

## A Practical Synthesis of (+)-Muscarine from L-Rhamnose

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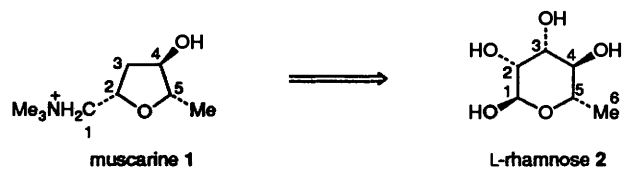
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A practical seven-step synthesis of muscarine tosylate {[[(2*S*,4*R*,5*S*)-4-hydroxy-5-methyltetrahydrofuran-2-ylmethyl](trimethyl)ammonium tosylate} from L-rhamnose is described, which does not require the use of any protecting group.

*Amanita muscaria* looks among the most appetising of the mushrooms that grow in autumnal woods; its beauty belies the treachery of an active principle, muscarine **1**.<sup>1</sup> An excellent and wide-ranging review of muscarine<sup>2</sup> in 1984 surveys the isolation, pharmacology and synthesis of muscarine and its analogues, including the first attempts at its synthesis in 1811; a solution to a murder mystery in a novel in 1930<sup>3</sup> turned on the difference in the optical activity of synthetic and natural muscarine, some 27 years before the X-ray structure of muscarine firmly established its structure.<sup>4</sup>

In recent years, the isolation and characterisation of subtypes of muscarinic receptor have allowed a greater understanding of the chemotherapeutic potential of specific muscarinic agonists;<sup>5</sup> accordingly, current interest in exploring compounds which may be specific agonists or antagonists of individual muscarinic receptors is intense.<sup>6</sup> Efforts have also continued to improve the synthesis of muscarine itself;<sup>7</sup> thus, non-stereospecific syntheses of muscarine have been reported recently by photochemical ring expansion of a cyclobutanone,<sup>8</sup> by rhodium(II)-catalysed carbenoid insertion cyclisation of  $\alpha$ -alkoxy diazoketones,<sup>9</sup> and by a chemoenzymatic procedure.<sup>10</sup>

Muscarine has long been recognised as a suitable target from starting materials in the chiral pool.<sup>2</sup> The synthesis of muscarine from L-arabinose in 1957<sup>11</sup> is one of the outstanding early examples of the use of sugars in the synthesis of non-carbohydrate targets. More efficient syntheses of muscarine have been reported from D-mannitol<sup>12</sup> and D-mannonolactone,<sup>13</sup> although these routes need the separation of intermediate diastereo- or regio-isomers and have only been reported on a relatively small scale. This paper illustrates the value of



(All numbering refers to the carbons in L-rhamnose)

L-rhamnose **2** as a starting material for the synthesis of muscarine in a seven-step synthesis which allows the easy preparation of multi-gram amounts of the target; a preliminary account of this work has been published.<sup>14</sup>

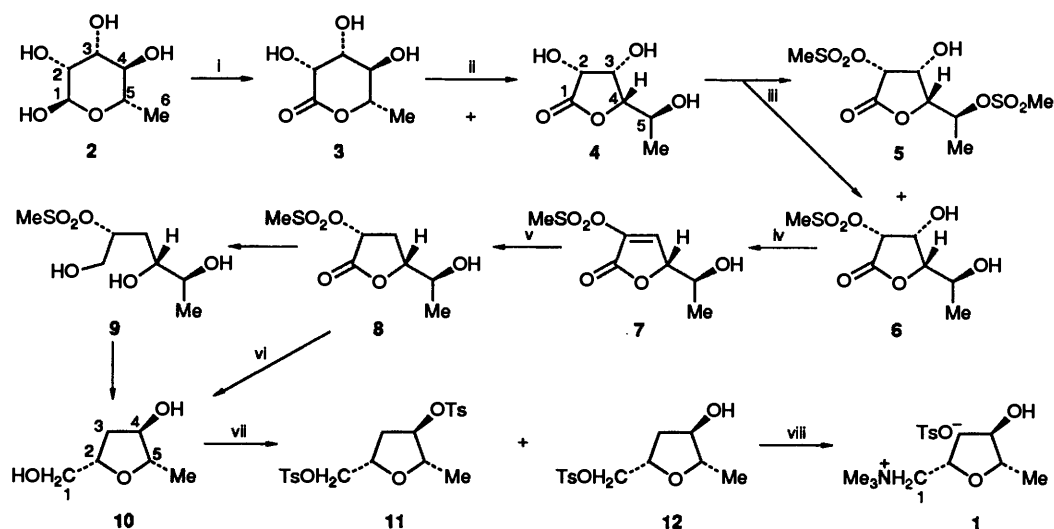
L-Rhamnose is the cheapest and most available L-hexose, and is one of the easiest sugars to handle experimentally since the replacement in the deoxysugar of the hydroxymethyl group by methyl means that any protected derivative of rhamnose is usually readily handled in organic solvents. The approach described in this paper involves the formation of the tetrahydrofuran ring of muscarine by the nucleophilic displacement,

with inversion, of a leaving group at C-2 of a rhamnose derivative by the oxygen function at C-5. For such a strategy, L-rhamnose has the correct stereochemistry and functionality at C-6, C-5, C-4 and C-2; the only functional group interconversions necessary are the removal of the 3-hydroxy group and the introduction of the quaternary ammonium group at C-1.

Carbohydrate lactones have very great potential in synthesis<sup>15</sup> and provide several easy and short strategies for the preparation of complex tetrahydrofurans.<sup>16</sup> In principle, either  $\delta$ -3 or  $\gamma$ -4 rhamnonolactones would be suitable for the preparation of muscarine but the removal of the C-3 oxygen function by elimination to an  $\alpha,\beta$ -unsaturated lactone makes the approach from the  $\gamma$ -lactone **4** more attractive since this allows easy control of the stereochemistry at C-2. One of the frequent problems associated with the use of carbohydrates in synthesis is the amount of time and effort invested in the protection of hydroxy groups; in this synthesis of muscarine (Scheme 1), there is no requirement for any protecting groups at all.

Oxidation of L-rhamnose **2** by buffered bromine water gave a mixture of  $\delta$ -3 and  $\gamma$ -4 lactones in a yield of 75%; about two thirds of the mixture is the  $\delta$ -lactone **3** but the crude mixture was quantitatively converted into rhamnono-1,4-lactone **4**<sup>17</sup> by treatment with 50% aqueous trifluoroacetic acid; this procedure is easy to accomplish on a large scale and requires no chromatographic separations. It is almost invariably the case that the  $\alpha$ -hydroxy groups in lactones are more easily esterified than any of the other secondary alcohols; thus, selective esterification of the 2-hydroxy group with methanesulfonyl chloride in pyridine in the presence of 4-(*N,N*-dimethylamino)pyridine gave the monomesylate **6** in 58% yield, together with the dimesylate **5** in 14% yield. The strategy adopted for the removal of the 3-hydroxy group was to convert the C-3 alcohol in the monomesylate **6** into a better leaving group so that an easy base-induced elimination would give the unsaturated lactone **7**, in an overall formal dehydration; it was anticipated that subsequent hydrogenation of the double bond in **7** would take place highly stereoselectively from the least hindered side and would re-establish the correct stereochemistry at C-2.

Unfortunately, the 5-OH group in **6** is more nucleophilic than the 3-OH group. Thus, the dehydration was achieved by the low-temperature esterification of both of the two remaining hydroxy groups with trifluoroacetic anhydride and triethylamine to give the corresponding bis-trifluoroacetate. Under the reaction conditions, it was possible to eliminate only one of the trifluoroacetates; concomitant quenching and deprotection by treatment with acetic acid and methanol removed the remaining trifluoroacetyl group to afford the vinyl mesylate **7** in 79% overall yield from **6**. The hydrogenation of **7** in ethyl acetate in the presence of 10% palladium on carbon occurred highly stereoselectively to give the required 3-deoxymethanesulfonate **8** in 76% yield. Hydrogenation for extended periods of time (or



(All numbering refers to the carbons in L-rhamnose)

**Scheme 1** Reagents: i,  $\text{Br}_2$ ,  $\text{BaCO}_3$ ,  $\text{H}_2\text{O}$ ; ii,  $\text{CF}_3\text{CO}_2\text{H}-\text{H}_2\text{O}$ ; iii,  $\text{MeSO}_2\text{Cl}$ , DMAP, pyridine; iv,  $(\text{CF}_3\text{CO})_2\text{O}$ ,  $\text{Et}_3\text{N}$ , THF; then AcOH, MeOH; v, 10% Pd-C, EtOAc; vi,  $\text{LiBH}_4$ , THF; then NaOAc, MeCN; vii, TsCl, THF, pyridine; viii,  $\text{Me}_3\text{N}$ , MeOH

with palladium black as the catalyst) resulted in hydrogenolysis of the methanesulfonate function.

The lactone **8** was reduced with lithium borohydride in tetrahydrofuran to give a relatively unstable intermediate with  $^1\text{H}$  NMR spectrum consistent with structure of the open-chain triol methanesulfonate **9**; because of the instability of **9**, the reaction mixture was treated with sodium acetate whilst heated under reflux in acetonitrile to give the required tetrahydrofuran **10** in the overall yield of 68% from **8**. The open-chain triol methanesulfonate **9** could close to form epoxides or oxetanes; however, neither of these alternative reaction pathways compete significantly with formation of the tetrahydrofuran **10** under these reaction conditions.

The diol **10** was converted into muscarine, using slight modifications of literature procedures.<sup>12</sup> Selective esterification of the primary hydroxy group in **10** by toluene-*p*-sulfonyl chloride in pyridine afforded the monotosylate **12** in 77% yield, with a smaller amount of ditosylated material **11** (7% yield). Reaction of the monotosylate **12** with trimethylamine in methanol gave (+)-muscarine tosylate **1** in 67% yield. The overall yield of recrystallised muscarine **1** from L-rhamnose **2** is 10%.

In summary, this paper reports a practical seven-step synthesis of (+)-muscarine from L-rhamnose, which does not require the use of protecting groups and makes possible the production of multi-gram quantities, and provides a good example of the value of lactones in the synthesis of complex tetrahydrofurans. An alternative approach to the synthesis of the muscarine nucleus from the ring contraction of rhamnono- $\delta$ -lactone allows the easy synthesis of analogues of muscarine with additional functionality at the unsubstituted position of the muscarine ring.<sup>18</sup>

## Experimental

Melting points were recorded on a Kofler hot block.  $^1\text{H}$  NMR ( $\delta_{\text{H}}$ ) spectra were recorded on Varian Gemini 200 (at 200 MHz) or Bruker AM 500 (500 MHz) spectrometers.  $^{13}\text{C}$  NMR ( $\delta_{\text{C}}$ ) spectra were recorded on a Varian Gemini 200 (50 MHz) or a Bruker AM 500 (125 MHz) spectrometer. The  $^1\text{H}$  NMR of **10** and **12** were assigned using a COSY sequence. Multiplicities were assigned using DEPT sequence. Spectra run in  $\text{D}_2\text{O}$  were referenced to dioxane ( $\delta$  67.3) as an internal standard. All chemical shifts are quoted on the  $\delta$ -scale. IR spectra were

recorded on a Perkin-Elmer 150 Fourier Transform spectrophotometer. Mass spectra were recorded on VG Micromass 30F, ZAB 1F, Masslab 20-250 or Trio-1 GCMS (DB-5 column) spectrometers using desorption chemical ionisation ( $\text{NH}_3$ ; DCI), electron impact (EI), chemical ionisation ( $\text{NH}_3$ ; CI) and fast atom bombardment (FAB) techniques, as stated. Optical rotations were measured on a Perkin-Elmer 241 polarimeter with a path length of 1 dm,  $[\alpha]_{\text{D}}$  values are given in  $10^{-1}$  deg  $\text{cm}^2 \text{g}^{-1}$ . Concentrations were given in  $\text{g}/100 \text{cm}^3$ . Hydrogenations were run under an atmosphere of hydrogen gas maintained by inflated balloon. Microanalyses were performed by the microanalysis service of the Dyson-Perrins laboratory. Thin layer chromatography (TLC) was carried out on aluminium sheets coated with 60F<sub>254</sub> silica. Plates were developed using 0.2% w/v cerium(IV) sulfate and 5% ammonium molybdate in 2 mol  $\text{dm}^{-3}$  sulfuric acid. Flash chromatography was carried out using Sorbsil C60 4/60 silica. Solvents and commercially available reagents were dried and purified before use according to standard procedures; methanol was distilled from magnesium methoxide, pyridine was distilled from calcium hydride and stored over potassium hydroxide and tetrahydrofuran was distilled from a purple solution of sodium benzophenone ketyl immediately before use. Hexane was distilled at 68 °C before use to remove involatile fractions. L-Rhamnose **2** was obtained from the Sigma Chemical Company.

**L-Rhamnono-1,4-lactone 4.**—Barium carbonate (81.4 g, 0.413 mol, 1.5 equiv.) was added to a solution of L-rhamnose monohydrate **2** (50 g, 0.275 mol) in distilled water (350  $\text{cm}^3$ ). Bromine (1.1 equiv., 0.303 mol, 15.4  $\text{cm}^3$ ) was added in three equal portions at 20 min intervals to the stirred mixture at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 6 h, when TLC (methanol-ethyl acetate, 1:9) indicated that the starting material ( $R_f$  0.1) had been replaced by the  $\gamma$ -lactone **4** ( $R_f$  0.35) and the  $\delta$ -lactone **3** ( $R_f$  0.4). Excess of barium carbonate was filtered off through Celite and the residual solid washed with distilled water ( $2 \times 50 \text{cm}^3$ ). The residual bromine was blown off with compressed air until all the colour had disappeared. The solvent was removed to give a white residue which was extracted with boiling acetone ( $3 \times 11$ ). Solvent removal afforded a mixture of the  $\delta$ -3 and  $\gamma$ -4 lactones (33.1 g, 75%) in approximately 2:1 ratio as estimated by  $^1\text{H}$  NMR integration of the methyl protons in the two lactones. Quantitative conversion of 20 g of this material into

L-rhamnono-1,4-lactone **4** was achieved by dissolving this material in hot aqueous trifluoroacetic acid (100 cm<sup>3</sup>, 1:1 w/v). The resulting solution was allowed to cool and then to stand at room temperature for 4 h at which point TLC (methanol–ethyl acetate, 1:9) indicated that conversion into the  $\gamma$ -lactone **4** ( $R_f$  0.35) was complete. The solvent was removed to give L-rhamnono-1,4-lactone **4**, which could be used without further purification in subsequent experiments, m.p. indeterminate (due to phase change);  $[\alpha]_D^{20} - 39.4$  (*c* 2.02 in water) {lit.,<sup>17</sup> m.p. 148–150 °C;  $[\alpha]_D^{24} - 40$  (*c* 2.0 in water)};  $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$  3300br (OH) and 1776 (C=O);  $\delta_{\text{H}}(500 \text{ MHz}; \text{D}_2\text{O})$  1.27 (3 H, d, *J* 6.4, 6-H), 4.06 (1 H, qd, *J* 6.4, 8.2, 5-H), 4.19 (1 H, dd, *J* 2.8, 8.2, 4-H), 4.55 (1 H, dd, *J* 2.8, 4.7, 3-H) and 4.67 (1 H, d, *J* 4.7, 2-H);  $\delta_{\text{C}}(50.3 \text{ MHz}; \text{D}_2\text{O})$  179.2 (s, C-1), 83.8 (d, C-4), 71.6, 70.1, 64.5 (3  $\times$  d, C-2, C-3, C-5) and 19.5 (q, C-6); *m/z* (DCI; NH<sub>3</sub>) 180 (M + NH<sub>4</sub><sup>+</sup>, 36), 163 (M + H<sup>+</sup>, 100) and 117 (68%).

**2-O-Methanesulfonyl-L-rhamnono-1,4-lactone 6.**—Methanesulfonyl chloride (9.45 cm<sup>3</sup>, 0.12 mol, 1.1 equiv.) was added dropwise to a stirred solution of a catalytic amount of 4-(*N,N*-dimethylamino)pyridine and rhamnono-1,4-lactone **4** (18.00 g, 0.11 mol) in dry pyridine (60 cm<sup>3</sup>) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 7 h, when TLC (methanol–ethyl acetate, 1:9) showed only a trace of starting material ( $R_f$  0.35) and the formation of both a minor product, the dimesylate **5** ( $R_f$  0.65) and the monomethanesulfonate **6** as the major product ( $R_f$  0.55). After the reaction was quenched by addition of methanol (20 cm<sup>3</sup>), the solvent was partially removed under reduced pressure. The crude liquor was partitioned between aqueous hydrochloric acid (2 mol dm<sup>-3</sup>, 100 cm<sup>3</sup>) and ethyl acetate (300 cm<sup>3</sup>). The aqueous layer was extracted with ethyl acetate (2  $\times$  100 cm<sup>3</sup>) and then the combined organic extracts were washed with brine (100 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>). The solvent was removed and the residue recrystallised from boiling methanol to afford 2,5-di-*O*-methanesulfonyl-L-rhamnono-1,4-lactone **5** (4.86 g, 0.015 mol, 14%), a white crystalline solid, m.p. 210–211 °C (Found: C, 30.0; H, 4.35. C<sub>8</sub>H<sub>14</sub>O<sub>9</sub>S<sub>2</sub> requires C, 30.19; H, 4.43%);  $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$  1795 (C=O str);  $[\alpha]_D^{20} + 3.6$  (*c* 1.0 in CH<sub>3</sub>CN);  $\delta_{\text{H}}(200 \text{ MHz}; \text{CD}_3\text{CN})$  (after D<sub>2</sub>O exchange) 1.53 (3 H, d, *J* 6.5, 6-H), 3.11 (3 H, s, MeSO<sub>2</sub>), 3.26 (3 H, s, MeSO<sub>2</sub>), 4.47 (1 H, dd, *J* 2.5, 8, 4-H), 4.71–4.74 (1 H, m, 3-H), 4.95–5.09 (1 H, m, 5-H) and 5.45 (1 H, d, *J* 4.5, 2-H);  $\delta_{\text{C}}(50.3 \text{ MHz}; [\text{H}_6]\text{DMSO})$  171.1 (s, C-1), 80.6, 76.2, 75.0, 67.9 (d, C-2, C-3, C-4, C-5), 38.4 (q, 2  $\times$  MeSO<sub>2</sub>) and 17.8 (q, C-6); *m/z* (DCI; NH<sub>3</sub>) 336 (M + NH<sub>4</sub><sup>+</sup>, 100) and 240 (25%). The methanolic solution was evaporated to give an oil which was purified by flash chromatography (ethyl acetate–hexane, 1:1 graded to 3:2) to give 2-*O*-methanesulfonyl-L-rhamnono-1,4-lactone **6** (15.1 g, 58%), m.p. 96–97 °C;  $[\alpha]_D^{20} - 9.1$  (*c* 1.1 in acetonitrile) (Found: C, 35.15; H, 4.9. C<sub>7</sub>H<sub>12</sub>O<sub>7</sub>S requires C, 35.00; H, 5.03%);  $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$  1795 (C=O);  $\delta_{\text{H}}(200 \text{ MHz}; \text{CD}_3\text{OD})$  1.31 (3 H, d, *J* 6, 6-H), 3.29 (3 H, s, MeSO<sub>2</sub>), 4.04–4.16 (2 H, m), 4.68 (1 H, dd, *J* 2, 4.5), 5.56 (1 H, d, *J* 4.5, 2-H);  $\delta_{\text{C}}(50.3 \text{ MHz}; \text{CD}_3\text{CN})$  171.8 (s, C-1), 83.5, 77.3 (2  $\times$  d, C-2, C-4), 69.5, 64.6 (2  $\times$  d, C-3, C-5), 39.3 (q, MeSO<sub>2</sub>) and 20.0 (q, C-6); *m/z* (DCI; NH<sub>3</sub>) 258 (M + NH<sub>4</sub><sup>+</sup>, 100) and 240 (M + H<sup>+</sup>, 8%).

**2-O-Methanesulfonyl-3,6-dideoxy-L-erythro-hex-2-enono-1,4-lactone 7.**—Trifluoroacetic anhydride (19.7 cm<sup>3</sup>, 0.14 mol, 2.2 equiv.) was added dropwise to a solution of triethylamine (28.3 ml, 0.203 mol, 3.2 equiv.) and the methanesulfonate **6** (14.13 g, 0.064 mol) in tetrahydrofuran (90 cm<sup>3</sup>) at –90 °C. After the addition was complete, the reaction mixture was stirred at –78 °C for 30 min and then at –25 °C for 30 min. The reaction mixture was then cooled to –78 °C, quenched by sequential addition of acetic acid (15 cm<sup>3</sup>) and methanol (30 cm<sup>3</sup>), and the resulting mixture allowed to stand at room

temperature for 3 h. TLC (ethyl acetate–hexane, 1:1) showed that a minor, intensely UV active spot ( $R_f$  0.5) and the major less UV active product **7** ( $R_f$  0.3) had been formed. Removal of solvent gave a residue which was partitioned between water (100 cm<sup>3</sup>) and ethyl acetate (200 cm<sup>3</sup>). The organic layer was removed and the aqueous layer then washed with ethyl acetate (2  $\times$  150 cm<sup>3</sup>). The organic layers were combined, washed with brine (50 cm<sup>3</sup>) and dried (MgSO<sub>4</sub>). The solvent was evaporated to yield an oil from which the remaining acetic acid was removed under reduced pressure before purification of the residue by flash chromatography (ethyl acetate–hexane, 7:13 graded to 3:2) to give 2-*O*-methanesulfonyl-3,6-dideoxy-L-erythro-hex-2-enono-1,4-lactone **7** (11.00 g, 0.05 mol, 79%), oil;  $[\alpha]_D^{20} + 58.1$  (*c* 2.1 in chloroform);  $\nu_{\max}(\text{neat})/\text{cm}^{-1}$  1776 (C=O) and 1650 (C=C) (Found: C, 38.05; H, 4.7. C<sub>7</sub>H<sub>10</sub>O<sub>6</sub>S requires C, 37.84; H, 4.54%);  $\delta_{\text{H}}(200 \text{ MHz}; \text{CDCl}_3)$  1.35 (3 H, d, *J* 6.5, 6-H), 3.38 (3 H, s, MeSO<sub>2</sub>), 4.09–4.18 (1 H, m, 5-H), 4.98 (1 H, dd, *J* 2, 4.5, 4-H) and 7.27 (1 H, d, *J* 2, 3-H);  $\delta_{\text{C}}(50.3 \text{ MHz}; \text{CD}_3\text{CN})$  167.3 (s, C-1), 138.9 (s, C-2), 135.8 (d, C-3), 83.7 (d, C-4), 67.7 (d, C-5), 38.9 (q, MeSO<sub>2</sub>) and 18.7 (q, C-6); *m/z* (DCI; NH<sub>3</sub>) 240 (M + NH<sub>4</sub><sup>+</sup>, 100) and 223 (M + H<sup>+</sup>, 6%).

**2-O-Methanesulfonyl-3,6-dideoxy-L-arabino-hexono-1,4-lactone 8.**—A solution of the unsaturated lactone **7** (9.00 g, 0.041 mol) in ethyl acetate (90 cm<sup>3</sup>) was stirred in an atmosphere of hydrogen in the presence of a catalyst of 10% palladium on carbon (0.90 g) for 3 h, after which time TLC (ethyl acetate–hexane, 1:1) showed the absence of any UV-active material. Magnesium sulfate (2 g) was then added and the catalyst was removed by filtration through Celite. The filter cake was washed with ethyl acetate (2  $\times$  50 cm<sup>3</sup>) and the solvent removed to give a white crystalline solid which was dissolved in ethyl acetate (50 cm<sup>3</sup>); diethyl ether (50 cm<sup>3</sup>) and hexane (50 cm<sup>3</sup>) were added to this solution and left to stand to allow the crystallisation of the lactone **8** (6.37 g) as a white crystalline solid; flash chromatography (ethyl acetate–hexane, 1:1) was performed on residue from evaporation of the mother liquor to give a further crop of 2-*O*-methanesulfonyl-3,6-dideoxy-L-arabino-hexono-1,4-lactone **8** (total amount 6.92 g, 0.031 mol, 76%), m.p. 94–95 °C;  $[\alpha]_D^{20} + 7.6$  (*c* 1.1 in CH<sub>3</sub>CN);  $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$  1794 (C=O) (Found: C, 37.25; H, 5.15. C<sub>7</sub>H<sub>12</sub>O<sub>6</sub>S requires C, 37.50; H, 5.39%);  $\delta_{\text{H}}(200 \text{ MHz}; \text{CD}_3\text{CN})$  1.10 (3 H, d, *J* 6.5, 6-H), 2.33 (1 H, dt, *J* 10, 12.5, 3-H), 2.73 (1 H, ddd, *J* 6, 9, 12.5, 3'-H), 3.21 (3 H, s, MeSO<sub>2</sub>), 4.02 (1 H, dq, *J* 3.5, 6.5, 5-H), 4.37 (1 H, m, *J* 3.5, 6, 10, 4-H) and 5.43 (1 H, dd, *J* 9, 10, 2-H);  $\delta_{\text{C}}(50.3 \text{ MHz}; \text{CD}_3\text{CN})$  171.7 (s, C-1), 80.2, 74.6, 66.0 (3  $\times$  d, C-2, C-4, C-5), 38.4 (q, MeSO<sub>2</sub>), 28.3 (t, C-3) and 17.1 (q, C-6); *m/z* (DCI; NH<sub>3</sub>) 242 (M + NH<sub>4</sub><sup>+</sup>, 100%).

**2,5-Anhydro-3,6-dideoxy-L-ribo-hexitol 10.**—Lithium borohydride (2 mol dm<sup>-3</sup> in tetrahydrofuran; 25.8 cm<sup>3</sup>, 0.0517 mol) was added to a solution of 2-*O*-methanesulfonyl-3,6-dideoxy-L-arabino-hexono-1,4-lactone **8** (9.01 g, 0.0404 mol) in tetrahydrofuran (120 cm<sup>3</sup>) at 0 °C. Vigorous effervescence and clouding of the solution occurred as the reaction mixture was allowed to warm to room temperature. After 15 min, TLC (methanol–ethyl acetate, 1:9) showed the starting material ( $R_f$  0.6) had been replaced by an open-chain hydroxymethanesulfonate **9** ( $R_f$  0.15); the reaction was quenched by addition of ammonium chloride (7.5 g) and the slow dropwise addition of methanol (25 cm<sup>3</sup>). The reaction mixture was filtered through Celite and the filter cake was washed with acetonitrile (2  $\times$  30 cm<sup>3</sup>). Removal of the combined solvents gave a solid, white residue that was pre-adsorbed on to silica prior to flash chromatography (ethyl acetate–hexane, 3:1 graded to methanol–ethyl acetate, 1:9) to give a mixture of uncyclised **9** ( $R_f$  0.15) and cyclised **10** ( $R_f$  0.25) products. The solvent was removed under reduced pressure and the residue redissolved in acetonitrile (100 cm<sup>3</sup>); the resulting

solution was treated with sodium acetate (5.00 g, 0.061 mol) and then heated under reflux for 8 h after which time only the cyclised product **10** ( $R_f$  0.25) was present. The reaction mixture was filtered and the solvents removed to give a residue which was purified by flash chromatography (ethyl acetate–hexane, 4:1 graded to pure ethyl acetate) to give 2,5-anhydro-3,6-dideoxy-L-ribo-hexitol **10** (3.67 g, 68%), oil;  $[\alpha]_D^{20} - 6.0$  ( $c$  0.5 in  $\text{CHCl}_3$ ) {lit.,<sup>12</sup>  $[\alpha]_D^{20} - 6.0$  ( $c$  0.5 in  $\text{CHCl}_3$ )};  $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$  3369 (OH str);  $\delta_{\text{H}}(200 \text{ MHz}; \text{CD}_3\text{CN})$  1.13 (3 H, d,  $J$  6.5, 6-H), 1.73 (1 H, ddd,  $J$  3.5, 6.5, 13, 3-H), 1.88 (1 H, ddd,  $J$  6.5, 8.5, 13, 3'-H), 3.39 (1 H, dd,  $J$  5, 11.5, 1-H), 3.52 (1 H, dd,  $J$  3.5, 11.5, 1'-H), 3.66–3.76 (1 H, m, 5-H), 3.78–3.86 (1 H, m, 4-H) and 4.00–4.12 (1 H, m, 2-H);  $\delta_{\text{C}}(50.3 \text{ MHz}; \text{CD}_3\text{CN})$  82.9, 79.4, 77.4 (3  $\times$  d, C-2, C-3, C-5), 65.2 (t, C-1), 36.7 (t, C-4) and 19.6 (q, C-6);  $m/z$  (DCI;  $\text{NH}_3$ ) 150 ( $\text{M} + \text{NH}_4^+$ , 100) and 133 ( $\text{M} + \text{H}^+$ , 44%).

**2,5-Anhydro-3,6-dideoxy-1-O-toluene-p-sulfonyl-L-ribo-hexitol 12.**—Toluene-*p*-sulfonyl chloride (1.1 equiv., 0.0306 mol, 5.83 g) in tetrahydrofuran (14  $\text{cm}^3$ ) was added dropwise to a stirred solution of 2,5-anhydro-3,6-dideoxy-L-ribo-hexitol **10** (3.67 g, 0.0278 mol) in pyridine (60  $\text{cm}^3$ ) at  $-10^\circ\text{C}$ . The reaction mixture was allowed to warm to room temperature and stirred for 16 h when TLC (ethyl acetate) indicated the presence of a trace of starting material ( $R_f$  0.15), the monotosylate **12** ( $R_f$  0.45) and a small amount of the ditosylate **11** ( $R_f$  0.7). The reaction was quenched by the addition of methanol (10  $\text{cm}^3$ ) and the solvent removed under reduced pressure. The residue was partitioned between aqueous hydrochloric acid (2 mol  $\text{dm}^{-3}$ ; 50  $\text{cm}^3$ ) and ethyl acetate (100  $\text{cm}^3$ ). The aqueous phase was extracted with ethyl acetate (2  $\times$  100  $\text{cm}^3$ ) and the combined organic extracts were washed with brine (50  $\text{cm}^3$ ) and dried ( $\text{MgSO}_4$ ). Solvent removal gave an oil which was purified by flash chromatography (diethyl ether–hexane, 7:3 graded to pure diethyl ether) to yield 1,4-di-O-toluene-*p*-sulfonyl-2,5-anhydro-3,6-dideoxy-L-ribo-hexitol **11** (0.90 g, 7%), m.p.  $74\text{--}75^\circ\text{C}$ ;  $[\alpha]_D^{20} - 13.3$  ( $c$  1.1 in  $\text{CH}_3\text{CN}$ ) (Found: C, 54.35; H, 5.5.  $\text{C}_{20}\text{H}_{24}\text{O}_7\text{S}_2$  requires C, 54.53; H, 5.49%);  $\delta_{\text{H}}(200 \text{ MHz}; \text{CDCl}_3)$  1.06 (3 H,  $J$  6.5, 6-H), 1.95–2.03 (2 H, m, 3-H), 2.44 (3 H, s, ArMe), 2.46 (3 H, s, ArMe), 3.94–4.11 (3 H, m), 4.16–4.26 (1 H, m), 4.53–4.59 (1 H, m), 7.34–7.38 (4 H, m, ArH) and 7.74–7.79 (4 H, m, ArH);  $\delta_{\text{C}}(50.3 \text{ MHz}; \text{CDCl}_3)$  145.4, 145.2 (s, ArC), 133.6, 132.8 (s, ArC), 130.2, 130.0 (d, ArC), 128.0, 127.9 (d, ArC), 85.1, 80.1, 75.3 (d, C-2, C-4, C-5), 70.1 (t, C-1), 33.7 (t, C-3), 21.5 (q, 2  $\times$  ArMe) and 18.7 (q, C-6);  $m/z$  (DCI;  $\text{NH}_3$ ) 458 ( $\text{M} + \text{NH}_4^+$ , 100) 441 ( $\text{M} + \text{H}^+$ , 3%), and 2,5-anhydro-3,6-dideoxy-1-O-toluene-*p*-sulfonyl-L-ribo-hexitol **12**, oil (6.11 g, 0.0213 mol, 77%);  $[\alpha]_D^{20} - 0.4$  ( $c$  0.5,  $\text{CHCl}_3$ ) {lit.,<sup>12</sup>  $[\alpha]_D^{20} + 3.6$  ( $c$  0.5  $\text{CHCl}_3$ )};  $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$  3425br (OH);  $\delta_{\text{H}}(500 \text{ MHz}; \text{CDCl}_3)$  1.16 (3 H, d,  $J$  6.4, 6-H), 1.91 (1 H, ddd,  $J$  3.4, 6.7, 13.2, 3-H), 2.01 (1 H, ddd,  $J$  6.3, 8.5, 13.2, 3'-H), 2.45 (3 H, s, ArMe), 3.86 (1 H, qd,  $J$  3.5, 6.4, 5-H), 3.99–4.01 (1 H, m, 4-H), 4.03 (1 H, dd,  $J$  4.7, 10.4, 1-H), 4.09 (1 H, dd,  $J$  4, 10.4, 1'-H), 4.28–4.32 (1 H, m, 2-H), 7.35 (2 H, d,  $J$  8, ArH) and 7.79–7.81 (2 H, m, ArH);  $\delta_{\text{C}}(50.3 \text{ MHz}; \text{CDCl}_3)$  145.2 (s, ArC), 132.8 (s, ArC), 130.0, 128.1 (2  $\times$  d, ArCH), 82.7, 76.8, 75.0 (3  $\times$  d, C-2, C-4, C-5), 71.4 (t, C-1), 36.2 (t, C-3), 21.5 (q, ArMe) and 19.2 (q, C-6);  $m/z$  (DCI;  $\text{NH}_3$ ) 304 ( $\text{M} + \text{NH}_4^+$ , 67) and 287 ( $\text{M} + \text{H}^+$ , 100%).

**(+)-Muscarine Toluene-*p*-sulfonate Salt 1.**—Trimethylamine (70  $\text{cm}^3$ ) was added to a solution of the tosylate **12** (6.44 g, 0.022 mol) in methanol (70  $\text{cm}^3$ ). The reaction mixture was poured into a pressurisable vessel and heated to  $80^\circ\text{C}$  for 6 h at which time TLC (ethyl acetate–hexane, 3:1) indicated the presence of only a trace of starting material ( $R_f$  0.75) and substantial amounts of baseline products. The solvent was removed under reduced pressure and the brown, oily residue partitioned between distilled water (100  $\text{cm}^3$ ) and ethyl acetate (80  $\text{cm}^3$ ).

After removal of the aqueous phase, the organic layer was washed with water (50  $\text{cm}^3$ ). The aqueous phases were combined and the solvent removed to yield a light brown crystalline solid which was recrystallised from hot acetone (50  $\text{cm}^3$ ) to give (+)-[(2*S*,4*R*,5*S*)-4-hydroxy-5-methyltetrahydrofuran-2-ylmethyl](trimethyl)ammonium toluene-*p*-sulfonate **1** as a white crystalline solid (5.01 g, 0.0147 mol, 67%), m.p.  $109\text{--}110^\circ\text{C}$ ;  $[\alpha]_D^{20} + 3.1$  ( $c$  3.6 EtOH) {lit.,<sup>12</sup> m.p.  $110\text{--}112^\circ\text{C}$ ;  $[\alpha]_D^{20} + 4$  ( $c$  4, EtOH)} (Found: C, 55.45; H, 8.0; N, 4.35.  $\text{C}_{16}\text{H}_{27}\text{NO}_5\text{S}$  requires C, 55.63; H, 7.88; N, 4.05%);  $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$  3410br (OH);  $\delta_{\text{H}}(500 \text{ MHz}; \text{D}_2\text{O})$  1.08 (3 H, d,  $J$  6.6, 6-H), 1.86 (1 H, ddd,  $J$  5.8, 9.7, 13.7, 3-H), 1.98 (1 H, ddd,  $J$  2.2, 6.2, 13.7, 3-H), 2.28 (3 H, s, ArMe), 3.07 (9 H, s, MeN), 3.32 (1 H, dd,  $J$  9.4, 14.0, 1-H), 3.45 (1 H, dd,  $J$  1.7, 14.0, 1-H), 3.93 (1 H, qd,  $J$  2.5, 6.7, 5-H), 3.98–4.00 (1 H, m), 4.50–4.59 (1 H, m), 7.26 (2 H, d,  $J$  8.0, ArH) and 7.57–7.58 (2 H, m, ArH);  $\delta_{\text{C}}(50.3 \text{ MHz}; \text{D}_2\text{O})$  142.5 (s, ArC), 140.0 (s, ArC), 130.1, 126.1 (2 d, ArCH), 84.7, 76.0, 72.6 (3 d, C-2, C-4, C-5), 71.3 (t, C-1), 54.8 (q, MeN), 38.4 (t, C-3), 21.1 (q, ArMe) and 19.8 (q, C-6);  $m/z$  (FAB) 174 ( $\text{M}^+$ , 100) and 58 (23%).

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