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Enantioselective total syntheses of cedrelin A and methylated paralycolin B using Pd-catalyzed asymmetric intramolecular Friedel–Crafts allylic alkylation of phenols

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ABSTRACT

We report the first enantioselective total syntheses of cedrelin A and methylated paralycolin B, wherein Pd-catalyzed asymmetric intramolecular Friedel–Crafts allylic alkylation of phenols was the key step.

1. Introduction

Highly oxygenated 9,10-dihydrophenanthrenes are ubiquitous structural motifs in biologically active natural products. In 1987, Delle Monache and co-workers reported the isolation of a novel dihydrophenanthrapyrane natural product from the root of *Clusia paralycola*, paralycolin A (**1a**), which exhibits cytotoxicity against KB and P388 cells (Fig. 1).[1a] The structurally related natural products cedrelin A (**2a**) and cedrelin B (**2b**) were isolated from the bark of *Cedrelinga catenaeformis* Duke by Kakisawa and co-workers in 1991. Cedrelin A has cytotoxic activity against *Staphylococcus aureus* (209P) and *Bacillus subtilis* (IAM1213).[1b] Paralycolin B (**1b**), whose oxidation pattern differs from that of paralycolin A and cedrelins, was also reported by Delle Monache et al. in 2002.[1c] This natural product was isolated only as a methylated derivative (**1c**) after treatment of an obtained mixture of paralycolin A and paralycolin B with diazomethane. In addition to multiple oxygen functionalities on the aromatic rings, these natural products commonly possess an isopropenyl group at the 10-position of the 9,10-dihydrophenanthrene skeleton. The reported bioactivities and characteristic structure make these natural products attractive targets in organic synthesis and medicinal chemistry. To date, however, synthetic studies of these natural products have not been reported. The development of an efficient and divergent synthetic method would facilitate detailed studies of the bioactivities of this class of dihydrophenanthrapyranes. Herein we report the first enantioselective total syntheses of cedrelin A and methylated paralycolin B using Pd-catalyzed asymmetric intramolecular Friedel–Crafts allylic alkylation of phenols.

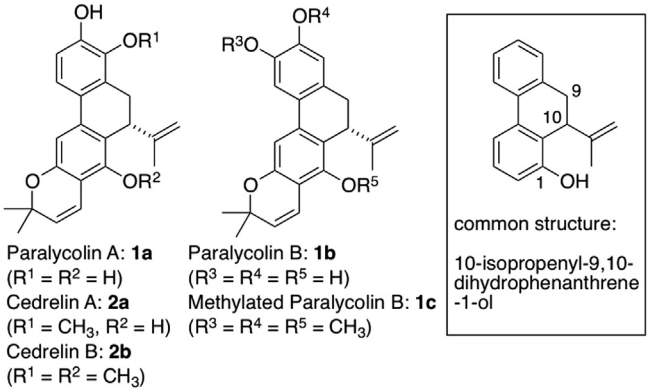

Fig. 1. Dihydrophenanthrapyrane natural products.

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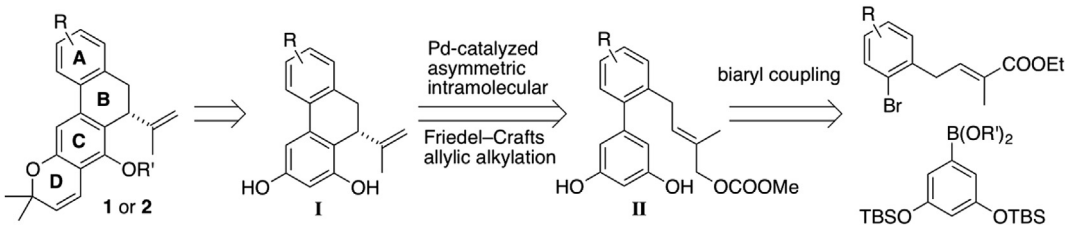
2. Results and discussions

Our plan for the enantioselective synthesis of cedrelins and paralycolins is shown in Scheme 1. As part of our ongoing studies aimed at developing novel synthetic methods based on intramolecular Friedel–Crafts-type reactions,[2] we recently reported a Pd-catalyzed asymmetric intramolecular Friedel–Crafts allylic alkylation of phenols that provides 10-vinyl- or 10-isopropenyl-substituted chiral 9,10-dihydrophenanthrenes in excellent yield with high enantioselectivity.[3,4] This catalytic asymmetric reaction can be a powerful tool for constructing the core structure of target natural products. We envisioned that the D-ring moiety could be constructed in the late stage of the synthesis using diphenol-type compounds **I** as key intermediates, which in turn would be obtained in optically active forms by the Pd-catalyzed asymmetric intramolecular Friedel–Crafts allylic alkylation of symmetric 3,5-dihydroxy biphenyl derivatives **II**. Biphenyl derivatives could be prepared from the corresponding aryl bromides and arylboronate using catalytic biaryl coupling reactions.

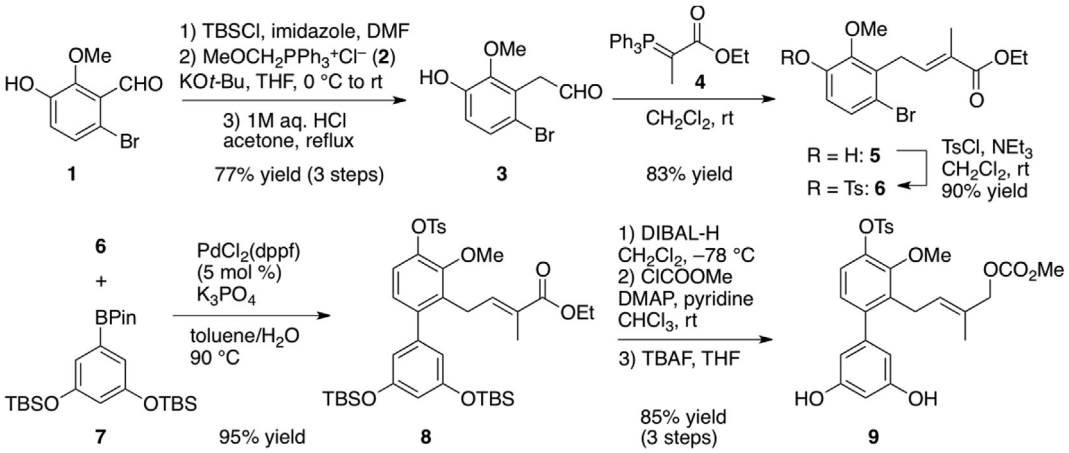


Scheme 1. Synthetic plan.

Synthetic studies toward cedrelin A started with the known aldehyde **1**[5] (Scheme 2). After temporary protection of the phenolic hydroxyl group with a TBS group, a methylene-unit homologation of the aldehyde moiety was performed via Wittig reaction using phosphonium salt **2**, followed by acidic hydrolysis, affording compound **3** in 77% yield in three steps. Compound **3** was reacted with stable ylide **4** to give α,β-unsaturated ester **5** (83% yield), which was then transformed into the corresponding tosylate **6** in 90% yield. Suzuki–Miyaura cross-coupling[6] of **6** with **7** proceeded smoothly using 5 mol % of $PdCl_2$(dppf) and K_3PO_4 as a base, affording biaryl derivative **8** in 95% yield. After reduction of the ester unit with DIBAL-H, the obtained alcohol was converted into allyl carbonate derivative **9** in 85% yield in three steps.

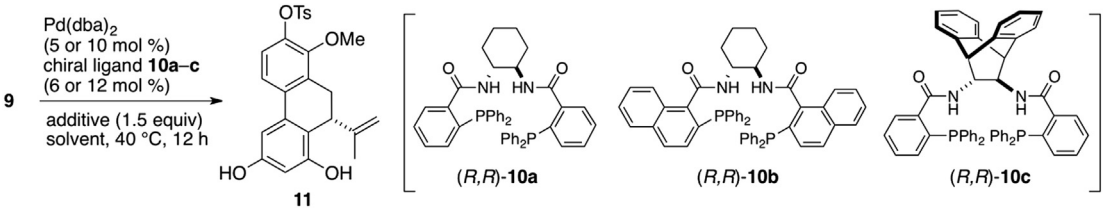
We next examined Pd-catalyzed asymmetric intramolecular Friedel–Crafts allylic alkylation of **9** (Table 1). First, we performed the reaction using 10 mol % of $Pd(dba)_2$ and 12 mol % of (*R*,*R*)-DCHA-phenyl Trost ligand[7] **10a** in CH_2Cl_2/MeOH mixed solvent at 40 °C, which were the optimum conditions for the previously reported chiral 9,10-dihydrophenanthrene synthesis. The reaction proceeded smoothly to give compound **11** in 94% yield, which was determined by ^1H NMR analysis of the crude mixture. Enantiomeric purity of the product was, however, 29% ee (Entry 1). The solvent system affected the reactivity, as well as the enantioselectivity. When the reaction was performed in THF/MeOH mixed solvent, the product was obtained in 88% yield with 60% ee (Entry 4). No reaction occurred when other commercially available Trost ligands were used (Entries 5 and 6).[8] The addition of acetate salts slightly increased the enantiomeric excess. Using 1.5 equiv of KOAc, the reaction proceeded smoothly to provide **11** in 98% yield (94% isolated yield after silica gel column purification) with 66% ee. Less satisfactory results were obtained when the reaction was performed using 5 mol % of the Pd catalyst (Entry 10).

With optically active intermediate **11** (66% ee) in hand, we examined the enantioselective total synthesis of cedrelin A (Scheme 3). First, to construct the D-ring moiety, **11** was reacted with 3,3-dimethylacrolein in the presence of ethylendiamine·2AcOH.[9] The tetracyclic adduct with the desired molecular skeleton **12** was obtained in 51% yield, accompanied by the formation of regioisomer **12′** in 38% yield. Deprotection of the tosyl



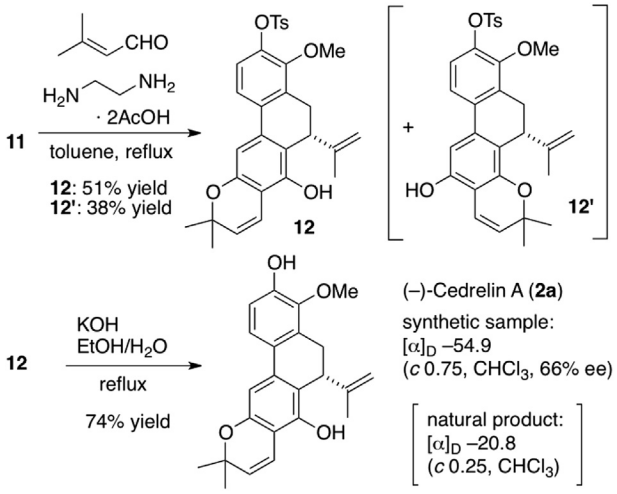
Scheme 2. Substrate preparation for the Pd-catalyzed asymmetric intramolecular Friedel–Crafts allylic alkylation.

Table 1
Pd-catalyzed asymmetric intramolecular Friedel–Crafts allylic alkylation of **9**



Entry	Pd cat. (mol %)	Solvent	Chiral ligand	Additive	Yield (%)[a]	Ee (% ee)[b]
1	10	CH_2Cl_2/MeOH (4/1)	(*R*,*R*)-**10a**	—	94	29
2	10	CH_3CN/MeOH (4/1)	(*R*,*R*)-**10a**	—	33	36
3	10	Toluene/MeOH (4/1)	(*R*,*R*)-**10a**	—	31	38
4	10	THF/MeOH (4/1)	(*R*,*R*)-**10a**	—	88	60
5	10	THF/MeOH (4/1)	(*R*,*R*)-**10b**	—	No reaction	—
6	10	THF/MeOH (4/1)	(*R*,*R*)-**10c**	—	No reaction	—
7	10	THF/MeOH (4/1)	(*R*,*R*)-**10a**	LiOAc	83	63
8	10	THF/MeOH (4/1)	(*R*,*R*)-**10a**	KOAc	98 (94)[c]	66
9	10	THF/MeOH (4/1)	(*R*,*R*)-**10a**	$Mg(OAc)_2$	75	65
10	5	THF/MeOH (4/1)	(*R*,*R*)-**10a**	KOAc	45	60

[a] Determined by ^{1}H NMR analysis of the crude sample.
[b] Determined by chiral HPLC analysis.
[c] Isolated yield.



Scheme 3. Total synthesis of cedrelin A.

group was performed under basic conditions to give cedrelin A in 74% yield (16.5% overall yield, 12 steps from **1**)($[\alpha]_D^{24}$ −54.9 [*c* 0.75, $CHCl_3$, 66% ee]; Literature data.[1b] $[\alpha]_D$ −20.8 [*c* 0.25, $CHCl_3$]).[10] The NMR data (^{1}H NMR and ^{13}C NMR) were identical to the reported data of **2a**.[1b]

We next turned our attention to enantioselective total synthesis of paralycolin B with different oxidation patterns on the A-ring (Scheme 4). Compound **17** was prepared from commercially available 6-bromoveratraldehyde **13** using the same synthetic method as that used for compound **9** (seven steps, 71% overall yield). Asymmetric intramolecular Friedel–Crafts allylic alkylation of **17** proceeded using 2.5 mol % of $Pd(dba)_2$ and 3 mol % of (*R*,*R*)-**10a** in CH_2Cl_2/MeOH mixed solvent, providing **18** in 98% yield with 92% ee. Subsequent D-ring formation gave a mixture of **19** ($[\alpha]_D^{23}$ −94.0 [*c* 0.44, $CHCl_3$]) and **19′** in 55% yield and 28% yield, respectively.[11] Finally, **19** was converted into methylated paralycolin B (**1c**) in 92% yield (35.2% overall yield, 10 steps from **13**).[1c] ^{1}H NMR and ^{13}C NMR analyses of the synthetic sample were identical to the literature data.[12,13]

3. Conclusion

In conclusion, we successfully achieved the first enantioselective total syntheses of cedrelin A and methylated paralycolin B by Pd-catalyzed asymmetric intramolecular Friedel–Crafts allylic alkylation of phenols. The present method provides access to synthetic analogues of this class of dihydrophenanthrapyranes that are of potential interest in medicinal chemistry. Further studies are in progress.

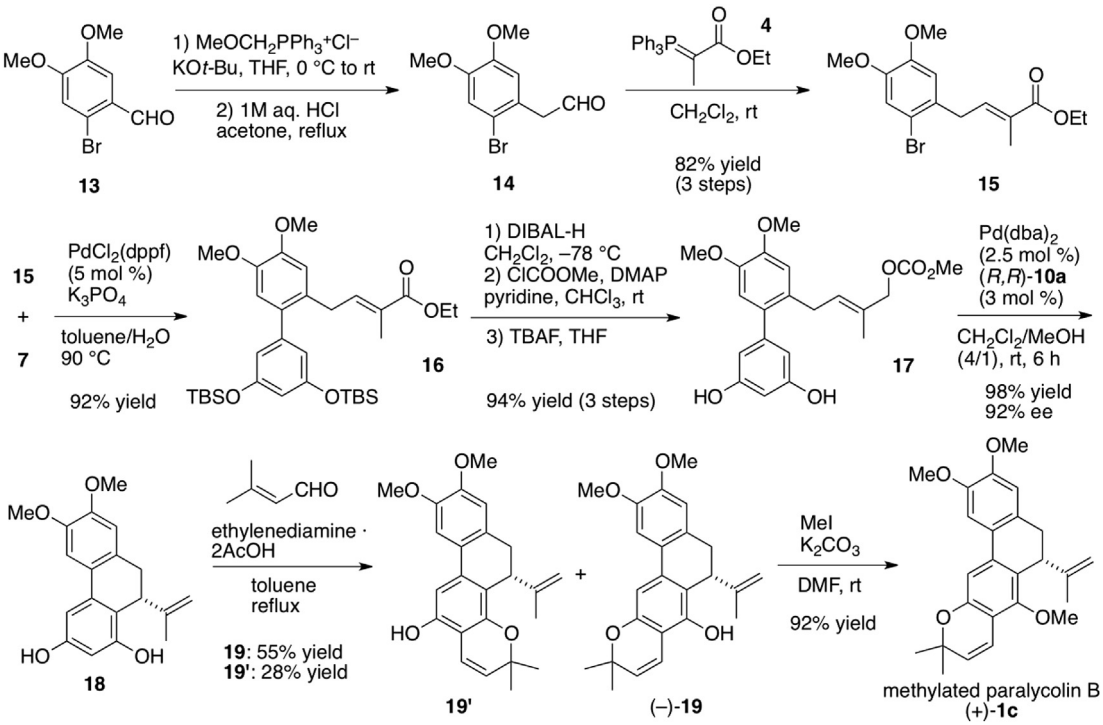
4. Experimental

4.1. General

Infrared (IR) spectra were recorded on a JASCO FT/IR 230 Fourier transform infrared spectrophotometer, equipped with ATR (Smiths Detection, DuraSample IR II). NMR spectra were recorded on a JEOL ecp 400 spectrometer, operating at 400 MHz for ^{1}H NMR, and 100 MHz for ^{13}C NMR. Chemical shifts in $CDCl_3$, were reported downfield from TMS (=0 ppm) for ^{1}H NMR. For ^{13}C NMR, chemical shifts were reported in the scale relative to the solvent signal [$CHCl_3$ (77.0 ppm)] as an internal reference. ESI mass spectra were measured on JEOL AccuTOF LC-plus JMS-T100L. The enantiomeric excess (ee) was determined by HPLC analysis. HPLC was performed on JASCO HPLC systems consisting of the following: pump, PU-980; detector, UV-970, measured at 254 nm; column, DAICEL CHIRALCEL OD-H; mobile phase: hexane/2-propanol. Reactions were carried out in dry solvent under argon atmosphere. Other reagents were purified by the usual methods.

4.2. Enantioselective synthesis of (−)-cedrelin A

*4.2.1. 2-(6-Bromo-3-hydroxy-2-methoxyphenyl)acetaldehyde (**3**).* To a stirred solution of **1** (7.44 g, 32.2 mmol) and imidazole (2.85 g, 41.9 mmol) in DMF (32.2 mL) at 0 °C was added TBSCl (7.28 g, 48.3 mmol), and the resulting mixture was stirred for 1 h at room temperature. After dilution with Et_2O, the mixture was washed with water (2 times), brine, and then dried over Na_2SO_4. After concentration in vacuo, the obtained crude silylated product was used for the next step without purification. To a stirred solution of (methoxymethyl)triphenyl phosphonium chloride



Scheme 4. Total synthesis of methylated paralycolin B.

(16.8 g, 48.9 mmol) in THF (120 mL) at 0 °C was added KO*t*-Bu (12.8 g, 114.0 mmol). The resulting mixture was stirred at the same temperature for 30 min. A solution of the crude silylated product in THF (40 mL) was added to the reaction, and then the resulting mixture was stirred at room temperature. After 2 h, the reaction was quenched with 1 N aq HCl, and the mixture was diluted with AcOEt. After separation of the aqueous layer, the organic layer was washed with brine, dried over Na_2SO_4, and then evaporated in vacuo. The obtained crude methyl vinyl ether derivative was used for the next step without purification. To a stirred solution of the crude product in THF (72 mL) at room temperature was added 1 N aq HCl (10 mL). The resulting solution was refluxed for 3 h. After evaporation of the organic solvent in vacuo, water was added to the mixture, and the resulting slurry was extracted with AcOEt. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The obtained residue was purified by flash column chromatography (SiO_2, hexane/AcOEt=3/1) to give **3** (7.10 g, 90% yield over three steps) as white solids. Mp 74–75 °C; IR (ATR) ν 3379, 2943, 2836, 1713, 1466, 1427, 1287, 1179, 1030, 998, 807 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.71 (s, 3H), 3.91 (d, J=1.2 Hz, 2H), 6.24 (br s, 1H), 6.80 (d, J=9.0 Hz, 1H), 7.23 (d, J=9.0 Hz, 1H), 9.75 (t, J=1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 44.8, 61.3, 114.8, 116.8, 126.9, 128.6, 146.8, 148.5, 199.0; (+)-ESI-LRMS m/z 267 ($M+Na^+$), 269 ($M+2+Na^+$); (+)-ESI-HRMS. Calcd for $C_9H_9BrNaO_3^+$ ($M+Na^+$): 266.9627. Found: 266.9628.

*4.2.2. (E)-Ethyl 4-(6-bromo-3-hydroxy-2-methoxyphenyl)-2-methylbut-2-enoate (**5**).* To a stirred solution of aldehyde **3** (980 mg, 4.00 mmol) in CH_2Cl_2 (20 mL) at room temperature was added a Wittig reagent **4** (1.66 g, 13.5 mmol), and the resulting mixture was stirred for 1 h at the same temperature. After evaporation of the solvent, the obtained residue was purified by flash column chromatography (SiO_2, hexane/AcOEt=4/1) to give **5** (1.09 g, 83% yield) as colorless oil. IR (ATR) ν 3370, 2981, 1685, 1467, 1293, 1257, 1176, 1001, 907, 808, 728 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.27 (t, J=7.2 Hz, 3H), 2.02 (d, J=1.6 Hz, 3H), 3.66 (d, J=7.0 Hz, 2H), 3.77 (s, 3H), 4.18 (q, J=7.2 Hz, 2H), 5.69 (br s, 1H), 6.71 (td, J=1.6 Hz, 7.0 Hz, 1H), 6.77 (d, J=8.4 Hz, 1H), 7.23 (d, J=8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 12.7, 14.1, 29.9, 60.7, 61.2, 114.3, 115.8, 128.2, 128.5, 132.4, 139.2, 146.4, 148.7, 168.4; (+)-ESI-LRMS m/z 351 ($M+Na^+$), 353 ($M+2+Na^+$); (+)-ESI-HRMS. Calcd for $C_{14}H_{17}BrNaO_4^+$ ($M+Na^+$): 351.0202. Found: 351.0184.

*4.2.3. (E)-Ethyl 4-(6-bromo-2-methoxy-3-(tosyloxy)phenyl)-2-methylbut-2-enoate (**6**).* To a stirred solution of **5** (1.09 g, 3.30 mmol) and triethylamine (0.55 mL, 3.96 mmol) in CH_2Cl_2 (6.6 mL) at 0 °C was added *p*-toluenesulfonyl chloride (1.66 g, 13.5 mmol), and the resulting mixture was stirred at room temperature. After 1 h, the reaction was quenched with water, and the mixture was diluted with AcOEt. After separation of the aqueous layer, the organic layer was washed with brine, dried over Na_2SO_4, and then evaporated in vacuo. The obtained residue was purified by flash column chromatography (SiO_2, hexane/AcOEt=4/1) to give **6** (1.42 g, 90% yield) as white solids. Mp 70–71 °C; IR (ATR) ν 2980, 1707, 1466, 1378, 1254, 1178, 1007, 818 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.28 (t, J=7.2 Hz, 3H), 1.94 (d, J=1.2 Hz, 3H), 2.46 (s, 3H), 3.59 (d, J=6.8 Hz, 2H), 3.71 (s, 3H), 4.18 (q, J=7.2 Hz, 2H), 6.55 (td, J=1.2 Hz, 6.8 Hz, 1H), 6.95 (d, J=8.8 Hz, 1H), 7.27 (d, J=8.8 Hz, 1H), 7.32 (d, J=8.6 Hz, 2H), 7.73 (d, J=8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 12.7, 14.3, 21.7, 30.2, 60.6, 61.5, 123.1, 123.3, 128.0, 128.4 (2C), 128.7, 129.7 (2C), 132.5, 134.4, 137.7, 145.7, 151.7, 167.9; (+)-ESI-LRMS m/z 505 ($M+Na^+$), 507 ($M+2+Na^+$); (+)-ESI-HRMS. Calcd for $C_{21}H_{23}BrNaO_6S^+$ ($M+Na^+$): 505.0291. Found: 505.0313.

*4.2.4. (E)-Ethyl 4-(3′,5′-bis((tert-butyldimethylsilyl)oxy)-3-methoxy-4-(tosyloxy)-[1,1′-biphenyl]-2-yl)-2-methylbut-2-enoate (**8**).* A mixture of **6** (2.78 g, 5.76 mmol), **7** (3.21 g, 6.91 mmol), $PdCl_2$(dppf) (170 mg, 0.29 mmol), and K_3PO_4 (3.67 g, 17.3 mmol) in toluene (5 mL) and H_2O (5 mL) was stirred for 24 h at 90 °C. After the reaction was quenched with water, AcOEt was added to the mixture. The aqueous layer was separated and the resulting organic layer was washed with brine, dried over Na_2SO_4, and then evaporated in

vacuo. The obtained residue was purified by flash column chromatography (SiO_2, hexane/AcOEt=30/1) to give **8** (4.18 g, 98% yield) as white solids. Mp 107–108 °C; IR (ATR) ν 2931, 1714, 1585, 1379, 1255, 1166, 1029, 831, 781 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.18 (s, 12H), 0.97 (s, 18H), 1.26 (t, J=6.8 Hz, 3H), 1.67 (d, J=1.2 Hz, 3H), 2.47 (s, 3H), 3.38 (d, J=6.8 Hz, 2H), 3.73 (s, 3H), 4.14 (q, J=6.8 Hz, 2H), 6.32 (s, 2H), 6.32 (s, 1H), 6.53 (dt, J=1.2 Hz, 6.8 Hz, 1H), 6.90 (d, J=8.2 Hz, 1H), 7.04 (d, J=8.2 Hz, 1H), 7.35 (d, J=8.4 Hz, 2H), 7.82 (d, J=8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ −4.5 (4C), 12.3, 14.3, 18.1 (2C), 21.7, 25.6 (6C), 27.6, 60.3, 61.1, 111.1, 114.4 (2C), 121.7, 125.1, 127.5, 128.4 (2C), 129.7 (2C), 132.3, 133.1, 140.2, 141.7, 141.9, 142.2, 145.4, 150.8, 156.3 (2C), 167.8; (+)-ESI-LRMS m/z 763 ($M+Na^+$); (+)-ESI-HRMS. Calcd for $C_{39}H_{56}NaO_8SSi_2^+$ ($M+Na^+$): 763.3127. Found: 763.3166.

*4.2.5. (E)-3′,5′-Dihydroxy-3-methoxy-2-(4-((methoxycarbonyl)oxy)-3-methylbut-2-en-1-yl)-[1,1′-biphenyl]-4-yl 4-methylbenzenesulfonate (**9**).* To a stirred solution of **8** (4.08 g, 6.95 mmol) in CH_2Cl_2 (35 mL) at −78 °C was added DIBAL-H (17.4 mL, 1 M solution in hexane, 17.4 mmol). After the solution was stirred for 2.5 h at −78 °C, and 30 min at room temperature, the reaction was quenched by the addition of aq 1 M Rochelle salt. After being stirred for 1 h, the mixture was extracted with AcOEt. The combined organic layers were washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. The obtained crude alcohol was used for the next step without purification. To a stirred solution of crude alcohol and DMAP (170 mg, 1.39 mmol) in $CHCl_3$ (11.6 mL) and pyridine (2.3 mL) at 0 °C was added methyl chloroformate (1.34 mL, 17.4 mmol), and the resulting mixture was kept stirring for 3 h at room temperature. The reaction was quenched with 1 N HCl at 0 °C, and then the resulting mixture was extracted with AcOEt. The combined organic layers were washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. The obtained residue was used for the next reaction without further purification. To a stirred solution of the crude sample in THF (35 mL) at 0 °C was added TBAF (17.4 mL, 1 M solution in THF, 0.73 mmol). After being stirred for 1 h at room temperature, the reaction mixture was diluted with AcOEt. The obtained mixture was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The obtained residue was purified by flash column chromatography (SiO_2, hexane/AcOEt=2/1) to give **9** (3.10 g, 85% yield over three steps) as amorphous solids. IR (ATR) ν 3420, 2955, 1721, 1598, 1472, 1442, 1370, 1254, 1189, 1174, 1154, 983, 749, 668 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.47 (s, 3H), 2.46 (s, 3H), 3.18 (d, J=5.6 Hz, 2H), 3.73 (s, 3H) 3.78 (s, 3H), 4.47 (s, 2H), 5.32 (t, J=5.6 Hz, 1H), 6.16–6.25 (m, 4H), 6.36 (d, J=2.0 Hz, 1H), 6.86 (d, J=8.4 Hz, 1H), 7.00 (d, J=8.4 Hz, 1H), 7.33 (d, J=7.6 Hz, 2H), 7.79 (d, J=7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 13.7, 21.7, 26.7, 55.1, 61.2, 73.6, 101.7, 108.8 (2C), 121.3, 125.1, 128.4 (2C), 129.2, 129.6, 129.7, 129.7 (2C), 132.9, 133.4, 141.6, 142.2, 145.4, 150.6, 156.2, 156.7 (2C); (+)-ESI-LRMS m/z 551 ($M+Na^+$); (+)-ESI-HRMS. Calcd for $C_{27}H_{28}NaO_9S^+$ ($M+Na^+$): 551.1346. Found: 551.1369.

*4.2.6. (R)-6,8-Dihydroxy-1-methoxy-9-(prop-1-en-2-yl)-9,10-dihydrophenanthren-2-yl 4-methylbenzenesulfonate (**11**).* Compound **9** (123 mg, 0.233 mmol), $Pd(dba)_2$ (13.4 mg, 0.0233 mmol), (*R*,*R*)-**10a** (19.3 mg, 0.0279 mmol), and KOAc (34.2 mg, 0.349 mmol) were dissolved in THF (3.7 mL) and MeOH (0.93 mL) under argon atmosphere, and the resulting solution was stirred at 40 °C. After 12 h, the reaction was quenched with water, and the mixture was extracted with AcOEt. The combined organic layers were washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. The obtained residue was purified by flash column chromatography (SiO_2, $CHCl_3$/MeOH=30/1) to give **11** (99.0 mg, 94% yield) as amorphous solids. IR (ATR) ν 3461, 1616, 1465, 1362, 1254, 1174, 1011, 967, 830, 754, 668 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.58 (s, 3H), 2.44 (s, 3H), 2.56–2.62 (m, 1H), 3.28 (d, J=16.0 Hz, 1H), 3.69 (s, 3H), 3.73 (d, J=6.0 Hz, 1H), 4.29 (s, 1H), 4.59 (s, 1H), 5.53 (br s, 1H), 5.80 (br s, 1H), 6.38 (d, J=2.4 Hz, 1H), 6.76 (d, J=8.0 Hz, 1H), 7.04 (d, J=8.0 Hz, 1H), 7.25 (d, J=2.4 Hz, 1H), 7.29 (d, J=8.4 Hz, 1H), 7.76 (d, J=8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 21.0, 21.7, 25.6, 37.1, 61.2, 103.1, 103.8, 112.2, 117.0, 119.8, 121.3, 128.4 (2C), 129.6 (2C), 130.2, 132.6, 134.4, 135.5, 141.8, 145.2, 145.3, 149.6, 154.1, 155.4; (+)-ESI-LRMS m/z 475 ($M+Na^+$); (+)-ESI-HRMS. Calcd for $C_{25}H_{24}NaO_6S^+$ ($M+Na^+$): 475.1186. Found: 475.1199; $[\alpha]_D^{14}$ −71.8 (c 1.27, $CHCl_3$, 66% ee). The enantiomeric excess was determined by chiral HPLC analysis (DAICEL CHIRALCEL OD-H, hexane/2-propanol=80/20, flow rate: 1.0 mL/min, t_R 9.3 min [(*R*)-(−)-isomer] and 13.1 min [(*S*)-(+)-isomer], detection at 254 nm).

*4.2.7. (R)-7-Hydroxy-4-methoxy-10,10-dimethyl-6-(prop-1-en-2-yl)-6,10-dihydro-5H-naphtho[2,1-g]chromen-3-yl 4-methylbenzenesulfonate (**12**).* To a stirred solution of **11** (25.3 mg, 0.081 mmol) and ethylendiamine diacetate (0.7 mg, 0.0041 mmol) in toluene (1.60 mL), was added 3-methyl crotonaldehyde (12.4 μL, 0.121 mmol), and the resulting mixture was refluxed for 6 h. Then, the solvent was removed in vacuo, and the obtained residue was purified by flash column chromatography (SiO_2, hexane/AcOEt=4/1 to 3/1) to give **12** (15.6 mg, 51% yield) as a brown oil, and **12′** (11.6 mg, 38% yield) as a brown oil. IR (ATR) ν 3528, 2925, 1470, 1373, 1255, 1175, 1122, 827, 771, 734 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.42 (s, 3H), 1.48 (s, 3H), 1.54 (s, 3H), 2.44 (s, 3H), 2.72 (dd, J=7.2 Hz, 16.0 Hz, 1H), 3.29 (dd, J=2.4 Hz, 16.0 Hz, 1H), 3.64 (dd, J=2.4 Hz, 7.2 Hz, 1H), 3.70 (s, 3H), 4.54 (s, 1H), 4.69 (s, 1H), 4.99 (br-s, 1H), 5.64 (d, J=10.0 Hz, 1H), 6.65 (d, J=10.0 Hz, 1H), 6.86 (s, 1H), 7.05 (d, J=8.6 Hz, 1H), 7.28 (d, J=8.4 Hz, 2H), 7.33 (d, J=8.6 Hz, 1H), 7.74 (d, J=8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 20.4, 21.7, 25.7, 27.5, 28.0, 38.5, 61.2, 75.9, 105.1, 110.0, 112.8, 116.1, 116.4, 119.7, 121.5, 128.5 (2C), 129.4, 129.5 (2C), 129.9, 132.8, 134.2, 134.3, 141.8, 145.2, 145.9, 148.9, 149.6, 152.7; (+)-ESI-LRMS m/z 541 ($M+Na^+$); (+)-ESI-HRMS. Calcd for $C_{30}H_{30}NaO_6S^+$ ($M+Na^+$): 541.1655. Found: 541.1635; $[\alpha]_D^{26}$ −68.8 (c 1.93, $CHCl_3$, 66% ee).

*4.2.8. (R)-12-Hydroxy-7-methoxy-3,3-dimethyl-5-(prop-1-en-2-yl)-5,6-dihydro-3H-naphtho[1,2-h]chromen-8-yl 4-methylbenzenesulfonate (**12′**).* IR (ATR) ν 3464, 2973, 1474, 1409, 1371, 1255, 1190, 1175, 1120, 1060, 967, 829, 775, 731 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.30 (s, 3H), 1.45 (s, 3H), 1.57 (s, 3H), 2.43 (s, 3H), 2.51 (dd, J=6.4 Hz, 15.6 Hz, 1H), 3.26 (d, J=16.0 Hz, 1H), 3.67 (s, 3H), 3.80 (d, J=6.4 Hz, 1H), 4.14 (s, 1H), 4.49 (s, 1H), 5.26 (br s, 1H), 5.62 (d, J=10.0 Hz, 1H), 6.62 (s, 1H), 6.66 (d, J=10.0 Hz, 1H), 7.07 (d, J=8.2 Hz, 1H), 7.22 (d, J=8.2 Hz, 1H), 7.27 (d, J=8.4 Hz, 2H), 7.75 (d, J=8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 21.5, 21.7, 25.5, 27.1, 28.1, 35.9, 61.2, 75.9, 103.0, 109.5, 111.4, 116.7, 119.1, 119.3, 121.2, 128.5 (2C), 129.5, 129.5 (2C), 130.7, 132.7, 133.9, 134.5, 141.7, 145.1, 145.2, 149.7, 150.2, 150.8; (+)-ESI-LRMS m/z 541 ($M+Na^+$); (+)-ESI-HRMS. Calcd for $C_{30}H_{30}NaO_6S^+$ ($M+Na^+$): 541.1655. Found: 541.1635; $[\alpha]_D^{26}$ −62.3 (c 1.64, $CHCl_3$, 66% ee).

4.2.9. (−)-Cedrelin A. Solution of potassium hydroxide (3.0 g) in water (50 mL) and ethanol (50 mL) was prepared. **12** (38.6 mg, 0.074 mmol) was dissolved in 2.0 mL of the alkaline solution, and the resulting mixture was stirred at 80 °C. After 1 h, the solution was cooled, and neutralized with acetic acid. The mixture was extracted with ether, washed with aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated in vacuo. The obtained residue was purified by flash column chromatography (SiO_2, hexane/AcOEt=7/1) to give cedrelin A (20.0 mg, 74% yield) as pale yellow oil; IR (ATR) ν 3441, 2973, 1604, 1558, 1474, 1291, 1167, 1121, 1027, 899, 753 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.43 (s, 3H), 1.48 (s, 3H), 1.62 (s, 3H), 2.89 (dd, J=7.2 Hz, 15.6 Hz, 1H), 3.32 (dd, J=2.8 Hz, 15.6 Hz, 1H), 3.96–3.71 (m, 1H), 3.78 (s, 3H), 4.64 (s, 1H), 4.73 (s, 1H), 4.98 (s, 1H), 5.62 (d, J=10.0 Hz, 1H), 5.64 (s, 1H), 6.65 (d, J=10.0 Hz, 1H), 6.86 (s, 1H), 6.86 (d, J=8.4 Hz, 1H), 7.35 (d, J=8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$):

δ 20.4, 26.4, 27.5, 28.0, 38.7, 61.2, 75.8, 104.3, 109.0, 112.8, 113.6, 115.1, 116.5, 120.9, 127.6, 127.7, 129.2, 135.2, 144.3, 146.4, 148.4, 148.9, 152.7; (+)-ESI-LRMS *m/z* 365 ($M+H^+$); (+)-ESI-HRMS. Calcd for $C_{23}H_{25}O_4^+$ ($M+H^+$): 365.1747. Found: 365.1761; $[\alpha]_D^{24}$ −54.9 (*c* 0.75, $CHCl_3$, 66% ee). The enantiomeric excess was determined by chiral HPLC analysis (DAICEL CHIRALCEL OD-H, hexane/2-propanol=90/10, flow rate: 0.75 mL/min, t_R 14.7 min [(*S*)-(+)-isomer] and 17.4 min [(*R*)-(−)-isomer], detection at 254 nm).

4.3. Enantioselective total synthesis of paralycolin B

*4.3.1. (E)-Ethyl 4-(2-bromo-4,5-dimethoxyphenyl)-2-methylbut-2-enoate (**15**).* Compound **15** was prepared from commercially available **13** according to the experimental procedures described in Sections 4.2.1 and 4.2.2 (82% yield, three steps). White solids. Mp 35–36 °C; IR (ATR) ν 2934, 1707, 1507, 1440, 1381, 1255, 1219, 1164, 1116, 1071, 1032, 800 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.29 (t, *J*=7.2 Hz, 3H), 1.98 (s, 3H), 3.56 (d, *J*=7.2 Hz, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 4.19 (q, *J*=7.2 Hz, 2H), 6.69 (s, 1H), 6.79 (t, *J*=7.2 Hz, 1H), 7.02 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 12.7, 14.2, 35.0, 56.1, 56.2, 60.6, 113.0, 114.2, 115.7, 128.8, 130.5, 138.9, 148.3, 148.6, 167.9; (+)-ESI-LRMS *m/z* 365 ($M+Na^+$), 367 ($M+2+Na^+$); (+)-ESI-HRMS. Calcd for $C_{15}H_{19}BrNaO_4^+$ ($M+Na^+$): 365.0359. Found: 365.0365.

*4.3.2. (E)-Ethyl 4-(3′,5′-bis((tert-butyldimethylsilyl)oxy)-4,5-dimethoxy-[1,1′-biphenyl]-2-yl)-2-methylbut-2-enoate (**16**).* Compound **16** was prepared from compound **15** and arylboronate **7** according to the experimental procedures described in 4.2.4 (92% yield). White solids. Mp 70–71 °C; IR (ATR) ν 2930, 1711, 1584, 1516, 1432, 1256, 1164, 1028, 832, 781 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.20 (s, 12H), 0.98 (s, 18H), 1.27 (t, *J*=7.2 Hz, 3H), 1.78 (d, *J*=1.2 Hz, 3H) 3.42 (d, *J*=7.2 Hz, 2H), 3.87 (s, 3H), 3.90 (s, 3H), 4.16 (q, *J*=7.2 Hz, 2H), 6.33 (t, *J*=2.4 Hz, 1H), 6.39 (d, *J*=2.4 Hz, 2H), 6.72 (s, 1H), 6.74 (s, 1H), 6.79 (td, *J*=1.2 Hz, 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ −4.4 (4C), 12.4, 14.2, 18.2 (2C), 25.6 (6C), 32.3, 56.0, 56.0, 60.4, 110.7, 112.3, 113.1, 114.7 (2C), 127.7, 128.7, 134.2, 141.0, 142.9, 147.2, 148.4, 156.2 (2C), 167.9; (+)-ESI-LRMS *m/z* 623 ($M+Na^+$); (+)-ESI-HRMS. Calcd for $C_{33}H_{52}NaO_6Si_2^+$ ($M+Na^+$): 623.3195. Found: 623.3222.

*4.3.3. (E)-4-(3′,5′-Dihydroxy-4,5-dimethoxy-[1,1′-biphenyl]-2-yl)-2-methylbut-2-en-1-yl methyl carbonate (**17**).* Compound **17** was prepared from compound **16** according to the experimental procedures described in Section 4.2.5 (94% yield). Amorphous solids; IR (ATR) ν 3418, 2959, 1724, 1600, 1507, 1442, 1255, 1156, 1059, 1000, 776 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.56 (s, 3H), 3.22 (d, *J*=6.4 Hz, 2H), 3.79 (s, 3H), 3.84 (s, 3H), 3.90 (s, 3H), 4.53 (s, 2H), 5.59 (t, *J*=6.4 Hz, 2H), 6.00 (br s, 2H), 6.33 (d, *J*=2.0 Hz, 2H), 6.36 (t, *J*=2.0 Hz, 1H), 6.72 (s, 1H), 6.73 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 13.8, 32.0, 55.0, 55.9, 55.9, 73.7, 101.2, 109.1 (2C), 112.6, 112.8, 129.1, 130.0, 130.6, 133.9, 143.5, 146.9, 148.1, 156.1, 156.6 (2C); (+)-ESI-LRMS *m/z* 411 ($M+Na^+$); (+)-ESI-HRMS. Calcd for $C_{21}H_{24}NaO_7^+$ ($M+Na^+$): 411.1414. Found: 411.1430.

*4.3.4. (R)-6,7-Dimethoxy-10-(prop-1-en-2-yl)-9,10-dihydrophenanthrene-1,3-diol (**18**).* Compound **18** was prepared from compound **17** according to the experimental procedures described in Section 4.2.6 (98% yield, 92% ee). White solid. Mp 139–140 °C; IR (ATR) ν 3409, 2938, 1606, 1578, 1515, 1464, 1257, 1205, 1139, 1012, 756 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.67 (s, 3H), 2.93 (dd, *J*=2.8 Hz, 15.2 Hz, 1H), 3.09 (dd, *J*=7.2 Hz, 15.2 Hz, 1H), 3.72 (dd, *J*=2.8 Hz, 7.2 Hz, 1H), 3.91 (s, 3H), 3.94 (s, 3H), 4.53 (s, 1H), 4.72 (s, 1H), 4.78 (s, 1H), 4.98 (s, 1H), 6.31 (d, *J*=2.6 Hz, 1H), 6.69 (s, 1H), 6.83 (d, *J*=2.6 Hz, 1H), 7.15 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 21.9, 33.8, 38.5, 56.4, 56.8, 102.2, 102.5, 109.2, 111.6, 113.4, 117.7, 128.8, 130.0, 137.4, 147.0, 149.0, 150.0, 156.6, 157.8 (+)-ESI-LRMS *m/z* 313 ($M+H^+$); (+)-ESI-HRMS. Calcd for $C_{19}H_{21}O_4^+$ ($M+H^+$): 313.1434. Found: 313.1454; $[\alpha]_D^{26}$ −105.5 (*c* 0.52, MeOH, 92% ee). The enantiomeric excess was determined by chiral HPLC analysis (DAICEL CHIRALCEL OD-H, hexane/2-propanol=80/20, flow rate: 1.0 mL/min, t_R 13.5 min [(*S*)-(+)-isomer] and 24.0 min [(*R*)-(−)-isomer], detection at 254 nm).

*4.3.5. (R)-2,3-Dimethoxy-10,10-dimethyl-6-(prop-1-en-2-yl)-6,10-dihydro-5H-naphtho[2,1-g]chromen-7-ol (**19**).* Compound **19** was prepared from compound **18** according to the experimental procedures described in Section 4.2.7 (**19**: 55% yield, **19′**: 28% yield). Pale brown amorphous solids; IR (ATR) ν 3431, 2970, 2926, 1606, 1552, 1515, 1433, 1258, 1216, 1126 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.44 (s, 3H), 1.50 (s, 3H), 1.63 (s, 3H), 2.91 (dd, *J*=2.4 Hz, 15.6 Hz, 1H), 3.11 (dd, *J*=7.0 Hz, 15.6 Hz, 1H), 3.65 (dd, *J*=2.4 Hz, 7.0 Hz, 1H), 3.89 (s, 3H), 3.91 (s, 3H), 4.67 (s, 1H), 4.75 (s, 1H), 5.06 (br s, 1H), 5.61 (d, *J*=9.6 Hz, 1H), 6.66 (s, 1H), 6.67 (d, *J*=9.6 Hz, 1H), 6.86 (s, 1H), 7.17 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 20.3, 27.6, 28.1, 33.1, 39.4, 55.9, 55.9, 75.9, 104.0, 107.1, 108.9, 111.1, 112.6, 115.3, 116.6, 126.3, 127.0, 128.9, 135.3, 146.9, 147.8, 148.7, 149.2, 152.6; (+)-ESI-LRMS *m/z* 379 ($M+H^+$); (+)-ESI-HRMS. Calcd for $C_{24}H_{27}O_4^+$ ($M+H^+$): 379.1904. Found: 379.1918; $[\alpha]_D^{23}$ −94.0 (*c* 0.44, $CHCl_3$, 92% ee).

*4.3.6. (R)-8,9-Dimethoxy-3,3-dimethyl-5-(prop-1-en-2-yl)-5,6-dihydro-3H-naphtho[1,2-h]chromen-12-ol (**19′**).* White solids mp 160–161 °C; IR (ATR) ν 3441, 2962, 1514, 1431, 1264, 1206, 1114, 1067, 1036 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.31 (s, 3H), 1.47 (s, 3H), 1.68 (s, 3H), 2.89 (dd, *J*=0 Hz, 15.6 Hz, 1H) 3.03 (dd, *J*=6.8 Hz, 15.6 Hz, 1H), 3.84 (dd, *J*=0 Hz, 6.8 Hz, 1H), 3.90 (s, 3H), 3.92 (s, 3H), 4.30 (s, 1H), 4.58 (s, 1H), 4.78 (br s, 1H), 5.62 (d, *J*=10.0 Hz, 1H), 6.65 (d, *J*=10.0 Hz, 1H), 6.68 (s, 1H), 6.70 (s, 1H), 7.12 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 21.6, 27.1, 28.2, 32.7, 36.8, 55.8, 56.0, 75.8, 102.1, 106.8, 108.4, 111.3, 111.7, 116.6, 118.7, 126.3, 128.5, 129.0, 135.1, 146.0, 147.6, 148.7, 150.0, 151.0; (+)-ESI-LRMS *m/z* 379 ($M+H^+$); (+)-ESI-HRMS. Calcd for $C_{24}H_{27}O_4^+$ ($M+H^+$): 379.1904. Found: 379.1919; $[\alpha]_D^{26}$ −27.2 (*c* 1.18, $CHCl_3$, 92% ee).

*4.3.7. (R)-2,3,7-Trimethoxy-10,10-dimethyl-6-(prop-1-en-2-yl)-6,10-dihydro-5H-naphtho[2,1-g]chromene (methylated paralycolin B) (**1c**).* To a stirred mixture of **19** (10.0 mg, 0.0264 mmol) and K_2CO_3 (11.0 mg, 0.0793 mmol) in DMF (0.5 mL) at 0 °C was added iodomethane (5.0 μL), and the resulting mixture was kept stirring for 5 h. After dilution of the reaction mixture with Et_2O, the mixture was washed with water and brine, and then dried over Na_2SO_4. After concentration under reduced pressure, the obtained residue was purified by flash column chromatography (SiO_2, hexane/AcOEt=6/1) to give **1c** (9.5 mg, 92% yield) as white solids. Mp 157–158 °C IR (ATR) ν 2958, 1604, 1550, 1514, 1469, 1455, 1261, 1224, 1080, 849 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.45 (s, 3H), 1.50 (s, 3H), 1.74 (s, 3H), 2.89 (dd, *J*=0 Hz, 15.6 Hz, 1H), 3.03 (d, *J*=6.4 Hz, 15.6 Hz, 1H), 3.76 (s, 3H), 3.81 (dd, *J*=0 Hz, 6.4 Hz, 1H), 3.89 (s, 3H), 3.92 (s, 3H), 4.26 (s, 1H), 4.64 (s, 1H), 5.65 (d, *J*=10.0 Hz, 1H), 6.60 (d, *J*=10.0 Hz, 1H), 6.66 (s, 1H), 6.98 (s, 1H), 7.18 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 21.7, 27.7, 28.0, 32.8, 37.9, 55.8, 55.9, 62.3, 75.9, 106.8, 107.0, 111.5, 112.9, 113.4, 117.4, 123.5, 126.5, 127.7, 129.8, 135.8, 146.1, 147.7, 148.6, 152.6, 153.6; (+)-ESI-LRMS *m/z* 393 ($M+H^+$); (+)-ESI-HRMS. Calcd for $C_{25}H_{29}O_4^+$ ($M+H^+$): 393.2060. Found: 393.2075; $[\alpha]_D^{26}$ +15.5 (*c* 0.36, $CHCl_3$, 92% ee).

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.05.007.

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11. Absolute configuration of (−)-**19** was assigned by comparing the CD spectrum with that of (−)-cedrelin B. See Supplementary data for the detail.
12. The ^{1}H and ^{13}C NMR data of methylated paralycolin B (**1c**), reported by Delle Monache and co-workers in 2002 (Ref. 1c), were measured in C_6D_6, not in $CDCl_3$. Prof. Delle Monache kindly informed us this error information and provided us the NMR charts of methylated paralycolin B, measured in both C_6D_6 and $CDCl_3$. NMR data of our synthetic sample were identical to the provided data.
13. We examined deprotection of the methyl groups in 19 under several reaction conditions. When **19** was treated with 5 mol % of $B(C_6F_5)$ and 3 equiv of Et_3SiH in CH_2Cl_2 at room temperature, paralycolin B (**1b**) was obtained in 52% yield, accompanied by the formation of 6-isopropyl derivative (21%) as inseparable mixtures. These yields were determined by ^{1}H NMR analysis of the isolated mixture. The use of other deprotection protocols gave unsatisfactory results.