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Reactions of D,L-Osmunda γ- and δ-Lactones. Synthesis of Megosaminic γ-Lactone

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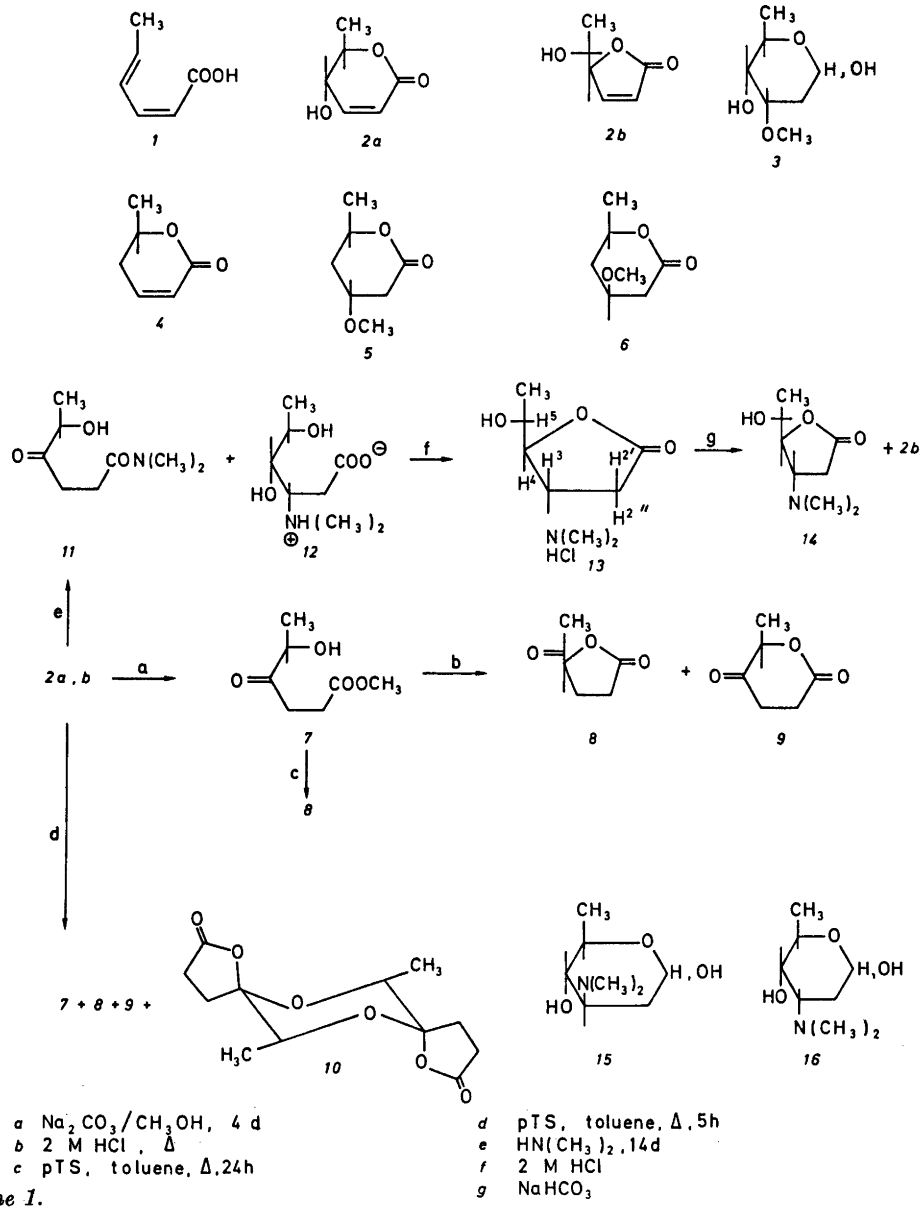
The synthesis of *cis-trans*-sorbic acid (*1*) from parasorbic acid *4* was optimized. Osmunda lactones *2a,b* rearranged to methyl 5-hydroxy-4-ketohexanoate *7* on treatment with base in methanol. *7* rearranged to the lactones *8*, *9*, and *10* in an acid catalyzed reaction. *7* – *9* are of interest as starting material for the synthesis of racemic 2,3,6-trideoxysugars. *2b* added dimethylamine giving racemic *11* and *12*, from which the hexonolactone of D,L-megalosamin *13* was prepared.

The facile conversion of *cis-trans*-sorbic acid *1* to D,L-osmunda lactone *2a* (δ-lactone) and its five-membered ring isomer *2b* (major product, γ-lactone)[1] by peracid oxidation led us to explore the reactions of *2a,b*. It appeared to us that this compound could be utilized in the synthesis of racemic hexoses. Selective reduction with diisobutylaluminium hydride, DIBAH, and hydroxylation of the double bond should lead to a variety of sugars.

Since the reaction conditions are crucial for the preparation of the starting material *cis-trans*-sorbic acid *1*, we set out to optimize the yield of *1*. Treatment of parasorbic acid *4* with catalytic amounts of sodium methoxide gave the *trans* adduct *5*; this gave on treatment with one equivalent of sodium methoxide for 5 – 10 min *1* as major product together with minor amounts of the *cis* adduct *6* that became the main product if *4* was treated with 1.2 equivalent of methoxide for 6 days. Treatment of *4* with one equivalent of methoxide in absolute methanol for 30 min at room temperature gave *1* in a yield of *ca.* 70 %,[2] contaminated by some *5* and *6*. A product of higher purity was obtained when the reaction was carried out at 0 °C. Small amounts of methyl sorbate were formed in all reactions.

It was hoped that addition of methanol to *2b* (the mixture of γ-, *2b*, and δ-lactone, *2a*, was used) in a *trans* fashion followed by reduction should give the 2,6-dideoxysugar cymarose *3*. In contrast to the facile addition of methanol to the unsaturated six-membered ring in parasorbic acid *4*, all attempts to bring about the same reaction with *2a,b* were unsuccessful. *2a,b* rearranged rapidly in excellent yield to the keto ester *7* by treatment with solid sodium carbonate in methanol for 4 days. *7* was cyclized to an inseparable mixture of lactones *8* and *9* (only spectroscopically detected) by treatment with warm 2 M hydrochloric acid but to rather pure *8* vith *para*-toluenesulfonic acid in refluxing toluene for 24 h. When *7* was refluxed with TsOH for a few hours in toluene, a small amount of a solid appeared in addition to *8*, *9*, and unreacted *7*. According to its mass spectrum the solid compound turned out to be a dimer of *7*, and it showed an IR absorption characteristic for a γ-lactone and had ^{1}H and ^{13}C NMR spectra in accordance with *10* (or a stereoisomer). We were unable to direct the cyclization toward the formation of *9* as single product. The facile rearrangement of *2b* to *7* is explicable in terms of tautomerism in the 2-hydroxyfuran system. Similar rearrangements have recently been observed.[3] *7* as well as *8* or *9* are interesting as starting materials for the synthesis of racemic 2,3,6-trideoxysugars.

In contrast, dimethylamine added across the double bond of *2b* giving a mixture of *11*, *12* and minor amounts of the dimethylamide of *12*. *12* was cyclized to *13* the hexonolactone of megosamine *16*,[4] with diluted aqueous hydrochloric acid. Analysis of the ^{1}H NMR spectrum proved conclusively that the addition had taken



Scheme 1.

place in a *trans* fashion. The *cis*-isomer – actually the one that by selective reduction was supposed to give angolosamine *15* – was not isolated.

We were unable to reduce *14* to *16* with DIBAH. Below −25 °C the starting material was recovered and at 0 °C presumably some of the corresponding tetrahydrofuran was formed together with the α-β-elimination product *2b*.

EXPERIMENTAL

cis-trans-Sorbic acid, 1. Cooled solutions of sodium methoxide (4.8 g Na in 170 ml of absolute methanol) and *4* (22.4 g) in methanol (170 ml) were slowly mixed at 0 °C. The methanol was immediately evaporated *in vacuo* at 25 – 30 °C and to the residue, water (200 ml) was added. Extraction with chloroform gave methyl sorbate (2.0 g, 8 %). The water phase was acidified with 2 M sulfuric acid with cooling

and extracted several times with chloroform. Drying (sodium sulfate) and evaporation of the solvent gave practically pure *1* in a yield of 70–80 %.

cis-4-Methoxy-6-methyl tetrahydropyran-2-one, 6. Parasorbic acid (5 g) *4* was treated with sodium methoxide (1.2 eqv.) in absolute methanol (100 ml) for 6 days at room temperature. The methanol was removed *in vacuo* at 25–30 °C. Water (25 ml) and 2 M sulfuric acid were added until the mixture was distinctly acid. Extraction with chloroform, separation of the acid components with aqueous sodium bicarbonate, and evaporation gave the pyrones *5* and *6* (~1:10, 2.8 g) as an inseparable mixture. They distilled together at 95–97 °C/1 mmHg (lit.[1] *5*, 101–103 °C/1.8 mmHg), 2.3 g. The bicarbonate phase gave *5* (2.3 g, crude) on acidification and extraction with methylene chloride. ^{1}H NMR ($CDCl_3$): *6* δ 1.41 (3 H, d, J_{56} 6.3 Hz), 1.70 (H_{4a}, br.m), 2.32 (H_{4e}, br.m), 2.68 ($H_{2a,e}$, m), 3.33 (3 H, s), 3.85 (H_{3a}, m), 4.37 (H_{5a}, m).

Treatment of 5 with sodium methoxide. 5 (1 g) was treated with sodium methoxide (1.0 eqv.) in absolute methanol (20 ml). The solution was worked-up as described under *cis-trans*-sorbic acid and gave methyl sorbate (70 mg) and a mixture of *1*, *5*, and *6* (810 mg, ~4:1:2).

Methyl 5-hydroxy-4-ketohexanoate, 7. Osmunda lactones *2a,b* (5 g) were dissolved in 100 ml absolute methanol and solid sodium carbonate (3 g) was added. After 4 days with occasional stirring at room temperature the sodium carbonate was filtered off and the methanol removed under reduced pressure at 25 °C. Chloroform (80 ml) and ice water (40 ml) were added and the phases separated. Drying over sodium sulfate and evaporation of the chloroform gave 5.0 g (80 %) of pure *7*. The ^{1}H and ^{13}C NMR spectra were identical with the published ones.[3] *7* slowly rearranged to *8* on attempted distillation.

Treatment of 7 with hydrochloric acid. 7 (1.0 g) was dissolved in 10 ml 2 M HCl. After 2 h the acid was removed *in vacuo* at 60 °C. Chloroform (25 ml) was added to the residue. Drying over sodium sulfate and evaporation of the solvent gave an oil (0.75 g). The ^{1}H NMR spectrum showed that it mainly consisted of *8* and *9* (~5:6). ^{1}H NMR ($CDCl_3$) *9*: δ 1.39 (3 H, d, *J* 7.0 Hz), 2.20–2.95 (4 H, br.m), 4.34 (1 H, q, *J* 7.0 Hz).

Preparation of 5-acetyl-butyrolactone, 8, 7 (0.5 g) was refluxed in toluene (25 ml) with $TsOH \cdot H_2O$ (20 mg) for 24 h. Filtration and evaporation of the solvent under reduced pressure at 30–40 °C gave *8* (0.38 g, crude), b.p. 102–104 °C/1.2 mmHg. IR (film): 1780, 1725 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.0–2.8 (4 H, m), 2.28 (3 H, s), 4.98 (1 H, dt, *J* 2 and 6 Hz). (Found: C 55.80, H 6.22. Calc. for $C_6H_8O_3$: C 56.25, H 6.29).

Formation of 10 (or stereoisomer). 7 (1.05 g) was refluxed in toluene (50 ml) for 5 h with $TsOH \cdot H_2O$ (30 mg). Evaporation of toluene gave an oil (0.94 g). The ^{1}H NMR spectrum showed that it contained in addition to *7*, *8* and *9* (~4:5:6) a fourth compound with a characteristic doublet at δ 1.19. Crystals separated from the product dissolved in a small amount of chloroform, m.p. 210–212 °C. IR (KBr): 1780, 1055 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.19 (3 H, d, *J* 6.5 Hz), 1.93–2.35 (2 H, m), 2.55–2.95 (2 H, m), 4.16 (1 H, q, *J* 6.5 Hz). ^{13}C NMR ($CDCl_3$): δ 15.0 (CH_3), 27,5 (CH_2), 29.9 (CH_2), 69.5 (CH_3-C-O), 105.7 ($O-C-O$) 175.6 ($C=O$). MS (M^+) 256, 212, 184, 171, 112.

4-Keto-5-hydroxyhexanoic acid dimethylamide, 11, 4,5-dihydroxy-3-dimethylaminohexanoic acid, 12, and hydrochloride of 2,3,6-trideoxy-3-dimethylaminohexonic acid γ-lactone, 13. 2a,b (10 g, 78,2 mmol) were kept in aqueous dimethylamine (50 ml, 40 %) at room temperature for 14 days. Evaporation *in vacuo* removed excess of dimethylamine and water. The residue was treated with chloroform (100 ml) and allowed to stand at 0 °C overnight. The crystals, *12*, were filtered off and washed with cold methanol. The chloroform phase was evaporated to 20 ml and again allowed to stand for 2 days at 0 °C which gave a further crop of crystals, m.p. 171–173 °C (from methanol, 5.76 g *12*, 41 %). IR (KBr): 1600 cm^{-1}. ^{1}H NMR (D_2O): δ 1.25 (3 H, d, J_{56} 6.0 Hz), 2.60 (2 H, m), 2.88 (6 H, s), 3.73 (3 H, br.m). (Found: C 50.01, H 8.88. Calc. for $C_8H_{17}O_4N$: C 50.25, H 8.96). The chloroform solution was evaporated to give mainly the amide *11* as an oil (5.90 g crude, 36 %). ^{1}H NMR ($CDCl_3$): δ 1.29 (3 H, d, *J* 7.0 Hz), 2.6–2.9 (4 H, m), 2.95 and 3.04 (6 H, d) 4.3 (1 H, q, *J* 7.0 Hz).

12 (5.76 g) was treated with hydrochloric acid (2 N, 25 ml) for 24 h. Evaporation to dryness gave *13* which was crystallized from methanol, m.p. 181–183 °C (6.54 g, 94 %). IR (KBr): 1770 cm^{-1}. ^{1}H NMR (D_2O): δ 1.28 (3 H, d, $J_{H^5H^6}$ 6.56 Hz), 2.92 (6 H, s), 2.70–3.35 ($H^{2'}$ $H^{2''}$, br.m. $J_{H^{2'}H^{2''}}$ – 19.85, $J_{H^{2'}H^3}$ 9.27, $J_{H^{2''}H^3}$ 1.94 Hz), 4.16 (H^5, dq, $J_{H^4H^5}$ 3.90 Hz), 4.34 (H^3, m, $J_{H^3H^4}$ 1.65 Hz), 4.92 (H^4, dd). (Found: C 45.84, H 7.21. Calc. for $C_8H_{16}O_3NCl$: C 45.83, H 7.69). Treatment of *13* with aqueous sodium bicarbonate and extraction with chloroform gave *14* as an oil.

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