An Expeditious Asymmetric Synthesis of the Polyketide Unit Present in HIV-Inhibitory Depsipeptides Aetheramide A and B

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Experimental:

General Procedures: Column chromatography was performed on Silica gel, Acme grade 100-200 mesh. TLC plates were visualized either with UV, in an iodine chamber, or with phosphomolybdic acid spray. All reagents were purchased from commercial sources and used without additional purification. THF was freshly distilled over Na-benzophenone ketyl. Melting points were uncorrected. $^1$H NMR and $^{13}$C NMR spectra were recorded either on a 400 MHz machine in CDCl$_3$ as solvent with TMS as reference. HRMS was obtained using a micromass-QTOF spectrometer using electrospray ionization (ESI).

Preparation of (R)-furan-2-yl(phenyl)methanol (++)-6: Resolution of (++)-6 was performed according to the procedure described earlier by Kusakabe et. al.$^7$ Resolution of (++)-6 (3.1 g, 17.8 mmol) afforded (++)-6 (1.32 g, 43%) as an yellow oil. [α]$^2$$_D$ +6.5 (c 1.2, CHCl$_3$); IR (neat): $\nu$ max 3377, 1627, 1143, 1010 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.50-7.25 (m, 6H), 6.33 (dd, $J = 2.9$, 1.8 Hz, 1H), 6.13 (d, $J = 3.2$ Hz, 1H), 5.83 (d, $J = 3.2$ Hz, 1H), 2.54 (bs, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$155.9, 142.5, 140.8, 128.4 (2 x C), 128.1, 126.6 (2 x C), 110.2, 107.4, 70.1; HRMS: m/z calcd for C$_{11}$H$_{10}$O$_2$+Na 197.0578; found: 197.0578.

Preparation of (R)-tert-butyl(furan-2-yl(phenyl)methoxy)dimethylsilane (5): To a stirred solution of the furyl carbinol (++)-6 (1.2 g, 6.89 mmol) in CH$_2$Cl$_2$ (12 mL) were added imidazole (0.94 g, 13.8 mmol), 4-(dimethylamino)pyridine (0.17 g, 1.4 mmol) and TBSCI (1.6 g, 10.3 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. After completion of the reaction (TLC), it was poured into water (50 mL) and was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine (50 mL) and dried over anhydrous Na$_2$SO$_4$. Silica gel column chromatography of the residue obtained after evaporation of the solvent, using petroleum ether: EtOAc (19:1) as eluent afforded the desired product 5 (2.5 g, 95%) as a colorless oil. [α]$^2$$_D$ +16.3 (c 0.74, CHCl$_3$); IR (neat): $\nu$ max 2956, 2931, 2858, 1598, 1471, 1256 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.41 (d, $J = 7.6$ Hz, 2H), 7.36-7.30 (m, 3H), 7.28-7.22 (m, 1H), 6.27 (d, $J = 1.2$ Hz, 1H), 6.06 (d, $J = 2.4$ Hz, 1H), 5.78 (s, 1H), 0.91 (s, 3H), 0.05 (s, 3H), 0.02 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$157.0, 142.04, 142.0, 128.1 (2 x C), 127.4, 126.3 (2 x C), 110.0, 106.7, 70.5, 25.8 (3 x C), 18.3, –5.03, –5.05; HRMS: m/z calcd for C$_{11}$H$_{14}$O$_2$Si+Na 311.1443; found: 311.1448.

Preparation of (R,E)-5-((tert-butldimethylsilyloxy)-4-oxo-5-phenylpent-2-enal (4): To a stirred solution of 5 (1.93 g, 6.7 mmol) in acetone/H$_2$O (9:1, 15 mL) was added NaHCO$_3$ (1.2 g, 13.4 mmol) and a solution of NBS (1.4 g, 8.0 mmol) in acetone/H$_2$O (9:1, 10 mL) at –15 °C. The reaction mixture was stirred at –15 °C for 20 min, and furan (0.96 mL, 13.1 mmol) was introduced into the reaction mixture to destroy excess NBS. After stirring for 0.5 h, pyridine (0.5 mL, 6.7 mmol) was added to reaction mixture at –15 °C, and the mixture was stirred at room temperature for 2 h. Brine (25 mL) and
EtOAc (30 mL) were added to the reaction mixture and the resulting mixture was acidified with phosphate buffer (pH ~ 4.0). The organic layer was separated from the aqueous layer, and the aqueous layer was extracted with EtOAc (2 × 25 mL). The combined organic extracts were dried over anhydrous Na2SO4. The residue thus obtained was purified by Silica gel column chromatography using petroleum ether:EtOAc (5:1) as eluent to afford the keto aldehyde 4 (1.63 g, 80%) as a pale yellow oil. [α]D24 +67.5 (c 0.80, CHCl3); IR (Neat): 2932, 2860, 2739, 1701, 1466; 1H NMR (400 MHz, CDCl3): δ 9.70 (d, J = 7.6 Hz, 1H), 7.45 (d, J = 7.6 Hz, 2H), 7.38 (t, J = 7.3 Hz, 2H), 7.37-7.25 (m, 2H), 6.90 (dd, J = 16.0, 7.6 Hz, 1H), 5.30 (s, 1H), 0.95 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); 13C NMR (100 MHz, CDCl3): δ 197.3, 192.8, 140.0, 138.8, 137.0, 128.9 (2 × C), 128.5, 125.8 (2 × C), 80.2, 25.7 (3 × C), 18.2, -4.9, -5.1; Anal: calcd for C67.06, H 7.95; found C 67.1928, H 8.0009.

**Preparation of ethyl (R,2E,4E)-7-((tert-butyldimethylsilyl)oxy)-2-methyl-6-oxo-7-phenylhepta-2,4-dienoate (7):** To a solution of ethyl diethylphosphonoacetate (1.32 g, 5.55 mmol) in THF (5 mL) was added LiHMDS (5.50 mL of 1M solution in toluene, 5.50 mmol) at −78 °C, and the reaction mixture was stirred for 30 min at −78 °C. Then solution of keto aldehyde 4 (1.30 g, 3.70 mmol) in THF (10 mL) was added dropwise at −78 °C. The reaction mixture was stirred at same temperature for 1.5 h and was cautiously quenched by addition of saturated aq. NH4Cl solution (20 mL). The reaction mixture was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na2SO4. Evaporation of the solvent gave the crude residue which was purified by silica gel column chromatography using petroleum ether:EtOAc (10:1) as eluent to furnish 7 (1.31 g, 91%) as a colorless oil. [α]D24 +40.6 (c 0.35, CHCl3); IR (Neat): 2957, 2933, 2859, 1713, 1692; 1H NMR (400 MHz, CDCl3): δ 7.57 (dd, J = 15.2, 12.0 Hz, 1H), 7.44 (d, J = 7.4 Hz, 2H), 7.34 (t, J = 7.3 Hz, 2H), 7.29 (d, J = 7.0 Hz, 1H), 7.18 (d, J = 12.1 Hz, 1H), 6.83 (d, J = 15.3 Hz, 1H), 5.22 (s, 1H), 4.22 (q, J = 7.0 Hz, 2H), 2.03 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H), 0.95 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); 13C NMR (100 MHz, CDCl3): δ 198.3, 167.5, 138.3, 137.6, 136.4, 135.0, 128.7, 128.6 (2 × C), 128.1, 125.8 (2 × C), 80.4, 61.1, 25.7 (3 × C), 18.2, 14.2, 13.3, -4.97, -5.02; HRMS: m/z calcd for C22H32O3Si+Na 411.1968; found: 411.1967.

**Preparation of ethyl (2E,4E,6R,7R)-7-((tert-butyldimethylsilyl)oxy)-6-hydroxy-2-methyl-7-phenylhepta-2,4-dienoate (8):** To a solution of the keto ester 7 (1.18 g, 3.05 mmol) in methanol (15 mL) was added CeCl3·7H2O (2.27 g, 6.10 mmol) at room temperature and stirred at the same temperature for 0.5 h. The reaction mixture was cooled to −78 °C and NaBH4 (0.17 g, 4.50 mmol) was added portion wise over a period of 15 min and the reaction mixture was stirred at −78 °C for 1 h. After completion of the reaction (TLC), it was cautiously quenched by addition of water (1 mL). After evaporation of MeOH in vacuo, the crude residue was washed with water and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried over Na2SO4, and concentrated. Silica gel column chromatography of the crude residue obtained after evaporation of the solvent, with petroleum ether:EtOAc (10:1) as eluent, gave desired alcohol 8 (1.03 g, 87%) as a colorless liquid. [α]D24 +71.5 (c 1.05, CHCl3); IR (Neat): 3442, 2954, 2929, 1700, 1587 cm⁻¹; 1H NMR (400 MHz, CDCl3): δ 7.40-7.22 (m, 5H), 7.08 (d, J = 11.2 Hz, 1H), 6.58-6.45 (m, 1H), 5.81 (dd, J = 15.2, 4.8 Hz, 1H), 4.44 (d, J = 7.2 Hz, 1H), 4.27 (bs, 1H), 4.20 (q, J = 7.2 Hz, 2H), 2.97 (d, J = 2.4 Hz, 1H), 1.89 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H), 0.90 (s, 9H), 0.05 (s, 3H), −0.18 (s, 3H); 13C NMR (100 MHz, CDCl3): δ 168.5, 140.5, 138.8, 137.3, 128.1 (2 × C), 127.8, 127.5, 127.1, 127.0 (2 × C), 78.1, 76.6, 60.6, 25.7 (3 × C), 18.1, 14.3, 12.6, −4.6, −5.0; HRMS: m/z calcd for C22H33OSi+Na 413.2124; found 413.2124.
Preparation of ethyl (2E,4E,6R,7R)-7-((tert-butylidimethylsilyl)oxy)-6-(methoxymethoxy)-2-methyl-7-phenylhepta-2,4-dienoate (9): To a precooled (0 °C) solution of a mixture of 8 (0.99 g, 2.54 mmol) in dichloromethane (6 mL) were added DMAP (0.062 g, 0.51 mmol) and Pr₂NEt (2.6 mL, 15.23 mmol) dropwise followed by MOMCl (0.58 mL, 7.61 mmol). The reaction mixture was slowly allowed to warm to room temperature and stirred at room temperature for 8 h. After completion of the reaction (TLC), it was poured into water (10 mL) and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine (5 mL) and dried over Na₂SO₄. Evaporation of solvent gave the crude residue which was purified and separated by silica gel column chromatography using petroleum ether:EtOAc (20:1) as eluent to furnish 9 (1.02 g, 93%) as a colorless oil. [α]ᵰ₂⁴⁺60.3 (c 0.75, CHCl₃); IR (Neat): νmax 2957, 2889, 2858, 1727, 1664, 1468 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.35-7.20 (m, 5H), 7.06 (d, J = 11.6 Hz, 1H), 6.42 (dd, J = 15.2, 12.0 Hz, 1H), 5.76 (dd, J = 15.6, 6.8 Hz, 1H), 4.71 (d, J = 5.6 Hz, 1H), 4.67 (s, 1H), 4.30 (t, J = 6.4 Hz, 2H), 4.20 (q, J = 7.2 Hz, 2H), 3.20 (s, 3H), 1.94 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 3H), -0.10 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 168.4, 141.0, 137.6, 137.1, 128.1, 127.7 (2 × C), 127.5, 127.4, 127.2 (2 × C), 95.1, 80.7, 77.5, 60.6, 55.4, 25.7 (3 × C), 18.2, 14.3, 12.6, -4.8, -4.9; HRMS: m/z calcd for C₂₅H₃₃O₅Si+Na 457.2386; found 457.2382.

Preparation of (2E,4E,6R,7R)-7-((tert-butylidimethylsilyl)oxy)-N-methoxy-6(methoxymethoxy)-N,2-dimethyl-7-phenylhepta-2,4-dienamide (10): To a stirred solution of the ester 9 (3.18 g, 7.34 mmol) in THF (20 mL) was added N, O-dimethylhydroxylamine hydrochloride (1.44 g, 14.68 mmol) at 0 °C. Isopropylmagnesium chloride (23.48 mmol, 33.4 mL of 0.7 M solution in THF) was added to the reaction mixture dropwise at 0 °C and the stirring was continued at the same temperature for 1 h. After completion of the reaction (TLC), it was quenched by addition of saturated NH₄Cl solution (30 mL) and was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄ and was concentrated to give the crude residue which was purified by Silica gel column chromatography using petroleum ether:EtOAc (5:1) as eluent to furnish the pure amide 10 (2.80 g, 85%) as a colorless oil. [α]ᵰ₂⁴+=53.7 (c 0.80, CHCl₃); IR (Neat): νmax 2932, 2890, 1646, 1468, 1255 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.38-7.20 (m, 5H), 6.42-6.25 (m, 2H), 5.59 (dd, J = 12.4, 6.4 Hz, 1H), 4.70 (d, J = 5.2 Hz, 1H), 4.06 and 4.61 (ABq, J = 6.4 Hz, 2H), 4.26 (t, J = 6.0 Hz, 1H), 3.60 (s, 3H), 3.20 (bs, 6H), 1.91 (s, 3H), 0.87 (s, 9H), 0.05 (s, 3H), -0.10 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 172.4, 141.2, 134.5, 131.3, 131.7 (2 × C), 127.67, 127.3, 127.1 (3 × C), 94.8, 80.6, 77.6, 61.0, 55.3, 33.6, 25.7 (3 × C), 18.2, 14.3, -4.8, -4.9; HRMS: m/z calcd for C₂₅H₃₉NO₂Si+Na 472.2498; found 472.2493.

Preparation of (6E,8E,10R,11R)-11-((tert-butylidimethylsilyl)oxy)-10-(methoxymethoxy)-6-methyl-11-phenyl-1-((tetrahydro-2H-pyran-2-yl)oxy)undec-6,8-dien-5-one (11): To a solution of the amide 10 (2.47 g, 5.50 mmol) in dry THF (15 mL) was added a freshly prepared solution of (4-((tetrahydro-2H-pyran-2-yl)oxy)butyl)magnesium bromide (20.6 mL of 0.40 M solution in THF, 8.25 mmol) at 0 °C. Progress of the reaction was monitored by TLC and after the reaction was complete
(−1 h), it was cautiously quenched by addition of sat. NH₄Cl solution (15 mL). It was then quenched with saturated NH₄Cl solution (20 mL) and was extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with brine (30 mL) and dried (Na₂SO₄). Evaporation of solvent followed by Silica gel column chromatography of the resultant residue with petroleum ether:EtOAc (10:1) as eluent yielded I (2.50 g, 83%) as a colorless oil. [α]D²⁰=−43.0 (c 1.0, CHCl₃); IR (Neat): νmax 2939, 2871, 1667, 1034 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.35-7.21 (m, 5H), 6.90 (d, J = 11.2 Hz, 1H), 6.50 (dd, J = 15.2, 11.2 Hz, 1H), 5.78 (dd, J = 15.2, 6.4 Hz, 1H), 4.71 (d, J = 5.6 Hz, 1H), 4.67 (s, 2H), 4.56 (bd, J = 4.0 Hz, 1H), 4.31 (t, J = 6.4 Hz, 1H), 3.90-3.82 (m, 1H), 3.78-3.70 (m, 1H), 3.55-3.45 (m, 1H), 3.39 (dt, J = 9.6, 6.2 Hz, 1H), 3.26 (s, 3H), 2.69 (t, J = 6.8 Hz, 2H), 1.82 (s, 3H), 1.75-1.45 (m, 10H), 0.87 (s, 9H), 0.06 (s, 3H), −0.10 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 201.8, 141.0, 138.1, 136.8, 136.2, 128.6, 127.8 (2 × C), 127.5, 127.1 (2 × C), 98.8, 95.2, 80.7, 77.5, 67.2, 62.3, 55.5, 37.0, 30.7, 29.3, 25.7 (3 × C), 25.4, 21.6, 19.6, 18.2, 11.6, −4.8, −4.9; HRMS: m/z calcd for C₃₁H₅₀O₄Si+Na 569.3274; found 569.3275.

Preparation of (5R,6E,8E,10R,11R)-11-((tert-butylimidemethylsilyl)oxy)-10-(methoxymethoxy)-6-methyl-11-phenyl-1-((tetrahydro-2H-pyran-2-yl)oxy)undeca-6,8-dien-5-ol (12): To a stirred solution of (5)-2-methyl-CBS-oxazaborolidine (0.95 mL, 1.0 M solution in toluene, 0.95 mmol) in THF (2 mL) was added BH₃·SMe₂ (2.1 mL, 2.0 M solution in THF, 4.28 mmol) at room temperature and stirred for 10 min. Then the reaction mixture was cooled to −20 °C and the solution of ketone I (1.3 g, 2.38 mmol) in THF (12 mL) was added dropwise over a period of 5 h and stirred at the same temperature for additional 5 h. After completion of the reaction (TLC), it was quenched by the addition of MeOH (5 mL) followed by evaporation of MeOH in vacuo furnished the crude residue. This was dissolved in EtOAc (10 mL) to which 1N cold HCl (10 mL) was added and was extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with brine (25 mL) and dried over Na₂SO₄ and concentrated. The crude residue obtained after evaporation of solvent was purified by silica gel column chromatography with petroleum ether:EtOAc (5:1) as eluent to give desired alcohol 12 (1.07 g, 82%) as a colorless oil. [α]D²⁰=−45.0 (c 0.65, CHCl₃); IR (Neat): νmax 3447, 2937, 2859, 1729, 1455 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.37-7.16 (m, 5H), 6.33 (dd, J = 15.2, 11.0 Hz, 1H), 5.92 (d, J = 11.0 Hz, 1H), 5.37 (dd, J = 15.2, 7.4 Hz, 1H), 4.69 (d, J = 5.4 Hz, 1H), 4.65 (d, J = 6.8 Hz, 1H), 4.61-4.54 (m, 2H), 4.20 (t, J = 6.8 Hz, 1H), 4.00 (t, J = 6.4 Hz, 1H), 3.90-3.82 (m, 1H), 3.77-3.69 (m, 1H), 3.53-3.46 (m, 1H), 3.42-3.34 (m, 1H), 3.16 (s, 3H), 1.88-1.69 (m, 2H), 1.67 (s, 3H), 1.65-1.45 (m, 8H), 1.42-1.30 (m, 2H), 0.87 (s, 9H), 0.05 (s, 3H), −0.10 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 141.5, 140.1, 129.8, 129.1, 127.6 (2 × C), 127.1 (3 × C), 124.6, 98.8, 94.4, 80.7, 77.7, 67.4, 62.3, 60.3, 55.2, 34.6, 30.7, 29.5, 25.7 (3 × C), 25.4, 22.4, 19.6, 18.2, 11.9, −4.8, −4.9; HRMS: m/z calcd for C₃₁H₅₂O₅Si+Na 571.3431; found 571.3431.

Preparation of (5R,6R)-5-((1E,3E,5R)-5-methoxy-4-methyl-9-((tetrahydro-2H-pyran-2-yl)oxy)nona-1,3-dien-1-yl)-8,8,9,9-tetramethyl-6-phenyl-2,4,7-trioxa-8-siladecane (13): To a pre-cooled solution of alcohol 12 (0.88 g, 1.6 mmol) in DMF (8 mL) was added NaH (0.13 g of 60% dispersed in mineral oil, 3.2 mmol) portion wise at 0 °C and stirred at same temperature for 1 h. Then methyl iodide (0.9 mL, 8.0 mmol) was introduced into the reaction mixture at 0 °C and slowly warmed to room temperature and stirred for additional 4 h. After completion of the reaction (TLC), this was cautiously quenched by addition of saturated NH₄Cl solution (20 mL). The reaction mixture was extracted...
with EtOAc (2 × 20 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na₂SO₄. Evaporation of the solvent gave the crude residue which was purified by silica gel column chromatography using petroleum ether:EtOAc (5:1) as eluent to furnish 13 (0.72 g, 80%) as a colorless oil. [α]D²⁴ +42.5 (c 0.60, CHCl₃); IR (Neat): v max 2936, 2891, 1731, 1457, 1256 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.36-7.19 (m, 5H), 6.35 (dd, J = 15.2, 11.0 Hz, 1H), 5.88 (dd, J = 11.0 Hz, 1H), 5.41 (dd, J = 15.2, 7.4 Hz, 1H), 4.70 (dd, J = 5.2 Hz, 2H), 4.66 (dd, J = 6.2 Hz, 1H), 4.63-4.50 (m, 2H), 4.21 (t, J = 6.2 Hz, 1H), 3.90-3.80 (m, 1H), 3.72 (dt, J = 9.2, 6.9 Hz, 1H), 3.53-3.45 (m, 1H), 3.43 (t, J = 6.8 Hz, 1H), 3.40-3.30 (m, 1H), 3.14 (s, 3H), 3.13 (s, 3H), 1.90-1.65 (m, 2H), 1.68 (s, 3H), 1.64-1.45 (m, 8H), 1.40-1.20 (m, 2H), 0.87 (s, 9H), 0.04 (s, 3H), −0.10 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 141.6, 137.5, 129.9, 128.8, 127.6 (2 × C), 127.1 (3 × C), 126.9, 98.8, 94.5, 87.0, 80.7, 77.8, 67.2, 62.3, 55.9, 55.2, 33.4, 30.7, 29.5, 25.7 (3 × C), 25.4 (2 × C), 19.6, 18.2, 11.0, −4.8, −5.0; HRMS: m/z calcd for C₁₂H₁₄O₂Si+Na 585.3587; found 585.3584.

Preparation of (5R,6R)-5-((1E,3E,5R)-5-methoxy-4-methyl-9-((tetrahydro-2H-pyran-2-yl)oxy)nona-1,3-dien-1-yl)-8,8,9,9-tetramethyl-6-phenyl-2,4,7-trioxo-8-siladecane (14): To a stirred solution of the diene 13 (0.56 g, 1.0 mmol) in MeOH (5 mL) was added PPTS (0.25 g, 1.0 mmol) at room temperature and stirred for 6 h. After completion of the reaction (TLC), it was quenched with solid NaHCO₃ (0.05 g). It was then filtered through a short pad of celite and the celite pad was washed with CH₄Cl₂ (20 mL). The solvent was evaporated off and the crude residue thus obtained was purified by silica gel column chromatography using petroleum ether:EtOAc (3:2) as eluent to afford 14 (0.40 g, 84%) as a colorless oil. [α]D²⁴ +48.8 (c 0.65, CHCl₃); IR (Neat): v max 3450, 2932, 2888, 1725, 1458, 1099 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.35-7.20 (m, 5H), 6.36 (dd, J = 15.0, 11.2 Hz, 1H), 5.89 (dd, J = 11.2 Hz, 1H), 5.43 (dd, J = 15.2, 7.2 Hz, 1H), 4.68 (dd, J = 5.2 Hz, 1H), 4.63 (dd, J = 6.8, 2.0 Hz, 1H), 4.55 (dd, J = 6.8, 2.0 Hz, 1H), 4.19 (t, J = 6.8 Hz, 1H), 3.62-3.52 (m, 2H), 3.40 (t, J = 7.2 Hz, 1H), 3.10 (bs, 6H), 2.31 (bs, 1H), 1.56 (bs, 3H), 1.55-1.45 (m, 2H), 1.44-1.20 (m, 4H), 0.84 (s, 9H), 0.02 (s, 3H), −0.12 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 141.4, 137.2, 129.9, 128.7, 127.5 (2 × C), 127.1, 127.0 (2 × C), 126.9, 94.3, 87.0, 80.7, 77.7, 62.3, 55.7, 55.1, 33.2, 32.4, 25.7 (3 × C), 21.9, 18.1, 10.9, −4.9, −5.1; HRMS: m/z calcd for C₂₂H₂₆O₂Si+Na 501.3012; found 501.3013.

Preparation of ethyl (2E,7R,8E,10E,12R,13R)-13-((tert-butyl(dimethylsilyl)oxy)-7-methoxy-12-(methoxy methoxy)-2,8-dimethyl-13-phenyltrideca-2,8,10-trieneoate (15): To a stirred solution of alcohol 14 (0.38 g, 0.80 mmol) in EtOAc (4 mL) was added IBX (0.68 g, 2.42mmol) and refluxed for 3 h. After completion of the reaction it was filtered through a short pad of Celite® and the celite pad was washed with EtOAc (25 mL). The organic layer was washed with saturated NaHCO₃ solution (15 mL), brine (15 mL), dried over Na₂SO₄, and concentrated. The crude aldehyde obtained was used in the next step without further purification.

To a stirred solution of the aldehyde (obtained above) in dry toluene (20 mL) was added (carbethoxymethylidene)triphenylphosphorane (0.58 g, 1.6 mmol) and refluxed for 1 h. After completion of the reaction (TLC), most of the solvent was evaporated off and the crude residue thus obtained was purified by column chromatography using petroleum ether:EtOAc (6:1) as eluent to afford 15 (0.43 g, 95% for 2 steps) as a colorless oil. [α]D²⁴ +48.8 (c 0.65, CHCl₃); IR (Neat): v max 2933, 2860, 2364, 1716,
1460 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.38-7.18 (m, 5H), 6.73 (t, J = 7.0 Hz, 1H), 6.35 (dd, J = 15.2, 11.2 Hz, 1H), 5.88 (d, J = 11.2 Hz, 1H), 5.42 (dd, J = 15.2, 7.2 Hz, 1H), 4.70 (d, J = 5.2 Hz, 1H), 4.67 (d, J = 6.4 Hz, 1H), 4.59 (d, J = 6.8 Hz, 1H), 4.30-4.15 (m, 3H), 3.43 (t, J = 6.4 Hz, 1H), 3.15 (s, 3H), 3.14 (s, 3H), 2.16 (dd, J = 14.0, 7.2 Hz, 2H), 1.81 (s, 3H), 1.60 (s, 3H), 1.55-1.40 (m, 2H), 1.35-1.25 (m, 5H), 0.87 (s, 9H), 0.04 (s, 3H), −0.10 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 168.2, 141.8, 141.5, 137.2, 130.1, 128.7, 127.9, 127.6 (2 × C), 127.15, 127.12 (2 × C), 127.07, 94.5, 86.8, 80.7, 77.8, 60.3, 55.9, 55.2, 33.2, 28.5, 25.7 (3 × C), 24.8, 18.2, 14.2, 12.3, 11.0, −4.8, −5.0; HRMS: m/z calcld for C₃₂H₃₂O₇Si+Na 583.3431; found 583.3430.

Preparation of (2E,7R,8E,10E,12R,13R)-13-((tert-butylidemethylyl)oxy)-7-methoxy-12-(methoxymethoxy)-2,8-dimethyl-13-phenyltrideca-2,8,10-trien-1-ol (16): To a stirred solution of the ester 15 (0.44 g, 0.78 mmol) in dry CH₂Cl₂ (8 mL) was added DiBAL-H (1.65 mL of 1.0 M solution in toluene, 1.64 mmol) dropwise at −78 °C for a period of 5 min under argon atmosphere. The reaction mixture was stirred at the same temperature for 30 min. After completion of the reaction (TLC), it was quenched by addition of a saturated aqueous solution of potassium sodium tartrate (10 mL), diluted with Et₂O (10 mL) and stirred for 1 h at room temperature. The aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄ and concentrated to yield the crude residue, thus obtained was purified by column chromatography using petroleum ether:EtOAc (5:1) as eluent to afford 16 (0.35 g, 87%) as a colorless oil. [α]D²⁴ −40.4 (c 0.45, CHCl₃); IR (Neat): νmax 3448, 2933, 2859, 1458, 1255 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ ¹H NMR (400 MHz, CDCl₃) 7.35-7.20 (m, 5H), 6.35 (dd, J = 15.2, 11.0 Hz, 1H), 5.87 (d, J = 10.8 Hz, 1H), 5.43 (d, J = 7.2 Hz, 1H), 5.42-5.32 (m, 1H), 4.70 (d, J = 5.2 Hz, 1H), 4.66 (d, J = 6.8 Hz, 1H), 4.58 (d, J = 6.6 Hz, 1H), 4.21 (t, J = 6.4 Hz, 1H), 3.97 (bs, 2H), 3.42 (t, J = 6.6 Hz, 1H), 3.14 (s, 3H), 3.13 (s, 3H), 2.50-1.80 (m, 2H), 1.64 (s, 3H), 1.58 (s, 3H), 1.50-1.20 (m, 4H), 0.87 (s, 9H), 0.04 (s, 3H), 0.10 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 141.5, 137.4, 134.8, 129.9, 128.8, 127.5 (2 × C), 127.11, 127.10 (2 × C), 127.0, 125.8, 94.4, 87.0, 80.7, 77.7, 68.7, 55.8, 55.2, 33.1, 27.3, 25.7 (3 × C), 25.6, 18.2, 13.6, 10.9, −4.9, −5.0; HRMS: m/z calcld for C₃₀H₃₀O₇Si+Na 541.3325; found 541.3325.

Preparation of (2S,3S,4E,9R,10E,12E,14R,15R)-15-((tert-butylidemethylyl)oxy)-3-hydroxy-1-((S)-4-isopropyl-2-thioxothiazolidin-3-yl)-9-methoxy-14-(methoxymethoxy)-2,4,10-trimethyl-15-phenylpentadeca-4,10,12-trien-1-one (18): To a stirred solution of the alcohol 16 (0.10 g, 0.19 mmol) in CH₂Cl₂ was added MnO₂ (0.17 g, 1.9 mmol) at room temperature and the resulting suspension was refluxed for 2 h. The reaction mixture was filtered through a Celite® pad and concentrated to afford the crude aldehyde, which was used as such in the next step without further purification. To a stirred solution of thioazolidinone thione 17 (0.08 g, 0.38 mmol) in freshly distilled CH₂Cl₂ (10 mL) was added, TiCl₄ (0.04 mL, 0.38 mmol) dropwise at −25 °C under inert atmosphere and was stirred for 5 min. Disisopropylethylamine (0.1 mL, 0.57 mmol) was introduced into the reaction mixture and the resulting mixture was refluxed for 3 min at −25 °C. The solution of crude aldehyde (obtained above) in CH₂Cl₂ (3 mL) was added dropwise at −25 °C and stirred at the same temperature.
After completion of the reaction (15 min), it was quenched by addition of saturated NH₄Cl solution (10 mL). The reaction mixture was extracted with EtOAc (2 × 10 mL). The organic layer was washed with brine, and then dried over Na₂SO₄. It was concentrated in vacuo to provide the crude residue which was purified by Silica gel column chromatography using petroleum ether:EtOAc (5:1) as eluent to afford the pure alcohol 18 (0.12 g, 90% for 2 steps) as an yellow oil. [α]D²⁴ +96.0 (c 0.15, CHCl₃); IR (Neat): νmax 3451, 2956, 2933, 1695, 1467 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.35-7.20 (m, 5H), 6.35 (dd, J = 15.2, 10.8 Hz, 1H), 5.87 (d, J = 10.8 Hz, 1H), 5.55 (t, J = 7.2 Hz, 1H), 5.40 (dd, J = 15.6, 7.2 Hz, 1H), 5.18 (t, J = 6.8 Hz, 1H), 5.04-4.96 (m, 1H), 4.70 (d, J = 5.2 Hz, 1H), 4.66 (d, J = 6.8 Hz, 1H), 4.58 (d, J = 6.8 Hz, 1H), 4.47 (bs, 1H), 4.21 (t, J = 6.4 Hz, 1H), 3.48 (dd, J = 11.6, 8.4 Hz, 1H), 3.41 (t, J = 6.4 Hz, 1H), 3.15 (s, 3H), 3.13 (s, 3H), 3.01 (d, J = 11.6 Hz, 1H), 2.84 (bs, 1H), 2.33 (dq, J = 13.2, 6.4 Hz, 1H), 2.09-1.95 (m, 2H), 1.59 (s, 3H), 1.58 (s, 3H), 1.50-1.20 (m, 4H), 1.07 (d, J = 7.2 Hz, 3H), 1.05 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 7.2 Hz, 3H), 0.87 (s, 9H), 0.04 (s, 3H), −0.10 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 202.9, 178.0, 141.5, 137.4, 133.5, 129.9, 128.8, 127.6 (2 × C), 127.1 (3 × C), 126.9, 126.1, 94.5, 87.0, 80.7, 77.8, 74.8, 71.8, 55.8, 55.2, 40.7, 33.3, 30.7, 29.6, 27.4, 25.7 (3 × C), 25.7, 19.0, 18.2, 17.4, 13.5, 11.0, 10.6, −4.8, −5.0; HRMS: m/z calc'd for C₃₅H₅₀NO₆S₅Si+Na 756.3764; found 756.3761.

Preparation of (2S,3S,4E,9S,10E,12E,14R,15R)-15-((tert-butyldimethylsilyloxy)-1-((S)-4-isopropyl-2-thioxothiazolidin-3-yl)-9-methoxy-14-(methoxymethoxy)-2,4,10-trimethyl-15-phenyl-3-((triethylsilyloxy)pentadeca-4,10,12-trien-1-one (19): To a solution of 18 (0.05 g, 0.07 mmol) and pyridine (0.02 mL, 0.21 mmol) in CH₂Cl₂ (1 mL) was added TESOtf (0.02 mL, 0.1 mmol) at −50°C. The mixture was allowed to warm up to room temperature and was stirred at room temperature for 2 h. After the reaction was complete (TLC), it was washed with saturated aqueous NaHCO₃ solution (5 mL) and was extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine (5 mL), dried over Na₂SO₄, and the solvent was evaporated off to give crude residue which was purified by Silica gel column chromatography using petroleum ether:EtOAc (6:1) as eluent to afford desired product 19 (0.054 g, 92%) as yellow oil. [α]D²⁴ +52.9 (c 1.05, CHCl₃); IR (Neat): νmax 2933, 2955, 1695, 1460, 1251 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.40-7.20 (m, 5H), 6.35 (dd, J = 15.2, 11.2 Hz, 1H), 5.87 (d, J = 10.8 Hz, 1H), 5.40 (dd, J = 15.2, 7.2 Hz, 1H), 5.33 (t, J = 6.8 Hz, 1H), 5.25-5.20 (m, 1H), 5.15-5.05 (m, 1H), 4.70 (d, J = 4.8 Hz, 1H), 4.66 (d, J = 6.4 Hz, 1H), 4.58 (d, J = 6.8 Hz, 1H), 4.30 (d, J = 9.2 Hz, 1H), 4.25-4.18 (m, 1H), 3.46-3.35 (m, 2H), 3.15 (s, 3H), 3.13 (s, 3H), 2.90 (d, J = 11.6 Hz, 1H), 2.14 (d, J = 12.8, 6.8 Hz, 1H), 2.05-1.92 (m, 1H), 1.90-1.75 (m, 1H), 1.58 (bs, 6H), 1.45-1.20 (m, 4H), 1.21 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 6.8, 3H), 1.0-0.85 (m, 12H), 0.87 (s, 9H), 0.57 (q, J = 7.6, 6H), 0.04 (s, 3H), −0.10 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 202.4, 176.0, 141.6, 137.6, 135.7, 129.9, 128.9, 128.6, 127.6 (2 × C), 127.2 (3 × C), 126.8, 94.5, 87.0, 80.8, 80.2, 77.5, 71.3, 55.9, 55.2, 42.7, 33.5, 30.8, 28.6, 27.5, 25.8 (3 × C), 25.4, 19.0, 18.3, 17.1, 15.3, 11.5, 6.9 (3 × C), 4.8 (3 × C), −4.8, −4.9; HRMS: m/z calc'd for C₄₉H₇₁NO₆S₂Si⁺Na 870.4629; found 870.4628.
4,10,12-trienoic acid (3): To a stirred solution of thione 19 (0.152 g, 0.18 mmol) in THF (2 mL) were added LiOH (0.5 mL of 1.0 M aq. solution, 0.54 mmol) followed by H₂O₂ (1.0 mL of 30% w/v solution in water). The reaction mixture was stirred for 2 h at room temperature and was acidified to pH = 7 carefully with 2N HCl. The reaction mixture was extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine (5 mL), dried over Na₂SO₄ and concentrated. The crude residue thus obtained was purified by Silica gel column chromatography using EtOAc as eluent to afford 3 (0.07 g, 60%) as a colorless oil. [α]D²⁵ −19.4 (c 0.5, CHCl₃); IR (Neat): ν max 3400, 2919, 1710, 1655, 1087 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.40-7.15 (m, 5H), 6.34 (dd, J = 15.2, 11.0 Hz, 1H), 5.87 (d, J = 10.8 Hz, 1H), 5.45-5.30 (m, 2H), 4.70 (d, J = 5.2 Hz, 1H), 4.66 (d, J = 6.8 Hz, 1H), 4.58 (d, J = 6.8 Hz, 1H), 4.21 (t, J = 6.2 Hz, 1H), 4.10 (d, J = 7.8 Hz, 1H), 3.42 (dd, J = 7.2, 4.0 Hz, 1H), 3.15 (s, 3H), 3.14 (s, 3H), 2.70-2.58 (m, 1H), 2.28-1.95 (m, 2H), 1.90-1.80 (m, 1H), 1.61 (s, 3H), 1.60 (s, 3H), 1.45-1.20 (m, 3H), 1.14 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 8.0 Hz, 9H), 0.87 (s, 9H), 0.58 (q, J = 8.0, 6H), 0.04 (s, 3H), −0.10 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 177.8, 141.6, 137.4, 137.3, 135.6, 130.1, 128.8, 127.6 (2 × C), 127.2 (3 × C), 127.1, 94.5, 87.6, 80.9, 80.4, 77.8, 55.7, 55.2, 33.8, 29.7, 26.8, 25.8 (3 × C), 25.7, 18.3, 12.9, 11.0, 10.9, 6.8 (3 × C), 4.7 (3 × C), −4.8, −4.9; HRMS: m/z calc for C₉₉H₉₇O₇Si₂+Na 727.4401; found 727.4401.
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 6

$^{13}$C NMR spectrum (400 MHz, CDCl$_3$) of 6
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 5

$^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 5
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 4

$^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 4
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 7

$^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 7
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 8

$^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 8
"\textsuperscript{1}H NMR spectrum (400 MHz, CDCl\textsubscript{3}) of 9"
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 10

$^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 10
$^{1}$H NMR spectrum (400 MHz, CDCl$_3$) of 12

$^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 12
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 13

$^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 13
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 14

$^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 14
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 16

$^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 16
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 19

$^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 19
$^1$H NMR spectrum (400 MHz, CDCl$_3$) of 3

$^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of 3