MATERIALS AND METHODS

Materials

Instrumentation

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

^{1}H and ^{13}C-NMR spectra were recorded on Bruker (300 MHz) spectrometer at Department of Chemistry, Srinakarinwiroth University and on Brucker (400 MHz) Advance DPX-400. Chemical shifts are reported as parts per million (δ) downfield from tetramethylsilane (TMS) as internal standard. Unless otherwise specified deuterochloroform ($CDCl_3$) and deuteracetone (CD_3COCD_3) were used as solvents. Coupling constants (J) are given in Hertz (Hz) and peak multiplicities are reported using the following abbreviations: s = singlet; d = doublet; t = triplet; q = quartet; br = broad; m = multiplet, dd = double doublet, dt = double triplet.

Mass spectra and accurate masses (HRMS) were obtained on a JEOL JMS-SX102 mass spectrometer, on a GCMS-QP-5050A in electron impact mode at 70 eV and on an Agilent 1100 Series LC/MSSD Trap in chemical ionization.

Infrared (IR) spectra were recorded on a FTIR Perkin-Elmer System 2000 as neat liquid or KBr pellet at Department of Chemistry, Kasetsart University.

Melting points data (mp) were determined on Fisher Johns apparatus at Department of Chemistry, Kasetsart University and are uncorrected.

Chromatographic system

Thin layer chromatography (TLC) was carried out on aluminum sheets coated with 200-300 mesh silica gel with a fluorescent indicator (254 nm) (Merck) for monitoring reaction progress. The chromatograms were visualized under ultraviolet light (254 nm) and/or by spraying with a solution of 3% vanillin in ethanol with 3% sulfuric acid following by heating on a hot plate.

Ultraviolet absorbtion spectra were recorded using a 3D spectra program of HPLC Agilent 1200 series with Eclipe XDB-C18 Pack column [150x406 mm., i.d. 5 μm].

Flash column chromatography was performed as described by Still W.C. employing less than 230 mesh silica gel.

The ratio of enatiomeric mixture of (±)-isagarin (11) was determined by chiral HPLC column (Chiralcel OD column 250 x 4.6 mm).

Chemical reagents

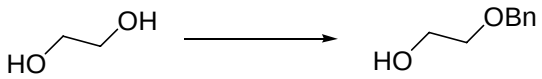
1-Naphthol, p-hydrobenzoquinone, vanillin were purchased from Fluka and Merck.

All other chemicals were obtained from Aldrich, Fluka and Merck Co. and were used without further purification. In the case of anhydrous solvent were dried according to the standard procedure outlined by Vogel (1989) in Vogel' Text Book of Practical Organic Chemistry.

Experimental details of the reactions that failed have not been reported, although they are discussed.

Methods

2-(Benzyloxy)ethanol (118)



(117) (118)

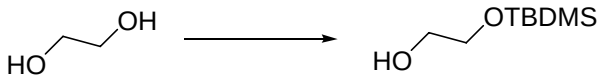
85% KOH (5.6 g, 0.25 mol) was dissolved in ethylene glycol (117) (15.5 mL, 0.25 mol). Benzyl chloride (12.6 mL, 0.1 mol) was added to the solution with stirring, during a period of 2 h and keeping the temperature of the reaction mixture at 90 ^{o}C. The temperature was then raised to 130 ^{o}C and kept at this point for 2 h. The cooled mixture was diluted with water and then extracted with diethyl ether (3x50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and filtrate distilled to removethe solvent. The crude product was purified by fractional distillation to give 2-(benzyloxy)ethanol (118) as colorless oil (7.7 g, 51 %) (Marshall, 1988).

FTIR (neat) ν_{max} ; 3400 (OH) , 1630 (C=C), 1455, 1360 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33 (m, 5H, phenyl H), 4.55 (s, 2H, $PhCH_2O$), 3.74 (m, 2H), 3.59 (m, 2H), 2.34 (m, 1H, CH_2OH)

MS (CI), m/z 153.2 (M+1)

(*tert*-Butyldimethylsilyloxy)ethanol (120)



(117) **(120)**

Sodium hydride (0.27 g, 5.6 mmol) was suspended in THF (11 mL) after being washed with ether. Ethylene glycol (117) (0.35 g, 5.6 mmol) was added to the

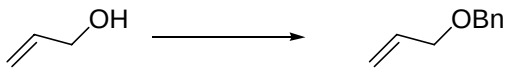
mixture at room temperature and stirred for 45 min during which a large amount of white precipitate formed. *tert*-Butyldimethylsilyl chloride (0.84 g, 5.6 mmol) was then added, and vigorous stirring was continued for 45 min. The mixture was poured into ether (100 mL) and washed with 10% aq. K_2CO_3 (2x30 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and the filtrate concentrated in vacuo. The residue was purified by flash column chromatography (1:9 ; EtOAc : Hexane) to obtain (*tert*-butyldimethylsilyloxy)ethanol (120) as colorless oil (0.7 g, 73%) (Lafontaine, 2003).

FTIR (neat) ν_{max} ; 3403 (OH) cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz) δ 3.68 (m, 2H), 3.51 (m, 2H), 1.87 (s, 9H), 0.03 (s, 6H)

MS (CI), m/z 177.3 (M+1)

Allyloxymethyl-benzene (124)



(122) **(123)**

Sodium hydride (0.49 g, 0.017 mmol) was suspended in THF after being washed with ether. Allyl alcohol (1 g, 0.017 mol) was added at room temperature and the mixture was stirred during 45 min during which time a large amount of a white precipitate had formed. The benzyl chloride (0.84 ml, 0.02 mol) was then added, and vigorous stirring was continued for 45 min. The mixture was poured into ether (100 mL) and washed with 10% aq. K_2CO_3 (30 mL). The organic layer was dried over Na_2SO_4, filtered and the filtrate concentrated under reduced pressure. The residue was purified by flash column chromatography to obtain colorless oil (1.2 g , 84%) (Menicagli, 1987).

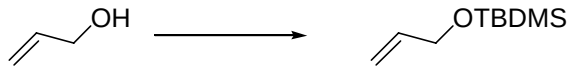
FTIR (neat) ν_{max} ; 1648 (C=C), 1637 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34 (m, 5H), 5.95 (m, 1H), 5.28 (m, 2H), 4.53 (s, 2H), 4.03 (m, 2H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.3, 134.71, 128.3 (2xC), 127.7 (2xC), 127.5, 117.0, 72.1, 71.1

MS (CI), m/z 150.2 (M+1)

Allyloxy-tert-butyl-dimethyl-silane (124)



(122) **(124)**

A stirred solution of allyl alcohol (122) (1 g, 0.017 mol) in CH_2Cl_2 (15 mL) was stirred at room temperature. Then a solution of *tert*-butyldimethylsilyl chloride (3.3 g, 0.022 mol) in DMF (3 mL) was added and stirred overnight. The reaction mixture was poured into ether (100 mL) and washed with 10% aq. K_2CO_3 (30 mL). The organic layer was dried over anhydrous Na_2SO_4, the filtrate filtered and concentrated in vacuo. The residue was purified by flash column chromatography (1:9 ; EtOAc : Hexane) to afford allyloxy-tert-butyl-dimethyl-silane (124) as colorless oil (0.95 g, 73%) (Van de Coevering, 2005).

FTIR (neat) ν_{max} ; 1645 (C=C), 1360 cm^{-1}

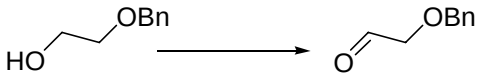
^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.90 (m, 1H), 5.24 (m, 1H), 5.06 (m, 1H), 4.15 (m, 2H), 0.90 (s, 9H), 0.05 (s, 6H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.5, 113.9, 64.1, 25.9, 18.4, -4.58

MS (CI), m/z 173.3 (M+1)

(Benzyloxy)acetaldehyde (119)

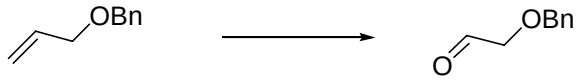
Method 1



(118) **(119)**

A solution of oxalyl chloride (0.6 mL, 6.9 mmol) in dry CH_2Cl_2 (20 mL) was stirred at -78 ^oC under nitrogen atmosphere and maintained at that temperature while DMSO (0.98 mL, 13.8 mmol) was added dropwise. After 30 min, a solution of monobenzyl ether (118) (0.7 g, 4.6 mmol) in dry CH_2Cl_2 (1 mL) was added to the reaction mixture, which was stirred at -78 ^oC for further 1 h. The mixture was treated dropwise over 10 min with Et_3N (3 mL, 20 mmol). After 30 min, the cold bath was removed and the reaction mixture was filtered through anhydrous Na_2SO_4 pad and the filtrate was concentrated in vacuo. The aldehyde was purified by fractional distillation (110-112 ^oC) to give (benzyloxy)acetaldehyde (119) as colorless oil (560 mg, 81%).

Method 2



(123) **(119)**

A solution of allyl ether (123) (500 mg 3.1 mmol) in CH_2Cl_2 (10 mL) was stirred at -78 ^oC while air was bubbled through the solution. After 15 min, ozone was bubbled through the solution until the color of solution change from colorless to blue Then, the air was bubbled through the reaction mixture until the solution was colorless. PPh_3 (2.3 g, 8.7 mmol) was then added. The reaction mixture was stirred at room temperature for a further 3 h and concentrated in vacuo. The residue was purified by flash column chromatography (1:9 ; EtOAc : Hexane) to obtain (benzyloxy)acetaldehyde (119) as colorless oil (417 mg, 82%) (Pollex, 2005).

FTIR (neat) ν_{max} ; 1699 (C=O), 1630 (C=C) cm^{-1}

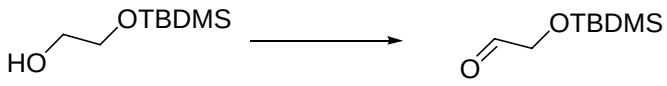
^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.74 (s, 1H), 7.36 (m, 5H), 4.65 (s, 2H), 4.12 (s, 2H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 200.5, 136.8, 128.6(2xC), 128.3, 127.9(2xC), 75.3, 73.7

MS (CI), m/z 151.1 (M+1)

(*tert*-Butyldimethylsilyloxy)acetaldehyde (121)

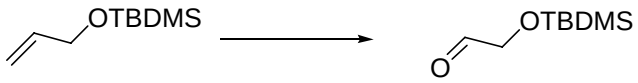
Method 1



(120) **(121)**

A solution of oxalyl chloride (0.6 mL, 6.9 mmol) in dry CH_2Cl_2 (20 mL) was stirred at -78 ^{o}C under nitrogen atmosphere and maintained at that temperature while DMSO (0.98 mL, 13.8 mmol) was added dropwise. After 30 min, a solution of silyl ether (120) (0.64 g, 4.6 mmol) in dry CH_2Cl_2 (1 mL) was added to the reaction mixture, which was stirred at -78 ^{o}C for further 1 h. The mixture was treated dropwise over 10 min with Et_3N (3 mL, 20 mmol). After 30 min, the cold bath was removed and the reaction mixture was filtered through anhydrous Na_2SO_4 pad and the filtrate was concentrated in vacuo. The residue was purified by fractional distillation to give *tert*-butyldimethylsilyloxy)acetaldehyde (121) as colorless oil (542 mg, 76%) (Lafontaine, 2003).

Method 2



(124) **(121)**

A solution of allyl ether (124) (500 mg 2.9 mmol) in CH_2Cl_2 (10 mL) was stirred at -78 ^oC while air was bubbled through the solution. After 15 min, ozone was bubbled through the solution until the color of solution change from colorless to blue color. Ozone was stopped. Then, the reaction mixture was bubbled with air until the color of the solution change to colorless solution and PPh_3 (2.3 g, 8.7 mmol) was added. The reaction mixture was stirred at room temperature for further 3 h and concentrated in vacuo. The residue was purified by flash column chromatography (1:9 ; EtOAc : Hexane) to obtain (*tert*-butyldimethylsilyloxy) acetaldehyde (121) as colorless oil (385 mg, 76%) (Lafontaine, 2003).

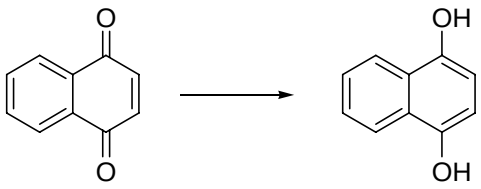
FTIR (neat) ν_{max} ; 1701 (C=O) cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz) δ 9.6 (s, 1H), 4.31 (s, 2H), 0.9 (s, 9H), 0.1 (s, 6H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 200.1, 75.3, 25.7, -4.1. -4.0

MS (CI), m/z 175.3 (M+1)

p-Hydronaphthoquinone (110)

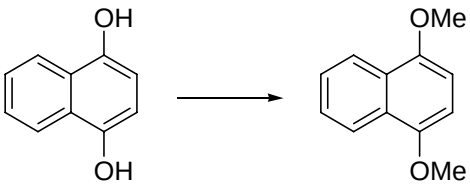


(110)

A solution of *p*-naphthoquinone (10 g, 63.3 mmol) in diethylether (250 mL) and EtOAc (70 mL) was stirred vigorously at room temperature. The solution of $Na_2S_2O_4$ (65 g, 316.5 mmol) in water (50 mL) was added and stirred for 30 min. The organic layer was separated, washed with water (2x100 mL), dried over anhydrous Na_2SO_4 and filtered. The resulting solution was concentrated in vacuo to give *p*-hydronaphthoquinone (110) as a brown crystal in quantitative yield ; mp 191-195 ^{0}C (Oatis *et al*., 1985, 191-193 ^{o}C).

FTIR (KBr) ν_{max} ; 3260 , 1648 cm^{-1}

1,4-Dimethoxynaphthalene (111)



(110) **(111)**

Method 1

To a stirred suspension of p-hydronaphthoquinone (110) (5 g, 31.25 mmol), anhydrous K_2CO_3 (12.7 g, 92.02 mmol) in dry acetone (100 mL) was added dimethyl sulfate (7.4 mL, 78.11 mmol). The reaction mixtiure was refluxed for 3 h. After cooling to room temperature, the mixture was filtered and the filtrate concentrated in vacuo. The residue was purified by quick column chromatography (hexane-CH_2Cl_2) to obtain the 1,4-dimethoxynaphthalene (111) as a colourless needles (4.32 g, 72 %) ; mp 84-85 ^{0}C (Harvey *et al*., 2004, 85-86 ^{0}C).

Method 2

To a stirred suspension of *p*-hydronaphthoquinone (110) (5 g, 31.25 mmol), anhydrous K_2CO_3 (12.7 g, 92.02 mmol) in dry acetone (100 mL) was added methyl

iodide (9.7 mL, 124 mmol). The reaction mixture was refluxed for 10 h. After cooling to room temperature, the reaction mixture was filtered and the filtrate concentrated in vacuo. The residue was purified by quick column chromatography (hexane-CH_2Cl_2) to obtain the 1,4-dimethoxynaphthalene (111) as a colourless needles (3.35 g, 57%) ; mp 84-85 ^{0}C (Harvey *et al*., 2004, 85-86 ^{0}C).

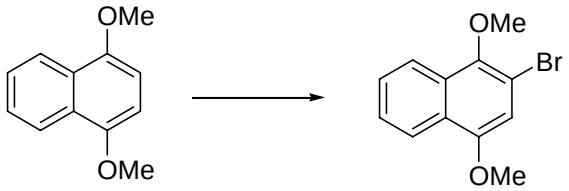
FTIR (KBr), ν_{max} 1593, 1272, 1235 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.20 (m, 2H), 7.50 (m, 2H) , 6.70 (s, 2H), 3.95 (s, 6H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.1 (2xC), 126.9 (2xC), 126.5 (2xC), 122.4 (2xC), 103.8 (2xC), 56.4(2xC)

MS m/e (M^+) (relative intensity) 188 (M^+, 70), 173 (100) , 145 (25)

2-Bromo-1,4-dimethoxynaphthalene (112)



(111) **(112)**

To a solution of 1,4-dimethoxynapthalene (111) (1 g, 4 mmol) in benzene (3 mL) was added bromine (0.25 mL). After being stirred at room temperature for 30 min, the reaction mixture was poured with 10% aq. Na_2CO_3 (10 mL). Benzene layer was separated and dried over anhydrous K_2CO_3 and filtered. The filtrate was concentrated in vacuo. The residue was purified by flash column chromatography (15:85 ; CH_2Cl_2 : Hexane) to give 2-bromo-1,4-dimethoxynaphthalene (112) as colorless oil (982 mg, 92%) (Harvey *et al*., 2004).

FTIR (KBr), ν_{max} 1581 (C=C), 1105(C-O) cm^{-1}

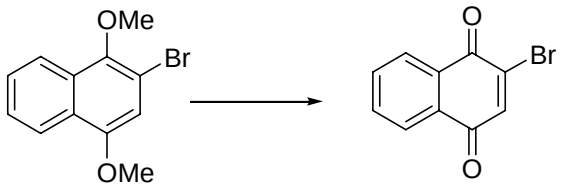
^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.11 (m, 1H), 7.97 (m, 1H), 7.45 (m, 2H), 6.79 (s, 1H), 3.88 (s, 3H), 3.87 (s, 3H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.9, 147.4, 129.6, 126.4, 123.2, 122.5, 112.5, 108.6, 62.1(OMe), 56.5(OMe)

MS (CI), m/z 268 (M+1, 60), 266(67), 253(100), 251(95), 129(63)

2-Bromo-1,4-naphthoquinone (114)

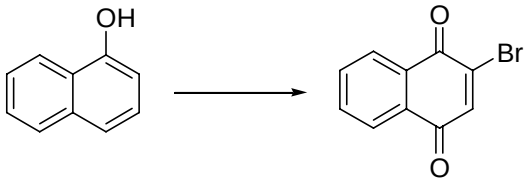
Method 1



(112) (114)

To an ice-cold solution of 2-bromo-1,4-dimethoxynaphthalene (112) (20 mg, 0.1 mmol) in acetonitrile (0.75 mL) was added dropwise a solution of CAN (143 mg, 0.26 mmol) in water (0.5 mL). The reaction mixture was stirred at 0 ^{o}C for 15 min, water (10 mL) was added and extracted with EtOAc (3x15 mL). The organic layers were separated and dried over anhydrous Mg_2SO_4 then concentrated under reduced pressure. The residue was purified by flash column chromatography (15: 85; CH_2Cl_2: Hexane) to obtain 2-bromo-1,4-naphthoquinone (114) in quantitative yield as a yellow plates ; mp 131-132 ^{0}C (De Kimpe *et al*., 2003, 130-132 ^{o}C).

Method 2



(113) **(114)**

A solution of 1-naphthol (113) (1 g, 6.94 mmol) in acetic acid (50 mL) was stirred at 45 ^{o}C. Then, a solution of *N*-bromosuccinamide (5 g, 27.8 mmol) in 50% acetic acid solution (150 mL) was added dropwise for 30 min. The resulting solution was stirred at 55-60 ^{o}C for 30 min. Subsequently, water (50 mL) was added to the solution, followed by extraction with CH_2Cl_2 (6x50 mL). The combined organic layers were washed with water (4x100 mL) and saturated $NaHCO_3$ (5x100 mL). The organic phase was dried over anhydrous Mg_2SO_4, filtered and the filtrated concentrated in vacuo. The residue was purified by flash column chromatography (15:85; CH_2Cl_2:Hexane) to provide 2-bromo-1,4-naphthoquinone (114) (1.2 g, 73%) as a yellow plats ; mp 131-132 ^{0}C (De Kimpe *et al*., 2003, 130-132 ^{o}C).

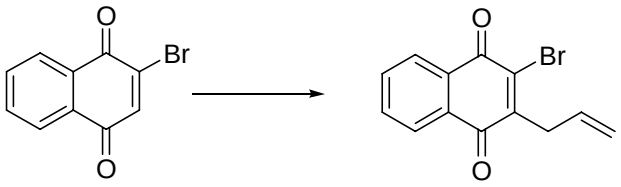
FTIR (KBr) ν_{max} 1679 (C=O), 1657 (C=O), 1590 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.16 (m, 1H), 8.01 (m, 1H), 7.77 (m, 2H), 7.51 (s, 1H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 182.8, 178.3, 140.8, 140.5, 134.9, 134.6, 132.1, 131.3, 128.2, 127.4

MS (CI), m/z 237.1 (M+1)

2-Allyl-3-bromo-1,4-naphthoquinone (115)



(114) **(115)**

To a stirred suspension of 2-bromo-1,4-naphthoquinone (114) (500 mg, 2.1 mmol), silver nitrate (110 mg, 1.05 mmol), and vinylacetic acid (270 mg, 3.15 mmol) in acetonitrile (50 mL) was added dropwise over 15 min a solution of ammonium persulfate (860 mg, 3.78 mmol) in water (25 mL). The reaction mixture was stirred at 60-70 ^{o}C for 8 h. Then, the resulting mixture was poured into cold water (25 mL) and extracted with EtOAc (4x50 mL). The combined organic layers were separated, washed with 10% aq. $NaHCO_3$ (2x50 mL), dried over anhydrous Mg_2SO_4 and filtered. The solution was concentrated in vacuo. The residue was purified by flash column chromatography (5: 95 ; EtOAc: Hexane) to obtain 2-allyl-3-bromo-1,4-naphthoquinone (115) (418 mg, 72%) as a yellow prisms ; mp 70-71 ^{0}C (Maruyama *et al*., 1986, 72-72 ^{o}C).

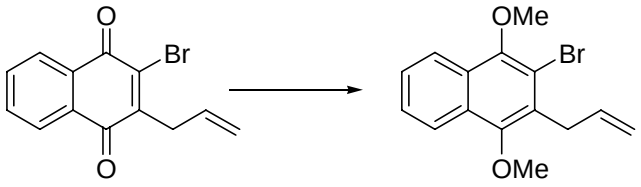
IR (KBr), ν_{max} 1665, 1590 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.10 (2H, m), 7.71 (2H, m), 5.85 (1H, ddt, J=17 Hz, 10 Hz, 6 Hz), 5.25 (1H, dd, J= 17Hz, 1.3 Hz), 5.14 (1H, dd, J=10 Hz, 1.3 Hz), 3.61 (2H, dt, J=6.6 Hz, 1.3 Hz)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 181.3, 177.7, 148.9, 139.3, 134.2, 133.9, 131.3, 131.1, 127.5, 127.1, 118.2, 35.4

MS (CI), m/z 278.2 (M+1)

2-Allyl-3-bromo-1,4-dimethoxynaphthalene (116)



(115) **(116)**

A solution of 2-allyl-3-bromo-1,4-naphthoquinone (115) (500 mg, 1.8 mmol) in 95% ethanol (20 mL) was added to a solution of tin(II)chloride (1.2 g, 6.34 mmol) in concentrated hydrochloric acid (1.2 mL) at 50 ^{o}C. Then, the reaction mixture was stirred for 30 min at the same temperature. After addition of cold water (100 mL), the appearing precipitate was filtered. The precipitate was mixed with dimethyl sulfate (3.42 g, 27 mmol). Then 50% aq. KOH (10 mL) was added dropwise at 0 ^{o}C. The reaction mixture was stirred at 65 ^{o}C for 3 h, and then the reaction mixture was poured into cold water (20 mL). The resulting mixture was extracted with diethyl ether (5x50 mL). The combined organic layers were separated, washed with 10% aq. $NaHCO_3$ (2x50 mL), dried over anhydrous Mg_2SO_4 and filtered. The organic extract was concentrated in vacuo. Flash column chromatography of the residue on silica gel (15:85 ; CH_2Cl_2 : Hexane) provided 2-allyl-3-bromo-1,4-dimethoxynaphthalene (116) as colourless (414 mg, 75%) ; mp 56-57 ^{o}C (De Kimpe *et al*., 1999, 57-59 ^{o}C).

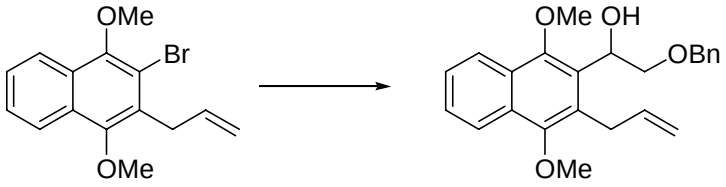
FTIR (KBr) ν_{max} 1612 (C=C), 1593 (C=C) cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.06 (2H, m), 7.51 (2H, m), 6.07 (1H, ddt, J=16.8 Hz, 10.2 Hz, 5.6 Hz), 5.09 (1H, dd, J=10.2 Hz, 1.7 Hz), 5.03 (1H, dd, J=16.8 Hz, 1.7 Hz), 3.97 (3H, s, OMe), 3.91 (3H, s, OMe), 3.79 (2H, dt, J=5.6 Hz, 1.7 Hz)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.9, 150.2, 135.7, 128.2, 127.9, 126.6, 126.5, 122.6, 122.5, 116.7, 115.8, 62.7, 61.34, 34.4

MS (EI), m/z ($M^{+\cdot}$ 5%) 307 (20), 277.1 (100), 257.3 (40), 198.2 (55)

2-Benzyloxy-1-(1,4-dimethoxy-naphthalen-2-yl)-ethanol (125)



(116) **(125)**

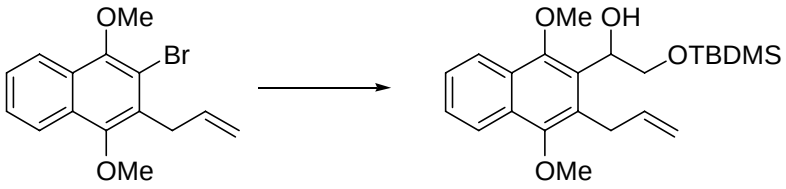
A solution of bromonaphthalene (116) (200 mg, 0.651 mmol) in dry THF (5 mL) was stirred at -78 ^{o}C under N_2 atmosphere. Then, *n*-BuLi (0.5 mL, 0.782 mmol) was added dropwise. Then a solution of (benzyloxy)acetaldehyde (119) (120 mg, 0.782 mmol) in dry THF (1mL) was added dropwise at the same temperature and stirred for an additional 30 min. The resulting mixture was poured into cold water and extracted with diethyl ether (4x30 mL). The combined organic layers were dried over anhydrous Mg_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (2:8 ; EtOAc: Hexane) to provide 2-benzyloxy-1-(1,4-dimethoxy-naphthalen-2-yl)-ethanol (125) as colorless oil (96 mg, 44%).

FTIR (neat), ν_{max} 3401 (OH) ,1615 (C=C) , 1595 (C=C) cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.0 (m, 2H), 7.45 (m,2H), 7.2 (m, 5H), 6.0 (m, 1H), 5.26 (dd, 1H, J=9, 3.5 Hz), 4.98 (dd, 1H, J= 10, 1.5 Hz), 4.83 (dd, 1H, J=10, 1.5 Hz), 4.55 (dd, 1H, J=12, 15 Hz), 4.2 (t, 2H, J=10 Hz), 3.91 (s, 3H), 3.82 (s, 3H), 3.65 (m,2H), 3.55 (m, 1H)

MS (CI), m/z 379.3 (M+1)

1-(3-Allyl-1,4-dimethoxy-naphthalen-2-yl)-2-(*tert*-butyl-dimethyl-silanyloxy)-ethanol (127)



(116) **(127)**

A solution of bromonaphthalene (116) (200 mg, 0.651 mmol) in dry THF (5 mL) was stirred at -78 ^{o}C under N_2 atmosphere. Then, *n*-BuLi (0.5 mL, 0.782 mmol) was added dropwise. Then a solution of aldehyde (121) (120 mg, 0.782 mmol) in dry THF (1mL) was added dropwise at the same temperature and stirred for an additional 30 min. The resulting was poured into cold water and extracted with diethyl ether (4x30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (2:8 ; EtOAc : Hexane) to obtain 1-(3-allyl-1,4-dimethoxy-naphthalen-2-yl)-2-(*tert*-butyl-dimethyl-silanyloxy)-ethanol (127) as colorless oil (184 mg , 70%).

FTIR (neat), ν_{max} 3413 (OH), 1612 (C=C) , 1593 (C=C) cm^{-1}

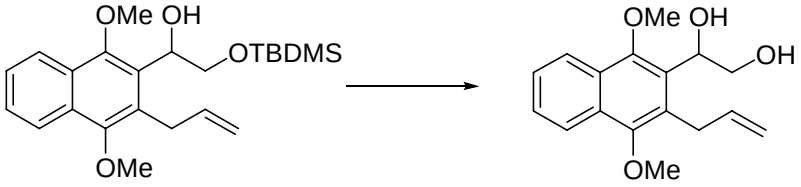
^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.05 (m, 2H) , 7.47 (m, 2H) 6.09 (m, 1H), 5.15 (dd, ,J= 4, 9 Hz, 1H), 5.05 (m, 1H), 4.80 (m, 1H), 4.15 (dd, J= 9, 8 Hz, 1H), 4.00 (s, 3H), 3.86 (s, 3H), 3.75 (m, 2H), 3.72 (1H), 0.88 (s, 9H), 0.04 (d, J=12 Hz, 3H)

^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.2, 131.2, 129.3, 126.9, 126.5, 123.5, 123.2, 115.4, 71.6, 68.2, 63.5, 62.3, 31.6, 26.3, -5.0, -5.1

MS (CI), m/z 403.4 (M+1)

1-(3-Allyl-1,4-dimethoxy-naphthalen-2-yl)-ethane-1,2-diol (126)

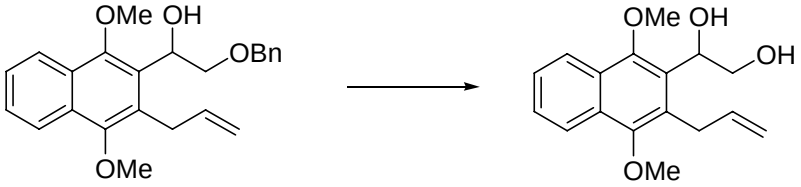
Method 1



(127) **(126)**

To a stirred solution of silylether (127) (300 mg, 0.8 mmol) in THF (15 mL) was added TBAF (756 mg, 2.4 mmol). The reaction mixture was stirred at room temperature for 30 min. Then water (50 mL) was added and extracted with diethyl ether (3x40 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduce pressure. The residue was purified by flash column chromatography (1:3 ; EtOAc : Hexane) to obtain 1-(3-allyl-1,4-dimethoxy-naphthalen-2-yl)-ethane-1,2-diol (126) as colorless oil (200 mg, 87%).

Method 2



(125) **(126)**

To a solution of naphthalene (350 mg, 2.8 mmol) in dry THF (12 mL), was added lithium metal (15 mg, 2.1 mmol) in small pieces. The reaction mixture was stirred at room temperature under N_2 atmosphere until lithium metal was completely dissolved (~3h). The resulting dark green solution of lithium naphthanide was cooled to -78 ^oC, followed by addition of a solution of benzyl ether (125) (100 mg, 0.26 mmol) in dry THF (4 mL) dropwise over 5 min. The reaction mixture was stirred at -78 ^oC for 30 min. Saturated aqueous ammonium chloride (5 mL) was added to the reaction mixture followed by addition of water (5 mL). The resulting solution was

extracted with ether (4x10 mL). The combined extracted was washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (4:6 ; EtOAc : Hexane) to obtain 1-(3-allyl-1,4-dimethoxy-naphthalen-2-yl)-ethane-1,2-diol (126) as colorless oil (31 mg, 41%).

FTIR (neat), ν_{max} 3415(OH), 1613(C=C), 1590 (C=C) cm^{-1}

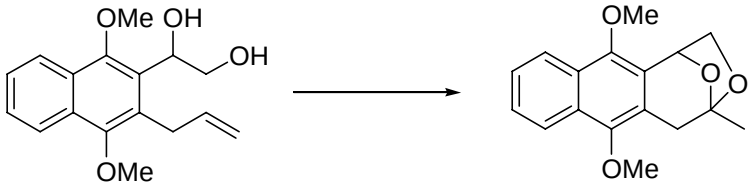
^1H NMR (acetone-d_6, 400 MHz) δ 8.00-8.09 (m, 2H), 7.50-7.54 (m, 2H), 6.10 (ddt, 1H, J=17.8 Hz, 7 Hz, 5.5 Hz), 5.31(m, 1H), 4.92-5.00 (m, 2H), 4.1 (dd, 1H, J=9 Hz, 10 Hz), 3.95 (s, 3H), 3.85 (s, 3H) 3.79-3.82 (m, 2H), 3.75 (dd, 1H, J=5 Hz, 10 Hz)

^{13}C NMR (acetone-d_6, 100 MHz) δ 152.3, 151.8, 139.2, 131.3, 129.3, 128.8, 126.9, 126.5, 123.5, 123.2, 115.3, 72.1, 66.9, 63.5, 62.3, 31.6

MS (CI), m/z 288.3 (M+)

Oxabicyclo compound (128)

Method 1



(126) **(128)**

A mixture of palladium chloride (4 mg, 0.023 mmol) and anhydrous cupric chloride (47 mg, 0.35 mmol) in dry dimethoxyethane (2 mL) was stirred and heat at 65 ^oC while oxygen was bubbled through the solution. A solution of diol (126) (100 mg, 0.35 mmol) in dry dimethoxyethane (1 mL) was added dropwise and stirred at 65 ^oC for further 30 min then cooled to room temperature. The reaction mixture was filtered through a short neutral alumina column and eluted with ether. The resulting

solution was concentrated in vacuo. The residue was purified by flash column chromatography (1:4 ; EtOAc : Hexane) to obtain oxabicyclo compound (128) (72 mg, 71%) as colourless plates : mp 71-72 ^{o}C.

Method 2

(127) **(128)**

A mixture of palladium chloride (1 mg, 0.0056 mmol) and anhydrous cupric chloride (10 mg, 0.074 mmol) in dry dimethoxyethane (2 mL) was stirred and heat at 65 ^{o}C while oxygen was bubbled through the solution. A solution of silyl ether (127) (30 mg, 0.074 mmol) in dry dimethoxyethane (0.5 mL) was added dropwise and the reaction mixture was stirred at 65 ^{o}C for further 30 min then cooled to room temperature. The reaction mixture was filtered through a short neutral alumina column and eluted with ether. The resulting solution was concentrated *in vacuo*. The residue was purified by flash column chromatography (2:8 ; EtOAc : Hexane) to obtain oxabicyclo compound (128) (15 mg, 67%) as colourless plates; mp 71-72 ^{o}C.

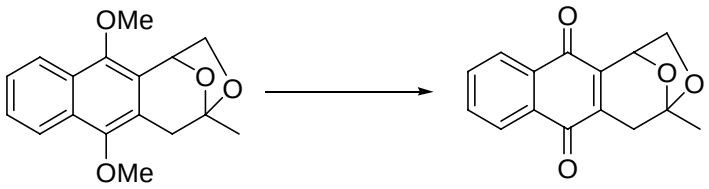
FTIR (KBr), ν_{max} 1600 (C=C), 1594 (C=C) cm^{-1}

^{1}H NMR (acetone-d_6, 400 MHz) δ 8.04-8.13 (m, 2H), 7.58-7.52 (m, 2H) , 5.79 (d, J=4 Hz, 1H), 3.88-4.01 (m, 2H), 3.95 (s, 3H), 3.88 (s, 3H), 3.17 (d, J=20, 1H), 3.04 (d, J=20 Hz, 1H), 1.65 (s, 3H)

^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.2, 146.8, 128.3, 127.3, 127.5, 126.1, 125.8, 122.3, 122.1, 121.9, 106.6, 73.4, 71.7, 62.6, 60.9, 36.3, 24.6

HRMS, Found: [M+Na], 309.1101. Calc. for $C_{17}H_{18}O_4$ + Na : 309.1103

(±)-Isagarin (11)



(128) (11)

To an ice-cold solution of oxabicyclo compound (128) (200 mg, 0.70 mmol) in acetonitrile (2 mL) was added dropwise a solution of CAN (30 mg, 0.051 mmol) in water (0.5 ml). After being stirred at at 0 ^{o}C for 15 min, the reaction mixture was poured into water (5 mL), extracted with EtOAc (3x10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the filtrate concentrated in vacuo. The residue was purified by flash column chromatography (2:8 ; EtOAc : Hexane) to obtain (±)-isagarin (11) (170 mg, 95%) as a yellow crystal ; mp 159-160 ^{0}C (De Kimpe *et al*., 1998, 159-160 ^{o}C). The enantiomeric mixture of (11) (ratio 1;1) was separated by chiral HPLC column (Chiralcel OD column 250 x 4.6 mm, hexane: isopropyl alcohol ; 95:5 as eluent, elution rate 1.0 ml/min).

IR (KBr), ν_{max} 1660 (C=O), 1632 (C=C), 1596 (C=C) cm^{-1}

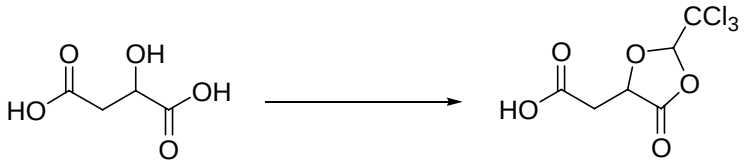
^{1}H NMR ($CDCl_3$, 400 MHz) δ. 8.04-8.13 (m, 2H), 7.70-7.8 (m, 2H), 5.58 (d, J=4 Hz, 1H), 3.93-4.05 (m, 2H), 2.87 (dd, J=1.9, 1.3 Hz, 1H), 2.73 (d, J=19 Hz, 1H), 1.68 (s, 3H)

^{13}C NMR ($CDCl_3$, 100 MHz) δ. 184.1, 182.6, 143.9, 141.7, 133.9, 132.0, 131.6, 133.9, 126.4, 126.3, 106.4, 73.0, 70.2, 36.3, 23.9

HRMS, Found: [M+H^{+}], 257.0818. Calc. for $C_{15}H_{12}O_4 + H^{+}$: 257.0814

Synthesis of Marticin

(5-Oxo-2-trichloromethyl-[1,3]dioxolan-4-yl)-acetic acid (132)



(131) **(132)**

A solution of *dl*-malic acid (131) (1.2 g, 8.9 mmol) in conc. H_2SO_4 (5 ml, 26 mmol) was stirred at 0 °C and treated with chloral (1.6 g, 12 mmol). The reaction mixture was maintained at 0 °C for 2 h and then at room temperature for another 12 h. After addition of ice water (20g), the precipitate was filtered and washed with water and crystallised from hexane-EtOAc to give (5-oxo-2-trichloromethyl-[1,3]dioxolan-4-yl)-acetic acid (132) (1.8 g, 79%) as colourless plates ; mp 175-176 °C (Shih *et al*., 1989, 176-178 °C).

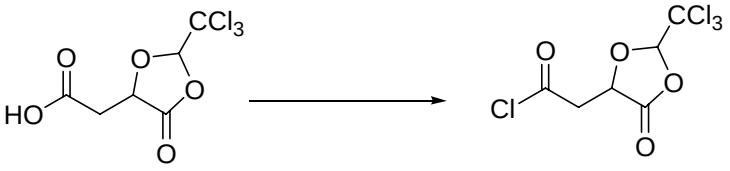
IR (KBr), ν_{max} 2973 (OH), 1873 (C=O), 1828 (C=O) cm^{-1}

^1H NMR ($CDCl_3$, DMSO, 400 MHz) ^1H NMR δ 5.8 (d, J=1.7 Hz , 1H , CH), 4.72 (m, 1H , CH), 2.91 (dd. J=4 Hz ,18 Hz , 1H , CH), 2.82 (dd, J=4 Hz,18 Hz, 1H , CH)

^{13}C NMR (acetone–d_6, 75 MHz) δ 171.7, 171.4, 106.0(CH), 99.4, 72.9, (CH), 36.4

MS m/e (M^++1) 269.2

(5-Oxo-2-trichloromethyl-[1,3]dioxolan-4-yl)-acetyl chloride (133)

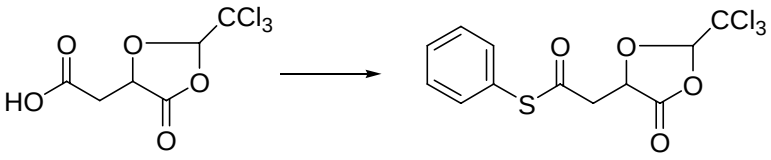


(132) **(133)**

A racemic mixture of protected malic acid (132) (3.4 g, 13 mmol) and thionyl chloride (15 mL, 207 mmol) was refluxed for 50 h. The reaction mixture was concentrated under vacuum to give a pale yellow solid. After washing the solid with dry petroleum ether, the product (133) was obtained as a white solid (3.6 g, 98%); mp 76-77 ^{o}C.

IR (KBr), ν_{max} 1808 (C=O), 1776 (C=O) cm^{-1}

(5-Oxo-2-trichloromethyl-[1,3]dioxolan-4-yl)-thioacetic acid S-phenyl ester (134)



(132) **(134)**

Method 1

A mixture of acid (132) (950 mg, 3.61 mmol), DMAP (530 mg, 4.33 mmol) and DCC (900 mg, 4.33 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature. Thiophenol (0.43 ml, 4.33 mmol) was added dropwise. After being stirred for 6 h, the reaction mixture was poured with water (30 mL) and extracted with CH_2Cl_2 (4x20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash column chromatography

(2:8 ; EtOAc : Hexane) to obtain (5-oxo-2-trichloromethyl-[1,3]dioxolan-4-yl)-thioacetic acid S-phenyl ester (134) (730 mg, 79%) as a colourless needles ; mp 78-80 ^{o}C.

Method 2

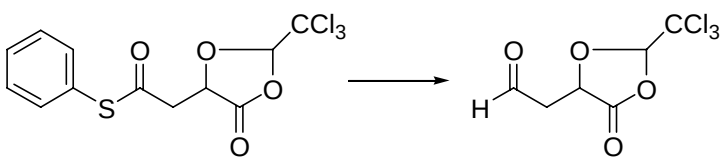
To a stirred solution of acid (132) (950 mg, 3.61 mmol) in benzene (20ml) was added oxalyl chloride (0.8 ml). DMF (2 drops) was added. The reaction mixture was stirred at room temperature for further 1 h and then concentrated under vacuo. The residue was dissolved in CH_2Cl_2 (20 mL). Thiophenol (0.43 ml, 4.33 mmol) and pyridine (0.2 mL) were added. The reaction mixture was stirred for futher 5 h. Then, water (30 mL) was added and extracted with CH_2Cl_2 (4x20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash column chromatography to obtain (5-oxo-2-trichloromethyl-[1,3]dioxolan-4-yl)-thioacetic acid S-phenyl ester (134) a coulourless needles ; mp 78-80 ^{o}C (780 mg, 85%).

IR KBr 1737 (C=O) ν_{max} 1699, 1673 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.19 (s, 5H), 5.78 (2s, 1H), 4.80-4.47 (m, 1H), 3.35 (dd, 1 H, J= 4.2, 17.8 Hz), 3.25 (dd, 1 H, J= 4.2, 17.8 Hz)

MS m/e (M^{+}+) 356, 281 (33), 207 (61), 110 (100)

(5-Oxo-2-trichloromethyl-[1,3]dioxolan-4-yl)-acetaldehyde (135)



(134) **(135)**

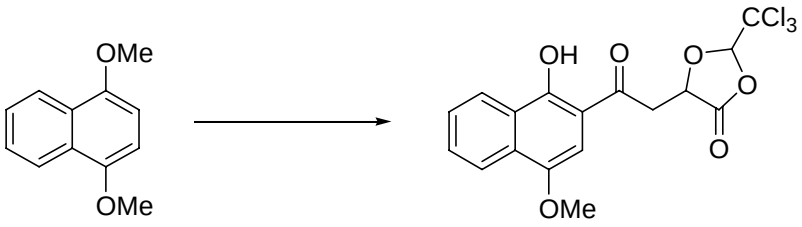
A mixture of thioester (134) (500 mg, 1.4 mmol) and 5% Pd/C (20 mol%, 90 mg) in CH_2Cl_2 (15 mL) was stirred at room temperature. Triethyl silane (4.2 mmol, 0.7 mL) was added dropwise. After stirring for 45 min, the reaction mixture was filtered through a short siliga gel column and eluted with ether. The resulting solution was concentrated in vacuo. The residue was purified by flash column chromatography (2:8 ; EtOAc : Hexane) to obtain (5-oxo-2-trichloromethyl-[1,3]dioxolan-4-yl)-acetaldehyde (135) (410 mg, 85%) as a coulourless needles; mp 91-93 ^oC.

IR (KBr), ν_{max} 1737 (C=O), 1699 (C=O), 1673 cm^{-1}

^1H NMR ($CDCl_3$, 400 MHz) δ 9.67 (s, 1H), 5.85 (2s, 1H), 4.81-4.79 (m, 1H), 3.25 (dd, 1 H, J= 4.2, 17.7 Hz), 3.05 (dd, 1 H, J= 4.2, 17.7 Hz)

MS m/e (M^++1) 247.6

5-[2-(1-Hydroxy-4-methoxy-naphthalene-2-yl)-2-oxo-ethyl]-2-trichloromethyl-[1,3]dioxolan-4-one (137)



(111) **(137)**

A mixture of 1,4-dimethoxynaphthalene (111) (500 mg, 27 mmol) and acid chloride (56) (2.3 g, 8.1 mmol) in dry CH_2Cl_2 (15 mL) was stirred at 0 °C under N_2 atmosphere. The solution of $AlCl_3$ (710 g, 50.4 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise during 10 min. The reaction mixture was stirred at 0 °C for 12 h. and cool water (30 mL) was added dropwise. The reaction was extracted with CH_2Cl_2 (3x30 mL). The combined organic layers were washed with water (2x40 mL), dried

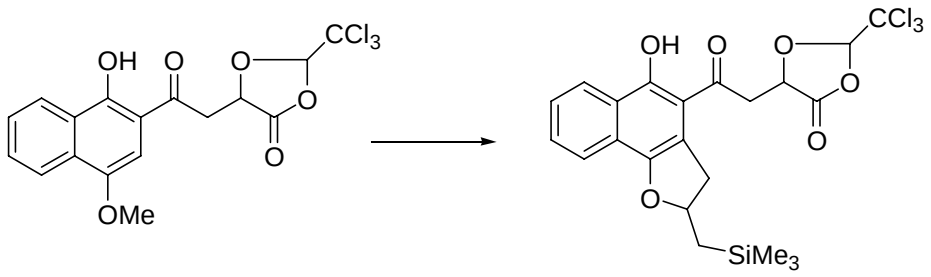
over anhydrous $MgSO_4$ and filtered. The resulting solution was concentrated under reduced pressure to give solid residue. The residue was purified by flash column chromatography (20:80 ; CH_2Cl_2 : Hexane) to yield 5-[2-(1-hydroxy-4-methoxy-naphthalene-2-yl)-2-oxo-ethyl]-2-trichloromethyl-[1,3]dioxolan-4-one (137) as a yellow plates (487 mg, 43%); mp 184-186 ^{0}C.

IR (KBr), ν_{max} 1814 (C=O), 1625 (C=O), 1599, (C=C) cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz) δ 13.05 (s, 1H), 8.39(d, J=8.3 Hz, 1H), 8.13(d, J=8.3 Hz, 1H), 7.63(m, 1H), 7.54(m, 1H), 6.63 (s, 1H) 5.96 (d, J= 1.7 Hz,1H), 4.97 (m, 1H), 3.92 (s, 1H), 3.88 (d, J=4, 1H), 3.83 (d, J=4, 1H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 199.0 (C=O), 170.9 (C=O), 158.2 (C-O), 147.9 (C-O), 130.4 (CHarom), 127.0 (CHarom), 125.8 (CHarom), 124.6 (CHarom), 122.0 (CHarom), 111.0, 105.2, 98.8, 97.8, 70.8, 55.7, 39.6

5-[2-(5-Hydroxy-2-trimethylsilanylmethyl-2,3-dihydro-naphtho[1,2-b]furan-4-yl)-2-oxo-ethyl]-2-trichloromethyl-[1,3]dioxolan-4-one (139).



(137) **(139)**

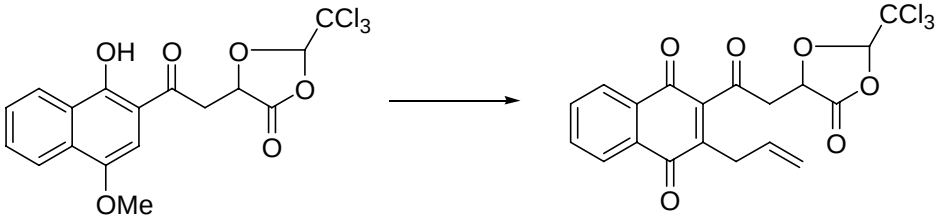
To an ice-cold solution of naphthol (137) (100 mg, 0.24 mmol) in acetonitrile (5 mL) was added dropwise a solution of CAN (390 mg, 0.71 mmol) in water (1.5 mL). The reaction mixture was stirred at 0 ^{o}C for 15 min, added water (10 mL) and extracted with EtOAc (3x15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give oil residue. The residue was dissolved with dry CH_2Cl_2 (3 mL) and $SnCl_4$ (0.03 mL, 0.24

mmol) was added dropwise followed by the addition of allyltrimethylsilane (0.06 mL, 0.72 mmol). After being stirred at –78 ^{o}C for 5 h. under N_2 atmosphere, the reaction mixture was poured into water (10 mL), extracted with CH_2Cl_2 (3x10 mL). The combined organic layers were over anhydrous $MgSO_4$, filtered and the filtrate concentrated under reduce pressure to obtain brown oily residue. The residue was purified by flash column chromatography(1:9 ; EtOAc : Hexane) to afford 5-[2-(5-hydroxy-2-trimethylsilanylmethyl-2,3-dihydro-naphtho[1,2-b]furan-4-yl)-2-oxo-ethyl]-2-trichloromethyl-[1,3]dioxolan-4-one (139) as a diastereomeric mixture (71 mg, 56%); mp 51-53 ^{0}C.

IR (KBr), ν_{max} 2922, 1824 (C=O) 1716 , 1670 , 1649 cm^{-1}

^{1}H NMR ($CDCl_3$) δ 13.57 (s, 1H), 8.45 (d, J=8.4 Hz, 1H), 7.88 (d, J=6.3 Hz, 1H), 7.67 (t, J=7.6 Hz 1H), 7.54 (t, J=7.6 Hz, 1H), 7.28 (s, 1H), 6.05 (s, 1H), 5.96 (d, J= 1.7 Hz, 1H), 5.14 (m, 1H), 5.01 (s), 4.97 (s, 1H), 3.62 (m, 2H), 3.25 (m 1H), 1.59 (s,1H), 1.41 (m, 1H), 0.19 (s, 9H)

2-Allyl-3-[2-(5-oxo-2-trichloromethyl-[1,3]dioxolan-4-yl)-acetyl]-[1,4]naphtho quinone (140)



(137) (140)

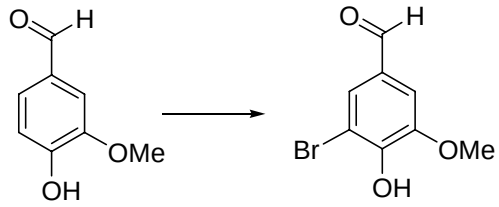
To an ice-cold solution of naphthol (137) (100 mg, 0.24 mmol) in acetonitrile (5 ml) was added dropwise a solution of CAN (390 mg, 0.71 mmol) in water (1.5 ml). After stirring at 0 ^{o}C for 15 min, the reaction mixture was poured with water (10 ml) and extracted with EtOAc (3x15 ml). The combined organic extracts were dried over anhydrous $MgSO_4$, filterd and concentrated under reduced pressure to give a oil residue. The solution of residue in acetonitrile (50 mL) was stirred at room

temperature. Silver nitrate (50 mg, 0.5 mmol) and vinylacetic acid (270 mg, 3.15 mmol) were added. Then a solution of ammonium persulfate (860 mg, 3.78 mmol) in water (25 mL) in was added dropwise over 15 min. After being stirred at 60-70 ^{o}C for 8 h, the reaction mixture was poured into cold water (25 mL) and extracted with ethyl acetate (4x50 mL). The combined organic layers were washed with 10% aq. $NaHCO_3$ (2x50 mL), dried over anhydrous Mg_2SO_4 and filtered. The organic extract was concentrated in vacuo. The residue was purified by flash column chromatography (2:8 ; EtOAc:Hexane) to obtain 2-allyl-3-[2-(5-oxo-2-trichloromethyl-[1,3]dioxolan-4-yl)-acetyl]-[1,4]naphtho quinone (140) (65 mg, 55 %) as a yellow plates; mp 73-75 ^{0}C.

FTIR (KBr), ν_{max} 1825 (C=O), 1740 (C=O), 1730 (C=O), 1615 (C=C) cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.15 (m, 2H), 7.92 (m, 2H), 6.21 (s, 1H), 5.83 (m, 1H), 5.25-5.12 (m, 2H), 3.88 (dd, J=4, 10 Hz, 1H), 3.52 (dd, J=4, 10 Hz, 1H), 3.25 (m, 2H)

3-Bromo-4-hydroxy-5-methoxy-benzaldehyde (142)



(141) **(142)**

To an ice-cold stirred solution of vanillin (141) (1.5 g, 10 mmol) in acetic acid (3 mL) was added rapidly a solution of Br_2 (0.5 mL, 10 mmol) in acetic acid (2 ml) with stirring for 30 min. After addition of water (20 mL), the appearing precipitate was filtered and washed with water (3x20 mL). The precipitate was purified by quick column chromatography to yield 3-bromo-4-hydroxy-5-methoxy-benzaldehyde (142) (2.18 g, 95%) as a colourless plates; mp 163-164 ^{o}C. (Henry *et al*., 1930, 166-169 ^{o}C).

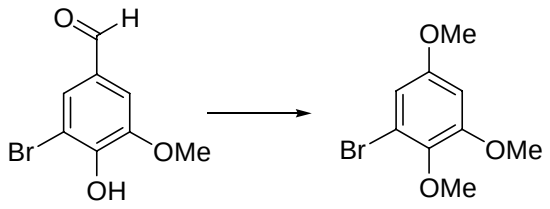
FTIR (KBr), ν_{max} 3291 (O-H) , 1683 (C=O), 1577 (C=C) cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.22 (s, 1H), 7.09 (d, J=1.6 Hz, 1H), 6.80 (d, J=1.6 Hz, 1H), 3.14 (s, 3H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 189.4, 149.3, 148.1, 130.2, 127.9, 114.7, 108.1, 57.2

MS m/e (M^{+}+) 230.8 (M+), 229.0 (M+1)

1-Bromo-2,3,5-trimethoxy-benzene (143)



(142) **(143)**

To a solution of bromovanillin (142) (1g, 4 mmol) in 1N NaOH (10 mL) was added 5% H_2O_2 (20 mL). After being stirred at room temperature for 20 min, the reaction mixture was acidified with 10% HCl and extracted with diethyl ether (3x30 mL). The combined organic layers were dry over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to give residue as brown solid. Then the residue was dissolved in dry acetone. K_2CO_3 (1.5g, 10.8 mmol) and dimethyl sulfate (1.3 ml, 13.6 mmol) were added. The reaction mixture was refluxed for 2 h. After cooling to room temperature, the reaction mixture was filterd and the resulting solution was concentrated under reduce pressure to obtain a black oil residue. The oil residue was purified by flash column chromatography (2:8 ; EtOAc : Hexane) to provide 1-bromo-2,3,5-trimethoxy-benzene (143) as colorless oil (794 mg, 81 %) (Crowther, 1984).

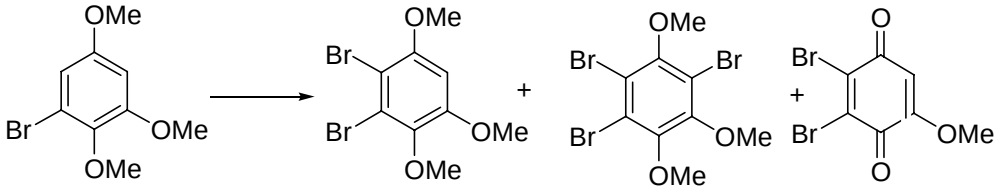
FTIR (KBr), ν_{max} 1570 (C=C) 1577 (C=C) cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.72 (s, 1H), 6.51 (s, 1H), 3.89 (s, 3H), 3.85(s, 3H), 3.74 (s, 3H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.3, 154.1, 140.8, 118.1, 108.0, 100.1, 60.6, 56.1, 55.9

MS m/e (M^{+}+) 246.1, 249.3, 248.1

2,3-Dibromo-1,4,5-trimethoxy-benzene (144)



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

To a stirred solution of trimethoxybromobenzene (143) (1 g, 4 mmol) in benzene (3 mL) was added bromine (0.25 mL). After stirring at room temperature for 30 min, the reaction mixture was and was poured with 10% aq. Na_2CO_3 (10 mL). Benzene layer was separated, dried over anhydrous K_2CO_3 and filtered. The filtrate was concentrated under reduce pressure. The residue was purified by flash column chromatography (15:85 ; CH_2Cl_2 : Hexane) to give (144) as a colourless plates (1.05 g, 81%) ; mp 96-98 ^{0}C (Crowther, 1984, 97-99 ^{o}C), (148) as a colourless plates (96 mg, 6%) ; mp 91-92 ^{0}C and (149) as yellow oil (58 mg, 5%).

2,3-Dibromo-1,4,5-trimethoxy-benzene (144)

FTIR (KBr), ν_{max} 2943 (C=O), 1634 (C=C) cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.51 (s, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.77 (s, 3H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.8, 153.1, 141.9, 122.1, 105,2, 97.3, 61.1, 57.2, 56.9

MS m/e (M^++) 318.3, 320.3

1,2,4-Tribromo-3,5,6-thimethoxy-benzene (148)

FTIR (KBr), ν_{max} 2974 (C-H), 2940 (C-H), 1561 (C=C) cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.90 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.1, 152.4, 149.3, 121.1, 112.5, 114.0, 61.3(2xC), 61.0

MS m/e (M^++) 401.2(M+)

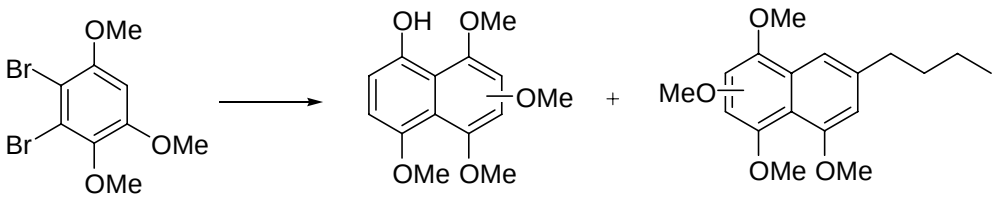
2,3 Dibromo-5-methoxy-[1,4]benzoquinone (149)

FTIR (neat), ν_{max} 1686 (C=O) , 1641 (C=C) cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.80 (s, 1H), 3.88 (s, 3H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.1, 172.5, 158.6, 141.1, 136.5, 106.9, 57.0

Regiomeric naphthol (145)



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

2,3-Dibromo-1,4,5-trimethoxybenzene (144) (150 mg, 0.46 mmol) and 2-methoxyfuran (0.06 mL, 0.5 mmol) were stirred in dry tetrahydrofuran (2 mL) at –78 ^{o}C under nitrogen. *n*-butyl lithium (0.05 mL, 0.41 mmol) was added dropwise at the same temperature during 10 min. The reaction mixture was allowed to warm to room temperature following the addition of water (10 mL) and extracted with ether (3x15 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduce pressure. The residue was purified by flash column chromatography (4:6 ; EtOAc : Hexane) to give regioisomeric naphthols (145) as a light brown oil (53 mg, 43%) and byproduct (146) as a light brown oil (37 mg, 27%) (Giles *et al*., 1988).

Regiomeric naphthol (145)

FTIR (neat), ν_{max} 3290 (0H), 1652 (C=C) cm^{-1}

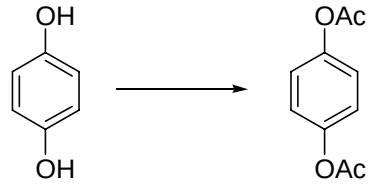
^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.63 (s, OH), 6.71 (m, 3H), 3.99 (s, 3H), 3.98 (s, 3H), 3.94 (s, 3H), 3.86 (s, 3H)

Byproduct (146)

FTIR (neat), ν_{max} 1661 (C=C), 1630 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.58 (d, J=2 Hz, 1H), 6.73 (d, J=2 Hz, 1H), 6.64 (s, 1H), 3.98 (s, 6H), 3.96 (s, 3H), 3.84 (s, 3H), 2.71 (t, J=7.7 Hz, 2H), 1.6-1.8 (m, 2H) 1.3-1.5 (m, 2H) and 0.95 (m,3H)

1, 4-Diactoxyphenylester (155)



(154) **(155)**

To a stirred solution of 1,4-dihydrobenzoquinone (10 g, 91 mmol) in acetic anhydride (20 ml) was added dropwise H_2SO_4 (1 drop) at room temperature. Then the reaction mixture was stirred for 30 min. After adding of cold water, the appearing precipitate was filtered and dried to give 1, 4-diactoxyphenylester (155) as a colourless needles (17 g, 100%); mp 121-122 ^oC (Prichard, 1955, 121-122 ^oC).

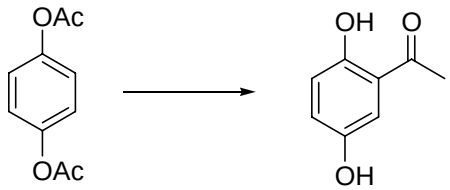
FTIR (KBr), ν_{max} 1740 (C=O), 1615 (C=C) cm^{-1}

^1H NMR ($CDCl_3$, 400 MHz) δ 7.0 (s, 4H), 2.22 (s, 6H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.1, 150.0, 121.5, 17.2

MS (CI), m/z 195.2 (M+1)

2,5-Dihydroxyacetophenone (156)



(155) **(156)**

A mixture of dry hydroquinone diacetate (155) (5 g, 0.026 mole) and anhydrous aluminum chloride (0.087 mol, 11.6 g) is finely powdered in a mortar and introduced into a dry 50-mL round-bottom flask fitted with an air condenser

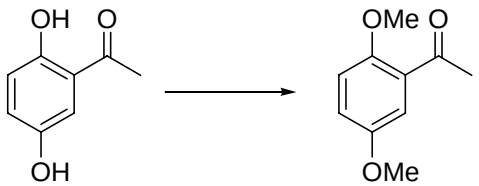
protected by a calcium chloride tube and connected to a gas-absorption trap. The flask was placed in an oil bath which was heated slowly from room temperature so that at the end of about 30 minutes the temperature of the oil reaches 110–120°C, at which point the evolution of hydrogen chloride begins. The temperature was then raised slowly to 160–165°C and maintained at that point for about 3 h; at the end of about 2 h the evolution of hydrogen chloride becomes very slow and the mass assumes a green color and becomes pasty in consistency. The reaction flask was removed from the oil bath and allowed to cool to room temperature. The excess aluminum chloride was decomposed by treating the reaction mixture with crushed ice (35 g) followed by concentrated hydrochloric acid (2.5 mL). The solid obtained was collected on a Büchner funnel and washed with two 10-mL portions of cold water. The crude product was purified by flash column chromatography (1:4 ; EtOAc: Hexane) to give 2,5-dihydroxyacetophenone (156) as a yellow needles (3.9 g, 71%) ; mp 201–202 ^{o}C (Amin and Shah, 1955, 201–202 ^{o}C).

FTIR (KBr), ν_{max} 3420 (OH), 1690 (C=O)cm^{-1}

^{1}H NMR ($CDCl_3$+DMSO-d6, 400 MHz) δ 11.63 (s, 1H), 7.12 (d, J= 3Hz, 1H), 7.00 (dd, J=3, 9Hz, 1H), 6.75 (d, J=9 Hz, 1H), 2.5 (s, 3H)

MS (CI), m/z 153.1 (M+1)

2,5-Dimethoxyacetophenone (157)



(156) **(157)**

Method 1

A mixture of 2,5-dihydroxyacetophenone (156) (5g, 31.25 mmol), dimethyl sulfate (7.4 ml, 78.11 mmol) and anhydrous K_2CO_3 (12.7g, 92.02 mmol) in dry acetone (100 ml) was refluxed for 5 h. The reaction mixture was concentrated under

reduced pressure. The residue was purified by quick column chromatography (hexane:CH_2Cl_2) to obtain 2,5 dimethoxyacetophenone (157) as a yellow oil (4.32 g, 72 %).

Method 2

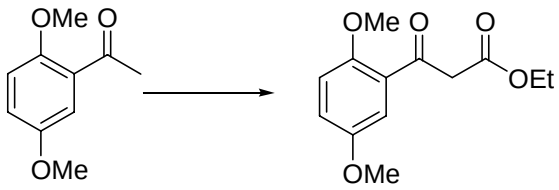
To a mixture of 2,5-dihydroxyacetophenone (156) (50 mg, 0.33 mmol) and tetrabutylammonium iodide (50 mg, 0.13 mmol) in THF (20 ml) was added a solution of 20% aq. KOH (30 mg, 0.43 mmol). After stirring for 5 min, dimethyl sulfate (0.5 mL, 0.1 mmol) was added. The reaction mixture was stirred for 10 h. Then the reaction mixture was extracted with ether (4x50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced presure. The residue was purified by flash column chromatography (2:3 ; EtOAc : Hexane) to obtain 2,5 dimethoxy acetophenone (157) as a yellow oil (71 %, 35 mg) (Amin and Shah, 1955).

FTIR (neat), ν_{max} 1674 (C=O), 1606 (C=C) cm^{-1}

^1H NMR ($CDCl_3$, 400 MHz) δ 7.31 (1H, d, J= 3.2 Hz), 7.12 (1H, dd, J= 7.6, 3.2 Hz), 6.91 (1H, d, J= 3.2 Hz), 3.85 (3H, s), 3.79 (3H, s), 2.4 (s, 3H)

MS (CI), m/z 181.2 (M+1)

Ethyl 3-(2,5-dimethoxyphenyl)-3-oxopropanoate (157)



(157) **(158)**

Sodium hydride (2.25 g, 93.5 mmol) was suspended in benzene (100 mL) under a N_2 atmosphere after being washed with ether. A solution of 2,5 dimethoxy acetophenone (157) (7.8 g, 42.6 mmol) and diethylcarbonate (9.75 ml) in benzene (20 mL) was added. The reaction mixture was refluxed at 80 ^oC for 4 h. After cooling

to room temperature, water (50 mL) was added dropwise. The reaction mixture was extracted with ether (5x50 mL), dried over anhydrous Na_2SO_4, filtered and the filtrate concentrated under reduced pressure. The residue was purified by flash column chromatography (2:8; EtOAc:Hexane) to give ethyl 3-(2,5-dimethoxyphenyl)-3-oxopropanoate (158) as a yellow oil (8.27 g, 77 %) (McPherson *et al*., 1976).

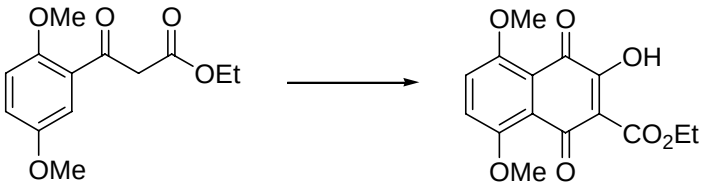
FTIR (neat), ν_{max} 3453 (OH), 1738 (C=O), 1672 (C=O) cm^{-1}

^1H NMR ($CDCl_3$, 400 MHz) δ 12.72 (s, OH), 7.23 (1H, d, J= 3.2 Hz), 7.07 (1H, dd, J= 7.6, 3.2 Hz), 6.91 (1H, d, J= 3.2 Hz), 4.19 (2H, q, J=6.8 Hz), 3.9 (2H, s), 3.86 (3H, s), 3.80 (3H, s), 1.24 (3H, t, J= 6.8 Hz)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 192.5, 168.0, 153.6, 153.4, 126.2, 121.5, 111.8, 112.5, 113.8, 112.9, 60.7, 55.6, 50.3, 13.9

MS (CI), m/z 253.3 (M+1)

2-Ethoxycarbonyl-3-hydroxy-5,8-dimethoxynaphthalene-1,4-dione (159)



(158) **(159)**

A mixture of keto ester (158) (2.5g, 0.01 mol) and aluminum chloride (4 g, 0.03 mol) was dissolved in dry nitromethane (60 mL) under nitrogen. After stirring for 15 min , a solution of oxalyl chloride (0.82 mL, 0.01 mol) in dry nitromethane (40 mL) was added dropwise. The reaction mixture was heated to 80 ^oC for 3 h. After cooling to room temperature, The reaction mixture was poured into 10% aqueous oxalic acid (30 mL), extracted with ether (3x70 mL). The combined extracts were washed with 10% aq. Na_2CO_3 (2x70 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrated was concentrated under reduced pressure. The residue was

purified by flash column chromatography (60:30:5 ; EtOAc : CH_2Cl_2 : AcOH) to give 2-ethoxycarbonyl-3-hydroxy-5,8-dimethoxynaphthalene-1,4-dione (159) as a red needles (2 g, 67%); mp 112- 113 ^oC (Sartori *et al*., 1993, 112-113 ^oC).

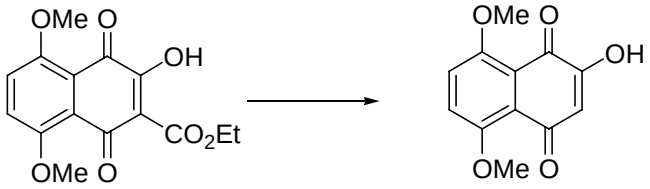
FTIR (KBr), ν_{max} 3430 (OH), 1735 (C=O), 1684 (C=O) cm^{-1}

^1H NMR ($CDCl_3$, 400 MHz) δ 7.41 (1H, d, J=9.6 Hz), 7.26 (1H, d, J=9.6 Hz), 4.46 (2H, q, J=7.1 Hz), 3.98 (3H, s, OMe), 3.95 (3H, s, OMe), 1.42 (3H, t, J=7.1 Hz)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 186.2, 180.1, 179.3, 176.2, 156.8, 155.4, 154.1, 153.7, 122.7, 121.5, 63.4, 57,3, 56.7, 14.1

MS (CI), m/z 278.9 (M+)

2-Hydroxy-5,8-dimethoxynaphthalene-1,4-dione (160)



(159) **(160)**

A solution of 2-ethoxycarbonyl-3-hydroxy-5,8-dimethoxynaphthalene-1,4-dione (160) (1.3 g, 0.005 mol) in 5% aqueous NaOH (50 mL) was stirred at 60 ^oC for 8 h. Then a solution of 10% aqueous HCl (50 mL) was added and heating was continued for further 30 min. After cooling to room temperature, the mixture was extracted with ether (4x50 mL), dried over anhydrous Na_2SO_4, filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with (50:40:5; EtOAc: CH_2Cl_2: AcOH) to give 2-hydroxy-5,8-dimethoxynaphthalene-1,4-dione (160) as a red needles (850 mg, 73%); mp 98-100 ^oC (Sartori *et al*., 1993, 102-104 ^oC).

FTIR (KBr), ν_{max} 3405 (OH), 1665 (C=O) cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (1H, d, J=9.0 Hz), 7.26 (1H, d, J=9.0 Hz), 6.22 (1H, s), 4.00 (3H, s, OMe), 3.96 (3H, s, OMe)

MS (CI), m/z 235.1 (M+1)

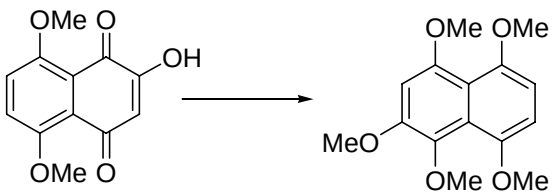
1,2,4,5,8-Pentamethoxynaphthalene (147)

Method 1

(145) **(147)**

A mixture of regiomeric naphthol (145) (100 mg, 0.43 mmol) and tetrabutylammonium bromide (200 mg, 0.83 mmol), 20% aq. KOH (30 mg, 0.43 mmol) in THF (10 mL) was stirred at room temperature. Dimethyl sulfate (0.5 mL, 0.1 mmol) was added. The mixture stirred for 8 h, the reaction mixture was extracted with ether (2x50 mL), dried over anhydrous Na_2SO_4, filtered and the filtrate concentrated under reduced pressure. The residue was purified by flash column chromatography (2:3 ; EtOAc : Hexane) to obtain 1,2,4,5,8-pentamethoxynaphthalene (147) as a yellow needles (70 %, 75 mg) ; mp 101-102 ^oC (Giles *et al*., 1988, 102-103 ^oC) .

Method 2



(160) **(147)**

A mixture of 2-hydroxy-5,8-dimethoxynaphthalene-1,4-dione (160) (10 mg, 0.043 mmol) and tetrabutylammonium bromide (20 mg, 0.083 mmol) in THF (1 mL) was stirred at room temperature. Then 10% aq. $Na_2S_2O_4$ (100 mg, 0.43 mmol) was added. After being stirred for 15 min, 20% aq. KOH (30 mg, 0.43 mmol) was added followed by the addition of dimethyl sulfate (0.5 mL, 0.1 mmol). The reaction mixture was stirred for further10 h. Then the mixture was extracted with ether (2x50 mL), dried over anhydrous Na_2SO_4, filtered and the filtrate concentrated under reduced pressure. The residue was purified by flash column chromatography (2:3 ; EtOAc : Hexane) to obtain 1,2,4,5,8-pentamethoxynaphthalene (147) as a yellow needles (71 %, 7 mg); mp 101-102 ^oC (Giles *et al*., 1988, 102-103 ^oC).

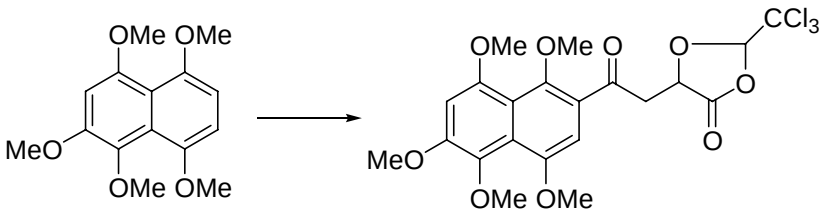
FTIR (KBr), ν_{max} 1601 (C=C) cm^{-1}

^1H NMR ($CDCl_3$, 400 MHz) δ 6.72 (1H, d, J= 8.5 Hz), 6.67 (1H, s), 6.58 (1H, d, J= 8.5 Hz), 3.91(3H, s), 3.87(3H, s), 3.84 (3H, s), 3.82, (3H, s), 3.75, (3H, s)

^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.9, 151.5, 150.1, 149.9, 138.1, 124.2, 115.5, 108.9, 105.2, 99.2, 61.9, 57.8, 57.6, 57.4, 57.3

MS (CI), m/z 279.2 (M+1)

5-[2-Oxo-2-(1,4,5,6,8-pentamethoxy-naphthalen-2-yl)-ethyl]-2-trichloromethyl-[1,3] dioxolan-4-one (161)



(147) **(161)**

A mixture of 1,2,4,5,8-pentamethoxy-naphthalene (147) (60 mg, 1.2 mmol) and acid (132) (1.3 g, 5 mmol) in CH_2Cl_2 (5 mL) was stirred at 0 ^oC under N_2

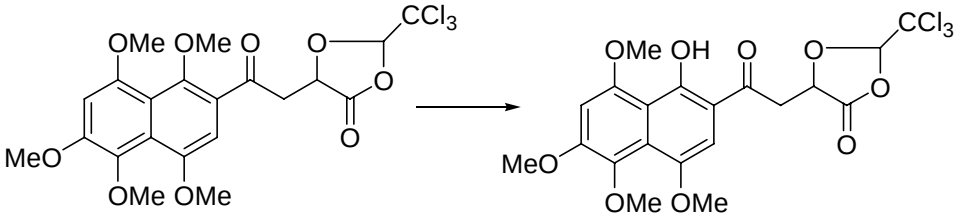
atmosphere. Then, TFAA (0.7 ml, 5 mmol) was added dropwise. The reaction mixture was stirred for further 3 h, then poured into cold water and extracted with CH_2Cl_2 (4x20 mL). The combined organic layers were dried over anh. Na_2SO_4, filtered and the filtrate concentrated in vacuo. The residue was purified by flash column chromatography (3 : ; Hexane : EtOAc) to obtain 5-[2-oxo-2-(1,4,5,6,8-pentamethoxy-naphthalen-2-yl)-ethyl]-2-trichloro methyl-[1,3] dioxolan-4-one (161) as a yellow plates (360 mg, 55%); mp 121-124 ^oC.

IR (KBr) 1810 ν_{max} (C=O) 1680, 1611 cm^{-1}

^1H NMR ($CDCl_3$, 400 MHz) δ 7.10 (s, 1H), 6.48 (s, 1H), 5.83 (s,1H), 4.79 (m, 1H) 3.88 (s,3H), 3.87 (s, 3H), 3.85 (s, 3H), 3.82 (s, 3H), 3.69 (s, 3H), 2.98 (dd, J=4.3 Hz, 18 Hz, 1H), 2.89 (dd, J=4.3 Hz, 18 Hz, 1H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 199.7, 185.3, 153.9, 152.5, 151.5, 137.8, 126.0, 116.2, 105.3, 97.6, 63.3, 61.5, 56.6, 56.6, 56.4, 56.3

5-[2-(1-Hydroxy-4,5,6,8-tetramethoxy-naphthalen-2-yl)-2-oxo-ethyl]-2-trichloro methyl-[1,3]dioxolan-4-one (163)



(161) **(163)**

To a solution of naphthalene (161) (150 mg, 0.29 mmol) in dry CH_2Cl_2 (5 mL) at –78 ^oC under N_2 was added dropwise a solution of BBr_3 in CH_2Cl_2 (1 N, 0.4 ml, 6.6 mmol). After being stirred for 10 min at same temperature, the reaction mixture was quenched with aqueous 10% NH_4Cl (10 mL) and extracted with CH_2Cl_2 (4x30 mL). The combined organic layers were washed with water (2x20 mL), dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by flash column

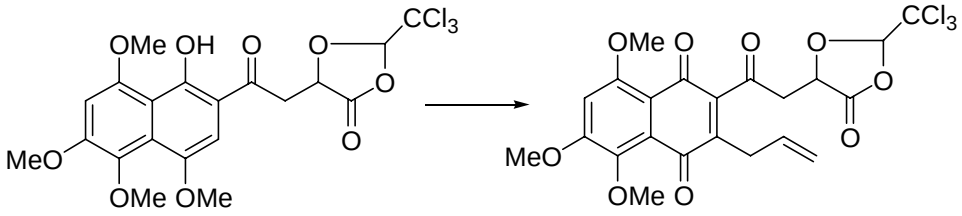
chromatography (3 : 2; Hexane : EtOAC) to give 5-[2-(1-hydroxy-4,5,6,8-tetramethoxy-naphthalen-2-yl)-2-oxo-ethyl]-2-trichloro methyl-[1,3]dioxolan-4-one (163) as a brown plates (105 mg, 71%); mp 72-74 ^{0}C.

IR (KBr) 3360 (OH), 2965, 1820 (C=O) cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz) δ 13.01 (s, 1H), 7.24 (s, 1H), 6.41 (s, 1H), 6.23(s, 1H), 4.97 (m, 1H), 3.92 (s, 1H), 3.80 (s, 3H), 3.74 (s, 3H), 3.70 (s, 3H), 3.52 (dd, J=4 Hz, 18 Hz, 1H), 3.21 (dd, J=4 Hz, 18 Hz, 1H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 198.2, 185.2, 153.5, 151.2, 151.5, 137.8, 124.1, 116.5, 105.2, 97.4, 60.1, 61.5, 56.2, 56.4, 56.4, 56.4

3-Allyl-5,6,8-trimethoxy-2-[2-(5-oxo-2-trichloromethyl-[1,3]dioxolan-4-yl)-acetyl]-[1,4]naphthoquinone (166)



(163) **(166)**

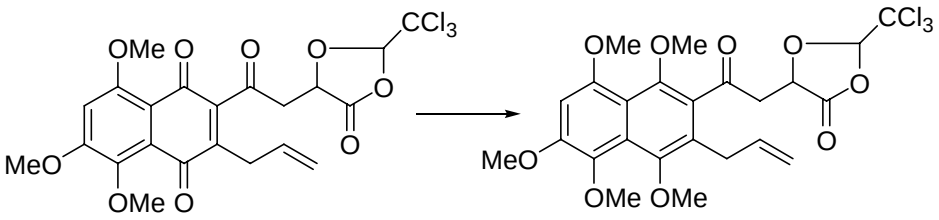
To a stirred ice-cold solution of naphthol (163) (105 mg, 0.24 mmol) in acetonitrile (5 mL) was added dropwise a solution of CAN (390 mg, 0.71 mmol) in water (1.5 mL and stirring was continued for 15 min at 0 ^{o}C, when water (10 mL) was added. The reaction mixture was extracted with EtOAc (3x15 mL), the combined organic layers were dried over anhydrous Mg_2SO_4, filtered and the filtrate concentrated under reduced pressure to give oil residue. The residue was dissolved with acetonitrile (30 ml). Then silver nitrate (45 mg, 0.48 mmol), and vinylacetic acid (135 mg, 1.5 mmol) was added. After 10 min, a solution of ammonium persulfate (430 mg, 1.6 mmol) in water (20 mL) was added dropwise. The reaction mixture was stirred at 60-70 ^{o}C for 8 h. Then, the reaction mixture was poured into cold water (20

mL) and extracted with ethyl acetate (4x 50 mL). The combined organic layers were washed with 10% a solution sodium hydrogen carbonate (2x50 mL), dried over anhydrous $MgSO_4$ and filtered. The organic extract was concentrated in vacuo. The residue was purified by flash column chromatography (95 : 5; Hexane : EtOAC) to obtain 3-allyl-5,6,8-trimethoxy-2-[2-(5-oxo-2-trichloromethyl-[1,3]dioxolan-4-yl)-acetyl]-[1,4]naphthoquinone (166) as a brown needles (61 mg, 50%); mp 81-83 ^{0}C.

IR (neat), ν_{max} 1799, 1675, 1595, 1471 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.24 (s, 1H), 5.92(s, 1H), 5.76 (ddt, J=17, 10.4, 6.7 Hz, 1H) 5.05-5.07 (m, 2H), 4.89 (m, 1H), 3.81 (s, 3H), 3.72 (s, 3H), 3.67 (s, 3H), 3.52 (dd, J=4, 19 Hz, 1H) 3.32 (dd, J=4, 19 Hz, 1H), 3.21 (m, 2H)

5-[2-(3-Allyl-1,4,5,6,8-pentamethoxy-naphthalen-2-yl)-2-oxo-ethyl]-2-trichloro methyl-[1,3]dioxolan-4-one (167)



(166) **(167)**

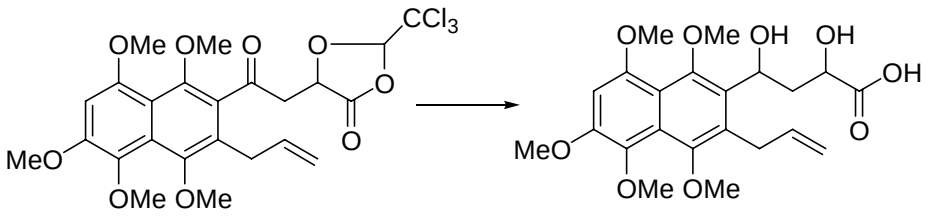
To a stirred solution of quinone (156) (10 mg, 0.019 mmol) in THF (1 ml) was added tetrabutylammonium iodide (20 mg, 0.083 mmol) and a solution of sodium dithionite (100 mg, 0.43 mmol) in water (0.5 mL). After being stirred for15 min at room temperature, K_2CO_3 (60 mg, 0.43 mmol) and dimethyl sulfate (0.5ml, 0.1 mmol) were added. The reaction mixture was stirred overnight. Then the reaction mixture was extracted with ether (4x20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the filtrate concentrated under reduced pressure. The residue was purified by flash column chromatography (6 : 4; Hexane : EtOAC) to give 5-[2-(3-allyl-1,4,5,6,8-pentamethoxy-naphthalen-2-yl)-2-oxo-ethyl]-2-

trichloro methyl-[1,3]dioxolan-4-one (167) as a yellow plates (6 mg, 55 %); mp 103-104 ^{0}C.

IR (KBr) ν_{max} 1812 (C=O) 1680, 1611 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.76 (s, 1H), 6.23(m, 1H), 5.81 (s, 1H), 5.14-5.28 (m, 2H), 4.81 (m, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.87(s, 3H), 3.75 (s, 3H), 3.72(s, 3H), 3.32 (m, 2H), 2.87 (dd, J=4, 18 Hz, 1H) 2.64 (dd, J=4, 18 Hz, 1H)

4-(3-Allyl-1,4,5,6,8-pentamethoxy-naphthalen-2-yl)-2,4-dihydroxy-butyric acid(169)



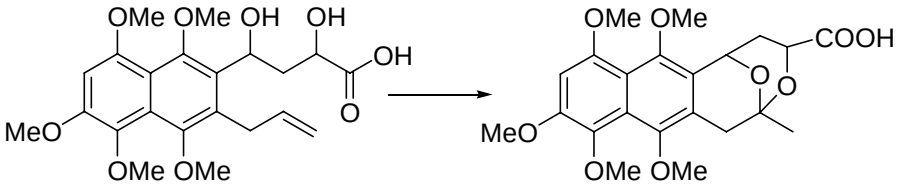
(167) **(169)**

To a stirred solution of naphthalene (157) (100 mg, 0.18 mmol) in EtOH (3 mL) was added a solution of $NaBH_4$ (17 mg, 4.5 mmol) in EtOH (0.25 mL). Stirring was at room temperature for 30 min. Then acetone (1 mL) was added. The reaction mixture was concentrated under reduced pressure. The residue was purified by short column chromatrography to give yellow oil. The oil was dissolved in ethanol (2 mL). A solution of 10% aq.NaOH (1 ml) was added. After being stirred overnight, the reaction mixture was acidified with 20% aq.HCl and extracted with ether (5x20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (1: 3; EtOH : EtOAC) to give 4-(3-allyl-1,4,5,6,8-pentamethoxy-naphthalen-2-yl)-2,4-dihydroxy-butyric acid (169) as a yellow oil (48 mg, 62%).

IR (KBr) ν_{max} 3370 (OH), 1731 (C=O) 1682 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz) δ 12.42 (s, 1H), 6.41 (s, 1H), 6.19 (m, 1H), 5.37 (m, 2H), 4.90 (m, 1H), 4.41 (m, 1H), 4.05 (s, 3H), 4.03 (s, 3H), 3.87(s, 3H), 3.75 (s, 3H), 3.55(s, 3H), 3.43 (m, 2H), 2.94(m, 1H), 2.89 (m, 1H)

Oxabicyclic compound (170)



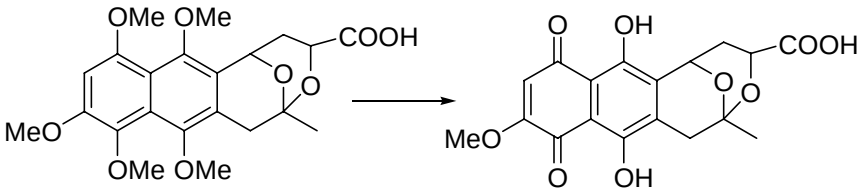
(169) **(170)**

A mixture of palladium chloride (1 mg, 0.0056 mmol) and anhydrous cupric chloride (10 mg, 0.074 mmol) in dry dimethoxyethane (2 mL) was heated at 65 ^{o}C while oxygen was bubbled through the solution. A solution of (169) (30 mg, 0.074 mmol) in dry dimethoxyethane (0.5 mL) was added dropwise and the reaction mixture was stirred at 65 ^{o}C for further 30 min then cooled to room temperature. The reaction mixture was filtered through a short neutral alumina column and eluted with ether. The resulting solution was concentrated in vacuo. The residue was purified by flash column chromatography (4:1 ; EtOAc : Hexane) to obtain oxabicyclic compound (170) (15 mg, 67%) as a mixture of diasteriomer.

IR (KBr) ν_{max} 3340 (OH), 1736 (C=O) cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.30(s, 2H), 5.74 (d, j=5 Hz, 1H), 5.31 (d, J=8 Hz, 1H), 4.90 (m, 1H), 4.52 (m, 1H), 4.41 (m, 1H), 4.37 (m, 1H), 4.05 (s, 6H), 4.03 (s, 6H), 3.87(s, 6H),3.51(s,6H), 3.33(s, 6H) 3.0 (d, J=17 Hz, 1H), 2.81(d, J=17 Hz, 1H), 2.63(d, J=17 Hz, 1H), 2.41 (d, J=17 Hz, 1H), 2.21 (m, 2H), 2.05(m, 2H), 1.57(s, 3H), 1.55(s, 3H)

Marticin (12) and its isomer (13)



(170) **(12)** and **(13)**

To stirred ice-cold solution of naphthol (170) (15 mg, 0.12 mmol) in acetonitrile (5 mL) was added a solution of CAN (202 mg, 0.35 mmol) in water (1.5 mL). The reaction mixture was stirred at 0 ^{o}C for 15 min and then water (10 mL) was added. The mixture was extracted with EtOAc (3x15 mL). The organic extract was separated and dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure to give oil residue. The residue was dissolved in dry CH_2Cl_2 (3 ml) at –78 ^{o}C under N_2 atmosphere. A solution of BBr_3 in CH_2Cl_2 (1 N, 6 ml, 6.0 mmol) was added dropwise. After being stirred for 10 min at –78 ^{o}C, the reaction mixture was quenched with 10% aq.NH_4Cl (5 mL) and extracted with CH_2Cl_2 (4x20 mL). The combined organic layers were washed with water (2x20 mL), dried over anhydrous Na_2SO_4 and filtered and the filtrate concentrated under reduced pressure. The residue was purified by flash column chromatography (1: 9; Hexane : EtOAC) to give a 1:1.2 mixture of marticin (12) and its isomer (13) in the ration 1: 1.2 (6 mg, 52%).

IR (KBr) ν_{max} 3325 (OH), 1665 (C=O) cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz) δ 12.92 and 12.93 (2s, 2H), 12.42, 12.43(2s, 2H), 6.15, 6.17(2s, 2H), 5.62 (d, j=5 Hz, 1H), 5.39 (d, J=9 Hz, 1H), 4.61 (m, 1H), 4.42(m, 1H), 3.97 (s, 6H), 3.13 (d, J=19 Hz, 1H), 3.09 (d, J=19 Hz, 1H), 2.71(d, J=19 Hz, 1H), 2.62 (d, J=19 Hz, 1H), 2.30(m, 2H), 2.21(m, 2H), 1.60 (s, 3H), 1.56(s, 3H)