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Asymmetric Total Synthesis of Cladosporin and Isocladosporin

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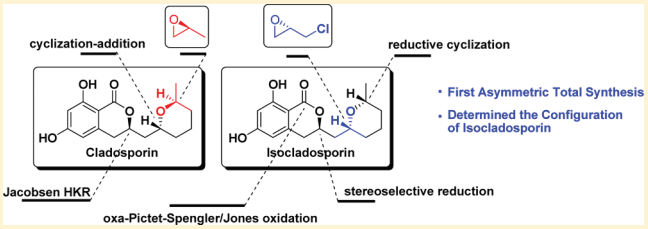
Supporting Information

ABSTRACT: The first asymmetric total syntheses of cladosporin and isocladosporin were accomplished in 8 steps with 8% overall yield and 10 steps with 26% overall yield, respectively. The relative configuration of isocladosporin was determined via this total synthesis.



INTRODUCTION

Cladosporin ((−)-**1**) (also known as asperentin) is an antifungal antibiotic and plant growth inhibitor produced by various fungal sources.[1,2] Vederas and other researchers at Merck assigned its absolute stereochemistry,[3,2e] and Grove et al. reported the general features of its biosynthesis in *Aspergillus flavus* by administration of [1-^{13}C]acetate and [2-^{14}C]-malonate.[4] Isocladosporin (**2** or **3**), whose structure was not determined on the basis of the available characterization data, was isolated from the fungus *Cladosporium cladosporioides* in 1993 (Figure 1).[5] Cladosporin ((−)-**1**) and isocladosporin (**2** or **3**) both feature a 2,6-disubstituted tetrahydropyran (THP) ring and a δ-valerolactone with a fused 1,3-dihydroxybenzene ring. Their favorable bioactivities as well as interesting structures inspired our interest in their syntheses. As part of our ongoing program toward the syntheses of bioactive pyran- and pyranone-type natural products,[6,7] we herein report the first asymmetric total synthesis of cladosporin and isocladosporin and also the efforts to determine the relative configuration of isocladosporin (given the lack of optical data for natural isocladosporin, the absolute configuration of the natural product cannot be deduced).

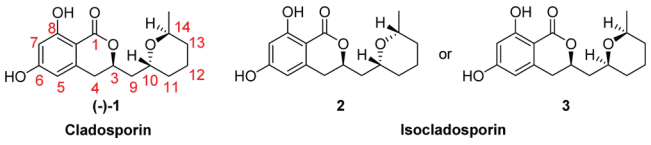


Figure 1. Structures of cladosporin (**1**) and isocladosporin (**2** or **3**).

RETROSYNTHETIC ANALYSIS

The stereodivergent construction of cyclic ethers remains an important area of synthetic interest,[8] in which 2,6-disubstituted tetrahydropyran systems are present in a large number of biologically active natural products such as leucascandrolide,[9] phorboxazole,[10] and spirastrellolide.[11] Based on the chemistry involving intramolecular tandem cyclization−addition[12] and reductive etherification[13] reactions, we envisioned that cladosporin and isocladosporin could be synthesized in short steps from tetrahydropyran (THP) oxocarbenium ions **6** and **10**, respectively (Scheme 1). In addition, the δ-valerolactone could be synthesized through a similar reaction sequence involving oxa-Pictet−Spengler cyclization[14] and Jones oxidation.[15]

RESULTS AND DISCUSSION

Our synthesis of (−)-**1** thus began with **7**, which was derived from ring-opening of (*S*)-propylene oxide **8** in one step (Scheme 2). Hydroxy dioxane **7** was treated with allyltrimethylsilane in the presence of a catalytic amount of TMSOTf to give **16** with 2,6-*trans*-THP selectivity. We then accessed the enantioenriched epoxide (−)-**17** using the Jacobsen hydrolytic kinetic resolution (HKR)[16] from the corresponding epoxide which was obtained as a 1:1 mixture by *m*-CPBA epoxidation of alkene **16**. Alcohol ***trans*-4** was obtained by reaction of epoxide **17** with the Grignard reagent and CuI at low temperature. Subsequently, the lactone **19** was furnished from ***trans*-4** by a two-step process involving oxa-Pictet−Spengler cyclization and Jones oxidation. Initially, the oxa-Pictet−Spengler reaction was found to be unsuccessful between ***trans*-4** and MOMCl/$ZnCl_2$, DMM/BF_3·Et_2O, or DMM/TMSOTf (DMM: dimethoxymethane). Finally, condensation of ***trans*-4** with trimethyl orthoformate under pTSA conditions yielded the desired acetal **18** in 89% yield, which was characterized to be a single diastereomer of *trans*-pyran.[17] Jones oxidation of **18** led to the

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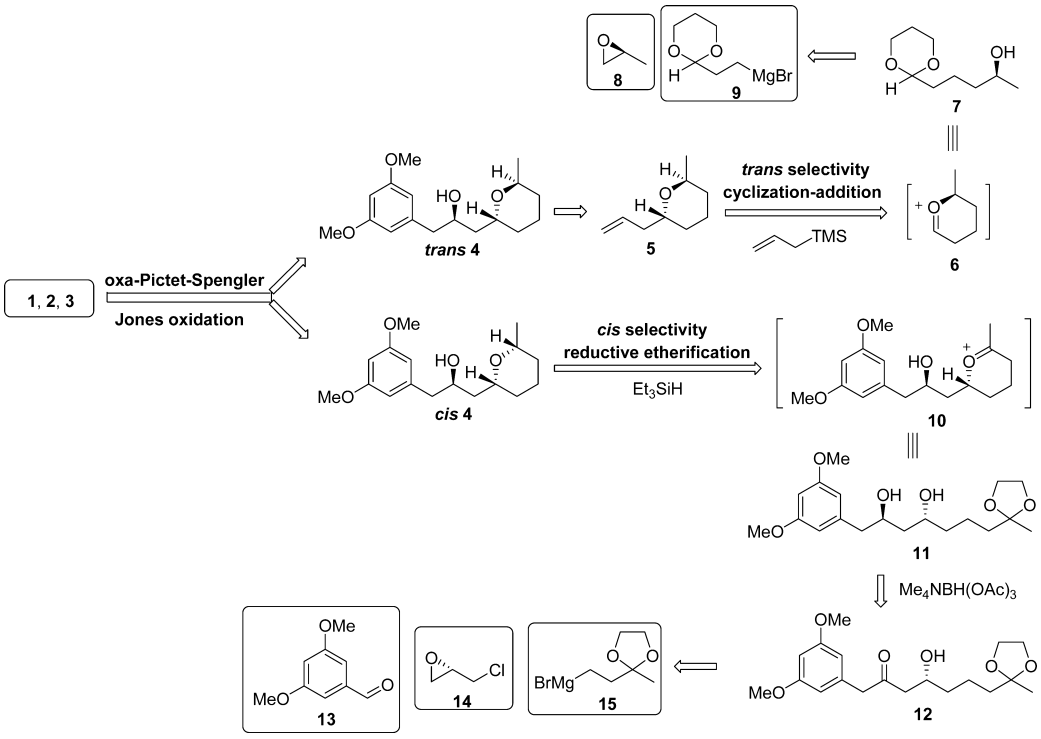
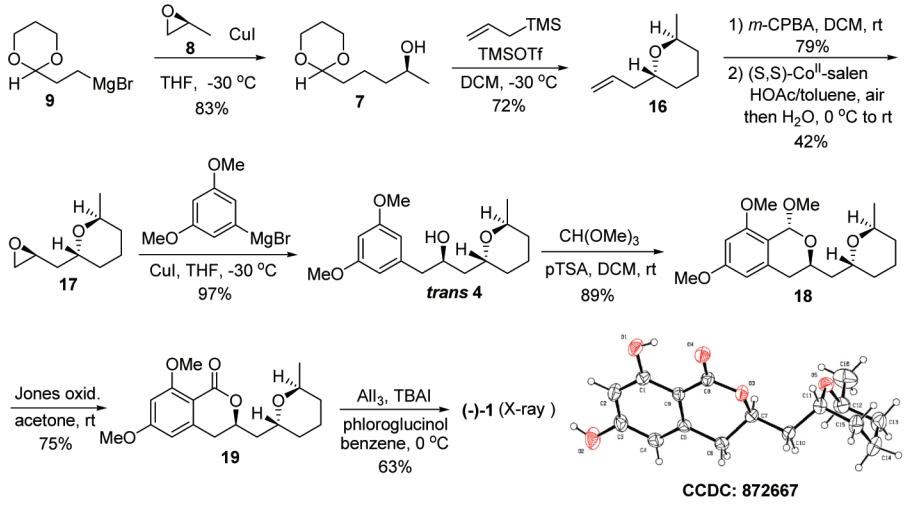
Scheme 1. Retrosynthetic Analysis of Cladosporin (1) and Isocladosporin (2 or 3)



Scheme 2. Total Synthesis of Cladosporin ((−)-1)



formation of lactone **19**, which was converted to the natural product (−)-**1** by removal of both aromatic methyl ether functions under Maier's conditions[18] (AlI_3, TBAI, and phloroglucinol). The crystal structure determination established the stereochemistry of the 2,6-*trans*-tetrahydropyran ring at positions C10 and C14 and the 1,3-*anti*-diol at positions C3 and C10 (for details, see the Supporting Information).[19]

Based on the successful synthesis of cladosporin, we then turned our attention to the synthesis of isocladosporin (Scheme 3). According to the structure of (−)-**2**, the more plausible configuration of isocladosporin according to the original literature,[5] aldehyde **13** was selected as the starting material. Homologation of **13** was performed via a Wittig reaction, and the resulting enol ether was directly treated with 1,3-propanedithiol and $BF_3{\cdot}Et_2O$ to give dithiane **20** in satisfactory yield.[20] Treatment of **20** with ^{t}BuLi in THF was followed by the ring-opening of (*S*)-epichlorohydrin and concurrent epoxide formation to afford **21**. The ring-opening of epoxide **21**, deprotection of the 1,3-dithiane group with I_2, and $Me_4NBH(OAc)_3$ reduction[21] of *β*-hydroxy ketone **12** gave the desired 1,3-*anti*-diol **11**. Then we turned to the reductive cyclization of hydroxy dioxolanes developed by Colobert and co-workers.[22] Treatment of **11** with an excess of Et_3SiH (5 equiv), followed by TMSOTf (1.3 equiv) in CH_2Cl_2 at 0 °C, led to the rapid (within 30 min) formation of the 2,6-*cis*-THP derivative ***cis*-4** as a sole diastereomer. The remaining steps involving oxa-Pictet−Spengler reaction, Jones oxidation, and deprotection of both aromatic methyl ether functions were conducted as depicted as the synthesis of cladosporin. The characterization data of (−)-**2** (^{1}H, ^{13}C NMR determined in $CDCl_3$, and melting point) were consistent with the structure reported for isocladosporin (the solvent was not mentioned in

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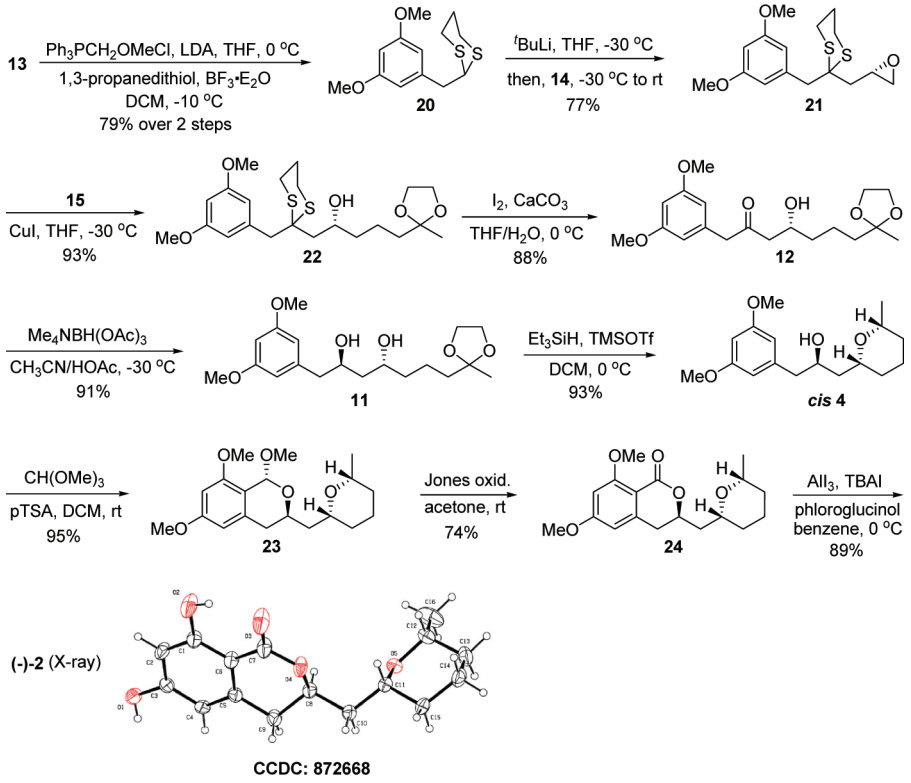
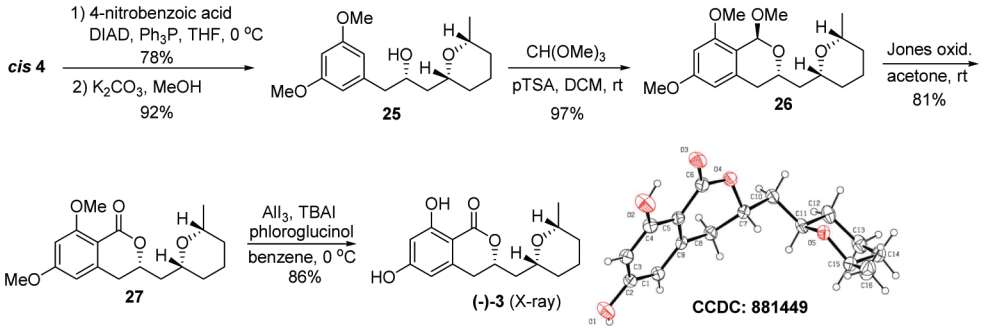
Scheme 3. Total Synthesis of (−)-2



Scheme 4. Synthesis of (−)-3



the original reference; however, the comparative analysis of ^{1}H and ^{13}C chemical shifts between Jacyno and Springer led us to believe that the data were collected in $CDCl_3$).

To further confirm the configuration of isocladosporin, the enantiomer of the other possible structure (−)-**3** was also synthesized (Scheme 4). Alcohol ***cis*-4** was first converted to alcohol **25** through Mitsunobu reaction[23] and deprotection of the ester by K_2CO_3 in MeOH. Subsequently, (−)-**3** was synthesized from **25** in three steps according to the previous route.

The principal differences between **2** and **3** were observed in ^{13}C NMR spectra and melting point (see Table 1). Specifically, the ^{13}C resonances at lower field for **3** ranging from 172.0 to 141.0 ppm and 78.0−73.0 ppm appears fairly diagnostic between **3** and **2**. It is worth mentioning that the NMR data of **3** were collected in CD_3OD solvent because of its insolubility in $CDCl_3$. In addition, the melting point of 196−202 °C for **3** was significantly different from the value of isocladosporin obtained by Jacyno or the value of **2**. Therefore, we confirmed that the configuration of isocladosporin is **2**.

CONCLUSION

In conclusion, we have accomplished the first asymmetric total synthesis of cladosporin ((−)-**1**) and isocladosporin ((−)-**2**) from commercially available (*S*)-propylene oxide and (*S*)-epichlorohydrin as chiral sources, respectively. The strategy was developed on the basis of a notion of concise enantioselective assembly of the tetrahydropyran ring. The relative configuration of isocladosporin was defined as the structure of **2** compared with **3** through this total synthesis.

EXPERIMENTAL SECTION

Materials and Methods. All chemicals were used as received. Solvent THF was refluxed with Na, and CH_2Cl_2 was refluxed with CaH_2 and freshly distilled prior to use. All reactions under standard conditions were monitored by thin-layer chromatography (TLC) on gel F254 plates. The silica gel (200−300 meshes) was used for column chromatography, and the distillation range of petroleum was 60−90 °C. ^{1}H and ^{13}C NMR spectral data were reported in ppm relative to tetramethylsilane (TMS) as internal standard. High-resolution mass

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Table 1. Analysis data of (−)-1, 2, and 3

		^{13}C NMR ($CDCl_3$)													mp (°C)
(−)-1	Jacyno et al.[5]	169.68	164.34	162.34	141.85	106.48	102.04	101.96	76.31	67.83	66.35	39.47	33.66	30.95	30.86	18.92	18.19	
	Springer et al.[2e]	169.5	164.4	163.9	141.2	106.8	101.4	100.4	76.0	66.9	66.2	38.7	33.5	31.1	30.5	19.2	18.2	180−184
	Vederas et al.[3]	169.7	164.5	162.5	141.9	106.6	102.0	128.4	76.4	67.9	66.5	39.5	33.7	31.00	30.97	19.0	18.3	187.5−188.5
	our work	170.1	164.1	163.7	141.6	106.9	101.8	101.0	76.3	67.8	66.6	38.8	33.4	30.9	30.6	19.0	18.0	175−177
2	Jacyno et al.[5]	170.10	164.30	162.84	141.94	106.67	101.92	101.69	75.94	74.02	73.16	41.79	33.64	33.17	31.86	23.47	22.02	164−166
	our work	170.3	164.2	163.3	141.9	106.8	101.9	101.3	76.0	74.1	73.2	41.7	33.6	33.1	31.6	23.4	22.0	159−160
3[a]		171.7	166.4	165.8	143.6	108.1	102.3	101.7	78.0	75.5	75.2	42.2	34.5	33.8	32.5	24.7	22.6	196−202

[a]NMR data was collected in CD_3OD.

spectra (HRMS) were recorded using a Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometer.

Preparation of (*S*)-5-(1,3-Dioxan-2-yl)pentan-2-ol (7). To a suspension of Mg (1.26 g, 0.052 g atom) in THF (10 mL) was added I_2 to activate Mg, and a solution of the bromide (9.75 g, 50.0 mmol) in THF (100 mL) was added dropwise. After the addition (about 1 h), the mixture was stirred at rt for 2 h and then cooled to −30 °C.

To this cold Grignard reagent solution was added CuI (0.95 g, 5 mmol), followed by the addition of (*S*)-propylene oxide (5.8 g, 100 mmol) in THF (30 mL). The mixture was stirred at −30 °C overnight and then quenched by addition of saturated aqueous NH_4Cl solution (50 mL). After 30 min of stirring, the mixture was extracted with Et_2O, and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting yellowish oil was purified by column chromatography to afford alcohol **7** as a colorless oil (7.22 g, 83%): $[\alpha]^{20}_D$ = +4.0 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.53 (t, *J* = 5.2 Hz, 1H), 4.10 (dd, *J* = 4.4, 11.2 Hz, 2H), 3.81−3.73 (m, 3H), 2.13−2.03 (m, 1H), 1.76−1.33 (m, 8H), 1.18 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 102.2, 67.8, 66.8, 39.0, 34.9, 25.8, 23.4, 20.1; HRMS (EIS) calcd for $C_9H_{19}O_3$ $[M + H]^+$ 175.1329, found 175.1335.

Preparation of (2*R*,6*S*)-2-Allyltetrahydro-6-methyl-2*H*-pyran (16). To a cooled (−40 °C) solution of **7** (10.0 g, 57.5 mmol) and allyltrimethylsilane (18.2 mL, 115 mmol) in CH_2Cl_2 (100 mL) was added TMSOTf (2.1 mL, 11.5 mmol). The reaction mixture was then warmed to −20 °C and stirred for 1 h. After quenching by addition of saturated aqueous $NaHCO_3$ solution, the resulting mixture was diluted with Et_2O. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography to afford **16** as a colorless oil (5.8 g, 72%): $[\alpha]^{20}_D$ = −40.0 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86−5.76 (m, 1H), 5.10−5.03 (m, 2H), 3.95−3.90 (m, 1H), 3.84−3.79 (m, 1H), 2.46−2.38 (m, 1H), 2.24−2.17 (m, 1H), 1.69−1.61 (m, 4H), 1.38−1.26 (m, 2H), 1.18 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5, 116.4, 70.6, 67.0, 37.9, 31.5, 29.2, 19.7, 18.3; HRMS (EIS) calcd for $C_9H_{17}O$ $[M + H]^+$ 141.1274, found 141.1265.

Preparation of (2*S*,6*R*)-Tetrahydro-2-methyl-6-(((*S*)-oxiran-2-yl)methyl)-2*H*-pyran (17). To a solution of alkene **16** (1.4 g, 10 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added 70% (m/m) *m*-CPBA (3.94 g, 16 mmol) in one portion. The reaction mixture was warmed to room temperature and stirred for 10 h. The reaction mixture was quenched with 1 N aqueous NaOH and saturated aqueous $Na_2S_2O_3$ and extracted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum to give a yellow liquid which was purified by column chromatography to afford the corresponding epoxide as a colorless liquid (1.27 g, 79%).

A flask open to air was charged with (*R*,*R*)-Co^{II} salen (24 mg, 0.04 mmol) and AcOH (27 mg, 0.45 mmol) in toluene (10 mL) at room temperature. The solution, initially red, turned brown within a few seconds. The solution was stirred under air atmosphere for 1 h and then concentrated under vacuum. The above epoxide was added neat. The solution was cooled to 0 °C, and water (80 mg, 5 mmol) was added dropwise while the temperature was controlled. After the addition, the reaction mixture was allowed to warm to room temperature (water bath was used to ensure temperature remains around 20 °C). The reaction mixture was stirred for 18 h and then directly purified by column chromatography to afford pure epoxide **17** (0.53 g, 42%) as a colorless oil: $[\alpha]^{20}_D$ = −59.0 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.04−3.88 (m, 2H), 3.05−3.01 (m, 1H), 2.79 (t, *J* = 4.4 Hz, 1H), 2.49−2.47 (m, 1H), 1.99−1.93 (m, 1H), 1.73−1.59 (m, 4H), 1.48−1.28 (m, 3H), 1.19 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 68.7, 67.2, 50.0, 47.2, 36.8, 31.3, 30.3, 19.5, 18.3; HRMS (EIS) calcd for $C_9H_{16}NaO_2$ $[M + Na]^+$ 179.1043, found 179.1050.

Preparation of (*R*)-1-((2*R*,6*S*)-Tetrahydro-6-methyl-2*H*-pyran-2-yl)-3-(3,5-dimethoxyphenyl)propan-2-ol (*trans*-4). To a cooled (−30 °C) THF solution of **10**, which had been prepared from Mg (0.6 g, 0.025 g atom), 1-bromo-3,5-dimethoxybenzene (5.0 g, 23

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mmol), I_2 (cat.), and THF in a similar manner as described above, was added CuI (0.44 g, 2.31 mmol) followed by the addition of epoxide **17** (0.83 g, 5.32 mmol) in THF (10 mL). The mixture was stirred at −30 °C overnight and then quenched by addition of saturated aqueous NH_4Cl solution (10 mL). After 30 min of stirring, the mixture was extracted with Et_2O, and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting yellowish oil was purified by column chromatography to afford alcohol ***trans*-4** as a colorless oil (1.52 g, 97%): $[\alpha]^{20}_D$ = −19.5 (*c* = 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.38 (d, *J* = 2.0 Hz, 2H), 6.33 (d, *J* = 2.0 Hz, 1H), 4.10−4.06 (m, 2H), 3.97−3.95 (m, 1H), 3.77 (s, 6H), 2.80 (br s, 1H), 2.71 (d, *J* = 6.4 Hz, 2H), 1.89−1.83 (m, 1H), 1.70−1.26 (m, 8H), 1.20 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 141.2, 107.2, 98.2, 69.5, 67.5, 67.5, 55.1, 44.3, 39.6, 30.8, 30.5, 18.7, 18.2; HRMS (EIS) calcd for $C_{17}H_{27}O_4$ $[M + H]^+$ 295.1904, found 295.1913.

Preparation of (1*R*,3*R*)-3,4-Dihydro-3-(((2*R*,6*S*)-tetrahydro-6-methyl-2*H*-pyran-2-yl)methyl)-1,6,8-trimethoxy-1*H*-isochromene (18). To a solution of ***trans*-4** (0.96 g, 3.26 mmol) and trimethyl orthoformate (8 mL) in CH_2Cl_2 (20 mL) was added pTSA (62 mg, 0.326 mmol). After being stirred for 1 h, the reaction mixture was quenched with addition of saturated aqueous $NaHCO_3$ solution, and the resulting mixture was diluted with Et_2O. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography to afford **18** (0.98 g, 89%) as a white solid: $[\alpha]^{20}_D$ = −35.0 (*c* = 2.0, $CHCl_3$); mp 62 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.29 (s, 1H), 6.20 (s, 1H), 5.52 (s, 1H), 4.40−4.33 (m, 1H), 4.16−4.11 (m, 1H), 3.94−3.91 (m, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 3.55 (s, 3H), 2.62 (d, *J* = 7.6 Hz, 2H), 1.99−1.93 (m, 1H), 1.74−1.56 (m, 5H), 1.42−1.30 (m, 2H), 1.21 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 158.0, 136.6, 115.9, 103.7, 96.7, 95.3, 67.0, 66.9, 63.0, 55.6, 55.2, 55.1, 39.7, 34.6, 31.5, 30.7, 19.4, 18.4; HRMS (EIS) calcd for $C_{19}H_{28}NaO_5$ $[M + Na]^+$ 359.1829, found 359.1822.

Preparation of (*R*)-3,4-Dihydro-3-(((2*R*,6*S*)-tetrahydro-6-methyl-2*H*-pyran-2-yl)methyl)-6,8-dimethoxyisochromen-1-one (19). To a cooled (0 °C) solution of **18** (0.80 g, 2.37 mmol) in acetone (12 mL) was added 3.0 M Jones oxidant (2.4 mL, 7.2 mmol). The reaction mixture was then warmed to rt and stirred for 1 h. After quenching by addition of water, the resulting mixture was diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography to afford **19** as a foamy solid (0.57 g, 75%): $[\alpha]^{20}_D$ = +76.5 (*c* = 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.34 (s, 1H), 6.24 (s, 1H), 4.53−4.51 (br m, 1H), 4.02 (br m, 1H), 3.85 (br m, 1H), 3.85 (s, 3H), 3.79 (s, 3H), 2.86−2.73 (m, 2H), 1.87−1.55 (m, 6H), 1.27 (br m, 2H), 1.13 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 162.8, 162.6, 143.8, 106.8, 103.7, 97.5, 74.2, 67.3, 65.9, 55.9, 55.3, 39.3, 35.3, 30.8, 30.7, 18.7, 18.1; HRMS (EIS) calcd for $C_{18}H_{24}NaO_5$ $[M + Na]^+$ 343.1516, found 343.1512.

Preparation of Cladosporin ((−)-1). A suspension of Al powder (1.81 g, 67 mmol) in dry benzene (10 mL) was treated with I_2 (6.35 g, 25 mmol) under Ar, and the violet mixture was stirred under reflux for 30 min until the color had changed to a colorless mixture. After the mixture was cooled to 0 °C, a few crystals of TBAI (58 mg, 0.157 mmol) and phloroglucinol (0.99 g, 7.85 mmol) were added before a solution of lactone **19** (0.5 g, 1.56 mmol) in dry benzene (3 mL) was added in one portion. The resulting green-brown suspension was stirred for 30 min at 0 °C before saturated $Na_2S_2O_3$ solution (15 mL) and ethyl acetate (15 mL) were added. After separation of the layers, the aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography to afford **1** (0.29 g, 63%) as a white solid: $[\alpha]^{20}_D$ = −14.0 (*c* = 1.0, EtOH); mp 175−177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.99 (d, *J* = 1.6 Hz, 1H), 8.46 (m, 1H), 6.29 (d, *J* = 2.0 Hz, 1H), 6.16 (d, *J* = 1.6 Hz, 1H), 4.71−4.66 (m, 1H), 4.13−4.10 (m, 1H), 3.97 (br s, 1H), 2.88−2.75 (m, 2H), 2.02−1.95 (m, 1H), 1.84−1.78 (m, 1H), 1.68−1.53 (m, 4H), 1.37−1.32 (m, 2H), 1.20 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 164.1, 163.7, 141.6, 106.9, 101.8, 101.0, 76.3, 67.8, 66.6, 38.8, 33.4, 30.9, 30.6, 19.0, 18.0; HRMS (EIS) calcd for $C_{16}H_{21}O_5$ $[M + H]^+$ 293.1384, found 293.1389.

Preparation of 2-(3,5-Dimethoxybenzyl)-1,3-dithiane (20). To a suspension of methoxymethylphosphonium chloride (20.5 g, 60 mmol) in 150 mL of THF was added LDA (2.0 M, 30 mL, 60 mmol) at 0 °C, and the mixture was stirred for 30 min at 0 °C. Aldehyde **13** (6.64 g, 40 mmol) in 50 mL of THF was added to the mixture. After being stirred for 1 h, the reaction mixture was quenched by addition of saturated aqueous NH_4Cl solution, and the resulting mixture was diluted with Et_2O. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was dissolved in petroleum ether; after removal of $Ph_3P{=}O$, the filtrate was concentrated in vacuo.

The crude residue was dissolved in CH_2Cl_2 (100 mL), and 1,3-propanedithiol (5.3 g, 48 mmol) was added at −10 °C. To the resultant solution was added $BF_3{\cdot}Et_2O$ (10 mL, 80 mol) dropwise and the solution stirred at −10 °C for 2 h. The reaction was then carefully quenched with saturated $NaHCO_3$ solution and extracted with Et_2O. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. MeOH was added to this residue; **20** (10.8 g, 79%) was then obtained as a white solid after filtration: mp 75−76 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.41 (d, *J* = 2.4 Hz, 2H), 6.36 (t, *J* = 2.4 Hz, 1H), 4.25 (t, *J* = 7.6 Hz, 1H), 3.78 (s, 6H), 2.96 (d, *J* = 7.6 Hz, 2H), 2.90−2.78 (m, 4H), 2.15−2.08 (m, 1H), 1.91−1.80 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 139.4, 107.2, 98.8, 55.1, 48.3, 42.0, 30.5, 25.7; HRMS (EIS) calcd for $C_{13}H_{19}O_2S_2$ $[M + H]^+$ 271.0821, found 271.0832.

Preparation of (*S*)-2-((2-(3,5-Dimethoxybenzyl)-1,3-dithian-2-yl)methyl)oxirane (21). To a solution of 1,3-dithiane **20** (3.80 g, 14 mmol) in anhydrous THF (10 mL) at −30 °C was added ^{t}BuLi (1.7 M in pentane, 12.4 mL, 21 mmol). After 30 min, (*S*)-epichlorohydrin (1.95 g, 21 mmol) was added dropwise, and the reaction mixture was stirred for a further 1 h at −30 °C and then allowed to warm to rt and stirred overnight. The reaction was quenched by saturated aqueous NH_4Cl solution and extracted with Et_2O. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography to give epoxide **21** as a white solid (3.52 g, 77%): $[\alpha]^{20}_D$ = +12.0 (*c* = 1.0, $CHCl_3$); mp 62 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.51 (d, *J* = 2.0 Hz, 2H), 6.34 (d, *J* = 2.0 Hz, 1H), 3.74 (s, 6H), 3.27−3.17 (m, 3H), 2.86−2.84 (m, 4H), 2.83−2.77 (m, 1H), 2.50−2.48 (m, 1H), 2.19 (dd, *J* = 4.4, 15.2 Hz, 1H), 2.01−1.91 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 137.2, 109.2, 98.6, 55.0, 52.0, 49.0, 46.4, 45.8, 40.5, 26.2, 24.5; HRMS (EIS) calcd for $C_{16}H_{22}NaO_3S_2$ $[M + Na]^+$ 349.0903, found 349.0905.

Preparation of (*R*)-1-(2-(3,5-Dimethoxybenzyl)-1,3-dithian-2-yl)-5-(2-methyl-1,3-dioxolan-2-yl)pentan-2-ol (22). To a cooled (−30 °C) THF solution of **15**, which had been prepared from Mg (0.40 g, 0.017 g atom), 2-(2-bromoethyl)-2-methyl-1,3-dioxolane (3.0 g, 15 mmol), I_2 (cat.), and THF in a similar manner as described above, was added CuI (0.286 g, 1.5 mmol) followed by the addition of epoxide **21** (1.63 g, 5 mmol) in THF (10 mL). The mixture was stirred at −30 °C overnight and then quenched by addition of saturated aqueous NH_4Cl solution (10 mL). After 30 min of stirring, the mixture was extracted with Et_2O, and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting yellowish oil was purified by column chromatography to afford alcohol **22** as a colorless oil (2.05 g, 93%): $[\alpha]^{20}_D$ = −31.0 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.47 (s, 2H), 6.37 (s, 1H), 4.08 (m, 1H), 3.93 (m, 4H), 3.77 (s, 6H), 3.50 (br s, 1H), 3.21 (dd, *J* = 14.0, 32.4 Hz, 2H), 3.08−3.02 (m, 1H), 2.96−2.90 (m, 1H), 2.83 (m, 2H), 2.28−2.21 (m, 1H), 2.02 (m, 1H), 1.93−1.85 (m, 2H), 1.65−1.37 (m, 6H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 137.2, 109.9, 109.3, 98.8, 68.5, 64.5, 55.2, 52.4, 46.2, 43.9, 39.0, 37.7, 26.8, 26.3, 24.5, 23.6, 20.0; HRMS (EIS) calcd for $C_{22}H_{34}NaO_5S_2$ $[M + Na]^+$ 465.1740, found 465.1744.

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Preparation of (*R*)-4-Hydroxy-1-(3,5-dimethoxyphenyl)-7-(2-methyl-1,3-dioxolan-2-yl)heptan-2-one (12). Dithiane **22** (1.50 g, 3.39 mmol) was dissolved in THF/H_2O (4:1, 35 mL) and $CaCO_3$ (3.39 g, 33.9 mmol) and then cooled to 0 °C, whereupon iodine (2.60 g, 10.2 mmol) was added portionwise. The reaction mixture was then allowed to stir for 30 min before quenching with saturated $Na_2S_2O_3$ (20 mL) solution. The aqueous phase was separated and extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by column chromatography to give hydroxy ketone **12** (1.05 g, 88%) as a colorless oil: $[\alpha]^{20}_D = -33.0$ (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.37 (s, 1H), 6.33 (d, J = 2.0 Hz, 2H), 4.01 (m, 1H), 3.95−3.86 (m, 4H), 3.78 (s, 6H), 3.63 (s, 2H), 3.01 (s, 1H), 2.66−2.52 (m, 2H), 1.67−1.33 (m, 6H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.3, 161.0, 135.7, 109.9, 107.4, 99.0, 67.4, 64.5, 55.2, 51.0, 48.1, 38.8, 36.4, 23.7, 19.9; HRMS (EIS) calcd for $C_{19}H_{28}NaO_6$ $[M + Na]^+$ 375.1778, found 375.1779.

Preparation of (2*R*,4*R*)-1-(3,5-Dimethoxyphenyl)-7-(2-methyl-1,3-dioxolan-2-yl)heptane-2,4-diol (11). To a stirred solution of $Me_4NBH(OAc)_3$ (4.2 g, 16 mmol) in acetonitrile (10 mL) was added acetic acid (12 mL), and the mixture was stirred at room temperature for 30 min. The mixture was cooled to −30 °C, and an acetonitrile solution of compound **12** (0.7 g, 2 mmol in 5 mL of acetonitrile) was added. The mixture was stirred at the same temperature for 12 h. The reaction was quenched with 1 N NaOH, and the resulting mixture was diluted with EtOAc. The layers were separated, and the aqueous layer extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography to give diol **11** (0.64 g, 91%) as a colorless oil: $[\alpha]^{20}_D = +3.5$ (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.35 (s, 2H), 6.31 (d, J = 1.6 Hz, 1H), 4.16−4.11 (m, 1H), 3.96−3.86 (m, 5H), 3.75 (s, 6H), 2.80 (br s, 2H), 2.69 (d, J = 6.8 Hz, 2H), 1.63−1.34 (m, 8H), 1.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 140.7, 109.9, 107.2, 98.3, 69.8, 68.8, 64.5, 55.2, 44.3, 42.0, 38.9, 37.4, 23.6, 20.1; HRMS (EIS) calcd for $C_{19}H_{31}O_6$ $[M + H]^+$ 355.2115, found 355.2111.

Preparation of (*R*)-1-((2*R*,6*R*)-Tetrahydro-6-methyl-2*H*-pyran-2-yl)-3-(3,5-dimethoxyphenyl)propan-2-ol (*cis*-4). To a cooled (0 °C) solution of **11** (0.4 g, 1.13 mmol) and triethylsilane (0.66 g, 5.65 mmol) in CH_2Cl_2 was added TMSOTf (0.33 g, 1.49 mmol). After being stirred for 30 min at 0 °C, the reaction was quenched with saturated aqueous $NaHCO_3$ solution, the resulting mixture was diluted with Et_2O. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography to afford ***cis* 4** as a colorless oil (0.31 g, 93%): $[\alpha]^{20}_D = -0.5$ (c = 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.40 (d, J = 2.0 Hz, 2H), 6.34 (dd, J = 2.0, 2.4 Hz, 1H), 4.19−4.13 (m, 1H), 3.79 (s, 6H), 3.72-.367 (m, 1H), 3.50−3.43 (m, 1H), 3.13 (d, J = 3.6 Hz, 1H), 2.72 (d, J = 6.4 Hz, 2H), 1.84−1.79 (m, 1H), 1.73−1.62 (m, 2H), 1.57−1.45 (m, 3H), 1.40−1.30 (m, 1H), 1.24−1.14 (m, 1H), 1.17 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 141.2, 107.2, 98.1, 75.4, 74.0, 69.4, 55.1, 44.2, 41.5, 33.0, 30.7, 23.5, 22.1; HRMS (EIS) calcd for $C_{17}H_{27}O_4$ $[M + H]^+$ 295.1904, found 295.1915.

Preparation of (1*R*,3*R*)-3,4-Dihydro-3-(((2*R*,6*R*)-tetrahydro-6-methyl-2*H*-pyran-2-yl)methyl)-1,6,8-trimethoxy-1*H*-isochromene (23). The same procedure as described above for the preparation of **18** was used in the preparation of **23**. To a solution of ***cis*-4** (0.282 g, 0.96 mmol) and trimethyl orthoformate (2.5 mL) in CH_2Cl_2 (10 mL) was added pTSA (19 mg, 0.096 mmol). After being stirred for 1 h, the reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ solution, and the resulting mixture was diluted with Et_2O. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography to afford **23** (0.306 g, 95%) as a white solid: $[\alpha]^{20}_D = -31.0$ (c = 1.0, $CHCl_3$); mp 104−105 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.29 (d, J = 2.0 Hz, 1H), 6.20 (d, J = 2.0 Hz, 1H), 5.53 (s, 1H), 4.53−4.47 (m, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 3.72−3.67 (m, 1H), 3.51 (s, 3H), 3.48−3.41 (m, 1H), 2.60 (d, J = 7.2 Hz, 2H), 1.86−1.50 (m, 6H), 1.30−1.18 (m, 2H), 1.17 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 157.9, 136.8, 115.9, 103.8, 96.7, 95.1, 73.9, 73.7, 62.2, 55.6, 55.2, 54.5, 42.4, 34.5, 33.3, 31.8, 23.8, 22.0; HRMS (EIS) calcd for $C_{19}H_{28}NaO_5$ $[M + Na]^+$ 359.1829, found 359.1826.

Preparation of (*R*)-3,4-Dihydro-3-(((2*R*,6*R*)-tetrahydro-6-methyl-2*H*-pyran-2-yl)methyl)-6,8-dimethoxyisochromen-1-one (24). The same procedure as described for the preparation of **19** was used in the preparation of **24**. To a cooled (0 °C) solution of **23** (0.166 g, 0.494 mmol) in acetone (2.5 mL) was added 3.0 M Jones oxidant (0.5 mL, 1.482 mmol). The reaction mixture was then warmed to rt and stirred for 1 h. After quenching by addition of water, the resulting mixture was diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography to afford **24** as a yellowish oil (0.117 g, 74%): $[\alpha]^{20}_D = +126.0$ (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.39 (s, 1H), 6.28 (s, 1H), 4.69−4.64 (m, 1H), 3.91 (s, 3H), 3.84 (s, 3H), 3.72−3.67 (m, 1H) 3.46−3.39 (m, 1H), 2.90−2.76 (m, 2H), 1.89−1.77 (m, 2H), 1.73−1.66 (m, 1H), 1.58−1.51 (m, 3H), 1.25−1.15 (m, 2H), 1.10 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 163.0, 162.9, 144.1, 107.1, 103.8, 97.7, 73.8, 73.6, 73.0, 56.1, 55.5, 41.7, 35.5, 33.2, 31.6, 23.5, 22.0; HRMS (EIS) calcd for $C_{18}H_{25}O_5$ $[M + H]^+$ 321.1697, found 321.1705.

Preparation of Isocladosporin ((−)-2). The same procedure as described for the preparation of **1** was used in the preparation of (−)-**2**. A suspension of Al powder (0.38 g, 14.1 mmol) in dry benzene (5 mL) was treated with I_2 (1.34 g, 5.27 mmol) under Ar, and the violet mixture was stirred under reflux for 30 min until the color had changed to a colorless mixture. After the mixture was cooled to 0 °C, a few crystals of TBAI (12 mg, 0.033 mmol) and phloroglucinol (0.21 g, 1.67 mmol) were added before a solution of lactone **24** (0.105 g, 0.328 mmol) in dry benzene (1 mL) was added in one portion. The resulting green-brown suspension was stirred for 30 min at 0 °C before saturated $Na_2S_2O_3$ solution (5 mL) and ethyl acetate (5 mL) were added. After separation of the layers, the aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography to afford (−)-**2** (0.085 g, 89%) as a white solid: $[\alpha]^{20}_D = -5.0$ (c = 1.0, $CHCl_3$); mp 158−159 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.07 (d, J = 2.0 Hz, 1H), 7.83 (m, 1H), 6.34 (d, J = 2.0 Hz, 1H), 6.17 (s, 1H), 4.83−4.78 (m, 1H), 3.72−3.66 (m, 1H), 3.49−3.45 (m, 1H), 2.84−2.71 (m, 2H), 1.92−1.71 (m, 3H), 1.60−1.50 (m, 3H), 1.27−1.20 (m, 2H), 1.15 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 164.2, 163.3, 141.9, 106.8, 101.9, 101.3, 76.0, 74.1, 73.2, 41.7, 33.6, 33.1, 31.6, 23.4, 22.0; HRMS (EIS) calcd for $C_{16}H_{21}O_5$ $[M + H]^+$ 293.1384, found 293.1394.

Preparation of (*S*)-1-((2*R*,6*R*)-Tetrahydro-6-methyl-2*H*-pyran-2-yl)-3-(3,5-dimethoxyphenyl)propan-2-ol (25). To a stirred, cooled (0 °C) mixture of ***cis*-4** (0.50 g, 1.7 mmol), triphenylphosphine (0.50 g, 2.57 mmol), and 4-nitrobenzoic acid (0.43 g, 2.57 mmol) in THF (20 mL) was added dropwise diisopropyl azodicarboxylate (0.41 g, 2.57 mmol), and the mixture was stirred at rt overnight. After removal of the solvent, the residue was loaded directly onto a silica gel column, and elution with PE and EtOAc yielded the desired 4-nitrobenzoate as a yellow oil (0.58 g, 78%).

To a MeOH solution of the 4-nitrobenzoate obtained above was added K_2CO_3 (0.36 g, 2.6 mmol), and the resulting mixture was stirred at rt for 1 h before water and EtOAc were added. After separation of the layers, the aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography to afford **25** (0.354 g, 92%) as a colorless oil: $[\alpha]^{20}_D = -18.0$ (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.39 (d, J = 2.0 Hz, 2H), 6.32 (d, J = 2.0 Hz, 1H), 4.31 (s, 1H), 4.12−4.05 (m, 1H), 3.78 (s, 6H), 3.59−3.44 (m, 2H), 2.79 (dd, J = 6.4, 13.2 Hz, 1H), 2.58 (dd, J = 6.4, 13.2 Hz, 1H), 1.80−1.75 (m, 1H), 1.58−1.43 (m, 5H), 1.27−1.17 (m, 2H), 1.15 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 141.2, 107.4, 98.1, 79.3, 74.0, 73.2, 55.2, 44.3,

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41.8, 32.8, 31.6, 23.3, 22.1; HRMS (EIS) calcd for $C_{17}H_{27}O_4$ $[M + H]^+$ 295.1904, found 295.1901.

Preparation of (1*S*,3*S*)-3,4-Dihydro-3-(((2*R*,6*R*)-tetrahydro-6-methyl-2*H*-pyran-2-yl)methyl)-1,6,8-trimethoxy-1*H*-isochromene (26). The same procedure as described for the preparation of **18** was used in the preparation of **26**. To a solution of **25** (0.235 g, 0.8 mmol) and trimethyl orthoformate (1.6 mL) in CH_2Cl_2 (5 mL) was added pTSA (16 mg, 0.08 mmol). After being stirred for 1 h, the reaction mixture was quenched with addition of saturated aqueous $NaHCO_3$ solution, and the resulting mixture was diluted with Et_2O. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography to afford **26** (0.261 g, 97%) as a white solid: $[\alpha]^{20}_D$ = +5.0 (*c* = 1.0, $CHCl_3$); mp 92 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.30 (d, *J* = 2.0 Hz, 1H), 6.22 (d, *J* = 2.0 Hz, 1H), 5.51 (s, 1H), 4.36−4.29 (m, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 3.66−3.59 (m, 1H), 3.52 (s, 3H), 3.49−3.44 (m, 1H), 2.65 (d, *J* = 6.8 Hz, 2H), 2.05−1.97 (m, 1H), 1.87−1.84 (m, 1H), 1.74−1.48 (m, 4H), 1.27−1.22 (m, 2H), 1.17 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 158.1, 136.6, 115.9, 103.8, 96.8, 95.5, 74.5, 74.0, 63.3, 55.6, 55.3, 55.2, 42.3, 34.1, 33.3, 31.1, 23.7, 22.2; HRMS (EIS) calcd for $C_{19}H_{29}O_5$ $[M + H]^+$ 337.2010, found 337.2016.

Preparation of (*S*)-3,4-Dihydro-3-(((2*R*,6*R*)-tetrahydro-6-methyl-2*H*-pyran-2-yl)methyl)-6,8-dimethoxyisochromen-1-one (27). The same procedure as described for the preparation of **19** was used in the preparation of **27**. To a cooled (0 °C) solution of **26** (0.18 g, 0.53 mmol) in acetone (3 mL) was added 3.0 M Jones oxidant (0.55 mL, 1.65 mmol). The reaction mixture was then warmed to rt and stirred for 1 h. After quenching by addition of water, the resulting mixture was diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography to afford **27** as a white solid (0.139 g, 81%): $[\alpha]^{20}_D$ = −70.0 (*c* = 1.0, $CHCl_3$); mp 123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.40 (s, 1H), 6.32 (s, 1H), 4.58−4.55 (m, 1H), 3.92 (s, 3H), 3.86 (s, 3H), 3.66−3.61 (m, 1H), 3.46−3.42 (m, 1H), 2.97 (dd, *J* = 11.2, 16.0 Hz, 1H), 2.84 (dd, *J* = 2.4, 16.0 Hz, 1H), 2.13−2.05 (m, 1H), 1.83−1.73 (m, 2H), 1.64−1.47 (m, 3H), 1.28−1.14 (m, 2H), 1.13 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 163.1, 162.7, 144.1, 107.0, 103.9, 97.7, 74.3, 73.8, 73.4, 56.1, 55.5, 40.8, 34.7, 33.1, 30.9, 23.5, 22.1; HRMS (EIS) calcd for $C_{18}H_{25}O_5$ $[M + H]^+$ 321.1697, found 321.1690.

Preparation of (*S*)-3,4-Dihydro-3-(((2*R*,6*R*)-tetrahydro-6-methyl-2*H*-pyran-2-yl)methyl)-6,8-dihydroxyisochromen-1-one ((−)-3). The same procedure as described for the preparation of (−)-**1** was used in the preparation of (−)-**3**. A suspension of Al powder (0.36 g, 13.4 mmol) in dry benzene (5 mL) was treated with I_2 (1.27 g, 5 mmol) under Ar, and the violet mixture was stirred under reflux for 30 min until the color had changed to a colorless mixture. After the mixture was cooled to 0 °C, a few crystals of TBAI (12 mg, 0.033 mmol) and phloroglucinol (0.197 g, 1.56 mmol) were added before a solution of lactone **27** (0.10 g, 0.313 mmol) in dry benzene (1 mL) was added in one portion. The resulting green-brown suspension was stirred for 30 min at 0 °C before saturated $Na_2S_2O_3$ solution (5 mL) and ethyl acetate (5 mL) were added. After separation of the layers, the aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography to afford (−)-**3** (0.079 g, 86%) as a white solid: $[\alpha]^{20}_D$ = −46.0 (*c* = 1.0, EtOH); mp 196−202 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 6.22 (s, 1H), 6.20 (s, 1H), 4.73−4.66 (m, 1H), 3.63−3.57 (m, 1H), 3.51−3.44 (m, 1H), 2.98−2.86 (m, 2H), 2.07−2.00 (m, 1H), 1.85−1.77 (m, 2H), 1.66−1.56 (m, 3H), 1.28−1.53 (m, 2H), 1.13 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 166.4, 165.8, 143.6, 108.1, 102.3, 101.7, 78.0, 75.5, 75.2, 42.2, 34.5, 33.8, 32.5, 24.7, 22.6; HRMS (EIS) calcd for $C_{16}H_{21}O_5$ $[M + H]^+$ 293.1384, found 293.1390.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Spectroscopic data for all new compounds and X-ray data for compounds **1**−**3** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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