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Fibrostatins의 부분 합성

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Partial Synthesis of Fibrostatins

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요 약. 알킬화제로 작용할 수 있는 naphthoquinones인 fibrostatin이 Streptomyces catanulae subsp. griseospora 배양액으로부터 추출되었다. 이들 quinone 화합물들의 합성은 이 화합물들의 생물학적 반응성 연구에 매우 중요하다. 본 논문에서는 효과적으로 치환체들의 위치를 조절할 수 있는 방법인 Hooker oxidation을 이용하여 fibrostatin B를 합성하였다.

주제어: Hook Oxidation, Fibrostatin, 알킬화제, 퀴논

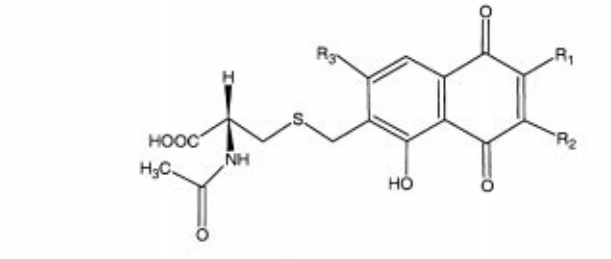
ABSTRACT. Fibrosstatins, which were isolated from the culture broth of *Streptomyces catanulae* subsp. *griseospora*, are naphthoquinones which can work as alkylating agents. It is important to synthesize these quinone compounds for the study of their biological activities. In this paper, an efficient method, Hooker oxidation, to control the regiochemistry in the synthesis of fibrostatin B is reported.

Key words: Hook Oxidation, Fibrostatin, Alkylating Agents, Quinones

INTRODUCTION

Fibrostatins were isolated as orange crystals from the culture broth of *Streptomyces catanulae* subsp. *griseospora*.[1] These compounds are the first naturally occurring 2,6,7- or 3,6,7-trisubstituted or 2,3,6,7-tetrasubstituted 5-hydroxy-1,4-naphthoquinones possessing an N-acetyl-L-cystein-S-yl moiety in the molecule.

These compounds show inhibitory activity against prolyl hydroxylase. Prolyl hydroxylase is an enzyme (M.W., 200,000) along with its cofactors (molecular oxygen, ascorbic acid and -ketoglutarate), which are responsible for hydroxylation of proline. The hydroxyl groups of hydroxyproline residues in collagen, the extracellular matrix protein in animals or cell walls in plants, help to maintain the triple helical structure interchain hydrogen bonding. Procollagen triple helices in which the prolines have not been hydroxylated are far less stable than their hydroxylated counterparts. The conditions that prevent proline hydroxylation like fibrostatins inhibit procollagen helix formation which leads to some diseases.[2] The *in vitro* inhibitory activity (IC_{50}) of fibrostatins A, B, C, D, E and F against prolyl hydroxylase of chick embroys was 23, 39, 29, 180, 10 and 14 μM, respectively. It is reported that acute toxicity (LD_{50}) of fibrostatins was 50-200 mg/kg when administered intraperitoneally to rats.[1] From these data, fibrostatins are regarded as potent inhibitors of prolyl hydroxylase.

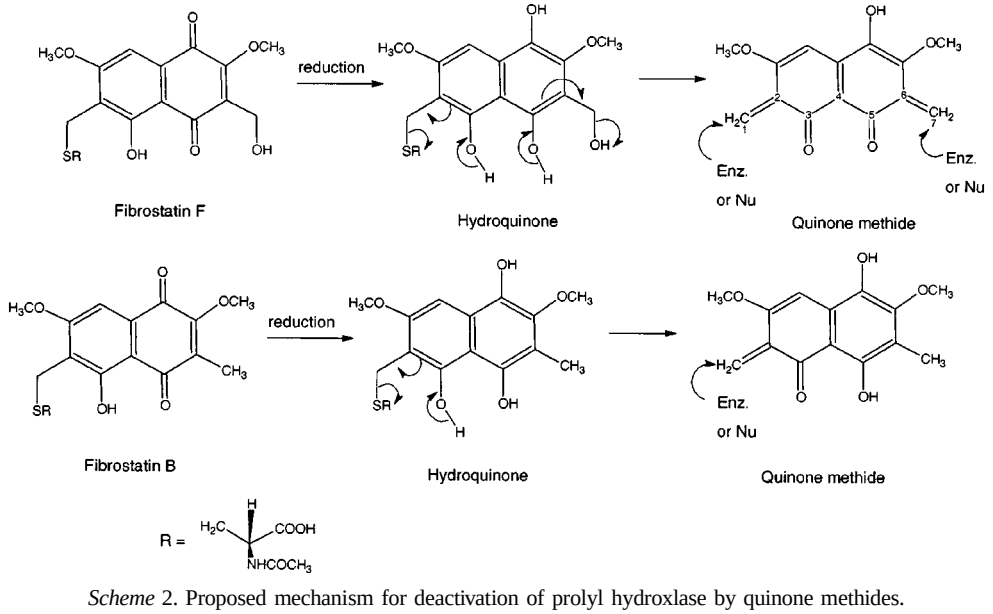


Fibrostatin		R_1	R_2	R_3
	A	H	CH_3	OCH_3
	B	OCH_3	CH_3	OCH_3
	C	OCH_3	H	OCH_3
	D	OCH_3	CH_3	OH
	E	H	CH_2OHOCH_3	
	F	OCH_3	CH_2OHOCH_3	

Scheme 1. Structures of fibrostatins.

The structures of these six fibrostatins were deduced from their chemical and spectroscopic properties.[3] The detailed structures of fibrostatins are shown in *Scheme* 1.

Examination of the structure reveals a benzylic thiol and alcohol which could be precursors to quinone methides and thus the natural products are classified as potent bioreductive alkylating agent. The inhibitory activity to the prolyl hydroxylase could be due to the formation of quinone methide *via* a bioreductive mode. Fibrostatins could be reduced *in vivo*, probably by enzymes such as NADPH, to the corresponding hydroquinone, which may then eliminate water and/or thio side chain to form the quinone methide intermediates. Conceivably the prolyl hydroxylase is trapped and deactivated by these quinone methides, which may function as alkylating agents (*Scheme* 2).



Scheme 2. Proposed mechanism for deactivation of prolyl hydroxlase by quinone methides.

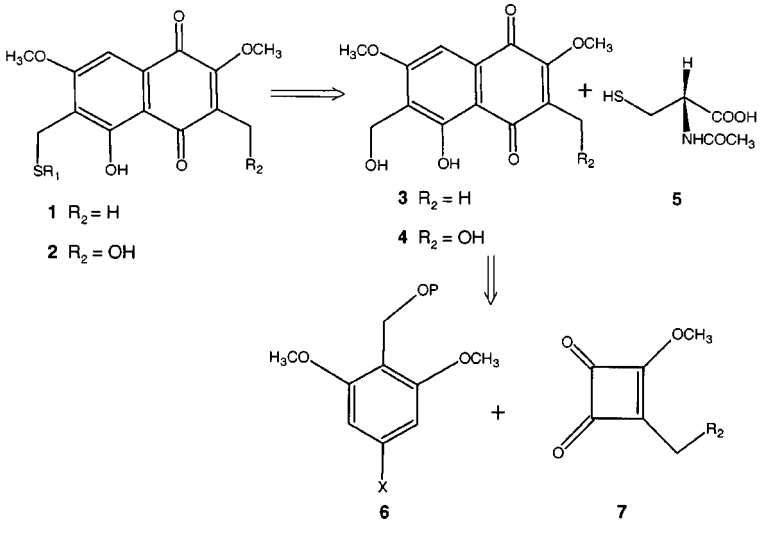
As one can see in *Scheme* 2, fibrostatin F could work as an 1,7-bisalkylating agent, and fibrostatin B could function as a monoalkylating agent. Since many anticancer agents are alkylating agents, it is conceivable that fibrostatins could also behave analogously. Therefore, the synthesis of fibrostatins is very important to test their biological activities and gain a better understanding of their chemistry. The synthesis of fibrostatin B will be discussed in this report.

RESULTS AND DISCUSSION

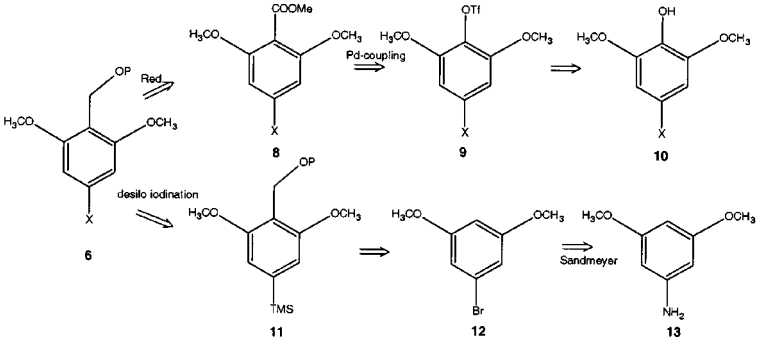
The synthetic strategy of fibrostatins outlined in *Scheme* 3. The key synthetic step is the addition of a suitably substituted aryl lithium reagent **6** to unsymmetrical cyclobutenone **7**.

The introduction of -CH_2OP into aromatic ring did not give promising results. The intermediate **6** could be prepared from 2,6-dimethoxyphenol (**10**) through palladium-catalyzed carbon monoxide insertion or from 3,5-dimethoxyaniline (**13**) through Sandmeyer reaction (*Scheme* 4).

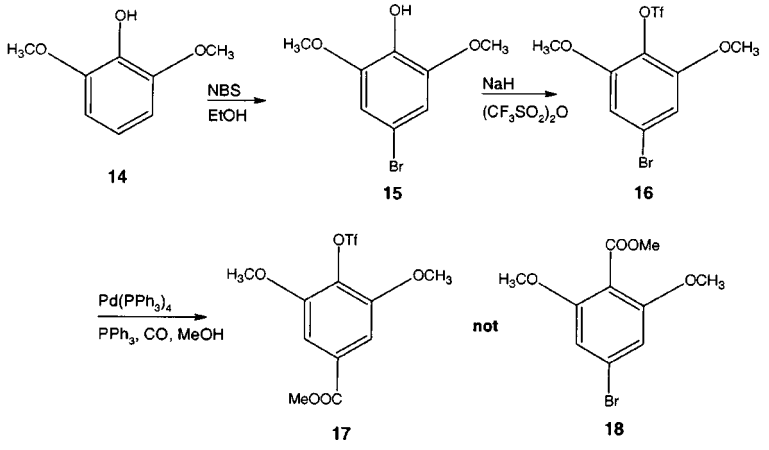
The first route examined was the preparation of aryl triflate **9**, an assumed precursor of methylbenzoate **8** as shown in *Scheme* 5. 4-Bromo-2,6-dimethoxyphenol (**15**), a good precursor for the aryl triflate **9**, was prepared in 76% yield by a procedure similar to that reported by Foley,[4] i.e. *N*-bromosuccinimide (NBS) was employed as a brominating reagent in $CHCl_3$ with 0.75% (v/v) ethanol. The resulting 4-bromo-2,6-dimethoxyphenol (**15**) was treated with trifluo-



Scheme 3. Retrosynthesis of fibrostatin B, F.



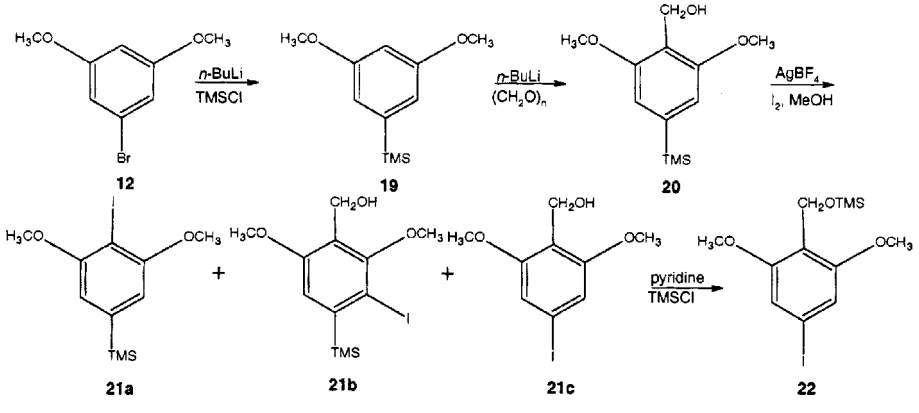
Scheme 4. Retrosynthesis of protected 2,6-dimethoxylbenzyl alcohol **6**.



Scheme 5. Synthesis of 3-bromo-2,6-dimethoxymethylbenzoate (**18**).

romethanesulfonic anhydride and base to give bromoaryl triflate **16** in 90% yield. Among the bases tried, sodium hydride gave the best result. The palladium-catalyzed carbon monoxide insertion was performed.[5] Unfortunately, the product obtained was compound **17**, not the desired compound **18** (*Scheme* 5). The insertion of palladium occurred at the C-Br bond. A possible explanation for this reaction could be that the aryl triflate **16** is more sterically hindered than those reactions described in other papers,[5] so the insertion of palladium took place at the less hindered site. Therefore, this approach was not successful.

The next route tried was the synthesis of protected 2,6-dimethoxy-4-iodobenzyl alcohol (**22**). 3,5-Dimethoxybromobenzene (**12**) was prepared from 3,5-dimethoxyaniline by Sandmeyer reaction (*Scheme* 6). 3,5-Dimethoxytrimethylsilylbenzene (**19**) was prepared from **12** in 97% yield upon treatment of **12** with butyllithium and trimethylsilyl chloride. Compound **19** was then converted into the benzyl alcohol **20** upon treatment with *n*-BuLi and paraformaldehyde in 79% yield. Following desilyloiodination with silver tetrafluoroborate,[6] 4-iodo-1,6-dimethoxybenzyl alcohol (**21c**) was isolated in 39% yield with **21b**(33%) and **21a**(17%). The formation of **21a** can be rationalized by the fact that the aromatic cation formed upon treatment with iodine might be stabilized by the adjacent methoxy groups leading to release of formaldehyde. Also, the formation of **21b** can be rationalized by the fact that the alkoxy aromatic substitution is usually occurred at *ortho* and *para*



Scheme 6. Synthesis of protected 2,6-dimethoxy-4-iodobenzyl alcohol **22**.

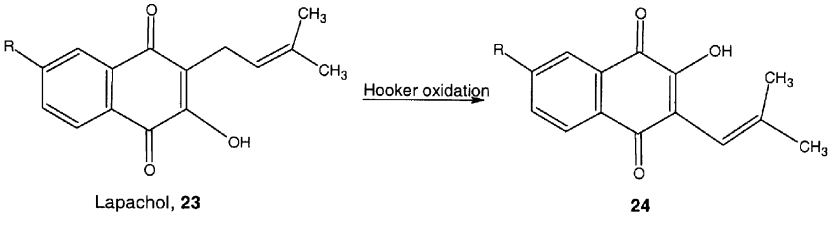
position of the alkoxy groups. Of course, the compound **21c** was converted into **22** successfully. However, this approach was not satisfactory because of the unwanted by-products in the iodination.

Since all attempts to synthesize were not successful or not efficient because of the difficulty introducing -CH_2OP (P=protecting group) group into aromatic ring, Hooker oxidation was introduced. In 1936, *Hooker* reported an unusual transformations of simple hydroxynaphthoquionones. Oxidation of lapachol (**23**) with alkaline permanganate resulted in a totally unexpected product **24** with the elimination of CH2 from the side chain and the change of the regiochemistry (*Scheme* 7).[7] Later Fieser *et al.* reported a new procedure using hydrogen peroxide and $CuSO_4$ under basic condition.[8] The mechanism of this reaction was proposed 50 years ago[8a,e], but it was not proved until our research group proved it with ^{13}C labeled NMR experiments.[9]

If the Hooker oxidation could be efficiently accomplished on highly substituted hydroxynaphthoquinones, one would have a particularly useful control of the regiochemistry. Generally, there are three major contributions for the regiochemical control in the synthesis of quinones: (1) the regiochemical control in the cyclobutenedione state by the regioselective 1,2-addition of lithium reagent to it;[10] (2) the regiochemical control in aryl, alkenyl or alkynyl lithium reagents by an incorporation of a halogen atom or stannyl derivatives at the specific position, or heteroatom directed lithiation;[11] (3) the regiochemical control in the quinone state, especially hydroxynaphthoquinones, by the Hooker oxidation.

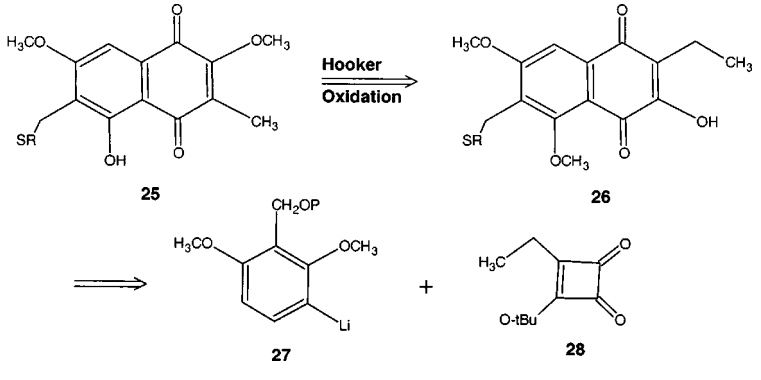
The synthetic strategy for fibrostatin B is proposed in *Scheme* 8. That is, fibrostatin B can be envisaged to ultimately arise from 2,6-dimethoxybenzyl alcohol (**27**) and 3-*t*-butoxy-2-ethyl-3-cyclobutene-1,2-dione (**28**), and both compounds are easy to be prepared in one or two steps from commercially available starting materials.

The aromatic compound was prepared from 1,3-dimethoxtbenzyl alcohol or 2,6-dimethoxybenzoic acid in high yields (*Scheme* 9). 2,6-Dimethoxybenzyl alcohol (**31)** was prepared from 2,6-dimethoxybenzene (**29**) in 92% yield or 2,6-dimethoxybenzoic acid (**30**) in 76% yield. It was then treated with *t*-butyldimethylsilyl chloride (TBDMSCl)[12] to give 2,6-dimethoxy-(*t*-butyldimethylsilyloxymethyl)benzene



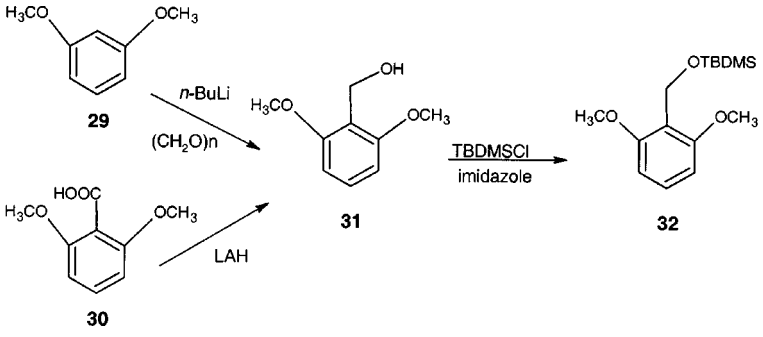
Lapachol, **23** **24**

Scheme 7. Hooker oxidation.

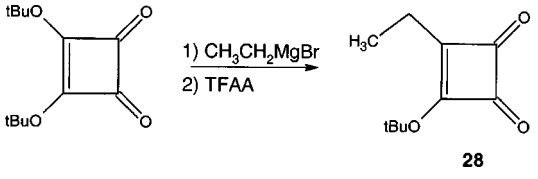


25 **26** **27** **28**

Scheme 8. Retrosynthesis of fibrostatin B.



Scheme 9. Synthesis of protected 2,6-dimethoxylbenzyl alcohol **32**.



Scheme 10. Synthesis of 3-t-butoxy-4-ethyl-3-cyclobutene-1,2-dione (**28**).

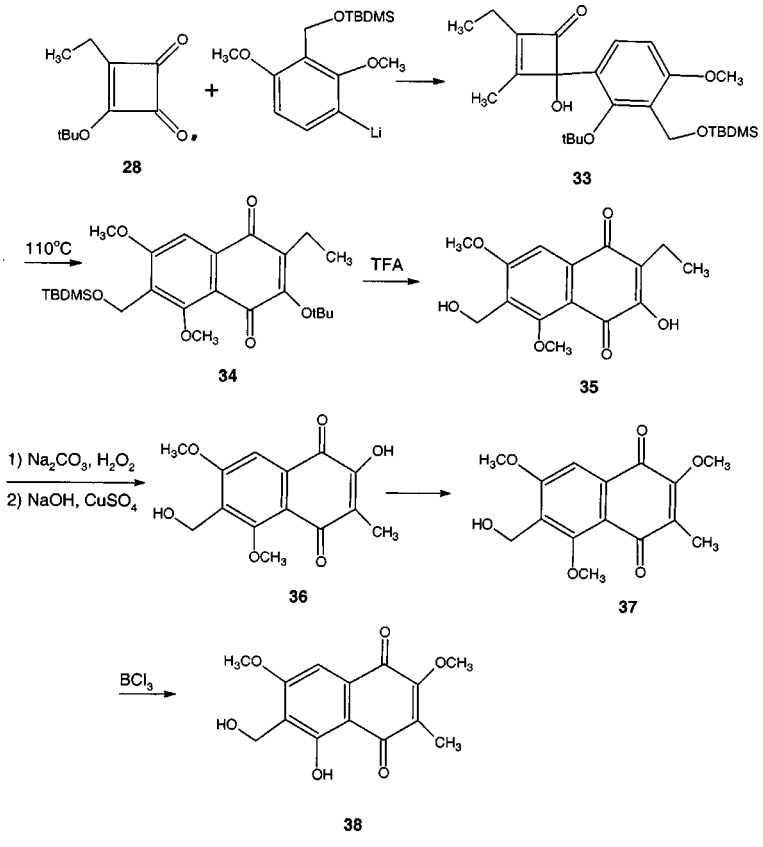
(**32**) in 92% yield.

3-*t*-Butoxy-4-ethyl-3-cyclobutene-1,2-dione (**28**) was prepared by the usual one pot procedure in 76% yield.[13] starting with di-*t*-butylsquarate and ethylmagnesiumbromide (*Scheme* 10).

The addition of the lithium salt of **32** to **28** was performed successfully only in hexane with TMEDA at 0 °C to afford 3-*t*-butoxy-2-ethyl-4-hydroxy-4-(2,4-dimethoxy-3-*t*-butyldimethylsilyloxymethylpheny)-2-cyclobuten-1-one (**33**) in 68% yield. In the absence of TMEDA, the reaction failed. Thermolysis of the resulting cyclobutenone **33** in toluene followed by Ag_2O oxidation of the resulting hydroquinone gave the desired 3-*t*-butoxy-6-(*t*-butyldimethylsilyloxymethyl)-5,7-dimethoxy-2-ethyl-1,4-naphthoquinone (**34**) in 85% overall yield. Removal of the *t*-butyl group was performed by trifluoroacetic acid (TFA) at 0 °C to give 5,7-dimethoxy-2-ethyl-3-hydroxy-6-hydroxymethyl-1,4-naphthoquinone (**35**)[14] in 85% yield. When Hooker oxidation of **35** was performed in alkaline potassium permanganate or hydrogen peroxide and $CuSO_4$. The first attempt employed alkaline potassium permanganate, 5,7-dimethoxy-2-hydroxy-6-hydroxymethyl-3-methyl-1,4-naphthoquinone (**36**) was not obtained in high yield. In addition, the reaction was hard to follow by TLC because both the starting naphthoquinone and the product has the same Rf value in the available eluents. We applied the conditions using hydrogen peroxide and CuSO4, and **36** was successfully obtained in 76% yield. The reaction could be followed easily by color changes, i.e., hydroxynaphthoquinones are red in basic condition and yellow in acidic condition, and ketols are colorless in basic condition. Methylation of **36** was performed by diazomethane15 to give **37** in 89% yield. Demethylation of methoxy group in **37** was selectively performed by boron trichloride to give **38** in 90% yield.[16] 2,7-Dimethoxy-5-hydroxy-6-hydroxymethyl-3-methyl-1,4-naphthoquinone (**38**) is an aglycone of fibrostatin B, but compound **38** can also work as an alkylating agent. So, biological study for this compound must be valuable, too.

EXPERIMENT

General procedure. Commercial reagents were used without further purification excepts as indicated below. Tetrahydrofuran and diethyl ether were distilled from sodium/benzophenone ketyl immediately before use. All air or water sensitive reactions were carried out in flame dried glassware under a positive pressure of argon or nitrogen. Air sensitive solutions were transferred *via* cannula and were introduced into the reaction vessel through rubber septa. Butyllithiums were introduced to the reaction vessels *via* syringe. Reaction solutions were concentrated by a Buchi rotary evaporator at 15-30 mmHg. Column chromatography was per-



Scheme 11. Synthesis of Fibrostatin B.

formed by using E. Merck silica gel (230-400 mesh) mostly with hexanes and ethyl acetate as eluents.

Instruments. Proton and carbon ^{13}C NMR were recorded on a Bruker WM 250, a General Electric QE 300, a General Electric Ω500 NMR or a General Electric GN 500 NMR spectrometer. Infrared spectra were recorded on a Perkin-Elmer FT IR spectrophotometer. Low-resolution mass spectra (MS) were recorded on a Finigan 4000 spectrometer and high-resolution mass spectra (HRMS) were measured with a VG Analytic 7070E spectrometer. Elemental Analysis were performed by Robertson Laboratory.

4-Bromo-2,6-dimethoxyphenol (15). A solution of 5.32 g (30.0 mmol) of N-bromosuccinimide (NBS) in 300 mL of $CHCl_3$ and 3.3 mL of ethanol (0.65 v/v%) at 0 °C was added to a solution of **14** (4.62 g, 30.0 mmol) in 150 mL of $CHCl_3$, and stirred for 5 hrs at 0 °C. The solvent was evaporated *in vacuo*, and diethyl ether was added and the solid was removed by filtration. Diethyl ether was added to the resulting solution and the solid was filtered again. The solution was washed with water (2×10 mL) and brine (10 mL), dried over magnesium sulfate, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (3/1 hexanes/ethyl acetate) to give 5.48 g (78%) of the desired 4-bromo-2,6-dimethoxyphenol **(15)**. Recrystalization of the solid in hexanes gave 5.34 g (76%) of **15** as white needles: m.p., 104.0-104.5 °C; IR ($CHCl_3$) 3540, 1610, 1505, 1455, 1450, 1360, 1240, 1210, 1120 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 6.72 (s, 2H), 5.45 (s, 1H), 3.87 (s, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 147.4, 133.8, 110.8, 108.3, 56.4; MS (CI), m/z 233 (MH^+); MS (EI), m/z (rel. intensity) 234(48), 232 (47), 217(20), 154(21), 110(24), 93(15), 79(30), 67(49), 66(28), 65(33), 53(70), 51(100); HRMS, m/z calcu-

lated for $C_8H_9BrO_3$, 231.9736; found, 231.9718. Anal. calculated for $C_8H_9BrO_3$: C, 41.38; H, 3.91. Found: C, 41.85; H, 3.91.

4-Bromo-2,6-dimethoxy-(trifluoromethanesulfonyl)-benzene (16). To a solution of 1.69 g (7.28 mmol) of **15** in 100 mL of dry diethyl ether was added a mixture of NaH (0.35 mg, 7.28 mmol, 50% in mineral oil)(prewashed with ether before use) in 30 mL of ether at 0 °C. The resulting mixture was stirred for 30 min until no more grey precipitate was formed at 0 °C. Trifluoromethanesulfonic anhydride (1.3 mL, 8.0 mmol) was slowly added to this solution over 3 min at 0 °C, stirred for 5 min and the ice bath was removed. The reaction mixture was heated at reflux for 4 hrs and then cooled to room temperature. The reaction was quenched with water by pouring the reaction mixture into a separatory funnel containing 50 mL of water. The aqueous layer was extracted with diethyl ether (2×100 mL) and the combined organic layer was washed with 50 mL of 5% NaOH solution, water (2×100 mL), and brine (50 mL), dried over magnesium sulfate, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (3/1 hexanes/ethyl acetate) to give 2.37 g (90%) of the desired arytriflate **16** as a white solid; m.p., 51.0-51.5 °C; IR ($CHCl_3$) 2950, 1605, 1575, 1495, 1465, 1450, 1420, 1230, 1140, 890, 830 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 6.87 (s, 2H), 3.87 (s, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 152.9, 127.1, 124.9, 116.4, 108.7, 56.5; MS (CI), m/z 365 (MH^+); MS (EI), m/z (rel. intensity) 366(3), 364(3), 233(85), 231(92), 205(24), 203(25), 190(21), 188(30), 152(22), 124(100), 119(32), 117 (34), 109(61), 66(86), 69(68); HRMS, m/z calculated for $C_9H_8BrO_5SF_3$, 363.9228; found, 363.9228. Anal. calculated for $C_9H_8BrO_5SF_3$: C, 29.61; H, 2.21. Found: C, 29.70; H, 2.07.

3,5-Dimethoxy-4-(trifluomethanesulfonyl)methylbenzoate (17). To a three neck round bottom flask (50 mL) equipped with a magnetic stirrer were added 364 mg (1.0 mmol) of **16**, 16.0 mg (0.06 mmol) of $P(Ph)_3$, 7.00 mg (0.03 mmol) of $Pd(OAc)_2$, 0.28 mL (2.0 mmol) of NEt_3 and 0.9 mL (20.0 mmol) of methanol, and CO was purged for 5 min. The reaction mixture was stirred at 60 °C for 2 hrs with bubbling of CO into the reaction flask, and then cooled to room temperature. The reaction mixture was poured into a separatory funnel containing diethyl ether (100 mL). The aqueous layer was extracted with diethyl ether (2×20 mL). The combined organic layer was washed with 5 mL of 1N HCl and then brine (10 mL) until neutral, dried over magnesium sulfate, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (3/1 hexanes/ethyl acetate) to give 203 mg (59%) of **17** as a white solid with 142 mg (39%) of starting material **16**; m.p., 86.0-87.0 °C; IR ($CHCl_3$), 2950, 1740, 1610, 1580, 1500, 1460, 1450, 1230, 890, 830 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.34 (s, 2H), 3.95 (s, 6H), 3.94 (s, 3H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 173.5, 154.3, 128.2, 125.3, 117.2, 109.1, 82.7, 56.5; MS (CI), m/z 345 (MH^+); MS (EI), m/z (rel. intensity) 344(6), 212(11), 211(100), 155(30), 125(23), 124(15), 109(15), 79(16), 69(51), 66(40), 59(69), 53(37); HRMS, m/z calculated for $C_{11}H_{11}O_7SF_3$, 344.0177; found 344.0186.

3,5-Dimethoxymethylsilylbenzene (19). To a solution of **12** (2.16 g, 10.0 mmol) was added *n*-BuLi (1.6 M in hexanes, 6.88 mL, 11.0 mmol) at -78 °C *via* syringe slowly. After stirred for 20 min at -78 °C, the reaction mixture was treated with excess amount of TMSCl (1.3 equiv). The resulting mixture was stirred for an additional 30 min, and the mixture was poured into a separatory funnel containing 120 mL of diethyl ether and 50 mL of water. The aqueous layer was extracted with diethyl ether (2×100 mL), dried over magnesium sulfate, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (1/1 hexanes/ethyl acetate) to give 2.04 g (97%) of the desired product **19** as a sticky oil: IR (neat) 3030, 3005, 2980, 2955, 1600, 1465, 1410, 1330, 1300, 1210, 1150 cm^{-1}; 1H NMR ($CDCl_3$, 300 MHz) δ 6.65 (d, *J*=2.5 Hz, 2H), 6.45 (t, *J*=2.5 Hz, 1H), 3.81 (s, 6H), 0.25 (s, 9H); ^{13}C NMR (Acetone-d_6, 300 MHz) δ 161.2, 142.8, 111.2, 100.9, 55.0, -1.5; MS (CI), m/z 211 (MH^+); MS (EI), m/z (rel. intensity) 210(34), 195(100), 165 (18), 150(4), 135(7), 97(8), 75(21), 73(16), 59(32): HRMS, m/z calculated for $C_{11}H_{18}SiO_2$, 210.1076; found 210.1055.

2,6-Dimethoxy-4-trimethylsilyibenzyl alcohol (20). A solution of 630 mg (3.0 mmol) of **19** in 30 mL of dry THF at 0 °C under argon was treated with *n*-BuLi (1.6 M in hexanes, 2.25 mL, 3.6 mmol). The reaction mixture was stirred for 2 hrs at room temperature, and then cooled to 0 °C and 108 mg (3.6 mmol) of *para* formaldehyde was added. The solution was stirred for 1 hr and quenched with 4 mL of a 10% NH_4Cl solution. The resulting solution was poured into a separatory funnel containing diethyl ether (100 mL) and water (20 mL). The organic layer was washed with water (2×20 mL) and brine (10 mL), dried over magnesium sulfate, and finally concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (3/1 hexanes/ethyl acetate) to give 700 mg (79%) of the desired product **20** as a white solid with 120 mg (20%) of starting material **19**: m.p., 50.0-50.5 °C; IR ($CHCl_3$) 3600, 3010, 2970, 1600, 1570, 1470, 1395, 1290, 1250, 1130, 840 cm^{-1}; ^1H NMR (Acetone-d_6, 500 MHz) δ 6.78 (s, 2H), 4.61 (d, *J*=6.7 Hz, 2H), 3.21 (t, *J*=6.7 Hz, 1H); ^{13}C NMR (Acetone-d_6, 500 MHz) δ 156.9, 140.1, 117.4, 107.0, 54.0, 51.8, -3.1; MS (CI), m/z 241 (MH^+); MS(EI), m/z (rel. intensity) 240(18), 225(35), 193(17), 91(21), 75(60), 73(100), 59(48); HRMS, m/z calculated for $C_{12}H_{20}SiO_3$, 240.1182; found, 240.1175. Anal. calculated for $C_{12}H_{20}SiO_4$: C, 59.96; H, 8.38. Found: C, 59.96; H, 8.36.

2,6-Dimethoxy-4-iodobenzyl alcohol (21c). To a solution of 800 mg (3.33 mmol) of **20** in 50 mL of dry MeOH was added 840 mg (4.29 mmol) of $AgBF_4$ and cooled the reaction mixture to 0 °C. Iodine (840 mg, 3.33 mmol) dissolved in 20 mL of dry MeOH was added to the mixture, and stirred for 1 1/2 hrs at 0 °C. The reaction mixture was poured into 200 mL of diethyl ether and filtered through a celite pad to remove AgI and washed the yellow cake (AgI) with ether (2×30 mL). The organic solution was washed with 10% sodium thiosulfate solution (2×10 mL) and brine (20 mL). dried over magnesium sulfate, and concentrated *in vacuo*. Flash column chromatography (3/1 hexanes/ethyl acetate) and following recrystalization in hexanes were performed to separate the mixture and 360 mg (39%) of the desired product **21c** as a white solid with 331 mg (33%) of **21b** and 170 mg(17%) of **21a** were obtained.

21c: m.p., 126.0-127.0 °C; IR ($CHCl_3$) 3600, 3040, 2970, 1595, 1475, 1420, 1250, 1205, 1190, 1140, 1010, 850, 830 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.89 (s, 2H), 4.71 (d, *J*=6.7 Hz, 2H), 3.82 (s, 6H), 2.34 (t, *J*=6.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 156.9, 140.1, 117.4, 107.0, 54.0, 51.8, -3.1; MS (CI), m/z 277 (MH^+-H_2O); MS (EI), m/z (rel. intensity) 294(65), 293(23), 262(31), 139(28), 138(32), 135(20), 124(17), 108(21), 107(22), 92(40), 91(34), 79(44), 78(53), 77(88), 75(45), 65(47), 64(52), 63(100), 53(87), 51(94); HRMS, m/z calculated for $C_9H_{11}IO_3$, 293.9755; found, 293.9733. Anal. calculated for $C_9H_{11}IO_3$: C, 36.76; H, 3.77. Found: C, 36.75; H, 3.62. **21b** as a white solid: m.p., 132.0-133.0 °C; IR ($CHCl_3$) 3600, 2900, 1595, 1470, 1250, 1200, 1140, 830 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.81 (s, 1H), 4.78 (d, *J*=5.7 Hz, 2H), 3.87 (s, 3H), 3.84 (s, 3H), 2.3 (t, *J*=6.7 Hz, 1H), 0.02 (s, 9H). **21a** colorless oil; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.87 (s, 2H), 4.78 (s, 2H), 3.81 (s, 6H), 0.02 (s, 9H).

2.6-Dimethoxy-4-iodotrimethylsilyloxymethylbenzene (22). To a solution of 352 mg (1.2 mmol) of **21.c** in dry THF (70 mL) were added 4 mL of dry pyridine and 0.4 mL (1.4 mmol) of TMSCl slowly at room temperature, and the reaction mixture was stirred for 1 hr at 35 °C. The reaction mixture was cooled to room temperature and 30 mL of diethyl ether was added, and the pyridinium hydrochloride salt was removed by filtration through a celite pad twice. The organic layer was washed with water (2×10 mL) and brine (10 mL), dried over magnesium sulfate, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (3:1 hexanes/ethyl acetate) to give 420 mg (96%) of the desired product **22** as a white solid**:** m.p., 72.0-73.0 °C; IR ($CHCl_3$) 2980, 1595, 1480, 1420, 1240, 1210, 1200, 1140, 850, 830 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.86 (s, 2H), 4.67 (s, 2H), 3.80 (s, 6H), 0.11 (s, 9H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 159.1, 116.6, 113.7, 93.7, 55.9, 53.1, -0.2; MS (CI), m/z 367 (MH^+); MS (EI), m/z (rel. intensity) 366(4), 277(31), 120(13), 89(21), 77(28), 75(23), 73(100), 59(27); HRMS, m/z calculated for $C_{12}H_{19}SiIO_3$, 366.0150; found, 366.0237.

3-*t*-Butoxy-4-ethyl-3-cyclobutene-1,2-dione (28). To a solution of Mg ribbon (2.3 g, 0.1 mol) in 100 mL of dry ethyl ether with a few crystals of iodine was added ethylbromide (5.4 g, 50.0 mmol) in dry ether (100 mL) dropwise for 30 min. The mixture was heated at reflux for 3 hrs, and then cooled to room temperature. The resulting grey solution was transferred into a solution of di-*t*-butyl squarate (9.0 g, 40.0 mmol) in dry THF (200 mL) at -78 °C *via* cannula slowly. After stirred for 30 min, the reaction mixture was treated with TFAA (8.5 mL, 60 mmol) at 0 °C. The mixture was stirred for another 30 min, and 20 mL of water was added to the reaction mixture. The reaction mixture was poured into a separatory funnel containing 300 mL of ether and 100 mL of water. The aqueous layer was extracted with ether (2×100 mL). The combined organic layer was washed with water (100 mL) and brine (20 mL), dried over magnesium sulfate, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (3/1 hexanes/ethyl acetate) to give 5.53 g (76%) of the desired dione **28** as clear crystals: m.p., 36.0-37.0 °C; IR ($CHCl_3$) 2980, 1792, 1750, 1579, 1464, 1387, 1309, 1266, 1155, 1080, 982 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.59 (q, *J*=7.1 Hz, 2H), 1.59 (s, 9H), 1.24 (t, *J*=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 200.3, 197.3, 193.1, 187.5, 88.5, 29.3, 19.1, 10.6; MS (CI), m/z 183 (MH^+); MS (EI), m/z (rel. intensity) 182(7), 167(5), 153(6), 140(10), 126(17), 111(11), 99(23), 97(100), 83(16); HRMS, m/z calculated for $C_{10}H_{14}O_3$, 182.0943; found, 183.1055(MH^+).

3-*t*-Butoxy-2-ethyl-4-hydroxy-4-(2,4-dimethoxy-3-*t*-butyldimethylsilyloxymethyl)-2-cyclobuten-1-one (33). To a solution of **32** (1.25 g, 4.4 mmol) in dry hexanes (120 mL) were added *n*-BuLi (1.6 M in hexanes, 2.75 mL, 4.4 mmol) and TMEDA (4.75 mmol) at -78 °C and the reaction mixture was warmed to 0 °C with stirring. After stirring for 1 hr at 0 °C (reaction mixture turned from colorless to yellow), the reaction was cooled to -78 °C and transferred to a solution of cyclobutenedione **28** (600 mg, 3.65 mmol) in dry THF (100 mL) *via* cannula at -78 °C. After stirring for 30 min at -78 °C, the reaction was quenched with 5% NH_4Cl solution (10 mL) and the resulting solution was poured into a separatory funnel containing 200 mL of ether and 30 mL of water. The aqueous layer was extracted with ether (2×100 mL). The combined organic solution was washed with water (100 mL) and brine (20 mL), dried over magnesium sulfate, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (3/1 hexanes/ethyl acetate) gave 1.15 g (68%) of the desired cyclobutenone **33** as a white solid: m.p., 89.0-90.0 °C; IR ($CDCl_3$) δ 3418, 2956, 2937, 2856, 1756, 1601, 1464, 1375, 1360, 1303, 1279, 1254, 1167, 1106, 1079, 836, 777 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) 7.08 (d, *J*=8.9Hz, 1H), 6.62 (d, *J*=8.9 Hz, 1H), 4.70 (s, 2H), 4.13 (s, 3H), 3.79 (s, 3H), 2.25 (q, *J*=7.8 Hz, 2H), 1.46 (s, 9H), 1.17 (t, *J*=7.8 Hz, 3H), 0.88 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 500 MHz) 192.1, 177.0, 158.9, 158.0, 130.7, 127.5, 122.72, 121.8, 106.5, 94.3, 83.7, 65.3, 55.2, 54.2, 28.3, 28.0, 25.6, 18.2, 16.9, 11.3, -5.6, -5.7; MS (CI), m/z 465 (MH^+); MS (EI), m/z (rel. intensity) 349(7), 276(5), 179(3), 163(4), 151(10), 75(100), 73(18), 56(58), 55(28); HRMS, m/z calculated for $C_{25}H_{40}SiO_6$, 464.2594; found, 465.2684(MH^+).

2-*t*-Butoxy-6,8-dimethoxy-3-ethyl-7-(*t*-butyldimethylsilyloxymethyl)-1,4-naphthoquinone (34). The hydroxycyclobutenone **33** (700 mg, 1.5 mmol) was heated under reflux in toluene (50 mL) for 1 hr. The reaction was cooled to room temperature, Ag_2O (4.0 mmol) and K_2CO_3 were added and stirred for 3 hrs. After the silver residues and K_2CO_3 were removed by filtration, the solution was concentrated *in vacuo* at 45 °C. The resulting residue was purified by flash column chromatography (3/1 hexanes/ethyl acetate) to give 590 mg (85%) of the desired naphthoquinone **34** as a yellow solid: m.p., 80.0-81.0 °C; IR ($CHCl_3$) 2936, 2895, 2857, 1668, 1608, 1582, 1464, 1411, 1369, 1340, 1298, 1260, 1224, 1138, 1093, 1067 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.43 (s, 1H), 4.74 (s, 2H), 3.96 (s, 3H), 3.92 (s, 3H), 2.57 (q, *J*=7.4 Hz, 2H), 1.46 (s, 9H), 1.11 (t, *J*=7.4 Hz, 3H), 0.877 (s, 9H), 0.09 (s, 6H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 185.3, 181.1, 162.3, 160.5, 157.2, 138.6, 135.1, 128.7, 117.7, 104.5, 84.0, 63.1, 55.7, 53.6, 29.3, 25.6, 18.2, 17.7, 12.7, -5.6; MS (CI), m/z (rel. intensity) 463 (MH^+,

21), 407(100), 349(15), 331(34), 275(84); HRMS, m/z calculated for $C_{25}H_{38}SiO_6$, 462.2437; found, 463.2531(MH^+).

5,7-Dimethoxy-2-ethyl-3-hydroxy-6-hydroxymethyl-1,4-naphthoquinone (35). The naphthoquinone **34** (500 mg, 1.1 mmol) was placed in a flame fried 100 mL round bottom flask, and cold TFA(40 mL) was added to this quinone slowly under argon atm. After the reaction mixture was stirred for 30 min, 30 mL of toluene was added to the mixture and then the solution was concentrated *in vacuo* at 40 °C. The resulting residue was purified by flash column chromatography (3/1 hexanes/ethyl acetate) gave 268 mg (85%) of the desired 5,7-dimethoxy-2-ethyl-3-hydroxy-6-hydroxymethyl-1,4-naphthoquinone (**35**) as a yellow solid: m.p., 166.0-167.0 °C; IR ($CHCl_3$) δ 3369, 2976, 2941, 1651, 1581, 1418, 1350, 1262, 1234, 1134 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.81 (s, 1H), 7.52 (s, 1H), 4.77 (s, 2H), 4.02 (s, 3H), 3.90 (s, 3H), 2.53 (q, *J*=7.4 Hz, 2H), 2.37 (brs, 1H, OH), 1.11 (t, *J*=7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 183.7, 178.4, 163.5, 160.9, 153.2, 136.08, 127.0, 115.3, 105.7, 62.5, 56.2, 54.1, 16.4, 12.3; MS (EI), m/z (rel. intensity) 292(100), 277(20), 274(75), 262 (52), 261(28), 259(74), 231(95), 205(21), 203(24), 201(36), 175(12), 149(13), 115(15), 91(16), 77(20); HRMS, m/z calculated for $C_{15}H_{16}O_6$, 292.0947; found, 292.0930.

5,7-Dimethoxy-2-hydroxy-3-methyl-6-hydroxymethyl-1,4-naphthoquinone (36). The hydroxyquinone **35** (292 mg, 1.0 mmol) was added to a 50 mL flame dried round bottom flask containing 3 mL of dioxane and 3 mL of water, and 128 mg (1.2 mmol) of Na_2CO_3 was added (reaction mixture becomes red). The reaction mixture was heated with 0.30 mL of 30% H_2O_2 under nitrogen at 60 °C until the solution was turned to a pale yellow. The reaction solution was then cooled in ice and treated with 10 drops of conc. hydrochloric acid and a sufficient amount of water solution saturated with SO_2. A stream of nitrogen was then bubbled into the solution for 30 min. The mixture was then treated with 2 mL of 25% NaOH solution and 6 mL of a aqueous $CuSO_4$ solution (1 g, 6.0 mmol) (blue) and heated at 70 °C until the solution became red (blue to red through brown). The solution was filtered through a pad of celite and the pad was washed with water until the red color disappeared. The red solution was treated with dilute hydrochloric acid to slightly acidic (yellow). The solution was poured into a separatory funnel containing $CHCl_3$ (150 mL) and water (10 mL) and separated the layers. The aqueous layer was extracted with $CHCl_3$ (100 mL). The combined organic layers were washed with brine (10 mL), dried over magnesium sulfate, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (3/1 hexanes/ethyl acetate) to give 211 mg (76%) of the desired rearranged 5,7-dimethoxy-2-hydroxy-3-methyl-6-hydroxymethyl-1,4-naphthoquinone (**36**) as a yellow solid: m.p., 187.0-188.0 °C; IR ($CHCl_3$) 3602, 3433, 2966, 2860, 1654, 1583, 1416, 1313, 1215 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.49 (s, 1H), 7.13 (s, 1H), 4.84 (s, 2H), 4.05 (s, 3H), 3.96 (s, 3H), 2.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 183.6, 180.9, 161.6, 160.0, 151.5, 132.1, 130.6, 121.9, 118.5, 104.8, 62.8, 56.3, 54.6, 8.9; MS (EI), m/z (rel. intensity) 278(11), 263(37), 248(100), 247(49), 235(39), 230(40), 219(30), 205 (19), 189(19), 91(14), 83(32), 77(19); HRMS, m/z calculated for $C_{14}H_{14}O_6$, 278.0790; found, 278.0755.

6-Hydroxymethyl-3-methyl-2,5,7-trimethyl-1,4-naphthoquinone (37). To the solution of diazald (10.0 g) in dry ether (10 mL) in 50 mL elrenmeyer flask was added ethanol (30 mL) which was saturated with KOH, and this solution was connected into a reaction flask containing quinone **36** (139 mg, 0.5 mmol) in 25 mL of dry ether with a nalgen tube. Excess diazomethane was passed through acetic acid. After the reaction was completed, the reaction mixture was stored in a hood overnight. The solvent was then removed *in vacuo* and the residue was purified through flash column chromatography (3/1 hexanes/ethyl acetate) to give 125 mg (89%) of the desired 6-hydroxymethyl-3-methyl-2,5,7-trimethyl-1,4-naphthoquinone (**37**) as a yellow solid: m.p., 152.0-15.0 °C; IR ($CHCl_3$) 3601, 2943, 2859, 1667, 1659, 1627, 1581, 1464, 1375, 1331, 1296, 1212, 1132 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.41 (s, 1H), 4.77 (s, 2H), 4.03 (s, 3H), 3.99 (s, 3H), 3.89 (s, 3H), 2.55 (s, 1H), OH), 2.05 (s, 3H);

^{13}C NMR ($CDCl_3$, 500 MHz) δ 183.9, 180.7, 161.8, 159.5, 156.1, 134.2, 133.5, 129.2, 118.0, 104.7, 62.6, 60.6, 56.2, 54.4, 9.5; MS (EI), m/z (rel. intensity) 292(21), 277(70), 262(100), 261(74), 249(28), 247(27), 234(32), 219(28), 203(27), 189(17), 175(15), 103(11), 91(11), 83(32); HRMS, m/z calculated for $C_{15}H_{16}O_6$, 292.0947; found, 293.1040(MH^+).

2,7-Dimethoxy-5-hydroxy-6-hydroxymethyl-3-methyl-1,4-naphthoquinone (38). To a solution of **37** (146 mg, 0.5 mmol) in dry CH_2Cl_2 (30 mL) was added BCl_3 (1.5 mmol) at -78 °C *via* syringe. After stirred for 20 min, the reaction was quenched with water, and the solution was poured into a separatory funnel containing 20 mL of CH_2Cl_2 and 10 mL of water. The organic layer was washed with water (10 mL) and brine (10 mL), dried over magnesium sulfate, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (3/1 hexanes/ethyl acetate) to give 125 mg (90%) of the desired product **38** as a yellow solid: m.p., 152.0-153.0 °C; IR ($CHCl_3$) 3603, 2948, 2853, 1670, 1630, 1602, 1490, 1376, 1324, 1298, 1214, 1108 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.18 (s, 1H), 4.82 (d, *J*=6 Hz, 2H), 4.11 (s, 3H), 3.99 (s, 3H), 2.55 (t, *J*=6 Hz, 1H, OH), 2.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 190.3, 180.5, 162.6, 160.7, 157.9, 132.3, 121.8, 109.4, 102.4, 61.1, 56.3, 54.0, 8.7; MS (CI), m/z 279 (MH^+), 261; HRMS, m/z calculated for $C_{14}H_{14}O_6$, 278.0790; found, 278.0815.

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