STEREOSPECIFIC SYNTHESIS OF (+)-MUSCARINE FROM D-GLUCOSE, SUITABLE FOR PREPARATION OF 5-SUBSTITUTED ANALOGUES

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Dedicated to Dr Jan Fajkos on the occasion of his 75th birthday.

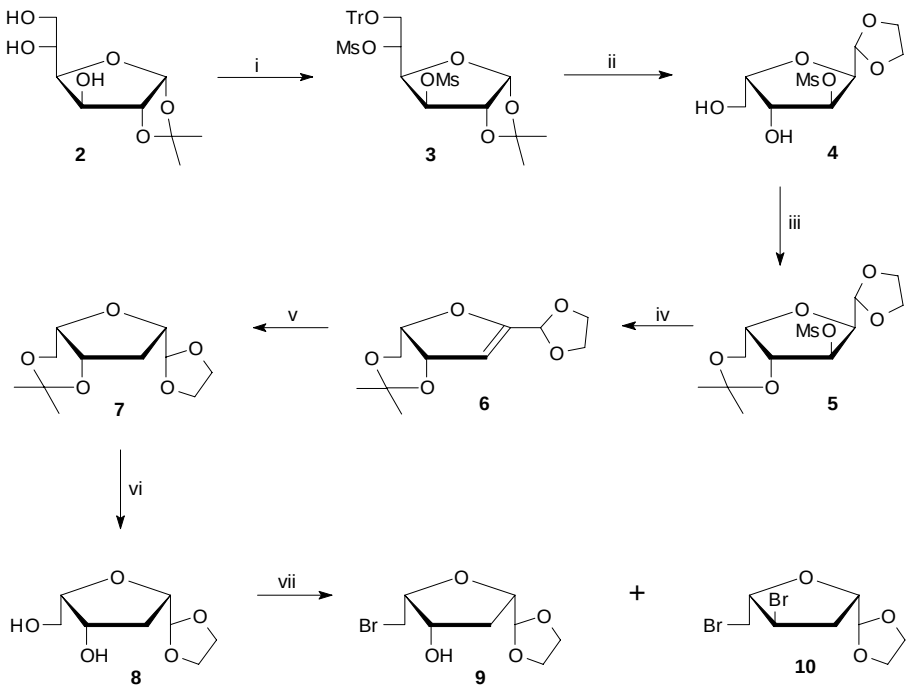
A stereospecific synthesis of (+)-muscarine iodide (**1**) has been achieved starting from D-glucose as a chiral precursor. The key steps of the synthesis involved a stereospecific cyclization of 3,5-di-*O*-mesyl derivative **3** into the 2,5-anhydride **4**, the stereospecific catalytic hydrogenation of unsaturated derivative **6**, and the C-4 epimerization of alcohol **12** by Mitsunobu reaction.
Key words: 2,5-Anhydro sugars; (+)-Muscarine, Stereospecific synthesis; Alkaloids, Carbohydrates.

(+)-Muscarine (**1**) is a principal alkaloid of the poisonous mushroom *Amanita muscaria*, which shows acetylcholine agonist activity towards the different subtypes of muscarinic receptors[1]. Recently, much progress has been made in the understanding of the muscarinic receptor sites and agonists or antagonists, which have a potential in the treatment of Alzheimer's disease[2]. Hence, synthetic activity in this area has been considerable and numerous syntheses of muscarine have been accomplished from different precursors[3]. Major drawbacks of most of these approaches are either lack of selectivity or the usage of relatively expensive reagents and/or starting compounds. Apart from a single synthesis of (–)-muscarine from (*S*)-malic acid[3d], none of the reported routes are suitable for the preparation of higher muscarine homologues. In the course of our studies related to preparation of optically pure muscarine stereoisomers by chirality transfer from D-glucose, the syntheses of (+)-epiallomuscarine[4], (–)-allomuscarine[5] and (+)-epimuscarine[6] were already accomplished. Herein we wish to report the first stereospecific synthesis of (+)-muscarine (**1**) based on D-glucose as a chiral precursor.

1,2-*O*-Isopropylidene-α-D-glucofuranose (**2**) readily available from D-glucose[7] was tritylated (TrCl, Py, rt, 72 h) and subsequently mesylated (MsCl, Py, +4 °C, 24 h) in a "one pot" procedure to afford a quantitative yield of the corresponding 3,5-di-*O*-mesyl-6-*O*-trityl derivative **3**. Treatment of compound **3** with ethylene glycol and *p*-toluene-

sulfonic acid, in refluxing benzene with azeotropic removal of water for 2 h gave the 2,5-anhydro-L-idose derivative **4** (51% from **2**). Reaction of **4** with 2,2-dimethoxypropane, in the presence of catalytic amounts of *p*-toluenesulfonic acid (rt, 24 h), afforded the corresponding 4,6-*O*-isopropyledene derivative **5** in 87% yield. Treatment of **5** with tetrabutylammonium fluoride, in boiling acetonitrile for 48 h, gave the corresponding 2,3-unsaturated derivative **6** in 76% yield. Catalytic hydrogenation of **6** (PtO_2, EtOH, rt, 24 h) took place stereospecifically (from the less hindered β-side) to afford the 3-deoxy derivative **7** as the only stereoisomer in high yield (94%). Selective removal of the 4,6-*O*-isopropylidene protective group in **7** was achieved with 10% trifluoroacetic acid in methanol (rt, 0.5 h) whereupon the corresponding diol **8** was obtained in 79% yield[8].

Comparing with the target molecule **1**, the intermediate **8** has the correct stereochemistry only at the C-2 and C-5 chiral centers. For the sake of better functional and stereochemical resemblance to the target, the molecule **8** must be further subjected to a C-6 deoxygenation and a Walden inversion at the C-4. This would lead to the key chiral

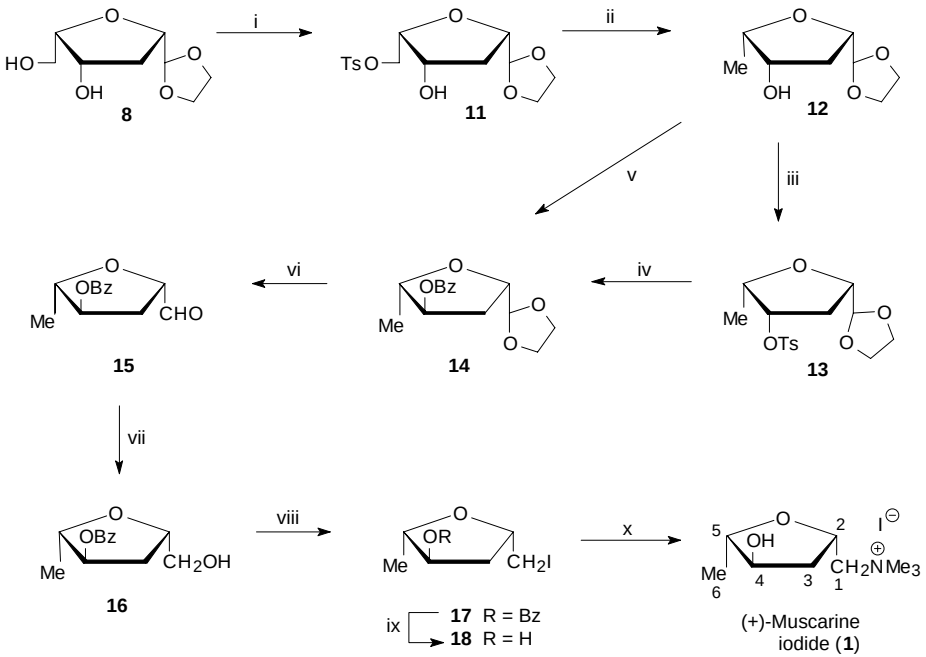


(i) TrCl, Py, rt, then MsCl, +4 °C (100%); (ii) Ethylene glycol, TsOH, benzene, reflux (51%); (iii) $Me_2C(OMe)_2$ TsOH, rt (87%); (iv)Bu_4NF, MeCN, reflux (76%); (v) H_2/PtO_2, EtOH, rt (94%); (vi) CF_3COOH, MeOH, rt (79%); (vii) CBr_4, Ph_3P, Py, rt (23% of **9** + 24% of **10**)

SCHEME 1

intermediate **14** with all stereocenters corresponding to (+)-muscarine. At first we have planned to deoxygenate the C-6 *via* the corresponding 6-bromo-6-deoxy derivative **9**. It was assumed that the diol **8** could be transformed to the bromo derivative **9** by using the $CBr_4/Ph_3P/Py$ reagent system which selectively reacted with the hydroxymethyl groups of certain sugar derivatives to give high yields of the corresponding primary bromodeoxy sugars. Conversely, the secondary hydroxyl groups remain unchanged under the recommended reaction conditions[9]. However, a treatment of the diol **8** with tetrabromomethane and triphenylphosphine (Py, rt) gave a low yield of the expected 6-bromo-6-deoxy derivative **9** (23%) accompanied by an equal amount of the 4,6-dibromo derivative **10**.

Obviously, the deoxy derivative **9** could be further converted to the advanced intermediate **12**, however a low yield of the preceding bromination forced us to use the known[6] but rather efficient two-step sequence for the preparation of compound **12**. It included previous conversion of diol **8** (TsCl, Py, 20 °C, 6 days) to the 6-*O*-tosyl deri-



(i) TsCl, Py, -20°C (80%); (ii) $LiAlH_4$, THF, reflux (90%); (iii) TsCl, Py, rt (80%); (iv) KOBz, DMF, 100 °C (66%); (v) PhCOOH, Ph_3P, DEAD, THF, rt; (vi) CF_3COOH, 6 M HCl, +4°C; (vii) $NaBH_4$, MeOH, RT (27% from **12**); (viii) I_2, Imidazole, Ph_3P, MePh, reflux (83%); (ix) K_2CO_3, MeOH, rt (83%); (x) Me_3N, EtOH, 80°C (76%)

SCHEME 2

vative **11** (80%), followed by reduction of **11** ($LiAlH_4$, THF↑↓, 4 h) to the desired intermediate **12** (90%).

Treatment of **12** with tosyl chloride (Py, rt, 48 h) gave the 4-*O*-tosyl derivative **13** in 80% yield. Compound **13** readily reacted with potassium benzoate (DMF, 100 °C, 24 h) to give the compound **14** (ref.[10]) (66%), with an absolute configuration of all stereogenic centers corresponding to (+)-muscarine. Compound **14** was alternatively prepared directly from **12** by using the standard Mitsunobu[11] conditions (PhCOOH, Ph_3P, DEAD, THF, rt, 24 h). However, thus obtained sample **14** was slightly contaminated with unidentified aromatic impurities that remained in the sample even after repeated chromatographic purification. Fortunately, these impurities did not affect the course of the following reaction directed to the hydrolytic removal of the dioxolane protective group.

Treatment of **14** with a mixture of trifluoroacetic and 6 M hydrochloric acid (4 : 1; +4 °C, 24 h) gave the unstable aldehyde **15** which was immediately reduced with sodium borohydride (MeOH, rt, 24 h) to afford the corresponding primary alcohol **16** (ref.[12]) (27% from **12**). Reaction of **16** with iodine, imidazole and triphenylphosphine (MePh↑↓, 3 h) gave the known[13] iodo derivative **17** (ref.[14]) in 83% yield. *O*-Debenzoylation of **17** with potassium carbonate (MeOH, THF, rt, 1.5 h) afforded the iodo alcohol **18** (ref.[15]) in 83% yield.

Finaly, compound **18** was converted to (+)-muscarine iodide (**1**) by treatment with trimethylamine (EtOH, 80 °C, 3 h). The ^1H and ^{13}C NMR spectral data (Table I) as well as physical constants of **1** thus obtained were in reasonable agreement with those already reported[13].

In conclusion, a practical multistep synthesis of (+)-muscarine was developed starting from D-glucose as a chiral precursor. Each step of the synthesis was realized in a

TABLE I
NMR Spectral data for (+)-muscarine iodide (**1**; in D_2O)

	Chemical shifts (δ) and *J* (Hz)								
	H-1a	H-1b	H-2	H-3a	H-3b	H-4	H-5	H-6	
This work	3.48	3.62	4.66	2.01	2.12	4.13	4.06	1.21	
Ref.[13]	3.39	3.49	4.57	1.91	2.01	4.03	3.96	1.11	
	$J_{1a,1b}$	$J_{1a,2}$	$J_{1b,2}$	$J_{2,3a}$	$J_{2,3b}$	$J_{3a,3b}$	$J_{3a,4}$	$J_{3b,4}$	$J_{4,5}$
This work	14.0	9.1	1.8	9.5	6.4	13.7	5.9	2.4	2.5
Ref.[13]	14.0	9.2	1.8	9.6	6.3	13.7	5.7	2.3	2.5
	C-1	C-2	C-3	C-4	C-5	C-6	NMe_3		
This work	73.21	74.66	40.23	77.87	86.77	21.89	56.70		
Ref.[13]	73.51	74.85	40.53	78.13	86.91	22.11	57.09		

fully regio- and stereospecific manner, using inexpensive reagents and a readily available starting material. This approach is potentially useful for the preparation of a variety of 5-substituted (+)-muscarine analogues, by starting from D-glucose derivatives bearing the appropriate functional groups at C-6.

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8. Compound **8** was synthesized earlier by an independent six-step route (ref.[6]) in 17.43% overall yield in respect to the starting triol **2**. The sequence presented here represents a more convenient route towards the intermediate **8**, because it provided higher overall yield of the desired product (25.04% in 6 steps).
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10. Compound **14** (syrup): $[\alpha]_D$ +0.53 (*c* 1.7, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.34 d, 3 H, *J*(5,6) = 6.6 Hz (Me-6), 2.15 ddd, 1 H, *J*(3a,3b) = 13.8, *J*(2,3a) = 6.3, *J*(3a,4) = 2.4 Hz (H-3a), 2.25 ddd, 1 H, *J*(2,3b) = 9.4, *J*(3b,4) = 5.9 Hz (H-3b), 3.82–4.07 m, 4 H (dioxolane CH_2), 4.14–4.29 m, 2 H, *J*(1,2) = 5.5, *J*(4,5) = 2.7 Hz (H-2 and H-5), 4.93 d, 1 H (H-1), 5.15 m, 1 H (H-4), 7.40-8.10 m, 5 H (Ph); ^{13}C NMR ($CDCl_3$): δ 19.78 (C-6), 32.97 (C-3), 65.43 and 65.56 (dioxolane CH_2), 79.07 (C-2), 79.88 (C-4), 81.01 (C-5), 104.73 (C-1), 128.45, 129.65, 129.97 and 133.22 (aromatic), 166.14 (C=O); CI MS (*i*-C_4H_{10}): *m/e* 278 (M^+).
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12. Alcohol **16** (syrup): $[\alpha]_D$ –7.85 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.35 d, 3 H, *J*(5,6) = 6.5 Hz (Me-6), 2.04 ddd, 1 H, *J*(3a,3b) = 13.7, *J*(2,3a) = 5.6, *J*(3a,4) = 1.9 Hz (H-3a), 2.24 ddd, overlapped with bs, 2 H, *J*(2,3b) = 10.2, *J*(3b,4) = 6.3 Hz (H-3b and OH), 3.59 m, after addition of D_2O dd, 1 H, *J*(1a,1b) = 11.9, *J*(1a,2) = 4.6 Hz (H-1a), 3.87 m, after addition of D_2O dd, 1 H, *J*(1b,2) = 2.9 Hz (H-1b), 4.22 dq, 1 H, *J*(4,5) = 2.6 Hz (H-5), 4.32 m, 1 H (H-2), 5.14 dt, 1 H (H-4), 7.40-8.08 m, 5 H (Ph); ^{13}C NMR ($CDCl_3$): δ 19.79 (C-6), 33.04 (C-3), 63.79 (C-1), 79.06 (C-5), 80.36 (C-2), 80.64 (C-4), 128.37, 129.55, 129.87 and 133.16 (aromatic), 166.11 (C=O); CI MS (*i*-C_4H_{10}): *m/e* 237 (M^+ + H).

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14. Iodo derivative **17**: $[\alpha]_D$ –7.57 (*c* 0.37, $CHCl_3$); m.p. 68 °C (from hexane). Ref.[13]: $[\alpha]_D$ –11.67 (*c* 0.93, $CHCl_3$); m.p. 68 °C (from hexane).
15. Iodo alcohol **18** (syrup): $[\alpha]_D$ –33.26 (*c* 0.87, $CHCl_3$). Ref.[13]: $[\alpha]_D$ –30.72 (*c* 0.87, $CHCl_3$).