Dichloromethylenation of Sugar γ-Lactones: a Stereospecific Synthesis of L-(+)-Muscarine and L-(+)-Epimuscarine Toluene-*p*-sulphonates

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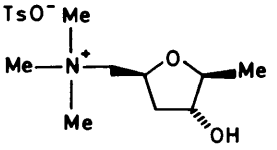
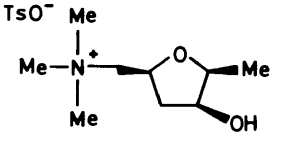
Treatment of di-isopropylidene-D-mannono-1,4-lactone (**3**) with hexamethylphosphorous triamide–tetrachloromethane gave the dichloro-olefin (**4**), which was converted into the ketone (**5**) by treatment with lithium di-isopropylamide. Reduction with Raney nickel gave the key intermediate (**7**) together with its isomer (**6**) (9:1 ratio). Compound (**7**) was transformed into L-(+)-epimuscarine (**2**) *via* glycol cleavage, reduction, tosylation, and treatment with trimethylamine. L-(+)-Muscarine (**1**) was synthesised from compound (**7**) by inversion of the hydroxy group configuration at C-3 followed by the above sequence.

L-(+)-Muscarine (**1**; OH instead of OTs) is an alkaloid isolated from several species of mushrooms, *e.g. Amanita muscaria* and many *Inocybes* and *Clitocybes*.[1] The cholinomimetic properties[2] of both this substance and its isomers stimulated much interest in the chemical synthesis of the natural compound[3,4] and analogues;[5] owing to its simple structure with three chiral centres, muscarine has been the target of several syntheses utilizing new synthetic methodologies.



(**1**)

Tosyl L-(+)-muscarine



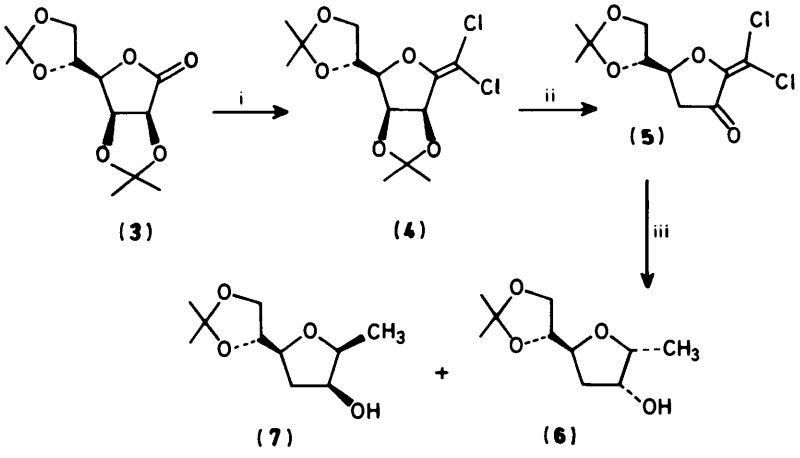
(**2**)

Tosyl L-(+)-epimuscarine

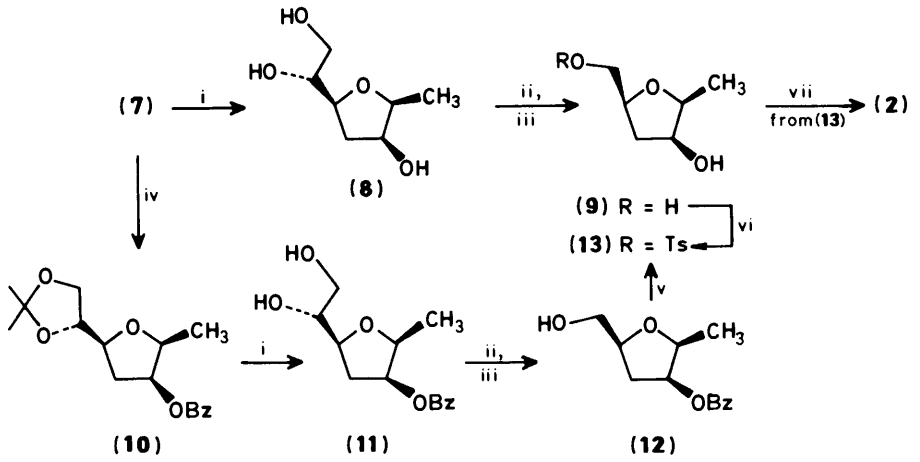
In order to obtain enantiomerically pure compounds, chiral starting materials, mainly carbohydrates[3a] and amino-acids,[3b] have been employed. We present here an alternative synthesis of L-(+)-muscarine toluene-*p*-sulphonate (**1**) and L-(+)-epimuscarine toluene-*p*-sulphonate (**2**), starting from D-mannono-lactone, which takes advantage of our recent methodology for synthesis of chiral substituted tetrahydrofurans.[6]

Reaction of di-*O*-isopropylidene-D-mannono-1,4-lactone (**3**) with hexamethylphosphorous triamide–tetrachloromethane afforded the corresponding dichloromethylene compound (**4**) in high yield. Treatment of compound (**4**) with lithium di-isopropylamide (LDA) gave the ketone (**5**) which was reduced to alcohols (**6**) and (**7**) with Raney nickel (Scheme 1). This sequence has been applied to several γ-lactones of sugars, thus opening a new route to 1-*C*-methyl *C*-glycosides.[7] Compound (**7**) is a key intermediate which presents all the stereochemical features of muscarine. Chemical manipulation of the C-5–C-6 carbon chain was necessary in order to complete the synthesis of the alkaloid. Thus exposure of compound (**7**) to acid hydrolysis gave the triol (**8**), which was submitted to glycol cleavage and subsequent sodium borohydride reduction to give the expected diol (**9**) in moderate yield. Another route was examined which gave almost identical results. Benzoylation of compound (**7**) with benzoyl chloride in pyridine gave the ester (**10**). Acid hydrolysis of the isopropylidene group, followed by glycol cleavage and reduction, gave the alcohol (**12**). Ester cleavage with methoxide then led to the crystalline diol (**9**). This compound was transformed into L-(+)-epimuscarine in two steps by the method of Mubarak and Brown.[4] Selective tosylation of the primary alcohol gave compound (**13**), reaction of which with trimethylamine in methanol gave (+)-epimuscarine tosylate (**2**) (Scheme 2).

The synthesis of L-(+)-muscarine required the same chemical manipulation but inversion of configuration at C-3 had to be



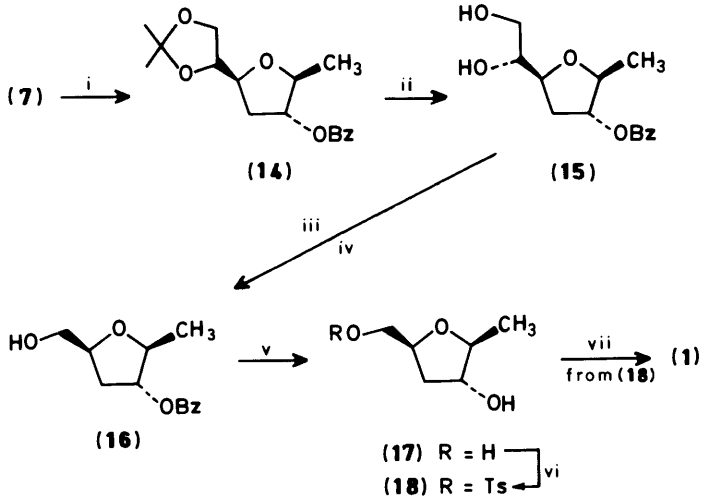
Scheme 1. *Reagents:* i, $P(NMe_2)_3$, CCl_4; ii, LDA; iii, Raney nickel



Scheme 2. *Reagents:* i, aq. AcOH; ii, $NaIO_4$; iii, $NaBH_4$; iv, BzCl, pyridine; v, NaOMe, MeOH; vi, TsCl, pyridine; vii, NMe_3, MeOH

secured. Treatment of compound (**7**) with triphenylphosphine–diethyl azodicarboxylate (DEAD) and benzoic acid cleanly afforded benzoate (**14**), with net inversion of configuration at C-3, in 90% yield. Compound (**14**) was clearly different from benzoate (**10**). This reaction opens the way to various substituted muscarines by use of different nucleophiles in place of benzoic acid. Transformation of benzoate (**14**) into L-(+)-muscarine was then accomplished as above (Scheme 3). The

from $SiMe_4$ as internal standard. I.r. spectra were recorded on a Perkin-Elmer 580 spectrometer. Optical measurements were performed on a Perkin-Elmer 141 automatic polarimeter. T.l.c. was performed on precoated Merck plates with visualisation under u.v. light and spraying with 50% H_2SO_4 in MeOH and heating under a i.r. lamp. M.p.s were measured on a Kofler block. Solvent evaporations were carried out under reduced pressure below 40 °C. Conventional work-up refers to solvent



Scheme 3. *Reagents:* i, PPh_3, DEAD, $PhCO_2H$; ii, aq. AcOH; iii, $NaIO_4$; iv, $NaBH_4$; v, NaOMe, MeOH; vi, TsCl, pyridine; vii, NMe_3, MeOH

structure of all the compounds described was determined by ^1H n.m.r. spectroscopy, and the physical properties of L-(+)-muscarine were in agreement with those previously reported.[3,4]

In conclusion, the proposed method offers a new route to L-(+)-muscarine and congeners with high stereospecificity. Starting from commercial D-gulonolactone would afford the D-isomer, all of these compounds being of interest in muscarinic receptor studies.

Experimental

High-field n.m.r. spectra were obtained using a Bruker Aspect 3000 spectrometer operating at 400 MHz in the Fourier-transform mode. Unless otherwise stated, the spectra were recorded for $CDCl_3$ solutions with chemical shifts (δ) downfield

extraction, washing of the organic layer successively with dil. hydrochloric acid (15%), water, dilute aqueous sodium hydroxide (1M), and water. The organic phase was then dried over anhydrous sodium sulphate, filtered, and evaporated under reduced pressure. Compounds (**4**)—(**7**) have been prepared according to our previously described procedure.[7]

General Procedures.—A. Hydrolysis of the isopropylidene group of compounds (**7**), (**10**), *and* (**14**). A solution of the isopropylidene derivative in aqueous acetic acid (70%) (10 ml per mmol) was heated at 60 °C until no starting material remained (t.l.c. monitoring). The solvent was removed under reduced pressure; two co-distillations with ethanol (25 ml) and toluene (25 ml) gave almost pure compounds.

B. Glycol cleavage and reduction of compounds (**8**), (**11**), *and*

(**15**). To a solution of the diol in a mixture of water and ethanol (1:1 v/v) (5 ml per mmol) was added a solution of sodium metaperiodate (1 mol equiv.) in water. T.l.c. showed complete reaction in 5 min. The white precipitate was filtered off and to the stirred filtrate was added a solution of sodium borohydride (2 mol equiv.) in water. The mixture was stirred for 2 h, then was neutralised with 1M-hydrochloric acid. Evaporation gave a residue, which was taken up in dichloromethane (100 ml). The insoluble solid was filtered off and washed thoroughly with dichloromethane (50 ml). The combined organic phases were concentrated to dryness. Column chromatography of the residue on silica gel afforded pure compounds (**9**), (**12**), and (**16**).

Synthesis of L-(+)-*Epimuscarine* (**2**).—*Anhydro*-1,4-*dideoxy*-D-gluco-*heptitol* (**8**). Compound (**7**) (372 mg, 2 mmol) was hydrolysed according to procedure A to give the *title compound* (**8**) (308 mg, 95%), which was used directly in the next step. An analytical sample (preparative t.l.c.) had $[\alpha]_D^{20}$ +15.2° (*c* 0.5 in $CHCl_3$) (Found: C, 51.6; H, 8.6. $C_7H_{14}O_4$ requires C, 51.84; H, 8.7%); δ 1.27 (3 H, d, *J* 6 Hz, Me), 1.96 (1 H, dd, $J_{4,5}$ 3, $J_{4,4'}$ 14 Hz, 4-H), 2.23 (1 H, ddd, $J_{4',5}$ 10, $J_{3,4'}$ 5 Hz, 4'-H), 3.48 (1 H, dd, $J_{6,7}$ 7.5, $J_{7,7'}$ 11.5 Hz, 7-H), 3.63 (1 H, dd, $J_{6,7'}$ 3.5 Hz, 7'-H), 3.79 (1 H, dq, $J_{2,3}$ 2.5 Hz, 2-H), 3.93 (1 H, m, $J_{5,6}$ 3 Hz, 6-H), 4.01 (1 H, dd, 3-H), 4.13 (1 H, ddd, 5-H), and 4.95 (3 H, br, OH).

2,5-*Anhydro*-1,4-*dideoxy*-D-xylo-*hexitol* (**9**). Compound (**8**) (308 mg, 1.9 mmol) was treated according to procedure B to give the title product (**9**) (158 mg, 60%), m.p. 63 °C (from CH_2Cl_2–hexane); $[\alpha]_D^{25}$ +51.6° (*c* 0.5 in $CHCl_3$); R_F 0.26 (ethyl acetate). Spectroscopic data were in agreement with those previously reported.[4]

2,5-*Anhydro*-3-O-*benzoyl*-1,4-*dideoxy*-6,7-O-*isopropylidene*-D-gluco-*heptitol* (**10**). To a solution of the alcohol (**7**) (372 mg, 2 mmol in pyridine (20 ml) at 0 °C was added benzoyl chloride (516 mg, 4 mmol). The mixture was allowed to warm to room temperature and was stirred for 1 h. Evaporation of the solvent, and work-up with diethyl ether, gave crude compound (**10**) which was purified by column chromatography to give the title benzoate (560 mg, 92%), $[\alpha]_D^{20}$ −6.8° (*c* 0.5 in $CHCl_3$); R_F 0.43 (hexane–ethyl acetate 3:1) (Found: C, 66.7; H, 7.35. $C_{17}H_{22}O_5$ requires C, 66.64; H, 7.23%); $\nu_{max.}$ 1 720 cm^{-1}; δ 1.3 (3 H, d, *J* 6.5 Hz, Me), 1.35 and 1.4 (each 3 H, s, together CMe_2), 2.11 (1 H, ddd, $J_{3,4}$ 1.5, $J_{4,5}$ 5.5, $J_{4,4'}$ 15 Hz, 4-H), 2.58 (1 H, ddd, $J_{3,4'}$ 6.5, $J_{4',5}$ 8 Hz, 4'-H), 3.92 (1 H, m, 6-H), 3.96 (1 H, m, 5-H), 4.08 (1 H, dq, $J_{2,3}$ 4 Hz, 2-H), 4.15 (2 H, m, 7-H_2), 5.48 (1 H, m, 3-H), 7.46 (2 H, m, ArH), 7.57 (1 H, m, ArH), and 8.05 (2 H, m, ArH).

2,5-*Anhydro*-3-O-*benzoyl*-1,4-*dideoxy*-D-gluco-*heptitol* (**11**). Compound (**10**) (535 mg, 1.7 mmol) was submitted to acid hydrolysis using procedure A to give the *title compound* (**11**) (449 mg, 95%) which was immediately used for the next step. An analytical sample (preparative t.l.c.) had $[\alpha]_D$ +4.10° (*c* 0.5 in $CHCl_3$); R_F 0.35 (ethyl acetate) (Found: C, 63.0; H, 6.7. $C_{14}H_{18}O_5$ requires C, 63.15; H, 6.81%); $\nu_{max.}$ 1 715 cm^{-1}; δ 1.3 (3 H, d, *J* 6.5 Hz, Me), 2.15 (1 H, ddd, $J_{3,4}$ 1, $J_{4,5}$ 6, $J_{4,4'}$ 14.5 Hz, 4-H), 2.5 (1 H, m, $J_{3,4'}$ 7, $J_{4',5}$ 8.5 Hz, 4'-H), 3.75—4.25 (7 H, m, 2-, 5-, and 6-H, 7-H_2, and 2 × OH), 5.5 (1 H, m, 3-H), 7.4 (2 H, m, ArH), 7.47 (1 H, m, ArH), and 8.05 (2 H, m, ArH).

2,5-*Anhydro*-3-O-*benzoyl*-1,4-*dideoxy*-D-xylo-*hexitol* (**12**). Compound (**11**) (440 mg, 1.6 mmol) was treated according to procedure B to give, after column chromatography, pure *title compound* (**12**) (272 mg, 72%), $[\alpha]_D^{25}$ +23.0° (*c* 0.5 in $CHCl_3$); R_F 0.66 (ethyl acetate) (Found: C, 65.8; H, 6.8. $C_{13}H_{16}O_4$ requires C, 66.08; H, 6.82%); $\nu_{max.}$ 3 700 and 1 715 cm^{-1}; δ 1.33 (3 H, d, *J* 6 Hz, Me), 1.97 (1 H, ddd, $J_{3,4}$ 2, $J_{4,5}$ 6, $J_{4,4'}$ 14.5 Hz, 4-H), 2.10 (1 H, br s, OH), 2.50 (1 H, ddd, $J_{3,4'}$ 6.5, $J_{4',5}$ 8.5 Hz, 4'-H), 3.65 (1 H, dd, $J_{5,6}$ 5.5, $J_{6,6'}$ 11.5 Hz, 6-H), 3.80 (1 H, dd, $J_{5,6'}$ 3 Hz, 6'-H), 4.09 (1 H, m, $J_{2,3}$ 3.5 Hz, 2-H), 4.14 (1 H, m, 5-H), 5.5 (1 H, m, 3-H), 7.4 (2 H, m, ArH), 7.6 (1 H, m, ArH), and 8.05 (2 H, m, ArH).

Treatment of compound (**12**) (260 mg, 1.1 mmol) with a catalytic amount of sodium methoxide in methanol (10 ml) gave, after neutralisation with Dowex 50W (H^+), crude diol (**9**). Column chromatography on silica gel gave pure diol (**9**) (140 mg, 97%).

2,5-*Anhydro*-1,4-*dideoxy*-6-O-(p-*tolylsulphonyl*)-D-xylo-*hexitol* (**13**). To a solution of the diol (**9**) (132 mg, 1 mmol) in dry pyridine (20 ml) at 0 °C was added toluene-*p*-sulphonyl chloride (285 mg, 1.5 mmol). The mixture was then stirred for 24 h at room temperature. The solvent was removed and conventional work-up gave crude compound (**13**).

Column chromatography on silica gel with hexane–ethyl acetate (2:1) gave pure title product (**13**) (214 mg, 75%), m.p. 70 °C (from CH_2Cl_2–hexane); $[\alpha]_D^{25}$ +37.4° (*c* 0.5 in $CHCl_3$); R_F 0.40 (hexane–ethyl acetate 2:1); (Found: C, 55.0; H, 6.4; S, 11.0. $C_{13}H_{18}O_5S$ requires C, 54.52; H, 6.33; S, 11.19%); δ 1.20 (3 H, s, *J* 6 Hz, Me), 1.78 (1 H, dd, $J_{4,4'}$ 14, $J_{4,5}$ 4 Hz, 4-H), 2.25 (1 H, m, OH), 2.32 (1 H, ddd, $J_{4',5}$ 8.5, $J_{3,4'}$ 6 Hz, 4'-H), 2.44 (3 H, s, Ar*Me*), 3.80 (1 H, m, $J_{2,3}$ 3 Hz, 2-H), 4.06 (1 H, dd, $J_{6,6'}$ 9, $J_{5,6}$ 4 Hz, 6-H), 4.09 (1 H, m, $J_{3,4'}$ 6 Hz, 3-H), 4.11 (1 H, m, $J_{5,6'}$ 3 Hz, 5-H), 4.17 (1 H, dd, 6'-H), and 7.35—7.8 (4 H, m, ArH).

L-(+)-*Epimuscarine toluene*-p-*sulphonate* (**2**). To a solution of the toluene-*p*-sulphonate (**13**) (110 mg, 3.9 mmol) in methanol (5 ml) was added trimethylamine (5 ml) and the stoppered flask was heated at 65 °C during 3 days. Evaporation of the solvent gave L-(+)-epimuscarine toluene-*p*-sulphonate (**2**), which crystallised from acetone (109 mg, 80%), m.p. 158 °C; $[\alpha]_D^{25}$ +36.5° (*c* 1 in EtOH) (Found: C, 55.1; H, 8.1; N, 4.1; S, 9.5. $C_{16}H_{27}NO_5S$ requires C, 55.62; H, 7.87; N, 4.05; S, 9.28%); δ 1.23 (1 H, d, *J* 6 Hz, Me), 1.59 (1 H, ddd, $J_{4,4'}$ 14, $J_{3,4}$ 1.5, $J_{4,5}$ 5.5 Hz, 4-H), 2.35 (3 H, s, Ar*Me*), 2.5 (1 H, ddd, $J_{4,4'}$ 14, $J_{3,4'}$ 5.5, $J_{4',5}$ 8.5 Hz, 4'-H), 3.17 (9 H, s, 3 × Me), 3.46 (1 H, dd, $J_{5,6}$ 1.5, $J_{6,6'}$ 13.5 Hz, 6-H), 3.57 (1 H, dd, $J_{5,6'}$ 10 Hz, 6'-H), 3.88 (1 H, dq, $J_{2,3}$ 3.5 Hz, 2-H), 4.11 (1 H, m, 3-H), 4.40 (1 H, m, 5-H), 4.88 (1 H, s, OH), and 7.23—7.71 (4 H, m, ArH).

Synthesis of L-(+)-*Muscarine* (**1**).—2,5-*Anhydro*-3-O-*benzoyl*-1,4-*dideoxy*-6,7-O-*isopropylidene*-D-allo-*heptitol* (**14**). To a stirred solution of compound (**7**) (372 mg, 2 mmol, triphenylphosphine (2.1 g, 8 mmol), and benzoic acid (488 mg, 4 mmol) in dry tetrahydrofuran (20 ml) was added a solution of DEAD (1.4 g, 8 mmol) in THF (5 ml). After 30 min the solvent was evaporated off and the residue was purified by column chromatography [hexane–ethyl acetate (3:1) as eluant] to give pure *title compound* (**14**), (550 mg, 90%), $[\alpha]_D^{25}$ +10.5° (*c* 0.5 in $CHCl_3$); R_F 0.55 (hexane–ethyl acetate 3:1) (Found: C, 66.7; H, 7.2. $C_{17}H_{22}O_5$ requires C, 66.64; H, 7.23%); $\nu_{max.}$ 1 720 cm^{-1}; δ 1.3 (3 H, d, *J* 6.5 Hz, Me), and 1.35 and 1.45 (both 3 H, s, together CMe_2), 2.17 (1 H, ddd, $J_{3,4}$ 6, $J_{4,5}$ 9, $J_{4,4'}$ 14 Hz, 4-H), 2.24 (1 H, ddd, $J_{3,4'}$ 2, $J_{4',5}$ 5.5 Hz, 4'-H), 3.88 (1 H, dd, $J_{6,7}$ 8, $J_{6,7'}$ 5 Hz, 6-H), 4.1 (3 H, m, 5-H and 7-H_2), 4.19 (1 H, m, $J_{2,3}$ 2 Hz, 2-H), 5.15 (1 H, m, 3-H), 7.43 (2 H, m, ArH), 7.60 (1 H, m, ArH), and 8.05 (2 H, m, ArH).

2,5-*Anhydro*-3-O-*benzoyl*-1,4-*dideoxy*-D-allo-*heptitol* (**15**). Compound (**14**) (520 mg, 1.7 mmol) was treated according to procedure A to give *compound* (**15**) (440 mg, 98%), which was used without purification for the next step. An analytical sample (preparative t.l.c.) had m.p. 83 °C (from CH_2Cl_2–hexane), $[\alpha]_D^{20}$ −8.7° (*c* 0.5 in $CHCl_3$); R_F 0.39 (ethyl acetate) (Found: C, 63.3; H, 7.0. $C_{14}H_{18}O_5$ requires C, 63.15; H, 6.81%); $\nu_{max.}$ 1 715 cm^{-1}; δ 1.26 (3 H, d, *J* 6 Hz, Me), 2.11 (1 H, ddd, $J_{3,4}$ 1, $J_{4,5}$ 5.5, $J_{4,4'}$ 14 Hz, 4-H), 2.26 (1 H, ddd, $J_{3,4'}$ 6, $J_{4',5}$ 10 Hz, 4'-H), 3.62 (1 H, dd, $J_{6,7}$ 6.5, $J_{7,7'}$ 11 Hz, 7-H), 3.68 (2 H, br m, OH), 3.76 (1 H, dd, $J_{6,7'}$ 3 Hz, 7'-H), 3.85 (1 H, m, $J_{5,6}$ 5 Hz, 6-H), 4.17 (2 H, m, 2- and 5-H), 5.1 (1 H, m, 3-H), 7.43 (2 H, m, ArH), 7.55 (1 H, m, ArH), and 8.02 (2 H, m, ArH).

2,5-*Anhydro*-3-O-*benzoyl*-1,4-*dideoxy*-D-ribo-*hexitol* (**16**). Compound (**15**) (440 mg, 1.6 mmol) was treated according to

procedure B to give pure *title compound* (**16**) after column chromatography (hexane–ethyl acetate 3:7) (254 mg, 65%), $[\alpha]_D$ −9.8° (*c* 0.5 in $CHCl_3$); R_F 0.67 (ethyl acetate) (Found: C, 65.9; H, 6.85. $C_{13}H_{16}O_4$ requires C, 66.08; H, 6.82%); $\nu_{max.}$ 1 715 cm^{-1}; δ 1.28 (3 H, d, $J_{1,2}$ 6.5 Hz, Me), 2.05 (1 H, ddd, $J_{3,4}$ 1.5, $J_{4,5}$ 5.5, $J_{4,4'}$ 14 Hz, 4-H), 2.22 (1 H, ddd, $J_{3,4'}$ 6, $J_{4',5}$ 10 Hz, 4′-H), 2.48 (1 H, br s, OH), 3.59 (1 H, dd, $J_{5,6}$ 4.5, $J_{6,6'}$ 12 Hz, 6-H), 3.86 (1 H, dd, $J_{5,6'}$ 3 Hz, 6′-H), 4.21 (1 H, dq, $J_{2,3}$ 2.5 Hz, 2-H), 4.31 (1 H, m, 5-H), 5.14 (1 H, m, 3-H), 7.45 (2 H, m, ArH), 7.58 (1 H, m, ArH), and 8.04 (2 H, m, ArH).

2,5-*Anhydro*-1,4-*dideoxy*-D-ribo-*hexitol* (**17**). Compound (**16**) (200 mg, 8.5 mmol) was dissolved in methanol (10 ml) and a catalytic amount of sodium methoxide was added. After the solution had been stirred for 3 h at room temperature, Dowex 50W (H^+) was added (to neutrality), when filtration and evaporation gave crude diol (**17**). Purification by column chromatography (ethyl acetate) gave pure diol (**17**) (108 mg, 97%), $[\alpha]_D^{25}$ −6.0° (*c* 0.5 in $CHCl_3$); R_F 0.13 (ethyl acetate); spectroscopic data were in agreement with those reported.[4]

2,5-*Anhydro*-1,4-*dideoxy*-6-O-(p-*tolylsulphonyl*)-D-ribo-*hexitol* (**18**). Compound (**17**) (95 mg, 7.2 mmol) was transformed into the title compound (**18**) as described above for the transformation of compound (**9**) into the ester (**13**). Column chromatography gave pure ester (**18**) (158 mg, 77%), $[\alpha]_D^{25}$ +3.6° (*c* 0.5 in $CHCl_3$); R_F 0.54 (ethyl acetate); spectroscopic data are in agreement with those reported.[4]

L-(+)-*Muscarine toluene*-p-*sulphonate* (**1**). Treatment of compound (**18**) (112 mg, 4 mmol) with trimethylamine in methanol according to ref. 4 gave the title salt (**1**) after crystallisation from acetone (127 mg, 94%), m.p. 114 °C; (lit.,[4] 110—112 °C); $[\alpha]_D^{25}$ + 6.2° (*c* 0.5 in EtOH) [lit.,[4] $[\alpha]_D$ +4° (*c* 4 in EtOH].

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