Stereoselective Synthesis of Premisakinolide A, the Monomeric Counterpart of the Marine 40-Membered Dimeric Macrolide Misakinolide

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Experimental

General. All reactions were carried out under a dry argon atmosphere. Flash chromatography was performed using 40-100 μm mesh KANTO silica gel 60N or 0.063-0.200 μm mesh Merck silica gel 60 for purification of products.

Materials. Diethyl ether and tetrahydrofuran were distilled from sodium and benzophenone immediately before use. DMF, toluene, benzene, and triethylamine were distilled from CaH_2 . Dehydrated CH_2Cl_2 was purchased from Kanto Chemical Co. Ltd.

Unsaturated aldehyde **6**

To a stirred solution of compound **3**¹ (2.94 g, 11.6 mmol) and 2nd Generation Grubbs' Catalyst (196 mg, 0.23 mmol, 2 mol%) in CH_2Cl_2 (100 mL) was added crotonaldehyde (1.92 mL, 23.1 mmol) at room temperature. After refluxing for 2 h, another portion of crotonaldehyde (0.96 mL, 11.6 mmol) was added and the resulting mixture was refluxed for additional 30 min. The reaction mixture was then concentrated and purified directly by silica gel column chromatography (EtOAc/hexane 20%, 30%, 40%, then 50%) to give the unsaturated aldehyde **6** (2.54 g, 78%) as an oil: IR (neat) 3490 (br), 2972, 2825, 1689, 1134, 1089, 977 cm^{-1} ; ^1H NMR δ (400 MHz,

CDCl₃) 9.53 (1 H, d, J = 8.0 Hz), 6.86 (1 H, dt, J = 15.6, 7.2 Hz), 6.19 (1 H, ddt, J = 15.6, 8.0, 1.2 Hz), 5.91 (1 H, dddt, J = 10.4, 2.8, 2.8, 2.4 Hz), 5.70 (1 H, dddd, J = 10.4, 2.8, 2.4, 2.0 Hz), 4.39 (1 H, br s), 3.98 (1 H, qd, J = 6.4, 2.0 Hz), 3.71-3.64 (1 H, m), 3.60 (1 H, ddd, J = 9.6, 4.0, 2.8 Hz), 3.36 (3 H, s), 3.16 (1 H, s), 2.65 (1 H, dddd, J = 15.6, 8.8, 7.2, 1.6 Hz), 2.52 (1 H, dddd, J = 15.6, 7.2, 4.8, 1.6 Hz), 2.09-2.00 (2 H, m), 1.95 (1 H, ddd, J = 14.4, 10.0, 4.0 Hz), 1.61 (1 H, ddd, J = 14.4, 9.6, 3.2 Hz), 1.54 (1 H, qdd, J = 7.2, 2.8, 2.0 Hz), 1.15 (3 H, d, J = 6.4 Hz), 0.91 (3 H, d, J = 7.2 Hz); ¹³C NMR δ (67.8 MHz, CDCl₃) 193.3, 154.3, 134.4, 127.8, 125.2, 82.4, 71.2, 71.0, 64.7, 56.3, 40.2, 37.1, 35.1, 30.8, 20.9, 5.6; HRMS (FD⁺) [M+H]⁺ found 283.1893, C₁₆H₂₇O₄ requires 283.1909.

Allyl alcohol **6'**

To a solution of unsaturated aldehyde **6** (2.54 g, 9.0 mmol) in dry THF (45 mL) was added DIBAL (0.94 M solution in hexane, 23 mL, 21.6 mmol) at 0 °C. After stirring for 20 min, the reaction mixture was quenched with satd. aq. potassium sodium tartrate solution, and then the mixture was separated. The organic layer was washed with brine and the aqueous layers were extracted with AcOEt (x4). The combined organic layers were dried (MgSO₄) and concentrated *in vacuo*. The crude oil was purified by neutral silica gel column chromatography (EtOAc/hexane 50%, 70%, then 80%) to give allyl alcohol **6'** (2.34 g, 92%) as an oil: IR (neat) 3400 (br), 2972, 2368, 1090, 970 cm⁻¹; ¹H NMR δ (400 MHz, CDCl₃) 5.87-5.81 (1 H, m), 5.77-5.67 (3 H, m), 4.27-4.20 (1 H, m), 4.16-4.08 (2 H, m), 4.02 (1 H, qd, J = 6.4, 2.0 Hz), 3.71-3.60 (2 H, m), 3.36 (3 H, s), 3.38-3.30 (1 H, m), 2.40-2.32 (1 H, m), 2.28-2.21 (1 H, m), 2.02-1.96 (2 H, m), 1.94 (1 H, ddd, J = 14.0, 10.0, 4.0 Hz), 1.80-1.69 (1 H, m), 1.65-1.55 (2 H, m), 1.17 (3 H, d, J = 6.4 Hz), 0.91 (3 H, d, J = 7.2 Hz); ¹³C NMR δ (67.8 MHz, CDCl₃) 131.6, 128.9, 128.5, 124.3, 82.3, 72.4, 71.6, 64.5, 63.3, 56.4, 40.2, 36.9, 35.3, 31.2, 20.8, 5.9; HRMS (FD⁺) [M+H]⁺ found 285.2050, C₁₆H₂₉O₄ requires 285.2066.

Epoxy alcohol **7**

To a suspension of powdered molecular sieves 4A (2.38 g) and CH₂Cl₂ (20 mL) was added titanium(IV) isopropoxide (2.72 mL, 9.87 mmol) and (D)-(-)-diethyl tartrate (1.7 mL, 9.87 mmol) at -25 °C and the mixture was stirred for 10 min. Then a solution of **6'** (2.34 g, 8.23 mmol) in CH₂Cl₂ (20 mL) was added and the mixture was further stirred for 20 min at the same temperature, to which *tert*-butyl hydroperoxide (2.20 M solution in toluene, 9.0 mL, 19.7 mmol) was added and the resulting mixture was stirred at -25 °C for an additional 2 h. The reaction mixture was treated with aqueous tartaric acid (10%) at -25 °C and warmed up to room temperature and stirred for an additional 30 min. The mixture was separated and the aqueous layer was extracted with CH₂Cl₂ (x8). The combined organic layers were concentrated *in vacuo*. The residue was dissolved in ether (80 mL) and treated with 1 N NaOH (30 mL) at 0 °C. After being stirred vigorously for 30 min, the mixture was separated and the organic layer was washed with brine. The aqueous washes were

extracted with CH_2Cl_2 (x5) and the combined organic layers were dried (MgSO_4) and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (EtOAc/hexane 80%, then 100%) to give epoxy alcohol **7** (2.43 g, 98%) as an oil: IR (neat) 3400 (br), 2974, 2929, 2827, 1460, 1184, 1090, 756 cm^{-1} ; ^1H NMR δ (400 MHz, CDCl_3) 5.86 (1 H, dddt, $J = 10.4, 2.8, 2.4, 2.0$ Hz), 5.69 (1 H, dm, $J = 10.4$ Hz), 4.46-4.39 (1 H, m), 4.01 (1 H, qd, $J = 6.4, 2.0$ Hz), 3.88 (1 H, ddd, $J = 12.0, 4.0, 2.8$ Hz), 3.72-3.61 (3 H, m), 3.37 (3 H, s), 3.14 (1 H, s), 3.12 (1 H, ddd, $J = 4.0, 3.2, 2.4$ Hz), 2.96 (1 H, ddd, $J = 4.0, 2.8, 2.8$ Hz), 2.05-1.94 (3 H, m), 1.89-1.82 (1 H, m), 1.64-1.56 (3 H, m), 1.49 (1 H, ddd, $J = 14.4, 8.0, 4.0$ Hz), 1.17 (3 H, d, $J = 6.4$ Hz), 0.92 (3 H, d, $J = 7.2$ Hz); ^{13}C NMR δ (67.8 MHz, CDCl_3) 128.8, 124.4, 77.3, 71.3, 70.2, 64.7, 61.6, 58.7, 56.4, 53.3, 40.5, 36.3, 35.4, 30.9, 20.8, 6.3; HRMS (FD^+) $[\text{M}]^+$ found 300.1957, $\text{C}_{16}\text{H}_{28}\text{O}_5$ requires 300.1937.

Epoxy aldehyde **7'**

To a solution of **7** (506.1 mg, 1.68 mmol) in dry CH_2Cl_2 (10 mL) was added Dess-Martin periodinane (2.57 g, 6.07 mmol). The mixture was stirred at room temperature for 1 h and treated with a 1:1 mixture of satd. NaHCO_3 and satd. $\text{Na}_2\text{S}_2\text{O}_3$. The organic layer was separated and the aqueous layer was extracted with AcOEt. The combined organic layers were dried (MgSO_4) and concentrated *in vacuo* to give epoxy aldehyde **7'** which was used for the next step without purification: ^1H NMR δ (270 MHz, CDCl_3) 9.04 (1H, d, $J = 6.3$ Hz), 5.88 (1H, ddt, $J = 10.2, 5.1, 2.5$ Hz), 5.67 (1H, ddt, $J = 10.1, 2.5, 1.6$ Hz), 4.45 (1H, br d, $J = 9.4$ Hz), 3.82-3.70 (1H, m), 3.64 (1H, ddd, $J = 5.8, 5.8, 5.1$ Hz), 3.50 (1H, ddd, $J = 7.7, 3.8, 2.0$ Hz), 3.34 (3H, s), 3.20 (1H, dd, $J = 6.3, 2.0$ Hz), 2.75 (1H, qd, $J = 7.3, 5.3$ Hz), 2.21-2.08 (1H, m), 2.20 (3H, s), 2.08-1.91 (2H, m), 1.83 (1H, ddd, $J = 14.2, 7.4, 6.8$ Hz), 1.65-1.52 (2H, m), 1.12 (3H, d, $J = 7.1$ Hz); ^{13}C NMR δ (67.8 MHz, CDCl_3) 211.3, 198.1, 128.2, 124.8, 78.8, 69.8, 65.0, 59.2, 57.2, 54.2, 49.5, 36.5, 35.8, 30.2, 29.5, 11.3.

Unsaturated ester **8'**

A solution of $\text{Na}[\text{PhSeB}(\text{OEt})_3]$ (0.4 M solution in EtOH, 10.1 mL, 4.04 mmol), which was prepared from $(\text{PhSe})_2$ (780.3 mg, 2.5 mmol) in EtOH (12.5 mL), NaBH_4 (189.2 mg, 5 mmol) and AcOH (429.3 μL , 7.5 mmol) by stirring for 5 min at 0 $^\circ\text{C}$, was added to a solution of crude **7'** in EtOH (7 mL) at 0 $^\circ\text{C}$. After stirring for 1 h, the reaction mixture was bubbled with O_2 , diluted with AcOEt and washed with brine, then the layers were separated. The aqueous layers were extracted with AcOEt (x3). The combined organic layers were dried (MgSO_4) and concentrated *in vacuo* to give hydroxy aldehyde **8**, which was used for the next step without purification.

To a solution of the crude aldehyde **8** in dry toluene (10 mL) was added $\text{Ph}_3\text{P}=\text{C}(\text{Me})\text{CO}_2\text{Me}$ (1.9 g, 5.46 mmol). After being stirred for 1.5 h at room temperature, the mixture was filtered through a pad of Celite by the aid of AcOEt and the filtrate was concentrated *in vacuo*. The residue was purified by neutral silica gel column chromatography (EtOAc/hexane 25%, 30%, 35%, 40%, 45%) to give unsaturated ester **8'** (427 mg, 69%) as a

colourless oil: $[\alpha]_D^{30} = -64.9^\circ$ (c 1.1, CHCl_3); IR (neat) 3500 (br), 2945, 1717, 1437, 1194, 1088, 752 cm^{-1} ; ^1H NMR δ (270 MHz, CDCl_3) 6.76 (1H, t, $J = 6.8$ Hz), 5.81-5.70 (1H, m), 5.56 (1H, d, $J = 10.1$ Hz), 4.43 (1H, br d, $J = 8.4$ Hz), 4.05-3.91 (1H, m), 3.83-3.71 (1H, m), 3.66 (3H, s), 3.57 (1H, ddd, $J = 6.3, 5.9, 5.6$ Hz), 3.27 (3H, s), 2.70-2.54 (1H, m), 2.69 (1H, ddd, $J = 14.0, 7.1, 4.8$ Hz), 2.44-2.22 (2H, m), 2.13 (3H, s), 2.12-2.03 (1H, m), 1.91-1.65 (3H, m), 1.79 (3H, s), 1.58-1.42 (2H, m), 1.04 (3H, d, $J = 7.1$ Hz); ^{13}C NMR δ (67.8 MHz, CDCl_3) 211.0, 168.3, 138.1, 129.3, 128.5, 123.7, 79.1, 68.6, 67.6, 65.7, 57.2, 51.6, 49.4, 39.9, 36.8, 35.7, 30.0, 29.5, 12.6, 11.2.

Segment A (**9**)

To a solution of alcohol **8'** (469 mg, 1.27 mmol) in dry CH_2Cl_2 (6 mL) was added 2,6-lutidine (0.44 mL, 3.82 mmol) and TBSOTf (0.38 mL, 1.65 mmol) at -78°C . After being stirred for 10 min at -78°C , the reaction was quenched with H_2O . The mixture was separated and the aqueous layer was extracted with ether (x6). The combined organic layers were dried (MgSO_4) and concentrated *in vacuo* to leave an oil which was purified by silica gel column chromatography (EtOAc/hexane 15%) to give segment A (**9**) (541.5 mg, 88%) as an oil: $[\alpha]_D^{30} = -62.6^\circ$ (c 1.4, CHCl_3); IR (neat) 3450 (br), 2936, 1717, 1256, 1088, 837, 777 cm^{-1} ; ^1H NMR δ (270 MHz, CDCl_3) 6.78 (1H, tq, $J = 7.5, 1.3$ Hz), 5.79 (1H, ddt, $J = 10.1, 4.9, 2.5$ Hz), 5.65 (1H, br d, $J = 10.4$ Hz), 4.35 (1H, br d, $J = 10.6$ Hz), 4.09 (1H, dtd, $J = 9.3, 5.6, 2.5$ Hz), 3.76 (1H, ddd, $J = 7.3, 5.8, 4.3$ Hz), 3.72 (3H, s), 3.58 (1H, ddt, $J = 8.4, 8.4, 4.3$ Hz), 3.31 (3H, s), 2.66 (1H, qd, $J = 7.0, 4.1$ Hz), 2.38 (2H, t, $J = 6.4$ Hz), 2.20 (3H, s), 2.08-1.89 (2H, m), 1.83 (3H, d, $J = 1.2$ Hz), 1.75 (1H, ddd, $J = 13.5, 8.2, 6.1$ Hz), 1.69-1.52 (2H, m), 1.41 (1H, ddd, $J = 14.4, 9.7, 2.8$ Hz), 1.11 (3H, d, $J = 7.1$ Hz), 0.90 (9H, s), 0.13 (3H, s), 0.12 (3H, s); ^{13}C NMR δ (67.8 MHz, CDCl_3) 211.0, 168.4, 138.2, 130.2, 129.0, 123.4, 78.5, 69.1, 67.7, 63.9, 57.1, 51.7, 49.5, 40.6, 37.6, 36.6, 30.9, 29.2, 25.8 (3C), 18.0, 12.7, 10.7, -4.4, -4.7.

Diol **13'**

To a solution of the crude silyl ether **13'** (7.31 mmol) in dry THF (15 mL) was added TBAF (0.98 M solution in THF, 9.7 mL, 9.5 mmol) at room temperature. After stirring for 1 h, the reaction mixture was quenched with

H₂O and THF was removed *in vacuo*. The residue was extracted with ether (x4). The combined organic layers were washed with brine, dried (MgSO₄) and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (EtOAc/hexane 15%) to give diol **13'** (2.61 g, 94% for 3 steps) as an oil: $[\alpha]_D^{28} = +14.4^\circ$ (c 1.2, CHCl₃); IR (neat) 3450 (br), 2970, 1726, 1479, 1286, 1165, 974 cm⁻¹; ¹H NMR δ (400 MHz, CDCl₃) 7.39-7.28 (5 H, m), 4.55 (1 H, d, *J* = 11.6 Hz), 4.51 (1 H, d, *J* = 11.6 Hz), 4.34 (1 H, dd, *J* = 10.8, 4.0 Hz), 4.28 (1 H, s), 4.17 (1 H, dd, *J* = 10.8, 6.4 Hz), 3.88 (1 H, d, *J* = 9.0 Hz), 3.63-3.59 (2 H, m), 3.51 (1 H, dd, *J* = 9.2, 9.2 Hz), 3.34 (1 H, ddd, *J* = 9.0, 8.4, 3.6 Hz), 2.12-1.99 (2 H, m), 1.85-1.78 (1 H, m), 1.21 (9 H, s), 1.08 (3 H, d, *J* = 7.2 Hz), 0.90 (3 H, d, *J* = 6.8 Hz), 0.77 (3 H, d, *J* = 7.2 Hz); ¹³C NMR δ (67.8 MHz, CDCl₃) 178.7, 137.4, 128.5 (2C), 127.9, 127.7 (2C), 77.9, 76.5, 73.6, 67.0, 38.9, 36.8, 35.7, 34.2, 27.2 (3C), 24.7, 14.1, 12.9, 10.7; HRMS (FD⁺) [M]⁺ found 380.2533, C₂₂H₃₆O₅ requires 380.2563.

Cyclic silyl ether **13''**

To a solution of diol **13'** (1.68 g, 4.43 mmol) in dry CH₂Cl₂ (22 mL) was added 2,6-lutidine (2.06 mL, 17.7 mmol) and di-*tert*-butylsilyl ditriflate (2.42 mL, 6.64 mmol) at room temperature. After being stirred for 66 h at 30 °C, the reaction was diluted with hexane and quenched with H₂O. The mixture was separated and the aqueous layer was extracted with hexane (x3). The combined organic layers were washed with brine, dried (MgSO₄) and concentrated *in vacuo* to leave an oil which was purified by silica gel column chromatography (EtOAc/hexane 5%) to give cyclic silyl ether **13''** (1.7 g, 74%) as an oil: $[\alpha]_D^{26} = -21.8^\circ$ (c 1.3, CHCl₃); IR (neat) 2970, 2935, 2860, 2360, 1730, 1477, 1285, 1157, 1099, 986 cm⁻¹; ¹H NMR δ (400 MHz, CDCl₃) 7.35-7.27 (5 H, m), 4.53 (1 H, d, *J* = 12.0 Hz), 4.47 (1 H, d, *J* = 12.0 Hz), 4.23 (1 H, dd, *J* = 10.4, 4.0 Hz), 4.09 (1 H, d, *J* = 10.4, 6.8 Hz), 3.97 (1 H, dd, *J* = 9.6, 3.2 Hz), 3.69 (1 H, dd, *J* = 7.6, 2.8 Hz), 3.67 (1 H, dd, *J* = 8.8, 3.2 Hz), 3.53 (1 H, dd, *J* = 7.6, 2.4 Hz), 2.01-1.84 (3 H, m), 1.21 (9 H, s), 1.05 (3 H, d, *J* = 7.2 Hz), 1.03 (9 H, s), 1.00 (9 H, s), 0.97 (1 H, d, *J* = 6.8 Hz), 0.93 (1 H, d, *J* = 6.8 Hz); ¹³C NMR δ (100.4 MHz, CDCl₃) 178.4, 138.7, 128.1 (2C), 127.6 (2C), 127.2, 80.8, 73.1, 73.0, 72.4, 66.2, 39.5, 38.9, 37.1, 35.7, 28.3 (3C), 27.8 (3C), 27.3 (3C), 22.1, 21.8, 13.9, 13.8, 13.8; HRMS (FD⁺) [M]⁺ found 520.3563, C₃₀H₅₂O₅Si requires 520.3584.

Alcohol **14**

To a solution of pivalate **13''** (1.95 g, 3.75 mmol) in dry THF (15 mL) was added DIBAL (0.95 M solution in hexane, 8.7 mL, 8.25 mmol) at 0 °C. After stirring for 30 min, the reaction mixture was quenched with satd. aq. potassium sodium tartrate solution, and then the mixture was separated. The organic layer was washed with brine and the aqueous layers were extracted with ether (x4). The combined organic layers were dried (MgSO₄) and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (EtOAc/hexane 5%, 10%) to give alcohol **14** (1.51 g, 92%) as an oil: $[\alpha]_D^{26} = -17.9^\circ$ (c 1.3, CHCl₃); IR (neat) 3450 (br), 2968, 2956, 2860, 1475, 1097, 986, 756 cm⁻¹; ¹H NMR δ (400 MHz, CDCl₃) 7.35-7.27 (5 H, m), 4.54

(1 H, d, $J = 11.6$ Hz), 4.46 (1 H, d, $J = 11.6$ Hz), 4.05 (1 H, dd, $J = 10.0, 3.2$ Hz), 3.75 (1 H, dd, $J = 7.2, 3.6$ Hz), 3.72 (1 H, dd, $J = 7.2, 3.6$ Hz), 3.67 (1 H, ddd, $J = 6.8, 4.0, 3.2$ Hz), 3.65 (1 H, ddd, $J = 7.2, 6.8, 4.0$ Hz), 3.56 (1 H, dd, $J = 8.4, 6.0$ Hz), 3.16 (1 H, dd, $J = 7.2, 4.0$ Hz), 1.94-1.78 (3 H, m), 1.06 (9 H, s), 1.04 (3 H, d, $J = 7.2$ Hz), 1.02 (9 H, s), 0.94 (3 H, d, $J = 6.8$ Hz), 0.89 (3 H, d, $J = 6.8$ Hz); ^{13}C NMR δ (100.4 MHz, CDCl_3) 138.6, 128.1 (2C), 127.5 (2C), 127.3, 85.4, 73.1, 72.9, 72.3, 67.6, 41.5, 37.3, 37.0, 28.4 (3C), 27.7 (3C), 21.9, 21.8, 13.8, 13.8, 13.8; HRMS (FD+) $[\text{M}+\text{H}]^+$ found 437.3067, $\text{C}_{25}\text{H}_{45}\text{O}_4\text{Si}$ requires 437.3087.

Aldehyde **14'**

To a solution of oxalyl chloride (0.36 mL, 4.07 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise DMSO (0.58 mL, 8.15 mmol) at -78°C and the mixture was stirred for 10 min. After a solution of alcohol **14** in CH_2Cl_2 (5 mL) was added to the mixture, stirring was continued at -78°C for 20 min, then triethylamine (1.7 mL, 12.2 mmol) was added, and the mixture was further stirred at room temperature for 30 min. The reaction mixture was treated with H_2O and separated. The aqueous layers were extracted with hexane (x4). The combined organic layers were dried (MgSO_4) and concentrated *in vacuo* to give the aldehyde **14'** which was used for the next step without purification: ^1H NMR δ (270 MHz, CDCl_3) 9.75 (1H, d, $J = 3.5$ Hz), 7.36-7.22 (5H, m), 4.54 (1H, d, $J = 11.9$ Hz), 4.46 (1H, d, $J = 11.8$ Hz), 4.05 (1H, dd, $J = 7.8, 5.0$ Hz), 4.03-4.00 (1H, m), 3.65 (1H, dd, $J = 8.5, 3.1$ Hz), 3.55 (1H, dd, $J = 8.5, 6.0$ Hz), 2.63-2.48 (1H, m), 1.96-1.81 (2H, m), 1.10 (3H, d, $J = 7.4$ Hz), 1.07 (3H, d, $J = 6.9$ Hz), 1.03 (9H, s), 0.98 (9H, s), 0.92 (3H, d, $J = 6.9$ Hz).

Dibromo olefin **14''**

To a mixture of triphenylphosphine (2.68 g, 10.2 mmol) and tetrabromomethane (1.35 g, 4.08 mmol) in dry CH_2Cl_2 (5 mL) was added pyridine (0.99 mL, 12.2 mmol) at 0°C and the reaction mixture was stirred for 5 min. After addition of a solution of the crude aldehyde **14'** in CH_2Cl_2 (5 mL) at 0°C , the mixture was stirred for 30 min, then quenched with satd. NaHCO_3 solution, and separated. The aqueous layers were extracted with CH_2Cl_2 (x3). The combined organic layers were dried (MgSO_4) and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (EtOAc /hexane 1%) to give **14''** (1.15 g, 96% from **14**) as a white solid: $[\alpha]_{\text{D}}^{25} = -3.8^\circ$ (c 1.2, CHCl_3); mp $47\text{--}52^\circ\text{C}$; IR (neat) 2968, 2933, 2860, 1475, 1007 cm^{-1} ; ^1H NMR δ (400 MHz, CDCl_3) 7.36-7.23 (5 H, m), 6.55 (1 H, d, $J = 9.6$ Hz), 4.53 (1 H, d, $J = 12.0$ Hz), 4.48 (1 H, d, $J = 12.0$ Hz), 3.89 (1 H, dd, $J = 9.6, 4.0$ Hz), 3.73 (1 H, dd, $J = 4.0, 4.0$ Hz), 3.71 (1 H, dd, $J = 8.8, 3.2$ Hz), 3.49 (1 H, dd, $J = 8.8, 2.8$ Hz), 2.54 (1 H, dqd, $J = 9.6, 6.8, 4.0$ Hz), 1.90 (1 H, qddd, $J = 6.8, 4.0, 3.2, 2.8$ Hz), 1.86 (1 H, dqd, $J = 9.6, 7.2, 4.0$ Hz), 1.08 (3 H, d, $J = 6.8$ Hz), 1.03 (9 H, s), 1.02 (3 H, d, $J = 7.2$ Hz), 1.01 (9 H, s), 0.95 (3 H, d, $J = 6.8$ Hz); ^{13}C NMR δ (67.8 MHz, CDCl_3) 140.6, 138.7, 128.1 (2C), 127.5 (2C), 127.2, 88.0, 81.6, 73.6, 73.0, 72.5, 45.2, 37.3, 36.8, 28.3 (3C), 27.7 (3C), 22.2, 21.9, 16.1, 14.1, 13.5; HRMS (FD+) $[\text{M}]^+$ found 588.1245, $\text{C}_{26}\text{H}_{42}\text{Br}_2\text{O}_3\text{Si}$ requires 588.1270.

Acetylene **5**

To a solution of **14''** (939 mg, 1.59 mmol) in dry THF (8 mL) was added *n*BuLi (1.29 *M* solution in hexane, 2.7 mL, 3.5 mmol) at -30 °C. After stirring for 30 min, the reaction mixture was quenched with satd. NH₄Cl and H₂O, and then the mixture was separated. The aqueous layers were extracted with ether (x4). The combined organic layers were dried (MgSO₄) and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (EtOAc/hexane 0.5%) to give acetylene **5** (617.7 mg, 90%) as an oil: $[\alpha]_D^{28} = -26.8^\circ$ (c 1.4, CHCl₃); IR (neat) 3311, 2970, 2858, 1477, 982 cm⁻¹; ¹H NMR δ (400 MHz, CDCl₃) 7.34-7.25 (5 H, m), 4.53 (1 H, d, *J* = 12.0 Hz), 4.48 (1 H, d, *J* = 12.0 Hz), 4.05 (1 H, dd, *J* = 9.6, 3.6 Hz), 3.76 (1 H, dd, *J* = 4.0, 3.6 Hz), 3.74 (1 H, dd, *J* = 8.8, 3.2 Hz), 3.47 (1 H, dd, *J* = 8.8, 2.8 Hz), 2.62 (1 H, qdd, *J* = 6.8, 3.6, 2.4 Hz), 2.11 (1 H, qddd, *J* = 7.2, 3.6, 3.2, 2.8 Hz), 1.99 (1 H, d, *J* = 2.4 Hz), 1.91 (1 H, dqd, *J* = 9.6, 6.8, 4.0 Hz), 1.24 (3 H, d, *J* = 6.8 Hz), 1.05 (3 H, d, *J* = 7.2 Hz), 1.04 (18 H, s), 0.96 (3 H, d, *J* = 6.8 Hz); ¹³C NMR δ (67.8 MHz, CDCl₃) 138.8, 128.2 (2C), 127.6 (2C), 127.3, 86.0, 80.1, 73.9, 73.0, 72.6, 69.4, 37.0, 36.8, 33.6, 28.2 (3C), 27.7 (3C), 22.2, 21.9, 16.6, 13.9, 13.9; HRMS (FD⁺) [M]⁺ found 430.2884, C₂₆H₄₂O₃Si requires 430.2903.

Ester **11**

To a solution of LDA prepared from *i*Pr₂NH (21 mL, 150 mmol) and *n*BuLi (2.64 *M* solution in hexane, 45.5 mL, 120 mmol) in THF (150 mL) by stirring for 15 min at 0 °C was added *tert*-butyl acetate (16.2 mL, 120 mmol) at -78 °C and the reaction mixture was stirred for 20 min. After dropwise addition of a solution of methyl (S)-3-hydroxybutanoate (**10**) in THF (15 mL) at -78 °C, the mixture was stirred for 2 h at -50 °C, and then stirred for 15 min at -15 °C. The reaction mixture was quenched with ice cold H₂O, and separated. The aqueous layers were extracted with ether (x3). The combined organic layers were washed with satd. NaHCO₃ solution and brine, then dried (MgSO₄) and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (EtOAc/hexane 20%, 25%) to give ester **11** (5.64 g, 93%) as an oil: $[\alpha]_D^{28} = +38.7^\circ$ (c 1.1, CHCl₃); IR (neat) 3450 (br), 2978, 1711, 1150 cm⁻¹; ¹H NMR δ (400 MHz, CDCl₃) 4.26 (1 H, dqdd, *J* = 8.8, 6.4, 3.2, 3.2 Hz), 3.37 (2 H, s), 2.86 (1 H, d, *J* = 3.2 Hz), 2.74 (1 H, dd, *J* = 17.6, 3.2 Hz), 2.64 (1 H, dd, *J* = 17.6, 8.8 Hz), 1.47 (9 H, s), 1.21 (3 H, d, *J* = 6.4 Hz); ¹³C NMR δ (67.8 MHz, CDCl₃) 204.0, 166.1, 82.1, 63.6, 51.0, 50.9, 27.8 (3C), 22.3; HRMS (FD⁺) [M+H]⁺ found 203.1283, C₁₀H₁₉O₄ requires 203.1283.

Dihydroxy ester **12**

To a solution of Me₄NBH(OAc)₃ (30.4 g, 115.5 mmol) in dry MeCN (91 mL) was added AcOH (91 mL) at

room temperature and the reaction mixture was stirred for 30 min. After addition of a solution of β -ketoester **11** (3.68 g, 18.2 mmol) in MeCN (27 mL) at -40 °C, the mixture was stirred for 94 h, then quenched with satd. aq. potassium sodium tartrate solution, and separated. The aqueous layers were extracted with CH₂Cl₂ (x4) and the combined organic layers were washed with satd. NaHCO₃ solution and brine, dried (MgSO₄), and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (EtOAc/hexane 25%, 30%, 35%, 40%, 45%) to give the dihydroxy ester **12** (3.69 g, 97%) as an oil: $[\alpha]_D^{19} = -4.7^\circ$ (c 1.4, CHCl₃); IR (neat) 3395 (br), 2976, 2934, 1728, 1369, 1155 cm⁻¹; ¹H NMR δ (400 MHz, CDCl₃) 4.31 (1H, dddd, $J = 8.8, 8.3, 3.7, 3.7$, 2.7 Hz), 4.18-4.08 (1H, m), 3.57 (1H, d, $J = 2.7$ Hz), 2.63-2.57 (1H, m), 2.46 (1H, dd, $J = 16.5, 8.8$ Hz), 2.39 (1H, dd, $J = 16.5, 3.7$ Hz), 1.68-1.53 (2H, m), 1.47 (9H, s), 1.24 (3H, d, $J = 6.3$ Hz); ¹³C NMR δ (67.8 MHz, CDCl₃) 172.1, 81.1, 65.5, 64.5, 43.7, 42.4, 27.9 (3C), 23.4; HRMS (EI⁺) [M-O'Bu]⁺ found 131.0718, C₆H₁₁O₃ requires 131.0708.

Lactone **12'**

A mixture of the dihydroxy ester **12** (2.01 g, 9.86 mmol) and PPTS (247.8 mg, 0.986 mmol) in dry ClCH₂CH₂Cl (50 mL) was refluxed for 4 h and then concentrated. The residue was filtered through a pad of silica gel by the aid of AcOEt and the filtrate was concentrated *in vacuo* to give lactone **12'** which was used for the next step without purification: $[\alpha]_D^{19} = -26.2^\circ$ (c 1.4, CHCl₃); IR (neat) 3410 (br), 2982, 2936, 1728, 1389, 1254, 1078 cm⁻¹; ¹H NMR δ (400 MHz, CDCl₃) 4.35 (1H, dqd, $J = 11.5, 6.3, 2.9$ Hz), 4.30-4.21 (1H, m), 2.91 (1H, dddd, $J = 17.1, 5.9, 1.5, 0.7$ Hz), 2.46 (1H, dd, $J = 17.1, 8.1$ Hz), 2.27 (1H, dddd, $J = 13.7, 5.4, 2.9, 1.5$ Hz), 2.14-2.05 (1H, m), 1.59 (1H, ddd, $J = 13.7, 11.5, 9.3$ Hz), 1.42 (3H, d, $J = 6.3$ Hz); ¹³C NMR δ (67.8 MHz, CDCl₃) 171.8, 73.9, 63.2, 39.1, 39.0, 21.2; HRMS (EI⁺) [M]⁺ found 130.0644, C₆H₁₀O₃ requires 131.0630.

Methyl ether **12''**

To a mixture of powdered molecular sieves 4A (22.8 g) and Ag₂O (15.1 g, 65.2 mmol) in ether was added MeI (18.4 mL, 295.8 mmol) at room temperature and the reaction mixture was stirred for 10 min. After addition of a solution of the crude lactone **12'** in dry CH₂Cl₂, the mixture was stirred for 1.5 h with ultra sound, then filtered through a pad of Celite by the aid of CH₂Cl₂ and the filtrate was concentrated *in vacuo*. The residue was purified by neutral silica gel column chromatography (EtOAc/hexane 50%) to give methyl ether **12''** (1.22 g, 86%) as an oil: $[\alpha]_D^{19} = -19.7^\circ$ (c 1.4, CHCl₃); IR (neat) 2982, 2936, 1740, 1389, 1256, 1065, 980 cm⁻¹; ¹H NMR δ (400 MHz, CDCl₃) 4.33 (1H, dqd, $J = 11.7, 6.2, 2.8$ Hz), 3.75 (1H, ddt, $J = 8.9, 7.3, 5.9$ Hz), 3.36 (3H, s), 2.86 (1H, ddd, $J = 17.1, 5.9, 1.2$ Hz), 2.50 (1H, dd, $J = 17.1, 7.3$ Hz), 2.31 (1H, dddd, $J = 13.9, 5.9, 2.8, 1.2$ Hz), 1.52 (1H, ddd, $J = 13.9, 11.7, 8.9$ Hz), 1.42 (3H, d, $J = 6.2$ Hz); ¹³C NMR δ (67.8 MHz, CDCl₃) 170.3, 73.1, 72.0, 55.6, 36.2, 35.7, 21.1; HRMS (FD⁺) [M]⁺ found 144.0770, C₇H₁₂O₃ requires 144.0786.

Acetate **4**

To a solution of lactone **12''** (2.98 g, 20.7 mmol) in dry CH_2Cl_2 (140 mL) was added DIBAL (1.01 M solution in toluene, 24.6 mL, 24.8 mmol) at -78°C and the reaction mixture was stirred for 1 h. After addition of pyridine (5 mL, 62.1 mmol), DMAP (3 g, 24.8 mmol) and acetic anhydride (7.8 mL, 82.8 mmol) at -78°C , the mixture was stirred for 1 h at room temperature, and then quenched with satd. aq. potassium sodium tartrate solution, and the mixture was separated. The organic layer was washed with brine and the aqueous layers were extracted with ether (x4). The combined organic layers were dried (MgSO_4) and concentrated in vacuo. The crude product was purified by silica gel column chromatography (EtOAc/hexane 20%) to give acetate **4** (3.11 g, 80%) as an oil: $[\alpha]_{\text{D}}^{30} = +5.8^\circ$ (c 1.1, CHCl_3); IR (neat) 2976, 2937, 1753, 1375, 1231, 1148, 1047 cm^{-1} ; ^1H NMR δ (400 MHz, CDCl_3) 5.64 (1 H, dd, $J = 10.4, 2.0\text{ Hz}$), 3.61 (1 H, dqd, $J = 11.6, 6.0, 2.0\text{ Hz}$), 3.44 (1 H, dddd, $J = 11.2, 11.2, 4.8, 4.4\text{ Hz}$), 3.36 (3 H, s), 2.25 (1 H, dddd, $J = 12.0, 4.4, 2.4, 2.0\text{ Hz}$), 2.12 (3 H, s), 2.01 (1 H, dddd, $J = 12.8, 4.8, 2.4, 2.0\text{ Hz}$), 1.40 (1 H, ddd, $J = 12.0, 11.2, 10.4\text{ Hz}$), 1.29 (3 H, d, $J = 6.0\text{ Hz}$), 1.18 (1 H, ddd, $J = 12.8, 11.6, 11.2\text{ Hz}$); ^{13}C NMR δ (67.8 MHz, CDCl_3) 169.0, 92.5, 74.7, 69.1, 55.4, 38.2, 35.9, 21.1, 21.0; HRMS (FD^+) $[\text{M}]^+$ found 188.1028, $\text{C}_9\text{H}_{16}\text{O}_4$ requires 188.1049.

Coupling compound **15**

To a solution of **4** (1.29 g, 3.0 mmol) in dry CH_2Cl_2 (7 mL) was added $n\text{BuLi}$ (1 M solution in hexane, 3 mL, 3 mmol) at -30°C and the mixture was stirred for 30 min. After addition of Me_2AlOTf (1 M solution in CH_2Cl_2 , 9.6 mL, 9.6 mmol), which was prepared from Me_3Al (2 M solution in hexane, 7.5 mL, 15 mmol) in dry CH_2Cl_2 (7.5 mL) and TfOH (1.33 mL, 15 mmol) by stirring for 20 min at 0°C , at -30°C , the mixture was stirred for 30 min. To the resulting alkynyl aluminum solution was added a solution of **5** (702 mg, 3.73 mmol) in CH_2Cl_2 (8 mL) at -30°C and the mixture was stirred for 30 min at -30°C , then stirred for 30 min at room temperature. The reaction was quenched with satd. aq. potassium sodium tartrate solution and NaHCO_3 , and the mixture was separated. The organic layer was washed with brine and the aqueous layers were extracted with hexane (x4).

The combined organic layers were dried (MgSO_4) and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (EtOAc/hexane 2%, 5%) to give the coupling compound **15** (1.33 g, 80%) as an oil: $[\alpha]_{\text{D}}^{28} = -35.6^\circ$ (c 1.0, CHCl_3); IR (neat) 2970, 2934, 2860, 1097, 756 cm^{-1} ; ^1H NMR δ (400 MHz, CDCl_3) 7.35-7.25 (5 H, m), 4.84-4.80 (1 H, m), 4.52 (1 H, d, $J = 12.0$ Hz), 4.46 (1 H, d, $J = 12.0$ Hz), 4.03 (1 H, dd, $J = 9.6, 3.2$ Hz), 3.99 (1 H, dqd, $J = 11.6, 6.0, 2.0$ Hz), 3.74 (1 H, dd, $J = 4.4, 4.0$ Hz), 3.70 (1 H, dd, $J = 8.4, 3.2$ Hz), 3.65 (1 H, dddd, $J = 11.2, 10.8, 4.4, 4.4$ Hz), 3.50 (1 H, dd, $J = 8.4, 6.4$ Hz), 3.31 (3 H, s), 2.67 (1 H, qdd, $J = 6.8, 3.2, 2.0$ Hz), 2.08 (1 H, qddd, $J = 7.2, 6.4, 4.0, 3.2$ Hz), 2.04 (1 H, dddd, $J = 12.4, 4.4, 2.4, 2.0$ Hz), 1.98 (1 H, dddd, $J = 12.4, 4.4, 2.4, 2.0$ Hz), 1.90 (1 H, dqd, $J = 9.6, 6.8, 4.4$ Hz), 1.53 (1 H, ddd, $J = 12.4, 11.2, 5.6$ Hz), 1.23 (3 H, d, $J = 6.8$ Hz), 1.18 (3 H, d, $J = 6.0$ Hz), 1.09 (1 H, ddd, $J = 12.4, 11.6, 10.8$ Hz), 1.04 (3 H, d, $J = 7.2$ Hz), 1.04 (18 H, s), 0.96 (3 H, d, $J = 6.8$ Hz); ^{13}C NMR δ (100.4 MHz, CDCl_3) 138.6, 128.1 (2C), 127.6 (2C), 127.3, 88.5, 80.2, 79.3, 73.9, 73.4, 73.1, 72.4, 66.6, 64.6, 55.2, 39.6, 37.0, 36.9, 36.4, 33.7, 28.2 (3C), 27.8 (3C), 22.1, 21.9, 21.8, 16.9, 14.0, 13.9; HRMS (FD+) $[\text{M}]^+$ found 558.3748, $\text{C}_{33}\text{H}_{54}\text{O}_5\text{Si}$ requires 558.3741.

Alcohol **15'**

A mixture of **15** (283.9 mg, 0.51 mmol) and 10% palladium hydroxide on carbon (28 mg) in ethyl acetate (4 mL) was stirred under a hydrogen atmosphere (1 atm) at room temperature for 22 h. The reaction mixture was filtered through a pad of Celite and the solvent was evaporated *in vacuo*. The crude product was purified by silica gel column chromatography (EtOAc/hexane 15%, 20%, 25%) to give the hydrogenated product **15'** (181.4 mg, 76%) as an oil: $[\alpha]_{\text{D}}^{26} = -24.1^\circ$ (c 1.5, CHCl_3); IR (neat) 3450 (br), 2968, 2936, 2860, 2361, 756 cm^{-1} ; ^1H NMR δ (400 MHz, CDCl_3) 4.06 (1 H, dd, $J = 10.0, 2.8$ Hz), 4.02-3.96 (1 H, m), 3.77-3.67 (3 H, m), 3.61 (1 H, dd, $J = 6.4, 3.2$ Hz), 3.58 (1 H, ddd, $J = 11.2, 10.8, 2.8$ Hz), 3.53 (1 H, dddd, $J = 10.4, 10.4, 4.4, 4.4$ Hz), 3.34 (3 H, s), 2.02-1.95 (2 H, m), 1.92-1.81 (3 H, m), 1.68-1.50 (3 H, m), 1.42-1.24 (2 H, m), 1.20 (3 H, d, $J = 6.0$ Hz), 1.18 (1 H, ddd, $J = 12.4, 10.4, 10.0$ Hz), 1.08 (3 H, d, $J = 7.2$ Hz), 1.08 (9 H, s), 1.06 (9 H, s), 0.92 (3 H, d, $J = 6.8$ Hz), 0.75 (3 H, d, $J = 6.8$ Hz); ^{13}C NMR δ (67.8 MHz, CDCl_3) 82.9, 79.8, 73.2, 72.1, 69.3, 64.6, 55.2, 39.5, 38.8, 37.4, 36.1, 34.9, 28.7, 28.2 (3C), 27.9 (3C), 27.7, 22.3, 21.9 (2C), 15.7, 14.2, 13.2; HRMS (FD+) $[\text{M}+\text{H}]^+$ found 473.3637, $\text{C}_{26}\text{H}_{53}\text{O}_5\text{Si}$ requires 473.3662.

Triol **15''**

A solution of $\text{HF} \cdot \text{py}$ was prepared from 1.52 g of pyridinium hydrofluoride, 4.13 mL of pyridine, and 7.24 mL of THF. A mixture of alcohol **15'** (296.8 mg, 0.63 mmol) and 5 mL of the solution of $\text{HF} \cdot \text{py}$ in THF (5 mL) was stirred at room temperature for 30 min, then quenched with satd. NaHCO_3 . The organic layer was separated and the aqueous layer was extracted with AcOEt (x6). The combined organic layers were washed with satd. CuSO_4 solution, H_2O and brine, dried (MgSO_4) and concentrated *in vacuo* to give triol **15''** which was used for

the next step without purification: $[\alpha]_D^{27} = -21.3^\circ$ (c 1.0, CHCl_3); IR (neat) 3400 (br), 2960, 2932, 2874, 2361, 1460, 1381, 1101 cm^{-1} ; ^1H NMR δ (270 MHz, CDCl_3) 4.21 (1H, s), 4.03 (1H, dddd, $J = 4.8, 4.6, 4.5, 4.1$ Hz), 3.90 (1H, d, $J = 9.4$ Hz), 3.74 (1H, dqd, $J = 9.5, 6.4, 3.0$ Hz), 3.70-3.64 (2H, m), 3.55 (1H, tt, $J = 9.6, 4.6$ Hz), 3.44 (1H, br s), 3.37-3.28 (1H, m), 3.34 (3H, s), 3.19 (1H, d, $J = 4.9$ Hz), 2.02-1.92 (1H, m), 1.92-1.74 (3H, m), 1.72 (1H, br s), 1.62 (1H, ddd, $J = 14.0, 8.7, 4.2$ Hz), 1.43-1.18 (5H, m), 1.23 (3H, d, $J = 6.3$ Hz), 1.07 (3H, d, $J = 7.1$ Hz), 0.85 (3H, d, $J = 6.8$ Hz), 0.74 (3H, d, $J = 6.9$ Hz); ^{13}C NMR δ (67.8 MHz, CDCl_3) 80.8, 77.0, 73.1, 71.8, 68.8, 64.8, 55.2, 38.3, 37.1, 35.6, 34.7, 34.5, 28.9, 28.8, 21.6, 16.2, 13.0, 10.9; HRMS (FD+) $[\text{M}+\text{H}]^+$ found 333.2626, $\text{C}_{18}\text{H}_{37}\text{O}_5$ requires 333.2641.

Acetal **16**

To a solution of the crude triol **15''** in dry DMF (6.3 mL) was added p-anisaldehyde dimethyl acetal (0.16 mL, 0.95 mmol) followed by CSA (14.6 mg, 0.063 mmol) at room temperature. After stirring for 2.5 h, the reaction mixture was diluted with a solution of hexane and CH_2Cl_2 (10 : 1) and quenched with H_2O and the mixture was separated. The aqueous layers were extracted with a solution of hexane and CH_2Cl_2 (10 : 1) (x3). The combined organic layers were dried (MgSO_4) and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (EtOAc/hexane 30%, 40%) to give acetal **16** (248 mg, 87% from **15''**) as an oil: $[\alpha]_D^{29} = 2.4^\circ$ (c 7.4, CHCl_3); IR (neat) 3500 (br), 2936, 2243, 1518, 1250, 910, 733 cm^{-1} ; ^1H NMR δ (270 MHz, CDCl_3) 7.36 (2H, d, $J = 8.6$ Hz), 6.88 (2H, d, $J = 8.7$ Hz), 5.48 (1H, s), 4.11 (1H, dd, $J = 11.2, 4.6$ Hz), 4.04-3.94 (1H, m), 3.86 (1H, dd, $J = 10.1, 1.7$ Hz), 3.80 (3H, s), 3.75-3.65 (1H, m), 3.59-3.44 (2H, m), 3.37-3.23 (1H, m), 3.33 (3H, s), 2.44 (1H, d, $J = 7.4$ Hz), 2.19-2.07 (1H, m), 2.04-1.91 (2H, m), 1.89-1.78 (2H, m), 1.73-1.51 (4H, m), 1.38-0.98 (2H, m), 1.20 (3H, d, $J = 6.3$ Hz), 1.11 (3H, d, $J = 7.1$ Hz), 0.92 (3H, d, $J = 6.8$ Hz), 0.76 (3H, d, $J = 6.6$ Hz); ^{13}C NMR δ (67.8 MHz, CDCl_3) 159.7, 130.8, 127.1 (2C), 113.4 (2C), 100.8, 82.8, 78.6, 73.1, 73.0, 71.8, 64.4, 55.0 (2C), 38.4, 35.6, 34.6, 34.4, 30.1, 29.0, 27.4, 21.6, 16.4, 11.7, 11.1; HRMS (FD+) $[\text{M}]^+$ found 450.2968, $\text{C}_{26}\text{H}_{42}\text{O}_6$ requires 450.2981.

MOM ether **16'**

To a solution of alcohol **16** (248 mg, 0.55 mmol) in dry $\text{ClCH}_2\text{CH}_2\text{Cl}$ (3 mL) was added $i\text{Pr}_2\text{NEt}$ (575.2 μL , 3.30 mmol) and MOMCl (250.8 μL , 3.30 mmol). After being stirred for 3 h at 50 $^\circ\text{C}$, the reaction was quenched with satd. NaHCO_3 solution. The mixture was separated and the aqueous layer was extracted with ether (x6). The combined organic layers were dried (MgSO_4) and concentrated *in vacuo* to give MOM ether **16'** which was used for the next step without purification: $[\alpha]_D^{30} = -0.64^\circ$ (c 1.1, CHCl_3); IR (neat) 2937, 2361, 1520, 1250, 1040, 912, 733 cm^{-1} ; ^1H NMR δ (270 MHz, CDCl_3) 7.39 (2H, dt, $J = 9.2, 2.4$ Hz), 6.88 (2H, dt, $J = 9.2, 2.3$ Hz), 5.42 (1H, s), 4.66 (2H, s), 4.12 (1H, dd, $J = 11.0, 4.6$ Hz), 4.07-3.95 (1H, m), 3.80 (3H, s), 3.75 (1H, dd, $J = 10.1, 1.5$ Hz), 3.74-3.63 (1H, m), 3.62-3.39 (3H, m), 3.40 (3H, s), 3.34 (3H, s), 2.17-1.77 (4H, m), 1.77-1.53

(3H, m), 1.53-1.38 (1H, m), 1.34-1.12 (3H, m), 1.21 (3H, d, $J = 6.3$ Hz), 1.01 (3H, d, $J = 6.9$ Hz), 0.91 (3H, d, $J = 7.1$ Hz), 0.75 (3H, d, $J = 6.6$ Hz); ^{13}C NMR δ (67.8 MHz, CDCl_3) 159.7, 131.5, 127.2 (2C), 113.4 (2C), 100.8, 99.1, 85.7, 81.6, 73.3, 73.2, 71.4, 64.5, 55.9, 55.1 (2C), 38.5, 36.2, 34.8, 33.8, 30.3, 29.5, 25.3, 21.7, 17.5, 11.9, 10.0; HRMS (FD+) $[\text{M}]^+$ found 494.3262, $\text{C}_{28}\text{H}_{46}\text{O}_7$ requires 494.3244.

Alcohol **16''**

To a solution of the crude acetal **16'** in dry CH_2Cl_2 (3 mL) was added DIBAL (1.01 M solution in toluene, 1.63 mL, 1.65 mmol) at 0 °C. After stirring for 30 min, the reaction mixture was quenched with satd. aq. potassium sodium tartrate solution, and then the mixture was separated. The aqueous layers were extracted with AcOEt (x4). The combined organic layers were dried (MgSO_4) and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (EtOAc/hexane 30%, 40%, 50%) to give alcohol **16''** (239.6 mg, 88% from **16**) as an oil: $[\alpha]_{\text{D}}^{30} = -1.26^\circ$ (c 1.2, CHCl_3); IR (neat) 3490 (br), 2937, 2361, 1514, 1248, 1038, 733 cm^{-1} ; ^1H NMR δ (270 MHz, CDCl_3) 7.28 (2H, d, $J = 5.6$ Hz), 6.87 (2H, d, $J = 8.7$ Hz), 4.67 (2H, s), 4.66 (1H, d, $J = 10.9$ Hz), 4.58 (1H, d, $J = 10.9$ Hz), 4.05-3.94 (1H, m), 3.80 (3H, s), 3.78-3.59 (4H, m), 3.53 (1H, tt, $J = 10.1, 4.3$ Hz), 3.41 (3H, s), 3.34 (3H, s), 3.30 (1H, dd, $J = 8.6, 2.6$ Hz), 3.01-2.92 (1H, m), 2.03-1.69 (6H, m), 1.60 (1H, ddd, $J = 13.0, 10.1, 5.6$ Hz), 1.53-1.39 (1H, m), 1.35-1.14 (3H, m), 1.22 (3H, d, $J = 6.3$ Hz), 0.97 (3H, d, $J = 6.8$ Hz), 0.95 (3H, d, $J = 7.1$ Hz), 0.92 (3H, d, $J = 7.1$ Hz); ^{13}C NMR δ (67.8 MHz, CDCl_3) 158.9, 131.0, 128.9 (2C), 113.6 (2C), 98.6, 87.7, 82.8, 82.8, 73.7, 73.1, 71.4, 64.5, 55.7, 55.1, 55.0, 39.0, 38.5, 38.4, 34.7, 34.6, 29.5, 26.2, 21.6, 17.1, 14.6, 11.1.

Segment B (**17**)

To a solution of **16''** (90.8 mg, 0.183 mmol) in dry CH_2Cl_2 (1 mL) was added Dess-Martin periodinane (116.3 g, 0.274 mmol). The mixture was stirred at room temperature for 30 min and treated with a 1:1 mixture of satd. NaHCO_3 and satd. $\text{Na}_2\text{S}_2\text{O}_3$. The organic layer was separated and the aqueous layer was extracted with ether (x4). The combined organic layers were dried (MgSO_4) and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (EtOAc/hexane 10%, 15%) to give segment B (**17**) (83.8 mg, 93%) as an oil: ^1H -NMR δ (270 MHz, CDCl_3) 9.84 (1H, d, $J = 2.6$ Hz), 7.22 (2H, dt, $J = 9.2, 2.4$ Hz), 6.86 (2H, dt, $J = 9.3, 2.5$ Hz), 4.69 (1H, d, $J = 6.6$ Hz), 4.66 (1H, d, $J = 6.8$ Hz), 4.56 (1H, d, $J = 10.9$ Hz), 4.47 (1H, d, $J = 10.9$ Hz), 4.04 (1H, dd, $J = 7.9, 1.6$ Hz), 4.03-3.94 (1H, m), 3.80 (3H, s), 3.70 (1H, tt, $J = 6.9, 2.8$ Hz), 3.53 (1H, tt, $J = 10.1, 4.5$ Hz), 3.41 (3H, s), 3.35 (1H, dd, $J = 8.6, 2.6$ Hz), 3.34 (3H, s), 2.72 (1H, dqd, $J = 7.1, 7.1, 2.6$ Hz), 1.98 (1H, br d, $J = 12.7$ Hz), 1.89-1.68 (3H, m), 1.66-1.53 (2H, m), 1.50-1.40 (1H, m), 1.32-1.14 (3H, m), 1.21 (3H, d, $J = 6.3$ Hz), 1.07 (3H, d, $J = 7.1$ Hz), 0.97 (3H, d, $J = 6.9$ Hz), 0.96 (3H, d, $J = 6.9$ Hz); ^{13}C NMR δ (67.8 MHz, CDCl_3) 204.8, 159.0, 130.8, 128.8 (2C), 113.6 (2C), 98.8, 87.2, 79.8, 73.2 (2C), 71.4, 64.7, 55.8, 55.2, 55.2, 50.2, 38.7, 38.4, 34.8, 34.6, 29.6, 26.2, 21.7, 17.2, 11.7, 10.8.

Aldol compound **19**

To a solution of segment A (**9**) (88.1 mg, 0.183 mmol) in THF (0.76 mL) was added a mixture of TMSCl and Et₃N (1:1 molar ratio, 0.49 mL, 1.83 mmol) followed by LHMDS (a 0.62 M solution in THF, 0.6 mL, 0.37 mmol) at -78 °C. After stirring for 20 min at -78 °C, another portion of LHMDS (1.02 mL, 0.62 mmol) and a mixture of TMSCl and Et₃N (0.24 mL, 0.913 mmol) were added and the resulting mixture was stirred for additional hour at the same temperature. The reaction mixture was treated with a pH 7 buffer solution, diluted with ether, and warmed up to room temperature. The organic layer was separated and the aqueous layer was extracted with ether (x4). The combined organic layers were dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by neutral silica gel column chromatography (EtOAc/hexane 5%) to give silyl enol ether **18** containing a small amount of impurities.

A stirred solution of the above silyl enol ether **18** and segment B (**17**) (79.8 mg, 0.161 mmol) in dry CH₂Cl₂ (2 mL) was cooled to -78 °C to which BF₃·OEt₂ (13.9 μL, 0.11 mmol) was added dropwise. After 10 min, another portion of BF₃·OEt₂ (13.9 μL, 0.11 mmol) was added and the mixture was stirred -78 °C for an additional hour. The reaction mixture was treated with satd. NaHCO₃, diluted with ether, and the aqueous layer was extracted with ether. The combined organic layers were dried (MgSO₄) and concentrated *in vacuo*. The oily residue was purified by neutral silica gel column chromatography (EtOAc/hexane 30%, 35%, then 40%) to give **19** (129.9 mg, 82%) as a colourless oil: [α]_D³⁰ = -28.7° (c 0.74, CHCl₃); IR (neat) 3500 (br), 2936, 1711, 1514, 1250, 1088, 1038, 910, 733 cm⁻¹; ¹H NMR δ (270 MHz, CDCl₃) 7.27 (2H, d, *J* = 7.1 Hz), 6.87-6.75 (1H, m),

6.84 (2H, d, $J = 8.6$ Hz), 5.77 (1H, d, $J = 10.2$ Hz), 5.64 (1H, d, $J = 10.2$ Hz), 4.74-4.61 (4H, m), 4.50 (1H, d, $J = 7.3$ Hz), 4.34 (1H, d, $J = 9.1$ Hz), 4.16-4.04 (1H, m), 4.04-3.94 (1H, m), 3.85 (1H, d, $J = 7.4$ Hz), 3.78 (3H, s), 3.75-3.64 (1H, m), 3.70 (3H, s), 3.63-3.47 (2H, m), 3.41 (3H, s), 3.37-3.21 (2H, m), 3.33 (3H, s), 3.28 (3H, s), 2.85-2.62 (2H, m), 2.53 (1H, d, $J = 17.5$ Hz), 2.37 (2H, t, $J = 6.0$ Hz), 2.02-1.88 (4H, m), 1.88-1.69 (4H, m), 1.83 (3H, s), 1.68-1.34 (7H, m), 1.32-1.14 (3H, m), 1.21 (3H, d, $J = 6.1$ Hz), 1.13-1.04 (1H, m), 1.09 (3H, d, $J = 6.9$ Hz), 0.96 (3H, d, $J = 6.8$ Hz), 0.93 (3H, d, $J = 6.1$ Hz), 0.89 (9H, s), 0.89 (3H, d, $J = 6.4$ Hz), 0.12 (3H, s), 0.11 (3H, s); ^{13}C NMR δ (67.8 MHz, CDCl_3) 214.0, 168.3, 158.9, 138.3, 131.5, 130.2, 128.9 (2C), 128.9, 123.6, 113.6 (2C), 98.6, 87.6, 81.0, 78.6, 74.1, 73.2, 71.6, 69.1, 67.7, 66.6, 64.6, 63.9, 57.0, 55.8, 55.1 (2C), 51.6, 49.4, 46.9, 41.1, 40.6, 38.5, 38.4, 37.6, 36.6, 34.8, 34.8, 30.7, 29.6, 26.6, 25.8 (3C), 21.7, 18.0, 17.2, 12.6, 11.2, 10.8, 10.7, -4.4, -4.7.

Diol **19'**

To a cooled solution of ketol **19** (115.2 mg, 0.118 mmol) in THF (10 mL) at -78 °C was added catecholborane (125.6 μL , 1.18 mmol) and the mixture was warmed gradually to -20 °C over 2 h and further stirred for 21 h, at -20 °C. A saturated potassium sodium tartrate solution (15 mL) was added and stirring was continued at room temperature for 4 h. The mixture was diluted with ether and separated. The organic layer was washed with 1N NaOH (x2), H_2O and brine and the aqueous layers were extracted with ether. The combined organic layers were dried (MgSO_4) and concentrated *in vacuo*. The crude oil was purified by neutral silica gel column chromatography (EtOAc/hexane 30%, 35%, then 40%) to give the *syn*-diol **19'** (73.4 mg, 64%) as a colourless oil: $[\alpha]_{\text{D}}^{28} = -34.7^\circ$ (c 0.65, CHCl_3); IR (neat) 3450 (br), 2936, 1713, 1514, 1462, 1250, 1086, 1038, 912, 733 cm^{-1} ; ^1H NMR δ (270 MHz, CDCl_3) 7.28 (2H, d, $J = 8.6$ Hz), 6.90-6.78 (1H, m), 6.86 (2H, d, $J = 8.7$ Hz), 5.83-5.74 (1H, m), 5.64 (1H, d, $J = 9.6$ Hz), 4.69 (1H, d, $J = 6.6$ Hz), 4.67 (2H, s), 4.65 (1H, d, $J = 6.8$ Hz), 4.39-4.23 (3H, m), 4.19-4.08 (1H, m), 4.03-3.94 (2H, m), 3.87-3.80 (1H, m), 3.79 (3H, s), 3.76-3.64 (2H, m), 3.71 (3H, s), 3.62-3.46 (2H, m), 3.42 (3H, s), 3.37 (3H, s), 3.36-3.27 (2H, m), 3.34 (3H, s), 2.41-2.32 (2H, m), 2.02-1.77 (5H, m), 1.82 (3H, s), 1.75-1.36 (11H, m), 1.30-1.05 (4H, m), 1.21 (3H, d, $J = 6.1$ Hz), 0.95 (3H, d, $J = 6.9$ Hz), 0.94 (3H, d, $J = 6.9$ Hz), 0.89 (9H, s), 0.88 (3H, d, $J = 6.3$ Hz), 0.83 (3H, d, $J = 7.1$ Hz), 0.12 (3H, s), 0.08 (3H, s); ^{13}C NMR δ (67.8 MHz, CDCl_3) 168.4, 159.0, 138.5, 131.5, 130.3, 128.9 (2C), 128.8, 123.6, 113.7 (2C), 98.5, 87.6, 81.8, 79.0, 75.4, 74.2, 73.2, 71.9, 71.7, 69.1, 67.4, 64.7, 64.0, 56.9, 55.9, 55.2, 55.2, 51.6, 42.2, 40.5, 40.4, 39.4, 38.6, 38.5, 37.5, 36.1, 34.9, 34.8, 31.0, 29.7, 26.8, 25.8 (3C), 21.7, 18.0, 17.2, 12.7, 11.5, 11.2, 10.9, -4.4, -4.7.

Protected pre-misakinolide A (**2**)

To a solution of diol **19'** (72.4 mg, 0.074 mmol) in dry CH_2Cl_2 (0.7 mL) was added 2,2-dimethoxypropane (54.5 μL , 0.44 mmol) followed by CSA (1.2 mg, 5.2 μmol) at room temperature. After stirring for 30 min, the

reaction mixture was quenched with satd. NaHCO_3 and the mixture was separated. The aqueous layer was extracted with ether (x4). The combined organic layers were dried (MgSO_4) and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (EtOAc/hexane 15%, 20%) to give protected pre-misakinolide A (**2**) (61.8 mg, 82%) as an oil: $[\alpha]_{\text{D}}^{28} = -38.3^\circ$ (c 0.35, CHCl_3); IR (neat) 2937, 1716, 1508, 1458, 1250, 1092, 1038, 910, 733 cm^{-1} ; ^1H NMR δ (270 MHz, CDCl_3) 7.26 (2H, d, $J = 8.6$ Hz), 6.93-6.83 (1H, m), 6.87 (2H, d, $J = 8.6$ Hz), 5.83-5.73 (1H, m), 5.64 (1H, d, $J = 8.9$ Hz), 4.68 (1H, d, $J = 6.9$ Hz), 4.66 (2H, s), 4.63 (1H, d, $J = 6.9$ Hz), 4.38-4.23 (2H, m), 4.18-4.05 (1H, m), 4.03-3.93 (1H, m), 3.89-3.74 (2H, m), 3.80 (3H, s), 3.73-3.66 (1H, m), 3.73 (3H, s), 3.61-3.45 (2H, m), 3.42 (3H, s), 3.37-3.26 (2H, m), 3.34 (3H, s), 3.32 (3H, s), 2.51-2.27 (2H, m), 2.02-1.91 (2H, m), 1.91-1.76 (3H, m), 1.83 (3H, s), 1.76-1.51 (4H, m), 1.51-1.33 (4H, m), 1.45 (3H, s), 1.38 (3H, s), 1.30-1.12 (7H, m), 1.21 (3H, d, $J = 6.1$ Hz), 0.94 (3H, d, $J = 6.8$ Hz), 0.89 (9H, s), 0.86 (3H, d, $J = 6.8$ Hz), 0.85 (3H, d, $J = 6.6$ Hz), 0.79 (3H, d, $J = 6.9$ Hz), 0.12 (3H, s), 0.09 (3H, s); ^{13}C NMR δ (67.8 MHz, CDCl_3) 168.4, 158.7, 138.4, 132.2, 130.3, 128.8, 128.2 (2C), 123.8, 113.6 (2C), 98.5, 98.1, 87.5, 79.0, 75.4, 73.3, 73.3, 71.6, 70.0, 69.1, 67.7, 67.5, 64.7, 64.0, 57.7, 55.7, 55.2 (2C), 51.6, 41.9, 41.2, 40.6, 38.6, 38.0, 37.4, 37.2, 34.8, 34.7, 33.0, 31.3, 30.6, 29.7, 25.9, 25.9 (3C), 21.7, 20.4, 18.0, 17.4, 12.7, 10.4, 10.2, 8.1, -4.3, -4.7.

¹ (a) Nakamura, R.; Tanino, K.; Miyashita, M. *Org. Lett.* **2003**, *5*, 3579. (b) Nakamura, R.; Tanino, K.; Miyashita, M. *Org. Lett.* **2003**, *5*, 3583.