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Intra- and Intermolecular Oxa-Pictet–Spengler Cyclization Strategy for the Enantioselective Synthesis of Deoxy Analogues of (+)-Nanomycin A Methyl Ester, (+)-Eleutherin, (+)-Allo-Eleutherin, and (+)-Thysanone

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Enantioselective synthesis of deoxy analogues of pyranonaphthoquinone antibiotics (+)-nanomycin A methyl ester, (+)-eleutherin, (+)-allo-eleutherin, and (+)-thysanone was achieved in good overall yield with high enantio- and diastereoselectivity from the common intermediate (*R*)-3-(2,5-dimethoxyphenyl)propane-1,2-diol. The intramolecular oxa-Pictet–Spengler cyclization of 6-aryl-1,3-dioxolone was developed for the first time and utilized in the enantioselective synthesis of (+)-deoxynanomycin A methyl ester, whereas the intermolecular oxa-Pictet–Spengler cyclization strategy was applied to the enantioselective synthesis of deoxy analogues of (+)-eleutherin, (+)-allo-eleutherin, and (+)-thysanone.

Introduction

A pyran ring fused to a naphthoquinone nucleus is a ubiquitous structural motif present in a number of natural products (Figure 1) that exhibit a wide range of biological activities, such as antibiotic, antiparasitic, antiviral, and antitumor activities.[1] Nanomycin A (**1**) belongs to the monomeric class of pyranonaphthoquinone antibiotics[1a] and was isolated from the fungus *Streptomyces rosa* in 1974;[2] it exhibits inhibitory activity against mycoplasma, fungi, and Gram-positive bacteria. It also shows inhibition of the platelet-aggregation agent adenosine diphosphate (ADP).[1,2] Due to the significant antitumor activity of **1**, several racemic syntheses of **1**[3] as well as methyl ester **6a**[3a] and its deoxy analogue **6b**[4] have been reported. Recently, Brimble and co-workers reported the asymmetric synthesis of (1*R*,3*R*)-deoxynanomycin A in 12 steps with 86%*ee*.[5] However, the enantioselective syntheses of **1** and analogues **6a** and **6b** are not known.

Eleutherin (**2**) and isoeleutherin (**3**) were first isolated from the bulbs of *Eleutherin bulbosa* (Iridaceae) in 1950[6] and 1951,[7] respectively. (+)-Eleutherin (**2**) possess C-1–C-3 *cis* stereochemistry on the pyran ring and is a reversible inhibitor of topoisomerase II–a target for anticancer agents.[8] (+)-Allo-eleutherin (**4**; Figure 1) is an enantiomer of (+)-isoelutherin (**3**), and both were first synthesized from (+)-eleutherin by treatment with H_3PO_4.[7] Several syntheses of **2** and **3** and their analogues have been reported in the literature.[4a,4b,9–11] However, existing methods are either limited to racemic syntheses[4a,4b,9] or are based on chiral pool synthesis[10] or enzymatic resolution,[11] whereas catalytic asymmetric methods are rather rare. Very few enantioselective syntheses of **2**,[10] **3**,[10c] and deoxyeleutherin (**6**)[11] have been reported. Recently, Fernandes and co-workers[10c] used ethyl (*S*)-3-hydroxybutyrate as a chiral template in the synthesis of (+)-**2** and (+)-**4**.

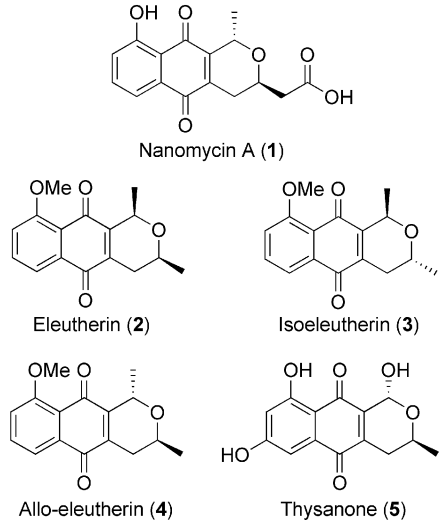

Figure 1. Biologically active pyranonaphthoquinones.

Thysanone (**5**) was isolated from the fungus *Thysanophora penicilloides* in 1991[12] and is one of the effective inhibitors of human rhinovirus 3C-protease; therefore, it should serve as a basis for the development of a chemotherapeutic agent for the common cold. Several racemic[13] and enantiopure[11,14a,15] syntheses of (1*R*,3*S*)-thysanone (**5**) and its analogues have been reported.

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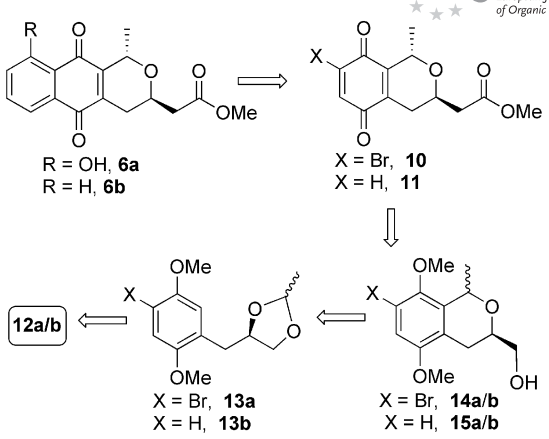
Bromopyranobenzoquinone intermediates **10** and **18a** are valuable immediate precursors in the synthesis of nanomycin A, eleutherin, and many other pyranonaphthoquinone natural products.[3a,10a] Moreover, Diels–Alder reaction[3a,4a,10a,15a,15b] of substituted 1,3-butadiene with bromopyranobenzoquinones or pyranobenzoquinones and the titanium tetrachloride promoted oxa-Pictet–Spengler rearrangement[16] of 5-aryl-1,3-dioxolanes have also been used for the construction of the aromatic and pyran rings of bioactive pyranonaphthoquinones, respectively. However, oxa-Pictet–Spengler rearrangement of 6-aryl-1,3-dioxolanes or an organocatalytic asymmetric approach has not been reported for the synthesis of the pyranonaphthoquinone class of compounds apart from our earlier report on the organocatalytic enantioselective formal synthesis of (1*R*,3*S*)-thysanone.[14a] Towards this end, a convenient, straightforward, and practical route to the synthesis of enantiomerically pure bromopyranobenzoquinone or pyranobenzoquinone intermediates and pyranonaphthoquinone antibiotics from easily available starting material is highly desirable.

As part of our research program aimed towards the development of new strategies for the organocatalytic enantioselective synthesis of biologically active compounds and their chiral key intermediates[14] on the basis of proline-catalyzed asymmetric α-aminooxylation of aldehydes,[17a] we were encouraged to design a convenient and effective route to the pyranonaphthoquinone antibiotic class of compounds. Herein we report a general, short, and efficient enantioselective synthesis of (+)-deoxynanomycin A methyl ester (**6b**), (+)-demethoxyeleutherin (**7**), (+)-demethoxyalloeleutherin (**8**), and (+)-deoxythysanone (**9**) by employing L-proline-catalyzed-asymmetric α-aminooxylation[17a] and oxa-Pictet–Spengler cyclization[16,18] as the key steps.

Results and Discussion

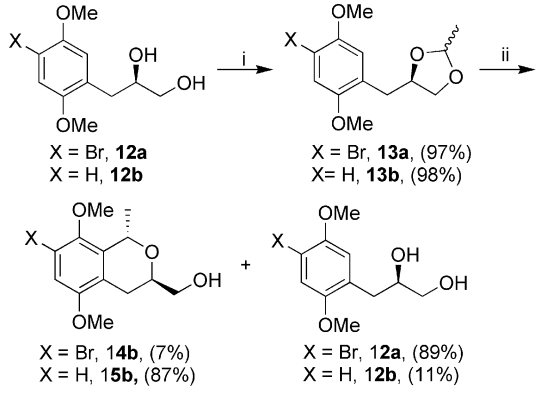
Synthesis of (1*S*,3*R*)-Nanomycin A Methyl Ester (6a) and (+)-Deoxynanomycin A Methyl Ester (6b)

The retrosynthetic strategy for the synthesis of **6a** and **6b** is outlined in Scheme 1. We envisage that **6a** and **6b** could be obtained from quinone intermediates **10** and **11**, as their racemic form has been synthesized by Kraus and Shi[3a] and Yoshii and Kometani,[4a] respectively. The synthetic challenge of this retrosynthetic pathway is to establish the two stereogenic center at C-1 and C-3 of quinones **10** and **11**. We realize that (*R*)-diol **12a/b**[14a,14b] would serve as a suitable precursor with the required C-3 stereocenter of **10** and **11**, which can be easily prepared by using L-proline-catalyzed asymmetric α-aminooxylation of the aldehyde.[14] Our plan was to generate the C-1 stereocenter by using intramolecular oxa-Pictet–Spengler cyclization[16] of 6-aryl-1,3-dioxolanes **13a/b** derived from (*R*)-diol **12a/b** to give pyrans **14a/b** and **15a/b**, which can be further transformed into quinones **10** and **11** by simple functional group interconversion (Scheme 1).



Scheme 1. Retrosynthetic analysis of **6a** and **6b**.

We began the synthesis of **6a** and **6b** with the preparation of 6-aryl-1,3-dioxolanes **13a/b**. (*R*)-Diols **12a**[14a] and **12b**[14b] were prepared in 98%*ee* by following our reported organocatalytic approach[14a,14b] that is based on L-proline-catalyzed asymmetric α-aminooxylation of aldehyde[17a] followed by treatment with 1,1′-diethoxyethane in the presence of *p*-TsA in CH_2Cl_2 to give 1,3-dioloxolanes **13a** and **13b** in excellent yield. The mixture of **13a** was subjected to intramolecular oxa-Pictet–Spengler cyclization[16] with $TiCl_4$ (2 equiv.) in dry CH_2Cl_2 at –30 °C to give *trans*-configured pyran **14b** in poor yield (7%) along with hydrolyzed product diol **12a** in 89% yield, whereas oxa-Pictet–Spengler rearrangement of **13b** proceeded smoothly to give exclusively *trans*-pyran **15b** in very good yield (87%) along with hydrolyzed product diol **12b** in 11% yield. The $TiCl_4$-promoted intramolecular oxa-Pictet–Spengler cyclization was found to be highly diastereoselective to give *trans*-pyran **14b** and **15b** as single diastereomers (Scheme 2).



Scheme 2. Reagents and conditions: (i) $CH_3CH(OEt)_2$, *p*-TsA, CH_2Cl_2, 0 °C – r.t., 7 h; (ii) $TiCl_4$, CH_2Cl_2, –30 °C, 3.5 h.

The *trans* stereochemical relationship between H^1 and H^3 on the pyran ring in **14b** and **15b** was assigned on the basis of NOESY proton NMR experiments. The H^3 proton showed strong NOE correlation to the methyl protons and very weak correlation to H^1, indicating that H^1 and H^3 are *trans* to each other (Figure 2).

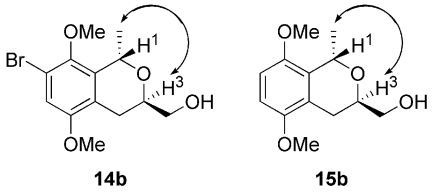
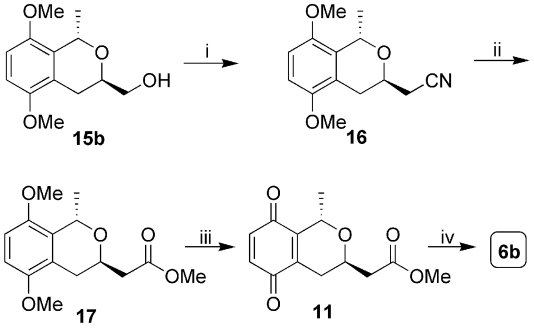


Figure 2. NOE observed in *trans*-**14b** and *trans*-**15b**.

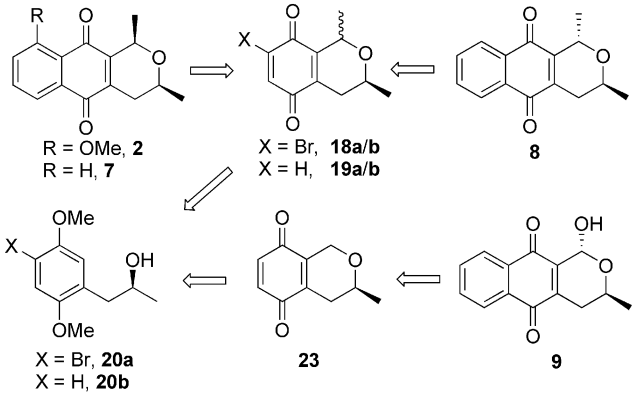
The poor yield in the oxa-Pictet–Spengler rearrangement of bromo-1,3-dioxolane **13a** into pyran **14b** may be due to the electron-withdrawing effect of the bromide substituent at C-4 of the aryl ring, which deactivates the aryl ring towards Friedel–Crafts electrophilic cyclization to give **14b**.[19] Due to the poor yield of pyran **14b**, our plan to prepare important intermediate **10** for the eventual synthesis of **6a** was unsuccessful. Thus, it was decided to complete the synthesis of (+)-**6b** from pyran **15b**. For one carbon homologation of alcohol **14b**, we adopted a two-step reaction sequence to convert alcohol **15b** into nitrile **16**, which involved tosylation of **15b** with *p*-toluenesulfonyl chloride by using Et_3N and DMAP in CH_2Cl_2, followed by nucleophilic displacement of the tosylate with NaCN and NaI in DMF at 80 °C to furnish nitrile **16** in 85% yield over the two steps. Compound **16** was hydrolyzed with aqueous 50% NaOH in MeOH to afford the carboxylic acid, which was treated with MeI by using anhydrous K_2CO_3 in DMF at room temperature to give ester **17** in 92% yield over two steps. Oxidative demethylation of pyran **17** with cerium(IV) ammonium nitrate (CAN) in aqueous CH_3CN gave quinone **11** in 82% yield. Quinone **11** was converted into **6b** in 78% yield by following a two-step (Diels–Alder followed by aromatization) literature procedure[4a] (Scheme 3). The physical and spectroscopic data of quinone (+)-**6b** are in accordance with the reported data of racemic **6b**.[4a]



Scheme 3. Reagents and conditions: (i) (a) *p*-TsCl, Et_3N, CH_2Cl_2, 0 °C to r.t., 30 h, (b) NaCN, NaI, DMF, 70 °C, 12 h, 85% (over two steps); (ii) (a) 50% NaOH, MeOH, 80 °C, 8 h, (b) MeI, K_2CO_3, DMF, r.t., 4.5 h, 92% (over two steps); (iii) CAN (3 equiv.), CH_3CN/H_2O (4:1), 0 °C to r.t., 20 min, 82%; (iv) see ref.[4a]: (a) 1-acetoxy-1,3-butadiene, toluene, r.t., 48 h; (b) 1% aq. Na_2CO_3, EtOH, r.t., 5 h;78% (over two steps).

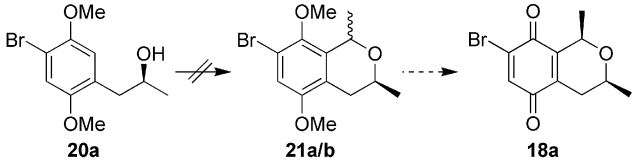
Synthesis of (+)-Eleutherin (2), (+)-Deoxyeleutherin (7), (+)-Deoxyallo-eleutherin (8), and (+)-Deoxythysanone (9)

The retrosynthetic strategy for the synthesis of pyranonaphthoquinones **2** and **7**–**9** is depicted in Scheme 4. Donner and co-workers[10a] and Yoshii and Kometani[4a] reported the enantiopure and racemic syntheses of quinone **18a** and **19a** as key intermediates for the total synthesis of (+)-eleutherin (**2**) and (±)-demethoxyeleutherin (**7**), respectively. We envisaged a new and short synthesis of important intermediate (+)-**18a**, (+)-**19a/b**, and (+)-**23** from (*S*)-alcohols **20a**[14a] and **20b**[14b] (98%*ee*) through oxa-Pictet–Spengler cyclization followed by oxidation of pyrans **21a/b** and **22a/b** (Scheme 5).



Scheme 4. Retrosynthetic analysis of **2** and **7**–**9**.

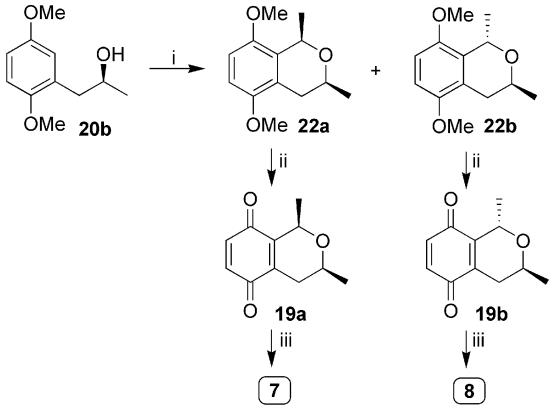
We focused initially on the synthesis of intermediate **18a** for the synthesis of (+)-eleutherin (**2**). Thus, alcohol (*S*)-**20a** was prepared by following our reported organocatalytic approach[14a,14b] and subjected to oxa-Pictet–Spengler cyclization with acetaldehyde or 1,1′-diethoxyethane under different reaction conditions by using different acids such as $BF_3{\cdot}Et_2O$, H_3PO_4, and HCl; unfortunately, all attempts were failed to give desire cyclized product **21a/b** required for the synthesis of intermediate **18a** to prepare **2**. The low reactivity of alcohol (*S*)-**20a** towards oxa-Pictet–Spengler cyclization is similar to our earlier observation in the cyclization of bromo-1,3-dioxolane **13a** into pyran **14a/b** (Scheme 5). This may be due to the electron-withdrawing effect of the bromide substituent at C-4 of the aryl ring, which deactivates the aryl ring towards Friedel–Crafts cyclization.[19]



Scheme 5. Attempted oxa-Pictet–Spengler cyclization on (*S*)-**20a**.

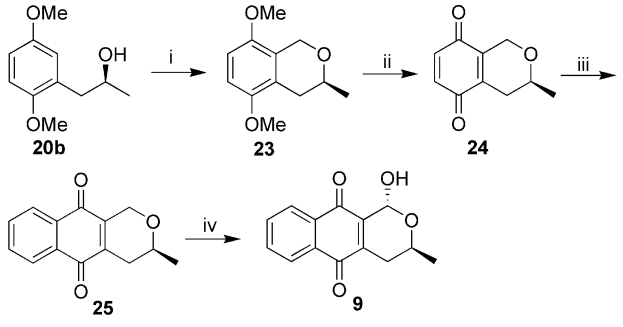
Then, we turned our attention to complete the synthesis of quinones **19a/b** in optically pure form (Scheme 6). Thus, (*S*)-alcohol **20b** was prepared by following our reported organocatalytic approach[14a,14b] and subjected to oxa-Pictet–Spengler cyclization with 1,1′-diethoxyethane in the presence of $BF_3{\cdot}Et_2O$ to give a mixture of pyrans **22a/b** (25:75 ratio) in 86% yield. The **22a/b** mixture was easily separated by column chromatography to give *cis*-**22a**[4a] (21%) and *trans*-**22b**[4a] (65%) from (*S*)-**20b**. The 1,3-relationship of the

newly generated stereocenter in pyrans **22a/b** was confirmed by comparing the ^{1}H NMR spectroscopic values with the those reported in the literature[4a] and converting nonpolar diastereomer **22a** into (+)-demethoxyeleutherin (**7**).[11] Oxidative demethylation of pyran **22a** with CAN in aqueous CH_3CN gave quinone **19a** in 84% yield. Quinone **19a** was converted into (+)-**7**[11] in 80% yield by following a two-step (Diels–Alder followed by aromatization) literature procedure.[4a] The physical and spectroscopic data of (+)-**19a** and (+)-**7** are in accordance with the literature data of racemic **19a**[4a] and (+)-**7**.[11] Similarly, (+)-demethoxyallo-eleutherin (**8**) was synthesized from *trans*-**22b** in 63% yield.



Scheme 6. Reagents and conditions: (i) $CH_3CH(OEt)_2$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C to r.t., 3.5 h, 21% (**22a**), 65% (**22b**); (ii) CAN (3 equiv.), CH_3CN/H_2O (4:1), 0 °C to r.t., 0.5 h; 84% (**19a**), 78% (**19b**); (iii) see ref.[4a]: (a) 1-acetoxy-1,3-butadiene, toluene, r.t., 48 h; (b) 1% aq. Na_2CO_3, EtOH, r.t., 5 h; 80% (**7**), 82% (**8**) (over two steps).

To demonstrate the further utility of (*S*)-alcohol **20b** for the synthesis of (+)-deoxythysanone (**9**), we subjected (*S*)-**20b** to oxa-Pictet–Spengler cyclization with methoxymethyl chloride in the presence of $ZnCl_2$ (30 mol-%) in dry Et_2O to afford pyran **23** in 80% yield. The oxidation of **23** with CAN in aqueous CH_3CN furnished quinone **24** in 81% yield. Diels–Alder reaction[4a] of quinone **24** with 1-acetoxy-1,3-butadiene in toluene followed by aromatization with 1% aqueous Na_2CO_3 solution in EtOH gave benz-annulated pyran **25** in 85% yield. Finally, (+)-deoxythysanone (**9**) was prepared in 77% yield from pyran **25** over a two-step reaction sequence involving radical bromination of pyran **25** and hydrolysis of the bromide intermediate in aqueous THF (Scheme 7). The physical and spectroscopic data of (+)-**9** are in good agreement with the reported data.[11,15c]



Scheme 7. Reagents and conditions: (i) $MeOCH_2Cl$ (2.1 equiv.), $ZnCl_2$ (30 mol-%), Et_2O, 0 °C to r.t., 7 h, 83%; (ii) CAN (3 equiv.), CH_3CN/H_2O (4:1), 0 °C to r.t., 25 min, 81%; (iii) (a) 1-acetoxy-1,3-butadiene, toluene, r.t., 48 h; (b) 1% aq. Na_2CO_3, EtOH, r.t., 5 h; 85%, (over two steps); (iv) Br_2 (1 equiv.), CCl_4, *hv*, 0.5 h; then THF/H_2O (3:1), r.t., 1 h, 77% (over two steps).

Conclusions

In conclusion, we have accomplished the first concise enantioselective synthesis of (+)-deoxynanomycin A methyl ester (**6b**) in nine steps by employing a novel intramolecular oxa-Pictet–Spengler cyclization of 6-aryl-1,3-dioxolone **13b**. We have also demonstrated the enantioselective four-step syntheses of (+)-demethoxyeleutherin (**7**) and (+)-demethoxyallo-eleutherin (**8**) and the six-step synthesis of (+)-deoxythysanone **9** by using an intermolecular oxa-Pictet–Spengler cyclization of (*S*)-1-(2,5-dimethoxyphenyl)propan-2-ol (**20b**). Good yields, ready availability of the starting materials, and high enantio- and diastereoselectivity are some of the salient features of our synthetic approach, which represents a good alternative to the known methods. Although, the present strategy failed to synthesize bromopyranobenzoquinone intermediates **10** and **18a** for the preparation of nanomycin A methyl ester (**6a**) and eleutherin (**2**), we believe that the present synthetic strategy could serve as a potential route for the synthesis of related pyranonaphthoquinone natural products. Efforts are in progress in this direction.

Experimental Section

General Methods: Melting points were recorded with a Thomas Hoover Capillary melting point apparatus. Thin-layer chromatography was performed on Merck $60F_{254}$ silica gel plates, and visualization was accomplished by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid (1.25 g) and $Ce(SO_4)_2{\cdot}H_2O$ (0.5 g) in concentrated H_2SO_4/H_2O (3.47 mL) followed by heating. Crude products were purified by column chromatography on silica gel of 100–200 mesh. IR spectra were recorded with a Shimadzu FTIR 8400 in $CHCl_3$ or as KBr pellets. Optical rotations were obtained with Jasco P-1020 digital polarimeter. ^{1}H and ^{13}C NMR spectra were recorded with a Varian Mercury spectrometer at 300 and 75 MHz, respectively, by using $CDCl_3$ as a solvent. Chemical shifts are reported in δ units (ppm) with reference to TMS as an internal standard. GC mass spectra were obtained with a Shimadzu GC–MS-QP5050A spectrometer. Elemental analyses were carried out with a Thermo-Electron Corporation CHNS Analyzer, FLASH-EA 1112. Analytical HPLC was performed on a chiral AD-H column (250 mm × 4.6 mm × 5 μ). Enantiomeric excesses were measured by using either chiral HPLC or by comparison with specific rotation. All solvents were purified and dried by standard procedures prior to use.

(*R*)-4-(4-Bromo-2,5-dimethoxybenzyl)-2-methyl-1,3-dioxolane (13a): To a stirred solution of (*R*)-diol **12a** (500 mg, 1.72 mmol) and 1,1′-diethoxyethane (1.23 mL, 8.62 mmol) in dry CH_2Cl_2 (20 mL) was added *p*-toluenesulfonic acid (32 mg, 0.17 mmol) at 0 °C, and the mixture was stirred at room temperature for 4 h. The reaction was

quenched with saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layer was washed with brine, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/hexane, 0.7:9.3) to give a 1:3 mixture of **13a** (529 mg, 97%) as a colorless oil. R_f = 0.35 (EtOAc/hexane, 1.5:8.5). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.33 (d, J = 5.1 Hz, 0.75 H, CH_3), 1.38 (d, J = 4.8 Hz, 2.25 H, CH_3), 2.74–2.93 (m, 2 H, CH_2), 3.54 (dd, J = 8.1, 6.9 Hz, 0.25 H, CH), 3.65 (dd, J = 8.1, 6.0 Hz, 0.75 H, CH), 3.76 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 3.79–3.85 (m, 0.75 H, CH), 4.01–4.06 (m, 0.25 H, CH), 4.24–4.39 (m, 0.75 H, CH), 5.05 (q, J = 4.8 Hz, 0.75, CH), 5.14 (q, J = 4.8 Hz, 0.25, CH), 6.79 (s, 1 H, ArH), 7.01 (s, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.0, 33.8, 34.6, 55.9, 56.8, 69.2, 69.9, 75.0, 75.6, 100.8, 101.6, 109.4, 115.2, 115.4, 115.6, 125.9, 149.7, 151.7 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2999, 2935, 1487, 1213 cm^{-1}. MS (EI): m/z = 317 $[M]^+$. $C_{13}H_{17}BrO_4$ (317.18): calcd. C 49.23, H 5.40; found C 49.32, H 5.47.

(*R*)-4-(2,5-Dimethoxybenzyl)-2-methyl-1,3-dioxolane (13b): The 1:1.5 mixture of **13b** (550 mg, 98%) was prepared as a colorless oil from **12b** (500 mg, 2.10 mmol) by using the same experimental procedure as that described for **13a**. R_f = 0.35 (EtOAc/hexane, 1.5:8.5). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.35 (d, J = 4.8 Hz, 1.2 H, CH_3), 1.40 (d, J = 5.1 Hz, 1.8 H, CH_3), 2.81 (dd, J = 12.6, 7.2 Hz, 1 H, CH), 2.96 (dd, J = 13.5, 6.3 Hz, 1 H, CH), 3.57 (dd, J = 8.4, 6.9 Hz, 0.4 H, CH), 3.68 (dd, J = 8.1, 6.0 Hz, 0.6 H, CH), 3.75 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 3.81 (dd, J = 7.8, 6.6 Hz, 0.6 H, CH), 4.02 (dd, J = 8.1, 6.0 Hz, 0.4 H, CH), 4.31–4.42 (m, 1 H, CH), 5.01 (q, J = 4.8 Hz, 0.6 H, CH), 5.17 (q, J = 4.8 Hz, 0.4 H, CH), 6.70–6.78 (m, 3 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.0, 34.0, 34.8, 55.5, 55.6, 69.3, 70.0, 75.2, 75.9, 100.7, 101.5, 111.0, 111.6, 111.7, 117.2, 126.7, 126.9, 151.6, 153.2 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2939, 1502, 1220, 1043 cm^{-1}. MS: m/z = 238 $[M]^+$. $C_{13}H_{18}O_4$ (238.28): calcd. C 65.53, H 5.31; found C 65.56, H 5.36.

(+)-(1*S*,3*R*)-7-Bromo-5,8-dimethoxy-1-methyl-3-hydroxymethy-l-3,4-dihydro-1*H*-benzo[*c*]pyran (14b): To a stirred solution of 1,3-dioxoalane **13a** (200 mg, 0.63 mmol) in CH_2Cl_2 (15 mL) under an atmosphere of nitrogen was added $TiCl_4$ (138 μL, 1.26 mmol) in dry CH_2Cl_2 (1 mL) dropwise over 5 min, and the mixture was stirred at the same temperature for 3.5 h. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2 of (3 × 15 mL). The combined organic layer was washed with brine, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure, and the residue was purified by column chromatography (EtOAc/hexane, 1.8:8.2) to give *trans*-**14b** (14 mg, 7%) as a colorless oil. R_f = 0.4 (EtOAc/hexane, 4:6). $[\alpha]_D^{26}$ = +35.9 (c = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.55 (d, J = 6.6 Hz, 3 H, CH_3), 2.34 (dd, J = 17.4, 11.4 Hz, 1 H, CH), 2.58 (dd, J = 17.1, 3.6 Hz, 1 H, CH), 3.69 (dd, J = 11.4, 4.5 Hz, 1 H, CH), 3.75–3.83 (m, 1 H, CH), 3.77 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 4.01–4.07 (m, 1 H, CH), 5.13 (q, J = 6.6 Hz, 1 H, CH), 6.80 (s, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.3, 23.8, 55.6, 60.7, 65.9, 66.7, 68.6, 112.5, 113.6, 121.9, 134.8, 146.5, 153.7 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3450, 2931, 1469, 1265 cm^{-1}. MS (EI): m/z = 317 $[M]^+$. $C_{13}H_{17}BrO_4$ (317.18): calcd. C 49.23, H 5.40; found C 49.31, H 5.46.

(+)-(1*S*,3*R*)-5,8-Dimethoxy-1-methyl-3-hydroxymethyl-3,4-dihydro-1*H*-benzo[*c*]pyran (15b): Product *trans*-**15b** (175 mg, 87%) was obtained as a colorless solid from **13a** (200 mg, 0.84 mmol) by using the same experimental procedure as that described for **14b**. R_f = 0.4 (EtOAc/hexane, 4:6). $[\alpha]_D^{26}$ = +23.2 (c = 1.0, $CHCl_3$). M.p. 67–69 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.51 (d, J = 6.6 Hz, 3 H, CH_3), 2.40 (dd, J = 17.1, 11.4 Hz, 1 H, CH), 2.65 (dd, J = 17.1, 3.3 Hz, 1 H, CH), 3.65 (dd, J = 11.4, 7.2 Hz, 1 H, CH), 3.33 (s, 6 H, OCH_3), 3.81–3.82 (m, 1 H, CH), 4.04–4.10 (m, 1 H, CH), 5.13 (q, J = 6.6 Hz, 1 H, CH), 6.66 (s, 2 H, ArH), ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.3, 24.1, 55.3, 55.4, 65.9, 66.9, 68.0, 107.1, 107.4, 122.3, 128.9, 149.2, 150.9 ppm. IR (KBr): $\tilde{\nu}$ = 3376, 2939, 1447, 1253, 1082, 1043 cm^{-1}. MS: m/z = 238 $[M]^+$. $C_{13}H_{18}O_4$ (238.28): calcd. C 65.53, H 5.31; found C 65.62, H 5.39.

(+)-2-[(1*S*,3*R*)-5,8-Dimethoxy-1-methyl-3,4-dihydro-1*H*-benzopyran-3-yl]acetonitrile (16): To as stirred solution of alcohol **15b** (255 mg, 1.07 mmol) in dry CH_2Cl_2 (15 mL) under an atmosphere of nitrogen was added Et_3N (195 μL, 1.39 mmol), DMAP (15 mg), and *p*-toluenesulfonyl chloride (223 mg, 1.17 mmol) at 0 °C, and the mixture was stirred at room temperature for 30 h. After completion of the reaction (monitored by TLC), saturated aqueous solution of NH_4Cl was added, and the solution was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layer was washed with brine, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure, and the residue was purified by column chromatography (EtOAc/hexane, 1.1 8:9) to afford the tosylate (94%, 395 mg) as a white solid. R_f = 0.30 (EtOAc/hexane, 2:8). $[\alpha]_D^{26}$ = +25.4 (c = 0.5, $CHCl_3$). M.p. 119–121 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.41 (d, J = 6.6 Hz, 1 H, CH_3), 2.22–2.35 (m, 3 H, CH), 2.44 (s, 3 H, CH_3), 2.59 (dd, J = 16.8, 2.7 Hz, 1 H, CH), 3.74 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 4.12–4.17 (m, 3 H, CH and CH_2), 5.03 (q, J = 6.6 Hz, 1 H, CH), 6.63 (s, 2 H, ArH), 7.33 (d, J = 8.4 Hz, 2 H, ArH), 7.82 (d, J = 8.1 Hz, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1, 21.6, 24.5, 55.4, 55.5, 64.5, 68.3, 72.3, 107.5, 107.6, 121.5, 128.0, 128.6, 129.7, 133.1, 144.7, 149.2, 150.9 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2937, 1483, 1217, 1072 cm^{-1}. MS: m/z = 392 $[M]^+$. $C_{20}H_{24}O_6S$ (392.47): calcd. C 61.21, H 6.16; found C 61.30, H 6.22. To a solution of tosylate (456 mg, 1.16 mmol) in anhydrous DMF (15 mL) under an atmosphere of nitrogen was added NaI (225 mg, 1.51 mmol) and NaCN (74 mg, 1.51 mmol), and the mixture was stirred at 80 °C for 12 h. The reaction mixture was cooled to room temperature, diluted with water, and extracted with EtOAc (3 × 25 mL). The combined organic layer was washed with brine, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure, and the residue was purified by column chromatography (EtOAc/hexane, 0.8:9.2) to give nitrile **16** (264 mg, 91%) as a colorless solid. R_f = 0.4 (EtOAc/hexane, 2:8). $[\alpha]_D^{26}$ = +41.8 (c = 0.50, $CHCl_3$). M.p. 63–65 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.51 (d, J = 6.6 Hz, 3 H, CH_3), 2.45 (dd, J = 17.1, 10.8 Hz, 1 H, CH), 2.67 (d, J = 6.0 Hz, 2 H, CH_2), 2.91 (dd, J = 17.1, 3.6 Hz, 1 H, CH), 3.77 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 4.18–4.24 (m, 1 H, CH), 5.13 (q, J = 6.6 Hz, 1 H, CH), 6.66 (s, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2, 24.7, 27.9, 55.3, 55.5, 62.8, 68.8, 107.7, 117.3, 121.3, 128.2, 149.2, 150.7 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2935, 2252, 1483, 1259, 1074 cm^{-1}. MS: m/z = 247 $[M]^+$. $C_{14}H_{17}NO_3$ (247.19): calcd. C 68.0, H 6.93, N 5.66; found C 68.09, H 6.96, N 5.72.

(+)-Methyl 2-[(1*S*,3*R*)-5,8-Dimethoxy-1-methyl-3,4-dihydro-1*H*-benzopyran-3-yl]acetate (17): To a solution of nitrile **16** (228 mg, 0.92 mmol) in MeOH (3 mL) was added 50% NaOH (3 mL), and the mixture was stirred for 8 h at 100 °C. The reaction mixture was cooled to room temperature and acidified with cold 5% HCl and extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure to give the carboxylic acid, which was used in the next step without purification. To a stirred solution of the crude acid in anhydrous DMF was added K_2CO_3 (165 mg, 1.19 mmol) and MeI (69 μL, 1.11 mmol) at room temperature, and the mixture was stirred for 3.5 h. The reaction mixture was diluted with water and extracted with EtOAc (3 × 15 mL). The combined

organic layer was washed with brine, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure, and the residue was purified by column chromatography (EtOAc/hexane, 0.7:9.3) to give ester **17** (238 mg, 98%) as a colorless oil. R_f = 0.5 (EtOAc/hexane, 2:8). $[\alpha]_D^{26}$ = –17.1 (c = 0.90, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.51 (d, J = 6.6 Hz, 3 H, CH_3), 2.37 (dd, J = 17.1, 11.4 Hz, 1 H, CH), 2.62–2.66 (m, 2 H, CH_2), 2.81 (dd, J = 17.1, 3.3 Hz, 1 H, CH), 3.73 (s, OCH_3), 3.76 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 4.34–4.43 (m, 1 H, CH), 5.07 (q, J = 6.6 Hz, 1 H, CH), 6.64 (s, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.0, 28.0, 40.9, 51.5, 55.2, 55.3, 63.2, 68.3, 107.2, 107.3, 122.4, 128.7, 149.2, 150.7, 171.5 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2941, 1737, 1600, 1479, 1255 cm^{-1}. MS: m/z = 280 $[M]^+$. $C_{15}H_{20}O_5$ (280.32): calcd. C 64.27, H 7.19; found C 64.35, H 7.23.

(+)-Methyl 2-(1*S*,3*R*)-(5,8-Dioxo-1-methyl-3,4-dihydro-1*H*-benzopyran-3-yl)acetate (11): To a precooled (0 °C) solution of (+)-pyran **17** (100 mg, 0.35 mmol) in CH_3CN (8 mL) was added dropwise a solution of CAN (587 mg, 1.07 mmol) in water (2 mL). The mixture was stirred for 20 min, then diluted with water, and extracted with ethyl acetate (3 × 15 mL). The combined organic layer were dried with Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (EtOAc/hexane, 1:9) to afford (+)-**11** as a pale-yellow solid (60 mg, 82%). R_f = 0.4 (EtOAc/hexane, 2:8). $[\alpha]_D^{25}$ = +61.2 (c = 1.0, $CHCl_3$). M.p. 77–79 °C (ref.[4a] 99–105.5 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48 (d, J = 6.6 Hz, 3 H, CH_3), 2.22 (dddd, J = 18.9, 12.6, 10.5, 2.1 Hz, 1 H, CH), 2.68–2.69 (m, 3 H, CH_2 and CH), 3.73 (s, 3 H, OCH_3), 4.24–4.31 (m, 1 H, CH), 4.82 (q, J = 6.4 Hz, 1 H, CH) 6.70 (d, J = 10.2 Hz, 1 H, olefinic CH), 6.75 (d, J = 10.2 Hz, 1 H, olefinic CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1, 27.1, 40.3, 51.8, 63.3, 67.0, 136.0, 136.4, 138.6, 144.1, 170.9, 185.4, 186.0 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2931, 1739, 1656, 1438, 1213, 1159 cm^{-1}. MS: m/z = 250 $[M]^+$. $C_{13}H_{14}O_5$ (250.25): calcd. C 62.39, H 5.64; found C 62.44, H 5.71.

(+)-Methyl 2-[(1*R*,3*R*)-1-Methyl-5,10-dioxo-3,4,5,10-tetrahydro-1*H*-naphtho[2,3-*c*]pyran-3-yl]acetate (6b): Compound (+)-**6b** (49 mg, 78%) was prepared from quinone **11** (53 mg, 0.21 mmol) as a pale-yellow solid by using a known procedure.[4a] R_f = 0.5 (EtOAc/hexane, 2:8). $[\alpha]_D^{25}$ = +37.0 (c = 0.30, $CHCl_3$). M.p. 184–186 °C (ref.[4a] 185–187 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.56 (d, J = 6.9 Hz, 3 H, CH_3), 2.35 (dddd, J = 19.2, 12.6, 10.8, 2.1 Hz, 1 H, CH), 2.65–2.68 (m, 2 H, CH_2), 2.82 (dd, J = 18.9, 3.6 Hz, 1 H, CH), 3.75 (s, 3 H), 4.29–4.38 (m, 1 H, CH), 5.02 (q, J = 6.6 Hz, 1 H, CH), 7.71–7.74 (m, 2 H, ArH), 8.05–8.09 (m, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.3, 27.1, 40.4, 51.8, 63.4, 67.4, 126.2, 131.7, 131.9, 133.6, 133.7, 140.9, 146.3, 171.0, 183.0, 183.7 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3020, 2928, 1734, 1662, 1438, 1215, 1074 cm^{-1}. MS: m/z = 300 $[M]^+$. $C_{17}H_{16}O_5$ (300.31): calcd. C 67.99, H 5.37; found C 68.06, H 5.42.

(+)-(1*R*,3*S*)- and (+)-(1*S*,3*S*)-5,8-Dimethoxy-1,3-dimethyl-3,4-dihydro-1*H*-benzo[*c*]pyran (22a and 22b): To a stirred solution of (*S*)-**20b**[14b] (122 mg, 0.62 mmol) and 1,1′-diethoxyethane (267 μL, 1.86 mmol) in CH_2Cl_2 (5 mL) was slowly added $BF_3{\cdot}Et_2O$ (118 μL, 0.93 mmol) at 0 °C, and the mixture was stirred at room temperature for 3.5 h. Saturated aqueous $NaHCO_3$ was added, and mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extract was washed with brine, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure to afford a mixture of **22a** and **22b**, which was purified by column chromatography (EtOAc/hexane, 0.1:9.9) to give nonpolar *cis*-isomer **22a** (30 mg, 21%) as a white solid. R_f = 0.52 (EtOAc/hexane, 0.5:9.5). M.p. 64–66 °C. $[\alpha]_D^{26}$ = +224.0 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.36 (d, J = 6.0 Hz, 3 H, CH_3), 1.55 (d, J = 6.6 Hz, 3 H, CH_3), 2.37 (dd, J = 16.8, 10.7 Hz, 1 H, CH), 2.86 (d, J = 6.0 Hz, 1 H, CH), 3.58–3.66 (m, 1 H, CH), 3.78 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 5.02 (q, J = 6.7 Hz, 1 H, CH), 6.69 (s, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6, 21.7, 31.1, 55.3, 55.6, 69.0, 70.8, 107.6, 107.7, 125.2, 129.3, 150.2, 150.5 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2970, 2931, 2835, 1491, 1437, 1257, 1074 cm^{-1}. MS: m/z = 222 $[M]^+$. $C_{13}H_{18}O_3$ (222.28): calcd. C 70.24, H 8.16; found C 70.30, H 8.23. Further elution (EtOAc/hexane, 0.2:9.8) gave polar *trans*-isomer **22b** (87 mg, 65%) as a colorless oil. R_f = 0.5 (EtOAc/hexane, 0.5:9.5). $[\alpha]_D^{26}$ = +32.8 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 (d, J = 6.3 Hz, 3 H, CH_3), 1.50 (d, J = 6.6 Hz, 3 H, CH_3), 2.30 (dd, J = 17.4, 10.8 Hz, 1 H, CH), 2.76 (dd, J = 17.4, 3.6 Hz, 1 H, CH), 3.76 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 4.05–4.07 (m, 1 H, CH), 5.08 (q, J = 6.6 Hz, 1 H, CH), 6.64 (s, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.5, 21.9, 30.3, 55.3, 55.5, 62.1, 68.2, 107.1, 107.4, 123.4, 129.0, 149.4, 150.8 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2935, 1493, 1263, 1066 cm^{-1}. MS: m/z = 222 $[M]^+$. $C_{13}H_{18}O_3$ (222.28): calcd. C 70.24, H 8.16; found C 70.32, H 8.25.

(+)-(1*R*,3*S*)-1,3-Dimethyl-3,4-dihydro-1*H*-benzo[*c*]pyran-5,8-dione (19a): To a precooled (0 °C) solution of (+)-pyran **22a** (29 mg, 0.13 mmol) in CH_3CN (4 mL) was added dropwise a solution of CAN (214 mg, 0.39 mmol) in water (1 mL). The mixture was stirred for 20 min at the same temperature, then diluted with water (5 mL), and extracted with ethyl acetate (3 × 12 mL). The combined organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (EtOAc/hexane, 0.4:9.6) to afford (+)-**19a** (21 mg, 84%) as a pale-yellow liquid. R_f = 0.45 (EtOAc/hexane, 1:9). $[\alpha]_D^{25}$ = +178.1 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (d, J = 6.3 Hz, 3 H, CH_3), 1.48 (d, J = 6.6 Hz, 3 H, CH_3), 2.1 (dddd, J = 18.6, 14.4, 10.2, 4.2 Hz, 1 H, CH), 2.60 (dt, J = 18.6, 2.7 Hz, 1 H, CH), 3.52–3.59 (m, 1 H, CH), 4.66–4.70 (m, 1 H, CH), 6.67 (d, J = 9.9 Hz, 1 H, olefinic CH), 6.73 (d, J = 10.2 Hz, 1 H, olefinic CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.6, 21.1, 29.8, 68.6, 69.5, 135.7, 136.9, 140.3, 144.2, 186.2, 186.3 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2926, 1654, 1600, 1462, 1386, 1170 cm^{-1}. MS: m/z = 192 $[M]^+$. $C_{11}H_{12}O_3$ (192.21): calcd. C 68.74, H 6.29; found C 68.82, H 6.34.

(+)-(1*R*,3*R*)-1,3-Dimethyl-3,4-dihydro-1*H*-benzo[*c*]pyran-5,8-d-ione (19b): Compound **19b** (57 mg, 78%) was prepared as a yellow crystalline solid from **22b** (85 mg, 0.38 mmol) by using the same procedure as that described for **19a**. R_f = 0.4 (EtOAc/hexane, 1.0:9.0). $[\alpha]_D^{26}$ = +145.9 (c = 1.0, $CHCl_3$). M.p. 123–125 °C (ref.[4a] 100–105 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (d, J = 6.0 Hz, 3 H, CH_3), 1.46 (d, J = 6.9 Hz, 3 H, CH_3), 2.11 (d, J = 19.2, 12.3, 10.2, 2.4 Hz, 1 H, CH), 3.89–3.99 (m, 1 H, CH), 4.83 (q, J = 6.9 Hz, 1 H, CH), 6.69 (d, J = 10.2 Hz, 1 H, olefinic CH), 6.74 (d, J = 10.2 Hz, 1 H, olefinic CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.5, 21.3, 29.2, 62.4, 66.8, 136.0, 136.4, 139.3, 144.1, 185.7, 186.3 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2983, 2935, 2854, 1660, 1597, 1311, 1138, 985, 844 cm^{-1}. MS: m/z = 192 $[M]^+$. $C_{11}H_{12}O_3$ (192.21): calcd. C 68.74, H 6.29; found C 68.85, H 6.36.

(+)-(1*R*,3*S*)-1,3-Dimethyl-3,4-dihydro-1*H*-naphtho-[2,3-*c*]pyran-5,10-dione (7):[11] Compound (+)-**7** (20 mg, 80%) was prepared from **19a** (20 mg, 0.10 mmol) as a yellow solid by using a known procedure,[4a] R_f = 0.52 (EtOAc/hexane, 1.5:8.5). $[\alpha]_D^{26}$ = +248.1 (c = 0.10, $CHCl_3$) {ref.[11] $[\alpha]_D^{20}$ = +227.2 (c = 0.10, $CHCl_3$)}. M.p. 121–123 °C (ref.[4a] 122–125 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38 (d, J = 6.6 Hz, 3 H, CH_3), 1.55 (d, J = 6.3 Hz, 3 H, CH_3), 2.27 (dddd, J = 18.0, 14.4, 9.9, 3.6 Hz, 1 H, CH), 2.79 (dd, J = 19.2, 2.7 Hz, 1 H, CH), 3.55–3.66 (m, 1 H, CH), 4.07–4.90 (m, 1

H, CH), 7.26–7.75 (m, 2 H, ArH), 8.02–8.10 (m, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.8, 21.2, 30.3, 68.7, 70.0, 126.2, 131.7, 132.4, 133.7, 142.5, 146.7, 183.9, 184.0 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2931, 1662, 1593, 1458, 1292, 1128 cm^{-1}. MS: *m*/*z* = 242 $[M]^+$. $C_{15}H_{14}O_3$ (242.27): calcd. C 74.36, H 5.82; found C 74.45, H 5.87. The physical and spectroscopic data of **7** are in accordance with the literature data.[11]

(+)-(1*R*,3*R*)-1,3-Dimethyl-3,4-dihydro-1*H*-naphtho[2,3-*c*]pyran-5,10-dione (8): Compound (+)-**8** (25 mg, 82%) was prepared as a yellow solid from **19b** (24 mg, 0.12 mmol) by using a known procedure.[4a] R_f = 0.60 (EtOAc/hexane, 2:8). $[\alpha]_D^{26}$ = +66.3 (*c* = 0.12, $CHCl_3$). M.p. 147–149 °C (ref.[4a] 146–148 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.36 (d, *J* = 6.0 Hz, 3 H, CH_3), 1.54 (d, *J* = 7.2 Hz, 3 H, CH_3), 2.26 (dddd, *J* = 19.5, 12.3, 9.9, 2.4 Hz, 1 H, CH), 2.76 (dd, *J* = 19.5, 3.6 Hz, 1 H, CH), 3.99–4.03 (m, 1 H, CH), 5.02 (q, *J* = 6.8 Hz, 1 H, CH), 7.27–7.73 (m, 2 H, ArH), 8.05–8.09 (m, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.6, 21.4, 29.8, 62.4, 67.1, 126.2, 131.7, 132.0, 133.6, 133.7, 141.6, 146.3, 183.2, 184.0 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2929, 1658, 1593, 1460, 1327, 1180 cm^{-1}. MS: *m*/*z* = 242 $[M]^+$. $C_{15}H_{14}O_3$ (242.27): calcd. C 74.36, H 5.82; found C 74.46, H 5.89.

(+)-(*S*)-5,8-Dimethoxy-3-methyl-3,4-dihydro-1*H*-benzo[*c*]pyran (23): To a precooled (0 °C) solution of (+)-alcohol **20b** (200 mg, 1.02 mmol) and methoxymethyl chloride (232 μL, 3.06 mmol) in dry diethyl ether (15 mL) was added anhydrous $ZnCl_2$ (41 mg, 0.30 mmol) under an atmosphere of nitrogen, and the mixture was stirred at room temperature for 4 h. To this reaction mixture was added water, and the mixture was stirred for 10 min and then extracted with EtOAc (3 × 25 mL). The combined extract was washed with aqueous $NaHCO_3$ solution, water, and brine, dried with Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography (EtOAc/hexane, 0.6:9.4) to give (+)-**23** (175 mg, 82%) as a colorless solid. R_f = 0.5 (EtOAc/hexane, 1.5:8.5). $[\alpha]_D^{26}$ = +149.9 (*c* = 1.0, $CHCl_3$). M.p. 49–51 °C (ref.[20] 68–69 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (d, *J* = 6.0 Hz, 3 H, CH_3), 2.39 (dd, *J* = 16.5, 10.8 Hz, 1 H, CH), 2.75 (dd, *J* = 17.1, 3.3 Hz, 1 H, CH), 3.65–3.72 (m, 1 H, CH) 3.74 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 4.59 (d, *J* = 15.9 Hz, 1 H, CH), 4.92 (d, *J* = 15.9 Hz, 1 H, CH), 6.58 (d, *J* = 8.7 Hz, 1 H, ArH), 6.63 (d, *J* = 8.7 Hz, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6, 30.2, 55.3, 55.4, 64.4, 69.9, 106.6, 107.3, 123.8, 124.5, 149.3, 150.7 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2935, 1604, 1485, 1257, 1072 cm^{-1}. MS: *m*/*z* = 208 $[M]^+$. $C_{12}H_{16}O_3$ (208.25): calcd. C 69.21, H 7.74; found C 69.25, H 7.78.

(+)-(*S*)-3-Methyl-3,4-dihydro-1*H*-benzo[*c*]pyran-5,8-dione (24): To a precooled (0 °C) solution of (+)-**23** (152 mg, 0.73 mmol) in CH_3CN (9 mL) was added dropwise a solution of CAN (1.2 g, 2.19 mmol) in water (3 mL). The mixture was stirred at the same temperature for 20 min and then diluted with water and extracted with ethyl acetate (3 × 10 mL). The combined layer was dried with Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (EtOAc/hexane, 0.7:9.3) to afford (+)-**24** (120 mg, 92%) as a yellow solid. R_f = 0.5 (EtOAc/hexane, 2:8). $[\alpha]_D^{26}$ = +270.8 (*c* = 0.5, $CHCl_3$). M.p. 101–103 °C (ref.[20] 89–91 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.36 (d, *J* = 6.0 Hz, 3 H, CH_3), 2.12–2.24 (m, 1 H, CH), 2.58 (d, 19.2, 2.7 Hz, 1 H, CH), 3.60–3.69 (m, 1 H, CH), 4.38 (dt, *J* = 18.3, 2.7 Hz, 1 H, CH), 4.68 (dt, *J* = 18.3, 2.7 Hz, 1 H, CH), 6.68 (d, *J* = 10.2 Hz, 1 H, olefinic CH), 6.73 (d, *J* = 10.2 Hz, 1 H, olefinic CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.1, 28.8, 62.7, 69.4, 136.0, 136.3, 139.5, 140.2, 185.7, 186.0 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2945, 1658, 1597, 1402, 1143 cm^{-1}. MS (EI): *m*/*z* = 179 $[M + 1]^+$. $C_{10}H_{10}O_3$ (178.18): calcd. C 67.41, H 5.66; found C 67.50, H 5.73.

(+)-(*S*)-3-Methyl-3,4-dihydro-1*H*-naphtho[2,3-*c*]pyran-5,10-dione (25): A solution of quinone **24** (115 mg, 0.64 mmol) and L-acetoxybutadiene (361 mg, 3.23 mmol) in toluene (1.2 mL) was kept at room temperature for 48 h. The mixture was evaporated to dryness under reduced pressure, and the obtained oil was dissolved in EtOH (7 mL). To this solution was added 1% aqueous Na_2CO_3 solution (1.5 mL), and the mixture was stirred at room temperature for 5 h, diluted with water, and extracted with EtOAc (3 × 15 mL). The combined organic layer was washed with brine, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure, and the residue was purified by column chromatography (EtOAc/hexane, 0.7:9.3) to afford (+)-**25** (126 mg, 85%) as a yellow solid. R_f = 0.5 (EtOAc/hexane, 2:8). $[\alpha]_D^{26}$ = +251.7 (*c* = 0.2, $CHCl_3$). M.p. 168–170 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38 (d, *J* = 6.6 Hz, 3 H, CH_3), 2.24–2.36 (m, 1 H), 2.75 (dt, *J* = 19.2, 2.7 Hz, 1 H, CH), 3.64–3.74 (m, 1 H, CH), 4.52 (dt, *J* = 19.2, 3.9 Hz, 1 H, CH), 4.84 (dd, *J* = 18.3, 1.8 Hz, 1 H, CH), 7.68–7.75 (m, 2 H, ArH), 8.03–8.09 (m, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.2, 29.4, 63.2, 69.5, 126.0, 126.2, 126.3, 131.7, 131.8, 133.7, 141.8, 142.3, 183.3, 183.6 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2924, 2854, 1658, 1591, 1452, 1296, 1074 cm^{-1}. MS: *m*/*z* = 228 $[M]^+$. $C_{14}H_{12}O_3$ (228.24): calcd. C 73.67, H 5.30; found C 73.73, H 5.35.

(+)-(1*R*,3*S*)-1-Hydroxy-3-methyl-3,4,5,10-tetrahydro-1*H*-naphtho-[2,3-*c*]pyran-5,10-dione (9):[11,15c] To a solution of pyran **25** (55 mg, 0.21 mmol) in CCl_4 (35 mL) was added bromine (11.3 μL, 0.21 mmol) in CCl_4 (1 mL) at room temperature, and the mixture was irradiated with 300 W tungsten lamp for 30 min. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. To this obtained residue was added THF (10 mL) and water (2 mL), and the mixture was stirred for 1 h at room temperature, diluted with water, and extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine, dried with anhydrous Na_2SO_4, and concentrated, and the residue was purified by column chromatography (EtOAc/hexane, 1.6:8.4) to give (+)-**9** (42 mg, 77%) as a yellow solid. R_f = 0.3 (EtOAc/hexane, 2.5:7.5). $[\alpha]_D^{26}$ = +138.8 (*c* = 0.80, CH_2Cl_2) {ref.[15c] $[\alpha]_D^{20}$ = +29.5 (*c* = 0.80, CH_2Cl_2); ref.[11] $[\alpha]_D^{20}$ = +139.3 (*c* = 0.76, CH_2Cl_2)}. M.p. 160–162 °C (ref.[11,15c] 161–162 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40 (d, *J* = 6.7 Hz, 3 H, CH_3), 2.27 (dd, *J* = 19.2, 10.8 Hz, 1 H, CH), 2.78 (dd, *J* = 19.5, 3.3 Hz, 1 H, CH), 3.63 (br. s, 1 H, OH), 4.30–4.39 (m, 1 H, CH), 6.07 (br. s, 1 H, CH), 7.74–7.78 (m, 2 H, ArH), 8.09–8.13 (m, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.9, 29.3, 62.6, 86.8, 126.3, 131.8, 133.8, 134.0, 140.2, 143.5, 183.2, 184.3 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3421, 2980, 2928, 1668, 1591, 1446, 1290, 1076 cm^{-1}. MS: *m*/*z* = 244 $[M]^+$. $C_{14}H_{12}O_4$ (244.24): calcd. C 68.85, H 4.95; found C 68.89, H 5.01. The physical and spectroscopic data of **9** are in accordance with the literature data.[11,15c]

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[19] A referee suggested that the poor reactivity of bromide derivatives **13a** and **20a** towards Friedel–Crafts electrophilic cyclization is not due to the electron-withdrawing effect of bromine but due to the bulky bromine substituent at C-4 of the aryl ring, which requires the methyl group of the neighboring methoxy moiety to adopt such a conformation (out of plane) as to allow substitution of the unoccupied *ortho* position. This results in a decrease in the amount of conjugation with the aromatic ring, which therefore diminishes the activation of **13a** and **20a** towards Friedel–Crafts cyclization. At this stage we cannot exclude this possibility.

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