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Stereospecific carbon–carbon bond formation at secondary carbons in cyclic sugars

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ABSTRACT

An excellent leaving-group, triflate, at C-4 of the benzylated hexopyranose glycosides **1** and **2** was used to study the introduction of carbon branches in sugars. By using a phase-transfer reagent, a one-carbon source, cyanide ion, was used to prepare the displacement products **3** and **4**. Direct displacement by a malonate ester ion was also successful and gave rise to the corresponding products **5** and **6**. A significant difference in the chemistry of **5** and **6** was noted in that the *galacto* isomer **5**, under neutral conditions, rearranged to its 1,6-anhydride **7** with loss of the O-6 benzyl group; a rationalization for the difference in stability of **5** and **6** is presented.

INTRODUCTION

The modification of natural sugars by attachment, through carbon–carbon bonds, of certain functional groups can result in intermediates to biologically important molecules, such as the C-nucleosides[1]. While such functionalization of cyclic sugars is relatively easily accomplished at C-1 and at most primary carbon atoms, it is much less readily carried out at the secondary carbons. The methods most commonly employed for establishing these carbon–carbon bonds are the opening of epoxides by carbon nucleophiles[2] including cyanide ion[3], reaction of epoxides with organometallics[4], and nucleophilic additions to sugar carbonyl groups with organometallics[5], cyanide ion[6], and carbanions[7]. With the methods just mentioned, there are questions about the regiospecificity or the stereospecificity of the reactions, and mixtures of products usually result. Sugar triflates[8,9] have been shown to undergo clean S_N2 displacements, thus with predictable stereochemistry, with a variety of nucleophiles[10,11], including one example, relevant to the work

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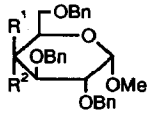
presented here, with cyanide ion[12], which effected carbon–carbon bond formation. Triflate displacement by cyanide ion, with inversion, has also been noted by Fleet et al., in a methyl 2-deoxy-α-D-*threo*-pentofuranoside derivative[13]. We have extended the study of these triflates with certain carbon nucleophiles to give modified sugars that may be visualized as precursors to heterocycles carbon-bonded to sugars and to carbon-linked disaccharides, as examples of interesting new molecules.

RESULTS AND DISCUSSION

All of our studies have used the 4-triflates of methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside[11] (**1**) and -galactopyranoside * (**2**). When either **1** or **2** was allowed



1, $R^1 = H$, $R^2 = OSO_2CF_3$
2, $R^1 = OSO_2CF_3$, $R^2 = H$
3, $R^1 = CN$, $R^2 = H$
4, $R^1 = H$, $R^2 = CN$
5, $R^1 = CH(CO_2Et)_2$, $R^2 = H$
6, $R^1 = H$, $R^2 = CH(CO_2Et)_2$

to react with a large excess of cyanide ion (from potassium cyanide) in dry THF in the presence of dicyclohexano-18-crown-6, excellent yields of the nitriles **3** and **4** were obtained. In the earlier study[12] just referred to, Durette had treated methyl 3-azido-2,3,6-trideoxy-4-*O*-triflyl-α-D-*lyxo*-hexopyranoside with tetrabutylammonium cyanide in acetonitrile to give ~21% of the inverted nitrile. ^1H NMR analysis permitted the assignments of **3** and **4** as *galacto* and *gluco* epimers; the ^{13}C spectra clearly showed them to be isomers. Thus, as expected, the reactions had occurred by clean inversion (see Tables I and II).

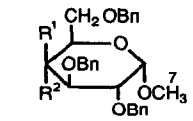
The reaction of **1** and **2** with a large excess of the anion of diethyl malonate for extended times at room temperature in dry THF gave good yields of the adducts **5** and **6**, respectively. The *gluco* adduct **6** was stable in the reaction medium and could be heated in dry THF (50°C) without change. The reaction to give **5**, however, showed by TLC, the formation of another product whose intensity increased as the reaction time was extended and which also formed slowly when **5** was heated in dry THF.

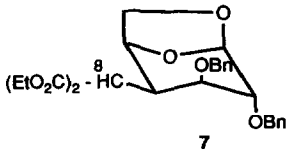
The transformation product from **5** was separated chromatographically and existed as an oil, shown by NMR to differ from **5** by the loss of one benzyl group and the anomeric methoxyl group, but retaining intact the diethyl malonate moiety. The bicyclic structure **7** was assigned on the basis of a detailed NMR study

* Prepared from methyl 2,3,6-tri-*O*-benzyl-α-D-galactopyranoside[18] by the same method as used for **1**.

TABLE I

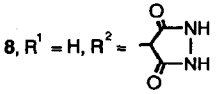
^{1}H NMR chemical shifts, multiplicities, and coupling constants [a,b,c,e]





7

3, R^1 = CN, R^2 = H
4, R^1 = H, R^2 = CN
5, R^1 = $CH(CO_2Et)_2$, R^2 = H
6, R^1 = H, R^2 = $CH(CO_2Et)_2$



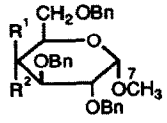
	3	4	5	6	7	8
H-1	4.62(3, *J*, 4.4)	4.63(d, *J*, 3.3)	4.67(d)	4.65(d, *J*, 3.3)	5.45(d, *J*, 1.8)	
H-2	3.78(dd, *J*, 4.4)	3.43(dd, *J*, 3.3, 9.3)		3.48(m, *J*, 3.3)	3.46(dd, *J*, 1.8)	
H-3	3.94(dd, *J*, 4.4)	4.09(dd, *J*, 9.3, 10.8)		4.23(q)	3.87(m, *J*, 1.8, 3.1)	
H-4	3.32(dd, *J*, 4.4, 1.6)	3.03(t, *J*, 10.8)		2.65(dt)	3.13(m)	2.53(dt)
H-5	3.98(m)	3.99(dt, *J*, 10.8, 2.7)		4.04(m)	4.38(m)	
H-6α					3.62(m, *J*, 12.0) [d]	
H-6β	3.64(m) [d]	3.69(m, *J*, 2.7, 12.0) [d]		3.61(m) [d]	4.21(m, *J*, 12.0) [d]	
H-7	3.33(s)	3.36(s)	3.39(s)	3.36(s)		3.27(s)
H-8				3.78(d)	3.66(d, *J*, 9.2)	
Ester CH_2			3.85(m)	3.97(m)	4.07(m)	
			4.03(m)	4.13(m)	4.17(m)	
Ester CH_3			1.09(t)	1.12(t)	1.16(t), 1.24(t)	

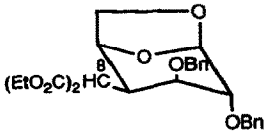
[a] The benzyl CH_2 groups were all AB quartets that occurred in the 4.25–4.90 ppm range. [b] The aromatic protons were multiplets that occurred in the 7.20–7.35 ppm range. [c] Small couplings were observed for most of the sugar protons and are not noted here. [d] The protons of H-6α and H-6β in compound **3**, **4**, and **6** were slightly broadened multiplets and the chemical shifts were simply given as the center of the peak for two protons. In **7**, H-6α and H-6β had very different chemical shifts. [e] In many cases the complexity of the spectra prevented the determination of meaningful coupling-constants.

of the compound. In the 1D carbon and proton spectra of the transformation product, the signals at 100.2 (Table II) and at 5.45 ppm (Table I) clearly could be assigned to the anomeric carbon and proton, respectively, which are deshielded by two oxygen atoms. The chemical shift of H-1 as compared to the same protons in **3**,

TABLE II

^{13}C NMR spectral data [a,b,c]





7

3, $R^1 = {}^8CN$, $R^2 = H$
4, $R^1 = H$, $R^2 = {}^8CN$
5, $R^1 = {}^8CH(CO_2Et)_2$, $R^2 = H$
6, $R^1 = H$, $R^2 = {}^8CH(CO_2Et)_2$

8, $R^1 = H$, $R^2 =$

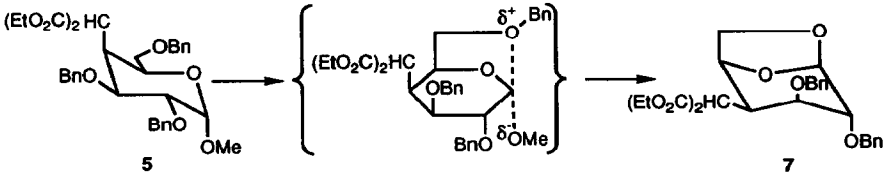
Atom	Chemical shifts					
	3	4	5	6	7	8
C-1	98.9	98.4	98.7	98.2	100.2	98.4
C-2	77.5	79.7	78.5	82.4	72.7	81.5
C-3	73.8	76.1	75.1	76.0	74.8	75.5
C-4	37.4	35.8	40.1	43.8	39.0	42.7
C-5	65.2	67.5	68.7	68.5	72.9	67.5
C-6	69.7	69.2	70.4	70.5	64.5	70.5
C-7	55.6	55.5	55.1	55.1		55.3
C-8	116.4	117.5	47.9	48.7	50.1	43.0
Ester and			169.1	168.1	168.4	170.7
Pyrazolone C=O			169.3	168.6	167.2	171.5
Ester CH_2			61.3	61.0	61.7	
			61.4	61.1	61.4	
Ester CH_3			13.8, 13.9	13.9	14.0	

[a] The benzyl methylenes appeared in the 72.0–75.7 ppm range. [b] The aromatic carbons appeared in the 137.3–139.0 ppm range. [c] In compounds, 3, 4, 5, and 8, 2D HETCORR spectra were not recorded, and the specific assignments were not rigorously established but are listed to correspond to the chemical shifts in 6.

4, 5, and 6 suggests a fundamental structural difference in the transformation product. The 2D COSY spectrum (^1H) then permitted the assignment (by correlation) of H-2, and, in turn, H-3, H-4, H-5, and H-6α, H-6β (not individually assigned) to account for all of the critical ring protons. The same 2D spectrum also correlated H-4 and the malonyl proton H-8. Again, it is significant that, in 7, H-6α, and H-6β resonate as separate, distinct signals (3.62 and 4.21 ppm) with a large chemical-shift difference, whereas in 3, 4, 5, and 6, these two protons resonate at almost identical chemical shifts as a somewhat broadened multiplet, emphasizing the structural difference between 7 and the simple methyl glycosides. The ring hydrogens were then correlated to the ring carbons by a 2D HETCORR spectrum which permitted the assignment of the latter. This spectrum also led to the definitive assignment of the malonyl carbon C-8 by correlation with H-8. A DEPT

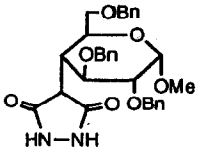
spectrum was used to distinguish CH_2– from CH–, and CH_3 groupings; conventional decoupling techniques were useful in verifying proton assignments. Finally, the key observation that showed that the 6-*O*-benzyl group had been lost in the cyclization at C-1 to give **7**, was a long-range coupling in the ^1H COSY spectrum of H-1 to H-6α and H-6β.

We rationalize the **5** to **7** transformation (and the resistance to cyclization of **6**) by assuming that **5** exists largely in the $^4C_1$ conformation, the anomeric effect dictating that the methoxyl group be axial which then fixes the diethylmalonyl group as an axial group. The driving force for the cyclization is



conformational change to the $^1C_4$ conformation in **7** which now possesses an equatorial diethylmalonyl group. An oxonium ion intermediate seems a reasonable postulation for the change. The fate of the lost benzyl group is obscure. When **5** was heated in dry THF containing excess methanol, it was converted completely into **7** (according to TLC) but we could not identify benzyl methyl ether as a reaction product. Similarly, rearrangement in the presence of ethanol gave no evidence for the formation of benzyl ethyl ether. A somewhat related cyclization with loss of the 6-*O*-benzyl group was noted in the reaction of 3,4,6-tri-*O*-benzyl-2-chloro-2-deoxy-α-D-glucopyranosyl chloride with silver cyanide where one of the products was a 1,6-anhydro-D-gluocopyranose[15]. Recently, an almost identical loss of an *O*-benzyl group under neutral conditions was noted by Dehmlow et al.,[16] who reported tetrahydrofuran formation with a variety of different compounds containing benzyl ethers with S_N2 active sites in the γ-position to give regio- and stereo-controlled cyclizations with concomitant debenzylation. Under strongly electrophilic conditions, similar benzyl ether participations have been noted by Mootoo and Fraser-Reid[17].

Our attempts to utilize the diethylmalonyl group to form heterocycles emphasized **6**, stable to cyclization by virtue of its equatorial diester group in the favored $^4C_1$ conformation. Glycoside **6** was quite unreactive with most of the reagents tried. The diester groups could not be hydrolyzed with aqueous 6 M NaOH at room temperature; heating with the base at 90°C caused extensive decomposition. Reaction with urea and sodium ethoxide gave no evidence for barbiturate formation. When **6** was heated with neat 97% hydrazine at 100°C, it was slowly converted in moderate yield into a crystalline compound identified as pyrazolidinedione **8** by NMR and elemental analysis. The latter, in particular, distinguished **8** from the other possible product, the dihydrazide. Similar treatment of **5** led to a complex mixture as shown by TLC.



8

EXPERIMENTAL

General methods.—Melting points were determined with a Meltemp apparatus (Laboratory Devices, Cambridge, MA) or a digital melting-point apparatus (Electrothermal Eng. Ltd., UK), and both are uncorrected. IR spectra were recorded on a Perkin–Elmer 281B infrared spectrophotometer using KBr solid pellets or neat liquids on salt plates. NMR spectra were recorded with Varian EM-360A (^{1}H), EM-390 (^{1}H), and Bruker AM-300 (^{1}H, ^{13}C, 2D) spectrometers in $CDCl_3$ containing 1% of Me_4Si. Chemical shifts are reported in δ units. Optical rotations of solutions in CH_2Cl_2 were measured with a Perkin–Elmer Model 141 automatic polarimeter at the sodium D line. Flash chromatography was performed with Merck grade 60 (60–230 mesh) silica gel. Thin-layer chromatography (TLC) separations were carried out using Brinkman Polygram Sil G/UV_{254} plates, with spot detection by UV light or with a 20% H_2SO_4–95% EtOH spray, followed by carbonization. The solvent systems used for both types of chromatography were 1:9 to 4:6 EtOAc–hexane mixtures unless otherwise noted. THF was dried over sodium ketyl. Powered 3A molecular sieves were employed in certain reactions and when the NaH in oil was used, the oil was removed by hexane washes. Elemental analyses were obtained from M-H-W Laboratories (P.O. Box 15149, Phoenix, AZ).

The general workup procedure for most reactions was to remove any excess volatile reagents by warming (65°C) under vacuum (either water aspirator or mechanical pump), then adding the residue to ice–water. Dichloromethane was the usual extraction solvent (20–25 mL/g of expected product), and combined extracts were usually washed with cold 3 M HCl, cold satd aq $NaHCO_3$, and cold water. The extracts were dried over anhyd $MgSO_4$, then filtered and evaporated in vacuo, usually below 65°C. Flash chromatography was used to isolate the products and the composition of the EtOAc–hexane eluants is noted for each chromatogram.

Methyl 2,3,6-tri-O-benzyl-4-O-triflyl-α-D-galactopyranoside (**2**).—The standard processing of a mixture of 2.0 g (4.31 mmol) of methyl 2,3,6-tri-*O*-benzyl-α-D-galactopyranoside[14] 1.0 mL of dry pyridine, 1.04 mL (6.18 mmol) of triflic anhydride, and 50 mL of CH_2Cl_2 yielded 2.55 g of light-brown oil, that, after chromatography (4:6), gave 2.44 g (98.2%) of **2** as an oil; $[\alpha]_D^{23.5}$ +57.5 (*c* 3.63). Anal. Calcd for $C_{29}H_{31}F_3O_8S$: C, 58.38; H, 5.24. Found: C, 58.41; H, 5.49.

Methyl 2,3,6-tri-O-benzyl-4-cyano-4-deoxy-α-D-galactopyranoside (**3**).—A mixture of 0.20 g (0.335 mmol) of **1**, 0.40 g (6.15 mmol) of KCN, 0.50 g of molecular sieves, 0.20 g (0.54 mmol) of *cis*-dicyclohexano-18-crown-6, and 50 mL of dry THF was stirred vigorously at room temperature for 48 h and then worked up conventionally to give, after flash chromatography (4:6) and recrystallization from 95%, EtOH, 0.127 g (85.0%) of white crystals; mp 93–94°C; $[\alpha]_D^{23.5}$ +89.7° (*c* 2.79); IR, 2243 cm^{-1} (very weak). Anal. Calcd for $C_{29}H_{31}NO_5$: C, 73.55; H, 6.60; N, 2.96. Found C, 73.80; H, 6.82; N, 2.89.

Methyl 2,3,6-tri-O-benzyl-4-cyano-4-deoxy-α-D-glucopyranoside (**4**).—Following the procedure described for **3** and employing 1.024 g (1.72 mmol) of **2**, 2.025 g (31.20 mmol) of KCN, 0.56 g of molecular sieves, 1.0 g (2.68 mmol) of *cis*-dicyclohexano-18-crown-6 and 50 mL of dry THF, 0.725 g (89.0%) of **4** was produced, after flash chromatography (4:6), as a colorless oil, $[\alpha]_D^{23.5}$ +57.4° (*c* 7.01); IR, 2242 cm^{-1} (very weak). Anal. Calcd for $C_{29}H_{31}NO_5$: C, 73.55; H, 6.60; N, 2.96. Found: C, 73.47; H, 6.79; N, 2.85.

Methyl 2,3,6-tri-O-benzyl-4-deoxy-4-bis(ethoxycarbonyl)methyl-α-D-galactopyranoside (**5**).—A solution of the malonate anion was prepared by adding 15 mL (98.80 mmol) of diethyl malonate, slowly, to an ice-cooled suspension of 3.24 g (67.5 mmol) of NaH (50% in oil) in 100 mL of dry THF with protection from atmospheric moisture. When hydrogen evolution had ceased, 2.69 g (4.51 mmol) of triflate (**1**) was added and the mixture was stirred for 3 days at room temperature, while monitoring the reaction with TLC. Most of the excess diethyl malonate was removed by high-vacuum evaporation at room temperature. After general workup, 2.40 g of crude product, which showed 2 spots on TLC, was obtained. Flash chromatography (1:9) yielded 1.35 g (49%) of compound **5** and 0.45 g (21%) of the transformation product **7**. In later experiments, the amount of **7** was minimized by using a reaction time of 36 h. Compound **5** was a colorless oil; $[\alpha]_D^{23.5}$ +48.1° (*c* 1.15). Anal. Calcd for $C_{35}H_{42}O_9$: C, 69.29; H, 6.98. Found: C, 70.05; H, 7.00.

1,6-Anhydro-2,3-di-O-benzyl-4-deoxy-4-bis(ethoxycarbonyl)methyl-β-D-galactopyranose (**7**).—Compound **7**, isolated from the preparation of **5**, was a colorless oil; $[\alpha]_D^{23.5}$ −27.1° (*c* 3.63). Anal. Calcd for $C_{27}H_{32}O_8$: C, 66.93; H, 6.66. Found: C, 66.68; H, 7.04.

Methyl 2,3,6-tri-O-benzyl-4-deoxy-4-bis(ethoxycarbonyl)methyl-α-D-glucopyranoside (**6**).—Using the procedure described for **5** but employing 12 mL (79.04 mmol) of diethyl malonate, 2.50 g (52.0 mmol) of 50% NaH, 50 mL of dry THF and 1.50 g (2.51 mmol) of **1**, crude **6** was obtained after removal of most of excess diethyl malonate by high-vacuum evaporation. The thermal stability of **6** permitted removal of the last traces of diethyl malonate by refluxing the crude product in abs EtOH containing NaOEt and urea. After filtration of the small amount of barbituric acid and flash chromatography (1:9), 1.335 g (87.7%) of **6** was obtained as a colorless oil; $[\alpha]_D^{23.5}$ +31.9° (*c* 3.35). Anal. Calcd for $C_{35}H_{42}O_9$: C, 69.29; H, 6.98. Found: C, 69.76; H, 7.09.

Methyl 2,3,6-tri-O-benzyl-4-deoxy-4-α-D-glucopyranosid-4-yl-3,5-pyrazolidinedione (**8**).—A mixture of 0.65 g (1.07 mmol) of diester **6** and 2.5 mL (76.50 mmol) of 97% hydrazine was heated for 18 h at 100–110°C. Most of excess hydrazine was removed at aspirator vacuum (50°C). The residue was treated with 3.0 mL of cold water and the mixture extracted with three 3.0 mL portions of CH_2Cl_2. The extracts were washed twice with 10 mL portions of water, dried and evaporated to give 0.39 g of residue. Flash chromatography (1:9) yielded 0.18 g (30.8%) of chromatographically homogeneous oil. The oil was dissolved in 0.5 mL of warm EtOAc, and then 1.5 mL of hexane was added giving a cloudy solution that on slow evaporation at room temperature yielded white crystals; mp 93–94.1°C; $[\alpha]_D^{23.5}$ +25.7° (*c* 3.25). Anal. Calcd for $C_{31}H_{34}N_2O_7$: C, 68.12; H, 6.27; N, 5.12. Found: C, 68.24; H, 6.30; N, 5.10.

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