A Stereospecific Synthesis of (+)-Muscarine

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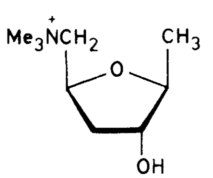
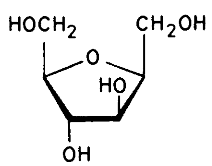
A stereospecific synthesis of (+)-muscarine (1) is described in which acid-catalysed cyclisation of D-mannitol gives 2,5-anhydro-D-glucitol, isolated as its 1,3-*O*-isopropylidene-4,6-dibenzoate (3); acid hydrolysis then tosylation gives the 1,3-di-*O*-tosyl derivative (7), converted by sodium methoxide–methanol into 2,5:3,4-dianhydro-1-tosyl-D-allitol (8). This epoxide with sodium bis-(2-methoxyethoxy)aluminium hydride gives 2,5-anhydro-1,4-dideoxy-D-*ribo*-hexitol (10) and its 1,3-dideoxy-isomer (11) (12:1). The former, with tosyl chloride then trimethylamine gives (+)-muscarine tosylate, also isolated as chloride and bromide salts.

THE toxic principles of mushrooms of the genus *Amanita* have received much study.[1] Of these, (+)-muscarine (1) has been of especial interest in view of its powerful activity as an acetylcholine agonist, an activity which defines the 'muscarinic' receptor sites for the neurotransmitter.[2-4] Many structurally related compounds have also been shown to be cholinomimetic.[3] Earlier syntheses of (+)-muscarine were overall very low yielding, and involved separations of enantiomers or diastereoisomers.[5-8] Our experiments in the synthesis of deoxy-*C*-nucleosides [9] suggested to us that a more direct route from a chiral precursor could be evolved, which would also be sufficiently flexible to permit the easy elaboration of structurally related compounds of possible pharmacological interest. A preliminary account of this work has been published.[10]

The acid-catalysed cyclisation of D-mannitol gives two major products, 2,5-anhydro-D-glucitol (2) (*ca.* 45%) and 1,4:3,6-dianhydro-D-mannitol (*ca.* 41%).[11-13] These are not readily separated, but acetonation [12] then benzoylation gives a mixture of the crystalline derivatives 1,3-*O*-isopropylidene-4,6-di-*O*-benzoyl-2,5-anhydro-D-glucitol (3) and 1,4:3,6-dianhydro-2,5-di-*O*-benzoyl-D-mannitol (4),[14] separable by fractional crystallisation.



(1)



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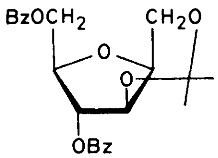

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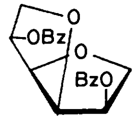


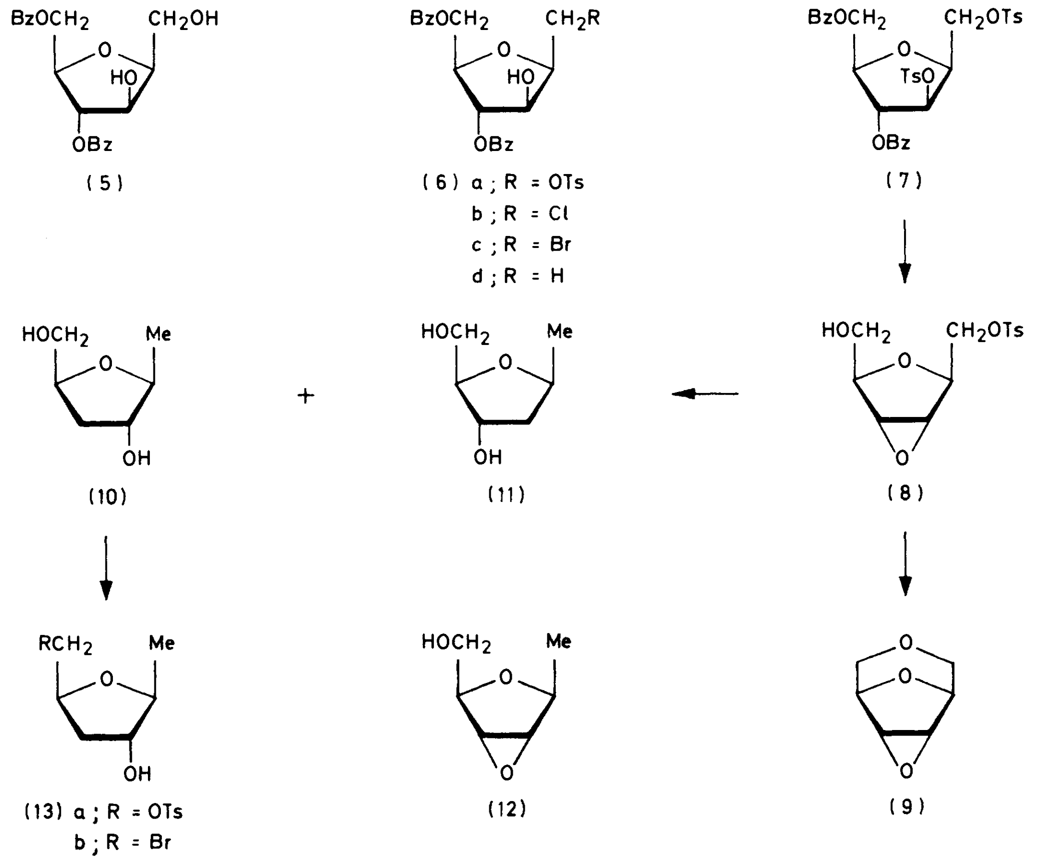
(4)

Alternatively, and more conveniently, mild acidic hydrolysis of the mixture of (3) and (4) removes the isopropylidene group from (3) to give (5), and this is easily isolated from (4). The diol (5) is a convenient precursor of muscarine, since both have the same carbon skeleton and the same chirality at C-2 and C-5. Moreover, the *trans*-3,4-diol system is available for a wide range of transformations. All the hydroxy-groups of (2) are conveniently differentiated in subsequent reactions of the dibenzoate (5).

Tosylation of (5) affords the 1-tosylate (6a) in high yield and, in a more prolonged reaction, the 1,3-ditosylate (7). Careful treatment of the latter with sodium methoxide (1.1 mol equiv.) in methanol gives the epoxide (8). However, if an excess of methoxide is used the crystalline, but volatile, trianhydroallitol (9) is formed. It was the sole product, too, in an experiment directed to the synthesis of a 1-fluoro-compound, in which (8) was treated with dry tetrabutylammonium fluoride in methyl cyanide at room temperature.

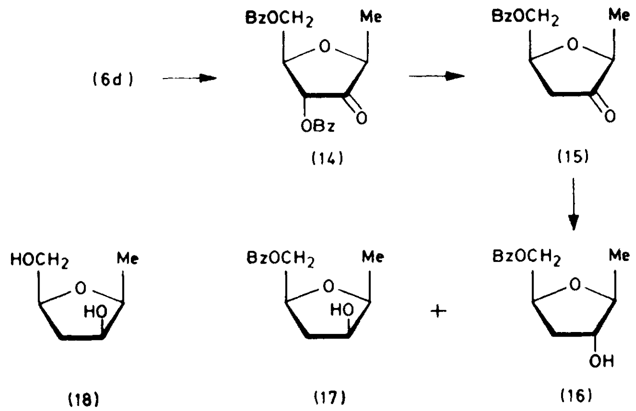
Reduction of the epoxide (8) could lead to ring opening in either of two ways, to give the isomeric deoxy-alcohols (10) and (11). We argued that the presence of a free hydroxy-group at C-6 would assist hydride transfer through the formation of an alkoxyaluminohydride, and models showed that transfer would occur *via* a six-membered ring intermediate preferentially to C-4, to give the 1,4-dideoxy-alcohol (10). This mode of hydride transfer is well documented in carbohydrate and alicyclic chemistry.[15] This view was confirmed when lithium aluminium hydride in tetrahydrofuran was used, and the 4- and 3-isomers (10) and (11) were formed in 3 : 1 ratio (n.m.r.) (compare ref. 16). This product ratio was unaltered when (12) was reduced by lithium aluminium hydride under the same conditions, suggesting that the initial step in the reduction of (8) is the hydride displacement of the tosyloxy-group. Compound (12) itself was obtained from the diol (5), which was selectively monohalogenated with triphenylphosphine and carbon tetrachloride or bromide [17] to give (6b or c), whence reduction with tributylstannane [18] gave (6d). Tosylation followed by treatment with methoxide then led to (12).

When the reduction of (8) was effected with sodium bis-(2-methoxyethoxy)aluminium hydride (Red-al) the ratio of (10) to (11) was increased to 12 : 1, and the muscarine synthesis was completed using this mixture. Monotosylation and silica gel chromatography gave (13a), reaction of which with trimethylamine in methanol gave (+)-muscarine tosylate (1). This was converted by ion-



exchange chromatography into the chloride, identical with that previously isolated.[1,19,20,*] Alternatively, but with lower yield, (10) was converted into the 6-bromo compound (13b), and this with trimethylamine gave (+)-muscarine bromide. The overall yield [30% from (5)] is much greater than in earlier published syntheses.

The regioselectivity in the reduction of the epoxide (8) was high and the major isomer was clearly (10), from its n.m.r. spectrum and because it led to muscarine. Nevertheless a structurally unambiguous synthesis of (10) was carried out by an alternative route. The alcohol (6d) was oxidised by pyridinium chlorochromate[21] in benzene to the ketone (14). The carbonyl function serves two purposes: it activates the neighbouring acyloxy-function for reductive cleavage to introduce the 4-methylene group, and it subsequently allows the inversion of the 3-hydroxy-group to give the *ribo*-configuration. When (14) was treated with zinc and acetic acid the deoxy-ketone (15) was obtained in 40% yield. House and Karlson[22] have shown that reductions with Cr^{II} salts can be more successful for cyclohexanone derivatives with α-acyloxy-functions; when applied to the present problem this approach gave an improved (70%) yield. Reduction of the deoxy-ketone with sodium borohydride then gave the two crystalline epimeric alcohols (16) and (17) in the ratio 3 : 2. The debenzoylation product of (16) had an n.m.r. spectrum identical with that of the product from the epoxide route, thus establishing its identity.



The ^1H n.m.r. spectra of all the compounds described in this paper (Experimental section) are fully in accord with the assigned structures. The n.m.r. spectra of the dideoxy-diols (10), (11), and (18) were similar, but the signals corresponding to the ring methylene protons were sufficiently different to warrant comment. In each compound they revealed an ABMX system consisting of 16 lines. However, the magnetic non-equivalence of the

* The tosylate showed full cholinomimetic activity on guinea pig ileum. We are grateful to Professor A. W. Cuthbert, Department of Pharmacology, Cambridge, for carrying out these assays.

A and B protons was not the same in each case. It was greatest in (18), where one proton is flanked on either side by a hydroxy-group, and this results in a maximum separation of the A and B parts ($\Delta\delta$ 0.58 p.p.m.). In (10) both protons have hydroxy-group neighbours, resulting in a small magnetic non-equivalence ($\Delta\delta$ 0.16). Compound (11) shows an intermediate pattern ($\Delta\delta$ 0.29), as only one proton has a hydroxy-group in a *cis*-relationship to it.

EXPERIMENTAL

Unless otherwise stated, the following methods and equipment were used. Solutions were normally dried over anhydrous $MgSO_4$ and evaporated below 50 °C. M.p.s were determined on a Kofler hot-stage apparatus. T.l.c. and p.l.c. were carried out on Merck plates precoated with silica GF_{254} [solvent CH_2Cl_2–Et_2O (9 : 1)], and Merck Kieselgel 60 (70—230 mesh) was used for column chromatography. G.l.c. was performed using derivatised (*O*-trimethylsilyl) samples on a Perkin-Elmer F11 instrument (6 ft 3% OV-1 column; N_2 at 17.5 lb in^{-2}) at 120 °C. N.m.r. spectra were obtained using Varian EM-360, HA-100, and XL-100 spectrometers with $CDCl_3$ solutions. Optical rotations were taken with a Perkin-Elmer 241 instrument and mass spectra were measured with A.E.I. MS9 and MS12 spectrometers.

*2,5-Anhydro-4,6-di-*O*-benzoyl-1,3-*O*-isopropylidene-*D*-glucitol* (3).—To the desiccated mixture of anhydrides resulting from the acid-catalysed dehydration of D-mannitol (250 g) [11-13] were added dry acetone (1 l), 2,2-dimethoxypropane (250 ml), and 65% perchloric acid (5 ml). After stirring at room temperature for 24 h, the mixture was neutralised with ammonia, passed through a Celite pad, evaporated *in vacuo*, and dried over P_2O_5 and paraffin to give a yellow viscous syrup (200 g). Treatment in pyridine (750 ml) at 0 °C with benzoyl chloride (120 ml), stirring at room temperature for 16 h, and then addition to ice–water (10 l) gave a precipitate. This was washed with water and crystallised from ethanol giving a colourless solid (130 g). T.l.c. showed two products: the *isopropylidene derivative* (3), R_F 0.5, and 1,4:3,6-dianhydro-2,5-di-*O*-benzoyl-D-mannitol (4), R_F 0.39, which was separated by fractional crystallisation (EtOH).

The isopropylidene derivative gave fine needles, m.p. 127—129°, $[\alpha]_D^{20}$ +20° (*c* 2.7, $CHCl_3$) (Found: C, 64.1; H, 6.1. $C_{23}H_{24}O_7,H_2O$ requires C, 64.1; H, 6.2%); *m/z* 413 (M^+ + 1), 412 (M^+), 397 ($M^+ - CH_3$); δ (C_6D_6) 1.10 and 1.37 (each 3 H, s, 2 × CH_3), 3.60 (1 H, m, H-2), 3.63 (1 H, dd, *J* 12 and 2.6 Hz, H_A-1), 3.94 (1 H, dd, *J* 12 and 2.2 Hz, H_B-1), 4.15 (1 H, d, *J* 2.5 Hz, H-3), 4.42 (1 H, ddd, *J* 7.3, 5.5, and 1.65 Hz, H-5), 4.70 (1 H, dd, *J* 11 and 5.5 Hz, H_A-6), 4.83 (1 H, dd, *J* 11 and 7.3 Hz, H_B-6), 5.50 (1 H, m, H-4), and 7.00—8.26 (10 H, m, ArH).

The dianhydride (4) had m.p. 132—133° (lit.,[14] 133°), $[\alpha]_D^{20}$ +226° (*c* 2, $CHCl_3$) (lit.,[14] +226°); *m/z* 354 (M^+); δ 3.99 (2 H, dd, *J* 10 and 6.2 Hz, H_A-1 and H_A-6), 4.13 (2 H, dd, *J* 10 and 6 Hz, H_B-1 and H_B-6), 4.86 (2 H, m, H-3 and -4), 5.33 (2 H, m, H-2 and -5), and 7.32—8.16 (10 H, m, ArH).

*2,5-Anhydro-4,6-di-*O*-benzoyl-*D*-glucitol* (5).—The foregoing mixture of isopropylidene derivative (3) and dianhydride (4) (10 g) in methanol (200 ml) was treated with 1% H_2SO_4 (75 ml) and stirred at 50 °C until t.l.c. showed complete hydrolysis (*ca.* 30 min). The mixture was cooled and the dianhydride removed by filtration. After concentration, the filtrate was extracted with CH_2Cl_2 and the extract washed with aq. $NaHCO_3$ and water, dried, and evaporated. The *dibenzoate* (5) formed an oil (4—5.5 g, 15—20% from D-mannitol), which was used for the next stage without further purification.

A specimen obtained by hydrolysis of the pure isopropylidene derivative (3) had $[\alpha]_D^{20}$ +21° (*c* 3, $CHCl_3$) (Found: C, 64.4; H, 5.4. $C_{20}H_{20}O_7$ requires C, 64.5; H, 5.4%); δ 1.82 (1 H, br, s, CHO*H*), 3.18 (1 H, br, t, exchangeable with D_2O, CH_2OH), 3.96—4.08 (2 H, m, H_2-1), 4.19 (1 H, br, q, *J* 4 Hz, H-2), 4.36 (1 H, m, H-5), 4.50 (1 H, dd, *J* 4 and 2 Hz, H-3), 4.53 (1 H, dd, *J* 11 and 4 Hz, H_A-6), 4.82 (1 H, dd, *J* 11 and 7 Hz, H_B-6), 5.21 (1 H, dd, *J* 4 and 2 Hz, H-4), and 7.30—8.14 (10 H, m, ArH).

*2,5-Anhydro-4,6-di-*O*-benzoyl-1,3-di-*O*-p-tolylsulphonyl-*D*-glucitol* (7).—To a solution of the dibenzoate (5) (5 g, 0.015 mol) in dry pyridine at 5 °C was added tosyl chloride (1.4 g, 0.06 mol) in pure chloroform (15 ml), with the temperature kept below 15 °C. After stirring overnight at room temperature, t.l.c. showed only the monotosyl derivative (R_F 0.47). The treatment was repeated with tosyl chloride (3.0 g) in chloroform (8 ml) three times during 100 h and led to complete tosylation. Water (5 ml) was added dropwise and, after being poured into ice–water (1 l), the product was extracted with dichloromethane (3 × 200 ml). The extract was washed with ice-cold 1.5M-H_2SO_4 and water, and dried. The *1,3-di-*O*-p-tolylsulphonyl* derivative, R_F 0.67, formed needles (7.8 g, 75%) (from EtOH), m.p. 65—69° (Found: .C, 60.4; H, 4.8; S, 9.3. $C_{34}H_{32}O_{11}S_2$ requires C, 60.0; H, 4.7; S, 9.4%); *m/z* 680 (M^+); δ 2.25 and 2.49 (each 3 H, s, $ArCH_3$), 4.1—4.5 (6 H, m), 5.12 and 5.24 (each 1 H, dd, H-3 and -4), and 7.1—7.8 (8 H, m, ArH).

The *1-*O*-p-tolylsulphonyl derivative* (6a) obtained after 12 h reaction formed needles (80%) (EtOH), m.p. 117—118° $[\alpha]_D^{20}$ +25 (*c* 1.4, $CHCl_3$) (Found: C, 61.9; H, 5.1; S, 6.1. $C_{27}H_{26}O_9S$ requires C, 61.6; H, 5.0; S, 6.1%); *m/z* 526 (M^+).

*2,5:3,4-Dianhydro-1-*O*-p-tolylsulphonyl-*D*-allitol* (8).—To a solution of the di-*O*-tosyl derivative (7) (9.0 g, 0.0132 mol) in dry benzene (50 ml) cooled to 0 °C was added freshly prepared sodium methoxide [from sodium (0.335 g, 0.0145 mol) in anhydrous methanol (10 ml)] precooled to 0 °C. After stirring for 3 h the solution was filtered and the filtrate evaporated to a syrup. This was dissolved in dichloromethane; the solution was washed with brine, and evaporated finally at 40 °C and 0.01 Torr. The product was recrystallised from ether to give the *epoxide* (8) as rhomboid crystals (3.9 g, 90%), m.p. 60—61°, $[\alpha]_D^{20}$ −15° (*c* 1.2, EtOH) (Found: C, 51.4; H, 5.3; S, 10.3. $C_{13}H_{16}O_6S$ requires C, 52.0; H, 5.4; S, 10.7%); *m/z* (no M^+) 173, 155, and 115; δ 2.35 (1 H, br, s, OH), 2.44 (3 H, s, $ArCH_3$), 3.66 (2 H, m, H_2-6), 3.72 and 3.77 (each 1 H, d, *J* 3 Hz, H-3 and -4), 4.00—4.40 (4 H, m, H_2-1, H-2 and -5), and 7.36 and 7.80 (each 2 H, d, *J* 8 Hz, ArH).

1,6:2,5:3,4-Trianhydroallitol (9).—To a solution of the epoxide (8) (0.5 g) in dry methyl cyanide (5 ml) was added a solution of dry tetrabutylammonium fluoride (2 g) in dry methyl cyanide (5 ml). The solution was stirred for 3 h at room temperature then poured into water, and the ether layer was washed with water and dried. Solvent was removed by distillation through a long column and the residue was sublimed to give crystals of the *trianhydride*, m.p. 73—75° (Found: M^+ 128. $C_6H_8O_3$ requires *M*, 128); δ 3.7 (6 H, m) and 4.1 (2 H, br, s).

The trianhydride was obtained in good yield when the di-*O*-tosyl derivative (7) was treated with an excess of methanolic sodium methoxide (3 equiv.).

Reduction of the Epoxide (8).—(a) *With lithium aluminium hydride*. To a stirred suspension of the hydride (0.4 g) in dry tetrahydrofuran (20 ml) was added a solution of the epoxide (2.6 g) in the same solvent (20 ml). After refluxing under nitrogen with stirring for 12 h then addition of a little water, the solution was filtered and filtrate and washings were evaporated. A solution of the residue in water was passed through an Amberlite MB-3 column and evaporated to give a syrupy mixture of 2,5-anhydro-1,4-dideoxy-D-*ribo*-hexitol (10) and 2,5-anhydro-1,3-dideoxy-D-*ribo*-hexitol (11) (1.2 g, 100%), in the ratio 3 : 1 (n.m.r.; by comparison with authentic samples).

(b) *With sodium dihydrobis-*(2-*methoxyethoxy*)*aluminate* (*Red-al*). Using the same conditions as above but with a solution of Red-al in toluene (15 ml; *ca.* 70%) as reducing agent, the dideoxy-isomers were obtained as a syrup (1.2 g, 100%) in the ratio 12 : 1 (n.m.r.). This mixture of diols was used in the next stage.

2,5-*Anhydro*-6-*bromo*-1,4-*dideoxy*-D-ribo-*hexitol* (13b).—A solution of the foregoing diol mixture (264 mg), triphenylphosphine (1.048 g), and carbon tetrabromide (662 mg) in dry methyl cyanide (7.5 ml) was refluxed for 3 h under nitrogen. Evaporation gave a syrup, purified by Kugelrohr distillation then p.l.c. The pure 6-*bromo-compound* (150 mg, 40%) had R_F 0.3 (Found: C, 36.8; H, 5.6; Br, 40.0. $C_6H_{11}BrO_2$ requires C, 36.9; H, 5.7; Br, 41.0%); δ 1.21 (1 H, br, s, OH), 3.2—3.60 (2 H, m, H_2-6), 3.88 (1 H, m, H-2), 4.00 (1 H, m, H-3), and 4.33 (1 H, m, H-5).

2,5-*Anhydro*-1,4-*dideoxy*-6-O-p-*tolylsulphonyl*-D-ribo-*hexitol* (13a).—To a solution of the diol mixture [(10) and (11)] (12 : 1) (0.5 g) in dry pyridine (10 ml), cooled to −20 °C, was added dropwise a solution of toluene-*p*-sulphonyl chloride (0.8 g) in pure chloroform (2 ml). After being stirred at −20 °C for 3 h and at room temperature overnight, the solution was poured into ice–water and the product extracted into CH_2Cl_2. After washing (1M-H_2SO_4, H_2O) and drying, the solution was evaporated and the syrup was used in the next reaction; for purification it was chromatographed in Et_2O–hexane (7 : 3). The 1,4-*dideoxy-product* was an oil (0.7 g, 65%), R_F 0.15 (Found: C, 54.3; H, 6.3; S, 11.0. $C_{13}H_{18}O_5S$ requires C, 54.5; H, 6.3; S, 11.2%); δ 1.11 (3 H, d, J 6 Hz, CH_3), 1.7—2.2 (2 H, m, H_2-4), 2.44 (3 H, s, $ArCH_3$), 3.02 (1 H, br, s, OH), 3.70 (1 H, m, H-2), 3.86—4.16 (3 H, m, H-3 and H_2-6), 4.26 (1 H, m, H-5), and 7.36 and 7.80 (each 2 H, d, J 8 Hz, ArH).

In an earlier fraction from the column was eluted 2,5-*anhydro*-1,3-*dideoxy*-6-O-p-*tolylsulphonyl*-D-ribo-*hexitol* (50 mg, 5%) (R_F 0.2) (Found: C, 54.4; H, 6.3; S, 11.1%); δ 1.19 (3 H, d, J 6 Hz, CH_3), 1.62 (1 H, ddd, J 14, 10, and 6 Hz, H_A-3), 1.94 (1 H, ddd, J 14, 6, and 2 Hz, H_B-3), 2.24 (1 H, br, s, OH), 2.44 (3 H, s, $ArCH_3$), 3.82—4.34 (5 H, m, H-2, -4, -5, and H_2-6), and 7.34 and 7.80 (each 2 H, d, J 8 Hz, ArH).

Salts of (+)-*Muscarine* (1).—To a solution of the *p*-tolylsulphonyl derivative (13a) (0.5 g) in anhydrous methanol (5 ml) was added, in the cold, a solution of trimethylamine (10 ml) in methanol (5 ml), and the stoppered flask was kept at 50 °C overnight. Evaporation afforded (+)-*muscarine toluene*-p-*sulphonate* (420 mg, 70%), which formed plates from acetone, m.p. 110—112°, $[\alpha]_D^{20}$ +4° (*c* 4, EtOH) (Found: C, 54.4; H, 8.0; N, 4.0; S, 9.1. $C_{16}H_{27}NO_5S$ requires C, 55.6; H, 7.9; N, 4.1; S, 9.3%).

An aqueous solution of the foregoing salt was percolated through a column of Amberlite AG-1 × 4 (chloride form) and the effluent and washings were evaporated. (+)-Muscarine chloride formed prismatic needles (100%), recrystallised from acetone–propan-2-ol; m.p. 182—183° (lit.,[1,19] 181—182°), $[\alpha]_D^{20}$ +8.4° (*c* 2.7, EtOH) (lit.,[1,7,20] +8.1°); δ (D_2O) 1.07 (3 H, d, $J_{1,2}$ 6.8 Hz, CH_3), 1.84 (1 H, ddd, $J_{4A,3}$ 5.2, $J_{4A,4B}$ 14, $J_{4A,5}$ 9.2 Hz, H_A-4), 1.96 (1 H, ddd, $J_{4B,3}$ 2.4, $J_{4A,4B}$ 14, $J_{4B,5}$ 7 Hz, H_B-4), 3.04 (9 H, s, $^+NMe_3$), 3.30 (1 H, dd, $J_{6A,5}$ 8.30, $J_{6A,6B}$ 13.5 Hz, H_A-6), 3.46 (1 H, dd, $J_{6B,5}$ 3.0, $J_{6A,6B}$ 13.5 Hz, H_B-6), 3.90 (1 H, dq, $J_{2,1}$ 6.8, $J_{2,3}$ 3 Hz, H-2), 3.93 (1 H, m, H-3), and 4.49 (1 H, br, q, H-5).

(+)-Muscarine bromide was obtained by treatment of 2,5-anhydro-6-bromo-1,4-dideoxy-D-*ribo*-hexitol (13b) with trimethylamine, as above. The crystalline *bromide* (70%), from acetone–propan-2-ol, had m.p. 169—171°, $[\alpha]_D^{20}$ +3.4° (*c* 1, H_2O) (Found: C, 42.4; H, 8.0; Br, 31.0; N, 5.3. $C_9H_{20}BrNO_2$ requires C, 42.5; H, 7.9; Br, 31.4; N, 5.5%).

2,5-*Anhydro*-4,6-*di*-O-*benzoyl*-1-*chloro*-1-*deoxy*-D-*glucitol* (6b).—The dibenzoate (5) (7.0 g), triphenylphosphine (10.2 g), and carbon tetrachloride (35 ml) were boiled under reflux in methyl cyanide (80 ml) under nitrogen until t.l.c. showed complete reaction. Evaporation and silicic acid chromatography (CH_2Cl_2–Et_2O, 9 : 1) afforded the *chloro-derivative* as fine needles from heptane–ether (6.2 g, 85%), m.p. 104—105°, $[\alpha]_D^{20}$ +25° (*c* 2, EtOH) (Found: C, 61.6; H, 4.9; Cl, 9.1. $C_{20}H_{19}ClO_6$ requires C, 61.5; H, 4.9; Cl, 9.1%); *m/z* (no M^+), 355 (M − Cl); δ 2.64 (1 H, br, s, OH), 3.74 (1 H, dd, J 12 and 6 Hz, H_A-1), 3.86 (1 H, dd, J 12 and 7 Hz, H_B-1), 4.28—4.56 (2 H, m, H-2 and -5), 4.51 (1 H, dd, J 4 and 1.5 Hz, H-3), 4.69 (2 H, m, H_2-6), and 7.3—8.1 (10 H, m, ArH).

The corresponding 1-*bromo-derivative* (6c) was prepared similarly using triphenylphosphine and carbon tetrabromide. It formed needles (heptane–ether), m.p. 103—105° (Found: C, 55.4; H, 4.6; Br, 18.7. $C_{20}H_{19}BrO_6$ requires C, 55.2; H, 4.4; Br, 18.4%); δ 2.90 (1 H, br, s, OH), 3.62 (1 H, dd, J 10 and 6 Hz, H_A-1), 3.72 (1 H, dd, J 10 and 1.5 Hz, H_B-1), 4.34—4.60 (3 H, m, H-2, -3, and -5), 4.70 (2 H, m, H_2-6), 5.38 (1 H, dd, J 3.5 and 1 Hz, H-4), and 7.3—8.1 (10 H, m, ArH).

2,5-*Anhydro*-4,6-*di*-O-*benzoyl*-1-*deoxy*-D-*glucitol* (6d).—To a solution of the chloro-compound (6b) (5.5 g) in dry benzene (100 ml) were added 2,2′-azobisisobutyronitrile (200 mg) and tri-n-butyltin hydride (10 ml), and the solution was boiled under reflux for 6 h. Removal of solvent left an oil, which was dissolved in methyl cyanide; the solution was washed with hexane (3 × 20 ml) and evaporated. Trituration with light petroleum gave a solid (5.0 g, 92%) which was recrystallised from heptane–ether affording the *deoxy-derivative* as needles, m.p. 66—68°, $[\alpha]_D^{20}$ +24° (*c* 3, EtOH) (Found: C, 67.3; H, 5.6. $C_{20}H_{20}O_6$ requires C, 67.4; H, 5.6%); *m/z* 356 (M^+); δ 1.42 (3 H, d, J 6 Hz, CH_3), 2.84 (1 H, br, d, J 4 Hz, OH), 4.12—4.38 (3 H, m, H-2, -3, and -5), 4.67 (2 H, m, H_2-6), 5.25 (1 H, m, H-4), and 7.3—8.15 (10 H, m, ArH).

2,5-*Anhydro*-4,6-*di*-O-*benzoyl*-1-*deoxy*-D-ribo-*hex*-3-*ulose* (14).—To a stirred solution of the 1-deoxy-compound (6d) (2.6 g) in dry benzene (60 ml) was added freshly prepared pyridinium chlorochromate (3 g). After refluxing for 5 h the cooled solution was filtered through Celite and evaporated. The resulting oil, in dry ether, was passed through a short Florisil column. Eluate and washings were evaporated to give 2,5-*anhydro*-4,6-*di*-O-*benzoyl*-1-*deoxy*-D-ribo-

hex-3-ulose (14) as a gum (2.3 g, 90%). A sample was purified by silicic acid chromatography (Found: C, 67.7; H, 5.1. $C_{20}H_{18}O_6$ requires C, 67.8; H, 5.1%); δ 1.40 (3 H, d, *J* 6 Hz, CH_3), 4.26 (1 H, q, *J* 6 Hz, H-2), 4.48—4.86 (3 H, m, H-5 and H_2-6), 5.46 (1 H, d, *J* 8 Hz, H-4), and 7.20—8.10 (10 H, m, ArH).

2,5-*Anhydro-6-O-benzoyl-1,4-dideoxy-*D-erythro-*hex-3-ulose* (15).—A solution of the unpurified ketone (14) (1.4 g) in acetone (65 ml) was deoxygenated by a stream of nitrogen; to it, under nitrogen, was added aqueous chromium(II) chloride (from 5 g of $CrCl_3,6H_2O$). The solution was stirred for 6 h at room temperature and concentrated, and the product was dissolved in ether and percolated through a column of Florisil. Evaporation of the effluent gave the *deoxy-ketone* as a gum (0.64 g, 70%), which was used in the next step without further purification. A sample purified by p.l.c. had *m/z* 234 (M^+) and 206 ($M^+ - CO$); δ 1.31 (3 H, d, *J* 6 Hz, CH_3), 2.30—2.74 (2 H, m, H_2-4), 3.90 (1 H, q, *J* 6 Hz, H-2), 4.34—4.64 (3 H, m, H-5 and H_2-6), and 7.3—8.1 (5 H, m, ArH).

2,5-*Anhydro-6-O-benzoyl-1,4-dideoxy-*D-ribo-*hexitol* (16) *and its* D-xylo-*Epimer* (17).—The deoxy-ketone (15) (1.30 g) was reduced with sodium borohydride (0.2 g) in aqueous ethanol (10 ml) for 1 h at room temperature. Removal of solvent and addition of water gave, on extraction with dichloromethane, an oil which was separated into the two epimers by p.l.c.

The ribo-*hexitol* (0.3 g, 23%) had R_F 0.42, m.p. 73—74° (Found: C, 66.0; H, 7.0. $C_{13}H_{16}O_4$ requires C, 66.1; H, 6.8%); *m/z* 237 ($M^+ + 1$), and 236 (M^+); δ 1.23 (3 H, d, *J* 6 Hz, CH_3), 1.96—2.10 (2 H, m, H_2-4), 2.74 (1 H, br, s, O*H*), 3.96 (1 H, dq, *J* 6 and 3 Hz, H-2), 4.04 (1 H, m, H-3), and 7.3—8.1 (5 H, m, ArH).

The xylo-*hexitol* (0.75 g, 60%) had R_F 0.51, m.p. 48—49° (Found: C, 65.8; H, 6.6%); *m/z* 237 ($M^+ + 1$) and 236 (M^+); δ 1.28 (3 H, d, *J* 6 Hz, CH_3), 1.84 (1 H, ddd, *J* 14, 6, and 2 Hz, H_A-4), 2.33 (1 H, ddd, *J* 14, 8, and 6 Hz, H_B-4), 2.87 (1 H, br, s, OH), 3.80 (1 H, dq, *J* 6 and 3 Hz, H-2), and 7.3—8.1 (5 H, m, ArH).

2,5-*Anhydro-1,4-dideoxy-*D-ribo-*hexitol* (10).—Debenzoylation of the benzoyl-*ribo*-hexitol (16) with sodium methoxide in methanol and work-up gave the *product* (10) as an oil (100%); *m/z* (no M^+) 102 ($M^+ - CH_2O$) and 101 ($M^+ - CH_2OH$); δ (CD_3OD) 1.20 (3 H, d, *J* 6.6 Hz, CH_3), 1.84 (1 H, ddd, *J* 13.2, 6.6, and 4.2 Hz, H_A-4), 2.00 (1 H, ddd, *J* 13.2, 8.4, and 6 Hz, H_B-4), 3.52 (1 H, dd, *J* 11 and 5 Hz, H_A-6), 3.65 (1 H, dd, *J* 11 and 4 Hz, H_B-6), 3.79—4.01 (2 H, m, H-2 and -3), and 4.19 (1 H, m, H-5). The trimethylsilyl derivative had a g.l.c. retention time identical with that of the major isomer obtained in the reduction of the epoxide (8).

2,5-*Anhydro-1,4-dideoxy-*D-xylo-*hexitol* (18).—Debenzoylation of (17), as above, gave the *product* (18) as an oil; *m/z* 114 ($M^+ - H_2O$), 102 ($M^+ - CH_2O$), and 101 ($M^+ - CH_2OH$); δ (CD_3OD) 1.26 (3 H, d, *J* 6 Hz, CH_3), 1.78 (1 H, ddd, *J* 14, 5, and 2 Hz, H_A-4), 2.36 (1 H, ddd, *J* 14, 9, and 6 Hz, H_B-4), 3.45—3.74 (2 H, m, H_2-6), 3.82 (1 H, dq, *J* 6 and 3 Hz, H-2), and 4.04 (2 H, m, H-3 and -5). The trimethylsilyl derivative had a g.l.c. retention time 1.1 times that of the epimer (10).

2,5-*Anhydro-1,3-dideoxy-*D-ribo-*hexitol* (11).—A solution of 2,5-anhydro-4,6-di-*O*-benzoyl-1-chloro-1,3-dideoxy-D-*ribo*-hexitol [9,23] was reduced in dry benzene with tri-n-butyltin hydride and azobisisobutyronitrile, as above. The resulting oil was debenzoylated with sodium methoxide in methanol, affording the 1,3-*dideoxy-*D-ribo-*derivative* as an oil; δ (CD_3OD) 1.25 (3 H, d, *J* 6 Hz, CH_3), 1.67 (1 H, ddd, *J* 13, 10, and 6 Hz, H_A-3), 1.96 (1 H, ddd, *J* 13, 6, and 2 Hz, H_B-3), 3.58 (2 H, m, H_2-6), 3.80 (1 H, m, H-2), and 4.15—4.49 (2 H, m, H-4 and -5). The retention time of the trimethylsilyl derivative was identical with that of the minor isomer (11) obtained on reducing the epoxide (8).

2,5:3,4-*Dianhydro-1-deoxy-*D-*allitol* (12).—A solution of 2,5-anhydro-4,6-di-*O*-benzoyl-1-deoxy-D-glucitol (6d) (3.5 g) in dry pyridine (50 ml) was treated with toluene-*p*-sulphonyl chloride (3.8 g) at room temperature for 6 h. The 3-*O*-*p*-tolylsulphonyl derivative was obtained as an oil (3.6 g, 70%), showing a single spot on t.l.c. A sample (2.5 g) was treated with sodium methoxide (1.1 equiv.) as in the synthesis of (8). The *dianhydro-allitol* was obtained as an oil (0.5 g, 80%) (Found: C, 55.3; H, 7.7. $C_6H_{10}O_3$ requires C, 55.4; H, 7.7%); *m/z* 130 (M^+); δ 1.27 (3 H, d, *J* 6 Hz, CH_3), 2.37 (1 H, br, s, OH), 3.58 and 3.76 (each 1 H, d, *J* 3 Hz, H-3 and H-4), 3.65 (2 H, d, *J* 5.8 Hz, H_2-6) 4.16 (1 H, t, *J* 5.8 Hz, H-5), and 4.28 (1 H, q, *J* 6 Hz, H-2).

Reduction with lithium aluminium hydride under the same conditions as used for the epoxide (8) gave a mixture of the 1,4- and the 1,3-dideoxy-*ribo*-hexitols (10) and (11) in the ratio 3 : 1 (n.m.r.).

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