Dispiroketals in Synthesis (Part 15): Simultaneous Enantioselective and Regioselective Protection of Glycerol by Reaction with C_2 Symmetric (4*S*,4'*S*)-Dimethyl-*bis*-dihydropyran

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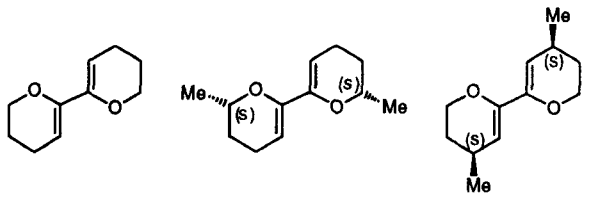
Abstract: Glycerol was simultaneously, enantioselectively and regioselectively protected by reaction with (4*S*,4'*S*)-4,4'-dimethyl-3,3',4,4'-tetrahydro-6,6'-*bis*-2*H*-pyran to afford a dispiroketal product.

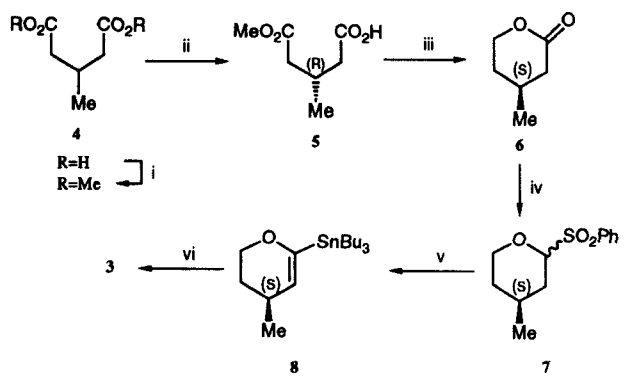
The desymmetrisation of *meso* polyols is an excellent method for the preparation of enantiomerically pure polyhydroxylated compounds.[1] We previously reported that *bis*-dihydropyran **1** reacts with various diols to form dispiroketal adducts.[2] The discovery led to the development of a new protecting group for carbohydrates.[3] More recently, we disclosed that incorporation of chirality into the *bis*-dihydropyran enables discrimination between two enantiotopic diol pairs. Hence, the C_2 symmetric disubstituted 2-dimethyldihydropyran **2** has been used to effect the disymmetric protection of glycerol.[4] We report herein that glycerol can also be similarly enantioselectively protected using the much more readily available disubstituted 4,4'-dimethyldihydropyran ((4*S*,4'*S*)MDHP) **3**.



1 **2** ((2*S*,2'*S*)MDHP) **3** ((4*S*,4'*S*)MDHP)

Figure 1

The synthesis of **3** is outlined in Scheme 1. Enzymatic hydrolysis of the *meso* diester **4**[5] followed by a regioselective reduction of the ester group afford the (4*S*)-methyl-δ-valerolactone **6**[6] in 92% *ee* (determined by chiral GC). Lactone **6** was then transformed into a mixture of anomeric sulfones **7** (*cis*/*trans*: 18/72), according to a two step sequence developed in our laboratory.[7] Deprotonation of the sulfones, alkylation of the resulting anion with *n*-tributyltin chloride and elimination of phenylsulfenic acid, gave the vinylstannane **8** in 70% overall yield from **7**. Transmetallation of **8** with *n*-butyllithium, followed by palladium(II) catalysed homocoupling of the resulting vinyllithium provided **3** in greater than 99% *ee*.[8]

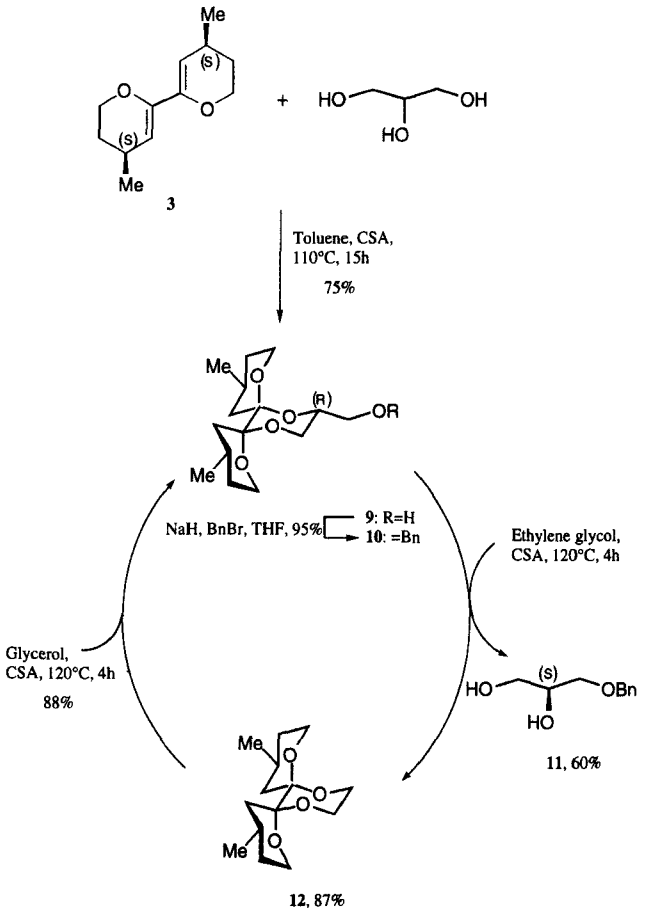


(i) H_2SO_4, MeOH, 70°C, 3 days, 92%, (ii) PLE, phosphate buffer (10% MeOH), pH 7, 0°C, 5 days, 90%, (iii) a) LiOH, MeOH, b) $LiBH_4$, THF, 67%, (iv) DIBAL, toluene, -78°C, then $PhSO_2H$, $CaCl_2$, CH_2Cl_2, r.t., 88%, (v) *n*-BuLi, *n*-Bu_3SnCl, THF, -78°C, then (*i*-Pr)$_2$EtN, $CHCl_3$, Δ, 70%, (vi) *n*-BuLi, then $PdCl_2(MeCN)_2$, $CuCl_2$, THF, 50%

Scheme 1

Reaction of **3** with glycerol, in the presence of a catalytic amount of camphorsulfonic acid (CSA), in boiling toluene gave the dispiroketal **9** (Scheme 2). The selective formation of **9** can be explained by a combination of anomeric and steric effects. Both the methyl groups and the hydroxymethylene substituent adopt an equatorial orientation. The equatorial position of the hydroxymethylene substituent is the result of thermodynamic control. Initially, a mixture of two isomers was formed, but after 15 h, only a small amount (less than 5%) of the axial isomer still remained in the crude reaction mixture. Prolonged reaction time did not alter the ratio. After purification by flash chromatography, **9** was isolated in 75% yield as a single diastereoisomer.

Benzylation of the hydroxyl group of **9**, followed by treatment of **10** in neat ethylene glycol, furnished (*S*)-1-*O*-benzylglycerol **11** and **12** in 60% and 87% yields respectively. The Moshers' ester[9] of **11** was



Scheme 2

prepared and the diastereoisomeric excesses were determined by 500 MHz ^{1}H NMR. Only one isomer could be detected and the absolute configuration was determined by comparison with the ^{1}H NMR spectrum of an authentic sample prepared from (*S*)-(+)-2,2-dimethyl-1,3-dioxolane-4-methanol.[10]

In order to devise a recycling process[11], compound **12** was heated in glycerol with CSA. As expected, **9** was obtained diastereoisomerically pure in 88% yield, after purification by flash chromatography. What we have achieved therefore is a chirality multiplication through the control of the multiple operating anomeric effects.

Experimental Section

(4*S*)-4-Methyl-2-phenylsulfonyltetrahydro-2*H*-pyran (7)

Lactone **6** (13 g, 0.112 mol) was dissolved in dry toluene (350 mL) under an argon atmosphere. The solution was cooled at -78°C and DIBAL (90 mL, 0.134 mol) 1.5 M in toluene was added dropwise. The reaction mixture was stirred for 2h at -78°C, warmed to -10°C, quenched with water (15 mL) and then poured into EtOAc (500 mL). The solution was dried over sodium bicarbonate-sodium sulfate and concentrated, to give 14 g of crude lactol which was used without further purification in the next step.

The crude lactol was added to DCM (200 mL) containing calcium chloride (31.7 g). Freshly prepared benzenesulfinic acid (16.2 g, 0.114 mol) was added in one portion and the reaction mixture was stirred for 15h at room temperature. The reaction mixture was diluted with DCM (50 mL), filtered and washed with saturated sodium bicarbonate (150 mL). The aqueous phase was extracted with DCM (3 x 100 mL). The combined organic extracts were dried over magnesium sulfate and concentrated. The resulting pale yellow oil was purified by rapid filtration on Florisil® (hexane/EtOAc: 70/30, Rf: 0.36 and 0.28) to give a mixture (*cis*/*trans*: 18/72) of anomeric sulfones **7** (23.6 g, 88% yield).

Trans isomer (recrystallized from ether): m.p 94-96°C

^{1}H NMR (200 MHz, $CDCl_3$): δ= 7.91 (d, ^2J=6.0, 2H, $H_{arom,}$), 7.60-7.50 (m, 3H, $H_{arom,}$), 4.66 (dd, ^3J=6.2, 2.4, 1H, H-6), 4.38 (ddd, ^2J=11.2, ^3J=11.2, 2.9, 1H, H-2_{ax}), 3.77 (ddd, ^2J=11.2, ^3J=7.8, 4.0, 1H, H-2_{eq}), 2.60-2.46 (m, 1H, H-5_{eq}), 2.44-2.27 (m, 1H, H-4), 1.80-1.65 (m, 1H, H-3_{eq}), 1.64-1.48 (m, 1H, H-5_{ax}), 1.37-1.21 (m, 1H, H-3_{ax}), 0.99 (d, ^3J=6.4, 3H, Me).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ= 137.77, 133.87, 129.17, 129.03 (C_{arom}), 89.24 (C-6), 64.31 (C-2), 32.91, 30.34 (C-3, C-5) 24.59 (C-4), 21.80 (Me).

MS (E/I) *m/z*: 142, 125, 99.

Ana. calc. for $C_{12}H_{13}O_3S$: C, 59.98; H, 6.71. Found: C, 59.76; H, 6.75%.

Cis isomer (recrystallized from ether): m.p 88-90°C

^{1}H NMR (200 MHz, $CDCl_3$): δ= 7.91 (d, ^2J=6.0, 2H, H_{arom}), 7.60-7.50 (m, 3H, H_{arom}), 4.33 (dd, ^3J=11.6, 2.3, 1H, H-6), 4.05 (ddd, ^2J=11.5, ^3J=4.7, 1.4, 1H, H-2_{eq}), 3.38 (ddd, ^2J=11.5, ^3J=12.2, 2.4, 1H, H-2_{ax}), 2.25-2.11 (m, 1H, H-5_{eq}), 1.80-1.65 (m, 1H, H-4), 1.64-1.45 (m, 1H, H-3_{eq}), 1.42-1.19 (m, 2H, H-3_{ax}, H-5_{ax}), 0.99 (d, ^3J=6.6, 3H, Me).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ= 136.51, 134.03, 129.73, 129.02 (C_{arom}), 91.72 (C-6), 69.34 (C-2), 33.46, 32.05 (C-3, C-5) 29.68 (C-4), 22.19 (Me).

MS (E/I) *m/z*: 241, 142, 125, 99.

Ana. calc. for $C_{12}H_{13}O_3S$: C, 59.98; H, 6.71. Found: C, 59.85; H, 6.72%.

(4*S*)-3,4-Dihydro-4-methyl-6-tri-*n*-butylstannyl-2*H*-pyran (8)

To a mixture of sulfone anomers **7** (7 g, 29 mmol) dissolved in dry THF (100 mL) was added dropwise at -78°C, under argon atmosphere, *n*-butyllithium (19 mL, 30.6 mmol) 1.7 M in hexanes. After 30 min at -78°C, tri-*n*-butyltin chloride (8.3 mL, 30.6 mmol) was added slowly and the reaction mixture stirred at -78°C for 1h and at -10°C for 2h. The solution was evaporated to dryness and taken up in chloroform (150 mL). Hünig's base (7.42 mL, 43.5 mmol) was added and the resulting mixture was heated at 70°C for 4h, then cooled to room temperature, filtered through a short pad of Florisil® and evaporated. The residue was partitioned between hexane (100 mL) and acetonitrile (100 mL) and the acetonitrile was further extracted with hexane (2 x 100 mL). The combined hexane phases were concentrated and the crude product was purified by column chromatography on Florisil® (hexane, Rf: 0.44) to give the vinyl stannane **8** as a colourless oil; yield: 8 g (70%).

^{1}H NMR (500 MHz, C_6D_6): δ= 4.92 (dd, ^3J= 2.0, J_{Sn-H}=12.9, 1H, H-5), 3.93 (ddd, ^2J=10.6, ^3J=6.1, 3.2, 1H, H-2), 3.86 (ddd, ^2J=10.6, ^3J=8.9, 2.7, 1H, H-2'), 2.26-2.23 (m, 1H, H-4), 1.84-1.71 (m, 7H, CH_2, H-3), 1.53-1.40 (m, 7H, CH_2, H-3'), 1.17 (t, 6H, CH_2), 1.05-1.01 (m, 12H, Me).

^{13}C NMR (100 MHz, C_6D_6): δ= 161.61 (C-6), 119.24 (C-5), 64.67 (C-2), 31.775 (C-4), 29.46, 27.59, 9.82 (CH_2), 26.75 (C-3), 22.45, 13.91 (CH_3).

MS (E/I) *m/z*: 388 (M^+), 331, 273, 219, 97.

HRMS calculated for $C_{18}H_{37}OSn$: 388.1788. Found: 388.1792.

(4*S*,4'*S*)-4,4'-Dimethyl-3,3',4,4'-tetrahydro-6,6'-*bis*-2*H*-pyran (3)

n-Butyllithium (13.1 mL, 21 mmol) 1.7 M in hexanes was added dropwise to a cooled (-78°C) solution of vinyl stannane **8** (7.5 g, 20 mmol) in dry THF (100 mL) under an argon atmosphere. After 30 min, a mixture of anhydrous copper (II) chloride (2.95 g, 22 mmoL) and palladium dichloride bis-acetonitrile (100 mg, 0.4 mmol) was added in one portion. The reaction mixture was stirred at -78°C for 3h, then allowed to warm to -10°C and poured into a mixed solution of saturated ammonium chloride and ammonia (150 mL). The aqueous phase was extracted with ether (3 x 50 mL) and the combined organic phases were dried over sodium sulfate and concentrated. The residue was purified by column chromatography (silica gel, hexane/triethylamine: 99/1, Rf: 0.18) to give **3** as a colourless oil; yield: 0.93 g (50%).

^{1}H NMR (200 MHz, C_6D_6): δ= 5.09 (d, ^3J=3.1, 1H, H-5), 4.01 (ddd, ^2J=10.6, ^3J=5.9, 3.4, 1H, H-2), 3.88 (ddd, ^2J=10.6, ^3J=8.5 , 2.8, 1H, H-2'), 2.34-2.26 (m, 1H, H-4), 1.71-1.61 (m, 1H, H-3), 1.42-1.30 (m, 1H, H-3'), 1.03 (d, ^3J=7.0, 3H, Me).

^{13}C NMR (50 MHz, $CDCl_3$): δ= 146.76 (C-6), 103.62 (C-5), 65.02 (C-2), 30.97 (C-3), 25.91 (C-4), 22.08 (Me).

[MS (E/I) *m/z*: 194 (M^+), 179, 97, 84.

HRMS calculated for $C_{12}H_{18}O_2$: 194.1306. Found: 194.1298.

$[\alpha]^{28}_D$: -59.5 (c=0.39, $CHCl_3$)

(4*S*, 6*S*, 7*R*, 11*S*, 14*R*) 14-Hydroxymethyl-4,11-dimethyl-1,8,13,16-tetraoxa-dispiro[5.0.5.4]hexadecane (9)

Chiral *bis*-DHP **3** (250 mg, 1.55 mmol), glycerol (1.42 g, 15.65 mmol) and CSA (35.87 mg, 0.156 mmol) were dissolved in dry toluene (3 mL) and the solution was heated under reflux for 15h. The reaction mixture was then cooled to room temperature and the toluene was evaporated. The crude was purified by column chromatography (silica gel, hexane/EtOAc: 70/30, Rf: 0.22) to give **9** as an oil; yield: 270 mg (75%).

^{1}H NMR (500 MHz, $CDCl_3$): δ= 4.06-4.02 (m, 1H, H-14), 3.72-3.67 (m, 3H, H-2, H-9, H-15_{ax}), 3.61 (ABX, ^2J=10.4, ^3J=5.6, 2H, CH_2OH), 3.46 (dd, ^3J= 11.9, 3.0, 1H, H-15_{eq}), 1.98-1.90 (m, 2H, H-4, H-11), 1.81-1.75 (m, 2H, H-3_{eq}, H-10_{eq}), 1.54-1.51 (m, 2H, H-5_{eq}, H-12_{eq}),1.24-1.15 (m, 2H, H-3_{ax}, H-10_{ax}), 1.13-1.08 (m, 2H, H-5_{ax}, H-12_{ax}), 0.91 (d, ^3J=6.6, 3H, Me), 0.89 (d, ^3J=6.6, 3H, Me).

^{13}C NMR (100 MHz, $CDCl_3$): δ= 96.79, 95.78 (C-6, C-7), 67.14 (C-14), 62.11 (C-15), 60.82, 60.79 (C-2, C-9), 59.44 (CH_2OH), 36.94, 33.49, 33.46 (C-3, C-5, C-10, C-12), 24.51, 24.48 (C-4, C-11), 22.22, 22.18 (Me).

MS (E/I) *m/z*: 287 (M^+), 195, 143, 129, 115.

HRMS calculated for $C_{15}H_{26}O_5$: 286.1780 Found: 286.1773.

$[\alpha]^{25}_D$: +125.0 (c=1.25, $CHCl_3$).

(4*S*, 6*S*, 7*R*, 11*S*, 14*R*) 14-Benzyloxymethyl-4,11-dimethyl-1,8,13,16-tetraoxa-dispiro[5.0.5.4]hexadecane (10)

To a suspended solution of sodium hydride (105 mg 60% in mineral oil, 2.755 mmol) in dry THF (10 mL), cooled at 0°C, was added, under argon atmosphere, a solution of **9** (270 mg, 0.918 mmol) and benzyl bromide (327 µl, 2.755 mmol) dissolved in dry THF. The reaction mixture was stirred at room temperature for 8h and then poured into water (15 mL). The aqueous phase was extracted with ether (3 x 10 mL). The combined organic phases were dried with sodium sulfate and concentrated. The residue was purified by column chromatography (silica gel, hexane/Et_2O: 80/20, Rf: 0.18) to give **10** as a oil; yield: 328 mg (95%).

^1H NMR (500 MHz, $CDCl_3$): δ= 7.35-7.26 (m, 5H, H_{arom}), 4.56 (AB, 2H, OCH_2Ph,), 4.21-4.17 (m, 1H, H-14), 3.73 (m, 3H, H-2, H-9, H-15_{ax}), 3.56 (dd, ^3J= 11.8, 3.1, 1H, H-15_{eq}), 3.54, 3.45 (2xdd, ^2J=10.4, ^3J=5.6, 2H, CH_2OBn), 2.04-1.96 (m, 2H, H-4, H-11), 1.86-1.77 (m, 2H, H-3_{eq}, H-10_{eq}), 1.54-1.43 (m, 2H, H-5_{eq}, H-12_{eq}), 1.18-1.15 (m, 2H, H-3_{ax}, H-10_{ax}), 1.14-1.06 (m, 2H, H-5_{ax}, H-12_{ax}), 0.90 (d, 6H, Me).

^{13}C NMR (100 MHz, $CDCl_3$): δ=138.23, 128.32, 127.54 (C_{arom}), 96.76, 95.81 (C-6, C-7), 73.39 (OCH_2Ph), 70.03 (CH_2OBn), 66.11 (C-14), 60.79, 60.72, 60.67 (C-2, C-9, C-15), 37.00, 37.05 (C-3, C-5, C-10, C-12), 24.52, 24.39 (C-4, C-11), 22.24 (Me).

MS (E/I) *m/z*: 376 (M^+), 229, 115, 91.

HRMS calculated for $C_{22}H_{32}O_5$: 376.2249. Found: 376.2247.

$[\alpha]^{25}_D$: +104.9 (c=3.2, $CHCl_3$).

(*S*)-1-O-Benzylglycerol (11) and (4*S*, 6*S*, 7*R*, 11*S*)-4,11-Dimethyl-1,8,13,16-tetraoxa-dispiro[5.0.5.4]hexadecane (12)

The benzylated dispiroketal **10** (65 mg, 0.173 mmol) and CSA (4 mg, 0.0173 mmol) were dissolved into glycerol (1 mL) and the reaction mixture was heated at 120°C for 4h and then cooled to room temperature. The crude material was directly loaded onto a column and chromatographed (silica gel, hex/AcOEt: 90/10, Rf **12**: 0.27, then hexane/EtOAc: 50/50, Rf **11**: 0.43) to give **11** (18.8 mg, 60%) and **12** (28.1 mg, 88%).

^1H NMR (500 MHz, $CDCl_3$): δ= 4.03-3.96 (m, 2H, H-14_{ax}, H-15_{ax}), 3.77-3.68 (m, 4H, H-2, H-9), 3.48-3.42 (m, 2H, H-14_{eq}, H-15_{eq}), 1.97-1.89 (m, 2H, H-4, H-11), 1.78-1.75 (m, 2H, H-3_{eq}, H-10_{eq}), 1.54 (dd, ^2J=12.7, ^3J=1.5, 2H, H-5_{eq}, H-12_{eq}), 1.25-1.14 (m, 2H, H-3_{ax}, H-10_{ax}), 1.11 (dd, ^2J=12.7, ^3J=12.7, 2H, H-5_{ax}, H-12_{ax}), 0.89 (d, ^3J=6.6, 6H, Me).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ= 96.29 (C-6, C-7), 60.84, 58.32 (C-2, C-9, C-14, C-15), 37.34 (C-5, C-12), 33.58 (C-3, C-10), 24.44 (C-4, C-11), 22.24 (Me).

MS (E/I) *m/z*: 256 (M^+), 196, 142, 122, 115.

HRMS calculated for $C_{14}H_{24}O_4$: 256.1674. Found: 256.1668.

$[\alpha]^{25}_D$: +147.7 (c=1.9, $CHCl_3$).

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(8) The homocoupling process enhanced the *ee* of the C_2 symmetric bis-DHP with respect to the starting stannane. However, the cost of this enhancement was the production of 7% of meso diene.

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(11) Reaction of **10** with glycerol in the presence of CSA procceeded sluggishly giving poor yields of **9**.