A Concise Enantioselective Synthesis of a Key A-Ring Synthon for 1α-Hydroxyvitamin D$_3$ Compounds

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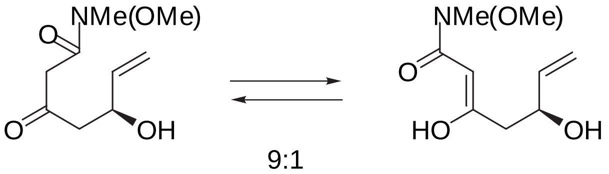
Supporting Information

General Procedure. Where appropriate, reactions were performed in flame-dried glassware under an argon atmosphere. All extracts were dried over $MgSO_4$ and concentrated by rotary evaporation below 30 °C at ca. 25 Torr. Analytical and preparative thin-layer chromatography were performed with Merck F-254 TLC plates. Column chromatography was performed employing silica gel 60 (230-400 mesh ASTM, Merk).

Materials. Commercial reagents and solvents were used as supplied with the following exceptions. Tetrahydrofuran (THF) and ether (Et_2O) were distilled from sodium benzophenone ketyl. Dichloromethane (CH_2Cl_2), triethylamine (Et_3N), and *N*,*N*-dimethyformamide (DMF) were distilled from calcium hydride. 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine was purified by kugelrohr distillation after washing with 10% NaOH just prior to use.

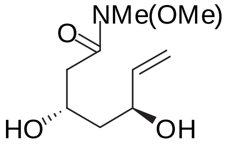
Instrumentation. Infrared spectra were measured on a JASCO FT/IR-230 spectrometer. Optical rotations were recorded on a JASCO DIP-370 polarimeter at ambient temperature. ^{1}H and ^{13}C NMR spectra were measured on a Varian Gemini 300 or a Varian Unity plus 500 spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) in δ units and coupling constants are given in hertz. TMS was defined as 0 ppm for ^{1}H NMR spectra and the center line of the triplet of $CDCl_3$ was also defined as 77.10 ppm for ^{13}C NMR spectra. High resolution Mass spectra were measured on a JEOL JMS-DX303.

(5*S*)-*N*-Methoxy-*N*-methyl-5-hydroxy-3-oxo-6-heptenamide (10).



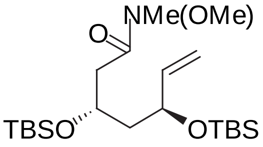
To an ice-cooled solution of N,O-dimethylhydroxylamine hydeochloride (737mg, 7.56mmol) in CH_2Cl_2 (10 ml) was added Me_2AlCl (0.98 M in hexane, 7.7 ml, 7.56 mmol) and the mixture was stirred for 1 h after removal of the cooling bath. To the resulting mixture was added a solution of **9** (97% ee)[1] (500mg, 2.52mmol) in CH_2Cl_2 (15ml). After being stirred at room temperature for 18 h, the reaction mixture was quenched with water and extracted with $CHCl_3$. The extract was washed with brine, dried, and concentrated. The residue was purified by silica gel column chromatography (hexane:EtOAc = 2:1) to give **10** (390 mg, 77%) as a colorless oil: $[\alpha]_D^{24}$ –18.8° (*c* 1.01, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.40 (dd, *J* = 7.8, 14.1 Hz, 0.1H), 2.49 (dd, *J* = 4.5, 14.1 Hz, 0.1H), 2.75 (dd, *J* = 3.3, 12.3 Hz, 0.9H), 2.81 (d, *J* = 12.3 Hz, 0.9H), 2.97 (br s, 1H), 3.21 (s, 0.3H), 3.22 (s, 2.7H), 3.62 (s, 1.8H), 3.69 (s, 3H), 4.53 (br q, 0.1H), 4.62 (br q, *J* = 5.7 Hz, 0.9H), 5.15 (dt, *J* = 1.5, 10.5 Hz, 0.9H), 5.16 (dt, *J* = 1.5, 10.5 Hz, 0.1H), 5.31 (dt, *J* = 1.5, 17.4 Hz, 0.9H), 5.33 (dt, *J* = 1.5, 17.1 Hz, 0.1H), 5.47 (br s, 0.1H), 5.87 (ddd, *J* = 5.4, 10.5, 17.4 Hz, 0.9H), 5.91 (ddd, *J* = 5.7, 10.5, 17.1 Hz, 0.1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.1 (minor), 43.4 (minor), 48.4, 49.5, 61.5, 68.6, 70.3 (minor), 88.3, 115.1, 139.0, 139.6 (minor), 167.8, 203.8; FT-IR (neat) 3417, 1718, 1641, 1429, 1390 cm^{-1}; HRMS (EI) calcd for $C_9H_{15}NO_4$ (M^+): 201.1001, found: 201.0988.

(3*S*,5*S*)-*N*-Methoxy-*N*-methyl-3,5-dihydroxy-6-heptenamide (11).



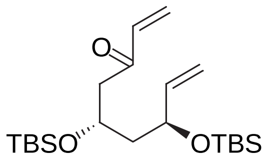
A mixture of $Me_4NBH(OAc)_3$ (2.54 g, 9.66 mmol) in acetone-AcOH (1:1 mixture, 10 ml) was stirred at room temperature for 30 min. The resulting mixture was cooled to –40 °C and a solution of **10** (160 mg, 0.80 mmol) in acetone (5 ml) was added. After being stirred at –40 °C for 34 h, the reaction mixture was quenched by the addition of 20% potassium sodium tartrate and saturated $NaHCO_3$ and extracted with $CHCl_3$. The extract was washed with brine, dried, and concentrated. The residue was purified by silica gel column chromatography (hexane:EtOAc = 1:1) to give **11** (143 mg, 88%) as a colorless oil: $[\alpha]_D^{27}$ +39.2° (*c* 1.37, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$)) δ 1.64 (ddd, *J* = 3.0, 7.8, 14.1 Hz, 1H), 1.82 (ddd, *J* = 3.3, 9.3, 14.1 Hz, 1H), 2.57 (dd, *J* = 9.0, 17.1 Hz, 1H), 2.65 (br d, *J* = 17.1 Hz, 1H), 3.19 (s, 3H), 3.68 (s, 3H), 4.20 (br s, 1H), 4.37 (br t, *J* = 9.3 Hz, 1H), 4.46 (br s, 1H), 5.13 (dt, *J* = 1.5, 10.2 Hz, 1H), 5.31 (dt, *J* = 1.5, 17.0 Hz, 1H), 5.93 (ddd, *J* = 5.1, 10.2, 17.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.9, 38.2, 42.1, 61.3, 65.6, 70.0, 114.2, 140.8, (C=O was not detected); FT-IR (neat) 3365, 1630, 1423, 1390, 1063 cm^{-1}.

(3*S*,5*S*)-*N*-Methoxy-*N*-methyl-3,5-di[(*tert*-butyldimethylsilyl)oxy]-6-heptenamide (12).



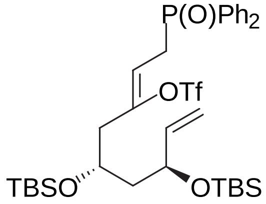
A solution of **11** (63 mg, 0.30 mmol), *tert*-butyldimethylsilyl chloride (310 mg, 2.06 mmol), and imidazole (130 mg, 1.91 mmol) in DMF (5 ml) was stirred at room temperature for 10 h. The reaction mixture was diluted with Et_2O, washed with water and brine, dried, and concentrated. The residue was purified by silica gel column chromatography (hexane:EtOAc = 20:1) to give **12** (117 mg, 87%) as a colorless oil; $[\alpha]_D^{24}$ +21.1° (*c* 1.01, $CHCl_3$); ^{1}H NMR (300MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.04 (s, 3H), 0.07 (s, 3H), 0.08 (s, 3H), 0.86 (s, 9H), 0.89 (s, 9H), 1.64-1.85 (m, 2H), 1.69 (dt, *J* = 13.8, 5.1 Hz, 1H), 1.80 (dt, *J* = 13.8, 6.6 Hz, 1H), 2.44 (dd, *J* = 4.8, 14.7 Hz, 1H), 2.77 (br dd, *J* = 7.8, 14.7 Hz, 1H), 3.17 (s, 3H), 3.69 (s, 3H), 4.18 (q, *J* = 6.6 Hz, 1H), 4.27-4.35 (m, 1H), 5.05 (ddd, *J* = 0.9, 1.8, 10.2 Hz), 5.25 (dt, *J* = 1.2, 17.1 Hz, 1H), 5.83 (ddd, *J* = 6.9, 10.2, 17.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –4.53, –4.41, –4.36, –3.85, 18.1, 18.3, 25.9, 26.0, 32.1, 40.6, 47.0, 61.3, (66.9), 67.2, 71.9, 114.4, 141.9; FT-IR (neat) 1668, 1466,1254, 1084 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{45}NO_4Si_2$ (M^+): 431.2887, found: 431.2934.

(5*S*,7*S*)-5,7-Di[(*tert*-butyldimethylsilyl)oxy]nona-1,8-diene-3-one (4).



To an ice-cooled solution of **12** (230 mg, 0.53 mmol) in THF (5 ml) was added vinylmagnesium bromide (1.12 M in THF, 1.5 ml, 1.68 mmol). After being stirred at 0 °C for 7h, the reaction mixture was quenched with saturated NH_4Cl and extracted with $CHCl_3$. The extract was washed with brine, dried over, and concentrated. The residue was purified by silica gel column chromatography (hexane:EtOAc = 100:1) to give **4** (206 mg, 98%) as a colorless oil; $[\alpha]_D^{23}$ +20.4° (*c* 1.19, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.00 (s, 3H), 0.03 (s, 3H), 0.06 (s, 3H), 0.07 (s, 3H), 0.84 (s, 9H), 0.88 (s, 9H), 1.68 (ddd, *J* = 14.0, 6.0, 5.5, Hz, 1H), 1.75 (dt, *J* = 14.0, 6.5, Hz, 1H), 2.68 (dd, *J* = 4.5, 14.5 Hz, 1H), 2.82 (dd, *J* = 7.5, 14.5 Hz, 1H), 4.18 (q, *J* = 6.5 Hz, 1H), 4.30 (tt, *J* = 5.0, 7.5 Hz, 1H), 5.05 (ddd, *J* = 1.0, 1.5, 10.5 Hz, 1H), 5.15 (dt, *J* = 1.5, 17.0 Hz, 1H), 5.81 (ddd, *J* = 7.0, 10.5, 17.0 Hz, 1H), 5.82 (dd, J= 1.0, 10.5 Hz, 1H), 6.19 (dd, *J* = 1.0, 17.5 Hz, 1H), 6.35 (dd, *J* = 10.5, 17.5 Hz, 1H); ^{13}C NMR (75MHz, $CDCl_3$) δ -4.6, -4.4, -4.3, –3.9, 18.1, 18.3, 25.9, 26.0, 46.8, 48.0, 67.0, 71.8, 114.5, 128.3, 137.5, 141.8, 199.4; FT-IR (neat) 1687, 1468, 1403, 1254, 1082 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{39}O_3Si_2$ (M^+–CH_3) 383.2438, found 383.2437.

(*Z*,5*S*,7*S*)-[5,7-Di[(*tert*-butyldimethylsilyl)oxy]-3-[(trifluoromethanesulfonyl)oxy]nona-2,8-dienyl]diphenylphosphine Oxide (7).



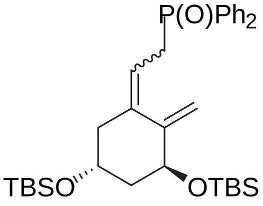
To an ice-cooled solution of $Ph_2P(O)H$ (88 mg, 0.436 mmol) in THF (1.3 ml) was added *n*-BuLi (1.59 M in hexane, 0.27 ml, 0.429 mmol) and the mixture was stirred at 0 °C for 1 h. The mixture was cooled to –78 °C and a solution of **4** (144 mg, 0.362 mmol) in THF (2 ml) was added. The resulting mixture was stirred at –78 °C for 30 min and a solution of 2-[*N,N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine[2] (227 mg, 0.578 mmol) in THF (1.7 ml) was added. After being stirred at –78 °C for 20 h, the reaction mixture was diluted with Et_2O, washed with water and brine, dried over, and concentrated. The residue was purified by silica gel column chromatography (hexane:EtOAc = 2:1) to give **7** (236 mg, 89%) and **13** (16 mg, 7%) each as a colorless oil.

Enol triflate **7**: $[\alpha]_D^{24}$ +13.7° (*c* 1.44, $CHCl_3$); ^{1}H NMR (500 MHz, CDCl3) δ –0.02 (s, 3H), 0.02 (s, 3H), 0.03 (s, 6H), 0.83 (s, 9H), 0.87 (s, 9H), 1.40 (ddd, *J* = 14.0, 6.9, 4.8 Hz, 1H), 1.47 (ddd, *J* = 14.0, 7.5, 5.0 Hz, 1H), 2.45 (dd, *J* = 14.0, 6.6 Hz, 1H), 2.50 (dd, *J* = 14.0, 5.3 Hz, 1H), 3.14 (dt, *J* = 15.5, 6.0 Hz, 1H), 3.33 (ddd, *J* = 5.5, 11.7, 8.9 Hz, 1H), 3.98 (quint, *J* = 6.4 Hz, 1H), 4.12 (dt, *J* = 7.5, 5.0 Hz, 1H), 5.01 (ddd, *J* = 11.0, 1.6, 0.7 Hz, 1H), 5.08 (dt, *J* = 17.0, 1.6 Hz, 1H), 5.61-5.68 (m, 2H), 7.46-7.56 (m, 2H), 7.71-7.76 (m, 4H); ^{13}C NMR (75 MHz, CDCl3) δ –4.7, –4.3, –4.1, –3.6, 18.0, 18.2, 25.9, 28.5 29.4, 42.4, 45.6, 66.2, 71.4, 113.6, 113.7, 114.7, 128.8, 129.0, 130.8, 130.9, 131.0, 132.3, 141.7, 148.8; FT-IR (neat) 1410, 1252, 1211, 1134, 1090 cm-1; HRMS (EI) calcd for $C_{30}H_{43}F_3O_6PSSi_2$ (M^+–C_4H_9) 675.2009, found 675.2021.

Ketone **13**: $[\alpha]_D^{24}$ +12.6° (*c* 1.11, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ –0.08 (s, 3H), 0.00

(s, 3H), 0.01 (s, 3H), 0.03 (s, 3H), 0.77 (s, 9H), 0.85 (s, 9H), 1.54-1.71 (m, 2H), 2.40-2.86 (m, 6H), 4.09 (q, *J* = 6.6 Hz, 1H), 4.18 (tt, *J* = 6.9, 5.1 Hz, 1H), 5.02 (d, *J* = 10.2 Hz, 1H), 5.09 (dt, *J* = 17.1, 1.2 Hz, 1H), 5.74 (ddd, *J* = 17.1, 10.2, 6.6 Hz, 1H), 7.41-7.54 (m, 6H), 7.68-7.76 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –4.6, –4.5, –4.3, –3.9, 17.9, 18.2, 22.7, 23.7, 25.8, 25.9, 36.1, 36.2, 46.4, 50.7, 66.8, 71.7, 114.6, 128.8, 128.9, 130.7, 130.9, 131.9, 132.0, 141.5, 206.9, 207.1; FT-IR (neat) 1716, 1468, 1437, 1409, 1254, 1188, 1074 cm^{-1}; HRMS (EI) calcd for $C_{32}H_{50}O_4PSi_2$ ($M^+–CH_3$) 585.2985, found 585.3044.

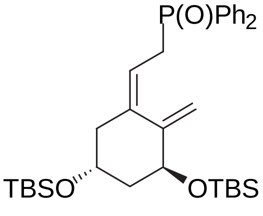
Palladium-Catalyzed Cyclization of Enol Triflate 7.



Z/*E* = 86/14

A solution of **7** (288 mg, 0.393 mmol) in THF (8 ml) was degassed thoroughly by three times repetition of filling up with argon after suction. To this solution were added Ph_3P (10 mg, 0.038 mmol), Et_3N (66 µl, 0.474 mmol), and $Pd(OAc)_2$ (9 mg, 0.039 mmol) and the mixture was stirred at room temperature for 6.5 h. The reaction mixture was diluted with Et_2O, filtered through Celite, and concentrated. The residue was purified by silica gel column chromatography (hexane:EtOAc = 2:1) to give a 86:14 mixture of **2** and its *E*-isomer (215 mg, 94 %); ^{1}H NMR (300 MHz, $CDCl_3$) δ –0.05 (s, 3H), –0.01 (s, 3H), 0.01 (s, 3H), 0.03 (s, 3H), 0.80 (s, 9H), 0.87 (s, 9H), 1.64-1.77 (m, 1H), 1.82-1.90 (m, 1H), 2.15 (br d, *J* = 11.7 Hz, 1H), 2.32 (br d, *J* = 12.9 Hz, 1H), 3.14 (dt, *J* = 6.9, 15.0 Hz, 1H), 3.38 (dt, *J* = 8.7, 15.0 Hz, 1H), 4.11 (m, 1H), 4.35 (m, 1H), 4.73 (s, 1H), 4.79 (s, 0.14H), 5.14 (s, 0.86H), 5.33 (dt, *J* = 8.0, 6.9 Hz, 0.86H), 5.54 (dt, *J* = 9.0, 6.6 Hz, 0.14H), 7.38-7.53 (m, 6H), 7.65-7.76 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –4.9, –4.8, –4.7, 18.1, 18.3, 25.8, (30.5), 30.9, (31.4), 31.8, (37.1), (43.9), 44.8, 45.6, (66.7), 67.5, (70.6), 70.9, (108.6), 110.3, (114.8), (114.9), 115.1, 115.2, 128.5, 128.7, 131.0, 131.1, 131.2, 131.8, (132.1), 132.4, 133.4, (133.7), 141.0, 141.1, 147.8, peaks in parentheses are attributed to the *E*-isomer; FT-IR (neat) 1469, 1254, 1084 cm^{-1}; HRMS (EI) calcd for $C_{33}H_{51}O_3PSi_2$ (M^+) 582.3114, found 582.3083.

(Z,3S,5R)-2-[[3,5-Di(*tert*-butyldimethylsilyl)oxy-2-methylenecyclohexylidene]ethyl]diphenylphosphine oxide (2).



A solution of the above-mentioned Z/E-mixture (97 mg, 0.167 mmol) and 9-fluorenone (3.1 mg, 0.017 mol) in *t*-BuOMe (6.6 ml) was irradiated with a medium pressure mercury arc lamp for 3 h. The reaction mixture was concentrated and chromatographed (hexane:EtOAc = 2:1) to give **2** (92 mg, 95 %); $[\alpha]_D^{24}$ –2.9° (*c* 1.43, $CHCl_3$), $[\alpha]_D^{24}$ –2.6°(*c* 1.21,EtOH) [lit.[3] $[\alpha]_D^{25}$ –2.3°(*c* 0.5, EtOH)]; ^{1}H NMR (500 MHz, $CDCl_3$) δ –0.03 (s, 3H), 0.01 (s, 3H), 0.03 (s, 3H), 0.05 (s, 3H), 0.82 (s, 9H), 0.89 (s, 9H), 1.71 (ddd, *J* = 2.5, 8.5, 9.5 Hz, 1H), 1.84-1.89 (m, 1H), 2.17 (dd, *J* = 5.0, 13.3, 1H), 2.33 (d, *J* = 13.3 Hz, 1H), 3.16 (dt, *J* = 6.6, 15.3 Hz, 1H), 3.39 (dt, *J* = 8.7, 15.3 Hz, 1H), 4.12

(quint. *J* = 2.5 Hz, 1H), 4.36 (q, *J* = 4.1 Hz, 1H), 4.74 (dd, *J* = 1.6, 2.0 Hz, 1H), 5.15 (dd, *J* = 1.8, 2.0 Hz, 1H), 5.34 (dt, *J* = 8.0, 6.9, Hz, 1H), 7.43-7.47 (m, 4H), 7.49-7.53 (m, 2H), 7.69-7.74 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –4.9, –4.8, –4.7, 18.2, 18.3, 25.9, 31.0, 31.9, 44.9, 45.6, 67.5, 70.9, 110.3, 115.1, 115.2, 128.5, 128.7, 131.1, 131.2, 131.8, 132.5, 133.5, 141.0, 141.1, 147.8; FT-IR (neat) 1467, 1253, 1201, 1083 cm^{-1}; HRMS (EI) calcd for $C_{33}H_{51}O_3PSi_2$ (M^+) 582.3114, found 582.3098.

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