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Synthesis of 1,2-anhydro-3,4,5-tri-*O*-benzyl-β-D-fructopyranose

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ABSTRACT

A synthesis of the anomeric spiro-epoxide **15** from D-fructose, in 7 steps in an overall 13% yield, is described. The key intermediate in the synthesis, 3,4,5-tri-*O*-benzyl-1-deoxy-1-iodo-β-D-fructopyranose (**14**), was prepared from the corresponding methyl fructopyranoside by reaction with the iodine–triphenylphosphine–imidazole reagent complex, followed by acid hydrolysis. Ring closure of the iodohydrin **14** was achieved under extremely mild conditions on treatment with silver(I) oxide in anhydrous THF. The ^{13}C NMR spectrum of **15** exhibited a large upfield shift of the resonances assigned to C-1 and C-2, indicative of an oxirane ring involving these two carbon atoms.

INTRODUCTION

The synthesis and reactivity of 1,2-anhydro-D-hexopyranoses has generated considerable interest[1,2]. In the majority of cases, the synthesis of these compounds has been achieved by an intramolecular S_N2 displacement of a leaving group on the anomeric carbon atom by an ionised hydroxyl group on the adjacent carbon atom[1]. An important advance in this field was made by Halcomb and Danishefsky[2] who reported the direct epoxidation of glycals with anhydrous 3,3-dimethyldioxirane[3]. Previous attempts to achieve this reaction using peroxy acids were unsuccessful because of the acid sensitivity of the initially formed 1,2-anhydro sugar[4].

However, the use of 3,3-dimethyldioxirane has largely been confined to endocyclic glycals. Recently, Russo et al. demonstrated the applicability of this methodology to the epoxidation of exocyclic glycals[5]. Methylenation of 2,3,5-tri-*O*-benzyl-D-arabinonolactone, using the Tebbe reagent[6], followed by epoxidation with 3,3-dimethyldioxirane afforded 1,2-anhydro-3,4,6-tri-*O*-benzyl-D-fructofuranose (**1**) as an 11:1 diastereomeric mixture of α and β anomers, respectively. The anomeric

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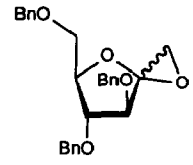

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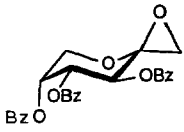

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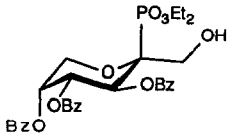

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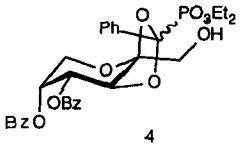

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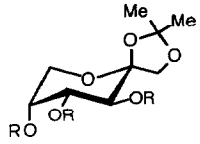
spiro-epoxide **1** reacted with alcohols under Lewis acid catalysis regioselectively at C-2 affording fructofuranosyl glycosides.

Previously, we had reported the synthesis of 1,2-anhydro-3,4,5-tri-*O*-benzoyl-β-D-fructopyranose (**2**) and its reaction with a phosphorus nucleophile, affording **3**, an "isopolar" phosphonate analogue of D-fructose 1-phosphate[7]. Base-catalysed nucleophilic ring opening of **2** occurred cleanly at the least sterically hindered, terminal end of the epoxide with a variety of nucleophiles[8]. However, Lewis acid catalysed reaction of **2** was complicated by the "participating" benzoate protecting group at C-3. Reaction of **2** with diethyl trimethylsilylphosphite catalysed by $ZnCl_2$ did not yield the expected anomeric phosphonate **3**, but instead gave the 1′-diethoxyphosphinoyl benzylidene compound **4** due to participation of the C-3 benzoate group. We now report the synthesis of 1,2-anhydro-3,4,5-tri-*O*-benzyl-β-D-fructopyranose (**15**) containing only non-participating protecting groups.

RESULTS AND DISCUSSION

The key step in our synthesis of **2** involved ring closure of the iodohydrin **12** under extremely mild conditions employing silver(I) oxide to facilitate iodide removal. We thus envisaged an analogous synthesis of the tribenzyl-protected anomeric epoxide **15** from the iodohydrin **14**.

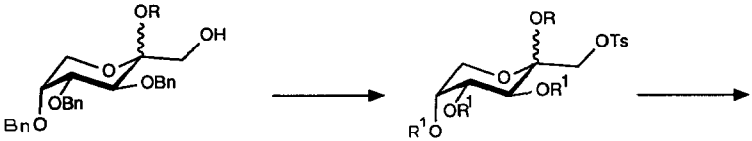
1,2-*O*-isopropylidene-β-D-fructopyranose[9] (**5**) was protected as the tribenzyl ether **6** on treatment with 3 equiv of sodium hydride and benzyl bromide in THF, incorporating tetrabutylammonium iodide as phase transfer catalyst[10]. The acetonide protecting group of **6** proved resistant to acid-catalysed hydrolysis under standard conditions[11]. Cleavage was finally achieved on treatment with aq 50% trifluoroacetic acid to afford the diol **7**, with an $\alpha:\beta$ ratio of 1:2.5, in moderate yield. Reaction of **7** with *p*-toluenesulphonyl chloride in pyridine yielded exclusively the primary tosylate **9** with a measured $\alpha:\beta$ ratio of 1:2.8.



5 R=H
6 R=Bn

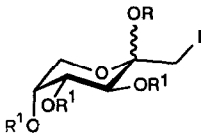
In the related series[7], displacement of the leaving group from the tribenzoate-protected tosylate **10** was readily achieved with potassium iodide in DMF at 70°C to afford the iodohydrin **12**. Unfortunately, the tosylate **9**, now lacking the anchimeric assistance provided by the benzoate protecting groups, failed to react with potassium iodide at 150°C in DMF over an extended time period. This was not unexpected as the tosylate **9** is neopentyl in nature, and the reluctance of similar primary tosylates derived from 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose to undergo nucleophilic displacement has been reported by Richardson[12].

Ring closure of **9** could, however, be achieved on treatment with potassium *tert*-butoxide in THF at room temperature for 1 h to afford a diasteromeric mixture of epoxides **15** and **16**, in 6:1 ratio. The anomeric spiro-epoxides **15** and **16** proved to be very much more unstable than the analogous spiro-epoxide **2** incorporating benzoate protecting groups. The epoxides were especially acid labile, complete decomposition occurring during TLC; the formation of the epoxides was demonstrated by the presence of the corresponding diol in TLC. Special care had to be taken in preparing the samples of the spiro-epoxides for NMR analysis. The deuteriochloroform had first to be passed through a small column of basic alumina in order to remove all traces of hydrochloric acid before use. However, despite the use of rigorous anhydrous conditions, the anomeric epoxides were always obtained contaminated with ca. 10% of the diol **7**. Thus, a practical synthesis of the iodohydrin **14** still remained a priority.

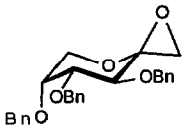


7 R=H
8 R=Me (β anomer)

9 R=H, R¹=Bn
10 R=H, R¹=Bz (β anomer)
11 R=Me, R¹=Bn (β anomer)



12 R=H (β anomer), R¹=Bz
13 R=Me, R¹=Bn
14 R=H, R¹=Bn



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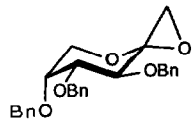

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It had proved possible to synthesise directly 1-deoxy-1-iodo-2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose from 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose on reaction with the triphenylphosphine–imidazole–iodine reagent system[7]. Since Garegg and Samuelsson's reagent mixture is known to form olefins from vicinal diols[13], application of this strategy would necessitate protection of the anomeric hydroxyl group.

Cleavage of the acetal in **5** on treatment with 1% w/v iodine in refluxing methanol[14] for 4 h afforded the methyl fructopyranoside **8** exclusively as the β anomer in excellent yield (95%). The effectiveness of iodine in methanol for this particular acetal cleavage can be gauged by the fact that deprotection with a 1% w/v *p*-toluenesulphonic acid solution in methanol was complete only after 24 h at reflux, yielding a moderate (40%) yield of methyl glycoside **8**. Reaction of the primary alcohol **8** with iodine, triphenylphosphine, and imidazole in refluxing toluene afforded cleanly the primary iodide **13** in good yield. The methyl glycoside **13** was hydrolysed under mild conditions on treatment with aq 80% acetic acid at 100°C to yield the required iodohydrin **14**, with an $\alpha:\beta$ ratio of 1:5. Epoxide formation was then achieved under neutral conditions utilising silver(I) oxide[15] to give the anomeric spiro-epoxides **15** and **16**, free from contamination with the diol, with the same anomeric ratio as the starting material. A single crystallisation of the crude product from diethyl ether–pentane afforded the pure β anomer in 63% yield.

The spiro-epoxides were characterised by a large upfield shift of the C-1 methylene protons in the ^{1}H NMR spectrum. The β anomer **15** exhibited a broad singlet at δ 2.92, whilst the α anomer **16** exhibited an AB system at δ 2.81, with a small geminal coupling constant of −5.3 Hz. The ^{13}C NMR spectrum was also indicative of an oxirane ring involving C-1 and C-2. The C-2 resonance, which normally lies between δ 95 and 105 for fructopyranose derivatives, occurred at δ 83.99 for the β anomer **15** and at δ 82.48 for the α anomer **16**. The C-2 resonances were also shifted upfield to δ 50.37 (β anomer) and δ 49.46 (α anomer).

EXPERIMENTAL

3,4,5-Tri-O-benzyl-1,2-O-isopropylidene-β-D-fructopyranose (**6**).—To a suspension of 60% NaH dispersion (7.21 g, 0.18 mol) and tetrabutylammonium iodide (6.65 g, 0.018 mol) in dry THF (100 mL) at 0°C under N_2 was added dropwise a solution of **5** (ref 9b) (12.01 g, 54.60 mmol) in dry THF (100 mL). After 1 h at 0°C, benzyl bromide (21.5 mL, 0.18 mol) was added dropwise and the mixture stirred at room temperature for 18 h. The reaction was quenched by the addition of MeOH (10 mL), filtered through a pad of Celite, and concentrated under vacuum. A solution of the residue in diethyl ether (500 mL) was washed with satd brine (2 × 300 mL), dried over $MgSO_4$, filtered, and concentrated. Chromatography on silica gel wth 3:17 EtOAc–petroleum ether as eluant gave **6** (21.19 g, 17%) as a colourless syrup that crystallised; mp 76–77°C (from diethyl ether–petroleum

ether); $[\alpha]_D$ −81.2° (*c* 0.92, $CHCl_3$); ν_{max} ($CHCl_3$) 2966, 2912, 2850, 1446, 1360, 1107, 1074, 885, and 865 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ 7.41–7.26 (m, 15 H, Ar-H), 5.04 (d, 1 H, *J* −11.5 Hz, ArCH_2), 4.73 (AB q, 2 H, *J* −12,5 Hz, ArCH_2), 4.66 (d, 1 H, *J* −11.5 Hz, ArCH_2), 4.62 (AB q, 2 H, *J* −11.5 Hz, ArCH_2), 3.98 (AB q, 2 H, *J* −8.6 Hz, H-1a,1b), 3.92 (m, 2 H, H-4,5), 3.79 (m, 3 H, H-3, H-6a,6b), 1.47 (s, 3 H, CH_3), and 1.42 (s, 3 H, CH_3); *m/z* (c.i.) 475 ($MH^+ - CH_4$), 433 ($MH^+ - CH_3COCH_3$), and 399 ($MH^+ - C_6H_5CH_3$). Anal. Calcd for $C_{30}H_{34}O_6$: C, 73.45; H, 7.0. Found: C, 73.5; H, 6.95

3,4,5-Tri-O-benzyl-α,β-D-fructopyranose (**7**).—A solution of **6** (7.72 g, 15.76 mmol) in CF_3CO_2H (100 mL) and water (100 mL) was stirred at room temperature for 24 h. The solvent was removed under vacuum and the residue dissolved in diethyl ether (500 mL). The organic solution was washed with satd aq $NaHCO_3$ (3 × 300 mL) and satd brine (400 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. Chromatography on silica gel with 1:1 EtOAc–petroleum ether as eluant gave **7** (3.47 g, 49%) as a colourless syrup with an α:β ratio of 1:25; $[\alpha]_D$ −42.6° (*c* 0.71, $CHCl_3$); ν_{max} (film) 3444 (OH), 3064, 3032, 2930, 2878, 1454, 1084, 1028, 737, and 698 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ 7.37–7.24 (m, 15 H, Ar-H), 5.69–4.47 (m, 6 H, 3 × ArCH_2), 4.04–3.35 (m, 9 H); *m/z* (CI) 433 ($MH^+ - H_2O$), and 341 ($MH^+ - H_2O - C_6H_5CH_3$).

3,4,5-Tri-O-benzyl-1-O-p-toluenesulphonyl-α,β-D-fructopyranose (**9**).—A solution of **7** (3.16 g, 7.02 mmol) and *p*-toluenesulphonyl chloride (1.47 g, 7.72 mmol) in dry pyridine (50 mL) was stirred at room temperature for 24 h under N_2. The mixture was poured into diethyl ether (500 mL), washed with 2 M HCl (3 × 250 mL) and satd brine (250 mL), dried over $MgSO_4$, and concentrated under vacuum. Chromatography on silica gel with 7:13 EtOAc–petroleum ether as eluant gave **9** (2.97 g, 70%) as a colourless syrup with an α:β ratio of 1:28; $[\alpha]_D$ −25.0° (*c* 0.42, $CHCl_3$); ν_{max} (film) 3430 (OH), 3068, 3038, 2934, 2876, 1597, 1450, 1364, 1180, and 1089 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ 7.79–7.74 (m, 2 H, Ar-H), 7.40–7.15 (m, 17 H, Ar-H), 4.96–4.22 (m, 6 H, 3 × ArCH_2), 4.19–3.65 (m, 7 H), and 2.39 (s, 3 H, ArCH_3); *m/z* (FAB) 601 ($MH^+ - H_2O$), and 495 ($MH^+ - H_2O - C_6H_5CH_3$).

Methyl 3,4,5-tri-O-benzyl-β-D-fructopyranoside (**8**).—To a stirred solution of iodine (2.5 g, 9.85 mmol, 1% w/v) in dry MeOH (150 mL) was added a solution of **6** in dry MeOH (100 mL), and the mixture was refluxed for 4 h under N_2. The mixture was concentrated under vacuum to ca. 50 mL, poured into diethyl ether (800 mL), washed with aq 10% $Na_2S_2O_3$ (2 × 400 mL) and satd brine (500 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. Chromatography on silica gel with 2:3 EtOAc–petroleum ether as eluant gave **8** (4.52 g, 95%) as a colourless syrup; $[\alpha]_D$ −51.3° (*c* 1.06, $CHCl_3$); ν_{max} (film) 3476 (OH), 3050, 3022, 2922, 2858, 1457, 1356, 1104, 1068, and 749 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ 7.41–7.45 (m, 15 H, Ar-H), 5.00 (d 1 H, *J* −10.9 Hz, ArCH_2), 4.75 (d, 1 H, *J* −10.0 Hz, ArCH_2), 4.74 (br s, 2 H, ArCH_2), 4.66 (AB q, 2 H, *J* −11.6 Hz, ArCH_2), 4.21 (d, 1 H, *J* 10.1 Hz, H-3), 4.00 (dd, 1 H, *J* 3.1 Hz, H-4), 3.79 (dd, 1 H, *J* 2.0, $J_{6a,6b}$ −12.8 Hz, H-6a), 3.78 (m, 1 H, H-5), 3.69 (br s, 2 H, H-1a,1b), 3.53 (dd,

1 H, *J* 1.7 Hz, H-6b), 3.29 (s, 3 H, OCH_3), and 2.00 (br s, 1 H), OH); *m/z* (CI) 482 (MNH_4^+), and 450 ($MH^+ - CH_3$). Anal. Calcd for $C_{28}H_{32}O_6$: C, 72.4; H, 6.9. Found C, 72.1; H, 7.0.

*Methyl 3,4,5-tri-*O*-benzyl-1-deoxy-1-iodo-β-*D*-fructopyranose* (**13**).—To a stirred solution of iodine (3.13 g, 12.33 mmol), Ph_3P (3.46 g, 13.19 mmol), and imidazole (1.80 g, 26.44 mmol) in dry toluene (250 mL) was added a solution of **8** (4.08 g, 8.79 mmol) in dry toluene (50 mL), and the mixture was refluxed for 5 h under N_2. The mixture was poured into diethyl ether (700 mL), washed with aq 10% $Na_2S_2O_3$ (2 × 300 mL) and satd brine (2 × 300 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. Chromatography on silica gel with 1:5 EtOAc–petroleum ether as eluant gave **11** (3.48 g, 69%) as a colourless syrup; $[\alpha]_D$ −51.7° (*c* 0.68, $CHCl_3$); ν_{max} (film) 3066, 2032, 2934, 2878, 1496, 1452, 1092, 1057, 741, and 701 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.47–7.24 (m, 15 H, Ar-H), 5.05 (d, 1 H, *J* −11.0 Hz, ArCH_2), 4.83 (d, 1 H, *J* −11.0 Hz, ArCH_2), 4.75 (br s, 2 H, ArCH_2), 4.65 (AB q, 2 H, *J* −11.8 Hz, ArCH_2), 4.51 (d, 1 H, $J_{3,4}$ 9.9 Hz, H-3), 3.92 (dd, 1 H, $J_{4,5}$ 3.2, H-4), 3.84 (dd, 1 H, *J* 1.9, $J_{6a,6b}$ −12.6 Hz, H-6a), 3.77 (m, 1 H, H-5), 3.56 (d, 1 H, $J_{1a,1b}$ −10 Hz, H-1a), 3.46 (d, 1 H, H-1b), 3.38 (dd, 1 H, $J_{5,6b}$ 1.0 Hz, H-6b), and 3.24 (s, 3 H, OCH_3); *m/z* (CI) 592 (MNH_4^+), and 560 ($MH^+ - CH_3$). Anal. Calcd for $C_{28}H_{31}IO_5$: C, 58.5; H, 5.4. Found: C, 58.4; H, 5.4.

*3,4,5-Tri-*O*-benzyl-1-deoxy-1-iodo-α,β-*D*-fructopyranose* (**14**).—A solution of **13** (2.68 g, 4.67 mmol) in acetic acid (200 mL) and water (40 mL) was heated at 100°C for 2 h. The mixture was poured into water (400 mL) and extracted with CH_2Cl_2 (4 × 250 mL). The combined organic extracts were washed with satd aq $NaHCO_3$ (2 × 500 mL), aq 10% NaS_2O_3 (250 mL), and satd brine (250 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. Chromatography on silica gel with 1:4 EtOAc–petroleum ether as eluant gave **14** (2.13 g, 81%) as a colourless syrup with an α:β ratio of 1:45; $[\alpha]_D$ −30.8° (*c* 1.37, $CHCl_3$); ν_{max} (film) 3422 (OH), 3066, 3032, 2926, 2882, 1454, 1088, 752, and 694 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): α anomer, δ 7.41–7.17 (m, 15 H, Ar-H), 4.85–4.40 (m, 6 H, 3 × ArCH_2), 4.05–3.53 (m, 5 H), and 3.33 (br s, 2 H, H-1a,1b); β anomer, δ 7.41–7.16 (m, 15 H, Ar-H), 5.02 (d, 1 H, *J* −11.2 Hz, ArCH_2), 4.77–4.54 (m, 5 H, ArCH_2), 4.14 (d, 1 H, $J_{3,4}$ 9.4 Hz, H-3), 3.88 (dd, 1 H, $J_{4,5}$ 2.9 Hz, H-4), 3.76–3.71 (m, 3 H, H-5,6a, 6b), 3.49 (d, 1 H, $J_{1a,1b}$ −10.5 Hz, H-1a), 3.30 (d, 1 H, H-1b), and 2.98 (br s, 1 H, OH); *m/z* (CI) 578 (MNH_4^+), and 450 ($M^+ - H_2O$-$C_6H_5CH_3$). Anal. Calcd for $C_{27}H_{29}IO_5$: C, 57.9; H, 5.2. Found: C, 58.3; H, 5.3.

*1,2-Anhydro-3,4,5-tri-*O*-benzyl-β-*D*-fructopyranose* (**15**) *and 1,2-anhydro-3,4,5-tri-*O*-benzyl-α-*D*-fructopyranose* (**16**).—(*i*) To a suspension of silver(I) oxide (167 mg, 0.72 mmol) in dry THF (5 mL) was added a solution of **14** in dry THF (5 mL). The mixture was stirred for 72 h at room temperature in the dark, filtered through a pad of Celite, and concentrated under vacuum to give the spiro-epoxides **15** and **16** (87 mg, 84%) as a colourless syrup that partially crystallised , with an α:β ratio of 1:5; $[\alpha]_D$ −28.3° (*c* 0.79, $CHCl_3$); ν_{max} (film) 3058, 2032, 2908, 2854, 1451, 1215, 1206, 1102, 1024, 745, and 699 cm^{-1}; **16**, ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.40–7.22

(m, 15 H, Ar-H), 4.60-4.54 (m, 6 H, $3 \times ArCH_2$), 4.13 (dd, 1 H, $J_{5,6a}$ 6.2, $J_{6a,6b}$ −11.6 Hz, H-6a), 3.94–3.87 (m, 2 H, H-3,5), 3.78 (dd, 1 H, $J_{4,5}$ 2.8, $J_{3,4}$ 6.8 Hz, H-4), 3.57 (dd, 1 H, $J_{5,6b}$ 2.6 Hz, H-6b), and 2.81 (AB q, 2 H, J −5.3 Hz, H-1a,1b); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 131.10–123.97 (m, Ar), 82.48 (s, C-2, 77.36, 75.54, and 73.69 (3 d, C-3,4,5), 72.40 and 71.49 (2 t, $ArCH_2$), 64.16 (t, C-6), and 49.46 (t, C-1); **15**, ^1H NMR (270 MHz, $CDCl_3$): δ 7.40–7.22 (m, 15 H, Ar-H), 4.91 (d, 1 H, J −11.5 Hz, $ArCH_2$), 4.74–4.60 (m, 5 H, $ArCH_2$), 4.38 (d, 1 H, $J_{3,4}$ 9.5 Hz, H-3), 3.94–3.87 (m, 3 H, H-4,5,6a), 3.69 (br d, 1 H, $J_{5,6b}$ −11.5 Hz, H-6b), and 2.92 (br s, 2 H, H-1a,1b); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 138.17, 138.06, and 137.86 (3 s, Ar), 131.10–123.97 (m, Ar), 83.39 (s, C-2), 80.05 (d), 74.96 (t, $ArCH_2$), 73.47 and 73.14 (2 d), 72.53 and 71.78 (2 t, $ArCH_2$), 64.94 (t, C-6), and 50.37 (t, C-1); m/z (CI) 433 (MH^+), and 341 ($MH^+ - C_6H_5CH_3$.

Recrystallisation afforded exclusively the β anomer **15** (65 mg, 63%) as colourless needles; mp 79°C (from diethyl ether–petroleum ether); $[\alpha]_D$ −35.8° (c 1.39, $CHCl_3$). MS: Calc. for $C_{27}H_{28}O_5$ (M^+): m/z 432.1937. Found: m/z 432.1947.

(*ii*) To a solution of potassium *tert*-butoxide (240 mg, 2.14 mmol) in dry THF (15 mL) at 0°C under N_2 was added dropwise a solution of **9** (1.23 g, 2.04 mmol) in dry THF (15 mL). The mixture was stirred at room temperature for 1 h, filtered, and concentrated in vacuum. A solution of the residue in dry diethyl ether (50 mL) was filtered through a pad of Celite and concentrated in vacuum to give the spiro-epoxides **15** and **16** (0.765 g, 87%), with an $\alpha:\beta$ ratio of 1:6, identical with those described above.

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