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Organocatalytic enantioselective formal synthesis of HRV 3C-protease inhibitor (1*R*,3*S*)-thysanone

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ABSTRACT

A short and efficient organocatalytic enantioselective formal synthesis of HRV 3C-protease inhibitor (1*R*,3*S*)-thysanone is achieved in a nine-step with 98.7% enantiomeric excess, by employing L-proline-catalyzed asymmetric α-aminooxylation of aldehyde and Oxa-Pictet–Spengler cyclization as the key steps.

1. Introduction

Pyran ring fused to a naphthoquinone nucleus is a ubiquitous structural sub-unit present in a number of biologically active natural products (Fig. 1).[1] Thysanone **1**, eleutherin **2**, ventiloquinone **3**, and nanomycin **4** are naturally occurring pyranonaphthoquinones, which exhibits wide range of biological acivity.[1c] Thysanone **1**, possess C-1–C-3 trans stereochemistry on the pyran ring, which shows promising antibiotic activity.[1c] It was isolated from the fungus *Thysanophora penicilloides* by Singh and co-workers[2] and is one of the effective inhibitors of human rhinovirus 3C-protease and therefore provides a lead compound for understanding the mechanism of 3C-protease inhibition. Due to significant biological activity of **1**, several approaches for the synthesis of **1** and its analogues have been reported.[3–9] Recently, Brimble and Sperry reported stereospecific synthesis of (−)-**1** using an *o*-toluate anion addition to chiral α,β-unsaturated δ-lactone.[9] The reported methods (except Brimble and Sperry[9]) are either based on lengthy chiral pool approach[3] or enzymatic resolution[4] while catalytic asymmetric methods are rather rare.[5]

Due to their interesting structural features and the biological significance of this class of compounds, we were encouraged to design a short and effective route for the synthesis of (1*R*,3*S*)-thysanone using proline-catalyzed asymmetric α-aminooxylation as the source of chirality.

Over past few years, the field of asymmetric organocatalysis is an emerging area of research in organic synthesis to obtain chiral compounds in high optical purity.[10] Among the different organocatalysts; proline, a readily available (in both D and L forms) bi-functional amino acid, has been found to be an excellent organocatalyst.[11] It has also been found to be an versatile organocatalyst for the asymmetric α-hydroxylation of aldehydes and ketones.[12] Herein we report for the first time a short and efficient organocatalytic enantioselective formal synthesis of (1*R*,3*S*)-thysanone **1** by using L-proline-catalyzed asymmetric α-aminooxylation of aldehyde[12a] and Oxa-Pictet–Spengler cyclization[13] as the key steps (Scheme 2).

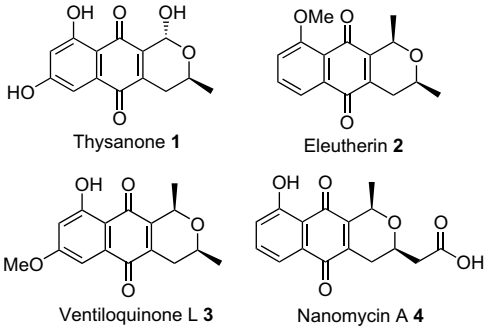

Figure 1. Structure of some pyranonaphthoquinone antibiotics.

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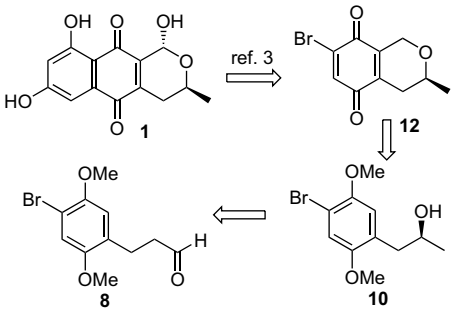
2. Result and discussion

Retrosynthetic strategy for the synthesis of (1*R*,3*S*)-thysanone is outlined in Scheme 1. Gill and Donner[3] have reported 15-step synthesis of (*S*)-bromopyranobenzoquinone **12** as a key intermediate starting from ethyl (*S*)-lactate in 4.7% yield for the total synthesis of (1*R*,3*S*)-thysanone **1**. We envisaged a new and short synthesis of important intermediate (+)-**12** from alcohol **10** through Oxa-Pictet–Spengler cyclization followed by oxidative demethylation of pyran **11**. Intermediate **10** can be prepared from chiral diol **9**, which in turn would be obtained by using L-proline-catalyzed asymmetric α-aminooxylation of aldehyde **8**. The aryl propanaldehyde **8** can be easily prepared from known aryl propanoate **5**[14] (Scheme 1).



Scheme 1. Retrosynthesis of (1*R*,3*S*)-thysanone.

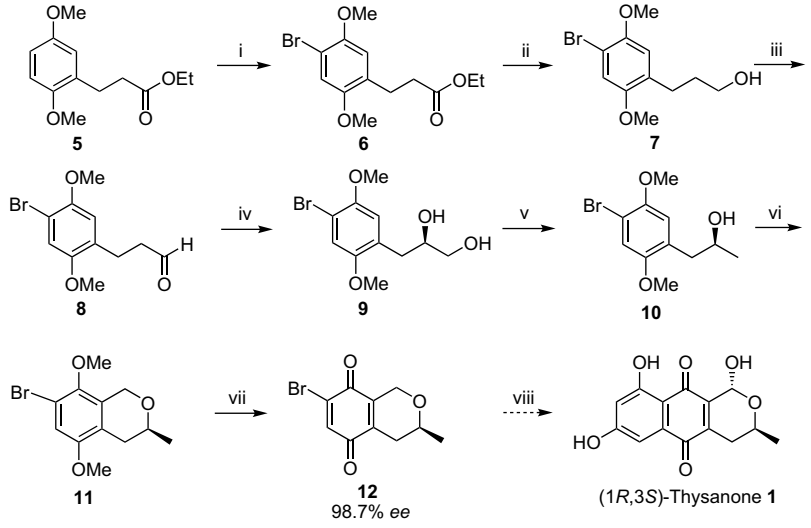
The synthesis of (1*R*,3*S*)-thysanone intermediate **12** is depicted in Scheme 2. Ethyl 3-(2,5-dimethoxyphenyl)propionate[14] **5** was easily prepared from 2,5-dimethoxy benzaldehyde by Wittig olefination followed by hydrogenation. The regioselective aromatic bromination of ester **5** using *N*-bromo succinimide (NBS) in CH_3CN at room temperature gave bromo compound **6** in 96% yield. Ester **6** was converted in to corresponding aldehyde **8** in high yield by following two-step reaction sequences. Initially, bromo ester **6** was reduced to alcohol **7** using $LiAlH_4$ in dry THF in 81% yield, subsequently, it was oxidized to corresponding aldehyde **8** with IBX in DMSO at room temperature in 87% yield. Aldehyde **8** was converted in to diol **9** by using L-proline-catalyzed asymmetric α-aminooxylation[12a] in a two-step reaction sequence: (i) reaction of **8** with nitrosobenzene as a source of oxygen in the presence of L-proline (25 mol %) in CH_3CN at −20 °C followed by treatment with $NaBH_4$ in MeOH gave the crude aminooxy alcohol and (ii) subsequent reduction of the crude aminooxy alcohol with 30 mol % $CuSO_4 \cdot 5H_2O$ afforded chiral diol **9** $[\alpha]_D^{25}$ +20.7 (*c* 1, EtOH) in 73% yield. Selective tosylation of primary hydroxyl functionality of diol **9** was carried out using catalytic amount of dibutyltin oxide (2 mol %) and *p*-toluenesulfonyl chloride.[15] The crude monotosylate was reduced with $LiAlH_4$ (4 equiv) in dry THF to afford the (+)-alcohol **10** $[\alpha]_D^{25}$ +21.0 (*c* 1, $CHCl_3$) in 90% yield. The enantiomeric excess was 98.7%, determined by HPLC equipped with chiral AD-H column.

Our next aim was to construct pyran ring of **11** through Oxa-Pictet–Spengler reaction.[13] We subjected alcohol **10** to the Oxa-Pictet–Spengler reaction with methoxymethyl chloride in presence of $ZnCl_2$ (30 mol %) in dry Et_2O to afford pyran **11**, mp 41–42 °C $[\alpha]_D^{25}$ +102.9 (*c* 1.1, $CHCl_3$) in 80% yield. Although synthesis of racemic pyran **11** is reported in the literature, its physical constant and optical rotation are not known.[3b] The oxidative demethylation of **11** with cerium(IV) ammonium nitrate (CAN) in aqueous CH_3CN furnished quinone **12**, mp 101–104 °C, $[\alpha]_D^{25}$ +192.4 (*c* 0.64, $CHCl_3$) {lit.[3b] mp 100–103 °C $[\alpha]_D$ +195 (*c* 0.64, $CHCl_3$)} as a yellow, crystalline solid in 77% yield and >98.7% ee (Scheme 2). The physical and spectroscopic data of the quinone **12** is in accordance with the literature data.[3b]

We have executed a nine-step organocatalytic enantioselective synthesis of (1*R*,3*S*)-thysanone intermediate (+)-**12** with an overall yield of 27.3% and high optical purity (98.7% ee) from ester **5**. Since, the conversion of (+)-**12** to (1*R*,3*S*)-thysanone **1** through regioselective Diels–Alder reaction and radical bromination followed by hydroxylation has already been reported in the literature.[3] Thus, an organocatalytic formal enantioselective synthesis of **1** has been accomplished. All compounds **5**–**12** have been fully characterized by spectroscopic techniques.

3. Conclusions

In summary, we have demonstrated a successful application of L-proline-catalyzed asymmetric α-aminooxylation and Oxa-Pictet–Spengler cyclization strategy to the asymmetric formal total synthesis of HRV 3C-protease inhibitor (1*R*,3*S*)-thysanone in 27.3%



Scheme 2. Reagents and conditions: (i) NBS, CH_3CN, rt, 12 h, 96%; (ii) $LiAlH_4$, THF, 0 °C to rt, 8 h, 81%; (iii) IBX, DMSO, rt, 4 h, 87%; (iv) (a) PhNO, L-proline (25 mol %), CH_3CN, −20 °C, 24 h then MeOH, $NaBH_4$, 30 min; (b) $CuSO_4 \cdot 5H_2O$ (30 mol %), 0 °C MeOH, 12 h, 73% (two steps); (v) (a) Bu_2SnO (2 mol %), *p*-TsCl (1.02 equiv), Et_3N, CH_2Cl_2, 0 °C to rt, 1 h; (b) $LiAlH_4$ (4 equiv) THF, 0 °C to rt, 5 h, 90% (two steps); (vi) $MeOCH_2Cl$ (20 equiv), $ZnCl_2$ (30 mol %), Et_2O, 0 °C to rt, 6 h, 80%; (vii) CAN (3 equiv), CH_3CN/H_2O (4:1), 0 °C to rt, 25 min, 77%; (viii) See Ref. 3. (a) 1-Methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene, toluene, reflux, 3 h; (b) Br_2 (1 equiv), $CC1_4$, *hν*, 0.5 h; then THF, H_2O, rt, 1 h, 62% (two steps).

yield with 98.7% ee. Good yield, environmentally friendly reaction procedures and high enantioselectivity are some of the salient features of our synthetic approach and represent a good alternative to the known methods. We believe that the present synthetic strategy would be potential route for the synthesis of related pyranonaphthoquinones compounds such as eleutherin and nanomycin A. Efforts are in progress in this direction.

4. Experimental section

4.1. General experimental details

All solvents were purified and dried by standard procedures prior to use. Melting points were recorded with Thomas Hoover Capillary melting point apparatus and are uncorrected. Thin layer chromatography was performed on Merck 60 F_{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) solution in concd 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 on Shimadzu FTIR 8400 as a thin film or KBr pellets and are expressed in cm^{-1}. Optical rotations were obtained on Jasco P-1020 digital polarimeter. ^1H and ^{13}C NMR spectra were recorded on Varian Mercury spectrometer on 300 and 75 MHz, respectively, using $CDCl_3$ as a solvent. Chemical shifts were reported in δ units (parts per million) with reference to TMS as an internal standard and coupling constants (J) are given in hertz. GC mass spectra were obtained on Shimadzu GCMS-QP5050A spectrometer. Elemental analyses were carried out with Thermo-Electron Corporation CHNS Analyzer, FLASH-EA 1112 at Shimadzu Analytical Centre, University of Pune. Analytical HPLC was performed on chiral AD-H column (250 mm×4.6 mm×5 μ).

4.2. Ethyl 3-(2,5-dimethoxyphenyl)propionate (5)[14]

A mixture of 2,5-dimethoxy benzaldehyde (7.0 g, 42.16 mmol) and ethyl (triphenylphosphoranylidiene) acetate (17.6 g, 50.60 mmol) in toluene (120 mL) was stirred at 100 °C. After 4 h, reaction mixture was cooled to room temperature and solvent was removed under reduced pressure and solid residue was purified over silica gel column chromatography using ethyl acetate/hexane (08:92) gave α,β-unsaturated ester (9.9 g) as green oil. To a solution of unsaturated ester (9.9 g) in MeOH (60 mL) was added 10% Pd/C (0.4 g). The reaction mixture was stirred for 12 h under hydrogen (1 atm) and then catalyst was filtered off and filtrate concentrated under reduced pressure. The crude product was purified over silica gel column chromatography (5% ethyl acetate/hexane) to yield ester **5** (9.8 g, 98% for two steps) as a colorless oil. [Found C, 65.62; H, 7.65%. $C_{13}H_{18}O_4$ requires C, 65.53; H, 7.61%.] R_f (10% ethyl acetate/hexane) 0.40; ν_{max} (film) 1732, 1500, 1224, 1051, 864, 802 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.23 (t, 3H, J=7.2 Hz, CH_3), 2.57 (t, 2H, J=7.5 Hz, CH_2CO), 2.89 (t, 2H, J=7.2 Hz, CH_2Ar), 3.73 (s, 3H, OMe), 3.76 (s, 3H, OMe), 4.11 (q, 2H, J=7.2 Hz, OCH_2CH_3), 6.66–6.75 (m, 3H, ArH); δ_C (75 MHz, $CDCl_3$) 14.3, 26.3, 34.2, 55.6, 55.7, 60.2, 110.9, 111.3, 116.1, 129.9, 151.5, 153.1, 173.1; MS: (m/z)=238 (M^+).

4.3. Ethyl 3-(4-bromo 2,5-dimethoxyphenyl)propionate (6)

A solution of ester **5** (5 g, 21.0 mmol) and NBS (3.74 g, 21.0 mmol) in CH_3CN (35 mL) was stirred at room temperature for 12 h, then diluted with water (25 mL) and extracted with ethyl acetate (3×25 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (5% ethyl acetate/hexane) to give pure bromo ester **6** (6.4 g, 96%) as a pale yellow solid; mp 55–57 °C. [Found C, 49.14; H, 5.46%. $C_{13}H_{17}BrO_4$ requires C, 49.23; H, 5.40.] R_f (10% ethyl acetate/hexane) 0.41; ν_{max} (KBr) 1732, 1213, 1043, 964, 860, 786 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.25 (t, 3H, J=7.2 Hz, CH_3), 2.55 (t, 2H, J=7.8 Hz, CH_2CO), 2.86 (t, 2H, J=7.4 Hz, CH_2Ar), 3.75 (s, 3H, OMe), 3.81 (s, 3H, OMe), 4.09 (q, 2H, J=7.2 Hz, OCH_2), 6.74 (s, 1H, ArH), 6.98 (s, 1H, ArH); δ_C (75 MHz, $CDCl_3$) 14.2, 26.1, 34.0, 55.8, 56.8, 60.3, 108.8, 114.3, 115.4, 128.8, 149.5, 151.6, 172.7; MS: (m/z)=318 (M^+) ^{81}Br, 316 (M^+) ^{79}Br.

4.4. 3-(4-Bromo 2,5-dimethoxyphenyl)propan-1-ol (7)

A solution of ester **6** (11.7 g, 37.0 mmol) in dry THF (25 mL) was added dropwise to a cold (0 °C) suspension of $LiAlH_4$ (1.54 g, 40.7 mmol) in dry THF (90 mL). After stirring this suspension for 8 h at room temperature, it was cooled to 0 °C then quenched with wet Na_2SO_4. The reaction mass was diluted with ethyl acetate (100 mL), filtered through pad of Celite under vacuum and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using (18% ethyl acetate/hexane) to give pure alcohol **7** (8.25 g, 81%) as a colorless oil. [Found C, 49.10; H, 5.41%. $C_{11}H_{15}BrO_3$ requires C, 48.02; H, 5.50%.] R_f (25% ethyl acetate/hexane) 0.25; ν_{max} (film) 3398, 2939, 1593, 1215, 1041, 910, 856, 856 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.81 (quin, 2H, J=6.6 Hz, CH_2CH_2Ar), 2.19 (br s, 1H, OH), 2.65 (t, 2H, J=7.1 Hz, CH_2Ar), 3.56–3.60 (t, 2H, J=6.3 Hz, CH_2OH), 3.76 (s, 3H, OMe), 3.8 (s, 3H, OMe), 6.72 (s, 1H, ArH), 7.0 (s, 1H, ArH); δ_C (75 MHz, $CDCl_3$) 26.1, 32.7, 56.1, 56.8, 61.6, 108.3, 114.2, 115.6, 130.1, 149.7, 151.5; MS: (m/z)=276 (M^+) ^{81}Br, 274 (M^+) ^{79}Br.

4.5. 3-(4-Bromo 2,5-dimehoxyphenyl)propanal (8)

A mixture of alcohol **7** (3 g, 10.94 mmol) and IBX (3.98 g, 14.23 mmol) in DMSO (25 mL) was stirred for 4 h at room temperature, then water was added to the reaction mixture and 2-iodobenzoic acid was filtered off. The filtrate was extracted with ether (3×40 mL), combined organic layer washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure and the crude product was purified by silica gel column chromatography (13% ethyl acetate/hexane) to afford pure aldehyde **8** (2.59 g, 87%) as a colorless oil. [Found C, 49.31; H, 5.92%. $C_{11}H_{13}BrO_3$ requires C, 48.37; H, 5.80%.] R_f (30% ethyl acetate/hexane) 0.55; ν_{max} (film) 1722, 1213, 1037, 910, 853, 736 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.70 (t, 2H, J=7.2 Hz, CH_2CHO), 2.88 (t, 2H, J=7.2 Hz, CH_2Ar), 3.75 (s, 1H, OMe), 3.81 (s, 1H, OMe), 6.74 (s, 1H, ArH), 6.99 (s, 1H, ArH), 9.75 (s, 1H, CHO); δ_C (75 MHz, $CDCl_3$) 23.4, 43.5, 55.8, 56.7, 108.8, 114.3, 115.4, 128.6, 149.5, 151.4, 201.5; MS: m/z=274 (M^+) ^{81}Br, 272 (M^+) ^{79}Br.

4.6. (*R*)-3-(4-Bromo 2,5-dimehoxyphenyl)1,2-propanediol (9)

To a stirred solution of aldehyde **8** (3.3 g, 12.14 mmol) and nitrosobenzene (1.0 g, 9.34 mmol) in CH_3CN (40 mL) was added L-proline (0.268 g, 2.33 mmol) at −20 °C. The reaction was stirred at the same temperature for 24 h and then diluted with MeOH (15 mL) and to this solution $NaBH_4$ (1.06 g, 28.03 mmol) was added. After 25 min, the reaction mixture was quenched with saturated aqueous $NaHCO_3$, extracted with ethyl acetate (3×30 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The $CuSO_4 \cdot 5H_2O$ (0.7 g, 2.8 mmol) was added at 0 °C to the suspension of crude product in MeOH (30 mL) and stirred for 10 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (30 mL) and extracted with ethyl acetate (3×40 mL), washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (40–50% ethyl acetate/hexane) to yield pure (+)-diol **9** (1.97 g, 73%) as a white solid; mp 123–125 °C. [Found C, 45.31; H,

5.26%. $C_{11}H_{15}BrO_4$ requires C, 45.38; H, 5.19%.] R_f (50% ethyl acetate/hexane) 0.12; $[\alpha]_D^{25}$ +20.7 (*c* 1, EtOH); ν_{max} (KBr) 3319, 2847, 1577, 1496, 1388, 1211, 1080, 1032, 958, 852, 796 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.17 (br s, 1H, OH), 2.35 (br s, 1H, OH), 2.71–2.86 (m, 2H, CH_2Ar), 3.49 (m, 1H, CH_2OH), 3.61 (m, 1H, CH_2OH), 3.79 (s, 3H, OMe), 3.84 (s, 3H, OMe), 3.91 (m, 1H, CHOH), 6.75 (s, 1H, ArH), 7.04 (s, 1H, ArH); δ_C (75 MHz, $CDCl_3$) 34.3, 56.1, 56.8, 65.8, 71.7, 109.1, 115.4, 115.6, 126.4, 149.7, 151.5; MS: (*m*/*z*)=292 (M^+) ^{81}Br, 290 (M^+) ^{79}Br.

4.7. (*S*)-3-(4-Bromo 2,5-dimehoxyphenyl)-2-propanol (10)

To a stirred solution of (+)-diol **9** (1.1 g, 3.79 mmol) in dry DCM (15 mL), dibutyltin oxide (0.020 g, 0.079 mmol), triethylamine (565 μL, 4.03 mmol), and *p*-toluenesulfonyl chloride (0.769 g, 4.03 mmol) was added at 0 °C. The reaction mixture was stirred for 1 h at room temperature, diluted with water (20 mL), and the reaction mixture was extracted with DCM (3×25 ml). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford crude monotosylate. The crude monotosylate was used for next step without any purification.

The solution of crude tosylate (1.68 g, 3.79 mmol) in dry THF (15 mL) was added dropwise to the cooled (0 °C) suspension of $LiAlH_4$ (0.576 g, 15.1 mmol) in dry THF (20 mL) and stirred for 5 h at room temperature. The reaction mixture was quenched with wet Na_2SO_4, diluted with ethyl acetate (40 mL), filtered through pad of Celite under vacuum, and concentrated under reduced pressure. The crude alcohol was purified by silica gel column chromatography (20% ethyl acetate/hexane) to afford pure (+)-alcohol **10** (0.92 g, 90%) as a white solid; mp 111–112 °C. The enantiomeric excess was found to be 98.7% (ee was determined by chiral HPLC equipped with chiral AD-H column (250 mm×4.6 mm×5 μ) with hexane/EtOH/TFA (90:9.9:0.1 v/v/v) as a eluent (flow rate 1.2 mL/min)). The retention time for major and minor isomers was 7.3 and 9.1 min, respectively. [Found C, 49.14; H, 5.42%. $C_{11}H_{15}BrO_3$ requires C, 48.02; H, 5.50%.] R_f (30% ethyl acetate/hexane) 0.30; $[\alpha]_D^{25}$ +21.0 (*c* 1, $CHCl_3$); ν_{max} (KBr) 3389, 2935, 2843, 1620, 1496, 1437, 1386, 1118, 1030, 943, 852 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.21 (d, 2H, *J*=6.3 Hz, CH_3), 2.02 (br s, 1H, OH), 2.64 (dd, 1H, *J*=13.4, 7.9 Hz, CH_2Ar), 2.76–2.82 (dd, 1H, *J*=13.4, 4.4 Hz, CH_2Ar), 3.76 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.99–4.03 (m, 1H, CHOH), 6.73 (s, 1H, ArH), 7.02 (s, 1H, ArH); δ_C (75 MHz, $CDCl_3$) 23.0, 40.3, 56.0, 56.8, 67.6, 109.1, 115.4, 115.7, 127.1, 149.6, 151.7; MS: (*m*/*z*)=276 (M^+) ^{81}Br, 274 (M^+) ^{79}Br.

4.8. (*S*)-7-Bromo-1-hydroxy-5,8-dimethoxy-3-methyl-3,4-dihydro-1*H*-2-benzopyran (11)

To a pre-cooled (0 °C) solution of (+)-alcohol **10** (0.4 g, 1.45 mmol) and methoxymethyl chloride (2.21 mL, 29.1 mmol) in dry diethyl ether (15 mL) was added anhydrous $ZnCl_2$ (0.06 g, 0.43 mmol) under nitrogen and stirred at room temperature for 6 h. To this reaction mixture water was added, stirred for 10 min and extracted with diethyl ether (3×25 mL). The combined organic layers were washed with aqueous solution of $NaHCO_3$, water, brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (6% ethyl acetate/hexane) to give (+)-pyran **1** (0.33 g, 80%) as colorless solid; mp 41–42 °C. The spectroscopic data of (+)-**11** is in full agreement with reported data of racemic pyran **11**.[3b] [Found C, 50.11; H, 5.33%. $C_{12}H_{15}BrO_3$ requires C, 50.19; H, 5.27%.] R_f (20% ethyl acetate/hexane) 0.50; $[\alpha]_D^{25}$ +102.9 (*c* 1.1, $CHCl_3$); ν_{max} (KBr) 777, 952, 1130, 1180, 1230, 1471, 2893, 2933, 2962 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.37 (d, 3H, *J*=6.0 Hz, CH_3), 2.31 (dd, 1H, *J*=16.5, 10.4 Hz, CH_2Ar), 2.70 (d, 1H, *J*=17.1, 4.4 Hz, CH_2Ar), 3.69–3.70 (m, 1H, $CHOCH_3$), 3.76 (s, 3H, OMe), 3.78 (s, 3H, OMe), 4.68 (d, 1H, *J*=15.6 Hz, $ArCH_2O$), 4.96 (d, 1H, *J*=15.7 Hz, $ArCH_2O$), 6.85 (s, 1H, ArH); δ_C (75 MHz, $CDCl_3$) 21.6, 30.1, 55.6, 60.4, 64.6, 70.1, 112.0, 113.1, 123.2, 130.4, 146.2, 153.3; MS: (*m*/*z*)=288 (M^+) ^{81}Br, 286 (M^+) ^{79}Br.

4.9. (*S*)-7-Bromo-3-methyl-3,4-dihydro-1*H*-2-benzopyran-5,8-dione (12)[3b]

To a pre-cooled (0 °C) solution of the (+)-pyran **11** (0.11 g, 0.384 mmol) in CH_3CN (8 mL) was added dropwise a solution of CAN (0.632 g, 1.15 mmol) in water (2 mL). The mixture was stirred for 25 min at room temperature, then diluted with water (10 mL), extracted with ethyl acetate (3×10 mL). The combined layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (8% ethyl acetate/hexane) to afford (+)-bromobenzoquinone **12** (0.076 g, 77%); as a yellow crystalline solid; mp 101–104 °C; {lit.[3b] mp 100–103 °C}. [Found C, 46.64; H, 3.62%. $C_{10}H_9BrO_3$ requires C, 46.72; H, 3.53%.] R_f (20% ethyl acetate/hexane) 0.45; $[\alpha]_D^{25}$ +192.4 (*c* 0.64, $CHCl_3$); {lit.[3b] $[\alpha]_D$ +195 (*c* 0.64, $CHCl_3$)}; ν_{max} (KBr) 2983, 2929, 2856, 1660, 1591, 1386, 1263, 1139 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.35 (d, 3H, *J*=6.0 Hz, CH_3), 2.15–2.25 (m, 1H, CH_2), 2.59 (d, 1H, *J*=19.2 Hz, CH_2), 3.62–3.65 (m, 1H, $CHOCH_3$), 4.41 (d, 1H, *J*=18.7 Hz, CH_2O), 4.72 (d, 1H, *J*=18.4 Hz, CH_2O), 7.25 (s, 1H, CH); δ_C (75 MHz, $CDCl_3$) δ 21.1, 29.1, 63.2, 69.4, 136.8, 137.7, 140.1 (2C), 177.7, 183.2; MS: (*m*/*z*)=258 (M^+) ^{81}Br, 256 (M^+) ^{79}Br.

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