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A Carbohydrate-Based Total Syntheses of (+)-Pyrenolide D and (−)-4-*epi*-Pyrenolide D

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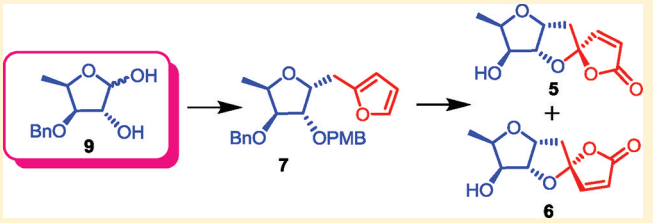
Supporting Information

ABSTRACT: Efficient total syntheses of (+)-pyrenolide D (**5**) and (−)-4-*epi*-pyrenolide D (**6**) have been achieved from a known 5-deoxy-D-xylose derivative **9** in ten steps with 19% overall yield either exclusively as **5** or as pure **5** and **6** in a 3:2 ratio. Key steps involved are one-pot epoxidation−cyclization by Corey−Chaykvosky reagent, reductive Barton−McCombie deoxygenation, and per-acid mediated oxidative spiroketalization.



The γ-spiroketal lactones are an indispensible structural motif, as they exist in a number of biologically important natural products, which include the cephalosporolide class of natural products[1] and crassalactone D (**1**).[2a,b] The phytopathogenic fungus *Pyrenophora teres* (Diedicke) Drechsler (IFO 7508) has been a rich source of a number of fungal metabolites, and among them, pyrenoloides A−C (**2**−**4**)[3] have simple macrolide structures with potent growth-inhibitory and morphogenic activities toward fungi. A new tricyclic compound with cytotoxic activity named pyrenolide D (**5**)[4] was isolated from the ethyl acetate extracts of a culture broth of the same fungus (Figure 1), which is structurally distinct from the other

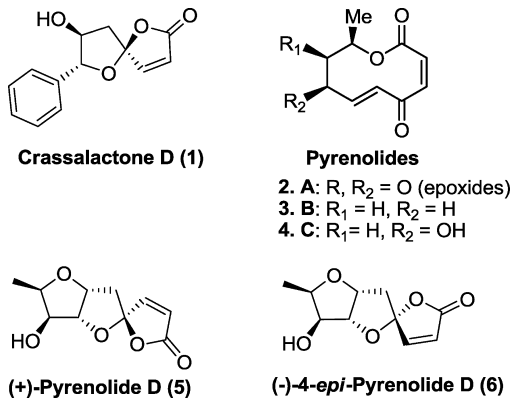


Figure 1. Structures of crassalactone D, pyrenolides A−D, and 4-*epi*-pyrenolide D.

members of the family. It possesses a spiroketal chiral center along with a highly oxygenated tricyclic spiro-γ-lactone. It shows significant cytotoxicity against HL-60 cells (IC_{50} 4 μg mL^{-1}). Its interesting structural features as well as intriguing biological profile attracted the attention of synthetic and medicinal chemists. The first elegant total synthesis of pyrenolide D was achieved by Gin et al.[5] in 2001. Recently, 4,9-*epi*-pyrenolide[2b] and various analogues[6] have been reported by Vassilikogiannakis et al. and Robertson et al., respectively.

As part of our ongoing research of highly substituted tetrahydrofuran ring system bearing natural products from carbohydrates,[7] we report herein the total syntheses of (+)-pyrenolide D (**5**) and (−)-4-*epi*-pyrenolide D (**6**) starting from a known 5-deoxy-D-xylose **9** derivative in ten steps. From a retrosynthetic perspective, we envisaged that the γ-spirolactone system present in **5** could be achieved by oxidative spiroketalization of furan derivative **7** by *m*-chloroperoxybenzoic acid (*m*-CPBA), followed by pyridinium dichromate (PDC) oxidation as reported by Vassilikogiannakis et al. and Robertson et al.[2b,6] The furan moiety of the compound **7** could be installed through coupling of 2-furyllithium with the aldehyde derived from the carbohydrate fragment **8** (Scheme 1). Compound **8** could readily be obtained by treatment of lactol **9**, a known 5-deoxy-D-xylose derivative serving as the key intermediate in the present synthesis with Corey−Chaykvosky reagent. Lactol **9** in turn could be obtained from D-glucose.

Accordingly, our synthesis started from commercially available D-glucose diacetonide (**10**). Compound **10** was converted to **9**[8] following standard literature protocol in five steps with good overall yield (51%) (Scheme 2). To construct the crucial tetrahydrofuran ring system from lactol **9**, Corey−Chaykovsky reagent[9] ($Me_3S^+OI^-$) was used. Among the bases (NaH, *n*-BuLi, LiHMDS, NaHMDS, LDA, *t*-BuOK) tried, *t*-BuOK gave the best result for **11** in terms of yield (65%) as an inseparable mixture of diastereomers. Here, the lactol moiety reacted with the in situ generated dimethyloxosulfonium methylide to form an epoxide,[10] which undergoes a favorable 5-*exotet*-cyclization (Baldwin's rule[11] 6-*endo-tet* cyclization is unfavorable) to furnish the desired tetrahydrofuran ring. Next,

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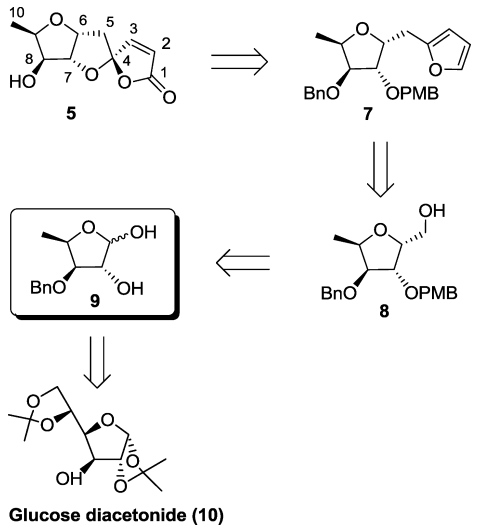
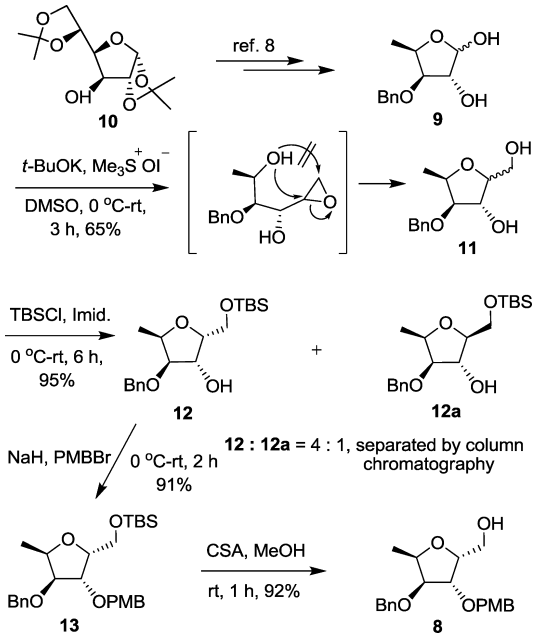
Scheme 1. Retrosynthetic Analysis



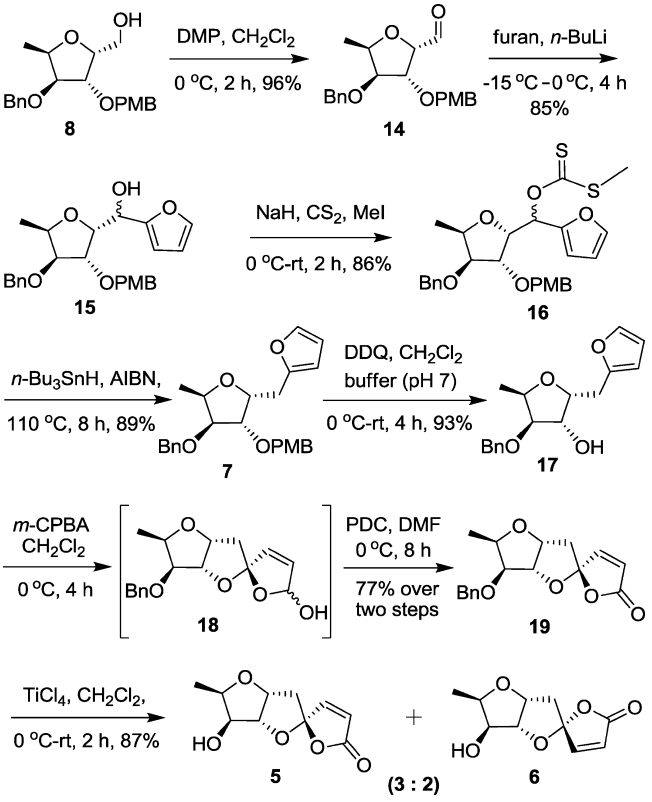
Scheme 2. Synthesis of Intermediate 8



the primary hydroxyl group was selectively protected in the presence of a secondary hydroxyl group as its TBDMS ether in excellent yield (95%). It is noteworthy to mention here that the two diastereomers **12** and **12a** (as a 4:1 diastereomeric mixture), which easily separated at this stage. The secondary hydroxyl group present in the major isomer **12** was then converted to its PMB-ether with NaH, PMB-Br to provide compound **13** in 91% yield. Deprotection of the *tert*-butyldimehtysilyl group was smoothly achieved by camphorsulphonic acid (CSA) in methanol in 92% yield.

To incorporate the furan, alcohol **8** was converted to its corresponding aldehyde **14** with Dess-Martin periodinane (DMP)[12] and subsequently treated with 2-lithiofuran to get the desired coupled product **15** in 82% yield over two steps as a diastereomeric mixture (≈3:2).[13] Our next task, reductive deoxygenation of **15**, was achieved by the Barton–McCombie protocol.[14] Accordingly, **15** was first treated with NaH, CS_2, and MeI to obtain the xanthate derivative **16** as a diastereomeric mixture (≈3:2), which, on treatment with *n*-Bu_3SnH and catalytic amount of AIBN in refluxing toluene, afforded compound **7** in 76% yield over two steps (Scheme 3).

Scheme 3. Synthesis of (+)-Pyrenolide D (5) and (−)-4-*epi*-Pyrenolide D (6)



PMB group was selectively deprotected by careful treatment of DDQ[15] in CH_2Cl_2/phosphate buffer mixture (9:1) to produce compound **17** in 93% yield. Compound **17** sets the stage for oxidative spiroketalization, which was smoothly achieved with *m*-CPBA in dichloromethane to afford the highly unstable lactol **18**, and the crude product was immediately taken up for oxidation with PDC in DMF to furnish the desired γ-spiroketal γ-lactone **19** as a major product (by NMR) in 77% yield over two steps.[2c,6] We did not find any evidence of the stereoisomer with opposite configuration at spiro carbon 4 in the reaction mixture generating **19**. In spite of the instability of the lactol precursor **18**, its absolute configuration at the spiro-chiral carbon could be assigned with high degree of certainty on the basis of the known configuration in **19**. The noteworthy formation of the lactol precursor in high stereospecificity suggests that it could have been formed with highly favorable stereoelectronic conditions, possibly with the oxidation and cyclization occurring in a concerted manner with lowered transition state energy. The instability of the lactol is likely initiated by ring-opening to give keto aldehyde that undergoes further transformations subsequent to, but not during, the formation of the lactol. The structure and stereochemistry of the compound **19** was characterized with the support of an NMR experiment including 2D nuclear Overhauser effect spectroscopy (NOESY) and double quantum filtered correlation spectroscopy (DQFCOSY). From the one-dimensional ^1H NMR experiments, $^3J_{H2-H3}$ = 5.6, $^3J_{H5(pro\text{-}R)-H6}$ = 3.4 Hz, $^3J_{H5(pro\text{-}S)-H6}$ = 7.4, $^3J_{H6-H7}$ = 4.9 and $^3J_{H8-H9}$ = 3.4 Hz were

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determined. The conformation of the fused five-membered with spiro ring supported by the NOESY cross peak H5(*pro-S*)/H9, H5(*pro-S*)/H3, and H8/H10 are shown in energy minimized structures in Figure 2.[16]

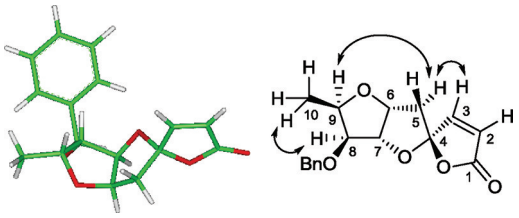
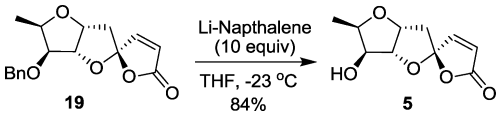


Figure 2. Energy-minimum structure and *NOE* interactions for **19**.

Finally, Lewis acid mediated benzyl group deprotection was carried out with excess $TiCl_4$ (10 equiv) to afford (+)-pyrenolide D (**5**) and (−)-4-*epi*-pyrenolide D (**6**) as 3:2 diastereomeric mixtures, which easily separated by silica gel column chromatography. It is noteworthy to mention here that the deprotection of benzyl ether with Li-napthalenide[17] (10 equiv) afforded **5** as major product (84%) with minor quantities (2−3%) of **6** obtained through epimerization at the spirocyclic carbon (Scheme 4). The spectral (^{1}H, ^{13}C NMR) and analytical data {$[\alpha]_D^{27}$ +68.7 (*c* = 1.2, $CHCl_3$); lit.:[5] $[\alpha]_D^{23}$ +64.3 (*c* = 0.4, $CHCl_3$)} of the synthetic (+)-pyrenolide D (**5**) were in good agreement with the reported values.[4,5]

Scheme 4. Synthesis of (+)-Pyrenolide D (5) from 19



In conclusion, we demonstrated a highly efficient carbohydrate-based approach for the total synthesis of (+)-pyrenolide D (**5**) and (−)-4-*epi*-pyrenolide D (**6**) in ten steps with 19% overall yield either exclusively as **5** or as pure **5** and **6** in a 3:2 ratio starting from a known 5-deoxy-D-xylose derivative **9** and utilizing sequential one-pot epoxidation-cyclization by Corey−Chaykvosky reagent, reductive Barton−McCombie deoxygenation, and per-acid mediated oxidative spiroketalization as key steps.

EXPERIMENTAL SECTION

All reactions were performed under an inert atmosphere if argon is mentioned. All glassware apparatus used for reactions were perfectly oven/flame-dried. Anhydrous solvents were distilled prior to use: THF, toluene, and *t*-butyl methyl ether from Na and benzophenone; CH_2Cl_2, DMSO from CaH_2; MeOH from Mg cake. Commercial reagents were used without purification. Column chromatography was carried out by using silica gel (60−120 mesh) unless otherwise mentioned. Analytical thin layer chromatography (TLC) was run on Merck silica gel 60 F254 precoated plates (250 μm thickness). Specific optical rotations $[\alpha]_D$ were measured on a Perkin-Elmer 343 polarimeter and given in 10^{-1} deg cm^2 g^{-1}. Infrared spectra were recorded in $CHCl_3$/neat (as mentioned) and reported in wavenumber (cm^{-1}). Mass spectral data were obtained using MS (EI) ESI, HRMS mass spectrometers. ^{1}H NMR spectra were recorded at 200, 300, 400, 500 and ^{13}C NMR spectra 50, 75, 100 MHz in $CDCl_3$ solution unless otherwise mentioned; chemical shifts are in ppm downfield from tetramethylsilane and coupling constants (*J*) are reported in hertz (Hz). The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.

(4*R*,5*R*)-4-(Benzyloxy-2-(hydroxymethyl)-5-methyl-tetrahydrofuran-3-ol (11). To a stirred solution of ^{t}BuOK (15.0 g, 140.6 mmol) in anhydrous DMSO (42 mL) was added trimethyl sulfoxonium iodide (31.5 g, 140.6 mmol) portion-wise at 0 °C under a nitrogen atmosphere. The resulting mixture was stirred for 30 min at the same temperature and then 30 min at room temperature. To this well stirred solution, lactol **9** (21 g, 93.0 mmol) dissolved in dry DMSO (25 mL) was added dropwise at 0 °C and stirred for 3 h at room temperature. After completion of the reaction (monitored by TLC), it was carefully quenched with saturated NH_4Cl solution (200 mL) at 0 °C and diluted with ethyl acetate (200 mL). The two layers separated, and the aqueous layer was extracted with ethyl acetate (3 × 200 mL). The combined organic layer was back washed with water (2 × 100 mL) and brine (2 × 150 mL) and dried over anhydrous Na_2SO_4. After removal of the organic solvent under reduced pressure, the crude alcohol was purified by flash column chromatography over silica gel (ethyl acetate/hexane = 1:2) to furnish the desired diol **11** (14.4 g, 65%) as yellow oil: $[\alpha]_D^{27}$ −22.0 (*c* = 1.0, $CHCl_3$); IR (neat) 3401, 3031, 2928, 1639, 1453, 1380.02, 1210, 1068, 741, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 10H), 4.64 (dd, *J* = 11.89, 26.6 Hz, 2H), 4.51 (dd, *J* = 8.1, 12.0 Hz, 2H), 4.38 (dd, *J* = 3.9, 6.4 Hz, 1H), 4.24 (dd, *J* = 2.0, 3.7 Hz, 1H), 4.04−4.18 (m, 2H), 3.97(dd, *J* = 3.7, 16.0 Hz, 1H), 3.63−3.9 (m, 7H), 2.90−3.11 (m, 2H), 2.05 (d, *J* = 13.0 Hz, 2H), 1.23−1.31 (m, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) 138.4, 138.1, 128.8, 128.4, 128.1, 128.0, 128.0, 127.8, 86.0, 85.6, 77.4, 77.1, 76.8, 72.8, 72.4, 71.9, 68.6, 63.0, 61.9, 61.5, 57.0, 55.1, 14.9, 14.7 ppm; HRMS (ESI) *m*/*z* calcd. for $C_{13}H_{18}O_4$ [M + Na]$^+$ 261.1102, found 261.1098.

Other five bases such as LiHMDS, NaHMDS, *n*-BuLi, NaH, and LDA have been similarly tried but failed to give any hint of reaction according to TLC.

(2*R*,3*S*,4*R*,5*R*)-4-(Benzyloxy)-2-((*tert*-butyldimethylsilyl-oxy)-methyl)-5-methyl-tetrahydro-furan-3-ol (12). To a stirred solution of a diastereomeric mixture of diols **11** (12.0 g, 50.4 mmol) in dry CH_2Cl_2 (150 mL) was added imidazole (7.5 g, 110.9 mmol) at 0 °C under nitrogen atmosphere. After 30 min, a solution of TBDMS-Cl (9.0 g, 60.4 mmol) dissolved in CH_2Cl_2 (50 mL) was added dropwise. After completion of the reaction (monitored by TLC), H_2O (100 mL) was added to the reaction mixture, and two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL), and the combined organic layer was washed with brine (2 × 150 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to get the crude product, which was purified by flash column chromatography over silica gel (ethyl acetate/hexane = 1:19) to furnish the desired TBS-ether **12** and **12a** (16.23 g, 95%) (**12** = 12.98 g and **12a** = 3.25 g) as yellow oils.

12: $[\alpha]_D^{27}$ −26.4 (*c* = 1.06, $CHCl_3$); IR (neat) 3423, 3032, 2953, 2929, 2857, 1496, 1254, 1209, 1085, 837, 779 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.25 (m, 5H), 4.71−4.50 (AB_q, *J* = 12.0, 46.4 Hz, 2H), 4.22−4.13 (m, 2H), 3.83 (d, *J* = 4.9 Hz, 1H), 3.78 (dd, *J* = 3.0, 5.2 Hz, 1H), 3.66−3.58 (m, 2H), 1.97 (br s, 1H), 1.26 (d, *J* = 6.4 Hz, 3H), 0. 90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 138.2, 128.3, 127.6, 127.4, 85.5, 83.7, 78.8, 76.5, 71.5, 64.3, 26.0, 15.0, −5.3; HRMS (ESI) *m*/*z* calcd. for $C_{19}H_{32}O_4Si$ [M + Na]$^+$ 375.1967, found 375.1974.

12a: $[\alpha]_D^{27}$ −20.4 (*c* = 1.5, $CHCl_3$); IR (neat) 3553, 3376, 2979, 2934, 2857, 1683, 1386, 1172, 1030, 854, 743 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.23 (m, 5H), 4.73−4.50 (AB_q, *J* = 12.1, 45.1 Hz, 2H), 4.40 (br s, 1H), 4.32 (m, 1H), 4.15−4.04 (m, 2H), 3.99 (d, *J* = 3.7 Hz, 2H), 3.74 (dd, *J* = 1.5, 3.9 Hz, 1H), 1.28 (d, *J* = 6.4 Hz, 3H), 0. 89 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 138.2, 128.3, 127.5, 127.3, 85.7, 77.9, 77.2, 76.3, 71.9, 63.1, 25.6, 14.4, −5.6; HRMS (ESI) *m*/*z* calcd. for $C_{19}H_{32}O_4Si$ [M + Na]$^+$ 375.1967, found 375.1963.

(((2*R*,3*S*,4*S*,5*R*)4-(Benzyloxy)-3-(4-methoxybenzyloxy)-5-methyl-tetrahydrofuran-2-yl)methoxy)(*tert*-butyl)-dimethylsilane (13). To a solution of alcohol **12** (8.1 g, 23.0 mmol) in THF (70 mL), NaH (1.1 g, 46.0 mmol, 60% in mineral oil) was

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added at 0 °C under nitrogen atmosphere, and the mixture was allowed to stir for 30 min at room temperature. Thereafter, 4-methoxy benzyl bromide (5.49 g, 27.6 mmol) dissolved in dry THF (50 mL) was added dropwise to the above reaction mixture. After completion of the reaction (monitored by TLC), it was carefully quenched with ice pieces at 0 °C and then with a saturated solution of NH_4Cl (100 mL). The reaction mixture was diluted with ethyl acetate (150 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layer was washed with brine (2 × 150 mL), dried over anhydrous Na_2SO_4, and evaporated to dryness under reduced pressure to get the crude product, which was purified by column chromatography over silica gel (ethyl acetate/hexane = 1:49) to afford the desired product **13** (7.3 g, 91%) as a colorless liquid: $[\alpha]_D^{27}$ −14.5 (c = 0.9, $CHCl_3$); IR (neat) 2930, 2859, 1612, 1512, 1462, 1362, 1096, 1036, 778, 741, 589 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32−7.22 (m, 5H), 7.19 (d, J = 8.3 Hz, 2H), 6.81 (d, J = 9.0 Hz, 2H), 4.50 (AB_q, J = 12.0, 18.8 Hz, 2H), 4.38 (dd, J = 3.7, 12.0 Hz, 2H), 4.43−4.05 (m, 1H), 3.91 (d, J = 3.7 Hz, 1H), 3.83 (dd, J = 3.0, 5.2 Hz, 1H), 3.79 (s, 3H), 3.81−3.78 (m, 1H), 3.73−3.66 (m, 2H), 3.54 (dd, J = 7.5, 9.8 Hz, 1H), 1.25 (d, J = 6.7 Hz, 3H), 0.89 (s, 9H), 0.04 (d, J = 1.5 Hz, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) 159.2, 138.1, 130.1, 129.3, 128.3, 127.5, 127.4, 113.8, 84.0, 83.9, 71.3, 71.0, 63.8, 55.2, 25.4, 18.3, 14.1, −5.4; HRMS (ESI) m/z calcd. for $C_{27}H_{40}O_5Si$ $[M + Na]^+$ 495.2542, found 495.2532.

(2*S*((2*R*,3*S*,4*S*,5*R*)-4-(Benzyloxy)-3-(4-methoxybenzyloxy)-5-methyl-tetrohydrofuran-2-yl)methanol (8). To a stirred solution of TBS-ether **13** (7.1 g, 15 mmol) in methanol (40 mL) at 0 °C was added camphorsulfonic acid (0.17 g, 0.75 mmol) and, the mixture was stirred for 4 h at room temperature. After completion of the reaction (monitored by TLC), it was quenched with saturated $NaHCO_3$ solution (25 mL). Methanol was removed under reduced pressure, and the residual reaction mixture was diluted with ethyl acetate (100 mL) and water (50 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 100 mL). The combined organic layer was washed with brine (2 × 100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to get the crude product, which was purified by silica gel column chromatography (ethyl acetate/hexane = 1:5) to afford alcohol **8** (4.82 g, 92%) as a light yellow liquid: $[\alpha]_D^{27}$ −61.4 (c = 1.01, $CHCl_3$); IR (neat) 3447, 2929, 2868, 1718, 1513, 1389, 1248, 1070, 1033, 821, 742, 588 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34−7.24 (m, 5H), 7.17 (d, J = 8.3 Hz, 2H), 6.83 (d, J = 8.4 Hz, 2H), 4.59 (d, J = 12.0 Hz, 1H), 4.42 (s, 2H), 4.38 (d, J = 12.0 Hz, 1H), 4.13−4.04 (m, 1H), 3.97 (d, J = 3.7 Hz, 1H), 3.90 (dd, J = 3.0, 6.7 Hz, 1H), 3.80 (s, 3H), 3.74 (d, J = 12.0 Hz, 1H), 3.67 (d, J = 3.7 Hz, 1H), 3.56 (m, 1H), 2.09 (br s, 1H), 1.29 (d, J = 6.0 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) 159.3, 137.6, 129.6, 129.1, 129.2, 128.4, 127.7, 127.6, 113.9, 84.2, 83.2, 77.4,76.5, 71.5, 71.2, 63.1, 55.2, 13.8 ppm; HRMS (ESI) m/z calcd. for $C_{21}H_{26}O_5$ $[M+Na]^+$ 381.1677, found 381.1665.

((2*S*,3*R*,4*S*,5*R*)-4-(Benzyloxy)-3-(4-methoxybenzyloxy)-5-methyl-tetrahydrofuran-2-carbaldehyde (14). To a stirred solution of alcohol **8** (4.1 g, 11.45 mmol) in dry CH_2Cl_2 (50 mL) was added Dess−Martin periodinane (7.2 g, 17.1 mmol) at 0 °C under a nitrogen atmosphere. After 1 h (monitored by TLC), the reaction mixture was filtered through a Celite bed and washed thoroughly with CH_2Cl_2 (2 × 50 mL). The filtrate was washed with sodium thiosulphate (2 × 50 mL) and brine (2 × 50 mL) and dried over anhydrous Na_2SO_4. After removal of the organic layer under reduced pressure, the crude aldehyde **14** was obtained (3.85 g, 96%) as a light red liquid and immediately used for the next step: $[\alpha]_D^{27}$ −8.0 (c = 1.3, $CHCl_3$); IR (neat) 2929, 1724, 1610, 1512, 1455, 1249, 1082, 1032, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.56 (s, 1H), 7.32−7.13 (m, 7H), 6.84 (d, J = 8.7 Hz, 2H), 4.55 (d, J = 11.7 Hz, 1H), 4.42 (dd, J = 11.7, 15.6 Hz, 2H), 4.33 (m, 1H), 4.21 (d, J = 13.7 Hz, 1H), 4.10 (br s, 1H), 3.80 (s, 3H), 3.61 (d, J = 2.97 Hz, 1H), 1.32 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) 203.7, 159.4, 129.4, 128.4, 127.9, 127.6, 113.9, 87.0, 85.0, 81.1, 78.3, 71.4, 71.3, 55.2, 13.9 ppm; HRMS (ESI) m/z calcd. for $C_{21}H_{24}O_5$ $[M + Na]^+$ 379.1526, found 379.1532.

((4*S*,5*R*)-4-(Benzyloxy)-3-(4-methoxybenzyloxy)-5-methyl-tetrahydrofuran-2yl)(furan-2-yl)methanol (15). To a stirred solution of furan (2.6 mL, 34.4 mmol) in dry diethyl ether (52 mL) was added *n*-BuLi (12 mL, 24 mmol, 2 M in hexane) dropwise at −15 °C under an argon atmosphere. The reaction mixture was slowly warmed to 20 °C and stirred for 1 h and then again cooled to 0 °C. Thereafter, the aldehyde **14** (3.5 g, 9.8 mmol) dissolved in dry diethyl ether (15 mL) was added to the above reaction mixture, and it was allowed to stir for 5 h at room temperature. After completion of the reaction (monitored by TLC), it was cooled to 0 °C and carefully quenched with saturated NH_4Cl solution (50 mL). The two layers were separated, and the aqueous layer was extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine (2 × 100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get the crude oil, which on purification over silica gel column chromatography (ethyl acetate/hexane = 1:9) afforded alcohol **15** (3.54 g, 85%) as a colorless liquid: IR (neat) 3410, 2924, 2855, 1713, 1636, 1507, 1453, 1050, 752, 742, 600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39−7.25 (m, 5H), 7.02 (d, J = 9.0 Hz, 1H), 6.76−6.8 (m, 2H), 6.41−6.24 (m, 3H), 6.21−6.16 (m, 1H), 4.62 (dd, J = 13.5 Hz, 0.6H), 4.60 (dd, J = 6.7, 12.0 Hz, 0.6H), 4.33 (d, J = 6.7 Hz, 0.4H), 4.27 (d, J = 13.5 Hz, 0.4H), 4.07−4.21 (m, 2.7H), 3.97 (dd, J = 3.0, 12.0, 20.3 Hz, 0.7H), 3.79 (d, J = 2.2 Hz, 1H), 3.78 (s, 3H), 3.59 (dd, J = 3.0, 4.5 Hz, 0.8H), 1.31 (d, J = 6.7 Hz, 1.5H), 1.28 (d, J = 6.0 Hz, 1.2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) 159.3 153.7, 153.6, 142.1, 142.0, 137.6, 137.3, 129.6, 129.5, 129.4, 129.2, 128.5, 128.4, 127.9, 127.8, 127.6, 127.4, 113.8, 113.7, 110.2, 107.6, 107.0, 86.6, 85.3, 83.4, 83.3, 82.7, 81.1, 77.7, 77.3, 71.4, 71.2, 71.1, 71.1, 68.7, 68.2, 55.2, 13.9, 13.4 ppm; MS (ESI) m/z $C_{25}H_{28}O_6$ $[M + Na]^+$ 447.

2-(((4*S*,5*R*,4*S*)-4-(Benzyloxy)-3-(4-methoxybenzyloxy)-5-methyl-tetrahydrofuran-2-yl)methyl)furan (16). To a suspension of NaH (0.31 g, 13.0 mmol, 60% in mineral oil) in anhydrous THF (20 mL) was added alcohol **15** (3.1 g, 7.3 mmol) dissolved in THF (20 mL) at 0 °C under nitrogen atmosphere, and the mixture was stirred for 30 min at room temperature. To this reaction mixture, carbon disulfide (0.7 mL, 10.9 mmol) was added at 0 °C, and the mixture was stirred for 30 min. Methyl iodide (0.75 mL, 12.2 mmol) was added, and the mixture was slowly warmed to room temperature. After completion of the reaction (monitored by TLC), it was quenched with ice pieces at 0 °C. The reaction mixture was diluted with ethyl acetate (50 mL) and water (30 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 70 mL). The combined organic layers were washed with brine (2 × 75 mL) and dried over anhydrous Na_2SO_4. After removal of the organic solvents under reduced pressure, the crude was purified by silica gel column chromatography (ethyl acetate/hexanes = 1:19) to afford xanthate **16** (3.4 g, 90%) as a colorless liquid: IR (neat) 3446.6, 2925, 2866, 1646, 1511, 1456, 1247, 1075, 1034, 866, 742, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35−7.26 (m, 5H), 7.25−7.15 (m, 2H), 6.82 (dd, J = 4.5, 8.3 Hz, 1H), 6.81 (dd, J = 2.2, 6.7 Hz, 1H), 6.25 (dd, J = 3.7, 11.3 Hz, 0.7H), 6.24 (dd J = 3.7, 9.8 Hz, 0.7H), 5.07 (d, J = 8.3 Hz, 1H), 4.36−4.60 (m, 3H), 4.28 (dd, J = 6.7, 12.0 Hz, 1H), 4.21−4.05 (m, 2H), 3.90 (d, J = 3.0, 3.8 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 1H), 3.70 (dd, J = 3.7, 14.3 Hz, 1H), 3.70 (dd, J = 3.7, 14.3 Hz, 1H), 3.69 (dd, J = 2.2, 18.8 Hz, 1H), 2.42 (2 × s, 3H), 1.28 (m, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) 188.6, 188.2, 159.3, 159.2, 152.3, 150.8, 142.1, 142.0, 141.8, 138.0, 129.7, 129.6, 129.4, 129.3, 129.3, 128.3, 128.2, 127.7, 127.6, 127.5, 127.4, 113.8, 113.7, 110.5, 110.4, 110.2, 110.1, 108.8, 108.2, 108.1, 108.0, 85.3, 85.1, 84.7, 84.2, 84.1, 83.6, 83.5, 83.4, 82.8, 78.0, 77.8, 77.7, 71.6, 71.3, 71.2, 55.2, 47.5, 44.4, 44.3, 14.4, 14.3, 14.2 ppm; HRMS (ESI) m/z calcd. for $C_{27}H_{30}O_6S_2$ $[M + Na]^+$ 537.1381, found 537.1372.

2-(((4*S*,5*R*)-4-(Benzyloxy)-3-(4-methoxybenzyloxy)-5-methyl-tetrahydrofuran-2-yl)methyl)furan (7). Compound **15** (3.8 g, 7.3 mmol) was taken in toluene (50 mL) and Bu_3SnH (3.2 g, 11.0 mmol) followed by a catalytic amount of AIBN (100 mg, 0.6 mmol) added under a nitrogen atmosphere, and the mixture was stirred under reflux conditions for 8 h. After completion of the reaction (monitored by TLC), toluene was removed under reduced pressure, and the

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residual product was purified by column chromatography over silica gel (ethyl acetate/hexane = 1:12) to furnish the desired compound **7** (2.47 g, 89%) as brown syrup: $[\alpha]_D^{27}$ −7.5 (*c* = 1.1, $CHCl_3$); IR (neat) 3450, 2924, 2862, 1612, 1512, 1457, 1034, 737, 596 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34−7.27 (m, 5H), 7.25 (s, 1H), 7.05 (d, *J* = 9.0 Hz, 2H), 6.79 (d, *J* = 8.3 Hz, 2H), 6.25 (dd, *J* = 1.5, 3.0 Hz, 1H), 6.01 (d, *J* = 3.0 Hz, 1H), 4.46 (AB_q, *J* = 12.0, 42.3 Hz, 2H), 4.21 (dd, *J* = 11.3, 24.1 Hz, 2H), 4.10−3.99 (m, 2H), 3.78 (s, 3H), 3.77 (s, 1H), 3.65 (dd, *J* = 3.0, 6.0 Hz, 1H), 2.99 (dd, *J* = 6.0, 15.1 Hz, 1H), 2.8 (dd, *J* = 8.3, 15.1 Hz, 1H), 1.29 (d, *J* = 6.7 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) 159.2, 152.4, 141.2, 138.1, 129.8, 129.2, 128.3, 127.6, 127.5, 113.7, 110.2, 106.7, 85.8, 83.9, 82.0, 77.1, 71.4, 71.0, 55.2, 32.9, 14.0 ppm; HRMS (ESI) *m*/*z* calcd. for $C_{25}H_{28}O_5$ $[M + Na]^+$ 431.1834, found 431.1829.

(2*R*,3*S*,4*R*,5*R*)-4-(Benzyloxy)-2-(furan-2-ylmethyl)-5-methyltetrahydrofuran-3-ol (17). To a stirred solution of PMB-ether **7** (1.7 g, 0.4 mmol) in a mixture of CH_2Cl_2 (15 mL) and phosphate buffer (pH 7) (1.5 mL) was added DDQ (1.73 g, 0.62 mmol) at 0 °C, and the mixture was allowed to stir at room temperature. After 1 h (monitored by TLC), the reaction was quenched with a saturated solution of $NaHCO_3$ (20 mL) and diluted with CH_2Cl_2 (20 mL). After separation of two layers, the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL) and the combined organic layer was washed with brine (2 × 30 mL), dried over anhydrous Na_2SO_4, filtered, and then concentrated to dryness under reduced pressure to get the crude alcohol. The alcohol was purified by column chromatography over silica gel (neutralized with 0.5% Et_3N, ethyl acetate/hexanes = 3:7) to produce **17** (0.8 g, 66%) as a colorless liquid: $[\alpha]_D^{27}$ −5.9 (*c* = 0.95, $CHCl_3$); IR (neat) 3427, 2926, 1715, 1065, 749 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34−7.28 (m, 6H), 6.27 (t, *J* = 2.8 Hz, 1H), 6.08 (d, *J* = 3.0 Hz, 1H), 4.59 (AB_q, *J* = 12.0, 44.0 Hz, 2H), 4.12 (m, 1H), 4.05 (dd, *J* = 2.0, 4.3 Hz, 1H), 3.80 (m, 1H), 3.71 (dd, *J* = 2.3, 4.9 Hz, 2H), 3.03 (dd, *J* = 5.6, 14.9 Hz, 1H), 2.88 (dd, *J* = 8.3, 14.9 Hz, 1H), 1.27 (d, *J* = 3.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) 152.1, 141.4, 138.0, 128.3, 127.7, 127.4, 110.3, 106.8, 85.9, 82.8, 80.0, 71.6, 32.4, 14.7 ppm; HRMS (ESI) *m*/*z* calcd. for $C_{17}H_{20}O_4$ $[M + H]^+$ 289.1434, found 289.1428.

(2*R*,3a′*R*,5′*R*,6′*S*,6a′*S*)-6′-(Benzyloxy)-5′-methyl-3a′,5′,6′,6a′-tetrahydro-3′*H*,5*H*-spiro-[furan-2,2′-furo[3,2-*b*]furan]-5-one (19). To a stirred solution of the compound **17** (0.6 g, 1.8 mmol) in CH_2Cl_2 (10 mL) was added *m*-CPBA (0.78 g, 3.9 mmol, 77%) in six portions at 0 °C under nitrogen atmosphere. After completion of the reaction (monitored by TLC), it was quenched with solid $NaHCO_3$, diluted with CH_2Cl_2 (40 mL), and washed with a saturated solution of $NaHCO_3$ (2 × 30 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layer was washed with brine (2 × 50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford the crude product **18** (0.63 g), which was immediately used for the next step without further purification and characterization.

To a stirred solution of crude lactol **18** (0.63 g, 2.03 mmol) in dry DMF (15 mL) was added 3 Å molecular sieves (0.5 g) followed by PDC (2.29 g, 6.09 mmol) at 0 °C under nitrogen atmosphere, and the mixture was stirred for 8 h at the same temperature. After completion of the reaction (monitored by TLC), it was diluted with diethyl ether (50 mL) and washed with water (2 × 40 mL). The aqueous phase was extracted with diethyl ether (2 × 40 mL). The combined organic layer was washed with brine (2 × 60 mL) and dried over anhydrous Na_2SO_4. After removal of the organic solvent under reduced pressure, the crude lactone was purified by flash column chromatography over silica gel (ethyl acetate/hexane = 3:7) to provide **19** (0.48 g, 77% over two steps) as a colorless liquid: $[\alpha]_D^{27}$ −6.0 (*c* = 1.0, $CHCl_3$); IR (neat) 3427, 2920, 2851, 1729, 1632, 1084, 749 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38−7.29 (m, 5H), 7.11 (d, *J* = 5.6 Hz, 1H), 6.15 (d, *J* = 5.4 Hz, 1H), 5.13 (m, 1H), 4.88 (d, *J* = 4.7 Hz, 1H), 4.61 (AB_q, *J* = 12.2, 64.0 Hz, 2H), 4.13 (m, 1H), 3.81 (d, *J* = 3.3 Hz, 1H), 2.62 (dd, *J* = 7.1, 14.7 Hz, 1H), 2.28 (m, 1H), 1.30 (d, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) 170.1, 150.9, 129.8, 128.4, 127.9, 127.6, 124.3, 115.2, 88.1, 82.3, 80.7, 72.2, 71.8, 42.2, 29, 13.5 ppm; HRMS (ESI) *m*/*z* calcd. $C_{17}H_{18}O_5$ $[M + Na]^+$ 325.1051, found 325.1038.

(+)-Pyrenolide D (5) and (−)-4-*epi*-Pyrenolide D (6). To a stirred solution of **19** (0.1 g, 0.33 mmol) in CH_2Cl_2 (5 mL) was added $TiCl_4$ (3.3 mL, 3.3 mmol, 1 M in CH_2Cl_2) at 0 °C, and the mixture was allowed to stir at room temperature. After completion of the reaction (monitored by TLC), it was quenched with a saturated solution of $NaHCO_3$ (5 mL). After separation of the two layers, the aqueous phase was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layer was washed with brine (2 × 30 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to get the crude product, which was purified by column chromatography over silica gel (ethyl acetate/hexane = 4:7) to afford **5** (37 mg) and **6** (24 mg) in 87% yield as white solids.

Data for **5**: mp 154−155 °C; $[\alpha]_D^{27}$ +68.7 (*c* = 1.2, $CHCl_3$); IR (neat) 3447, 2923, 2853, 1742, 1654, 1458, 1258, 1079, 1025, 862, 738 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.15 (d, *J* = 6.4 Hz, 1H), 6.18 (d, *J* = 5.2 Hz, 1H) 5.14 (ddd, *J* = 0.75, 3.7, 8.3 Hz, 1H), 4.78 (d, *J* = 5.2 Hz, 1H), 4.14 (m, 1H), 4.1 (br s, 1H), 3.81 (dd, *J* = 6.7, 12.0 Hz, 1H), 2.64 (dd, *J* = 6.7, 14.3 Hz, 1H), 2.34 (m, 1H), 1.39 (d, *J* = 7.5 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) 171.2, 150.8, 124.5, 114.8, 90.6, 80.4, 76.0, 75.7, 42.3, 13.6 ppm; MS (ESI) *m*/*z* $C_{10}H_{12}O_5$ $[M + Na]^+$ 235; HRMS (ESI) *m*/*z* calcd. $C_{10}H_{12}O_5Na$ $[M + Na]^+$ 235. 0582, found 235. 0585.

Data for **6**: mp 139−140 °C; $[\alpha]_D^{27}$ −12.0 (*c* = 1.15, $CHCl_3$); IR (neat) 3449, 2923, 2853, 1750, 1461, 1217, 1082, 922 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.04 (d, *J* = 5.2 Hz, 1H), 6.16 (d, *J* = 5.2 Hz, 1H), 5.04 (t, *J* = 5.6 Hz, 1H), 4.77 (d, *J* = 4.5 Hz, 1H), 4.16 (m, 1H), 3.79 (dd, *J* = 2.2, 6.0 Hz, 1H), 3.65 (t, *J* = 4.5 Hz, 1H), 2.48−2.26 (m, 2H), 1.29 (d, *J* = 6.0 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) 171.2, 151.9, 123.9, 114.9, 92.8, 80.5, 61.8, 60.4, 42.9, 13.3; MS (ESI) *m*/*z* $C_{10}H_{12}O_5$ $[M + Na]^+$ 235; HRMS (ESI) *m*/*z* calcd. $C_{10}H_{12}O_5Na$ $[M + Na]^+$ 235. 0582, found 235. 0587.

(+)-Pyrenolide D (5). To a stirred solution of naphthalene (0.052 g, 0.411 mmol) in THF (3 mL) at room temperature were added lithium granules (0.012 g, 1.65 mmol), and the mixture was allowed to stir at room temperature for 45 min to generate Li-naphthalenide. To the resulting dark green colored solution was added benzyl ether **19** (0.025 g, 0.083 mmol) at −23 °C, and the mixture was allowed to stir at the same temperature for 30 min. After complete consumption of the starting material, the reaction was quenched with saturated aqueous NH_4Cl solution (5 mL), extracted with ethyl acetate (3 × 10 mL), dried over Na_2SO_4, concentrated under reduced pressure, and purified on silica gel (ethyl acetate/hexane = 1:1) to obtain compound **5** (0.015 g, 84%) as white powder, identical to that described above according to the analytical and spectral data.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and ^{13}C NMR and HRMS spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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