Synthesis of the Four Stereoisomers of 4,5-Dihydroxy-N,N,N-trimethylhexanamminium 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., and from other natural sources. It was characterized as the tetrachloroaurate. Degradation experiments indicated that it was a 4,5-dihydroxy-N,N,N-trimethylhexanamminium 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-o-tartarates and then converted into the chiral chlorides, obtained as hygroscopic syrups. 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. 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-

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deoxaldonolactones⁴⁻⁸ 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 ¹³C 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 benzylation. 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 D-rhamnonolactone.⁵

Treatment of D-gulono-lactone with hydrogen bromide in acetic acid gave the known 2,6-dibromo-2,6-dideoxy-D-idono-1,4-lactone (7) 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-gulono-lactone 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 trideoxy lactones (2b, 3b, 8b and 9b) with aqueous dimethylamine gave the amides 11a−d as syrups, which were characterized only through their ¹³C 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-trimethylhexanammin iodides (1a−d).

In order to compare these products with muscaridin the D-erythro iside (1a−1) and the D-threo iside (1c−1) 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, 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 deuterochloroform solutions and dioxane (67.4 ppm) for ¹³C 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 (MgSO₄) 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, [α]₂⁰° = −21.6° (c 1.6, CHCl₃). A ¹³C NMR spectrum was identical with that of the enantiomer (2a). Anal. C₆H₄OBr₂. C, H, Br.

In a separate experiment the reaction of 2a with potassium hydroxide was monitored by ¹³C NMR spectroscopy in a mixture of D₂O and H₂O. 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.¹³C 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, [α]₂⁰° + 10.1° (c 1.2, CHCl₃). Anal. C₁₅H₁₈O₆: 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 benzyolated with benzoyl chloride in pyridine. Work-up and crystallization from ethanol gave 25% of the title compound, m.p. 98–100°C, [α]_D^20 = -10.0° (c 0.8, CHCl_3). Anal. C_{30}H_{40}O_8. C, H.

6-Bromo-2,3,6-trIDEOXY-3-d-threo-hexono-1,4-lactone (8a). Crude, syrupy 2,6-dibromo-2,3-dIDEOXY-3-d-idono-1,4-lactone (7) was prepared as described previously² by treatment of α-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, [α]_D^20 = 32.6° (c 1.8. H_2O). ¹³C NMR (CDCl₃): 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_{13}H_{12}BrO_3. C, H, Br.

6-Bromo-2,3,6-trIDEOXY-L-threo-hexono-1,4-lactone (9a) was prepared from i-gulono-1,4-lactone via 10 in 45% yield as described above, m.p. 72–74°C, [α]_D^20 = 32.1° (c 1.9, H_2O); reported¹⁰ [α]_D^20 = 31.0°. A ¹³C 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 ¹³C NMR spectrum. Distillation gave 2.2 g (88%), b.p. 105°C (0.5 mmHg), [α]_D^20 = -8.5° (c 2.3, CHCl₃); reported¹¹ [α]_D^20 = -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), [α]_D^20 = -63.1° (c 2.4, CHCl₃). ¹H NMR (500 MHz, CDCl₃): δ 4.26 (dt, J_3,4 = J_4,5 7.3 Hz, H-4), 3.69 (dd, J_4,5 5.0, J_5,6 6.5, H-5), 2.48 (m, J_5,6 17.8, J_5,5 5.2, J_5,5 9.9, H-2), 2.43 (m, J_5,5 9.6, J_5,5 8.6, H-2'), 2.14 (m, J_5,5 12.8, H-3'), 1.95 (m, H-3'), 1.12 (d, H-6). ¹³C 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_{14}H_{10}O_3. C, H.

2,3,6-TrIDEOXY-D-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), [α]_D^20 = 63.9° (c 1.5, CHCl₃); reported¹¹¹,¹² +56.1 and +51.6. NMR spectra were identical with those described above.

1-Dimethylamino-4,5-diIDEOXY-D-erythro-hexane hydroiodide (12a·HI). Treatment of the triideoxy lactone 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-diIDEOXY-N,N-dimethyl-D-erythro-hexamidine (11a, 4.0 g) as a syrup. ¹¹C NMR (D_2O): δ 176.6 (C-1), 75.2, 71.0 (C-4,5), 38.4, 36.3 (NMe₂), 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 coevaporation 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, [α]_D^20 = 13.8° (c 2.7, H_2O). ¹¹C NMR (D_2O): δ 75.1, 71.0 (C-4,5), 58.9 (C-1), 43.5 (NMe₂), 29.0, 21.7 (C-2,3), 17.5 (C-6). Anal. C_{14}H_{20}INO₂. C, H, N.

1-Dimethylamino-4,5-diIDEOXY-L-erythro-hexane hydroiodide (12b·HI) was prepared similarly from 3b via the amide 11b. The recrystallized product had m.p. 112–114°C, [α]_D^20 = 14.1° (c 2.1, H_2O). A ¹¹C NMR spectrum was identical with that of 12a·HI. Anal. C_{14}H_{20}INO₂. C, H, N.

1-Dimethylamino-4,5-diIDEOXY-D-threo-hexane hydroiodide (12c·HI) was obtained from the triideoxy lactone 8b (2.0 g), which, with dimethylamine, gave crude 4,5-diIDEOXY-N,N-dimethyl-D-threo-hexamidine (11c). ¹¹C NMR (D_2O): δ 176.5 (C-1), 75.3 (C-4), 71.0 (C-5), 38.4, 36.3 (NMe₂), 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, [α]_D^20 = 12.5° (c 3.0, H_2O). ¹¹C NMR (D_2O): δ 75.2 (C-4), 70.9 (C-5), 58.5 (C-1), 43.5 (NMe₂), 29.5 (C-2), 21.5 (C-3), 18.7 (C-6). Anal. C_{14}H_{20}INO₂. C, H, N.

1-Dimethylamino-4,5-diIDEOXY-L-threo-hexane hydroiodide (12d·HI) was prepared from 9b (3.0 g) which, with dimethylamine, gave the amide (11d, 4.0 g). A ¹¹C 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·Hl, m.p. 114–116°C. Recrystallization gave a product with m.p. 117–119°C, [α]D20 = 12.5° (c 1.8, H2O). A 13C NMR spectrum was identical with that of 12c·Hl. Anal. C12H20INO2: C, H, N.

4.5-Dihydroxy-d-erythro-N,N,N-trimethylhexanaminium iodide (1a·I). An aqueous solution of 12a·Hl (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., [α]D20 + 14.7° (c 2.3, H2O). 13C NMR (H2O): δ 75.0 (C-4), 71.0 (C-5), 67.2 (C-1), 53.7 (NMe3), 28.9 (C-2), 20.1 (C-3), 17.5 (C-6). Anal. C12H22INO2· 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·AuCl3, which was recrystallized from water and dried, m.p. 128–130°C, [α]D20 = 9.0° (c 0.6, H2O); reported m.p. 129–131°C, [α]D20 + 20.0° (c 2.3) for natural muscaradin.1 The product is not sufficiently soluble in water at 20°C to measure the rotation at the concentration reported in Ref. 1. A 13C 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·Hl (1.5 g) to give 1.34 g (85%), m.p. 101–103°C. Recrystallization gave a product with unchanged m.p., [α]D20 + 14.7° (c 1.8, H2O). A 13C NMR spectrum was identical with that of 1a·I. Anal. C12H22INO2· C, H, N.

4.5-Dihydroxy-d-threo-N,N,N-trimethylhexanaminium iodide (1c·I) was prepared from 12c·Hl (2.5 g) to give 2.22 g (85%), m.p. 98–100°C. Recrystallization gave a product with m.p. 99–100°C, [α]D20 + 14.2° (c 2.8, H2O). 13C NMR (D2O): δ 75.1 (C-4), 70.9 (C-5), 67.2 (C-1), 53.7 (NMe3), 29.3 (C-2), 19.9 (C-3), 18.7 (C-6). Anal. C12H22INO2· C, H, N.

The tetrachloroaurate (1d·AuCl4) was prepared as described for the d-erythro isomer, yellow crystals, m.p. 98–101°C, [α]D20 + 6.2° (c 0.5, H2O); reported m.p. 97–102°C for the d,1-threo salt.3

4.5-Dihydroxy-L-threo-N,N,N-trimethylhexanaminium iodide (1d·I) was prepared from 12d·Hl (3.0 g). Recrystallization from ethanol-ethyl acetate gave 2.7 g (86%), m.p. 96–98°C. Recrystallization gave a product with m.p. 97–98°C, [α]D20 = 14.9° (c 1.2, H2O). A 13C NMR spectrum was identical with that of 1c·I. Anal. C12H22INO2· C, H, N.

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References

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