Supporting Information

Total Synthesis of Natural (+)-(2'S,3'R)-Zoapatanol

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General

TLC was performed on Merck 60F₂₅₄ silica gel plates and visualized either with a UV lamp (254 nm), or by using a solution of *p*-anisaldehyde/sulfuric acid/acetic acid in EtOH followed by heating.

Flash chromatography was performed with Merck Geduran Si60 silica gel (40-63 μ m).

Infrared (IR) spectra were recorded on a Perkin-Elmer 298, wave-numbers are indicated in cm^{-1} . ^1H NMR spectra were recorded on a Bruker AC 300 at 300 MHz and data are reported as follows: chemical shift in ppm from tetramethylsilane as an internal standard, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or overlap of non equivalent resonances), integration. ^{13}C NMR spectra were recorded on a Bruker AC 300 at 75 MHz and data are reported as follows: chemical shift in ppm from tetramethylsilane with the solvent as an internal indicator (CDCl_3 δ 77.0 ppm), multiplicity with respect to proton (deduced from DEPT experiments, s = quaternary C, d = CH, t = CH_2 , q = CH_3). Mass spectra with electronic impact (MS-EI) were recorded from a Hewlett-Packard tandem 5890A GC (12 m capillary column) – 5971 MS (70 eV). Mass spectra with chemical ionization (MS-CI⁺) and high resolution mass spectra (HRMS) were performed by the Centre de Spectrochimie Organique de l'Ecole Normale Supérieure Ulm (Paris). Elemental analyses were performed by the Centre Régional de Microanalyses (Université Pierre et Marie Curie, Paris VI).

Spectral data of key intermediates

(Z)-Ethyl 8-(tert-butyldiphenylsilyloxy)-3,7-dimethyl-oct-2-enoate (12): To *tert*-butyl(2-methylpent-4-enyloxy)diphenylsilane (1.55 g, 4.58 mmol, 1.1 equiv) at 0 °C was added dropwise a solution of 9-BBN dimer (0.615 g, 2.52 mmol, 0.6 equiv) in anhydrous THF (10 mL, 0.5 M). The solution was stirred at 0 °C until complete conversion of the starting alkene (approximately 2 h, followed by TLC). Besides, a suspension of K₃PO₄ (1.33 g, 6.26 mmol, 1.50 equiv) and iodide **9** (1.0 g, 4.2 mmol, 1 equiv) in freshly distilled dioxane (12 mL) was degased 30 min by argon bubbling. The solution of borane and Pd(PPh₃)₄ (0.12 g, 0.10 mmol, 2.5 mol%) were then added to the iodide and the reaction mixture was heated 5 h at 85 °C. After cooling to room temperature, the unreacted borane was oxidized by addition of an aqueous solution of sodium acetate (1.2 mL, 3 mol.L⁻¹) and hydrogen peroxide (30%, 1.2 mL). After 1 h of stirring at room temperature, the red solution was diluted with ether (50 mL), washed with a saturated aqueous solution of NH₄Cl (25 mL) and with a saturated aqueous solution of NaCl (2x20 mL). The combined organic extracts were dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (petroleum ether/diethyl ether: 95/05 to 80/20) afforded 1.40 g of alkene **12** (74%) as a colorless oil; IR (film) 1710, 1645, 1425, 1255, 1150, 1110 cm⁻¹; ¹H NMR (CDCl₃) δ 7.74-7.64 (m, 4H), 7.48-7.34 (m, 6H), 5.67 (br s, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.54 (dd, *J* = 9.6 and *J* = 5.7 Hz, 1H), 3.47 (dd, *J* = 9.6 and *J* = 6.3 Hz, 1H), 2.62 (br t, *J* = 7.4 Hz, 2H), 1.88 (d, *J* = 1.5 Hz, 3H), 1.77-1.15 (m, 5H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.09 (s, 9H), 0.96 (d, *J* = 6.6 Hz, 3H); ¹³C RMN (CDCl₃) δ 166.2 (s), 160.3 (s), 135.5 (d, 4C), 134.0 (s, 2C), 129.3 (d, 2C), 127.4 (d, 4C), 116.0 (d), 68.8 (t), 59.2 (t), 35.5 (d), 33.4 (t), 33.0 (t), 26.8 (q, 3C), 25.5 (t), 25.0 (q), 19.2 (s), 16.7 (q), 14.2 (q); MS-EI *m/z* (%): 437 (1), 407 (3), 397 (9), 396 (32), 395 (M-(*t*-Bu)⁺, 100), 349 (8), 245 (8), 227 (17), 199 (34), 183 (14), 181 (11), 123 (12), 95 (11); HRMS (Cl⁺, CH₄) Calcd C₂₈H₄₁O₃Si (M+H⁺): 453.2825. Found: 453.2815.

(2S,3S)-Ethyl 8-(*tert*-butyldiphenylsilanyloxy)-2,3-dihydroxy-3,7-dimethyloctanoate (13**):**

To a stirred mixture of water and *tert*-butanol (1/1, 7 mL) at room temperature was added AD-mix β (0.976 g). Once the two phases were clear, the mixture was cooled at 0 °C and solid methanesulfonamide (67 mg, 0.67 mmol, 1 equiv) was added in one portion. After 20 min at 0 °C, a solution of alkene **12** (0.32 g, 0.71 mmol, 1 equiv) in toluene (1 mL) was added *via* cannula and the reaction mixture was vigorously stirred 30 h at 0 °C. After dilution with EtOAc (3 mL) at 0 °C and addition of solid sodium sulfite (*ca* 1 g), the mixture was stirred 1 h at room temperature. The aqueous layer was then extracted with EtOAc (3×15 mL) and the combined organic extracts were washed with water, dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (petroleum ether/EtOAc : 80/20) afforded 0.222 g of diol **13** (65%) as a colorless oil; $[\alpha]_D^{20} + 6.9$ (*c* 1.10, CHCl₃); IR (film) 3460 (br), 2850, 1730, 1470, 1460, 1425, 1385, 1110, 710, 700 cm⁻¹; ¹H NMR (CDCl₃) rotamers δ 7.71-7.65 (m, 4H), 7.47-7.35 (m, 6H), 4.31 (m, 2H), 4.02 (2d, *J* = 6.6 Hz, 1H), 3.53 (dd, *J* = 9.7 and *J* = 5.7 Hz, 1H), 3.47 (dd, *J* = 9.7 and *J* = 5.7 Hz, 1H), 3.16 (d, *J* = 6.6 Hz, 1H), 2.53 (s, 1H), 1.75-1.26 (m, 7H), 1.34 and 1.33 (2t, *J* = 7.2 Hz, 3H), 1.23 (s, 3H), 1.07 (s, 9H), 0.95 (d, *J* = 7.0 Hz, 3H); ¹³C RMN (CDCl₃) rotamers δ 173.3 (s), 135.5 (d, 4C), 134.0 (s, 2C), 129.4 (d, 2C), 127.4 (d, 4C), 76.2 and 76.1 (d), 73.8 (s), 68.8 (t), 61.9 (t), 38.1 and 38.0 (t), 35.6 and 35.5 (d), 33.5 (t), 26.8 (q, 3C), 22.8 and 22.7 (q), 20.5 (t), 19.2 (s), 16.7 and 16.6 (q), 14.1 (q) ; MS-EI *m/z* (%): 367 (1), 326 (12), 325 (42), 269 (7), 200 (19), 199 (100), 181 (12), 139 (24), 109 (12); Anal Calcd for C₂₈H₄₂O₅Si: C, 69.10 ; H, 8.70. Found: C, 68.79 ; H, 9.01.

Dimethyl 3-[(1S)-1-[(1S)-1-benzyloxy-2-methoxymethoxyethyl]-6-(tert-butyldiphenylsilyloxy)-1,5-dimethylhexyloxy]-2-oxopropylphosphonate (15): To a solution of methyldimethylphosphonate (145 μ L, 1.33 mmol, 10.1 equiv) in anhydrous THF (2 mL) at -78°C was added a solution of *n*-butyllithium in hexanes (530 μ L, 2.5 M, 1.32 mmol, 10 equiv). After 30 min at -78°C , a solution of the ester resulting from the insertion of ethyldiazoacetate on alcohol **14** (88 mg, 0.13 mmol, 1 equiv) in dry THF (1 mL) was added *via* cannula to the solution of phosphonate anion and the mixture was stirred 1 h at -78°C . The reaction mixture was then poured into an aqueous solution of citric acid (5%, 5 mL) and the aqueous layer was extracted with diethyl ether (3 $\times$ 15 mL). The combined organic extracts were dried over MgSO_4 , filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (EtOAc) afforded 55 mg of phosphonate **15** (56%) as a colorless oil; $[\alpha]_{\text{D}}^{20}$ - 2.8 (*c* 1.0, CHCl_3); IR (film) : 1720, 1460, 1425, 1260, 1110, 1030, 740, 710, 700 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.69-7.61 (m, 4H), 7.45-7.22 (m, 11H), 4.87 (d, J = 11.4 Hz, 1H), 4.65 (s, 2H), 4.54 (d, J = 11.4 Hz, 1H), 4.17-3.96 (m, 3H), 3.73 (m, 1H), 3.77 (s, 3H), 3.73 (s, 3H), 3.59 (dd, J = 6.6 and J = 1.8 Hz, 1H), 3.53-3.39 (m, 2H), 3.37 (s, 3H), 3.18 (br d, $J_{\text{H-P}}$ = 22.4 Hz, 2H), 1.77-1.18 (m, 7H), 1.16 (s, 3H), 1.05 (s, 9H), 0.89 (2d, J = 6.6 Hz, 3H); ^{13}C NMR (CDCl_3) δ 200.8 and 200.7 (s), 138.6 (s), 135.5 (d, 4C), 133.9 (s, 2C), 129.4 (d, 2C), 128.1 (d, 2C), 127.5 (d, 2C), 127.4 (d, 4C), 127.3 (d), 96.7 (t), 81.8 and 81.7 (d), 79.6 (s), 73.5 and 73.4 (t), 69.1 (t), 68.9 and 68.8 (t), 68.3 (t), 55.2 (q), 52.9 (q), 52.8 (q), 36.8 (t, $J_{\text{C-P}}$ = 121.6 Hz), 35.9 (t), 35.6 and 35.5 (d), 33.5 (t), 26.8 (q, 3C), 20.4 and 20.3 (t), 19.2 (q), 18.8 (s), 16.6 and 16.5 (q); MS- CI^+ (NH_3) m/z (%): 760 ($\text{M}+\text{NH}_4^+$, 100), 184 (13); HRMS (CI^+ , NH_3) Calcd for ($\text{M}+\text{NH}_4^+$): 760.4010. Found: 760.4017; Anal Calcd for $\text{C}_{40}\text{H}_{59}\text{O}_9\text{SiP}$: C, 64.66 ; H, 8.00. Found: C, 64.30 ; H, 8.22.

(6*R*,7*S*)-6-Benzoyloxy-7-[5-(*tert*-butyldiphenylsilyloxy)-4-methylpentyl]-7-methyl-6,7-dihydrooxepin-3-one (17): To a stirred solution of the alcohol resulting from removal of the methoxymethyl ether protecting group in **15** (50 mg, 72 μ mol, 1 equiv) in dry dichloromethane (2 mL) were added pyridinium dichromate (82 mg, 22 μ mol, 3 equiv) and molecular sieves 4Å (164 mg). After stirring for 2 h at room temperature, the reaction mixture was diluted with ether (20 mL) and stirring was pursued 20 min. The resulting suspension was filtered through a pad of Celite (washed with of 2x20 mL diethyl ether) and filtrate was concentrated *in vacuo* to afford the crude aldehyde which was used in the next step without further purification. A solution of the crude aldehyde in anhydrous THF (20 mL) was then added dropwise *via* cannula to a suspension of sodium hydride (60% dispersion in oil, 29 mg, 0.72 mmol, 10 equiv) in dry THF (15 mL) at 0 °C. After 15 min at 0 °C, the cooling bath was removed and the reaction mixture was stirred 1 h at room temperature. The reaction mixture was then poured into a saturated aqueous solution of NH₄Cl (10 mL) and the aqueous layer was extracted with diethyl ether (3x20 mL). The combined organic extracts were dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 90/10) afforded 19 mg of cyclic enone **17** (46%) as a colorless oil; $[\alpha]_D^{20}$ - 64.0 (*c* 1.0, CHCl₃); IR (film) 1685, 1465, 1455, 1425, 1385, 1375, 1265, 1105, 740, 710, 700 cm⁻¹; ¹H NMR (CDCl₃) δ 7.69-7.63 (m, 4H), 7.45-7.24 (m, 11H), 6.71 (dd, *J* = 12.0 and *J* = 4.0 Hz, 1H), 6.12 (d, *J* = 12.0 Hz, 1H), 4.67 (d, *J* = 11.8 Hz, 1H), 4.41 (d, *J* = 11.8 Hz, 1H), 4.20 (br d, *J* = 18.0 Hz, 1H), 4.07-3.97 (m, 2H), 3.50 (dd, *J* = 10.1 and *J* = 6.1 Hz, 1H), 3.45 (dd, *J* = 10.1 and *J* = 6.8 Hz, 1H), 1.73-1.22 (m, 7H), 1.20 (s, 3H), 1.05 (s, 9H), 0.92 (2d, *J* = 6.6 Hz, 3H); ¹³C NMR (CDCl₃) δ 205.5 (s), 146.3 (d), 137.2 (s), 135.5 (d, 4C), 133.9 (s, 2C), 131.0 (d), 129.4 (d, 2C), 128.3 (d, 2C), 127.8 (d, C), 127.7 (d, 2C), 127.4 (d, 4C), 82.0 (d), 79.3 (s), 72.5 (t), 69.9 (t), 68.7 (t), 37.7 (t), 35.6 and 35.5 (d.), 33.5 (t), 26.8 (q, 3C), 20.6 (t), 19.2 (q), 19.1 (s), 16.8 (q); MS-EI *m/z* (%): 513 (M-(*t*-Bu)⁺, 6), 357 (9), 281 (10), 253 (16), 208 (10), 207 (49), 200 (18), 199 (100), 197 (12), 183 (13), 181 (16), 139 (18), 135 (14), 117 (19), 109 (14), 91 (72); Anal Calcd for C₃₆H₄₆O₄Si: C, 75.75 ; H, 8.12. Found: C, 75.71 ; H, 8.22.

(+)-(2'S,3'R)-Zoapatanol (1): To a solution of phenyl prenyl ether (162 mg, 1.00 mmol, 20 equiv) in a mixture of anhydrous diethyl ether and tetrahydrofuran (1/1, 2 mL,) was added lithium (235 mg, 34 mmol) portionwise. A few drops of anhydrous methanol to clean the surface of lithium were first added. The mixture was then vigorously stirred at room temperature until the solution turned to yellow. The reaction mixture was then cooled to 15 °C and stirring was maintained 2 h at 15 °C. The supernatant solution of organolithium reagent was then added *via* cannula to a solution of the Weinreb amide **22** (25 mg, 49 μmol, 1 equiv) in dry THF (1 mL) at -78 °C. After 10 min at -78 °C (conversion of **22** was monitored by TLC), the reaction mixture was added dropwise to a solution of lithium (108 mg, 15.6 mmol) in ammoniac (*ca* 20 mL) at -78 °C, in the presence of a mixture of *tert*-butanol and tetrahydrofurane (1/4, 0.5 mL). After 5 min at -78 °C, solid NH₄Cl was added portionwise until complete disparition of the dark blue coloration. The reaction mixture was then diluted with diethyl ether (10 mL) and ammoniac was evaporated. Water (10 mL) was further added and the aqueous layer was extracted with diethyl ether (3×15 mL). The combined organic extracts were dried over MgSO₄, filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (EtOAc) and zoapatanol **1** (11 mg, 33 μmol, 66%) was isolated as a colorless oil. Physical and spectral data match those previously reported;^{1,2} *R*_f 0.6 (EtOAc); [α]_D²⁰ + 4.16 (*c* 0.31, CHCl₃) {lit.² [α]_D²⁰ + 12.00 (*c* 0.31, CHCl₃)}; IR (film) 3390 (br), 1707, 1450, 1375, 1100, 1060, 1025, 740 cm⁻¹; ¹H NMR (CDCl₃) δ 5.47 (br t, *J* = 7.0 Hz, 1H), 5.30 (br t, *J* = 7.0 Hz, 1H), 4.20 (d, *J* = 7.0 Hz, 2H), 4.13 (br s, 2H), 3.55 (m, 1H), 3.16 (d, *J* = 7.0 Hz, 2H), 2.59 (q, *J* = 7.0 Hz, 1H), 2.48 (m, 1H), 2.23 (m, 1H), 1.73 (br s, 3H), 1.63 (apparent s, 3H), 1.85-1.20 (m, 10H), 1.16 and 1.15 (2s, 2×1.5H), 1.09 (d, *J* = 7.0 Hz, 3H); ¹³C RMN (CDCl₃) δ 213.1 (s), 143.3 (s), 135.4 (s), 123.1 (d), 115.9 (d), 79.7 (s), 76.3 and 76.1 (d), 69.1 (t), 58.6 (t), 45.7 (d), 40.8 and 40.7 (t), 38.0

¹ (a) Kanojia, R. M.; Wachter, M. P.; Levine, S. D.; Adams, R. E.; Chen, R.; Chin, E.; Cotter, M. L.; Hirsch, A. F.; Huettelman, R.; Kane, V. V.; Ostrowski, P.; Shaw, C. J. *J. Org. Chem.* **1982**, *47*, 1310-1319; (b) Nicolaou, K. C.; Claremon, D. E.; Barnett, W. E. *J. Am. Chem. Soc.* **1980**, *102*, 6611-6612; (c) Kocienski, P. J.; Love, C. J.; Whitby, R. J. *Tetrahedron* **1989**, *45*, 3839-3848.

² Trost, B. M.; Greenspan, P. D.; Geissler, H.; Kim, J. H.; Greeves, N. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2182-2184.

and 37.9 (t), 33.3 (t), 31.5 (t), 25.6 (q), 23.3 and 23.2 (t), 20.9 and 20.8 (t), 18.3 (q), 18.0 (q), 16.5 (q); MS- CI^+ (NH_3) m/z (%): 356 ($\text{M}+\text{NH}_4^+$, 100), 341 (8), 321 (9), 274 (7), 228 (10), 124 (7); HRMS (CI^+ , NH_3) Calcd for $\text{C}_{20}\text{H}_{34}\text{O}_4\text{N}$ ($\text{M}+\text{NH}_4^+$): 356.2801. Found: 356.2806.

Comparison with the literature data reported for **1** (Nicolaou et al. *J. Am. Chem. Soc.* **1980**, *102*, 6611-6612)

Observed data for 1	Literature data reported for 1
¹ H NMR (300 MHz, CDCl ₃) δ	¹ H NMR (500 MHz, CDCl ₃) δ
5.47 (br t, $J = 7.0$ Hz, 1H)	5.47 (t, $J = 7.0$ Hz, 1H)
5.30 (br t, $J = 7.0$ Hz, 1H)	5.31 (t, $J = 7.0$ Hz, 1H)
4.20 (d, $J = 7.0$ Hz, 2H)	4.20 (d, $J = 7.0$ Hz, 2H)
4.13 (br s, 2H)	4.13 (s, 2H)
3.55 (m, 1H)	3.55 (dd, $J = 8.4$ Hz, 1H)
3.16 (d, $J = 7.0$ Hz, 2H)	3.16 (d, $J = 7.0$ Hz, 2H)
2.59 (q, $J = 7.0$ Hz, 1H)	2.67-2.15 (m, 3H)
2.48 (m, 1H)	1.77 (s, 3H)
2.23 (m, 1H)	1.65 (s, 3H)
1.73 (br s, 3H)	1.90-1.00 (m, 10H)
1.63 (apparent s, 3H)	1.17 and 1.16 (2s, 2×1.5H)
1.85-1.20 (m, 10H)	0.99 (d, $J = 7.0$ Hz, 3H)
1.16 and 1.15 (2s, 2×1.5H)	
1.09 (d, $J = 7.0$ Hz, 3H)	

Copies of the ¹H and ¹³C NMR spectra of zoapatanol **1**:

(+)-(2'S,3'R)-zoapatanol **1**