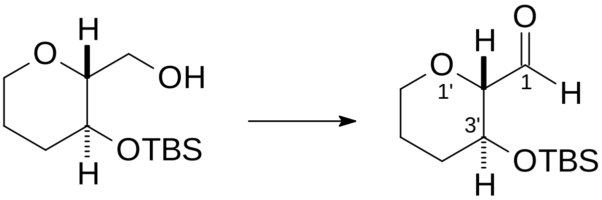
Synthesis of Novel Polyethers in a Geometrically Precise Conformation

Supporting Information

Experimental Procedures.

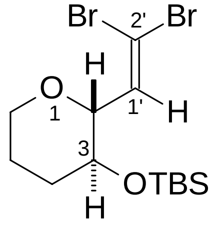
(2’S, 3’S)-3’.(*tert*-Butyldimethylsiloxy)-tetrahydropyran-2’-carbaldehyde (10). To a solution of alcohol **9** (21.1 g, 87 mmol), DMSO (55 mL, 774 mmol, 9 equiv) and Et_3N (60 mL, 430 mmol, 5 equiv) in CH_2Cl_2 (204 mL) at 0 ºC was added $SO_3{\cdot}py$ complex (68 g, 430 mmol). After 2 h, the reaction mixture was diluted with ether (2 x 100 mL), washed with aqueous saturated NH_4Cl (2 x 100 mL), and dried ($MgSO_4$). Filtration, concentration and flash chromatography (silica, 20% EtOAc in *n*-hexane) gave aldehyde **10** (15.9 g, 65.2 mmol, 75%).



9 **10**

10: colorless oil; R_f = 0.4 (silica, 10% EtOAc in n-hexane); IR (film) ν_{max} 2955, 2930, 2858, 1738, 1388, 1362, 1253, 1079 cm^{-1}; $[\alpha]_D^{25}$ + 58.8 (*c* 0.7, $CHCl_3$); ^{1}HNMR (400 MHz, $CDCl_3$) δ 9.75 (s, 1H, H_1), 3.95 (ddd, J = 11.3, 3.3, 2.5 Hz, 1H, $H_{6'}$), 3.69 (ddd, J = 9.1, 9.1, 4.4 Hz, 1H, $H_{3'}$), 3.65 (d, J = 9.1 Hz, 1 H, $H_{2'}$), 3.35 (ddd, J = 11.3, 6.6, 3.9 Hz, 1H, $H_{6'}$), 2.02-2.07 (m, 1H, $He_{4'}$), 1.58-1.68 (m, 2H, 2 x $H_{5'}$), 1.51-1.56 (m, 1H, $Ha_{4'}$), 0.84 (s, 9H, $(C\underline{H}_3)_3CSi$), 0.04 (s, 3H, $C\underline{H}_3Si$), 0.01 (s, 3H, $C\underline{H}_3Si$); ^{13}CNMR (100 MHz, $CDCl_3$) δ 199.9 (d, C_1), 85.9 (d, $C_{2'}$), 68.2 (d, $C_{3'}$), 67.7 (t, $C_{6'}$), 33.9 (t, $C_{4'}$), 26.1 (q, $(\underline{C}H_3)_3CSi$), 24.8 (t, $C_{5'}$), 18.2 (s, $(CH_3)_3\underline{C}Si$), -3.7 (q, $\underline{C}H_3Si$), -4.6 (q, $\underline{C}H_3Si$); MS at *m/z* (rel int) 215 ($[M\text{-}COH]^+$, 17), 187 (100), 185 (59), 173 (57); HRMS calcd for $C_{12}H_{23}O_3Si$ $(M\text{-}H)^+$ 243.14165, found 243.14068.

(2R, 3S)-2-(2’-2’-Dibromovinyl)-3(*tert*-butyldimethylsiloxy)tetrahydropyran (7). Triphenylphosphine (34.4 g, 131 mmol) was added to a stirred solution of carbon tetrabromide (21.8 g, 65.6 mmol) in dry CH_2Cl_2 (218 mL) at 0 ºC. After 10 min the bright orange solution was cooled to -78 ºC and treated dropwise with the aldehyde **10** (8 g, 32.8 mmol) in CH_2Cl_2 (109 mL) over a 3 min period. After 20 min at 0 ºC, the reaction was treated with Et_3N (22.8 mL, 164 mmol) and then poured into stirring hexanes (329 mL). The solids were removed by filtration, the filtrate was concentrated, and the residue was chromatographed (silica, 10% EtOAc in *n*-hexane) to afford the vinyl dibromide **7** (11 g, 27.2 mmol, 83%).

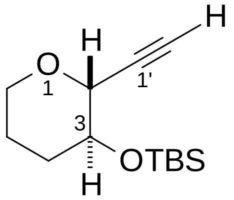


7

7: oil; R_f = 0.75 (silica, 10% EtOAc in n-hexane); IR ($CHCl_3$) ν_{max} 2940, 2930, 2858, 1258, 1226, 1116, 1004, 1079, 856, cm^{-1}; $[\alpha]_D^{25}$ - 3.4 (*c* 3.2, $CHCl_3$); ^{1}HNMR (400 MHz, $CDCl_3$) δ 6.34 (d, J = 8.6 Hz, 1H, $H_{1'}$), 3.89 (br dd, J = 9.5, 1.6 Hz, 1H, He_6), 3.78 (dd, J = 8.6, 8.6 Hz, 1H, H_2), 3.36-3.44 (m, 2H, H_3, Ha_6), 2.04 (br d, J = 12.5 Hz, 1H, He_4), 1.65-1.69 (m, 2H, 2 x H_5), 1.5 (dddd, J = 12.5, 12.5, 12.5, 2.2 Hz, 1H, Ha_4), 0.9 (s, 9H, $(C\underline{H}_3)_3CSi$), 0.06 (s, 6H, 2 x $C\underline{H}_3Si$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.4 (d, $C_{1'}$), 94.2

(s, $C_{2'}$), 82.7 (d, C_2), 70.4 (d, C_3), 67.5 (t, C_6), 33.3 (t, C_4), 25.7 (q, $(\underline{C}H_3)_3CSi$)., 25.2 (t, C_5), 17.9(s, $CH_3)_3\underline{C}Si$), -4.4 (q, $\underline{C}H_3Si$), -4.7 (q, $\underline{C}H_3Si$); MS at *m/z* (rel int) 343($[M-{}^tBu]^+$, 41), 341 (20), 199 (16), 183 (21), 139 (18), 137 (16), 131 (16), 101 (38), 75 (94), 73 (100), 59 (50), 57 (50); HRMS, calcd for $C_{13}H_{23}O_2SiBr_2$ (M^+) 402.99496, found 402.99130.

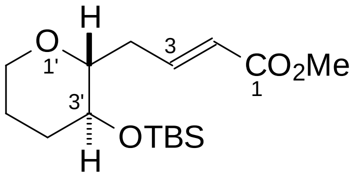
(2R, 3S)-2-Ethynyl-3-*tert*-butyldimethylsiloxy-tetrahydropyran (11). The vinyl dibromide **7** (23.4 g, 58 mmol) in a stirred solution of THF (580 mL) at -78 ºC was treated dropwise with *n*-BuLi (77.4 mL, 116 mmol, 1.5 M in *n*-hexane). After being stirred for 20 min, the reaction mixture was quenched with aqueous salurated NH_4Cl solution and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic phases were washed with H_2O (2 x 100 mL) and then dried ($MgSO_4$). The solvent was evaporated under reduced pressure and the residue chromatographed on a silica gel column (eluant 5% EtOAc in *n*-hexane) to give **11** (11.3 g, 47.5 mmol, 82%).



11

11: colorless oil; R_f = 0.40 (silica, 5% EtOAc in *n*-hexano). IR ($CHCl_3$) ν_{max} 3014, 2956, 2856, 2885, 1472, 1362, 1320, 1258, 1130, 1088, 1026, 950, 861, 840 cm^{-1}; $[\alpha]_D^{25}$ + 29.3 (*c* 1.18, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 3.91 (dddd, J = 11.4, 4.2, 3.8, 1.2 Hz, 1H, Ha_6), 3.87 (dd, J = 7.7, 2.0 Hz, 1H, H_2), 3.61 (ddd, J = 9.1, 7.7, 4.2 Hz, 1H, H_3), 3.39 (ddd, J = 11.4, 10.1, 2.8 Hz, 1H, He_6), 2.42 (d, J = 2.0 Hz, 1H, $H_{2'}$), 2.04 (dddd, J = 13.1, 5.1, 4.2, 3.8, 1.1 Hz, 1H, He_4), 1.72 (br ddd, J = 11.8, 4.2, 3.8 Hz, 1H, He_5), 1.56-1.63 (m, 1H, Ha_5), 1.45 (dddd, J = 13.1, 11.2, 9.1, 4.2 Hz, 1H, Ha_4), 0.89 (s, 9H, $(C\underline{H}_3)_3CSi$), 0.10 (s, 3H, $C\underline{H}_3Si$), 0.08, (s, 3H, $C\underline{H}_3Si$); ^{13}C NMR(100 MHz, $CDCl_3$) δ 82.1 (d, $C_{2'}$), 73.7 (s, $C_{1'}$), 72.8 (d, C_2), 70.3 (d, C_3), 66.8 (t, C_6), 32.1 (t, C_4), 25.7 (q, $(\underline{C}H_3)_3CSi$), 24.0 (t, C_5), 18.0 (s, $(CH_3)_3\underline{C}Si$), -4.47 (q, $\underline{C}H_3Si$), -4.6 (q, $\underline{C}H_3Si$); MS at *m/z* (rel int) 183($[M-{}^tBu]^+$,66), 141 (100), 101 (77), 75 (100), 73 (100), 71 (46), 59 (97), 57 (51); HRMS calcd for $C_{13}H_{23}O_2Si$ $(M+H)^+$ 239.14638, found 239.14359.

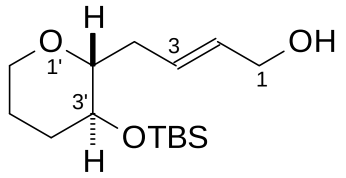
(2'R, 3'S)-Methyl(E)-4-[3'-(*tert*-butyldimethylsiloxy)tetrahydropyran-2'-yl]buteno-ate (13). A stirred solution of $BH_3{\cdot}SMe_2$ (50.2 mL, 100 mmol), 2 M in THF at 0 ºC, was treated dropwise with 2-methyl-2-butene (21.3 mL, 200 mmol), and stirring was continued for 3 h. Acetylene **11** (12 g, 50.2 mmol) in dry THF (100 mL) was added, and the reaction mixture was stirred at 25 ºC for 12 h. Excess disiamylborane was carefully quenched with H_2O (15 mL) followed by dropwise addition of a mixture of 3N NaOH (35 mL) and 30% hydrogen peroxide (15 mL) over a 30 min period, removal of the cooling bath, and continued stirring for 2 h. The reaction mixture was diluted with ether (2 x 100 mL) and washed with H_2O (2 x 100 mL) and brine (100 mL). Drying ($MgSO_4$) and concentration followed by flash chromatography (silica, 10% EtOAc in *n*-hexane) gave the acetaldehyde **12** (11.3 g, 44.1 mmol, 88%) which was used directly for the next step. Aldehyde **12** (11 g, 42.6 mmol) was dissolved in benzene (100 mL) and added dropwise to a stirred mixture of NaH (1.4 g, 56.3 mmol) and trimethyl phosphonoacetate (8.3 mL, 51.2 mmol) in benzene (463 mL). The reaction mixture was stirred for 15 min at 25 ºC before dilution with ether (2 x 200 mL) and washed with an aqueous saturated NaCl solution (2 x 200 mL), H_2O (200 mL) and dried ($MgSO_4$). Concentration followed by flash column chromatography (silica, 15% EtOAc in *n*-hexane) gave compound **13** (11.8 g, 37.5 mmol, 88%).



13

13: colorless foam; R_f = 0.38 (silica, 10% EtOAc in *n*-hexane); IR ($CHCl_3$) ν_{max} 3006, 2953, 2931, 2885, 2858, 1716, 1661, 1438, 1324, 1279, 1260, 1127, 1097, 871, 838 cm^{-1}; $[\alpha]_D^{25}$ + 31.86 (*c* 4.31, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$,) δ 6.99 (dddd, J = 15.6, 7.5, 6.8, 1.1 Hz, 1H, H_3), 5.86 (dd, J = 15.6, 1.4 Hz, 1H, H_2), 3.83 (ddd, J = 10.5, 2.0, 2.0 Hz, 1H, $He_{6'}$), 3.68 (s, 3H, $OC\underline{H}_3$), 3.26-3.30 (m, 1H, $H_{3'}$), 3.25 (ddd, J = 11.0, 10.5, 5.0 Hz, 1H, $Ha_{6'}$), 3.11 (ddd, J = 8.6, 8.6, 2.8 Hz, 1H, $H_{2'}$), 2.67 (br dd, J = 15.1, 6.8 Hz, 1H, H_4), 2.23 (dddd, J = 15.1, 8.6, 7.5, 1.1 Hz, 1H, H_4), 1.98 (br dd, J = 12.1, 3.0, 1H, $He_{4'}$), 1.58-1.64 (m, 2H, 2 x $H_{5'}$), 1.37-1.44 (m, 1H, $Ha_{4'}$), 0.89 (s, 9H, $(C\underline{H}_3)_3$ CSi), 0.06 (s, 6H, 2 x $C\underline{H}_3Si$); ^{13}C NMR ($CDCl_3$) δ 166.8 (s, C_1), 146.6 (d, C_3), 122.5 (d, C_2), 81.4 (d, $C_{2'}$), 70.9 (d, $C_{3'}$), 67.8 (t, $C_{6'}$), 51.2 (q, $O\underline{C}H_3$), 35.5 (t, C_4), 33.5 (t, $C_{4'}$), 25.7 (q, $(\underline{C}H_3)_3CSi$), 25.5 (t, $C_{5'}$), 17.8 (s, $(CH_3)_3\underline{C}Si$), -3.9 (q, $\underline{C}H_3Si$), -4.8(q, $\underline{C}H_3Si$); MS at *m/z* (rel int) 257 ($[M-{}^tBu]^+$, 66), 173 (61), 157 (55), 129 (22), 105 (27), 100 (34), 89 (47), 75 (46), 59 (53), 57 (46). Anal. Calcd for $C_{16}H_{30}O_4Si$: C, 61.11; H, 9.62. Found: C, 61.20; H, 9.75.

(2'R, 3'S)-4-[3'-(*tert*-Butyldimethylsiloxy)tetrahydropyran-2'-yl]-2-buten-1-ol (14).
DIBALH (74.6 mL, 186 mmol, 1 M in hexanes) was added dropwise to a stirred solution of the ester **13** (11.7 g, 37.3 mmol) in dry ether (373 mL) at 0 ºC over a 15 min period. After 1 h, the reaction mixture was quenched by treatment with H_2O (200 mL) and NaOH (100 mL, 3 N). Extractive workup with ether (3 x 200 mL) gave, after drying ($MgSO_4$), concentration, and flash chromatography (silica, 20% EtOAc in *n*-hexane), the allylic alcohol **14** (10.5 g, 36.7 mmol, 98%).

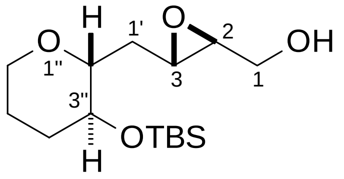


14

14: colorless oil; R_f = 0.25 (silica, 20% EtOAc in *n*-hexane); IR ($CHCl_3$) ν_{max} 3500, 3006, 2955, 2930, 2858, 1472, 1463, 1259, 1127, 1097, 1006, 971, 878, 860 cm^{-1}; $[\alpha]_D^{25}$ + 41.85 (*c* 4.21, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.64-5.71 (m, 2H, H_2, H_3), 4.04 (br s, 2H, 2 x H_1), 3.82 (ddd, J = 12.5, 2.0, 1.5 Hz, 1H, $He_{6'}$), 3.22-3.28 (m, 2H, $H_{3'}$, $Ha_{6'}$), 3.04 (ddd, J = 8.7, 8.7, 2.6 Hz, 1H, $H_{2'}$), 2.56 (br d, J = 14.0 Hz, 1H, H_4), 2.27 (br s, 1H, $O\underline{H}$), 2.06 (ddd, J = 14.5, 8.1, 6.0 Hz, 1H, H_4), 1.96 (br dd, J = 12.2, 2.8 Hz, 1H, $He_{4'}$), 1.57-1.64 (m, 2H, 2 x $H_{5'}$), 1.39 (dddd, J = 12.2, 11.7, 11.0, 5.4 Hz, 1H, $Ha_{4'}$), 0.85 (s, 9H, $(C\underline{H}_3)_3$ CSi), 0.03 (s, 6H, 2 x $C\underline{H}_3Si$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.1 (d, C_3), 129.4 (d, C_2), 82.4 (d, $C_{2'}$), 70.9 (d, $C_{3'}$), 67.8 (t, $C_{6'}$), 63.5 (t, C_1), 34.9 (t, C_4), 35.5 (t, $C_{4'}$), 25.8 (q, $(\underline{C}H_3)_3CSi$), 25.6 (t, $C_{5'}$), 17.9 (s, $(CH_3)_3\underline{C}Si$), -3.9 (q, $\underline{C}H_3Si$), -4.7(q, $\underline{C}H_3Si$); MS at *m/z* (rel int) 285 ($[M-H)]^+$, 1), 229 ($[M-{}^tBu]^+$, 6), 175 (73), 157 (94), 137 (51), 129 (52), 101 (37), 83 (100), 75 (100), 57 (51), 55 (42). Anal. Calcd for $C_{15}H_{30}O_3Si$: C, 62.89; H, 10.55. Found: C, 62.81; H, 10.75.

(2S, 3S, 2''R, 3''S)-{3-[3''-(*tert*-Butyldimethylsiloxy)tetrahydropyran-2''-yl-methyl]-oxiran-2-yl}-methanol (15). A solution of allylic alcohol **14** (9.96 g, 34.8 mmol) in CH_2Cl_2 (100 mL) was added dropwise to a mixture of (+)-diethyl-D-tartrate (2.14 mL, 12.5 mmol), 4 Å molecular sieves (2 g), and titanium isopropoxide (3.1 mL, 10.4 mmol) in CH_2Cl_2 (130 mL) at -20 ºC. After 1 h, *tert*-butyl hydroperoxide (11.38 mL, 62.6 mmol, 5-6 M in decane) was added and the reaction mixture was stored at -20 ºC for 12 h. Cooling was stopped and the reaction mixture was filtered. The filtrate was diluted with

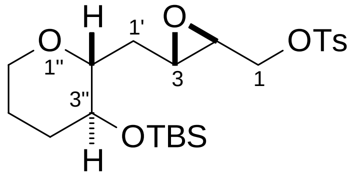
EtOAc (100 mL), washed with aqueous saturated sodium sulfate (100 mL), dried ($MgSO_4$), and filtered throught Celite. The filtrate was concentrated and chromatographed (silica 10→30 % EtOAc in *n*-hexane) to give epoxide **15** (9.98 g, 33 mmol, 95%).



15

15: colorless foam; R_f = 0.42 (silica, 30% EtOAc in *n*-hexane); IR ($CHCl_3$) ν_{max} 3500, 3041, 3002, 2954, 2931, 2858, 1253, 1215, 1100 cm^{-1}; $[\alpha]_D^{25}$ + 32.38 (*c* 2.56, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 3.89 (br d, J = 12.1 Hz, 1H, H_1), 3.86 (br d, J = 14.0 Hz, 1H, $He_{6''}$), 3.60 (ddd, J = 12.1, 6.4, 4.6 Hz, 1H, H_1), 3.27-3.34 (m, 2H, $Ha_{6''}$, $H_{3''}$), 3.13 (ddd, J = 8.8, 8.8, 2.8 Hz, 1H, $H_{2''}$), 3.12 (br s, 1H, H_3), 2.90 (ddd, J = 4.6, 2.5, 2.5 Hz, 1H, H_2), 2.10 (dd, J = 6.4, 6.4, Hz, 1H, $O\underline{H}$), 1.95-2.00 (m, 2H, $He_{4''}$, $H_{1'}$), 1.83 (ddd, J = 14.3, 8.8, 5.7 Hz, 1H, $H_{1'}$), 1.67-1.72 (m, 2H, 2 x $H_{5''}$), 1.62 (dddd, J = 12.0, 11.0, 11.0, 5.4 Hz, 1H, $Ha_{4''}$), 0.85 (s, 9H, $(C\underline{H}_3)_3$ CSi), 0.04 (s, 6H, 2 x $C\underline{H}_3Si$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 80.7 (d, $C_{2''}$), 70.8 (d, $C_{3''}$), 67.7 (t, $C_{6''}$), 61.8 (t, C_1), 57.8 (d, C_2), 53.8 (d, C_3), 34.1 (t, $C_{1'}$), 33.5 (t, $C_{4''}$), 25.8 (q, $(\underline{C}H_3)_3CSi$), 25.5 (t, $C_{5''}$), 17.9 (s, $(CH_3)_3\underline{C}Si$), -3.9 (q, $\underline{C}H_3Si$), -4.8 (q, $\underline{C}H_3Si$); MS at *m/z* (rel int) 303 ($[M+H]^+$, 3), 245 ($[M-{}^tBu]^+$, 2), 157 (26), 145 (52), 117 (38), 97 (49), 74 (100), 71 (100), 57 (47), 55 (32). Anal. Calcd for $C_{15}H_{30}O_4Si$: C, 59.56; H, 10.00. Found: C, 59.45; H, 10.26.

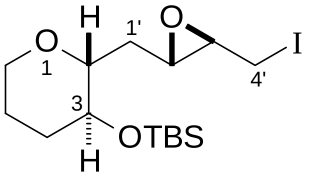
(2S, 3S, 2’’R, 3’’S)- *p*-Toluenesulfonic acid-3-[3’’-(*tert*-butyldimethylsiloxy)tetra-hydropyran-2’’-yl-methyl]-oxiran-2-yl-methyl-ester. (16). *p*-Toluenesulfonyl chloride (6.7 g, 35.3 mmol) was added to a cold (0 ºC) and stirred solution of alcohol **15** (9.7 g, 32.1 mmol), 4-(dimethylamino)pyridine (183 mg, 1.5 mmol) and Et_3N (11.2 mL, 80.3 mmol) in dry CH_2Cl_2 (320 mL). After 8 h, the reaction mixture was allowed to reach room temperature and was stirred for 1 h before dilution with MeOH (20 mL) and CH_2Cl_2 (100 mL). The mixture was washed with aqueous saturated NH_4Cl solution (2 x 200 mL), H_2O (200 mL), and brine (100 mL) and then dried ($MgSO_4$). Concentration followed by flash column chromatography (silica, 25%, EtOAc in *n*-hexane) gave compound **16** (13.6 g, 29.8 mmol, 93%).



16

16: oil; R_f = 0.61 (silica, 30% EtOAc in *n*-hexane); IR ($CHCl_3$) ν_{max} 3021, 3007, 2955, 2931, 2858, 1463, 1365, 1254, 1225, 1206, 1190, 1177 cm^{-1}; $[\alpha]_D^{25}$ + 8.8 (*c* 1.51, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 8.0 Hz, 2H, $Ph\underline{H}$), 7.34 (d, J = 8.0 Hz, 2H, $Ph\underline{H}$), 4.22 (dd, J = 11.3, 3.5 Hz, 1H, H_1), 3.94 (dd, J = 11.3, 6.0 Hz, 1H, Ha_1), 3.85 (br d, J = 13.7 Hz, 1H, $He_{6''}$), 3.26-3.32 (m, 2H, $H_{3''}$, $Ha_{6''}$), 3.10 (ddd, J = 8.6, 8.6, 2.7 Hz, 1H, $H_{2''}$), 2.96-2.98 (m, 2H, H_3, H_2), 2.45 (s, 3H, $C\underline{H}_3Ph$), 1.98 (br d, J = 14.3, 1H, $H_{1'}$), 1.92 (dddd, J = 11.3, 2.8, 2.8, 2.8 Hz, 1H, $He_{4''}$), 1.68 (ddd, J = 14.3, 8.6, 5.4 Hz, 1H, $H_{1'}$), 1.63 (br d, J = 11.5 Hz, 2H, 2 x $H_{5''}$), 1.37-1.44 (m, 1H, $Ha_{4''}$), 0.83 (s, 9H, $(C\underline{H}_3)_3$ CSi), 0.05 (s, 3H, $C\underline{H}_3Si$), 0.03 (s, 3H, $C\underline{H}_3Si$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9 (s), 132.8 (s), 129.9 (d), 129.9 (d), 127.9 (d), 127.9(d) [Ph], 80.3 (d, $C_{2''}$), 70.8 (d, $C_{3''}$), 70.4(t, C_1), 67.7 (t, $C_{6''}$), 54.3 (d, C_2), 53.9 (d, C_3), 33.8 (t, $C_{1'}$), 33.5 (t, $C_{4''}$), 25.7 (q, $(\underline{C}H_3)_3CSi$), 25.5 (t, $C_{5''}$), 21.6 (q, $\underline{C}H_3Ph$) 17.9 (s, $(CH_3)_3\underline{C}Si$), -3.9 (q, $\underline{C}H_3Si$), -4.8(q, $\underline{C}H_3Si$); MS at *m/z* (rel int) 229 ($[M-{}^tBu-OSO_2Ph]^+$, 100), 155 (25), 129 (19), 91 (71), 75 (51), 73 (58), 71 (68), 65 (22), 59 (22), 57 (22). Anal. Calcd for $C_{22}H_{36}O_6SSi$: C, 57.87; H, 7.95. Found: C, 57.74; H, 7.81.

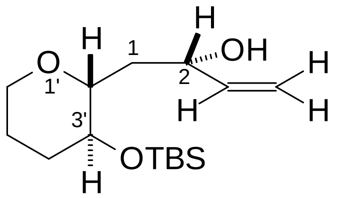
(2R, 3S, 2S, 3’R)-3-(*tert*-Butyldimethylsiloxy)-2-(3’-iodomethyl-oxiran-2’-ylme-thyl)tetrahydropyrane (17). $NaHCO_3$ (4 g, 48 mmol) and NaI (8.2 g 55 mmol) were added to a solution of the tosylate **16** (11 g, 24 mmol) in freshly distilled butanone (125 mL). The mixture was refluxed (60 ºC) for 1 h, then allowed to reach room temperature and filtered. Concentration followed by flash column chromatography (silica, 10% EtOAc in *n*-hexane) gave the iodide **17** (9.6 g, 23.3 mmol, 97%).



17

17: oil; R_f = 0.33 (silica, 5% EtOAc in *n*-hexane); IR ($CHCl_3$) ν_{max} 3019, 3010, 2955, 2930, 2858, 1602, 1463, 1256, 1224, 1208, 1130, 1100, 943, 894, 877 cm^{-1}; $[\alpha]_D^{25}$ + 41.9 (*c* 1.09, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 3.90 (ddd, J = 11.2, 2.0, 2.0 Hz, 1H, He_6), 3.30-3.37 (m, 2H, Ha_6, H_3), 3.26 (dd, J = 8.9, 4.7 Hz, 1H, $H_{4'}$), 3.17 (ddd, J = 8.8, 8.8, 3.0 Hz, 1H, H_2), 2.99-3.07 (m, 3H, $H_{4'}$, $H_{2'}$, $H_{3'}$), 2.01 (br dd, J = 12.4, 3.1 Hz, 1H, He_4), 1.91 (dddd, J = 14.3, 5.8, 3.0 Hz, 1H, $H_{1'}$), 1.76 (br d, J = 14.3, 8.8, 5.5 Hz, 1H, $H_{1'}$), 1.63-1.69 (m, 2H, 2 x H_5), 1.42 (dddd, J = 12.4, 11.0, 11.0, 5.3 Hz, 1H, Ha_4), 0.87 (s, 9H, $(C\underline{H}_3)_3$ CSi), 0.06 (s, 6H, 2 x $C\underline{H}_3Si$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 80.7 (d, C_2), 70.9 (d, C_3), 67.7 (t, C_6), 60.4 (d, $C_{3'}$), 57.7 (d, $C_{2'}$), 34.4 (t, $C_{1'}$), 33.5 (t, C_4), 25.8 (q, $(\underline{C}H_3)_3CSi$), 25.5 (t, C_5), 17.9 (s, $(CH_3)_3\underline{C}Si$), 5.1 (t, $C_{4'}$), -4.0 (q, $\underline{C}H_3Si$), -4.8 (q, $\underline{C}H_3Si$); MS at *m/z* (rel int) 355 ($[M-{}^tBu]^+$, 4), 227 (27), 185 (29), 155 (11), 127 (42), 101 (43), 75 (100), 73 (82), 71 (41), 59 (42), 57 (47). Anal. Calcd for $C_{15}H_{29}O_3ISi$: C, 43.68; H, 7.09. Found: C, 43.39; H, 7.05.

(2’R, 3’S, 2S)-1-[3’-(*tert*-Butyldimethylsiloxy)tetrahydropyran-2’yl]but-3-en-2-ol (18). The iodide **17** (9.6 g, 23.3 mmol) in a stirred solution of dry Et_2O (235 mL) at -78 ºC was treated dropwise with *t*-BuLi (39 mL, 47 mmol, 1.2 M in *n*-hexane). After 2 h the cooling bath was removed, and stirring was continued for 5 min. Dilution with ether (100 mL), followed by washing with saturated $NaHCO_3$ (100 mL) and brine (2 x 50 mL), drying ($MgSO_4$), concentration, and flash chromatography (silica, 20% EtOAc in *n*-hexane) afforded the allyl alcohol **18** (6.6 g, 23.1, 99%).

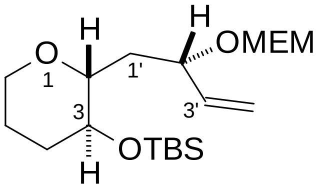


18

18: oil; R_f = 0.68 (silica, 30% EtOAc in *n*-hexane); IR ($CHCl_3$) ν_{max} 3490, 3009, 2955, 2884, 2857, 1439, 1278, 1257, 1212, 1125, 1096, 1060, 944, 924, 850 cm^{-1}; $[\alpha]_D^{25}$ + 51.1 (*c* 2.43, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_{3,}$) δ 5.84 (ddd, J = 17.0, 10.5, 6.0 Hz, 1H, H_3), 5.24 (d, J = 17.0 Hz, 1H, H_{4trans}), 5.05 (d, J = 10.5, 1H, H_{4cis}), 4.31-4.33 (m, 1H, H_2), 3.89 (ddd, J = 11.0, 2.0, 2.0 Hz, 1H, $He_{6'}$), 3.71 (s, 1H, OH), 3.35 (ddd, J = 11.0, 11.0, 3.8 Hz, 1H, $Ha_{6'}$), 3.24-3.28 (m, 2H, $H_{2'}$, $H_{3'}$), 2.10 (br d, J = 14.3, 1H, H_1), 1.98 (br d, J = 10.5 Hz, 1H, $He_{4'}$), 1.64-1.69 (m, 2H, 2 x $H_{5'}$), 1.40-1.50 (m, 2H, H_1, $H_{4'}$), 0.86 (s, 9H, $(C\underline{H}_3)_3$ CSi), 0.04 (s, 6H, 2 x CH_3Si); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7 (d, C_3), 113.9 (t, C_4), 83.7 (d, $C_{2'}$), 72.8 (d, C_2), 71.3 (d, $C_{3'}$), 67.6 (t, $C_{6'}$), 39.1 (t, C_1), 33.2 (t, $C_{4'}$), 25.7 (q, $(\underline{C}H_3)_3CSi$), 25.5 (t, $C_{5'}$), 17.9 (s, $(CH_3)_3\underline{C}Si$), -4.1 (q, $\underline{C}H_3Si$), -4.7 (q, $\underline{C}H_3Si$); MS at *m/z* (rel int) 285 ($[M-H]^+$, 2), 229 ($[M-{}^tBu])^+$, 3), 175

(51), 157 (61), 101 (38), 83 (99), 75 (100), 73 (78), 57 (84), 55 (47). Anal. Calcd for $C_{15}H_{30}O_3Si$; C, 62.89.; H, 10.56. Found: C, 62.67; H, 10.74.

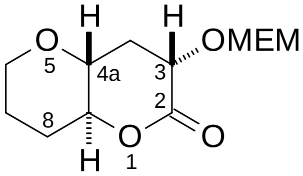
(2R, 3S, 2'S)-3-(*tert*-Butyldimethylsiloxy)-2-(2'-methoxy-methoxy-but-3'-enyl)-tetrahydropyran (19). A solution of **18** (6.4 g, 22.4 mmol), *i*-Pr_2NEt (15.6 mL, 89.5 mmol), MEMCl (3.4 mL, 44.8 mmol), and DMAP (250 mg, 2 mmol) in CH_2Cl_2 (225 mL) was stirred at 25 ºC for 5 h. The mixture was then poured into 10% aqueous citric acid (200 mL) and was extracted with ether (3 x 150 mL). The combined extracts were washed with water (150 mL) and brine (150 mL), dried ($MgSO_4$) and concentrated. Flash column chromatography gave (silica, 10% EtOAc in *n*-hexane) **19** (7 g, 21.2 mmol, 95%).



19

19: oil; R_f = 0.40 (silica, 10% EtOAc in *n*-hexane); IR ($CHCl_3$) ν_{max} 3019, 3010, 2955, 2887, 2857, 1439, 1256, 1216, 1210, 1131, 1097, 1067, 994, 933 cm^{-1}; $[\alpha]_D^{25}$ - 3.56 (*c* 1.72, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.65 (ddd, J = 17.1, 10.4, 8.7 Hz, 1H, $H_{3'}$), 5.22 (d, J = 17.1 Hz, 1H, $H_{4'trans}$), 5.21 (d, J = 10.4, 1H, $H_{4'cis}$), 4.70 (d, J = 6.6 Hz, 1H, $OC\underline{H}_2O$), 4.55 (d, J = 6.6 Hz, 1H, $OC\underline{H}_2O$), 4.22 (ddd, J = 8.7, 8.7, 5.0 Hz, 1H, $H_{2'}$), 3.84 (ddd, J = 11.1, 2.0, 2.0 Hz, 1H, He_6), 3.36 (s, 3H, $OC\underline{H}_3$), 3.30 (ddd, J = 10.4, 9.0, 4.5 Hz, 1H, H_3), 3.22 (ddd, J = 11.1, 11.1, 3.3 Hz, 1H, Ha_6), 2.99 (ddd, J = 10.4, 10.4, 2.1 Hz, 1H, H_2), 1.98-2.04 (m, 2H, Ha_4, $H_{1'}$), 1.61-1.70 (m, 3H, $H_{1'}$, 2 x H_5), 1.39 (br dd, J = 10.7, 4.5 Hz, 1H, He_4), 0.87 (s, 9H, $(C\underline{H}_3)_3CSi$), 0.05 (s, 6H, 2 x $C\underline{H}_3Si$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1 (d, $C_{3'}$), 117.8 (t, $C_{4'}$), 93.7 (t, $O\underline{C}H_2O$), 79.6 (d, C_2), 75.2 (d, $C_{2'}$), 71.3 (d, C_3), 67.5 (t, C_6), 55.3 (q, $O\underline{C}H_3$), 37.8 (t, $C_{1'}$), 33.6 (t, C_4), 25.7 (q, $(\underline{C}H_3)_3CSi$), 25.6 (t, C_5), 17.9 (s, $(CH_3)_3\underline{C}Si$), -3.9 (q, $\underline{C}H_3Si$), -4.7 (q, $\underline{C}H_3Si$); MS at *m/z* (rel int) 285 ($[M\text{-}OCH_3]^+$, 4), 269 ($[M\text{-}OCH_2OCH_3])^+$, 23), 211 (43), 157 (73), 137 (71), 101 (47), 89 (64), 75 (96), 73 (94), 71 (100), 57 (63). Anal. Calcd for $C_{17}H_{34}O_4Si$: C, 61.77; H, 10.37. Found: C, 61.67; H, 10.47.

Preparation of (3S, 4aR, 8aS)-3-methoxymethoxy-hexahydro pyrane [3-2b] pyran-2-one (8). To a stirred solution mixture of 4-methylmorpholine N-oxide (8.6 g, 63.6 mmol) and H_2O (66 mL) at 25 ºC was added OsO_4 (25.4 mg, 0.1 mmol) followed by slow addition of **19** (7 g, 21.2 mmol) in THF-acetone (1:1) (132 mL). After 12 h at 25 ºC the reaction mixture was treated with an aqueous saturated solution of $Na_2S_2O_3$ (75 mL), diluted with EtOAc (500 mL), washed with H_2O (2 x 100 mL), and dried ($MgSO_4$). Concentration followed by flash column chromatography (silica, 60% EtOAc in *n*-hexane) afforded the expected diol (5.8 g, 15.9 mmol, 75%), which was dissolved in dry THF (160 mL) and treated with (*n*-Bu)$_4$NF (5 g, 19.1 mmol). The reaction mixture was stirred at 25 ºC for 6 h, after which the solvent was removed. The residue was dissolved in MeOH:H_2O (4:1) (160 mL), treated with (*n*-Bu)$_4$$NIO_4$ (13.8 g, 39.1 mmol) and the mixture stirred at 0 ºC for 3 h. The quenched reaction was taken with H_2O (500 mL) and extracted with ether (2 x 200 mL). The combined organic layers were washed with 5% $NaHCO_3$ aqueous solution (2 x 200 mL) and water (2 x 200 mL). The organic phase was dried ($MgSO_4$) and concentrate to give hemiacetals **20** (2.8 g, 12.9 mmol, 81 %). **20**: Anal. Calcd for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31. Found: C, 55.04; H, 8.56. To a stirred mixture of pyridinium chlorochromate (PCC, 4 g, 18.9 mmol), NaOAc (207 mg, 2.5 mmol) in CH_2Cl_2 (50 mL), was added a solution of **20** (2.75 g, 12.6 mmol) and CH_2Cl_2 (12.5 mL) dropwise over ca. 5 min. After 12 h, the reaction was diluted with 50 mL of dry pentane-Et_2O (2:1, v/v, from Na_2SO_4) and the supernatent was filtered through a plug of silica gel. The chromium salts were washed with additional pentane-Et_2O (2 x 100 mL), and the washing were passed through the plug of silica gel. Concentration afforded **8** (1.8 g, 8.3 mmol, 66 %).



8

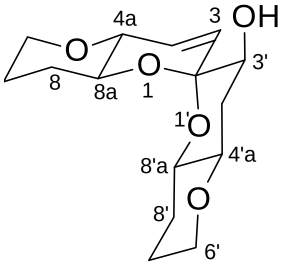
8: oil; R_f = 0.55 (silica, 50% EtOAc in *n*-hexane); IR ($CHCl_3$) ν_{max} 3031, 3010, 2954, 1752, 1464, 1441, 1264, 1232, 1187, 1153, 1092, 1057, 964 cm^{-1}; $[\alpha]_D^{25}$ - 124.3 (*c* 2.77, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.90 (d, J = 6.8 Hz, 1H, $OC\underline{H}_2O$), 4.67 (d, J = 6.8 Hz, 1H, $OC\underline{H}_2O$), 4.27 (dd, J = 8.5, 7.0 Hz, 1H, H_3), 4.10 (ddd, J = 11.0, 9.5, 4.0 Hz, 1H, H_{8a}), 3.92 (br d, J = 11.7 Hz, 1H, He_6), 3.38-3.43 (m, 1H, Ha_6), 3.36 (s, 3H, $O\underline{C}H_3$), 3.31 (br ddd, J = 11.0, 10.6, 5.6 Hz, 1H, H_{4a}), 2.49 (ddd, J = 12.7, 7.0, 5.6 Hz, 1H, H_4), 2.20 (br dd, J = 12.0, 4.0, 1H, He_8), 1.93 (ddd, J = 12.7, 10.6, 8.5 Hz, 1H, H_4), 1.70-1.76 (m, 2H, 2 x H_7), 1.53-1.58 (m, 1H, Ha_8); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7 (s, C_2), 96.0 (t, $O\underline{C}H_2O$), 77.9 (d, C_{8a}), 74.2 (d, C_{4a}), 70.2 (d, C_3), 67.9 (t, C_6), 55.9 (q, $O\underline{C}H_3$), 34.1 (t, C_4), 29.2 (t, C_8), 24.7 (t, C_7); MS at *m/z* (rel int) 217 ($[M+H]^+$, 4), 185 (18), 127 (21), 97 (17), 84 (41), 71 (100), 57 (20), 55 (51). Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.53; H, 7.46. Found: C, 55.46; H, 7.51.

Preparation of (2S, 4aR, 8aS, 3'S, 4'aR, 8'aS)-spiro |(2, 4a, 6, 7, 8, 8a)-hexahydropyran [3, 2-b]pyrane-2,2'-octahydro[3, 2-b]pyran-3'ol. (23). Both lactone **8** and dibromo olefin **7** were azeotroped with benzene and then dried over P_2O_5 under high vacuum overnight. *n*-BuLi (9.45 mL, 1.5 M in *n*-hexane, 14.1 mmol) was added dropwise to a solution of **7** (2.85 g, 7.09 mmol) in dry THF (60 mL) at -78 ºC. The resulting mixture was stirred at -78 ºC for 1 h, warmed to 0 ºC and stirred at 0 ºC for 5 min, and then cooled back to -35 ºC. To this mixture was introduced the lactone **8** (1.5 g, 6.75 mmol) in THF (11 mL) via cannula and the resulting mixture was stirred for 30 min. The cooling bath was removed and the reaction was quenched by the addition of sat. NH_4Cl (10 mL) and H_2O (10 mL). The reaction was warmed to room temperature and diluted with Et_2O (20 mL). The aqueous layer was extracted with Et_2O (3 x 20 mL), and the combined organic layers were dried ($MgSO_4$), filtered and concentrated. Flash column chromatography (silica, 30% EtOAc in *n*-hexane) gave **21** (2.35 g, 5.2 mmol, 77%). **21**: Anal. Calcd for $C_{23}H_{40}O_7Si$: C, 60.50; H, 8.83. Found: C, 60.57; H, 8.97.

A solution of **21** (2 g, 4.42 mmol) in 0.5% CSA solution of MeOH (442 mL) was stirred at 25 ºC for 24 h. The reaction was quenched by addition of $NaHCO_3$ (10 g), stirred for 15 min, diluted with Et_2O (100 mL), filtered through Celite and filtrate concentrated. Flash column chromatography (silica, EtOAc) gave 1:1 mixture of diols **6** (1.1 g, 3.52 mmol, 80%). **6**: Anal. Calcd for $C_{16}H_{24}O_6$: C, 61.54; H, 7.7. Found: C, 61.64; H, 8.0.

A mixture of **6** (1 g, 3.2 mmol), quinoline (0.07 equiv) and Lindlar catalyst (10 wt% of 10% Pd-$CaCO_3$) in EtOAc was degassed four times under H_2 and then stirred at 25 ºC under H_2 for 10 h. The reaction mixture was filtered through Celite with the aid of EtOAc and the filtrate was concentrated to give **22** (954 mg, 3.1 mmol, 95%). **22**: Anal. Calcd for $C_{16}H_{26}O_6$: C, 61.14; H, 8.30. Found: C, 61.10; H, 8.47.

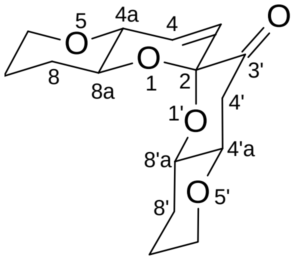
To a solution of **22** (630 mg, 2.0 mmol) in freshly distilled CH_3CN (200 mL) at -30 ºC was added $BF_3{\cdot}Et_2O$ (0.35 mL), 2.2 mmol) and the resulting mixture was stirred at -30 ºC for 20 min. The reaction was quenched by the addition of aqueous $NaHCO_3$ solution (100 mL) and Et_2O (200 mL). The layers were separated and aq. layer was extracted with Et_2O (2 x 100 mL). The combined extract were dried ($MgSO_4$), filtered and concentrated. The resulting oil was purified by flash column chromatography (silica, 90% EtOAc in *n*-hexane) to give **23** (500 mg, 1.77 mmol, 88%).



23

23: colorless foam; R_f = 0.59 (silica, 10% EtOAc in *n*-hexane); IR ($CHCl_3$) ν_{max} 3692, 3587, 3022, 3012, 2950, 2857, 1602, 1493, 1395, 1353, 1223, 1184, 1116, 1020, 980 cm^{-1}; $[\alpha]_D^{25}$ - 33.8 (*c* 2.61, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.06 (d, J = 10.2, 1H, H_3), 5.53 (d, J = 10.2, 2.1 Hz, 1H, H_4), 3.94 (br d, J = 10.7 Hz, 1H, He_6), 3.88 (br d, J = 10.9 Hz, 1H, $He_{6'}$), 3.53-3.62 (m, 3H, H_{8a}, H_{4a}, $H_{3'}$), 3.45 (ddd, J = 10.7, 9.7, 4.1 Hz, 1H, Ha_6), 3.41 (ddd, J = 11.5, 11.5, 4.1 Hz, 1H, $H_{8'a}$), 3.31-3.37 (m, 1H, $Ha_{6'}$), 2.98 (ddd, J = 11.5, 9.5, 4.1 Hz, 1H, $H_{4'a}$), 2.12-2.17 (m, 1H, $H_{4'}$), 1.96-2.02 (m, 3H, He_8, $He_{8'}$, $H_{7'}$), 1.67-1.78 (m, 4H, 2 x H_7, $H_{7'}$, $H_{4'}$), 1.55 (dddd, J = 11.5, 11.5, 11.5, 5.8 Hz, 1H, Ha_8), 1.41 (dddd, J = 11.6, 11.6, 10.6,5.8 Hz, 1H, $Ha_{8'}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.5(d, C_3), 128.3 (d, C_4), 96.5 (s, C_2), 76.7 (d, $C_{4'a}$), 75.5 (d, C_{4a}), 70.7 (d, $C_{3'}$), 70.0 (d, C_{8a}), 69.6 (d, $C_{8'a}$), 68.3 (t, C_6), 67.8 (t, $C_{6'}$), 34.1 (t, $C_{4'}$), 29.0 (t, $C_{8'}$), 28.9 (t, C_8), 25.6 (t, $C_{7'}$ or C_7), 25.5 (t, $C_{7'}$ or C_7); MS at *m/z* (rel int) 282 (M^+, 9), 155 (83), 97 (26), 84 (95), 83 (16), 81 (17), 71 (100), 55 (49). Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.83; H, 7.99.

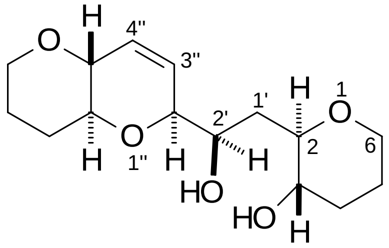
(2S, 4aR, 8aS, 4’aR, 8’aS)-Spiro |(2, 4a, 6, 7, 8, 8a)-hexahydropyran [3, 2-b]pyrane-2,2’-octahydropyrane[3, 2-b]pyran-3’-one (5). A solution of **23** (500 mg, 1.8 mmol) in CH_2Cl_2 (18 mL) was added to a mixture of NMO (359.5 mg, 2.66 mmol) and 4 Å-molecular sieves. The mixture was stirred at 25 ºC for 10 min and added tetrapropylammonium perruthenate (TPAP) (70 mg, 0.2 mmol). After stirring at 25 ºC for 2 h, the mixture was diluted with CH_2Cl_2 (60 mL) and washed with a saturated aqueous solution of Na_2SO_3 (2 x 50 mL) and H_2O (2 x 50 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated, and subjected to flash chromatography column (silica, 50% EtOAc in *n*-hexane) to give spiroketone **5** (437 mg, 1.56 mmol, 88%).



5

5: crystalline solid; mp 118-119 ºC (*n*-hexane); R_f = 0.78 (silica, 75% EtOAc in *n*-hexane); IR ($CHCl_3$) ν_{max} 3020, 3012, 2951, 2857, 1729, 1283, 1223, 1216, 1159, 1113, 1092, 1077, 1040, 1002, 984, 962 cm^{-1}; $[\alpha]_D^{25}$ - 18.27 (*c* 1.95, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.10 (d, J = 10.4, 1H, H_3), 5.58 (dd, J = 10.4, 2.0 Hz, 1H, H_4), 3.83-3.92 (m, 3H, He_6, $He_{6'}$, $H_{8'a}$), 3.64 (ddd, J = 9.0, 9.0, 4.0 Hz, 1H, H_{8a}), 3.57 (dd, J = 9.0, 2.0 Hz, 1H, H_{4a}), 3.26-3.44 (m, 2H, $Ha_{6'}$, Ha_6), 3.24 (ddd, J = 12.1, 9.4, 5.0 Hz, 1H, $H_{4'a}$), 2.87 (dd, J = 13.4, 12.2 Hz, 1H, $H_{4'}$), 2.80 (dd, J = 13.4, 5.0 Hz, 1H, $H_{4'}$), 2.08 (dd, J = 8.5, 3.5 Hz, 1H, $He_{8'}$), 2.02 (br dd, J = 12.0, 3.0 Hz, 1H, He_8), 1.74-1.82 (m, 4H, 2 x H_7, 2 x $H_{7'}$), 1.43-1.59 (m, 2H, $Ha_{8'}$, Ha_8); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.5 (s, $C_{3'}$)133.3(d, C_3), 124.8 (d, C_4), 96.7 (s, C_2), 78.0 (d, $C_{4'a}$), 75.1 (d, C_{4a}), 70.5 (d, C_{8a}), 70.1 (d, $C_{8'a}$), 68.3 (t, C_6 or $C_{6'}$), 67.8 (t, $C_{6'}$ or C_6), 42.8 (t, $C_{4'}$), 28.9 (t, $C_{8'}$ or C_8), 28.9 (t, C_8 or $C_{8'}$), 25.6 (t, $C_{7'}$ or C_7), 25.3 (t, $C_{7'}$ or C_7); MS at *m/z* (rel int) 281 ($[M+H]^+$, 3), 252 (26), 155 (41), 148 (34), 98 (100), 97 (63), 84 (75), 83 (100), 71 (100), 69 (41), 57 (55), 56 (98), 55 (99). Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.18; H, 7.32.

(2R, 3S, 2’R, 2’’S, 4’’aR, 8’’aS)-2-[2’-(2’’, 4’’a, 6’’, 7’’, 8’’, 8’’a)-Hexhydropyrane [3, 2-b]pyran-2’’-yl)-2’-hydroxyethyl]-tetrahydropyran-3-ol (4). To a solution of **5** (355 mg, 1.27 mmol) in freshly distilled CH_3CN (12 mL) at -15 ºC were added Et_3SiH (1.63 mL, 10.2 mmol) and then $BF_3{\cdot}Et_2O$ (0.8 mL, 6.35 mmol). The resulting solution was stirred at -15 ºC for 20-min. The reaction mixture was then diluted with Et_2O (100 mL) and washed with saturated $NaHCO_3$ (2 x 50 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$) and concentrated under vacuum. Flash column chromatography (silica, EtOAc) produced diol **4** (301 mg, 1.06 mmol, 83.5%) and its less polar $C_{2'}$-epimer (**4a**) (10 mg, 0.03 mmol, 24%).



4

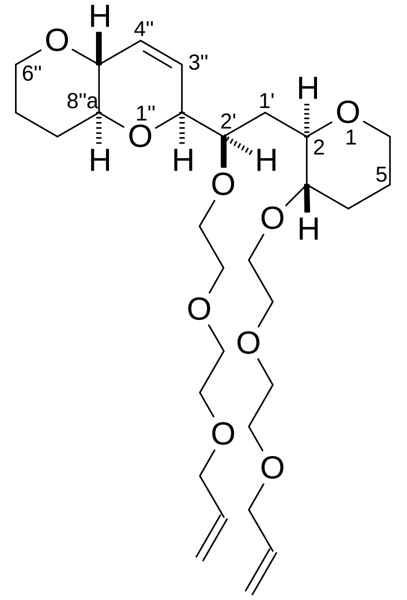
4: crystalline solid; mp 148-150 ºC; R_f = 0.28 (silica, 75% EtOAc in *n*-hexane); IR ($CHCl_3$) ν_{max} 3460, 3011, 2947, 2857, 1456, 1272, 1232, 1216, 1094, 1057, 967 cm^{-1}; $[\alpha]_D^{25}$ - 46.33 (*c* 0.6, $CHCl_3$); ^1H NMR (500MHz, $CDCl_3$) δ 5.87 (d, J = 10.4 Hz, 1H, $H_{3''}$), 5.69 (ddd, J =10.4, 2.0, 2.0 Hz, 1H, $H_{4''}$), 4.24 (br s, 1H, $H_{2''}$), 3.89 (br d, J =11.1 Hz, 1H, $He_{6''}$), 3.82-3.85 (m, 2H, $H_{2'}$, He_6), 3.41 (br d, J = 8.3 Hz, 1H, $H_{4''a}$), 3.27 (ddd, J = 11.1, 11.1, 3.6 Hz, 1H, $Ha_{6''}$), 3.19-3.29 (m, 4H, Ha_6, H_3, $H_{8''a}$, H_2), 2.07 (br dd, J = 12.4, 2.8 Hz, 1H, He_4), 2.01 (br dd, J = 12.1, 3.3 Hz, 1H, $He_{8''}$), 1.90 (ddd, J = 14.8, 9.8, 5.1 Hz, 1H, $H_{1'}$), 1.67-1.72 (m, 3H, $H_{1'}$, 2 x $H_{7''}$), 1.61-1.63 (m, 2H, 2 x H_5), 1.48 (dddd, J = 12.0, 12.0, 12.0, 5.3 Hz, 1H, $Ha_{8''}$), 1.35 (br ddd, J = 12.4, 12.0, 11.0 Hz, 1H, Ha_4); ^{13}C NMR (125 MHz, $CDCl_3$) δ 129.6 (d, $C_{3''}$), 127.1 (d, $C_{4''}$), 80.7 (d, C_2), 78.8 (d, $C_{2''}$), 75.6 (d, $C_{4''a}$), 75.2 (d, $C_{8''a}$), 70.8 (d, $C_{2'}$), 70.5 (d, C_3), 68.2 (t, $C_{6''}$), 67.7 (t, C_6), 35.7 (t, $C_{1'}$), 32.6 (t, C_4), 29.3 (t, $C_{8''}$), 25.7 (t, $C_{7''}$), 25.6 (t, C_5); ^1H NMR (500MHz, C_6D_6,) δ 5.98 (d, J = 10.4 Hz, 1H, $H_{3''}$), 5.68 (ddd, J = 10.5, 2.2, 2.2 Hz, 1H, $H_{4''}$), 4.16 (br s, 1H, $H_{2''}$), 3.93 (br s, 1H, $H_{2'}$), 3.75 (ddd, J = 11.5, 4.7, 3.8 Hz, 1H, $He_{6''}$), 3.71 (br d, J = 10.2 Hz, 1H, He_6), 3.52 (br s, 1H, $H_{4''a}$), 3.21 (m, 4H, $H_{8''a}$, $Ha_{6''}$, H_2, H_3), 3.11 (br dd, J = 11.9, 10.1, 1H, Ha_6), 2.88 (br s, 1H, OH), 2.48 (br s, 1H, OH), 2.02 (ddd, J = 14.2, 9.6, 4.5 Hz, 1H, $H_{1'}$), 1.84-1.90 (m, 3H, $H_{8''}$, H_4, $H_{1'}$), 1.38-1.47 (m, 2H, 2 x H_5), 1.32-1.37 (m, 3H, 2 x $H_{7''}$, $H_{8''}$), 1.21-1.29 (m, 1H, H_4); ^{13}C NMR (125 MHz, C_6D_6) δ 129.5 (d, $C_{3''}$), 127.3 (d, $C_{4''}$), 80.8 (d, C_2), 78.9 (d, $C_{2''}$), 75.8(d, $C_{4''a}$), 75.2 (d, $C_{8''a}$), 70.9(d, $C_{2'}$), 70.5 (d, C_3), 67.8 (t, $C_{6''}$), 67.4 (t, C_6), 35.9 (t, $C_{1'}$), 32.8 (t, C_4), 29.4 (t, $C_{8''}$), 25.8 (t, $C_{7''}$ or C_5), 25.6 (t, $C_{7''}$ or C_5); MS at *m/z* (rel int) 266($[M-H_2O]^+$, 1), 248(1), 140 (36), 127 (36), 101 (31), 81 (100), 71 (66), 57 (15), 55 (28). Anal. Calcd for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found: C, 63.24; H, 8.54.

4a: oil; R_f = 0.36 (silica, 75% AcOEt in *n*-hexane); IR ($CHCl_3$) ν_{max} 3476, 3022, 3011, 2947, 2857, 1456, 1369, 1264, 1223, 1211, 1094, 1049, 1011, 968 cm^{-1}; $[\alpha]_D^{25}$ - 4.76 (*c* 0.55, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$,) δ 5.90 (d, J = 10.5 Hz, 1H, $H_{3''}$), 5.79 (ddd, J =10.5, 2.0, 2.0 Hz, 1H, $H_{4''}$), 4.25 (br s, 1H, $H_{2''}$), 3.87-3.95 (m, 3H, $H_{2'}$, $He_{6''}$, He_6), 3.59 (br d, J = 11.9 Hz, 1H, $H_{4''a}$), 3.46 (ddd, J = 11.6, 11.0, 3.6 Hz, 1H, $Ha_{6''}$), 3.36-3.43 (m, 2H, Ha_6, H_3), 3.23-3.26 (m, 2H, H_2, $H_{8''a}$), 2.02-2.12 (m, 3H, $H_{1'}$, $He_{8''}$, H_4), 1.67-1.77 (m, 5H, $H_{1'}$, 2 x $H_{7''}$, 2 x H_5), 1.53 (dddd, J = 11.7, 11.7, 11.7, 5.3 Hz, 1H, $Ha_{8''}$) 1.39-1.43 (m, 1H, Ha_4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.3 (d, $C_{3''}$), 127.6 (d, $C_{4''}$), 82.4 (d, C_2), 77.9 (d, $C_{2''}$), 75.6 (d, $C_{4''a}$), 75.1 (d, $C_{8''a}$), 72.4 (d, $C_{2'}$), 70.2 (d, C_3), 68.2 (t, $C_{6''}$), 67.7 (t, C_6), 34.2 (t, $C_{1'}$), 32.4 (t, C_4), 29.3 (t, $C_{8''}$), 25.8 (t, $C_{7''}$ or C_5), 25.5 (t, C_5 or $C_{7''}$). ^1H NMR (400 MHz, C_6D_6) δ 6.08 (d, J = 10.4 Hz, 1H, $H_{3''}$), 5.93 (ddd, J = 10.4, 2.0, 2.0 Hz, 1H, $H_{4''}$), 4.43 (ddd, J = 5.1, 2.0, 2.0 Hz, 1H, $H_{2''}$), 4.17 (ddd, J = 9.1, 5.1, 2.0 Hz, 1H, $H_{2'}$), 3.75 (dd, J = 11.4, 4.7 Hz, 1H, $He_{6''}$), 3.52-3.60 (m, 2H, $H_{4''a}$, He_6), 3.24-3.27 (m, 2H, $H_{8''a}$, H_3), 3.10-3.21 (m, 2H, $Ha_{6''}$, H_2), 2.94 (ddd, J = 12.3, 2.0,2.0 Hz, 1H, Ha_6), 2.32 (ddd, J = 14.5, 2.3, 2.0 Hz, 1H, $H_{1'}$), 1.77-1.88 (m, 3H, $H_{8''}$, H_4, $H_{1'}$), 1.39-1.51 (m, 3H, H_5, $H_{7''}$, $H_{8''}$), 1.34-1.38 (m, 3H, $H_{7''}$, H_4, H_5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.6 (d, $C_{3''}$), 128.0 (d, $C_{4''}$), 82.8 (d, C_2), 78.2 (d, $C_{2''}$), 75.9 (d, $C_{4''a}$), 75.3 (d, $C_{8''a}$), 72.6 (d, $C_{2'}$), 70.0 (d, C_3), 67.7 (t, $C_{6''}$), 67.2 (t, C_6), 34.3 (t, $C_{1'}$), 32.6

(t, C_4), 29.5 (t, $C_{8''}$), 25.8 (t, $C_{7''}$ or C_5), 25.5 (t, C_5 or $C_{7''}$); MS at *m/z* (rel int) 285 ($[M+H]^+$, 1), 266 ($[M-H_2O]^+$, 2), 145 (44), 140 (100), 127 (78), 101 (33), 83 (20), 81 (73), 71 (46), 55 (19). Anal. Calcd for $C_{15}H_{24}O_5$: C, 63.36.; H, 8.51. Found: C, 63.41; H, 8.68.

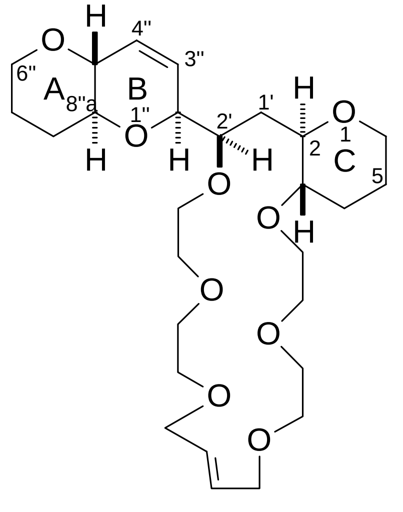
4 (Diacetate). ^{1}H NMR (500 MHz, $CDCl_3$,) δ 5.86 (d, J = 10.4 Hz, 1H, $H_{3''}$), 5.54 (ddd, J =10.4, 1.9, 1.9 Hz, 1H, $H_{4''}$), 5.10 (ddd, J = 10.5, 2.4, 2.2 Hz, 1H, $H_{2'}$), 4.39 (bs s, 1H, $H_{2''}$), 4.39 (ddd, J=12.5, 9.2, 3.5 Hz, 1H, H_3), 3.86 (br dd, J = 11.4, 4.1 Hz, 1H, $He_{6''}$), 3.82 (ddd, J = 11.6, 2.1, 2.1 Hz, He_6), 3.50 (br d, J = 8.1 Hz, 1H, $H_{4''a}$), 3.39 (ddd, J = 11.4, 11.4, 4.0 Hz, 1H, $Ha_{6''}$), 3.20 (ddd, J = 11.6, 11.6, 2.6 Hz, 1H, Ha_6), 3.14 (ddd, J=11.9, 8.1, 4.0 Hz, 1H, $H_{8''a}$), 3.11 (ddd, J=10.8, 9.2, 2.5 Hz, 1H, H_2), 2.10 (br ddd, J = 12.5, 3.5, 3.5 Hz, 1H, He_4), 2.09 (s, 3H, $C\underline{H}_3CO_2$), 2.03 (s, 3H, $C\underline{H}_3CO_2$), 1.90-2.03 (m, 1H, $He_{8''}$), 1.87 (ddd, J = 14.8, 10.5, 2.5 Hz, 1H, H(*pro*-S)$_{1'}$), 1.69-1.72 (m, 2H, 2 x $H_{7''}$), 1.60-1.63 (m, 2H, 2 x H_5), 1.49 (dddd, J = 12.5, 11.9, 11.6, 6.0 Hz, 1H, $Ha_{8''}$), 1.43 (ddd, J = 14.8, 10.8, 2.2 Hz, 1H, H(*pro*-R)$_{1'}$), 1.34 (dddd, J = 12.5, 12.5, 12.5, 4.6 Hz, 1H, Ha_4); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7 (s, $CH_3\underline{C}O_2$), 170.4(s, $CH_3\underline{C}O_2$), 129.9 (d, $C_{3''}$), 126.9 (d, $C_{4''}$), 76.7 (d, $C_{2''}$), 75.6 (d, C_2), 75.3 (d, $C_{4''a}$), 75.2 (d, $C_{8''a}$), 72.1 (d, $C_{2'}$), 71.7 (d, C_3), 68.2 (t, $C_{6''}$), 67.6 (t, C_6), 31.1 (t, $C_{1'}$), 29.4 (t, $C_{8''}$), 29.3 (t, C_4), 25.8 (t, $C_{7''}$), 25.1 (C_5), 21.4 (q, $\underline{C}H_3CO_2$), 21.3 (q, $\underline{C}H_3CO_2$). **4a** (Diacetate). ^{1}H NMR (500MHz, $CDCl_3$,) δ 5.89 (d, J = 10.3 Hz, 1H, $H_{3''}$), 5.66 (ddd, J =10.3, 2.0, 2.0 Hz, 1H, $H_{4''}$), 5.18-5.22 (m, 1H, $H_{2'}$), 4.46-4.48 (m, 1H, H_3), 4.35 (br s, 1H, $H_{2''}$), 3.86-3.93 (m, 2H, $He_{6'}$, $He_{6''}$), 3.58 (br d, J = 7.0 Hz, 1H, $H_{4''a}$), 3.43 (ddd, J = 11.5, 9.8, 3.2 Hz, 1H, $Ha_{6''}$), 3.36 (ddd, J = 10.5, 8.8, 3.1 Hz, 1H, H_2), 3.28 (br s, 1H, Ha_6), 3.26-3.29 (m, 1H, $H_{8''a}$), 2.12-2.16 (m,, 1H, He_4), 2.05-2.09 (m, 1H, $He_{8''}$), 2.03 (br s, 1H, $H_{1'}$), 2.01 (s, 6H, 2 x $C\underline{H}_3CO_2$), 1.66-1.77 (m, 6H, $H_{1'}$, 2 x $H_{7''}$, 2 x H_5, $Ha_{8''}$), 1.40-1.46 (m, 1H, Ha_4); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2 (s, $CH_3\underline{C}O_2$), 166.7 (s, $CH_3\underline{C}O_2$), 129.8 (d, $C_{3''}$), 127.2 (d, $C_{4''}$), 77.2 (d, $C_{2''}$), 75.6 (d, C_2), 75.4 (d, $C_{4''a}$), 75.1 (d, $C_{8''a}$), 72.1 (d, C_3), 71.7 (d, $C_{2'}$), 68.2 (t, $C_{6''}$), 67.4 (t, C_6), 32.1 (t, $C_{1'}$), 29.3 (t, C_4), 29.2 (t, $C_{8''}$), 25.7 (t, $C_{7''}$), 24.9 (C_5), 21.2 (q, $\underline{C}H_3CO_2$), 21.1 (q, $\underline{C}H_3CO_2$).

Compound 2. To a solution of diol **4** (25.8 mg, 0.091 mmol) in 2 mL of dry THF was added KO^{t}Bu (22 mg, 0.196 mmol, 0.2 mL of 1.0 M solution in THF). After being the mixture stirred at 25 ºC for 2 h, a solution of allyl diethylene glycol toluene-*p*-sulfonate (60 mg, 0.2 mmol), in THF (2 mL) was added via cannula. The resulting solution was stirred at 50 ºC for another 4 h, when TLC analysis showed full disappearance of starting material. Water (50 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 x 25 mL), dried ($MgSO_4$) and filtered. After evaporation of the solvent, the residue was purified by chromatography (silica, gradient from 50% EtOAc in *n*-hexane to 100% EtOAc) to yield **3** (31.2 mg, 0.058 mmol, 64%).



3

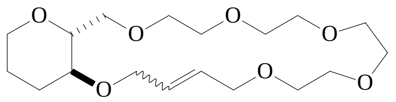
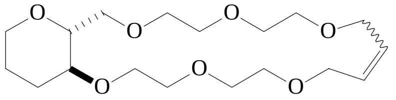
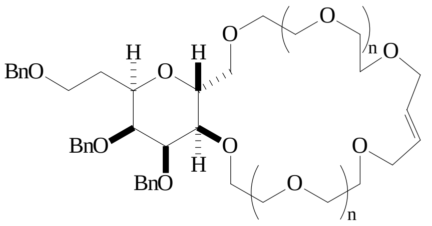
3: colorless oil; R_f = 0.59 (silica, EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (dddd, J = 17.2, 10.4, 5.7, 5.7 Hz, 2H, $C\underline{H}=CH_2$), 5.82 (br d, J = 10.4 Hz, 1H, $H_{3''}$), 5.74 (ddd, J = 10.4, 2.0. 2.0 Hz, 1H, $H_{4''}$), 5.25 (dddd, J = 17.2, 1.6, 1.6, 1.6 Hz, 2H, $CH=C\underline{H}_2$), 5.15 (d, J = 10.4 Hz, 2H, $CH=C\underline{H}_2$), 4.27 (br s, 1H, $H_{2''}$), 4.00 (dddd, J = 5.7, 1.2, 1.2, 1.2 Hz, 4H, - $OC\underline{H}_2CH=CH_2$), 3.90 (brd, J = 11.4 Hz, 1H, $He_{6''}$), 3.82 (brd, J = 11.4 Hz, 1H, He_6), 3.75-3.79 (m, 1H, $-OC\underline{H}_2CH_2O-$), 3.68-3.72 (m, 1H, $-OC\underline{H}_2CH_2O-$), 3.55-3.63 (m, 15H, 13 x $-OC\underline{H}_2CH_2O-$, $H_{2'}$, $H_{4''a}$), 3.48-3.51 (m, 1H, $-OC\underline{H}_2CH_2O-$), 3.42 (ddd, J = 11.4, 11.4, 3.3 Hz, 1H, $Ha_{6''}$), 3.28 (ddd, J = 10.7, 8.7, 2.0 Hz, 1H, H_2), 3.26 (ddd, J = 11.4, 11,4, 2.8 Hz, 1H, Ha_6), 3,17 (ddd, J = 11.6, 8.3, 4.1 Hz, 1H, $H_{8''a}$), 2.95 (ddd, J = 10.5, 8.7, 4.4 Hz, 1H, H_3), 2.17 (br dddd, J = 12.2, 4.4, 3.0, 3.0 Hz, 1H, He_4), 2.07 (ddd, J = 14.4, 10.7, 2.0 Hz, 1H, H(*pro*-S)$_{1'}$), 2.02 (br dddd, J = 12.2, 4.1, 3.3, 3.3 Hz, 1H, $He_{8''}$), 1.63-1.70 (m, 2H, 2 x $H_{7''}$), 1.47-1.60 (m, 2H, 2 x H_5), 1.51 (dddd, J = 12.2, 12.2, 11.6, 4.5 Hz, 1H, $Ha_{8''}$), 1.43 (ddd, J = 14.4, 10.7, 2.3 Hz, 1H, H (*pro*-R)$_{1'}$), 1.34 (dddd, J = 12.2, 12.2, 10.5, 4.8 Hz, 1H, Ha_4); ^{13}CNMR (125 MHz, $CDCl_3$) δ 134.83 (d, $\underline{C}H=CH_2$), 134.80 (d, $\underline{C}H$=CH2), 128.62 (d, $C_{3''}$), 128.33 (d, $C_{4''}$), 117.07 (t, 2 x C, $CH=\underline{C}H_{2)}$,, 78.70 (d, C_3), 78.21 (d, $C_{4''a}$), 78.02 (d, $C_{2''}$), 77.03 (d, C_2), 75.73 (d, $C_{2'}$), 75.15 (d, $C_{8''a}$), 72.28 (t, $-O\underline{C}H_2C=$), 72.25 (t, $-O\underline{C}H_2C=$), 70.92 (t), 70.73 (t), 70.70 (t), 70.65 (t), 70.62 (t), 70.55 (t), 69.50 (t), 69.45 (t), (1 c each, 4 x $O\underline{C}H_2\underline{C}H_2O-$), 68.21 (t, $C_{6''}$), 67.32 (t, C_6), 33.94 (t, $C_{1'}$), 29.47 (t, $C_{8''}$), 29.38 (t, C_4), 25.84 (t, $C_{7''}$), 25.47 (t, C_5). To a solution of bis(tricyclohexylphosphine)benzylidene ruthenium dichloride (5 mg, 0.004 mmol) predissolved in 4 mL of CH_2Cl_2 was added via cannula a solution of acyclic diene **3** (17 mg, 0.031 mmol) in CH_2Cl_2 (3 mL). The purple solution was stirred at 25 ºC and turned orange-brown in color over a 2 h period. The solution was stirred at 25 ºC for 12 h. The solution was then concentrated under pressure to afford an oily brown residue. Purification by chromatography (silica, gradient from 50% EtOAc in *n*-hexane to 100% EtOAc) gave **2** (12.8 mg, 0.025 mmol, 81%).



2

2: oil; R_f = 0.17 (silica, 100% EtOAc); IR ($CHCl_3$) ν_{max} 2960, 2927, 2854, 2360, 1463, 1262, 1096, 1014, 865 cm^{-1}; $[\alpha]_D^{25}$ + 8.5 (*c* 0.16, $CHCl_3$); ^{1}HNMR (500 MHz, $CDCl_3$) δ 5.76-5.87 (m, 4H, $H_{3''}$, $H_{4''}$, -$OCH_2C\underline{H}=$), 4.26 (br s, 1H, $H_{2''}$), 4.05-4.17 (m, 4H, $OC\underline{H}_2CH=$), 3.90 (br dd, J = 12.0, 4.2 Hz, 1H, $He_{6''}$), 3.82 (br d, J = 11.4 Hz, 1H, He_6), 3.46-3.80 (m, 18H, $H_{2'}$, $H_{4''a}$, $-OC\underline{H}_2C\underline{H}_2O-$), 3.42 (ddd, J = 12.0, 12.0, 3.5 Hz, 1H, $Ha_{6''}$), 3.37 (br dd, J = 10.7, 9.1 Hz, 1H, Hz), 3.32 (ddd, J = 11.4, 11.4, 2.4 Hz, 1H, Ha_6), 3.17 (ddd, J = 12.0, 8.4, 4.0 Hz, 1H, $H_{8''a}$), 2.93 (ddd, J = 10.2, 9.1, 4.4 Hz, 1H, H_3), 2.20 (br dd, J = 12.4, 3.1 Hz, 1H, He_4), 2.10 (br dd, J =12.4, 12.0, 3.1 Hz, 1H, H(*pro*-S)$_{1'}$, 2.03 (br d, J = 12.2 Hz, 1H, $He_{8''}$), 1.61-1.70 (m, 2H, 2 x $H_{7''}$), 1.51-1.57 (m, 2H, 2 x H_5), 1.49 (br dddd, J = 12.2, 12.2, 12.0, 4.5 Hz, 1H, $Ha_{8''}$), 1.47 (ddd, J = 12.4, 10.7, 2.0 Hz, 1H, H(*pro*-R)$_{1'}$), 1.35 (dddd, J = 12.4, 12.2, 10.2, 4.5 Hz, 1H, Ha_4); ^{13}CNMR (125 MHz, $CDCl_3$) δ 129.80 (d, $-OCH_2\underline{C}H=$), 129.64 (d, $-OCH_2\underline{C}H=$), 128.56 (d, $C_{3''}$), 128.38 (d, $C_{4''}$), 78.21 (d, C_3), 78.21 (d, $C_{4''a}$), 78.16 (d, $C_{2''}$), 76.97 (d, C_2), 75.76 (d, $C_{2'}$), 75.16 (d, $C_{8''a}$), 71.06, 70.92, 70.88, 70.87, 70.82, 70.75, 70.72, 70.71, 68.98, 68.21 (10 x C, t, $-O\underline{C}H_2$), 68.10 (t, $C_{6''}$), 67.24 (t, C_6), 34.26 (t, $C_{1'}$), 29.48 (t, $C_{8''}$), 29.07 (t, C_4), 25.85 (t, $C_{7''}$), 25.40 (t, C_5); HRMS, calcd for $C_{27}H_{44}O_9$ (M^+) 512.2985, found 512.2975.

Asociation Constants of Ionophore-Analogues and Alkali Metal or Ammonium Cations by the Picrate Extraction Method. (-ΔGº Kcal/mol)

Compound	Li^+	Na^+	K^+	Rb^+	Cs^+	$CH_3NH_3^+$	$PhCH(CH_3)NH_3^+$
	3.2×10^4 (6.2)	------	6.1×10^3 (5.2)	------	6.4×10^3 (5.2)	1.6×10^3 (4.3)	------
	9.4×10^4 (6.8)	4.9×10^4 (6.4)	3.5×10^4 (6.2)	2.5×10^4 (6.0)	2.7×10^4 (6.1)	6.5×10^3 (5.2)	------
							
n = 1	2.9×10^4 (6.1)	1.5×10^4 (5.7)	1.4×10^3 (4.3)	1.7×10^3 (4.4)	4.9×10^3 (5.0)	2.1×10^3 (4.5)	------
2	4.5×10^4 (6.3)	5.0×10^3 (5.0)	1.8×10^4 (5.8)	1.4×10^4 (5.6)	1.1×10^4 (5.5)	2.0×10^3 (4.5)	------
Dicyclohexyl-18-crown-6	1.9×10^5 (7.2)	2.3×10^6 (8.6)	2.0×10^8 (11.3)	5.0×10^6 (9.1)	1.8×10^6 (8.5)	8.3×10^6 (9.4)	------
2,3-Naphto-18-crown-6	2.2×10^4 (5.9)	1.2×10^6 (8.3)	8.6×10^7 (10.8)	1.1×10^7 (9.6)	1.2×10^6 (8.3)	3.3×10^5 (7.5)	------

NMR Studies

2D-Noesy spectra were recorded up to six different mixing times: 750, 1000, 1250, 1500, 2000 and 3000 msec. Cross-relaxation rates were obtained by linear extrapolation of $[I_{ij}(\tau m)/I_{ii}(\tau m)]/\tau m$ vs. τm at zero mixing time,[1] where I_{ij} and I_{ii} are the intensities of the NOE-enhanced and the selectively excited signals, respectively. Interproton distances were calculated from the formula $r_{ij}=(\sigma_{ref}/\sigma_{ij})^{1/6}r_{ref}$ when σ_{ref} and r_{ref} are the cross-relaxation rate and the distance of the reference pair of protons. We used σ_{ij} ($H_{4''}$-$H_{4''a}$) as σ_{ref} and 2.7 Å ($H_{4''}$-$H_{4''a}$) as r_{ref}. The regression analysis was done only with marked (*) rows.

Proton Pairs	τm	NOE (%)		σ_{ij}	R^2	Dst. Å
$H_{4''}$-$H_{4''a}$	750	1.41		2.48E-5	0.9472	2.7
	1000	2.85	*			
	1250	3.62	*			
	1500	4.54	*			
	2000	3.14				
	3000	7.86				
$H_{3''}$-$H_{2'}$	750	2.02		5.11E-5	0.9905	2.40
	1000	4.16	*			
	1250	5.06	*			
	1500	5.87	*			
	2000	7.84				
	3000	7.48	*			
$H_{3''}$-$H_{1'\mathit{proR}}$	750	0.69	*	5.70 E-6	0.8135	3.46
	1000	1.48				
	1250	1.52	*			
	1500	1.62	*			
	2000	3.06	*			
	3000	1.40				
$H_{2'}$-H_2	750	1.64	*	2.34 E-5	0.9435	2.73
	1000	2.14	*			
	1250	2.31				
	1500	2.84	*			
	2000	3.89				
	3000	4.93	*			
$H_{2'}$-$H_{1'\mathit{proS}}$	750	1.46	*	2.51 E-5	0.9969	2.70
	1000	0.59				
	1250	1.93	*			
	1500	0.69				
	2000	1.79	*			
	3000	0.63	*			
$H_{2'}$-$H_{1'\mathit{proR}}$	750	3.10		5.41E-5	0.9999	2.38
	1000	3.81	*			
	1250	4.23				
	1500	4.58	*			
	2000	5.40	*			
	3000	6.18				

Cont.

H_2-$H_{1'\mathit{proS}}$	750	5.92	*	8.63E-5	0.9941	2.20
	1000	4.57				
	1250	8.93	*			
	1500	6.20				
	2000	7.44				
	3000	16.04	*			

Ref.

1. Macura, S; Farmer, B.J.; Brown, L.R. J. Mag. Reson. 1983, 70, 493-499.

Population, Angles α, β and γ and Interproton Distances for compound **4**: conformers 1 to 9 and experimental values from 2D-NOESY experiments.

Conformer	Population	α	β	γ	$H_{3''}$-$H_{2'}$	$H_{3''}$-$H_{1'\mathit{proR}}$	$H_{2'}$-H_{2}	$H_{2'}$-$H_{1'\mathit{proS}}$	$H_{2'}$-$H_{1'\mathit{proR}}$	H_{2}-$H_{1'\mathit{proS}}$
1	54.63	-173	-178	-180	2.5	3.0	3.1	3.1	2.5	2.5
2	14.55	52	-174	-178	3.9	3.2	3.0	3.1	2.6	2.5
3	8.90	-172	-170	63	2.5	3.0	3.8	3.1	2.6	2.4
4	5.85	-60	-179	-179	3.1	4.8	3.1	3.1	2.5	2.5
5	2.77	-177	78	-166	2.5	4.1	3.9	2.6	2.3	2.7
6	2.42	57	-66	-168	3.9	2.3	2.5	2.5	3.1	2.6
7	1.24	-59	-174	60	3.1	4.8	3.9	3.1	2.6	2.4
8	1.05	52	-173	62	3.9	3.2	3.8	3.1	2.6	2.4
9	0.91	-66	53	-179	3.0	4.9	3.8	2.4	2.5	2.5
exp.					2.4	2.9	2.7	2.8	2.4	2.3

Calculation Details

Conformational Searches: Conformational searches of compound **4** were performed using systematic Monte Carlo method as implemented on Macromodel V6.0. For each search, 10000 starting structures were generated and minimized (MM3*) until the gradient was less than 0.05 (kJ/mol)Å using the truncated Newton-Raphson method (TNCG). Duplicate conformations and those with an energy greater than 10 kcal/mol above the global minimum were discarded.

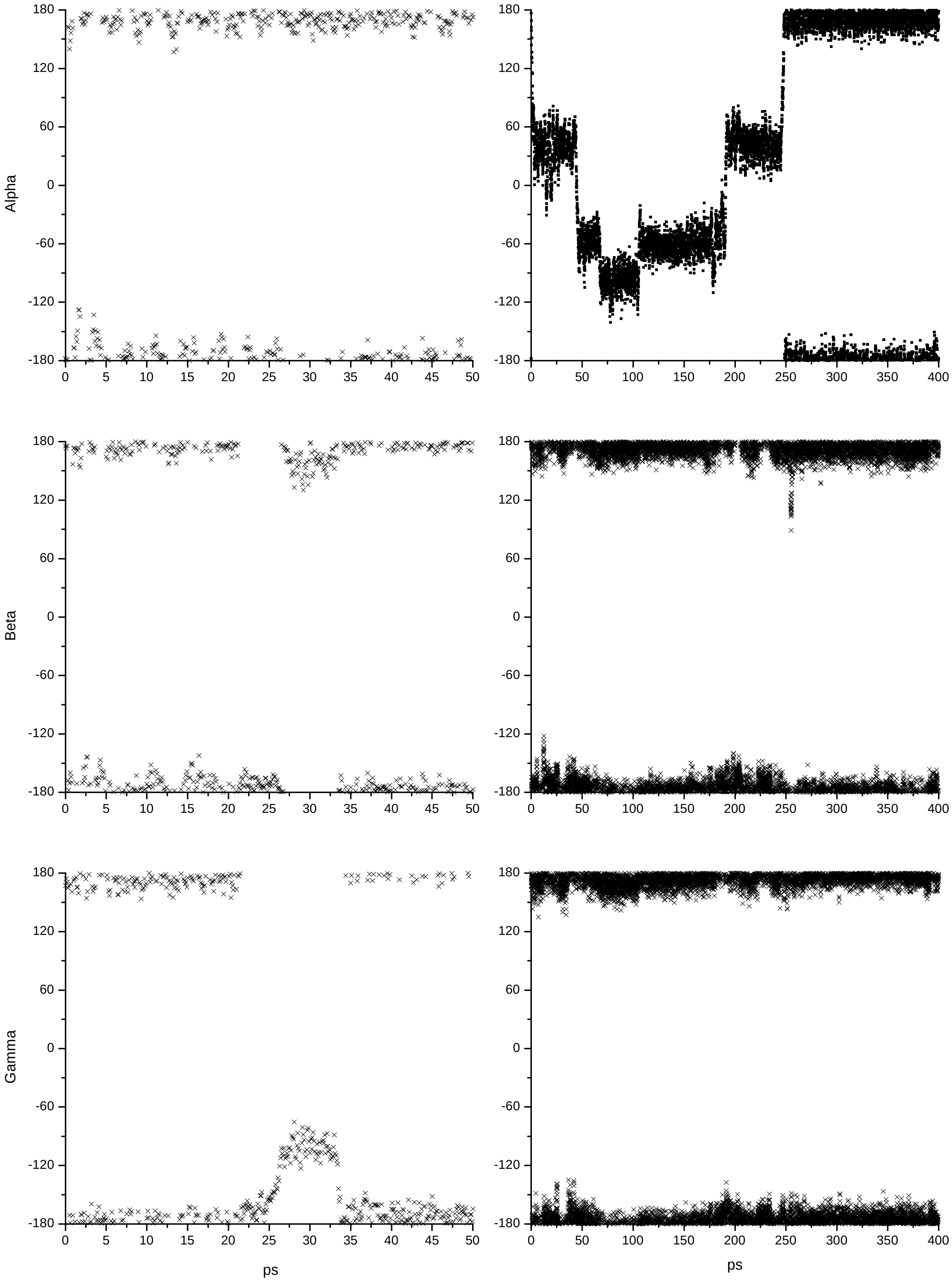
Calculated coupling constants (Hz) for compound **4**:
H_{a6}–H_{a5}: 11.9, H_{a6}–H_{e5}: 2.5, H_{e6}–H_{a5}: 4.5, H_{e6}–H_{e5}: 1.5, H_{a5}–H_{a4}: 13.4, H_{a5}–H_{e4}: 4.3, H_{e5}–H_{a4}: 4.3, H_{e5}–H_{e4}: 2.3, H_{a4}–H_3: 11.1, H_{e4}–H_3: 4.9, H_3–H_2: 8.9, H_2–$H_{1'\mathit{proR}}$: 10.0, H_2–$H_{1'\mathit{proS}}$: 2.2, $H_{1'\mathit{proR}}$–$H_{2'}$: 2.2, $H_{1'\mathit{proS}}$–$H_{2'}$: 10.5, $H_{2'}$–$H_{2''}$: 2.5, $H_{2''}$–$H_{3''}$: 3.2, $H_{2''}$–$H_{4''}$: –2.5, $H_{2''}$–$H_{4''a}$: 4.3, $H_{3''}$–$H_{4''a}$: –2.6, $H_{4''}$–$H_{4''a}$: 2.7, $H_{4''a}$–$H_{8''a}$: 9.0, $H_{a6''}$–$H_{a7''}$: 11.9, $H_{a6''}$–$H_{e7''}$: 2.9, $H_{e6''}$–$H_{a7''}$: 4.8, $H_{e6''}$–$H_{e7''}$: 1.3, $H_{a7''}$–$H_{a8''}$: 13.3, $H_{a7''}$–$H_{e8''}$: 4.6, $H_{e7''}$–$H_{a8''}$: 4.4, $H_{e7''}$–$H_{e8''}$: 2.1, $H_{a8''}$–$H_{8''a}$: 11.2, $H_{e8''}$–$H_{8''a}$: 4.7

MM calculations and MD simulations: Molecular Mechanics calculations and Molecular Dynamics simulations of compounds **2** and **three-units oligomer** were performed using Sybyl 6.3. MD simulations of these compounds were done at 300 K using Tripos FF with a time step of 1.5 fs. Simulations were carried out over charged compounds (Gastiger-Huckel) in a continuum solvent model with a dielectric constant as a distance function.

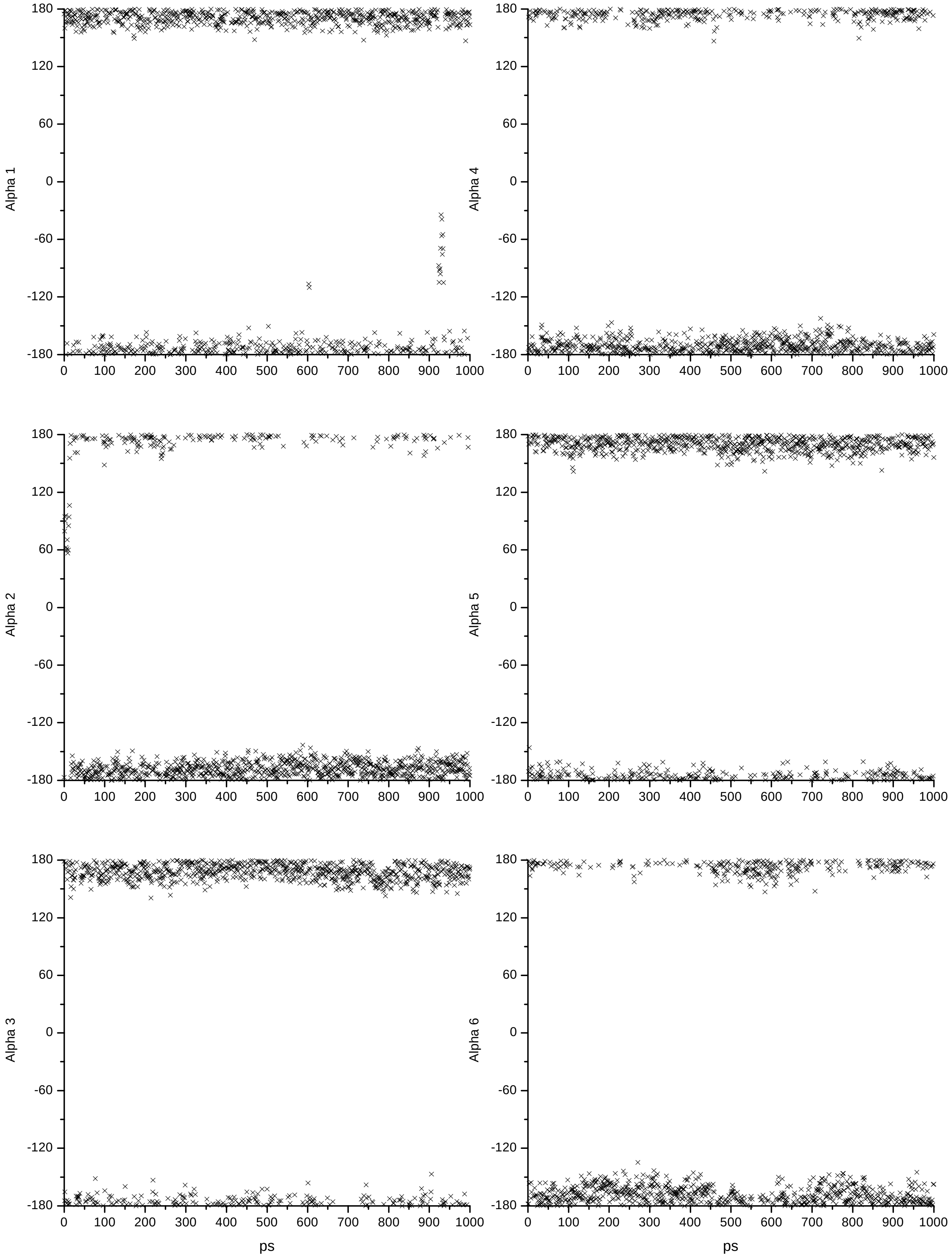
For **the three-units oligomer**, alpha 1, alpha 2, …., beta 1, beta 2, … and gamma 1, gamma 2, … are the equivalents to compound **4** for each unit.

Variation of alpha, beta and gamma angles for compound **2**, both in $CHCl_3$ (ε 4.0) and MeOH (ε 33.0)

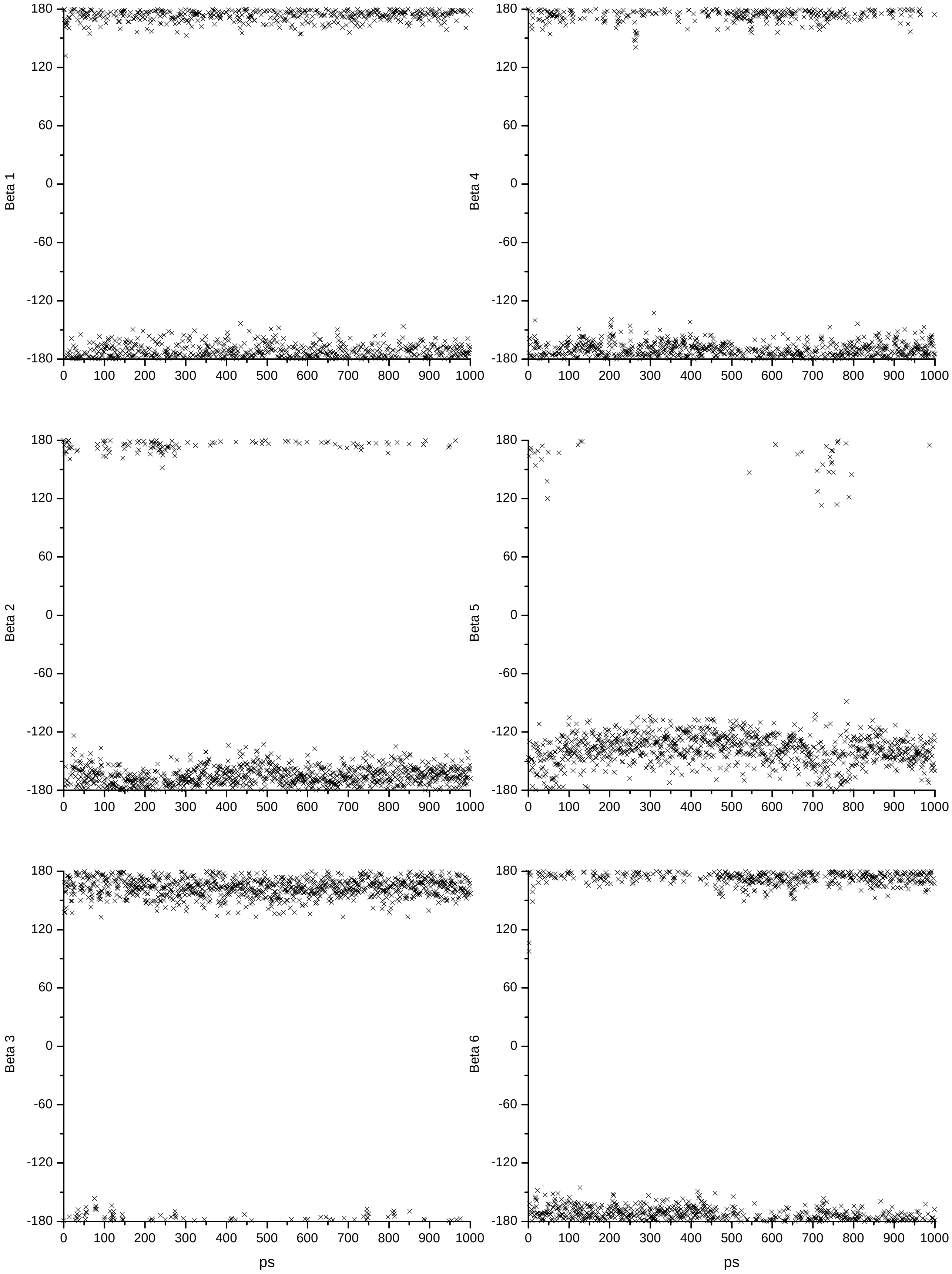
$CHCl_3$ (ε 4.0) MeOH (ε 33.0)



Alpha angles for three-units oligomer



Beta angles for three-units oligomer



Gamma angles for three-units oligomer