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NOVEL TOTAL SYNTHESIS OF THE 2-AZAANTHRAQUINONE ALKALOID SCORPINONE USING A TANDEM OXIDATION AND AZAELECTROCYCLIC REACTION

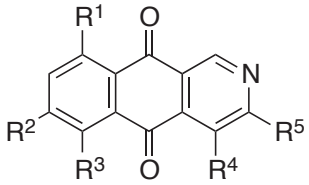
Tominari Choshi,[a]* Miharu Hironaka,[a] Miki Goto,[a] Kaori Shimizu,[a] Yuhki Kurata,[a] Takashi Nishiyama,[a] Noriyuki Hatae,[b] and Satoshi Hibino[a]*

[a]Faculty of Pharmaceutical Sciences, Fukuyama University, Fukuyama, Hiroshima 729-0292, Japan; [b]School of Pharmaceutical Sciences, Health Sciences University of Hokkaido, Ishikari-Tobetsu, Hokkaido 061-0293, Japan: E-mail, hibino@fupharm.fukuyama-u.ac.jp andchoshi@fupharm.fukuyama-u.ac.jp

Abstract – A new tandem oxidation and electrocyclic reaction of a 1-aza 6π-electron system derived from a known 3-hydroxynaphthalene derivative was developed for the synthesis of 2-azaanthraquinones. Total synthesis of scorpinone (**1a**) was achieved in seven steps using this new tandem reaction. In addition, the positional isomer, 7,9-dimethoxy-4-methylbenzo[*g*]isoquinoline-5,10-dione (**1b**) was also synthesized in the same way.

INTRODUCTION

Naturally occurring 2-azaanthraquinones are a class of polyketide-derived heterocycles produced by fungi or lichens[1-3] and are of special interest due to their important biologic properties,[4,5] includimg anti-HIV activity.[6] Bostrycoidin, tolypocladin, scopinone and their related natural compounds are members of the 2-azaanthraquinone family based on studies of their biosynthesis.[1-3] An unsubstituted 2-azaanthraquinone, benz[*g*]isoquinoline-5,10-dione, that inhibits the growth of multi-drug resistant pathogens has also been isolated from *Psychotria componutans* and *Mitracarpus scaber*.[4,5]



1a: scorpinone (R^1=R^2=OMe, R^3= R^4=H, R^5=Me)
1b: R^1=R^2=OMe, R^3=R^5=H, R^4=Me
2: bostrycoidin (R^1=R^3=OH, R^2=OMe, R^4=H, R^5=Me)
3: tolypocladin (R^1=R^2=R^3=OH, R^4=H, R^5=Me)

Figure 1

In 1954, naturally occurring 2-azaanthraquinone bostrycoidin (**2**) possessing antibiotic properties was first

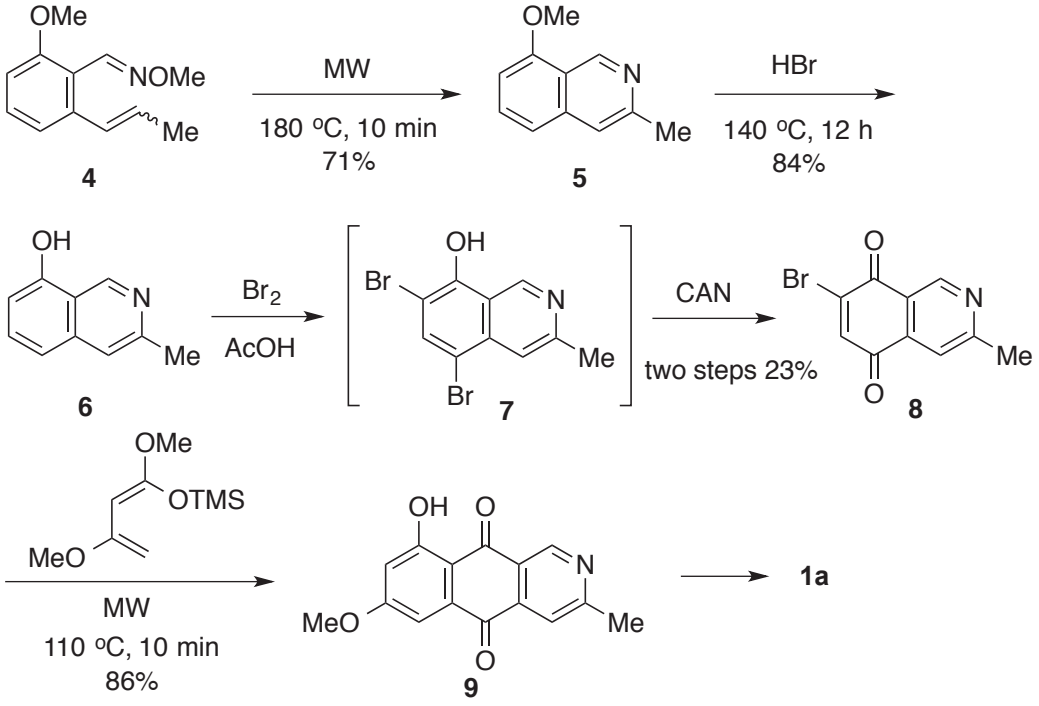
isolated from *Fusarium bostrycoides*[7] and the structure was assigned by Arsenault in 1965.[8] Bostrycoidin was subsequently also isolated from several *Fusarium* species[8-10] and produced from *Nectria haematococca*.[11] The physiologic importance of 2-azaanthraquinones led to the development of several synthetic methods. The first total synthesis of bostrycoidin (**2**) was reported by Cameron.[12] In 1987, Watanabe reported the formal total synthesis of **2** using 4-selective lithiation of *N*,*N*-diisopropylnicotinamide, followed by condensation with *N*,*N*-dimethyl-2,3,5-trimethoxybenzamide.[13] Most pathways involved a Diels-Alder cycloaddition reaction, followed by an intramolecular Friedel-Crafts reaction to obtain the appropriate building blocks, in which the nitrogen is already incorporated.[14-17]

The metal-chelating properties of tolypocladin (**3**), from the mycelium of the cyclosporine producing fungus *Tolypocladium inflatum*, was demonstrated in 1990.[18a] Graefe also reported that bostrycoidin (**2**) and tolypocladin (**3**) inhibit Ca^{2+} - and calmodulin-dependent cAMP phosphodiesterase.[18b] In 1997, the intermolecular Friedel-Crafts acylation of 1,2,4-trimethoxybenzene and 2-methylpyridine-4,5-dicarboxylic acid anhydride, followed by the subsequent intramolecular Friedel-Crafts reaction, was used for the first synthesis of tolypocladin (**3**).[15] The synthesis of tolypocladin (**3**) was also reported by Krapcho[16] and De Kimpe,[17] using the synthetic route for bostrycoidin (**2**).

Scopinone (**1a**) was isolated from the mycelium of a *Bispora*-like tropical fungus,[19] and from cultures of the mycobionts of the lichen *Haematomma* sp., respectively, in 2001.[20] Scorpinone (**1a**) was also recently independently isolated from the fungus *Amorosia littoralis*[21] and from the fungus *Ascomycete* IBWF79B-90A.[22] Anke[22] reported that scorpinone (**1a**) exhibited cytotoxic activities against several cell lines. In 2005, the first total synthesis of scorpinone (**1a**) was established by De Kimpe[17] through the construction of a naphthoquinone skeleton based on a [4 + 2] cycloaddition of an appropriate electron-rich and oxygenated diene, followed by cyclization of 2-phenoxymethyl-3-acetonylnaphthoquinones with ammonia according to the modified Parisot procedure.[23]

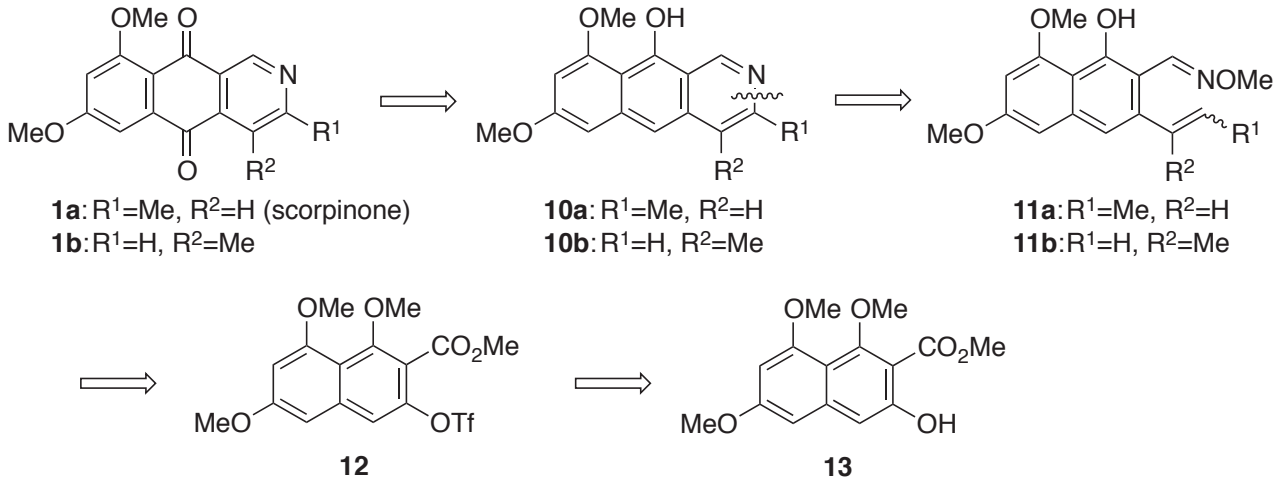
We are performing the synthesis of bioactive nitrogen-containing fused-heteroaromatic compounds including natural products with a thermal electrocyclic reaction using either a 6π- or aza 6π-electron system including an aromatic or heteroaromatic double bond in principle.[24] Among them, we reported the total synthesis of furo[3,2-*h*]isoquinoline,[25] phenanthridine,[26] β-carboline,[27] 2-azaanthraquinone,[28] benzo[*c*]phenanthridine,[29] indolo[3,2-*c*]quinolone,[30] and pyrano[2,3,4-*ij*]isoquinoline[31] alkaloids by the construction of fused pyridine ring systems using a microwave-assisted thermal electrocyclic reaction of an aza 6π-electron system. In 2008, we reported the total synthesis of the 2-azanthraquinone alkaloid scopinone (**1a**) in nine steps (8% overall yield) using two key reactions of a microwave-assisted thermal electrocyclic reaction for the synthesis of 8-oxygenated isoquinoline skeleton from a 1-azahexatriene system, followed by a regioselective microwave-assisted [4+2] cycloaddition for construction of the

2-azaanthraquinone framework (Scheme 1). The 7-bromoisoquinolinequinone **8** was obtained from the 8-hydroxyisoquinoline **6** in somewhat low yield (23% in two steps), because the 5,7-dibromo-isoquinoline **7** was very unstable. Therefore, we planned a new synthetic route.



Scheme 1

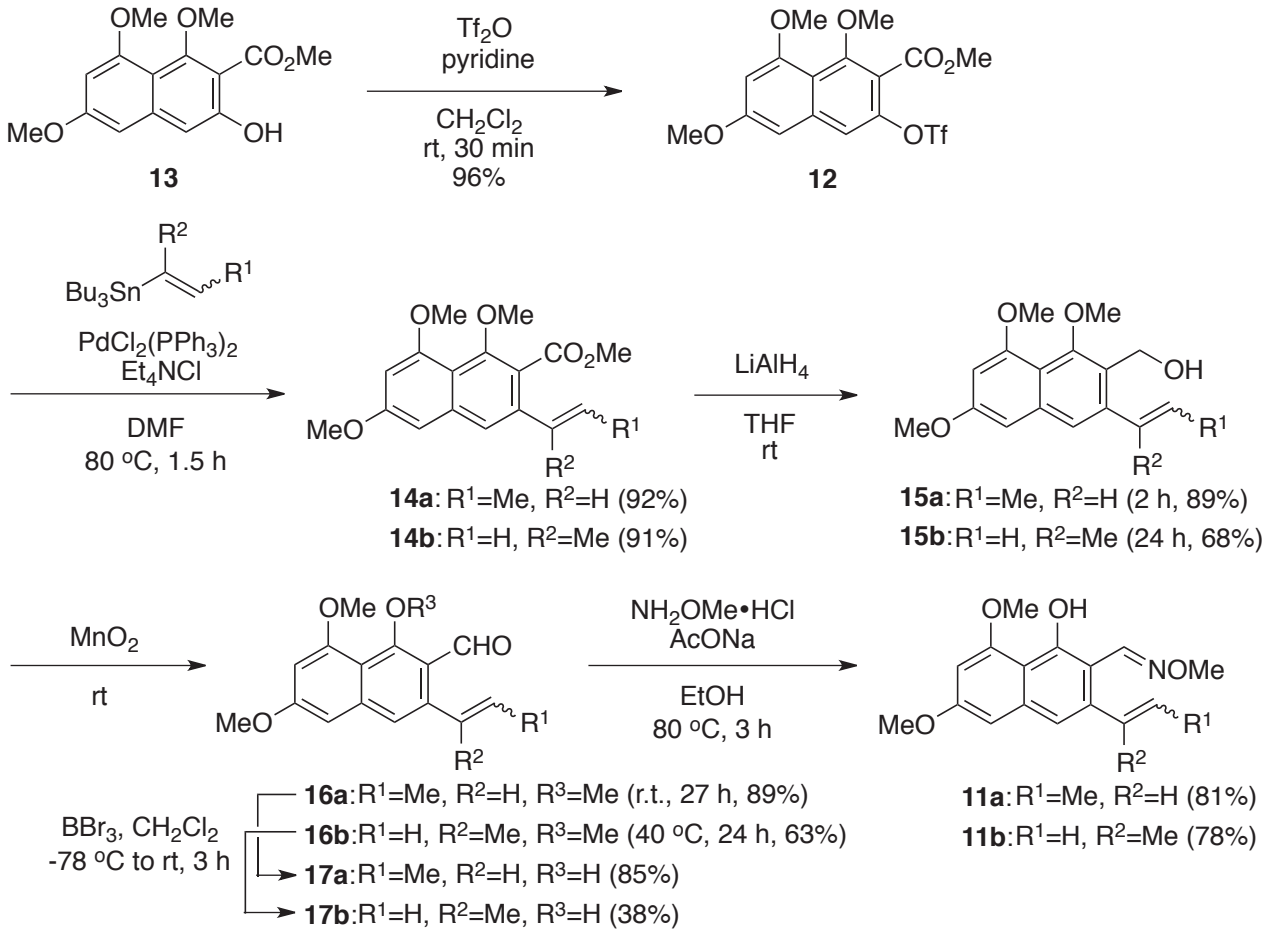
In this report, we describe an alternative synthesis of scorpinone (**1a**) together with its positional isomer of the methyl group, 7,9-dimethoxy-4-methylbenzo[*g*]isoquinoline-5,10-dione (**1b**) by the construction of the 2-azaanthraquinone ring system based on a new tandem oxidation and a thermal electrocyclic reaction of a 1-aza 6π electron system.



Scheme 2

RESULTS AND DISCUSSION

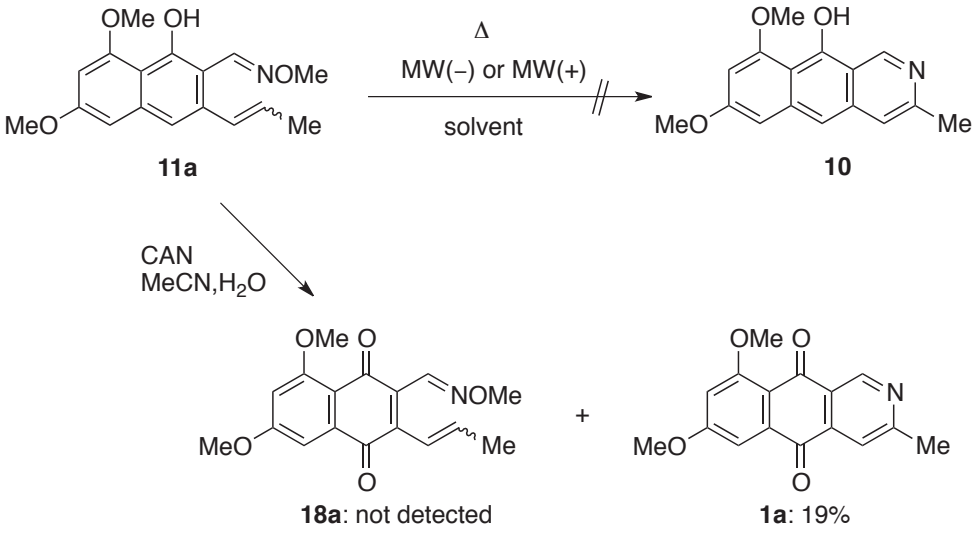
In the retrosynthetic analysis (Scheme 2), we envisaged that scorpinone (**1a**) and its positional isomer (**1b**) of methyl group could be derived from 5-oxyganated 2-azaanthracene **10** by oxidation. 2-Azaanthracene **10** might be obtained by a microwave-assisted thermal electrocyclic reaction of 3-alkenylnaphtharene-2-aldoxime methyl ether **11**, 1-azahexatriene system**,** derived from a cleavage of the 2,3-bond of the 2-azaanthracene framework. The aldoxime methyl ether **11** could be easily obtained from the known naphthalene **13**.[32]



Scheme 3

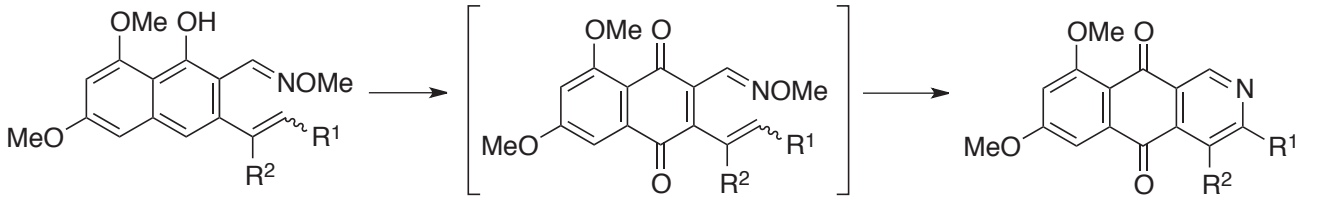
To synthesize an 1-azahexatriene system, the naphthalene **13** was prepared according to Greene's procedure.[32] As shown in Scheme 3, treatment of 3-hydroxynaphthalene **13** with trifluoromethanesulfonic anhydride (Tf_2O) afforded the triflate **12** (96%), which was subjected to the Stille reaction with two kind of alkenyltributyltins in the presence of $PdCl_2(PPh_3)_2$ to give 3-alkenylnaphthalenes **14a** (92%) and **14b** (91%), respectively. The reduction of naphthalenes **14** with $LiAlH_4$ followed by oxidation with active MnO_2 gave naphthalene-2-carbaldehydes **16a** and **16b** in 89% and 63% yields. Subsequent cleavage of methyl ethers of **16a** and **16b** with BBr_3 afforded 1-hydroxynaphthalenes **17a** (85%) and **17b** (38%), which were treated with *O*-methylhydroxylamine to produce aldoximes **11a** (81%) and **11b** (78%), respectively.

We next examined the construction of 2-azaanthracene **10** using a microwave (MW)-assisted thermal electrocyclic reaction to the aldoxime **11a** (Scheme 4). However, the desired 2-azaanthracene **10** could not be yielded. Therefore, we attempted to convert the naphthalene aldoxime **11a** into a naphoquinone aldoxime **18a** by an oxidation. The naphthalene aldoxime **11a** was subjected to the oxidation reaction using cerium ammonium nitrate (CAN). As a result, scorpinone (**1a**) was isolated as the sole product in 19% yield, however the expected naphth-1,4-quinone **18a** could be not detected. This experimental fact suggested that not only the oxidation reaction occurred, but an azaelectrocyclic ring closure also occurred at the room temperature, consecutively.



Scheme 4

Table 1. One-pot Synthesis of 2-Azaanthraquinone



Run	R^1	R^2	Conditions	Solvent	Time (h)	Temp (°C)	Yield (%)
1	Me	H	CAN	MeCN, H_2O	1.5	rt	**1a**: 19
2	Me	H	$ON(SO_3K)_2$	acetone, H_2O	4	rt	**1a**: 20
3	Me	H	Salcomine, O_2	DMF	3	rt	**1a**: 64
4	Me	H	Salcomine, O_2	DMF	1.5	50	**1a**: 21
5	Me	H	Salcomine, O_2	DMF	3	50	**1a**: 33
6	Me	H	Salcomine, O_2	MeCN	3	rt	**1a**: 42
7	Me	H	Salcomine, O_2	DMSO	3	rt	**1a**: 61
8	H	Me	Salcomine, O_2	DMF	3	rt	**1b**: 49

As shown in Table 1, treatment of **11a** with Fremy's salt afforded scorpinone (**1a**) in low yield (run 2). When salcomine with oxygen[33] was used, product **1a** was obtained in 64% yield (run 3). Although oxidation reactions at slightly high temperatures under the same conditions were investigated (runs 4 and 5), yields of both reactions were not improved. When MeCN or DMSO was used as a solvent instead of DMF was used under the same conditions (runs 6, 7), scorpinone (**1a**) was obtained in 42% and 61% yields, respectively. The condition of run 3 was the most effective procedure in terms of the yield. The physical and spectroscopic data of our synthetic scorpinone (**1a**) were identical to the previously reported data. Furthermore, treatment of the aldoxime **11b** with the best conditions (run 3) afforded the positional isomer of the methyl group, 7,9-dimethoxy-4-methylbenzo[*g*]isoquinoline-5,10-dione (**1b**) in 49% yield (run 8).

In this experiment, the azaelectrocyclic reaction of 1-azahexatriene containing 2,3-double bond of naphthalene **11** did not proceed at 180 ºC in 1,2-dichlorobenzene[25-28] with or without microwave irradiation due to the stable naphthalene **11** of the 10π electron system. By contrast, we have considered that the azaelectrocyclic reaction of naphthoquinone **18** proceeded at room temperature due to the lack of aromaticity.

CONCLUSION

In the present study, we achieved a new and efficient total synthesis of scorpinone (**1a**) in 31% overall yield in seven steps from the readily available known starting material **13**, using a new tandem oxidation and azaelectrocyclic reaction. The overall yield was remarkably improved over that of our earlier report (8% in nine steps).[28] In addition, this new tandem reaction was applied to the synthesis of the positional isomer **1b** of the methyl group. This new tandem reaction would be applicable procedure for a synthesis of other alkaloid possessing a fused pyridine ring system.

EXPERIMENTAL

General Methods: All non-aqueous reactions were carried out under an atmosphere of nitrogen in dried glassware unless otherwise noted. Solvents were dried and distilled according to standard protocols. Analytical thin-layer chromatography was performed with Silica gel $60PF_{254}$ (Merck). Silica gel column chromatography was performed with Silica gel 60N (63-210 mm, KANTO CHEMICAL Co. Ltd.). All melting points were determined on Yanagimoto micro melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a JEOL AL-300 at 300 MHz. Chemical shifts are reported relative to Me_4Si (δ 0.00). NMR spectra were measured with $CDCl_3$ unless otherwise noted. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a JEOL AL-300 at 75 MHz. Chemical shifts are reported relative to $CDCl_3$ (δ 77.0). Infrared spectra were

recorded with ATR method using a Shimadzu FTIR-8000 spectrophotometer and technologies DuraScop. Low and high resolution mass spectra were recorded on JEOL JMS-700 spectrometers by direct inlet system. The reaction of microwave (MW) irradiation was carried out by Discover of CEM Co. Ltd. with 2450 MHz.

Methyl 3-trifluoromethylsulfonyloxy-1,6,8-trimethoxynaphthalene-2-carboxylate 12

Trifluoromethanesulfonic anhydride (0.34 mL, 2.0 mmol) was added to a solution of the 2-naphthol **13** (0.54 mg, 1.9 mmol) and pyridine (0.29 mL, 3.7 mmol) in CH_2Cl_2 (30 mL) under cooling with ice-water. After stirring at rt for 30 min, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2. The organic layer was washed with water, brine, and dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc-hexane (2:8) as an eluent to give the triflate **12** (750 mg, 96%). mp 119-120 ºC. IR (ATR) ν: 1724, 1619 cm^{-1}. ^1H NMR (300 MHz $CDCl_3$) δ: 3.92 (3H, s), 3.93 (3H, s), 3.96 (3H, s), 3.98 (3H, s), 6.59 (1H, d, *J*=2.0 Hz), 6.73 (1H, d, *J*= 2.0 Hz), 7.39 (1H, s). ^{13}C NMR (75 MHz $CDCl_3$) δ: 52.7, 55.5, 56.2, 64.5, 99.2, 100.5, 100.5, 114.6, 115.0, 138.1, 143.9, 157.45, 157.8, 160.4, 164.2. MS (EI) *m/z*: 424 (M^+); HRMS (EI) Calcd for $C_{16}H_{15}F_3O_8S$: 424.0440. Found: 424.0450.

Methyl 1,6,8-trimethoxy-3-(prop-1-en-1-yl)naphthalene-2-carboxylate 14a

A solution of tributyl(propenyl)tin (1.34 g, 4.1 mmol) was added to a mixture of the triflate **12** (1.15 g, 2.7 mmol), $PdCl_2(PPh_3)_2$ (51 mg, 0.27 mmol), and Et_4NCl (674 mg, 4.1 mmol) in DMF (25 mL) at rt under an argon atmosphere. The stirred mixture was heated at 80 ºC for 1.5 h, which was cooled to rt. After being quenched with an aqueous solution of 30% KF (20 mL), and then the mixture was stirred at rt for 30 min. The mixture was filtered off through Celite pad and the filtrate was extracted with EtOAc. The EtOAc layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc-hexane (1:4 v/v) as an eluent to give 3-propenylnaphthalene **14a** (790 mg, 92%). mp 60-62 ºC. IR (ATR) ν: 1731 cm^{-1}. ^1H NMR (300 MHz $CDCl_3$) δ: 1.87 (3H/2, dd, *J*= 1.7, 7.5 Hz), 1.90 (3H/2, d, *J*= 5.6 Hz), 3.86 (3H/2, s), 3.87 (3H/2, s), 3.90 (3H/2, s), 3.91 (3H, s), 3.95 (3H/2, s), 3.96 (3H/2, s), 3.97 (3H/2, s), 5.85-5.96 (1H/2, m), 6.24-6.45 (3H/2, m), 6.49 (1H/2, d, *J*= 2.1 Hz), 6.52 (1H/2, d, *J*= 2.1 Hz), 6.70 (1H/2, d, *J*= 2.1 Hz), 6.71 (1H/2, d, *J*= 2.1 Hz), 7.36 (1H/2, s), 7.53 (1H/2, s). MS (EI) *m/z*: 316 (M^+); HRMS (EI) Calcd for $C_{18}H_{20}O_5$: 316.1311. Found: 316.1318.

Methyl 3-isopropenyl-1,6,8-trimethoxynaphthalene-2-carboxylate 14b

The same procedure as above was carried out using the triflate **12** (100 mg, 0.24 mmol) and tributyl(isopropenyl)tin (0.12 g, 0.35 mmol) to give the 3-isopropenylnaphthalene **14b** (68 mg, 91%). mp 99-100 ºC. IR (ATR) ν: 1724 cm^{-1}. ^1H NMR (300 MHz $CDCl_3$) δ: 2.13 (3H, br s), 3.87 (3H, s), 3.88 (3H, s), 3.90 (3H, s), 3.96 (3H, s), 5.06-5.07 (1H, m), 5.175.18 (1H, m), 6.52 (1H, d, *J*= 2.1 Hz), 6.70 (1H, d, *J*= 2.1 Hz), 7.34 (1H, s). ^{13}C NMR (75 MHz $CDCl_3$) δ: 23.8, 52.1, 55.3, 56.1, 64.0, 98.8, 99.3, 114.4, 115.5, 121.7, 123.4, 138.1, 140.0, 143.6, 154.3, 157.4, 159.1, 169.0. MS (EI) *m/z*: 316 (M^+); HRMS (EI) Calcd for $C_{18}H_{20}O_5$: 316.1311. Found: 316.1291.

[1,6,8-Trimethoxy-3-(prop-1-en-1-yl)naphthalen-2-yl]methanol 15a

A solution of 3-propenylnaphthalene **14a** (1.21 g, 3.84 mmol) in THF (20 mL) was added to a suspension of $LiAlH_4$ (291 mg, 7.68 mmol) in THF (20 mL) under ice-water. The mixture was stirred at rt for 2 h, which was quenched with water, and then the mixture was extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc-hexane (3:7 v/v) as an eluent to give the alcohol **15a** (1 g, 89 %). mp 61-63 ºC. IR (ATR) ν: 2938 cm^{-1}. ^1H NMR (300 MHz $CDCl_3$) δ: 1.80 (6H/5, dd, *J*=1.2, 6.8 Hz), 1.94 (9H/5, dd, *J*=1.7, 6.4 Hz), 3.86 (9H/5, s), 3.89 (6H/5, s), 3.89 (9H/5, s), 3.90 (6H/5, s), 3.97 (9H/5, s), 3.99 (6H/5, s), 4.82 (4H/5, s), 4.89 (6H/5, s), 5.96 (2H/5, dq, *J*=7.2, 11.4 Hz), 6.24 (3H/5, dq, *J*=6.6, 15.6 Hz), 6.48 (3H/5, d, *J*=2.3 Hz), 6.52 (2H/5, d, *J*=2.3 Hz), 6.69 (1H, d, *J*=2.3 Hz), 6.70 (2H/5, d, *J*=11.4 Hz), 6.83 (3H/5, d, *J*=15.6 Hz), 7.31 (2H/5, s), 7.51 (3H/5, s). MS (EI) *m/z*: 288 (M^+); HRMS (EI) Calcd for $C_{17}H_{20}O_4$: 288.1362. Found: 288.1364.

[3-Isopropenyl-1,6,8-trimethoxynaphthalen-2-yl]methanol 15b

The same procedure as above was carried out using the 3-isopropenylnaphthalene **14b** (739 mg, 2.34 mmol) to give the oily alcohol **15b** (458 mg, 68%). IR (ATR) ν: 2939 cm^{-1}. ^1H NMR (300 MHz $CDCl_3$) δ: 2.14-2.15 (3H, m), 2.49 (1H, t, *J*=5.8 Hz), 3.90 (3H, s), 3.92 (3H, s), 3.99 (3H, s), 4.79 (2H, d, *J*=5.8 Hz), 5.00-5.01 (1H, m), 5.27-5.28 (1H, m), 6.52 (1H, d, *J*=2.1 Hz), 6.70 (1H, d, *J*=2.1 Hz), 7.28 (1H, s). ^{13}C NMR (75 MHz $CDCl_3$) δ: 25.3, 55.3, 56.0, 58.5, 62.9, 98.7, 98.9, 114.7, 115.7, 122.1, 126.5, 137.5, 143.9, 145.0, 155.7, 156.9, 158.4. MS (EI) *m/z*: 288 (M^+); HRMS (EI) Calcd for $C_{17}H_{20}O_4$: 288.1362. Found: 288.1376.

1,6,8-Trimethoxy-3-(prop-1-en-1-yl)naphthalene-2-carbaldehyde 16a

A mixture of the alcohol **15a** (374 mg, 1.3 mmol) and activated MnO_2 (1.13 g, 13 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature for 27 h. The reaction mixture was then filtered through a Celite pad and the Celite pad was washed with CH_2Cl_2. The combined CH_2Cl_2 was concentrated under reduced

pressure. The residue was purified by column chromatography (silica gel, 30 g) using EtOAc-hexane (1:9) as an eluent to give the aldehyde **16a** (331 mg, 89%). mp 61-63 ºC. IR (ATR) ν: 1670 cm^{-1}. ^1H NMR (300 MHz $CDCl_3$) δ: 1.82 (21H/37, dd, *J*=2.0, 7.2 Hz), 1.95 (90H/37, dd, *J*=2.0, 6.0 Hz), 3.93 (180H/37, s), 3.94 (21H/37, s), 3.95 (21H/37, s), 4.01 (90H/37, s), 4.02 (21H/37, s), 5.90 (7H/37, dq, *J*=7.2, 11.8 Hz), 6.18 (30H/37, dq, *J*=6.0, 15.5 Hz), 6.15 (30H/37, d, *J*=2.8 Hz), 6.54 (7H/37, d, *J*=2.8 Hz), 6.71 (1H, d, *J*=2.8 Hz), 6.94 (7H/37, d, *J*=11.8 Hz), 7.29 (30H/37, d, *J*=15.5 Hz), 7.47 (1H, s), 10.62 (7H/37, s), 10.65 (30H/37, s). MS (EI) *m/z*: 286 (M^+); HRMS (EI) Calcd for$C_{17}H_{18}O_4$: 286.1205. Found: 286.1180.

3-Isopropenyl-1,6,8-trimethoxynaphthalene-2-carbaldehyde 16b

The same procedure as above was carried out using the alcohol **15b** (384 mg, 1.33 mmol) to give the oily aldehyde **16b** (260 mg, 63%). IR (ATR) ν: 1678 cm^{-1}. ^1H NMR (300 MHz $CDCl_3$) δ: 2.05-2.06 (3H, m), 3.92 (3H, s), 3.95 (3H, s), 4.01 (3H, s), 4.92-4.93 (1H, m), 5.15-5.16 (1H, m), 6.54 (1H, d, *J*=2.2 Hz), 6.71 (1H, d, *J*=2.2 Hz), 7.24 (1H, s), 10.55 (1H, s). ^{13}C NMR (75 MHz $CDCl_3$) δ: 24.1, 55.5, 56.2, 65.1, 99.3, 99.4, 113.5, 14.3, 123.0, 123.8, 140.9, 143.0, 146.8, 158.3, 161.0, 163.7, 190.9. MS (EI) *m/z*: 286 (M^+); HRMS (EI) Calcd for$C_{17}H_{18}O_4$: 286.1205. Found: 286.1216.

1-Hydroxy-6,8-dimethoxy-3-(prop-1-en-1-yl)naphthalene-2-carbaldehyde 17a

To a solution of aldehyde **16a** (331 mg, 1.16 mmol) in CH_2Cl_2 (15 mL) at -78 ºC was added BBr_3 (165 mL, 1.74 mmol), and then the mixture was stirred at an ambient temperature for 3 h. The reaction mixture was quenched with aqueous NH_4Cl, and the mixture was extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc-hexane (3:17 v/v) as an eluent to give the 1-hydroxynaphthalene **17a** (267 mg, 85%). mp 62-64 ºC. IR (ATR) ν: 2938, 1600 cm^{-1}. ^1H NMR (300 MHz $CDCl_3$) δ: 1.75 (3H/3, dd, *J*=2.0, 7.0 Hz), 1.95 (6H/3, dd, *J*=2.0, 7.6 Hz), 3.92 (6H/3, s), 3.93 (3H/3, s), 4.00 (6H/3, s), 4.01 (3H/3, s), 4.02 (21H/37, s), 6.03 (1H/3, dq, *J*=7.0, 11.4 Hz), 6.17 (2H/3, dq, *J*=7.6, 15.5 Hz), 6.45 (2H/3, d, *J*=2.6 Hz), 6.49 (1H/3, d, *J*=2.6 Hz), 6.62 (1H, d, *J*=2.6 Hz), 6.68 (1H/3, d, *J*=11.4 Hz), 6.86 (1H/3, s), 6.89 (2H/3, d, *J*=15.5 Hz), 7.03 (2H/3, s), 10.05 (1H/3, s), 10.21 (2H/3, s), 14.05 (2H/3, br s), 14.25 (1H/3, br s). MS (EI) *m/z*: 272 (M^+); HRMS (EI) Calcd for $C_{16}H_{16}O_4$: 272.1049. Found: 272.1023.

1-Hydroxy-3-isopropenyl-6,8-dimethoxynaphthalene-2-carbaldehyde 17b

The same procedure as above was carried out using the aldehyde **15b** (365 mg, 1.27 mmol) to give the 1-hydroxynaphthalene **17b** (132 mg, 38%). mp 84-85 ºC. IR (ATR) ν: 2939, 1604 cm^{-1}. ^1H NMR (300

MHz $CDCl_3$) δ: 2.15-2.16 (3H, m), 3.91 (3H, s), 4.00 (3H, s), 5.03-5.04 (1H, m), 5.38-5.39 (1H, m), 6.47 (1H, d, *J*=2.2 Hz), 6.62 (1H, d, *J*=2.2 Hz), 6.90 (1H, s), 10.00 (1H, s), 14.28 (1H, s). ^{13}C NMR (75 MHz $CDCl_3$) δ: 25.6, 55.5, 56.2, 98.5, 99.6, 110.3, 111.4, 117.0, 117.0, 117.8, 141.8, 142.2, 144.1, 161.1, 162.4, 162.4, 165.7, 195.0. MS (EI) *m/z*: 272 (M^+); HRMS (EI) Calcd for $C_{16}H_{16}O_4$: 272.1049. Found: 272.1068.

1-Hydroxy-6,8-dimethoxy-3-(prop-1-en-1-yl)naphthalene-2-carbaldehyde *O*-methyloxime 11a

A mixture of the 1-hydroxynaphthalene **17a** (267 mg, 0.98 mmol), $MeONH_2$•HCl (164 mg, 1.96 mmol), and AcONa (161 mg, 1.96 mmol) in EtOH (20 mL) was heated at 80 ºC for 3 h. After removal of solvent followed by addition of water, the mixture was extracted with EtOAc. The EtOAc layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc-hexane (1:4 v/v) as an eluent to give the oxime **11a** (238 mg, 81%). IR (ATR) ν: 2935 cm^{-1}. ^{1}H NMR (300 MHz $CDCl_3$) δ: 1.63 (9H/4, dd, *J*=1.8, 6.9 Hz), 1.85 (3H/4, dd, *J*=1.8, 6.7 Hz), 3.82 (3H/4, s), 3.82 (9H/4, s), 3.90 (9H/4, s), 3.92 (3H/4, s), 3.93 (3H/4, s), 3.93 (9H/4, s), 5.86 (3H/4, dq, *J*=6.9, 11.4 Hz), 6.05 (1H/4, dq, *J*=6.7, 16.5 Hz), 6.37 (1H/4, d, *J*=2.0 Hz), 6.40 (3H/4, d, *J*=2.0 Hz), 6.49 (3H/4, d, *J*=11.4 Hz), 6.55 (3H/4, d, *J*=2.0 Hz), 6.56 (1H/4, d, *J*=2.0 Hz), 6.70 (1H/4, d, *J*=16.5 Hz), 6.89 (1H, s), 7.08 (1H/4, s), 7.19 (3H/4, s), 11.12 (1H/4, br s), 11.49 (3H/4, br s). MS (EI) *m/z*: 301 (M^+); HRMS (EI) Calcd for $C_{17}H_{19}NO_4$: 301.1314. Found: 301.1318.

1-Hydroxy-3-isopropenyl-6,8-dimethoxynaphthalene-2-carbaldehyde *O*-methyloxime 11b

The same procedure as above was carried out using the 1-hydroxynaphthalene **17b** (87 mg, 0.32 mmol) to give the oxime **11b** (76 mg, 78%). mp 72-74 ºC. IR (ATR) ν: 2935 cm^{-1}. ^{1}H NMR (300 MHz $CDCl_3$) δ: 2.08 (3H, br s), 3.90 (3H, s), 3.97 (3H, s), 4.01 (3H, s), 4.95-6.96 (1H, m), 5.30-5.31 (1H, m), 6.48 (1H, d, *J*=2.2 Hz), 6.62 (1H, d, *J*=2.2 Hz), 6.98 (1H, s), 8.45 (1H, s), 11.67 (1H, s). ^{13}C NMR (75 MHz $CDCl_3$) δ: 25.4, 55.3, 56.2, 62.3, 98.4, 98.8, 106.8, 111.0, 116.8, 117.1, 138.4, 143.2, 143.9, 150.5, 157.1, 159.3, 159.7. MS (EI) *m/z*: 301 (M^+); HRMS (EI) Calcd for $C_{17}H_{19}NO_4$: 301.1314. Found: 301.1325.

Scorpinone 1a

A mixture of oxime **11a** (20 mg, 0.066 mmol) and salcomine (4.3 mg, 0.013 mmol) in DMF (5 mL) under bubbling O_2 was stirred at rt for 3 h. After being quenched with water, a reaction mixture was extracted with EtOAc. The EtOAc layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc-hexane (1:1 v/v) as an eluent to give scorpinone **1a** (12 mg, 64%). mp 193-196 ºC. IR (ATR) ν: 1678, 1673 cm^{-1}. ^{1}H NMR (300 MHz $CDCl_3$) δ: 2.79 (3H, s), 3.99 (3H, s), 4.03 (3H, s), 6.82 (1H, d, *J*=2.7 Hz), 7.44 (1H, d, *J*=2.7 Hz), 7.81 (1H, s), 9.41 (1H, s). ^{13}C NMR (75 MHz $CDCl_3$) δ: 25.1, 56.1,

56.6, 103.6, 105.5, 115.7, 117.5, 125.5, 137.0, 137.5, 149.8, 162.8, 164.2, 165.0, 180.6, 183.6. MS (EI) *m/z*: 283 (M^+); HRMS (EI) Calcd for $C_{16}H_{13}NO_4$: 283.0845. Found: 283.0819.

7,9-Dimethoxy-4-methylbenzo[*g*]isoquinoline-5,10-quinone 1b

The same procedure as above was carried out using the oxime **11b** (25 mg, 0.086 mmol) to give the benzoisoquinoline-5,10-dione **13** (12 mg, 49%). mp 235-237 ºC. IR (ATR) ν: 1655, 1577 cm^{-1}. ^1H NMR (300 MHz $CDCl_3$) δ: 2.75 (3H, s), 4.00 (3H, s), 4.03 (3H, s), 6.82 (1H, d, *J*=2.7 Hz), 7.40 (1H, d, *J*=2.7 Hz), 8.81 (1H, s), 9.41 (1H, s). ^{13}C NMR (75 MHz $CDCl_3$) δ: 19.1, 56.0, 56.6, 103.4, 104.9, 115.3, 128.2, 132.4, 134.7, 138.0, 148.3, 157.0, 162.4, 165.2, 180.9, 185.2. MS (EI) *m/z*: 283 (M^+); HRMS (EI) Calcd for $C_{16}H_{13}NO_4$: 283.0845. Found: 283.0833.

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