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Synthesis of (+)-2,8-dihydroxyethyl-1,4,7,10-tetraoxaspiro[5.5]undecane from (*R*)-4-hydroxymethyl-2,2-dimethyl-1,3-dioxane

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Abstract: Selective transformations of diethyl (*R*)-malate afforded (*R*)-4-hydroxymethyl-2,2-dimethyl-1,3-dioxane **7** in reasonable yield. Subsequent synthesis of (2*S*,6*R*,8*S*)-2,8-dihydroxyethyl-1,4,7,10-tetraoxaspiro[5.5]undecane **11** was achieved using precursor **7**.

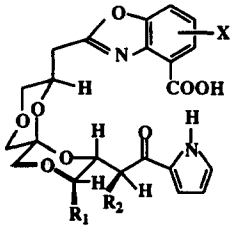
In work on the design of hydrophilic models of calcimycin (or A.23187) (Scheme 1), a calcium ionophore widely used as a biochemical tool[1], we reported a straightforward route to the 2,8-functionalized (+)-E,E-spirobidioxane skeleton[2].

For the model with R_1=R_2=H, to reduce the number of steps in the synthesis, one approach is *via* the symmetrical spiroacetal bearing CH_2–CH_2OH arms, which can subsequently be added to. This paper describes the synthesis of intermediate (+)-2,8-dihydroxyethyl-1,4,7,10-tetraoxaspiro[5.5] undecane **11**. The subsequent steps, comprising the addition of the benzoxazole and ketopyrrole moieties have been examined in several studies by other authors[3] and by ourselves[4].

In our previous work[2], a commercial D-(+)-α,β-isopropylideneglycerol fragment, bearing the secondary alcohol function with the appropriate configuration for the final cyclodehydration, was used. Access to the target molecule **11** needed an equivalent four-carbon precursor, namely (*R*)-4-hydroxymethyl-2,2-dimethyl-1,3-dioxane **7**. The preparation of this compound was achieved in six steps from diethyl D-(+)-malic acid **1**. Double condensation of **7** on epichlorhydrin and oxidation of the central secondary alcohol finally yielded the expected enantiopure spirobidioxane in four steps.

(*R*)-4-Hydroxymethyl-2,2-dimethyl-1,3-dioxane 7

Saito[5] *et al.* developed a regioselective reduction of the ester group α to the hydroxyl group in diethyl (*S*)-malate. This reaction, using a borane–dimethyl sulfide complex (BMS) allowed the preferential formation of a five-membered ring transition state involving the boron atom bound to the OH as an



R_1, R_2 = H or CH_3

Scheme 1.

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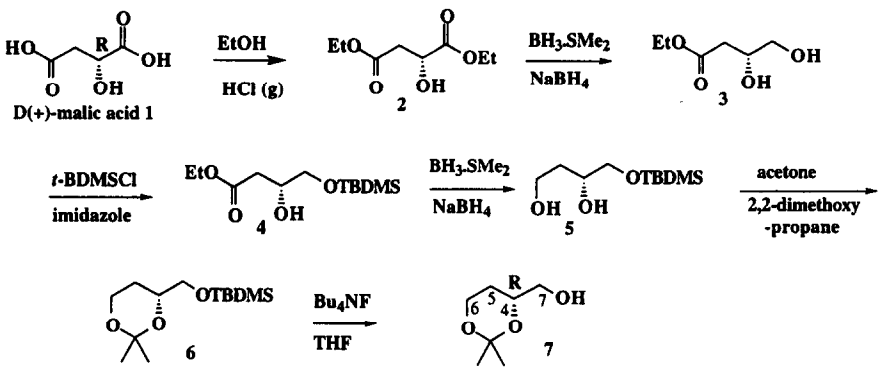
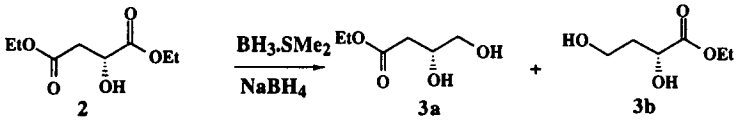


Scheme 2.



Scheme 3.

OBH_2 group and the carbonyl of the ester group in the α position; subsequent addition of $NaBH_4$ in catalytic amounts led to the reduction of this ester. The expected 4-hydroxymethyl-2,2-dimethyl-1,3-dioxane can then be obtained by appropriate protection–deprotection reactions.

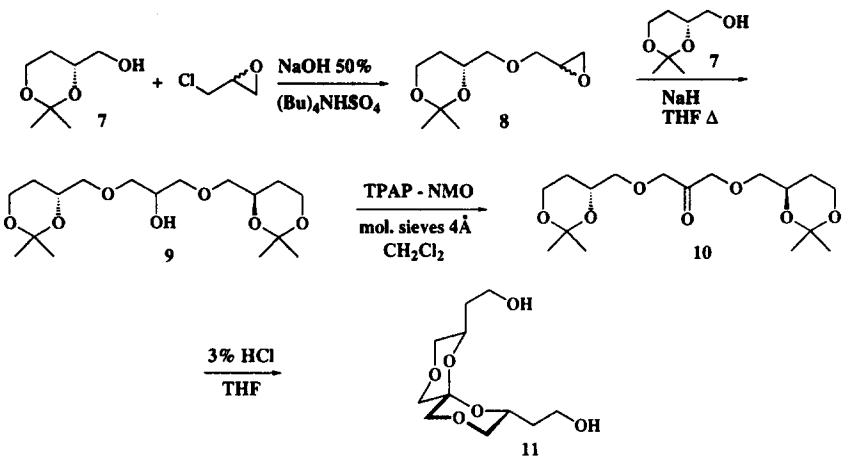
After several unsuccessful attemps by other different synthetic methods, we applied Saito's reaction to diethyl (*R*)-malate **2** (Scheme 2).

Compound **2** was treated with exactly one equivalent of BMS in THF at room temperature. Evolution of hydrogen gas took place immediately and ceased after 45 minutes. After addition of $NaBH_4$ (5 mol%), the reduction required one hour at room temperature for completion. The reaction was then quenched by addition of EtOH and *p*-toluene sulfonic acid. The solvent was evaporated after neutralization of the sodium ethoxide from the catalyst. A mixture of compounds **3a**:**3b** (97:3) (Scheme 3) was isolated, characterized by NMR spectroscopy, and the ratio was determined by a ^{13}C Jmod experiment. Ethyl (3R)-3,4-dihydroxybutanoate **3a** was present in 86% yield. A small amount of butanetriol (<2%) was also detected.

The selective silylation of the primary alcohol was carried out with *t*-butyldimethylsilylchloride in the presence of imidazole[6] at 0°C giving, after purification by column chromatography, ethyl (3R) 4-(*t*-butyldimethyl-silyloxy)-3-hydroxybutanoate **4** (84%). Subsequent reduction to give compound **5** (86%) was achieved with BMS. As expected, it required longer than the previous reaction and 10 mol% of $NaBH_4$ was added. The solution was stirred overnight at room temperature.

Treatment of **5** with 2,2-dimethoxypropane in acetone in the presence of camphorsulfonic acid gave compound **6**, which reacted with tetrabutylammonium fluoride in THF to give the (*R*)-4-hydroxymethyl-2,2-dimethyl-1,3-dioxane **7** in 85% yield ($[\alpha]_D^{25}=-13$ (c=0.087; $CHCl_3$)). ^1H NMR spectra showed that H5A was axial, H5B equatorial and H4 axial ($J_{5Be\text{-}6Be}$=1.6 Hz, $J_{5Be\text{-}6Aa}=J_{5Be\text{-}4}$=3.0 Hz, $J_{5Be\text{-}5Aa}$=12.0 Hz, $J_{5Aa\text{-}6Be}$=5.5 Hz, $J_{5Aa\text{-}6Aa}$=11.9 Hz, $J_{5Aa\text{-}4}=J_{5Aa\text{-}5Be}$=12.0 Hz).

To determine the enantiomeric purity, we synthesized (±)-**7** (synthesis not described), which gave identical NMR spectra to (−)-**7**. The e.e. values were determined by NMR, (±)-**7** gave duplicate resonance signals (^1H spectra) for the H4 proton in the presence of the chiral shift reagent $Eu(tfc)_3$



Scheme 4.

while only one signal was observed with (−)-**7**. Therefore, the e.e. was estimated to be greater than 97%.

(2*R*,6*S*,8*R*)-2,8-Dihydroxyethyl-1,4,7,10-tetraoxaspiro[5.5]undecane E,E 11

The procedure depicted in Scheme 4 was applied, following the original approach previously described[2].

Epoxide **8** was prepared using phase transfer conditions. (±)-Epichlorydrin, 50% aqueous NaOH and $(Bu)_4NHSO_4$ were first mixed, and synthon **7** was then added. Purification of the reaction products by column chromatography yielded 89% **8** as a mixture of diastereoisomers (4R,2R) and (4R,2S), identified by NMR as the two isomers had different chemical shifts for the H7A, H7B, H1′A, H1′B protons, which were not assigned. Treatment of (*R*)-**7** with NaH in THF, followed by addition of epoxide **8**, led to the alcohol (2RS,4′R,4″R)-**9** in 45% yield. It was the only step with a poor yield, which we were unable to improve.

The enantiopure ketone (4′R,4″R)-**10** ($[\alpha]_D^{25}$=+30 (c=0.046, MeOH)) was obtained from **9** by specific oxidation using Ley's conditions[7]. A very good yield (95%) was obtained on leaving the reaction overnight at room temperature.

The deprotection followed by cyclodehydration was achieved in 3% HCl/THF affording (2R,6S,8R)-2,8-dihydroxyethyl-1,4,7,10-tetraoxaspiro[5.5]undecane E,E-**11** with 70% yield ($[\alpha]_D^{25}$=+79 (c=0.117, $CHCl_3$)). 1D and 2D NMR analysis for ^1H and ^{13}C confirmed the C2 symmetry of the molecule corresponding to an E,E structure with two stabilizing anomeric effects, as already discussed in detail for parent compounds in a previous paper[8].

Hence (+)-E,E-spirobidioxane **11** bearing two CH_2CH_2OH arms was obtained in ten steps from D(+)-malic acid of the chiral pool, by highly reproducible reactions with fair-to-good yields for each step. This approach can be conveniently adapted for the preparation of unsymmetrical spiroacetals with R_1=CH_3, R_2=H and R_1=R_2=CH_3, with respectively four and five asymmetric centers, as will be described in forthcoming papers.

Experimental

Optical rotation values were measured on a JASCO DJP-370 polarimeter for the mercury D line (λ=589 nm) at 25°C (c in g/mL). Infrared (IR) spectra were obtained using a Perkin–Elmer 881 spectrometer and band positions are expressed in frequency units (ν cm^{-1}). NMR spectra were recorded at 400 MHz for ^1H and 100 MHz for ^{13}C on a Bruker AC 400 spectrometer. All chemical shifts

are expressed in ppm. Assignment of the spectra of spiroacetal **11** was made by 2D ^1H–^1H experiments. The following abbreviations are used: singlet (s), doublet (d), triplet (t), multiplet (m), axial (*a*), equatorial (*e*). Satisfactory analytical data were obtained for all new compounds (±0.3%) at the Service Central d'Analyse du CNRS, Solaize, France. Tris-[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]-europium III ($Eu(hfc)_3$) was used as a shift reagent for enantiomeric excess determination. Merck silica gel (40–63 μ) was used for column chromatography and commercial Kieselgel 60F254 plates were used for thin layer chromatography (TLC).

Diethyl (R)-malate 2

The procedure was that of Börjesson and Welch[9], from 10 g (0.0746 mol) of R-malic acid 11.91 g (0.062 mol) of the diethylester **2** were obtained (yield: 84%, colorless liquid).

$[\alpha]_D^{25}$=+6 (c=0.049, $CHCl_3$). IR: 3480, 1740, 1370, 1175–1045 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.22 (t, 3H, CH_3); 1.25 (t, 3H, CH_3); 2.75 (d, 2H, H2); 3.41 (d, 1H, OH); 4.12 (q, 2H, CH_2–CH_3); 4.21 (qd, 2H, CH_2–CH_3); 4.45 (dd, 1H, H3). ^{13}C-NMR ($CDCl_3$) δ: 13.9 (2 CH_3); 38.6 (C2); 60.8–61.7 (2 CH_2–CH_3); 67.2 (C3); 170.4 (C1); 173.2 (C4).

*Ethyl (R) 3,4-dihydroxybutanoate **3a***

In a 100 mL, two-necked, round-bottomed flask fitted with a short condenser was placed a solution of 11.91 g (62.68 mmol) of (*R*)-malate diethylester **2** (DEM) in 135 mL of THF. To this solution was added dropwise 5.7 mL of borane–dimethyl sulfide (1.03 eq), at 20°C, with stirring for 30 min. The solution was stirred at this temperature until evolution of hydrogen ceased (45 min). The flask was then cooled in a water–ice bath (10°C) and stirring was continued for 10 min. 118 mg of $NaBH_4$ powder (5 mol%) was added in one portion (exothermic) with vigorous stirring. When the exothermic reaction stopped (10 min), the water bath was removed and the reaction was continued at room temperature until the disappearance of DEM (1 h). To the reaction mixture were added 21.3 mL of ethanol and 600 mg of *p*-TsOH. The resulting slightly cloudy solution was stirred for 30 min at room temperature, followed by concentration to give a colorless gum. It was dissolved in benzene–ethanol (1:1) and the resulting solution was concentrated. This was done repeatedly to eliminate EtOH and $B(OEt)_3$ as completely as possible to give a clear colorless gum. The residue was chromatographed on silica gel with ethyl acetate/cyclohexane 40/60 and **3a** was obtained in 86% yield (7.98 g, 53.92 mmol). White wax. $[\alpha]_D^{25}$=+30 (c=0.005; $CHCl_3$). IR: 3400, 1735, 1175–1045 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.43 (t, 3H, CH_3); 2.45 (dd, 2H, H2); 3.40 (dd, 1H, H4B); 3.52 (dd, 1H, H4A); 3.55 (s, 1H, OH); 4.20 (m, 4H, OH,CH_2–CH_3, H3). ^{13}C-NMR ($CDCl_3$) δ: 14.0 (CH_3); 37.9 (C2); 60.8 (CH_2–CH_3); 65.6 (C4); 68.6 (C3); 172.4 (C1). Anal. Calcd. for $C_6H_{12}O_4$ (148): C 48.64, H 8.16. Found: C 48.72, H 8.08. MS FAB$^+$ m/z (%): 155.2 (MLi^+) (100.0); 133.2 $(M\text{-}CH_3)^+$ (4.7).

*Ethyl (R) 4-tert-butyldimethylsilyloxy-3-hydroxybutanoate **4***

4.62 g of imidazole (1.3 eq) and 8.7 g of TBDMSi–Cl were added at 0°C to a stirred solution of 7.98 g (53.92 mmol) of **3a** in 55 mL of THF. The mixture became immediately milky and was stirred for 3 h at 0°C. After dilution with ether followed by addition of water, the organic phase was washed with a saturated solution of sodium chloride. Evaporation of the solvent after drying gave a pale yellow oil, which was chromatographed on silica gel with ethyl acetate/cyclohexane 40/60 and afforded in 83.5% (11.8 g) yield. Colorless wax. $[\alpha]_D^{25}$=+15 (c=0.042; $CHCl_3$). IR: 3480, 1745, 1265–1125, 840, 785 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.10 (s, 6H, $Si(CH_3)_2$); 0.88 (s, 9H, $SiC(CH_3)_3$); 1.25 (t, 3H, CH_3); 2.49 (pt, 2H, H2); 2.94 (s, 1H, OH); 3.60 (ddd, 2H, H4); 4.08 (m, 1H, H3); 4.15 (q, 2H, CH_2–CH_3). ^{13}C-NMR ($CDCl_3$) δ:−3,2 ($Si(CH_3)_2$); 14.2 (CH_3); 18.3 (Si–C(q)); 25.9 ($SiC(CH_3)_3$); 38.1 (C2); 60.6 (CH_2–CH_3); 66.2 (C4); 68.6 (C3); 172.2 (C1). Anal. Calcd. for $C_{12}H_{26}O_4Si$ (262): C: 54.92, H: 9.99, Si: 10.70. Found: C: 55.06, H: 9.89, Si: 10.78. MS FAB$^+$ m/z (%): 531.6 ($2MLi^+$) (5.3); 269.3 (MLi^+) (100.0); 160.2 (4.6).

(R) 4-tert-Butyldimethylsilyloxy-butan-1,3-diol 5

To a stirred solution of 11.8 g (45.04 mmol) of product **4** in 134 mL of THF was added dropwise 4 mL of borane–dimethyl sulfide. The solution was stirred for 45 min at room temperature until evolution of hydrogen ceased. It was then cooled in a water–ice bath (10°C) for 10 min, and 220 mg of $NaBH_4$ was added in one portion. The solution was stirred for 10 min at 10°C then 12 h at room temperature. To the reaction were added 22 mL of ethanol and 600 mg of *p*-TsOH. The resulting solution was stirred for 30 min at room temperature, followed by concentration to give a colorless gum. This was dissolved in benzene–ethanol (1:1) and the resulting solution reconcentrated. This operation was repeated to eliminate EtOH and $B(OEt)_3$ and to obtain a colorless product. The residue was chromatographed on silica gel with ethyl acetate/cyclohexane 40/60 to afford 8.47 g (38.5 mmol) of **5** in 85.5% yield. Colorless wax. $[\alpha]_D^{25}=-1$ (c=0.038; $CHCl_3$). IR: 3485, 1255–1090, 840, 780 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.01 (s, 6H, $Si(CH_3)_2$); 0.83 (s, 9H, $SiC(CH_3)_3$); 1.60 (m, 2H, H2); 3.05 (d, 1H, OH); 3.13 (s, 1H, OH); 3.43 (dd, 1H, H4B); 3.52 (dd, 1H, H4A); 3.72 (m, 2H, H1); 3.79 (m, 1H, H3). ^{13}C-NMR ($CDCl_3$) δ: −5.4 ($Si(CH_3)_2$); 18.3 (Si–C(q)); 25.9 ($SiC(CH_3)_3$); 34.7 (C2); 61.0 (C1); 67.2 (C4); 71.7 (C3). Anal. Calcd. for $C_{10}H_{24}O_3Si$ (220): C: 54.50, H: 10.98, Si: 12.74. Found: C: 54.76, H: 10.82, Si: 12.88. MS FAB$^+$ m/z (%): 227.3 (MLi^+) (100.0); 226.3 (MLi^+-H) (9.0); 160.2 (3.8).

(R) 4-tert-Butyldimethylsilyloxymethyl-2,2-dimethyl-1,3-dioxane 6

To a solution of diol **5** (7.30 g, 33.18 mmol) were added 25.2 mL of 2,2-dimethoxypropane in 300 mL of acetone and 0.80 g of camphorsulfonic acid. The solution was stirred for 4 h at room temperature. The solvant was then evaporated and the residue was chromatographed on silica gel with ethyl acetate/cyclohexane 10/90 to give **6** (7.46 g, 28.69 mmol) in 86.5% yield. Colorless wax. $[\alpha]_D^{25}=+7$ (c=0.052; $CHCl_3$). IR: 1380–1370, 1250–1050, 840, 780 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.10 (s, 6H, $Si(CH_3)_2$); 0.75 (s, 9H, $SiC(CH_3)_3$); 1.30 (s, 3H, CH_3 acetonide); 1.45 (s, 3H, CH_3 acetonide); 1.55 (m, 2H, H5); 3.45 (dd, 1H, H7B); 3.60 (dd, 1H, H7A); 3.83 (m, 1H, H4); 3.95 (m, 2H, H6). ^{13}C-NMR ($CDCl_3$) δ: −5.2 ($Si(CH_3)_2$); 18.4 (Si–C(q)); 19.2 (CH_3 acetonide); 25.9 ($SiC(CH_3)_3$); 28.2 (C5); 29.8 (CH_3 acetonide); 59.8 (C6); 67.0 (C7); 69.7 (C4); 98.1 (C q. acetonide). Anal. Calcd. for $C_{13}H_{28}O_3Si$ (260): C: 59.95, H: 10.83, Si: 10.78. Found: C: 59.93, H: 10.82, Si: 10.80. MS FAB$^+$ m/z (%): 267.3 (MLi^+) (13.6); 202.2 (19.2); 160.2 (3.8); 202.2 (19.2); 185.3 (23.4); 161.2 (17.0); 160.2 (100.0).

(R) 4-Hydroxymethyl-2,2-dimethyl-1,3-dioxane 7

5.8 mL of tetrabutylammonium fluoride was added to **6** (2.48 g, 9.54 mmol) dissolved in 43 mL of THF. The resulting mixture was stirred at room temperature for 2 h, washed with brine and extracted with ethyl acetate.

The residue was chromatographed on silica gel with ethyl acetate/cyclohexane 70/30 to give **7** (1.18 g, 8.08 mmol) in 85% yield. Colorless liquid. $[\alpha]_D^{25}=-13$ (c=0.087; $CHCl_3$)[10]. IR: 3340, 1385, 1225–1030 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.45 (tdd, 1H, H5B, $J_{5Be\text{-}6Be}$ 1.6 Hz, $J_{5Be\text{-}6Aa}=J_{5Be\text{-}4}$ 3.0 Hz, $J_{5Be\text{-}5Aa}$ 12.0 Hz); 1.47 (s, 3H, CH_3 acetonide); 1.56 (s, 3H, CH_3 acetonide); 1.76 (tdd, 1H, H5A, $J_{5Aa\text{-}6Be}$ 5.5 Hz, $J_{5Aa\text{-}6Aa}$ 11.9 Hz, $J_{5Aa\text{-}4}=J_{5Aa\text{-}5Be}$ 12.0 Hz); 2.80 (s, 1H, OH); 3.58 (dd, 1H, H7B, $J_{7B\text{-}4a}$ 6.5 Hz, $J_{7B\text{-}7A}$ 11.5 Hz); 3.64 (dd, 1H, H7A, $J_{7A\text{-}4a}$ 3.0 Hz, $J_{7A\text{-}7B}$ 11.5 Hz); 3.92 (ddd, 1H, H6B, $J_{6Be\text{-}5Be}$ 1.6 Hz, $J_{6Be\text{-}5Aa}$ 5.5 Hz, $J_{6Be\text{-}6Aa}$ 11.9 Hz); 4.06 (td, 1H, H6A, $J_{6Aa\text{-}5Be}$ 3.0 Hz, $J_{6Aa\text{-}5Aa}=J_{6Aa\text{-}6Be}$ 11.9 Hz); 4,08 (m, 1H, H4). ^{13}C-NMR ($CDCl_3$) δ: 19.3 (CH_3 acetonide); 26.6 (C5); 29.7 (CH_3 acetonide); 59.4 (C6); 66.1 (C7); 69.6 (C4); 98.5 (C q. acetonide). Anal. Calcd. for $C_7H_{14}O_3$ (146): C: 57.51, H: 9.65. Found: C: 57.26, H: 9.60. MS EI m/z (%): 147.2 $(M+H)^+$ (77.9); 129.2 (24.3); 113.1 (24.9).

(R)-2,2-Dimethyl-4-[(2',3'-epoxypropoxy)methylene]-1,3-dioxane ***8***

A mixture of 50% aqueous NaOH (4.6 mL), epichlorhydrin (2.9 mL) and tetrabutylammonium hydrogen sulfate (97 mg) was vigorously stirred at room temperature. Compound **7** (1 g, 6.85 mmol) was added slowly while the temperature was maintained below 25°C. The resulting mixture was stirred at room temperature for 4 h and poured into water+ice (35 mL). The solution was extracted with ethyl acetate. The combined extracts were washed with brine and dried over $MgSO_4$. The residue was chromatographed on silica gel with ethyl acetate/cyclohexane 20/80 to give two diastereoisomers **8** (1.19 g, 5.9 mmol) in 86% yield the absolute configurations of which were not assigned. Colorless liquid.$[\alpha]_D^{25}=-3$ (c=0.086; $CHCl_3$). IR: 1385–1375, 1275–1000 cm^{-1}.

First diastereoisomer

^{1}H-NMR ($CDCl_3$) δ: 1.33 (s, 3H, CH_3 acetonide); 1.44 (m, 1H, H5B); 1.42 (s, 3H, CH_3 acetonide); 1.60 (m, 1H, H5A); 2.57 (td, 1H, H3'B); 2.77 (dd, 1H, H3'A); 3.12 (m, 1H, H2'); *3.38* (m, 1H, H7B); *3.42* (dd, 1H, H1'B); *3.54* (dd, 1H, H7A); 3.78 (m, 1H, H1'A); 3.82 (m, 1H, H6B); 3.95 (td, 1H, H6A); 4.05 (m, 1H, H4).

Second diastereoisomer

^{1}H-NMR ($CDCl_3$) δ: 1.33 (s, 3H, CH_3 acetonide); 1.44 (m, 1H, H5B); 1.42 (s, 3H, CH_3 acetonide); 1.60 (m, 1H, H5A); 2.57 (td, 1H, H3'B); 2.77 (dd, 1H, H3'A); 3.12 (m, 1H, H2'); *3.36* (m, 1H, H1'B); *3.45* (m, 2H, H7A, H7B); *3.80* (m, 1H, H1'A); 3.82 (m, 1H, H6B); 3.95 (td, 1H, H6A); 4.05 (m, 1H, H4).

^{13}C-NMR ($CDCl_3$) δ: 19.1 (CH_3 acetonide); 27.7 (C5); 29.8 (CH_3 acetonide); 44.1* (C3'); 50.7* (C2'); 59.4 (C6); 68.2* (C4); 72.0* (C1'); 74.8* (C7); 98.2 (C q. acetonide) (* double signal).

Anal. Calcd. for $C_{10}H_{18}O_4$ (202): C: 59.39, H: 8.97. Found: C: 59.39, H: 8.97. SM FAB^+ m/z (%): 209.0 (MLi^+) (100.0).

(4'R,4''R)-1-[2',2'-Dimethyl-4'-methylene-1',3'-dioxane]-3-[2'',2''-dimethyl-4''-methylene-1'',3''-dioxane]dioxy-propan-2-ol ***9***

Compound **7** (0.53 g, 3.6 mmol) was added to a suspension of NaH (0.21 g of a suspension at 50% in oil) in anhydrous THF (14 mL). The mixture was stirred and heated to 50°C under argon until the evolution of hydrogen ceased. Epoxide **8** (0.64 g, 3.17 mmol) was then added. The resulting mixture was refluxed and the reaction was followed by TLC (about 18 h). Water with ice were added, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over $MgSO_4$. After evaporation to dryness, the residue was chromatographed on silica gel with ethyl acetate/cyclohexane 30/70 to give **9** (496 mg, 1.42 mmol) in 45% yield. Colorless liquid. $[\alpha]_D^{25}=-7$ (c=0.047; $CHCl_3$). IR: 3420, 1385–1375, 1275–1000 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.34 (s, 6H, 2 CH_3 acetonide); 1.38 (m, 2H, H5'B–H5''B); 1.42 (s, 6H, 2 CH_3 acetonide); 1.60 (ddd, 2H, H5'A–H5''A); 3.20 (s, 1H, OH); 3.37–3.55 (m, 8H, H1–H3–H7'–H7''); 3.80 (ddd, 2H, H6'B–H6''B, part AB of ABXY spectrum, $J_{6'Be,5'Be}$ 1.6 Hz, $J_{6'Be,5'Aa}$ 5.5 Hz, $J_{6'Be,6'A}$ 12.1 Hz); 3.90 (m, 1H, H2); 3.94 (ddd, 2H, H6'A–H6''A, part AB of ABXY spectrum, $J_{6'Aa,5'Be}$ 3.0 Hz, $J_{6'Aa,5'Aa}=J_{6'Aa,6'B}$ 12.1 Hz); 4.05 (m, 2H, H4'–H4''). ^{13}C-NMR ($CDCl_3$) δ: 19.2 (2 CH_3 acetonide); 27.7 (C5'–C5''); 29.8 (2 CH_3 acetonide); 59.5 (C6'–C6''); 68.4 (C4'–C4''); 69.6 (C2); 72.9 (C1–C3); 75.1 (C7'–C7''); 98.4 (C q. acetonide). Anal. Calcd. for $C_{17}H_{32}O_7$ (348): C: 58.60, H: 9.26. Found: C: 58.84, H: 9.06.

(4'R,4''R)-1-[2',2'-Dimethyl-4'-methylene-1',3'-dioxane]-3-[2'',2''-dimethyl-4''-methylene-1'',3''-dioxane]dioxy-propanone ***10***

To a suspension of 4Å molecular sieve (powder) in anhydrous CH_2Cl_2 (6 mL), 190 mg of N-methyl morpholine N-oxide (NMO) and 300 mg (0.862 mmol) of alcohol **9** were added. The mixture was stirred vigorously for 1 h 30 min at room temperature. 20 mg of tetrapropyl ammonium perruthenate (TPAP) was added, and the resulting mixture was stirred overnight at room temperature. The

molecular sieve was filtered and washed several times with CH_2Cl_2. The combined filtrates were then concentrated. The residue was column chromatographed on silica gel with ethyl acetate/cyclohexane 50/50 to give ketone **10** (285 mg, 0.824 mmol) in 95% yield. Colorless liquid. $[\alpha]_D^{25}$=+30 (c=0.046; MeOH). IR: 1650–1640, 1380, 1130–1050 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.35 (s, 6H, 2 CH_3 acetonide); 1.41 (m, 2H, H5′B–H5″B); 1.43 (s, 6H, 2 CH_3 acetonide); 1.63 (ttd, 2H, H5′A–H5″A, $J_{5'Aa,6'Be}$ 5.5 Hz, $J_{5'Aa,4'a}$=$J_{5'Aa,6'Aa}$=$J_{5'Aa,5'B}$ 12.6 Hz); 3.46 (dd, 2H, H7′B–H7″B, $J_{7'B,4'a}$ 4.3 Hz, $J_{7'B,7'A}$ 10.4 Hz); 3.49 (dd, 2H, H7′A–H7″A, $J_{7'A,4'a}$ 5.6 Hz, $J_{7'A,7'B}$ 10.4 Hz); 3.82 (ddd, 2H, H6′B–H6″B, $J_{6'Be,5'Be}$ 1.6 Hz, $J_{6'Be,5'Aa}$ 5.4 Hz, $J_{6'Be,6A}$ 12.1 Hz); 3.97 (td, 2H, H6′A–H6″A, $J_{6'Aa,5'Be}$ 2.9 Hz, $J_{6'Aa,5'Aa}$=$J_{6'A,6B}$ 12.1 Hz); 4.10 (m, 2H, H4′–H4″, $J_{4'a,5'Be}$ 3.1 Hz, $J_{4'a,7'B}$ 4.3 Hz, $J_{4'a,7'A}$ 5.6 Hz, $J_{4'a,5'Aa}$ 12.1 Hz); 4.29 (d, 4H, H1 and H3). ^{13}C-NMR ($CDCl_3$) δ: 19.2 (2 CH_3 acetonide); 27.4 (C5′–C5″); 29.9 (2 CH_3 acetonide); 59.4 (C6′–C6″); 68.5 (C4′–C4″); 75.2 (C1–C3); 75.4 (C7′–C7″); 98.3 (C q. acetonide); 206.3 (C2). Anal. Calcd. for $C_{17}H_{30}O_7$ (346): C: 58.95, H: 8.73. Found: C: 58.71, H: 8.75.

(2R,6S,8R)-2,8-(Dihydroxyethyl)-1,4,7,10-tetraoxaspiro[5.5]undecane E,E ***11***

To a solution of 3.5 mL of THF and concentrated HCl (0.35 mL of 10 N HCl), 285 mg (0.82 mmol) of ketone **10** was added. The resulting mixture was stirred overnight at room temperature. To neutralize the hydrochloric acid, sodium hydroxide pellets were added. After filtration of the salt, the filtrate was evaporated to dryness. The residue was chromatographed on silica gel with ethyl acetate to give the spiroacetal E,E **11** (140 mg, 0.56 mmol) in 68.5% yield. White solid. $[\alpha]_D^{25}$=+79 (c=0.0117; $CHCl_3$). IR: 3400, 3195, 1150 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.56 (m, 4H, 12A, 12B, 12′A, 12′B); 3.25 (d, 2H, H5B, H11B); 3.30 (t, 2H, H3B,H9B, $J_{3Ba,2}$=$J_{3B,3A}$ 10.9 Hz); 3.49 (s, 1H, OH); 3.58 (d, 2H, H5A, H11A); 3,68 (m, 2H, H13B, H13′B); 3.72 (m, 2H, H3A, H9A); 3.88 (m, 2H, H13A, H13′A); 4.23 (m, 2H, H2, H8). ^{13}C-NMR ($CDCl_3$) δ: 33.2 (C12,C12′); 58.1 (C13,C13′); 65.1 (C2,C8); 68.4 (C5, C11); 70.4 (C3, C9); 91.9 (C6). Anal. Calcd. for $C_{11}H_{20}O_6$ (248): C: 53.21, H: 8.12. Found: C: 52.96, H: 8.27. Exact mass: C11H20O6: calc. 248.2730; found 248.2720. MS EI m/z (%): 248.1 (M^+) (5.2); 147.1 (32.5); 146.0 (35.7); 71.0 (100.0).

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