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Studies on the oxidative cyclization of 3-hydroxyalkyl-1,2,4-trialkoxynaphthalenes and synthetic application for the biologically active natural compound rhinacanthone

Tokutaro Ogata [a], Misae Doe [a], Aya Matsubara [a], Eri Torii [a], Chiaki Nishiura [a], Arisa Nishiuchi [a], Yusuke Kobayashi [b], Tetsutaro Kimachi [a,*]

[a] School of Pharmaceutical Sciences, Mukogawa Women's University, 11-68 Koshien Kyu-bancho, Nishinomiya 663-8179, Hyogo, Japan
[b] Graduate School and Faculty of Pharmaceutical Sciences, Kyoto University, 46-29 Yoshida Shimoadachicho, Sakyo-ku, Kyoto 606-8501, Japan

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ABSTRACT

The oxidative intramolecular cyclization of 3-hydroxyalkyl-1,2,4-trimethoxynaphthalenes was investigated. A series of 1,2-naphthoquinone fused cyclic ethers were synthesized directly from 3-hydroxyalkyl-1,2,4-trimethoxynaphthalenes by exposure to diammonium cerium (IV) nitrate. To understand the reaction mechanism, the intramolecular cyclization of 3-hydroxyalkyl-naphthoquinones that were formed as reaction intermediates was also examined. The results suggested that the reaction proceeds by a stepwise oxidation–cyclization mechanism. Using this methodology, five-step synthesis of rhinacanthone was achieved with high yield.

1. Introduction

We previously reported that CAN (diammonium cerium (IV) nitrate) oxidation of 3-hydroxyalkyl-1,2,4-trialkoxynaphthalene derivative (**1**) regarded as the reduced 2-hydroxy-1,4-naphthoquinone (lawsone) equivalent afforded (*R*)-(−)-dehydroiso-β-lapachone (**4**) in high yield.[1] Initially, we considered that the CAN oxidation would give a mixture of **2**, **3**, **4**, and **5**. Contrary to expectation, **2** and **3** were not obtained, but (*R*)-(−)-dehydroiso-β-lapachone (**4**) was obtained with a small amount of **5** (Fig. 1).

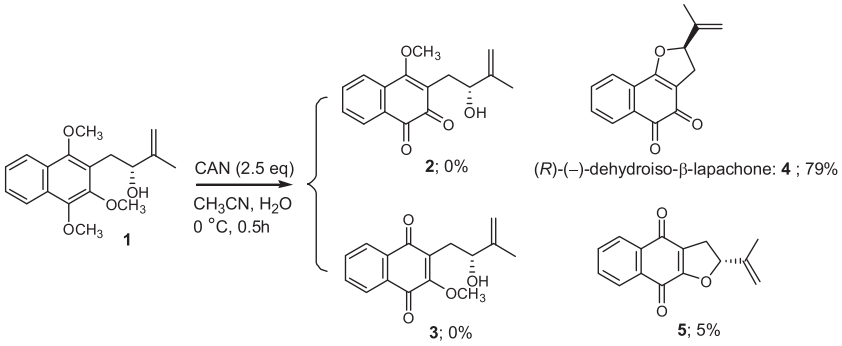

Fig. 1. Previous study of the synthesis of (−)-dehydroiso-β-lapachone.[1]

This interesting result prompted us to continue development of the new method to synthesize 1,2-naphthoquinones containing cyclic ether functions by CAN oxidation of the naphthalene

* Corresponding author. Tel./fax: +81 798 45 9952; e-mail address: tkimachi@mukogawa-u.ac.jp (T. Kimachi).

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derivatives having the hydroxyl group at side chains and accompanying intramolecular cyclization. In this study, four 3-hydroxyalkyl-1,2,4-trimethoxynaphthalenes (**8**, **9**, **11**, and **13**), which have a hydroxyl group at the end of each alkyl side chain, were prepared as substrates and subjected to CAN oxidation (Fig. 2). The brief consideration of the reaction mechanism of this oxidation including intramolecular cyclization is also described. We applied this method to the convenient synthesis of the biologically active natural product rhinacanthone.

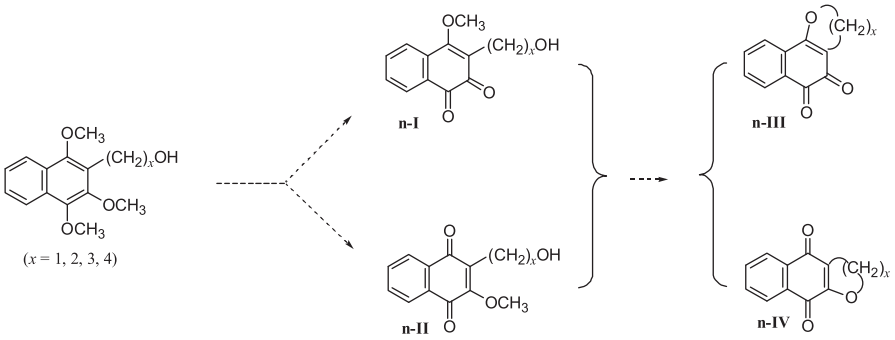


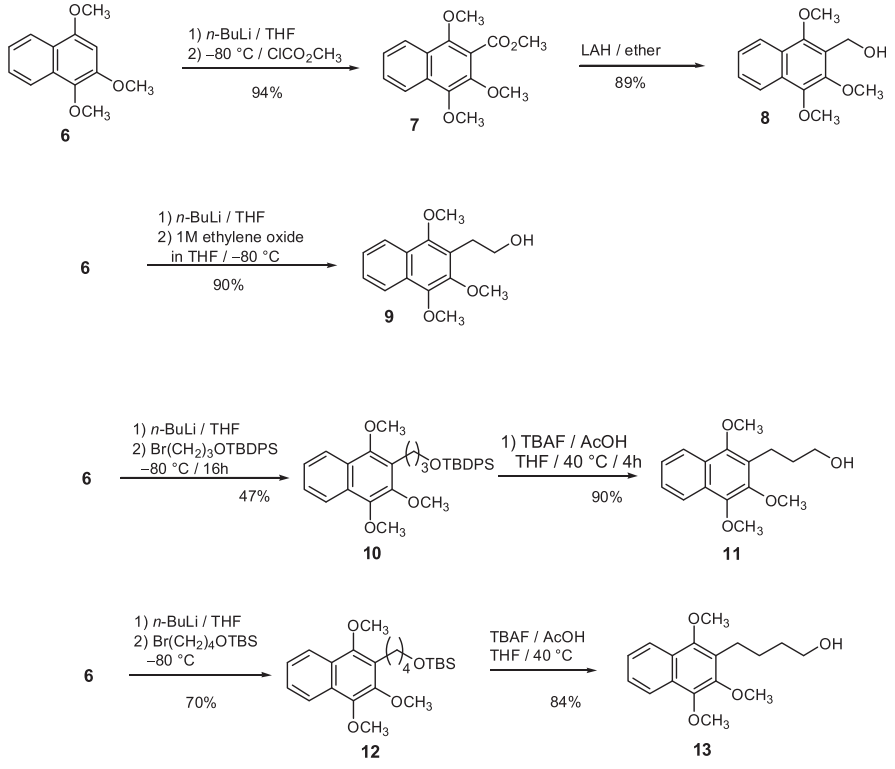
Fig. 2. Development of the synthesis of novel oxidative naphthoquinones linked by intramolecular ether bond formation (this study).

2. Results and discussion

Initial study began with the synthesis of compounds **8**, **9**, **11**, and **13** from 1,2,4-trimethoxynaphthalene (**6**). According to the known procedure, directed ortho lithiation–substitution reaction of **6** and subsequent quenching with suitable electrophiles afforded the corresponding 3-substituted-1,2,4-trimethoxynaphthalenes (**7**, **9**, **10**, and **12**).[2] Compound **9** was directly used as the starting substrate. Ester **7** was converted to **8** by lithium aluminum hydride ($LiAlH_4$) reduction. The silyl ethers **10** and **12** were treated with acidic tetrabutylammonium fluoride (TBAF) to lead to **11** and **13**, respectively. The spectroscopic data of all derived compounds (**8**, **9**, **11** and **13**) supported their chemical structures (Scheme 1) (For details, see the Experimental procedures).

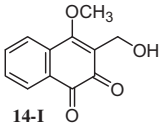
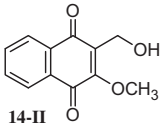
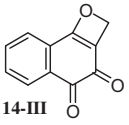
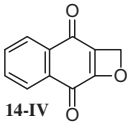
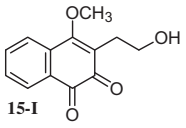
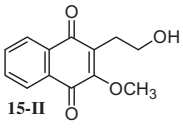
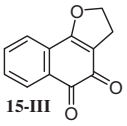
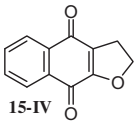
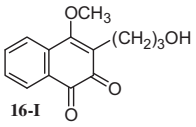
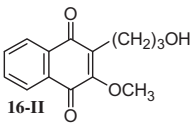
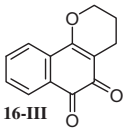
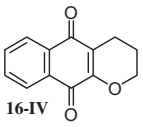
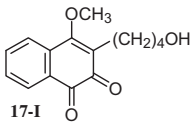
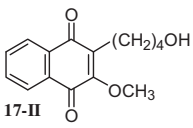
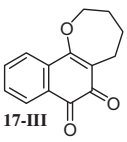
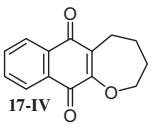
We carried out CAN oxidation of naphthalenes (**8**, **9**, **11**, and **13**) according to our reported procedure.[1] Acetonitrile solution of each compound was stirred at 0 °C with aqueous CAN solution. The reaction mixture was worked up and purified to give the corresponding products in pure form. The structures of the compounds have been elucidated by spectroscopic analyses. The results summarized in Table 1 showed that we obtained two sets of isomers. One of them was a pair of naphthoquinones having hydroxyalkyl side chains, such as *n*-**I** and *n*-**II** (*n*=**14**–**17**), and the other was a pair of naphthoquinones, such as *n*-**III** and *n*-**IV**, (*n*=**14**–**17**) containing the fused cyclic ether function.

CAN oxidation of naphthalene derivative **8** afforded equal amounts of **14-I** and **14-II**, but did not afford four-membered ring compounds, such as **14-III** and **14-IV** (entry 1). Oxidation of **9** and **11** mainly afforded naphthoquinones **15-III** and **16-III** with small amounts of **15-IV** and **16-IV**, respectively (entries 2 and 3). On the other hand, from these same entries, *n*-**I** and *n*-**II** (*n*=**15** and **16**)



Scheme 1. Synthesis of four 3-hydroxyalkyl-1,2,4-trimethoxynaphthalenes (**8**, **9**, **11**, and **13**).

Table 1
Oxidation of naphthalene derivatives (**8**, **9**, **11**, and **13**) with CAN

Entry			Compounds (yield%)			
1	**8**	condition →	 **14-I** (46%)	 **14-II** (40%)	 **14-III** (0%)	 **14-IV** (0%)
2	**9**	condition →	 **15-I** (0%)	 **15-II** (8%)	 **15-III** (56%)	 **15-IV** (6%)
3	**11**	condition →	 **16-I** (0%)	 **16-II** (0%)	 **16-III** (67%)	 **16-IV** (7%)
4	**13**	condition →	 **17-I** (8%)	 **17-II** (34%)	 **17-III** (20%)	 **17-IV** (8%)

Reaction conditions: CAN (2.5 equiv), CH_3CN/H_2O=1:1, 0 °C, 0.5 h.

were not isolated except a small amount of **15-II**. The results of these three entries suggest that the naphthalene derivatives initially oxidized by CAN and then the derived naphthoquinones (*n*-**I** and *n*-**II**, *n*=**15** and **16**) are facilitated to be cyclized in intramolecular manner. The disappearance of *n*-**I** and *n*-**II** could be interpreted on the ease of cyclization to form five- or six-membered ring compounds, which could be supported from the basis of the Baldwin's rules. Furthermore, the oxidation of **9** and **11** mainly afforded the corresponding *o*-quinone derivatives (**15-III** and **16-III**) rather than *p*-quinone derivatives (**15-IV** and **16-IV**). In the intramolecular cyclization, nucleophilic OH attack of the carbon located at the benzylic position and also the β-position of the conjugated system must be preferred.[3] To ensure the hypothesis described above, CAN oxidation of **13** was carried out. The formation of seven-membered ring is also favorable, but the cyclization is slower than that of five- or six-membered system according to the Baldwin's rules. Thus, it may be possible to isolate **17-I** and **17-II** as the intermediates of the oxidative cyclization. This is the reason why we prepared **13**. The result was illustrated in entry 4 in Table 1.

CAN oxidation of **13** gave conceivable products with substantial amounts of **17-II** relative to **17-I**, **17-III**, and **17-IV** (entry 4). The prolonged reaction time, or the reaction under the elevated temperature in the oxidation of **13** did not improve the yield of cyclic ethers (**17-III** and **17-IV**). Furthermore, the same reaction with the excess amount of CAN afforded decomposed complex mixtures. The result that **17-I** and **17-II** were accumulated and isolated strongly support stepwise oxidation–cyclization reaction. It is noteworthy that seven-membered ring compounds were directly formed by the oxidative intramolecular cyclization with a linear alkyl side chain, although the yields of the cyclized products (**17-III** and **17-IV**) were not satisfactory. The plausible reaction path of the oxidative intramolecular cyclization is visualized in Fig. 3. It shows that the starting 1,2,4-trimethoxynaphthalene derivatives were oxidized to naphthoquinone intermediates *n*-**I** and *n*-**II** (*n*=**14**, **15**, **16**, and **17**) with subsequent cyclization to produce *n*-**III** and *n*-**IV**, if possible. In order to support this hypothesis, additional experiments were carried out and the results were summarized in Table 2. Isolated or separately prepared *n*-**I** and *n*-**II** (*n*=**15** and **16**) were

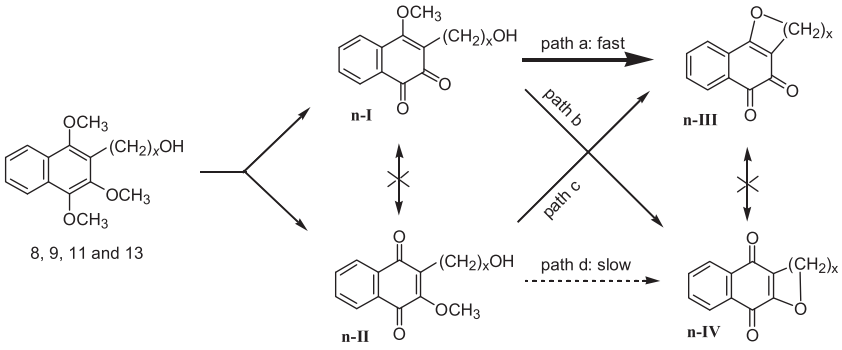


Fig. 3. Plausible reaction paths of the oxidative intramolecular cyclization.

Table 2
Additional experiments for the intramolecular cyclization and ring re-opening of *n*-**I**, *n*-**II**, *n*-**III**, and *n*-**IV** with CAN[a]

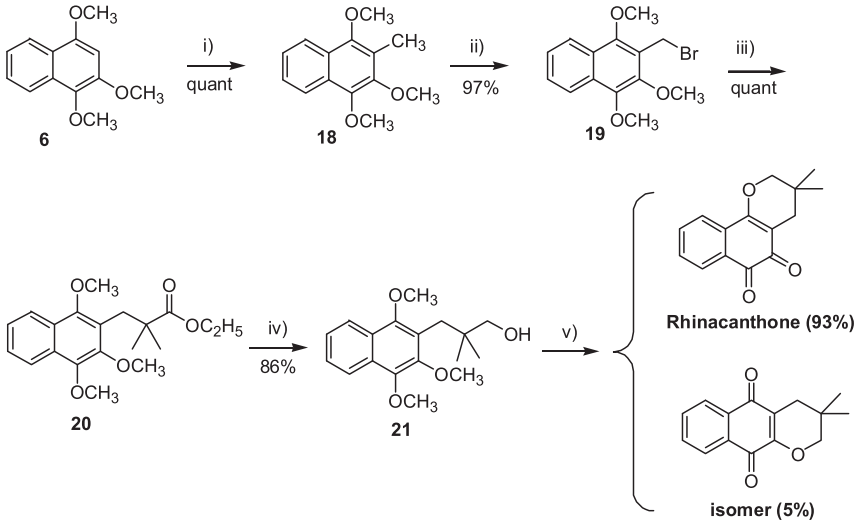
Entry	Substrate	Product ratio (%)[b]			
		I	**II**	**III**	**IV**
1	**14-I**	100	—	—	—
2	**14-II**	—	100	—	—
3	**15-I**	—	—	83	17
4[c]	**15-II**	—	—	—	—
5	**16-I**	5	—	95	—
6	**16-II**	—	81	19	—
7[d]	**16-II**	—	29	71	—
8	**17-I**	62	—	38	—
9[d]	**17-I**	50	—	50	—
10	**17-II**	—	100	—	—
11[e]	*n*-**III**	—	—	100	—
12[e]	*n*-**IV**	—	—	—	100

[a] Reaction conditions: CAN (2.5 equiv), CH_3CN/H_2O=5:3, 0 °C, 0.5 h.
[b] The ratio of these compounds was calculated from the crude mixture of the products by ^1H NMR analysis.
[c] A complex mixture was formed with no assignable product.
[d] The reaction was performed in the absence of H_2O.
[e] *n*=**15**, **16**, **17**.

Also, it was found that the water in the reaction might slow the cyclization, probably due to the nucleophilicity of the oxygen atom in a water molecule to the alcohol moiety of naphthoquinones (*n*-**I** and *n*-**II**). Thus, these results indicate that the one-pot reaction of 1,2,4-trimethoxynaphthalene derivatives with CAN proceeds by an initial oxidation to form naphthoquinones followed by highly regioselective intramolecular cyclization.

With the aim of advancing this methodology based on the new CAN oxidation intramolecular cyclization connection, we report an application for the synthesis of 3,4-dihydro-3,3-dimethyl-2*H*-naphtho[1,2-*b*]pyran-5,6-dione (rhinacanthone) (Scheme 2).

Rhinacanthone, which is isolated from a shrub widely distributed in Southeast Asia; *Rhinacanthus nasutus*, is a naturally occurring biologically active compound having antitumor activity against various cancer cells.[5] To date, there have been reports on the synthesis of rhinacanthone by two groups.[6,7] Both groups reported eight-step synthesis in 17% and 48% total yields, respectively. However, the reported methods are insufficient to enable expansion of the study of rhinacanthone and its analogs from the medicinal chemistry viewpoint. Improvement of the chemical yield and shortening of the reaction steps for the synthesis of this natural



Scheme 2. Five-step synthesis of rhinacanthone. Reagents and conditions: i) 1) *n*-BuLi, THF, 0 °C to rt. 2) CH_3I, −80 °C. ii) NBS, $CHCl_3$, reflux, 3 h. iii) LDA, ethyl isobutyrate, −80 °C. iv) $LiAlH_4$, THF, rt. v) CAN (2.5 equiv), CH_3CN/H_2O (1/1), 0 °C, 0.5 h.

solely mixed with aqueous CAN solution.[4] Further reaction of **14-I** or **14-II** did not occur (entries 1, 2). The reaction of **15-I** with aqueous CAN gave cyclized compound **15-III** as a major product with a small amount of **15-IV** (entry 3). Similar reaction of **16-I** or **16-II** with aqueous CAN gave the cyclized compound **16-III** with complete selectivity against the compound **16-IV** (entries 5, 6). On the other hand, oxidation of **17-I** afforded **17-III** with recovery of the starting material, while **17-II** was intact against the reaction mixture containing CAN (entries 8, 10). The cyclization of 1,4-naphthoquinones *n*-**II** was effectively accelerated when the reaction was carried out in the absence of water (entries 7, 9). In addition, the probability of inter-conversion between *n*-**III** and *n*-**IV** was tested, but the ring re-opening reaction of *n*-**III** and *n*-**IV** was not observed under the same conditions (entries 11, 12). These results suggest that cyclization of naphthoquinone intermediates *n*-**I** and *n*-**II** (except **17-II**) proceeds smoothly to afford *n*-**III** (*n*=**15**, **16**, and **17**) but intramolecular cyclization of **17-II** occurs very slowly. In particular, the reaction pathway from *n*-**I** to *n*-**III** (path a) seems much faster than the others. The order of the rate of this intramolecular cyclization is considered to be path a>path b, c>>path d.

product are needed. The construction of this naphthopyrandione structure was initiated by novel four-step synthesis of **21** using a conventional ortho-lithiation method through the known precursors **18**, **19**, and **20** shown in Scheme 2. Precursor **21** was converted to rhinacanthone by exposure to CAN oxidation. The obtained rhinacanthone and a small amount of the isomer showed analytical and spectroscopic data consistent with those reported elsewhere.[6] Finally, five-step synthesis of rhinacanthone in excellent yield (78% overall) proved the utility of this methodology.

3. Conclusion

Four 3-hydroxyalkyl-1,2,4-trimethoxynaphthalenes (**8**, **9**, **11**, and **13**), which have a hydroxyl group at the end of each alkyl side chain, were prepared and subjected to CAN oxidation reaction to afford naphthoquinone derivatives containing a fused cyclic ether function. The reaction was suggested to proceed by the stepwise oxidation–cyclization mechanism. Using this methodology, five-step synthesis of rhinacanthone from known 1,2,4-trimethoxynaphthalene was achieved in high yield.

4. Experimental

4.1. General

All materials not explicitly mentioned were purchased from Wako Pure Chemical Products Co., Kanto Chemical Co., TCI Laboratory Chemical Co., and Aldrich Chemical Co. ^{1}H NMR spectra were recorded on a JEOL JNM-ECP400 or JNM-ECP500 spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts are recorded in parts per million (ppm) relative to TMS. ^{13}C NMR spectra were proton decoupled and recorded on a JEOL JNM-ECP400 or JNM-ECP500 spectrometer using the carbon signal of the deuterated solvent as the internal standard. Mass spectra (MS) were obtained on JEOL JMS-700 instruments. Melting points were measured on a Yanaco micro melting point apparatus and are uncorrected. Flash chromatography was performed with silica gel (Wakosil C-200) obtained from Wako Pure Chemical Products Co. Analytical thin layer chromatography was performed on Merck Silica Gel 60 F_{254} aluminum sheets and the visualization was performed using a UV lamp.

*4.1.1. 1,3,4-Trimethoxy-2-naphthalenecarboxylic acid methyl ester (**7**).* A frame-dried round bottom flask was charged with a solution of 1,2,4-trimethoxynaphthalene (**6**) (2.18 g, 10 mmol) in anhydrous tetrahydrofuran (THF) (12 mL) under argon atmosphere. *n*-BuLi (7.5 mL, 12 mmol, 1.6 M in *n*-hexane solution) was added to the solution prepared above at 0 °C and the reaction mixture was stirred for 2 h at room temperature. The mixture was re-cooled to 0 °C and methyl chloroformate (3.1 mL, d=1.22 g/cm^3, 40 mmol) was added dropwise. After checking by thin layer chromatography (TLC), the reaction mixture was worked up with addition of satd aqueous NH_4Cl and AcOEt. The mixture was separated and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with 1% aqueous $Na_2S_2O_3$, water, brine and dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by flash chromatography (hexane/AcOEt=8:1) to afford 2.58 g (93%) of 1,3,4-trimethoxy-2-naphthalenecarboxylic acid methyl ester (**7**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.98 (s, 3H, OCH_3), 3.99 (s, 6H, OCH_3 ×2), 4.00 (s, 3H, OCH_3), 7.47 (t, 1H, J=8.2 Hz, aryl–H), 7.54 (t, 1H, J=8.2 Hz, aryl–H), 8.06 (d, 1H, J=8.2 Hz, aryl–H), 8.11 (d, 1H, J=8.2 Hz, aryl–H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 52.5 (CH_3), 61.1 (CH_3), 61.6 (CH_3), 63.3 (CH_3), 121.1 (CH), 121.9 (CH), 122.8 (CH), 125.3 (CH), 125.5 (C), 127.4 (C), 130.2 (C), 143.5 (C), 145.3 (C), 149.8 (C), 166.6 (C). IR (cm^{-1}) ν 2940, 1728, 1620, 1598, 1230, 1060. HRMS calcd for $C_{15}H_{16}O_5$: 276.0998. Found: 276.1002.

*4.1.2. (1,3,4-Trimethoxynaphthalen-2-yl)-methanol (**8**).* To a stirred 60 mL ethereal solution of methyl ester (**7**) (2.58 g, 9.3 mmol), was added lithium aluminum hydride (LAH) (777 mg, 20.4 mmol) at 0 °C. The ice bath was removed and the mixture was stirred for 2 h at room temperature. The excess LAH was quenched with addition of AcOEt. The mixture was extracted three times with diethyl ether. The combined ether layer was washed with water, brine, and then dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (hexane/AcOEt=3:1) to afford (1,3,4-trimethoxynaphthalen-2-yl)-methanol (**8**) (2.2 g, 8.8 mmol) (95%). ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.62 (m, 1H, CH_2OH), 3.98 (s, 6H, OCH_3 ×2), 4.07 (s, 3H, OCH_3), 7.43–7.54 (m, 2H, aryl–H), 8.03–8.12 (m, 2H, aryl–H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 56.4 (CH_3), 61.0 (CH_3), 61.3 (CH_3), 121.7 (CH), 122.5 (CH ×2), 125.3 (C), 125.5 (CH), 126.5 (C), 129.5 (C), 143.5 (C), 147.9 (C), 150.7 (C). IR (cm^{-1}) ν 3500, 2920, 1620, 1598, 1360, 1060. HRMS calcd for $C_{14}H_{16}O_4$: 248.1049. Found: 248.1055. LRMS (EI) m/z 248 (M+100), 233 (62), 205 (45), 173 (11), 161 (12), 15 (7), 129 (7).

*4.1.3. 2-(1,3,4-Trimethoxynaphthalen-2-yl)-ethanol (**9**).* A frame-dried round bottom flask was charged with a solution of **6** (1.1 g, 5 mmol) in anhydrous tetrahydrofuran (THF) (6 mL) under argon atmosphere. *n*-BuLi (3.75 mL, 6 mmol, 1.6 M in *n*-hexane solution) was added to the solution prepared above at 0 °C and the reaction mixture was stirred for 2 h at room temperature. The mixture was cooled to −80 °C and ethylene oxide solution (6.0 mL, 1 M solution in THF) was added. The dry ice bath was removed and the mixture was warmed to room temperature. After checking by TLC, the reaction mixture was worked up with addition of satd aqueous NH_4Cl and AcOEt. The mixture was separated and the aqueous layer was extracted three times with AcOEt. The combined organic layer was washed with water, brine and dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by flash chromatography (hexane/AcOEt=2:1) to afford 1.17 g, 90% of 2-(1,3,4-trimethoxynaphthalen-2-yl)-ethanol (**9**) as a white solid. Mp 56–61 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (br s, 1H, OH), 3.13 (t, 2H, J=6.2 Hz, CH_2), 3.89 (t, 2H, J=6.2 Hz, CH_2), 3.92 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 7.43 (m, 1H, aryl–H), 7.47 (m, 1H, aryl–H), 7.99 (dd, 1H, J=1.5, 7.0 Hz, aryl–H), 8.09 (dd, 1H, J=1.0, 7.0 Hz, aryl–H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3 (CH_2), 60.85 (CH_3), 60.9 (CH_3), 62.2 (CH_3), 63.4 (CH_2), 121.7 (CH), 122.1 (CH), 124.0 (CH), 125.1 (CH), 125.4 (C), 125.9 (CH), 128.7 (C), 143.7 (C), 148.0 (C), 150.7 (C). HRMS calcd for $C_{15}H_{18}O_4$: 262.1205. Found: 262.1202.

*4.1.4. tert-Butyl-diphenyl-[3-(1,3,4-trimethoxynaphthalen-2-yl)-propoxy]-silane (**10**).* A frame-dried round bottom flask was charged with a solution of **6** (872 mg, 4.0 mmol) in anhydrous tetrahydrofuran (THF) (5 mL) under argon atmosphere. *n*-BuLi (3.7 mL, 4 mmol, 1.6 M *n*-hexane solution) was added to the solution prepared above at 0 °C and the reaction mixture was stirred for 2 h at room temperature. Next, the mixture was cooled to −80 °C, and (3-bromo-propoxy)-*tert*-butyl-diphenylsilane (1.9 g, 6.0 mmol) solution in THF (5 mL) was added via cannula and the mixture was stirred for 15 h. The reaction mixture was worked up by addition of satd aqueous NH_4Cl and AcOEt. The mixture was separated and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with water, brine and dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by flash chromatography (hexane/AcOEt=6:1) to afford 975 mg (47%) of *tert*-butyl-diphenyl-[3-(1,3,4-trimethoxynaphthalen-2-yl)-propoxy]-silane (**10**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (s, 9H, Si(CH_3)$_3$), 1.88 (m, 2H, CH_2), 2.90 (m, 2H, CH_2), 3.81 (t, 2H, J=6.2 Hz, CH_2OH), 3.88 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 7.35–7.47 (m, 8H, aryl–H), 7.71 (m, 4H, aryl–H), 8.00 (m, 1H, aryl–H), 8.07 (m, 1H, aryl–H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3 (C), 21.8 (CH_2), 26.9 (CH_3), 33.7 (CH_2), 60.8 (CH_3), 62.2 (CH_3), 64.3 (CH_2), 121.5 (CH), 122.1 (CH), 124.8 (CH), 125.5 (CH), 127.6 (CH), 127.8 (CH), 128.2 (CH), 129.5 (C), 134.2 (C), 135.5 (C), 135.6 (C), 143.5 (C), 148.5 (C), 150.2 (C). HRMS calcd for $C_{32}H_{38}O_4Si$: 514.2539. Found: 514.2537. LRMS (EI) m/z 514 (M+53), 457 (86), 442 (100), 427 (30), 333 (22).

*4.1.5. 3-(1,3,4-Trimethoxynaphthalen-2-yl)-propan-1-ol (**11**).* TBDPS ether (**10**) (900 mg, 1.75 mmol) was dissolved in THF (10 mL) and cooled in ice bath. To the mixture, was added tetrabutylammonium fluoride (TBAF) (5.3 mL, 5.3 mmol, 1 M solution in THF) and acetic acid (0.2 mL, 3.5 mmol) followed by stirring for 40 min at 40 °C and working up. AcOEt and water was added to the mixture and separated. The aqueous layer was saturated by the addition of NaCl solid and then extracted twice with AcOEt. The combined organic layer was washed with satd aqueous $NaHCO_3$, brine and dried over $MgSO_4$. The filtrate was concentrated in vacuo and purified by flash chromatography (AcOEt) to afford 433 mg (1.57 mmol, 90%) of 3-(1,3,4-trimethoxynaphthalen-2-yl)-propan-1-ol (**11**) as a white solid. Mp 72–73 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89 (quint, 2H, J=7.0 Hz, CH_2), 2.51 (t, 1H, J=7.0 Hz, OH), 2.94 (t, 2H, J=7.0 Hz, CH_2), 3.54 (q, 2H, J=5.9 Hz, CH_2), 3.93 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 4.0

(s, 3H, OCH_3), 7.45 (m, 2H, Ar*H*), 8.04 (m, 2H, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5 (CH_2), 32.7 (CH_2), 60.9 (CH_3), 61.0 (CH_3), 61.3 (CH_2), 62.3 (CH_3), 121.7 (CH), 122.0 (CH), 125.0 (CH), 125.7 (CH), 126.3 (C), 128.4 (C), 143.7 (C), 148.2 (C), 150.2 (C). HRMS calcd for $C_{16}H_{20}O_4$: 276.1362. Found: 276.1361.

*4.1.6. tert-Butyldimethyl-[4-(1,3,4-trimethoxynaphthalen-2-yl)-butoxy]-silane (**12**).* A frame-dried round bottom flask was charged with a solution of **6** (1.09 g, 5.0 mmol) in anhydrous THF (7 mL) under argon atmosphere. *n*-BuLi (3.6 mL, 6 mmol, 1.6 M *n*-hexane solution) was added to the solution prepared above at 0 °C and the reaction mixture was stirred for 2 h at room temperature. The mixture was cooled to −80 °C and (4-bromobutoxy)-*tert*-butyldimethylsilane (1.9 g, 5.1 mmol) solution in THF (1 mL) was added via cannula and the mixture was stirred for 48 h. The reaction mixture was worked up by addition of satd aqueous NH_4Cl and AcOEt. The mixture was separated and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with water, brine and dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by flash chromatography (hexane/AcOEt=6:1) to afford 1.42 g (70%) of desired *tert*-butyldimethyl-[4-(1,3,4-trimethoxynaphthalen-2-yl)-butoxy]-silane (**12**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 6H, Si(CH_3)$_2$), 0.89 (s, 9H, Si-*tert*-C(CH_3)$_3$), 1.62–1.71 (m, 4H, CH_2 ×2), 2.81 (t, 2H, *J*=7.3 Hz, CH_2), 3.66 (m, 2H, CH_2OSi), 3.90 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 7.39 (td, 2H, *J*=6.0, 2.0 Hz, aryl–*H* ×2), 7.99 (dd, 1H, *J*=2.0, 7.0 Hz, aryl–*H*), 8.08 (dd, 1H, *J*=2.0, 7.0 Hz, aryl–*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ −2.9 (CH_3), 18.3 (C), 26.0 (CH_3), 60.8 (CH_3), 62.3 (CH_3), 63.1 (CH_3), 121.6 (CH), 122.1 (CH), 124.8 (CH), 125.4 (C), 125.5 (CH), 128.0 (C), 128.2 (C), 143.5 (C), 148.5 (C), 150.1 (C). HRMS calcd for $C_{23}H_{36}O_4Si$: 404.2383. Found: 404.2382.

*4.1.7. 4-(1,3,4-Trimethoxynaphthalen-2-yl)-butanol (**13**).* TBS ether (**12**) (1.37 g, 3.4 mmol) was dissolved in THF (20 mL) and cooled in an ice bath. To the mixture, was added TBAF (9.5 mL, 9.5 mmol, 1 M solution in THF) and acetic acid (0.4 mL, 6.8 mmol), and the mixture was stirred for 40 min at 40 °C then for 18 h at room temperature and worked up. AcOEt and water were added to the mixture, and after separation, the aqueous layer was saturated by the addition of NaCl solid and then extracted twice with AcOEt. The combined organic layer was washed with satd aqueous $NaHCO_3$, brine and dried over $MgSO_4$. The filtrate was concentrated in vacuo and purified by flash chromatography (AcOEt) to afford 830 mg (2.86 mmol, 84%) of 4-(1,3,4-trimethoxynaphthalen-2-yl)-butan-1-ol (**13**) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (t, 1H, *J*=6.0 Hz, O*H*), 1.71 (m, 4H, CH_2 ×2), 2.83 (t, 2H, *J*=7.3 Hz, CH_2), 3.72 (quint, 2H, *J*=6.0 Hz, CH_2), 3.91 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 7.43 (td, 2H, *J*=7.0, 1.5 Hz, Ar*H* ×2), 7.99 (dd, 1H, *J*=2.0, 7.0 Hz, Ar*H*), 8.08 (dd, 1H, *J*=2.0, 7.0 Hz, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.5 (CH_2), 26.7 (CH_2), 32.7 (CH_2), 60.8 (CH_3), 60.9 (CH_3), 62.2 (CH_3), 62.6 (CH_2), 121.6 (CH), 122.1 (CH), 124.8 (CH), 125.3 (C), 125.5 (CH), 127.6 (C), 128.2 (C), 143.5 (C), 148.3 (C), 150.0 (C). HRMS calcd for $C_{17}H_{22}O_4$: 290.1518. Found: 290.1516.

*4.1.8. CAN oxidation of **8**.* To a stirred solution of **8** (100 mg, 0.4 mmol) in acetonitrile (CH_3CN) (6.0 mL) at 0 °C, diammonium cerium (IV) nitrate (CAN) (548 mg, 1.0 mmol) in water (4.0 mL) was added dropwise. The red-orange solution was stirred for 30 min at 0 °C, and worked up by addition of $CHCl_3$ and water. The aqueous layer was extracted with $CHCl_3$. The combined organic layer was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexane/AcOEt=1:2) to provide **14-I** (40.1 mg, 46%) and **14-II** (34.8 mg, 40%). Compound (**14-I**); mp 105–112 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.26 (s, 3H, CH_3), 4.65 (s, 2H, CH_2), 7.65 (td, 1H, *J*=8.0, 1.5 Hz, Ar*H*), 7.70 (td, 1H, *J*=8.0, 1.5 Hz, Ar*H*), 7.80 (dd, 1H, *J*=8.0, 1.5 Hz, Ar*H*), 8.09 (dd, 1H, *J*=8.0, 1.5 Hz, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.0 (CH_2), 63.1 (CH_3), 123.8 (C), 125.8 (CH), 129.4 (CH), 130.2 (C), 131.3 (C), 133.1 (CH), 135.4 (CH), 167.8 (C), 178.6 (C), 182.1 (C). HRMS calcd for $C_{12}H_{10}O_4$: 218.0579. Found: 218.0579. Compound (**14-II**); mp 100–106 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.95 (s, 1H, OH), 4.22 (s, 3H, CH_3), 4.70 (s, 2H, CH_2), 7.72 (m, 2H, ArH ×2), 8.05 (m, 2H, ArH ×2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.2 (CH2), 61.7 (CH3), 126.0 (CH), 126.3 (CH), 130.5 (C), 131.5 (C), 131.7 (C), 133.5 (CH), 134.1 (CH), 157.4 (C), 181.6 (C), 186.3 (C). HRMS calcd for $C_{12}H_{10}O_4$: 218.0579. Found: 218.0580.

*4.1.9. CAN oxidation of **9**.* According to the procedure described for CAN oxidation of **8**, CAN (1.37 g, 2.5 mmol) in water (9.0 mL) was added to a stirred solution of **9** (262 mg, 1.0 mmol) in CH_3CN (14.0 mL) at 0 °C. The crude mixture was purified by flash chromatography (hexane/AcOEt=1:2) to provide **15-II** (17.3 mg, 8%), **15-III** (112.6 mg, 56%), and **15-IV** (12.3 mg, 6%). Compound (**15-II**); mp 107–108 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.92 (t, 2H, *J*=6.2 Hz, CH_2), 3.81 (t, 2H, *J*=6.2 Hz, CH_2), 4.17 (s, 3H, OCH_3), 7.70 (m, 2H, Ar*H*), 8.06 (m, 2H, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.4 (CH_2), 61.4 (CH_3), 62.0 (CH_2), 125.2 (CH), 126.0 (C), 129.6 (CH), 130.1 (C), 130.7 (CH), 132.9 (C), 135.4 (CH), 167.6 (C), 178.8 (C), 182.1 (C). HRMS calcd for $C_{13}H_{12}O_4$: 232.0736. Found: 232.0734. Compound (**15-III**); mp 229–236 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.21 (t, 2H, *J*=9.9 Hz, CH_2), 4.78 (t, 2H, *J*=9.9 Hz, OCH_2), 7.66 (td, 1H, *J*=8.0, 1.5 Hz, Ar*H*), 7.71 (td, 1H, *J*=8.0, 1.5 Hz, Ar*H*), 8.06 (dd, 2H, *J*=8.0, 1.5 Hz, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.5 (CH_2), 74.8 (CH_2), 115.6 (C), 124.5 (CH), 127.5 (C), 129.4 (CH), 130.7 (C), 131.9 (CH), 134.5 (CH), 170.5 (C), 175.4 (C), 181.2 (C). HRMS calcd for $C_{12}H_8O_3$: 200.0473. Found: 200.0473. Compound (**15-IV**); mp 194–200 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.16 (t, 2H, *J*=9.2 Hz, CH_2), 4.88 (t, 2H, *J*=9.2 Hz, OCH_2), 7.58 (td, 1H, *J*=8.0, 2.6 Hz), 7.64 (m, 2H, ArH), 8.09 (d, 1H, *J*=8.0 Hz, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.4 (CH_2), 73.3 (CH_2), 124.5 (C), 126.1 (CH), 126.3 (CH), 131.6 (C), 133.0 (C), 133.1 (C), 134.1 (C), 145.1 (C), 160.8 (C), 177.8 (C). HRMS calcd for $C_{12}H_8O_3$: 200.0473. Found: 200.0470.

*4.1.10. CAN oxidation of **11**.* According to the procedure described for CAN oxidation of **8**, diammonium cerium (IV) nitrate (CAN) (493 mg, 0.9 mmol) in water (3.0 mL) was added to a stirred solution of **11** (100 mg, 0.36 mmol) in acetonitrile (CH_3CN) (5.0 mL) at 0 °C. The crude mixture was purified by flash chromatography (hexane/AcOEt=1:2) to provide **16-III** (51.6 mg, 67%), **16-IV** (5.2 mg, 7%). Compound (**16-III**); mp 168–176 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.05 (m, 2H, CH_2), 2.62 (t, 2H, *J*=6.2 Hz, CH_2), 4.34 (t, 2H, *J*=5.5 Hz, CH_2), 7.68 (td, 1H, *J*=7.0, 1.5 Hz, Ar*H*), 7.71 (td, 1H, *J*=7.0, 1.5 Hz, Ar*H*), 8.08 (dd, 1H, *J*=7.0, 1.5 Hz, Ar*H*), 8.10 (dd, 1H, *J*=7.0, 1.5 Hz, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8 (CH_2), 20.7 (CH_2), 68.3 (CH_2), 114.0 (C), 123.9 (CH), 128.4 (CH), 129.9 (C), 130.6 (CH), 132.1 (C), 134.7 (CH), 162.9 (C), 178.5 (C), 179.5 (C). HRMS calcd for $C_{13}H_{10}O_3$: 214.0630. Found: 214.0628. Compound (**16-IV**); mp 216–218 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.05 (m, 2H, CH_2), 2.63 (t, 2H, *J*=6.3 Hz, CH_2), 4.36 (t, 2H, *J*=5.3 Hz, CH_2), 7.69 (td, 1H, *J*=7.0, 1.5 Hz, C*H*), 7.73 (td, 1H, *J*=7.0, 1.5 Hz, C*H*), 8.09 (dd, 1H, *J*=7.0, 1.5 Hz, C*H*), 8.11 (dd, 1H, *J*=7.0, 1.5 Hz, C*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.0 (CH_2), 21.1 (CH_2), 68.3 (CH_2), 122.3 (C), 126.7 (CH), 126.9 (CH), 131.5 (C), 132.6 (C), 133.3 (C), 134.6 (C), 156.1 (C), 180.3 (C), 184.8 (C). HRMS calcd for $C_{13}H_{10}O_3$: 214.0630 Found: 214.0630.

*4.1.11. CAN oxidation of **13**.* According to the procedure described for CAN oxidation of **8**, CAN (411 mg, 0.75 mmol) in water (3.0 mL) was added to a stirred solution of **13** (87 mg, 0.3 mmol) in CH_3CN (4.0 mL) at 0 °C. The crude mixture was purified by flash chromatography (hexane/AcOEt=1:2) to provide **17-I** (26.8 mg, 34%), **17-II** (6.5 mg, 8%), **17-III** (13.8 mg, 20%), and **17-IV** (5.7 mg, 8%). Compound (**17-I**): mp 88–95 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61 (m, 4H, CH_2 ×2), 2.62 (t, 2H, *J*=6.6 Hz, CH_2), 3.69 (t, 2H, *J*=6.6 Hz, CH_2), 4.13 (s, 3H,

OCH_3), 7.68 (td, 2H, J=7.5, 2.0 Hz, ArH ×2), 8.03 (m, 2H, ArH ×2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2 (CH_2), 25.0 (CH_2), 32.5 (CH_2), 61.2 (CH_2), 62.4 (CH_3), 126.0 (CH), 126.1 (CH), 131.5 (C), 131.9 (C), 133.2 (CH), 133.7 (CH), 135.3 (C), 157.8 (C), 181.4 (C), 185.4 (C). HRMS calcd for $C_{15}H_{16}O_4$: 260.1049. Found: 260.1048. Compound (**17-II**): yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.63 (m, 4H, CH_2 ×2), 2.56 (t, 2H, J=7.0 Hz, CH_2), 3.70 (t, 2H, J=6.2 Hz, CH_2), 4.00 (s, 3H, OCH_3), 7.50 (td, 1H, J=1.5, 7.0 Hz, ArH), 7.64 (dd, 1H, J=1.5, 7.0 Hz, ArH), 7.68 (dt, 1H, J=1.5, 7.0 Hz, ArH), 8.07 (dd, 1H, J=1.5, 7.0 Hz, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.4 (CH_2), 25.1 (CH_2), 32.5 (CH_2), 61.6 (CH_2), 62.5 (CH_3), 125.1 (CH), 129.2 (C), 129.6 (CH), 130.1 (C), 130.4 (CH), 133.2 (C), 135.4 (CH), 166.2 (C), 178.9 (C), 181.8 (C). HRMS calcd for $C_{15}H_{16}O_4$: 260.1049. Found: 260.1048. Compound: (**17-III**): 133–138 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.91 (quint, 2H, J=6.2 Hz, CH_2), 2.09 (quint, 2H, J=6.2 Hz, CH_2), 2.80 (t, 2H, J=6.2 Hz, CH_2), 4.51 (t, 2H, J=6.2 Hz, OCH_2) 7.48 (td, 1H, J=1.1, 7.7 Hz, ArH), 7.64 (dt, 1H, J=1.1, 7.7 Hz, ArH), 7.80 (dd, 1H, J=7.7, 1.1 Hz, ArH), 8.03 (dd, 1H, J=1.1, 7.7 Hz, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.4 (CH_2), 23.5 (CH_2), 28.9 (CH_2), 73.2 (CH_2), 122.0 (C), 124.9 (CH), 128.6 (CH), 129.4 (C), 130.4 (CH), 134.0 (C), 135.0 (C), 167.5 (C), 179.1 (C), 180.6 (C). H-MS calcd for $C_{14}H_{12}O_3$: 228.0786. Found: 228.0786. Compound: (**17-IV**): mp 83–91 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.91 (quint, 2H, J=6.2 Hz, CH_2), 2.06 (quint, 2H, J=6.2 Hz, CH_2), 2.88 (t, 2H, J=6.2 Hz, CH_2), 4.40 (t, 2H, J=6.2 Hz, OCH_2), 7.67 (dt, 1H, J=1.5, 7.3 Hz, ArH), 7.70 (dt, 1H, J=1.5, 7.3 Hz, ArH), 7.80 (m, 2H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.1 (CH_2), 23.3 (CH_2), 29.1 (CH_2), 73.3 (CH_2), 126.2 (CH), 126.4 (CH), 129.9 (C), 131.0 (C), 132.1 (C), 133.1 (CH), 133.8 (CH), 160.2 (C), 180.9 (C), 185.5 (C). HRMS calcd for $C_{14}H_{12}O_3$: 228.0786. Found: 228.0788.

*4.1.12. Additional experiments for cyclization of n-**I**, n-**II** and for the inter-conversion between n-**III** and n-**IV** (a typical procedure for the listed reactions in Table 2) (entries 1–12).* To a stirred solution of **15-I** (9.3 mg, 0.04 mmol) in CH_3CN (0.5 mL) at 0 °C, CAN (55 mg, 0.1 mmol) in water (0.3 mL) was added dropwise. The red-orange solution was stirred for 30 min at 0 °C, and worked up by addition of $CHCl_3$ and water. The aqueous layer was extracted with $CHCl_3$. The combined organic layer was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The crude mixture was directly dissolved in $CDCl_3$, and analyzed by ^{1}H NMR. The ratio of the products is listed in Table 2.

*4.1.13. 1,2,4-Trimethoxy-3-methylnaphthalene **18**.* A frame-dried round bottom flask was charged with a solution of 1,2,4-trimethoxynaphthalene (**6**) (2.5 g, 11.5 mmol) in anhydrous THF (25 mL) under argon atmosphere. *n*-BuLi (8.8 mL, 13 mmol, 1.57 M in *n*-hexane solution) was added to the solution prepared above at 0 °C and the reaction mixture was stirred for 2 h at room temperature. The mixture was cooled to −80 °C and added iodomethane (2.2 mL, d=2.28 g/cm^3, 34 mmol) dropwise. After 30 min and checking by TLC, the reaction mixture was warmed up to room temperature and worked up with addition of satd aqueous NH_4Cl and AcOEt. The mixture was separated and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with 1% aqueous $Na_2S_2O_3$, water, brine and dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by flash chromatography (hexane/AcOEt=6:1) to afford 2.7 g (>99%) of 1,2,4-trimethoxy-3-methylnaphthalene (**18**) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (s, 3H, CH_3), 3.88 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 7.42 (m, 2H, ArH), 8.01 (m, 1H, ArH), 8.08 (m, 1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.8 (CH_3), 60.5 (CH_3), 61.0 (CH_3), 61.3 (CH_3), 121.6 (CH), 121.8 (CH), 123.1 (C), 124.9 (CH), 125.4 (CH), 125.5 (C), 127.9 (C), 143.6 (C), 148.4 (C), 150.2 (C). HRMS calcd for $C_{14}H_{16}O_3$: 232.1099. Found: 232.1100.

*4.1.14. 2-Bromomethyl-1,3,4-trimethoxynaphthalene **19**.* To a stirred solution of **18** (464 mg, 2 mmol) in carbon tetrachloride (CCl_4) (6.25 mL), *N*-bromosuccinimide (NBS) (356 mg, 2 mmol) was added and the mixture was heated under reflux for 3 h. After removing the precipitates by filtration, the filtrate was washed with 1% sodium thiosulfate solution, 2 M NaOH, and then dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to afford 2-bromomethyl-1,3,4-trimethoxynaphthalene (616 mg, 99%) as a colorless solid. Mp 45.5–50 °C ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.97 (s, 3H, OCH_3), 4.07 (s, 3H, OCH_3), 4.13 (s, 3H, OCH_3), 4.83 (s, 2H, CH_2), 7.44 (m, 2H, ArH), 8.12 (m, 2H, ArH). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 23.4 (CH_2), 60.9 (CH_3), 61.2 (CH_3), 62.6 (CH_3), 121.8 (CH), 122.7 (CH), 123.7 (C), 125.3 (CH), 127.1 (CH), 130.0 (C), 143.8 (C), 147.4 (C), 151.4 (C). IR (cm^{-1}) ν 2920, 1620, 1590, 1460, 1360, 1060, 1000. HRMS calcd for $C_{14}H_{15}O_3Br$: 310.0205, 312.0186. Found: 310.0204, 312.0186. LRMS (EI) m/z 312 (55), 310 (56), 297 (4), 231 (100), 216 (34), 201 (41), 200 (50), 173 (21), 143 (13).

*4.1.15. Ethyl 2,2-dimethyl-3-(1,3,4-trimethoxynaphthalen-2-yl)propanoate **20**.* A frame-dried round bottom flask was charged with diisopropylamine (4.5 mL, 31.8 mmol) in anhydrous THF (140 mL) under argon atmosphere, and added *n*-BuLi (21 mL, 31.8 mmol, 1.54 M in *n*-hexane) at 0 °C. The mixture was cooled to −80 °C and ethyl isobutyrate (4.2 mL, 31.8 mmol) was added via cannula. After 30 min stirring at this temperature, 2-bromomethyl-1,3,4-trimethoxynaphthalene (4.95 g, 15.9 mmol) in THF (70 mL) was slowly added via cannula. The mixture was warmed to room temperature and worked up as follows. The mixture was cooled in an ice bath then satd aqueous NH_4Cl was added, and the mixture was concentrated to remove THF. The aqueous layer was extracted three times with AcOEt, and the combined organic layer was washed with water, brine and dried over $MgSO_4$. Filtration and concentration of the organic solvent under reduced pressure afforded a crude product (5.69 g).

Purification by flash chromatography (hexane/AcOEt=8:1) gave 5.5 g of ethyl 2,2-dimethyl-3-(1,3,4-trimethoxynaphthalen-2-yl) propanoate (**20**) as a colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.17 (s, 6H, CH_3), 1.24 (t, 3H, J=7.3 Hz, CH_3), 3.09 (s, 2H, CH_2), 3.84 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 4.14 (q, 2H, J=7.3 Hz, CH_2), 7.44 (m, 2H, ArH ×2), 7.99 (dd, 1H, J=7.0, 1.5 Hz, ArH), 8.07 (dd, 1H, J=7.0, 1.5 Hz, ArH). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 14.1 (CH_3), 25.1 (CH_3), 34.4 (CH_2), 43.5 (C), 60.4 (CH_3 ×2), 60.8 (CH_2), 61.5 (CH_3), 121.5 (CH), 122.4 (CH), 123.5 (C), 124.8 (CH), 125.2 (C), 125.8 (CH), 128.8 (C), 143.2 (C), 148.8 (C), 151.5 (C), 178.0 (C=O). IR (cm^{-1}) ν 2920, 1710, 1590, 1460, 1360, 1140, 1060, 1000. HRMS calcd for $C_{20}H_{26}O_5$; 346.17808. Found: 346.1774. LRMS (EI) m/z 346 (M+100), 331 (12), 301 (3), 273 (10), 231 (86), 216 (24), 200 (37).

*4.1.16. 2,2-Dimethyl-3-(1,3,4-trimethoxynaphthalen-2-yl)propan-1-ol (**21**).* To a stirred THF (87 mL) solution of lithium aluminum hydride (LAH) (456 mg, 12 mmol) at 0 °C, ethyl ester (**20**) (3.44 g, 10 mmol) in THF (87 mL) was slowly added. The ice bath was removed and the mixture was stirred for 2 h at room temperature. The excess LAH was quenched with addition of AcOEt and water. The mixture was extracted three times with diethyl ether. The combined ether layer was washed with water, brine, and then dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by crystallization (hexane/AcOEt) to afford 2,2-dimethyl-3-(1,3,4-trimethoxynaphthalen-2-yl)propan-1-ol (**21**) (2.61 g, 8.6 mmol) (86%) as a colorless solid. Mp 138–141 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (s, 6H, CH_3 ×2), 2.77 (s, 2H, CH_2), 3.01 (d, 2H, J=6.3 Hz, CH_2), 3.75 (t, 1H, J=6.3 Hz, OH), 3.89 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 7.47 (m, 2H, ArH), 7.98 (m, 1H, ArH), 8.10 (m, 1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.2 (CH_3), 32.0 (CH_2), 38.4 (C), 60.8 (CH_3), 61.0 (CH_3), 62.0 (CH_3), 69.7 (CH_2), 121.7 (CH), 122.2 (CH), 124.0 (C), 125.0 (C), 125.2 (CH), 126.0 (CH), 128.6 (C), 143.6 (C), 148.6 (C), 150.9 (C). IR (cm^{-1}) δ 3470, 2920, 1590, 1450, 1360, 1060, 1000. HRMS calcd for $C_{18}H_{24}O_4$

304.1675. Found: 304.1674. LRMS (EI) *m*/*z* 304 (M+100), 273 (3), 257 (25), 231 (43), 200 (26), 173 (10).

4.1.17. 3,4-Dihydro-3,3-dimethyl-2H-naphtho[1,2-b]pyran-5,6-dione; rhinacanthone. To a stirred solution of **21** (304 mg, 1.0 mmol) in CH_3CN (14.3 mL) at 0 °C, CAN (1.37 g, 2.5 mmol) in water (8.6 mL) was added dropwise. The red-orange solution was stirred for 30 min at 0 °C, and worked up by addition of $CHCl_3$ and water. The aqueous layer was extracted with $CHCl_3$. The combined organic layer was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography (chloroform) to provide 3,4-dihydro-3,3-dimethyl-2*H*-naphtho[1,2-*b*]pyran-5,6-dione; rhinacanthone as an orange solid (224.2 mg, 93%). Mp 152–153 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (s, 6H, C*H*$_3$ ×2), 2.35 (s, 2H, C*H*$_2$–C), 3.97 (s, 2H, C*H*$_2$–O), 7.52 (td, 1H, *J*=6.6, 1.1 Hz, Ar*H*), 7.65 (td, 1H, *J*=6.6, 1.1 Hz, Ar*H*), 7.80 (dd, 1H, *J*=6.6, 1.1 Hz, Ar*H*), 8.07 (dd, 1H, *J*=6.6, 1.1 Hz, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8 (CH_3), 28.0 (C), 32.0 (CH_2), 77.2 (CH_2), 113.3 (C), 124.1 (CH), 128.7 (CH), 129.9 (C), 130.7 (CH), 131.9 (C), 134.8 (CH), 161.9 (C), 179.0 (C), 179.6 (C). HRMS calcd for $C_{15}H_{14}O_3$: 242.0943. Found: 242.0941. The isomer of rhinacanthone was included in less polar crude mixture of the fraction (12 mg, 5% yield by ^{1}H NMR analysis). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (s, 6H, C*H*$_3$ ×2), 2.39 (s, 2H, C*H*$_2$–C), 3.90 (s, 2H, C*H*$_2$–O), 7.66–7.75 (m, 2H, Ar*H* ×2), 8.07–8.12 (m, 2H, Ar*H* ×2).[7i]

References and notes

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4. The prepared benzyl ethers of **9**, **11**, **13** were oxidized by CAN at first to obtain *O*-benzyl protected *o*- and *p*-naphthoquinones, and then debenzylation by catalytic hydrogenolysis was carried out to afford **15-I** and **15-II**, **16-I** and **16-II**, **17-I** and **17-II** in pure form, respectively.
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