Organocuprate-mediated Alkylation of Sugar Epoxides. New Stereospecific Route to 3-*C*-Alkyl-3-deoxy-α-D-glucose[1]

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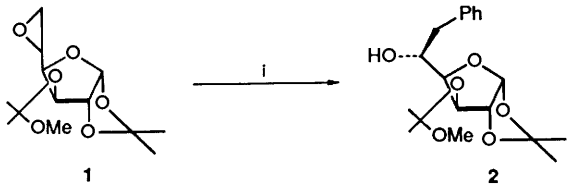
The reactivity of the 5,6-anhydroglucofuranose derivatives **1** and **3**, readily prepared from D-glucose, toward different cyanocuprates was examined. The former epoxide led to the corresponding C-6 chain-extended sugars, *e.g.*, **2**. Alkylation of 5,6-anhydro-3-deoxy-1,2-*O*-isopropylidene-α-D-*erythro*-hex-3-enofuranose **3** with mixed cyanocuprates RCu(CN)Li [R = Me, Bu] provided a convenient and stereospecific route to 3-*C*-alkyl (methyl, butyl)-3-deoxy-α-D-glucofuranose derivatives **12** and **14** *via* 1,4-addition followed by hydroboration–oxidation.

Regio- and stereo-selective alkylation of suitably protected carbohydrate substrates constitutes a convenient procedure for the preparation[2] of branched- as well as extended-chain sugars which occur as components of many biologically important natural products. This approach has been efficiently employed for the construction of highly functionalised chiral synthons which could be potential intermediates in the synthesis of diverse natural products[3] such as macrolide antibiotics. Stereoselective deoxyalkylation of D-glucose at different sites is of significance in this context.

In an attempt to develop rapid access to these sugar derivatives, we undertook a study on the reactivity of cyanocuprates toward the two epoxides[4] **1** and **3** (Schemes 1 and 2), readily available from D-glucose. The initial stage of our investigation was concerned with the 1,2-addition of higher-order cyanocuprates[5] to the terminal epoxide **1**.[4a]



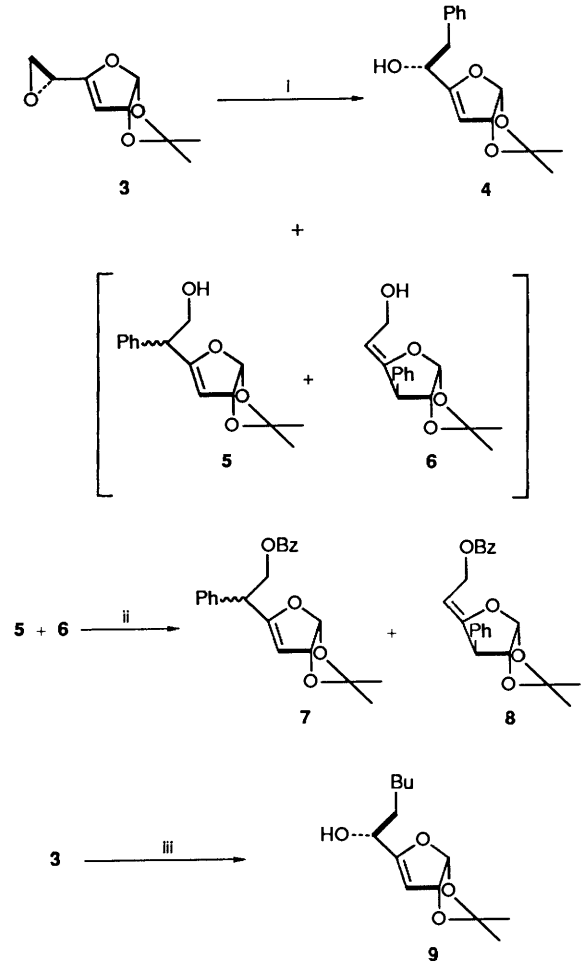
1 **2**

Scheme 1 *Reagents and conditions:* i, $Ph_2Cu(CN)Li_2$, Et_2O, −78 to −20 °C

Chain-extension at C-6 and C-5 of pyranosides and furanosides, respectively, through the use of organocuprate chemistry, had previously involved both conjugate addition to allylic mesyl esters[6] in the former case and S_N2 displacement of primary tosyl esters[7] in the latter. Accordingly, we devised a model experiment in which the epoxide **1** was treated with the less reactive $Ph_2Cu(CN)Li_2$, as compared with its alkyl analogues, at −78 to −20 °C in diethyl ether. The chain-extended sugar **2** (Scheme 1) was thus obtained in a fairly good yield (84%), thereby demonstrating the efficacy of this approach to C-6 chain-extended α-D-*gluco*-hexoses.[8]

The vinylic oxirane **3** was next examined in the hope of performing a stereospecific alkylation at the C-3 position. Whereas 3-*C*-alkyl-3-deoxy-D-allose derivatives could be conveniently obtained[9] by way of Wittig olefination of 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexo-3-ulose followed by catalytic hydrogenation, so far no stereospecific[10] method is available for the preparation of 3-*C*-alkyl-3-deoxy-D-glucose derivatives. Previous syntheses[11] of 3-deoxy-3-*C*-methyl-D-glucose derivatives involved a base-promoted equilibration at C-3 of a 2-keto intermediate.

The epoxide **3** was first treated with the higher order cyanocuprates $Ph_2Cu(CN)Li_2$ and $Bu_2Cu(CN)Li_2$. The reaction with $Ph_2Cu(CN)Li_2$ was devoid of any regioselectivity, and provided products corresponding to the three possible modes of epoxide opening. Compound **4** was the minor product (8% yield) whereas compounds **5** and **6** (74% combined yield) were obtained as an inseparable mixture in a 3:1 ratio as evidenced by ^1H NMR spectroscopy; these two compounds could, however, be separated as their benzoate derivatives **7** and **8** (Scheme 2).



3 **4** **5** **6** **7** **8** **9**

Scheme 2 *Reagents and conditions:* i, $Ph_2Cu(CN)Li_2$, Et_2O, −78 to −20 °C; ii, BzCl, Et_3N, DMAP, CH_2Cl_2, room temp.; iii, $Bu_2Cu(CN)Li_2$, Et_2O, −78 to −20 °C

The structure of the benzoate **7** was supported by its ^1H NMR spectrum, which displayed the following characteristic

features; a doublet ($J_{3,2}$ 2 Hz) at δ 5.15 for the proton 3-H, a triplet ($J_{5,6} = J_{5,6'}$ = 7 Hz) at δ 4.02 for the proton 5-H, and a pair of doublets of doublets at δ 4.78 and 4.63, respectively, for the 6-H protons. The stereochemistry at the C-5 position could not, however, be secured from these spectroscopic data. Nevertheless, inversion at this centre might be expected to have occurred, considering the likelihood of an S_N2 mechanism whether through initial formation of a π-complex or by direct attack of the organocuprate at the C-5 centre. Such a mechanism has been considered for the alkylation at the allylic position of vinylic oxiranes.[12]

Structure assignment for compound **8** resulted from analysis of its spectral data; of diagnostic significance were the chemical shift (δ 4.8) for the olefinic proton 5-H, which matched well that of the corresponding proton of compound **19**[4] (δ 4.6), as well as the absence of coupling[13] between 3-H and 2-H. These data are consistent with alkylation occurring from the face opposite to the isopropylidene group and the *Z*-configuration for the C-4–C-5 double bond, in full accordance with the well documented *anti*-S_N2' mechanism.[14]

In contrast to these results, alkylation occurred exclusively at C-6 when $Bu_2Cu(CN)Li_2$ was used, thereby leading to compound **9**. This outcome was unexpected in view of the well known ability of this type of organocuprate to undergo 1,4-addition with allylic epoxides.[5,15] The discrepancies observed between our results and those reported in the literature might be a result of the structure of our substrate, in which the olefinic part of the vinylic oxirane is also an enol ether.

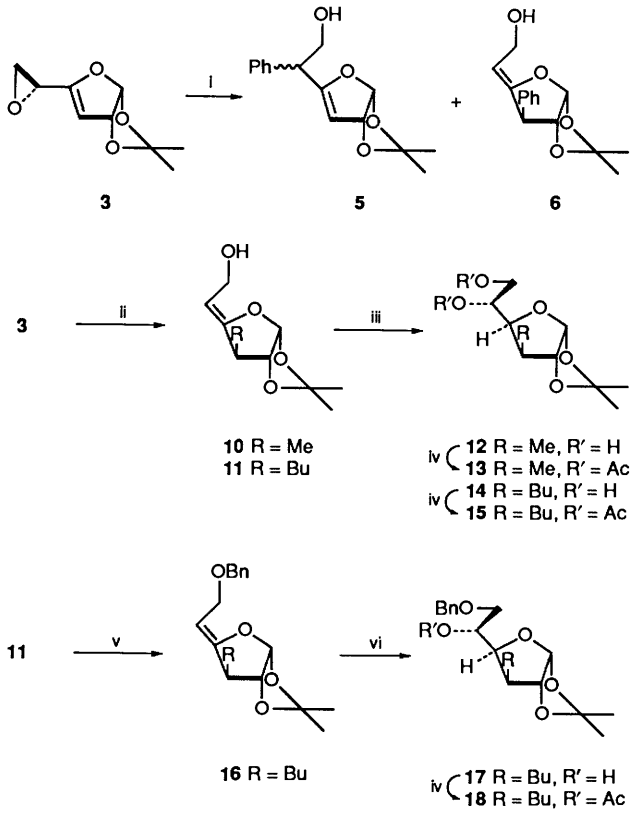
In order to overcome these difficulties and to achieve stereospecific alkylation at C-3, we resorted to the use of mixed cyanocuprates[16] recently developed by Marino. To this end, the vinylic oxirane **3** was first treated with PhCu(CN)Li to afford the previously obtained mixture of compounds **5** and **6** (Scheme 3). In striking difference to the case of $Ph_2Cu(CN)Li_2$, no alkylation at C-6 could be detected in the present case. This result might reflect the greater nucleophilicity of higher order cyanocuprates as compared with their mixed cyanocuprate counterparts.[5]

Treatment of the epoxide **3** with the cyanoalkylcuprates RCu(CN)Li [R = Me, Bu] proved more effective, achieving exclusive alkylation at the C-3 position.[17] Thus, reaction of compound **3** with MeCu(CN)Li in diethyl ether at −78 to 0 °C gave the allylic alcohol **10** in 62% yield, whereas BuCu(CN)Li furnished compound **11** in 76% yield (Scheme 3).

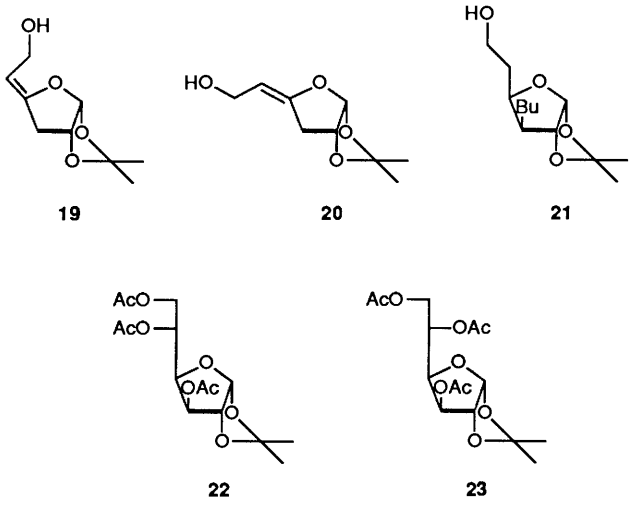
That the alkylation had indeed occurred as depicted in Scheme 3 was confirmed from an analysis of the ^1H NMR data of the two compounds. Noticeable in this regard were the 3-H resonances at δ 2.83 for **10** and at δ 2.67 for **11**, with no coupling with 2-H, thereby establishing the β-configuration for the incoming alkyl groups. Furthermore, correlation of the chemical shifts of proton 5-H (δ 4.56 for **10** and δ 4.6 for **11**) with the data obtained for the known alcohols[4] **19** and **20** established the *Z*-configuration for the C-4–C-5 double bond in products **10** and **11**.

Access to the 3-*C*-alkyl-3-deoxy-α-D-glucohexose rested upon the hydration of the C-4–C-5 double bond. Accordingly, the hydroboration–oxidation of compounds **10** and **11** was attempted. Treatment of compound **10** with BH_3Me_2S[18] in tetrahydrofuran (THF) at room temperature for 18 h, followed by alkaline oxidation ($NaOH–H_2O_2$), furnished the diol **12** in rather poor yield (27%). Stereochemical assignment at C-4 was based on the measurement of the $J_{3,4}$ coupling constant, the value of which ($J_{3,4}$ 4 Hz) implies a *cis*-relationship[11b,13] between protons 3-H and 4-H. The complete α-face selectivity obtained in the hydroboration step should be the result of steric hindrance exerted by the alkyl group at C-3.

Careful examination of the reaction products in the hydroboration–oxidation of the alcohol **11** revealed the presence



Scheme 3 *Reagents and conditions:* i, PhCu(CN)Li, Et_2O, −78 to −20 °C; ii, MeCu(CN)Li, Et_2O, −78 to 0 °C for R = Me; BuCu(CN)Li, Et_2O, −78 to −40 °C for R = Bu; iii, BH_3·Me_2S, THF, room temp. on **10**; thexylborane, THF, 0 °C, 1 h; then BH_3·Me_2S, 0 °C, 3 h on **11**; iv, Ac_2O, pyridine, room temp.; v, NaH, BnCl, DMF, room temp.; vi, BH_3·Me_2S, THF, −30 °C to room temp.



of the alcohol **21** [(HR, EIMS) *m/z* 229.1436 ($M^{\cdot+}$ − Me). $C_{12}H_{21}O_4$ requires *m/z* 229.1440] as a by-product. This compound should arise from β-elimination followed by rehydroboration–oxidation, a process which has been occasionally encountered in the hydroboration of heteroatom-substituted allylic systems.[19] To minimise the extent of this side-reaction, several modifications of the original hydroboration procedure were attempted. First, we considered protecting the hydroxy group of the allylic alcohol **11** as the benzyl ether **16**. Low-temperature hydroboration–oxidation of the latter furnished the alcohol **17** in an improved (63%) yield (Scheme 3).

Next, the C-6-unprotected derivative **14** was obtained through the use of the procedure developed by Brown and Gallivan[19a] for the hydroboration of allylic alcohols. Thus, treatment of the allylic alcohol **11** with thexylborane[20] at 0 °C in THF led to a borinate intermediate, the bulkiness of which was expected to prevent elimination. Indeed, when this intermediate was treated *in situ* with excess of BH_3·Me_2S in THF from 0 °C to room temperature, the diol **14** was obtained in a fairly decent 54% yield (Scheme 3).

The configuration of the newly created asymmetric centre C-5 in compounds **13**, **15** and **18** was unambiguously assigned by comparison of their $J_{4,5}$ coupling constants with those of the two representative compounds **22** and **23**, which were prepared from 1,2-*O*-isopropylidene-α-D-glucofuranose according to literature procedure.[21] The values observed for compounds **13** ($J_{4,5}$ = 9.8 Hz), **15** ($J_{4,5}$ 9.77 Hz) and **18** ($J_{4,5}$ 9.6 Hz) matched well that obtained for compound **22** ($J_{4,5}$ 9.4 Hz), whereas the corresponding coupling constant for compound **23** ($J_{4,5}$ 7.4 Hz) was much lower. From these data it follows that the C-5 stereocentre must possess the (*R*) absolute configuration as in D-glucose. Exclusive access to this configuration at C-5 should be the result of both the stereochemical outcome of the hydroboration process and the *Z*-configuration of our substrates.

In conclusion, we have developed a regio- and stereo-specific method for an expedient (five steps) synthesis of 3-*C*-alkyl-3-deoxy-α-D-gluco-hexose derivatives from the commercially available 1,2-*O*-isopropylidene-α-D-glucofuranose.

Experimental

M.p.s were determined on a Kofler hot-stage apparatus and are uncorrected. Optical rotations were measured on a Jouan and Roussel Quick polarimeter. ^{1}H NMR spectra were obtained with a Bruker W80 spectrometer (80 MHz) (unless otherwise stated) for solutions in deuteriochloroform containing tetramethylsilane as internal standard. Chemical shifts (^{1}H) are quoted in δ-values relative to the reference (doubly primed numbers in the NMR attribution of compounds **7** and **8** refer to the benzoate group). *J*-Values are given in Hz. Electron-impact mass spectra (EIMS), including high-resolution (HR) spectra, were recorded on a KRATOS/AEI MS50, and a modified AEI MS9 instrument was used for recording chemical ionisation mass spectra (CIMS) for which the indicated reactant gases were employed. TLC was conducted on 'F 1500 LS 2S4' (Schleicher & Schüll) precoated silica gel plates. Preparative TLC (PLC) was run on (20 × 20 cm) 1 mm thick layers. Silica gel columns for chromatography utilised E. Merck 'silicagel 60', 70–230 mesh ASTM. Solvents were distilled shortly before use from an appropriate drying agent. All reactions were run under an inert atmosphere (nitrogen) in oven-dried glassware which was cooled before use under a stream of dry nitrogen.

6-*Deoxy*-1,2-O-*isopropylidene*-3-O-(1-*methoxy*-1-*methylethyl*)-6-C-*phenyl*-α-D-*glucofuranose* **2**.—A suspension of CuCN (116 mg, 1.3 mmol) in dry diethyl ether (2 cm^3) was maintained under nitrogen at −78 °C. Phenyllithium [1.58 cm^3 of a 1.7 mol dm^{-3} solution in cyclohexane–Et_2O (70:30); 2.7 mmol] was added dropwise and the reaction mixture was warmed slowly to −30 °C when a slightly turbid solution was obtained. To this stirred solution, cooled to −78 °C, was added dropwise, a solution of the epoxide **1** (272 mg, 0.99 mmol). The reaction mixture was warmed to −20 °C (during 2 h) and stirred at this temperature for 4 h. After being quenched at −30 °C by addition of aq. 10% NaOH saturated with NH_4Cl (5 cm^3), the mixture was stirred at room temperature for 0.5 h and diluted with diethyl ether (30 cm^3). The organic phase was decanted and washed with aq. 10% NaOH saturated with NH_4Cl until disappearance of the blue colour of the aq. phase. Usual work-up furnished an oily residue (370 mg), which was purified by column chromatography to afford the title compound (298 mg, 84%) as an oil; $[\alpha]_D^{20}$ −7° (*c* 2.1, CH_2Cl_2); R_f 0.37 [hexane–ethyl acetate (3:1)]; δ 7.22 (5 H, m, Ph), 5.90 (1 H, d, $J_{1,2}$ 4, 1-H), 4.47 (1 H, d, $J_{2,1}$ 4, 2-H), 4.35 (1 H, d, $J_{3,4}$ 3, 3-H), 4.07–3.85 (2 H, m, 4- and 5-H), 3.4 (1 H, d, $J_{OH,5}$ 4, OH), 3.2 (3 H, s, OMe), 2.95 (1 H, dd, $J_{6,6'}$ 14, $J_{6,5}$ 4, 6-H), 2.75 (1 H, dd, $J_{6',6}$ 14, $J_{6',5}$ 7, 6-H'), and 1.47, 1.37 and 1.3 (12 H, together 3 s, 4 × Me); (HR, EIMS) *m/z* 337.1659 (5, $M^{\bullet+}$ − Me. $C_{18}H_{25}O_6$ requires *m/z* 337.1651), 321 (7, $M^{\bullet+}$ − OMe), 320 (2, $M^{\bullet+}$ − MeOH), 305 (10, 337 − MeOH), 279 (5, $M^{\bullet+}$ − C_4H_9O), 262 (70, $M^{\bullet+}$ − $C_4H_{10}O_2$), 247 (30, 262 − Me), 229 (80, 247 − H_2O), 129 (75, $C_6H_9O_3^+$), 121 (52, $PhCH_2CHOH^+$), 77 (60, $C_6H_5^+$) and 73 (100, $C_3H_6OMe^+$); (CIMS, NH_3) *m/z* 370 (22, MNH_4^+), 338 (100, MNH_4^+ − MeOH) and 298 (50, MNH_4^+ − C_4H_8O).

3,6-*Dideoxy*-1,2-O-*isopropylidene*-6-C-*phenyl*-α-D-erythro-*hex*-3-*enofuranose* **4**.—CuCN (79 mg, 0.88 mmol) was suspended in Et_2O (1.5 cm^3) under nitrogen. The stirred suspension was cooled to −78 °C and phenyllithium [1.1 cm^3 of a 1.7 mol dm^{-3} solution in hexane–Et_2O (7:3); 1.87 mmol] was added dropwise. The mixture was warmed to −40 °C and was maintained at this temperature for 10 min. The solution thus obtained was cooled to −78 °C and a solution of the epoxide **3** (125 mg, 0.68 mmol) in diethyl ether (2 cm^3) was added dropwise. The reaction mixture was warmed to −30 °C and stirred at this temperature for 1 h, then treated with aq. 10% NaOH saturated with NH_4Cl (5 cm^3) and stirred at room temperature for 45 min. Extraction with diethyl ether (2 × 20 cm^3) followed by usual work-up furnished an oily residue (205 mg), which was purified by column chromatography [hexane–ethyl acetate (3:2)] to afford compound **4** (15 mg, 8%) as an oil, along with an inseparable mixture of compounds **5** and **6** (132 mg, 74%). *Compound* **4**; $[\alpha]_D^{20}$ −11° (*c* 1.3, CH_2Cl_2); R_f 0.52 [hexane–ethyl acetate (3:2)]; δ 7.25 (5 H, s, Ph), 6.06 (1 H, d, $J_{1,2}$ 4, 1-H), 5.25 (1 H, dd, $J_{2,1}$ 4, $J_{2,3}$ 3, 2-H), 5.12 (1 H, d, $J_{3,2}$ 3, 3-H), 4.5–4.25 (1 H, m, $J_{5,6}$ 4, $J_{5,6'}$ 8, $J_{5,OH}$ 5, 5-H), 3.25–3.0 (1 H, dd, $J_{6,5}$ 4, $J_{6,6'}$ 14, 6-H), 2.95–2.65 (1 H, dd, $J_{6',5}$ 8, $J_{6',6}$ 14, 6-H'), 2.0 (1 H, d, $J_{OH,5}$ 5, OH) and 1.5 and 1.47 (6 H, together 2 s, 2 × Me); (HR, EIMS) *m/z* 262.1210 (10, $M^{\bullet+}$. $C_{15}H_{18}O_4$ requires M, 262.1205), 247 (15, $M^{\bullet+}$ − Me), 233 (100, $M^{\bullet+}$ − CHO), 215 (10, 233 − H_2O), 205 (20, 247 − CH_2CO), 187 (95, 247 − CH_3CO_2H), 175 (70, 233 − Me_2CO) and 91 (100, $C_7H_7^+$).

6-O-*Benzoyl*-3,5-*dideoxy*-1,2-O-*isopropylidene*-3-C-*phenyl*-β-L-*threo*-*hex*-4-*enofuranose* **8**.—The mixture of compounds **5** and **6** (132 mg, 0.5 mmol) was dissolved in dry dichloromethane (5 cm^3). To this solution were added successively at room temperature triethylamine (0.085 cm^3, 0.6 mmol), benzoyl chloride (80 mg, 0.55 mmol) and 4-dimethylaminopyridine (DMAP) (3 mg). The reaction mixture was stirred at room temperature for 4 h and then diluted with dichloromethane (20 cm^3). Usual work-up furnished an oily residue, which upon column chromatography [hexane–ethyl acetate (9:1)] afforded the *benzoates* **7** (solid, 101 mg, 54%) and **8** (oil, 46 mg, 25%).

Benzoate **7**. M.p. 88 °C (Found: C, 72.1; H, 6.2. $C_{22}H_{22}O_5$ requires C, 72.11; H, 6.05%); $[\alpha]_D^{20}$ − 8° (*c* 0.9, CH_2Cl_2); R_f 0.26 [hexane–ethyl acetate (9:1)]; δ(400 MHz) 8.00 (2 H, d, $J_{2'',3''} = J_{6'',5''}$ = 8, 2″- and 6″-H), 7.56 (1 H, t, $J_{4'',3''} = J_{4'',5''}$ = 8, 4″-H), 7.43 (2 H, t, $J_{3'',2''} = J_{3'',4''} = J_{5'',4''} = J_{5'',6''}$ = 8, 3″- and 5″-H), 7.38–7.28 (5 H, m, Ph), 6.08 (1 H, d, $J_{1,2}$ 4, 1-H), 5.28 (1 H, dd, $J_{2,1}$ 4, $J_{2,3}$ 2, 2-H), 5.15 (1 H, d, $J_{3,2}$ 2, 3-H), 4.78 (1 H, dd, $J_{6,6'}$ 12, $J_{6,5}$ 7, 6-H), 4.63 (1 H, dd, $J_{6',6}$ 12, $J_{6',5}$ 7, 6-H'), 4.02 (1 H, t, $J_{5,6} = J_{5,6'}$ = 7, 5-H) and 1.4 and 1.37 (6 H, together 2 s, 2 × Me); (HR, EIMS) *m/z* 366.1462 (2, $M^{\bullet+}$.

$C_{22}H_{22}O_5$ requires M, 366.1467), 337 (4, $M^{\bullet+}$ − CHO), 308 (5, $M^{\bullet+}$ − Me_2CO),244(82,$M^{\bullet+}$ − $PhCO_2H$),229(68,244 − Me), 215 (100, 244 − CHO), 186 (80, 244 − Me_2CO), 105 (100, $PhCO^+$) and 77 (90, $C_6H_5^+$).

Benzoate **8**. $[\alpha]_D^{20}$ −86° (*c* 0.8, CH_2Cl_2); R_f 0.31 [hexane–ethyl acetate (9:1)]; δ(400 MHz) 8.03 (2 H, d, $J_{2'',3''} = J_{6'',5''} = 8$, 2″- and 6″-H), 7.54 (1 H, t, $J_{4'',3''} = J_{4'',5''} = 8$, 4″-H), 7.42 (2 H, t, $J_{3'',4''} = J_{3'',2''} = J_{5'',4''} = J_{5'',6''} = 8$, 3″- and 5″-H), 7.37–7.2 (5 H, m, Ph), 6.12 (1 H, d, $J_{1,2}$ 4, 1-H), 5.03 (1 H, dd, $J_{6,6'}$ 12, $J_{6,5}$ 7, 6-H), 4.98 (1 H, dd, $J_{6',6}$ 12, $J_{6',5}$ 7, 6-H′), 4.80 (1 H, t, $J_{5,6} = J_{5,6'}$ = 7, 5-H), 4.61 (1 H, d, $J_{2,1}$ 4, 2-H), 4.13 (1 H, s, 3-H) and 1.55 and 1.41 (6 H, together 2 s, 2 × Me); (HR, EIMS) *m/z* 366.1462 (40, $M^{\bullet+}$. $C_{22}H_{22}O_5$ requires M, 366.1467), 351 (18, $M^{\bullet+}$ − Me), 337 (4, $M^{\bullet+}$ − CHO), 308 (18, $M^{\bullet+}$ − Me_2CO), 279 (80, 308 − CHO), 266 (82, $M^{\bullet+}$ − $C_5H_8O_2$), 261 (43, $M^{\bullet+}$ − PhCO), 245 (47, $M^{\bullet+}$ − $PhCO_2$), 244 (45, $M^{\bullet+}$ − $PhCO_2H$), 187 (81, 245 − Me_2CO), 186 (45, 244 − Me_2CO), 157 (75, 186 − CHO), 105 (100, $PhCO^+$) and 77 (90, $C_6H_5^+$).

3,6,7,8,9,10-*Hexadeoxy*-1,2-O-*isopropylidene*-α-D-erythro-*dec*-3-*enofuranose* **9**.—To a suspension of CuCN (70 mg, 0.78 mmol) in dry diethyl ether (3 cm^3) cooled to −78 °C was added dropwise, under nitrogen, butyllithium (1 cm^3 of a 1.5 mol dm^{-3} solution in hexane; 1.5 mmol). The mixture was allowed to warm to −40 °C and was stirred at this temperature for 45 min. A solution of the allylic epoxide **3** (110 mg, 0.6 mmol) in dry diethyl ether (2 cm^3) was then added dropwise at −78 °C and the resulting mixture was warmed to −20 °C during 1 h and was stirred at this temperature for 45 min. The reaction mixture was quenched at −30 °C with aq. 10% NaOH saturated with NH_4Cl (5 cm^3), and was stirred at room temperature for 0.5 h. Dilution with diethyl ether (25 cm^3) and usual work-up afforded an oily residue (135 mg), which was purified by column chromatography [hexane–ethyl acetate (3:1)] to afford *compound* **9** (112 mg, 77%) as an oil; $[\alpha]_D^{20}$ − 10° (*c* 0.6, CH_2Cl_2); R_f 0.4 [hexane–ethyl acetate (3:1)]; δ 6.02 (1 H, d, $J_{1,2}$ 5, 1-H), 5.25 (1 H, dd, $J_{2,1}$ 5, $J_{2,3}$ 3, 2-H), 5.10 (1 H, d, $J_{3,2}$ 3, 3-H), 4.63 (1 H, dd, $J_{6',6}$ 12, $J_{6',5}$ 7, 6-H′), 4.12 (1 H, m, $J_{6,6'}$ 12, $J_{6,5}$ 7, 6-H), 4.02 (1 H, m, $J_{5,OH}$ 6, 5-H), 2.05 (1 H, d, $J_{OH,5}$ 6, OH), 1.5 (6 H, s, 2 × Me) and 1.6–0.75 (11 H, m, 6-H_2 and Bu); (HR, EIMS) *m/z* 242.1524 (40, $M^{\bullet+}$. $C_{13}H_{22}O_4$ requires M, 242.1518), 227 (15, $M^{\bullet+}$ − Me), 213 (100, $M^{\bullet+}$ − CHO), 195 (22, 213 − H_2O), 167 (50, 227 − CH_3CO_2H) and 155 (70, 213 − Me_2CO); (CIMS, isobutane) *m/z* 243 (20, MH^+), 225 (8, MH^+ − H_2O), 185 (100, MH^+ − Me_2CO) and 167 (53, 185 − H_2O).

3,5-*Dideoxy*-1,2-O-*isopropylidene*-3-C-*methyl*-β-L-threo-*hex*-4-*enofuranose* **10**.—A suspension of CuCN (215 mg, 2.4 mmol) in dry diethyl ether (5 cm^3) was cooled to −78 °C under nitrogen. A solution of MeLi (1.7 cm^3 of a 1.42 mol dm^{-3} solution in diethyl ether; 2.41 mmol) was added dropwise and the mixture was stirred at this temperature for 1 h. To the yellow solution thus obtained was added dropwise a solution of the epoxide **3** (100 mg, 0.54 mmol) in dry diethyl ether (2 cm^3). The reaction mixture was slowly (during 4 h) warmed to 0 °C, stirred at this temperature for an additional 0.5 h, cooled to −20 °C, and then quenched by addition of aq. 10% NaOH saturated with NH_4Cl (5 cm^3). Usual work-up followed by column chromatography [hexane–ethyl acetate (3:1)] of the residue (91 mg) furnished *compound* **10** (67 mg, 62%) as an oil; $[\alpha]_D^{20}$ −100° (*c* 0.8, CH_2Cl_2); R_f 0.34 [hexane–ethyl acetate (3:1)]; δ 5.96 (1 H, d, $J_{1,2}$ 4, 1-H), 4.56 (1 H, t, $J_{5,6} = J_{5,6'} = 8$, 5-H), 4.30 (1 H, d, $J_{2,1}$ 4, 2-H), 4.16 (2 H, d, $J_{6,5} = J_{5,6'} = 8$, 6-H_2), 2.83 (1 H, q, $J_{3,Me}$ 8, 3-H), 1.7 (1 H, br s, OH), 1.41 and 1.32 (6 H, together 2 s, 2 × Me) and 1.09 (3 H, d, $J_{Me,3}$ 8, Me); (HR, EIMS) *m/z* 200.1045 (45, $M^{\bullet+}$. $C_{10}H_{16}O_4$ requires M, 200.1049), 185 (100, $M^{\bullet+}$ − Me), 171 (40, $M^{\bullet+}$ − CHO) and 125 (58, 185 − CH_3CO_2H).

3-C-*Butyl*-3,5-*dideoxy*-1,2-O-*isopropylidene*-β-L-threo-*hex*-4-*enofuranose* **11**.—To a suspension of CuCN (100 mg, 1.23 mmol) in dry diethyl ether (2 cm^3) cooled to −78 °C was added dropwise BuLi (0.8 cm^3 of a 1.5 mol dm^{-3} solution in hexane; 1.23 mmol). The mixture was allowed to warm to −40 °C and was stirred at this temperature for 0.5 h. To the slightly turbid solution thus obtained was added dropwise at −78 °C a solution of the epoxide **3** (110 mg, 0.6 mmol) in dry diethyl ether (2 cm^3). The reaction mixture was slowly (during 3 h) warmed to −40 °C and was stirred at this temperature for 1 h. Work-up as previously described furnished an oily residue, which upon purification by column chromatography [hexane–ethyl acetate (3:1)] afforded *compound* **11** (110 mg, 76%) as an oil; $[\alpha]_D^{20}$ −67° (*c* 1.3, CH_2Cl_2); R_f 0.28 [hexane–ethyl acetate (3:1)]; δ 5.92 (1 H, d, $J_{1,2}$ 4, 1-H), 4.6 (1 H, br t, $J_{5,6}$ 8, 5-H), 4.4 (1 H, d, $J_{2,1}$ 4, 2-H), 4.2 (2 H, d, $J_{6,5}$ 8, 6-H_2), 2.85–2.67 (1 H, m, 3-H), 1.77 (1 H, s, OH) and 1.57–0.82 (15 H, m, 2 × Me and Bu); (HR, EIMS) *m/z* 242.1516 (55, $M^{\bullet+}$. $C_{13}H_{22}O_4$ requires M, 242.1518), 227 (82, $M^{\bullet+}$ − Me) and 213 (25, $M^{\bullet+}$ − CHO); (CIMS, isobutane) *m/z* 243 (35, MH^+), 225 (100, MH^+ − H_2O), 185 (32, MH^+ − Me_2CO) and 167 (40, 185 − H_2O).

3-*Deoxy*-1,2-O-*isopropylidene*-3-C-*methyl*-α-D-*glucofuranose* **12**.—To a stirred solution of the alcohol **10** (140 mg, 0.7 mmol) in dry THF (10 cm^3) was added dropwise at 0 °C a solution of the complex BH_3·Me_2S (1.5 cm^3 of a 2 mol dm^{-3} solution in THF, 3 mmol). The reaction mixture was stirred at room temperature for 18 h, then cooled to 0 °C, and the excess of hydride was destroyed by addition of water (0.5 cm^3). Oxidation was carried out by successive addition of aq. 3 mol dm^{-3} NaOH (0.8 cm^3) and 30% H_2O_2 (1 cm^3) to the stirred mixture at room temperature for 5 h. The mixture was then saturated with solid anhydrous K_2CO_3; the organic phase was decanted and the residue was extracted with THF (4 × 10 cm^3). The organic phases were collected and dried over sodium sulphate. Evaporation to dryness furnished a residue (200 mg), which was purified by column chromatography [hexane–ethyl acetate 3:2)] to afford the title compound (41 mg, 27%) as an oil; $[\alpha]_D^{20}$ −16° (*c* 2.5, CH_2Cl_2) (lit.,[11b] $[\alpha]_D^{20}$ −17°); R_f 0.23 [diethyl ether–ethyl acetate (85:15)]; δ 5.72 (1 H, d, $J_{1,2}$ 4, 1-H), 4.32 (1 H, d, $J_{2,1}$ 4, 2-H), 4.07 (1 H, dd, $J_{4,3}$ 4, $J_{4,5}$ 8, 4-H), 3.82–3.52 (3 H, m, 5-H and 6-H_2), 2.92 (2 H, br s, 2 × OH), 2.43 (1 H, dq, $J_{3,Me}$ 8, $J_{3,4}$ 4, 3-H), 1.52 and 1.32 (6 H, together 2 s, 2 × Me) and 0.95 (3 H, d, $J_{Me,3}$ 8, Me); (HR, EIMS) *m/z* 203.0925 (100, $M^{\bullet+}$ − Me. $C_9H_{15}O_5$ requires *m/z* 203.0919), 157 (95, oxonium) and 99 (80, 157 − Me_2CO); (CIMS, isobutane) *m/z* 219 (100, MH^+) and 161 (60, MH^+ − Me_2CO).

5,6-*Di*-O-*acetyl*-3-*deoxy*-1,2-O-*isopropylidene*-3-C-*methyl*-α-D-*glucofuranose* **13**.—The diol **12** (32 mg, 0.14 mmol) was dissolved in dry dichloromethane (5 cm^3) under nitrogen. To this solution were added successively triethylamine (0.14 cm^3, 1 mmol), DMAP (3 mg) and acetic anhydride (0.1 cm^3, 1 mmol). The reaction mixture was stirred at room temperature for 4 h then poured into ice-cold, saturated aq. $NaHCO_3$. Extraction with diethyl ether followed by the usual work-up furnished a residue, which was purified by PLC [hexane–ethyl acetate (3:1)] to give compound **13** (35 mg, 83%) as an oil; $[\alpha]_D^{20}$ +19° (*c* 2.2, CH_2Cl_2); R_f 0.30 [hexane–ethyl acetate (3:1)]; δ(200 MHz) 5.80 (1 H, d, $J_{1,2}$ 4, 1-H), 5.06 (1 H, ddd, $J_{5,6}$ 2.6, $J_{5,6'}$ 5.7, $J_{5,4}$ 9.8, 5-H), 4.6 (1 H, dd, $J_{6,5}$ 2.6, $J_{6,6'}$ 13, 6-H), 4.36 (1 H, d, $J_{2,1}$ 4, 2-H), 4.34 (1 H, dd, $J_{4,3}$ 4, $J_{4,5}$ 9.8, 4-H), 4.11 (1 H, dd, $J_{6',5}$ 6, $J_{6',6}$ 13, 6-H′), 2.35 (1 H, qd, $J_{3,4}$ 4, $J_{3,Me}$ 7.3 3-H), 2.07 (6 H, s, 2 × OAc), 1.52 and 1.31 (6 H, together 2 s, 2 × Me), 0.84 (3 H, d, $J_{Me,3}$ 7.3, Me); (HR, EIMS) *m/z* 287.1125 (100, $M^{\bullet+}$ − Me. $C_{13}H_{19}O_7$ requires *m/z* 287.1131) and 157 (82, oxonium); (CIMS, isobutane) *m/z* 303 (100, MH^+), 245 (21, MH^+ − Me_2CO) and 243 (45, MH^+ − CH_3CO_2H).

3-C-*Butyl*-3-*deoxy*-1,2-O-*isopropylidene*-α-D-*glucofuranose* **14**.—A solution of compound **11** (45 mg, 0.18 mmol) in dry THF (3 cm^3) was added dropwise to a cold (0 °C), stirred solution of thexylborane (0.25 cm^3 of a 1 mol dm^{-3} solution in THF; 0.25 mmol) in THF (2 cm^3). After 1 h a solution of the complex BH_3·Me_2S (0.3 cm^3 of a 2 mol dm^{-3} solution in THF; 0.6 mmol) was added dropwise and the mixture was stirred for 3 h at 0 °C. Oxidation of the mixture was carried out by successive addition of water (0.3 cm^3), aq. 4 mol dm^{-3} NaOH (0.6 cm^3) and 30% H_2O_2 (0.35 cm^3) and stirring of the mixture at room temperature for 4 h. Excess of anhydrous K_2CO_3 was then added and the organic phase was decanted; the residue was further extracted with THF (3 × 10 cm^3). The organic phases were collected and the solvent was evaporated off under reduced pressure to give a residue (60 mg). Purification by column chromatography [hexane–ethyl acetate (3:2)] afforded the diol **14** (26 mg, 54%) as an oil. When the hydroboration of compound **11** was conducted according to the procedure used for compound **10** the diol **14** was obtained in 26% yield; $[\alpha]_D^{20}$ −24° (*c* 1.6, CH_2Cl_2); R_f 0.49 [diethyl ether–ethyl acetate (3:2)]; δ 5.7 (1 H, d, $J_{1,2}$ 4, 1-H), 4.48 (1 H, d, $J_{2,1}$ 4, 2-H), 4.0 (1 H, dd, $J_{4,3}$ 4, $J_{4,5}$ 8.5, 4-H), 3.37 (3 H, m, 5-H and 6-H_2), 2.9 (2 H, m, 2 × OH), 2.36–2.0 (1 H, m, 3-H), 1.45 and 1.25 (6 H, together 2 s, 2 × Me) and 1.25–0.85 (9 H, m, Bu); (HR, EIMS) *m/z* 245.1395 (100, $M^{\bullet+}$ − Me. $C_{12}H_{21}O_5$ requires *m/z* 245.1398), 185 (65, oxonium) and 141 (47, 199 − Me_2CO); (CIMS, isobutane) *m/z* 261 (100, MH^+), 203 (70, MH^+ − Me_2CO) and 185 (75, 203 − H_2O).

5,6-*Di*-O-*acetyl*-3-C-*butyl*-3-*deoxy*-1,2-O-*isopropylidene*-α-D-*glucofuranose* **15**.—Acetylation of compound **14** was carried out under standard conditions (acetic anhydride, pyridine; 25 °C). Purification by column chromatography [hexane–ethyl acetate (3:1)] furnished the diacetate **15** (81%) as an oil; $[\alpha]_D^{20}$ +1.4° (*c* 2.9, CH_2Cl_2); R_f 0.40 [hexane–ethyl acetate (3:1)]; δ(250 MHz) 5.81 (1 H, d, $J_{1,2}$ 4, 1-H), 5.11 (1 H, ddd, $J_{5,4}$ 9.77, $J_{5,6}$ 2.5, $J_{5,6'}$ 5.5, 5-H), 4.63 (1 H, dd, $J_{6,5}$ 2.5, $J_{6,6'}$ 12.5, 6-H), 4.56 (1 H, d, $J_{2,1}$ 4, 2-H), 4.38 (1 H, dd, $J_{4,3}$ 4.5, $J_{4,5}$ 9.77, 4-H), 4.12 (1 H, dd, $J_{6',5}$ 5.5, $J_{6,6}$ 12.5, 6-H'), 2.2 (1 H, m, $J_{3,4}$ 4.5, 3-H), 2.09 (6 H, s, 2 × OAc), 1.58 and 1.35 (6 H, together 2 s, 2 × Me) and 1.35–0.9 (9 H, m, Bu); (HR, EIMS) *m/z* 329.1610 (100, $M^{\bullet+}$ − Me. $C_{16}H_{25}O_7$ requires *m/z* 329.1600), 284 (6, $M^{\bullet+}$ − CH_3CO_2H), 269 (5, 329 − CH_3CO_2H) and 199 (15, oxonium).

6-O-*Benzyl*-3-C-*butyl*-3,5-*dideoxy*-1,2-O-*isopropylidene*-β-L-threo-*hex*-4-*enofuranose* **16**.—A suspension of NaH (50 mg, 2 mmol) in dry dimethylformamide (DMF) (1 cm^3) was cooled to 0 °C under nitrogen. A solution of the alcohol **11** (114 mg, 0.47 mmol) in DMF (1 cm^3) was added dropwise and the mixture was stirred for 20 min; benzyl bromide (0.2 cm^3, 1.67 mmol) was then added and the reaction mixture was stirred overnight at room temperature. The reaction mixture was poured into ice and extracted with diethyl ether (15 cm^3). Usual work-up furnished a residue, which was purified by column chromatography [hexane–ethyl acetate (9:1)] to afford *compound* **16** (129 mg, 82%) as an oil; $[\alpha]_D^{20}$ −64° (*c* 1.8, CH_2Cl_2); R_f 0.22 [hexane–ethyl acetate (9:1)]; δ 7.3 (5 H, m, Ph), 5.94 (1 H, d, $J_{1,2}$ 4, 1-H), 4.60–4.34 (4 H, m, $J_{2,1}$ 4, 2- and 5-H, CH_2Ph), 4.6 (2 H, d, $J_{6,5}$ 7, 6-H_2), 2.8 (1 H, m, 3-H) and 1.5–0.9 (15 H, m, 2 × Me, Bu); (HR, EIMS) *m/z* 332.1986 (42, $M^{\bullet+}$. $C_{20}H_{28}O_4$ requires M, 332.1987), 317 (58, $M^{\bullet+}$ − Me), 303 (28, $M^{\bullet+}$ − CHO), 274 (7, $M^{\bullet+}$ − Me_2CO), 211 (39, 317 − PhCHO), 209 (60, 317 − $PhCH_2OH$) and 91 (100, $C_7H_7^+$).

6-O-*Benzyl*-3-C-*butyl*-3-*deoxy*-1,2-O-*isopropylidene*-α-D-*glucofuranose* **17**.—A stirred solution of compound **16** (90 mg, 0.27 mmol) in dry THF (5 cm^3) was cooled to −30 °C. To this solution was added dropwise a solution of the complex BH_3·Me_2S (0.5 cm^3 of a 2 mol dm^{-3} solution in THF; 1 mmol) and the mixture was warmed up slowly to room temperature. After 3 h at room temperature the mixture was cooled to −10 °C and then treated successively with water (0.5 cm^3), aq. 4 mol dm^{-3} NaOH (0.6 cm^3) and 30% H_2O_2 (0.5 cm^3); the mixture was stirred for a further 2 h. Extraction with dichloromethane (2 × 20 cm^3) and usual work-up furnished a residue (125 mg), which was purified by column chromatography [hexane–ethyl acetate (4:1)] to afford the *title compound* (60 mg, 63%) as an oil. When the hydroboration–oxidation of compound **16** was carried out as described for compound **10**, the yield of compound **17** was 27%; $[\alpha]_D^{20}$ −21.6° (*c* 3.0, CH_2Cl_2); R_f 0.49 [hexane–ethyl acetate (3:1)]; δ 7.37 (5 H, m, Ph), 5.82 (1 H, d, $J_{1,2}$ 4, 1-H), 4.62 (2 H, s, CH_2Ph), 4.55 (1 H, d, $J_{2,1}$ 4, 2-H), 4.17 (1 H, dd, $J_{4,3}$ 4, $J_{4,5}$ 9, 4-H), 4.0–3.5 (3 H, m, 5- and 6-H_2), 2.5 (1 H, d, $J_{OH,5}$ 5, OH), 2.45–2.1 (1 H, m, 3-H), 1.5 and 1.32 (6 H, together 2 s, 2 × Me) and 1.32 and 0.87 (9 H, m, Bu); (HR, EIMS) *m/z* 350.2101 (60, $M^{\bullet+}$. $C_{20}H_{30}O_5$ requires M, 350.2093), 335 (60, $M^{\bullet+}$ − Me), 292 (56, $M^{\bullet+}$ − Me_2CO), 199 (91, oxonium), 141 (90, 199 − Me_2CO) and 91 (100, $C_7H_7^+$).

5-O-*Acetyl*-6-O-*benzyl*-3-C-*butyl*-3-*deoxy*-1,2-O-*isopropylidene*-α-D-*glucofuranose* **18**.—Acetylation of compound **17** was carried out under standard conditions with acetic anhydride and pyridine. Purification by column chromatography [hexane–ethyl acetate (4:1)] furnished *compound* **18** in 85% yield as an oil; $[\alpha]_D^{20}$ −29° (*c* 1.1, CH_2Cl_2); R_f 0.38 [hexane–ethyl acetate (4:1)]; δ(250 MHz) 7.30 (5 H, m, Ph), 5.77 (1 H, d, $J_{1,2}$ 4, 1-H), 5.08 (1 H, ddd, $J_{5,4}$ 9.6, $J_{5,6}$ 5, $J_{5,6'}$ 2.5, 5-H), 4.7 (2 H, d, J_{gem} 9, CH_2Ph), 4.51 (1 H, d, $J_{2,1}$ 4, 2-H), 4.47 (1 H, dd, $J_{4,3}$ 4, $J_{4,5}$ 9.6, 4-H), 3.81 (1 H, dd, $J_{6',6}$ 11, $J_{6',5}$ 2.5, 6-H'), 3.67 (1 H, dd, $J_{6,6'}$ 11, $J_{6,5}$ 5, 6-H), 2.1 (1 H, ddd, $J_{3,4}$ 4, $J_{3,Bu}$ 11, 3-H), 2.07 (3 H, s, OAc), 1.52 and 1.33 (6 H, together 2 s, 2 × Me) and 1.41, 1.18 (9 H, m, Bu); (HR, EIMS) *m/z* 392.2191 (40, $M^{\bullet+}$. $C_{22}H_{32}O_6$ requires M, 392.2199), 377 (33, $M^{\bullet+}$ − Me), 199 (30, oxonium), 141 (57, oxonium − Me_2CO) and 91 (100, $C_7H_7^+$).

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