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Synthesis of the Four Stereoisomers of 4,5-Dihydroxy-*N,N,N*-trimethylhexanaminium Iodide (Muscaridin) from Aldonolactones

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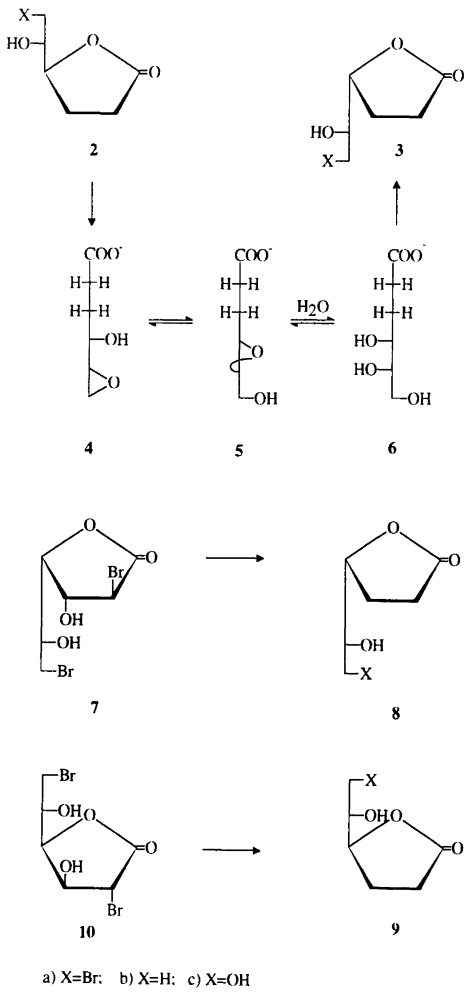
The D- and L-*erythro*- and D- and L-*threo*-isomers of 4,5-dihydroxy-*N,N,N*-trimethylhexanaminium iodide have been synthesized from D-glucono-, and D- and L-gulono-lactone via 2,6-dibromo-2,6-dideoxy-hexono-1,4-lactones. The aminium salts in the form of tetrachloroaurates were compared with that of muscaridin, which has been reported to have the L-*erythro*-configuration. This could, however, not be confirmed.

A nitrogen-containing product, named muscaridin, has been isolated from *Amanita muscaria L*,[1–3] and from other natural sources.[4] It was characterized as the tetrachloroaurate.[1] Degradation experiments indicated that it was a 4,5-dihydroxy-*N,N,N*-trimethylhexanaminium salt (**1**) and the four stereoisomers were synthesized from the corresponding unsaturated compound, *trans*-*N,N,N*-trimethylhex-4-enaminium chloride. *trans*-Hydroxylation of the latter gave the racemic *erythro* product while *cis*-hydroxylation yielded the racemic *threo* isomer. The two racemic products were resolved by fractional crystallization of their di-*p*-toluoyl D-tartrates and then converted into the chiral chlorides, obtained as hygroscopic syrups.[2,3] These were, unfortunately, not characterized as their tetrachloroaurates, neither was the chloride of the natural muscaridin prepared. The stereochemistry of the latter was therefore not established. The four stereoisomers (**1**) have now been synthesized from the readily available aldonolactones, D-glucono-, and D- and L-gulono-lactone.

Results and discussion

The 2,3,6-trideoxyhexonolactones (**2b**, **3b**, **8b** and **9b**) seemed to be obvious starting materials for the syntheses of the isomers of (**1**). The D-*erythro* isomer (**2b**) has already been prepared by hydrogenolysis of the 6-bromo lactone (**2a**), which in turn was obtained from D-gluconolactone.[5] Treatment of **2a** with aqueous potassium hydroxide resulted in the rapid formation of the L-*erythro*-carboxylate **6**. By analogy with previously studied base-catalyzed rearrangements of bromo-



Scheme 1.

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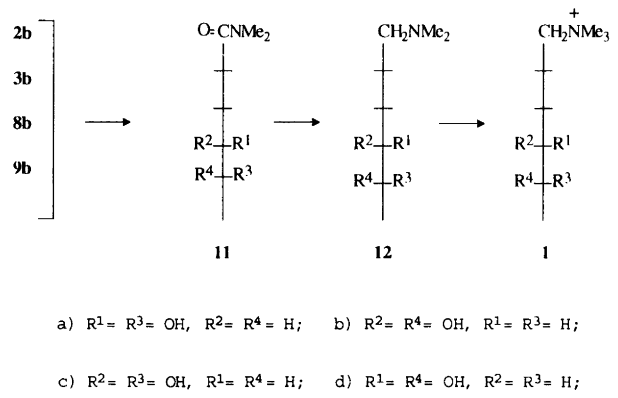

Scheme 2.

deoxyaldonolactones[6–8] the reaction of **2a** with base should initially give the 5,6-epoxide **4** which might be in equilibrium with the 4,5-epoxide **5**. The latter should then undergo a rapid intramolecular substitution at C-4 to give **6**, probably via a five-membered transition state. When the reaction of **2a** with potassium hydroxide was monitored by ^{13}C NMR spectroscopy, the intermediates, **4** and **5**, were actually observed. Acidification of **6** gave 2,3-dideoxy-L-*erythro*-hexono-1,4-lactone (**3c**), which was characterized as the crystalline dibenzoate. For comparison, the enantiomeric 5,6-di-*O*-benzoyl-2,3-dideoxy-D-*erythro*-hexono-1,4-lactone was prepared from **2a** by treatment with silver benzoate and subsequent benzoylation. The 6-bromo lactone (**3a**) was prepared from crude **3c** by treatment with hydrogen bromide in acetic acid. Hydrogenolysis of **3a** yielded 2,3,6-trideoxy-L-*erythro*-hexono-1,4-lactone (**3b**), identical with the product prepared from L-rhamnonolactone.[5]

Treatment of D-gulonolactone with hydrogen bromide in acetic acid gave the known 2,6-dibromo-2,6-dideoxy-D-idono-1,4-lactone (**7**)[9] which, on hydrogenolysis in ethanol, yielded 6-bromo-2,3,6-trideoxy-D-*threo*-hexono-1,4-lactone (**8a**). The same procedure gave the enantiomer (**9a**) from L-gulonolactone *via* the dibromolactone **10**.[10] The 6-bromolactones, **8a** and **9a**, were converted into the 2,3,6-trideoxy-D- and -L-*threo*-hexono-1,4-lactones, **8b** and **9b**, respectively, by catalytic hydrogenolysis in the presence of triethylamine.

Treatment of the four trideoxylactones (**2b**, **3b**, **8b** and **9b**) with aqueous dimethylamine gave the amides **11a–d** as syrups, which were characterized only through their ^{13}C NMR spectra. Reduction of **11** with the borane–dimethyl sulfide complex in dioxane yielded the corresponding tertiary amines **12a–d**, which were isolated as the crystalline hydroiodides. Finally, methylation of **12a–d**, as the free bases, with methyl iodide gave the four crystalline 4,5-dihydroxy-*N*,*N*,*N*-trimethylhexanaminium iodides (**1a–d**).

In order to compare these products with muscaridin the D-*erythro* iodide (**1a** · I) and the D-*threo* iodide (**1c** · I) were converted into the corresponding tetrachloroaurates. The D-*erythro* isomer gave a product which had the same m.p. as that of the tetrachloroaurate of muscaridin; the specific rotation (−9.0°) was, however, quite different from the reported value (+20.5°).[1] The D-*threo* isomer yielded a tetrachloroaurate with an m.p. similar to that of the racemic *threo*-product,[3] but its rotation was also different from that of the natural product. These data indicate that muscaridin may have the *erythro* configuration as suggested:[1] whether it is the D- or L-form can, however, not yet be decided.

Experimental

Melting points are uncorrected. Optical rotations were measured with a Perkin-Elmer 141 polarimeter. NMR spectra were recorded on Bruker AC-250 and A0-500 instruments.

Tetramethylsilane was used as an internal reference for deuteriochloroform solutions and dioxane (67.4 ppm) for ^{13}C NMR spectra measured in deuterium oxide solutions.

6-Bromo-2,3,6-trideoxy-L-erythro-*hexono-1,4-lactone* (**3a**). The bromo lactone (**2a**, 9.2 g) was dissolved in a solution of potassium hydroxide (7.4 g, 2.5 equiv.) in water (20 ml) and kept for 2 h. It was then acidified with hydrochloric acid, concentrated and coevaporated three times with toluene. The residue was stirred with 30% HBr–HOAc (50 ml) for 3 h. Methanol (200 ml) was added with stirring and the mixture was kept overnight. It was then concentrated and the residue was coevaporated twice with water. The residue in water (20 ml) was extracted continuously with ether for 4 h. The ether extract was dried ($MgSO_4$) and concentrated and the residue was crystallized from ether to give 5.7 g (62%) of **3a**, m.p. 72–74°C. Recrystallization from water gave 4.8 g (52%) of product, m.p. 75–77°C, $[\alpha]_D^{20} - 21.6°$ (*c* 1.6, $CHCl_3$). A ^{13}C NMR spectrum was identical with that of the enantiomer (**2a**). Anal. $C_9H_9BrO_3$: C, H, Br.

In a separate experiment the reaction of **2a** with potassium hydroxide was monitored by ^{13}C NMR spectroscopy in a mixture of D_2O and H_2O. After 3 min the solution contained a mixture of the two epoxides, **4** and **5**, and the final product **6**, and after ca. 30 min only **6** was observed. ^{13}C NMR for **4**: δ 70.6 (C-4), 56.0 (C-5), 46.2 (C-6), 34.2 (C-2), 31.0 (C-3); **5**: δ 62.3 (C-6), 60.7, 57.9 (C-4,5), 34.4 (C-2), 28.7 (C-3); **6**: δ 75.4, 72.7 (C-4,5), 63.5 (C-6), 34.7 (C-2), 29.6 (C-3).

5,6-Di-O-*benzoyl-2,3-dideoxy*-L-erythro-*hexono-1,4-lactone.* The 6-bromo-D-*erythro*-lactone (**2a**, 1 g) was treated with aqueous potassium hydroxide for 2 h. The solution was then acidified with hydrochloric acid and concentrated. The residue was coevaporated with toluene and then treated with benzoyl chloride (4.5 ml) in pyridine (10 ml). Work-up in the usual way and crystallization from ether–pentane gave 1.4 g (88%) of product which was recrystallized from ethanol, m.p. 100–101°C, $[\alpha]_D^{20} + 10.1°$ (*c* 1.2, $CHCl_3$). Anal. $C_{20}H_{18}O_6$: C, H.

*5,6-Di-O-benzoyl-2,3-dideoxy-*D-erythro-*hexono-1,4-lactone.* A mixture of **2a** (0.5 g) and silver benzoate (2 g) was boiled in acetonitrile (15 ml) for 4 h. The mixture was filtered and evaporated and the residue was benzoylated with benzoyl chloride in pyridine. Work-up and crystallization from ethanol gave 25% of the title compound, m.p. 98–100°C, $[\alpha]_D^{20} - 10.0°$ (*c* 0.8, $CHCl_3$). Anal. $C_{20}H_{18}O_6$: C, H.

*6-Bromo-2,3,6-trideoxy-*D-threo-*hexono-1,4-lactone* (**8a**). Crude, syrupy 2,6-dibromo-2,6-dideoxy-D-idono-1,4-lactone (**7**) was prepared as described previously[9] by treatment of D-gulono-1,4-lactone with HBr–HOAc for 3 h followed by addition of methanol. The subsequent evaporation was carried out at 30°C since a higher temperature led to formation of considerable amounts of 3,6-anhydro-2-bromo-2-deoxy-D-idono-1,4-lactone. Hydrogenation of crude **7** (32 g) for 48 h in ethanol (500 ml) in the presence of 5% palladium-on-carbon followed by filtration and concentration gave a residue which was dissolved in water (50 ml) and extracted continuously with ether for 4 h. The ether phase was dried and concentrated and the residue was crystallized from either to give 12 g of **8a**, m.p. 67–70°C. Recrystallization from ethyl acetate–pentane gave 10.8 g (42%), m.p. 72–74°C, $[\alpha]_D^{20} - 32.6°$ (*c* 1.8, H_2O). ^{13}C NMR ($CDCl_3$): δ 177.4 (C-1), 79.5 (C-4), 72.9 (C-5), 33.3 (C-6), 28.3 (C-2), 23.8 (C-3). Anal. $C_6H_9BrO_3$: C, H, Br.

*6-Bromo-2,3,6-trideoxy-*L-threo-*hexono-1,4-lactone* (**9a**) was prepared from L-gulono-1,4-lactone via **10** in 45% yield as described above, m.p. 72–74°C, $[\alpha]_D^{20} + 32.1°$ (*c* 1.9, H_2O); reported[10] $[\alpha]_D + 31.0°$. A ^{13}C NMR spectrum was identical with that of the enantiomer (**8a**).

*2,3,6-Trideoxy-*L-erythro-*hexono-1,4-lactone* (**3b**). A solution of **3a** (4.0 g) in ethyl acetate (75 ml) and triethylamine (8 ml) was hydrogenated for 20 h in the presence of 5% palladium-on-carbon (0.3 g). The mixture was then filtered and evaporated; the residue was acidified with hydrochloric acid, concentrated and dissolved in chloroform. The solution was dried, filtered and concentrated to leave 2.5 g (100%) of **3b**, pure as seen from a ^{13}C NMR spectrum. Distillation gave 2.2 g (88%), b.p. 105°C (0.5 mmHg), $[\alpha]_D^{20} - 8.5°$ (*c* 2.3, $CHCl_3$); reported[5] $[\alpha]_D - 8.7°$.

*2,3,6-Trideoxy-*D-threo-*hexono-1,4-lactone* (**8b**). Hydrogenolysis of **8a** (5.0 g) as described above gave 3.0 g (96%) of crude **8b** which was distilled to give 2.4 g (77%), b.p. 108°C (0.5–1 mmHg), $[\alpha]_D^{20} - 63.1°$ (*c* 2.4, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 4.26 (dt, $J_{3,4} = J_{3',4}$ 7.3 Hz, H-4), 3.69 (dq, $J_{4,5}$ 5.0, $J_{5,6}$ 6.5, H-5), 2.48 (m, $J_{2,2'}$ 17.8, $J_{2,3}$ 5.2, $J_{2,3'}$ 9.9, H-2), 2.43 (m, $J_{2',3}$ 9.6, $J_{2',3'}$ 8.6, H-2'), 2.14 (m, $J_{3,3'}$ 12.8, H-3), 1.95 (m, H-3'), 1.12 (d, H-6). ^{13}C NMR: δ 177.7 (C-1), 84.1 (C-4), 69.3 (C-5), 28.4 (C-2), 23.7 (C-3), 18.2 (C-6). Anal. $C_6H_{10}O_3$: C, H.

*2,3,6-Trideoxy-*L-threo-*hexono-1,4-lactone* (**9b**) was obtained analogously from **9a** (7.3 g), to give 4.2 g (93%) of crude product and 3.1 g (69%) of distilled material, b.p. 108°C (1 mmHg), $[\alpha]_D^{20} + 63.9°$ (*c* 1.5, $CHCl_3$); reported[11,12] +56.1 and +51.6. NMR spectra were identical with those described above.

*1-Dimethylamino-4,5-dihydroxy-*D-erythro-*hexane hydroiodide* (**12a** · HI). Treatment of the trideoxylactone **2b** (2.0 g) with 40% aqueous dimethylamine (12 ml) for 2 h at room temperature followed by concentration and coevaporation with toluene gave crude 4,5-dihydroxy-*N,N*-dimethyl-D-*erythro*-hexanamide (**11a**, 4.0 g) as a syrup. ^{13}C NMR (D_2O): δ 176.6 (C-1), 75.2, 71.0 (C-4,5), 38.4, 36.3 (NMe_2), 30.2, 28.2 (C-2,3), 17.6 (C-6).

After being dried under vacuum over potassium hydroxide **11a** was dissolved in dioxane (35 ml) and borane–dimethyl sulfide complex (12 ml, 4 mol equiv.) was added slowly with stirring. The solution was heated to 60°C for 4 h and kept overnight at room temperature. Methanol was then added slowly with stirring until the hydrogen evolution ceased. The solution was evaporated and coevaporated with methanol and acidified with an excess of aqueous hydrogen iodide. Concentration and evaporation with methanol to remove boric acid and water left **12a** · HI as a syrup, which crystallized from ethanol–ethyl acetate to give 5.1 g (77%) of product, m.p. 107–110°C. Recrystallization from the same solvent gave **12a** · HI, m.p. 112–114°C, $[\alpha]_D^{20} - 13.8°$ (*c* 2.7, H_2O). ^{13}C NMR (D_2O): δ 75.1, 71.0 (C-4,5), 58.9 (C-1), 43.5 (NMe_2), 29.0, 21.7 (C-2,3), 17.5 (C-6). Anal. $C_8H_{20}INO_2$: C, H, N.

*1-Dimethylamino-4,5-dihydroxy-*L-erythro-*hexane hydroiodide* (**12b** · HI) was prepared similarly from **3b** via the amide **11b**. The recrystallized product had m.p. 112–114°C, $[\alpha]_D^{20} + 14.1°$ (*c* 2.1, H_2O). A ^{13}C NMR spectrum was identical with that of **12a** · HI. Anal. $C_8H_{20}INO_2$: C, H, N.

*1-Dimethylamino-4,5-dihydroxy-*D-threo-*hexane hydroiodide* (**12c** · HI) was obtained from the trideoxylactone (**8b**, 2.0 g) which, with dimethylamine, gave crude 4,5-dihydroxy-*N,N*-dimethyl-D-*threo*-hexanamide (**11c**). ^{13}C NMR (D_2O): δ 176.5 (C-1), 75.3 (C-4), 71.0 (C-5), 38.4, 36.3 (NMe_2), 30.1, 28.6 (C-2,3), 18.7 (C-6). Reduction of the dried amide with borane as described above yielded 3.4 g (77%) of **12c** · HI, m.p. 116–120°C. Recrystallization from ethanol–ethyl acetate gave a product with m.p. 118–120°C, $[\alpha]_D^{20} + 12{,}5°$ (*c* 3.0, H_2O). ^{13}C NMR (D_2O): δ 75.2 (C-4), 70.9 (C-5), 58.5 (C-1), 43.5 (NMe_2), 29.5 (C-2), 21.5 (C-3), 18.7 (C-6). Anal. $C_8H_{20}INO_2$: C, H, N.

*1-Dimethylamino-4,5-dihydroxy-*L-threo-*hexane hydroiodide* (**12d** · HI) was prepared from **9b** (3.0 g) which, with dimethylamine, gave the amide (**11d**, 4.0 g). A ^{13}C NMR spectrum was identical with that of **11c**. Reduction as

described for the *erythro* isomer and crystallization from ethanol–ethyl acetate yielded 5.0 g (76%) of **12d** · HI, m.p. 114–116°C. Recrystallization gave a product with m.p. 117–119°C, $[\alpha]_D^{20} - 12.5°$ (*c* 1.8, H_2O). A ^{13}C NMR spectrum was identical with that of **12c** · HI. Anal. $C_8H_{20}INO_2$: C, H, N.

4,5-Dihydroxy-D-erythro-N,N,N-*trimethylhexanaminium iodide* (**1a** · I). An aqueous solution of **12a** · HI (2.0 g) was poured through Amberlite IRA-400 (OH^-) and the eluate was evaporated. To the residue in methanol (15 ml) was added methyl iodide (8 ml) and the solution was kept overnight. Evaporation and crystallization from ethanol–ethyl acetate gave the title product, 1.63 g (78%), m.p. 101–103°C. Further recrystallization did not change the m.p., $[\alpha]_D^{20} + 14.7°$ (*c* 2.3, H_2O). ^{13}C NMR (H_2O): δ 75.0 (C-4), 71.0 (C-5), 67.2 (C-1), 53.7 (NMe_3), 28.9 (C-2), 20.1 (C-3), 17.5 (C-6). Anal. $C_9H_{22}INO_2$: C, H, N.

The iodide (150 mg) was poured through Amberlite IRA-400 and the eluate was concentrated and acidified with hydrochloric acid. Addition of gold trichloride (150 mg) gave yellow crystals of **1a** · $AuCl_4$ which was recrystallized from water and dried, m.p. 128–130°C, $[\alpha]_D^{20} - 9.0°$ (*c* 0.6, H_2O); reported m.p. 129–131°C, $[\alpha]_D + 20.0°$ (*c* 8.3) for natural muscaridin.[1] The product is not sufficiently soluble in water at 20°C to measure the rotation at the concentration reported in Ref. 1. A ^{13}C NMR spectrum was identical with that of the iodide.

4,5-Dihydroxy-L-erythro-N,N,N-*trimethylhexanaminium iodide* (**1b** · I) was prepared as described above for **12b** · HI (1.5 g) to give 1.34 g (85%), m.p. 101–103°C. Recrystallization gave a product with unchanged m.p., $[\alpha]_D^{20} + 14.7°$ (*c* 1.8, H_2O). A ^{13}C NMR spectrum was identical with that of **1a** · I. Anal. $C_9H_{22}INO_2$: C, H, N.

4,5-Dihydroxy-D-threo-N,N,N-*trimethylhexanaminium iodide* (**1c** · I) was prepared from **12c** · HI (2.5 g) to give 2.22 g (85%), m.p. 98–100°C. Recrystallization gave a product with m.p. 99–100°C, $[\alpha]_D^{20} + 14.2°$ (*c* 2.8, H_2O). ^{13}C NMR (D_2O): δ 75.1 (C-4), 70.9 (C-5), 67.2 (C-1), 53.7 (NMe_3), 29.3 (C-2), 19.9 (C-3), 18.7 (C-6). Anal. $C_9H_{22}INO_2$: C, H, N.

The tetrachloroaurate (**1d** · $AuCl_4$) was prepared as described for the D-*erythro* isomer, yellow crystals, m.p. 98–101°C, $[\alpha]_D^{20} + 6.2°$ (*c* 0.5, H_2O); reported m.p. 97–102°C for the D,L-*threo* salt.[3]

4,5-Dihydroxy-L-threo-N,N,N-*trimethylhexanaminium iodide* (**1d** · I) was prepared from **12d** · HI (3.0 g). Crystallization from ethanol–ethyl acetate gave 2.7 g (86%), m.p. 96–98°C. Recrystallization gave a product with m.p. 97–98°C, $[\alpha]_D^{20} - 14.9°$ (*c* 1.2, H_2O). A ^{13}C NMR spectrum was identical with that of **1c** · I. Anal. $C_9H_{22}INO_2$: C, H, N.

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