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3R-HYDROXYMUSCARINE FROM L-RHAMNOSE WITHOUT PROTECTION

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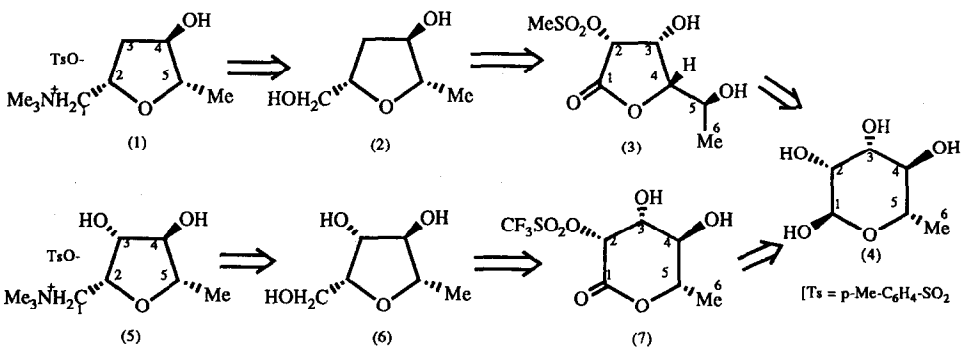
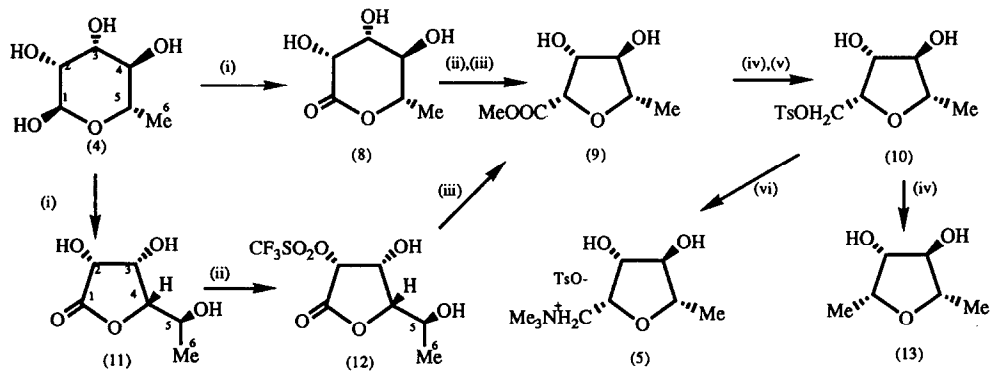
Abstract: The synthesis of the muscarine analogue 3R-3-hydroxymuscarine [(2S,3R,4R,5S)-3,4-dihydroxy-tetrahydro-N,N,N,5-tetramethyl-2-furanmethanimium tosylate] from L-rhamnose does not require the use of any protecting group.

The action of the neurotransmitter acetylcholine is mediated by several different receptors in a number of different tissues.[1,2] There is much current interest in the design and mechanism of action of agents which are specific agonists or antagonists of individual muscarinic receptors.[3] For example, a centrally active selective muscarinic agonist may relieve the memory loss associated with Alzheimer's disease;[4,5,6] also, selective muscarinic receptor antagonistic,[7] antispasmodic and local anaesthetic activities rationalise the effectiveness of oxybutynin in the treatment of the relief of symptoms in neurogenic bladder.[8] Although much effort has been invested in the synthesis of analogues of muscarine (1),[9] there are no examples of compounds - such as hydroxymuscarine (5) - which have a substituent at C-3,[10] the unsubstituted position of the tetrahydrofuran ring. Muscarine (1)[11,12] may be efficiently prepared from L-rhamnose (4) by a strategy in which the tetrahydrofuran ring is constructed by nucleophilic displacement of a leaving group at C-2 by the oxygen function at C-5 of the sugar; reduction of the 2-O-mesylate of γ-rhamnonolactone (3) and subsequent cyclisation afforded the diol (2)[13] which has previously been converted into muscarine.[14] This paper reports the synthesis of 3-hydroxymuscarine (5) in which the 2-O-triflate of δ-rhamnonolactone (7) is converted into the tetrahydrofuran carboxylate (9) by a novel ring contraction[15] and followed by reduction to the triol (6). An alternative approach from γ-rhamnonolactone (11) which proceeds *via* a common open chain trihydroxy triflate, is also described.



For the synthesis of 3-hydroxymuscarine (5), oxidation of L-rhamnose (4) with aqueous bromine in the presence of a barium carbonate buffer gave a mixture of the δ- (8) and γ- (11) lactones in 75% yield in a ratio of 2:1; recrystallisation from acetone afforded pure L-rhamnono-1,5-lactone (8),[16] $[\alpha]_D^{20}$ -104.9 (*c* 3 in water), [lit.[17] $[\alpha]_D^{20}$ -98 (*c* 3 in water). Under the kinetic conditions of buffered bromine water oxidation, the major product is the δ-lactone (8); if the mixture of lactones is subsequently subjected to treatment with aqueous trifluoroacetic acid, only the thermodynamic γ-lactone (11) is formed. Treatment of the δ–lactone (8) with trifluoromethanesulphonic (triflic) anhydride (1.2 equiv.) in tetrahydrofuran:pyridine (2:1) caused selective esterification of the hydroxyl group at C-2 to give the unstable lactone triflate (7); when the reaction mixture was worked up in the presence of methanol, the tetrahydrofuran carboxylic ester (9),[18,19] m.p. 83-84°C, $[\alpha]_D^{20}$ -12.4 (*c* 1.0 in acetonitrile) was formed in an overall yield of 62% from (8). The formal ring contraction of (7) to (9) involves nucleophilic attack by methoxide on the carbonyl of (3) to give an open chain trihydroxytriflate which cyclises by nucleophilic displacement of the triflate by the C-5 hydroxyl function with inversion of configuration at C-2. The same open chain trihydroxytriflate intermediate may also be generated from the 2-O-triflate of rhamnono-1,4-lactone (12),[20] m.p. 128-130°C, $[\alpha]_D^{20}$ -7.3 (*c* 1.0 in acetonitrile), prepared in 85% yield by selective esterification of γ-lactone (11) by triflic anhydride (1.4 equiv); reaction of (12) with pyridine in methanol also gave the tetrahydrofuran carboxylate (9) in 71% yield. The reaction of the γ-lactone triflate (12) was slower than that of the corresponding δ-lactone (7), indicating that the ring opening reaction of the γ-lactone is relatively difficult. The stereochemistry in methyl 2,5-anhydro-6-deoxy-L-gluconate (9) was firmly established by single X-ray crystallographic analysis (Figure).[21]



(i) bromine water, $BaCO_3$ buffer (ii) $(CF_3SO_2)_2O$, pyridine, THF (iii) pyridine in MeOH
(iv) $LiAlH_4$ in THF (v) TsCl in pyridine (vi) Me_3N in MeOH

Reduction of the methyl ester (9) with lithium aluminum hydride in tetrahydrofuran gave the triol (6)[22] [71% yield] which, with *p*-toluenesulphonyl chloride (0.8 equiv) in pyridine, afforded the tosylate (10), m.p. 132-133°C, $[\alpha]_D^{20}$ +4.0 (*c* 0.9 in acetonitrile) in 38% yield. It was just possible that epimerisation at C-2 might have occurred during the reduction of the ester (9) to the triol (6); however, reaction of the tosylate (10) with lithium aluminum hydride in tetrahydrofuran gave (13); the ^{13}C NMR of (13)[23] shows six different signals for the carbon atoms indicating that the stereochemistry at C-2 has not been affected by the reduction as the alternative product would possess a two-fold rotation axis of symmetry. Reaction of the tosylate (10) with trimethylamine in methanol gave 3-hydroxymuscarine (5),[24] oil, $[\alpha]_D^{20}$ -0.1 (*c* 1.8 in MeOH) in 82% yield.

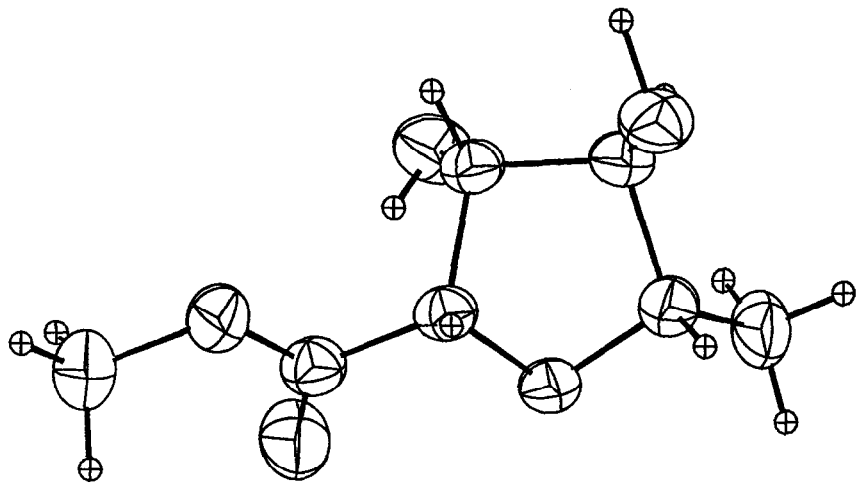


Figure: X-Ray molecular structure of methyl 2,5-anhydro-6-deoxy-L-gluconate (9)

It is noteworthy that in these syntheses of 3-hydroxymuscarine from L-rhamnose there is no need for the use of any protecting group at any stage; thus, there is considerable selectivity of the secondary hydroxyl groups of the rhamnonolactones in their reaction with triflic anhydride and additionally the resulting diolmonotriflates are relatively stable and easy to manipulate. It is clear that the strategies outlined in this paper will permit easy access to analogues of muscarine with a wide variety of substituent at C-3 in which the absolute and relative stereochemistry at all the other positions matches the natural product; such an approach will allow the evaluation of the interaction of a novel set of muscarine analogues with individual muscarinic receptors. The biological activity of 3-hydroxymuscarine and other 3-substituted analogues of muscarine will be reported in due course.

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10 All numbering in this paper refers to the carbons in L-rhamnose

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16 For (8): δ_C (D_2O): 176.6 (s, C-1), 77.5, 76.8, 75.6, 69.3 (4 x d, C-2, C-3, C-4, C-5), 19.1 (q, C-6) [dioxan (δ_C 67.8) as an internal standard].

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18 All new compounds reported in this paper have spectroscopic data consistent with the structures proposed. Satisfactory microanalytical data (CHN) has been obtained for all new compounds other than the unstable triflate (7); the very hygroscopic triol (6) was fully characterised as the corresponding triacetate. ^{13}C NMR spectra were obtained at 50.3 or 125 MHz for spectra.

19 For (9): δ_C (CD_3CN): 170.42 (s, C-1), 82.13, 81.29, 80.34, 78.88 (4 x d, C-2, C-3, C-4, C-5), 51.20 (q, CO_2Me), 18.18 (q, C-6).

20 For (12): δ_C (CD_3CN): 169.7 (s, C-1), 118.5 (q, CF_3), 83.6, 82.0, 69.3, 64.5 (4 x d, C-2, C-3, C-4, C-5), 19.9 (q, C-6).

21 The crystal data, atomic coordinates, bond lengths and thermal parameters for methyl 2,5-anhydro-6-deoxy-L-gluconate (9) have been deposited at the Cambridge Crystallographic Data Centre.

22 For (6): δ_C (CD_3CN): 82.6 (x 2), 79.7, 74.9 (4 x d, C-2, C-3, C-4, C-5), 61.6 (t, C-1), 19.0 (q, C-6).

23 For (13): δ_C ($CDCl_3$): 84.8, 80.5, 80.4, 76.5 (4 x d, C-2, C-3, C-4, C-5), 19.0 (q, C-6), 13.9 (q, C-1).

24 For (5): δC (D_2O): 143.1 (s, ArC),140.6 (s, ArC), 130.2 (d, ArC), 126.2 (d, ArC), 83.0, 82.5, 81.6, 75.0 (4 x d, C-2, C-3, C-4, C-5), 67.2 (t, C-1), 54.9 (q, NMe3), 21.2 (q, ArMe), 19.0 (q, Me). [methanol (δ_C 49.7) as an internal standard].

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