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Total synthesis of (±)-lantalucratins A and B by CAN-mediated oxidative cyclization

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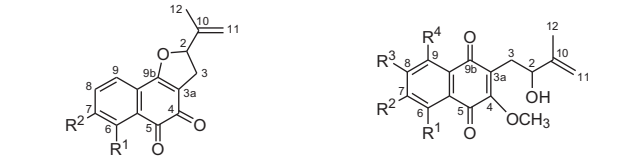
ABSTRACT

The first total synthesis of (±)-lantalucratins A and B is described. Introduction of an alkyl side chain at the 6-position was proceeded by directed *ortho*-lithiation and subsequent alkylation reaction to afford 6-alkyl-5,7,8-trimethoxy-1-naphthol as a synthetically important intermediate for (±)-lantalucratins A and B in excellent yield with complete regioselectivity. The 1,2-naphthoquinone fused five-membered cyclic ether framework was constructed directly from 3-hydroxyalkyl-naphthalenes by oxidative intramolecular cyclization reaction with diammonium cerium(IV) nitrate. (±)-Lantalucratins A and B were obtained in 69% and 45% overall yields, respectively.

1. Introduction

Biologically active natural products containing the naphthoquinone skeleton have been widely found in extensive regions around the world from many years ago.[1] Recently, lantalucratins and related compounds were isolated from rainforest plants such as *Lantana involucrata*, and they were found to possess cytotoxic activity against various human tumor cell lines.[2] Among the naphthoquinone derivatives, lantalucratins A–C consist of 1,2-naphthoquinone including the cyclic ether moiety as a central backbone and having an oxygen function at the 6- or 7-position (Fig. 1). Other lantalucratins D–F have a 1,4-naphthoquinone skeleton bearing a 3-(hydroxyalkyl) side chain with an oxygen function at the aromatic ring. Although the structure of these compounds has been determined by 2D NMR spectroscopic analysis and X-ray crystallographic analysis, as reported by Lee and coworkers, their absolute configuration at the stereogenic C2 carbon centers were not specified, and there has been no report of the synthesis of these compounds. In our previous report, we demonstrated the asymmetric synthesis of the natural product (*R*)-(−)-dehydroiso-β-lapachone that possesses the same structural backbone as lantalucratins A–C except for the oxygen functions.[3a]



Lantalucratin A (**1a**): R^1=OCH_3, R^2=H
B (**1b**): R^1=OH, R^2=H
C (**1c**): R^1=H, R^2=OH
Dehydroiso-β-lapachone: R^1=H, R^2=H

D (**1d**): R^1=OCH_3, R^2=H, R^3=H, R^4=H
E (**1e**): R^1=OCH_3, R^2=H, R^3=H, R^4=OH
F (**1f**): R^1=H, R^2=OCH_3, R^3=OH, R^4=OH

Fig. 1. Biologically active naphthoquinone derivatives: lantalucratins A–F.

During the study, we found that the 1,2-naphthoquinones fused five-membered cyclic ether (dihydrofuranyl) moieties, which could be directly constructed from 3-(hydroxyalkyl)-1,2,4-trimethoxynaphthalenes by exposure to diammonium cerium(IV) nitrate (CAN)[4] in high yields with good regioselectivities. We expected that the CAN-mediated oxidative cyclization method could be applied to the synthesis of lantalucratins. Moreover, we considered that the convenient synthesis of these compounds could be achieved if the oxygen functional group could be appropriately introduced. Herein, we describe the first, short step total synthesis of (±)-lantalucratins A and B.

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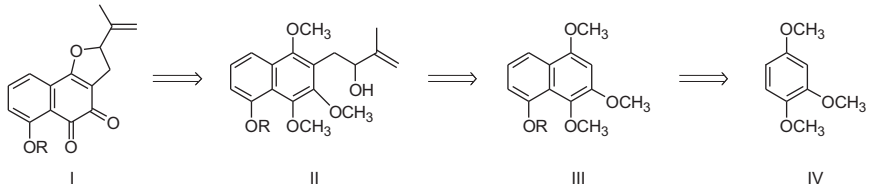
2. Results and discussion

2.1. Retrosynthetic analysis of (±)-lantalucratins A and B

Initially, we planned the synthetic route to the target compounds **1a** and **1b** as shown in Scheme 1.

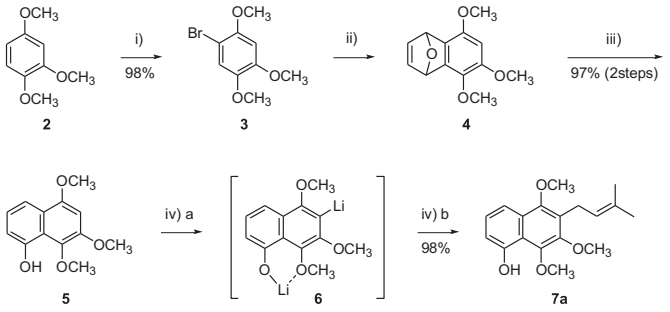
The fused five-membered cyclic ether moiety of the lantalucratins (I) can be constructed by CAN-mediated oxidative intramolecular cyclization from 3-(hydroxyalkyl)-1,2,4-trimethoxyn aphthalenes (II). This seems to be the most reliable and effective method for creating the dihydrofuranyl-1,2-naphthoquinone skeletons. The hydroxyalkyl fragment connecting at the C3 position of compound II is introduced by directed *ortho*-lithiation[5] of naphthalenes (III) and subsequent alkylation reaction. Compounds (III), regarded as the 'reduced naphthoquinone equivalent', are synthesized by benzyne-mediated [4+2] cycloaddition reaction starting from 1,2,4-trimethoxybenzene (IV).



Scheme 1. Synthetic strategies toward lantalucratins A and B.

2.2. Total synthesis of (±)-lantalucratin A

Based on the retrosynthetic analysis described in Section 2.1, we began to plan the synthesis of the racemate of the natural products **1a** and **1b**. The 3-alkyl substituted α-naphthol derivative **7a**, which is a synthetically important building block for **1a** and **1b**, was synthesized and the results are summarized in Scheme 2.



Reaction conditions: i) Br_2, $CHCl_3$, 0°C, 1 h ii) LDA, furan, THF, -78°C to rt iii) cat. $HClO_4$, THF, rt, 1 h iv) a) *n*-BuLi, THF, 0°C to rt b) prenyl bromide, -80°C to rt, 1 h

Scheme 2. Synthetic route to compound **7a**.

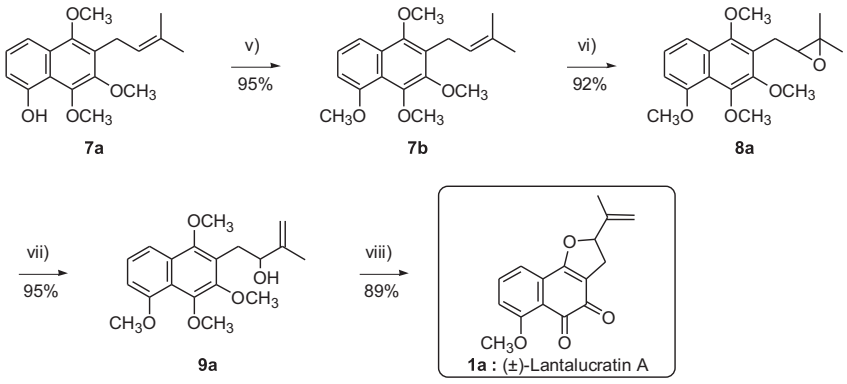
In accordance with the literature protocols,[6] 1-naphthol derivative **5** was prepared from commercially available 1,2,4-trimethoxybenzene **2** within three steps in quantitative yield. The $HClO_4$-catalyzed epoxy-ring opening reaction was accomplished with complete regioselectivity, in the same manner as well as the reported one confirmed by ^1H and ^{13}C NMR analysis. Directed *ortho*-lithiation of **5** was carried out with more than twice the excess amount of *n*-butyllithium against the substrate to generate the dianion intermediate **6**, and subsequent treatment with prenyl bromide afforded the alkylated product **7a** in excellent yield. The regioselectivity of the directed *ortho*-lithiation reaction was absolutely controlled; it might be explainable by the coordination property difference with the lone pair at the oxygen atoms of **6**. First, the deprotonation of compound **5** proceeds at the hydroxyl group, and the subsequent second deprotonation at the aromatic ring occurs to generate a dianion intermediate **6**. In the latter process, the deprotonation reaction occurs at the C6 position in preference to the C2 position, because the C6 position is surrounded by two methoxy groups, and a stronger coordination effect can be obtained than at the C2 position. In addition, the deprotonation reaction hardly occurs at the C2 position,[7] probably because electrical repulsion exists between the hydroxyl anion and the butyl anion of *n*-butyllithium when the deprotonation occurs at the C2 position. Although there is a possibility that the deprotonation reaction by alkyllithium reagent also occurs potentially at the C4 position, actually, the lithiation occurred selectively at the C6 position probably due to the difference of the coordination effect.[8]

The synthetically important compound **7a** was obtained briefly within four steps at over 90% yield. We next tried to focus on the synthesis of the natural product **1a**. The successful approach is summarized in Scheme 3. After methylation of the hydroxyl group of **7a**, an oxygen atom was introduced by alkene epoxidation with 3-chloroperoxybenzoic acid to afford 2-epoxyalkyl-1,3,4,5-tetramethoxynaphthalene **8a** in excellent yield. The epoxy-ring opening reaction[3a] was carried out in the presence of camphorsulfonic acid to yield the desired product **9a** as a (±)-lantalucratin A precursor. The target compound **1a** was finally obtained from **9a** by exposure to CAN in water in 89% yield. Although the side product, which is a regioisomer of **1a**,[9] was formed in less than 1% yield, the major product was easily separated by silica gel column chromatography. In addition, all measured data of the spectroscopic analysis of the product **1a** were identical with those of the compounds derived from natural products except for the optical rotation value.[2] The melting point of the synthesized compound **1a** was different from that of the compound derived from natural product because of the difference between the racemic compound and chiral one. Thus, we succeeded in the total synthesis of (±)-lantalucratin A in a total of eight steps with a 69% overall yield.

2.3. Total synthesis of (±)-lantalucratin B

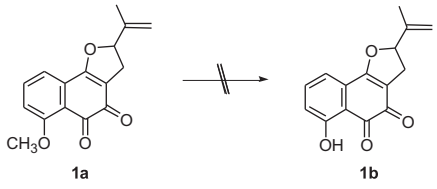
One of the most efficient synthetic routes will be the direct conversion from **1a** to **1b** by deprotection of methyl ether when synthesizing both target compounds. Hence, we decided to examine the *O*-demethylation of **1a** (Scheme 4).

First, we attempted to select some typical Lewis acids, such as boron tribromide or aluminum trichloride, for the *O*-demethylation of **1a**. Unfortunately, the desired molecule **1b** was not obtained and some of the side products were formed probably due to a halogenation reaction occurring at the terminal alkene of **1a**.[10] We assumed that the side reaction would be caused by the hydrogen



Reaction conditions: v) Me_2SO_4, KOH, TBAB, THF/H_2O, 0°C, 1 h vi) *m*-CPBA, $NaHCO_3$, CH_2Cl_2 rt, 0.5 h vii) CSA, TBAB, CH_2Cl_2, rt, 2 h viii) CAN (2.5 equiv), CH_3CN/H_2O, 0°C, 1 h.

Scheme 3. Total synthesis of (±)-lantalucratin A (**1a**).

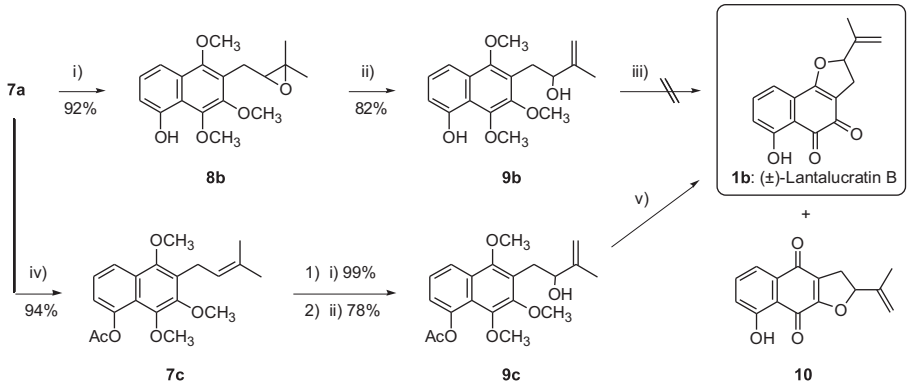


reagents: BBr_3, $AlCl_3$, PhSH, PhSLi, PhSNa
additives: 2-methyl-2-butene, DBU, HMPA, etc.

Scheme 4. Direct conversion of **1a** into **1b** by *O*-demethylation.

halides, which were generated from Lewis acids. In order to interrupt the side reaction processes, a large excess of 2-methyl-2-butene was added to the reaction mixture as an acid scavenger. However, this was not effective and the same side products were formed and identified by TLC analysis. These results indicated that the terminal alkene moiety of compound **1a** was extremely sensitive to the acidic conditions, and therefore, it might be difficult to remove the *O*-methyl group by utilizing typical Lewis acids. During the study, we found a similar case reported in a recent publication.[11] We also examined another method for the *O*-demethylation of **1a** by nucleophilic substitution of thiolates under basic conditions.[12] However, all attempts met with failure under those conditions, and only the recovery of starting material **1a** and/or decomposition was observed. Thus, we concluded that is too difficult to convert **1b** directly from **1a** by *O*-demethylation reaction.

On consideration of the above results, we decided to retrace the synthetic route to naphthol **7a**, which has a free hydroxy group at the C1 position. Fortunately, the epoxidation of **7a** and the following ring opening reaction proceeded smoothly in the presence of free hydroxyl group under conditions similar to those described in Scheme 3, and the desired products were produced in high yields. However, in contrast to the former reaction, the oxidative CAN cyclization of **9b** did not occur to furnish the desired product. In order to achieve the total synthesis of (±)-lantalucratin B, protection of the hydroxyl group at the C1 position of **9b** was needed when the compounds are treated with CAN. The acetyl group, which seems to be suitable protecting group for **9b** because it can be survived under acidic conditions and it can be removed easily under basic conditions. The hydroxyl group of **7a** was protected with acetic anhydride and sodium acetate under thermal conditions to afford the corresponding acetate **7c** in excellent yield. As expected, introduction of the oxygen functional group to the internal alkene moiety was successful using the same method without cleavage of the acetyl ester as shown in Scheme 5. The oxidative cyclization of **9c** was carried out with a stoichiometric



Reaction conditions: i) *m*-CPBA, CH_2Cl_2 rt, 0.5 h ii) CSA, TBAB, CH_2Cl_2, rt, 2 h iii) CAN (2.5 equiv), CH_3CN/H_2O, 0°C, 1 h iv) Ac_2O, AcONa, 120°C, 0.5 h v) CAN (2.5 equiv), CH_3CN/H_2O, 0°C, 0.5 h, then 1% Na_2CO_3 aq, rt, 2 h, **1b**: 66%, **10**: 8%.

Scheme 5. Total synthesis of (±)-lantalucratin B (**1b**).

amount of CAN. Thereafter, subsequent deprotection of the acetyl group was done by treatment with 1 wt/v% Na_2CO_3 aq solution, with the formation of the target compound **1b**. The regioisomer **10** was also obtained as a minor product in 8% yield, and the precise structure of this molecule was confirmed by ^1H and ^{13}C NMR analysis. The major product **1b** could be easily separated and isolated by flash column chromatography on silica gel. Moreover, all measured data of the spectroscopic analysis of product **1b** were identical with compounds derived from natural products except for the optical rotation value.[2] The melting point of the synthesized compound **1b** was very different from that of the compound derived from natural product because of the difference between the racemic compound and chiral one. Thus, we first established the synthetic route of (±)-lantalucratin B in a total of eight steps for 45% overall yield.

3. Conclusion

Total synthesis of (±)-lantalucratins A and B was accomplished in high yield. The alkyl side chain was successfully introduced by directed *ortho*-lithiation alkylation methodology to afford the synthetically important 1-naphthol derivative **7a** in excellent yield with complete regioselectivity. The dihydrofuranyl-1,2-naphthoquinone skeleton was constructed directly from 3-(hydroxyalkyl)-naphthalenes (**9a**, **9c**) by CAN-mediated oxidative intramolecular cyclization reaction. The asymmetric total synthesis of these compounds is currently in progress.

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., Nacalai Tesque Co., and Aldrich Chemical Co. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a JEOL JNM-ECP400 spectrometer. Chemical shift values were expressed in parts per million (ppm) relative to an internal reference of tetramethylsilane (0 ppm) in ^1H NMR and $CDCl_3$ (77.0 ppm) in ^{13}C NMR. Coupling constants are shown in hertz (Hz). Abbreviations are as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. IR spectra were recorded on a JASCO IR Report-100. 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 done using an UV lamp.

4.2. 1-Bromo-2,4,5-trimethoxybenzene (3)

According to a literature procedure,[6] to a solution of 1,2,4-trimethoxybenzene (1.68 g, 10 mmol) in 20 mL of $CHCl_3$ was added dropwise a solution of bromine (1.6 g, 10 mmol) in 10 mL of $CHCl_3$ over 45 min at 0 °C (in an ice-water bath) under an argon atmosphere. After stirring for 45 min at the same temperature, the reaction mixture was treated with 1 wt/v% $Na_2S_2O_3$ aq, and was then extracted with $CHCl_3$ (×3). The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography eluting with AcOEt and hexane in 1:10 ratio to give 2.41 g (98%) of the title compound as a white solid. ^1H NMR ($CDCl_3$) δ: 3.83 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 6.57 (1H, s, Ar–H), 7.04 (1H, s, Ar–H).

4.3. 1,4-Dihydro-5,6,8-trimethoxy-1,4-epoxynaphthalene (4)

According to a literature procedure,[6] a solution of **3** (2.47 g, 10 mmol) and furan (21.8 mL) in anhydrous THF (39 mL) was cooled to −78 °C under an argon atmosphere. To the solution was added LDA in THF dropwise via cannula over 1 h after preparation in situ from diisopropylamine (1.7 g, 16.8 mmol) and 1.6 M *n*-butyllithium solution in hexane (10 mL, 16 mmol) in anhydrous THF (21.5 mL) and precooling to −78 °C. The reaction mixture was stirred at −78 °C for 4 h, and then stirring was continued at room temperature for 15 h. The reaction was quenched with water and extracted with AcOEt (×2). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated to give the title compound in quantitative yield. It was used for the next step without further purification. ^1H NMR ($CDCl_3$) δ: 3.81 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 5.90–5.95 (2H, m), 6.12 (1H, s, Ar–H), 6.98–7.00 (1H, m), 7.03–7.05 (1H, m).

4.4. 5,7,8-Trimethoxynaphthalen-1-ol (5)

According to a literature procedure,[6] to a solution of **4** (2.34 g, 10 mmol) in anhydrous THF (21 mL) was slowly added 70 wt/v% $HClO_4$ aq (0.22 mL, 0.92 mmol) under ice-water bath cooling, and was stirred at room temperature for 75 min. The reaction mixture was diluted with ether, and then was successively washed with water and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography eluting with AcOEt and hexane in 1:3 ratio gave 2.26 g (97%) of the title compound as a yellow solid. A small portion of the solid was separated and recrystallized from AcOEt and hexane to give greenish-yellow cubic crystals of mp 92.5–94.0 °C. ^1H NMR ($CDCl_3$) δ: 3.96 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 4.01 (3H, s, OCH_3), 6.60 (1H, s, Ar–H), 6.88 (1H, dd, J=1.1, 7.7, Ar–H), 7.21 (1H, dd, J=7.7, 8.4, Ar–H), 7.64 (1H, dd, J=1.1, 8.4, Ar–H), 9.66 (1H, s, OH). ^{13}C NMR ($CDCl_3$) δ: 55.8, 57.4, 62.1, 95.6, 111.3, 113.1, 118.1, 123.2, 124.8, 136.9, 147.1, 153.0, 153.3.

4.5. 5,7,8-Trimethoxy-6-(3-methylbut-2-enyl)naphthalen-1-ol (7a)

Under an argon atmosphere, to a solution of **5** (7.02 g, 30 mmol) in anhydrous THF (75 mL) was added dropwise 1.6 M *n*-butyllithium in hexane solution (42 mL, 66 mmol) at 0 °C. The reaction mixture was warmed to room temperature, and then was stirred for 2 h until a white precipitate formed. The reaction mixture was cooled back to −80 °C, and prenyl bromide (11.7 g, 30 mmol) was slowly added with stirring for 10 min. The reaction mixture was warmed to room temperature again, with stirring for 30 min. The reaction was quenched with satd NH_4Cl aq under ice bath cooling, and the entire mixture was extracted with AcOEt (×3). The organic layer was separated and successively washed with water and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography eluting with AcOEt and hexane in 1:6 ratio to obtain 8.86 g (98%) of the title compound as an orange oil. IR (neat): 3360, 2945, 2850, 1605, 1505, 1455, 1375, 1360, 1245, 1200, 1115, 1080, 1058, 1005, 960, 840, 820, 770 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.70 (3H, s, CH_3), 1.83 (3H, s, CH_3), 3.51 (2H, d, J=6.8), 3.86 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 4.06 (3H, s, OCH_3), 5.21 (1H, t, J=6.8), 6.83 (1H, dd, J=1.1, 7.7, Ar–H), 7.29 (1H, t, J=7.7, 8.4, Ar–H), 7.49 (1H, dd, J=1.1, 8.4, Ar–H), 9.57 (1H, s, OH). ^{13}C NMR ($CDCl_3$) δ: 17.9, 24.0, 25.7, 60.7, 61.6, 61.9, 110.1, 113.2, 116.9, 123.0, 126.3, 127.51, 127.55, 131.8, 143.9, 147.4, 150.6, 154.0. EIMS m/z: 302 (M^+). HRMS-EI m/z: (M^+) calcd for $C_{18}H_{22}O_4$, 302.1518; found, 302.1515.

4.6. 1,3,4,5-Tetramethoxy-2-(3-methylbut-2-enyl)naphthalene (7b)

To a solution of **7a** (151 mg, 0.5 mmol) and tetra-*n*-butylammonium bromide (21 mg, 0.065 mmol) in anhydrous THF (0.15 mL) was added KOH (90 mg, 1.6 mmol) in water (54 μL) and dimethylsulfate (80 μL, 0.8 mmol) at 0 °C (ice-water bath) under an argon atmosphere, and the mixture was stirred for 1 h at the same temperature. The complete consumption of the starting material was confirmed by TLC analysis. To the reaction mixture was added 10 wt/v% NaOH aq and the entire mixture was extracted with AcOEt (×3), and the combined organic layer was washed successively with water and brine. The organic extracts were dried over $MgSO_4$, filtered, concentrated in vacuo, and subjected to flash column chromatography eluting with AcOEt and hexane in 1:30 ratio gave 150 mg (95%) of the title compound as a pale yellow oil. IR (neat): 2935, 2840, 1598, 1587, 1500, 1460, 1400, 1372, 1347, 1262, 1124, 1070, 1015, 760 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.70 (3H, s, CH_3), 1.83 (3H, s, CH_3), 3.52 (2H, d, J=6.2), 3.86 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 4.00 (3H, s, OCH_3), 5.24 (1H, t, J=6.2), 6.81 (1H, d, J=7.7, Ar−H), 7.30 (1H, t, J=7.7, 8.4, Ar−H), 7.63 (1H, d, J=8.4, Ar−H). ^{13}C NMR ($CDCl_3$) δ: 17.9, 24.2, 25.7, 56.1, 61.1, 61.5, 62.0, 105.6, 114.8, 120.2, 123.3, 124.8, 127.8, 127.9, 131.5, 145.1, 149.97, 150.02, 156.2. EIMS m/z: 316 (M^+). HRMS-EI m/z: (M^+) calcd for $C_{19}H_{24}O_4$, 316.1675; found, 316.1678.

4.7. 2,2-Dimethyl-3-(1,3,4,5-tetramethoxynaphthalen-2-ylmethyl)oxirane (8a)

To a solution of **7b** (1.40 g, 4.43 mmol) in CH_2Cl_2 (13.3 mL) was slowly added satd $NaHCO_3$ aq (13.3 mL), and was cooled to 0 °C (ice-water bath) equipped with an argon gas balloon. 3-Chloroperoxybenzoic acid (1.15 g, 6.6 mmol) was added portionwise for 4–5 times to the reaction mixture, and stirring of the solution was continued for 30 min at room temperature until the starting material was fully consumed, which was checked by TLC analysis. The reaction mixture was added water and $CHCl_3$ under ice-water bath cooling, and the entire mixture was extracted with $CHCl_3$. The organic layer was successively washed with 1 wt/v% $Na_2S_2O_3$ aq, 0.5 N $NaHCO_3$ aq, and water. The resulting organic extracts were dried over $MgSO_4$, filtered, and was subjected to flash column chromatography eluting with AcOEt and hexane in 1:10 ratio gave 1.35 g (92%) of the title compound as a pale yellow oil. IR (neat): 2940, 2848, 1718, 1600, 1580, 1500, 1460, 1400, 1370, 1348, 1261, 1125, 1100, 1070, 1012, 761 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.31 (3H, s, CH_3), 1.46 (3H, s, CH_3), 2.98–3.14 (3H, m), 3.88 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 4.01 (3H, s, OCH_3), 4.02 (3H, s, OCH_3), 6.84 (1H, d, J=7.7, Ar−H), 7.32 (1H, t, J=7.7, 8.1, Ar−H), 7.63 (1H, d, J=8.1, Ar−H). ^{13}C NMR ($CDCl_3$) δ: 19.0, 24.8, 25.0, 56.2, 59.1, 61.2, 61.6, 62.2, 64.0, 105.9, 114.9, 120.7, 124.1, 125.0, 127.8, 145.0, 150.0, 150.7, 156.2. EIMS m/z: 332 (M^+). HRMS-EI m/z: (M^+) calcd for $C_{19}H_{24}O_5$, 332.1624; found, 332.1621.

4.8. 3-Methyl-1-(1,3,4,5-tetramethoxynaphthalen-2-yl)but-3-en-2-ol (9a)

To a solution of **8a** (332 mg, 1.0 mmol) in CH_2Cl_2 (9.2 mL) was added 1 M camphorsulfonic acid solution in water (1.15 mL, 1.15 mmol) under ice-water bath cooling. After stirring for 30 min at room temperature, tetra-*n*-butylammonium bromide (16 mg, 0.05 mmol) was added to the flask, and stirring was continued for 1.5 h at the same temperature. The reaction was quenched with satd NH_4Cl aq, and diluted with water. The entire mixture was extracted with $CHCl_3$, and the combined organic layer was washed with water, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography and elution with AcOEt and hexane in 1:3 ratio gave 316 mg (95%) of the title compound as a pale yellow oil. IR (neat): 3500, 2945, 2850, 1598, 1500, 1450, 1400, 1360, 1260, 1200, 1120, 1020 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.89 (3H, s, CH_3), 2.95 (1H, dd, J=9.2, 13.5), 3.10 (1H, br s), 3.19 (1H, dd, J=2.9, 13.5), 3.88 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 4.01 (3H, s, OCH_3), 4.02 (3H, s, OCH_3), 4.86 (1H, s), 5.06 (1H, s), 6.84 (1H, d, J=7.3, Ar−H), 7.33 (1H, t, J=7.3, 8.4, Ar−H), 7.62 (1H, d, J=8.4, Ar−H). ^{13}C NMR ($CDCl_3$) δ: 18.1, 31.9, 56.1, 61.2, 61.6, 61.9, 76.3, 106.0, 110.2, 114.8, 120.6, 124.7, 125.2, 127.8, 145.2, 147.8, 149.5, 150.6, 156.3. EIMS m/z: 332 (M^+). HRMS-EI m/z: (M^+) calcd for $C_{19}H_{24}O_5$, 332.1624; found, 332.1627.

4.9. 2-Isopropenyl-6-methoxy-2,3-dihydronaphtho[1,2-*b*]furan-4,5-dione (lantalucratin A: 1a)

To a solution of **9a** (500 mg, 1.51 mmol) in acetonitrile (21.6 mL) was gently added cerium ammonium nitrate (2.06 g, 3.77 mmol) in 13 mL of water at 0 °C. After stirring for 1 h at the same temperature, the reaction mixture was diluted with water and $CHCl_3$, and the entire mixture was extracted with $CHCl_3$ (×3). The combined organic layer was washed with water, dried over $MgSO_4$, filtered, concentrated in vacuo, and subjected to flash column chromatography eluting with $CHCl_3$ and methanol in 100:1 ratio gave 343 mg (84%) of the title compound as a dark orange solid. A small portion of the solid was separated and recrystallized from AcOEt and hexane gave dark orange crystals of mp 156.4–158.9 °C (lit.:[2] mp146–158 °C). IR (KBr): 2980, 2955, 1687, 1650, 1630, 1580, 1465, 1358, 1297, 1205, 1070, 1004, 902, 799 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.80 (3H, s, CH_3), 2.94 (1H, dd, J=8.4, 16.0), 3.24–3.31 (1H, m), 3.99 (3H, s, OCH_3), 5.01 (1H, s), 5.12 (1H, s), 5.44 (1H, dd, J=8.4, 10.8), 7.18 (1H, d, J=8.1, Ar−H), 7.33 (1H, d, J=7.5, Ar−H), 7.59 (1H, t, J=7.5, 8.1, Ar−H). ^{13}C NMR ($CDCl_3$) δ: 16.8 (CH_3), 31.2 (CH_2), 56.4 (CH_3), 89.4 (CH), 113.6 (CH_2), 114.6 (C), 116.8 (CH), 117.2 (CH), 118.1 (C), 129.4 (C), 135.8 (CH), 142.1 (C), 161.9 (C), 169.2 (C), 175.4 (C), 180.0 (C). EIMS m/z: 270 (M^+). HRMS-EI m/z: (M^+) calcd for $C_{16}H_{14}O_4$, 270.0892; found, 270.0890.

4.10. 6-(3,3-Dimethyl-oxiranylmethyl)-5,7,8-trimethoxynaphthalen-1-ol (8b)

To a solution of **7a** (1.51 g, 5.0 mmol) in CH_2Cl_2 (15 mL) was added 3-chloroperoxybenzoic acid (1.29 g, 7.5 mmol) at 0 °C. The reaction mixture was allowed to reach room temperature and stirred for 0.5 min. The reaction was quenched with water at 0 °C, and the entire mixture was extracted with $CHCl_3$ (×3). The organic extracts were washed successively with 1 wt/v% $Na_2S_2O_3$, brine, and then dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography eluting with AcOEt and hexane in 1:5 ratio gave 1.46 g (92%) of the title compound as a pale yellow oil. IR (neat): 3360, 2945, 2850, 1608, 1506, 1459, 1375, 1361, 1245, 1120, 1058, 1006, 905, 760, 739 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.31 (3H, s, CH_3), 1.46 (3H, s, CH_3), 2.98–3.10 (3H, m), 3.90 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 4.06 (3H, s, OCH_3), 6.86 (1H, dd, J=1.1, 7.7, Ar−H), 7.30 (1H, t, J=7.7, 8.4, Ar−H), 7.50 (1H, dd, J=1.1, 8.4, Ar−H), 9.55 (1H, s, OH). ^{13}C NMR ($CDCl_3$) δ: 19.0 (CH_3), 24.77 (CH_3), 24.81 (CH_2), 59.1 (C), 60.8 (CH_3), 61.6 (CH_3), 62.2 (CH_3), 63.9 (CH), 110.5 (CH), 113.3 (CH), 117.4 (C), 123.9 (C), 126.4 (CH), 127.4 (C), 143.9 (C), 147.3 (C), 151.5 (C), 154.0 (C). EIMS m/z: 318 (M^+). HRMS-EI m/z: (M^+) calcd for $C_{18}H_{22}O_5$, 318.1467; found, 318.1467.

4.11. 6-(2-Hydroxy-3-methylbut-3-enyl)-5,7,8-trimethoxynaphthalen-1-ol (9b)

The reaction was conducted in the same manner for the preparation of **9a**. Flash column chromatography was carried out using

AcOEt and hexane in 2:3 ratio as an eluant to give 82% of the title compound as a pale yellow oil. IR (neat): 3500, 3370, 3080, 2950, 2850, 1610, 1580, 1510, 1450, 1370, 1320, 1250, 1200, 1120, 1060, 950, 900, 870, 820, 770, 730 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.88 (3H, s, CH_3), 2.81 (1H, d, J=4.1), 2.96 (1H, dd, J=9.2, 13.6), 3.15 (1H, dd, J=3.7, 13.6), 3.91 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 4.06 (3H, s, OCH_3), 4.31–4.35 (1H, m), 4.86 (1H, s), 5.04 (1H, s), 6.86 (1H, dd, J=1.1, 7.7, Ar–H), 7.31 (1H, t, J=7.7, 8.4, Ar–H), 7.49 (1H, dd, J=1.1, 8.4, Ar–H). ^{13}C NMR ($CDCl_3$) δ: 18.0 (CH_3), 31.6 (CH_2), 60.8 (CH_3), 61.6 (CH_3), 61.8 (CH_3), 76.1 (CH), 110.4 (CH_2), 110.5 (CH), 113.2 (CH), 117.3 (C), 124.4 (C), 126.6 (CH), 127.3 (C), 144.0 (C), 147.0 (C), 147.6 (C), 151.3 (C), 154.0 (C). EIMS m/z: 318 (M^+). HRMS-EI m/z: (M^+) calcd for $C_{18}H_{22}O_5$, 318.1467; found, 318.1469.

4.12. 5,7,8-Trimethoxy-6-(3-methylbut-2-enyl)-naphthalen-1-yl acetate (7c)

A solution of **7a** (2.02 g, 6.70 mmol) and sodium acetate (6.9 g, 83.1 mmol) in acetic anhydride (23.1 mL) was heated at 120 °C and stirred for 0.5 h. To the reaction mixture was added pH 7.4 phosphate buffer until a white suspension was formed in the reaction mixture. The entire mixture was extracted with $CHCl_3$ (×2) and the organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography eluting with AcOEt and hexane in 1:3 ratio to give 2.16 g (94%) of the title compound as a pale yellow solid. A small portion of the solid was separated and recrystallization from hexane gave colorless needles of mp 82.1–85.0 °C. IR (KBr): 2940, 2875, 1700, 1600, 1500, 1441, 1401, 1345, 1305, 1235, 1121, 1090, 1062, 1012, 920, 898, 781 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.70 (3H, s, CH_3), 1.82 (3H, s, CH_3), 2.38 (3H, s, CH_3), 3.51 (2H, d, J=7.0), 3.86 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 5.18–5.23 (1H, m), 7.04 (1H, dd, J=1.1, 7.7, Ar–H), 7.35 (1H, t, J=7.7, 8.5, Ar–H), 7.92 (1H, dd, J=1.1, 8.5, Ar–H). ^{13}C NMR ($CDCl_3$) δ: 17.9 (CH_3), 20.9 (CH_3), 24.1 (CH_2), 25.7 (CH_3), 60.9 (CH_3), 61.2 (CH_3), 62.2 (CH_3), 119.5 (CH), 120.7 (CH), 121.4 (C), 123.0 (CH), 124.3 (CH), 127.8 (C), 128.1 (C), 131.7 (C), 143.3 (C), 145.9 (C), 150.3 (C), 150.4 (C), 170.0 (C). EIMS m/z: 344 (M^+). HRMS-EI m/z: (M^+) calcd for $C_{20}H_{24}O_5$, 344.1624; found, 344.1624.

4.13. 6-(3,3-Dimethyl-oxiranylmethyl)-5,7,8-trimethoxynaphthalen-1-yl acetate (8c)

The reaction was conducted in the same manner as the preparation of **8b**. Flash column chromatography was carried out using AcOEt and hexane in 1:3 ratio as an eluant to give 99% of the title compound as a white solid of mp 69.3–71.4 °C. IR (KBr): 3090, 2950, 2850, 1765, 1700, 1600, 1455, 1370, 1230, 1125, 1060, 1008, 898, 780 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.31 (3H, s, CH_3), 1.46 (3H, s, CH_3), 2.39 (3H, s, CH_3), 2.97–3.12 (3H, m), 3.86 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 7.07 (1H, d, J=7.3, Ar–H), 7.37 (1H, dd, J=7.3, 8.4, Ar–H), 7.93 (1H, d, J=8.4, Ar–H). ^{13}C NMR ($CDCl_3$) δ: 19.0 (CH_3), 20.8 (CH_3), 24.8 (CH_3), 24.9 (CH_2), 59.1 (C), 60.9 (CH_3), 61.2 (CH_3), 62.4 (CH_3), 63.9 (CH), 119.9 (CH), 120.8 (CH), 121.9 (C), 124.46 (C), 124.52 (CH), 127.6 (C), 143.2 (C), 145.9 (C), 150.2 (C), 151.1 (C), 170.0 (C). EIMS m/z: 360 (M^+). HRMS-EI m/z: (M^+) calcd for $C_{20}H_{24}O_6$, 360.1573; found, 360.1576.

4.14. 6-(2-Hydroxy-3-methylbut-3-enyl)-5,7,8-trimethoxynaphthalen-1-yl acetate (9c)

The reaction was conducted in the same manner as the preparation of **9b**. The product was obtained in 78% yield of a colorless oil. IR (neat): 3451, 2860, 2820, 1763, 1653, 1600, 1458, 1400, 1360, 1220, 1122, 1062, 972, 910, 780, 738 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.88 (3H, s, CH_3), 2.38 (3H, s, CH_3), 2.96 (1H, dd, J=9.2, 13.5), 3.16 (1H, dd, J=3.2, 13.5), 3.86 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 4.32 (1H, dd, J=3.2, 9.2), 4.85 (1H, s), 5.04 (1H, s), 7.07 (1H, d, J=7.3, Ar–H), 7.38 (1H, t, J=7.3, 8.4, Ar–H), 7.92 (1H, d, J=8.4, Ar–H). ^{13}C NMR ($CDCl_3$) δ: 19.0 (CH_3), 20.8 (CH_3), 24.8 (CH_3), 24.9 (CH_2), 59.1 (C), 60.9 (CH_3), 61.2 (CH_3), 62.4 (CH_3), 63.9 (CH), 119.9 (C), 120.8 (CH), 121.9 (C), 124.46 (C), 124.52 (CH), 127.6 (C), 143.2 (C), 145.9 (C), 150.2 (C), 151.1 (C), 170.0 (C). EIMS m/z: 360 (M^+). HRMS-EI m/z: (M^+) calcd for $C_{20}H_{24}O_6$, 360.1573; found, 360.1576.

4.15. CAN-mediated oxidative intramolecular cyclization of 9c

To a solution of **9c** (108 mg, 0.3 mmol) in acetonitrile (4.3 mL) was gently added diammonium cerium(IV) nitrate (411 mg, 0.75 mmol) in 2.6 mL of water at 0 °C. After stirring for 0.5 h at the same temperature, the reaction mixture was basified with 1 wt/v% Na_2CO_3 aq, and was allowed to reach room temperature with stirring continuing for 2 h. The reaction mixture was cooled to 0 °C and acidified with 1 M HCl. The acidic solution was extracted with $CHCl_3$ (×3) and the combined organic layer was successively washed with water and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude red solid was purified by flash column chromatography eluting with $CHCl_3$ and AcOEt in 30:1 ratio gave 51 mg (66%) of **1b** as a red solid and 6 mg (8%) of **10** as a reddish-orange solid of mp 120.6–122.9 °C. A small portion of the **1b** was separated and recrystallized from AcOEt and hexane gave red crystals of mp 153.2–153.6 °C (lit.:[2] mp 179–181 °C).

*4.15.1. 6-Hydroxy-2-isopropenyl-2,3-dihydronaphtho[1,2-b]furan-4,5-dione (lantalucratin B: **1b**).* IR (KBr): 3470, 2965, 1765, 1650, 1619, 1590, 1500, 1459, 1412, 1365, 1250, 1213, 1185, 935, 768 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.80 (3H, s, CH_3), 2.95 (1H, dd, J=7.7, 15.6), 3.28 (1H, dd, J=10.6, 15.6), 5.03 (1H, s), 5.13 (1H, s), 5.46 (1H, dd, J=7.7, 10.6), 7.14 (1H, d, J=8.8, Ar–H), 7.24 (1H, d, J=7.3, Ar–H), 7.54 (1H, t, J=7.3, 8.8, Ar–H), 11.93 (1H, s, OH). ^{13}C NMR ($CDCl_3$) δ: 16.8 (CH_3), 31.0 (CH_2), 89.8 (CH), 113.4 (C), 113.9 (CH_2), 115.2 (C), 117.5 (CH), 123.4 (CH), 127.2 (C), 137.6 (CH), 141.9 (C), 164.5 (C), 169.1 (C), 174.8 (C), 185.2 (C). EIMS m/z: 256 (M^+). HRMS-EI m/z: (M^+) calcd for $C_{15}H_{12}O_4$, 256.0736; found, 256.0736.

*4.15.2. 6-Hydroxy-2-isopropenyl-2,3-dihydronaphtho[1,2-b]furan-4,5-dione (**10**).* IR (KBr): 3450, 2940, 2828, 1732, 1650, 1620, 1580, 1460, 1412, 1383, 1320, 1275, 1253, 1187, 909, 742 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.81 (3H, s, CH_3), 3.02 (1H, dd, J=8.8, 17.6), 3.34 (1H, dd, J=10.6, 17.6), 5.01 (1H, s), 5.14 (1H, s), 5.42 (1H, t, J=8.8, 10.6), 7.20 (1H, dd, J=1.8, 7.7, Ar–H), 7.57–7.63 (2H, m, Ar–H), 11.65 (1H, s, OH). ^{13}C NMR ($CDCl_3$) δ: 17.0 (CH_3), 32.0 (CH_2), 88.8 (CH), 114.1 (CH_2), 114.7 (C), 119.1 (CH), 124.1 (CH), 124.9 (C), 133.3 (C), 136.9 (CH), 141.6 (C), 159.9 (C), 162.1 (C), 181.3 (C), 182.5 (C). EIMS m/z: 256 (M^+). HRMS-EI m/z: (M^+) calcd for $C_{15}H_{12}O_4$, 256.0736; found, 256.0736.

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