Efficient Syntheses of 3-Hetero-13,14-dihydro Prostaglandin $F_{1\alpha}$ Analogues

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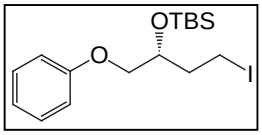
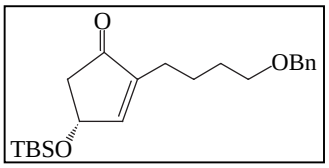
Supporting Information



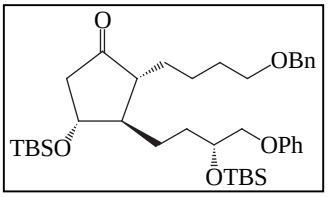
(*R*)-2-(*tert*-Butyldimethylsilyloxy)-4-iodo-1-phenoxybutane [(+)-3]: To a mixture of (Salen)Co[$OC(CF_3)_3$] catalyst (215 mg, 0.25 mmol) and molecular seives 4Å (250 mg) was added epoxide **4** (1.89 g, 12.5 mmol) and phenol (536 mg, 5.7 mmol) followed by *tert*-butyl methyl ether (0.5 mL) at -20 °C. After the mixture was stirred for 16 h at -20 °C , the resulting deep-colored semi-solid was dissolved in 3:1 hexane/ether and the mixture was filtered through a pad of silica gel and washed with 3:1 hexane/ether. The filtrate was concentrated and purified by chromatography on silica gel with 3:1 hexane/ether as eluent to give **5** (1.39 g, 99%) as a white solid. A sample recrystallized from hexane at -20 °C provided colorless needles: mp 40-41 °C, $[\alpha]_D^{23}$ = 8.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.33-7.26 (m, 2H), 7.02-6.90 (m, 3H), 4.28-4.20 (m, 1H), 4.03-3.99 (dd, J = 3.9, 9.0 Hz, 1H), 3.92-3.86 (dd, J = 6.6-9.0 Hz, 1H), 3.69-3.56 (m, 2H), 2.47 (bs, 1H), 2.22-2.01 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 158.28, 129.52, 121.25, 114.46, 71.49, 68.03, 35.90, 29.77; HRMS (EI) calcd. For $C_{10}H_{13}BrO_2$: (M+) 244.0099, found: 244.0098

A solution of **5** (2.0 g, 8.2 mmol) in dry DMF (40 mL) was treated with imidazole (1.0 g, 14.7 mmol) and TBSCl (2.0 g, 13.3 mmol) at 0 °C. The mixture was warmed to rt and stirred for 48 h at room temperature. The mixture was poured into water and extracted with hexane-ether (5:1). The organic layers were washed with brine and dried with $MgSO_4$. After concentration, without purification, the resulted crude product was dissolved in acetone (40 mL), NaI (8 g) was added, and the mixture was refluxed overnight under Ar. After acetone was removed under reduced pressure, the residue was

dissolved in water and extracted with hexane. The combined organic layers were washed with water, 10% Na_2SO_3, brine and dried over $MgSO_4$. Filtration and concentration gave a light yellow oil; purification by flash chromatography (20:1 hexane/ether) gave 3.21 g (97%) of **3** as a low melting point white solid: mp 28 °C, $[\alpha]_D^{23}$ = 19.3 (*c* 1.16, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.31-7.26 (m, 2H), 6.98-6.87 (m, 3H), 4.14-4.09 (m, 1H), 3.92-3.80 (m, 2H), 3.38-3.23 (m, 2H), 2.22-2.01 (m, 2H), 0.90 (s, 9H), 0.17 (s, 3H), 0.12 (s, 3H); ^{13} C NMR ($CDCl_3$): δ 158.54, 129.48, 120.88, 114.35, 71.39, 70.86, 38.57, 25.87, 18.14, 2.50, -4.22, -4.60; HRMS (EI) calcd. for $C_{16}H_{27}IO_2Si$: (M-C_4H_9) 349.0121, found: 349.0115.

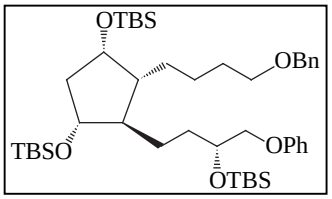


(4*R*)-2-[4-(Benzyloxy)butyl]-4-(*tert*-butyldimethylsilyloxy) -2-cyclopenten-1-one (7): A solution of benzyl 3-butenyl ether (1.62 g, 10 mmol) in dry THF (8 mL) was cooled to 0 °C and 9-BBN (20 mL of a 0.5 M solution in THF, 10 mmol) was added dropwise. The reaction mixture was allowed to warm to rt and stirred for a total of 4 h. In a separate flask, was placed α-iodoenone **6** (2.26 g, 6.7 mmol), $PdCl_2$(dppf) (328 mg, 0.4 mmol) and DMF (20 mL). To this stirred solution was then quickly added the above THF solution of borane followed immediately by 3 M aqueous K_3PO_4 (4.5 mL, 13.4 mmol). Vigorous stirring was continued at rt for 30 min. The mixture was poured into a separatory funnel containing 100 mL of water, extracted with Et_2O, the combined organic layers were washed with H_2O, brine, and dried over $MgSO_4$. Concentration and Purification by column chromatography (10:1, hexane:EtOAc) gave **7** (1.75g, 70%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.35-7.25 (m, 5H), 7.05-7.04 (m, 1H), 4.89-4.86 (m, 1H), 4.49 (s, 2H), 3.49-3.47 (t, J = 6 Hz, 2H), 2.75-2.70 (dd, J = 6.5, 17.5 Hz, 1H), 2.28-2.24 (dd, J = 2.5, 18.5 Hz, 1H), 2.21-2.17 (m, 2H), 1.66-1.57 (m, 4H), 0.91 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H); ^{13} C NMR ($CDCl_3$) δ 206.12, 156.72, 146.83, 138.47, 128.28, 127.54, 127.44, 72.83, 69.87, 68.91, 45.42, 29.40, 25.74, 24.17, 23.99, 18.07, -4.74; HRMS (EI) calcd. For $C_{22}H_{34}O_3Si$: (M^+) 374.2277, (M- C_4H_9)$^+$ 317.1573, found: 317.1571



2-[4-(Benzyloxy)butyl]-4-(*tert*-butyldimethylsilyloxy)-3-[3-(*tert*-butyldimethylsilyloxy)-4-phenoxybutyl]-cyclopentan-1-one (8): A solution of iodide **3** (1.42 g, 3.5

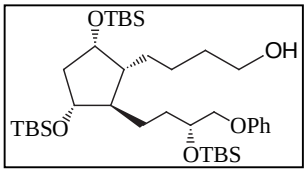
mmol) in Et_2O (30 mL) at -78 °C was treated with *tert*-BuLi (4.3 mL, 1.7 M in pentane, 7.35 mmol, 2.1 equiv.). After completion of the addition, the mixture was stirred 10 min. at -78 °C, then freshly prepared (2-thienyl)Cu(CN)Li (12 mL, 0.25M in THF, 3 mmol) was added dropwise. The mixture was slowly warmed to -40 °C during a period of 30 min, then was re-cooled to -78 °C. To this mixture was added dropwise a solution of enone **7** (1.0 g, 2.7 mmol) in Et_2O (15 mL). After completion of the addition, the flask was immediately brought to a -45 °C cooling bath, and then warmed to -20 °C over 20-30 min. Saturated NH_4Cl was added and the mixture was extracted with Et_2O. The organic layers were washed with water, brine and dried over $MgSO_4$, Concentration and purification by flash chromatography (5:1 hexane/ether with Et_3N) gave **8** (1.45 g, 83%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.34-7.25 (m, 7H), 6.97-6.86 (m, 3H), 4.49 (s, 2H), 4.10-3.99 (m, 2H), 3.89-3.77 (m, 2H), 3.48-3.44 (t, J = 6 Hz, 2H), 2.61-2.53 (dd, J = 6.3, 18.3 Hz, 1H), 2.21-2.13 (dd, J = 6.3, 18.3 Hz, 1H), 1.96-1.81 (m, 2H), 1.71-1.34 (m, 10H), 0.90 (s, 9H), 0.88 (s, 9H), 0.11 (s, 3H), 0.1 (s, 3H), 0.09 (s, 3H), 0.05 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 217.86, 158.66, 138.57, 129.44, 128.33, 127.60, 127.46, 120.71, 114.29. 73.08, 72.85, 71.60, 70.99, 70.15, 53.22, 49.42, 47.59, 31.91, 29.91, 29.27, 27.52, 25.87, 25.72, 23.73, 18.14, 17.86, -4.22, -4.48, -4.70, -4.81; HRMS (EI) calcd. For $C_{38}H_{62}O_5Si_2$: 654.4136, (M^+-C_4H_9) 597.3431, found: 597.3435.



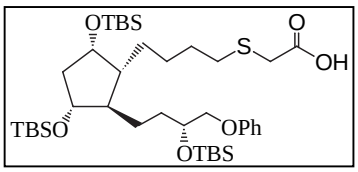
2-[4-(Benzyloxy)butyl]-1,4-bis(*tert*-butyldimethylsilyloxy)-3-[3-(*tert*-butyldimethylsilyloxy)-4-phenoxybutyl]-cyclopentane (2): A solution of **8** (2.40 g, 3.67 mmol) in THF (40 mL) at -78 °C was treated with L-Selectride (7.35 mL, 1 M solution in THF, 7.35 mmol, 2 equiv.). After the mixture was stirred at -78 °C for 4 h, the reaction was quenched with H_2O. H_2O_2 (1.8 mL, 30% in H_2O, 16 mmol) was added and the mixture was stirred for 30 min at 0 °C. The mixture was extracted with Et_2O. The combined organic layers were washed with H_2O, brine, and dried ($MgSO_4$). Filtration and concentration gave a light yellow oil.

The crude product was dissolved in anhydrous DMF (50 mL) and was treated with imidazole (496 mg, 7.3 mmol) and TBSCl (1.054 g, 7.0 mmol) at 0 °C. The mixture was allowed to warm to room temperature and was stirred for 36 h. Routine work up and purification on silica gel column (20:1, hexane:EtOAc) gave **2** (2.43 g, 86%) as a colorless oil. $[\alpha]_D$ = 11.1 (*c* 3.2, $CHCl_3$), ^{1}H NMR ($CDCl_3$): δ 7.35-7.25 (m, 7H), 6.96-

6.86 (m, 3H), 4.50 (s, 2H), 4.08-4.03 (m, 1H), 4.01-3.95 (m, 1H), 3.86-3.74 (m, 3H), 3.49-3.44 (m, 2H), 2.16-2.07 (m, 1H), 1.77-1.21 (m, 13H), 0.9 (s, 9H), 0.88 (s, 9H), 0.87 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H), 0.04 (s, 6H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 158.50, 138.66, 129.36, 128.29, 127.54, 127.39, 120.49, 114.28, 76.80, 72.80, 71.94, 71.62, 71.39, 70.58, 49.77, 47.91, 44.50, 31.63, 30.21, 27.21, 26.65, 25.93, 25.86, 25.83, 24.48, 18.18, 18.00, 17.85, -4.07, -4.19, -4.23, -4.68, -4.79, -5.10; HRMS calcd. For $C_{44}H_{78}O_5Si_3$: (M^+) 770.5157, ($M-C_4H_9$) 713.4453, found: 713.4455.

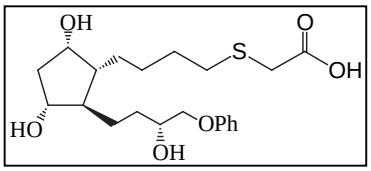


4-{3,5-Bis(*tert*-butyldimethylsilyloxy)-2-[3-(*tert*-butyldimethylsilyloxy)-4-phenoxybutyl]cyclopentyl}-1-butanol (9): A mixture of **2** (1.8 g, 2.34 mmol) and 5% Pd/C (400 mg) in EtOAc (80 mL) was stirred under a hydrogen atmosphere until the reaction was completed as ascertained by TLC (about 2 days). The suspension was filtered through a pad of Celite. Concentration and purification by column chromatography (5:1, hexane:EtOAc) gave 1.41 g (89%) of **9** as a colorless oil. $[\alpha]_D^{23}$ = 11.0 (*c* 1.4, $CHCl_3$), ^{1}H NMR ($CDCl_3$): δ 7.30-7.25 (m, 2H), 6.96-6.86 (m, 3H), 4.08-4.04 (m, 1H), 4.01-3.95 (m, 1H), 3.84-3.74 (m, 3H), 3.65-3.60 (t, J = 6 Hz, 2H), 2.16-2.07 (m, 1H), 1.79-1.21 (m, 13H); ^{13}C NMR ($CDCl_3$): δ 158.79, 129.38, 120.52, 114.28, 76.71, 71.89, 71.61, 71.38, 63.12, 49.77, 47.86, 44.48, 33.30, 31.57, 27.18, 26..55, 25.91, 25.86, 25.82, 24.06, 18.20, 18.01, 17.86, -4.07, -4.18, -4.23, -4.68, -4.78, -5.08; HRMS (EI) calcd. for $C_{37}H_{72}O_5Si_3$: (M^+) 680.4688, $(M-C_4H_9)^+$ 623.3983, found: 623.3984.

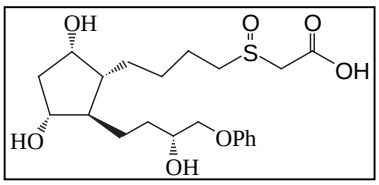


{4-[3,5-Bis(*tert*-butyldimethylsilyloxy)-2-[3-(*tert*-butyldimethylsilyloxy)-4-phenoxybutyl]cyclopentyl]-butylthio}acetic acid (10): A solution of **9** (168 mg, 0.25 mmol) and Et_3N (0.08 mL, 0.57 mmol) at 0 °C was treated with MsCl (0.04 mL, 0.5 mmol). After 1 h at 0 °C, the solution was poured into water and extracted with Et_2O. The ether layers were washed with brine and dried over $MgSO_4$. Concentration gave crude mesylate which was used without purification.

Thioglycolic acid (74 mg, 0.8 mmol) was added dropwise to a mixture of NaH (60 mg, 60% in oil, 1.5 mmol) in DMSO (1.5 mL) at rt. After 30 min, crude mesylate in DMSO (1.5 mL) was added. After 2.5 h, the solution was poured into water and the pH was adjusted to about 3 with aqueous HCl (0.5N). The mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over $MgSO_4$. Concentration and purification by column chromatography (20:1, CH_2Cl_2:MeOH) gave 146 mg (80%) of **10** as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.31-7.25 (m, 2H), 6.96-6.87 (m, 3H), 4.08-3.98 (m, 2H), 3.88-3.75 (m, 3H), 3.22 (s, 2H), 2.68-2.63 (t, J = 7.2Hz, 2H), 2.17-2.08 (m, 1H), 1.78-1.20 (m, 13H), 0.91 (s, 9H), 0.89 (s, 9H), 0.87 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H), 0.05 (s, 6H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 176.03, 158.76, 129.37, 120.52, 114.27, 76.59, 71.85, 71.54, 71.50, 49.67, 47.73, 44.44, 33.55, 32.72, 31.48, 29.21, 27.01, 26.87, 26.51, 25.91, 25.85, 25.82, 18.21, 17.98, 17.85, -4.10, -4.16, -4.24, -4.67, -4.79, -5.07.

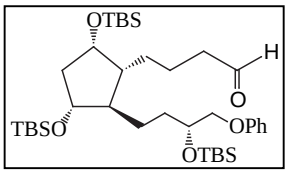


{4-[3,5-Dihydroxy-2-(3-hydroxy-4-phenoxybutyl)-cyclopentyl]butylthio}acetic acid (1a): A solution of **10** (60 mg, 0.08 mmol) in CH_3CN (3 mL) was treated at 0 °C with H_2SiF_6 (0.5 mL, 25% wt in H_2O). The solution was warmed to rt and stirred for a total of 4 h. The solution was poured into water. The mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over $MgSO_4$. Concentration and purification by column chromatography (20:1, CH_2Cl_2:MeOH) gave 31 mg (94%) of **1a** as a white foam. ^{1}H NMR (CD_3OD): δ 7.27-7.23 (m, 2H), 6.94-6.88 (m, 3H), 4.13-4.09 (m, 1H), 3.94-3.85 (m, 4H), 3.17 (s, 2H), 2.65-2.61 (t, J = 6.4 Hz, 2H), 2.13-2.06 (m, 1H), 1.70-1.33 (m, 13H); ^{13}C NMR (CD_3OD): δ 159.28, 129.27, 120.57, 114.41, 77.28, 72.44, 71.99, 69.96, 51.24, 50.02, 42.63, 35.04, 32.36, 31.28, 29.30, 28.65, 27.76, 27.09

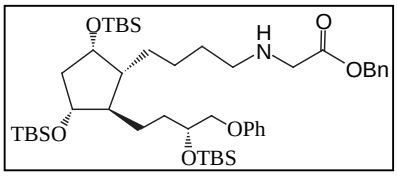


{4-[3,5-Dihydroxy-2-(3-hydroxy-4-phenoxybutyl)-cyclopentyl]butylsulfinyl}acetic acid (1b): A solution **1a**

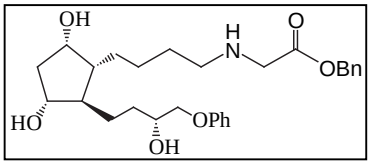
(18 mg) in CH_2Cl_2 (2 mL) and MeOH (0.2 ml) was treated with Bu_4NIO_4 (36 mg). After 16 h at rt, another portion of Bu_4NIO_4 (36 mg) was added and the mixture was stirred for another 24 h. Brine (1 mL) containing a few drops of saturated aqueous Na_2SO_3 was added at 0 °C and the mixture was stirred for a few minutes before a few drops of CH_3COOH was added to adjust its pH to acidic. The mixture was extracted with $CHCl_3$:MeOH (5:1). The combined organic layers were washed with brine and dried over $MgSO_4$. Concentration and purification by column chromatography (3:1, CH_2Cl_2:MeOH) gave 16 mg (86%) of **1b** as a syrup. ^{1}H NMR (CD_3OD): δ 7.28-7.23 (m, 2H), 6.94-6.88 (m, 3H), 4.15-4.08 (m, 1H), 3.94-3.87 (m, 4H), 3.77-3.51 (AB, J = 15, 63 Hz, 2H), 2.97-2.92 (t, J = 7.5 Hz, 2H), 2.17-2.08 (m, 1H), 1.8-1.38 (m, 13H); ^{13}C NMR (CD_3OD): δ 170.70, 159.27, 129.28, 120.59, 114.38, 77.12, 72.22, 71.97, 69.90, 51.08, 50.50, 49.73,42.76, 31.15, 28.49, 27.86, 27.05, 22.92, 21.86.



4-{3,5-Bis(*tert*-butyldimethylsilyloxy)-2-[3-(*tert*-butyldimethylsilyloxy)-4-phenoxybutyl]cyclopentyl}butanal (11): To a solution of oxalyl chloride (0.17 mL, 1.9 mmol) in CH_2Cl_2 (8 mL) at -78 °C was added dropwise DMSO (0.22 mL, 3.04 mmol). After 10 min, a solution of **9** (370 mg, 0.54 mmol) in CH_2Cl_2 (3 mL) was added dropwise. The mixture was then stirred for 45 min at -78 °C, Et_3N (0.62 mL, 4.4 mmol) was added and the solution was allowed to warm to 0 °C during a period of 30 min. After an additional 30 min at 0 °C, the mixture was poured into water and extracted with Et_2O. The combined organic layers were washed with brine and dried over $MgSO_4$. Concentration afforded crude aldehyde **11** (380 mg) which was used in next step without further purification. An analytical sample was obtained as a colorless oil by column chromatography (10:1, Hexane:EtOAc). ^{1}H NMR ($CDCl_3$): δ 9.76-9.74 (t, J = 1.2 Hz, 1H), 7.31-7.25 (m, 2H), 6.96-6.87 (m, 3H), 4.11-4.06 (m, 1H), 4.04-3.96 (m, 1H), 3.87-3.75 (m, 3H), 2.41-2.37 (t, J = 6.6 Hz, 2H), 2.19-2.10 (m, 1H), 1.80-1.25 (m, 11H), 0.91 (s, 9H), 0.89 (s, 9H), 0.87 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 202.63, 158.78, 129.38, 120.55, 114.27, 76.60, 71.83, 71.49, 71.31, 49.82, 47.72, 44.44, 44.40, 31.59, 27.12, 26.57, 25.91, 25.85, 25.82, 20.51, 18.19, 17.99, 17.86, -4.08, -4.15, -4.23, -4.69, -4.80, -5.09

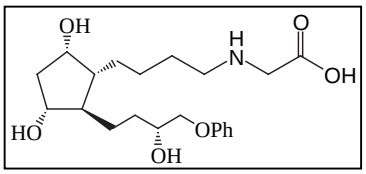


Benzyl {4-[3,5-Bis(*tert*-butyldimethylsilyloxy)-2-[3-(*tert*-butyldimethylsilyloxy)-4-phenoxybutyl]-cyclopentyl]butylamino}acetate (12): To a solution of **11** (370 mg, 0.54 mmol) in MeOH:Et_2O (4 mL, 3:2 v/v) at 0 °C was added dropwise Et_3N (0.47 mL, 3.24 mmol) followed by a solution of glycine, benzyl ester hydrochloride (652 mg, 3.24 mmol) in MeOH (1.5 mL). After 5 min, $NaCNBH_3$ (62 mg, 0.97 mmol) in MeOH (0.5 mL) was added and the cooling bath was removed. After 10 min at rt, the solution was poured into aqueous $NaHCO_3$ (5%). The mixture was extracted with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$. Concentration and purification by column chromatography (5:1, Hexane:EtOAc) gave 305 mg (66%) of **12** as a clear oil. $[\alpha]_D^{23}$ = 10.73 (c 1.0, $CHCl_3$), ^{1}H NMR ($CDCl_3$): δ 7.36-7.33 (m, 5H), 7.30-7.26 (m, 2H), 6.95-6.87 (m, 3H), 5.17 (s, 2H), 4.06-3.99 (m, 2H), 3.86-3.76 (m, 3H), 3.45 (s, 2H), 2.61-2.58 (t, J = 8 Hz, 2H), 2.15-2.08 (m, 1H), 1.78-1.76 (m, 1H), 1.63-1.21 (m, 13H), 0.91 (s, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.12 (s, 3H), 0.1 (s, 3H), 0.05 (s, 6H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 172.39, 158.78, 135.58, 129.35, 128.55, 128.32, 120.47, 114.25, 76.76, 71.90, 71.59, 71.38, 66.44, 50.90, 49.74, 47.90, 44.48, 31.60, 30.54, 27.20, 26.59, 25.91, 25.85, 25.81, 25.58, 18.19, 17.99, 17.84, -4.07, -4.18, -4.23, -4.69, -4.80, -5.08; MS (EI): 828 $(M+H)^+$

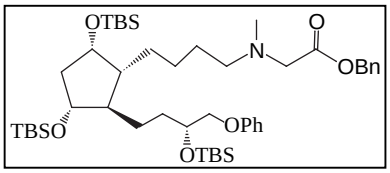


Benzyl {4-[3,5-Dihydroxy-2-(3-hydroxy-4-phenoxy-butyl)cyclopentyl]butylamino}acetate (13): A solution of **12** (30 mg, 0.036 mmol) in CH_3CN (1.5 mL) was treated at 0°C with H_2SiF_6 (0.4 mL, 25% wt in H_2O). The solution was warmed to rt and stirred for a total of 4 h. Aqueous $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2. The combined CH_2Cl_2 layers were washed with H_2O, brine and dried over $MgSO_4$. Filtration and concentration gave 18 mg (100%) of **13** as a single spot on TLC. ^{1}H NMR ($CDCl_3$): δ 7.38-7.33 (m, 5H), 7.30-7.26 (m, 2H), 6.98-6.90 (m, 3H), 5.16 (s, 2H), 4.23-4.20 (m, 1H), 4.06-4.02 (m, 1H), 3.98-3.94 (m, 2H), 3.86-3.82 (m, 1H), 3.44 (s, 2H), 2.69-2.60 (m, 2H), 1.87-1.86 (m, 1H), 1.74-1.25 (m, 12H); ^{13}C NMR ($CDCl_3$): δ 172.34, 158.52, 135.49, 129.50, 128.58, 128.39, 128.32,

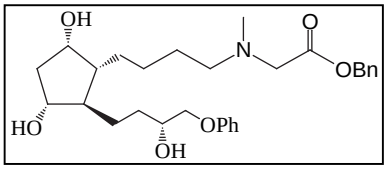
121.09, 114.53, 78.80, 74.36, 72.11, 69.95, 66.61, 53.33, 51.77, 50.61, 48.60, 42.31, 31.46, 29.67, 29.13, 28.22, 25.10.



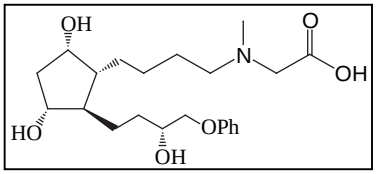
{4-[3,5-Dihydroxy-2-(3-hydroxy-4-phenoxybutyl)-cyclopentyl]butylamino}acetic acid (1c): To a solution of **13** (18 mg, 0.036 mmol) in EtOH (2 mL) was added 10% Pd/C (20 mg) followed by 1,4-cyclohexadiene (0.1 mL). The mixture was stirred under an Ar atmosphere for 1.5 h at rt. The suspension was filtered through a pad of Celite and the celite was throughly washed with EtOH. The solvent was removed and the residue was purified by column chromatography (5:1, CH_2Cl_2:MeOH) to give **1c** (15 mg, 100%) as a white foam. ^{1}H NMR (CD_3OD): δ 7.28-7.23 (m, 2H), 6.94-6.88 (m, 3H), 4.23-4.09 (m, 1H), 3.94-3.85 (m, 4H), 3.47 (s, 2H), 3.01-2.96 (t, J = 7.8 Hz, 2H), 2.18-2.09 (m, 1H), 1.71-1.28 (m, 13H); ^{13}C NMR (CD_3OD): δ 169.67, 159.27, 129.28, 120.60, 114.36, 77.07, 72.13, 71.97, 69.87, 50.98, 49.64, 49.40, 47.35, 42.82, 31.07, 28.41, 27.71, 26.38, 24.81



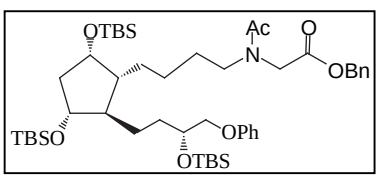
Benzyl *N*-methyl-{4-[3,5-bis(*tert*-butyldimethyl-silyloxy)-2-[3-(*tertt*-butyldimethylsilyloxy)-4-phenoxy-butyl]cyclopentyl]butylamino}acetate (14d): To a solution of **12** (28 mg, 0.034 mmol) in MeOH (2.5 mL) was added aqueous formaldehyde (0.15 mL, 37% in H_2O) followed by $NaCNBH_3$ (12 mg, 0.19 mmol) in MeOH (0.1 mL) at rt. The mixture was stirred for 15 min. The solution was poured into water and extracted with Et_2O. The combined Et_2O layers were washed with H_2O and brine and dried over $MgSO_4$. Concentration gave 28 mg (98%) **14d** as a clear oil (single spot on TLC, 5:1 Hexane/EtOAc). ^{1}H NMR ($CDCl_3$): δ 7.37-7.34 (m, 5H), 7.30-7.25 (m, 2H), 6.95-6.86 (m, 3H), 5.16 (s, 2H), 4.06-3.97 (m, 2H), 3.83-3.73 (m, 3H), 3.28 (s, 2H), 2.48 (t, J = 7.5 Hz, 2H), 2.36 (s, 3H), 2.15-2.06 (m, 1H), 1.77-1.18 (m, 13H), 0.90 (s, 9H), 0.88 (s, 9H), 0.86 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H), 0.03 (s, 6H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 170.88, 158.79, 135.78, 129.37, 128.53, 128.34, 128.26, 120.49, 114.27, 77.41, 71.93, 71.61, 71.39, 66.15, 58.46, 57.39, 49.73, 47.93, 44.48, 42.41, 31.61, 27.89, 27.26, 26.61, 25.91, 25.85, 25.82, 25.70, 18.20, 18.01, 17.85, -4.07, -4.16, -4.23, -4.68, -4.80, -5.10; MS (FAB): 865 $(M+Na)^+$.



Benzyl *N*-methyl-{4-[3,5-dihydroxy-2-(3-hydroxy-4-phenoxybutyl)cyclopentyl]butylamino}acetate: A solution of above crude product (28 mg) in CH_3CN (2 mL) was treated with H_2SiF_6 (0.5 mL, 25% wt in H_2O) at rt. After 4 h, aqueous $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with H_2O and brine and dried over $MgSO_4$. Filtration and concentration gave an oil (17 mg) as a single spot on TLC which was used without purification. ^{1}H NMR ($CDCl_3$): δ 7.36-7.32 (m, 5H), 7.30-7.26 (m, 2H), 6.98-6.90 (m, 3H), 5.15 (s, 2H), 4.24-4.23 (m, 1H), 4.07-4.02 (m, 1H), 3.98-3.94 (m, 2H), 3.86-3.83 (m, 1H), 3.32-3.21 (q, AB,J = 16.5, 250 Hz, 2H), 2.59-2.54 (m, 1H), 2.48-2.43 (m, 1H), 2.34 (s, 3H), 1.89-1.31 (m, 14H); ^{13}C NMR ($CDCl_3$): δ 170.75, 158.51, 135.65, 129.51, 128.56, 128.36, 128.31, 121.10, 114.53, 78.85, 74.36, 72.09, 70.02, 66.31, 58.18, 55.81, 53.41, 51.83, 42.44, 42.21, 31.47, 29.70, 28.08, 26.67, 24.96.

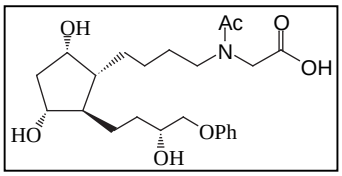


***N*-Methyl-{4-[3,5-dihydroxy-2-(3-hydroxy-4-phenoxybutyl)cyclopentyl]butylamino}acetic acid (1d):** To a solution of above crude product (17 mg, 0.034 mmol) in EtOH (2 mL) were added 100% Pd/C (20 mg) and 1,4-cyclohexadiene(0.1 mL). The mixture was stirred under an Ar atmosphere for 2 h. The suspension was filtered through a pad of Celite and the Celite pad was throughly washed with EtOH. The solvent was removed and the residue was purified by column chromatography (5:1, CH_2Cl_2:MeOH) to give 14 mg (100%) of **1d** as a white foam. ^{1}H NMR (CD_3OD): δ 7.27-7.24 (m, 2H), 6.94-6.89 (m, 3H), 4.11-4.09 (m, 1H), 3.94-3.86 (m, 4H), 3.61 (s, 2H), 3.16-3.09 (m, 2H), 2.87 (s, 3H), 2.16-2.10 (m, 1H), 1.77-1.35 (m, 13H); ^{13}C NMR (CD_3OD): δ 168.68, 159.29, 129.28, 120.60, 114.40, 77.11, 72.13, 72.00, 69.89, 58.56, 56.82, 51.05, 49.66, 42.81, 40.73, 31.12, 28.43, 27.72, 24.82, 24.57.



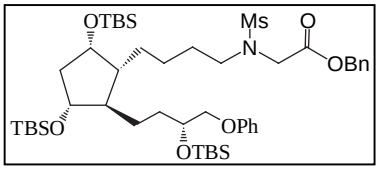
Benzyl *N*-Acetyl-{4-[3,5-bis(*tert*-butyldimethylsilyl-oxy)-2-[3-(*tert*-butyldimethylsilyloxy)-4-phenoxybutyl]-cyclopentyl]butylamino}acetate (14e): To a solution of

12 (30 mg, 0.036 mmol) in CH_2Cl_2 (1 mL) at 0 °C was added DMAP (1 mg) and Et_3N (8 mg), followed by Ac_2O (6 mg). The solution was slowly warmed to rt and stirred for a total of 4 h. After routine work up, purification by column chromatography (3:1, Hexane:EtOAc) gave 31 mg (99%) of **14e** as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.38-7.32 (m, 5H), 7.26-7.23 (m, 2H), 6.95-6.86 (m, 3H), 5.20 and 5.16 (s, 2H), 4.09 and 4.08 (s, 2H), 4.05-3.97 (m, 2H), 3.85-3.74 (m, 3H), 3.31-3.28 (m, 2H), 2.14 and 2.01 (s, 3H), 2.15-2.10 (m, 1H), 1.76-1.29 (m, 13H), 0.90 (s, 9H), 0.88 (s, 9H), 0.87 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H), 0.04 (s, 6H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 170.82, 169.30, 158.78, 135.48, 129.40, 128.56, 128.32, 128.25, 120.58, 114.29, 76.62, 71.84, 71.58, 71.32, 66.82, 50.04, 49.87, 47.78, 47.41, 44.44, 31.61, 29.17, 27.31, 26.59, 25.92, 25.85, 25.79, 25.17, 20.96, 18.19, 18.01, 17.87, -4.08, -4.22, -4.67, -4.78, -5.09; MS (FAB): 892 $(M+Na)^+$.

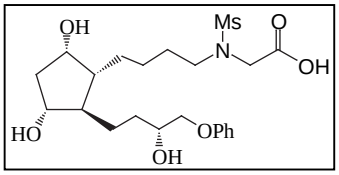


***N*-Acetyl-{4-[3,5-dihydroxy-2-(3-hydroxy-4-phenoxy-butyl)cyclopentyl]butylamino}acetic acid (1e):** A solution of **14e** (31 mg, 0.036 mmol) in CH_3CN (1.5 mL) at rt was treated with H_2SiF_6 (0.5 mL, 25% wt in H_2O). After 4 h, aqueous $NaHCO_3$ (2 mL) was added and the mixture was extracted with CH_2Cl_2. The combined CH_2Cl_2 layers were washed with H_2O and brine and dried over $MgSO_4$. Filtration and concentration gave crude product which was used without purification.

The above crude product (20 mg) was dissolved in EtOH (2 mL) and 10% Pd/C (20 mg) and 1,4-cyclohexadiene (0.15 mL) were added. The mixture was stirred under an Ar atmosphere at rt for 2 h. The suspension was filtered through a pad of Celite and the Celite layers were throughly washed with EtOH. The solvent was removed and the residue was purified by column chromatography (5:1, CH_2Cl_2:MeOH) to give **1e** (15 mg, 100%) as a white foam (mixture of rotamers from NMR). ^{1}H NMR (CD_3OD): δ 7.27-7.23 (m, 2H), 6.94-66.89 (m, 3H), 4.14 and 4.04 (s, 2H), 4.12-4.09 (m, 1H), 3.94-3.85 (m, 4H), 3.41-3.37 (m, 2H), 2.14 and 2.02 (s, 3H), 2.16-2.08 (m, 1H), 1.69-1.28 (m, 13H); ^{13}C NMR (CD_3OD): δ 172.49 (172.92), 171.60, 159.28, 129.27, 120.58, 114.39, 77.22 (77.16), 72.22, 71.96, 69.96 (69.91), 51.04, 50.17, 49.86, 42.77 (42.70), 31.14, 28.73, 28.47, 27.98 (27.86), 27.61, 25.11 (25.17), 19.86 (20.32)



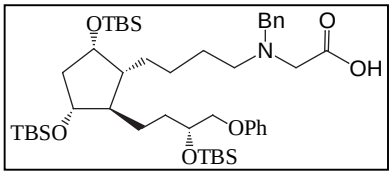
Benzyl *N*-methylsulfonyl-{4-[3,5-bis(*tert*-butyldimethyl silyloxy)-2-[3-(*tert*-butyldimethylsilyloxy)-4-phenoxy-butyl]cyclopentyl]butylamino}acetate (14f): A solution of **12** (25 mg, 0.03 mmol) in CH_2Cl_2 (1 mL) was treated at 0 °C with Et_3N (15 mg, 0.15 mmol) and $(MeSO_2)_2O$ (10 mg, 0.06 mmol). After 1 h, the mixture was poured into H_2O and extracted with EtOAc. The combined EtOAc was washed with H_2O and brine, dried over $MgSO_4$. Concentration afforded product (25 mg, 93%) as a clear oil. ^{1}H NMR ($CDCl_3$): δ 7.4-7.33 (m, 5H), 7.29-7.25 (m, 2H), 6.95-6.86 (m, 3H), 5.19 and 5.17 (s, 2H), 4.14 and 4.10 (s, 2H), 4.05-3.97 (m, 2H), 3.87-3.74 (m, 3H), 3.25-3.21 (t, J = 8 Hz, 2H), 2.98 (s, 3H), 2.15-2.08 (m, 1H), 1.75-1.67 (m, 13H), 0.90 (s, 9H), 0.88 (s, 9H), 0.86 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H), 0.04 (s, 6H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 169.60, 158.83, 134.93, 129.38, 128.72, 128.67, 128.38, 120.53, 114.33, 76.68, 71.96, 71.60, 71.42, 67.22, 49.90, 47.84, 47.76, 47.64, 44.46, 39.69, 31.72, 28.56, 27.17, 26.74, 25.94, 25.87, 25.83, 24.97, 18.22, 18.02, 17.87, -4.06, -4.14, -4.20, -4.64, -4.77, -5.06; MS (FAB): 929 $(M+Na)^+$.



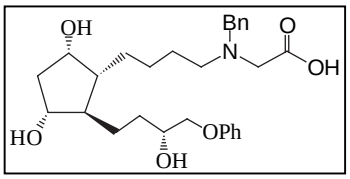
***N*-Methylsulfonyl-{4-[3,5-dihydroxy-2-(3-hydroxy-4-phenoxybutyl)cyclopentyl]butylamino}acetic acid (1f):** A solution of above crude product (25 mg, 0.028 mmol) in CH_3CN (1.5 mL) was treated with H_2SiF_6 (0.4 mL, 25% wt in H_2O) at rt. After 4 h, the mixture was poured into water and extracted with CH_2Cl_2. The combined organic layers were washed with H_2O and brine and dried over $MgSO_4$. Filtration and concentration gave a product (15 mg) as a single spot on TLC which was used without purification. ^{1}H NMR ($CDCl_3$): δ 7.38-7.33 (m, 5H), 7.31-7.26 (m, 2H), 6.99-6.89 (m, 3H), 5.30 and 5.17 (s, 2H), 4.26 and 4.20 (s, 2H), 4.09-3.81 (m, 5H), 3.36-3.22 (m, 1H), 2.99 (s, 3H), 2.61 (m, 1H), 1.87-1.25 (m, 13H); ^{13}C NMR ($CDCl_3$): δ 169.52, 158.48, 134.80, 129.50, 128.83, 128.71, 128.43, 121.09, 114.51, 78.65, 74.25, 72.01, 69.99, 67.33, 53.21, 52.08, 47.30, 46.63, 42.41, 39.57, 31.41, 29.53, 28.20, 27.61, 24.56.

The above crude product (15 mg) was dissolved in EtOH (1.5 mL) and 10% Pd/C (15mg) and 1,4-cyclohexadiene(0.1 mL) were added. The mixture was stirred under an Ar atmosphere for 2 h. The suspension was filtered through a pad of Celite and the Celite layers were throughly washed with EtOH. The solvent was removed and the residue was

purified by column chromatography (10:1, CH_2Cl_2:MeOH) to give **1f** (12 mg, 92%) as a white foam. ^{1}H NMR (CD_3OD): 7.28-7.23 (m, 2H), 6.96-6.88 (m, 3H), 4.11-4.09 (m, 1H), 4.05 (s, 2H), 3.95-3.84 (m, 4H), 3.31-3.26 (t, J = 7.2 Hz, 2H), 2.99(s, 3H), 2.16-2.07 (m, 1H), 1.70-1.28 (m, 13H); ^{13}C NMR ($CDCl_3$): δ 171.81, 159.30, 129.26, 120.55, 114.39, 77.22, 72.25, 71.97, 69.98, 51.05, 49.86, 47.81, 47.67, 42.71, 38.28, 31.18, 28.48, 28.24, 27.70, 24.85; MS (FAB): 496 $(M+Na)^+$.



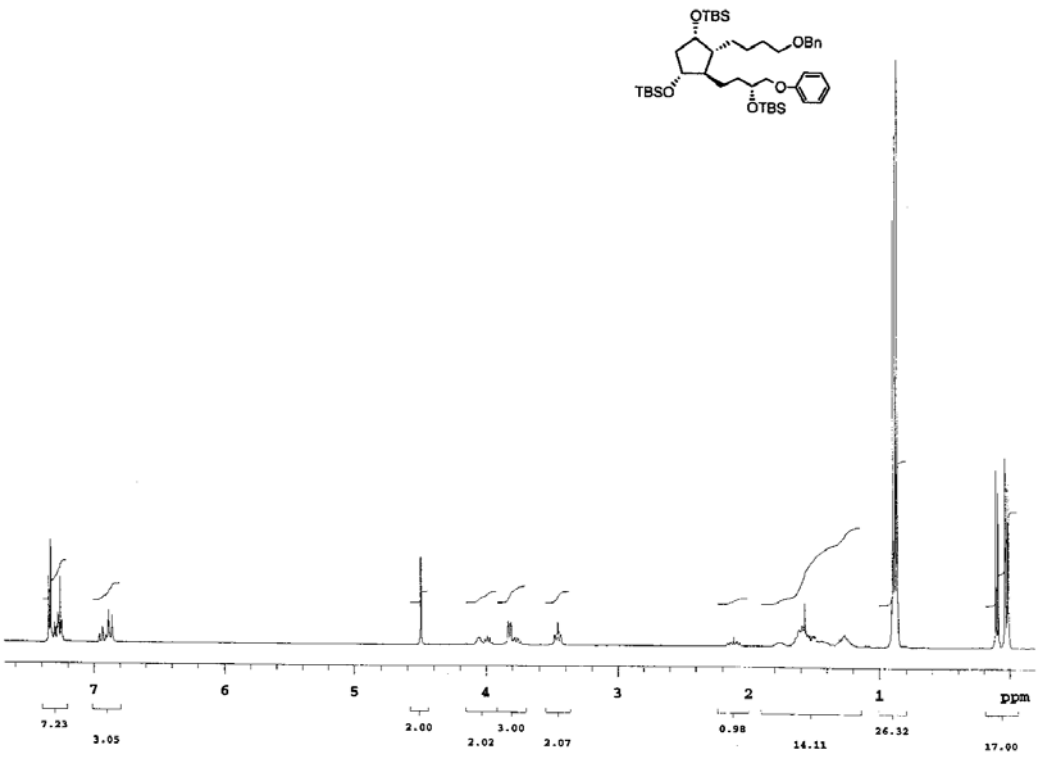
***N*-Benzyl-{4-[3,5-bis(*tert*-butyldimethylsilyloxy)-2-[3-(*tert*-butyldimethylsilyloxy)-4-phenoxybutyl]-cyclopentyl]butylamino}acetic acid (15):** To a solution of **11** (85 mg. 0.125 mmol) in MeOH:Et_2O (4 mL, 3:1 v/v) was added Et_3N (0.11 mL, 0.75 mmol), *N*-benzyl glycine hydrochloride (152 mg, 0.75 mmol) followed by $NaCNBH_3$ (24 mg, 0.37 mmol). After 15 min at rt, the mixture was diluted with pH4 buffer and the pH was adjusted to about 5. The mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over $MgSO_4$. Concentration and purification by column chromatography (10:1, CH_2Cl_2:MeOH) gave 58 mg (56%) of **15** as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.36-7.34 (m, 5H), 7.29-7.25 (m, 2H), 6.95-6.86 (m, 3H), 4.02-3.95 (m, 4H), 3.85-3.73 (m, 3H), 3.32 (s, 2H), 2.78-2.74 (t, J = 8 Hz, 2H), 2.14-2.07 (m, 1H), 1.72-1.21 (m, 13H), 0.91 (s, 9H), 0.89 (s, 9H), 0.86 (s, 9H), 0.1 (s, 3H), 0.09 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H), -0.03 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 169.22, 158.79, 130.02, 129.40, 129.12, 120.56, 114.30, 76.74, 71.88, 71.56, 71.36, 58.24, 55.56, 54.27, 49.90, 47.86, 44.39, 31.75, 27.23, 26.82, 25.93, 25.86, 25.81, 25.28, 18.20, 18.00, 17.86, -4.07, -4.14, -4.21, -4.63, -4.80, -5.00; MS (FAB): 850 $(M+Na)^+$.



***N*-Benzyl-{4-[3,5-dihydroxy-2-(3-hydroxy-4-phenoxy-butyl)cyclopentyl]butylamino}acetic acid (1g):** A solution of **15** (33 mg) in CH_3CN (2 mL) was treated with H_2SiF_6 (0.5 mL, 25% wt in H_2O) at rt. After 4 h, phosphate buffer (pH 5.5) was added to adjust the pH of aqueous layers to about 5, the mixture was saturated with NaCl and extracted with THF. The combined THF layers were washed with brine, dried over $MgSO_4$ and concentrated. The residue was co-evaporated with

MeOH to remove a remaining small amount of H_2O. The residue was pass through a short silica gel pad eluting with CH_2Cl_2:MeOH (3:1) to gave 18 mg (95%) of **1g** as a white foam. ^{1}H NMR (CD_3OD): δ 7.56-7.54 (m, 2H), 7.48-7.45 (m, 3H), 7.27-7.24 (m, 2H), 6.94-6.89 (m, 3H), 4.41 (s, 2H), 4.10-4.08 (m, 1H), 3.94-3.86 (m, 4H), 3.64 (m, 2H), 3.18-3.15 (t, J = 8 Hz, 2H), 2.15-2.09 (m, 1H), 1.83-1.29 (m, 13H), ^{13}C NMR (CD_3OD): δ 169.54, 159.28, 131.03, 129.96, 129.88, 129.29, 129.18, 120.62, 114.41, 77.10, 72.17, 72.01, 69.90, 57.91, 54.56, 54.41, 51.09, 49.67, 42.77, 31.14, 28.47, 27.76, 24.92, 24.16; MS (FAB): 508 $(M+Na)^+$.

Unity 300 spectrometer



Unity 300 spectrometer