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TETRAHEDRON: *ASYMMETRY*

Chiral building-blocks by chemoenzymatic desymmetrization of 2-ethyl-1,3-propanediol for the preparation of biologically active natural products

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Abstract

2-Ethyl-1,3-propanediol **1** and its related di-*O*-acetate **2** were desymmetrized by partial chemoenzymatic acetylation and deacetylation, by *Pseudomonas fluorescens* lipase (Amano P.; PFL), to (*R*)-1-*O*-acetyl-2-ethyl-1,3-propanediol **3**. On treatment of **3** with I_2/Ph_3P/imidazole the related (*S*)-1-*O*-acetyl-2-ethyl-3-iodopropanol **4** was obtained and transformed into the corresponding triphenylphosphonium salt **5**. Reaction of [(*S*)-3-acetoxy-2-ethylpropylidene]triphenylphosphorane **6**, prepared from **5**, with 2,3:4,5-di-*O*-isopropylidene-β-D-*arabino*-hexos-2-ulopyranose **7** gave (*Z*)-3-*C*-acetoxymethyl-1,2,3,4,5-pentadeoxy-6,7:8,9-di-*O*-isopropylidene-β-D-*manno*-dec-4-ene-6-ulo-6,10-pyranose **8** which was hydrogenated to **9** and subsequently deacylated to **10**. Treatment of **10** with Me_2CO/H^+ caused a rearrangement to (3*R*,4*R*,5*S*,6*R*,9*R*)-9-ethyl-5-hydroxy-3,4-isopropylidenedioxy-1,7-dioxaspiro[5.5]undecane **11**, which closely matched the skeleton of the talaromycins.

1. Introduction

Scheme 1 clearly shows that chiral moieties derived from 1,3-propanediol are commonly present in many molecules exhibiting important biological activities, such as β-blockers,[1] antifungal agents,[2] toxins,[3] etc., and hence there is much interest in finding simple synthetic methods for such moieties: those methods using chemoenzymatic routes have attracted the attention of many groups in recent years.[4] On the other hand, the synthesis of the dioxaspiro compound **11** (see Scheme 3) and its C-9 epimer have been reported[5] by our group but this approach was flawed in the stereoselectivity achieved during formation of branching at the 1,3-diol moiety, and required the use of tedious chromotography. Therein lies the convenience of exploring new methodologies for the preparation of those molecules from easily

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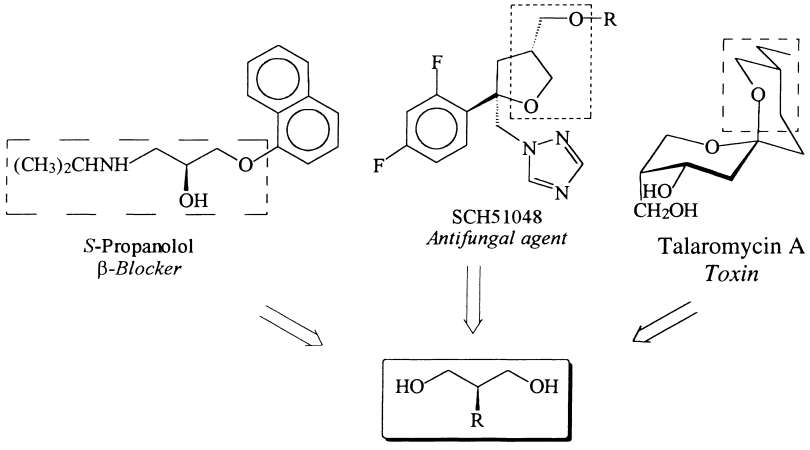
available chirons as starting materials in the stereospecific synthesis of such moieties. The results of this new approach are reported below.



Scheme 1.

2. Results and discussion

Treatment of 2-ethyl-1,3-propanediol **1**[6] with vinyl acetate in CH_2Cl_2 under the presence of lipase from *Pseudomonas fluorescens* (Amano P.; PFL) at room temperature, caused its desymmetrization to afford (*R*)-1-*O*-acetyl-2-ethyl-1,3-propanediol **3**,[6] isolated in 72% yield with a 46% *ee*, determined by GLC (*B*) on a β-DEX™ column (see Fig. 1). These findings differed from those recently reported,[7] where a lower *ee* (19%) was obtained and isolation of the products was not described. On the other hand, when 1,3-di-*O*-acetyl-2-ethyl-1,3-propanediol (**2**)[6] was subjected to partial hydrolysis catalyzed by PFL, compound **3** was obtained in 65% yield, after 1.5 h, with a 94% *ee* (see Fig. 2).

Although partial enzymatically catalyzed acylation of 2-substituted-1,3-propanediols and hydrolysis of the corresponding diesters by lipases usually display the same prochiral selectivity[8] and result in products of opposite absolute stereochemistry, this was not the case in the present work where only the *R*-isomer was obtained. This behaviour has been reported in other cases.[2]

Treatment of **3**, from partial hydrolysis of **2**, with I_2/Ph_3P/imidazole[9] gave (*S*)-1-*O*-acetyl-2-ethyl-3-iodopropanol **4** that was straightforwardly transformed into the corresponding phosphonium salt **5** by reaction with Ph_3P in toluene and subsequently into [(*S*)-3-acetoxy-2-

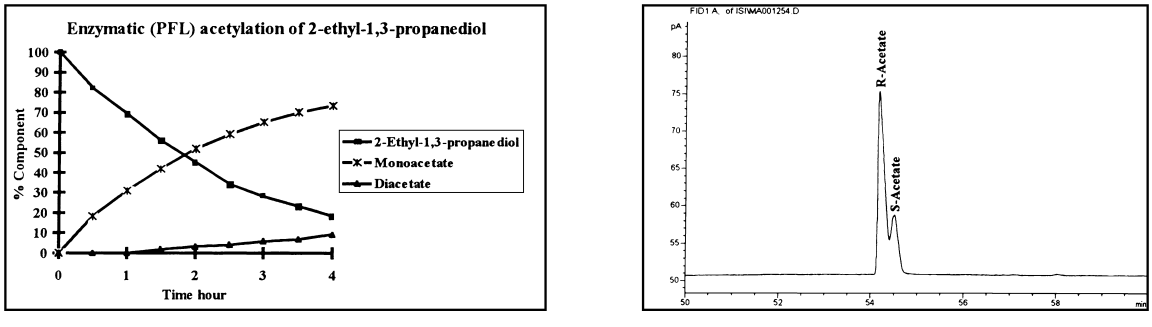


Figure 1. Kinetic data for enzymatically (PFL) catalyzed monoacetylation of **1** and GLC analysis (ee) on a β-DEX™ column

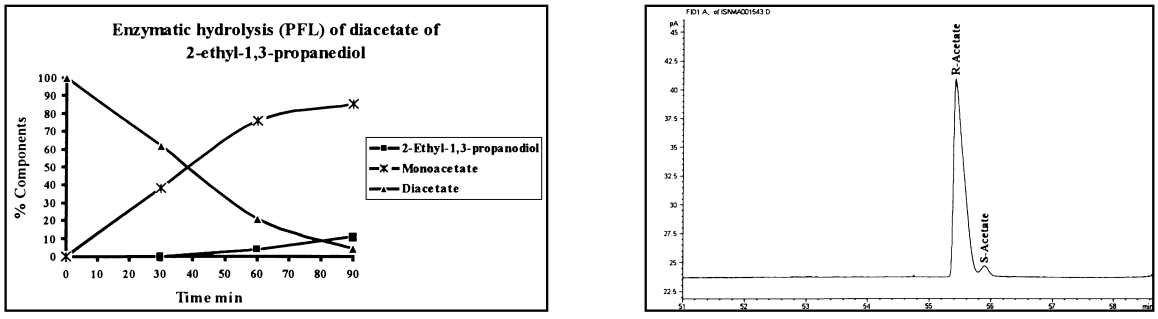
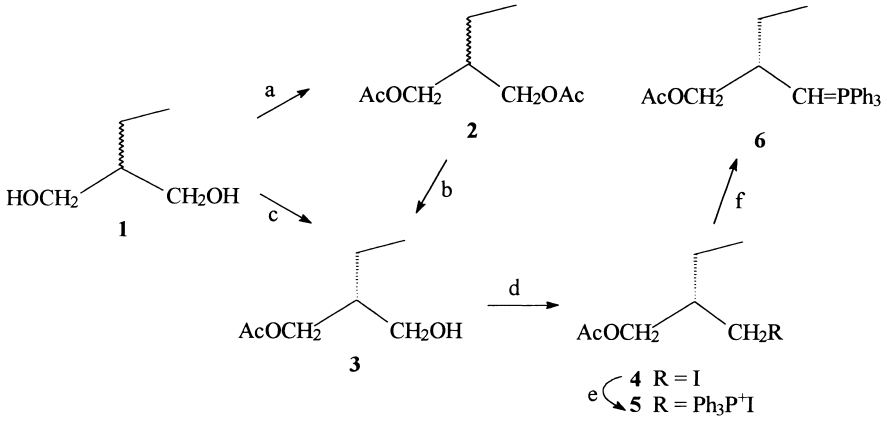


Figure 2. Kinetic data for enzymatically (PFL) catalyzed partial hydrolysis of **2** and GLC analysis (ee) on a β-DEX™ column

ethylpropylidene]triphenylphosphorane **6** (Scheme 2). Reaction of **6** with 2,3:4,5-di-*O*-isopropylidene-β-D-*arabino*-hexos-2-ulopyranose[5] (**7**) gave (*Z*)-3-*C*-acetoxymethyl-1,2,3,4,5-pentadeoxy-6,7:8,9-di-*O*-isopropylidene-β-D-*manno*-dec-4-ene-6-ulo-6,10-pyranose **8** which was hydrogenated to **9** and subsequently deacylated to **10** (Scheme 3). Treatment of **10** with Me_2CO/H^+ caused its rearrangement to afford (3*R*,4*R*,5*S*,6*R*,9*R*)-9-ethyl-5-hydroxy-3,4-isopropylidenedioxy-1,7-dioxaspiro[5.5]undecane (**11**), which showed the same physical and spectroscopic data as those previously reported[5] and where its transformation into talaromycin A and B was described.

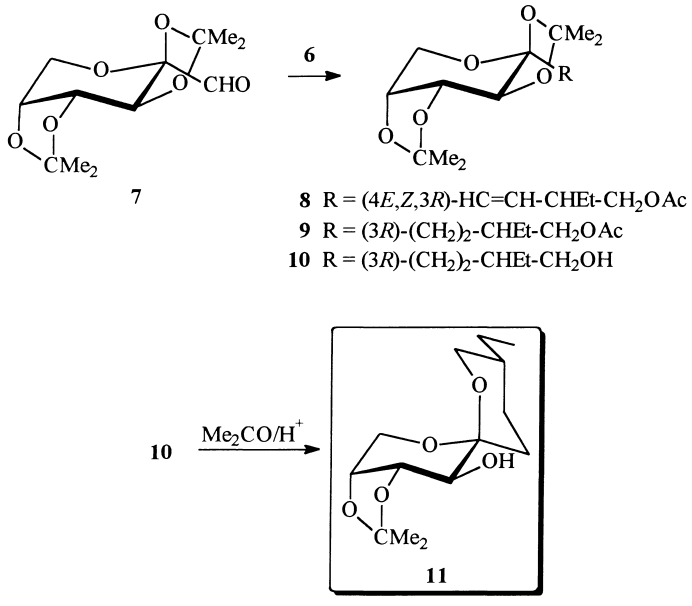


a) Ac_2)/Et3N/CH_2Cl_2; b) *Pseudomonas Fluorescens Lipase* (PFL)/buffer (pH7)/r.t.;
c) PFL/ vinyl acetate CH_2Cl_2/r.t.; d)I_2/Ph_3/P/imidazole; e) Ph_3P/MePh/reflux, f) diglyme/E-BuOK

Scheme 2.

3. Conclusions

The results described above, indicate that the use of the chiral pool (carbohydrates) combined with chiral catalysts (enzymes), both from natural sources, could be an excellent methodology in order to overcome many problems in the stereoselective synthesis of complex biologically active natural products.



Scheme 3.

4. Experimental

4.1. General

Melting points were determined with a Gallenkamp apparatus and are uncorrected. Solutions were dried over $MgSO_4$ before concentration under reduced pressure. The ^1H and ^{13}C NMR spectra were recorded with Bruker AMX-300, AM-300, and ARX-400 spectrometers for solutions in $CDCl_3$ (internal Me_4Si). IR spectra were recorded with a Perkin–Elmer 782 instrument and mass spectra with a Hewlett–Packard 5988A and Fisons Platform II and VG Autospec-Q mass spectrometers. Optical rotations were measured for solutions in $CHCl_3$ (1 dm tube) with a Jasco DIP-370 polarimeter. GLC was performed on a Hewlett–Packard 6890 gas chromatograph equipped with split/splitless injector, a flame-ionization detector, and: (*A*) a capillary HP-5 column (30 m×0.25 mm i.d.×0.25 μm film thickness) at 110°C; or (*B*) a β-DEX™ 325 (Supelco™) capillary column (30 m×0.25 mm i.d.×0.25 μm film thickness) 50 min at 80°C, program to 110°C, 10°C/min. The He flow rate was 1.1 mL/min, the injection port and the zone-detector temperatures were 275°C. TLC was performed on precoated silica gel 60 F_{254} aluminium sheets and detection by charring with H_2SO_4. Column chromatography was performed on silica gel (Merck, 7734). The noncrystalline compounds were shown to be homogeneous by chromatography and characterized by NMR and HRMS.

*4.2. Partial enzymatic (PFL) acetylation of 2-ethyl-1,3-propanediol **1***

To a gently stirred solution of **1** (1.25 g, 12 mmol) in dry dichloromethane (25 mL) and vinyl acetate (2.5 mL, 27 mmol) was added PFL (Amano P., 600 mg), and the mixture maintained at room temperature for 4 h. The reaction was monitored by GLC analysis (*A*). The enzyme was removed by filtering, thoroughly washed with dichloromethane, and the filtrate and washings concentrated to a residue that was chromatographed (ether:hexane=1:4 → 1:1) to afford first 1,3-di-*O*-acetyl-2-ethyl-1,3-propanediol (**2**, 116 mg), t_R 9.57 min (*A*). The second fraction was (*R*)-1-*O*-acetyl-2-ethyl-1,3-propanediol (**3**, 1 g,

72%), t_R 5.45 min (*A*), $[\alpha]_D^{25}$ +7.5, $[\alpha]_{405}^{25}$ +14.7 (c 1.7), t_R 54.18 min (*B*), *ee* 46% (see Fig. 1). The spectroscopic data for **2** and **3** were identical to those previously reported.[6] Finally, compound **1** (257 mg), t_R 3.72 min (*A*) was recovered.

4.3. 1,3-Di-O-acetyl-2-ethyl-1,3-propanediol **2**

To a cooled solution of **1** (1.5 g, 14.4 mmol), Et_3N (6.3 mL, 45 mmol), DMAP (100 mg) in dry dichloromethane (30 mL), and acetic anhydride (4.3 mL, 45 mmol) were added and the mixture was left at room temperature for 6 h. Work-up of the reaction mixture as usual gave, after column chromatography (ether:hexane=1:4), **2** (2.55 g, 94%) whose physical and spectroscopic data were the same as those previously reported.[6]

4.4. Partial enzymatic (PFL) hydrolysis of **2**

To a gently stirred suspension of **2** (2 g, 10.6 mmol) in 100 mL of a buffered (pH 7) aqueous 0.5 M phosphate solution (KH_2PO_4) was added PFL (500 mg). Stirring was maintained for 1.5 h. GLC analysis (*A*) of the mixture then revealed the presence of **1** (10.6%), **2** (4%), and **3** (85.1%). The enzyme was filtered off and the filtrate saturated with sodium chloride and extracted with ethyl acetate. The combined extracts were concentrated. Column chromatography (ether:hexane=1:2) of the residue gave **3** (1 g, 65%); $[\alpha]_D^{23}$ +11, $[\alpha]_{405}^{25}$ +26 (c 1.4), t_R 55.38 min (*B*), *ee* 94% (see Fig. 2).

4.5. (S)-1-O-Acetyl-2-ethyl-3-iodopropanol **4**

To a stirred solution of I_2 (2.1 g, 8.3 mmol) in dry dichloromethane (20 mL) was added Ph_3P (2.15 g, 8.2 mmol) and then imidazole (1.07 g, 16 mmol) at room temperature. After 5 min, compound **3** (*ee* 94%) (950 mg, 6.5 mmol) was added and the mixture was stirred for 30 min. GLC analysis (*A*) then showed the presence of a new compound (t_R 11.39 min). The reaction mixture was washed with aqueous 10% $KHSO_4$, brine and concentrated. The residue was extracted with ether:hexane=1:5 to remove most of the Ph_3PO and the combined extracts concentrated. Column chromatography (ether:hexane=1:9) of the residue gave **4** (1.54 g, 93%) as an oil; $[\alpha]_D^{24}$ +5.5, $[\alpha]_{405}^{25}$ +14 (c 1.8), t_R 17.15 min (*B* at 115°C); ν_{max}^{film} 1744 cm^{-1} ($MeCO_2$). NMR data: ^1H, δ 4.16 (dd, 1H, $J_{1a,1b}$=11.2, $J_{1a,2}$=4.8 Hz, H-1a), 3.98 (dd, 1H, $J_{1b,2}$=7.2 Hz, H-1b), 3.37 (dd, 1H, $J_{3a,3b}$=10.4, $J_{2,3a}$=4.6 Hz, H-3a), 3.32 (dd, 1H, $J_{2,3b}$=5.1 Hz, H-3b), 2.11 (s, 3H, Ac), 1.57 (m, 1H, H-2), 1.45 (m, 2H, H-1′), and 0.98 (t, 3H, J=7.4 Hz, H-2′); ^{13}C, δ 170.92 (Me*C*O), 66.47 (C-1), 40.12 (C-2), 24.25 (C-1′), 20.94 (*Me*CO), 10.97 (C-2′), and 10.53 (C-3). Mass spectrum (CI, CH_4): *m/z* 257 (20.9%, M^++1), 255 (9.0, M^+−1), 229 (9.8, M^++1−C_2H_4), 197 (23.1, M^++1−AcOH), 143 (49.4, CH_3IH^+), 129 (25.5, IH_2^+) and 57 (100, $C_4H_9^+$).

4.6. [(S)-3-Acetoxy-2-ethylpropyl]triphenylphosphonium iodide **5**

A stirred solution of **4** (1.35 g, 5.3 mmol) and Ph_3P (1.5 g, 5.7 mmol) in dry toluene (15 mL) was refluxed for 3 days. After cooling, a crystalline precipitate appeared, the solid was filtered and washed with ether to afford crystalline **5** (2.6 g, quantitative): mp: 81–83°C; $[\alpha]_D^{27}$ −13, $[\alpha]_{405}^{28}$ −30 (c 1.2, methanol). NMR data (d_3-MeOD): ^1H, δ 7.92–7.87 and 7.78–7.73 (2m, 15H, 3Ph), 3.98 (dd, 1H, $J_{3a,3b}$=11.5, $J_{2,3a}$=5.9 Hz, H-3a), 3.94 (dd, 1H, $J_{2,3b}$=4.8 Hz, H-3b), 3.62 (ddd, 1H, $J_{1a,1b}$=14.3, $J_{1a,2}$=5.6, $J_{1a,P}$=15.9 Hz, H-1a), 3.37 (dd, 1H, $J_{1b,2}$=6.3, $J_{1b,P}$=15.9 Hz, H-1b), 2.18 (m, 1H, H-2), 2.00 (s, 3H, Ac), 1.43 (m, 1H, H-1′a), 1.25 (m, 1H, H-1′b), and 0.79 (t, 3H, J=7.5 Hz, H-2′); ^{13}C, δ 172.35 (Me*C*O),

66.53 (C-3), 35.40 (C-2), 26.61 (C-1), 25.37 (C-1′), 20.78 (*Me*CO), and 10.97 (C-2′). Anal. calcd for $C_{25}H_{28}IO_2P$: C, 57.92; H, 5.44. Found: C, 58.21; H, 5.32. S, 3.21.

*4.7. (Z)-3-*C*-Acetoxymethyl-1,2,3,4,5-pentadeoxy-6,7:8,9-di-*O*-isopropylidene-β-*D*-manno-dec-4-ene-6-ulo-6,10-pyranose* **8**

To a stirred solution of 2,3:4,5-di-*O*-isopropylidene-β-D-*arabino*-hexos-2-ulopyranose[5] (**7**, 1.06 g, 4.1 mmol) in dry diglyme (7 mL) under argon, potassium *tert*-butoxide (500 mg, 4.5 mmol) was added at room temperature. Compound **5** (2.2 g, 4.2 mmol) was added and the mixture was left for 30 min. TLC (ether:hexane=3:2) then revealed the presence of a faster-running compound. The mixture was diluted with ether (50 mL) and the resulting solution was washed with brine, then concentrated. Column chromatography (ether:hexane=1:3) of the residue gave **8** (470 mg, 31%) as a colourless oil; $[\alpha]_D^{25}$ −23, $[\alpha]_{405}^{26}$ −57 (c 1.7), t_R 6.56 min (*A*); ν_{max}^{film} 1741 ($MeCO_2$), 1384 and 1373 cm^{-1} (CMe_2). NMR data: ^{1}H, δ 5.62 (d, 1H, $J_{4,5}$=11.6 Hz, H-5), 5.29 (t, 1H, $J_{3,4}$=11.6 Hz, H-4), 4.57 (dd, 1H, $J_{7,8}$=2.4, $J_{8,9}$=7.9 Hz, H-8), 4.20–4.17 (m, 2H, H-7,9), 4.07 (dd, 1H, $J_{1'a,1'b}$=10.7, $J_{1'a,3}$=5.7 Hz, H-1′a), 3.91 (dd, 1H, $J_{1'b,3}$=7.0 Hz, H-1′b), 3.81 (dd, 1H, $J_{9,10ax}$=1.9, $J_{10ax,10eq}$=12.9 Hz, H-10ax), 3.67 (d, 1H, H-10eq), 3.33 (m, 1H, H-3), 2.01 (s, 3H, Ac), 1.50, 1.45, and 1.32 (3s, 12H, $2CMe_2$), 1.57–1.18 (m, 2H, H-2), and 0.87 (t, 3H, J=7.5 Hz, H-1); ^{13}C, δ 175.39 (Me*C*O), 135.18 (C-5), 131.16 (C-4), 109.13 and 108.19 ($2CMe_2$), 74.85 (C-7), 70.67 and 70.56 (C-8,9), 67.20 (C-1′), 60.83 (C-10), 38.64 (C-3), 26.26, 25.99, 25.03, and 24.80 ($2CMe_2$), 24.38 (C-2), 21.12 (*Me*CO), and 11.58 (C-1). Mass spectrum (LSIMS): *m/z* 393.19027 (M^++Na). For $C_{19}H_{30}O_7Na$ 393.18892 (deviation −3.4 ppm).

*4.8. 3-*C*-Acetoxymethyl-1,2,3,4,5-pentadeoxy-6,7:8,9-di-*O*-isopropylidene-β-*D*-manno-dec-6-ulo-6,10-pyranose* **9**

A solution of **8** (1.06 g, 2.83 mmol) in dry methanol (20 mL) was hydrogenated over 10% Pd–C (220 mg) at 75 psi for 24 h. GLC (*A*) then revealed the presence of a new compound (t_R 7.60 min). The catalyst was filtered off, washed with methanol and the combined filtrate and washings concentrated to a residue which chromatographed (ether:hexane=1:3) to afford **9** (880 mg, 85%) as a colourless syrup; $[\alpha]_D^{26}$ −10 (c 1.2). NMR data: ^{1}H, δ 4.55 (dd, 1H, $J_{7,8}$=2, $J_{8,9}$=8 Hz, H-8), 4.20 (bd, 1H, H-9), 4.07 (d, 1H, H-7), 3.98 (m, 2H, CH_2OAc), 3.83 (bd, 1H, H-10ax), 3.70 (d, 1H, $J_{10ax,10eq}$=13 Hz, H-10eq), 2.02 (s, 3H, Ac), 1.90–1.30 (m, 7H, H-2,3,4,5), 1.50, 1.46, and 1.33 (3s, 12H, $2CMe_2$), and 0.88 (t, 3H, $J_{1,2}$=7.4 Hz, H-1); ^{13}C, δ 171.34 (Me*C*O), 108.97 and 107.48 ($2CMe_2$), 104.21 (C-6), 74.93 (C-7), 70.95 and 70.72 (C-8,9), 66.70 (C-1′), 61.02 (C-10), 38.77 (C-3), 38.13 (C-5), 26.49, 25.88, 25.19, and 24.20 ($2CMe_2$), 23.98 and 23.62 (C-2,4), 21.04 (*Me*CO), and 10.90 (C-1). Mass spectrum (LSIMS): *m/z* 395.20472 (M^++Na). For $C_{19}H_{32}O_7Na$ 395.20457 (deviation −0.4 ppm).

*4.9. 1,2,3,4,5-Pentadeoxy-3-*C*-hydroxymethyl-6,7:8,9-di-*O*-isopropylidene-β-*D*-manno-dec-6-ulo-6,10-pyranose* **10**

To a solution of **9** (480 mg, 1.29 mmol) in dry methanol (15 mL) 0.5 M sodium methoxide (0.25 mL) was added and the mixture left at room temperature for 24 h. TLC (ether:hexane=2:1) then revealed a slower-running compound. The mixture was neutralized and concentrated. The residue was partitioned in ether–water and the organic phase was separated and the aqueous phase extracted with ether. Concentration of the combined extracts gave a residue which was chromatographed (ether:hexane=1:1) to

give **10** (310 mg, 73%) as a colourless oil which showed the same spectroscopic data as those previously reported;[5] t_R 6.10 min (*A* at 210°C); $[\alpha]_D^{29}$ −11 (c 0.5).

*4.10. (3*R*,4*R*,5*S*,6*R*,9*R*)-9-Ethyl-5-hydroxy-3,4-isopropylidenedioxy-1,7-dioxaspiro[5.5]undecane **11***

To a stirred solution of **10** (310 mg, 0.94 mmol) in dry acetone (20 mL) was added anhydrous copper sulfate (250 mg) and *p*-toluenesulfonic acid (70 mg), and the mixture was kept at room temperature for 70 h. GLC (*A* at 210°C) then revealed the presence of **11** by comparison with an authentic sample (t_R 3.90 min). The reaction mixture was neutralized (K_2CO_3) filtered and concentrated. Column chromatography (ether:hexane=1:2) of the residue gave crystalline **11** (147 mg, 58%) which had the same physical spectroscopic data as those previously reported.[5]

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