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Note

# An alternative synthesis of (+)-*epiallo*-muscarine from D-glucose

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Preparation of muscarine and its analogues in optically pure form has attracted considerable interest mainly due to their marked biological activity [1]. Several syntheses of muscarine stereoisomers have been achieved so far [2], including the synthesis of (+)-*epiallo*-muscarine (**1**) from D-glucose [3]. However, the last synthesis [3] included a non-regiospecific step so that the separation of two structural isomers was needed.

By utilizing a similar 'chiron approach' we have accomplished an alternative synthesis of (+)-*epiallo*-muscarine from D-glucose, in which each step of the synthesis was realized in a fully regio- and stereo-specific manner.

Trimesylate **2**, readily available from D-glucose [4], reacted with ethylene glycol in the presence of toluene-*p*-sulfonic acid as a catalyst (8.5 h at 100°C) to afford the 2,5-anhydro-L-idose derivative **3** in 62% yield. Similar cyclizations of sugar 5-sulfonates have already been described in the literature [5]. Treatment of **3** with benzoyl chloride in pyridine for 3.5 h at room temperature gave the corresponding 4-*O*-benzoyl derivative **4** in a yield of 87%. Inter- and intra-molecular attack of hydrogensulfide anion on **4** (NaSH, DMF, 80°C) led to the bicyclic oxathiane derivative **5** isolated after silica gel column chromatography in 67% yield. However, when the process was carried out without purification of intermediate **4**, the desired product **5** was obtained in an overall yield of 74% with respect to compound **3**. Raney nickel desulfurization of **5** in ethanol for 1.5 h at 80°C afforded the key chiral synthon **6** (63%), with all chiral centres corresponding to (+)-*epiallo*-muscarine (**1**).

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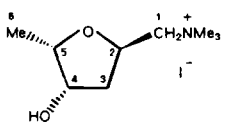
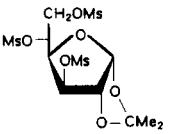


(+)-epiallo-Muscarine iodide (1)



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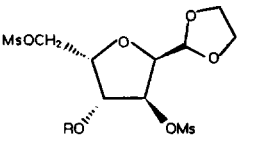
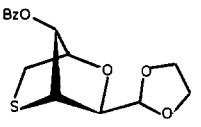


3 R = H

4 R = Bz



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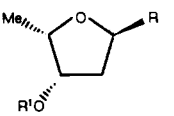

6 R =  ; R' = Bz

7 R = CHO; R' = Bz

8 R = $CH_2OH$; R' = Bz

9 R = $CH_2I$; R' = Bz

10 R = $CH_2NMe_2$; R' = H

Treatment of **6** with 18:1:1 trifluoroacetic acid–concd hydrochloric acid–water for 24 h at room temperature gave the unstable aldehyde **7** which was immediately reduced with sodium borohydride in methanol for 30 min at room temperature, to afford the corresponding alcohol **8** (46% from **6**). Reaction of **8** with iodine, imidazole, and triphenylphosphine [6] in refluxing toluene for 2 h afforded the corresponding iodo derivative **9** in 91% yield. Treatment of **9** with dimethylamine in alcohol at 80°C overnight, followed by subsequent debenzoylation, gave the known [2] (+)-*epiallo*-normuscarine (**10**) in 62% yield. Tertiary amine **10** was converted into (+)-*epiallo*-muscarine iodide (**1**) according to the described procedure [2]. The $^{1}H$ and $^{13}C$ NMR data as well as the melting point and optical rotation of **1** thus obtained were in agreement with those already reported [2].

## 1. Experimental

*General methods.*—Melting points were determined on a Büchi SMP 20 apparatus and were not corrected. Optical rotations were measured on an automatic polarimeter Polamat A (Karl Zeiss, Jena). NMR spectra were recorded on a Bruker AC 250 E instrument and chemical shifts are expressed in ppm downfield from tetramethylsilane. TLC was performed on DC Alufolien Kieselgel 60 $F_{254}$ (Merck) and column chromatography was carried out using Kieselgel 60 (under 0.063 mm; Merck). Flash chromatography was performed using ICN silica 32–63. All organic extracts were dried with anhydrous $Na_2SO_4$.

*2,5-Anhydro-3,6-di-*O*-methanesulfonyl-*L*-idose ethylene acetal* (**3**).—A solution of trimesylate [4] **2** (22 g, 48.46 mmol) and toluene-*p*-sulfonic acid (2.2 g, 11 mmol) in ethylene glycol (200 mL) was stirred at 100°C for 8.5 h. The mixture was then poured into satd aq NaCl (200 mL), neutralized with $NaHCO_3$ (7 g), and extracted with $CH_2Cl_2$ (4 × 100 mL). The combined extracts were dried and evaporated in vacuo. The solid residue (20 g) was recrystallized from MeOH to afford pure **3** (10.95 g, 62%) as white needles; mp 126°C; $[\alpha]_D$ −32.34° (*c* 1.0, $CHCl_3$). $^1$H NMR (pyridine-$d_5$): δ 3.32 and 3.4 (2 s, each 3 H, 2 $CH_3SO_2$), 3.65–4.05 (m, 4 H, dioxolane), 4.6 (dd, 1 H, $J_{2,3}$ 3.8, $J_{1,2}$ 6.6 Hz, H-2), 4.8 (m, 1 H, H-5), 4.9 (m, 2 H, H-6a and H-6b), 4.99 (dd, 1 H, $J_{3,4}$ 1.6, $J_{4,5}$ 3 Hz, H-4), 5.12 (bs, 1 H, OH), 5.36 (d, 1 H, H-1), 5.5 (dd, 1 H, H-3). $^{13}$C NMR (pyridine-$d_5$): δ 37.41 and 38.27 (2 $CH_3SO_2$), 65.33 and 65.43 (2 $CH_2$, dioxolane), 69.94 (C-6), 75.33, 79.91, 80.19, and 86.47 (C-2, C-3, C-4, and C-5), 102.61 (C-1). Anal. Calcd for $C_{10}H_{18}O_{10}S_2$: C, 33.15; H, 5.01; S, 17.69. Found: C, 33.04; H, 5.05; S, 17.48.

*2,5-Anhydro-4-*O*-benzoyl-3,6-di-*O*-methanesulfonyl-*L*-idose ethylene acetal* (**4**).—To a solution of **3** (2.32 g, 6.41 mmol) in dry pyridine (21 mL) was added benzoyl chloride (2.5 mL, 21.54 mmol). The mixture was kept at room temperature for 3.5 h, then acidified with aq 10% HCl (150 mL) and extracted with $CH_2Cl_2$ (5 × 30 mL). The extracts were combined, washed with water and satd aq $NaHCO_3$, dried, and concentrated to a yellow syrup. Crystallization from dry MeOH afforded pure **4** (2.6 g, 87%) as white needles; mp 116–117°C; $[\alpha]_D$ −22.12° (*c* 1.0, $CHCl_3$). $^1$H NMR ($CDCl_3$): δ 3.01 and 3.19 (2 $CH_3SO_2$), 3.8–4.15 (m, 4 H, dioxolane), 4.25 (dd, 1 H, $J_{2,3}$ 4.3, $J_{1,2}$ 5.8 Hz, H-2), 4.44 (d, 2 H, H-6a and H-6b), 4.78 (m, 1 H, H-5), 5.16 (d, 1 H, H-1), 5.27 (dd, 1 H, $J_{3,4}$ 2.1, $J_{4,5}$ 4.3 Hz, H-4), 7.44–8.02 (m, 5 H, aromatic). $^{13}$C NMR ($CDCl_3$): δ 37.72 and 38.39 (2 $CH_3SO_2$), 65.44 (2 $CH_2$, dioxolane), 66.29 (C-6), 76.32, 77.0, 79.69, and 81.76 (C-2, C-3, C-4, and C-5), 101.51 (C-1), 128.71, 129.84, and 134.0 (aromatic), 165.14 (C = O). Anal. Calcd for $C_{17}H_{22}O_{11}S_2$: C, 43.77; H, 4.75; S, 13.75. Found: C, 43.59; H, 4.82; S, 13.61.

*2,5-Anhydro-4-*O*-benzoyl-3,6-thioanhydro-*L*-talose ethylene acetal* (**5**).—(*a*). To a solution of **4** (1.75 g, 3.8 mmol) in *N*,*N*-dimethylformamide (20 mL) was added NaSH monohydrate (1.55 g; 21.5 mmol). The mixture was stirred in an atmosphere of $N_2$, at 80°C for 4 h, then poured into satd aq $NH_4Cl$ and extracted with $CH_2Cl_2$ (3 × 50 mL). The combined extracts were washed with water, dried, and concentrated to a brown syrup (1.7 g). Column chromatography on silica gel (100 g, 9:1 toluene–acetone) afforded pure **5** (0.78 g, 67%), as a pale-yellow syrup.

(*b*) A solution of **3** (5 g, 13.88 mmol) and benzoyl chloride (4 mL, 34.5 mmol) in dry pyridine (35 mL) was left at room temperature for 20 h. After the usual workup, the residue (8.4 g) was treated with NaSH monohydrate (7 g, 94.6 mmol) in *N*,*N*-dimethylformamide (85 mL) according to the above-described procedure to give crude **5** (6.8 g). Column chromatography on silica gel (180 g, 9:1 toluene–acetone) gave pure **5** (3.15 g, 74%) as a pale-yellow syrup; $[\alpha]_D$ −14.3° (*c* 1.3, $CHCl_3$). $^1$H NMR ($CDCl_3$): δ 3.13 (dd, 1 H, $J_{6a,6b}$ 10.8, $J_{5,6a}$ 1.2 Hz, H-6a), 3.17 (dd, 1 H, $J_{5,6b}$ 1.9 Hz, H-6b), 3.75 (d, 1 H, $J_{2,3}$ 0, $J_{3,4}$ 2.2 Hz, H-3), 3.89–4.18 (m, 4 H, 2 $CH_2$, dioxolane), 4.35 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-2), 4.72 (m, 1 H, H-5), 4.9 (d, 1 H, H-1), 5.71 (dd, 1 H, $J_{4,5}$ 2.9 Hz, H-4), 7.4–8.0 (m, 5 H, aromatic). $^{13}$C NMR ($CDCl_3$): δ 35.46 (C-6), 46.62 (C-3), 65.35 and

65.4 (2 $CH_2$, dioxolane), 75.26 and 76.4 (C-4 and C-5), 89.0 (C-2), 102.65 (C-1), 128.49, 129.4, 129.71, and 133.41 (aromatic), 165.7 (C = O).

*2,5-Anhydro-4-*O*-benzoyl-3,6-dideoxy-*L*-lyxo-hexose ethylene acetal* (**6**).—A suspension of compound **5** (1.07 g, 3.4 mmol) and Raney Ni (10 mL) in EtOH (30 mL) was hydrogenated at 80°C and normal pressure of $H_2$ for 1.5 h. The mixture was filtered through a Celite pad and the catalyst was washed successively with EtOH (40 mL) and EtOAc (40 mL). The filtrate and washings were combined and evaporated in vacuo. The residue was treated with $CH_2Cl_2$ (20 mL), then filtered, and the solvent evaporated. Silica gel column chromatography (60 g, 49:1 $CH_2Cl_2$–EtOAc) of the residue (0.7 g) afforded pure **6** (0.61 g, 63%) as a colourless oil; $[\alpha]_D$ +9.04° (*c* 3.2, $CHCl_3$). $^1$H NMR ($CDCl_3$): $\delta$ 1.29 (d, 3 H, $J_{5,6}$ 6.4 Hz, H-6), 2.23 (ddd, 1 H, $J_{2,3a}$ 7.3, $J_{3a,4}$ 1.68, $J_{3a,3b}$ 14.1 Hz, H-3a), 2.33 (ddd, 1 H, $J_{2,3b}$ 8.3, $J_{3b,4}$ 4.9 Hz, H-3b), 3.87–4.11 (m, 4 H, dioxolane), 4.31 (m, 1 H, H-5), 4.32 (ddd, 1 H, $J_{1,2}$ 3.9 Hz, H-2), 4.94 (d, 1 H, H-1), 5.54 (ddd, 1 H, $J_{4,5}$ 3.5 Hz, H-4), 7.4–8.11 (m, 5 H, aromatic). $^{13}$C NMR ($CDCl_3$): $\delta$ 14.56 (C-6), 33.92 (C-3), 65.14 and 65.42 (2 $CH_2$, dioxolane), 76.11 (C-4), 77.51 (C-2), 77.87 (C-5), 104.52 (C-1), 128.28, 129.47, 129.83, and 133.01 (aromatic), 165.7 (C = O).

*2,5-Anhydro-4-*O*-benzoyl-3,6-dideoxy-*L*-lyxo-hexitol* (**8**).—To a solution of **6** (1.8 g, 6.47 mmol) in trifluoroacetic acid (18 mL) was added aq HCl (6 M, 4.5 mL). The mixture was kept at +4°C for 24 h and then concentrated in vacuo by co-distillation with toluene. Silica gel flash chromatography (19:1 $CHCl_3$–acetone) of the residue (2 g) yielded the unstable aldehyde **7** (0.85 g) which was immediately dissolved in MeOH (9 mL) and treated with $NaBH_4$ (0.2 g). The mixture was stirred at room temperature for 30 min, then poured into satd aq NaCl (20 mL) and extracted with $CHCl_3$ (4 × 20 mL). The extracts were combined, washed with brine, dried, and evaporated. Silica gel column chromatography (70 g, $CHCl_3$) of the residue gave pure **8** (0.71 g, 46%) as a colourless syrup; $[\alpha]_D$ +20.7° (*c* 1.15, $CHCl_3$). $^1$H NMR ($CDCl_3$): $\delta$ 1.33 (d, 3 H, $J_{5,6}$ 6.4 Hz, H-6), 2.05 (bs, 1 H, OH), 2.21 (m, 2 H, H-3a and H-3b), 3.57 (dd, 1 H, $J_{1a,1b}$ 11.8, $J_{1a,2}$ 5.4 Hz, H-1a), 3.79 (dd, 1 H, $J_{1b,2}$ 2.7 Hz, H-1b), 4.31 (ddd, 1 H, $J_{4,5}$ 3.4 Hz, H-5), 4.4 (m, 1 H, H-2), 5.56 (m, 1 H, H-4), 7.44–8.11 (m, 5 H, aromatic). $^{13}$C NMR ($CDCl_3$): $\delta$ 14.8 (C-6), 34.7 (C-3), 64.55 (C-1), 76.61, 77.51, and 77.91 (C-2, C-4, and C-5), 128.45, 129.63, 129.93, and 133.21 (aromatic), 165.89 (C = O).

*2,5-Anhydro-4-*O*-benzoyl-1,3,6-trideoxy-1-iodo-*L*-lyxo-hexitol* (**9**).—To a solution of alcohol **8** (0.5 g, 2.12 mmol) in dry toluene (25 mL) were added successively imidazole (0.32 g, 4.68 mmol), $Ph_3P$ (1.2 g, 4.56 mmol), and $I_2$ (0.92 g, 3.6 mmol). The mixture was refluxed while stirring for 2 h and then concentrated in vacuo. Silica gel column chromatography (70 g, 19:1 toluene–acetone) of the residue afforded pure **9** (0.67 g, 91%) as a pale-yellow oil; $[\alpha]_D$ +15.9° (*c* 1.09, $CHCl_3$). $^1$H NMR ($CDCl_3$): $\delta$ 1.3 (d, 3 H, $J_{5,6}$ 6.4 Hz, H-6), 2.13 (ddd, 1 H, $J_{3a,3b}$14.0, $J_{2,3}$ 4.9, $J_{3a,4}$ 8.8 Hz, H-3a), 2.42 (ddd, 1 H, $J_{2,3b}$ 6.1, $J_{3b,4}$ 1.2 Hz, H-3b), 3.32 (dd, 1 H, $J_{1a,1b}$ 10.1, $J_{1a,2}$ 6.4 Hz, H-1a), 3.36 (dd, 1 H, $J_{1b,2}$ 4.9 Hz, H-1b), 4.36 (m, 1 H, H-2), 4.42 (ddd, 1 H, $J_{4,5}$ 3.4 Hz, H-5), 5.58 (m, 1 H, H-4), 7.34–8.16 (m, 5 H, aromatic). $^{13}$C NMR ($CDCl_3$): $\delta$ 10.86 (C-1), 14.82 (C-6), 76.61, 76.76, and 78.15 (C-2, C-4, and C-5), 128.4, 128.57, 128.63, and 132.16 (aromatic), 165.79 (C = O).

*(+)-epiallo-Normuscarine* (**10**).—A sealed tube charged with a solution of the iodo

derivative **9** (0.45 g, 1.3 mmol) in ethanolic 20% dimethylamine (30 mL) was heated at 80°C overnight. The mixture was evaporated in vacuo, and the residue treated with aq 10% HCl (10 mL) and extracted with ether. The aqueous layer was rendered alkaline with aq 30% NaOH to pH 9 and stirred at 80°C for 40 min. The mixture was cooled to room temperature and extracted with $CH_2Cl_2$ (5 × 25 mL). The combined extracts were dried and evaporated to afford chromatographically homogeneous **10** (0.129 g, 62%) as a colourless syrup; $[\alpha]_D$ +13.23° (*c* 0.9, EtOH); lit. [2] $[\alpha]_D$ +16.26° (*c* 1, EtOH). $^1$H NMR ($CDCl_3$): δ 1.23 (d, 3 H, $J_{5,6}$ 6.4 Hz, H-6), 1.77 (ddd, 1 H, $J_{3a,3b}$ 13.5, $J_{2,3a}$ 8.8, $J_{3a,4}$ 4.8 Hz, H-3a), 2.09 (ddd. 1 H, $J_{2,3b}$ 6.4, $J_{3b,4}$ 1.0 Hz, H-3b), 2.24 (dd, 1 H, $J_{1a,1b}$ 12.5, $J_{1a,2}$ 4.3 Hz, H-1a), 2.26 (s, 6 H, $Me_2N$), 2.44 (m, 2 H, H-1b and OH), 3.97 (ddd, 1 H, $J_{4,5}$ 3.1 Hz, H-5), 4.15 (ddd, 1 H, H-4), 4.36 (dddd, 1 H, $J_{1b,2}$ 7.9 Hz, H-2). $^{13}$C NMR ($CDCl_3$): δ 14.15 (C-6), 40.36 (C-3), 45.95 ($Me_2N$), 64.54 (C-1), 73.66 (C-4), 74.59 (C-2), 77.55 (C-5).

*(+)-epiallo-Muscarine iodide [2]* (**1**).—A solution of tertiary amine **10** (0.107 g, 0.67 mmol) in dry ether (5 mL) was treated with an excess of MeI (1 mL) for 3 h at room temperature. The precipitate was recrystallized from 2-propanol to afford pure **1** (0.144 g, 56.5%); mp 199–200°C; $[\alpha]_D$ 0° (*c* 0.7, EtOH); lit. [2] mp 199.17°C; $[\alpha]_D$ 0° (*c* 0.7, EtOH). $^1$H NMR ($D_2O$): δ 1.23 (d, 3 H, $J_{5,6}$ 6.4 Hz, H-6), 1.96 (ddd, 1 H, $J_{3a,3b}$ 14.2, $J_{2,3a}$ 8.7, $J_{3a,4}$ 4.7 Hz, H-3a), 2.24 (dd, 1 H, $J_{3b,4} < 1$, $J_{2,3b}$ 7.2 Hz, H-3b), 3.2 (s, 9 H, $Me_3N^+$), 3.4 (dd, 1 H, $J_{1a,1b}$ 14, $J_{1a,2}$ 2 Hz, H-1a), 3.54 (dd, 1 H, $J_{1b,2}$ 9.5 Hz, H-1b), 4.11 (ddd, 1 H, $J_{4,5}$ 3.1 Hz, H-5), 4.24 (dd, 1 H, H-4), 4.75 (m, 1 H, H-2). $^{13}$C NMR ($D_2O$): δ 16.06 (C-6), 41.81 (C-3), 54.92 ($Me_3N^+$), 72.22 (C-1), 74.01 (C-4), 74.86 (C-2), 81.93 (C-5).

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