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Synthesis of D,L-Chalcose and D,L-Desosamine

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Cyclization of methyl 2-*cis*-5-hexadienoate (*1*) with polyphosphoric acid (PPA) gives parasorbic acid (*2*) which on epoxidation, acid catalyzed opening of the epoxide ring in refluxing methanol and reduction with diisobutylaluminium hydride (DIBAH), gives D,L-chalcose (*6*). Treatment of the epoxide *3* with aqueous dimethyl amine results in a mixture of the amino acid *8* and the amide *7*. The lactone *11* is reduced to D,L-desosamine (*9*) by DIBAH.

It seemed to us that methyl 2-*cis*-5-hexadienoate [1a] (*1*), a product of the Ni-catalyzed reaction of carbon monoxide, allyl chloride, and acetylene, could serve as a suitable starting material for a general synthesis of several hexoses. The *cis*-structure should enable a facile acid catalyzed ring closure to the δ-lactone parasorbic acid (*2*) and further hydroxylations, rearrangements, and reductions would then lead to sugar derivatives.

It turned out that cold conc. sulfuric acid [1b] or polyphosphoric acid (PPA) at 70 – 80 °C was a suitable reagent for accomplishing the cyclization. The epoxidation of *2* had been carried out earlier [2] but in our hands the method gave variable yields. Reliable yields of the epoxide *3* were obtained by epoxidation at *ca.* 20 °C with 1.9 equiv. of H_2O_2 in methanol using solid sodium bicarbonate as catalyst. By controlling reaction time and temperature the formation of the methyl ester *4*, which occurs as a side product, could be brought to a minimum. Only the *trans* isomer *3* was formed and the crude product was used without purification for the further reactions. Refluxing *3* in methanol with a small amount of *p*-toluenesulfonic acid opened the epoxide ring in the expected direction and afforded the lactone *5* in a good yield. Reduction with diisobutylaluminium hydride (DIBAH) gave D,L-chalcose *6*, Scheme 1. Lithium aluminium hydride or sodium bis[2-methoxyethoxy]aluminium hydride gave lower yields. The ^{1}H NMR spectrum of *6* in D_2O was identical to that published earlier.[3] Chalcose has been prepared earlier by several routes.[4–10]

Opening of the epoxide ring with dimethylamine was accomplished by heating *3* in an autoclave with anhydrous dimethylamine.[11] We found that this reaction could be carried out simply by letting *3* stand for 10 days in aqueous dimethylamine. A mixture of the amide *7* and the carboxylate *8* was obtained with the latter as major product which by treatment with hydrochloric acid gave the lactone *11*. This was then reduced by DIBAH to D,L-desosamine (*12*), the ^{1}H NMR spectrum of which was identical to that published by Woo *et al.*[12] (the scale of the published spectrum is shifted by *ca.* 0.45 ppm).

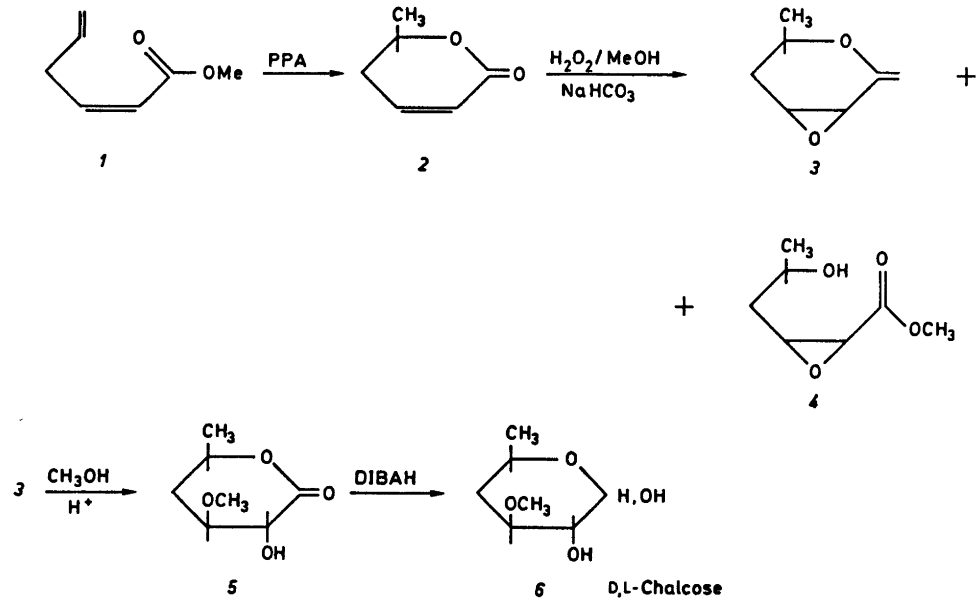
Treatment of *3* with concentrated ammonia gave the analogous amino compounds *9* and *10*.

Synthesis of desosamine has been accomplished earlier by several groups.[9,11,13–17]

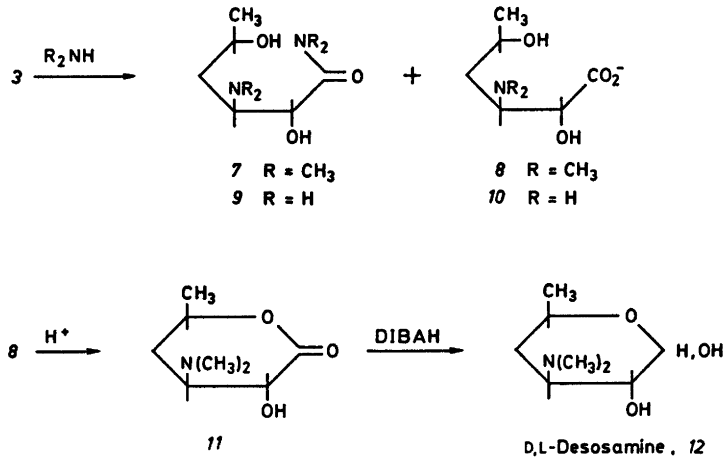
EXPERIMENTAL

Boiling and melting points are uncorrected. *J*-values given are first order splittings.

Parasorbic acid (*2*). A mixture of PPA (400 g) and methyl 2,5-hexadienoate *1* (50 g) was heated in an oil bath (70 – 80 °C) for 4 h with vigorous stirring. The reaction mixture was allowed to cool down to 30 – 35 °C and the PPA hydrolyzed by adding excess of crushed ice – water to the reaction flask. The organic material was extracted several times with CH_2Cl_2. The combined extract was washed



Scheme 1.



Scheme 2.

with water, dried over Na_2SO_4, and the solvent evaporated under reduced pressure. On distillation the residue gave pure parasorbic acid, *2*, b.p. 102–104 °C/12 mmHg (lit.[2] 110–113 °C/13 mmHg); yield 35 g (70 %). ^{1}H NMR (CCl_4): δ 1.39 (CH_3, d, J_{56} 6.3 Hz), 2.3 (2 H_4, m), 4.5 (H_5, m), 5.87 (H_2, d, t, J_{23} 9.7 Hz, $J_{24a} = J_{24e} = 1.5$ Hz), 6.90 (H_3, ddd, J_{34ae} 5.0 and 3.4 Hz).

Epoxidation of parasorbic acid. (A) *Sodium hydroxide method.*[2] To parasorbic acid (5.6 g, 0.05 mol) was added a solution of H_2O_2 (8 g, 40 % solution, 0.094 mol) dissolved in methanol (25 ml). The mixture was cooled to 10 °C and stirred. Sodium hydroxide solution (10 M, 1.75 ml) was added to the stirred mixture during 90 min so that the pH did not exceed 8, and the temperature was kept below 15 °C.

After stirring the reaction mixture for an additional period of 2 h, it was diluted with water (20 ml), saturated with $(NH_4)_2SO_4$ and extracted with ether (6 × 25 ml). The ether extract was cooled in an ice-water bath and the peroxide destroyed by gradually adding $NaHSO_3$ in excess while stirring. The decanted ether was dried with Na_2SO_4, solvent evaporated under vacuum, and the residue distilled to give pure epoxide *3*, b.p. 90 – 94 °C/2 mmHg (lit.[2] 59 °C/0.1 mmHg); yield 2 g (31 %). IR (film): 1745, 1270, 850 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.32 (CH_3, d, J_{56} 6.4 Hz), 1.95 (H_{4a}, dd, J_{4ae} 15.2 Hz, J_{4a5} 11.2 Hz, $J_{4a3} \sim 0$ Hz), 2.39 (H_{4e}, d, t, J_{4e3} 2.9 Hz, J_{4e5} 3.4 Hz), 3.55 (H_3, d, J_{23} 3.8 Hz), 3.70 (H_5, dd), 4.66 (H_6, ddq).

(B) *Sodium bicarbonate method.* To a cooled mixture of parasorbic acid (5.6 g, 0.05 mol), methanol (15 ml), sodium bicarbonate (4.2 g, 0.05 mol) was added in one portion a solution of H_2O_2 (9 g, 35 %) in methanol (25 ml). The reaction mixture was stirred for 48 h at 14 – 16 °C, diluted with water (40 ml), saturated with solid $(NH_4)_2SO_4$, and extracted with ether (6 × 25 ml). The extract, on working up as described in method (A), gave 3.8 g (60 %) of pure epoxide *3* which required no distillation.

trans-*3-Hydroxy-4-methoxy-tetrahydro-pyran-2-one*, *5*. A mixture of epoxide *3* (2.56 g), methanol (50 ml), and *p*-toluenesulfonic acid (100 mg) was refluxed for 48 h and methanol removed under reduced pressure. The residue was taken up in CH_2Cl_2, washed twice with sodium bicarbonate solution (10 %) and then with water, dried over Na_2SO_4, and solvent evaporated under vacuum. The residue distilled to provide *trans*-3-hydroxy-4-methoxy-6-methyl-tetrahydropyran-2-one, *5*, b.p. 104 – 105 °C/0.44 mmHg; yield 1.8 g (56 %). Calc. for $C_7H_{12}O_4$: C 52.50; H 7.5. Found: C 52.82; H 7.66. IR (film) 3450, 1740, 965, 850 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.41 (CH_3, d, J_{56} 6.5 Hz), 1.67 (H_{4a}, J_{4ae} 14.0 Hz, J_{4a3} 10.7 Hz, J_{4a5} 11.3 Hz), 2.33 (H_{4e}, J_{4e3} 4.5 Hz, J_{4e5} 3.0 Hz), 3.65 (H_3, J_{32} 9.0 Hz), 4.08 (H_2, d), 4.46 (H_6, ddq).

Chalcose (2,3-dihydroxy-4-methoxy-6-methyl-tetrahydropyran). A solution of *trans*-3-hydroxy-4-methoxy-6-methyl-tetrahydropyran-2-one (1.6 g, 0.01 mol) in dry THF (15 ml) was cooled to – 25 to – 30 °C under N_2 and a solution of DIBAH (18 ml, 20 % toluene solution, 3.06 g, 0.021 mol) was added whilst stirring for 40 min. After additional stirring for 2 h at – 25 to – 30 °C the temperature was allowed to rise to 0 °C and the complex decomposed by adding $Na_2SO_4.10H_2O$:celite mixture so that the temperature did not exceed 20 °C. The reaction mixture was filtered and the residue extracted a few times with boiling chloroform. The chloroform solution, dried with Na_2SO_4, was evaporated under vacuum, and the residue (800 mg) on chromatographic separation (TLC silica/$CHCl_3$) gave (500 mg) of pure chalcose as the first fraction (31 %). The IR in $CHCl_3$ and ^1H NMR in D_2O were identical with the spectra of a reference sample of natural D-chalcose.

Reaction of parasorbic acid epoxide 3 *with dimethylamine.* A mixture of epoxide *3* (5.0 g) and dimethylamine solution (12 g, 40 %) was kept at room temperature for 10 days. The excess of dimethylamine and water were removed under vacuum at 50 °C. The syrupy residue was allowed to stand at room temperature for a few hours and then chloroform was added. A solid separated (2.8 g) which was removed by filtration. The filtrate on keeping in the cold room for 2 days deposited further 0.8 g of the same solid, D,L-2,5-dihydroxy-3-*N*-dimethylaminohexonic acid *8*. It was recrystallized from ethanol, m.p. 145 – 147 °C; yield 3.5 g (50 %). IR (Nujol): 1630 cm^{-1} (COO^-); (KBr), 1630 cm^{-1} (lit.[11] 1600 cm^{-1}, L-configuration). ^1H NMR (D_2O): δ 1.24 (CH_3, d, J_{56} 6.2 Hz), 1.96 (2 H_4, t, $J_{34} = J_{45} = 6.1$ Hz), 2.90 [$N(CH_3)_2$, s], 3.55 (H_2, q, $J_{23} \sim J_{43} \sim 6$ Hz), 4.02 (H_5, m), 4.16 (H_3, d, J_{23} 5.7 Hz), 4.7 (OH, s).

The chloroform solution on removal of the solvent furnished 2,5-dihydroxy-3-dimethylaminohexonic acid dimethylamide *7* as a thick syrup (2.5 g, 25 %). ^1H NMR ($CDCl_3$): 1.17 (CH_3, d, *J* 6.1 Hz), 2.41 [$N(CH_3)_2$, s], 2.99 and 3.13 [$CON(CH_3)_2$, d]. *7* was not hydrolyzed by boiling water.

Hydrochloride of the 3,4,6-trideoxy-3-dimethylaminohexonic acid lactone 11. A solution of 2,5-dihydroxy-3-dimethylaminohexonic acid (2 g) and hydrochloric acid (21 ml, 0.5 M) was evaporated to dryness to give 3,4,6-trideoxy-3-dimethylaminohexonic acid lactone hydrochloride (1.8 g, 90 %). It crystallized from methanol, m.p. 213 – 216 °C. IR (Nujol): 1740 cm^{-1} (δ-lactone). The ^1H NMR D_2O agreed with literature values.[11]

Desosamine. A DIBAH solution (4.4 ml, 0.0044 mol, 20 % in toluene) was gradually added to *11* (420 mg, 0.002 mol) in dry THF (20 ml) at – 20 °C with stirring. After stirring the reaction mixture for another hour at – 20 to – 25 °C the complex was decomposed by adding celite and sodium sulfate decahydrate mixture so that the temperature did not rise above 20 °C. The mixture was filtered and the residue washed a few times with hot chloroform. The combined filtrate was dried over sodium sulfate, the solvent evaporated under vacuum to give desosamine (130 mg, 30 %), the ^1H NMR spectrum of which was identical with the published one.[12]

Reaction of parasorbic acid epoxide 3 *with ammonia.* A mixture of epoxy parasorbic acid *3* (4 g) and ammonia solution (50 ml, 25 %) was kept at room temperature for 10 days. Excess base and water was removed under vacuum at 50 °C. The thick syrupy residue was treated with methanol and the insoluble portion separated by filtration. On crystalliza-

tion from ethanol, water mixture (3:1) it gave pure 2,5-dihydroxy-3-amino-hexoic acid, (*10*), m.p. 215–217 °C; yield 2.4 g, 48 %. Found: C 43.70; H 8.09. Calc. for $C_6H_{13}NO_4$: C 44.11; H 7.97. IR (KBr): 1640, 1575 cm^{-1} (COO^-, lit.[11] 1640 cm^{-1}). ^1H NMR (D_2O): δ 1.23 (CH_3, d, J_{56} 6.3 Hz), 1.83 (H_4, t, $J_{34} \sim J_{45} \sim 6.3$ Hz), 3.67 (H_5, m), 4.10 (H_3, m), 4.72 (NH_3^+, OH, s) The methanol solution gave on evaporation of the solvent under vacuum a solid which was not investigated.

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