Complex Aldol Reactions for the Construction of Dense Polyol Stereoarrays: Synthesis of the C₃₃-C₃₆ Region of Aflastatin A

David A. Evans,* Frank Glorius, and Jason D. Burch

Department of Chemistry & Chemical Biology, Harvard University, Cambridge, Massachusetts, 02138

Supporting Information

General Information: All reactions were carried out under an atmosphere of nitrogen in flame- or oven-dried glassware with magnetic stirring, unless otherwise noted. THF, Et₂O, CH₂Cl₂ and toluene are purified by filtration through a column of activated alumina under an argon atmosphere.¹ Reagents were purified prior to use following the guidelines of Perrin and Armarego.² Analytical thin layer chromatography (TLC) was performed on EM Reagent 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and exposure to aqueous ceric ammonium molybdate solution or anisaldehyde followed by heating. Flash chromatography was performed using EM silica gel 60 (230-240 mesh). Solvents for extraction and chromatography were HPLC grade. Optical rotations were measured on a Jasco DIP-0181 digital polarimeter with a sodium lamp and reported as follows: $[\alpha]_D^{25}$ (c g/100 ml, solvent). Infrared spectra were recorded on a Perkin Elmer model 1600 FT-IR spectrometer. Low or high resolution mass spectra were obtained on a JEOL AX-505 or SX-102 high resolution magnetic sector mass spectrometer by the Harvard University Mass Spectrometry Laboratory. ¹H NMR spectra were recorded on Inova-500 (500 MHz) or Mercury-400 (400 MHz) spectrometers. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (CDCl₃: δ 7.26 ppm, C₆D₆: δ 7.15 ppm, CD₃OD: δ 3.30 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, bs = broad singlet, m = multiplet), coupling constants (Hz), integration. ¹³C NMR spectra were recorded on Varian INOVA-500 (125 MHz) or Mercury-400 (100 MHz) spectrometers with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard (CDCl₃: δ 77.0 ppm, C₆D₆: δ 128.0 ppm, CD₃OD: δ 49.0 ppm).

¹ Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics*, **1996**, *15*, 1518.

² Perrin, D. D. and Armarego, W. L. *Purification of Laboratory Chemicals*; 3rd ed., Pergamon Press, Oxford, 1988.

Synthesis of ketone 2

Reaction Conditions: (a) TBSCl, imid, CH₂Cl₂. (b) KOH, MeOH, H₂O, THF. (c) (COCl)₂, PhH. (d) Me(MeO)NH·HCl, pyr, THF. (e) ⁱBuMgCl, THF.

N-Methoxy-N-methyl-2-(1,1,2,2-tetramethyl-1-silapropoxy)acetamide. The corresponding acid chloride³ (14.8 g, 70.9 mmol) and Me(MeO)NH₂Cl (7.6 g, 78.0 mmol) were dissolved in CHCl₃ (400 mL) and pyridine (12.6 mL, 156 mmol) was added at 0 °C. The reaction mixture was stirred at rt for 24 h, the solvent evaporated in vacuo and the residue partitioned between brine (250 mL) and a 1:1 mixture of CH₂Cl₂ and Et₂O (500 mL). The layers were separated and the organic layer dried (Na₂SO₄), filtered and the solvent evaporated. Purification by flash chromatography (5:1 hexanes:EtOAc) provided the Weinreb amide (13.3 g, 80%) as a colorless oil.

R_f = 0.56 (2:1 hexanes/EtOAc); IR (NaCl) 2954, 2930, 2897, 2857, 1695, 1472, 1329, 1254, 1161, 1088, 997, 839, 779 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.42 (s, 2H, CH₂), 3.67 (s, 3H, OCH₃), 3.17 (s, 3H, NCH₃), 0.90 (s, 9H, CCH₃), 0.11 (s, 6H, SiCH₃); ¹³C NMR (100 MHz, CDCl₃) δ 172.2, 61.8, 61.4, 32.5, 25.9, 18.6, -5.2; LRMS (CI) *m/z* 234 MH⁺; HRMS (CI) calcd. for (C₁₀H₂₃NO₃Si + H) *m/z* 234.1526, found: *m/z* 234.1539.

4-Methyl-1-(1,1,2,2-tetramethyl-1-silapropoxy)pentan-2-one (2). To a solution of the Weinreb amide (13.0 g, 55.7 mmol) in THF (500 mL) was added a 2.0 M solution of *iso*-butyl magnesium chloride in ether (66.0 mL, 132.0 mmol) at 0 °C. The resulting reaction mixture was stirred at 0 °C for 1.5 h and finally cooled to -20 °C. It was then poured into a solution of 6 M aq. HCl (100 mL) in EtOH (300 mL) which was prechilled to 0 °C. After stirring this mixture for 15 min brine (300 mL) was added. The layers were separated and the aq. layer was extracted with ether (250 mL). The combined organic layers were dried (Na₂SO₄), filtered and the solvent evaporated in vacuo. Purification by flash chromatography (9:1 hexanes:EtOAc) yielded **2** as a colorless oil (11.50 g, 90%).

³ Bischofberger, N.; Waldmann, H.; Saito, T.; Simon, E. S.; Lees, W.; Bednarski, M. D.; Whitesides, G. M. J. *Org. Chem.* **1988**, 53, 3457.

$R_f = 0.36$ (19:1 hexanes/EtOAc); IR (NaCl) 2957, 2931, 2897, 2859, 1721, 1471, 1363, 1255, 1173, 1121, 1042, 1007, 940, 840, 779 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 4.14 (s, 2H, CH_2O), 2.34 (d, 2H, $J = 6.8$ Hz, CH_2CH), 2.15 (m, 1H, CH), 0.92 (d, $J = 6.8$ Hz, 6H, CHCH_3), 0.92 (s, 9H, CCH_3), 0.08 (s, 6H, SiCH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 210.2, 69.7, 47.2, 25.9, 24.3, 22.8, 18.5, -5.3; LRMS (CI) m/z 248 MNH^+ ; HRMS (EI) calcd. for ($\text{C}_{12}\text{H}_{26}\text{O}_2\text{Si} + \text{NH}_4$) m/z 248.2046, found: m/z 248.2042.

General Procedure for Aldol Reactions: Enolization Method A⁴

To a stirred solution of Cy_2BCl (74.0 μL , 0.338 mmol) in ether (1.0 mL) at -78°C was added dropwise NEt_3 (56.4 μL , 0.405 mmol), followed by the addition of ketone (0.225 mmol) in ether (1.0 mL), whereupon a white precipitate formed. After 30 min at -78°C the solution was allowed to warm to 0°C , was stirred for 1 h and then recooled to -78°C . The freshly distilled aldehyde (44.6 μL , 0.338 mmol) was added and the resulting mixture stirred at -78°C for 3 h and at -20°C for 12 h. The mixture was partitioned between a pH 7 buffer solution (5 mL) and ether (3×15 mL). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo. The resulting oil was dissolved in MeOH (0.5 mL), a pH 7 phosphate buffer (1 mL), and H_2O_2 (30%, 0.5 mL) at 0°C ; warmed to rt and stirred for 1 h. It was partitioned between H_2O (5 mL) and CH_2Cl_2 (3×20 mL). The combined extracts were washed with sat. aq. NaHCO_3 (5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated in vacuo. Isolation of the aldol product was achieved by column chromatography, and diastereomeric ratios were determined by ^1H NMR analysis. All aldol products were obtained as colorless oils.

General Procedure for Aldol Reactions: Method B⁵

To a cooled (0°C) solution of ketone (0.450 mmol) in pentane (9 mL) was added dropwise Cy_2BCl (108.4 μL , 0.495 mmol) and EtNMe_2 (97.6 μL , 0.900 mmol). The resulting white suspension was stirred at 0°C for 10 min and at room temperature for 15 h before it was cooled to -78°C . The freshly distilled aldehyde (89.2 μL , 0.675 mmol) was added and the resulting mixture stirred at -78°C for 4 h and at -20°C for 5 h. The mixture was partitioned between a pH 7 buffer solution (5 mL) and ether (3×15 mL). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo. The resulting oil was dissolved in MeOH (1.0 mL), a pH 7 phosphate buffer (2.0 mL), and H_2O_2 (30%, 1.0 mL) at 0°C ; warmed to rt and stirred for 1 h. It was partitioned between H_2O (5 mL) and CH_2Cl_2 (3×20 mL). The combined extracts were washed with sat. aq. NaHCO_3 (5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated in vacuo. Isolation of the aldol products was achieved by column chromatography, and diastereomeric ratios were determined by ^1H NMR analysis. All aldol products were obtained as colorless oils.

⁴ Marco, J. A.; Carda, M.; Falomir, E.; Palomo, C.; Oiarbide, M.; Ortiz, J. A.; Linden, A. *Tetrahedron Lett.* **1999**, *40*, 1065.

⁵ Galobardes, M.; Gascón, M.; Mena, M.; Romea, P.; Urpí, F.; Vilarassa, J. *Org. Lett.* **2000**, *2*, 2599.

(5*R,6*R**)-6-Hydroxy-2-methyl-8-phenyl-5-(1,1,2,2-tetramethyl-1-silapropoxy)octan-4-one (3)** and **(3*S**,4*R**)-4-Hydroxy-3-(methylethyl)-6-phenyl-1-(1,1,2,2-tetramethyl-1-silapropoxy)hexan-2-one (4)**. These compounds were formed as mixtures using Method A or B or modifications (see Table 1). Purification by flash column chromatography (19:1 hexanes:EtOAc) provided pure **3** and **4**.

3: R_f = 0.36 (19:1 hexanes/EtOAc); R_f = 0.79 (2:1 hexanes/EtOAc); IR (NaCl) 3480, 3028, 2956, 2931, 2859, 1714, 1604, 1472, 1363, 1254, 1102, 1046, 838, 779, 748, 699 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.33-7.20 (m, 5H, Ph), 4.01 (d, J = 4.4 Hz, 1H, CHOTBS), 3.78 (dt, J = 4.9, 7.8 Hz, 1H, CHOH), 2.91-2.86 (m, 1H, CH₂Ph), 2.75-2.69 (m, 1H, CH₂Ph), 2.45 (m, 2H, CH₂CO), 2.32 (s, 1H, OH), 2.19 (m, 1H, CHCH₃), 1.79-1.74 (m, 2H, CH₂CH₂Ph), 0.97 (s, 9H, CCH₃), 0.94 (d, J = 2.9 Hz, 3H, CHCH₃), 0.92 (d, J = 2.9 Hz, 3H, CHCH₃), 0.10 (s, 3H, SiCH₃), 0.09 (s, 3H, SiCH₃); ^{13}C NMR (100 MHz, CDCl_3) δ 211.6, 141.6, 128.4, 128.4, 125.9, 81.7, 72.7, 48.1, 33.5, 31.9, 25.7, 23.1, 22.6, 18.1, -4.8, -5.0; LRMS (CI) m/z 382 MNH_4^+ ; HRMS (CI) calcd. for ($\text{C}_{21}\text{H}_{28}\text{O}_3 + \text{NH}_4$) m/z 382.2778, found: m/z 382.2788.

4: R_f = 0.70 (2:1 hexanes/EtOAc); IR (NaCl) 3482, 3063, 3027, 2957, 2930, 2857, 1719, 1604, 1472, 1255, 1146, 1047, 939, 837, 780, 747, 699 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.30-7.18 (m, 5H, Ph), 4.19 (AB quartet, ν_B = 4.22, ν_A = 4.16, J = 18.1 Hz, 2H, CH₂OTBS), 3.93-3.89 (m, 1H, CH(OH)), 2.89-2.81 (m, 2H, CHCO and CH₂Ph), 2.66-2.60 (m, 1H, CH₂Ph), 2.35 (s, 1H, OH), 2.12 (m, 1H, CHCH₃), 1.82-1.68 (m, 2H, CH₂CH₂Ph), 0.94 (s, 9H, CCH₃), 0.90 (d, J = 1.5 Hz, 3H, CHCH₃), 0.89 (d, J = 1.5 Hz, 3H, CHCH₃), 0.12 (s, 3H, SiCH₃), 0.11 (s, 3H, SiCH₃); ^{13}C NMR (100 MHz, CDCl_3) δ 212.7, 141.7, 128.4, 128.4, 125.9, 71.7, 70.6, 58.0, 34.9, 32.4, 27.0, 25.8, 20.9, 20.7, 18.4, -5.4; LRMS (CI) m/z 382 MNH_4^+ ; HRMS (CI) calcd. for ($\text{C}_{21}\text{H}_{36}\text{O}_3\text{Si} + \text{NH}_4$) m/z 382.2778, found: m/z 382.2788.

(4*R*)-3-[(2*R*,3*R*)-3-Hydroxy-5-phenyl-2-(phenylmethoxy)pentanoyl]-4-benzyl-1,3-oxazolidin-2-one (6). To a solution of $\text{Sn}(\text{OTf})_2$ (194 mg, 0.466 mmol) in CH_2Cl_2 (1.5 mL) was added NEt_3 (65 μL , 0.466). The resulting faintly yellow suspension was immediately cooled to -78°C . After 5 min a solution of the acylimide (101 mg, 0.311) in CH_2Cl_2 (0.5 mL) was added via cannula. The resulting solution was stirred at -78°C for 1 h and then TMEDA (70 μL , 0.466) was added. After 5 min the freshly distilled dihydrocinnamaldehyde (49.3 μL , 0.373) was added and the solution stirred for 4 h. The reaction mixture was poured on a vigorously stirred mixture of 1 N NaHSO_4 (20 mL) and CH_2Cl_2 (20 mL) at 0°C . After stirring for 5 min the layers were separated and the

aq. layer extracted with CH_2Cl_2 (2×10 mL). The combined org. layers were washed with NaHCO_3 (10 mL), brine (10 mL) and dried (Na_2SO_4). Purification by column chromatography (2:1 hexanes/EtOAc) yielded **6** (82.5 mg, 58%) as a colorless oil.

$R_f = 0.21$ (2:1 hexanes/EtOAc); $[\alpha]_D^{20} -17.2$ ($c = 1.33$, CHCl_3); IR (NaCl) 3482, 3062, 3028, 2923, 2862, 1780, 1704, 1496, 1455, 1393, 1350, 1211, 1111, 922, 822, 751, 700 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.43-7.22 (m, 15H, Ph), 5.33 (d, $J = 6.4$ Hz, 1H, $\text{CH}(\text{OBn})$), 4.68-4.64 (m, 1H, CHN), 4.63 (AB quartet, $\nu_B = 4.65$, $\nu_A = 4.60$, $J = 11.5$ Hz, 2H, OCH_2Ph), 4.16 (d, $J = 4.9$ Hz, 2H, OCH_2), 3.95-3.90 (m, 1H, $\text{CH}(\text{OH})$), 3.22 (dd, $J = 3.4$, 13.2 Hz, 1H, CHCH_2Ph), 2.90 (ddd, $J = 5.4$, 9.8, 14.3 Hz, 1H, $\text{CH}_2\text{CH}_2\text{Ph}$), 2.71 (ddd, $J = 7.3$, 9.3, 14.3 Hz, 1H, $\text{CH}_2\text{CH}_2\text{Ph}$), 2.63 (dd, $J = 0.8$, 13.7 Hz, 1H, CHCH_2Ph), 2.18 (d, $J = 8.8$ Hz, 1H, OH), 2.12-2.06 (m, 1H, $\text{CH}_2\text{CH}_2\text{Ph}$), 1.88 (m, 1H, $\text{CH}_2\text{CH}_2\text{Ph}$); ^{13}C NMR (100 MHz, CDCl_3) δ 171.5, 153.6, 141.4, 136.9, 134.9, 129.2, 128.8, 128.4, 128.4, 128.3, 128.3, 128.0, 127.3, 125.8, 79.8, 73.1, 72.2, 66.7, 55.5, 37.9, 35.3, 31.6; LRMS (ESI) m/z 460 MH^+ ; HRMS (ESI) calcd. for ($\text{C}_{28}\text{H}_{29}\text{NO}_5 + \text{Na}$) m/z 482.1943, found: m/z 482.1960.

(2R,3R)-3-Hydroxy-N-methoxy-N-methyl-5-phenyl-2-(phenylmethoxy)pentanamide. To a suspension of $\text{Me}(\text{MeO})\text{NH}_2\text{Cl}$ (31.9 mg, 0.327 mmol) in THF (0.5 mL) was added a 2.0 M solution of AlMe_3 in toluene (0.166 mL, 0.332 mmol) at 0 °C. The resulting solution was stirred at r.t. for 30 min and then cooled to -20 °C. A solution of the aldol adduct **6** (50 mg, 0.109 mmol) in THF (0.5 mL) was slowly added and the solution was stirred at 0 °C for 1 h and at r.t. for an additional hour. The reaction mixture was kept at -20 °C overnight, diluted with CH_2Cl_2 (2.5 mL) and after the addition of 0.5 N HCl (1.7 mL) stirred for 1 h. The reaction was extracted with CH_2Cl_2 (3×15 mL) and dried (Na_2SO_4) providing an inseparable 1:1 mixture of the title compound with (*R*)-benzyl oxazolidinone (55 mg, $\approx 97\%$).

$R_f = 0.23$ (1:1 hexanes/EtOAc); IR (NaCl) 3403, 3304, 3062, 3028, 2928, 2862, 1748, 1652, 1496, 1455, 1404, 1242, 1100, 1029, 935, 822, 751, 700 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.35-7.16 (m, 10H, Ph), 4.67 (d, $J = 11.7$ Hz, 1H, OCH_2Ph), 4.45-4.39 (m, 2H, CHOBN and OCH_2Ph), 3.97 (ddd, $J = 2.4$, 5.4, 8.8 Hz, 1H, $\text{CH}(\text{OH})$), 3.56 (s, 3H, OCH_3), 3.20 (s, 3H, NCH_3), 2.90-2.83 (m, 1H, CH_2Ph), 2.68 (ddd, $J = 6.8$, 9.3, 13.7 Hz, 1H, CH_2Ph), 1.97-1.94 (m, 1H, $\text{CH}_2\text{CH}(\text{OH})$), 1.84-1.78 (m, 1H, $\text{CH}_2\text{CH}(\text{OH})$); ^{13}C NMR (100 MHz, CDCl_3) δ 171.7, 141.9, 137.3, 128.9, 128.3, 128.3, 128.0, 127.9, 125.7, 94.2, 77.7, 71.8, 70.7, 61.3, 34.7, 31.7; LRMS (ESI) m/z 344 MH^+ ; HRMS (ESI) calcd. for ($\text{C}_{20}\text{H}_{25}\text{NO}_4 + \text{H}$) m/z 344.1862, found: m/z 344.1849.

(2R,3R)-3-(2,2-dimethyl-1,1-diphenyl-1-silapropoxy)-N-methoxy-N-methyl-5-phenyl-2-(phenylmethoxy)pentanamide. A stirred solution of the aldol adduct (Inseparable 1:1 mixture with (*R*)-benzyl oxazolidinone, 2.90 g) in DMF (56 mL) was cooled to 0 °C prior to the sequential addition of imidazole (3.8 g, 55.7 mmol) and TBDPSCl (7.66 g,

27.9 mmol). The reaction was stirred at rt for 27 h, at which time the reaction was poured into ether (300 mL) and washed with water (4 × 30 mL) and brine (30 mL). The ether layer was dried (Na₂SO₄), filtered and concentrated in vacuo. Purification by column chromatography provided the title compound (2.78 g, 84% over two steps) as a colorless oil.

R_f = 0.45 (2:1 hexanes/EtOAc); $[\alpha]_D^{20}$ -34.0 (c = 0.65, CHCl₃); IR (NaCl) 3069, 3028, 2956, 2933, 2894, 2857, 1673, 1603, 1589, 1496, 1455, 1428, 1390, 1177, 1111, 996, 940, 822, 739, 701 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.74-7.64 (m, 4H, **Ph**), 7.45-7.07 (m, 14H, **Ph**), 6.82-6.80 (m, 2H, **Ph**), 4.52 (AB quartet, ν_B = 4.68, ν_A = 4.38, J = 12.2 Hz, 2H, OCH₂Ph), 4.52 (m, 1H, CHOBn), 4.27-4.23 (m, 1H, CHOTBDPS), 3.35 (s, 3H, OCH₃), 3.13 (s, 3H, NCH₃), 2.51-2.45 (m, 1H, CH₂Ph), 2.34-2.28 (m, 1H, CH₂Ph), 1.97-1.90 (m, 1H, CH₂CH₂Ph), 1.83-1.76 (m, 1H, CH₂CH₂Ph), 1.06 (s, 9H, CCH₃); ¹³C NMR (100 MHz, CDCl₃) δ 170.0, 142.3, 137.9, 136.1, 136.1, 134.0, 133.6, 129.6, 129.6, 128.3, 128.0, 128.0, 127.7, 127.5, 127.5, 125.4, 78.1, 73.0, 71.7, 61.1, 34.4, 32.0, 31.0, 27.0, 19.4; LRMS (ESI) m/z 604 MNa⁺; HRMS (ESI) calcd. for (C₃₆H₄₃NO₄Si + Na) m/z 604.2859, found: m/z 604.2882.

(2S,3R)-3-Methoxy-N-methoxy-N-methyl-2-(methylethoxy)-4-(1,1,2,2-tetramethyl-1-silapropoxy)butanamide. To a suspension of Me(MeO)NH₂Cl (5.55 g, 56.9 mmol) in THF (100 mL) was added a 2.0 M solution of AlMe₃ in toluene (29.2 mL, 58.4 mmol) at 0 °C. The resulting solution was stirred at rt for 30 min and then cooled to -15 °C. A solution of the 2,3-O-isopropylidene-D-erythrone (4.50 g, 28.4 mmol) in THF (80 mL) was slowly added and the solution was stirred at 0 °C for 2 h and at rt for 15 h. The reaction mixture was quenched by careful addition of ether (100 mL) and sat. aq. sodium potassium tartrate (200 mL) and extracted with EtOAc (4 × 150 mL). The organic layer was dried (Na₂SO₄) and the solvent evaporated in vacuo. The residue was dissolved in CH₂Cl₂ (150 mL) and cooled to 0 °C prior to the sequential addition of 2,6 lutidine (4.2 mL, 35.8 mmol) and TBSOTf (7.06 mL, 30.7 mmol). After stirring at 0 °C for 2 h sat. aq. NaHCO₃ (30 mL) was added. The biphasic mixture was diluted with CH₂Cl₂ (100 mL) before the two layers were separated. The aq. layer was extracted with CH₂Cl₂ (2 × 100 mL) and the combined organic layers were washed with 1 N NaHSO₄ (20 mL) and dried (Na₂SO₄). Purification by flash chromatography (4:1 hexanes/EtOAc) provided the title compound (6.21 g, 66%) as a white solid.

R_f = 0.39 (2:1 hexanes/EtOAc); [α]_D²⁰ +55.0 (*c* = 1.15, CHCl₃); IR (NaCl) 2932, 2858, 1692, 1463, 1380, 1252, 1093, 993, 836, 779 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.97 (d, *J* = 6.3 Hz, 1H, CHCO), 4.41 (t, *J* = 6.3 Hz, 1H, CHCH₂), 3.71 (s, 3H, OCH₃), 3.70 (dd, *J* = 6.3, 10.6 Hz, 1H, CH₂OTBS), 3.59 (dd, *J* = 5.6, 10.6 Hz, 1H, CH₂OTBS), 3.17 (s, 3H, NCH₃), 1.57 (s, 3H, CCH₃), 1.39 (s, 3H, CCH₃), 0.87 (s, 9H, SiCCH₃), 0.04 (s, 3H, SiCH₃), 0.03 (s, 3H, SiCH₃); ¹³C NMR (100 MHz, CDCl₃) δ 169.3, 109.9, 78.1, 73.8, 62.5, 61.3, 32.4, 27.5, 25.9, 25.6, 18.5, -5.3; LRMS (ESI) *m/z* 356 MNa⁺; HRMS (ESI) calcd. for (C₁₅H₃₁NO₅Si + Na) *m/z* 356.1869, found: *m/z* 356.1880.

(2S,3R)-3-Methoxy-2-(methylethoxy)-4-(1,1,2,2-tetramethyl-1-silapropoxy)butanal (7). To a solution of the Weinreb amide (380.0 mg, 1.14 mmol) in THF (3.0 mL) at -78 °C was added a 1.0 M solution of DIBAL-H in toluene (5.7 mL, 5.7 mmol) dropwise. The reaction was stirred at -78 °C for 0.5 h and then quenched by the dropwise addition of EtOAc (2.5 mL). After 5 min ether (12 mL) and sat. aq. sodium potassium tartrate (12 mL) were added, the reaction warmed to r.t. and stirred for 0.5 h. Water (10 mL) was added and the mixture extracted with ether (3 × 60 mL) and dried (Na₂SO₄). Purification by column chromatography (9:1 hexanes/EtOAc) provided **7** (300.5 mg, 96%) as a colorless oil.

R_f = 0.68 (2:1 hexanes/EtOAc); [α]_D²⁰ +51.8 (*c* = 1.16, CHCl₃); IR (NaCl) 2989, 2956, 2931, 2887, 2859, 2714, 1733, 1479, 1464, 1382, 1255, 1214, 1147, 1091, 1016, 873, 838, 779, 715 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 9.68 (d, *J* = 2.2 Hz, 1H, CHO), 4.49-4.41 (m, 2H, CH),

3.73 (d of a AB quartet, $\nu_B = 3.78$, $\nu_A = 3.69$, $J = 3.7$ Hz, $J_{AB} = 11.3$ Hz, 2H, OCH_2TBS), 1.57 (s, 3H, CCH_3), 1.38 (s, 3H, CCH_3), 0.88 (s, 9H, CCH_3), 0.05 (s, 3H, SiCH_3), 0.04 (s, 3H, SiCH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 200.3, 110.6, 80.8, 79.7, 60.5, 26.8, 25.7, 25.0, 18.1, -5.5, -5.7; LRMS (CI) m/z 292 MNH_4^+ ; HRMS (CI) calcd. for $(\text{C}_{13}\text{H}_{26}\text{O}_4\text{Si} + \text{NH}_4)$ m/z 292.1944, found: m/z 292.1940.

(5R,6R,7S,8R)-8-(2,2-dimethyl-1,1-diphenyl-1-silapropoxy)-6-hydroxy-2-methyl-10-phenyl-7-(phenylmethoxy)-5-(1,1,2,2-tetramethyl-1-silapropoxy)decan-4-one (8b). Aldol adduct **8b** was prepared according to Method B. ^1H NMR analysis of the unpurified reaction mixture indicated a 79:21 mixture of diastereomers. Purification by flash column chromatography (33:1 hexanes:EtOAc) provided the title compound as a clear colorless oil.

$R_f = 0.85$ (2:1 hexanes/EtOAc); IR (NaCl) 3063, 3029, 2956, 2930, 2894, 2856, 1721, 1710, 1497, 1471, 1427, 1362, 1253, 1111, 836 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.83-6.89 (m, 20H, **Ph**), 4.51 (AB quartet, $\nu_B = 4.61$, $\nu_A = 4.41$, $J = 11.0$ Hz, 2H, OCH_2Ph), 4.34 (d, $J = 1.9$ Hz, 1H, $\text{CH}(\text{OTBS})$), 4.27 (ddd, $J = 2.0$, 6.3, 9.3 Hz, 1H, $\text{CH}(\text{OH})$), 4.21-4.18 (m, 1H, $\text{CH}(\text{OTBDPS})$), 3.83 (d, $J = 9.3$ Hz, 1H, $\text{CH}(\text{OBn})$), 2.44-2.25 (m, 5H, OH and $\text{CH}_2\text{CH}_2\text{Ph}$ and CH_3CHCH_2), 2.06-1.79 (m, 3H, $\text{CH}_2\text{CH}_2\text{Ph}$ and CHCH_3), 1.16 (s, 9H, CCH_3), 1.04 (s, 9H, CCH_3), 0.87 (d, $J = 6.8$ Hz, 3H, CHCH_3), 0.83 (d, $J = 6.3$ Hz, 3H, CHCH_3), 0.22 (s, 3H, SiCH_3), 0.14 (s, 3H, SiCH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 208.5, 141.9, 138.3, 136.2, 136.0, 134.1, 133.0, 129.8, 129.7, 128.2, 128.2, 128.0, 127.8, 127.6, 127.6, 127.2, 125.6, 80.8, 80.2, 75.0, 74.3, 72.5, 48.1, 35.5, 27.1, 25.9, 23.6, 22.7, 22.6, 22.4, 19.4, 18.4, -4.6, -5.0; LRMS (ESI) m/z 753 MH^+ ; HRMS (ESI) calcd. for $(\text{C}_{46}\text{H}_{64}\text{O}_5\text{Si}_2 + \text{H})$ m/z 753.4370, found: m/z 753.4370.

(1S,2S)-1-((4S,5R)-2,2-Dimethyl-5-[(1,1,2,2-tetramethyl-1-silapropoxy)methyl](1,3-dioxolan-4-yl))-1-hydroxy-5-methyl-2-(1,1,2,2-tetramethyl-1-silapropoxy)hexane-3-one (9a). Aldol adduct **9a** was prepared according to Method B. ^1H NMR analysis of the unpurified reaction mixture indicated **9a** was present as a single diastereomer. Purification by flash column chromatography (19:1 hexanes:EtOAc) provided the title compound as a clear colorless oil.

$R_f = 0.42$ (9:1 hexanes/EtOAc); $[\alpha]_D^{20} -36.1$ ($c = 0.955$, CHCl_3); IR (NaCl) 3481, 2956, 2931, 2887, 2859, 1723, 1472, 1363, 1256, 1212, 1099, 938, 891, 838, 778 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 4.33 (d, $J = 7.3$ Hz, 1H, CH_2CHCH), 4.23 (ddd, $J = 4.4, 7.3, 7.3$ Hz, 1H, CHCH_2OTBS), 3.98-3.87 (m, 3H, CH_2OTBS and $\text{CH}(\text{OH})$ and CHOTBS), 3.78 (dd, $J = 4.2, 10.5$ Hz, 1H, CH_2OTBS), 2.98 (d, $J = 7.3$ Hz, 1H, OH), 2.56 (dd, $J = 7.3, 18.0$ Hz, 1H, CH_3CHCH_2), 2.39 (dd, $J = 6.3, 18.0$ Hz, 1H, CH_3CHCH_2), 2.20 (m, 1H, CHCH_3), 1.47 (s, 3H, CCH_3), 1.34 (s, 3H, CCH_3), 0.92 (d, $J = 6.8$ Hz, 3H, CHCH_3), 0.91 (d, $J = 6.8$ Hz, 3H, CHCH_3), 0.90 (s, 9H, SiCCH_3), 0.90 (s, 9H, SiCCH_3), 0.09 (s, 3H, SiCH_3), 0.08 (s, 3H, SiCH_3), 0.07 (s, 3H, SiCH_3), 0.02 (s, 3H, SiCH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 210.6, 108.2, 78.4, 76.8, 74.4, 70.0, 61.7, 46.4, 26.8, 25.8, 25.6, 24.6, 23.1, 22.6, 18.2, 18.0, -4.8, -5.3, -5.5, -5.5; LRMS (ESI) m/z 527 MNa^+ ; HRMS (ESI) calcd. for $(\text{C}_{25}\text{H}_{52}\text{O}_6\text{Si}_2 + \text{Na})$ m/z 527.3200, found: m/z 527.3178.

1-(((4R)-2,2-Dimethyl(1,3-dioxolan-4-yl))(1S)(tert-butyldimethylsilyloxy)methyl) (1S,2R)-3-{5-[(1S,2S,5R)-2,5-bis(tert-butyldimethylsilyloxy)-1-hydroxy-3-oxotetradecyl] (5S,4R)-2,2-dimethyl(1,3-dioxolan-4-yl)}-2-phenylcarbonyloxypropyl benzoate (12). A solution of ketone **10** (359 mg, 0.782 mmol) in 1.5 mL of freshly distilled pentane was chilled to 0 °C, and Cy_2BCl (163 μL , 0.744 mmol) followed by EtNMe_2 (141 μL , 1.30 mmol) were added dropwise. The resulting suspension was stirred for 15 hours at 0 °C to rt, and then chilled to -78 °C. A solution of aldehyde **11** (245 mg, 0.373 mmol) in 0.5 mL of pentane and 0.2 mL of toluene was then added to the enolate solution slowly via cannula, followed by a 0.3 mL pentane + 0.1 mL toluene rinse. This mixture was stirred for 4 hours at -78 °C and 20 hours at -20 °C, and then the reaction was quenched by the addition of a few drops of pH 7 buffer. Upon warming to room temperature, 1.5 mL each of pH 7 buffer, MeOH and 30% aqueous H_2O_2 were added, and the heterogeneous mixture was stirred vigorously for 2 hours. This mixture was poured into 50 mL of sat. $\text{NaHCO}_3(\text{aq})$, and extracted with 3×50 mL of Et_2O . Hexanes (50 mL) were added, and the organic solution was dried (Na_2SO_4) and concentrated in vacuo. Purification by flash column chromatography (0 $\rightarrow$ 10% EtOAc/hexanes; linear gradient) provided 310 mg (0.272 mmol, 73%) of the title compound as clear, colorless oil.

TLC R_f 0.8 (20% EtOAc/hexanes); $[\alpha]_D^{23} -9.2$ (c 0.7, CH_2Cl_2); IR (neat) 2929, 2857, 1727, 1472, 1380, 1258, 1094, 838 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.94-7.91 (m, 4H, BzH), 7.48-7.45 (m, 2H, BzH), 7.36-7.32 (m, 4H, BzH), 5.93-5.89 (m, 1H, $\text{C}_{31}\text{-H}$), 5.35 (dd, $J = 6.8, 3.9$ Hz, 1H, $\text{C}_{30}\text{-H}$), 4.34 (ddd, $J = 9.8, 7.3, 2.4$ Hz, 1H, $\text{C}_{33}\text{-H}$), 4.20-4.16 (m, 3H, $\text{C}_{28}\text{-H} + \text{C}_{34}\text{-H} + \text{C}_{39}\text{-H}$), 4.10 (dd, $J = 8.3, 6.3$ Hz, 1H, one of $\text{C}_{27}\text{-H}$), 4.00 (dd, $J = 6.8, 3.4$ Hz, 1H, $\text{C}_{29}\text{-H}$), 3.86 (d, $J = 8.3$ Hz, 1H, $\text{C}_{36}\text{-H}$), 3.76 (t, $J = 7.8$ Hz, 1H, one of $\text{C}_{27}\text{-H}$), 3.57 (dd, $J = 9.3, 8.3$ Hz, 1H, $\text{C}_{35}\text{-H}$), 2.87 (dd, $J = 18.6, 5.9$ Hz, 1H, one of $\text{C}_{38}\text{-H}$), 2.60 (dd, $J = 18.6, 6.8$ Hz, 1H, one of $\text{C}_{38}\text{-H}$), 2.51 (ddd, $J = 14.2, 9.8, 4.4$ Hz, 1H, one of $\text{C}_{32}\text{-H}$), 2.18 (d, $J = 9.8$ Hz, 1H, $\text{C}_{35}\text{-OH}$), 2.03 (ddd, $J = 14.2, 8.8, 2.4$ Hz, 1H, one of $\text{C}_{32}\text{-H}$), 1.51-1.47 (m, 1H, one

of C₄₀-H), 1.42 (s, 3H, one of C(CH₃)₂), 1.38 (s, 3H, one of C(CH₃)₂), 1.37-1.25 (m, 18H, one of C₄₀-H + C₄₁₋₄₇-H₁₄ + one of C(CH₃)₂), 1.22 (s, 3H, one of C(CH₃)₂), 0.94 (s, 9H, one of SiC(CH₃)₃), 0.88 (t, 3H, *J* = 6.8 Hz, C₄₈-H₃), 0.85 (s, 9H, one of SiC(CH₃)₃), 0.84 (s, 9H, one of SiC(CH₃)₃), 0.16 (s, 3H, one of Si(CH₃)₂), 0.11 (s, 3H, one of Si(CH₃)₂), 0.06 (s, 3H, one of Si(CH₃)₂), 0.01 (s, 3H, one of Si(CH₃)₂), 0.01 (s, 3H, one of Si(CH₃)₂), -0.01 (s, 3H, one of Si(CH₃)₂); ¹³C NMR (100 MHz, CDCl₃) δ 209.9, 165.7, 165.6, 133.0, 132.9, 129.8, 129.7, 129.6, 129.5, 128.3, 128.3, 109.0, 107.9, 79.0, 75.2, 74.5, 73.6, 72.2, 71.1, 70.8, 67.5, 65.9, 45.6, 37.4, 32.1, 31.9, 29.7, 29.6, 29.6, 29.3, 26.8, 26.4, 25.9, 25.9, 25.7, 25.2, 25.0, 24.1, 22.7, 18.2, 18.0, 18.0, 14.1, -4.3, -4.5, -4.8, -4.8, -4.9, -5.2; exact mass calc. for C₆₀H₁₀₆NO₁₃Si₃ [(M+NH₄)⁺]: 1132.6972; found: 1132.6992.

Stereochemical Proofs

Compound 3:

Compound 4:

Compound 6:

Reaction Conditions: (a) LiBH_4 , H_2O , EtOH ; (b) DMB, CSA.

Consistent with closely related substrates: *anti* $J_{1,2} = 9 \text{ Hz}$ (Evans, D.A. et al. *J. Org. Chem.* **1992**, 1961); *cf. syn* $J_{1,2} = 3 \text{ Hz}$ (Mukaiyama, T. et al. *Chem. Lett.* **1984**, 753).

Compound 8b:

Reaction Conditions: (a) TBAF, THF.

Compound 9a:

Reaction Conditions: (a) 80% AcOH(aq) .

Compound 12: