(+)-Muscarine From L-Rhamnose

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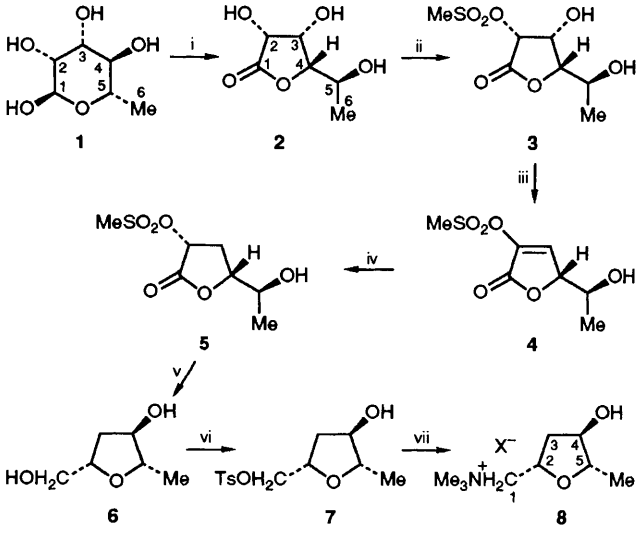
A short synthesis of (+)-muscarine from L-rhamnose which does not require the use of any protecting group is described.

The pharmacological properties of (+)-muscarine **8** as a cholinergic agonist have ensured long standing studies of the synthesis of muscarine itself and of its stereoisomers.[1] These interests have been heightened by the discovery of a relationship between cholinergic deficits in cortical and hippocampal areas and the pathology of Alzheimer's disease,[2] and by the promise of cholinomimetics as potential therapeutic agents in the symptomatic treatment of senile cognitive decline.[3,4] Moreover, recent advances identifying subtypes of the muscarinic receptor have led to renewed focus on the search for selective muscarinic agonists. Among a variety of approaches to muscarine,[5] a synthesis from L-arabinose in 1957[6] provides an outstanding example of the use of carbohydrates as chiral starting materials. More efficient routes from D-mannitol[7,8] and D-mannonolactone[9] have been described, though these syntheses require a chromatographic separation of intermediate stereoisomers and/or regioisomers. There remains a need for simple syntheses of muscarine and its analogues; this paper reports a short synthesis of muscarine from rhamnose.

L-Rhamnose **1** is a uniquely attractive starting material for the synthesis of muscarine by a strategy in which the tetrahydrofuran (THF) ring is constructed by nucleophilic displacement of a leaving group at C-2 by the oxygen function at C-5 of the sugar; the functionality and chirality is correct at all the carbons of rhamnose, other than the need for the removal of the hydroxy group at C-3. The sugar is even more ideally substituted for the construction of analogues of muscarine in which the three substituents of muscarine itself have the correct stereochemistry and functionality, and there is an additional substituent at C-3.

For the synthesis of (+)-muscarine **8**, L-rhamnose **1** is treated with aqueous bromine in the presence of a barium carbonate buffer, followed by treatment with aqueous trifluoroacetic acid, to give the γ-lactone **2**,† $[\alpha]_D^{20}$ −39.4 (*c* 2.02 in water), {lit.[10] $[\alpha]_D^{20}$ −40 (*c* 1.97 in water)}, in 70% yield. The hydroxy group at C-2 in **2** may be selectively esterified by methanesulphonyl chloride in pyridine at 0 °C to give the mesylate **3**,‡ m.p. 96–97 °C, $[\alpha]_D^{20}$ −9.1 (*c* 1.08 in acetonitrile) in 60% yield. The diol **3** was reacted with trifluoroacetic anhydride and triethylamine in THF to give the corresponding bis(trifluoroacetate) which under the reaction conditions underwent base catalysed elimination; work up in the presence of acetic acid and methanol resulted in deesterification of the remaining trifluoroacetate ester to give the vinyl mesylate **4**,‡ $[\alpha]_D^{20}$ + 58.1° (*c* 2.1 in chloroform) (76% yield from **3**). Hydrogenation of the unsaturated lactone **4** in ethyl acetate in the presence of 10% palladium on carbon resulted in a highly stereoselective reduction to afford the 3-deoxyrhamnose derivative **5**,‡ m.p. 94–95 °C, $[\alpha]_D^{20}$ −15.1 (*c* 1.0 acetonitrile), in 81% yield. Further reduction of the lactone **5** by lithium borohydride in THF, followed by cyclisation induced by sodium acetate in acetonitrile, gave the alcohol **6**,‡ {$[\alpha]_D^{20}$ −6.0 (*c* 0.5 in chloroform), lit.[8] $[\alpha]_D^{20}$ −6.0 (*c* 0.5 in $CHCl_3$)}, in 76% yield (28% overall yield from **3**). Selective tosylation of the primary alcohol function in **6** by tosyl chloride in pyridine afforded the tosylate **7**[7,8]‡ $[\alpha]_D^{20}$ −0.4 (*c* 0.5 in $CHCl_3$), {lit.[8] $[\alpha]_D^{20}$ +3.6 (*c* 0.5 in $CHCl_3$)}, (78% yield); subsequent reaction of the tosylate with trimethylamine in methanol, gave muscarine tosylate (**8**: X = *p*-$MeC_6H_4SO_3^-$; 78% yield),‡ m.p. 109–110 °C, $[\alpha]_D^{20}$ +3.1 (*c* 3.6 in EtOH), {lit.[7] m.p. 110–112 °C, $[\alpha]_D^{20}$ +4 (*c* 4 in EtOH)}, previously obtained[8] in 95% yield.

In summary, no protecting group is necessary in this seven step synthesis of muscarine from rhamnose; more importantly, it is clear that analogues with ready control of substituents at the unsubstituted position of (+)-muscarine **8** may be readily prepared by using the oxygen function at C-3 of rhamnose.



Scheme 1 *Reagents and conditions*: i, bromine water, $BaCO_3$ buffer; aq. CF_3CO_2H; ii, $MeSO_2Cl$, pyridine, 4-dimethylaminopyridine, 0 °C; iii, $(CF_3CO)_2O$, Et_3N in THF; AcOH, MeOH; iv, H_2, 10% Pd/C, EtOAc; v, $LiBH_4$ in THF; then $MeCO_2Na$ in MeCN; vi, TsCl in pyridine; vii, Me_3N in MeOH

† For **2**: ^{13}C NMR (D_2O) δ_C 179.27 (s, C-1), 83.84 (d, C-4), 71.60, 70.14, 64.52 (3d, C-2, C-3, C-5), 19.51 (q, C-6).

‡ All new compounds reported in this paper have spectroscopic data consistent with the structures proposed; satisfactory microanalytical data (C, H and N) have been obtained for **3**, **4**, **5**, **7** and **8**. NMR spectra were obtained in CD_3CN unless otherwise stated .

For **3** δ_C 171.83 (s, C-1), 83.49, 77.30 (2d C-2, C-4), 69.52, 64.64 (2d, C-3, C-5), 39.34 (q, $MeSO_2$), 19.99 (q, C-6).

For **4** δ_C 167.30 (s, C-1), 138.94 (s, C-2), 135.77 (d, C-3), 83.69 (d, C-4), 67.49 (d, C-5), 39.87 (q, $MeSO_2$), 18.71 (q, C-6).

For **5** δ_C 172.56 (s, C-1), 81.02, 75.48 (2d, C-2, C-4), 66.87 (d, C-5), 39.27 (q, $MeSO_2$), 29.20 (t, C-3), 18.02 (q, C-6).

For **6** δ_C 82.92, 79.40, 77.41 (3d, C-2, C-4, C-5), 65.15 (t, C-1) 36.72 (t, C-3), 19.61 (q, C-6).

For **7** δ_C ($CDCl_3$) 132.93 (s, ArC), 129.99, 128.10 (2d, ArCH), 82.73, 76.8, 75.03 (3d, C-2, C-4, C-5), 71.27 (t, C-1), 36.14 (t, C-3), 21.48 (q, ArMe), 19.22 (q, C-6).

For **8**; X = TsO δ_C (D_2O) 145.15 (s, ArC), 142.47 (s, ArC), 140.01 (s, ArC), 130.10, 126.14 (2d, ArCH), 84.70, 75.98, 72.62 (3d, C-2, C-4, C-5), 71.34 (t, C-1), 54.81 (q, MeN), 38.36 (t, C-3), 21.14 (q, ArMe), 19.78 (q, C-6); for **8**; X = Cl δ_C (D_2O) 84.83, 75.92, 72.70 (3d, C-2, C-4, C-5), 71.16 (t, C-1), 54.60 (q, MeN), 38.15 (t, C-3), 19.77 (q, C-6).

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