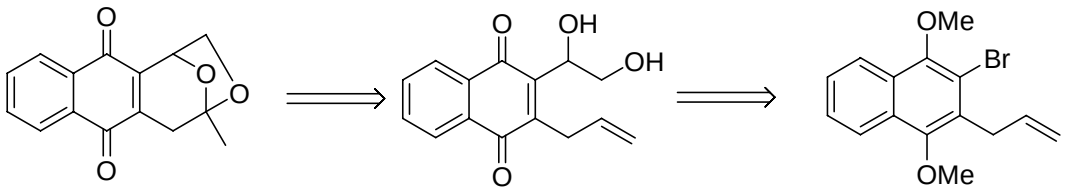
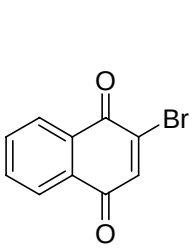
DISCUSSION

Isagarin

Pentas longiflora Oliv. (Rubiaceae) is woody herb which is reputed to possess medicinal properties. In Rwanda, where it is known as the traditional medicine under the name “Isagara”, the powdered roots of *P. longiflora* are used to treat the skin disease *Pityriasis versicolor*. The tetracyclic naphthoqiunone isagarin (11), 1,4-epoxy-4-methyl-1,2,4,5-tetrahydronaphtho [2,3-d]oxepin-6,11-dione was isolated from the roots of *P. longiflora* and subsequently synthesized by Kimpe *et al.* in 1999. We have shown that bicyclic ketals of this type can be obtained by palladium catalysed cyclization of the corresponding diol onto a proximal terminal alkene. Our new synthetic approach of isagarin (11) involving the Wacker ($PdCl_2$, $CuCl_2$, O_2) cyclization of (129) to (11), was demonstrated by the retrosynthetic sequence outlined in Scheme 17.



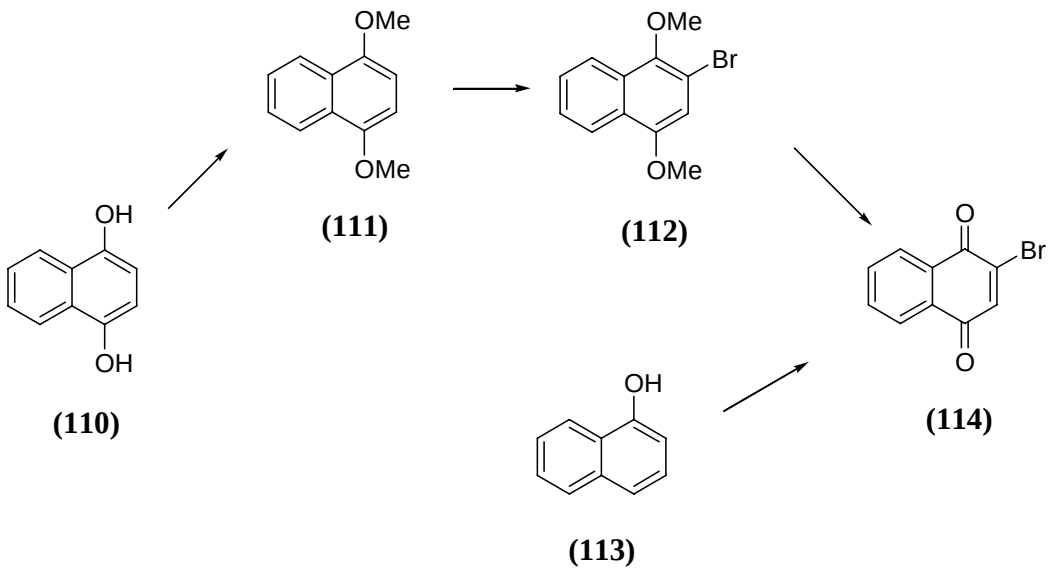
(11) (129) (116)



(114)

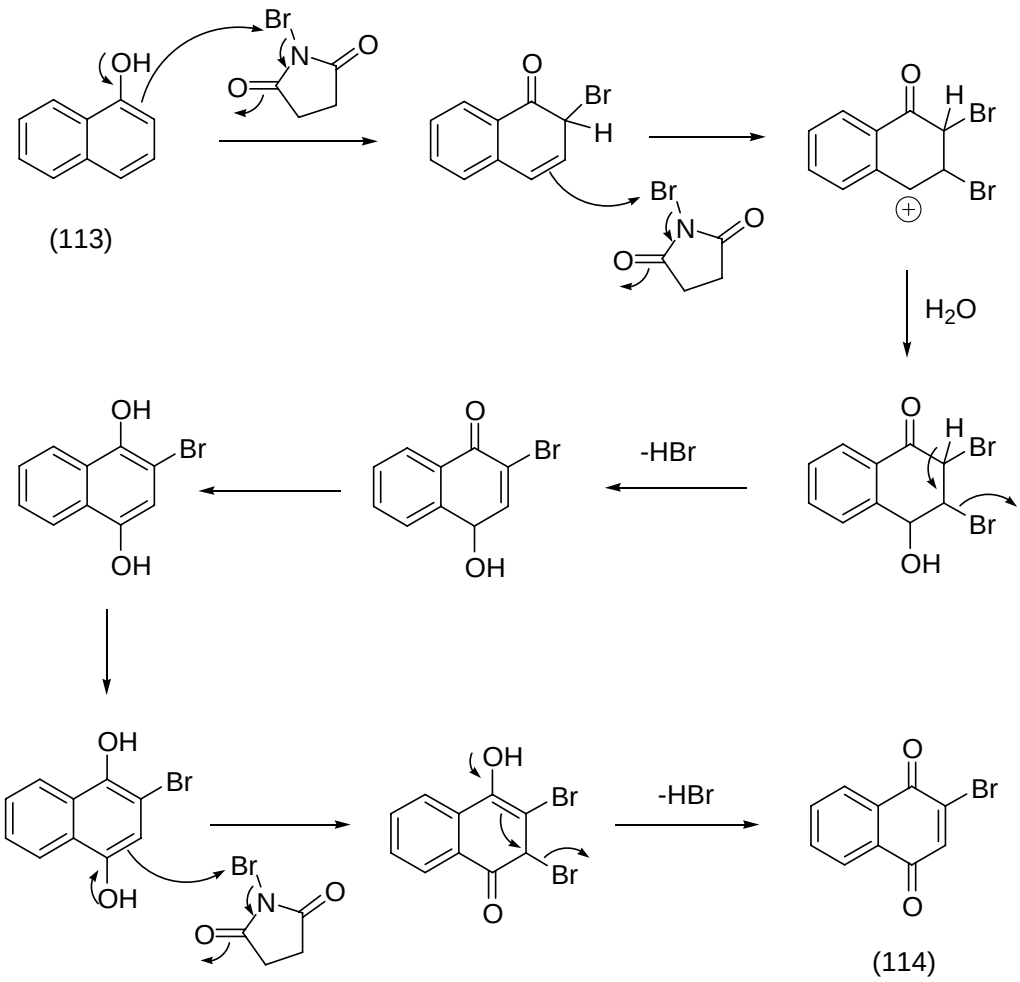
Scheme 17

2-Bromo-1,4-naphthoquinone (114) was prepared from p-hydro naphthoquinone (110) in three steps. Methylation of p-hydronaphthoquinone (110) has been studied under two reaction conditions. Dimethylsulfate, K_2CO_3 in acetone gave 1,4-dimethoxy-naphthalene (111) in 72% yield whilst MeI and K_2CO_3, in acetone afforded the methylated product in 57% yield. The results indicated that dimethylsulfate is a better methylating agent than MeI. Bromination of (111) gave 1,4-dimethoxy-2-bromo-naphthalene (112) which was oxidized to 2-bromo-1,4-naphthoquinone (114) by ceric(IV) ammonium nitrate (CAN) (Scheme 18). Alternatively, (114) can be prepared from 1-naphthol (113) by oxidative bromination according to the procedure of Butler *et al*. (Scheme 19).



(110) **(111)** **(112)** **(114)** **(113)**

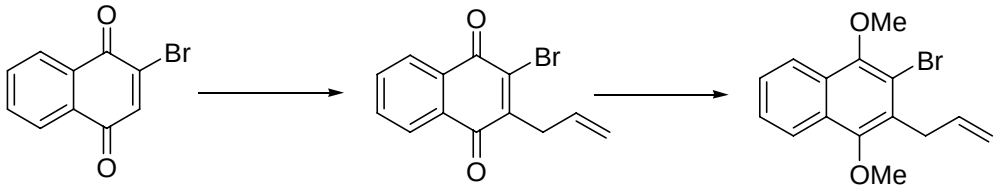
Scheme 18



Scheme 19

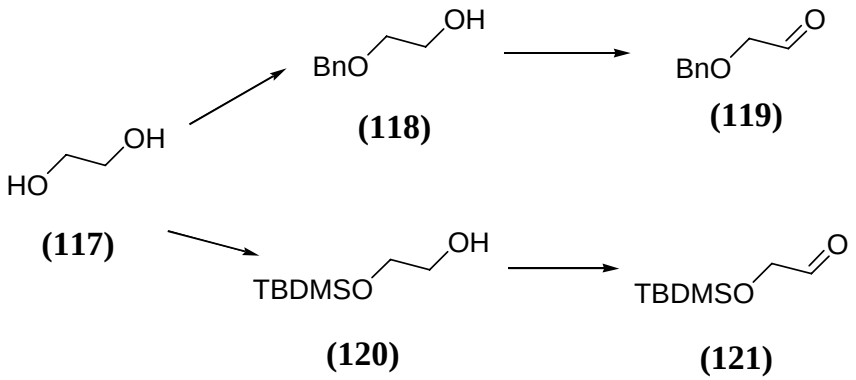
Radical allylation of naphthoquinone (114) with vinyl acetic acid, using ammonium persulfate and silver nitrate in aqueous acetonitrile, allowed the introduction of an allyl side chain at C(**3**) to give allylnaphthoquinone (115) in 72% yield. Reductive methylation of (115) by means of tin (II) chloride and dimethyl sulfate afforded 2-allyl-3-bromo-1,4-dimethoxynaphthalene (116) in 75% yield. The IR spectrum of 2-allyl-3-bromo-1,4-dimethoxynaphthalene (116) showed intense absorption bands at 1612 (C=C) and 1593 (C=C) cm^{-1}.The ^{1}H NMR spectrum ($CDCl_3$) with two-proton multiplets at δ 8.06 (Ar-H) and δ 7.51 (Ar-H) indicated the presence of a naphthalene moiety. The ^{1}H NMR data also showed the presence of the allyl moiety: three olefenic protons at δ 6.07 (ddt, J= 16.8 Hz, 10.2 Hz and 5.6 Hz), 5.09 (dd, J=10.2 Hz and1.7 Hz) and 5.03 (dd, J=16.8 Hz and 1.7 Hz) and methylene protons (at δ 3.79, showing double of doublet with J=5.6 Hz and 1.7 Hz). The ^{1}H

NMR spectrum with two singlet signals δ at 3.97 and 3.91 was identified as the two methoxy proton.



(114) **(115)** **(116)**

Benzyloxy-acetaldehyde (119) and (tert-butyl-dimethyl-silanyloxy)-acetaldehyde (121), the intermediates for coupling with 2-allyl-3-bromo-1,4-dimethoxynaphthalene (116), were synthesized by two approaches (Schemes 20, 21). Selective protection of ethylene glycol (117) with benzyl chloride or tert-butyl-dimethylsilyl chloride gave 2-benzyloxy-ethanol (118) and 2-(tert-butyl-dimethyl-silanyloxy)-ethanol (120) in 51% and 73% yield, respectively. Oxidation of 2-benzyloxy-ethanol (118) was investigated by several different methods as summarized in Table 4.



(118) **(119)** **(117)** **(120)** **(121)**

Scheme 20

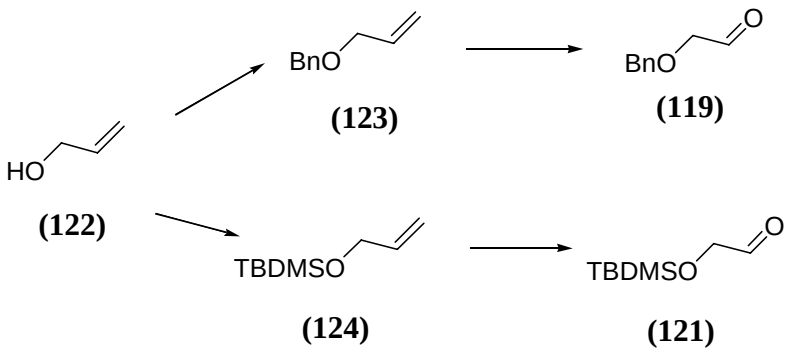
Due to the instability of benzyloxy-acetaldehyde (119), oxidation of 2-benzyloxy-ethanol (118) with IBX, PCC, PDC or P_2O_5,/DMSO provided complex

mixtures or trace amounts of benzyloxy-acetaldehyde (119). Therefore Swern oxidation (oxalyl chloride, DMSO, Et_3N), a mild oxidation method was used to oxidize 2-benzyloxy-ethanol (118) to benzyloxy-acetaldehyde (119) in 81% yield. 2-(tert-Butyl-dimethyl-silanyloxy)-ethanol (120) was also subjected to Swern reaction to obtain (tert-butyl-dimethyl-silanyloxy)-acetaldehyde (121) in 76% yield.

Table 4 Reaction conditions for oxidation of 2-(benzyloxy)ethanol (118)

Reaction Conditions	Results
IBX /DMSO, RT	complex mixture
PCC/ CH_2Cl_2, RT	complex mixture
PDC/ CH_2Cl_2	complex mixture
P_2O_5, DMSO, CH_2Cl_2	trace amount of aldehyde (119)
Oxalyl chloride, DMSO, Et_3N (Swern Oxidation)	aldehyde (119) (76%)

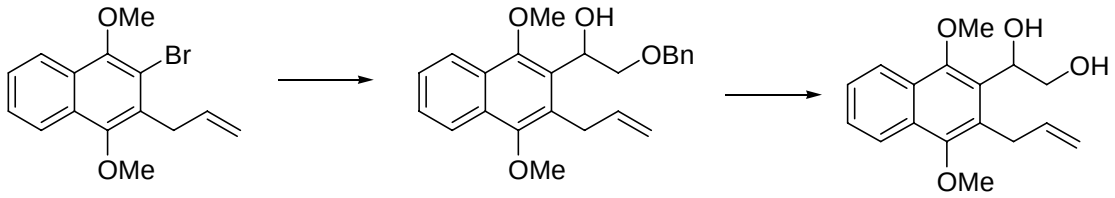
Alternatively, (119) or (121) were easily prepared from protection of allyl alcohol (122) via (123) or (124 by ozonolysis in good yield (Scheme 21).



(122) **(123)** **(119)** **(124)** **(121)**

Scheme 21

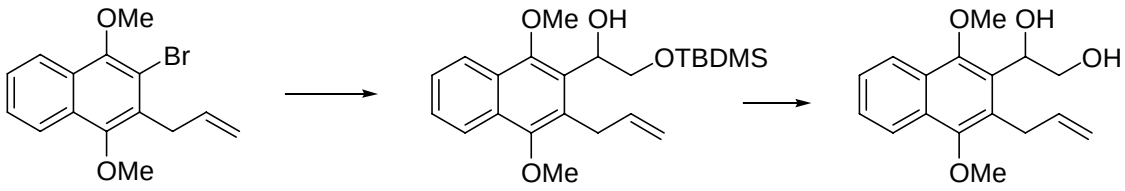
With aldehyde (119) in hand, bromide-lithium exchange of (116) with *n*-butyllithium at low temperature gave the corresponding lithium salt, which was immediately trapped with (119) affording (125) as a racemic mixture in 70% yield.Radical debenzylation of (125) with lithium naphthalenide furnished the desired diol (126) in poor yield because of the difficulty of controlling the mol amount of lithium naphthalinide generated *in situ*. The structure of (126) was elucidated from spectroscopic data. The IR spectrum with absorptions at 1613 cm^{-1} (C=C) and 1590 cm^{-1} and the ^1H NMR spectrum ($CDCl_3$) with two-proton multiplets at δ 8.00-8.09 and 7.50-7.54 (m, 2H) indicated the presence of a naphthalene moiety. The characteristic peaks of the allyl moiety appeared at δ 6.10 (ddt, 1H, J=17.8 Hz, 7 Hz, 5.5 Hz), δ 4.92-5.00 (m, 2H and δ 3.79-3.82 (m, 2H). The one proton multiplt at δ 5.31 is indicative of a CH-OH unit. The two-proton signals of CH_2OH unit occurred at δ 4.1 (dd, 1H, J=9 Hz, 10 Hz) and 3.75 (dd, , J=5 Hz, 10 Hz).



(116) **(125)** **(126)**

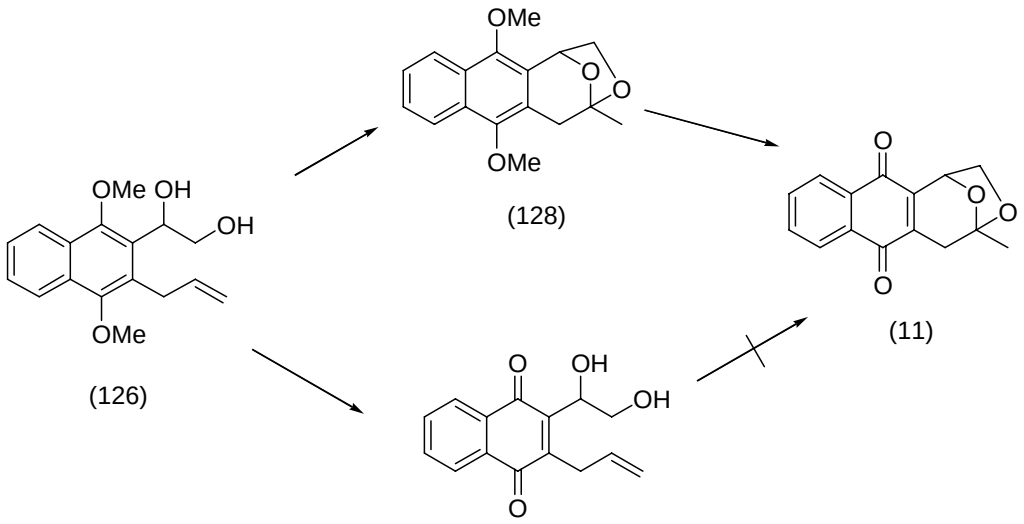
Debenzylation of diol (126) gave an unsatisfactory yield. The silyl group (TBDMS) was considered since it is stable in basis condition and easy to remove with fluoride ion. Coupling of 2-allyl-3-bromo-1,4-dimethoxynaphthalene (116) with

aldehyde (121) using *n*-BuLi provided silyl ether (127) in 70% yield. Desilylation of (127) using TBAF gave the key intermediate (126) as colorless oil in 87% yield after chromatographic purification.



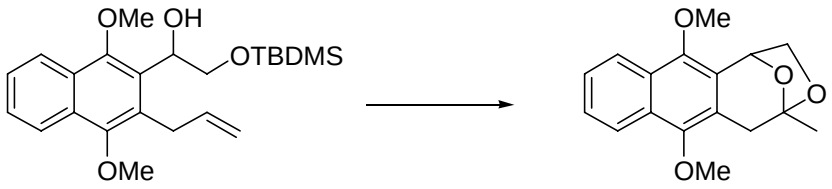
(**116)** **(127)** **(126)**

The Pd(II) promoted cyclization of (126) proceeded at 65^{o}C in anhydrous dimethoxyethane in the presence of 0.02 mol equivalent of Pd chloride, cupric chloride (4.0 mol. eq) and air bubbling to afford racemic (128) in 71%. Finally, oxidative demethylation of (128) with ceric(IV) ammonium nitrate (CAN) gave the desired isagarin (11) as a racemic mixture in 95% yield (Scheme 22). isagarin (11) was identified on the basis of its spectral properties. The IR spectrum with absorptions at 1596 cm^{-1} (C=C) and 1632, 1661 cm^{-1} (C=O) and the ^{1}H NMR spectrum ($CDCl_3$) with two-proton multiplets at δ 7.70-7.8 (Ar-H) and δ 8.04-8.13 (Ar-H) indicated the presence of a naphthoquinone moiety. The ^{1}H NMR data also showed the presence of a singlet signal of a methyl group (δ 1.68, 3H) and a methylene group (δ 2.73 and 2.87, d), the with a geminal coupling constant of 19.6 Hz. The one proton doublet at δ 5.58 with J = 4.0 Hz, is indicative for a CH-O unit substituted at the carbon adjacent to one of the carbonyl groups of the naphthoquinone nucleus. This oxygenated methine group holds a position adjacent to a CH_2O unit, which shows a degenerate spin system at δ 3.93-4.05.



Scheme 22

It was found that direct ring closure of mono silylether (127) proceeded as efficiently as that of (126), obviating the need for desilylation prior to ring closure (Scheme 23). Presumably the HCl generated during the Wacker oxidation is sufficient to promote desilylation of the primary silylether.

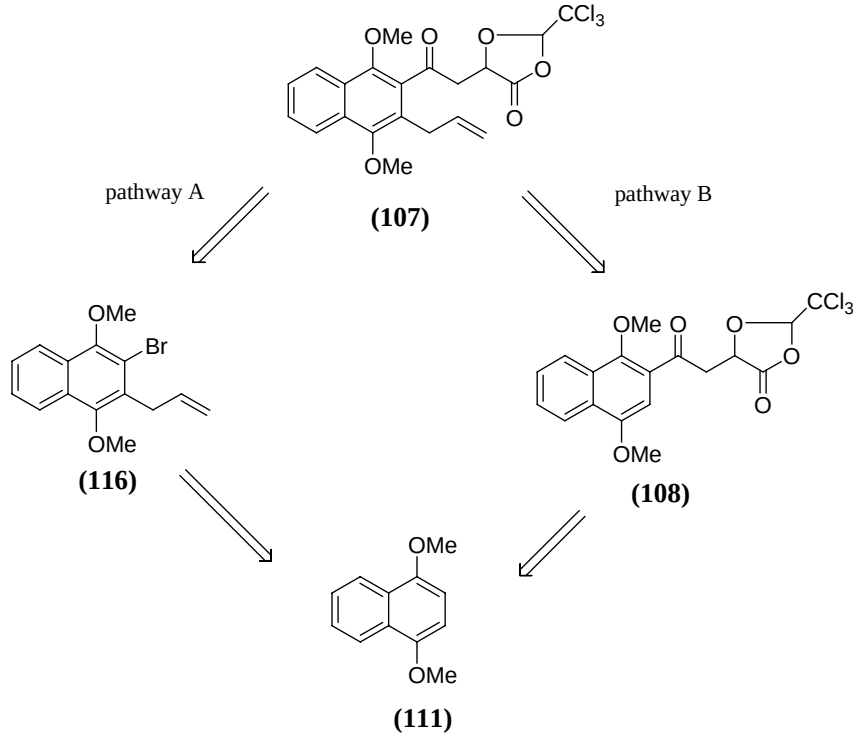


(127) **(11)**

Our synthetic methodology for (±)-isagarin (11) starting from 2-bromo-1,4-naphthoquinone (6) has been achieved in 5 steps with 24.1% overall yield whereas synthesis of (±)-isagarin (11) by De Kimpe *et al.* which started from 1,4-dimethoxynaphthaldehyde was accomplished in 4 steps with 64.6% overall yield.

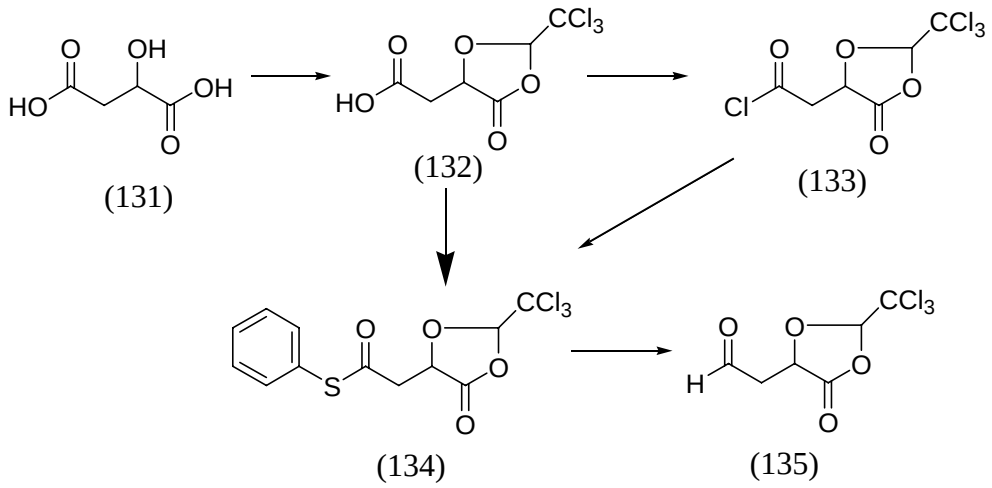
(±)-Marticin (12) and (±)- isomarticin (13)

We investigated the introduction allyl and acyl side chains onto the aromatic ring via the synthesis of model compound (107). The synthetic plan of (107) was divided into two pathways and is illustrated by the retrosynthetic sequence outlined in Scheme 24.



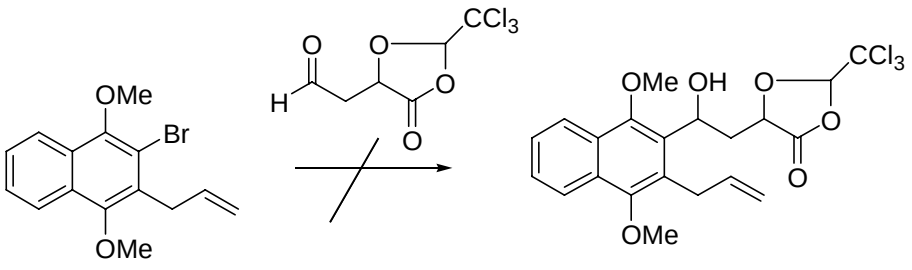
Scheme 24

Acid chloride (133) required for the acyl side chain was prepared from *dl*-malic acid (131) according to the procedure of Eggerer (1964). Aldehyde (135), another reagent for introduction of a side chain, was also prepared from (132) via thio ester (134), then hydrogenation using triethylsilane in the presence of 5% Pd/C to provide (135) in high yield (Scheme 25).

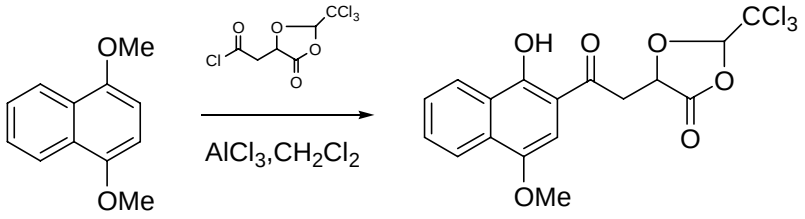


Scheme 25

In our plan, allyl side chain will be introduced onto naphthalene (111) followed by the introduction of the acyl side chain. With allyl naphthalene (116) in hand, an attempt to couple aldehyde (135) using *n*-BuLi was unsuccessful due to the instability of aldehyde (135) to the basis condition.

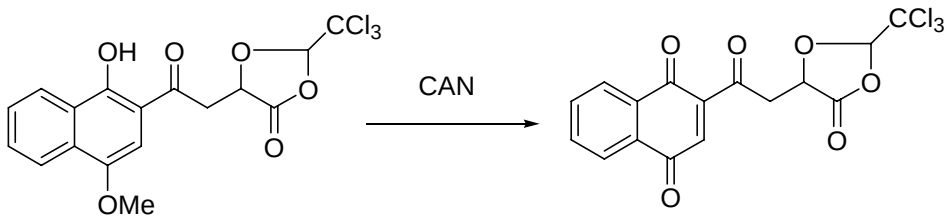


We next attempted the introduction of the acyl side chain via Fridel-Craft acylation using acid chloride (133) in the presence of 3 mol of $AlCl_3$ in CH_2Cl_2 which afforded product (137) in 43% yield.



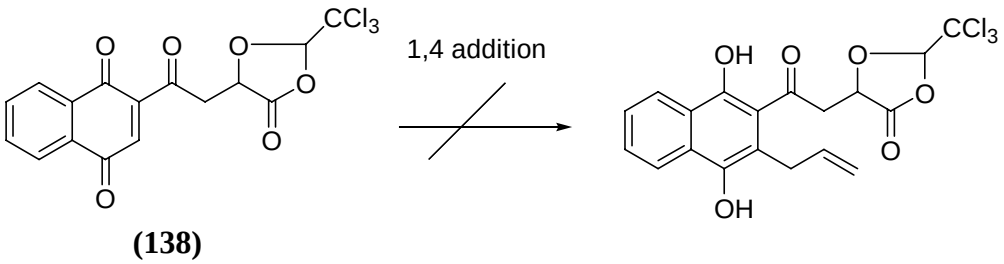
(111) **(137)**

Oxidation of the naphthol (137) by CAN provided unstable quinone (138) after chromatographic separation therefore the crude product was used in the next reaction without further purification.



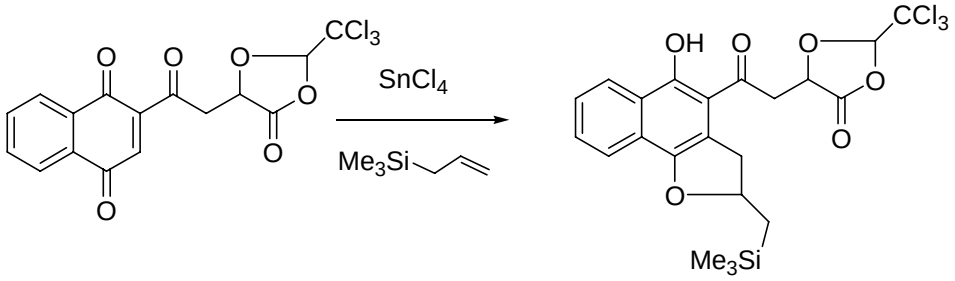
(137) **(138)**

Several attempts to introduce allyl group onto the unpurified quinone (138) by 1,4-addition an allyl cuprate complex failed. Probably, because this reaction still contained the oxidizing agent (CAN) from the previous step.



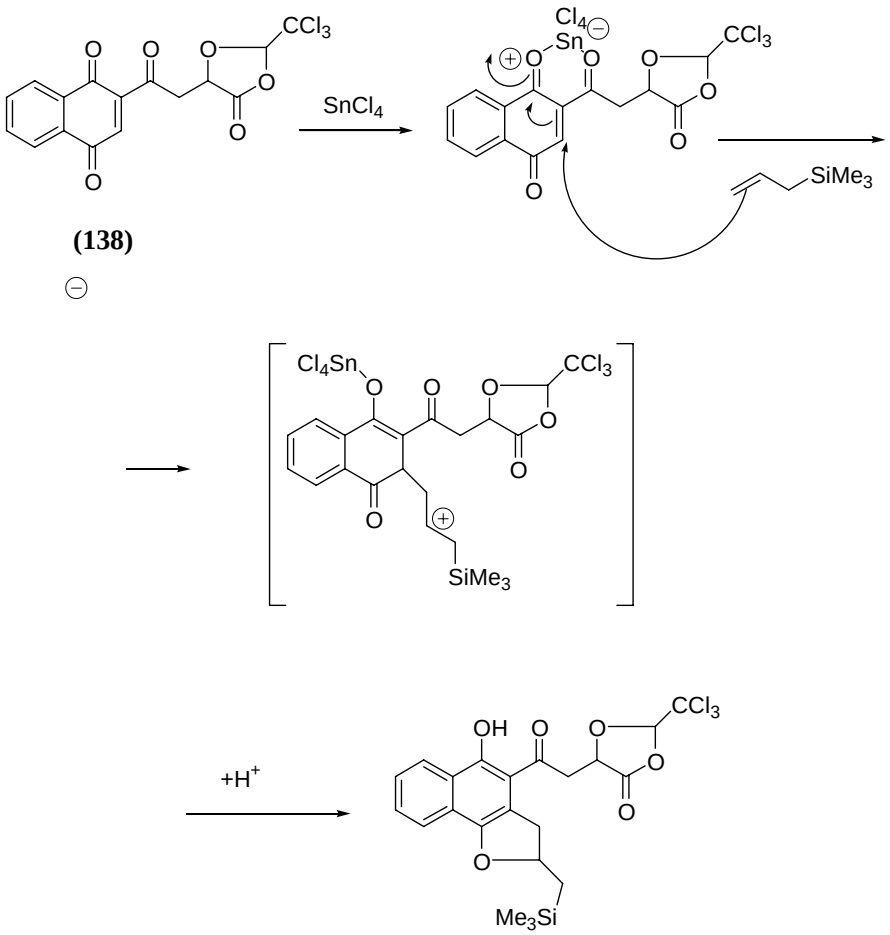
(138)

The1,4-addition to naphthoquinone (138) using allyl silane and $SnCl_4$ as catalyst, was all also investigated. Surprisingly, the reaction did not give the allyl quinone product (140); the furan naphthol (139) was obtained instead.



(138) **(139)**

The plausible mechanism for the above reaction is illustrated in Scheme 26.

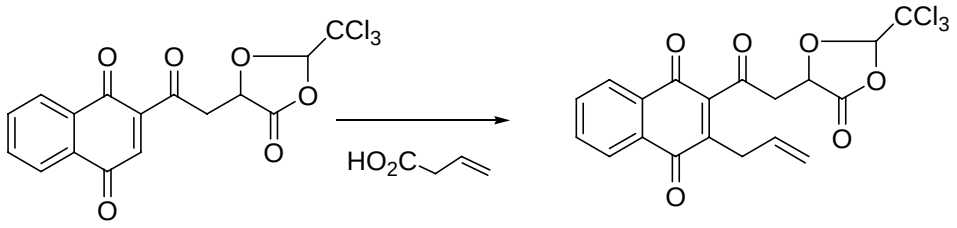


(138)

(139)

Scheme 26

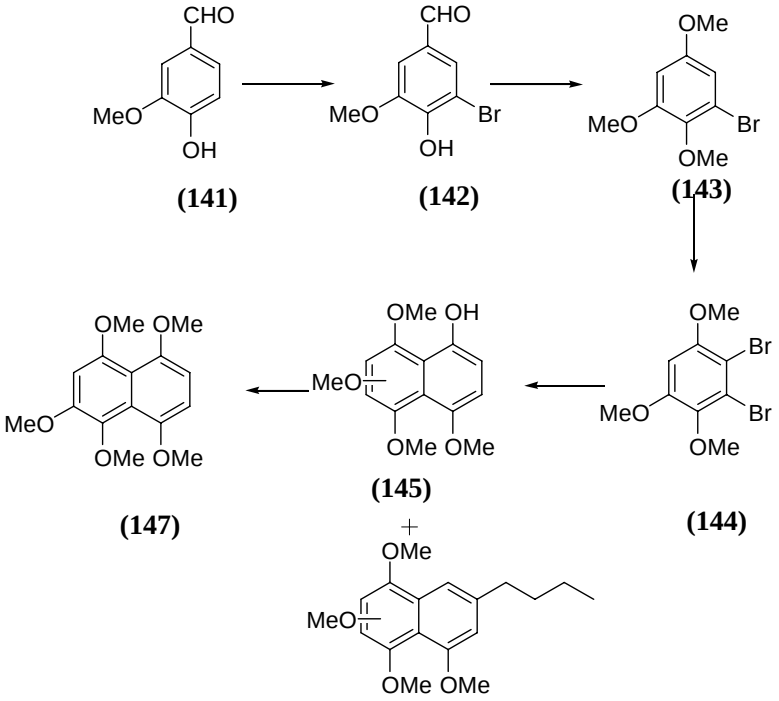
However, radical allylation of naphthoquinone (138) with vinyl acetic acid, using ammonium persulfate and silver nitrate in acetonitrile, allowed the introduction of the allyl side chain at C(**3**). The product (140) was obtained in 72% yield (2 steps). The IR spectrum with absorptions at 1730 cm^{-1} (C=O) and 1615 (C=C) cm^{-1} indicated the naphthoquinone moiety and the characteristic peaks of naphthoquinone moiety appeared at δ 8.15 (m, 2H) and 7.92 (m, 2H). ^1H NMR signals of (140) at δ 5.83 (m, 1H), 5.25-5.12 (m, 2H) and 3.25 (m, 2H) support the 1,4- addition of the allyl group onto the naphthoquinone ring.



(138) **(140)**

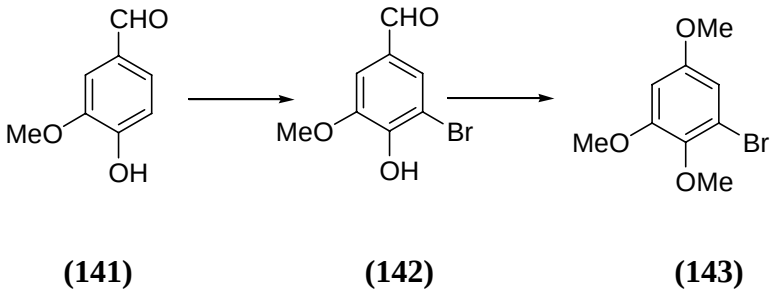
Synthesis of 1,2,4,5,8-pentamethoxynaphthalene (147)

After the successful synthesis of model compound (140), we next studied on the synthesis of 1,2,4,5,8-pentamethoxynaphthalene (147) via two pathways. In the first pathway, the synthetic plan started from vanillin (141) (Scheme 27).



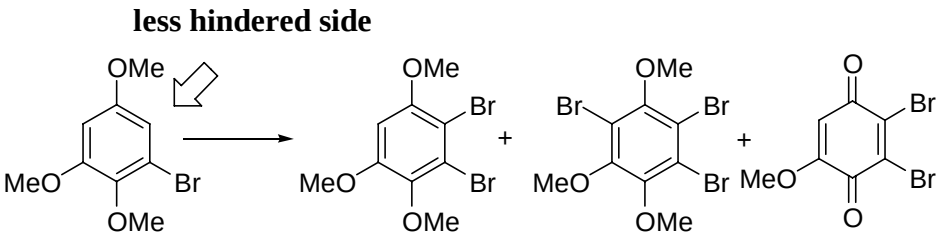
Scheme 27

Bromination of commercially available vanillin (141) provided bromovanillin (142) in 95% yield. Bayer-Villiger oxidation and methylation of bromovanillin (142) provided 3-bromo-1,2,5-trimethoxybenzene (143) in 81% yield.



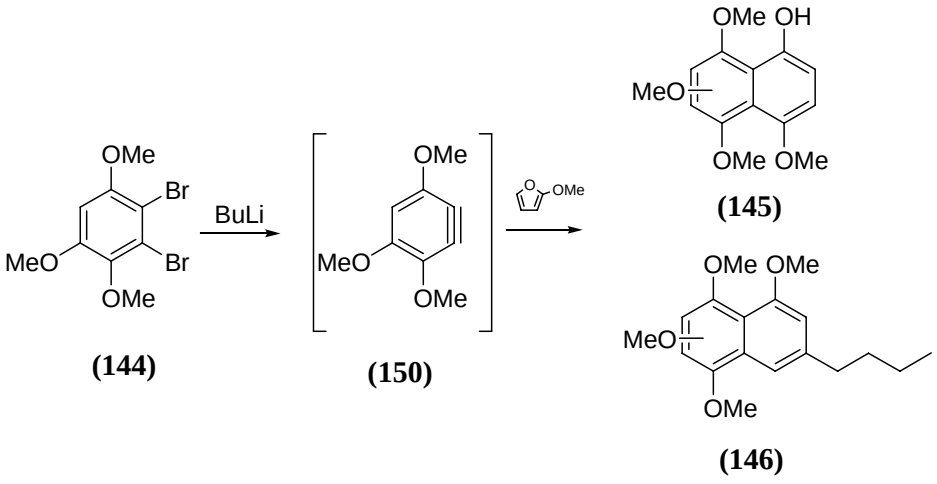
Bromination of 3-bromo-1,2,5-trimethoxybenzene (143) by treatment with Br_2 in benzene resulted in a mixture of 2,3-dibromo-1,4,5-trimethoxy-benzene (144) (81%), 1,2,4-tribromo-3,5,6-trimethoxy-benzene (148) (6%) and 2,3-dibromo-5-

methoxy-[1,4]benzoquinone (149) (5%). Bromination occurred mainly at the less hindered site of 3-bromo-1,2,5-trimethoxybenzene (143) affording (144) as the major product. Some oxadative demethylation of (144) occurred under the reaction conditions.



(143) **(144)** **(148)** **(149)**

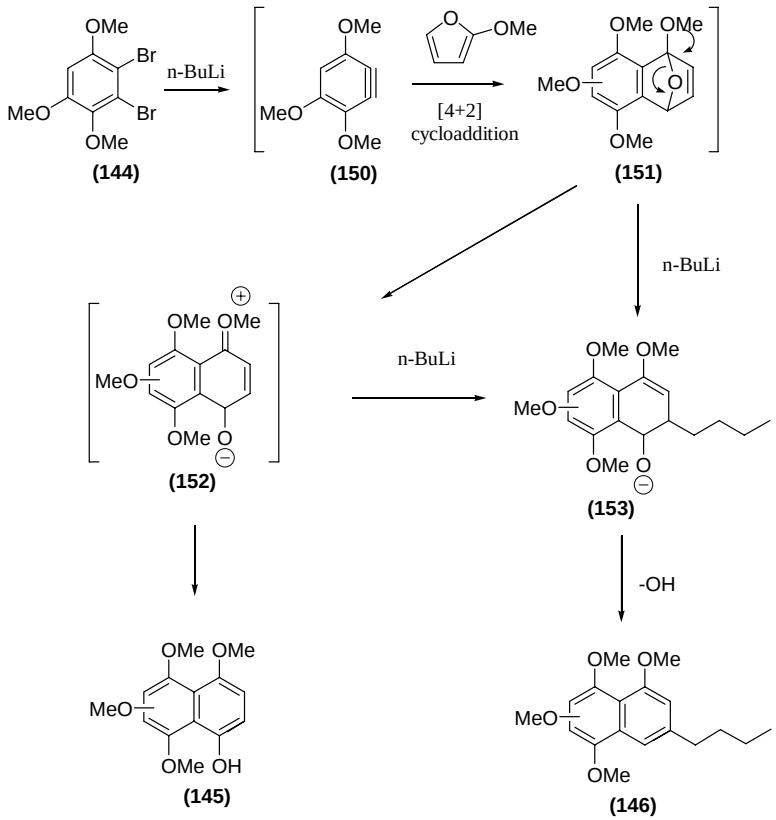
Naphthol (145) was synthesized from 3,4-dibromo-1,2,5-trimethoxybenzene (144). In this reaction, benzyne (150) was generated in situ and immediately trapped with commercially available 2-methoxyfuran to afford regiomeric naphthol (145) (33%) as a mixture of regioisomers and undesired byproduct (146) (21%).



(144) **(150)** **(145)** **(146)**

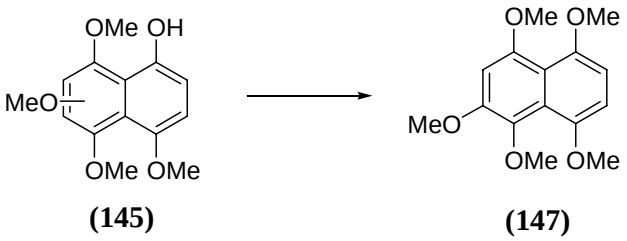
A plausible mechanism for formation of (145) and (146) have been proposed involves [4+2] cycloaddition of benzyne (150) and 2-methoxyfuran to give intermediate (151) which subsequently undergoes furan ring opening to give regioisomeric naphthols (145). The ^{1}H NMR spectrum of (145) showed butyl group at δ 0.95 (m,3H), 1.3-1.5 (m, 2H), 1.6-1.8 (m, 2H) and 2.71 (t, J=7.7 Hz, 2H). This

proton signals supported attract of butyl anion onto aromatic ring. The byproduct can be rationalized by attack of the butyl carbanion on the adduct (151) or (152), which would lead to ring opening to afford intermediate (153), and this could protonate oxygen and dehydrate **(**Scheme 28) (Giles *et al*., 1988).



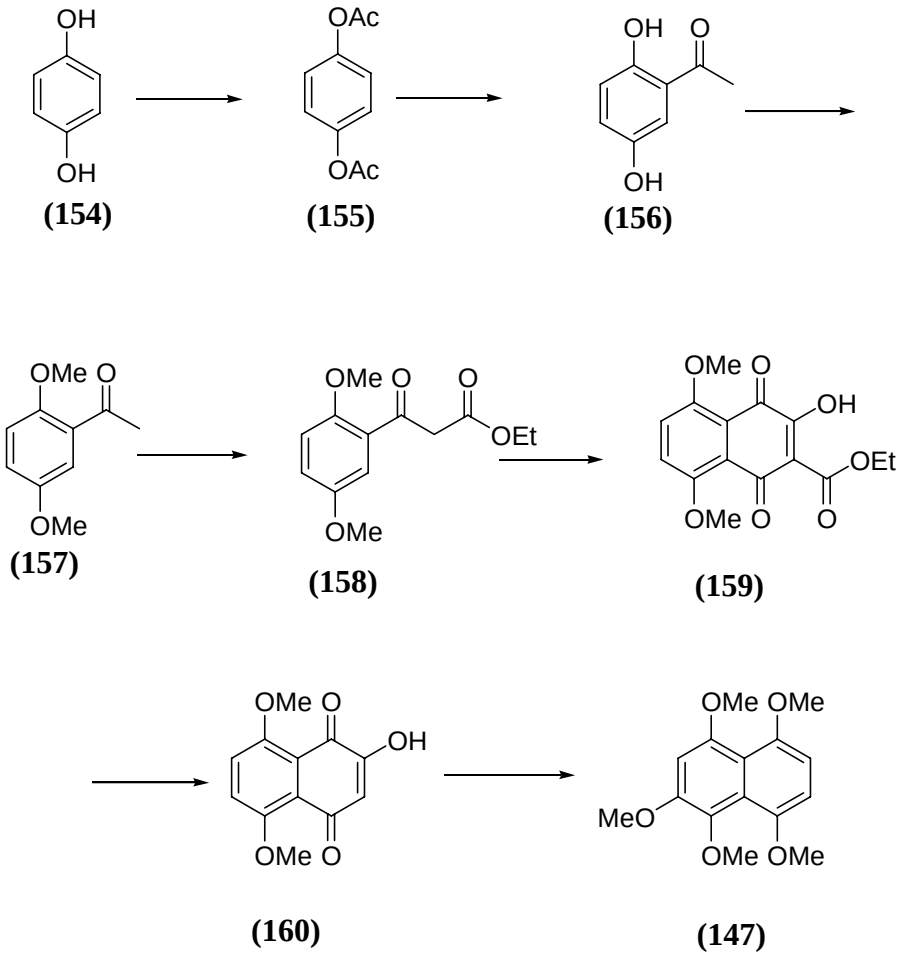
Scheme 28

Finally, methylation of the regioisomeric mixture of naphthols (145) using Me_2SO_4 gave 1,2,4,5,8-pentamethoxynaphthalene (147) in 43% yield.



(145) **(147)**

The second synthesis of 1,2,4,5,8-pentamethoxynaphthalene (147) started from hydroquinone (154) as shown in Scheme 29.



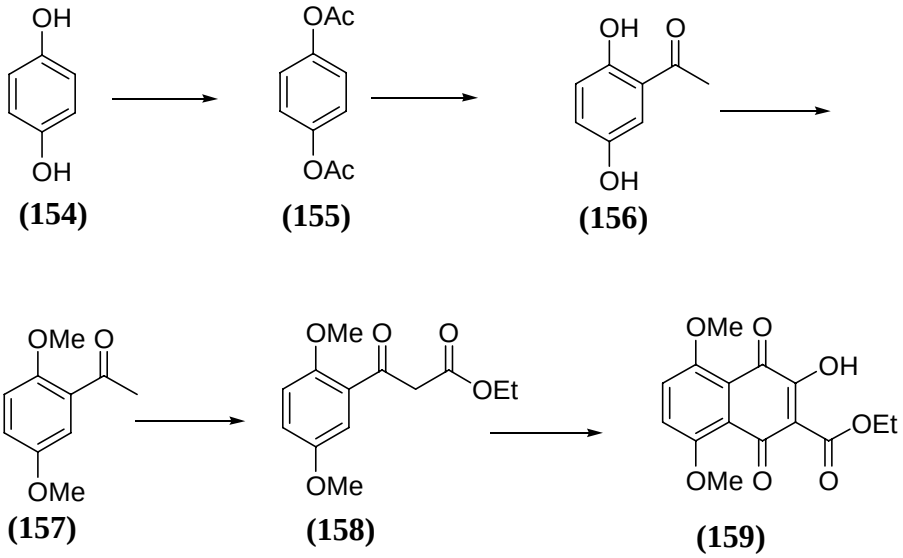
(154) **(155)** **(156)**

(157) **(158)** **(159)**

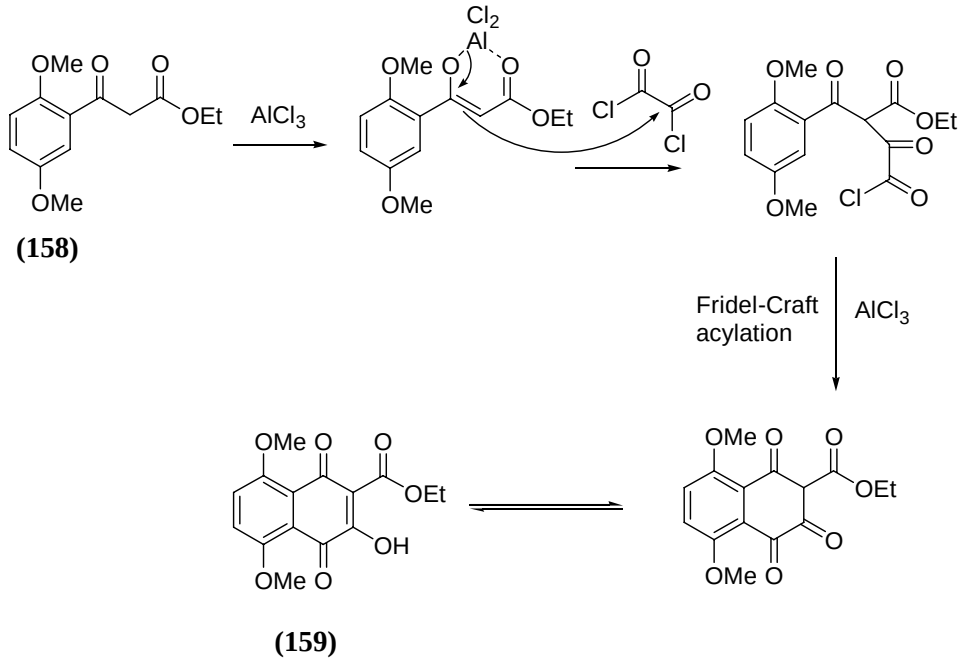
(160) **(147)**

Scheme 29

Acetylation of p-hydrobenzoquinone (154) using acetic anhydride in H_2SO_4 provided diacetate (155) in quantitative yield. Fried rearrangement of (155) was carried out at 165 ^oC using $AlCl_3$ to give 2,5-dihydroxyacrtophenone (156) in 71%. Methylation of (156) using dimethyl sulfate, K_2CO_3, in actone afforded 2,5-dimethoxy acetophenone (157) in 71% yield over two steps. Alternatively, the conversion of (156) to (157) has been accomplished in 71 yield% by using dimethyl sulfate, TBAI, KOH, H_2O. Treatment of (157) with NaH and diethyl carbonate furnished (2,5-dimethoxyphenyl)-3-oxopropanoate (158) in 81% yield.

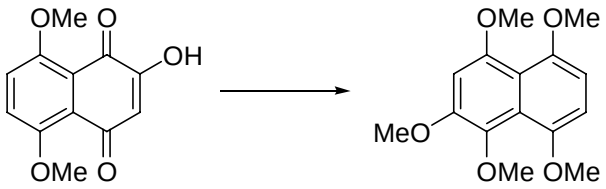


The next step of the reaction sequence was to construct the naphthoquinone ring via intramolecular Fridel-Craft acylation. Treatment of 158 with oxalyl chloride and $AlCl_3$, in refluxing $MeNO_2$ provided naphthoquinone (159) in 74% yield. This conversion is rationalized in Scheme 30.



Scheme 30

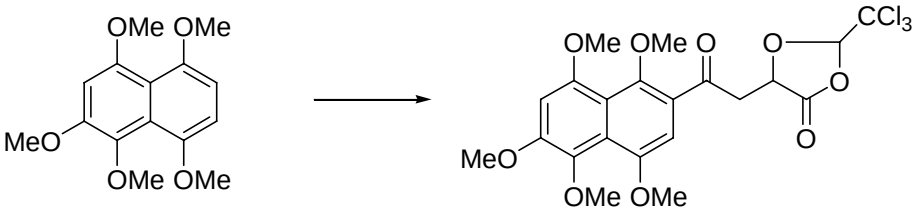
Finally, reductive methylation of 159 using dimethyl sulfate, $Na_2S_2O_4$, KOH, and TBAI, in THF, H_20 provided the desired 1,2,4,5,8-pentamethoxynaphthalene in 43% yield.



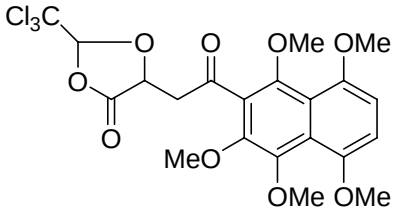
(160) **(147)**

Synthesis of (±)-marticin (12) and (±)-isomarticin (13)

With 1,2,4,5,8-pentamethoxynaphthalene(147) and side chains (132 or 133) in hand, we next investigated the connection of both compounds via Fridel-Craft acylation. Unfortunately, Fridel-Craft acylation of (147) using 2 mol of acid chloride (133) in the presence of 3 mol of $AlCl_3$ in CH_2Cl_2 provided 1:1 mixture of (161) and (162) as a inseparable product. (161) arises from acylation at the less hindered position (right hand side) whilst (162) arises from acylation at the more hindered and more electron rich position (left hand side). The mixture of (161) and (162) was characterized on the basis of ^{1}H NMR spectra. ^{1}H NMR spectrum ($CDCl_3$) exhibited two-proton doublets (J= 7.5 Hz) at δ 6.57 (Ar-H) and δ 6.45 (Ar-H) which indicated the presence of the naphthalene moiety of (162) whilst the signals of the naphthalene moiety of (162) appeared at 7.10 (d, J= 2.4 Hz) and 6.47 (d, J= 2.4 Hz).

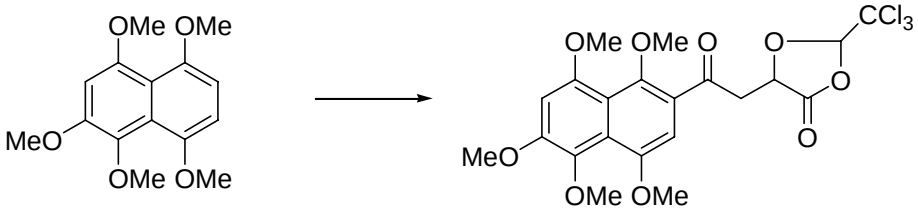


(147) **(161)**



(162)

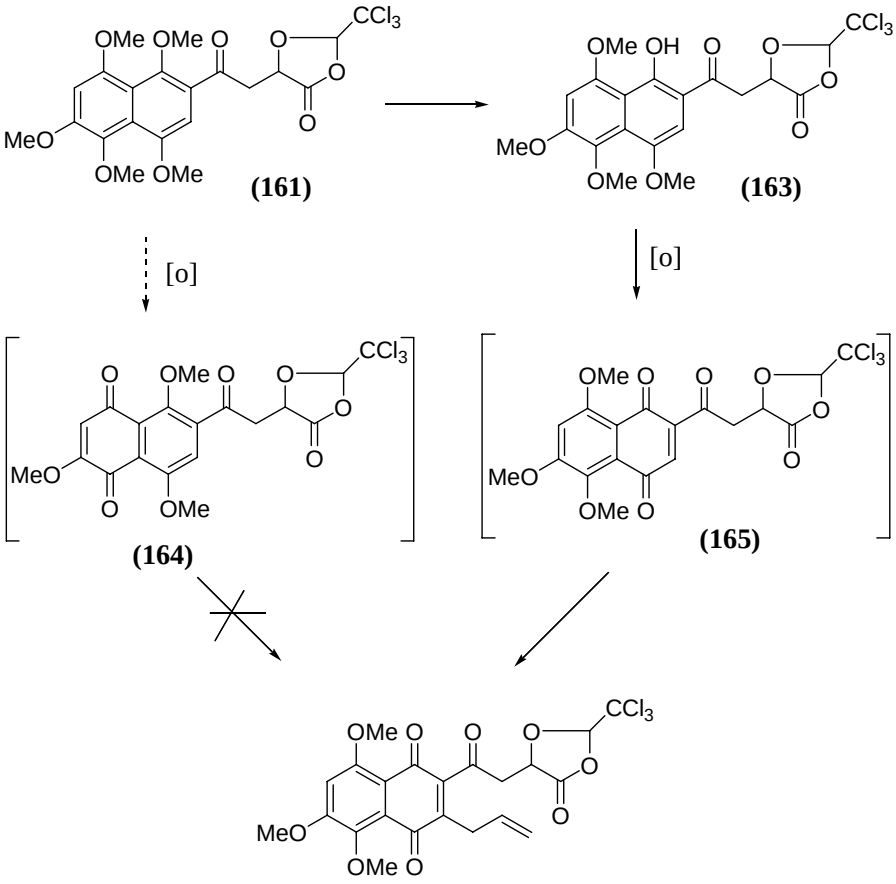
Possibly, byproduct (162) occur form the use of too active an acylating agent. To overcome the problem, a less active acylating agent was used without a Lewis acid catalyst. Treatment of acid (132) in TFAA generated acid anhydride *in situ* which was subsequently reacted with (147) to give only the desired (161) in 55% yield.



(147) **(161)**

In the next step of the reaction sequence, we planned to introduce an allyl group onto (161) via radical allylation. From Giles's report (1988), oxidation of 1,2,4,5,8-pentamethoxynaphthalene derivatives using CAN led to the oxidation at the ring that has most electron density (left hand side of naphthalene ring). If (161) is

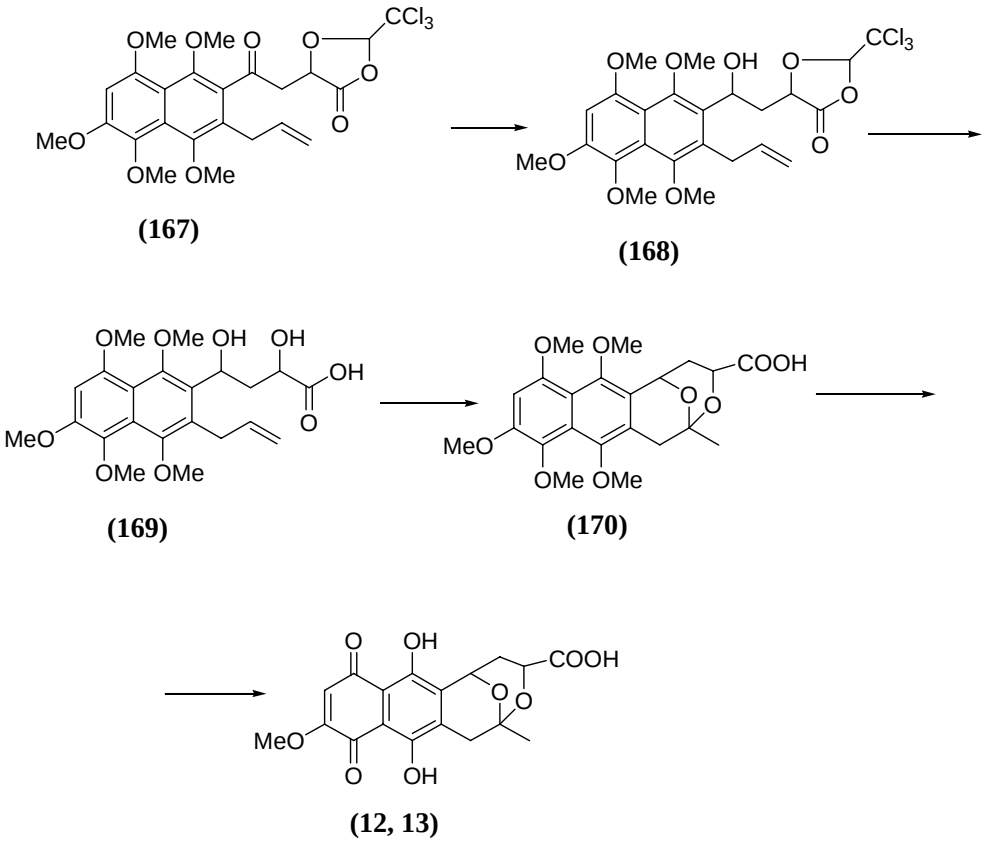
oxidized with CAN, unwanted naphthoquinone (164) will be formed. This problem was solved by making the right side of naphthalene ring more electron rich by selective demethylation of (161) using BBr_3 which gave (163) in 71% yield. Oxidation of (163) with CAN then provided (165) which was used in the next step without further purification. Radical allylation of naphthoquinone (165) with vinyl acetic acid, using ammonium persulfate and silver nitrate in acetonitrile, furnished allylnaphthoquinone (166) in Scheme 31.



Scheme 31

Several attempts to reductivly methylate (166) using dimethyl sulfate, $Na_2S_2O_4$, KOH, TBAI, in THF, H_20 were unsuccessful. This is probably because KOH could removes the side chain protecting group. By using K_2CO_3 as a milder base KOH, (167) was obtained in 55% yield.

Reduction of (167) using $NaBH_4$ gave alcohol (168) as a distereomeric mixture which was used in the next step without further purification. Deprotection of unpurifiled (168) with KOH furnished (169). The Pd(II) promoted cyclization of (159) proceeded at 65^{o}C in anhydrous dimethoxyethane with 0.02 mol equivalent of Pd chloride, cupric chloride (4.0 mol. eq) and air bubbling into the reaction to afford (170) as a diastereomer in 67% yield. Finally, oxidation of (170) using CAN followed by demethylation using BBr_3 gave the desired marticin (12) and isomarticin (13) as a 1 :1.2 mixture in 52% yield (Scheme 32). The ratio of products was confirmed by ^{1}H NMR and HPLC.



Scheme 32

The ^{1}H NMR of both products (12), (13) were compared with reference spectra as shown in Table 5.

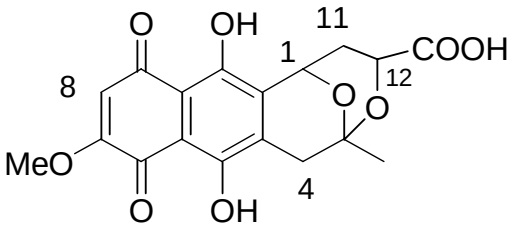


Table 5 ^{1}H NMR data of marticin (12) and isomarticin (13)

position	Marticin	Isomaticin	Marticin (Holenstein *et al*. in 1984)	Isomaticin (Holenstein *et al*. in 1984)
OH	12.93 (S)	12.92 (S)	12.93 (S)	12.91 (S)
OH	12.43 (S)	12.42 (S)	12.53 (S)	12.51 (S)
CH-8	6.15 (S)	6.17 (S)	6.18 (S)	6.20 (S)
CH-1 (eq)	4.61 (m)	4.42(m)	4.58 (m)	4.31(dd) (J=12, 3 Hz)
OMe	3.97 (S)	3.97 (S)	3.94 (S)	3.97 (S)
CH-12 (ax)	5.39 (d, J=9 Hz)	5.62 (d, J=5 Hz)	5.42 (d, J=9 Hz)	5.62 (d, J=5 Hz)
CH-11 (ax)	2.30 (m)	2.30 (m)	2.30 (m)	2.30 (m)
CH-11(eq)	2.21 (m)	2.21 (m)	2.22 (m)	2.21 (m)

CH-4 (eq)	3.09 (d, J=19 Hz)	3.13 (d, J=19 Hz)	3.02 (d, J=19 Hz)	3.13 (d, J=19 Hz)
CH-4 (ax)	2.71 (d, J=19 Hz)	2.62 (d, J=19 Hz)	2.73 (d, J=19 Hz)	2.67 (d, J=19 Hz)
Me	1.56 (S)	1.60 (S)	1.68(S)	1.70 (S)