Displacement of Sugar Chlorosulphates by Bromide, Azide, and Acetate; a Convenient Synthesis of Methyl 3,6-Dideoxy-β-D-*ribo*-hexopyranoside [1]

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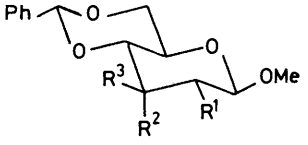
The displacement of chlorosulphate esters by a nucleophile other than chloride is demonstrated by the synthesis of methyl 4,6-*O*-benzylidene-3-bromo-3-deoxy-β-D-allopyranoside from methyl 4,6-*O*-benzylidene-β-D-glucopyranoside 2,3-bischlorosulphate. This reaction is used as the basis for a convenient and efficient synthesis of methyl 3,6-dideoxy-β-D-*ribo*-hexopyranoside (paratose). Displacement of primary and secondary chlorosulphate groups has also been achieved with bromide and azide, and in one case by acetate. The reactions proceed with inversion of configuration and in some instances require the use of aprotic solvents or crown ethers.

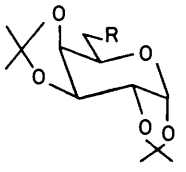
THE potential of chlorosulphate esters as intermediates leading to chloro-deoxy-sugars was established by Jennings and Jones.[2-4] A feature of this work was the ease with which the transformations were achieved. Although generally stable and highly crystalline, sugar per(chlorosulphate) esters were not isolated but allowed to react above −30 °C with chloride ion generated during the esterification. At temperatures above 0 °C displacement of secondary esters by chloride occurs at those centres possessing the appropriate stereochemistry.[4,5] Chloro-deoxy-sugars generated under these conditions have been utilised for further nucleophilic substitution, thus providing products, with retained configuration,[6] or valuable deoxy-sugars after either selective [6,7] or complete reduction.[8-10]

Despite the fact that sugar chlorosulphates may be isolated as stable crystalline compounds, few attempts have been made to employ nucleophiles other than chloride for displacement of this reactive leaving group. In those cases where this has been attempted [11,12] limited success has ensued. In the expectation that chlorosulphate esters should be prone to displacement by strong nucleophiles such as bromide, various chlorosulphate esters were treated with tetraethylammonium bromide. Azide and acetate were used in related reactions. After this work was completed, a report of crown-ether-mediated azide displacement of chlorosulphates appeared.[13]

Chlorosulphation of methyl 4,6-*O*-benzylidene-β-D-glucopyranoside (1) under controlled conditions gave crystalline 2,3 bischlorosulphate (2) in 77% yield. Reaction of the diester (2) with tetraethylammonium bromide in chloroform yielded crystalline methyl 4,6-*O*-benzylidene-3-bromo-3-deoxy-β-D-allopyranoside 2-chlorosulphate (3) in 84% yield. In the presence of 2 mol. equiv. of bromide ion in chloroform solution, (2) gives the bromo-derivative (3) in 3 h; however, in dimethylformamide (DMF) reaction is complete within 5 and 30 min at 20 and 0 °C, respectively. In DMF formation of the 3-bromo-3-deoxy-allopyranoside (3) is accompanied by cyclic 2,3-sulphate formation. This side reaction, which is known to occur under mildly basic conditions,[3] was not minimised by removal of amine impurities from the solvent. It appears that DMF is sufficiently basic to catalyse the hydrolysis and intramolecular cyclisation of chlorosulphate esters.

The product (3) of bromide attack on the bischlorosulphate (2) was expected [1,3] to possess the *allo*-configuration and this was firmly established by ^{1}H n.m.r. Methyl 4,6-*O*-benzylidene-3-bromo-3-deoxy-β-D-allopyranoside (4) and its chlorosulphated precursor (3) gave spectra at 220 MHz that were amenable to first-order analysis. Assignments were confirmed by spin-decoupling and establish that H-3 is weakly coupled to H-2 and H-4 ($J_{2,3} \approx J_{3,4} = 3.5$ Hz), thus confirming the *gluco* to *allo* inversion. The ease with which this displacement was achieved prompted investigation of the displacement with other nucleophiles. Acetate and azide as the tetraethylammonium and sodium salts did not react with the bischlorosulphate (2) in chloroform, and in DMF cyclic 2,3-sulphate formation predominated. However, in acetonitrile in the presence of dicyclohexano-18-crown-6 the respective potassium salts reacted with the 2,3-bischlorosulphate (2) to give the 3-*O*-acetyl- and 3-azido-3-deoxy-allopyranoside derivatives (6) and (7). Proton n.m.r. established the *allo*-configuration for the 3-*O*-acetyl-pyranoside (6), but for the azido derivative (7) the inversion of configuration was assumed since the H-3 resonance could not be clearly identified. However, the specific rotation was consistent with the assigned structure. Substantial amounts (20—30%) of cyclic 2,3-sulphate accompanied the low yields of acetate (6) (24%) and azide (7) (30%) and presumably result from the basic nature of the acetate and azide nucleophiles.





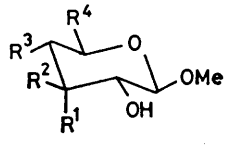
(1) $R^1 = R^3 = OH$, $R^2 = H$
(2) $R^1 = R^3 = OSO_2Cl$, $R^2 = H$
(3) $R^1 = OSO_2Cl$, $R^2 = Br$, $R^3 = H$
(4) $R^1 = OH$, $R^2 = Br$, $R^3 = H$
(5) $R^1 = OH$, $R^2 = R^3 = H$
(6) $R^1 = OSO_2Cl$, $R^2 = OAc$, $R^3 = H$
(7) $R^1 = OSO_2N_3$, $R^2 = N_3$, $R^3 = H$

(8) R = OH
(9) R = OSO_2Cl
(10) R = Br
(11) R = N_3

The utility of chlorosulphates for similar reactions

leading to bromo-deoxy-derivatives and azido-deoxy-derivatives in pyranose systems other than the gluco-pyranoside bischlorosulphate (2) was investigated. Chlorosulphation of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (8) provided the mono-chlorosulphate (9), an unstable syrup at 20 °C. Reaction of the chloro-sulphate (9) with bromide in chloroform gave only decomposition products. In DMF reaction with tetra-ethylammonium bromide proceeded over 2 days to give the 6-bromo-6-deoxy-galactopyranose (10) in 45% yield. Similarly sodium azide in DMF reacted with (9) to give the 6-azido-6-deoxy-derivative (11).[13] However in both instances the hydrolysis product, 1,2:3,4-di-*O*-isopropyl-idene-α-D-galactopyranose (8) (at least 30% yield) accompanied the products of substitution. Methyl α- and β-D-hexopyranoside 2,3,4,6-tetrakischlorosulphates possessing the *gluco-*, *galacto-*, and *manno*-configurations, were also treated with tetraethylammonium bromide in chloroform and in DMF. Although formation of bromo-deoxy-derivatives (as judged by t.l.c. and ^{13}C n.m.r. of crude products) occurred, de-chlorosulphated side-products made isolation tedious and inefficient.

The ease with which the 3-bromo-allose derivative (3) can be prepared from methyl β-D-glucopyranoside provides an attractive and simplified route to the 3,6-dideoxy-sugar, paratose. This procedure is well suited to large-scale reactions which provide 10—20 g quantities of methyl 3,6-dideoxy-β-D-*ribo*-hexopyranoside (15), in which form the derivatisation for subsequent α-glycoside synthesis is most conveniently achieved.[14,15] Two alternatives are available: either the 3-bromo-allopyranoside (4) is converted into the 3,6-dibromo-allopyranoside (13), or the 3-deoxy-*ribo*-hexopyranoside (5) is prepared from (4) and treated with *N*-bromo-succinimide to give the 6-bromo-derivative (12) as previously described.[9] Reduction of the bromo-sugar (12) or (13) with palladium on charcoal gives the dideoxy sugar as its 4-benzoate (14). De-*O*-benzoylation pro-



(12) $R^1 = R^2 = H$, $R^3 = OBz$, $R^4 = CH_2Br$

(13) $R^1 = Br$, $R^2 = H$, $R^3 = OBz$, $R^4 = CH_2Br$

(14) $R^1 = R^2 = H$, $R^3 = OBz$, $R^4 = Me$

(15) $R^1 = R^2 = H$, $R^3 = OH$, $R^4 = Me$

vides crystalline methyl 3,6-dideoxy-β-D-*ribo*-hexopyranoside (15). Recent syntheses of paratose as the free aldose [16] and also as the terminal sugar in a disaccharide [17] have been reported.

The mechanism of chlorosulphate displacement was originally recognised [4] as a typical S_N2 reaction of sulphonate esters involving carbon–oxygen bond fission. However, an intramolecular attack of chloride akin to an S_Ni mechanism has been suggested more recently.[12] The observations reported here are not consistent with a mechanism of this type. The conversion of the glucopyranoside (2) into the allopyranoside (3) by nucleophilic attack of bromide immediately rules out an S_Ni mechanism. The available evidence suggests that chlorosulphate displacement proceeds *via* an S_N2 mechanism as originally proposed.[4]

The use of nucleophiles other than chloride to displace chlorosulphate esters has been shown here to be an effective synthetic process in limited circumstances. The use of crown ethers demonstrated here and by Naidoo and Paralis [13] can improve yields by avoiding solvents such as DMF, which promote side reactions. A particularly convenient displacement to yield 3-bromo-3-deoxy-allose derivatives is the most notable success to date, allowing efficient and rapid synthesis of paratose. Crystals of the glycoside (15) obtained in this way have provided the first *X*-ray crystal structure for this class of sugars.[18] We have also found that chlorosulphate esters of 2-amino-2-deoxy-hexoses are conveniently prepared when the amino group is protected in a phthal-imido function. In such derivatives displacement by bromide ion can provide access to bromo-deoxy-amino-sugars.[19]

EXPERIMENTAL

T.l.c. was performed with Merck precoated silica gel 60 F-254 plates; compounds were detected by quenching of u.v. fluorescence and by charring after spraying with 5% sulphuric acid in ethanol. Merck silica gel G60 (70—230 mesh) and redistilled solvents were used for column chromatography. Identical but more rapid separations were achieved with a Waters Prep 500 high-pressure liquid chromatograph. Skellysolve B refers to hexane supplied by Getty Refining and Marketing Company, Tulsa, Oklahoma. Palladium (10% on charcoal) was purchased from Engelhard Industries, Newark, New Jersey. Solvents were purified and dried according to standard procedures.[20] Processed solutions were dried over anhydrous sodium sulphate and solvent removal was achieved at bath temperatures of 40 °C or lower unless otherwise stated. M.p.s were determined with a Fisher–Johns apparatus. Optical rotations were measured at 589 nm in a 1-dm cell at 20—23 °C. Carbon-13 and ^1H n.m.r. spectra were recorded at 20 and 79.9 MHz, respectively, in the pulsed Fourier-transform mode on a Varian CFT-20 spectrometer. Proton chemical shifts are expressed relative to 1% tetramethylsilane (TMS) for deuteriochloroform and relative to sodium 3-trimethylsilyl[2,2,3,3-$^2H_4$]propionate for deuterium oxide solutions. Carbon-13 shifts are expressed relative to internal TMS for deuteriochloroform solutions and to external TMS for deuterium oxide solutions. Proton spectra recorded at 220 MHz were obtained from the University of Toronto N.M.R. Centre. Assignments of ^{13}C resonances are tentative.

Methyl 4,6-O-*Benzylidene*-β-D-*glucopyranoside* (1).—Methyl β-D-glucopyranoside (100 g, 0.52 mol) was added in several portions to a solution of αα-dimethoxytoluene (110 ml, 0.72 mol) in dry acetonitrile (800 ml) containing toluene-*p*-sulphonic acid (800 mg). The suspension was vigorously stirred and warmed briefly to 50 °C. The methyl glycoside dissolved after *ca.* 10 min, and almost immediately crystals of (1) began to form. The suspension was stirred

for 18 h, then cooled to 4 °C for 5 h and the crystals (122.8 g) were collected (yields 79—84%), m.p. 196.5—198°, $[\alpha]_D$ −79.4° (*c* 1.0, methanol) {lit.,[21] m.p. 205°, $[\alpha]_D$ −75° (methanol)}.

Methyl 4,6-O-*Benzylidene*-β-D-*glucopyranoside* 2,3-*Bischlorosulphate* (2).—Methyl 4,6-*O*-benzylidene-β-D-glucopyranoside (1) (53.6 g, 190 mmol) was dissolved in dry pyridine (38 ml) and absolute chloroform (380 ml). The solution was stirred, and cooled to −70 °C in acetone–solid CO_2. Sulphuryl chloride (38 ml, 470 mmol) was then added dropwise over 30 min. After 4 h the mixture was allowed to warm to −10 °C and poured into 10% sulphuric acid (500 ml). Extraction of the precipitated oil with chloroform (400 ml) followed by washings with 5% potassium hydrogencarbonate and water gave a crystalline mass (90 g) after processing in the usual manner. Recrystallisation from ethyl acetate–Skellysolve B or chloroform–Skellysolve B gave *crystals* (70.5 g, 77%), m.p. 114—116° (decomp.), $[\alpha]_D$ −81.7° (*c* 1.6, $CHCl_3$), δ($CDCl_3$) 3.25—3.65 (4 H, m, H-5, OCH_3), 3.84 (1 H, t, $J_{5,6a} \approx J_{6e,6a}$ = 10.0 Hz, H-6a), 3.88 (1 H, t, $J_{3,4} \approx J_{4,5}$ = 9.0 Hz, H-4), 4.43 (1 H, q, $J_{5,6e}$ 4.4, $J_{6e,6a}$ 10.0 Hz, H-6e), 4.60 (1 H, d, $J_{1,2}$ 7.3 Hz, H-1), 4.84 (1 H, q, $J_{1,2}$ 7.3, $J_{2,3}$ 8.8 Hz, H-2), 5.18 (1 H, t, $J_{2,3} \approx J_{3,4}$ = 8.8 Hz, H-3), 5.59 (1 H, s, PhC*H*), and 7.30—7.55 (5 H, m, aromatic) (Found: C, 35.2; H, 3.35; Cl, 14.95; S, 13.5. $C_{14}H_{16}Cl_2O_{10}S_2$ requires C, 35.1; H, 3.35; Cl, 14.8; S, 13.3%).

Methyl 4,6-O-*Benzylidene*-3-*bromo*-3-*deoxy*-β-D-*allopyranoside* 2-*Chlorosulphate* (3).—Tetraethylammonium bromide (45 g, 213 mmol) was added to a stirred suspension of the bischlorosulphate (2) (40.9 g, 85.4 mmol) in dry absolute chloroform (600 ml). Dissolution of both compounds ensued rapidly, accompanied by a yellow colouration. The reaction was monitored by t.l.c. in Skellysolve B–ethyl acetate (2 : 1) until no starting material remained (2—3 h for the molar ratio used). The chloroform solution was extracted with 5% potassium hydrogencarbonate solution to remove liberated acid, and finally with water. Concentration of the processed solution gave a syrup (31.8 g) that crystallised spontaneously. The *crystals* (31.6 g, 84%) were collected by washing with ethyl acetate–Skellysolve B. Recrystallisation from ethyl acetate–Skellysolve B failed to raise the m.p. [103—104° (decomp.)]; $[\alpha]_D$ −83.3° (*c* 1.5, $CHCl_3$), δ($CDCl_3$) 3.58 (3 H, s, OCH_3), 3.70 (1 H, dd, $J_{3,4}$ 3.0, $J_{4,5}$ 8.9 Hz, H-4), 3.83 (1 H, t, $J_{6a,6e} \approx J_{5,6a}$ = 9.8 Hz, H-6a), 4.14 (1 H, m, H-5), 4.42 (1 H, dd, $J_{5,6e}$ 5.7, $J_{6a,6e}$ 9.8 Hz, H-6e), 4.68 (1 H, dd, $J_{2,3}$ 3.5, $J_{1,2}$ 7.6 Hz, H-2), 4.92 (1 H, d, $J_{1,2}$ 7.6 Hz, H-1), 5.02 (1 H, t, $J_{2,3} \approx J_{3,4}$ = 3.5 Hz, H-3), 5.64 (1 H, s, PhC*H*), and 7.32—7.68 (5 H, m, aromatic) (Found: C, 37.7; H, 3.75; Br, 18.05; Cl, 8.0; S, 7.1. $C_{14}H_{16}BrClO_7S$ requires C, 37.9; H, 3.65; Br, 18.0; Cl, 8.0; S, 7.25%).

Methyl 4,6-O-*Benzylidene*-3-*bromo*-3-*deoxy*-β-D-*allopyranoside* (4).—The chlorosulphate (3) (19.9 g) was dissolved in methanol (400 ml) and a catalytic amount of potassium iodide (200 mg) in methanol (5 ml) was added to the stirred solution in the presence of solid potassium hydrogencarbonate (30 g) and water (5 ml). After 15 min the dechlorosulphation was complete and the solution was filtered and evaporated. The resulting syrup was dissolved in ethyl acetate and washed with water. After concentration of the processed solution the syrup (15.5 g) was crystallised from ethyl acetate–Skellysolve B. The *crystals* (13.1 g, 85%) had m.p. 97—99°, $[\alpha]_D$ −23.0° (*c* 1.5, $CHCl_3$), δ($CDCl_3$) 3.54—3.61 (4 H, m, OCH_3, H-2), 3.66 (1 H, dd, $J_{3,4}$ 3.1, $J_{4,5}$ 9.0 Hz, H-4), 4.03 (1 H, t, $J_{6a,6e} \approx J_{5,6a}$ = 10.0 Hz, H-6a), 4.09 (1 H, m, H-5), 4.39 (1 H, dd, $J_{5,6e}$ 4.7, $J_{6e,6a}$ 10.0 Hz, H-6e), 4.67 (1 H, d, $J_{1,2}$ 7.0 Hz, H-1), 4.80 (1 H, t, $J_{2,3} \approx J_{3,4}$ = 3.5 Hz, H-3), 5.61 (1 H, s, PhC*H*), and 7.52—7.64 (5 H, m, aromatic) (Found: C, 49.05; H, 5.0; Br, 23.3. $C_{14}H_{17}BrO_5$ requires C, 48.7; H, 4.95; Br, 23.15%).

Methyl 4,6-O-*Benzylidene*-3-*deoxy*-β-D-ribo-*hexopyranoside* (5).—A solution of the bromo-sugar (4) (5 g) in ethanol (120 ml) was hydrogenated for 8 h at atmospheric pressure in the presence of solid potassium hydrogencarbonate (2 g) and palladium–charcoal (700 mg). The mixture was filtered, the filtrate was concentrated, and the residue was dissolved in ethyl acetate (150 ml) and extracted with water. The processed solution yielded crystals (3 g, 78%) from ether–Skellysolve B, m.p. 173—174.5°, $[\alpha]_D$ −61.5° (*c* 1.2, $CHCl_3$) {lit.,[9] m.p. 174°, $[\alpha]_D$ −61° (chloroform)}.

Alternatively sodium hydroxide was used as base. A solution of (4) (12 g, 348 mmol) in 75% ethanol solution (200 ml) containing 40 ml of 1M-sodium hydroxide was hydrogenated over palladium–charcoal (1 g). Uptake of hydrogen (800 ml) ceased after 15 min, and work-up as described above gave recrystallised *product* (8 g, 86%), m.p. 173—174°, δ($CDCl_3$) 1.74 (1 H, q, $J_{2,3a} \approx J_{3a,4} \approx J_{3e,3a}$ = 11.6 Hz, H-3a), 2.45 (1 H, dt, $J_{2,3e} \approx J_{3e,4}$ = 4.5 Hz, H-3e), 3.40—3.90 (7 H, m, OCH_3, H-4, H-5, H-2, H-6a), 4.20—4.43 (1 H, m, H-65), 4.25 (1 H, d, $J_{1,2}$ 7.6 Hz, H-1), 5.52 (1 H, s, PhC*H*), and 7.25—7.57 (5 H, m, aromatic).

Methyl 3-O-*Acetyl*-4,6-O-*benzylidene*-β-D-*allopyranoside* 2-*Chlorosulphate* (6).—Anhydrous potassium acetate (4 g, 50 mmol) was stirred in dry acetonitrile (20 ml) with dicyclohexano-18-crown-6 (0.7 g) for 1 h. The bischlorosulphate (2) (4.78 g, 10 mmol) was added to this stirred solution and after 3 h the solution was poured into dichloromethane (150 ml) and washed with 5% potassium hydrogencarbonate (50 ml) and water. Concentration of the processed solution gave 4 g of crude material which was applied to 250 g of silica gel. Elution with Skellysolve B–ethyl acetate (3 : 1) gave two fractions. The title compound (1 g, 24%) was eluted first, followed by the cyclic 2,3-sulphate (0.8 g, 23%). The 3-*acetate* (6), recrystallised from ethyl acetate–Skellysolve B (yield 600 mg), had m.p. 95—97°, $[\alpha]$ −93.9° (*c* 1.2, $CHCl_3$), δ($CDCl_3$) 2.08 (3 H, s, CH_3CO), 3.40—4.83 (6 H, m, H-1, H-2, H-4, H-5, H-6), 3.50 (3 H, s, OCH_3), 5.43 (1 H, s, PhC*H*), 5.98 (1 H, t, $J_{2,3} \approx J_{3,4}$ = 2.4 Hz, H-3), and 7.18—7.38br (5 H, s, aromatic), δ_C($CDCl_3$) 169.0 (C=O), 136.6, 129.2, 128.3, and 125.0 (aromatic), 101.6 (PhCH), 99.1 (C-1), 81.1 (C-4) 76.5 (C-2), 68.8 (C-6), 67.6 (C-3), 64.2 (C-5), 57.7 (OCH_3), and 20.7 (CH_3CO) (Found: C, 45.25; H, 4.6; Cl, 8.5; S, 7.45. $C_{16}H_{19}ClO_9S$ requires C, 45.45; H, 4.55; Cl, 8.35; S, 7.6%).

Methyl 3-*Azido*-4,6-O-*benzylidene*-3-*deoxy*-β-D-*allopyranoside* 2-*Azidosulphate* (7).—Potassium azide (7 g, 86 mmol) was stirred in dry acetonitrile (100 ml) with dicyclohexano-18-crown-6 (1 g) for 1 h. The bischlorosulphate (2) (7 g, 14.6 mmol) was added and the solution was stirred for 18 h at room temperature, then worked up as for compound (6) to yield crude syrup (6.9 g). This was chromatographed on silica gel (300 g); elution with Skellysolve B–ethyl acetate (3 : 1) gave pure 3-*azido*-*allopyranoside* (7) (1.8 g, 30%), m.p. 119—121° (from ethanol–Skellysolve B), $[\alpha]_D$ −143.3° (*c* 1.1, $CHCl_3$), δ_H($CDCl_3$) 3.59 (3 H, s, OCH_3), 3.68—4.21 (3 H, m, H-5, H-4, H-6a), 4.21—5.63 (3 H, m, H-2, H-3, H-6e), 4.74 (1 H, d, $J_{1,2}$ 7.5 Hz, H-1), 5.53 (1 H, s, PhC*H*), and 7.25—7.51 (5 H, m, aromatic), δ_C($CDCl_3$) 136.6, 129.5,

128.5, and 126.2 (aromatic), 102.0 (PhCH), 98.7 (C-1), 79.6 (C-4), 77.5 (C-2), 68.6 (C-6), 64.1 (C-5), 60.9 (C-3), and 57.7 (OCH_3) (Found: C, 40.7; H, 4.0; N, 20.7; S, 8.4. $C_{14}H_{16}N_6O_7S$ requires C, 40.8; H, 3.9; N, 20.4; S, 7.8%).

1,2:3,4-*Di*-O-*isopropylidene*-α-D-*galactopyranose* 6-*Chlorosulphate* (9).—Di-*O*-isopropylidenegalactose (8) (40 g) in chloroform (200 ml) containing dry pyridine (20 ml) was cooled to −70 °C. Sulphuryl chloride (16 ml) was added dropwise and after 2 h at −70 °C, the mixture was poured into 0.2M-sulphuric acid (300 ml). Chloroform (200 ml) was added and the organic phase was extracted with 5% potassium hydrogencarbonate and water. T.l.c. in Skellysolve B–ethyl acetate (2 : 1) indicated a homogeneous product. However concentration provided a semicrystalline mass which was unstable at room temperature and resisted attempts at recrystallisation. Carbon-13 n.m.r. indicated the syrup to be substantially >95% pure: $\delta(CDCl_3)$ 110.1 and 109.18 (acetal), 96.2 (C-1), 74.7 (C-4), 70.7, and 70.6 (C-2, C-3), 70.3 (C-6), 65.6 (C-5), and 26.0, 25.9, 24.9, and 24.2 (CH_3–C).

At 0 °C the compound rapidly darkens to a black residue. During this period substantial amounts of 6-chloro-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose are formed.

6-*Bromo*-6-*deoxy*-1,2:3,4-di-O-*isopropylidene*-α-D-*galactopyranose* (10).—The 6-chlorosulphate (9) (7.4 g) was dissolved in DMF (50 ml; dried with activated silica gel) containing 5 ml of chloroform and stirred with tetraethylammonium bromide (8.9 g) for 2 days at 20 °C. The solution was poured into water and the mixture was extracted (3 ×) with chloroform. The combined extracts were dried and concentrated to a syrup (6.2 g). The material was purified by preparative high-pressure liquid chromatography on a Waters LC 500 machine (solvent Skellysolve B–ethyl acetate, 2 : 1). A homogeneous syrup (3 g) of *compound* (10) was obtained which was recrystallised from methanol (30% yield), m.p. 52—53.5°, $[\alpha]_D$ −58.9° (*c* 1.15, $CHCl_3$), $\delta_H(CHCl_3)$ 1.34 [6 H, s, $(CH_3)_2C$], 1.43 [3 H, s, $(CH_3)_2C$], 1.53 [3 H, s, $(CH_3)_2C$], 3.35—3.66 (2 H, m, H-6), 3.97 (1 H, m, H-5), 4.33 (2 H, m, H-2, H-4), 4.63 (1 H, dd, $J_{2,3}$ 2.4, $J_{3,4}$ 7.8 Hz, H-3), and 5.53 (1 H, d, $J_{1,2}$ 5.0 Hz, H-1), $\delta_C(CDCl_3)$ 109.6 and 108.9 (acetal), 96.6 (C-1), 71.1, 71.0, and 70.6 (C-2, C-3, C-4), 68.5 (C-5), 29.7 (C-6), and 26.0, 24.9, and 24.50 (CH_3C) (Found: C, 44.8; H, 6.0; Br, 24.4. $C_{12}H_{19}BrO_5$ requires C, 44.6; H, 5.95; Br, 24.7%). Also isolated was the 1,2:3,4-di-*O*-isopropylidenegalactopyranose (8) (2 g).

6-*Azido*-6-*deoxy*-1,2:3,4-*di*-O-*isopropylidene*-α-D-*galactopyranose* (11).—The 6-chlorosulphate (9) (7.2 g) was dissolved in DMF and sodium azide (3.6 g) was added with stirring. After 3 days at 20 °C the mixture was worked up as for compound (10). Crude syrup (4.7 g) was applied to a preparative high-pressure chromatograph and 1,2:3,4-di-*O*-isopropylidenegalactopyranose (8) (2 g) was isolated, together with two components (2.5 g) with similar mobilities. Re-chromatography gave pure (11) (1.5 g), which resisted attempts at recrystallisation. The homogeneous *syrup* (11) (26%) had $[\alpha]_D$ −96.9° (*c* 1.1, $CHCl_3$) (*cf.* ref. 13), $\delta_H(CDCl_3)$ 1.30 [6 H, s, $(CH_3)_2C$], 1.41 [3 H, s, $(CH_3)_2C$], 1.51 [3 H, s, $(CH_3)_2C$], 3.39 (2 H, m, H-6), 3.85 (1 H, m, H-5), 4.15 (1 H, q, $J_{3,4}$ 7.8, $J_{4,5}$ 1.8 Hz, H-4), 4.29 (1 H, q, $J_{1,2}$ 5.0, $J_{2,3}$ 2.4 Hz, H-2), 4.59 (1 H, q, $J_{2,3}$ 2.4, $J_{3,4}$ 7.8 Hz, H-3), and 5.50 (1 H, d, $J_{1,2}$ 5.0 Hz, H-1), $\delta_C(CDCl_3)$ 109.4 and 108.5 (acetal), 96.2 (C-1), 71.1, 70.7, and 70.3 (C-2, C-3, C-4), 66.9 (C-5), 50.5 (C-6), and 25.8, 24.7, and 24.2 (CH_3-C) (Found: C, 50.45; H, 6.8; N, 14.5. $C_{12}H_{19}N_3O_5$ requires C, 50.5; H, 6.7; N, 14.75%).

Methyl 4-O-*Benzoyl*-6-*bromo*-3,6-*dideoxy*-β-D-ribo-*hexopyranoside* (12).—The 3-deoxy-*ribo*-hexopyranoside (5) (8.3 g) was refluxed with *N*-bromosuccinimide (NBS) (6.9 g) in carbon tetrachloride (215 ml) for 30 min. The solution was filtered hot and concentrated to a syrup, which was dissolved in ether (500 ml) and washed twice with water (50 ml). The syrup (9.1 g) obtained on concentration from the dried ether solution was crystallised from ether–Skellysolve B to give the 6-*bromo-derivative* (12) (5 g), m.p. 96.5—98.0°, $[\alpha]_D$ +11.4° (*c* 1.02, $CHCl_3$), $\delta_H(CDCl_3)$ 1.68 (1 H, q $J_{2,3a} \approx J_{3a,4} \approx J_{3e,3a} = 11.3$ Hz, H-3a), 2.59 (1 H, dt, $J_{2,3e} \approx J_{3e,4} = 5.0$, $J_{3e,3a} = 12.3$ Hz, H-3e), 3.35—4.00 (7 H, m, OCH_3, H-2, H-5, H-6), 4.27 (1 H, d, $J_{1,2}$ 7.5 Hz, H-1), 4.94 (1 H, octet, H-4), and 7.45—8.07 (5 H, m, aromatic) (Found: C, 48.7; H, 4.8; Br, 23.45. $C_{14}H_{17}BrO_5$ requires C, 48.7; H, 4.95; Br, 23.15%).

Methyl 4-O-*Benzoyl*-3,6-*dideoxy*-β-D-ribo-*hexopyranoside* (14).—(A) *From* (12). The 6-bromo-*ribo*-hexopyranoside (12) (8 g) was dissolved in ethanol (200 ml) and palladium–charcoal (1 g) was added. Solid potassium hydrogencarbonate (2 g) was added to the vigorously stirred suspension, which was then hydrogenated at atmospheric pressure for 18 h. Filtration and concentration gave a syrup which was taken up in ethyl acetate (300 ml) and washed with water. The crude product from the organic phase was purified on a silica gel column (300 g) by elution with Skellysolve B–ethyl acetate (1 : 1). The product crystallised spontaneously after concentration but resisted recrystallisation. The purified material had $[\alpha]_D$ +2.1° (*c* 1.0, $CHCl_3$), δ_H 1.28 (3 H, d, $J_{5,6}$ 6.3 Hz, H-6), 1.64 (1 H, q, $J_{2,3a} \approx J_{3a,4} \approx J_{3e,3a} = 11.6$ Hz, H-3a), 2.56 (1 H, d, t, $J_{2,3e} \approx J_{3e,4} = 4.7$, $J_{3e,3a}$ 12.2 Hz, H-3e), 3.56 (3 H, s, OCH_3), 3.44—3.70 (2 H, m, H-2, H-5), 4.20 (1 H, d, $J_{1,2}$ 7.4 Hz, H-1), 4.78 (1 H, m, H-4), and 7.23—8.01 (5 H, m, aromatic), $\delta_C(CDCl_3)$ 133.2, 129.8, 129.6, and 128.4 (aromatic), 105.9 (C-1), 73.5 (C-5), 72.2 (C-4), 68.3 (C-2), 56.8 (OCH_3), 35.4 (C-3), and 17.7 (C-6).

(B) via *Dibromo-allopyranose* (13). Methyl 4,6-*O*-benzylidene-3-bromo-3-deoxy-β-D-allopyranoside (4) (5.2 g, 15 mmol) in dry carbon tetrachloride (150 ml) was refluxed with NBS (3.6 g, 20 mmol) in the presence of barium carbonate (2.9 g). After 20 min the orange-red colour changed to a faint yellow and t.l.c. confirmed the completion of the reaction. The mixture was filtered hot and concentrated. The syrup, dissolved in ether (300 ml), was washed twice with water and dried. Concentration provided methyl 4-*O*-benzoyl 3,6-dibromo-3,6-dideoxy-β-D-allopyranoside (13) (6 g) as a syrup which was not purified but was hydrogenated immediately. The syrup was dissolved in ethanol containing 15 ml of 1M-sodium hydroxide and hydrogenated at 505 kPa over palladium–charcoal (2.0 g). After 18 h the solution was filtered and concentrated. The solid residue was partitioned between water (50 ml) and ethyl acetate (200 ml). The organic phase was washed with water (50 ml) and dried. Concentration gave a residue (3.8 g) which, after chromatography on silica gel (300 g) with ethyl acetate–Skellysolve B, gave the title *compound* (3.1 g, 77%). The syrup crystallised spontaneously but resisted attempts to recrystallise; $[\alpha]_D$ +2.2° (*c* 2.1, $CHCl_3$) (Found: C, 62.95; H, 6.6. $C_{14}H_{18}O_5$ requires, C. 63.15; H, 6.75%).

Methyl 3,6-*Dideoxy*-β-D-ribo-*hexopyranoside* (15).—The 4-benzoate (14) (8.6 g) was dissolved in dry methanol (200 ml) and a freshly prepared solution of sodium methoxide

[from sodium (50 mg)] in methanol (10 ml) was added. After 18 h at room temperature the solution was stirred with Rexyn (H^+) resin until neutral. Filtration and concentration gave a syrup which was chromatographed on silica gel (450 g) (solvent ethyl acetate–methanol–water, 85 : 10 : 5). The pure syrup (4.5 g, 86%) was crystallised from ethyl acetate–Skellysolve B; $[\alpha]_D$ −64° (*c* 1.0, H_2O), m.p. 51—53°, $\delta_H(D_2O)$ 1.26 (3 H, d, $J_{5,6}$ 6.0 Hz, H-6), 1.42 (1 H, q, $J_{2,3a} \approx J_{3a,4} = 10.5$, $J_{3e,3a}$ 11.8 Hz, H-3a), 2.36 (1 H, dt, $J_{2,3e} \approx J_{3e,4} = 3.7$, $J_{3e,3a}$ 11.8 Hz, H-3e), and 4.26 (1 H, d, $J_{1,2}$ 8.7 Hz, H-1), $\delta_C(D_2O)$ 106.6 (C-1), 77.0 (C-5), 71.0 (C-4), 69.2 (C-2), 58.2 (OCH_3), 39.6 (C-3), and 18.0 (C-6).

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