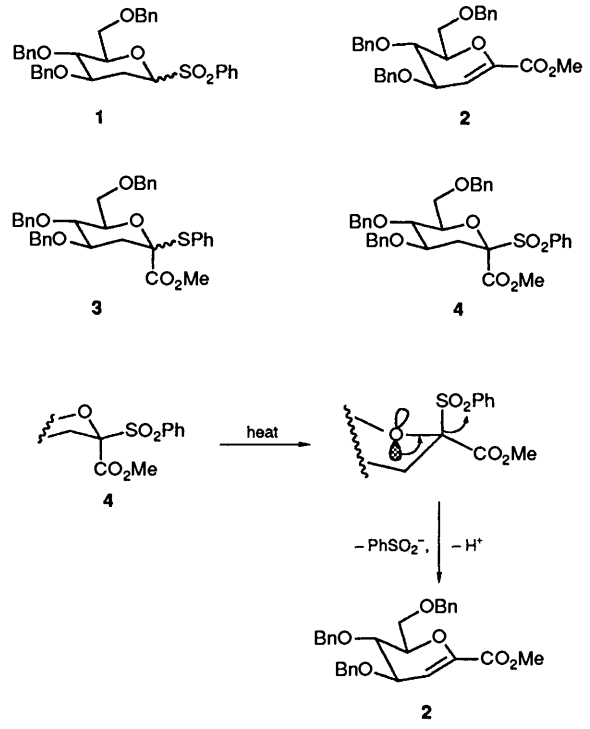
Diastereoselective Free-Radical Reactions. Part 3.† The Methyl Glucopyranos-1-yl and the 1,2-*O*-Isopropylideneglucopyranos-1-yl Radicals: Conformational Effects on Diastereoselectivity

David Crich*,‡,[a,b] and Linda B. L. Lim[a]
[a] *Department of Chemistry, University College London, 20 Gordon Street, London WC1H 0AJ, UK*
[b] *Department of Chemistry (M/C 111), University of Illinois at Chicago, Box 4348, Chicago, IL 60680, USA*

The 3,4,6-tri-*O*-benzyl-2-*O*-t-butyldimethylsilyl-1-*O*-methyl-D-glucopyranos-1-yl and the 3,4,6-tri-*O*-benzyl-1,2-*O*-isopropylidene-D-glucopyranos-1-yl radicals are quenched with high selectivity (>25:1) from the α- and β-face, respectively, by t-dodecanethiol. The reasons for this selectivity are discussed and the preparation of the radical precursors is presented. An improved preparation of 3,4,6-tri-*O*-benzyl-D-glucopyranose is described.

Previous papers in this series have concentrated on the formation of 2-deoxy-β-*O*-[1] and 2-deoxy-β-*C*-[2] glycopyranosides by a process involving diastereoselective hydrogen-atom transfer to the correspondingly functionalised glycopyranos-1-yl radicals which were themselves generated from the appropriate 3-deoxyulosonic acids by the Barton *O*-acyl thiohydroxamate[3] methodology. In this paper we describe, in full, studies directed towards the extension of this approach to the formation of glucopyranosides with particular reference to the reversal of selectivity observed in going from the simple 1-methoxy system to the constrained 1,2-*O*-isopropylidene system.[4] In designing an entry into 1-alkoxyglucopyranosyl radicals we were naturally attracted to the possibility of pursuing a parallel approach to the one adopted in the 2-deoxy series[1,2]; that is, formation of the radical by decarboxylation of the corresponding ulosonic acid. In this previous work the requisite radical precursors (ulosonic acids) had been formed from the 1-phenylsulphonyl-1,2-dideoxyglucose derivatives **1** by deprotonation at the anomeric centre followed by quenching with dimethyl carbonate. Further manipulations, leading ultimately to the 2-deoxy-*O*- and -*C*-glycosides, also involved the generation of carbanionic species at the anomeric centre. Clearly, in the context of the normal *gluco*- (and *manno*-) pyranosides, this strategy would have to be modified so as to allow introduction of the alcohol function at C-2 (glucose numbering) after the completion of any anionic chemistry at C-1, otherwise elimination would result. Ultimately we determined to investigate the hydroxylation of 1-methoxycarbonylglucals with osmium tetraoxide-based systems and thus the problem was reduced to one of the efficient preparation of compound **2** which had been previously isolated in this laboratory as a by-product from the use of the ester **3** as a glycosyl donor in coupling reactions.[1] Seemingly direct approaches involving C-1 metallation of glucals[5] followed by quenching with electrophiles were considered but rejected on grounds of the limited range of sufficiently reactive electrophiles and potential problems with protecting groups as previously observed[6] in this laboratory. In the event, and encouraged by the work of Ley on the deprotonation of 2-arylsulphonyltetrahydropyrans followed by quenching with a diverse range of electrophiles and subsequent spontaneous elimination of the arenesulphinic acid,[7] we opted to eliminate benzenesulphinic acid from the sulphone ester **4**, which itself was available in multigram quantities as a crystalline solid by lithium diisopropylamide deprotonation of **1** followed by quenching with dimethyl carbonate.[1] The sulphone **4** was assigned[1] the configuration illustrated by comparison with Ley's study[7] in which the use of similar electrophiles led to a stable 2-alkoxycarbonyl-2-sulphonyltetrahydropyran whose structure, with the equatorial sulphonyl group, was demonstrated crystallographically. Attempts at the base-promoted elimination of benzenesulphinic acid from compound **4** were mostly unsuccessful. Similarly, the use of Lewis acids, again as suggested by Ley for the promotion of glycosylation reactions involving glycosyl sulphones as glycosyl donors,[8] failed.We reasoned that our inability to bring about elimination of benzenesulphinic acid from compound **4** was due to the unfavourable equatorial disposition of the leaving group and consequently that the problem could be overcome by inversion of conformation of the pyranose ring to an alternative chair or boat conformation in which the sulphonyl moiety would be both axial and antiperiplanar to a ring oxygen lone pair as illustrated in Scheme 1. In the event, pyrolysis of compound **4**, on a gram scale, in a kugelrohr apparatus at



Scheme 1

† Part 2, preceding paper.
‡ Address correspondence to this author in Chicago.

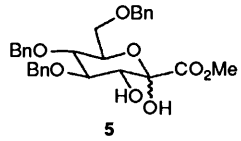
200 °C under reduced pressure brought about the desired elimination and resulted in the isolation of crystalline glycal **2** in 89% yield.

Attention was now turned to the osmium tetraoxide-mediated hydroxylation of compound **2**. Literature reports indicated that the stoicheiometric reaction of D-glucal and its triacetate with osmium tetraoxide results in the preferential formation of glucose rather than mannose derivatives.[9] Likewise, oxyamination of glucal with osmium tetraoxide and chloramine T provides a mixture of regioisomers, all of which have the *gluco*-configuration.[10] These observations are at variance with the empirical rule of Kishi in which hydroxylation of allylic alcohols and ethers takes place with preferential formation of the isomer in which the relative configuration of the pre-existing hydroxy or alkoxy group and the newly introduced adjacent hydroxy group is *erythro*.[11] We suggest that OsO_4 hydroxylation of glycals is dominated by the ring oxygen lone pairs and that attack takes place on the $^4H_5$ half-chair conformation, that conformation which triacetylglucal is known to adopt in the solid state and in solution,[12] and antiperiplanar to the pseudo-axial lone pair. Reaction of glycal **2** with a catalytic quantity of OsO_4 in a mixture of tetrahydrofuran (THF) and t-butyl alcohol at reflux with *N*-methylmorpholine *N*-oxide as overall oxidant, essentially according to the general procedure of Van Rheenan,[13] gave a 92% isolated yield of a single crystalline diol, compound **5**. At room temperature the reaction was prohibitively slow. The diol **5** was assigned the *gluco*-configuration on the basis of the above literature precedent and this was subsequently confirmed (*vide infra*) by correlation with literature compounds.

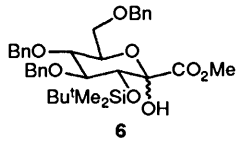
The secondary hydroxy group of compound **5** was protected in essentially quantitative yield as the silyl ether **6** by brief treatment with t-butyldimethylsilyl triflate (TBDMSOTf) in dichloromethane in the presence of *sym*-collidine (2,4,6-trimethylpyridine) at room temperature.[14] Use of the more standard t-butyldimethylsilyl chloride–imidazole combination in dimethylformamide required prolonged reaction times: attempts to force the reaction by heating resulted in a loss of regioselectivity. In view of recent reports on the activation of sialic acids as their derived glycosyl fluorides[15] we converted the alcohol **6** into the fluoride **7** in 94% yield, by treatment at 0 °C in dichloromethane, with (diethylamino)sulphur trifluoride (DAST)[16]: cleavage of the silyl ether group was not a problem under these conditions. Unfortunately, however, attempted coupling of the glycosyl donor **7** with methanol as a model alcohol with a range of standard activators ($SnCl_2$; $AgClO_4$; $BF_3{\cdot}OEt_2$; AgCl; TBDMSOTf; AgOTf; $MgBr_2$; SbF_5; $ZrCp_2Cl_2$) recommended for use with glycosyl fluorides was fruitless, with substrate **7** being recovered intact in all cases. Given the success of other workers[15] with sialic ester fluorides we are led to the conclusion that the 3-siloxy residue has a detrimental effect on reactivity in the present case. As a consequence of this lack of reactivity we turned to the correspondig chloride **8**, which was prepared in 97% yield by reaction of the alcohol **6** with thionyl chloride and pyridine. Like the fluoride **7** this chloride proved to be somewhat unreactive but eventually the methyl glycoside **9** was obtained in 80% yield as an unassigned, but separable, mixture of anomers in the ratio 1:3.4 by heating to reflux with methanol and magnesium bromide–diethyl ether under argon in 1,4-dioxane. Saponification of this anomeric mixture gave the acid **10**.

The key decarboxylation step was carried out by reaction of acid **10** as its triethylammonium salt with the commercial heterocyclic salt **11**,[3] giving the instantly recognisable bright yellow *O*-acyl thiohydroxamate **12**, which was not isolated but was immediately subjected to white-light photolysis in the presence of t-dodecanethiol. In this manner the methyl β-glucopyranoside **13** was formed in 65% isolated yield. Significantly, no evidence was found for the formation of the corresponding α-anomer and we estimate that the selectivity of this radical reaction was at least 25:1 in favour of the β-anomer. Inspection of the ^1H NMR spectrum of compound **13**, and in particular of the anomeric proton signal at δ 4.1, was complicated in deuteriochloroform solution owing to virtual coupling within the 1-H; 2-H; 3-H; 4-H spin-system; however, in perdeuteriotoluene the same signal appeared at δ 4.15 and was a simple doublet with $J_{1,2}$ 7.52 Hz. This coupling constant is entirely consistent with the assignment of compound **13** as the methyl β-glucopyranoside as the $^4C_1$ conformer indicated. Further verification was obtained when compound **13** was treated with tetrabutylammonium fluoride to give the crystalline alcohol **14** whose physical data matched well with those recorded in the literature for the identical substance prepared by an alternative route.[17] The establishment of the *gluco*-configuration for compound **13** confirmed that the osmium tetraoxide hydroxylation of the glycal **2** had taken place in accordance with literature precedent for simple glycals, giving the *gluco*-diol **5**.

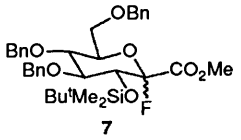
In a second reaction sequence the diol **5** was converted into its acetonide **15** by reaction with 2,2-dimethoxypropane in 76% isolated yield. Careful study of the ^1H NMR spectrum of compound **15** indicated that it exists in the $^OS_3$ twist-boat conformation (**A**), the $^4J_{3,5}$ coupling of approximately 1 Hz



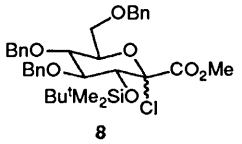
5



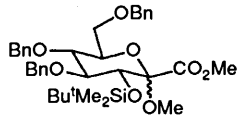
6



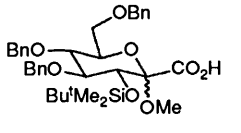
7



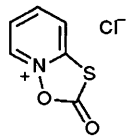
8



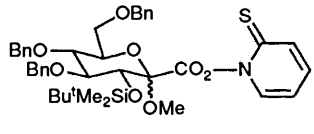
9



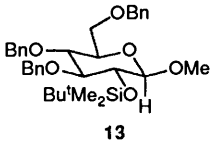
10



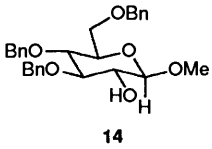
11



12

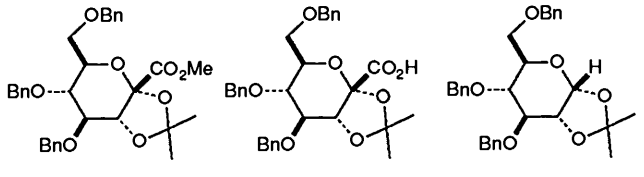


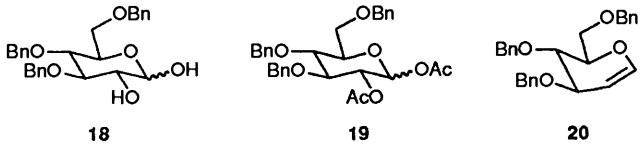
13

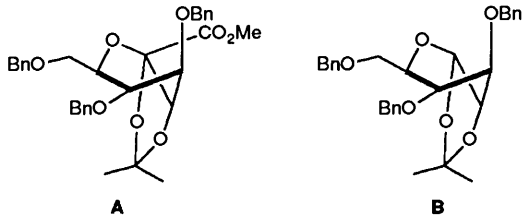


14

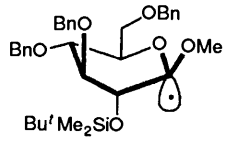
being particularly revealing. Saponification of **15** gave the acid **16**, which was in turn subjected to the reductive decarboxylation procedure by sequential reaction of its triethylammonium salt with the salt **11** followed by photolysis in the presence of the tertiary thiol. From this radical reaction the acetonide **17** was isolated in 75% yield. Once again no evidence was found for the formation of the alternative diastereoisomer. As with compound **15** the ^{1}H NMR spectrum indicated a twist-boat conformation (**B**, $^{O}S_2$) for compound **17**. Correlation of the physical data of compound **17**, especially the ^{1}H NMR spectrum, with literature values[18] was confusing: in our hands the coupling constant $J_{2,3}$ was found to have a value of 3.79 Hz, consistent with the twist boat **B**, whereas the literature value[18] for the same coupling constant is given as 9.8 Hz, consistent with the $^4C_1$ conformation. Further inspection led us to the conclusion that the literature spectrum is misassigned and that the 'quartet' observed at δ 4.49 with J 9.8 Hz is in fact half of an AB-quartet due to a pair of diastereotopic benzylic hydrogens such as we observe in our own spectrum at δ 4.51. The assignment of compound **17** as a twist-boat is fully consistent with the conformation assigned to related cyclic orthoester derivatives of 3,4,6-tri-*O*-acetyl-α-glucopyranose.[19] Nevertheless, in view of this discrepancy we were inclined to seek further proof of the structure of compound **17**. In the first instance the isopropylidene group was cleaved from compound **17** to give the alcohol **18**, whose physical data did correspond with those cited in the literature.[20] Unfortunately the anomeric proton signals of compound **18** were obscured by those of the benzylic protons. However, microscale acetylation gave the diacetate **19** in which the signals due to the 1-H and 2-H of both the α- and β-anomer were cleanly resolved and exhibited coupling constants in agreement with the $^4C_1$ glucopyranose structure. Reaction of the glucal **20** with a catalytic quantity of osmium tetraoxide and *N*-methylmorpholine *N*-oxide cleanly gave the diol **18** in essentially quantitative yield. The diol obtained in this manner, and its diacetate **19**, were identical with those obtained above. We note in passing that this latter one-step preparation of diol **18** from tribenzylglucal is far superior to the multistep procedure reported in the literature.[20] Finally, reaction of diol **18** with acetone and a catalytic quantity of camphor-10-sulphonic acid in benzene at reflux, with azeotropic removal of water, for three days gave compound **17** in 45% yield, identical in all respects with the sample isolated above. There can be little doubt as to the *cis*-fused nature of compound **17** formed under these equilibrating conditions.

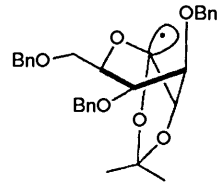






The very high diastereoselectivities observed in the two reductive decarboxylation reactions outlined above deserve comment. In Part 1 of this series we observed diastereoselectivities in the approximate range 8–20:1 in favour of quenching from the axial direction for the 1-alkoxy-2-deoxyglucopyranos-1-yl radicals under essentially the same conditions. As noted above the inclusion of an equatorial silyl ether function at the 2-position results in an improved selectivity to at least 25:1. This increased selectivity in the simple glucosyl series as compared with the 2-deoxyglucosyl series was also observed by Kahne in a closely related system.[21] We see no reason to assume the radical **C** intermediate between species **12** and **13** is anything other than a σ-radical with a preference for the axial site as observed in other 2-alkoxytetrahydropyran-2-yl radicals.[22] It is possible that radical **C** adopts a boat-like conformation, as indicated, similar to that proposed by Giese and Sustmann[23] for simple π-type glucopyranosyl radicals in which the orbital containing the single electron is periplanar with, and apparently stabilised by, the C-2–oxygen bond with selective quenching from the *exo*-face. This hypothesis is clearly subject to verification by ESR spectroscopy. Whatever the reason it is clear that the high diastereoselectivities observed are comparable with those recently reported by the Curran, Giese and Porter groups for other intermolecular radical reactions.[24]





With respect to the equally diastereoselective formation of compound **17** on decarboxylation of the acid **16** we believe that the intermediate radical **D** is best viewed as being of the σ-type and adopting a conformation like that observed for the product, with quenching taking place from the outside face of the bicyclic system. There is ample evidence in the literature that, whenever possible, 1,3-dioxolane rings exhibit a thermodynamic preference to be *cis*- rather than *trans*-fused to 6-membered rings:[25] indeed, special procedures have to be adopted for the formation and isolation of the kinetic *trans*-fused isomers.[26] We are, of course, aware of the possibility that the *trans*-fused isomer of compound **17** may have been formed in the course of the radical reaction and have undergone isomerisation under the reaction conditions or on silica gel chromatography. However, we consider that this is unlikely on the grounds that the process of isomerisation would almost certainly result in the competitive formation of the diol **18**, which was not the case; furthermore, comparison of the ^{1}H NMR spectrum of the crude reaction mixture and that of the pure product after chromatography revealed no difference in the chemical shift and coupling pattern of the anomeric proton signal. Once again the suggested conformation of radical **D** should be verifiable by ESR spectroscopy.

Experimental

General.—The general experimental conditions are as in Parts 1[1] and 2.[2]

3,4,6-*Tri*-O-*benzyl*-1-*methoxycarbonyl*-D-*glucal** **2**.—The sulphone ester **4**[1] (1.26 g, 2.04 mmol) was mixed with finely

* *Systematic name: methyl* 2,6-*anhydro*-4,5,7-*tri*-O-*benzyl*-3-*deoxy*-D-arabino-*hept*-2-*enonate*.

ground calcium oxide (0.13 g, 2.4 mmol) in a kugelrohr apparatus and the mixture was heated, at 15 mmHg, to 200 °C until TLC (SiO_2; light petroleum–diethyl ether, 1:1) of an aliquot showed the reaction to be complete (typically 1–2 h). After cooling, the reaction mixture was taken up in chloroform (50 cm^3), filtered on Celite, then washed successively with 5% aq. sodium hydrogen carbonate and water, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the crude product on silica gel [eluent (40–60) light petroleum–diethyl ether (3:2)] gave the title product as a crystalline solid (0.86 g, 89%), m.p. 70–71 °C (lit.,[1] 70–71 °C). In many instances the starting material **4** could be isolated from the crude reaction mixture, without recourse to chromatography, by simple crystallisation from diethyl ether–light petroleum.

Methyl 4,5,7-*Tri*-O-*benzyl*-α-D-gluco-*hep*-2-*ulopyranosonate* **5**.—The methoxycarbonylglucal **2** (1.2 g, 2.53 mmol) was dissolved in a mixture of THF (3 cm^3), and t-butyl alcohol (4 cm^3) and treated with pyridine (0.2 cm^3), *N*-methylmorpholine *N*-oxide (0.39 g, 2.87 mmol) and water (1.3 cm^3). A catalytic amount (1 crystal) of osmium tetraoxide was then added and the mixture was stirred and heated to reflux under nitrogen for 2.5 h. After cooling to room temperature the solution was treated with aq. sodium metabisulphite (20%; 10 cm^3) and the mixture was stirred for 5 min before the bulk of the t-butyl alcohol and THF were removed under reduced pressure. After dilution with dil. aq. sodium chloride the reaction mixture was extracted repeatedly with diethyl ether and the combined extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Crystallisation from diethyl ether–light petroleum gave the *title compound* as a crystalline solid (1.19 g, 92%), m.p. 97–99 °C; $[\alpha]_D^{20}$ +51.3° (*c* 1, $CHCl_3$); δ(400 MHz) 2.06 (1 H, d, *J* 8.8, 3-OH), 3.63–3.79 (4 H, m, 4- and 5-H, and 7-H_2), 3.88 (3 H, s), 4.03–4.06 (2 H, m, 3- and 6-H), 4.26 (1 H, d, *J* 1.23, 2-OH), 4.49–4.88 (6 H, m, CH_2Ph) and 7.16–7.38 (15 H, m, Ph); $\nu_{max}(CHCl_3)/cm^{-1}$ 3689, 3560, 3512, 1744, 1600, 1160 and 1088; *m/z* 418 ($M^{\bullet+}$ + H − CH_2Ph), 327, 221, 205, 181, 107 and 91 (Found: C, 68.2; H, 6.2. $C_{29}H_{32}O_8$ requires C, 68.49; H, 6.34%).

Methyl 4,5,7-*Tri*-O-*benzyl*-3-O-*t-butyldimethylsilyl*-α-D-gluco-*hept*-2-*ulopyranosonate* **6**.—A solution of diol **5** (0.72 g, 1.42 mmol) in dry dichloromethane (1.42 cm^3) was stirred at 0 °C under nitrogen. To this solution was added 2,4,6-collidine (0.41 cm^3, 3.11 mmol) followed by TBDMSOTf (0.33 cm^3, 1.42 mmol). After being stirred for 10 min at 0 °C the reaction mixture was diluted with diethyl ether (20 cm^3) and washed successively with 2 mol dm^{-3} HCl and brine, dried ($MgSO_4$), and concentrated under reduced pressure. Purification by chromatography on silica gel [eluent (40–60) light petroleum–diethyl ether (3:2)] afforded the *title product* in the form of a single anomer as an oil (0.82 g, 93%) with $[\alpha]_D^{20}$ +19.6° (*c* 1, $CHCl_3$); δ (400 MHz) −0.04 (3 H, s), 0.01 (3 H, s), 0.81 (9 H, s), 3.64 (1 H, dd, $J_{6,7a}$ 1.7, J_{gem} 11.1, 7-H[a]), 3.63–3.87 (3 H, m, 4-and 5-H, and 7-H[b]), 3.85 (3 H, s), 4.05 (1 H, ddd, $J_{5,6}$ 9.6, $J_{6,7a}$ 1.7, $J_{6,7b}$ 3.8, 6-H), 4.13 (1 H, d, $J_{3,4}$ 7.9, 3-H), 4.51–5.04 (6 H, m, CH_2Ph) and 6.99–7.36 (15 H, m, Ph); $\nu_{max}(CHCl_3)/cm^{-1}$ 3686, 3519, 1745, 1251, 1171, 1151 and 1070; *m/z* 565 ($M^{\bullet+}$ − Bu[t]), 547, 259, 181 and 91 (Found: C, 67.8; H, 7.4. $C_{35}H_{46}O_8Si$ requires C, 67.50; H, 7.44%).

Methyl 4,5,7-*Tri*-O-*benzyl*-3-O-*t-butyldimethylsilyl*-2-*deoxy*-2-*fluoro*-α/β-D-gluco-*hept*-2-*ulopyranosonate* **7**.—To a stirred solution of alcohol **6** (0.65 g, 1.04 mmol) in dry dichloromethane (1 cm^3) under nitrogen at 0 °C was added DAST (0.41 cm^3, 3.13 mmol). The mixture was stirred for a further 10 min before the reaction was quenched by the addition of cold water (3 cm^3). The reaction mixture was then extracted with dichloromethane and the extracts were washed with water, dried ($MgSO_4$), concentrated, and purified by chromatography on silica gel [eluent (40–60) light petroleum–diethyl ether (9:1)] to give the *title product* as an oil (0.61 g, 94%), as an unassigned mixture of anomers (1:3) with $[\alpha]_D^{26}$ +6° (*c* 0.5, $CHCl_3$); δ (400 MHz; major isomer) 0.01 (3 H, s), 0.09 (3 H, s), 0.82 (9 H, s) and 3.80 (3 H, s); (minor isomer) −0.05 (3 H, s), 0.00 (3 H, s), 0.80 (9 H, s) and 3.82 (3 H, s); (common) 3.67–3.78 (3 H, m, 5-H and 7-H_2), 3.82–4.23 (3 H, m, 3-, 4- and 6-H), 4.49–4.83 (6 H, m, CH_2Ph) and 7.06–7.32 (15 H, m, Ph); $\nu_{max}(CHCl_3)/cm^{-1}$ 1765, 1745, 1117 and 1084 (Found: C, 67.2; H, 7.4. $C_{35}H_{45}FO_7Si$ requires C, 67.28; H, 7.26%).

Methyl 4,5,7-*Tri*-O-*benzyl*-3-O-*t-butyldimethylsilyl*-2-*chloro*-2-*deoxy*-α/β-D-gluco-*hept*-2-*ulopyranosonate* **8**.—A stirred solution of **6** (0.26 g, 0.42 mmol) in dry dichloromethane (2 cm^3) under argon at room temperature was treated with pyridine (0.03 cm^3, 0.42 mmol) and subsequently with thionyl dichloride (0.03 cm^3, 0.42 mmol). After 10 min the reaction mixture was diluted with dichloromethane, washed with 2 mol dm^{-3} HCl, dried ($MgSO_4$), concentrated, and purified by chromatography on silica gel [eluent (40–60) light petroleum–diethyl ether (5:1)] to give the *title product* as an oil (0.26 g, 97%), as a (1:3) unassigned mixture of anomers with $[\alpha]_D^{20}$ +22° (*c* 1, $CHCl_3$); δ(400 MHz; major isomer) 0.05 (6 H, s), 0.81 (9 H, s) and 4.20 (1 H, m, 6-H); (minor isomer) 0.07 (6 H, s), 0.82 (9 H, s) and 4.11 (1 H, m, 6-H); (common) 3.82 (3 H, s), 3.64–3.86 (5 H, m, 4-H, 5-H, and 7-H_2), 4.26–4.98 (7 H, m, 3 × CH_2Ph and 3-H) and 6.99–7.38 (15 H, m, Ph); $\nu_{max}(CHCl_3)/cm^{-1}$ 1768, 1748, 1451, 1361, 1251 and 1091 (Found: C, 65.7; H, 7.0; Cl, 5.7. $C_{35}H_{45}ClO_7Si$ requires C, 65.55; H, 7.07; Cl, 5.53%).

Methyl (*Methyl* 4,5,7-*Tri*-O-*benzyl*-3-O-*t-butyldimethylsilyl*-α/β-D-gluco-*hept*-2-*ulopyranosid*)*onate* **9**.—To a stirred solution of the glycosyl chloride **8** (0.500 g, 0.78 mmol) in dry 1,4-dioxane (4 cm^3) under argon at room temperature were added powdered 4 Å molecular sieves followed by magnesium bromide–diethyl etherate (1.01 g, 3.9 mmol). Anhydrous methanol (3 cm^3) was then added and the whole was heated to reflux for 24 h. After cooling to room temperature the reaction mixture was diluted with diethyl ether, washed successively with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by chromatography on silica gel [eluent (40–60) light petroleum–diethyl ether (9:1)] to give two separate, but unassigned, anomers in the ratio (1:3.4) (0.400 g, 80%). The *major anomer* had $[\alpha]_D^{25}$ +27° (*c* 1, CCl_4); δ(400 MHz) −0.08 (3 H, s), 0.03 (3 H, s), 0.82 (9 H, s), 3.42 (3 H, s, OMe), 3.70 (2 H, m, 7-H_2), 3.78 (3 H, s, CO_2Me), 3.81–3.99 (3 H, m, 3-, 4- and 5-H), 4.51 (1 H, m, 6-H), 4.62–4.97 (6 H, m, CH_2Ph) and 6.96–7.35 (15 H, m, Ph); $\nu_{max}(CHCl_3)/cm^{-1}$ 1752, 1495, 1451, 1435, 1256, 1207, 1112, 1071 and 1053; *m/z* 579 ($M^{\bullet+}$ − Bu[t]), 578, 547, 457, 277, 271, 259, 231, 207, 181 and 91 (Found: C, 67.8; H, 7.7. $C_{36}H_{48}O_8Si$ requires C, 67.90; H, 7.60%).

The *minor anomer* had $[\alpha]_D^{25}$ +24° (*c* 1, CCl_4); δ(400 MHz) −0.02 (3 H, s), 0.06 (3 H, s), 0.81 (9 H, s), 3.37 (3 H, s, OMe), 3.39–3.75 (2 H, m, 7-H_2), 3.76 (3 H, s, CO_2Me), 3.77–3.94 (3 H, m, 3-, 4- and 5-H), 4.25 (1 H, dt, $J_{5,6}$ 10, $J_{6,7}$ 2), 4.51–4.79 (6 H, m, CH_2Ph) and 7.09–7.33 (15 H, m, Ph); $\nu_{max}(CHCl_3)/cm^{-1}$ 1759, 1736, 1451, 1360, 1253, 1249 and 1097 (Found: C, 67.5; H, 7.5%).

Methyl 3,4,6-*Tri*-O-*benzyl*-2-O-*t-butyldimethylsilyl*-β-D-*glucopyranoside* **13**.—A solution of the ester **9** (major anomer, 100 mg, 0.16 mmol) in methanol (0.5 cm^3) was treated with aq. potassium hydroxide (26 mg in 0.3 cm^3). After being stirred at room temperature for 2 h the reaction mixture was diluted with

chloroform, washed with 2 mol dm^{-3} HCl, dried ($MgSO_4$), and concentrated under reduced pressure to give the crude acid **10** (96 mg, 98%), which was used without further purification in the next step.

A solution of acid **10** (90 mg, 0.15 cm^3) in dry dichloromethane (1 cm^3) containing triethylamine (0.022 cm^3) was stirred under argon in the dark at room temperature with the heterocyclic salt **11** (34 mg, 0.18 mmol) for 2.5 h, after which t-dodecanethiol (0.1 cm^3) was added and the reaction mixture was photolysed at 0 °C with a 500 W tungsten lamp until TLC (SiO_2; light petroleum–diethyl ether, 2:1) control showed no further evolution. The reaction mixture was concentrated under reduced pressure and was then purified by chromatography on silica gel [eluent (40–60) light petroleum–diethyl ether (8:1)] to give the *title product* as a single anomer in the form of a viscous oil (55 mg, 65%) with $[\alpha]_D^{20}$ −24° (*c* 1, $CHCl_3$); δ(400 MHz; [$^2H_8$]toluene) 0.32 (3 H, s), 0.39 (3 H, s), 1.19 (9 H, s), 3.48 (1 H, dt, $J_{4,5}$ 9, $J_{5,6}$ 3.3, 5-H), 3.52 (3 H, s, OMe), 3.62 (1 H, dd, $J_{2,3}$, $J_{3,4}$ 8.1, 3-H), 3.79 (1 H, dd, $J_{3,4}$ 8.1, $J_{4,5}$ 9.0, 4-H), 3.81 (1 H, dd, $J_{1,2}$ 7.5, $J_{2,3}$ 8.1, 2-H), 3.83 (2 H, d, $J_{5,6}$ 3.3, 6-H_2), 4.15 (1 H, d, $J_{1,2}$ 7.52, 1-H) 4.57–5.08 (6 H, m, CH_2Ph) and 7.16–7.53 (15 H, m, Ph); ν_{max} ($CHCl_3$)/cm^{-1} 2925, 2845, 1598, 1495, 1448, 1358, 1254, 1124 and 1067; *m/z* 577 ($M^{\bullet+}$ − H), 547, 487, 455, 277, 207, 181, 91, 73 and 57 (Found: C, 70.3; H, 8.2. $C_{34}H_{46}O_6Si$ requires C, 70.55; H, 8.01%).

Methyl 3,4,6-*Tri*-O-*benzyl*-β-D-*glucopyranoside* **14**.—To a stirred solution of the silyl ether **13** (43 mg, 0.07 mmol) in dry THF (0.5 cm^3) in the presence of powdered 4 Å molecular sieves under argon at room temperature was added tetrabutylammonium fluoride (1 mol dm^{-3} in THF; 0.15 cm^3, 0.15 mmol). The reaction mixture was stirred for 24 h at room temperature and then poured onto water and repeatedly extracted with ethyl acetate. The combined extracts were washed successively with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. Purification by chromatography on silica gel [eluent (40–60) light petroleum–diethyl ether (3:2)] gave the title compound as a crystalline solid (26 mg, 74%), m.p. 74–75 °C; $[\alpha]_D^{20}$ −5° (*c* 1.1, $CHCl_3$) (lit.,[17] m.p. 72–75 °C; $[\alpha]_D$ −5°); δ(400 MHz) 2.35 (1 H, d, *J* 1.7, OH), 3.48 (1 H, ddd, $J_{4,5}$ 9.3, $J_{5,6a}$ 2.78, $J_{5,6b}$ 4.77, 5-H), 3.55 (3 H, s), 3.50–3.62 (3 H, m, 2-, 3- and 4-H), 3.74 (1 H, dd, $J_{5,6a}$ 2.78, J_{gem} 10.6, 6-H^a), 3.70 (1 H, dd, $J_{5,6b}$ 4.77, J_{gem} 10.6, 6-H^b), 4.17 (1 H, d, $J_{1,2}$ 7.48, 1-H), 4.50–4.91 (6 H, m, CH_2Ph) and 7.14–7.37 (15 H, m, Ph).

Methyl 4,5,7-*Tri*-O-*benzyl*-2,3-O-*isopropylidene*-α-D-gluco-*hept*-2-*ulopyranosonate* **15**.—To a solution of the diol **5** (0.200 g, 0.39 mmol) in dry toluene (6 cm^3) at 0 °C was added 2,2-dimethoxypropane (4 cm^3). A slow stream of hydrogen chloride was then bubbled through the solution for 5 min. The reaction mixture was then evaporated to dryness under reduced pressure and the residue was purified by chromatography on silica gel [eluent (40–60) light petroleum–diethyl ether (7:3)] to give the *title product* as an oil (0.160 g, 76%) with $[\alpha]_D^{20}$ +15° (*c* 0.5, $CHCl_3$); δ(400 MHz) 1.46 (3 H, s, CMe), 1.59 (3 H, s, CMe), 3.65 (3 H, m, $J_{4,5}$ 1.8, $J_{5,6}$ 9.5, 5-H and 7-H_2), 3.82 (3 H, s, CO_2Me), 3.98 (2 H, m, 4- and 6-H), 4.26–4.65 (6 H, m, CH_2Ph), 4.90 (1 H, dd, $J_{3,4}$ 1.8, $J_{3,5}$ 1, 3-H) and 7.15–7.36 (15 H, m, Ph); ν_{max}($CHCl_3$)/cm^{-1} 1744, 1460, 1384, 1375, 1110 and 1070; *m/z* 548 ($M^{\bullet+}$), 492, 458, 399, 351, 181 and 91 (Found: C, 69.8; H, 6.5. $C_{32}H_{36}O_8$ requires C, 70.06; H, 6.61%).

3,4,6-*Tri*-O-*benzyl*-1,2-O-*isopropylidene*-α-D-*glucopyranose* **17**.—A solution of the ester **15** (0.15 g, 0.27 mmol) in methanol (0.4 cm^3)–THF (2.1 cm^3) was treated with aq. potassium hydroxide (31 mg, 0.55 mmol in 0.2 cm^3) and stirred at room temperature for 1.5 h before dilution with dichloromethane, washing with 2 mol dm^{-3} HCl, drying ($MgSO_4$), and concentration under reduced pressure to give the crude acid **16** (0.13 g, 89%).

A solution of this crude acid (0.16 g, 0.3 mmol) in dry dichloromethane (3 cm^3) was stirred with triethylamine (0.05 cm^3, 0.36 mmol) and the heterocyclic salt **11** (68 mg, 0.36 mmol) under argon in the dark at room temperature for 3.5 h. t-Dodecanethiol (0.35 cm^3, 1.5 mmol) was then added and the mixture was photolysed at 0 °C under argon for 1 h. Concentration of the reaction mixture under reduced pressure and chromatography of the residue on silica gel [eluent (40–60) light petroleum–diethyl ether (17:3)] gave the title product as a crystalline solid (0.11 g, 75%), m.p. 55 °C; $[\alpha]_D^{20}$ +39.4° (*c* 1, $CHCl_3$) {lit.,[18] m.p. 71 °C; $[\alpha]_D$ +37.3° (*c* 2.9, $CHCl_3$)} δ(400 MHz) 1.36 (3 H, s, CMe), 1.54 (3 H, s, CMe), 3.65 (2 H, m, 6-H_2), 3.72 (1 H, dd, $J_{3,4}$ 3.79, $J_{4,5}$ 9.6, 4-H), 3.91 (1 H, m, 5-H), 3.93 (1 H, dd, $J_{2,3}$ = $J_{3,4}$ = 3.79, 3-H), 4.27 (1 H, dd, $J_{1,2}$ 4.88, $J_{2,3}$ 3.79, 2-H), 4.38–4.64 (5 H, m, CH_2Ph), 4.51 (1 H, d, *J* 11, C*H*HPh), 5.65 (1 H, d, $J_{1,2}$ 4.88, 1-H) and 7.19–7.39 (15 H, m, Ph); ν_{max}($CHCl_3$)/cm^{-1} 1495, 1450, 1381, 1368 and 1100; *m/z* 490 ($M^{\bullet+}$), 489, 475, 432, 423, 399, 341 and 91 (Found: C, 73.3; H, 6.8. Calc. for $C_{30}H_{34}O_6$: C, 73.45; H, 6.99%).

3,4,6-*Tri*-O-*benzyl*-α/β-D-*glucopyranose* **18**.—A solution of the acetonide **17** (25 mg, 0.051 mmol) in THF (0.5 cm^3) was stirred at room temperature with 2 mol dm^{-3} HCl (0.5 cm^3) for 24 h. The solution was then neutralised (pH 7) with 5% aq. sodium hydrogen carbonate and repeatedly extracted with ethyl acetate. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography on silica gel [eluent (40–60) light petroleum–diethyl ether (1:4)] gave the title product, a ~1:2 α:β mixture of anomers, as a solid (17 mg, 74%), m.p. 88–90 °C; $[\alpha]_D^{20}$ +58° (*c* 0.9, $CHCl_3$) {lit.,[20] m.p. 85–86 °C; $[\alpha]_D$ +57.1° (*c* 0.9, $CHCl_3$)}; δ(400 MHz) 5.25 (1 H, dd, $J_{1,2}$ 3.36, $J_{1,OH}$ 2.24, 1-H of α-anomer); the anomeric signal of the β-anomer was obscured by the benzylic hydrogens. The anomeric ratio of the product was estimated by integration of the anomeric OH signals at δ 2.44 (α-anomer, *J* 2.24 Hz) and 3.31 (β-anomer, *J* 3.36 Hz) which themselves were assigned by double irradiation of the signal at δ 5.25.

In a microscale acetylation reaction the diol **18** (3 mg) was dissolved in pyridine (0.5 cm^3) and treated with acetic anhydride (4 mg) at room temperature until TLC control (SiO_2; light petroleum–diethyl ether, 1:4) indicated complete reaction. The solvent was removed under reduced pressure and the residue was dried at 50 °C and 0.1 mmHg. In this manner a 2:1 α:β mixture of the diacetate **19** was obtained in essentially quantitative yield: it was characterised by δ 6.27 (d, *J* 3.55, 1-H of α-anomer) and 5.58 (d, *J* 8.23, 1-H of β-anomer) in the 400 MHz ^1H NMR spectrum.

Preparation of an Authentic Sample of 3,4,6-*Tri*-O-*benzyl*-α/β-D-*glucopyranose* **18**.—Tri-*O*-benzyl-D-glucal **20**[27] (416 mg, 1 mmol) was dissolved in THF (2 cm^3) and t-butyl alcohol (2 cm^3) and treated with pyridine (2 drops) and water (1 cm^3). *N*-Methylmorpholine *N*-oxide (130 mg, 1.1 mmol) was added followed by osmium tetraoxide (1 crystal), resulting in the immediate formation of a light brown solution. Little or no reaction occurred on storage at room temperature for 18 h, but on heating to reflux for 1.5 h all the starting material was consumed. After cooling to room temperature the reaction mixture was worked up as described above for compound **5**. The crude extracts were essentially pure compound **18** as demonstrated by TLC and 200 MHz ^1H NMR spectroscopy. The spectral characteristics were identical with those described above. Microscale acetylation also gave a sample of the diacetate **19** in the same anomeric ratio as that described above and with identical spectral characteristics.

Preparation of an Authentic Sample of 3,4,6-*Tri*-O-*benzyl*-1,2-O-*isopropylidene*-α-D-*glucopyranose* **17**.—The diol **18** (150 mg) was dissolved in benzene (5 cm^3) containing acetone (0.5 cm^3). Camphor-10-sulphonic acid (5 mg) was added and the mixture was heated to reflux in a Dean–Stark apparatus for 3 days. The reaction mixture was then cooled to room temperature and concentrated under reduced pressure prior to purification by chromatography on silica gel [eluent hexane–diethyl ether (1:1)] to give the acetonide **17** (77 mg, 45%), whose spectral data were identical with those of the sample obtained above.

Acknowledgements

We thank the Brunei Government for a studentship to L. B. L. L., Professor P. M. Collins (Birkbeck College London) for helpful and stimulating discussions and Dr. G. Williams for help with NMR spectra.

References

1 Part 1: D. Crich and T. J. Ritchie, *J. Chem. Soc., Perkin Trans. 1*, 1990, 945.
2 Part D. Crich and L. B. L. Lim, preceding paper.
3 D. H. R. Barton, D. Crich and W. B. Motherwell, *Tetrahedron*, 1985, **41**, 3901; D. Crich and L. Quintero, *Chem. Rev.*, 1989, **89**, 1413.
4 For a preliminary communication see: D. Crich and L. B. L. Lim, *Tetrahedron Lett.*, 1991, **32**, 2565.
5 K. C. Nicolaou, C.-K. Huang and M. E. Duggan, *J. Chem. Soc., Chem. Commun.*, 1986, 925; P. Lesimple, J. M. Beau, G. Jaurand and P. Sinaÿ, *Tetrahedron Lett.*, 1986, **27**, 6201; S. Hanessian, M. Martin and R. C. Desai, *J. Chem. Soc., Chem. Commun.*, 1986, 926.
6 D. Crich and T. J. Ritchie, *Tetrahedron*, 1988, **44**, 2319.
7 S. V. Ley, B. Lygo, F. Sternfeld and A. Wonnacott, *Tetrahedron*, 1986, **42**, 4333; see also ref. 6.
8 D. S. Brown, S. V. Ley and S. Vile, *Tetrahedron Lett.*, 1988, **29**, 4873.
9 R. C. Hockett, A. C. Sapp and S. R. Millman, *J. Am. Chem. Soc.*, 1941, **63**, 2051; V. Bilik and S. Kucar, *Carbohydr. Res.*, 1970, **13**, 311.
10 I. Dyong, G. Schulte, Q. Lam-Chi and H. Friege, *Carbohydr. Res.*, 1979, **68**, 257.
11 J. K. Cha, W. J. Christ and Y. Kishi, *Tetrahedron*, 1984, **40**, 2247.
12 K. Vangehr, P. Luger and H. Paulsen, *Carbohydr. Res.*, 1979, **70**, 1; see also W. Korytnyk and O. Dodson-Simmons, *Carbohydr. Res.*, 1984, **131**, 157.
13 V. Van Rheenan, D. Y. Cha and W. M. Hartley, *Org. Synth.*, 1988, Coll. vol. 6, 342; J. P. McCormick, J. Pachlatko and T. R. Schafer, *Tetrahedron Lett.*, 1978, 3993.
14 R. F. Stewart and L. L. Miller, *J. Am. Chem. Soc.*, 1980, **102**, 4999.
15 Y. Ito and T. Ogawa, *Tetrahedron Lett.*, 1988, **29**, 3987; S. Kusumoto, N. Kusumose, T. Kamikawa and T. Shiba, *Tetrahedron Lett.*, 1988, **29**, 6325; H. Kunz, H. Waldmann and U. Klinkhammer, *Helv. Chim. Acta*, 1988, **71**, 1868.
16 W. J. Middleton, *J. Org. Chem.*, 1975, **40**, 574.
17 G. Ekborg, B. Lindberg and J. Lönngrenn, *Acta Chem. Scand.*, 1972, **26**, 3287.
18 P. Boulanger, J. C. Martin and G. Descotes, *J. Heterocycl. Chem.*, 1975, **12**, 91.
19 B. Coxon and L. D. Hall, *Tetrahedron*, 1964, **20**, 1685.
20 P. A. Gent and R. Gigg, *Carbohydr. Res.*, 1976, **49**, 325.
21 D. Kahne, D. Yang, J. J. Lim, R. Miller and E. Paguaga, *J. Am. Chem. Soc.*, 1988, **110**, 8716.
22 A. L. J. Beckwith and P. K. Tindall, *Aust. J. Chem.*, 1971, **24**, 2099; V. Malatesta, R. D. McKelvey, R. W. Babcock and K. U. Ingold, *J. Org. Chem.*, 1979, **44**, 1872; A. R. Gregory and V. Malatesta, *J. Org. Chem.*, 1980, **45**, 122.
23 H. G. Korth, R. Sustmann, B. Giese and J. Dupuis, *J. Chem. Soc., Perkin Trans. 2*, 1986, 453, 615; H. G. Korth, R. Sustmann, K. S. Groninger, T. Witzel and B. Giese, *J. Chem. Soc., Perkin Trans. 2*, 1986, 1461; R. Sustmann and H. G. Korth, *J. Chem. Soc., Faraday Trans. 1*,1987, 95; H. G. Korth, R. Sustmann, B. Giese, B. Ruckert and K. S. Groninger, *Chem. Ber.*, 1990, **123**, 1891.
24 D. P. Curran, W. Shen, J. Zhang and T. A. Heffner, *J. Am. Chem. Soc.*, 1990, **112**, 6738; B. Giese, M. Zehnder, M. Roth and H. G. Zeitz, *J. Am. Chem. Soc.*, 1990, **112**, 6741; N. A. Porter, E. Swann, J. Nally and A. T. McPhaill, *J. Am. Chem. Soc.*, 1990, **112**, 6740, and references therein.
25 See, for example: J. Mills, *Adv. Carbohydr. Chem.*, 1955, **10**, 1; A. N. Debelder, *Adv. Carbohydr. Chem. Biochem.*, 1977, **34**, 179; P. H. Hermans and C. J. Maan, *Rec. Trav. Chim. Pays-Bas*, 1938, **57**, 643; J. Gigg, R. Gigg, S. Payne and R. Conant, *J. Chem. Soc., Perkin Trans. 1*, 1987, 1757.
26 See, for example: F. H. Bissett, M. E. Evans and F. W. Parrish, *Carbohydr. Res.*, 1967, **5**, 184; J. S. Brimacombe, A. B. Foster, B. D. Jones and J. J. Willard, *J. Chem. Soc. C*, 1967, 2404.
27 I. D. Blackburne, P. M. Fredericks and R. D. Guthrie, *Aust. J. Chem.*, 1976, **29**, 381.

Paper 1/01393I
Received 22*nd March* 1991
Accepted 15*th April* 1991