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THESIS

SYNTHESIS OF ADVANCED INTERMEDIATES TO ANTI-CANCER OSW-1 AND SYNTHESIS OF CYCLIC SULFAMIDATES FOR *N*-HETEROCYCLE CONSTRUCTION

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A Thesis Submitted in Partial Fulfillment of
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Janjira Rujirawanich 2012: Synthesis of Advanced Intermediates to Anti-cancer OSW-1 and Synthesis of Cyclic Sulfamidates for *N*-Heterocycle Construction. Doctor of Philosophy (Chemistry), Major Field: Chemistry, Department of Chemistry. Thesis Advisor: Associate Professor Boonsong Kongkathip, Ph.D. 458 pages.

OSW-1, a natural product isolated from the bulbs of *Ornithogalum saundersiae*, exhibited extremely potent cytotoxicity against the NCI 60-cell *in vitro* screen, with a mean IC_{50} of 0.78 nM. Its *in vitro* anticancer activity is from 10 to 1000 times more potent than many well-known anticancer agents in clinical use, including mitomycin C, adriamycin, cisplatin, camptothecin and even pacilitaxel. In addition, its toxicity to normal human pulmonary cells is significantly lower (IC_{50} 1500 nM). The structure of saponin OSW-1 contains the steroidal aglycone with a sugar residue at the 16β-hydroxy.

Synthesis of the protected OSW-1 aglycone by the intramolecular reaction of the keto ester steroid intermediate has been investigated. The key intermediate, 3β-benzyloxy-16β-(isobutyl-monomethyl ester malonate-ester)-17α-hydroxy-pregnenolone, has been successfully synthesized in 10 steps with 10.4% overall yield from a commercially available diosgenin. Intramolecular McMurry coupling or samarium diiodide-promoted keto-ester coupling reaction of our key intermediate did not provide the expected β-keto lactone intermediate, and only 5-pregnene-20-one derivative or 16-dehydropregnenolone were obtained.

The facile syntheses of three partially protected OSW-1 disaccharide moieties, having 2-*O*-*p*-methoxybenzoyl-β-D-xylopyranosyl-(1→3)-2-*O*-acetyl-L-arabinopyranoside structure, were elaborated by glycosylation of xylopyranose donors and arabinopyranose acceptors. The xylopyranose donors were synthesized by a short synthetic approach *via* convenient selective 1,2-diacetal protection of 3,4-*trans*-diequatorial hydroxyl group. Additionally, three arabinose acceptors were prepared in a three steps sequence from benzyl, *p*-methoxybenzyl and thiophenyl α/β-L-arabinopyranosides by using regioselective reductive ring opening of benzylidene acetals as the key feature.

The synthesis of benzannulated *N*-heterocyclic compounds which are the class of privileged structures having a wide range of biological activities, bearing stereodefined substituents has been accomplished based on enantiomerically pure 1,2- and 1,3-cyclic sulfamidates towards a range of nucleophiles. The enantiomerically pure 1,2- and 1,3-cyclic sulfamidates were prepared from 1,2- and 1,3-amino alcohols. The nucleophilic cleavage of 1,2-cyclic sulfamidates with the sodium anion of 2-bromophenols (and related anilines and thiophenols), followed by Pd(0)-mediated amination provided the substituted and enantiomerically pure benzoxazine, benzothiazine and quinoxaline derivatives. Moreover, 1,2- and 1,3-cyclic sulfamidates undergo efficient nucleophilic cleavage with 2-hydroxybenzyl alcohol (and related 2-aminobenzyl alcohols and 2-mercaptobenzyl alcohols), followed by Mitsunobu reaction also furnishing substituted and enantiopure benzoxazepine, benzodiazepine, benzothiazepine, benzoxazocine, benzodiazocine and benzothiazocine derivatives.

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Student's signature Thesis Advisor's signature

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Janjira Rujirawanich

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LIST OF ABBREVIATIONS

Ac	=	Acetyl
Bn	=	Benzyl
DBU	=	1, 8-Diazabicyclo[5.4.0]undec-7-ene
DCM	=	Dichloromethane
DMAP	=	*N*, *N*-Dimethylpyridine
DMF	=	*N*, *N*-Dimethylformamide
PCC	=	Pyridinium chlorochromate
Ph	=	Phenyl
TBS	=	*tert*-Butyldimethylsilyl
TES	=	Triethylsilyl
Tf	=	Trifluoromethanesulfonate
δ	=	Chemical shift (ppm)
J	=	Coupling constant
υ_{max}	=	Maximum absorption frequency
cm^{-1}	=	Reciprocal centimeter (wave number)
m	=	Multiplet
s	=	Singlet
t	=	Triplet
q	=	Quartet
d	=	Doublet
dd	=	Doublet of doublets
ddd	=	Doublet of doublet of doublets
Hz	=	Hertz
FTIR	=	Fourier transform infrared spectroscopy
MS	=	Mass spectroscopy
CI	=	Chemical ionization
EI	=	Electron impact
HRMS	=	High resolution mass spectroscopy
m.p.	=	Melting point
m/z	=	A value of mass divided by charge

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LIST OF ABBREVIATIONS (Continued)

NMR	=	Nuclear magnetic resonance
h	=	Hour

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SYNTHESIS OF ADVANCED INTERMEDIATE TO ANTI-CANCER OSW-1 AND SYNTHESIS OF CYCLIC SULFAMIDATES FOR *N*-HETEROCYCLE CONSTRUCTION

INTRODUCTION

Synthesis of an anti-cancer OSW-1

Cancer is a leading cause of death worldwide. The control of cancer may benefit from the potential that exists in natural products. Some of them, originating from plants, have been involved in cancer treatment without recognizable side effects (Reddy *et al.*, 2003). One of such very promising natural products is the steroidal saponin OSW-1 (1), isolated in 1992 by Sashida and co-workers at Tokyo University from the bulbs of *Ornithogalum saundersiae*, a perennial cultivated in southern Africa as a cut flower and garden plant. OSW-1 is the main component of a group of cholestane glycosides from methanolic extract of *Ornithogalum saundersiae* (Figure 1). The structure of OSW-1 was characterized as 3β,16β,17α- trihydroxycholest-5-en-22-one 16-*O*-{*O*-(2-*O*-(4-methoxybenzoyl)-β-D-xylopyranoxyl)-(1→3)-2-*O*-acetyl-α-L-arabinopyranoside}. It was investigated that OSW-1 showed exceptional cytostatic activity against various malignant tumor cells, such as leukemia HL-60, mouse mastrocarcinoma, human pulmonary adenocarcinoma, human pulmonary large cell carcinoma, and human pulmonary squamous cell carcinoma including adriamycin-resistant P388 leukemia and camptothecin-resistant P388. OSW-1 showed highly cytotoxicity with IC_{50} values ranging between 0.1 and 0.7 nM, which means about 10-100 times more potent than of the clinically applied anticancer agents, such as mitomycin C, adriamycin, cisplatin, camptothecin, and taxol. Furthermore, OSW-1 represented very little toxicity (IC_{50} 1500 nM) to normal human pulmonary cells and it does not show obvious hemolytic effect to human erythrocytes at 100 μg/mL (Mimaki *et al.*, 1997).

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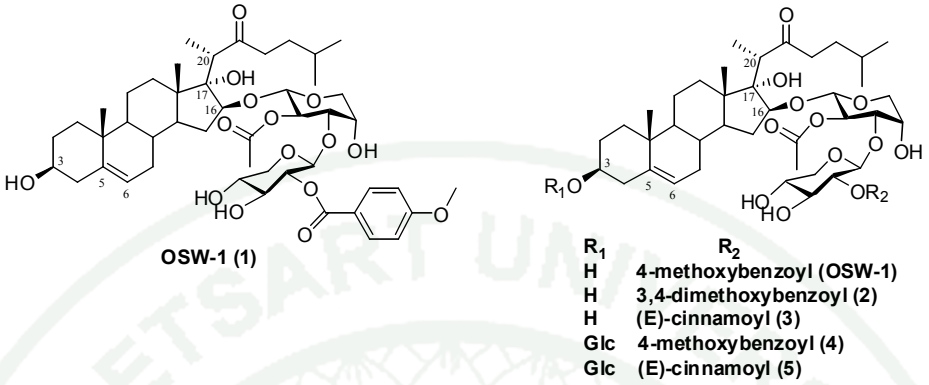
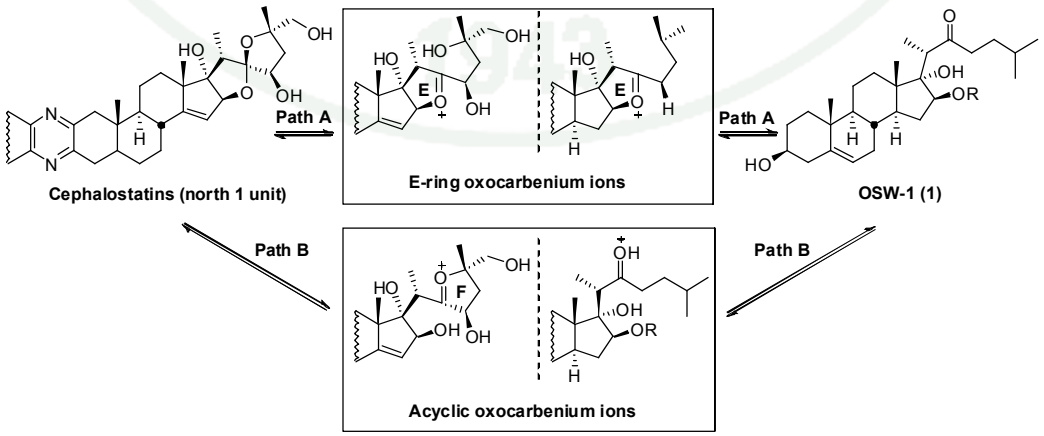


Figure 1 A group of cholestane glycosides from methanolic extract of *Ornithogalum saundersiae*.

The mechanism by which OSW-1 exerts its anticancer activity is poorly understood. However the cytotoxicity profile of OSW-1 is remarkably similar to that of cephalostatins, a group of dimeric steroid-pyrazines from marine organisms (Gryszkiewicz-Wojtkielewicz *et al.*, 2003) with Pearson correlation coefficients between 0.60 and 0.83. Initially, Guo and Fuchs (1998) hypothesized that the mechanism of action of OSW-1 and cephalostatins was proceeded *via* the same active intermediate E-ring oxonium ion (Scheme 1, path A), which could be generated from both types of them whereas the OSW-1 disaccharide moiety is function of a recognition element or a polarity modifier.



Scheme 1 The putative mechanisms of action of OSW-1 and Cephalostatins

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They further studied on the modes of action of several intermediates in their synthetic pathway for the anti-tumor activities. The cytotoxicity data of OSW-1 and its analogues concisely indicated that an acyclic oxocarbenium ion is the possible active intermediate which is more facilitated to generate from a ketal than the parent ketone (Scheme 1, path B) (Guo *et al.*, 1999). Therefore, the presence of both a 16β, 17α-diol and a C-22 carbonyl group is crucial for the biological activity of OSW-1.

Recently, Zhou and Garcia-Prieto (2005) investigated the anticancer activity and selectivity of OSW-1 and its underlying mechanisms of action using various human cancer and nonmalignant cell lines and found that OSW-1 damaged the mitochondrial membrane and cristae in both leukemia and pancreatic cancer cells, leading to the loss of transmembrane potential, increase of cytosolic calcium, and activation of calcium-dependent apoptosis. *In vitro* analysis showed that OSW-1 effectively killed primary leukemia cells from chromic lymphocytic leukemia patients with disease refractory to fludarabine. They concluded that OSW-1 exhibited a unique mechanism of action, in which structural and functional damage to mitochondria triggers activation of the Ca^{2+}-dependent apoptosis pathway. Nevertheless the exact mechanisms responsible for such selectivity are still unclear.

Immediately saponin OSW-1 was accepted in the high cytotoxic activity, numerous chemist groups around the world have paid attention to the synthesis of this compound including our group. Saponin OSW-1 could be plausibly disconnected into two parts: the cholestane aglycone and the disaccharide part. Studies on the structure-activity relationships (SAR) of this novel type of anticancer agent have so far been explored on both steroidal part and disaccharide part. Consequently short and convenient synthetic approaches have been required for synthesis of saponin OSW-1 and its analogues.

Over the past few decades, our research group (Kongkathip's group) have been studying on the synthesis of many noticeable steroidal compounds and several interesting steroid drugs, such as prednisolone (Mongkolsripatana, 1997; Noimai, 2001), triamcinolone (B. Kongkathip *et al.*, 1998), estradiol (Hasakunpaisan, 2000),

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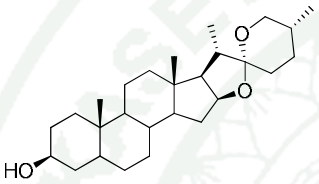
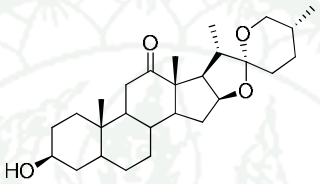
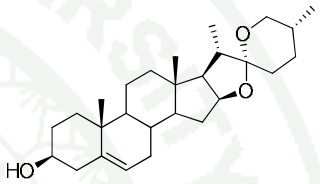
cyproterone acetate and its derivatives (Sakee *et al.*, 2003), OSW-1 aglycone (Chaosuancharoen *et al.*, 2004), betamethasone (N. Kongkathip *et al.*, 2006), polyoxygenated steroids and geodisterol (Boonananwong *et al.*, 2008) and antiviral sterol orthoesters and new polyhydroxy sterols (Bunyathaworn *et al.*, 2010; Bunyathaworn *et al.*, 2011) from the naturally occurring steroidal sapogenin tigogenin (6), hecogenin (7) or diosgenin (8).



Tigogenin (6)



Hecogenin (7)



Diosgenin (8)

This research is focused on the synthesis of saponin OSW-1 which is divided into two parts. The cholestane aglycone part could be synthesized from the naturally occurring diosgenin (8), isolated from *Dioscorea* plant. Diosgenin is also commercially inexpensive available and its cholestane skeleton is flexible for the synthesis of the steroidal part of OSW-1. Another part, disaccharide moiety, is obtained by alternative synthetic pathways from commercially available L-arabinose and D-xylose.

Synthesis of cyclic sulfamidates for *N*-heterocycle construction

Cyclic sulfamidates have served important roles for the synthesis of various products possessing heteroatomic functional groups. Cyclic sulfamidates are accessible *via* readily available 1,2- and 1,3-amino alcohols that are easily prepared from enantiomerically pure amino acids. Nucleophilic addition of cyclic sulfamidate at the oxygen-bearing carbon furnishes an *N*-sulfate intermediate in a stereospecific manner (S_N2). The addition products are achieved by hydrolysis of *N*-sulfate intermediate under acidic conditions (HCl, H_2SO_4, BF_3/thiol) (Scheme 2) (Bower, 2007).

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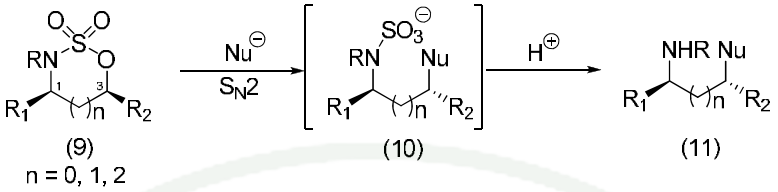
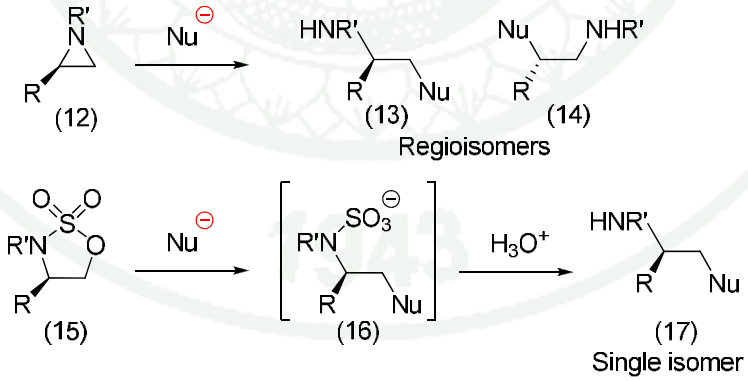


Scheme 2

Cyclic sulfamidates can function as potentially versatile intermediates more than the aziridines and azetidines for the synthesis of functionalized *N*-heterocycle compounds due to the combination of reduced ring strain and competing S_N1 reaction. Furthermore, cyclic sulfamidates allow flexibility with regard to the protecting group employed on nitrogen. For example, whereas aziridines often require activating protecting groups (such as *N*-tosyl or *N*-P(O)Ph_2), a variety of nitrogen protecting groups can be tolerated on cyclic sulfamidates (*e.g.* Boc, Cbz, benzyl) with only relatively small effects upon their susceptibility to nucleophilic cleavage (Bower, 2007). Importantly, the regioselectivity of nucleophilic attack occurs preferentially at the oxygen-bearing carbon, and attack at C-1 is never observed (Scheme 3 and 4).



Scheme 3

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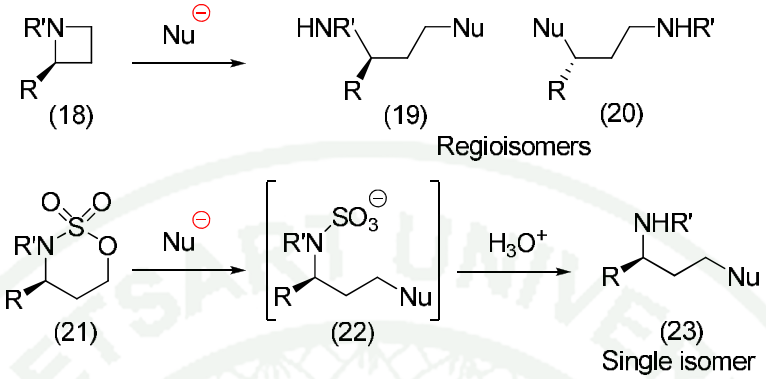

Scheme 4

There are many strategies to synthesize cyclic sulfamidates, for instance, from 1,2- or 1,3-amino alcohols, from 1,2-diol (Nicolaou *et al.*, 2002), *via* metal-catalysed nitrene insertion (Espino *et al.*, 2001; Liang *et al.*, 2002) and *via* tethered aminohydroxylation. The interesting one is the synthesis of cyclic sulfamidate starting from enantiomerically pure amino acid derivatives which are commercially available and easy to convert to amino alcohols (Scheme 5).

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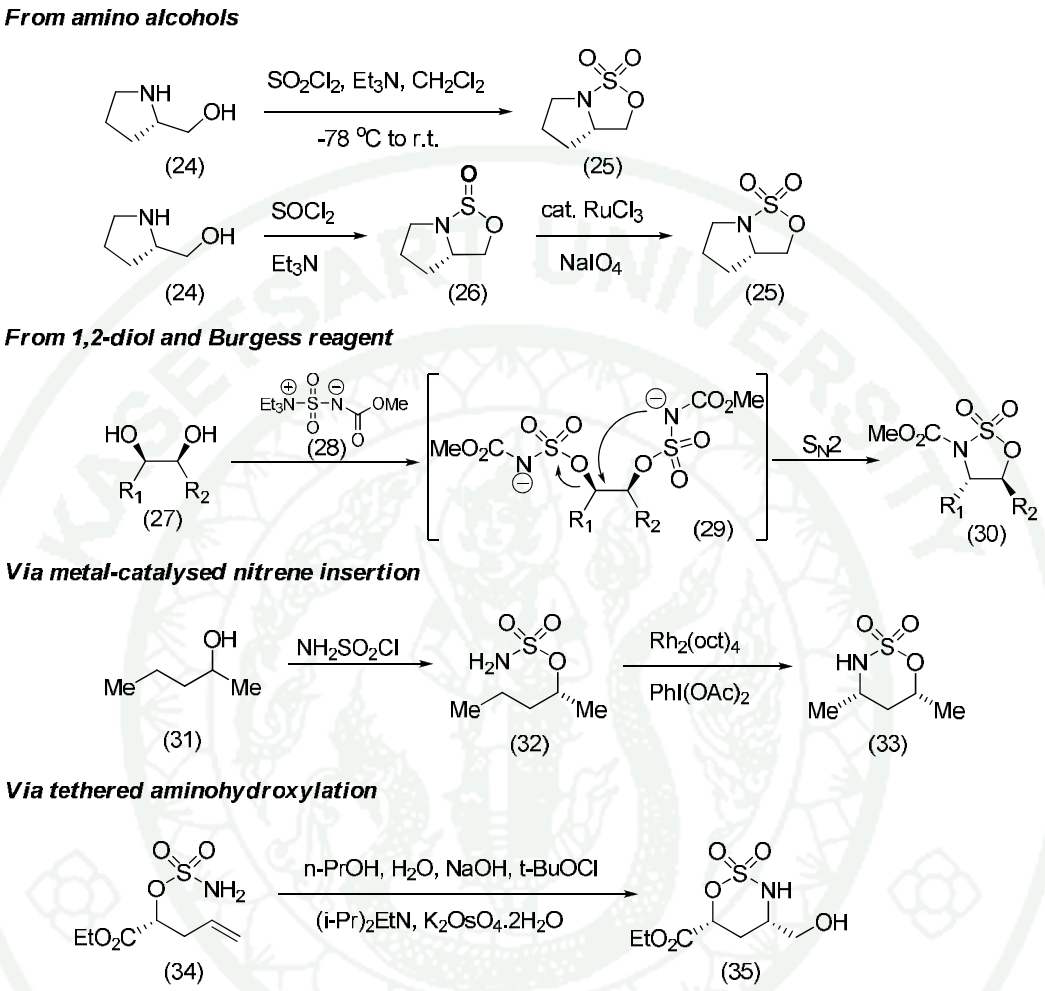

Scheme 5

Cyclic sulfamidates (36), which are readily available in enantiomerically pure form (Meléndez and Lubell, 2003), provide the basis of a flexible entry to a range of substituted heterocyclic scaffolds (Bower *et al.*, 2010). These include benzofused systems **39**, representing substituted tetrahydrobenzoxazines, benzothiazines, and quinoxalines, and the sequence outlined in Scheme 6 provides a general entry to these heterocyclic targets.

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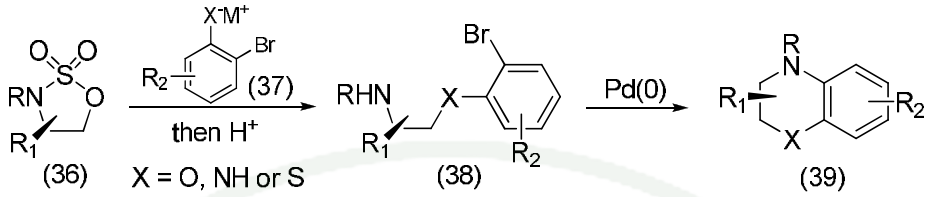

Scheme 6

More generally, these structures represent "rule of three" (Lipinski, 2000; Lipinski *et al.*, 1997) compatible fragments, and we were interested to extend the scope of this chemistry to provide access to other, heterocyclic targets with medicinal potential.

Over the past decades, the design and synthesis of medium ring heterocycles having a ring size in the range of 6-11 have received a lot of attention in synthetic organic chemistry as a consequence of a wide variety of applications such as biologically active natural products, drug candidates, materials, and for catalysis (Mishra and Panda, 2007) (Figure 2). Among them, the corresponding seven-ring variants (tetrahydro-benzoxazepines, benzothiazepines, and benzodiazepines) have also attracted a great deal of interest from the pharmaceutical sector, for example, the tetrahydro-1,4-benzothiazepines S107 (40) and JTV519 (41) are being evaluated for treating conditions linked to stabilization of cardiac ryanodine receptors (RyR1), which leak Ca^{2+} when subjected to stress (Bellinger, Mongillo *et al.*, 2008; Bellinger *et al.*, 2009; Bellinger, Reiken *et al.*, 2008). In addition, benzodiazepines are the class of privileged structures having a wide range of biological activities. Benzoxazepines show pharmacological activities such as antipsychotic for the central nervous system along with antibreast cancer (Díaz-Gavilán *et al.*, 2004; Liao *et al.*, 1999). Benzothiazepines are active constituents of an important class of biologically active compounds such as bradykinin agonists (Amblard *et al.*, 1999; Milligan, 1993). Eight-membered benzannulated heterocycle benzodiazocine, such as Teleocidines, activate protein kinase C (PKC) isozymes (Kazanietz *et al.*, 2000). Benzoxazocine, such as Nefopam hydrochloride, is a nonnarcotic analgesic drug with antidepressant properties. The abundance of medium ring heterocycles continues to ensure that they

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are attractive targets for synthetic organic chemists. Despite their wide occurrence and bioactivity, benzannulated medium ring heterocycles are not sufficiently investigated, one barrier to their access generally being unsatisfactory synthetic procedures. Thus, the development of novel and efficient methods leading to medium size heterocycles is an important area of research. However, only few methodologies for construction of medium ring heterocycles are available.

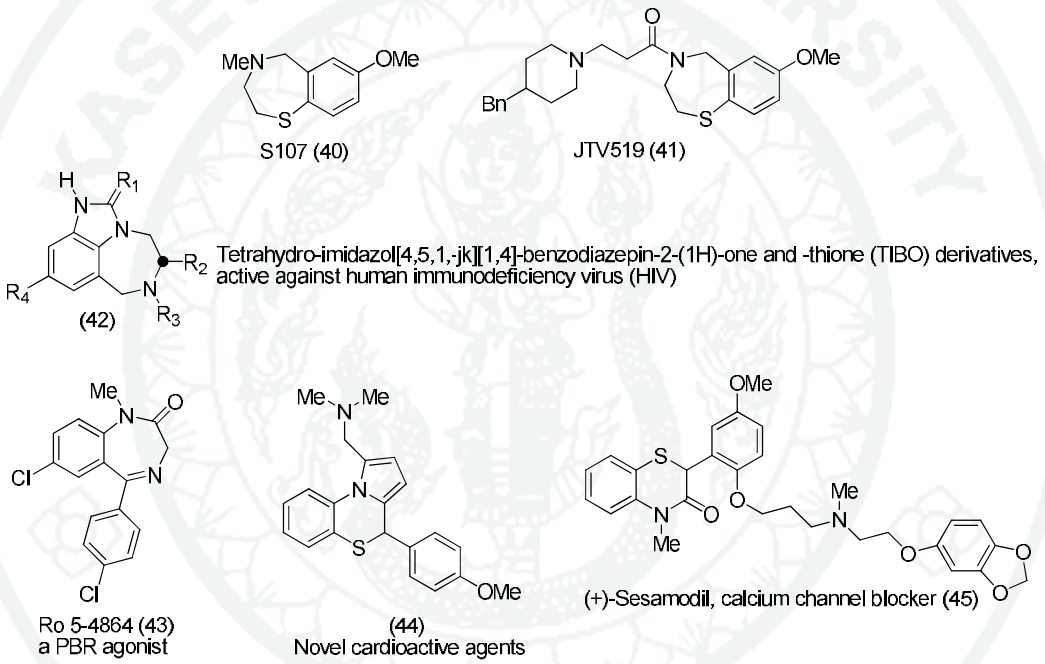

Figure 2 Biologically active heterocyclic compounds**.**

In this research we focused on the application of cyclic sulfamidates to the synthesis of seven- and eight-ring heterocyclic systems based on a departure from the chemistry outlined in Scheme 6.

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OBJECTIVES

1. To synthesize steroidal OSW-1 key intermediates for intramolecular cyclization studies

2. To study intramolecular McMurry reaction and samarium diiodide-promoted intramolecular ketone-ester coupling reaction of OSW-1 intermediates

3. To synthesize disaccharide moieties of OSW-1

4. To synthesize the enantiomerically pure substituted and unsubstituted five- and six-membered cyclic sulfamidates containing two protecting groups, benzyl and tosyl groups.

5. To synthesize benzannulated *N*-heterocyclic compounds bearing stereo-defined substituents based upon readily available and enantiomerically pure 1,2- and 1,3-cyclic sulfamidates.

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LITERATURE REVIEW

Biological activity of OSW-1 and related compounds

Over the past decade, a group of mono- and bisdesmosidic cholestane glycosides was isolated from the bulbs of *Ornithogalum saundersiae*, a species of the lily family, and has shown significant inhibitory activity on cyclic AMP phosphodiesterase with IC_{50} value of 5.5×10^{-5} M (Kubo *et al.*, 1992).

A few years later it has been reported that a methanolic extract of *Ornithogalum saundersiae* has showed exceptional cytostatic activity against various malignant tumor cells (Table 1) (Mimaki *et al.*, 1997). The major component, OSW-1 and a group of cholestane glycosides were isolated from the methanolic extract.

Table 1 Cytostatic activities of OSW-1 and clinically applied anticancer agents on various malignant tumor cells.

Malignant cells	IC_{50} (μg/ml)					
	OSW-1	MMC	ADM	CDDP	CPT	TAX
CCD-19Lu	1.5	2	2	10	2	2
P388	0.00013	0.01	0.003	0.05	0.005	0.01
P388/ADM	0.00077	-	-	-	-	-
P388/CPT	0.00010	-	-	-	-	-
FM3A	0.00016	-	-	-	-	-
A-549	0.00068	-	-	-	-	-
Lu-65	0.00020	-	-	-	-	-
Lu-99	0.00020	0.01	0.002	0.001	0.001	0.002
RERF-LC-AI	0.00026	-	-	-	-	-
CCRF-CEM	0.00016	0.02	0.01	0.005	0.005	0.001

*MMC = Mitomycin C; *ADM = Adriamycin; *CDDP = Cisplatin
*CPT = Camptothecin; *TAX = Taxol

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Table 1 (Continued)

CCD-19Lu (human normal pulmonary cell)
P388 (mouse leukemia)
P388/ADM (adriamycin-resistant P388)
P388/CPT (camptothecin-resistant P388)
FM3A (mouse mastrocarcinoma)
A-549 (human pulmonary adenocarcinoma)
Lu-65 (human pulmonary large cell carcinoma)
Lu-99 (human pulmonary large cell carcinoma)
RERF-LC-AI (human pulmonary squamous cell carcinoma)
CCRF-CEM (human leukemia)

Source: Mimaki *et al.* (1997)

There are several interesting publications for studying on the mechanism of action of anticancer activity and selectivity of OSW-1. In 2005, Zhu and co-workers reported that OSW-1 induced apoptosis of mammalian cells in concentration- and time-dependent manners. Apoptosis is a general cellular process which serves an important role in normal development as well as pathology of a number of human diseases. The resistance to apoptosis is common feature of cancer cells. Later, Zhou *et al.* (2005) also investigated the underlying mechanism of action of OSW-1. They summarized that OSW-1 possesses highly potent anticancer activity against several human malignant cell lines and primary leukemia cells from patients with chronic lymphocytic leukemia (CLL). Their results demonstrated that this compound displayed a unique mechanism of action, in which structural and functional damage to mitochondria triggers activation of the Ca^{2+}-dependent apoptosis pathway. However the distinctive mechanisms responsible for such selectivity remain unclear. The chemists have still been researching for its unique mechanism of action and further investigating for its potential to overcome drug resistance.

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Early reported syntheses of OSW-1 aglycone and OSW-1

Since OSW-1 has shown an outstanding cytotoxicity profile against various malignant tumor cell lines, there are numerous groups of chemists around the world interested in the synthesis of this compound until now. OSW-1 aglycone, OSW-1 and its derivatives have been synthesized for three main reasons: the mechanism of action study on cancer cells, the structure biological activity relationships (SAR) and the new excellent methodology in the synthesis. In general retrosynthetic analysis, OSW-1 can be logically disconnected into two distinctive parts: the cholestane aglycone and the disaccharide parts (Figure 3). Clearly, a major challenge synthesis of OSW-1 aglycone and its derivatives was the elaboration of the 16β,17α-diol and the incorporation of the side chain into the tetracyclic steroid nucleus. Until today, there are two major starting materials used in the synthesis of OSW-1: an industrial material (+) dehydroisoandrosterone (48) and 16-dehydropregnenolone acetate (49) which can be prepared through the degradation of inexpensive commercial diosgenin. The disaccharide moiety could be derived from commercial available D-xylose (53) and L-arabinose (54).

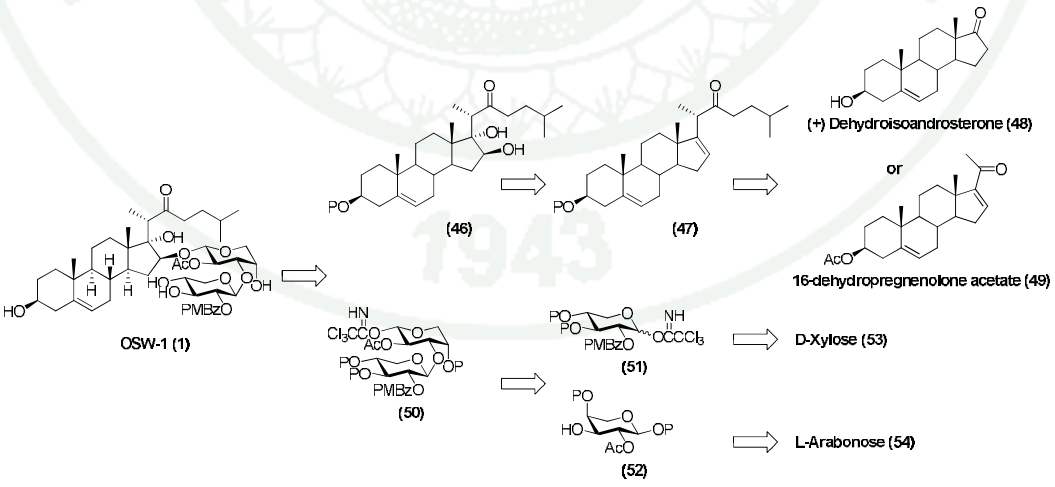

Figure 3 Retrosynthesis of OSW-1.

Owing to the correlative cytotoxicity profile between OSW-1 and cephalostatins, Guo and Fuchs hypothesize that both of them might have the same

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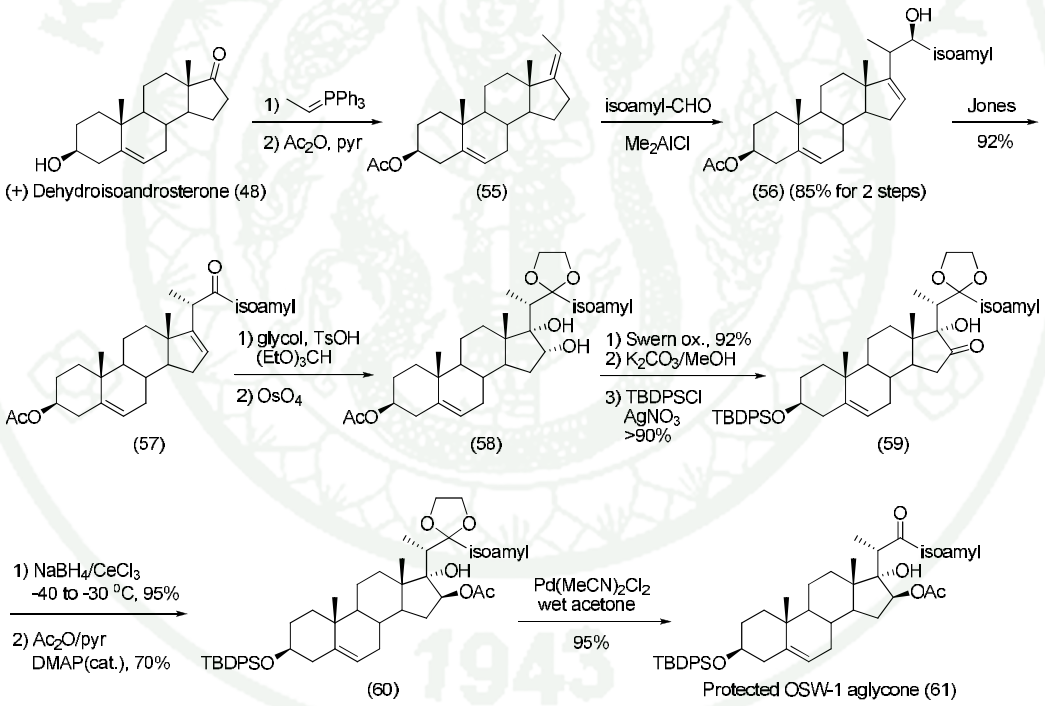
mechanism of action and the active intermediate might be an oxonium ion, which could be generated from both types of compounds (Scheme 1), whereas the disaccharide unit might serve as a recognition element or a polarity modifier. To investigate their hypothesis, the first protected OSW-1 aglycone was synthesized in 9 steps with about 55% overall yield starting from the commercial available (+) dehydroisoandrosterone (48). The considerable step in this synthesis was introduction of the C22 oxygenated side chain by diastereoselective ene reaction with 3-methylbutyraldehyde after Wittig olefination of ketone as shown in Scheme 7 (Guo and Fuchs, 1998).



Scheme 7 Fuch's synthesis of the OSW-1 aglycone

Year later, Guo *et al.* (1999) further studied on the anti-tumor activities of several intermediates of their synthetic compounds to examine their hypothesis. They concluded pathway that OSW-1 and the cephalostatin family appear to share similar modes of action. The SAR data of their synthetic compounds indicated that the probable intermediate responsible for cytotoxicity is an acyclic oxocarbenium ion (Scheme 1), which is more easily generated from ketal than the parent ketone.

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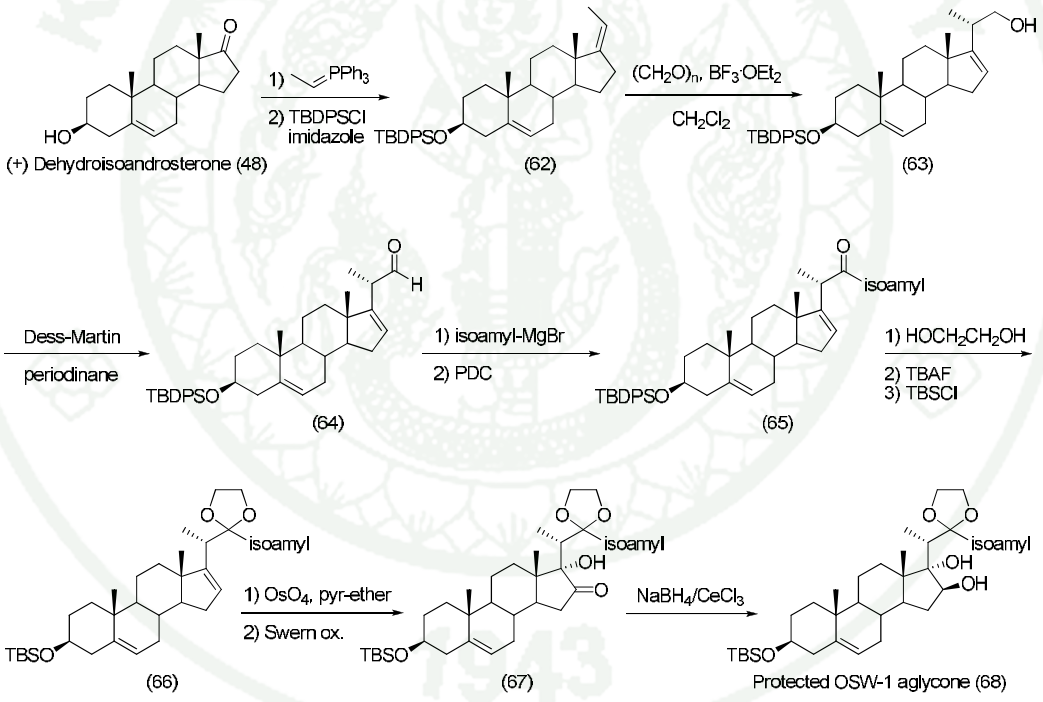
In 1999, Deng *et al.* accomplished the first total synthesis of OSW-1. The steroid aglycone was also synthesized from (+) dehydroandrosterone (48) using a strategy similar to that employed by Fuchs. The considerable difference consist in the introduction of the C22-functionalized side chain, where the diastereoselective ene reaction was carried out with paraformaldehyde (in Fuch's synthesis with 4-methylvaleraldehyde). The subsequent side chain elongation through oxidation and Grinard addition furnished the 16,17-en-22-ketone (65). The trans-16β,17α-diol was also created by the same methodology using by Fuchs to give the protected OSW-1 aglycone **68** in 12 linear steps in 10% overall yield (Scheme 8) (Deng *et al.*, 1999).



Scheme 8 Deng's synthesis of the OSW-1 aglycone

They proposed a very concise and straightforward manner to synthesize the disaccharide moiety which consists of 2-*O*-*p*-methoxybenzoyl-D-xylopyranose and 2-*O*-acetyl-L-arabinopyranose units. The xylose donor was prepared by regioselective introduction of a *p*-methoxybenzoate at the 2-hydroxyl group after protection of the anomeric position as a benzyl ether. Then, the rest of the hydroxyl groups (3-OH and

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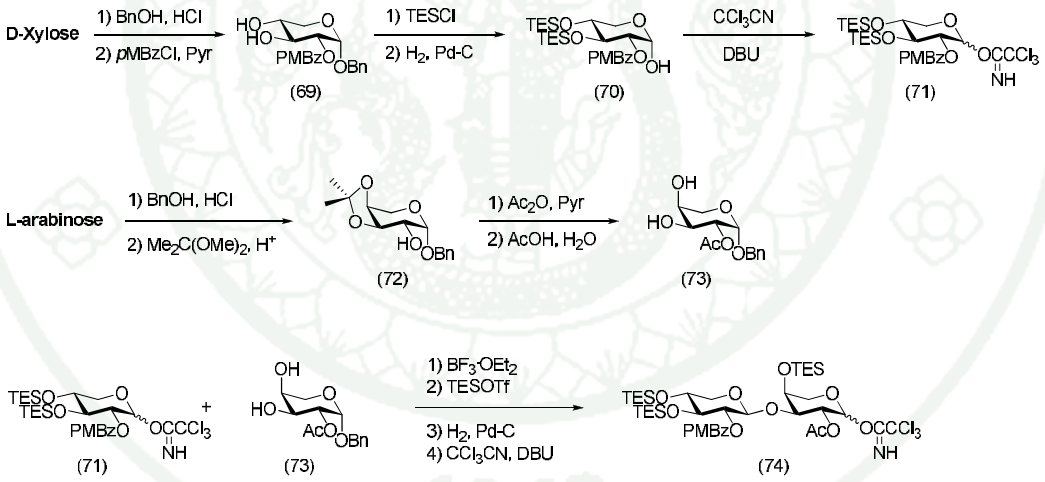
4-OH) were turned into the bis-TES ether. The following removal of the anomeric benzyl group was employed to generate the hemiacetal which was then converted to the corresponding trichloroacetimidate **71**. The L-arabinosyl acceptor **73** was synthesized from L-arabinose in four steps and in 67% yield: benzylation of anomeric hydroxyl group, isopropylidenation of 3,4-hydroxyl groups, acetylation of the 2-hydroxyl group and final removal of the acetonide protection. Although the L-arabinosyl acceptor prepared in this method contains two hydroxyl groups, a regioselective glycosylation with the xylosyl donor under $BF_3{\cdot}OEt_2$ catalysis (Schmidt and Michel, 1980) furnished the desired disaccharide as a major product. The remaining hydroxyl group was protected as a TES-ether. Then removal of benzyl group provided the hemiacetal which was converted to trichloroacetimidate **74** (Scheme 9).



Scheme 9 Deng's synthesis of the disaccharide moiety

The glycosylation of the steroidal aglycone **68** with the disaccharide imidate **74** under TMSOTf catalysis (Schmidt and Toepfer, 1991) proceeded smoothly providing the fully protected OSW-1. Removal of all protecting groups (TBS, TES, ethylene glycol ketal) in only one step with $Pd(MeCN)_2Cl_2$ catalyst (Lipshutz *et al.*, 1985) completed the first total synthesis of saponin OSW-1 in 27 steps in 6% overall yield (Scheme 10).

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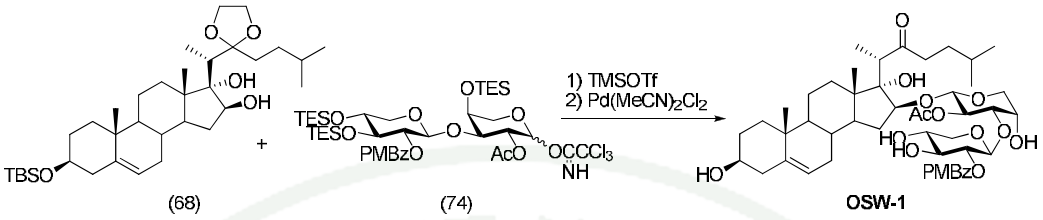
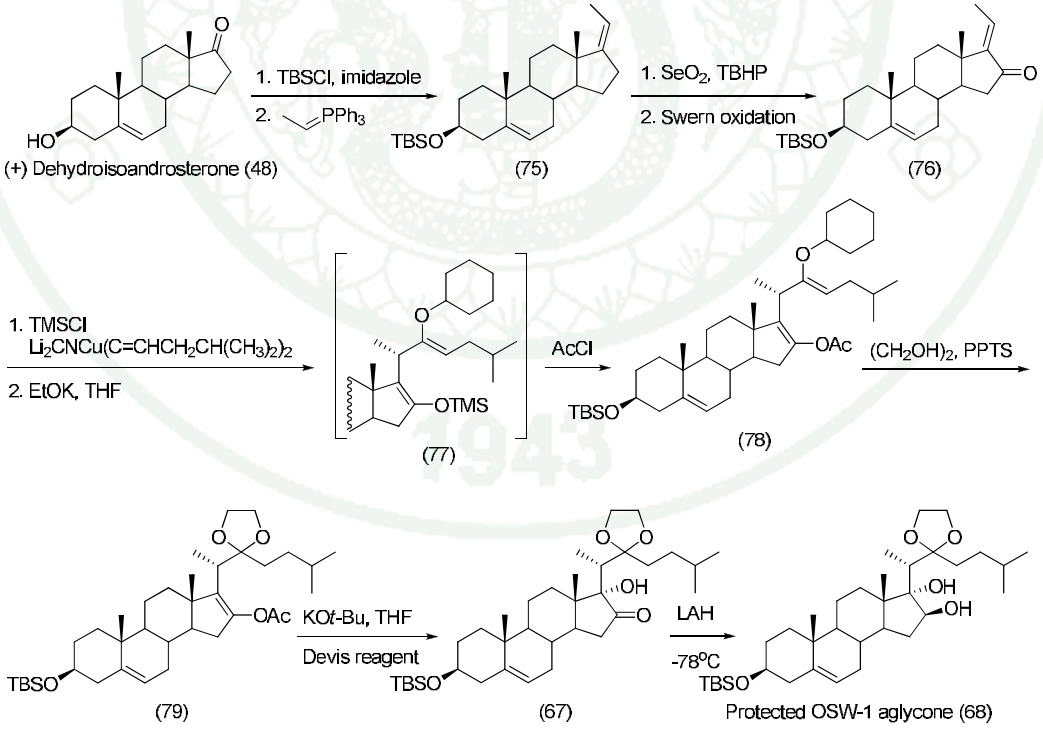


Scheme 10

Yu and Jin (2001) reported a completely different approach for the total synthesis of OSW-1. The strategy was based on stereoselective introduction of the steroid side chain *via* 1,4-addition of an α-alkoxy vinyl cuprate to steroid enone **76** (Scheme 11). The starting material was (+) dehydroisoandrosterone (48), as in the previous works. This methodology provided OSW-1 in only 10 linear operations from starting in 28% overall yield (Yu and Jin, 2001).



Scheme 11 Yu's synthesis of the OSW-1 aglycone

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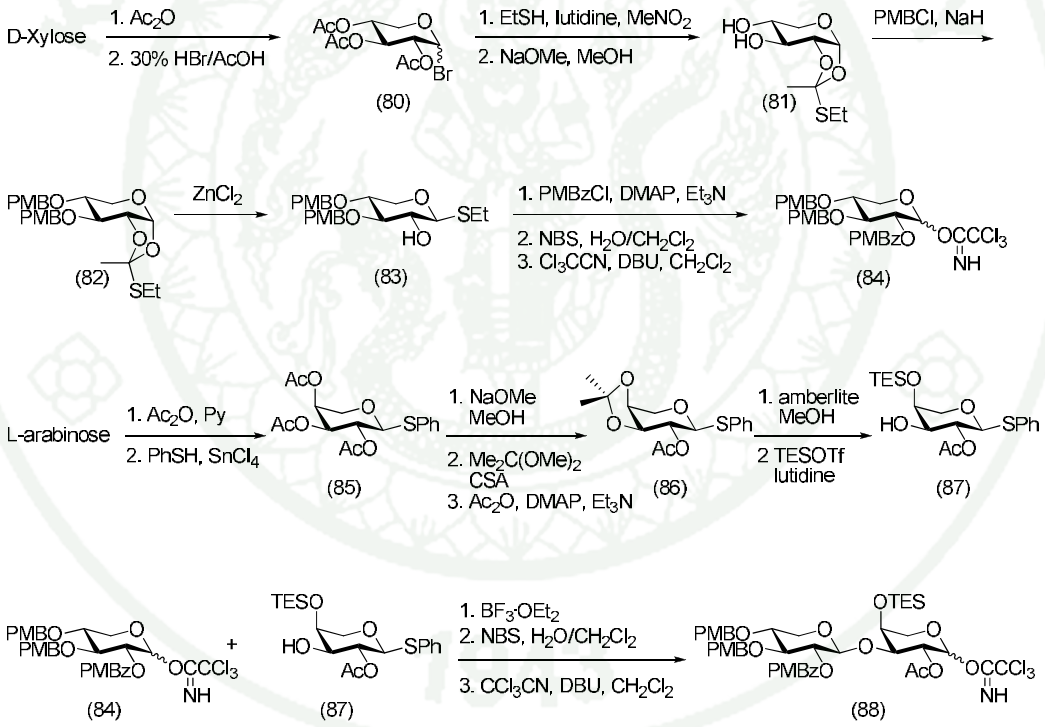
They also elaborated a new method for the synthesis of the disaccharide moiety shown in Scheme 12. The active xylose derivative **84** was synthesized in 8 steps from tetraacetyl-D-xylose *via* a key intermediate, the thio ortho ester (82). Tetraacetyl-L-arabinose was converted to a thioglycoside **87** *via* 6 steps sequentially; thioglycosylation, hydrolysis of the rest acetyl group, protection of 3-OH and 4-OH as acetonide and 2-OH as an acetate, removal of acetonide, finally regioselective triethylsilylation of the axial hydroxyl group at C4. The saccharide coupling reaction and glycosylation of the OSW-1 aglycone **68** were accomplished under conditions comparable to those in the synthesis described by Guo and Fuch.



Scheme 12 Yu's synthesis of the disaccharide moiety

In 2000, Morzycki *et al.* proposed a distinct method to the synthesis of OSW-1 aglycone through the key intermediate, 16α, 17α-oxido-steroids (Scheme 13). They studied on the cleavage of the 16α, 17α-epoxide (90) ring to trans diol in ring D using LiOH, H_2O_2, EtOH to give 16β, 17α-dihydroxy-22-carboxylic acid, which was spontaneously cyclized to the key precursor, 17α-hydroxy lactone **91** (Morzycki *et*

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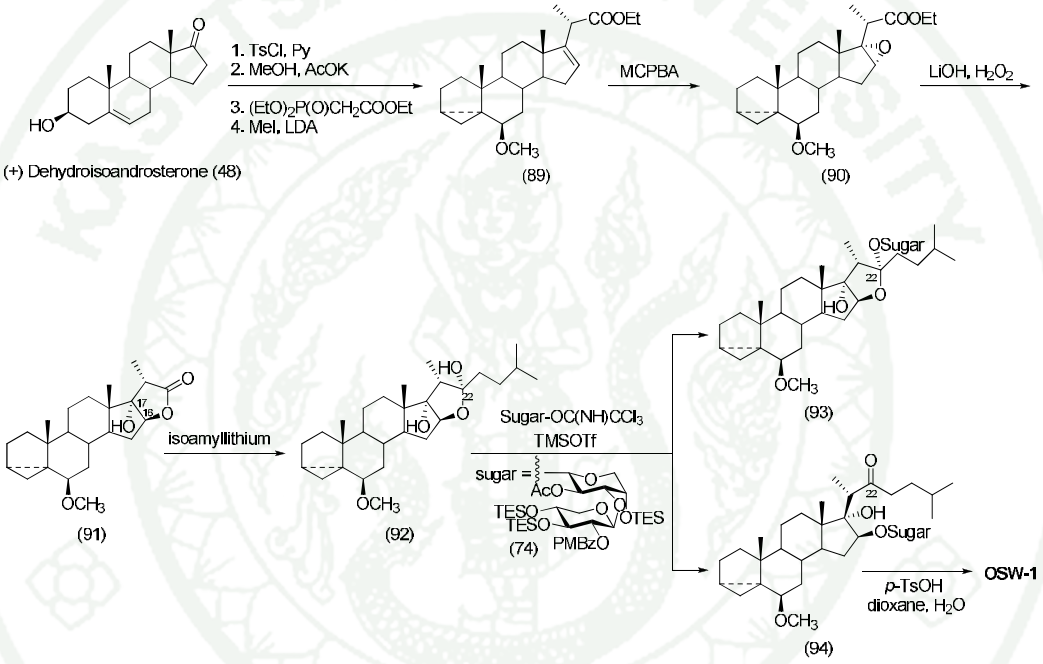
al., 2000). Treatment of lactone **91** with isoamyllithium provided hemiketal **92** which was exposed to glycosylation with the disaccharide trichloroacetimidate **74** under standard condition (Schmidt and Toepfer, 1991) to give two products, the protected saponin OSW-1 **94** and the 22-*O*-glycoside of the hemiketal **93**, in the ratio of about 1:1.



Scheme 13 Morzycki's synthesis of OSW-1

There are two more routes from the lactone **91** to the saponin OSW-1 (Scheme 14) (Morzycki *et al.*, 2001; Morzycki and Wojtkielewicz, 2002). In one of them, lactone **91** was reduced with DIBAL-H to give the lactol **95**, which was then glycosylated with the disaccharide to give 16*β*-*O*-glycoside aldehyde **96** along with the side products, the 22-*O*-glycoside **97** and ortho-acetate **98**. The 16*β*-*O*-glycoside **96** was converted to OSW-1 by treatment with isoamylmagnesium bromide, oxidation with PDC and removal of all protecting groups. The weakness of this approach was side reaction when **96** was treated with the Grignard reagent, retroaldol fragmentation was occurred to give 17-keto steroid (100). In the second route, the saponin OSW-1 was synthesized from the 22-*O*-benzylether **101** which was obtained in three steps

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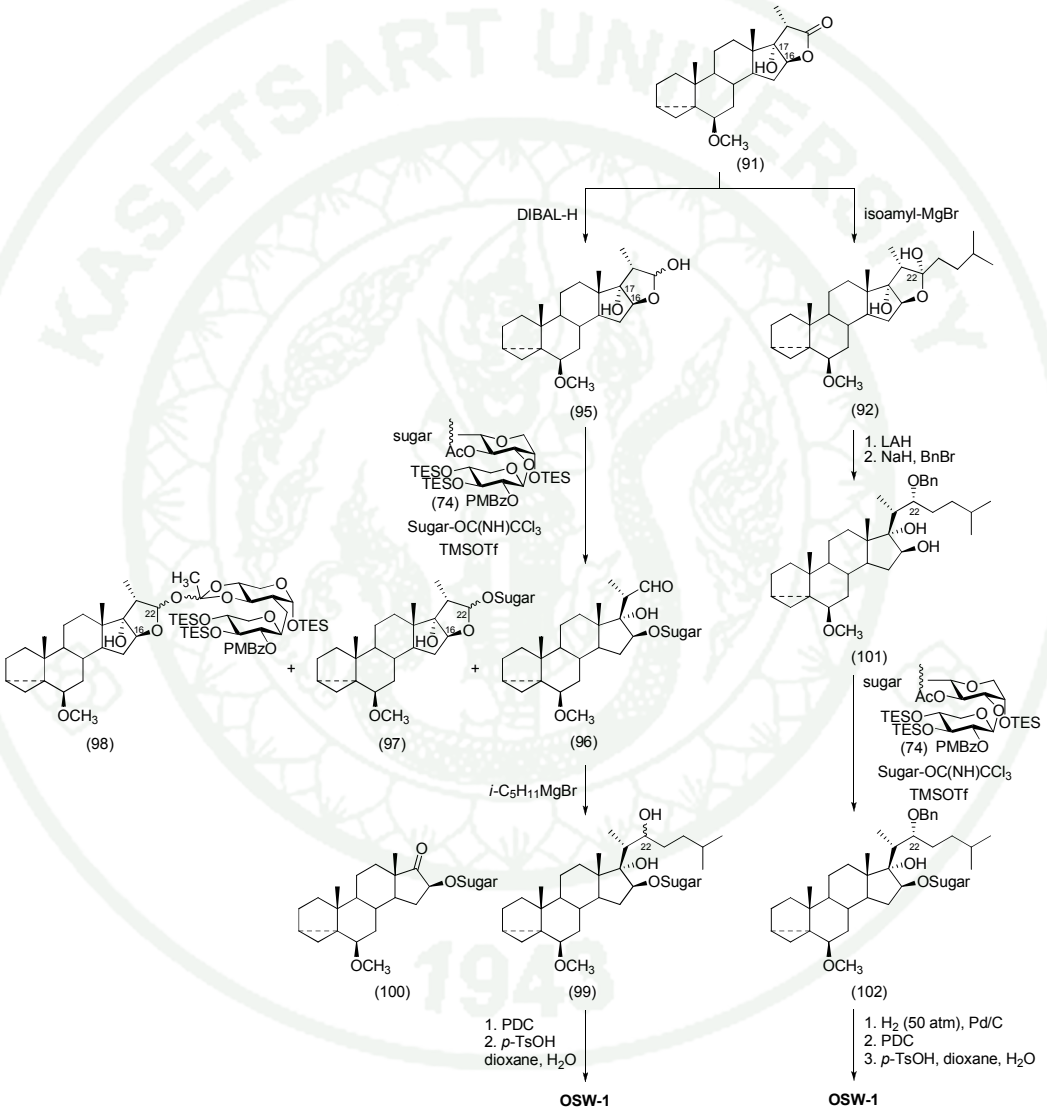
from lactone **91**. Glycosylation of **101** with the disaccharide imidate followed by hydrolysis of benzyl ether, PDC oxidation of 22-alcohol to the ketone and final removal of the protecting group provided OSW-1.



Scheme 14 Morzycki's alternative syntheses of OSW-1

Tian's group proposed a new strategy for synthesis the aglycone of OSW-1 by using the intact skeleton of diosgenin which is an easily available and cheap substrate (Scheme 15) (Xu *et al.*, 2003).

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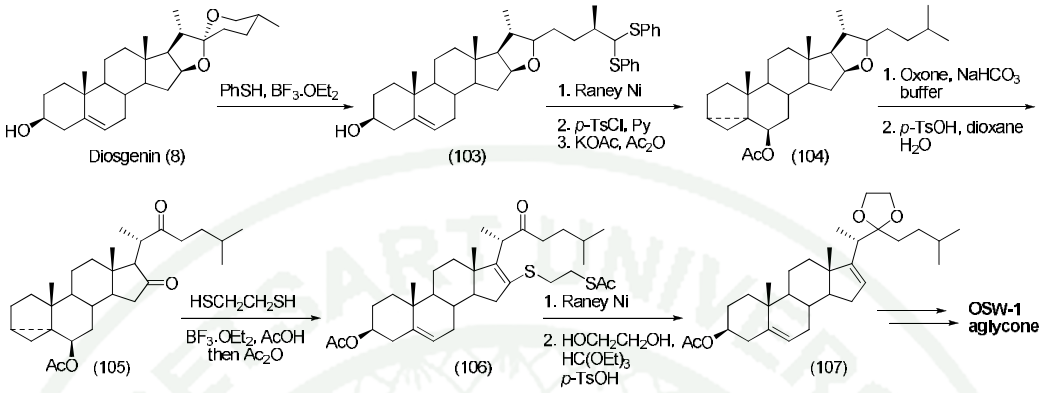

Scheme 15 Tian's synthesis of the OSW-1 aglycone

Treatment of diosgenin with PhSH in the presence of $BF_3 \cdot OEt_2$ opened ring F to dithiol (103) which was underwent reductive desulfurization catalyzed by Raney nickel. The double bond at C-5 and the 3α-hydroxyl group of **103** were protected as an *i*-steroid ether (104) before further modification of the ring E. Oxidation of the resulted compound **104** with dimethyldioxirane opened E-ring to give the diketone **105**. The regioselective conversion of 16, 22-diketone **105** with ethanedithiol in the presence of $BF_3 \cdot OEt_2$ afforded a 16-thioketal which was acetylated with Ac_2O to yield an enol thioether **106**. The known intermediate **107** in the earlier presented synthetic strategies, 16-en-22-one, was obtained by desulfurization of this enol thioether and protected ketone as cyclic ketal. This known compound (107) was further transformed to the protected OSW-1 aglycone according to Fuch's method. The aglycone was synthesized in 13 linear steps in 9.5% overall yield (Scheme 15).

Chaosuancharoen *et al.* (2005) reported the synthesis of the protected aglycones of OSW-1 from commercially available diosgenin (8) in 15 steps in about 0.5% overall yield (Scheme 16). The synthetic strategy is pointed at creating the cholesterol side chain from the spiro-ring without any carbon addition being required.

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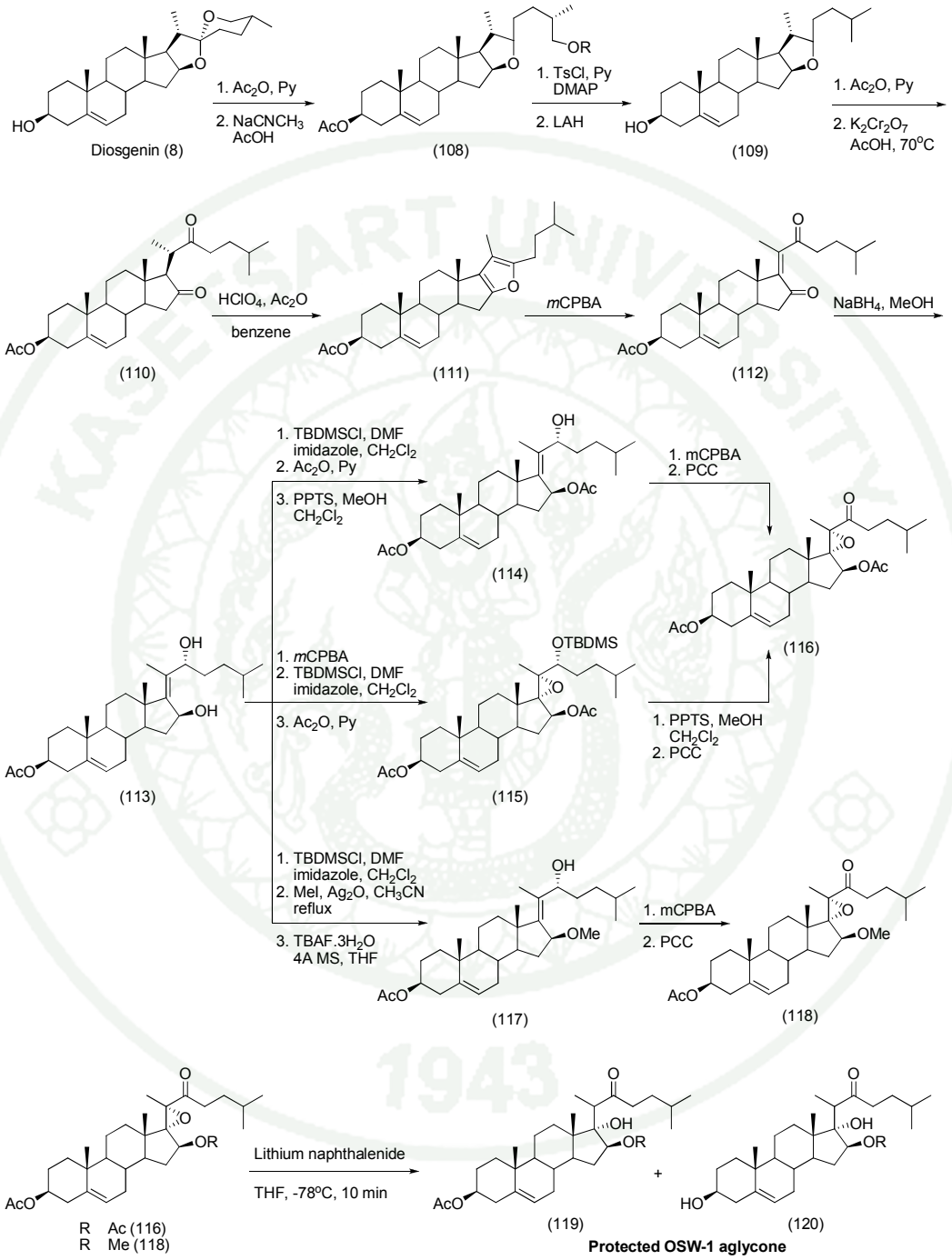

Scheme 16 Kongkathip's synthesis of the OSW-1 aglycones

The crucial synthetic method consists of two key steps. The first is construction of the cholesterol side chain from the spiro ring of diosgenin which could

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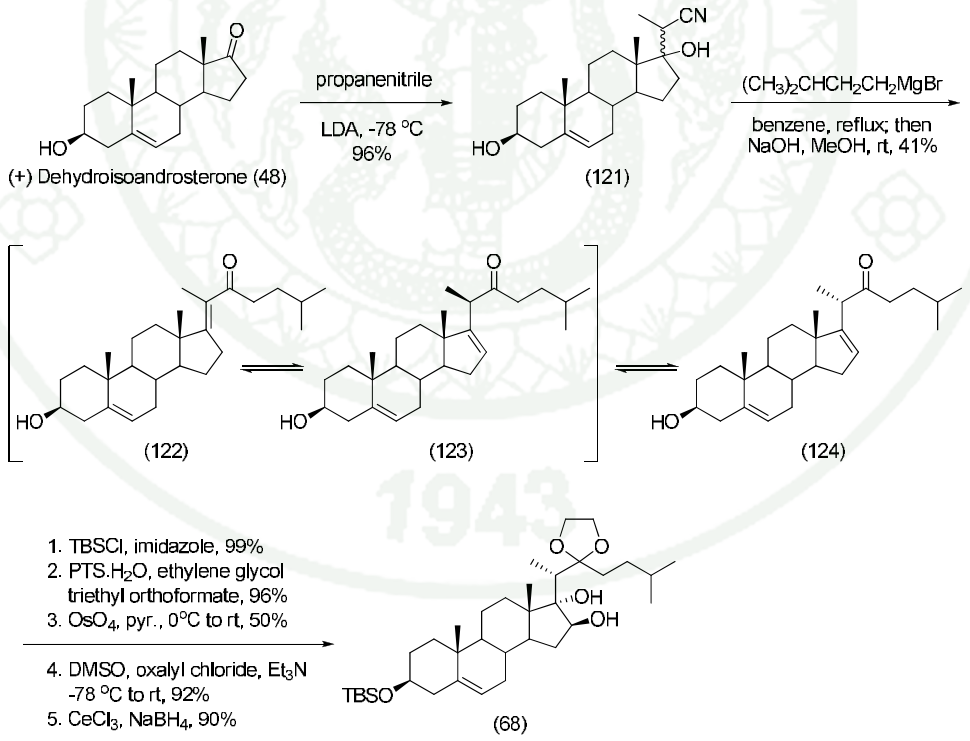
be accomplished by reductive opening of sapogenin spiroketal followed by the oxidative cleavage of the tetrahydrofuran moiety to yield the cholesterol side chain. The second is reductive cleavage of an α, β-epoxy ketone (116 and 118) to a β-hydroxy ketone (119 and 120) using lithium naphthalenide generated in situ from lithium metal and naphthalene (Scheme 16) (Chaosuancharoen, 2004).

In 2008, Xue and co-workers completed the total synthesis of OSW-1 from (+)-dehydroisoandrosterone, L-arabinose and D-xylose on gram scale. Aldol condensation reaction of (+)-dehydroisoandrosterone (48) with propanenitrile and LDA gave an epimeric mixture of **121** which was subjected to a key Grignard reaction describing by Yu and Jin (2001) to introduce a side chain at the C-17 to afford the thermodynamically more stable **124** as the major product (Scheme 17).



Scheme 17 Xue's synthesis of the OSW-1 aglycone

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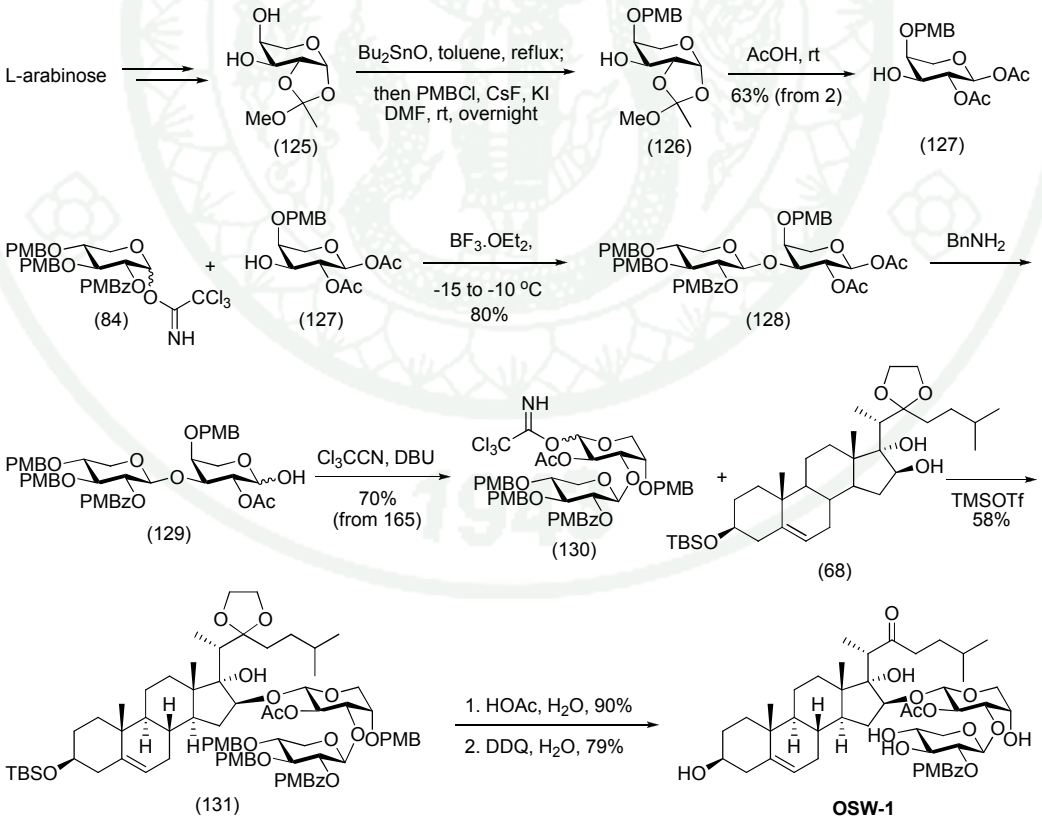
The desired glycosyl L-arabinopyranoside acceptor was prepared from **125** which was obtained from L-arabinose as reported (Magnus *et al.*, 1983). It was regioselectively *p*-methoxybenzylated with the assist of dibutyltin complex to yield **126**, which was exposure to acetolysis to give the acceptor **127**. The other glycosyl donor was prepared according to Jin's method with modified work-up procedures. Glycosylation of donor and acceptor was accomplished by using $BF_3{\cdot}OEt_2$ to give **128** which was converted to trichloroacetamide **130**. Protected OSW-1 aglycone (68) and trichloroacetamidate (130) were subjected to glycosylation under TMSOTf as promoter to give protected OSW-1 (131). After removal of all protecting groups, OSW-1 was obtained from (+)-dehydroisoandrosterone in 10 linear steps and an overall yield of 64% (Scheme 18). The highlight in this synthesis is the reliability of all involved transformations and the simple work-up procedures (Xue *et al.*, 2008).



Scheme 18 Xue's synthesis of the disaccharide moiety and OSW-1

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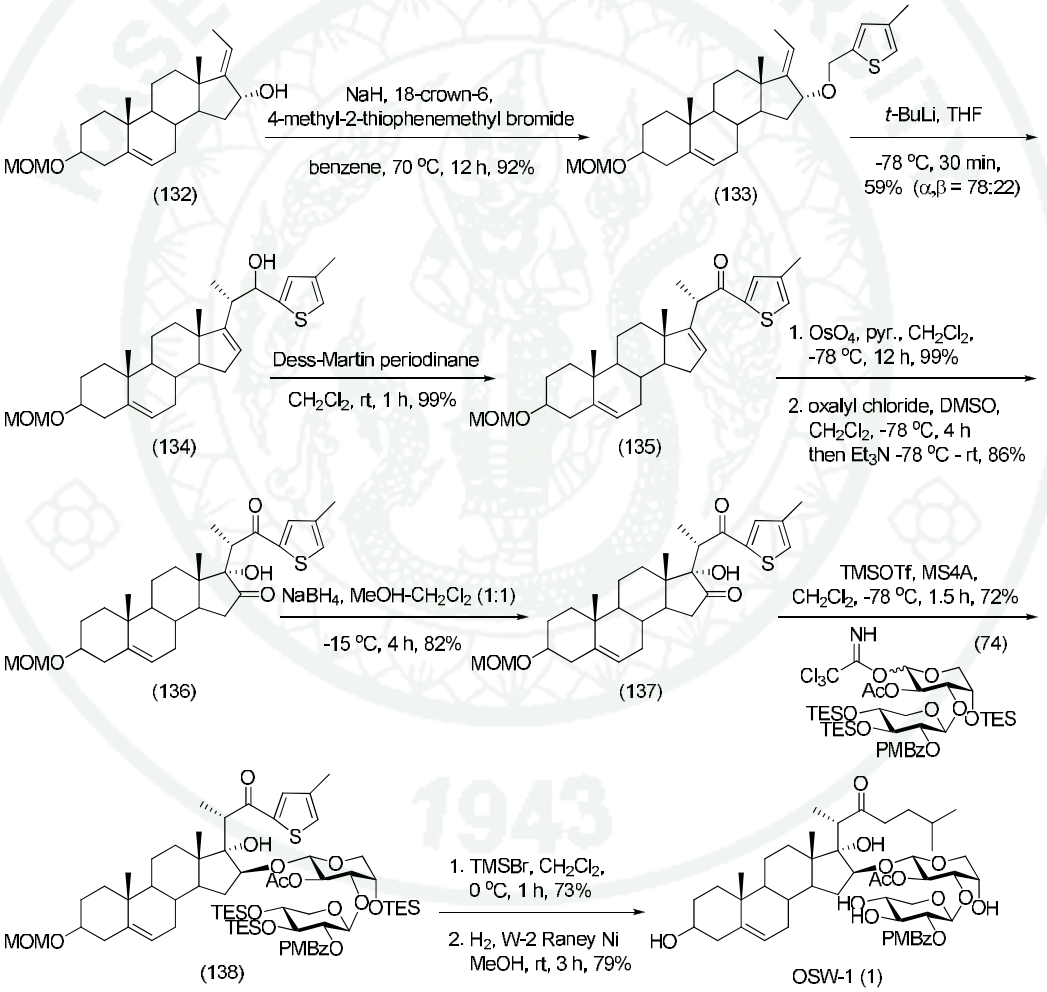
Tsubuki *et al.* reported a new synthesis of OSW-1 in which thiophene ring was introduced at the side chain required 9 steps from the known 17*E* (20)-ethylidene-16α-hydroxy steroid (132) in 15.6% overall yield. The key feature of this synthesis is employed Wittig rearrangement of 17*E* (20)-ethylidene-16α-(4′-methyl-2′-thienyl)methyloxy steroid (133) to introduce the side chain (Scheme 19) (Tsubuki *et al.*, 2008).



Scheme 19 Tsubuki's synthesis of OSW-1

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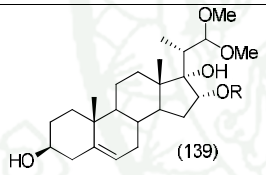
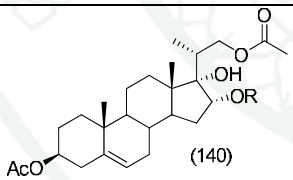
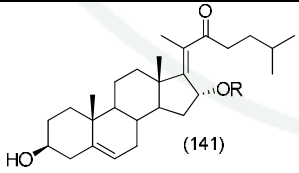
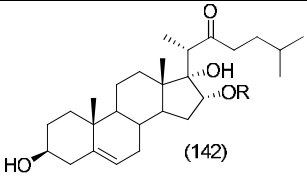
Early reported syntheses of OSW-1 analogues and their biological activity

Ma *et al.* undertook the task of synthesizing a great number of OSW-1 analogues and steroidal glycosides bearing the disaccharide moiety of OSW-1 or its 1→4-linked analogue and determined the cytotoxic activity of these compounds against two of cancer cell lines: mice leukemia P388 and human pulmonary adenocarcinoma A549 as shown in Table 2 (Ma *et al.*, 2001a, 2001b; Ma *et al.*, 2000).

Table 2 Growth inhibition ratio (%) of saponin OSW-1 and its analogues on tumor cells (P388 and A-549).

Compound	P388			A-549		
	10^{-6} M	10^{-7} M	10^{-8} M	10^{-6} M	10^{-7} M	10^{-8} M
OSW-1 (1)	100	100	100	99.3	99.1	98.2
 (139)	-	-	-	-	-	-
 (140)	20.4	15.5	17.9	6.2	0.8	-
 (141)	-	-	-	-	-	-
 (142)	66.7	35.4	15.5	53.8	29.5	-

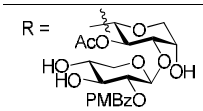
R = 

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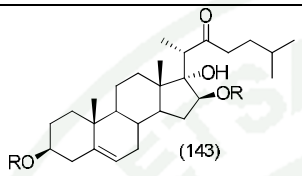
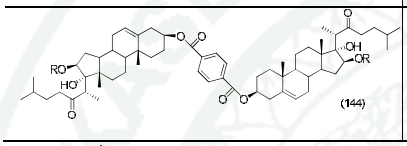
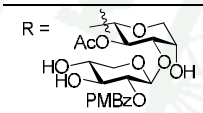
Table 2 (Continued)

Compound	P388			A-549		
	10^{-6} M	10^{-7} M	10^{-8} M	10^{-6} M	10^{-7} M	10^{-8} M
 (143)	90.7	52.0	-	80.9	6.7	0.7
 (144)	99.7	98.7	65.6	89.7	74.1	52.8

R = 

Most of the synthesized compounds are less active than the original OSW-1. From their tests, they demonstrated that a free 3-hydroxyl group and the configuration of the hydroxyl group at C16 are significance to the cytotoxic activity. The modified side chain derivatives of OSW-1 showed lower activity than the saponin OSW-1. Its analogues with a disaccharide connected to 3 and 16 positions are about 1000 times less active. On the other hand, the dimer (144) had much higher activity than other analogues and also showed slightly different inhibition ratio of the growth of cancer cells for P388 and A549 compared to OSW-1. This group also synthesized analogues of OSW-1 in which D-xylose and L-arabinose were connected as disaccharides through 1→4 but not through 1→3 as in the naturally occurring compound. Unfortunately, all of them were not biologically active.

Matsuya and co-workers reported the total synthesis of A-nor B-aromatic OSW-1 aglycone from benzocyclobutene derivative **145**. The key strategy involved a new enantioselective approach to the trans-4,5-benzhydrindane skeleton by intramolecular cycloaddition of *o*-quinodimethane which is generated by thermolysis of a benzocyclobutene derivative **147** (Scheme 20) (Matsuya *et al.*, 2003).

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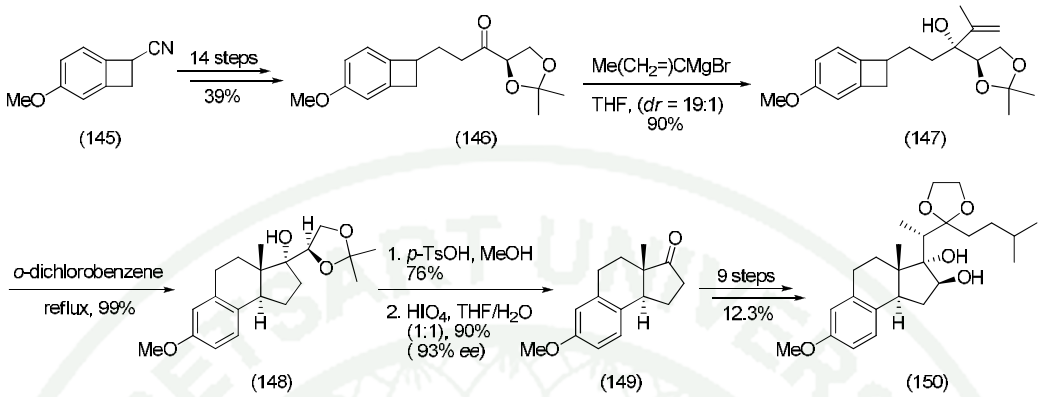

Scheme 20

In 2004, Morzycki *et al.* synthesized a series of side chain analogues, a 22-glycosylate isomer and 16*β*-*O*-L-arabinosyl or 16*β*-*O*-D-xylosyl analogues of OSW-1 (Figure 4) and tested their anti-tumor activities. It was found that all analogues are much less cytotoxic against breast and endometrial cancer cell lines than the natural product (Morzycki *et al.*, 2004).

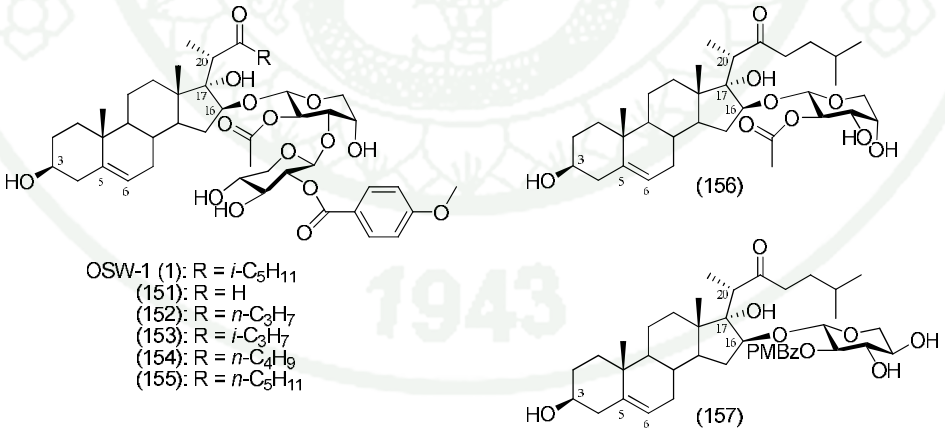

Figure 4 The analogues of OSW-1 by Morzycki *et al.*

Deng *et al.* (2004) reported the synthesis of four analogues of OSW-1 with modified side chains on the steroidal skeleton (Figure 5). These analogues and 5,6-dihydro-OSW-1 were synthesized following modification of their previous method for the total synthesis of OSW-1 and also were examined cytotoxicity against to

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tumor cells. They found that the 22-one function and the full length of the side chain of OSW-1 were not required for the antitumor action of OSW-1. Moreover, the 5,6-dihydro-OSW-1 showed slightly stronger potency than that of OSW-1 against the growth of cancer cells (Deng *et al.*, 2004).

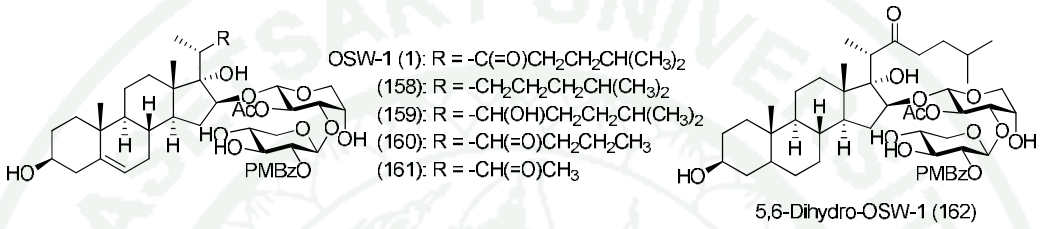

Figure 5 The analogues of OSW-1 by Deng *et al.*

Afterwards, Shi and co-workers published a novel and efficient approach to synthesize of 23-oxa-analogues of the saponin OSW-1. The key reaction involved an aldol condensation between **163** and **164** to give the 23-oxa-analogues of OSW-1 in about 20-30% overall yield from (+) dehydroisoandrosterone (48) (Figure 6). These 23-oxa-OSW-1 analogues were examined an antitumor activity. They found that the 23-oxa-OSW-1 showed similar antitumor potency to that of OSW-1, while dodecyl ester was even higher activity than OSW-1 (Shi *et al.*, 2005).

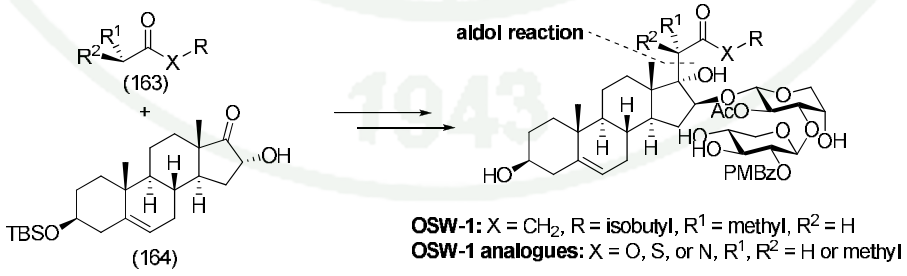

Figure 6 The analogues of OSW-1 by Shi *et al.*

Year later, for progress toward an understanding of the SAR and an antitumor mechanism of OSW-1 saponin they developed their earlier strategy to synthesize a new type of 23-oxa-analogues of OSW-1 and determined their cytotoxicity against the

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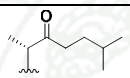
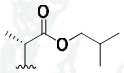
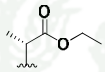
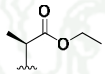
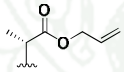
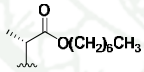
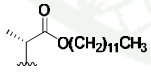
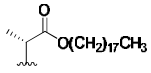
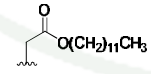
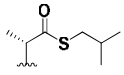
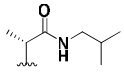
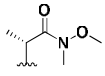
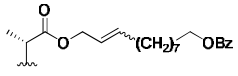
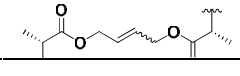
proliferation of several human cancer cell lines including HeLa, Jurkat T cells and human MCF-7 breast cancer cell line. The results showed that these new synthetic compounds of this family have exceptionally potent antitumor activities as shown in Table 3.

Table 3 Antitumor activities of the synthetic OSW-1 and its side chain modified analogues.

Compounds	C17 side chain	IC_{50} (μM)		
		HeLa	JurKat T	MCF-7
OSW-1		0.012	0.0022	0.094
165		0.23	0.00068	0.9
166		0.24	0.0053	>10
167		0.034	0.042	0.13
168		0.065	0.0027	0.1
169		0.002	0.0014	2.6
170		0.0033	0.0073	0.14
171		>10	>10	>10
172		10	0.073	1.4
173		0.0013	0.0009	5.2
174		0.0084	0.0053	1.8
175		0.012	0.035	16.5
176		0.04	0.003	0.19
177		0.07	0.066	2.8

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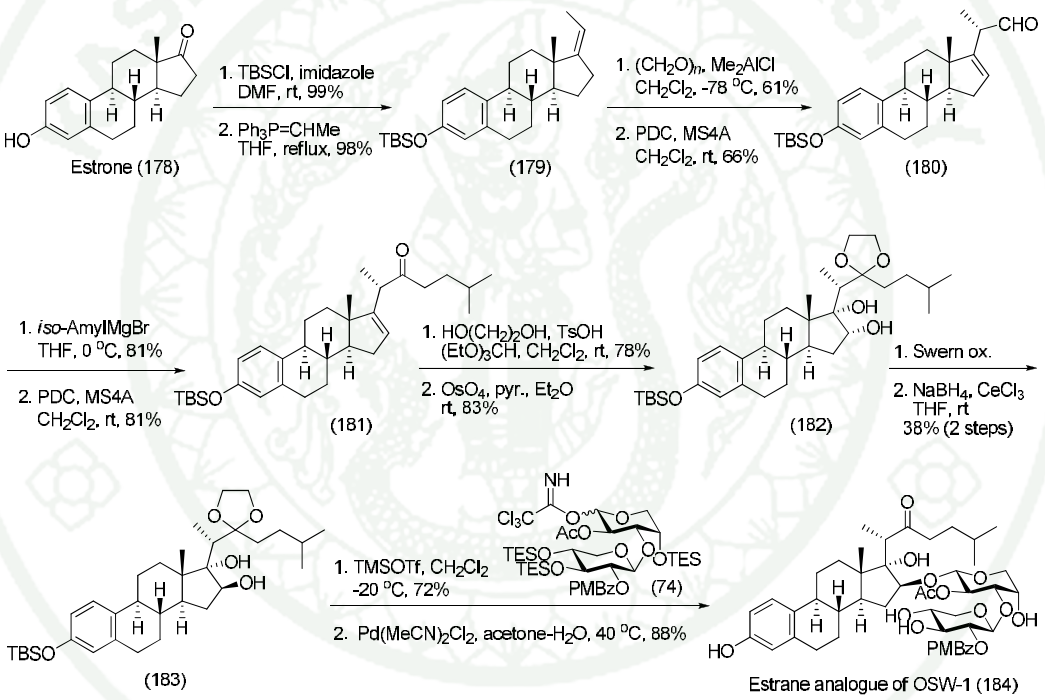
In 2005, Matsuya *et al.* also published synthesis of the estrange analogue of OSW-1 based on a highly effective method for the first construction of the OSW-1 aglycone by Yu and his co-workers (Scheme 21). The estrange analogue of OSW-1 was tested the cytostatic activity against several human malignant tumor cells and compared to those of natural OSW-1 and cisplatin (Table 4). The results suggested that the modification of the steroidal component could be an effective approach in the search for new candidates of anticancer drugs (Matsuya *et al.*, 2005).



Scheme 21 Matsuya's synthesis of the estrange analogue of OSW-1

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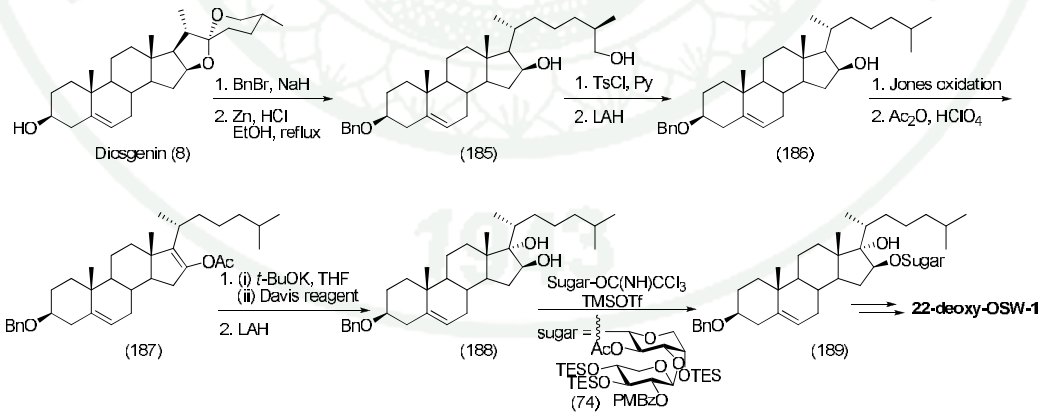
Table 4 Cytotoxic activity of OSW-1 analogues *in vitro* (NT: not tested).

Cell	IC_{50} Value (μM)		
	Cisplatin	Estrane Analogue (184)	OSW-1 aglycon
NCI-H460	0.660	0.439	> 10
T-47D	11.5	0.709	NT
MDA-MB-231	7.85	1.01	NT
A498	2.11	0.430	NT
PC-3	3.62	1.40	> 10
DLD-1	2.21	1.18	> 10

In 2006, Tian's group reported the synthesis of 22-deoxy-OSW-1 by also utilizing the intact skeleton of diosgenin. The key feature is treatment of 3-*O*-benzyl-diosgenin with Zn-Hg and HCl acid in refluxing ethanol to afford the E/F ring-opening reduction product, 16*β*-26-dihydroxyl cholesterol **185** which was then converted to 22-deoxy-OSW-1 in 11 steps in 13.7% overall yield as shown in Scheme 22 (Qin *et al.*, 2006).



Scheme 22 Tian's synthesis of 22-deoxy-OSW-1

In 2007, Wojtkielewicz and co-workers synthesized a number of analogues of OSW-1 with modified side chain, glycosylated with various monosaccharides, and also structural isomer of OSW-1. Cytotoxicity evaluation of these compounds

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demonstrated that modification of the steroidal aglycone may lead to compounds with high cytotoxicity (Wojtkielewicz *et al.*, 2007).

In the same year, Tang *et al.* published the synthesis of eight OSW-1 saponin analogues with modified sugar residues and their antiproliferative activities. The 23-oxa-OSW-1 aglycone was synthesized using the earlier synthetic strategy. Among of them, 2-*O*-acetyl-α-L-arabinopyranoside **191** showed activity comparable to that of the disaccharide derivative **170** against the Jurkat cells (IC_{50} = 0.078 nM). While other analogues did not show antiproliferation activity against cancer cell lines tested. These results demonstrated that the sugar moiety in the OSW-1 saponin is essential for their potent antitumor activity (Table 5) (Tang *et al.*, 2007).

Table 5 The antiproliferative activity of the synthetic OSW-1 analogs against tumor cells.

		IC_{50} (μM)		
		HeLa	Jurkat	RKO
1	R = Ac, R^1 = -2-*O*-MBz-D-xylosyl (170)	0.071	0.015	0.0007
2	R = Ac, R^1 = -$(CH_2)_2$OMBz (190)	ND	ND	ND
3	R = Ac, R^1 = H (191)	1.2	0.078	ND
4	R = Ac, R^1 = All (192)	1.1	ND	1.7

ND, IC_{50} not determined.

Later, Peng and co-workers synthesized the A,B-ring-truncated OSW-1 saponin analogs and tested their antitumor activities. Synthesis of the desired A,B-ring-truncated aglycone **193**, **194**, and **195** was successful starting from the ready available optically pure Hajos-Parrish ketone (Hajos and Parrish, 1984). These A,B-ring-truncated OSW-1 saponin analogs retained considerable inhibitory activity against the growth of HaLa and Jurkat cells (IC_{50} = 0.8 – 21.1 μM). The results

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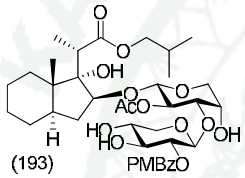
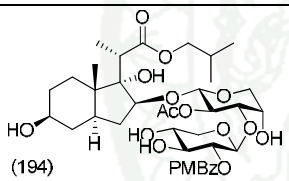
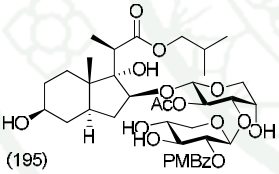
suggest that an intact steroid ring is not absolutely required for the biological activity of the OSW-1 family of saponin analogs (Peng *et al.*, 2007) (Table 6).

Table 6 The inhibitory activity of the A,B-ring-truncated OSW-1 analogs against the growth of tumor cells.

	IC_{50} (μM)	
	Jurkat	HeLa
23-Oxa-OSW-1 (165)	0.0013	0.24
 (193)	8.9	14.9
 (194)	14.5	2.6
 (195)	21.1	0.8

Tschamber and co-workers prepared four OSW-1 analogues featuring modified carbohydrate (Figure 7) and examined biological activity. They concluded that the modification of the disaccharide part of an analogue of OSW-1 let to dramatic changes in biological activity. From their works, OH-4 of L-arabinose unit clearly appears to be crucial and the integrity of the acylated xylopyranoside moiety is equally important, besides the two acyl groups (Ac and PMBz), in which role is already documented (Tschamber *et al.*, 2007).

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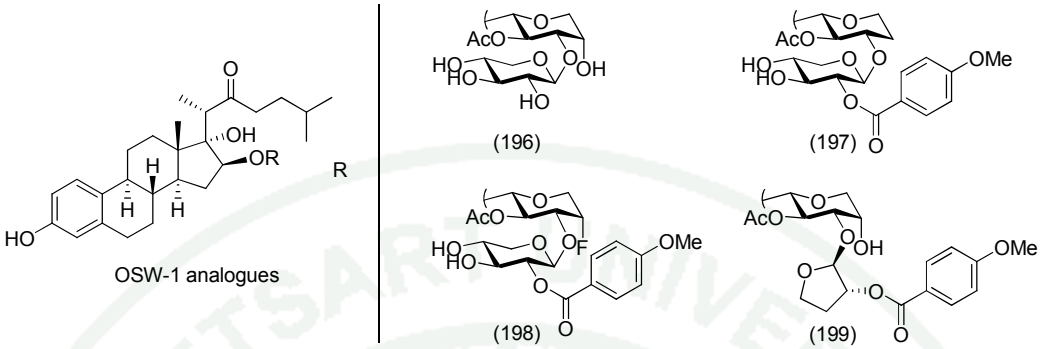
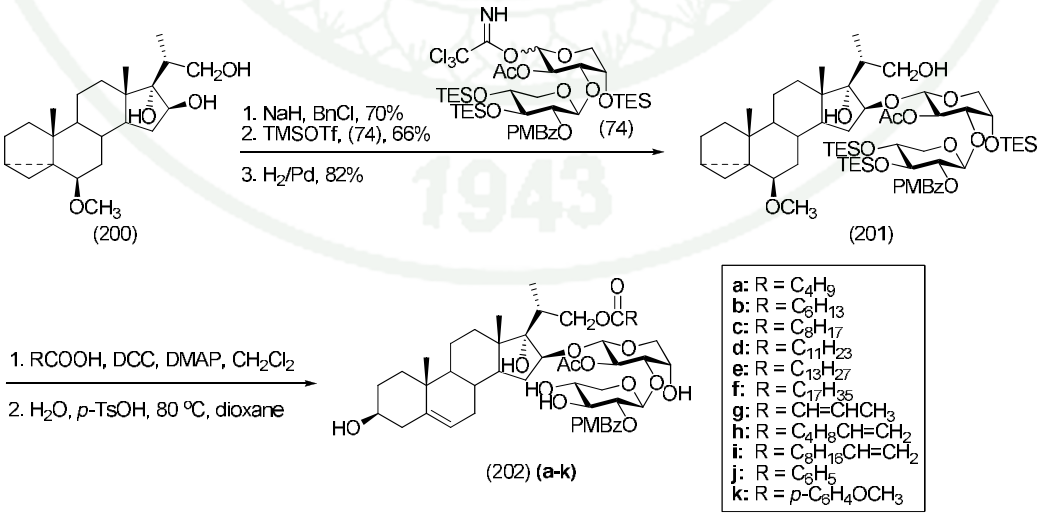


Figure 7 The analogues of OSW-1 by Tschamber *et al.*

Recently, Maj *et al*. synthesized the new 22-deoxo-23-oxa analogues of OSW-1 (Scheme 23) from the readily available steroidal 16β, 17α, 22-triol (200) (Morzycki *et al.*, 2001) and screened against eight cancer cell lines and normal human fibroblasts. They found that a series of OSW-1 analogues which are easier to obtain by chemical synthesis than the natural product are slightly less active than OSW-1 but have a much wider therapeutic window, since they are less toxic to normal cells. These analogues (like OSW-1) induce apoptosis of mammalian cancer cells in a concentration-dependent manner (Maj *et al.*, 2011) (Table 7).



Scheme 23

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Table 7 IC_{50} (μM) obtained from the calcein AM assays with the tested cancer and normal cell lines[a].

OSW-1 derivative	Cell line, IC_{50} (nM)								
	CEM	MCF7	G 361	HeLa	HOS	A 549	T98	HCL116	BJ
OSW-1	0.3±0.03	2.4±0.2	1000±100	3.4±0.3	8200±400	27±3	70±6	8400±500	0.2±0.01
5	20±1	600±100	750±80	200±10	-	100±50	-	-	300±40
202a	60±10	500±70	390±60	170±10	-	160±40	-	-	500±60
202b	10±2	400±40	1280±200	30±2	-	20±5	-	-	600±70
202c	7.2±0.4	26±8	15±1	47±4	2800±900	590±60	11±3	4900±800	7±1
202d	6.3±0.5	21±1	8±2	42±18	1900±700	930±300	7±1	2800±600	5±1
202e	16±5	48±22	30±10	67±2	2700±600	720±70	28±1	2800±400	83±5
202f	58±1	195±21	300±100	435±64	>50000	550±180	210±50	>50000	80±4
202g	340±40	840±51	890±90	1940±50	>50000	550±200	940±20	>50000	230±80
202h	21±3	54±9	44±4	61±6	6500±1400	840±300	43±9	11000±700	20±10
202i	6.1±1.2	29±12	6.7±0.5	103±88	1940 ± 50	600±100	7±1	2600±700	3±0.8
202j	70±10	700±100	1660±90	240±60	-	170±40	-	-	100±20
202k	57±19	410±120	170±60	340±10	5400±1500	570±190	55±4	5000±400	39±6

[a]The cells were treated for 72 h with serial concentrations of the compounds. Mean ± SD values were obtained from three in dependent experiments performed in triplicate. OSW-1 was used as positive control.

According to the research work of the Cao and co-workers (Guan *et al.*, 2008), the 15-OH of 5(6)-dihydro-OSW-1 analogs might play a role in the anti-tumor activities, thus Guan and co-workers synthesized of 5(6)-dihydro-OSW-1, eight 15(α)β-*O*-glycosyl analogs carrying three kinds of disaccharides including [β-D-Xyl*p*-(1-3)-α-L-Ara*p*], [β-D-Xyl*p*-(1-4)-α-L-Ara*p*] and [α-L-Rha*p*-(1-2)-(α)β-D-Glc*p*] from tigogenin (6) in order to study the SAR. The 5(6)-dihydro-OSW-1 analogs were tested *in vitro* antitumor activities by standard MTT assay and the results clearly demonstrated that the disaccharide [β-D-Xyl*p*-(1-3)-α-L-Ara*p*] and the β configuration of 15-OH are essential to the antitumor activities of 15-*O*-glycosyl 5(6)-dihydro-OSW-1 analogs (Guan *et al.*, 2011).

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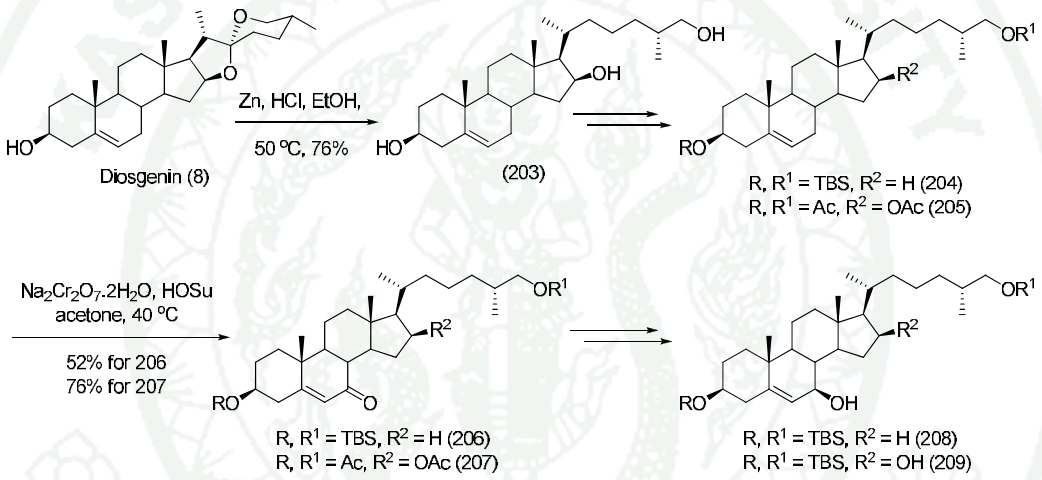
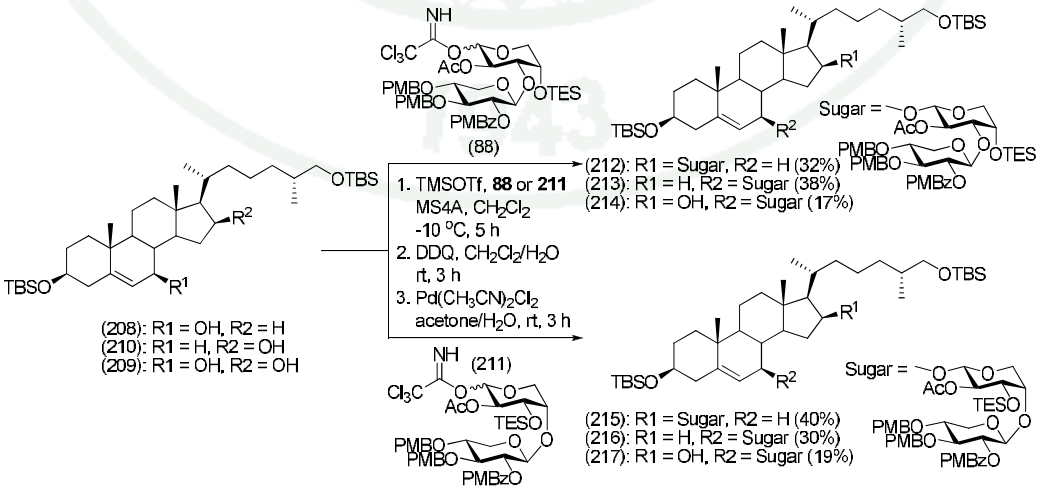
Very recently, Zheng *et al.* reported the synthesis of cholestane saponins as mimics of OSW-1 and their cytotoxic activities. They prepared six cholestane saponins by introducing OSW-1 disaccharide (2-*O*-4-methoxybenzoyl-*β*-D-xylopyranosyl-(1→3)-2-*O*-acetyl-*α*-L-arabinopyranosyl) and its 1→4 linked analogue to the 7-hydroxy or 16-hydroxy of steroidal sapogenins (Scheme 25). The key reaction is the modified Clemmensen reduction, reported by Williams *et al.*, to construct the sapogenin part in a facile way (Scheme 24) (Zheng *et al.*, 2011).



Scheme 24



Scheme 25

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The cytotoxicity results showed that the 22-one function was not necessary to the cytotoxicity. The disaccharide part could be connected to other position apart from 16-OH, but the oxygen-bearing substituent at C-16 might be required for the anti-tumor activity. Moreover, compound **212** which is the most simplified synthetic analogue preserves high potency and it could be a potential candidate for a new anti-tumor agent (Table 8) (Zheng *et al.*, 2011).

Table 8 Cytotoxic activities of compounds 212-217 against tumor cells[a].

Compounds	IC_{50} (M)				
	HCT-8	BEL-7402	BGC-823	A2780	A-549
212	7.0×10^{-8}	2.3×10^{-8}	2.0×10^{-9}	6.0×10^{-9}	9.3×10^{-9}
213	$>10^{-5}$	$>10^{-5}$	$>10^{-5}$	$>10^{-5}$	$>10^{-5}$
214	7.5×10^{-8}	5.0×10^{-7}	7.8×10^{-8}	1.9×10^{-6}	8.7×10^{-8}
215	$>10^{-5}$	$>10^{-5}$	$>10^{-5}$	$>10^{-5}$	$>10^{-5}$
216	$>10^{-5}$	$>10^{-5}$	$>10^{-5}$	$>10^{-5}$	$>10^{-5}$
217	$>10^{-5}$	$>10^{-5}$	$>10^{-5}$	$>10^{-5}$	$>10^{-5}$
Taxol	5.1×10^{-8}	6.0×10^{-9}	$<1.0 \times 10^{-9}$	$<1.0 \times 10^{-9}$	1.6×10^{-8}

[a]The *in vitro* cytotoxicities against HCT-8 (colon carcinoma), BEL-7402 (liver cancer), BGC-823 (stomach carcinoma), A2780 (ovarian cancer) and A549 (lung carcinoma) cell lines were evaluated by the stardard MTT assay.

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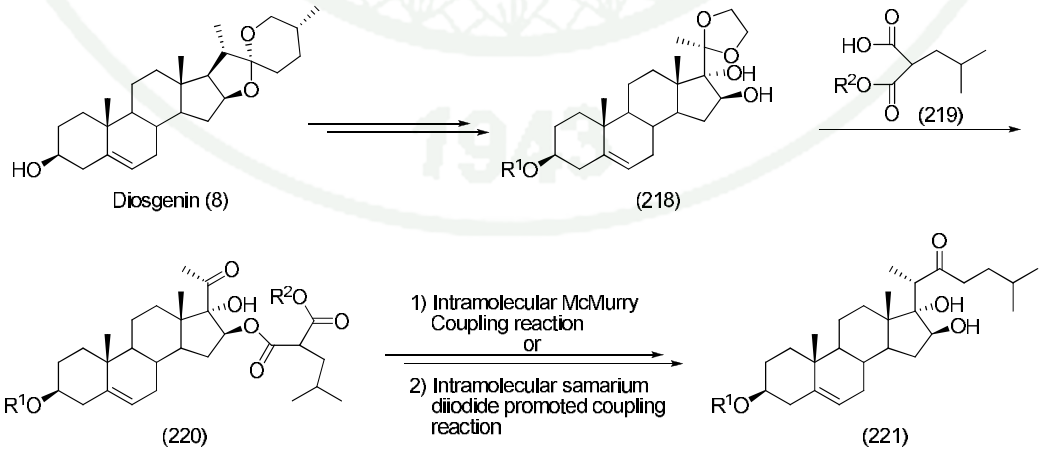
Synthetic Methodology for the Synthesis of OSW-1 Aglycone

The evaluation of the anti-cancer activity and the mechanism of action of the naturally occurring OSW-1 and its derivatives have been interested until now. There are many reports for the synthesis of OSW-1 and its analogues. However the convenient synthetic strategies to introduce the side chain into the steroid nucleus have still required. In our studies, the strategies for the synthesis of OSW-1 aglycones are different from these previous reports.

We proposed the synthetic strategy to synthesize the OSW-1 by synthesis of the core steroid intermediate **218** connected with the monoester carboxylic acid **219** which contains the same carbon number of the side chain (Scheme 26). The core steroid intermediate **218** could be synthesized from an easily available and cheap substrate diosgenin (8). The key feature of our studies is the introduction of the side chain to C-20 by two approaches; 1) intramolecular McMurry coupling reaction between C-20 ketone and malonate ester and 2) samarium diiodide-promoted intramolecular ketone-ester coupling reaction. Our strategies allow the synthesis of the side chain analogues of OSW-1 by varying the alkyl substituent at the α-carbon of the malonate ester.



Scheme 26

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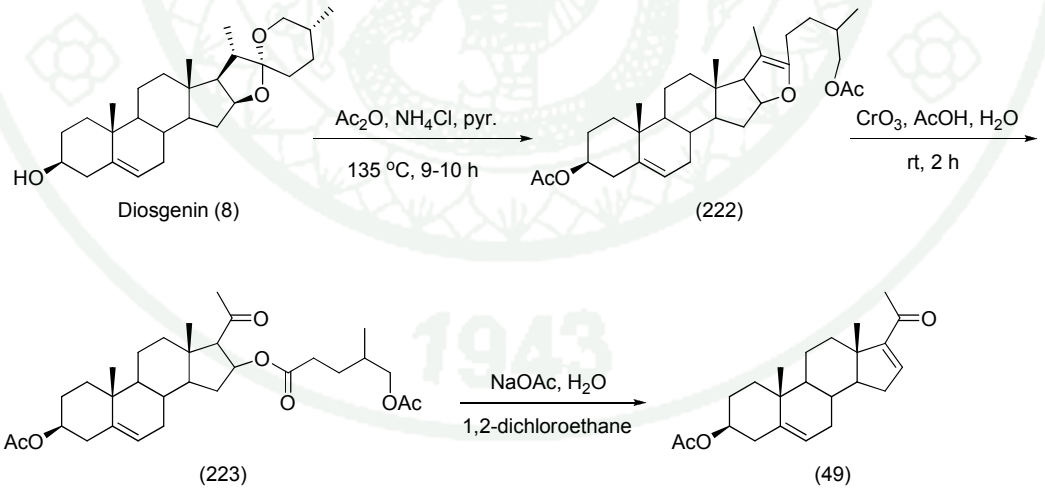
Conversion of steroid sapogenin to Δ^{16}-pregn-3β-ol-20-one-3-acetate (49)

In 1990, Mićović *et al.* reported the simplified preparation of 16-dehydropregnenolone acetate (49) from diosgenin (8) by using normal pressure and reduced temperature one-pot reaction (Scheme 27). The efficient one-pot process was performed by following reaction sequence.

a) Treatment of steroidal sapogenin with acetic anhydride at 135°C for 10 hours opened the spiroketal ring system to give pseudosapogenin acetate (222).

b) Oxidation of the resultant pseudodiosgenin using chromium trioxide in acetic acid gave intermediate **223**.

c) Hydrolysis of intermediate 223 by heating with dilute acid or alkali provided 3β-acetoxypregna-5, 16-dien-20-one (49).



Scheme 27

Later, Goswami (2003) have developed a new procedure for the preparation of 16-dehydropregnenolone acetate (49) from diosgenin (8). The reaction was performed by replacing the highly toxic chromiumtrioxide with potassium permanganate in the presence of tetraethylammonium iodide under acid condition (pH 3) at 0-5°C. Under

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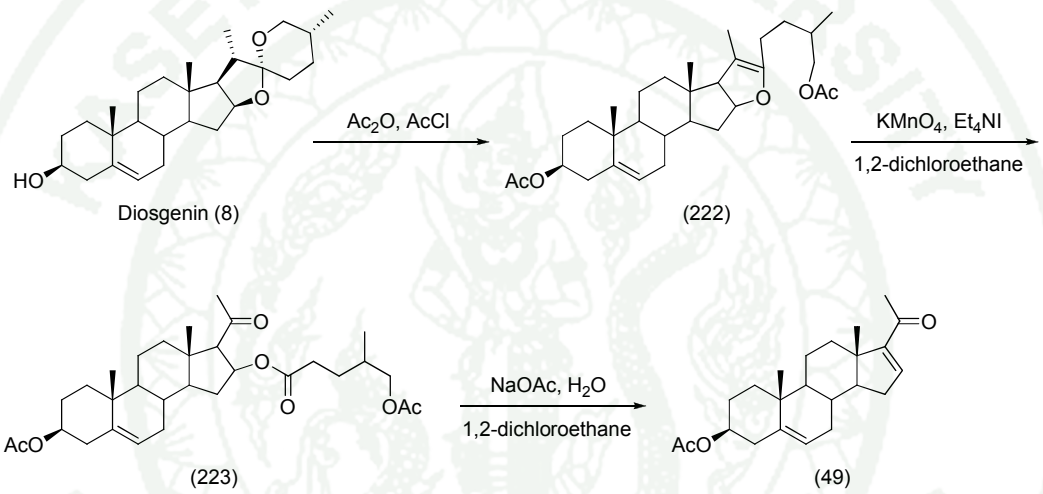
this condition, the double bond in the substrate furan ring **222** was cleavaged to form keto-ester (223) without any effects to the 5, 6-double bond. The advantages of this one-pot process are (i) there are no exotic and highly toxic reagents used in the reaction, (ii) the chromatographic purification was not required throughout the synthesis, and (iii) the final product was obtained in 75% yield, if compared to those of the previously report (Scheme 28).



Scheme 28

Keto-ester coupling reaction

A key aspect of this research is using the intramolecular reductive coupling reaction of keto-ester to introduce the side chain into C-20 of steroid intermediate. Although intramolecular coupling reactions are mainly limited to reaction between ketones and esters, there are some representative examples of titanium-induced cyclization of ketone-ester (McMurry reaction) and samarium diiodide-promoted intramolecular ketone-ester coupling reaction reported over decades.

McMurry Reaction

McMurry reaction is possibly the most important reaction to form carbon-carbon bonds from the carbonyl compounds. According to McMurry, this reaction

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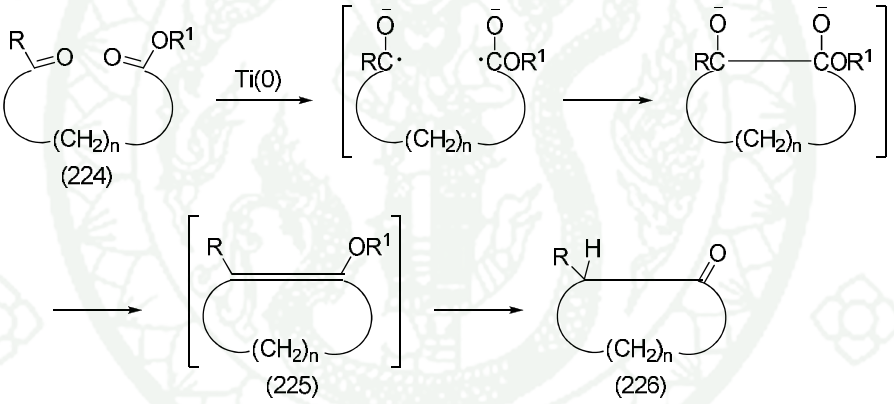
uses low-valent titanium reagents (Ti(II) and Ti(0)) which could be generated from $TiCl_4$ or $TiCl_3$ and the reducing reagents such as $LiAlH_4$, Zn, Zn-Cu, Li and K.

Extension to intramolecular keto-ester coupling reaction to form a cyclic ketone compound works particularly well for the construction of five-, six-, and seven-membered rings, but other ring sizes are obtained in lower yield. The reaction mechanism undergoes *via* two-steps the same as in carbonyl coupling reactions of diketone, dialdehyde or keto aldehyde substrates, but an enol-ether intermediate (225) was formed instead of an alkene. This acid-sensitive intermediate (225) was hydrolyzed to produce cyclic ketone (226) (Scheme 29).



Scheme 29

Some remarkable examples of intramolecular cyclizaions between keto-esters using the McMurry reaction to afford the cyclic ketone are shown in Scheme 30.

In 1983, McMurry *et al.* extended the dicarbonyl coupling reaction to the coupling reaction with a substrate of higher oxidation state (keto-ester). Titanium-induced cyclization of keto-esters was employed by using $TiCl_3/LiAlH_4$ in dry dimethoxyethane (DME) in the presence of triethylamine to access four through seventeen ring sizes of cycloalkanones. Not only the medium-sized rings were produced in good yield but also eight through fourteen ring sizes were obtained in synthetically useful yields (Scheme 30) (McMurry and Miller, 1983).

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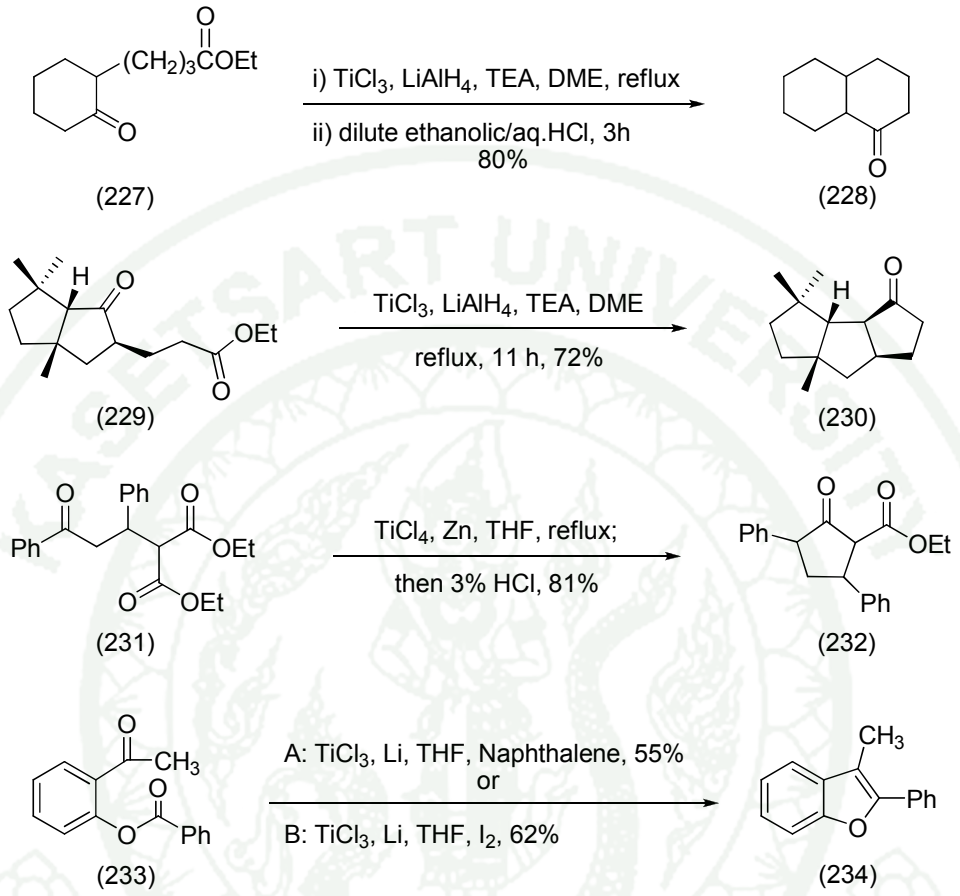

Scheme 30 Intramolecular McMurry reaction between ketone and ester

Several years later, cyclopentanone **230**, the key intermediate for synthesis of capnellene, was synthesized in good yield utilizing titanium-induced intramolecular coupling reaction of keto-ester **229** (Iyoda *et al.*, 1987).

Keto-diethyl malonate ester **231** was reacted with activated Zn and $TiCl_4$ followed by hydrolysis with aqueous HCl to give cyclopentano-ethyl ester derivative **232** in good yield (Shi *et al.*, 1993).

Moreover, the highly reactive low-valent titanium (LVT) reagents have been developed and utilized in intramolecular keto-ester cyclization reaction. Banerji and co-workers have reported an efficient low-valent titanium-iodine (LVT-I_2) system which could be generated by the addition of substoichiometric amounts of iodine to

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the LVT species prepared by Rieke's method ($TiCl_3$-Li-THF). Intramolecular keto-ester coupling of *o*-aroyloxyacetophenone **233** proceeded in LVT-I_2 systems at 25°C to afford benzofuran **234** in 62% yield (Scheme 30) (Talukdar *et al.*, 1998).

The other highly reactive low-valent titanium (LVT) reagents are prepared by refluxing a mixture of substoichiometric amounts of arenes, $TiCl_3$, and Li/Mg in THF or DME. The best condition for coupling of *o*-aroyloxyacetophenone **233** is using $TiCl_3$-Li-naphthalene-THF reagent system at room temperature to give benzofuran **234** in moderate yield (Rele *et al.*, 2001).

Samarium diiodide

Intramolecular samarium diiodide-promoted keto-ester coupling reactions have emerged as importance strategies for the formation of carbon-carbon bonds. The first example of this reaction has been reported by Zhang and co-workers in 2001. The reaction of SmI_2 with keto-diester **235** at room temperature produced substituted 2-hydroxy-5-ethoxycarbonylcyclopentanone **236** in moderate yield. In addition, substituted 5-ethoxycarbonylcyclopentenone **237** was obtained as a major compound when the reaction was performed at reflux.

Later, Hasegawa *et al.* have reported intramolecular ketone-ester reductive coupling reaction of ethyl 2-substituted-1-indanone-2-carboxylate **238** promoted by SmI_2 at room temperature to deliver ring expansion products, 3-substituted-1,2-naphthoquinone **239** and also a mixture of *cis*- and *trans*-isomers of hydroxyl substituent **240** (Scheme 31).

In 2006, they also have published on samarium diiodide-promoted intramolecular ketone-ester coupling of some cyclic and acyclic ketones tethering acyloxyalkyl side chains to afford 2-hydroxy cyclic hemiacetals **242** in moderate to good yields (Scheme 31).

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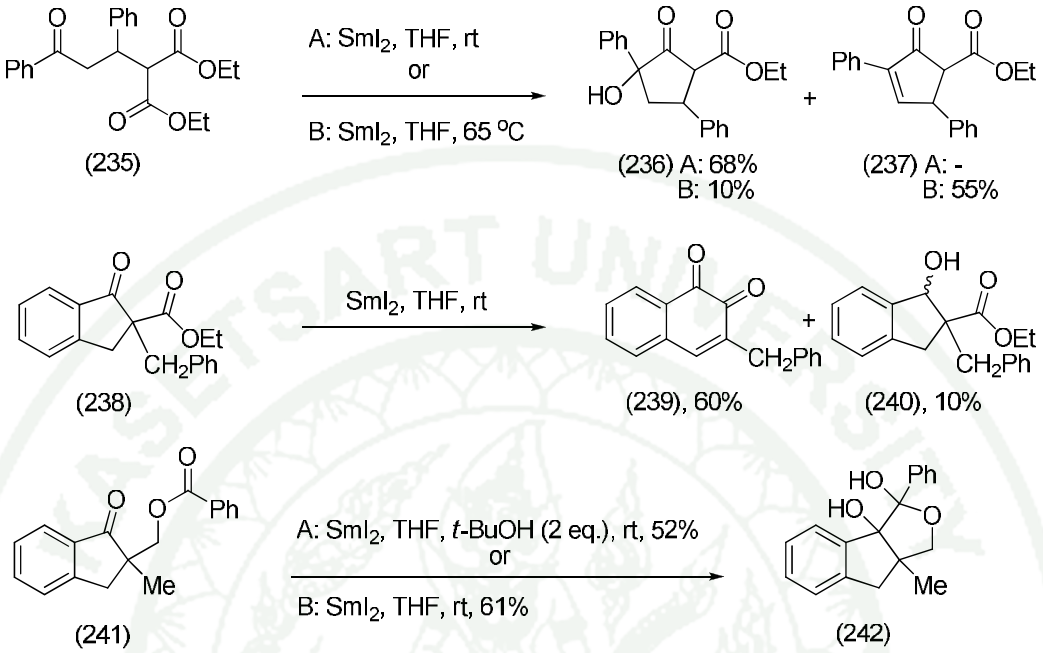

Scheme 31 Samarium diiodide-promoted intramolecular keto-ester coupling reaction

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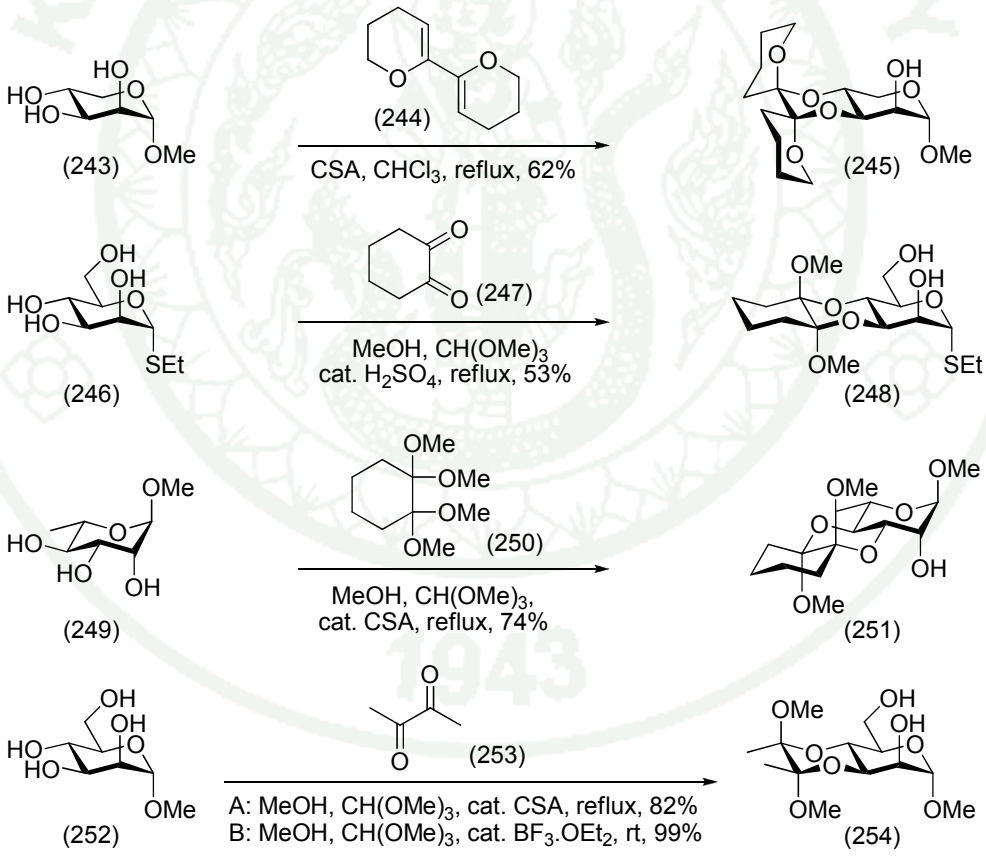
Synthetic Methodology for the Synthesis of Disaccharide Moiety

Conversion of D-xylose to D-xylopyranoside donor

Selective protection of diequatorial vicinal diols

A large number of highly effective protecting groups for *trans*-1,2-diols of monosaccharides and oligosaccharides *via* 1,2-diacetal formation were reported by Ley and co-workers.



Scheme 32 1,2-Diacetal protection of diequatorial vicinal diols

The commercially available 3,3′,4,4′-tetrahydro-6,6′-bi-*2H*-pyran (bis-DHP, 244), 1,2-cyclohexadione (247), 1,1,2,2-tetramethoxycyclohexane (250) and butane-

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2,3-dione (253) have been particularly utilized in selective protection of 1,2-diequatorial diols, even in the presence of further unprotected hydroxyl groups, employing catalytic either camphorsulfonic acid (CSA) or $BF_3 \cdot OEt_2$ in the presence of trimethyl orthoformate in MeOH at room temperature or refluxing. Some of examples are shown in Scheme 32.

Conversion of L-arabinose to L-arabinopyranoside acceptor

Reductive ring opening of benzylidene acetal

The reductive ring opening reaction of benzylidene protected glycosides serves an important role in organic synthesis utilizing carbohydrates. A great number of reagents for regioselective reductive opening of benzylidene acetals have been reported, such as $LiAlH_4$-$AlCl_3$, $BH_3 \cdot Me_3N$-$AlCl_3$, $BH_3 \cdot Me_2NH$-$BF_3 \cdot OEt_2$, Et_3SiH-$BF_3 \cdot OEt_2$, Et_3SiH-$Cu(OTf)_2$, $BH_3 \cdot THF$-$Cu(OTf)_2$ and DIBAL-H.

Lipták and co-workers originated hydrogenolysis of the alkylidene acetals such as benzylidene, methylene, ethylidene, isopropylidene and 1-phenylethylidene acetals of various pyranosides.

Hydrogenolysis of ethylidene and isopropylidene derivatives **255a-c** and **258a-b** with $LiAlH_4$-$AlCl_3$ furnished axial ethers almost in a regioselective manner. In some cases, equatorial ethers were observed as a major compound and in low yield (Scheme 33) (András Lipták *et al.*, 1985).

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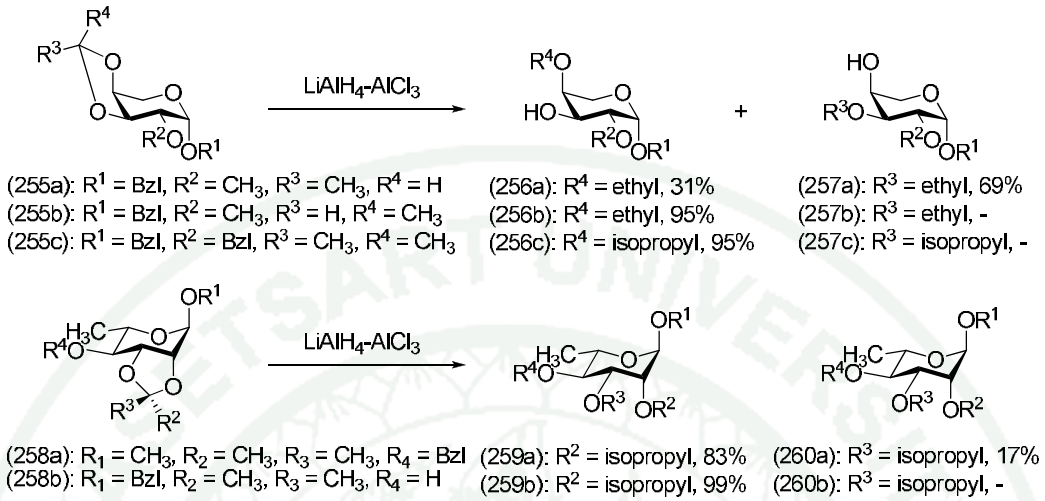
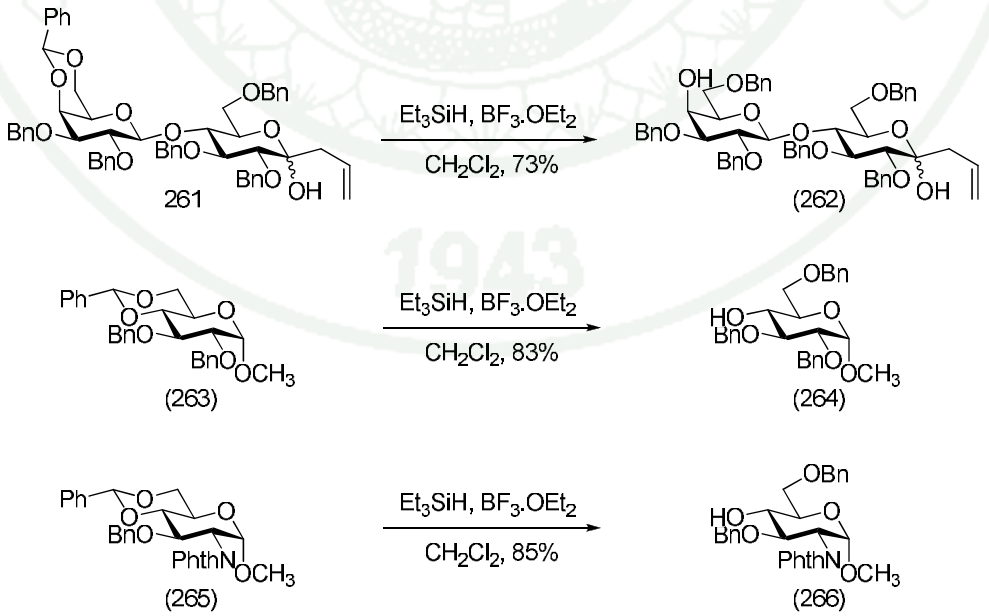


Scheme 33

In 2000, regioselective reduction of 4,6-di-*O*-benzylidene acetals of glucose, mannose, galactose and glucosamine was employed by using triethylsilane in the presence of $BF_3{\cdot}OEt_2$ to produce the 6-*O*-benzyl ethers in high yield (Scheme 34) (Debenham and Toone, 2000).



Scheme 34

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A few years ago, Tanaka *et al.* summarized the selective cleavage of 4,6-*O*-benzylidene acetal **263** to 4-*O*-benzyl derivative **267** and 6-*O*-benzyl derivative **264** (Table 9). The reason for the distinctive selectivity of these reactions is still unclear. It is possible to be depending on the particular reaction conditions involving the kind and the amount of Lewis acid and reducing reagents, reaction solvent, temperature and time as shown in Table 9.

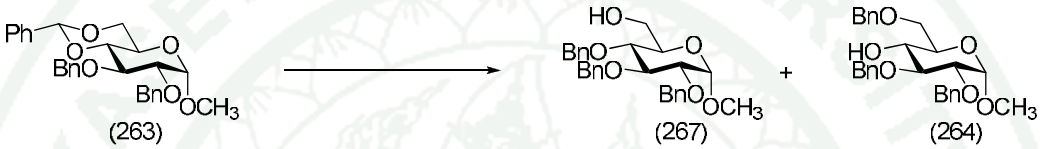

Table 9 Selective cleavage of 4,6-*O*-benzylidene acetal **263** to 4-*O*-benzyl ether **267** and 6-*O*-benzyl ether **264**.

Entry	Reagents	Solvent	Temp (°C)	Time	Yield (%)		Reference
					267	**264**	
1	DIBAL-H (5)	CH_2Cl_2	-30	21 h	88	4	24a
2	LAH-$AlCl_3$ (4.75/4.06)	CH_2Cl_2-ether	Reflux	2 h	94	-	24b
3	BH_3·THF-Bu_2BOTf (10/1)	CH_2Cl_2	0	1 h	87	-	24c
4	BH_3·THF-$CoCl_2$ (3/3)		rt	10 min	quant	-	24d
5	BH_3·THF-$V(O)(OTf)_2$ (5/0.15)	CH_2Cl_2	rt	3 h	94	-	24e
6	BH_3·THF-$Cu(OTf)_2$ (5/0.05)	-	rt	2.5 h	95	-	24f
7	BH_3·Me_3N-$Cu(OTf)_2$ (5/0.05)	CH_2Cl_2	rt	25 h	-	40	24f
8	BH_3·Me_2NH-BF_3·OEt_2 (5/5)	CH_2Cl_2	0	<1 h	73	3	24g
9	BH_3·Me_3N-$AlCl_3$ (5/5)	toluene	rt		50	-	24h
10	BH_3·Me_3N-$AlCl_3$ (6/6)	THF	rt		-	71	24h
11	$NaCNBH_3$-HCl·OEt_2 (12.5/?)	THF	rt	5 min	-	81	25a, 25b
12	Et_3SiH-CF_3COOH (5/5)	CH_2Cl_2	0-rt	2-4 h	-	81	25c
13	Et_3SiH-BF_3·OEt_2 (12/2)	CH_2Cl_2	0-25	4 h	-	83	25d
14	Me_2EtSiH-$Cu(OTf)_2$ (2/0.01)	CH_3CN	rt	0.5 h	-	84	24f

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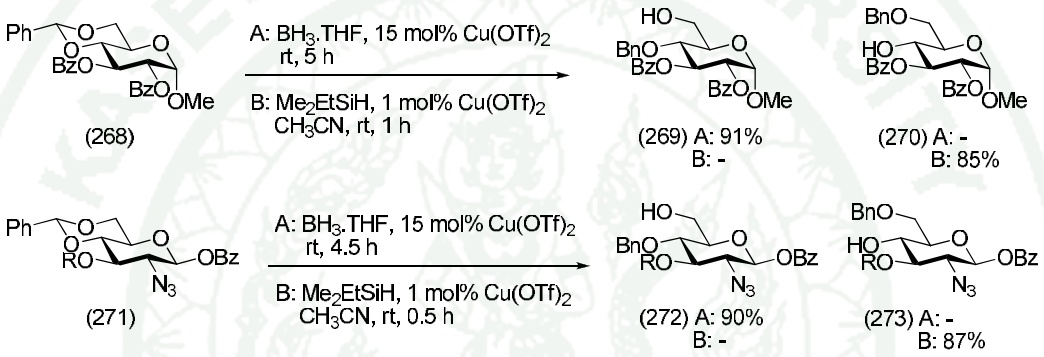
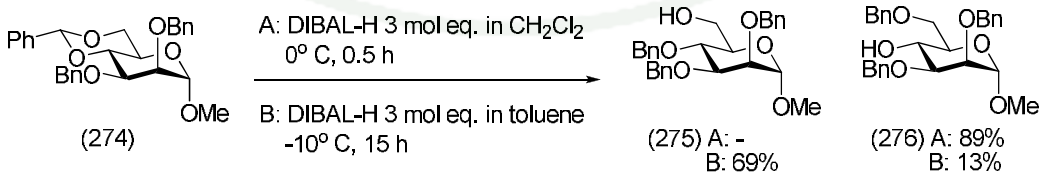
Hung and co-workers have published on regioselective reductive ring opening of various benzylidene acetals by the use of an efficient catalyst $Cu(OTf)_2$ with BH_3·THF and Me_2EtSiH to deliver the corresponding primary and secondary alcohols, respectively. Their mechanistic studies demonstrated that neither O6- nor O4-cleavage of the benzylidene ring undergoes the S_N2 reaction pathway when borane or triethylsilane attacks the carbon center of acetal (Scheme 35).



Scheme 35

DIBAL-H in a toluene solution and a dichloromethane solution efficiently reductive ring opened of benzylidene acetals protecting groups of glucosides and mannosides without a Lewis acid to furnish the corresponding 4- or 6-*O*-benzyl-protected hexapyranoside derivative highly regioselectivity. The regioselectivity of ring opening using DIBAL-H depends on the solvent used in reaction (Scheme 36) (Tanaka *et al.*, 2008).



Scheme 36

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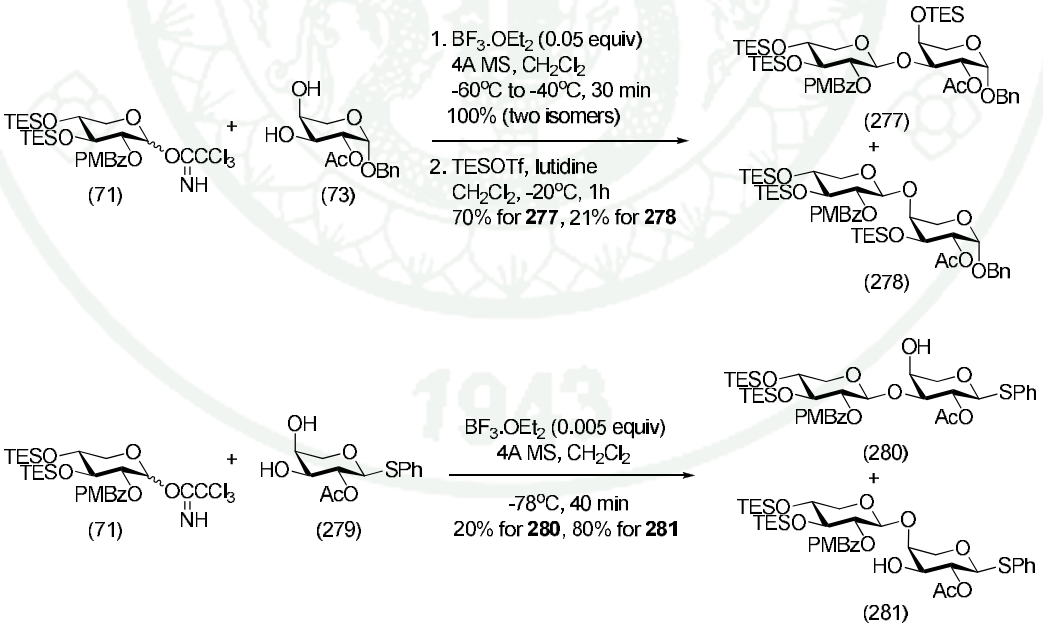
Synthesis of the disaccharide moiety

Glycosylation

A large number of methodologies have been published on glycosylation of monosaccharides to furnish the corresponding disaccharide moiety.

1. Trichloroacetimidate

The first general method for the glycosylation of D-xylopyranoside donor and L-arabinopyranoside acceptor in the synthesis of disaccharide moiety of OSW-1 was accomplished by using trichloroacetimidate intermediates **71** and **84**. There are several crucial conditions for the glycosylation using trichloroacetimidate intermediate (Scheme 37 and 38).



Scheme 37

A regioselective glycosylation between xylosyl trichloroacetimidate **71** and arabinosyl acceptor **73** under $BF_3{\cdot}OEt_2$ catalysis underwent the more active equatorial

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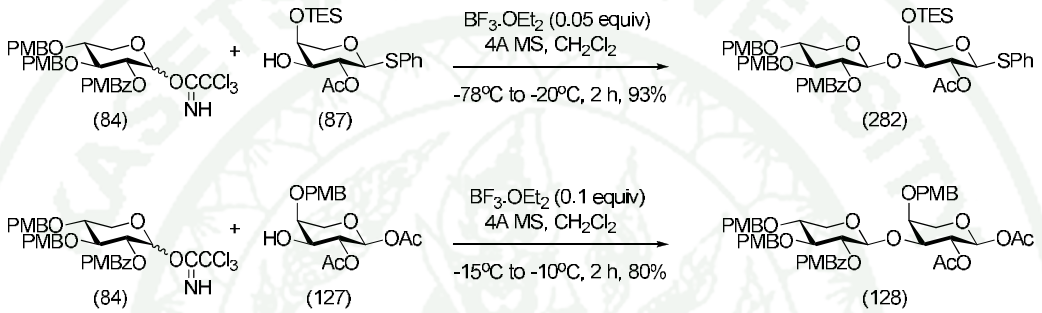
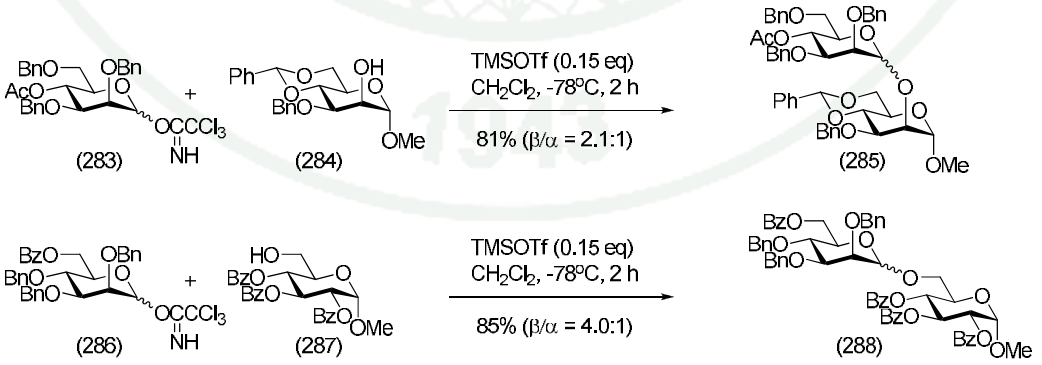
3-OH coupling to give the desire 1→3 linked disaccharide as the major product (Deng *et al.*, 1999). On the other hand, coupling reaction of trichloroacetimidate **71** with thioglycosyl acceptor **279** under the similar condition to the previous reaction gave a reversed regioselectivity which the 1→4 coupling product **281** was obtained in 80% yield and the 1→3 coupling product **280** in 20% yield (Scheme 37) (Ma *et al.*, 2000).



Scheme 38

The high yield of disaccharide moiety was obtained when trichloroacetimidate **84** and either 4-*O*-protected glycosyl acceptor **87** or **127** were subjected to the glycosylation using $BF_3{\cdot}OEt_2$ catalysis (Scheme 38) (Xue *et al.*, 2008; Yu and Jin, 2001).



Scheme 39

Trimethylsilyl trifluoromethanesulfonate (TMSOTf) has been used to activate the trichloroacetimidate donors processing an electron-withdrawing group at *O*-3, *O*-

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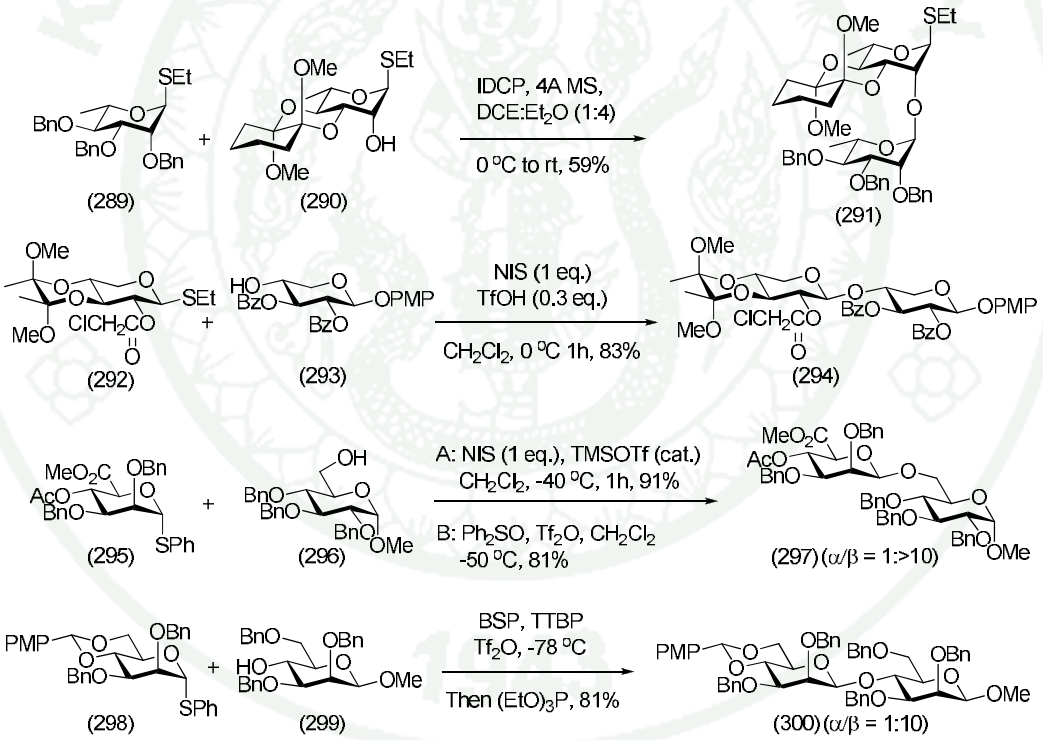
4, or *O*-6 positions for the mannosylations with various acceptors. Some of examples are shown in Scheme 39.

2. Thioglycoside

An efficient strategy for glycosylation of monosaccharides is using 1-thioglycosyl donors, activated with sulfonium ion based promoter systems, to couple with various acceptors. The stereochemical outcome of these condensations depends on the conformational change of six-membered transition state.



Scheme 40

Thioethyl and thiophenyl glycosides **289**, **292**, **295** and **298** were condensed with acceptor **290**, **293**, **296** and **299**, respectively, under a variety of activator such as iodonium dicollidine perchlorate (IDCP) (Ley and Priepke, 1994), NIS/TfOH (Oscarson and Svahnberg, 2001), NIS/TMSOTf, Ph_2SO/Tf_2O (van den Bos *et al.*,

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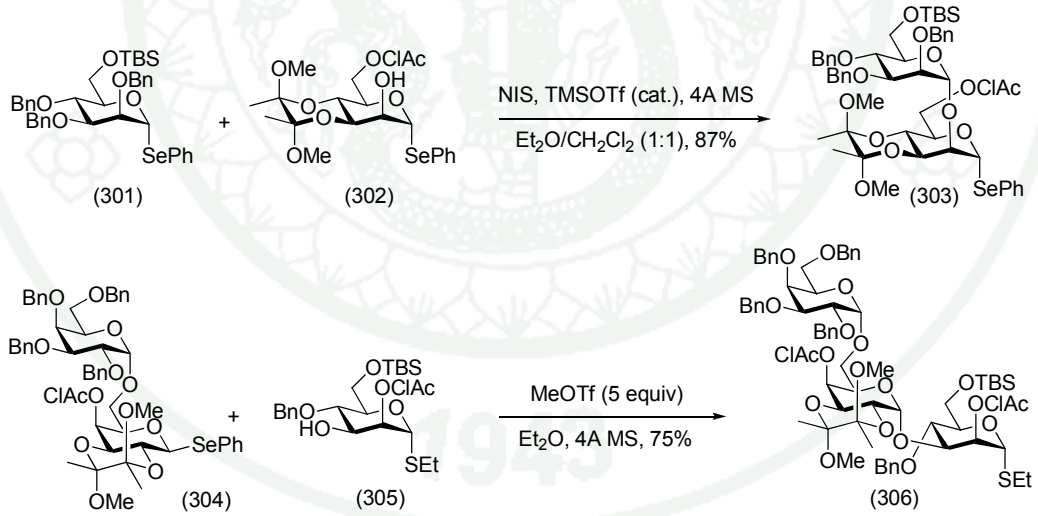
2006) and BSP/TTBP/Tf_2O (Crich *et al.*, 2004) to furnish β-linked disaccharides **291**, **294**, **297** and **300** in good yield and stereoselectivity (Scheme 40).

3. Selenyl glycosides

The benzeneselenyl glycoside **301** was selectively activated with *N*-iodosuccinimide (NIS) and catalytic amounts of triflic acid (TfOH) or trimethylsilyl triflate (TMSOTf) in the presence of deactivating BDA-acceptor **302** to give the α-linked disaccharide **303** in 87% yield and only trace amount of β-linked isomer was detected. In addition, the reactivity of selenyl group toward activating agent methyl triflate (MeOTf) is much more active than thionyl group. For example, trisaccharide **306** was formed by the couple of selenyl disaccharide donor **304** and thionyl acceptor **305** in the presence of 5 equivalents of MeOTf (Scheme 41) (Baeschlin *et al.*, 2000).



Scheme 41

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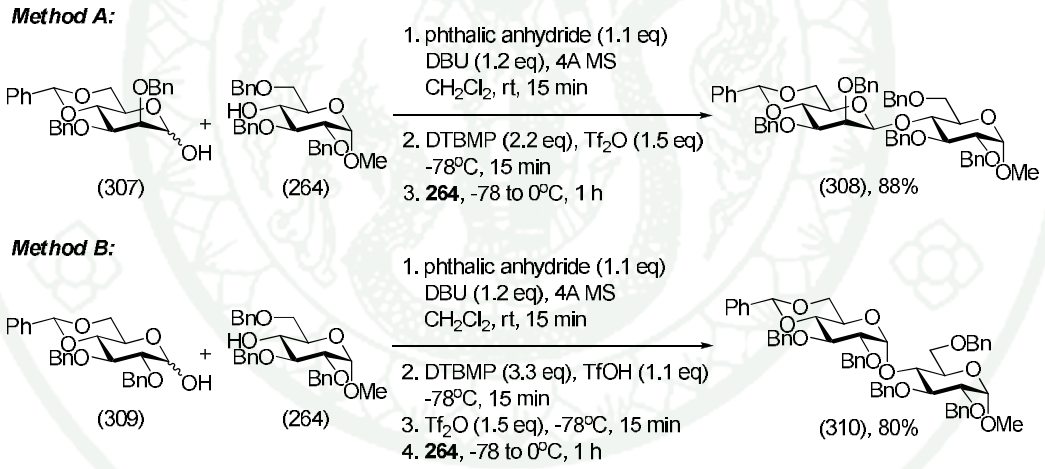
4. Anomeric hydroxyl glycoside

Kim and co-workers have reported the stereoselective direct glycosylation with anomeric hydroxy sugars by activation with phthalic anhydride and trifluoromethanesulfonic anhydride (Tf_2O). The β-glycosylations were achieved in a highly stereoselctive manner by employing with phthalic anhydride in the presence of DBU at room temperature followed by sequential addition of DTBMP and Tf_2O and glycosyl acceptors to the reaction mixture at -78°C in one pot (method A). Furthermore, the modified one-pot glycosylation protocol, in which TfOH was treated as the proton source together with DTBMP just before addition of Tf_2O (method B), gave the α-glycosyl disaccharide in stereoselectivity (Scheme 42).



Scheme 42

Very recently, an efficient and direct glycosylation with anomeric hydroxyl sugars in a one-pot reaction has been developed by operating 3-fluorophthalic anhydride and Tf_2O as activating agents. Some of examples were shown in Scheme 43 (Baek *et al.*, 2010).

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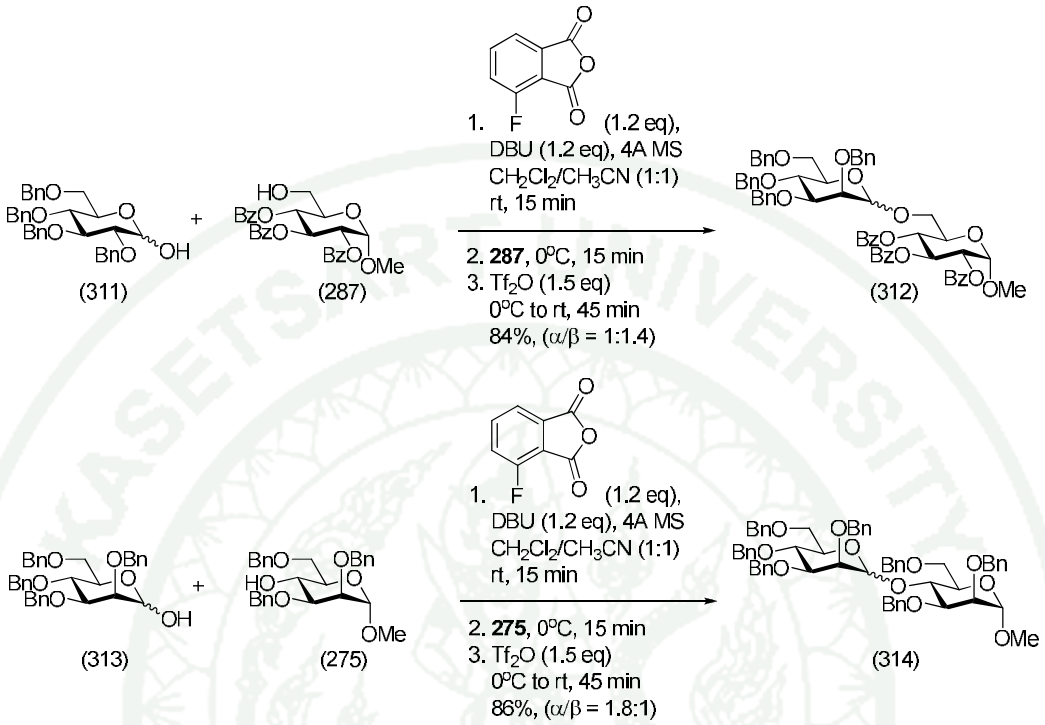
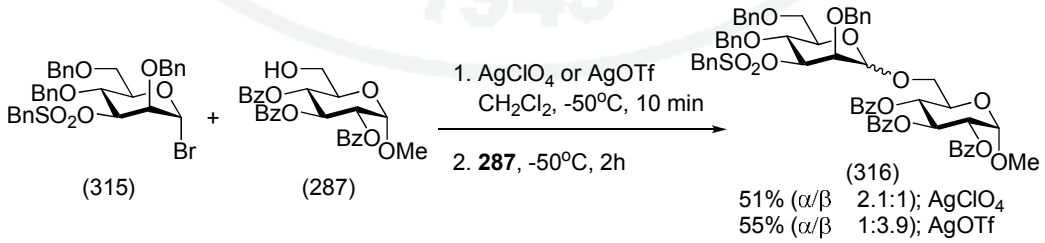


Scheme 43

5. Glycosyl bromide

Glycosylation of glycosyl bromide was achieved by employing either $AgClO_4$ or AgOTf as promoter (Baek *et al.*, 2009). The example of this reaction condition was shown in Scheme 44.



Scheme 44

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Synthesis of cyclic sulfamidates for *N*-heterocycle construction

We have explored the efficient methodology to synthesize the enantiomerically pure substituted and unsubstituted five- and six-membered cyclic sulfamidates from readily available 1,2- and 1,3-amino alcohols. Furthermore, application of cyclic sulfamidates to the construction of benzannulated *N*-heterocyclic compounds bearing stereodefined substituents have also been studied in the literatures.

Synthesis of cyclic sulfamidates

Cyclic sulfamidates are well known as versatile electrophile compounds which are accessible *via* 1,2- and 1,3-amino alcohols. Due to their stability and extraordinary reactivity profile, the extensive reviews for the synthesis of cyclic sulfamidates have been reported. In this context, we have focused on the construction of cyclic sulfamidates from amino alcohol derivatives.

1. Sulfuryl chloride

The most direct synthetic method to cyclic sulfamidates involve the treatment of an amino alcohol with sulfuryl chloride (SO_2Cl_2) to directly introduce the $–SO_2-$ moiety. However this method is only effective for conformationally rigid amino alcohols. For example cyclic sulfamidate **25** was synthesized in 63% yield on treatment of prolinol **24** with sulfuryl chloride (Alker *et al.*, 1990). The amino alcohol **317a** also reacted under similar condition to afford 3-(*p*-toluenesulfonyl)-1,2,3-benzoxathiazole 2,2-dioxide **318a** in 85% yield. A series of different aromatic substituted analogs **318b-g** were later synthesized by this method (Scheme 45) (Andersen *et al.*, 1991).

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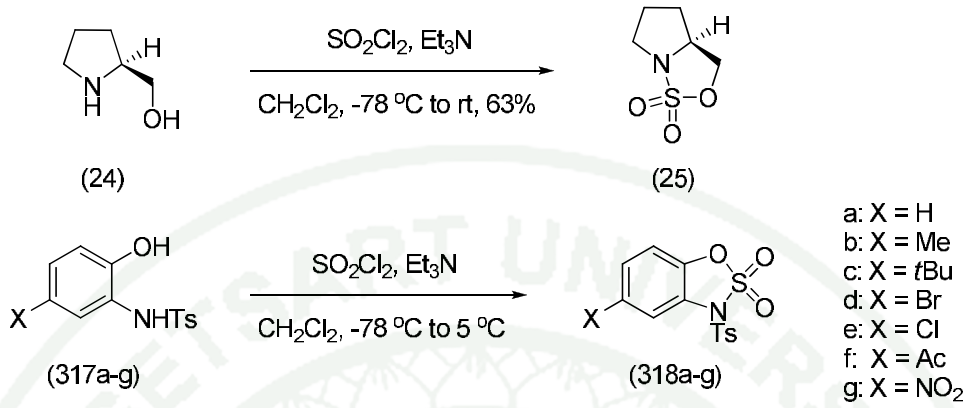
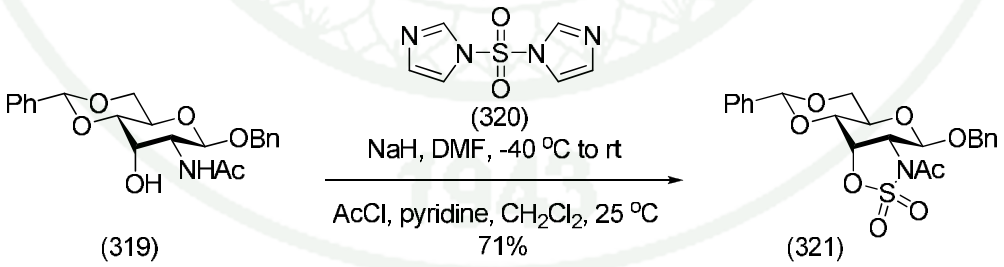


Scheme 45

2. Sulfuryl diimidazole

The commercially available sulfuryl diimidazole (320) was utilized to convert D-allosamine **319** to cyclic sulfamidate **321** which could not be prepared by using sulfuryl chloride. However the acetyl group in **319** was removed by sodium imidazolate, generated in the reaction. After re-acetylation, the target cyclic sulfamidate **321** was obtained in 71% yield (Scheme 46) (Aguilera *et al.*, 1997).



Scheme 46

3. O-sulfate and N-trifluoromethanesulfonamido intermediates

The installation of the -SO_2- moiety into an amino alcohol has been performed without oxidation through *O*-sulfate and *N*-trifluoromethanesulfonamido analogs of the starting *β*-amino alcohol. For example, L-serine *O*-sulfate **322** which was prepared

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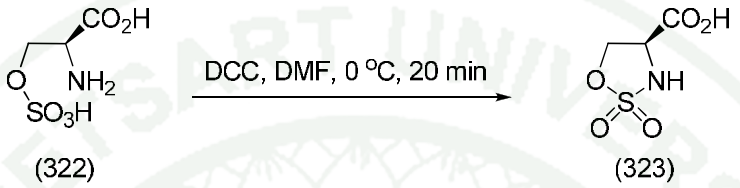
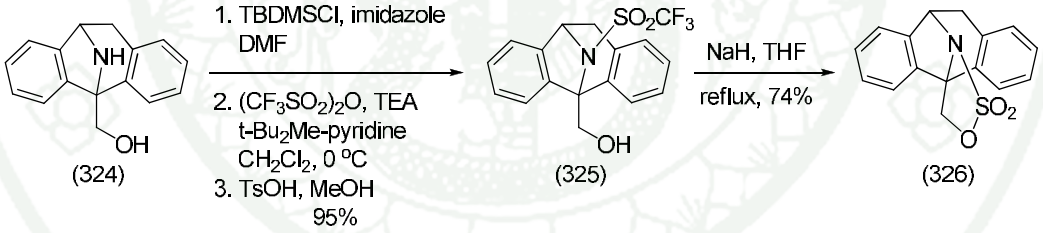
in 40% yield from L-serine by the Dodgson's method (Dodgson *et al.*, 1961) was converted to the cyclic sulfamidate **323** by treatment with dicyclohexylcarbodiimide (DCC) in DMF at 0°C (Scheme 47).



Scheme 47

The cyclic sulfamidate **326** was achieved by intramolecular nucleophilic attack of alkoxide at sulfone of the intermediate **325** which could be prepared by treatment of amino alcohol **324** with triflic anhydride (Scheme 48) (Lyle *et al.*, 1987).



Scheme 48

4. A two-step process via an intermediate cyclic sulfamidite

A two step approach featuring oxidation of a cyclic sulfamidite intermediate to cyclic sulfamidate has been explored owing to the directly installation of -SO_2- moiety is efficient only in conformationally rigid 1,2-amino alcohols. In case of more conformationally flexible amino alcohols tend to react with sulfuryl chloride leading to competitive chlorination (Vanhessche and Sharpless, 1997), aziridination (Scheme 49) (Kuyl-Yeheskiely *et al.*, 1992; Pilkington and Wallis, 1993) and also polymerization instead of the desired cyclic sulfamidates.

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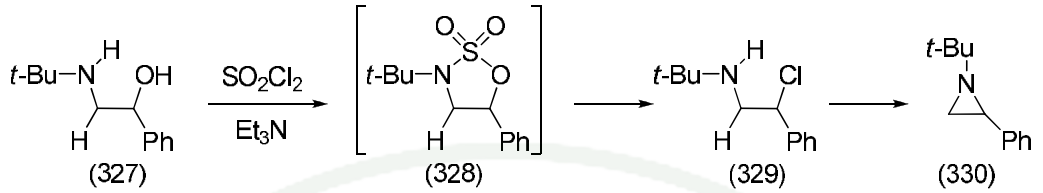
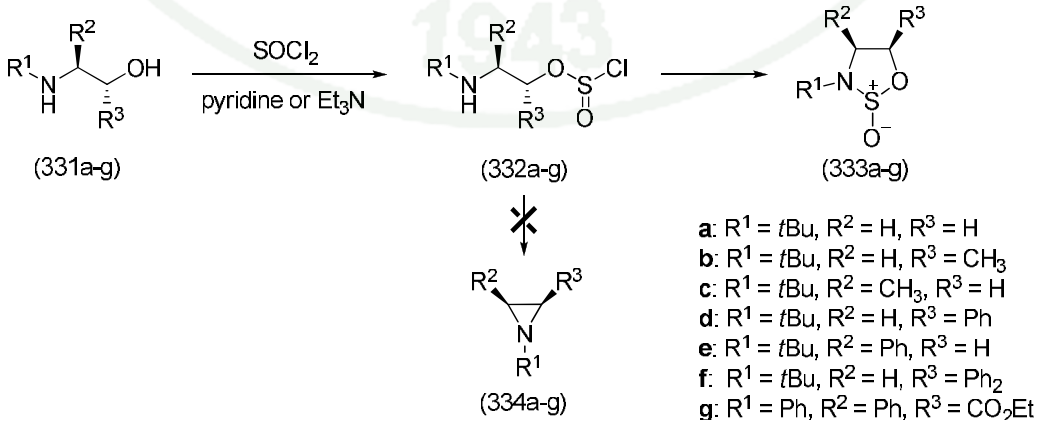


Scheme 49

Cyclic sulfamidates are widely synthesized by a two-step process, which proceeds *via* an intermediate cyclic sulfamidite. In some case, cyclic sulfamidites represent as electrophiles themselves, however, they are generally considered to be less reactive than the corresponding cyclic sulfamidates.

Over past decades, several approaches have been explored for the synthesis of cyclic sulfamidite. These manners were carried out by treatment of a variety of amino alcohols with thionyl chloride.

A variety of cyclic sulfamidite**s 333a-g** has been prepared from amino alcohols **331a-g** having various bulky or electron-withdrawing groups on nitrogen. The reactions were performed by using thionyl chloride in the presence of tertiary amines in nonpolar solvents. In addition, this method was extendable to larger rings (Deyrup and Moyer, 1969) (Scheme 50).



Scheme 50

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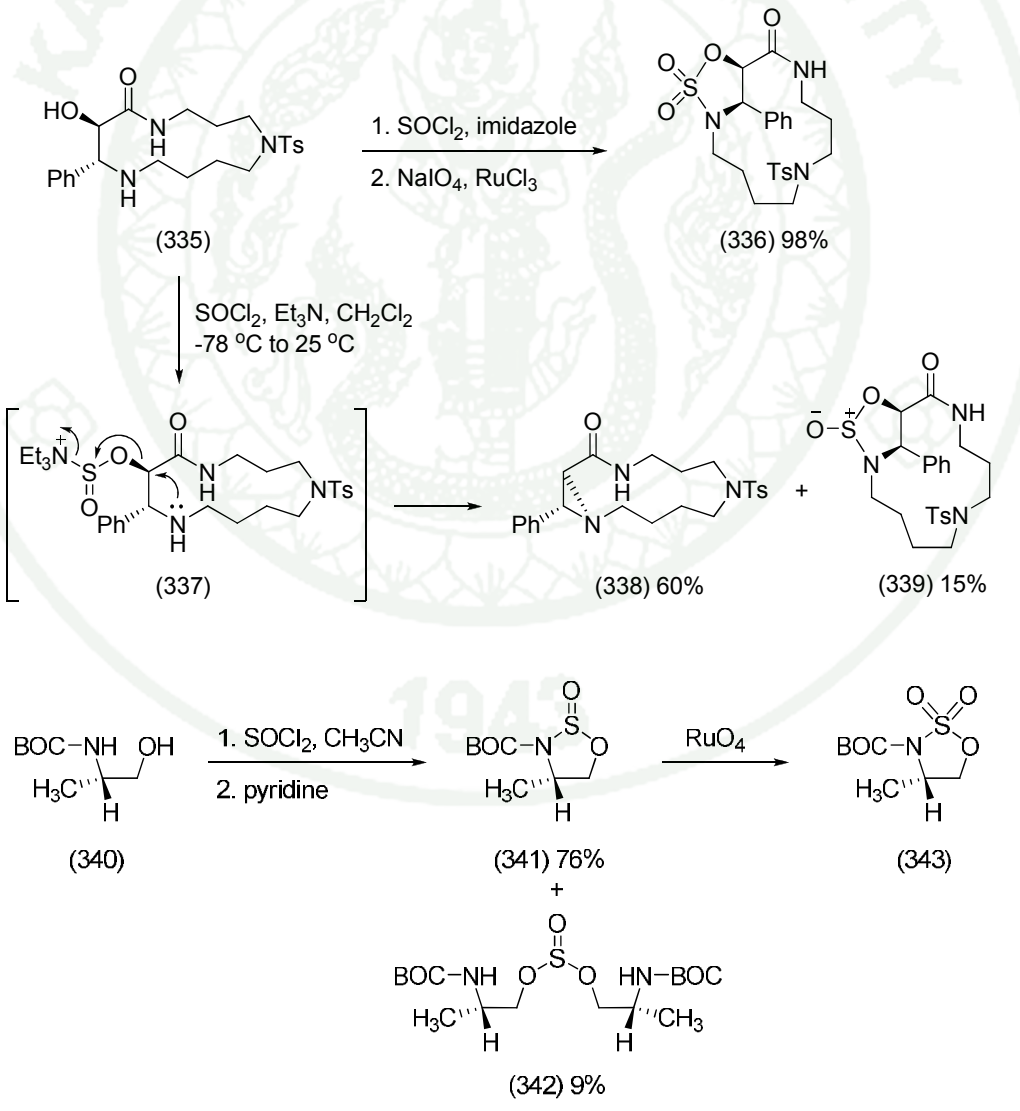
Although, the reaction of *β*-amino alcohols with thionyl chloride in the presence of tertiary amines in nonpolar solvent can potentially synthesized cyclic sulfamidites, in some cases, this condition has proven to be inefficient due to the rearrangement or the dimerization occurred to give aziridine **338** or dimer **342**. Therefore the methods for preparation of a range of 1,2- and 1,3-cyclic sulfamidites have been optimized by employing lower temperatures (-78 °C to 0 °C), more polar solvent systems, such as MeCN or CH_2Cl_2, and imidazole as a nucleophilic catalyst (Scheme 51) (Khanjin and Hesse, 2003; Posakony *et al.*, 2002).



Scheme 51

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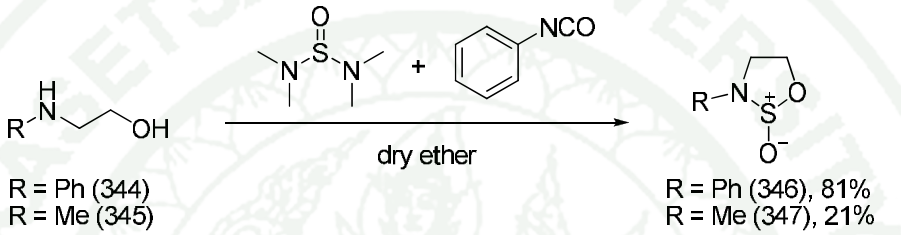
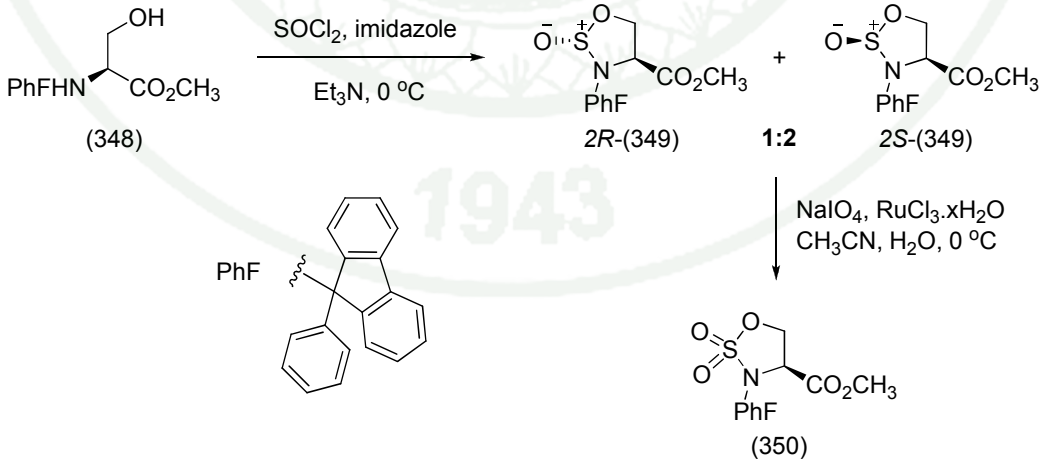
An alternative approach has been described for the preparation of 3-phenyl and 3-methyl 1,2,3-oxathiazolidine-2-oxides **346** and **347** by treatment of the corresponding *N*-(alkyl)amino alcohols **344** and **345** with the adduct generated from *N,N,N′,N′*-tetramethylsulfurous diamine and phenyl isocyanate in ether subsequently heating the oily resultant at 120-130 °C for 10 min (Scheme 52) (Takei *et al.*, 1968).



Scheme 52

The amino alcohol **348** having a bulky group (9-(9-phenylfluorenyl)) on the nitrogen was used to prepare diastereoisomers cyclic sulfamidites 2*R*-**349** and 2*S*-**349** which could be separated by chromatographic method (Scheme 53) (Wei and Lubell, 2001).



Scheme 53

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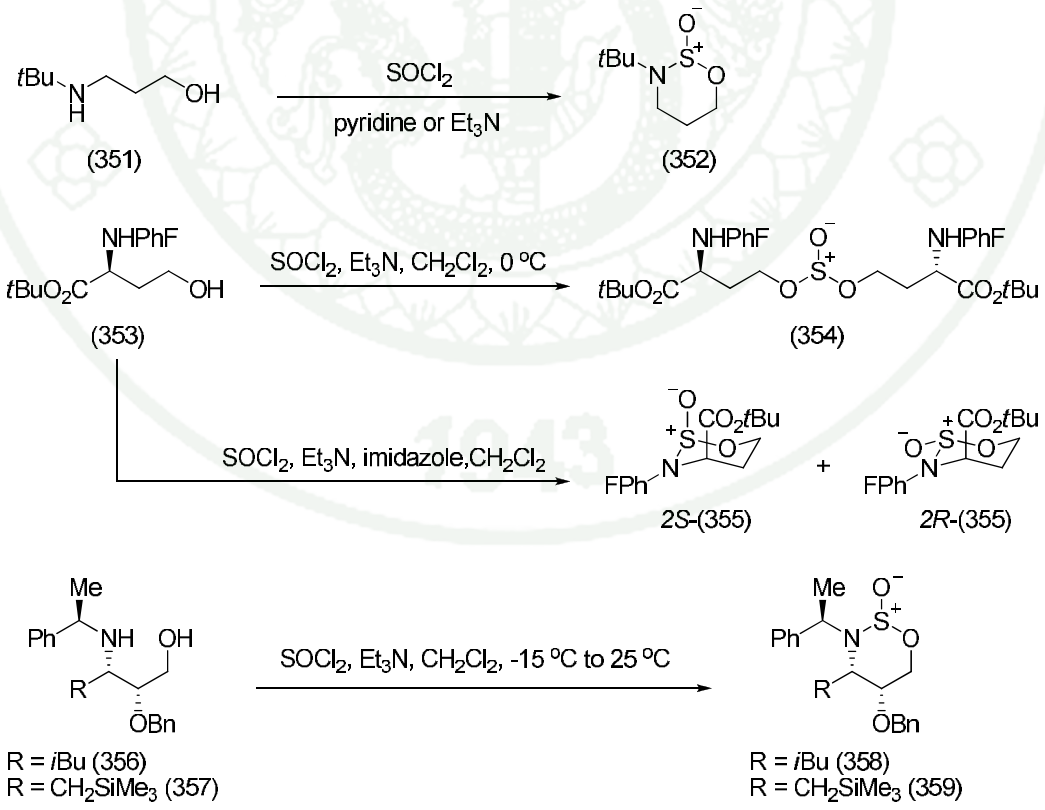
The two steps reaction was extending to synthesize six-membered cyclic sulfamidates from *γ*-amino alcohols. The 3-*t*-butyl amino propanol (351) was converted to the corresponding 2-oxo-1,2,3-tetrahydro-oxathiazin (352) by the original procedure (Scheme 54) (Deyrup and Moyer, 1969).

When the more sterically demanding 1,3-amino alcohol **353** was treated under similar conditions ($SOCl_2$, Et_3N, CH_2Cl_2 at 0°C), the sulfamidite was not obtained, instead, the dimer **354** was isolated as the major product. However the desired cyclic sulfamidite **355** was formed in a 4:1 mixture of diastereomers in excellent yield by the addition of excess imidazole to the high diluted reaction mixture (Scheme 54) (Atfani *et al.*, 2001). In addition, this procedure was extended to synthesize the disubstituted six-membered cyclic sulfamidites **358** and **359** as shown in Scheme 54 (Meunier *et al.*, 1996).



Scheme 54

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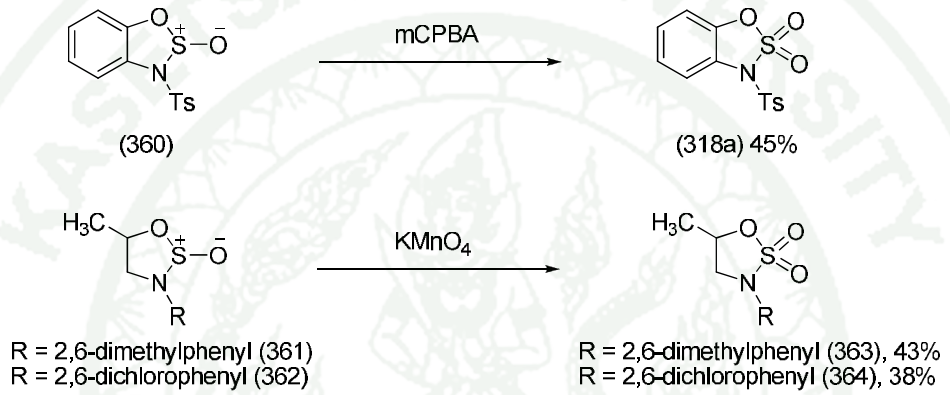
Several oxidizing reagents have been investigated for transformation of cyclic sulfamidites to cyclic sulfamidates. For example, m-chloroperoxybenzoic acid (Andersen *et al.*, 1991) or $KMnO_4$ (Zubovics *et al.*, 1986) was used to oxidize cyclic sulfamidites **360**, **361** and **362** to their sulfamidates **318a**, **363** and **364** in low to moderate yield (Scheme 55).



Scheme 55

The most effective reagent systems have utilized a combination of either catalytic RuO_4 or $RuCl_3$ and $NaIO_4$ in acetonitrile/water to furnish the desired product in generally more than 85% yields. The examples of five-membered cyclic sulfamidates prepared under this condition were shown in Figure 8.

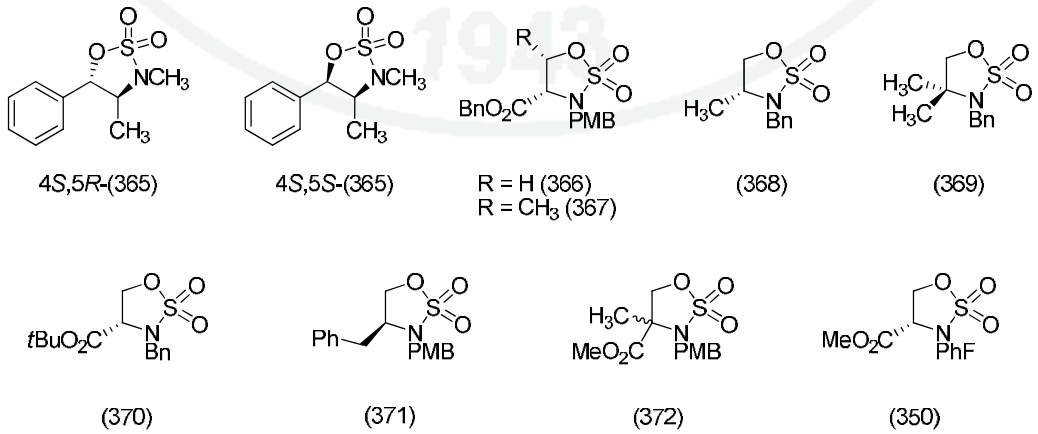


Figure 8 Five-membered cyclic sulfamidates.

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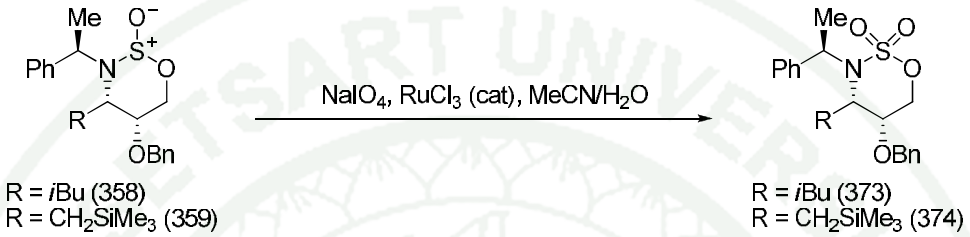
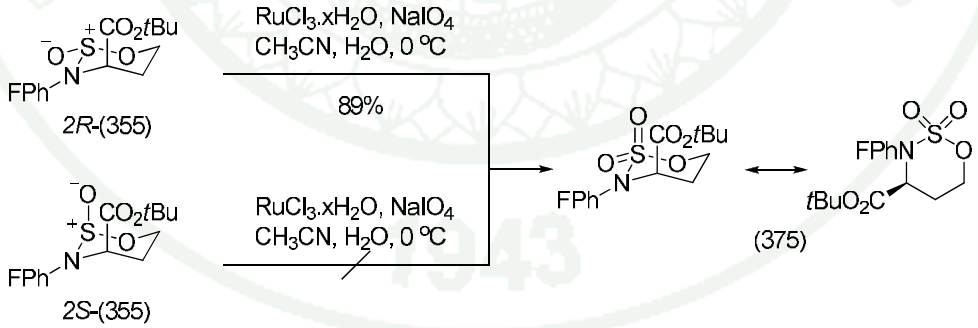
This manner could be applicable to the oxidation of six-membered cyclic sulfamidites **358** and **359** to the expected sulfamidates **373** and **374** in good yield (Scheme 56) (Meunier *et al.*, 1996).



Scheme 56

In case of oxidation of *N*-(PhF)homoserine-derived six-membered cyclic sulfamidite, the sterically hindered 2*S*-isomer **355** did not access to its sulfamidate under the catalytic $RuCl_3$ conditions, whereas, the major 2*R*,4*S*-sulfamidite **355** was smoothly oxidized under this condition to afford the desired product **375** in 89% yield (Scheme 57) (Atfani *et al.*, 2001).



Scheme 57

Gallagher and co-workers reported the efficient procedures to synthesize a range of structurally representative cyclic sulfamidates in enantiopure form and on large scale (30 g) from the corresponding amino alcohol *via* cyclic sulfamidite intermediate (Bower *et al.*, 2010). The two-steps reaction was carried out by treating amino alcohol with $SOCl_2$ in the presence of imidazole and then subsequent oxidation

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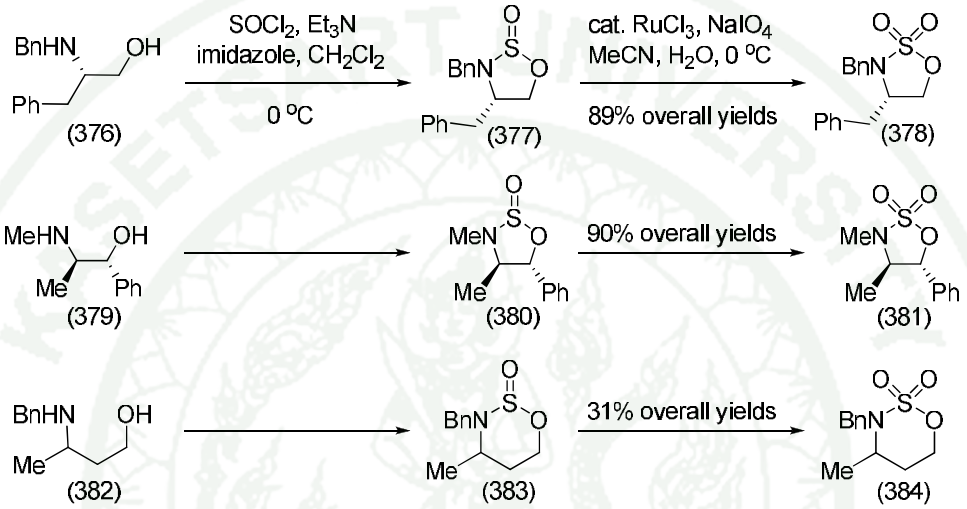
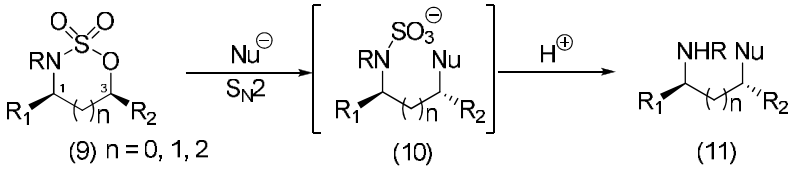
using catalytic $RuCl_3$, $NaIO_4$. Addition of DMSO prior to chromatographic purification can easily removed residual ruthenium from the crude product. A number of examples were shown in Scheme 58.



Scheme 58 Cyclic sulfamidates from amino alcohol using two-steps protocol

Synthesis of *N*-heterocycles *via* cyclic sulfamidates

The 1,2 and 1,3-cyclic sulfamidates with multiple chiral centers are synthetically valuable electrophiles in which nucleophilic attack occurs preferentially at the oxygen-bearing carbon centre in a stereospecific process (S_N2). The final product is formed after hydrolyzed an *N*-sulfate intermediate **10** under either protic (HCl, H_2SO_4, NaH_2PO_4) or Lewis acidic (BF_3/thiol) conditions. Moreover, cyclic sulfamidate serves as a key intermediate for the construction of enantiomeric chiral enriched heterocyclic compounds.



Scheme 2

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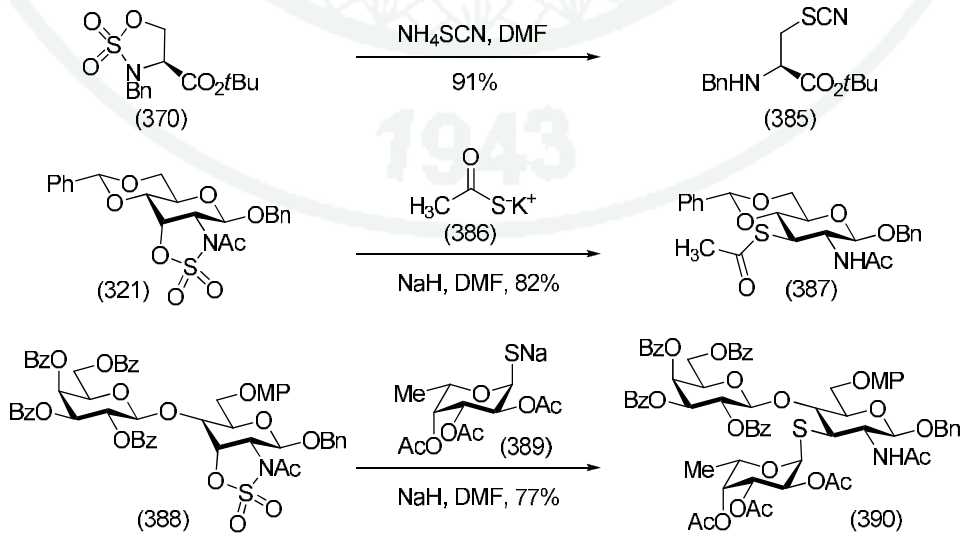
Nucleophilic ring opening of cyclic sulfamidates by heteroatom nucleophiles has been extensively studied and reviewed. Some examples of various hetero- and carbon-nucleophiles used in this reaction were shown as following.

1. Sulfur nucleophiles

Thiocyanate ion, thioacetate ion and also alkyl- or glycosylthiolate ion do react usually as nucleophile to cyclic sulfamidates under different conditions. For example, nucleophilic ring opening of serine-derived sulfamidate **370** with thiocyanate ion in DMF at room temperature provided *S*-cyano-cysteine **385** in 91% yield (Wei and Lubell, 2001). In addition, thioacetate ion **386** reacted with D-allosamine-derived sulfamidate **321** under the same condition to give thioester **387** in 82% yield (Aguilera *et al.*, 1997). In cases when five-membered cyclic sulfamidates did not react with alkylthiols under neutral conditions, the reaction under alkaline conditions proceeds quite well (Boulton *et al.*, 1999). The reactions between a series of glycosylthiolate ions with D-allosamine-, serine- and threonine-derived sulfamidates have been utilized to prepare a variety of polysaccharides. For example, trisaccharide **390** was prepared from the reaction of disaccharide **388** and monosaccharide **389** (Scheme 59) (Aguilera and Fernández-Mayoralas, 1998).



Scheme 59

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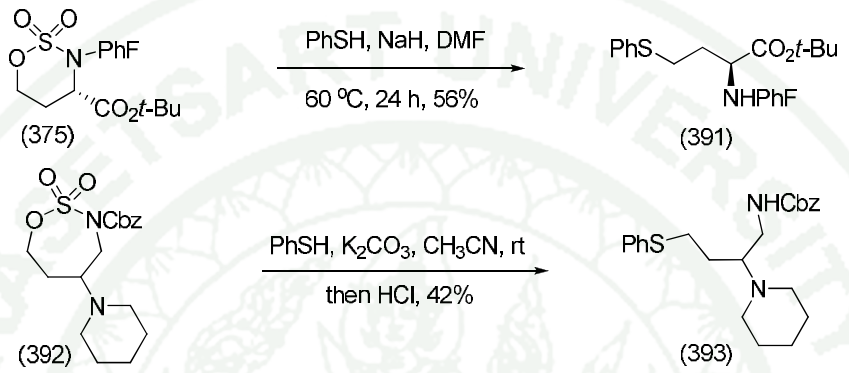
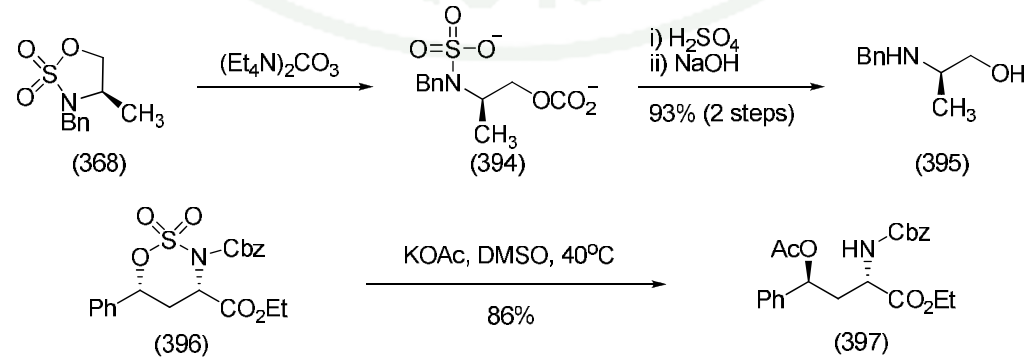
Six- and seven-membered cyclic sulfamidates have also reacted with thiophenol under basic conditions to deliver thioether in moderate yield (Scheme 60) (Atfani *et al.*, 2001; Duran *et al.*, 2002).



Scheme 60

2. Oxygen nucleophiles

Sulfamidates could be hydrolyzed under either acidic or basic conditions (*e.g.* aq. HCl in dioxane, aq. NaOH in CH_3CN and NaOMe in MeOH) to the corresponding amino alcohol. Furthermore, some weakly basic oxygen nucleophiles such as carbonate ion and acetate can react with cyclic sulfamidates **368** and **396** to provide the corresponding acetate or carbonate products in good yield (Scheme 61) (Aguilera *et al.*, 1997; Espino *et al.*, 2001; Posakony and Tewson, 2002).



Scheme 61

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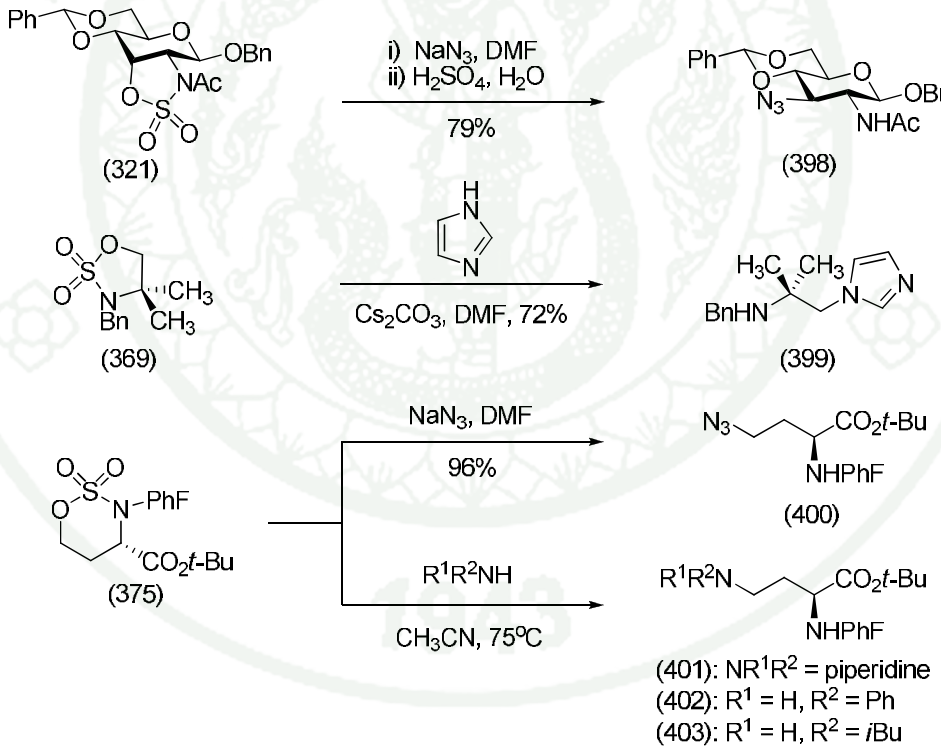
3. Nitrogen nucleophiles

Azide ion, an effective nucleophile, reacts with five- and six-membered cyclic sulfamidates **321** and **375** under mild conditions to afford amino azides **398** and **400** in high yield (Atfani *et al.*, 2001; Espino *et al.*, 2001). The reaction of imidazole with sulfamidate **369** was carried out by heating (60-80°C) in polar solvent (DMF) to produce azole-alanine **399** in 72% yield (Posakonya and Tewson, 2002). Moreover, both primary and secondary amines have efficiently reacted with five- and six-membered cyclic sulfamidates to the corresponding diamines in good yields (Alker *et al.*, 1990).



Scheme 62

4. Carbon nucleophiles

Cyanide ion reacts with a number of 1,2-cyclic sulfamidates in DMF at room temperature to deliver their nitrile counterparts in 22% to 100% yields relying on the

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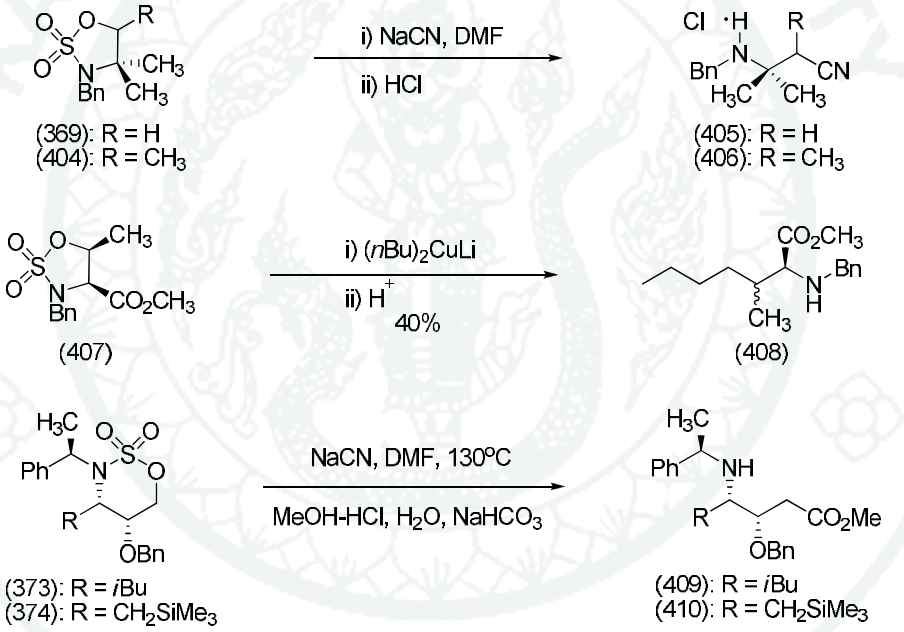
steric hindrance of substrates (Posakony and Tewson, 2002). In addition, lithium di(*n*-butyl)cuprate reacted with threonine-derived sulfamidate **407** by attack at the *β*-carbon *via* S_N2 process and attack the side elimination product *via* Michael addition mechanism to provide a 3:1 mixture of diastereomers **408** in 40% yield (Pound *et al.*, 2002). Six-membered cyclic sulfamidates **373** and **374** were opened with sodium cyanide in DMF at 130°C and then underwent hydrolysis of the sulfamic acids and nitrile groups with MeOH·HCl provided methyl esters **409** and **410** in 67 and 65% yields, respectively (Scheme 63) (Meunier *et al.*, 1996).



Scheme 63

5. Halogen nucleophiles

In advance, ^{18}F-labeled compounds, biological tools for imaging with the use of Position Emission Tomography (PET), were prepared by nucleophilic substitution of fluoride ion to five-membered cyclic sulfamidates. Sulfamidate 4*S*,5*S*-**365** was treated with a 1:4 KF/CaF_2 mix in dry acetonitrile in the presence of Kryptofix[2.2.2]® at 80°C to produce (1*R*,2*S*)-**411** in 54% yield after aqueous H_2SO_4 work-up (VanDort *et al.*, 1995). Tetrabutylammonium fluoride has been generally

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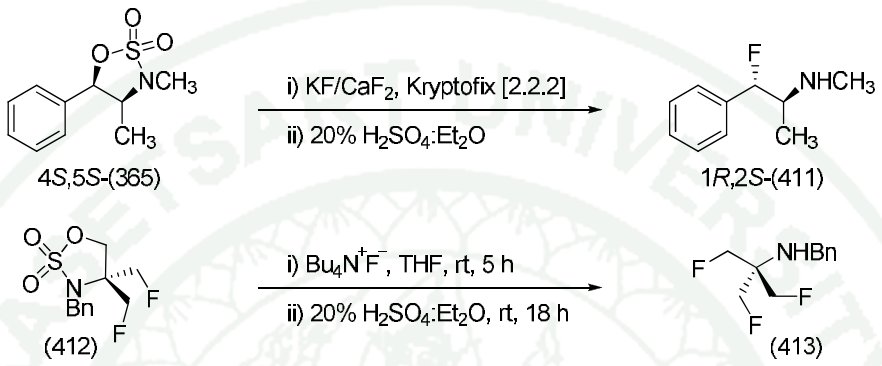
used to open five- and six-membered cyclic sulfamidates, such as sulfamidate **412** (Ok *et al.*, 1999).

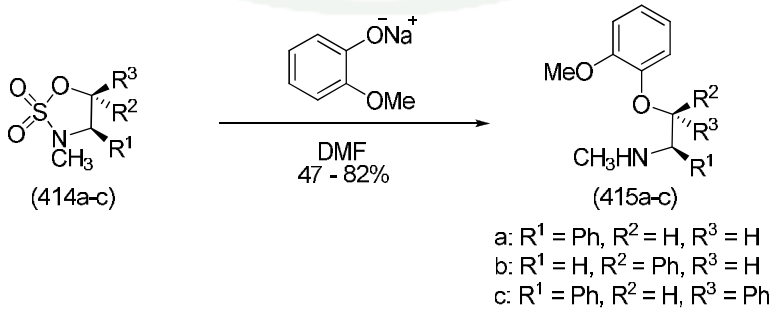


Scheme 64

Among numerous applications of cyclic sulfamidates, we focus upon the synthesis of related benzofused heterocycles *via* five- and six-membered cyclic sulfamidates due to these core structures are important toward the development of biological drug synthetic methods.

Aromatic nucleophiles

Okuda and Tomioka utilized 2-methoxyphenolate to open 1,2-cyclic sulfamidates **414a-c** to deliver the corresponding adducts **415a-c** in moderate to good yield (1994).



Scheme 65

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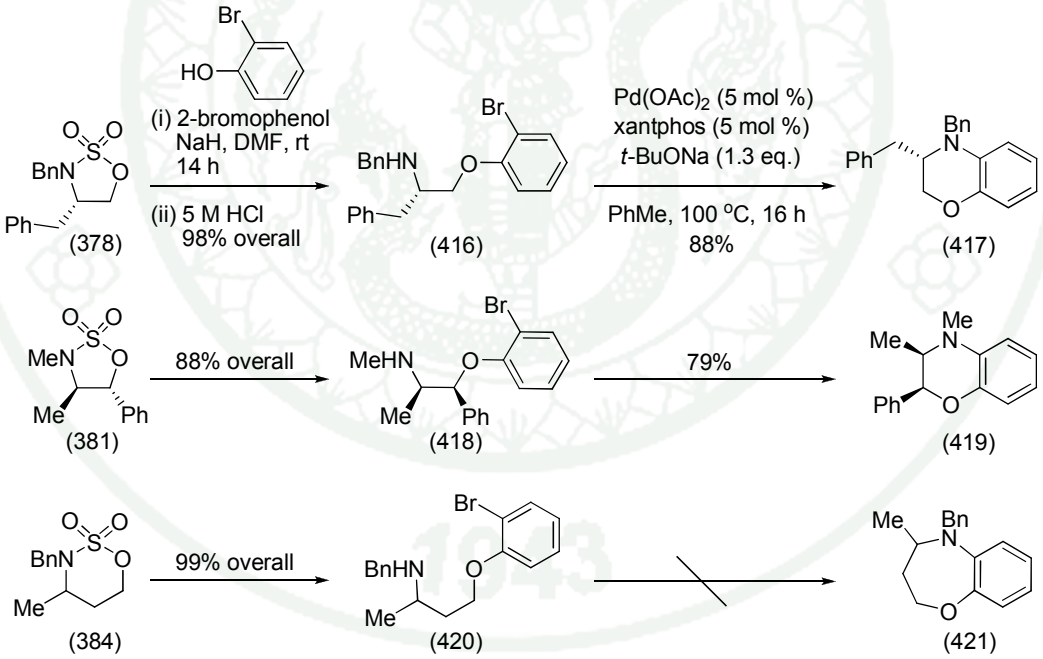
Recently, Bower and Gallagher have synthesized a number of substituted and enantiopure 1,4-benzoxazines and related benzofused heterocycles by the opening of a cyclic sulfamidate with 2-bromophenol and related species followed by *N*-sulfate hydrolysis, and annulation by Pd catalyst.

In their study, nucleophilic cleavage of various cyclic sulfamidates with the sodium anion of 2-bromophenol proceeded smoothly between room temperature to 60°C to afford the corresponding adducts in excellent yield (88-99%) after *N*-sulfate hydrolysis. The following cyclization reaction, $Pd(OAc)_2$ was employed as catalyst. The best yield of substituted benzoxazines were achieved when using 5 mol% of $Pd(OAc)_2$, xantphos as ligand and *t*-BuONa in toluene at 100°C (Scheme 66).



Scheme 66

The limitation of this condition toward amination product is the difficulty formation of 7-ring product **421** from **420** which was obtained from 1,3-cyclic sulfamidate **384** (Scheme 66).

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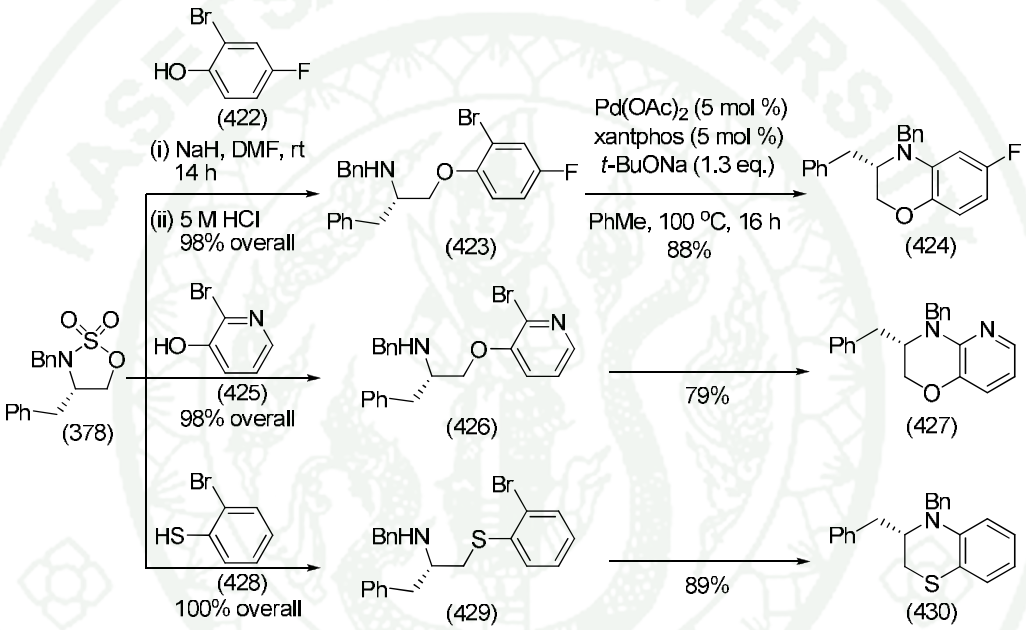
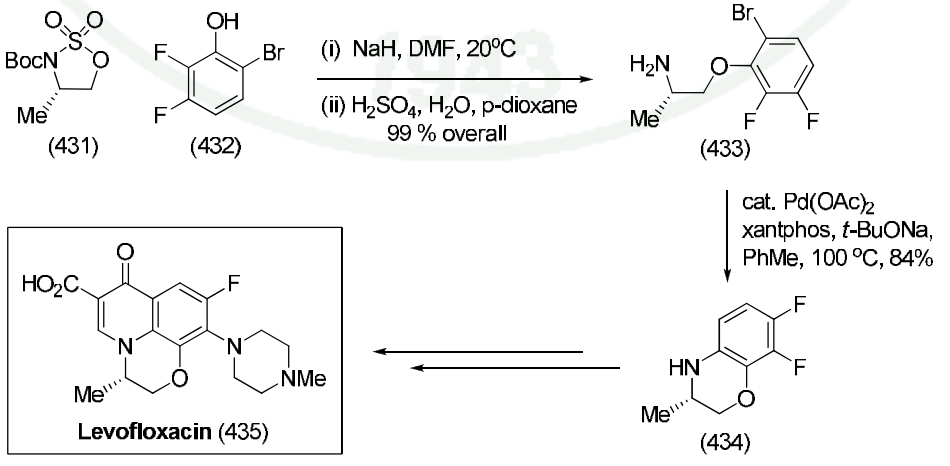
Extension of this methodology allows them to construct substituted aromatic 1,4-benzoxazines, 1,4-benzothiazines and 1,4-quinoxalines from the reaction of cyclic sulfamidate **378** (Scheme 67) with various nucleophiles and also to synthesize levofloxacin **435**, a significant antibiotic drug marketed in Europe by Sanofi-Aventis from sulfamidate **431** (Scheme 68) (Bower *et al.*, 2010).



Scheme 67



Scheme 68 Synthesis of Levofloxacin *via* cyclic sulfamidate

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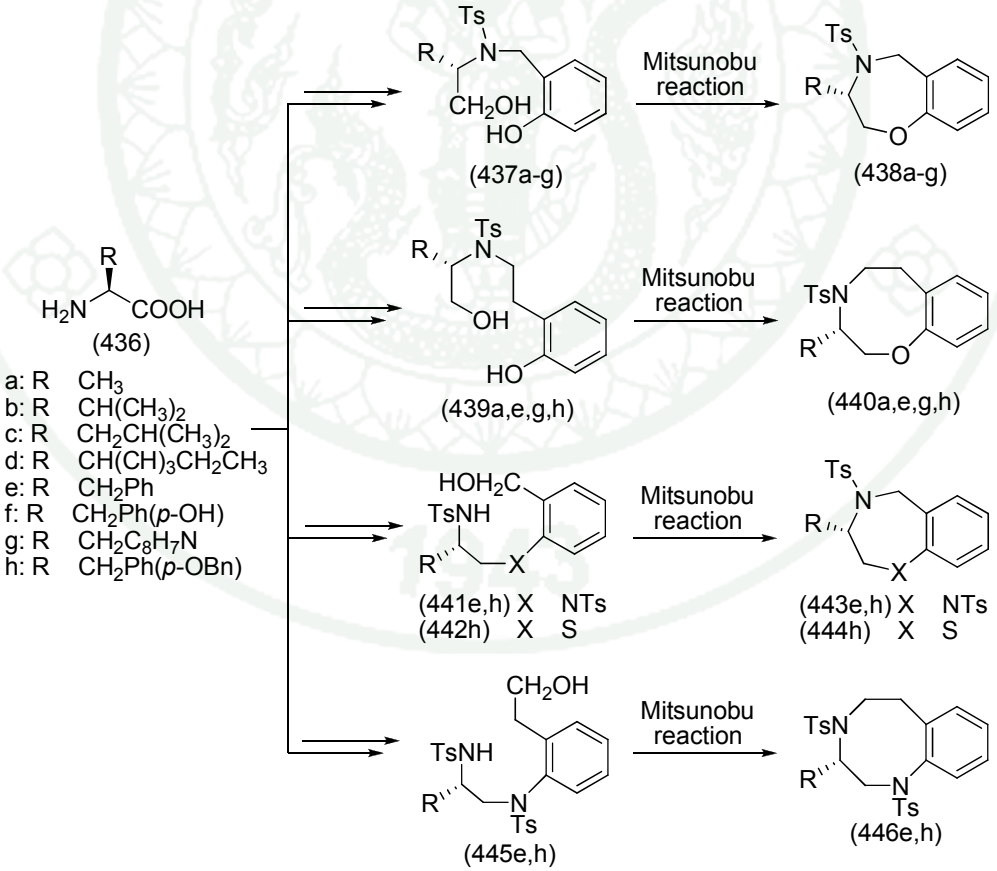
Intramolecular Mitsunobu reaction

An alternative approach to generate enantiomerically pure benzoannulated oxazepine, diazepine, thiazepine, oxazocine and diazocine scaffolds was reported by Mishra and Panda using intramolecular Mitsunobu reaction. They have prepared a number of precursors for the Mitsunobu cyclisation from naturally abundant chiral amino acids **436a-h**. Cyclisation of their precursors under standard Mitsunobu condition (DEAD, PPh_3, THF, 0°C to rt) is accessible for production of benzoannulated 7- and 8-membered ring heterocycles in moderate to good yield. However, the diverse multi-steps organic reactions were used for the preparation a variety of pre-cyclised intermediates (Scheme 69) (Mishra and Panda, 2007).



Scheme 69

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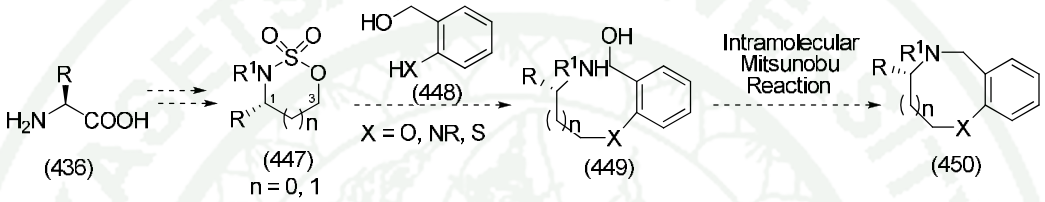
These chiral intermediate precursors could be created by nucleophilic attack of either five- or six-membered cyclic sulfamidates with 2-(hydroxymethyl)phenol (and related anilines and thiophenols) (Scheme 70). A number of cyclic sulfamidates can be also achieved in several steps reaction from the *S*-amino acid by the protocol described in the previous reviews (Bower *et al.*, 2010).



Scheme 70

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MATERIALS AND METHODS

Materials

Instrumentation

The following analytical methods were used throughout this work, unless otherwise indicated.

Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a VARIAN^{UTITY} INOVA 400 MHz NMR spectrometer at the Department of Chemistry, Faculty of Science, Kasetsart University, JEOL GX400, JEOL Eclipse 400 or JEOL Alpha 500 spectrometer at the School of Chemistry, University of Bristol. Chemical shifts were recorded as δ values in ppm. Spectra were acquired in $CDCl_3$ unless otherwise stated. The peak due to residual $CHCl_3$ (7.26 ppm for ^{1}H and 77.2 ppm for ^{13}C) was used as the internal reference. Coupling constants (*J*) are given in Hz, and multiplicity is defined as follows: br = broad, s = singlet, d = doublet, dd = doublet of doublet, dt = doublet of triplet, t = triplet, q = quartet, quint = quintet, m = multiplet.

Optical rotations were measured using a JASCO P-2000 polarimeter at the Government Pharmaceutical Organization or a Perkin-Elmer 241 polarimeter at the School of Chemistry, University of Bristol.

Infrared (IR) spectra were recorded in the range 4000-400 cm^{-1} on a Perkin-Elmer 2000 Fourier transform infrared spectrophotometer at the Department of Chemistry, Faculty of Science, Kasetsart University or a Perkin-Elmer Fourier transform infrared spectrophotometer at the School of Chemistry, University of Bristol. Samples were analyzed as neat liquid or KBr disks.

Mass spectra were obtained on an Agilent Technology 1100 series LL/MSD Trap; the first number denoted *m/z* value and the ion assignment and abundance are

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given in parentheses and on a GCMS-QP-5050QA spectrometer in electrospray ionization mode (ESI^+) at the Scientific Equipment Center, Faculty of Science, Kasetsart University and a Fisons VG Analytical Autospec spectrometer in electron impact (EI^+) or chemical ionization (CI^+) at the School of Chemistry, University of Bristol. Accurate masses (HRMS) were recorded on Q-TOF2 hybrid quadrupole time-of-flight mass spectrometer from Mass Spectrometry Research Laboratory at Department of Chemistry, Faculty of Science, Chiang Mai University and the University of Bristol mass spectrometry service by electrospray ionization (ESI^+) using a Brüker Daltonics Apex IV spectrometer.

Unless otherwise stated, concentration under reduced pressure refers to a rotary evaporator at water aspirator pressure at the Department of Chemistry, Faculty of Science, Kasetsart University and a Büchi rotary evaporator (bath temperatures up to 40 °C) at a pressure of either 15 mmHg (diaphragm pump) or 0.1 mmHg (oil pump), as appropriate, and a high vacuum line at room temperature at the School of Chemistry, University of Bristol.

Melting points (m.p.) were determined on a MeI-Temp electrothermal apparatus at the Department of Chemistry, Faculty of Science, Kasetsart University and were reported uncorrected in °C.

Chromatographic system

Analytical thin-layer chromatography (TLC) was conducted on aluminum-backed 0.2 mm thick silica gel 60 F254 plates (Merck) and the chromatograms were visualized under a 254 nm UV lamp and/or by spraying with a solution of vanillin (3% in ethanol with 3% sulfuric acid) followed by heating.

Flash column chromatography was conducted according to the method of Still and co-workers (1978) using silica gel 60 (mesh size 0.040-0.063 mm).

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Column chromatography was performed on silica gel 60 (70-230 mesh, Merck) and the column was packed by slurry method.

Chemical reagents

Starting materials sourced from commercial suppliers were used as received unless otherwise stated. Analytical grade solvents and reagents used for synthesis were obtained from commercial source and used directly without further purification unless noted. Dry tetrahydrofuran (THF) was freshly distilled under nitrogen atmosphere from sodium with benzophenone ketyl as an indicator. Dichloromethane was dried over anhydrous calcium chloride and distilled from calcium hydride immediately prior to use.

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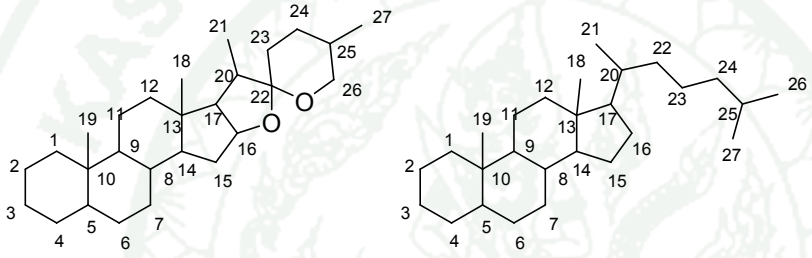
Methods

Numbering of tetracyclic steroid carbon skeleton

The spectral data of all synthesized compounds reported throughout this work were referred to the numbered of tetracyclic steroid carbon skeletons as shown below. The additional carbons would be numbered in each case.



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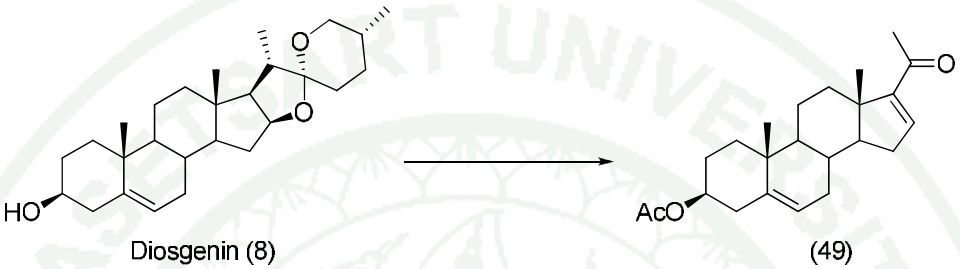
Synthesis of steroidal OSW-1 intermediates

3β-Acetoxy-5,16-pregnadiene-20-one (49)



A mixture of diosgenin (8) (1.0 g, 2.41 mmol), ammonium chloride (129 mg, 2.41 mmol), acetic anhydride (8 mL), and pyridine (0.4 mL, 4.82 mmol) was refluxed (135 °C) for 12 h. After cooling down, the reaction mixture was added acetic acid (2 mL), 1,2-dichloroethane (2 mL) and water (0.25 mL) and cooled to 0 °C. A cooled solution of chromium trioxide (0.84 g, 8.40 mmol) in water (0.6 mL) and acetic acid (0.2 mL) was added dropwise, while the temperature was kept at 7-10 °C. When 90% of the solution has been added, cooling is discontinued. After remaining portion has been added, the mixture was stirred for 2 h at room temperature. Then a saturated solution of sodium hydrogen carbonate was introduced and the stirring was continued for two additional hours. Then water was added and the reaction mixture was extracted with 1,2-dichloroethane and the combined extract was washed with water to remove the residual chromium salts, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. To a solution of the residue and alumina base (1:25) in benzene was stirred overnight at room temperature. The reaction mixture was washed with CH_2Cl_2 and filtered by silica gel 9385. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/hexane, 1:4) to provide 3β-acetoxy-5,16-pregnadiene-20-one (49) as a white solid (413 mg, 48%); m.p. 171-173 °C. (Mićović *et al.*, 1990, m.p. 170-172 °C)

FTIR (KBr), ν_{max}, cm^{-1}: 2965, 2944, 2904, 2864, 1730, 1662, 1372, 1246, 1036

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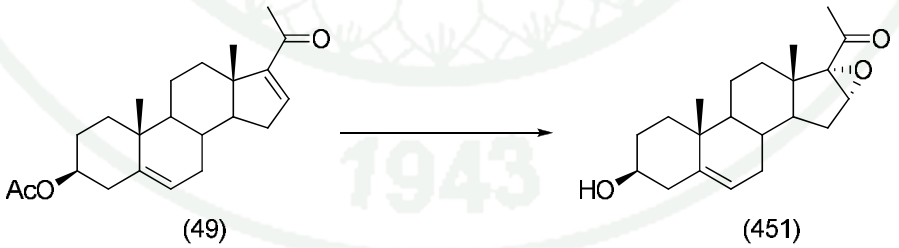
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.69 (d, *J* = 1.9, 3.3 Hz, 1H, H-16), 5.37 (d, *J* = 5.2 Hz, 1H, H-6), 4.55-4.63 (m, 1H, H-3), 2.39 (ddd, *J* = 2.7, 4.3, 12.7 Hz, 1H, H-4), 2.30-2.35 (m, 2H, H-4, H-15), 2.28 (dd, *J* = 3.4, 6.6 Hz, 1H, H-15), 2.25 (s, 3H, H-21), 2.05 (dd, *J* = 1.9, 12.2 Hz, 1H, H-7), 2.02 (s, 3H, -$OCOCH_3$), 1.98 (dd, *J* = 1.9, 8.2 Hz, 1H, H-7), 1.87 (dd, *J* = 3.3, 5.8 Hz, 1H, H-1), 1.84 (dd, *J* = 3.8, 5.5 Hz, 1H, H-2), 1.70 (ddd, *J* = 4.4, 10.5, 10.5 Hz, 1H, H-12), 1.50-1.66 (m, 4H, H-2, H-11, H-12), 1.42 (ddd, *J* = 6.6, 11.5, 11.5 Hz, 1H, H-14), 1.33 (ddd, *J* = 6.0, 12.1, 12.1 Hz, 1H, H-8), 1.12 (dd, *J* = 9.6, 14.0 Hz, 1H, H-1), 1.03 (ddd, *J* = 6.2, 10.5, 10.5 Hz, 1H, H-9), 1.05 (s, 3H, H-19), 0.91 (s, 3H, H-18)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 196.8 (C-20), 170.5 (C=O), 155.3 (C-17), 144.4 (C-16), 140.2 (C-5), 121.9 (C-6), 73.8 (C-3), 56.3 (C-14), 50.4 (C-9), 46.0 (C-13), 38.1 (C-4), 36.8 (C-1), 36.7 (C-10), 34.6 (C-15), 32.2 (C-7), 31.5 (C-2), 30.1 (C-8), 27.7 (C-12), 27.1 (C-21), 21.4 (OCO<u>C</u>H_3), 20.6 (C-11), 19.2 (C-19), 15.7 (C-18)

MS (ESI^+), *m/z* (relative intensity): 357.3 ($[M+H]^+$, 100 %)

3β-Hydroxy-16α,17α-epoxy-5-pregnene-20-one (451)



(49) (451)

To a cooled (0 °C) solution of 3β-acetoxy-5,16-pregnadiene-20-one (49) (413 mg, 1.16 mmol) in methanol (8 mL) was added dropwise 40% H_2O_2 (1.6 mL) and 2.5N NaOH (1.6 mL). After the reaction mixture was stirred at room temperature for 24 h, saturated aqueous NaCl was added and methanol was removed under vacuum. The residue was added with water and extracted with CH_2Cl_2. The combined organic layer was washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated

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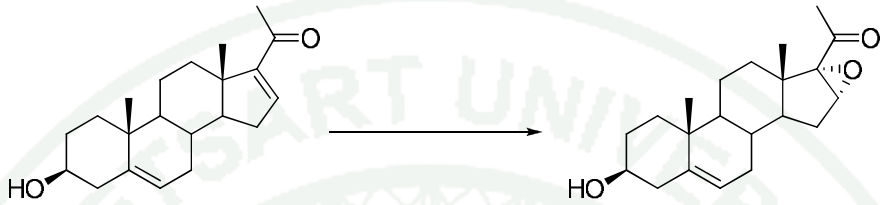
under reduced pressure to afford 3β-hydroxy-16α,17α-epoxy-5-pregnene-20-one (451) as a white solid (371 mg, 97%); m.p. 176-178 °C.



(452) (451)

To a cooled (0 °C) stirred solution of 5,16-pregnadiene-3β-ol-20-one (452) (2 g, 6.40 mmol) in methanol (50 mL) was added 30% H_2O_2 (10 mL), and treated dropwise with 2.5N NaOH (10 mL). After the resulting reaction mixture was stirred at room temperature for 24 h, the reaction was added with saturated aqueous NaCl. The solvent was removed under vacuum. The residue was dissolved in water and extracted with CH_2Cl_2. The combined organic layer was washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/hexane, 1:4) to provide 3β-hydroxy-16α,17α-epoxy-5-pregnene-20-one (451) (1.84 g, 88%) as a white solid or give upon crystallizations from ether-petroleum ether and from acetone of white needles; m.p. 177-179 °C. (Litvinovskaya *et al.*, 2001, m.p. 179-180°C (methanol) and Sakee *et al.*, 2003, m.p. 175-177°C)

FTIR (KBr), ν_{max}, cm^{-1}: 3378, 2970, 2936, 2864, 1693, 1376, 1055

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.28 (d, *J* = 5.2 Hz, 1H, H-6), 3.64 (s, 1H, H-16), 3.42–3.50 (m, 1H, H-3), 2.14-2.21 (m, 1H, H-4), 2.25 (ddd, *J* = 1.6, 5.1, 13.0 Hz, 1H, H-4), 2.12 (brs, 1H, OH), 1.97-2.01 (m, 1H, H-7), 1.98 (s, 3H, H-21), 1.91 (dd, *J* = 6.3, 13.5 Hz, 1H, H-15), 1.85-1.92 (m, 1H, H-12), 1.76-1.81 (m, 2H, H-1, H-2), 1.42-1.60 (m, 5H, H-2, H-7, H-8, H-11), 1.36 (ddd, *J* = 4.6, 12.6, 12.6 Hz, 1H, H-15), 1.28 (ddd, *J* = 0.6, 12.6, 12.6 Hz, 1H, H-12), 1.11 (ddd, *J* = 6.1, 11.4, 11.4 Hz, 1H, H-14), 1.04 (dd, *J* = 4.3, 14.4 Hz, 1H, H-1), 1.00 (s, 3H, H-19), 0.97 (s, 3H, H-18), 0.87-0.95 (m, 1H, H-9)

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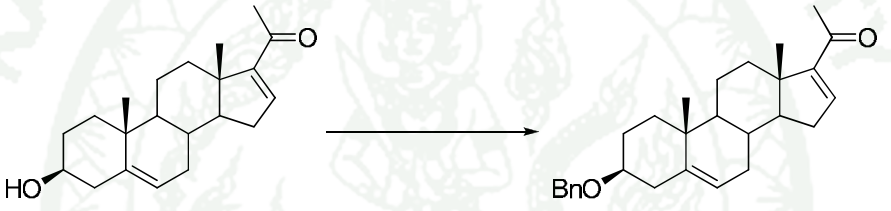
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 204.9 (C-20), 141.1 (C-5), 120.8 (C-6), 71.4 (C-3), 70.9 (C-17), 60.4 (C-16), 50.2 (C-9), 45.4 (C-14), 42.1 (C-4), 41.4 (C-13), 37.0 (C-1), 36.6 (C-10), 31.4 (C-7), 31.3 (C-15), 31.3 (C-2), 29.6 (C-8), 27.1 (C-12), 25.9 (C-21), 20.3 (C-11), 19.2 (C-19), 15.0 (C-18)

MS (ESI^+), *m/z* (relative intensity): 353.3 ($[M+Na]^+$, 100 %)

3β-Benzyloxy-5,16-pregnadiene-20-one (453)



To a suspension of NaH (51 mg of a 60% mineral oil suspension, 1.27 mmol) in dry THF (2 mL) was added dropwise a solution of 5,16-pregnadiene-3β-ol-20-one (452) (80 mg, 0.25 mmol) in THF (3 mL) under nitrogen atmosphere. After stirring at room temperature for 2 h, benzyl bromide (0.044 mL, 0.38 mmol) was added. The reaction mixture was heated to reflux for 12 h. After removal of most of the solvent and benzyl bromide under reduced pressure, the residue was diluted with EtOAc and water was added to decompose the rest of NaH. Then the mixture was sequentially washed with 1N HCl and saturated aqueous $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/hexane, 1:24) to provide 3β-benzyloxy-5,16-pregnadiene-20-one (453) (40 mg, 39%) as a white solid.

FTIR (KBr), ν_{max}, cm^{-1}: 2926, 2849, 1703, 1660, 1453, 1364, 1234, 1110, 1070, 1033

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^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.18-7.30 (m, 5H, Ar(H)), 6.63 (dd, *J* = 1.9, 3.4 Hz, 1H, H-16), 5.28 (d, *J* = 5.4 Hz, 1H, H-6), 4.49 (s, 2H, OCH_2Ar), 3.17-3.25 (m, 1H, H-3), 2.36 (ddd, *J* = 2.3, 3.6, 13.2 Hz, 1H, H-4), 2.33 (ddd, *J* = 3.9, 3.9, 12.3 Hz, 1H, H-15), 2.26 (dd, *J* = 3.4, 6.5 Hz, 1H, H-15), 2.22 (dd, *J* = 3.4, 6.5 Hz, 1H, H-4), 2.20- 2.23 (m, 1H, H-7), 2.19 (s, 3H, H-21), 1.99 (dd, *J* = 2.0, 12.1 Hz, 1H, H-7), 1.96 (dd, *J* = 3.1, 5.0 Hz, 1H, H-2), 1.94 (dd, *J* = 2.9, 4.8 Hz, 1H, H-12), 1.80 (ddd, *J* = 3.6, 3.6, 13.3 Hz, 1H, H-1), 1.63 (dd, *J* = 4.7, 11.0 Hz, 1H, H-2), 1.58 (dd, *J* = 2.7, 5.1 Hz, 1H, H-12), 1.51-1.55 (m, 2H, H-11), 1.31 (dd, *J* = 6.3, 9.0 Hz, 1H, H-14), 1.25 (dd, *J* = 6.2, 11.9 Hz, 1H, H-8), 0.98 (dd, *J* = 3.6, 13.7 Hz, 1H, H-1), 0.98 (s, 3H, H-19), 0.92 (dd, *J* = 6.8, 10.5 Hz, 1H, H-9), 0.85 (s, 3H, H-18)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 196.8 (C-20), 155.4 (C-17), 144.4 (C-16), 141.6 (C-5), 139.0 (C-Ar), 128.3×2 (CH-Ar), 127.6×2 (CH-Ar), 127.4 (CH-Ar), 120.9 (C-6), 78.5 (C-3), 69.9 (OCH_2Ar), 56.5 (C-14), 50.4 (C-9), 46.1 (C-13), 39.2 (C-4), 37.1 (C-1), 37.1 (C-10), 34.7 (C-15), 32.2 (C-7), 31.6 (C-2), 30.2 (C-8), 28.4 (C-12), 27.1 (C-21), 20.7 (C-11), 19.3 (C-19), 15.7 (C-18)

MS (ESI^+), *m/z* (relative intensity): 427.2 ($[M+Na]^+$, 100 %)

3β-Benzyloxy-16α,17α-epoxy-5-pregnene-20-one (454)

(451) (454)

To a suspension of NaH (13.6 mg of a 60% mineral oil suspension, 0.33 mmol) in dry THF (2 mL) and dry DMF (5 mL) was added dropwise a solution of 3β-hydroxy-16α,17α-epoxy-5-pregnene-20-one (451) (40 mg, 0.12 mmol) in THF (3 mL) under nitrogen atmosphere. After stirring at room temperature for 1 h, benzyl

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bromide (0.022 mL, 0.18 mmol) was added. The reaction mixture was heated to reflux for 12 h. After removal of most of the solvent and benzyl bromide under reduced pressure, the residue was diluted with EtOAc and water was added to decompose the rest of NaH. Then the mixture was sequentially washed with 1N HCl and saturated aqueous $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/hexane, 7:93) to provide 3β-benzyloxy-16α,17α-epoxy-5-pregnene-20-one (454) (21 mg, 42%) as a white solid**;** m.p. 127-128 °C**.**

(453) (454)

To a cooled (0 °C) stirred solution of 3β-benzyloxy-5,16-pregnadiene-20-one (453) (30 mg, 0.074 mmol) in methanol (0.75 mL) was added 30% H_2O_2 (0.15 mL), and treated dropwise with 2.5N NaOH (0.15 mL). After the resulting reaction mixture was stirred at room temperature for 4 h, the reaction was added with saturated aqueous NaCl. The solvent was removed under reduced pressure. The residue was dissolved in water and extracted with CH_2Cl_2. The combined organic layer was washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/hexane, 7:93) to provide 3β-benzyloxy-16α,17α-epoxy-5-pregnene-20-one (454) (25 mg, 80%) as a white solid**;** m.p. 127-128 °C**.**

FTIR (KBr), ν_{max}, cm^{-1}: 2973, 2934, 2864, 1703, 1364, 1116, 1073

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.16-7.25 (m, 5H, Ar(H)), 5.24 (d, *J* = 5.3 Hz, 1H, H-6), 4.46 (s, 2H, OCH_2Ar), 3.57 (s, 1H, H-16), 3.19 (m, 1H, H-3), 2.36 (dd, *J* = 2.3, 4.7 Hz, 1H, H-4), 2.32 (dd, *J* = 2.3, 4.8 Hz, 1H, H-4), 1.97 (m, 1H, H-7), 1.93 (s, 3H, H-21), 1.89 (m, 1H, H-2), 1.85 (m, 1H, H-15), 1.85 (dd, *J* = 6.1, 13.2 Hz, 1H, H-

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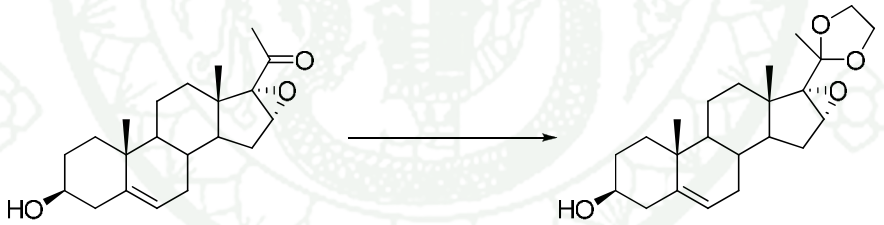
12), 1.76 (dt, *J* = 13.5, 3.3 Hz, 1H, H-1), 1.52 (m, 1H, H-11), 1.51 (m, 1H, H-7), 1.49 (m, 1H, H-8), 1.42 (m, 1H, H-2), 1.39 (dd, *J* = 3.7, 3.7 Hz, 1H, H-11), 1.32 (m, 1H, H-15), 1.22 (td, *J* = 0.8, 12.6 Hz, 1H, H-12), 1.03-1.08 (m, 1H, H-14), 0.96 (s, 3H, H-19), 0.94 (s, 3H, H-18), 0.94-0.99 (m, 1H, H-1), 0.83-0.91 (m, 1H, H-9)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 204.6 (C-20), 141.1 (C-5), 138.9 (C-Ar), 128.2 (CH-Ar), 127.4 (CH-Ar), 127.2 (CH-Ar), 120.7 (C-6), 78.3 (C-3), 70.8 (C-17), 69.8 (OCH_2Ar), 60.3 (C-16), 50.2 (C-9) 45.4 (C-14), 41.4 (C-13), 39.0 (C-4), 37.0 (C-1), 36.9 (C-10), 31.4 (C-7), 31.2 (C-15), 29.6 (C-8), 28.2 (C-2), 27.4 (C-12), 25.8 (C-21), 20.3 (C-11), 19.2 (C-19), 15.0 (C-18)

HRMS (ESI^+) *m/z*: $C_{28}H_{36}O_3Na$ $[M+Na]^+$, calcd 443.2562, found 443.2564

3β-Hydroxy-16α,17α-epoxy-20,20-(ethylenedioxy)-5-pregnene (455)



(451) (455)

To a solution of 3β-hydroxy-16α,17α-epoxy-5-pregnene-20-one (451) (50 mg, 0.15 mmol) in dichloromethane (3 mL) was added ethylene glycol (0.5 mL, 9.08 mmol), triethylorthoformate (0.76 mL, 4.54 mmol) and *p*-toluenesulfonic acid monohydrate (3 mg, 0.015 mmol). The reaction mixture was stirred at room temperature for 3 h. After addition of triethylamine and water, the product was extracted into EtOAc. The combined organic layers were washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (EtOAc/hexane, 1:3) to afford 3β-hydroxy-16α,17α-epoxy-20,20-(ethylenedioxy)-5-pregnene (455) (46 mg, 81%) as a white solid; m.p. 185-187 °C. (Herzog *et al.*, 1959, m.p. 184-186 °C)

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FTIR (KBr), ν_{max}, cm^{-1}: 3474, 2938, 2858

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.27 (d, *J* = 5.3, 1H, H-6), 3.86 (m, 4H, OCH_2CH_2O), 3.45 (m, 1H, H-3), 3.31 (s, 1H, H-16), 2.22 (ddd, *J* = 2.0, 5.2, 13.0, 1H, H-4), 2.15 (m, 1H, H-4), 1.86 (m, 1H, H-15), 1.83 (m, 1H, H-7), 1.79 (m, 1H, H-12), 1.76 (m, 1H, H-2), 1.74 (m, 1H, H-1), 1.56 (m, 1H, H-11), 1.49 (m, 1H, H-8), 1.48 (m, 1H, H-15), 1.45 (m, 1H, H-2), 1.42 (m, 1H, H-11), 1.41 (m, 1H, H-7), 1.36 (s, 3H, H-21), 1.19 (m, 1H, H-12), 1.11 (ddd, *J* = 0.9, 11.9, 11.9, 1H, H-14), 1.02 (dd, *J* = 4.4, 14.4, 1H, H-1), 0.95 (s, 3H, H-19), 0.92 (s, 3H, H-18), 0.86 (m, 1H, H-9)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 141.0 (C-5), 121.2 (C-6), 109.2 (C-20), 71.6 (C-3), 70.8 (C-17), 65.1, 64.6 (OCH_2CH_2O), 58.6 (C-16), 50.2 (C-9), 46.1 (C-14), 42.2 (C-4), 41.6 (C-13), 37.1 (C-1), 36.6 (C-10), 32.7 (C-15), 31.5 (C-2), 31.4 (C-7), 29.9 (C-8), 27.0 (C-12), 23.7 (C-21), 20.5 (C-11), 19.3 (C-19), 15.7 (C-18)

HRMS (ESI^+) *m/z*: $C_{23}H_{34}O_4Na$ $[M+Na]^+$, calcd 397.2355, found 397.2364

3β-Benzyloxy-16α,17α-epoxy-20,20-(ethylenedioxy)-5-pregnene (456)

(455) (456)

To a suspension of NaH (8 mg of a 60% mineral oil suspension, 0.21 mmol) in dry THF (2 mL) and dry DMF (2 mL) was added dropwise a solution of 3β-hydroxy-16α,17α-epoxy-20,20-(ethylenedioxy)-5-pregnene (455) (35 mg, 0.093 mmol) in THF (2 mL) under nitrogen atmosphere. After stirring at room temperature for 2 h, benzyl bromide (0.014 mL, 0.12 mmol) was added. The reaction mixture was stirred at room temperature for 24 h. Then saturated aqueous NH_4Cl solution was added

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dropwise and the reaction mixture was extracted with diethylether. The combined organic extracts were washed with water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/hexane, 1:9) to provide 3β-benzyloxy-16α,17α-epoxy-20,20-(ethylenedioxy)-5-pregnene (456) (40 mg, 92%) as a white solid; m.p. 148-150 °C.

FTIR (KBr), ν_{max}, cm^{-1}: 2935, 2856, 1109, 1049

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.16-7.30 (m, 5H, Ar(H)), 5.26 (d, *J* = 5.3 Hz, 1H, H-6), 4.48 (s, 2H, OCH_2Ar), 3.80-3.92 (m, 4H, OCH_2CH_2O), 3.30 (s, 1H, H-16), 3.17-3.25 (m, 1H, H-3), 2.35 (dd, *J* = 2.3, 13.2 Hz, 1H, H-4), 2.16-2.24 (m, 1H, H-4), 1.82-1.91 (m, 3H, H-7, H-12, H-15), 1.76 (ddd, *J* = 3.2, 3.2, 12.3 Hz, 1H, H-1), 1.76 (dd, *J* = 5.5, 12.3 Hz, 1H, H-2), 1.40-1.55 (m, 6H, H-2, H-7, H-8, H-11, H-15), 1.36 (s, 3H, H-21), 1.15-1.22 (m, 1H, H-12), 1.11 (ddd, *J* = 0.7, 11.8, 11.8 Hz, 1H, H-14), 0.96-0.99 (m, 1H, H-1), 0.96 (s, 3H, H-19), 0.92 (s, 3H, H-18), 0.85-0.94 (m, 1H, H-9)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 141.2 (C-5), 139.0 (C-Ar), 128.3×2 (CH-Ar), 127.5×2 (CH-Ar), 127.4 (CH-Ar), 121.1 (C-6), 109.2 (C-20), 78.4 (C-3), 70.8 (C-17), 69.9 (OCH_2Ar), 65.1, 64.6 (OCH_2CH_2O), 58.6 (C-16), 50.3 (C-9), 46.1 (C-14), 41.6 (C-13), 39.1 (C-4), 37.1 (C-1), 37.0 (C-10), 32.7 (C-15), 31.5 (C-7), 29.9 (C-8), 28.4 (C-2), 27.0 (C-12), 23.7 (C-21), 20.5 (C-11), 19.3 (C-19), 15.7 (C-18)

HRMS (ESI^+) *m/z*: $C_{30}H_{40}O_4Na$ $[M+Na]^+$, calcd 487.2824, found 487.2826

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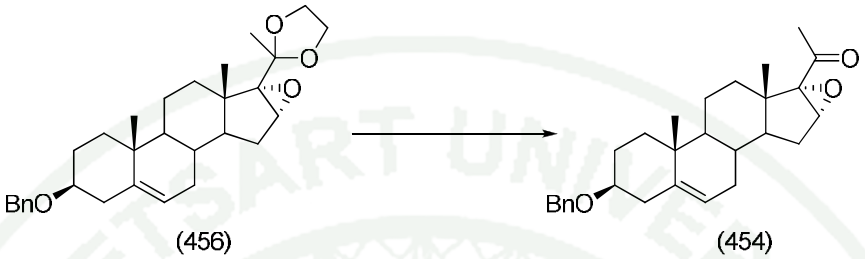
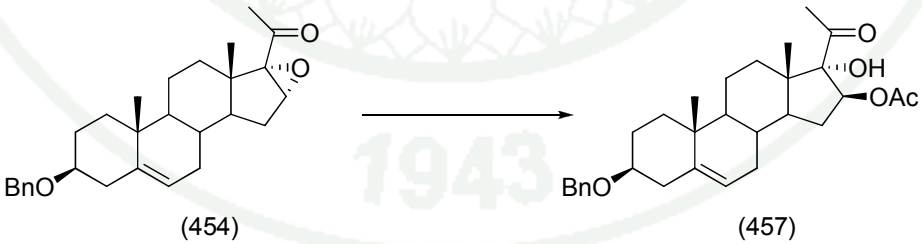
3β-Benzyloxy-16α,17α-epoxy-5-pregnene-20-one (454)



(456) (454)

To a solution of 3β-benzyloxy-16α,17α-epoxy-20,20-(ethylenedioxy)-5-pregnene (456) (40 mg, 0.086 mmol) in dichloromethane (5 mL) was added *p*-toluenesulfonic acid monohydrate (2 mg, 0.0086 mmol). The reaction mixture was stirred at room temperature for 2 h. The residue was dissolved in water and extracted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (EtOAc/hexane, 7:93) to give 3β-benzyloxy-16α,17α-epoxy-5-pregnene-20-one (454) (31 mg, 86%) as a white solid**;** m.p. 127-128 °C**.**

3β-Benzyloxy-16β-acetyloxy-17α-hydroxy-5-pregnene-20-one (457)



(454) (457)

To a solution of 3β-benzyloxy-16α,17α-epoxy-5-pregnene-20-one (454) (20 mg, 0.047 mmol) in acetic acid (0.4 mL) was added slowly a solution of 20% sulfuric acid in acetic acid (0.05 mL). The resulting reaction mixture was stirred for 2 h at room temperature. Then water was added and the product was extracted into EtOAc. The combined organic layer was washed with saturated aqueous $NaHCO_3$ and water and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (EtOAc/hexane,

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1:9) to provide 3β-benzyloxy-16β-acetyloxy-17α-hydroxy-5-pregnene-20-one (457) (11 mg, 48%) as a white solid; m.p. 128-129 °C.

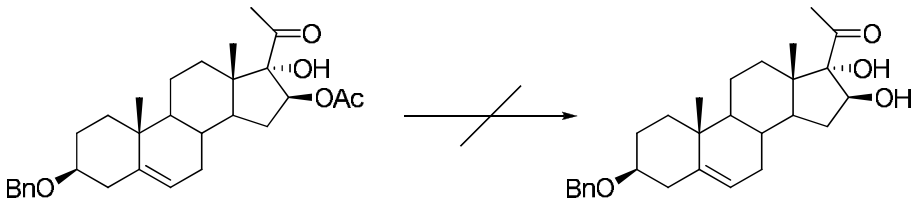
FTIR (KBr), ν_{max}, cm^{-1}: 3430, 2934, 2863, 1714, 1251

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.23 (m, 5H, Ar(H)), 5.28 (d, *J* = 5.1 Hz, 1H, H-6), 4.75 (dd, *J* = 6.7, 7.8 Hz, 1H, H-16), 4.49 (s, 2H, OCH_2Ar), 3.28 (d, *J* = 4.5 Hz, 1H, OH), 3.21 (m, 1H, H-3), 2.38 (dd, *J* = 2.3, 4.7 Hz, 1H, H-4), 2.35 (dd, *J* = 2.2, 4.7 Hz, 1H, H-4), 2.28 (dd, *J* = 7.8, 5.3 Hz, 1H, H-15), 2.17 (s, 3H, $OCOCH_3$), 1.99 (s, 3H, H-21), 1.92-1.95 (m, 1H, H-7), 1.89 (m, 1H, H-2), 1.80 (ddd, *J* = 3.5, 3.5, 13.4 Hz, 1H, H-1), 1.62 (m, 1H, H-14), 1.55 (m, 1H, H-11), 1.48-1.52 (m, 1H, H-8), 1.43 (m, 1H, H-2), 1.41 (m, 1H, H-7), 1.37 (m, 1H, H-15), 1.34 (m, 1H, H-11), 1.18 (m, 2H, H-12), 0.98 (m, 1H, H-1), 0.96 (s, 3H, H-19), 0.92 (m, 1H, H-9), 0.88 (s, 3H, H-18)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 208.7 (C-20), 171.2 ($O\underline{C}OCH_3$), 141.0 (C-5), 139.0 (C-Ar), 128.3×2 (CH-Ar), 127.5×2 (CH-Ar), 127.4 (CH-Ar), 121.0 (C-6), 88.1 (C-17), 83.4 (C-16), 78.4 (C-3), 70.0 (OCH_2Ar), 49.6 (C-9), 47.8 (C-14), 47.4 (C-13), 39.1 (C-4), 37.2 (C-1), 36.9 (C-10), 33.2 (C-15), 31.9 (C-7), 31.2 (C-8), 30.8 (C-12), 29.1 (C-21), 28.4 (C-2), 21.2 ($OCO\underline{C}H_3$), 20.2 (C-11), 19.4 (C-19), 15.2 (C-18)

HRMS (ESI^+) *m/z*: $C_{30}H_{40}O_5Na$ $[M+Na]^+$, calcd 503.2773, found 503.2777

3β-Benzyloxy-16β,17α-dihydroxy-5-pregnene-20-one (458)



(457) (458)

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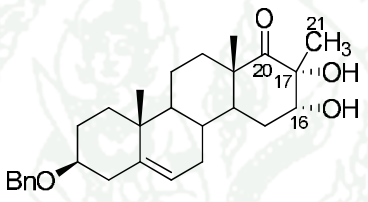
3β-Benzyloxy-16β-acetyloxy-17α-hydroxy-5-pregnene-20-one (457) (53 mg, 0.10 mmol) was dissolved in methanol (1.5 mL) and, then treated dropwise with 2.5N KOH (5.0 mL) and stirred at room temperature for 12 h. The mixture was evaporated under reduced pressure to remove methanol, then saturated aqueous NaCl solution was added and extracted with CH_2Cl_2. The combined organic extract was washed with water, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 1:4) to give only rearranged product (459) (27 mg, 55%) as a white solid.



(459)

D-Homoandrost-5-en-17a-one, 3β-benzyloxy-16α,17α-dihydroxy-17-methyl-(7CI,8CI) (459)

FTIR (KBr), ν_{max}, cm^{-1}: 3431, 2885, 2925, 2850, 1701

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.26 (m, 4H, Ar(H)), 7.20 (m, 1H, Ar(H)), 5.28 (d, *J* = 5.3 Hz, 1H, H-6), 4.49 (s, 2H, OCH_2Ar), 3.56 (dd, *J* = 4.6, 11.9 Hz, 1H, H-16), 3.20 (m, 1H, H-3), 2.37 (ddd, *J* = 2.3, 4.7, 13.2 Hz, 1H, H-4), 2.22 (m, 1H, H-4), 2.14 (m, 1H, H-7), 1.97 (ddd, *J* = 2.7, 4.6, 13.5 Hz, 1H, H-15), 1.92 (m, 1H, H-12), 1.86 (dt, *J* = 12.8, 3.0 Hz, 1H, H-2), 1.80 (dt, *J* = 13.5, 3.5 Hz, 1H, H-1), 1.55 (dd, *J* = 4.4, 10.4 Hz, 1H, H-12), 1.51 (m, 1H, H-7), 1.48 (m, 1H, H-15), 1.45 (m, 1H, H-2), 1.32 (s, 3H, H-21), 1.18 (s, 2H, H-11), 1.18 (s, 1H, H-14), 1.05 (s, 3H, H-19), 1.01 (m, 1H, H-8), 0.95 (s, 3H, H-18), 0.91 (m, 1H, H-1), 0.88 (m, 1H, H-9)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 216.5 (C-20), 140.8 (C-5), 138.9 (C-Ar), 128.3×2 (CH-Ar), 127.5×2 (CH-Ar), 127.4 (CH-Ar), 120.6 (C-6), 80.6 (C-17), 78.2 (C-3), 78.2 (C-16), 70.0 (OCH_2Ar), 49.2 (C-9), 46.3 (C-14), 46.1 (C-13), 38.8 (C-4),

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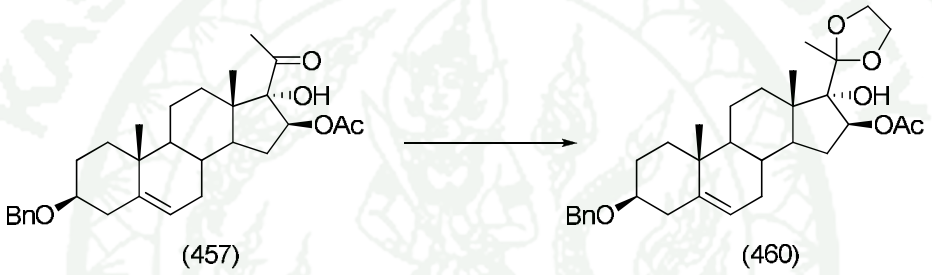
37.2 (C-1), 36.8 (C-10), 32.8 (C-2), 31.7 (C-7), 30.6 (C-8), 29.7 (C-11), 28.6 (C-12), 28.3 (C-15), 21.4 (C-21), 19.3 (C-18), 15.8 (C-19)

MS (ESI^+), *m/z* (relative intensity): 439.8 ($[M+H]^+$, 42 %), 403.3 (100 %)

3β-Benzyloxy-16β-acetyloxy-17α-hydroxy-20,20-(ethylenedioxy)-5-pregnene (460)



3β-Benzyloxy-16β-acetyloxy-17α-hydroxy-5-pregnene-20-one (457) (40 mg, 0.083 mmol) was dissolved in dichloromethane (2.4 mL). Ethylene glycol (0.28 mL, 5.0 mmol), triethylorthoformate (0.42 mL, 2.5 mmol) and *p*-toluenesulfonic acid monohydrate (2 mg, 0.0083 mmol) was added to the above solution and stirred at room temperature for 12 h. The reaction mixture was neutralized with triethylamine and extracted with diethylether. The organic layer was combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (EtOAc/hexane, 3:17) to give 3β-benzyloxy-16β-acetyloxy-17α-hydroxy-20,20-(ethylenedioxy)-5-pregnene (460) (28 mg, 64%) as a white solid; m.p. 192-193 °C.

FTIR (KBr), ν_{max}, cm^{-1}: 3416, 2935, 2900, 2863, 1728, 1371, 1249, 1088, 1026

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.25 (m, 4H, Ar(H)), 7.18 (m, 1H, Ar(H)), 5.26 (d, *J* = 5.2 Hz, 1H, H-6), 4.85 (dd, *J* = 4.8, 8.1 Hz, 1H, H-16), 4.48 (s, 2H, OCH_2Ar), 3.88 (m, 4H, OCH_2CH_2O), 3.20 (m, 1H, H-3), 2.31-2.38 (m, 1H, H-4),

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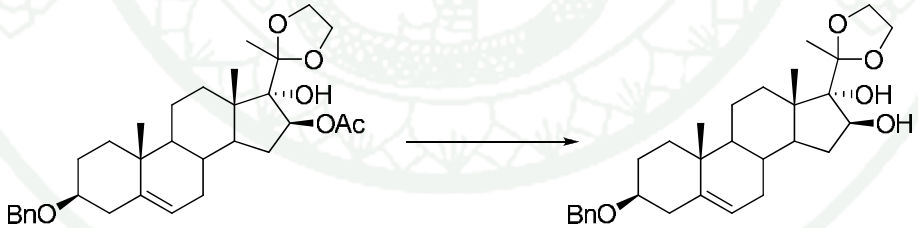
2.31-2.38 (m, 1H, H-15), 2.16-2.23 (m, 1H, H-4), 1.97 (s, 3H, $OCOCH_3$), 1.85-1.92 (m, 2H, H-2, H-7), 1.78 (ddd, *J* = 3.4, 3.4, 13.4 Hz, 1H, H-1), 1.65 (m, 1H, H-14), 1.52-1.59 (m, 4H, H-7, H-8, H-12), 1.50 (m, 1H, H-11), 1.47 (m, 1H, H-11), 1.44 (m, 1H, H-2), 1.31 (s, 3H, H-21), 1.03 (dd, *J* = 4.9, 13.1 Hz, 1H, H-15), 0.98 (s, 3H, H-19), 0.97 (m, 1H, H-1), 0.95 (s, 3H, H-18), 0.88 (m, 1H, H-9)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 169.8 ($O\underline{C}OCH_3$), 140.8 (C-5), 139.0 (C-Ar), 128.2×2 (CH-Ar), 127.5×2 (CH-Ar), 127.3 (CH-Ar), 121.3 (C-6), 112.9 (C-20), 86.4 (C-17), 80.3 (C-16), 78.4 (C-3), 69.9 (OCH_2Ar), 64.6, 63.8 (OCH_2CH_2O), 49.7 (C-9), 48.0 (C-14), 46.1 (C-13), 39.0 (C-4), 37.1 (C-1), 36.8 (C-10), 33.9 (C-15), 32.0 (C-7), 31.6 (C-12), 31.1 (C-8), 28.3 (C-2), 22.2 (C-21), 21.3 ($OCO\underline{C}H_3$), 20.2 (C-11), 19.3 (C-19), 14.8 (C-18)

HRMS (ESI^+) *m/z*: $C_{32}H_{44}O_6Na$ $[M+Na]^+$, calcd 547.3036, found 547.3035

3β-Benzyloxy-16β,17α-dihydroxy-20,20-(ethylenedioxy)-5-pregnene (461)



(460) (461)

3β-Benzyloxy-16β-acetyloxy-17α-hydroxy-20,20-(ethylenedioxy)-5-pregnene (460) (150 mg, 0.29 mmol) was dissolved in methanol (5 mL) and, then treated with 2.5N KOH (0.23 mL) and stirred overnight at room temperature. The reaction mixture was evaporated under reduced pressure to remove methanol, then saturated aqueous NaCl solution was added and extracted with CH_2Cl_2. The combined organic extract was washed with water, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography (EtOAc/hexane, 1:3) to

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afford 3β-benzyloxy-16β,17α-dihydroxy-20,20-(ethylenedioxy)-5-pregnene (461) as a colorless solid (120 mg, 87%); m.p. 194-195 °C.

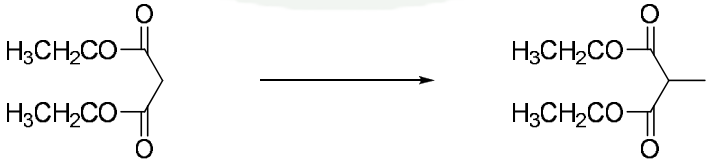
FTIR (KBr), ν_{max}, cm^{-1}: 3515, 3350, 2961, 2930, 2896, 1090, 1029

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.26 (m, 4H, Ar(H)), 7.19 (m, 1H, Ar(H)), 5.28 (d, *J* = 5.2 Hz, 1H, H-6), 4.49 (s, 2H, OCH_2Ar), 3.98 (m, 4H, OCH_2CH_2O), 3.94 (m, 1H, H-16), 3.52 (d, *J* = 4.8 Hz, 1H, OH), 3.21 (m, 1H, H-3), 2.36 (ddd, *J* = 2.3, 4.7, 13.2 Hz, 1H, H-4), 2.19-2.25 (m, 2H, H-4, H-15), 1.85-1.95 (m, 2H, H-2, H-7), 1.79 (ddd, *J* = 3.5, 3.5, 13.4 Hz, 1H, H-1), 1.52-1.56 (m, 4H, H-8, H-12, H-14), 1.47-1.51 (m, 2H, H-11), 1.45 (m, 1H, H-7), 1.44 (m, 1H, H-2), 1.41 (s, 3H, H-21), 1.14-1.22 (m, 1H, H-15), 0.99 (m, 1H, H-1), 0.97 (s, 3H, H-19), 0.96 (s, 3H, H-18), 0.89 (m, 1H, H-9)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 140.9 (C-5), 139.0 (C-Ar), 128.3×2 (CH-Ar), 127.6×2 (CH-Ar), 127.4 (CH-Ar), 121.4 (C-6), 113.9 (C-20), 85.3 (C-17), 80.8 (C-16), 78.5 (C-3), 69.9 (OCH_2Ar), 64.3, 63.8 (OCH_2CH_2O), 49.8 (C-9), 48.1 (C-14), 45.7 (C-13), 39.1 (C-4), 37.2 (C-1), 36.9 (C-10), 35.9 (C-15), 32.0 (C-7), 31.8 (C-12), 31.3 (C-8), 28.4 (C-2), 21.8 (C-21), 20.2 (C-11), 19.4 (C-19), 14.7 (C-18)

HRMS (ESI^+) *m/z*: $C_{30}H_{42}O_5Na$ $[M+Na]^+$, calcd 505.2930, found 505.2935

2-Methyl-malonic acid diethyl ester (463)



(462) (463)

A mixture of diethyl malonate (462) (1 mL, 7.04 mmol), methyl iodide (0.44 mL, 7.04 mmol) and potassium carbonate (1.17 g, 8.45 mmol) in acetone (30 mL) was stirred at room temperature for 3 h. The reaction mixture was monitored by TLC,

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only starting material was observed. The reaction mixture was heated at 50-60 °C for 8 h. The resulting was filtered through celite under suction and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 1:19) to provide monomethylated product (463) (572 mg, 51%) as a colorless oil and recovered starting material (462) (306 mg, 27 %).

FTIR (neat), ν_{max}, cm^{-1}: 1749, 1733, 1460, 1369, 1329, 1303, 1256, 1219, 1158, 1174, 1096, 1039

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.17 (q, *J* = 7.2 Hz, 2H, $OC\underline{H}_2CH_3$), 4.16 (q, *J* = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 3.39 (q, *J* = 7.3 Hz, 1H, $C\underline{H}CH_3$), 1.38 (d, *J* = 7.3 Hz, 3H, $CHC\underline{H}_3$), 1.24 (t, *J* = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 1.24 (t, *J* = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.1×2 (C=O), 61.2×2 ($O\underline{C}H_2CH_3$), 46.1 ($\underline{C}HCH_3$), 13.9×2 ($OCH_2\underline{C}H_3$), 13.4 ($CH\underline{C}H_3$)

MS (ESI^+), *m/z* (relative intensity): 197.1 ($[M+Na]^+$, 100 %)

2-Benzyl-malonic acid diethyl ester (464)

(462) (464)

To a mixture of diethyl malonate (462) (1.0 mL, 7.04 mmol) in dry THF (6.52 mL) was sequentially added NaH (296 mg of a 60% mineral oil suspension, 7.39 mmol) and benzyl bromide (0.79 mL, 7.04 mmol). The resulting mixture was refluxed for 18 h and solvent was removed under reduced pressure, followed by addition of 2.5 mL of water. The mixture was extracted with diethyl ether, and the extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was

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purified by flash column chromatography (EtOAc/hexane, 1:9) to provide 2-benzyl-malonic acid diethyl ester (464) (1.0 g, 57%) as a colorless oil.

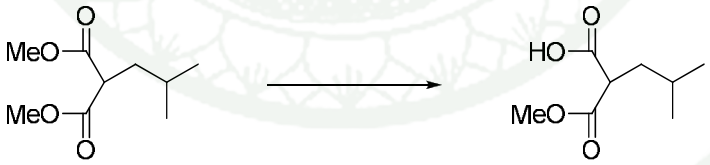
FTIR (neat), ν_{max}, cm^{-1}: 2970, 2885, 1749, 1740, 1457, 1380, 1329, 1233, 1158, 1039

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.12-7.23 (m, 5H, Ar(H)), 4.09 (q, *J* = 7.2 Hz, 2H, $OC\underline{H}_2CH_3$), 4.09 (q, *J* = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 3.58 (t, *J* = 7.9 Hz, 1H, $C\underline{H}CH_2Ar$), 3.15 (d, *J* = 7.9 Hz, 2H, $CHC\underline{H}_2Ar$), 1.14 (t, *J* = 7.1 Hz, 6H, $OCH_2C\underline{H}_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.8×2 (C=O), 137.9 (C-Ar), 128.8×2 (CH-Ar), 128.4×2 (CH-Ar), 126.7 (CH-Ar), 61.4×2 ($O\underline{C}H_2CH_3$), 53.8 ($\underline{C}HCH_2Ar$), 34.7 ($CH\underline{C}H_2Ar$), 14.0×2 ($OCH_2\underline{C}H_3$)

MS (ESI^+), *m/z* (relative intensity): 273.2 ($[M+Na]^+$, 100 %)

2-Isobutyl-malonic acid monomethyl ester (466)



(465) (466)

An aqueous solution of 1.8M KOH (3.2 mL, 5.77 mmol) was added to dimethyl isobutylmalonate (465) (1.05 g, 5.60 mmol), which was dissolved in 7 mL of methanol, at 0 °C. After 5-7 h, most of the methanol was removed by evaporation, water was added to dissolve all solids, then the solution was washed with EtOAc and the pH was carefully adjusted to 2 at 0 °C. The aqueous solution was extracted with EtOAc. The organic extracts were combined, washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified

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by flash column chromatography (EtOH/EtOAc/hexane, 1:7:12) to provide 2-isobutyl-malonic acid monomethyl ester (466) (732 mg, 75%) as a colorless oil.

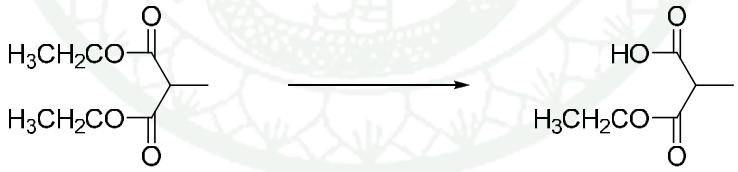
FTIR (neat), ν_{max}, cm^{-1}: 3188, 2960, 2873, 1741, 1714

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.70 (s, 3H, OCH_3), 3.42 (t, *J* = 7.6 Hz, 1H, $C\underline{H}CH_2CH(CH_3)_2$), 1.76 (td, *J* = 7.5, 2.5, 2H, $CHC\underline{H}_2CH(CH_3)_2$), 1.54 (m, 1H, $CHCH_2C\underline{H}(CH_3)_2$), 0.87 (d, *J* = 6.6, 6H, $CHCH_2CH(C\underline{H}_3)_2$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 175.3 ($\underline{C}OOH$), 169.9 ($\underline{C}OOCH_3$), 52.6 (OCH_3), 49.9 ($\underline{C}HCH_2CH(CH_3)_2$), 37.5 ($CH\underline{C}H_2CH(CH_3)_2$), 26.1 ($CHCH_2\underline{C}H(CH_3)_2$), 22.1×2 ($CHCH_2CH(\underline{C}H_3)_2$)

MS (ESI^+), *m/z* (relative intensity): 198.0 ($[M+Na]^+$, 100 %)

2-Methyl-malonic acid monoethyl ester (467)



(463) (467)

An aqueous solution of 1.8M KOH (6.7 mL, 12.1 mmol) was added to 2-methyl-malonic acid diethyl ester (463) (2.4 g, 11.7 mmol), which was dissolved in 15 mL of ethanol, at 0 °C. After 5-7 h, most of the ethanol was removed by evaporation, water was added to dissolve all solids, then the solution was washed with EtOAc and the pH was carefully adjusted to 2 at 0 °C. The aqueous solution was extracted with EtOAc. The organic extracts were combined, washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOH/EtOAc/hexane, 1:6:13) to give 2-methyl-malonic acid monoethyl ester (467) (1.33 g, 78%) as a colorless oil.

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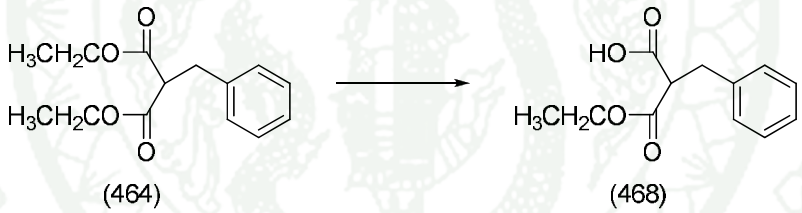
FTIR (neat), ν_{max}, cm^{-1}: 3422, 1725, 1591

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 9.42 (brs, 1H, COOH), 4.18 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 3.45 (q, *J* = 7.3 Hz, 1H, $CHCH_3$), 1.41 (d, *J* = 7.3 Hz, 3H, $CHCH_3$), 1.24 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 175.5, 174.9 (COOH), 170.0 ($COOCH_2CH_3$), 61.7 (OCH_2CH_3), 45.9 ($CHCH_3$), 13.8 (OCH_2CH_3), 13.4 ($CHCH_3$)

MS (ESI^+), *m/z* (relative intensity): 169.0 ($[M+Na]^+$, 14 %), 170.5 (100)

2-Benzyl-malonic acid monoethyl ester (468)



(464) (468)

An aqueous solution of 1.8M KOH (1.23 mL, 2.22 mmol) was added to 2-benzyl-malonic acid diethyl ester (464) (540 mg, 2.16 mmol), which was dissolved in 2.77 mL of ethanol at 0 °C. After 5-7 h, most of the ethanol was removed by evaporation, water was added to dissolve all solids, then the solution was washed with EtOAc and the pH was carefully adjusted to 2 at 0 °C. The aqueous solution was extracted with EtOAc. The organic extracts were combined, washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOH/EtOAc/hexane, 1:7:12) to provide 2-benzyl-malonic acid monoethyl ester (468) (364 mg, 76%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.16-7.29 (m, 5H, Ar(H)), 4.14 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 3.69 (t, *J* = 7.7 Hz, 1H, $CHCH_2Ar$), 3.22 (d, *J* = 7.8 Hz, 2H, $CHCH_2Ar$), 1.18 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3)

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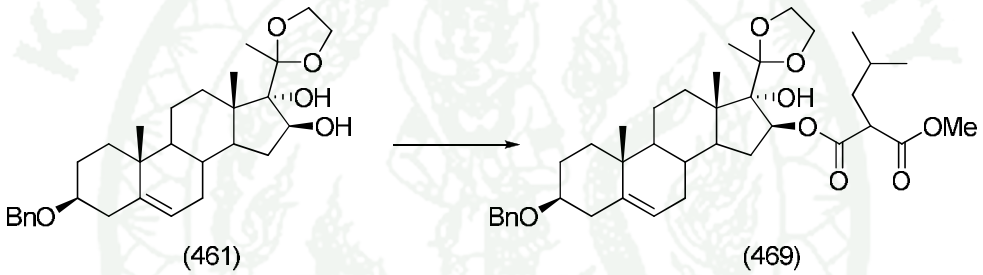
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 173.8 (COOH), 168.8 ($\underline{C}OOCH_2CH_3$), 137.4 (C-Ar), 128.8×2 (CH-Ar), 128.5×2 (CH-Ar), 126.8 (CH-Ar), 61.8 ($O\underline{C}H_2CH_3$), 53.5 ($\underline{C}HCH_2Ar$), 34.6 ($CH\underline{C}H_2Ar$), 13.9 ($OCH_2\underline{C}H_3$)

MS (ESI^+), *m/z* (relative intensity): 246.5 ($[M+Na]^+$, 35 %), 247.5 (100 %)

3β-Benzyloxy-16β-(isobutyl-monomethyl ester malonate-ester)-17α-hydroxy-20,20-(ethylenedioxy)-5-pregnene (469)



To a solution of 2-isobutyl-malonic acid monomethyl ester (466) (17 mg, 0.099 mmol) and *N,N*-dimethylaminopyridine (DMAP) (2 mg, 0.017 mmol) in dry dichloromethane (0.5 mL) was added a solution of 3β-benzyloxy-16β,17α-dihydroxy-20,20-(ethylenedioxy)-5-pregnene (461) (32 mg, 0.066 mmol) in dry dichloromethane (1.5 mL) at room temperature. After the reaction was stirred for 5 minutes, the solution of *N,N*-dicyclohexylcarbodiimide (20 mg, 0.099 mmol) in dry dichloromethane (1.5 mL) was introduced. The reaction was stirred at room temperature for 3 hours and then filtered and rinsed successively with CH_2Cl_2. The combined CH_2Cl_2 was extracted with saturated aqueous NH_4Cl. The combined organic layers were dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (EtOAc/hexane, 1:9) to give 3β-benzyloxy-16β-(isobutyl-monomethyl ester malonate-ester)-17α-hydroxy-20,20-(ethylenedioxy)-5-pregnene (469) as a colorless solid (42 mg, 100%); m.p. 129-131 °C.

FTIR (KBr), ν_{max}, cm^{-1}: 3392, 1749, 1731

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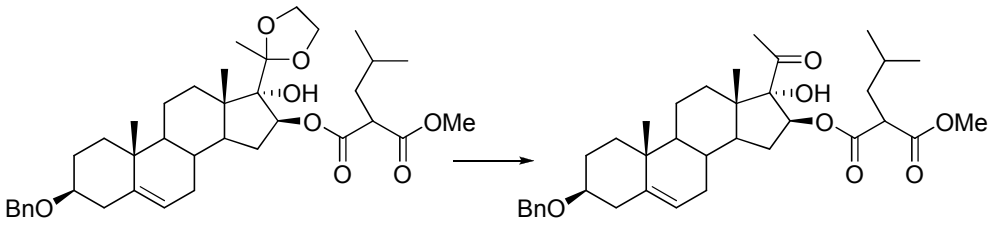
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.24-7.27 (m, 4H, Ar(H)), 7.18-7.21 (m, 1H, Ar(H)), 5.27 (d, *J* = 5.1 Hz, 1H, H-6), 4.82 (dd, *J* = 2.1, 4.5 Hz, 1H, H-16), 4.80 (dd, *J* = 2.2, 4.6 Hz, 1H, H-16), 4.49 (s, 2H, OCH_2Ar), 3.88 (m, 4H, OCH_2CH_2O), 3.64 (s, 3H, OCH_3), 3.35 (t, *J* = 7.7 Hz, 1H, $C\underline{H}CH_2CH(CH_3)_2$), 3.18-3.24 (m, 1H, H-3), 2.38-2.43 (m, 1H, H-15), 2.36 (ddd, *J* = 2.0, 4.7, 11.4 Hz, 1H, H-4), 2.17-2.23 (m, 1H, H-4), 1.83-1.91 (m, 3H, H-2, H-12, H-15), 1.76 (ddd, *J* = 4.0, 4.0, 13.9 Hz, 1H, H-1), 1.72 (m, 2H, $CHC\underline{H}_2CH(CH_3)_2$), 1.56-1.63 (m, 3H, H-7, H-14), 1.46-1.56 (m, 5H, H-2, H-8, H-11, H-12), 1.49 (m, 1H, $CHCH_2C\underline{H}(CH_3)_2$), 1.29 (s, 3H, H-21), 0.97-1.01 (m, 1H, H-1), 0.96 (s, 3H, H-19), 0.95 (s, 3H, H-18), 0.89 (m, 1H, H-9), 0.85 (d, *J* = 6.6 Hz, 3H, $CHCH_2CH(C\underline{H}_3)_2$), 0.84 (d, *J* = 6.6 Hz, 3H, $CHCH_2CH(C\underline{H}_3)_2$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.1, 169.9, 168.6, 168.4 ($\underline{C}OO$), 140.9, 140.8 (C-5), 139.0 (C-Ar), 128.3×2 (CH-Ar), 127.6×2 (CH-Ar), 127.4 (CH-Ar), 121.3 (C-6), 112.8 (C-20), 86.3 (C-17), 81.1, 81.0 (C-16), 78.5 (C-3), 70.0 (OCH_2Ar), 64.9, 64.8, 63.5, 63.4 (OCH_2CH_2O), 52.3, 52.2 (OCH_3), 50.4, 50.3 ($\underline{C}HCH_2CH(CH_3)_2$), 49.7 (C-9), 48.0 (C-14), 46.2 (C-13), 39.1 (C-4), 37.4, 37.2 (C-1), 37.3, 36.9 (C-10), 33.9, 33.8 (C-15), 32.1, 32.0 (C-7), 31.6 (C-12), 31.2, 31.1 (C-8), 28.4 (C-2), 26.0 ($CH\underline{C}H_2CH(CH_3)_2$), 25.6, 24.9 ($CHCH_2\underline{C}H(CH_3)_2$), 22.3, 22.0, 21.9 ($CHCH_2CH(\underline{C}H_3)_2$), 22.1 (C-21), 20.2 (C-11), 19.4, 19.3 (C-19), 14.7 (C-18)

HRMS (ESI^+) *m/z*: $C_{38}H_{54}O_8Na$ $[M+Na]^+$, calcd 661.3716, found 661.3706

3β-Benzyloxy-16β-(isobutyl-monomethyl ester malonate-ester)-17α-hydroxy-5-pregnene-20-one (470)



(469) (470)

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To a solution of 3β-benzyloxy-16β-(isobutyl-monomethyl ester malonate-ester)-17α-hydroxy-20,20-(ethylenedioxy)-5-pregnene (469) (40 mg, 0.063 mmol) in THF (2 mL) was added *p*-toluenesulfonic acid monohydrate (1 mg, 0.0063 mmol). The reaction mixture was stirred at room temperature for 2 h. The residue was added with water, extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (EtOAc/hexane, 3:17) to provide 3β-benzyloxy-16β-(isobutyl-monomethyl ester malonate-ester)-17α-hydroxy-5-pregnene-20-one (470) as a colorless viscous oil (23 mg, 62%) which could slowly become a colorless solid.

FTIR (KBr), ν_{max}, cm^{-1}: 3404, 2935, 2869, 1734, 1715, 1659, 1452, 1386, 1351, 1273, 1240, 1159, 1070

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.24-7.27 (m, 4H, Ar(H)), 7.19-7.21 (m, 1H, Ar(H)), 5.27 (d, *J* = 5.2 Hz, 1H, H-6), 4.86 (dd, *J* = 5.7, 7.9 Hz, 1H, H-16), 4.82 (dd, *J* = 5.8, 7.9 Hz, 1H, H-16), 4.49 (s, 2H, OCH_2Ar), 3.65, 3.68 (s, 3H, OCH_3), 3.36 (t, *J* = 7.7 Hz, 1H, C<u>H</u>$CH_2CH(CH_3)_2$), 3.37 (t, *J* = 7.6 Hz, 1H, C<u>H</u>$CH_2CH(CH_3)_2$), 3.17-3.25 (m, 1H, H-3), 2.36-2.48 (m, 1H, H-15), 2.36 (ddd, *J* = 2.3, 4.8, 13.0 Hz, 1H, H-4), 2.20-2.24 (m, 1H, H-4), 2.17 (s, 3H, H-21), 1.84-1.93 (m, 2H, H-2, H-7), 1.74-1.81 (m, 1H, H-12), 1.76 (ddd, *J* = 3.5, 3.5, 13.4 Hz, 1H, H-1), 1.77 (t, *J* = 7.4 Hz, 2H, CHC<u>H$_2$</u>$CH(CH_3)_2$), 1.75 (t, *J* = 7.7 Hz, 2H, CHC<u>H$_2$</u>$CH(CH_3)_2$), 1.60-1.64 (m, 1H, $CHCH_2$C<u>H</u>$(CH_3)_2$), 1.40-1.57 (m, 6H, H-2, H-8, H-11, H-12, H-14), 1.22-1.27 (m, 1H, H-15), 1.16-1.20 (m, 1H, H-7), 0.99-1.05 (m, 1H, H-1), 1.00 (s, 3H, H-19), 0.97-1.00 (m, 1H, H-9), 0.97, 0.94 (s, 3H, H-18), 0.89 (d, *J* = 6.6 Hz, 3H, $CHCH_2CH(C$<u>H$_3$</u>$)_2$), 0.88 (d, *J* = 6.6 Hz, 3H, $CHCH_2CH(C$<u>H$_3$</u>$)_2$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 207.9, 207.8 (C-20), 169.8, 169.6, 168.9 (<u>C</u>OO), 141.0 (C-5), 139.0 (C-Ar), 128.3×2 (CH-Ar), 127.6×2 (CH-Ar), 127.4 (CH-Ar), 121.0 (C-6), 88.2 (C-17), 83.6, 83.3 (C-16), 78.4 (C-3), 70.0 (OCH_2Ar), 52.7, 52.4 (OCH_3), 50.2, 50.1 (<u>C</u>$HCH_2CH(CH_3)_2$), 49.6 (C-9), 48.0 (C-14), 47.2 (C-13), 39.1 (C-4), 37.2, 37.1 (C-1), 36.9 (C-10), 33.9, 33.6 (C-15), 32.7, 32.1 (C-7), 31.8, 31.4 (C-12), 31.2 (C-8), 29.0, 28.9 (C-21), 28.3 (C-2), 26.0 (CH<u>C</u>$H_2CH(CH_3)_2$), 25.4,

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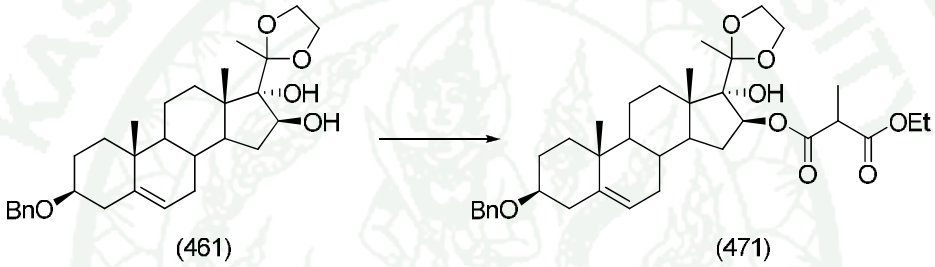
25.3 ($CHCH_2\underline{C}H(CH_3)_2$), 22.9, 22.2, 22.1 ($CHCH_2CH(\underline{C}H_3)_2$), 20.1 (C-11), 19.4 (C-19), 14.9 (C-18)

HRMS (ESI^+) *m/z*: $C_{36}H_{51}O_7$ $[M+H]^+$, calcd 595.3635, found 595.3640

3β-Benzyloxy-16β-(2-methyl-monoethyl ester malonate-ester)-17α-hydroxy-20,20-(ethylenedioxy)-5-pregnene (471)



To a solution of 2-methyl-malonic acid monoethyl ester (467) (32 mg, 0.22 mmol) and *N,N*-dimethylaminopyridine (DMAP) (4 mg, 0.037 mmol) in dry dichloromethane (3.2 mL) was added a solution of 3β-benzyloxy-16β,17α-dihydroxy-20,20-(ethylenedioxy)-5-pregnene (461) (72 mg, 0.15 mmol) in dry dichloromethane (1.6 mL) at room temperature. After the reaction was stirred for 5 minutes, the solution of *N,N*-dicyclohexylcarbodiimide (46 mg, 0.22 mmol) in dry dichloromethane (1.6 mL) was introduced. The reaction was stirred at room temperature for 5 hours and then filtered and rinsed successively with CH_2Cl_2. The combined CH_2Cl_2 was extracted with saturated aqueous NH_4Cl. The combined organic layers were dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (EtOAc/hexane, 1:9) to give 3β-benzyloxy-16β-(2-methyl-monoethyl ester malonate-ester)-17α-hydroxy-20,20-(ethylenedioxy)-5-pregnene (471) as a colorless solid (90 mg, 100%).

FTIR (KBr), ν_{max}, cm^{-1}: 3452, 2936, 2856, 2360, 1726, 1705, 1658, 1451, 1380, 1365, 1325, 1274, 1255, 1222, 1174, 1096, 1034

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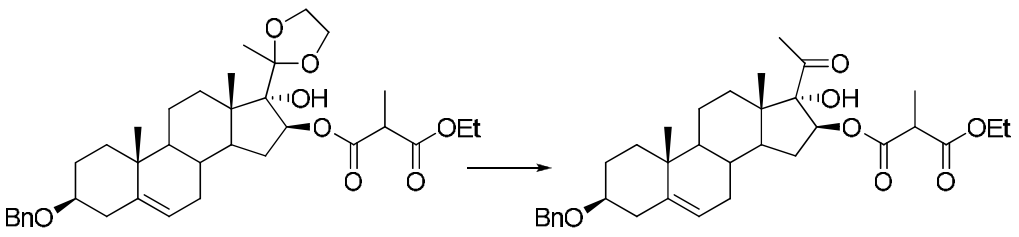
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.27 (m, 4H, Ar(H)), 7.17 (m, 1H, Ar(H)), 5.25 (d, *J* = 5.1 Hz, 1H, H-6), 4.82 (dd, *J* = 8.1, 4.5 Hz, 1H, H-16), 4.47 (s, 2H, $OC\underline{H}_2Ar$), 4.10 (q, *J* = 7.1 Hz, 1H, $OC\underline{H}_2CH_3$), 4.09 (q, *J* = 7.1 Hz, 1H, $OC\underline{H}_2CH_3$), 4.07 (q, *J* = 7.1 Hz, 1H, $OC\underline{H}_2CH_3$), 4.06 (q, *J* = 7.2 Hz, 1H, $OC\underline{H}_2CH_3$), 3.86 (m, 4H, OCH_2CH_2O), 3.32 (q, *J* = 7.3 Hz, 1H, $C\underline{H}CH_3$), 3.32 (q, *J* = 7.3 Hz, 1H, $C\underline{H}CH_3$), 3.19 (m, 1H, H-3), 2.35-2.41 (m, 1H, H-15), 2.36 (ddd, *J* = 2.1, 4.6, 12.2 Hz, H-4), 2.15-2.21 (m, 1H, H-4), 1.87 (m, 1H, H-2), 1.84 (m, 1H, H-7), 1.76 (ddd, *J* = 3.4, 3.4, 13.4 Hz, H-1), 1.55 (m, 1H, H-14), 1.39-1.54 (m, 7H, H-2, H-7, H-8, H-11, H-12), 1.34 (d, *J* = 7.3 Hz, 3H, $OCHC\underline{H}_3$), 1.32 (d, *J* = 7.2 Hz, 3H, $OCHC\underline{H}_3$), 1.28 (s, 3H, H-21), 1.27 (s, 3H, H-21), 1.17 (t, *J* = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 1.17 (t, *J* = 7.2 Hz, 3H, $OCH_2C\underline{H}_3$), 0.95-1.05 (m, 1H, H-15), 0.97 (m, 1H, H-1), 0.93 (s, 3H, H-19), 0.93 (s, 3H, H-18), 0.92 (m, 1H, H-9)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.0, 169.8, 169.1, 168.9 ($\underline{C}OO$), 140.8 (C-5), 139.0 (C-Ar), 128.3×2 (CH-Ar), 127.5×2 (CH-Ar), 127.4 (CH-Ar), 121.3 (C-6), 112.8 (C-20), 86.3 (C-17), 81.0, 80.9 (C-16), 78.5 (C-3), 69.9 (OCH_2Ar), 64.8, 63.6 (OCH_2CH_2O), 61.4, 61.3 ($O\underline{C}H_2CH_3$), 49.7 (C-9), 48.0 (C-14), 46.5 (C-13), 46.2 ($\underline{C}HCH_3$), 39.1 (C-4), 37.2 (C-1), 36.8 (C-10), 33.9, 33.7 (C-15), 32.1, 32.0 (C-7), 31.6 (C-12), 31.1 (C-8), 28.4 (C-2), 22.2, 21.9 (C-21), 20.2 (C-11), 19.3 (C-19), 14.6 (C-18), 14.0 ($OCH_2\underline{C}H_3$), 13.5, 13.3 ($CH\underline{C}H_3$)

MS (ESI^+), *m/z* (relative intensity): 633.3 ($[M+Na]^+$, 100 %)

3β-Benzyloxy-16β-(2-methyl-monoethyl ester malonate-ester)-17α-hydroxy-5-pregnene-20-one (472)



(471) (472)

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To a solution of 3β-benzyloxy-16β-(2-methyl-monoethyl ester malonate-ester)-17α-hydroxy-20,20-(ethylenedioxy)-5-pregnene (471) (70 mg, 0.11 mmol) in dry dichloromethane (4 mL) was added *p*-toluenesulfonic acid monohydrate (2 mg, 0.011 mmol). The reaction mixture was stirred at room temperature for 2 h. The residue was added with water, extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/hexane, 1:4) to provide 3β-benzyloxy-16β-(2-methyl-monoethyl ester malonate-ester)-17α-hydroxy-5-pregnene-20-one (472) as a colorless syrup (52 mg, 80%).

FTIR (neat), ν_{max}, cm^{-1}: 3447, 1749, 1733, 1716

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.16-7.28 (m, 5H, Ar(H)), 5.27 (d, *J* = 5.2 Hz, 1H, H-6), 4.85 (dd, *J* = 7.9, 5.6 Hz, 1H, H-16), 4.82 (dd, *J* = 7.9, 5.9 Hz, 1H, H-16), 4.49 (s, 2H, OC$\underline{H}_2$Ar), 4.11 (q, *J* = 7.2 Hz, 1H, OC$\underline{H}_2CH_3$), 4.11 (q, *J* = 7.2 Hz, 1H, OC$\underline{H}_2CH_3$), 4.10 (q, *J* = 7.1 Hz, 1H, OC$\underline{H}_2CH_3$), 4.09 (q, *J* = 7.1 Hz, 1H, OC$\underline{H}_2CH_3$), 3.36 (q, *J* = 7.3 Hz, 1H, C$\underline{H}CH_3$), 3.34 (q, *J* = 7.3 Hz, 1H, C$\underline{H}CH_3$), 3.21 (m, 1H, H-3), 2.36 (ddd, *J* = 2.2, 4.5, 13.0 Hz, H-4), 2.33 (m, 1H, H-15), 2.20-2.24 (m, 1H, H-4), 2.16 (s, 3H, H-21), 2.17 (s, 3H, H-21), 1.92 (m, 1H, H-7), 1.88 (m, 1H, H-2), 1.79 (ddd, *J* = 3.4, 3.4, 13.4 Hz, 1H, H-1), 1.56 (m, 1H, H-7), 1.44-1.52 (m, 6H, H-2, H-8, H-11, H-12, H-14), 1.40 (m, 1H, H-11), 1.35 (d, *J* = 7.3 Hz, 3H, CHC$\underline{H}_3$), 1.33 (d, *J* = 7.3 Hz, 3H, CHC$\underline{H}_3$), 1.27 (m, 1H, H-15), 1.19 (t, *J* = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 0.99 (m, 1H, H-1), 0.96 (s, 3H, H-19), 0.93, 0.90 (s, 3H, H-18), 0.92 (m, 1H, H-9)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 208.0, 207.6 (C-20), 169.8, 169.6, 169.5, 169.4 ($\underline{C}OO$), 140.9 (C-5), 139.0 (C-Ar), 128.3×2 (CH-Ar), 127.5×2 (CH-Ar), 127.4 (CH-Ar), 120.9 (C-6), 88.1 (C-17), 83.5, 83.3 (C-16), 78.4 (C-3), 69.9 (OCH_2Ar), 61.5 ($O\underline{C}H_2CH_3$), 49.6 (C-9), 48.0, 47.9 (C-14), 47.2, 47.1 (C-13), 46.3, 46.0 ($\underline{C}HCH_3$), 39.0 (C-4), 37.1 (C-1), 36.9 (C-10), 33.7, 33.4 (C-15), 31.8, 31.7 (C-7), 31.2 (C-8), 30.6 (C-12), 29.0, 28.9 (C-21), 28.3 (C-2), 20.1 (C-11), 19.3 (C-19), 14.8 (C-18), 14.0 ($OCH_2\underline{C}H_3$), 13.4, 13.3 ($CH\underline{C}H_3$)

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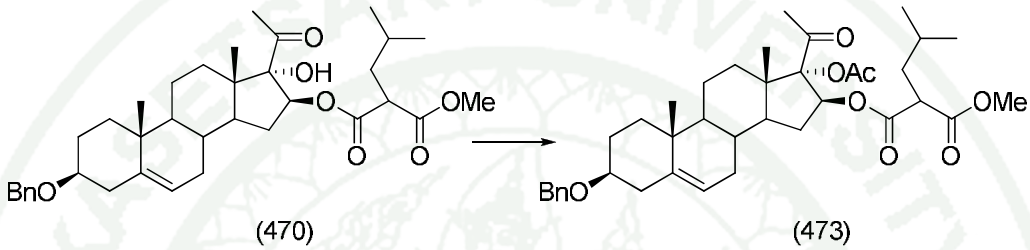
MS (ESI^+), *m/z* (relative intensity): 589.5 ($[M+Na]^+$, 100 %)

3β-Benzyloxy-16β-(isobutyl-monomethyl ester malonate-ester)-17α-acetoxy-5-pregnene-20-one (473)



Method I:

To a solution of 3β-benzyloxy-16β-(isobutyl-monomethyl ester malonate-ester)-17α-hydroxy-5-pregnene-20-one (470) (30 mg, 0.05 mmol) in acetic anhydride (0.25 mL) and dioxane (1 mL) was added 60% perchloric acid (1 µl), and the mixture was stirred for 20 minutes at room temperature. After addition of water, the product was extracted with CH_2Cl_2. The organic layer was washed with 5% $NaHCO_3$ and water, dried over anhydrous Na_2SO_4, and concentrated to dryness. The crude product was purified by flash column chromatography (EtOAc/hexane, 3:17) to give 3β-benzyloxy-16β-(isobutyl-monomethyl ester malonate-ester)-17α-acetoxy-5-pregnene-20-one (473) as a colorless syrup (20 mg, 62%) and recovered starting material (6 mg, 21%).

Method II:

Under N_2 atmosphere, acetic acid (0.065 mL, 1.09 mmol) was added to a well stirred mixture of trifluoroacetic anhydride (TFAA) (0.15 mL, 2.61 mmol) in dichloromethane (1.1 mL) and the mixture was stirred at room temperature for 30 minutes. *p*-Toluenesulfonic acid monohydrate (10 mg, 0.054 mmol) was then added and the mixture was cooled to 0 °C. 3β-Benzyloxy-16β-(isobutyl-monomethyl ester

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malonate-ester)-17α-hydroxy-5-pregnene-20-one (470) (32 mg, 0.054 mmol) was dissolved in dichloromethane (0.65 mL), cooled in an ice bath and added to the stirred mixed anhydride with stirring at 0 °C for 20 minutes. Cold 20% aqueous K_2CO_3 was added carefully until the mixture was basic. The mixture was diluted with water until the CH_2Cl_2 phase became the lower phase. The mixture was extracted with CH_2Cl_2 and washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 3:17) to give 3β-benzyloxy-16β-(isobutyl-monomethyl ester malonate-ester)-17α-acetoxy-5-pregnene-20-one (473) as a colorless syrup (24 mg, 71%) and recovered starting material (7 mg, 23%).

FTIR (neat), ν_{max}, cm^{-1}: 1735, 1716, 1697, 1242

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.22-7.29 (m, 4H, Ar(H)), 7.17-7.21 (m, 1H, Ar(H)), 5.27 (d, *J* = 5.1 Hz, 1H, H-6), 5.11 (dd, *J* = 3.5, 5.4 Hz, 1H, H-16), 5.09 (dd, *J* = 3.5, 5.4 Hz, 1H, H-16), 4.49 (s, 2H, OCH_2Ar), 3.68 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 3.41 (t, *J* = 7.7 Hz, 1H, C<u>H</u>$CH_2CH(CH_3)_2$), 3.38 (t, *J* = 7.7 Hz, 1H, C<u>H</u>$CH_2CH(CH_3)_2$), 3.17-3.24 (m, 1H, H-3), 2.44 (ddd, *J* = 7.8, 13.5, 14.8 Hz, 1H, H-15), 2.36 (ddd, *J* = 2.2, 4.9, 13.3 Hz, 1H, H-4), 2.17-2.23 (m, 1H, H-4), 2.09 (s, 3H, H-21), 2.07 (s, 3H, H-21), 2.03 (s, 3H, $COOCH_3$), 1.87-1.95 (m, 2H, H-2, H-15), 1.85-1.88 (m, 1H, H-12), 1.80 (ddd, *J* = 3.4, 3.4, 13.1 Hz, 1H, H-1), 1.74 (dd, *J* = 7.4, 12.2 Hz, 2H, CHC<u>H</u>$_2$$CH(CH_3)_2$), 1.73 (dd, *J* = 7.5, 8.2 Hz, 2H, CHC<u>H</u>$_2$$CH(CH_3)_2$), 1.44-1.64 (m, 9H, H-2, H-7, H-8, H-11, H-12, H-14, $CHCH_2C$<u>H</u>$(CH_3)_2$), 0.94-1.01 (m, 1H, H-1), 0.96 (CH_3-19, s, 3H), 0.95 (CH_3-18, s, 3H), 0.88-0.94 (m, 1H, H-9), 0.85 (d, *J* = 6.6 Hz, 3H, $CHCH_2CH(C$<u>H</u>$_3)_2$), 0.83 (d, *J* = 6.3 Hz, 3H, $CHCH_2CH(C$<u>H</u>$_3)_2$), 0.82 (d, *J* = 6.6 Hz, 3H, $CHCH_2CH(C$<u>H</u>$_3)_2$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 201.2, 201.0 (C-20), 170.1, 169.9 (<u>C</u>$OOCH_3$), 169.9, 169.6, 168.1, 167.9 (<u>C</u>OO), 141.1 (C-5), 139.0 (C-Ar), 128.4×2 (CH-Ar), 127.6 (CH-Ar), 127.5 (CH-Ar), 127.4 (CH-Ar), 120.8 (C-6), 93.6, 93.3 (C-17), 80.4, 80.1 (C-16), 78.4 (CH-3), 70.0, 69.9 (OCH_2Ar), 52.4 (OCH_3), 50.3, 50.2 (<u>C</u>$HCH_2CH(CH_3)_2$), 49.6 (C-9), 48.3, 48.2 (C-14), 47.5, 47.6 (C-13), 39.1 (C-4), 37.3

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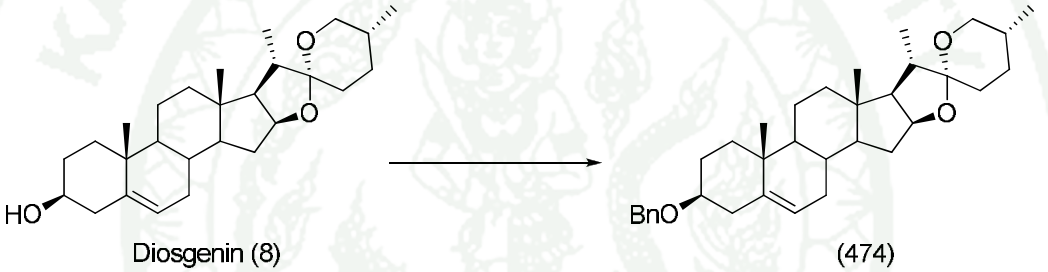
(C-1), 36.9 (C-10), 32.2, 32.1 (C-7), 31.9, 31.7 (C-8), 31.3 (C-12), 29.8, 29.4 (C-21), 28.4, 28.3 (C-2), 26.0 ($CHCH_2\underline{C}H(CH_3)_2$), 26.1 (C-15), 24.6, 23.0 ($CH\underline{C}H_2CH(CH_3)_2$), 22.2, 22.1, 21.7 ($CHCH_2CH(\underline{C}H_3)_2$), 21.0, 20.9 ($COO\underline{C}H_3$), 20.2 (C-11), 19.4 (C-19), 14.1, 13.9 (C-18)

MS (ESI^+), *m/z* (relative intensity): 661.6 ($[M+Na]^+$, 100 %)

3β-Benzyloxy-5-spirostene (474)



To a suspension of diosgenin (8) (200 mg, 0.48 mmol) and NaH (52.6 mg of a 60% mineral oil suspension, 1.32 mmol) in THF (1 mL) and DMF (1 mL), which had been stirred for 1 hour at room temperature, benzyl bromide (0.095 mL, 0.79 mmol) was slowly added under the positive pressure of nitrogen. After additional 2 hours, the reaction was heated to reflux for 4 hours. After removal of most of the solvents and benzyl bromide under reduced pressure, the residue was diluted with EtOAc and water was added to decompose the rest of NaH. Then the mixture was sequentially washed with 1N HCl and saturated aqueous $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4 and then filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 1:9) to give 3β-benzyloxy-5-spirostene (474) as a white solid (244 mg, 100%); m.p. 114-116 °C.

FTIR (KBr), ν_{max}, cm^{-1}: 2927, 2849, 1453, 1376, 1095, 1072, 1051

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.17-7.30 (m, 5H, Ar(H)), 5.27 (d, *J* = 5.3 Hz, 1H, H-6), 4.50 (d, AB, *J* = 12.0 Hz, 1H, OCH_2Ar), 4.47 (d, AB, *J* = 12.0 Hz, 1H,

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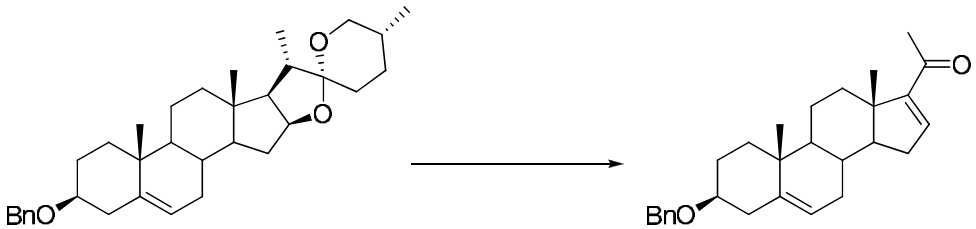
OCH_2Ar), 4.33 (dd, *J* = 7.5, 15.0 Hz, 1H, H-16), 3.40 (ddd, *J* = 1.9, 4.4, 10.9 Hz, 1H, H-26α), 3.30 (dd, *J* = 10.9, 10.9 Hz, 1H, H-26β), 3.16-3.24 (m, 1H, H-3), 2.36 (ddd, *J* = 2.3, 4.8, 13.2 Hz, 1H, H-4β), 2.21 (dddd, *J* = 2.8, 5.1, 12.2, 12.2 Hz, 1H, H-4α), 1.94 (ddd, *J* = 2.7, 5.0, 16.8 Hz, 1H, H-15α), 1.85-1.94 (m, 3H, H-1β, H-2α, H-7β), 1.79 (dd, *J* = 4.7, 13.8 Hz, 1H, H-20), 1.78 (dd, *J* = 6.8, 13.9 Hz, 1H, H-17), 1.70 (dd, *J* = 6.8, 8.6 Hz, 1H, H-12β), 1.66 (ddd, *J* = 3.3, 3.3, 12.6 Hz, 1H, H-23β), 1.59 (dd, *J* = 4.7, 7.5 Hz, 1H, H-24α), 1.36-1.57 (m, 7H, H-2β, H-7α, H-8, H-11α,β, H-23α, H-24β), 1.23 (dd, *J* = 6.5, 13.7 Hz, 1H, H-15β), 1.20 (dd, *J* = 6.4, 13.6 Hz, 1H, H-25), 1.11 (dd, *J* = 5.0, 12.5 Hz, 1H, H-12α), 1.04 (dd, *J* = 5.4, 10.7 Hz, 1H, H-14), 1.01 (dd, *J* = 5.1, 11.0 Hz, 1H, H-1α), 0.96 (s, 3H, H-19), 0.90 (d, *J* = 7.0 Hz, 3H, H-21), 0.87 (dd, *J* = 5.8, 11.0 Hz, 1H, H-9), 0.72 (s, 3H, H-18), 0.72 (d, *J* = 6.4 Hz, 3H, H-27)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 141.0 (C-5), 139.0 (C-Ar), 128.4 (CH-Ar), 128.3×2 (CH-Ar), 127.5×2 (CH-Ar), 121.3 (C-6), 109.2 (C-22), 80.8 (C-16), 78.5 (C-3), 69.9 (OCH_2Ar), 66.8 (C-26), 62.1 (C-17), 56.5 (C-14), 50.1 (C-9), 41.6 (C-4), 40.2 (C-20), 39.8 (C-12), 39.1 (C-13), 37.2 (C-1), 37.0 (C-10), 32.1 (C-15), 31.8 (C-2), 31.4 (C-7), 31.4 (C-23), 30.3 (C-25), 29.7 (C-8), 28.8 (C-24), 20.8 (C-11), 19.4 (C-19), 17.1 (C-27), 16.3 (C-18), 14.5 (C-21)

MS (ESI^+), *m/z* (relative intensity): 505.3 ($[M+H]^+$, 100 %)

3β-Benzyloxy-5,16-pregnadiene-20-one (453)



(474) (453)

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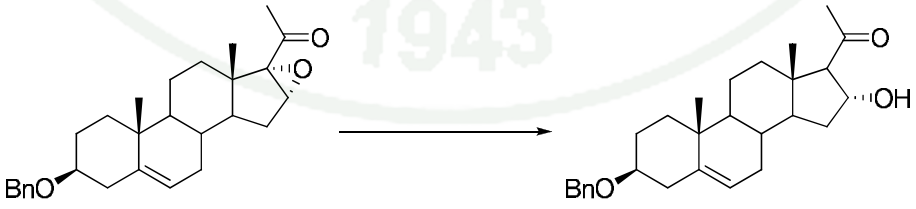
A mixture of 3β-benzyloxy-5-spirostene (474) (243 mg, 0.48 mmol), ammonium chloride (59 mg, 1.10 mmol), acetic anhydride (1.8 mL), and pyridine (0.46 mL, 4.82 mmol) was refluxed (135 °C) for 12 h. After cooling down, the reaction mixture was added acetic acid (0.4 mL), 1,2-dichloroethane (0.4 mL) and water (0.05 mL) and cooled to 0 °C. A cooled solution of chromium trioxide (168 mg, 1.68 mmol) in water (0.12 mL) and acetic acid (0.04 mL) was added, while the temperature was kept at 7-10 °C. When 90% of the solution has been added, cooling is discontinued. After remaining portion has been added, the mixture was stirred for 2 hours at room temperature. Then a saturated solution of $NaHCO_3$ was introduced and the stirring was continued for two additional hours. Then water was added and the reaction mixture was extracted with 1,2-dichloroethane and the combined extract was washed wish water to remove the residual chromium salts, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. A solution of the residue and alumina base (1:25) in benzene was stirred overnight at room temperature. The reaction mixture was washed with CH_2Cl_2 and filtered by silica gel 9385. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/hexane, 1:9) to provide 3β-benzyloxy-5,16-pregnadiene-20-one (453) as a white solid (68 mg, 35%).

3β-Benzyloxy-16α-hydroxy-5-pregnene-20-one (475)



(454) (475)

To a solution of 3β-benzyloxy-16α,17α-epoxy-5-pregnene-20-one (454) (248 mg, 0.59 mmol) in ethanol (9.0 mL) and dichloromethane (1.8 mL) was added hydrazine hydrate (1.14 mL, 23.5 mmol) at room temperature. After stirring for 5 hours, the solvent was evaporated and stirred vigorously for 30 minutes with the

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mixture of EtOAc (27 mL), 10% aqueous HCl acid (27 mL). The organic layer was separated and the aqueous layer was washed with EtOAc. The combined organic layer was washed with brine and water, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/hexane, 1:1) to provide 3β-benzyloxy-16α-hydroxy-5-pregnene-20-one (475) (132 mg, 53%) as a white solid; m.p. 172-174 °C.

FTIR (KBr), ν_{max}, cm^{-1}: 3262, 2934, 2849, 2361, 1702, 1452, 1357, 1112, 1057, 1052

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.17-7.30 (m, 5H, Ar(H)), 5.27 (d, *J* = 5.3 Hz, 1H, H-6), 4.78 (ddd, *J* = 1.8, 6.6, 8.5 Hz, 1H, H-16), 4.51 (d, AB, *J* = 12.0 Hz, 1H, OCH_2Ar), 4.48 (d, AB, *J* = 12.0 Hz, 1H, OCH_2Ar), 3.18-3.26 (m, 1H, H-3), 2.45 (d, *J* = 6.5 Hz, 1H, H-17), 2.36 (ddd, *J* = 13.3, 4.8, 2.4 Hz, 1H, H-4), 2.20 (dddd, *J* = 12.3, 12.3, 5.3, 2.8 Hz, 1H, H-4), 2.10 (s, 3H, H-21), 1.86-1.95 (m, 3H, H-2, H-7, H-12), 1.80 (ddd, *J* = 13.3, 3.6, 3.6 Hz, 1H, H-1), 1.35-1.67 (m, 9H, H-2, H-7, H-8, H-11, H-12, H-14, H-15), 1.01 (dd, *J* = 13.5, 3.7 Hz, 1H, H-1), 0.95 (dd, *J* = 7.7, 4.3 Hz, 1H, H-9), 0.94 (s, 3H, H-19) , 0.57 (s, 3H, H-18)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 208.6 (C-20), 140.9 (C-5), 139.0 (C-Ar), 128.3×2 (CH-Ar), 127.6×2 (CH-Ar), 127.4 (CH-Ar), 121.1 (C-6), 78.4 (C-3), 73.7 (C-16), 72.1 (C-17), 69.9 (OCH_2Ar), 54.5 (C-14), 49.9 (C-9), 44.8 (C-13), 39.1 (C-4), 38.7 (C-12), 37.1 (C-1), 36.9 (C-10), 35.2 (C-15), 31.7 (C-7), 31.6 (C-8), 31.4 (C-21), 28.4 (C-2), 20.6 (C-11), 19.3 (C-19), 14.3 (C-18)

MS (ESI^+), *m/z* (relative intensity): 445.4 ($[M+Na]^+$, 100 %)

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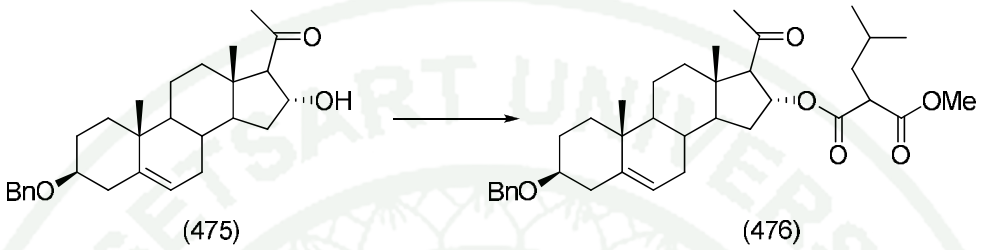
3β-Benzyloxy-16α-(isobutyl-monomethyl ester malonate-ester)-5-pregnene-20-one (476)



To a solution of 2-isobutyl-malonic acid monomethyl ester (466) (31 mg, 0.18 mmol) and *N,N*-dimethylaminopyridine (DMAP) (4 mg, 0.03 mmol) in dichloromethane (2.6 mL) was added a solution of 3β-benzyloxy-16α-hydroxy-5-pregnene-20-one (475) (50 mg, 0.12 mmol) in dichloromethane (2.6 mL) at room temperature. After the reaction was stirred for 5 minutes, *N,N*-dicyclohexylcarbodiimide (37 mg, 0.18 mmol) was introduced. The reaction was stirred at room temperature for 3 hours and then filtered and rinsed successively with CH_2Cl_2. The combined CH_2Cl_2 was extracted with saturated aqueous NH_4Cl. The combined organic layers were dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (EtOAc/hexane, 1:4) to give 3β-benzyloxy-16α-(isobutyl-monomethyl ester malonate-ester)-5-pregnene-20-one (476) (44 mg, 64%) as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.24-7.29 (m, 4H, Ar(H)), 7.17-7.22 (m, 1H, Ar(H)), 5.43-5.50 (m, 1H, H-16), 5.26 (d, *J* = 5.2 Hz, 1H, H-6), 4.49 (s, 2H, OCH_2Ar), 3.63 (s, 3H, OCH_3), 3.31 (t, *J* = 7.7 Hz, 1H, C<u>H</u>$CH_2CH(CH_3)_2$), 3.30 (t, *J* = 7.7 Hz, 1H, C<u>H</u>$CH_2CH(CH_3)_2$), 3.18-3.25 (m, 1H, H-3), 2.58 (dd, *J* = 6.2, 6.2 Hz, 1H, H-17), 2.36 (ddd, *J* = 13.3, 4.7, 2.2 Hz, 1H, H-4), 2.17-2.24 (m, 1H, H-4), 2.08 (s, 3H, H-21), 1.87-1.96 (m, 2H, H-2, H-7), 1.80 (ddd, *J* = 13.2, 3.5, 3.5 Hz, 1H, H-1), 1.76-1.80 (m, 2H, H-12), 1.72-1.77 (m, 1H, H-15), 1.69 (td, *J* = 7.3, 1.5 Hz, 2H, CHC<u>H$_2$</u>$CH(CH_3)_2$), 1.68 (td, *J* = 7.2, 2.5 Hz, 2H, CHC<u>H$_2$</u>$CH(CH_3)_2$), 1.61 (ddd, *J* = 6.9, 2.9, 1.5 Hz, 1H, H-15), 1.36-1.60 (m, 7H, H-2, H-7, H-8, H-11, H-14,

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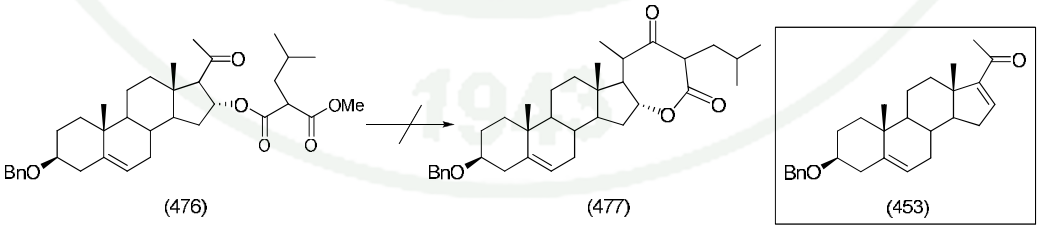
$CHCH_2C\underline{H}(CH_3)_2$), 0.99 (dd, *J* = 13.5, 3.6 Hz, 1H, H-1), 0.92-0.96 (m, 1H, H-9), 0.94 (s, 3H, H-19), 0.83 (d, *J* = 6.6 Hz, 3H, $CHCH_2CH(C\underline{H}_3)_2$), 0.82 (d, *J* = 6.6 Hz, 3H, $CHCH_2CH(C\underline{H}_3)_2$), 0.60 (s, 3H, H-18)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 206.2, 206.1 (C-20), 170.1, 169.2 (C=O), 141.0 (C-5), 138.9 (C-Ar), 128.3×2 (CH-Ar), 127.5×2 (CH-Ar), 127.4 (CH-Ar), 120.9, 120.8 (C-6), 78.3 (C-3), 77.0, 76.8 (C-16), 69.9 (OCH_2Ar), 69.8 (C-17), 54.5, 54.4 (C-14), 52.3 (OCH_3), 50.1, 50.0 ($\underline{C}HCH_2CH(CH_3)_2$), 49.8 (C-9), 44.5 (C-13), 39.0 (C-4), 38.7 ($CH\underline{C}H_2CH(CH_3)_2$), 37.4, 37.3 (C-1), 37.1 (C-12), 36.8 (C-10), 33.2, 33.1 (C-15), 31.6 (C-7), 31.4 (C-8), 31.2, 31.1 (C-21), 28.3 (C-2), 26.1 ($CHCH_2\underline{C}H(CH_3)_2$), 22.3, 22.2, 22.1, 22.0 ($CHCH_2CH(\underline{C}H_3)_2$), 20.6 (C-11), 19.3 (C-19), 14.3 (C-18)

MS (ESI^+), *m/z* (relative intensity): 601.9 ($[M+Na]^+$, 12 %), 387.4 (100)

Intramolecular McMurry Reaction

Intramolecular McMurry coupling of 3β-benzyloxy-16α-(isobutyl-monomethyl ester malonate-ester)-5-pregnene-20-one (476)



Under an inert atmosphere of nitrogen, a stirred mixture of THF (1.3 mL) and $TiCl_4$ (0.11 mL, 0.98 mmol) at 0 °C was treated with $LiAlH_4$ (11 mg, 0.33 mmol). The resulting black slurry was allowed to reflux for an hour, then the reaction mixture was gradually cooled to 0 °C. To this mixture was added a mixture of 3β-benzyloxy-16α-(isobutyl-monomethyl ester malonate-ester)-5-pregnene-20-one (476) (44 mg, 0.078 mmol) in dry THF (1.3 mL). The reaction mixture was refluxed at 70 °C for 12 h. On

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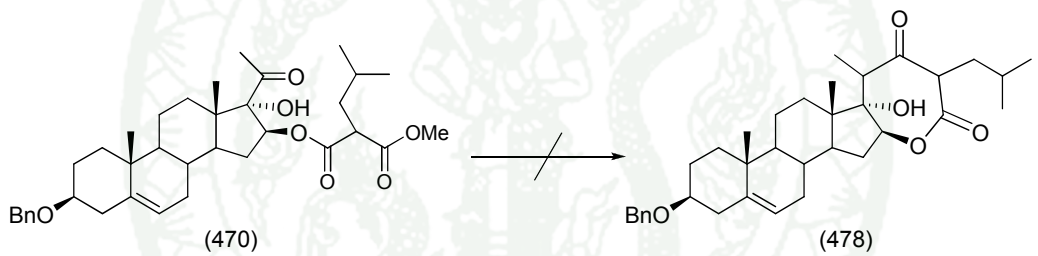
completion of reaction, the mixture was poured onto 10% aqueous solution of potassium carbonate. The whole content was then filtered through silica gel under suction. Filtrate was extracted with EtOAc, the organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (EtOAc/hexane, 1:9). However the desired product (477) was not observed, only 3β-benzyloxy-5,16-pregnadiene-20-one (453) was obtained as a white solid (28 mg, 88%).

Intramolecular McMurry coupling of 3β-benzyloxy-16β-(isobutyl-monomethyl ester malonate-ester)-17α-hydroxy-5-pregnene-20-one (470)



Using $TiCl_4$/Zn

Under nitrogen atmosphere, a three-necked flask was charged with zinc powder (67 mg, 1.01 mmol) and THF (1.7 mL). The mixture was cooled to -5 to 0 °C, and $TiCl_4$ (0.055 mL, 0.50 mmol) was slowly added by a syringe with the temperature kept under 10 °C. The suspending mixture was warmed to room temperature and stirred for 0.5 h, then heated at reflux for 2.5 h. The mixture was again cooled to -5 to 0 °C, charged with pyridine (0.021 mL, 0.25 mmol) and stirred for 10 min. The solution of 3β-benzyloxy-16β-(isobutyl-monomethyl ester malonate-ester)-17α-hydroxy-5-pregnene-20-one (470) (60 mg, 0.10 mmol) in THF (1.0 mL) was added slowly. After addition, the reaction mixture was heated at reflux for 8 h. The reaction was quenched with 10% K_2CO_3 aqueous solution and take up with CH_2Cl_2. The organic layer was collected, dried over anhydrous Na_2SO_4 and concentrated. The crude material was purified by flash column chromatography (EtOAc/hexane, 1:9) to give an unexpected product (479) (7 mg, 17%) as a white solid, an uninterpreted

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product (5 mg) as a colorless syrup and recovered starting material (470) (41 mg, 69%).

Using $TiCl_4$/Zn-Cu

$TiCl_4$ (0.055 mL, 0.50 mmol) and Zn-Cu couple (63 mg) were covered with dry THF (5.0 mL). The mixture was refluxed for 1 hour with effective stirring under nitrogen atmosphere. A solution of 3β-benzyloxy-16β-(isobutyl-monomethyl ester malonate-ester)-17α-hydroxy-5-pregnene-20-one (470) (60 mg, 0.10 mmol) in dry THF (2.0 mL) was added at once, and refluxing was continued for only 10 minutes. To the reaction mixture was added silica gel (746 mg), and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (EtOAc/hexane, 1:9) to give an unexpected product (479) (28 mg, 67%) as a white solid.

Using $TiCl_4$/$LiAlH_4$

Under nitrogen atmosphere, a stirred mixture of THF (1.5 mL) and $TiCl_4$ (0.11 mL, 1.06 mmol) at 0 °C was treated with $LiAlH_4$ (12 mg, 0.35 mmol). The resulting black slurry was allowed to reflux for an hour, then the reaction mixture was gradually cooled to 0 °C. To this mixture was added 3β-benzyloxy-16β-(isobutyl-monomethyl ester malonate-ester)-17α-hydroxy-5-pregnene-20-one (470) (51 mg, 0.085 mmol) in dry THF. The reaction mixture was refluxed at 70 °C for 8 h. On completion of reaction, the mixture was poured onto 10% aqueous solution of K_2CO_3. The whole content was then filtered through silica gel under suction. Filtrate was extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by flash column chromatography (EtOAc/hexane, 1:9) to give a white solid and recovered starting material (9 mg, 18%). However, NMR experiment showed the mixture of two uninterpreted compounds.

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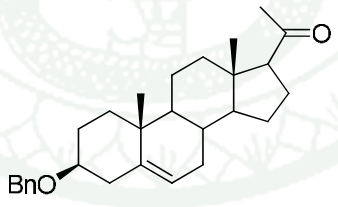
Using $TiCl_4$/Mg-Naphthalene

To a stirred suspension of Mg (16 mg, 0.66 mmol) and naphthalene (7 mg, 0.05 mmol) in dry THF (0.8 mL) under nitrogen atmosphere was successively added $TiCl_4$ (0.022 mL, 0.20 mmol) in THF (0.8 mL) at room temperature. After refluxing for 3 h, a thick dense homogeneous black mass of activated Ti species was obtained and then allowed to cool to ambient temperature. To a stirred solution of the reagent was added 3β-benzyloxy-16β-(isobutyl-monomethyl ester malonate-ester)-17α-hydroxy-5-pregnene-20-one (470) (30 mg, 0.05 mmol) in THF (1.0 mL) and the reaction mixture was stirred at room temperature for 12 h. Then the mixture was diluted with hexane and quenched with saturated aqueous NH_4Cl and the supernatant was passed through a bed of celite. The eluent was extracted with CH_2Cl_2, washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 3:17) to give 3β-benzyloxy-5-pregnene-20-one (479) as a white solid (17 mg, 85%), and the desired product (478) was not observed.



(479)

3β-Benzyloxy-5-pregnene-20-one (479)

FTIR (KBr), ν_{max}, cm^{-1}: 2928, 2852, 1702

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.17-7.33 (m, 5H, Ar(H)), 5.28 (d, *J* = 5.3 Hz, 1H, H-6), 4.50 (s, 2H, OCH_2Ar), 3.17-3.25 (m, 1H, H-3), 2.46 (dd, *J* = 9.0, 9.0 Hz, 1H, H-17), 2.36 (ddd, *J* = 2.4, 4.7, 13.2 Hz, 1H, H-4), 2.21 (dddd, *J* = 2.8, 5.2, 12.3, 12.3 Hz, 1H, H-4), 2.12 (dd, *J* = 9.3, 11.2 Hz, 1H, H-4), 2.05 (s, 3H, $OCOCH_3$), 1.87-2.00 (m, 3H, H-2, H-7, H-12), 1.81 (ddd, *J* = 3.5, 3.5, 13.2 Hz, 1H, H-1), 1.30-1.66

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(m, 9H, H-2, H-7, H-8, H-11, H-12, H-15, H-16), 1.07 (ddd, *J* = 6.4, 10.2, 12.4 Hz, 1H, H-14), 1.00 (dd, *J* = 3.7, 13.7 Hz, 1H, H-1), 0.95 (s, 3H, H-19), 0.87-0.93 (m, 1H, H-9), 0.56 (s, 3H, H-18)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 209.5 (C-20), 141.0 (C-5), 139.0 (C-Ar), 128.3×2 (CH-Ar), 127.6×2 (CH-Ar), 127.4 (CH-Ar), 121.3 (C-6), 78.5 (C-3), 69.9 (OCH_2Ar), 63.7 (C-17), 56.9 (C-14), 50.1 (C-9), 44.0 (C-13), 39.1 (C-4), 38.8 (C-12), 37.2 (C-1), 36.9 (C-10), 31.9 (C-8), 31.8 (C-7), 31.5 (C-21), 28.4 (C-2), 24.5 (C-15), 22.8 (C-16), 21.1 (C-11), 19.4 (C-19), 13.2 (C-18)

MS (ESI^+), *m/z* (relative intensity): 429.5 ($[M+Na]^+$, 100 %)

Uninterpreted compound 480

FTIR (neat), ν_{max}, cm^{-1}: 3347, 2929, 2853, 2360, 1737, 1710

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.22 (m, 5H), 5.49 (m, 1H), 5.28 (d, *J* = 5.2 Hz, 1H), 4.49 (s, 2H), 3.68 (s, 1H), 3.62 (s, 3H), 3.33, 3.32 (t, t, *J* = 7.6, 7.7 Hz, 1H) (may be two isomers), 3.20 (m, 1H), 2.00, 1.99 (s, s, 3H), 0.98 (s, 3H), 0.96 (s, 3H), 0.84 (s, 3H), 0.83 (s, 3H)

Uninterpreted compound 481

FTIR (KBr), ν_{max}, cm^{-1}: 3489, 2955, 2931, 2870, 1750, 1734, 1701

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.24 (m, 5H), 5.79 (m, 0.4H), 5.26 (d, *J* = 5.2 Hz, 1H), 4.78 (m, 0.6H), 4.50, 4.49 (s, s, 2H), 3.94 (s, 0.25H), 3.91 (s, 0.27H), 3.70 (s, 0.52H), 3.68 (m, 2.25H), 3.47 (m, 1H), 3.21 (m, 1H), 2.17 (s, 0.35H), 1.54 (s, 5H), 1.33 (s, s, 1.82H), 1.16 (s, 1.11H), 1.07 (s, 1.72H), 0.94 (s, 2H), 0.92 (s, 1.3H), 0.87 (s, 1.79H), 0.86 (s, 1.59H)

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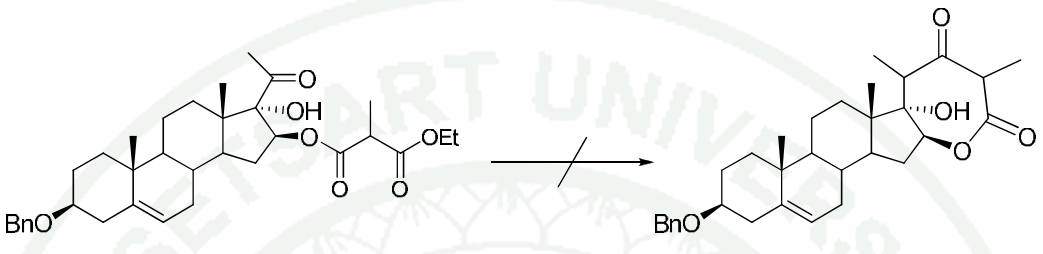
Intramolecular McMurry coupling of 3β-benzyloxy-16β-(2-methyl-monoethyl ester malonate-ester)-17α-hydroxy-5-pregnene-20-one (472)



Using $TiCl_4/LiAlH_4$

Under a nitrogen atmosphere, a stirred mixture of THF (3.3 mL) and $TiCl_4$ (0.09 mL, 0.94 mmol) at 0 °C was treated with $LiAlH_4$ (19 mg, 0.56 mmol). The resulting black slurry was allowed to reflux for an hour then the reaction mixture was gradually cooled to 0 °C. To this mixture was added 3β-benzyloxy-16β-(2-methyl-monoethyl ester malonate-ester)-17α-hydroxy-5-pregnene-20-one (472) (42 mg, 0.075 mmol) in dry THF (2.0 mL). The reaction mixture was refluxed at 70 °C for 8 h. On completion of reaction, the mixture was poured onto 10% aqueous solution of K_2CO_3. The whole content was then filtered through silica gel under suction. Filtrate was extracted with EtOAc and CH_2Cl_2, the organic layer was dried over anhydrous Na_2SO_4 and concentrated to residue. TLC of the crude product showed a complex mixture.

Using $TiCl_4$/Li-Naphthalene

To a stirred suspension of lithium (7 mg, 0.98 mmol) in THF (0.6 mL) was added naphthalene (10 mg, 0.074 mmol) at room temperature. After refluxing for 3 hours, a thick dense homogeneous black mass of activated Ti species was obtained. The reagent was then allowed to cool to ambient temperature. To a stirred solution of the reagent was added 3β-benzyloxy-16β-(2-methyl-monoethyl ester malonate-ester)-17α-hydroxy-5-pregnene-20-one (472) (42 mg, 0.074 mmol) in THF (0.6 mL) and the

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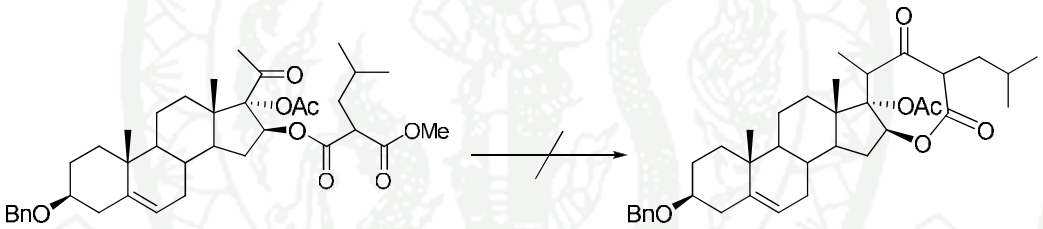
reaction mixture was stirred at refluxing for 5 hours. The reaction mixture was diluted with hexane and quenched with saturated aqueous NH_4Cl solution and the supernatant was passed through a bed of celite. Filtrate was extracted with EtOAc and CH_2Cl_2, the organic layer was dried over anhydrous Na_2SO_4 and concentrated to residue. TLC of the crude product showed a complex mixture. However, the residue was purified by flash column chromatography (EtOAc/hexane, 3:17) to give 3β-benzyloxy-5-pregnene-20-one (479) as a white solid (5.3 mg, 17.5%), and the desired product was not observed.

Intramolecular McMurry coupling of 3β-benzyloxy-16β-(isobutyl-monomethyl ester malonate ester)-17α-acetyloxy-5-pregnene-20-one (473)



(473) (483)

Using $TiCl_4/LiAlH_4$

Under a nitrogen atmosphere, a stirred mixture of THF (1.0 mL) and $TiCl_4$ (0.052 mL, 0.47 mmol) at 0 °C was treated with $LiAlH_4$ (6 mg, 0.16 mmol). The resulting black slurry was allowed to reflux for an hour then the reaction mixture was gradually cooled to 0 °C. To this mixture was added 3β-benzyloxy-16β-(isobutyl-monomethyl ester malonate ester)-17α-acetyloxy-5-pregnene-20-one (473) (24 mg, 0.038 mmol) in dry THF (1.0 mL). The reaction mixture was refluxed at 70 °C for 8 h. Then, the mixture was poured onto 10% aqueous solution of K_2CO_3. The whole content was then filtered through silica gel under suction. Filtrate was extracted with EtOAc and CH_2Cl_2, the organic layer was dried over anhydrous Na_2SO_4 and concentrated to residue. The residue was purified by flash column chromatography (EtOAc/hexane, 3:17) to give only recovered starting material (473) as a colorless syrup (21 mg, 87%).

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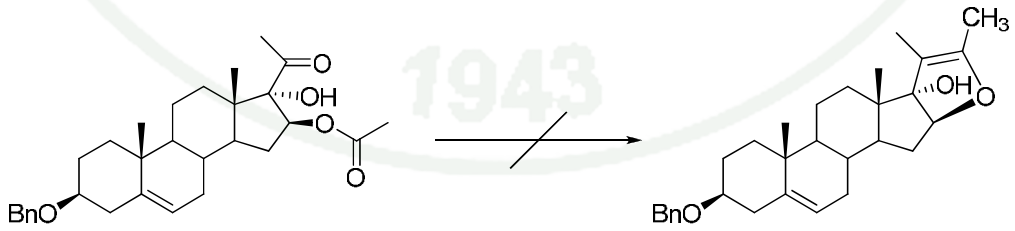
Using $TiCl_4$/Mg-Naphthalene

To a stirred suspension of magnesium (12 mg, 0.48 mmol) and naphthalene (5 mg, 0.036 mmol) in dry THF (0.58 mL) under nitrogen was successively added $TiCl_4$ (0.016 mL, 0.14 mmol) in THF (0.58 mL) at room temperature. After refluxing for 3 h, a thick dense homogeneous black mass of activated Ti species was obtained and then allowed to cool to ambient temperature. To a stirred solution of the reagent was added 3β-benzyloxy-16β-(isobutyl-monomethyl ester malonate ester)-17α-acetyloxy-5-pregnene-20-one (473) (23 mg, 0.036 mmol) in THF (0.72 mL) and the reaction mixture was stirred at room temperature for 12 h. Then the mixture was diluted with hexane and quenched with saturated aqueous NH_4Cl and the supernatant was passed through a bed of celite. The eluent was extracted with a mixture of EtOAc and hexane (1:4), washed with brine and dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 1:9) to give starting material (473) as a colorless syrup (6 mg, 27%). The desired product (483) was not observed, only 3β-benzyloxy-5-pregnene-20-one (479) was obtained as a white solid (6 mg, 42%).

Intramolecular McMurry coupling of 3β-benzyloxy-16β-acetyloxy-17α-hydroxy-5-pregnene-20-one (457)



(457) (484)

Under a nitrogen atmosphere, a three-necked flask equipped with a magnetic stirrer was charged with zinc powder (83 mg, 1.25 mmol) and dry THF (2.1 mL). The mixture was cooled to 0 °C, and $TiCl_4$ (0.068 ml, 0.62 mmol) was slowly added with the temperature kept under 10 °C. The suspending mixture was warmed to room

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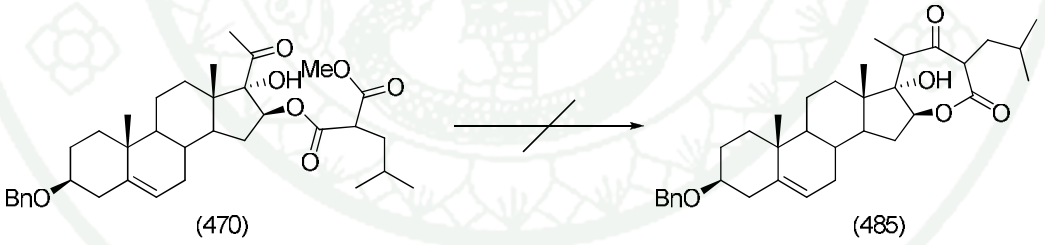
temperature and stirred for 30 minutes, then heated at reflux for 2.5 hours. The mixture was again cooled to 0 °C, charged with pyridine (0.02 mL, 0.31 mmol) and stirred for 10 minutes. The solution of 3β-benzyloxy-16β-acetyloxy-17α-hydroxy-5-pregnene-20-one (457) (60 mg, 0.12 mmol) in THF (0.8 mL) was added slowly. After addition, the reaction mixture was heated at reflux for 5 hours. The reaction was quenched with 10% K_2CO_3 aqueous solution and take up with CH_2Cl_2. The organic layer was collected and concentrated. The residue was purified by flash column chromatography (EtOAc/hexane, 1:9) to give starting material (457) as a white solid (25 mg, 41%). The desired product (484) was not observed, only 3β-benzyloxy-5-pregnene-20-one (479) was obtained as a white solid (12 mg, 23%).

Samarium diiodide-promoted intramolecular ketone-ester coupling reaction

Samarium diiodide-promoted intramolecular coupling of 3β-benzyloxy-16β-(isobutyl-monomethyl ester malonate ester)-17α-hydroxy-5-pregnene-20-one (470)



(470) (485)

Using SmI_2 at -78 °C

A THF solution (0.5 mL) of 3β-benzyloxy-16β-(isobutyl-monomethyl ester malonate ester)-17α-hydroxy-5-pregnene-20-one (470) (48 mg, 0.08 mmol) was added dropwise under nitrogen during 3 min to the THF solution (2.0 mL) of SmI_2 (72 mg, 0.18 mmol) at -78 °C. The reaction mixture was stirred for 3 hours, and then it was quenched with saturated aqueous $NaHCO_3$ solution, and the solution was stirred under air for 10 min. The solution was extracted with Et_2O, and then organic layer was washed with saturated aqueous $NaHCO_3$, $Na_2S_2O_3$ and NaCl, and dried over anhydrous Na_2SO_4. The crude reaction mixture obtained by the concentration of the

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extract was separated by flash column chromatography (EtOAc/hexane, 1:9). Unfortunately none product was observed, only starting material (470) was recovered (46 mg, 95%).

Using SmI_2 at 0 °C

A THF solution (0.7 mL) of 3β-benzyloxy-16β-(isobutyl-monomethyl ester malonate ester)-17α-hydroxy-5-pregnene-20-one (470) (54 mg, 0.09 mmol) was added dropwise under nitrogen during 3 min to the THF solution (2.2 mL) of SmI_2 (81 mg, 0.20 mmol) at 0 °C. The reaction mixture was stirred for 10 min, and then it was quenched with saturated aqueous $NaHCO_3$ solution, and the solution was stirred under air for 10 min. The solution was extracted with Et_2O, and then organic layer was washed with saturated aqueous $NaHCO_3$, $Na_2S_2O_3$ and NaCl, and dried over anhydrous Na_2SO_4. The crude reaction mixture obtained by the concentration of the extract was separated by flash column chromatography (EtOAc/hexane, 1:9). Unfortunately only 3β-benzyloxy-5,16-pregnadiene-20-one (453) was obtained as a white solid (15 mg, 41%) and starting material was recovered (21 mg, 38%).

Using SmI_2 at room temperature

A THF solution (1.0 mL) of 3β-benzyloxy-16β-(isobutyl-monomethyl ester malonate ester)-17α-hydroxy-5-pregnene-20-one (470) (100 mg, 0.17 mmol) was added dropwise under nitrogen during 3 min to the THF solution (3.7 mL) of SmI_2 (150 mg, 0.37 mmol) at room temperature. The reaction mixture was stirred for 30 minutes, and then it was quenched with saturated aqueous $NaHCO_3$ solution, and the solution was stirred under air for 10 min. The solution was extracted with Et_2O, and then organic layer was washed with saturated aqueous $NaHCO_3$, $Na_2S_2O_3$ and NaCl, and dried over anhydrous Na_2SO_4. The crude reaction mixture obtained by the concentration of the extract was separated by flash column chromatography (EtOAc/hexane, 1:9). Unfortunately only 3β-benzyloxy-5-pregnene-20-one (479) was obtained as a white solid (52 mg, 76%).

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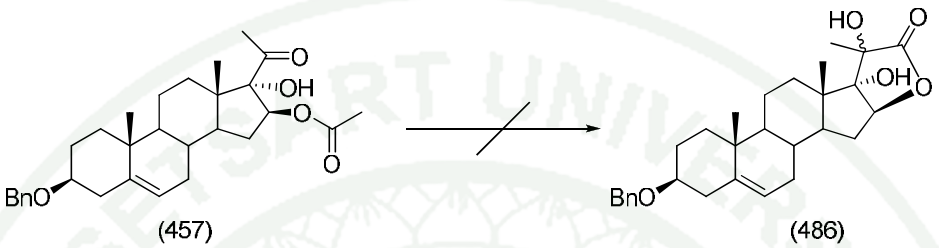
Samarium diiodide-promoted intramolecular coupling of 3β-benzyloxy-16β-acetyloxy-17α-hydroxy-pregnenolone (457)



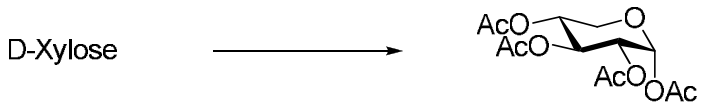
(457) (486)

A THF solution (0.5 mL) of 3β-benzyloxy-16β-acetyloxy-17α-hydroxy-pregnenolone (457) (21 mg, 0.044 mmol) was added dropwise under nitrogen during 3 min to the THF solution (1.0 mL) of SmI_2 (39 mg, 0.096 mmol) at room temperature. The reaction mixture was stirred for 30 minutes, and then it was quenched with saturated aqueous $NaHCO_3$ solution, and the solution was stirred under air for 10 min. The solution was extracted with Et_2O, and then organic layer was washed with saturated aqueous $NaHCO_3$, $Na_2S_2O_3$ and NaCl, and dried over anhydrous Na_2SO_4. The crude reaction mixture obtained by the concentration of the extract was separated by flash column chromatography (EtOAc/hexane, 1:9). Unfortunately only 3β-benzyloxy-5,16-pregnadiene-20-one (453) was obtained as a white solid (2 mg, 11%) and starting material was recovered (18 mg, 84%).

Synthesis of disaccharide moiety of OSW-1

Synthesis of D-xylopyranoside donor

1,2,3,4-*O*-tetraacetyl-D-xylopyranoside (487)



(53) (487)

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Acetyl chloride (3.0 mL, 42 mmol) was added dropwise to a solution of D-xylose (53) (1.0 g, 6.7 mmol) in dichloromethane (25 mL) and pyridine (2.6 mL, 32 mmol) at 0 °C. The mixture was allowed to stir at room temperature for 24 hours, and then quenched with water (50 mL). The organic layer was washed with 2M aqueous HCl (2 x 50 mL), saturated aqueous $NaHCO_3$ (50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/hexane, 3:7) to give 1,2,3,4-*O*-tetraacetyl-D-xylopyranoside (487) (2.1 g, 99%) as colorless syrup; $[\alpha]_D^{25}$ +71.11, (c = 0.58, $CHCl_3$).

FTIR (neat), ν_{max}, cm^{-1}: 1755, 1370, 1228

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.21 (d, *J* = 3.6 Hz, 1H, H-1), 5.42 (t, *J* = 9.8 Hz, 1H, H-2), 4.99 (m, 2H, H-3,4), 3.89 (dd, *J* = 5.6, 11.2 Hz, 1H, H-5), 3.67 (dd, *J* = 11.2, 11.2, 1H, H-5), 2.13 (s, 3H, $OCOCH_3$), 2.00 (s, 3H, $OCOCH_3$), 2.00 (s, 3H, $OCOCH_3$), 1.98 (s, 3H, $OCOCH_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.0, 169.7, 169.6, 168.9 ($O\underline{C}OCH_3$), 89.2 (C-1), 69.3 (C-2), 69.3 (C-3), 68.6 (C-4), 60.6 (C-5), 20.8, 20.6, 20.6, 20.4 ($OCO\underline{C}H_3$)

Thiophenyl-2,3,4-*O*-triacetyl-D-xylopyranoside (488)

(487) (488)

A solution of 1,2,3,4-*O*-tetraacetyl-D-xylopyranoside (487) (3.0 g, 9.43 mmol) in dry dichloromethane (50 mL) was cooled to 0 °C. Thiophenol (1.12 mL, 11.3 mmol) was added followed by the addition of $SnCl_4$ (0.77 mL, 6.60 mmol). The reaction solution was stirred at room temperature for 4 hours until the starting material disappeared on TLC. Saturated aqueous $NaHCO_3$ was added. The organic layer was separated and the water layer was extracted with CH_2Cl_2 three times. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4.

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The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (EtOAc/hexane, 1:4) to afford thiophenyl-2,3,4-*O*-triacetyl-D-xylopyranoside (488) (2.1 g, 60%) as pale yellow syrup; $[\alpha]_D^{25}$ -38.33, (c = 0.96, $CHCl_3$).

FTIR (neat), ν_{max}, cm^{-1}: 1767, 1756, 1748, 1583, 1372, 1248, 1070

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.40 (m, 2H, Ar(H)), 7.22 (m, 3H, Ar(H)), 5.11 (dd, *J* = 8.2, 8.2 Hz, 1H, H-3), 4.87 (dd, *J* = 8.2, 8.2 Hz, 1H, H-2), 4.85 (td, *J* = 8.5, 4.9 Hz, 1H, H-4), 4.74 (d, *J* = 8.4 Hz, 1H, H-1), 4.20 (dd, *J* = 11.8, 4.9 Hz, 1H, H-5), 3.35 (dd, *J* = 11.8, 8.7 Hz, 1H, H-5), 2.01 (s, 3H, $OCOCH_3$), 1.97 (s, 3H, $OCOCH_3$), 1.96 (s, 3H, $OCOCH_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 169.7, 169.6, 169.2 ($O\underline{C}OCH_3$), 132.6×2 (CH-Ar), 132.1 (C-Ar), 128.9×2 (CH-Ar), 128.1 (CH-Ar), 86.1 (C-1), 70.9 (C-3), 69.7 (C-2), 68.3 (C-4), 65.1 (C-5), 20.65, 20.59, 20.57 ($OCO\underline{C}H_3$)

1-Thiophenyl-D-xylopyranoside (489)

(488) (489)

Method I

Thiophenyl-2,3,4-*O*-triacetyl-D-xylopyranoside (488) (1.13 g, 3.07 mmol) was dissolved in methanol (15 mL) followed by the addition of sodium methoxide (10 mg, 0.15 mmol). The reaction mixture was stirred at room temperature for 12 hours then saturated aqueous NH_4Cl was added. The organic layer was separated and the water layer was extracted with EtOAc three times. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced

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pressure and the crude product was purified by flash column chromatography (100%EtOAc) to give 1-thiophenyl-D-xylopyranoside (489) (393 mg, 53%) as a white solid.

Method II

Thiophenyl-2,3,4-*O*-triacetyl-D-xylopyranoside (488) (3.56 g, 9.66 mmol) was dissolved in methanol (44 mL) followed by the addition of sodium methoxide (31 mg, 0.48 mmol). The reaction mixture was stirred at room temperature for 12 hours. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (100%EtOAc) to give 1-thiophenyl-α/β-D-xylopyranoside (489) (α/β, 5:3) (1.90 g, 81%) as a white solid. $[\alpha]_D^{25}$ +55.30, (c = 1.02, $CHCl_3$).

FTIR (KBr), ν_{max}, cm^{-1}: 3391, 1047

^{1}H NMR ($(CD_3)_2CO$, 400 MHz) δ: 7.49 (m, 4H, Ar(H)), 7.27 (m, 6H, Ar(H)), 5.52 (d, *J* = 4.3 Hz, 1H, H-1β), 4.70 (d, *J* = 8.7 Hz, 1H, H-1α), 4.54 (brm, 4H, O-H), 4.46 (brm, 1H, O-H), 4.38 (brm, 1H, O-H), 3.97 (dd, *J* = 4.8, 11.3 Hz, 1H, H-5α), 3.93 (dd, *J* = 8.4, 11.4 Hz, 1H, H-5β), 3.82 (m, 1H, H-2α), 3.73 (dd, *J* = 4.6, 11.5 Hz, 1H, H-5β), 3.68 (td, *J* = 7.8, 3.2 Hz, 1H, H-3β), 3.60 (m, 1H, H-4β), 3.54 (m, 1H, H-4α), 3.49 (td, *J* = 8.0, 3.3 Hz, 1H, H-3α), 3.34 (dd, *J* = 5.0, 8.3 Hz, 1H, H-2α), 3.30 (dd, *J* = 9.3, 11.4 Hz, 1H, H-5α)

^{13}C NMR ($(CD_3)_2CO$, 100 MHz) δ: 136.5 (C-Ar(β)), 135.3 (C-Ar(α)), 132.0×2 (CH-Ar(α)), 131.5×2 (CH-Ar(β)), 129.6×2 (CH-Ar(β)), 129.5×2 (CH-Ar(α)), 127.8 (CH-Ar(α)), 127.4 (CH-Ar(β)), 89.6 (C-1β), 89.2 (C-1α), 78.3 (C-3α), 74.4 (C-3β), 73.3 (C-2α), 73.0 (C-2β), 70.6 (C-4β), 70.5 (C-4α), 69.4 (C-5α), 64.9 (C-5β)

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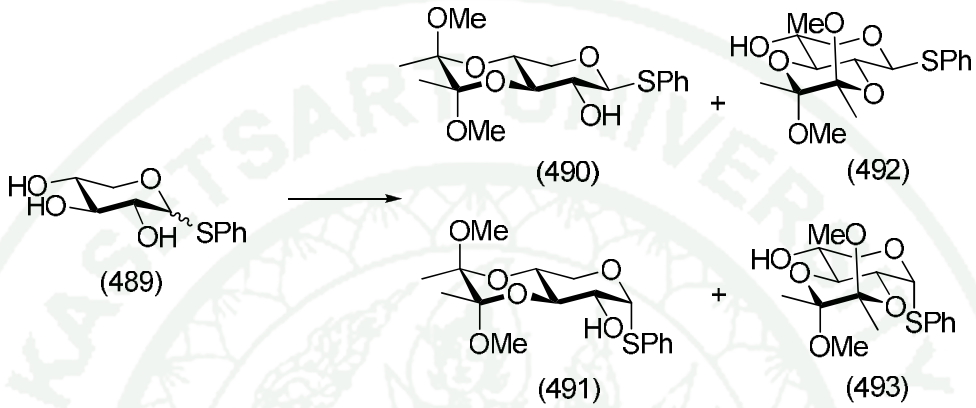
Thiophenyl-(2'S,3'S)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-α-D-xylopyranoside (490)



Method I

BF_3•OEt_2 (8 µl, 0.059 mmol) was added to a solution of 1-thiophenyl-α/β-D-xylopyranoside (489) (132 mg, 0.54 mmol), butane-2,3-dione (49.5 µl, 0.60 mmol) and triethyl orthoformate (0.30 mL, 1.79 mmol), in methanol (16.5 mL). The mixture was stirred at room temperature for 17 hours and then neutralized by the addition of triethylamine. The reaction was concentrated under reduced pressure and purified by flash column chromatography (EtOAc/hexane, 1:4) to yield thiophenyl-(2'S,3'S)-methyl-3,4-*O*-(2',3'-dimethoxy butane-2',3'-diyl)-α-D-xylopyranoside (490) (44 mg, 23%) as a colorless syrup; $[\alpha]_D^{25}$ +114.42, (c = 0.24, $CHCl_3$), thiophenyl-(2'S,3'S)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-β-D-xylopyranoside (491) (22 mg, 11 %) as a colorless syrup; $[\alpha]_D^{25}$ +370.09, (c = 0.79, $CHCl_3$), thiophenyl-(2'S,3'S)-methyl-2,3-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-α-D-xylopyranoside (492) (11 mg, 6%) as a white solid; m.p. 158-160 °C; $[\alpha]_D^{25}$ -125.76, (c = 0.66, $CHCl_3$) and thiophenyl-(2'S,3'S)-methyl-2,3-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-β-D-xylopyranoside (493) (5 mg, 3%) as a white solid; m.p. 161-163 °C; $[\alpha]_D^{25}$ +67.03, (c = 0.78, $CHCl_3$).

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Method II

BF_3•OEt_2 (1.9 mL, 14.85 mmol) was added to a solution of 1-thiophenyl-α/β-D-xylopyranoside (489) (1.80 g, 7.42 mmol), butane-2,3-dione (0.7 mL, 8.17 mmol) and trimethyl orthoformate (2.7 mL, 24.52 mmol), in methanol (225 mL). The mixture was stirred at room temperature for 12 hours and then neutralized by the addition of triethylamine. The reaction was concentrated under reduced pressure and purified by flash column chromatography (EtOAc/hexane, 1:4) to yield thiophenyl-(2'S,3'S)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-α-D-xylopyranoside (490) (1.98 g, 75%).

Thiophenyl-(2'S,3'S)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-α-D-xylopyranoside (490)

FTIR (neat), ν_{max}, cm^{-1}: 3479, 1584, 1131

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.49 (m, 2H, Ar(H)), 7.26 (m, 3H, Ar(H)), 4.42 (d, *J* = 9.3 Hz, 1H, H-1), 3.92 (dd, *J* = 4.6, 10.8 Hz, 1H, H-5), 3.67 (ddd, *J* = 9.8, 9.8, 4.6 Hz, 1H, H-4), 3.62 (dd, *J* = 10.1, 10.1 Hz, 1H, H-3), 3.43 (ddd, *J* = 9.0, 9.0, 1.9 Hz, 1H, H-2), 3.39 (dd, *J* = 10.5, 10.5 Hz, 1H, H-5), 3.25 (s, 3H, OCH_3), 3.19 (s, 3H, OCH_3), 2.46 (brs, 1H, OH), 1.28 (s, 3H, CCH_3), 1.23 (s, 3H, CCH_3)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 133.4×2 (CH-Ar), 131.2 (C-Ar), 129.0×2 (CH-Ar), 128.4 (CH-Ar), 99.9 ($\underline{C}CH_3$), 99.5 ($\underline{C}CH_3$), 89.3 (C-1), 74.0 (C-3), 69.2 (C-2), 68.0 (C-5), 65.5 (C-4), 48.0 (OCH_3), 47.9 (OCH_3), 17.7 ($C\underline{C}H_3$), 17.5 ($C\underline{C}H_3$)

HRMS (ESI^+) *m/z*: $C_{17}H_{24}O_6SNa$ $[M+Na]^+$, calcd 379.1191, found 379.1191

Thiophenyl-(2'S,3'S)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-β-D-xylopyranoside (491)

FTIR (neat), ν_{max}, cm^{-1}: 3466, 1584, 1142

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^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.47-7.50 (m, 2H, Ar(H)), 7.23-7.31 (m, 3H, Ar(H)), 5.58 (d, *J* = 5.4 Hz, 1H, H-1), 4.13 (dd, *J* = 10.4, 10.4 Hz, 1H, H-5), 4.02 (dd, *J* = 5.7, 8.8 Hz, 1H, H-2), 3.77 (ddd, *J* = 4.9, 9.7, 9.8 Hz, 1H, H-4), 3.72 (dd, *J* = 9.4, 9.4 Hz, 1H, H-3), 3.68 (dd, *J* = 4.9, 11.0 Hz, 1H, H-5), 3.31 (s, 3H, OCH_3), 3.26 (s, 3H, OCH_3), 2.49 (brs, 1H, OH), 1.34 (s, 3H, CCH_3), 1.30 (s, 3H, CCH_3)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 134.1 (C-Ar), 131.9×2 (CH-Ar), 129.0×2 (CH-Ar), 127.5 (CH-Ar), 100.0 ($\underline{C}CH_3$), 99.6 ($\underline{C}CH_3$), 91.3 (C-1), 71.5 (C-3), 69.6 (C-2), 66.1 (C-4), 61.0 (C-5), 48.0 (OCH_3), 47.9 (OCH_3), 17.7 ($C\underline{C}H_3$), 17.6 ($C\underline{C}H_3$)

MS (ESI^+), *m/z* (relative intensity): 379.2 ($[M+Na]^+$, 100 %)

Thiophenyl-(2'S,3'S)-methyl-2,3-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-α-D-xylopyranoside (492)

FTIR (neat), ν_{max}, cm^{-1}: 3472, 1584, 1137

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.47-7.50 (m, 2H, Ar(H)), 7.20-7.28 (m, 3H, Ar(H)), 4.73 (d, *J* = 9.7 Hz, 1H, H-1), 4.07 (dd, *J* = 11.4, 5.3 Hz, 1H, H-5), 3.86 (ddd, *J* = 5.4, 9.5, 9.5 Hz, 1H, H-4), 3.66 (dd, *J* = 9.4, 9.4 Hz, 1H, H-3), 3.57 (dd, *J* = 9.7, 9.7 Hz, 1H, H-2), 3.28 (dd, *J* = 10.0, 11.4 Hz, 1H, H-5), 3.27 (s, 3H, OCH_3), 3.19 (s, 3H, OCH_3), 1.32 (s, 3H, CCH_3), 1.31 (s, 3H, CCH_3)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 133.2 (C-Ar), 131.7×2 (CH-Ar), 128.8×2 (CH-Ar), 127.4 (CH-Ar), 100.1 ($\underline{C}CH_3$), 99.6 ($\underline{C}CH_3$), 85.9 (C-1), 74.8 (C-3), 69.6 (C-5), 67.9 (C-2), 67.1 (C-4), 48.1 (OCH_3), 47.9 (OCH_3), 17.6 ($C\underline{C}H_3$), 17.5 ($C\underline{C}H_3$)

MS (ESI^+), *m/z* (relative intensity): 379.1 ($[M+Na]^+$, 100 %)

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Thiophenyl-(2'S,3'S)-methyl-2,3-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-β-D-xylopyranoside (493)

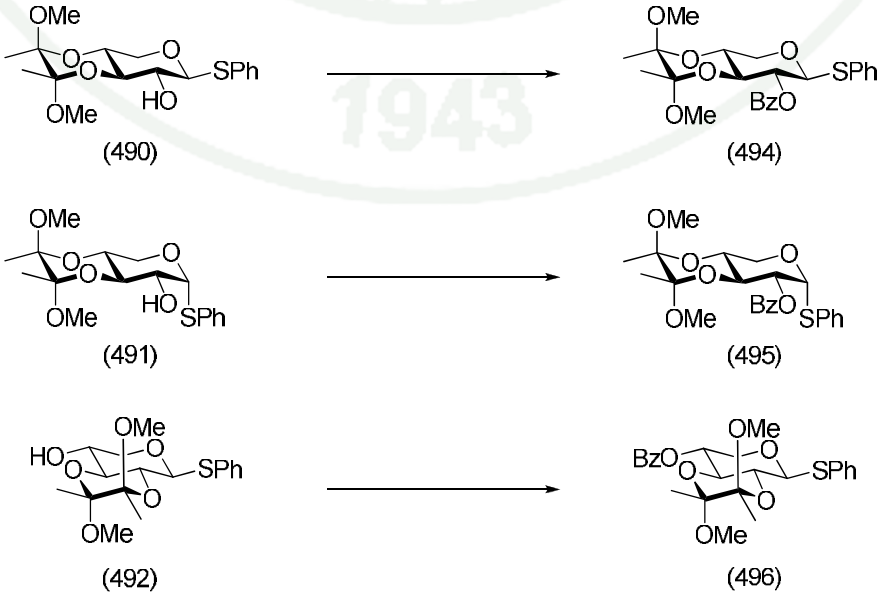
FTIR (neat), ν_{max}, cm^{-1}: 3470, 1584, 1138

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.47-7.50 (m, 2H, Ar(H)), 7.20-7.30 (m, 3H, Ar(H)), 5.53 (d, *J* = 5.3 Hz, 1H, H-1), 4.00-4.08 (m, 1H, H-4), 4.01 (dd, *J* = 5.3, 10.3 Hz, 1H, H-5), 3.88 (dd, *J* = 9.3, 9.3 Hz, 1H, H-2), 3.87 (dd, *J* = 2.6, 7.5 Hz, 1H, H-3), 3.78 (dd, *J* = 5.0, 11.0 Hz, 1H, H-5), 3.32 (s, 3H, OCH_3), 3.27 (s, 3H, OCH_3), 2.60 (brs, 1H, OH), 1.35 (s, 3H, CCH_3), 1.33 (s, 3H, CCH_3)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 134.3 (C-Ar), 131.0×2 (CH-Ar), 128.8×2 (CH-Ar), 126.9 (CH-Ar), 100.0 ($\underline{C}CH_3$), 99.4 ($\underline{C}CH_3$), 85.7 (C-1), 71.0 (C-2), 67.8 (C-4), 67.7 (C-3), 62.4 (C-5), 48.0 (OCH_3), 47.9 (OCH_3), 17.6×2 ($C\underline{C}H_3$)

MS (ESI^+), *m/z* (relative intensity): 379.4 ($[M+Na]^+$, 100 %)

To investigate the position of trans-diequatorial 1,2-diols protection, compound **490**, **491**, **492** and **493** were benzoylated



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(493) (497)

General procedure

To a solution of thiophenyl-(2'S,3'S)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-α-D-xylopyranoside (490) (30 mg, 0.084 mmol), and triethylamine (0.018 mL, 0.13 mmol) in dichloromethane (2 mL) was added benzoyl chloride (0.015 mL, 0.11 mmol) and DMAP (1 mg, 0.0042 mmol). The reaction was stirred at 25 °C for 5 hours. The reaction was quenched with saturated aqueous $NaHCO_3$. The organic layer was separated and the water layer was extracted with CH_2Cl_2 three times. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the product was isolated by flash column chromatography (EtOAc/hexane, 1:9) to afford thiophenyl-2-*O*-benzoyl-(2'S,3'S)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-α-D-xylopyranoside (494) (36 mg, 92%) as a white solid.

Thiophenyl-2-*O*-benzoyl-(2'S,3'S)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-α-D-xylopyranoside (494)

FTIR (KBr), ν_{max}, cm^{-1}: 1724, 1583, 1263

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.06-8.09 (m, 2H, Ar(H)), 7.56-7.61 (m, 1H, Ar(H)), 7.44-7.48 (m, 4H, Ar(H)), 7.26-7.30 (m, 3H, Ar(H)), 5.22 (dd, *J* = 9.5, 9.5 Hz, 1H, H-2), 4.76 (d, *J* = 9.6 Hz, 1H, H-1), 4.04 (dd, *J* = 4.6, 10.8 Hz, 1H, H-5), 3.94 (dd, *J* = 9.5, 9.5 Hz, 1H, H-3), 3.90 (ddd, *J* = 9.9, 9.9, 4.8 Hz, 1H, H-4), 3.50 (dd, *J* = 10.5, 10.5 Hz, 1H, H-5), 3.26 (s, 3H, OCH_3), 3.18 (s, 3H, OCH_3), 1.27 (s, 3H, CCH_3), 1.22 (s, 3H, CCH_3)

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^{13}C NMR ($CDCl_3$, 100 MHz) δ: 164.8 (C=O), 133.1 (CH-Ar), 132.8×2 (CH-Ar), 132.5 (C-Ar), 129.9 (C-Ar), 129.8×2 (CH-Ar), 128.9×2 (CH-Ar), 128.4×2 (CH-Ar), 128.0 (CH-Ar), 100.0 ($\underline{C}CH_3$), 99.6 ($\underline{C}CH_3$), 85.7 (C-1), 72.4 (C-2), 69.9 (C-3), 67.8 (C-5), 65.8 (C-4), 48.0 (OCH_3), 47.7 (OCH_3), 17.6 ($C\underline{C}H_3$), 17.5 ($C\underline{C}H_3$)

MS (ESI^+), *m/z* (relative intensity): 483.3 ($[M+Na]^+$, 10 %), 475.5 (100)

Thiophenyl-2-*O*-benzoyl-(2'S,3'S)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-β-D-xylopyranoside (495)

FTIR (neat), ν_{max}, cm^{-1}: 1725, 1599, 1272

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.07-8.10 (m, 2H, Ar(H)), 7.57-7.61 (m, 1H, Ar(H)), 7.45-7.49 (m, 2H, Ar(H)), 7.38-7.41 (m, 2H, Ar(H)), 7.21-7.27 (m, 3H, Ar(H)), 6.04 (d, *J* = 5.6 Hz, 1H, H-1), 5.29 (dd, *J* = 5.6, 10.7 Hz, 1H, H-2), 4.25 (dd, *J* = 10.1, 10.1 Hz, 1H, H-5), 4.21 (dd, *J* = 10.2, 10.2 Hz, 1H, H-3), 3.96 (ddd, *J* = 5.1, 9.8, 10.9 Hz, 1H, H-4), 3.72 (dd, *J* = 5.1, 10.8 Hz, 1H, H-5), 3.40 (s, 3H, OCH_3), 3.30 (s, 3H, OCH_3), 1.35 (s, 3H, CCH_3), 1.32 (s, 3H, CCH_3)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 165.5 (C=O), 133.5 (C-Ar), 133.2 (CH-Ar), 131.8×2 (CH-Ar), 129.8×2 (CH-Ar), 129.7 (C-Ar), 128.9×2 (CH-Ar), 128.4×2 (CH-Ar), 127.3 (CH-Ar), 100.0 ($\underline{C}CH_3$), 99.6 ($\underline{C}CH_3$), 86.8 (C-1), 70.9 (C-2), 68.3 (C-3), 66.4 (C-4), 60.3 (C-5), 48.0 (OCH_3), 47.8 (OCH_3), 17.6 ($C\underline{C}H_3$), 17.5 ($C\underline{C}H_3$)

MS (ESI^+), *m/z* (relative intensity): 484.0 ($[M+Na]^+$, 100 %)

Thiophenyl-(2'S,3'S)-methyl-2,3-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-4-*O*-benzoyl-α-D-xylopyranoside (496)

FTIR (neat), ν_{max}, cm^{-1}: 1685, 1453, 1326, 1292, 1179, 1128, 1073

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^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.11-8.13 (m, 2H, Ar(H)), 7.99-8.01 (m, 2H, Ar(H)), 7.42-7.64 (m, 5H, Ar(H)), 7.25-7.32 (m, 1H, Ar(H)), 5.22 (ddd, *J* = 5.4, 9.2, 9.2 Hz, 1H, H-4), 4.85 (d, *J* = 9.7 Hz, 1H, H-1), 4.37 (dd, *J* = 5.4, 11.6 Hz, 1H, H-5), 4.10 (dd, *J* = 9.6, 9.6 Hz, 1H, H-3), 3.78 (dd, *J* = 9.7, 9.7 Hz, 1H, H-2), 3.42 (dd, *J* = 8.9, 11.6 Hz, 1H, H-5), 3.32 (s, 3H, OCH_3), 3.23 (s, 3H, OCH_3), 1.35 (s, 3H, CCH_3), 1.28 (s, 3H, CCH_3)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 165.5 (C=O), 133.8 (C-Ar), 133.2 (CH-Ar), 131.9 (CH-Ar), 130.2×2 (CH-Ar), 129.7 (C-Ar), 129.6×2 (CH-Ar), 128.9 (CH-Ar), 128.5 (CH-Ar), 128.4 (CH-Ar), 127.5 (CH-Ar), 100.3 ($\underline{C}CH_3$), 99.7 ($\underline{C}CH_3$), 86.0 (C-1), 71.5 (C-4), 69.3 (C-3), 68.2 (C-2), 67.0 (C-5), 48.2 (OCH_3), 47.8 (OCH_3), 17.6 ($C\underline{C}H_3$), 17.5 ($C\underline{C}H_3$)

MS (ESI^+), *m/z* (relative intensity): 483.3 ($[M+Na]^+$, 100 %)

Thiophenyl-(2'S,3'S)-methyl-2,3-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-4-*O*-benzoyl-β-D-xylopyranoside (497)

FTIR (neat), ν_{max}, cm^{-1}: 1694, 1455, 1326, 1291, 1157, 1072

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.43-7.52 (m, 5H, Ar(H)), 7.21-7.31 (m, 5H, Ar(H)), 5.60 (d, *J* = 4.7 Hz, 1H, H-1), 5.21 (ddd, *J* = 5.9, 9.6, 9.6 Hz, 1H, H-4), 4.23 (dd, *J* = 10.1, 10.1 Hz, 1H, H-3), 4.19 (dd, *J* = 5.1, 10.2 Hz, 1H, H-2), 4.13 (dd, *J* = 10.8, 10.8 Hz, 1H, H-5), 4.05 (dd, *J* = 6.0, 11.2 Hz, 1H, H-5), 3.30 (s, 3H, OCH_3), 3.22 (s, 3H, OCH_3), 1.29 (s, 3H, CCH_3), 1.21 (s, 3H, CCH_3)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 165.6 (C=O), 134.1 (C-Ar), 133.2 (CH-Ar), 131.9 (C-Ar), 131.1×2 (CH-Ar), 129.7×2 (CH-Ar), 128.9×2 (CH-Ar), 128.4×2 (CH-Ar), 127.1 (CH-Ar), 100.1 ($\underline{C}CH_3$), 99.6 ($\underline{C}CH_3$), 85.6 (C-1), 69.4 (C-4), 68.1 (C-3), 67.8 (C-2), 59.9 (C-5), 48.1 (OCH_3), 47.8 (OCH_3), 17.6×2 ($C\underline{C}H_3$)

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MS (ESI^+), *m/z* (relative intensity): 483.1 ($[M+Na]^+$, 95 %), 481.3 (100)

Thiophenyl-2-*O*-methoxybenzoyl-(2'S,3'S)-methyl-3,4-*O*-(2',3'-dimethoxy-butane-2',3'-diyl)-α-D-xylopyranoside (498)

(490) (498)

To a solution of 2-methoxybenzoic acid (38 mg, 0.25 mmol) and *N,N*-dimethylaminopyridine (DMAP) (5 mg, 0.042 mmol) in dichloromethane (2.45 mL) was added a solution of thiophenyl-(2'S,3'S)-methyl-3,4-*O*-(2',3'-dimethoxy butane-2',3'-diyl)-α-D-xylopyranoside (490) (60 mg, 0.17 mmol) in dichloromethane (3.6 mL) at room temperature. After the reaction was stirred for 5 minutes, the solution of *N,N*-dicyclohexylcarbodiimide (DCC) (52 mg, 0.25 mmol) in dichloromethane (1.5 mL) was introduced. The reaction was stirred at room temperature for 12 hours and then filtered and rinsed successively with CH_2Cl_2. The combined CH_2Cl_2 was extracted with saturated aqueous NH_4Cl. The combined organic layers were dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (EtOAc/hexane, 1:9) to give thiophenyl-2-*O*-methoxybenzoyl-(2'S,3'S)-methyl-3,4-*O*-(2',3'-dimethoxy-butane-2',3'-diyl)-α-D-xylopyranoside (498) as a pale yellow syrup (77 mg, 93%); $[\alpha]_D^{25}$ +145.17, (c = 1.52, $CHCl_3$).

FTIR (neat), ν_{max}, cm^{-1}: 1724, 1605, 1258

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.95 (d, *J* = 9.0 Hz, 2H, Ar(H)), 7.38 (m, 2H, Ar(H)), 7.20 (m, 3H, Ar(H)), 6.86 (d, *J* = 9.0 Hz, 2H, Ar(H)), 5.12 (dd, *J* = 9.6, 9.6 Hz, 1H, H-2), 4.68 (d, *J* = 9.6 Hz, 1H, H-1), 3.96 (dd, *J* = 4.6, 10.8 Hz, 1H, H-5), 3.84 (dd, *J* = 9.7, 9.7 Hz, 1H, H-3), 3.82 (ddd, *J* = 8.1, 8.1, 4.2 Hz, 1H, H-4), 3.42 (dd, *J* =

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10.5, 10.5 Hz, 1H, H-5), 3.79 (s, 3H, $ArOCH_3$), 3.18 (s, 3H, OCH_3), 3.10 (s, 3H, OCH_3), 1.20 (s, 3H, CCH_3), 1.15 (s, 3H, CCH_3)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 164.6 (C=O), 163.5 (C-Ar), 132.7×2 (CH-Ar), 132.6 (C-Ar), 131.8 (CH-Ar), 128.8×2 (CH-Ar), 127.9×2 (CH-Ar), 122.2 (C-Ar), 113.7×2 (CH-Ar), 99.9 ($\underline{C}CH_3$), 99.5 ($\underline{C}CH_3$), 87.6 (C-1), 72.4 (C-3), 69.6 (C-2), 67.8 (C-5), 65.8 (C-4), 55.4 ($ArOCH_3$), 47.9 (OCH_3), 47.6 (OCH_3), 17.6 ($C\underline{C}H_3$), 17.5 ($C\underline{C}H_3$)

HRMS (ESI^+) *m/z*: $C_{25}H_{30}O_8SNa$ $[M+Na]^+$, calcd 513.1559, found 513.1557

2-*O*-Methoxybenzoyl-(2'S,3'S)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-α/β-D-xylopyranoside (499)

(498) (499)

To a solution of thiophenyl-2-*O*-methoxybenzoyl-(2'S,3'S)-methyl-3,4-*O*-(2',3'-dimethoxy-butane-2',3'-diyl)-α-D-xylopyranoside (498) (39 mg, 0.080 mmol) in dichloromethane (1.8 mL) and water (0.2 mL) was added NBS (16 mg, 0.087 mmol) in one portion. After the reaction was stirred at 25 °C for 1 hour, saturated aqueous Na_2SO_3 was added. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (EtOAc/hexane, 3:7) to give 2-*O*-methoxybenzoyl-(2'S,3'S)-methyl-3,4-*O*-(2',3'-dimethoxy-butane-2',3'-diyl)-α/β-D-xylopyranoside (499) as a colorless oil (25 mg, 79%); $[\alpha]_D^{25}$ +194.93, (c = 0.49, $CHCl_3$).

FTIR (neat), ν_{max}, cm^{-1}: 3421, 1716, 1606, 1258, 1169, 1131, 1082, 1034

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^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.95 (d, *J* = 9.0 Hz, 2H, Ar(Hβ)), 7.92 (d, *J* = 9.0 Hz, 2H, Ar(Hα)), 6.85 (d, *J* = 9.1 Hz, 2H, Ar(Hβ)), 6.84 (d, *J* = 9.0 Hz, 2H, Ar(Hα)), 6.33 (d, *J* = 3.4 Hz, 1H, H-1β), 5.50 (d, *J* = 3.7 Hz, 1H, H-1α), 4.90 (dd, *J* = 3.7, 10.6 Hz, 1H, H-2β), 4.22 (dd, *J* = 10.0, 10.0 Hz, 1H, H-2α), 3.78-3.99 (m, 6H, H-3α,β, H-4α,β, H-5α,β), 3.79 (s, 3H, $ArOCH_3$), 3.77 (s, 3H, $ArOCH_3$), 3.66 (dd, *J* = 2.5, 5.3 Hz, 1H, H-5β), 3.55 (dd, *J* = 4.6, 9.9 Hz, 1H, H-5α), 3.28 (s, 3H, OCH_3β), 3.27 (s, 3H, OCH_3α), 3.22 (s, 3H, OCH_3β), 3.20 (s, 3H, OCH_3α), 1.28 (s, 3H, CCH_3β), 1.26 (s, 3H, CCH_3β), 1.23 (s, 3H, CCH_3α), 1.20 (s, 3H, CCH_3α)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.8, 165.6 (C=O), 164.9, 163.8 (C-Ar), 132.0×2 (CH-Ar), 131.8×2 (CH-Ar), 121.7, 122.2 (C-Ar), 113.8×2 (CH-Ar), 113.6×2 (CH-Ar), 100.0, 99.7 ($\underline{C}CH_3$), 99.9, 99.6 ($\underline{C}CH_3$), 92.3 (C-1β), 90.9 (C-1α), 71.4 (C-2β), 70.7, 69.1, 66.4, 65.7 (C-3β,α, C-4β,α), 67.1 (C-2α), 62.1 (C-5β), 59.4 (C-5α), 55.4×2 ($ArOCH_3$), 48.1, 48.0 (OCH_3), 47.9, 47.8 (OCH_3), 17.7, 17.4 ($C\underline{C}H_3$), 17.5×2 ($C\underline{C}H_3$)

MS (ESI^+), *m/z* (relative intensity): 421.2 ($[M+Na]^+$, 100 %)

Trichloroacetimidyl-2-*O*-methoxybenzoyl-(2'S,3'S)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-α/β-D-xylopyranoside (500)

2-*O*-Methoxybenzoyl-(2'S,3'S)-methyl-3,4-*O*-(2',3'-dimethoxy-butane-2',3'-diyl)-α/β-D-xylopyranoside (499) (20 mg, 0.05 mmol) was dissolved in dry dichloromethane (2.0 mL). Trichloroacetonitrile (0.025 mL, 0.25 mmol) and DBU (1 drop) were added. The reaction was stirred at 25 °C for 12 hours. The solvent was removed and the product was isolated by silica gel short column chromatography

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(EtOAC/hexane/Et_3N, 15:4:1) to afford trichloroacetimidyl-2-*O*-methoxybenzoyl-(2'S,3'S)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-α/β-D-xylopyranoside (500) as a pale yellow oil (26 mg, 96%).

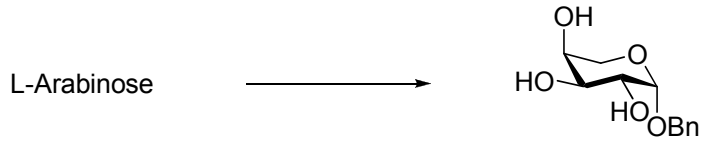
FTIR (neat), ν_{max}, cm^{-1}: 3342, 1720, 1606, 1257, 1169, 1138, 1085, 1030

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.49 (brs, 1H, NHα), 8.45 (brs, 1H, NHβ), 7.99 (d, *J* = 9.0 Hz, 2H, Ar(Hβ)), 7.94 (d, *J* = 9.0 Hz, 2H, Ar(Hα)), 6.91 (d, *J* = 9.0 Hz, 2H, Ar(Hβ)), 6.88 (d, *J* = 9.0 Hz, 2H, Ar(Hα)), 6.76 (d, *J* = 3.8 Hz, 1H, H-1β), 6.61 (d, *J* = 3.7 Hz, 1H, H-1α), 5.26 (dd, *J* = 3.7, 10.6 Hz, 1H, H-2α), 5.18 (dd, *J* = 3.8, 10.6 Hz, 1H, H-2β), 4.36 (dd, *J* = 8.3, 9.6 Hz, 1H, H-3β), 4.33 (dd, *J* = 9.6, 10.4 Hz, 1H, H-3α), 4.01 (dd, *J* = 5.1, 10.9 Hz, 1H, H-4β), 3.98 (dd, *J* = 4.7, 10.8 Hz, 1H, H-4α), 3.92 (dd, *J* = 10.5, 10.5 Hz, 1H, H-5α,β), 3.86 (s, 3H, $ArOCH_3$β), 3.84 (s, 3H, $ArOCH_3$α), 3.82 (dd, *J* = 4.9, 10.3 Hz, 1H, H-5α,β), 3.37 (s, 3H, OCH_3β), 3.32 (s, 3H, OCH_3α), 3.30 (s, 3H, OCH_3β), 3.30 (s, 3H, OCH_3α), 1.34 (s, 3H, CCH_3β), 1.33 (s, 3H, CCH_3β), 1.32 (s, 3H, CCH_3α), 1.28 (s, 3H, CCH_3α)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 165.2 (C=O), 163.6, 160.8 (C-Ar), 131.8×2 (CH-Ar), 131.7×2 (CH-Ar), 121.7 (C-Ar), 113.8×2 (CH-Arβ), 113.6×2 (CH-Arα), 100.0, 99.7 ($\underline{C}CH_3$), 94.1 (C-1), 88.9 (CCl_3), 69.8 (C-4), 67.5 (C-2), 65.8 (C-3), 62.2 (C-5), 55.4 ($ArOCH_3$), 48.1 (OCH_3), 47.6 (OCH_3), 17.7 ($C\underline{C}H_3$), 17.5 ($C\underline{C}H_3$)

MS (ESI^+), *m/z* (relative intensity): 564.0 ($[M+Na]^+$, 100 %)

Benzyl-*β*-L-arabinopyranoside (501)



(54) (501)

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Method I

Benzyl alcohol (50 ml) was saturated with hydrogen chloride for 40 minutes at 0 °C, then L-arabinose (10 g, 0.067 mol) was added and the mixture was stirred at room temperature for 10 h. During this time, benzyl-*β*-L-arabinopyranoside (314) precipitated. EtOAc (75 ml) was slowly added while stirring for additional precipitation. The precipitate was filtered and washed with EtOAc, and dried under vacuum, to give benzyl-*β*-L-arabinopyranoside (501) as a white solid (12 g, 75%); m.p. 171-173 °C; $[\alpha]_D^{20}$ +202.67, (c = 0.20, MeOH).

Method II

Acetyl chloride (3.0 mL, 43.8 mmol) was added dropwise to benzyl alcohol (52.0 mL, 0.52 mol) which was cooled in an ice-water bath with stirring. L-arabinose (10.0 g, 66.6 mmol) was added and the reaction temperature was raised to room temperature. The resulting mixture was vigorously stirred at room temperature for 5 days. Et_2O (200 mL) was then added to precipitate the benzyl glycoside that was filtered and the crude white solid washed with Et_2O (40 mL). Recrystallization from EtOH gave benzyl-*β*-L-arabinopyranoside (501) as white crystals (14.1 g, 88%); m.p. 171-173 °C**.** (Fletcher *et al.*, 1963, m.p. 172-173 °C)

FTIR (KBr), ν_{max}, cm^{-1}: 3421, 1258, 1137, 1076, 1059, 1000

^{1}H NMR (CD_3SOCD_3, 400 MHz) δ: 7.25-7.38 (m, 5H, Ar(H)), 4.74 (d, *J* = 1.6 Hz, 1H, H-1), 4.65 (d, *J* = 12.4 Hz, 1H, OCH_2Ar), 4.60-4.61 (m, 1H, OH-2), 4.54-4.56 (m, 1H, OH-3), 4.50 (d, *J* = 4.0 Hz, 1H, OH-4), 4.44 (d, *J* = 12.4 Hz, 1H, OCH_2Ar), 3.71-3.72 (m, 1H, H-4), 3.67 (d, *J* = 11.9 Hz, 1H, H-5), 3.62-3.63 (m, 2H, H-2, H-3), 3.46 (dd, *J* = 2.9, 11.8 Hz, 1H, H-5)

^{13}C NMR (CD_3SOCD_3, 100 MHz) δ: 138.2 (C-Ar), 128.1×2 (CH-Ar), 127.4×2 (CH-Ar), 127.3 (CH-Ar), 98.9 (C-1), 69.1, 68.6 (C-2, C-3), 68.4 (OCH_2Ar), 68.3 (C-4), 63.3 (C-5)

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HRMS (ESI$^+$) *m/z*: $C_{12}H_{16}O_5Na$ $[M+Na]^+$, calcd 263.0895, found 263.0898

Benzyl-3,4-acetonide-β-L-arabinopyranoside (72)

(501) (72)

To a solution of benzyl-β-L-arabinopyranoside (501) (40 mg, 0.16 mmol) in DMF (0.8 mL) was added 2,2-dimethoxypropane (0.024 mL, 0.20 mmol) and *p*-toluenesulfonic acid (3 mg, 0.016 mmol) at room temperature. The reaction mixture was stirred at room temperature for 5 hours and was quenched with saturated aqueous $NaHCO_3$. The organic layer was separated and the water layer was extracted with CH_2Cl_2 three times. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 3:2) to benzyl-3,4-acetonide-β-L-arabinopyranoside (72) (38 mg, 82%) as a colorless syrup; $[\alpha]_D^{20}$ +271.78, (c = 0.20, $CHCl_3$).

FTIR (neat), ν_{max}, cm^{-1}: 3444, 1245, 1218, 1063

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.20-7.29 (m, 5H, Ar(H)), 4.83 (d, *J* = 3.6 Hz, 1H, H-1), 4.69 and 4.46 (AB, *J* = 11.8 Hz, 2H, OCH_2Ar), 4.10-4.14 (m, 2H, H-3, H-4), 3.90 (dd, *J* = 2.2, 13.2 Hz, 1H, H-5), 3.83 (dd, *J* = 1.0, 13.1 Hz, 1H, H-5), 3.68-3.72 (m, 1H, H-2), 1.44 (s, 3H, $C(C\underline{H}_3)_2$), 1.27 (s, 3H, $C(C\underline{H}_3)_2$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 136.9 (C-Ar), 128.3×2 (CH-Ar), 127.8×3 (CH-Ar), 108.9 ($\underline{C}(CH_3)_2$), 96.9 (C-1), 75.7 (C-3), 72.8 (C-4), 69.8 (C-2), 69.4 (OCH_2Ar), 59.6 (C-5), 27.7 ($C(\underline{C}H_3)_2$), 25.8 ($C(\underline{C}H_3)_2$)

HRMS (ESI$^+$) *m/z*: $C_{15}H_{20}O_5Na$ $[M+Na]^+$, calcd 303.1208, found 303.1210

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Benzyl-2-*O*-acetyl-3,4-acetonide-*β*-L-arabinopyranoside (502)

(72) (502)

Benzyl-3,4-acetonide-*β*-L-arabinopyranoside (72) (20 mg, 0.071 mmol) was dissolved in dichloromethane (1.0 mL). Triethylamine (0.015 mL, 0.11 mmol), acetic anhydride (0.008 mL, 0.085 mmol), and DMAP (1 mg) were added. The reaction mixture was stirred at room temperature for 2 hours then was quenched with saturated aqueous $NaHCO_3$. The organic layer was separated and the water layer was extracted with CH_2Cl_2 three times. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (EtOAc/hexane, 1:4) to give benzyl-2-*O*-acetyl-3,4-acetonide-*β*-L-arabinopyranoside (502) (21 mg, 91%) as pale yellow syrup; $[\alpha]_D^{20}$ +216.50, (c = 0.28, $CHCl_3$)**.**

FTIR (neat), ν_{max}, cm^{-1}: 1753, 1222, 1052

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.25-7.35 (m, 5H, Ar(H)), 4.97 (d, *J* = 3.4 Hz, 1H, H-1), 4.89 (dd, *J* = 3.4, 8.2 Hz, 1H, H-2), 4.71 and 4.48 (AB, *J* = 12.3 Hz, 2H, OCH_2Ar), 4.36 (dd, *J* = 5.6, 8.2 Hz, 1H, H-3), 4.24 (ddd, *J* = 1.9, 1.9, 5.6 Hz, 1H, H-4), 3.94-4.05 (m, 2H, H-5), 2.06 (s, 3H, $OCOCH_3$), 1.52 (s, 3H, $C(C\underline{H}_3)_2$), 1.34 (s, 3H, $C(C\underline{H}_3)_2$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.4 (C=O), 137.1 (C-Ar), 128.4×2 (CH-Ar), 127.9 (CH-Ar), 127.6×2 (CH-Ar), 109.3 ($\underline{C}(CH_3)_2$), 95.2 (C-1), 73.5 (C-4), 72.8 (C-3), 72.2 (C-2), 69.4 (OCH_2Ar), 58.8 (C-5), 27.9 ($C(\underline{C}H_3)_2$), 26.3 ($C(\underline{C}H_3)_2$), 20.9 ($OCO\underline{C}H_3$)

HRMS (ESI^+) *m/z*: $C_{17}H_{22}O_6Na$ $[M+Na]^+$, calcd 345.1314, found 345.1302

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Benzyl-2-*O*-acetyl-*β*-L-arabinopyranoside (73)

(502) (73)

A solution of benzyl-2-*O*-acetyl-3,4-acetonide-*β*-L-arabinopyranoside (502) (312 mg, 0.96 mmol) in 70% aqueous acetic acid (4.68 mL) was stirred at 70 °C for 1 h and then concentrated *in vacuo*, and the traces of acetic acid and water were removed by co-evaporation with toluene several times. The residue was purified by flash column chromatography (EtOAc/hexane, 7:3) to afford benzyl-2-*O*-acetyl-*β*-L-arabinopyranoside (73) (264 mg, 96%) as a colorless syrup, which slowly became a solid; $[\alpha]_D^{20}$ +230.27, (c = 0.20, CH_2Cl_2)**.**

FTIR (neat), ν_{max}, cm^{-1}: 3428, 1732, 1372, 1244, 1059

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.20-7.31 (m, 5H, Ar(H)), 4.99 (d, *J* = 3.7 Hz, 1H, H-1), 4.94 (dd, *J* = 3.7, 9.9 Hz, 1H, H-2), 4.66 and 4.44 (AB, *J* = 12.3 Hz, 2H, OCH_2Ar), 4.01 (dd, *J* = 3.5, 9.9 Hz, 1H, H-3), 3.93-3.94 (m, 1H, H-4), 3.85 (dd, *J* = 1.4, 12.6 Hz, 1H, H-5), 3.68 (dd, *J* = 2.0, 12.6 Hz, 1H, H-5), 2.03 (s, 3H, $OCOCH_3$), 2.95 (brs, 2H, OH)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.4 (C=O), 137.1 (C-Ar), 128.4×2 (CH-Ar), 127.9 (CH-Ar), 127.6×2 (CH-Ar), 95.2 (C-1), 73.5 (C-4), 72.8 (C-3), 72.2 (C-2), 69.4 (OCH_2Ar), 58.8 (C-5), 20.87 ($OCO\underline{C}H_3$)

HRMS (ESI^+) *m/z*: $C_{14}H_{18}O_6Na$ $[M+Na]^+$, calcd 305.1001, found 305.1005

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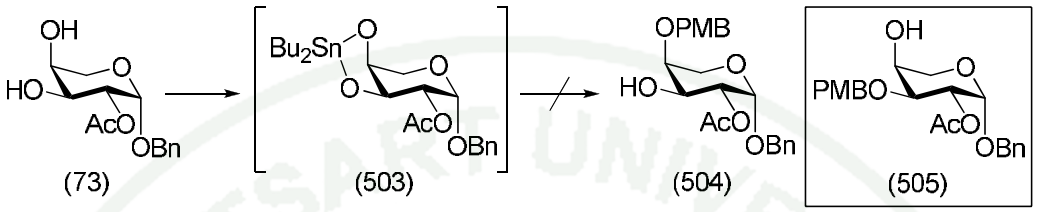
Benzyl 2-*O*-acetyl-4-*O*-paramethoxybenzyl-*β*-L-arabinopyranoside (504)



A mixture of benzyl-2-*O*-acetyl-*β*-L-arabinopyranoside (73) (50 mg, 0.18 mmol) and Bu_2SnO (45 mg, 0.18 mmol) in toluene (0.66 mL) was refluxed for 2 h. The reaction mixture was concentrated under reduced pressure. To the residue were added DMF (0.33 mL), CsF (50 mg, 0.33 mmol), KI (40 mg, 0.26 mmol) and PMBCl (0.03 mL, 0.21 mmol) at 0 °C. The mixture was stirred at room temperature overnight and then diluted with CH_2Cl_2. The organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 3:7). Benzyl 2-*O*-acetyl-4-*O*-paramethoxy benzyl-*β*-L-arabinopyranoside (504) was not observed, only benzyl 2-*O*-acetyl-3-*O*-paramethoxybenzyl-*β*-L-arabinopyranoside (505) was obtained as a yellow oil (17 mg, 24%); $[\alpha]_D^{25}$ +111.84, (c = 0.09, $CHCl_3$)**.**

Benzyl 2-*O*-acetyl-3-*O*-paramethoxybenzyl-*β*-L-arabinopyranoside (505)

FTIR (neat), ν_{max}, cm^{-1}: 3435, 1733, 1642, 1660, 1541, 1244, 1063, 1024

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.20-7.30 (m, 5H, Ar(H)), 7.17 (d, *J* = 8.7 Hz, 2H, Ar(H)), 6.81 (d, *J* = 8.7 Hz, 2H, Ar(H)), 5.08 (dd, *J* = 9.8, 3.6 Hz, 1H, H-2), 5.00 (d, *J* = 3.6 Hz, 1H, H-1), 4.65 (d, *J* = 12.3 Hz, 1H, OCH_2Ar), 4.54 (d, *J* = 11.5 Hz, 1H, $OC\underline{H}_2ArOCH_3$), 4.50 (d, *J* = 11.5 Hz, 1H, $OC\underline{H}_2ArOCH_3$), 4.44 (d, *J* = 12.3 Hz, 1H, OCH_2Ar), 3.91-3.92 (m, 1H, H-4), 3.86 (dd, *J* = 9.8, 3.6 Hz, 1H, H-3), 3.74-3.75 (m, 1H, H-5), 3.73 (s, 3H, OCH_3), 3.69-3.72 (m, 1H, H-5), 2.52 (s, 1H, OH), 1.99 (s, 3H, $OCOCH_3$)

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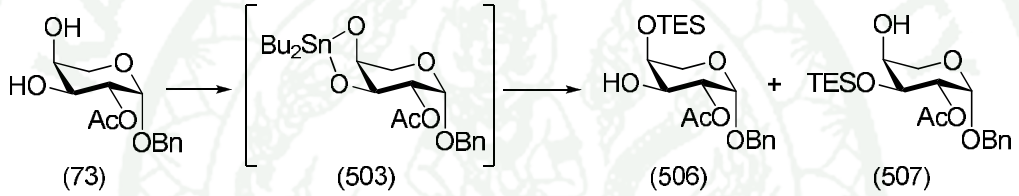
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.3 (C=O), 159.5 (C-Ar), 137.3×2 (C-Ar), 129.2×2 (CH-Ar), 128.4×2 (CH-Ar), 127.9 (CH-Ar), 127.7×2 (CH-Ar), 113.9×2 (CH-Ar), 95.9 (C-1), 74.6 (C-3), 72.1 ($O\underline{C}H_2ArOCH_3$), 70.2 (C-2), 69.4 (OCH_2Ar), 67.3 (C-4), 61.8 (C-5), 55.3 (OCH_3), 20.9 ($OCO\underline{C}H_3$)

HRMS (ESI^+) *m/z*: $C_{22}H_{26}O_7Na$ $[M+Na]^+$, calcd 425.1576, found 425.1574

Benzyl 2-*O*-acetyl-4-*O*-triethylsilyloxy-*β*-L-arabinopyranoside (506)



Method I

A mixture of benzyl-2-*O*-acetyl-*β*-L-arabinopyranoside (73) (50 mg, 0.18 mmol) and Bu_2SnO (45 mg, 0.18 mmol) in toluene (0.66 mL) was refluxed for 2 h. The reaction mixture was concentrated under reduced pressure. To the residue were added TESCl (0.036 mL, 0.21 mmol) and triethylamine (0.5 mL) at room temperature. The mixture was stirred at room temperature overnight and then diluted with CH_2Cl_2. The organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 3:17) to give benzyl 2-*O*-acetyl-4-*O*-triethylsilyloxy-*β*-L-arabinopyranoside (506) as a colorless oil (42 mg, 60%); $[\alpha]_D^{25}$ +108.33, (c = 0.25, $CHCl_3$) and benzyl 2-*O*-acetyl-3-*O*-triethylsilyloxy-*β*-L-arabinopyranoside (507) as a colorless oil (16 mg, 23%); $[\alpha]_D^{25}$ +123.65, (c = 0.12, $CHCl_3$).

Method II

A mixture of benzyl-2-*O*-acetyl-*β*-L-arabinopyranoside (654) (50 mg, 0.18 mmol) and Bu_2SnO (45 mg, 0.18 mmol) in toluene (0.66 mL) was refluxed for 2 h.

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The reaction mixture was concentrated under reduced pressure. The residue was dissolved in dichloromethane (1.0 mL) and then TESCl (0.036 mL, 0.21 mmol) and triethylamine (0.5 mL) were added at room temperature. The mixture was stirred at room temperature overnight and then diluted with CH_2Cl_2. The organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 3:17) to give benzyl 2-*O*-acetyl-4-*O*-triethylsilyloxy-*β*-L-arabinopyranoside (506) as a colorless oil (44 mg, 63%) and benzyl 2-*O*-acetyl-3-*O*-triethylsilyloxy-*β*-L-arabinopyranoside (507) as a colorless oil (2 mg, 23%).

Benzyl 2-*O*-acetyl-4-*O*-triethylsilyloxy-*β*-L-arabinopyranoside (506)

FTIR (neat), ν_{max}, cm^{-1}: 3418, 1732, 1372, 1242, 1141, 1063, 1015

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.20-7.29 (m, 5H, Ar(H)), 4.99 (d, *J* = 3.6 Hz, 1H, H-1), 4.90 (dd, *J* = 9.5, 3.5 Hz, 1H, H-2), 4.66 (d, *J* = 12.4 Hz, 1H, OCH_2Ar), 4.43 (d, *J* = 12.5 Hz, 1H, OCH_2Ar), 4.10 (dd, *J* = 9.5, 3.6 Hz, 1H, H-3), 3.77-3.80 (m, 2H, H-4, H-5), 3.71 (dd, *J* = 2.4, 12.8 Hz, 1H, H-5), 2.67 (brs, 1H, OH), 1.98 (s, 3H, $OCOCH_3$), 0.89 (t, *J* = 7.9 Hz, 9H, $(C\underline{H}_3CH_2)_3Si$), 0.57 (q, *J* = 7.9 Hz, 6H, $(CH_3C\underline{H}_2)_3Si$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.2 (C=O), 137.5 (C-Ar), 128.3×2 (CH-Ar), 127.7 (CH-Ar), 127.5×2 (CH-Ar), 95.8 (C-1), 71.4 (C-4), 70.0 (C-2), 69.3 (OCH_2Ar), 68.2 (C-3), 61.5 (C-5), 20.8 ($OCO\underline{C}H_3$), 6.6×3 ($(\underline{C}H_3CH_2)_3Si$), 4.8×3, 4.7 ($(CH_3\underline{C}H_2)_3Si$)

HRMS (ESI^+) *m/z*: $C_{20}H_{32}O_6SiNa$ $[M+Na]^+$, calcd 419.1866, found 419.1863

Benzyl 2-*O*-acetyl-3-*O*-triethylsilyloxy-*β*-L-arabinopyranoside (507)

FTIR (neat), ν_{max}, cm^{-1}: 3475, 1737, 1455, 1371, 1237, 1145, 1059, 1025

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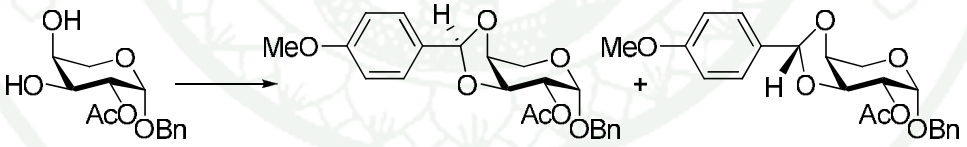
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.20-7.31 (m, 5H, Ar(H)), 4.97 (dd, *J* = 9.2, 3.5 Hz, 1H, H-2), 4.95 (d, *J* = 3.6 Hz, 1H, H-1), 4.66 (d, *J* = 12.3 Hz, 1H, OCH_2Ar), 4.45 (d, *J* = 12.4 Hz, 1H, OCH_2Ar), 3.96-3.98 (m, 1H, H-4), 3.89 (ddd, *J* = 9.6, 9.6, 3.5 Hz, 1H, H-3), 3.79 (dd, *J* = 1.5, 12.5 Hz, 1H, H-5), 3.55 (dd, *J* = 2.5, 12.5 Hz, 1H, H-5), 2.11 (brd, *J* = 10.2 Hz, 1H, OH), 2.03 (s, 3H, $OCOCH_3$), 0.92 (t, *J* = 7.9 Hz, 9H, $(C\underline{H}_3CH_2)_3Si$), 0.59 (q, *J* = 8.0 Hz, 6H, $(CH_3C\underline{H}_2)_3Si$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 171.1 (C=O), 137.4 (C-Ar), 128.4×2 (CH-Ar), 127.8 (CH-Ar), 127.6×2 (CH-Ar), 96.1 (C-1), 71.5 (C-3), 70.6 (C-2), 69.4 (OCH_2Ar), 67.9 (C-4), 63.4 (C-5), 21.0 ($OCO\underline{C}H_3$), 6.7×3 ($(\underline{C}H_3CH_2)_3Si$), 4.9×2, 4.8 ($(CH_3\underline{C}H_2)_3Si$)

MS (ESI^+), *m/z* (relative intensity): 397.2 ($[M+H]^+$, 100 %)

Benzyl 2-*O*-acetyl-exo/endo-3,4-*O*-parametho xybenzylidene-*β*-L-arabinopyranosides (508)



(73) *exo*-(508) *endo*-(508)

Method I

Benzyl-2-*O*-acetyl-*β*-L-arabinopyranoside (73) (50 mg, 0.18 mmol) was suspended in dry dichloromethane (2.0 mL) and *p*-methoxybenzaldehyde (0.032 mL, 0.27 mmol) and pyridinium toluene-4-sulfonate (0.4 mg, 0.0018 mmol) were added. The resulting mixture was heated at reflux for 5 hours. $NaHCO_3$ (0.6 mg) was added and the solvent was evaporated. Then, the residue was extracted with CH_2Cl_2 and the combined organic layer was washed with saturated aqueous $NaHCO_3$, water, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash

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column chromatography (EtOAc/hexane, 7:3) to give only recovered starting material (44 mg, 89%).

Method II

To a solution of benzyl-2-*O*-acetyl-*β*-L-arabinopyranoside (73) (100 mg, 0.35 mmol) in dry dichloromethane (2.0 mL) were added *p*-methoxybenzaldehyde (0.086 mL, 0.71 mmol), trimethylorthoformate (0.078 mL, 0.71 mmol) and *p*-toluenesulfonic acid (7 mg, 0.035 mmol). The reaction mixture was stirred at room temperature for 16 h. Triethylamine was added before concentration and the syrup which was dissolved in CH_2Cl_2 was extracted with saturated aqueous $NaHCO_3$, water, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 1:4) to afford benzyl 2-*O*-acetyl-exo-3,4-*O*-paramethoxybenzylidene-*β*-L-arabinopyranoside (*exo*-508) as a yellow syrup (20 mg, 14%); $[\alpha]_D^{25}$ +144.92, (c = 0.22, $CHCl_3$) and benzyl 2-*O*-acetyl-endo-3,4-*O*-paramethoxybenzylidene-*β*-L-arabinopyranoside (*endo*-508) as a yellow syrup (26 mg, 18%); $[\alpha]_D^{25}$ +247.16, (c = 0.05, $CHCl_3$).

Method III

To a solution of benzyl-2-*O*-acetyl-*β*-L-arabinopyranoside (73) (30 mg, 0.11 mmol) in dry DMF (0.5 mL) were added *p*-methoxybenzaldehyde (0.016 mL, 0.13 mmol), trimethylorthoformate (0.014 mL, 0.13 mmol) and *p*-toluenesulfonic acid (2 mg, 0.011 mmol). The reaction mixture was stirred at room temperature for 16 h. Triethylamine was added before concentration and the syrup which was dissolved in CH_2Cl_2 was extracted with saturated aqueous $NaHCO_3$, water, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 1:4) to afford benzyl 2-*O*-acetyl-exo-3,4-*O*-paramethoxybenzylidene-*β*-L-arabinopyranoside (*exo*-508) as a yellow syrup (8 mg, 18%) and benzyl 2-*O*-acetyl-endo-3,4-*O*-paramethoxybenzylidene-*β*-L-arabinopyranoside (*endo*-508) as a yellow syrup (21 mg, 50%).

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Method IV

To a solution of benzyl-2-*O*-acetyl-*β*-L-arabinopyranoside (73) (50 mg, 0.35 mmol) in dry dichloromethane (1.0 mL) were added *p*-methoxybenzaldehyde (0.04 mL, 0.35 mmol), triethylorthoformate (0.06 mL, 0.35 mmol) and *p*-toluenesulfonic acid (3 mg, 0.018 mmol). The reaction mixture was stirred at room temperature for 16 h. Triethylamine was added before concentration and the syrup which was dissolved in CH_2Cl_2 was extracted with saturated aqueous $NaHCO_3$, water, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 1:4) to afford benzyl 2-*O*-acetyl-exo-3,4-*O*-paramethoxybenzylidene-*β*-L-arabinopyranoside (*exo*-508) as a yellow syrup (48 mg, 34%) and benzyl 2-*O*-acetyl-endo-3,4-*O*-paramethoxybenzylidene-*β*-L-arabinopyranoside (*endo*-508) as a yellow syrup (57 mg, 40%).

Benzyl 2-*O*-acetyl-exo-3,4-*O*-paramethoxybenzylidene-*β*-L-arabinopyranoside (*exo*-508)

FTIR (neat), ν_{max}, cm^{-1}: 1731, 1371, 1248, 1140, 1060, 1017

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.29 (d, *J* = 8.8 Hz, 2H, Ar(H)), 7.21–7.31 (m, 5H, Ar(H)), 6.81 (d, *J* = 8.8 Hz, 2H, Ar(H)), 6.08 (s, 1H, C<u>H</u>ArOCH$_3$), 5.01 (d, *J* = 3.5 Hz, 1H, H-1), 4.99 (dd, *J* = 3.5, 5.3 Hz, 1H, H-2), 4.68 (d, *J* = 12.3 Hz, 1H, OCH_2Ar), 4.60 (dd, *J* = 5.3, 7.9 Hz, 1H, H-3), 4.46 (d, *J* = 12.3 Hz, 1H, OCH_2Ar), 4.19 (dd, *J* = 5.3, 2.0 Hz, 1H, H-4), 4.00 (d, *J* = 13.3 Hz, 1H, H-5), 3.92 (dd, *J* = 13.4, 2.5 Hz, 1H, H-5), 3.72 (s, 3H, $ArOCH_3$), 2.03 (s, 3H, $OCOCH_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.5 (C=O), 160.3 (C-Ar), 137.0 (C-Ar), 130.9 (C-Ar), 128.5×2 (CH-Ar), 128.0 (CH-Ar), 127.6×2 (CH-Ar), 127.5×2 (CH-Ar), 113.8×2 (CH-Ar), 102.8 (<u>C</u>HArOCH$_3$), 95.1 (C-1), 74.1 (C-3), 73.3 (C-4), 69.6 (OCH_2Ar), 69.3 (C-2), 58.9 (C-5), 55.3 ($ArOCH_3$), 20.9 (OCO<u>C</u>H$_3$)

HRMS (ESI^+) *m/z*: $C_{22}H_{24}O_7Na$ $[M+Na]^+$, calcd 423.1420, found 423.1421

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Benzyl 2-*O*-acetyl-endo-3,4-*O*-paramethoxybenzylidene-*β*-L-arabinopyranoside (*endo*-508)

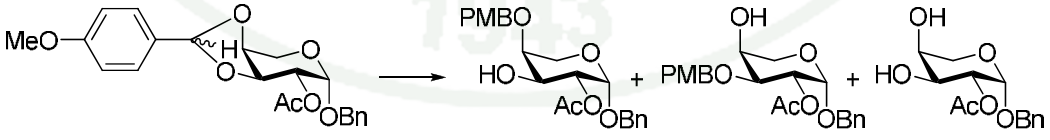
FTIR (neat), ν_{max}, cm^{-1}: 1735, 1613, 1370, 1247, 1135, 1087, 1057, 1031

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.43 (d, *J* = 8.8 Hz, 2H, Ar(H)), 7.28 – 7.37 (m, 5H, Ar(H)), 6.90 (d, *J* = 8.7 Hz, 2H, Ar(H)), 5.84 (s, 1H, C<u>H</u>ArOCH$_3$), 5.05 (d, *J* = 3.4 Hz, 1H, H-1), 5.00 (dd, *J* = 3.4, 7.8 Hz, 1H, H-2), 4.74 (d, *J* = 12.3 Hz, 1H, OCH_2Ar), 4.51 (d, *J* = 12.2 Hz, 1H, OCH_2Ar), 4.50 (dd, *J* = 6.3, 7.7 Hz, 1H, H-3), 4.30 (dd, *J* = 6.2, 2.5 Hz, 1H, H-4), 4.14 (d, *J* = 13.4 Hz, 1H, H-5), 4.07 (dd, *J* = 13.5, 3.1 Hz, 1H, H-5), 3.78 (s, 3H, $ArOCH_3$), 2.07 (s, 3H, $OCOCH_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.3 (C=O), 160.6 (C-ArO), 137.0 (C-Ar), 128.7 (C-Ar), 128.4×2 (CH-Ar), 128.3×2 (CH-Ar), 127.6×2 (CH-Ar), 127.9 (CH-Ar), 113.9×2 (CH-Ar), 104.4 (<u>C</u>HArOCH$_3$), 95.0 (C-1), 75.7 (C-4), 73.1 (C-2), 72.5 (C-3), 69.6 (OCH_2Ar), 58.7 (C-5), 55.2 ($ArOCH_3$), 20.9 ($OCO\underline{C}H_3$)

HRMS (ESI^+) *m/z*: $C_{22}H_{24}O_7Na$ $[M+Na]^+$, calcd 423.1420, found 423.1425

Reductive ring opening of benzyl 2-*O*-acetyl-exo/endo-3,4-*O*-paramethoxy benzylidene-*β*-L-arabinopyranosides (508)



(508) (504) (505) (73)

Using DIBAL-H (solution in THF) in CH_2Cl_2

To a solution of benzyl 2-*O*-acetyl-endo-3,4-*O*-paramethoxybenzylidene-*β*-L-arabinopyranoside (*endo*-508) (57 mg, 0.14 mmol) in dichloromethane (3.0 mL) was added DIBAL-H (0.17 mL, 1.07 mmol, 0.7-1.3 M in THF solution) at room

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temperature. After the reaction was stirred for 16 hours, the reaction was quenched with water, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography (EtOAc/hexane, 3:7). None product was observed, only starting material was recovered (39 mg, 69%).

Using $NaCNBH_3$/CF_3COOH in DMF

To a solution of benzyl 2-*O*-acetyl-exo-3,4-*O*-paramethoxybenzylidene-*β*-L-arabinopyranoside (*exo*-508) (20 mg, 0.050 mmol) in DMF (1.0 mL) were added $NaCNBH_3$ (6 mg, 0.10 mmol) and trifluoroacetic acid (0.004 mL, 0.05 mmol) at 15 °C. After the reaction was stirred for 15 minutes at 15 °C, the reaction was quenched with water, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography (EtOAc/hexane, 3:7) to afford benzyl 2-*O*-acetyl-3-*O*-paramethoxybenzyl-*β*-L-arabinopyranoside (505) as a colorless oil (9 mg, 46%) and hydrolysis product (73) as a white solid (5 mg, 38%). Benzyl 2-*O*-acetyl-4-*O*-paramethoxybenzyl-*β*-L-arabinopyranoside (504) was not observed.

Using $Et_3SiH/BF_3{\cdot}OEt_2$ in CH_2Cl_2

To a solution of benzyl 2-*O*-acetyl-exo-3,4-*O*-paramethoxybenzylidene-*β*-L-arabinopyranoside (*exo*-508) (48 mg, 0.12 mmol) in dichloromethane (2.94 mL) was added triethylsilane (0.23 mL, 1.43 mmol). The reaction mixture was cooled to 0 °C and slowly added $BF_3{\cdot}Et_2O$ (0.03 ml, 0.24 mmol). The reaction was stirred at 0 °C for 20 minutes. The mixture was diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 7:3) to give only hydrolysis product (73) (26 mg, 78%).

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Using $NaCNBH_3/BF_3{\cdot}OEt_2$ in CH_2Cl_2

To a solution of benzyl 2-*O*-acetyl-exo-3,4-*O*-paramethoxybenzylidene-*β*-L-arabinopyranoside (*exo*-508) (50 mg, 0.12 mmol) in dichloromethane (2.0 mL) were added $NaCNBH_3$ (16 mg, 0.25 mmol) and $BF_3{\cdot}Et_2O$ (0.016 mL, 0.12 mmol) at 0 °C. After the reaction was stirred for 1 hour at 0 °C, the reaction was quenched with triethylamine, and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography (EtOAc/hexane, 3:7). None product was observed, only starting material was recovered (12 mg, 25%).

Using $NaCNBH_3/BF_3{\cdot}OEt_2$ in THF

To a solution of benzyl 2-*O*-acetyl-exo-3,4-*O*-paramethoxybenzylidene-*β*-L-arabinopyranoside (*exo*-508) (44 mg, 0.11 mmol) in THF (2.0 mL) were added $NaCNBH_3$ (14 mg, 0.22 mmol) and $BF_3{\cdot}Et_2O$ (0.014 mL, 0.11 mmol) at 0 °C. After the reaction was stirred for 1 hour at 0 °C, the reaction was quenched with triethylamine, and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography (EtOAc/hexane, 3:7) to afford benzyl 2-*O*-acetyl-4-*O*-paramethoxybenzyl-*β*-L-arabinopyranoside (504) as a white solid (1 mg, 3%); $[\alpha]_D^{25}$ +183.20, (c = 0.12, $CHCl_3$) and recovered starting material (32 mg, 73%).

Using $NaCNBH_3$/TMSOTf in THF

To a solution of benzyl 2-*O*-acetyl-endo-3,4-*O*-paramethoxybenzylidene-*β*-L-arabinopyranoside (*endo*-508) (30 mg, 0.075 mmol) in THF (1.0 mL) were added $NaCNBH_3$ (9 mg, 0.15 mmol) and TMSOTf (0.014 mL, 0.075 mmol) at 0 °C. After the reaction was stirred for 15 minutes at 0 °C, the reaction was quenched with triethylamine, and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography (EtOAc/hexane, 3:7) to afford benzyl 2-*O*-

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acetyl-4-*O*-paramethoxybenzyl-*β*-L-arabinopyranoside (504) as a white solid (20 mg, 67%) and recovered starting material (4 mg, 13%).

Using BH_3·THF/TMSOTf in CH_2Cl_2

To a solution of benzyl 2-*O*-acetyl-endo-3,4-*O*-paramethoxybenzylidene-*β*-L-arabinopyranoside (*endo*-508) (39 mg, 0.098 mmol) in dry dichloromethane (1.0 mL) were added BH_3·THF (0.5 mL, 1M solution in THF, 0.49 mmol) and TMSOTf (0.003 mL, 0.015 mmol) at room temperature. After the reaction was stirred for 4 hours, the reaction was quenched with triethylamine followed by careful addition of methanol until the evalution of hydrogen gas ceased. The mixture was coevaporated with methanol under reduced pressure. Purification of the residue by flash column chromatography (EtOAc/Hexane, 7:13) afforded benzyl 2-*O*-acetyl-4-*O*-paramethoxybenzyl-*β*-L-arabinopyranoside (504) as a white solid (12 mg, 30%) and hydrolysis product (73) (17 mg, 61%).

Benzyl 2-*O*-acetyl-4-*O*-paramethoxybenzyl-*β*-L-arabinopyranosides (504)

FTIR (neat), ν_{max}, cm^{-1}: 3435, 1733, 1644, 1371, 1244, 1143, 1063, 1024

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.20-7.30 (m, 5H, Ar(H)), 7.17 (d, *J* = 8.7 Hz, 2H, Ar(H)), 6.81 (d, *J* = 8.7 Hz, 2H, Ar(H)), 5.08 (dd, *J* = 9.8, 3.6 Hz, 1H, H-2), 5.00 (d, *J* = 3.6 Hz, 1H, H-1), 4.65 (d, *J* = 12.3 Hz, 1H, OCH_2Ar), 4.54 (d, *J* = 11.5 Hz, 1H, $OC\underline{H}_2ArOCH_3$), 4.50 (d, *J* = 11.5 Hz, 1H, $OC\underline{H}_2ArOCH_3$), 4.44 (d, *J* = 12.3 Hz, 1H, OCH_2Ar), 3.91-3.92 (m, 1H, H-4), 3.86 (dd, *J* = 9.8, 3.6 Hz, 1H, H-3), 3.74-3.75 (m, 1H, H-5), 3.73 (s, 3H, $ArOCH_3$), 3.69 (dd, *J* = 2.2, 12.6 Hz, 1H, H-5), 2.52 (s, 1H, OH), 1.99 (s, 3H, $OCOCH_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.3 (C=O), 159.5 (C-Ar), 137.3×2 (C-Ar), 129.2×2 (CH-Ar), 128.4×2 (CH-Ar), 127.9 (CH-Ar), 127.7×2 (CH-Ar), 113.9×2 (CH-Ar), 95.9 (C-1), 74.6 (C-3), 72.1 ($O\underline{C}H_2ArOCH_3$), 70.2 (C-2), 69.4 (OCH_2Ar), 67.3 (C-4), 61.8 (C-5), 55.3 ($ArOCH_3$), 20.9 ($OCO\underline{C}H_3$)

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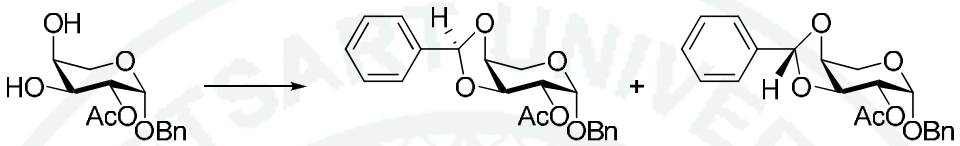
HRMS (ESI$^+$) *m/z*: $C_{22}H_{26}O_7Na$ $[M+Na]^+$, calcd 425.1576, found 425.1575

Benzyl 2-*O*-acetyl-exo/endo-3,4-*O*-benzylidene-*β*-L-arabinopyranosides (509)



(73) *exo*-(509) endo-(509)

To a solution of benzyl-2-*O*-acetyl-*β*-L-arabinopyranoside (73) (200 mg, 0.71 mmol) in dry acetonitrile (2.5 mL) were added α,α-dimethoxytoluene (0.16 mL, 1.13 mmol) and *p*-toluenesulfonic acid (1 mg, 0.007 mmol). The reaction mixture was stirred at room temperature for 6 h. Triethylamine was added before concentration and the syrup which was dissolved in EtOAc was extracted with saturated aqueous $NaHCO_3$, water, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 3:17) to afford benzyl 2-*O*-acetyl-exo-3,4-*O*-benzylidene-*β*-L-arabinopyranoside (*exo*-509) as a yellow syrup (42 mg, 16%); $[\alpha]_D^{20}$ +177.35, (c = 0.295, CH_2Cl_2) and benzyl 2-*O*-acetyl-endo-3,4-*O*-benzylidene-*β*-L-arabinopyranoside (*endo*-509) as a yellow syrup (168 mg, 64%); $[\alpha]_D^{20}$ +205.54, (c = 0.30, CH_2Cl_2) and recovered starting material (10 mg, 5%).

Benzyl 2-*O*-acetyl-exo-3,4-*O*-benzylidene-*β*-L-arabinopyranoside (*exo*-509)

FTIR (neat), ν_{max}, cm^{-1}: 1749, 1370, 1272, 1089, 1026

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.41-7.44 (m, 2H, Ar(H)), 7.21-7.38 (m, 8H, Ar(H)), 6.12 (s, 1H, C<u>H</u>Ar), 5.01 (d, *J* = 4.0 Hz, 1H, H-1), 5.00 (dd, *J* = 11.8, 4.0 Hz, 1H, H-2), 4.60 (dd, *J* = 7.7, 5.3 Hz, 1H, H-3), 4.67 (d, *J* = 12.3 Hz, 1H, OCH_2Ar), 4.44 (d, *J* = 12.3 Hz, 1H, OCH_2Ar), 4.18 (dd, *J* = 5.6, 2.5 Hz, 1H, H-4), 3.92 (dd, *J* = 13.4, 2.6 Hz, 1H, H-5), 4.00 (d, *J* = 13.5 Hz, 1H, H-5), 2.03 (s, 3H, $OCOCH_3$)

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^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.5 (C=O), 137.0 (C-Ar), 138.7 (C-Ar), 129.6 (CH-Ar), 128.6 (CH-Ar), 128.5×2 (CH-Ar), 127.6 (CH-Ar), 126.8×3 (CH-Ar), 126.1×2 (CH-Ar), 102.8 (CHAr), 95.1 (C-1), 74.1 (C-3), 73.4 (C-4), 69.5 (C-2), 69.6 (OCH_2Ar), 58.8 (C-5), 20.9 ($OCOCH_3$)

HRMS (ESI^+) *m/z*: $C_{21}H_{22}O_6Na$ $[M+Na]^+$, calcd 393.1314, found 393.1313

Benzyl 2-*O*-acetyl-endo-3,4-*O*-benzylidene-*β*-L-arabinopyranoside (*endo*-509)

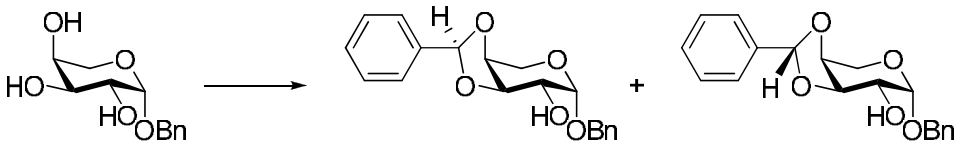
FTIR (neat), ν_{max}, cm^{-1}: 1736, 1370, 1233, 1067

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.41 – 7.44 (m, 2H, Ar(H)), 7.21-7.38 (m, 8H, Ar(H)), 5.82 (s, 1H, CHAr), 4.98 (d, *J* = 3.5 Hz, 1H, H-1), 4.90 (dd, *J* = 7.8, 3.5 Hz, 1H, H-2), 4.46 (dd, *J* = 7.6, 6.4 Hz, 1H, H-3), 4.67 (d, *J* = 12.3 Hz, 1H, OCH_2Ar), 4.44 (d, *J* = 12.3 Hz, 1H, OCH_2Ar), 4.25 (dd, *J* = 6.1, 2.3 Hz, 1H, H-4), 4.00 (dd, *J* = 13.5, 3.0 Hz, 1H, H-5), 4.08 (d, *J* = 13.2 Hz, 1H, H-6), 1.99 (s, 3H, $OCOCH_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.3 (C=O), 137.0 (C-Ar), 136.6 (C-Ar), 129.1 (CH-Ar), 128.5×2 (CH-Ar), 127.6×2 (CH-Ar), 126.8×3 (CH-Ar), 126.1×2 (CH-Ar), 104.4 (CHAr), 95.0 (C-1), 75.8 (C-4), 72.7 (C-2), 72.6 (C-3), 69.6 (OCH_2Ar), 58.7 (C-5), 20.9 ($OCOCH_3$)

HRMS (ESI^+) *m/z*: $C_{21}H_{22}O_6Na$ $[M+Na]^+$, calcd 393.1314, found 393.1310

Benzyl exo/endo-3,4-*O*-benzylidene-*β*-L-arabinopyranosides (510)



(501) *exo*-(510) *endo*-(510)

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To a solution of benzyl *β*-L-arabinopyranoside (501) (100 mg, 0.42 mmol) in dry DMF (1.5 mL) were added α,α-dimethoxytoluene (0.09 mL, 0.67 mmol) and *p*-toluenesulfonic acid (1 mg, 0.004 mmol). The reaction mixture was stirred at room temperature for 24 h. Triethylamine was added before concentration and the syrup which was dissolved in EtOAc was extracted with saturated aqueous $NaHCO_3$, water, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 1:4) to afford benzyl exo/endo-3,4-*O*-benzylidene-*β*-L-arabinopyranosides (510) as a white solid (106 mg, 77%); m.p. 98-100 °C; $[\alpha]_D^{20}$ +138.64, (c = 0.21, CH_2Cl_2).

FTIR (neat), ν_{max}, cm^{-1}: 3436, 1091, 1067, 1022

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.48-7.53 (m, 16H, Ar(H)), 7.43-7.44 (m, 2H, Ar(H)), 7.27-7.40 (m, 2H, Ar(H)), 6.16 (s, 1H, CHAr-exo), 5.85 (s, 1H, CHAr-endo), 4.96 (d, *J* = 3.7 Hz, 1H, H-1-exo), 4.91 (d, *J* = 3.6 Hz, 1H, H-1-endo), 4.53 (d, *J* = 11.8 Hz, 2H, OCH_2Ar-exo), 4.75 (d, *J* = 11.8 Hz, 2H, OCH_2Ar-exo), 4.54 (d, *J* = 11.8 Hz, 2H, OCH_2Ar-endo), 4.78 (d, *J* = 11.7 Hz, 2H, OCH_2Ar-endo), 4.41 (dd, *J* = 7.1, 5.6 Hz, 1H, H-3-exo), 4.33 (dd, *J* = 6.4, 6.4 Hz, 1H, H-3-endo), 4.14-4.16 (m, 1H, H-4-exo), 4.23-4.25 (m, 1H, H-4-endo), 3.89 (dd, *J* = 7.2, 3.7 Hz, 1H, H-2-exo), 3.86 (dd, *J* = 6.2, 3.6 Hz, 1H, H-2-endo), 3.93 (dd, *J* = 13.3, 2.5 Hz, 1H, H-5-exo), 4.04 (dd, *J* = 13.3, 2.4 Hz, 1H, H-5-exo), 3.98 (dd, *J* = 13.2, 1.0 Hz, 1H, H-5-endo), 4.00 (d, *J* = 13.2, 1.6 Hz, 1H, H-5-endo)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 137.0, 138.9 (C-Ar-endo), 136.8, 136.9 (C-Ar-exo), 129.6, 129.4, 129.3, 128.9, 128.8, 128.5×3, 128.4, 127.9, 126.6, 125.9 (CH-Ar-exo, endo), 102.8 (CHAr-exo), 103.8 (CHAr-endo), 97.0 (C-1-exo), 96.5 (C-1-endo), 76.9 (C-3-exo), 75.7 (C-3-endo), 73.0 (C-4-exo), 74.7 (C-4-endo), 69.6 (OCH_2Ar-exo), 69.6 (OCH_2Ar-endo), 67.9 (C-2-exo), 69.7 (C-2-endo), 59.4 (C-5-exo), 59.8 (C-5-endo)

HRMS (ESI^+) *m/z*: $C_{19}H_{20}O_5Na$ $[M+Na]^+$, calcd 351.1208, found 351.1209

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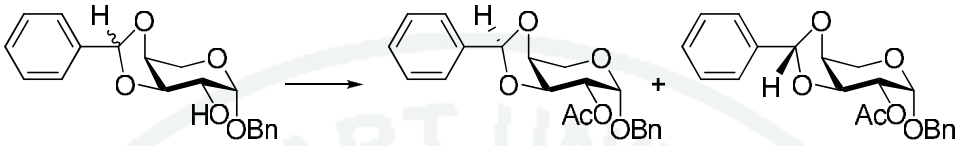
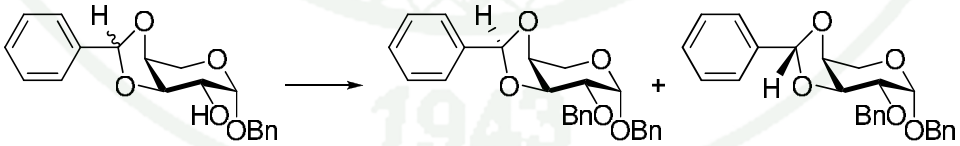
Benzyl 2-*O*-acetyl-exo/endo-3,4-*O*-benzylidene-*β*-L-arabinopyranosides (509)



(510) *exo*-(509) *endo*-(509)

Benzyl exo/endo-3,4-*O*-benzylidene-*β*-L-arabinopyranosides (510) (80 mg, 0.24 mmol) was dissolved in dichloromethane (1.3 mL). Triethylamine (0.05 mL, 0.36 mmol), acetyl anhydride (0.03 mL, 0.29 mmol) and DMAP (1 mg, 0.006 mmol) were added. The reaction mixture was stirred at room temperature for 1 hour then was quenched with saturated aqueous $NaHCO_3$. The organic layer was separated and the water layer was extracted with CH_2Cl_2 three times. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the product was purified by flash column chromatography (EtOAc/hexane, 1:4) to give benzyl 2-*O*-acetyl-exo/endo-3,4-*O*-benzylidene-*β*-L-arabinopyranosides (509) (90 mg, 100%) as pale yellow syrup**.**

Benzyl 2-*O*-benzyl-exo/endo-3,4-*O*-benzylidene-*β*-L-arabinopyranosides (511)



(510) *exo*-(511) *endo*-(511)

Benzyl exo/endo-3,4-*O*-benzylidene-*β*-L-arabinopyranosides (510) (100 mg, 0.30 mmol) was treated with benzyl bromide (1.09 mL, 9.14 mmol) in the presence of potassium hydroxide (205 mg, 3.65 mmol) for 5 h at 50 °C. The reaction mixture was diluted with dichloromethane and filtered, and benzyl bromide was removed under reduced pressure. The oily residue was purified by flash column chromatography (EtOAc/hexane, 1:9) to afford benzyl 2-*O*-benzyl-exo-3,4-*O*-benzylidene-*β*-L-arabinopyranoside (*exo*-511) as a yellow syrup (44 mg, 35%); $[\alpha]_D^{20}$ +134.43, (c =

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0.45, CH_2Cl_2) and benzyl 2-*O*-benzyl-endo-3,4-*O*-benzylidene-*β*-L-arabinopyranoside (*endo*-511) as a yellow syrup (54 mg, 43%); $[\alpha]_D^{20}$ +169.52, (c = 0.24, CH_2Cl_2).

Benzyl 2-*O*-benzyl-exo-3,4-*O*-benzylidene-*β*-L-arabinopyranoside (*exo*-511)

FTIR (neat), ν_{max}, cm^{-1}: 1274, 1099, 1045, 1019

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.18 – 7.38 (m, 15H, Ar(H)), 5.95 (s, 1H, CHAr), 4.88 (d, *J* = 3.4 Hz, 1H, H-1), 4.71 (d, *J* = 12.5 Hz, 1H, OCH_2Ar), 4.64 (d, *J* = 11.6 Hz, 1H, OCH_2Ar), 4.63 (d, *J* = 12.2 Hz, 1H, OCH_2Ar), 4.62 (dd, *J* = 8.0, 5.4 Hz, 1H, H-3), 4.48 (d, *J* = 12.3 Hz, 1H, OCH_2Ar), 4.13 (m, 1H, H-4), 3.92 (dd, *J* = 13.4, 1.0 Hz, 1H, H-5), 3.88 (dd, *J* = 13.3, 2.4 Hz, 1H, H-5), 3.62 (dd, *J* = 8.0, 3.5 Hz, 1H, H-2)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 139.0 (C-Ar), 138.1 (C-Ar), 137.1 (C-Ar), 129.0 (CH-Ar), 128.4×3 (CH-Ar), 128.3×3 (CH-Ar), 127.9×2 (CH-Ar), 127.8×3 (CH-Ar), 127.7×2 (CH-Ar), 126.1 (CH-Ar), 102.6 (CHAr), 95.8 (C-1), 76.6 (C-3), 73.8 (C-2), 73.4 (C-4), 72.2, 69.3 (OCH_2Ar), 58.9 (C-5)

HRMS (ESI^+) *m/z*: $C_{26}H_{26}O_5Na$ $[M+Na]^+$, calcd 441.1678, found 441.1680

Benzyl 2-*O*-benzyl-endo-3,4-*O*-benzylidene-*β*-L-arabinopyranoside (*endo*-511)

FTIR (neat), ν_{max}, cm^{-1}: 1272, 1090, 1068, 1022

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.10 – 7.37 (m, 15H, Ar(H)), 5.84 (s, 1H, CHAr), 4.77 (d, *J* = 3.4 Hz, 1H, H-1), 4.68 (d, *J* = 12.3 Hz, 1H, OCH_2Ar), 4.59 (d, *J* = 12.3 Hz, 1H, OCH_2Ar), 4.47 (d, *J* = 12.6 Hz, 1H, OCH_2Ar), 4.46 (d, *J* = 12.3 Hz, 1H, OCH_2Ar), 4.44 (dd, *J* = 6.0, 1.8 Hz, 1H, H-3), 4.23 (ddd, *J* = 6.2, 2.8, 1.3 Hz, 1H, H-4), 4.01 (dd, *J* = 13.4, 1.2 Hz, 1H, H-5), 3.96 (dd, *J* = 13.3, 3.0 Hz, 1H, H-5), 3.52 (dd, *J* = 7.5, 3.4 Hz, 1H, H-2)

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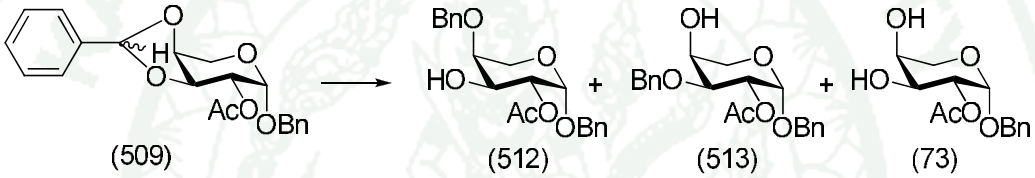
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 138.1 (C-Ar), 137.5 (C-Ar), 137.2 (C-Ar), 129.2 (CH-Ar), 128.4×3 (CH-Ar), 128.3×2 (CH-Ar), 128.2×2 (CH-Ar), 127.9×2 (CH-Ar), 127.8×2 (CH-Ar), 127.6×2 (CH-Ar), 126.6 (CH-Ar), 103.8 (CHAr), 95.8 (C-1), 76.7 (C-2), 75.9 (C-4), 75.3 (C-3), 72.0, 69.3 (OCH_2Ar), 58.9 (C-5)

HRMS (ESI^+) *m/z*: $C_{26}H_{26}O_5Na$ $[M+Na]^+$, calcd 441.1678, found 441.1681

Benzyl 2-*O*-acetyl-4-*O*-benzyl-*β*-L-arabinopyranoside (512)



Using $TiCl_4$/Et_3SiH in CH_2Cl_2

To a solution of benzyl 2-*O*-acetyl-exo/endo-3,4-*O*-benzylidene-*β*-L-arabinopyranosides (509) (110 mg, 0.30 mmol) in dichloromethane (3.0 mL) was added Et_3SiH (0.065 mL, 0.40 mmol). The reaction mixture was cooled to -78 °C and slowly added a solution of $TiCl_4$ (0.037 ml, 0.33 mmol) in dichloromethane (0.3 mL). The reaction was stirred at -78 °C for 5 h. The reaction mixture was poured into ice and extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 3:7) to afford benzyl 2-*O*-acetyl-4-*O*-benzyl-*β*-L-arabinopyranoside (512) as a yellow syrup (46 mg, 41%); $[\alpha]_D^{20}$ +217.95, (c = 0.30, CH_2Cl_2), benzyl 2-*O*-acetyl-3-*O*-benzyl-*β*-L-arabinopyranoside (513) as a yellow syrup (22 mg, 20%); $[\alpha]_D^{20}$ +160.97, (c = 0.40, CH_2Cl_2) and recovered starting material (19 mg, 17%).

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Using BF_3·Et_2O/Et_3SiH in CH_2Cl_2

To a solution of benzyl 2-*O*-acetyl-exo/endo-3,4-*O*-benzylidene-*β*-L-arabinopyranosides (509) (60 mg, 0.16 mmol) in dichloromethane (3.0 mL) at 0 °C was added Et_3SiH (0.32 mL, 1.96 mmol) and BF_3·Et_2O (0.04 mL, 0.33 mmol). The reaction was stirred at 0 °C for 1 h. The mixture was diluted with CH_2Cl_2, washed with saturated $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 3:7) to afford benzyl 2-*O*-acetyl-4-*O*-benzyl-*β*-L-arabinopyranoside (512) as a yellow syrup (32 mg, 52%) and benzyl 2-*O*-acetyl-3-*O*-benzyl-*β*-L-arabinopyranoside (513) as a white solid (10 mg, 22%).

Using $Cu(OTf)_2$/Et_3SiH in CH_3CN

To a solution of benzyl 2-*O*-acetyl-exo/endo-3,4-*O*-benzylidene-*β*-L-arabinopyranosides (509) (56 mg, 0.15 mmol) in acetonitrile (3.0 mL) and Et_3SiH (0.049 ml, 0.30 mmol) at 0 °C was added $Cu(OTf)_2$ (5 mg, 0.015 mmol). The reaction was warmed to room temperature and stirred for 30 minutes. The mixture was diluted with CH_2Cl_2, washed with saturated $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 1:4) to afford benzyl 2-*O*-acetyl-*β*-L-arabino pyranoside (73) as a white solid (27 mg, 64%).

Using $Cu(OTf)_2$/BH_3·THF

A 1M solution of borane/tetrahydrofuran complex in tetrahydrofuran (0.23 mL, 0.23 mmol) was added to a benzyl 2-*O*-acetyl-exo/endo-3,4-*O*-benzylidene-*β*-L-arabinopyranosides (509) (17 mg, 0.046 mmol) at room temperature under nitrogen. The mixture was stirred for 10 minutes, and $Cu(OTf)_2$ (2 mg, 0.0046 mmol) was added to the solution. After stirring for 30 minutes, the mixture was cooled down to 0 °C, and the reaction was quenched by sequential additions of triethylamine and methanol (*caution*: hydrogen gas was evolved). The resulting mixture was

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concentrated under reduced pressure followed by coevaporation with methanol. The residue was purified by flash column chromatography (EtOAc/hexane, 3:7) to afford benzyl 2-*O*-acetyl-4-*O*-benzyl-*β*-L-arabinopyranoside (512) as a yellow syrup (8 mg, 46%) and benzyl 2-*O*-acetyl-3-*O*-benzyl-*β*-L-arabinopyranoside (513) as a yellow syrup (5 mg, 29%).

Benzyl 2-*O*-acetyl-4-*O*-benzyl-*β*-L-arabinopyranoside (512)

FTIR (neat), ν_{max}, cm^{-1}: 3462, 1735, 1371, 1239, 1140, 1057, 1026

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.19 – 7.28 (m, 10H, Ar(H)), 4.99 (dd, *J* = 11.4, 3.6 Hz, 1H, H-2), 4.98 (d, *J* = 8.7 Hz, 1H, H-1), 4.66 (d, *J* = 11.8 Hz, 1H, OCH_2Ar), 4.65 (d, *J* = 12.4 Hz, 1H, OCH_2Ar), 4.46 (d, *J* = 11.8 Hz, 1H, OCH_2Ar), 4.44 (d, *J* = 12.3 Hz, 1H, OCH_2Ar), 3.96-4.02 (m, 1H, H-3), 3.71 (dd, *J* = 3.5, 2.1 Hz, 1H, H-4), 3.75 (dd, *J* = 12.6, 1.9 Hz, 1H, H-5), 3.68 (dd, *J* = 12.6, 1.1 Hz, 1H, H-5), 2.36 (brd, *J* = 10.3 Hz, 1H, OH), 2.01 (s, 3H, $OCOCH_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.9 (C=O), 137.3 (C-Ar), 137.5 (C-Ar), 128.5×2 (CH-Ar), 128.4×2 (CH-Ar), 127.9 (CH-Ar), 127.8×3 (CH-Ar), 127.6×2 (CH-Ar), 95.9 (C-1), 76.7 (C-2), 76.6 (C-4), 71.5 (OCH_2Ar), 69.4 (OCH_2Ar), 67.3 (C-3), 59.0 (C-5), 20.9 ($OCO\underline{C}H_3$)

HRMS (ESI^+) *m/z*: $C_{21}H_{24}O_6Na$ $[M+Na]^+$, calcd 395.1471, found 395.1460

Benzyl 2-*O*-acetyl-3-*O*-benzyl-*β*-L-arabinopyranoside (513)

FTIR (neat), ν_{max}, cm^{-1}: 3470, 1737, 1370, 1238, 1143, 1061, 1023

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.20 – 7.30 (m, 10H, Ar(H)), 5.10 (dd, *J* = 9.9, 3.6 Hz, 1H, H-2), 5.00 (d, *J* = 3.6 Hz, 1H, H-1), 4.65 (d, *J* = 12.3 Hz, 1H, OCH_2Ar), 4.60 (s, 2H, OCH_2Ar), 4.44 (d, *J* = 12.3 Hz, 1H, OCH_2Ar), 3.95-3.96 (m,

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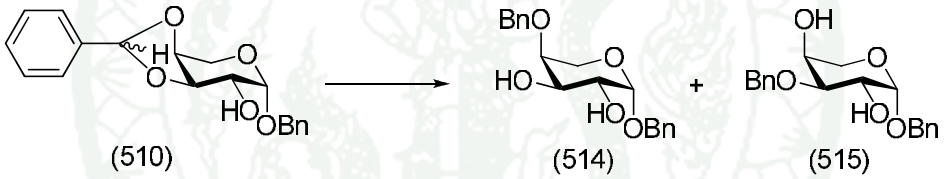
1H, H-4), 3.88 (dd, *J* = 9.8, 3.5 Hz, 1H, H-3), 3.77 (dd, *J* = 12.6, 1.5 Hz, 1H, H-5), 3.70 (dd, *J* = 12.6, 2.2 Hz, 1H, H-5), 2.54 (s, 1H, OH), 1.98 (s, 3H, $OCOCH_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.3 (C=O), 137.3 (C-Ar), 137.8 (C-Ar), 128.5×2 (CH-Ar), 128.4×2 (CH-Ar), 128.0 (CH-Ar), 127.9 (CH-Ar), 127.7×2 (CH-Ar), 127.5×2 (CH-Ar), 95.9 (C-1), 75.0 (C-2), 72.4 (OCH_2Ar), 69.4 (OCH_2Ar), 70.2 (C-3), 67.3 (C-4), 61.8 (C-5), 20.9 ($OCO\underline{C}H_3$)

HRMS (ESI^+) *m/z*: $C_{21}H_{24}O_6Na$ $[M+Na]^+$, calcd 395.1471, found 395.1471

Benzyl 4-*O*-benzyl-*β*-L-arabinopyranoside (514)



To a solution of benzyl exo/endo-3,4-*O*-benzylidene-*β*-L-arabinopyranosides (510) (442 mg, 1.35 mmol) in dry acetonitrile (3.0 mL) at 0 °C was added Et_3SiH (2.61 mL, 16.16 mmol) and $BF_3{\cdot}Et_2O$ (0.34 mL, 2.69 mmol). The reaction was stirred at 0 °C for 10 minutes. The mixture was diluted with CH_2Cl_2, washed with saturated $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 7:3) to afford benzyl 4-*O*-benzyl-*β*-L-arabinopyranoside (514) as a white solid (92 mg, 21%); m.p. 114-116 °C; $[\alpha]_D^{20}$ +165.20, (c = 0.18, CH_2Cl_2) and benzyl 3-*O*-benzyl-*β*-L-arabinopyranoside (515) as a white solid (40 mg, 9%); m.p. 118-120 °C; $[\alpha]_D^{20}$ +146.65, (c = 0.08, CH_2Cl_2).

Benzyl 4-*O*-benzyl-*β*-L-arabinopyranoside (514)

FTIR (neat), ν_{max}, cm^{-1}: 3430, 1344, 1266, 1140, 1077, 1048, 1025

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^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.22 – 7.32 (m, 10H, Ar(H)), 4.94 (d, *J* = 3.3 Hz, 1H, H-1), 4.69 (d, *J* = 12.0 Hz, 1H, OCH_2Ar), 4.66 (d, *J* = 12.3 Hz, 1H, OCH_2Ar), 4.62 (d, *J* = 11.7 Hz, 1H, OCH_2Ar), 4.51 (d, *J* = 11.5 Hz, 1H, OCH_2Ar), 3.92-3.94 (m, 1H, H-3), 3.79-3.80 (m, 1H, H-4), 3.74 (dd, *J* = 12.2, 2.4 Hz, 1H, H-5), 3.71-3.72 (m, 1H, H-5), 3.62 (dd, *J* = 3.5, 9.4 Hz, 1H, H-2)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 137.7 (C-Ar), 137.1 (C-Ar), 128.6×4 (CH-Ar), 128.5 (CH-Ar), 128.0×2 (CH-Ar), 127.9 (CH-Ar), 127.8×2 (CH-Ar), 98.0 (C-1), 70.4 (C-2), 71.7 (OCH_2Ar), 69.8 (OCH_2Ar), 70.4 (C-3), 78.1 (C-4), 59.8 (C-5)

HRMS (ESI^+) *m/z*: $C_{19}H_{22}O_5Na$ $[M+Na]^+$, calcd 353.1365, found 353.1367

Benzyl 3-*O*-benzyl-*β*-L-arabinopyranoside (515)

FTIR (neat), ν_{max}, cm^{-1}: 3437, 1257, 1137, 1092, 1063, 1015

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.20 – 7.33 (m, 10H, Ar(H)), 4.89 (d, *J* = 3.4 Hz, 1H, H-1), 4.66 (d, *J* = 12.2 Hz, 1H, OCH_2Ar), 4.49 (d, *J* = 11.7 Hz, 1H, OCH_2Ar), 4.43 (d, *J* = 11.8 Hz, 1H, OCH_2Ar), 4.42 (d, *J* = 12.2 Hz, 1H, OCH_2Ar), 4.02 (ddd, *J* = 0.3, 3.2, 9.4 Hz, 1H, H-4), 3.94-3.95 (m, 1H, H-3), 3.80 (dd, *J* = 12.7, 1.3 Hz, 1H, H-5), 3.67 (dd, *J* = 9.7, 3.5 Hz, 1H, H-2), 3.66 (dd, *J* = 12.6, 1.8 Hz, 1H, H-5), 2.46 (s, 1H, OH), 2.43 (s, 1H, OH)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 137.8 (C-Ar), 137.3 (C-Ar), 130.0 (CH-Ar), 128.6×2 (CH-Ar), 128.4×2 (CH-Ar), 128.1×2 (CH-Ar), 128.0×2 (CH-Ar), 127.9 (CH-Ar), 95.4 (C-1), 69.0 (C-2), 72.3 (OCH_2Ar), 69.2 (OCH_2Ar), 76.5 (C-3), 68.5 (C-4), 62.0 (C-5)

HRMS (ESI^+) *m/z*: $C_{19}H_{22}O_5Na$ $[M+Na]^+$, calcd 353.1365, found 353.1363

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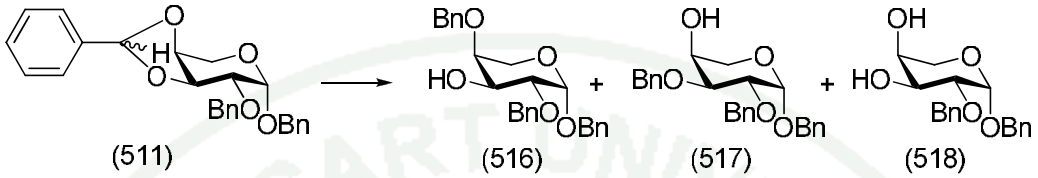
Benzyl 2-*O*-benzyl-4-*O*-benzyl-*β*-L-arabinopyranoside (516)



To a solution of benzyl 2-*O*-benzyl-endo-3,4-*O*-benzylidene-*β*-L-arabinopyra noside (*endo*-511) (29 mg, 0.069 mmol) in dichloromethane (1.7 mL) at 0 °C was added Et_3SiH (0.13 mL, 0.83 mmol) and $BF_3{\cdot}Et_2O$ (0.017 mL, 0.14 mmol). The reaction was stirred at 0 °C for 30 minutes. The mixture was diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 1:3) to afford benzyl 2-*O*-benzyl-4-*O*-benzyl-*β*-L-arabinopyranoside (516) as a yellow solid (10 mg, 36%); m.p. 64-66 °C; $[\alpha]_D^{20}$ +128.20, (c = 0.23, CH_2Cl_2), benzyl 2-*O*-benzyl-3-*O*-benzyl-*β*-L-arabinopyranoside (517) as a pale yellow syrup (4 mg, 13%); $[\alpha]_D^{20}$ +131.57, (c = 0.11, CH_2Cl_2) and benzyl 2-*O*-benzyl-*β*-L-arabinopyranoside (518) as a white solid (7 mg, 30%); m.p. 113-115 °C; $[\alpha]_D^{20}$ +176.10, (c = 0.21, CH_2Cl_2).

Benzyl 2-*O*-benzyl-4-*O*-benzyl-*β*-L-arabinopyranoside (516)

FTIR (neat), ν_{max}, cm^{-1}: 3453, 1344, 1260, 1093, 1048, 1025

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.20 – 7.32 (m, 15H, Ar(H)), 4.86 (d, *J* = 3.4 Hz, 1H, H-1), 4.65 (d, *J* = 11.9 Hz, 1H, OCH_2Ar), 4.64 (d, *J* = 12.2 Hz, 1H, OCH_2Ar), 4.59 (d, *J* = 11.9 Hz, 1H, OCH_2Ar), 4.55 (d, *J* = 12.1 Hz, 1H, OCH_2Ar), 4.50 (d, *J* = 11.9 Hz, 1H, OCH_2Ar), 4.42 (d, *J* = 12.2 Hz, 1H, OCH_2Ar), 4.00-4.06 (m, 1H, H-3), 3.74 (ddd, *J* = 3.6, 1.8, 1.8 Hz, 1H, H-4), 3.70 (dd, *J* = 9.6, 3.4 Hz, 1H, H-2), 3.67-3.68 (m, 2H, H-5), 2.36 (brd, *J* = 6.6 Hz, 1H, OH)

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^{13}C NMR ($CDCl_3$, 100 MHz) δ: 138.3 (C-Ar), 138.0 (C-Ar), 137.4 (C-Ar), 128.0×3 (CH-Ar), 128.4×3 (CH-Ar), 128.5×3 (CH-Ar), 127.9×2 (CH-Ar), 127.8×3 (CH-Ar), 127.7 (CH-Ar), 96.2 (C-1), 76.6 (C-2), 76.2 (C-4), 72.8 (OCH_2Ar), 71.9 (OCH_2Ar), 69.2 (OCH_2Ar), 69.0 (C-3), 59.8 (C-5)

HRMS (ESI^+) *m/z*: $C_{26}H_{28}O_5Na$ $[M+Na]^+$, calcd 443.1834, found 443.1834

Benzyl 2-*O*-benzyl-3-*O*-benzyl-*β*-L-arabinopyranoside (517)

FTIR (neat), ν_{max}, cm^{-1}: 3467, 1342, 1261, 1140, 1098, 1067, 1024

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.21 – 7.34 (m, 15H, Ar(H)), 4.82 (d, *J* = 3.6 Hz, 1H, H-1), 4.75 (d, *J* = 11.5 Hz, 1H, OCH_2Ar), 4.66 (d, *J* = 12.3 Hz, 1H, OCH_2Ar), 4.63 (d, *J* = 12.0 Hz, 1H, OCH_2Ar), 4.62 (d, *J* = 11.5 Hz, 1H, OCH_2Ar), 4.50 (d, *J* = 12.0 Hz, 1H, OCH_2Ar), 4.48 (d, *J* = 12.3 Hz, 1H, OCH_2Ar), 3.93-4.94 (m, 1H, H-4), 3.88 (dd, *J* = 9.5, 3.5 Hz, 1H, H-3), 3.76 (dd, *J* = 9.5, 3.5 Hz, 1H, H-2), 3.73-3.77 (m, 1H, H-5), 3.64 (dd, *J* = 12.5, 2.0 Hz, 1H, H-5), 2.50 (s, 1H, OH)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 138.4 (C-Ar), 138.2 (C-Ar), 137.3 (C-Ar), 128.5×2 (CH-Ar), 128.4×2 (CH-Ar), 128.3×2 (CH-Ar), 128.2×2 (CH-Ar), 127.9 (CH-Ar), 127.8×4 (CH-Ar), 127.6×2 (CH-Ar), 96.3 (C-1), 77.2 (C-3), 76.7 (C-2), 73.1 (OCH_2Ar), 72.9 (OCH_2Ar), 69.0 (OCH_2Ar), 67.7 (C-4), 61.8 (C-5)

HRMS (ESI^+) *m/z*: $C_{26}H_{28}O_5Na$ $[M+Na]^+$, calcd 443.1834, found 443.1839

Benzyl 2-*O*-benzyl-*β*-L-arabinopyranoside (518)

FTIR (neat), ν_{max}, cm^{-1}: 3357, 3272, 1261, 1129, 1099, 1066, 1020

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.20 – 7.33 (m, 10H, Ar(H)), 4.89 (d, *J* = 3.4 Hz, 1H, H-1), 4.66 (d, *J* = 12.2 Hz, 1H, OCH_2Ar), 4.49 (d, *J* = 11.8 Hz, 1H,

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OCH_2Ar), 4.43 (d, *J* = 11.8 Hz, 1H, OCH_2Ar), 4.41 (d, *J* = 12.2 Hz, 1H, OCH_2Ar), 3.99-4.03 (m, 1H, H-3), 3.93-3.94 (m, 1H, H-4), 3.79 (d, *J* = 12.4 Hz, 1H, H-5), 3.67 (dd, *J* = 9.7, 3.5 Hz, 1H, H-2), 3.65 (dd, *J* = 12.6, 1.8 Hz, 1H, H-5), 2.49 (d, *J* = 12.4 Hz, 1H, OH), 2.48 (d, *J* = 10.7 Hz, 1H, OH)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 137.8 (C-Ar), 137.3 (C-Ar), 128.6×2 (CH-Ar), 128.4×2 (CH-Ar), 128.1 (CH-Ar), 128.0×4 (CH-Ar), 127.9 (CH-Ar), 95.4 (C-1), 76.6 (C-2), 72.2 (OCH_2Ar), 69.2 (OCH_2Ar), 68.9 (C-4), 68.5 (C-3), 62.1 (C-5)

HRMS (ESI^+) *m/z*: $C_{19}H_{22}O_5Na$ $[M+Na]^+$, calcd 353.1365, found 353.1359

1,2,3,4-*O*-Tetraacetyl-β-L-arabinopyranoside (519)

(54) (519)

Method I

Acetyl chloride (1.5 mL, 21 mmol) was added dropwise to a solution at 0 °C of L-arabinose (54) (500 mg, 3.33 mmol) in dichloromethane (13 mL) and pyridine (1.3 mL, 16 mmol). The mixture was allowed to stir at room temperature for 24 hours, and then quenched with water (25 mL). The organic layer was washed with 2M aqueous HCl (2 x 25 mL), saturated aqueous $NaHCO_3$ (25 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude was purified by flash column chromatography (EtOAc/hexane, 3:7) to give 1,2,3,4-*O*-tetraacetyl-β-L-arabinopyranoside (519) (1.03 g, 98%) as pale yellow syrup; $[\alpha]_D^{25}$ +83.13, (c = 0.522, CH_2Cl_2).

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Method II

Acetic anhydride (15.7 mL, 166.5 mmol) was slowly added to a solution of L-arabinose (5.0 g, 33.3 mmol) and pyridine (26.9 mL, 333.0 mmol) at 0 °C. After 48 h, toluene was added (×3) and the solvent was evaporated under reduced pressure until the oil was obtained. The residue was purified by flash column chromatography (EtOAc/hexane, 3:7) to afford 1,2,3,4-*O*-tetraacetyl-L-arabinopyranoside (519) (10.6 g, 100%) as a pale yellow syrup; $[\alpha]_D^{25}$ +83.13, (c = 0.522, CH_2Cl_2).

FTIR (neat), ν_{max}, cm^{-1}: 1748, 1372, 1223, 1071

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.27 (d, *J* = 2.8 Hz, 1H, H-1), 5.31 (m, 1H, H-3), 5.28 (m, 1H, H-4), 5.27 (d, *J* = 2.6 Hz, 1H, H-2), 4.00 (dd, *J* = 1.0, 13.2 Hz, 1H, H-5), 3.75 (dd, *J* = 2.0, 13.2 Hz, 1H, H-5), 2.08 (s, 6H, $OCOCH_3$), 1.95 (s, 6H, $OCOCH_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.0 (C=O), 169.9 (C=O), 169.6 (C=O), 168.9 (C=O), 89.9 (C-1), 68.2 (C-2), 66.8 (C-3), 66.5 (C-4), 62.5 (C-5), 20.6 ($OCO\underline{C}H_3$), 20.6 ($OCO\underline{C}H_3$), 20.4 ($OCO\underline{C}H_3$), 20.3 ($OCO\underline{C}H_3$)

1-Thiophenyl-2,3,4-*O*-triacetyl-α-L-arabinopyranoside (85)

(519) (85)

A solution of 1,2,3,4-*O*-tetraacetyl-β-L-arabinopyranoside (519) (6.46 g, 20.3 mmol) in dry dichloromethane (90 mL) was cooled to 0 °C. Thiophenol (2.20 mL, 22.1 mmol) was added followed by the addition of $SnCl_4$ (1.66 mL, 14.2 mmol). The reaction solution was stirred at room temperature for 4 hours until the starting material disappeared on TLC. Saturated aqueous $NaHCO_3$ was added. The organic

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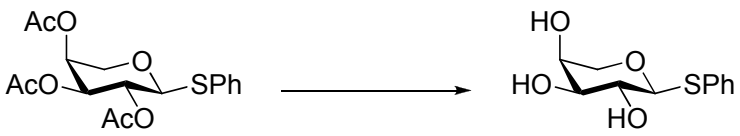
layer was separated and the water layer was extracted with CH_2Cl_2 three times. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (EtOAc/hexane, 1:9) to afford 1-thiophenyl-2,3,4-*O*-triacetyl-α/β-L-arabinopyranoside (85) (α/β, 4:1) (6.0 g, 80%) as pale yellow syrup; $[\alpha]_D^{25}$ -26.83, (c = 1.409, CH_2Cl_2).

FTIR (neat), ν_{max}, cm^{-1}: 1746, 1370, 1220, 1055

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.40 – 7.44 (m, 4H, Ar(H), α,β), 7.18 – 7.25 (m, 6H, Ar(H), α,β), 5.46 (ddd, *J* = 0.6, 0.6, 2.0 Hz, 1H, H-1β), 5.18 – 5.20 (m, 1H, H-4α, H-4β), 5.19 (dd, *J* = 8.2, 8.2 Hz, 1H, H-2α), 5.03 (dd, *J* = 3.4, 8.4 Hz, 1H, H-3α), 5.00 (ddd, *J* = 0.7, 2.2, 5.3 Hz, 1H, H-2β), 4.76 (d, *J* = 7.8 Hz, 1H, H-1α), 4.38 – 4.42 (m, 1H, H-3β), 4.31 (dd, *J* = 3.7, 12.0 Hz, 1H, H-5β), 4.20 (dd, *J* = 5.5, 12.0 Hz, 1H, H-5β), 4.10 (dd, *J* = 4.3, 12.7 Hz, 1H, H-5α), 3.61 (dd, *J* = 2.1, 12.6 Hz, 1H, H-5α), 2.01 (s, 6H, $OCOCH_3$, α), 2.00 (s, 6H, $OCOCH_3$, β), 1.96 (s, 3H, $OCOCH_3$, α), 1.94 (s, 3H, $OCOCH_3$, β)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.3 ($O\underline{C}OCH_3$-β), 169.9 ($O\underline{C}OCH_3$-α), 169.8 ($O\underline{C}OCH_3$-β), 169.7 ($O\underline{C}OCH_3$-α), 169.3 ($O\underline{C}OCH_3$-β), 169.1 ($O\underline{C}OCH_3$-α), 133.3 (C-Ar-β), 133.1 (C-Ar-α), 132.0×2 (CH-Ar-α), 131.8×2 (CH-Ar-β), 128.8×4 (CH-Ar-α, β), 127.7 (CH-Ar-α), 127.6 (CH-Ar-β), 90.6 (C-1β), 86.5 (C-1α), 81.3 (C-3β), 79.9 (C-2β), 77.0 (C-4β), 70.3 (C-3α), 68.3 (C-2α), 67.4 (C-4α), 65.1 (C-5β), 62.6 (C-5α), 20.6×2 ($OCO\underline{C}H_3$-α,β), 20.5 ($OCO\underline{C}H_3$-α,β)

1-Thiophenyl-α-L-arabinopyranoside (520)



(85) (520)

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1-Thiophenyl-2,3,4-*O*-triacetyl-α/β-L-arabinopyranoside (85) (α/β, 4:1) (1.10 g, 3.00 mmol) was dissolved in methanol (15 mL) followed by the addition of sodium methoxide (8 mg, 0.15 mmol). The reaction mixture was stirred at room temperature for 3 h. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (EtOAc/hexane, 9:1) to give 1-thiophenyl-α-L-arabinopyranoside (520α) (517 mg, 71%) as a white solid; m.p. 117-119 °C; $[\alpha]_D^{25}$ -24.52, (c = 0.324, CH_2Cl_2) and 1-thiophenyl-β-L-arabinopyranoside (520β) (95 mg, 13%) as a white solid.

1-Thiophenyl-α-L-arabinopyranoside (520α)

FTIR (neat), ν_{max}, cm^{-1}: 3392, 1080

^{1}H NMR ($(CD_3)_2CO$, 400 MHz) δ: 7.49 (m, 2H, Ar(H)), 7.26 (m, 3H, Ar(H)), 4.76 (d, *J* = 7.4 Hz, 1H, H-1), 4.40 (d, *J* = 4.8 Hz, 1H, OH), 4.23 (d, *J* = 5.0 Hz, 1H, OH), 3.99 (dd, *J* = 4.1, 11.9 Hz, 1H, H-5), 3.94 (m, 1H, H-4), 3.88 (dd, *J* = 0.6, 4.5 Hz, 1H, OH), 3.79 (ddd, *J* = 4.8, 7.5, 7.5 Hz, 1H, H-2), 3.69 (ddd, *J* = 3.3, 4.8, 7.8 Hz, 1H, H-3), 3.59 (dd, *J* = 1.9, 12.0 Hz, 1H, H-5)

^{13}C NMR ($(CD_3)_2CO$, 100 MHz) δ: 136.4 (C-Ar), 131.5×2 (CH-Ar), 129.5×2 (CH-Ar), 127.4 (CH-Ar), 89.3 (C-1), 74.3 (C-3), 71.5 (C-2), 68.5 (C-4), 68.2 (C-5)

HRMS (ESI^+) *m/z*: $C_{11}H_{14}O_4SNa$ $[M+Na]^+$, calcd 265.0511, found 265.0509

1-Thiophenyl-β-L-arabinopyranoside (520β)

FTIR (neat), ν_{max}, cm^{-1}: 3394, 1083

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.44 (m, 2H, Ar(H)), 7.20 (m, 3H, Ar(H)), 5.36 (d, *J* = 3.9 Hz, 1H, H-1), 5.11 (m, 1H, OH), 4.74 (m, 1H, OH), 4.09 – 4.13 (m,

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2H, H-2, H-4), 4.02 – 4.05 (m, 1H, H-3), 3.99 (m, 1H, OH), 3.76 (dd, *J* = 2.4, 12.4 Hz, 1H, H-5), 3.68 (dd, *J* = 0.3, 12.3 Hz, 1H, H-5)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 133.4 (C-Ar), 132.0×2 (CH-Ar), 129.1×2 (CH-Ar), 127.7 (CH-Ar), 92.6 (C-1), 85.1 (C-3), 81.7 (C-2), 78.0 (C-4), 61.8 (C-5)

MS (ESI^+), *m/z* (relative intensity): 265.5 ($[M+Na]^+$, 100 %)

1-Thiophenyl-3,4-acetonide-α-L-arabinopyranoside (521)

(520) (521)

To a solution of 1-thiophenyl-α-L-arabinopyranoside (520) (40 mg, 0.16 mmol) in dichloromethane (0.8 mL) was added 2,2-dimethoxypropane (0.024 mL, 0.20 mmol) and *p*-toluenesulfonic acid monohydrate (3 mg, 0.016 mmol) at room temperature. The reaction mixture was stirred at room temperature for 3 hours and was quenched with saturated aqueous $NaHCO_3$. The organic layer was separated and the water layer was extracted with CH_2Cl_2 three times. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 3:2) to give 1-thiophenyl-3,4-acetonide-α-L-arabinopyranoside (521) (38 mg, 82%) as a colorless syrup.

FTIR (neat), ν_{max}, cm^{-1}: 3437, 1219, 1079

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.44 (m, 2H, Ar(H)), 7.19 (m, 3H, Ar(H)), 4.49 (d, *J* = 9.0 Hz, 1H, H-1), 4.16 (m, 1H, H-4), 4.14 (m, 1H, H-5), 4.01 (dd, *J* = 6.1,

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6.1 Hz, 1H, H-3), 3.68 (m, 1H, H-5), 3.58 (ddd, *J* = 3.5, 6.6, 9.0 Hz, 1H, H-2), 1.37 (s, 3H, C(C$\underline{H}_3$)$_2$), 1.26 (s, 3H, C(C$\underline{H}_3$)$_2$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 132.5 (C-Ar), 132.2×2 (CH-Ar), 128.8×2 (CH-Ar), 127.7 (CH-Ar), 109.9 (C(CH$_3$)$_2$), 87.8 (C-1), 78.1 (C-3), 72.6 (C-4), 71.2 (C-2), 65.2 (C-5), 27.7 (C(CH$_3$)$_2$), 25.9 (C(CH$_3$)$_2$)

1-Thiophenyl-2-*O*-acetyl-3,4-acetonide-α-L-arabinopyranoside (86)

(521) (86)

1-Thiophenyl-3,4-acetonide-α-L-arabinopyranoside (521) (20 mg, 0.071 mmol) was dissolved in dichloromethane (1 mL). Triethylamine (0.015 mL, 0.11 mmol), acetic anhydride (0.008 mL, 0.085 mmol), and DMAP (0.2 mg) were added. The reaction mixture was stirred at room temperature for 2 hours then was quenched with saturated aqueous $NaHCO_3$. The organic layer was separated and the water layer was extracted with CH_2Cl_2 three times. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed and the residue was purified by flash column chromatography (EtOAc/hexane, 1:4) to give 1-thiophenyl-2-*O*-acetyl-3,4-acetonide-α-L-arabinopyranoside (86) (21 mg, 91%) as pale yellow syrup.

FTIR (neat), ν_{max}, cm^{-1}: 1753, 1373, 1222, 1052

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.40 (m, 2H, Ar(H)), 7.19 (m, 3H, Ar(H)), 5.06 (dd, *J* = 6.1, 7.4 Hz, 1H, H-2), 4.76 (d, *J* = 7.5 Hz, 1H, H-1), 4.20 (m, 1H, H-4), 4.15 (m, 1H, H-5), 4.09 (dd, *J* = 5.6, 5.6 Hz, 1H, H-3), 3.70 (dd, *J* = 3.7, 12.5 Hz, 1H, H-5), 2.03 (s, 3H, $OCOCH_3$), 1.48 (s, 3H, C(C$\underline{H}_3$)$_2$), 1.27 (s, 3H, C(C$\underline{H}_3$)$_2$)

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^{13}C NMR ($CDCl_3$, 100 MHz) δ: 169.4 (O<u>C</u>OCH_3), 133.9 (C-Ar), 131.6×2 (CH-Ar), 128.8×2 (CH-Ar), 127.4 (CH-Ar), 110.3 (<u>C</u>(CH_3)$_2$), 85.6 (C-1), 75.4 (C-3), 71.9 (C-4), 71.1 (C-2), 64.0 (C-5), 27.5 (C(<u>C</u>H_3)$_2$), 26.2 (C(<u>C</u>H_3)$_2$), 20.8 (OCO<u>C</u>H_3)

1-Thiophenyl-2-*O*-acetyl-α-L-arabinopyranoside (279)

(86) (279)

A solution of 1-thiophenyl-2-*O*-acetyl-3,4-acetonide-α-L-arabinopyranoside (86) (312 mg, 0.96 mmol) in 70% aqueous acetic acid (4.7 mL) was stirred at 70 °C for 1 hour and then concentrated *in vacuo*, and the traces of acetic acid and water were removed by co-evaporation with toluene several times. The residue was purified by flash column chromatography (EtOAc/hexane, 7:3) to afford 1-thiophenyl-2-*O*-acetyl-α-L-arabinopyranoside (279) (264 mg, 96%) as a white solid; m.p. 132-134 °C; $[\alpha]_D^{25}$ +1.39, (c = 0.31, CH_2Cl_2).

FTIR (KBr), ν_{max}, cm^{-1}: 3384, 1735, 1371, 1234, 1052

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.39 (m, 2H, Ar(H)), 7.19 (m, 3H, Ar(H)), 5.02 (dd, *J* = 7.9, 7.9 Hz, 1H, H-2), 4.67 (d, *J* = 8.0 Hz, 1H, H-1), 4.06 (dd, *J* = 4.1, 12.4 Hz, 1H, H-5), 3.96 (brs, 1H, H-4), 3.72 (m, 1H, H-3), 3.49 (dd, *J* = 2.1, 12.3 Hz, 1H, H-5), 2.05 (s, 3H, OCOCH_3)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.9 (O<u>C</u>OCH_3), 133.8 (C-Ar), 131.7×2 (CH-Ar), 128.9×2 (CH-Ar), 127.5 (CH-Ar), 86.4 (C-1), 71.7 (C-2), 71.6 (C-3), 67.8 (C-4), 67.6 (C-5), 21.0 (OCO<u>C</u>H_3)

HRMS (ESI^+) *m/z*: $C_{13}H_{16}O_5SNa$ $[M+Na]^+$, calcd 307.0616, found 307.0619

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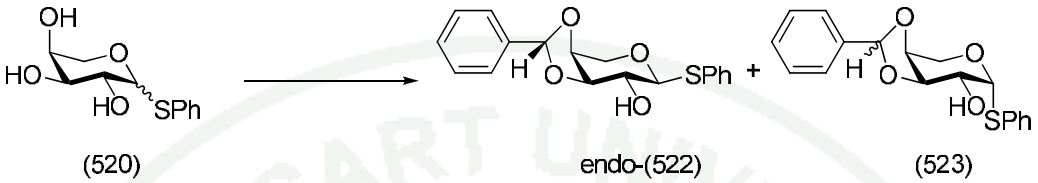
Thiophenyl-endo-3,4-*O*-benzylidene-α-L-arabinopyranoside (*endo*-522)



To a solution of 1-thiophenyl-α/β-L-arabinopyranoside (520) (217 mg, 0.89 mmol) in dry DMF (1.7 mL) were added α,α-dimethoxytoluene (0.2 mL, 1.43 mmol) and *p*-toluenesulfonic acid monohydrate (17 mg, 0.089 mmol). The reaction mixture was stirred at room temperature for 12 hours. Triethylamine was added before concentration and the syrup which was dissolved in EtOAc was extracted with saturated aqueous $NaHCO_3$, water, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 1:4) to afford thiophenyl-endo-3,4-*O*-benzylidene-*α*-L-arabinopyranoside (*endo*-522) as a white solid (145 mg, 49%); m.p. 96-98 °C; $[\alpha]_D^{25}$ -15.86, (c = 1.457, CH_2Cl_2) and thiophenyl-exo/endo-3,4-*O*-benzylidene-*β*-L-arabinopyranosides (523) (exo:endo = 0.7:1) as a white solid (66 mg, 22%); m.p. 134-136 °C; $[\alpha]_D^{25}$ +182.42, (c = 0.819, CH_2Cl_2).

Thiophenyl-endo-3,4-*O*-benzylidene-*α*-L-arabinopyranoside (*endo*-522)

FTIR (KBr), ν_{max}, cm^{-1}: 3447, 1107, 1088

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.47 – 7.50 (m, 2H, Ar(H)), 7.23-7.32 (m, 8H, Ar(H)), 5.84 (s, 1H, C<u>H</u>Ar), 4.48 (d, *J* = 9.4 Hz, 1H, H-1), 4.33 (dd, *J* = 13.4, 2.6 Hz, 1H, H-5), 4.22 (ddd, *J* = 3.1, 3.1, 6.2 Hz, 1H, H-4), 4.15 (dd, *J* = 6.5, 6.5 Hz, 1H, H-3), 3.80 (dd, *J* = 13.4, 3.4 Hz, 1H, H-5), 3.60 (dd, *J* = 9.4, 6.7 Hz, 1H, H-2)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 136.9 (C-Ar), 131.7 (C-Ar), 133.1×2 (CH-Ar), 129.5 (CH-Ar), 129.0×2 (CH-Ar), 128.4×2 (CH-Ar), 128.2 (CH-Ar), 126.7×2 (CH-Ar), 104.7 (<u>C</u>HAr), 87.8 (C-1), 75.2 (C-4), 78.1 (C-3), 71.8 (C-2), 65.6 (C-5)

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HRMS (ESI$^+$) *m/z*: $C_{18}H_{18}O_4SNa$ $[M+Na]^+$, calcd 353.0818, found 353.0826

Thiophenyl-exo/endo-3,4-*O*-benzylidene-*β*-L-arabinopyranosides (523) (exo:endo = 0.7:1)

FTIR (KBr), ν_{max}, cm^{-1}: 3421, 1095, 1066

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.79 – 7.82 (m, 2H, Ar(H)), 7.35-7.57 (m, 8H, Ar(H)), 7.16-7.33 (m, 10H, Ar(H)), 6.16 (s, 1H, CHAr-exo), 5.84 (s, 1H, CHAr-endo), 5.49 (d, *J* = 4.6 Hz, 1H, H-1-exo), 5.45 (d, *J* = 4.5 Hz, 1H, H-1-endo), 4.37 (dd, *J* = 13.3, 3.0 Hz, 1H, H-5-endo), 4.33 (dd, *J* = 13.5, 2.9 Hz, 1H, H-5-exo), 4.28 – 4.32 (m, 1H, H-4-endo), 4.27 (dd, *J* = 3.1, 1.7 Hz, 1H, H-4-exo), 4.23 (dd, *J* = 6.2, 6.2 Hz, 1H, H-3-endo), 4.23 (dd, *J* = 5.0, 5.0 Hz, 1H, H-2-exo), 4.20 (dd, *J* = 6.8, 4.9 Hz, 1H, H-3-exo), 4.12 (dd, *J* = 6.0, 4.6 Hz, 1H, H-2-endo), 4.01 (d, *J* = 13.4, 1.7 Hz, 1H, H-5-endo), 3.97 (dd, *J* = 13.4, 1.8 Hz, 1H, H-5-exo)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 138.8, 136.9 (C-Ar-endo), 134.4, 133.7 (C-Ar-exo), 132.5×2, 129.5, 129.1, 129.0, 128.4×2, 127.5, 126.0×2 (CH-Ar-exo), 131.4×2, 129.7, 129.1×2, 128.5×2, 127.4, 126.6×2 (CH-Ar-endo), 104.1 (CHAr-endo), 103.2 (CHAr-exo), 88.3 (C-1-exo), 87.7 (C-1-endo), 76.6 (C-4-endo), 76.0 (C-3-endo), 74.4 (C-4-exo), 72.8 (C-2-exo), 70.3 (C-2-endo), 68.5 (C-3-exo), 61.6 (C-5-endo), 61.5 (C-5-exo)

HRMS (ESI$^+$) *m/z*: $C_{18}H_{18}O_4SNa$ $[M+Na]^+$, calcd 353.0818, found 353.0824

Thiophenyl 2-*O*-acetyl-endo-3,4-*O*-benzylidene-*α*-L-arabinopyranoside (524)

(522) (524)

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Thiophenyl-endo-3,4-*O*-benzylidene-α-L-arabinopyranoside (*endo*-522) (50 mg, 0.15 mmol) was dissolved in dichloromethane (0.79 mL). Triethylamine (0.03 mL, 0.22 mmol), acetic anhydride (0.02 mL, 0.18 mmol), and DMAP (0.4 mg, 0.0036 mmol) were added. The reaction mixture was stirred at room temperature for 1 hour then was quenched with saturated aqueous $NaHCO_3$. The organic layer was separated and the water layer was extracted with CH_2Cl_2 three times. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed and the residue was purified by flash column chromatography (EtOAc/hexane, 1:4) to give thiophenyl 2-*O*-acetyl-endo-3,4-*O*-benzylidene-α-L-arabinopyranoside (524) (53 mg, 95%) as a white solid; m.p. 130-132 °C; $[\alpha]_D^{25}$ +2.19, (c = 0.292, CH_2Cl_2).

FTIR (KBr), ν_{max}, cm^{-1}: 1747, 1374, 1226, 1089, 1047

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.46 – 7.49 (m, 2H, Ar(H)), 7.40-7.44 (m, 2H, Ar(H)), 7.30 – 7.34 (m, 3H, Ar(H)), 7.18 – 7.25 (m, 3H, Ar(H)), 5.84 (s, 1H, C<u>H</u>Ar), 5.19 (dd, *J* = 7.2, 5.7 Hz, 1H, H-2), 4.88 (d, *J* = 7.2 Hz, 1H, H-1), 4.31 – 4.38 (m, 1H, H-3), 4.26 (dd, *J* = 12.3, 6.0 Hz, 1H, H-4), 4.26 (dd, *J* = 12.6, 4.7 Hz, 1H, H-5), 3.80 (dd, *J* = 12.9, 4.4 Hz, 1H, H-5), 2.06 (s, 3H, $OCOCH_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 169.4 ($O\underline{C}OCH_3$), 136.3 (C-Ar), 133.7 (C-Ar), 132.0×2 (CH-Ar), 129.6 (CH-Ar), 128.9×2 (CH-Ar), 128.4×2 (CH-Ar), 127.7 (CH-Ar), 126.9×2 (CH-Ar), 105.1 (<u>C</u>HAr), 85.6 (C-1), 75.9 (C-4), 73.2 (C-3), 71.7 (C-2), 63.8 (C-5), 21.0 ($OCO\underline{C}H_3$)

HRMS (ESI^+) *m/z*: $C_{20}H_{20}O_5SNa$ $[M+Na]^+$, calcd 395.0929, found 395.0943

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Thiophenyl 2-*O*-acetyl-exo/endo-3,4-*O*-benzylidene-*β*-L-arabinopyranosides (525)

(523) (525)

Thiophenyl-exo/endo-3,4-*O*-benzylidene-*β*-L-arabinopyranosides (523) (85 mg, 0.26 mmol) was dissolved in dichloromethane (1.35 mL). Triethylamine (0.05 mL, 0.38 mmol), acetic anhydride (0.03 mL, 0.31 mmol), and DMAP (1 mg, 0.006 mmol) were added. The reaction mixture was stirred at room temperature for 1 hour then was quenched with saturated aqueous $NaHCO_3$. The organic layer was separated and the water layer was extracted with CH_2Cl_2 three times. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (EtOAc/hexane, 1:4) to give thiophenyl 2-*O*-acetyl-exo/endo-3,4-*O*-benzylidene-*β*-L-arabinopyranosides (525) (exo:endo, 1:6) (91 mg, 95%) as a white solid; m.p. 78-80 °C; $[\alpha]_D^{25}$ +187.11, (c = 0.547, CH_2Cl_2)**.**

FTIR (neat), ν_{max}, cm^{-1}: 1742, 1372, 1232, 1096, 1056

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.42-7.45 (m, 4H, Ar(H)), 7.37-7.40 (m, 4H, Ar(H)), 7.28-7.34 (m, 6H, Ar(H)), 7.16-7.26 (m, 6H, Ar(H)), 6.19 (s, 1H, C<u>H</u>Ar-exo), 5.83 (s, 1H, C<u>H</u>Ar-endo), 5.71 (d, *J* = 4.8 Hz, 1H, H-1-exo), 5.70 (d, *J* = 5.0 Hz, 1H, H-1-endo), 5.24 (dd, *J* = 6.5, 5.0 Hz, 1H, H-2-endo), 5.14 (dd, *J* = 9.1, 4.8 Hz, 1H, H-2-exo), 4.39 (dd, *J* = 13.5, 3.0 Hz, 1H, H-5-endo), 4.33-4.38 (m, 1H, H-4-exo), 4.35 (dd, *J* = 6.4, 3.9 Hz, 1H, H-3-endo), 4.31 (ddd, *J* = 6.4, 3.0, 1.4 Hz, 1H, H-4-endo), 4.23 (dd, *J* = 12.6, 2.1 Hz, 1H, H-5-exo), 4.05 (dd, *J* = 13.5, 1.4 Hz, 1H, H-5-endo), 3.99 (dd, *J* = 3.4, 2.0 Hz, 1H, H-3-exo), 3.72 (dd, *J* = 12.7, 3.3 Hz, 1H, H-5-exo), 2.09 (s, 3H, OCOC<u>H</u>$_3$-exo), 2.08 (s, 3H, OCOC<u>H</u>$_3$-endo)

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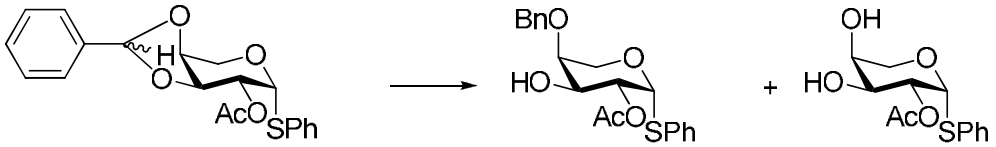
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.7 (O<u>C</u>OCH_3-exo), 170.0 (O<u>C</u>OCH_3-endo), 136.4, 134.4 (C-Ar-endo), 136.1, 133.6 (C-Ar-exo), 131.4×2, 129.7, 129.0×2, 128.4×2, 127.4, 126.1×2 (CH-Ar-exo), 131.1×2, 129.7, 129.1×2, 128.5×2, 127.4, 126.8×2 (CH-Ar-endo), 104.5 (<u>C</u>HAr-endo), 103.3 (<u>C</u>HAr-exo), 85.5 (C-1-exo), 84.1 (C-1-endo), 74.7 (C-4-endo), 73.5 (C-4-exo), 72.8 (C-3-endo), 72.1 (C-3-exo), 71.8 (C-2-endo), 68.3 (CH-2-exo), 63.5 (C-5-exo), 60.8 (C-5-endo), 21.0 (OCO<u>C</u>H_3-exo), 20.9 (OCO<u>C</u>H_3-endo)

Thiophenyl 2-*O*-acetyl-endo-3,4-*O*-benzylidene-*α*-L-arabinopyranoside (524)

(279) (524)

To a solution of 1-thiophenyl-2-*O*-acetyl-α-L-arabinopyranoside (279) (1.0 g, 3.52 mmol) in dry DMF (9.99 mL) were added α,α-dimethoxytoluene (0.58 mL, 4.22 mmol) and *p*-toluenesulfonic acid monohydrate (67 mg, 0.35 mmol). The reaction mixture was stirred at room temperature for 12 h. Triethylamine was added before concentration and the syrup which was dissolved in EtOAc was extracted with saturated aqueous $NaHCO_3$, water, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 1:4) to afford thiophenyl 2-*O*-acetyl-endo-3,4-*O*-benzylidene-*α*-L-arabinopyranoside (524) (986 mg, 75%) as a white solid; m.p. 130-132 °C; $[\alpha]_D^{25}$ +2.19, (c = 0.292, CH_2Cl_2).

Thiophenyl 2-*O*-acetyl-4-*O*-benzyl-*β*-L-arabinopyranoside (526)



(525) (526) (527)

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To a solution of thiophenyl 2-*O*-acetyl-exo/endo-3,4-*O*-benzylidene-*β*-L-arabinopyranosides (525) (88 mg, 0.24 mmol) in dichloromethane (5.8 mL) at 0 °C was added Et_3SiH (0.46 mL, 2.82 mmol) and $BF_3{\cdot}Et_2O$ (0.06 mL, 0.47 mmol). The reaction was stirred at 0 °C for 30 minutes. The mixture was diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 3:7) to afford thiophenyl 2-*O*-acetyl-4-*O*-benzyl-*β*-L-arabinopyranoside (526) as a white solid (57 mg, 65%); m.p. 83-85 °C; $[\alpha]_D^{25}$ +219.37, (c = 0.194, CH_2Cl_2) and thiophenyl 2-*O*-acetyl-*β*-L-arabinopyranoside (527) as a white solid (15 mg, 22%); $[\alpha]_D^{25}$ +193.80, (c = 0.50, CH_2Cl_2)**.**

Thiophenyl 2-*O*-acetyl-4-*O*-benzyl-*β*-L-arabinopyranoside (526)

FTIR (KBr), ν_{max}, cm^{-1}: 3367, 1730, 1459, 1374, 1249, 1085, 1063

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.35 – 7.38 (m, 2H, Ar(H)), 7.15 – 7.30 (m, 8H, Ar(H)), 5.61 (d, *J* = 4.3 Hz, 1H, H-1), 5.19 (dd, *J* = 8.4, 4.3 Hz, 1H, H-2), 4.62 (d, *J* = 11.6 Hz, 1H, OCH_2Ar), 4.47 (d, *J* = 11.7 Hz, 1H, OCH_2Ar), 4.04 (dd, *J* = 13.9, 3.8 Hz, 1H, H-5), 3.91 (ddd, *J* = 7.9, 7.9, 3.0 Hz, 1H, H-3), 3.76 (dd, *J* = 14.1, 4.4 Hz, 1H, H-5), 3.75 (dd, *J* = 7.3, 4.2 Hz, 1H, H-4), 2.46 (d, *J* = 7.6 Hz, 1H, OH), 2.04 (s, 3H, $OCOCH_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.4 ($O\underline{C}OCH_3$), 137.3 (C-Ar), 133.7 (C-Ar), 131.4×2 (CH-Ar), 129.0×2 (CH-Ar), 128.6×2 (CH-Ar), 128.1 (CH-Ar), 127.8×2 (CH-Ar), 127.3 (CH-Ar), 85.3 (C-1), 74.8 (C-4), 72.1 (C-2), 71.5 (OCH_2Ar), 67.6 (C-3), 60.8 (C-5), 20.9 ($OCO\underline{C}H_3$)

HRMS (ESI^+) *m/z*: $C_{20}H_{22}O_5SNa$ $[M+Na]^+$, calcd 397.1086, found 397.1086

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Thiophenyl 2-*O*-acetyl-β-L-arabinopyranoside (527)

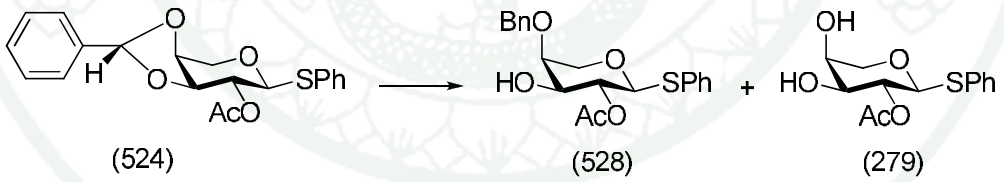
FTIR (neat), ν_{max}, cm^{-1}: 3412, 1732, 1373, 1245, 1062

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.40 – 7.44 (m, 2H, Ar(H)), 7.21 – 7.30 (m, 3H, Ar(H)), 5.75 (d, *J* = 4.8 Hz, 1H, H-1), 5.20 (dd, *J* = 9.1, 4.9 Hz, 1H, H-2), 4.28 (dd, *J* = 12.6, 2.1 Hz, 1H, H-5), 4.04 – 4.06 (m, 1H, H-4), 3.97 (dd, *J* = 9.1, 3.5 Hz, 1H, H-3), 3.77 (dd, *J* = 12.6, 3.4 Hz, 1H, H-5), 2.15 (s, 3H, $OCOCH_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.8 ($O\underline{C}OCH_3$), 133.6 (C-Ar), 131.4×2 (CH-Ar), 129.1×2 (CH-Ar), 127.4 (CH-Ar), 85.5 (C-1), 72.1 (C-2), 68.4 (C-4), 68.4 (C-3), 63.5 (C-5), 21.0 ($OCO\underline{C}H_3$)

MS (ESI^+), *m/z* (relative intensity): 307 ($[M+Na]^+$, 100%)

Thiophenyl 2-*O*-acetyl-4-*O*-benzyl-α-L-arabinopyranoside (528)



To a solution of thiophenyl 2-*O*-acetyl-endo-3,4-*O*-benzylidene-α-L-arabinopyranoside (524) (986 mg, 2.65 mmol) in dichloromethane (26.5 mL) at 0 °C was added Et_3SiH (5.14 mL, 31.8 mmol) and $BF_3{\cdot}Et_2O$ (0.67 mL, 5.30 mmol). The reaction was stirred at 0 °C for 30 minutes. The mixture was diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 3:7) to afford thiophenyl 2-*O*-acetyl-4-*O*-benzyl-α-L-arabinopyranoside (528) as a white solid (722 mg, 73%); m.p. 101-103 °C; $[\alpha]_D^{25}$ +6.52, (c = 0.32, CH_2Cl_2) and thiophenyl 2-*O*-acetyl-α-L-arabinopyranoside (279) as a white solid (146 mg, 19%).

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Thiophenyl 2-*O*-acetyl-4-*O*-benzyl-α-L-arabinopyranoside (528)

FTIR (KBr), ν_{max}, cm^{-1}: 3377, 1731, 1372, 1247, 1084, 1057

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.40 – 7.43 (m, 2H, Ar(H)), 7.14 – 7.32 (m, 8H, Ar(H)), 5.07 (dd, *J* = 6.9, 6.9 Hz, 1H, H-2), 4.74 (d, *J* = 6.9 Hz, 1H, H-1), 4.63 (d, *J* = 11.7 Hz, 1H, OCH_2Ar), 4.47 (d, *J* = 11.7 Hz, 1H, OCH_2Ar), 4.20 (dd, *J* = 12.6, 4.8 Hz, 1H, H-5), 3.71 – 3.75 (m, 2H, H-3, H-4), 3.43 (dd, *J* = 12.4, 2.3 Hz, 1H, H-5), 2.04 (s, 3H, $OCOCH_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.0 ($O\underline{C}OCH_3$), 137.3 (C-Ar), 134.1 (C-Ar), 131.9×2 (CH-Ar), 128.8 (CH-Ar), 128.5×2 (CH-Ar), 128.0×2 (CH-Ar), 127.8×2 (CH-Ar), 127.5 (CH-Ar), 86.0 (C-1), 74.3 (C-4), 71.7 (C-2), 71.3 (OCH_2Ar), 70.6 (C-3), 63.1 (C-5), 21.0 ($OCO\underline{C}H_3$)

HRMS (ESI^+) *m/z*: $C_{20}H_{22}O_5SNa$ $[M+Na]^+$, calcd 397.1086, found 397.1085

Bromo 2,3,4-*O*-triacetyl-α/β-L-arabinopyranoside (529)

(519) (529)

The 1,2,3,4-*O*-tetraacetyl-L-arabinopyranoside (519) (5.46 g, 17.2 mmol) was then dissolved in 95.7 mL of acetic acid followed by the dropwise addition of phosphorustribromide (1M in CH_2Cl_2, 164.9 mL, 164.9 mmol). After stirring at room temperature for 4 h the mixture was diluted with CH_2Cl_2, poured into ice-water, and extracted with more CH_2Cl_2. The organic extracts were dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to give the bromide (529) as a white solid (4.63 g, 80%). The crude product was immediately used in the next step without purification.

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4-Methoxybenzyl 2,3,4-*O*-triacetyl-α-L-arabinopyranoside (530)

(529) (530)

The bromide (529) (4.63 g, 13.7 mmol) was then mixed with toluene (58.2 mL) and 4Å MS (10.2 g) for 40 minutes before adding 4-methoxybenzyl alcohol (8.61 mL, 68.4 mmol), I_2 (5.19 g, 20.5 mmol), and Ag_2CO_3 (7.54 g, 27.2 mmol). After stirring overnight, the reaction mixture was filtered through celite and the pad was washed with toluene. The organic layer was then washed with 20% $Na_2S_2O_3$ (115 mL), H_2O (115 mL) and saturated aqueous NaCl (115 mL). The organic extract was dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 3:7) to afford 4-methoxybenzyl 2,3,4-*O*-triacetyl-α-L-arabinopyranoside (530) (3.73 g, 70%) as a colorless syrup; $[\alpha]_D^{25}$ -20.2, (c = 0.31, $CHCl_3$).

FTIR (neat), ν_{max}, cm^{-1}: 1747, 1612, 1514, 1370, 1249, 1224, 1103, 1056, 1023

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.20 (d, *J* = 8.7 Hz, 2H, Ar(H)), 6.85 (d, *J* = 8.7 Hz, 2H, Ar(H)), 5.22 - 5.24 (m, 1H, H-4), 5.20 (dd, *J* = 9.4, 6.9 Hz, 1H, H-2), 4.98 (dd, *J* = 9.2, 3.6 Hz, 1H, H-3), 4.79 (d, *J* = 11.9 Hz, 1H, OC$\underline{H}_2$ArOCH$_3$), 4.51 (d, *J* = 11.9 Hz, 1H, OC$\underline{H}_2$ArOCH$_3$), 4.44 (d, *J* = 6.8 Hz, 1H, H-1), 4.03 (dd, *J* = 13.0, 3.5 Hz, 1H, H-5), 3.78 (s, 3H, OCH_3), 3.59 (dd, *J* = 12.9, 1.9 Hz, 1H, H-5), 2.11 (s, 3H, $OCOCH_3$), 2.00 (s, 3H, $OCOCH_3$), 1.98 (s, 3H, $OCOCH_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.2 (O$\underline{C}$OCH$_3$), 170.0 (O$\underline{C}$OCH$_3$), 169.3 (O$\underline{C}$OCH$_3$), 159.3 (C-Ar), 129.2×2 (CH-Ar), 128.8 (C-Ar), 113.7×2 (CH-Ar), 99.1 (C-1), 70.0 (C-3), 70.0 (O$\underline{C}$H$_2$ArOCH$_3$), 69.1 (C-2), 67.5 (C-4), 62.9 (C-5), 55.1 (OCH_3), 20.6 (OCO$\underline{C}$H$_3$), 20.5 (OCO$\underline{C}$H$_3$), 20.4 (OCO$\underline{C}$H$_3$)

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MS (ESI$^+$), *m/z* (relative intensity): 419 ([M+Na]$^+$, 100%)

4-Methoxybenzyl α-L-arabinopyranoside (531)

(530) (531)

4-Methoxybenzyl 2,3,4-*O*-triacetyl-α-L-arabinopyranoside (530) (3.73 g, 9.42 mmol) was stirred overnight in a mixture of MeOH/Et_3N/H_2O (8:1:1, 45 mL). The reaction mixture was evaporated under reduced pressure and the crude residue was purified by flash column chromatography (EtOAc then EtOAc/MeOH, 9:1) to give 4-methoxybenzyl α-L-arabinopyranoside (531) as a white solid (2.54 g, 100%); m.p. 107-109 °C; $[\alpha]_D^{20}$ -26.1, (c = 1.0, CH_3OH).

FTIR (KBr), ν_{max}, cm^{-1}: 3269, 1611, 1514, 1257, 1088, 1075, 1004

^{1}H NMR (CD_3OD, 400 MHz) δ: 7.30 (d, *J* = 8.5 Hz, 2H, Ar(H)), 6.86 (d, *J* = 8.6 Hz, 2H, Ar(H)), 4.76 (d, *J* = 11.4 Hz, 1H, OC$\underline{H}_2$ArOCH$_3$), 4.52 (d, *J* = 11.3 Hz, 1H, OC$\underline{H}_2$ArOCH$_3$), 4.26 (d, *J* = 6.8 Hz, 1H, H-1), 3.88 (dd, *J* = 12.5, 3.1 Hz, 1H, H-5), 3.79 – 3.81 (m, 1H, H-4), 3.76 (s, 3H, OCH_3), 3.59 (dd, *J* = 8.7, 6.9 Hz, 1H, H-2), 3.51 (dd, *J* = 12.6, 1.6 Hz, 1H, H-5), 3.50 (dd, *J* = 8.6, 3.6 Hz, 1H, H-3)

^{13}C NMR (CD_3OD, 100 MHz) δ: 159.7 (C-Ar), 129.8 (C-Ar), 129.7×2 (CH-Ar), 113.6×2 (CH-Ar), 102.3 (C-1), 73.0 (C-3), 71.2 (C-2), 70.1 (O$\underline{C}$H$_2$ArOCH$_3$), 68.4 (C-4), 65.6 (C-5), 54.6 (OCH_3)

MS (ESI$^+$), *m/z* (relative intensity): 293 ([M+Na]$^+$, 100%)

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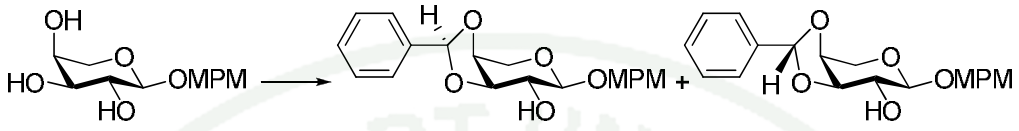
4-Methoxybenzyl exo/endo-3,4-*O*-benzylidene-α-L-arabinopyranosides (532)



(531) *exo*-(532) *endo*-(532)

To a solution of 4-methoxybenzyl α-L-arabinopyranoside (531) (4.28 g, 15.84 mmol) in dry *N,N*-dimethylformamide (35.3 mL) were added α,α-dimethoxytoluene (3.53 mL, 25.39 mmol) and *p*-toluenesulfonic acid monohydrate (30 mg, 0.16 mmol). The reaction mixture was stirred at room temperature for 24 h. Triethylamine was added before concentration and the syrup which was dissolved in EtOAc was extracted with saturated aqueous $NaHCO_3$, water, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 3:7) to afford 4-methoxybenzyl exo-3,4-*O*-benzylidene-α-L-arabinopyranoside (*exo*-532) as a white solid (647 mg, 11%); m.p. 118-119 °C; $[\alpha]_D^{25}$ -12.43, (c = 0.2, CH_2Cl_2) and 4-methoxybenzyl endo-3,4-*O*-benzylidene-α-L-arabinopyranoside (*endo*-532) as a white solid (4.14 g, 73%); m.p. 119-121 °C; $[\alpha]_D^{25}$ +6.33, (c = 0.12, $CHCl_3$).

4-Methoxybenzyl exo-3,4-*O*-benzylidene-α-L-arabinopyranoside (*exo*-532)

FTIR (KBr), ν_{max}, cm^{-1}: 3452, 1515, 1251, 1102, 1075

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.44 – 7.47 (m, 2H, Ar(H)), 7.34-7.40 (m, 3H, Ar(H)), 7.30 (d, *J* = 8.4 Hz, 2H, Ar(H)), 6.90 (d, *J* = 8.8 Hz, 2H, Ar(H)), 6.19 (s, 1H, C<u>H</u>Ar), 4.87 (d, *J* = 11.2 Hz, 1H, OC<u>H</u>$_2$ArOCH$_3$), 4.55 (d, *J* = 11.2 Hz, 1H, OC<u>H</u>$_2$ArOCH$_3$), 4.36 (dd, *J* = 7.4, 5.7 Hz, 1H, H-3), 4.31 (dd, *J* = 13.4, 2.4 Hz, 1H, H-5), 4.29 (d, *J* = 7.7 Hz, 1H, H-1), 4.18 - 4.21 (m, 1H, H-4), 3.82 (dd, *J* = 9.1, 7.5 Hz, 1H, H-2), 3.81 (s, 3H, OCH_3), 3.74 (dd, *J* = 13.4, 2.9 Hz, 1H, H-5)

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^{13}C NMR ($CDCl_3$, 100 MHz) δ: 159.5 (C-Ar), 138.5 (C-Ar), 129.9×2 (CH-Ar), 129.1 (CH-Ar), 128.9 (C-Ar), 128.3×2 (CH-Ar), 126.1×2 (CH-Ar), 113.9×2 (CH-Ar), 103.3 (CHAr), 100.6 (C-1), 79.2 (C-3), 73.0 (C-4), 71.0 (C-2), 70.3 (OCH_2ArOCH_3), 63.2 (C-5), 55.2 (OCH_3)

MS (ESI$^+$), *m/z* (relative intensity): 381 ($[M+Na]^+$, 100%)

4-Methoxybenzyl endo-3,4-*O*-benzylidene-α-L-arabinopyranoside (*endo*-532)

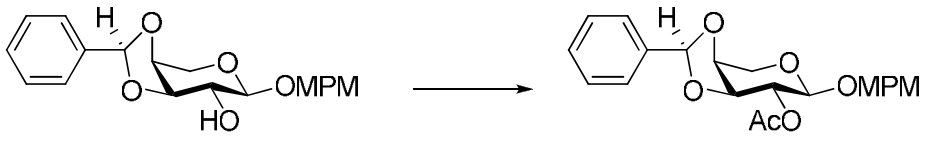
FTIR (KBr), ν_{max}, cm^{-1}: 3452, 1513, 1249, 1118, 1093

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.50 – 7.52 (m, 2H, Ar(H)), 7.35-7.38 (m, 3H, Ar(H)), 7.29 (d, *J* = 8.4 Hz, 2H, Ar(H)), 6.89 (d, *J* = 8.7 Hz, 2H, Ar(H)), 5.94 (s, 1H, CHAr), 4.83 (d, *J* = 11.2 Hz, 1H, OCH_2ArOCH_3), 4.53 (d, *J* = 11.2 Hz, 1H, OCH_2ArOCH_3), 4.36 (d, *J* = 7.4 Hz, 1H, H-1), 4.31 (dd, *J* = 14.0, 3.3 Hz, 1H, H-5), 4.30 (dd, *J* = 6.3, 4.7 Hz, 1H, H-4), 4.20 (dd, *J* = 7.2, 6.3 Hz, 1H, H-3), 3.87 (dd, *J* = 14.0, 4.7 Hz, 1H, H-5), 3.80 (s, 3H, OCH_3), 3.76 (dd, *J* = 7.3, 7.3 Hz, 1H, H-2)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 159.3 (C-Ar), 136.9 (C-Ar), 129.8×2 (CH-Ar), 129.3 (CH-Ar), 129.0 (C-Ar), 128.3×2 (CH-Ar), 126.6×2 (CH-Ar), 113.8×2 (CH-Ar), 104.5 (CHAr), 100.5 (C-1), 77.8 (C-3), 74.8 (C-4), 73.4 (C-2), 70.0 (OCH_2ArOCH_3), 62.5 (C-5), 55.1 (OCH_3)

MS (ESI$^+$), *m/z* (relative intensity): 381 ($[M+Na]^+$, 100%)

4-Methoxybenzyl 2-*O*-acetyl-exo-3,4-*O*-benzylidene-α-L-arabinopyranoside (*exo*-533)



exo-(532) *exo*-(533)

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4-Methoxybenzyl exo-3,4-*O*-benzylidene-α-L-arabinopyranoside (*exo*-532) (647 mg, 1.81 mmol) was dissolved in dichloromethane (9.44 mL). Triethylamine (0.37 mL, 2.71 mmol), acetic anhydride (0.20 mL, 2.17 mmol), and DMAP (5 mg, 0.04 mmol) were added. The reaction mixture was stirred at room temperature for 1 hour then was quenched with saturated aqueous $NaHCO_3$. The organic layer was separated and the water layer was extracted with CH_2Cl_2 three times. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (EtOAc/hexane, 3:7) to give 4-methoxybenzyl 2-*O*-acetyl-exo-3,4-*O*-benzylidene-α-L-arabinopyranoside (*exo*-533) (624 mg, 86%) as a colorless syrup then became a white solid; m.p. 99-101 °C; $[\alpha]_D^{25}$ -33.02, (c = 0.40, CH_2Cl_2).

FTIR (neat), ν_{max}, cm^{-1}: 1746, 1612, 1514, 1247, 1229, 1099, 1061

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.43 – 7.45 (m, 2H, Ar(H)), 7.35-7.38 (m, 3H, Ar(H)), 7.26 (d, *J* = 8.4 Hz, 2H, Ar(H)), 6.89 (d, *J* = 8.8 Hz, 2H, Ar(H)), 6.22 (s, 1H, C<u>H</u>Ar), 5.25 (dd, *J* = 6.2, 6.2 Hz, 1H, H-2), 4.80 (d, *J* = 12.0 Hz, 1H, OC<u>H</u>$_2$ArOCH$_3$), 4.55 (d, *J* = 12.0 Hz, 1H, OC<u>H</u>$_2$ArOCH$_3$), 4.49 (d, *J* = 6.2 Hz, 1H, H-1), 4.36 – 4.38 (m, 2H, H-3, H-4), 4.19 (dd, *J* = 13.0, 3.8 Hz, 1H, H-5), 3.81 (s, 3H, OCH_3), 3.78 (dd, *J* = 13.0, 4.2 Hz, 1H, H-5), 2.08 (s, 3H, $OCOCH_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 169.6 (O<u>C</u>OCH$_3$), 159.3 (C-Ar), 138.1 (C-Ar), 129.4×2 (CH-Ar), 129.2 (CH-Ar), 129.1 (C-Ar), 128.4×2 (CH-Ar), 126.2×2 (CH-Ar), 113.8×2 (CH-Ar), 103.4 (<u>C</u>HAr), 97.6 (C-1), 76.7 (C-3), 72.3 (C-4), 70.1 (C-2), 69.3 (O<u>C</u>H$_2$ArOCH$_3$), 61.6 (C-5), 55.2 (OCH_3), 20.9 (OCO<u>C</u>H$_3$)

MS (ESI$^+$), *m/z* (relative intensity): 423 ($[M+Na]^+$, 100%)

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4-Methoxybenzyl 2-*O*-acetyl-endo-3,4-*O*-benzylidene-α-L-arabinopyranoside (*endo*-533)

4-Methoxybenzyl endo-3,4-*O*-benzylidene-α-L-arabinopyranoside (*endo*-532) (4.14 g, 11.6 mmol) was dissolved in dichloromethane (60.5 mL). Triethylamine (2.4 mL, 17.4 mmol), acetic anhydride (1.3 mL, 13.9 mmol), and DMAP (34 mg, 0.28 mmol) were added. The reaction mixture was stirred at room temperature for 1 hour then was quenched with saturated aqueous $NaHCO_3$. The organic layer was separated and the water layer was extracted with CH_2Cl_2 three times. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (EtOAc/hexane, 3:7) to give 4-methoxybenzyl 2-*O*-acetyl-endo-3,4-*O*-benzylidene-α-L-arabinopyranoside (*endo*-533) (4.05 g, 88%) as a colorless syrup; $[\alpha]_D^{25}$ 21.80, (c = 0.60, CH_2Cl_2).

FTIR (neat), ν_{max}, cm^{-1}: 1744, 1612, 1514, 1244, 1232, 1119, 1091, 1066

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.51-7.55 (m, 2H, Ar(H)), 7.34-7.39 (m, 3H, Ar(H)), 7.25 (d, *J* = 8.9 Hz, 2H, Ar(H)), 6.88 (d, *J* = 8.7 Hz, 2H, Ar(H)), 5.89 (s, 1H, C<u>H</u>Ar), 5.24 (dd, *J* = 5.7, 5.7 Hz, 1H, H-2), 4.75 (d, *J* = 11.8 Hz, 1H, OC<u>H</u>$_2$ArOCH$_3$), 4.57 (d, *J* = 5.5 Hz, 1H, H-1), 4.52 (d, *J* = 11.8 Hz, 1H, OC<u>H</u>$_2$ArOCH$_3$), 4.38 (dd, *J* = 5.5, 11.6 Hz, 1H, H-4), 4.27 (dd, *J* = 6.2, 6.2 Hz, 1H, H-3), 4.12 (dd, *J* = 12.7, 5.7 Hz, 1H, H-5), 3.84 (dd, *J* = 12.6, 5.0 Hz, 1H, H-5), 3.81 (s, 3H, OCH_3), 2.09 (s, 3H, $OCOCH_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 169.4 (O<u>C</u>OCH$_3$), 159.3 (C-Ar), 136.4 (C-Ar), 129.5 (CH-Ar), 129.4×2 (CH-Ar), 129.1 (C-Ar), 128.4×2 (CH-Ar), 126.9×2

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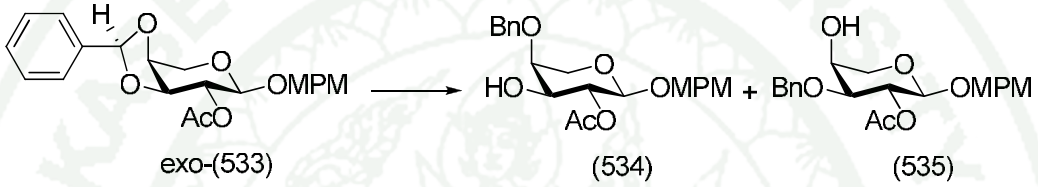
(CH-Ar), 113.7×2 (CH-Ar), 104.9 (CHAr), 97.5 (C-1), 75.8 (C-3), 72.8 (C-4), 72.2 (C-2), 69.3 (OCH_2ArOCH_3), 61.3 (C-5), 55.2 (OCH_3), 20.9 ($OCOCH_3$)

MS (ESI$^+$), *m/z* (relative intensity): 423 ($[M+Na]^+$, 100%)

4-Methoxybenzyl 2-*O*-acetyl-4-*O*-benzyl-α-L-arabinopyranoside (534)



Using $BF_3{\cdot}OEt_2$/Et_3SiH in CH_2Cl_2

To a solution of 4-methoxybenzyl 2-*O*-acetyl-exo-3,4-*O*-benzylidene-α-L-arabinopyranoside (*exo*-533) (874 mg, 2.18 mmol) in dichloromethane (21.8 mL) at 0 °C was added Et_3SiH (4.23 mL, 26.2 mmol) and $BF_3{\cdot}Et_2O$ (0.55 mL, 4.37 mmol). The reaction was stirred at 0 °C for 5 h. The mixture was diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 2:3) to afford 4-methoxybenzyl 2-*O*-acetyl-4-*O*-benzyl-α-L-arabinopyranoside (534) as a white solid (123 mg, 14%); $[\alpha]_D^{25}$ -29.44, (c = 0.60, CH_2Cl_2), 2-*O*-acetyl-4-*O*-benzyl-α/*β*-L-arabinopyranoside (536) as a white solid (333 mg, 54%) and 4-methoxybenzyl 2-*O*-acetyl-α-L-arabinopyranoside (538) as a white solid (150 mg, 22%); $[\alpha]_D^{25}$ -23.80, (c = 0.2, $CHCl_3$).

Using $Cu(OTf)_2$/$BH_3{\cdot}THF$

A 1M solution of borane/tetrahydrofuran complex in tetrahydrofuran (0.69 mL, 0.69 mmol) was added to 4-methoxybenzyl 2-*O*-acetyl-exo-3,4-*O*-benzylidene-α-L-arabinopyranoside (*exo*-533) (55 mg, 0.14 mmol) at room temperature under nitrogen. The mixture was stirred for 10 minutes, and $Cu(OTf)_2$ (5 mg, 0.014 mmol)

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was added to the solution. After stirring for 5 minutes, the mixture was cooled down to 0 °C, and the reaction was quenched by sequential additions of triethylamine and methanol (*caution*: hydrogen gas was evolved). The resulting mixture was concentrated under reduced pressure followed by coevaporation with methanol. The residue was purified by flash column chromatography (EtOAc/hexane, 2:3) to afford 4-methoxybenzyl 2-*O*-acetyl-4-*O*-benzyl-α-L-arabinopyranoside (534) as a white solid (2 mg, 4%), 4-methoxybenzyl 2-*O*-acetyl-3-*O*-benzyl-α-L-arabinopyranoside (535) as a white solid; $[\alpha]_D^{25}$ -47.38, (c = 0.08, $CHCl_3$) (4 mg, 7%) and 4-methoxybenzyl 3-*O*-benzyl-α-L-arabinopyranoside (537) as a white solid (6 mg, 12%).

Using $TiCl_4$/Et_3SiH in CH_2Cl_2

To a solution of 4-methoxybenzyl 2-*O*-acetyl-exo-3,4-*O*-benzylidene-α-L-arabinopyranoside (*exo*-533) (173 mg, 0.43 mmol) in dichloromethane (1.73 mL) was added Et_3SiH (0.09 mL, 0.58 mmol). The reaction mixture was cooled to -78 °C and slowly added a solution of $TiCl_4$ (0.05 ml, 0.49 mmol) in dichloromethane (0.54 mL). The reaction was stirred at -78 °C for 5 h. The reaction mixture was poured into ice and extracted with EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 2:3) to afford 4-methoxybenzyl 2-*O*-acetyl-4-*O*-benzyl-α-L-arabinopyranoside (534) as a white solid (75 mg, 43%), 4-methoxybenzyl 2-*O*-acetyl-3-*O*-benzyl-α-L-arabinopyranoside (535) as a white solid (20 mg, 11%) and 2-*O*-acetyl-4-*O*-benzyl-α/*β*-L-arabinopyranoside (536) as a white solid (26 mg, 21%).

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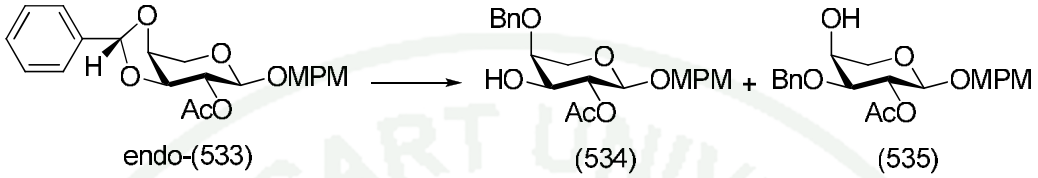
4-Methoxybenzyl 2-*O*-acetyl-4-*O*-benzyl-α-L-arabinopyranoside (534)



To a solution of 4-methoxybenzyl 2-*O*-acetyl-endo-3,4-*O*-benzylidene-α-L-arabinopyranoside (*endo*-533) (3.02 g, 7.55 mmol) in dichloromethane (30.2 mL) was added Et_3SiH (1.65 mL, 10.2 mmol). The reaction mixture was cooled to -78 °C and slowly added a solution of $TiCl_4$ (0.93 ml, 8.46 mmol) in dichloromethane (9.3 mL). The reaction was stirred at -78 °C for 5 h. The reaction mixture was poured into ice and extracted with EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 2:3) to afford 4-methoxybenzyl 2-*O*-acetyl-4-*O*-benzyl-α-L-arabinopyranoside (534) as a white solid (2.21 g, 73%), 4-methoxybenzyl 2-*O*-acetyl-3-*O*-benzyl-α-L-arabinopyranoside (535) as a white solid (428 mg, 14%) and 2-*O*-acetyl-4-*O*-benzyl-α/*β*-L-arabinopyranoside (536) as a white solid (106 mg, 5%).

4-Methoxybenzyl 2-*O*-acetyl-4-*O*-benzyl-α-L-arabinopyranoside (534)

FTIR (neat), ν_{max}, cm^{-1}: 3481, 1738, 1612, 1514, 1244, 1088, 1057

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.22 – 7.30 (m, 5H, Ar(H)), 7.18 (d, *J* = 8.4 Hz, 2H, Ar(H)), 6.81 (d, *J* = 8.7 Hz, 2H, Ar(H)), 4.97 (dd, *J* = 4.8, 6.8 Hz, 1H, H-2), 4.69 (d, *J* = 11.8 Hz, 1H, $OC\underline{H}_2ArOCH_3$), 4.62 (d, *J* = 11.8 Hz, 1H, $OC\underline{H}_2Ar$), 4.53 (d, *J* = 11.8 Hz, 1H, $OC\underline{H}_2Ar$), 4.45 (d, *J* = 5.1 Hz, 1H, H-1), 4.45 (d, *J* = 11.3 Hz, 1H, $OC\underline{H}_2ArOCH_3$), 3.98 (dd, *J* = 6.2, 12.3 Hz, 1H, H-5), 3.75 – 3.78 (m, 1H, H-4), 3.74 (s, 3H, OCH_3), 3.67 (ddd, *J* = 3.2, 3.2, 6.3 Hz, 1H, H-3), 3.41 (dd, *J* = 3.1, 12.3 Hz, 1H, H-5), 1.99 (s, 3H, $OCOCH_3$)

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^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.0 (O<u>C</u>OCH$_3$), 159.4 (C-Ar), 137.5 (C-Ar), 129.5×2 (CH-Ar), 128.8 (C-Ar), 128.5×2 (CH-Ar), 127.9 (CH-Ar), 127.8×2 (CH-Ar), 113.8×2 (CH-Ar), 97.8 (C-1), 73.4 (C-3), 71.8 (C-2), 71.2 (O<u>C</u>H$_2$Ar), 69.6 (O<u>C</u>H$_2$ArOCH$_3$), 69.4 (C-4), 59.6 (C-5), 55.2 (OCH$_3$), 20.9 (OCO<u>C</u>H$_3$)

MS (ESI$^+$), *m/z* (relative intensity): 425 ([M+Na]$^+$, 100%)

4-Methoxybenzyl 2-*O*-acetyl-3-*O*-benzyl-α-L-arabinopyranoside (535)

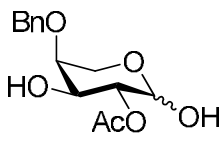
FTIR (neat), ν_{max}, cm^{-1}: 3478, 1739, 1612, 1514, 1243, 1084, 1052

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.24 – 7.34 (m, 5H, Ar(H)), 7.22 (d, *J* = 8.5 Hz, 2H, Ar(H)), 6.84 (d, *J* = 8.5 Hz, 2H, Ar(H)), 5.21 (dd, *J* = 6.0, 5.0 Hz, 1H, H-2), 4.74 (d, *J* = 11.5 Hz, 1H, OC<u>H</u>$_2$ArOCH$_3$), 4.68 (d, *J* = 11.5 Hz, 1H, OC<u>H</u>$_2$Ar), 4.56 (d, *J* = 11.5 Hz, 1H, OC<u>H</u>$_2$Ar), 4.50 (d, *J* = 4.5 Hz, 1H, H-1), 4.46 (d, *J* = 11.5 Hz, 1H, OC<u>H</u>$_2$ArOCH$_3$), 3.98 (dd, *J* = 11.3, 6.3 Hz, 1H, H-5), 3.93 (m, 1H, H-4), 3.79 (s, 3H, OCH$_3$), 3.59 (dd, *J* = 5.8, 3.3 Hz, 1H, H-3), 3.46 (dd, *J* = 11.0, 9.0 Hz, 1H, H-5), 2.03 (s, 3H, OCOCH$_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 169.7 (O<u>C</u>OCH$_3$), 159.2 (C-Ar), 137.4 (C-Ar), 129.4×2 (CH-Ar), 129.4 (C-Ar), 128.4×2 (CH-Ar), 128.0 (CH-Ar), 127.9×2 (CH-Ar), 113.7×2 (CH-Ar), 97.8 (C-1), 76.5 (C-3), 71.7 (O<u>C</u>H$_2$Ar), 69.4 (C-2), 69.2 (O<u>C</u>H$_2$ArOCH$_3$), 65.0 (C-4), 62.6 (C-5), 55.2 (OCH$_3$), 20.9 (OCO<u>C</u>H$_3$)

MS (ESI$^+$), *m/z* (relative intensity): 425 ([M+Na]$^+$, 100%)

2-*O*-Acetyl-4-*O*-benzyl-α/*β*-L-arabinopyranoside (536)



(536)

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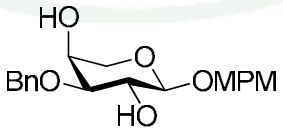
FTIR (neat), ν_{max}, cm^{-1}: 3424, 1728, 1248, 1140, 1082, 1055

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.28 – 7.39 (m, 10H, Ar(H)-α,β), 5.33 (d, *J* = 3.3 Hz, 1H, H-1β), 5.05 (dd, *J* = 3.3, 9.4 Hz, 1H, H-2β), 4.95 (dd, *J* = 4.9, 7.0 Hz, 1H, H-2α), 4.72 (d, *J* = 11.8 Hz, 1H, OC$\underline{H}_2$Ar-α), 4.68 (d, *J* = 11.7 Hz, 1H, OC$\underline{H}_2$Ar-β), 4.67 (d, *J* = 4.9 Hz, 1H, H-1α), 4.56 (d, *J* = 11.1 Hz, 1H, OC$\underline{H}_2$Ar-α), 4.53 (d, *J* = 11.6 Hz, 1H, OC$\underline{H}_2$Ar-β), 4.06 (dd, *J* = 5.8, 12.6 Hz, 1H, H-5β), 4.04 (dd, *J* = 3.8, 5.8 Hz, 1H, H-3β), 3.93 (dd, *J* = 1.6, 10.9 Hz, 1H, H-5α), 3.90 (dd, *J* = 3.3, 6.9 Hz, 1H, H-3α), 3.81 (dd, *J* = 3.0, 12.7 Hz, 1H, H-5α), 3.78 (dd, *J* = 1.7, 3.5 Hz, 1H, H-4α), 3.75 (dd, *J* = 3.3, 6.2 Hz, 1H, H-4β), 3.52 (dd, *J* = 3.1, 12.5 Hz, 1H, H-5β), 2.13 (s, 3H, OCOCH_3-β), 2.10 (s, 3H, OCOCH_3-α)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 171.1 (O$\underline{C}$OCH_3-α), 170.9 (O$\underline{C}$OCH_3-β), 137.4 (C-Ar-β), 137.2 (C-Ar-α), 128.6×2 (CH-Ar), 128.5×2 (CH-Ar), 128.2 (CH-Ar), 128.0 (CH-Ar), 127.9×2 (CH-Ar), 127.8×2 (CH-Ar), 94.0 (C-1β), 91.1 (C-1α), 75.9 (C-4α), 73.3 (C-4β), 72.6 (C-2α), 71.9 (C-2β), 71.5 (O$\underline{C}H_2$Ar-α), 71.4 (O$\underline{C}H_2$Ar-β), 69.4 (C-3α), 67.0 (C-3β), 59.5 (C-5β), 59.0 (C-5α), 21.0 (OCO$\underline{C}H_3$-α), 20.9 (OCO$\underline{C}H_3$-β)

MS (ESI$^+$), *m/z* (relative intensity): 305 ($[M+Na]^+$, 100%)

4-Methoxybenzyl 3-*O*-benzyl-α-L-arabinopyranoside (537)



(537)

FTIR (neat), ν_{max}, cm^{-1}: 3430, 1612, 1514, 1249, 1084, 1029

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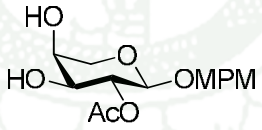
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.27-7.38 (m, 5H, Ar(H)), 7.29 (d, *J* = 8.7 Hz, 2H, Ar(H)), 6.88 (d, *J* = 8.7 Hz, 2H, Ar(H)), 4.86 (d, *J* = 11.3 Hz, 1H, $OC\underline{H}_2ArOCH_3$), 4.78 (d, *J* = 11.9 Hz, 1H, $OC\underline{H}_2Ar$), 4.72 (d, *J* = 11.9 Hz, 1H, $OC\underline{H}_2Ar$), 4.53 (d, *J* = 11.4 Hz, 1H, $OC\underline{H}_2ArOCH_3$), 4.23 (d, *J* = 7.5 Hz, 1H, H-1), 4.08 (dd, *J* = 2.3, 12.9 Hz, 1H, H-5), 3.91-3.93 (m, 1H, H-4), 3.84 (dd, *J* = 1.4, 7.6 Hz, 1H, H-2), 3.80 (s, 3H, OCH_3), 3.45 (dd, *J* = 1.5, 12.9 Hz, 1H, H-5), 3.44 (dd, *J* = 3.6, 9.1 Hz, 1H, H-3)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 159.4 (C-Ar), 137.7 (C-Ar), 129.9×2 (CH-Ar), 129.1 (C-Ar), 128.6×2 (CH-Ar), 128.0 (CH-Ar), 127.9×2 (CH-Ar), 113.9×2 (CH-Ar), 101.7 (C-1), 79.8 (C-3), 72.3 ($O\underline{C}H_2Ar$), 71.2 (C-2), 70.3 ($O\underline{C}H_2ArOCH_3$), 66.5 (C-4), 65.7 (C-5), 55.3 (OCH_3)

MS (ESI$^+$), *m/z* (relative intensity): 383 ($[M+Na]^+$, 100%)

4-Methoxybenzyl 2-*O*-acetyl-α-L-arabinopyranoside (538)



(538)

FTIR (neat), ν_{max}, cm^{-1}: 3413, 1734, 1453, 1374, 1247, 1139, 1082, 1055

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.25 (d, *J* = 8.7 Hz, 2H, Ar(H)), 6.88 (d, *J* = 8.7 Hz, 2H, Ar(H)), 4.98 (dd, *J* = 3.6, 5.5 Hz, 1H, H-2), 4.73 (d, *J* = 11.5 Hz, 1H, $OC\underline{H}_2ArOCH_3$), 4.65 (d, *J* = 3.5 Hz, 1H, H-1), 4.50 (d, *J* = 11.5 Hz, 1H, $OC\underline{H}_2ArOCH_3$), 3.89-3.92 (m, 1H, H-4), 3.81 (s, 3H, OCH_3), 3.78 (dd, *J* = 1.1, 12.0 Hz, 1H, H-5), 3.75-3.78 (m, 1H, H-3), 3.64 (dd, *J* = 4.3, 11.8 Hz, 1H, H-5), 2.09 (s, 3H, $OCOCH_3$)

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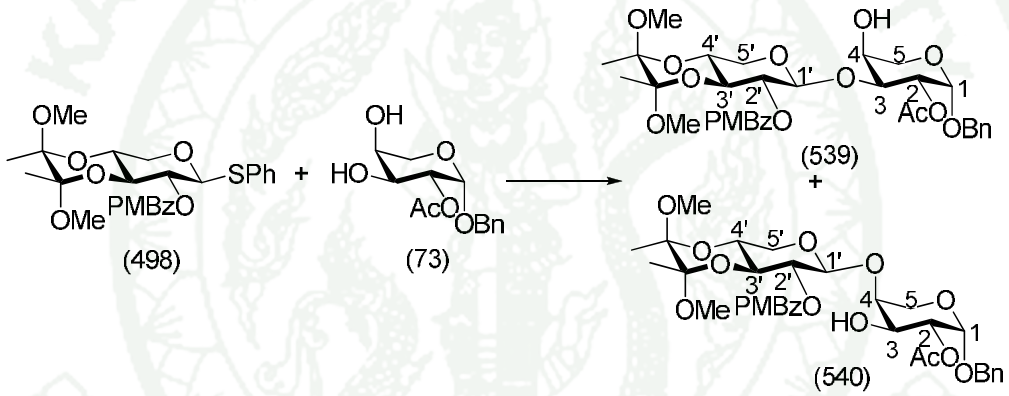
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 159.6 (C-Ar), 129.7×2 (CH-Ar), 128.4 (C-Ar), 114.0×2 (CH-Ar), 96.8 (C-1), 71.1 (C-2), 69.7 ($O\underline{C}H_2ArOCH_3$), 65.4 (C-4), 61.2 (C-5), 60.7 (C-3), 55.3 (OCH_3)

MS (ESI$^+$), *m/z* (relative intensity): 335 ($[M+Na]^+$, 100%)

Benzyl 2-*O*-acetyl-3-*O*-(2-*O*-methoxybenzoyl-(2'*S*,3'*S*)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-β-D-xylopyranosyl)-β-L-arabinopyranoside (539)



Using NIS/TMSOTf

A solution of 1-thiophenyl-2-*O*-methoxybenzoyl-(2'S,3'S)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-α-D-xylopyranoside (498) (30 mg, 0.06 mmol) and benzyl 2-*O*-acetyl-β-L-arabinopyranoside (73) (26 mg, 0.09 mmol) in dry dichloromethane (3.06 mL) was stirred over activated MS 3Å for 30 minutes before *N*-iodosuccinimide (18 mg, 0.08 mmol) was added. The mixture was cooled to -40 °C before trimethylsilyl trifluoromethanesulfonate (0.014 mL, 0.08 mmol) was added. Stirring was continued and the reaction mixture was allowed to warm to -20 °C for 2 h. Triethylamine was added and the reaction mixture was diluted with CH_2Cl_2, washed with water, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 1:1) to afford benzyl 2-*O*-acetyl-3-*O*-(2-*O*-methoxybenzoyl-(2'*S*,3'*S*)-methyl-3,4-*O*-(2',3'-dimethoxy butane-2',3'-diyl)-β-D-xylopyranosyl)-β-L-arabinopyranoside (539) as a white solid

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(32 mg, 78.1%) and benzyl 2-*O*-acetyl-4-*O*-(2-*O*-methoxybenzoyl-(2'*S*,3'*S*)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-β-D-xylopyranosyl)-β-L-arabinopyranoside (540) as a white solid (6 mg, 15.0%).

Using NIS/TfOH

A solution of 1-thiophenyl-2-*O*-methoxybenzoyl-(2'S,3'S)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-α-D-xylopyranoside (498) (50 mg, 0.10 mmol) and benzyl 2-*O*-acetyl-β-L-arabinopyranoside (73) (43 mg, 0.15 mmol) in dry dichloromethane (1.0 mL) was stirred over activated MS 4Å for 30 minutes. The mixture was cooled to -30 °C before *N*-iodosuccinimide (28 mg, 0.12 mmol) and trifluoromethanesulfonic acid (0.90 μL, 0.01 mmol) were added. Stirring was continued for 2 hour at -30 °C. Triethylamine was added and the reaction mixture was diluted with CH_2Cl_2 and successively washed with 1 M aqueous Na_2CO_3 and 1M aqueous $Na_2S_2O_3$ and then water, dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue was purified by flash column chromatography (EtOAc/hexane, 1:1) to afford benzyl 2-*O*-acetyl-3-*O*-(2-*O*-methoxybenzoyl-(2'*S*,3'*S*)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-β-D-xylopyranosyl)-β-L-arabinopyranoside (539) as a white solid (49 mg, 72.4%) and benzyl 2-*O*-acetyl-4-*O*-(2-*O*-methoxybenzoyl-(2'*S*,3'*S*)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-β-D-xylopyranosyl)-β-L-arabinopyranoside (540) as a white solid (13 mg, 21.2%).

Benzyl 2-*O*-acetyl-3-*O*-(2-*O*-methoxybenzoyl-(2'*S*,3'*S*)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-β-D-xylopyranosyl)-β-L-arabinopyranoside (539)

FTIR (KBr), ν_{max}, cm^{-1}: 3458, 1732, 1605, 1509, 1456, 1372, 1258, 1169, 1140, 1110, 1051

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.95 (d, *J* = 9.0 Hz, 2H, Ar(H)), 7.22 – 7.32 (m, 5H, Ar(H)), 6.90 (d, *J* = 9.0 Hz, 2H, Ar(H)), 5.17 (dd, *J* = 9.8, 7.6 Hz, 1H, H-2′), 5.00 (dd, *J* = 9.5, 3.5 Hz, 1H, H-2), 4.97 (d, *J* = 3.5 Hz, 1H, H-1), 4.66 (d, *J* = 7.6 Hz, 1H, H-1′), 4.65 (d, *J* = 12.2 Hz, 1H, C^1OCH_2Ar), 4.38 (d, *J* = 12.1 Hz, 1H,

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C^1OCH_2Ar), 4.10 – 4.12 (m, 1H, H-4), 4.03 (dd, *J* = 9.5, 3.4 Hz, 1H, H-3), 3.86 – 3.94 (m, 3H, H-4′, 5′, 5), 3.84 (dd, *J* = 6.2, 2.7 Hz, 1H, H-3′), 3.83 (s, 3H, OCH_3), 3.74 (dd, *J* = 2.5, 12.5 Hz, 1H, H-5), 3.42 – 3.48 (m, 1H, H-5′), 3.26 (s, 3H, OCH_3), 3.19 (s, 3H, OCH_3), 1.50 (s, 3H, $OCOC\underline{H}_3$), 1.27 (s, 3H, $CC\underline{H}_3$), 1.26 (s, 3H, $CC\underline{H}_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 169.9 ($O\underline{C}OCH_3$), 164.4 ($O\underline{C}OArOCH_3$), 163.5 (C-Ar), 137.2 (C-Ar), 131.7×2 (CH-Ar), 128.3×2 (CH-Ar), 127.8 (CH-Ar), 127.7×2 (CH-Ar), 122.1 (C-Ar), 113.7×2 (CH-Ar), 103.4 (C-1′), 99.8, 99.6 ($\underline{C}CH_3$), 95.8 (C-1), 70.8 (C-3′), 70.5 (C-4), 69.5 ($-C^1O\underline{C}H_2Ar$), 69.5×2 (C-2′, 3), 68.7 (C-2), 65.7 (C-4′), 64.0 (C-5′), 61.7 (C-5), 55.4 ($ArO\underline{C}H_3$), 47.9, 47.6 ($O\underline{C}H_3$), 20.0 ($OCO\underline{C}H_3$), 17.6, 17.5 ($C\underline{C}H_3$)

HRMS (ESI^+) *m/z*: $C_{33}H_{42}O_{14}Na$ $[M+Na]^+$, calcd 685.2467, found 685.2489

Benzyl 2-*O*-acetyl-4-*O*-(2-*O*-methoxybenzoyl-(2'*S*,3'*S*)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-β-D-xylopyranosyl)-β-L-arabinopyranoside (540)

FTIR (KBr), ν_{max}, cm^{-1}: 3460, 1730, 1603, 1514, 1456, 1372, 1259, 1169, 1135, 1108, 1049

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.98 (d, *J* = 9.0 Hz, 2H, Ar(H)), 7.27 – 7.35 (m, 5H, Ar(H)), 6.90 (d, *J* = 9.0 Hz, 2H, Ar(H)), 5.19 (dd, *J* = 9.7, 6.7 Hz, 1H, H-2′), 5.07 (d, *J* = 3.6 Hz, 1H, H-1), 4.90 (dd, *J* = 10.1, 3.6 Hz, 1H, H-2), 4.68 (d, *J* = 12.4 Hz, 1H, C^1OCH_2Ar), 4.67 (d, *J* = 6.6 Hz, 1H, H-1′), 4.48 (d, *J* = 12.3 Hz, 1H, C^1OCH_2Ar), 3.92 – 4.03 (m, 4H, H-3, 4′, 5, 5′), 3.85 – 3.90 (m, 2H, H-3′, 4), 3.84 (s, 3H, OCH_3), 3.75 (dd, *J* = 1.7, 12.8 Hz, 1H, H-5), 3.48 – 3.53 (m, 1H, H-5′), 3.26 (s, 3H, OCH_3), 3.25 (s, 3H, OCH_3), 2.02 (s, 3H, $OCOC\underline{H}_3$), 1.28 (s, 3H, $CC\underline{H}_3$), 1.27 (s, 3H, $CC\underline{H}_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.5 ($O\underline{C}OCH_3$), 165.5 ($O\underline{C}OArOCH_3$), 163.6 (C-Ar), 137.3 (C-Ar), 131.8×2 (CH-Ar), 128.4×2 (CH-Ar), 127.8 (CH-Ar),

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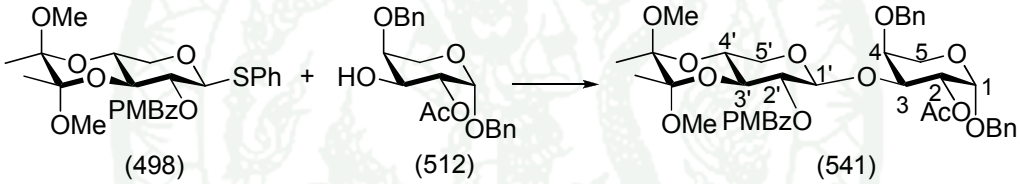
127.7×2 (CH-Ar), 121.8 (C-Ar), 113.8×2 (CH-Ar), 104.2 (C-1′), 99.8, 99.5 ($\underline{C}CH_3$), 95.8 (C-1), 79.4 (C-4), 72.2 (C-2′), 71.8 (C-2), 70.0 (C-3′), 69.5 (-$C^1O\underline{C}H_2Ar$), 67.1 (C-3), 65.2 (C-4′), 64.0 (C-5′), 61.5 (C-5), 55.4 (Ar$O\underline{C}H_3$), 47.9, 47.7 ($O\underline{C}H_3$), 20.8 ($OCO\underline{C}H_3$), 17.6, 17.5 ($C\underline{C}H_3$)

HRMS (ESI^+) *m/z*: $C_{33}H_{42}O_{14}Na$ $[M+Na]^+$, calcd 685.2467, found 685.2475

Benzyl 2-*O*-acetyl-3-*O*-(2-*O*-methoxybenzoyl-(2'*S*,3'*S*)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-β-D-xylopyranosyl)-4-*O*-benzyl-β-L-arabinopyranoside (541)



Using NIS/TMSOTf

A solution of 1-thiophenyl-2-*O*-methoxybenzoyl-(2'S,3'S)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-α-D-xylopyranoside (498) (190 mg, 0.39 mmol) and benzyl 2-*O*-acetyl-4-*O*-benzyl-β-L-arabinopyranoside (512) (96 mg, 0.26 mmol) in dry dichloromethane (9.47 mL) was stirred over activated MS 3Å for 30 minutes before *N*-iodosuccinimide (93 mg, 0.41 mmol) was added. The mixture was cooled to -78 °C before trimethylsilyl trifluoromethanesulfonate (0.07 mL, 0.39 mmol) was added. Stirring was continued and the reaction mixture was allowed to warm to -20 °C for 2 h. Triethylamine was added and the reaction mixture was diluted with CH_2Cl_2, washed with water, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 3:7) to afford benzyl 2-*O*-acetyl-3-*O*-(2-*O*-methoxybenzoyl-(2'*S*,3'*S*)-methyl-3,4-*O*-(2',3'-dimethoxy butane-2',3'-diyl)-β-D-xylopyranosyl)-4-*O*-benzyl-β-L-arabinopyranoside (541) as a white solid (127 mg, 65%); m.p. 175-177 °C; $[\alpha]_D^{25}$ +167.93, (c = 0.295, CH_2Cl_2).

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Using NIS/TfOH

A stirred 0.05 M solution of 1-thiophenyl-2-*O*-methoxybenzoyl-(2'S,3'S)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-α-D-xylopyranoside (498) (38 mg, 0.077 mmol) and benzyl 2-*O*-acetyl-4-*O*-benzyl-β-L-arabinopyranoside (512) (43 mg, 0.12 mmol) in dry dichloromethane (3.0 mL) under nitrogen atmosphere was stirred over activated MS 3Å for 30 minutes. The mixture was cooled to -30 °C before *N*-iodosuccinimide (21 mg, 0.093 mmol) was added, followed by trifluoromethanesulfonic acid (0.68 μL, 0.008 mmol). After stirring for 1 hour at this temperature, the reaction mixture was then diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The combine organic portion was washed with aqueous $Na_2S_2O_3$ and then brine, dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue was purified by flash column chromatography (EtOAc/hexane, 3:7) to afford benzyl 2-*O*-acetyl-3-*O*-(2-*O*-methoxybenzoyl-(2'*S*,3'*S*)-methyl-3,4-*O*-(2',3'-dimethoxy butane-2',3'-diyl)-β-D-xylopyranosyl)-4-*O*-benzyl-β-L-arabinopyranoside (541) as a white solid (28 mg,48%); m.p. 175-177 °C; $[\alpha]_D^{25}$ +167.93, (c = 0.295, CH_2Cl_2).

FTIR (KBr), ν_{max}, cm^{-1}: 1731, 1605, 1509, 1456, 1372, 1258, 1169, 1140, 1113, 1100, 1051

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.89 (d, *J* = 9.0 Hz, 2H, Ar(H)), 7.34 (d, *J* = 6.9 Hz, 2H, Ar(H)), 7.15 – 7.28 (m, 8H, Ar(H)), 6.82 (d, *J* = 9.0 Hz, 2H, Ar(H)), 5.16 (dd, *J* = 9.4, 7.6 Hz, 1H, H-2′), 5.03 (dd, *J* = 10.0, 3.6 Hz, 1H, H-2), 4.95 (d, *J* = 3.6 Hz, 1H, H-1), 4.80 (d, *J* = 12.2 Hz, 1H, C^4OCH_2Ar), 4.65 (d, *J* = 7.4 Hz, 1H, H-1′), 4.63 (d, *J* = 12.2 Hz, 1H, C^4OCH_2Ar), 4.56 (d, *J* = 12.1 Hz, 1H, C^1OCH_2Ar), 4.29 (d, *J* = 12.1 Hz, 1H, C^1OCH_2Ar), 4.01 (dd, *J* = 10.0, 3.1 Hz, 1H, H-3), 3.80 – 3.87 (m, 3H, H-3′, 4′, 4), 3.78 (dd, *J* = 5.4, 5.4 Hz, 1H, H-5), 3.75 (s, 3H, OCH_3), 3.70 (dd, *J* = 12.3, 1.2 Hz, 1H, H-5′), 3.57 (dd, *J* = 12.2, 2.7 Hz, 1H, H-5′), 3.35 – 3.40 (m, 1H, H-5), 3.21 (s, 3H, OCH_3), 3.13 (s, 3H, OCH_3), 1.48 (s, 3H, $OCOCH_3$), 1.21 (s, 3H, $CC\underline{H}_3$), 1.16 (s, 3H, $CC\underline{H}_3$)

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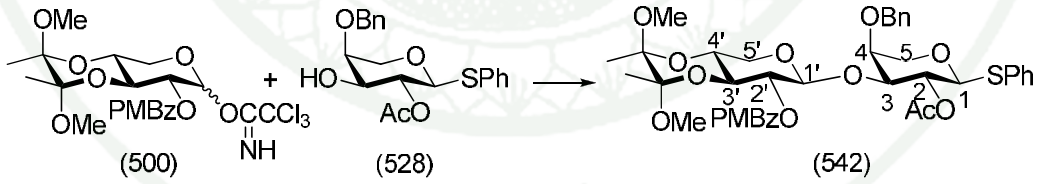
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 169.8 (O<u>C</u>OCH$_3$), 164.3 (O<u>C</u>OArOCH$_3$), 163.4 (C-Ar), 138.8 (C-Ar), 137.4 (C-Ar), 131.6×2 (CH-Ar), 128.3×2 (CH-Ar), 128.2×2 (CH-Ar), 128.1×2 (CH-Ar), 127.8×2 (CH-Ar), 127.8 (CH-Ar), 127.4 (CH-Ar), 122.5 (C-Ar), 113.6×2 (CH-Ar), 103.6 (C-1′), 99.8, 99.6 (<u>C</u>CH$_3$), 95.9 (C-1), 76.0 (C-3′), 75.7 (C-3), 72.8 (C^{4}O<u>C</u>H$_2$Ar), 71.2 (C-2′), 70.7 (C-4), 70.4 (C-2), 69.6 (-C^{1}O<u>C</u>H$_2$Ar), 65.9 (C-4′), 63.9 (C-5), 61.8 (C-5′), 55.4 (ArO<u>C</u>H$_3$), 47.9, 47.7 (O<u>C</u>H$_3$), 20.2 (OCO<u>C</u>H$_3$), 17.6, 17.5 (C<u>C</u>H$_3$)

MS (ESI$^+$), *m/z* (relative intensity): 775.3 ([M+Na]$^+$, 100%)

HRMS (ESI$^+$) *m/z*: $C_{40}H_{48}O_{14}Na$ [M+Na]$^+$, calcd 775.2936, found 775.2935

Thiophenyl 2-*O*-acetyl-3-*O*-(2-*O*-methoxybenzoyl-(2'*S*,3'*S*)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-β-D-xylopyranosyl)-4-*O*-benzyl-α-L-arabinopyranoside (542)

Method I



A solution of 1-α/β-trichloroacetimidyl-2-*O*-methoxybenzoyl-(2'*S*,3'*S*)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-D-xylopyranoside (500) (90 mg, 0.17 mmol) and thiophenyl 2-*O*-acetyl-4-*O*-benzyl-α-L-arabinopyranoside (528) (41 mg, 0.11 mmol) in dry dichloromethane (5.52 mL) was stirred for 5 minutes at room temperature and cooled to -78 °C. After the addition of trimethylsilyl trifluoromethanesulfonate (0.03 mL, 0.17 mmol), the reaction mixture was stirred at -78 °C to -20 °C for 2 h, quenched with triethylamine and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 1:4) to afford thiophenyl 2-*O*-acetyl-3-*O*-(2-*O*-methoxybenzoyl-(2'*S*,3'*S*)-methyl-3,4-*O*-(2',3'-

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dimethoxybutane-2',3'-diyl)-β-D-xylopyranosyl)-4-*O*-benzyl-α-L-arabinopyranoside (542) as a white solid (15 mg, 18%); $[\alpha]_D^{25}$ +10.72, (c = 0.119, CH_2Cl_2).

FTIR (KBr), ν_{max}, cm^{-1}: 1734, 1697, 1606, 1509, 1458, 1375, 1257, 1168, 1138, 1110, 1073, 1044

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.98 (d, *J* = 9.0 Hz, 2H, Ar(H)), 7.36 – 7.39 (m, 2H, Ar(H)), 7.12 – 7.28 (m, 6H, Ar(H)), 6.95 – 6.97 (m, 2H, Ar(H)), 6.80 (d, *J* = 9.0 Hz, 2H, Ar(H)), 5.31 (d, *J* = 1.5 Hz, 1H, H-1), 5.14 (dd, *J* = 9.9, 7.5 Hz, 1H, H-2′), 5.00 (dd, *J* = 3.5, 3.5 Hz, 1H, H-2), 4.62 (d, *J* = 7.5 Hz, 1H, H-1′), 4.11 (dd, *J* = 10.5, 10.5 Hz, 1H, H-5′), 4.08 (dd, *J* = 4.0, 1.9 Hz, 1H, H-3′), 3.91 (d, *J* = 11.4 Hz, 1H, OCH_2Ar), 3.80 – 3.88 (m, 3H, H-3, H-4, H-5), 3.76 (d, *J* = 11.3 Hz, 1H, OCH_2Ar), 3.63 (s, 3H, OCH_3), 3.61 – 3.66 (m, 1H, H-4′), 3.48 (dd, *J* = 11.3, 4.2 Hz, 1H, H-5′), 3.36 – 3.42 (m, 1H, H-5), 3.18 (s, 3H, OCH_3), 3.13 (s, 3H, OCH_3), 2.07 (s, 3H, $OCOC\underline{H}_3$), 1.21 (s, 3H, $CC\underline{H}_3$), 1.17 (s, 3H, $CC\underline{H}_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.3 ($O\underline{C}OCH_3$), 164.5 ($O\underline{C}OArOCH_3$), 163.6 (C-Ar), 137.7 (C-Ar), 136.1 (C-Ar), 131.8×2 (CH-Ar), 130.6×2 (CH-Ar), 128.9×2 (CH-Ar), 128.2×2 (CH-Ar), 127.6 (CH-Ar), 127.5×2 (CH-Ar), 126.9 (CH-Ar), 122.1 (C-Ar), 113.9×2 (CH-Ar), 103.1 (C-1′), 99.8, 99.5 ($\underline{C}CH_3$), 86.5 (C-1), 76.6 (C-3′), 70.9 ($O\underline{C}H_2Ar$), 70.9 (C-2′), 70.8 (C-4′), 70.6 (C-4), 67.7 (C-2), 65.7 (C-3), 64.2 (C-5), 58.8 (C-5′), 55.3 ($ArO\underline{C}H_3$), 47.9, 47.7 ($O\underline{C}H_3$), 21.1 ($OCO\underline{C}H_3$), 17.6, 17.5 ($C\underline{C}H_3$)

HRMS (ESI^+) *m/z*: $C_{39}H_{46}O_{13}SNa$ $[M+Na]^+$, calcd 777.2551, found 777.2567

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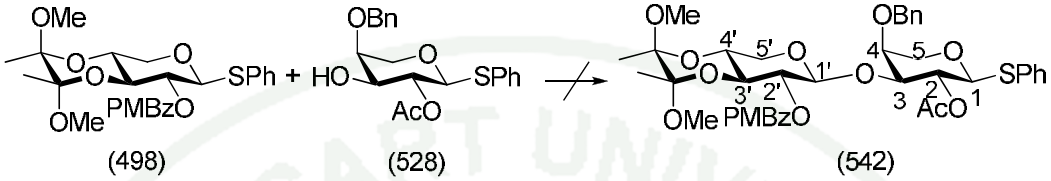
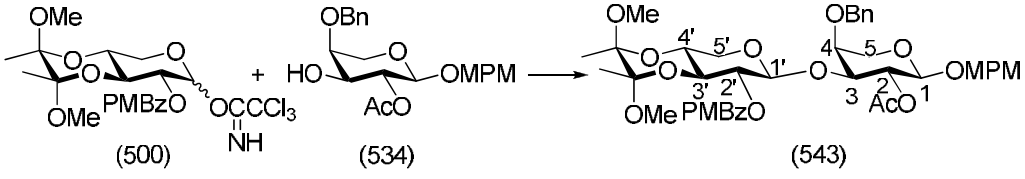
Method II



A solution of 1-thiophenyl-2-*O*-methoxybenzoyl-(2'S,3'S)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-α-D-xylopyranoside (498) (48 mg, 0.098 mmol) and thiophenyl 2-*O*-acetyl-4-*O*-benzyl-α-L-arabinopyranoside (528) (24 mg, 0.065 mmol) in dry dichloromethane (2.39 mL) was stirred over activated MS 3Å for 30 minutes before *N*-iodosuccinimide (24 mg, 0.10 mmol) was added. The mixture was cooled to -78 °C before trimethylsilyl trifluoromethanesulfonate (0.018 mL, 0.098 mmol) was added. Stirring was continued and the reaction mixture was allowed to warm to -20 °C for 2 h. Triethylamine was added and the reaction mixture was diluted with CH_2Cl_2, washed with water, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 3:7). Unfortunately, the desired product (542) and also starting material were not observed under this condition. Only 2-*O*-methoxybenzoyl-(2'S,3'S)-methyl-3,4-*O*-(2',3'-dimethoxy-butane-2',3'-diyl)-α/β-D-xylopyranoside (499) was obtained.

4-Methoxybenzyl 2-*O*-acetyl-3-*O*-(2-*O*-methoxybenzoyl-(2'*S*,3'*S*)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-β-D-xylopyranosyl)-4-*O*-benzyl-α-L-arabinopyranoside (543)

Method I



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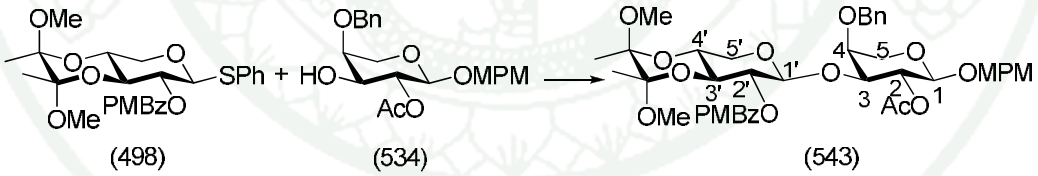
A solution of 4-methoxybenzyl 2-*O*-acetyl-4-*O*-benzyl-α-L-arabinopyranoside (534) (163 mg, 0.40 mmol), 1-α/β-trichloroacetimidyl-2-*O*-methoxybenzoyl-(2'*S*,3'*S*)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-D-xylopyranoside (500) (514 mg, 0.95 mmol), and activated MS 4Å (1.65 g) in dry dichloromethane (24.8 mL) was stirred for 1 h at room temperature. The mixture was cooled to -78 °C for 30 minutes followed by the dropwise addition of a 0.1M solution of TMSOTf in dry dichloromethane (0.066 mL, 0.007 mmol). Stirring was continued and the reaction mixture was allowed to warm to -20 °C for 2 h. Then the reaction mixture was quenched with triethylamine, filtered through Celite, and the solvents were evaporated. Purification by flash column chromatography (EtOAc/hexane, 3:7) gave 4-methoxybenzyl 2-*O*-acetyl-3-*O*-(2-*O*-methoxybenzoyl-(2'*S*,3'*S*)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-β-D-xylopyranosyl)-4-*O*-benzyl-*α*-L-arabinopyranoside (543) (152 mg, 49%) as a white solid; m.p. 84-86 °C; $[\alpha]_D^{25}$ +44.97, (c = 0.23, $CHCl_3$).

Method II



1-Thiophenyl-2-*O*-methoxybenzoyl-(2'S,3'S)-methyl-3,4-*O*-(2',3'-dimethoxy butane-2',3'-diyl)-α-D-xylopyranoside (498) (257 mg, 0.52 mmol), diphenylsulfoxide (Ph_2SO) (117 mg, 0.58 mmol), and tri-*tert*-butylpyrimidine (TTBP) (326 mg, 1.31 mmol) were dissolved in dry dichloromethane (10.5 mL) and stirred over activated molecular sieves 3Å for 30 minutes. At -60 °C, triflic anhydride (Tf_2O) (0.097 mL, 0.58 mmol) was added and the resulting mixture was allowed to warm to -45 °C over 15 minutes. Subsequently, 4-methoxybenzyl 2-*O*-acetyl-4-*O*-benzyl-α-L-arabinopyranoside (534) (148 mg, 0.37 mmol), dissolved in dry dichloromethane (7.36 mL), was added at -60 °C and the reaction mixture was allowed to warm to -20 °C for 2 h. The reaction mixture was quenched by addition of triethylamine, diluted

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with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (EtOAc/hexane, 3:7) provided 4-methoxybenzyl 2-*O*-acetyl-3-*O*-(2-*O*-methoxybenzoyl-(2'*S*,3'*S*)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-β-D-xylopyranosyl)-4-*O*-benzyl-*α*-L-arabinopyranoside (543) (109 mg, 38%) as a white solid.

FTIR (KBr), ν_{max}, cm^{-1}: 1745, 1726, 1606, 1513, 1456, 1371, 1256, 1168, 1138, 1111, 1098, 1048

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.98 (d, *J* = 9.0 Hz, 2H, Ar(H)), 7.38 – 7.40 (m, 2H, Ar(H)), 7.30 – 7.34 (m, 2H, Ar(H)), 7.23 – 7.28 (m, 1H, Ar(H)), 7.02 (d, *J* = 8.6 Hz, 2H, Ar(H)), 6.90 (d, *J* = 9.0 Hz, 2H, Ar(H)), 6.76 (d, *J* = 8.7 Hz, 2H, Ar(H)), 5.22 (dd, *J* = 7.3, 9.6 Hz, 1H, H-2′), 5.14 (dd, *J* = 6.1, 7.5 Hz, 1H, H-2), 4.82 (d, *J* = 12.3 Hz, 1H, OC$\underline{H}_2$ArOCH$_3$), 4.67 (d, *J* = 12.2 Hz, 1H, OC$\underline{H}_2$ArOCH$_3$), 4.67 (d, *J* = 7.4 Hz, 1H, H-1′), 4.50 (d, *J* = 12.2 Hz, 1H, OC$\underline{H}_2$Ar), 4.37 (d, *J* = 12.2 Hz, 1H, OC$\underline{H}_2$Ar), 4.25 (d, *J* = 5.9 Hz, 1H, H-1), 3.85 – 3.96 (m, 4H, H-3′, H-4′, H-5, H-5′), 3.83 (s, 3H, ArOC$\underline{H}_3$), 3.75 – 3.81 (m, 2H, H-3, H-4), 3.76 (s, 3H, ArOC$\underline{H}_3$), 3.40 – 3.46 (m, 1H, H-5′), 3.35 (dd, *J* = 1.8, 12.1 Hz, 1H, H-5), 3.27 (s, 3H, OCH$_3$), 3.18 (s, 3H, OCH$_3$), 1.67 (s, 3H, OCOC$\underline{H}_3$), 1.28 (s, 3H, CC$\underline{H}_3$), 1.22 (s, 3H, CC$\underline{H}_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 169.0 (O$\underline{C}$OCH$_3$), 164.3 (O$\underline{C}$OArOCH$_3$), 163.3 (C-Ar), 159.0 (C-Ar), 138.5 (C-Ar), 131.7×2 (CH-Ar), 129.3×2 (CH-Ar), 129.3 (C-Ar), 128.1×2 (CH-Ar), 128.0×2 (CH-Ar), 127.4 (CH-Ar), 122.6 (C-Ar), 113.6×2 (CH-Ar), 113.5×2 (CH-Ar), 102.9 (C-1′), 99.7, 99.5 (C$\underline{C}$H$_3$), 98.4 (C-1), 77.6 (C-4), 73.6 (C-3), 71.9 (O$\underline{C}$H$_2$ArOCH$_3$), 70.1 (C-2′), 70.7 (C-3′), 70.5 (C-2), 68.5 (O$\underline{C}$H$_2$Ar), 65.7 (C-4′), 63.9 (C-5), 62.7 (C-5′), 55.4 (OCOArO$\underline{C}$H$_3$), 55.2 (ArO$\underline{C}$H$_3$), 47.9, 47.6 (O$\underline{C}$H$_3$), 20.5 (OCO$\underline{C}$H$_3$), 17.6, 17.5 (C$\underline{C}$H$_3$)

MS (ESI$^+$), *m/z* (relative intensity): 805 ([M+Na]$^+$, 100%)

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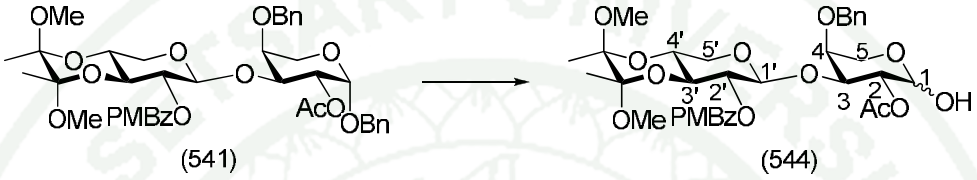
HRMS (ESI^+) *m/z*: $C_{41}H_{50}O_{15}Na$ $[M+Na]^+$, calcd 805.3042, found 805.3066

2-*O*-Acetyl-3-*O*-(2-*O*-methoxybenzoyl-(2'*S*,3'*S*)-methyl-3,4-*O*-(2',3'-dimethoxy butane-2',3'-diyl)-β-D-xylopyranosyl)-4-*O*-benzyl-α/β-L-arabinopyranoside (544)



Using 10%Pd/C/H_2 in EtOAc/EtOH

A suspension of benzyl 2-*O*-acetyl-3-*O*-(2-*O*-methoxybenzoyl-(2'*S*,3'*S*)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-β-D-xylopyranosyl)-4-*O*-benzyl-β-L-arabinopyranoside (541) (53 mg, 0.07 mmol), 10%Pd/C (72 mg) and triethylamine (0.036 mL) in ethylacetate (0.48 mL) and ethanol (0.48 mL) was stirred under hydrogen atmosphere at room temperature for 1 day and then filtered. The filtrate was concentrated *in vacuo* to give a residue which was purified by flash column chromatography (EtOAc/hexane, 1:1) to provide 2-*O*-acetyl-3-*O*-(2-*O*-methoxybenzoyl-(2'*S*,3'*S*)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-β-D-xylopyranosyl)-4-*O*-benzyl-α/β-L-arabinopyranoside (544) (15 mg, 32%) as a white solid, 2-*O*-acetyl-3-*O*-(2-*O*-methoxybenzoyl-(2'*S*,3'*S*)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-β-D-xylopyranosyl)-α/β-L-arabinopyranoside (545) (21 mg, 53%) as a white solid.

Using 4M HCl/CH_3CN

A solution of benzyl 2-*O*-acetyl-3-*O*-(2-*O*-methoxybenzoyl-(2'*S*,3'*S*)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-β-D-xylopyranosyl)-4-*O*-benzyl-β-L-arabinopyranoside (541) (19 mg, 0.025 mmol) in a mixture of 4 M HCl-acetonitrile 8:5 (3 mL) was heated at 80 °C for 2 h. The mixture was concentrated to dryness and extracted with CH_2Cl_2. The extracts were washed with saturated aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4, and concentrated to dryness. The residue was purified

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by flash column chromatography (EtOAc/hexane, 3:2) to give benzyl 3-*O*-(2-*O*-methoxybenzoyl-β-D-xylopyranosyl)-4-*O*-benzyl-α/β-L-arabinopyranoside (546) (2 mg, 16%); $[\alpha]_D^{25}$ +83.6, (c = 0.15, $CHCl_3$) and recovered starting material (13 mg, 68%).

Using 10%Pd/C/Et_3SiH in MeOH

A suspension of benzyl 2-*O*-acetyl-3-*O*-(2-*O*-methoxybenzoyl-(2'*S*,3'*S*)-methyl-3,4-*O*-(2',3'-dimethoxy butane-2',3'-diyl)-β-D-xylopyranosyl)-4-*O*-benzyl-β-L-arabinopyranoside (541) (30 mg, 0.04 mmol), 10%Pd/C (6 mg) in methanol (0.2 mL) under hydrogen atmosphere was added Et_3SiH (0.064 mL, 0.40 mmol) and stirred at room temperature for 1h and then filtered. The filtrate was concentrated *in vacuo* to give a residue which was purified by flash column chromatography (EtOAc/hexane, 1:1) to provide benzyl 2-*O*-acetyl-3-*O*-(2-*O*-methoxybenzoyl-(2'*S*,3'*S*)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-β-D-xylopyranosyl)-β-L-arabinopyranoside (547) (5 mg, 19%). The desired product (544) was not obtained.

Using anh.$FeCl_3$ in CH_2Cl_2

Benzyl 2-*O*-acetyl-3-*O*-(2-*O*-methoxybenzoyl-(2'*S*,3'*S*)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-β-D-xylopyranosyl)-4-*O*-benzyl-β-L-arabinopyranoside (541) (30 mg, 0.04 mmol) was dissolved in dry dichloromethane (1.07 mL) under nitrogen atmosphere and anhydrous $FeCl_3$ added. The reaction was stirred at room temperature for 5 minutes and then quenched with water and diluted with CH_2Cl_2. The organic layer was extracted with brine, and the aqueous layer was re-extracted with EtOAc. The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/hexane, 3:2) to give benzyl 2-*O*-acetyl-3-*O*-(2-*O*-methoxybenzoyl-β-D-xylopyranosyl)-4-*O*-benzyl-β-L-arabinopyranoside (548) (25 mg, 96%) as a white solid; $[\alpha]_D^{25}$ +83.60, (c = 0.15, $CHCl_3$).

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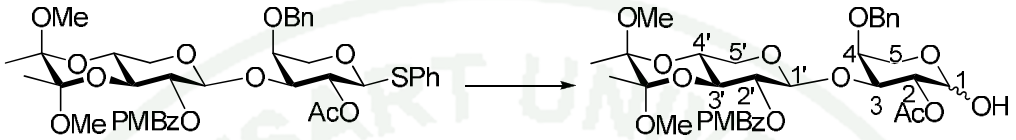
2-*O*-Acetyl-3-*O*-(2-*O*-methoxybenzoyl-(2'*S*,3'*S*)-methyl-3,4-*O*-(2',3'-dimethoxy butane-2',3'-diyl)-β-D-xylopyranosyl)-4-*O*-benzyl-α/β-L-arabinopyranoside (544)



(542) (544)

To a solution of thiophenyl 2-*O*-acetyl-3-*O*-(2-*O*-methoxybenzoyl-(2'*S*,3'*S*)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-β-D-xylopyranosyl)-4-*O*-benzyl-α-L-arabinopyranoside (542) (47 mg, 0.063 mmol) in dichloromethane (0.38 mL) and water (0.05 mL) was added NBS (12 mg, 0.069 mmol) in one portion. After the reaction was stirred at room temperature for 1 hour, saturated aqueous Na_2SO_3 was added. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (EtOAc/hexane, 1:1) to give 2-*O*-acetyl-3-*O*-(2-*O*-methoxybenzoyl-(2'*S*,3'*S*)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-β-D-xylopyranosyl)-4-*O*-benzyl-α/β-L-arabinopyranoside (544) as a white solid (7 mg, 17%).

2-*O*-Acetyl-3-*O*-(2-*O*-methoxybenzoyl-(2'*S*,3'*S*)-methyl-3,4-*O*-(2',3'-dimethoxy butane-2',3'-diyl)-β-D-xylopyranosyl)-4-*O*-benzyl-α/β-L-arabinopyranoside (544)

FTIR (KBr), ν_{max}, cm^{-1}: 3421, 1742, 1724, 1605, 1513, 1456, 1371, 1257, 1168, 1138, 1110, 1095, 1048

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.98 (d, *J* = 8.9 Hz, 2H, Ar(H)-α,β), 7.27 – 7.41 (m, 5H, Ar(H)-α,β), 6.92 (d, *J* = 9.0 Hz, 2H, Ar(H)-α), 6.91 (d, *J* = 9.0 Hz, 2H, Ar(H)-β), 5.28 (brd, *J* = 2.6 Hz, 1H, H-1β), 5.24 (dd, *J* = 7.4, 9.7 Hz, 1H, H-2′β), 5.21 (dd, *J* = 6.9, 9.6 Hz, 1H, H-2′α), 5.07 (dd, *J* = 3.1, 9.3 Hz, 1H, H-2β), 4.97 (dd, *J* = 5.6, 7.9 Hz, 1H, H-2α), 4.85 (d, *J* = 12.2 Hz, 1H, OC$\underline{H}_2$Ar-β), 4.80 (d, *J* = 11.9 Hz, 1H, OC$\underline{H}_2$Ar-α), 4.73 (d, *J* = 7.0 Hz, 1H, H-1′α), 4.72 (d, *J* = 7.4 Hz, 1H, H-1′β),

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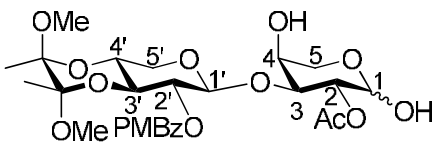
4.68 (d, *J* = 12.2 Hz, 1H, OC$\underline{H}_2$Ar-β), 4.66 (d, *J* = 12.0 Hz, 1H, OC$\underline{H}_2$Ar-α), 4.49 (d, *J* = 5.3 Hz, 1H, H-1α), 4.12 (dd, *J* = 3.0, 9.2 Hz, 1H, H-3β), 3.97 (dd, *J* = 5.0, 12.6 Hz, 1H, H-5α), 3.86 – 3.96 (m, 8H, H-3α, H-3′β, H-4β, H-4′α, H-4′β, H-5β, H-5′α, H-5′β), 3.86 (s, 3H, ArOC$\underline{H}_3$-α), 3.85 (s, 3H, ArOC$\underline{H}_3$-β), 3.81 – 3.84 (m, 1H, H-4α), 3.67 (dd, *J* = 3.7, 11.9 Hz, 1H, H-5β), 3.49 (dd, *J* = 2.6, 12.3 Hz, 1H, H-5α), 3.46 – 3.49 (m, 2H, H-5′α,β), 3.44 (dd, *J* = 3.0, 7.4 Hz, 1H, H-3′α), 3.28 (s, 3H, OCH_3-β), 3.26 (s, 3H, OCH_3-α), 3.22 (s, 3H, OCH_3-α), 3.21 (s, 3H, OCH_3-β), 1.75 (s, 3H, OCOC$\underline{H}_3$-α), 1.68 (s, 3H, OCOC$\underline{H}_3$-β), 1.29 (s, 3H, CC$\underline{H}_3$-β), 1.28 (s, 3H, CC$\underline{H}_3$-α), 1.24 (s, 3H, CC$\underline{H}_3$-α,β)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.6 (O$\underline{C}$OCH$_3$-α), 169.9 (O$\underline{C}$OCH$_3$-β), 164.4 (O$\underline{C}$OArOCH$_3$-β), 163.5 (O$\underline{C}$OArOCH$_3$-α), 163.4 (C-Ar), 138.6 (C-Ar), 138.2 (C-Ar), 131.8×2 (CH-Ar-α), 131.7×2 (CH-Ar-β), 128.3×2 (CH-Ar-α), 128.2×2 (CH-Ar-β), 128.1×2 (CH-Ar-β), 128.0×2 (CH-Ar-α), 127.6 (CH-Ar-α), 127.5 (CH-Ar-β), 113.7×2 (CH-Ar-α,β), 122.4, 122.2 (C-Ar-α,β), 103.4 (C-1′β), 103.0 (C-1′α), 99.8, 99.6 (C$\underline{C}$H$_3$-α,β), 95.2 (C-1α), 91.0 (C-1β), 75.1, 74.9 (C-3α,β, C-3′α,β), 72.6, 71.6, 71.2 (C-4α,β, C-4′α,β), 70.7, 70.5, 70.4 (C-2α,β, C-2′α,β), 65.8 (O$\underline{C}$H$_2$Ar-β), 65.6 (O$\underline{C}$H$_2$Ar-α), 63.9, 61.8 (C-4α,β, C-4′α,β), 55.4 (OCOArO$\underline{C}$H$_3$-α,β), 48.0, 47.7 (O$\underline{C}$H$_3$-α,β), 20.5 (OCO$\underline{C}$H$_3$-α), 20.4 (OCO$\underline{C}$H$_3$-β), 17.6, 17.5 (C$\underline{C}$H$_3$-α,β)

MS (ESI$^+$), *m/z* (relative intensity): 685 ([M+Na]$^+$, 100%)

HRMS (ESI$^+$) *m/z*: $C_{33}H_{42}O_{14}Na$ [M+Na]$^+$, calcd 685.2467, found 685.2478

2-*O*-Acetyl-3-*O*-(2-*O*-methoxybenzoyl-(2'*S*,3'*S*)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-β-D-xylopyranosyl)-α/β-L-arabinopyranoside (545)



(545)

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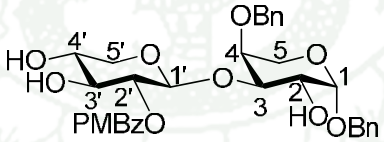
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.92 (d, *J* = 9.0 Hz, 2H, Ar(H)-β), 7.90 (d, *J* = 9.0 Hz, 2H, Ar(H)-α), 6.86 (d, *J* = 9.0 Hz, 2H, Ar(H)-β), 6.85 (d, *J* = 9.0 Hz, 2H, Ar(H)-α), 5.14 (d, *J* = 4.3 Hz, 1H, H-1β), 5.13 (dd, *J* = 3.2, 5.1 Hz, 1H, H-2′β), 5.13 (dd, *J* = 2.2, 6.5 Hz, 1H, H-2β), 5.10 (dd, *J* = 2.8, 3.8 Hz, 1H, H-2′α), 5.07 (dd, *J* = 7.6, 10.0 Hz, 1H, H-2α), 4.84 – 4.88 (m, 1H, H-β), 4.70 – 4.74 (m, 1H, H-β), 4.59 (d, *J* = 7.6 Hz, 1H, H-1′β), 4.55 (d, *J* = 7.6 Hz, 1H, H-1′α), 4.47 (d, *J* = 4.7 Hz, 1H, H-1α), 3.96 – 4.00 (m, 3H, H-5α, H-5′α, H-5′β), 3.80 – 3.93 (m, 5H, H-4α, H-4β, H-4′α, H-4′β, H-5β), 3.79 (s, 3H, ArOC$\underline{H}_3$-α), 3.78 (s, 3H, ArOC$\underline{H}_3$-β), 3.69 (dd, *J* = 2.5, 4.4 Hz, 1H, H-3′α), 3.63 (dd, *J* = 3.6, 12.3 Hz, 1H, H-5β), 3.37 – 3.49 (m, 6H, H-3α, H-3β, H-3′β, H-5α, H-5′α, H-5′β), 3.20 (s, 3H, OCH_3-β), 3.19 (s, 3H, OCH_3-α), 3.17 (s, 3H, OCH_3-α), 3.14 (s, 3H, OCH_3-β), 1.71 (s, 3H, OCOC$\underline{H}_3$-α), 1.60 (s, 3H, OCOC$\underline{H}_3$-β), 1.22 (s, 3H, CC$\underline{H}_3$-α), 1.21 (s, 3H, CC$\underline{H}_3$-β), 1.16 (s, 3H, CC$\underline{H}_3$-α,β)

Benzyl 3-*O*-(2-*O*-methoxybenzoyl-β-D-xylopyranosyl)-4-*O*-benzyl-α/β-L-arabino pyranoside (546)



(546)

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.03 (d, *J* = 9.0 Hz, 2H, Ar(H)), 7.25 – 7.36 (m, 10H, Ar(H)), 6.92 (d, *J* = 9.0 Hz, 2H, Ar(H)), 5.02 (d, *J* = 5.9 Hz, 1H, H-1), 4.96 – 4.99 (m, 1H, H-2′), 4.98 (d, *J* = 3.5 Hz, 1H, H-1′), 4.73 (d, *J* = 11.6 Hz, 1H, OC$\underline{H}_2$Ar), 4.70 (d, *J* = 12.2 Hz, 1H, OC$\underline{H}_2$Ar), 4.66 (d, *J* = 12.2 Hz, 1H, OC$\underline{H}_2$Ar), 4.50 (d, *J* = 11.7 Hz, 1H, OC$\underline{H}_2$Ar), 4.04 – 4.08 (m, 1H, H-4), 4.06 (dd, *J* = 3.9, 11.8 Hz, 1H, H-5′), 3.95 (dd, *J* = 3.2, 9.5 Hz, 1H, H-2), 3.85 (s, 3H, ArOC$\underline{H}_3$), 3.83 – 3.86 (m, 1H, H-3), 3.75 – 3.78 (m, 3H, H-3′, H-4′, H-5), 3.72 (d, *J* = 1.5 Hz, 1H, OH), 3.69 (dd, *J* = 2.6, 12.3 Hz, 1H, H-5), 3.37 (dd, *J* = 8.0, 11.9 Hz, 1H, H-5′)

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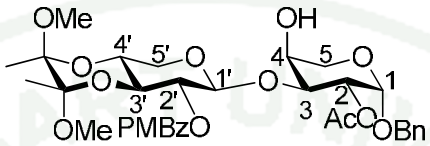
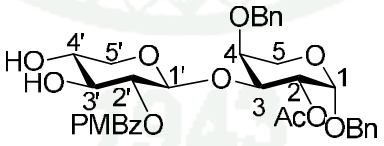
Benzyl 2-*O*-acetyl-3-*O*-(2-*O*-methoxybenzoyl-(2'*S*,3'*S*)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-β-D-xylopyranosyl)-β-L-arabinopyranoside (547)



(547)

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.96 (d, *J* = 9.0 Hz, 2H, Ar(H)), 7.21 – 7.35 (m, 5H, Ar(H)), 6.90 (d, *J* = 8.9 Hz, 2H, Ar(H)), 5.18 (dd, *J* = 7.6, 9.8 Hz, 1H, H-2′), 5.00 (dd, *J* = 3.5, 9.2 Hz, 1H, H-2), 4.97 (d, *J* = 3.6 Hz, 1H, H-1), 4.67 (d, *J* = 7.5 Hz, 1H, H-1′), 4.66 (d, *J* = 12.3 Hz, 1H, OC$\underline{H}_2$Ar), 4.38 (d, *J* = 12.1 Hz, 1H, OC$\underline{H}_2$Ar), 4.06 – 4.11 (m, 1H, H-4′), 4.04 (dd, *J* = 3.5, 9.2 Hz, 1H, H-3′), 3.91 (dd, *J* = 2.3, 4.7 Hz, 1H, H-3), 3.85 – 3.89 (m, 3H, H-4, H-5′), 3.84 (s, 3H, ArOC$\underline{H}_3$), 3.74 (dd, *J* = 2.6, 12.4 Hz, 1H, H-5), 3.43 – 3.49 (m, 1H, H-5), 3.26 (s, 3H, OCH_3), 3.20 (s, 3H, OCH_3), 1.51 (s, 3H, OCOC$\underline{H}_3$), 1.28 (s, 3H, CC$\underline{H}_3$), 1.23 (s, 3H, CC$\underline{H}_3$)

Benzyl 2-*O*-acetyl-3-*O*-(2-*O*-methoxybenzoyl-β-D-xylopyranosyl)-4-*O*-benzyl-β-L-arabinopyranoside (548)



(548)

FTIR (KBr), ν_{max}, cm^{-1}: 3422, 1719, 1605, 1511, 1455, 1372, 1318, 1258, 1170, 1138, 1096, 1063, 1026

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.92 (d, *J* = 8.3 Hz, 2H, Ar(H)), 7.23 – 7.36 (m, 10H, Ar(H)), 6.87 (d, *J* = 8.2 Hz, 2H, Ar(H)), 5.19 (dd, *J* = 3.5, 10.1 Hz, 1H, H-2), 5.07 (d, *J* = 3.6 Hz, 1H, H-1), 4.94 (dd, *J* = 5.8, 5.8 Hz, 1H, H-2′), 4.89 (d, *J* = 5.2

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Hz, 1H, H-1′), 4.69 (s, 2H, OC$\underline{H}_2$Ar), 4.66 (d, *J* = 12.4 Hz, 1H, OC$\underline{H}_2$Ar), 4.42 (d, *J* = 12.2 Hz, 1H, OC$\underline{H}_2$Ar), 4.15 (dd, *J* = 3.1, 10.1 Hz, 1H, H-3), 3.99 (dd, *J* = 3.6, 12.0 Hz, 1H, H-5′), 3.86 – 3.87 (m, 1H, H-4), 3.81 (s, 3H, ArOC$\underline{H}_3$), 3.68 – 3.76 (m, 4H, H-3′, H-4′, H-5), 3.35 (dd, *J* = 6.7, 12.0 Hz, 1H, H-5′), 1.88 (s, 3H, OCOC$\underline{H}_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.3 (O$\underline{C}$OCH$_3$), 165.6 (O$\underline{C}$OArOCH$_3$), 163.9 (C-Ar), 138.0 (C-Ar), 137.3 (C-Ar), 131.9×2 (CH-Ar), 128.4×2 (CH-Ar), 128.3×2 (CH-Ar), 128.1×2 (CH-Ar), 127.9 (CH-Ar), 127.8×2 (CH-Ar), 127.7 (CH-Ar), 121.6 (C-Ar), 113.8×2 (CH-Ar), 100.9 (C-1′), 95.8 (C-1), 75.6 (C-3′), 74.9 (C-3), 72.7 (C-4′), 72.5 (C-2′), 71.9 (C^{4}O$\underline{C}$H$_2$Ar), 70.4 (C-2), 69.7 (C-4), 69.6 (-C^{1}O$\underline{C}$H$_2$Ar), 63.2 (C-5′), 60.3 (C-5), 55.4 (ArO$\underline{C}$H$_3$), 20.6 (OCO$\underline{C}$H$_3$)

MS (ESI$^+$), *m/z* (relative intensity): 661.2 ([M+Na]$^+$, 100%)

Benzyl 2-*O*-acetyl-3-*O*-(2-*O*-methoxybenzoyl-β-D-xylopyranosyl)-4-*O*-benzyl-β-L-arabinopyranoside (548)

(541) (548)

A solution of trifluoroacetic acid in water (TFA/H_2O, 2:1, 0.74 mL) was added to benzyl 2-*O*-acetyl-3-*O*-(2-*O*-methoxybenzoyl-(2'*S*,3'*S*)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-β-D-xylopyranosyl)-4-*O*-benzyl-β-L-arabinopyranoside (541) (48 mg, 0.064 mmol) at room temperature. After stirring at the same temperature for 2 h, the solution was evaporated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 1:1) to afford benzyl 2-*O*-acetyl-3-*O*-(2-*O*-methoxybenzoyl-β-D-xylopyranosyl)-4-*O*-benzyl-β-L-arabinopyranoside (548) (32 mg, 79%) as a white solid.

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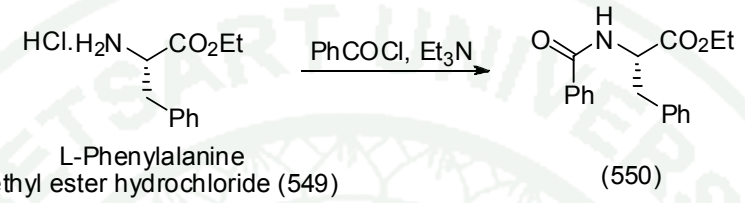
Synthesis of five- and six-membered cyclic sulfamidates

(2S)-Ethyl-2-benzoylamino-3-phenylpropionate (550)



L-Phenylalanine ethyl ester hydrochloride (549)

(550)

To an ice-cooled (0 °C) of L-phenylalanine ethyl ester hydrochloride (549) (4.0 g, 17.4 mmol) in CH_2Cl_2 (33.0 mL) was added Et_3N (5.24 mL, 37.6 mmol) dropwise over 5 minutes. A solution of benzoyl chloride (2.28 mL, 19.7 mmol) in CH_2Cl_2 (9.0 mL) was then added dropwise over 10 minutes. The mixture was warmed to r.t. and stirred for 2 h prior to the addition of water (33.0 mL). The organic portion was isolated, washed sequentially with aqueous 1 M HCl (33.0 mL), saturated aqueous $NaHCO_3$ (33.0 mL) and brine (33.0 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford a colourless solid. This material was recrystallised from CH_2Cl_2/petrol (4 crops) to afford the title compound **550** (5.07 g, 98 %) as a fluffy, white solid; m.p. 102-104 °C (CH_2Cl_2-petrol).

FTIR (neat), ν_{max}, cm^{-1}: 3423, 1737, 1639

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.73 (m, 2H, Ar(H)), 7.14-7.52 (m, 8H, Ar(H)), 6.61 (brd, *J* = 8.0 Hz, 1H, NH), 5.07 (m, 1H, H-2), 4.21 (q, *J* = 8.0 Hz, 2H, OCH_2), 3.21-3.31 (m, 2H, CH_2Ph), 1.27 (t, *J* = 8.0 Hz, 3H, CH_3)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 171.6 (C=O), 166.8 (C=O), 135.9 (C-Ar), 134.0 (C-Ar), 131.7 (CH-Ar), 129.4×3 (CH-Ar), 128.6×3 (CH-Ar), 127.0×3 (CH-Ar), 61.6 (O-CH_2CH_3), 53.5 ($CHCH_2Ph$), 38.0 ($CHCH_2Ph$), 14.2 (O-CH_2CH_3)

HRMS (ESI^+) *m/z*: $C_{18}H_{19}NO_3Na$ $[M+Na]^+$, calcd 320.1257, found 320.1269

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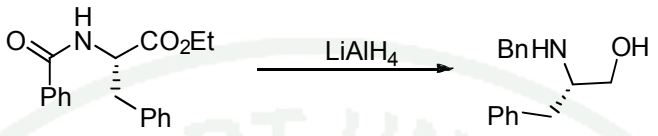
(S)-2-Benzylamino-3-phenylpropan-1-ol (376)

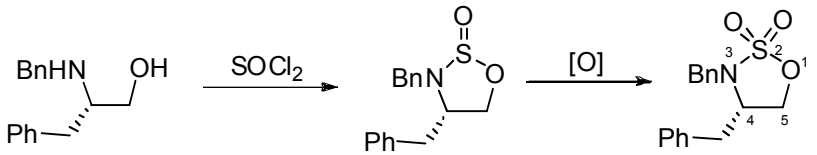


(550) (376)

To an ice-cooled (0 °C) slurry of benzoylated phenylalanine ethyl ester (550) (5.07 g, 17.1 mmol) in anhydrous THF (20 mL) was added, *via* cannula, a solution of $LiAlH_4$ in THF (1.0 M, 28.7 mmol) dropwise over 30 minutes (caution: exotherm). The mixture was heated at reflux for 4 h and then cooled to 0 °C. Water (7.0 mL), aqueous 4 M NaOH (7.0 mL) and then water (21 mL) were added dropwise (caution: exotherm and vigorous gas evolution) to form a crisp, colourless precipitate and the mixture was filtered through Celite ®, washing with EtOAc (80 mL). The mother liquors were then washed with brine (60 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford amino alcohol **376** (4.04 g, 98 %) as a pale yellow solid. This material was used in the next step without further purification.

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.14-7.32 (m, 10H, Ar(H)), 3.78 (s, 2H, NCH_2Ph), 3.65 (dd, J = 10.6, 3.8 Hz, 1H, H-1), 3.34 (dd, J = 10.6, 5.6 Hz, 1H, H-1), 2.97 (m, 1H, H-2), 2.77-2.82 (m, 2H, CCH_2Ph), signals attributable to NH and OH were not observed.

(S)-3,4-Dibenzyl[1,2,3]oxathiazolidine-2,2-dioxide (378)



(376) (377) (378)

To an ice-cooled (0 °C) solution of amino alcohol **376** (4.04 g, 16.8 mmol), Et_3N (5.10 mL, 36.6 mmol) and imidazole (4.56 g, 66.9 mmol) in anhydrous CH_2Cl_2

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(150 mL) was added *via* syringe a solution of $SOCl_2$ (1.40 mL, 19.1 mmol) in anhydrous CH_2Cl_2 (20 mL) dropwise over 10 minutes. The mixture was stirred at 0 °C for 1.5 h and then poured into water (100 mL). The organic portion was isolated, washed with water (75 mL) and then brine (75 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford intermediate cyclic sulfamidite **377** (4.82 g, 100 %) as a yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.06-7.45 (m, 20H, Ar(H)), 4.65 (dd, *J* = 10.0, 6.0 Hz, 2H, H-5), 4.39 (d, *J* = 16.0 Hz, 1H, NCH_2Ph), 4.33 (dd, *J* = 10.0, 6.0 Hz, 1H, H-5), 4.09-4.27 (m, 4H, H-5 and NCH_2Ph×3), 3.86 (m, 1H, H-4), 3.59 (m, 1H, H-4), 3.19 (dd, *J* = 12.0, 4.0 Hz, 1H, C4-CH_2Ph), 2.97 (dd, *J* = 12.0, 4.0 Hz, 1H, C4-CH_2Ph), 2.91 (dd, *J* = 14.0, 10.0 Hz, 1H, C4-CH_2Ph), 2.61 (dd, *J* = 14.0, 10.0 Hz, 1H, C4-CH_2Ph)

To an ice-cooled (0 °C) solution of cyclic sulfamidite **377** (4.82 g, 16.8 mmol) in MeCN (120 mL) was added $RuCl_3$ (28.6 mg, 0.25 mol %), $NaIO_4$ (5.55 g, 25.9 mmol) and then water (90 mL). The mixture was stirred at 0 °C for 1.25 h and then poured into water (100 mL). The mixture was extracted with Et_2O (3 × 150 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford a brown oil. This material was dissolved in CH_2Cl_2 (25 mL) and DMSO (800 μL) was added. After stirring at r.t. for 2 h the mixture was pre-adsorbed onto SiO_2 (60) and purified by flash column chromatography (Et_2O/Petrol, 1:1) to afford cyclic sulfamidate **378** (4.48 g, 88 %) as a colourless, crystalline solid; m.p. 65-66 °C (Et_2O-hexanes); $[\alpha]_D^{20}$ -38.4, (c = 1.2, $CHCl_3$).

FTIR (neat), ν_{max}, cm^{-1}: 1343, 1186

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.23-7.39 (m, 8H, Ar(H)), 7.02 (m, 2H, Ar(H)), 4.30-4.34 (m, 3H, H-5 and NCH_2Ph×2), 4.23 (dd, *J* = 9.1, 5.2 Hz, 1H, H-5), 3.76 (m, 1H, H-4), 3.01 (dd, *J* = 13.5, 9.1 Hz, 1H, C4-CH_2Ph), 2.73 (dd, *J* = 13.5, 5.2 Hz, 1H, C4-CH_2Ph)

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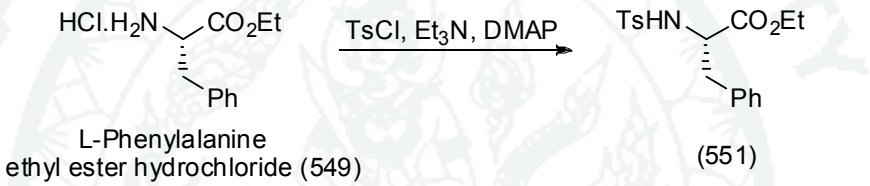
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 135.3 (C-Ar), 134.7 (C-Ar), 129.1×4 (CH-Ar), 129.0×4 (CH-Ar), 128.6 (CH-Ar), 127.5 (CH-Ar), 70.5 (C-5), 60.1 (C-4), 50.8 (NCH_2Ph), 38.5 (C4-CH_2Ph)

MS (CI^+), *m/z* (relative intensity): 304.1 ($[M+H]^+$, 5%), 91.0 (100)

(2*S*)-Ethyl-2-tosylamino-3-phenylpropionate (551)



L-Phenylalanine ethyl ester hydrochloride (549)

(551)

To an ice-cooled (0 °C) of L-phenylalanine ethyl ester hydrochloride (549) (2.0 g, 8.71 mmol) and DMAP (212.74 g, 1.74 mmol) in CH_2Cl_2 (16 mL) was added Et_3N (2.67 mL, 19.2 mmol) dropwise over 5 minutes. A solution of tosylchloride (1.99 g, 10.4 mmol) in CH_2Cl_2 (4.0 mL) was then added dropwise over 10 minutes. The mixture was warmed to r.t. and stirred for 2 h prior to the addition of water (20 mL). The organic portion was isolated, washed sequentially with aqueous 1 M HCl (20 mL), saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 3:7) to afford (2*S*)-ethyl-2-tosylamino-3-phenylpropionate (551) (3.02 g, 100 %) as a colourless crystalline solid; m.p. 81-83 °C.

FTIR (neat), ν_{max}, cm^{-1}: 3277, 1737, 1340, 1161

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.69 (m, 2H, Ar(H)), 7.26-7.30 (m, 5H, Ar(H)), 7.13 (m, 2H, Ar(H)), 5.10 (brd, *J* = 9.3 Hz, 1H, N$\underline{H}$), 4.22 (dt, *J* = 6.0, 6.0 Hz, 1H, H-2), 3.95 (q, *J* = 7.2 Hz, 2H, OC$\underline{H}_2$), 3.07 (d, *J* = 6.0 Hz, 2H, C$\underline{H}_2$Ph), 2.44 (s, 3H, ArC$\underline{H}_3$), 1.10 (t, *J* = 7.0 Hz, 3H, $CH_2C\underline{H}_3$)

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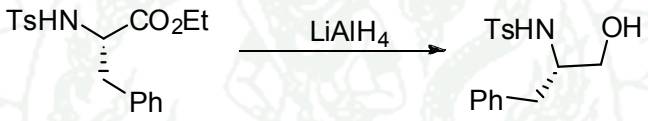
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.8 (C=O), 143.7 (C-Ar), 135.1 (C-Ar), 129.7 (CH-Ar), 129.6×2 (CH-Ar), 128.6×3 (CH-Ar), 127.3×3 (CH-Ar), 61.7 ($O\underline{C}H_2CH_3$), 56.7 ($\underline{C}HCH_2Ph$), 39.6 ($CH\underline{C}H_2Ph$), 21.6 ($Ar\underline{C}H_3$), 14.0 ($CCH_2\underline{C}H_3$)

MS (CI^+), *m/z* (relative intensity): 348.1 ($[M+H]^+$, 77 %), 274.1 (100)

HRMS (ESI^+) *m/z*: $C_{18}H_{21}NO_4SNa$ $[M+Na]^+$, calcd 370.1083, found 370.1081

(*S*)-2-Tosylamino-3-phenylpropan-1-ol (552)



(551) (552)

To an ice-cooled (0 °C) slurry of tosylated phenylalanine ethyl ester (551) (3.02 g, 8.71 mmol) in anhydrous THF (50 mL) was added, *via* cannula, a solution of $LiAlH_4$ in THF (1.0 M, 14.4 mmol) dropwise over 30 minutes (**caution:** exotherm). The mixture was heated at reflux for 4 h and then cooled to 0 °C. Water (5.0 mL), aqueous 4 M NaOH (5.0 mL) and then water (15 mL) were added dropwise (**caution:** exotherm and vigorous gas evolution) to form a crisp, colourless precipitate and the mixture was filtered through Celite ®, washing with EtOAc (75 mL). The mother liquors were then washed with brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford amino alcohol **552** (2.65 g, 100 %) as a pale yellow oil. This material was used in the next step without further purification.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.59 (m, 2H, Ar(H)), 7.17-7.22 (m, 5H, Ar(H)), 6.99 (m, 2H, Ar(H)), 4.97 (brd, *J* = 6.9 Hz, 1H, N$\underline{H}$), 3.64 (m, 1H, H-2), 3.50 (m, 2H, $CHC\underline{H}_2Ph$), 2.79 (dd, *J* = 13.8, 6.9 Hz, 1H, H-1), 2.68 (dd, *J* = 13.8, 7.2 Hz, 1H, H-1), 2.42 (s, 3H, $ArC\underline{H}_3$)

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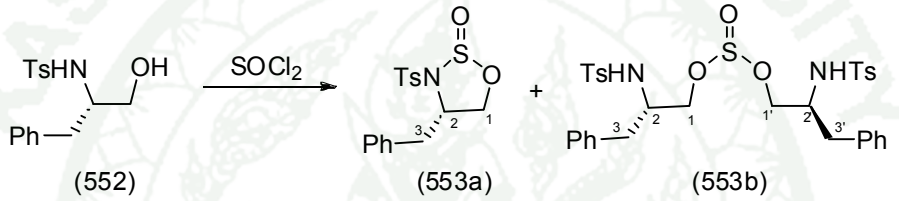
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 143.5 (C-Ar), 136.8 (C-Ar), 129.8×2 (CH-Ar), 129.2×2 (CH-Ar), 128.8×2 (CH-Ar), 127.1×2 (CH-Ar), 126.8 (CH-Ar), 64.1 ($\underline{C}H_2OH$), 56.7 ($\underline{C}HCH_2Ph$), 37.9 ($CH\underline{C}H_2Ph$), 21.6 ($Ar\underline{C}H_3$) (signals attributable to O$\underline{H}$ was not observed)

(*S*)-3-Tosyl-4-benzyl[1,2,3]oxathiazolidine-2,2-dioxide (553a)



(552) (553a) (553b)

Method I:

To an ice-cooled (0 °C) solution of amino alcohol **552** (2.65 g, 8.71 mmol) in dry THF (16.0 mL) was added *via* syringe $SOCl_2$ (0.89 mL, 12.2 mmol) slowly in one portion, followed by addition of pyridine (1.76 mL, 21.77 mmol) solution in THF (4.0 mL) over 30 minutes. The reaction mixture was warmed to room temperature and stirred for 1.5 h. The reaction was quenched by slow addition of saturated aqueous $NaHCO_3$ solution. The organic portion was isolated, washed with water (50 mL) and then brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford intermediate cyclic sulfamidite **553a** (1.10 g, 36.1 %) as a yellow oil; $[\alpha]_D^{25}$ -40.0 (c = 1.0, CH_2Cl_2) and dimeric compound **553b** (1.58 g, 55.4%).

***Method II*:**

To a cooled (-78 °C) solution of amino alcohol **552** (2.29 g, 7.49 mmol) in dry THF (40.0 mL) was added *via* syringe $SOCl_2$ (0.76 mL, 10.46 mmol) slowly in one

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portion, followed by addition of pyridine (1.52 mL, 18.73 mmol) solution in THF (7.0 mL) over 30 minutes. The reaction mixture was stirred at this temperature for a further 4 h. The reaction was quenched by slow addition of saturated aqueous $NaHCO_3$ solution. The organic portion was isolated, washed with water (50 mL) and then brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford intermediate cyclic sulfamidite **553a** (2.48 g, 97.1 %) as a yellow oil.

(*S*)-3-Tosyl-4-benzyl[1,2,3]oxathiazolidine-2,2-dioxide (553a)

FTIR (neat), ν_{max}, cm^{-1}: 1455, 1323, 1158, 1093

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.97 (d, *J* = 8.4 Hz, 2H, Ar(H)), 7.84 (d, *J* = 8.0 Hz, 2H, Ar(H)), 7.32-7.40 (m, 5H, Ar(H)), 7.25-7.30 (m, 5H, Ar(H)), 7.19 (d, *J* = 6.8 Hz, 2H, Ar(H)), 7.12 (d, *J* = 6.8 Hz, 2H, Ar(H)), 4.83 (dd, *J* = 9.0, 9.0 Hz, 1H, H-5), 4.63 (ddd, *J* = 9.6, 5.6, 1.2 Hz, 1H, H-5), 4.46 (d, *J* = 9.2 Hz, 1H, H-5), 4.41 (dd, *J* = 9.2, 6.4 Hz, 1H, H-5), 3.90 (m, 1H, H-4), 3.81 (m, 1H, H-4), 3.39 (dd, *J* = 13.8, 4.2 Hz, 1H, C4-C$\underline{H}_2$Ph), 3.32 (dd, *J* = 13.6, 3.2 Hz, 1H, C4-C$\underline{H}_2$Ph), 2.77 (dd, *J* = 13.8, 10.6 Hz, 1H, C4-C$\underline{H}_2$Ph), 2.81 (dd, *J* = 13.8, 10.6 Hz, 1H, C4-C$\underline{H}_2$Ph), 2.47 (s, 3H, ArC$\underline{H}_3$), 2.46 (s, 3H, ArC$\underline{H}_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 136.2 (C-Ar), 136.1 (C-Ar), 130.4 (C-Ar), 130.1 (CH-Ar), 129.5 (CH-Ar), 129.1×2 (CH-Ar), 128.9 (CH-Ar), 128.3×2 (CH-Ar), 127.7 (CH-Ar), 127.4 (CH-Ar), 73.9 ($\underline{C}H_2O$), 59.1 ($\underline{C}$4-CH_2Ph), 39.3 (C4-$\underline{C}H_2$Ph), 39.2 (C4-$\underline{C}H_2$Ph), 21.2 (Ar$\underline{C}H_3$), 21.8 (Ar$\underline{C}H_3$)

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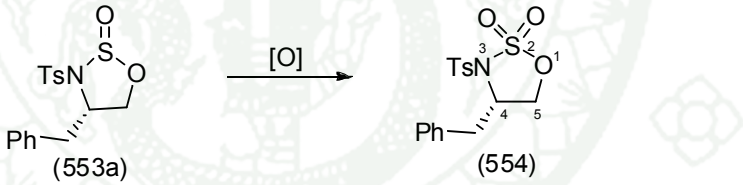
Compound 553b

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.97 (d, *J* = 8.4 Hz, 2H, Ar(H)), 7.84 (d, *J* = 8.0 Hz, 2H, Ar(H)), 7.32-7.40 (m, 5H, Ar(H)), 7.25-7.30 (m, 5H, Ar(H)), 7.19 (d, *J* = 6.8 Hz, 2H, Ar(H)), 7.12 (d, *J* = 6.8 Hz, 2H, Ar(H)), 4.83 (dd, *J* = 9.0, 9.0 Hz, 1H, H-5), 4.63 (ddd, *J* = 9.6, 5.6, 1.2 Hz, 1H, H-5), 4.46 (d, *J* = 9.2 Hz, 1H, H-5), 4.41 (dd, *J* = 9.2, 6.4 Hz, 1H, H-5), 3.90 (m, 1H, H-4), 3.81 (m, 1H, H-4), 3.39 (dd, *J* = 13.8, 4.2 Hz, 1H, C4-C$\underline{H}_2$Ph), 3.32 (dd, *J* = 13.6, 3.2 Hz, 1H, C4-C$\underline{H}_2$Ph), 2.77 (dd, *J* = 13.8, 10.6 Hz, 1H, C4-C$\underline{H}_2$Ph), 2.81 (dd, *J* = 13.8, 10.6 Hz, 1H, C4-C$\underline{H}_2$Ph), 2.46 (s, 3H, ArC$\underline{H}_3$), 2.41 (s, 3H, ArC$\underline{H}_3$)

(*S*)-3-Tosyl-4-benzyl[1,2,3]oxathiazolidine-2,2-dioxide (554)



To an ice-cooled (0 °C) solution of cyclic sulfamidite **553a** (2.48 g, 7.06 mmol) in MeCN (50 mL) was added $RuCl_3$ (11.6 mg, 0.25 mol %), $NaIO_4$ (2.25 g, 10.52 mmol) and then water (38 mL). The mixture was stirred at 0 °C for 1.25 h and then poured into water (20 mL). The mixture was extracted with Et_2O (3 × 100 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford a brown oil. This material was dissolved in CH_2Cl_2 (10 mL) and DMSO (300 μL) was added. After stirring at room temperature for 2 h the mixture was pre-adsorbed onto SiO_2 and purified by flash column chromatography (EtOAc/hexane, 1:4) to afford cyclic sulfamidate **554** (1.33 g, 51.3%) as a white solid; m.p. 130-132 °C; $[\alpha]_D^{25}$ +28.0 (c = 0.5 ,CH_2Cl_2).

FTIR (neat), ν_{max}, cm^{-1}: 1376, 1205, 1166

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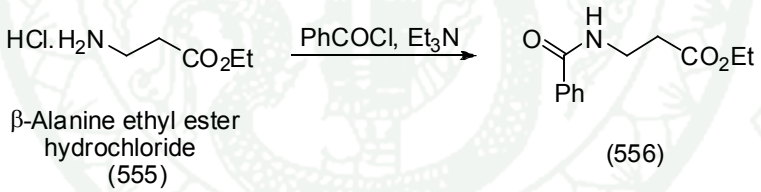
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.99-8.02 (m, 2H, Ar(H)), 7.29-7.42 (m, 5H, Ar(H)), 7.20-7.22 (m, 2H, Ar(H)), 4.24 (dd, *J* = 8.0, 4.0 Hz, 1H, H-5), 4.14 (ddd, *J* = 8.0, 4.0, 2.0 Hz, 1H, H-5), 4.19 (m, 1H, H-4), 3.44 (dd, *J* = 4.0, 16.0 Hz, 1H, C4-C$\underline{H}_2$Ph), 3.05 (dd, *J* = 8.0, 16.0 Hz, 1H, C4-C$\underline{H}_2$Ph), 2.48 (s, 3H, ArC$\underline{H}_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 146.2 (C-Ar), 134.5 (C-Ar), 133.7 (C-Ar), 130.1×2 (CH-Ar), 129.2×2 (CH-Ar), 128.7×3 (CH-Ar), 127.8×2 (CH-Ar), 68.8 (C-5), 61.0 (C-4), 39.1 (C4-$\underline{C}H_2$Ph), 21.7 (Ar$\underline{C}H_3$)

HRMS (ESI^+) *m/z*: $C_{16}H_{17}NO_5S_2Na$ $[M+Na]^+$, calcd 390.0440, found 390.0456

Ethyl-3-benzamidopropanoate (556)



β-Alanine ethyl ester hydrochloride (555)

(556)

To an ice-cooled (0 °C) of β-alanine ethyl ester hydrochloride (555) (1.0 g, 6.51 mmol) in CH_2Cl_2 (12.0 mL) was added Et_3N (1.96 mL, 14.06 mmol) dropwise over 5 minutes. A solution of benzoyl chloride (0.85 mL, 7.36 mmol) in CH_2Cl_2 (3.0 mL) was then added dropwise over 10 minutes. The mixture was warmed to room temperature and stirred for 2 h prior to the addition of water (10.0 mL). The organic portion was isolated, washed sequentially with aqueous 1 M HCl (10.0 mL), saturated aqueous $NaHCO_3$ (10.0 mL) and brine (10.0 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 2:3) to afford ethyl-3-benzamidopropanoate (556) (1.37 g, 95.3 %) as a colourless oil; $[\alpha]_D^{25}$ +20.9 (c = 3.2, CH_2Cl_2).

FTIR (neat), ν_{max}, cm^{-1}: 3322, 1731, 1639, 1538, 1183

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^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.73-7.76 (m, 2H, Ar(H)), 7.43-7.47 (m, 1H, Ar(H)), 7.35-7.40 (m, 2H, Ar(H)), 4.12 (q, *J* = 7.2 Hz, 2H, $OC\underline{H}_2CH_3$), 3.68 (q, *J* = 6.0 Hz, 2H, H-1), 2.61 (t, *J* = 6.2 Hz, 2H, H-2), 1.23 (t, *J* = 7.2 Hz, 3H, $OCH_2C\underline{H}_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 172.9 (C=O), 167.5 (C=O), 134.5 (C-Ar), 131.6×2 (CH-Ar), 128.6×2 (CH-Ar), 127.1 (CH-Ar), 60.8 ($O\underline{C}H_2CH_3$), 35.5 (C-1), 34.1 (C-2), 14.3 ($OCH_2\underline{C}H_3$)

HRMS (ESI^+) *m/z*: $C_{12}H_{15}NO_3Na$ $[M+Na]^+$, calcd 244.0944, found 244.0954

3-(Benzylamino)propan-1-ol (557)

(556) (557)

To an ice-cooled (0 °C) of benzoylated phenyl-*β*-alanine ethyl ester (556) (1.23 g, 5.55 mmol) in anhydrous THF (27.5 mL) was added a solution of $LiAlH_4$ in THF (1.0 M, 9.15 mmol) dropwise over 30 minutes (**caution:** exotherm). The mixture was heated at reflux for 4 h and then cooled to 0 °C. Water (7.0 mL), aqueous 4 M NaOH (7.0 mL) and then water (21 mL) were added dropwise (**caution:** exotherm and vigorous gas evolution) to form a crisp, colourless precipitate and the mixture was filtered through Celite ®, washing with EtOAc (80 mL). The mother liquors were then washed with brine (30 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford amino alcohol **557** (0.92 g, 100 %) as a pale yellow oil. This material was used in the next step without further purification.

FTIR (neat), ν_{max}, cm^{-1}: 3420

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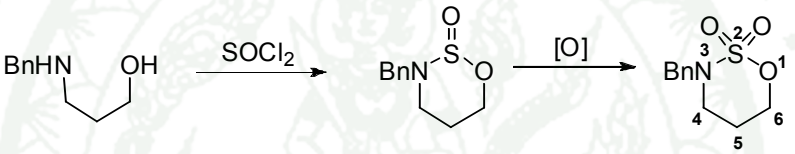
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.25-7.36 (m, 5H, Ar(H)), 3.82 (dd, *J* = 8.0, 4.0 Hz, 2H, H-1), 3.79 (s, 2H, $NC\underline{H}_2Ph$), 2.90 (dd, *J* = 8.0, 4.0 Hz, 2H, H-3), 1.73 (2H, quin, *J* = 6.0 Hz, C2-$\underline{H}$) (signals attributable to N$\underline{H}$ and O$\underline{H}$ were not observed)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 139.7 (C-Ar), 128.6×2 (CH-Ar), 128.3×2 (CH-Ar), 127.3 (CH-Ar), 64.4 (C-1), 54.1 ($N\underline{C}H_2Ph$), 49.5 (C-3), 31.0 (C-2)

3-Benzyl[1,2,3]oxathiazinane-2,2-dioxide (559)



(557) (558) (559)

To an ice-cooled (0 °C) solution of amino alcohol **557** (730.0 mg, 4.42 mmol), Et_3N (1.85 mL, 13.25 mmol) and imidazole (1.18 g, 17.38 mmol) in anhydrous CH_2Cl_2 (30.0 mL) was added *via* syringe a solution of $SOCl_2$ (0.39 mL, 5.30 mmol) in anhydrous CH_2Cl_2 (3.0 mL) dropwise over 10 minutes. The mixture was stirred at 0 °C for 12 h and then poured into water (10 mL). The organic portion was isolated, washed with water (20 mL) and then brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford intermediate cyclic sulfamidite **558** (933.8 mg, 100 %) as a yellow oil.

FTIR (neat), ν_{max}, cm^{-1}: 1376, 1205, 1166

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.29-7.41 (m, 5H, Ar(H)), 4.82 (ddd, *J* = 14.0, 12.0, 4.0 Hz, 1H, H-6), 4.18 (d, *J* = 12.0 Hz, 1H, $NC\underline{H}_2Ph$), 3.86 (ddt, *J* = 12.0, 4.0, 2.0 Hz, 1H, H-6), 3.82 (d, *J* = 16.0 Hz, 1H, $NC\underline{H}_2Ph$), 3.64 (ddd, *J* = 12.0, 12.0, 2.0 Hz, 1H, H-4), 2.68 (dddd, *J* = 12.0, 4.0, 4.0, 2.0 Hz, 1H, H-4), 2.28 (m, 1H, H-5), 1.55 (dh, *J* = 12.0, 2.0 Hz, 1H, H-5)

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^{13}C NMR ($CDCl_3$, 100 MHz) δ: 135.8 (C-Ar), 128.6×4 (CH-Ar), 127.8 (CH-Ar), 57.4 (C-6), 52.6 (N<u>C</u>H_2Ph), 37.6 (C-4), 23.1 (C-5)

HRMS (ESI^+) *m/z*: $C_{10}H_{13}NO_2SNa$ $[M+Na]^+$, calcd 234.0559, found 234.0566

To an ice-cooled (0 °C) solution of cyclic sulfamidite **558** (933.8 g, 4.42 mmol) in MeCN (26 mL) was added $RuCl_3$ (7.16 mg, 0.25 mol %), $NaIO_4$ (1.41 g, 6.59 mmol) and then water (18 mL). The mixture was stirred at 0 °C for 12 h and then poured into water (20 mL). The mixture was extracted with Et_2O (3 × 50 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford a brown oil. This material was dissolved in CH_2Cl_2 (5 mL) and DMSO (210 μL) was added. After stirring at room temperature for 2 h the mixture was pre-adsorbed onto SiO_2 (60) and purified by flash column chromatography (EtOAc/hexane, 3:7) to afford cyclic sulfamidate **559** (588.7 mg, 58.6 %) as a white solid; m.p. 94-96 °C.

FTIR (neat), ν_{max}, cm^{-1}: 1384, 1357, 1184, 788

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.31-7.40 (m, 5H, Ar(H)), 4.66 (dd, *J* = 8.0, 4.0 Hz, 2H, H-6), 4.35 (s, 2H, NC<u>H</u>$_2$Ph), 3.42 (dd, *J* = 8.0, 4.0 Hz, 2H, H-4), 1.84 (quin, *J* = 8.0 Hz, 2H, H-5)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 134.9 (C-Ar), 128.7 (CH-Ar), 128.5×2 (CH-Ar), 128.1×2 (CH-Ar), 73.2 (C-6), 52.1 (N<u>C</u>H_2Ph), 47.0 (C-4), 19.9 (C-5)

HRMS (ESI^+) *m/z*: $C_{10}H_{13}NO_3SNa$ $[M+Na]^+$, calcd 250.0508, found 250.0516

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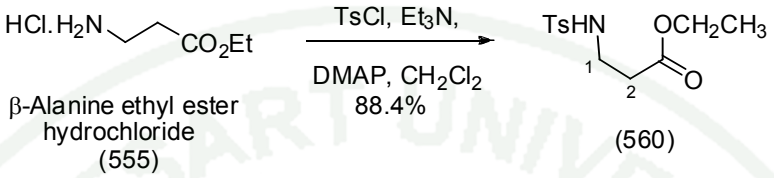
Ethyl 3-(4-methylphenylsulfonamido)propanoate (560)



To an ice-cooled (0 °C) of β-alanine ethyl ester hydrochloride (555) (500 mg, 3.26 mmol) and DMAP (79.53 mg, 0.65 mmol) in CH_2Cl_2 (7.5 mL) was added Et_3N (1.00 mL, 7.16 mmol) dropwise over 5 minutes. A solution of tosylchloride (744.68 mg, 3.91 mmol) in CH_2Cl_2 (1.5 mL) was then added dropwise over 10 minutes. The mixture was warmed to room temperature and stirred for 12 h prior to the addition of water (10 mL). The organic portion was isolated, washed sequentially with aqueous 1 M HCl (10 mL), saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 3:7) to afford ethyl 3-(4-methylphenylsulfonamido) propanoate (560) (780.8 mg, 88.4 %) as a colourless crystalline solid; m.p. 94-96 °C; $[\alpha]_D^{25}$ -3.3 (c = 1.2, CH_2Cl_2).

FTIR (neat), ν_{max}, cm^{-1}: 3292, 1732, 1328, 1160

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.75 (d, *J* = 8.0 Hz, 2H, Ar(H)), 7.31 (d, *J* = 8.0 Hz, 2H, Ar(H)), 5.19 (brt, *J* = 4.0 Hz, 1H, N<u>H</u>), 4.12 (q, *J* = 8.0 Hz, 2H, O<u>CH</u>$_2$), 3.18 (dd, *J* = 8.0, 12.0 Hz, 2H, H-1), 2.52 (dd, *J* = 8.0, 8.0 Hz, 2H, H-2), 2.43 (s, 3H, Ar<u>CH</u>$_3$), 1.24 (t, *J* = 8.0 Hz, 3H, CH_2<u>CH</u>$_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 172.1 (C=O), 143.5 (C-Ar), 137.0 (C-Ar), 129.8×2 (CH-Ar), 127.0×2 (CH-Ar), 61.0 (O<u>C</u>H_2CH_3), 38.8 (C-1), 34.0 (C-2), 21.5 (Ar<u>C</u>H_3), 14.1 (CCH_2<u>C</u>H_3)

HRMS (ESI^+) *m/z*: $C_{12}H_{17}NO_4SNa$ $[M+Na]^+$, calcd 294.0770, found 294.0775

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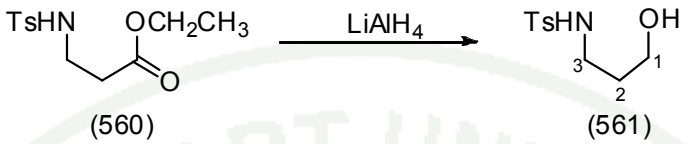
3-(Tosylamino)propan-1-ol (561)



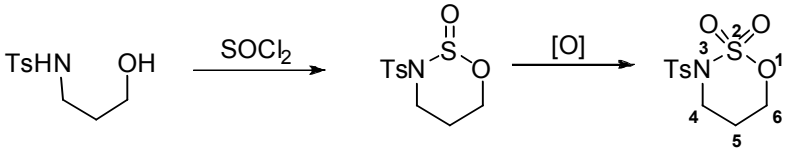
(560) (561)

To an ice-cooled (0 °C) of tosylated β-alanine ethyl ester (560) (740.8 mg, 2.73 mmol) in anhydrous THF (15.0 mL) was added a solution of $LiAlH_4$ in THF (1.0 M, 4.50 mmol) dropwise over 30 minutes (**caution:** exotherm). The mixture was heated at reflux for 4 h and then cooled to 0 °C. Water (7.0 mL), aqueous 4 M NaOH (7.0 mL) and then water (21 mL) were added dropwise (**caution:** exotherm and vigorous gas evolution) to form a crisp, colourless precipitate and the mixture was filtered through Celite ®, washing with EtOAc (40 mL). The mother liquors were then washed with brine (15 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford amino alcohol **561** (577.2 mg, 92.2 %) as a colorless oil. This material was used in the next step without further purification.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.75 (d, *J* = 8.0 Hz, 2H, Ar(H)), 7.31 (d, *J* = 8.0 Hz, 2H, Ar(H)), 3.73 (dd, *J* = 5.6, 5.6 Hz, 2H, H-1), 3.09 (dd, *J* = 6.2, 6.2 Hz, 2H, H-3), 2.43 (s, 3H, ArC<u>H</u>$_3$), 1.70 (quin, *J* = 6.0 Hz, 2H, H-2), (signals attributable to N<u>H</u> and O<u>H</u> were not observed)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 143.4 (C-Ar), 136.8 (C-Ar), 129.8×2 (CH-Ar), 127.1×2 (CH-Ar), 60.5 (C-1), 41.0 (C-3), 31.5 (C-2), 21.5 (Ar<u>C</u>H$_3$)

3-Tosyl[1,2,3]oxathiazinane-2,2-dioxide (563)



(561) (562) (563)

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To a cooled (-78 °C) solution of amino alcohol **561** (447.7 mg, 1.95 mmol) in dry THF (15.0 mL) was added *via* syringe $SOCl_2$ (0.24 mL, 3.31 mmol) slowly in one portion, followed by addition of pyridine (0.48 mL, 5.93 mmol) solution in THF (5.0 mL) over 30 minutes. The reaction mixture was stirred at this temperature for a further 4 h. The reaction was quenched by slow addition of saturated aqueous $NaHCO_3$ solution. The organic portion was isolated, washed with water (20 mL) and then brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 4:6) to afford intermediate cyclic sulfamidite **562** (354.0 g, 65.8 %) as a white solid.

FTIR (neat), ν_{max}, cm^{-1}: 3287, 1598, 1331, 1162, 1092

^{1}H NMR ($CDCl_3$, 400 MHz) δ: (58:58′ = 2:1), 7.74-7.77 (m, 6H, Ar(H) and Ar(H′)), 7.36 (d, *J* = 8.0 Hz, 2H, Ar(H)), 7.32 (d, *J* = 8.0 Hz, 2H, Ar(H′)), 4.73 (ddd, *J* = 13.0, 11.6, 2.6 Hz, 1H, H-6), 4.09 (dd, *J* = 6.0, 6.0 Hz, 2H, H-6′), 3.89 (ddt, *J* = 11.4, 4.6, 1.6 Hz, 1H, H-6), 3.58 (ddd, *J* = 12.6, 12.6, 2.8 Hz, 1H, H-4), 3.48 (m, 1H, H-4), 3.02 (q, *J* = 6.0 Hz, 2H, H-4′), 2.45 (s, 3H, ArC$\underline{H}_3$), 2.43 (s, 3H, ArC$\underline{H}_3$), 2.22 (m, 1H, H-5), 1.80 (quin, *J* = 6.0 Hz, 2H, H-5′), 1.65 (dquin, *J* = 16.0, 4.0 Hz, 1H, H-5)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 144.9 (C-Ar), 143.5 (C-Ar), 138.9 (C-Ar), 134.6 (C-Ar), 129.9×2 (CH-Ar), 129.8×2 (CH-Ar), 127.9×2 (CH-Ar), 127.1×2 (CH-Ar), 61.4 (C′-6), 57.4 (C-6), 40.0 (C′-4), 37.5 (C-4), 28.9 (C′-5), 23.9 (C-5), 21.6 (Ar$\underline{C}H_3$), 21.5 (Ar$\underline{C}'H_3$)

HRMS (ESI^+) *m/z*: $C_{10}H_{13}NO_4S_2Na$ $[M+Na]^+$, calcd 298.0178, found 298.0180

To an ice-cooled (0 °C) solution of cyclic sulfamidite **562** (319.0 mg, 1.16 mmol) in MeCN (8.0 mL) was added $RuCl_3$ (1.90 mg, 0.25 mol %), $NaIO_4$ (369.29

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mg, 1.73 mmol) and then water (6 mL). The mixture was stirred at 0 °C for 12 h and then poured into water (6 mL). The mixture was extracted with Et_2O (3 × 20 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford a brown oil. This material was dissolved in CH_2Cl_2 (5 mL) and DMSO (210 μL) was added. After stirring at room temperature for 2 h the mixture was pre-adsorbed onto SiO_2 (60) and purified by flash column chromatography (EtOAc/hexane, 1:1) to afford cyclic sulfamidate **563** (279.2 mg, 82.7 %) as a white solid; m.p. 137-139 °C.

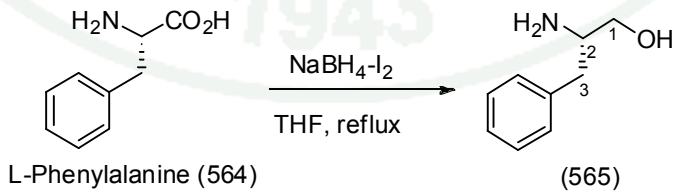
FTIR (neat), ν_{max}, cm^{-1}: 1399, 1364, 1196, 1168

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.85 (d, *J* = 8.0 Hz, 2H, Ar(H)), 7.35 (d, *J* = 8.0 Hz, 2H, Ar(H)), 4.70 (dd, *J* = 8.0, 4.0 Hz, 2H, H-6), 4.26 (dd, *J* = 8.0, 4.0 Hz, 2H, H-4), 2.45 (s, 3H, ArC$\underline{H}_3$), 2.03 (quin, *J* = 4.0 Hz, 2H, H-5)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 145.6 (C-Ar), 135.6 (C-Ar), 129.8×2 (CH-Ar), 128.4×2 (CH-Ar), 74.8 (C-6), 48.4 (C-4), 24.0 (C-5), 21.7 (Ar$\underline{C}H_3$)

HRMS (ESI^+) *m/z*: $C_{10}H_{13}NO_5S_2Na$ $[M+Na]^+$, calcd 314.0127, found 314.0135

L-Phenylalaninol (565)



L-Phenylalanine (564) (565)

A three-neck round-bottom flask was fitted with a magnetic stirbar and a reflux condenser. The flask was charged with 2.21 g (58.31 mmol) sodium borohydride and 64.0 mL of dry THF. L-Phenylalanine (564) (4.0 g, 24.21 mmol) was added in one portion. The remaining neck was sealed with a septum and a nitrogen line attached, and the flask was cooled to 0 °C in an ice bath. A solution of 6.15 g

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(24.21 mmol) of iodine dissolved in 16 mL of THF was added slowly and dropwise over 30 minutes resulting in vigorous evolution of hydrogen. After addition of the iodine was complete and gas evolution had ceased, the flask was heated to reflux for 18 h and then cooled to room temperature, and methanol was added cautiously until the mixture became clear. After stirring 30 minutes, the solvent was removed by rotary evaporation leaving a white paste which was dissolved by addition of 48 mL of 20% aqueous KOH. The solution was stirred for 4 h and extracted with 3×50 mL of CH_2Cl_2. The organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*, affording amino alcohol **565** as a white solid (3.29 g, 90%) which was recrystallized from toluene to afford colorless crystals; m.p. 91-93 °C (lit. 92-94 °C); $[\alpha]_D^{20}$ -62.0 (c = 1.0, CH_2Cl_2).

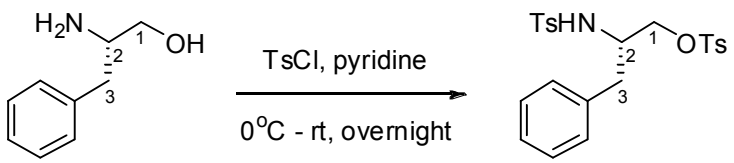
FTIR (neat), ν_{max}, cm^{-1}: 3351, 3283, 3025, 1583, 1496, 1454

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.26-7.32 (m, 2H, Ar(H)), 7.17-7.24 (m, 3H, Ar(H)), 3.62 (dd, *J* = 12.0, 4.0 Hz, 1H, H-1), 3.38 (dd, *J* = 12.0, 8.0 Hz, 1H, H-1), 3.07-3.13 (m, 1H, H-2), 2.78 (dd, *J* = 12.0, 4.0 Hz, 1H, C2-C$\underline{H}_2$Ar), 2.50 (dd, *J* = 12.0, 8.0 Hz, 1H, C2-C$\underline{H}_2$Ar)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 138.6 (C-Ar), 129.1×2 (CH-Ar), 128.5×2 (CH-Ar), 126.3 (CH-Ar), 66.0 (C-1), 54.1 (C-2), 40.6 (C2-$\underline{C}H_2$Ar)

HRMS (ESI^+) *m/z*: $C_9H_{13}NONa$ $[M+Na]^+$, calcd 174.0889, found 174.0889

(*S*)-2-(4-methylphenylsulfonamido)-3-phenylpropyl 4-methyl benzenesulfonate (566)



(565) (566)

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To an ice-cooled (0 °C) of L-phenylalaninol (565) (3.29 g, 21.79 mmol) in excess pyridine (16.0 mL) was added TsCl (9.14 g, 47.94 mmol). The mixture was warmed to r.t. and stirred for 12 h prior to the addition of saturated aqueous $NaHCO_3$ (30 mL). The mixture was extracted with CH_2Cl_2 (3 × 25 mL). The organic extracts were combined, washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 1:4) to afford the product **566** (9.20 g, 92 %) as a colorless syrup; $[\alpha]_D^{20}$ -64.6 (c = 1.3, CH_2Cl_2).

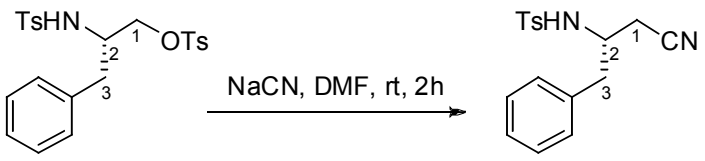
FTIR (neat), ν_{max}, cm^{-1}: 3292, 1598, 1362, 1336, 1176, 1161

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.75 (d, *J* = 8.0 Hz, 2H, Ar(H)), 7.52 (d, *J* = 8.0 Hz, 2H, Ar(H)), 7.36 (d, *J* = 8.0 Hz, 2H, Ar(H)), 7.10-7.18 (m, 5H, Ar(H)), 6.87 (d, *J* = 8.0 Hz, 2H, Ar(H)), 4.71 (d, *J* = 8.0 Hz, 1H, N<u>H</u>), 3.98 (dd, *J* = 8.0, 4.0 Hz, 1H, H-1), 3.86 (dd, *J* = 8.0, 4.0 Hz, 1H, H-1), 3.54-3.60 (m, 1H, H-2), 2.81 (dd, *J* = 16.0, 8.0 Hz, 1H, C2-C<u>H</u>$_2$Ar), 2.66 (dd, *J* = 16.0, 8.0 Hz, 1H, C2-C<u>H</u>$_2$Ar), 2.47 (s, 3H, ArC<u>H</u>$_3$), 2.40 (s, 3H, ArC<u>H</u>$_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 145.2 (C-Ar), 143.5 (C-Ar), 136.7 (C-Ar), 135.6 (C-Ar), 132.2 (C-Ar), 130.0×2 (CH-Ar), 129.7×2 (CH-Ar), 129.1×2 (CH-Ar), 128.7×2 (CH-Ar), 128.0×2 (CH-Ar), 126.9×3 (CH-Ar), 70.0 (C-1), 53.5 (C-2), 37.5 (C2-<u>C</u>H$_2$Ar), 21.7 (Ar<u>C</u>H$_3$), 21.5 (Ar<u>C</u>H$_3$)

HRMS (ESI^+) *m/z*: $C_{23}H_{25}NO_5S_2Na$ $[M+Na]^+$, calcd 482.1066, found 482.1058

(*S*)-*N*-(1-cyano-3-phenylpropan-2-yl)-4-methylbenzenesulfonamide (567)



(566) (567)

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To a solution of tosylated-L-phenylalaninol (566) (9.20 g, 20.04 mmol) in dry DMF (40.0 mL) was added NaCN (1.18 g, 24.05 mmol). The reaction mixture was stirred at room temperature for 2 h. The mixture was quenched with water, and the solvent was removed under vacuum. The residue was diluted in water and extracted with EtOAc (3 × 150 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 1:4) to afford nitrile compound **567** (5.66 g, 90 %) as a colorless syrup; $[\alpha]_D^{25}$ -43.9 (c = 1.8, CH_2Cl_2).

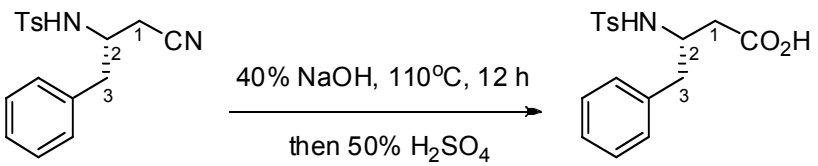
FTIR (neat), ν_{max}, cm^{-1}: 3276, 2252, 1599, 1496, 1456, 1420, 1333, 1305, 1292, 1161, 1089

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.56 (d, *J* = 8.0 Hz, 2H, Ar(H)), 7.20-7.22 (m, 5H, Ar(H)), 6.98 (dd, *J* = 8.0, 4.0 Hz, 2H, Ar(H)), 4.99 (brd, *J* = 4.0 Hz, 1H, NH), 3.60-3.67 (m, 1H, H-2), 2.90 (dd, *J* = 12.0, 8.0 Hz, 1H, C2-CH$_2$Ar), 2.78 (dd, *J* = 12.0, 8.0 Hz, 1H, C2-CH$_2$Ar), 2.66 (dd, *J* = 16.0, 8.0 Hz, 1H, H-1), 2.56 (dd, *J* = 20.0, 4.0 Hz, 1H, H-1), 2.42 (s, 3H, ArCH$_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 143.8 (C-Ar), 136.4 (C-Ar), 135.1 (C-Ar), 129.8×2 (CH-Ar), 129.0×4 (CH-Ar), 127.4 (CH-Ar), 126.9×2 (CH-Ar), 116.8 (CN), 51.4 (C-2), 39.8 (C2-CH$_2$Ar), 24.2 (C-1), 21.6 (ArCH$_3$)

HRMS (ESI^+) *m/z*: $C_{17}H_{18}N_2O_2SNa$ $[M+Na]^+$, calcd 337.0981, found 337.0978

(*S*)-3-(4-methylphenylsulfonamido)-4-phenylbutanoic acid (568)



(567) (568)

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Nitrile (567) (5.66 g, 18.02 mmol) was suspended in 70 mL of 40% aqueous NaOH and refluxed overnight. The reaction mixture was treated with 50% H_2SO_4, diluted with water and extracted with CH_2Cl_2 (3 × 25 mL). The organic extracts were combined, washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to afford compound **568** (5.98 g, 100 %) as a yellow oil; $[\alpha]_D^{25}$ -7.0 (c = 1.0, CH_2Cl_2).

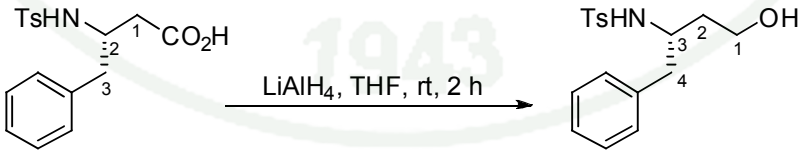
FTIR (neat), ν_{max}, cm^{-1}: 3272, 1712, 1325, 1305, 1291, 1157, 1091

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 9.77 (brs, 1H, COO<u>H</u>), 7.62 (brs, 2H, Ar(H)), 7.20-7.26 (brm, 5H, Ar(H)), 7.02 (brs, 2H, Ar(H)), 5.59 (s, 1H, N<u>H</u>), 3.75 (s, 1H, H-2), 2.82 (d, *J* = 20.0 Hz, 2H, C2-C<u>H</u>$_2$Ar), 2.55 (s, 2H, H-1), 2.40 (s, 3H, ArC<u>H</u>$_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 176.4 (C=O), 143.4 (C-Ar), 137.1 (C-Ar), 136.7 (C-Ar), 129.7×2 (CH-Ar), 129.2×2 (CH-Ar), 128.7×2 (CH-Ar), 127.0×2 (CH-Ar), 126.8 (CH-Ar), 51.7 (C-2), 40.5 (C2-<u>C</u>H$_2$Ar), 37.8 (C-1), 21.5 (Ar<u>C</u>H$_3$)

HRMS (ESI^+) *m/z*: $C_{17}H_{19}NO_4SNa$ $[M+Na]^+$, calcd 356.0927, found 356.0925

(*S*)-*N*-(4-hydroxy-1-phenylbutan-2-yl)-4-methylbenzenesulfonamide (569)



(568) (569)

To an ice-cooled (0 °C) of carboxylic acid (568) (5.98 g, 17.95 mmol) in anhydrous THF (75.0 mL) was added a solution of $LiAlH_4$ in THF (1.0 M, 28.72 mmol) dropwise over 30 minutes (**caution:** exotherm). The mixture was heated at reflux for 4 h and then cooled to 0 °C. Water (30.0 mL), aqueous 4 M NaOH (30.0 mL) and then water (30 mL) were added dropwise (**caution:** exotherm and vigorous

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gas evolution) to form a crisp, colourless precipitate and the mixture was filtered through Celite ®, washing with EtOAc (3×150 mL). The mother liquors were then washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to afford amino alcohol **569** (5.61 g, 98%) as a colorless syrup; $[\alpha]_D^{25}$ +10.6 (c = 1.6, CH_2Cl_2).

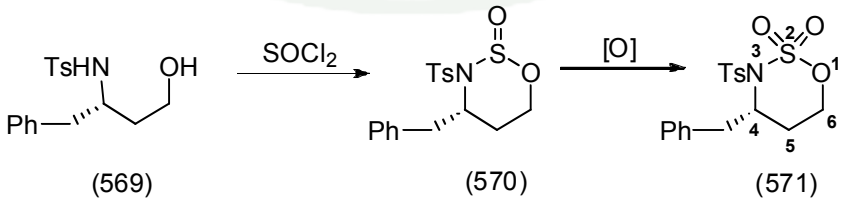
FTIR (neat), ν_{max}, cm^{-1}: 3503, 3281, 1323, 1304, 1290, 1157, 1091

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.68 (d, *J* = 8.0 Hz, 2H, Ar(H)), 7.23 (d, *J* = 8.0 Hz, 2H, Ar(H)), 7.13-7.19 (m, 3H, Ar(H)), 6.95 (d, *J* = 8.0 Hz, 2H, Ar(H)), 3.79 (ddd, *J* = 12.0, 8.0, 4.0 Hz, 1H, H-1), 3.55-3.66 (m, 2H, H-1 and H-3), 2.67 (dd, *J* = 12.0, 8.0 Hz, 1H, C3-C$\underline{H}_2$Ar), 2.60 (dd, *J* = 12.0, 8.0 Hz, 1H, C3-C$\underline{H}_2$Ar), 2.40 (s, 3H, ArC$\underline{H}_3$), 1.70-1.78 (m, 1H, H-2), 1.41-1.49 (m, 1H, H-2)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 143.2 (C-Ar), 137.4 (C-Ar), 137.0 (C-Ar), 129.6×2 (CH-Ar), 129.3×2 (CH-Ar), 128.4×2 (CH-Ar), 126.9×2 (CH-Ar), 126.4 (CH-Ar), 58.9 (C-1), 52.7 (C-3), 41.6 (C3-$\underline{C}H_2$Ar), 36.5 (C-2), 21.4 (Ar$\underline{C}H_3$)

HRMS (ESI^+) *m/z*: $C_{17}H_{21}NO_3SNa$ $[M+Na]^+$, calcd 342.1134, found 342.1130

4-Benzyl-3-tosyl[1,2,3]oxathiazinane-2,2-dioxide (571)



To a cooled (-78 °C) solution of amino alcohol **569** (2.63 g, 8.25 mmol) in dry THF (70 mL) was added *via* syringe $SOCl_2$ (0.67 mL, 9.24 mmol) slowly in one

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portion, followed by addition of pyridine (1.67 mL, 20.63 mmol) solution in THF (17 mL) over 30 minutes. The reaction mixture was stirred at this temperature for a further 4 h and allowed to room temperature for 12 h. The reaction was quenched by slow addition of saturated aqueous $NaHCO_3$ solution. The organic portion was isolated, washed with water (50 mL) and then brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 1:4) to afford intermediate cyclic sulfamidite **570** (2.10 g, 70%) as a white solid; $[\alpha]_D^{25}$ +77.7 (c = 2.3, CH_2Cl_2).

FTIR (neat), ν_{max}, cm^{-1}: 1353, 1162, 1040

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.75 (d, *J* = 8.0 Hz, 2H, Ar(H)), 7.22-7.34 (m, 5H, Ar(H)), 7.12 (d, *J* = 8.0 Hz, 2H, Ar(H)), 5.01 (t, *J* = 12.0 Hz, 1H, H-6), 4.00-4.03 (m, 1H, H-4), 3.82-3.85 (m, 1H, H-6), 3.32 (dd, *J* = 24.0, 12.0 Hz, 1H, C4-C$\underline{H}_2$Ar), 3.27 (dd, *J* = 12.0, 4.0 Hz, 1H, C4-C$\underline{H}_2$Ar), 2.44 (s, 3H, ArC$\underline{H}_3$), 1.81-1.87 (m, 1H, H-5), 1.60 (d, *J* = 16.0 Hz, 1H, H-5)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 144.6 (C-Ar), 137.9 (C-Ar), 136.5 (C-Ar), 130.0×2 (CH-Ar), 129.2×2 (CH-Ar), 128.7×2 (CH-Ar), 127.2×2 (CH-Ar), 126.8 (CH-Ar), 55.3 (C-4), 53.9 (C-6), 40.8 (C4-$\underline{C}H_2$Ar), 24.1 (C-5), 21.6 (Ar$\underline{C}H_3$)

HRMS (ESI^+) *m/z*: $C_{17}H_{19}NO_4S_2Na$ $[M+Na]^+$, calcd 388.0648, found 388.0646

To an ice-cooled (0 °C) solution of cyclic sulfamidite **570** (1.67 g, 4.57 mmol) in MeCN (40 mL) was added $RuCl_3$ (7.52 mg, 0.25 mol %), $NaIO_4$ (1.46 g, 6.81 mmol) and then water (30 mL). The mixture was stirred at 0 °C for 12 h and then poured into water (30 mL). The mixture was extracted with Et_2O (3 × 50 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford a brown oil. This material was dissolved in CH_2Cl_2 (25 mL) and DMSO (1.0 mL) was added. After stirring at room

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temperature for 2 h the mixture was pre-adsorbed onto SiO_2 and purified by flash column chromatography (EtOAc/hexane, 1:4) to afford cyclic sulfamidate **571** (1.27 g, 73%) as a colourless, crystalline solid; m.p. 176-178 °C (CH_2Cl_2-hexanes); $[\alpha]_D^{25}$ +10.0 (c = 0.6, CH_2Cl_2).

FTIR (neat), ν_{max}, cm^{-1}: 1400, 1362, 1196, 1186, 1166, 1030

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.42 (d, *J* = 8.0 Hz, 2H, Ar(H))**,** 7.29-7.38 (m, 5H, Ar(H)), 7.21 (d, *J* = 8.0 Hz, 2H, Ar(H)), 5.17 (m, 1H, H-4), 5.04 (ddd, *J* = 12.0, 12.0, 4.0 Hz, 1H, H-6), 4.55 (dddd, *J* = 12.0, 4.0, 2.0, 2.0 Hz, 1H, H-6), 3.51 (dd, *J* = 16.0, 8.0 Hz, 1H, C4-C$\underline{H}_2$Ar), 3.16 (dd, *J* = 12.0, 8.0 Hz, 1H, C4-C$\underline{H}_2$Ar), 2.40 (s, 3H, ArC$\underline{H}_3$), 2.26 (m, 1H, H-5), 1.83 (dq, *J* = 16.0, 4.0 Hz, 1H, H-5)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 145.1 (C-Ar), 137.2 (C-Ar), 136.2 (C-Ar), 129.6×2 (CH-Ar), 129.5×2 (CH-Ar), 128.8×2 (CH-Ar), 128.4×2 (CH-Ar), 127.0 (CH-Ar), 70.9 (C-6), 60.4 (C-4), 38.7 (C4-$\underline{C}H_2$Ar), 26.3 (C-5), 21.6 (Ar$\underline{C}H_3$)

MS (CI^+), *m/z* (relative intensity): 382 ($[M+H]^+$, 45%), 155 (100)

HRMS (CI^+) *m/z*: $C_{17}H_{20}NO_5S_2$ $[M+H]^+$, calcd 382.0783, found 382.0786

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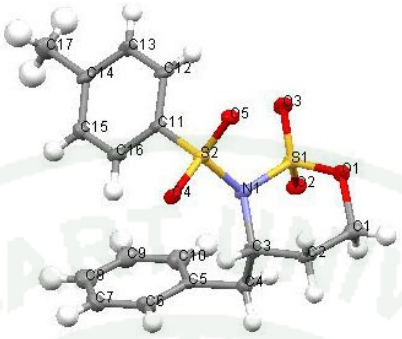
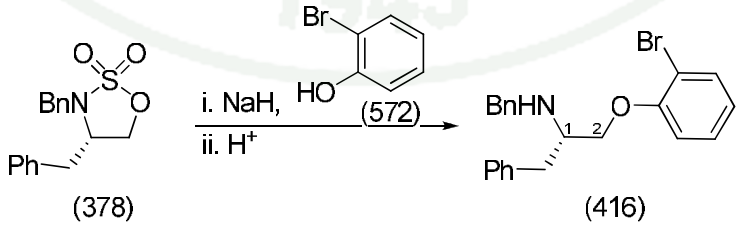


Figure 9 The X-ray crystal structure of 4-benzyl-3-tosyl[1,2,3]oxathiazinane-2,2-dioxide (571); Crystal data for **571**: $C_{17}H_{19}NO_5S_2$, MW = 381.45, lath, space group $P2_1$, a = 7.3117(7), b = 6.5064(6), c = 17.977(2) Å, V = 850.05(15) $Å^3$, α = 90.00, β = 96.292(7), γ = 90.00 °, Z = 2, D_c = 1.490 g cm^{-1}, Mo-Kα radiation, λ = 0.71073 Å, μ = 0.342 mm^{-1}, T = 100 K; monoclinic, 0.36×0.06×0.01mm, Bruker-AXS D8 diffractometer, 8584 reflections were collected, 3624 were unique, R_{int} = 0.0647; refinement on F2 gave R = 0.0827 and R_w = 0.2114, GOF = 0.764 for refined parameters

Synthesis of *N*-heterocycle *via* cyclic sulfamidates

Benzyl[(*S*)-1-benzyl-2-(2-bromophenoxy)ethyl]amine (416)



To a solution of 2-bromophenol (572) (114 mg, 0.66 mmol) in anhydrous DMF (3.8 mL) was added NaH (60 % dispersion in mineral oil, 26 mg, 0.66 mmol) and the mixture was stirred at room temperature for 15 minutes. Cyclic sulfamidate **378** (100 mg, 0.33 mmol) was added and the mixture was stirred at room temperature

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for a further 16.5 h prior to the addition of aqueous 5 M HCl (0.33 mL). The mixture was stirred at room temperature for 2 h, then diluted with aqueous 1 M NaOH (30 mL) and extracted with Et_2O (3 × 25 mL). The organic extracts were combined, washed with aqueous 1 M NaOH (3 × 25 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by short flash column chromatography (hexane 100% - EtOAc/MeOH, 9:1) to afford the product **416** (119.2 mg, 91 %) as a colourless oil; $[\alpha]_D^{20}$ +8.3 (c = 1.0, $CHCl_3$).

FTIR (neat), ν_{max}, cm^{-1}: 2924, 1481, 1442, 1277, 1248, 1125, 1051, 1030

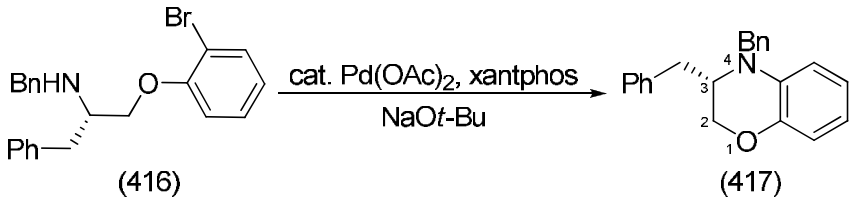
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.52 (dd, *J* = 7.6, 1.6, 1H, Ar(H)), 7.16-7.28 (m, 11H, Ar(H)), 6.80 (ddd, *J* = 8.2, 8.2, 1.6 Hz, 1H, Ar(H)), 6.75 (dd, *J* = 8.2, 1.4 Hz, 1H, Ar(H)), 3.92 (dd, *J* = 9.2, 4.8 Hz, 1H, H-2), 3.91 (s, 2H, NC$\underline{H}_2$Ar), 3.87 (dd, *J* = 9.0, 5.4 Hz, 1H, H-2), 3.23-3.28 (m, 1H, H-1), 2.99 (dd, *J* = 13.6, 6.0 Hz, 1H, C1-C$\underline{H}_2$Ar), 2.94 (dd, *J* = 13.6, 7.6 Hz, 1H, C1-C$\underline{H}_2$Ar), 1.85 (brs, 1H, N$\underline{H}$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 155.2 (C-Ar), 140.4 (C-Ar), 138.7 (C-Ar), 133.4×2 (CH-Ar), 129.5×2 (CH-Ar), 128.7×2 (CH-Ar), 128.6×2 (CH-Ar), 128.2×2 (CH-Ar), 127.1 (CH-Ar), 126.5 (CH-Ar), 122.1 (CH-Ar), 113.3 (CH-Ar), 112.4 (C-Ar), 70.1 (C-2), 57.6 (C-1), 51.6 (N$\underline{C}H_2$Ar), 38.0 (C1-$\underline{C}H_2$Ar)

MS (CI^+), *m/z* (relative intensity): 396.2 ($[M+H]^+$, 100%)

HRMS (ESI^+) *m/z*: $C_{22}H_{23}NO^{79}Br$ $[M+H]^+$, calcd 396.0958, found 396.0965

(*S*)-3,4-Dibenzyl-3,4-dihydro-2*H*-benzo[1,4]oxazine (417)



(416) (417)

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$Pd(OAc)_2$ (1.3 mg, 5 mol %), xantphos (3.5 mg, 5 mol %), *t*-BuONa (15 mg, 0.15 mmol) and amine **416** (40 mg, 0.10 mmol) were dissolved in anhydrous toluene (1.4 mL), placed in a re-sealable tube and heated at 100 °C for 16 h. The mixture was cooled to room temperature, diluted with EtOAc (20 mL), washed with water (10 mL) and then brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by short flash column chromatography (EtOAc/hexane, 1:1) to afford benzoxazine **417** (28 mg, 88 %) as a colourless oil; $[\alpha]_D^{20}$ +21.5 (c = 0.4, $CHCl_3$).

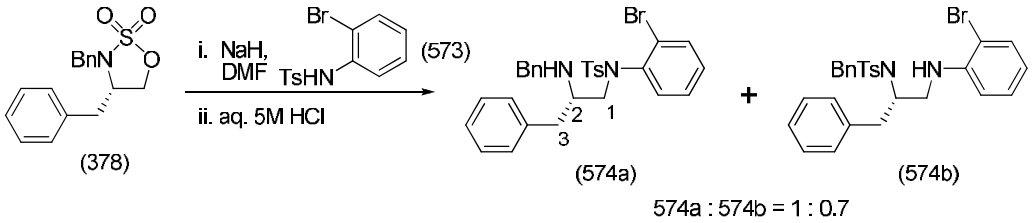
FTIR (neat), ν_{max}, cm^{-1}: 2923, 1604, 1501, 1453, 1249, 1215

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.17-7.42 (m, 10H, Ar(H)), 6.70 (dd, *J* = 8.0, 4.0 Hz, 1H, Ar(H)), 6.64 (ddd, *J* = 8.0, 8.0, 4.0 Hz, 1H, Ar(H)), 6.62-6.70 (m, 2H, Ar(H)), 4.58 (d, *J* = 16.0 Hz, 1H, NC$\underline{H_2}$Ar), 4.34 (d, *J* = 16.0 Hz, 1H, NC$\underline{H_2}$Ar), 4.12 (dd, *J* = 12.0, 4.0 Hz, 1H, H-2), 4.00 (ddd, *J* = 12.0, 4.0, 2.0 Hz, 1H, H-2), 3.50 (dddd, *J* = 12.0, 8.0, 4.0, 4.0 Hz, 1H, H-3), 2.98 (dd, *J* = 12.0, 8.0 Hz, 1H, C3-C$\underline{H_2}$Ar), 2.89 (dd, *J* = 12.0, 12.0 Hz, 1H, C3-C$\underline{H_2}$Ar)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 143.7 (C-Ar), 138.5 (C-Ar), 138.3 (C-Ar), 134.2 (C-Ar), 129.6×2 (CH-Ar), 128.8×2 (CH-Ar), 128.7 (CH-Ar), 128.4×2 (CH-Ar), 127.3×2 (CH-Ar), 126.6 (CH-Ar), 122.1 (CH-Ar), 117.5 (CH-Ar), 116.4 (CH-Ar), 112.9 (CH-Ar), 65.2 (C-2), 58.0 (C-3), 53.8 (N$\underline{C}H_2$Ar), 35.9 (C3-$\underline{C}H_2$Ar)

HRMS (ESI^+) *m/z*: $C_{22}H_{22}NO$ $[M+H]^+$, calcd 316.1696, found 316.1699

(*S*)-*N*-(2-(benzylamino)-3-phenylpropyl)-*N*-(2-bromophenyl)-4-methylbenzene sulfonamide (574a)



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To a solution of *N*-tosyl-2-bromoaniline (573) (215 mg, 0.66 mmol) in anhydrous DMF (3.14 mL) was added NaH (60% dispersion in mineral oil, 26 mg, 0.66 mmol) and the mixture was stirred at room temperature for 15 minutes. Cyclic sulfamidate **378** (100 mg, 0.33 mmol) was added and the mixture was stirred at room temperature for a further 16.5 h prior to the addition of aqueous 5 M HCl (1.0 mL). The mixture was stirred at room temperature for 2 h, then diluted with aqueous 1 M NaOH (30 mL) and extracted with Et_2O (3 × 25 mL). The organic extracts were combined, washed with aqueous 1 M NaOH (3 × 25 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 3:7) to afford the product **574a** and **574b** (137 mg, 76%) as a colourless oil.

FTIR (neat), ν_{max}, cm^{-1}: 1472, 1352, 1164

^{1}H NMR ($CDCl_3$, 400 MHz) δ: (7a:7b, 1:0.7) 7.60-7.65 (m, 2H, Ar(H)^{a,b}), 7.55 (d, *J* = 8.0 Hz, 2H, Ar(H)^b), 7.53 (d, *J* = 8.0 Hz, 2H, Ar(H)^a), 7.15-7.25 (m, 20H, Ar(H)^{a,b}), 7.09-7.11 (m, 2H, Ar(H)^b), 7.04-7.06 (m, 2H, Ar(H)^a), 6.97-7.00 (m, 2H, Ar(H)^b), 6.91-6.94 (m, 2H, Ar(H)^a), 6.88 (d, *J* = 2.0 Hz, 1H, Ar(H)^a), 6.86 (d, *J* = 2.0 Hz, 1H, Ar(H)^b), 3.76 (dd, *J* = 12.0, 4.0 Hz, 1H, H-1^b), 3.68 (d, *J* = 16.0 Hz, 1H, TsN^{b}C$\underline{H}_2$Ar), 3.64 (dd, *J* = 16.0, 8.0 Hz, 1H, H-1^a), 3.63 (d, *J* = 16.0 Hz, 1H, TsN^{b}C$\underline{H}_2$Ar), 3.58 (d, *J* = 12.0 Hz, 1H, HN^{a}C$\underline{H}_2$Ar), 3.50 (d, *J* = 12.0 Hz, 1H, HN^{a}C$\underline{H}_2$Ar), 3.41 (dd, *J* = 16.0, 8.0 Hz, 1H, H-1^a), 3.31 (dd, *J* = 12.0, 4.0 Hz, 1H, H-1^b), 3.12 (dd, *J* = 16.0, 8.0 Hz, 1H, C2-^{a}C$\underline{H}_2$Ar), 2.87 (m, 1H, H-2^b), 2.83 (m, 1H, H-2^a), 2.74 (d, *J* = 8.0 Hz, 2H, C2-^{b}C$\underline{H}_2$Ar), 2.63 (dd, *J* = 16.0, 8.0 Hz, 1H, C2-^{a}C$\underline{H}_2$Ar), 2.42 (s, 3H, Ar^{a}C$\underline{H}_3$), 2.41 (s, 3H, Ar^{b}C$\underline{H}_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 143.8 (C-Ar), 143.7 (C-Ar), 140.1 (C-Ar), 139.8 (C-Ar), 138.9 (C-Ar), 138.7 (C-Ar), 138.4×2 (C-Ar), 135.6 (C-Ar), 135.5 (C-Ar), 134.1×2 (C-Ar), 130.8×4 (CH-Ar), 129.6×4 (CH-Ar), 129.5×4 (CH-Ar), 129.1 (CH-Ar), 129.0 (CH-Ar), 128.4 (CH-Ar), 128.3 (CH-Ar), 128.2 (CH-Ar), 128.1×4 (CH-Ar), 128.0×6 (CH-Ar), 126.8×2 (CH-Ar), (CH-Ar), 126.7 (CH-Ar), 126.2×4

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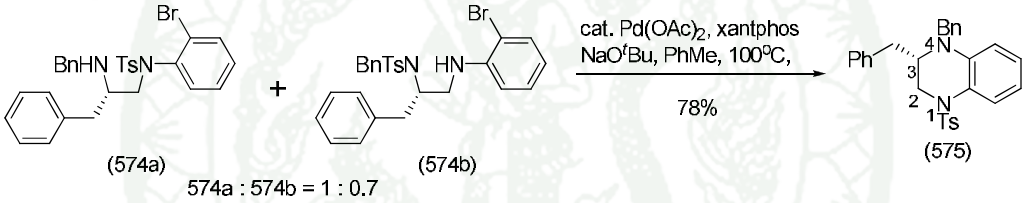
(CH-Ar), 125.9 (CH-Ar), 125.8 (CH-Ar), 57.6 (^{b}C-2), 56.4 (^{a}C-2), 55.2 (^{a}C-1), 54.6 (^{b}C-1), 51.4 (TsN^{b}$\underline{C}$H$_2$Ar), 51.2 (HN^{a}$\underline{C}$H$_2$Ar), 39.0 (C2-^{a}$\underline{C}$H$_2$Ar), 38.8 (C2-^{b}$\underline{C}$H$_2$Ar), 22.0×2 (Ar^{a,b}$\underline{C}$H$_3$)

HRMS (ESI$^+$) *m/z*: $C_{29}H_{30}N_2O_2S^{79}Br$ $[M+H]^+$, calcd 549.1206, found 549.1229; $C_{29}H_{30}N_2O_2S^{81}Br$ $[M+H]^+$, calcd 551.1185, found 551.1207; $C_{29}H_{29}N_2O_2S^{79}BrNa$ $[M+Na]^+$, calcd 571.1025, found 571.1047; $C_{29}H_{29}N_2O_2S^{81}BrNa$ $[M+Na]^+$, calcd 573.1005, found 573.1027

(*S*)-1,2-dibenzyl-4-tosyl-1,2,3,4-tetrahydroquinoxaline (575)



$Pd(OAc)_2$ (1.18 mg, 5 mol %), xantphos (2.63 mg, 5 mol %), *t*-BuONa (13.1 mg, 0.14 mmol) and the mixture of amine **574a** and **574b** (50 mg, 0.091 mmol) were dissolved in anhydrous toluene (1.30 mL), placed in a re-sealable tube and heated at 100 °C for 16 h. The mixture was cooled to room temperature, diluted with EtOAc (20 mL), washed with water (10 mL) and then brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 1:4) to afford quinoxaline derivative **575** (33.3 mg, 78%) as a colourless solid; m.p. 142-144 °C; $[\alpha]_D^{25}$ -86.8 (c = 1.3, CH_2Cl_2).

FTIR (neat), ν_{max}, cm^{-1}: 1599, 1495, 1452, 1350, 1165, 1091

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.54 (d, *J* = 8.0 Hz, 2H, Ar(H)), 7.52 (dd, *J* = 8.0, 4.0 Hz, 1H, Ar(H)), 7.20-7.34 (m, 8H, Ar(H)), 7.08-7.13 (m, 4H, Ar(H)), 6.93 (ddd, *J* = 8.0, 8.0, 2.0 Hz, 1H, Ar(H)), 6.67 (ddd, *J* = 8.0, 8.0, 2.0 Hz, 1H, Ar(H)), 6.51 (dd, *J* = 8.0, 2.0 Hz, 1H, Ar(H)), 4.37 (d, *J* = 16.0 Hz, 1H, NC$\underline{H}_2$Ar), 4.22 (d, *J* =

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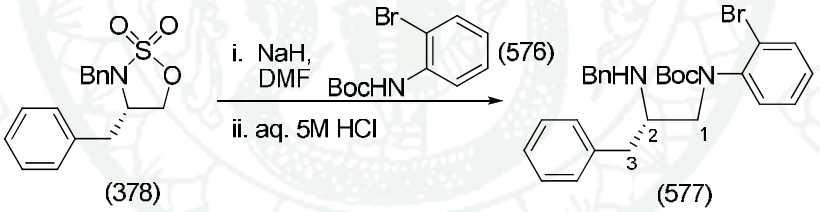
16.0 Hz, 1H, NC<u>H</u>$_2$Ar), 3.90 (dd, *J* = 12.0, 8.0 Hz, 1H, H-2), 3.65 (dd, *J* = 12.0, 4.0 Hz, 1H, H-2), 3.34 (m, 1H, H-3), 2.91 (dd, *J* = 12.0, 4.0 Hz, 1H, C3-C<u>H</u>$_2$Ar), 2.64 (dd, *J* = 12.0, 8.0 Hz, 1H, C3-C<u>H</u>$_2$Ar), 2.44 (s, 3H, ArC<u>H</u>$_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 143.6 (C-Ar), 141.4 (C-Ar), 139.2 (C-Ar), 138.8 (C-Ar), 138.2 (C-Ar), 136.6 (C-Ar), 129.6×2 (CH-Ar), 129.3×2 (CH-Ar), 128.6×2 (CH-Ar), 127.2×2 (CH-Ar), 127.0×2 (CH-Ar), 126.3×2 (CH-Ar), 125.9×2 (CH-Ar), 125.5 (CH-Ar), 122.4 (CH-Ar), 117.8 (CH-Ar), 112.2 (CH-Ar), 72.0 (C-3), 61.7 (N<u>C</u>H$_2$Ar), 48.1 (C-2), 35.8 (C3-<u>C</u>H$_2$Ar), 21.6 (Ar<u>C</u>H$_3$)

HRMS (ESI$^+$) *m/z*: $C_{29}H_{28}N_2O_2SNa$ $[M+Na]^+$, calcd 491.1764, found 491.1770; $C_{29}H_{29}N_2O_2S$ $[M+H]^+$, calcd 469.1944, found 469.1952

***(S)-tert*-butyl 2-(benzylamino)-3-phenylpropyl(2-bromophenyl) carbamate (577)**



To a solution of *N*-(*tert*-butoxycarbonyl)-2-bromoaniline (576) (135 mg, 0.49 mmol) in anhydrous DMF (3.14 mL) was added NaH (60 % dispersion in mineral oil, 20 mg, 0.49 mmol) and the mixture was stirred at room temperature for 15 minutes. Cyclic sulfamidate **378** (100 mg, 0.33 mmol) was added and the mixture was stirred at room temperature for a further 16.5 h prior to the addition of aqueous 5 M HCl (1.0 mL). The mixture was stirred at room temperature for 2 h, then diluted with aqueous 1 M NaOH (30 mL) and extracted with Et_2O (3 × 25 mL). The organic extracts were combined, washed with aqueous 1 M NaOH (3 × 25 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 3:7) to afford the product **577** (130 mg, 80%) as a colorless oil; $[\alpha]_D^{25}$ +4.0 (c = 0.6, CH_2Cl_2).

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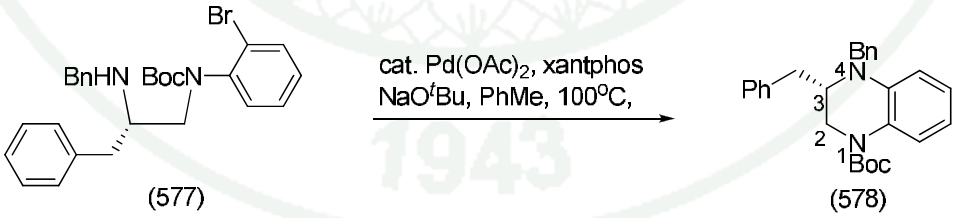
FTIR (neat), ν_{max}, cm^{-1}: 1701, 1477, 1391, 1366

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.58 (dd, *J* = 12.0, 8.0 Hz, 1H, Ar(H)), 7.04-7.26 (m, 13H, Ar(H)), 3.73-3.84 (m, 1H, H-1), 3.68 (d, *J* = 12.0 Hz, 1H, ArC$\underline{H}_2$NH), 3.62 (d, *J* = 12.0 Hz, 1H, ArC$\underline{H}_2$NH), 3.43-3.46 (m, 1H, H-1), 2.87-3.05 (m, 2H, C2-C$\underline{H}_2$Ar, H-2), 2.66 (dd, *J* = 12.0, 8.0 Hz, 1H, C2-C$\underline{H}_2$Ar), 1.66 (brs, 1H, N$\underline{H}$), 1.46 (s, 3H, OC(C$\underline{H}_3$)$_3$), 1.34 (s, 6H, OC(C$\underline{H}_3$)$_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 154.8 (C=O), 143.2 (C-Ar), 136.5 (C-Ar), 136.4 (C-Ar), 136.2 (C-Ar), 133.1 (C-Ar), 129.2×3 (CH-Ar), 129.1 (CH-Ar), 128.4 (CH-Ar), 128.3 (CH-Ar), 128.2×3 (CH-Ar), 128.0×3 (CH-Ar), 126.2 (CH-Ar), 126.1 (CH-Ar), 67.0 (C-2) , 55.3 (C-1), 51.6 (Ar$\underline{C}H_2$NH) 39.2 (C2-$\underline{C}H_2$Ar), 28.3 (OC($\underline{C}H_3$)$_3$), 28.1 (OC($\underline{C}H_3$)$_3$)

HRMS (ESI^+) *m/z*: $C_{27}H_{32}N_2O_2{}^{79}Br$ $[M+H]^+$, calcd 495.1642, found 495.1644; $C_{27}H_{32}N_2O_2{}^{81}Br$ $[M+H]^+$, calcd 497.1621, found 497.1622

***(S)-tert*-butyl 3,4-dibenzyl-3,4-dihydroquinoxaline-1*(2H)*-carboxylate (578)**



$Pd(OAc)_2$ (1.31 mg, 5 mol %), xantphos (3.53 mg, 5 mol %), *t*-BuONa (14.55 mg, 0.15 mmol) and amine **577** (50 mg, 0.10 mmol) were dissolved in anhydrous toluene (1.41 mL), placed in a re-sealable tube and heated at 100 °C for 16 h. The mixture was cooled to room temperature, diluted with EtOAc (20 mL), washed with water (10 mL) and then brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 1:19) to

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afford quinoxaline derivative **578** (39.7 mg, 95%) as a colourless oil; $[\alpha]_D^{25}$ -10.0 (c = 0.3, CH_2Cl_2).

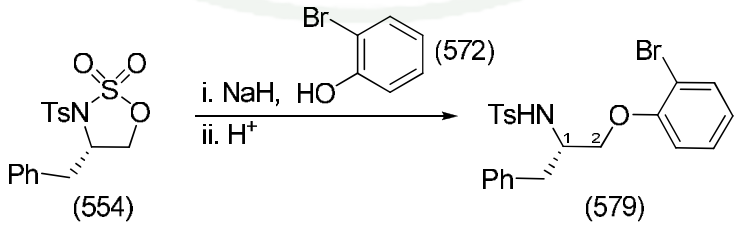
FTIR (neat), ν_{max}, cm^{-1}: 1693, 1507, 1381, 1164, 1144

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.17-7.31 (m, 11H, Ar(H)), 6.88 (ddd, *J* = 8.0, 8.0, 2.0 Hz, 1H, Ar(H)), 6.65 (ddd, *J* = 8.0, 8.0, 1.0 Hz, 1H, Ar(H)), 4.63 (d, *J* = 16.0 Hz, 1H, NC$\underline{H}_2$Ar), 6.54 (d, *J* = 8.0 Hz, 1H, Ar(H)), 4.38 (d, *J* = 16.0 Hz, 2H, H-2, NC$\underline{H}_2$Ar), 3.68-3.69 (m, 1H, H-3), 3.12 (d, *J* = 12.0 Hz, 1H, H-2), 2.92 (dd, *J* = 16.0, 4.0 Hz, 1H, C3-C$\underline{H}_2$Ar), 2.70 (dd, *J* = 16.0, 8.0 Hz, 1H, C3-C$\underline{H}_2$Ar), 1.56 (s, 9H, OC(C$\underline{H}_3$)$_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 154.8 (C=O), 138.3 (C-Ar), 138.2 (C-Ar), 137.0 (C-Ar), 129.4×2 (CH-Ar), 128.7×2 (CH-Ar), 128.5×2 (CH-Ar), 127.0×2 (CH-Ar), 126.4×2 (CH-Ar), 124.8×2 (CH-Ar), 124.5 (C-Ar), 115.7 (CH-Ar), 111.7 (CH-Ar), 81.0 (O$\underline{C}$(CH$_3$)$_3$), 61.0 (C-3), 53.2 (N$\underline{C}$H$_2$Ar), 44.4 (C-2), 38.4 (C3-$\underline{C}$H$_2$Ar), 28.4 (OC($\underline{C}$H$_3$)$_3$)

HRMS (ESI$^+$) *m/z*: $C_{27}H_{30}N_2O_2Na$ $[M+Na]^+$, calcd 437.2199, found 437.2212; $C_{27}H_{31}N_2O_2$ $[M+H]^+$, calcd 415.2380, found 415.2394

Tosyl[(*S*)-1-benzyl-2-(2-bromophenoxy)ethyl]amine (579)



To a solution of 2-bromophenol (572) (94.2 mg, 0.54 mmol) in anhydrous DMF (3.14 mL) was added NaH (60 % dispersion in mineral oil, 21.8 mg, 0.54

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mmol) and the mixture was stirred at room temperature for 15 minutes. Cyclic sulfamidate **554** (100 mg, 0.27 mmol) was added and the mixture was stirred at room temperature for a further 16.5 hours prior to the addition of aqueous 5 M HCl (0.27 mL). The mixture was stirred at room temperature for 2 hours, then diluted with aqueous 1 M NaOH (30 mL) and extracted with Et_2O (3 × 25 mL). The organic extracts were combined, washed with aqueous 1 M NaOH (3 × 25 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 1:3) to afford the product **579** (99.5 mg, 80 %) as a colourless oil; $[\alpha]_D^{25}$ -19.0 (c = 1.0, CH_2Cl_2).

FTIR (neat), ν_{max}, cm^{-1}: 3285, 1482, 1329, 1278, 1249, 1160, 1093, 1031

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.67 (dd, *J* = 8.0, 4.0 Hz, 1H, Ar(H)), 7.66 (d, *J* = 8.0 Hz, 1H, Ar(H)), 7.55 (dd, *J* = 8.0, 2.0 Hz, 1H, Ar(H)), 7.17-7.23 (m, 6H, Ar(H)), 7.06-7.08 (m, 2H, Ar(H)), 6.86 (ddd, *J* = 8.0, 8.0, 2.0 Hz, 1H, Ar(H)), 6.65 (dd, *J* = 8.0, 2.0 Hz, 1H, Ar(H)), 5.02 (brd, *J* = 4.0 Hz, 1H, N<u>H</u>), 3.90 (dd, *J* = 8.0, 4.0 Hz, 1H, H-2), 3.80 (m, 1H, H-1), 3.76 (dd, *J* = 8.0, 4.0 Hz, 1H, H-2), 3.06 (dd, *J* = 16.0, 8.0 Hz, 1H, C1-C<u>H</u>$_2$Ar), 2.94 (dd, *J* = 16.0, 8.0 Hz, 1H, C1-C<u>H</u>$_2$Ar), 2.38 (s, 3H, ArC<u>H</u>$_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 154.3 (C-Ar), 143.3 (C-Ar), 137.4 (C-Ar), 136.6 (C-Ar), 133.3 (CH-Ar), 129.6×2 (CH-Ar), 129.3×2 (CH-Ar), 128.7×2 (CH-Ar), 126.9×2 (CH-Ar), 126.8 (CH-Ar), 122.4 (CH-Ar), 113.2×2 (CH-Ar), 112.2 (C-Ar), 68.5 (C-2), 54.2 (C-1), 38.1 (C1-<u>C</u>H$_2$Ar), 21.4 (Ar<u>C</u>H$_3$)

HRMS (ESI$^+$) *m/z*: $C_{22}H_{22}NO_3S^{79}Br$ $[M+Na]^+$, calcd 482.0396, found 482.0390; $C_{22}H_{22}NO_3S^{81}Br$ $[M+Na]^+$, calcd 484.0376, found 484.0368

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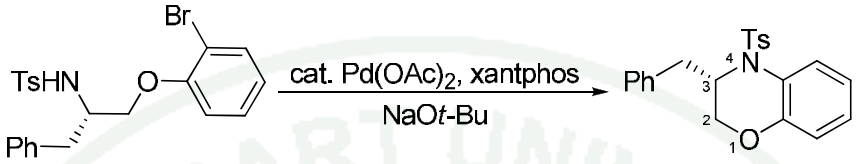
(*S*)-3-Benzyl-4-(toluene-4-sulfonyl)-3,4-dihydro-2*H*-benzo[1,4]oxazine (580)



(579) (580)

$Pd(OAc)_2$ (1.13 mg, 5 mol %), xantphos (3.04 mg, 5 mol %), *t*-BuONa (12.5 mg, 0.13 mmol) and amine **579** (40 mg, 0.09 mmol) were dissolved in anhydrous toluene (1.21 mL), placed in a re-sealable tube and heated at 100 °C for 16 hours. The mixture was cooled to room temperature, diluted with EtOAc (20 mL), washed with water (10 mL) and then brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 1:4) to afford benzoxazine derivative **580** (18.8 mg, 55%) as a colourless oil; $[\alpha]_D^{25}$ +179.0 (c = 1.0, CH_2Cl_2).

FTIR (neat), ν_{max}, cm^{-1}: 1490, 1354, 1245, 1167, 1090

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.88 (dd, *J* = 8.0, 2.0 Hz, 1H, Ar(H)), 7.41 (d, *J* = 8.0 Hz, 2H, Ar(H)), 6.95-7.32 (m, 9H, Ar(H)), 6.87 (dd, *J* = 8.0, 2.0 Hz, 1H, Ar(H)), 4.43 (m, 1H, H-3), 3.84 (dd, *J* = 12.0, 2.0 Hz, 1H, H-2), 3.15 (dd, *J* = 12.0, 4.0 Hz, 1H, H-2), 2.90 (dd, *J* = 16.0, 4.0 Hz, 1H, C3-C$\underline{H}_2$Ar), 2.70 (dd, *J* = 12.0, 8.0 Hz, 1H, C3-C$\underline{H}_2$Ar), 2.36 (s, 3H, ArC$\underline{H}_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 160.7 (C-Ar), 154.3 (C-Ar), 148.4 (C-Ar), 142.4 (C-Ar), 139.9 (C-Ar), 129.8×4 (CH-Ar), 128.6×4 (CH-Ar), 127.2×2 (CH-Ar), 126.8 (CH-Ar), 126.3 (CH-Ar), 121.3 (CH-Ar), 64.2 (C-2), 54.3 (C-3), 36.7 (C3-$\underline{C}H_2$Ar), 21.6 (Ar$\underline{C}H_3$)

HRMS (ESI^+) *m/z*: $C_{22}H_{21}NO_3SNa$ $[M+Na]^+$, calcd 402.1134, found 402.1149

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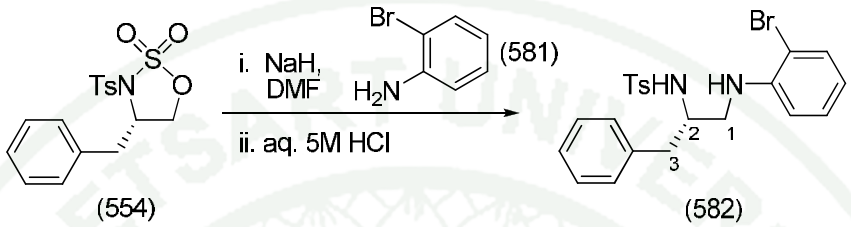
(*S*)-*N*-(1-(2-Bromophenylamino)-3-phenylpropan-2-yl)-4-methyl benzenesulfonamide (582)



To a solution of 2-bromoaniline (581) (93.6 mg, 0.54 mmol) in anhydrous DMF (3.14 mL) was added NaH (60 % dispersion in mineral oil, 10.9 mg, 0.27 mmol) and the mixture was stirred at room temperature for 15 minutes. Cyclic sulfamidate **554** (100 mg, 0.27 mmol) was added and the mixture was stirred at room temperature for a further 16.5 hours prior to the addition of aqueous 5 M HCl (0.27 mL). The mixture was stirred at room temperature for 2 hours, then diluted with aqueous 1 M NaOH (30 mL) and extracted with Et_2O (3 × 25 mL). The organic extracts were combined, washed with aqueous 1 M NaOH (3 × 25 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 1:9) to afford the product **582** (13.6 mg, 11.0 %) as a white solid; m.p. 136-138 °C; $[\alpha]_D^{25}$ -20.0 (c = 0.3, CH_2Cl_2).

FTIR (neat), ν_{max}, cm^{-1}: 3277, 1598, 1513, 1321, 1158, 1090

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.59 (d, *J* = 8.0 Hz, 2H, Ar(H)), 7.38 (dd, *J* = 7.8, 1.4 Hz, 1H, Ar(H)), 7.22-7.24 (m, 4H, Ar(H)), 7.15 (d, *J* = 8.4 Hz, 2H, Ar(H)), 7.09 (ddd, *J* = 7.8, 7.8, 1.6 Hz, 1H, Ar(H)), 7.02-7.05 (m, 2H, Ar(H)), 6.57 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H, Ar(H)), 6.46 (dd, *J* = 8.2, 1.0 Hz, 1H, Ar(H)), 4.53 (brd, *J* = 7.2 Hz, 1H, C2-N<u>H</u>), 4.45 (brt, *J* = 5.8 Hz, 1H, C1-N<u>H</u>), 3.63 (m, 1H, H-2), 3.22 (d, *J* = 6.0 Hz, 1H, H-1), 3.21 (d, *J* = 6.0 Hz, 1H, H-1), 2.88 (dd, *J* = 13.8, 6.2 Hz, 1H, C2-C<u>H</u>$_2$Ar), 2.82 (dd, *J* = 13.8, 6.2 Hz, 1H, C2-C<u>H</u>$_2$Ar), 2.37 (s, 3H, ArC<u>H</u>$_3$)

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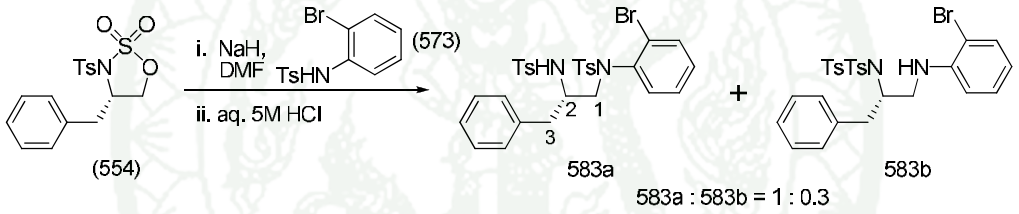
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 144.1 (C-Ar), 143.9 (C-Ar), 143.4 (C-Ar), 132.4 (C-Ar), 129.7×4 (CH-Ar), 129.3×4 (CH-Ar), 128.8 (CH-Ar), 128.4 (CH-Ar), 126.9×2 (CH-Ar), 118.3 (CH-Ar), 111.3 (C-Ar), 53.7 (C-2), 46.8 (C-1), 39.4 (C2-$\underline{C}H_2Ar$), 21.5 (Ar$\underline{C}H_3$)

HRMS (ESI^+) *m/z*: $C_{22}H_{23}N_2O_2S^{79}BrNa$ $[M+Na]^+$, calcd 481.0556, found 481.0572; $C_{22}H_{23}N_2O_2S^{81}BrNa$ $[M+Na]^+$, calcd 483.0535, found 483.0549

(*S*)-*N*-(2-Bromophenyl)-4-methyl-*N*-(2-(4-methylphenylsulfonamido)-3-phenyl propyl)benzenesulfonamide (583a)



To a solution of *N*-tosyl-2-bromoaniline (573) (177.6 mg, 0.54 mmol) in anhydrous DMF (3.14 mL) was added NaH (60 % dispersion in mineral oil, 21.77 mg, 0.54 mmol) and the mixture was stirred at room temperature for 15 minutes. Cyclic sulfamidate **554** (100 mg, 0.27 mmol) was added and the mixture was stirred at room temperature for a further 16.5 hours prior to the addition of aqueous 5 M HCl (1.0 mL). The mixture was stirred at room temperature for 2 hours, then diluted with aqueous 1 M NaOH (30 mL) and extracted with Et_2O (3 × 25 mL). The organic extracts were combined, washed with aqueous 1 M NaOH (3 × 25 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 3:7) to afford the product **583a** and **583b** (1:0.3) (108.4 mg, 73%) as a colourless oil then became a white solid.

FTIR (neat), ν_{max}, cm^{-1}: 1338, 1162, 1090

^{1}H NMR ($CDCl_3$, 400 MHz) δ: (8a:8b, 1:0.3), 7.53-7.58 (m, 2H, Ar(H)), 7.48 (d, *J* = 8.0 Hz, 1H, Ar(H)), 7.45 (d, *J* = 8.0 Hz, 1H, Ar(H)), 7.09-7.26 (m, 14H,

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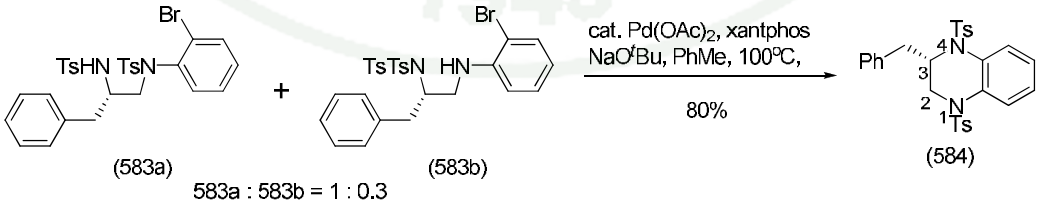
Ar(H)), 6.96-7.06 (m, 9H, Ar(H)), 6.92 (dd, *J* = 8.0, 4.0 Hz, 2H, Ar(H)), 6.86 (dd, *J* = 8.0, 4.0 Hz, 1H, Ar(H)), 6.75 (dd, *J* = 8.0, 8.0 Hz, 2H, Ar(H)), 6.64 (dd, *J* = 8.0, 4.0 Hz, 2H, Ar(H)), 4.83 (d, *J* = 8.0 Hz, 1H, NH), 4.74 (d, *J* = 4.0 Hz, 1H, NH), 3.64 (dd, *J* = 16.0, 4.0 Hz, 1H, ^{b}H-1), 3.64 (dd, *J* = 12.0, 4.0 Hz, 1H, ^{a}H-1), 3.59 (dd, *J* = 12.0, 4.0 Hz, 1H, ^{a}H-1), 3.48-3.51 (m, 1H, ^{b}H-2), 3.40 (dd, *J* = 12.0, 8.0 Hz, 1H, ^{b}H-1), 3.27 (dd, *J* = 16.0, 8.0 Hz, 1H, C2-C^{a}H$_2$Ar), 3.04-3.12 (m, 2H, C2-C^{b}H$_2$Ar, ^{a}H-2), 2.60 (dd, *J* = 16.0, 8.0 Hz, 1H, C2-C^{b}H$_2$Ar), 2.56 (dd, *J* = 16.0, 8.0 Hz, 1H, C2-C^{a}H$_2$Ar), 2.36 (s, 6H, ArC^{a}H$_3$), 2.33 (s, 6H, ArC^{b}H$_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 144.2 (C-Ar), 144.1 (C-Ar), 143.2×2 (C-Ar), 138.2 (C-Ar), 137.7 (C-Ar), 137.0 (C-Ar), 136.2 (C-Ar), 135.6 (C-Ar), 135.1 (C-Ar), 137.7 (C-Ar), 134.3 (C-Ar), 134.1 (C-Ar), 131.5 (C-Ar), 129.9×2 (CH-Ar), 129.7×4 (CH-Ar), 129.6 (CH-Ar), 129.5×4 (CH-Ar), 129.2 (CH-Ar), 128.9×4 (CH-Ar), 128.6×4 (CH-Ar), 128.4 (CH-Ar), 128.2×2 (CH-Ar), 128.1×3 (CH-Ar), 124.1×3 (CH-Ar), 127.0 (CH-Ar), 126.9 (CH-Ar), 126.6×2 (CH-Ar), 125.5 (CH-Ar), 55.7 (^{b}C-1), 55.2 (^{a}C-1), 54.9 (^{b}C-2), 53.0 (^{a}C-2), 38.7 (C2-^{a}CH$_2$Ar), 38.4 (C2-^{b}CH$_2$Ar), 21.6×2 (Ar^{a}CH$_3$), 21.5×2 (Ar^{b}CH$_3$)

HRMS (ESI$^+$) *m/z*: $C_{29}H_{29}N_2O_4S_2{}^{79}BrNa$ $[M+Na]^+$, calcd 635.0644, found 635.0655; $C_{29}H_{29}N_2O_4S_2{}^{81}BrNa$ $[M+Na]^+$, calcd 637.0624, found 637.0634

(*S*)-2-Benzyl-1,4-ditosyl-1,2,3,4-tetrahydroquinoxaline (584)



583a : 583b = 1 : 0.3

$Pd(OAc)_2$ (0.63 mg, 5 mol %), xantphos (1.41 mg, 5 mol %), *t*-BuONa (7.05 mg, 0.073 mmol) and the mixture of amine **583a** and **583b** (30 mg, 0.049 mmol) were dissolved in anhydrous toluene (0.70 mL), placed in a re-sealable tube and heated at 100 °C for 16 hours. The mixture was cooled to room temperature, diluted with

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EtOAc (20 mL), washed with water (10 mL) and then brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 1:4) to afford quinoxaline derivative **584** (20.9 mg, 80%) as a colourless oil; $[\alpha]_D^{25}$ -16.7 (c = 0.3, CH_2Cl_2).

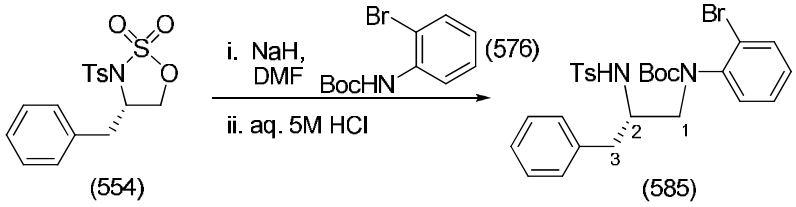
FTIR (neat), ν_{max}, cm^{-1}: 1492, 1353, 1166, 1090

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.66 (dd, *J* = 8.0, 4.0 Hz, 1H, Ar(H)), 7.59 (dd, *J* = 8.0, 2.0 Hz, 1H, Ar(H)), 7.52 (d, *J* = 8.0 Hz, 2H, Ar(H)), 7.21-7.35 (m, 6H, Ar(H)), 7.03-7.14 (m, 7H, Ar(H), 4.62 (m, 1H, H-3), 3.96 (dd, *J* = 12.0, 4.0 Hz, 1H, H-2), 3.26 (dd, *J* = 12.0, 4.0 Hz, 1H, H-2), 2.78 (dd, *J* = 12.0, 8.0 Hz, 1H, C3-C$\underline{H}_2$Ar), 2.70 (dd, *J* = 16.0, 8.0 Hz, 1H, C3-C$\underline{H}_2$Ar), 2.41 (s, 3H, ArC$\underline{H}_3$), 2.39 (s, 3H, ArC$\underline{H}_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 144.2 (C-Ar), 143.8 (C-Ar), 137.0 (C-Ar), 136.7 (C-Ar), 135.7 (C-Ar), 117.6 (C-Ar), 99.9 (C-Ar), 129.8×2 (CH-Ar), 129.7×2 (CH-Ar), 129.4 (CH-Ar), 128.6×2 (CH-Ar), 127.4 (CH-Ar), 127.3×2 (CH-Ar), 127.0×2 (CH-Ar), 126.8×2 (CH-Ar), 126.3×2 (CH-Ar), 119.0 (CH-Ar), 55.2 (C-3), 47.6 (C-2), 38.1 (C3-$\underline{C}H_2$Ar), 21.6×2 (Ar$\underline{C}H_3$)

HRMS (ESI^+) *m/z*: $C_{29}H_{28}N_2O_4S_2Na$ $[M+Na]^+$, calcd 555.1383, found 555.1400

***(S)-tert*-Butyl-2-bromophenyl(2-(4-methylphenylsulfonamido)-3-phenylpropyl) carbamate (585)**



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To a solution of *N*-(*tert*-butoxycarbonyl)-2-bromoaniline (576) (148.1 mg, 0.54 mmol) in anhydrous DMF (3.14 mL) was added NaH (60% dispersion in mineral oil, 21.8 mg, 0.54 mmol) and the mixture was stirred at room temperature for 15 minutes. Cyclic sulfamidate **554** (100 mg, 0.27 mmol) was added and the mixture was stirred at r.t. for a further 16.5 h prior to the addition of aq. 5 M HCl (1.0 mL). The mixture was stirred at room temperature for 2 hours, then diluted with aqueous 1 M NaOH (30 mL) and extracted with Et_2O (3 × 25 mL). The organic extracts were combined, washed with aqueous 1 M NaOH (3 × 25 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 1:4) to afford the product **585** (101.8 mg, 67%) as a colorless oil; $[\alpha]_D^{25}$ +4.5 (c = 1.1, CH_2Cl_2).

FTIR (neat), ν_{max}, cm^{-1}: 3281, 1743, 1280, 1161

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.67 (dd, *J* = 8.0, 8.0 Hz, 1H, Ar(H)), 7.61 (d, *J* = 8.0 Hz, 2H, Ar(H)), 7.10-7.27 (m, 8H, Ar(H)), 6.98-7.02 (m, 2H, Ar(H)), 4.74 (brd, *J* = 4.0 Hz, 1H, N<u>H</u>), 3.99 (dd, *J* = 12.0, 4.0 Hz, 1H, H-1), 3.92 (dd, *J* = 12.0, 4.0 Hz, 1H, H-1), 3.63-3.69 (m, 1H, H-2), 2.82 (dd, *J* = 12.0, 8.0 Hz, 1H, C2-C<u>H</u>$_2$Ar), 2.76 (dd, *J* = 12.0, 8.0 Hz, 1H, C2-C<u>H</u>$_2$Ar), 2.40 (s, 3H, ArC<u>H</u>$_3$), 1.48 (s, 6H, OC(C<u>H</u>$_3$)$_3$), 1.33 (s, 3H, OC(C<u>H</u>$_3$)$_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 153.1 (C=O), 143.3 (C-Ar), 140.6 (C-Ar), 137.2 (C-Ar), 136.2 (C-Ar), 133.0 (C-Ar), 129.2×2 (CH-Ar), 128.7×2 (CH-Ar), 128.4 (CH-Ar), 128.0 (CH-Ar), 127.8 (CH-Ar), 127.2 (CH-Ar), 126.9×4 (CH-Ar), 126.8 (CH-Ar), 82.7 (O<u>C</u>(CH$_3$)$_3$), 67.1 (C-1), 53.8 (C-2), 38.1 (C2-<u>C</u>H$_2$Ar), 28.0 (OC(<u>C</u>H$_3$)$_3$), 27.7 (OC(<u>C</u>H$_3$)$_3$), 21.5 (Ar<u>C</u>H$_3$)

HRMS (ESI^+) *m/z*: $C_{27}H_{31}N_2O_4S^{79}BrNa$ $[M+Na]^+$, calcd 581.1080, found 581.1102; $C_{27}H_{31}N_2O_4S^{81}BrNa$ $[M+Na]^+$, calcd 583.1060, found 583.1082

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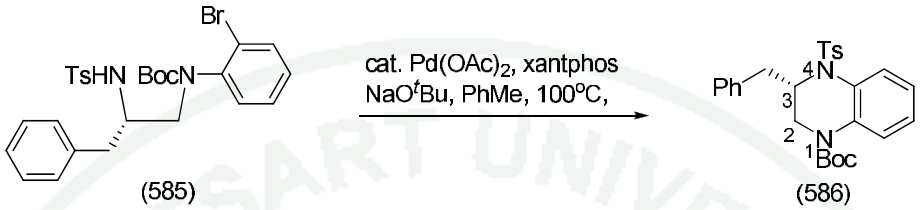
***(S)-tert*-Butyl 3-benzyl-4-tosyl-3,4-dihydroquinoxaline-1(*2H*)-carboxylate (586)**



(585) (586)

$Pd(OAc)_2$ (0.70 mg, 5 mol %), xantphos (1.88 mg, 5 mol %), *t*-BuONa (7.75 mg, 0.081 mmol) and amine **585** (30.0 mg, 0.054 mmol) were dissolved in anhydrous toluene (mL), placed in a re-sealable tube and heated at 100 °C for 16 hours. The mixture was cooled to room temperature, diluted with EtOAc (20 mL), washed with water (10 mL) and then brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 1:4) to afford quinoxaline derivative **586** (20.14 mg, 78%) as a colorless oil; $[\alpha]_D^{25}$ +69.7 (c = 0.3, CH_2Cl_2).

FTIR (neat), ν_{max}, cm^{-1}: 1703, 1495, 1352, 1166

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.72 (dd, *J* = 8.0, 2.0 Hz, 1H, Ar(H)), 7.58 (d, *J* = 8.0 Hz, 1H, Ar(H)), 7.09-7.32 (m, 11H, Ar(H)), 4.53-4.60 (m, 1H, H-3), 3.51 (dd, *J* = 12.0, 4.0 Hz, 1H, H-2), 3.28 (dd, *J* = 12.0, 8.0 Hz, 1H, H-2), 3.06 (dd, *J* = 12.0, 8.0 Hz, 1H, C3-C$\underline{H}_2$Ar), 2.74 (dd, *J* = 12.0, 8.0 Hz, 1H, C3-C$\underline{H}_2$Ar), 2.33 (s, 3H, ArC$\underline{H}_3$), 1.34 (s, 9H, OC(C$\underline{H}_3$)$_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 153.5 (C=O), 147.3 (C-Ar), 144.6 (C-Ar), 143.3 (C-Ar), 142.8 (C-Ar), 136.9 (C-Ar), 132.2 (CH-Ar), 130.6 (CH-Ar), 129.6 (CH-Ar), 129.4×2 (CH-Ar), 128.6×2 (CH-Ar), 127.2×2 (CH-Ar), 127.0 (CH-Ar), 126.8 (CH-Ar), 126.0 (CH-Ar), 122.9 (CH-Ar), 81.3 (O$\underline{C}$(CH$_3$)$_3$), 57.8 (C-3), 46.8 (C-2), 40.2 (C3-$\underline{C}$H$_2$Ar), 28.1 (OC($\underline{C}$H$_3$)$_3$), 21.5 (Ar$\underline{C}$H$_3$)

HRMS (ESI^+) *m/z*: $C_{27}H_{30}N_2O_4SNa$ $[M+Na]^+$, calcd 501.1818, found 501.1823

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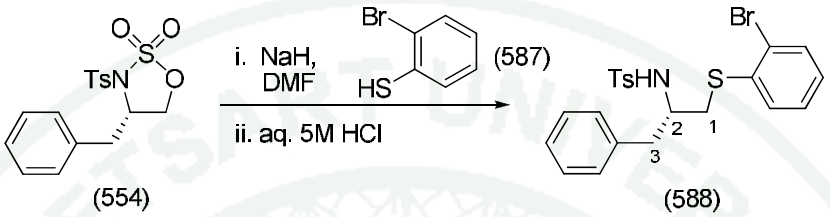
(*S*)-*N*-(1-(2-Bromophenylthio)-3-phenylpropan-2-yl)-4-methyl benzenesulfonamide (588)



To a solution of 2-bromothiophenol (587) (102.9 mg, 0.54 mmol) in anhydrous DMF (3.14 mL) was added NaH (60 % dispersion in mineral oil, 21.8 mg, 0.54 mmol) and the mixture was stirred at room temperature for 15 minutes. Cyclic sulfamidate **554** (100 mg, 0.27 mmol) was added and the mixture was stirred at room temperature for a further 16.5 hours prior to the addition of aqueous 5 M HCl (0.27 mL). The mixture was stirred at room temperature for 2 hours, then diluted with aqueous 1 M NaOH (30 mL) and extracted with Et_2O (3 × 25 mL). The organic extracts were combined, washed with aqueous 1 M NaOH (3 × 25 mL), dried (Na_2SO_4) and concentrated *in vacuo.* The residue was purified by flash column chromatography (EtOAc/hexane, 1:4) to afford the product **588** (90.0 mg, 70%) as a white solid; m.p. 119-121 °C; $[\alpha]_D^{25}$ -10.0 (c = 0.3, CH_2Cl_2).

FTIR (neat), ν_{max}, cm^{-1}: 3272, 1450, 1427, 1328, 1157, 1085

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.53 (dd, *J* = 8.0, 2.0 Hz, 1H, Ar(H)), 7.47 (d, *J* = 8.0 Hz, 2H, Ar(H)), 7.18-7.21 (m, 4H, Ar(H)), 7.14 (dd, *J* = 8.0, 4.0 Hz, 1H, Ar(H)), 7.09 (d, *J* = 8.0 Hz, 2H, Ar(H)), 7.04 (ddd, *J* = 8.0, 8.0, 4.0 Hz, 1H, Ar(H)), 7.00-7.02 (m, 2H, Ar(H)), 3.54 (m, 1H, H-2), 3.14 (dd, *J* = 14.0, 6.0 Hz, 1H, C2-C$\underline{H}_2$Ar), 3.00 (dd, *J* = 16.0, 8.0 Hz, 1H, H-1), 2.89 (dd, *J* = 16.0, 8.0 Hz, 1H, H-1), 2.86 (dd, *J* = 14.0, 6.0 Hz, 1H, C2-C$\underline{H}_2$Ar), 2.36 (s, 3H, ArC$\underline{H}_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 143.2 (C-Ar), 136.5 (C-Ar), 136.4 (C-Ar), 136.2 (C-Ar), 133.1 (C-Ar), 129.6×2 (CH-Ar), 129.3×2 (CH-Ar), 128.9 (CH-Ar),

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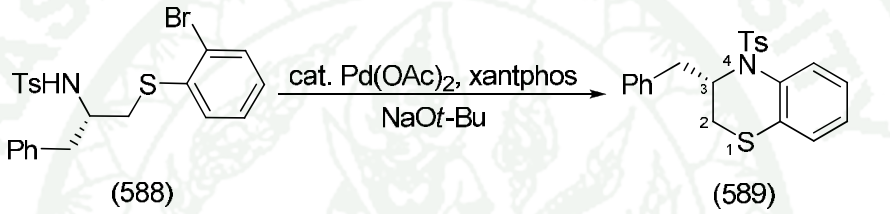
128.7×2 (CH-Ar), 127.9×2 (CH-Ar), 127.1×2 (CH-Ar), 126.9×2 (CH-Ar), 53.6 (C-2), 39.8 (C-1), 37.3 (C2-$\underline{C}H_2Ar$), 21.5 (Ar$\underline{C}H_3$)

HRMS (ESI^+) *m/z*: $C_{22}H_{22}NO_2S_2{}^{79}BrNa$ $[M+Na]^+$, calcd 498.0168, found 498.0174; $C_{22}H_{22}NO_2S_2{}^{81}BrNa$ $[M+Na]^+$, calcd 500.0147, found 500.0153

(*S*)-3-Benzyl-4-tosyl-3,4-dihydro-2H-benzo[*b*][1,4]thiazine (589)



$Pd(OAc)_2$ (1.36 mg, 5 mol %), xantphos (3.03 mg, 5 mol %), *t*-BuONa (15.13 mg, 0.16 mmol) and amine **588** (50 mg, 0.10 mmol) were dissolved in anhydrous toluene (1.47 mL), placed in a re-sealable tube and heated at 100 °C for 24 hours. The mixture was cooled to room temperature, diluted with EtOAc (20 mL), washed with water (10 mL) and then brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 1:4) to afford benzothiazine derivative **589** (31.9 mg, 77%) as a white solid; m.p. 93-95 °C; $[\alpha]_D^{25}$ +53.3 (c = 0.3, CH_2Cl_2).

FTIR (neat), ν_{max}, cm^{-1}: 1473, 1348, 1163, 1092

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.26 (d, *J* = 8.0 Hz, 2H, Ar(H)), 7.13-7.22 (m, 4H, Ar(H)), 7.02-7.09 (m, 7H, Ar(H)), 4.70-4.76 (m, 1H, H-3), 2.82 (dd, *J* = 12.0, 8.0 Hz, 1H, C3-C$\underline{H}_2$Ar), 2.81 (dd, *J* = 12.0, 4.0 Hz, 1H, H-2), 2.64 (dd, *J* = 12.0, 8.0 Hz, 1H, C3-C$\underline{H}_2$Ar), 2.48 (dd, *J* = 12.0, 4.0 Hz, 1H, H-2), 2.30 (s, 3H, ArC$\underline{H}_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 143.7 (C-Ar), 137.3 (C-Ar), 136.6 (C-Ar), 131.4 (C-Ar), 128.5 (C-Ar), 129.7 (CH-Ar), 129.6×2 (CH-Ar), 129.3×2 (CH-Ar),

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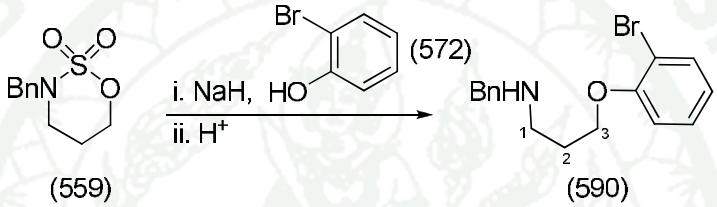
128.6×2 (CH-Ar), 127.2×2 (CH-Ar), 126.8 (CH-Ar), 126.7 (CH-Ar), 126.3 (CH-Ar), 124.8 (CH-Ar), 53.8 (C-3), 38.8 (C3-$\underline{C}H_2$Ar), 28.3 (C-2), 21.6 (Ar$\underline{C}H_3$)

HRMS (ESI^+) *m/z*: $C_{22}H_{21}NO_2S_2Na$ $[M+Na]^+$, calcd 418.0906, found 418.0917

Benzyl[3-(2-bromophenoxy)propyl]amine (590)



To a solution of 2-bromophenol (572) (152.4 mg, 0.88 mmol) in anhydrous DMF (5.1 mL) was added NaH (60% dispersion in mineral oil, 35.2 mg, 0.88 mmol) and the mixture was stirred at room temperature for 15 minutes. Cyclic sulfamidate **559** (100 mg, 0.44 mmol) was added and the mixture was stirred at room temperature for a further 16.5 hours prior to the addition of aqueous 5 M HCl (0.44 mL). The mixture was stirred at room temperature for 2 hours, then diluted with aqueous 1 M NaOH (30 mL) and extracted with Et_2O (3 × 25 mL). The organic extracts were combined, washed with aqueous 1 M NaOH (3 × 25 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/MeOH, 1:1 – MeOH 100%) to afford the product **590** (52.4 mg, 37%) as a white solid; m.p. 96-98 °C.

FTIR (neat), ν_{max}, cm^{-1}: 1482, 1466, 1440, 1276, 1248, 1049, 1029, 747

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.53 (dd, *J* = 8.0, 4.0 Hz, 1H, Ar(H)), 7.23-7.37 (m, 6H, Ar(H)), 6.90 (dd, *J* = 8.0, 4.0 Hz, 1H, Ar(H)), 6.84 (ddd, *J* = 12.0, 8.0, 4.0 Hz, 1H, Ar(H)), 4.13 (t, *J* = 8.0 Hz, 2H, H-3), 3.86 (s, 2H, NC$\underline{H}_2$Ar), 2.92 (t, *J* = 8.0 Hz, 2H, H-1), 2.27 (brs, 1H, N$\underline{H}$), 2.08 (quin, d, *J* = 8.0 Hz, 2H, H-2)

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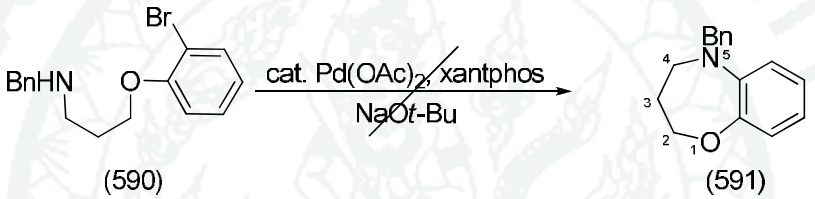
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 155.0 (C-Ar), 140.2 (C-Ar), 138.5 (C-Ar), 128.4×2 (CH-Ar), 128.2×2 (CH-Ar), 127.0×2 (CH-Ar), 121.8×2 (CH-Ar), 113.1 (CH-Ar), 99.9 (C-Ar), 67.7 (C-3), 53.9 (N<u>C</u>H_2Ar), 46.5 (C-1), 29.2 (C-2)

HRMS (ESI$^+$) *m/z*: $C_{16}H_{18}NO^{79}Br$ $[M+H]^+$, calcd 320.0644, found 320.0655; $C_{16}H_{18}NO^{81}Br$ $[M+H]^+$, calcd 322.0624, found 322.0634

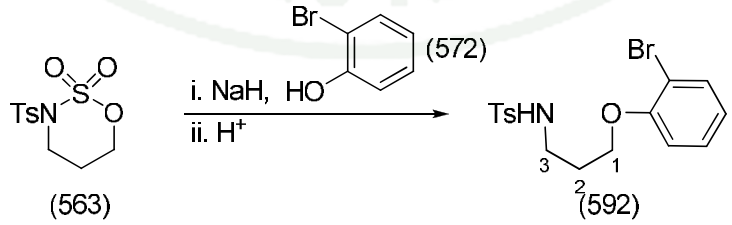
5-Benzyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepine (591)



(590) (591)

$Pd(OAc)_2$ (1.22 mg, 5 mol%), xantphos (3.28 mg, 5 mol%), *t*-BuONa (13.5 mg, 0.14 mmol) and amine **590** (30 mg, 0.09 mmol) were dissolved in anhydrous toluene (1.3 mL), placed in a re-sealable tube and heated at 100 °C for 16 hours. The mixture was cooled to room temperature, diluted with EtOAc (20 mL), washed with water (10 mL) and then brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The product (591) was not observed, only recovered starting material was observed.

***N*-(3-(2-Bromophenoxy)propyl)-4-methylbenzenesulfonamide (592)**



(563) (592)

To a solution of 2-bromophenol (572) (118.8 mg, 0.69 mmol) in anhydrous DMF (3.14 mL) was added NaH (60 % dispersion in mineral oil, 27.5 mg, 0.69 mmol) and the mixture was stirred at room temperature for 15 minutes. Cyclic

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sulfamidate **563** (100 mg, 0.34 mmol) was added and the mixture was stirred at room temperature for a further 16.5 hours prior to the addition of aqueous 5 M HCl (1.0 mL). The mixture was stirred at room temperature for 2 hours, then diluted with aqueous 1 M NaOH (30 mL) and extracted with Et_2O (3 × 25 mL). The organic extracts were combined, washed with aqueous 1 M NaOH (3 × 25 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 3:7) to afford the product **592** (109.1 mg, 83 %) as a white solid; m.p. 116-118 °C.

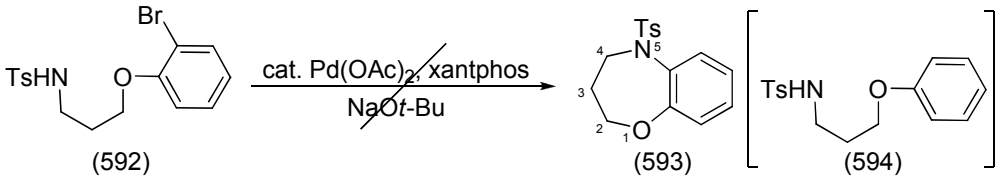
FTIR (neat), ν_{max}, cm^{-1}: 3309, 1328, 1160

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.76 (d, *J* = 8.0 Hz, 2H, Ar(H)), 7.53 (dd, *J* = 8.0, 2.0 Hz, 1H, Ar(H)), 7.25 (d, *J* = 8.0 Hz, 2H, Ar(H)), 7.24 (ddd, *J* = 8.0, 8.0, 2.0 Hz, 1H, Ar(H)), 6.85 (ddd, *J* = 8.0, 8.0, 2.0 Hz, 1H, Ar(H)), 6.80 (dd, *J* = 8.0, 2.0 Hz, 1H, Ar(H)), 5.45 (brt, *J* = 4.0 Hz, 1H, NH), 4.02 (dd, *J* = 4.0, 4.0 Hz, 2H, H-1), 3.24 (dd, *J* = 12.0, 4.0 Hz, 2H, H-3), 2.39 (s, 3H, ArCH_3), 2.00 (quin, *J* = 4.0 Hz, 2H, H-2)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 154.6 (C-Ar), 143.2 (C-Ar), 137.0 (C-Ar), 133.2 (CH-Ar), 129.6×2 (CH-Ar), 128.5 (CH-Ar), 127.1×2 (CH-Ar), 122.3 (CH-Ar), 112.6 (CH-Ar), 111.9 (C-Ar), 67.7 (C-1), 41.6 (C-3), 28.6 (C-2), 21.5 (Ar$\underline{C}H_3$)

HRMS (ESI^+) *m/z*: $C_{16}H_{18}NO_3S^{79}BrNa$ $[M+Na]^+$, calcd 406.0083, found 406.0098; $C_{16}H_{18}NO_3S^{81}BrNa$ $[M+Na]^+$, calcd 408.0062, found 408.0076

5-Tosyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepine (593)



(592) (593) (594)

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$Pd(OAc)_2$ (1.7 mg, 5 mol %), xantphos (4.6 mg, 5 mol %), *t*-BuONa (18.8 mg, 0.19 mmol) and amine **592** (50.0 mg, 0.13 mmol) were dissolved in anhydrous toluene (1.82 mL), placed in a re-sealable tube and heated at 100 °C for 16 hours. The mixture was cooled to room temperature, diluted with EtOAc (20 mL), washed with water (10 mL) and then brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The product **593** was not observed, only debrominated product **594** was observed as a colorless oil (39.8 mg, 100%).

Compound 594

FTIR (neat), ν_{max}, cm^{-1}: 3283, 1599, 1496, 1326, 1160

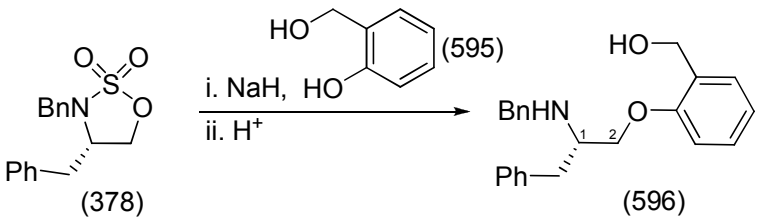
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.73 (d, *J* = 8.0 Hz, 2H, Ar(H)), 7.21-7.46 (m, 4H, Ar(H)), 6.96 (ddd, *J* = 8.0, 8.0, 2.0 Hz, 1H, Ar(H)), 6.82 (d, *J* = 8.0 Hz, 2H, Ar(H)), 4.77 (brt, *J* = 4.0 Hz, 1H, N<u>H</u>), 3.96 (dd, *J* = 12.0, 8.0 Hz, 2H, H-1), 3.18 (dd, *J* = 12.0, 4.0 Hz, 2H, H-3), 2.40 (s, 3H, ArC<u>H</u>$_3$), 1.95 (quin, *J* = 4.0 Hz, 2H, H-2)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 158.4 (C-Ar), 129.7×3 (CH-Ar), 129.5 (CH-Ar), 128.2 (C-Ar), 127.1×2 (CH-Ar), 127.0 (C-Ar), 121.1 (CH-Ar), 114.4×2 (CH-Ar), 65.6 (C-1), 41.1 (C-3), 29.0 (C-2), 21.5 (Ar<u>C</u>H$_3$)

MS (CI^+), *m/z* (relative intensity): 306 ($[M+H]^+$, 45%), 212 (100)

HRMS (CI^+) *m/z*: $C_{16}H_{20}NO_3S$ $[M+H]^+$, calcd 306.1164, found 306.1156

Benzyl[(*S*)-1-benzyl-2-(2-methylalcoholphenoxy)ethyl]amine (596)



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To a solution of 2-hydroxy benzyl alcohol (595) (81.8 mg, 0.66 mmol) in anhydrous DMF (3.8 mL) was added NaH (60% dispersion in mineral oil, 26.4 mg, 0.66 mmol) and the mixture was stirred at room temperature for 15 minutes. Cyclic sulfamidate **378** (100 mg, 0.33 mmol) was added and the mixture was stirred at room temperature for a further 16.5 h prior to the addition of aqueous 5 M HCl (0.33 mL). The mixture was stirred at room temperature for 2 h, then diluted with aqueous 1 M NaOH (30 mL) and extracted with Et_2O (3 × 25 mL). The organic extracts were combined, washed with aqueous 1 M NaOH (3 × 25 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 1:1) to afford the product **596** (113.1 mg, 99 %) as a colourless oil; $[\alpha]_D^{25}$ +3.0 (c = 1.0, CH_2Cl_2).

FTIR (neat), ν_{max}, cm^{-1}: 1491, 1452, 1236

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.18-7.34 (m, 12H, Ar(H)), 6.96 (td, *J* = 8.0, 4.0 Hz, 1H, Ar(H)), 6.83 (d, *J* = 8.0 Hz, 1H, Ar(H)), 4.87 (d, *J* = 16.0 Hz, 1H, ArC$\underline{H}_2$OH), 4.58 (d, *J* = 12.0 Hz, 1H, ArC$\underline{H}_2$OH), 4.04 (dd, *J* = 8.0, 4.0 Hz, 1H, H-2), 3.98 (dd, *J* = 8.0, 4.0 Hz, 1H, H-2), 3.88 (d, *J* = 12.0 Hz, 1H, NC$\underline{H}_2$Ar), 3.78 (d, *J* = 12.0 Hz, 1H, NC$\underline{H}_2$Ar), 3.20 (m, 1H, H-1), 2.96 (dd, *J* = 8.0, 4.0 Hz, 2H, C1-C$\underline{H}_2$Ar)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 139.4 (C-Ar), 138.1 (C-Ar), 130.6 (C-Ar), 129.2×2 (CH-Ar), 129.1 (CH-Ar), 128.9 (CH-Ar), 128.6×2 (CH-Ar), 128.5×2 (CH-Ar), 128.1×2 (CH-Ar), 127.1×2 (CH-Ar), 126.6 (CH-Ar), 121.1 (CH-Ar), 112.6 (C-Ar), 69.0 (C-2), 62.1 (Ar$\underline{C}H_2$OH), 57.8 (C-1), 51.2 (N$\underline{C}H_2$Ar), 38.0 (C1-$\underline{C}H_2$Ar)

HRMS (ESI^+) *m/z*: $C_{23}H_{25}NO_2Na$ $[M+Na]^+$, calcd 370.1778, found 370.1787; $C_{23}H_{25}NO_2$ $[M+H]^+$, calcd 348.1958, found 348.1969

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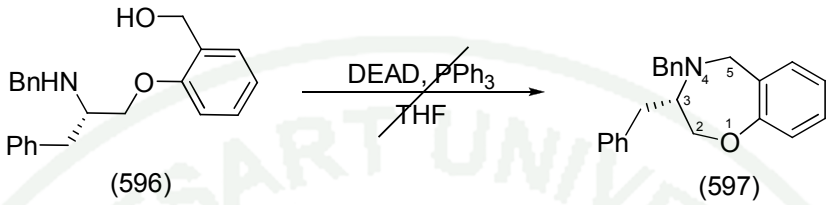
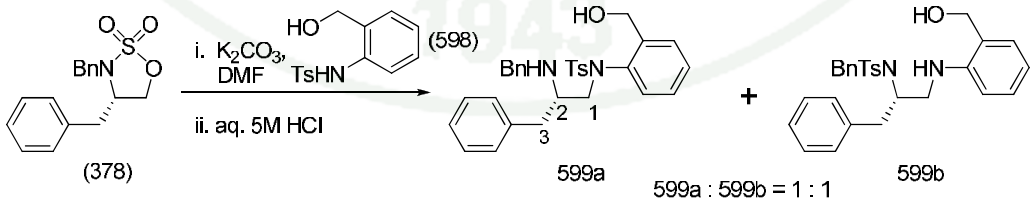
(*S*)-3-Benzyl-4-benzyl-2,3,4,5-tetrahydro-benzo[*f*][1,4]oxazepine (597)



To a stirred solution of amine **596** (30.0 mg, 0.09 mmol) and triphenylphosphine (22.6 mg, 0.09 mmol) in anhydrous THF (2.0 mL) under atmosphere of nitrogen was added DEAD (0.014 mL, 0.09 mmol, in THF (2.0 mL)) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 1 additional hour. It was then allowed to warm to room temperature and was stirred for an additional 14 hour. The reaction mixture was stirred with a 1:1 mixture of hexane:diethylether, and the triphenylphosphine oxide that precipitated was filtered off. The organic solvent was removed in vacuum, the mixture was diluted with 30 mL of water, then extracted with EtOAc (3 x 50 mL), and dried over anhydrous Na_2SO_4. Concentration under reduced pressure and column chromatography of the crude product over silica gel furnished only starting material.

(*S*)-*N*-(2-(benzylamino)-3-phenylpropyl)-*N*-(2-(hydroxymethyl) phenyl)-4-methylbenzenesulfonamide (599a)



To a solution of *N*-tosyl-2-hydroxymethylaniline (598) (182.8 mg, 0.66 mmol) in anhydrous DMF (3.14 mL) was added K_2CO_3 (91.1 mg, 0.66 mmol) and the mixture was stirred at room temperature for 15 minutes. Cyclic sulfamidate **378** (100 mg, 0.33 mmol) was added and the mixture was stirred at room temperature for a further 24 hours prior to the addition of aqueous 5 M HCl (1.0 mL). The mixture was

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stirred at room temperature for 2 hours, then diluted with aqueous 1 M NaOH (30 mL) and extracted with Et_2O (3 × 25 mL). The organic extracts were combined, washed with aqueous 1 M NaOH (3 × 25 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 1:1) to afford the product **599a** and **599b** (1:1) (147.0 mg, 89%) as a white solid.

FTIR (neat), ν_{max}, cm^{-1}: 3063, 3028, 1598, 1494, 1453, 1346, 1163

^{1}H NMR ($CDCl_3$, 400 MHz) δ: (8a:8b, 1:0.7) 7.60 (ddd, *J* = 8.0, 8.0, 2.0 Hz, 2H, Ar(H)), 7.52 (d, *J* = 8.0 Hz, 2H, Ar(H)), 7.23-7.42 (m, 21H, Ar(H)), 7.19 (ddd, *J* = 8.0, 8.0, 4.0 Hz, 1H, Ar(H)), 7.15 (ddd, *J* = 8.0, 8.0, 2.0 Hz, 1H, Ar(H)), 6.99-7.10 (m, 7H, Ar(H)), 6.46 (dd, *J* = 8.0, 2.0 Hz, 1H, Ar(H)), 6.41 (dd, *J* = 8.0, 2.0 Hz, 1H, Ar(H)), 5.32 (d, *J* = 12.0 Hz, 1H, ArC^b$\underline{H_2}$OH), 5.18 (d, *J* = 12.0 Hz, 1H, ArC^b$\underline{H_2}$OH), 4.66 (d, *J* = 12.0 Hz, 1H, ArC^a$\underline{H_2}$OH), 4.54 (d, *J* = 12.0 Hz, 1H, ArC^a$\underline{H_2}$OH), 4.05 (dd, *J* = 16.0, 8.0 Hz, 1H, ^{a}H-1), 3.88 (m, 1H, ^{b}H-1), 3.80 (d, *J* = 12.0 Hz, 1H, TsN^{b}C$\underline{H_2}$Ar), 3.66 (d, *J* = 12.0 Hz, 1H, TsNC^b$\underline{H_2}$Ar), 3.64 (d, *J* = 12.0 Hz, 1H, HN^{a}C$\underline{H_2}$Ar), 3.52 (d, *J* = 12.0 Hz, 1H, HNC^a$\underline{H_2}$Ar), 3.30 (dd, *J* = 12.0, 4.0 Hz, 1H, ^{a}H-1), 3.14 (m, 2H, ^{b}H-1 and ^{b}H-2), 2.94 (m, 2H, C2-C^b$\underline{H_2}$Ar and ^{a}H-2), 2.81 (dd, *J* = 12.0, 4.0 Hz, 1H, C2-C^b$\underline{H_2}$Ar), 2.71 (dd, *J* = 12.0, 4.0 Hz, 1H, C2-C^a$\underline{H_2}$Ar), 2.67 (dd, *J* = 12.0, 4.0 Hz, 1H, C2-C^a$\underline{H_2}$Ar), 2.49 (s, 3H, ArC^a$\underline{H_3}$), 2.47 (s, 3H, ArC^b$\underline{H_3}$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 144.0 (C-Ar), 143.9 (C-Ar), 143.4 (C-Ar), 142.9 (C-Ar), 139.8 (C-Ar), 138.9 (C-Ar), 138.7 (C-Ar), 138.4 (C-Ar), 138.0 (C-Ar), 137.6 (C-Ar), 133.9 (C-Ar), 133.6 (C-Ar), 129.4×4 (CH-Ar), 129.1×2 (CH-Ar), 129.0×2 (CH-Ar), 128.9×2 (CH-Ar), 128.6×4 (CH-Ar), 128.4×6 (CH-Ar), 128.2×4 (CH-Ar), 127.2×2 (CH-Ar), 127.1×2 (CH-Ar), 126.7×2 (CH-Ar), 126.6×2 (CH-Ar), 126.5×2 (CH-Ar), 126.2×2 (CH-Ar), 61.8×2 (Ar^{a,b}$\underline{C}$H$_2$OH), 57.2 (^{b}C-2), 56.4 (^{a}C-2), 54.8 (^{b}C-1), 53.5 (^{a}C-1), 50.5 (TsN^b$\underline{C}$H$_2$Ar), 48.6 (HN^a$\underline{C}$H$_2$Ar), 38.8 (C2-^{a}$\underline{C}$H$_2$Ar), 38.2 (C2-^{b}$\underline{C}$H$_2$Ar), 21.6×2 (Ar^{a,b}$\underline{C}$H$_3$)

HRMS (ESI$^+$) *m/z*: $C_{30}H_{32}N_2O_3SNa$ $[M+Na]^+$, calcd 523.2026, found 523.2022

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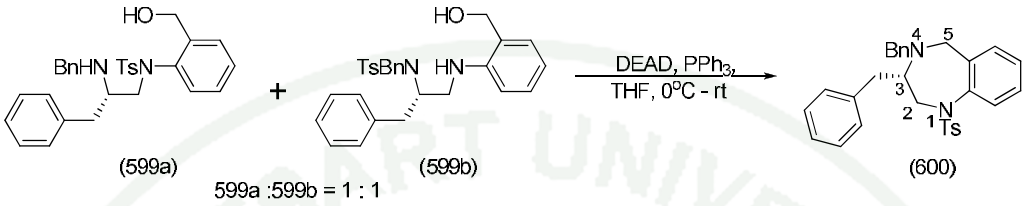
(*S*)-3,4-Dibenzyl-1-tosyl-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4] diazepine (600)



To a stirred solution of the mixture of amine **599a** and **599b** (90.0 mg, 0.18 mmol) and triphenylphosphine (47.16 mg, 0.18 mmol) in anhydrous THF (2.5 mL) under atmosphere of nitrogen was added DEAD (0.028 mL, 0.18 mmol, in THF (2.5 mL)) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 1 additional hour. It was then allowed to warm to room temperature and was stirred for an additional 14 hours. The reaction mixture was stirred with a 1:1 mixture of hexane:diethylether, and the triphenylphosphine oxide that precipitated was filtered off. The organic solvent was removed in vacuum, the mixture was diluted with 30 mL of water, then extracted with EtOAc (3 x 50 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 1:4) to afford the benzodiazepine derivative **600** (30.8 mg, 71%) as a colorless oil; $[\alpha]_D^{25}$ -38.0 (c = 1.0, CH_2Cl_2).

FTIR (neat), ν_{max}, cm^{-1}: 1494, 1453, 1347, 1163, 1092

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.34-7.46 (m, 5H, Ar(H)), 7.29 (ddd, *J* = 8.0, 8.0, 2.0 Hz, 2H, Ar(H)), 7.16-7.21 (m, 8H, Ar(H)), 6.93-6.95 (m, 2H, Ar(H)), 6.81 (d, *J* = 4.0 Hz, 1H, Ar(H)), 4.07 (brm, 2H, NC$\underline{H}_2$Ar), 3.55 (d, *J* = 16.0 Hz, 2H, H-5), 3.34 (d, *J* = 16.0 Hz, 2H, H-2), 3.04 (d, *J* = 12.0 Hz, 1H, H-3), 2.95 (dd, *J* = 12.0, 8.0 Hz, 1H, C3-C$\underline{H}_2$Ar), 2.74 (dd, *J* = 12.0, 8.0 Hz, 1H, C3-C$\underline{H}_2$Ar), 2.40 (s, 3H, ArC$\underline{H}_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 143.3 (C-Ar), 138.6×2 (C-Ar), 138.5 (C-Ar), 131.3 (C-Ar), 129.6×2 (CH-Ar), 129.3×2 (CH-Ar), 129.0 (C-Ar), 128.6×2 (CH-Ar), 128.4×2 (CH-Ar), 128.1×2 (CH-Ar), 128.0×2 (CH-Ar), 127.3×2 (CH-Ar), 127.1×2

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(CH-Ar), 126.9 (CH-Ar), 126.4 (CH-Ar), 64.2 (C-3), 48.7×2 (C-5, N<u>C</u>H_2Ar), 38.5×2 (C-2, C3-<u>C</u>H_2Ar), 21.6 (Ar<u>C</u>H_3)

HRMS (ESI^+) *m/z*: $C_{30}H_{30}N_2O_2SNa$ $[M+Na]^+$, calcd 505.1920, found 505.1939; $C_{30}H_{31}N_2O_2S$ $[M+H]^+$, calcd 483.2101, found 483.2111

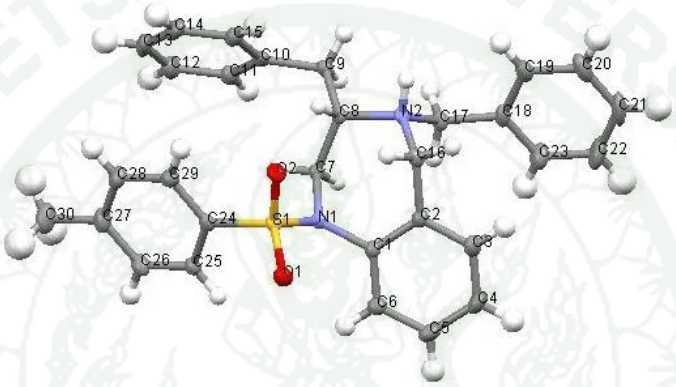
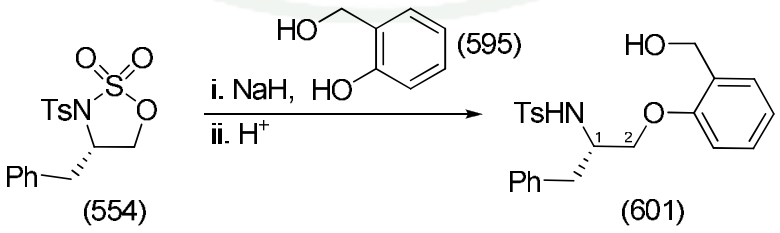


Figure 10 The X-ray crystal structure of (*S*)-3,4-Dibenzyl-1-tosyl-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4] diazepine (600): Crystal data for **600**; $C_{30}H_{31}ClN_2O_2S$, MW = 519.08, lath, space group $P2_12_12_1$, a = 10.671(5), b = 15.104(6), c = 16.813(7) Å, V = 2710(2) $Å^3$, α = 90.00, β = 90.00, γ = 90.00 °, Z = 4, D_c = 1.276 g cm^{-1}, Mo-Kα radiation, λ = 0.71073 Å, μ = 0.248 mm^{-1}, T = 100 K; orthorhombic.

Tosyl[(*S*)-1-benzyl-2-(2-methylalcoholphenoxy)ethyl]amine (601)



To a solution of 2-hydroxy benzyl alcohol (595) (67.6 mg, 0.54 mmol) in anhydrous DMF (3.14 mL) was added NaH (60% dispersion in mineral oil, 21.8 mg,

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0.54 mmol) and the mixture was stirred at room temperature for 15 minutes. Cyclic sulfamidate **554** (100 mg, 0.27 mmol) was added and the mixture was stirred at room temperature for a further 16.5 hours prior to the addition of aqueous 5 M HCl (0.27 mL). The mixture was stirred at room temperature for 12 hours, then diluted with aqueous 1 M NaOH (30 mL) and extracted with Et_2O (3 × 25 mL). The organic extracts were combined, washed with aqueous 1 M NaOH (3 × 25 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 3:7) to afford the product **601** (72.0 mg, 64%) as a white solid; m.p. 97-99 °C; $[\alpha]_D^{24}$ -18.2 (c = 0.3, CH_2Cl_2).

FTIR (neat), ν_{max}, cm^{-1}: 3490, 3272, 1495, 1455, 1322, 1241, 1157, 1092

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.64 (d, *J* = 12.0 Hz, 2H, Ar(H)), 7.29 (dd, *J* = 8.0, 4.0 Hz, 1H, Ar(H)), 7.18-7.24 (m, 4H, Ar(H)), 7.16 (d, *J* = 8.0 Hz, 2H, Ar(H)), 7.05-7.08 (m, 2H, Ar(H)), 6.96 (ddd, *J* = 8.0, 8.0, 2.0 Hz, 1H, Ar(H)), 6.65 (d, *J* = 8.0 Hz, 1H, Ar(H)), 5.82 (brd, *J* = 8.0 Hz, 1H, N<u>H</u>), 4.80 (d, *J* = 16.0 Hz, 1H, ArC<u>H</u>$_2$OH), 4.64 (d, *J* = 12.0 Hz, 1H, ArC<u>H</u>$_2$OH), 3.91 (m, 1H, H-2), 3.81 (m, 2H, H-1 and H-2), 2.94 (dd, *J* = 12.0, 8.0 Hz, 1H, C1-C<u>H</u>$_2$Ar), 2.88 (dd, *J* = 16.0, 8.0 Hz, 1H, C1-C<u>H</u>$_2$Ar), 2.38 (s, 3H, ArC<u>H</u>$_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 156.7 (C-Ar), 143.2 (C-Ar), 137.7 (C-Ar), 136.8 (C-Ar), 129.6 (CH-Ar), 129.3×2 (CH-Ar), 129.2 (CH-Ar), 129.1×2 (CH-Ar), 128.7×2 (CH-Ar), 126.8×2 (CH-Ar), 126.7×2 (CH-Ar), 121.2 (CH-Ar), 112.0 (C-Ar), 68.5 (C-2), 61.7 (Ar<u>C</u>H$_2$OH), 54.6 (C-1), 38.4 (C1-<u>C</u>H$_2$Ar), 21.5 (Ar<u>C</u>H$_3$)

HRMS (ESI^+) *m/z*: $C_{23}H_{25}NO_4SNa$ $[M+Na]^+$, calcd 434.1396, found 434.1390

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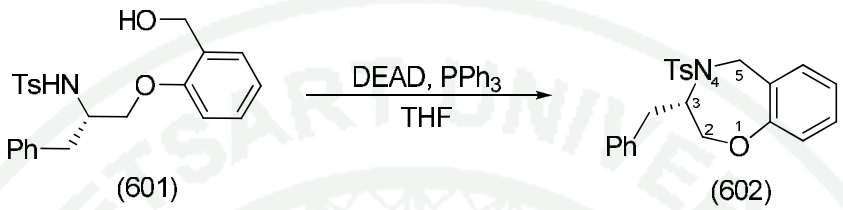
(*S*)-3-Benzyl-4-(toluene-4-sulfonyl)-2,3,4,5-tetrahydro-benzo[*f*][1,4]oxazepine (602)



(601) (602)

To a stirred solution of amine **601** (50.0 mg, 0.12 mmol) and triphenylphosphine (31.9 mg, 0.12 mmol) in anhydrous THF (2.0 mL) under atmosphere of nitrogen was added DEAD (0.019 mL, 0.12 mmol, in THF (1.5 mL)) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 1 additional hour. It was then allowed to warm to room temperature and was stirred for an additional 14 hours. The reaction mixture was stirred with a 1:1 mixture of hexane:diethylether, and the triphenylphosphine oxide that precipitated was filtered off. The organic solvent was removed in vacuum, the mixture was diluted with 30 mL of water, then extracted with EtOAc (3 x 50 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 2:3) to afford benzoxazepine derivative **602** (37.5 mg, 78 %) as a white solid; m.p. 96-98 °C; $[\alpha]_D^{24}$ +56.7 (c = 0.3, CH_2Cl_2).

FTIR (neat), ν_{max}, cm^{-1}: 1490, 1454, 1336, 1157, 1090

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.23-7.36 (m, 7H, Ar(H)), 7.08 (d, *J* = 8.0 Hz, 1H, Ar(H)), 7.04 (ddd, *J* = 8.0, 8.0, 2.0 Hz, 1H, Ar(H)), 6.97 (d, *J* = 8.0 Hz, 2H, Ar(H)), 6.91 (ddd, *J* = 8.0, 8.0, 2.0 Hz, 1H, Ar(H)), 6.57 (d, *J* = 8.0 Hz, 1H, Ar(H)), 4.69 (d, *J* = 16.0 Hz, 1H, H-2), 4.49 (d, *J* = 16.0 Hz, 1H, H-2), 4.34 (m, 1H, H-3), 4.06 (dd, *J* = 16.0, 8.0 Hz, 1H, H-5), 3.79 (dd, *J* = 12.0, 4.0 Hz, 1H, H-5), 3.12 (dd, *J* = 16.0, 12.0 Hz, 1H, C3-C$\underline{H}_2$Ar), 3.03 (dd, *J* = 12.0, 4.0 Hz, 1H, C3-C$\underline{H}_2$Ar), 2.28 (s, 3H, ArC$\underline{H}_3$)

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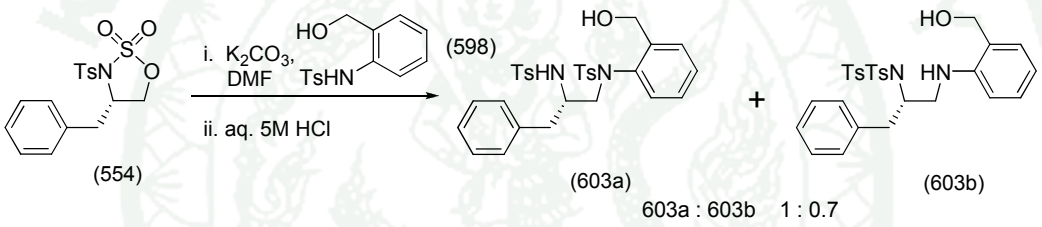
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 158.3 (C-Ar), 142.8 (C-Ar), 137.0×2 (C-Ar), 136.8 (C-Ar), 129.6 (CH-Ar), 129.4×2 (CH-Ar), 129.0×2 (CH-Ar), 128.7×2 (CH-Ar), 128.6×2 (CH-Ar), 127.1 (CH-Ar), 126.8 (CH-Ar), 122.8 (CH-Ar), 119.7 (CH-Ar), 71.8 (C-5), 59.2 (C-3), 45.7 (C-2), 37.2 (C3-$\underline{C}H_2$Ar), 21.4 (Ar$\underline{C}H_3$)

HRMS (ESI^+) *m/z*: $C_{23}H_{23}NO_3SNa$ $[M+Na]^+$, calcd 416.1291, found 416.1285

(*S*)-*N*-(2-(Hydroxymethyl)phenyl)-4-methyl-*N*-(2-(4-methylphenylsulfonamido)-3-phenylpropyl)benzenesulfonamide (603a)



To a solution of *N*-tosyl-2-hydroxymethylaniline (598) (75.5 mg, 0.27 mmol) in anhydrous DMF (3.14 mL) was added K_2CO_3 (37.6 mg, 0.27 mmol) and the mixture was stirred at room temperature for 15 minutes. Cyclic sulfamidate **554** (100 mg, 0.27 mmol) was added and the mixture was stirred at room temperature for a further 24 hours prior to the addition of aqueous 5 M HCl (1.0 mL). The mixture was stirred at room temperature for 2 hours, then diluted with aqueous 1 M NaOH (30 mL) and extracted with Et_2O (3 × 25 mL). The organic extracts were combined, washed with aqueous 1 M NaOH (3 × 25 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 3:7) to afford the mixture of product **603a** and **603b** (1:0.7) (99.1 mg, 65%) as a white solid.

FTIR (neat), ν_{max}, cm^{-1}: 3524, 3292, 1339, 1162, 1090

^{1}H NMR ($CDCl_3$, 400 MHz) δ: (8a:8b, 1:0.7) 7.68 (dd, *J* = 8.0, 4.0 Hz, 1H, Ar(H)), 7.62 (dd, *J* = 8.0, 4.0 Hz, 1H, Ar(H)), 7.36-7.49 (m, 7H, Ar(H)), 7.25-7.30

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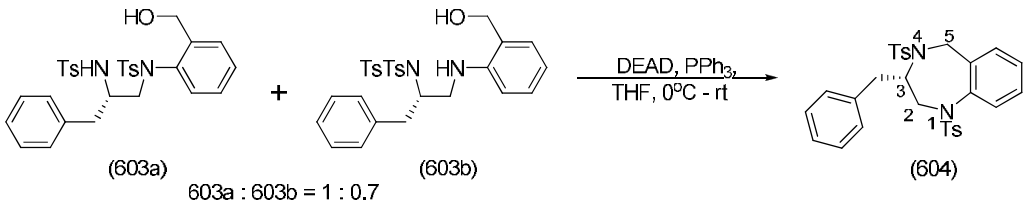
(m, 7H, Ar(H)), 7.04-7.18 (m, 8H, Ar(H)), 6.96-7.01 (m, 4H, Ar(H)), 6.80 (d, *J* = 8.0 Hz, 2H, Ar(H)), 6.68 (d, *J* = 8.0 Hz, 2H, Ar(H)), 6.56 (d, *J* = 8.0 Hz, 1H, Ar(H)), 6.41 (d, *J* = 8.0 Hz, 1H, Ar(H)), 5.05 (d, *J* = 4.0 Hz, 1H, NH), 4.96 (dd, *J* = 12.0, 4.0 Hz, 1H, $ArC^{a}H_2OH$), 4.76 (dd, *J* = 8.0, 4.0 Hz, 1H, $ArC^{b}H_2OH$), 4.61 (dd, *J* = 12.0, 8.0 Hz, 2H, $ArC^{a}H_2OH$, NH), 4.02 (dd, *J* = 16.0, 4.0 Hz, 1H, $ArC^{b}H_2OH$), 3.84 (dd, *J* = 16.0, 8.0 Hz, 1H, ^{a}H-1), 3.57-3.62 (m, 1H, ^{b}H-1), 3.56 (dd, *J* = 12.0, 4.0 Hz, 1H, ^{a}H-1), 3.33 (dd, *J* = 16.0, 8.0 Hz, 1H, ^{b}H-1), 3.10 (dd, *J* = 16.0, 4.0 Hz, 1H, C2-$C^{a}H_2Ar$), 2.96-3.02 (m, 2H, ^{a,b}H-2), 2.91-2.95 (m, 1H, C2-$C^{b}H_2Ar$), 2.62 (dd, *J* = 16.0, 8.0 Hz, 1H, C2-$C^{b}H_2Ar$), 2.54 (dd, *J* = 16.0, 8.0 Hz, 1H, C2-$C^{a}H_2Ar$), 2.46 (s, 3H, $ArC^{a}H_3$), 2.45 (s, 3H, $ArC^{b}H_3$), 2.40 (s, 3H, $ArC^{b}H_3$), 2.36 (s, 3H, $ArC^{a}H_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 144.4 (C-Ar), 144.3 (C-Ar), 143.2 (C-Ar), 143.1 (C-Ar), 141.8 (C-Ar), 141.4 (C-Ar), 138.9 (C-Ar), 137.3 (C-Ar), 135.8 (C-Ar), 135.2 (C-Ar), 133.2 (C-Ar), 133.1 (C-Ar), 131.4 (C-Ar), 131.3 (C-Ar), 129.7×2 (CH-Ar), 129.6×2 (CH-Ar), 129.5×2 (CH-Ar), 129.4×2 (CH-Ar), 129.0 (CH-Ar), 128.9×2 (CH-Ar), 128.8×4 (CH-Ar), 128.7×3 (CH-Ar), 128.6×2 (CH-Ar), 128.4×2 (CH-Ar), 128.3×2 (CH-Ar), 127.3×2 (CH-Ar), 127.2×2 (CH-Ar), 126.9×2 (CH-Ar), 126.8×2 (CH-Ar), 126.63×2 (CH-Ar), 61.0 ($Ar^{b}CH_2OH$), 60.4 ($Ar^{a}CH_2OH$), 55.3 (^{b}C-1), 54.5 (^{a}C-1), 52.9×2 (^{a,b}C-2), 38.5 (C2-$^{b}CH_2Ar$), 38.4 (C2-$^{a}CH_2Ar$), 21.6×2 ($Ar^{a,b}CH_3$), 21.5 ($Ar^{a}CH_3$), 21.0 ($Ar^{b}CH_3$)

HRMS (ESI^+) *m/z*: $C_{30}H_{32}N_2O_5S_2Na$ $[M+Na]^+$, calcd 587.1645, found 587.1654

(*S*)-3-Benzyl-1,4-ditosyl-2,3,4,5-tetrahydro-1H-benzo[*e*][1,4]diaze-pine (604)



(603a) (603b) (604)

603a : 603b = 1 : 0.7

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To a stirred solution of a mixture of amine **603a** and **603b** (39.8 mg, 0.07 mmol) and triphenylphosphine (18.5 mg, 0.07 mmol) in anhydrous THF (2.0 mL) under atmosphere of nitrogen was added DEAD (0.019 mL, 0.11 mmol, in THF (1.5 mL)) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 1 additional hour. It was then allowed to warm to room temperature and was stirred for an additional 14 hours. The reaction mixture was stirred with a 1:1 mixture of hexane:diethylether, and the triphenylphosphine oxide that precipitated was filtered off. The organic solvent was removed in vacuum, the mixture was diluted with 30 mL of water, then extracted with EtOAc (3 x 50 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 3:7) to afford benzodiazepine derivative **604** (32.2 mg, 84 %) as a white solid; m.p. 174-176 °C; $[\alpha]_D^{25}$ +14.0 (c = 0.5, CH_2Cl_2).

FTIR (neat), ν_{max}, cm^{-1}: 1339, 1160, 1090

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.63 (d, *J* = 8.0 Hz, 2H, Ar(H)), 7.38 (dd, *J* = 8.0, 2.0 Hz, 1H, Ar(H)), 7.13-7.28 (m, 11H, Ar(H)), 7.08 (dd, *J* = 8.0, 2.0 Hz, 1H, Ar(H)), 6.97 (d, *J* = 8.0 Hz, 2H, Ar(H)), 4.43 (s, 2H, H-5), 4.30-4.35 (m, 1H, H-2), 4.11-4.18 (m, 1H, H-3), 3.22 (dd, *J* = 16.0, 8.0 Hz, 1H, C3-C$\underline{H}_2$Ar), 3.18 (dd, *J* = 12.0, 4.0 Hz, 1H, H-2), 3.08 (dd, *J* = 16.0, 8.0 Hz, 1H, C3-C$\underline{H}_2$Ar), 2.43 (s, 3H, ArC$\underline{H}_3$), 2.31 (s, 3H, ArC$\underline{H}_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 143.8×2 (C-Ar), 142.9 (C-Ar), 140.2 (C-Ar), 138.1 (C-Ar), 137.8 (C-Ar), 136.7 (C-Ar), 130.4 (CH-Ar), 129.8×2 (CH-Ar), 129.3×3 (CH-Ar), 128.5 (CH-Ar), 128.4×2 (CH-Ar), 127.6 (CH-Ar), 127.3×2 (CH-Ar), 127.2×3 (CH-Ar), 126.4 (CH-Ar), 126.3 (CH-Ar), 58.0 (C-3), 52.3 (C-2), 45.4 (C-5), 37.1 (C3-$\underline{C}H_2$Ar), 21.6 (Ar$\underline{C}H_3$), 21.4 (Ar$\underline{C}H_3$)

HRMS (ESI^+) *m/z*: $C_{30}H_{30}N_2O_4S_2Na$ $[M+Na]^+$, calcd 569.1539, found 569.1539

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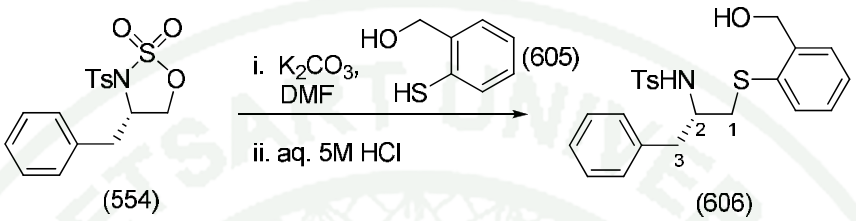
***(S)-N*-(1-(2-(Hydroxymethyl)phenylthio)-3-phenylpropan-2-yl)-4-methylbenzene sulfonamide (606)**



To a solution of 2-mercaptobenzyl alcohol (605) (76.3 mg, 0.5443 mmol) in anhydrous DMF (3.14 mL) was added K_2CO_3 (75.2 mg, 0.5443 mmol) and the mixture was stirred at room temperature for 15 minutes. Cyclic sulfamidate **554** (100 mg, 0.2722 mmol) was added and the mixture was stirred at room temperature for a further 24 hours prior to the addition of aqueous 5 M HCl (1.0 mL). The mixture was stirred at room temperature for 2 hours, then diluted with aqueous 1 M NaOH (30 mL) and extracted with Et_2O (3 × 25 mL). The organic extracts were combined, washed with aqueous 1 M NaOH (3 × 25 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 1:1) to afford the product **606** (94.2 mg, 81%) as a colorless oil; $[\alpha]_D^{25}$ -30.0 (c = 0.2, CH_2Cl_2).

FTIR (neat), ν_{max}, cm^{-1}: 3501, 3281, 1325, 1157

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.40 (d, *J* = 8.0 Hz, 2H, Ar(H)), 7.17-7.29 (m, 7H, Ar(H)), 7.08 (d, *J* = 8.0 Hz, 2H, Ar(H)), 6.94-7.00 (m, 2H, Ar(H)), 5.28 (brs, 1H, NH), 4.84 (dd, *J* = 12.0, 8.0 Hz, 1H, ArCH_2OH), 4.71 (dd, *J* = 12.0, 8.0 Hz, 1H, ArCH_2OH), 3.52 (m, 1H, H-2), 3.11 (dd, *J* = 12.0, 4.0 Hz, 1H, H-1), 2.94 (dd, *J* = 12.0, 8.0 Hz, 1H, H-1), 2.86 (dd, *J* = 16.0, 8.0 Hz, 1H, H-3), 2.77 (dd, *J* = 16.0, 8.0 Hz, 1H, H-3), 2.42 (dd, *J* = 12.0, 8.0 Hz, 1H, OH), 2.36 (s, 3H, ArCH_3)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 143.1 (C-Ar), 141.1 (C-Ar), 136.9 (C-Ar), 133.9 (C-Ar), 131.4 (C-Ar), 129.5×2 (CH-Ar), 129.2×2 (CH-Ar), 129.0 (CH-Ar),

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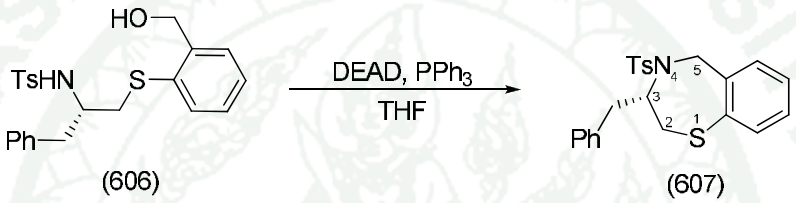
128.7×2 (CH-Ar), 128.6 (CH-Ar), 127.3 (CH-Ar), 126.9×3 (CH-Ar), 126.8 (CH-Ar), 63.7 (Ar<u>C</u>H_2OH), 54.2 (C-2), 39.8 (C-3), 39.0 (C-1), 21.5 (Ar<u>C</u>H_3)

HRMS (ESI^+) *m/z*: $C_{23}H_{25}NO_3S_2Na$ $[M+Na]^+$, calcd 450.1168, found 450.1186

(*S*)-3-Benzyl-4-tosyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]thiazepine (607)



(606) (607)

To a stirred solution of amine **606** (30.0 mg, 0.07 mmol) and triphenylphosphine (18.4 mg, 0.07 mmol) in anhydrous THF (1.0 mL) under atmosphere of nitrogen was added DEAD (0.011 mL, 0.07 mmol, in THF (1.0 mL)) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 1 additional hour. It was then allowed to warm to room temperature and was stirred for an additional 14 hours. The reaction mixture was stirred with a 1:1 mixture of hexane:diethyl ether, and the triphenylphosphine oxide that precipitated was filtered off. The organic solvent was removed in vacuum, the mixture was diluted with 30 mL of water, then extracted with EtOAc (50 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 1:9) to afford benzothiazepine derivative **607** (20.0 mg, 70%) as a colorless oil; $[\alpha]_D^{25}$ +27.5 (c = 0.4, CH_2Cl_2).

FTIR (neat), ν_{max}, cm^{-1}: 1336, 1156, 1091

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.46 (dd, *J* = 8.0, 2.0 Hz, 1H, Ar(H)), 7.38-7.42 (m, 2H, Ar(H)), 7.18 (d, *J* = 4.0 Hz, 1H, Ar(H)), 7.20-7.30 (m, 5H, Ar(H)), 7.16 (ddd, *J* = 8.0, 8.0, 4.0 Hz, 2H, Ar(H)), 7.08 (d, *J* = 8.0 Hz, 2H, Ar(H)), 4.77 (d, *J* =

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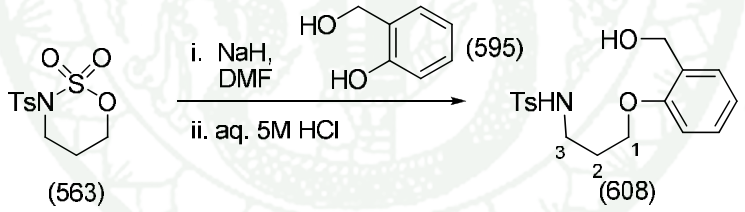
16.0 Hz, 1H, H-5), 4.70 (d, *J* = 16.0 Hz, 1H, H-5), 4.32 (h, *J* = 4.0 Hz, 1H, H-3), 3.38 (dd, *J* = 12.0, 8.0 Hz, 1H, H-2), 2.95 (dd, *J* = 12.0, 4.0 Hz, 1H, H-2), 2.64 (dd, *J* = 12.0, 4.0 Hz, 1H, C3-C$\underline{H}_2$Ar), 2.56 (ddd, *J* = 12.0, 4.0, 1.0 Hz, 1H, C3-C$\underline{H}_2$Ar), 2.34 (s, 3H, ArC$\underline{H}_3$)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 143.0 (C-Ar), 138.7 (C-Ar), 137.5 (C-Ar), 137.4 (C-Ar), 136.2 (C-Ar), 130.6×2 (CH-Ar), 129.4×2 (CH-Ar), 129.3×2 (CH-Ar), 128.7×2 (CH-Ar), 127.9 (CH-Ar), 127.8 (CH-Ar), 127.2×2 (CH-Ar), 126.7 (CH-Ar), 53.5 (C-3), 47.1 (C-5), 35.8×2 (C3-$\underline{C}H_2$Ar, C-2), 21.4 (Ar$\underline{C}H_3$)

HRMS (ESI$^+$) *m/z*: $C_{23}H_{23}NO_2S_2Na$ $[M+Na]^+$, calcd 432.1062, found 432.1075

***N*-(3-(2-(Hydroxymethyl)phenoxy)propyl)-4-methylbenzenesulfonamide (608)**



(563) (608)

To a solution of 2-hydroxybenzyl alcohol (595) (85.2 mg, 0.69 mmol) in anhydrous DMF (3.14 mL) was added NaH (60% dispersion in mineral oil, 27.5 mg, 0.69 mmol) and the mixture was stirred at room temperature for 15 minutes. Cyclic sulfamidate **563** (100 mg, 0.34 mmol) was added and the mixture was stirred at room temperature for a further 24 hours prior to the addition of aqueous 5 M HCl (1.0 mL). The mixture was stirred at room temperature for 2 hours, then diluted with aqueous 1 M NaOH (30 mL) and extracted with Et_2O (3 × 25 mL). The organic extracts were combined, washed with aqueous 1 M NaOH (3 × 25 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 1:1) to afford the product **608** (103.7 mg, 90.1%) as a white solid; m.p. 98-100 °C.

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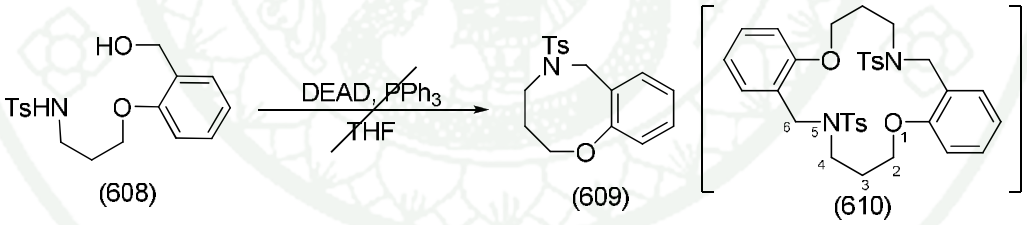
FTIR (neat), ν_{max}, cm^{-1}: 3514, 3278, 1602, 149, 1455, 1323, 1243, 1158, 1093

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.71 (d, *J* = 8.0 Hz, 2H, Ar(H)), 7.22-7.28 (m, 4H, Ar(H)), 6.93 (ddd, *J* = 8.0, 8.0, 2.0 Hz, 1H, Ar(H)), 6.79 (d, *J* = 8.0 Hz, 1H, Ar(H)), 6.23 (t, *J* = 4.0 Hz, 1H, NH), 4.69 (d, *J* = 4.0 Hz, 2H, $ArCH_2OH$), 4.04 (dd, *J* = 8.0, 4.0 Hz, 2H, H-1), 3.15 (dd, *J* = 12.0, 8.0 Hz, 2H, H-3), 2.62 (brs, 1H, OH), 2.38 (s, 3H, $ArCH_3$), 2.00 (quin, *J* = 4.0 Hz, 2H, H-2)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 156.7 (C-Ar), 143.1×2 (C-Ar), 137.1 (C-Ar), 129.9 (CH-Ar), 129.6×2 (CH-Ar), 129.4 (CH-Ar), 127.0×2 (CH-Ar), 120.7 (CH-Ar), 110.8 (CH-Ar), 66.6 (C-1), 62.0 ($ArCH_2OH$), 41.7 (C-3), 28.8 (C-2), 21.4 ($ArCH_3$)

HRMS (ESI^+) *m/z*: $C_{17}H_{21}NO_4SNa$ $[M+Na]^+$, calcd 358.1083, found 358.1096

5-Tosyl-3,4,5,6-tetrahydro-2*H*-benzo[*b*][1,5]oxazocine (609)



(608) (609) (610)

To a stirred solution of amine **608** (35.0 mg, 0.104 mmol) and triphenylphosphine (27.37 mg, 0.104 mmol) in anhydrous THF (1.5 mL) under atmosphere of nitrogen was added DEAD (0.016 mL, 0.104 mmol, in THF (1.5 mL)) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 1 additional hour. It was then allowed to warm to room temperature and was stirred for an additional 14 hours. The reaction mixture was stirred with a 1:1 mixture of hexane:diethyl ether, and the triphenylphosphine oxide that precipitated was filtered off. The organic solvent was removed in vacuum, the mixture was diluted with 15 mL of water, then extracted with EtOAc (3 x 25 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane,

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3:7). The benzoxazocine derivative **609** was not observed, only 16-membered compound **610** was obtained (24.76 mg, 75%) as a white solid; m.p. 204-206 °C.

Compound 610

FTIR (neat), ν_{max}, cm^{-1}: 1494, 1454, 1337, 1245, 1158, 1090

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.62 (d, *J* = 8.0 Hz, 4H, Ar(H)), 7.47 (dd, *J* = 8.0, 2.0 Hz, 2H, Ar(H)), 7.24-7.30 (m, 4H, Ar(H)), 7.13 (ddd, *J* = 8.0, 8.0, 2.0 Hz, 2H, Ar(H)), 6.92 (dd, *J* = 8.0, 8.0 Hz, 2H, Ar(H)), 6.42 (d, *J* = 8.0 Hz, 2H, Ar(H)), 4.31 (s, 4H, H-6), 3.69 (t, *J* = 6.0 Hz, 4H, H-2), 3.32 (t, *J* = 8.0 Hz, 4H, H-4), 2.41 (s, 6H, ArC$\underline{H}_3$), 1.98 (quin, *J* = 6.0 Hz, 4H, H-3)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 156.1 (C-Ar), 143.1 (C-Ar), 137.0 (C-Ar), 131.9 (C-Ar), 129.7 (CH-Ar), 129.6 (CH-Ar), 129.2 (CH-Ar), 127.2 (CH-Ar), 127.0 (CH-Ar), 124.7 (CH-Ar), 120.8 (CH-Ar), 111.3 (CH-Ar), 64.9 (C-2), 47.3 (C-4), 47.1 (C-6), 29.8 (C-3), 21.5 (ArC$\underline{H}_3$)

HRMS (ESI^+) *m/z*: $C_{34}H_{38}N_2O_6S_2Na$ $[M+Na]^+$, calcd 657.2063, found 657.2055

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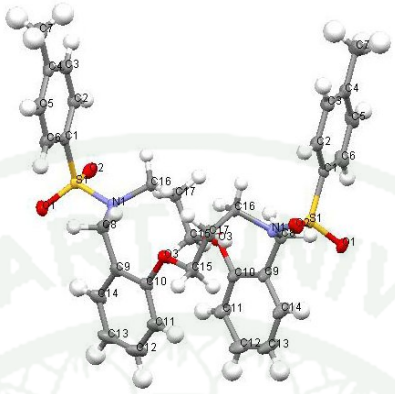
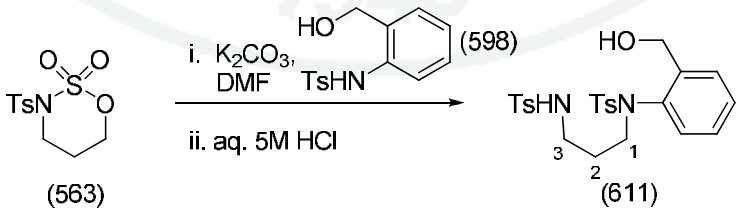


Figure 11 The X-ray crystal structure of 9,19-ditosyl-6,7,8,9,10,16,17,18,19,20-decahydrodibenzo[b,j] [1,9,5,13]dioxadiazacyclohexadecine (610); Crystal data for **610**: $C_{34}H_{38}N_2O_6S_2$, MW = 634.78, tetragonal, space group $I4_1/a$, a = 14.0817(2), b = 14.0817(2), c = 31.4227(6) Å, V = 6230.94(17) $Å^3$, α = 90.00, β = 90.00, γ = 90.00 °, Z = 8, D_c = 1.353 g cm^{-1}, Mo-Kα radiation, λ = 0.71073 Å, μ = 0.220 mm^{-1}, T = 100 K; colourless octahedron, 0.383×0.377×0.309 mm, Bruker-AXS D8 diffractometer, 26837 reflections were collected, 3572 were unique, R_{int} = 0.0254; refinement on F2 gave R = 0.0374 and R_w = 0.1090, GOF = 0.291 for refinement parameters.

_N_-(2-(Hydroxymethyl)phenyl)-4-methyl-_N_-(3-(4-methylphenylsulfonamido) propyl)benzenesulfonamide (611)



To a solution of *N*-tosyl-2-hydroxymethylaniline (598) (95.2 mg, 0.34 mmol) in anhydrous DMF (3.14 mL) was added K_2CO_3 (47.4 mg, 0.34 mmol) and the mixture was stirred at room temperature for 15 minutes. Cyclic sulfamidate **563** (100 mg, 0.34 mmol) was added and the mixture was stirred at room temperature for a

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further 24 hours prior to the addition of aqueous 5 M HCl (1.0 mL). The mixture was stirred at room temperature for 2 hours, then diluted with aqueous 1 M NaOH (30 mL) and extracted with Et_2O (3 × 25 mL). The organic extracts were combined, washed with aqueous 1 M NaOH (3 × 25 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 1:1) to afford the product **611** (106.3 mg, 64%) as a colorless oil.

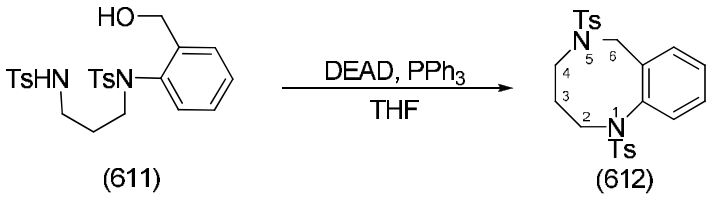
FTIR (neat), ν_{max}, cm^{-1}: 3518, 1333, 1159

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.73 (d, *J* = 8.0 Hz, 2H, Ar(H)), 7.59 (dd, *J* = 8.0, 2.0 Hz, 1H, Ar(H)), 7.49 (d, *J* = 8.0 Hz, 2H, Ar(H)), 7.29-7.37 (m, 5H, Ar(H)), 7.15 (t, *J* = 8.0 Hz, 1H, Ar(H)), 6.44 (d, *J* = 8.0 Hz, 1H, Ar(H)), 5.01 (brs, 1H, NH), 4.78 (dd, *J* = 8.0, 2.0 Hz, 1H, ArCH_2OH), 4.48 (dd, *J* = 12.0, 8.0 Hz, 1H, ArCH_2OH), 3.95 (ddd, *J* = 16.0, 8.0, 4.0 Hz, 1H, H-3), 3.16 (dt, *J* = 16.0, 4.0 Hz, 1H, H-3), 3.01-3.06 (m, 2H, H-1), 2.96-2.99 (m, 1H, OH), 2.46 (s, 3H, ArCH_3), 2.44 (s, 3H, ArCH_3), 1.55-1.66 (m, 2H, H-2)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 144.2 (C-Ar), 143.5 (C-Ar), 142.2 (C-Ar), 137.2 (C-Ar), 136.8 (C-Ar), 133.8 (C-Ar), 131.2×2 (CH-Ar), 129.8×2 (CH-Ar), 129.6×2 (CH-Ar), 129.1×2 (CH-Ar), 128.6 (CH-Ar), 128.1×2 (CH-Ar), 127.0 (CH-Ar), 60.9 (ArCH$_2$OH), 49.3 (C-3), 40.0 (C-1), 28.5 (C-2), 21.6 (ArCH$_3$), 21.5 (ArCH$_3$)

HRMS (ESI^+) *m/z*: $C_{24}H_{28}N_2O_5S_2Na$ $[M+Na]^+$, calcd 511.1332, found 511.1334

1,5-Ditosyl-1,2,3,4,5,6-hexahydrobenzo[*b*][1,5]diazocine (612)



(611) (612)

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To a stirred solution of amine **611** (71.1 mg, 0.146 mmol) and triphenylphosphine (38.2 mg, 0.146 mmol) in anhydrous THF (2.0 mL) under atmosphere of nitrogen was added DEAD (0.023 mL, 0.146 mmol, in THF (2.0 mL)) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 1 additional hour. It was then allowed to warm to room temperature and was stirred for an additional 14 hours. The reaction mixture was stirred with a 1:1 mixture of hexane:diethyl ether, and the triphenylphosphine oxide that precipitated was filtered off. The organic solvent was removed in vacuum, the mixture was diluted with 15 mL of water, then extracted with EtOAc (3 x 25 mL), and dried over anhydrous Na_2SO_4. Concentration under vacuum and flash column chromatography of the crude product over silica gel furnished benzodiazocine derivative **612** (56.1 mg, 82%) as a white solid; m.p. 174-176 °C.

FTIR (neat), ν_{max}, cm^{-1}: 1344, 1159

^{1}H NMR (DMSO-d6 at 100.0 °C, 500 MHz) δ: 7.68 (d, *J* = 8.0 Hz, 2H, Ar(H)), 7.62 (d, *J* = 8.0 Hz, 2H, Ar(H)), 7.38-7.45 (m, 6H, Ar(H)), 7.31 (ddd, *J* = 8.0, 8.0, 1.0 Hz, 1H, Ar(H)), 6.72-6.78 (m, 1H, Ar(H)), 4.37 (brs, 2H, H-6), 3.52 (brm, 2H, H-2), 3.34 (brm, 2H, H-4), 2.43 (s, 3H, ArC$\underline{H}_3$), 2.41 (s, 3H, ArC$\underline{H}_3$), 1.58 (brm, 2H, H-3)

^{13}C NMR (DMSO-d6 at 100.0 °C, 125 MHz) δ: 144.2 (C-Ar), 143.7 (C-Ar), 139.0 (C-Ar), 138.5 (C-Ar), 136.9 (C-Ar), 131.7 (CH-Ar), 130.5×2 (CH-Ar), 130.4×2 (CH-Ar), 130.2 (CH-Ar), 129.9 (CH-Ar), 128.1 (C-Ar), 127.6×3 (CH-Ar), 127.2×2 (CH-Ar), 51.6 (C-6), 49.9 (C-2), 48.0 (C-4), 28.1 (C-3), 21.5×2 (Ar$\underline{C}H_3$)

HRMS (ESI^+) *m/z*: $C_{24}H_{26}N_2O_4S_2Na$ $[M+Na]^+$, calcd 493.1226, found 493.1227

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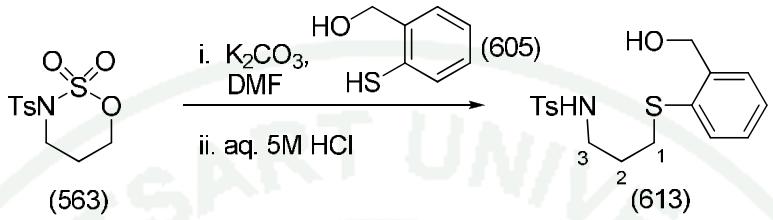
***N*-(3-(2-(Hydroxymethyl)phenylthio)propyl)-4-methylbenzenesulfonamide (613)**



To a solution of 2-mercaptobenzyl alcohol (605) (96.2 mg, 0.69 mmol) in anhydrous DMF (3.14 mL) was added K_2CO_3 (94.9 mg, 0.69 mmol) and the mixture was stirred at room temperature for 15 minutes. Cyclic sulfamidate **563** (100 mg, 0.34 mmol) was added and the mixture was stirred at room temperature for a further 24 hours prior to the addition of aqueous 5 M HCl (1.0 mL). The mixture was stirred at room temperature for 2 hours, then diluted with aqueous 1 M NaOH (30 mL) and extracted with Et_2O (3 × 25 mL). The organic extracts were combined, washed with aqueous 1 M NaOH (3 × 25 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 3:2) to afford the product **613** (96.7 mg, 81%) as a white solid; m.p. 117-119 °C.

FTIR (neat), ν_{max}, cm^{-1}: 3462, 3272, 1320, 1155

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.71 (d, *J* = 8.0 Hz, 2H, Ar(H)), 7.39-7.41 (m, 1H, Ar(H)), 7.28-7.34 (m, 4H, Ar(H)), 7.23-7.25 (m, 1H, Ar(H)), 4.75 (d, *J* = 8.0 Hz, 2H, ArC$\underline{H}_2$OH), 3.07 (dd, *J* = 16.0, 8.0 Hz, 2H, H-3), 2.93 (dd, *J* = 8.0, 8.0 Hz, 2H, H-1), 2.42 (s, 3H, ArC$\underline{H}_3$), 2.25 (dd, *J* = 8.0, 4.0 Hz, 1H, O$\underline{H}$), 1.79 (quin, *J* = 4.0 Hz, 2H, H-2)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 143.5 (C-Ar), 137.9 (C-Ar), 134.0 (C-Ar), 132.8 (C-Ar), 130.5 (CH-Ar), 129.7×2 (CH-Ar), 128.7 (CH-Ar), 128.4 (CH-Ar), 127.0×3 (CH-Ar), 63.7 (Ar$\underline{C}H_2$OH), 41.9 (C-3), 31.3 (C-1), 28.8 (C-2), 21.5 (Ar$\underline{C}H_3$)

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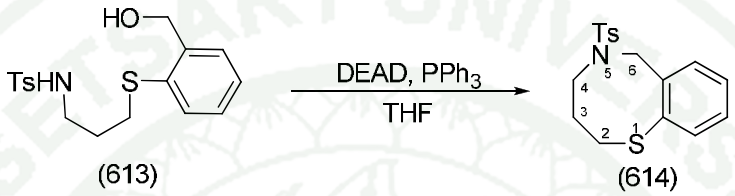
HRMS (ESI^+) *m/z*: $C_{17}H_{21}NO_3S_2Na$ $[M+Na]^+$, calcd 374.0855, found 374.0861

5-Tosyl-3,4,5,6-tetrahydro-*2H*-benzo[*b*][1,5]thiazocine (614)



(613) (614)

To a stirred solution of amine `**613** (30.0 mg, 0.085 mmol) and triphenylphosphine (22.4 mg, 0.085 mmol) in anhydrous THF (1.2 mL) under atmosphere of nitrogen was added DEAD (0.013 mL, 0.085 mmol, in THF (1.2 mL)) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 1 additional hour. It was then allowed to warm to room temperature and was stirred for an additional 14 hours. The reaction mixture was stirred with a 1:1 mixture of hexane:diethyl ether, and the triphenylphosphine oxide that precipitated was filtered off. The organic solvent was removed in vacuum, the mixture was diluted with 15 mL of water, then extracted with EtOAc (3 x 25 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 1:9) to afford benzothiazocine derivative **614** (22.37 mg, 79%) as a white solid; m.p. 102-104 °C.

FTIR (neat), ν_{max}, cm^{-1}: 1337, 1326, 1157, 1093

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.73 (dt, *J* = 8.0, 2.0 Hz, 2H, Ar(H)), 7.60 (dd, *J* = 8.0, 2.0 Hz, 1H, Ar(H)), 7.49 (dd, *J* = 8.0, 2.0 Hz, 1H, Ar(H)), 7.36 (ddd, *J* = 8.0, 8.0, 4.0 Hz, 1H, Ar(H)), 7.32 (dd, *J* = 8.0, 2.0 Hz, 2H, Ar(H)), 7.28 (dd, *J* = 8.0, 4.0 Hz, 1H, Ar(H)), 4.68 (s, 2H, H-6), 3.45 (dd, *J* = 6.0, 6.0 Hz, 2H, H-4), 2.72 (dd, *J* = 6.0, 6.0 Hz, 2H, H-2), 2.44 (s, 3H, ArC$\underline{H}_3$), 1.80 (dquin, *J* = 4.0, 2.0 Hz, 2H, H-3)

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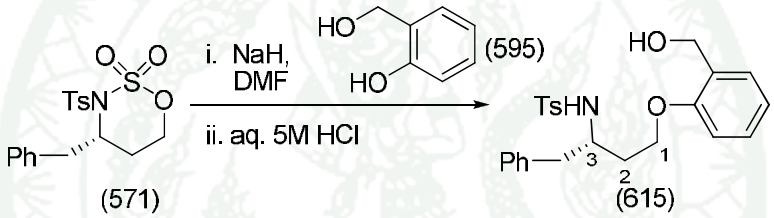
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 143.2 (C-Ar), 141.7 (C-Ar), 137.2 (C-Ar), 134.9 (C-Ar), 136.6 (CH-Ar), 131.4×2 (CH-Ar), 129.8×2 (CH-Ar), 129.1 (CH-Ar), 127.1×2 (CH-Ar), 51.8 (C-6), 47.1 (C-4), 36.6 (C-2), 29.3 (C-3), 21.5 (Ar$C\underline{H}_3$)

HRMS (ESI^+) *m/z*: $C_{17}H_{19}NO_2S_2Na$ $[M+Na]^+$, calcd 356.0749, found 356.0763

***(S)-N*-(4-(2-(Hydroxymethyl)phenoxy)-1-phenylbutan-2-yl)-4-methylbenzene sulfonamide (615)**



To a solution of 2-hydroxybenzyl alcohol (595) (65.2 mg, 0.52 mmol) in anhydrous DMF (3.14 mL) was added NaH (60% dispersion in mineral oil, 21.0 mg, 0.52 mmol) and the mixture was stirred at room temperature for 15 minutes. Cyclic sulfamidate **571** (100 mg, 0.26 mmol) was added and the mixture was stirred at room temperature for a further 24 hours prior to the addition of aqueous 5 M HCl (1.0 mL). The mixture was stirred at room temperature for 2 hours, then diluted with aqueous 1 M NaOH (30 mL) and extracted with Et_2O (3 × 25 mL). The organic extracts were combined, washed with aqueous 1 M NaOH (3 × 25 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 1:4) to afford the product **615** (46.7 mg, 42%) as a white solid; m.p. 140-142 °C; $[\alpha]_D^{24}$ -12.8 (c = 0.7, CH_2Cl_2).

FTIR (neat), ν_{max}, cm^{-1}: 3281, 1455, 1327, 1305, 1160, 1095

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.63 (d, *J* = 8.0 Hz, 2H, Ar(H)), 7.17-7.29 (m, 5H, Ar(H)), 7.11 (d, *J* = 8.0 Hz, 2H, Ar(H)), 7.07 (d, *J* = 8.0 Hz, 2H, Ar(H)), 6.95

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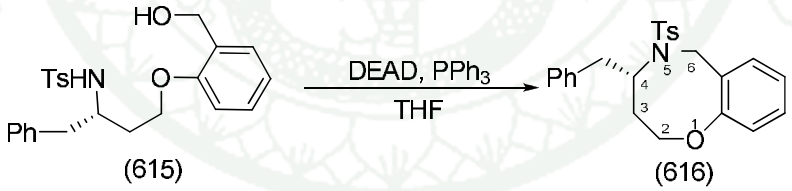
(ddd, *J* = 8.0, 8.0, 1.0 Hz, 1H, Ar(H)), 6.69 (d, *J* = 8.0 Hz, 1H, Ar(H)), 5.60 (dd, *J* = 8.0, 4.0 Hz, 1H, N<u>H</u>), 4.73 (dd, *J* = 12.0, 4.0 Hz, 1H, ArC<u>H</u>$_2$OH), 4.64 (1H, dd, *J* = 12.0, 4.0 Hz, ArC<u>H</u>$_2$OH), 4.01 (ddd, *J* = 8.0, 8.0, 4.0 Hz, 1H, H-1), 3.88 (ddd, *J* = 12.0, 4.0, 4.0 Hz, 1H, H-1), 3.70-3.79 (m, 1H, H-3), 2.87 (dd, *J* = 14.0, 8.0 Hz, 1H, ArC<u>H</u>$_2$C3), 2.72 (dd, *J* = 14.0, 8.0 Hz, 1H, ArC<u>H</u>$_2$C3), 2.48 (brd, *J* = 4.0 Hz, 1H, O<u>H</u>), 2.33 (s, 3H, ArC<u>H</u>$_3$), 2.03 (ddd, *J* = 16.0, 8.0, 4.0 Hz, 1H, H-2), 1.71-1.78 (m, 1H, H-2)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 156.5 (C-Ar), 137.7×2 (C-Ar), 137.2×2 (C-Ar), 129.6×3 (CH-Ar), 129.3×2 (CH-Ar), 128.6×3 (CH-Ar), 126.9×2 (CH-Ar), 126.6 (CH-Ar), 120.7 (CH-Ar), 110.7 (CH-Ar), 64.1 (C-1), 62.0 (Ar<u>C</u>H$_2$OH), 53.0 (C-3), 41.3 (Ar<u>C</u>H$_2$C3), 32.7 (C-2), 21.4 (Ar<u>C</u>H$_3$)

HRMS (ESI$^+$) *m/z*: $C_{24}H_{27}NO_4SNa$ $[M+Na]^+$, calcd 448.1553, found 448.1551

***(S)*-4-Benzyl-5-tosyl-3,4,5,6-tetrahydro-2H-benzo[*b*][1,5]oxazocine (616)**



To a stirred solution of amine **615** (18 mg, 0.04 mmol) and triphenylphosphine (11.1 mg, 0.04 mmol) in anhydrous THF (1.5 mL) under atmosphere of nitrogen was added DEAD (0.007 mL, 0.04 mmol, in THF (1.5 mL)) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 1 additional hour. It was then allowed to warm to room temperature and was stirred for an additional 14 hours. The reaction mixture was stirred with a 1:1 mixture of hexane:diethyl ether, and the triphenylphosphine oxide that precipitated was filtered off. The organic solvent was removed in vacuum, the mixture was diluted with 5 mL of water, then extracted with EtOAc (3 x 10 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 3:7) to afford benzoxazocine

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derivative **616** (10 mg, 58%) as a white solid; m.p. 246-248 °C; $[\alpha]_D^{24}$ -45.0 (c = 0.2, CH_2Cl_2).

FTIR (neat), ν_{max}, cm^{-1}: 1494, 1454, 1341, 1155, 1091

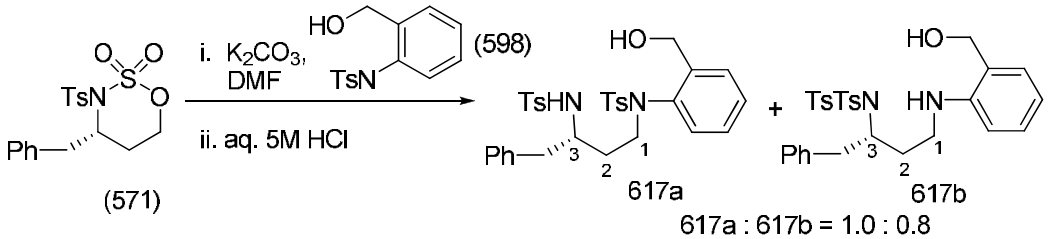
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.62 (d, *J* = 8.0 Hz, 2H, Ar(H)), 7.30-7.32 (m, 1H, Ar(H)), 7.16 (d, *J* = 8.0 Hz, 2H, Ar(H)), 7.02-7.08 (m, 4H, Ar(H)), 6.79-6.84 (m, 3H, Ar(H)), 6.26 (d, *J* = 8.0 Hz, 1H, Ar(H)), 4.40 (d, *J* = 16.0 Hz, 1H, TsNC$\underline{H}_2$Ar), 4.22 (d, *J* = 16.0 Hz, 1H, TsNC$\underline{H}_2$Ar), 3.79-3.87 (m, 1H, H-2), 3.56-3.57 (m, 1H, H-2), 3.14 (m, 1H, H-4), 3.00 (dd, *J* = 12.0, 4.0 Hz, 1H, C4-C$\underline{H}_2$Ar), 2.32-2.39 (m, 1H, C4-C$\underline{H}_2$Ar), 2.32 (s, 3H, ArC$\underline{H}_3$), 2.16-2.26 (m, 1H, H-3), 1.90-1.97 (m, 1H, H-3)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 155.9 (C-Ar), 143.2 (C-Ar), 139.0 (C-Ar), 138.4 (C-Ar), 131.2 (C-Ar), 129.6 (CH-Ar), 129.1×3 (CH-Ar), 128.6 (CH-Ar), 128.3×3 (CH-Ar), 127.1×2 (CH-Ar), 126.3 (CH-Ar), 121.1 (CH-Ar), 111.3 (CH-Ar), 65.6 (C-2), 59.3 (C-4), 42.9 (TsN$\underline{C}H_2$Ar), 30.2 (C4-$\underline{C}H_2$Ar), 29.7 (C-3), 21.5 (Ar$\underline{C}H_3$)

MS (CI^+), *m/z* (relative intensity): 408 ($[M+H]^+$, 24%), 316 (84), 237 (100)

HRMS (CI^+) *m/z*: $C_{24}H_{26}NO_3S$ $[M+H]^+$, calcd 408.1633, found 408.1626

(*S*)-*N*-(2-(Hydroxymethyl)phenyl)-4-methyl-*N*-(3-(4-methylphenylsulfonamido)-4-phenylbutyl)benzenesulfonamide (617a)



To a solution of *N*-tosyl-2-hydroxymethyl aniline (598) (145.6 mg, 0.52 mmol) in anhydrous DMF (3.14 mL) was added K_2CO_3 (72.5 mg, 0.52 mmol) and the

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mixture was stirred at room temperature for 15 minutes. Cyclic sulfamidate **571** (100 mg, 0.26 mmol) was added and the mixture was stirred at room temperature for a further 24 hours prior to the addition of aqueous 5 M HCl (1.0 mL). The mixture was stirred at room temperature for 2 hour, then diluted with aqueous 1 M NaOH (30 mL) and extracted with Et_2O (3 × 25 mL). The organic extracts were combined, washed with aqueous 1 M NaOH (3 × 25 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 2:3) to afford the product **617a** and **617b** (1.0:0.8) (140.6 mg, 93%) as a white solid.

FTIR (neat), ν_{max}, cm^{-1}: 3514, 3292, 1454, 1334, 1159, 1090

^{1}H NMR ($CDCl_3$, 400 MHz) δ: (a:b, 1:0.8) 7.60 (d, *J* = 8.0 Hz, 2H, Ar(H)), 7.56 (d, *J* = 8.0 Hz, 1H, Ar(H)), 7.52 (d, *J* = 8.0 Hz, 2H, Ar(H)), 7.46 (dd, *J* = 8.0, 4.0 Hz, 2H, Ar(H)), 7.34 (q, *J* = 8.0 Hz, 2H, Ar(H)), 7.28 (d, *J* = 8.0 Hz, 2H, Ar(H)), 7.09-7.23 (m, 9H, Ar(H)), 6.84-6.89 (m, 3H, Ar(H)), 6.36 (d, *J* = 8.0 Hz, 2H, Ar(H)), 4.84 (dd, *J* = 16.0, 4.0 Hz, 1H, ArC^{a}$\underline{H}_2$OH), 4.76 (dd, *J* = 12.0, 4.0 Hz, 1H, ArC^{b}$\underline{H}_2$OH), 4.54 (dd, *J* = 12.0, 8.0 Hz, 1H, ArC^{a}$\underline{H}_2$OH), 4.46-4.56 (m, 1H, N$\underline{H}$), 4.40 (dd, *J* = 12.0, 8.0 Hz, 1H, ArC^{b}$\underline{H}_2$OH), 3.98 (ddd, *J* = 16.0, 8.0, 4.0 Hz, 1H, ^{a}H-1), 3.84 (ddd, *J* = 12.0, 8.0, 4.0 Hz, 1H, ^{a}H-1), 3.40-3.44 (m, 2H, ^{a,b}H-3), 3.19 (ddd, *J* = 16.0, 12.0, 4.0 Hz, 1H, ^{b}H-1), 3.05-3.12 (m, 2H, ^{b}H-1), 2.97-3.02 (m, 1H, O$\underline{H}$), 2.68 (dd, *J* = 16.0, 8.0 Hz, 1H, C3-C^{a}$\underline{H}_2$Ar), 2.47-2.59 (m, 3H, C3-C^{a,b}$\underline{H}_2$Ar), 2.45 (s, 6H, ArC^{a,b}$\underline{H}_3$), 2.41 (s, 6H, ArC^{a,b}$\underline{H}_3$), 1.68-1.78 (m, 2H, ^{b}H-2), 1.52-1.58 (m, 1H, ^{a}H-2), 1.35-1.43 (m, 1H, ^{a}H-2)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 144.0 (C-Ar), 143.4 (C-Ar), 142.4 (C-Ar), 142.1 (C-Ar), 137.7 (C-Ar), 137.6 (C-Ar), 137.2×2 (C-Ar), 136.2×2 (C-Ar), 134.1 (C-Ar), 133.9 (C-Ar), 131.1 (C-Ar), 131.0 (C-Ar), 129.7×5 (CH-Ar), 129.6×4 (CH-Ar), 129.3×6 (CH-Ar), 128.9×2 (CH-Ar), 128.6×4 (CH-Ar), 128.3 (CH-Ar), 128.1×4 (CH-Ar), 127.2 (CH-Ar), 126.9×2 (CH-Ar), 126.8×3 (CH-Ar), 117.2 (CH-Ar), 116.0 (CH-Ar), 60.9×2 (Ar^{a,b}$\underline{C}H_2$OH), 52.9 and 53.0 (^{a,b}C-3×2), 49.3 (^{a}C-1), 49.1 (^{b}C-1), 41.3 (C2-^{a}$\underline{C}H_2$Ar), 40.7 (C3-^{b}$\underline{C}H_2$Ar), 33.7 (^{a}C-2), 33.6 (^{b}C-2), 21.6 (Ar^{a,b}$\underline{C}H_3$), 21.5 (Ar^{a,b}$\underline{C}H_3$)

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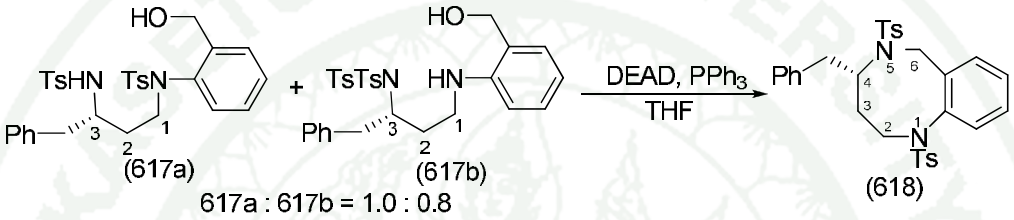
MS (CI^+), *m/z* (relative intensity): 579 ($[M+H]^+$, 8 %), 561 (100), 260 (82)

HRMS (CI^+) *m/z*: $C_{31}H_{35}N_2O_5S_2$ $[M+H]^+$, calcd 579.1987, found 579.1974

(*S*)-4-Benzyl-1,5-ditosyl-1,2,3,4,5,6-hexahydrobenzo[*b*][1,5]diazocine (618)



To a stirred solution of a mixture of amine **617a** and **617b** (90 mg, 0.16 mmol) and triphenylphosphine (40.8 mg, 0.16 mmol) in anhydrous THF (3.0 mL) under atmosphere of nitrogen was added DEAD (0.024 mL, 0.16 mmol, in THF (3.0 mL)) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 1 additional hour. It was then allowed to warm to room temperature and was stirred for an additional 14 hours. The reaction mixture was stirred with a 1:1 mixture of hexane:diethyl ether, and the triphenylphosphine oxide that precipitated was filtered off. The organic solvent was removed in vacuum, the mixture was diluted with 15 mL of water, then extracted with EtOAc (3 x 25 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 1:4) to afford benzodiazocine derivative **618** (75.9 mg, 87%) as a white solid; m.p. 174-176°C; $[\alpha]_D^{25}$ -4.0 (c = 1.0, CH_2Cl_2).

FTIR (neat), ν_{max}, cm^{-1}: 1494, 1340, 1157, 1089

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.78 (d, *J* = 8.0 Hz, 1H, Ar(H)), 7.66 (d, *J* = 8.0 Hz, 2H, Ar(H)), 7.59 (d, *J* = 8.0 Hz, 2H, Ar(H)), 7.39 (ddd, *J* = 8.0, 8.0, 2.0 Hz, 1H, Ar(H)), 7.33 (d, *J* = 8.0 Hz, 2H, Ar(H)), 7.19-7.29 (m, 8H, Ar(H)), 6.55 (d, *J* = 8.0 Hz, 1H, Ar(H)), 4.74 (s, 2H, H-6), 4.31-4.38 (m, 2H, H-2 and H-4), 3.49 (dd, *J* = 12.0, 12.0 Hz, 1H, C4-C$\underline{H}_2$Ar), 2.97 (dd, *J* = 12.0, 4.0 Hz, 1H, H-2), 2.74 (dd, *J* =

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12.0, 4.0 Hz, 1H, C4-C$\underline{H}_2$Ar), 2.47 (s, 3H, ArC$\underline{H}_3$), 2.39 (s, 3H, ArC$\underline{H}_3$), 1.66-1.69 (m, 1H, H-3), 1.46-1.56 (m, 1H, H-3)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 143.9 (C-Ar), 143.1 (C-Ar), 140.6 (C-Ar), 138.0 (C-Ar), 137.8 (C-Ar), 137.6 (C-Ar), 132.2 (C-Ar), 129.7×4 (CH-Ar), 129.6×3 (CH-Ar), 129.5 (CH-Ar), 128.9×3 (CH-Ar), 128.6×2 (CH-Ar), 127.7 (CH-Ar), 127.0×2 (CH-Ar), 126.4 (CH-Ar), 56.1 (C-4), 48.5 (C-2), 43.6 (C-6), 34.3 (C4-$\underline{C}H_2$Ar), 29.1 (C-3), 21.6 (Ar$\underline{C}H_3$), 21.5 (Ar$\underline{C}H_3$)

MS (CI^+), *m/z* (relative intensity): 561 ($[M+H]^+$, 90 %), 469 (100), 85 (68)

HRMS (CI^+) *m/z*: $C_{31}H_{33}N_2O_4S_2$ $[M+H]^+$, calcd 561.1882, found 561.1865

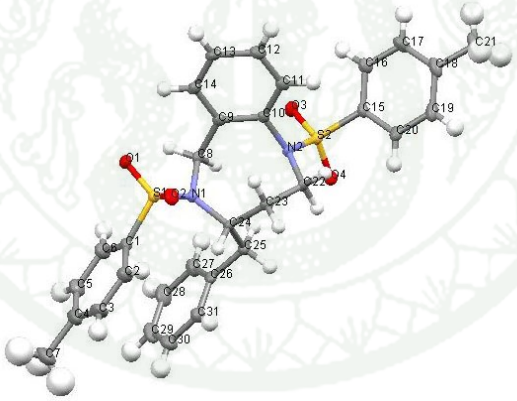

Figure 12 The X-ray crystal structure of (*S*)-4-benzyl-1,5-ditosyl-1,2,3,4,5,6-hexahydrobenzo[*b*][1,5] diazocine (618): Crystal data for **618**: $C_{32}H_{34}Cl_2N_2O_4S_2$, MW = 645.63, monoclinic, space group $P2_1$, a = 15.7605(7), 6.5470(3), c = 15.9408(7) Å, V = 1555.27(12) Å^3, α = 90.00, β = 108.995(2), γ = 90.00 ^{o}, Z = 2, D_c = 1.379 g cm^{-1}, Cu-Kα radiation, λ = 1.5418 Å, μ = 0.383 mm^{-1}, T = 100 K; colourless prism, 0.50×0.02×0.02mm, Bruker-AXS D8 diffractometer, 27151 reflections were collected, 7049 were unique, R_{int} = 0.0486; refinement on F2 gave R = 0.0436 and R_w = 0.1023, GOF = 1.087 for refined parameters.

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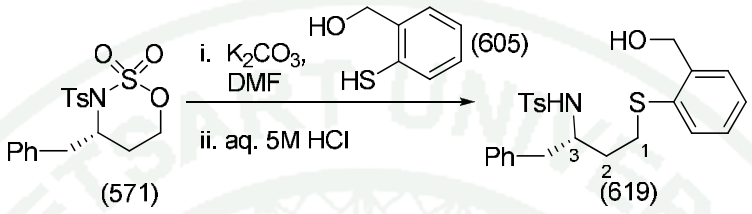
(*S*)-*N*-(4-(2-(Hydroxymethyl)phenylthio)-1-phenylbutan-2-yl)-4-methylbenzene sulfonamide (619)



To a solution of 2-mercaptobenzyl alcohol (605) (73.6 mg, 0.52 mmol) in anhydrous DMF (3.14 mL) was added K_2CO_3 (72.5 mg, 0.52 mmol) and the mixture was stirred at room temperature for 15 minutes. Cyclic sulfamidate **571** (100 mg, 0.26 mmol) was added and the mixture was stirred at room temperature for a further 24 hours prior to the addition of aqueous 5 M HCl (1.0 mL). The mixture was stirred at room temperature for 2 hours, then diluted with aqueous 1 M NaOH (30 mL) and extracted with Et_2O (3 × 25 mL). The organic extracts were combined, washed with aqueous 1 M NaOH (3 × 25 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 2:3) to afford the product **619** (97.8 mg, 84%) as a colorless oil; $[\alpha]_D^{25}$ -15.0 (c = 1.9, CH_2Cl_2).

FTIR (neat), ν_{max}, cm^{-1}: 3496, 3272, 1454, 1440, 1320, 1155, 1088

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.74 (d, *J* = 8.0 Hz, 2H, Ar(H)), 7.44-7.46 (m, 1H, Ar(H)), 7.22-7.34 (m, 8H, Ar(H)), 7.04 (d, *J* = 8.0 Hz, 1H, Ar(H)), 7.03 (d, *J* = 8.0 Hz, 1H, Ar(H)), 4.77-4.85 (m, 1H, NH), 4.78 (d, *J* = 8.0 Hz, 2H, ArCH_2OH), 3.66-3.69 (m, 1H, H-3), 2.96 (ddd, *J* = 9.0, 8.0, 4.0 Hz, 1H, H-1), 2.80-2.87 (m, 1H, H-1), 2.76 (dd, *J* = 16.0, 4.0 Hz, 1H, C3-CH_2Ar), 2.70 (dd, *J* = 12.0, 8.0 Hz, 1H, C3-CH_2Ar), 2.48 (s, 3H, ArCH_3), 2.40-2.44 (m, 1H, OH), 1.80-1.87 (m, 1H, H-2), 1.65-1.78 (m, 1H, H-2)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 143.5 (C-Ar), 140.9 (C-Ar), 137.7 (C-Ar), 134.3 (C-Ar), 130.2 (C-Ar), 129.9×3 (CH-Ar), 129.6×2 (CH-Ar), 128.8×2 (CH-Ar),

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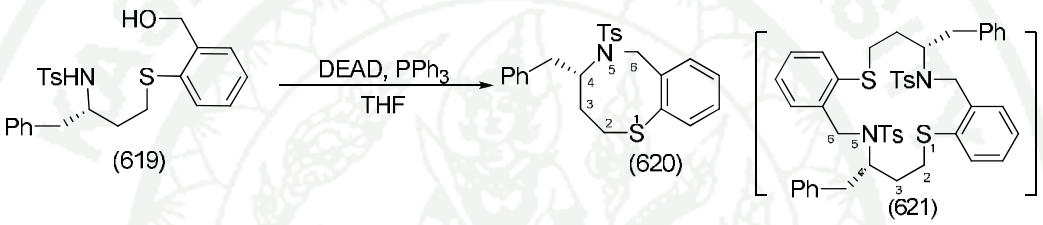
128.6 (CH-Ar), 128.4 (CH-Ar), 127.1×2 (CH-Ar), 126.9 (CH-Ar), 126.8 (CH-Ar), 63.7 (Ar<u>C</u>H_2OH), 54.3 (C-3), 41.7 (C3-<u>C</u>H_2Ar), 33.6 (C-2), 30.4 (C-1), 21.7 (Ar<u>C</u>H_3)

HRMS (ESI$^+$) *m/z*: $C_{24}H_{27}NO_3S_2Na$ $[M+Na]^+$, calcd 464.1324, found 464.1318

(*S*)-4-Benzyl-5-tosyl-3,4,5,6-tetrahydro-2H-benzo[*b*][1,5]thiazocine (620)



To a stirred solution of amine **619** (40.0 mg, 0.09 mmol) and triphenylphosphine (23.8 mg, 0.09 mmol) in anhydrous THF (2.0 mL) under atmosphere of nitrogen was added DEAD (0.014 mL, 0.09 mmol, in THF (2.0 mL)) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 1 additional hour. It was then allowed to warm to room temperature and was stirred for an additional 14 hours. The reaction mixture was stirred with a 1:1 mixture of hexane:diethyl ether, and the triphenylphosphine oxide that precipitated was filtered off. The organic solvent was removed in vacuum, the mixture was diluted with 15 mL of water, then extracted with EtOAc (3 x 25 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane, 1:4). The benzothiazocine derivative **620** was not observed, only 16-membered compound **621** was obtained as a white solid (27.6 mg, 72%); m.p. 85-87 °C; $[\alpha]_D^{24}$ +26.7 (c = 0.3, CH_2Cl_2).

Compound 621

FTIR (neat), ν_{max}, cm^{-1}: 1340, 1157, 1093

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^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.80 (d, *J* = 8.0 Hz, 4H, Ar(H)), 7.76 (d, *J* = 8.0 Hz, 2H, Ar(H)), 7.33 (d, *J* = 8.0 Hz, 4H, Ar(H)), 7.17-7.24 (m, 8H, Ar(H)), 7.09 (ddd, *J* = 8.0, 8.0, 2.0 Hz, 2H, Ar(H)), 6.99 (dd, *J* = 8.0, 2.0 Hz, 2H, Ar(H)), 6.92 (dd, *J* = 8.0, 4.0 Hz, 4H, Ar(H)), 4.59 (d, *J* = 16.0 Hz, 2H, TsNC$\underline{H}_2$Ar), 4.45 (d, *J* = 16.0 Hz, 2H, TsNC$\underline{H}_2$Ar), 3.80-3.86 (m, 2H, H-4), 2.82 (dd, *J* = 12.0, 4.0 Hz, 2H, C4-C$\underline{H}_2$Ar), 2.38 (s, 6H, ArC$\underline{H}_3$), 2.13-2.26 (m, 4H, H-2, C4-C$\underline{H}_2$Ar), 1.65-1.81 (m, 4H, H-2, H-3), 1.22-1.33 (m, 2H, H-3)

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 143.7 (C-Ar), 138.3 (C-Ar), 137.8 (C-Ar), 130.6 (C-Ar), 130.4 (C-Ar), 129.9×3 (CH-Ar), 129.0×2 (CH-Ar), 128.5×3 (CH-Ar), 128.1 (CH-Ar), 127.0×3 (CH-Ar), 126.6 (CH-Ar), 60.5 (C-4), 44.4 (TsN$\underline{C}H_2$Ar), 42.6 (C4-$\underline{C}H_2$Ar), 31.5 (C-3), 31.3 (C-2), 21.5 (Ar$\underline{C}H_3$)

HRMS (ESI^+) *m/z*: $C_{48}H_{50}N_2O_4S_4Na$ $[M+Na]^+$, calcd 869.2546, found 869.2523

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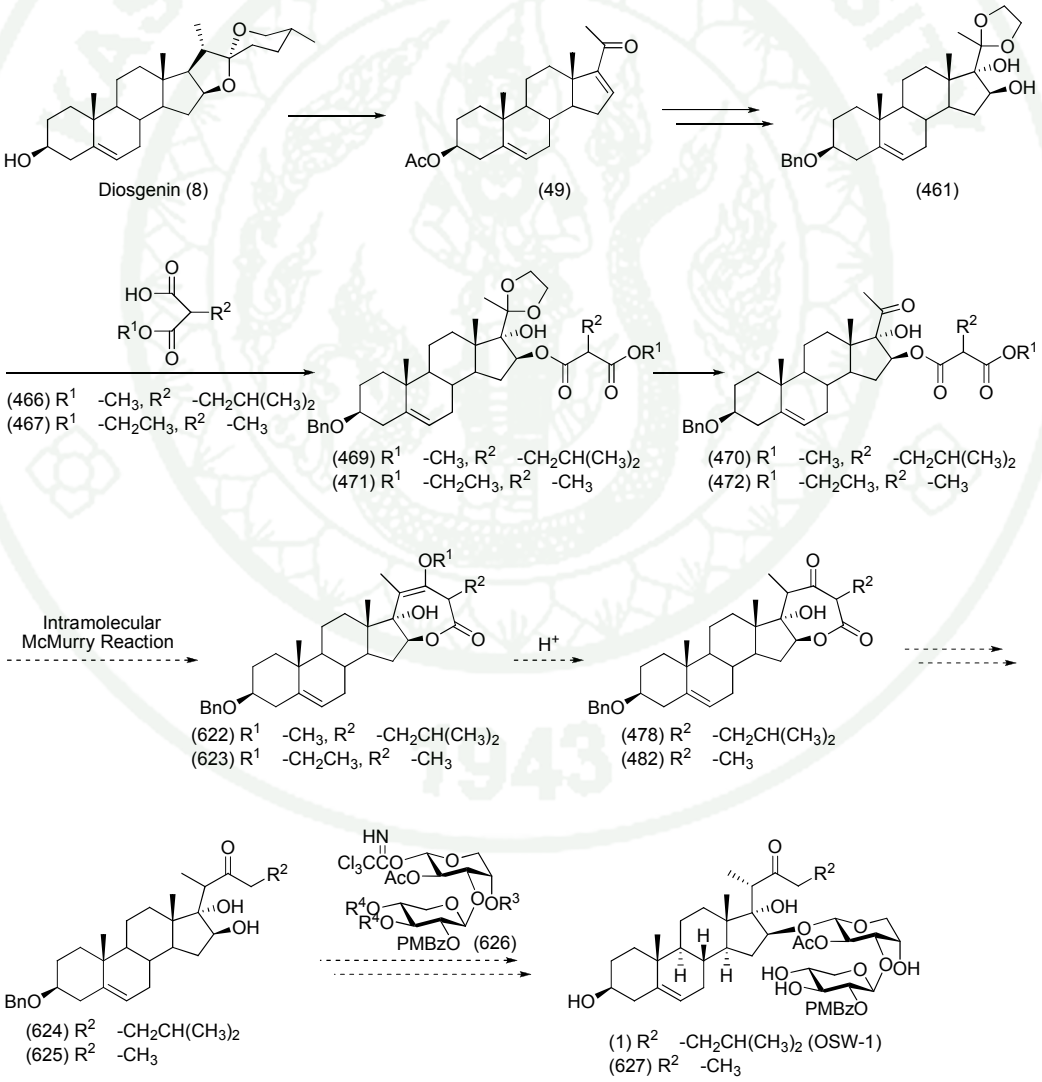
RESULTS AND DISCUSSION

Results

1. Synthesis of steroidal OSW-1 intermediates

1.1 Synthesis of steroidal OSW-1 intermediates for intramolecular strategy



Scheme 71

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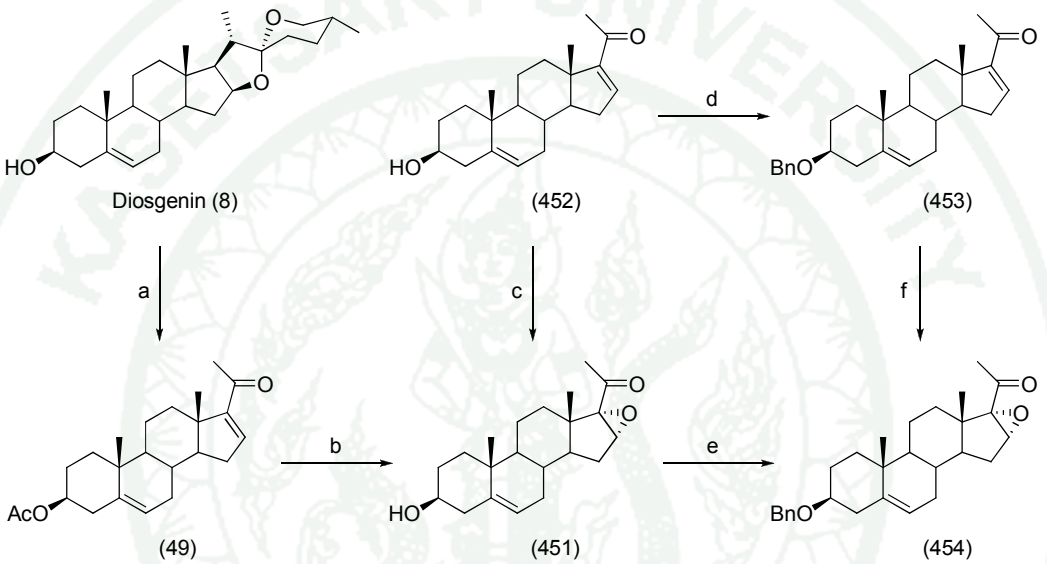
Preparation of 20-ketal-3β-benzyloxy-16β,17α-dihydroxy-pregnenolone (461)

Conversion of diosgenin (8) and 16-dehydropregnenolone (452) to 3β-benzyloxy-16α,17α-epoxy-pregnenolone (454) was shown in Scheme 72.



Scheme 72

Reagents and conditions:

a) i) Ac_2O, pyr., NH_4Cl, 135°C, 12h

ii) CrO_3, AcOH, 1, 2-dichloroethane, H_2O, 0°C-rt, 2h

iii) Al_2O_3, benzene, rt, 16h, 48% (3 steps)

b) 30% H_2O_2, 2.5M NaOH, MeOH, rt, 16h, 97%

c) 30% H_2O_2, 2.5M NaOH, MeOH, rt, 16h, 87%

d) NaH, BnBr, THF, reflux, 12h, 39%

e) NaH, BnBr, THF, DMF, reflux, 12h, 42%

f) 30% H_2O_2, 2.5M NaOH, MeOH, rt, 4h, 80%

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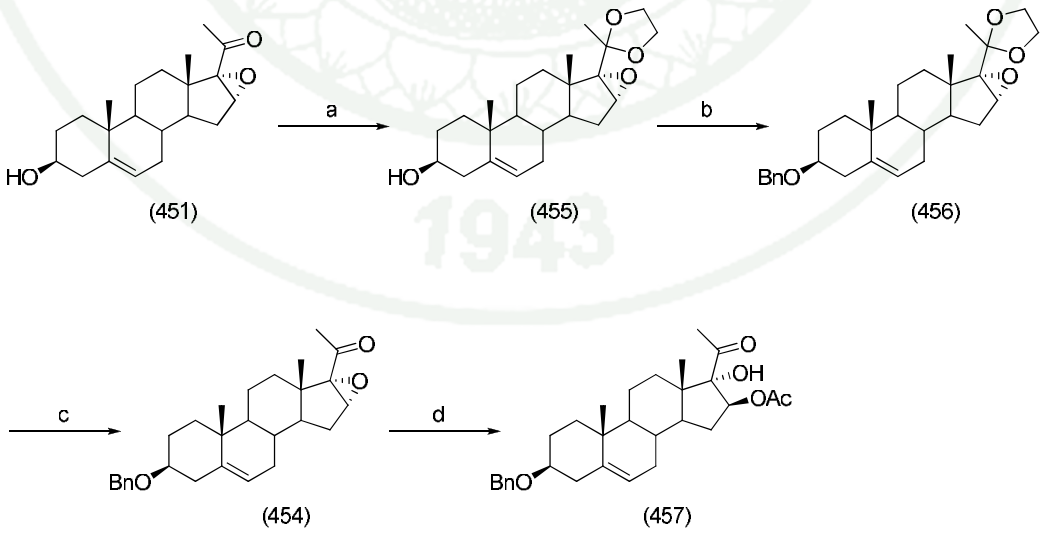
Table 10 Benzylation of 16-dehydropregnenolone (452) and 16α,17α-epoxy-pregnenolone (451).

Entry	Starting material	conditions	Results
1	**452**	NaH, BnBr, THF, DMF, rt, 12h	complex mixture
2	**452**	NaH, BnBr, THF, DMF, *n*BuNI, rt, 48h	complex mixture
3	**452**	NaH, BnBr, THF, reflux, 12h	39%, unknown compound and recovered starting material
4	**451**	NaH, BnBr, THF, HMPA, *n*BuNBr, 0°C – rt, 5h	complex mixture and recovered starting material
5	**451**	NaH, BnBr, THF, DMF, reflux, 6h	42% and recovered starting material

Conversion of 16α,17α-epoxy-pregnenolone (451) to 3β-benzyloxy-16β-acetyloxy-17α-hydroxy-pregnenolone (457) was shown in Scheme 73.



Scheme 73

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Reagents and conditions:

a) 1, 2-ethanediol, *p*-TsOH·H_2O, $CH(OEt)_3$, CH_2Cl_2, rt, 7h, 100%

b) NaH, BnBr, THF, DMF, rt, 16h, 92%

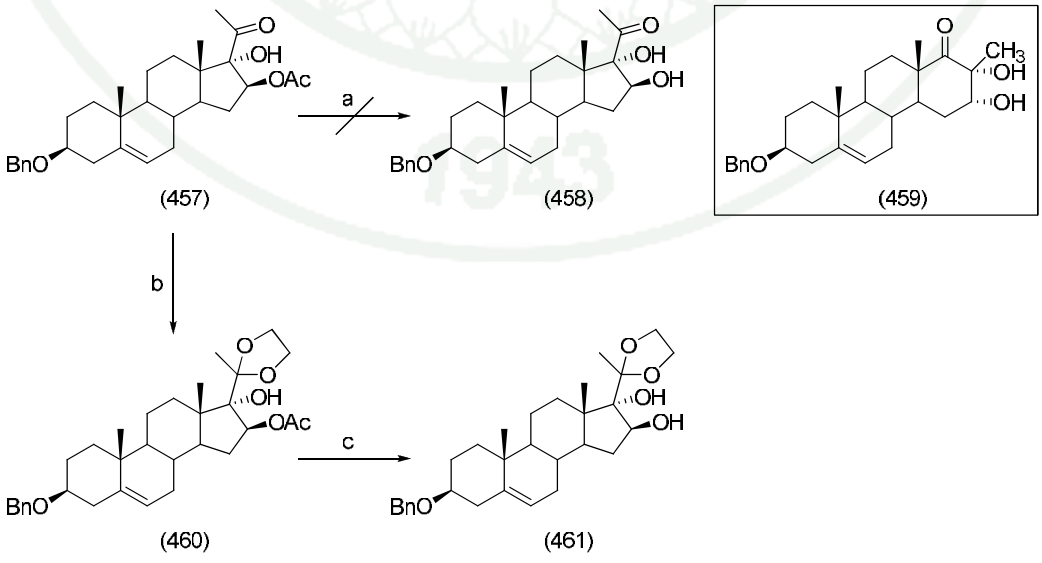
c) *p*-TsOH·H_2O, CH_2Cl_2 (86%) or THF, rt, 3h, 100%

d) 20%H_2SO_4 in AcOH, rt, 2h, 48%

Table 11 Epoxide ring opening of 3β-benzyloxy-16α,17α-epoxy-pregnenolone (454) to 3β-benzyloxy-16β-acetyloxy-17α-hydroxy-pregnenolone (457).

Entry	conditions	Results
1	20%H_2SO_4 in Ac_2O, rt, 2h	complex mixture
2	NaOAc, AcOH, 65°C, 7h	small amout of product and unknown compound
3	20%H_2SO_4 in AcOH, rt, 2h	48%

Conversion of 3β-benzyloxy-16β-acetyloxy-17α-hydroxy-pregnenolone (457) to 20-ketal-3β-benzyloxy-16β,17α-dihydroxy-pregnenolone (461) was shown in Scheme 74.



Scheme 74

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Reagents and conditions:

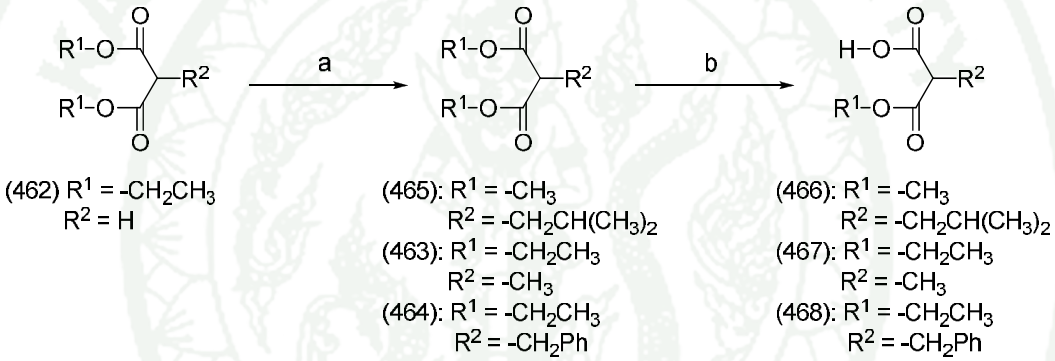
a) 2.5N KOH, MeOH, THF, rt, 6h, 55%

b) 1, 2-ethanediol, *p*-TsOH·H_2O, $CH(OEt)_3$, CH_2Cl_2, rt, 10h, 94%

c) 2.5N KOH, MeOH, THF, rt, 5h, 87%

Preparation of side chain part

The preparations of side chain moieties were shown in Scheme 75



Scheme 75

Reagents and conditions:

a) **463**; MeI, K_2CO_3, acetone, 60°C, 6h, 51%

464; NaH, BnBr, THF, reflux, 18h, 57%

b) **466**; 1.8N KOH, MeOH, 0°C, 6h, 75%

467; 1.8N KOH, EtOH, 0°C, 6h, 78%

468; 1.8N KOH, EtOH, 0°C, 6h, 76%

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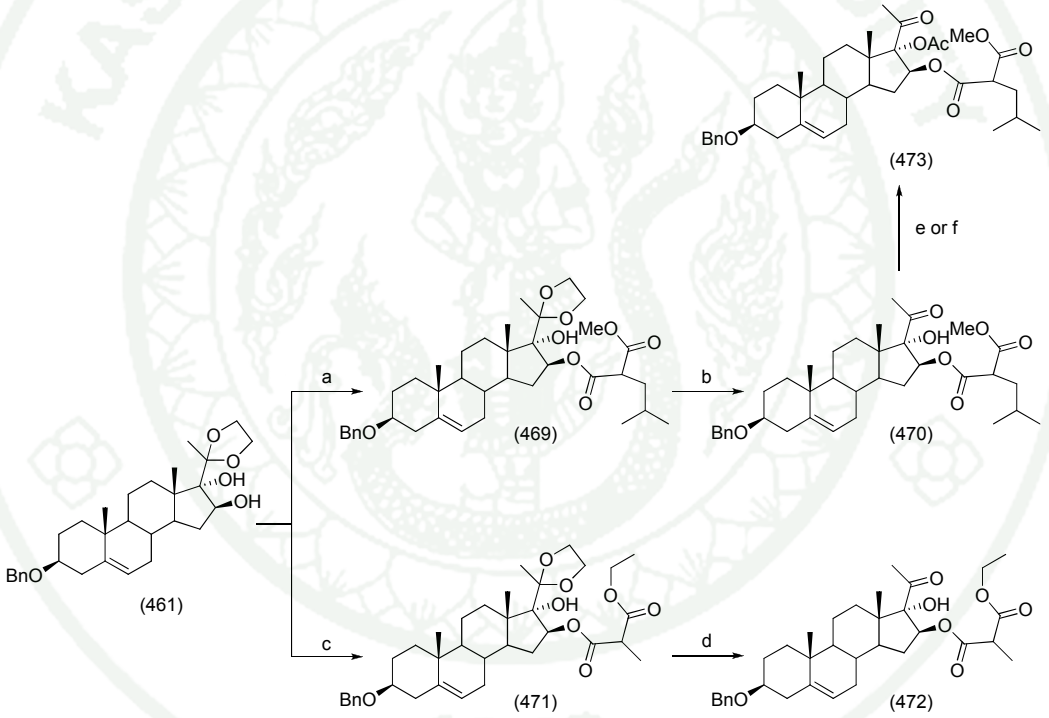
Conversion of 20-ketal-3β-benzyloxy-16β,17α-dihydroxy-pregnenolone (461) to 3β-benzyloxy-16β-(isobutyl-monomethyl ester malonate-ester)-17α-hydroxy-pregnenolone (470), 3β-benzyloxy-16β-(2-methyl-monoethyl ester malonate-ester)-17α-hydroxy-pregnenolone (472) and 3β-benzyloxy-16β-(isobutyl-monomethyl ester malonate-ester)-17α-acetyloxy-pregnenolone (473) was shown in Scheme 76.



Scheme 76

Reagents and conditions:

a) 2-Isobutyl-malonic acid monomethyl ester (466), DCC, DMAP, CH_2Cl_2, rt, 3h, 100%

b) *p*-TsOH·H_2O, THF, rt, 2h, 62%

c) 2-methyl-malonic acid monoethyl ester (467), DCC, DMAP, CH_2Cl_2, rt, 5h, 100%

d) *p*-TsOH·H_2O, CH_2Cl_2, rt, 12h, 80%

e) Ac_2O, 70%$HClO_4$, dioxane, rt, 20 min, 62% and 21% recovered starting material

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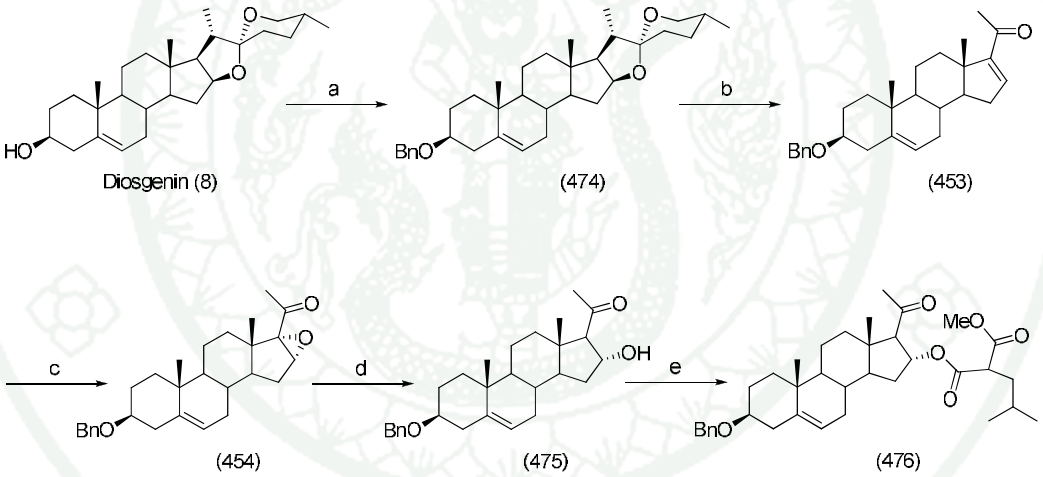
f) TFAA, AcOH, *p*-TsOH·H_2O, CH_2Cl_2, 0°C, 20 min, 71% and 23% recovered starting material

Preparation of 3β-benzyloxy-16α-(isobutyl-monomethyl ester malonate-ester)-pregnenolone (476)

Steroid part, 3β-benzyloxy-16α-hydroxy-pregnenolone (475), synthesized from diosgenin (8), coupled with side chain moiety, 2-isobutyl-malonic acid monomethyl ester (466) to give 3β-benzyloxy-16α-(isobutyl-monomethyl ester malonate-ester)-pregnenolone (476) as presented in Scheme 77.



Scheme 77

Reagents and conditions:

a) NaH, BnBr, THF, DMF, reflux, 4h, 100%

b) i) Ac_2O, pyr., NH_4Cl, 135°C, 12h

ii) CrO_3, AcOH, 1, 2-dichloroethane, H_2O, 0°C-rt, 2h

iii) Al_2O_3, benzene, rt, 24h, 35% (3 steps)

c) 30% H_2O_2, 2.5M NaOH, MeOH, rt, 4h, 80%

d) $NH_2NH_2·H_2O$, EtOH, CH_2Cl_2, 0°C – rt, 5h, 53%

e) 2-Isobutyl-malonic acid monomethyl ester (466), DCC, DMAP, CH_2Cl_2, rt, 3h, 64%

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1.2 Intramolecular McMurry Reaction

The results of intramolecular McMurry coupling reaction of steroidal intermediates **457**, **470**, **472**, **473** and **476** were summarized in Table 12.

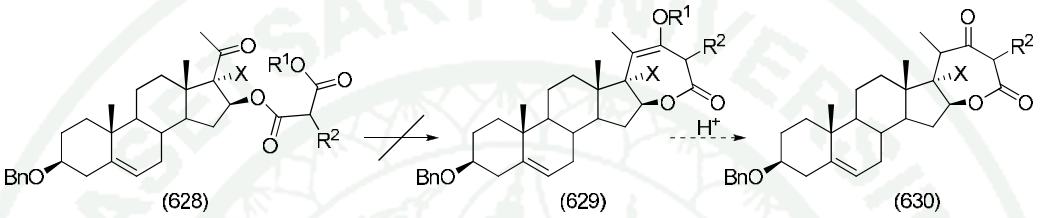


Table 12 Intramolecular McMurry reactions of steroidal intermediates **457**, **470**, **472**, **473** and **476**.

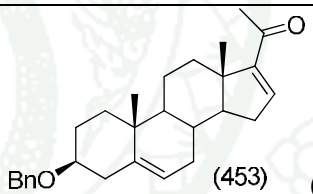
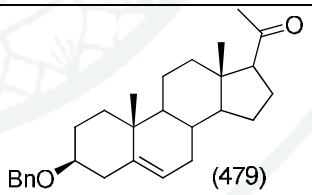
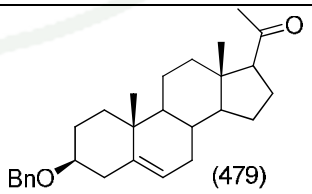
Entry	Starting material	conditions	Results
1	**476**: 16α-isomer X = H, R^1 = -CH_3, R^2 = -$CH_2CH(CH_3)_2$	$TiCl_4$, $LiAlH_4$, THF, reflux, 24h	 (453) (100%)
2	**470**: X = OH, R^1 = -CH_3, R^2 = -$CH_2CH(CH_3)_2$	$TiCl_4$, Zn, pyridine, THF, reflux, 8h	 (479) (17%) recovered starting material (69%)
3	**470**: X = OH, R^1 = -CH_3, R^2 = -$CH_2CH(CH_3)_2$	$TiCl_4$, Zn-Cu, THF, reflux, 10 min	 (479) (67%)
4	**470**: X = OH, R^1 = -CH_3, R^2 = -$CH_2CH(CH_3)_2$	$TiCl_4$, $LiAlH_4$, THF, reflux, 8h	un-interpreted compounds (480) and (481) (16%) recovered starting material (38%)

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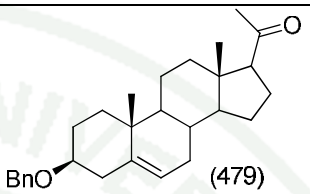
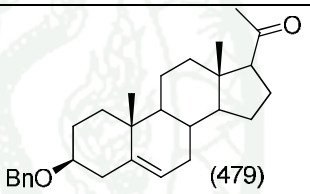
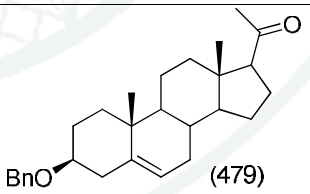
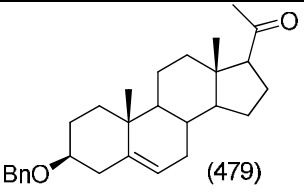
Table 12 (Continued)

Entry	Starting material	conditions	Results
5	**470**: X = OH, R^1 = -CH_3, R^2 = -$CH_2CH(CH_3)_2$	$TiCl_4$, Mg, Naphthalene, THF, reflux,	 (479) (85%)
6	**472**: X = OH, R^1 = -CH_2CH_3, R^2 = -CH_3	$TiCl_4$, $LiAlH_4$, THF, reflux,	complex mixture
7	**472**: X = OH, R^1 = -CH_2CH_3, R^2 = -CH_3	$TiCl_4$, Li, Naphthalene, THF, reflux,	 (479) (18%)
8	**473**: X = OAc, R^1 = -CH_3, R^2 = -$CH_2CH(CH_3)_2$	$TiCl_4$, $LiAlH_4$, THF, reflux,	recovered starting material (87%)
9	**473**: X = OAc, R^1 = -CH_3, R^2 = -$CH_2CH(CH_3)_2$	$TiCl_4$, Mg, Naphthalene, THF, reflux,	 (479) (42%) recovered starting material (27%)
10	**457**: 16β-OAc X = OH	$TiCl_4$, Zn, pyridine, THF, reflux	 (479) (23%) un-interpreted compound (11%) recovered starting material (41%)

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1.3 Samarium diiodide-promoted intramolecular keto-ester coupling reaction

The results of samarium diiodide-promoted intramolecular keto-ester coupling reaction of steroidal intermediates **457** and **470** were summarized in Table 13.

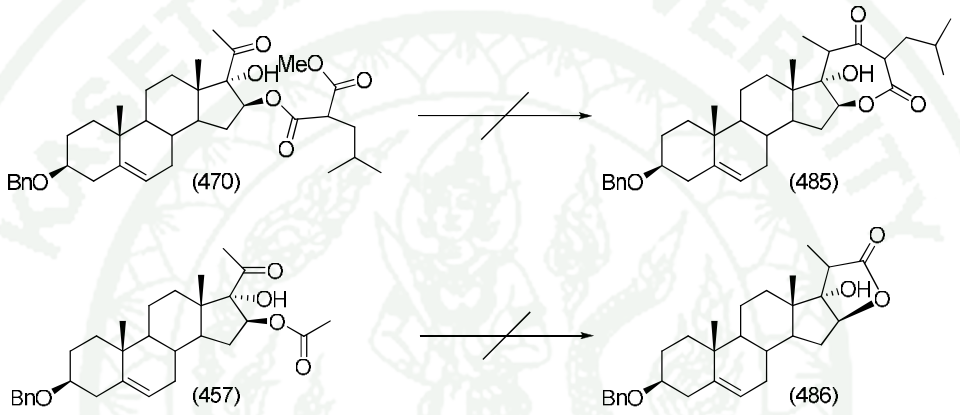
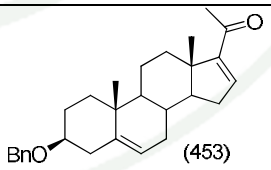
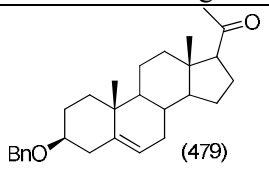
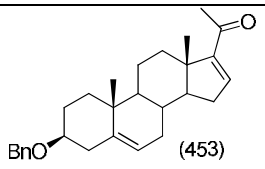


Table 13 The reaction conditions for samarium diiodide-promoted intramolecular ketone-ester coupling reaction.

Entry	Starting	Conditions	Results
1	**470**	SmI_2, THF, -78°C, 3h	recovered starting material (95%)
2	**470**	SmI_2, THF, 0°C, 10 min	 (453) (41%) and recovered starting material (38%)
3	**470**	SmI_2, THF, rt, 30 min	 (479) (76%)
4	**457**	SmI_2, THF, rt, 30 min	 (453) (11%) and recovered starting material (84%)

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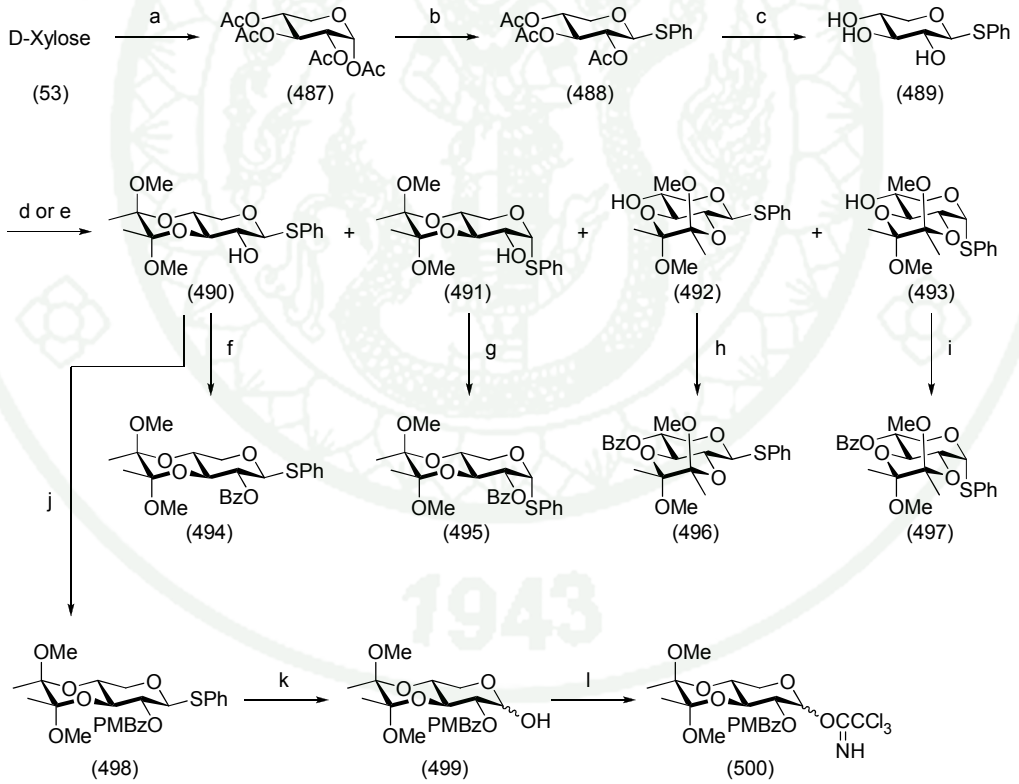
2. Synthesis of disaccharide moiety

2.1 Synthesis of D-xylopyranoside donor

Preparation of 1-α/β-trichloroacetimidyl-2-O-methoxybenzoyl-(2'S,3'S)-methyl-3,4-O-(2',3'-dimethoxybutane-2',3'-diyl)-D-xylopyranoside (500)

Conversion of D-xylose (53) to trichloroacetimidate **500** and esterification of butanediacetal isomers **490**, **491**, **492** and **493** to confirm the definite structures were shown in Scheme 78.



Scheme 78

Reagents and conditions:

a) AcCl, pyridine, CH_2Cl_2, rt, 24h, 99%

b) PhSH, $SnCl_4$, CH_2Cl_2, 0°C - rt, 5h, 60%

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Reagents and conditions: (Continued)

c) NaOMe, MeOH, rt, 12h, 81%

d) 2,3-butadione, $CH(OEt)_3$, $BF_3{\cdot}OEt_2$, MeOH, 0°C – rt, 12h, 23% for **490**; 11% for **491**; 6% for **492**; 3% for **493**

e) 2,3-butadione, $CH(OMe)_3$, $BF_3{\cdot}OEt_2$, MeOH, rt, 12h, 75% for **490**

f) BzCl, DMAP, Et_3N, CH_2Cl_2, rt, 5h, 92%

g) BzCl, DMAP, Et_3N, CH_2Cl_2, rt, 2h, 99%

h) BzCl, DMAP, Et_3N, CH_2Cl_2, rt, 5h, 33%

i) BzCl, DMAP, Et_3N, CH_2Cl_2, rt, 5h, 30%

j) *p*-methoxybenzoic acid, DCC, DMAP, CH_2Cl_2, rt, 12h, 97%

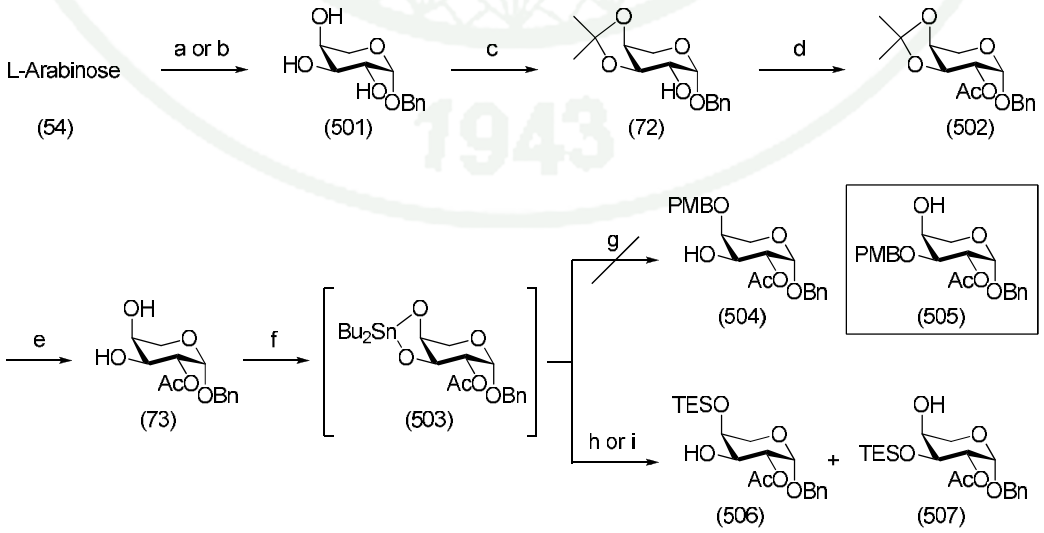
k) NBS, CH_2Cl_2:H_2O (9:1), rt, 1h, 79%

l) CCl_3CN, DBU, CH_2Cl_2, rt, 12h, 96%

2.2 Synthesis of L-arabinopyranoside acceptor

Preparation of benzyl 2-O-acetyl-4-O-triethylsilyl-β-L-arabinopyranoside (506)

Conversion of L-arabinose (54) to benzyl 2-*O*-acetyl-4-*O*-triethylsilyloxy-*β*-L-arabinopyranoside (506) *via* 3,4-stannylene **503** was shown in Scheme 79.



Scheme 79

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Reagents and conditions:

a) BnOH, HCl (g), rt, 24h, 70%

b) BnOH, AcCl, rt, 5h, 88%

c) $Me_2C(OMe)_2$, *p*-TsOH·H_2O, DMF, rt, 12h, 82%

d) Ac_2O, pyr., rt, 12h, 91%

e) 70%AcOH, 70°C, 1h, 96%

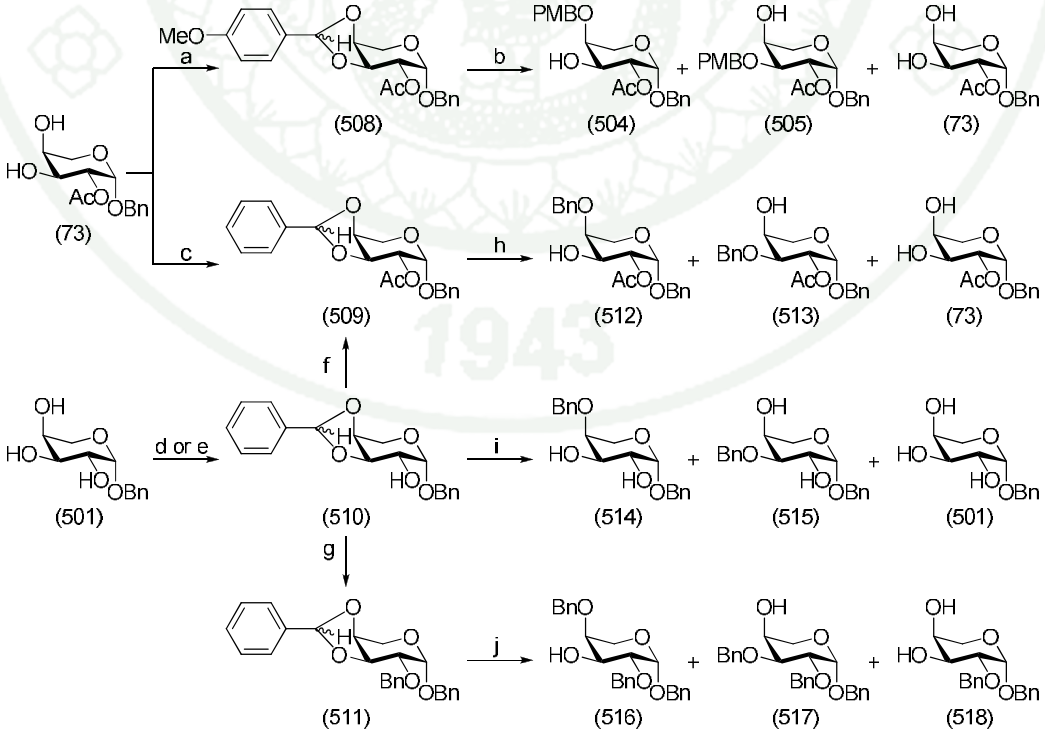
f) Bu_2SnO, toluene, reflux, 2h

g) PMBCl, CsF, KI, DMF, rt, 12h, 27% for **505**

h) TESCl, Et_3N, rt, 12h, 60% for **506**, 23% for **507**

i) TESCl, Et_3N, CH_2Cl_2, 63% for **506**, 3% for **507**

Preparation of benzyl 2-O-acetyl-4-O-p-methoxybenzyl-β-L-arabinopyranoside (504), benzyl 2-O-acetyl-4-O-benzyl-β-L-arabinopyranoside (512), benzyl 4-O-benzyl-β-L-arabinopyranoside (514) and benzyl 2-O-benzyl-4-O-benzyl-β-L-arabinopyranoside (516)



Scheme 80

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Reagents and conditions:

a) Anisaldehyde, *p*-TsOH·H_2O, $CH(OEt)_3$, CH_2Cl_2, rt, 16h, 34% for *exo*-isomer, 40% for *endo*-isomer

b) TMSOTf, $NaCNBH_3$, THF, 0°C, 15 min, 67% for **504** and 13% for recovered starting material

c) $C_6H_5CH(OMe)_2$, *p*-TsOH·H_2O, CH_3CN, rt, 6h, 16% for *exo*-isomer, 64% for *endo*-isomer and 5% for recovered starting material

d) $C_6H_5CH(OMe)_2$, *p*-TsOH·H_2O, CH_3CN, rt, 24h, 47% for a mixture of *exo*- and *endo*-isomer (4:5) and 37% for recovered starting material

e) $C_6H_5CH(OMe)_2$, *p*-TsOH·H_2O, DMF, rt, 24h, 77% for a mixture of *exo*- and *endo*-isomer (4:5) and 19% for recovered starting material

f) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 1h, 100%

g) BnBr, KOH, 50°C, 5h, 35% for *exo*-isomer and 43% for *endo*-isomer

h) $BF_3{\cdot}OEt_2$, Et_3SiH, CH_3CN, 0°C, 30 min, 69% for **512**

i) $BF_3{\cdot}OEt_2$, Et_3SiH, CH_3CN, 0°C, 10 min, 21% for **514** and 9% for **515**

j) $BF_3{\cdot}OEt_2$, Et_3SiH, CH_2Cl_2, 0°C, 30 min, 36% for **516**, 13% for **517** and 29% for **518**

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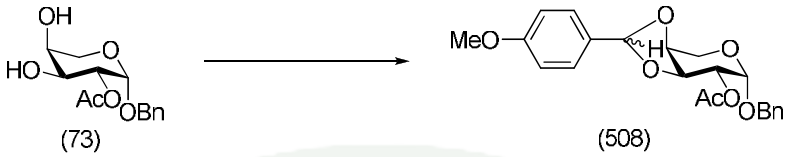

Table 14 The reaction conditions for conversion of benzyl 2-*O*-acetyl-*β*-L-arabino-pyranoside (73) to benzyl 2-*O*-acetyl-*exo*/*endo*-3,4-*O*-paramethoxy-benzylidene-*β*-L-arabinopyranosides (508).

Entry	conditions	Results		
		Exo-**508**	*Endo*-**508**	Starting material
1	Anisaldehyde, PPTS, CH_2Cl_2, reflux, 5h	-	-	89%
2	Anisaldehyde, *p*-TsOH·H_2O, $CH(OMe)_3$, CH_2Cl_2, rt, 16h	14%	18%	trace
3	Anisaldehyde, *p*-TsOH·H_2O, $CH(OMe)_3$, DMF, rt, 16h	18%	50%	trace
4	Anisaldehyde, *p*-TsOH·H_2O, $CH(OEt)_3$, CH_2Cl_2, rt, 16h	34%	40%	trace

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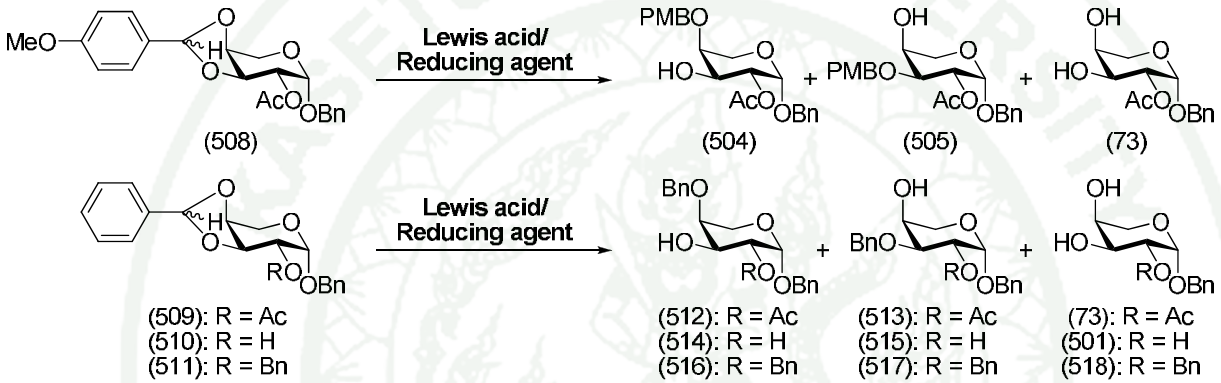


Table 15 Reductive cleavage of 3,4-*O*-paramethoxybenzylidene and 3,4-*O*-benzylidene acetals of benzyl *β*-L-arabinose derivatives.

Entry	Substrate (ratio)	Lewis acid	Reducing agent	Quantity (equiv)	Solv.	Temp(°C)/ time	Yield (%)			
							4-*O*-PMB or 4-*O*-Bzy type	3-*O*-PMB or 3-*O*-Bzy type	Hydrolysis type	Starting compd (%) (*exo:endo*)
1	**508***endo*	-	DIBAL-H	7.5	CH_2Cl_2	rt/16 h	-	-	-	69.0
2	**508***exo*	TFA	$NaCNBH_3$	2.0	DMF	15/15 min	-	46.0	38.0	-
3	**508***exo*	$BF_3{\cdot}OEt_2$	Et_3SiH	12.0	CH_2Cl_2	0/20 min	-	-	78.0	-
4	**508***exo*	$BF_3{\cdot}OEt_2$	$NaCNBH_3$	2.0	CH_2Cl_2	0/1 h	-	-	-	25.0
5	**508***exo*	$BF_3{\cdot}OEt_2$	$NaCNBH_3$	2.0	THF	0/1 h	3.0	-	-	73.0
6	**508***endo*	TMSOTf	$NaCNBH_3$	2.0	THF	0/15 min	67.0	-	-	13.0

Table 15 (Continued)

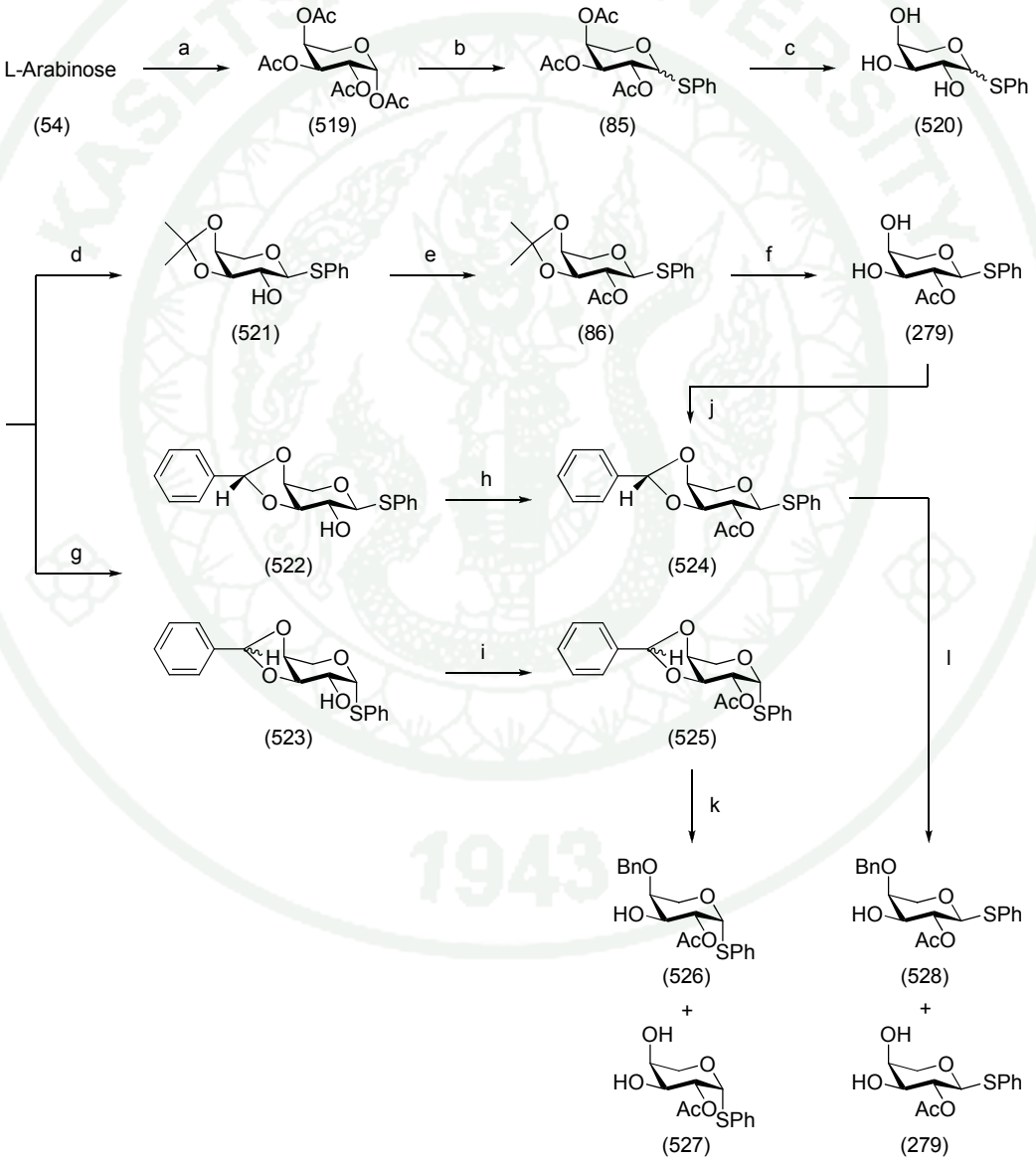
Entry	Substrate (ratio)	Lewis acid	Reducing agent	Quantity (equiv)	Solv.	Temp(°C)/ time	Yield (%)			
							4-*O*-PMB or 4-*O*-Bzy type	3-*O*-PMB or 3-*O*-Bzy type	Hydrolysis type	Starting compd (%) (*exo:endo*)
7	**508***endo*	TMSOTf	BH_3·THF	5.0	CH_2Cl_2	0/4 h	30.0	-	61.0	-
8	**509***exo/endo* (1:4)	$TiCl_4$	Et_3SiH	1.35	CH_2Cl_2	-78/5 h	41.0	20.2	-	17.0
9	**509***exo/endo* (1:4)	BF_3·OEt_2	Et_3SiH	12.0	CH_2Cl_2	-78/10 min	53.3	Trace	5.43	-
10	**509***exo/endo* (1:4)	BF_3·OEt_2	Et_3SiH	12.0	CH_2Cl_2	0/1 h	52.5	Trace	21.6	-
11	**509***exo/endo* (1:4)	BF_3·OEt_2	Et_3SiH	12.0	CH_3CN	0/30 min	69.4	Trace	trace	-
12	**509***endo*	BF_3·OEt_2	Et_3SiH	12.0	CH_3CN	0/30 min	57.9	Trace	31.0	-
13	**509***exo*	BF_3·OEt_2	Et_3SiH	12.0	CH_3CN	0/30 min	64.3	Trace	20.5	-
14	**509***exo/endo* (1:4)	$Cu(OTf)_2$	Et_3SiH	2.0	CH_3CN	0/30 min	-	-	64.2	-
15	**509***endo*	$Cu(OTf)_2$	Et_3SiH	2.0	CH_2Cl_2	rt/24 h	-	-	48.5	Trace (1:1)
16	**509***endo*	$Cu(OTf)_2$	Et_3SiH	12.0	CH_2Cl_2	rt/24 h	-	-	58.4	-
17	**509***exo/endo* (1:4)	$Cu(OTf)_2$	BH_3·THF	5.0	CH_3CN	rt/24 h	18.1	-	23.4	54.7 (2:1)
18	**509***exo/endo* (1:4)	$Cu(OTf)_2$	BH_3·THF	5.0	CH_2Cl_2	rt/1.25 min	47.6	28.7	-	-
19	**509***exo/endo* (1:4)	$Cu(OTf)_2$	BH_3·THF	5.0	-	rt/24 h	45.6	28.7	-	-
20	**510***exo/endo* (4:5)	BF_3·OEt_2	Et_3SiH	12.0	CH_3CN	0/10 min	20.7	9.1	-	-

Table 15 (Continued)

Entry	Substrate (ratio)	Lewis acid	Reducing agent	Quantity (equiv)	Solv.	Temp(°C)/ time	Yield (%)			
							4-*O*-PMB or 4-*O*-Bzy type	3-*O*-PMB or 3-*O*-Bzy type	Hydrolysis type	Starting compd (%) (*exo:endo*)
21	**511***endo*	$BF_3{\cdot}OEt_2$	Et_3SiH	12.0	CH_2Cl_2	0/30 min	36.3	12.8	29.5	-
22	**511***exo*	$BF_3{\cdot}OEt_2$	Et_3SiH	12.0	CH_2Cl_2	0/30 min	25.9	23.4	35.5	-

Preparation of thiophenyl 2-O-acetyl-4-O-benzyl-β/α-L-arabinopyranoside (526 and 528)

Conversion of L-arabinose (54) to thiophenyl 2-*O*-acetyl-4-*O*-benzyl-*β*/*α*-L-arabinopyranoside (526 and 528) was shown in Scheme 81.



Scheme 81

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Reagents and conditions:

a) AcCl, pyridine, CH_2Cl_2, rt, 24h, 100%

b) PhSH, $SnCl_4$, CH_2Cl_2, 0°C - rt, 4h, 82%

c) NaOMe, MeOH, 0°C - rt, 3h, 71%

d) $Me_2C(OMe)_2$, *p*-TsOH·H_2O, CH_2Cl_2, rt, 3h, 86%

e) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 2h, 91%

f) 70%AcOH, 70°C, 1h, 96%

g) $C_6H_5CH(OMe)_2$, *p*-TsOH·H_2O, DMF, rt, 12h, 49% for **522** and 22% for **523**

h) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 2h, 95%

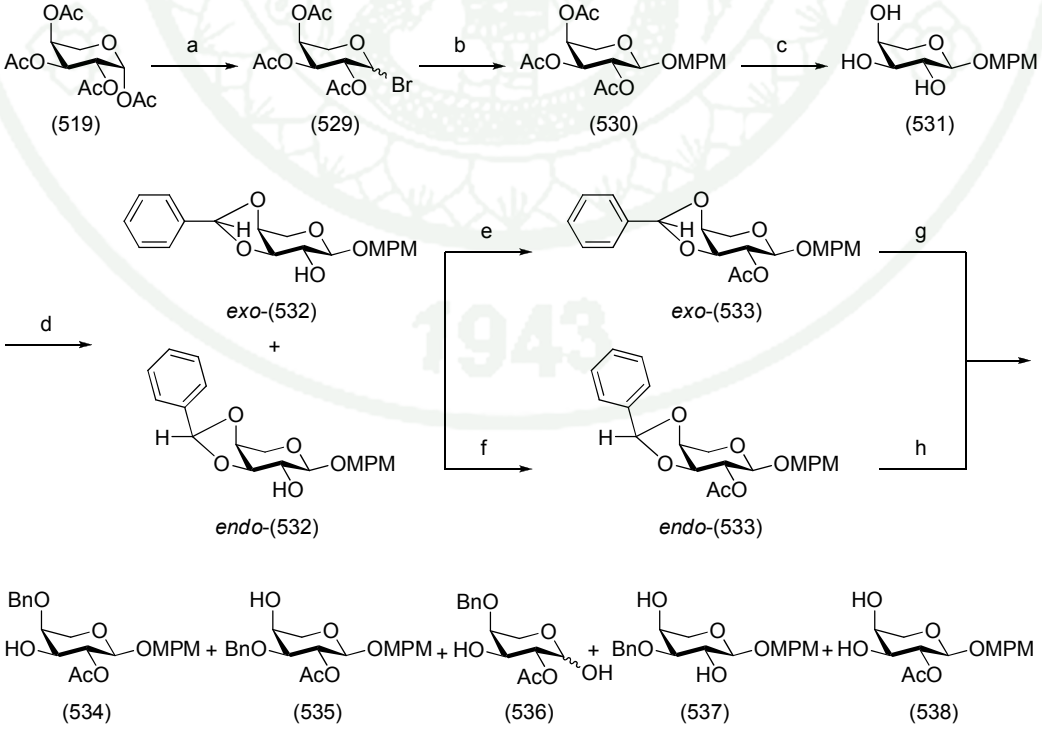
i) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 2h, 95%

j) $C_6H_5CH(OMe)_2$, *p*-TsOH·H_2O, DMF, rt, 12h, 75% for **524**

k) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0°C, 30 min, 65% for **526** and 22% for **527**

l) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0°C, 30 min, 73% for **528** and 19% for **279**

Preparation of p-methoxybenzyl 2-O-acetyl-4-O-benzyl-α-L-arabinopyranoside (534)



Scheme 82

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Reagents and conditions:

a) PBr_3 (1M in CH_2Cl_2), AcOH, rt, 4h,

b) *p*-methoxybenzyl alcohol, I_2, Ag_2CO_3, MS 4Å, toluene, rt, 16h, 55% (2 steps)

c) MeOH, Et_3N, H_2O, rt, 16h, 100%

d) $C_6H_5CH(OMe)_2$, *p*-TsOH·H_2O, DMF, rt, 24h, 16% for *exo*-isomer and 58% for *endo*-isomer

e) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 1h, 97%

f) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 1h, 100%

g) $TiCl_4$, Et_3SiH, CH_2Cl_2, -78°C, 5h, 43% for **534** and 11% for **535**

h) $TiCl_4$, Et_3SiH, CH_2Cl_2, -78°C, 5h, 72% for **534** and 14% for **535**

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2.2 Synthesis of disaccharide moiety

Preparation of disaccharide moieties ***539, 540, 541, 542*** *and* ***543***

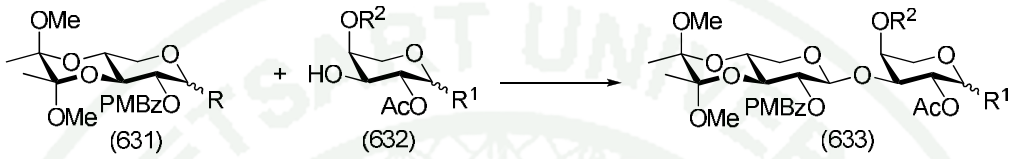

Table 16 Glycosylation of D-xylopyranoside donor and L-arabinopyranoside acceptor.

Entry	Donor	Acceptor		conditions	Results
	R	R^1	R^2		
1	α-SPh	β-OBn	OH	NIS, TMSOTf, 3Å MS, CH_2Cl_2, -40°C to rt	78.1% (1→3) 15.0% (1→4)
				NIS, TfOH, 3Å MS, CH_2Cl_2, -30°C	72.4% (1→3) 21.2% (1→4)
2	α-SPh	β-OBn	OBn	NIS, TMSOTf, 3Å MS, CH_2Cl_2, -78 to -20°C	65.2%
				NIS, TfOH, 3Å MS, CH_2Cl_2, 0°C to rt	48.0%
3	α-SPh	α-SPh	OBn	NIS, TMSOTf, 3Å MS, CH_2Cl_2, -78 to -20°C	None of product
4	$OC(=NH)CCl_3$	α-SPh	OBn	$BF_3{\cdot}OEt_2$, 4Å MS, CH_2Cl_2, -78 to -40°C	None of product
				TMSOTf, 3Å MS, CH_2Cl_2, -78 to -40°C	None of product
				TMSOTf, CH_2Cl_2 -78 to -20°C	18.5%
5	$OC(=NH)CCl_3$	α-OMPM	OBn	NIS, TMSOTf, 4Å MS, CH_2Cl_2, -78 to -20°C	49.0%
6	α-SPh	α-OMPM	OBn	Ph_2SO, TTBP, Tf_2O, 3Å MS CH_2Cl_2, -60 to -20°C	38.1%

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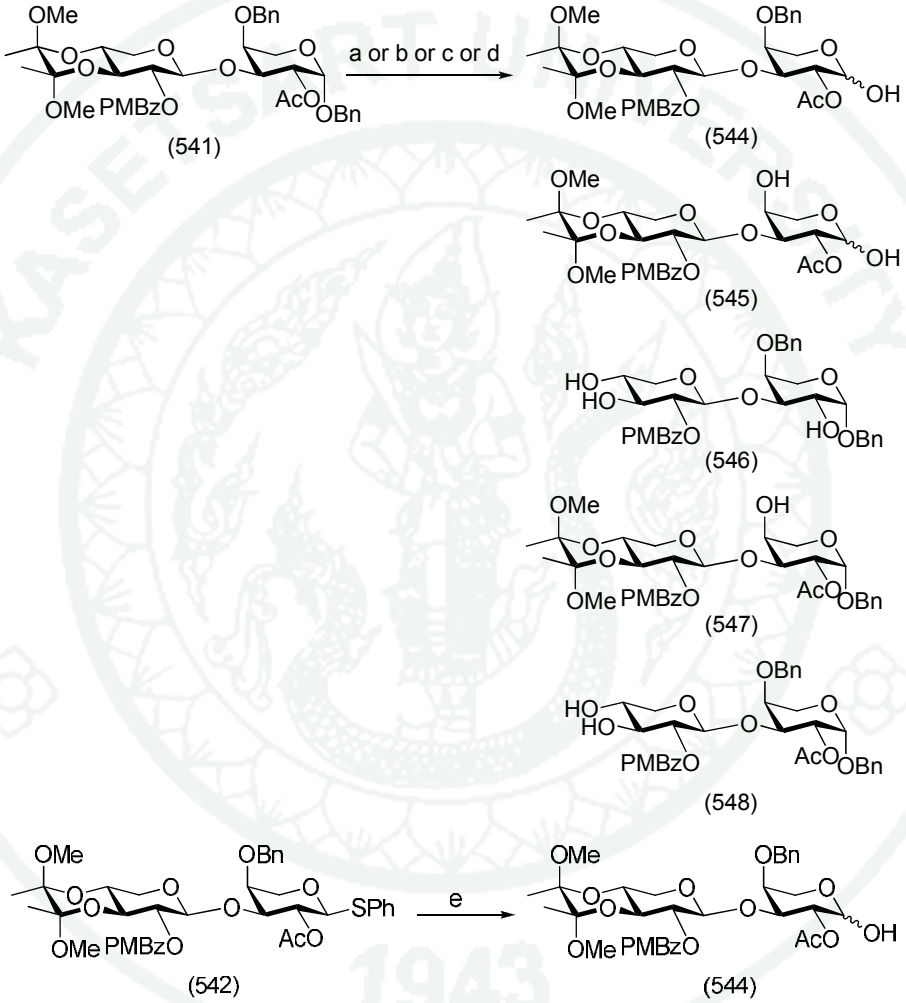
Preparation of 2-O-acetyl-3-O-(2-O-methoxybenzoyl-(2'S,3'S)-methyl-3,4-O-(2',3'-dimethoxybutane-2',3'-diyl)-β-D-xylopyranosyl)-4-O-benzyl-α/β-L-arabinopyranoside (544)



Scheme 83

Reagents and conditions:

a) 10%Pd/C, H_2, EtOAc, EtOH, rt, 1d, **544** (32%), **545** (53%)

b) 4M HCl, CH_3CN, 80°C, 2h, **546** (16%), recovered starting material (68%)

c) 10%Pd/C, Et_3SiH, MeOH, rt, 1h, **547** (19%)

d) anh. $FeCl_3$, CH_2Cl_2, rt, 5 min, **548** (96%)

e) NBS, CH_2Cl_2:H_2O (9:1), rt, 1h, **544** (17%)

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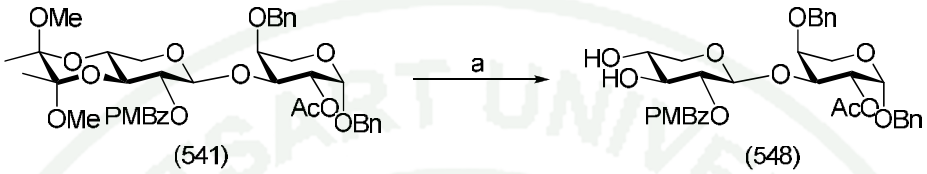
Preparation of benzyl 2-O-acetyl-3-O-(2-O-methoxybenzoyl-β-D-xylopyranosyl)-4-O-benzyl-β-L-arabinopyranoside (548)



Scheme 84

Reagents and conditions:

a) TFA/H_2O (2:1), rt, 2h, 79%

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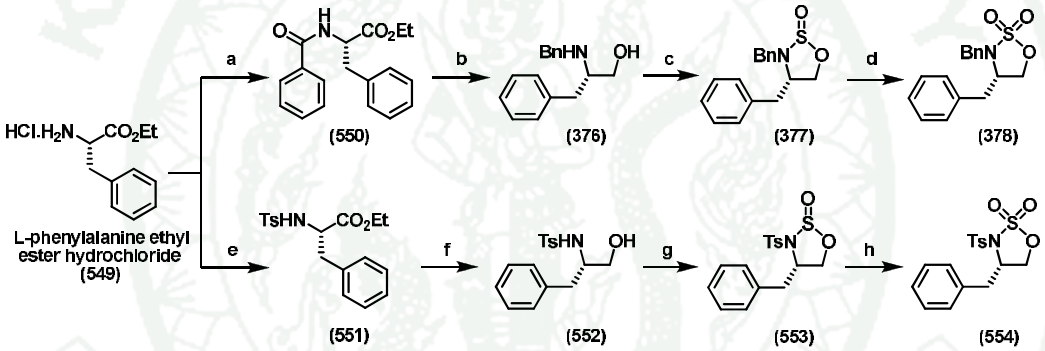
3. Synthesis of five- and six-membered cyclic sulfamidates

Preparation of (S)-3,4-dibenzyl[1,2,3]oxathiazolidine-2,2-dioxide (378) and (S)-3-tosyl-4-benzyl[1,2,3]oxathiazolidine-2,2-dioxide (554)

Conversion of L-phenylalanine ethyl ester hydrochloride (549) to (*S*)-3,4-dibenzyl[1,2,3]oxathiazolidine-2,2-dioxide (378) and (*S*)-3-tosyl-4-benzyl[1,2,3]oxa thiazolidine-2,2-dioxide (554) using sequential four steps reactions was shown in Scheme 85.



Scheme 85

Reagents and conditions:

a) PhCOCl, Et_3N, CH_2Cl_2, 0°C to rt, 2h, 98%

b) $LiAlH_4$ (1.0 M solution in THF), THF, reflux, 4h, 98%

c) $SOCl_2$, Et_3N, imidazole, CH_2Cl_2, 0°C, 1.5h, 100%

d) $RuCl_3$, $NaIO_4$, CH_3CN, H_2O, 0°C, 1.25h, 88%

e) TsCl, Et_3N, DMAP, CH_2Cl_2, rt, 2h, 100%

f) $LiAlH_4$ (1.0 M solution in THF), THF, reflux, 4h, 100%

g) $SOCl_2$, pyridine, THF, -78°C to rt, 4h, 97%

h) $RuCl_3$, $NaIO_4$, CH_3CN, H_2O, 0°C, 1.25h, 51%

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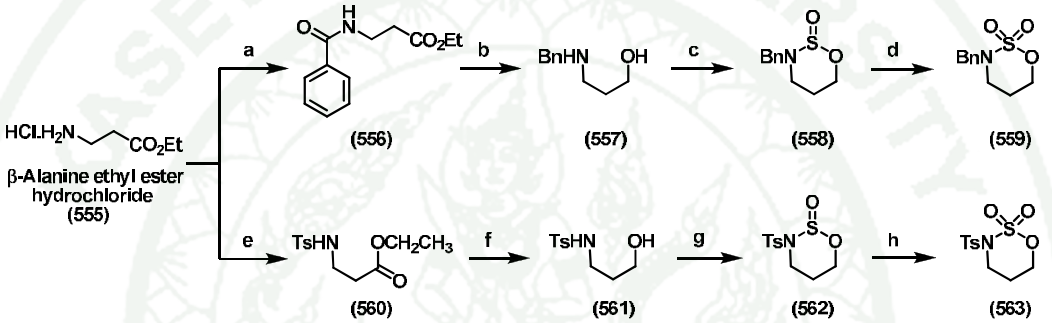
Preparation of 3-benzyl[1,2,3]oxathiazinane-2,2-dioxide (559) and 3-tosyl[1,2,3]oxathiazinane-2,2-dioxide (563)

Conversion of *β*-alanine ethyl ester hydrochloride (555) to 3-benzyl[1,2,3] oxathiazinane-2,2-dioxide (559) and 3-tosyl[1,2,3]oxathiazinane-2,2-dioxide (563) *via* four steps sequent reaction was shown in Scheme 86.



Scheme 86

Reagents and conditions:

a) PhCOCl, Et_3N, CH_2Cl_2, 0°C to rt, 2h, 95%

b) $LiAlH_4$ (1.0 M solution in THF), THF, reflux, 4h, 100%

c) $SOCl_2$, Et_3N, imidazole, CH_2Cl_2, 0°C, 12h, 100%

d) $RuCl_3$, $NaIO_4$, CH_3CN, H_2O, 0°C, 12h, 58.6%

e) TsCl, Et_3N, DMAP, CH_2Cl_2, rt, 12h, 88.4%

f) $LiAlH_4$ (1.0 M solution in THF), THF, reflux, 4h, 92.2%

g) $SOCl_2$, pyridine, THF, -78°C to rt, 4h, 65.8%

h) $RuCl_3$, $NaIO_4$, CH_3CN, H_2O, 0°C, 12h, 82.7%

Preparation of 4-benzyl-3-tosyl[1,2,3]oxathiazinane-2,2-dioxide (571)

Synthesis of 4-benzyl-3-tosyl[1,2,3]oxathiazinane-2,2-dioxide (571) using two steps from *γ*-amino alcohol (569), prepared from L-phenylalanine (564) *via* five steps sequent reaction, was presented in Scheme 87.

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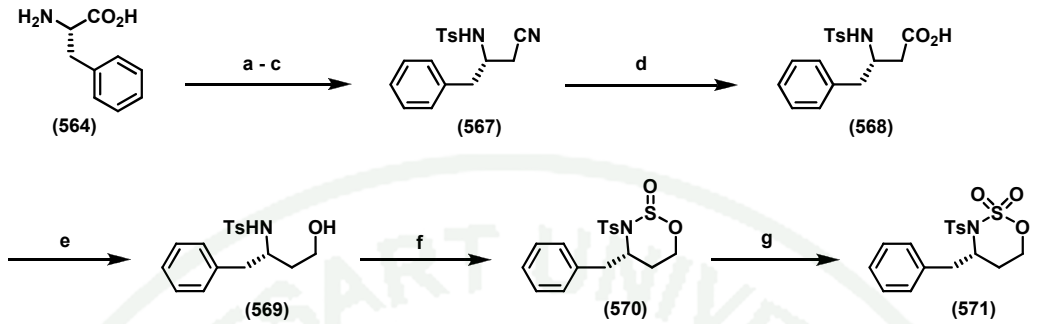

Scheme 87

Reagents and conditions:

a) $NaBH_4 \cdot I_2$, THF, 0°C to reflux, 18h, 90%

b) TsCl, pyridine, 0°C to rt, overnight, 92%

c) NaCN, DMF, rt, 2h, 90%

d) 40% NaOH, 110°C, 15h, then 50% H_2SO_4, 100%

e) $LiAlH_4$ (1.0 M solution in THF), THF, 0°C to rt, 2h, 98%

f) $SOCl_2$, pyridine, THF, -78°C to rt, 16h, 70%

g) $RuCl_3$, $NaIO_4$, CH_3CN, H_2O, 0°C, 12h, 73%

4. Synthesis of *N*-heterocycle *via* cyclic sulfamidates

Preparation of substituted benzoxazines, benzothiazines and quinoxalines

Conversion of (*S*)-3,4-dibenzyl[1,2,3]oxathiazolidine-2,2-dioxide (378) and (*S*)-3-tosyl-4-benzyl[1,2,3]oxathiazolidine-2,2-dioxide (554) to substituted benzoxazines, benzothiazines and quinoxalines using a two pot sequence of annulation, *N*-sulfate hydrolysis, and Pd catalyzed amination was summarized in Table 17.

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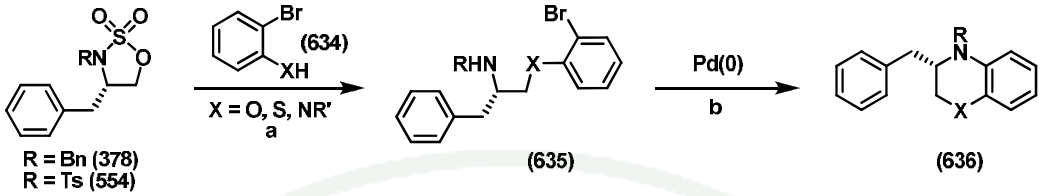


Scheme 88

Reagents and conditions:

a) (i) NaH, DMF, rt

(ii) aq. 5M HCl

b) cat. $Pd(OAc)_2$, xantphos, NaO*t*Bu, toluene, 100°C

Table 17 Synthesis of 2-substituted 1,4-benzoxazines, benzothiazines and quinoxalines.

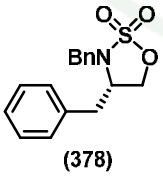
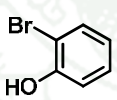
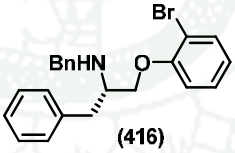
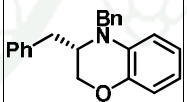
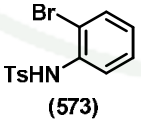
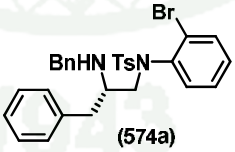
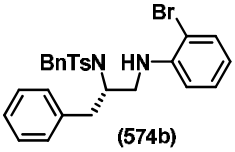
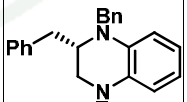
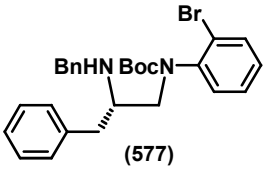
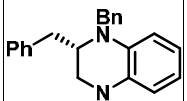
Entry	Sulfamidate	Nucleophile	Addition product	Yield (%)	Heterocycle	Yield (%)
1	 (378)	 (572)	 (416)	88	 (417)	88
2		 (573)	 (574a) and  (574b)	76 a:b 1.0:0.7	 (575)	78
3		(576)	 (577)	80	 (578)	95

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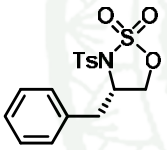
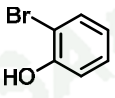
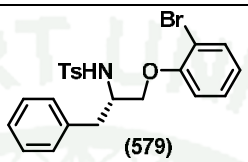
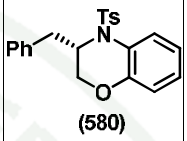
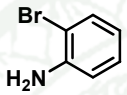
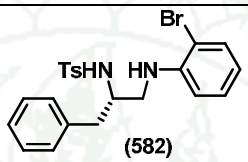
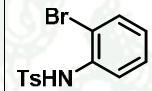
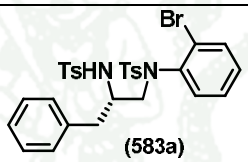
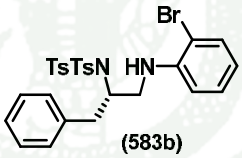
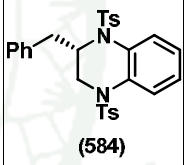
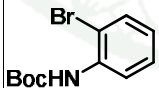
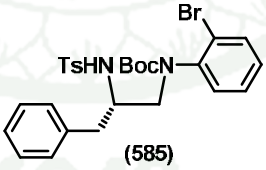
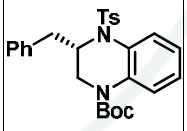
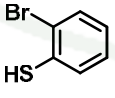
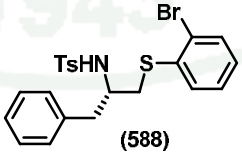
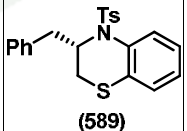
Table 17 (Continued)

Entry	Sulfamidate	Nucleophile	Addition product	Yield (%)	Heterocycle	Yield (%)
4	 (554)	 (572)	 (579)	80	 (580)	55
5		 (581)	 (582)	11		
6		 (573)	 (583a) and  (583b)	73 a:b 1.0:0.3	 (584)	80
7		 (576)	 (585)	67	 (586)	78
8		 (587)	 (588)	69	 (589)	77

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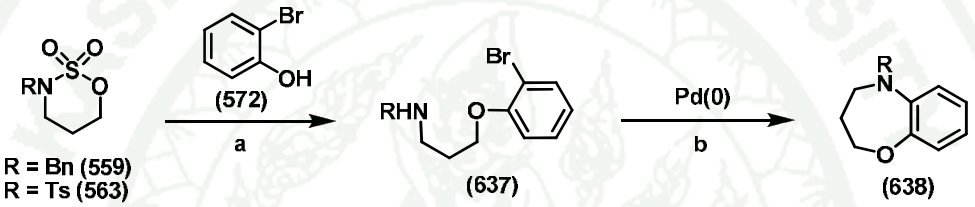
Preparation of 1,4-benzoxazepines

Conversion of 3-benzyl[1,2,3]oxathiazinane-2,2-dioxide (559) and 3-tosyl[1,2,3]oxathiazinane-2,2-dioxide (563) to 1,4-benzoxazepines using a two pot sequence of annulation, *N*-sulfate hydrolysis, and Pd catalyzed amination was not successful, recovered starting material and reductive product were observed as presented in Table 18.



Scheme 89

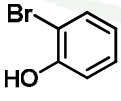
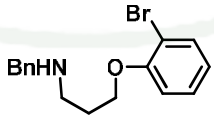
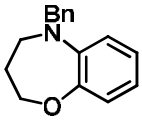
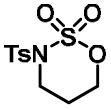
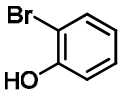
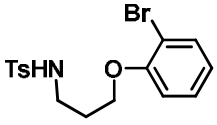
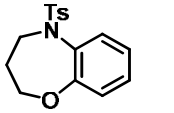
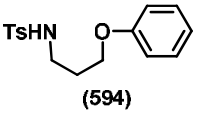
Reagents and conditions:

a) (i) NaH, DMF, rt

(ii) aq. 5M HCl

b) cat. $Pd(OAc)_2$, xantphos, NaO*t*Bu, toluene, 100°C

Table 18 Synthesis of 1,4-benzoxazepines.

Entry	Sulfamidate	Nucleophile	Addition product	Yield (%)	Heterocycle	Yield (%)
1	(559)	 (572)	 (590)	37	 (591)	-
2	 (563)	 (572)	 (592)	88	 (593)  (594)	- 100

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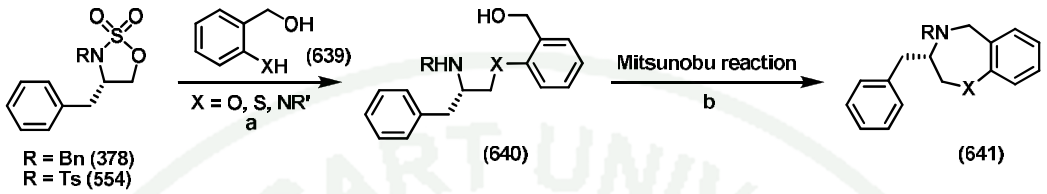


Scheme 90

Reagents and conditions:

a) (i) K_2CO_3, DMF, rt

(ii) aq. 5M HCl

b) DEAD, PPh_3, THF, 0°C to rt

Table 19 Synthesis of 3-substituted benzoxazepines, benzodiazepines and benzothiazepines.

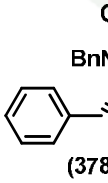
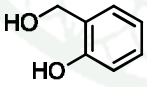
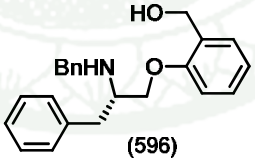
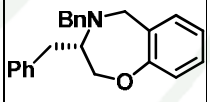
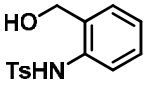
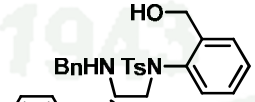
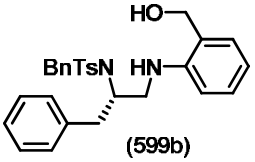
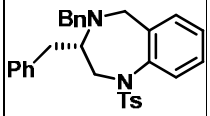
Entry	Sulfamidate	Nucleophile	Addition product	Yield (%)	Heterocycle	Yield (%)
1	 (378)	 (595)	 (596)	99	 (597)	-
2		 (598)	 (599a) and  (599b)	89 a:b 1:1	 (600)	96

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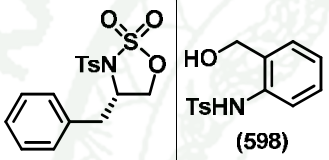
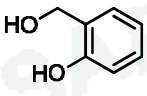
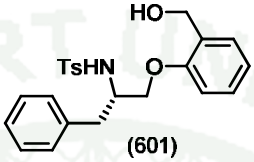
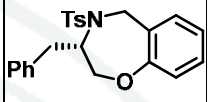
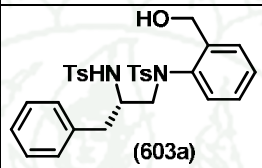
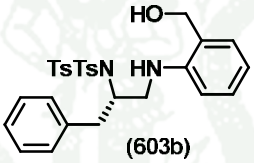
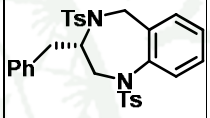
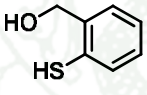
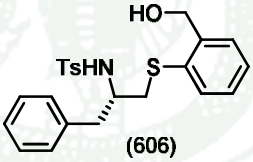
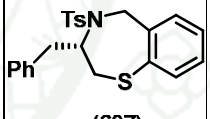
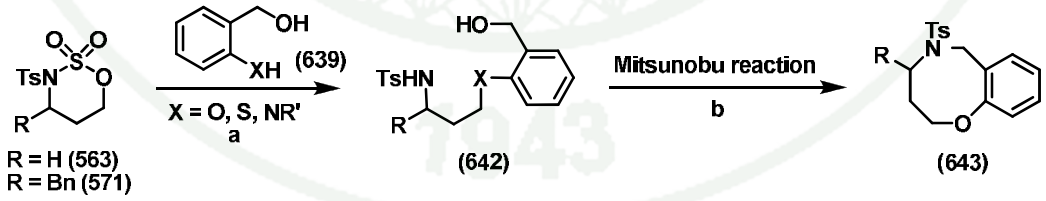
Table 19 (Continued)

Entry	Sulfamidate	Nucleophile	Addition product	Yield (%)	Heterocycle	Yield (%)
3	 (554)	 (595)	 (601)	64	 (602)	78
4		(598)	 (603a) and  (603b)	65 a:b 1.0:0.7	 (604)	84
5		 (605)	 (606)	78	 (607)	70



Scheme 91

Reagents and conditions:

a) (i) K_2CO_3, DMF, rt

(ii) aq. 5M HCl

b) DEAD, PPh_3, THF, 0°C to rt

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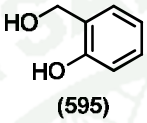
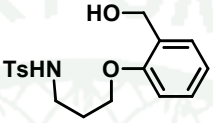
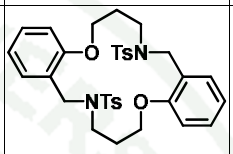
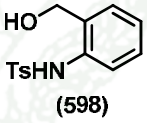
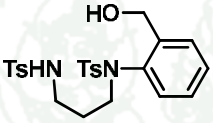
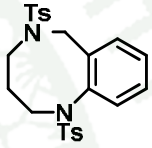
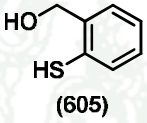
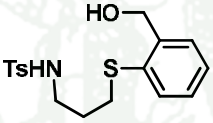
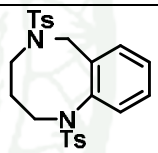
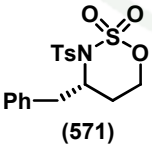
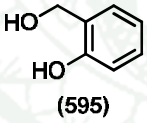
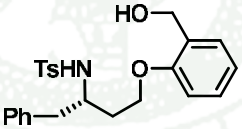
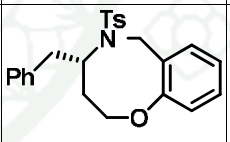
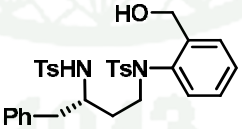
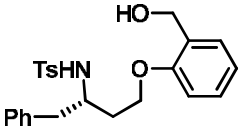
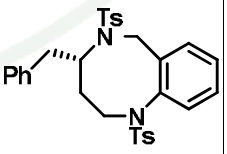
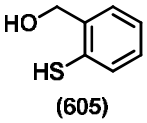
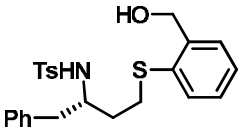
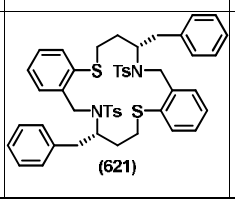
Table 20 Synthesis of unsubstituted and 4-substituted 1,5-benzoxazocines, benzodiazocines and benzothiazocines.

Entry	Sulfamidate	Nucleophile	Addition product	Yield (%)	Heterocycle	Yield (%)
1	(563)	 (595)	 (608)	90	 (610)	75
2		 (598)	 (611)	64	 (612)	82
3		 (605)	 (613)	81	 (614)	79
4	 (571)	 (595)	 (615)	42	 (616)	58
5		(598)	 (617a) and  (617b)	93	 (618)	87
6		 (605)	 (619)	84	 (621)	72

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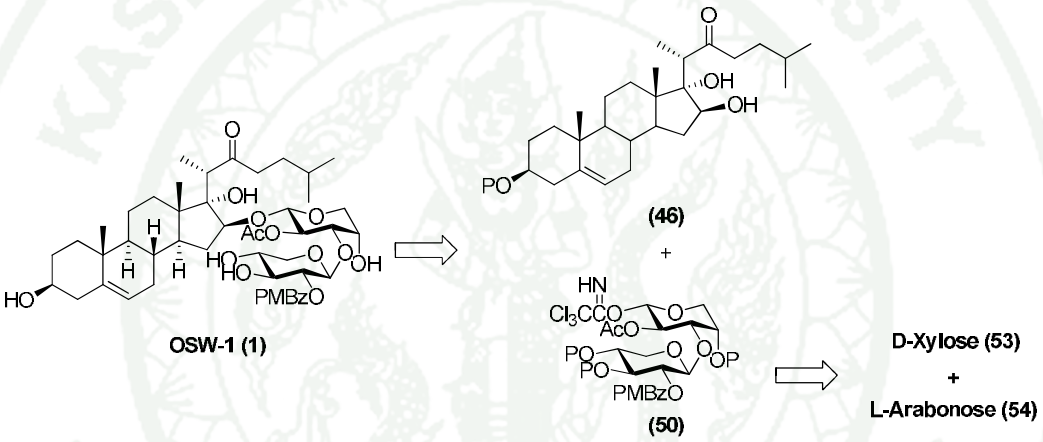
Discussion

Herein we report the synthetic studies of an anticancer OSW-1 which was disconnected into two distinctive parts. The first part is the steroidal OSW-1 aglycone which contained the 16β,17α-dihydroxycholest-22-one structure (46). The second part is the disaccharide moiety (50) which could be derived from the commercially available D-xylose (53) and L-arabinose (54) (Scheme 92).



Scheme 92

1. Synthesis of steroidal OSW-1 intermediate

The protected OSW-1 aglycone (46) would be synthesized by hydrolysis and decarboxylation of cyclic β-keto lactone **644**. Lactone **644** will be constructed by McMurry coupling of keto ester **645**, which was prepared from esterification of sterol **646** with monoacid malonate methyl ester **466**. The sterol (646) should be obtained from diosgenin (8) (Scheme 93).

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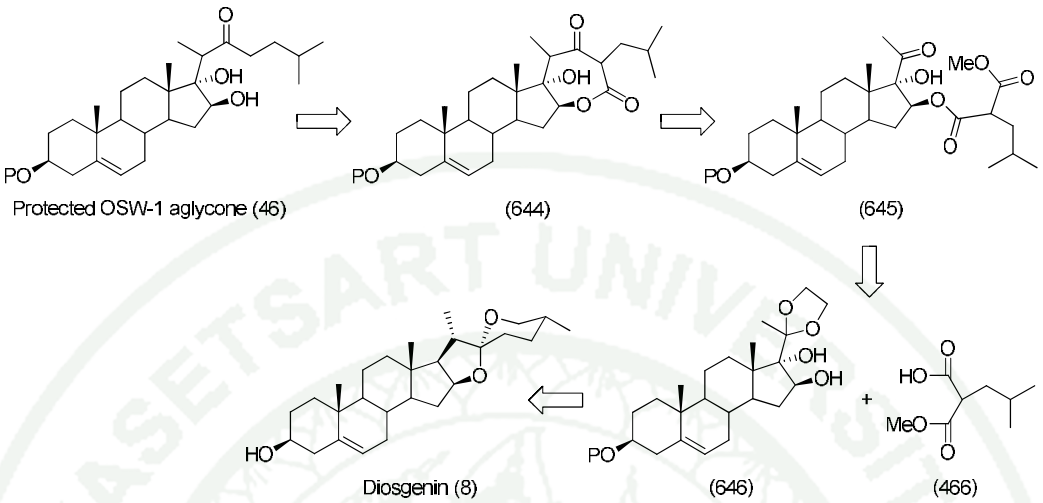
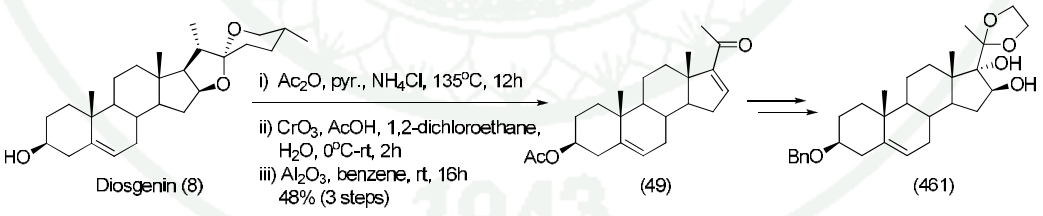


Scheme 93

Synthesis of 3β-benzyloxy-16β,17α-dihydroxy-20-ketal-pregnenolone (461)

Preparation of key intermediate 16β,17α-dihydroxy-steroid **461**, we need to synthesize α,β-unsaturated ketone (49) by one-pot degradation of the spiro-ring of diosgenin (8) using modified Mićović method (Scheme 94) (Mićović *et al.*, 1990).



Scheme 94

As described in Scheme 72, 16α,17α-epoxy ketone steroid **454** was prepared by two similar pathways. The first pathway was performed by benzylation of the epoxide **451** which could be synthesized by epoxidation of 16-dehydropregnenolone acetate (49) or 16-dehydropregnenolone (452). Only 16α,17α-epoxy ketone **451** was obtained because of the steric effect of 18β-angular methyl group in the molecule. Many attempts to benzylate compound **451** provided the desired product **454** in low

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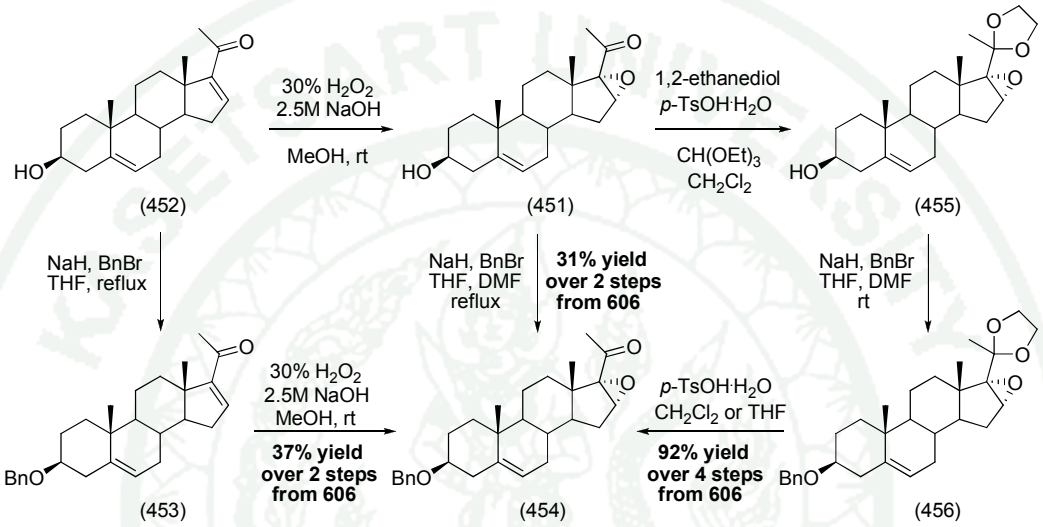
yield. Another pathway, we reversely synthesized the epoxide **454** by sequential benzylation and epoxidation. However the total yield of 3β-benzyloxy-16α,17α-epoxy ketone steroid (454) was still low.



Scheme 95

To overcome this problem, we decided to protect C-20 ketone as a ketal in quantitative yield before benzylation. The total yield of the protected ketone (456) from **452** was 92% which was higher than two previous pathways (36.5% and 31.0%) as shown in Scheme 95.

Installation of 16β-acetyloxy-17α-hydroxyl group to pregnenolone **454** was carried out by treatment with a mixture of 20% sulfuric acid and acetic acid to furnish 3β-benzyloxy-16β-acetyloxy-17α-hydroxy-pregnenolone (457) in only 48% yield. To improve the yield of product, the reaction with a mixture of 20% sulfuric acid and acetic anhydride, and with sodium acetate in acetic acid at 65°C have been tried. However, only small amount of product was obtained along with the unknown compound from both methods. The stereochemical assignments of the product were made on the basis of ^{1}H-NMR spectrum and were confirmed by diagnostic nuclear Overhauser effect (nOe) experiments. ^{1}H NMR data of 16-position (4.75 ppm) were in good agreement with the reported for 16β-acetyloxy-17α-hydroxy ketone steroid

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(4.85 ppm) (Takegawa *et al.*, 1993). Moreover the configuration at C-16 of **457** was established based on a nOe between the angular methyl proton at C-18 and acetate at C-16 (Figure 9).

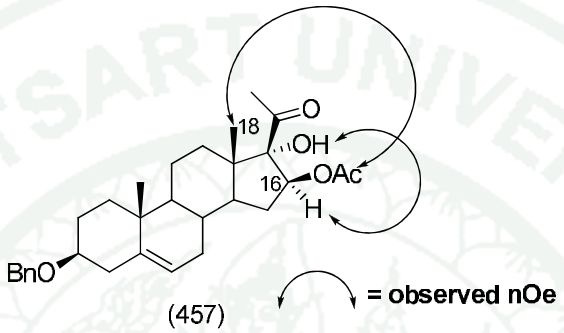
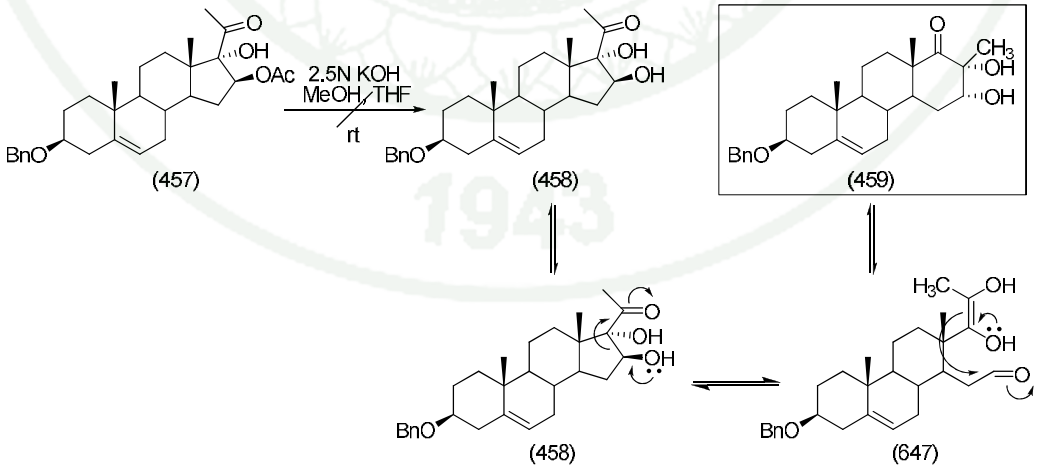


Figure 13 NOE effect of the steroid **457**.

Hydrolysis of 16β-acetyloxy-17α-hydroxy ketone **457** by using KOH in methanol was not successful due to the retro-aldol rearrangement of the resulting 16β,17α-dihydroxy ketone **458** to **459** (Akhrem *et al.*, 1969). The plausible mechanism was shown in Scheme 96.



Scheme 96

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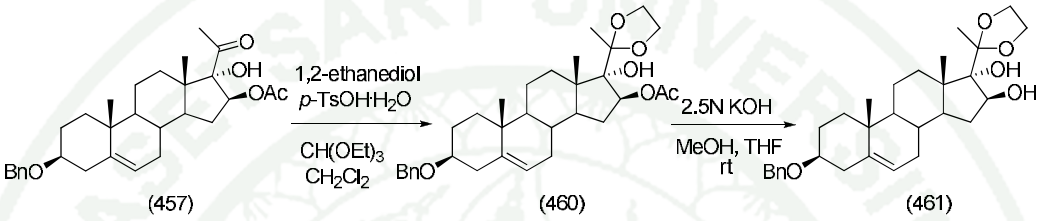
To solve the problem, C-20 ketone was again protected as cyclic ketal before removal of acetate group. Hydrolysis of 16β-acetyloxy-17α-hydroxy-20-ketal **460** proceeded smoothly to the desired 16β,17α-dihydroxy steroid **461** in good yield (Scheme 97).



Scheme 97

Synthesis of side chain

Isobutyl-malonic acid monomethyl ester (466) was prepared by partial hydrolysis of the commercially available isobutyl dimethylmalonate ester (465), whereas methyl- and benzyl-diethylmalonate esters (463 and 464) were obtained by mono-alkylation of diethylmalonate ester **462**. It was noted that mol amount of alkylating agents, temperature and time were crucial for controlling the mono-alkylation. The optimized condition of mono-methylation was using 1.2 equivalent of methyl iodide in the presence of potassium carbonate in acetone at 60°C for 6 hours to afford methyl malonate ethylester (463) in moderate yield (51%) without dialkylated product. In the same way, the optimized mono-benzylation condition of diethylmalonate ester (462) provided the expected monobenzylated product **464** in 57% yield by using benzyl bromide in the presence of sodium hydride in THF at refluxing for 18 hours. Partial hydrolysis of both methyl- and benzyl-malonate diethylester was performed under the same condition, potassium hydroxide (1.8 N) in ethanol at 0°C, to give the desired product **467** and **468** in 78% and 76% respectively. The temperature had to be kept at 0°C for partial hydrolysis (Scheme 98).

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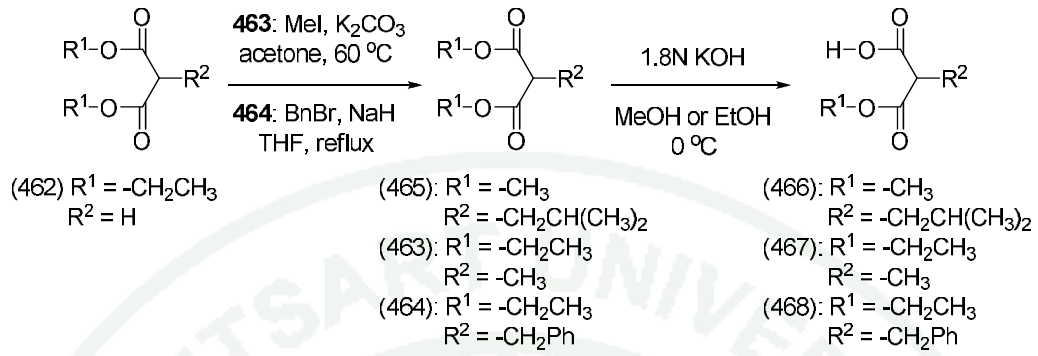

Scheme 98

Synthesis of steroidal OSW-1 intermediates and its analogues

Esterification between 2-isobutyl-malonic acid monomethyl ester **466** and 16β,17α-dihydroxy steroid **461** under standard condition using DCC and DMAP efficiently achieved the expected ester product **469** in quantitative yield. Removal of C-20 ketal with *p*-toluenesulfonic acid monohydrate in THF at room temperature afforded 16β-(isobutyl-monomethyl ester malonate-ester)-17α-hydroxy ketone steroid **470** which then was acetylated of 17α-tertiary hydroxyl group by two different methods. One of those was using acetic anhydride in the presence of 70% perchloric acid in dioxane at room temperature for 20 minutes to provide the acetylated product **473** in 62% yield and 21% of starting material was recovered. Another reaction condition was carried out under trifluoroacetic anhydride in the presence of acetic acid and *p*-toluenesulfonic acid monohydrate in dichloromethane at 0°C for 20 minutes to give **473** in 71% yield, that is more than the previous one, and also 23% of recovered starting material. Condensation between 2-methyl-malonic acid monoethyl ester (467) and 16β,17α-dihydroxy steroid (461) followed by removal of C-20 ketal under the same representative condition afforded **472** in 80% yield over 2 steps (Scheme 99).

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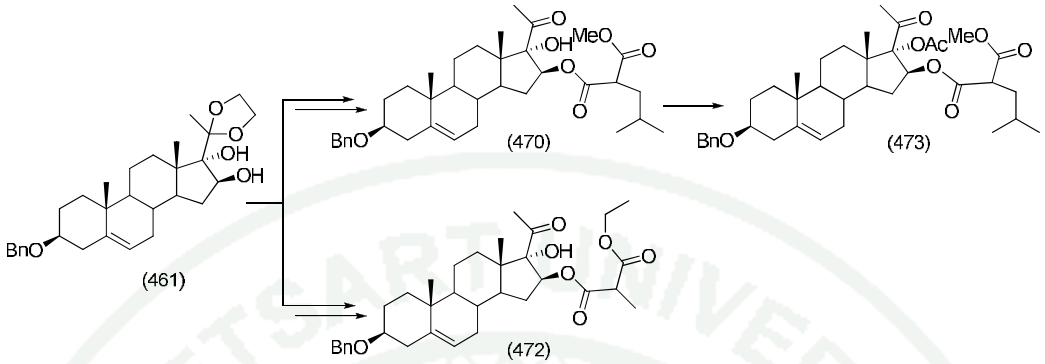
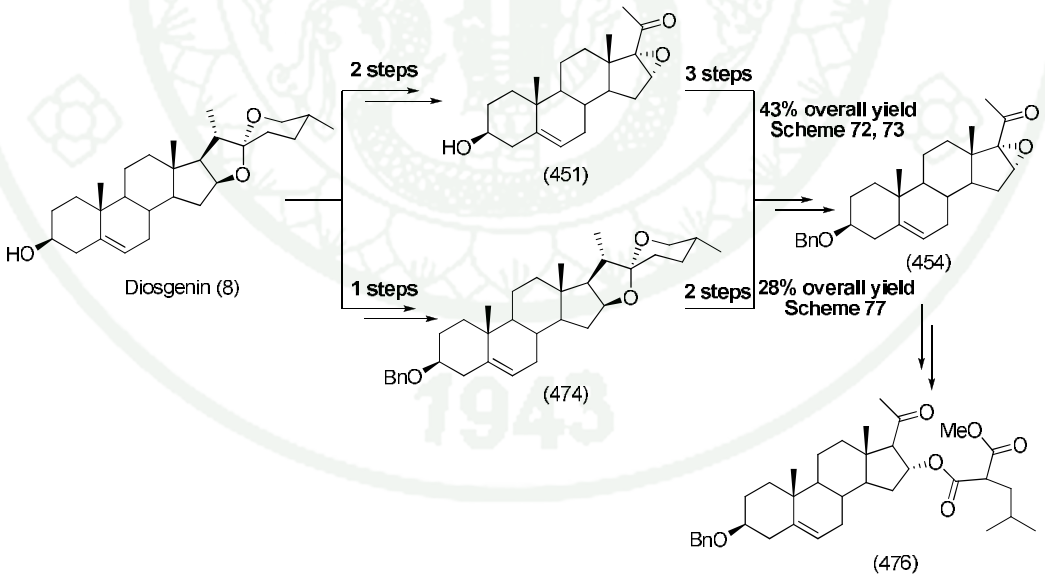


Scheme 99

To investigate that the 17α-hydroxy group would be represented the steric hindrance to intramolecular McMurry coupling reaction of keto-ester **470**, 16α-(isobutyl-monomethyl ester malonate ester)-pregnenolone **476** would be synthesized through intermediate **454** (Scheme 100).



Scheme 100

We proposed an alternative pathway to synthesize epoxide **454** directly from diosgenin (8) *via* three steps sequentially; benzylation of diosgenin, one-pot degradation and epoxidation. The final epoxide product was obtained in 28% yield

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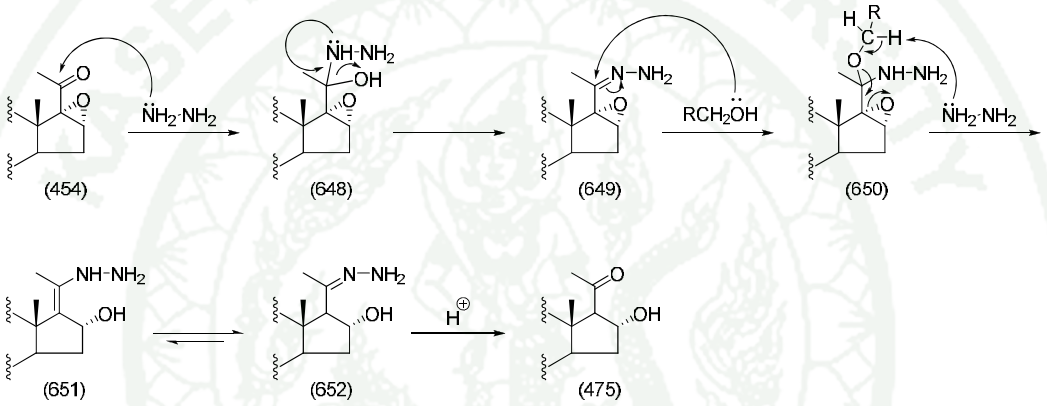
which was less than the previous method (43% yield), although a number of reaction steps were less than the previous one (5 steps) as shown in Scheme 100.

Reductive cleavage of 16α,17α-epoxy ketone **454** was accomplished by using hydrazine hydrate to afford 16α-hydroxy ketone **475** in moderate yield. The possible mechanism was shown in Scheme 101.



Scheme 101

We tried to inverse 16α-hydroxy to 16β-hydroxy configuration by ketalization, oxidation and reduction with a small amount of 16α-hydroxy-ketone steroid **475**. Ketalization of **475** was not convenient when using ethylene glycol and triethylorthoformate in the presence of *p*-toluenesulfonic acid monohydrate in dichloromethane. The desired product **653** was isolated in only 29% yield together with the eliminated product **654** in 58% yield. Oxidation of **653** with pyridinium chlorochromate in the presence of sodium acetate in dichloromethane at 0°C for 1 hour was failed, only diketone **656** was obtained in 35% yield (Scheme 102).

We turned our attention to condense our side chain with 16α-hydroxy steroid **475** under standard condition (DCC, DMAP, CH_2Cl_2) to give the desired ester **476** in 77% yield (Scheme 102). We hoped, seven membered ring intermediate would offer an opportunity for the intramolecular McMurry reaction of trans-16α-(isobutyl monomethyl ester malonate ester)-17β-acetyl steroid **476**.

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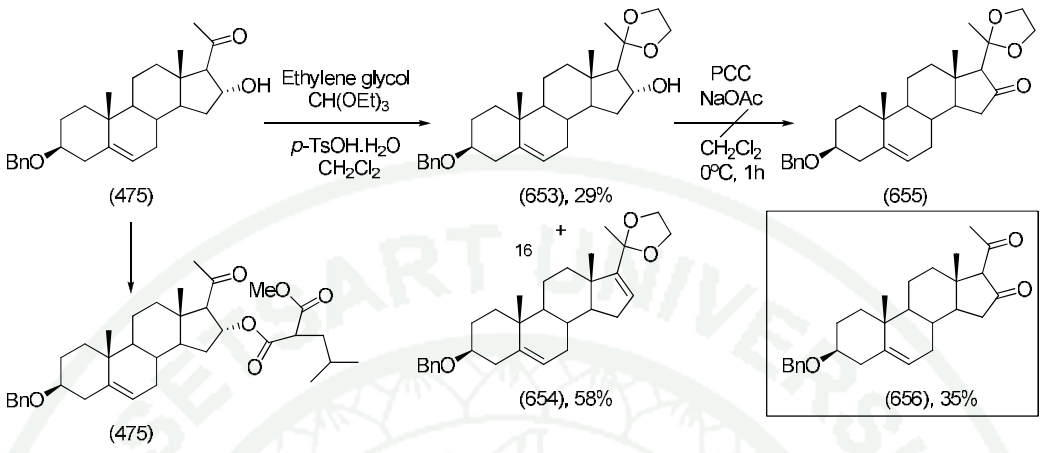

Scheme 102

Intramolecular McMurry reaction

Intramolecular McMurry reactions of **470** (Table 12, entries 2-5) using titanium(IV) chloride with various reducing reagents, such as Zn, Zn-Cu, $LiAlH_4$, Mg or Li-naphthalenide, were unsuccessful, dehydroxygenated product **479** was obtained and starting material was recovered. The intramolecular coupling reaction would not be occurred probably due to the steric hindrance of isobutyl group on the side chain. In order to prove our assumption, intramolecular McMurry coupling of **472** (entries 6 and 7) which contains less sterically side chain, 2-methyl monoethyl malonate ester, was performed under similar conditions. However several attempts were still failure, only eliminated side chain product **479** was isolated. These results indicated that 17α-hydroxy group might be involved in the McMurry reaction mechanism leading to the undesired product **479** as shown in Scheme 104. Therefore, the 17α-acetoxyl steroid **473** (entries 8 and 9) has been subjected to intramolecular McMurry reaction but only starting material was again recovered when using titanium(IV) chloride and $LiAlH_4$ in THF at refluxing. Whereas, McMurry coupling of **473** with titanium(IV) chloride and magnesium naphthalenide provided both recovered starting material and the unexpected product **479** in 42% yield. Final attempt was still not successful. Intramolecular coupling reaction of 16β-acetyloxy-17α-hydroxy-pregnenolone (457) also delivered the same product as the previous reaction (entry 10) (Scheme 103).

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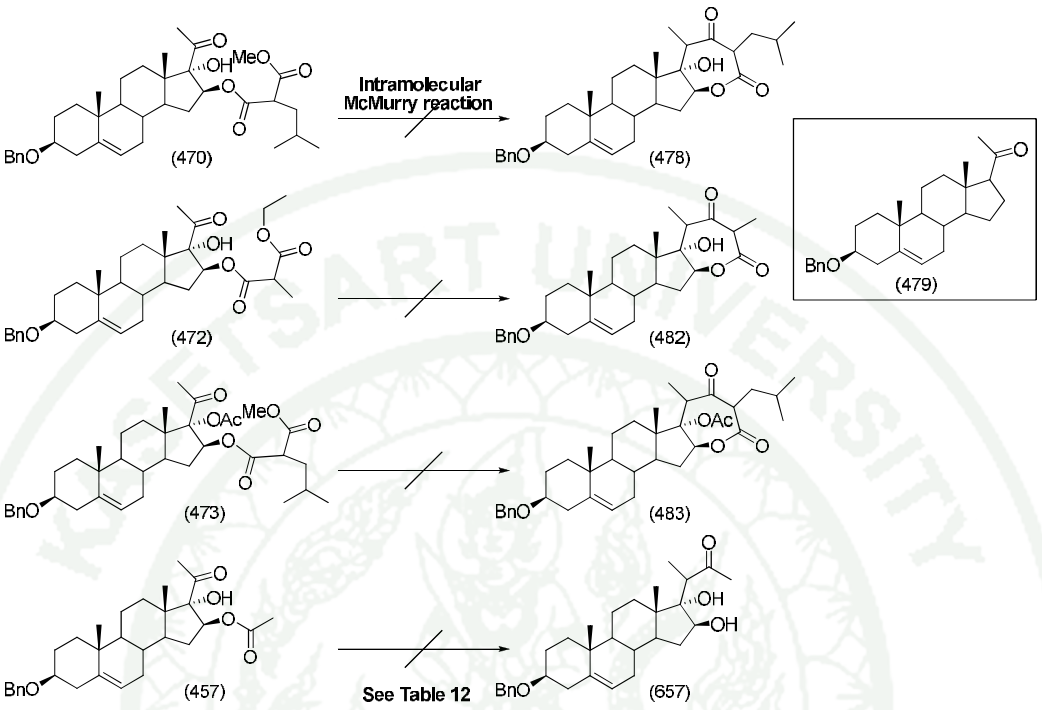
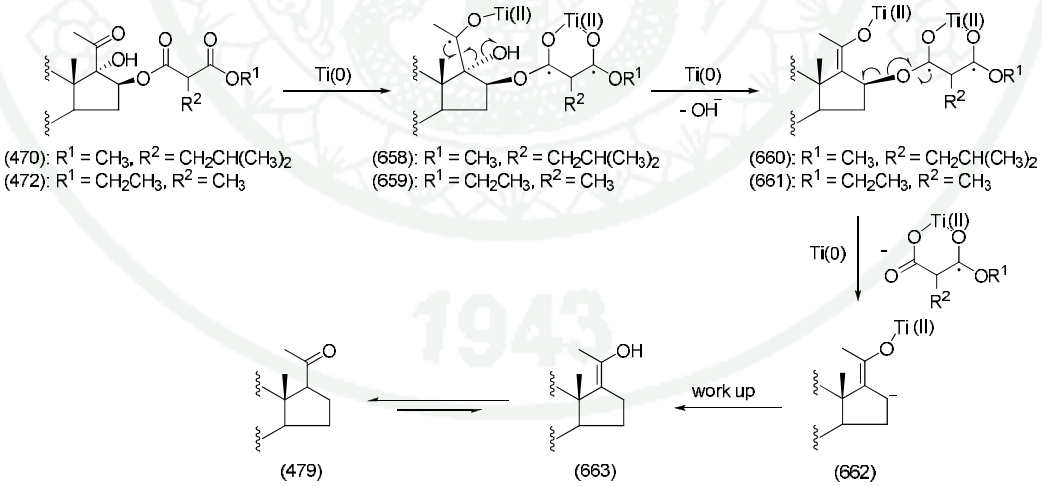


Scheme 103



Scheme 104

In case of trans-16α-(isobutyl monomethyl ester malonate ester) steroid (476), intramolecular McMurry reaction gave only elimination product **453**, 3β-benzyloxy-16-dehydropregnenolone (Scheme 105).

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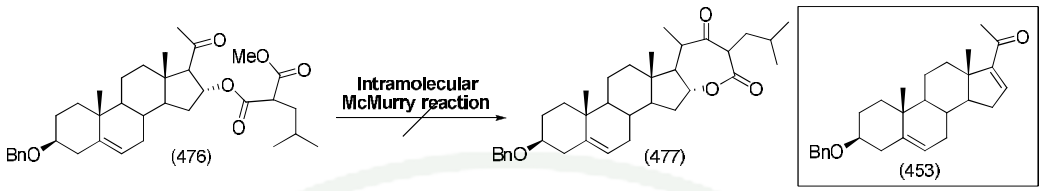

Scheme 105

The alternative strategy for intramolecular coupling between ketone and ester has been described using samarium diiodide (Iwaya *et al.*, 2002). Nevertheless, the expected product was not observed, eliminated product **453** and dehydroxylated **479** were obtained along with recovered starting material (Table 13).

2. Synthesis of disaccharide moiety

We proposed a new efficient methodology to synthesize the disaccharide moiety of OSW-1. Prudent choice of protecting groups is of great prominent, especially considering the presence of two ester functional groups in the final target, which restrict the final deprotection conditions to near neutral.

Synthesis of D-xylopyranoside donor

Our plan was to use thioglycoside **498** and xylosyl trichloroacetimidate **500** as D-xylopyranoside donor (Scheme 106). Thus, the thio-α-D-xylose **489** was prepared from D-xylose by using three sequence steps reaction as following tetraacetylation, thioglycosylation and methanolysis to give 48% yield of product.

To install a 2-*O*-*p*-methoxybenzoyl group, the selective protection of 3,4-*trans*-diequatorial hydroxyl group was required. Since triol **489** having both 2,3- and 3,4-*trans*-diequatorial hydroxyl group, the butanediacetal protection had proven especially useful for the protection of our compound. We supposed that butane-3,4-diacetal would be attributed to the thermodynamic stability greater than butane-2,3-diacetal. The first attempt to protect 3,4-*trans*-diequatorial hydroxyl group using 2,3-butadione, triethylorthoformate in the presence of borontrifluoride dietherate in

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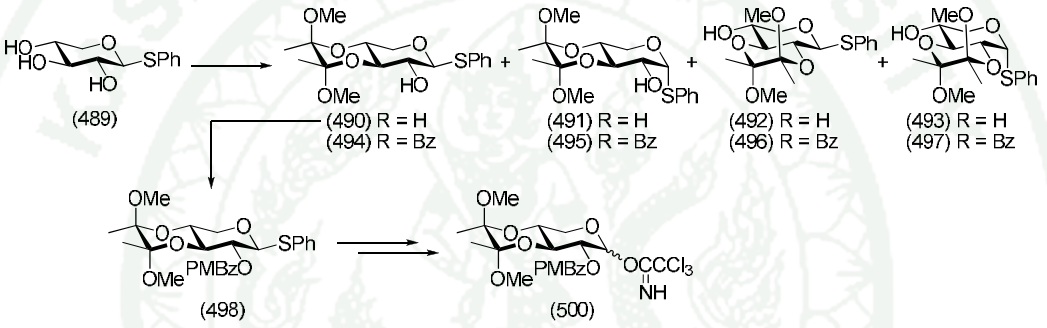
methanol was not proceeded in a selective manner. The desired product, thio-3,4-butadiacetal-α-D-xylopyranoside (490), was isolated in only 23% yield together with three side products, thio-3,4-butadiacetal-β-D-xylose (491, 11%) and thio-2,3-butadiacetal-α/β-D-xylose (492, 6% and 493, 3%). Therefore, we adjusted reaction condition by changing triethylorthoformate to trimethylorthoformate to access selective 3,4-*trans*-diequatorial hydroxy protection in good yield and only trace amount of side products were detected (Scheme 106).



Scheme 106

The structural assignments of all diacetal **490**, **491**, **492** and **493** were made on the basis of ^{1}H-NMR (α-H: 4.42, 4.68 ppm; β-H: 5.52, 5.47 ppm) and were reinforced by shifting of proton chemical shift of H-2 and H-4 positions after benzoylation. Free hydroxyl group at C-2 of **490** and **491**, and at C-4 of **492** and **493** were esterified with benzoylchloride in the presence of DMAP and triethylamine in dichloromethane to give 2-*O*- and 4-*O*-benzoyl products, respectively. The proton chemical shift of H-2 of **494** and **495** moved from 3.38 and 3.97 ppm to 5.15 and 5.14 ppm. In the same way, the proton chemical shift of H-4 of **496** and **497** shifted from 3.53 and 3.96 ppm to 5.15 and 5.13 ppm. The α- and β-protons at anomeric position were comfirmed by comparing the ^{1}H and ^{13}C NMR spectra with those of other α- and β-anomeric protons of thioglycoside (Yu and Jin, 2001).

Installation of *p*-methoxybenzoyl group at C-2 position was carried out with *p*-methoxybenzoic acid, DCC and DMAP in dichloromethane to afford thio-α-D-

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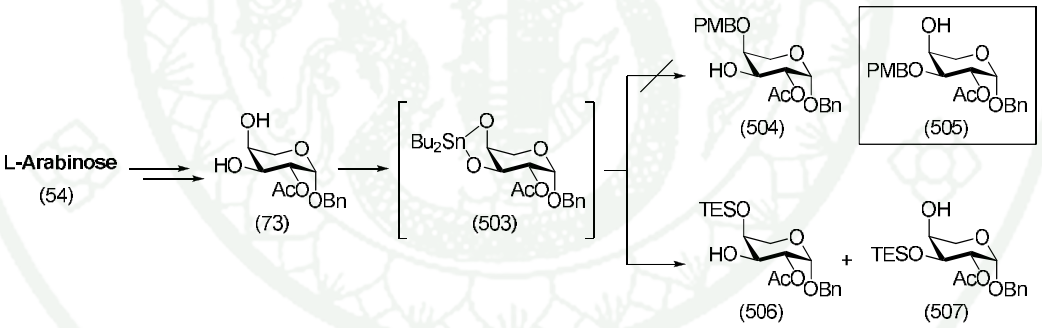
xylopyranoside donor **498** in excellent yield. Moreover, the synthetic flexibility of the thioglycoside allowed a facile preparation of the highly reactive trichloroacetimidate **500** in good yield. Conversion of thiophenyl group to hydroxyl group using *N*-bromosuccinimide followed by treatment with trichloroacetimidate and DBU easily gave the desired product (500) (Scheme 106).

Synthesis of L-arabinopyranoside acceptor

Initial attention focused upon the use of benzyl 4-*O*-protected-*β*-L-arabinopyranose as the glycosyl acceptor. The benzyl-2-*O*-acetyl-*β*-L-arabinose (73) was prepared from *β*-L-arabinose in four steps involving i.e., benzylation of 1-OH (501), isopropylidenation of 3,4-diOH (72), acetylation of 2-OH (502), and final removal of isopropylidene as shown in Scheme 79 (Deng *et al.*, 1999).



Scheme 107

Although it is well-known that the equatorial 3-hydroxy group is much more reactive than the axial 4-hydroxy, regioselective protection of 4-*O*-position had still required. In order to get the better yield of product and also reduce separable problem of regioisomer, we planned to selectively protect 4-hydroxyl group as p-methoxybenzyl ether *via* the 3,4-stannylene intermediate **503** which was generated with dibutyltin oxide under refluxing toluene. Unfortunately, treatment of 3,4-stannylene **503** with *p*-methoxybenzoyl chloride, cesium fluoride and potassium iodide in dimethylformamide at room temperature gave only thermodynamically more stable regioisomer **505** in low yield. Once again, treatment with triethylsilyl chloride

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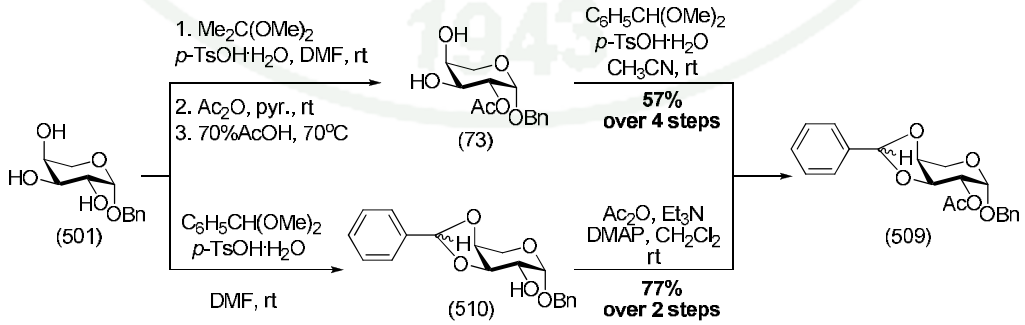
in the presence of triethylamine without solvent at room temperature afforded a ca. 3:1 mixture of monosilyl ethers **506** and **507**. Eventhough, this reaction was carried out in dichloromethane, the yield of desired product was not increased but diminished for the side product (Scheme 107).

We finally overcame this problem by the use of regioselective reductive ring opening of benzylidene acetal to protect 4-*O*-hydroxyl group of L-arabinose acceptor as benzyl ether or *p*-methoxybenzyl ether.

In the investigation of the reductive opening of 3,4-benzylidene acetal, a model system was designed using the 3,4-*O*-benzylidene derivative of *β*-L-arabinopyranoside, varying protecting groups at C-2. The 2-acetyl derivative **509** was prepared from the corresponding unprotected syn-1,2-diol **73** by the modified method described by Josephson (Bundle and Josephson, 1978). Thus treatment of **73** with benzaldehyde dimethyl acetal in the presence of *p*-toluenesulfonic acid provided an 1:4 mixture (nmr) of benzyl 2-*O*-acetyl-*exo/endo*-3,4-*O*-benzylidene-*β*-L-arabinopyranosides (**509***exo* and **509***endo*) (Harangi *et al.*, 1985) in 80% yield. These compounds could also be prepared in high yield directly from triol **501** by selective protection of 3,4*β*-dihydroxyl group under the similar condition to form a mixture of *exo*- and *endo*-**510** in 4:5 ratio which then was acetylated at C-2 position (Scheme 108). Compound **509***exo* and **509***endo* were separated by column chromatography.



Scheme 108

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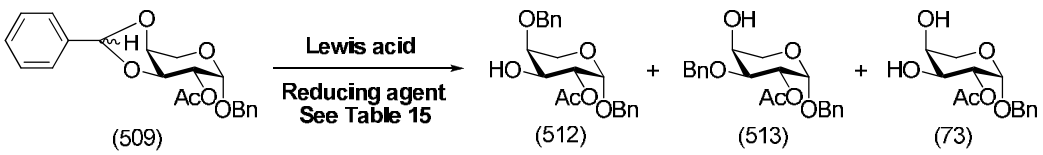
The *endo*-configuration of the benzylidene ring of **509***endo* was confirmed on the basis of ^{1}H and ^{13}C NMR spectroscopic data; the benzylidene proton resonated at δ 5.82 ppm, the signal of the acetalic carbon atom appeared at 104.39 ppm, whereas the benzylidene proton of the *exo*-isomer **509***exo* was found at δ 6.12 ppm and the signal of the acetalic carbon atom appeared at 102.78 ppm. These values are in good agreement with the corresponding data reported in the literatures (A. Lipták *et al.*, 1982).

With 3,4-benzylidene acetal in hand, regioselective reductive ring opening were explored with various reducing agents and Lewis acids (Scheme 109). In our initial studies the mixture of **509***exo* and **509***endo* (1:4) obtained directly from the synthesis was employed. $TiCl_4$ in conjugation with Et_3SiH was found to be effective in the reductive ring opening of our benzylidene acetal compound at -78 °C to give **512** and **513** but regioselectivity was low and some starting material was recovered (Table 15, entry 8). When $BF_3{\cdot}OEt_2$, a weaker Lewis acid was used and the amount of Et_3SiH was increased, the reaction was completed in 10 min at -78 °C to give 53.3% of 4-*O*-benzyl-3-hydroxy derivative (512) and only trace amount of other isomer **513** was detected (entry 9). This reagent at 0 °C gave a similar yield of **512** but the hydrolyzed product (73) was increased (entry 10). The best result was obtained when the isomeric mixture **509***exo*/**509***endo* was treated with $BF_3{\cdot}OEt_2/Et_3SiH$ in acetonitrile at 0 °C the benzyl 4-*O*-benzyl derivative **512** in 69.4% yield, with only trace amount of the **513** isomer and hydrolysis product **73** (entry 11), while the pure **509***exo* or **509***endo* isomer gave similar selectivity but a significant amount of hydrolysis product was isolated (entries 12 and 13).



Scheme 109

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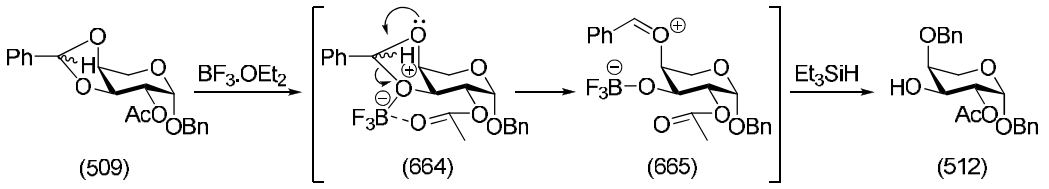
$Cu(OTf)_2$, a catalyst which was used to alter the ring opening of the 4,6-benzylidene compound (Shie *et al.*, 2005) was also examined in our 3,4-benzylidene compounds. The reaction of the isomeric mixture **509***exo* and **509***endo* with $Cu(OTf)_2/Et_3SiH$ in CH_3CN at 0 °C gave only hydrolyzed product, no ring opening product was obtained (entry 14). Pure **509***endo* in CH_2Cl_2 also yielded similar result to that of entry 14, only hydrolyzed product was obtained and trace amount of starting compound (**509***exo*/**509***endo* = 1:1) was detected (entry 15). Increasing the reducing agent (entry 16) provided slight increase of hydrolyzed product. Since only hydrolyzed products were obtained when using this reagent system, it may be assumed that the reducing agent Et_3SiH is not strong enough. Indeed when $Cu(OTf)_2$ was used with BH_3·THF in CH_3CN, benzyl 4-*O*-benzyl derivative **512** was the only isomer obtained as a minor product (18.1%) together with the hydrolyzed product **73** (23.4%) and the major product was resulted from the isomerization of the starting compound (entry 17). However when the reaction was carried out in CH_2Cl_2 or without solvent, a mixture of **512** and **513** was obtained in 5:3 ratio (entries 18 and 19).

From the above result, the regioselective ring opening of **509***exo* and **509***endo* may be altered by the presence of 2-OAc functional group which is capable of coordinating with the BF_3 to form the bidentate complex **664** (Scheme 110), which allows cleavage of the C4-*O* bond to give benzyl 4-*O*-benzyl isomer **512** as a major product whereas $TiCl_4$ and $Cu(OTf)_2$ can form complex at both *O*-3 and *O*-4 of the benzylidene ring to permit O-C cleavage to give a mixture of both benzyl 3-*O*- and 4-*O*-benzyl isomers.



Scheme 110 Transition state of benzylidene acetal cleavage of **509** by BF_3·OEt_2

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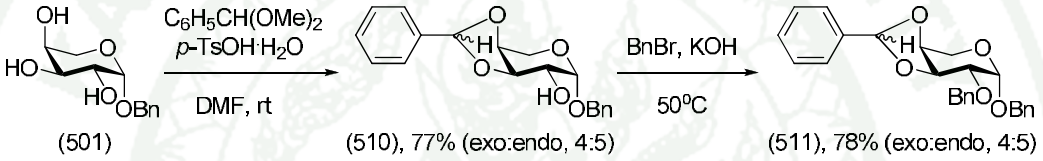
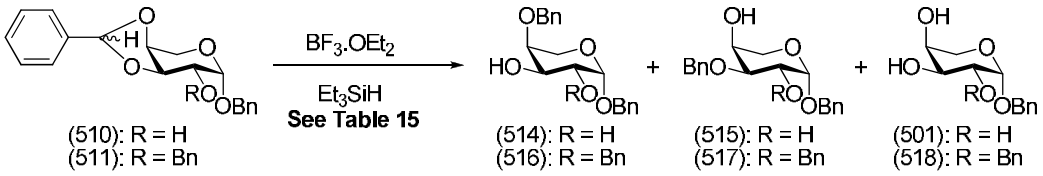
To prove our assumption, the free hydroxyl 3,4-benzylidene acetal compound **510** (Lipták *et al.*, 1982; Matsuzawa *et al.*, 1981) and the benzyl substituted compound **511** were prepared by the method described by Lipták (Lipták, 1978). Treatment of benzyl β-L-arabinose (501) with α,α-dimethoxytoluene resulted in a 4:5 mixture of the **510***exo* and **510***endo* isomers in good yield. Since these isomers could not be completely separated by column chromatography, the mixture was then benzylated and the separation of the resulting mixture of **511***exo* and **511***endo* was successful (Scheme 111).



Scheme 111

We examined the cleavage of **510** and **511** by using $BF_3{\cdot}OEt_2/Et_3SiH$ at 0 °C; the results are shown in Table 15. Treatment of **510***exo* and **510***endo* with $BF_3{\cdot}OEt_2/Et_3SiH$ in CH_3CN at 0 °C gave 4-*O*-benzyl ether (514) and 3-*O*-benzyl ether derivative (515) in 2:1 ratio (entry 20) whereas the benzyl substitution of both **511***endo* and **511***exo* isomers yielded a mixture of **516** and **517** (Matsuzawa *et al.*, 1981) in 3:1 and 1:1 ratios, respectively as well as considerable amount of hydrolyzed product **518** (entries 21 and 22). These results clearly indicated that the direction of ring cleavage by $BF_3{\cdot}OEt_2/Et_3SiH$ is strongly influenced by the acetate substitution at C-2.



Scheme 112

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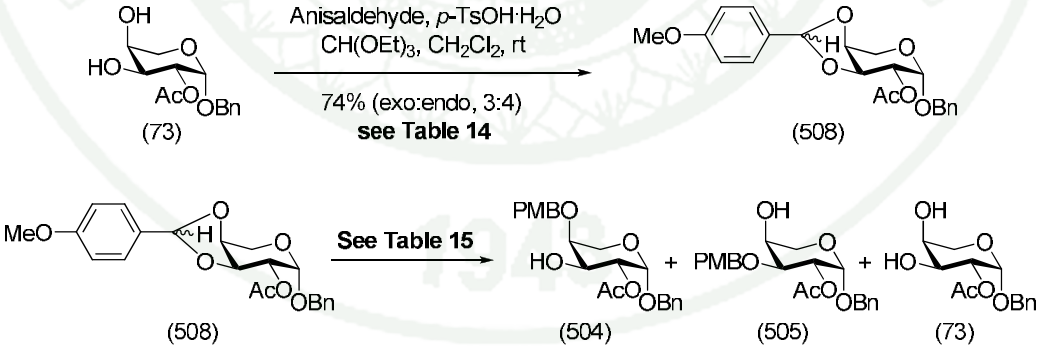
In conclusion, we have found that among the Lewis acids, $BF_3{\cdot}OEt_2/Et_3SiH$ in acetonitrile gave the best result for highly regioselective ring opening of 3,4-*O*-benzylidene acetals of arabinoside derivatives bearing 2-acetoxyl, to furnish the corresponding 4-*O*-benzyl ethers with the 3-hydroxy unsubstituted. The reaction condition is mild, and benzyl or ester protecting groups in the substrates are tolerated. Our investigation also revealed that the regioselective ring opening was not directed by the stereochemistry of the acetalic center but was altered by an adjacent-acetyl group which could coordinate with the BF_3 to form a bidentate metal complex intermediate.

We have also prepared 3,4-*O*-*p*-methoxybenzylidene acetal from diol **73** for the regioselective reductive ring opening studies. The optimized reaction condition was using excess anisaldehyde in the presence of *p*-toluenesulfonic acid monohydrate and triethylorthoformate in dichloromethane at room temperature to furnish *exo* and *endo* products **508** in about 3:4 ratio. The structures of *exo*- and *endo*-**508** were confirmed by the ^{1}H-NMR, the methine proton of the benzylidene group resonated at 5.84 for *endo* isomer and at 6.08 for *exo* isomer (Suzuki *et al.*, 2004).



Scheme 113

The results of reductive ring opening of *p*-methoxybenzylidene acetal derivative clearly showed that when $BF_3{\cdot}OEt_2$ was used as Lewis acids even with triethylsilane or sodium cyanoborohydride as reducing agents, the reaction did not provide the *p*-methoxybenzyl ether (Table 15), only starting material (entries 4 and 5) and hydrolyzed product (entry 3) were obtained. On the other hand, when

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trifluoroacetic acid was used instead of $BF_3 \cdot OEt_2$ with sodium cyanoborohydride as a reducing agent, the 3-*O*-*p*-methoxybenzyl ether was obtained in 46% yield along with hydrolyzed product 38% yield (entry 2). However the desired product, 4-*O*-*p*-methoxybenzyl ether was not observed under this condition. Changing Lewis acid to TMSOTf and $BH_3 \cdot THF$ in dichloromethane at 0°C, the expected product **504** was obtained in 30% yield along with 61% of hydrolysis product (entry 7). Finally, yield of product **504** was increased to 67% when using sodium cyanoborohydride as reducing agent in THF at 0°C (entry 6).

Application of this strategy to synthesize thio- and *p*-methoxybenzyl-4-*O*-benzyl-α-L-arabinopyranoside acceptors has been described.

Thio 2-*O*-acetyl-*exo/endo*-3,4-benzylidene-α-L-arabinose (524 and 525) was synthesized by two pathways from thio β,α-L-arabinose (520) and thio-2-*O*-acetyl-α-L-arabinose (279) as shown in Scheme 114. Thio *endo*-3,4-benzylidene-α-L-arabinose (522) and a mixture of thio *exo/endo*-3,4-benzylidene-β-L-arabinose (523) was obtained in 49% and 22% yield, respectively when treatment of **520** with α,α-dimethoxytoluene in the presence of *p*-toluenesulfonic acid monohydrate in DMF. Acetylation of **522** and **523** with acetic anhydride, triethylamine and DMAP in dichloromethane afforded **524** and **525** in excellent yield. The other pathway from **279,** which was obtained from L-arabinose (54) (Yu and Jin, 2001), by directly reacted **279** with α,α-dimethoxytoluene in the presence of *p*-toluenesulfonic acid monohydrate in DMF gave thio 2-*O*-acetyl-*endo*-3,4-benzylidene-α-L-arabinose (524) in 75% yield (Scheme 114).

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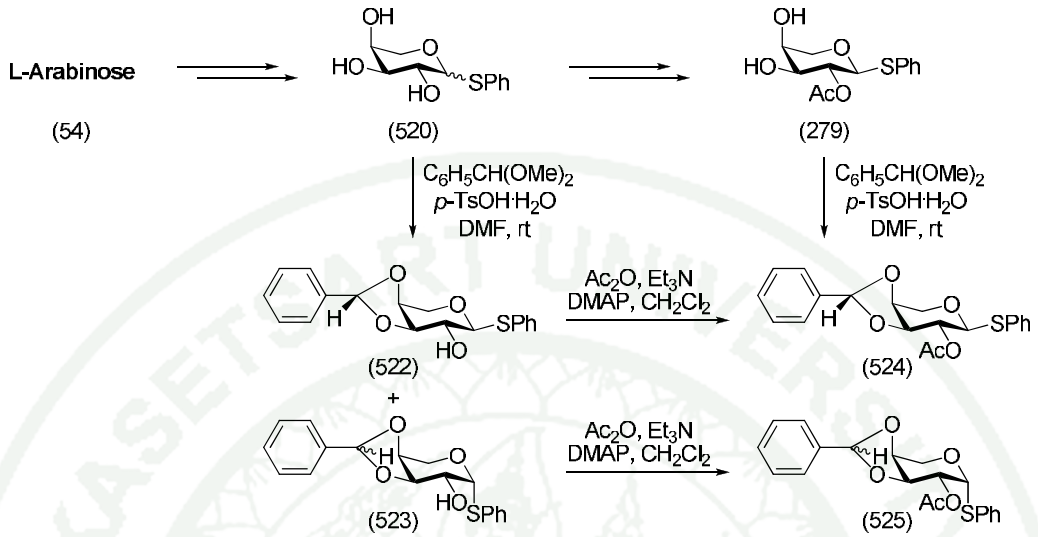
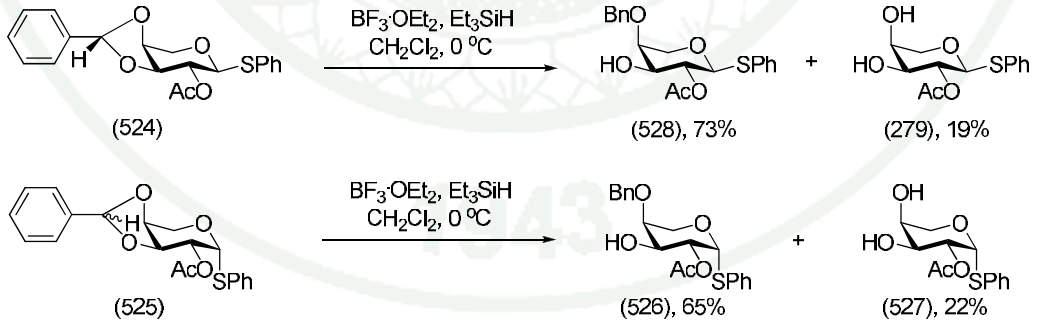


Scheme 114

Regioselective reductive ring opening of either **524** or **525** with $BF_3{\cdot}OEt_2/Et_3SiH$ in CH_2Cl_2 at 0°C was successful produced 4-*O*-benzyl ether **528** and **526** as a major product. However, a significant of hydrolysis by-product **279** and **527** were also obtained (Scheme 115).



Scheme 115

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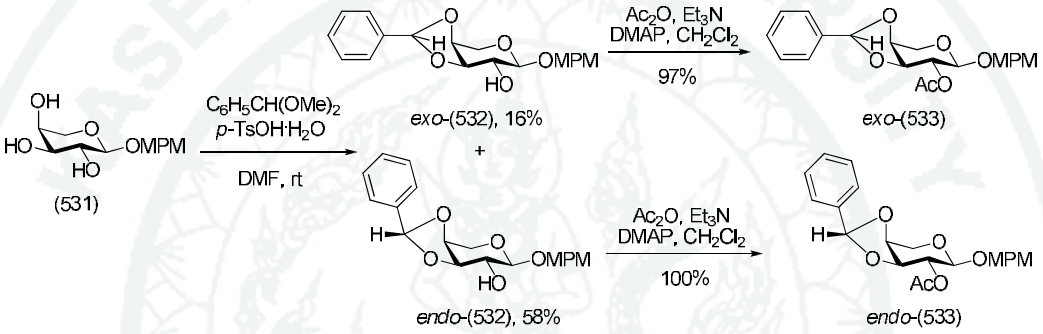
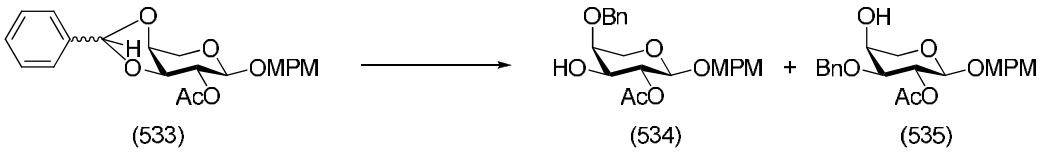
The *p*-methoxybenzyl α-L-arabinopyranoside (531) was easily synthesized from L-arabinose (54) in 4 steps and in 55% yield by Plé's method (Ple´ *et al.*, 2004). Selective benzylidene acetal formation of 3,4-β-dihydroxy of **531** was accomplished by treatment with α,α-dimethoxytoluene in the presence of *p*-toluenesulfonic acid to yield *exo*- and *endo*-3,4-*O*-benzylidene acetal **532** in 16% and 58% yield, respectively.



Scheme 116

As discussed above, reductive opening of the benzylidene acetals **509**, **524** and **525** with a combination of borontrifluoride dietherate and triethylsilane in dichloromethane or acetonitrile proceeded well in a regioselective manner to give 4-*O*-benzyl isomer as a major product. Therefore, we first tried to convert *p*-methoxybenzyl 2-*O*-acetyl-*exo*-3,4-*O*-benzylidene-α-L-arabinopyranose (533) to 4-*O*-benzyl ether **534** under this condition but the desired product was obtained in only 13.8% yield. The unexpected results were found to be removal of *p*-methoxybenzyl group at anomeric position to **536** (53.7%) and removal of benzylidene acetal to diol **538** (22.1%) (Table 21, entry 1).



Scheme 117

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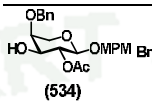
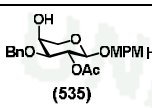
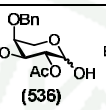
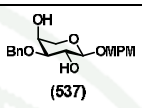
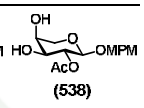
Table 21 Reductive cleavage of 3,4-*O*-benzylidene acetal of *p*-methoxybenzyl 2-*O*-acetyl-*exo/endo*-3,4-*O*-benzylidene-α-L-arabinopyranose (533).

Entry	**533**	conditions	Yield (%)				
			 (534)	 (535)	 (536)	 (537)	 (538)
1	*exo*	$BF_3{\cdot}OEt_2$, Et_3SiH CH_2Cl_2, 0°C, 5 min	13.8	-	53.7	-	22.1
2	*exo*	$Cu(OTf)_2$, $BH_3{\cdot}THF$ rt, 10 min	3.6	6.7	-	12.3	-
3	*exo*	$TiCl_4$, Et_3SiH CH_2Cl_2, -78°C, 5h	42.9	11.2	21.0	-	-
4	*endo*	$TiCl_4$, Et_3SiH CH_2Cl_2, -78°C, 5h	72.8	14.1	5.0	-	-

$Cu(OTf)_2$ in conjugation with $BH_3{\cdot}THF$, another choice of reductive reagent system, has been tried for our compound (533). However, the reaction gave only small amount of the product 4-*O*-benzyl ether **534** (3.6%), together with the other isomer **535** (6.7%) and deacetylated product **537** (12.3%) (Table 21, entry 2).

The final attempt, $TiCl_4$ was used with Et_3SiH for reductive ring opening of *endo*-isomer **533**. This reaction provided 4-*O*-benzyl ether **534** as the main product (72.8%). Nevertheless compounds **535** and **536** were also isolated in 14.1 and 5.0% yield, respectively (Table 21, entries 3 and 4).

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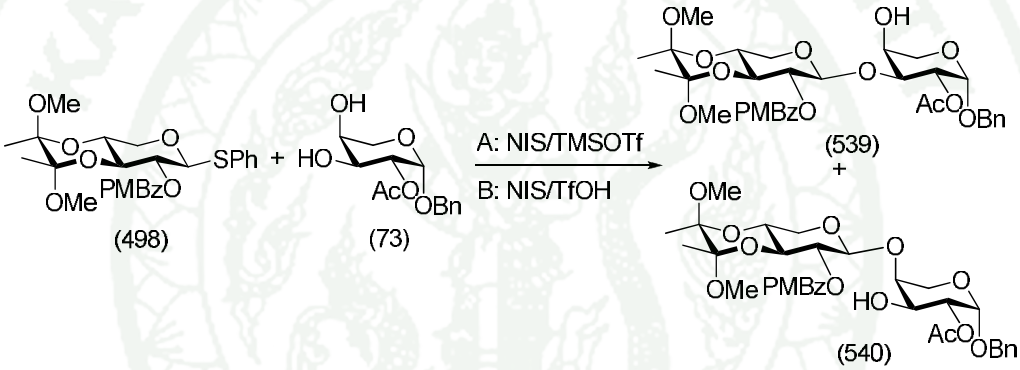
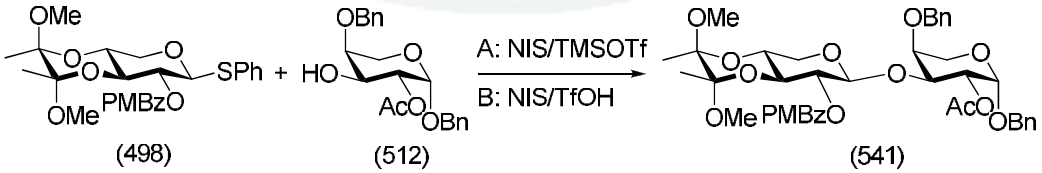
Synthesis of disaccharide moiety

A regioselective glycosylation of diol **73** with thioglycoside donor **498** was carried out by using *N*-iodosuccunimide (NIS) with trimethylsilyl triflate (TMSOTf) or triflic acid (TfOH) in dry dichloromethane at temperature range from -40°C to -30 °C to give the 1→3 coupling product **539** in 75% yield and the 1→4 coupling product **540** in 20% yield (Scheme 118). The major product **539** could be separated from **540** by column chromatography.



Scheme 118

The xylose donor **498** was successfully reacted with benzyl 2-*O*-acetyl-4-*O*-benzyl-β-L-arabinopyranoside (512) under the promotion of NIS/TMSOTf or NIS/TfOH to give the protected disaccharide product **541** in about 65% and 48% yield, respectively.



Scheme 119

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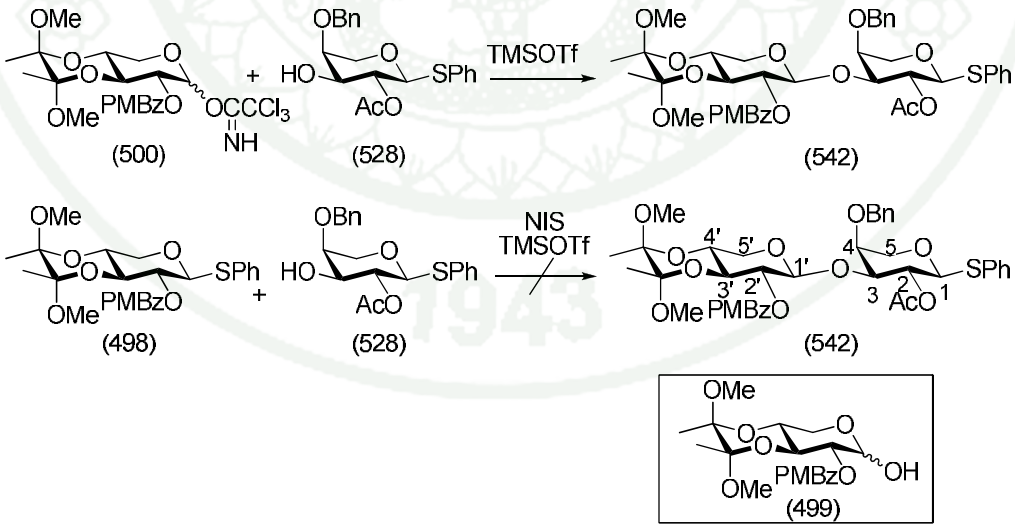
The notable problem in this reaction was the difficulty to monitor the reaction by TLC and to separate the product from the starting compound by column chromatography due to the R_f value of glycosyl acceptor and the disaccharide product are very close. Therefore an excess of glycosyl donor **498** (more than 2 equivalents of glycosyl acceptor **512)** was used in order to get the reaction complete. During the reaction, slowly warming up temperature from -78°C to -20°C to complete the glycosylation and the maintainable temperature at -20°C were crucial to prevent the removal of protecting group.

Glycosylation of the xylosyl trichloroacetimidate **500** and thio 2-*O*-acetyl-4-*O*-benzyl-α-L-arabinopyranoside (528) under TMSOTf catalysis in dry dichloromethane at -78°C to -20°C afforded the disaccharide moiety **542** in only 18% yield. In contrast, thiol activation of **498** by NIS with TMSOTf did not react with arabinosyl acceptor **528** to form the disaccharide unit, only xylopyranoside **499** was isolated. It is possible that thiol group of arabinose acceptor **528** may react with the rest of reagent (NIS/TMSOTf) in the reaction faster than coupling reaction.



Scheme 120

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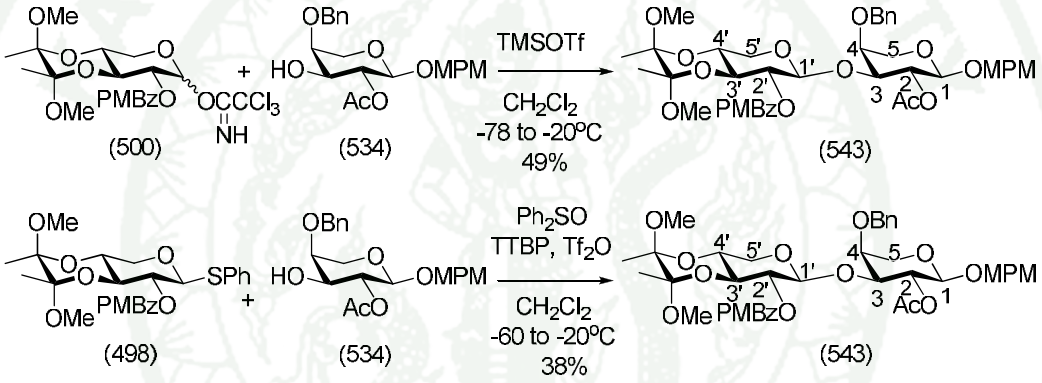
4-Methoxybenzyl 2-*O*-acetyl-3-*O*-(2-*O*-methoxybenzoyl-(2'*S*,3'*S*)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-β-D-xylopyranosyl)-4-*O*-benzyl-α-L-arabinopyranoside (543) was achieved by two glycosylation approaches. The first one was coupling between xylosyl trichloroacetimidate **500** and the arabinosyl acceptor **534** in the presence of TMSOTf to provide disaccharide moiety **543** in moderate yield. The second method was assessed in the diphenylsulfoxide (Ph_2SO)-triflic anhydride (Tf_2O) mediated condensation to produce the protected disaccharide **543** in 38% yield.



Scheme 121

Many attempts to transform disaccharide **541** to the desired product **544** by selective debenzylation at anomeric position under various conditions gave unsatisfied results. The disaccharide **544** was isolated in only 32% yield together with the side product **545** in 53% yield when using 10%Pd/C, hydrogen gas in ethyl acetate and ethanol at room temperature (Scheme 122). Other reagent systems (4M HCl/CH_3CN, 10%Pd/C/Et_3SiH, anh. $FeCl_3$) did not provide the desired product **544**.

The disaccharide **544** was also synthesized from glycoside **542** by using NBS in dichloromethane and water (9:1) at room temperature, howver, the product was obtained in very low yield (17%) (Scheme 122).

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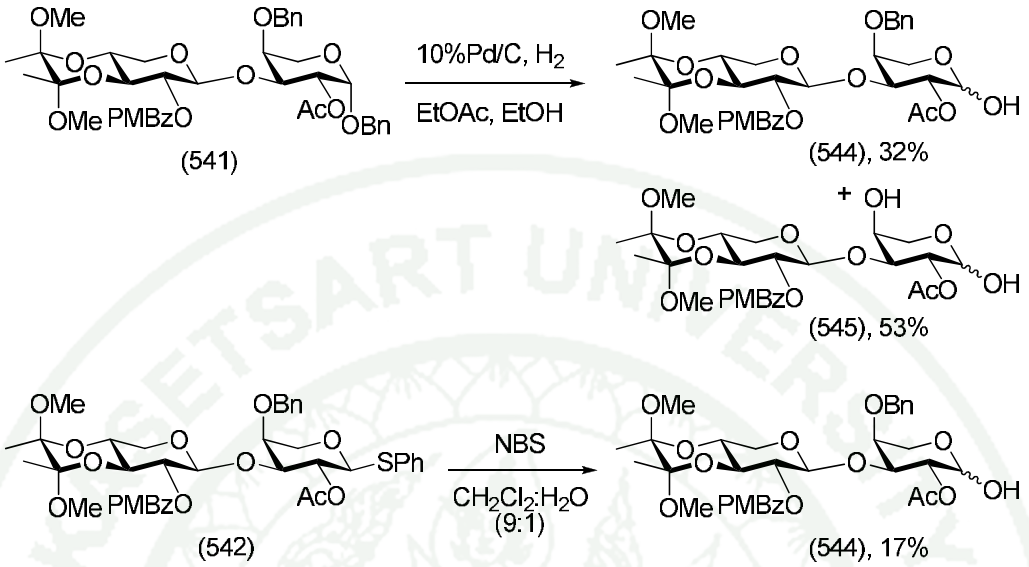
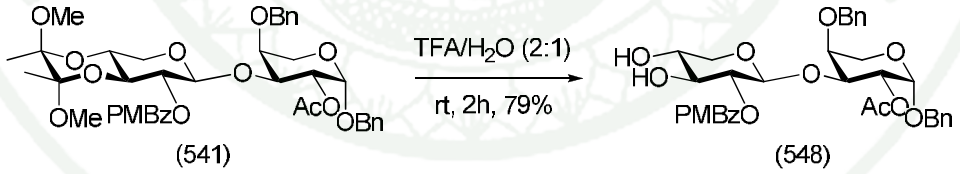


Scheme 122

3,4-Butanediacetal protecting group of disaccharide **541** was easily removed by using trifluoroacetic acid and water (2:1) at room temperature to deliver the diol **548** in 79% yield (Scheme 123).



Scheme 123

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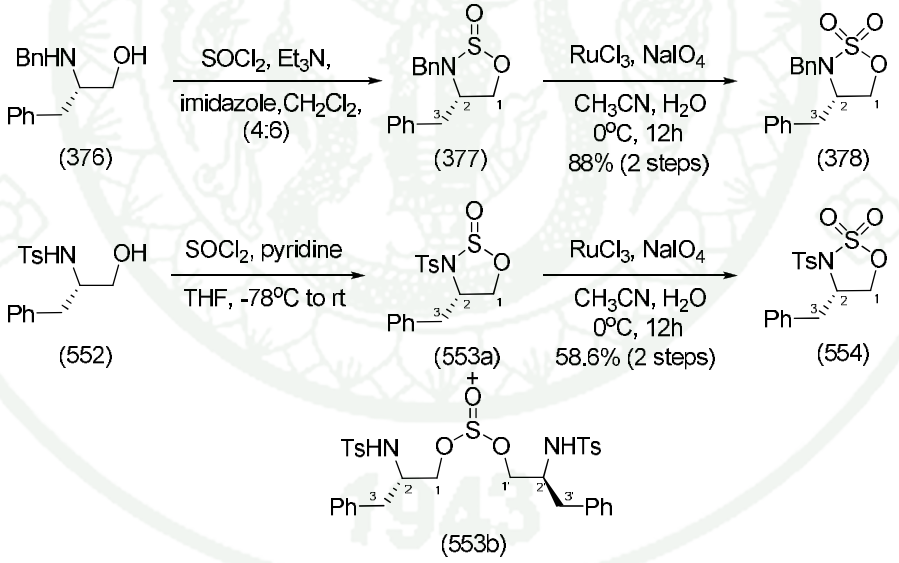
3. Synthesis of five- and six-membered cyclic sulfamidates

The enantiopure five- and six-membered cyclic sulfamidates were conveniently synthesized in two steps from the corresponding *β*- and *γ*-amino alcohols which were readily prepared from the enantiopure amino acid derivatives. Five-membered cyclic sulfamidate **378** was readily obtained in good yield by treating amino alcohol **376** with $SOCl_2$ in the presence of imidazole and then subsequent oxidation (cat. $RuCl_3$, $NaIO_4$). Unfortunately it was found that synthesis of tosylated cyclic sulfamidate **554** using the same condition afforded the mixture of cyclic sulfamidite **553a** and dimer product **553b** (Scheme 124). The optimized condition to synthesize cyclic sulfamidite **553a** was obtained by using $SOCl_2$, pyridine in THF at low temperature (-78 °C) in high dilution (Han *et al.*, 2005).



Scheme 124

Unsubstituted six-membered cyclic sulfamidates **559** and **563** could be prepared from *β*-alanine derivative **555** in moderate overall yield using the same methodology (Scheme 86).

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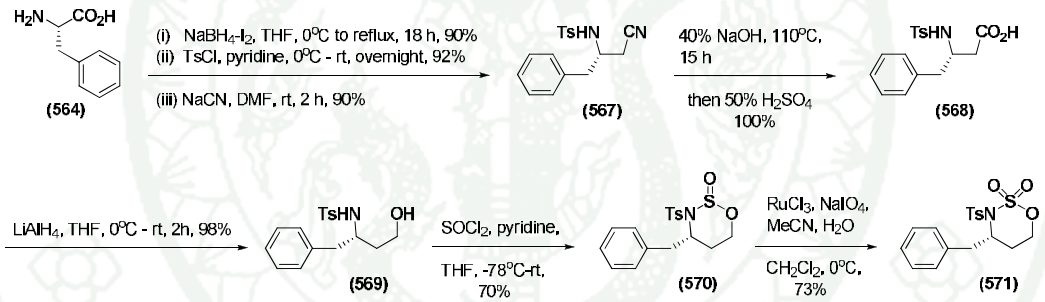
The enantiopure six-membered cyclic sulfamidate **571** could be synthesized from L-phenylalanine *via* γ-amino alcohol **569** which was easily prepared by reduction of α-amino acid to the corresponding β-amino alcohol (McKennon *et al.*, 1993), tosylation of β-amino alcohol followed by treatment with NaCN in DMF gave *N*-tosyl β-amino nitrile **567** in high yield (Ghorai *et al.*, 2007). β-Amino nitrile **567** was hydrolyzed to the corresponding acid **568** subsequently, reduction of acid **568** provided γ-amino alcohol **709** in excellent yield. The γ-amino alcohol was converted to substituented six-membered cyclic sulfamidate **571** in about 51% yield by treating the thionyl chloride/tertiary amine/non-polar solvent condition subsequent oxidation (cat. $RuCl_3$, $NaIO_4$) (Scheme 125). The absolute configuration of compound **571** was confirmed by X-ray crystallography as shown in Figure 14.



Scheme 125

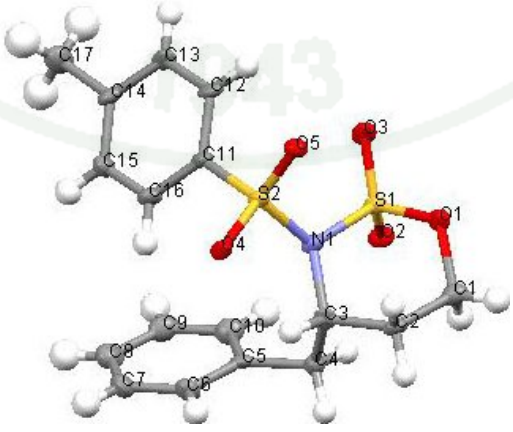


Figure 14 The X-ray crystal structure of compound **571**.

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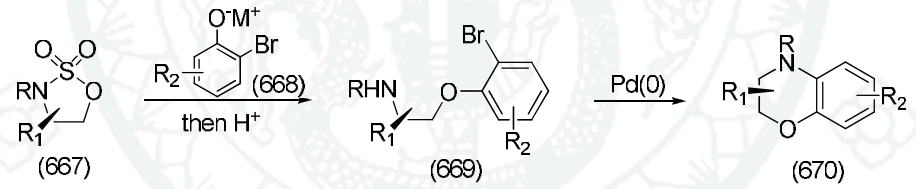
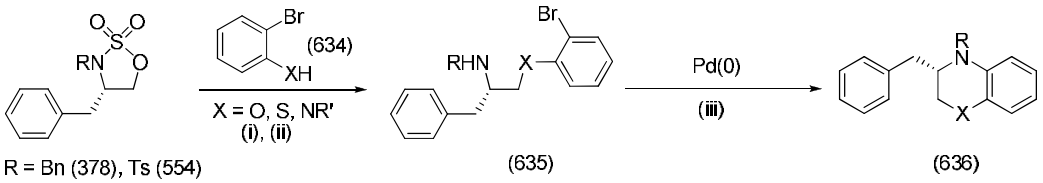
4. Synthesis of *N*-heterocycle *via* cyclic sulfamidates

Cyclic sulfamidates function as excellent precursors to establish a variety of *N*-heterocyclic compounds by ring opening with a suitable nucleophile. Over the past decades, many nucleophilic displacements of 1,2- and 1,3-cyclic sulfamidates were explored, for example, opening of cyclic sulfamidates with malonate enolates, aryl-stabilised enolates and heteroatom-stabilised enolates (N, S). Herein, we focus on reactions of cyclic sulfamidates with heteroatom nucleophiles followed by a cyclisation to deliver chiral benzannulated medium ring heterocyclic scaffolds. In 2007, John F. Bower and co-worker reported synthesis of enantiopure 1,4-benzoxazines *via* 1,2-cyclic sulfamidates (Scheme 126) using a two pot sequence of annulation, *N*-sulfate hydrolysis, and Pd catalysed amination (Bower *et al.*, 2007). These compounds represent subunits of natural products and also are of medicinal value.



Scheme 126

Following this methodology, various benzoxazines, benzothiazines and quinoxalines were synthesized *via* two different protected 1,2-cyclic sulfamidates (Table 17).



Reagents and conditions: (i) NaH, DMF, rt; (ii). aq. 5M HCl; (iii) cat. $Pd(OAc)_2$, xantphos, NaO^tBu, PhMe, 100°C

Scheme 127

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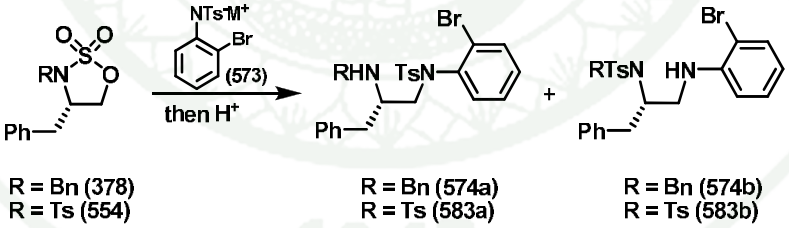
Nucleophilic addition and cyclization under Pd(0)-mediated Buchwald-Hartwig amination conditions of *N*-benzyl and *N*-tosyl cyclic sulfamidates (378 and 554) based on 2-bromophenol, 2-bromothiophenol and *N*-protected 2-bromoaniline provided direct access to substituted and enantiomerically pure 1,4-benzoxazine, 1,4-benzothiazine and quinoxaline variants, respectively, in moderate to high yields (Table 17). Opening of **554** with anion of aniline **581** was less efficient, possibly due to competing elimination, and adduct **582** was isolated in very low yield (11%) (entry 5) (Bower *et al.*, 2007).

We found that the migration of tosyl group from nitrogen atom of 2-bromoaniline to nitrogen atom of *N*-protected cyclic sulfamidates was observed in nucleophilic displacement of cyclic sulfamidates **378** and **554** (entries 2 and 6) with *N*-tosyl-2-bromoaniline (Krolski *et al.*, 1988). It is possible to obtain the tosyl-migrated product (574b and 583b) upon hydrolysis of *N*-sulfate intermediate under acidic conditions (Scheme 128). The ratio of addition product and tosyl migrated product depends on competition between reversible tosyl migration to the other nitrogen atom and protonation of the secondary amine.



Scheme 128

The proposed mechanism for the tosyl migrated product involves intramolecular nucleoplilic attack of secondary amine to sulfonamide (671) and releasing aromatic amine (672) due to the mesomeric effect of aromatic ring stabilized the lone pair of electrons on nitrogen into the ring. The secondary amine in addition product could be protonated under acidic condition easier than tertiary aromatic amine arised from inductive effect of alkyl groups raises the energy of the lone pair of

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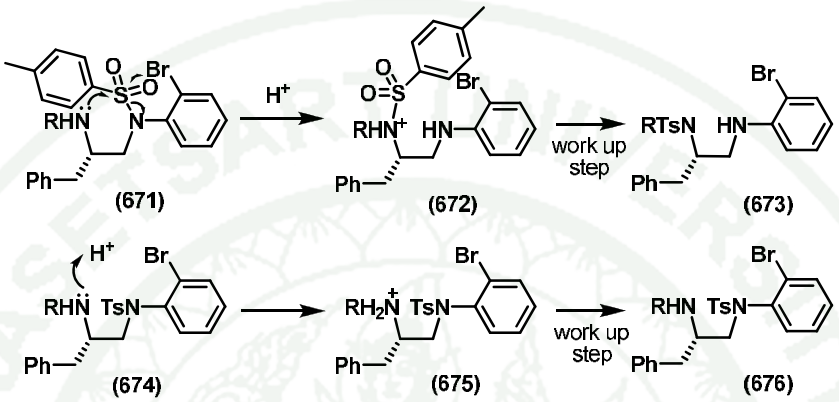
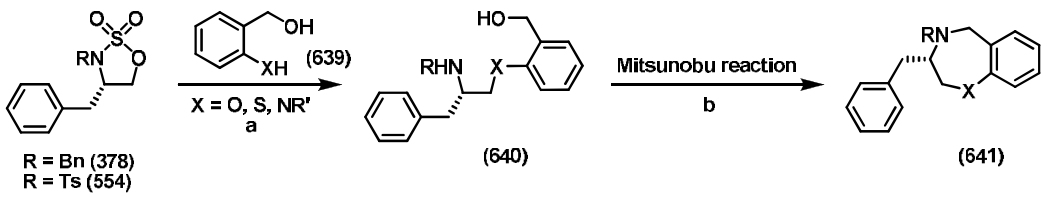
electrons, thus elevating the basicity of secondary amine, and also predominant steric hindrance of the aromatic tertiary amine (Scheme 129).



Scheme 129

The attempts to synthesize seven-membered *N*-heterocyclic compound starting from 1,3-cyclic sulfamidates **559** and **563** under Pd(0)-mediated Buchwald-Hartwig amination conditions were unsuccessful, only starting compound and reduction product **594** were observed (Table 18).

As previously attempted, we have searched another approach for the construction of seven- and eight-membered ring heterocycles *via* 1,2 and 1,3-cyclic sulfamidates. The Mitsunobu approach for the formation of the carbonheteroatom bond offers a better and more convenient route to the synthesis of benzannulated medium ring heterocycles in an optically pure form. We can synthesize the precursors for Mitsunobu reaction by nucleophilic addition of 1,2 and 1,3-cyclic sulfamidates based on 2-hydroxybenzyl alcohol, 2-mercaptobenzyl alcohol and *N*-tosyl-2-hydroxymethylaniline (Hechavarría Fonseca *et al.*, 2003) (Table 19).



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Many attempts to synthesize benzoxazepine **597** from addition product precursor **596**, which contains *N*-benzyl protecting group, were unsuccessful (Tsunoda *et al.*, 1996). However, exposure of compound **599** to Mitsunobu reaction condition resulted in formation of desired enantiomerically pure benzodiazepine derivative **600** in excellent yield (Table 19, entries 1 and 2). The absolute configuration of compound **600** was confirmed by X-ray crystallography as shown in Figure 15.

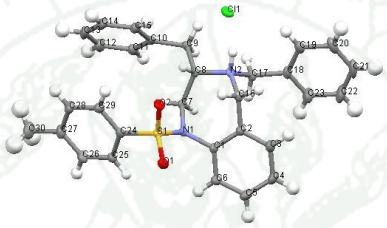
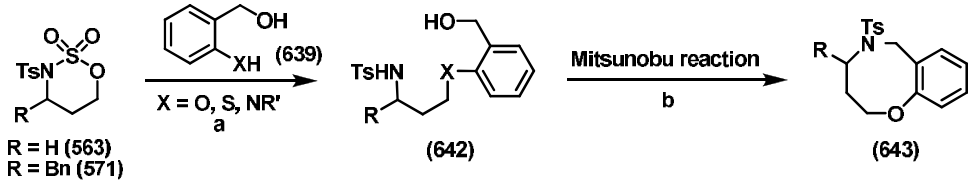


Figure 15 The X-ray crystal structure of compound **600**.

The introduction of a tosyl group on *N*-cyclic sulfamidate addition product made the proton attached to nitrogen acidic enough to participate in Mitsunobu reaction (Mishra and Panda, 2007). Synthesis of benzoxazepine, benzodiazepine and benzothiazepine derivatives were accomplished by using a two pot sequence of annulation, *N*-sulfate hydrolysis and Mitsunobu reaction in moderate to high yield (Table 19, entries 3-5).

These conditions have been successfully applied to the other adducts derived from 1,3-cyclic sulfamidates to deliver the eight-membered ring heterocycles in moderate to good yield (Table 20). Unfortunately, construction of the eight-membered ring heterocycles by cyclization of the ring cleavage products **608** and **619** was not accomplished, only 16-membered rings **610** and **621** were observed.



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CONCLUSIONS

1. Synthesis of steroidal OSW-1 intermediate

The key intermediate for the intramolecular strategy, 3β-benzyloxy-16β-(isobutyl-monomethyl ester malonate-ester)-17α-hydroxy-pregnenolone, was successfully synthesized in 10 steps with 10.4% overall yield from a commercially available diosgenin.

Intramolecular McMurry coupling or samarium diiodide-promoted keto-ester coupling reaction of our key intermediate did not provide the expected β-keto lactone intermediate, only 5-pregnene-20-one derivative or 16-dehydropregnenolone was obtained.

2. Synthesis of disaccharide moieties

The facile syntheses of three partially protected OSW-1 disaccharide moieties, having 2-*O*-*p*-methoxybenzoyl-β-D-xylopyranosyl-(1→3)-2-*O*-acetyl-L-arabinopyranoside structure, were favorably elaborated by glycosylation of xylopyranose donors and arabinopyranose acceptors.

The xylopyranose donors were synthesized by a short synthetic approach *via* convenient selective 1,2-diacetal protection of 3,4-*trans*-diequatorial hydroxyl group. Also, three arabinose acceptors were prepared in a three steps sequence from easily available benzyl, *p*-methoxybenzyl and thiophenyl α/β-L-arabinopyranosides in 44.5, 53.3 and 28.5% yield, respectively, by using regioselective reductive ring opening of benzylidene acetals as the key feature.

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3. Synthesis of five- and six-membered cyclic sulfamidates

Synthesis of cyclic sulfamidates with two different protecting group (benzyl and tosyl) were accomplished in two steps from amino alcohols which were obtained from enantiomerically pure α- and β-amino acids.

4. Synthesis of *N*-heterocycles *via* cyclic sulfamidates

1,2- and 1,3-cyclic sulfamidates react efficiently with a variety of nucleophiles to deliver annulated intermediates which are converted to six-, seven- and eight-membered benzannulated heterocycles. Pd(0)-catalysed cyclisation of annulated intermediates under standard condition (*t*-BuONa, PhMe, $Pd(OAc)_2$, 100°C) was successful to produce six-membered heterocycles but was not succeed with seven-membered heterocycles. Mitsunobu reaction of annulated intermediates was a convenient route to synthesize enantiomerically pure seven- and eight-membered heterocycles.

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APPENDIX

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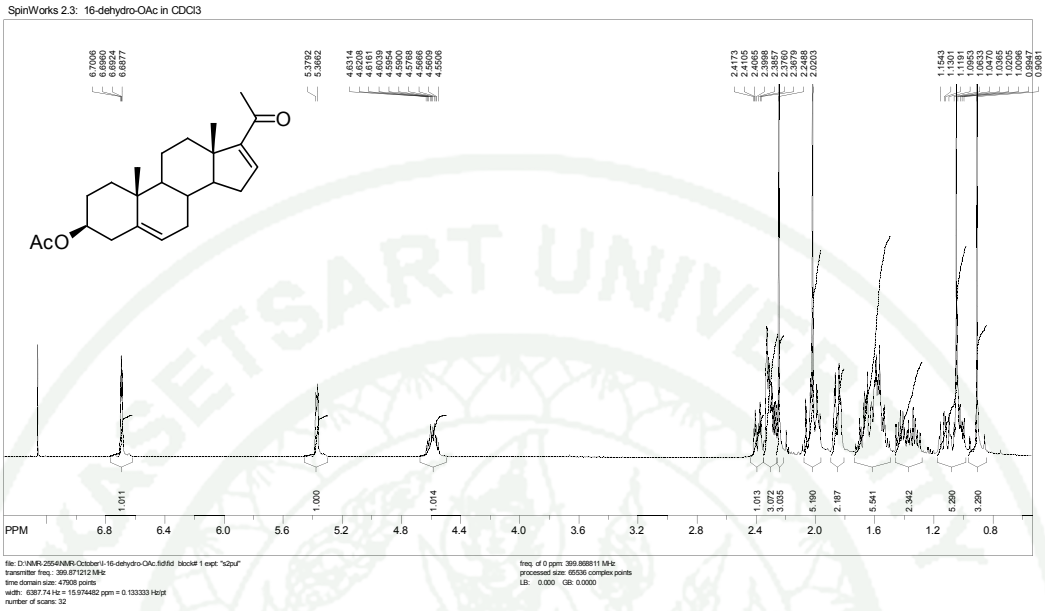
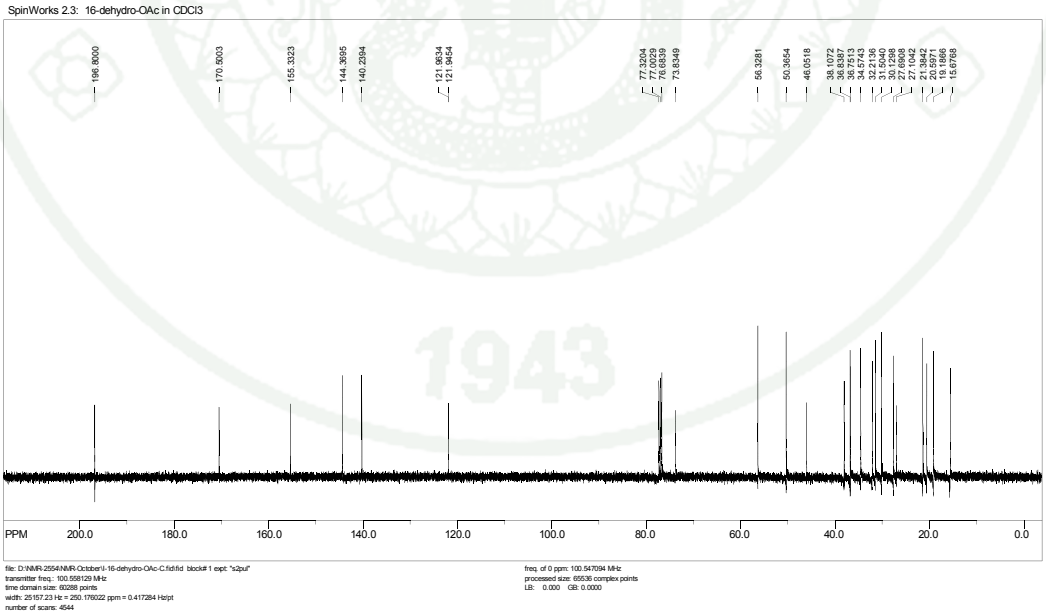


Appendix Figure 1 400 MHz ^{1}H NMR spectrum: 3β-acetoxy-5,16-pregnadiene-20-one (49)



Appendix Figure 2 100 MHz ^{13}C NMR spectrum: 3β-acetoxy-5,16-pregnadiene-20-one (49)

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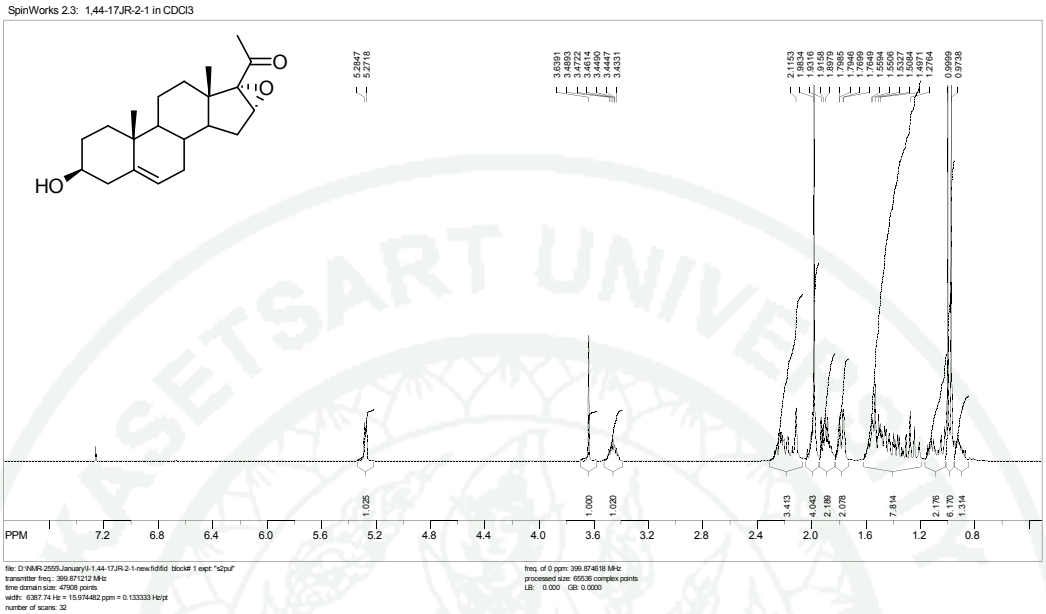
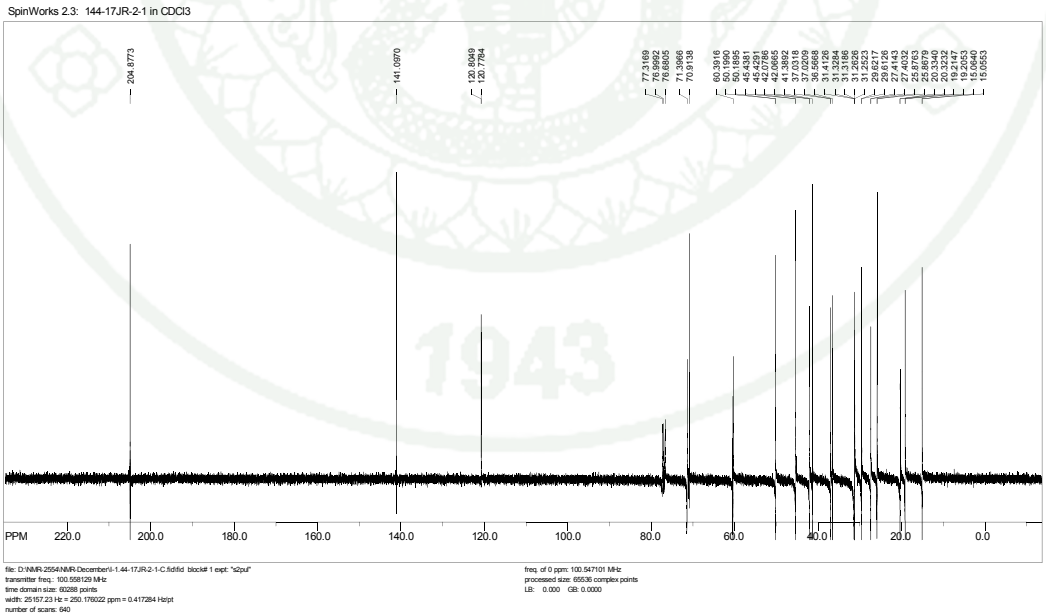


Appendix Figure 3 400 MHz ^{1}H NMR spectrum: 3β-hydroxy-16α,17α-epoxy-5-pregnene-20-one (451)



Appendix Figure 4 100 MHz ^{13}C NMR spectrum: 3β-hydroxy-16α,17α-epoxy-5-pregnene-20-one (451)

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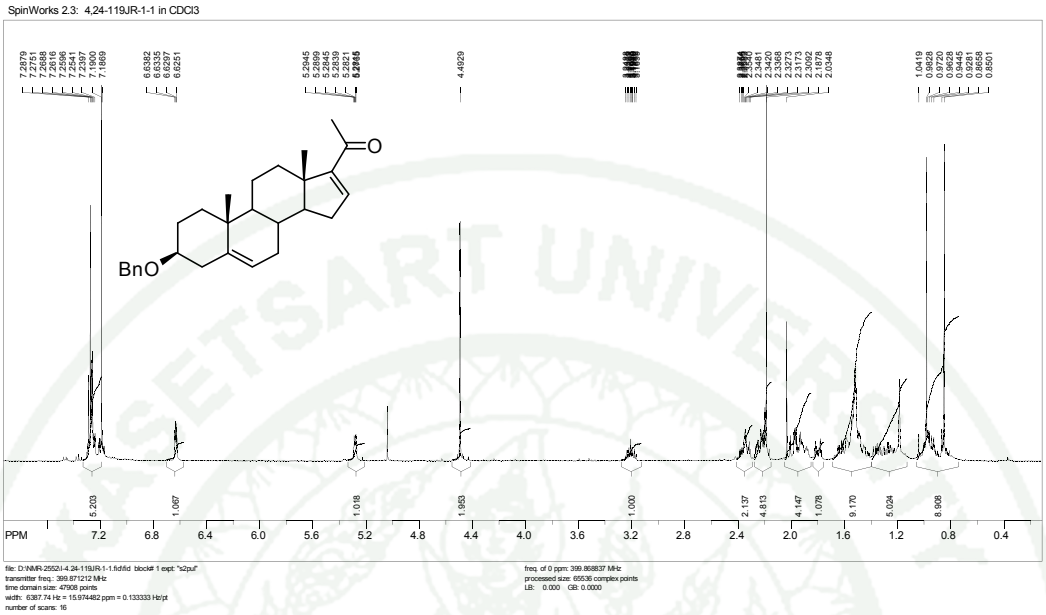
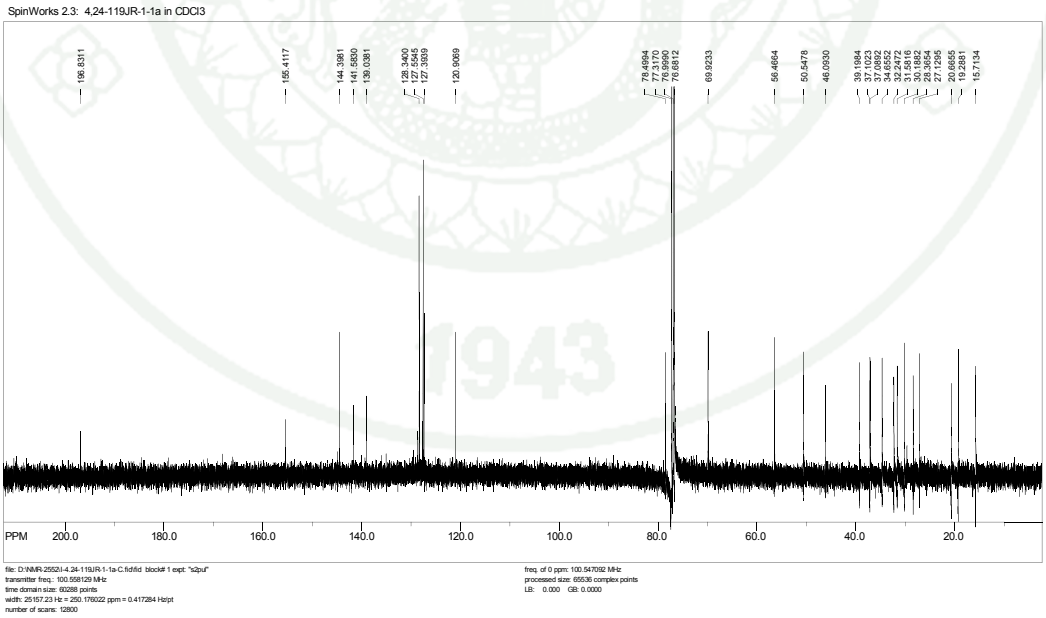


Appendix Figure 5 400 MHz ^{1}H NMR spectrum: 3β-benzyloxy-5,16-pregnadiene-20-one (453)



Appendix Figure 6 100 MHz ^{13}C NMR spectrum: 3β-benzyloxy-5,16-pregnadiene-20-one (453)

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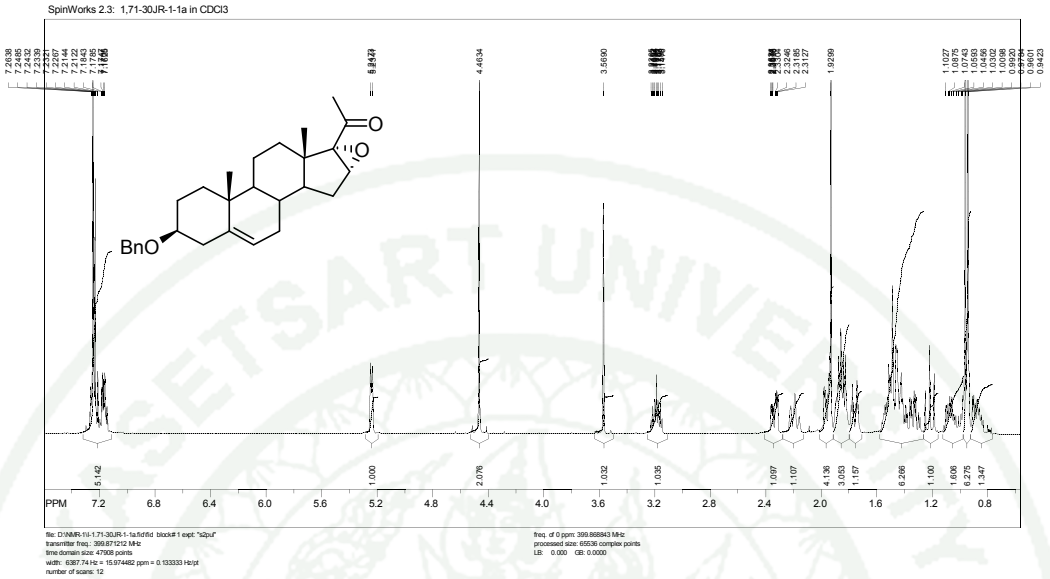
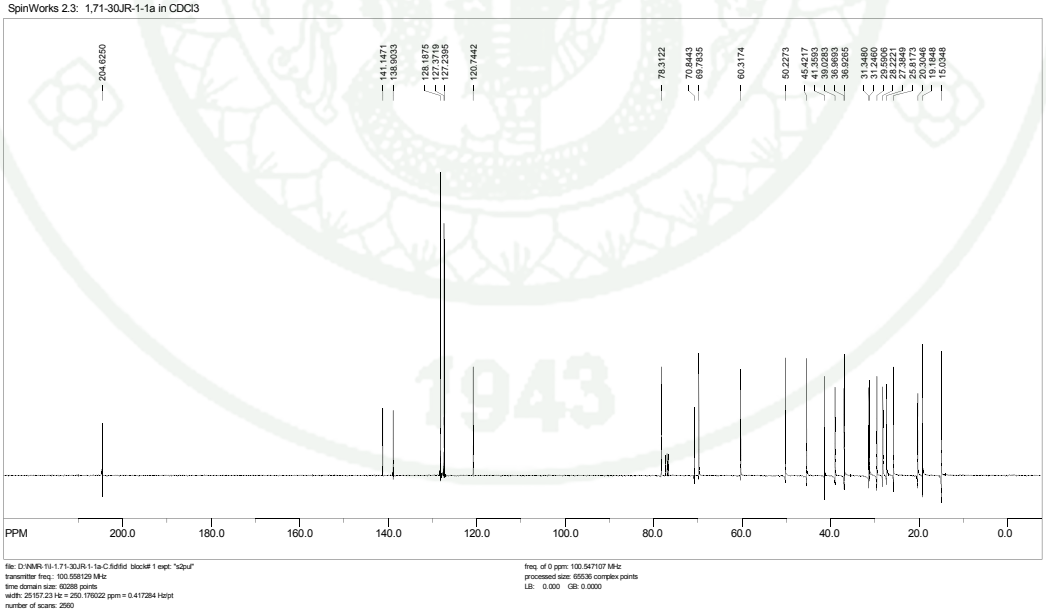


Appendix Figure 7 400 MHz ^{1}H NMR spectrum: 3β-benzyloxy-16α,17α-epoxy-5-pregnene-20-one (454)



Appendix Figure 8 100 MHz ^{13}C NMR spectrum: 3β-benzyloxy-16α,17α-epoxy-5-pregnene-20-one (454)

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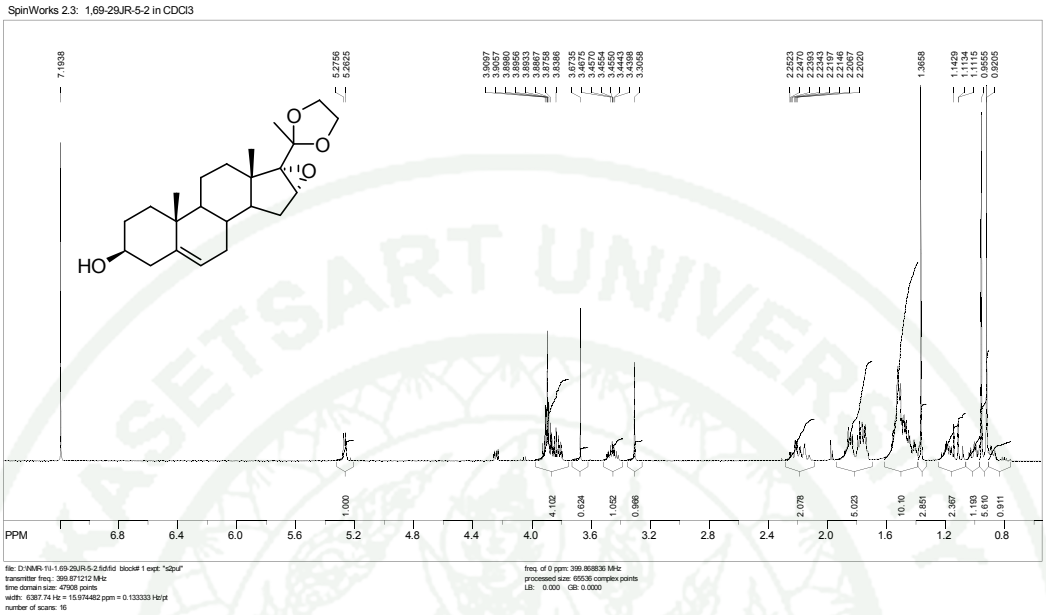
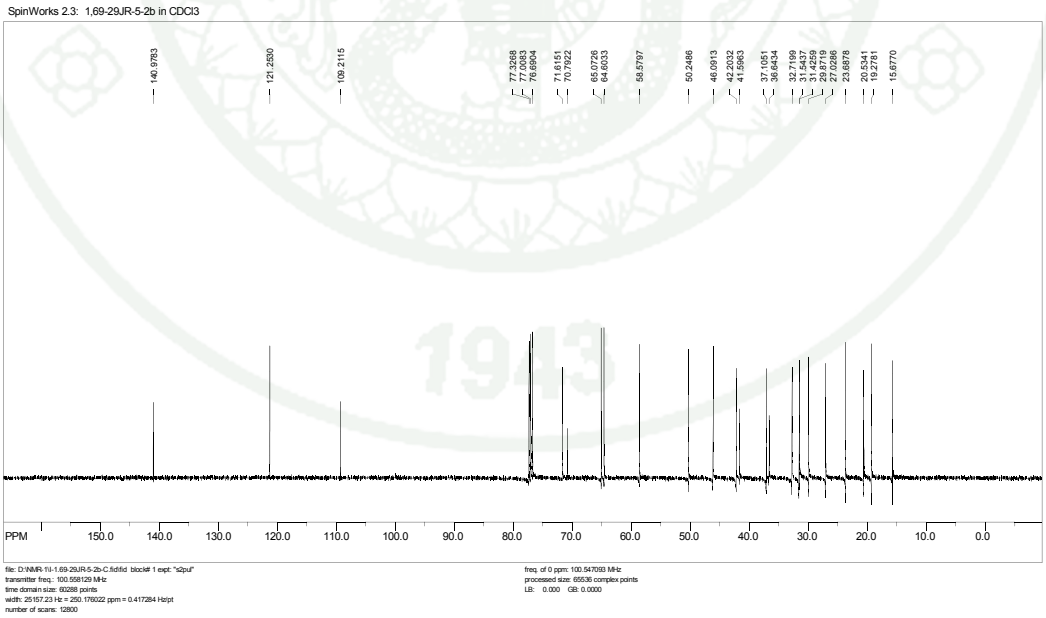


Appendix Figure 9 400 MHz ^{1}H NMR spectrum: 3β-hydroxy-16α,17α-epoxy-20,20-(ethylenedioxy)-5-pregnene (455)



Appendix Figure 10 100 MHz ^{13}C NMR spectrum: 3β-hydroxy-16α,17α-epoxy-20,20-(ethylenedioxy)-5-pregnene (455)

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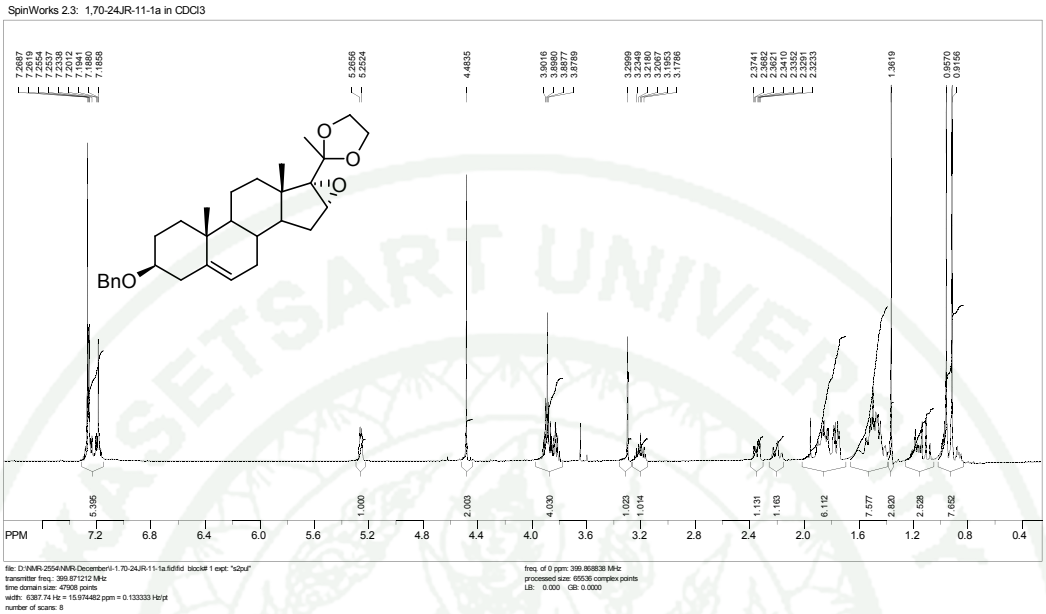
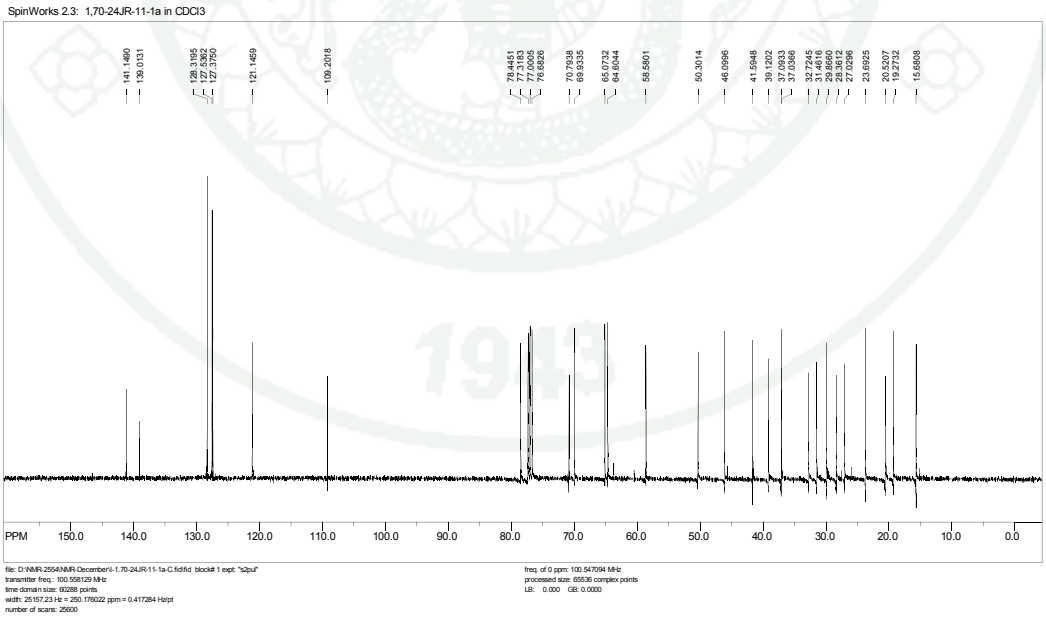


Appendix Figure 11 400 MHz ^{1}H NMR spectrum: 3β-benzyloxy-16α,17α-epoxy-20,20-(ethylenedioxy)-5-pregnene (456)



Appendix Figure 12 100 MHz ^{13}C NMR spectrum: 3β-benzyloxy-16α,17α-epoxy-20,20-(ethylenedioxy)-5-pregnene (456)

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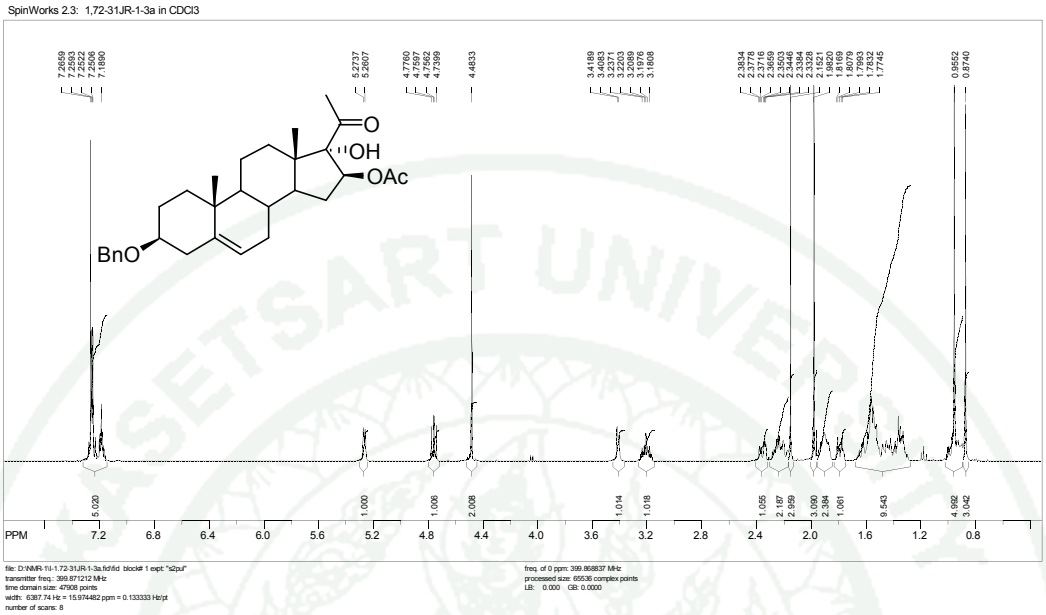
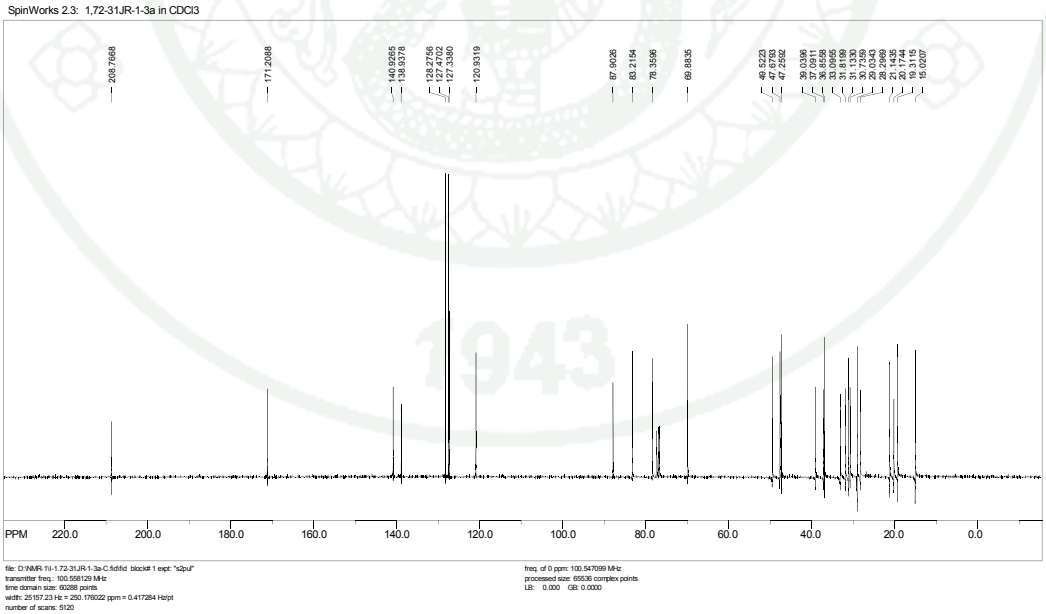


Appendix Figure 13 400 MHz ^{1}H NMR spectrum: 3β-benzyloxy-16β-acetyloxy-17α-hydroxy-5-pregnene-20-one (457)



Appendix Figure 14 100 MHz ^{13}C NMR spectrum: 3β-benzyloxy-16β-acetyloxy-17α-hydroxy-5-pregnene-20-one (457)

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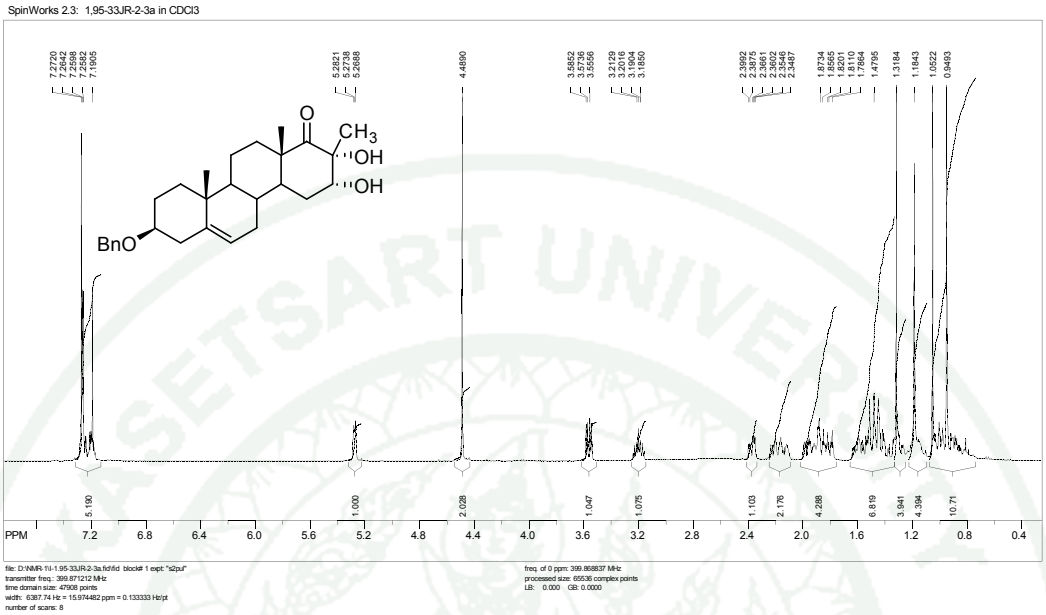
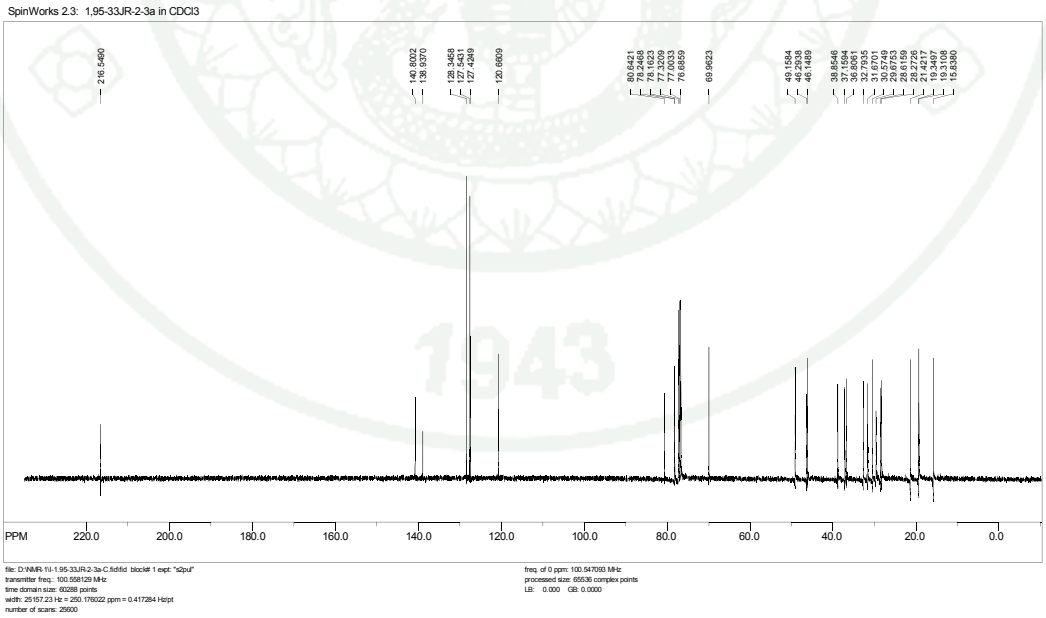


Appendix Figure 15 400 MHz ^{1}H NMR spectrum: D-homoandrost-5-en-17a-one, 3β-benzyloxy-16α,17α-dihydroxy-17-methyl- (7CI,8CI) (459)



Appendix Figure 16 100 MHz ^{13}C NMR spectrum: D-homoandrost-5-en-17a-one, 3β-benzyloxy-16α,17α-dihydroxy-17-methyl- (7CI,8CI) (459)

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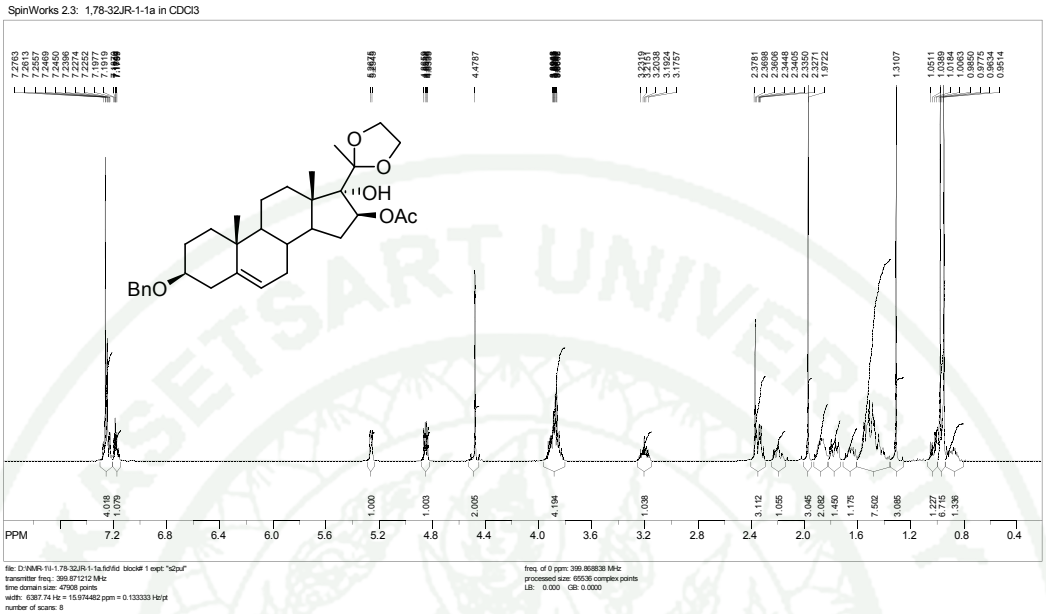
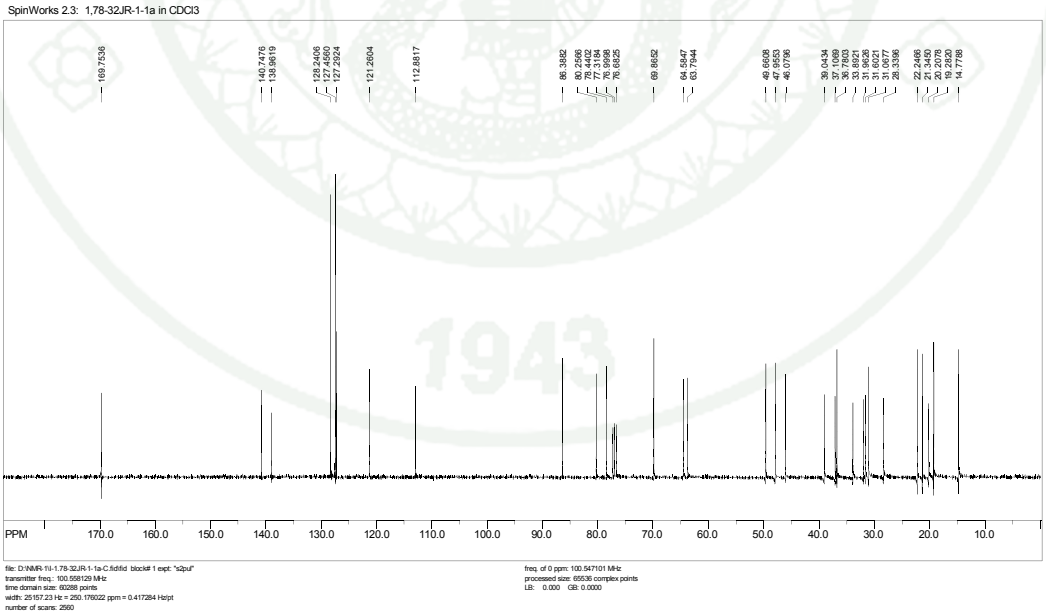


Appendix Figure 17 400 MHz ^{1}H NMR spectrum: 3β-benzyloxy-16β-acetyloxy-17α-hydroxy-20,20-(ethylenedioxy)-5-pregnene (460)



Appendix Figure 18 100 MHz ^{13}C NMR spectrum: 3β-benzyloxy-16β-acetyloxy-17α-hydroxy-20,20-(ethylenedioxy)-5-pregnene (460)

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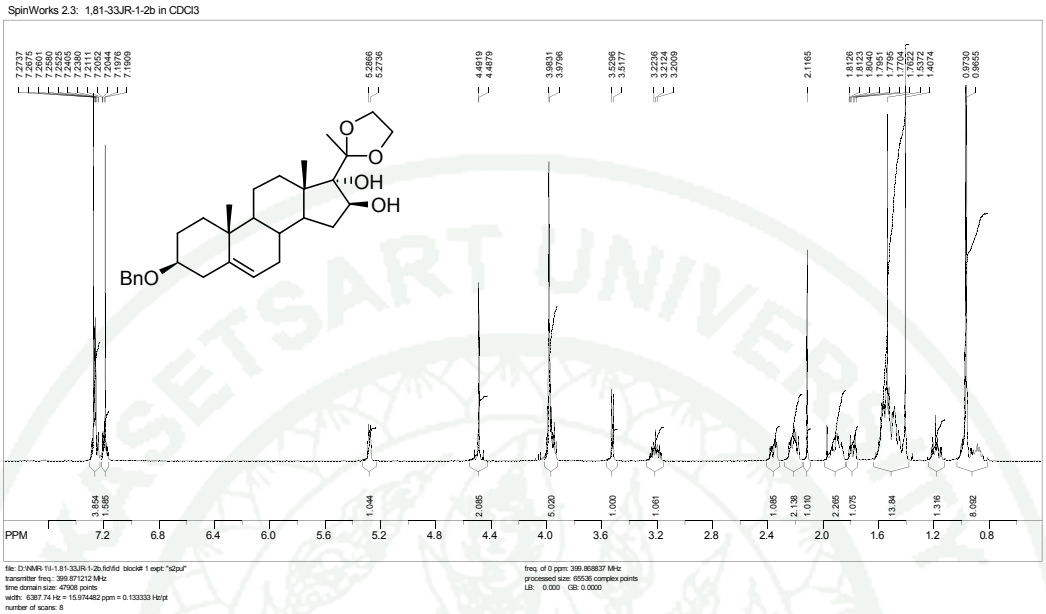
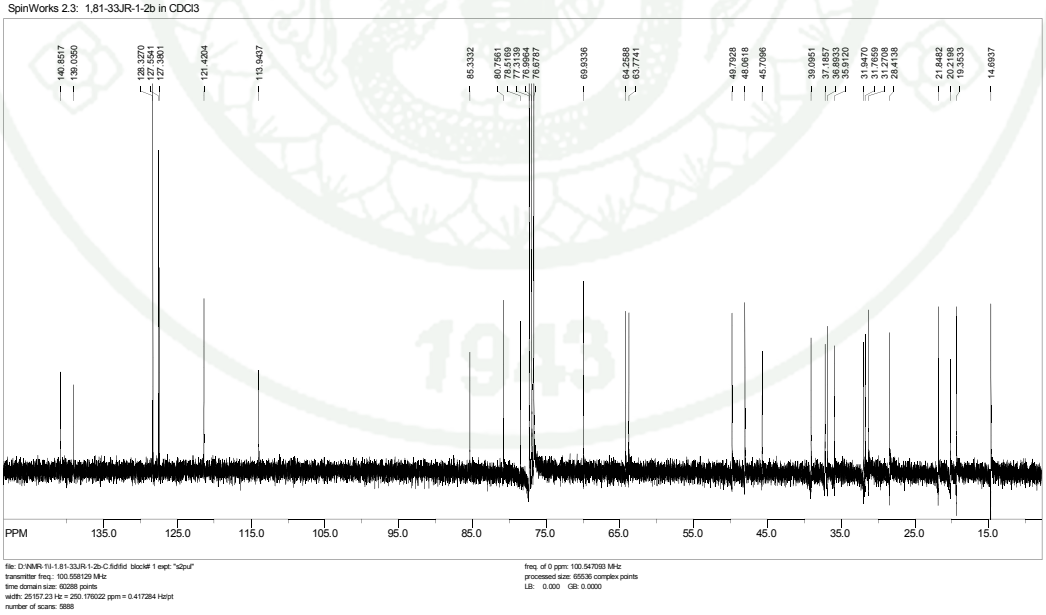


Appendix Figure 19 400 MHz ^{1}H NMR spectrum: 3β-benzyloxy-16β,17α-dihydroxy-20,20-(ethylenedioxy)-5-pregnene (461)



Appendix Figure 20 100 MHz ^{13}C NMR spectrum: 3β-benzyloxy-16β,17α-dihydroxy-20,20-(ethylenedioxy)-5-pregnene (461)

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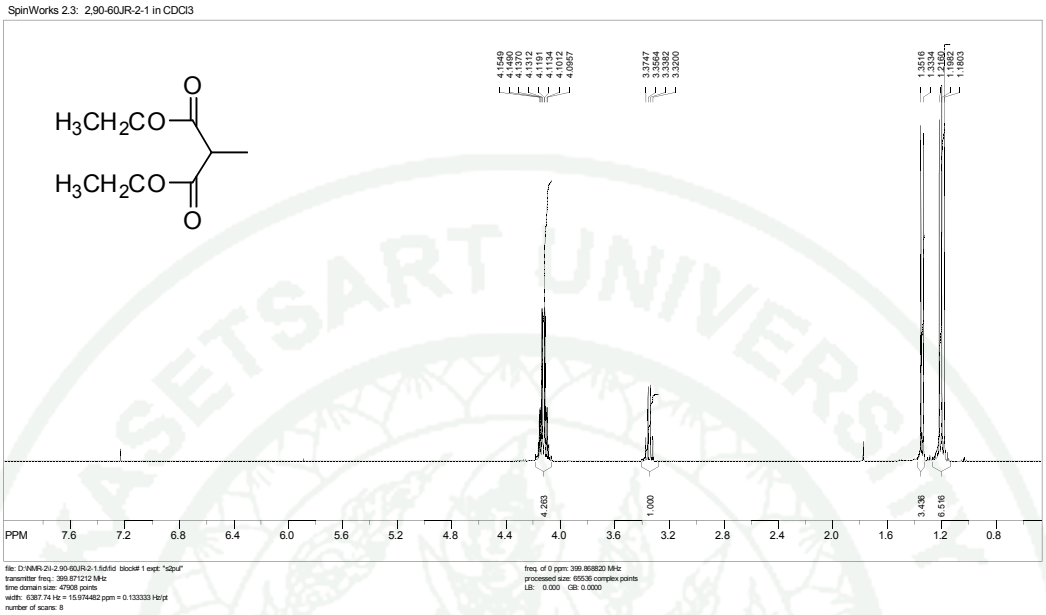
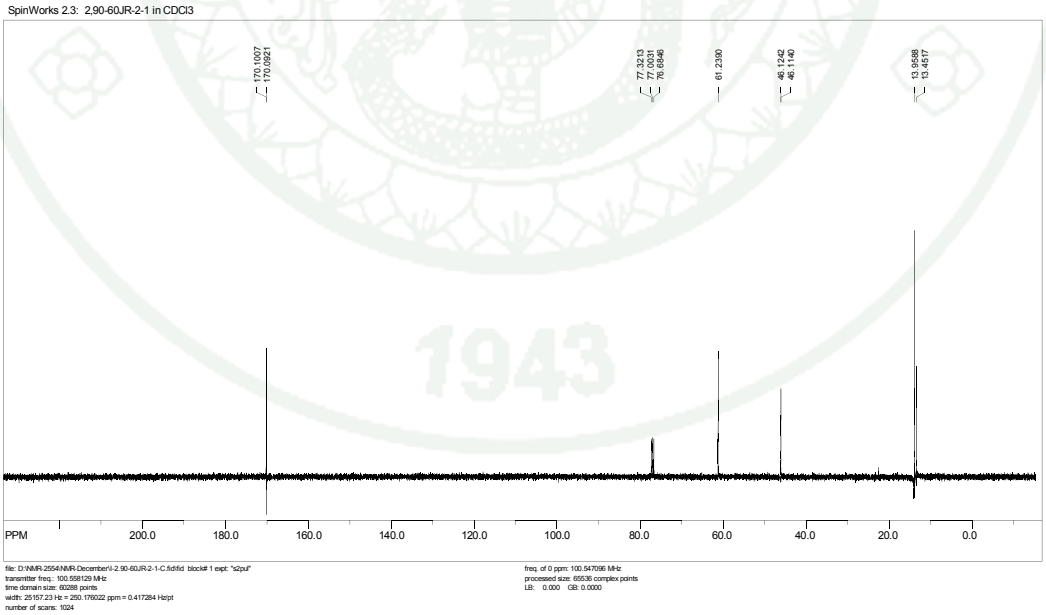


Appendix Figure 21 400 MHz ^{1}H NMR spectrum: 2-methyl-malonic acid diethyl ester (463)



Appendix Figure 22 100 MHz ^{13}C NMR spectrum: 2-methyl-malonic acid diethyl ester (463)

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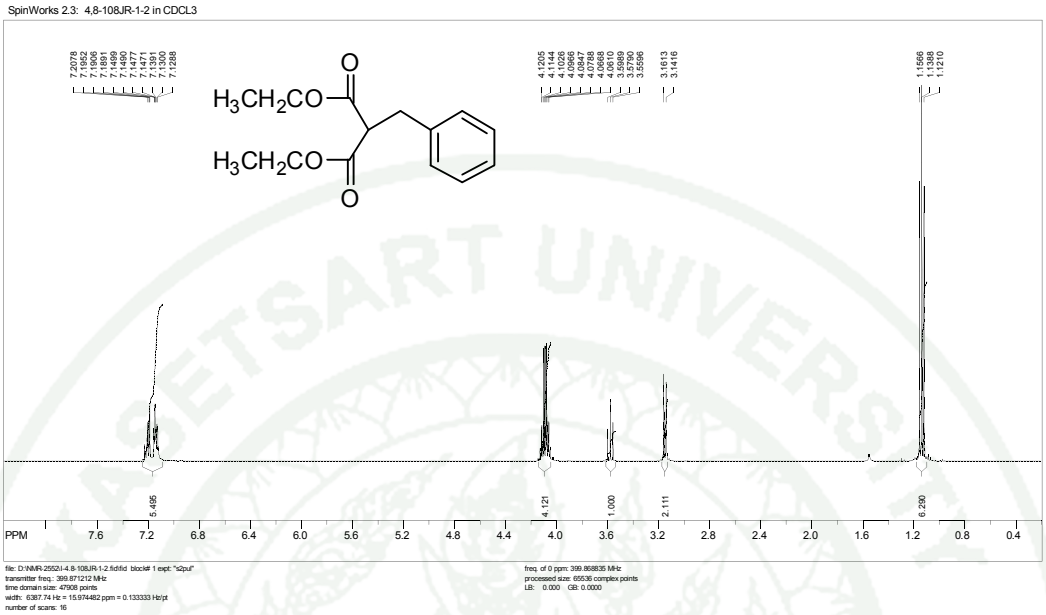
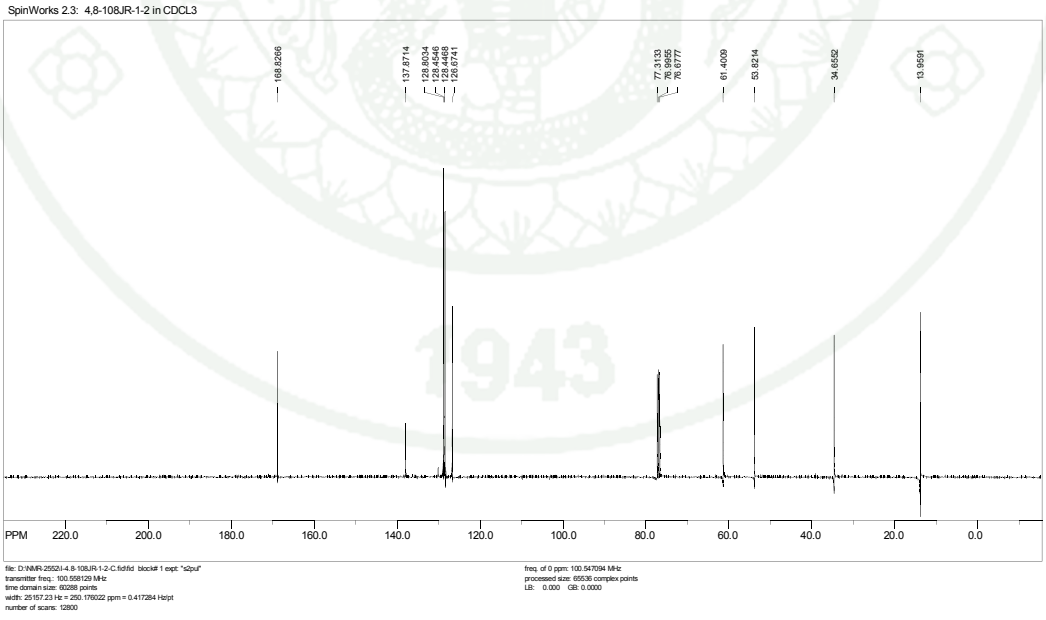


Appendix Figure 23 400 MHz ^{1}H NMR spectrum: 2-benzyl-malonic acid diethyl ester (464)



Appendix Figure 24 100 MHz ^{13}C NMR spectrum: 2-benzyl-malonic acid diethyl ester (464)

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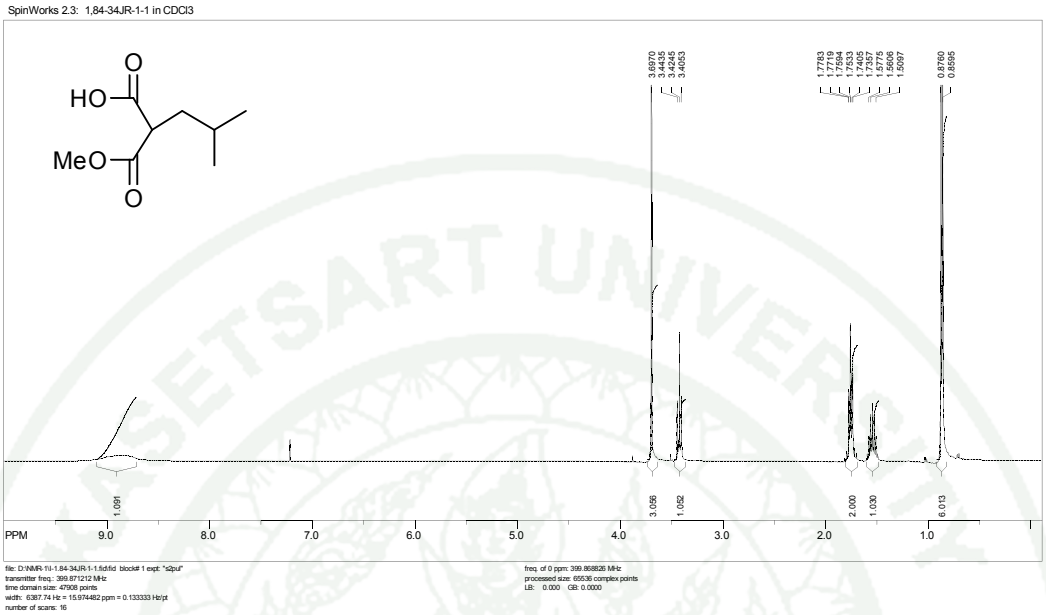
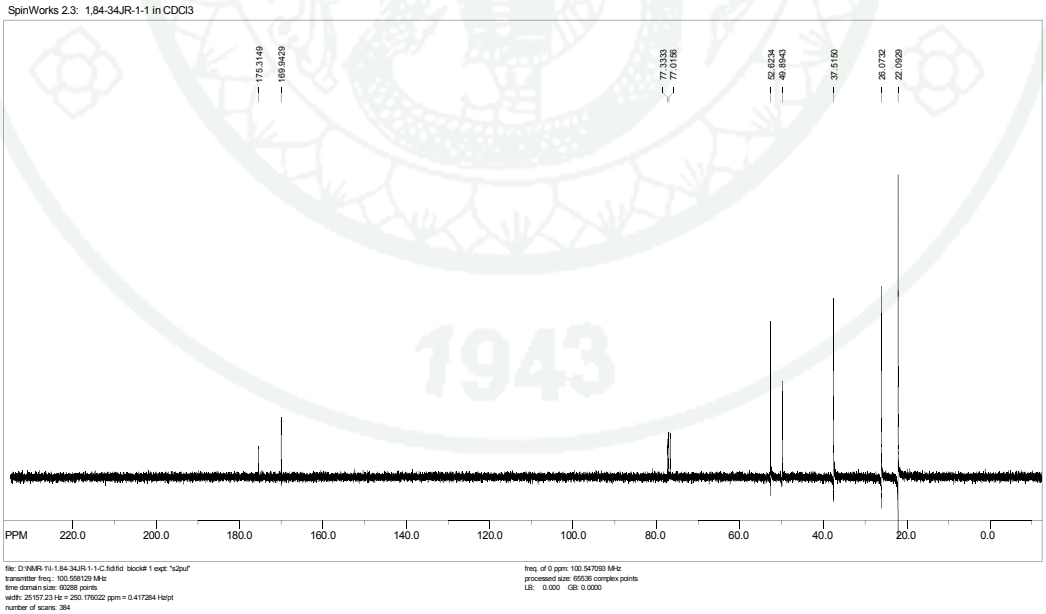


Appendix Figure 25 400 MHz ^{1}H NMR spectrum: 2-isobutyl-malonic acid monomethyl ester (466)



Appendix Figure 26 100 MHz ^{13}C NMR spectrum: 2-isobutyl-malonic acid monomethyl ester (466)

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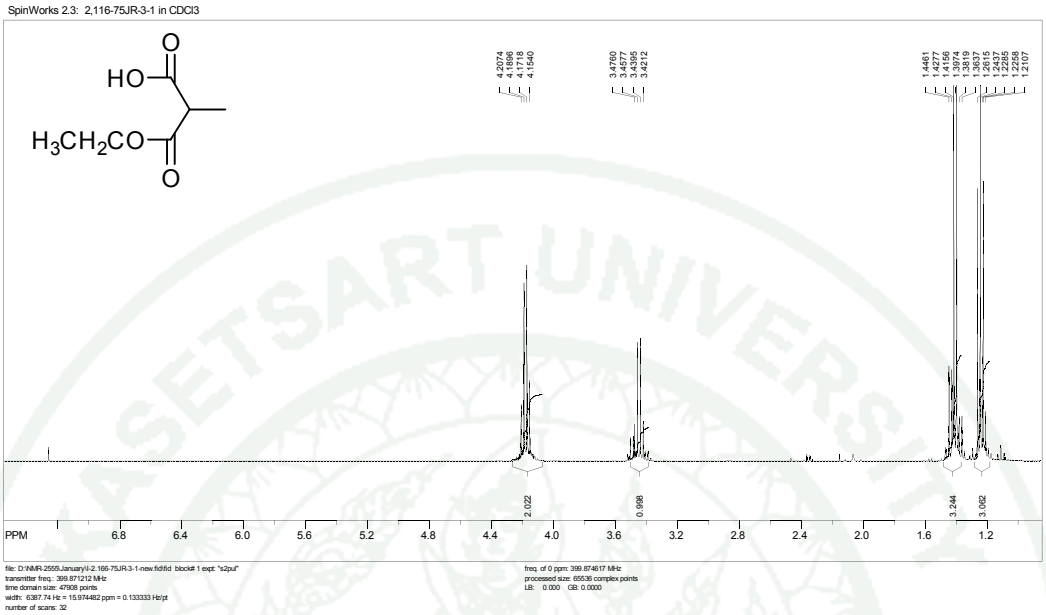
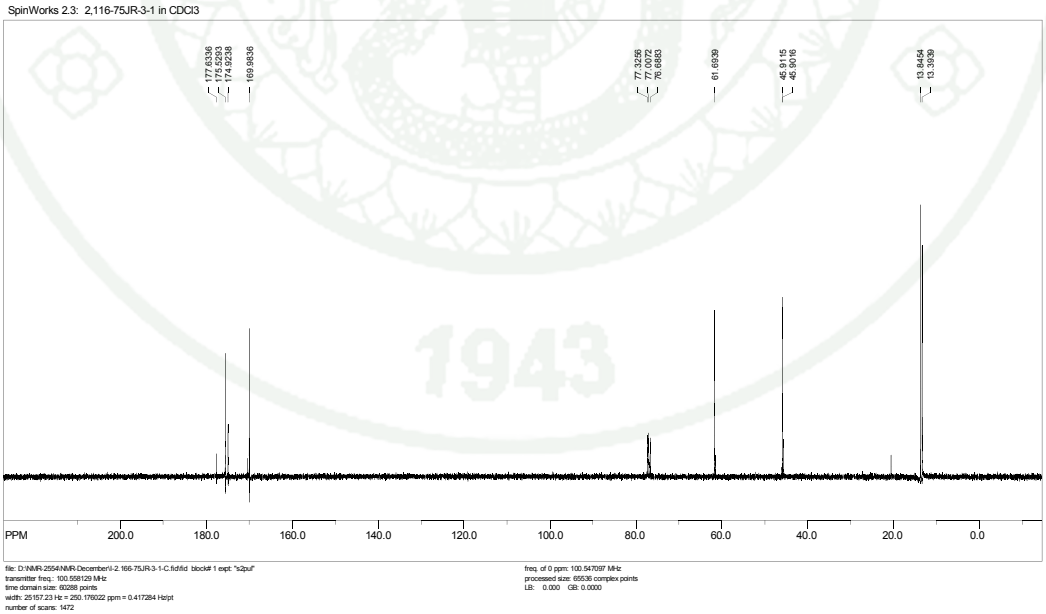


Appendix Figure 27 400 MHz ^{1}H NMR spectrum: 2-methyl-malonic acid monoethyl ester (467)



Appendix Figure 28 100 MHz ^{13}C NMR spectrum: 2-methyl-malonic acid monoethyl ester (467)

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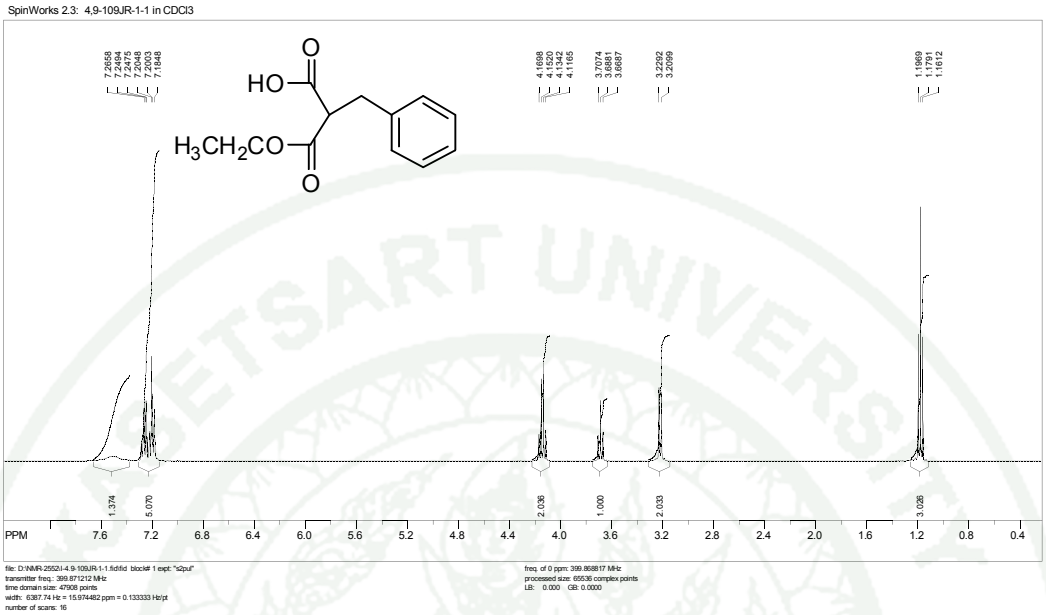
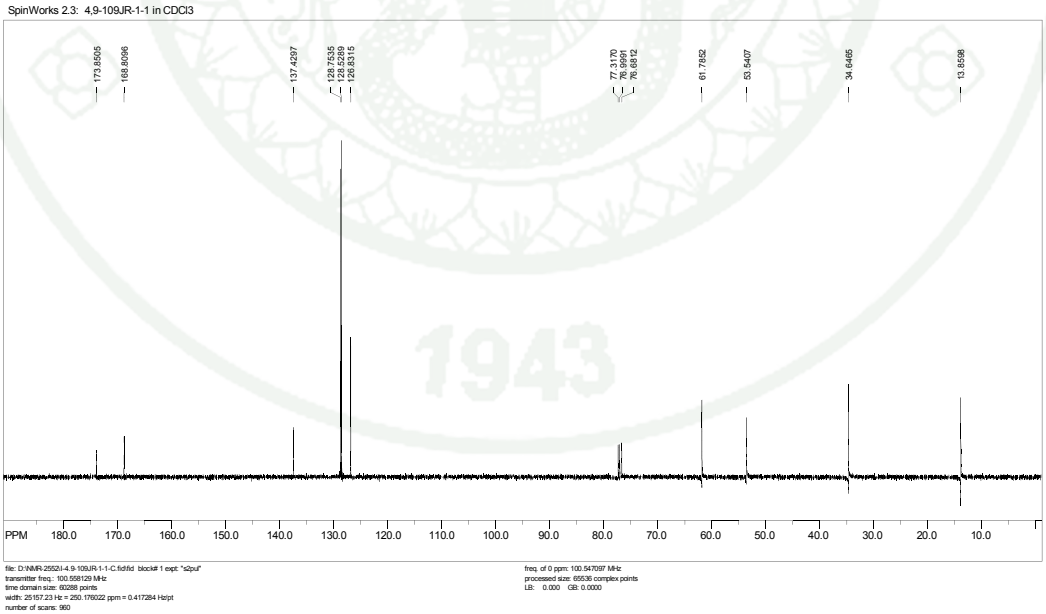


Appendix Figure 29 400 MHz ^{1}H NMR spectrum: 2-benzyl-malonic acid monoethyl ester (468)



Appendix Figure 30 100 MHz ^{13}C NMR spectrum: 2-benzyl-malonic acid monoethyl ester (468)

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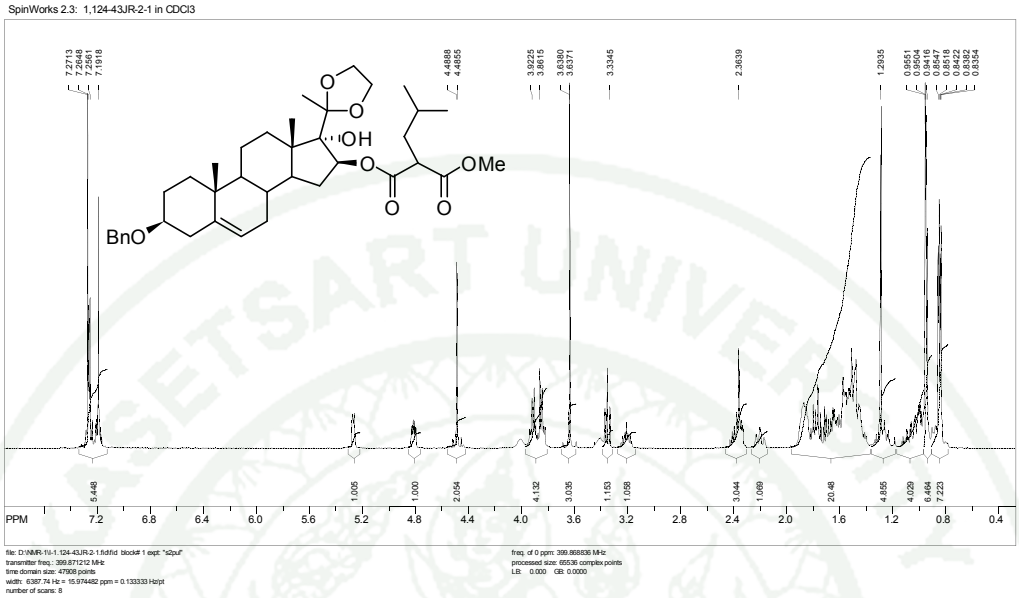
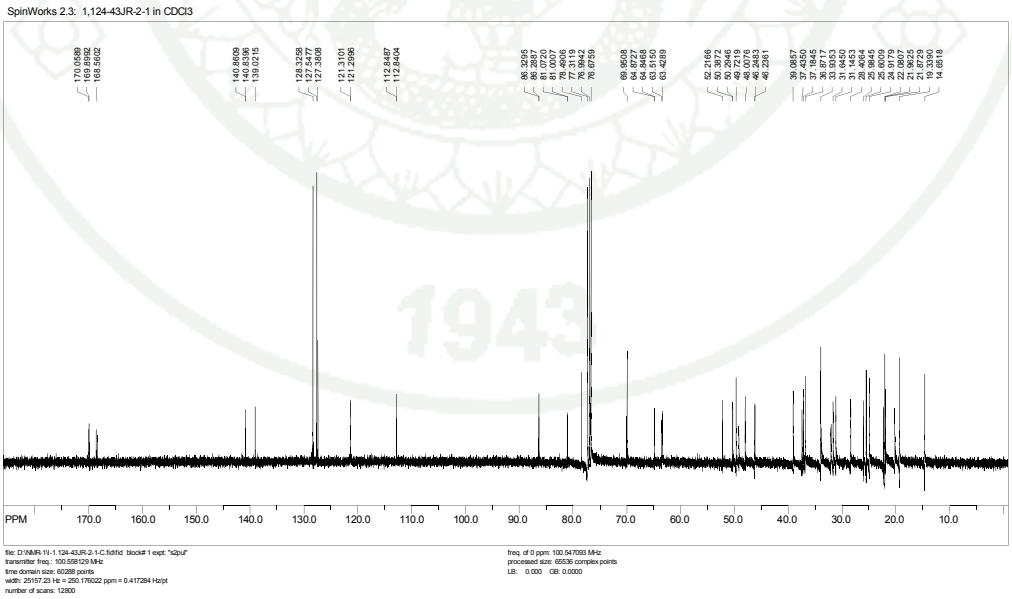


Appendix Figure 31 400 MHz ^{1}H NMR spectrum: 3β-benzyloxy-16β-(isobutyl-monomethyl ester malonate-ester)-17α-hydroxy-20,20-(ethylenedioxy)-5-pregnene (469)



Appendix Figure 32 100 MHz ^{13}C NMR spectrum: 3β-benzyloxy-16β-(isobutyl-monomethyl ester malonate-ester)-17α-hydroxy-20,20-(ethylenedioxy)-5-pregnene (469)

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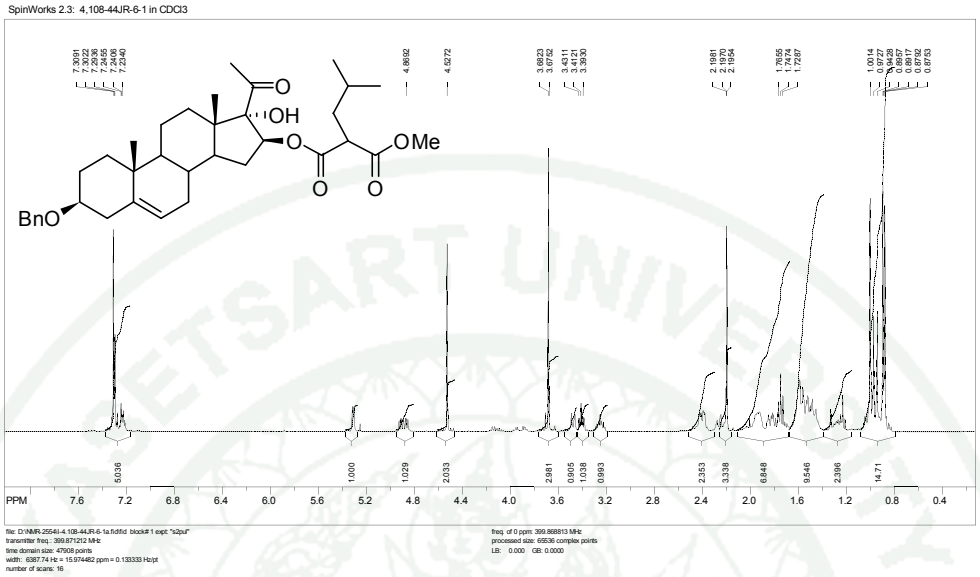
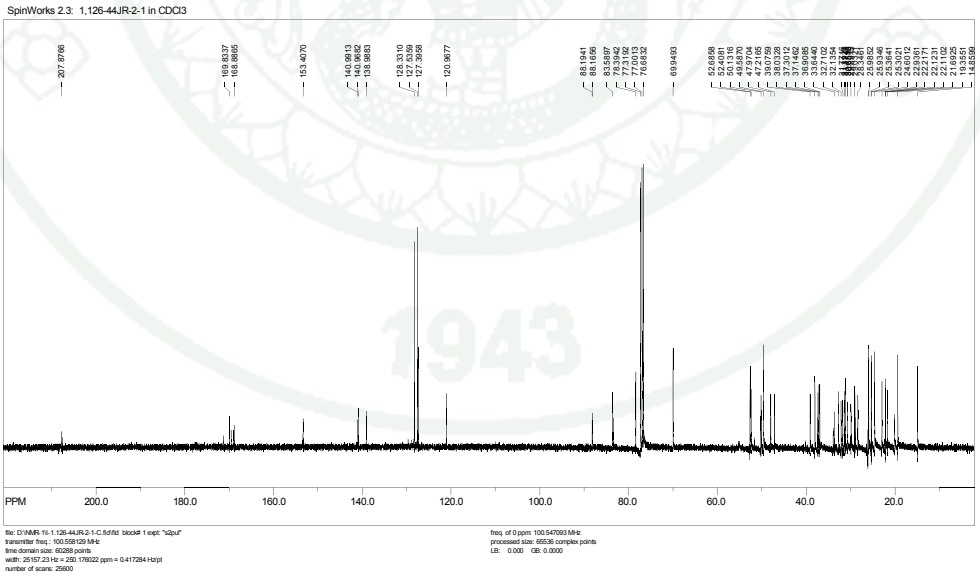


Appendix Figure 33 400 MHz ^{1}H NMR spectrum: 3β-benzyloxy-16β-(isobutyl-monomethyl ester malonate-ester)-17α-hydroxy-5-pregnene-20-one (470)



Appendix Figure 34 100 MHz ^{13}C NMR spectrum: 3β-benzyloxy-16β-(isobutyl-monomethyl ester malonate-ester)-17α-hydroxy-5-pregnene-20-one (470)

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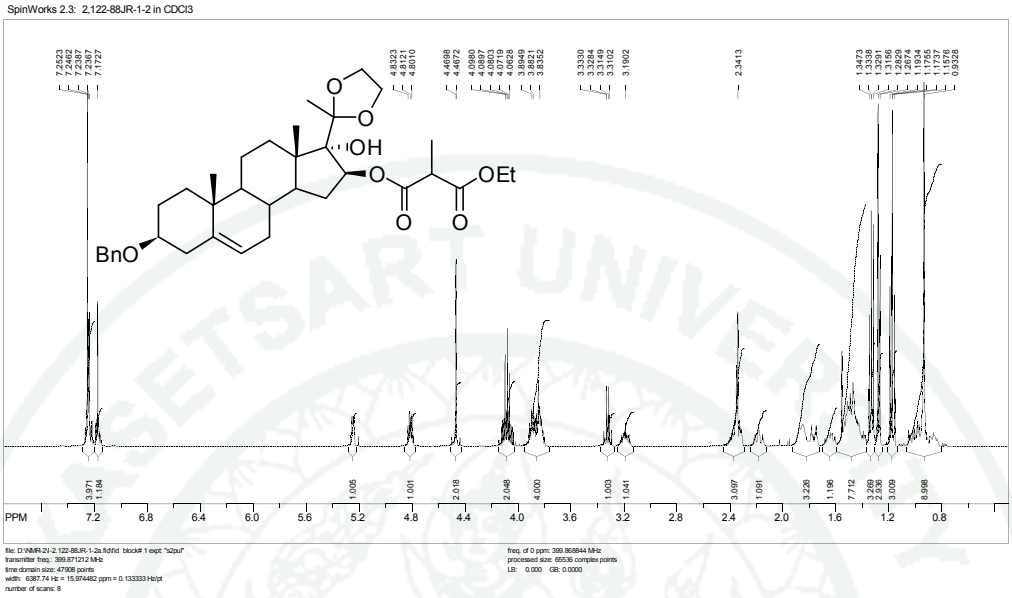
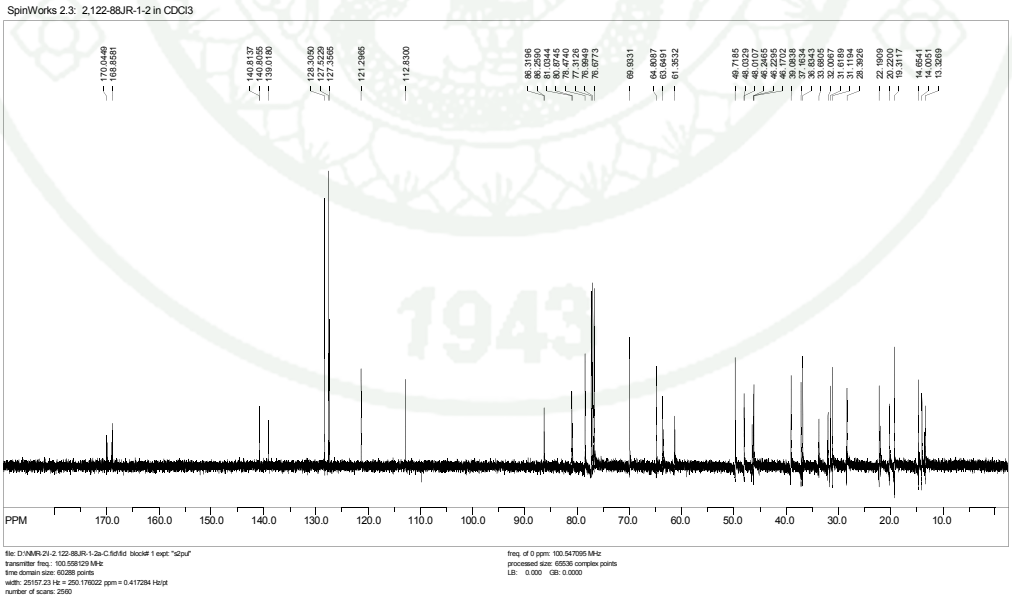


Appendix Figure 35 400 MHz ^{1}H NMR spectrum: 3β-benzyloxy-16β-(2-methyl-monoethyl ester malonate-ester)-17α-hydroxy-20,20-(ethylenedioxy)-5-pregnene (471)



Appendix Figure 36 100 MHz ^{13}C NMR spectrum: 3β-benzyloxy-16β-(2-methyl-monoethyl ester malonate-ester)-17α-hydroxy-20,20-(ethylenedioxy)-5-pregnene (471)

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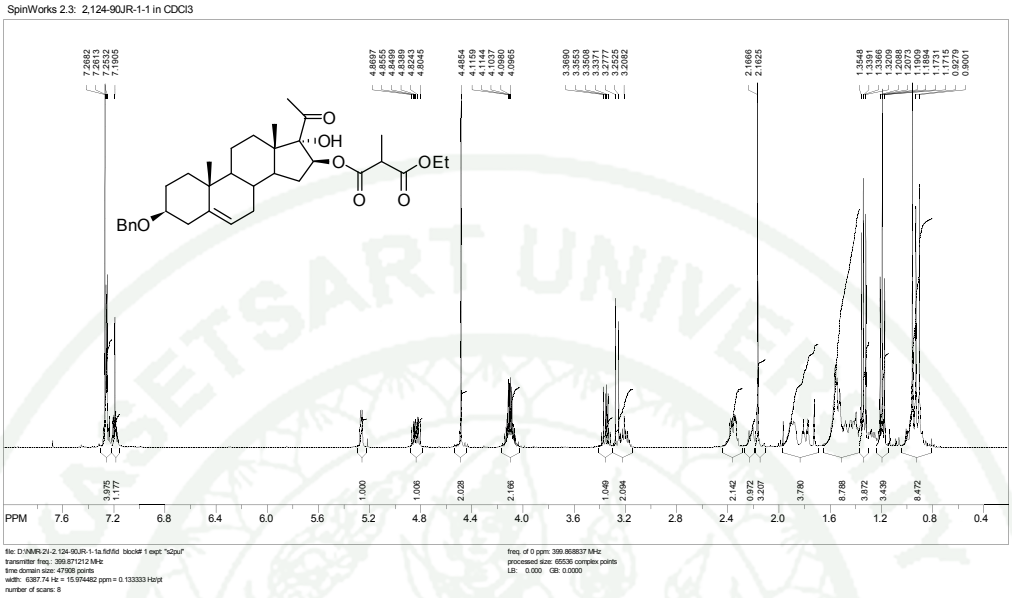
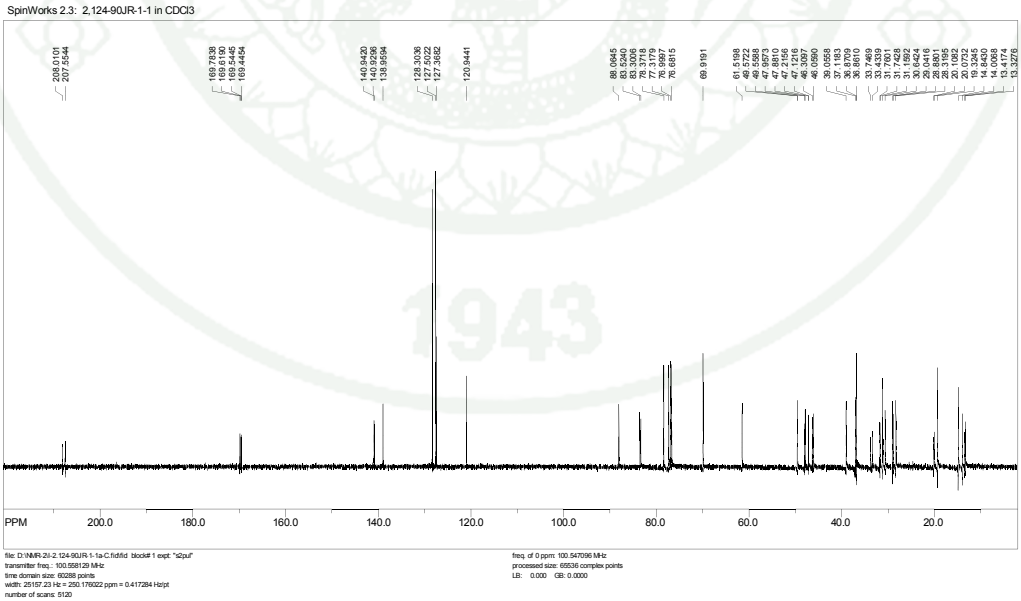


Appendix Figure 37 400 MHz ^{1}H NMR spectrum: 3β-benzyloxy-16β-(2-methyl-monoethyl ester malonate-ester)-17α-hydroxy-5-pregnene-20-one (472)



Appendix Figure 38 100 MHz ^{13}C NMR spectrum: 3β-benzyloxy-16β-(2-methyl-monoethyl ester malonate-ester)-17α-hydroxy-5-pregnene-20-one (472)

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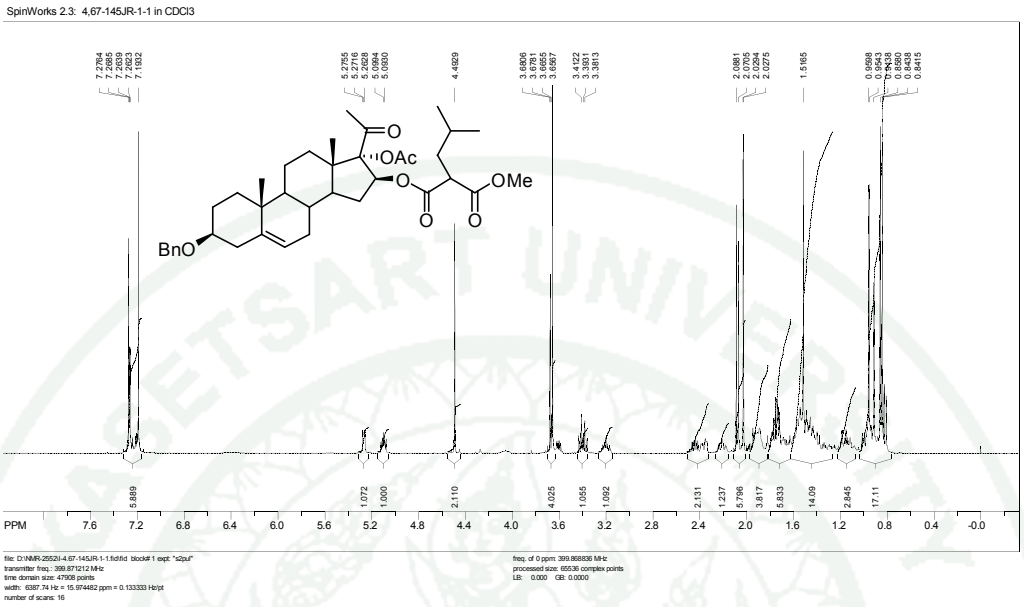
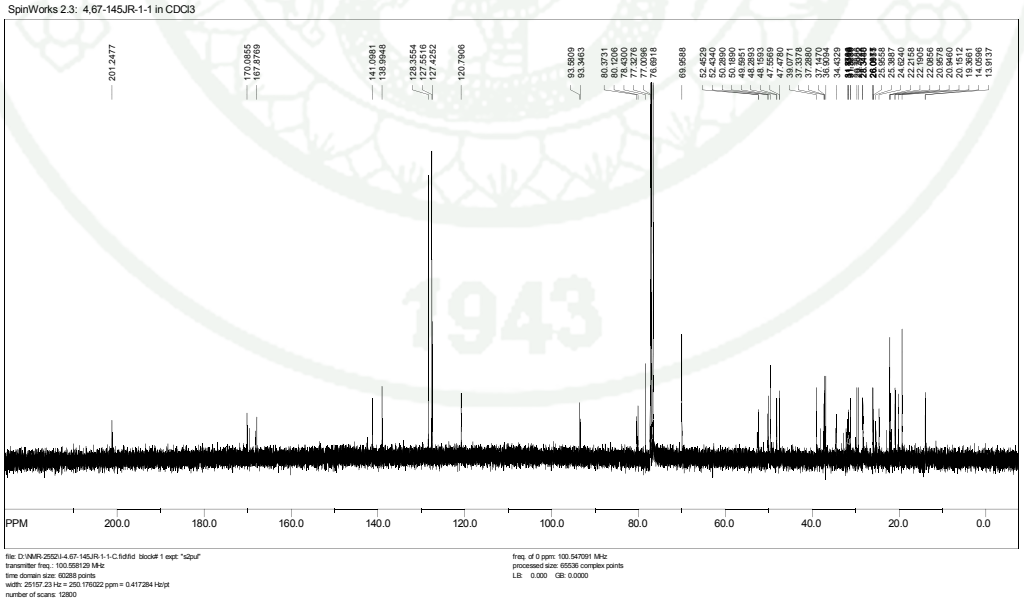


Appendix Figure 39 400 MHz ^{1}H NMR spectrum: 3β-benzyloxy-16β-(isobutyl-monomethyl ester malonate-ester)-17α-acetoxy-5-pregnene-20-one (473)



Appendix Figure 40 100 MHz ^{13}C NMR spectrum: 3β-benzyloxy-16β-(isobutyl-monomethyl ester malonate-ester)-17α-acetoxy-5-pregnene-20-one (473)

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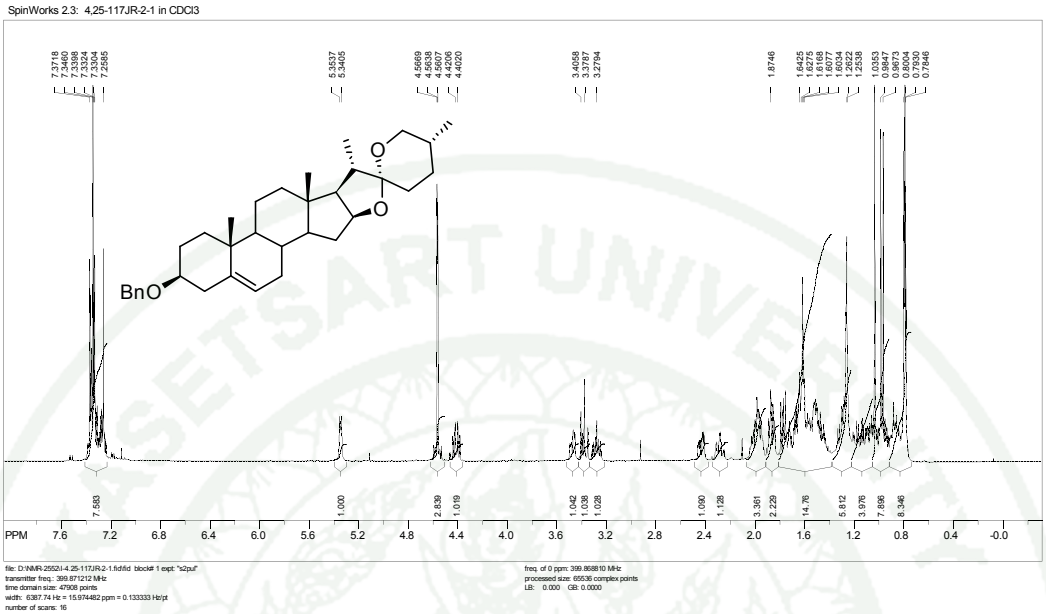
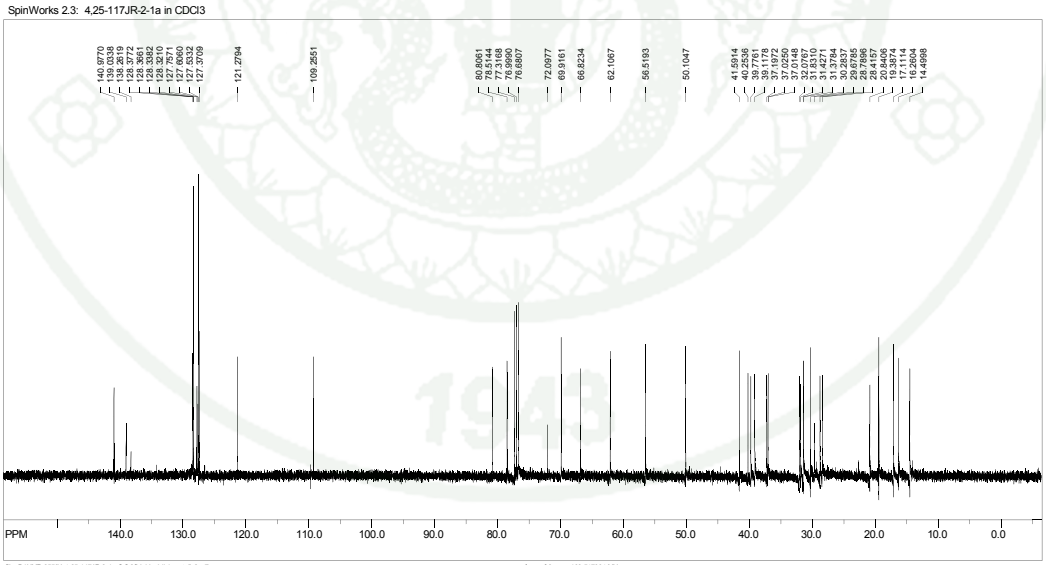


Appendix Figure 41 400 MHz ^{1}H NMR spectrum: 3β-benzyloxy-5-spirostene (474)



Appendix Figure 42 100 MHz ^{13}C NMR spectrum: 3β-benzyloxy-5-spirostene (474)

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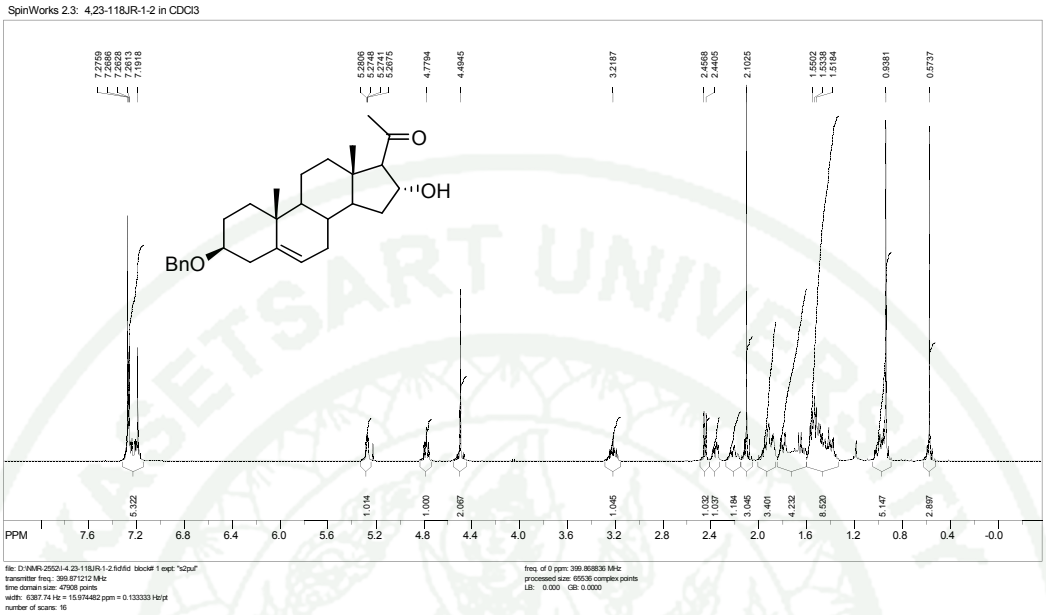
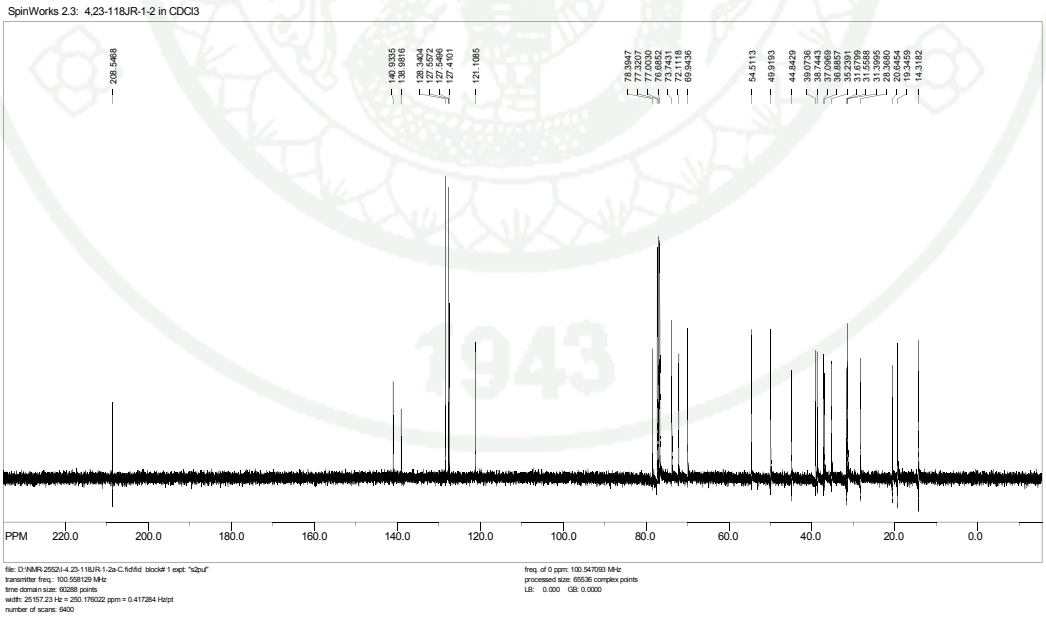


Appendix Figure 43 400 MHz ^{1}H NMR spectrum: 3β-benzyloxy-16α-hydroxy-5-pregnene-20-one (475)



Appendix Figure 44 100 MHz ^{13}C NMR spectrum: 3β-benzyloxy-16α-hydroxy-5-pregnene-20-one (475)

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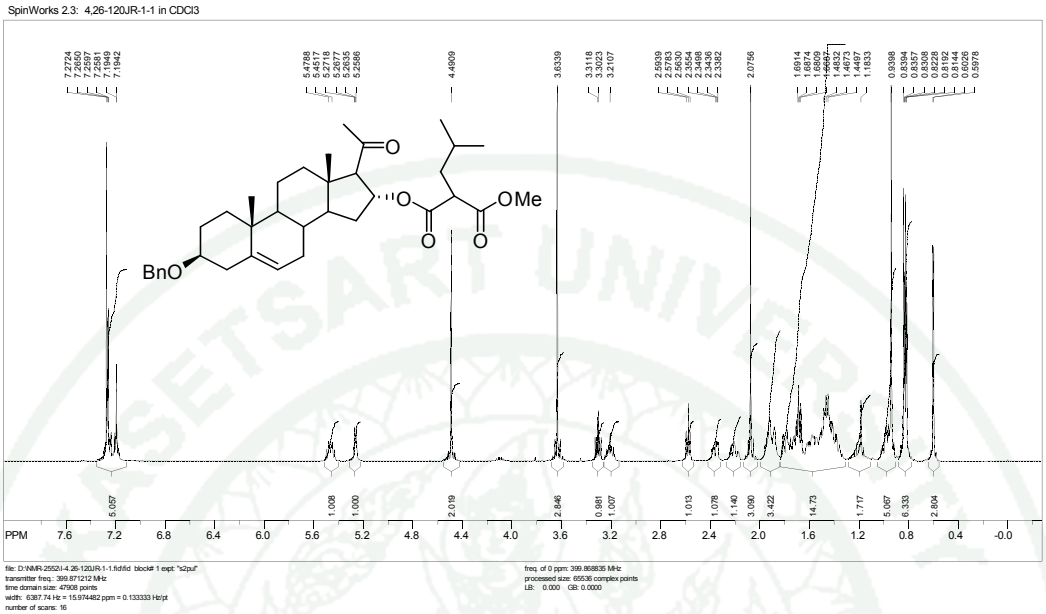
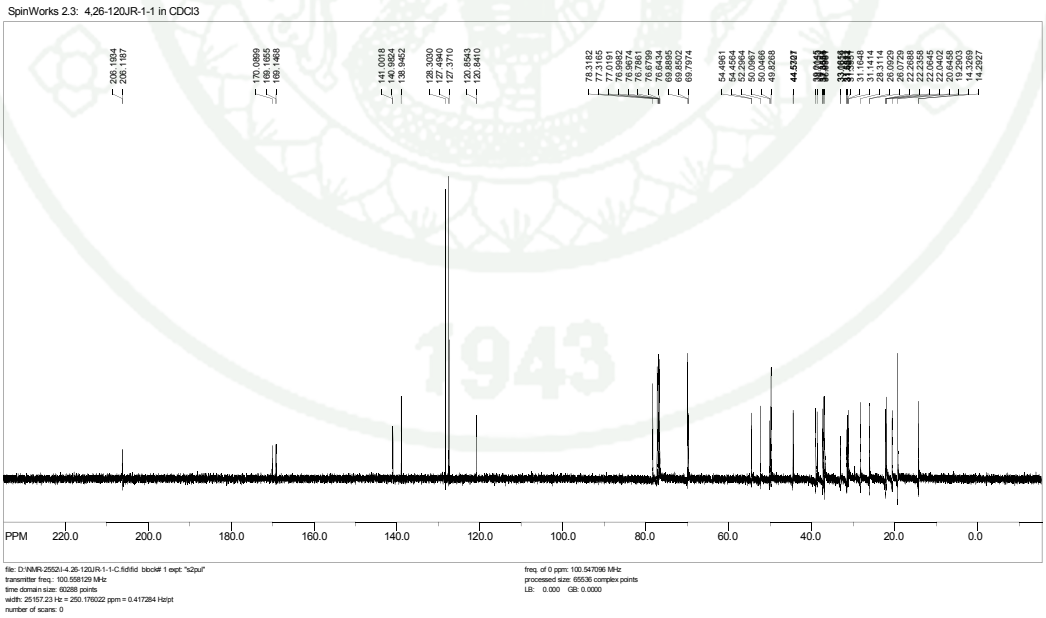


Appendix Figure 45 400 MHz ^{1}H NMR spectrum: 3β-benzyloxy-16α-(isobutyl-monomethyl ester malonate-ester)-5-pregnene-20-one (476)



Appendix Figure 46 100 MHz ^{13}C NMR spectrum: 3β-benzyloxy-16α-(isobutyl-monomethyl ester malonate-ester)-5-pregnene-20-one (476)

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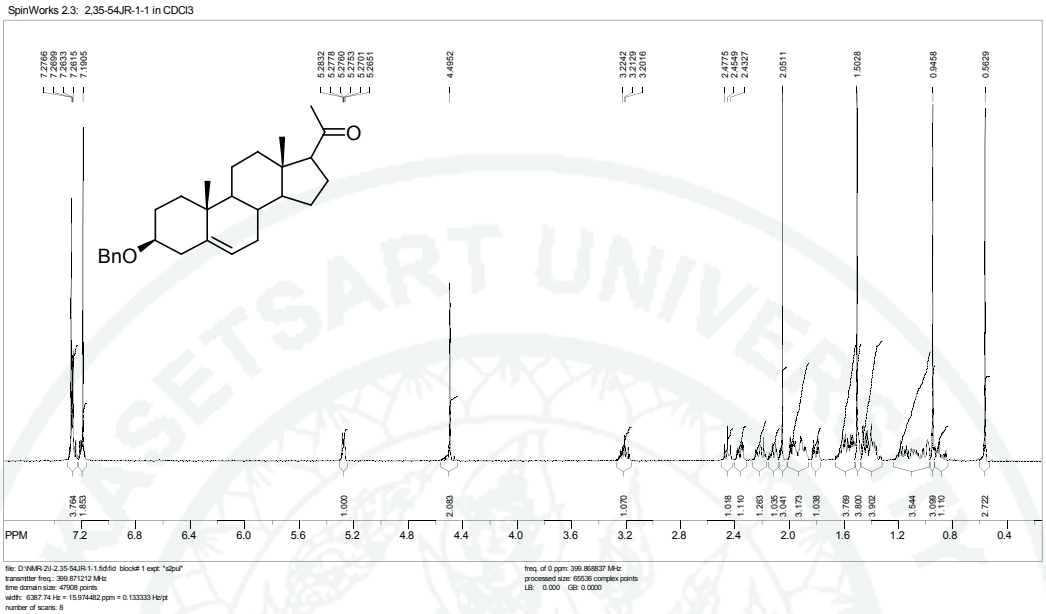
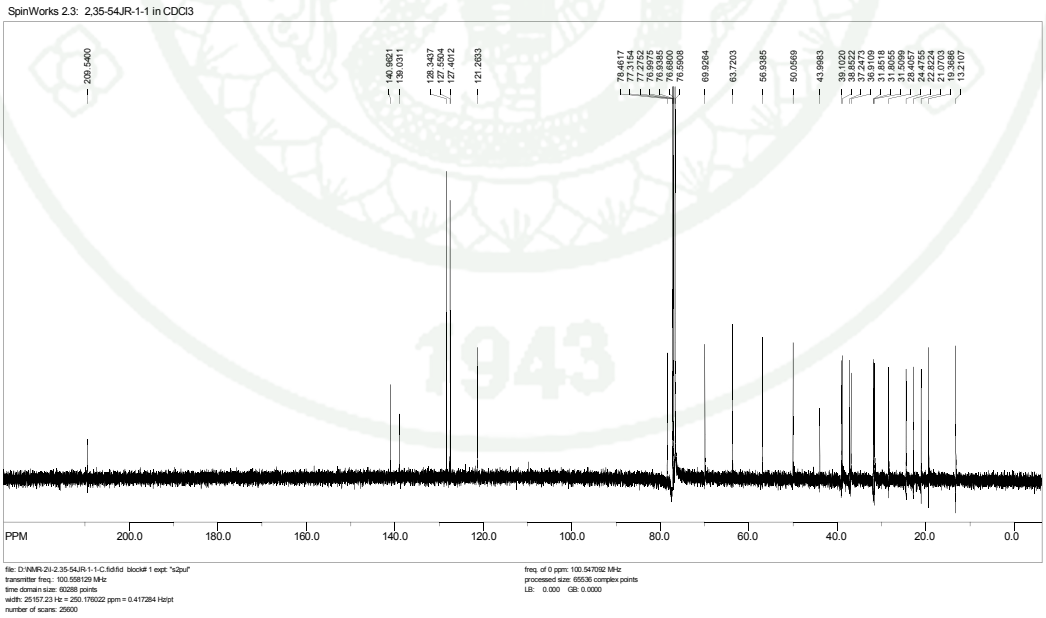


Appendix Figure 47 400 MHz ^{1}H NMR spectrum: 3β-benzyloxy-5-pregnene-20-one (479)



Appendix Figure 48 100 MHz ^{13}C NMR spectrum: 3β-benzyloxy-5-pregnene-20-one (479)

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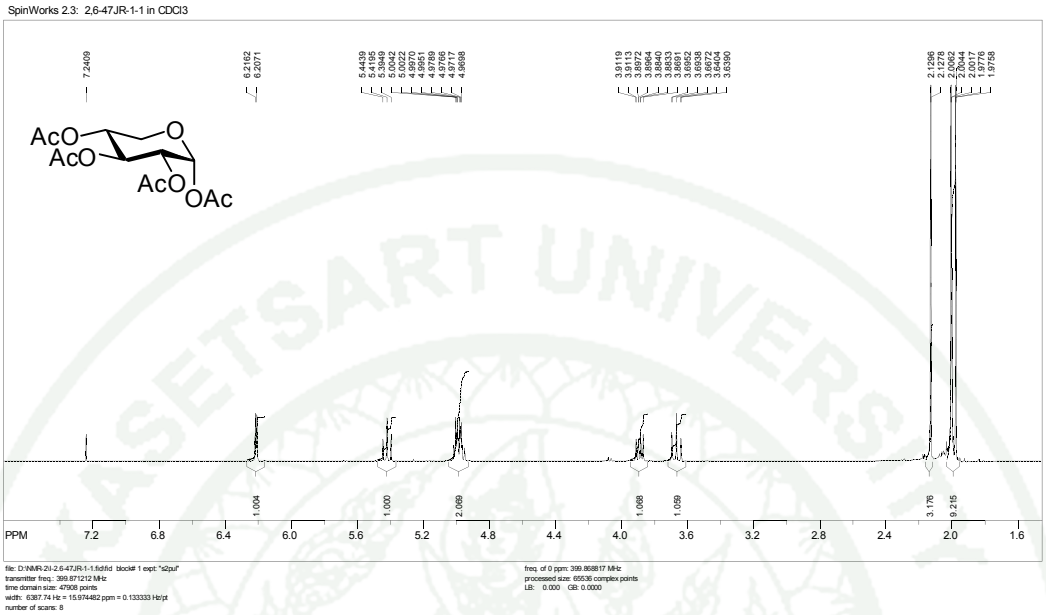
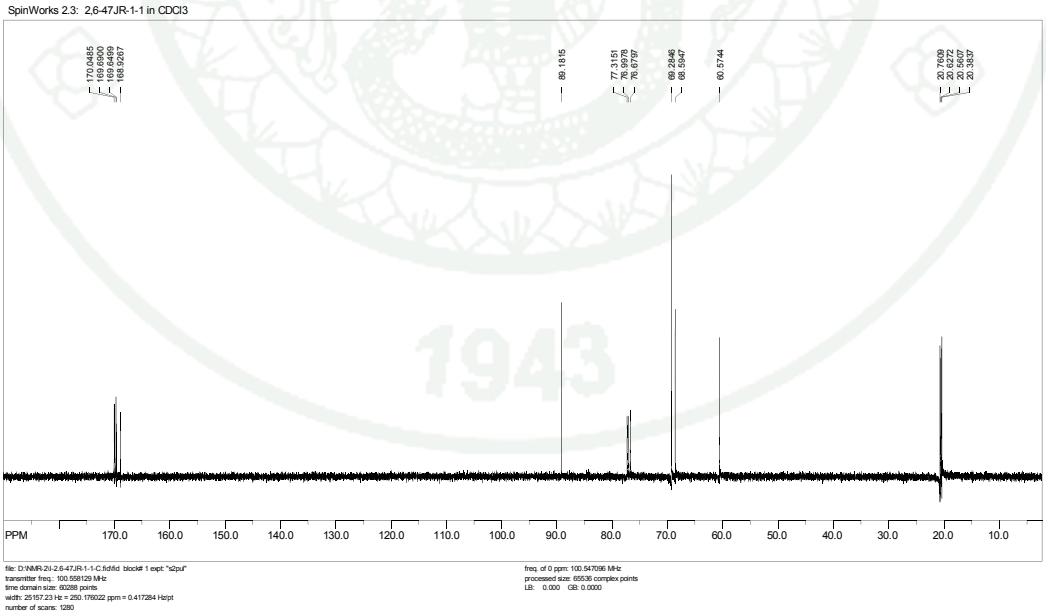


Appendix Figure 49 400 MHz ^{1}H NMR spectrum: 1,2,3,4-*O*-tetraacetyl-D-xylopyranoside (487)



Appendix Figure 50 100 MHz ^{13}C NMR spectrum: 1,2,3,4-*O*-tetraacetyl-D-xylopyranoside (487)

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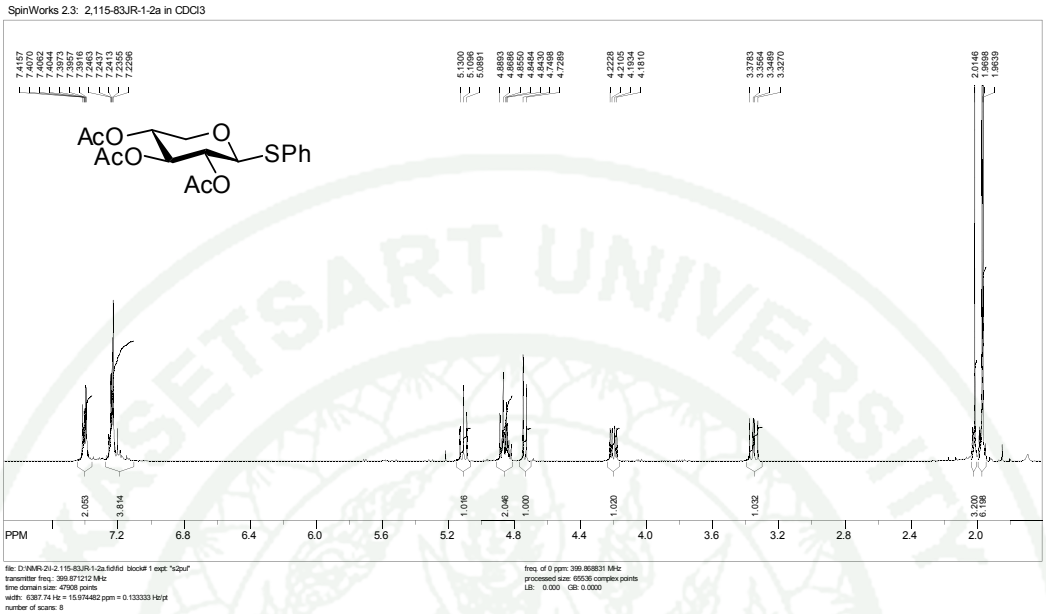
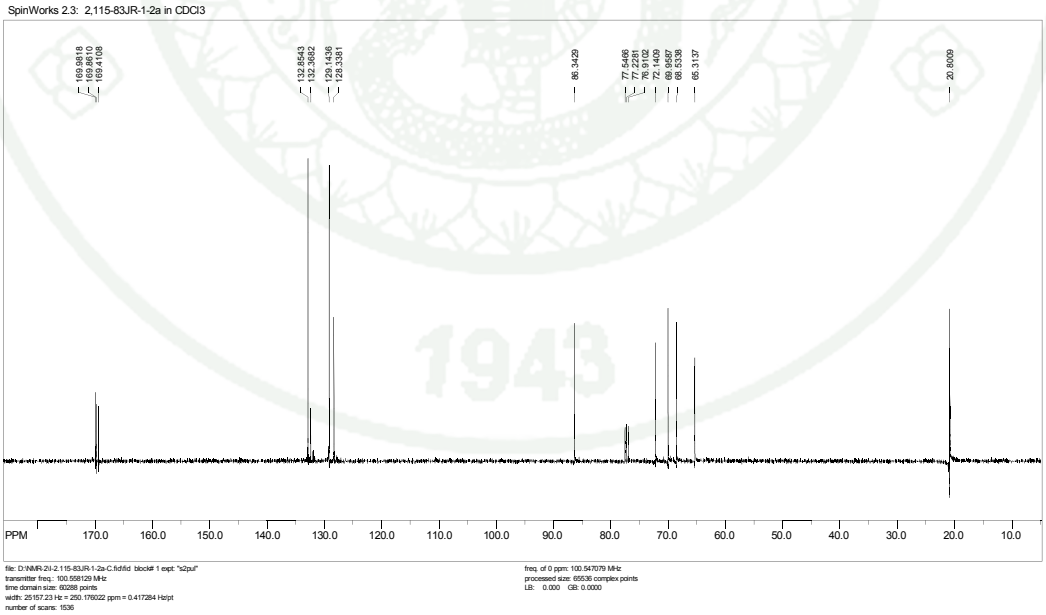


Appendix Figure 51 400 MHz ^{1}H NMR spectrum: thiophenyl-2,3,4-*O*-triacetyl-D-xylopyranoside (488)



Appendix Figure 52 100 MHz ^{13}C NMR spectrum: thiophenyl-2,3,4-*O*-triacetyl-D-xylopyranoside (488)

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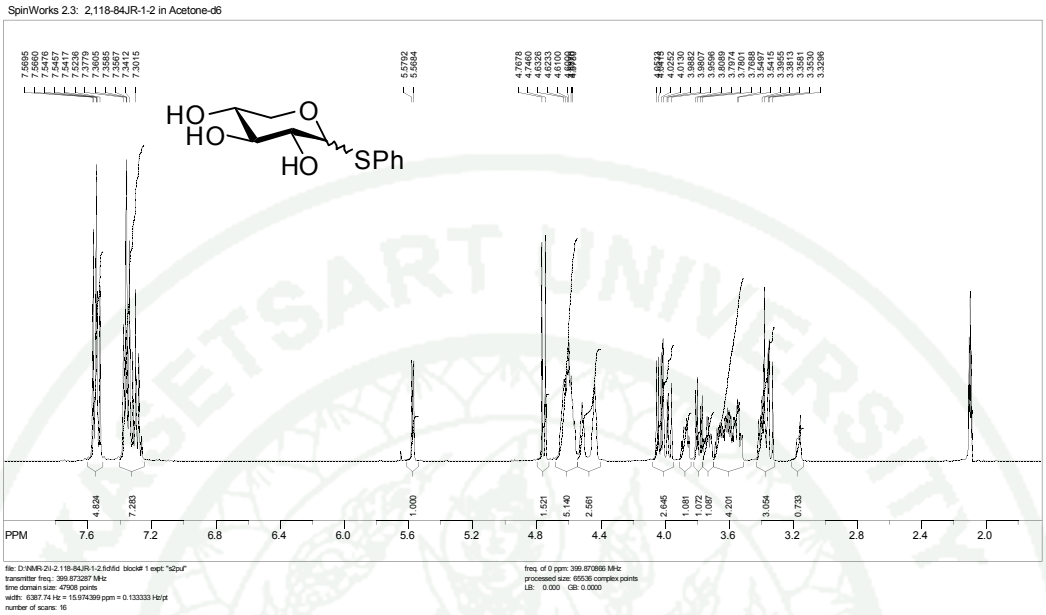
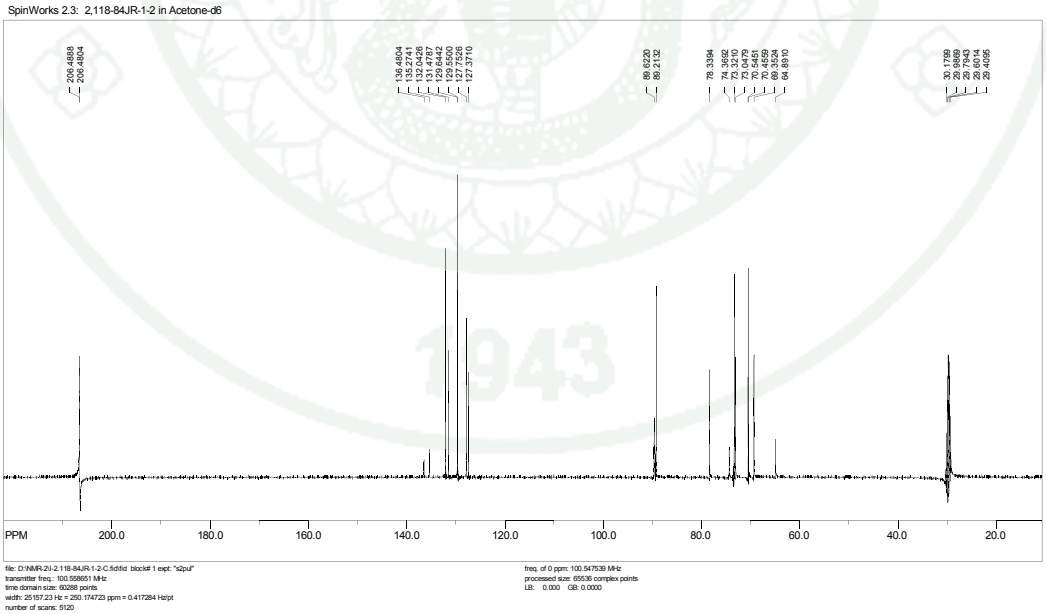


Appendix Figure 53 400 MHz ^{1}H NMR spectrum: 1-thiophenyl-D-xylopyranoside (489)



Appendix Figure 54 100 MHz ^{13}C NMR spectrum: 1-thiophenyl-D-xylopyranoside (489)

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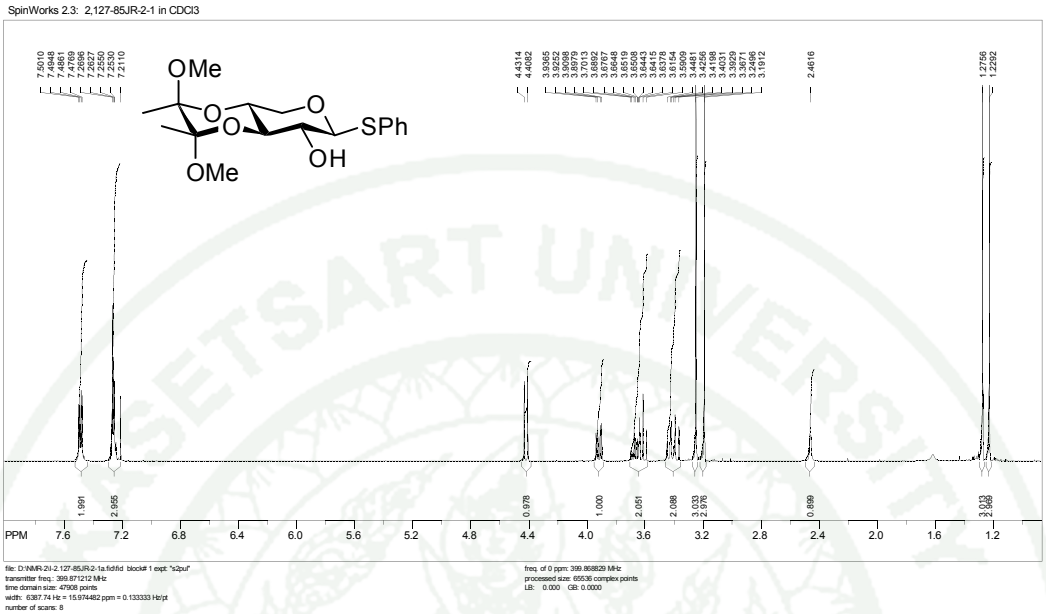
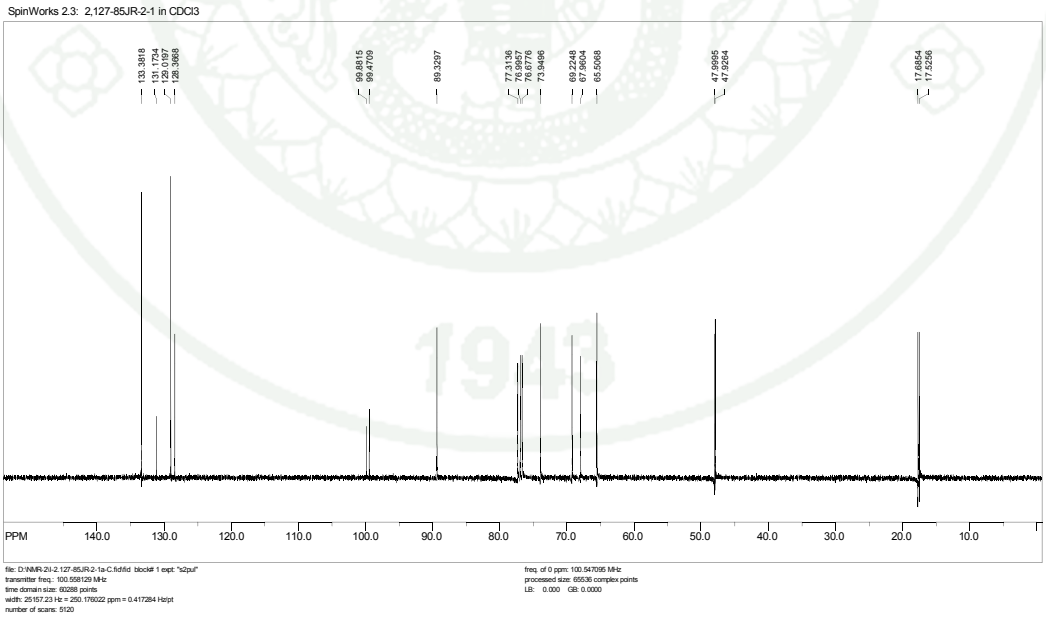


Appendix Figure 55 400 MHz ^{1}H NMR spectrum: thiophenyl-(2'S,3'S)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-α-D-xylopyranoside (490)



Appendix Figure 56 100 MHz ^{13}C NMR spectrum: thiophenyl-(2'S,3'S)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-α-D-xylopyranoside (490)

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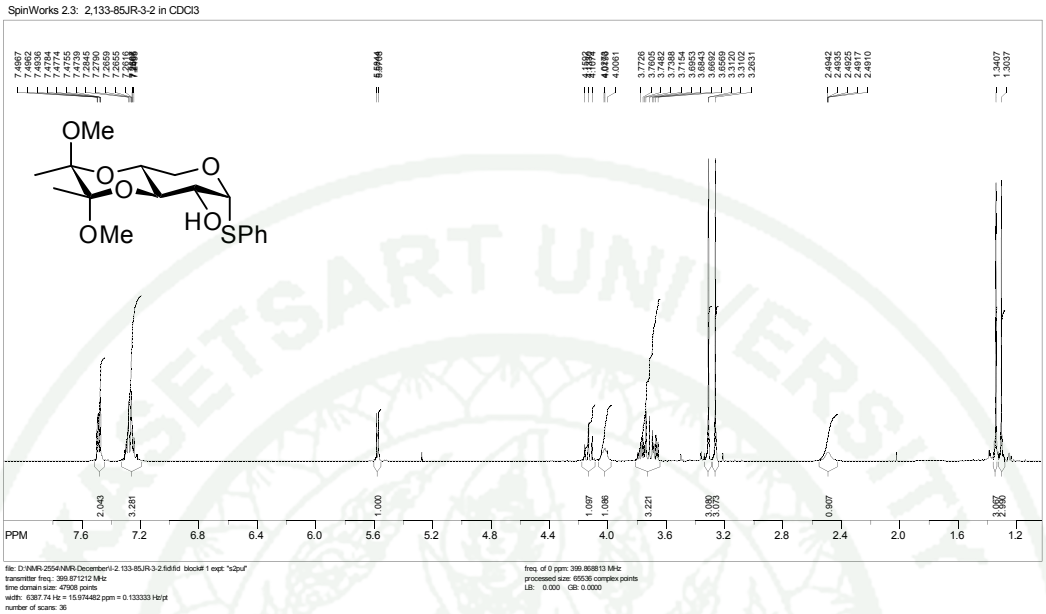
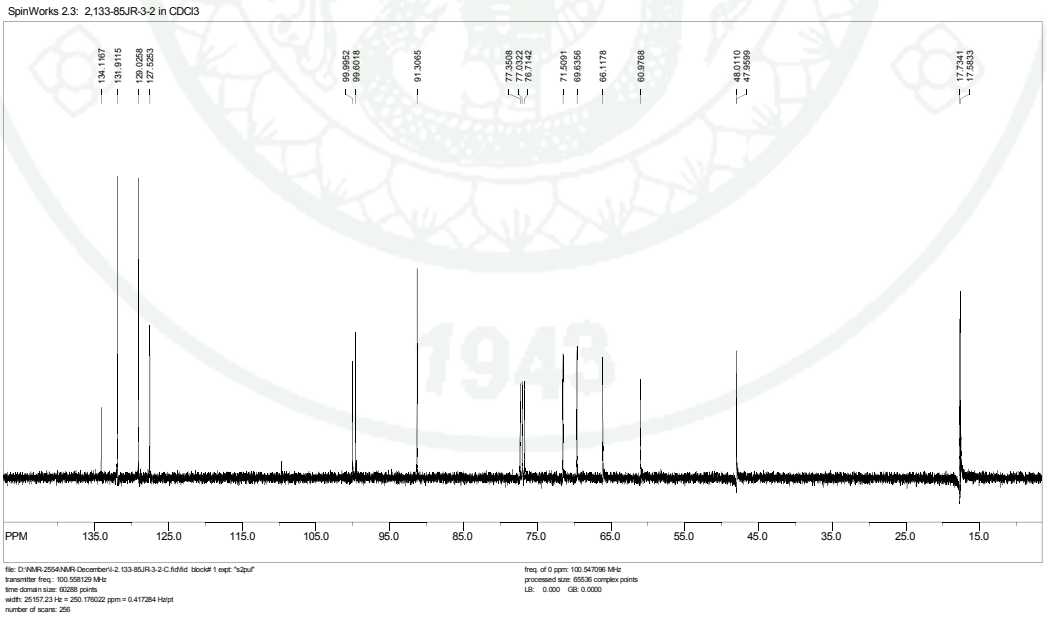


Appendix Figure 57 400 MHz ^{1}H NMR spectrum: thiophenyl-(2'S,3'S)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-β-D-xylopyranoside (491)



Appendix Figure 58 100 MHz ^{13}C NMR spectrum: thiophenyl-(2'S,3'S)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-β-D-xylopyranoside (491)

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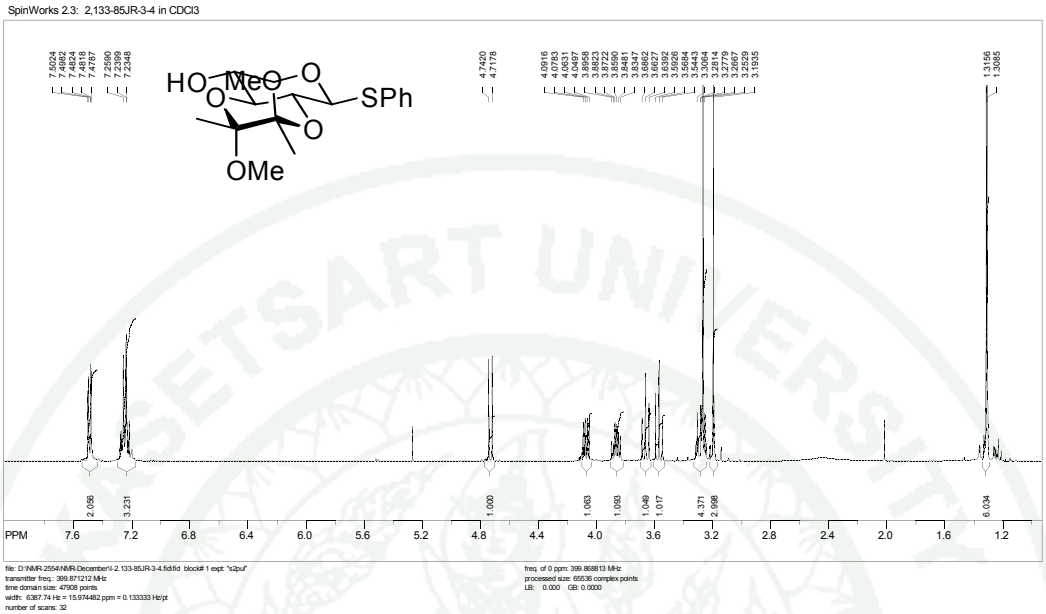
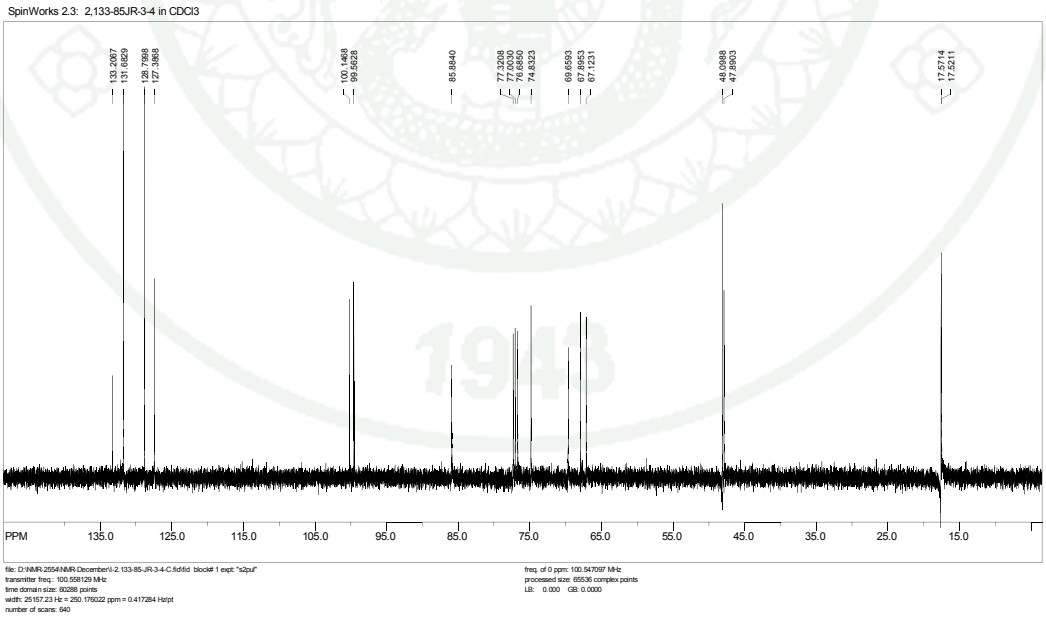


Appendix Figure 59 400 MHz ^{1}H NMR spectrum: thiophenyl-(2'S,3'S)-methyl-2,3-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-α-D-xylopyranoside (492)



Appendix Figure 60 100 MHz ^{13}C NMR spectrum: thiophenyl-(2'S,3'S)-methyl-2,3-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-α-D-xylopyranoside (492)

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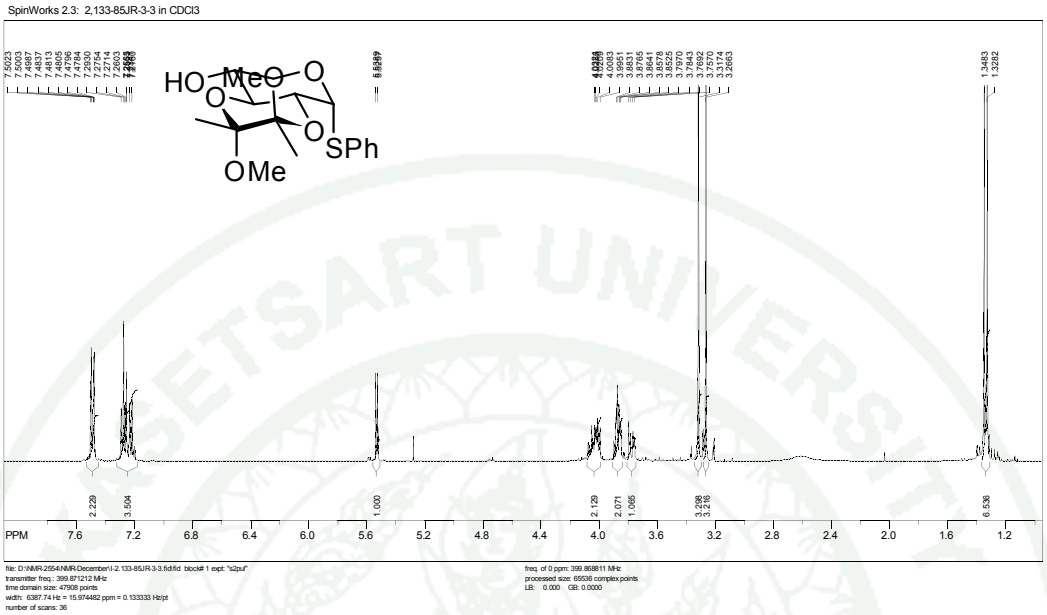
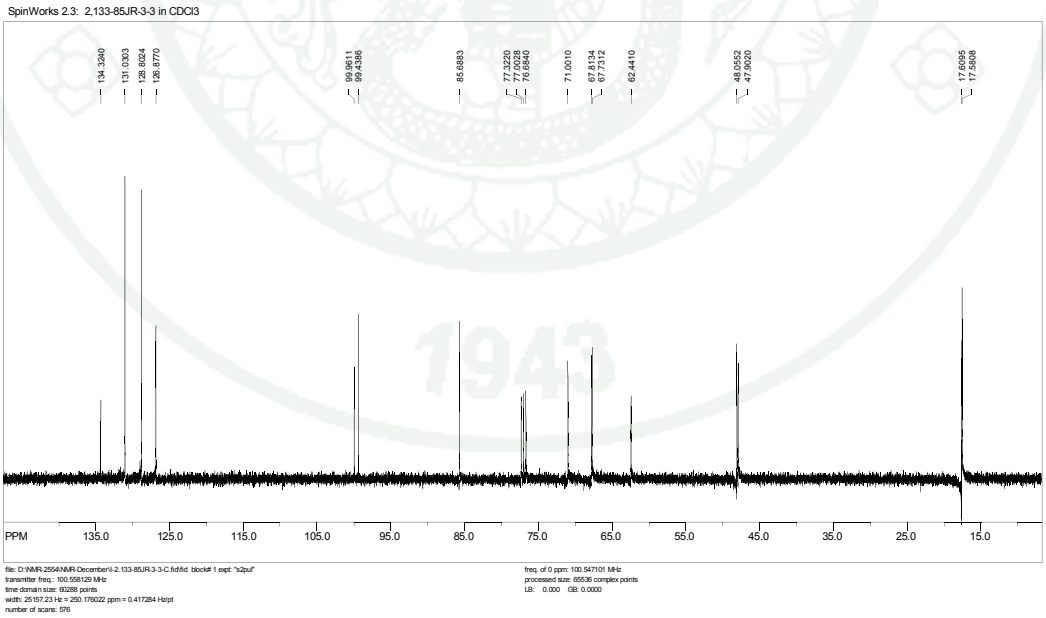


Appendix Figure 61 400 MHz ^{1}H NMR spectrum: thiophenyl-(2'S,3'S)-methyl-2,3-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-β-D-xylopyranoside (493)



Appendix Figure 62 100 MHz ^{13}C NMR spectrum: thiophenyl-(2'S,3'S)-methyl-2,3-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-β-D-xylopyranoside (493)

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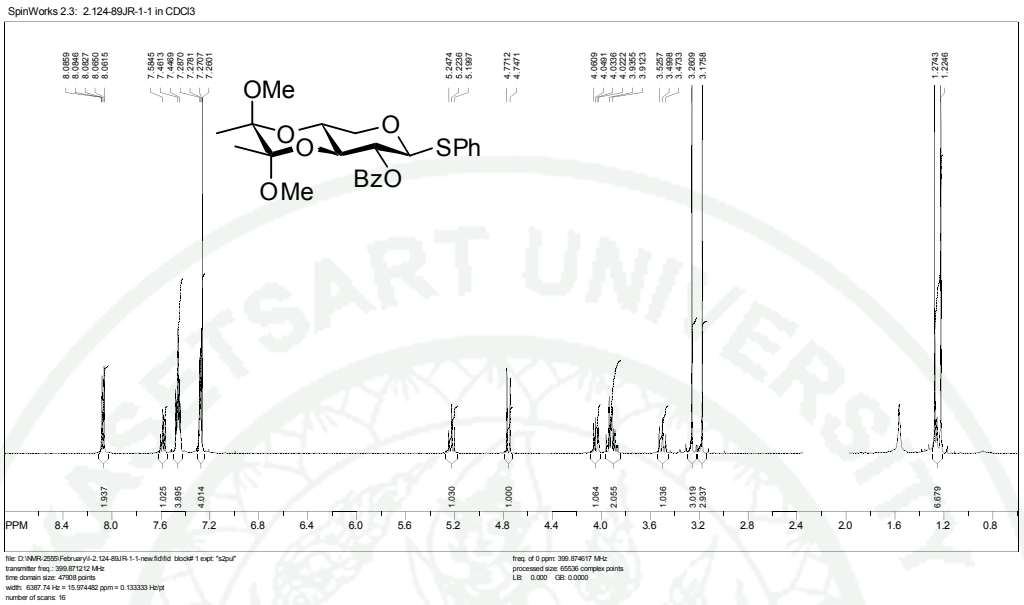
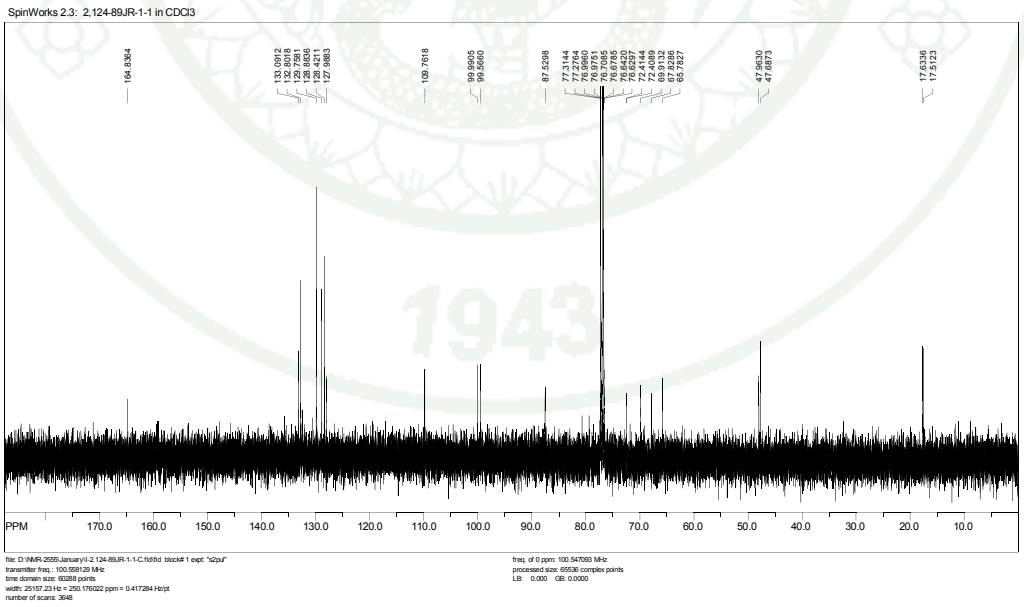


Appendix Figure 63 400 MHz ^{1}H NMR spectrum: thiophenyl-2-*O*-benzoyl-(2'S,3'S)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3' -diyl)-α-D-xylopyranoside (494)



Appendix Figure 64 100 MHz ^{13}C NMR spectrum: thiophenyl-2-*O*-benzoyl-(2'S,3'S)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-α-D-xylopyranoside (494)

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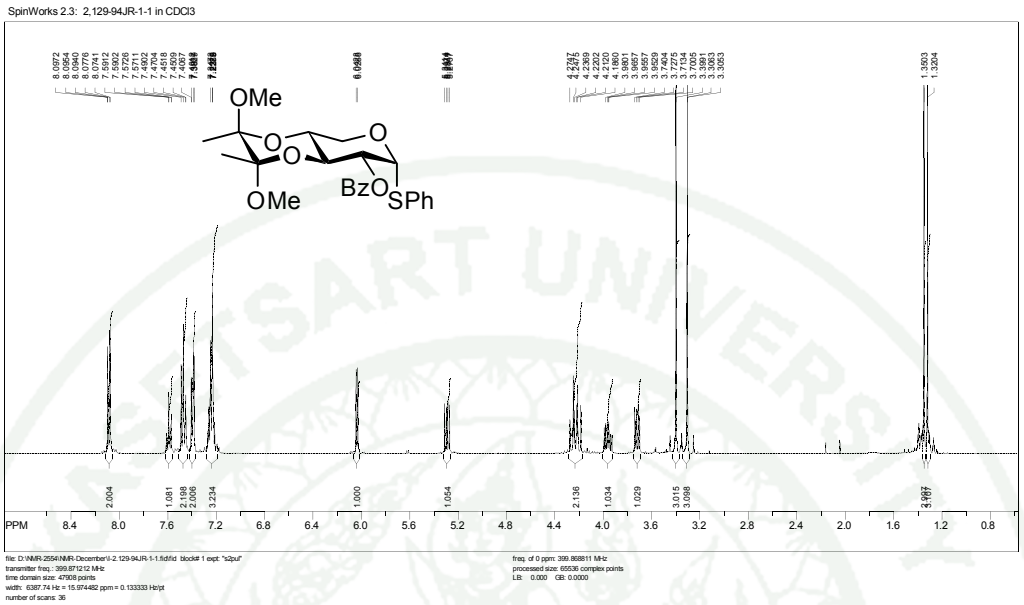
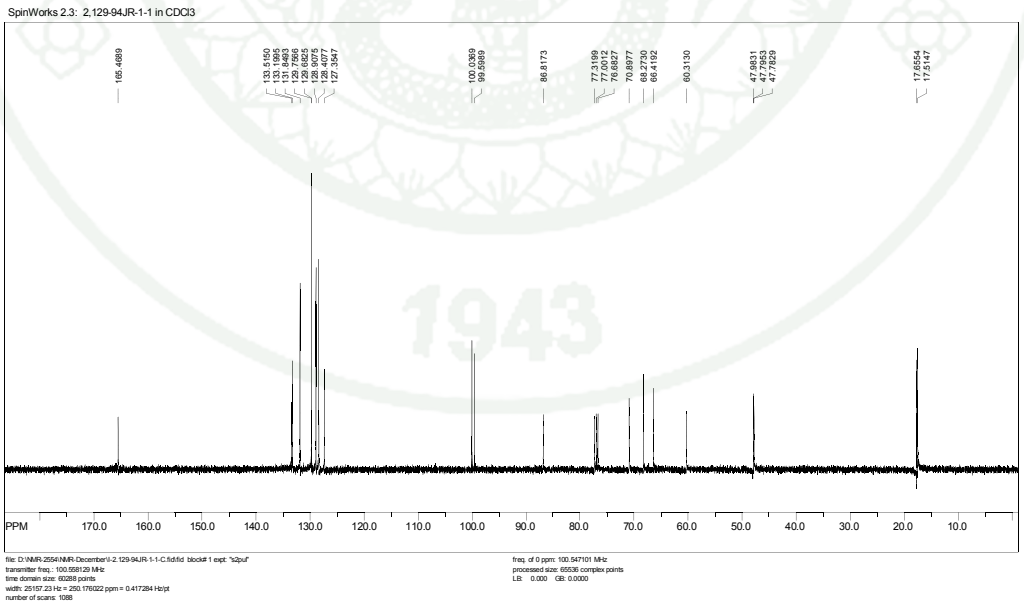


Appendix Figure 65 400 MHz ^{1}H NMR spectrum: thiophenyl-2-*O*-benzoyl-(2'S,3'S)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-d iyl)-β-D-xylopyranoside (495)



Appendix Figure 66 100 MHz ^{13}C NMR spectrum: thiophenyl-2-*O*-benzoyl-(2'S,3'S)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-β-D-xylopyranoside (495)

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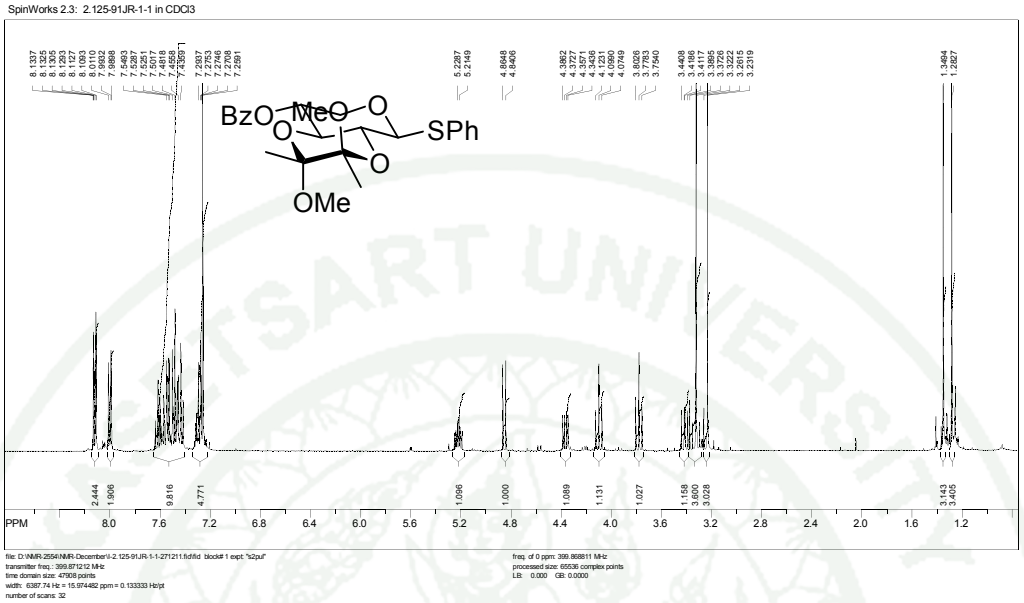
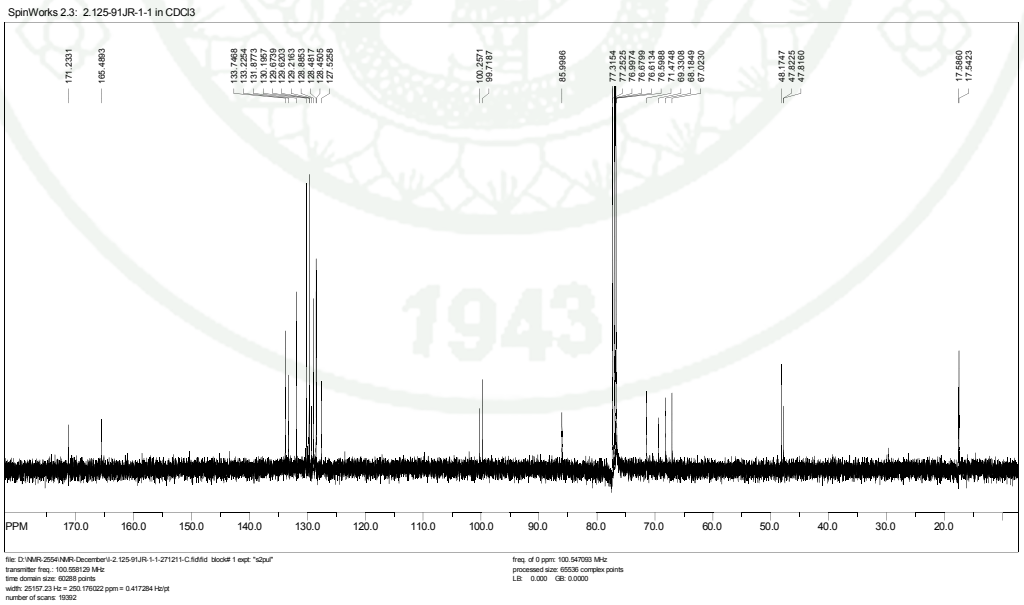


Appendix Figure 67 400 MHz ^{1}H NMR spectrum: thiophenyl-(2'S,3'S)-methyl-2,3-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-4-*O*-benzoyl-α-D-xylopyranoside (496)



Appendix Figure 68 100 MHz ^{13}C NMR spectrum: thiophenyl-(2'S,3'S)-methyl-2,3-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-4-*O*-benzoyl-α-D-xylopyranoside (496)

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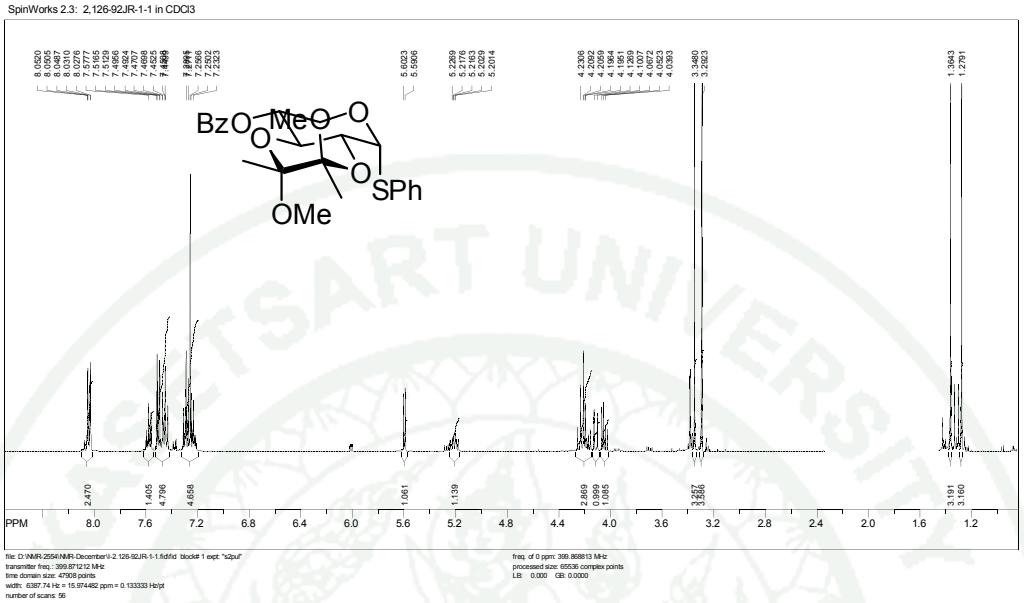
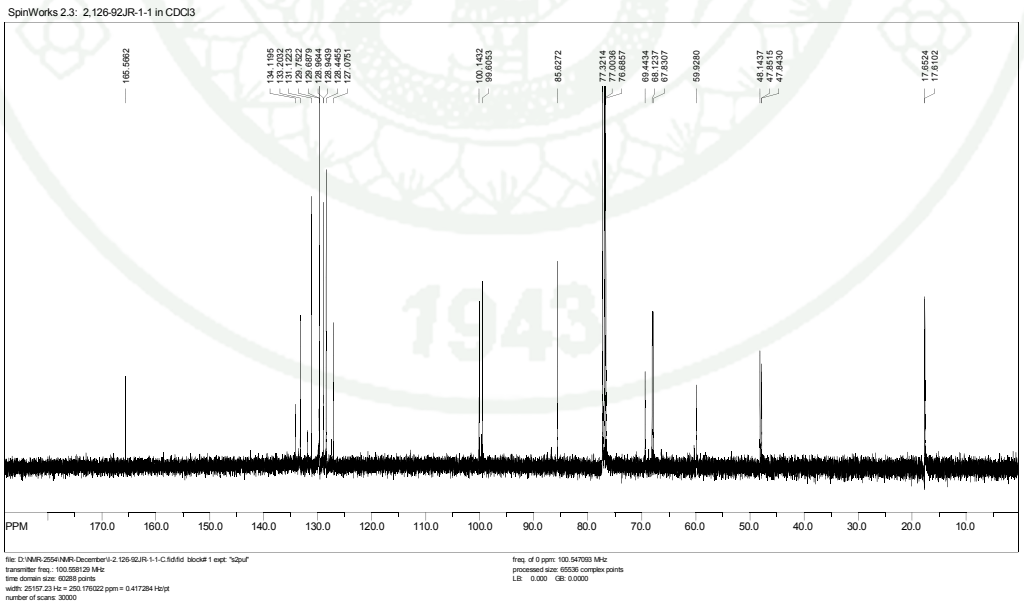


Appendix Figure 69 400 MHz ^{1}H NMR spectrum: thiophenyl-(2'S,3'S)-methyl-2,3-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-4-*O*-benzoyl-β-D-xylopyranoside (497)



Appendix Figure 70 100 MHz ^{13}C NMR spectrum: thiophenyl-(2'S,3'S)-methyl-2,3-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-4-*O*-benzoyl-β-D-xylopyranoside (497)

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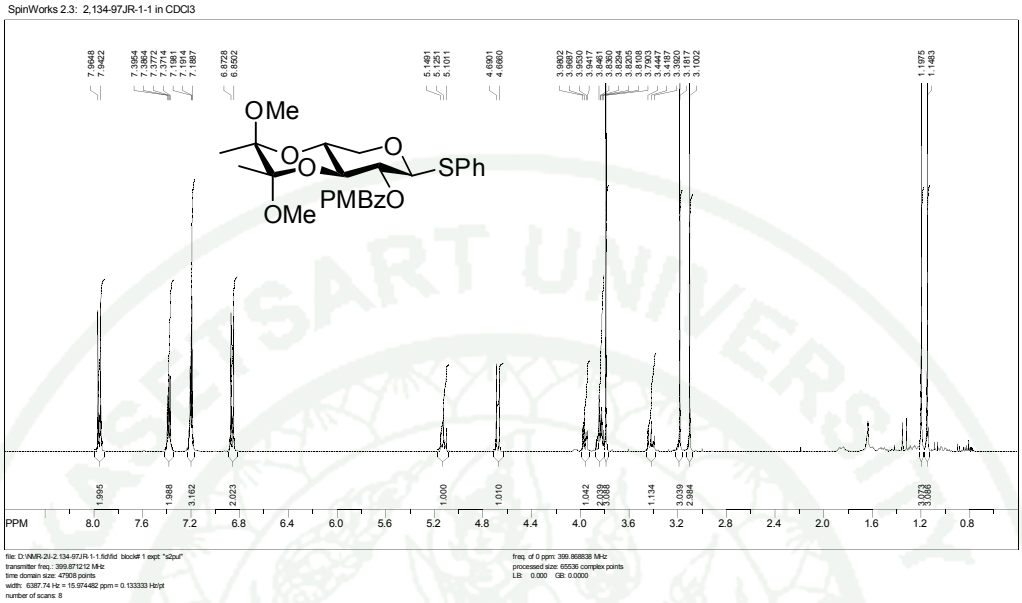
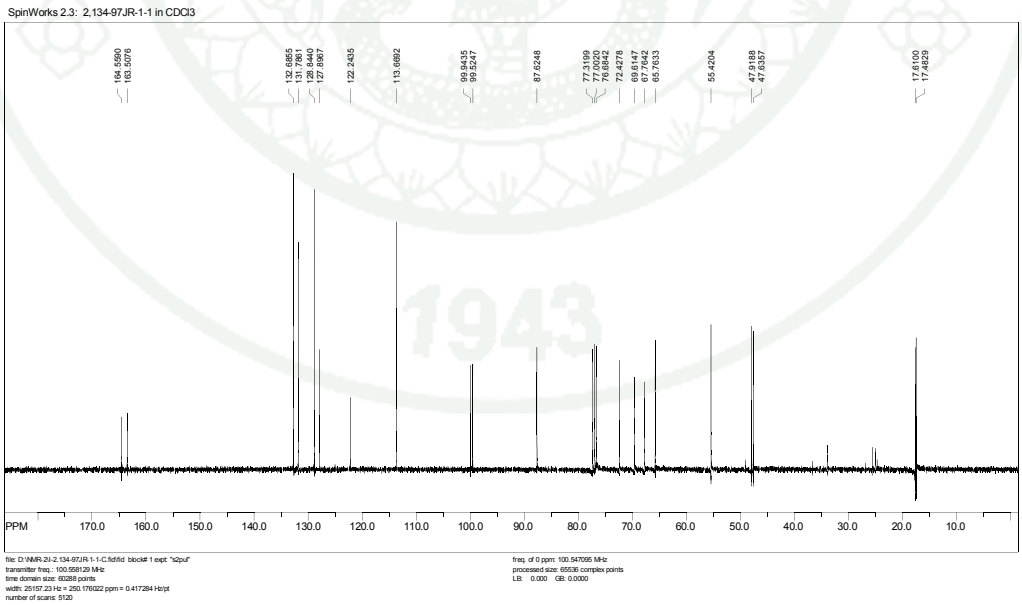


Appendix Figure 71 400 MHz ^{1}H NMR spectrum: thiophenyl-2-*O*-methoxybenzoyl-(2'S,3'S)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-α-D-xylopyranoside (498)



Appendix Figure 72 100 MHz ^{13}C NMR spectrum: thiophenyl-2-*O*-methoxybenzoyl-(2'S,3'S)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-α-D-xylopyranoside (498)

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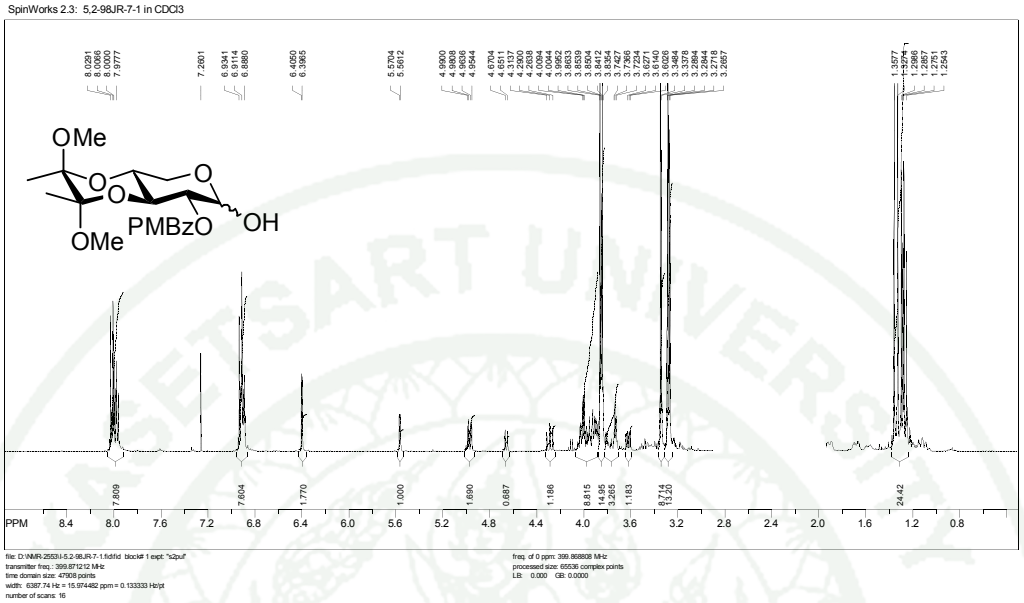
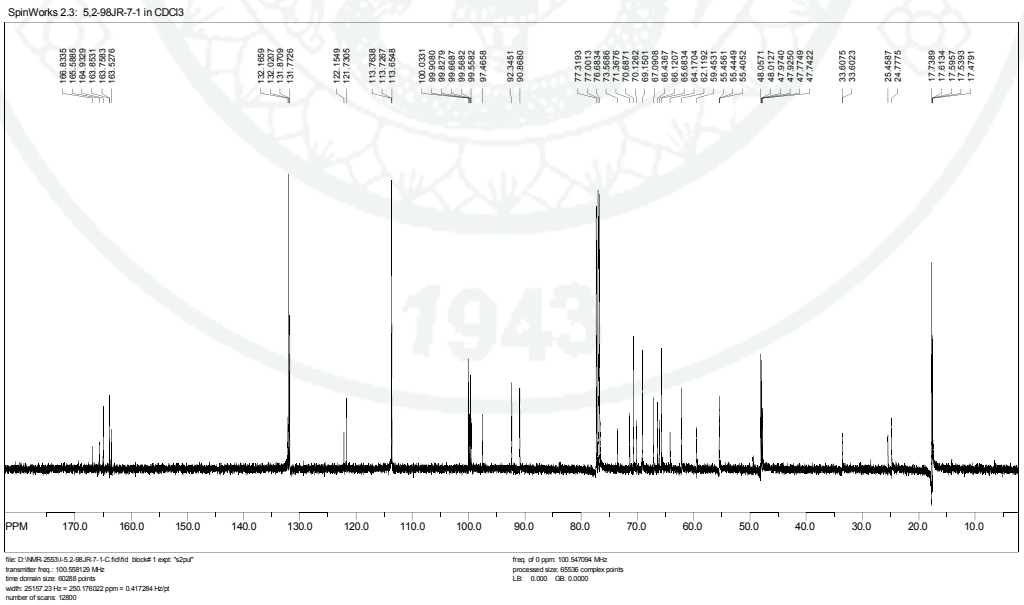


Appendix Figure 73 400 MHz ^{1}H NMR spectrum: 2-*O*-methoxybenzoyl-(2'S,3'S)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-α/β-D-xylopyranoside (499)



Appendix Figure 74 100 MHz ^{13}C NMR spectrum: 2-*O*-methoxybenzoyl-(2'S,3'S)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-α/β-D-xylopyranoside (499)

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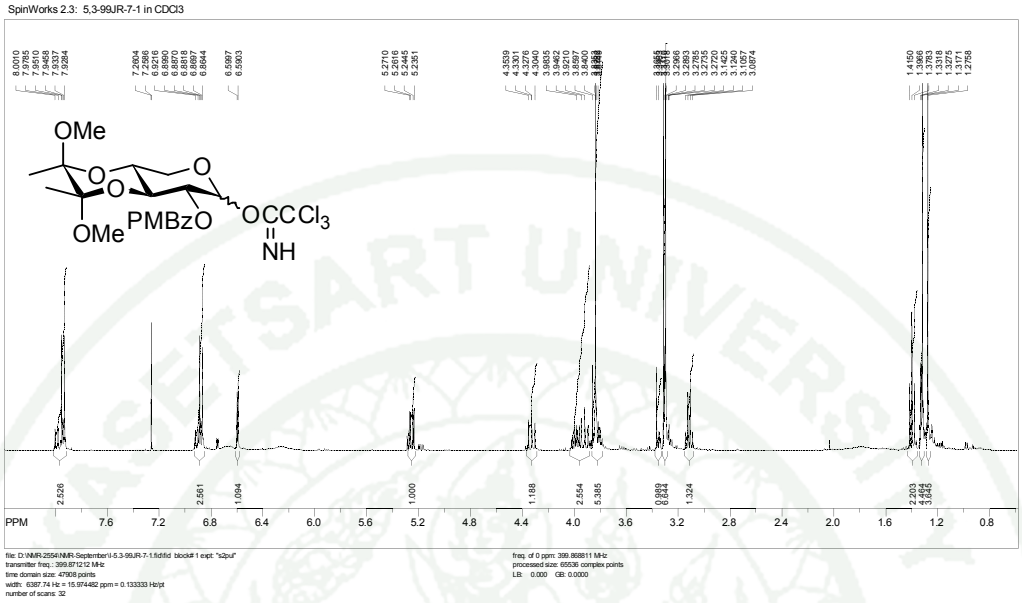
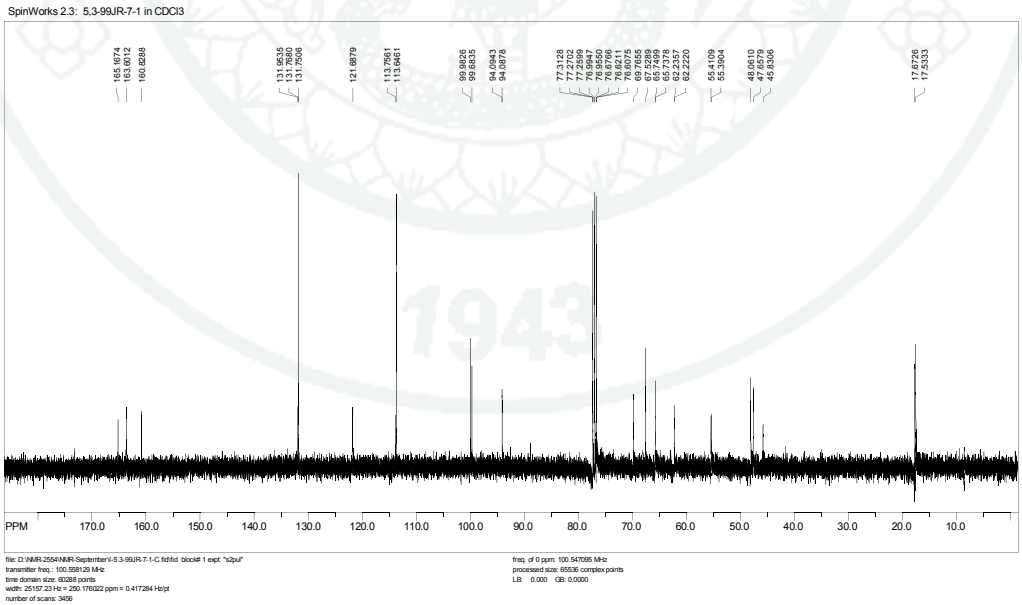


Appendix Figure 75 400 MHz ^{1}H NMR spectrum: trichloroacetimidyl-2-*O*-methoxybenzoyl-(2'S,3'S)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-α/β-D-xylopyranoside (500)



Appendix Figure 76 100 MHz ^{13}C NMR spectrum: trichloroacetimidyl-2-*O*-methoxybenzoyl-(2'S,3'S)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-α/β-D-xylopyranoside (500)

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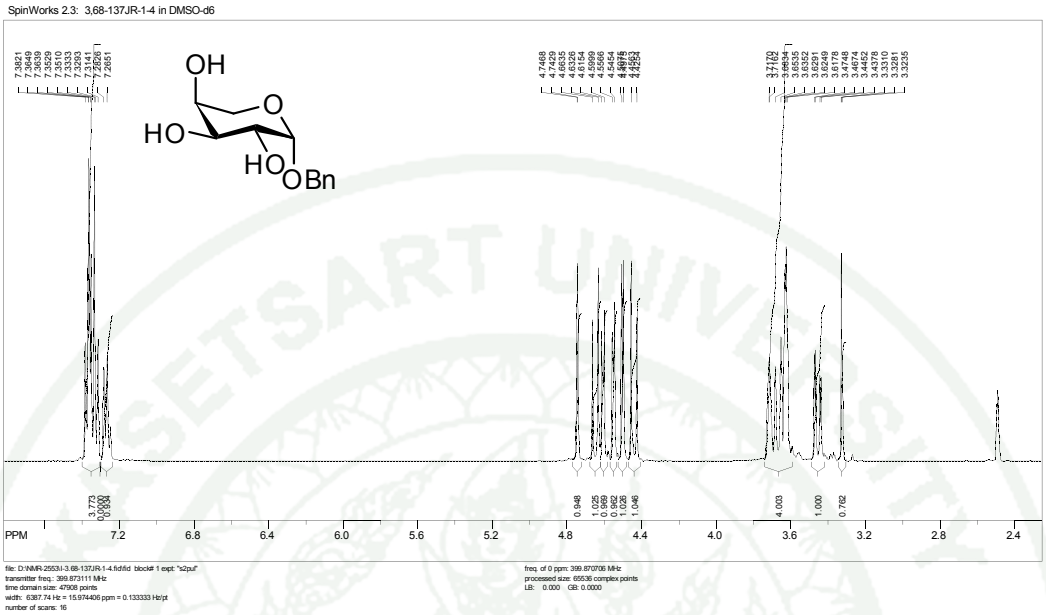
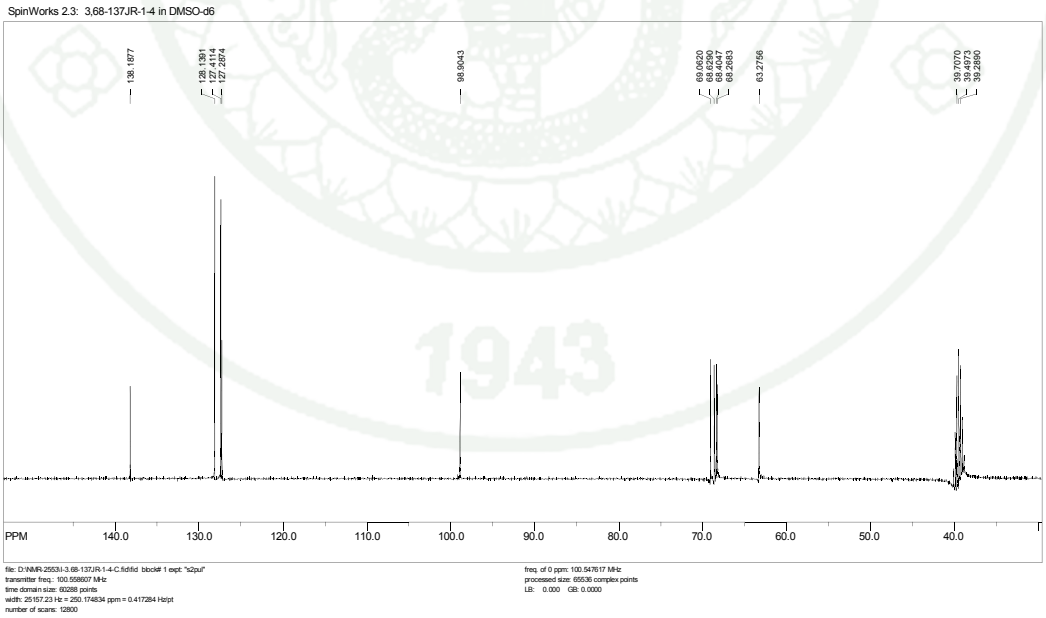


Appendix Figure 77 400 MHz ^{1}H NMR spectrum: benzyl-β-L-arabinopyranoside (501)



Appendix Figure 78 100 MHz ^{13}C NMR spectrum: benzyl-β-L-arabinopyranoside (501)

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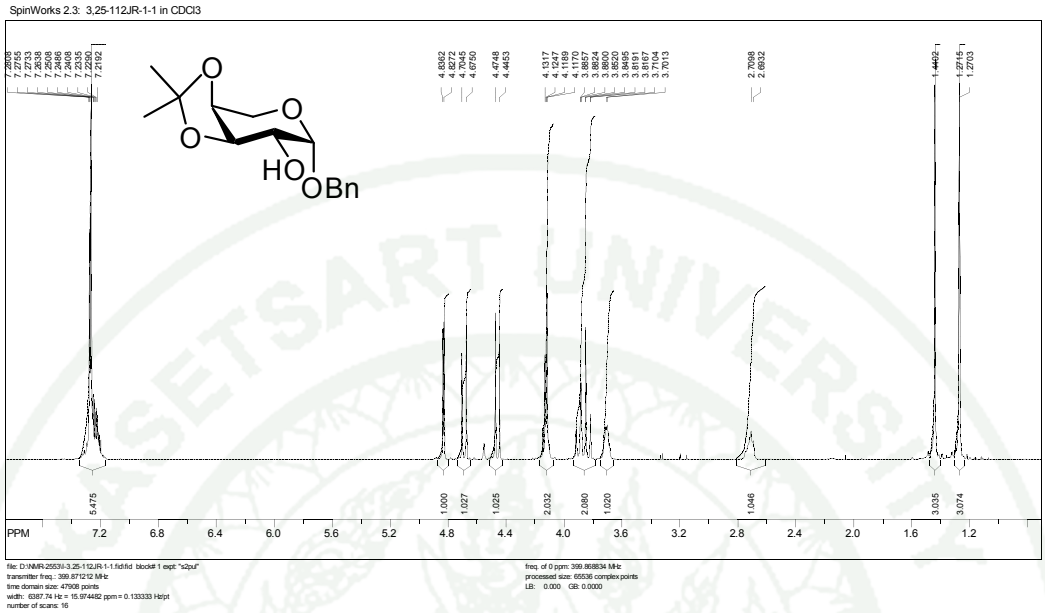
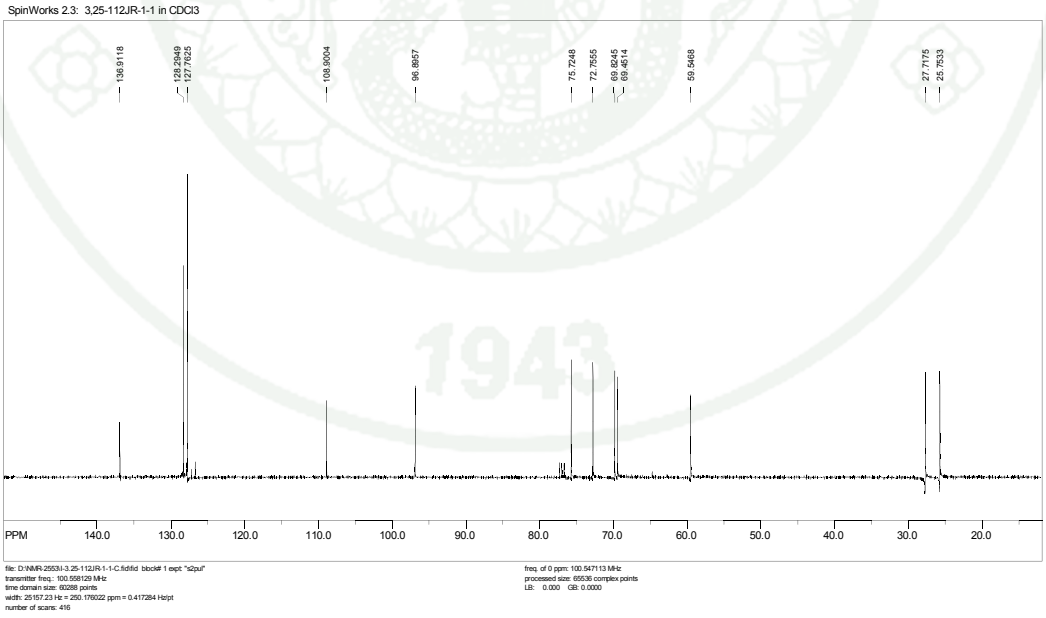


Appendix Figure 79 400 MHz ^{1}H NMR spectrum: benzyl-3,4-acetonide-β-L-arabinopyranoside (72)



Appendix Figure 80 100 MHz ^{13}C NMR spectrum: benzyl-3,4-acetonide-β-L-arabinopyranoside (72)

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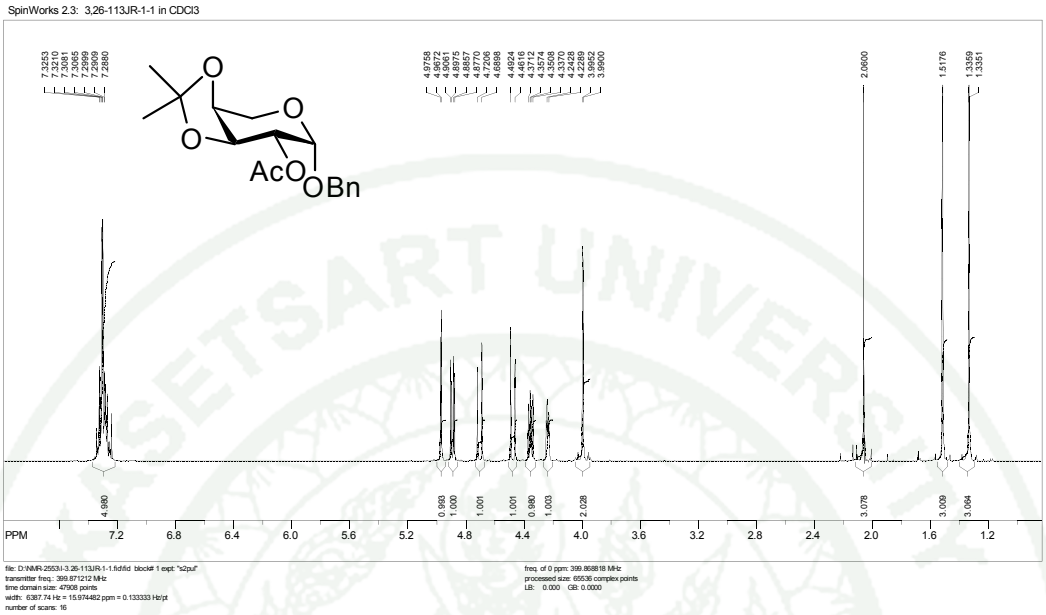
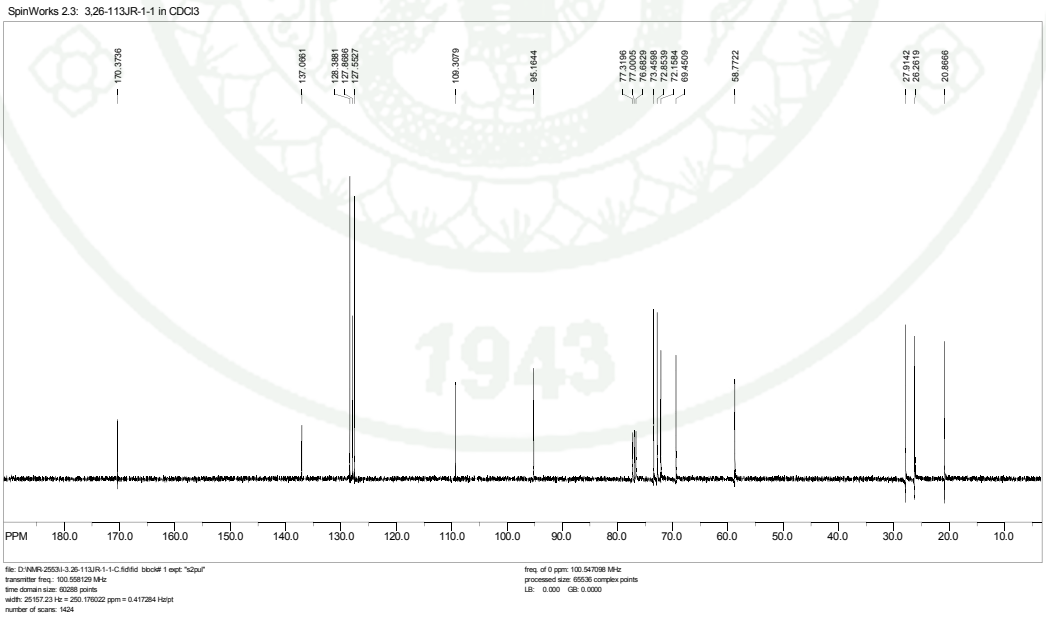


Appendix Figure 81 400 MHz ^{1}H NMR spectrum: benzyl-2-*O*-acetyl-3,4-acetonide-*β*-L-arabinopyranoside (502)



Appendix Figure 82 100 MHz ^{13}C NMR spectrum: benzyl-2-*O*-acetyl-3,4-acetonide-*β*-L-arabinopyranoside (502)

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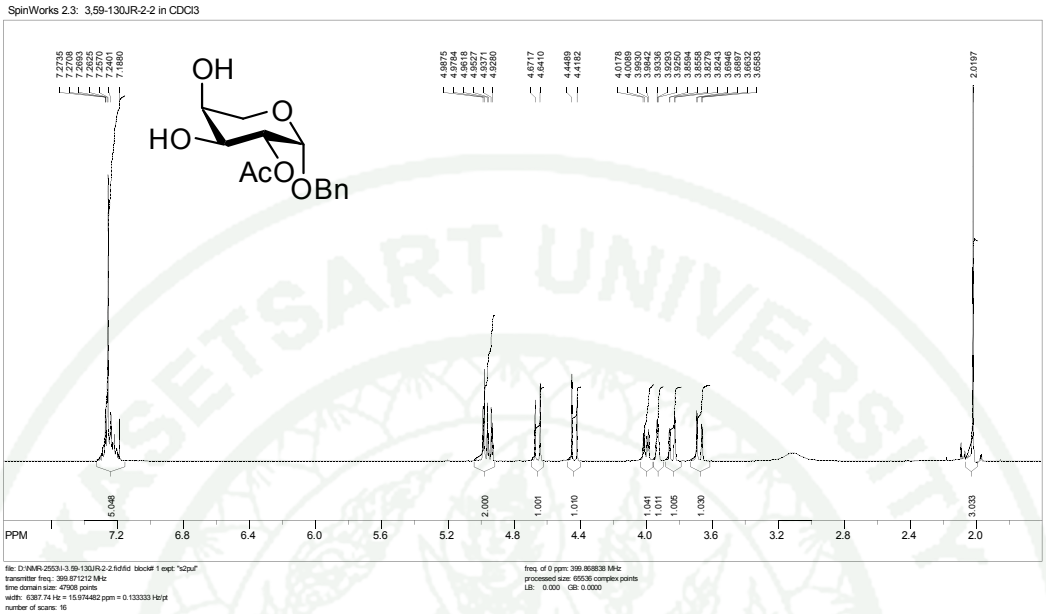
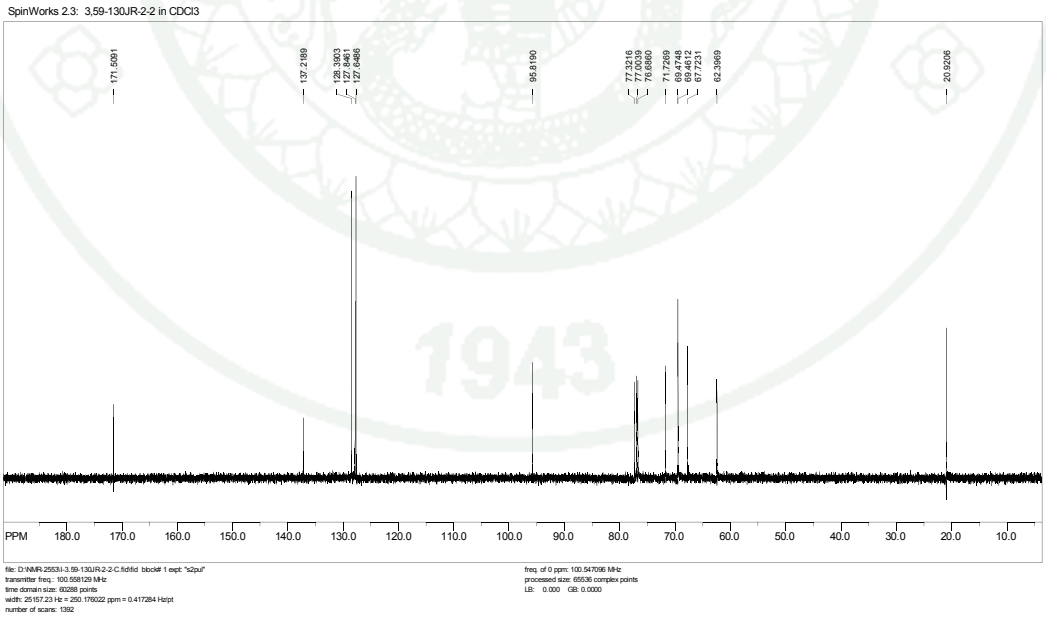


Appendix Figure 83 400 MHz ^{1}H NMR spectrum: benzyl-2-*O*-acetyl-*β*-L-arabinopyranoside (73)



Appendix Figure 84 100 MHz ^{13}C NMR spectrum: benzyl-2-*O*-acetyl-*β*-L-arabinopyranoside (73)

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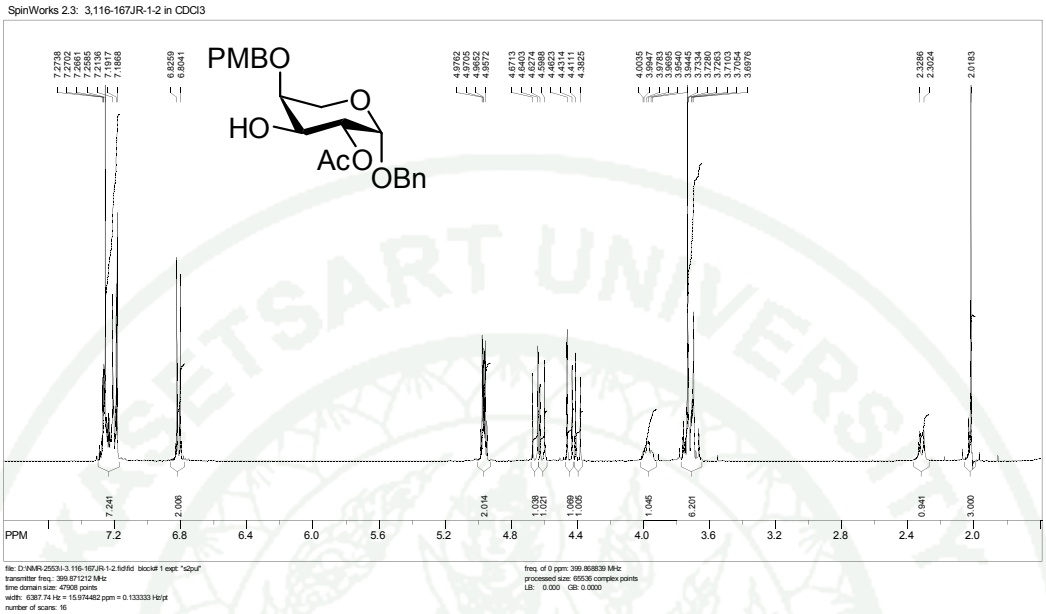
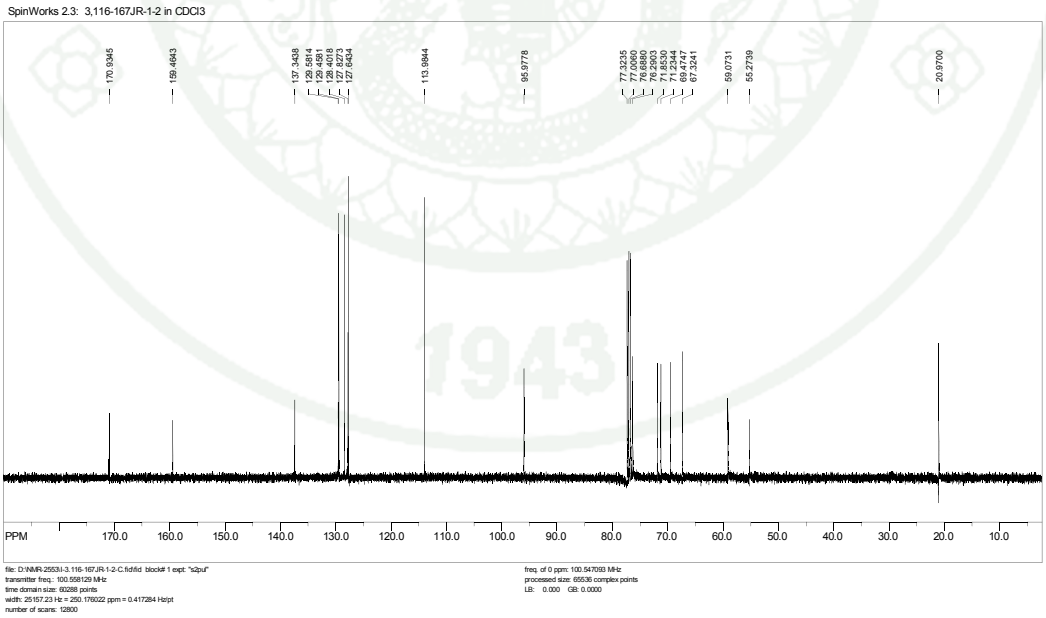


Appendix Figure 85 400 MHz ^{1}H NMR spectrum: benzyl 2-*O*-acetyl-4-*O*-paramethoxybenzyl-β-L-arabinopyranoside (504)



Appendix Figure 86 100 MHz ^{13}C NMR spectrum: benzyl 2-*O*-acetyl-4-*O*-paramethoxybenzyl-β-L-arabinopyranoside (504)

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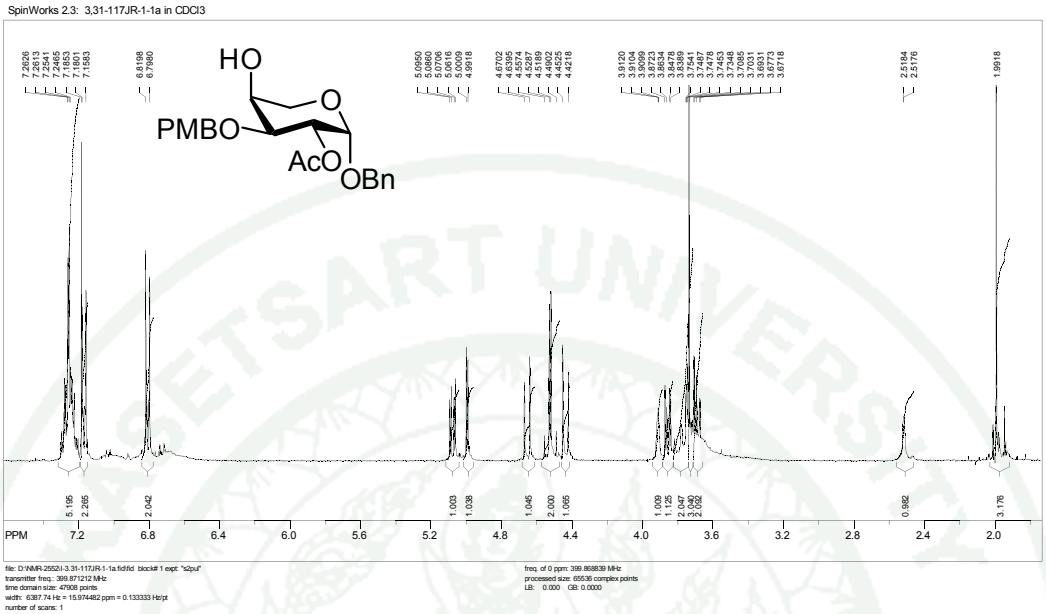
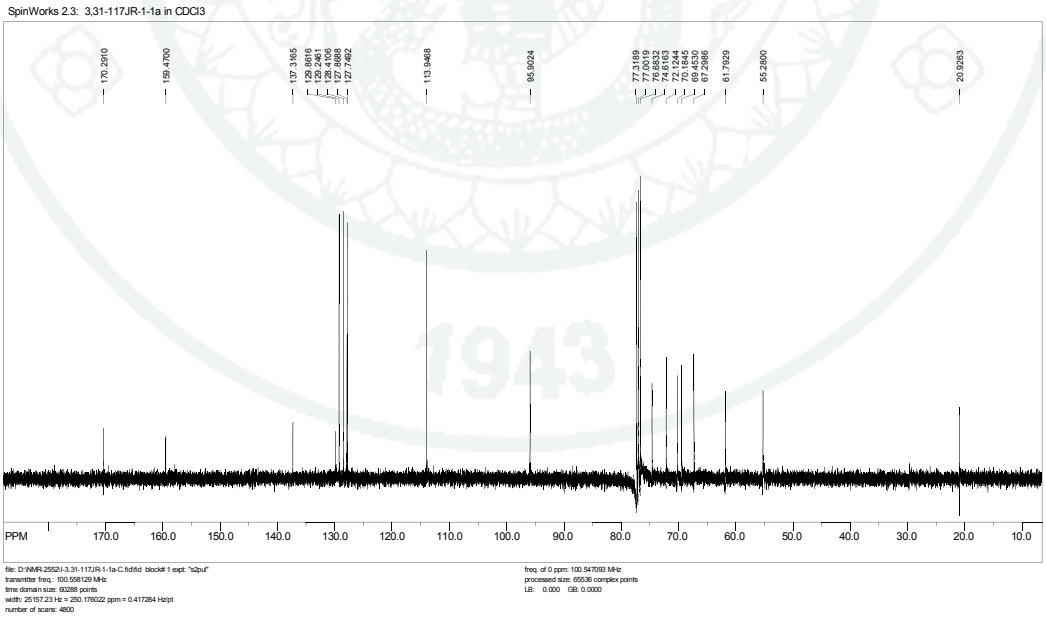


Appendix Figure 87 400 MHz ^{1}H NMR spectrum: benzyl 2-*O*-acetyl-3-*O*-parametho xybenzyl-*β*-L-arabinopyranoside (505)



Appendix Figure 88 100 MHz ^{13}C NMR spectrum: benzyl 2-*O*-acetyl-3-*O*-parametho xybenzyl-*β*-L-arabinopyranoside (505)

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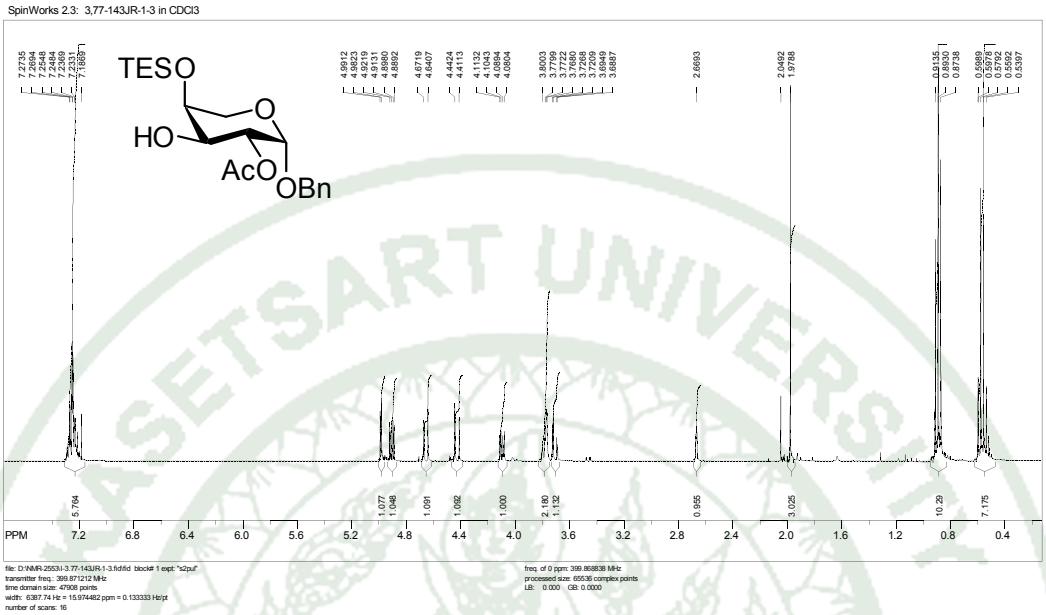
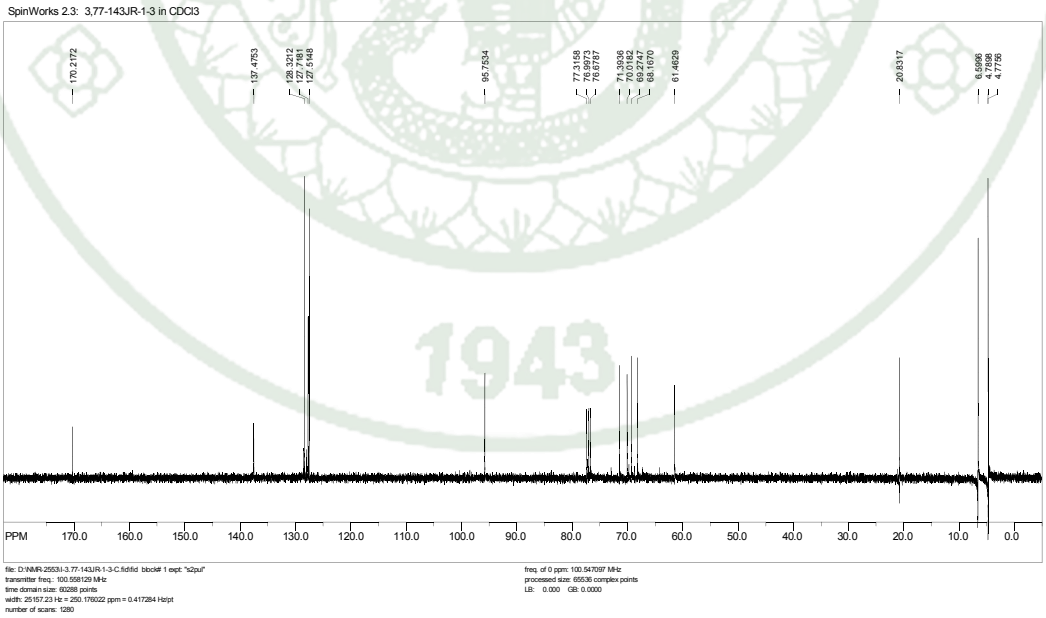


Appendix Figure 89 400 MHz ^{1}H NMR spectrum: benzyl 2-*O*-acetyl-4-*O*-triethylsilyloxy-*β*-L-arabinopyranoside (506)



Appendix Figure 90 100 MHz ^{13}C NMR spectrum: benzyl 2-*O*-acetyl-4-*O*-triethylsilyloxy-*β*-L-arabinopyranoside (506)

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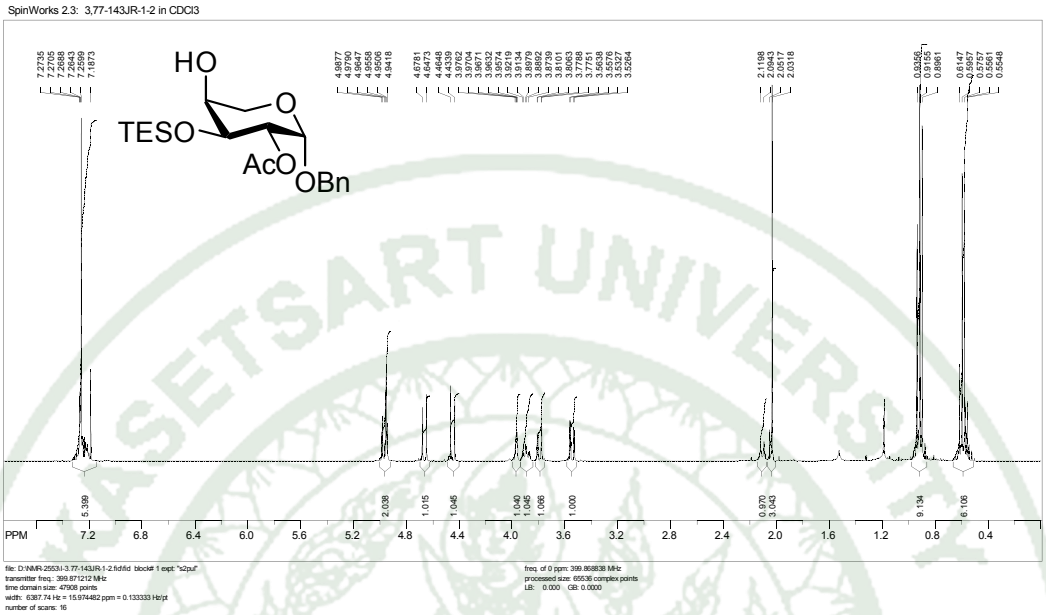
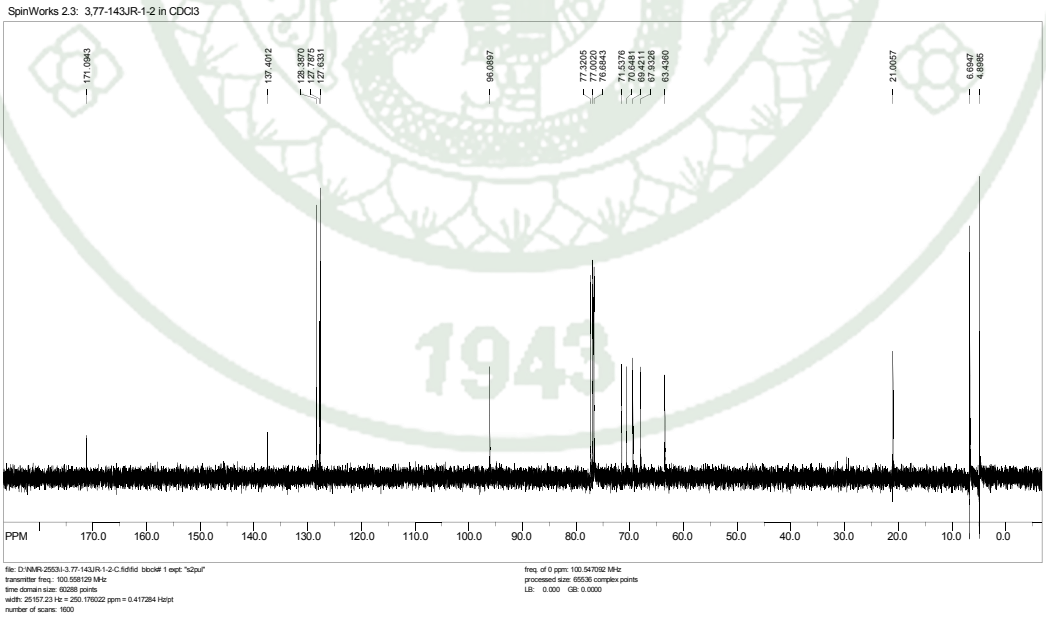


Appendix Figure 91 400 MHz ^{1}H NMR spectrum: benzyl 2-*O*-acetyl-3-*O*-triethylsilyloxy-*β*-L-arabinopyranoside (507)



Appendix Figure 92 100 MHz ^{13}C NMR spectrum: benzyl 2-*O*-acetyl-3-*O*-triethylsilyloxy-*β*-L-arabinopyranoside (507)

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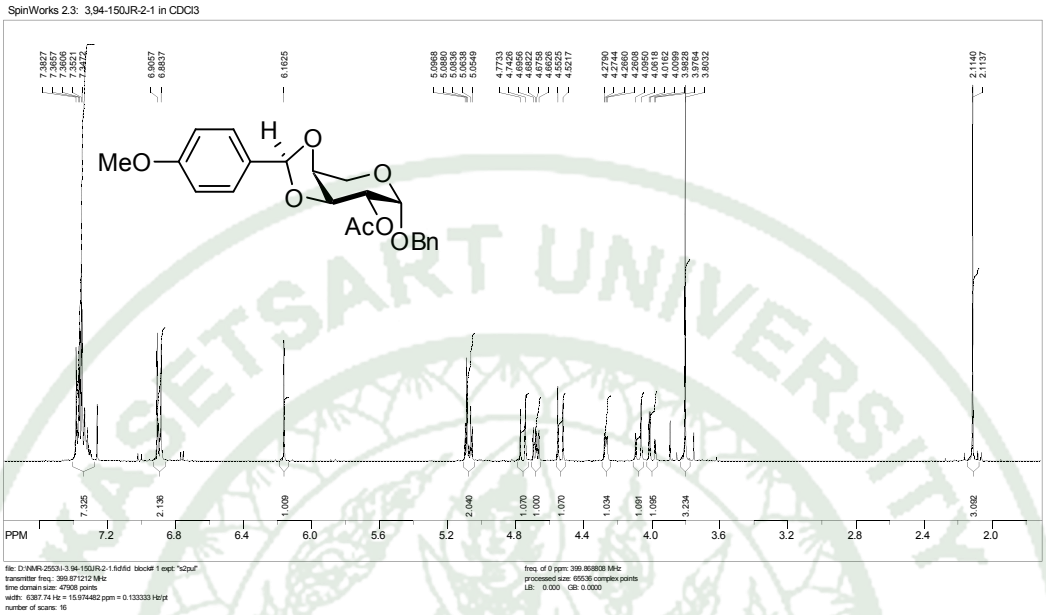
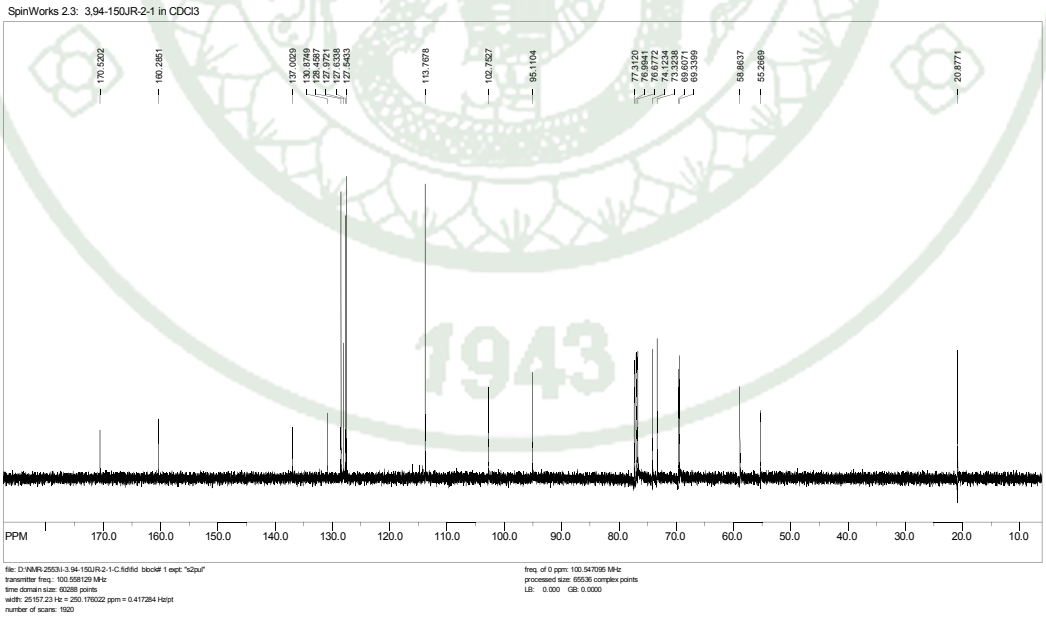


Appendix Figure 93 400 MHz ^{1}H NMR spectrum: benzyl 2-*O*-acetyl-exo-3,4-*O*-paramethoxybenzylidene-*β*-L-arabinopyranoside (*exo*-508)



Appendix Figure 94 100 MHz ^{13}C NMR spectrum: benzyl 2-*O*-acetyl-exo-3,4-*O*-paramethoxybenzylidene-*β*-L-arabinopyranoside (*exo*-508)

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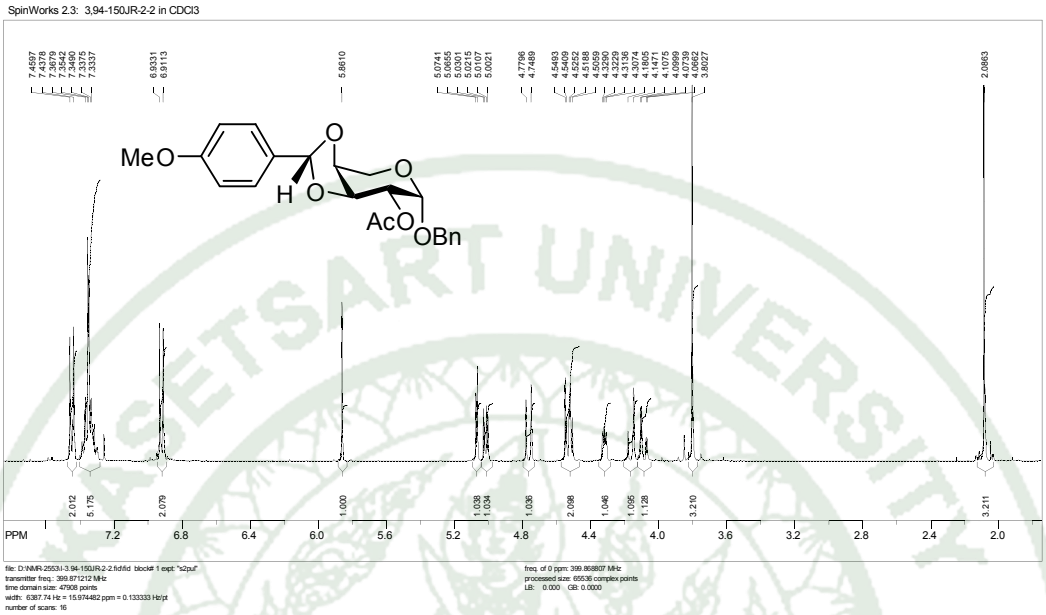
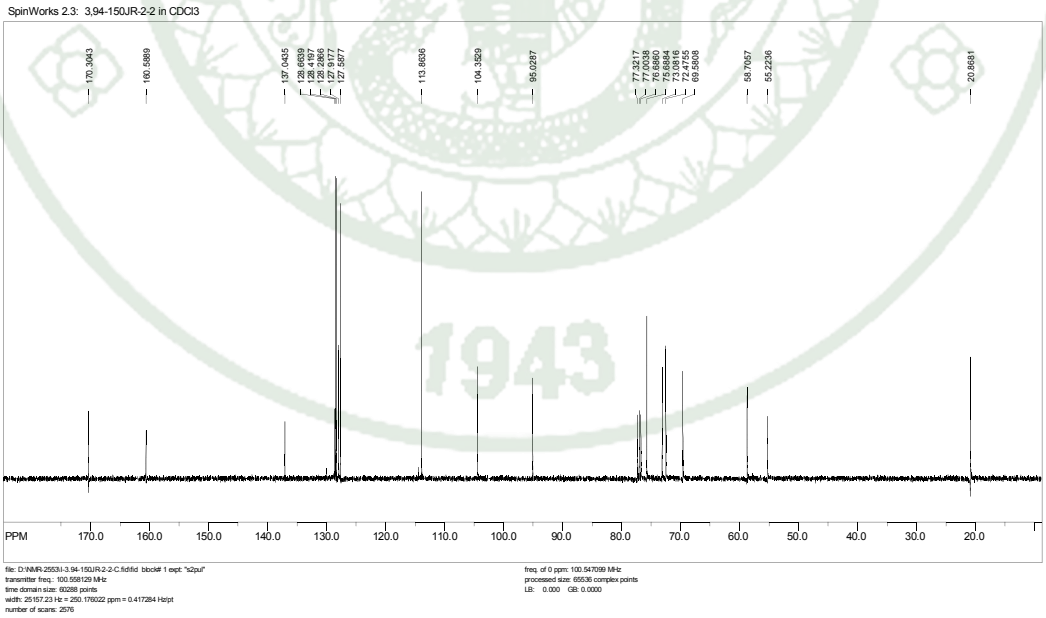


Appendix Figure 95 400 MHz ^{1}H NMR spectrum: benzyl 2-*O*-acetyl-endo-3,4-*O*-paramethoxybenzylidene-*β*-L-arabinopyranoside (*endo*-508)



Appendix Figure 96 100 MHz ^{13}C NMR spectrum: benzyl 2-*O*-acetyl-endo-3,4-*O*-paramethoxybenzylidene-*β*-L-arabinopyranoside (*endo*-508)

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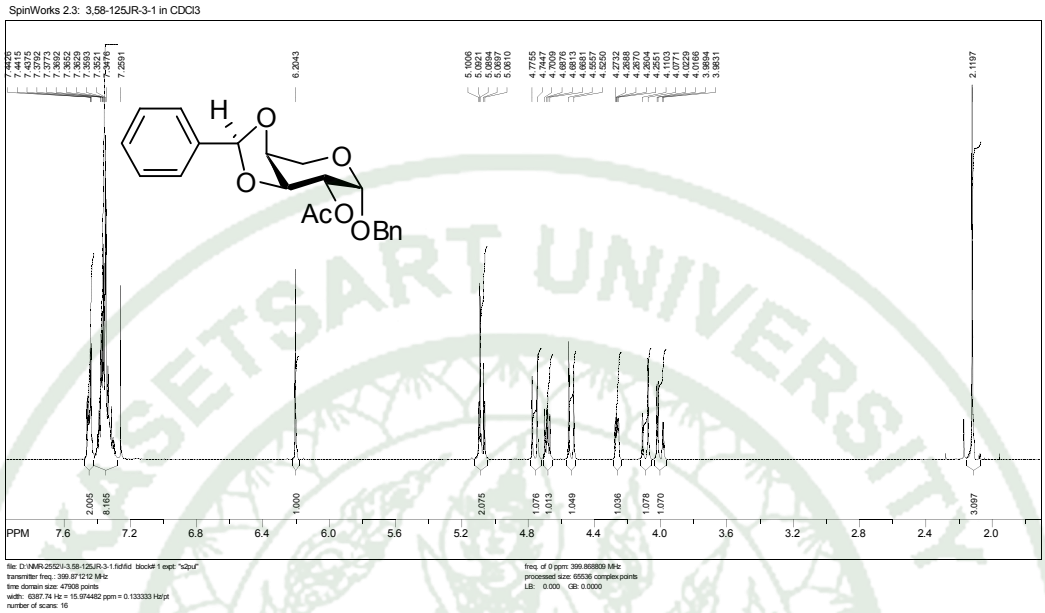
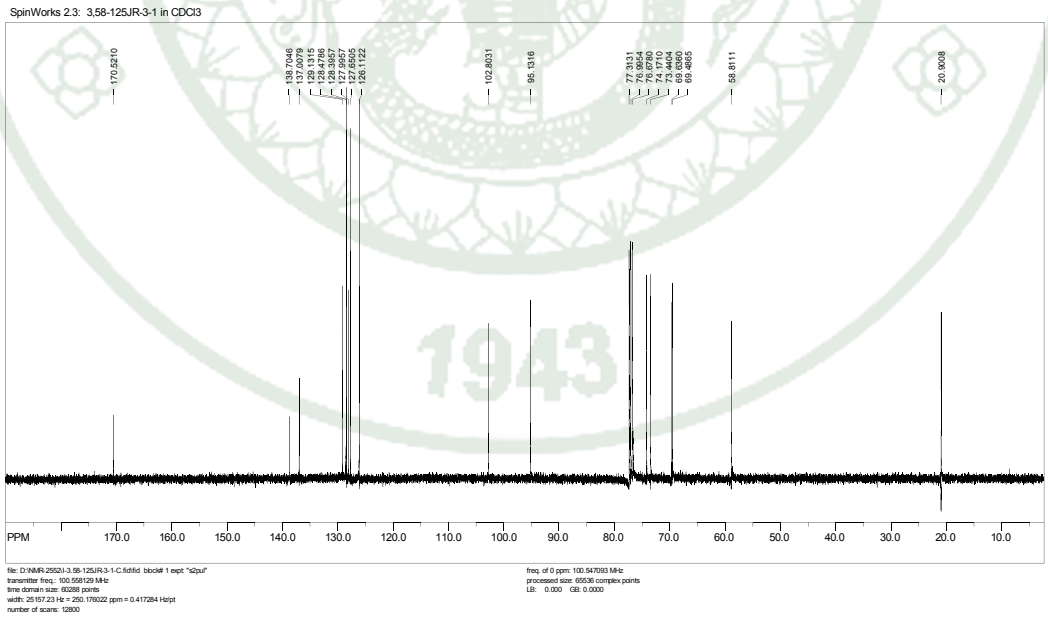


Appendix Figure 97 400 MHz ^{1}H NMR spectrum: benzyl 2-*O*-acetyl-exo-3,4-*O*-benzylidene-*β*-L-arabinopyranoside (*exo*-509)



Appendix Figure 98 100 MHz ^{13}C NMR spectrum: benzyl 2-*O*-acetyl-exo-3,4-*O*-benzylidene-*β*-L-arabinopyranoside (*exo*-509)

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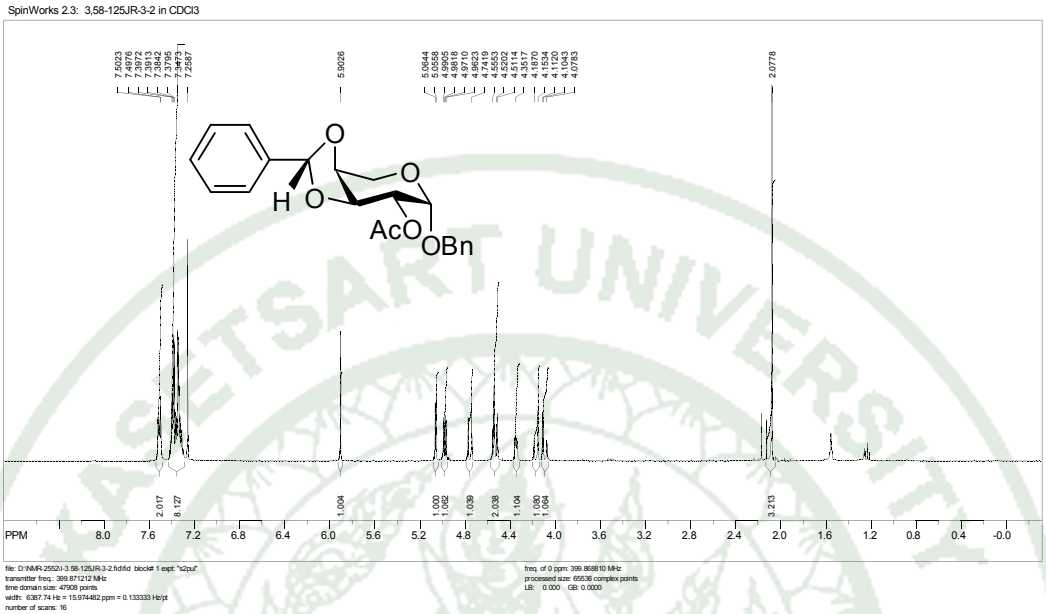
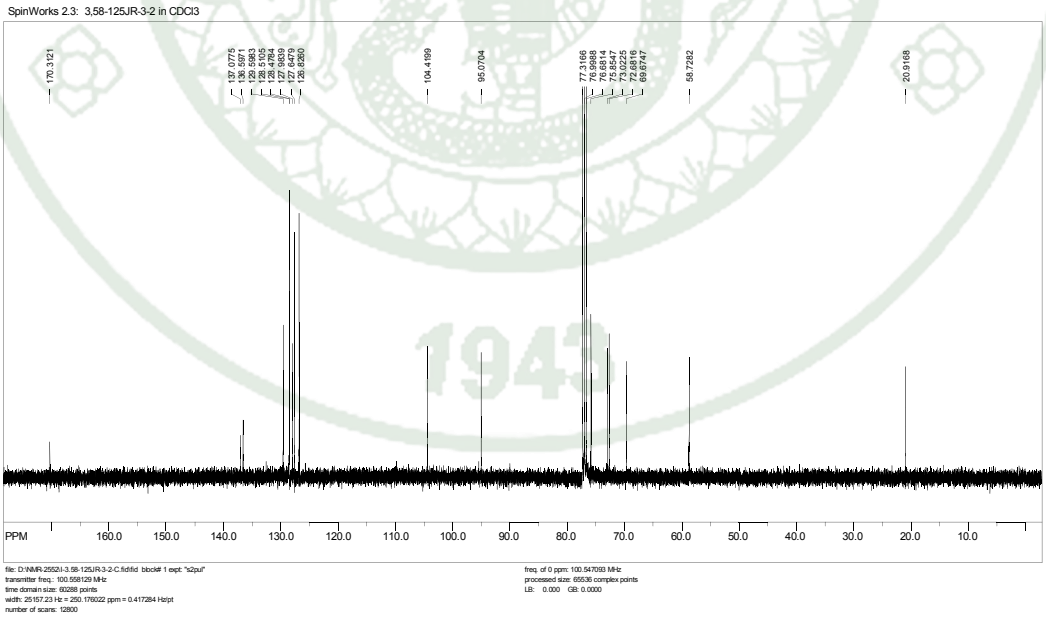


Appendix Figure 99 400 MHz ^{1}H NMR spectrum: benzyl 2-*O*-acetyl-endo-3,4-*O*-benzylidene-*β*-L-arabinopyranoside (*endo*-509)



Appendix Figure 100 100 MHz ^{13}C NMR spectrum: benzyl 2-*O*-acetyl-endo-3,4-*O*-benzylidene-*β*-L-arabinopyranoside (*endo*-509)

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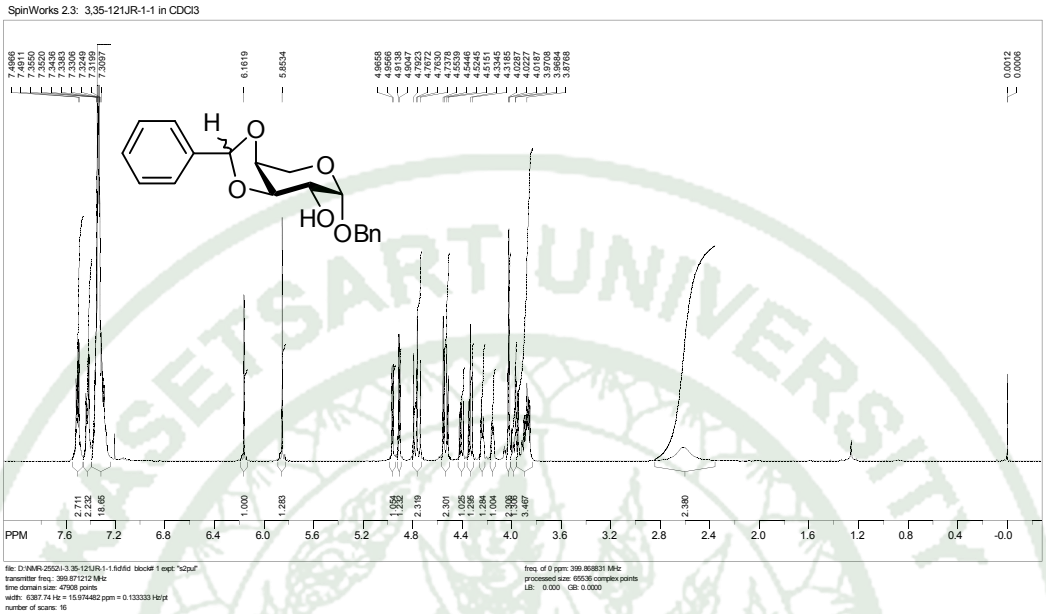
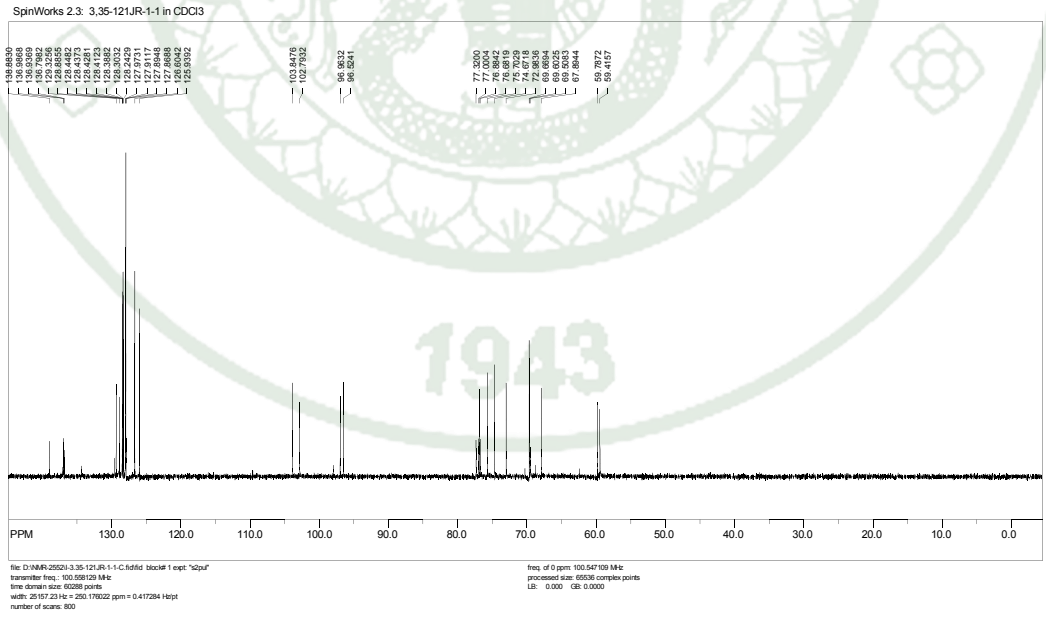


Appendix Figure 101 400 MHz ^{1}H NMR spectrum: benzyl exo/endo-3,4-*O*-benzylidene-*β*-L-arabinopyranosides (510)



Appendix Figure 102 100 MHz ^{13}C NMR spectrum: benzyl exo/endo-3,4-*O*-benzylidene-*β*-L-arabinopyranosides (510)

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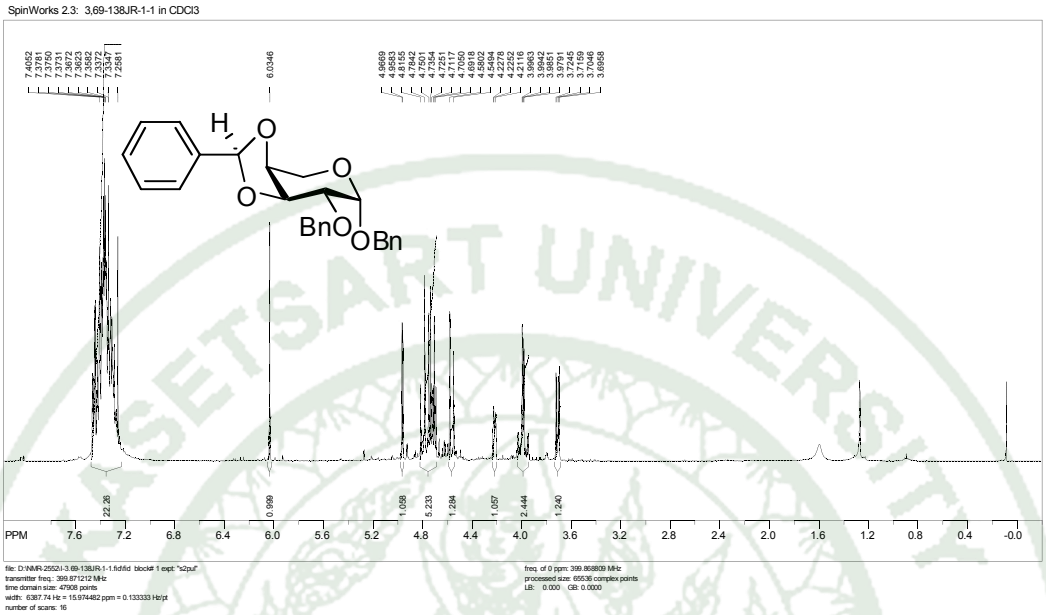
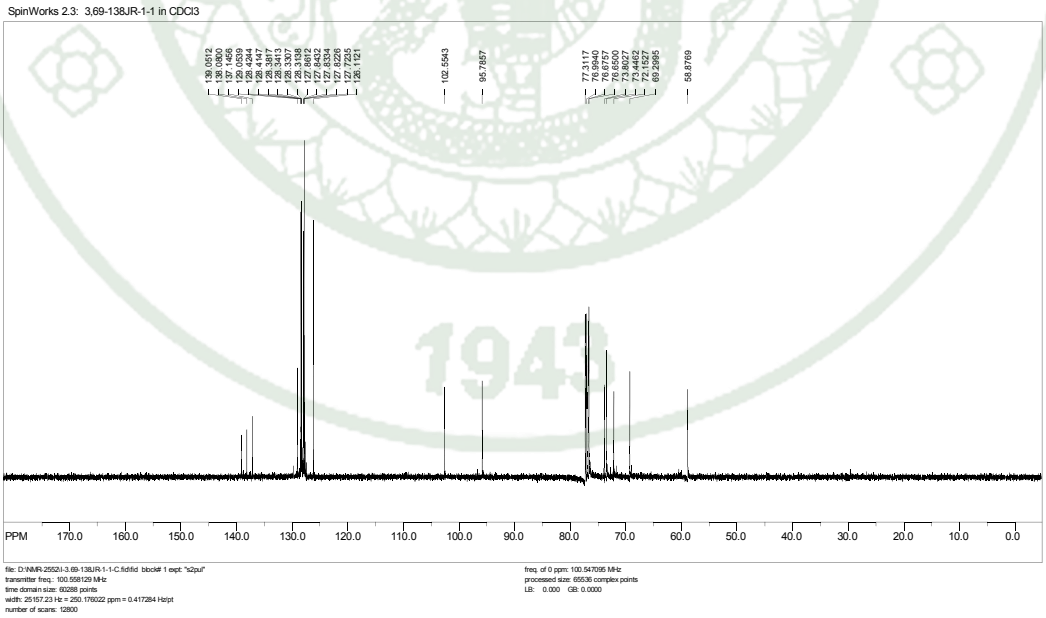


Appendix Figure 103 400 MHz ^{1}H NMR spectrum: benzyl 2-*O*-benzyl-exo-3,4-*O*-benzylidene-*β*-L-arabinopyranoside (*exo*-511)



Appendix Figure 104 100 MHz ^{13}C NMR spectrum: benzyl 2-*O*-benzyl-exo-3,4-*O*-benzylidene-*β*-L-arabinopyranoside (*exo*-511)

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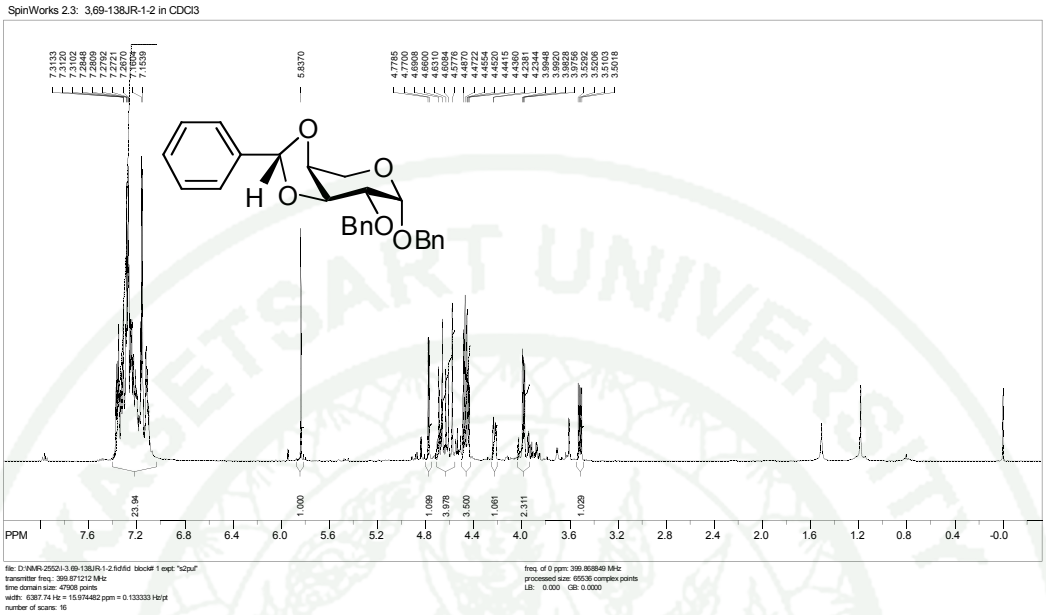
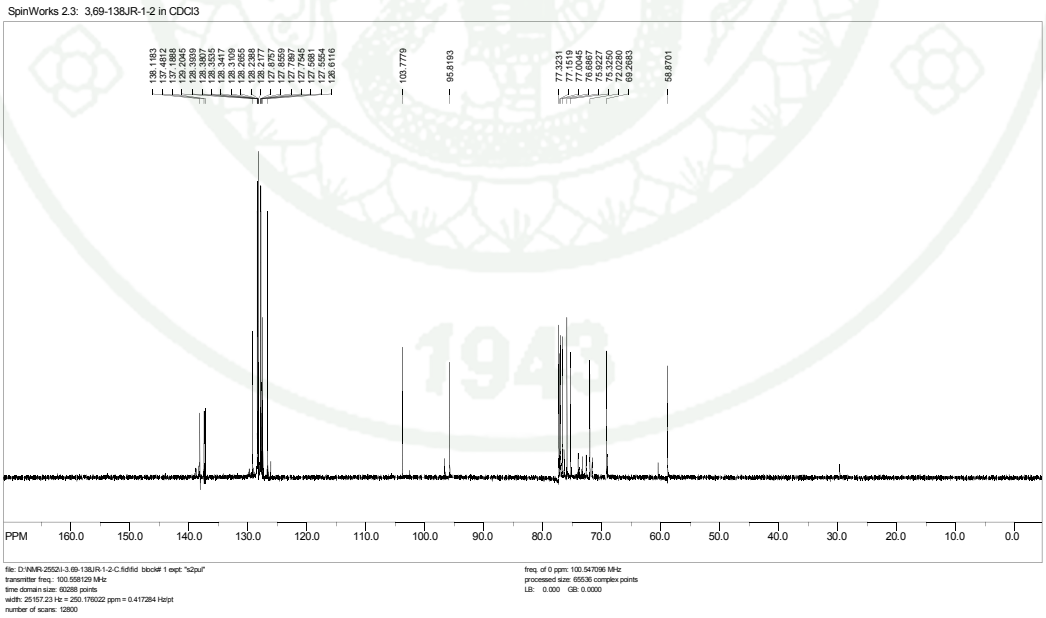


Appendix Figure 105 400 MHz ^{1}H NMR spectrum: benzyl 2-*O*-benzyl-endo-3,4-*O*-benzylidene-*β*-L-arabinopyranoside (*endo*-511)



Appendix Figure 106 100 MHz ^{13}C NMR spectrum: benzyl 2-*O*-benzyl-endo-3,4-*O*-benzylidene-*β*-L-arabinopyranoside (*endo*-511)

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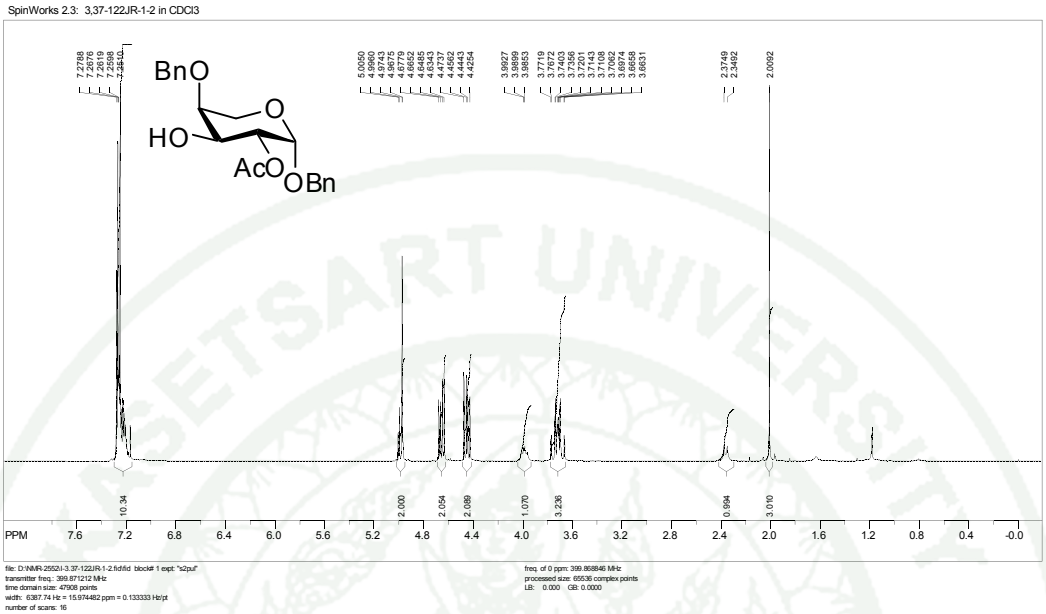
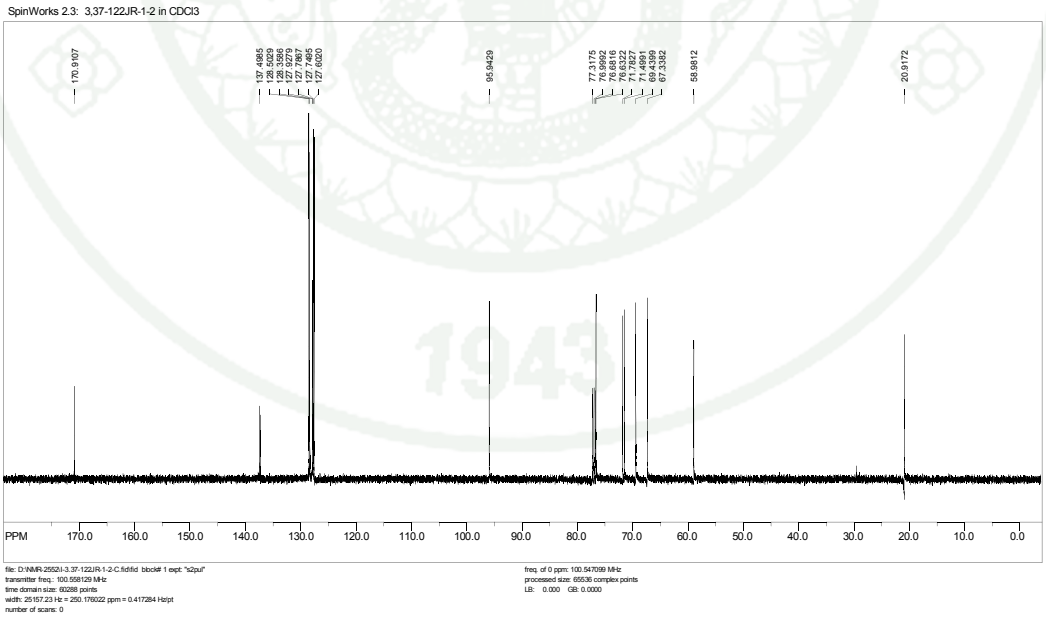


Appendix Figure 107 400 MHz ^{1}H NMR spectrum: benzyl 2-*O*-acetyl-4-*O*-benzyl-*β*-L-arabinopyranoside (512)



Appendix Figure 108 100 MHz ^{13}C NMR spectrum: benzyl 2-*O*-acetyl-4-*O*-benzyl-*β*-L-arabinopyranoside (512)

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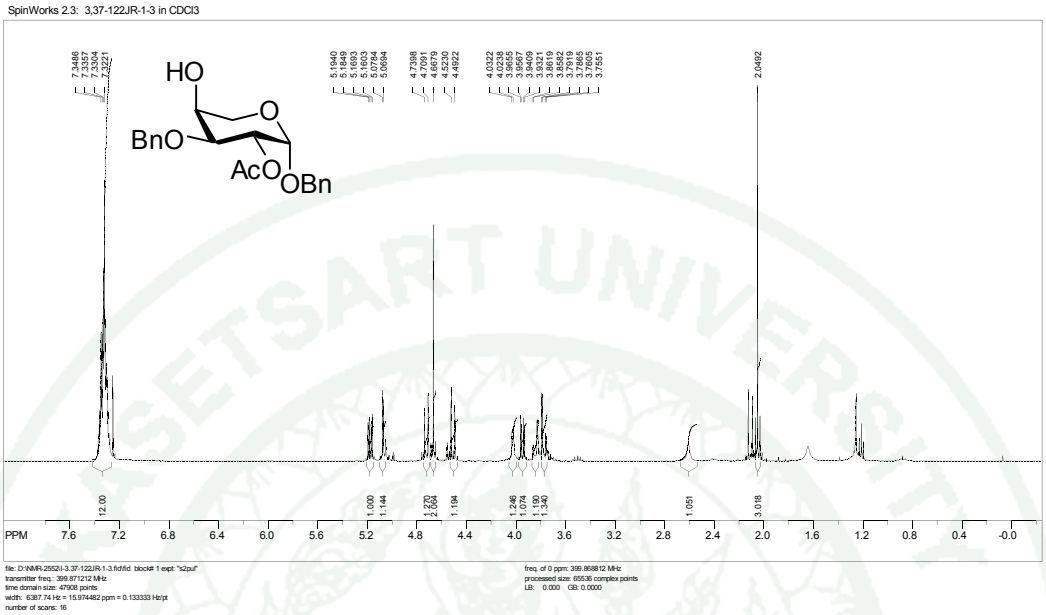
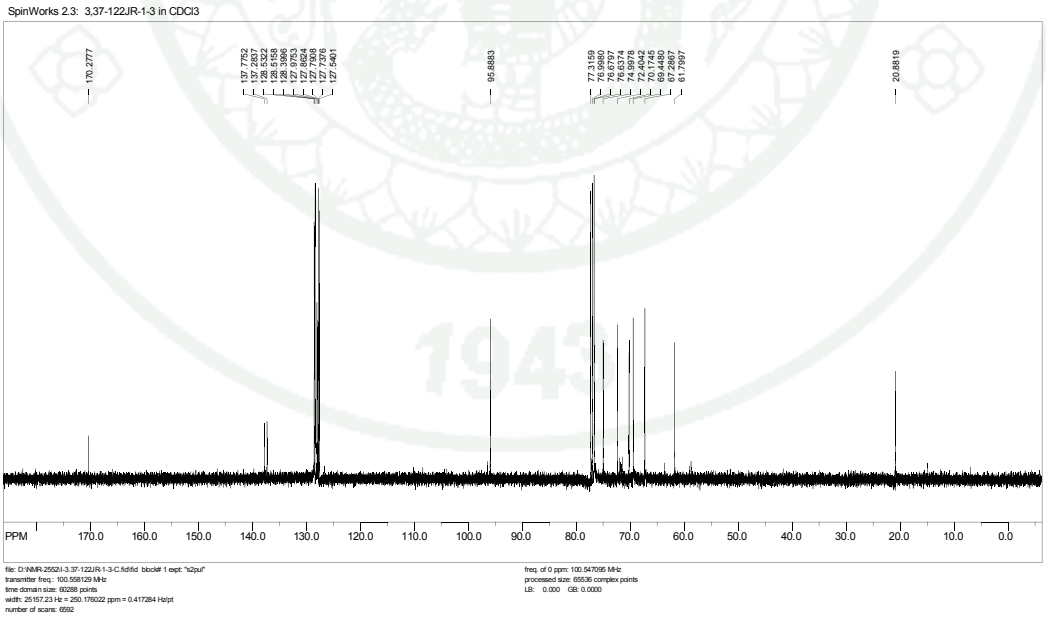


Appendix Figure 109 400 MHz ^{1}H NMR spectrum: benzyl 2-*O*-acetyl-3-*O*-benzyl-*β*-L-arabinopyranoside (513)



Appendix Figure 110 100 MHz ^{13}C NMR spectrum: benzyl 2-*O*-acetyl-3-*O*-benzyl-*β*-L-arabinopyranoside (513)

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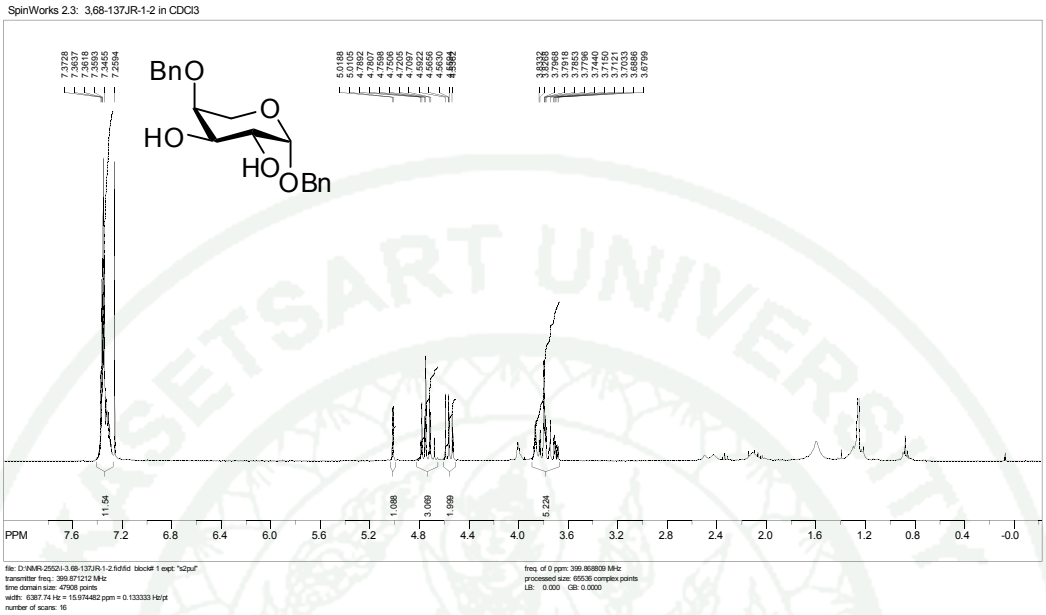
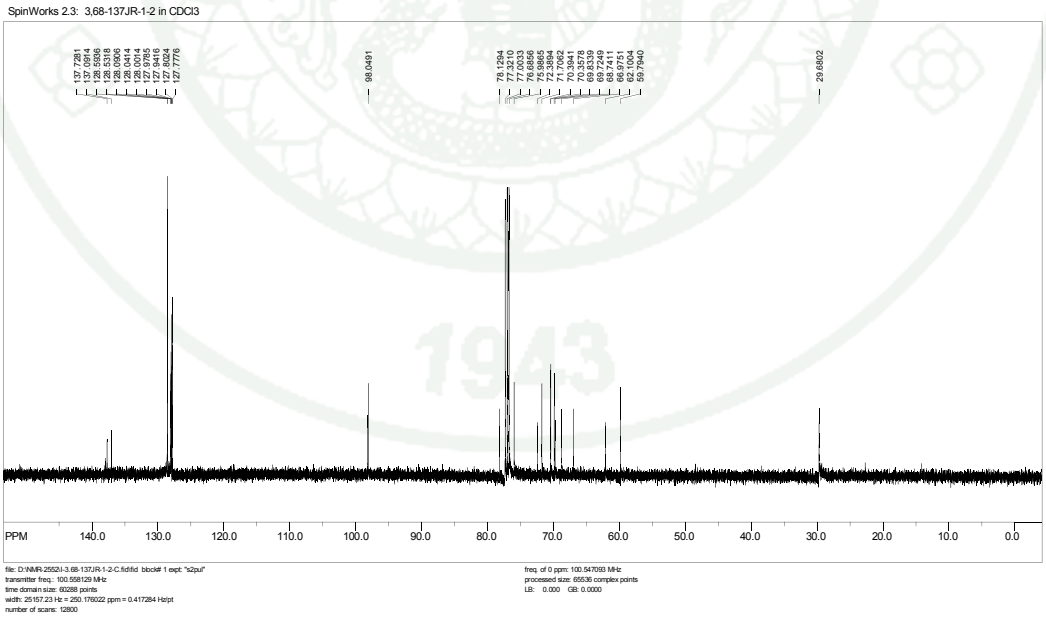


Appendix Figure 111 400 MHz ^{1}H NMR spectrum: benzyl 4-*O*-benzyl-*β*-L-arabinopyranoside (514)



Appendix Figure 112 100 MHz ^{13}C NMR spectrum: benzyl 4-*O*-benzyl-*β*-L-arabinopyranoside (514)

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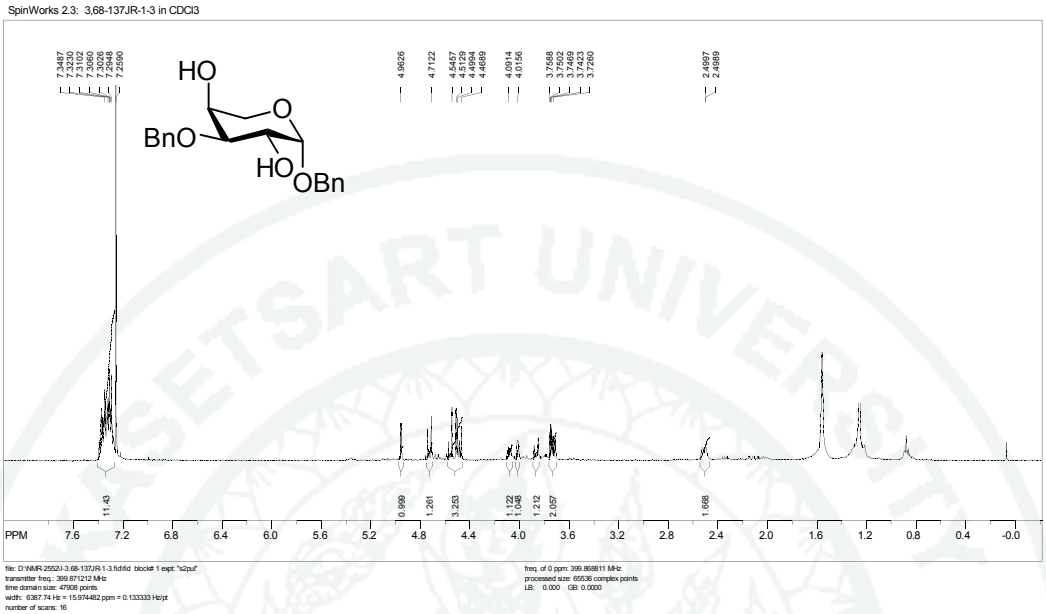
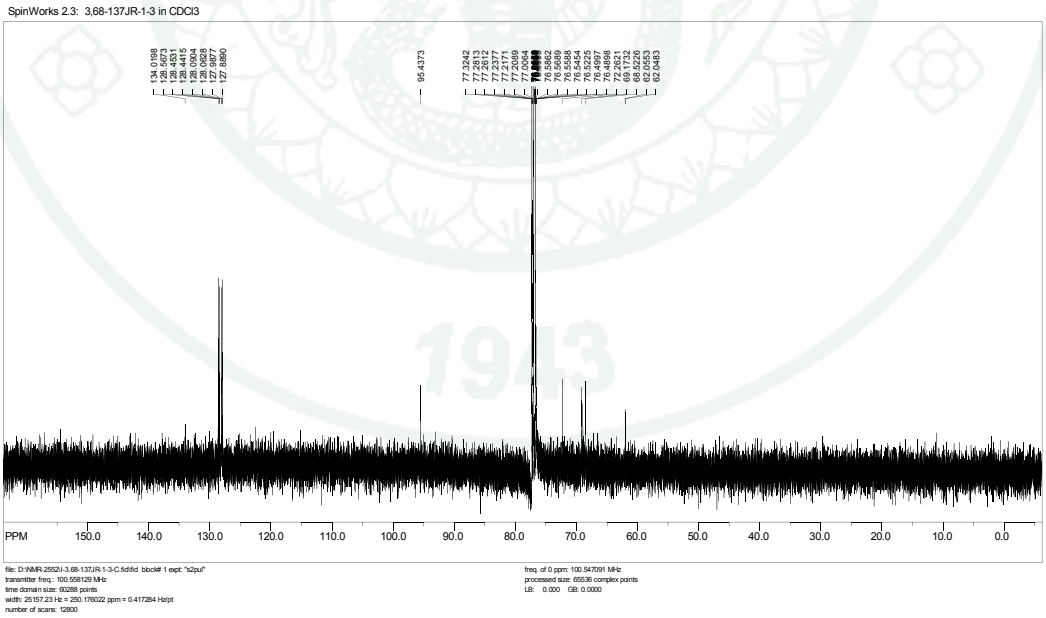


Appendix Figure 113 400 MHz ^{1}H NMR spectrum: benzyl 3-*O*-benzyl-*β*-L-arabinopyranoside (515)



Appendix Figure 114 100 MHz ^{13}C NMR spectrum: benzyl 3-*O*-benzyl-*β*-L-arabinopyranoside (515)

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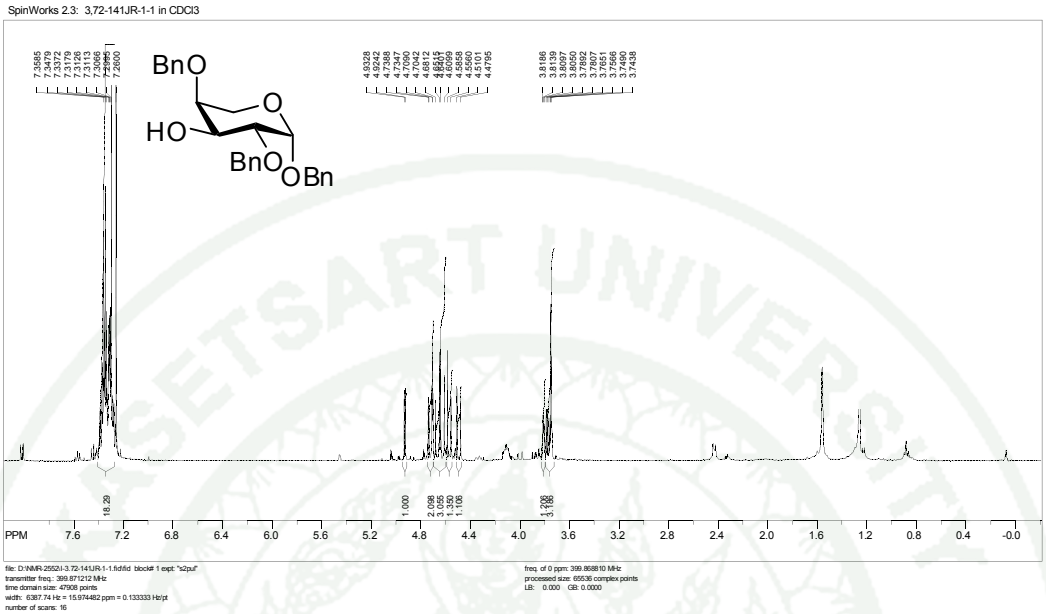
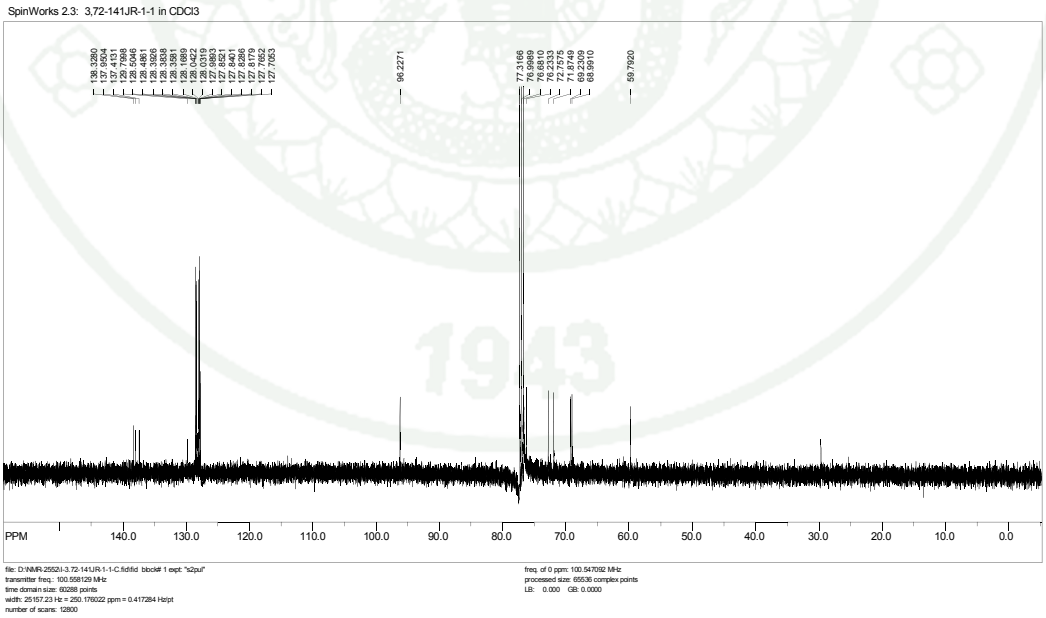


Appendix Figure 115 400 MHz ^{1}H NMR spectrum: benzyl 2-*O*-benzyl-4-*O*-benzyl-*β*-L-arabinopyranoside (516)



Appendix Figure 116 100 MHz ^{13}C NMR spectrum: benzyl 2-*O*-benzyl-4-*O*-benzyl-*β*-L-arabinopyranoside (516)

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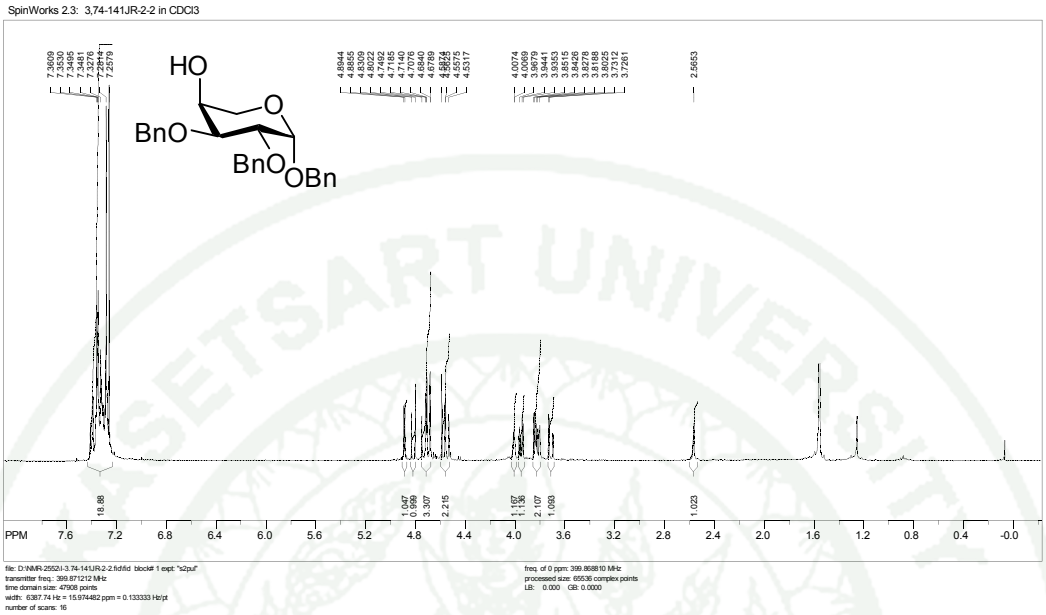
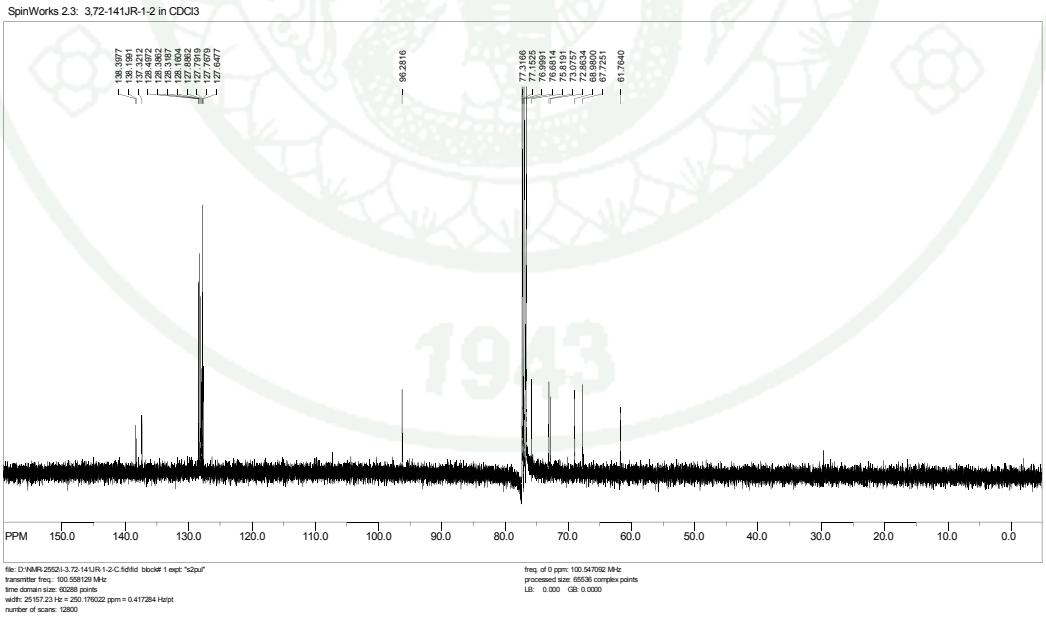


Appendix Figure 117 400 MHz ^{1}H NMR spectrum: benzyl 2-*O*-benzyl-3-*O*-benzyl-*β*-L-arabinopyranoside (517)



Appendix Figure 118 100 MHz ^{13}C NMR spectrum: benzyl 2-*O*-benzyl-3-*O*-benzyl-*β*-L-arabinopyranoside (517)

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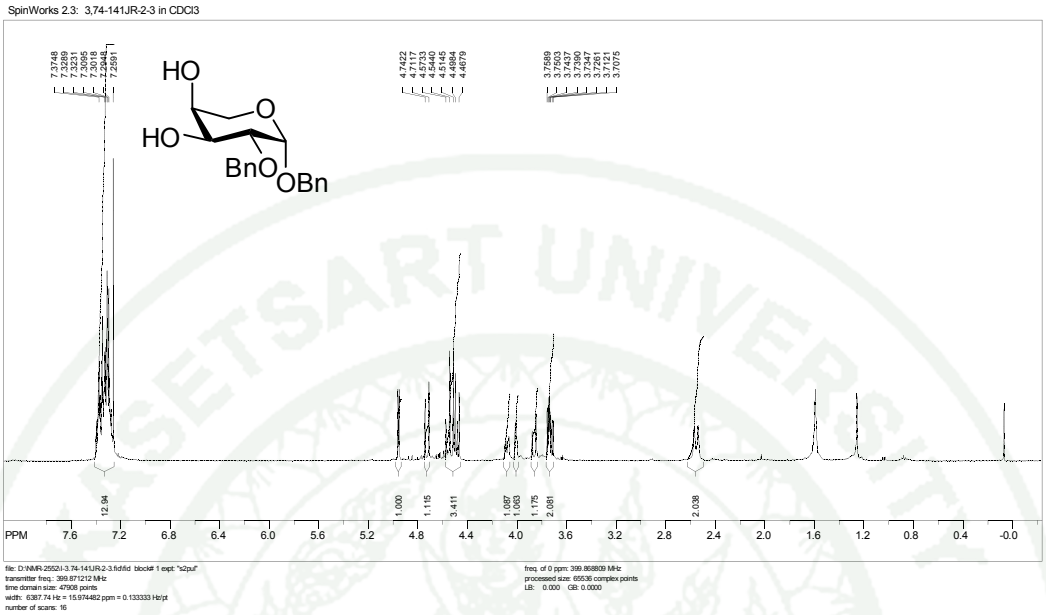
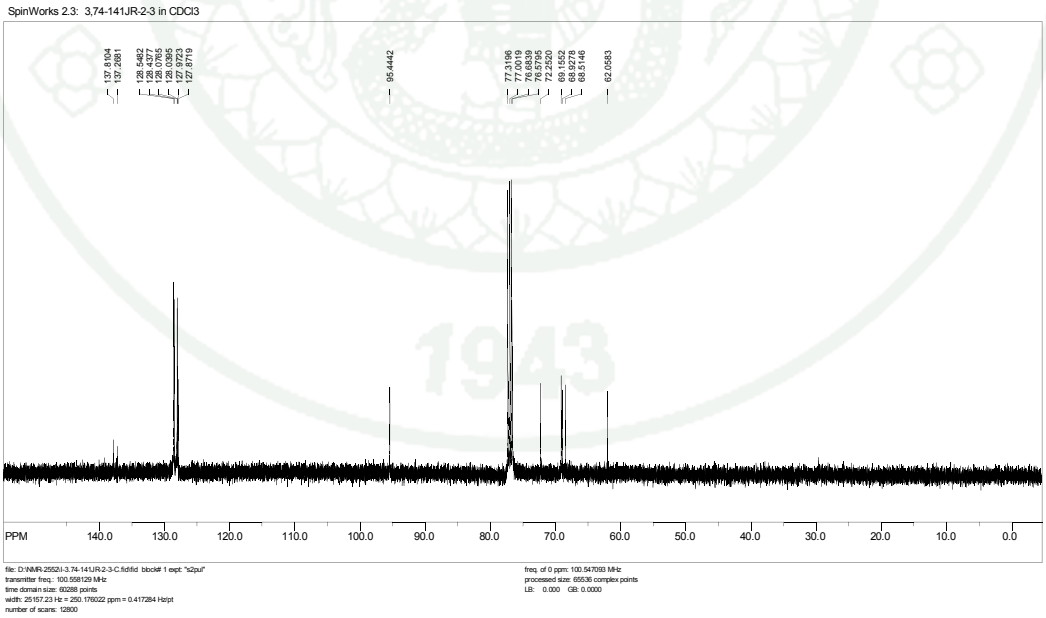


Appendix Figure 119 400 MHz ^{1}H NMR spectrum: benzyl 2-*O*-benzyl-*β*-L-arabinopyranoside (518)



Appendix Figure 120 100 MHz ^{13}C NMR spectrum: benzyl 2-*O*-benzyl-*β*-L-arabinopyranoside (518)

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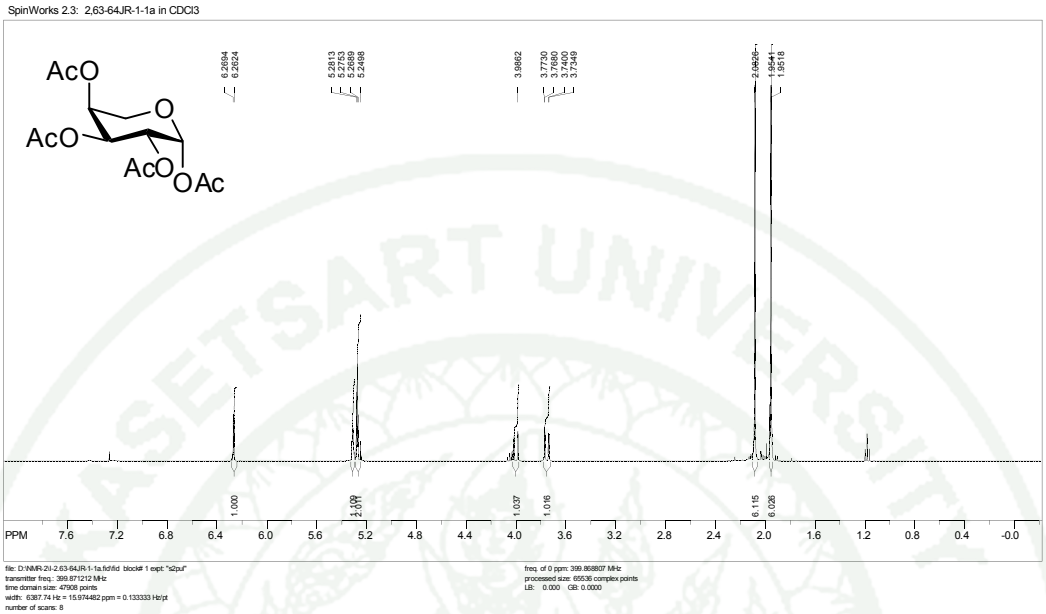
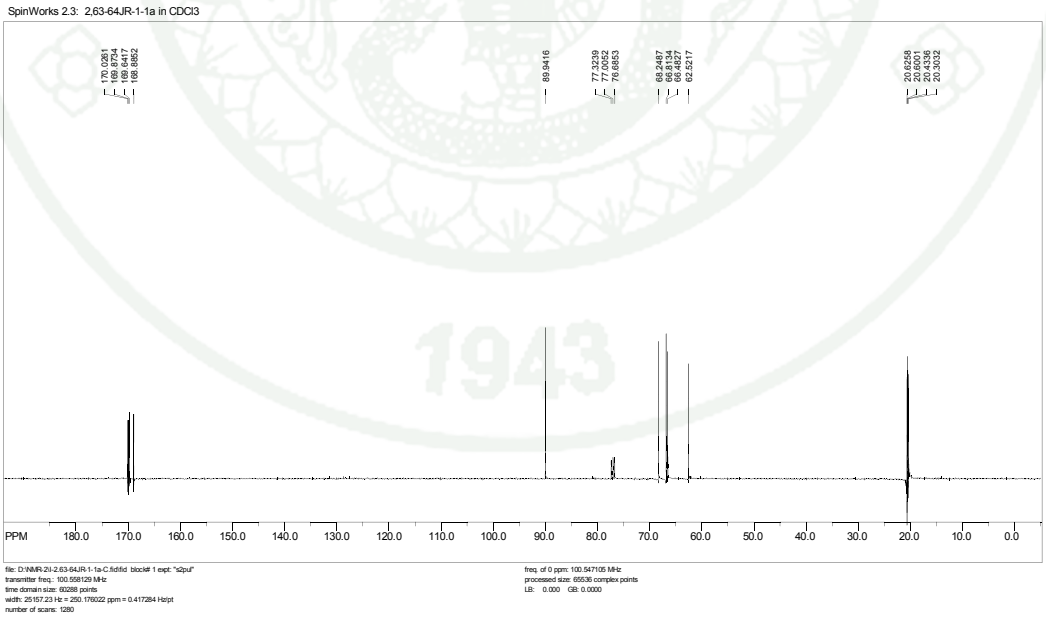


Appendix Figure 121 400 MHz ^{1}H NMR spectrum: 1,2,3,4-*O*-tetraacetyl-β-L-arabinopyranoside (519)



Appendix Figure 122 100 MHz ^{13}C NMR spectrum: 1,2,3,4-*O*-tetraacetyl-β-L-arabinopyranoside (519)

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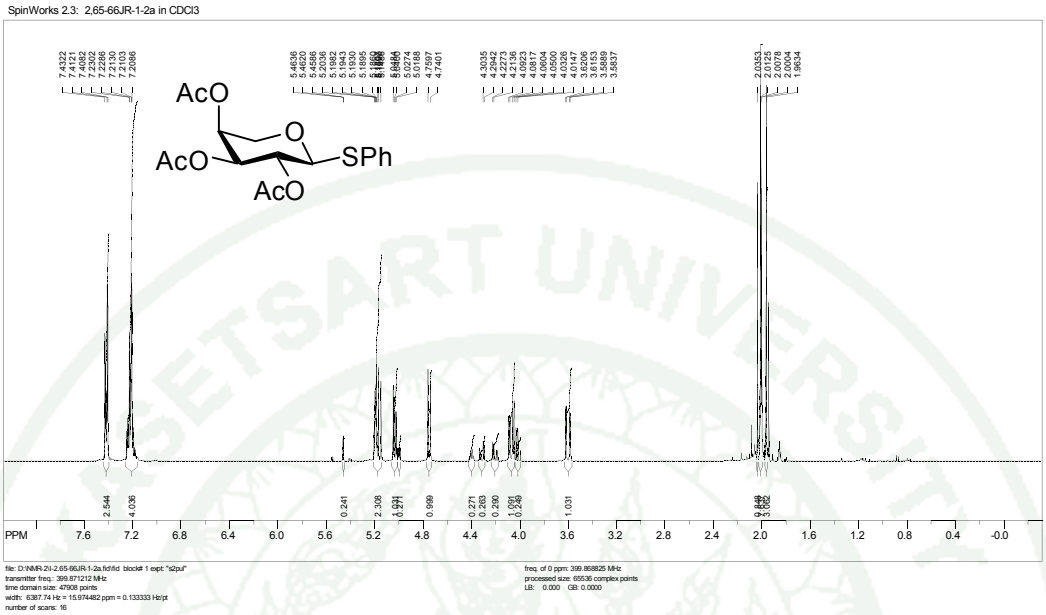
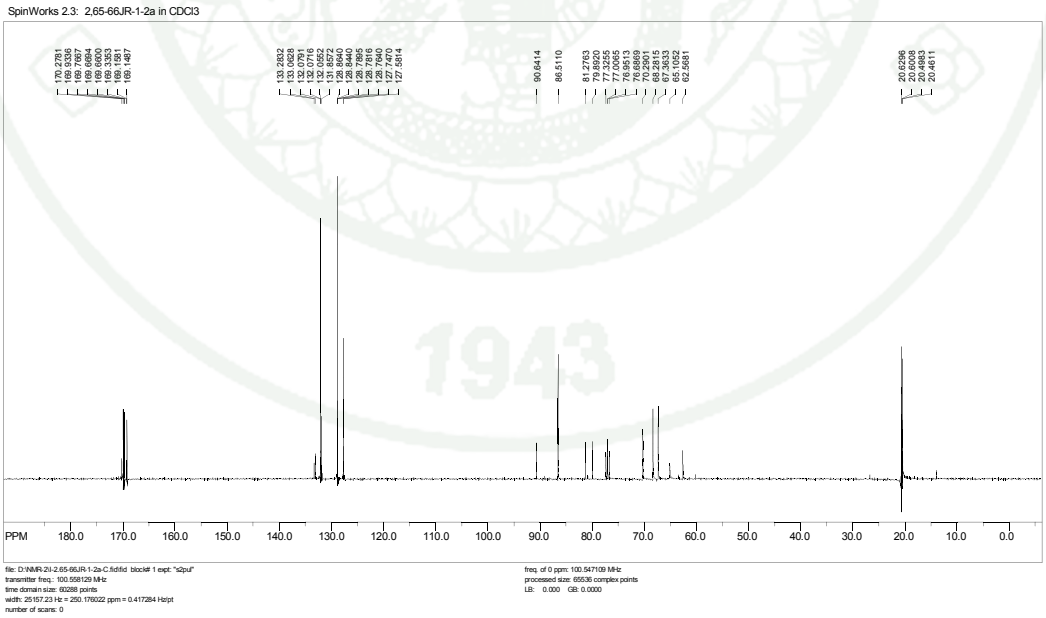


Appendix Figure 123 400 MHz ^{1}H NMR spectrum: 1-thiophenyl-2,3,4-*O*-triacetyl-α-L-arabinopyranoside (85)



Appendix Figure 124 100 MHz ^{13}C NMR spectrum: 1-thiophenyl-2,3,4-*O*-triacetyl-α-L-arabinopyranoside (85)

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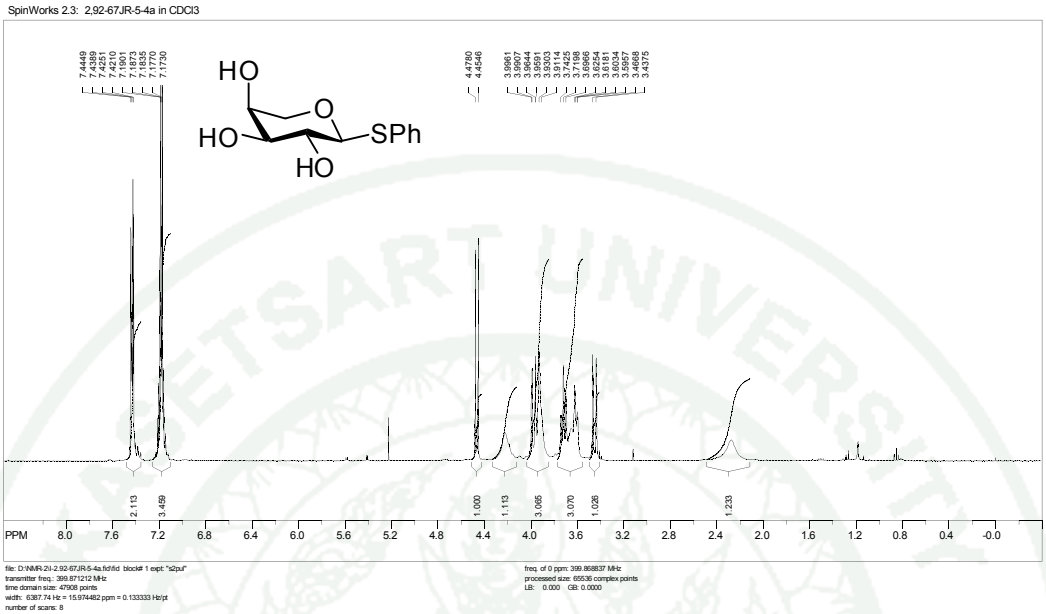
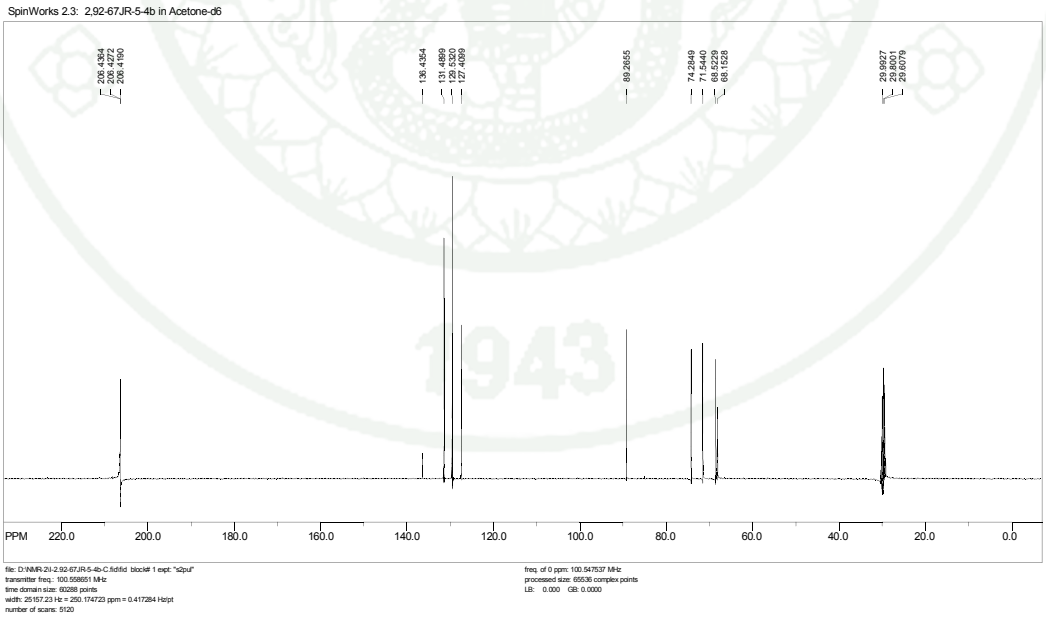


Appendix Figure 125 400 MHz ^{1}H NMR spectrum: 1-thiophenyl-α-L-arabino pyranoside (520)



Appendix Figure 126 100 MHz ^{13}C NMR spectrum: 1-thiophenyl-α-L-arabino pyranoside (520)

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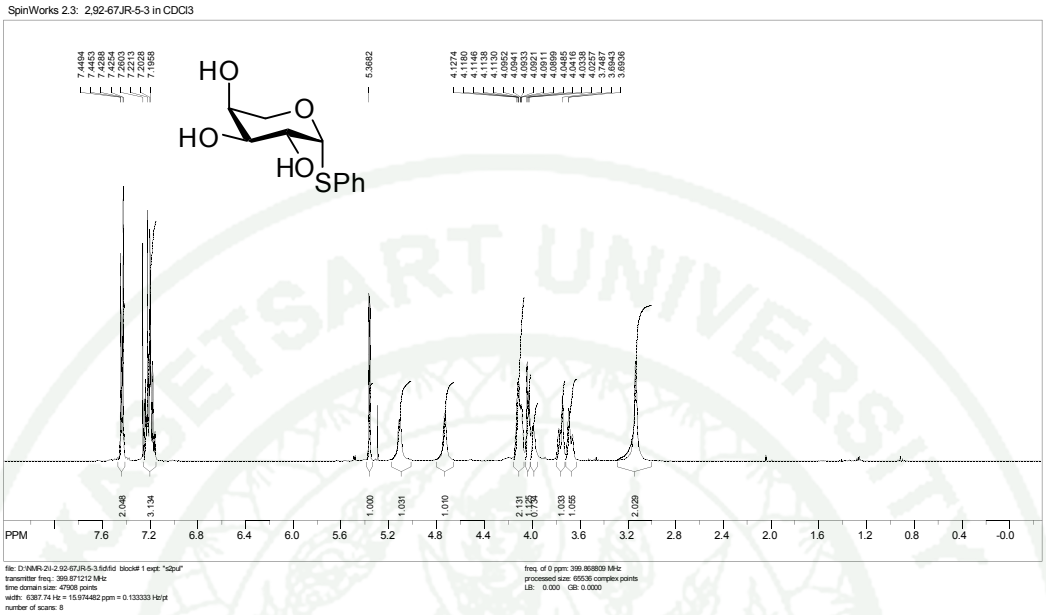
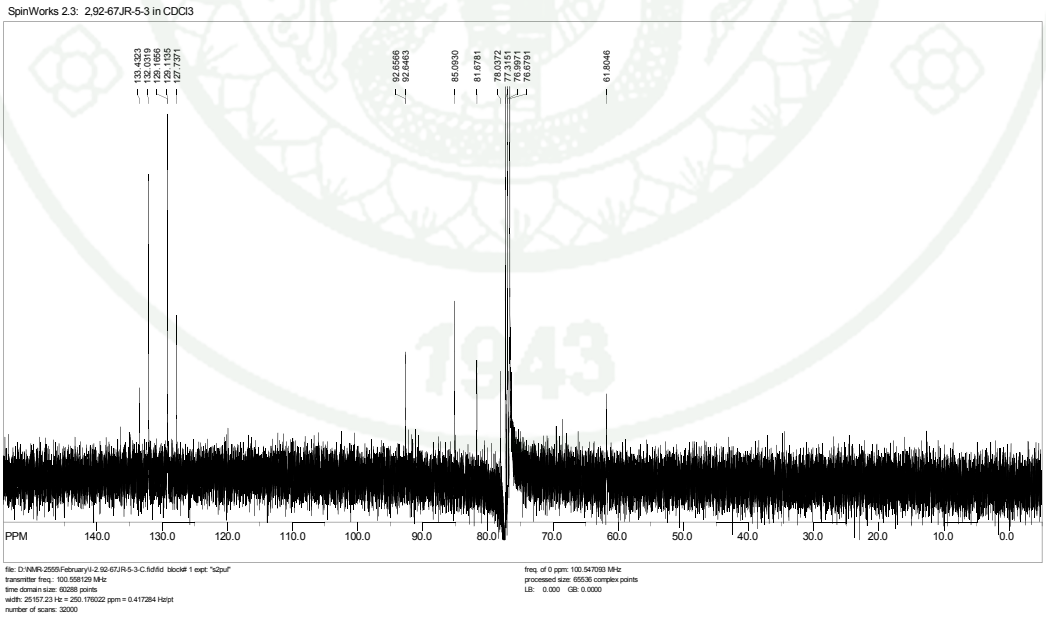


Appendix Figure 127 400 MHz ^{1}H NMR spectrum: 1-thiophenyl-β-L-arabino pyranoside (520)



Appendix Figure 128 100 MHz ^{13}C NMR spectrum: 1-thiophenyl-β-L-arabino pyranoside (520)

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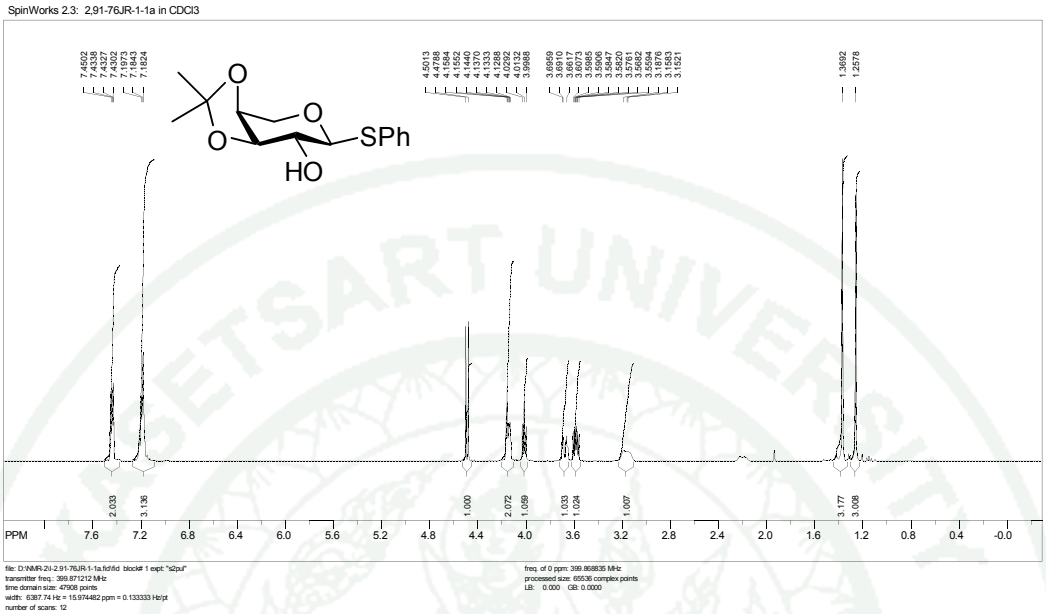
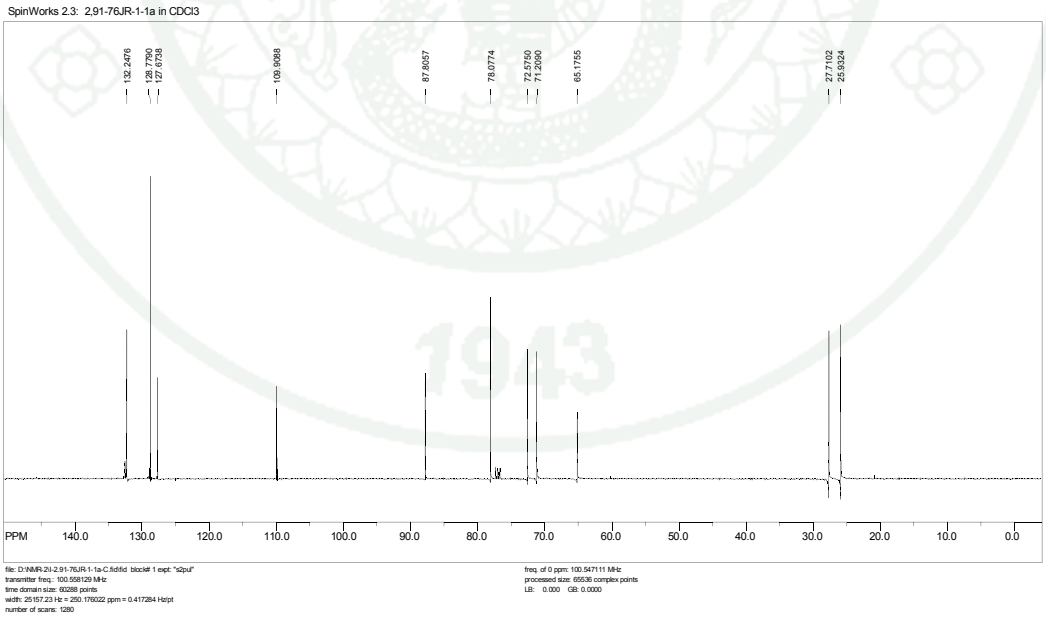


Appendix Figure 129 400 MHz ^{1}H NMR spectrum: 1-thiophenyl-3,4-acetonide-α-L-arabinopyranoside (521)



Appendix Figure 130 100 MHz ^{13}C NMR spectrum: 1-thiophenyl-3,4-acetonide-α-L-arabinopyranoside (521)

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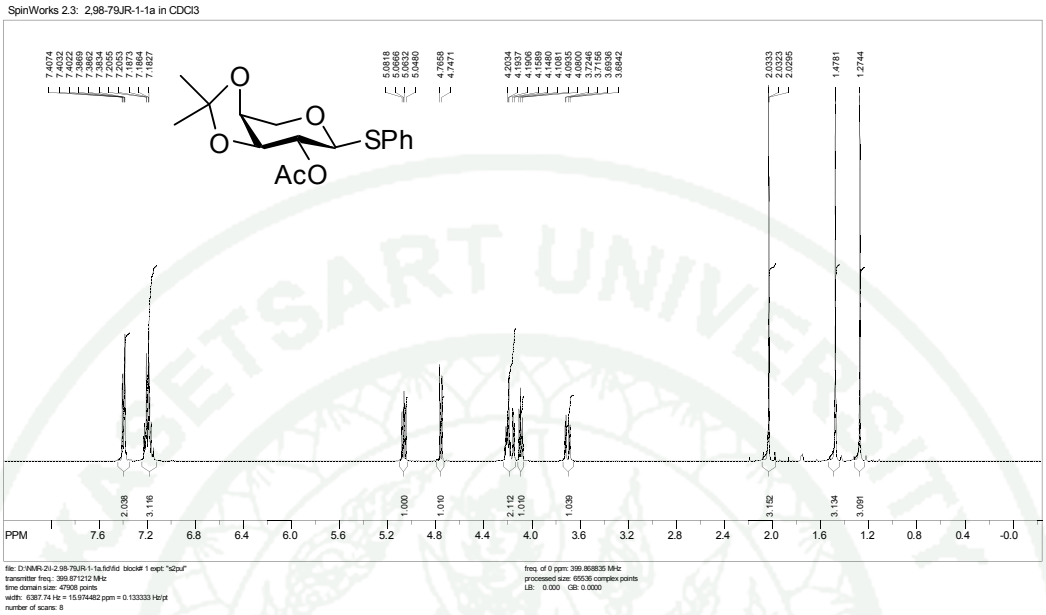
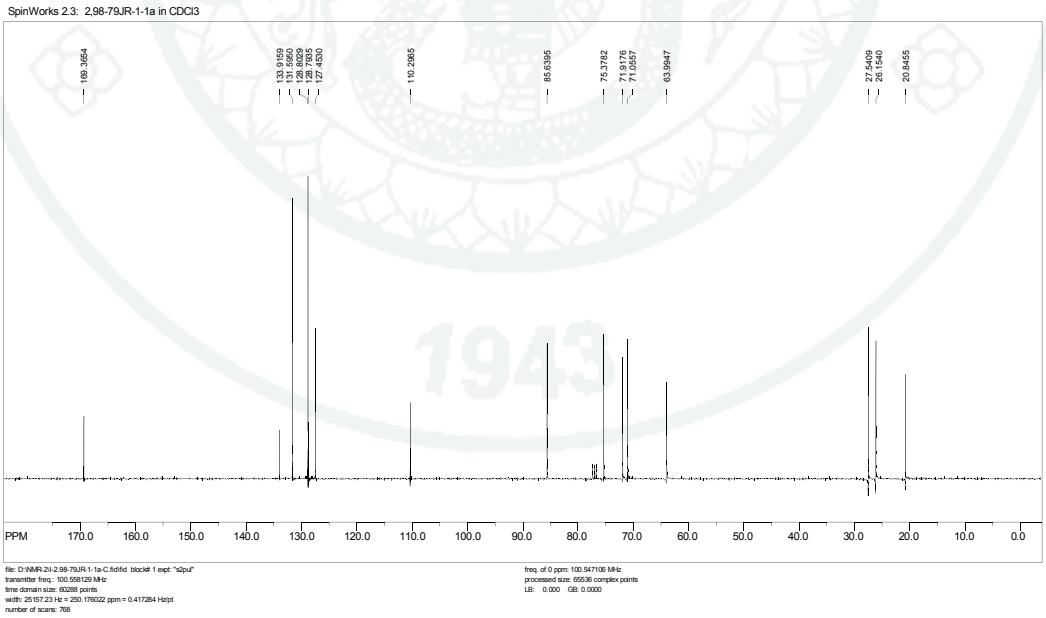


Appendix Figure 131 400 MHz ^{1}H NMR spectrum: 1-thiophenyl-2-*O*-acetyl-3,4-acetonide-α-L-arabinopyranoside (86)



Appendix Figure 132 100 MHz ^{13}C NMR spectrum: 1-thiophenyl-2-*O*-acetyl-3,4-acetonide-α-L-arabinopyranoside (86)

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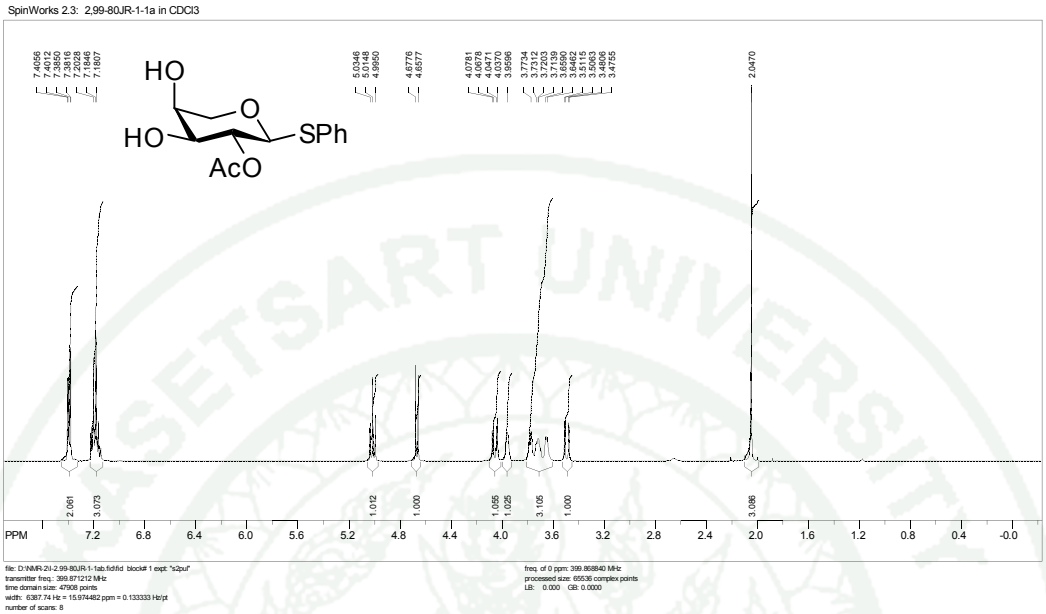
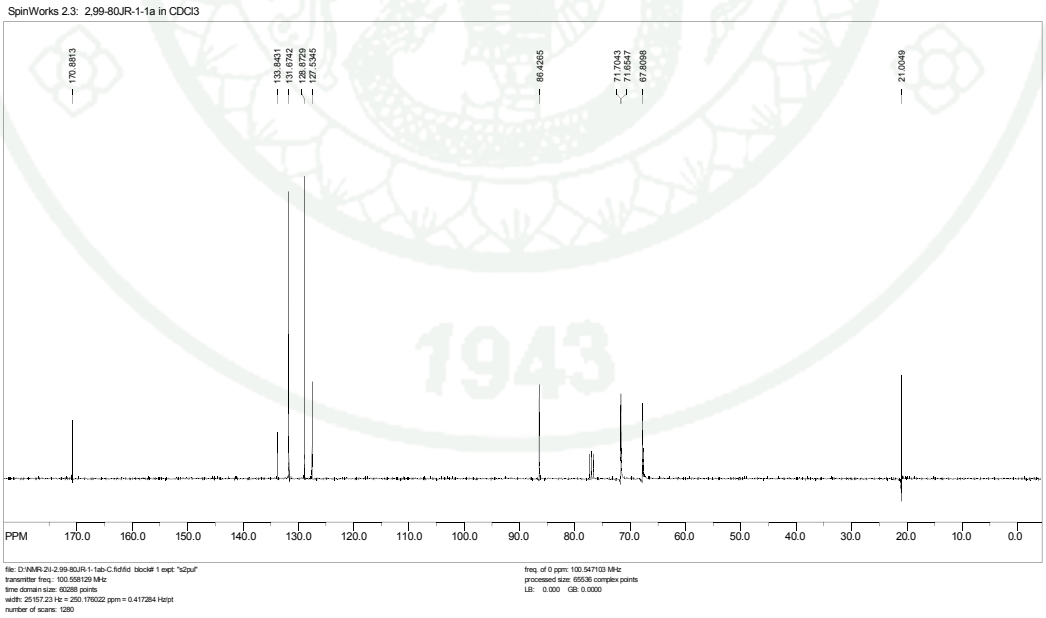


Appendix Figure 133 400 MHz ^{1}H NMR spectrum: 1-thiophenyl-2-*O*-acetyl-α-L-arabinopyranoside (279)



Appendix Figure 134 100 MHz ^{13}C NMR spectrum: 1-thiophenyl-2-*O*-acetyl-α-L-arabinopyranoside (279)

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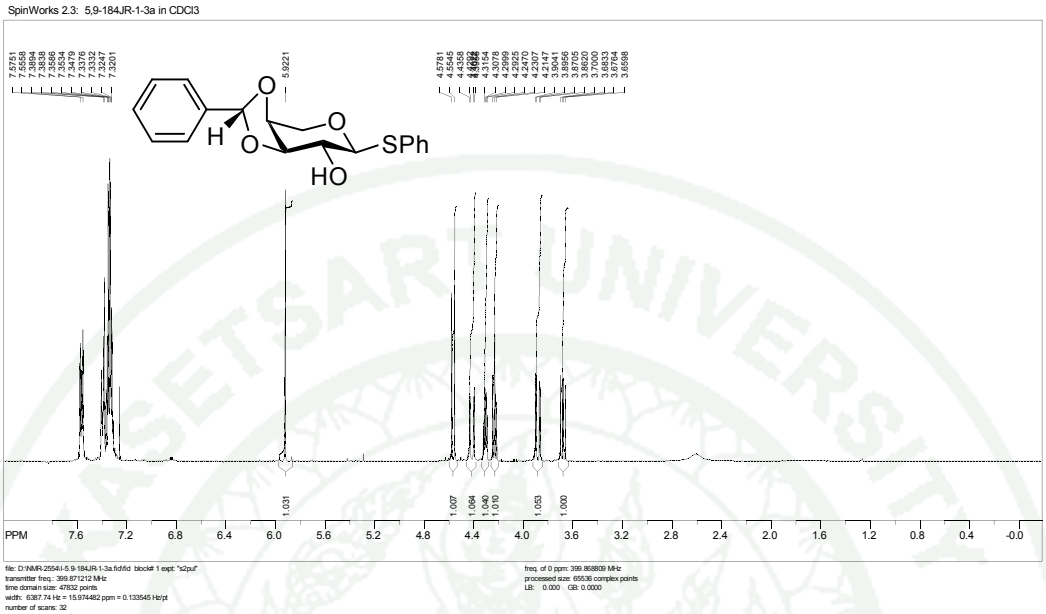
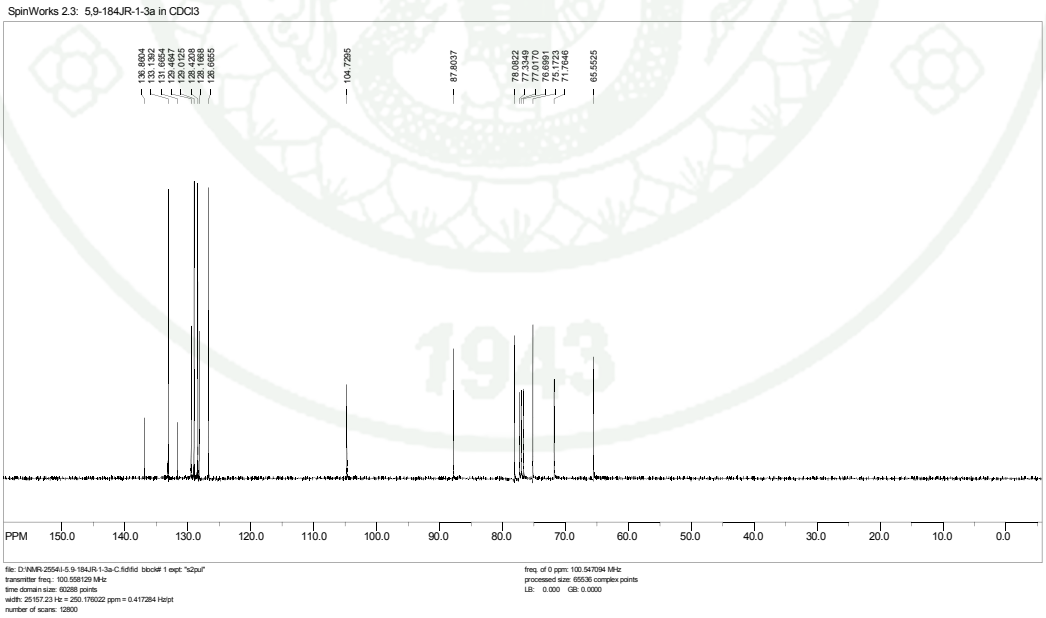


Appendix Figure 135 400 MHz ^{1}H NMR spectrum: thiophenyl-endo-3,4-*O*-benzylidene-α-L-arabinopyranoside (*endo*-522)



Appendix Figure 136 100 MHz ^{13}C NMR spectrum: thiophenyl-endo-3,4-*O*-benzylidene-α-L-arabinopyranoside (*endo*-522)

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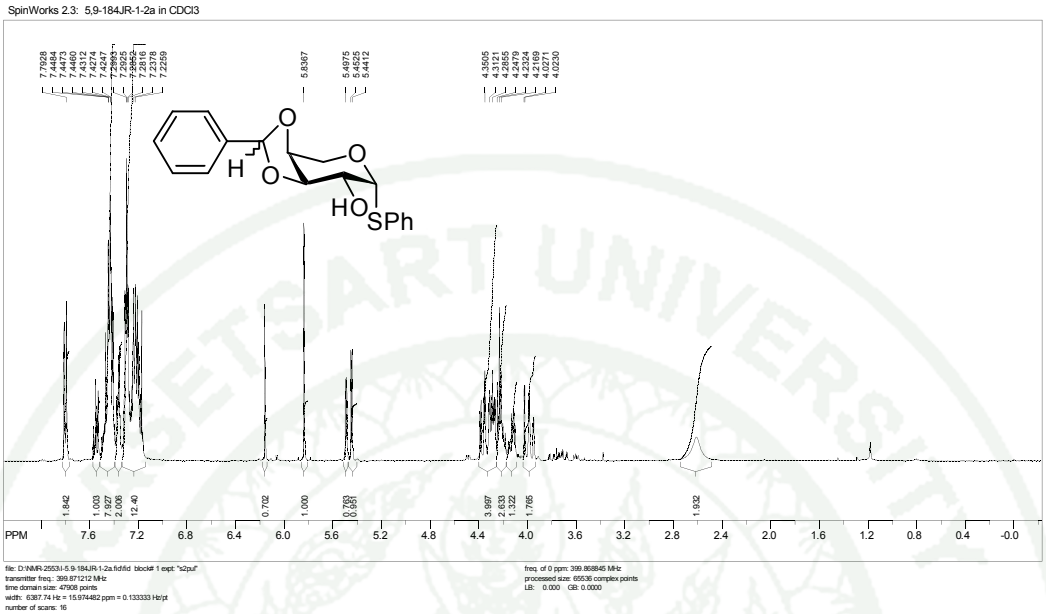
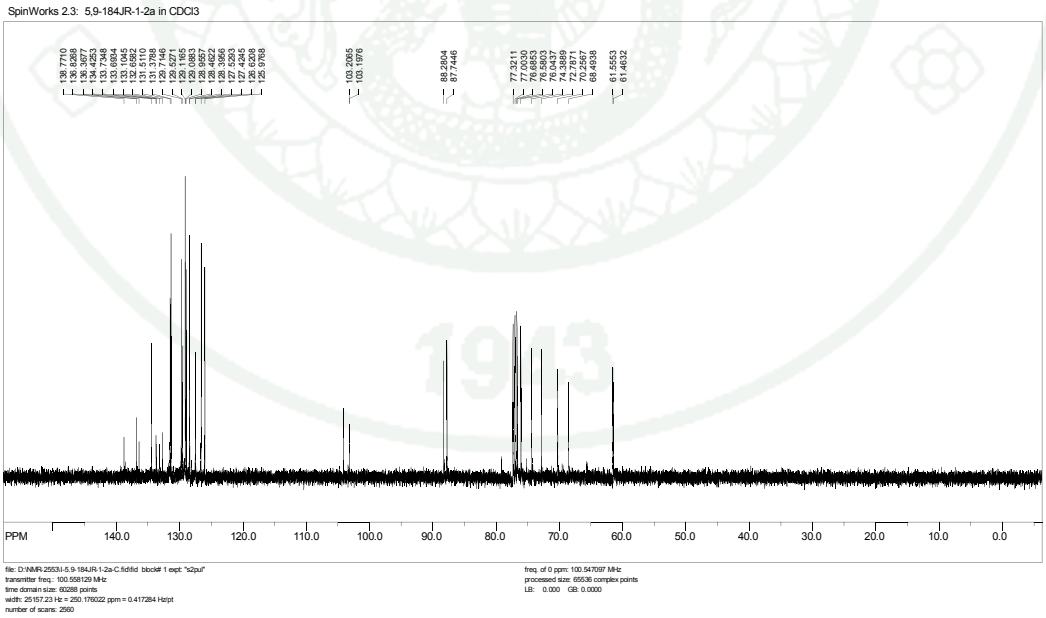


Appendix Figure 137 400 MHz ^{1}H NMR spectrum: thiophenyl-exo/endo-3,4-*O*-benzylidene-*β*-L-arabinopyranosides (523)



Appendix Figure 138 100 MHz ^{13}C NMR spectrum: thiophenyl-exo/endo-3,4-*O*-benzylidene-*β*-L-arabinopyranosides (523)

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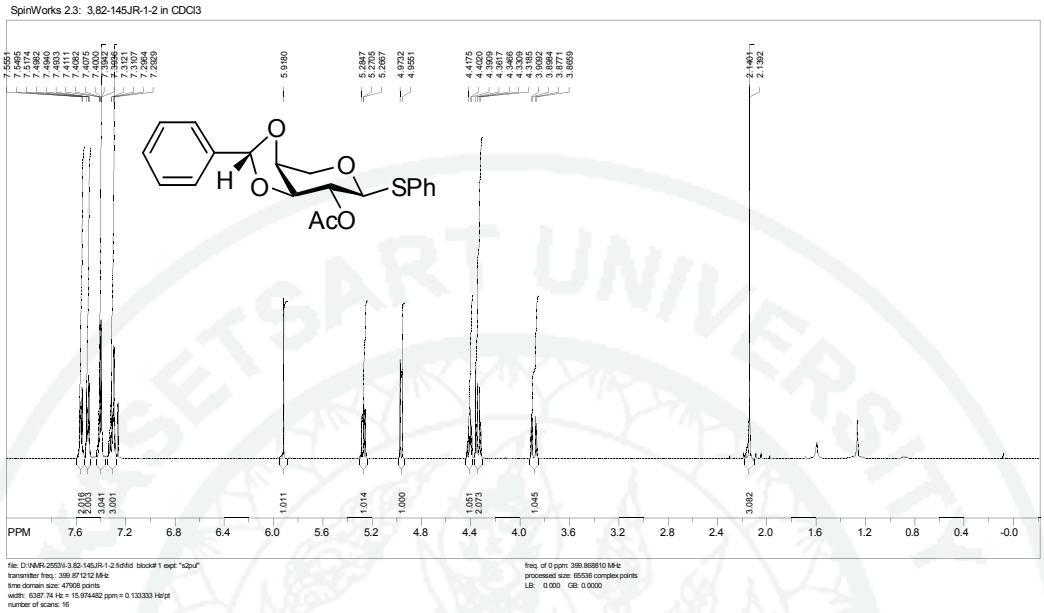
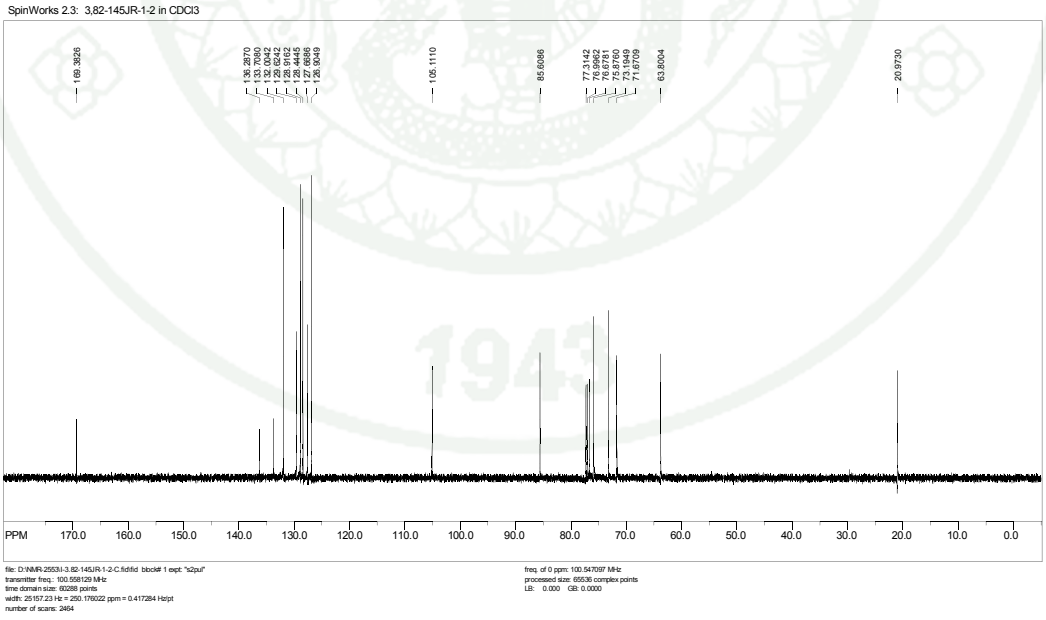


Appendix Figure 139 400 MHz ^{1}H NMR spectrum: thiophenyl 2-*O*-acetyl-endo-3,4-*O*-benzylidene-α-L-arabinopyranoside (524)



Appendix Figure 140 100 MHz ^{13}C NMR spectrum: thiophenyl 2-*O*-acetyl-endo-3,4-*O*-benzylidene-α-L-arabinopyranoside (524)

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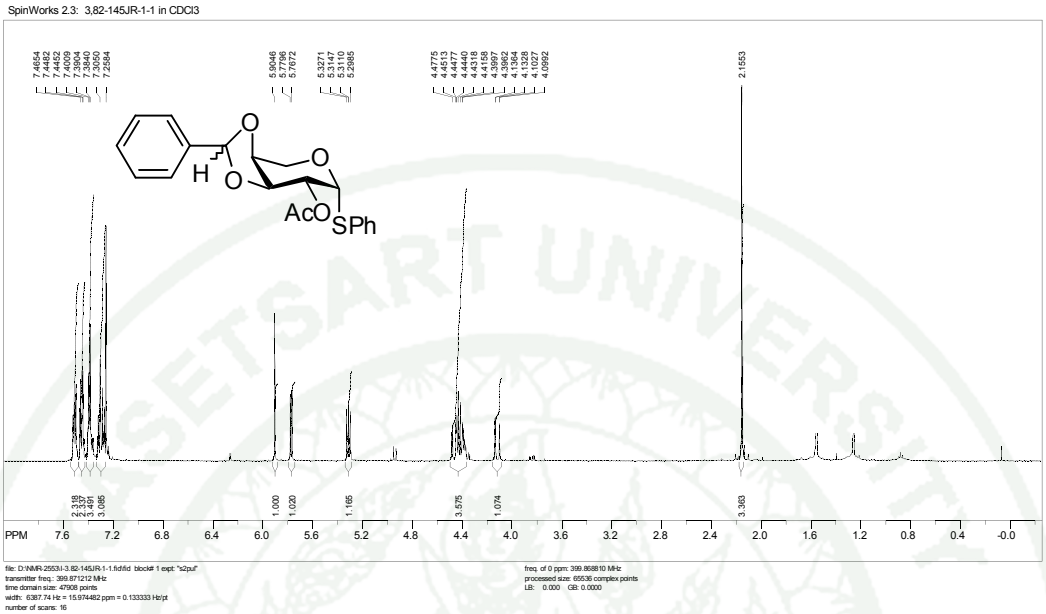
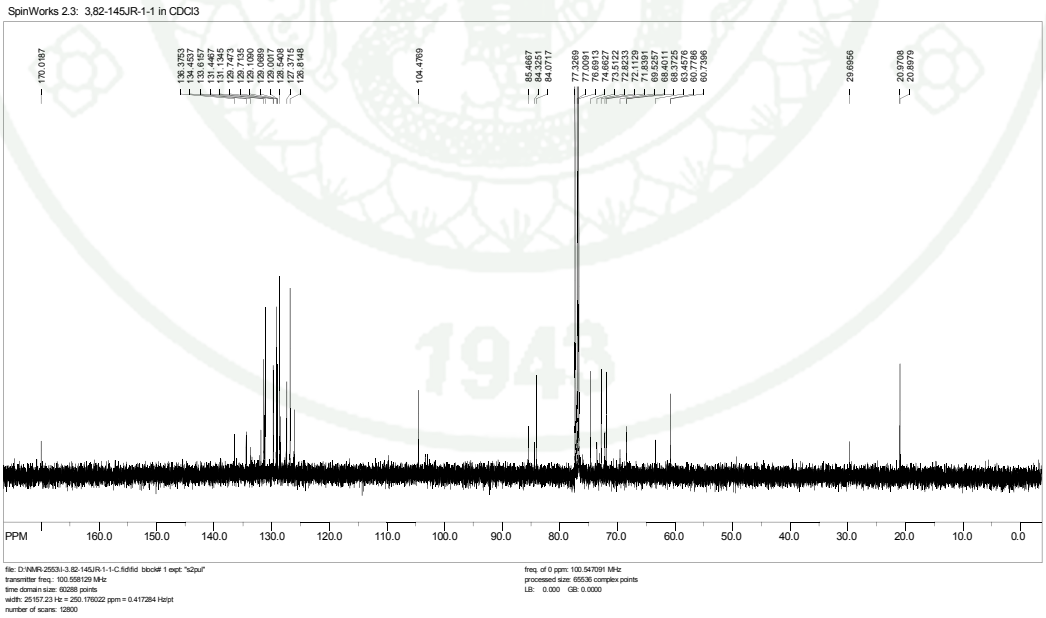


Appendix Figure 141 400 MHz ^{1}H NMR spectrum: thiophenyl 2-*O*-acetyl-exo/endo-3,4-*O*-benzylidene-*β*-L-arabinopyranosides (525)



Appendix Figure 142 100 MHz ^{13}C NMR spectrum: thiophenyl 2-*O*-acetyl-exo/endo-3,4-*O*-benzylidene-*β*-L-arabinopyranosides (525)

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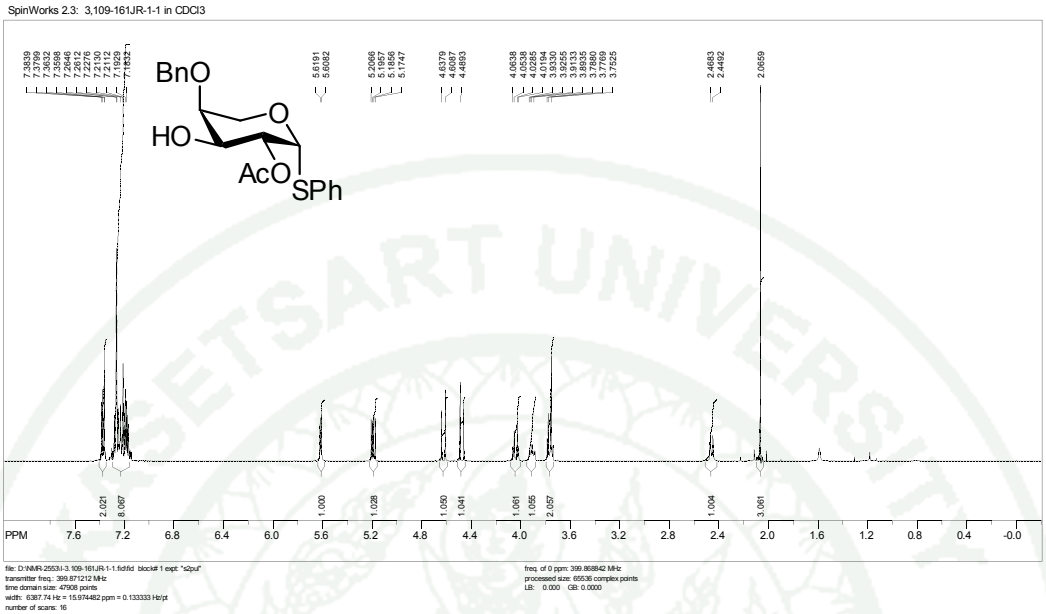
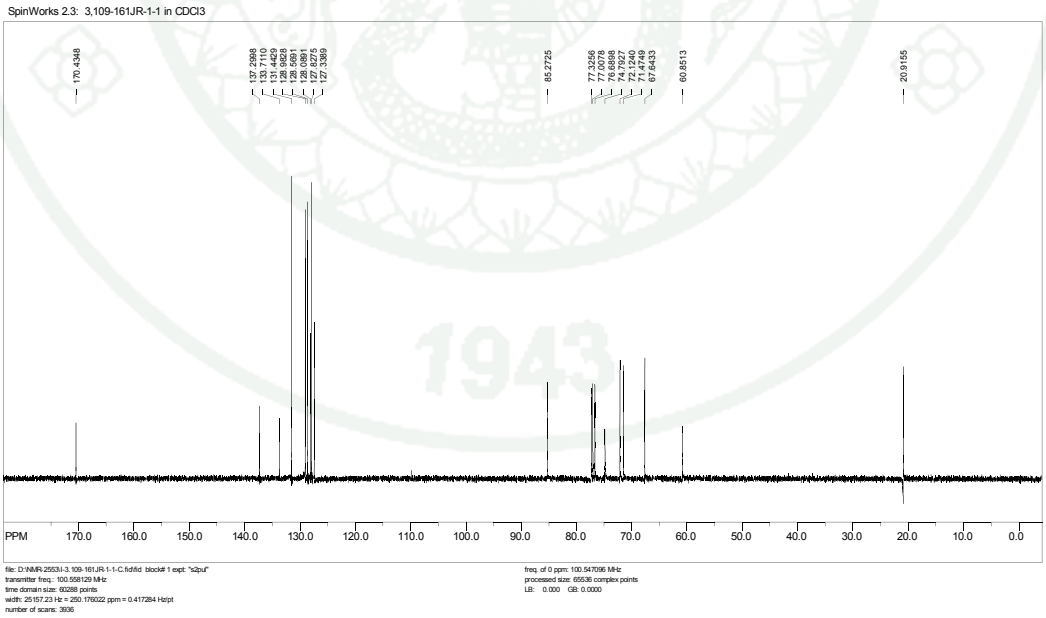


Appendix Figure 143 400 MHz ^{1}H NMR spectrum: thiophenyl 2-*O*-acetyl-4-*O*-benzyl-*β*-L-arabinopyranoside (526)



Appendix Figure 144 100 MHz ^{13}C NMR spectrum: thiophenyl 2-*O*-acetyl-4-*O*-benzyl-*β*-L-arabinopyranoside (526)

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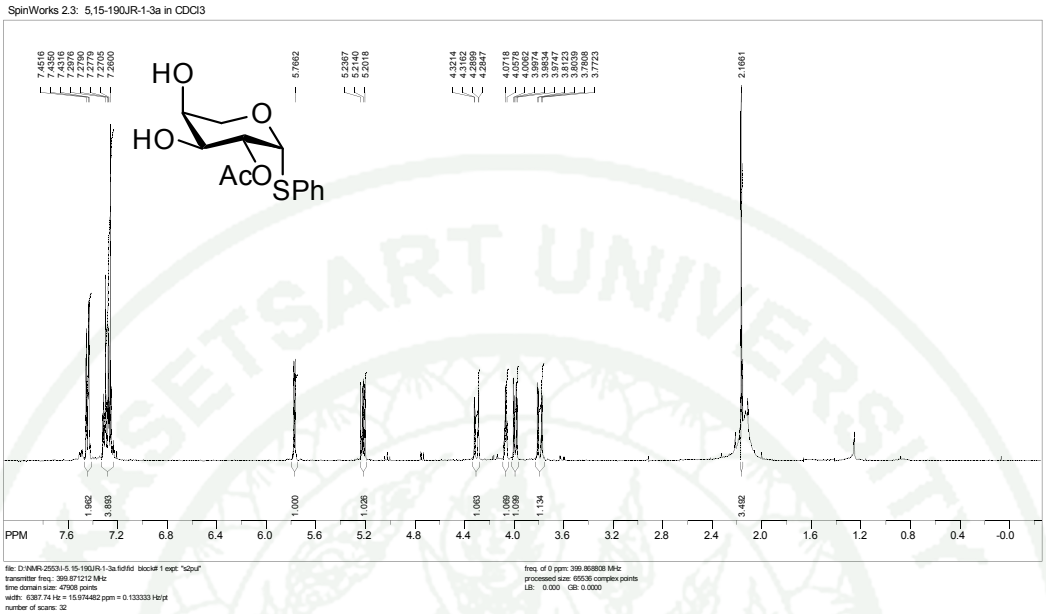
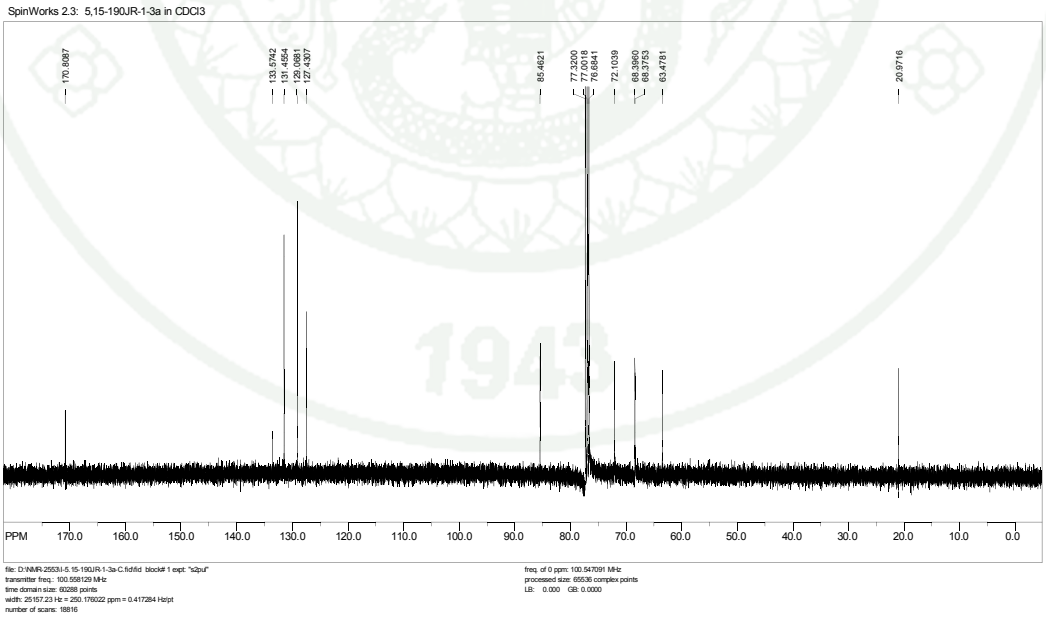


Appendix Figure 145 400 MHz ^{1}H NMR spectrum: thiophenyl 2-*O*-acetyl-*β*-L-arabinopyranoside (527)



Appendix Figure 146 100 MHz ^{13}C NMR spectrum: thiophenyl 2-*O*-acetyl-*β*-L-arabinopyranoside (527)

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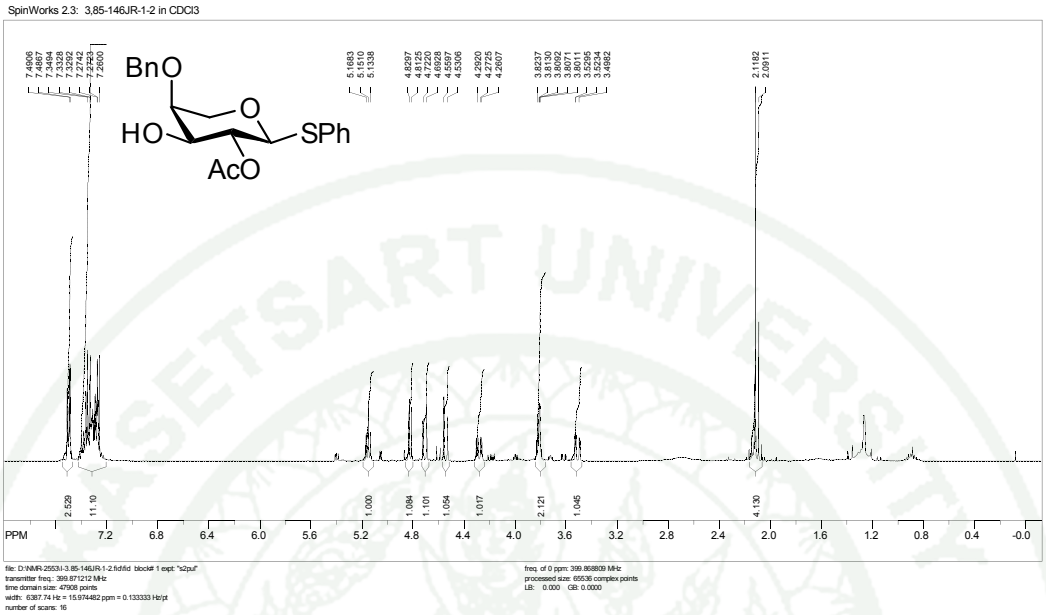
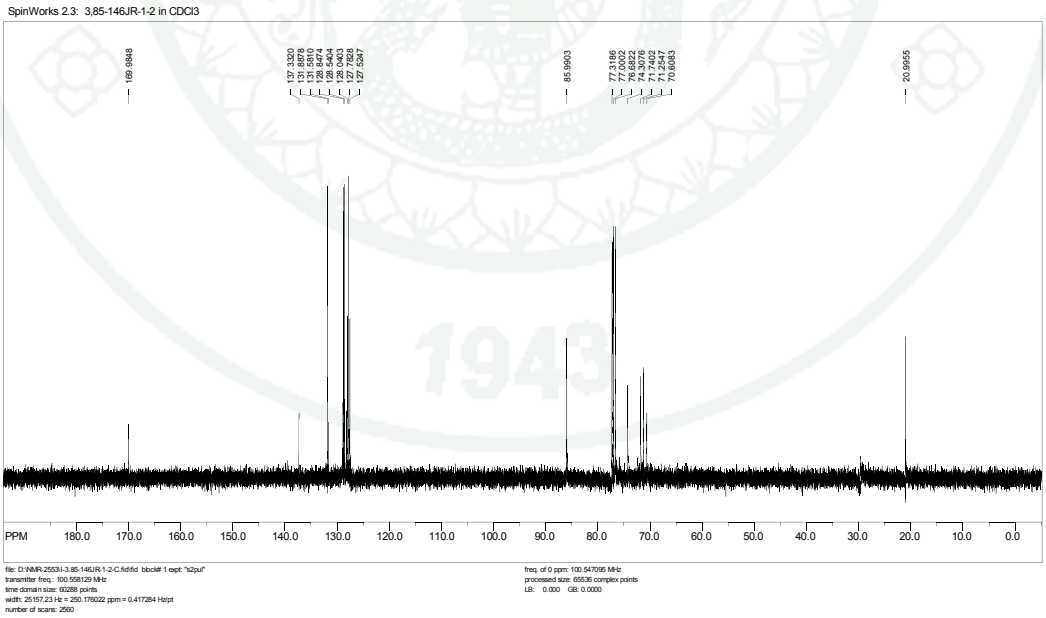


Appendix Figure 147 400 MHz ^{1}H NMR spectrum: thiophenyl 2-*O*-acetyl-4-*O*-benzyl-α-L-arabinopyranoside (528)



Appendix Figure 148 100 MHz ^{13}C NMR spectrum: thiophenyl 2-*O*-acetyl-4-*O*-benzyl-α-L-arabinopyranoside (528)

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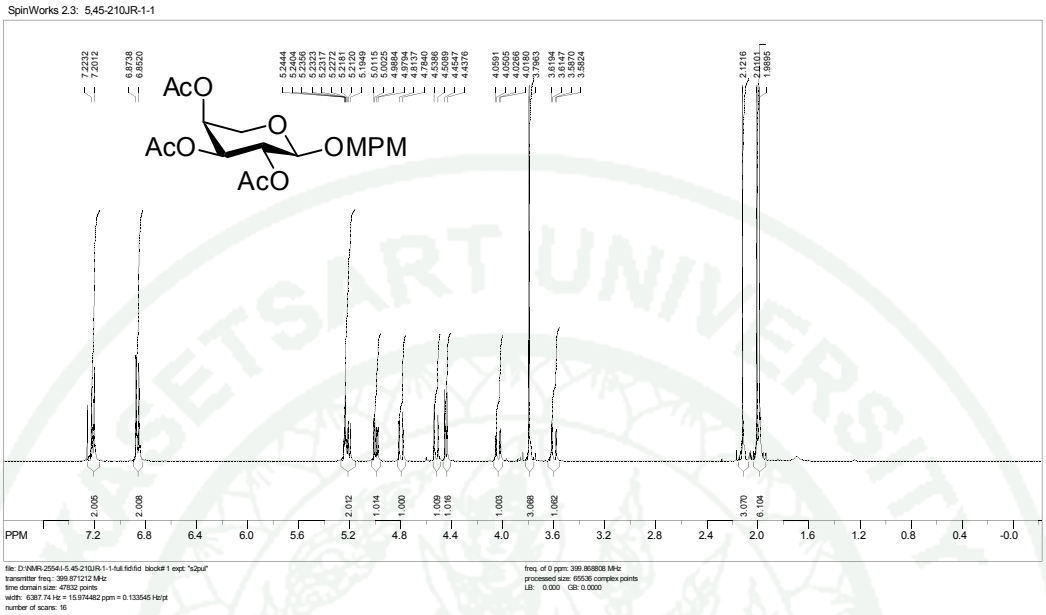
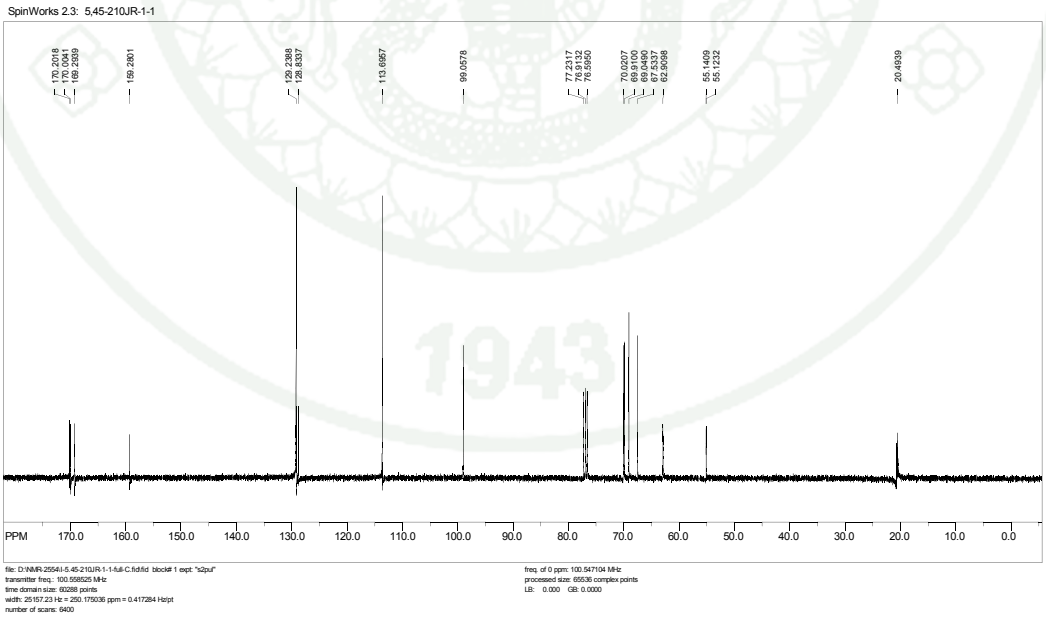


Appendix Figure 149 400 MHz ^{1}H NMR spectrum: 4-methoxybenzyl 2,3,4-*O*-triacetyl-α-L-arabinopyranoside (530)



Appendix Figure 150 100 MHz ^{13}C NMR spectrum: 4-methoxybenzyl 2,3,4-*O*-triacetyl-α-L-arabinopyranoside (530)

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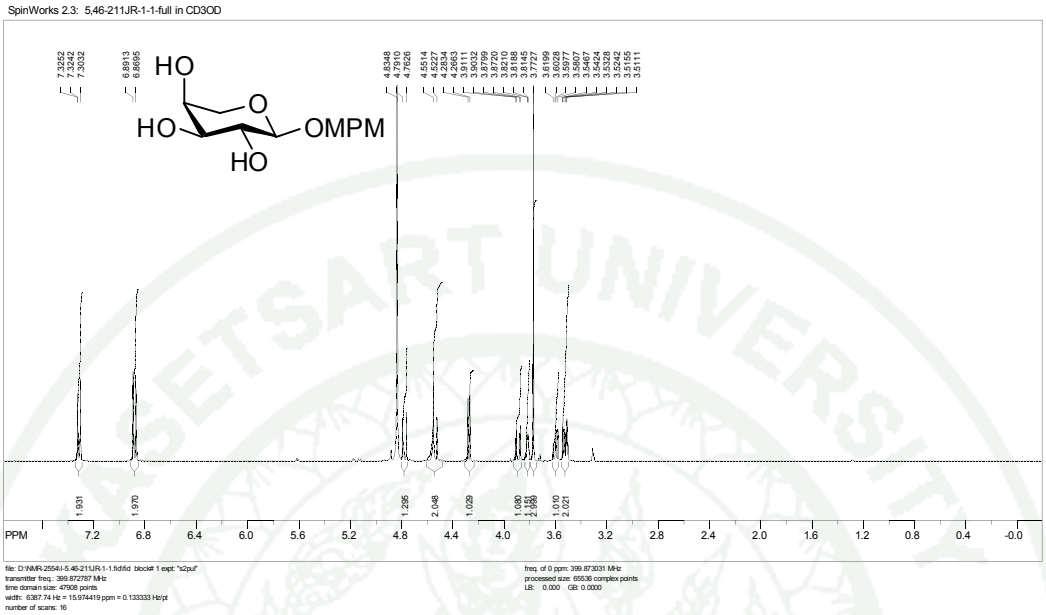
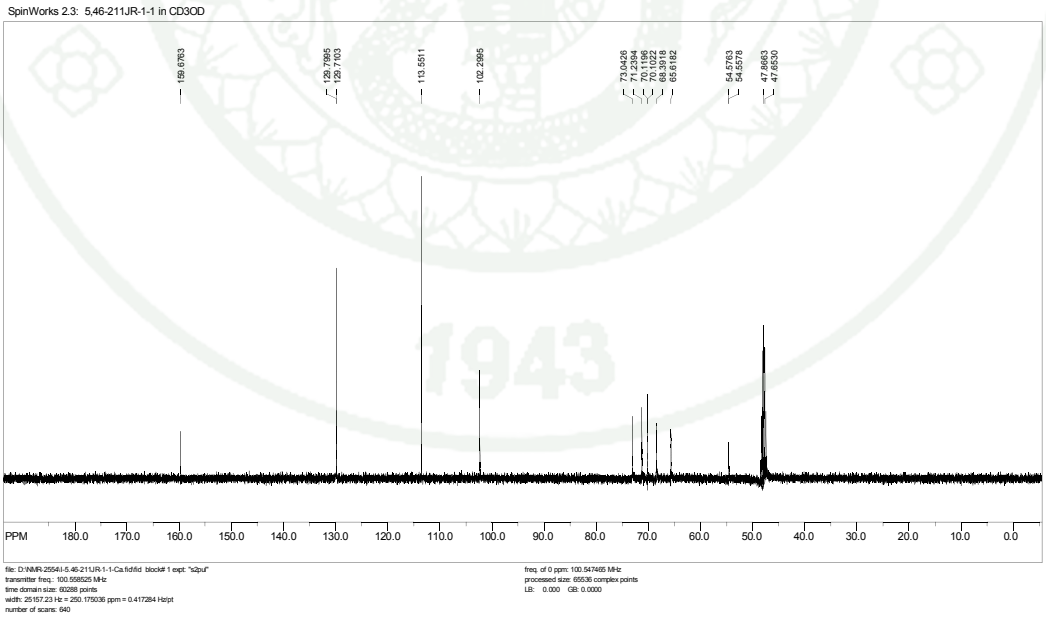


Appendix Figure 151 400 MHz ^{1}H NMR spectrum: 4-methoxybenzyl α-L-arabinopyranoside (531)



Appendix Figure 152 100 MHz ^{13}C NMR spectrum: 4-methoxybenzyl α-L-arabinopyranoside (531)

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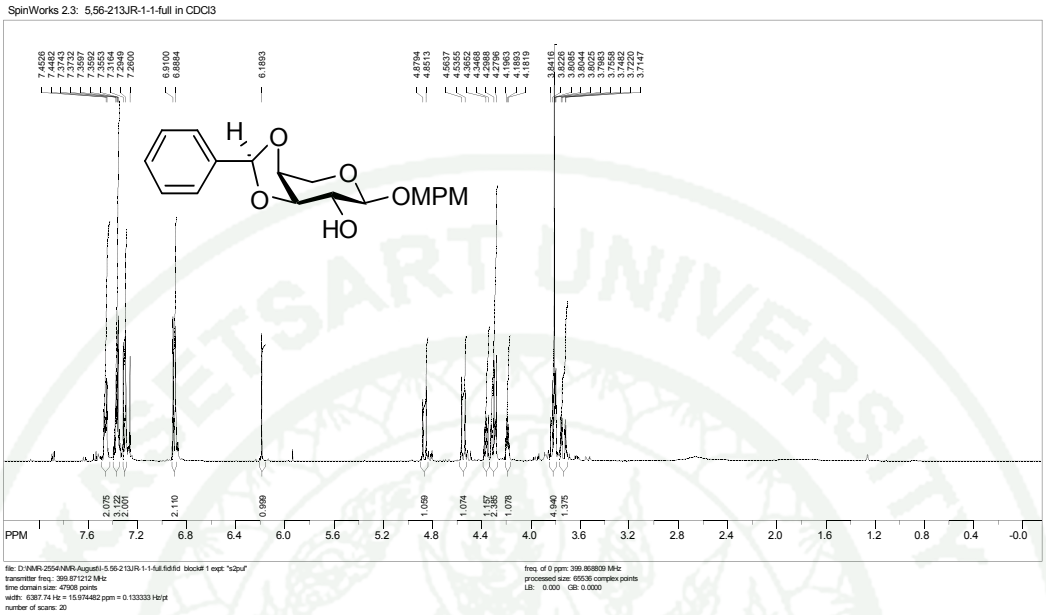
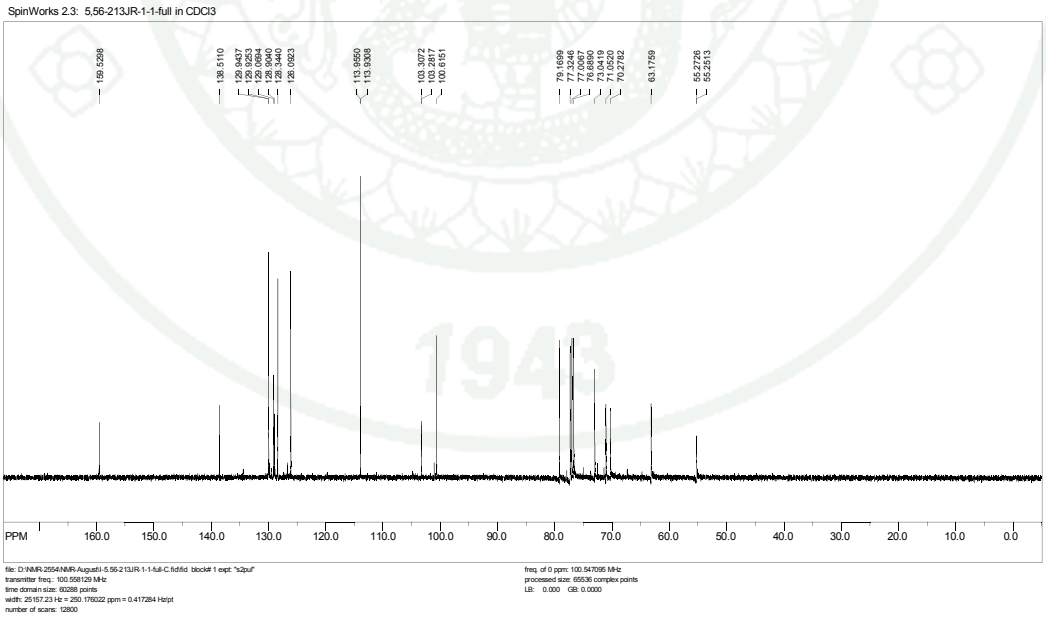


Appendix Figure 153 400 MHz ^{1}H NMR spectrum: 4-methoxybenzyl exo-3,4-*O*-benzylidene-α-L-arabinopyranoside (*exo*-532)



Appendix Figure 154 100 MHz ^{13}C NMR spectrum: 4-methoxybenzyl exo-3,4-*O*-benzylidene-α-L-arabinopyranoside (*exo*-532)

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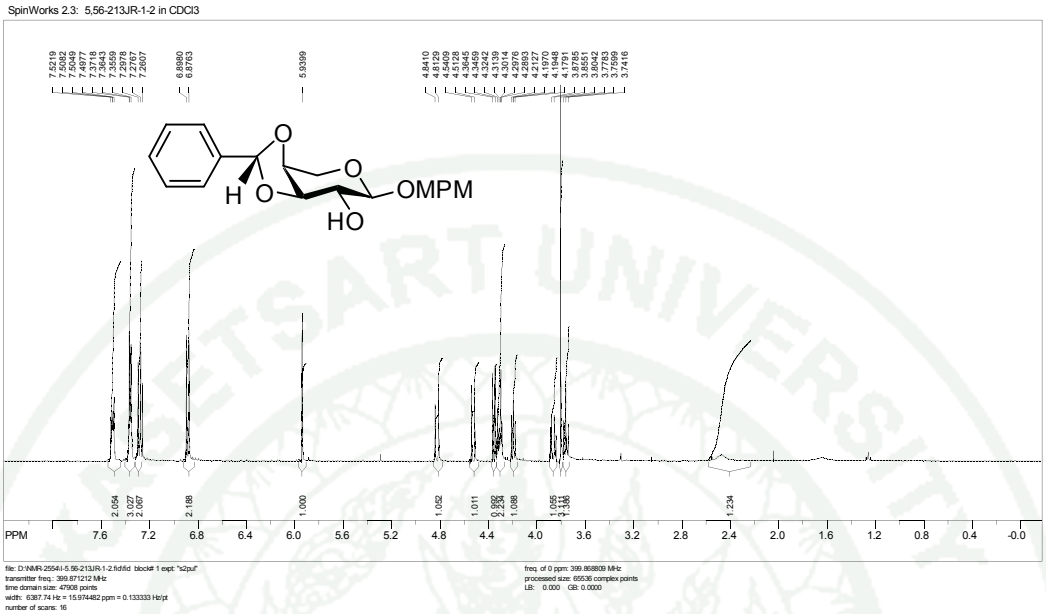
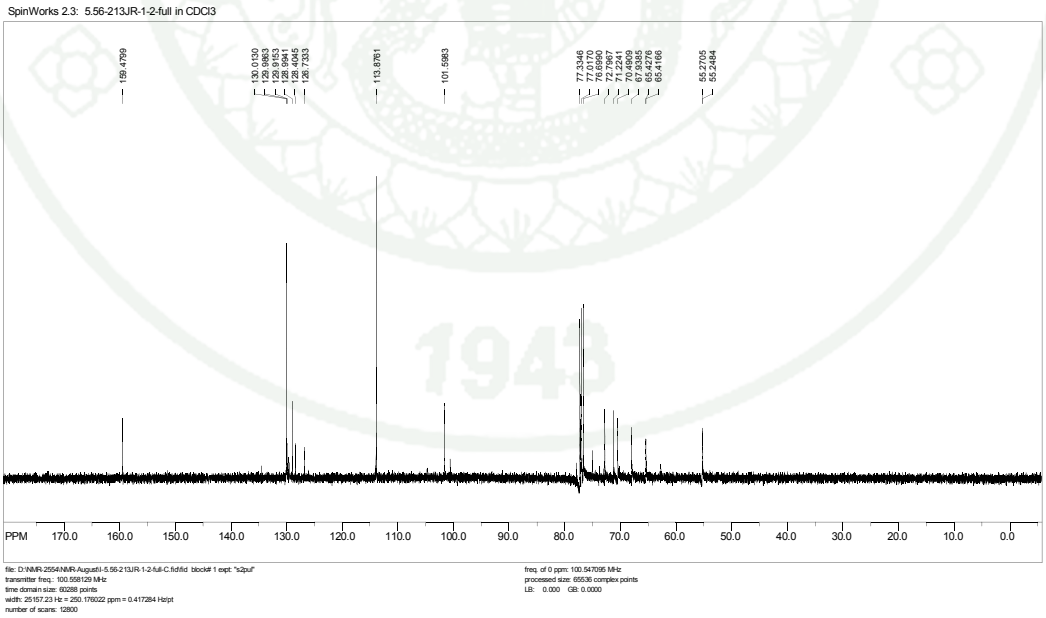


Appendix Figure 155 400 MHz ^{1}H NMR spectrum: 4-methoxybenzyl endo-3,4-*O*-benzylidene-α-L-arabinopyranoside (*endo*-532)



Appendix Figure 156 100 MHz ^{13}C NMR spectrum: 4-methoxybenzyl endo-3,4-*O*-benzylidene-α-L-arabinopyranoside (*endo*-532)

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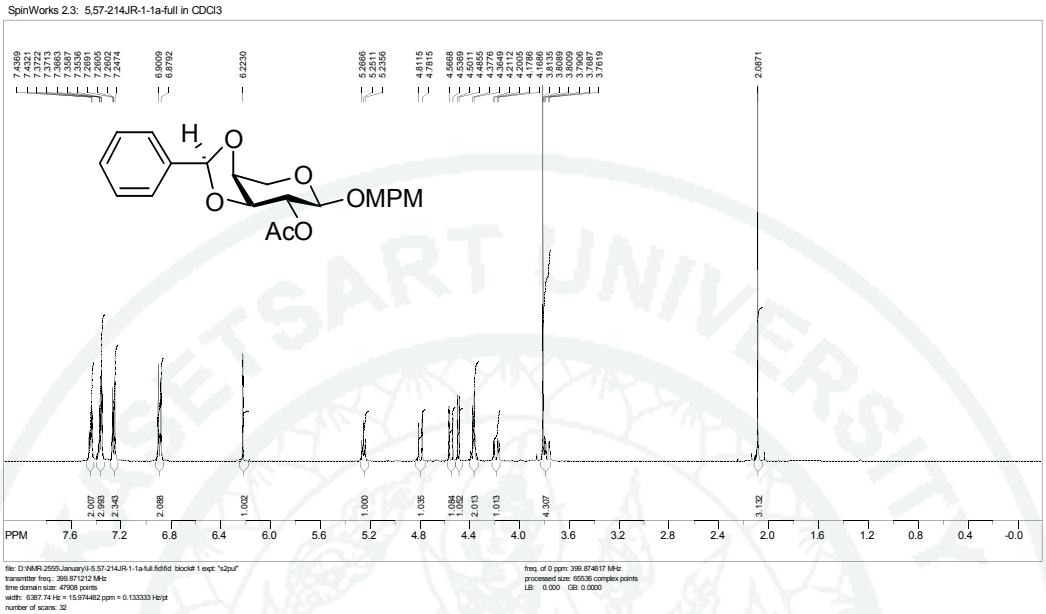
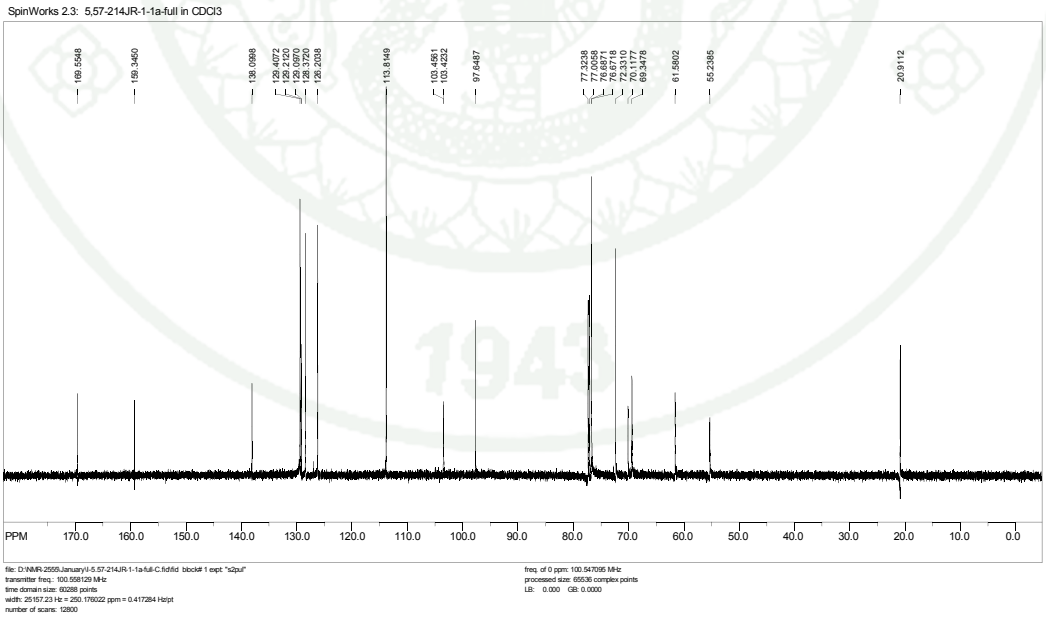


Appendix Figure 157 400 MHz ^{1}H NMR spectrum: 4-methoxybenzyl 2-*O*-acetyl-exo-3,4-*O*-benzylidene-α-L-arabinopyranoside (*exo*-533)



Appendix Figure 158 100 MHz ^{13}C NMR spectrum: 4-methoxybenzyl 2-*O*-acetyl-exo-3,4-*O*-benzylidene-α-L-arabinopyranoside (*exo*-533)

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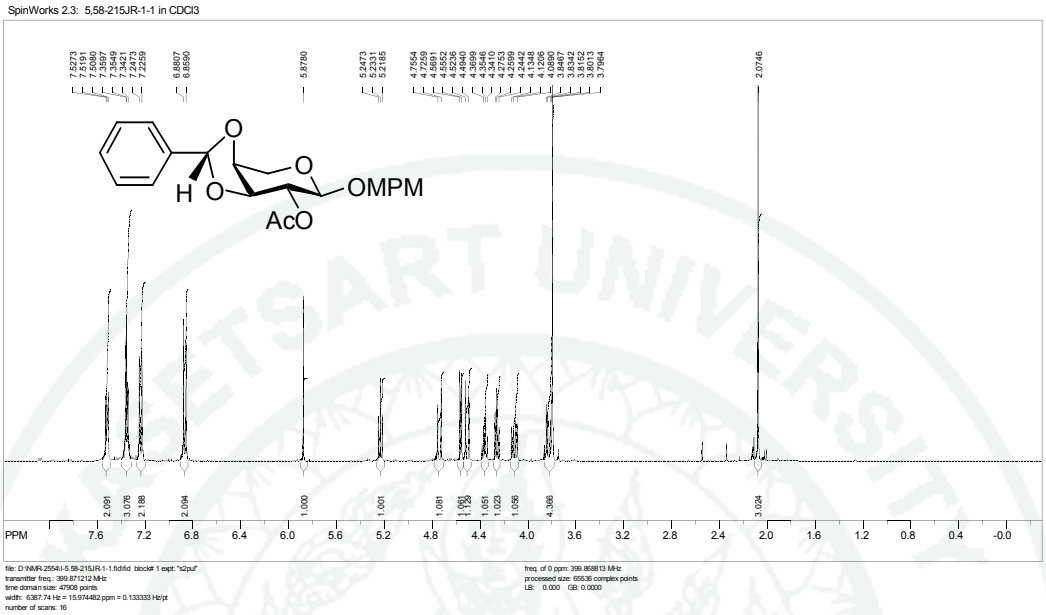
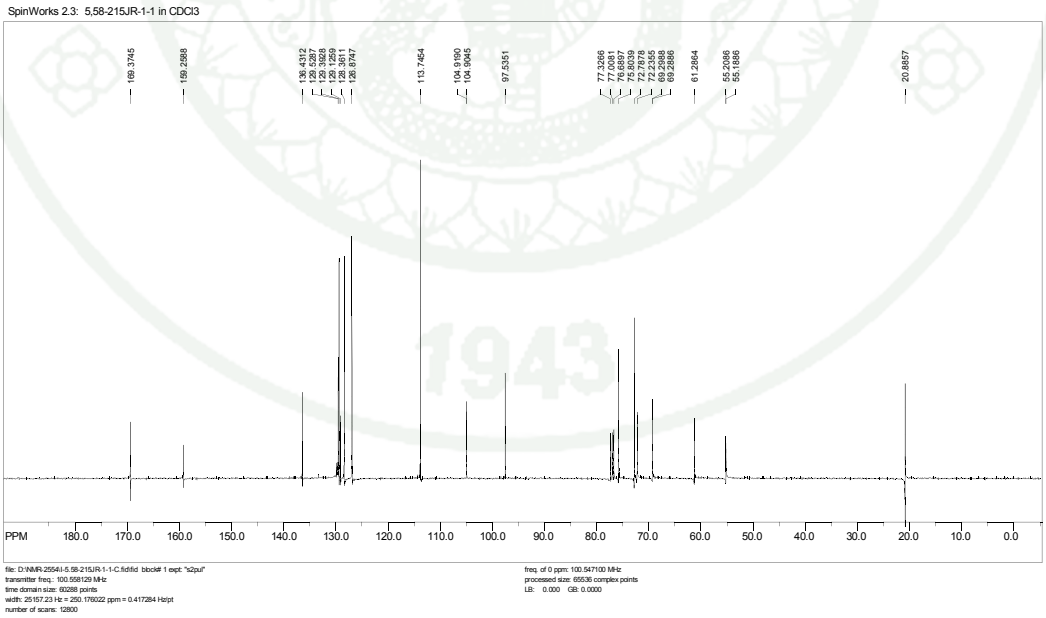


Appendix Figure 159 400 MHz ^{1}H NMR spectrum: 4-methoxybenzyl 2-*O*-acetyl-endo-3,4-*O*-benzylidene-α-L-arabinopyranoside (*endo*-533)



Appendix Figure 160 100 MHz ^{13}C NMR spectrum: 4-methoxybenzyl 2-*O*-acetyl-endo-3,4-*O*-benzylidene-α-L-arabinopyranoside (*endo*-533)

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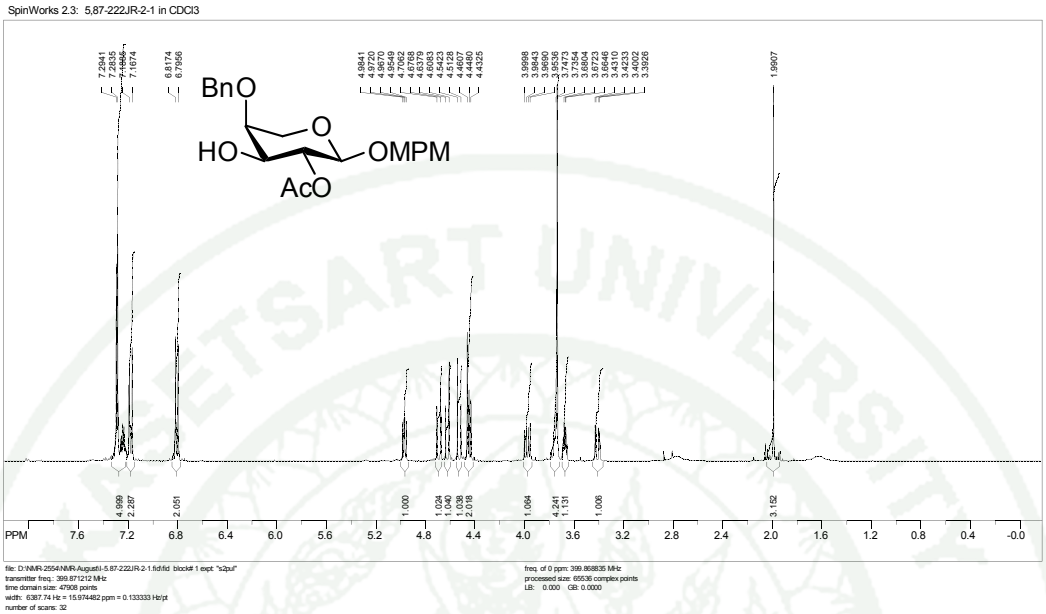
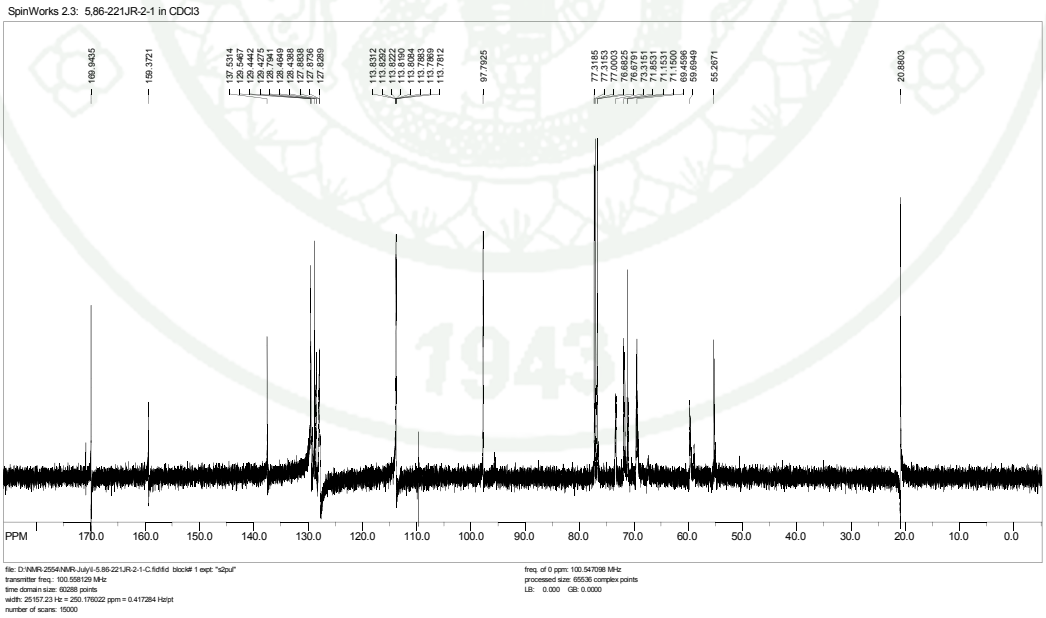


Appendix Figure 161 400 MHz ^{1}H NMR spectrum: 4-methoxybenzyl 2-*O*-acetyl-4-*O*-benzyl-α-L-arabinopyranoside (534)



Appendix Figure 162 100 MHz ^{13}C NMR spectrum: 4-methoxybenzyl 2-*O*-acetyl-4-*O*-benzyl-α-L-arabinopyranoside (534)

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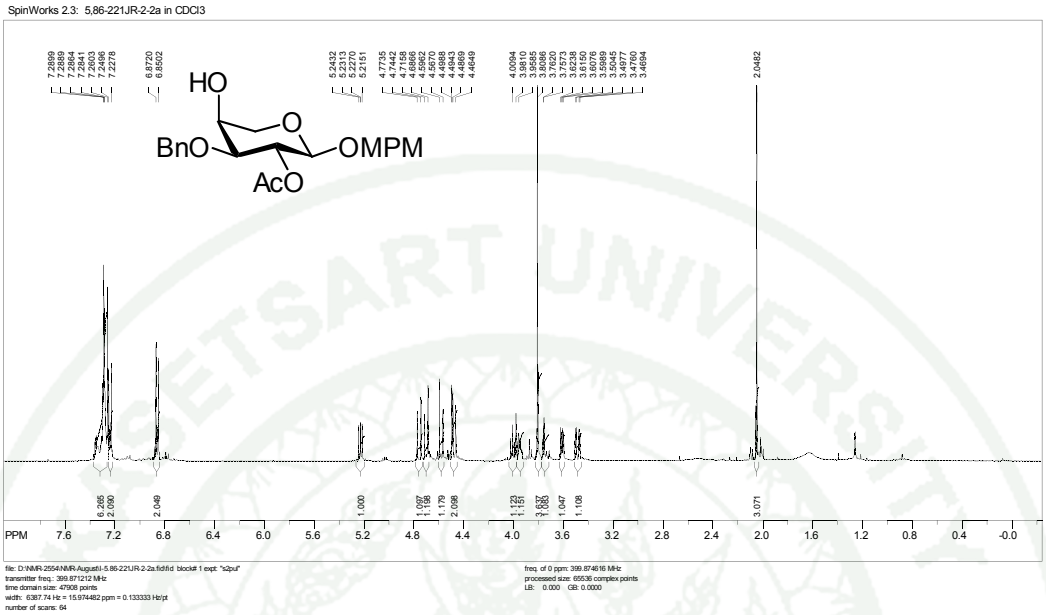
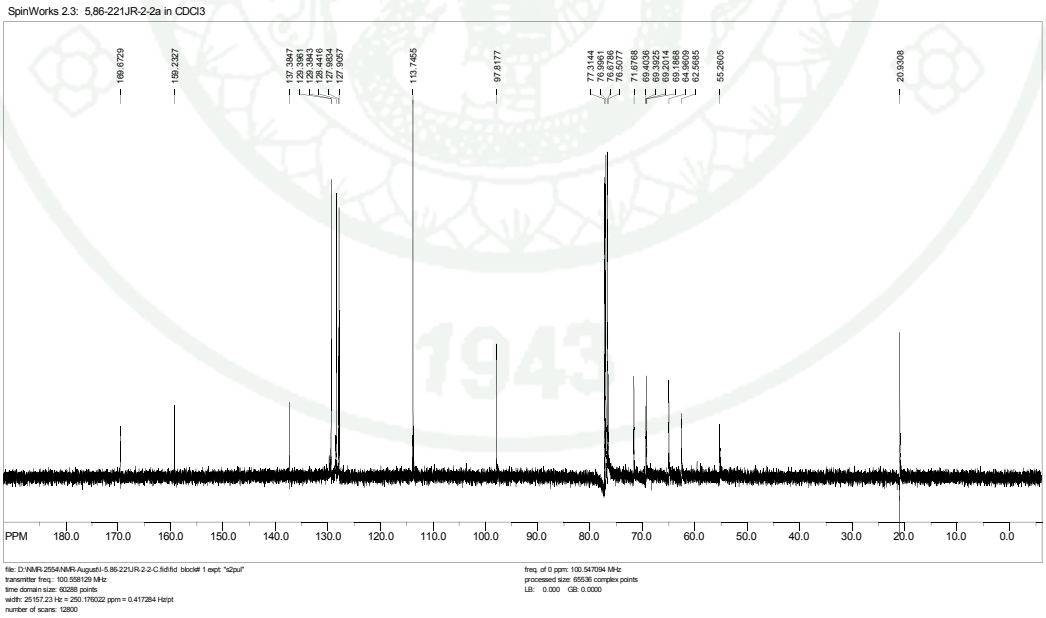


Appendix Figure 163 400 MHz ^{1}H NMR spectrum: 4-methoxybenzyl 2-*O*-acetyl-3-*O*-benzyl-α-L-arabinopyranoside (535)



Appendix Figure 164 100 MHz ^{13}C NMR spectrum: 4-methoxybenzyl 2-*O*-acetyl-3-*O*-benzyl-α-L-arabinopyranoside (535)

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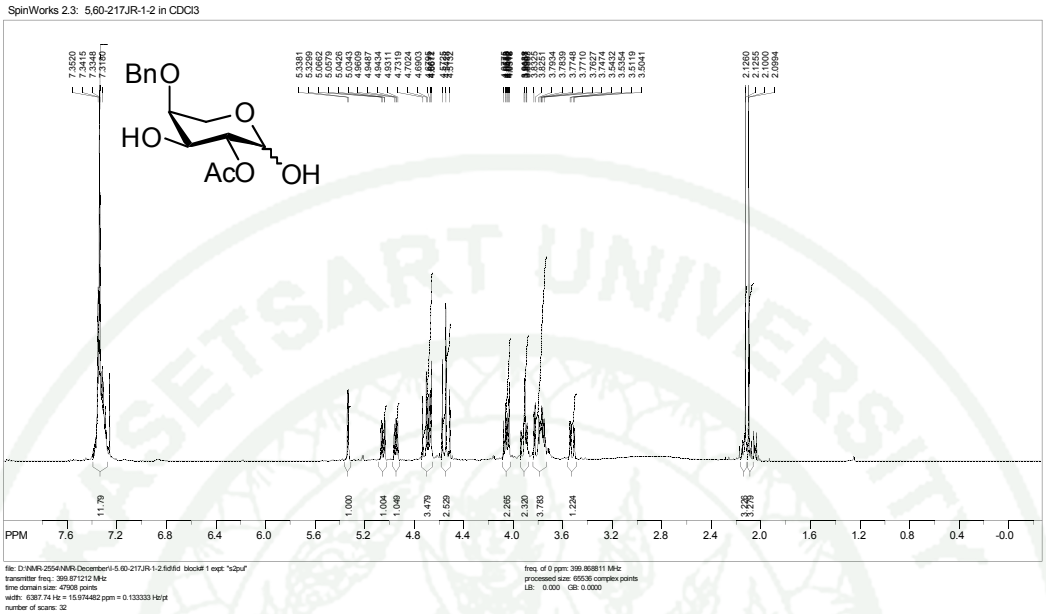
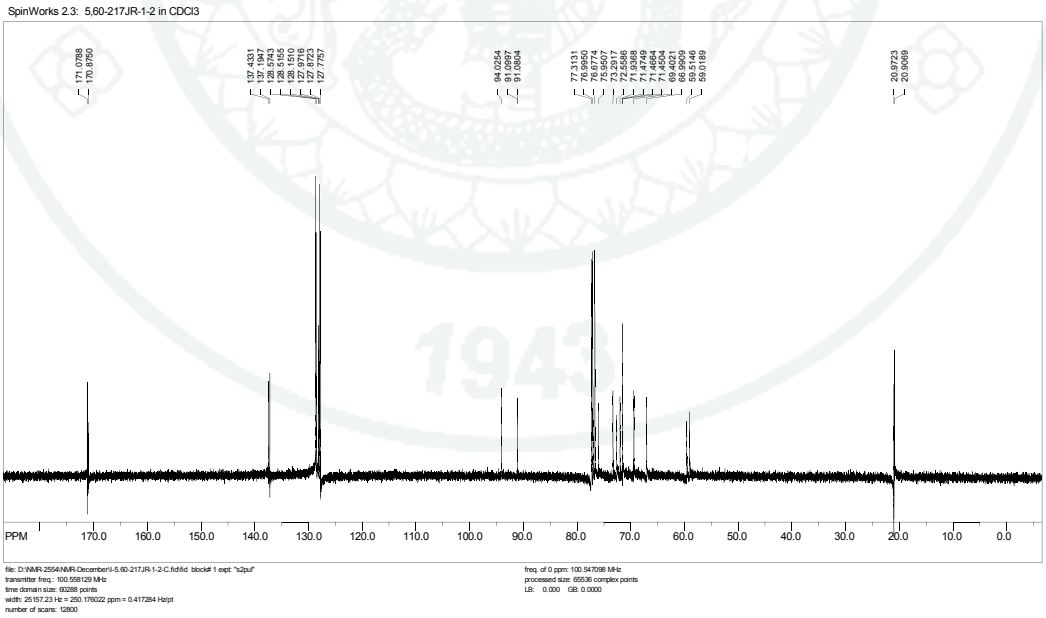


Appendix Figure 165 400 MHz ^{1}H NMR spectrum: 2-*O*-acetyl-4-*O*-benzyl-α/*β*-L-arabinopyranoside (536)



Appendix Figure 166 100 MHz ^{13}C NMR spectrum: 2-*O*-acetyl-4-*O*-benzyl-α/*β*-L-arabinopyranoside (536)

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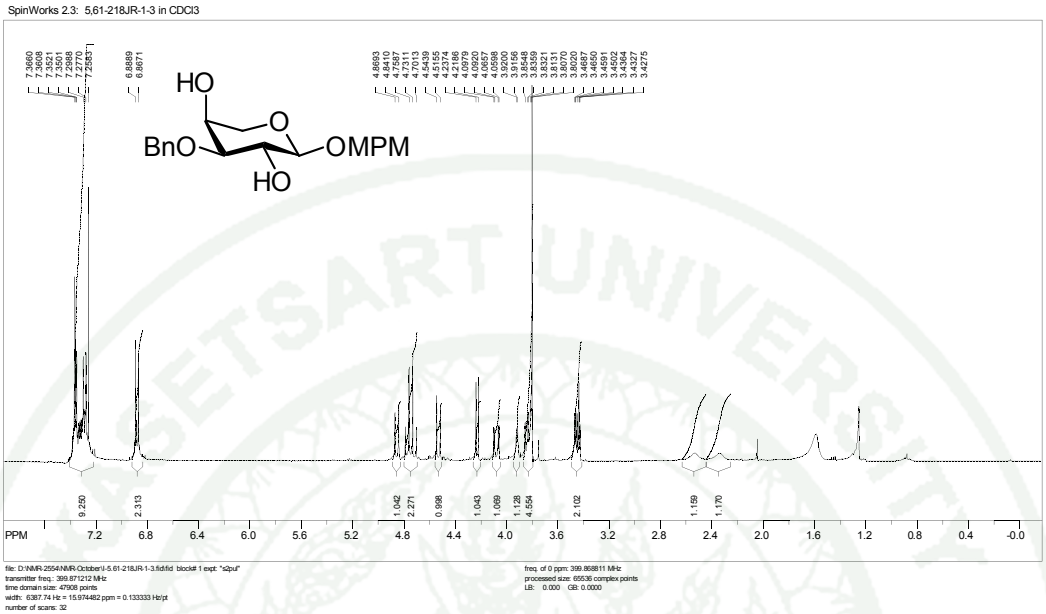
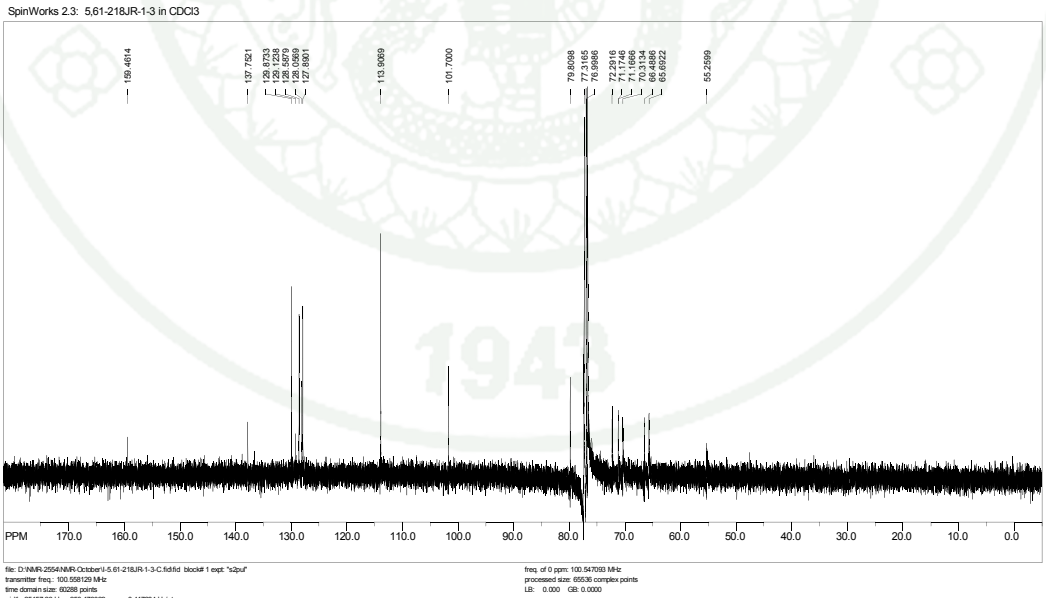


Appendix Figure 167 400 MHz ^{1}H NMR spectrum: 4-methoxybenzyl 3-*O*-benzyl-α-L-arabinopyranoside (537)



Appendix Figure 168 100 MHz ^{13}C NMR spectrum: 4-methoxybenzyl 3-*O*-benzyl-α-L-arabinopyranoside (537)

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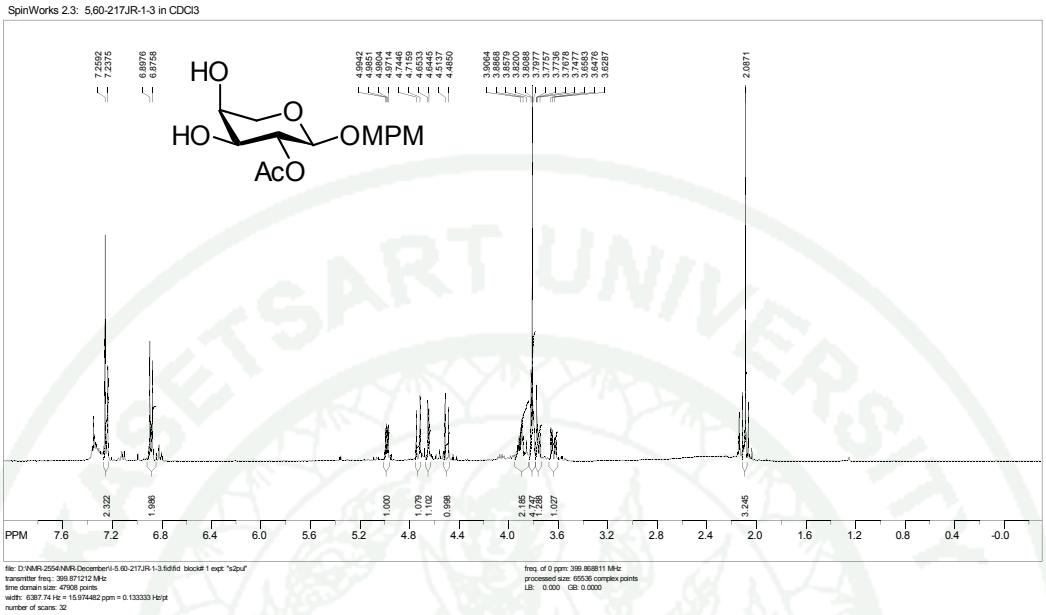
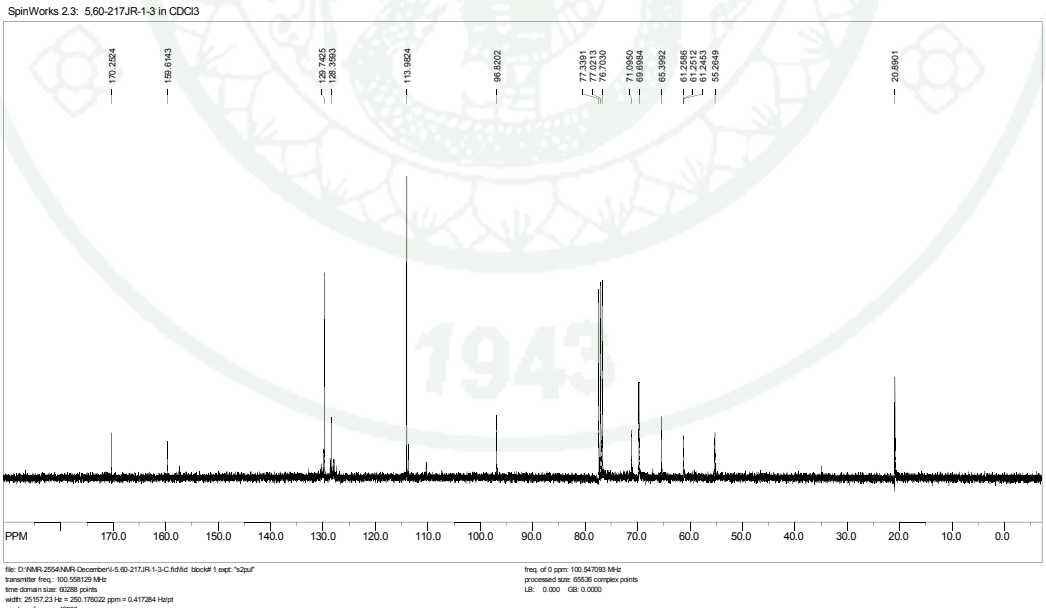


Appendix Figure 169 400 MHz ^{1}H NMR spectrum: 4-methoxybenzyl 2-*O*-acetyl-α-L-arabinopyranoside (538)



Appendix Figure 170 100 MHz ^{13}C NMR spectrum: 4-methoxybenzyl 2-*O*-acetyl-α-L-arabinopyranoside (538)

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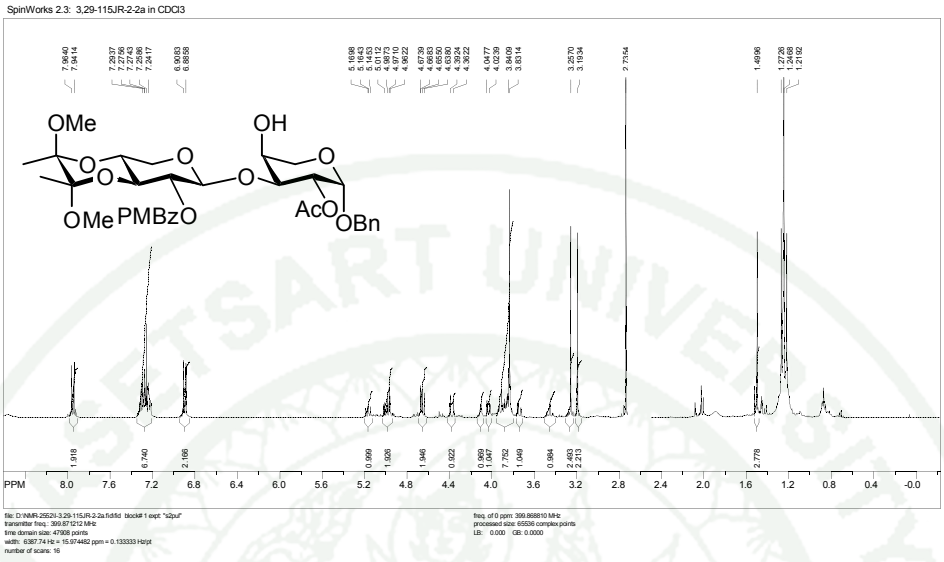
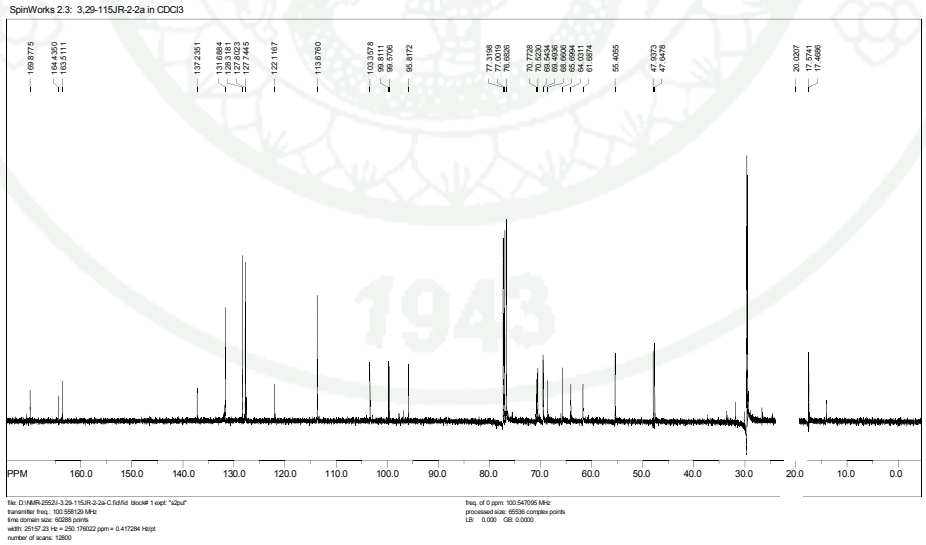


Appendix Figure 171 400 MHz ^{1}H NMR spectrum: benzyl 2-*O*-acetyl-3-*O*-(2-*O*-methoxybenzoyl-(2'*S*,3'*S*)-methyl-3,4-*O*-(2',3'-dimethoxy butane-2',3'-diyl)-β-D-xylopyranosyl)-β-L-arabinopyranoside (539)



Appendix Figure 172 100 MHz ^{13}C NMR spectrum: benzyl 2-*O*-acetyl-3-*O*-(2-*O*-methoxybenzoyl-(2'*S*,3'*S*)-methyl-3,4-*O*-(2',3'-dimethoxy butane-2',3'-diyl)-β-D-xylopyranosyl)-β-L-arabinopyranoside (539)

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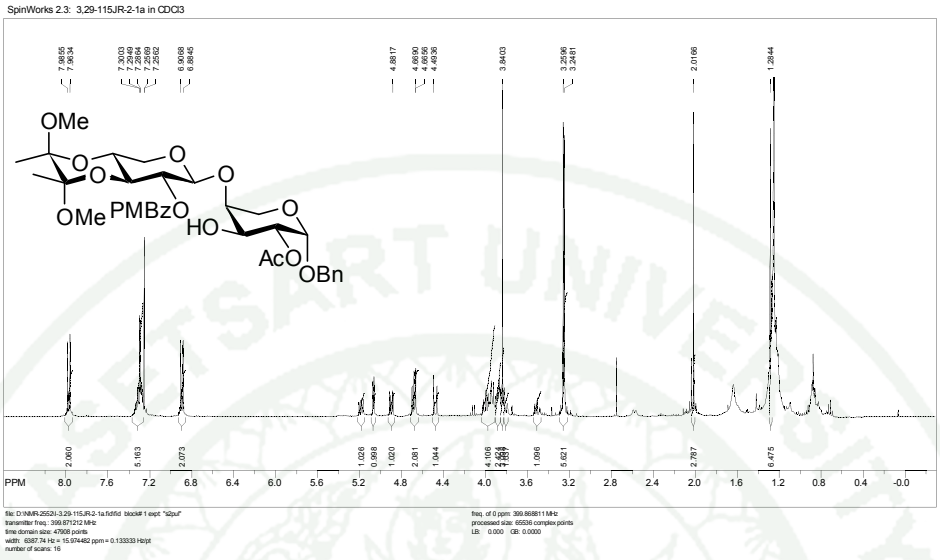
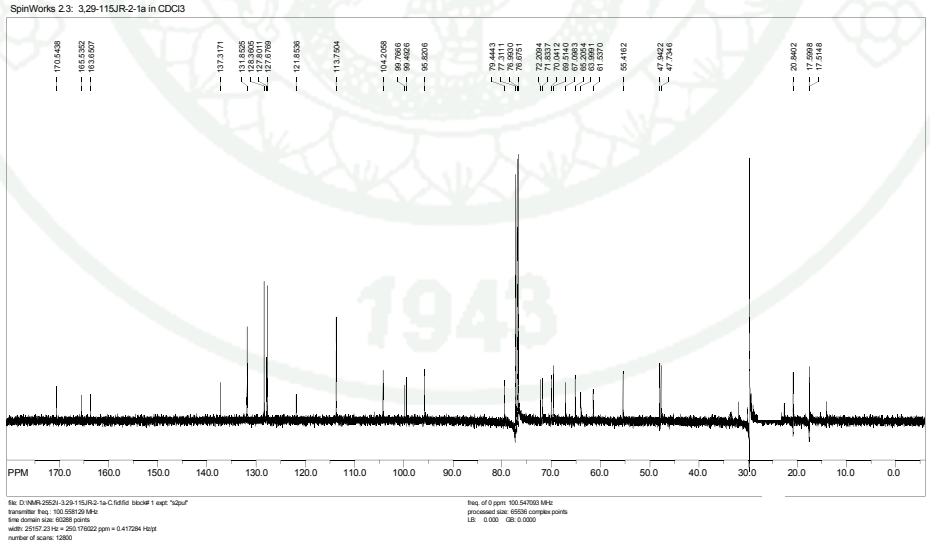


Appendix Figure 173 400 MHz ^{1}H NMR spectrum: benzyl 2-*O*-acetyl-4-*O*-(2-*O*-methoxybenzoyl-(2'*S*,3'*S*)-methyl-3,4-*O*-(2',3'-dimethoxy butane-2',3'-diyl)-β-D-xylopyranosyl)-β-L-arabinopyranoside (540)



Appendix Figure 174 100 MHz ^{13}C NMR spectrum: benzyl 2-*O*-acetyl-3-*O*-(2-*O*-methoxybenzoyl-(2'*S*,3'*S*)-methyl-3,4-*O*-(2',3'-dimethoxy butane-2',3'-diyl)-β-D-xylopyranosyl)-4-*O*-benzyl-β-L-arabinopyranoside (540)

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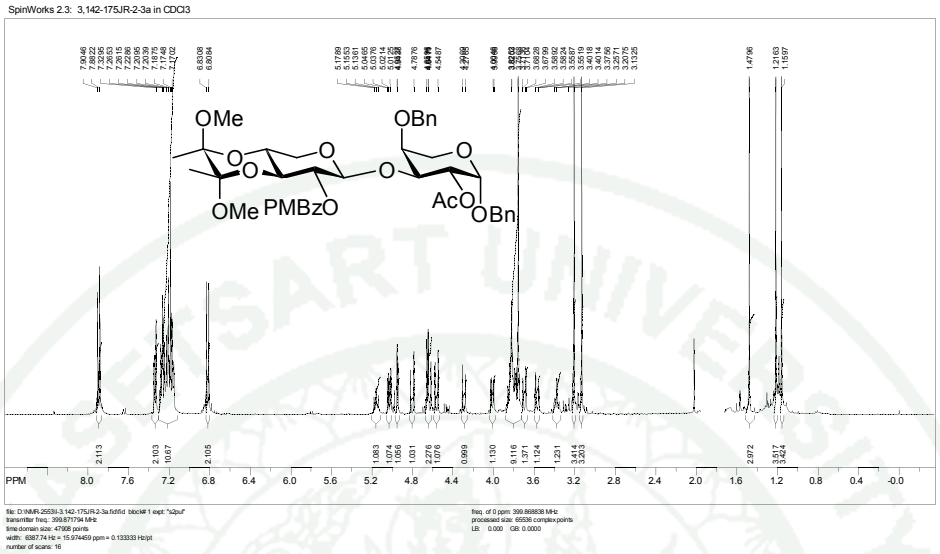
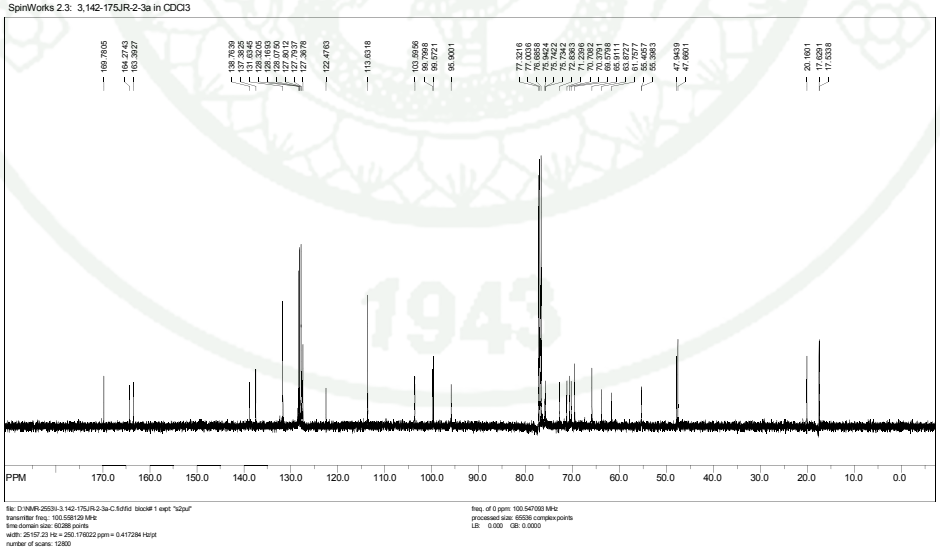


Appendix Figure 175 400 MHz ^{1}H NMR spectrum: benzyl 2-*O*-acetyl-3-*O*-(2-*O*-methoxybenzoyl-(2'*S*,3'*S*)-methyl-3,4-*O*-(2',3'-dimethoxy butane-2',3'-diyl)-β-D-xylopyranosyl)-4-*O*-benzyl-β-L-arabinopyranoside (541)



Appendix Figure 176 100 MHz ^{13}C NMR spectrum: benzyl 2-*O*-acetyl-3-*O*-(2-*O*-methoxybenzoyl-(2'*S*,3'*S*)-methyl-3,4-*O*-(2',3'-dimethoxy butane-2',3'-diyl)-β-D-xylopyranosyl)-4-*O*-benzyl-β-L-arabinopyranoside (541)

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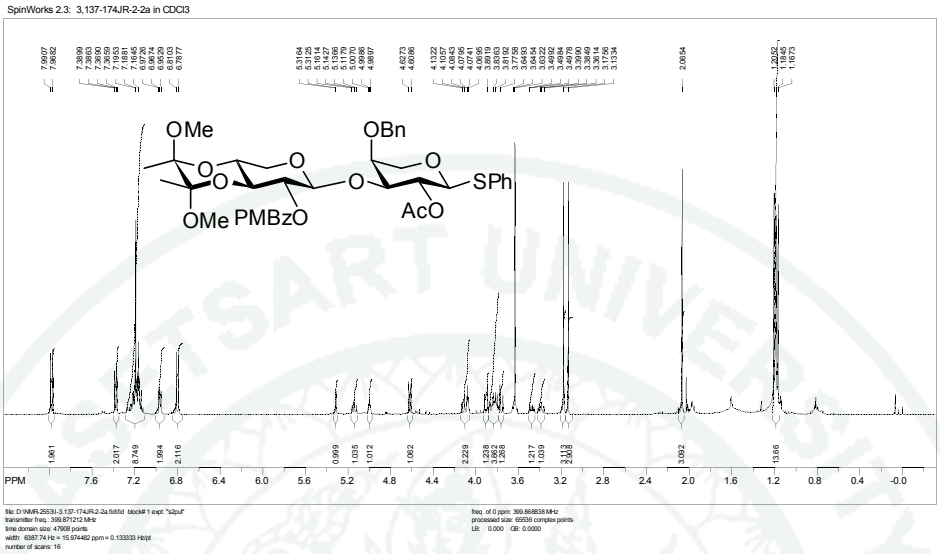
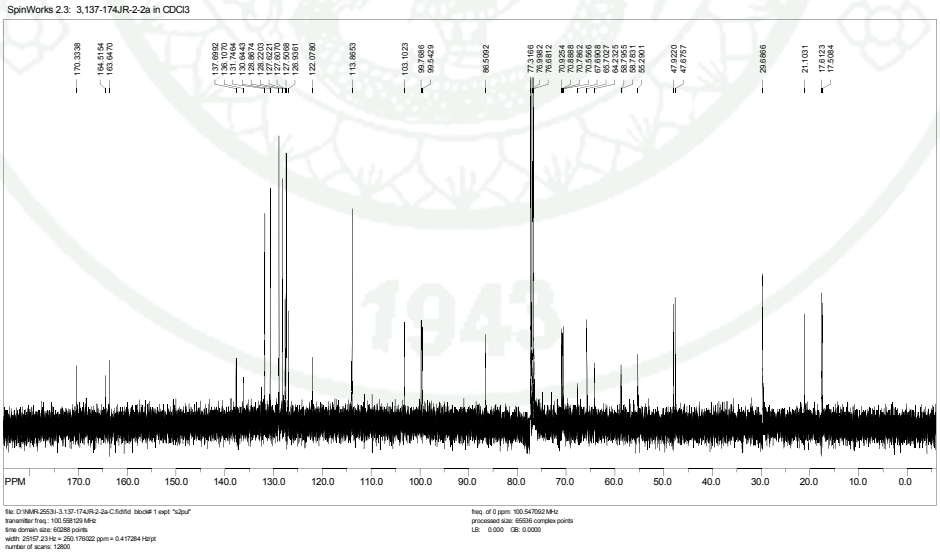


Appendix Figure 177 400 MHz ^{1}H NMR spectrum: thiophenyl 2-*O*-acetyl-3-*O*-(2-*O*-methoxybenzoyl-(2'*S*,3'*S*)-methyl-3,4-*O*-(2',3'-dimethoxy butane-2',3'-diyl)-β-D-xylopyranosyl)-4-*O*-benzyl-α-L-arabinopyranoside (542)



Appendix Figure 178 100 MHz ^{13}C NMR spectrum: thiophenyl 2-*O*-acetyl-3-*O*-(2-*O*-methoxybenzoyl-(2'*S*,3'*S*)-methyl-3,4-*O*-(2',3'-dimethoxy butane-2',3'-diyl)-β-D-xylopyranosyl)-4-*O*-benzyl-α-L-arabinopyranoside (542)

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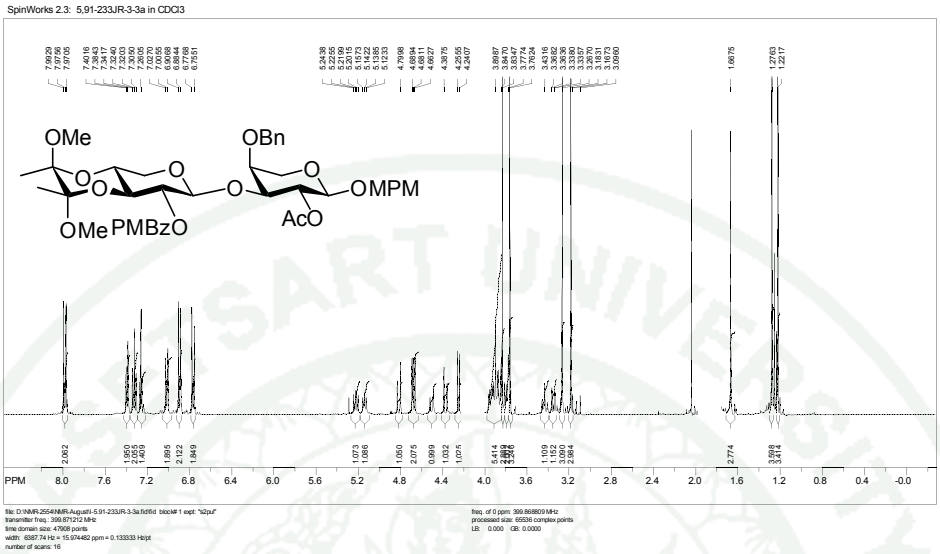
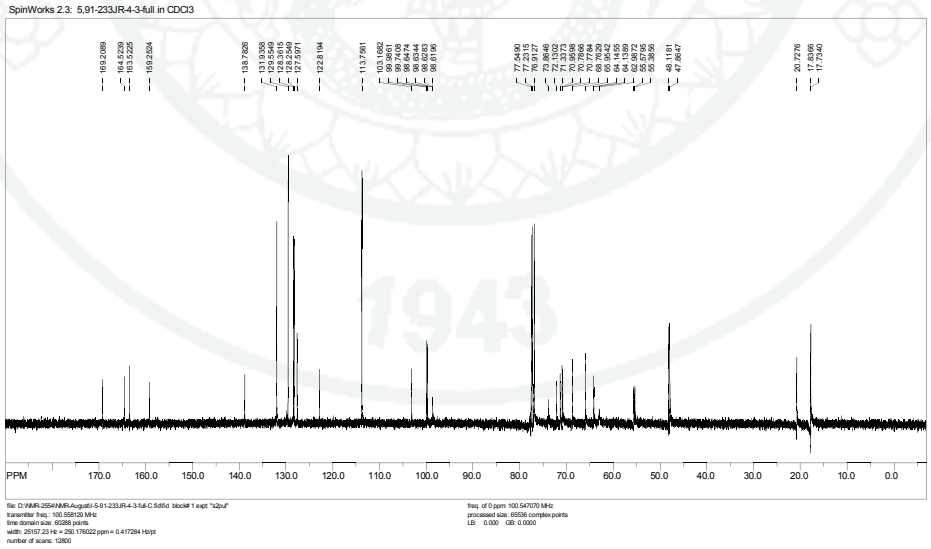


Appendix Figure 179 400 MHz ^{1}H NMR spectrum: 4-methoxybenzyl 2-*O*-acetyl-3-*O*-(2-*O*-methoxybenzoyl-(2'*S*,3'*S*)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-β-D-xylopyranosyl)-4-*O*-benzyl-*α*-L-arabinopyranoside (543)



Appendix Figure 180 100 MHz ^{13}C NMR spectrum: 4-methoxybenzyl 2-*O*-acetyl-3-*O*-(2-*O*-methoxybenzoyl-(2'*S*,3'*S*)-methyl-3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-β-D-xylopyranosyl)-4-*O*-benzyl-*α*-L-arabinopyranoside (543)

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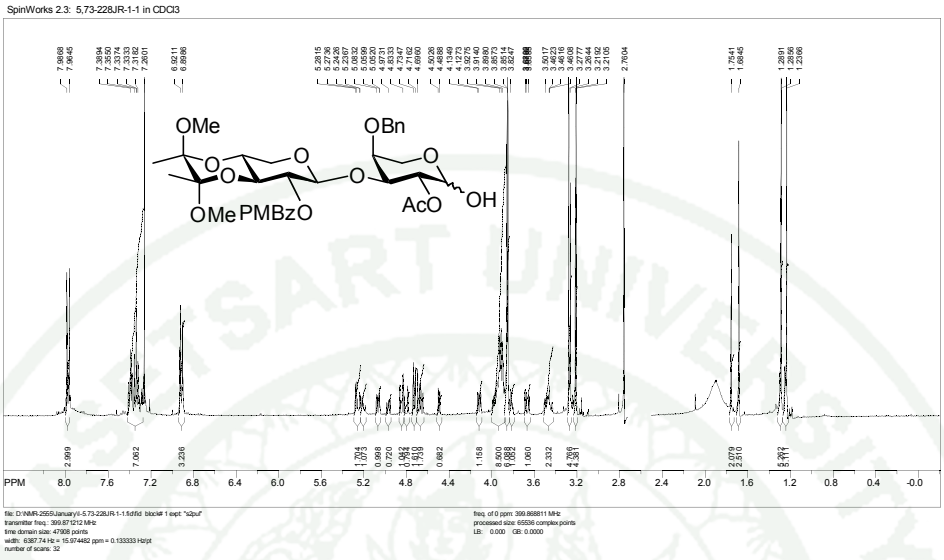
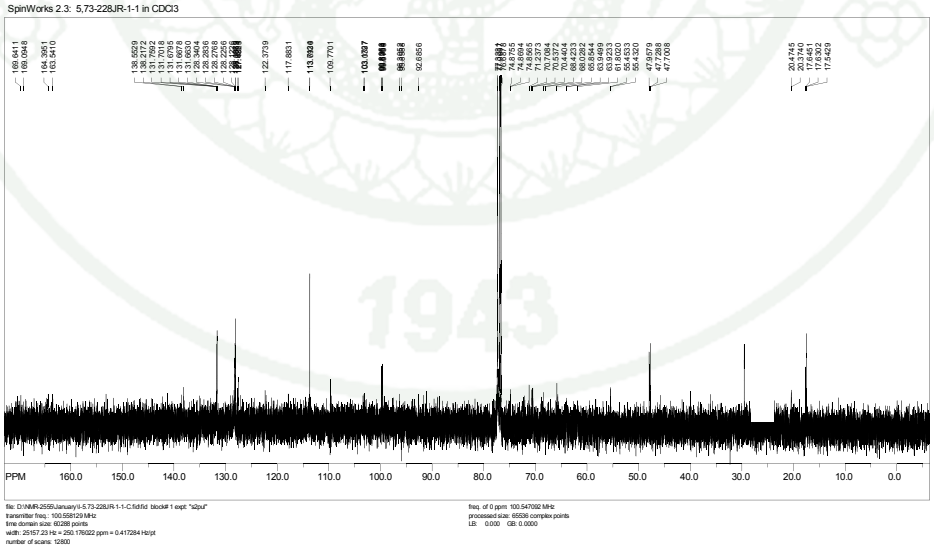


Appendix Figure 181 400 MHz ^{1}H NMR spectrum: 2-*O*-acetyl-3-*O*-(2-*O*-methoxybenzoyl-(2'*S*,3'*S*)-methyl-3,4-*O*-(2',3'-dimethoxy butane-2',3'-diyl)-β-D-xylopyranosyl)-4-*O*-benzyl-α/β-L-arabinopyranoside (544)



Appendix Figure 182 100 MHz ^{13}C NMR spectrum: 2-*O*-acetyl-3-*O*-(2-*O*-methoxybenzoyl-(2'*S*,3'*S*)-methyl-3,4-*O*-(2',3'-dimethoxy butane-2',3'-diyl)-β-D-xylopyranosyl)-4-*O*-benzyl-α/β-L-arabinopyranoside (544)

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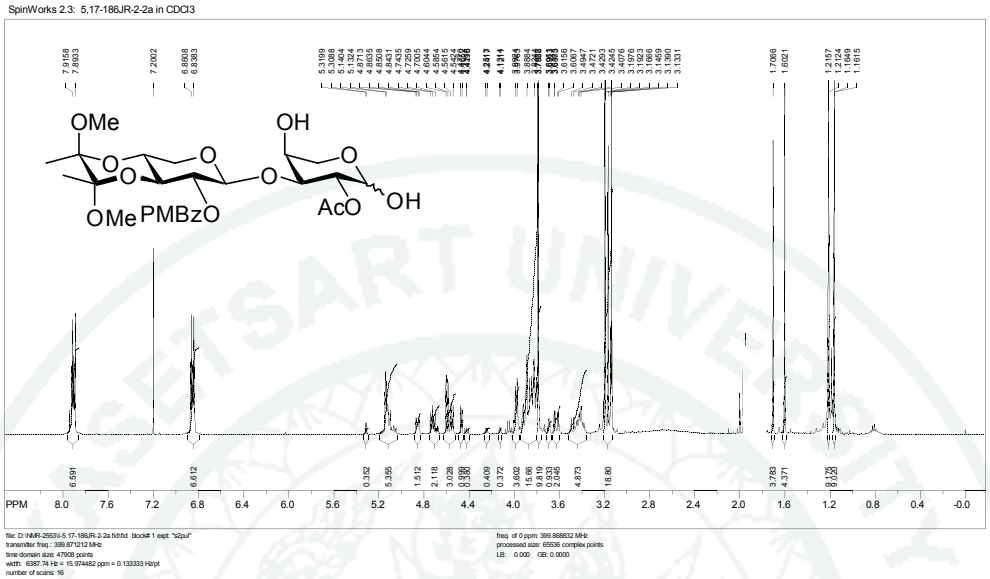
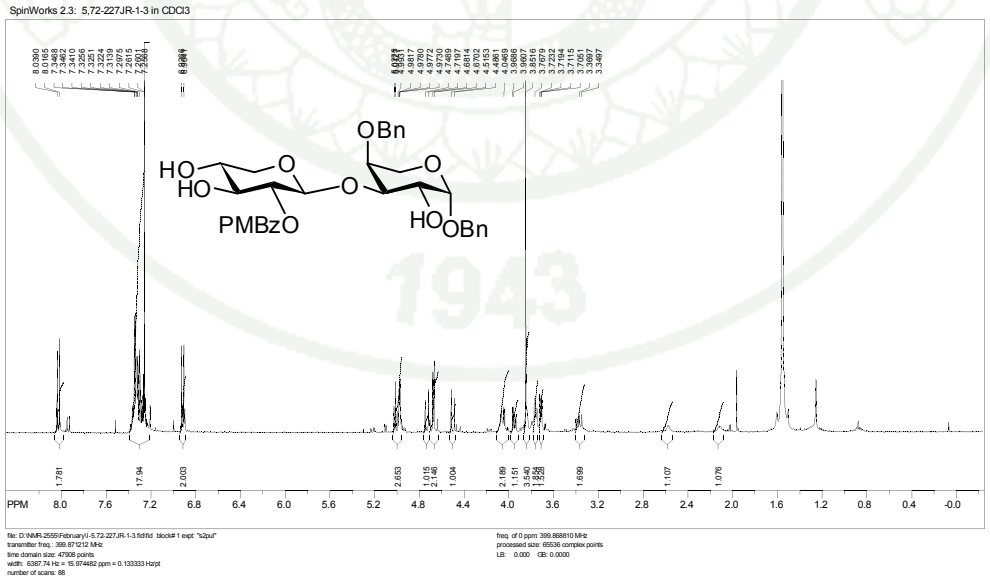


Appendix Figure 183 400 MHz ^{1}H NMR spectrum: 2-*O*-acetyl-3-*O*-(2-*O*-methoxybenzoyl-(2'*S*,3'*S*)-methyl-3,4-*O*-(2',3'-dimethoxy butane-2',3'-diyl)-β-D-xylopyranosyl)-α/β-L-arabinopyranoside (545)



Appendix Figure 184 400 MHz ^{1}H NMR spectrum: benzyl 3-*O*-(2-*O*-methoxybenzoyl-β-D-xylopyranosyl)-4-*O*-benzyl-β-L-arabinopyranoside (546)

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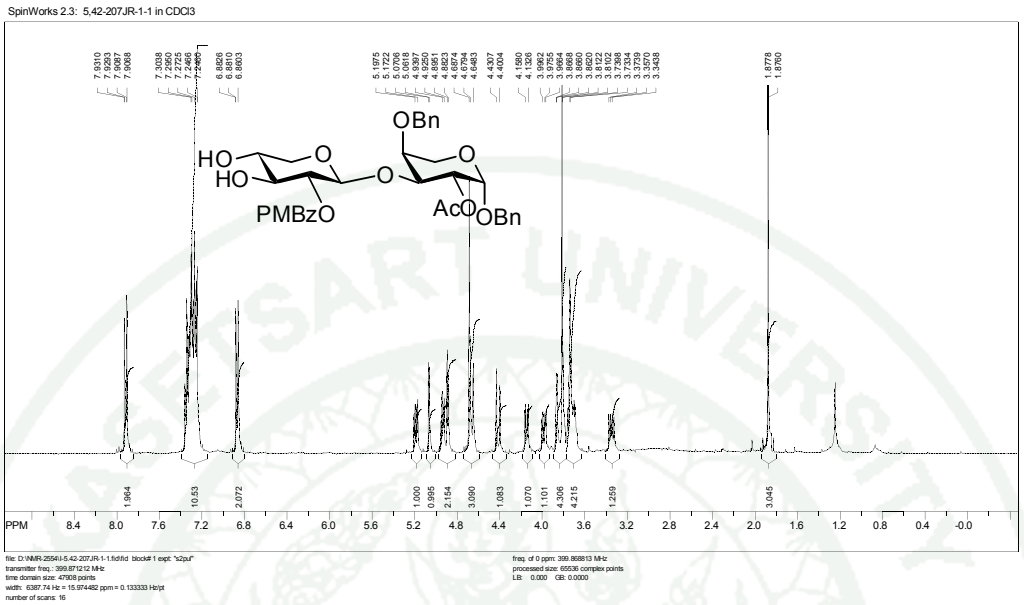
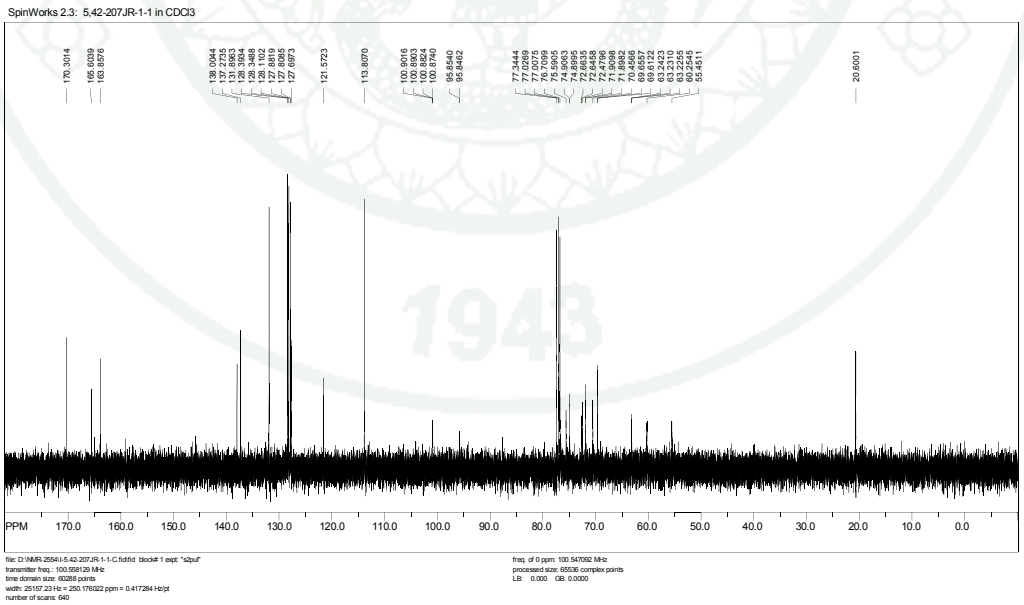


Appendix Figure 185 400 MHz ^{1}H NMR spectrum: benzyl 2-*O*-acetyl-3-*O*-(2-*O*-methoxybenzoyl-β-D-xylopyranosyl)-4-*O*-benzyl-β-L-arabinopyranoside (548)



Appendix Figure 186 100 MHz ^{13}C NMR spectrum: benzyl 2-*O*-acetyl-3-*O*-(2-*O*-methoxybenzoyl-β-D-xylopyranosyl)-4-*O*-benzyl-β-L-arabinopyranoside (548)

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: PERCH-CIC Congress V, May 6-9, 2007
: PERCH-CIC Congress VII, May 6-9, 2011
: PACCON Congress, Jan 5-7, 2011

PUBLICATION : Rujirawanich, J. and T. Gallagher. 2009. Substituted 1,4-benzoxazepines, 1,5-benzoxazocines, and *N*- and *S*-variants. **Organic Letters**. 11(23): 5494-5496.
: Rujirawanich, J., B. Kongkathip and N. Kongkathip. 2011. Regioselective ring opening of exo- and endo-3,4-benzylidene acetals of arabinopyranoside derivatives with Lewis acids and reducing agents. **Carbohydrate Research.** 346: 927-932.

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