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THESIS

TOTAL SYNTHESIS OF AN ANTI-AVIAN INFLUENZA DRUG OSELTAMIVIR PHOSPHATE (TAMIFLU) AND ADVANCE INTERMEDIATE TO TAMIPHOSPHOR FROM D-RIBOSE

PAWINEE WICHIENUKUL

A Thesis Submitted in Partial Fulfillment of
the Requirements for the Degree of
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Oseltamivir phosphate (Tamiflu) is used as an orally active drug for treatment and prevention of influenza viruses infections. It is hydrolyzed by an esterase enzyme to the corresponding carboxylic acid, which is a potent inhibitor of neuraminidases A and B. Recently Tamiphosphor, a phosphonate congener of Tamiflu, has been synthesized and showed more potent activity against the wild-type neuraminidase of H5N1 and H1N1 viruses. The current manufacturing process of Tamiflu uses (-)-shikimic acid as the starting compound which is not always readily available in consistently pure form. Thus, alternative approaches starting from other substrates were explored. Herein, we report a synthesis of Tamiflu and advance intermediate to Tamiphosphor from an alternative starting material D-ribose which is cheap and commercially available.

The main features of this approach comprise a metal (Zn, In)-mediated domino reaction of 5-iodo derivative of D-ribofuranose and ring-closing olefin metathesis (RCM) of the resultant functionalized dienes to produce the Tamiflu skeleton. The synthesis represents a new and efficient transformation of a 5-epi-hydroxy shikimate derivative into a 1,2-diamino compound which involved oxidation of an alcohol followed by reductive amination, regioselective reductive ring opening of 3-pentylidene ketal and stereospecific nucleophilic replacement of a triflate with an azide.

In summary, we have accomplished an efficient synthesis of Tamiflu in 14 steps and advance intermediate to Tamiphosphor in 9 steps with 5% and 2% overall yield respectively, using cheap and abundant D-ribose as the starting material. The key features of the synthesis include a metal-mediated domino reaction, ring-closing olefin metathesis (RCM), reductive amination and regioselective reductive ring opening of 3-pentylidene ketal.

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Student's signature Thesis Advisor's signature

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My appreciation is also extended to the Natural Products and Organic Synthesis Research Unit (NPOS), Department of Chemistry, Faculty of Science, Kasetsart University, and the staff of the Chemistry Department. Moreover, I would like to thank all of my friends and colleagues for helping me get through the hard times.

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Pawinee Wichienukul

May 2011

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LIST OF ABBREVIATIONS

α	=	alpha
β	=	beta
δ	=	chemical shift (ppm)
υ_{max}	=	maximum absorption frequency
Ac	=	acetyl
Ar	=	aryl
Boc	=	*tert*-butoxycarbonyl
br s	=	broad singlet
BSA	=	benzenesulfonic acid
Calcd.	=	calculated
cm^{-1}	=	reciprocal centimeter (wave number)
d	=	doublet
dd	=	doublet of doublets
ddd	=	doublet of doublet of doublets
dt	=	doublet of triplets
DMAP	=	4-dimethylaminopyridine
EI	=	electron impact
Et	=	ethyl
FTIR	=	fourier transform infrared spectroscopy
g	=	gram
h	=	hour
HRMS	=	high resolution mass spectroscopy
Hz	=	Hertz
J	=	coupling constant
m	=	multiplet
Me	=	methyl
mg	=	milligram
min	=	minute
mL	=	milliliter

LIST OF ABBREVIATIONS (Continued)

MS	=	mass spectrometry
Ms	=	methanesulfonyl
m/z	=	a value of mass divided by charge
NOESY	=	nuclear overhauser effect spectroscopy
NMR	=	nuclear magnetic resonance
ppm	=	part per million
Py	=	pyridine
q	=	quartet
quint	=	quintet
RCM	=	ring-closing olefin metathesis
rt	=	room temperature
s	=	singlet
t	=	triplet
t-Bu	=	tertiary butyl
TCCA	=	trichloroisocyanuric acid
TEMPO	=	2,2,6,6-tetramethylpiperidine 1-oxyl
Tf	=	trifluoromethanesulfonyl
TFA	=	trifluoroacetic acid
THF	=	tetrahydrofuran
TLC	=	thin layer chromatography
Tr	=	trityl chloride
Ts	=	4-toluenesulfonyl

TOTAL SYNTHESIS OF AN ANTI-AVIAN INFLUENZA DRUG OSELTAMIVIR PHOSPHATE (TAMIFLU) AND ADVANCE INTERMEDIATE TO TAMIPHOSPHOR FROM D-RIBOSE

INTRODUCTION

Influenza, commonly referred to as the flu, is a disease caused by the influenza viruses that affects birds and mammals. Influenza is a more severe disease than the common cold, although common symptoms are alike, and is caused by a different type of virus. There are three types of influenza viruses which are influenza A, B and C. The most commonly found type of flu virus is influenza A virus that causes infection in a variety of animal species including humans. The virus particles contain two main types of glycoproteins, hemagglutinin (HA) and neuraminidase (NA) (Figure 1). HA allows the recognition of target cells and facilitates the entry of the viral genome into the target, while NA is involved in the release of progeny virus from infected cells. Based on antibody responses to HA and NA, influenza A viruses are classified into subtypes labeling on an H number (H1 to H16 for the type of hemagglutinin) and an N number (N1 to N9 for the type of neuraminidase).

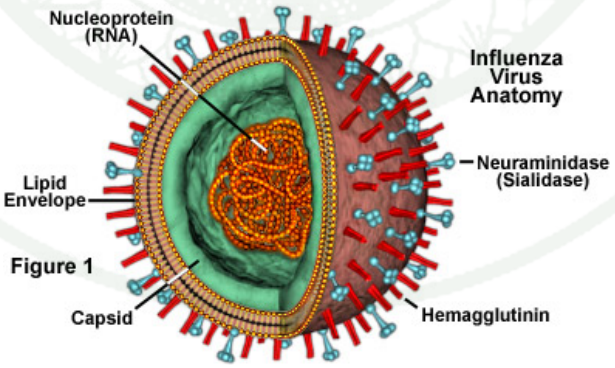


Figure 1 Influenza virus anatomy.

Source: Michael W. Davidson and The Florida State University (2005)

Since 20th century, the world have seen many influenza pandemics, for example Spanish flu (1918), Asian flu (1957) and Hong Kong flu (1968), resulting in the deaths of more than 50 million of people worldwide and each of these pandemics being caused by the appearance of a new strain of the virus in humans (Table 1) (Hilleman, 2002). The new strain of the virus appear when an existing human flu virus picks up new genes from a virus that usually infects other animal species, such as birds or pigs, or in contrast an existing animal flu virus spreads to humans.

Table 1 Influenza pandemics in the 1900s.

Name of pandemic	Date	Deaths	Subtype involved
Spanish Flu	1918	20-50 million	H1N1
Asian Flu	1957	1 to 2 million	H2N2
Hong Kong Flu	1968	1 million	H3N2

Source: Maurice R. Hilleman (2002)

The first H5N1, a bird-adapted strain commonly known as “avian flu” or “bird flu”, emerged in Asia in 1987, spread throughout the continent in 2003 and reached Europe in 2005 and the Middle East as well as Africa the following year. The virus transmitted from birds to humans and it has not evolved to a form that spreads easily between humans. Combined genes from human, pig, and bird flu, a novel flu strain H1N1 evolved in April 2009. This virus was called by many names such as “swine flu” or “2009 H1N1 flu”. Although it was first informally called “swine flu”, the virus cannot be spread by eating pork. The H1N1 influenza virus is mainly transmitted from human-to-human through the respiratory system.

There have been many attempts to prevent and slow down a flu pandemic. Vaccination is used as a strategy to prevent flu. A vaccine probably would not be available in the initial stages of population infection as it cannot be developed to protect against a virus which does not exist yet. And since the influenza virus evolves rapidly, a vaccine formulated for one year may be ineffective in the following year.

Antiviral drugs have also been used to treat influenza. The viral neuraminidase enzyme is a target for the development of antiviral therapeutics. Neuraminidases, also called sialidases, catalyze the hydrolysis of terminal sialic acid residues to release the newly formed viral particles from the host cell. Using computational chemistry techniques, the neuraminidase inhibitor was designed based on the structure of sialic acid (1) which is the target of neuraminidase enzyme (Figure 2) (Magano, 2009). The first neuraminidase inhibitor commercially developed was zanamivir (2). It is marketed under the trade name "Relenza" as a powder for oral inhalation. Another neuraminidase inhibitor available in store is oseltamivir (3). It was developed by Gilead Sciences Inc. and is marketed by F. Hoffmann-La Roche Ltd. (Roche) under the trade name "Tamiflu" in form of phosphate salt. Oseltamivir phosphate (4), or Tamiflu, is a prodrug that is converted into its active form, oseltamivir carboxylic acid (5), by metabolic process after it is taken into the body (Figure 3). The key interactions between oseltamivir carboxylate and the active site of neuraminidase enzyme were divided into five subsites (Maring *et al.*, 2005; Stoll *et al.*, 2003) (Figure 4).

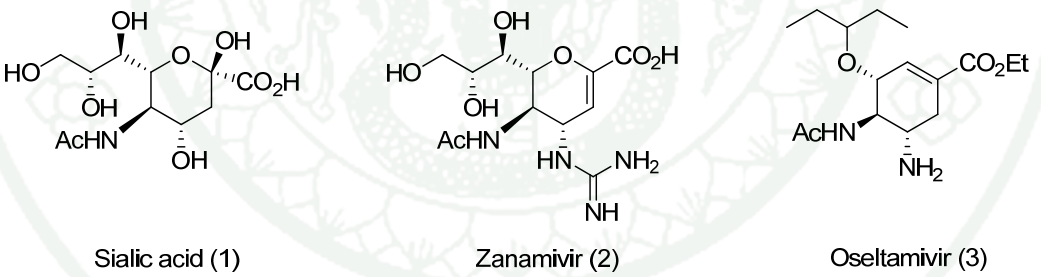


Figure 2 Structure of sialic acid (1), zanamivir (2) and oseltamivir (3).

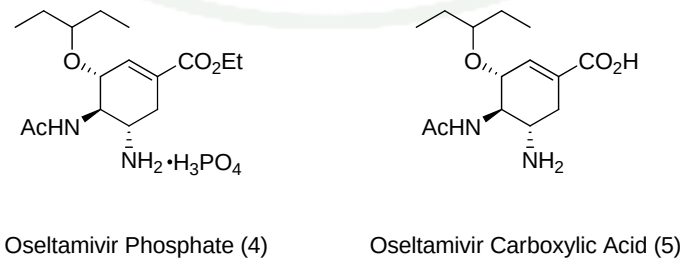


Figure 3 Structure of oseltamivir phosphate (4) and its active form (5).

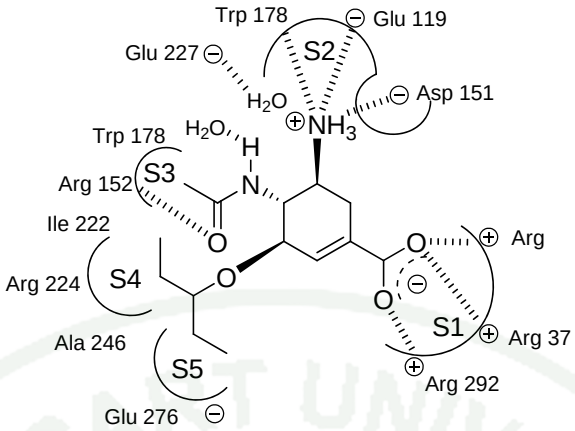
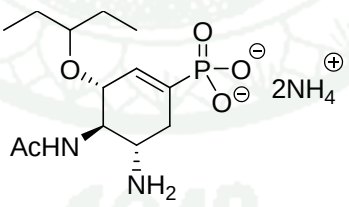


Figure 4 The key interactions of oseltamivir carboxylate and the active site of the neuraminidase enzyme.

To develop the influenza neuraminidase inhibitors, Tamiphosphor (6), the phosphonate congener of Tamiflu, was investigated since the phosphonate group is generally used as a bioisostere of carboxylate in drug design (Shie *et al.*, 2007) (Figure 5). Tamiphosphor (6) provides more extensive hydrogen bonding interactions in the neuraminidase active site resulting in the higher affinity in the enzyme inhibition and better anti-influenza activity. It is more potent than Tamiflu by 19- and 7-folds, respectively, in the enzyme inhibition and cell-based anti-flu assays.



Tamiphosphor (6)

Figure 5 Structure of Tamiphosphor (6).

Many nations are working to stockpile antiviral drugs in preparation for a possible pandemic. Due to the lack of (-)-shikimic acid which is the starting material in the current manufacturing process, concerns have been raised about the capacity of the existing production process to meet world demand. Thus, there has been intense

effort from the chemical community in developing alternative approaches which start from cheap and readily available substrates.

To synthesize oseltamivir phosphate (4), our research group considers that monosaccharides would be appropriate candidates for the use as a starting material in the manufacturing process. Besides being cheap and commercially available, monosaccharides have a number of structures variable in the stereoisomer that would be suitable for the synthesis. We plan to use D-ribose (7) as a starting material for our synthetic approach. Using a metal-mediated domino reaction and ring-closing olefin metathesis (RCM), the core structure was formed. The synthesis was accomplished by reductive amination, nucleophilic replacement and phosphate salt formation (Figure 6). A similar strategy was also used to synthesize Tamiphosphor (6) *via* the intermediate **46b** (Shie *et al.*, 2008) (Figure 7).

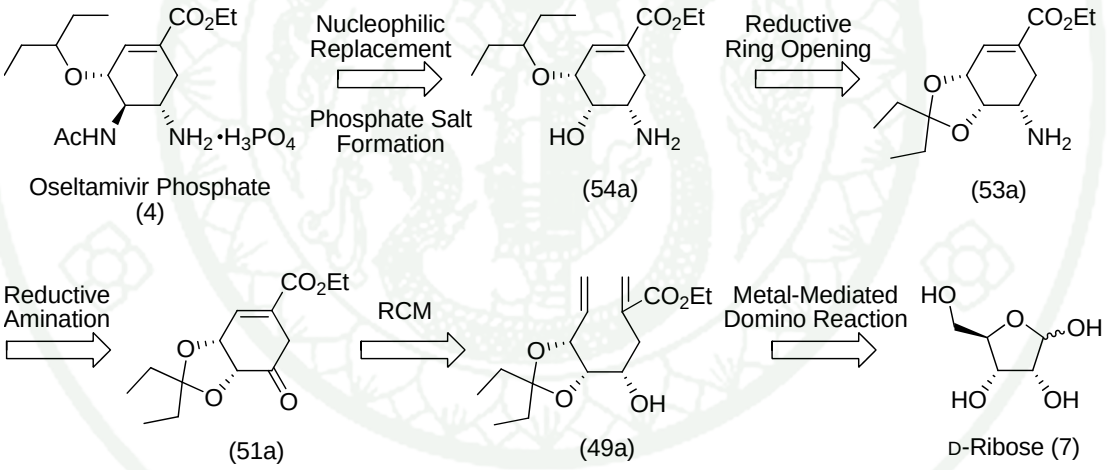


Figure 6 Retrosynthetic analysis of oseltamivir phosphate (4) from D-ribose (7).

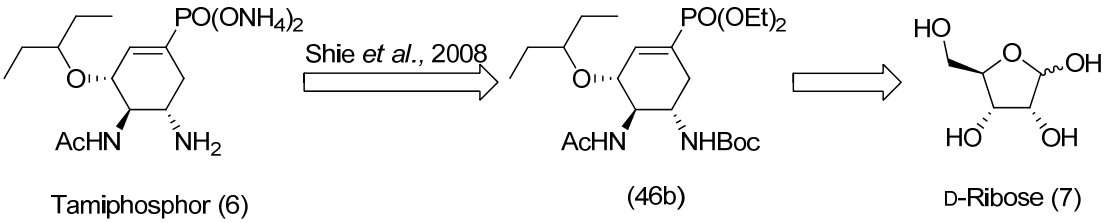


Figure 7 Retrosynthetic analysis of Tamiphosphor (6) from D-ribose (7).

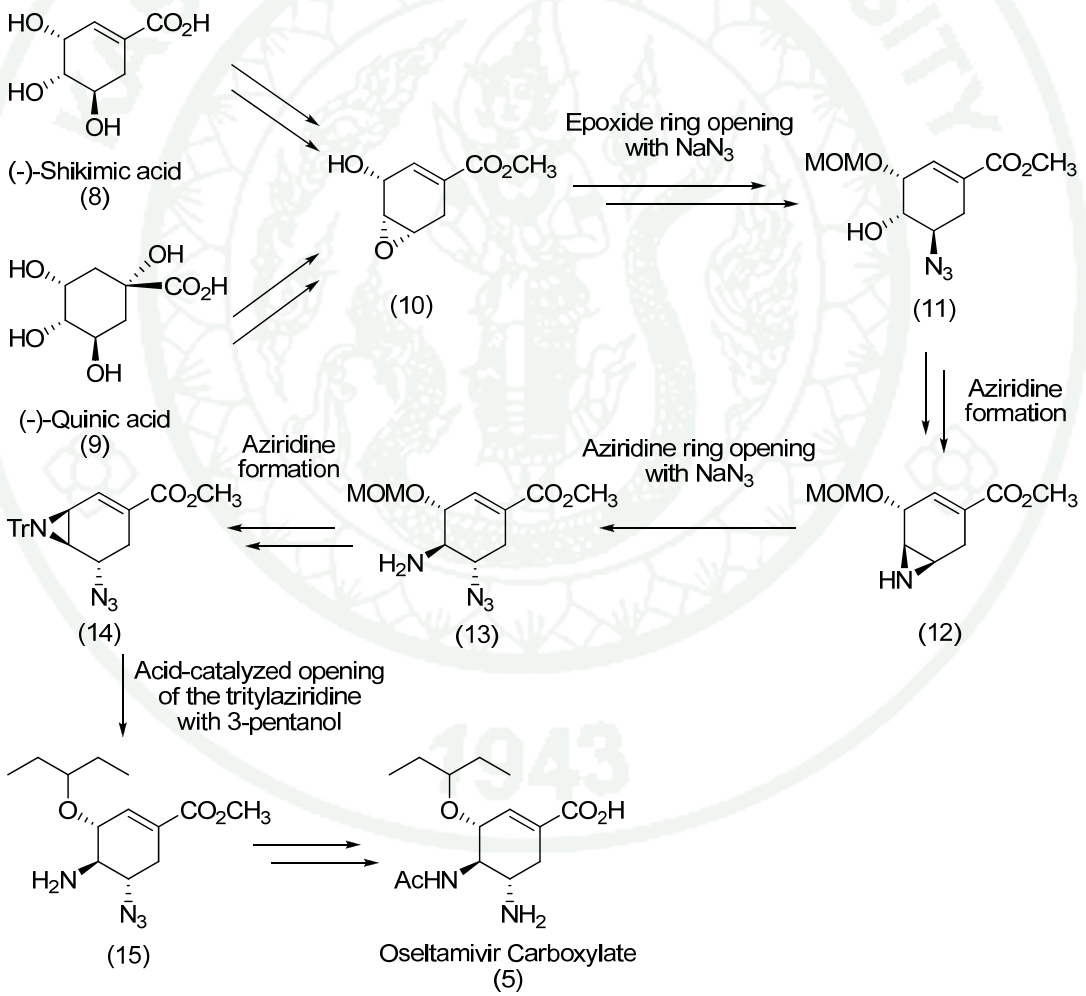
OBJECTIVES

To synthesize Tamiflu (oseltamivir phosphate) (4) and advance intermediate (55b) to Tamiphosphor from cheap and commercially available D-ribose (7).

LITERATURE REVIEW

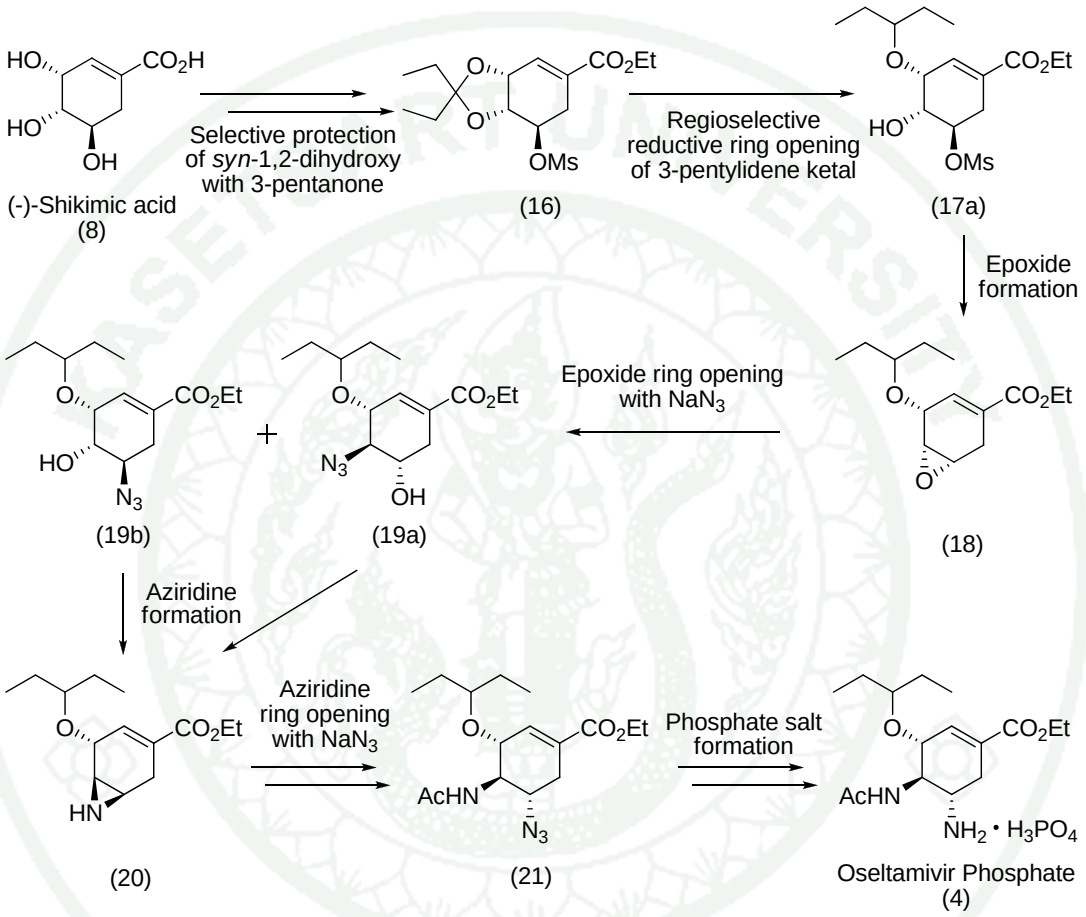
1. Synthesis of oseltamivir phosphate (4)

Oseltamivir carboxylate (5) was the first molecule synthesized by Gilead Science Inc. (Kim *et al.*, 1997) using (-)-shikimic acid (8) as a starting material. However, due to the high cost and low availability of (-)-shikimic acid (8), Gilead Science Inc. had developed the scalable synthesis starting from more readily available (-)-quinic acid (9) (Rohloff *et al.*, 1998) (Scheme 1).



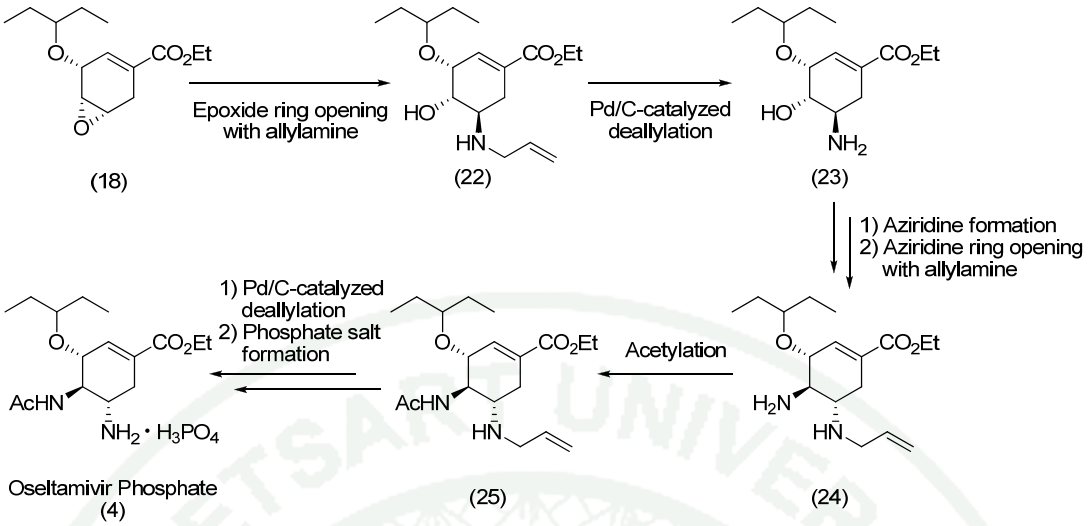
Scheme 1 First synthesis of oseltamivir carboxylate (5) from (-)-shikimic acid (8) and (-)-quinic acid (9).

To prepare the industrial scale of drug, Gilead Science Inc. and F. Hoffmann-La Roche Ltd. had co-develop the route to synthesize oseltamivir phosphate (4) *via* the key intermediate epoxide **18** (Federspiel *et al.*, 1999; Rohloff *et al.*, 1998) (Scheme 2).



Scheme 2 Industrial synthesis oseltamivir phosphate (4) from (-)-shikimic acid (8).

The previously reported methods utilized two reaction steps with potentially hazardous azides. Therefore F. Hoffmann-La Roche Ltd. had an attempt to find a non-azide nitrogen nucleophile that could be compatible with the rest of the functional groups in the molecule and published the azide-free route using an allylamine instead of a sodium azide *via* the key intermediate epoxide **18** (Karpf and Trussardi, 2001) (Scheme 3).



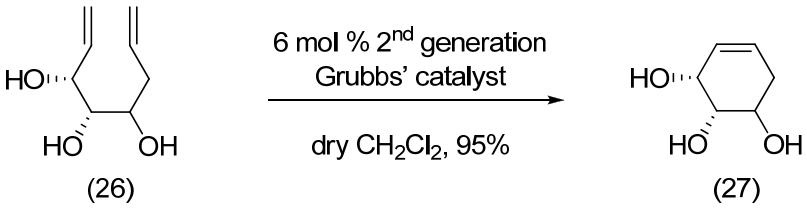
Scheme 3 Azide-free synthesis of oseltamivir phosphate (4).

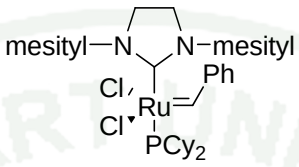
To synthesize oseltamivir phosphate (4), there are three main parts that should be considered which are the construction of cyclohexene core structure, the method to introduce pentyl ether as well as two amino groups in stereospecific manner.

1.1 Synthesis of the cyclohexene core structure

(-)-Shikimic acid (8) and (-)-quinic acid (9) were used as starting materials because they either contain or can be easily converted to the cyclohexene core structure of Tamiflu (4). Lately, the researchers have attempted to use others compound to synthesize the drug. In several new syntheses, the starting material does not contain core structure of Tamiflu (4), therefore the reactions to establish the cyclohexene core structure were explored.

In 2000, Hyldtoft and Madsen reported the method to construct the cyclohexene ring (27) from diene (25) using ring-closing olefin metathesis (RCM) with second generation Grubbs' catalyst (28) (Figure 8).

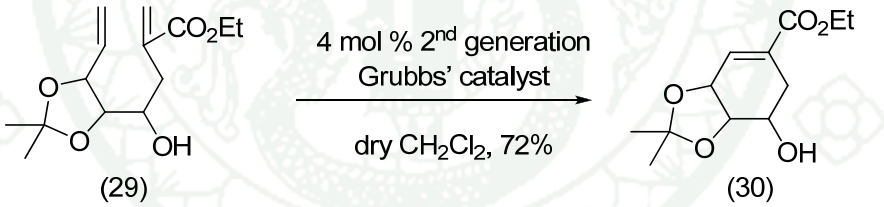




2nd generation
Grubbs' catalyst
(28)

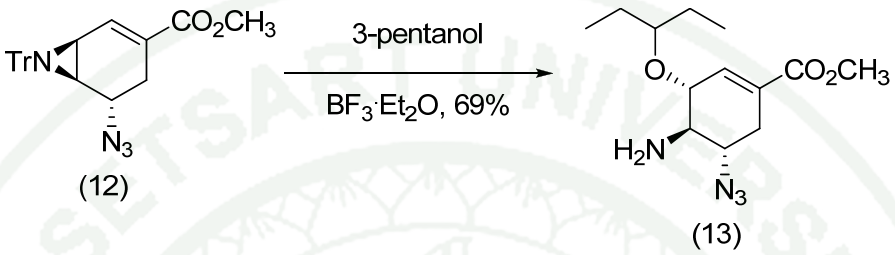
Figure 8 The structure of second generation Grubbs' catalyst (28).

In 2009, Kancharla *et al.* utilized RCM with second generation Grubbs' catalyst (28) to construct shikimic acid skeleton (30) from diene (29).

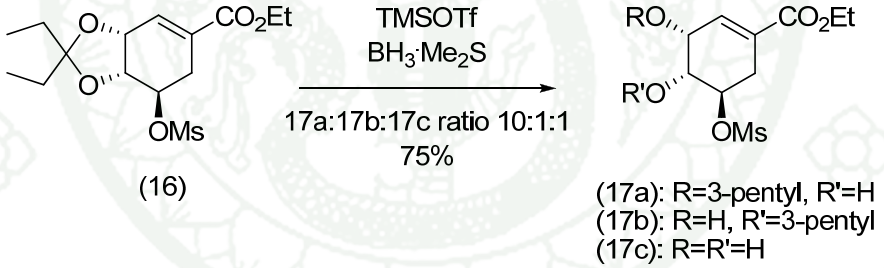


1.2 Introduction of the pentyl ether moiety

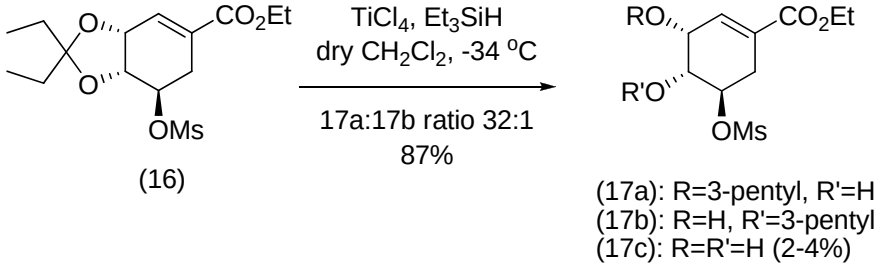
Another important part in the molecule was the pentyl ether moiety. In 1997, Kim *et al.* used the Lewis acid catalyzed nucleophilic attack to open the aziridine ring with 3-pentanol to introduce the pentyl ether group.



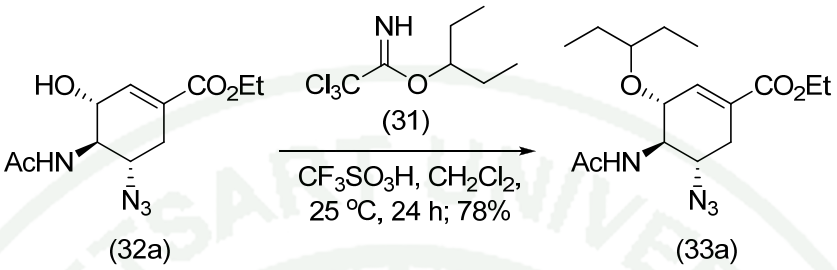
In 1998, Rohloff *et al.* reported an efficient method to introduce the pentyl ether moiety *via* regioselective reductive ring opening of a quinic or shikimic acid derived 3,4-pentylidene ketal to give **17a** and **17b** in 10:1 ratio.



In 1999, Federspiel *et al.* reported the optimized condition of reductive ring opening of pentylidene ketal using titanium tetrachloride and triethylsilane to give a much better selectivity (**17a**:**17b**=32:1).

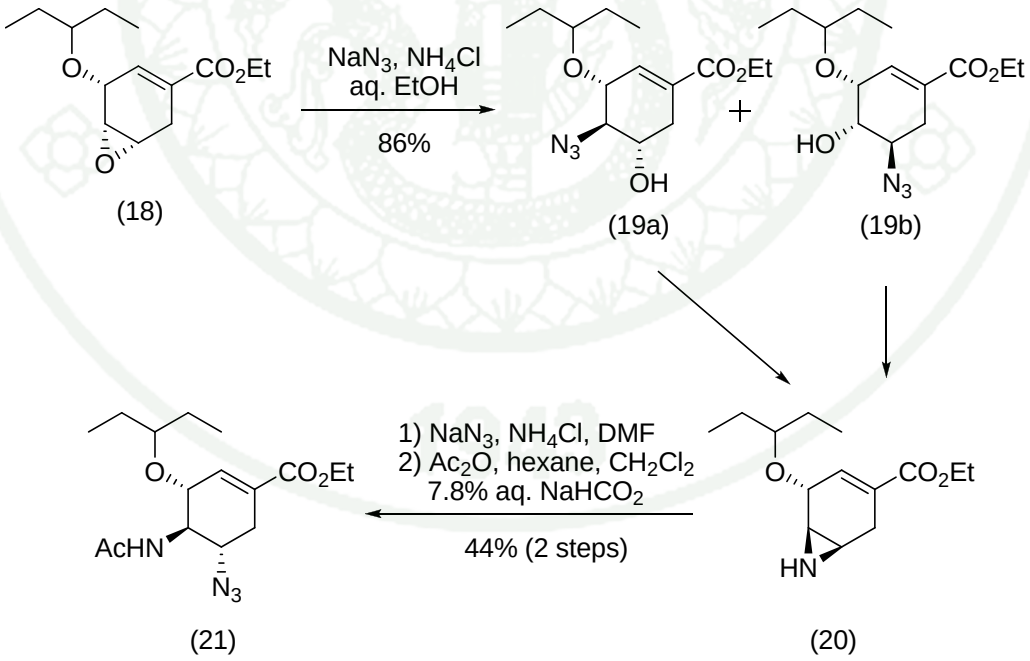


Fang's group (Shie *et al.*, 2007) reported the use of 3-pentyl trichloroacetimidate (31) as an active electrophile to introduce the pentyl ether moiety.

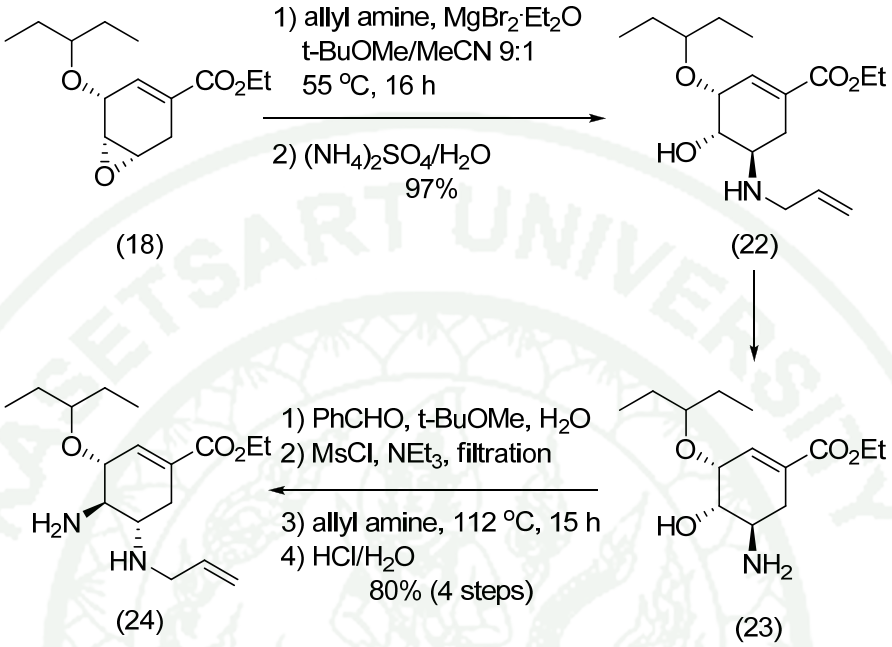


1.3 Introduction of the amino group

To introduce the amino groups, addition or substitution of *N*-nucleophile were employed. In the production of Tamiflu (4), sodium azide was used as an *N*-nucleophile (Federspiel *et al.*, 1999; Rohloff *et al.*, 1998).

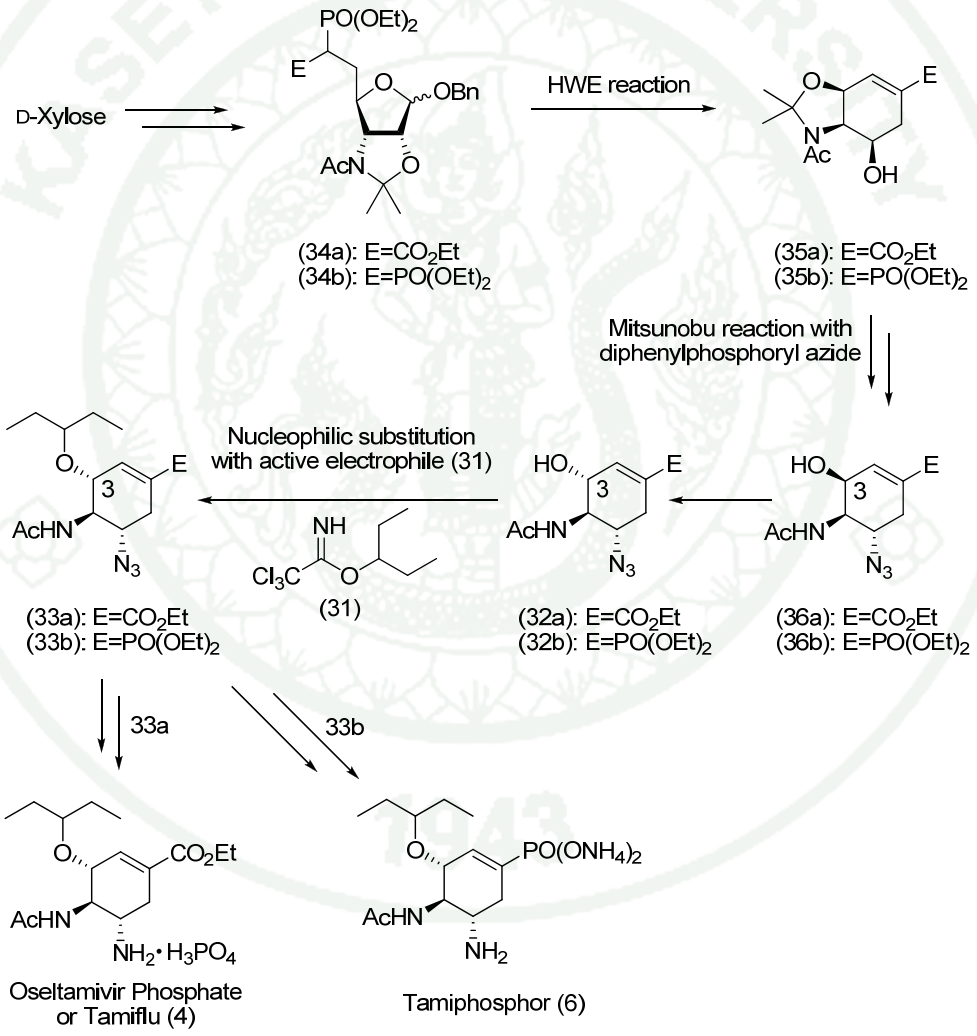


In 2001, Karpf and Trussardi reported the use of allylamine as an *N*-nucleophile instead of a sodium azide.



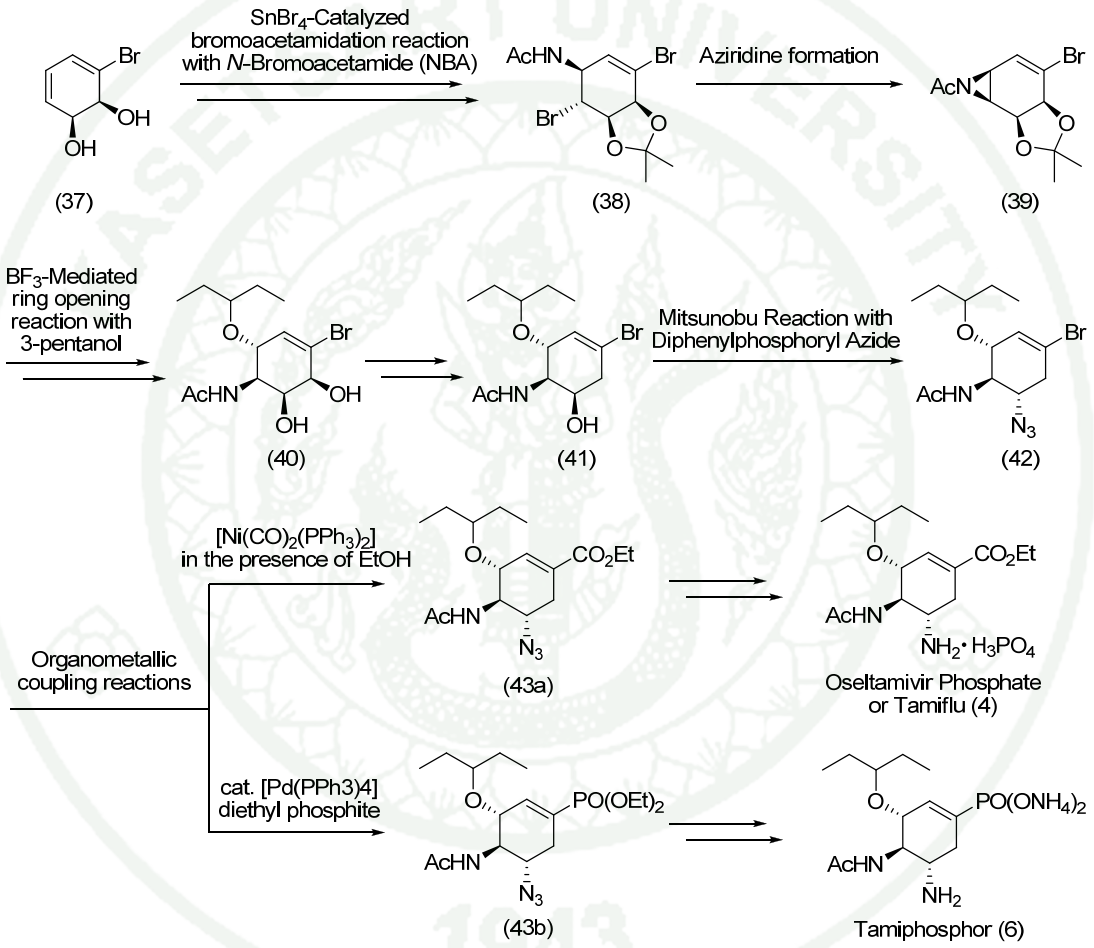
2. Synthesis of Tamiphosphor (6) by Fang's group

Fang's group (Shie *et al.*, 2007) reported the new synthetic approach to synthesize Tamiflu (4) and its phosphonate congeners Tamiphosphor (6) using D-xylose as an appropriate chiral precursor. An intramolecular Horner-Wadsworth-Emmons reaction (HWE) was utilized to construct the cyclohexene core structure. Mitsunobu's method with diphenylphosphoryl azide was employed to introduce an azido group in attempt to avoid the use of sodium azide (Scheme 4).



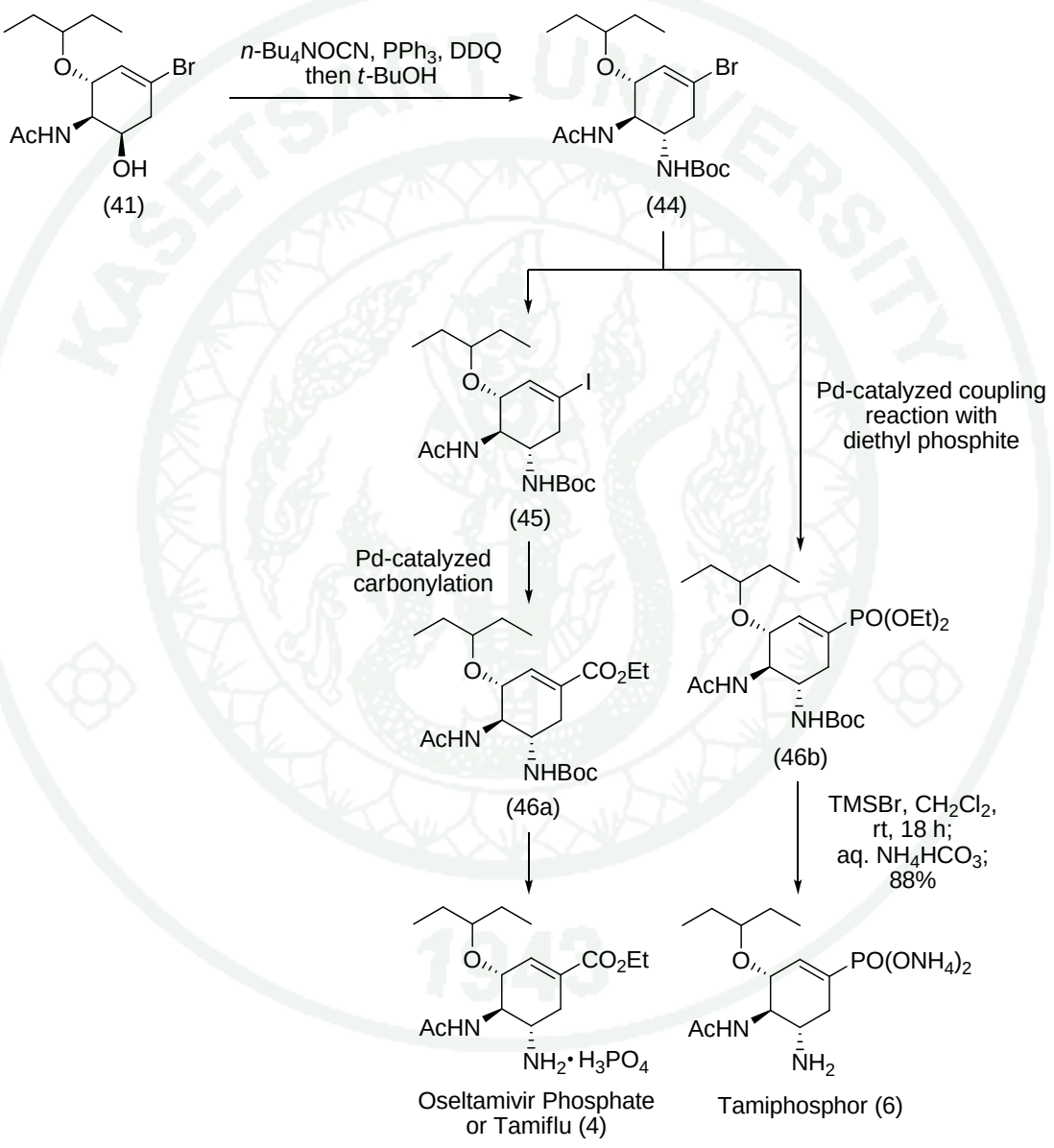
Scheme 4 Synthesis of Tamiflu (4) and Tamiphosphor (6) from D-xylose.

In the following year, Fang's group (Shie *et al.*, 2008) published more concise and practical synthetic route to Tamiflu (4) and Tamiphosphor (6) using bromoarene *cis*-1,2-dihydrodiol (37) as a starting material. The advantage of this synthetic strategy is that the bromine atom presented in starting material can be transformed into various functional groups, including carboxylate and phosphonate, at a late stage of the synthetic sequence (Scheme 5).



Scheme 5 Synthesis of Tamiflu (4) and Tamiphosphor (6) from bromoarene *cis*-1,2-dihydrodiol (37).

An azide-free process of the above synthetic method was also reported in the same publication. Employing tetrabutylammonium cyanate as a source for the amine functionality, the intermediate **41** was converted into carbamate **44**. The bromine atom was transformed to carboxylate and phosphonate in a late stage of the synthesis (Scheme 6).



Scheme 6 Synthesis of Tamiflu (4) and Tamiphosphor (6) from intermediate **41**.

MATERIALS AND METHODS

Materials

Instrument

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

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

Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were determined on a VARIAN^{UNITY} INOVA 400 MHz NMR spectrometer at the Chemistry Department, Faculty of Science, Kasetsart University. 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 77.23 ppm for ^{13}C) was used as an 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, ddd = doublet of doublet of doublet, dt = double of triplet, t = triplet, q = quartet, quint = quintet, m = multiplet.

Accurate masses (HRMS) were obtained from PERCH-CIC Mass Spectrometry Research Laboratory, Department of Chemistry, Faculty of Science, Chiang Mai University.

Unless otherwise stated, concentration under reduced pressure refers to a rotary evaporator at water aspirator pressure.

Chromatographic system

Analytical thin-layer chromatography (TLC) was conducted on aluminum-backed 0.2 mm thick silica gel 60 F_{254} plates (Merck). The chromatograms were visualized under a 254 nm UV lamp and then sprayed with vanillin solution followed by heating or with basic solution of potassium permanganate.

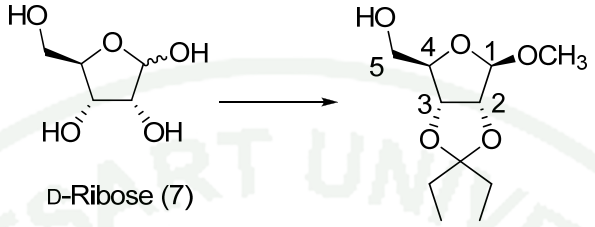
Flash column chromatography was conducted according to the method of Still and co-workers (1978) using silica gel 60 (mesh size 0.040-0.063 mm). Column chromatography was performed on silica gel 60 (70-230 mesh, Merck).

Chemical reagents

Analytical grade solvents and reagents used for synthesis were obtained from commercial sources and used directly without further purification unless noted. Dry tetrahydrofuran (THF) was freshly distilled under a 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.

Methods

Methyl 2,3-*O*-isopentylidene-β-D-ribofuranose (47)



To a suspension of D-ribose (7) (5 g, 33.30 mmol) in 3-pentanone (50 mL) was added trimethyl orthoformate (8 mL), methanol (20 mL) and methanol saturated with hydrogen chloride gas (2 mL). The reaction was stirred overnight at room temperature. The reaction mixture was neutralized with saturated aqueous sodium hydrogen carbonate and the solvent was removed under reduced pressure. The residue was partitioned between water (200 mL) and diethyl ether (150 mL). The aqueous layer was extracted with diethyl ether (3x100 mL) and the combined diethyl ether extracts were dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The residue was purified by flash column chromatography (15:85 ethyl acetate:hexane) to yield methyl 2,3-*O*-isopentylidene-β-D-ribofuranose (47) (7.63 g, 98%) as a colorless oil.

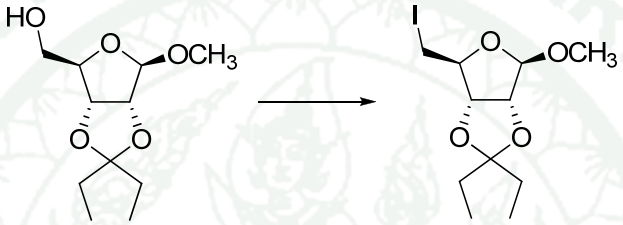
FTIR (neat), υ_{max}, cm^{-1}: 3435, 2941, 1463, 1098.

^{1}H NMR (400 MHz, $CDCl_3$), δ 4.91 (s, 1H, H-1), 4.75 (d, *J* = 6.0 Hz, 1H, H-3), 4.52 (d, *J* = 6.0 Hz, 1H, H-2), 4.36 (dd, *J* = 3.6, 3.1 Hz, 1H, H-4), 3.60 (ddd, *J* = 12.4, 3.2, 3.1 Hz, 1H, H-5), 3.53 (ddd, *J* = 12.4, 9.8, 3.6 Hz, 1H, H-5), 3.35 (s, 3H, OCH_3), 3.22 (dd, *J* = 9.8, 3.2 Hz, OH), 1.63 (q, *J* = 7.5, 2H, $CC\underline{H}_2CH_3$), 1.51 (q, *J* = 7.6, 2H, $CC\underline{H}_2CH_3$), 0.85 (t, *J* = 7.5, 3H, $CCH_2C\underline{H}_3$), 0.80 (t, *J* = 7.6, 3H, $CCH_2C\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$), δ 116.3 ($\underline{C}(CH_2CH_3)_2$), 109.9 (C-1), 88.4 (C-4), 86.0 (C-2), 81.6 (C-3), 63.8 (C-5), 55.2 (OCH_3), 29.2 ($C\underline{C}H_2CH_3$), 28.7 ($C\underline{C}H_2CH_3$), 8.3 ($CCH_2\underline{C}H_3$), 7.2 ($CCH_2\underline{C}H_3$).

HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd. for $C_{11}H_{20}O_5Na$: 255.1208, Found: 255.1208.

Methyl 5-deoxy-5-iodo-2,3-*O*-isopentylidene-β-D-ribofuranose (48)



(47) (48)

A solution of methyl 2,3-*O*-isopentylidene-β-D-ribofuranose (47) (5 g, 21.53 mmol), imidazole (2.20 g, 32.29 mmol) and triphenylphosphine (6.70 g, 25.83 mmol) in toluene (100 mL) and acetonitrile (20 mL) was treated portionwise with iodine (6.54 g, 25.83 mmol). The reaction mixture was refluxed for 3 h and cooled to room temperature. The reaction mixture was diluted with diethyl ether (100 mL) and the organic layer was washed with 10% sodium thiosulfate solution (3x100 mL), water (150 mL) and brine (150 mL). The organic phase was dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The residue was purified by flash column chromatography (5:95 ethyl acetate:hexane) to give methyl 5-deoxy-5-iodo-2,3-*O*-isopentylidene-β-D-ribofuranose (48) (5.82 g, 79%) as a colorless oil.

FTIR (neat), υ_{max}, cm^{-1}: 2937, 1463, 1104.

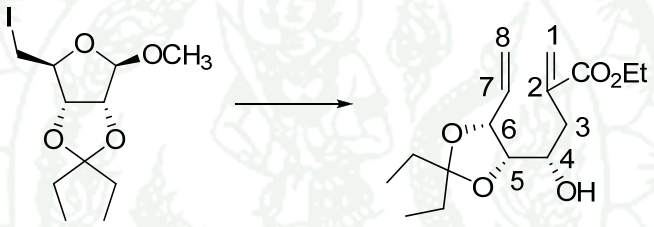
^{1}H NMR (400 MHz, $CDCl_3$), δ 4.99 (s, 1H, H-1), 4.69 (dd, *J* = 6.0, 0.5 Hz, 1H, H-3), 4.56 (d, *J* = 6.0 Hz, 1H, H-2), 4.39 (ddd, *J* = 9.6, 6.4, 0.5 Hz, 1H, H-4), 3.31 (s, 3H, OCH_3), 3.21 (dd, *J* = 9.9, 6.4 Hz, 1H, H-5), 3.10 (dd, *J* = 9.9, 9.7 Hz, 1H, H-

5), 1.63 (q, *J* = 7.5, 2H, CC<u>H</u>$_2$CH$_3$), 1.51 (q, *J* = 7.6, 2H, CC<u>H</u>$_2$CH$_3$), 0.84 (t, *J* = 7.5, 3H, CCH$_2$C<u>H</u>$_3$), 0.81 (t, *J* = 7.6, 3H, CCH$_2$C<u>H</u>$_3$).

^{13}C NMR (100 MHz, $CDCl_3$), δ 116.9 (<u>C</u>(CH$_2$CH$_3$)$_2$), 109.8 (C-1), 87.5 (C-4), 85.6 (C-2), 83.2 (C-3), 55.2 (OCH_3), 29.5 (C<u>C</u>H$_2$CH$_3$), 28.9 (C<u>C</u>H$_2$CH$_3$), 8.3 (CCH$_2$<u>C</u>H$_3$), 7.3 (CCH$_2$<u>C</u>H$_3$), 6.7 (C-5).

HRMS (ESI-TOF) *m/z* [M+Na]$^+$ calcd. for $C_{11}H_{19}O_4NaI$: 365.0226, Found: 365.0226.

2-Carboethoxy-4-hydroxy-5,6-*O*-isopentylidene-1,7-octadiene (49a)



(48) (49a)

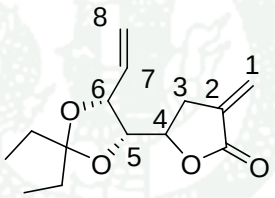
To a solution of methyl 5-deoxy-5-iodo-2,3-*O*-isopentylidene-β-D-ribofuranose (48) (1 g, 2.92 mmol) in 2:1 tetrahydrofuran/water (22 mL) was added zinc powder (1.91 g, 29.22 mmol). The mixture was sonicated at 50 °C for 3 h during which time ethyl 2-(bromomethyl) acrylate (1.61 mL, 11.69 mmol) was added dropwise. The sonication was continued for an additional 1 h and the reaction mixture was then filtered through celite and washed with diethyl ether (100 mL). The filtrate was evaporated and the remaining aqueous solution was extracted with dichloromethane (3x50 mL). The combined organic phases were dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The residue was purified by flash column chromatography (15:85 ethyl acetate:hexane) to provide 2-carboethoxy-4-hydroxy-5,6-*O*-isopentylidene-1,7-octadiene (49a) (0.62 g, 71%) as a colorless oil.

FTIR (neat), υ_{max}, cm^{-1}: 3465, 3079, 2974, 1719.

^{1}H NMR (400 MHz, $CDCl_3$), δ 6.21 (d, *J* = 1.6 Hz, 1H, H-1), 5.97 (m, 1H, H-7), 5.65 (d, *J* = 1.6 Hz, 1H, H-1), 5.35 (ddd, *J* = 17.1, 1.7, 1.3 Hz, 1H, H-8), 5.20 (ddd, *J* = 10.4, 1.7, 1.1 Hz, 1H, H-8), 4.63 (ddd, *J* = 7.0, 6.7, 1.0 Hz, 1H, H-6), 4.16 (dq, *J* = 7.1, 1.7 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 3.89 (dd, *J* = 8.7, 6.7 Hz, 1H, H-5), 3.70 (m, 1H, H-4), 2.80 (ddd, *J* = 14.3, 2.9, 1.0 Hz, 1H, H-3), 2.37 (ddd, *J* = 14.3, 8.4, 0.5 Hz, 1H, H-3), 1.64 (q, *J* = 7.5 Hz, 2H, $CC\underline{H}_2CH_3$), 1.57 (q, *J* = 7.5 Hz, 2H, $CC\underline{H}_2CH_3$), 1.24 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 0.88 (t, *J* = 7.5 Hz, 3H, $CCH_2C\underline{H}_3$), 0.83 (t, *J* = 7.5 Hz, 3H, $CCH_2C\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$), δ 167.2 ($\underline{C}O_2CH_2CH_3$), 136.9 (C-2), 134.4 (C-7), 127.5 (C-1), 119.3 (C-8), 112.3 ($\underline{C}(CH_2CH_3)_2$), 79.9 (C-6), 79.1 (C-5), 68.4 (C-4), 60.7 ($CO_2\underline{C}H_2CH_3$), 37.1 (C-3), 29.2 ($C\underline{C}H_2CH_3$), 28.2 ($C\underline{C}H_2CH_3$), 14.1 ($CO_2CH_2\underline{C}H_3$), 8.6 ($CCH_2\underline{C}H_3$), 7.9 ($CCH_2\underline{C}H_3$).

Spectroscopic data of lactone compound **62**

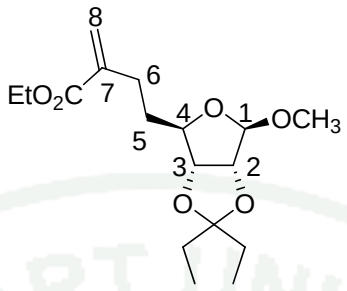


(62)

^{1}H NMR (400 MHz, $CDCl_3$), δ 6.19 (t, *J* = 2.9 Hz, 1H, H-1), 5.87 (m, 1H, H-7), 5.60 (dt, *J* = 2.7, 0.4 Hz, 1H, H-1), 5.43 (dt, *J* = 17.1, 1.5 Hz, 1H, H-8), 5.27 (dt, *J* = 10.5, 1.4 Hz, 1H, H-8), 4.72 (m, 1H, H-6), 4.44 (q, *J* = 7.1 Hz, 1H, H-4), 4.12 (t, *J* = 7.1, 1H, H-5), 2.95 (m, 2H, H-3), 1.66 (dd, *J* = 7.5, 2.1 Hz, 2H, $CC\underline{H}_2CH_3$), 1.60 (t, *J* = 7.5 Hz, 3H, $CC\underline{H}_2CH_3$), 0.89 (t, *J* = 7.5, 3H, $CCH_2C\underline{H}_3$), 0.85 (t, *J* = 7.5, 3H, $CCH_2C\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$), δ 169.9 ($\underline{C}O$), 133.9 (C-2), 132.6 (C-7), 122.2 (C-1), 118.3 (C-8), 112.9 ($\underline{C}(CH_2CH_3)_2$), 78.6 (C-5), 77.6 (C-6), 74.8 (C-4), 30.1 (C-3), 29.2 ($C\underline{C}H_2CH_3$), 28.3 ($C\underline{C}H_2CH_3$), 8.5 ($CCH_2\underline{C}H_3$), 7.8 ($CCH_2\underline{C}H_3$)

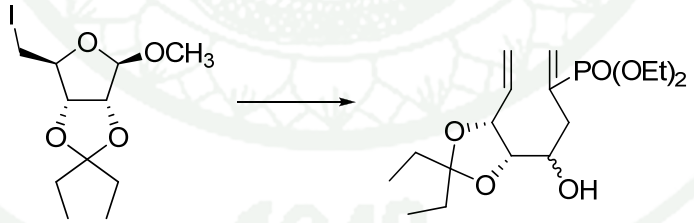
Spectroscopic data of compound **63**



(63)

^{1}H NMR (400 MHz, $CDCl_3$), δ 6.10 (d, *J* = 1.3 Hz, 1H, H-8), 5.49 (q, *J* = 1.3 Hz, 1H, H-8), 4.90 (s, 1H, H-1), 4.54 (d, *J* = 6.0 Hz, 1H, H-3), 4.48 (dd, *J* = 6.0, 0.5 Hz, 1H, H-2), 4.14 (q, *J* = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.11 (m, 1H, H-4), 3.28 (s, 3H, OCH_3), 2.46-2.39 (m, 1H, H-6), 2.35-2.27 (m, 1H, H-6), 1.73-1.57 (m, 1H, H-5), 1.62 (t, *J* = 7.4 Hz, 2H, $CC\underline{H}_2CH_3$), 1.50 (q, *J* = 7.4 Hz, 2H, $CC\underline{H}_2CH_3$), 1.23 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 0.85 (t, *J* = 7.3 Hz, 3H, $CCH_2C\underline{H}_3$), 0.80 (t, *J* = 7.3 Hz, 3H, $CCH_2C\underline{H}_3$).

2-Phosphodiethoxy-4-hydroxy-5,6-*O*-isopentylidene-1,7-octadiene (49b)



(48) (49b)

To a solution of methyl 5-deoxy-5-iodo-2,3-*O*-isopentylidene-β-D-ribofuranose (48) (100 mg, 0.29 mmol) in 2:1 tetrahydrofuran/water (2.5 mL) was added zinc powder (191 mg, 2.92 mmol). The mixture was sonicated at 50 °C for 3 h during which time diethyl 3-bromoprop-1-en-2-ylphosphonate (225 mg, 0.88 mmol) was added dropwise. The sonication was continued for an additional 1 h and the reaction mixture was then filtered through celite and washed with ethyl ether (30 mL).

The filtrate was evaporated and the residue was partitioned between water (25 mL) and ethyl acetate (20 mL). The aqueous layer was extracted with ethyl acetate (3x20 mL). The combined organic phases were dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The residue was purified by flash column chromatography (1:99 methanol:dichloromethane) to provide 2-phosphodiethoxy-4-hydroxy-5,6-*O*-isopentylidene-1,7-octadiene (49b) (72 mg, 68%) (α:β=1:3) as a colorless oil.

Spectroscopic data of **β-49b**

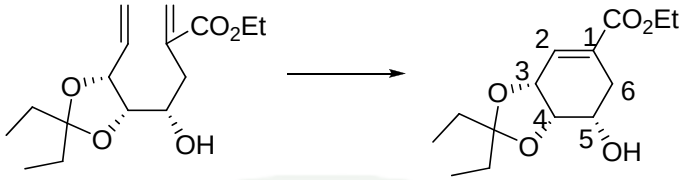
FTIR (neat), υ_{max}, cm^{-1}: 3378, 2977, 1443 1222, 1024.

^{1}H NMR (400 MHz, $CDCl_3$), δ 5.99 (m, 1H, H-7), 5.92 (d, *J* = 1.1 Hz, 1H, H-1), 5.80 (d, *J* = 1.1 Hz, 1H, H-1), 5.38 (ddd, *J* = 17.2, 1.7, 1.3 Hz, 1H, H-8), 5.21 (ddd, *J* = 10.4, 1.6, 1.3 Hz, 1H, H-8), 4.68 (t, *J* = 6.7 Hz, 1H, H-6), 4.16 (dq, *J* = 7.1, 1.6 Hz, 4H, $PO(OC\underline{H}_2CH_3)_2$), 3.93 (dd, *J* = 8.8, 6.6 Hz, 1H, H-4), 3.76 (t, *J* = 8.8 Hz, 1H, H-5), 2.80 (dt, *J* = 14.3, 0.8 Hz, 1H, H-3), 2.40 (m, 1H, H-3), 1.66 (q, *J* = 7.5, 2H, $CC\underline{H}_2CH_3$), 1.61 (q, *J* = 7.5, 2H, $CC\underline{H}_2CH_3$), 1.31 (t, *J* = 7.0, 6H, $PO(OCH_2C\underline{H}_3)_2$), 0.91 (t, *J* = 7.5, 3H, $CCH_2C\underline{H}_3$), 0.86 (t, *J* = 7.5, 3H, $CCH_2C\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$), δ 136.4 (C-2), 134.4 (C-7), 132.3 (C-1), 117.3 (C-8), 112.4 ($\underline{C}(CH_2CH_3)_2$), 79.9 (C-5), 78.7 (C-6), 69.1 (C-4), 62.5 ($PO\underline{C}H_2CH_3$), 62.4 ($PO\underline{C}H_2CH_3$), 38.2 (C-3), 29.8 ($C\underline{C}H_2CH_3$), 28.7 ($C\underline{C}H_2CH_3$), 16.3 ($POCH_2\underline{C}H_3$), 16.2 ($POCH_2\underline{C}H_3$), 8.1 ($CH_2\underline{C}H_3$), 8.6 ($CH_2\underline{C}H_3$).

HRMS (ESI-TOF) *m/z* $[M+Na]_+$ calcd. for $C_{17}H_{31}O_6NaP$: 385.1756, Found: 385.1750.

Ethyl 3,4-*O*-isopentylidene-5-epi-hydroxy shikimate (50a)



(49a) (50a)

To a solution of 2-carboethoxy-4-hydroxy-5,6-*O*-isopentylidene-1,7-octadiene (49a) (60 mg, 0.20 mmol) in dry dichloromethane (5 mL) under nitrogen atmosphere was added a solution of 2nd generation Grubbs' catalyst (17 mg, 10 mol%) in dry dichloromethane (1 mL). The reaction mixture was stirred at refluxing temperature for 4 h. The reaction mixture was concentrated and the residue was purified by flash column chromatography (15:85 ethyl acetate:hexane) to give ethyl 3,4-*O*-isopentylidene-5-epi-hydroxy shikimate (50a) (33 mg, 60%) as a colorless oil.

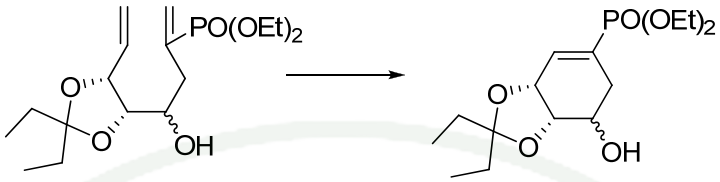
FTIR (neat), υ_{max}, cm^{-1}: 3435, 2977, 1723, 1652, 1237.

^{1}H NMR (400 MHz, $CDCl_3$), δ 6.68 (m, 1H, H-2), 4.68 (m, 1H, H-3), 4.37 (dd, *J* = 5.8, 2.4 Hz, 1H, H-4), 4.14 (dq, *J* = 7.2, 1.3 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 3.83 (m, 1H, H-5), 2.61 (dd, *J* = 16.5, 5.1 Hz, 1H, H-6), 2.37-2.30 (m, 1H, H-6), 1.63-1.50 (m, 4H, $C(C\underline{H}_2CH_3)_2$), 1.23 (dt, *J* = 7.2, 1.3 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 0.85 (dt, *J* = 7.5, 1.2 Hz, 3H, $CCH_2C\underline{H}_3$), 0.77 (dt, *J* = 7.5, 1.4 Hz, 3H, $CCH_2C\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$), δ 166.3 ($\underline{C}O_2CH_2CH_3$), 134.7 (C-2), 129.4 (C-1), 113.6 ($\underline{C}(CH_2CH_3)_2$), 75.5 (C-4), 73.0 (C-3), 67.6 (C-5), 60.9 ($CO_2\underline{C}H_2CH_3$), 29.9 ($C\underline{C}H_2CH_3$), 29.3 ($C\underline{C}H_2CH_3$), 27.4 (C-6), 14.0 ($CO_2CH_2\underline{C}H_3$), 8.3 ($CCH_2\underline{C}H_3$), 7.8 ($CCH_2\underline{C}H_3$).

HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd. for $C_{14}H_{23}O_5H$: 271.1548, Found: 271.1548.

Diethyl (3*R*,4*S*)-3,4-*O*-isopentylidene-5-hydroxy-1-cyclohexene-1-phosphonate (50b)



(49b) (50b)

To a solution of 2-phosphodiethoxy-4-hydroxy-5,6-*O*-isopentylidene-1,7-octadiene (49b) (50 mg, 0.14 mmol) in dry dichloromethane (5 mL) under nitrogen atmosphere was added a solution of 2nd generation Grubbs' catalyst (12 mg, 10 mol%) in dry dichloromethane (1 mL). The reaction mixture was stirred at refluxing temperature for 4 h. The reaction mixture was concentrated and the residue was purified by flash column chromatography (100% acetate:hexane) to give diethyl (3*R*,4*S*)-3,4-*O*-isopentylidene-5-hydroxy-1-cyclohexene-1-phosphonate (50b) (26 mg, 57%) as a colorless oil.

Spectroscopic data of **β-50b**

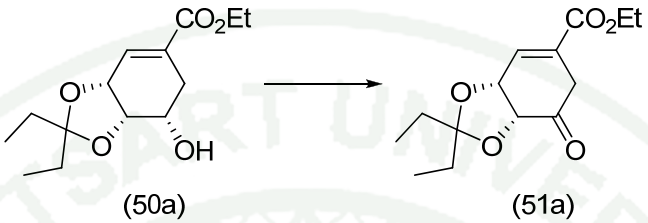
FTIR (neat), υ_{max}, cm^{-1}: 3412, 2982, 1640, 1265, 1025, 738.

^{1}H NMR (400 MHz, $CDCl_3$), δ 6.66 (m, 1H, H-2), 4.63 (m, 1H, H-3), 4.07 (m, 1H, H-4), 4.03 (m, 4H, $PO(OC\underline{H}_2CH_3)_2$), 3.84 (ddd, *J* = 11.7, 7.5, 4.3 Hz, 1H, H-5), 2.55-2.48 (m, 1H, H-6), 2.17-2.09 (m, 1H, H-6), 1.63-1.55 (m, 4H, $C(C\underline{H}_2CH_3)_2$), 1.26 (m, 6H, $PO(OCH_2C\underline{H}_3)_2$), 0.85 (t, *J* = 7.5 Hz, 3H, $CCH_2C\underline{H}_3$), 0.81 (t, *J* = 7.3 Hz, 3H, $CCH_2C\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$), δ 137.9 (C-2), 128.9 (d, *J* = 160.0 Hz, C-1), 113.2 ($\underline{C}(CH_2CH_3)_2$), 76.3 (C-4), 71.9 (C-3), 67.8 (C-5), 62.2 ($PO\underline{C}H_2CH_3$), 62.1 ($PO\underline{C}H_2CH_3$), 29.3 ($C\underline{C}H_2CH_3$), 29.1 ($C\underline{C}H_2CH_3$), 28.9 (C-6), 16.2 ($POCH_2\underline{C}H_3$), 16.1 ($POCH_2\underline{C}H_3$), 8.2 ($CCH_2\underline{C}H_3$), 7.8 ($CCH_2\underline{C}H_3$).

HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd. for $C_{15}H_{27}O_6NaP$: 357.1443, Found: 357.1447.

Ethyl 3,4-*O*-isopentylidene-5-keto shikimate (51a)



To a cooled suspension of trichloroisocyanuric acid (3.44 g, 14.82 mmol) in dry dichloromethane (38 mL) was added 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) (11.6 mg, 0.074 mmol) followed by solution of ethyl 3,4-*O*-isopentylidene-5-epi-hydroxy shikimate (50a) (2.00 g, 7.41 mmol) in dry dichloromethane (5 mL). The mixture was stirred at room temperature for 45 min. After this time, the reaction mixture was filtered through celite and concentrated under reduced pressure. The crude ethyl 3,4-*O*-isopentylidene-5-keto shikimate (51a) was used in the next step without further purification (for spectroscopic data : the crude ethyl 3,4-*O*-isopentylidene-5-keto shikimate (51a) was purified by flash column chromatography (20:80 ethyl acetate:hexane) to give ethyl 3,4-*O*-isopentylidene-5-keto shikimate (51a) as a colorless oil).

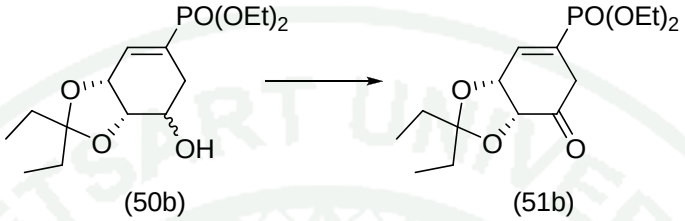
FTIR (neat), υ_{max}, cm^{-1}: 2976, 1720, 1659, 1463, 1251.

^{1}H NMR (400 MHz, $CDCl_3$), δ 6.89(m, 1H, H-2), 5.00 (m, 1H, H-3), 4.38 (d, *J* = 6.5, 1H, H-4), 4.18 (q, *J* = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 3.36-3.29 (dt, *J* = 19.5, 1.8 Hz, 1H, H-6), 3.17-3.10 (d, *J* = 19.5 Hz, 1H, H-6), 1.60 (m, 4H, $C(C\underline{H}_2CH_3)_2$), 1.25 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 0.85 (t, *J* = 7.5 Hz, 3H, $CCH_2C\underline{H}_3$), 0.81 (t, *J*=7.5 Hz, 3H, $CCH_2C\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$), δ 203.2 (C-5), 165.0 ($\underline{C}O_2CH_2CH_3$), 133.7 (C-2), 129.1 (C-1), 115.5 ($\underline{C}(CH_2CH_3)_2$), 77.4 (C-4), 75.9 (C-3), 61.4 ($CO_2\underline{C}H_2CH_3$),

36.5 (C-6), 29.9 (C<u>C</u>H$_2$CH$_3$), 29.2 (C<u>C</u>H$_2$CH$_3$), 14.0 (CO$_2$CH$_2$<u>C</u>H$_3$), 8.2 (CCH$_2$<u>C</u>H$_3$), 8.0 (CCH$_2$<u>C</u>H$_3$).

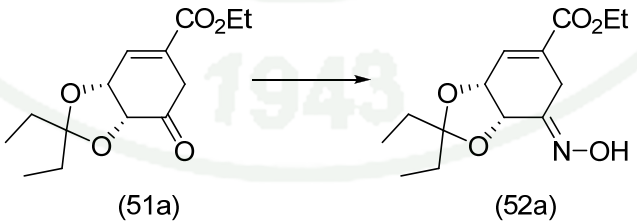
Diethyl (3*R*,4*S*)-3,4-*O*-isopentylidene-5-keto-1-cyclohexene-1-phosphonate (51b)



(50b) (51b)

To a cooled suspension of trichloroisocyanuric acid (0.69 g, 2.99 mmol) in dry dichloromethane (3.5 mL) was added 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) (11.5 mg, 0.075 mmol) followed by solution of diethyl (3*R*,4*S*)-3,4-*O*-isopentylidene-5-hydroxy-1-cyclohexene-1-phosphonate (50b) (500 mg, 1.50 mmol) in dry dichloromethane (1 mL). The mixture was stirred at room temperature for 45 min. After this time, the reaction mixture was filtered through celite and concentrated under reduced pressure. The crude diethyl (3*R*,4*S*)-3,4-*O*-isopentylidene-5-keto-1-cyclohexene-1-phosphonate (51b) (507 mg) was used in the next step without further purification.

Ethyl 3,4-*O*-isopentylidene-5-oxime shikimate (52a)



(51a) (52a)

To the crude ethyl 3,4-*O*-isopentylidene-5-keto shikimate (51a) (7.41 mmol) in ethanol (14 mL) was added hydroxylamine hydrochloride (1.43 g, 14.81 mmol) followed by pyridine (14 mL). The reaction mixture was stirred at room temperature for 2 h. The solution was poured into water and extracted with dry dichloromethane (3x50 mL). The combined organic layers were dried over anhydrous sodium sulfate,

filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (20:80 ethyl acetate:hexane) to give ethyl 3,4-*O*-isopentylidene-5-oxime shikimate (52a) (1.55 g, 71%, 2 steps) as a yellow oil.

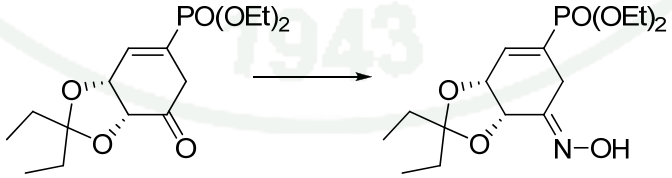
FTIR (neat), υ_{max}, cm^{-1}: 3382, 2976, 1716, 1661, 1241.

^{1}H NMR (400 MHz, $CDCl_3$), δ 6.80 (s, 1H, H-2), 4.85 (s, 1H, H-3), 4.69 (d, *J* = 5.4 Hz, 1H, H-4), 4.25 (q, *J* = 7.2 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 3.81 (dt, *J* = 21.6 Hz, 1H, H-6), 3.00 (d, *J* = 21.6 Hz, 1H, H-6), 1.65 (m, 4H, $C(C\underline{H}_2CH_3)_2$), 1.33 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 0.93 (t, *J* = 7.5 Hz, 3H, $CCH_2C\underline{H}_3$), 0.85 (t, *J*=7.5 Hz, 3H, $CCH_2C\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$), δ 166.1 ($\underline{C}O_2CH_2CH_3$), 152.5 (C-5), 135.6 (C-2), 126.8 (C-1), 114.3 ($\underline{C}(CH_2CH_3)_2$), 73.5 (C-3), 73.4 (C-4), 61.1 ($CO_2\underline{C}H_2CH_3$), 30.3 ($C\underline{C}H_2CH_3$), 29.5 ($C\underline{C}H_2CH_3$), 20.8 (C-6), 14.0 ($CO_2CH_2\underline{C}H_3$), 8.1 ($CCH_2\underline{C}H_3$), 8.0 ($CCH_2\underline{C}H_3$).

HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd. for $C_{14}H_{22}NO_4H$: 284.1498, Found: 284.1498.

Diethyl (3*R*,4*S*)-3,4-*O*-isopentylidene-5-oxime-1-cyclohexene-1-phosphonate (52b)



(51b) (52b)

To the crude diethyl (3*R*,4*S*)-3,4-*O*-isopentylidene-5-keto-1-cyclohexene-1-phosphonate (51b) (507 mg) in ethanol (3 mL) was added hydroxylamine hydrochloride (208 mg, 2.99 mmol) followed by pyridine (3 mL). The reaction mixture was stirred at room temperature for 2 h. The solution was poured into water

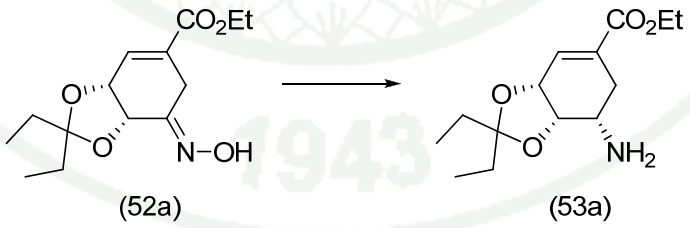
and extracted with ethyl acetate (3x30 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (100% ethyl acetate) to give diethyl (3*R*,4*S*)-3,4-*O*-isopentylidene-5-oxime-1-cyclohexene-1-phosphonate (52b) (260 mg, 50%, 2 steps) as a yellow oil.

FTIR (neat), υ_{max}, cm^{-1}: 3224, 2979, 2360, 1620, 1463, 1227, 1021.

^{1}H NMR (400 MHz, $CDCl_3$), δ 6.58 (dd, *J* = 21.7, 0.9 Hz, 1H, H-2), 4.77 (s, 1H, H-3), 4.66 (d, *J* = 5.5 Hz, 1H, H-4), 4.09 (q, *J* = 7.3 Hz, 4H, $PO(OC\underline{H}_2CH_3)_2$), 3.69 (dd, *J* = 21.0, 6.7 Hz, 1H, H-6), 2.86 (m, 1H, H-6), 1.65 (m 4H, $C(C\underline{H}_2CH_3)_2$), 1.32 (dt, *J* = 7.0, 2.1 Hz, 6H, $PO(OCH_2C\underline{H}_3)_2$), 0.91 (t, *J* = 7.4 Hz, 3H, $CCH_2C\underline{H}_3$), 0.85 (t, *J*=7.4 Hz, 3H, $CCH_2C\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$), δ 152.0 (C-5), 139.6 (C-2), 125.2 (d, *J* = 190.0 Hz, C-1), 114.3 ($\underline{C}(CH_2CH_3)_2$), 73.9 (C-3), 73.8 (C-4), 62.2 ($PO\underline{C}H_2CH_3$), 62.1 ($PO\underline{C}H_2CH_3$), 30.3 ($C\underline{C}H_2CH_3$), 29.8 ($C\underline{C}H_2CH_3$), 20.3 (C-6), 16.3 ($POCH_2\underline{C}H_3$), 16.2 ($POCH_2\underline{C}H_3$), 8.2 ($CCH_2\underline{C}H_3$), 8.1 ($CCH_2\underline{C}H_3$).

Ethyl 3,4-*O*-isopentylidene-5α-amino shikimate (53a)



(52a) (53a)

To a suspension of ethyl 3,4-*O*-isopentylidene-5-oxime shikimate (52a) (511 mg, 1.73 mmol) and molybdenum(VI) oxide (344 mg, 2.39 mmol) in methanol (17 mL) was added sodium borohydride (654 mg, 17.3 mmol) portionwise. An exothermic reaction occurred with vigorous gas. The reaction mixture was stirred at room temperature for 30 min or TLC complete. To the reaction mixture was added brine and the precipitate was filtered off. The filtrate was extracted with ethyl acetate

(3x10mL). The combined organic layer were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give ethyl 3,4-*O*-isopentylidene-5α-amino shikimate (53a) (448 mg, 92 %) as a yellow-brown oil.

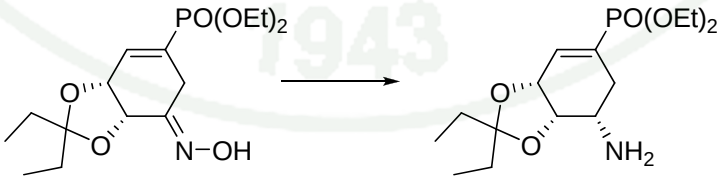
FTIR (neat), υ_{max}, cm^{-1}: 3364, 2974, 1718, 1651, 1463, 1246.

^{1}H NMR (400 MHz, $CDCl_3$), δ 6.66 (t, *J*= 2.8 Hz, 1H, H-2), 4.66 (m, 1H, H-3), 4.26 (d, *J*= 4.9 Hz, 1H, H-4), 4.14 (q, *J*= 7.2 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 2.95 (m, 1H, H-5), 2.51 (dt, *J*= 5.2, 11.9 Hz, 1H, H-6), 2.13 (m, 1H, H-6), 1.59 (m, 2H, $CC\underline{H}_2CH_3$), 1.50 (q, *J*= 7.54 Hz, 2H, $CC\underline{H}_2CH_3$),1.23 (t, *J*= 7.2 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 0.85 (t, *J*=7.54 Hz, 3H, $CCH_2C\underline{H}_3$), 0.75 (t, *J*=7.54 Hz, 3H, $CCH_2C\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$), δ 166.5 ($\underline{C}O_2CH_2CH_3$), 134.9 (C-2), 130.5 (C-1), 113.1 ($\underline{C}(CH_2CH_3)_2$), 76.6 (C-4), 73.1 (C-3), 60.8 ($CO_2\underline{C}H_2CH_3$), 49.3 (C-5), 30.0 (C-6), 29.5 ($C\underline{C}H_2CH_3$), 28.7 ($C\underline{C}H_2CH_3$), 14.1 ($CO_2CH_2\underline{C}H_3$), 8.4 ($CCH_2\underline{C}H_3$), 7.9 ($CCH_2\underline{C}H_3$).

HRMS (ESI-TOF) *m/z* $[M+H]_+$ calcd. for $C_{14}H_{24}NO_4H$: 270.1705, Found: 270.1705.

Diethyl (3*R*,4*R*,5*S*)-3,4-*O*-isopentylidene-5-amino-1-cyclohexene-1-phosphonate (53b)



(52b) (53b)

To a suspension of ethyl diethyl (3*R*,4*S*)-3,4-*O*-isopentylidene-5-oxime-1-cyclohexene-1-phosphonate (52b) (150 mg, 1.43 mmol) and molybdenum(VI) oxide (866 mg, 0.60 mmol) in methanol (5 mL) was added sodium borohydride (164 mg, 4.3 mmol) portionwise. An exothermic reaction occurred with vigorous gas. The

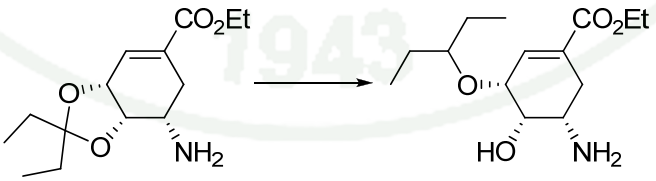
reaction mixture was stirred at room temperature for 2 h. To the reaction mixture was added brine and the precipitate was filtered off. The filtrate was extracted with ethyl acetate (3x30mL). The combined organic layer were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give diethyl (3*R*,4*R*,5*S*)-3,4-*O*-isopentylidene-5-amino-1-cyclohexene-1-phosphonate (53b) (73 mg, 51%) as a yellow oil.

FTIR (neat), υ_{max}, cm^{-1}: 3434, 2977, 1641, 1463, 1236, 1022.

^{1}H NMR (300 MHz, $CDCl_3$), δ 6.52 (dt, *J* = 20.9, 2.9 Hz, 1H, H-2), 4.68 (m, 1H, H-3), 4.34 (d, *J* = 2.9, 1H, H-4), 4.17 (m, 4H, $PO(OC\underline{H}_2CH_3)_2$), 3.05 (m, 1H, H-5), 2.45-2.15 (m, 2H, H-6), 1.70-1.55 (m, 4H, $C(C\underline{H}_2CH_3)_2$), 1.31 (m, 6H, $PO(OCH_2C\underline{H}_3)_2$), 0.91 (t, *J* = 7.9 Hz, 3H, $CCH_2C\underline{H}_3$), 0.83 (t, *J* = 7.4 Hz, 3H, $CCH_2C\underline{H}_3$).

^{13}C NMR (75 MHz, $CDCl_3$), δ 138.8 (C-2), 128.8 (d, *J* = 179.3 Hz, C-1), 113.3 ($\underline{C}(CH_2CH_3)_2$), 76.5 (C-4), 73.4 (C-3), 62.0 ($PO\underline{C}H_2CH_3$), 61.9 ($PO\underline{C}H_2CH_3$), 49.2 (C-5), 30.1 ($C\underline{C}H_2CH_3$), 29.7 ($C\underline{C}H_2CH_3$), 28.9 (C-6), 16.4 ($POCH_2\underline{C}H_3$), 16.3 ($POCH_2\underline{C}H_3$), 8.4 ($CCH_2\underline{C}H_3$), 8.0 ($CCH_2\underline{C}H_3$).

Ethyl (3*R*,4*S*,5*S*)-3-(1-ethyl-propoxy)-4-hydroxy-5-amino-1-cyclohexene-1-carboxylate (54a)



(53a) (54a)

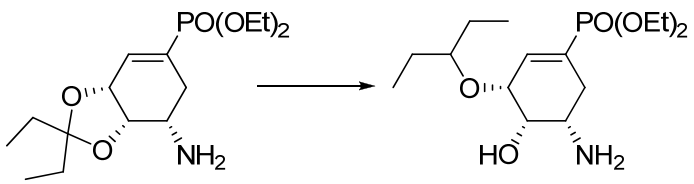
To a solution of ethyl 3,4-*O*-isopentylidene-5α-amino shikimate (53a) (2 g, 7.12 mmol) in dry dichloromethane (20 mL) under nitrogen atmosphere at -78 °C was added triethylsilane (1.5 mL, 9.26 mmol). A solution of titanium tetrachloride (0.97 mL, 8.54 mmol) was added dropwise. The reaction mixture was warmed to -10 °C

and stirred at this temperature for 16 h. Titanium tetrachloride (0.23 mL, 2.14 mmol) was added and stirred for 1 h. 10% Ammonium hydroxide solution (5 mL) was added and the suspension was filtered. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3x50mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude ethyl (3*R*,4*S*,5*S*)-3-(1-ethyl-propoxy)-4-hydroxy-5-amino-1-cyclohexene-1-carboxylate (54a) was used in the next step without further purification (for the spectroscopic data : the crude product was purified by flash column chromatography (10:90 methanol:dichloromethane) to give ethyl (3*R*,4*S*,5*S*)-3-(1-ethyl-propoxy)-4-hydroxy-5-amino-1-cyclohexene-1-carboxylate (54a) as a yellow solid).

^{1}H NMR (400 MHz, $CDCl_3$), δ 6.60 (s, 1H, H-2), 4.13 (q, *J*= 7.2 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.03 (m, 1H, H-3), 3.94 (m, 1H, H-4), 3.35 (quint, *J*= 5.7 Hz, 1H, $C\underline{H}(CH_2CH_3)_2$), 2.91 (q, *J*= 5.9, 2.5 Hz, 1H, H-5), 2.46 (dd, *J*= 5.3, 12.1 Hz, 1H, H-6), 2.20 (m, 1H, H-6), 1.50 (m, 4H,$CH(C\underline{H}_2CH_3)_2$), 1.22 (t, *J*= 7.2 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 0.87 (t, *J*=7.4 Hz, 3H, $CHCH_2C\underline{H}_3$), 0.86 (t, *J*=7.4 Hz, 3H, $CHCH_2C\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$), δ 166.4 ($\underline{C}O_2CH_2CH_3$), 135.8 (C-2), 130.6 (C-1), 81.6 ($\underline{C}H(CH_2CH_3)_2$), 74.4 (C-3), 69.8 (C-4), 60.7 ($CO_2\underline{C}H_2CH_3$), 49.7 (C-5), 29.7 (C-6), 26.3 ($CH\underline{C}H_2CH_3$), 26.1 ($CH\underline{C}H_2CH_3$), 14.2 ($CO_2CH_2\underline{C}H_3$), 9.7 ($CHCH_2\underline{C}H_3$), 9.4 ($CHCH_2\underline{C}H_3$).

Diethyl (3*R*,4*S*,5*S*)-3-(1-ethyl-propoxy)-4-hydroxy-5-amino-1-cyclohexene-1-phosphonate (54b)

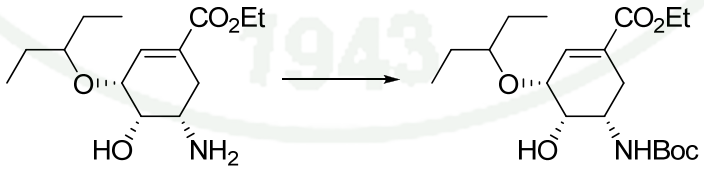


(53b) (54b)

To a solution of diethyl (3*R*,4*R*,5*S*)-3,4-*O*-isopentylidene-5-amino-1-cyclohexene-1-phosphonate (53b) (95 mg, 0.28 mmol) in dry dichloromethane (1 mL) under nitrogen atmosphere at -78 °C was added triethylsilane (0.08 mL, 0.49 mmol). A solution of titanium tetrachloride (0.04 mL, 0.32 mmol) was added dropwise. The reaction mixture was warmed to -10 °C and stirred at this temperature for 16 h. 10% Ammonium hydroxide solution (1 mL) was added and the suspension was filtered. Ethanol (2 mL) was added to the filtrate and the mixture was concentrated under reduced pressure. The crude diethyl (3*R*,4*S*,5*S*)-3-(1-ethyl-propoxy)-4-hydroxy-5-amino-1-cyclohexene-1-phosphonate (54b) was used in the next step without further purification (for the spectroscopic data : the crude product was purified by flash column chromatography (10:90 methanol:dichloromethane) to give diethyl (3*R*,4*S*,5*S*)-3-(1-ethyl-propoxy)-4-hydroxy-5-amino-1-cyclohexene-1-phosphonate (54b) as a yellow oil).

^{1}H NMR (400 MHz, $CDCl_3$), δ 6.40 (d, *J* = 21.4 Hz, 1H, H-2), 4.19 (br s, 1H, H-3) 3.99 (m, 4H, $PO(OC\underline{H}_2CH_3)_2$), 3.92 (br s, 1H, H-4), 3.54 (m, 1H, H-5), 3.33 (quint, *J*= 5.6 Hz, 1H, $C\underline{H}(CH_2CH_3)_2$), 2.37-2.27 (m, 1H, H-6), 2.18-2.09 (m, 1H, H-6), 1.63 (m, 4H, $CH(C\underline{H}_2CH_3)_2$), 1.26 (m, 6H, $PO(OCH_2C\underline{H}_3)_2$), 0.85 (t, *J* = 7.5 Hz, 3H, $CHCH_2C\underline{H}_3$), 0.83 (t, *J* = 7.3 Hz, 3H, $CHCH_2C\underline{H}_3$).

Ethyl (3*R*,4*S*,5*S*)-3-(1-ethyl-propoxy)-4-hydroxy-5-*tert*-butoxycarbonylamino-1-cyclohexene-1-carboxylate (55a)



(54a) (55a)

To a solution of crude ethyl (3*R*,4*S*,5*S*)-3-(1-ethyl-propoxy)-4-hydroxy-5-amino-1-cyclohexene-1-carboxylate (54a) (7.12 mmol) in methanol (30 mL) was added di-*tert*-butyl dicarbonate (2.33 g, 10.7 mmol) and stirred at room temperature for 3 h. The solvent was removed under reduced pressure. The crude product was

purified by flash column chromatography (80:20 ethyl acetate:hexane) to give ethyl (3*R*,4*S*,5*S*)-3-(1-ethyl-propoxy)-4-hydroxy-5-*tert*-butoxycarbonylamino-1-cyclohexene-1-carboxylate (55a) as a yellow solid (2.72 g, 66%, 2 steps).

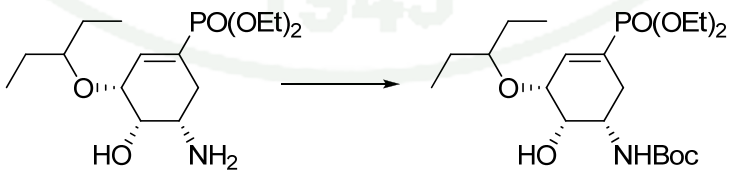
FTIR (KBr), υ_{max}, cm^{-1}: 3390, 2973, 1714, 1505, 1246.

^{1}H NMR (400 MHz, $CDCl_3$), δ 6.65 (s, 1H, H-2), 5.16 (d, *J* = 8.1 Hz, 1H, NH), 4.18(q, *J* = 7.2 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.13 (s, 1H, H-3), 4.02 (s, 1H, H-4), 3.85 (q, *J* = 9.1, 6.1 Hz, 1H, H-5), 3.40 (quint, *J* = 5.7 Hz, 1H, $C\underline{H}(CH_2CH_3)_2$), 2.57 (dd, *J* = 5.7, 11.8 Hz, 1H, H-6), 2.51 (br s, 1H, OH), 2.30(m, 1H, H-6), 1.54 (m, 4H, $CH(C\underline{H}_2CH_3)_2$), 1.43 (s, 9H, $C(C\underline{H}_3)_3$), 1.27 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 0.91 (t, *J* = 7.4 Hz, 6H, $CH(CH_2C\underline{H}_3)_2$).

^{13}C NMR (100 MHz, $CDCl_3$), δ 166.1 ($\underline{C}O_2CH_2CH_3$), 155.4 ($NH\underline{C}O_2t$-Bu), 135.6 (C-2), 130.5 (C-1), 81.6 ($\underline{C}H(CH_2CH_3)_2$), 79.5 ($\underline{C}(CH_3)_3$), 73.7 ($CO_2\underline{C}H_2CH_3$), 68.0 (C-4), 60.8 (C-3), 48.6 (C-5), 28.3 ($C(\underline{C}H_3)_3$), 27.0 (C-6), 26.2 ($CH\underline{C}H_2CH_3$), 26.0 ($CH\underline{C}H_2CH_3$), 14.1 ($CO_2CH_2\underline{C}H_3$), 9.6 ($CH\underline{C}H_2CH_3$), 9.3 ($CHCH_2\underline{C}H_3$).

HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd. for $C_{19}H_{33}NO_6Na$: 394.2206, Found: 394.2206.

Diethyl (3*R*,4*S*,5*S*)-3-(1-ethyl-propoxy)-4-hydroxy-5-*tert*-butoxycarbonylamino-1-cyclohexene-1-phosphate (55b)



(54b) (55b)

To a solution of crude diethyl (3*R*,4*S*,5*S*)-3-(1-ethyl-propoxy)-4-hydroxy-5-amino-1-cyclohexene-1-phosphonate (54b) (0.28 mmol) in methanol (2 mL) was added di-*tert*-butyl dicarbonate (98 mg, 0.45 mmol) and stirred at room temperature

for 3 h. The solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (100% ethyl acetate) to give diethyl (3*R*,4*S*,5*S*)-3-(1-ethyl-propoxy)-4-hydroxy-5-*tert*-butoxycarbonylamino-1-cyclohexene-1-phosphate (55b) (31 mg, 25%, 2 steps) as a pale yellow oil.

FTIR (neat), υ_{max}, cm^{-1}: 3429, 2976, 1642, 1503, 1244, 1021.

^{1}H NMR (400 MHz, $CDCl_3$), δ 6.42 (d, *J* = 21.1 Hz, 1H, H-2), 5.07 (d, *J*= 8.1 Hz, 1H, NH), 4.04-3.92 (m, 6H, H-3, H-4, $PO(OC\underline{H}_2CH_3)_2$), 3.54 (quint, *J* = 5.7 Hz, 1H, $C\underline{H}(CH_2CH_3)_2$), 2.39-2.30 (m, 1H, H-6), 2.21-2.15 (m, 1H, H-6), 1.43 (m, 4H, $C(C\underline{H}_2CH_3)_2$), 1.23 (m, 6H, $PO(OCH_2C\underline{H}_3)_2$), 0.83 (t, *J* = 7.5 Hz, 3H, $CHCH_2C\underline{H}_3$), 0.79 (t, *J* = 7.3 Hz, 3H, $CHCH_2C\underline{H}_3$).

^{13}C NMR (75 MHz, $CDCl_3$), δ 155.3 ($NH\underline{C}O_2t$-Bu), 139.6 (C-2), 128.6 (d, *J* = 179.3 Hz, C-1), 81.7 ($\underline{C}H(CH_2CH_3)_2$), 79.8 ($\underline{C}(CH_3)_3$), 73.7 (C-4), 68.1 (C-3), 62.0 ($PO\underline{C}H_2CH_3$), 61.9 ($PO\underline{C}H_2CH_3$), 48.7 (C-5), 31.2 ($CH\underline{C}H_2CH_3$), 30.7 ($CH\underline{C}H_2CH_3$), 28.4 ($C(\underline{C}H_3)_3$), 26.1 (C-6), 16.4 ($POCH_2\underline{C}H_3$), 16.3 ($POCH_2\underline{C}H_3$), 9.9 ($CHCH_2\underline{C}H_3$), 9.8 ($CHCH_2\underline{C}H_3$).

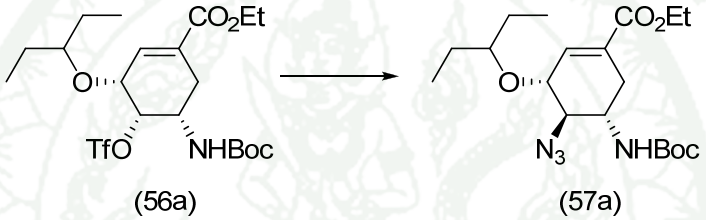
Ethyl (3*R*,4*S*,5*S*)-3-(1-ethyl-propoxy)-4-trifluoromethanesulfonyloxy-5-*tert*-butoxycarbonylamino-1-cyclohexene-1-carboxylate (56a)

(55a) (56a)

To a solution of ethyl (3*R*,4*S*,5*S*)-3-(1-ethyl-propoxy)-4-hydroxy-5-*tert*-butoxycarbonylamino-1-cyclohexene-1-carboxylate (55a) (0.62 g, 1.67 mmol) and pyridine (0.27 mL, 3.33 mmol) in dry dichloromethane (8.5 mL) at -10 °C under nitrogen atmosphere was added dropwise trifluoromethanesulfonic anhydride (0.33 mL, 1.83 mmol). The mixture was stirred at 0 °C for 30 min. To the cooled reaction

mixture was added water (10 mL). The organic phase was separated and aqueous phase was extracted with dichloromethane (3x30 mL). The combined organic phases were washed with saturated aqueous sodium hydrogen carbonate (50 mL) and brine (50 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to dryness to provide the crude ethyl (3*R*,4*S*,5*S*)-3-(1-ethyl-propoxy)-4-trifluoromethanesulfonyloxy-5-*tert*-butoxycarbonylamino-1-cyclohexene-1-carboxylate (56a).

Ethyl (3*R*,4*R*,5*S*)-3-(1-ethyl-propoxy)-4-azido-5-*tert*-butoxycarbonylamino-1-cyclohexene-1-carboxylate (57a)



The crude ethyl (3*R*,4*S*,5*S*)-3-(1-ethyl-propoxy)-4-trifluoromethanesulfonyl oxy-5-*tert*-butoxycarbonylamino-1-cyclohexene-1-carboxylate (56a) was dissolved in 9:1 acetone/water (5 mL) and sodium azide (0.12 g, 1.83 mmol) was added to the solution. The reaction mixture was stirred at room temperature for 15 h. The solvent was evaporated and the residue was dissolved in ethyl acetate (50 mL). The organic phase was washed with water (2x30 mL) and brine (30 mL). The aqueous phase was extracted with ethyl acetate (50 mL) and the combined organic phases were dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The crude ethyl (3*R*,4*R*,5*S*)-3-(1-ethyl-propoxy)-4-azido-5-*tert*-butoxycarbonylamino-1-cyclohexene-1-carboxylate (57a) (0.8291 g) was used in the next step without further purification.

FTIR (neat), υ_{max}, cm^{-1}: 3343, 2937, 2108, 1715, 1687, 1530, 1255.

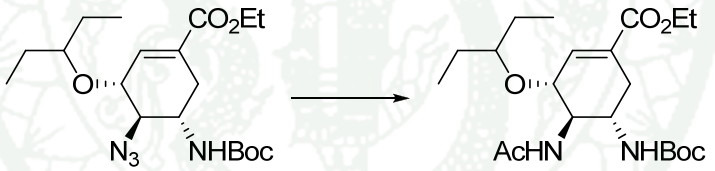
^{1}H NMR (400 MHz, $CDCl_3$), δ 6.70 (ddd, *J* = 3.7, 2.5, 1.5 Hz, 1H, H-2), 4.85 (d, *J* = 6.2 Hz, 1H, N<u>H</u>Boc), 4.52 (q, *J* = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 3.94 (m, 1H, H-3), 3.75 (m, 1H, H-4), 3.53 (dd, *J* = 9.6, 6.8 Hz, 1H, H-5), 3.39 (quint, *J* = 5.7 Hz, 1H,

C<u>H</u>(CH_2CH_3)$_2$), 2.70 (ddd, *J* = 18.0, 5.5, 1.5 Hz, 1H, H-6), 2.26 (ddd, *J* = 18.0, 8.6, 2.5 Hz, 1H, H-6), 1.44-1.54 (m, 4H, CH(C<u>H</u>$_2$CH$_3$)$_2$), 1.39 (s, 9H, C(C<u>H</u>$_3$)$_3$), 1.22 (t, *J* = 7.1, 3H, CO_2CH_2C<u>H</u>$_3$), 0.87 (t, *J* = 7.3, 3H, $CHCH_2C$<u>H</u>$_3$), 0.85 (t, *J* = 7.4, 3H, $CHCH_2C$<u>H</u>$_3$).

^{13}C NMR (100 MHz, $CDCl_3$), δ 165.9 (<u>C</u>$O_2CH_2CH_3$), 155.2 (NH<u>C</u>O_2*t*-Bu), 135.8 (C-2), 129.4 (C-1), 82.1 (<u>C</u>H(CH_2CH_3)$_2$), 80.0 (<u>C</u>(CH_3)$_3$), 75.3 (CO_2<u>C</u>H_2CH_3), 65.1 (C-3), 61.0 (C-4), 48.4 (C-5), 30.2 (C-6), 28.3 (C(<u>C</u>H_3)$_3$), 26.2 (CH<u>C</u>H_2CH_3), 25.6 (CH<u>C</u>H_2CH_3), 14.2 (CO_2CH_2<u>C</u>H_3), 9.5 ($CHCH_2$<u>C</u>H_3), 9.4 ($CHCH_2$<u>C</u>H_3).

HRMS (ESI-TOF) *m/z* [M+Na]$^+$ calcd. for $C_{19}H_{32}N_4O_5Na$: 419.2270, Found: 419.2265.

Ethyl (3*R*,4*R*,5*S*)-3-(1-ethyl-propoxy)-4-acetamido-5-*tert*-butoxycarbonylamino-1-cyclohexene-1-carboxylate (46a)



(57a) (46a)

The crude ethyl (3*R*,4*R*,5*S*)-3-(1-ethyl-propoxy)-4-azido-5-*tert*-butoxy carbonylamino-1-cyclohexene-1-carboxylate (57a) (0.83 g) and 2,6-lutidine (1.94 mL, 16.67 mmol) in chloroform (3 mL) was added thioacetic acid (1.19 mL, 16.67 mmol) and stirred for 5 h at refluxing temperature. The solvent was evaporated and the residue was purified by flash column chromatography (1:99 methanol:dichloromethane) to give ethyl (3*R*,4*R*,5*S*)-3-(1-ethyl-propoxy)-4-acetamido-5-*tert*-butoxycarbonylamino-1-cyclohexene-1-carboxylate (46a) (5.82 g, 71%) as a white solid.

FTIR (KBr), υ_{max}, cm^{-1}: 3312, 2958, 1714, 1685, 1246.

^{1}H NMR (400 MHz, $CDCl_3$), δ 6.72 (dd, *J* = 2.3, 1.6 Hz, 1H, H-2), 5.72 (d, *J* = 9.2 Hz, 1H, NHAc), 5.04 (d, *J* = 9.0 Hz, 1H, NHBoc), 4.13 (dq, *J* = 7.1, 1.6 Hz, 2H, $CO_2CH_2CH_3$), 4.00 (q, *J* = 9.2 Hz, 1H, H-3), 3.53 (d, *J* = 7.7 Hz, 1H, H-4), 3.72 (m, 1H, H-5), 3.28 (quint, *J* = 5.7 Hz, 1H, $CH(CH_2CH_3)_2$), 2.67 (dd, *J* = 17.5, 5.2Hz, 1H, H-6), 2.22 (ddd, *J* = 17.5, 9.8, 2.5 Hz, 1H, H-6), 1.91 (s, 3H, $NHCOCH_3$), 1.43 (m, 4H, $CH(CH_2CH_3)_2$), 1.35 (s, 9H, $C(CH_3)_3$), 1.22 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 0.83 (t, *J* = 7.4, 3H, $CHCH_2CH_3$), 0.81 (t, *J* = 7.6, 3H, $CHCH_2CH_3$).

^{13}C NMR (100 MHz, $CDCl_3$), δ 170.8 ($NHCOCH_3$), 166.0 ($CO_2CH_2CH_3$), 156.3 ($NHCO_2t$-Bu), 137.6 (C-2), 129.3 (C-1), 82.2 ($CH(CH_2CH_3)_2$), 79.7 ($C(CH_3)_3$), 75.9 ($CO_2CH_2CH_3$), 60.9 (C-3), 54.4 (C-4), 49.0 (C-5), 31.0 (C-6), 28.3 ($CHCH_2CH_3$), 26.1 ($CHCH_2CH_3$), 25.7 (C-6), 23.4 ($NHCOCH_3$), 14.2 ($CO_2CH_2CH_3$), 9.5 ($CHCH_2CH_3$), 9.2 ($CHCH_2CH_3$).

HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd. for $C_{21}H_{36}N_2O_6Na$: 435.2471, Found: 435.2471.

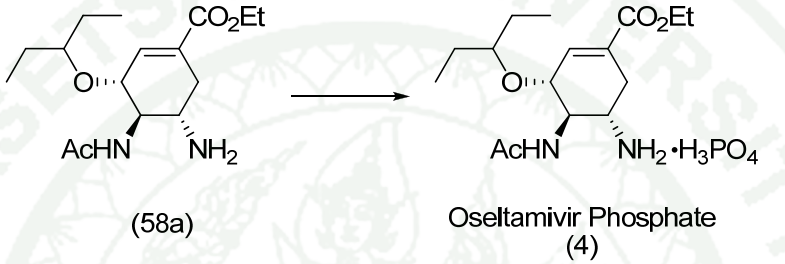
Ethyl (3*R*,4*R*,5*S*)-3-(1-ethyl-propoxy)-4-acetamido-5-amino-1-cyclohexene-1-carboxylate (58a)

(46a) (58a)

To an ice-cooled solution of ethyl (3*R*,4*R*,5*S*)-3-(1-ethyl-propoxy)-4-acetamido-5-*tert*-butoxycarbonylamino-1-cyclohexene-1-carboxylate (46a) (100 mg, 0.24 mmol) in dry dichloromethane (1 mL) was added trifluoroacetic acid (0.24 mL, 3.23 mmol) and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was cooled and diluted with dichloeomethane (5 mL), water (3 mL) and toluene (10 mL). The mixture was evaporated and the residue was partitioned between water (30 mL) and ethyl acetate (25 mL). The aqueous layer was extracted

with ethyl acetate (3x25 mL) and the combined organic layers were washed with saturated aqueous sodium hydrogen carbonate (25 mL). The separated organic phase was dried over anhydrous sodium sulfate, filtered and evaporated to dryness to provide crude ethyl (3*R*,4*R*,5*S*)-3-(1-ethyl-propoxy)-4-acetamido-5-amino-1-cyclohexene-1-carboxylate (58a).

Oseltamivir phosphate (4)



The crude ethyl (3*R*,4*R*,5*S*)-3-(1-ethyl-propoxy)-4-acetamido-5-amino-1-cyclohexene-1-carboxylate (58a) in ethanol (1.5 mL) was added 1.0 M phosphoric acid in ethanol (0.29 mL, 0.29 mmol). The mixture was warmed to 55 °C until white crystals were formed. The mixture was slowly cooled down to 0 °C. The crystals were collected and washed with acetone and hexane to yield oseltamivir phosphate (4) (0.0746 g, 75%) as white crystals.

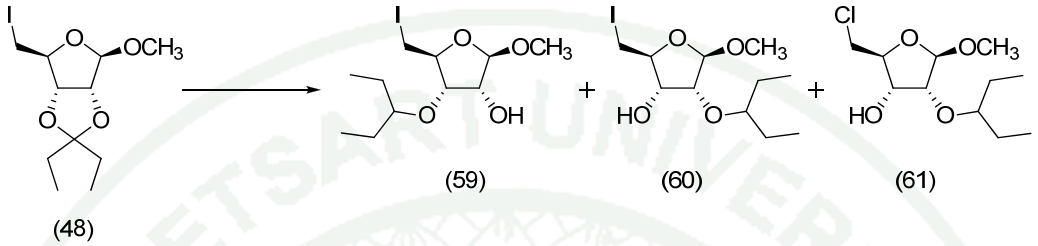
FTIR (KBr), υ_{max}, cm^{-1}: 3508, 1735, 1607, 1142.

^{1}H NMR (400 MHz, D_2O), δ 6.72 (m, 1H, H-2), 4.22-4.19 (m, 1H, H-3), 4.15-4.09 (m, 2H, $CO_2C\underline{H}_2CH_3$), 3.92 (m, 1H, H-4), 3.47 (m, 1H, H-5), 3.41 (quint, *J* = 5.7 Hz, 1H, $C\underline{H}(CH_2CH_3)_2$), 2.84 (dd, *J* = 17.4, 5.5 Hz, 1H, H-6), 2.40 (m, 1H, H-6), 1.96 (s, 3H, $NHCOC\underline{H}_3$), 1.46-1.39 (m, 3H, $CH(C\underline{H}_2CH_3)_2$), 1.38-1.29 (m, 1H, $CH(C\underline{H}_2CH_3)_2$), 1.16 (m, 3H, $CO_2CH_2C\underline{H}_3$), 0.76 (t, *J* = 7.4, 3H, $CHCH_2C\underline{H}_3$), 0.71 (t, *J* = 7.4, 3H, $CHCH_2C\underline{H}_3$).

^{13}C NMR (100 MHz, D_2O), δ 175.4 ($NH\underline{C}OCH_3$), 167.6 ($\underline{C}O_2CH_2CH_3$), 138.1 (C-2), 127.8 (C-1), 84.4 ($\underline{C}H(CH_2CH_3)_2$), 75.3 ($CO_2\underline{C}H_2CH_3$), 62.6 (C-3), 52.8 (C-4),

49.3 (C-5), 28.3 (C-6), 25.6 ($CH\underline{C}H_2CH_3$), 25.2 ($CH\underline{C}H_2CH_3$), 22.6 ($NHCO\underline{C}H_3$), 13.5 ($CO_2CH_2\underline{C}H_3$), 8.7 ($CHCH_2\underline{C}H_3$), 8.6 ($CHCH_2\underline{C}H_3$).

Methyl 5-deoxy-5-iodo-2-hydroxy-3-(1-ethyl-propoxy)-β-D-ribofuranose (59)



Procedure A

To a solution of methyl 5-deoxy-5-iodo-2,3-*O*-isopentylidene-β-D-ribofuranose (48) (200 mg, 0.58 mmol) in dry dichloromethane (2 mL) under nitrogen atmosphere at -78 °C was added triethylsilane (0.12 mL, 0.79 mmol). A solution of titanium tetrachloride (0.04 mL, 0.33 mmol) was added dropwise. The reaction mixture was warmed to -10 °C and stirred at this temperature for 4 h. 10% Ammonium hydroxide solution (1 mL) was added and the suspension was filtered. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3x10mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (5:95 ethyl acetate:hexane) to give methyl 5-deoxy-5-iodo-2-hydroxy-3-(1-ethyl-propoxy)-β-D-ribofuranose (59) (54 mg, 27%) as a colorless oil, methyl 5-deoxy-5-iodo-3-hydroxy-2-(1-ethyl-propoxy)-β-D-ribofuranose (60) (30 mg, 15%) as a colorless oil and methyl 5-deoxy-5-chloro-3-hydroxy-2-(1-ethyl-propoxy)-β-D-ribofuranose (61) (47 mg, 32%) as a colorless oil.

Procedure B

To a solution of methyl 5-deoxy-5-iodo-2,3-*O*-isopentylidene-β-D-ribofuranose (48) (100 mg, 0.29 mmol) and 1 M. borane tetrahydrofuran complex (3 mL) was added copper(II) triflate (21 mg, 0.058 mmol) and stirred at room

temperature for 2 h. The reaction mixture was cooled to 0 °C and triethylamine (0.04 mL) and methanol (0.50 mL) was added to the solution. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography (5:95 ethyl acetate:hexane) to give methyl 5-deoxy-5-iodo-2-hydroxy-3-(1-ethyl-propoxy)-β-D-ribofuranose (59) (45 mg, 45% based on 61% recovery) as a colorless oil and methyl 5-deoxy-5-iodo-3-hydroxy-2-(1-ethyl-propoxy)-β-D-ribofuranose (60) (43 mg, 43% based on 61% recovery) as a colorless oil.

Spectroscopic data of compound **59**

FTIR (neat), υ_{max}, cm^{-1}: 3491, 2963, 2359, 1462, 1103.

^{1}H NMR (400 MHz, $CDCl_3$), δ 4.88 (d, *J* = 4.5 Hz, 1H, H-1), 4.09 (m, 1H, H-2), 3.87 (dd, *J* = 8.6, 4.5 Hz, 1H, H-4), 3.65 (dd, *J* = 7.1, 3.5 Hz, 1H, H-3), 3.42 (s, 3H, OCH_3), 3.34-3.30 (m, 3H, H-5, C<u>H</u>$(CH_2CH_3)_2$), 2.88 (d, *J* = 10.3 Hz, OH), 1.57-1.47 (m, 4H, CH(C<u>H</u>$_2$$CH_3)_2$), 0.90 (m, 6H, CH($CH_2$C<u>H</u>$_3)_2$).

^{13}C NMR (100 MHz, $CDCl_3$), δ 103.2 (C-1), 82.6 (<u>C</u>H$(CH_2CH_3)_2$), 81.0 (C-2), 78.4 (C-3), 71.3 (C-4), 55.5 (OCH_3), 26.0 (CH<u>C</u>H_2CH_3), 25.8 (CH<u>C</u>H_2CH_3), 9.8 (CHCH_2<u>C</u>H_3), 9.6 (CHCH_2<u>C</u>H_3), 8.2 (C-5).

HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd. for $C_{11}H_{21}O_4NaI$: 367.0382, Found: 367.0388.

Spectroscopic data of compound **60**

^{1}H NMR (400 MHz, $CDCl_3$), δ 4.77 (s, 1H, H-1), 4.03 (m, 1H, H-3), 3.90 (m, 1H, H-4), 3.80 (d, *J* = 5.2 Hz, 1H, H-2), 3.33 (s, 3H, OCH_3), 3.32-3.29 (m, 2H, H-5, C<u>H</u>$(CH_2CH_3)_2$), 3.32-3.20 (dd, *J* = 10.3, 6.7 Hz, 1H, H-5), 2.70 (d, *J* = 9.2 Hz, OH), 1.53-1.42 (m, 4H, CH(C<u>H</u>$_2$$CH_3)_2$), 0.90 (q, *J* = 6.1 Hz, 6H, CH(CH_2C<u>H</u>$_3)_2$).

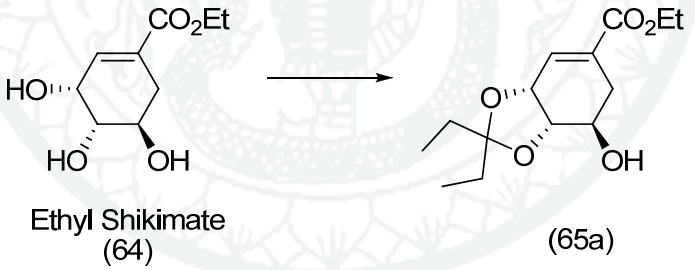
^{13}C NMR (100 MHz, $CDCl_3$),δ 106.6 (C-1), 84.0 (C-4), 82.7 ($\underline{C}H(CH_2CH_3)_2$), 81.0 (C-2), 74.6 (C-3), 55.3 (OCH_3), 26.3 ($CH\underline{C}H_2CH_3$), 25.8 ($CH\underline{C}H_2CH_3$), 9.7 ($CHCH_2\underline{C}H_3$), 9.3 ($CHCH_2\underline{C}H_3$), 7.9 (C-5).

Spectroscopic data of compound **61**

^{1}H NMR (400 MHz, $CDCl_3$), δ 4.88 (d, *J* = 4.1 Hz, 1H, H-1), 3.98 (m, 1H, H-4), 3.87 (dd, *J* = 6.7, 4.1 Hz, 1H, H-2), 3.80 (dd, *J* = 6.7, 2.6 Hz, 1H, H-3), 3.37 (s, 3H, OCH_3), 3.30-3.27 (m, 3H, H-5, $C\underline{H}(CH_2CH_3)_2$), 1.56-1.48 (m, 4H, $CH(C\underline{H}_2CH_3)_2$), 0.89-0.85 (m, 6H, $CH(CH_2C\underline{H}_3)_2$).

^{13}C NMR (100 MHz, $CDCl_3$),δ 103.0 (C-1), 83.3 (C-4), 83.8 ($\underline{C}H(CH_2CH_3)_2$), 76.8 (C-2), 73.0 (C-3), 55.2 (OCH_3), 26.2 ($CH\underline{C}H_2CH_3$), 26.0 ($CH\underline{C}H_2CH_3$), 9.8 ($CHCH_2\underline{C}H_3$), 9.3 ($CHCH_2\underline{C}H_3$), 7.9 (C-5).

Ethyl 3,4-*O*-isopentylidene-5β-hydroxy shikimate (65a)



To a solution of ethyl shikimte (10.0 g, 49.45 mmol) in 3-pentanone (30.4 mL, 287.35 mmol) and triethyl orthoformate (10) was added benzene sulfonic acid (1.064 g, 5.75 mmol). The reaction mixture was stirred at room temperature for 15 h. The reaction mixture was neutralized with saturated aqueous sodium hydrogen carbonate and the residue was extracted with dichloromethane (3x100 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The crude product was purified by flash column chromatography (35:65 ethyl acetate:hexane) to give ethyl 3,4-*O*-isopentylidene-5β-hydroxy shikimate (65a) (12.92 g, 97%) as a pale yellow oil.

FTIR (neat), υ_{max}, cm^{-1}: 3459, 2976, 1714, 1655, 1463, 1246.

^{1}H NMR (400 MHz, $CDCl_3$), δ 6.90 (t, *J* = 1.44Hz, 1H, H-2), 4.74 (m, 1H, H-3), 4.19 (q, *J* = 7.23 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.10 (t, *J* = 6.80 Hz, 1H, H-4), 3.90 (m, 1H, H-5), 2.80 (br s, 1H, OH), 2.73 (dd, *J* = 4.63, 12.60 Hz, 1H, H-6), 2.23 (ddt, *J* = 1.67, 7.97, 9.45 Hz, 1H, H-6), 1.64 (m, 4H, $C(C\underline{H}_2CH_3)_2$), 1.28 (t, *J* = 7.23 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 0.90 (t, *J* = 7.41Hz, 3H, $CCH_2C\underline{H}_3$), 0.86 (t, *J* = 7.41 Hz, 3H, $CCH_2C\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$), δ 166.2 ($\underline{C}O_2CH_2CH_3$), 134.1 (C-2), 130.2 (C-1), 113.5 ($\underline{C}(CH_2CH_3)_2$), 77.7 (C-4), 72.2 (C-3), 68.7 (C-5), 61.0 ($CO_2\underline{C}H_2CH_3$), 29.6 ($C\underline{C}H_2CH_3$), 29.3 ($C\underline{C}H_2CH_3$), 29.0 (C-6), 14.1 ($CO_2CH_2\underline{C}H_3$), 8.5 ($CCH_2\underline{C}H_3$), 7.9 ($CCH_2\underline{C}H_3$).

HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd. for $C_{14}H_{23}O_5H$: 271.1548, Found: 271.1548.

Ethyl 3,4-*O*-isopentylidene-5β-trifluoromethanesulfonyloxy shikimate (66a)

(65a) (66a)

To a solution of ethyl 3,4-*O*-isopentylidene-5β-hydroxy shikimate (65a) (2 g, 7.40 mmol) and pyridine (1.2 mL, 14.80 mmol) in dry dichloromethane (37 mL) at 0 °C under nitrogen atmosphere was added dropwise trifluoromethanesulfonic anhydride (1.5 mL, 8.88 mmol). The mixture was stirred at 0 °C for 20 min. To the cooled reaction mixture was added water (50 mL). The organic phase was separated and aqueous phase was extracted with dichloromethane (3x30 mL). The combined organic phases were washed with saturated aqueous sodium hydrogen carbonate (50

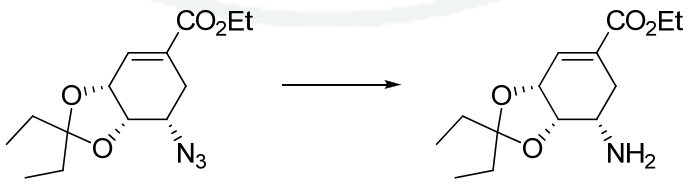
mL) and brine (50 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The crude ethyl 3,4-*O*-isopentylidene-5β-trifluoromethanesulfonyloxy shikimate (66a) (2.97 g) was used in the next step without purification.

Ethyl 3,4-*O*-isopentylidene-5α-azido shikimate (67a)

(66a) (67a)

The crude ethyl 3,4-*O*-isopentylidene-5β-trifluoromethanesulfonyloxy shikimate (66a) (2.97 g) was dissolved in 9:1 acetone/water (20 mL) and sodium azide (0.59 g, 9.04 mmol) was added to the solution. The reaction mixture was stirred at room temperature for 15 h. The solvent was evaporated and the residue was dissolved in ethyl acetate (50 mL). The organic phase was washed with water (2x30 mL) and brine (30 mL). The aqueous phase was extracted with ethyl acetate (50 mL) and the combined organic phases were dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The crude ethyl 3,4-*O*-isopentylidene-5α-azido shikimate (67a) (2.19 g) was used in the next step without further purification.

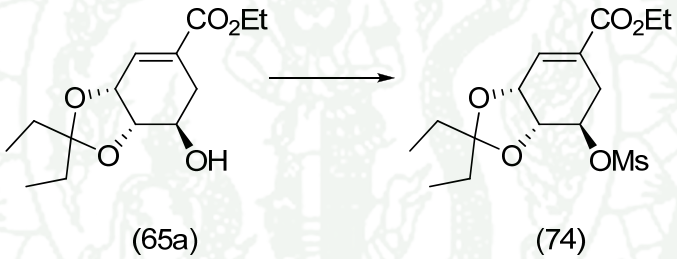
Ethyl 3,4-*O*-isopentylidene-5α-amino shikimate (53a)



(67a) (53a)

To a solution of a crude ethyl 3,4-*O*-isopentylidene-5α-azido shikimate (67a) (2.91 g) in dry tetrahydrofuran (80 mL) was added triphenylphosphene (3.87 g, 14.83 mmol) and stirred for 4 h at room temperature. To this solution were added triethylamine (3 mL, 22.25 mmol) and water (15 mL) and the reaction mixture was stirred for further 6 h. The solvent was evaporated and the residue was partitioned between water (100 mL) and ethyl acetate (100 mL). The aqueous layer was extracted with ethyl acetate (3x50 mL) and the combined ethyl acetate extracts were dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The residue was purified by flash column chromatography (5:95 methanol:dichloromethane) to yield ethyl 3,4-*O*-isopentylidene-5α-amino shikimate (53a) (0.92 g, 46%) as a colorless oil.

Ethyl 3,4-*O*-isopentylidene-5β-methanesulfonyloxy shikimate (74)



(65a) (74)

To a solution of ethyl 3,4-*O*-isopentylidene-5β-hydroxy shikimate (65a) (300 mg, 1.11 mmol) and triethylamine (0.31 mL, 2.22 mmol) in dry dichloromethane (6 mL) at 0 °C was added dropwise methanesulfonyl chloride(0.11 mL, 1.44 mmol). The mixture was stirred at 0 °C for 1 h. To the cooled reaction mixture was added water (15 mL). The organic phase was separated and aqueous phase was extracted with dichloromethane (3x10 mL). The combined organic phases were washed with saturated aqueous sodium hydrogen carbonate (15 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The residue was purified by flash column chromatography (100% dichloromethane) to yield ethyl 3,4-*O*-isopentylidene-5β-methanesulfonyloxy shikimate (74) (348 mg, 90%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ 6.89 (m, 1H, H-2), 4.77-4.72 (m, 2H, H-3, H-5), 4.25 (t, *J* = 7.2 Hz, 1H, H-4), 4.16 (q, *J* = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 3.05 (s, 3H, $SO_2C\underline{H}_3$), 2.90 (dd, *J* = 17.5, 4.8 Hz, 1H, H-6), 2.44 (m, 1H, H-6), 1.65-1.58 (m, 4H, $C(C\underline{H}_2CH_3)_2$), 1.24 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 0.86-0.81 (m, 6H, $C(CH_2C\underline{H}_3)_2$).

^{13}C NMR (100 MHz, $CDCl_3$), δ 165.3 ($\underline{C}O_2CH_2CH_3$), 134.0 (C-2), 129.3 (C-1), 114.4 ($\underline{C}(CH_2CH_3)_2$), 79.0 (C-5), 74.8 (C-4), 72.2 (C-3), 61.2 ($CO_2\underline{C}H_2CH_3$), 38.6 ($SO_2\underline{C}H_3$), 29.6 ($C\underline{C}H_2CH_3$), 28.8 ($C\underline{C}H_2CH_3$), 28.0 (C-6), 14.1 ($CO_2CH_2\underline{C}H_3$), 8.4 ($CH\underline{C}H_2CH_3$), 7.9 ($CHCH_2\underline{C}H_3$).

Ethyl 3,4-*O*-isopentylidene-5α-*tert*-butoxycarbonylamino shikimate (68)

(53a) (68)

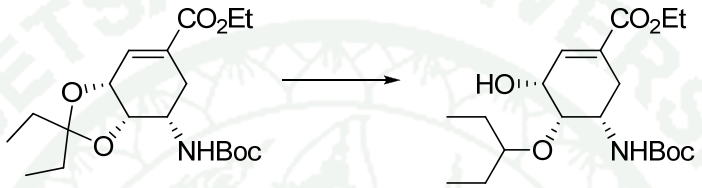
To a solution of ethyl 3,4-*O*-isopentylidene-5α-amino shikimate (53a) (237 mg, 0.88 mmol) in methanol (17.5 mL) was added di-*tert*-butyl dicarbonate (0.38 g, 1.76 mmol) and stirred at room temperature for 3 h. The solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (20:80 ethyl acetate:hexane) to give ethyl 3,4-*O*-isopentylidene-5α-*tert*-butoxycarbonylamino shikimate (68) (270 mg, 83%) as a white solid.

FTIR (KBr), υ_{max}, cm^{-1}: 3362, 2976, 1714, 1653, 1504, 1242.

^{1}H NMR (400 MHz, $CDCl_3$), δ 6.66 (t, *J* = 3.4 Hz 1H, H-2), 4.95 (d, *J* = 9.4 Hz, 1H, NH), 4.68 (m, 1H, H-3), 4.29 (m, 1H, H-4), 4.14 (q, *J* = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 3.85 (m, 1H, H-5), 2.62 (dd, *J* = 11.5 5.1, Hz, 1H, H-6), 2.10 (m, 1H, H-6), 1.57 (m, 4H, $C(C\underline{H}_2CH_3)_2$), 1.39 (s, 9H, $C(C\underline{H}_3)_3$), 1.23 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 0.84 (t, *J* = 7.5 Hz, 3H, $CCH_2C\underline{H}_3$), 0.74 (t, *J*=7.5 Hz, 3H, $CCH_2C\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$), δ 166.3 ($\underline{C}O_2CH_2CH_3$), 155.2 ($NH\underline{C}O_2t$-Bu), 134.8 (C-2), 130.2 (C-1), 113.6 ($\underline{C}(CH_2CH_3)_2$), 79.7 ($\underline{C}(CH_3)_3$), 74.7 (C-4), 72.9 (C-3), 60.9 ($CO_2\underline{C}H_2CH_3$), 48.1 (C-5), 30.1 ($C\underline{C}H_2CH_3$), 29.6 ($C\underline{C}H_2CH_3$), 28.4 ($C(\underline{C}H_3)_3$), 27.4 (C-6), 14.1 ($CO_2CH_2\underline{C}H_3$), 8.4 ($C\underline{C}H_2CH_3$), 7.9 ($CCH_2\underline{C}H_3$).

Ethyl (3*R*,4*S*,5*S*)-3-hydroxy -4-(1-ethyl-propoxy)-5-*tert*-butoxycarbonylamino-1-cyclohexene-1-carboxylate (69)



(68) (69)

To a solution of ethyl 3,4-*O*-isopentylidene-5α-*tert*-butoxycarbonylamino shikimate (68) (200 mg, 0.54 mmol) in dry dichloromethane (4 mL) under nitrogen atmosphere at -78 °C was added triethylsilane (0.12 mL, 0.73 mmol). A solution of titanium tetrachloride (0.07 mL, 0.61 mmol) was added dropwise. The reaction mixture was warmed to -10 °C and stirred at this temperature for 16 h. The solution was poured into an ice/water mixture. The mixture was partitioned between water (20 mL) and dichloromethane (15 mL). The aqueous layer was extracted with dichloromethane (3x10 mL) and the combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (15 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The residue was purification by flash column chromatography (1:99 methanol:dichloromethane) to give ethyl (3*R*,4*S*,5*S*)-3-hydroxy-4-(1-ethyl-propoxy)-5-*tert*-butoxycarbonylamino-1-cyclohexene-1-carboxylate (69) (133 mg, 65%) as a white solid.

FTIR (KBr), υ_{max}, cm^{-1}: 3371, 2967, 1719, 1681, 1654, 1530, 1245.

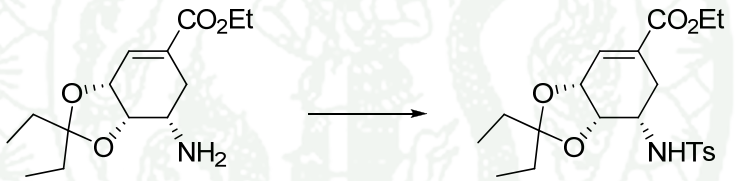
^{1}H NMR (400 MHz, $CDCl_3$), δ 6.72 (m, 1H, H-2), 5.18 (d, J = 6. Hz, 1H, NH), 4.30 (s, 1H, H-3), 4.13 (q, J = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 3.87 (m, 1H, H-4), 3.75 (m, 1H, H-5), 3.36 (quint, J = 5.6 Hz, 1H, $C\underline{H}(CH_2CH_3)_2$), 2.67 (m, 1H, H-6),

2.39 (m, 2H, H-6, OH), 1.45 (m, 4H, $CH(C\underline{H}_2CH_3)_2$), 1.36 (s, 9H, $C(C\underline{H}_3)_3$), 1.22 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 0.86 (t, *J* = 7.4 Hz, 3H, $CHCH_2C\underline{H}_3$), 0.80 (t, *J* = 7.4 Hz, 3H, $CHCH_2C\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$), δ 166.2 ($\underline{C}O_2CH_2CH_3$), 155.3 ($NH\underline{C}O_2t$-Bu), 137.2 (C-2), 129.8 (C-1), 82.1 ($\underline{C}H(CH_2CH_3)_2$), 79.2 ($\underline{C}(CH_3)_3$), 73.5 ($CO_2\underline{C}H_2CH_3$), 687.3 (C-4), 60.7 (C-3), 47.7 (C-5), 28.4 (C-6), 28.3 ($C(\underline{C}H_3)_3$), 26.2 ($CH\underline{C}H_2CH_3$), 26.0 ($CH\underline{C}H_2CH_3$), 14.1 ($CO_2CH_2\underline{C}H_3$), 9.8 ($CH\underline{C}H_2CH_3$), 9.4 ($CHCH_2\underline{C}H_3$).

HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd. for $C_{19}H_{33}NO_6Na$: 394.2206, Found: 394.2197.

Ethyl 3,4-*O*-isopentylidene-5α-*p*-toluenesulfonylamino shikimate (70)



(53a) (70)

To a solution of ethyl 3,4-*O*-isopentylidene-5α-amino shikimate (53a) (100 mg, 0.37 mmol), *N,N*-dimethylamino pyridine (9 mg, 0.07 mmol) and triethylamine (0.10 mL, 0.82 mmol) in dry dichloromethane (1.0 mL) (.12 mmol) was added *p*-toluenesulfonyl chloride (85 mg, 0.45 mmol) and stirred at room temperature for 12 h. To the cooled reaction mixture was added water (10 mL). The aqueous phase was extracted with dichloromethane (3x15 mL). The combined organic phases were washed with saturated aqueous sodium hydrogen carbonate (15 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The crude product was purified by flash column chromatography (20:80 ethyl acetate:hexane) to give ethyl 3,4-*O*-isopentylidene-5α-*p*-toluenesulfonylamino shikimate (70) (103 mg, 83%) as a white solid.

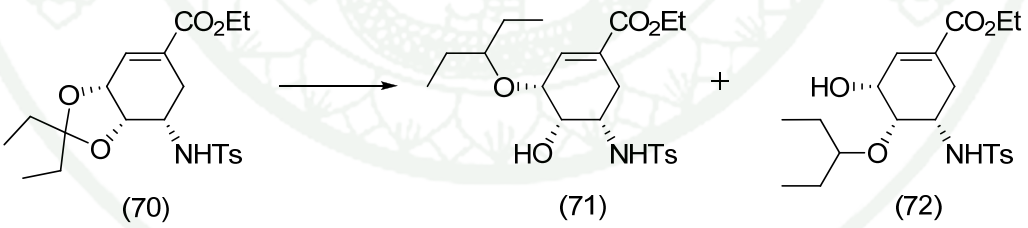
FTIR (KBr), υ_{max}, cm^{-1}: 3309, 2979, 1716, 1442, 1330, 1257.

^{1}H NMR (400 MHz, $CDCl_3$), δ 7.71 (d, *J* = 8.3 Hz, 2H, Ar), 7.27 (dd, *J* = 8.0, 0.4 Hz, 2H, Ar), 6.61 (t, *J* = 3.3 Hz, 1H, H-2), 5.03 (d, *J* = 9.8 Hz, 1H, NH), 4.58 (m, 1H, H-3), 4.10 (dq, *J* = 7.1, 0.8 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.02 (m, 1H, H-4), 3.53 (m, 1H, H-5), 2.45 (dd, *J*= 5.4, 11.4 Hz, 1H, H-6), 2.36 (s, 3H, $ArC\underline{H}_3$), 2.09 (m, 1H, H-6), 1.45 (q, *J* = 7.4 Hz, 4H, $C(C\underline{H}_2CH_3)_2$), 1.20 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 0.75 (t, *J* = 7.4 Hz, 3H, $CCH_2C\underline{H}_3$), 0.70 (t, *J* = 7.4 Hz, 3H, $CCH_2C\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$), δ 165.9 ($\underline{C}O_2CH_2CH_3$), 143.6 (Ar), 138.4 (Ar), 134.6 (C-2), 129.8 (C-1), 129.7 (Ar), 126.9 (Ar), 113.7 ($\underline{C}(CH_2CH_3)_2$), 74.2 (C-4), 72.7 (C-3), 61.0 ($CO_2\underline{C}H_2CH_3$), 51.2 (C-5), 30.0 ($C\underline{C}H_2CH_3$), 29.4 ($C\underline{C}H_2CH_3$), 25.8 (C-6), 21.5 ($ArC\underline{H}_3$), 14.1 ($CO_2CH_2\underline{C}H_3$), 8.3 ($C\underline{C}H_2CH_3$), 7.9 ($CCH_2\underline{C}H_3$).

HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd. for $C_{21}H_{29}NO_6NaS$: 446.1613, Found: 446.1615.

Ethyl (3*R*,4*S*,5*S*)-3-(1-ethyl-propoxy)- 4-hydroxy-5-*p*-toluenesulfonylamino-1-cyclohexene-1-carboxylate (71) and ethyl (3*R*,4*S*,5*S*)-3-hydroxy-4-(1-ethyl-propoxy)-5-*p*-toluenesulfonylamino-1-cyclohexene-1-carboxylate (72)



To a solution of ethyl 3,4-*O*-isopentylidene-5α-*p*-toluenesulfonylamino shikimate (70) (540 mg, 1.27 mmol) in dry dichloromethane (5.0 mL) under nitrogen atmosphere at -78 °C was added triethylsilane (0.30 mL, 1.86 mmol). A solution of titanium tetrachloride (0.16 mL, 1.45 mmol) was added dropwise. The reaction mixture was warmed to -10 °C and stirred at this temperature for 16 h. The solution was poured into an ice/water mixture. The mixture was partitioned between water (20 mL) and dichloromethane (15 mL). The aqueous layer was extracted with dichloromethane (3x10 mL) and the combined organic extracts were washed with

saturated aqueous sodium hydrogen carbonate (15 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The residue was purification by flash column chromatography (1:99 methanol:dichloromethane) to give ethyl (3*R*,4*S*,5*S*)-3-(1-ethyl-propoxy)- 4-hydroxy-5-*p*-toluenesulfonylamino-1-cyclohexene-1-carboxylate (71) (189 mg, 35%) as a white solid and ethyl (3*R*,4*S*,5*S*)-3-hydroxy-4-(1-ethyl-propoxy)-5-*p*-toluenesulfonylamino-1-cyclohexene-1-carboxylate (72) (160 mg, 30%) as a white solid.

Spectroscopic data of compound **71**

^{1}H NMR (400 MHz, $CDCl_3$), δ 7.76 (d, *J* = 8.3 Hz, 2H, Ar), 7.28 (dd, *J* = 8.0, 0.6 Hz, 2H, Ar), 6.63 (m, 1H, H-2), 5.50 (d, *J* = 9.6 Hz, 1H, NH), 4.14 (q, *J* = 7.1, 0.8 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.00 (m, 1H, H-3), 3.84 (m, 1H, H-4), 3.54 (m, 1H, H-5), 3.23 (quint, *J* = 5.8 Hz, 1H, $C\underline{H}(CH_2CH_3)_2$), 2.40 (s, 3H, $ArC\underline{H}_3$), 2.34 (m, 2H, H-6), 1.49 (m, 4H, $CH(C\underline{H}_2CH_3)_2$), 1.23 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 0.88 (t, *J* = 7.4 Hz, 3H, $CHCH_2C\underline{H}_3$), 0.85 (t, *J* = 7.4 Hz, 3H, $CHCH_2C\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$), δ 165.8 ($\underline{C}O_2CH_2CH_3$), 143.3 (Ar), 138.5 (Ar), 134.3 (C-2), 130.0 (C-1), 129.7 (Ar), 126.9 (Ar), 82.0 ($\underline{C}H(CH_2CH_3)_2$), 73.3 (C-4), 68.0 (C-3), 60.8 ($CO_2\underline{C}H_2CH_3$), 51.8 (C-5), 27.8 ($CH\underline{C}H_2CH_3$), 26.1 ($CH\underline{C}H_2CH_3$), 26.0 (C-6), 21.4 ($Ar\underline{C}H_3$), 14.1 ($CO_2CH_2\underline{C}H_3$), 9.5 ($CH\underline{C}H_2CH_3$), 9.3 ($CHCH_2\underline{C}H_3$).

HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd. for $C_{21}H_{31}NO_6NaS$: 448.1770 Found: 448.1759.

Spectroscopic data of compound **72**

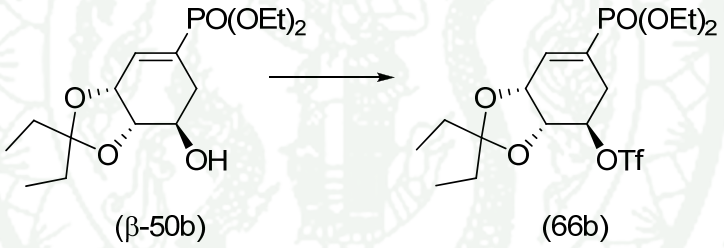
^{1}H NMR (400 MHz, $CDCl_3$), δ 7.76 (d, *J* = 8.3 Hz, 2H, Ar), 7.22 (d, *J* = 8.3 Hz, 2H, Ar), 6.68 (m, 1H, H-2), 5.22 (d, *J* = 7.9 Hz, 1H, NH), 4.24 (m, 1H, H-3), 4.07 (q, *J* = 7.2 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 3.67 (m, 1H, H-4), 3.51 (m, 1H, H-5), 3.39 (quint, *J* = 6.1 Hz, 1H, $C\underline{H}(CH_2CH_3)_2$), 2.51 (s, 1H, OH), 2.40 (m, 1H, H-6), 2.34 (s, 3H, $ArC\underline{H}_3$), 2.19 (m, 1H, H-6), 1.40 (m, 4H, $CH(C\underline{H}_2CH_3)_2$), 1.18 (t, *J* = 7.2 Hz, 3H,

$CO_2CH_2C\underline{H}_3$), 0.80 (t, *J* = 7.3 Hz, 3H, $CHCH_2C\underline{H}_3$), 0.76 (t, *J* = 7.3 Hz, 3H, $CHCH_2C\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$), δ 165.9 ($\underline{C}O_2CH_2CH_3$), 143.6 (Ar), 138.0 (Ar), 137.3 (C-2), 129.6 (C-1), 129.3 (Ar), 126.8 (Ar), 82.3 ($\underline{C}H(CH_2CH_3)_2$), 74.1 (C-4), 67.1 (C-3), 60.8 ($CO_2\underline{C}H_2CH_3$), 51.2 (C-5), 28.7 ($CH\underline{C}H_2CH_3$), 26.0 ($CH\underline{C}H_2CH_3$), 25.7 (C-6), 21.4 ($Ar\underline{C}H_3$), 14.0 ($CO_2CH_2\underline{C}H_3$), 9.8 ($CH\underline{C}H_2CH_3$), 9.2 ($CHCH_2\underline{C}H_3$).

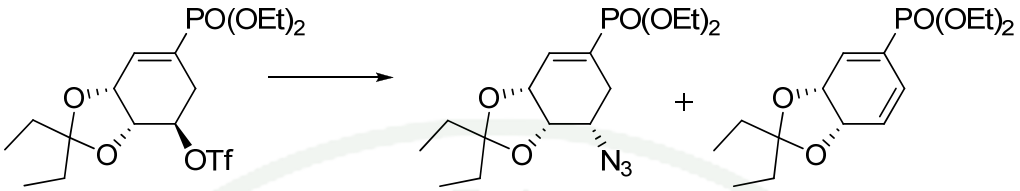
HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd. for $C_{21}H_{31}NO_6NaS$: 448.1770 Found: 448.1759.

Diethyl (3*R*,4*S*,5*R*)-3,4-*O*-isopentylidene-5-trifluoromethanesulfonyloxy-1-cyclohexene-1-phosphonate (66b)



To a solution of diethyl (3*R*,4*S*,5*R*)-3,4-*O*-isopentylidene-5-hydroxy-1-cyclohexene-1-phosphonate (β-50b) (50 mg, 0.15 mmol) and pyridine (0.03 mL, 0.30 mmol) in dry dichloromethane (1 mL) at 0 °C under nitrogen atmosphere was added dropwise trifluoromethanesulfonic anhydride (0.03 mL, 0.18 mmol). The mixture was stirred at 0 °C for 30 min. To the cooled reaction mixture was added water (10 mL). The organic phase was separated and aqueous phase was extracted with ethyl acetate (3x10 mL). The combined organic phases were washed with saturated aqueous sodium hydrogen carbonate (10 mL) and brine (10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The crude diethyl (3*R*,4*S*,5*R*)-3,4-*O*-isopentylidene-5-trifluoromethanesulfonyloxy-1-cyclohexene-1-phosphonate (66b) (63 mg) was used in the next step without purification.

Diethyl (3*R*,4*S*,5*S*)-3,4-*O*-isopentylidene-5-azido-1-cyclohexene-1-phosphonate (67b)



The crude diethyl (3*R*,4*S*,5*R*)-3,4-*O*-isopentylidene-5-trifluoromethane sulfonyloxy-1-cyclohexene-1-phosphonate (66b) (63 mg) was dissolved in 9:1 acetone/water (1 mL) and sodium azide (12 mg, 0.18 mmol) was added to the solution. The reaction mixture was stirred at room temperature for 15 h. The solvent was evaporated and the residue was dissolved in ethyl acetate (15 mL). The organic phase was washed with water (2x5 mL). The aqueous phase was extracted with ethyl acetate (15 mL) and the combined organic phases were dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The residue was purification by flash column chromatography (5:95 methanol:dichloromethane) to give diethyl (3*R*,4*S*,5*S*)-3,4-*O*-isopentylidene-5-azido-1-cyclohexene-1-phosphonate (67b) (18 mg, 34%) as a yellow oil.

Spectroscopic data of compound **67b**

FTIR (neat), υ_{max}, cm^{-1}: 2977, 2098, 1463, 1641, 1248, 1024.

^{1}H NMR (400 MHz, $CDCl_3$), δ 6.51 (d, *J* = 20.0 Hz,,1H, H-2), 4.64 (m, 1H, H-3), 4.45 (m, 1H, H-4), 4.07 (m, 4H, $PO(OC\underline{H}_2CH_3)_2$), 3.49 (m, 1H, H-5), 2.48 (m, 2H, H-6), 1.71-1.57 (m, 4H, $C(C\underline{H}_2CH_3)_2$), 1.29 (m, 6H, $PO(OCH_2C\underline{H}_3)_2$), 0.89 (t, *J* = 7.5 Hz, 3H, $CCH_2C\underline{H}_3$), 0.81 (t, *J* = 7.3 Hz, 3H, $CCH_2C\underline{H}_3$).

^{13}C NMR (75 MHz, $CDCl_3$), δ 138.8 (C-2), 127.8 (d, *J* = 182.2 Hz, C-1), 114.3 ($\underline{C}(CH_2CH_3)_2$), 74.2 (C-4), 73.0 (C-3), 62.3 ($PO\underline{C}H_2CH_3$), 62.1 ($PO\underline{C}H_2CH_3$),

57.2 (C-5), 30.1 ($C\underline{C}H_2CH_3$), 29.6 ($C\underline{C}H_2CH_3$), 24.0 (C-6), 16.4 ($POCH_2\underline{C}H_3$), 16.3 ($POCH_2\underline{C}H_3$), 8.3 ($CCH_2\underline{C}H_3$), 8.0 ($CCH_2\underline{C}H_3$).

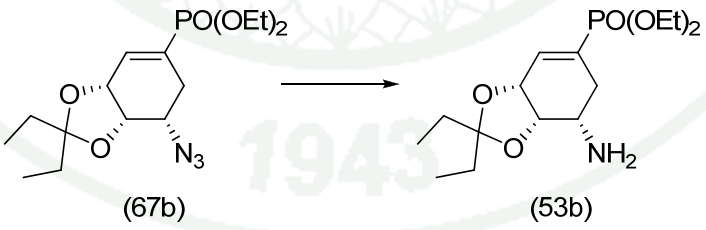
Spectroscopic data of compound **73**

FTIR (neat), υ_{max}, cm^{-1}: 2977, 1693, 1463, 1240, 1022.

^{1}H NMR (400 MHz, $CDCl_3$), δ 6.66 (m,1H, H-2), 6.12 (t, *J* = 8.4 Hz, 1H, H-6), 6.02 (m, 1H, H-5), 4.73 (m, 1H, H-3), 4.59 (dd, *J* = 9.2, 4.0 Hz, 1H, H-4), 4.13 (m, 4H, $PO(O\underline{C}H_2CH_3)_2$), 1.63 (q, *J* = 7.6 Hz, 2H, $CC\underline{H}_2CH_3$), 1.56 (q, *J* = 7.6 Hz, 2H, $CC\underline{H}_2CH_3$), 1.27 (m, 6H, $PO(OCH_2C\underline{H}_3)_2$), 0.90 (t, *J*=7.6 Hz, 3H, $CCH_2C\underline{H}_3$), 0.77 (t, *J*=7.6 Hz, 3H, $CCH_2C\underline{H}_3$).

^{13}C NMR (75 MHz, $CDCl_3$), δ 137.7 (C-2), 125.8 (C-6), 124.6 (d, *J* = 217.5 Hz, C-1), 121.8 (C-5), 109.3 ($\underline{C}(CH_2CH_3)_2$), 70.3 (C-3), 69.2 (C-4), 62.2 ($PO\underline{C}H_2CH_3$), 62.1 ($PO\underline{C}H_2CH_3$), 29.0 ($C\underline{C}H_2CH_3$), 28.7 ($C\underline{C}H_2CH_3$), 16.3 ($POCH_2\underline{C}H_3$), 16.2 ($POCH_2\underline{C}H_3$), 8.5 ($CCH_2\underline{C}H_3$), 7.8 ($CCH_2\underline{C}H_3$).

Diethyl (3*R*,4*R*,5*S*)-3,4-*O*-isopentylidene-5-amino-1-cyclohexene-1-phosphonate (53b)



(67b) (53b)

To a solution of diethyl (3*R*,4*S*,5*S*)-3,4-*O*-isopentylidene-5-azido-1-cyclohexene-1-phosphonate (67b) (18 mg, 0.05 mmol) in dry tetrahydrofuran (1 mL) was added triphenylphosphene (26 mg, 0.10 mmol) and stirred for 2 h at room temperature. To this solution were added triethylamine (0.02 mL, 0.15 mmol) and water (0.1 mL) and the reaction mixture was stirred for further 4 h. The solvent was evaporated and the residue was partitioned between water (10 mL) and ethyl acetate

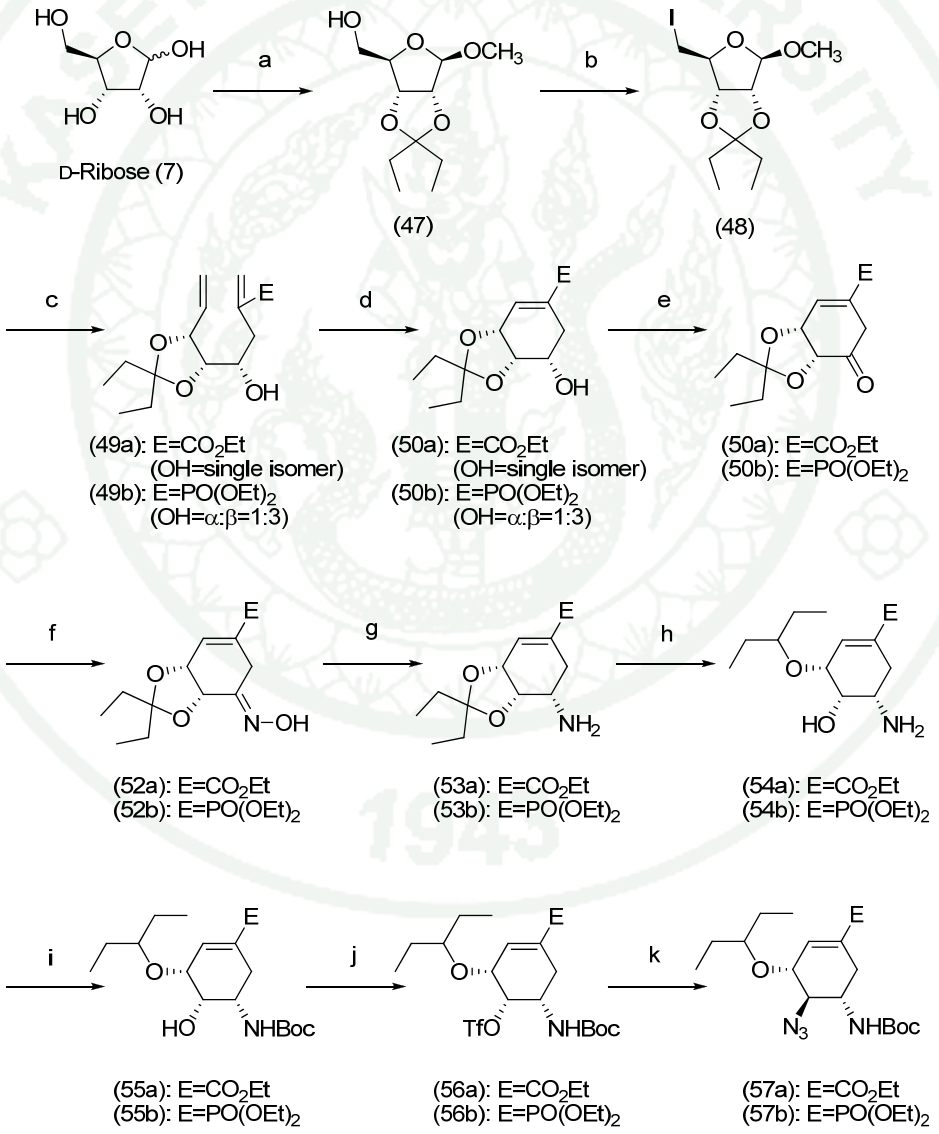
(10 mL). The aqueous layer was extracted with ethyl acetate (3x10 mL) and the combined ethyl acetate extracts were dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The residue was purified by flash column chromatography (10:90 methanol:dichloromethane) to yield diethyl (3*R*,4*R*,5*S*)-3,4-*O*-isopentylidene-5-amino-1-cyclohexene-1-phosphonate (53b) (5 mg, 30%) as a yellow oil.

RESULTS AND DISCUSSION

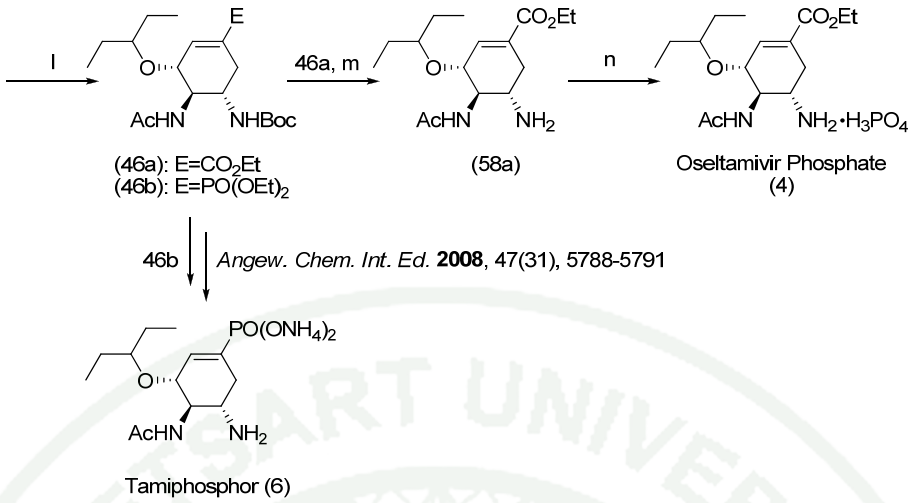
Results

1. Synthesis of Tamiflu (4) and Tamiphosphor (6) from D-ribose (7)

Oseltamivir phosphate (Tamiflu, 4) and Tamiphosphor (6) were synthesized starting from D-ribose (7) as shown in Scheme 7.



Scheme 7



Scheme 7 (Continued)

Reagents and conditions

a) 3-pentanone, MeOH, conc. HCl, $CH(OCH_3)_3$, rt, overnight, 98%

b) I_2, imidazole, PPh_3, toluene, MeCN, reflux, 3 h, 79%

c) Zn, ethyl 2-(bromomethyl) acrylate for **49a** and 3-bromoprop-1-en-2-ylphosphonate for **49b**, THF/H_2O (2:1), sonicate, 50 ºC, 3 h, **49a**=71% (single isomer), **49b**=68% (α:β=1:3)

d) 2nd generation Grubbs' catalyst, dry CH_2Cl_2, 40 ºC, 4 h, **50a**=60% (single isomer), **50b**=57% (α:β=1:3)

e) TEMPO, TCCA, dry CH_2Cl_2, 0 ºC to rt, 45 min

f) $NH_2OH{\cdot}HCl$, EtOH/Py (3:1), rt, 2 h, **52a**=71% (two steps), **52b**=50% (two steps)

g) $NaBH_4$, MoO_3, MeOH, rt, 30 min - 2 h, **53a**=92%, **53b**=51%

h) Et_3SiH, $TiCl_4$, dry CH_2Cl_2, -78 ºC to -10 ºC, 16 h

i) Boc_2O, MeOH, rt, 3 h, **55a**=66% (two steps), **55b**=25% (two steps)

j) Tf_2O, Py, dry CH_2Cl_2, -10 ºC, 30 min

k) NaN_3, acetone/H_2O (9:1), rt, 15 h

l) AcSH, 2,6-lutidine, $CHCl_3$, reflux, 5 h, **46a**=44% (three steps)

m) TFA, dry CH_2Cl_2, rt, 1 h

n) H_3PO_4, EtOH, 55 ºC to 0 ºC, **4**=75% (two steps)

2. An attempt to functionalize methyl 5-deoxy-5-iodo-2,3-*O*-isopentylidene-β-D-ribofuranose (48)

Methyl 5-deoxy-5-iodo-2,3-*O*-isopentylidene-β-D-ribofuranose (48) was subjected to regioselective reductive ring opening of pentylidene ketal as shown in Table 2.

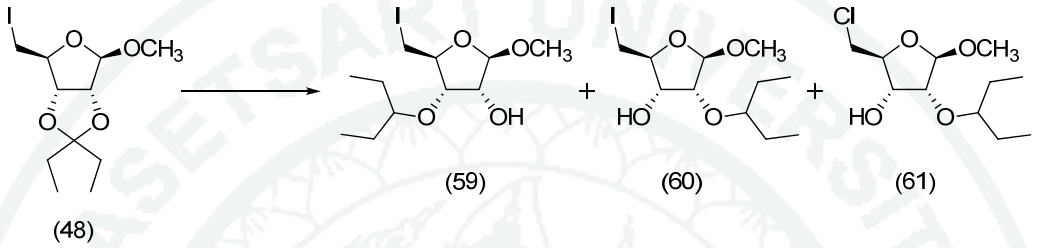


Table 2 Regioselective reductive ring opening of pentylidene ketal of methyl 5-deoxy-5-iodo-2,3-*O*-isopentylidene-β-D-ribofuranose (48).

Entry	Reagents	Yield of 59 (%)	Yield of 60 (%)	Yield of 61 (%)
1	Et_3SiH, $TiCl_4$, dry CH_2Cl_2, -78 ºC to -10 ºC, 4 h	27[a]	15[a]	32[a]
2	Et_3SiH, $TiCl_4$, dry CH_3CN, 0 ºC to rt, 5 h	No reaction		
3	Et_3SiH, $BF_3{\cdot}Et_2O$, dry CH_3CN, 0 ºC to rt, 2 h	-	-	-
4	Et_3SiH, $Cu(OTf)_2$, dry CH_2Cl_2, rt, 5 h	No reaction		
5	1 M. $BH_3{\cdot}THF$, $BF_3{\cdot}Et_2O$, dry CH_3CN, 0 ºC to rt, 24 h	trace	trace	-
6	1 M. $BH_3{\cdot}THF$, $Cu(OTf)_2$, rt, 2 h	45[b]	43[b]	-
7	1 M. $BH_3{\cdot}THF$, $Cu(OTf)_2$, dry CH_2Cl_2, rt, 5 h	trace	trace	-

[a] Isolated yield.

[b] Based on 61% recovery.

3. Metal-mediate domino reaction of methyl 5-deoxy-5-iodo-2,3-*O*-isopentylidene-β-D-ribofuranose (48)

3.1 Synthesis of diene intermediate **49a**

A metal-mediate domino reaction of methyl 5-deoxy-5-iodo-2,3-*O*-isopentylidene-β-D-ribofuranose (48) was examined as shown in Table 3.

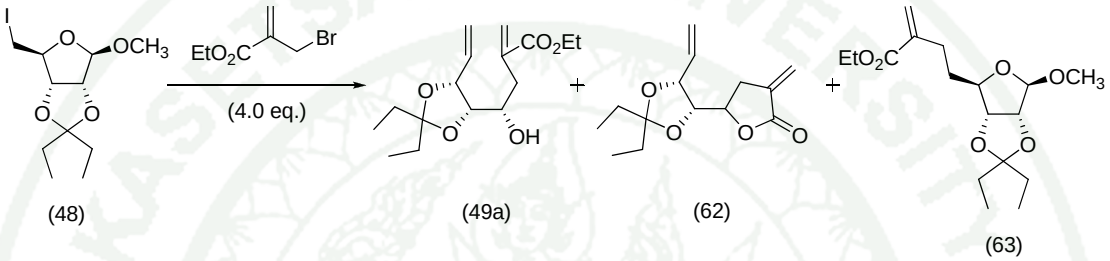


Table 3 Zinc- and indium-mediated elimination-allylation of methyl 5-deoxy-5-iodo-2,3-*O*-isopentylidene-β-D-ribofuranose (48).

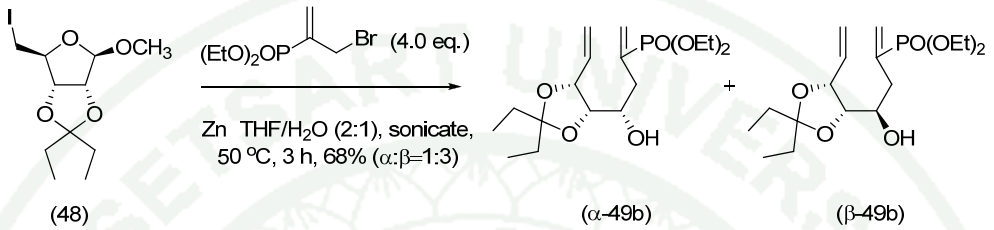
Entry	Metal	Reagents	Yield of 49a (%)[b]	Yield of 62 (%)[b]	Yield of 63 (%)[b]
1	Zn	THF/H_2O (2:1), sonicate, 50 ºC, 3 h	71	22	-
2	In	THF/H_2O (2:1), sonicate, 50 ºC, 3 h	45	-	30
3	In	THF/H_2O (2:1), AcOH sonicate, 50 ºC, 1 h[a]	70	-	7

[a] AcOH (0.01 eq.) was added and sonicated until the aldehyde intermediate formed (monitoring by TLC) then ethyl 2-(bromomethyl) acrylate was added and the reaction was sonicated for another 2 h.

[b] Isolated yield.

3.2 Synthesis of diene intermediate **49b**

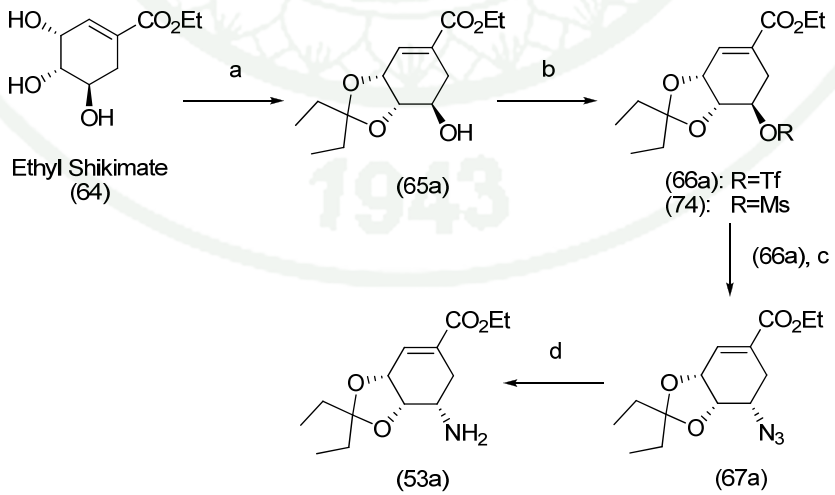
A metal-mediate domino reaction of methyl 5-deoxy-5-iodo-2,3-*O*-isopentylidene-β-D-ribofuranose (48) was employed to synthesize diene intermediate **49b** in the synthesis of Tamiphosphor (6) (Scheme 8).



Scheme 8

4. Synthesis of ethyl 3,4-*O*-isopentylidene-5α-amino shikimate (53a) from ethyl shikimate (64)

Using nucleophilic replacement of a triflate with an azide, ethyl 3,4-*O*-isopentylidene-5α-amino shikimate (53a) was synthesized starting from ethyl shikimate (64) as shown in Scheme 9.



Scheme 9

Reagents and conditions

a) 3-pentanone, BSA, $CH(OEt)_3$, rt, 15 h, 97%

b) **66a:** Tf_2O, Py, dry CH_2Cl_2, 0 ºC, 20 min,
74: MsCl, Et_3N, dry CH_2Cl_2, 0 ºC, 1 h, 90%

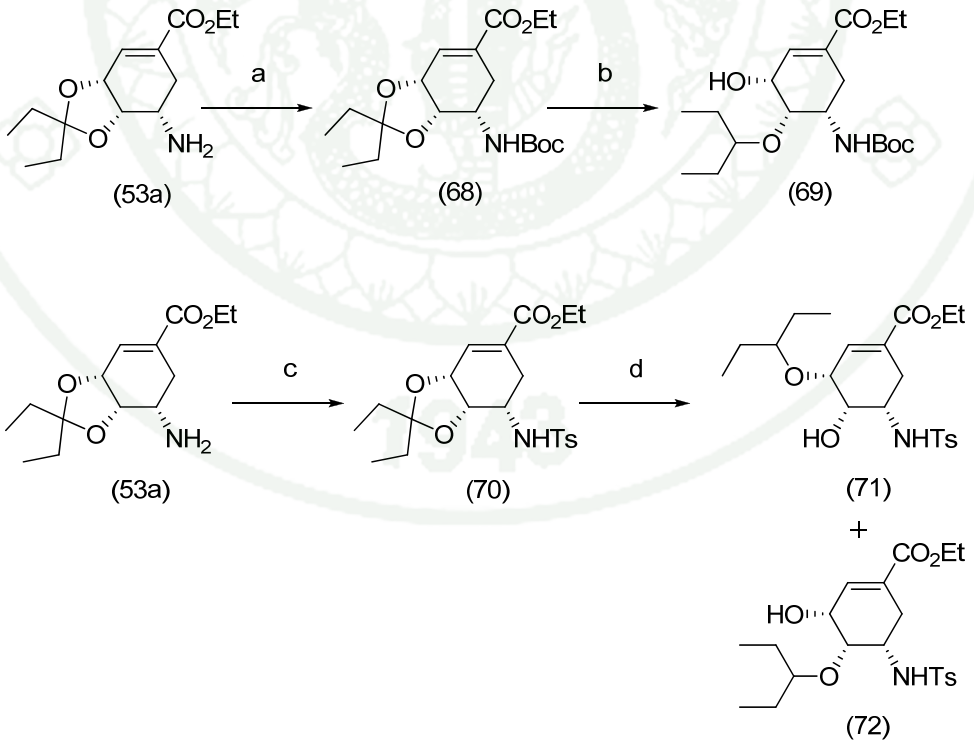
c) NaN_3, acetone/H_2O (9:1), rt, 15 h

d) PPh_3, dry THF, rt, 4 h, then Et_3N, H_2O, rt, 6 h, 46% (three steps)

5. Regioselective reductive ring opening of pentylidene ketal

5.1 *N*-Protected ethyl 3,4-*O*-isopentylidene-5α-amino shikimate

Regioselective reductive ring opening of pentylidene ketal of ethyl 3,4-*O*-isopentylidene-5α-*tert*-butoxycarbonylamino shikimate (68) and ethyl 3,4-*O*-isopentylidene-5α-tosylamino shikimate (70) was showed in Scheme 10.



Scheme 10

Reagents and conditions

a) Boc_2O, MeOH, rt, 3 h, 83%

b) Et_3SiH, $TiCl_4$, dry CH_2Cl_2, -78 ºC to -10 ºC, 16 h, 65%

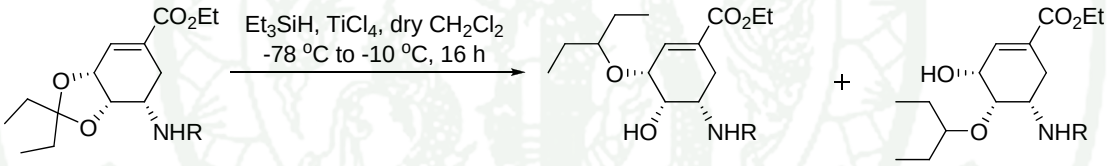
c) TsCl, DMAP, Et_3N, dry CH_2Cl_2, rt, 12 h, 65%

d) Et_3SiH, $TiCl_4$, dry CH_2Cl_2, -78 ºC to -10 ºC, 16 h, (**71**=35%, **72**=30%)

5.2 Result of the reaction

The result of regioselective reductive ring opening of pentylidene ketal was summarized as shown in Table 4.

Table 4 Regioselective reductive ring opening of pentylidene ketal of *N*-protected ethyl 3,4-*O*-isopentylidene-5α-amino shikimate



(53a): R = H
(68): R = Boc
(70): R = Ts

Product Type A

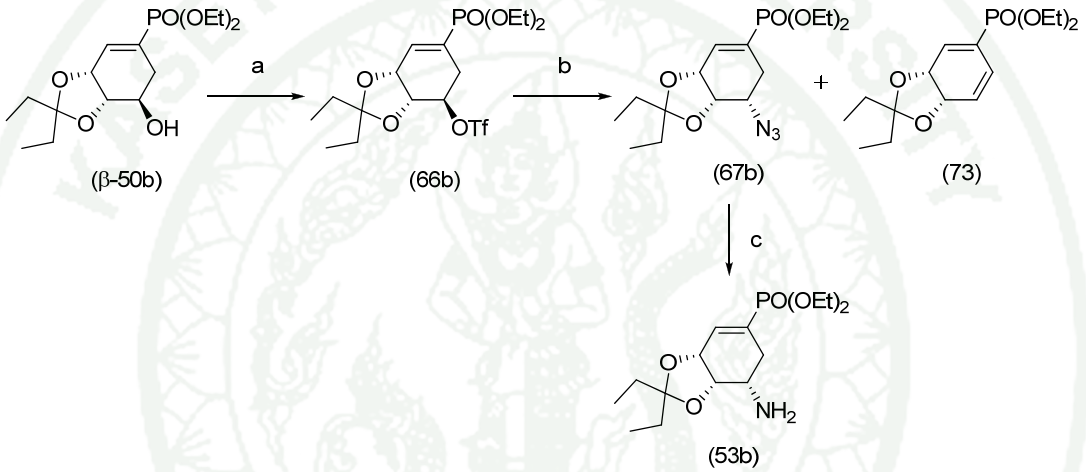
Product Type B

Entry	Ketal	Yield of Produce Type A[a]	Yield of Produce Type B[a]
1	**53a**: R = H	(**54a**: R = H) 70%	-
2	**68**: R = Boc	-	(**69**: R = Boc) 65%
3	**70**: R = Ts	(**71**: R = Ts) 35%	(**72**: R = Ts) 30%

[a] Isolated yield.

6. Synthesis of diethyl (3*R*,4*S*,5*S*)-3,4-*O*-isopentylidene-5-amino-1-cyclohexene phosphonate (53b) from diethyl (3*R*,4*S*,5*R*)-3,4-*O*-isopentylidene-5-hydroxy-1-cyclohexene phosphonate (β-50b)

The stereospecific synthesis of diethyl (3*R*,4*S*,5*S*)-3,4-*O*-isopentylidene-5-amino-1-cyclohexene phosphonate (53b) from diethyl (3*R*,4*S*,5*R*)-3,4-*O*-isopentylidene-5-hydroxy-1-cyclohexene phosphonate (β-50b) was showed in Scheme 11.



Scheme 11

Reagents and conditions

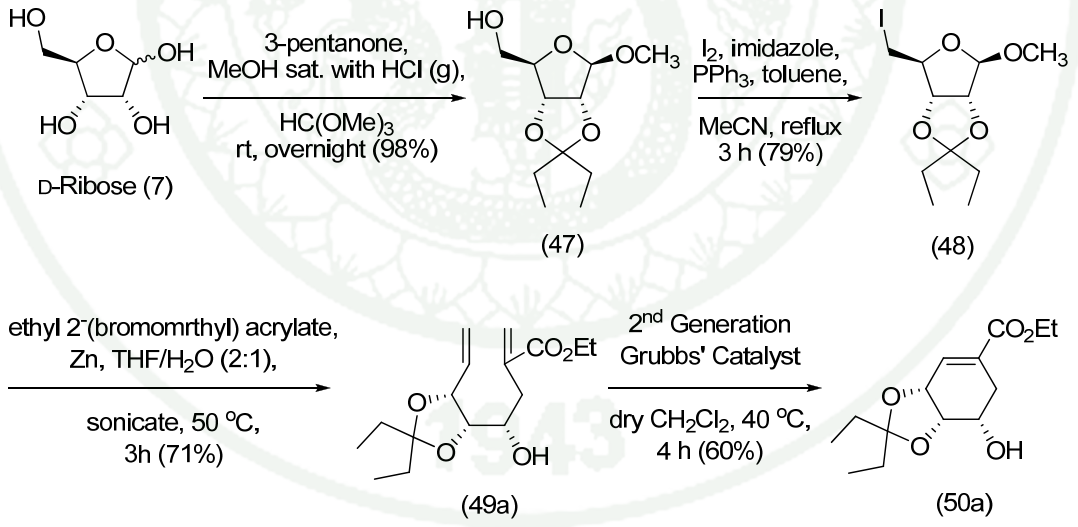
a) Tf_2O, Py, dry CH_2Cl_2, 0 ºC, 30 min

b) NaN_3, acetone/H_2O (9:1), rt, 15 h, (**67b**=34%, **73**=23%) (two steps)

c) PPh_3, dry THF, rt, 2 h, then Et_3N, H_2O, rt, 4 h, 30%

Discussion

The strategy to synthesize oseltamivir phosphate (4) started from D-ribose (7) was studied. The synthesis started from the selective protection of the *syn*-1,2-dihydroxy group of D-ribose (7) as 3-pentylidene ketal by reaction with 3-pentanone in methanolic saturated HCl(g) solution and trimethyl orthoformate. Methyl 2,3-*O*-isopentylidene-β-D-ribofuranose (47) was then converted to methyl 5-deoxy-5-iodo-2,3-*O*-isopentylidene-β-D-ribofuranose (48) by treatment with triphenylphosphine and iodine in the presence of imidazole. The iodinated intermediate **48** underwent a metal-mediate domino reaction in the presence of zinc and ethyl 2-(bromomethyl) acrylate under sonication to obtain the diene intermediate 2-carboethoxy-4-hydroxy-5,6-*O*-isopentylidene-1,7-octadiene (49a).Ring-closing olefin metathesis of diene **49a** using second generation Grubbs' catalyst provided ethyl 3,4-*O*-isopentylidene-5-epi-hydroxy shikimate (50a) (Scheme 12). The stereochemistry of compound **50a** was confirmed by 2D-NOESY NMR experiment (Figure 9).



Scheme 12

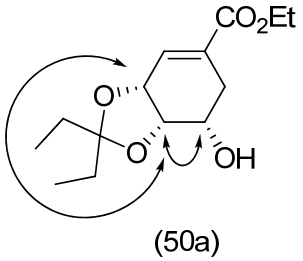
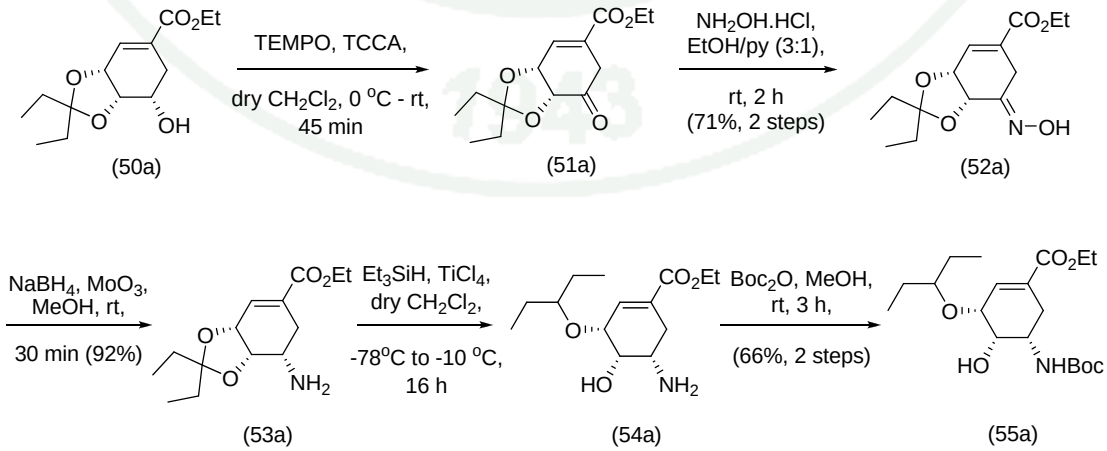
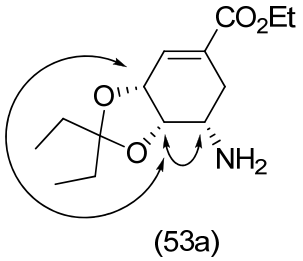


Figure 9 Correlations in 2D-NOESY NMR spectrum of compound **50a**.

After the construction of cyclohexene core structure, the secondary hydroxyl group of **50a** was converted into an amino group by oxidation with 2,2,6,6-tetramethylpiperidine 1-oxyl and trichloroisocyanuric acid, followed by oxime formation and then reduction of the oxime **52a** with sodium borohydride in the presence of molybdenum(VI) oxide to give ethyl (3*R*,4*S*,5*S*)-3-(1-ethyl-propoxy)-4-hydroxy-5-amino-cyclohex-1-ene-1-carboxylate (53a). The stereochemistry of compound **53a** was confirmed by 2D-NOESY NMR experiment (Figure 10). Regioselective reductive ring opening of the 5α-amino ketal **53a** with triethylsilane and titanium tetrachloride in dry dichloromethane at -78 to -10 ºC gave ethyl (3*R*,4*S*,5*S*)-3-(1-ethyl-propoxy)-4-hydroxy-5-amino-1-cyclohexene-1-carboxylate (54a). However, the polarity of amino alcohol **54a** was very high, made it very difficult to purify by column chromatography. Therefore, it was derivatized as *N*-Boc amino alcohol (55a) before purification (Scheme 13).



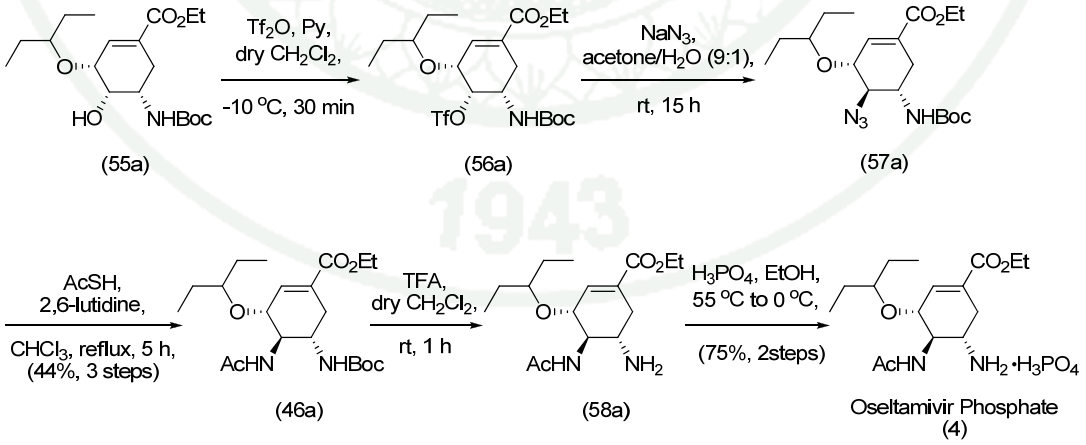
Scheme 13



(53a)

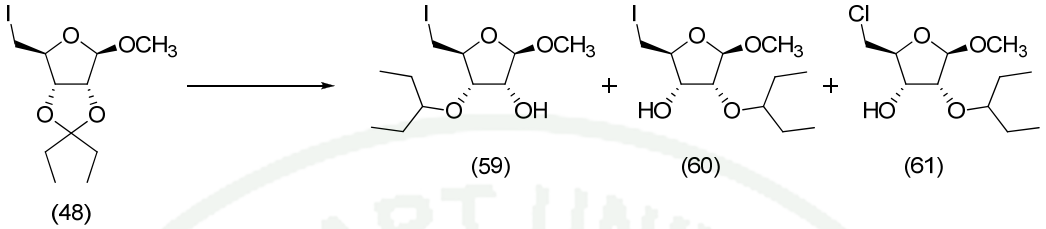
Figure 10 Correlations in 2D-NOESY NMR spectrum of compound **53a**.

The hydroxy group of **55a** was activated as the triflate and then underwent nucleophilic replacement with sodium azide in acetone/water (9:1) to provide ethyl (3*R*,4*R*,5*S*)-3-(1-ethyl-propoxy)-4-azido-5-*tert*-butoxycarbonylamino-cyclohex-1-ene-1-carboxylate (57a). The azide group of **57a** was transformed directly into an acetamide by treatment with thioacetic acid and 2,6-lutidine in chloroform at reflux to afford ethyl (3*R*,4*R*,5*S*)-3-(1-ethyl-propoxy)-4-acetamido-5-*tert*-butoxycarbonylamino -cyclohex-1-ene-1-carboxylate (46a). Finally, the Boc protecting group of **46a** was removed with trifluoroacetic acid to form an amine **58a**, which was directly exposed to 1.2 equiv. of phosphoric acid in ethanol at 55 ºC to afford oseltamivir phosphate (4) (Scheme 14). A similar synthetic approach was also used to synthesize Tamiphosphor (6).



Scheme 14

Table 5 Reaction conditions for the regioselective reductive ring opening of methyl 5-deoxy-5-iodo-2,3-*O*-isopentylidene-β-D-ribofuranose (48).



Entry	Reagents	Yield of 59 (%)	Yield of 60 (%)	Yield of 61 (%)
1	Et_3SiH, $TiCl_4$, dry CH_2Cl_2, -78 ºC to -10 ºC, 4 h	27[a]	15[a]	32[a]
2	Et_3SiH, $TiCl_4$, dry CH_3CN, 0 ºC to rt, 5 h	No reaction		
3	Et_3SiH, $BF_3{\cdot}Et_2O$, dry CH_3CN, 0 ºC to rt, 2 h	-	-	-
4	Et_3SiH, $Cu(OTf)_2$, dry CH_2Cl_2, rt, 5 h	No reaction		
5	1 M. $BH_3{\cdot}THF$, $BF_3{\cdot}Et_2O$, dry CH_3CN, 0 ºC to rt, 24 h	trace	trace	-
6	1 M. $BH_3{\cdot}THF$, $Cu(OTf)_2$, rt, 2 h	45[b]	43[b]	-
7	1 M. $BH_3{\cdot}THF$, $Cu(OTf)_2$, dry CH_2Cl_2, rt, 5 h	trace	trace	-

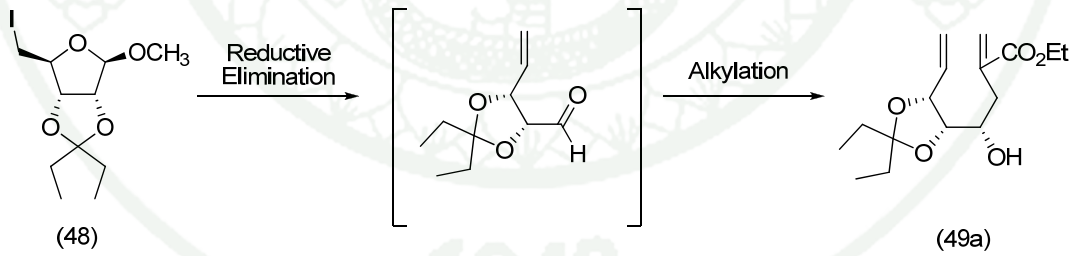
[a] Isolated yield.

[b] Based on 61% recovery.

An attempt to functionalize the starting material, D-ribose (7), before constructing the cyclohexene core structure was also studied (Table 5). Regioselective reductive ring-opening of pentylidene ketal of methyl 5-deoxy-5-iodo-2,3-*O*-isopentylidene-β-D-ribofuranose (48) using titanium tetrachloride and triethylsilane gave the mixture of the desired product **59** in low yield along with the regioisomer of the desired product **60** and the by product **61** resulting from the replacement of iodide in compound **60** with chloride (entry 1, Table 5). The unsatisfied result also obtain from the used of borane tetrahydrofuran complex and copper(II) triflate. The reaction

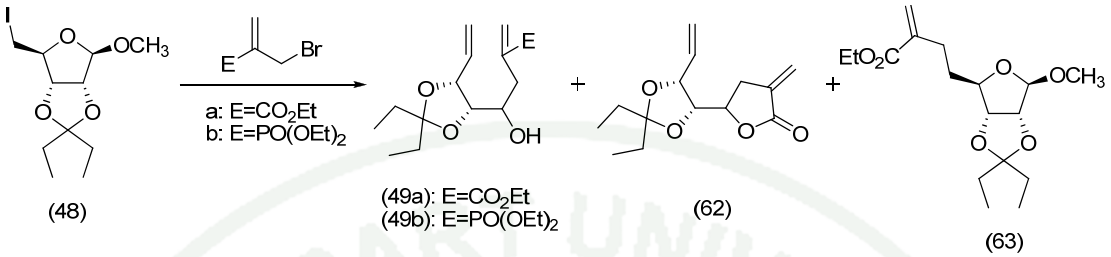
was not complete (39% conversion) while the approximately 1:1 of the isomer **59** and **60** was continuously degraded (entry 6, Table 5). Recombination of reducing agent (triethylsilane, borane tetrahydrofuran complex) and Lewis acid (titanium tetrachloride, boron trifluoride diethyl etherate, copper(II) triflate) in various solvent (dichloromethane, acetonitrile, tetrahydrofuran) result in either no reaction or no desired product.

A metal-mediate domino reaction of methyl 5-deoxy-5-iodo-2,3-*O*-isopentylidene-β-D-ribofuranose (48) was examined. This reaction consists of reductive elimination and alkylation steps (Scheme 15). The reaction with zinc gave diene **α-49a** along with lactone **62** resulting from cyclization of intermediate **49a** (entry 1, Table 6) while the reaction with indium provided diene **α-49a** and alkylated product **63** (entry 2, Table 6). These results indicated that reductive elimination occurred faster than alkylation in the presence of zinc whereas in the presence of indium, alkylation competed with reductive elimination. To avoid the formation of alkylated product **63** in the reaction with indium, catalytic amount of acetic acid was used to help accelerate the reductive elimination step and resulting in the higher ratio of **49a** and **63** (from 3:2 to 10:1) (entry 3, Table 6).



Scheme 15

Table 6 Metal-mediated domino reaction of methyl 5-deoxy-5-iodo-2,3-*O*-isopentylidene-β-D-ribofuranose (48).



Entry	Metal	Reagents	Yield of 49 (%)[b]	Yield of 62 (%)[b]	Yield of 63 (%)[b]
1	Zn	a, THF/H_2O (2:1), sonicate, 50 ºC, 3 h	**(α-49a)** 71	22	-
2	In	a, THF/H_2O (2:1), sonicate, 50 ºC, 3 h	**(α-49a)** 45	-	30
3	In	a, THF/H_2O (2:1), AcOH sonicate, 50 ºC, 1 h[a]	**(α-49a)** 70	-	7
4	Zn	b, THF/H_2O (2:1), sonicate, 50 ºC, 3 h	**(49b)** 68 (α:β=1:3)	-	-

[a] AcOH (0.01 eq.) was added and sonicated until the aldehyde intermediate formed (monitoring by TLC) then ethyl 2-(bromomethyl) acrylate was added and the reaction was sonicated for another 2 h.

[b] Isolated yield.

For the configuration of alcohol **49a**, the stereochemistry was assigned after cyclization. The stereoselectivity can be explained by Felkin Anh model which nucleophile attacks a carbonyl compound at the least steric side. In this case, nucleophile approach to the least hindered side between the H and C atom which is a *Si* face of aldehyde to give the alcohol **49a** (Figure 11).

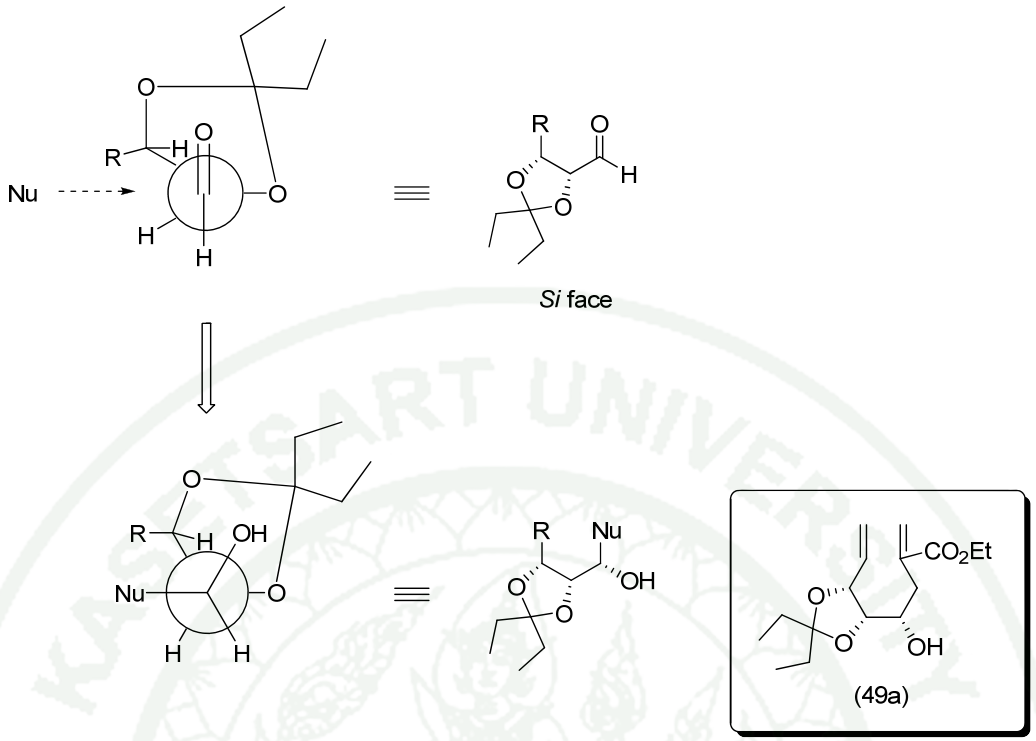
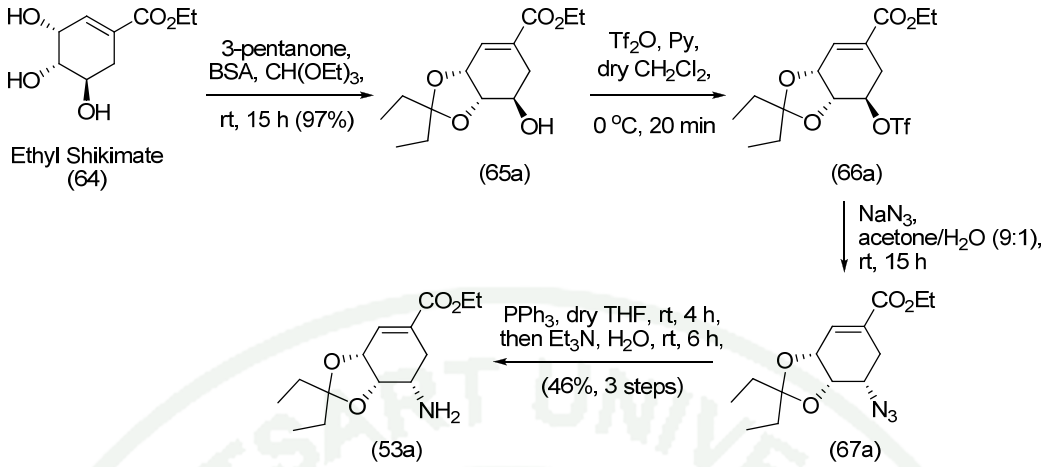


Figure 11 Felkin Anh model.

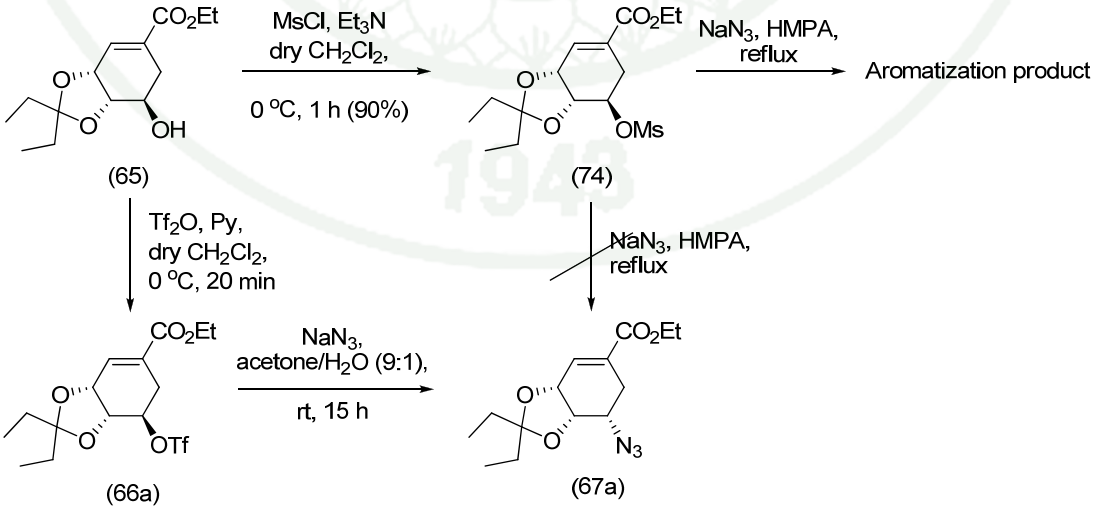
A similar synthetic approach toward the synthesis of Tamiflu (4) was also used to synthesize Tamiphosphor (6). The iodinated intermediate **48** underwent a metal-mediate domino reaction in the presence of zinc and diethyl 3-bromoprop-1-en-2-ylphosphonate under sonication to obtain the diene intermediate **49b** as an inseparable mixture of α and β isomer in ratio 1:3 (entry 4, Table 6) (the stereochemistry was determined after the construction of cyclohexene ring).

In addition to 2D-NOESY NMR experiment, the stereochemistry of ethyl 3,4-*O*-isopentylidene-5α-amino shikimate (53a) was also confirmed by stereospecific synthesis which ethyl shikimate (64) was used as a starting material for the stereo specific route. Ethyl shikimate (64) was subjected to the nucleophilic replacement using sodium azide as a nucleophile to give the desired stereoisomer of the amino group after the reduction of the azide (Scheme 16).



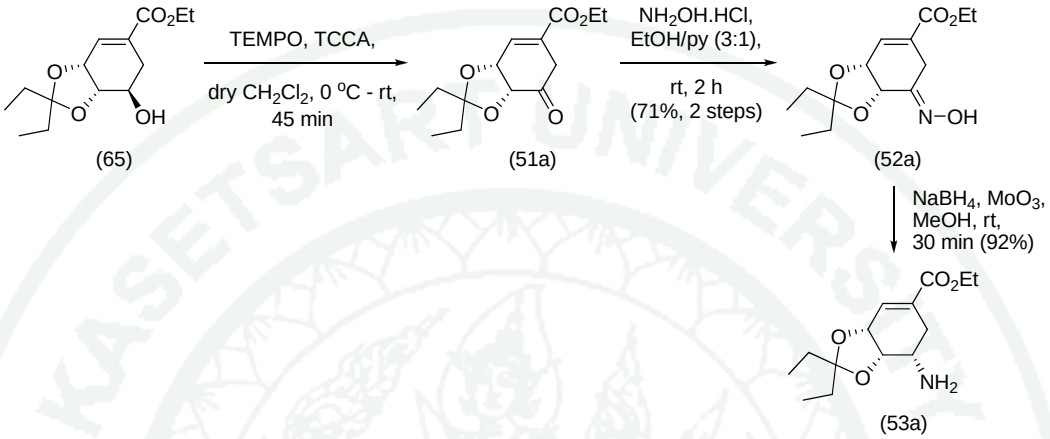
Scheme 16

To do the nucleophilic replacement with sodium azide, the hydroxyl group was converted to a good leaving group. Mesylate group was the first leaving group used in our investigation. The reaction was set at the refluxing temperature in hexamethylphosphoramide (HMPA) resulted in the aromatization of the mesylate intermediate **74**. Changing from mesylate to triflate group, the reaction was proceed in acetone/water at room temperature to give crude ethyl 3,4-*O*-isopentylidene-5α-azido shikimate (67a). The azido group in compound **67a** was reduced using Staudinger reaction to give the amine **53a** (Scheme 17).



Scheme 17

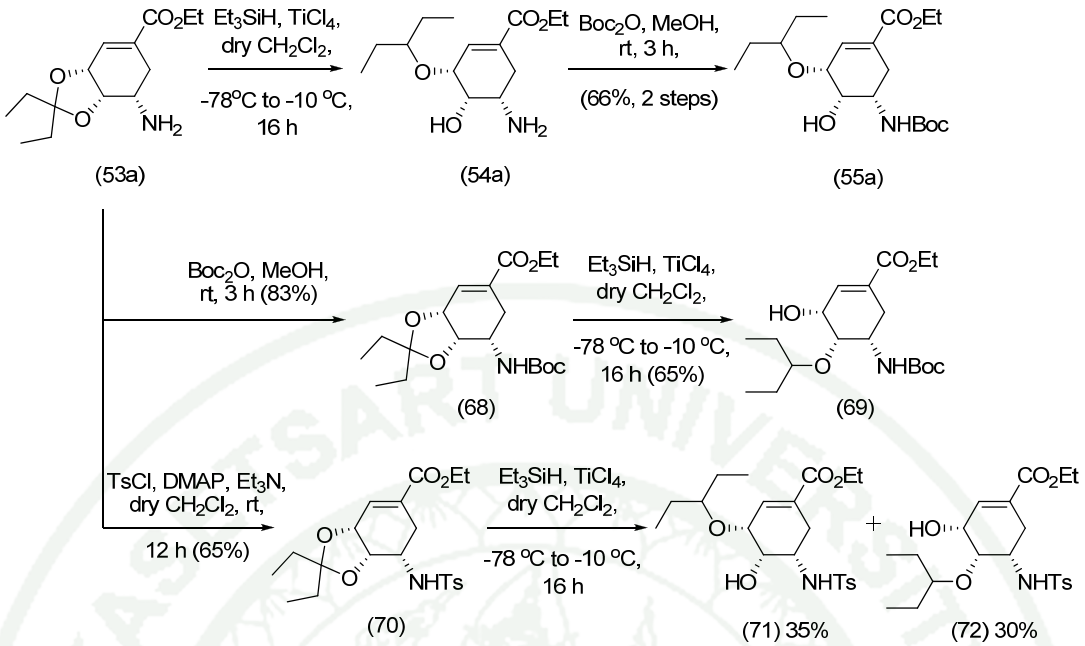
Using the same methodology as the ribose route, ethyl 3,4-*O*-isopentylidene-5-hydroxy shikimate (65) was oxidized, treated with hydroxylamine hydrochloride and reduced with sodium borohydride to provide the amine **53a** which its spectrum is identical to those obtained from the nucleophilic replacement (Scheme 18).



Scheme 18

The stereochemistry of the amine **53a** results from the steric hindrance of pentylidene ketal, allowing hydride to attack only the less steric side to give α-isomer of the amino group.

3-Pentyl ether moiety was introduced *via* the regioselective reductive ring opening of the pentylidene ketal to give the amino alcohol **54a** as the only product. Dew to its high polarity, the amino alcohol **54a** was derivatized as *N*-Boc amino alcohol **55a** before the purification. To reduce the polarity of the product from the regioselective reductive ring opening reaction, the amine **53a** was derivatized as *N*-Boc before subjected to the reaction. Surprisingly the only product obtained from the reaction was the alternate regioisomer **69**. Another protecting group utilized was tosyl group. However, the regioselective reductive ring opening reaction of *N*-Ts derivative **70** gave the mixture of the regioisomer **71** and **72** in approximately 1:1 ratio (Scheme 19).



Scheme 19

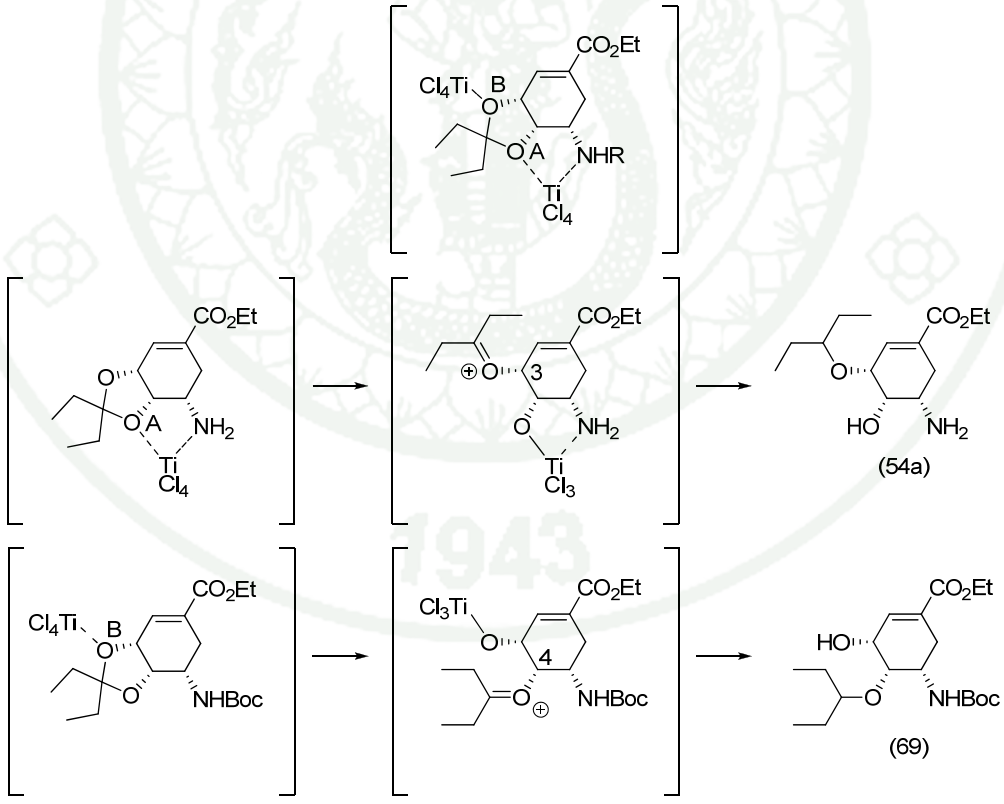
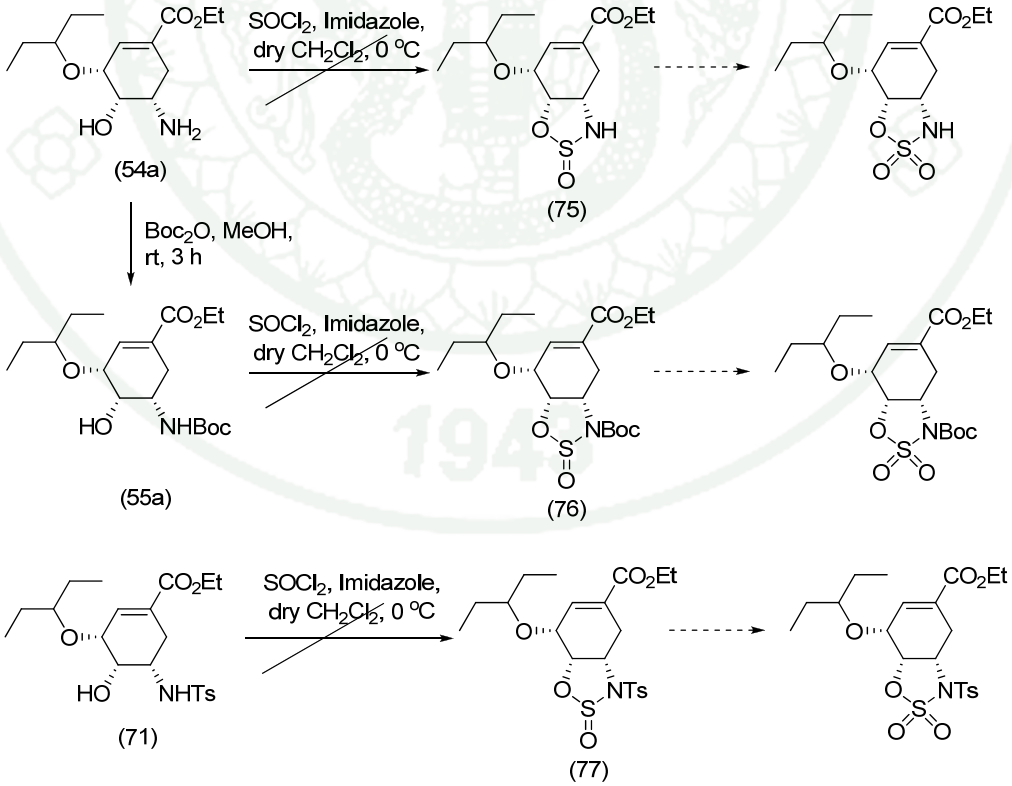


Figure 12 Coordination of Lewis acid in regioselective reductive ring opening reaction

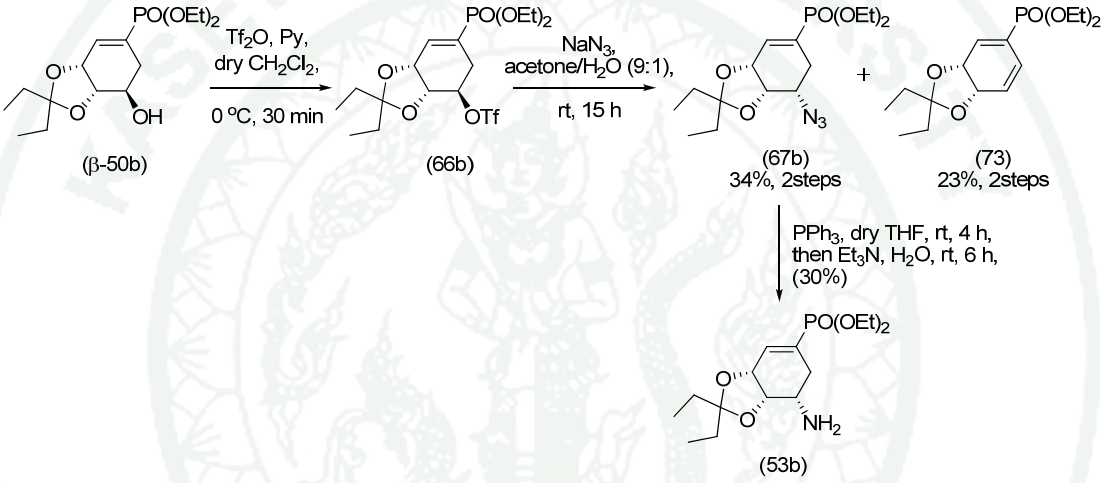
These result indicated that titanium tetrachloride which is Lewis acid can coordinate to both oxygen A and B. For the free amine **53a**, both oxygen A and nitrogen of the amino group coordinated to titanium tetrachloride to give the oxonium at C-3 position, leading to the desired product **54a**. But when the amino group was derivatized, the Boc protecting group make the amino less basicity and also increase the steric hindrance. Therefore, titanium tetrachloride coordinated to the less steric oxygen B to give the oxonium at C-4 position, leading to the undesired isomer **69** (Figure 12).

To introduce another amino group, the nucleophilic displacement of cyclic sulfamidate was considered. Preparation of the cyclic sulfamidite from the reaction of 1,2-amino alcohol **54a** and thionyl chloride was unsuccessful. *N*-Boc (55a) and *N*-tosyl (71) amino derivatives were also utilized. Unfortunately, both *N*-Boc (55a) and *N*-tosyl amino alcohol (71) failed to give cyclic sulfamidite **76** and **77** respectively (Scheme 20).



Scheme 20

Similar to the identification of ethyl 3,4-*O*-isopentylidene-5α-amino shikimate (53a), diethyl (3*R*,4*S*,5*S*)-3,4-*O*-isopentylidene-5-amino-1-cyclohexene phosphonate (53b) was synthesized from diethyl (3*R*,4*S*,5*R*)-3,4-*O*-isopentylidene-5-hydroxy-1-cyclohexene phosphonate (β-50b) using the stereospecific nucleophilic substitution. Replacement of a triflate group in **66b** with an azido group using sodium azide in 9:1 acetone/water at room temperature provided azido intermediate **67b** along with the triflate elimination product **73** (Scheme 21). The stereochemistry of compound **β-50b** and **53b** were confirmed by 2D-NOESY NMR experiment (Figure 13).



Scheme 21

Figure 13 Correlations in 2D-NOESY NMR spectra of compound **β-50b** and **53b.**

CONCLUSION

The syntheses of oseltamivir phosphate (Tamiflu, 4) and advance intermediate (55b) to Tamiphosphor have been accomplished. The synthesis used D-ribose as a starting material which is cheap and commercially available.

The main features of this approach comprise a metal (Zn, In)-mediated domino reaction of methyl 5-deoxy-5-iodo-2,3-*O*-isopentylidene-β-D-ribofuranose (48) and ring-closing olefin metathesis (RCM) of the resultant functionalized dienes to produce the Tamiflu skeleton.

The synthesis represents a new and efficient transformation of a 5-epi-hydroxy shikimate derivative into a 1,2-diamino compound which involved oxidation of an alcohol followed by reductive amination, regioselective reductive ring opening of a pentylidene ketal and stereospecific nucleophilic replacement of a triflate with an azide.

In summary, we have accomplished an efficient synthesis of Tamiflu (4) in 14 steps with 5% overall yield, using cheap and commercially D-ribose as the starting material. This synthetic approach was also utilized to synthesize an advance intermediate (55b) to Tamiphosphor in 9 steps with 2 % overall yield. Moreover, transformation of the 5-epi-hydroxy shikimate derivative into a 1,2-diamino compound represents a new and efficient synthetic route for the synthesis of Tamiflu (4) which has the potential to be developed as an industrial process in the future.

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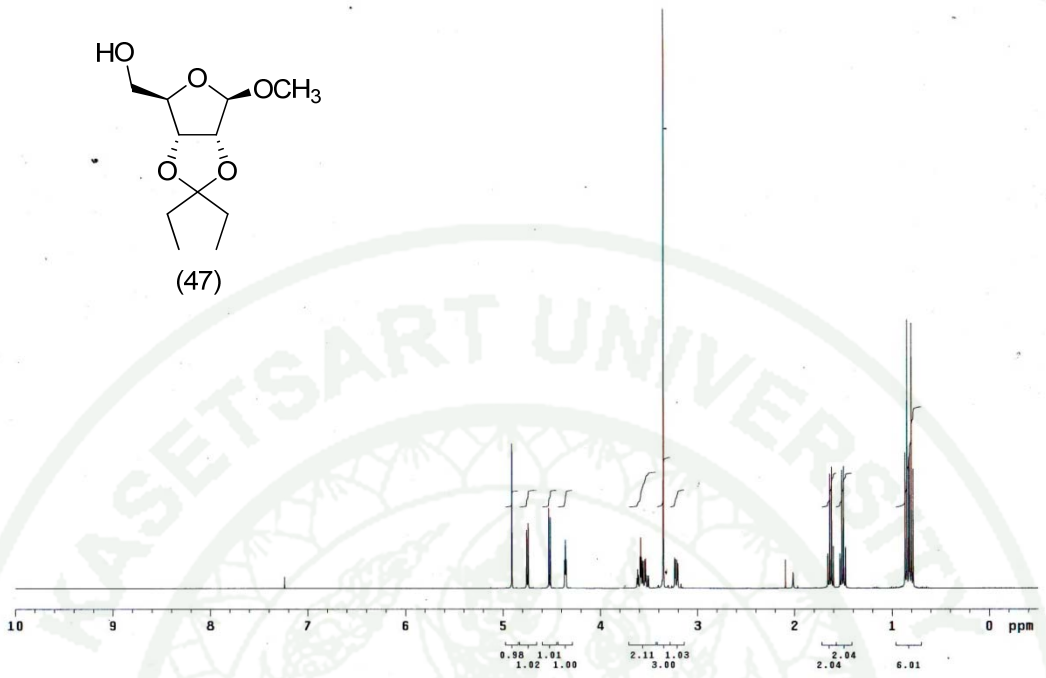
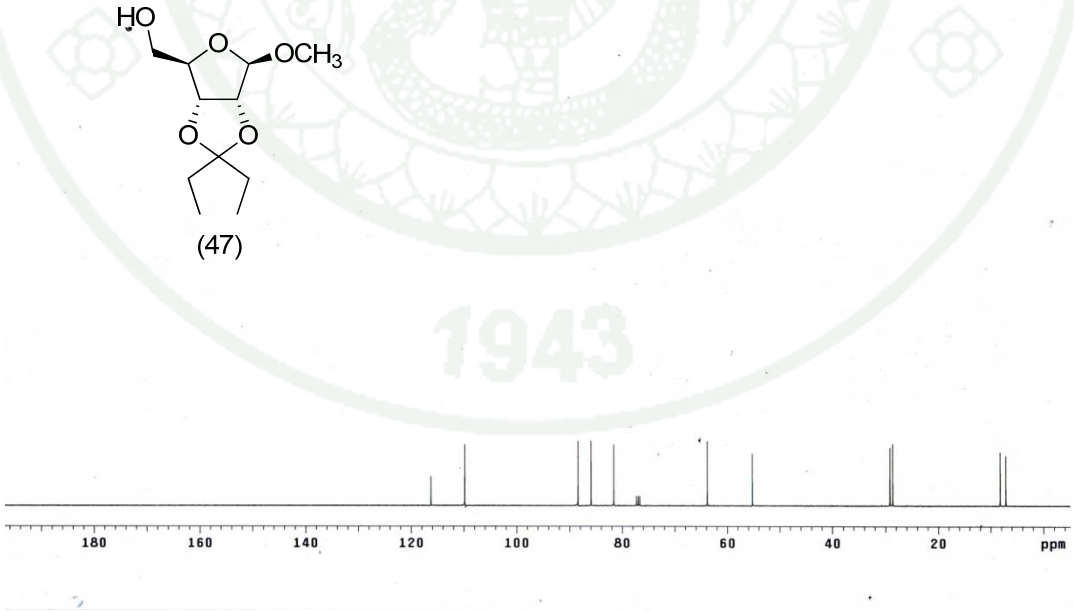
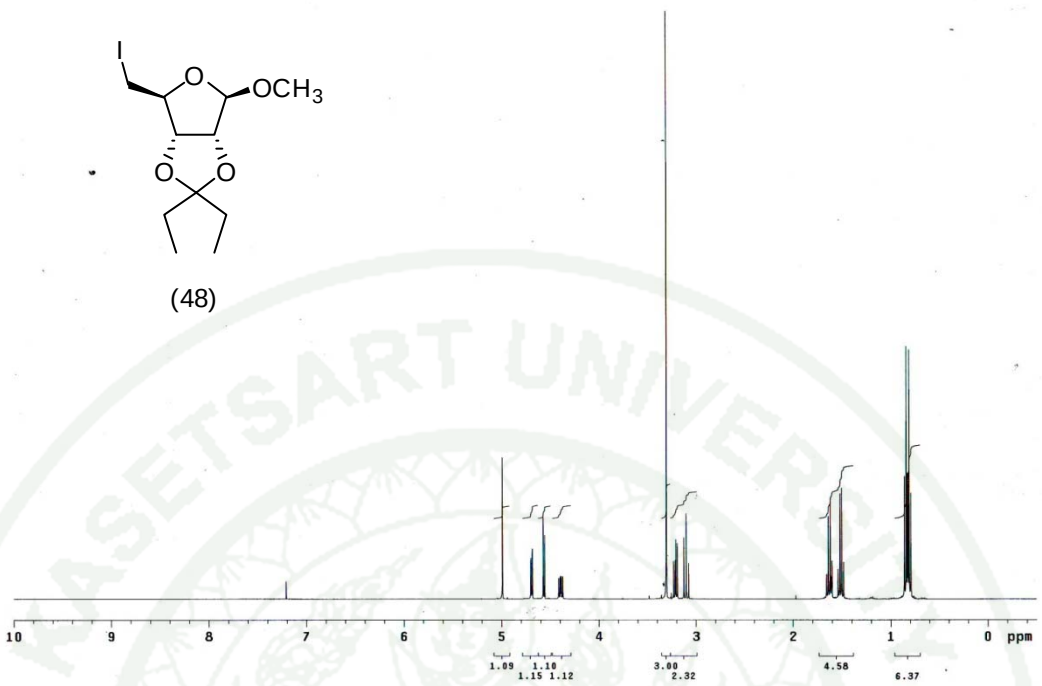
APPENDIX



Appendix Figure 1 400 MHz ^{1}H NMR spectrum of methyl 2,3-*O*-isopentylidene-β-D-ribofuranose (47)

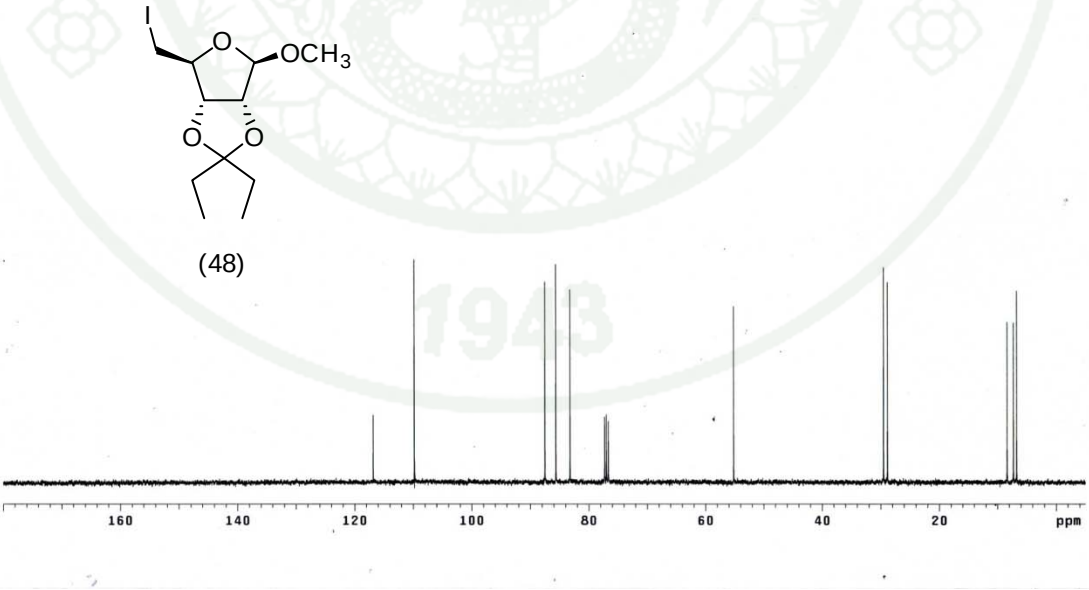


Appendix Figure 2 100 MHz ^{13}C NMR spectrum of methyl 2,3-*O*-isopentylidene-β-D-ribofuranose (47)



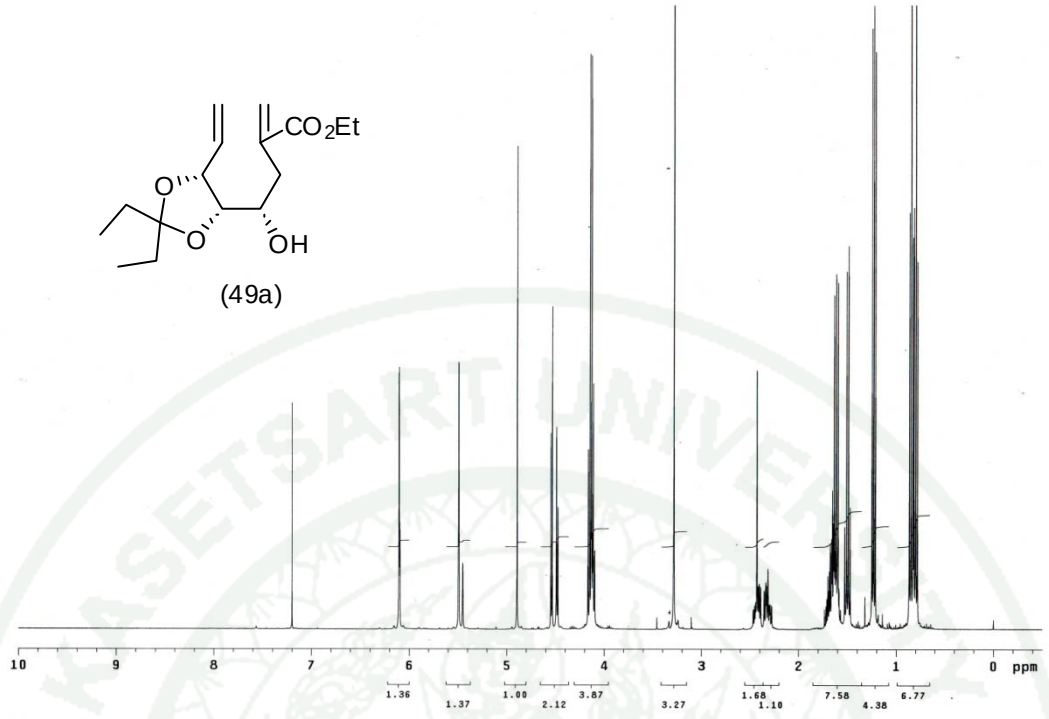
(48)

Appendix Figure 3 400 MHz ^{1}H NMR spectrum of methyl 5-deoxy-5-iodo-2,3-*O*-isopentylidene-β-D-ribofuranose (48)

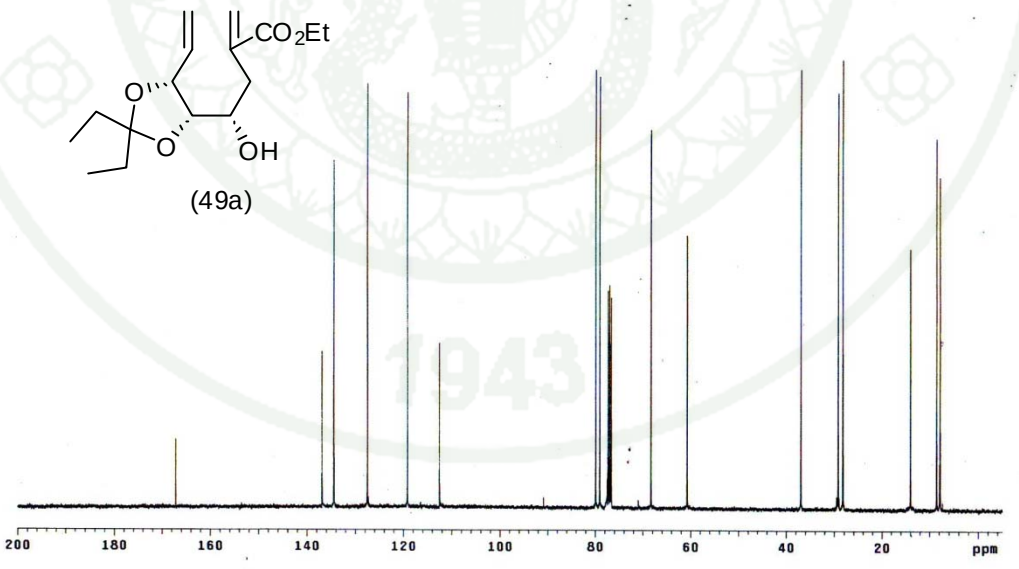


(48)

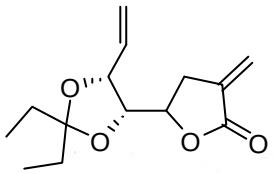
Appendix Figure 4 100 MHz ^{13}C NMR spectrum of methyl 5-deoxy-5-iodo-2,3-*O*-isopentylidene-β-D-ribofuranose (48)



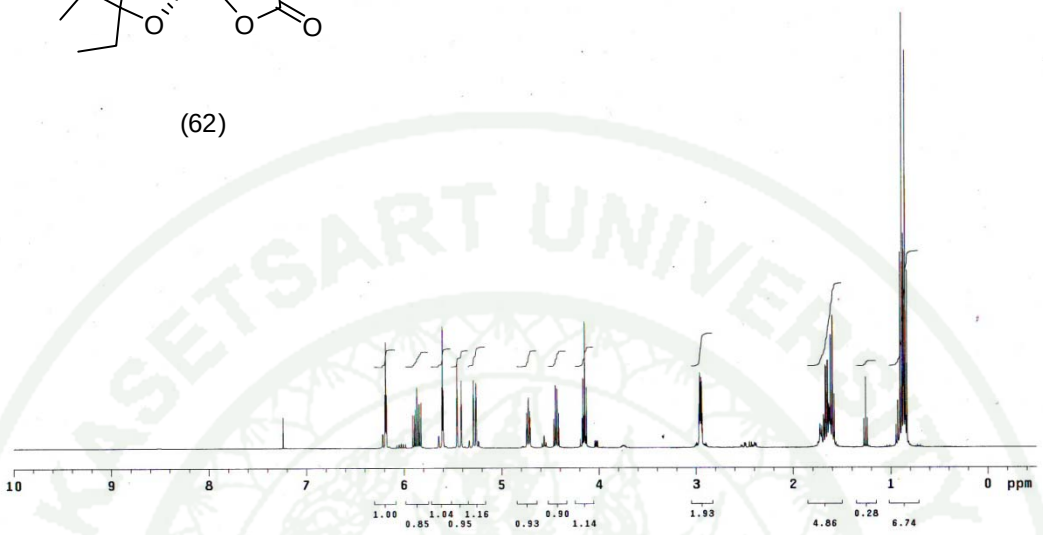
Appendix Figure 5 400 MHz ^{1}H NMR spectrum of 2-carboethoxy-4-hydroxy-5,6-*O*-isopentylidene-1,7-octadiene (49a)



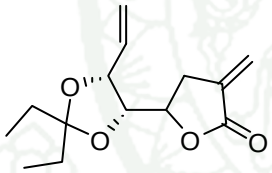
Appendix Figure 6 100 MHz ^{13}C NMR spectrum of 2-carboethoxy-4-hydroxy-5,6-*O*-isopentylidene-1,7-octadiene (49a)



(62)



Appendix Figure 7 400 MHz ^{1}H NMR spectrum of lactone compound **62**



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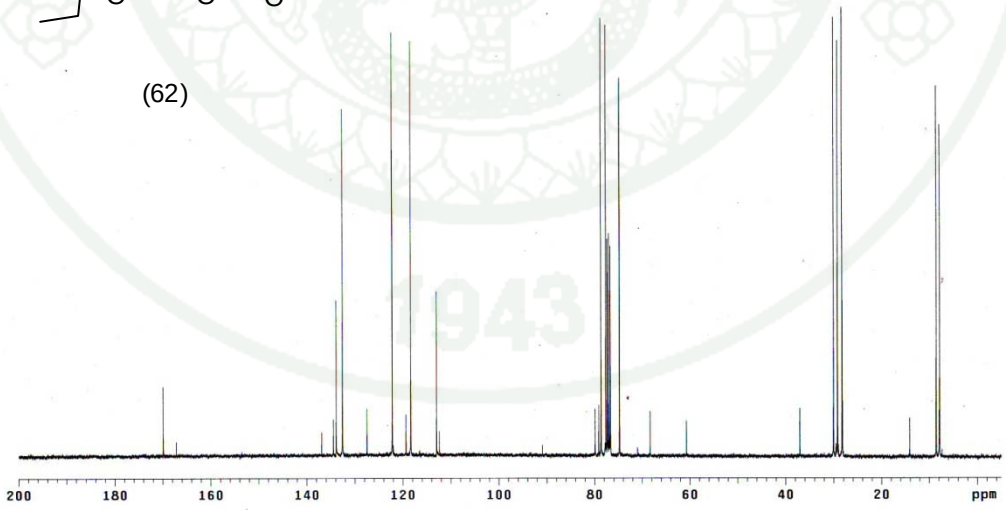
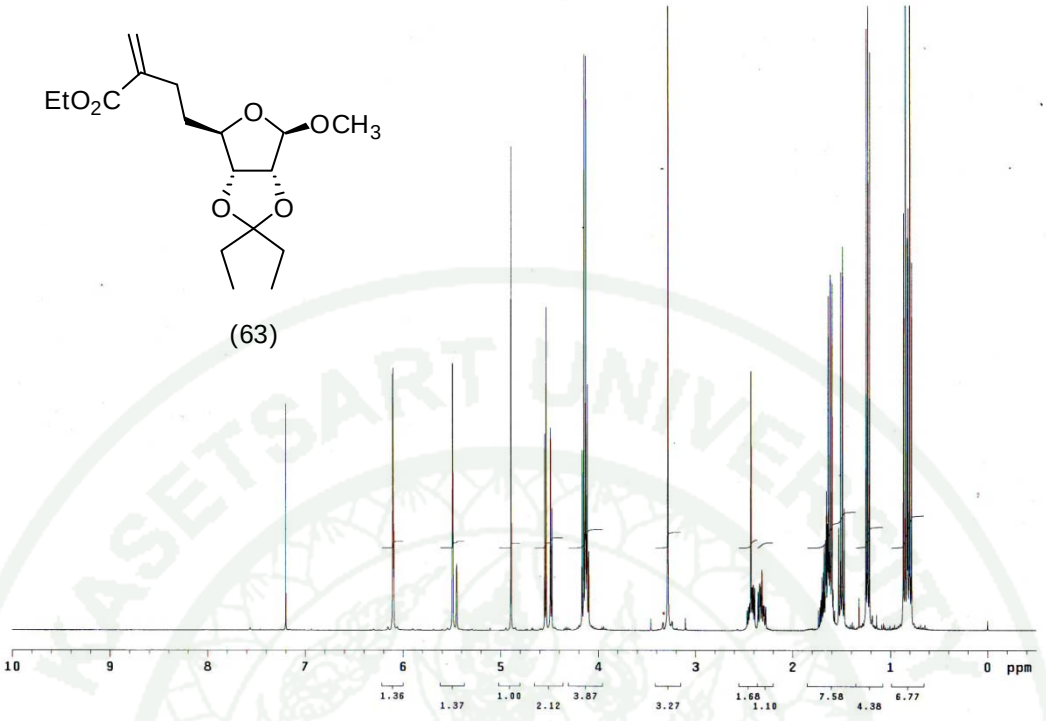
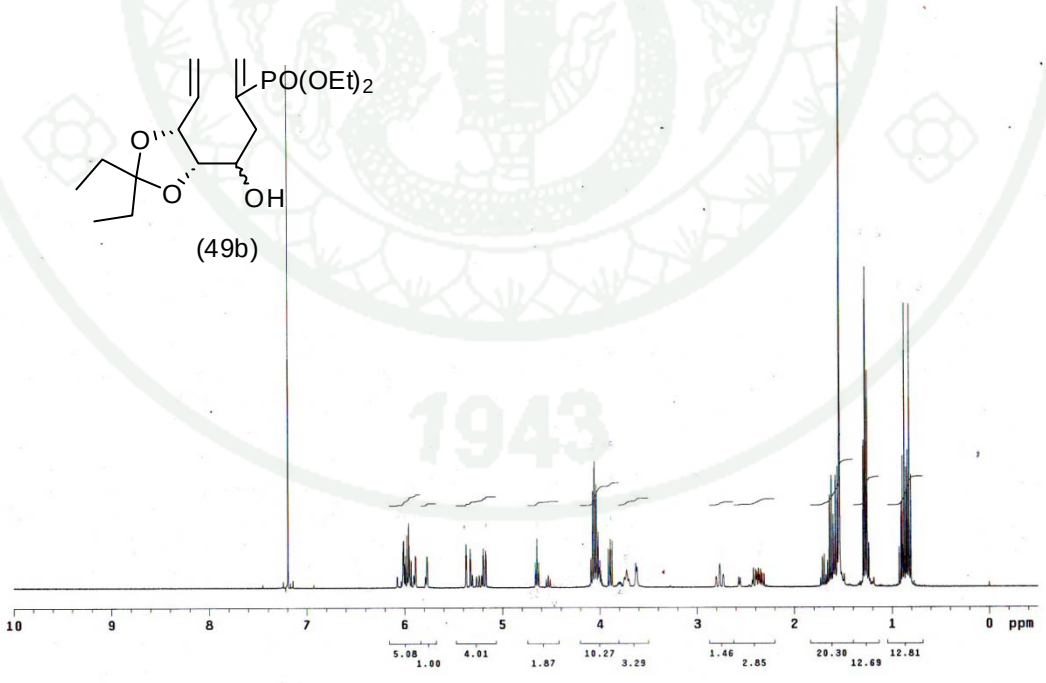


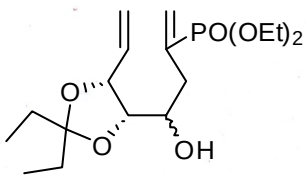
Appendix Figure 8 100 MHz ^{13}C NMR spectrum of lactone compound **62**



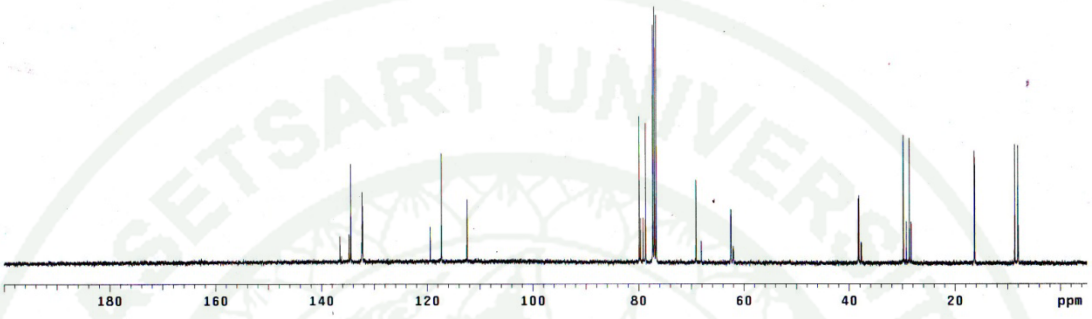
Appendix Figure 9 400 MHz ^{1}H NMR spectrum of compound **63**



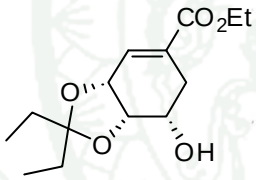
Appendix Figure 10 400 MHz ^{1}H NMR spectrum of 2-phosphodiethoxy-4-hydroxy-5,6-*O*-isopentylidene-1,7-octadiene (49b)



(49b)

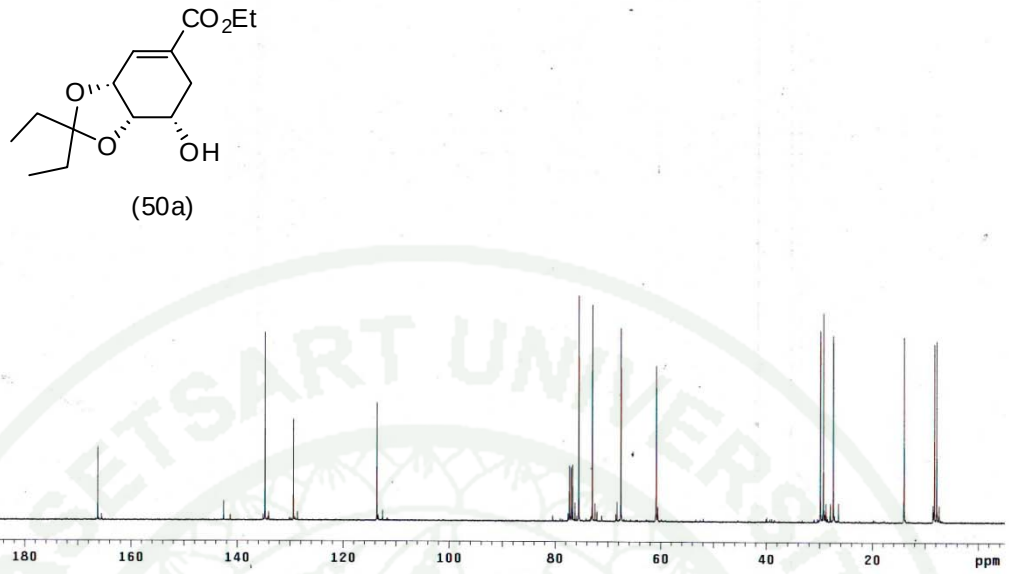


Appendix Figure 11 100 MHz ^{13}C NMR spectrum of 2-phosphodiethoxy-4-hvdroxy-5,6-*O*-isopentylidene-1,7-octadiene (49b)

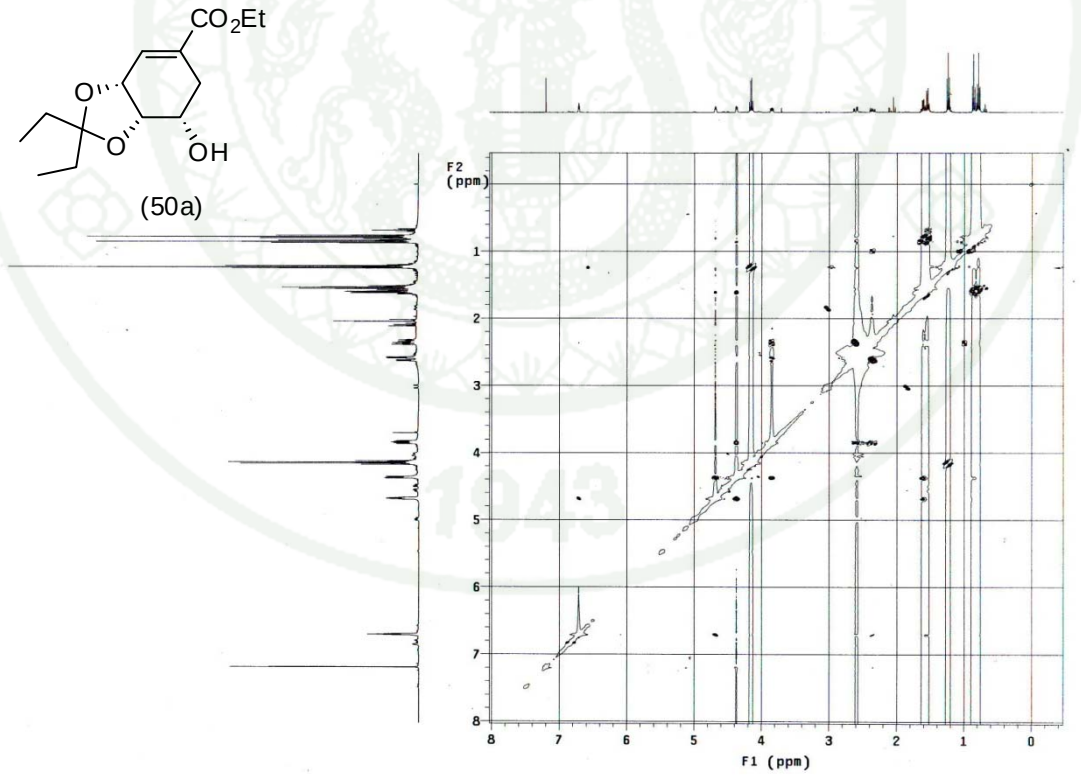


(50a)

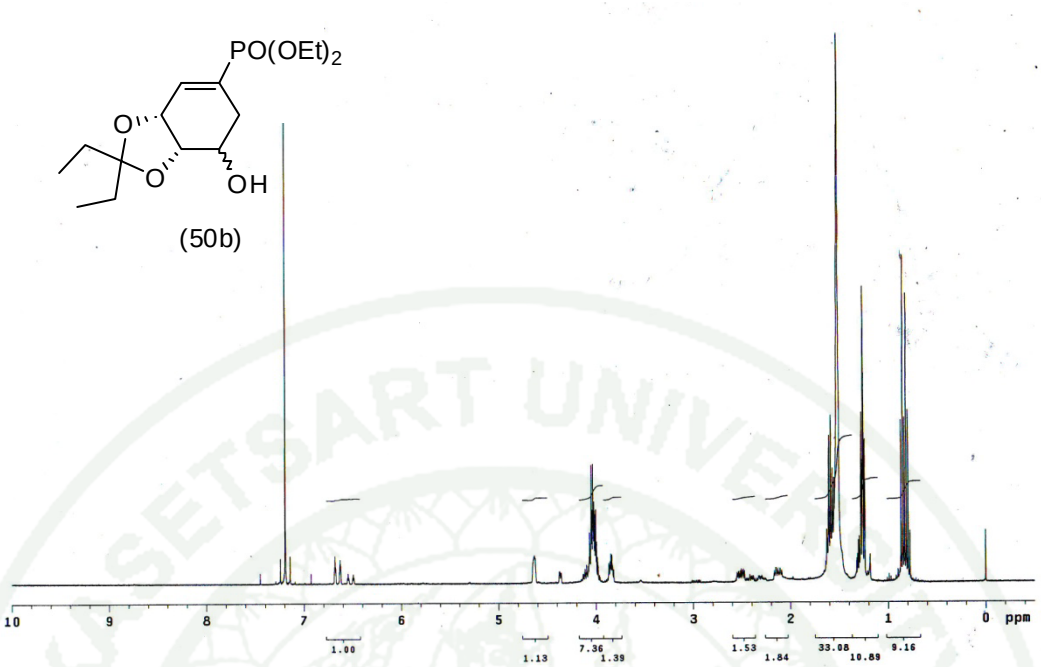
Appendix Figure 12 400 MHz ^{1}H NMR spectrum of ethyl 3,4-*O*-isopentylidene-5-epi-hydroxy shikimate (50a)



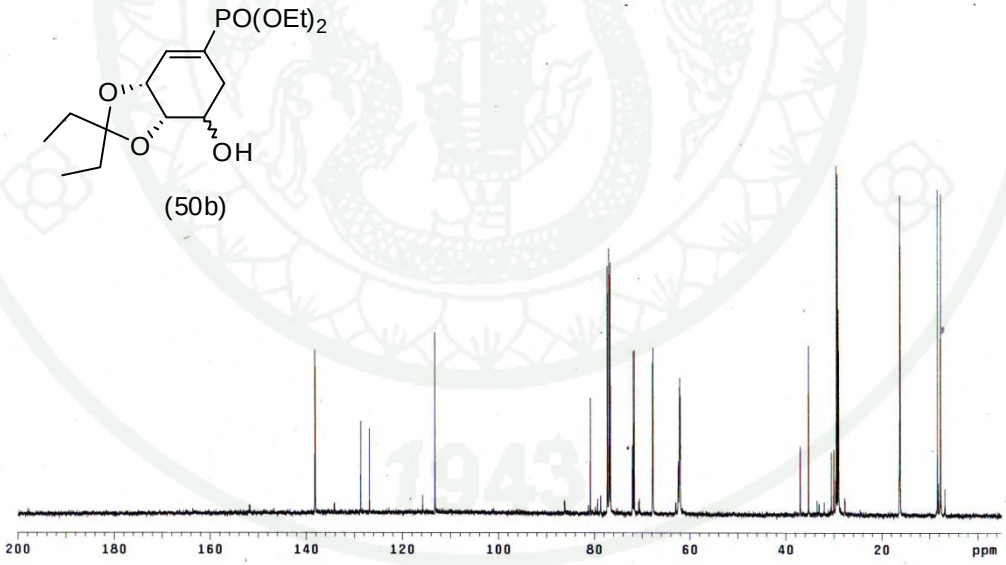
Appendix Figure 13 100 MHz ^{13}C NMR spectrum of ethyl 3,4-*O*-isopentylidene-5-epi-hydroxy shikimate (50a)



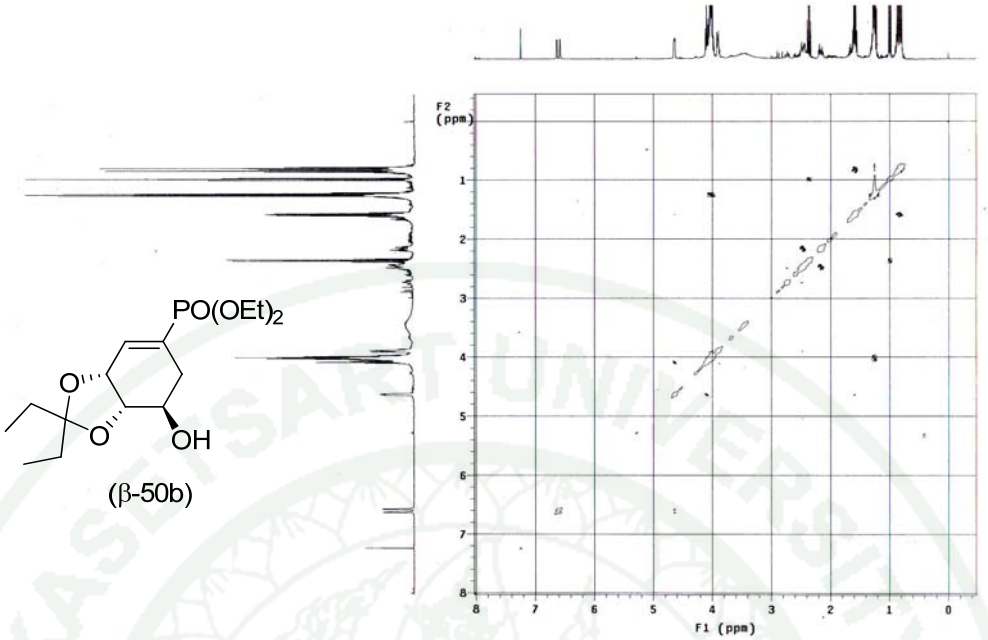
Appendix Figure 14 2D-NOESY spectrum of ethyl 3,4-*O*-isopentylidene-5-epi-hydroxy shikimate (50a)



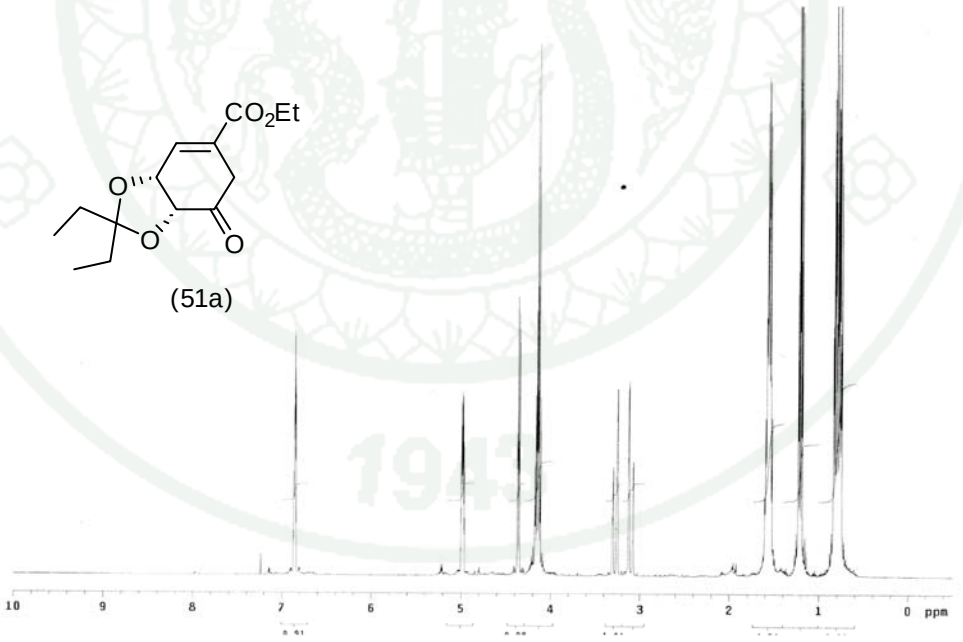
Appendix Figure 15 400 MHz ^{1}H NMR spectrum of diethyl (3*R*,4*S*)-3,4-*O*-isopentylidene-5-hydroxy-1-cyclohexene-1-phosphonate (50b)



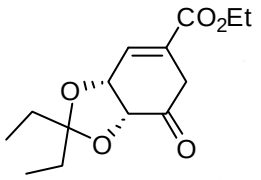
Appendix Figure 16 100 MHz ^{13}C NMR spectrum of diethyl (3*R*,4*S*)-3,4-*O*-isopentylidene-5-hydroxy-1-cyclohexene-1-phosphonate (50b)



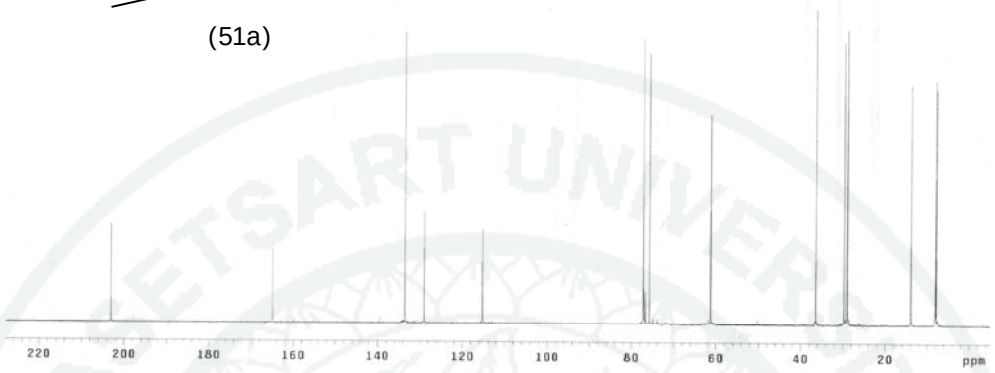
Appendix Figure 17 2D-NOESY spectrum of diethyl (3*R*,4*S*,5*R*)-3,4-*O*-isopentylidene-5-hydroxy-1-cyclohexene-1-phosphonate (β-50b)



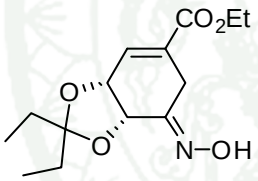
Appendix Figure 18 400 MHz ^{1}H NMR spectrum of ethyl 3,4-*O*-isopentylidene-5-keto shikimate (51a)



(51a)

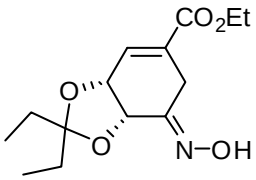


Appendix Figure 19 100 MHz ^{13}C NMR spectrum of ethyl 3,4-*O*-isopentylidene-5-keto shikimate (51a)

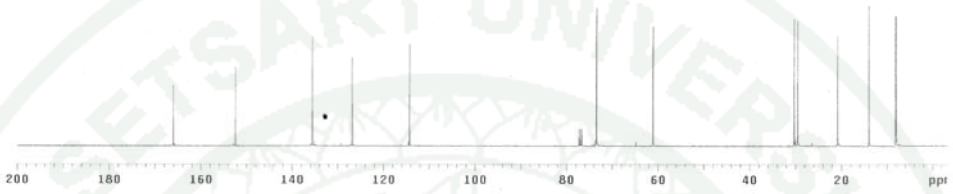


(52a)

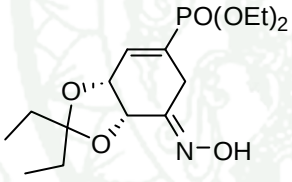
Appendix Figure 20 400 MHz ^{1}H NMR spectrum of ethyl 3,4-*O*-isopentylidene-5-oxime shikimate (52a)



(52a)

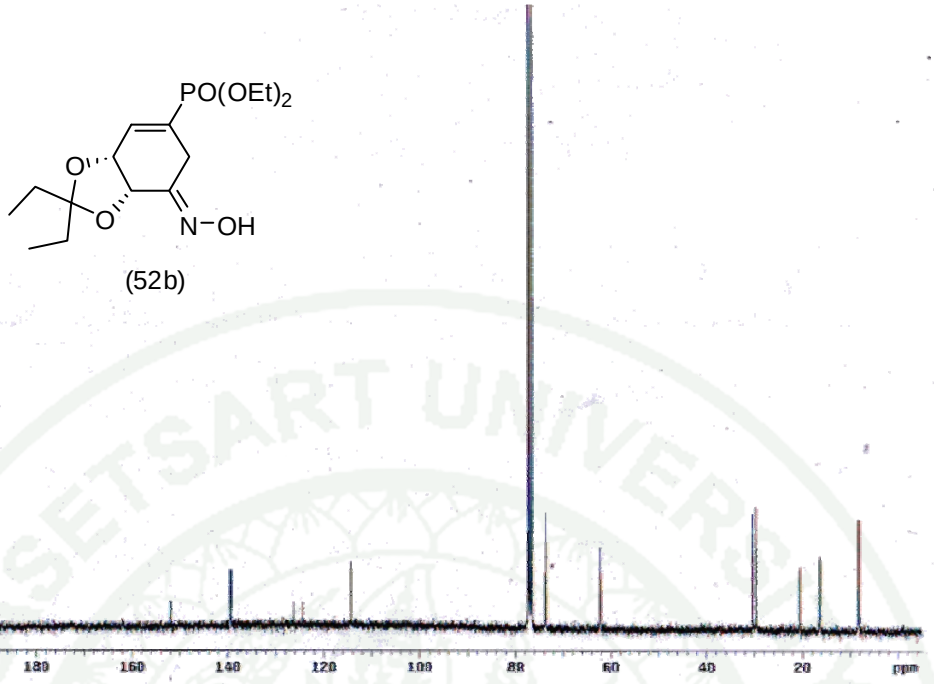


Appendix Figure 21 100 MHz ^{13}C NMR spectrum of ethyl 3,4-*O*-isopentylidene-5-oxime shikimate (52a)

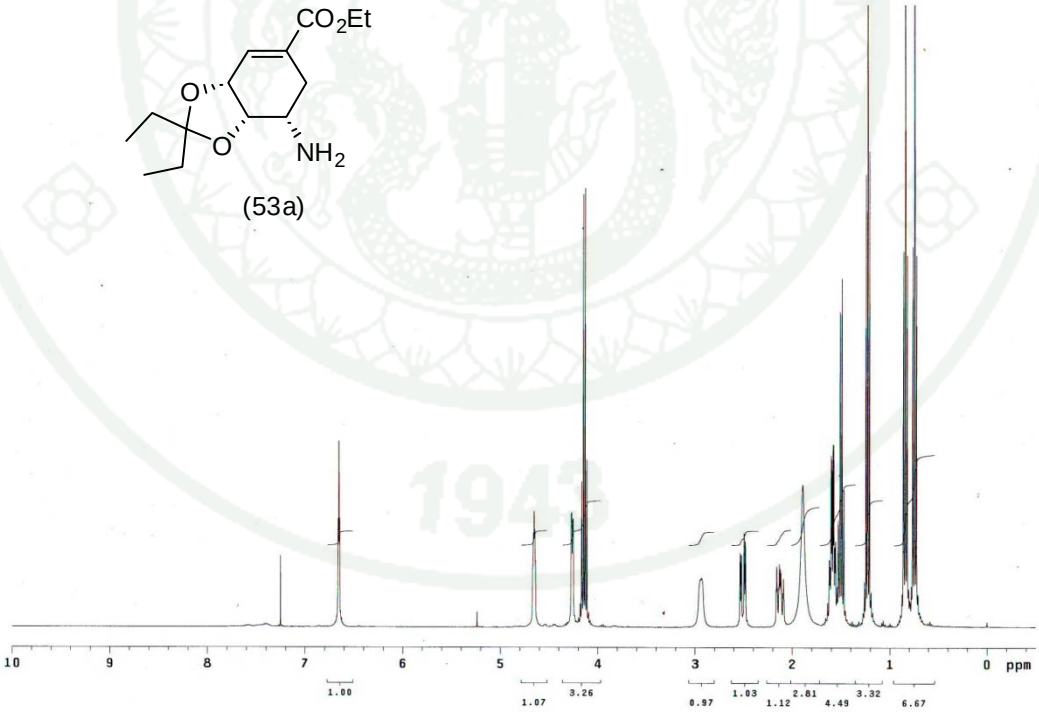


(52b)

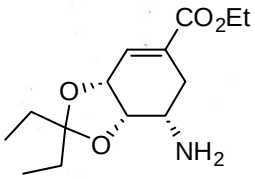
Appendix Figure 22 400 MHz ^{1}H NMR spectrum of diethyl (3*R*,4*S*)-3,4-*O*-isopentylidene-5-oxime-1-cyclohexene-1-phosphonate (52b)



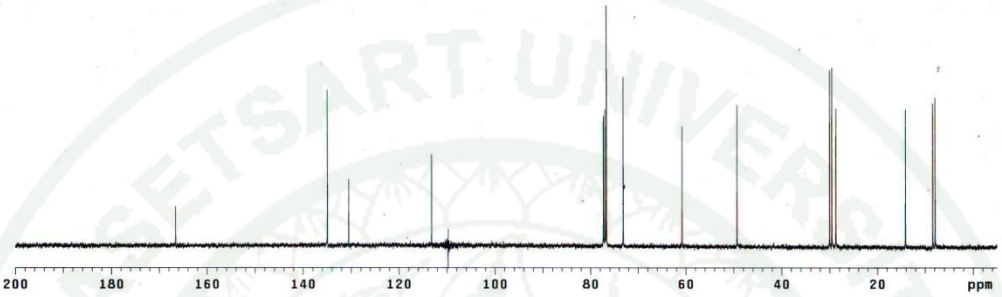
Appendix Figure 23 100 MHz ^{13}C NMR spectrum of diethyl (3*R*,4*S*)-3,4-*O*-isopentylidene-5-oxime-1-cyclohexene-1-phosphonate (52b)



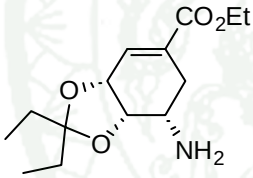
Appendix Figure 24 400 MHz ^{1}H NMR spectrum of ethyl 3,4-*O*-isopentylidene-5α-amino shikimate (53a)



(53a)

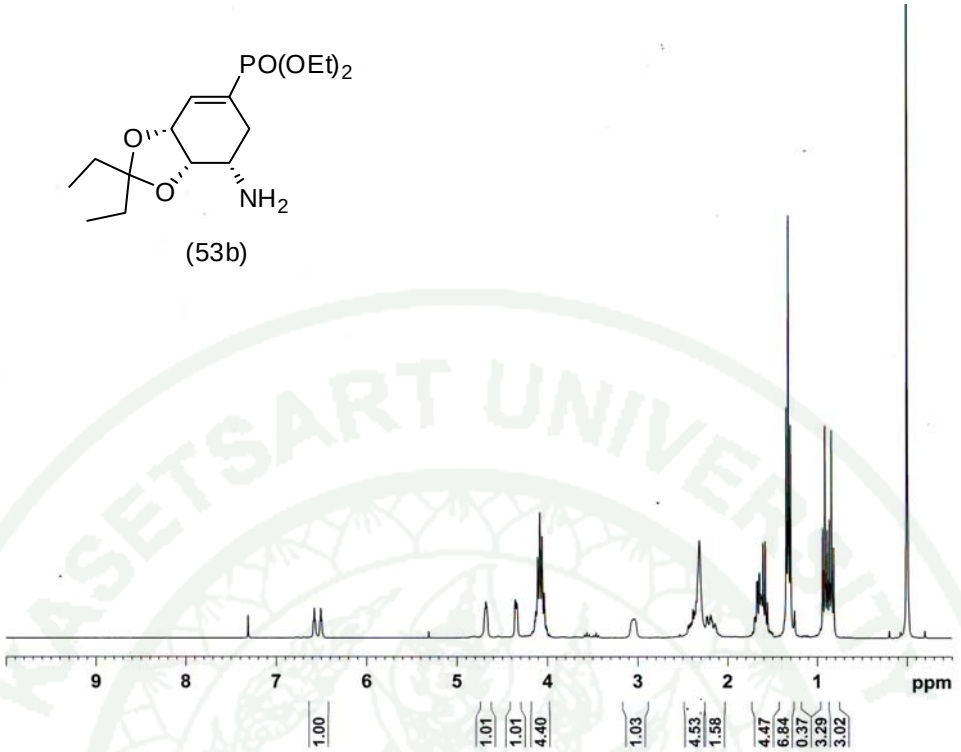


Appendix Figure 25 100 MHz ^{13}C NMR spectrum of ethyl 3,4-*O*-isopentylidene-5α-amino shikimate (53a)

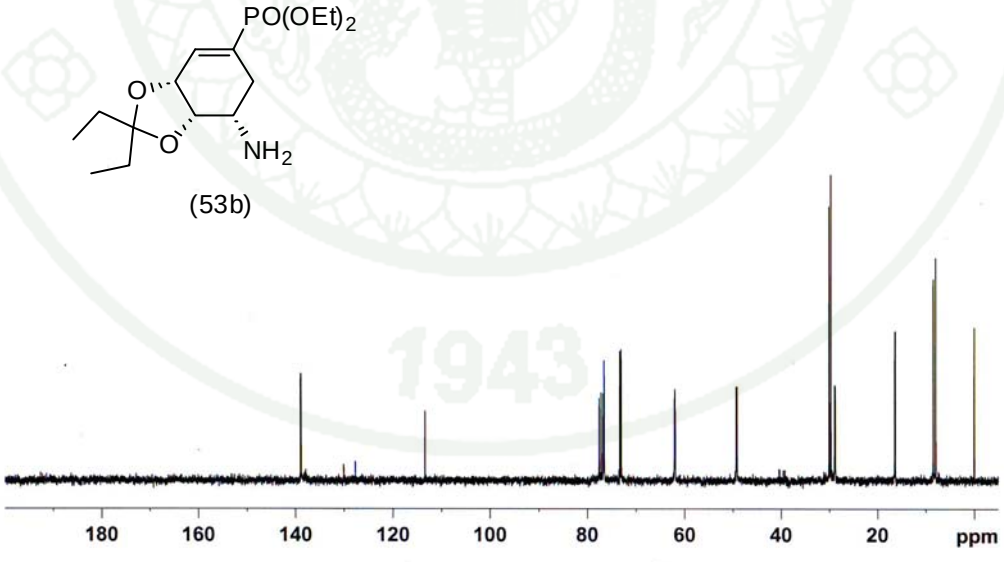


(53a)

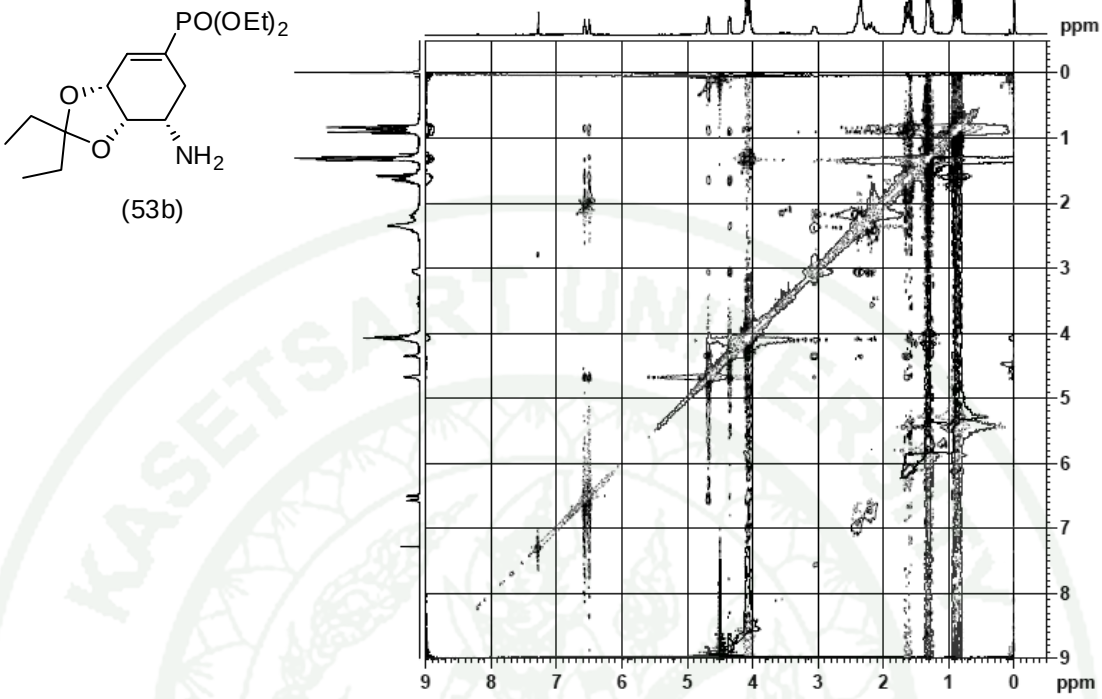
Appendix Figure 26 2D-NOESY spectrum of ethyl 3,4-*O*-isopentylidene-5α-amino shikimate (53a)



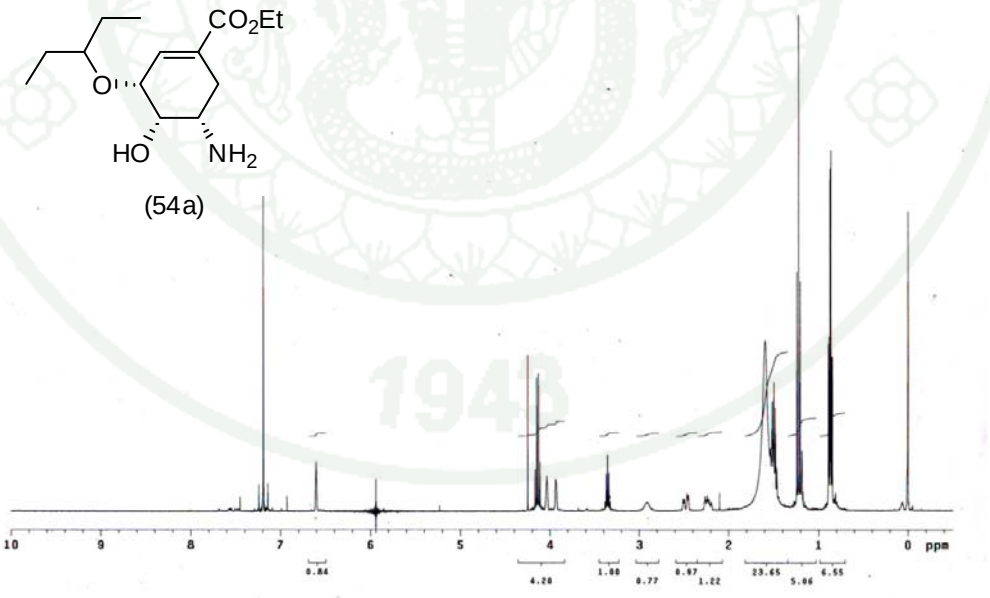
Appendix Figure 27 300 MHz ^{1}H NMR spectrum of diethyl (3*R*,4*R*,5*S*)-3,4-*O*-isopentylidene-5-amino-1-cyclohexene-1-phosphonate (53b)



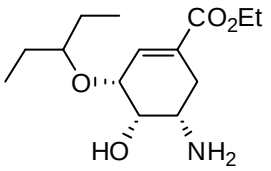
Appendix Figure 28 75 MHz ^{13}C NMR spectrum of diethyl (3*R*,4*R*,5*S*)-3,4-*O*-isopentylidene-5-amino-1-cyclohexene-1-phosphonate (53b)



Appendix Figure 29 2D-NOESY spectrum of diethyl (3*R*,4*R*,5*S*)-3,4-*O*-isopentylidene-5-amino-1-cyclohexene-1-phosphonate (53b)

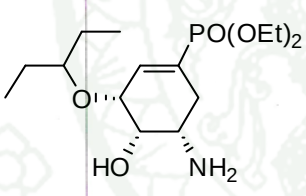


Appendix Figure 30 400 MHz ^{1}H NMR spectrum of ethyl (3*R*,4*S*,5*S*)-3-(1-ethyl-propoxy)-4-hydroxy-5-amino-1-cyclohexene-1-carboxylate (54a)



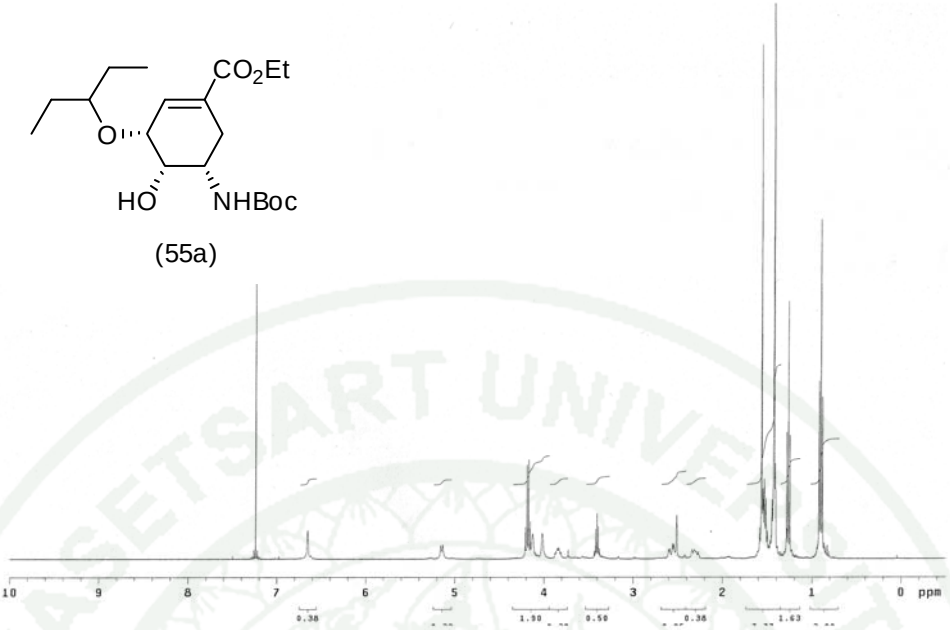
(54a)

Appendix Figure 31 100 MHz ^{13}C NMR spectrum of ethyl (3*R*,4*S*,5*S*)-3-(1-ethyl-propoxy)-4-hydroxy-5-amino-1-cyclohexene-1-carboxylate (54a)

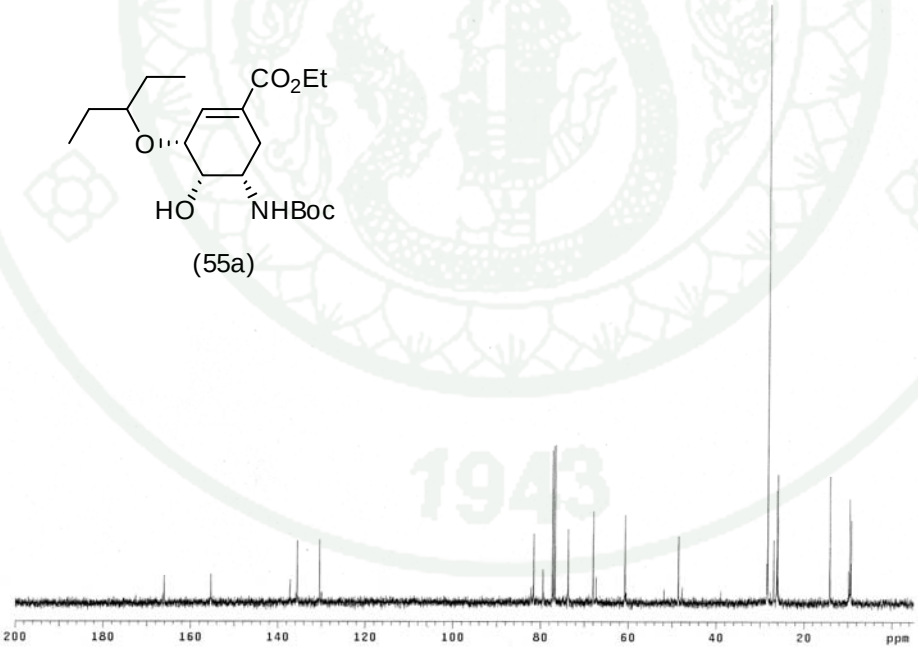


(54b)

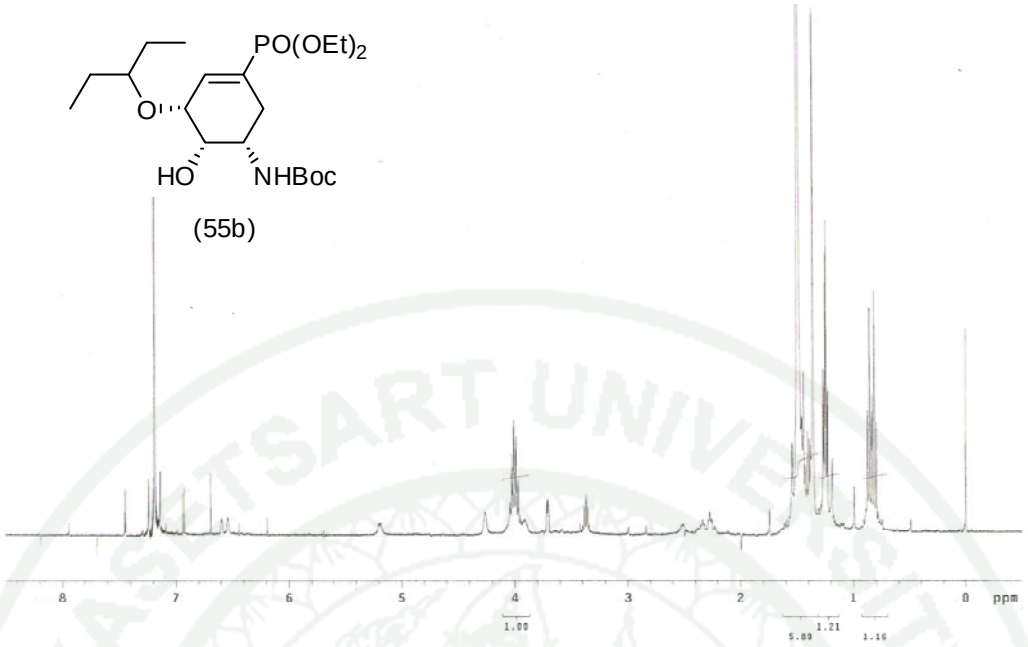
Appendix Figure 32 400 MHz ^{1}H NMR spectrum of diethyl (3*R*,4*S*,5*S*)-3-(1-ethyl-propoxy)-4-hydroxy-5-amino-1-cyclohexene-1-phosphonate (54b)



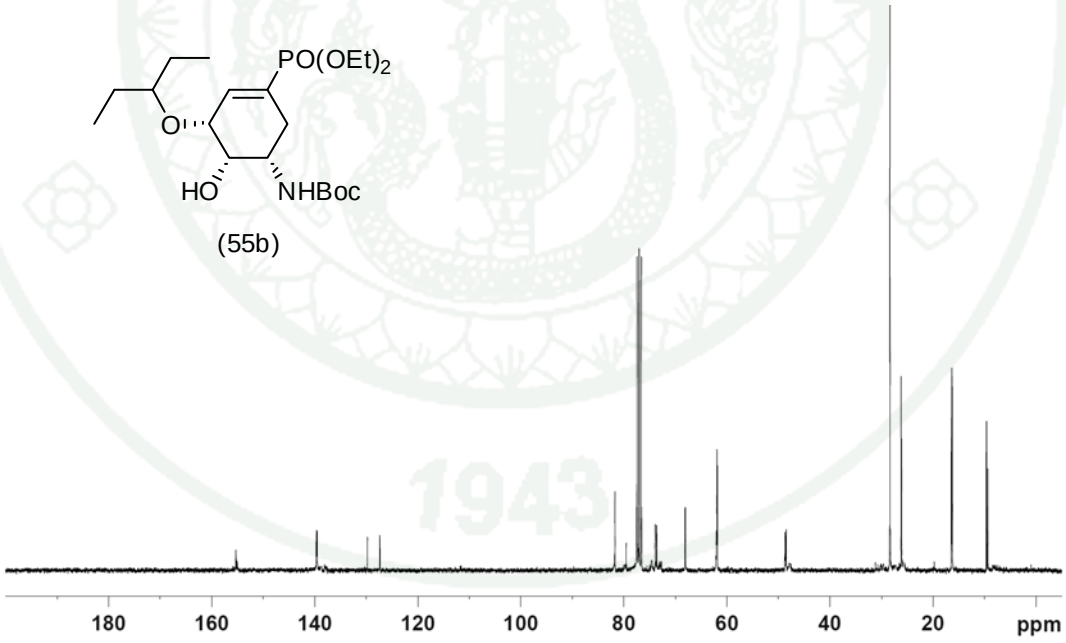
Appendix Figure 33 400 MHz ^{1}H NMR spectrum of ethyl (3*R*,4*S*,5*S*)-3-(1-ethyl-propoxy)-4-hydroxy-5-*tert*-butoxycarbonylamino-1-cyclohexene-1-carboxylate (55a)



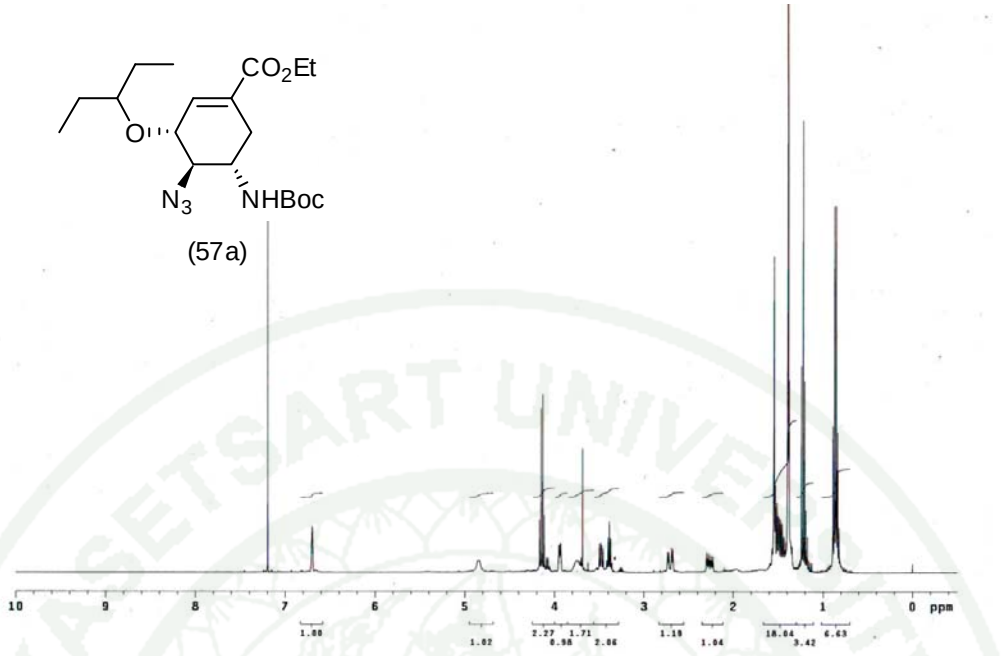
Appendix Figure 34 100 MHz ^{13}C NMR spectrum of ethyl (3*R*,4*S*,5*S*)-3-(1-ethyl-propoxy)-4-hydroxy-5-*tert*-butoxycarbonylamino-1-cyclohexene-1-carboxylate (55a)



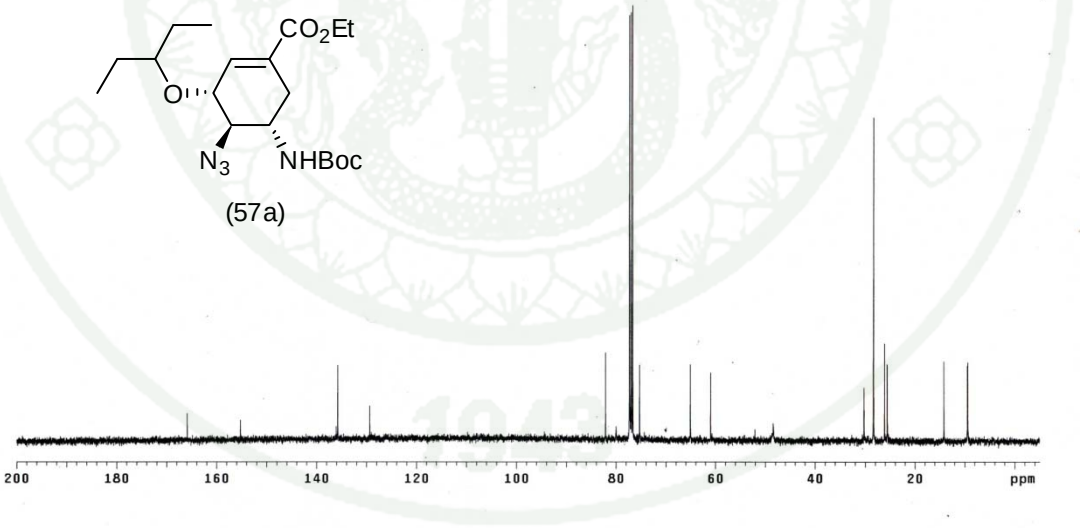
Appendix Figure 35 400 MHz ^{1}H NMR spectrum of diethyl (3*R*,4*S*,5*S*)-3-(1-ethyl-propoxy)-4-hydroxy-5-*tert*-butoxycarbonylamino-1-cyclohexene-1-phosphate (55b)



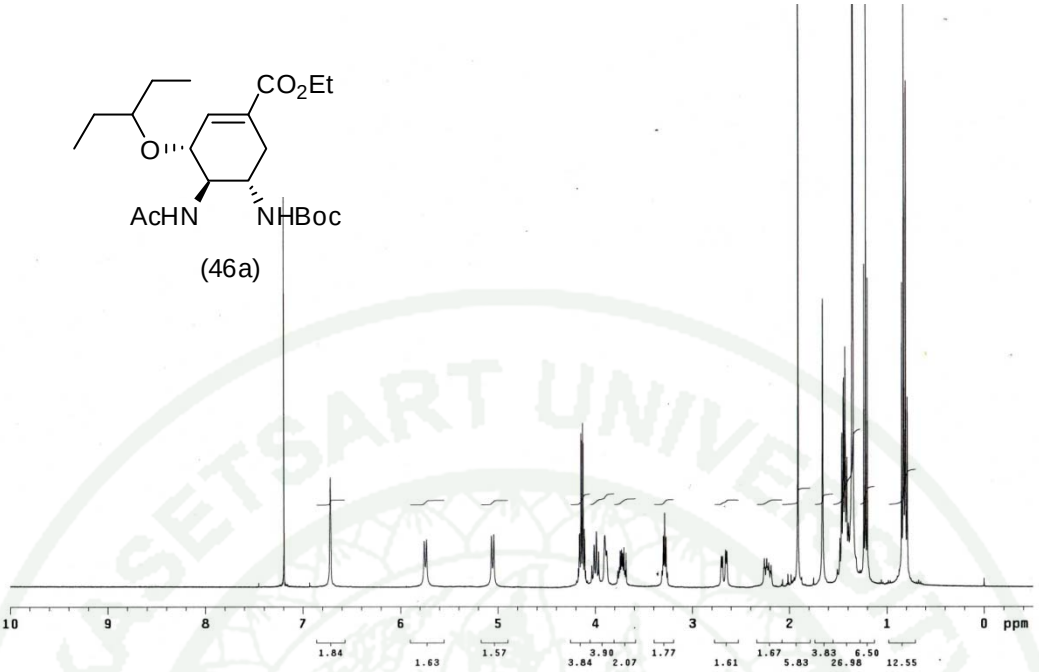
Appendix Figure 36 75 MHz ^{13}C NMR spectrum of diethyl (3*R*,4*S*,5*S*)-3-(1-ethyl-propoxy)-4-hydroxy-5-*tert*-butoxycarbonylamino-1-cyclohexene-1-phosphate (55b)



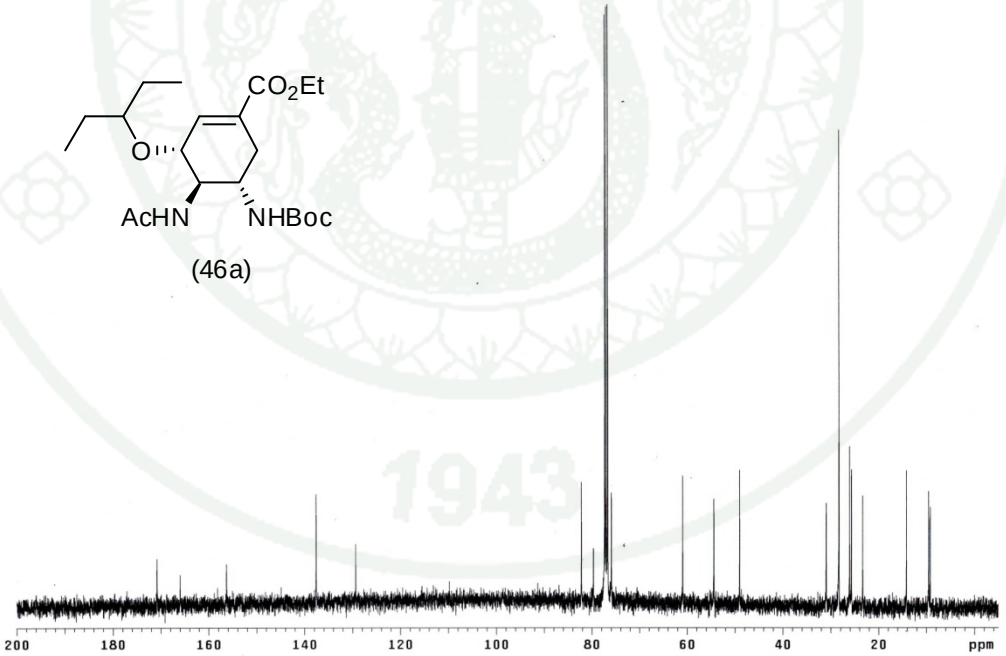
Appendix Figure 37 400 MHz ^{1}H NMR spectrum of ethyl (3*R*,4*R*,5*S*)-3-(1-ethyl-propoxy)-4-azido-5-*tert*-butoxycarbonylamino-1-cyclohexene-1-carboxylate (57a)



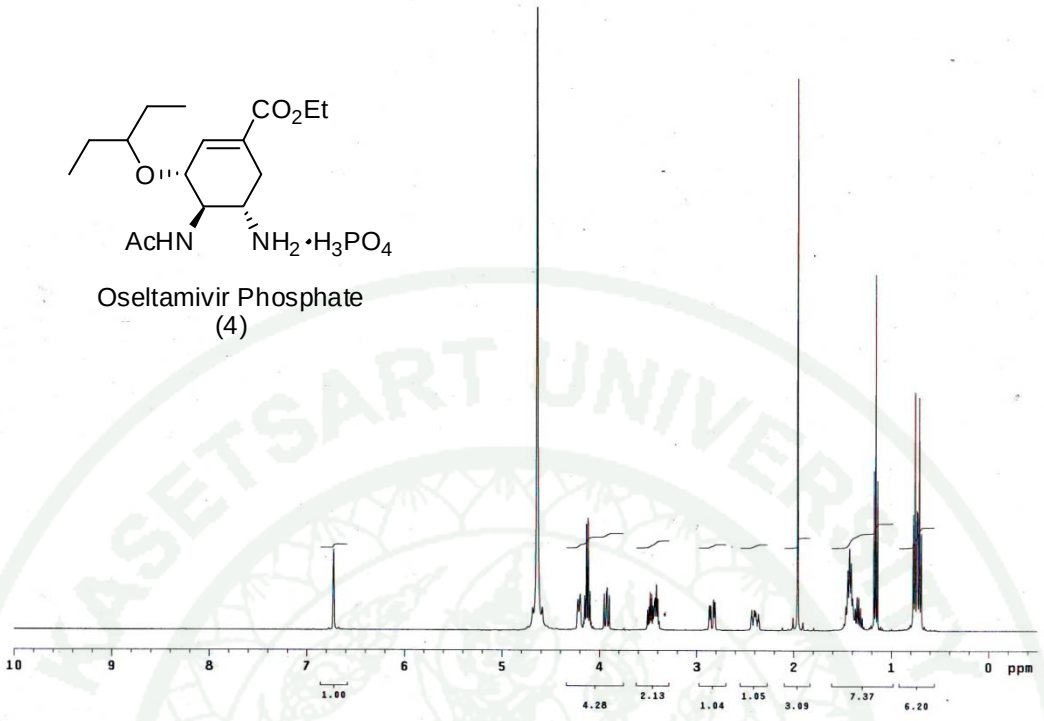
Appendix Figure 38 100 MHz ^{13}C NMR spectrum of ethyl (3*R*,4*R*,5*S*)-3-(1-ethyl-propoxy)-4-azido-5-*tert*-butoxycarbonylamino-1-cyclohexene-1-carboxylate (57a)



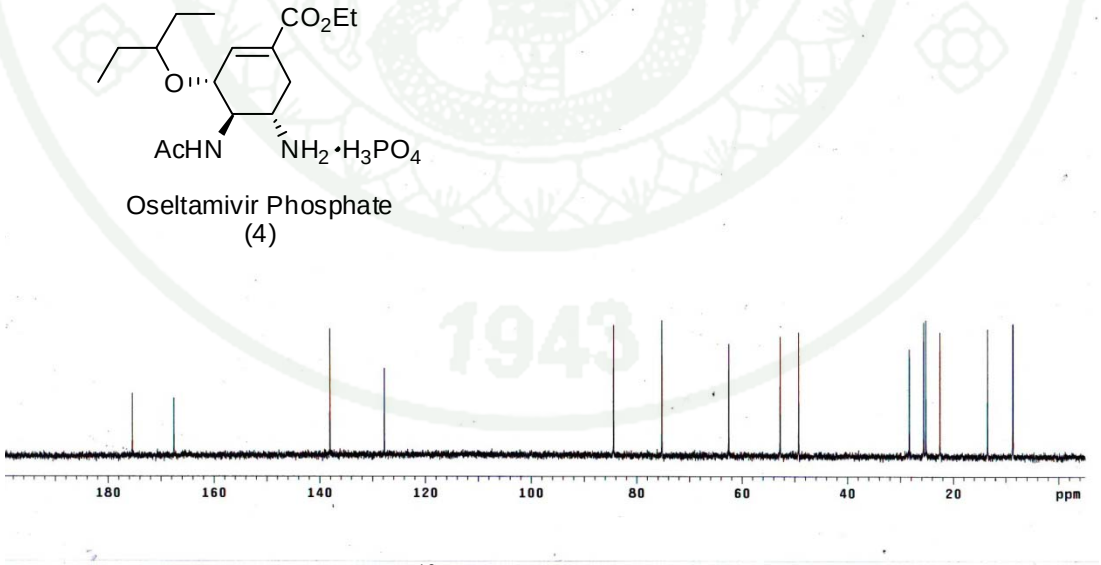
Appendix Figure 39 400 MHz ^{1}H NMR spectrum of ethyl (3*R*,4*R*,5*S*)-3-(1-ethyl-propoxy)-4-acetamido-5-*tert*-butoxycarbonylamino-1-cyclohexene-1-carboxylate (46a)



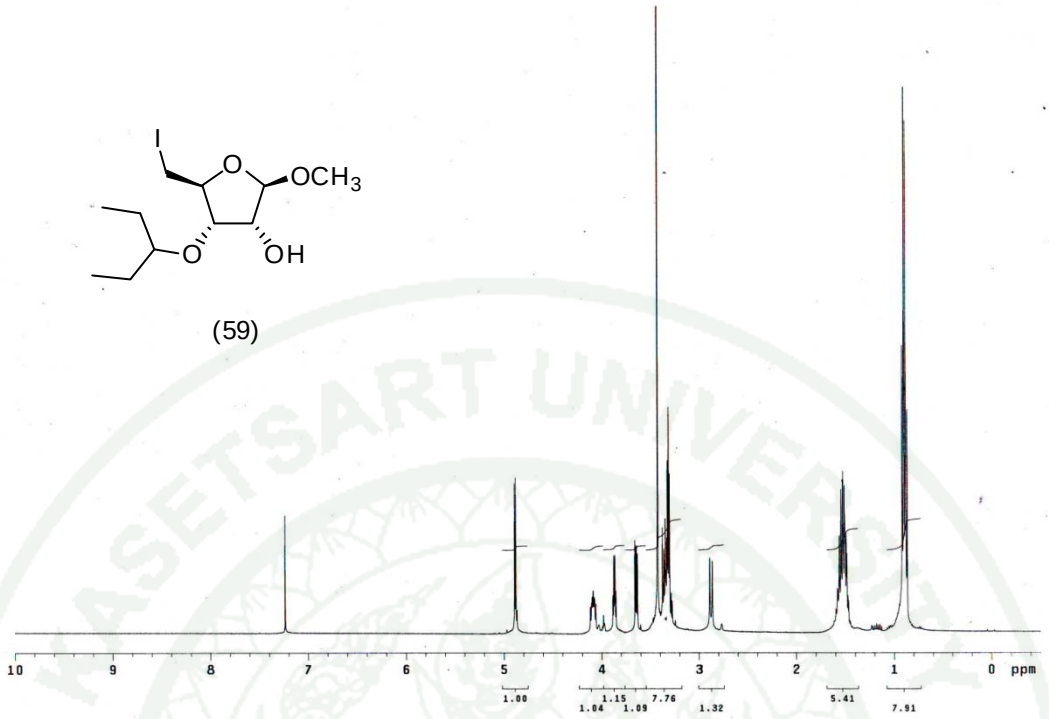
Appendix Figure 40 100 MHz ^{13}C NMR spectrum of ethyl (3*R*,4*R*,5*S*)-3-(1-ethyl-propoxy)-4-acetamido-5-*tert*-butoxycarbonylamino-1-cyclohexene-1-carboxylate (46a)



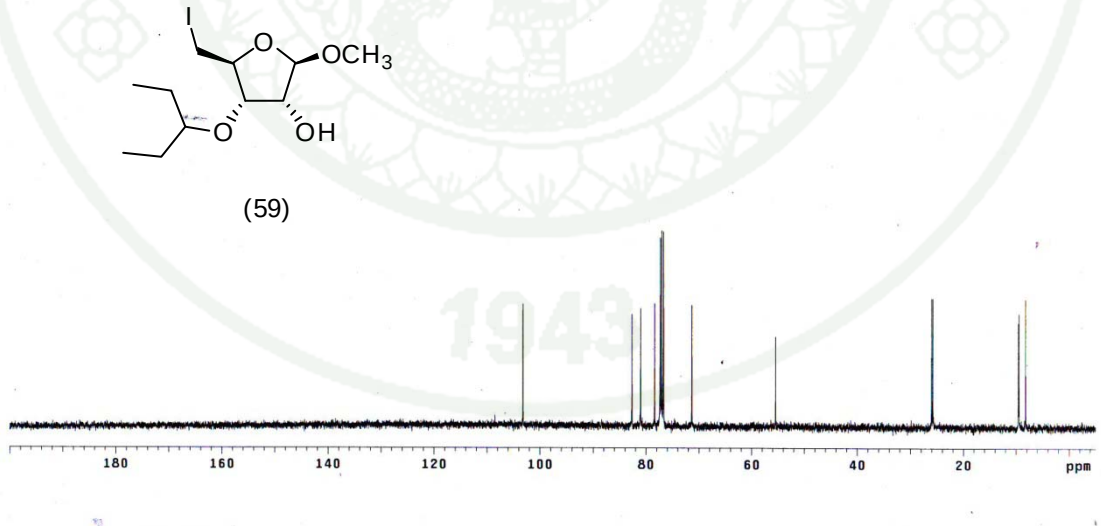
Appendix Figure 41 400 MHz ^{1}H NMR spectrum of oseltamivir phosphate (4)



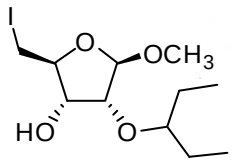
Appendix Figure 42 100 MHz ^{13}C NMR spectrum of oseltamivir phosphate (4)



Appendix Figure 43 400 MHz ^{1}H NMR spectrum of methyl 5-deoxy-5-iodo-2-hydroxy-3-(1-ethyl-propoxy)-β-D-ribofuranose (59)

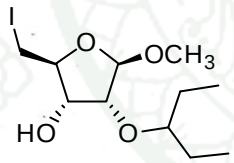


Appendix Figure 44 100 MHz ^{13}C NMR spectrum of methyl 5-deoxy-5-iodo-2-hydroxy-3-(1-ethyl-propoxy)-β-D-ribofuranose (59)

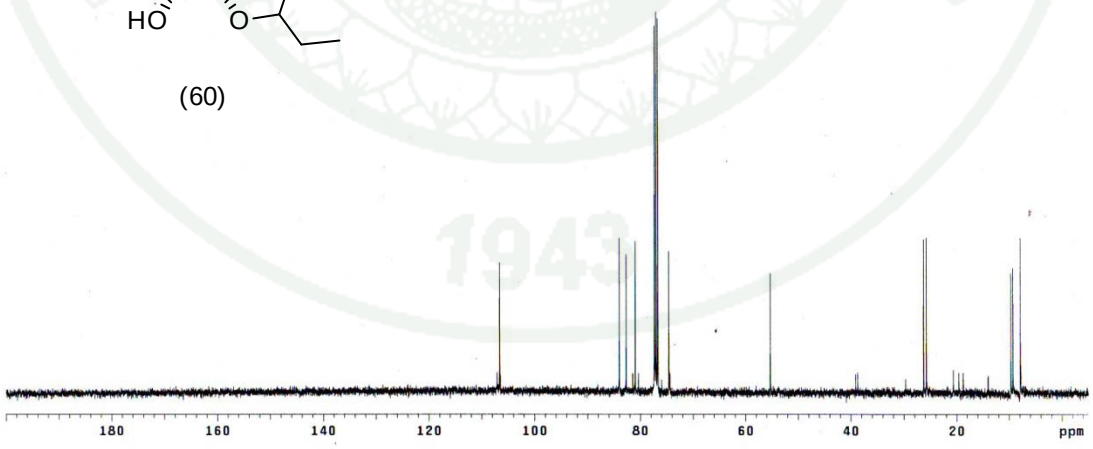


(60)

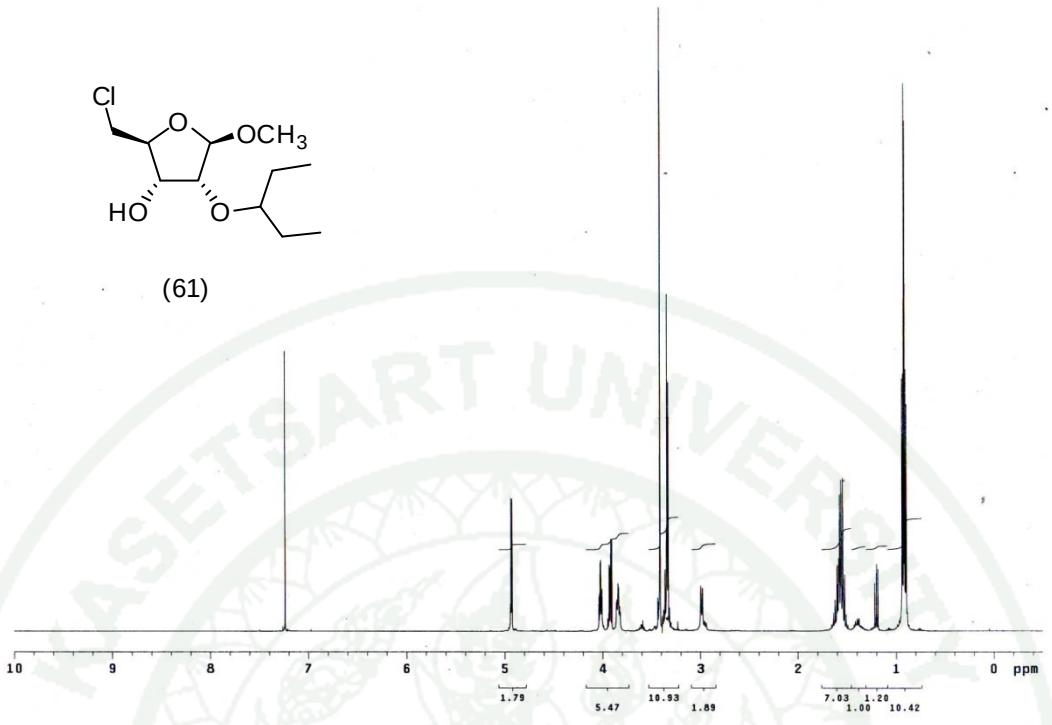
Appendix Figure 45 400 MHz ^{1}H NMR spectrum of methyl 5-deoxy-5-iodo-3-hydroxy-2-(1-ethyl-propoxy)-β-D-ribofuranose (60)



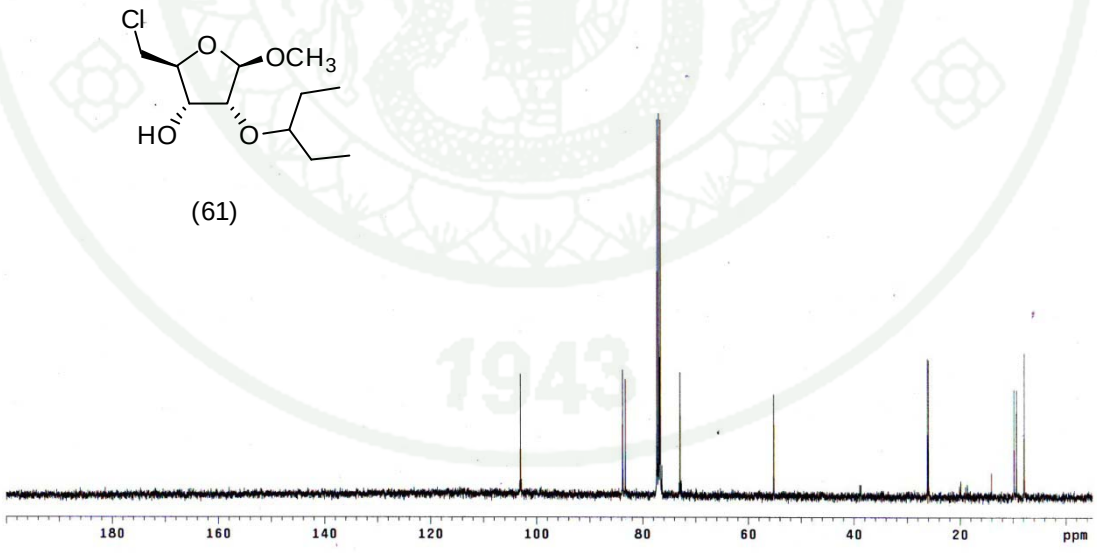
(60)



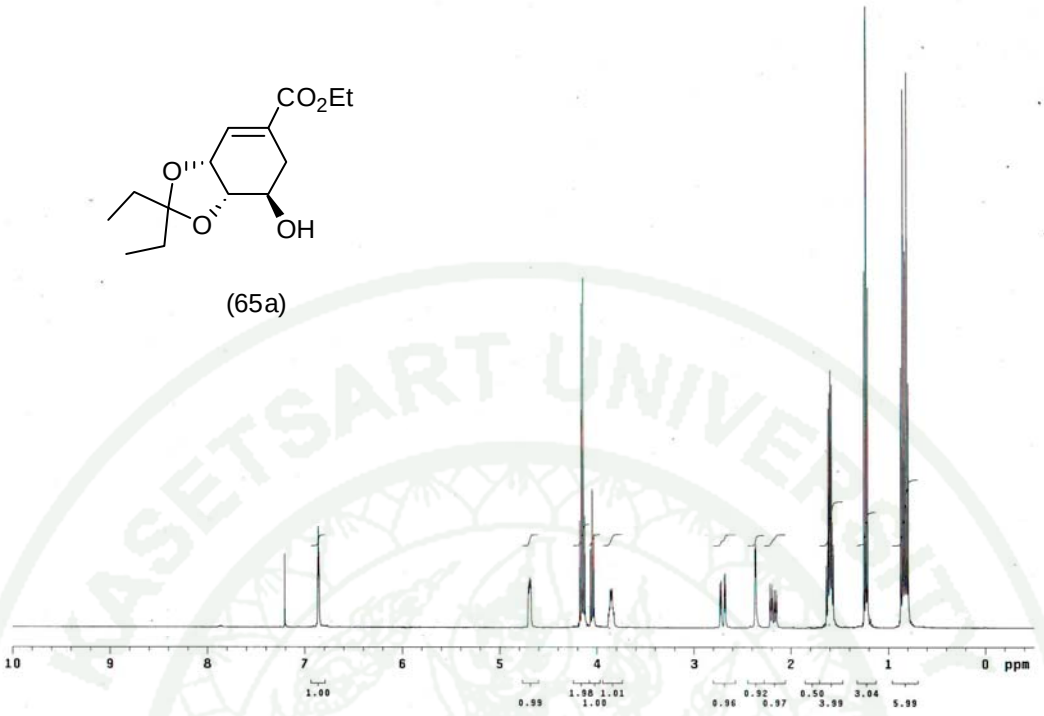
Appendix Figure 46 100 MHz ^{13}C NMR spectrum of methyl 5-deoxy-5-iodo-3-hydroxy-2-(1-ethyl-propoxy)-β-D-ribofuranose (60)



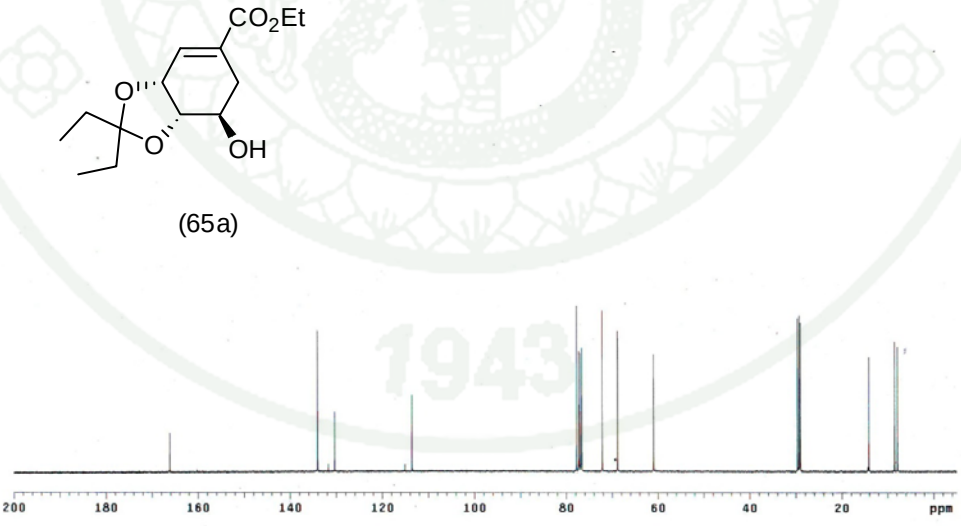
Appendix Figure 47 400 MHz ^{1}H NMR spectrum of methyl 5-deoxy-5-chloro-3-hydroxy-2-(1-ethyl-propoxy)-β-D-ribofuranose (61)



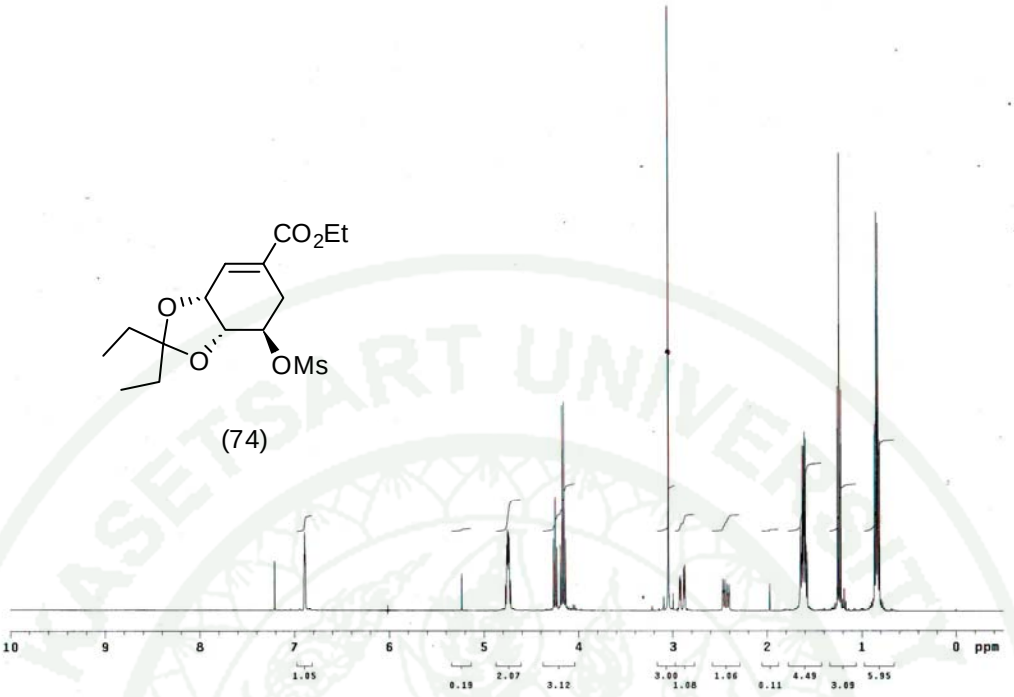
Appendix Figure 48 100 MHz ^{13}C NMR spectrum of methyl 5-deoxy-5-chloro-3-hydroxy-2-(1-ethyl-propoxy)-β-D-ribofuranose (61)



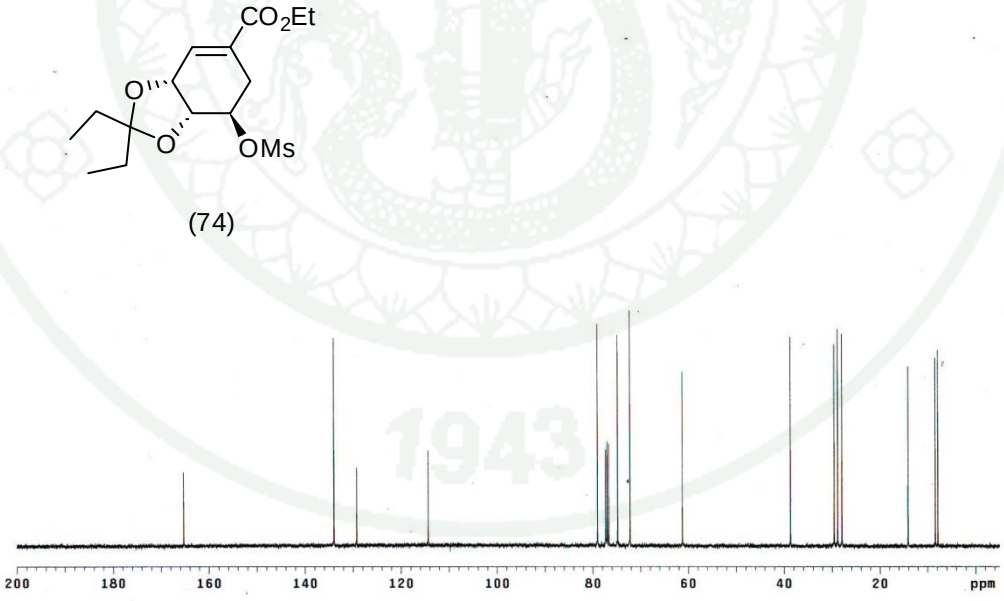
Appendix Figure 49 400 MHz ^{1}H NMR spectrum of ethyl 3,4-*O*-isopentylidene-5β-hydroxy shikimate (65a)



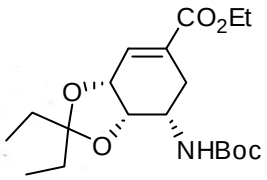
Appendix Figure 50 100 MHz ^{13}C NMR spectrum of ethyl 3,4-*O*-isopentylidene-5β-hydroxy shikimate (65a)



Appendix Figure 51 400 MHz ^{1}H NMR spectrum of ethyl 3,4-*O*-isopentylidene-5β-methanesulfonyloxy shikimate (74)

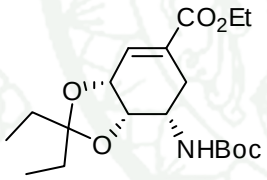


Appendix Figure 52 100 MHz ^{13}C NMR spectrum of ethyl 3,4-*O*-isopentylidene-5β-methanesulfonyloxy shikimate (74)



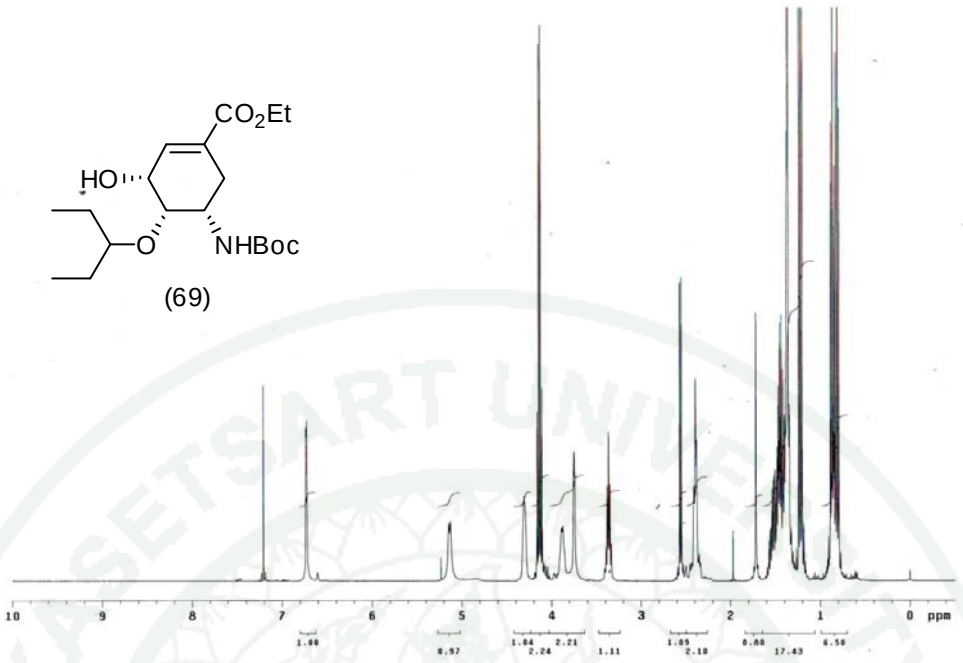
(68)

Appendix Figure 53 400 MHz ^{1}H NMR spectrum of ethyl 3,4-*O*-isopentylidene-5α-*tert*-butoxycarbonylamino shikimate (68)

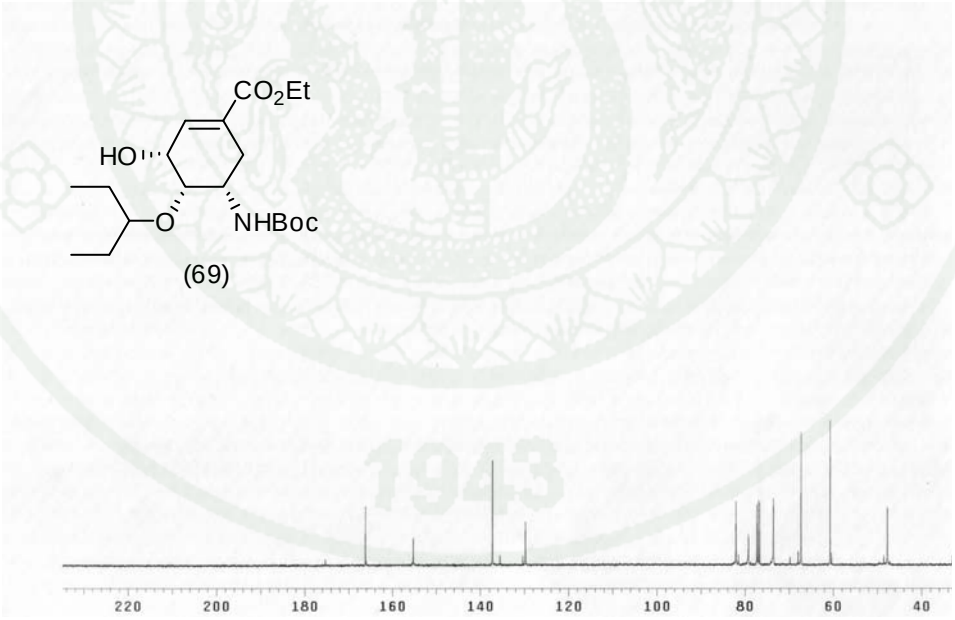


(68)

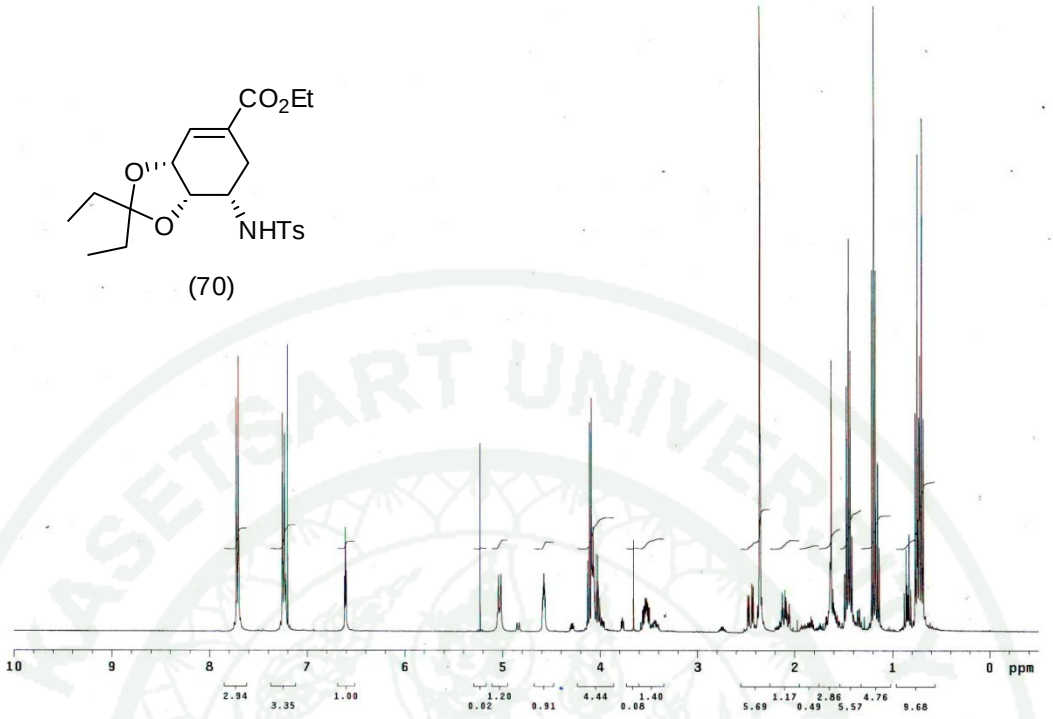
Appendix Figure 54 100 MHz ^{13}C NMR spectrum of ethyl 3,4-*O*-isopentylidene-5α-*tert*-butoxycarbonylamino shikimate (68)



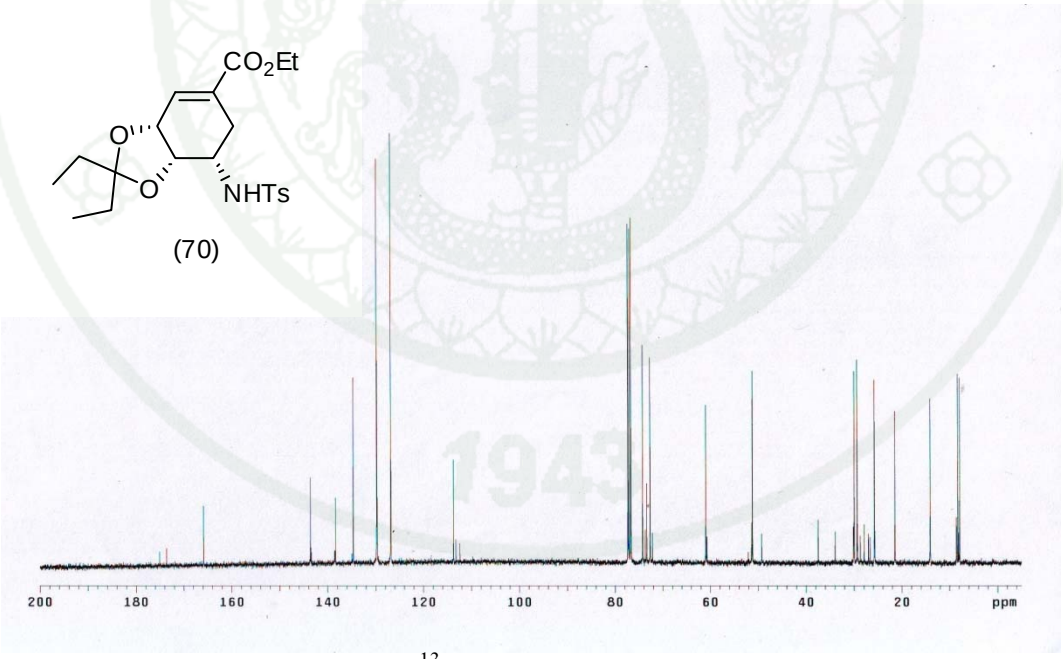
Appendix Figure 55 400 MHz ^{1}H NMR spectrum of ethyl (3*R*,4*S*,5*S*)-3-hydroxy-4-(1-ethyl-propoxy)-5-*tert*-butoxycarbonylamino-1-cyclohexene-1-carboxylate (69)



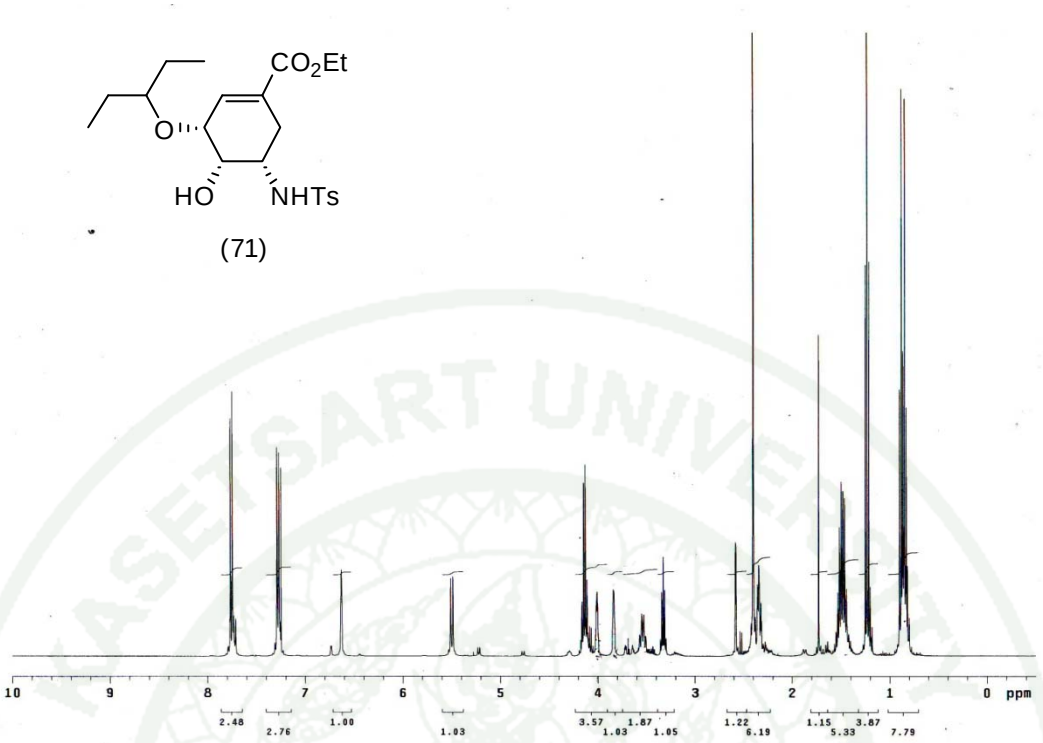
Appendix Figure 56 100 MHz ^{13}C NMR spectrum of ethyl (3*R*,4*S*,5*S*)-3-hydroxy-4-(1-ethyl-propoxy)-5-*tert*-butoxycarbonylamino-1-cyclohexene-1-carboxylate (69)



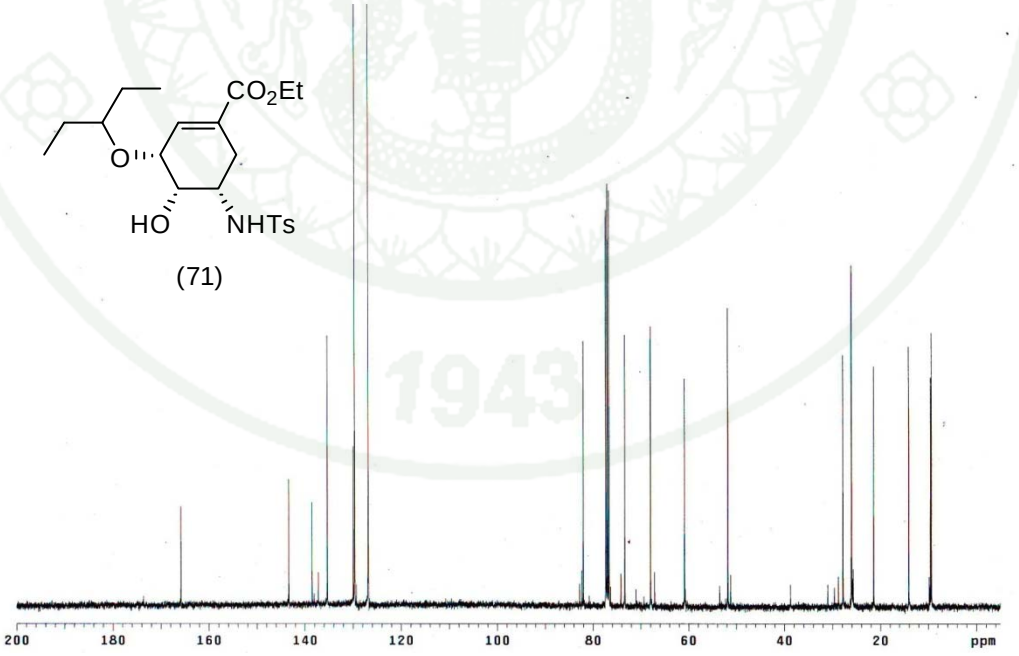
Appendix Figure 57 400 MHz ^{1}H NMR spectrum of ethyl 3,4-*O*-isopentylidene-5α-*p*-toluenesulfonylamino shikimate (70)



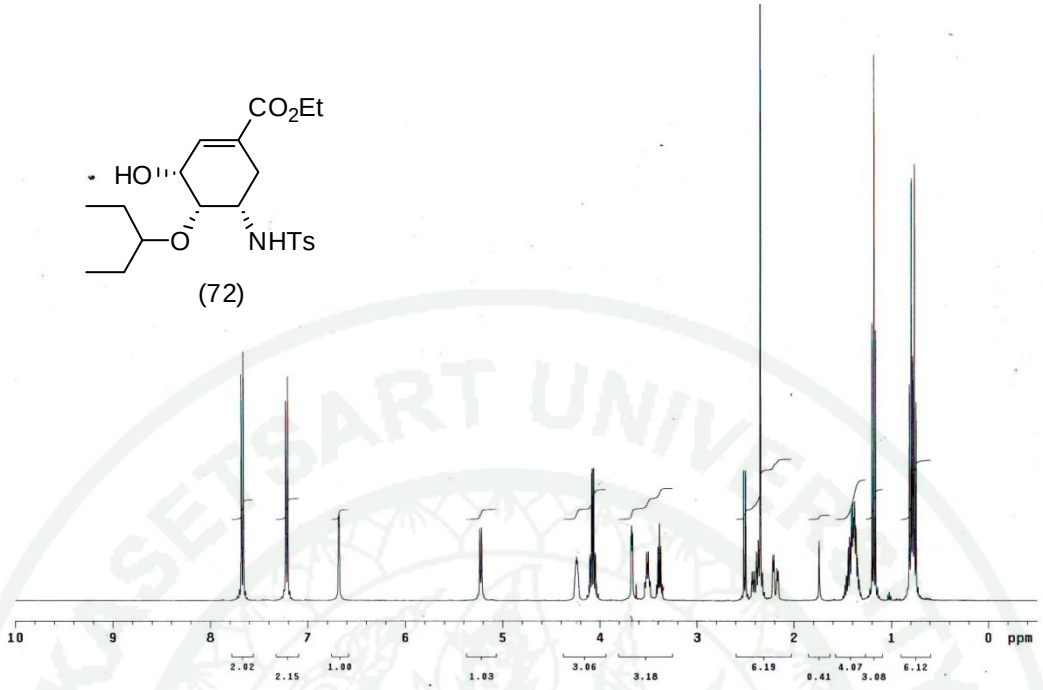
Appendix Figure 58 100 MHz ^{13}C NMR spectrum of ethyl 3,4-*O*-isopentylidene-5α-*p*-toluenesulfonylamino shikimate (70)



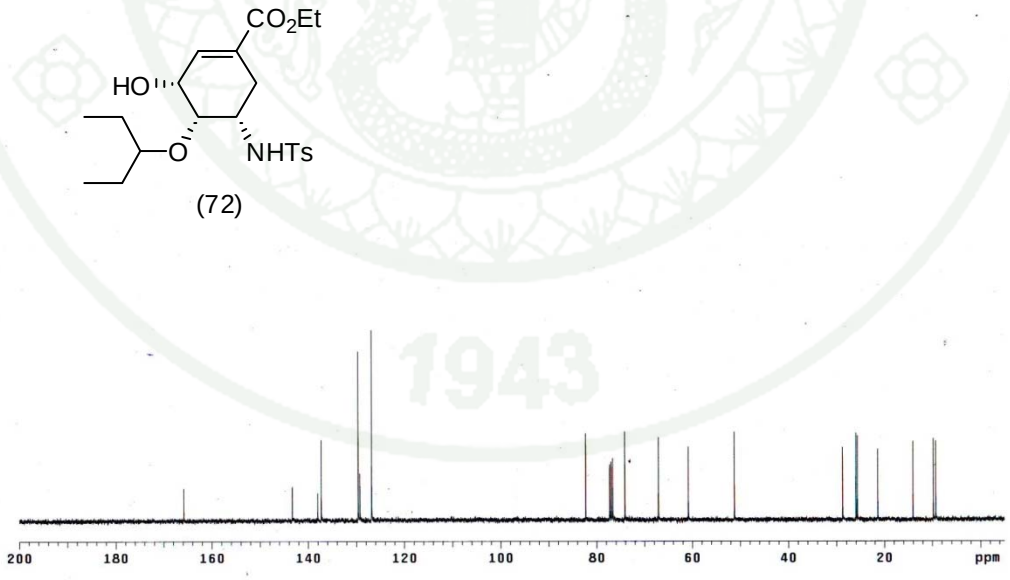
Appendix Figure 59 400 MHz ^{1}H NMR spectrum of ethyl (3*R*,4*S*,5*S*)-3-(1-ethyl-propoxy)- 4-hydroxy-5-*p*-toluenesulfonylamino-1-cvclohexene-1-carboxylate (71)



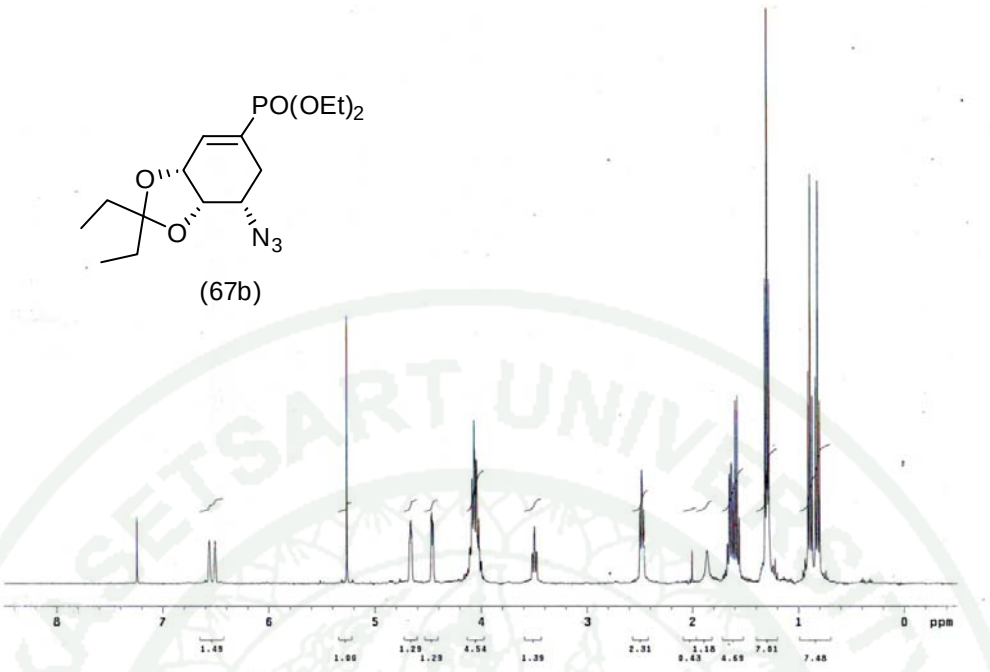
Appendix Figure 60 100 MHz ^{13}C NMR spectrum of ethyl (3*R*,4*S*,5*S*)-3-(1-ethyl-propoxy)- 4-hydroxy-5-*p*-toluenesulfonylamino-1-cyclohexene-1-carboxylate (71)



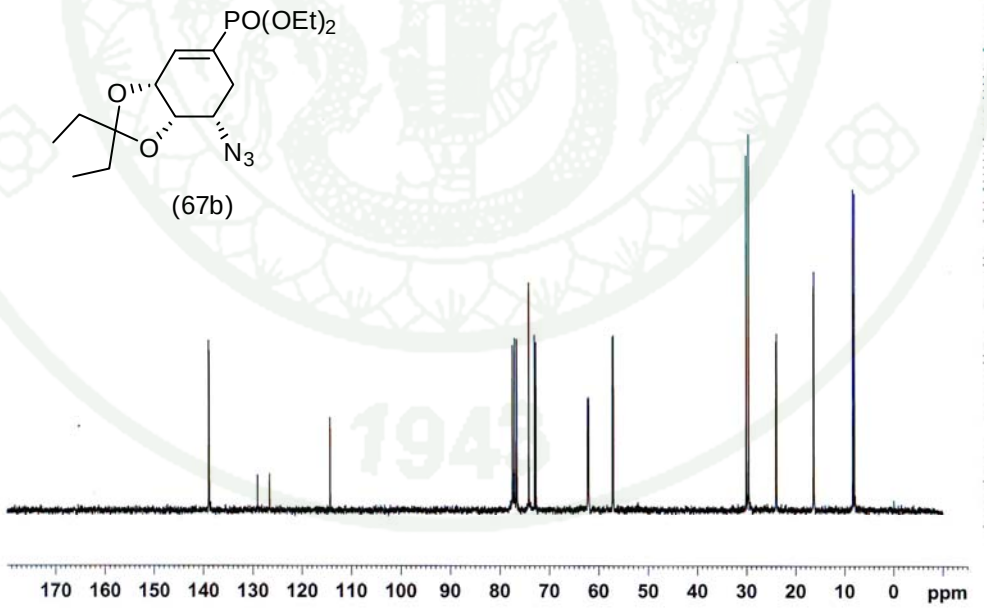
Appendix Figure 61 400 MHz ^{1}H NMR spectrum of ethyl (3*R*,4*S*,5*S*)-3-hydroxy-4-(1-ethyl-propoxy)-5-*p*-toluenesulfonylamino-1-cyclohexene-1-carboxylate (72)



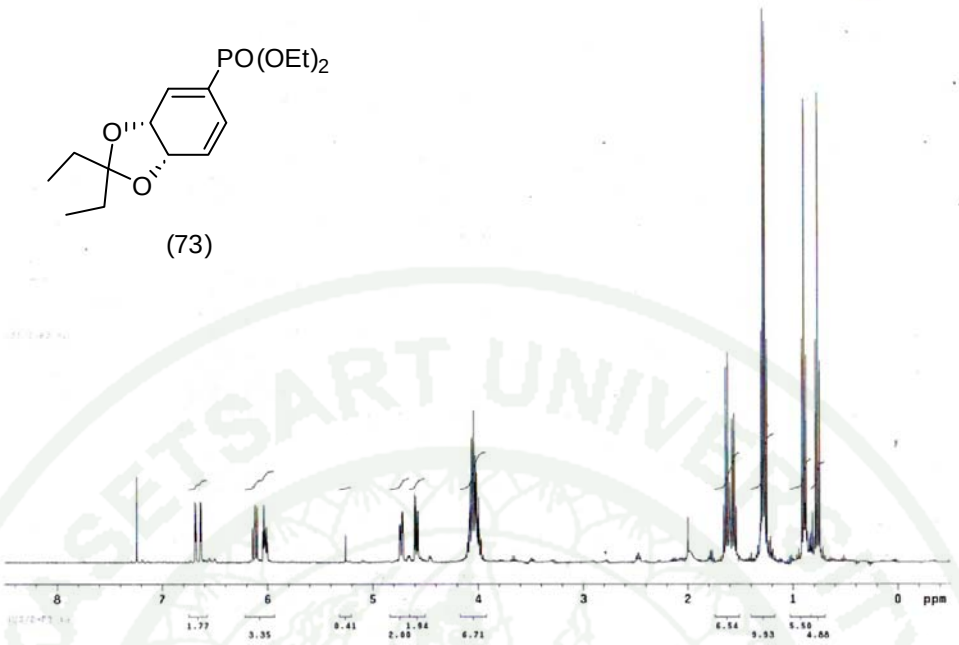
Appendix Figure 62 100 MHz ^{13}C NMR spectrum of ethyl (3*R*,4*S*,5*S*)-3-hydroxy-4-(1-ethyl-propoxy)-5-*p*-toluenesulfonylamino-1-cyclohexene-1-carboxylate (72)



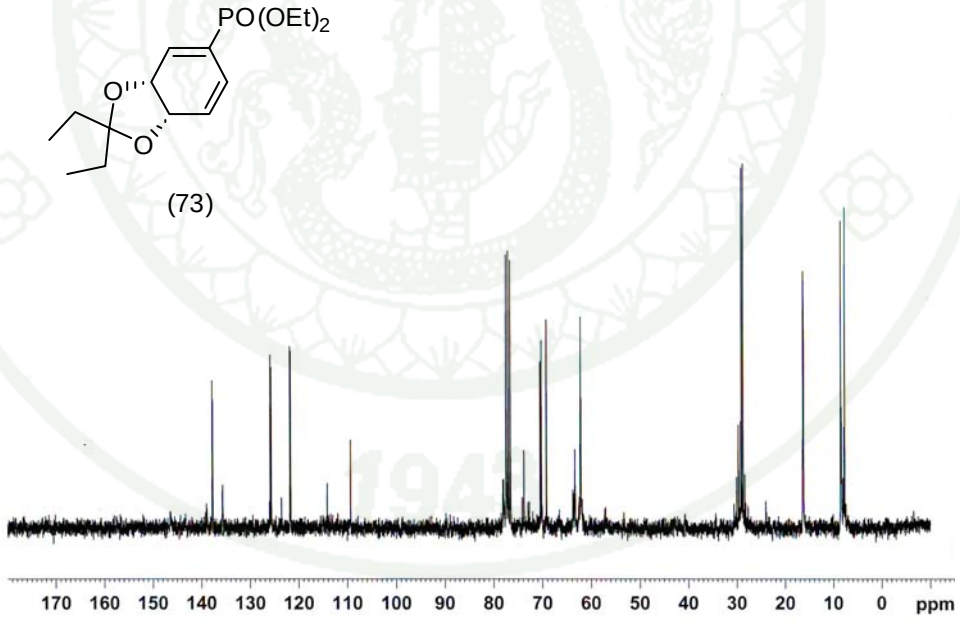
Appendix Figure 63 400 MHz ^{1}H NMR spectrum of diethyl (3*R*,4*S*,5*S*)-3,4-*O*-isopentylidene-5-azido-1-cyclohexene-1-phosphonate (67b)



Appendix Figure 64 75 MHz ^{13}C NMR spectrum of diethyl (3*R*,4*S*,5*S*)-3,4-*O*-isopentylidene-5-azido-1-cyclohexene-1-phosphonate (67b)



Appendix Figure 65 400 MHz ^{1}H NMR spectrum of compound **73**



Appendix Figure 66 75 MHz ^{13}C NMR spectrum of compound **73**

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