Stereoselective Total Synthesis of C₂-Symmetric Natural Products Pyrenophorol and its Derivatives

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Abstract: A stereoselective total synthesis of 16-membered C₂-symmetric macrodiolide Pyrenophorol, Tetrahydropyrenophorol and 4,4-diacetylpyrenophorol have been accomplished. The synthesis started from commercially available L-Aspartic acid and the key reactions involved are regioselective epoxide opening, CBS reduction, Pinnick oxidation and Mitsunobu dilactonization.

Experimental Section:

General Information: All the air and moisture sensitive reactions were carried out under inert atmosphere (nitrogen or argon). Oven-dried glass apparatus were used to perform all the reactions. Freshly distilled anhydrous solvents were used for air and moisture sensitive reactions. Commercially available reagents were used as such. Purification of compounds was carried out via column chromatography by using silica gel (100-200 mesh) packed in glass columns. ¹H NMR and ¹³C NMR were recorded in CDCl₃ an DMSO-d₆ solvents on 400 MHz and 500 MHz spectrometer respectively, using TMS as an internal standard. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectro photometer using KBr / Thin Film optics. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV. Optical rotation values were recorded on Horiba sepa 300 polarimeter using a 2 mL cell with a 10 mm path length. High resolution mass spectra (HRMS) [ESI+] were obtained using either a TOF or a double focusing spectrometer.
(S)-2-Bromosuccinic acid: (L)-Aspartic acid (10 g, 75.13 mmol) was dissolved in H$_2$SO$_4$ (300 mL, 2.5 M) and cooled to -10 °C, then added KBr (35.8 g, 301 mmol), followed by NaN$_2$ (9.8 g, 142 mol) which was dissolved in H$_2$O (30 mL) through additional funnel over 85 min. A brown color gas was evolved and then the reaction was warmed to room temperature and stirred for 5 hr. The mixture was extracted with EtOAc (3x100 mL), dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo. The resulting solid was dried under vacuum to give the title compound in 12.2 g (82.4%); White solid. Mp = 170-171 °C (lit, mp 176-179 °C); [α]$_D^{20}$ = -42.7 (c =1, H$_2$O).

(S)-2-Bromo-(1,4)-butanediol (3): The diacid compound (12 g, 71 mmol) was dissolved in dry THF (150 mL) under N$_2$ and cooled to -10 °C. Then BH$_3$·Me$_2$S (8.7 mL, 213 mmol) was added drop wise over 30 min. The mixture was warmed to room temperature and stirred for 12 hr. The reaction mixture was quenched with MeOH by adding drop wise at 0 °C then concentrated in vacuo. The crude product azeotrope with methanol (50 mL) by twice and purified by chromatography using silica gel (60-120 mesh) by eluting with Hexane-EtOAc (1:1) mixture to give the title compound (9.54g, 92.8%) as a colorless oil.; [α]$_D^{20}$ = -27.5 (c = 1, CHCl$_3$) (lit, -31.2 (c = 1.02, CDCl$_3$).; $^1$H NMR (400 MHz, CD$_3$Cl): 2.14 - 2.20 (m, 2H), 3.87 - 3.92 (m, 4H), 4.34 - 4.40 (m, 1H).; $^{13}$C NMR (100 MHz, CDCl$_3$): δ 66.9, 59.9, 54.5, 37.7.

(R)-[2-(Benzyloxy)ethyl]-oxirane (4): To a stirred solution of NaH (60% dispersion in oil, 5.4 g, 135 mmol) in dry THF (70 mL) under nitrogen atmosphere was added bromodiol (9.5g, 56.2 mmol), dissolved in dry THF (28 mL) drop wise and the reaction mixture was stirred for 75 minutes at 0 °C. Then added BnBr (9.34 mL, 78.7 mol) dissolved in dry THF (10 mL) at 0 °C and add catalytic amount of TBAI, and the reaction mixture was warmed to room temperature and stirred for 5hr. The reaction mixture was quenched with saturated NH$_4$Cl (50 mL) and solvent was removed under reduced pressure. The residue was extracted with EtOAc (3x50 mL). The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, and concentrated in vacuo. The crude product was purified by column chromatography using silica gel (60-120 mesh) by eluting with hexanes-EtOAc (9:1) mixture to afford epoxide 4, in 7 g (70%) as a colorless liquid.; [α]$_D^{25}$ +13.2 (c =1, CHCl$_3$).; IR (neat): ν 3036, 2924, 2856, 1494, 1096, 909,
695 cm$^{-1}$; $^1$H NMR (400 MHz, CD$_3$Cl): $\delta$ 7.37 - 7.27 (m, 5H), 4.52 - 4.60 (m, 2H), 3.65 - 3.58 (m, 2H), 3.09 - 3.04 (m, 1H), 2.78 (d, 1H, $J$ = 5.2 Hz), 2.53 (dd, 1H, $J$ = 4.2 Hz), 1.94 - 1.98 (m, 1H), 1.80 - 1.74 (m, 1H);$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 138.2, 128.3, 127.5, 73.0, 67.0, 50.0, 47.0, 32.9 ppm; MS (ESIMS) $m/z$ 201 (M+Na).$^+$

**(S)-4-(Benzyloxy)butan-2-ol (5):** To a stirred suspension of LAH (7 g, 39.3 mmol) in dry THF (30 mL) was added drop wise a solution of ($R$)- epoxide (7 g, 38.9 mmol) dissolved in dry THF (40 mL) at 0°C, and the reaction mixture was slowly warmed to room temperature and then stirred for 1hr. After completion of the reaction shown by TLC, then the reaction mixture was cooled to 0°C, and quenched with saturated sodium sulphate and then stirred for 5hr. Formation of crude white precipitate becomes free rated and filtered through celite bed and the filtrate was dried over Na$_2$SO$_4$ concentrated to vacuo. The crude product was purified by column chromatography using silica gel (60-120 mesh) by eluting with hexane-EtOAc (8:2) mixture to afford, compound 5 in 6.38 g (90.2%), as pale yellow liquid.; $[\alpha]_D^{25}$ +11.3 (c = 1, CHCl$_3$); IR (neat): $\nu$ 3397, 3049, 2931, 2857, 1426, 1217, 1105, 699 cm$^{-1}$; $^1$H NMR (400 MHz, CD$_3$Cl): $\delta$ 7.37 - 7.25 (m, 5H), 4.52 (s, 2H), 4.04 - 3.96 (m, 1H), 3.72 - 3.63 (m, 2H), 2.72 - 2.58 (brs, 1H, -OH), 1.81 - 1.67 (m, 2H), 1.19 (d, 3H, $J$ = 6.6 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 137.8, 128.4, 127.7, 127.6, 73.2, 69, 67.5, 38.0, 23.3; MS (ESIMS) $m/z$ 181 (M+H)$^+$, 198 (M+NH$_4$).$^+$

**(S)-[4-(Benzyloxy)butan-2-yl]oxy(tert-butyl)diphenyl silane (6):** To a stirred solution of hydroxy compound 5 (6.3g, 35 mmol), in dry CH$_2$Cl$_2$ (30 mL) was added imidazole (2.3g, 33.3 mmol), followed by TBDPS-Cl (10.2 mL, 38.5 mmol) and catalytic amount of DMAP at 0°C and stirring was continued for 2hr at room temperature. After completion of the reaction showed by TLC, then the reaction mixture was quenched by adding cold water and extracted with CH$_2$Cl$_2$ (2x50 mL). The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, and concentrated into vacuo. The crude product was purified by column chromatography using silica gel (60-120 mesh) by eluting with EtOAc-hexane (1:9) mixture to give pure compound 6, in 13.2g (90.2%) as colorless liquid.; $[\alpha]_D^{25}$ -6.19 (c = 1, CHCl$_3$); IR (neat): $\nu$ 2930, 2856, 1588, 1427, 1104, 1002, 821, 770, 696 cm$^{-1}$; $^1$H NMR (400 MHz, CD$_3$Cl): $\delta$ 7.70 - 7.65 (m, 4H), 7.44 - 7.22 (m, 11H), 4.42 (dd, 2H), 4.05 (q, 1H, $J$ = 12.4 Hz), 3.49-3.56 (m, 2H), 1.89 - 1.69 (m, 2H), 1.06 (d, 3H), 1.04 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 138.5, 135.8, 134.7, 134.2, 129.4, 129.3, 128.2, 127.5, 127.4, 1237.3, 72.7, 67.1, 39.4, 27, 23.7, 19.2; MS (ESIMS) $m/z$ 419
(M+H)^+: 436 (M+NH_4)^+. HRMS (ESI) calcd. for C_{27}H_{34}O_2NaSi (M+Na)^+ 441.2225, found 441.2220.

(S)-3-[(Tert-butyldiphenylsilyloxy)butan-1-ol (7): To a stirred solution of naphthalene crystals (21.5 g, 155.5 mmol) in dry THF (100 mL) was added lithium metal (0.56 g, 40.8 mmol). The reaction mixture was stirred for 2hr at room temperature and then cooled to -40 °C and the compound 6 (13 g, 31.1 mmol) was added, which was dissolved in dry THF (60 mL) and stirred for 1hr. After completion of the reaction, showed by TLC, the reaction mixture was quenched with saturated NH_4Cl and the solvent was removed under reduced pressure. The residue was extracted with ethyl acetate (2x200 mL). The combined organic layer were washed with water, followed by brine and dried over Na_2SO_4 and concentrated into vacuo. The crude product was purification by silica gel (60-120 mesh) column chromatography by eluting with Hexane-EtOAc (9:1) mixture to afford, compound 7, in 8.5 g (83.3%) as colorless liquid.; [α]_D^{25} +18.2 (c = 1, CHCl_3); IR (neat): υ 3334, 3016, 2923, 1604, 1492, 1381, 1248, 1195, 1027, 797, 735 cm.⁻¹; ^1H NMR (400 MHz, CDCl_3): δ 7.70 - 7.64 (m, 4H), 7.48 - 7.37 (m, 6H), 4.13 (dq, 1H, J = 12.3 Hz), 3.88 - 3.81 (m, 1H), 3.65 - 3.72 (m, 1H), 2.20 (brs, 1H), 1.87 - 1.78 (m,1H), 1.71 - 1.63 (m, 1H), 1.10 (d, 3H, J = 6.2 Hz), 1.08 (s, 9H); ^13C NMR (100 MHz, CDCl_3): δ 135.9, 135.8, 134.2, 133.7, 129.7, 129.3, 127.6, 127.5, 68.7, 59.9, 40.6, 26.9, 22.9, 19.1.; MS (ESIMS) m/z 329 (M+H^+): HRMS (ESI) calcd for C_{22}H_{28}O_2Si (M+Na)^+ 351.1755, found 351.1750.

(S)-3-[(Tert-butyldiphenylsilyloxy)butyl 4-methylbenzenesulfonate (8): To a stirred solution of alcohol 7 (8.4 g, 25.6) in dry CH_2Cl_2 (80 mL) was added Et_3N (7.1 mL, 51.2 mmol), p-TsCl (3.3g, 28.2 mmol) and catalytic amount of DMAP sequentially. The reaction mixture was stirred for 6hr at room temperature. After completion of the reaction showed by TLC, the reaction mixture was quenched with water and saturated NaHCO_3 and extracted with CH_2Cl_2 (2x40 mL). The combined organic layers were washed with brine and dried over Na_2SO_4 and concentrated into vacuo. The crude product was purified by silica gel (60-120) column chromatography by eluting with EtOAc-hexane (1:9) mixture to afford, compound 8, in 8.56 g (69%) as brown liquid.; IR (neat): υ 2930, 2857, 1597, 1427, 1360, 1176, 1003, 935, 773, 662 cm.⁻¹; ^1H NMR (400 MHz, CDCl_3): δ 7.73 - 7.64 (d, 2H, J = 8.2 Hz), 7.62 - 7.70 (m, 4H), 7.42 - 7.52 (m, 2H), 7.32 - 7.37 (m, 4H), 7.30 (d, 2H, J = 8.0 Hz), 4.17 - 4.08 (m, 2H), 3.92 (m, 1H, J = 12.5 Hz), 2.44 (s, 3H), 1.84 - 1.71 (m, 2H), 0.99 (d, 3H, J = 6.3 Hz), 0.97 (s, 9H); ^13C NMR (100 MHz,
CDCl₃): δ 144.5, 135.7, 134.2, 133.6, 133.1, 129.7, 129.6, 129.5, 127.8, 127.6, 127.4, 67.7, 66.2, 38.2, 26.8, 23.4, 21.6, 19.2.; MS (ESIMS) m/z 483 (M+H).+

(S)-4-[(Tert-butyldiphenylsilyl)oxy]pentanenitrile (9): To a stirred solution of tosyl compound 8 (8.5g, 17.6 mmol), in dry DMSO (40mL) was added sodium iodide (2.1g, 14.1 mmol), followed by sodium cyanide (6.8g, 140.8 mmol), at room temperature and slowly raised the temperature to 80 °C, and then stirred for 90 minutes. After completion of the reaction showed by TLC, reaction mixture was cooled room temperature. The reaction mixture was quenched with saturated Ferrous sulphate (20 mL) then added chilled water, and then extracted with ether (2x50 mL). The combined organic layers were washed with brine, and dried over anhydrous Na₂SO₄, and concentrated into vacuo. The crude product was purified by column chromatography using silica gel (60-120 mesh) by eluting with hexane-EtOAc (9:1) mixture to give cyano compound 9 (5.94 g, 88%) as pale yellow liquid.; [α]D²⁵ +9.25 (c = 2, CHCl₃); IR (neat): υ 2960, 2857, 2146, 1732, 1469, 1426, 1379, 1190, 1088, 989, 821 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.69 - 7.64 (m, 4H), 7.46 - 7.36 (m, 6H), 3.96 - 3.90 (m, 1H), 2.39 - 2.30 (m, 2H), 1.80 - 1.74 (m, 2H), 1.07 (d, 3H, J = 6.2 Hz), 1.05 (s, 9H).; ¹³C NMR (100 MHz, CDCl₃): 135.6, 134.0, 133.5, 129.8, 129.7, 127.7, 127.5, 119.9, 67.7, 34.6, 26.9, 22.8, 19.2, 12.9.; MS (ESIMS) m/z 338 (M+H⁺), 355 (M+NH₄⁺): HRMS (ESI) calcd for C₂₁H₂₇NOSi (M+Na⁺) 360.1757, found 360.1783.

(7S)-7-[(Tert-butyldiphenylsilyl)oxy]-1-[(tetrahydro-2H-pyran-2-yl)oxy]oct-2-yn-4-ol (11): To a stirred solution of cyano compound 9 (3g, 8.9 mmol), in dry CH₂Cl₂ (20 mL) at -78 °C was added DIBAL-H (29.2 mL, 25% in toluene, 33 mmol) slowly for 5 minutes. The reaction mixture was stirred for 1hr. After completion of the reaction showed by TLC, the reaction mixture was quenched with saturated solution of Rochelle's salt and allow to stir for 1hr. The reaction mixture was passed through celite-bed. The filtrate was extracted with CH₂Cl₂ (2x25mL) and washed with brine, and dried over Na₂SO₄ and concentrated into vacuo. The crude product was purified by flash column chromatography (60-120 mesh) by eluting with hexane-EtOAc (9:1) mixture to afford aldehyde compound 10 in 2.28 g (75%) as colorless viscous liquid.

To a stirred solution of propergyl compound (2.34g 16.7 mmol) in dry THF (20 mL) was added n-BuLi (8.36 mL, 13.4 mmol, 1.6 M, hexane), at -78 °C. After stirring for 45 minutes, the above
aldehyde 10 (2.28g, 6.7 mmol) was added, which was dissolved in dry THF (15 mL). The resulting reaction mixture was stirred for 2hr at -78 °C. After completion of the reaction, as showed by TLC, the reaction mixture was quenched with saturated NH₄Cl and the solvent was removed under reduced pressure. The residue was extracted with EtOAc (2x30 mL). The combined organic layers were washed with brine and dried over Na₂SO₄ and concentrated into vacuo. The crude product was purified by column chromatography using silica (60-120 mesh), by eluting with Hexane-EtOAc (8:2) mixture to give propergyl alcohol 11, 2.36g, (71.5%) as colorless liquid.; IR (neat): υ 3420, 3070, 2931, 2856, 1376, 1263, 1107, 1020, 901, 740 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.73 - 7.64 (m, 4H), 7.45 - 7.34 (m, 6H), 4.80 - 4.50 (m, 3H), 3.98 - 3.90 (m, 1H), 3.85 - 3.80 (m, 1H), 3.50 - 3.57 (m, 1H), 3.52 - 3.56 (m, 1H), 2.70 - 2.50 (m, 2H), 1.88 - 1.79 (m, 2H) 1.58 -1.68 (m, 4H), 1.05 (m, 12H).; ¹³C NMR (100 MHz, CDCl₃): δ 187.3, 135.8, 135.7, 134.5, 133.9, 129.6, 129.5, 127.6, 127.4, 97.1, 87.8, 84.8, 68.3, 53.7, 41.1, 32.9, 30.3, 27.0, 25.2, 23.1, 19.2, 18.8.; MS (ESIMS) m/z 503 (M+Na)⁺.
(4S,7S)-7-[(Tert-butyldiphenylsilyl)oxy]-1-[(tetrahydro-2H-pyran-2-yl)oxy]oct-2-yn-4-ol (13): To a stirred solution of keto compound 12 (1.9 g, 3.97 mmol) in dry THF (20 mL) was added R-(-)-2-methyl-CBS-oxazo borolidine (1.32 mL, 1.31 mmol, 1M toluene) at -40 °C and stirred for 30 minutes, then added BH₃-DMS (0.33 mL, 4.36 mmol) at the same temperature and stirring continued for 1 hr. The reaction mixture was quenched by adding methanol (0.1 mL in 5 mL ether) followed by saturated NaHCO₃ (15 mL). The solvent was removed under reduced pressure and the residue was extracted with ethyl acetate (2x15 mL) and the combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated into vacuum. The crude product was purified by flash column chromatography by eluting with Hexane-EtOAc (8:2) mixture to yield chiral alcohol compound 13, in 1.54 g (80.8%) yield, with excellent diastereomeric excess (92:8); [α]D²⁵ -16.79 (c = 1, CHCl₃); IR (neat): υ 3420, 3048, 2931, 2856, 1589, 1427, 1376, 1021, 901, 701 cm⁻¹; ¹H NMR (400 MHz, CDCl₃):  δ 7.71 - 7.65 (m, 4H), 7.44 - 7.34 (m, 6H), 4.80 (t, 1H, J = 6.9 Hz), 4.35 - 4.29 (m, 1H), 4.27 (dd, 1H, J = 8.8 Hz), 3.95 - 3.88 (m, 1H), 3.84 (dt, J = 9.5 Hz, 1H), 3.50 - 3.60 (m, 1H), 2.34 - 2.42 (m, 1H), 1.88 - 1.67 (m, 4H), 1.65 - 1.49 (m, 6H), 1.09 - 1.13 (m, 12H); ¹³C NMR (100 MHz, CDCl₃):  δ 135.9, 134.5, 134.0, 129.6, 127.5, 127.4, 96.8, 86.9, 80.7, 69.0, 62.3, 62, 54.3, 34.3, 32.8, 30.2, 27.0, 25.3, 22.7, 19.2, 19.0; MS (ESIMS) m/z 503 (M+Na)⁺: HRMS (ESI) calcd for C₂₉H₄₀O₅Si₃Na (M+Na)⁺ 503.2588, found 503.25884.

{[(2S,5S)-5-(Benzyloxy)-8-((tetrahydro-2H-pyran-2-yl)oxy)oct-6-yn-2-yl]oxy}(tert-butyl)di phenylsilane (14): To a stirred solution of NaH (250 mg, 6.3 mmol, 60% in hexane mineral oil) in dry THF (10 mL) was added the solution of alcohol compound (1.5 g, 3.1 mmol) in THF (10 mL) at 0 °C, then Bu₄N⁺I⁻ (10 mg) and BnBr (0.41 mL, 3.4 mmol) was added. The solution was warmed to room temperature and stirred for 4 hr. After completion of the reaction, as showed by TLC, then the reaction mixture was quenched with saturated NH₄Cl solution and extracted with EtOAc (3x20 mL), the combined organic layers were washed with brine (3x15 mL), dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography using silica (60-120 mesh) by eluting with hexanes-EtOAc (9:1) mixture to give compound 14, in 1.38 g (78%) as colorless liquid.; [α]D²⁵ +4.2 (c = 0.5, CHCl₃); IR (neat): υ 3066, 2929, 1427, 1375, 1109, 1001, 868, 701 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 7.69 - 7.64 (m, 4H), 7.43 - 7.27 (m, 11H), 4.82 - 4.87 (m, 1H), 4.75 (dd, 1H, J = 11.7 Hz), 4.45 (t, 1H, J =
11.1 Hz), 4.35 - 4.31 (m, 2H), 4.06 (q, 1H, J = 15.7 Hz), 3.92 - 3.82 (m, 2H), 3.57 - 3.50 (m, 1H), 1.93 - 1.69 (m, 4H), 1.68 - 1.50 (m, 6H), 1.05 - 1.02 (m, 12H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): δ 138, 135.8, 134.8, 134.3, 129.5, 129.4, 128.3, 127.8, 127.5, 127.4, 127.3, 96.7, 84.9, 81.7, 70.3, 69.1, 68.8, 62.0, 54.2, 34.8, 31.2, 30.3, 29.7, 27, 25.3, 23.2, 19.2, 19.1; MS (ESIMS) m/z 589 (M+NH\(_4\))^+.

\((4S,7S)-4-\{(Benzyloxy)-7-\{(tert-butylidiphenylsilyl)oxy\}oct-2-yn-1-ol\}(15): To a stirred solution of compound 14 (1.3g, 2.3 mmol) in dry methanol (10 mL) was added PPTS (100 mg, 0.23 m mol) at 0 °C, slowly reaction mixture warmed to room temperature and stirred for 12hr. After completion of the reaction, as showed by TLC, reaction mixture was quenched with TEA (1 mL) and methanol was removed under vacuo, and the residue was extracted with EtOAc (2x20 mL). The combined organic layers were washed with brine and dried over Na\(_2\)SO\(_4\) and concentrated under vacuo. The crude product was purified by flash column chromatography using silica (60-120 mesh) by eluting with Hexane-EtOAc (8:2) mixture to obtained, compound 15, in 0.98 g, (89%) as colorless liquid.; \([\alpha]_D^{25}+6.8 \ (c = 0.5, \text{CHCl}_3).; IR (neat): \nu 3334, 3016, 2862, 1492, 1381, 135.8, 134.8, 134.3, 129.5, 129.4, 128.3, 127.8, 127.5, 127.4, 127.3, 96.7, 84.9, 81.7, 70.3, 69.1, 68.8, 62.0, 54.2, 34.8, 31.2, 30.3, 29.7, 27, 25.3, 23.2, 19.2, 19.1.; MS (ESIMS) m/z 487 (M+H)^+. 504 (M+NH\(_4\))^+; HRMS (ESI) calcd for C\(_{31}\)H\(_{38}\)O\(_3\)NaSi (M+Na)^+ 509.2495, found 509.2482.

\((4S,7S,\text{E})-4-(Benzyloxy)-7-\{(tert-butylidiphenylsilyl)oxy\}oct-2-en-1-ol \ (16): To a stirred solution of compound 15 (0.9 g, 2 mmol), in dry THF (8 mL) under nitrogen at 0 °C was added Red-Al (0.3 mL, 3 mmol, 65% in toluene). The resulting mixture was warmed to room temperature and stirred for 1hr. After completion of reaction, mixture was cooled to 0 °C and quenched with saturated solution of Rochelle’s salt. And stirred for 1h, clear solution obtained, then the layers were separated. The combined organic layers were washed with brine and concentrated to vacuo. The crude product was purified by chromatography using silica (60-120 mesh) by eluting with Hexane-EtOAc (8:2) mixture to obtained, compound 16, in 0.82g (91%) as colorless liquid.; \([\alpha]_D^{25} -7.29 \ (c = 1, \text{CHCl}_3).; IR (neat): \nu 3396, 3030, 2928, 1741, 1427,
1218, 1108, 1067, 975, 822 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CD\(_3\)Cl): \(\delta\) 7.71 - 7.65 (m, 4H), 7.44 - 7.27 (m, 11H), 5.73 (dt, 1H, \(J = 17.4\) Hz), 5.53 (pentet, 1H, \(J = 17.2\) Hz), 4.52 (dd, 1H, \(J = 11.1, 6.4\) Hz), 4.31 (dd, 1H, \(J = 19.0, 11.9\) Hz), 4.15 - 4.11 (m, 2H), 3.85 - 3.81 (m, 1H), 3.66 (pentet, 1H, \(J = 12.4, 5.7\) Hz) 1.70 - 1.39 (m, 4H), 1.05 - 1.01 (m, 12H); \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 138.7, 135.8, 134.7, 134.4, 132, 131.7, 129.3, 128.3, 127.6, 127.4, 79.4, 70.0, 69.2, 62.9, 34.7, 30.7, 27.0, 23.0, 19.2.; MS (ESIMS) \(m/z\) 507 (M+NH\(_4\))\(^{+}\), 511 (M+Na\(^{+}\)). HRMS (ESI) calcd for C\(_{31}\)H\(_{40}\)O\(_3\)NaSi (M+Na\(^{+}\)) 511.2638, found 511.2642. 

\((4S,7S,E)-4\)-[(Benzyloxy)-7-(tert-butyldiphenylsilyl)oxy]oct-2-enoic acid (17): To a stirred solution of allylic alcohol compound 16 (0.6 g, 1.2 mmol) in dry Hexane (30 mL) was added activated MnO\(_2\) (2.1 g, 24.6 mmol) at room temperature and stirred for 20hr. After completion of reaction showed by TLC, then the reaction mixture filtered through the celite bed, the solvent removed under reduced pressure to give the aldehyde in quantitative yield, as pale yellow syrup, which was used for next reaction without purification. To a stirred solution of the above aldehyde (0.54 g, 1.15 mmol) in a mixture of \(\text{tert-BuOH-H}_2\text{O}\) (20 mL, 5:1) was added 2-methyl-2-butene (4 mL) at 0\(^\circ\)C. Then added a mixture of NaClO\(_2\) (208 mg, 2.3 mmol in 3mL, H\(_2\)O) and NaH\(_2\)PO\(_4\) (689 mg, 0.75 mmol, 3mL, H\(_2\)O) simultaneously drop wise at 0\(^\circ\)C. The reaction mixture was stirred for 1hr. After completion of reaction, the reaction mixture quenched with saturated brine (20 mL) and stirred for 30 min. The white turbidity given off and extracted with EtOAc (2x25 mL). The combined organic layers were separated and dried over Na\(_2\)SO\(_4\) concentrated \(\text{vacuo}\). The crude product was purified by column chromatography using silica gel (60-120 mesh) by eluting with Hexane-EtOAc (7:3) mixture to obtained, compound 17, in 528 mg, (92.2%) as pale yellow sticky liquid.; \([\alpha]_D\)\(^{25}\) +18.0 (c = 1, CHCl\(_3\)); IR (neat): \(\nu\) 3465, 3018, 2925, 1704, 1489, 1379, 1281, 1215, 1072, 912, 747 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CD\(_3\)Cl): \(\delta\) 7.68 - 7.62 (m, 4H), 7.44 - 7.26 (m, 11H), 6.92 (dq, 1H, \(J = 15.7, 6.1\) Hz), 5.98 (dd, 1H, \(J = 16.8\) Hz), 4.53 (dd, 1H, \(J = 19.1, 11.8\) Hz), 4.33 (dd, 1H, \(J = 11.8\) Hz), 3.82 - 3.86 (m, 2H), 1.70 - 1.57 (m, 2H), 1.55 - 1.40 (m, 2H), 1.02 - 1.06 (m, 12H); \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 171.1, 151.1, 137.9, 135.8, 134.6, 134.3, 129.5, 129.4, 128.3, 127.6, 125.7, 127.4, 120.9, 77.6, 70.9, 68.9, 34.4, 29.9, 27, 23.1, 19.2.; MS (ESIMS) \(m/z\) 501 (M-H\(^{+}\)). HRMS (ESI) calcd for C\(_{31}\)H\(_{40}\)O\(_3\)NaSi (M+Na\(^{+}\)) 525.5623 found 525.5512.
(4S,7S,E)-4-(Benzyloxy)-7-hydroxyoct-2-enoic acid (18): To a stirred solution of acid compound 17 (300 mg, 0.6 mmol) in dry THF (5mL) was added HF:pyridine (0.1 mL, 3 mmol, 70% HF:30% pyridine), at 0 °C. Then the reaction mixture slowly warmed to room temperature and stirred for 20hr. After completion of the reaction, showed TLC, then the reaction mixture was cooled to 0 °C and quenched with saturated NaHCO₃, followed by 1N HCl. The residue was extracted with EtOAc (2x20mL). The combined organic layers were washed with brine and dried over Na₂SO₄ concentrated into vacuo. The crude product was purified by Flash column chromatography using silica (60-120 mesh) by eluting with Hexane-EtOAc (7:3) mixture to afforded, compound 18 (128 mg, 85%) as colorless liquid.; [α]D²⁵ -8.7 (c = 0.8, CHCl₃); IR (neat): υ 3359, 2885, 1768, 1733, 1641, 1420, 1375, 1219, 1028, 893 cm.⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.39 - 7.27 (m, 5H), 6.98 (dd, 1H, J = 15.7, 6.2 Hz), 6.06 (dt, 1H, J = 15.8 Hz), 4.61 (dd, 1H, J = 11.4 Hz), 4.40 (dd, 1H, J = 11.4 Hz), 4.04 (q, 1H, J = 12.4, 6.4 Hz), 3.75 - 3.68 (m, 1H), 1.81 - 1.67 (m, 2H), 1.62 - 1.47 (m, 2H), 1.18 (d, 3H, J = 6.2 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 170.5, 150.3, 137.6, 128.4, 127.8, 121.5, 77.6, 71.2, 34.3, 30.8, 23.4. ; MS (ESIMS) m/z 265 (M+H)+, 287 (M+Na); HRMS (ESI) calcd for C₁₅H₂₀O₄NaSi (M+Na)+ 287.1253 found 287.1256.

(3E,5S,8R,11E,13S,16R)-5,13-bis(benzyloxy)-8,16-dimethyl-1,9-dioxacyclohexadeca-3,11-diene-2,10-dione (19): To stirred solution of acid compound 18 (100 mg, 0.4 mmol) in dry toluene-THF (110 mL, 10:1) mixture at -30 °C was added triphenyl phosphene (200 mg, 2 mmol) followed by diethylazodicarboxylate (300 mg, 2 mmol) under argon atmosphere. The reaction mixture was stirred at -30 °C for 18 hr. After completion of the reaction (indicated by TLC), solvent was removed under vacuo concentrated. The crude product was purified by column chromatography using silica gel (100-200 mesh) by eluting with EtOAc-Hexane (2:8) mixture to afford, 19 (52 mg, 55.8% yield) as low melting solid.; [α]D²⁵ -10.57 (c = 0.7, CHCl₃); IR (neat): υ 2943, 2853, 1725, 1550, 1516, 1415, 1378, 1281, 772 cm.⁻¹ ; ¹H NMR (400 MHz, CDCl₃): δ 7.38 - 7.27 (m, 10H), 6.83 (dq, 2H, J = 15.9 Hz), 5.87 (dd, 2H, J = 15.9 Hz), 5.19 - 5.10 (m, 1H), 5.10 - 4.95 (m, 1H), 4.61 - 4.53 (m, 2H, J = 11.7 Hz), 4.39 (dd, 1H, J = 11.7 Hz), 4.25 - 4.35 (m, 1H), 2.02 - 2.20 (m, 2H), 1.93 - 1.73 (m, 4H), 1.70 - 1.42 (m, 4H), 1.22 - 1.28 (m, 6H, J = 6.3 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 165.3, 165, 148.4, 147.7, 137.9, 128.3, 127.3,
To a stirred solution of compound 19 (45 mg, 0.1 mmol) in dry CH$_2$Cl$_2$ (2 mL) was added TiCl$_4$ (0.1 mL, 0.4 mmol) dissolved in dry CH$_2$Cl$_2$ (1 mL) drop wise at 0 °C. The reaction mixture was slowly warmed to room temperature and stirred for 2 hr. After completion of the reaction monitored by TLC, then the reaction mixture was quenched with saturated NaHCO$_3$ and extracted with CH$_2$Cl$_2$ (2x10 mL) the combined layers were washed with brine, dried over Na$_2$SO$_4$ and concentrated to vacuo. The crude product was purified by silica gel (100-200 mesh) by eluting with Hexane-EtOAc (4:6) mixture to afford Pyrenophorol (23 mg, 80% yield) as white solid; [α]$_D^{25}$ -10.5 (c = 1, CHCl$_3$). (lit -10.2 (c = 1.04, CHCl$_3$).; IR (neat): υ 3609, 3396, 2923, 2853, 1786, 1696, 1660, 1515, 1219, 1025, 772 cm.$^{-1}$; $^1$H NMR (400 MHz, CD$_3$Cl): δ 6.91 (dd, 2H, $J$ = 15.6, 5.1 Hz), 6.02 - 5.95 (m, 2H), 5.17 - 5.06 (m, 2H), 4.35 - 4.24 (m, 2H), 2.01 - 1.82 (m, 2H), 1.80 - 1.62 (m, 6H), 1.28 (d, 6H, $J$ = 6.6 Hz).; $^{13}$C NMR (100 MHz, CDCl$_3$): δ 164.8, 149.4, 122.1, 70.4, 69.7, 30.4, 28.9, 18.1.; MS (ESIMS) $m/z$ 312 (M+H)$^+$, 334 (M+Na)$^+$. HRMS (ESI) calcd for C$_{16}$H$_{25}$O$_6$Na $^{(M+Na)}$ 515.2404 found 515.2389.

(3E,5S,8R,11E,13S,16R)-5,13-dihydroxy-8,16-dimethyl-1,9-dioxacyclohexadeca-3,11-diene-2,10-dione (1): To a stirred solution of compound 19 (45 mg, 0.1 mmol) in dry CH$_2$Cl$_2$ (2 mL) was added TiCl$_4$ (0.1 mL, 0.4 mmol) dissolved in dry CH$_2$Cl$_2$ (1 mL) drop wise at 0 °C. The reaction mixture was slowly warmed to room temperature and stirred for 2 hr. After completion of the reaction monitored by TLC, then the reaction mixture was quenched with saturated NaHCO$_3$ and extracted with CH$_2$Cl$_2$ (2x10 mL) the combined layers were washed with brine, dried over Na$_2$SO$_4$ and concentrated to vacuo. The crude product was purified by silica gel (100-200 mesh) by eluting with Hexane-EtOAc (4:6) mixture to afford Pyrenophorol (23 mg, 80% yield) as white solid; [α]$_D^{25}$ -10.5 (c = 1, CHCl$_3$). (lit -10.2 (c = 1.04, CHCl$_3$).; IR (neat): υ 3609, 3396, 2923, 2853, 1786, 1696, 1660, 1515, 1219, 1025, 772 cm.$^{-1}$; $^1$H NMR (400 MHz, CD$_3$Cl): δ 6.91 (dd, 2H, $J$ = 15.6, 5.1 Hz), 6.02 - 5.95 (m, 2H), 5.17 - 5.06 (m, 2H), 4.35 - 4.24 (m, 2H), 2.01 - 1.82 (m, 2H), 1.80 - 1.62 (m, 6H), 1.28 (d, 6H, $J$ = 6.6 Hz).; $^{13}$C NMR (100 MHz, CDCl$_3$): δ 164.8, 149.4, 122.1, 70.4, 69.7, 30.4, 28.9, 18.1.; MS (ESIMS) $m/z$ 312 (M+H)$^+$, 334 (M+Na)$^+$; HRMS (ESI) calcd for C$_{16}$H$_{25}$O$_6$Na $^{(M+Na)}$ 515.2404 found 515.2389.

(5S,8R,13S,16R)-5,13-dihydroxy-8,16-dimethyl-1,9-dioxacyclohexadecane-2,10-dione (1b): To a stirred solution of Pyrenophorol (5 mg) in ethyl acetate (5 mL) was added catalytic amount of (Pd/C, 10%) and stirred under hydrogen atmosphere (25 psi) for a period of 8 hr. The completion of reaction was confirmed by TLC and filtered on celite bed, washed with ethyl acetate. The combined filtrate was concentrated under reduced pressure to afford the product, tetrahydropyrenophorol (4 mg, 78%) as a colorless crystals.; [α]$_D^{25}$ -55.6 (c = 0.4, CHCl$_3$). (lit - 68 (c = 0.14, CHCl$_3$).; IR (neat): υ 3359, 2930, 2885, 1768, 1733, 1641, 1420, 1375, 1028, 991, 893.; $^1$H NMR (400 MHz, CD$_3$Cl): δ 5.03 - 4.94 (m, 2H), 3.68 - 3.56 (m, 2H), 2.64 - 2.50 (m, 2H), 2.43 - 2.32 (m, 2H), 1.90 - 1.78 (m, 10H), 1.42 - 1.28 (m, 2H), 1.22 (d, $J$ = 6.23 Hz, 6H).; $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 172.4, 68.8, 66.6, 32.5, 31.3, 30.9, 29.7, 20.2.; MS (ESIMS) $m/z$ 339 (M+Na)$^+$ HRMS (ESI) calcd for C$_{16}$H$_{28}$O$_6$Na 339.1766 (M+Na)$^+$ found 339.1778.
(2R,5S,6E,10R,13S,14E)-2,10-dimethyl-8,16-dioxo-1,9-dioxacyclohexadeca-6,14-diene-5,13-diyl diacetate (1c): To stirred solution of Pyrenophorol (5mg) in pyridine (1 mL) at 0 °C was added acetic anhydride two drops and raise the temperature to rt and stirred for 24 hr. After completion of the reaction showed by TLC, pyridine was removed under reduced pressure. The crude product subjected to column chromatography by using silica gel (100-200 mesh) by eluting with Hexane-EtOAc (8:2) mixture to afford, 4,4'-diacetyl pyrenophorol (4 mg, 64%), as low melting solid.; [α]D
25 -35.5 (c = 0.4, CHCl3); IR (neat): ν 2958, 2853, 2313, 1726, 1549, 1451, 1284, 1074, 968, 772 cm⁻¹; ¹H NMR (400 MHz, CDCl3): δ 6.80 (dd, 2H, J = 15.7 Hz), 5.94 (dd, 2H, J = 15.7 Hz), 5.29 - 5.17 (m, 2H), 5.02 - 4.91 (m, 2H), 2.37 - 2.27 (m, 2H), 2.08 (s, 6H), 1.96 - 1.71 (m, 6H), 1.28 (d, 6H, J = 7.0 Hz); ¹³C NMR (100 MHz, CDCl3): δ 169.9, 164.9, 143.7, 124.1, 71.7, 69.9, 29.3, 27.0, 21.0, 18.4.; MS (ESIMS) m/z 419 (M+Na).+HRMS (ESI) calcd for C₂₀H₂₈O₈Na 416.16764 (M+Na)+ and found 416.16916.
$^1$H-NMR Specturm of (S)-2-bromosuccinic acid (400 MHz, DMSO-$d_6$)
$^{13}$C-NMR Spectrum of (S)-2-bromosuccinic acid (100 MHz, DMSO-$d_6$)
$^1$H-NMR Specturm of Compound 3 (400 MHz, CDCl$_3$)
$^{13}$C-NMR Spectrum of Compound 3 (100 MHz, CDCl$_3$)
$^1$H NMR - Spectrum of compound 4 (400 MHz, CDCl$_3$)
$^{13}$C NMR - Spectrum of Compound 4 (100 MHz, CDCl$_3$)
H NMR - Spectrum of Compound 5 (400 MHz, CDCl₃)
$^{13}$C NMR - Spectrum of Compound 5 (100 MHz, CDCl$_3$)
$^{1}H$ NMR - Spectrum of Compound 6 (400 MHz, CDCl$_3$)
$^{13}$C NMR - Spectrum of Compound 6 (100 MHz, CDCl$_3$)
$\text{H NMR - Spectrum of Compound 7 (400 MHz, CDCl}_3\text{)}$
\[^{13}\text{C} \text{ NMR} - \text{Spectrum of Compound 7 (100 MHz, CDCl}_3)\]
$^1$H NMR - Spectrum of Compound 8 (400 MHz, CDCl$_3$)
$^{13}$C NMR - Spectrum of Compound 8 (100 MHz, CDCl$_3$)
$^{1}$H NMR - Spectrum of Compound 9 (400 MHz, CDCl$_3$)
$^{13}$C NMR - Spectrum of Compound 9 (100 MHz, CDCl$_3$)
$^1$H NMR - Spectrum of Compound 11 (400 MHz, CDCl$_3$)
\[^{13}\text{C} \text{NMR - Spectrum of Compound 11 (100 MHz, CDCl}_3\text{)}\]
$^1$H NMR - Spectrum of Compound 12 (400 MHz, CDCl$_3$)
$^{13}$C NMR - Spectrum of Compound 12 (100 MHz, CDCl$_3$)
$^1$H NMR - Spectrum of Compound 13 (400 MHz, CDCl$_3$)
$^{13}$C NMR - Spectrum of Compound 13 (100 MHz, CDCl$_3$)
$^1$H NMR - Spectrum of Compound 14 (400 MHz, CDCl$_3$)
$^{13}$C NMR - Spectrum of Compound 14 (100 MHz, CDCl$_3$)
$^1$H NMR - Spectrum of Compound 15 (400 MHz, CDCl$_3$)
$^{13}$C NMR - Spectrum of Compound 15 (100 MHz, CDCl$_3$)
$^1$H NMR - Spectrum of Compound 16 (400 MHz, CDCl$_3$)
$^{13}$C NMR - Spectrum of Compound 16 (100 MHz, CDCl$_3$)
$^{1}$H NMR - Spectrum of Compound 17 (400 MHz, CDCl$_3$)
$^{13}$C NMR - Spectrum of Compound 17 (100 MHz, CDCl$_3$)
$^1$H NMR - Spectrum of Compound 18 (400 MHz, CDCl$_3$)
$^{13}$C NMR - Spectrum of Compound 18 (100 MHz, CDCl$_3$)
$^1$H NMR - Spectrum of Compound 19 (400 MHz, CDCl$_3$)
$^{13}$C NMR - Spectrum of Compound 19 (100 MHz, CDCl$_3$)
ESI-HRMS - Spectrum of compound 19
$^1$H NMR - Spectrum of Compound 1 (400 MHz, CDCl$_3$)
$^{13}$C NMR - Spectrum of Compound 1 (100 MHz, CDCl$_3$)
$^1$H NMR - Spectrum of Compound 1b (400 MHz, CDCl$_3$)
$^{13}$C NMR - Spectrum of Compound 1b (100 MHz, CDCl$_3$)
ESI-HRMS - Spectrum of Compound 1b
$^1$H NMR - Spectrum of Compound 1a (400 MHz, CDCl$_3$)
$^{13}$C NMR - Spectrum of Compound 1a (100 MHz, CDCl$_3$)
