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Reactions of Parasorbic Acid. Synthesis of 2-Alkoxy-5,6-dihydro-α-pyrans and D,L-Osmunda Lactone

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Parasorbic acid (*1*) is reduced by diisobutylaluminiumhydride to the unsaturated sugar *2* which on heating or influence of light rearranges to the *trans*-aldehyde *3*. Reaction of *2* with alcohols or orthoformates leads to 2-alkoxy-5,6-dihydro-α-pyrans which are useful intermediates in general sugar synthesis. Epoxidation of the 2-isopropoxy derivative gives mainly the lyxo-isomer *7*. Treatment of *2* with base gives *cis-trans*-sorbic acid which in one step can be transformed into osmunda lactone *19* by hydroxylation with peracid. Parasorbic acid adds methanol and aziridine in a *trans*-fashion.

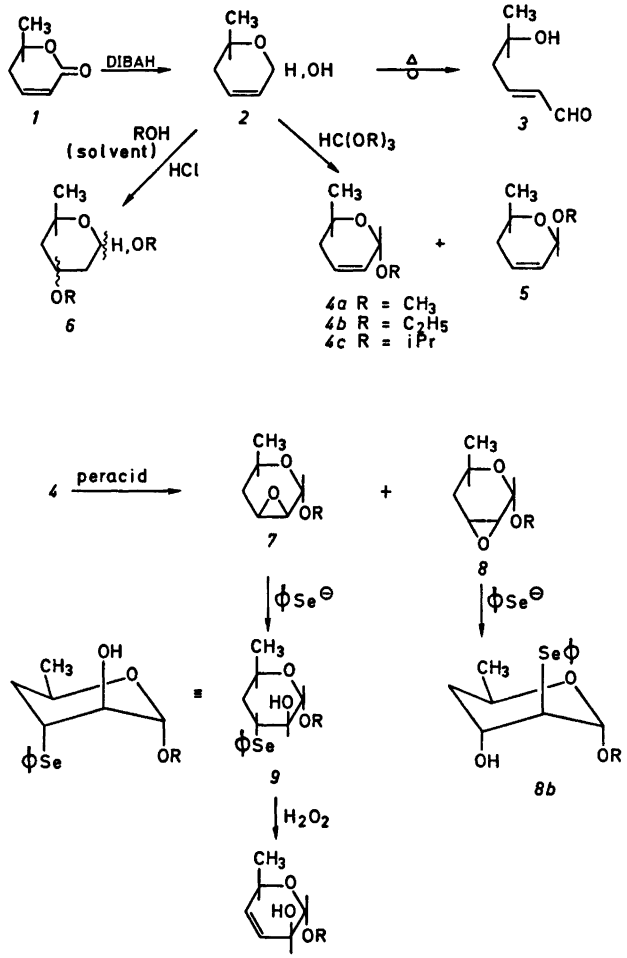
Parasorbic acid (*1*) was shown to be a useful intermediate for the preparation of some hexoses.[1] This work explores further reactions of *1* which lead to a variety of sugars.

Reduction with diisobutylaluminium hydride, DIBAH, converted *1* to 2-hydroxy-5,6-dihydro-pyran (*2*) which on distillation gave a mixture of products, the main component of which showed a rather strong carbonyl absorption at 1685 cm^{-1} in the IR. This was first believed to originate from free α,β-unsaturated *cis*-aldehyde but examination of the ^1H NMR spectrum showed the product to consist mainly of rearranged *trans*-aldehyde *3*, ($J_{2,3} = 16.0$ Hz). Inspection of the literature revealed that recently several similar rearrangements have been reported.[2–6] When *2* was left at room temperature for several weeks, it slowly rearranged to *3*, and a sample kept under the influence of light did so more rapidly than a sample kept in the dark. Even though the reaction is catalyzed by light and heat, an addition-elimination mechanism seems to be most plausible as evidenced by the addition reactions with methanol below. Because of its instability it was desirable to transfer *2* into the glycosides *4* and *5* which have been prepared by other routes and used for synthesis of 4,6-dideoxy sugars.[7–10]

Treatment of *2* with 2 % hydrochloric acid in methanol gave an anomeric mixture of *erythro*- and *threo*-isomers *6*. Ethanol gave the same result and it was not possible to prepare the glycoside by this procedure without adding alcohol across the double bond. When the *trans*-isomer *3* was treated in the same way, it also formed *6* which shows that Michael addition in this system is a facile reaction. Reaction of *2* with one equivalent of trimethyl or triethyl orthoformate gave the wanted glycosides, and later it was found that they could also be obtained more simply by reacting *2* with an equimolecular amount of alcohol in ether and with boron trifluoride etherate as catalyst. The anomeric effect favours the formation of the α-glycoside *4*.

GLC of a distilled sample of *4* showed only one main peak and minor impurities and the IR and ^1H NMR spectra were in agreement with data reported.[7] The ethyl and isopropyl glycosides *4b,c* were prepared similarly (Scheme 1).

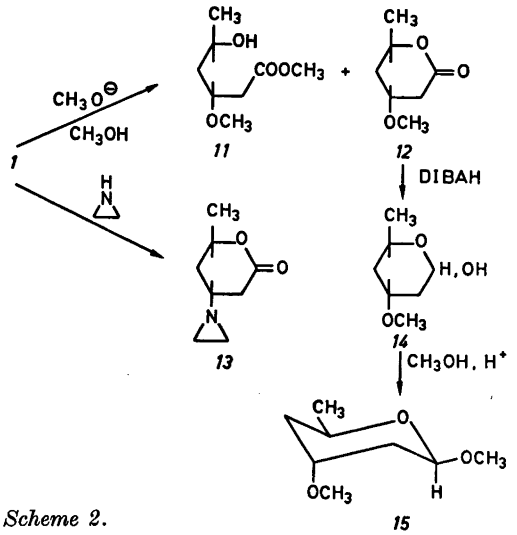
1 added methanol stereospecifically with simultaneous ring opening giving a mixture of the ester *11* and δ-lactone *12*. On acid treatment *11* cyclized to *12*. The ^1H NMR spectrum was in accordance with the *erythro*-structure. $J_{3e2ae} = 4.5$ Hz. Reduction of *12* and methylation gave predominantly β-glycoside, the conformation of which is represented by *15* ($_{1a2a}J = 9.5$, $J_{1a2e} = 2.6$, $J(^{13}C_1,H_{1a}) = 161$, $J(^{13}C_5H_{5a}) = 141.5$ Hz.



Scheme 1.

Aziridine added rapidly to *1* to give the *trans*-isomer *13* as proved by ^{1}H NMR (J_{3e2ae} = 5.1 Hz, H_5 shows both a – a and a – e couplings). GLC of the distilled product showed only one main peak and minor contaminations, *ca.* 10 % (Scheme 2). Epoxidation of *4a* and *4b* is reported to give mixtures of *ribo*, *8*, and *lyxo* derivatives *7* with increasing proportion of *7* with increasing size of R.[11] This was verified by our experiments and the isopropyl glucoside *4c* was therefore prepared and oxidized in order to obtain *7* in the purest possible state without resorting to chromatography. GLC of the product showed that *ca.* 10 – 15 % of the *ribo* isomer *8* was formed. This mixture was used in our further experiments directed towards the introduction of the 3,4 double bond. For that purpose we applied the phenyl selenide procedure.[12]

The epoxide opened in the expected direction and the selenium adduct *9* was obtained as the main product which on oxidation gave *10*, albeit in a poor yield. The corresponding methyl glycoside has been prepared earlier by a different route.[13] The structure and conformation of *9* was proved spectroscopically, J_{1e2e} = 2.3 Hz, $J_{^{13}C,H}$ = 165 Hz. $J_{^{13}C,H_5}$ = 144 Hz; H_3 appears as a quartet, $J_{2e3e} \sim J_{2e4ae} \sim$ 4.5 Hz and these data are only compatible with equatorial[14] H_1, H_3, and H_5 or slightly twisted conformation caused by 1,3 interaction at C_1 and C_3 formed by a *trans*-diaxial opening of the



Scheme 2.

epoxide ring at C_3. The selenium satellites that appeared in the ^{13}C NMR spectrum supported the assignment. By preparative TLC a small amount of an isomeric selenium adduct (*8b*) was also isolated, formed from the epoxide *8* by *trans* diaxial ring opening at C_2. The oxidative elimination of phenyl selenide was not performed at optimum conditions.

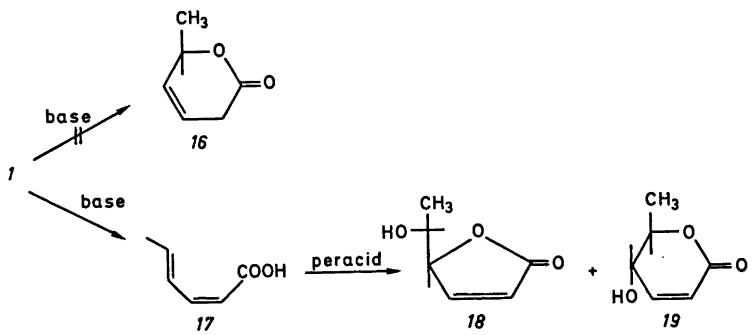
In order to make the application of parasorbic acid in sugar synthesis more useful, we tried to deconjugate its double bond. This would then easily make possible the preparation of several 2,6-deoxysugars and 6-deoxysugars after hydroxylations and reduction. To that effect *2* was treated with strong bases according to the method of Herrman *et al.*[15] However, *16* was not formed; instead 2-*cis*-4-*trans*-hexadienoic acid (*17*), an isomer of sorbic acid,[16,17] was obtained. This compound, which we had expected as an alternative product, is of utmost interest and can serve us in the same way as the desired compound *16*. Selective hydroxylation with peracid gave, *e.g.* directly the naturally occurring osmunda lactone (*19*) and its 5-membered ring isomer (*18*), 1:3. The ^1H NMR spectra of *18* and *19* were identical to those published earlier.[18] (Scheme 3).

EXPERIMENTAL

The melting and boiling points are uncorrected. The ^1H NMR couplings given are first order couplings.

2-Hydroxy-6-methyl-5,6-dihydro-α-pyran (2). Parasorbic acid (*1*) (5.6 g, 0.05 mol) was reduced with DIBAH (50 ml, 20 % toluene solution) at −25 °C under N_2. The reducing agent was added during a period of 1 h and after additional 2 h with stirring the temperature was allowed to rise to 0 °C; the excess of DIBAH decomposed by a sodium sulfate decahydrate: celite mixture below 20 °C. The organic phase was filtered and the residue washed with $CHCl_3$. The solution was dried over sodium sulfate and the solvent removed under vacuum to give 2-hydroxy-6-methyl-5,6-dihydro-α-pyran (*2*). It showed a weak carbonyl absorption at 1680 cm^{-1} that became more intense when the compound was left standing for a few weeks. The crude compound was directly used for the further reactions. ^1H NMR ($CDCl_3$): δ 1.23 (CH_3, d, J_{56} 6.2 Hz), 1.97 (H_4, m), 4.10 (H_5, sext., $J \sim 7$ Hz), 4.6 (OH, br.d), 5.39 (H_1, br.s), 5.79 (H_2, m), 6.00 (H_3, t, J_{34ae} 3.5 Hz, J_{23} 10 Hz).

On attempted distillation *2* gave the rearranged *trans*-aldehyde *3*, b.p. 87–89 °C/0.8 mmHg. IR (film): 1685 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.24 (CH_3, d, J_{56} 6.2 Hz), 2.51 (H_4, m, J_{34} 7.3 Hz, J_{45} 6.1 Hz, J_{24} 1.1 Hz), 4.04 (H_5, sext., J 6.1 Hz), 6.20 (H_2, ddt, J_{23} 16.0 Hz, J_{12} 7.8 Hz), 6.95 (H_3, dt).



Scheme 3.

2-Methoxy-6-methyl-5,6-dihydro-α-pyran (4a). Method A. To 2-hydroxy-6-methyl-5,6-dihydro-α-pyran (*2*) (1.14 g, 0.01 mol) and methanol (320 mg, 0.01 mol) in dry ether (20 ml) a few drops of BF_3/etherate were added. After keeping the mixture at room temperature for 45 min it was washed with sodium carbonate (10 %, 10 ml) and then with water. The ethereal solution was dried over sodium sulfate, the solvent evaporated under vacuum, and the residue distilled to give *4a*, b.p. 65–66 °C/55 mmHg. Yield: 900 mg, 70 %. The ^{1}H NMR and IR spectra agreed with the literature data.[7]

Method B. To *2* (2.85 g) and trimethyl orthoformate (3 g) in dry ether (30 ml), BF_3/etherate (0.5 ml) was added. The reaction mixture was kept at room temperature for 1 h. The ether solution was washed with sodium carbonate (10 %, 10 ml) and then with water, dried over sodium sulfate, and the solvent was removed under vacuum. The ^{1}H NMR spectrum of the residue was identical with that of the distilled product in Method A, yield: 75 %.

2-Ethoxy-6-methyl-5,6-dihydro-α-pyran (4b). Method A. B.p. 65–66 °C/35 mmHg yield: 70 %.

Method B. B.p. 65–66 °C/35 mmHg, yield: 75 %. The ^{1}H NMR spectrum of the ethyl glucoside shows the characteristic magnetic non-equivalence of the ethyl methylene group.

2-Isopropoxy-6-methyl-5,6-dihydro-α-pyran (4c), was prepared according to Method A using 3 mol of alcohol for 1 mol of *2* and the mixture was kept at room temperature for 1.5 h, b.p. 54–55 °C/15 mmHg, yield: 75 %. Calc. for $C_9H_{16}O_2$: C 69.23; H 10.26. Found: C 69.01; H 10.38. ^{1}H NMR ($CDCl_3$): δ 1.08, 1.19, and 1.22 (3 CH_3, d, J 6.2 Hz), 1.94 (H_4, m), 4.01 (H_{iPr}, hept.), 4.08 (H_5, sext.), 5.07 (H_1, br.s), 5.70 (H_2, m, J_{23} 10 Hz), 5.98 (H_3, t, J_{34ae} 3.4 Hz).

*Epoxidation of 2-isopropoxy-6-methyl-5,6-dihydro-α-pyran (4c) to isopropyl-2,3-anhydro-4,6-dioxy-α-*D,L*-lyxo-hexopyranoside.* To *4c* (1.56 g, 0.010 mol) in chloroform (40 ml) was added *m*-chloroperbenzoic acid (3.0 g, 0.014 mol, 80 %) and the mixture was stirred for 72 h at room temperature. The solid was filtered off, the filtrate washed with sodium carbonate (10 ml, 10 %) and water, and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was distilled, b.p. 86–89 °C/13 mmHg. The yield of the isopropyl-2,3-anhydro-4,6-dioxy-α-D,L-*lyxo*-hexopyranoside (*7*) was 76 %. Calc. for $C_9H_{16}O_3$: C 62.75; H 9.35. Found: C 62.27; H 9.53. ^{1}H NMR ($CDCl_3$): δ 1.09 and 1.19 (iPr, d, non-equivalent, J 6 Hz), 1.23 (CH_3, d, J_{56} 6.3 Hz), 1.6–1.9 (H_4, m), 2.92 (H_2, d, J_{23} 3.8 Hz), 3.3 (H_4, m), 3.6–4.3 (H_5, iPr, m), 5.10 (H_1, s). The spectrum shows *ca.* 10–15 % contamination of the *ribo*-isomer *8* (H_4 gives a considerably broader AB-system and H_1 appeared as a satellite, d, at *ca.* 5.13).

Addition of methanol to parasorbic acid; trans-4-methoxy-6-methyltetrahydropyran-2-one (12). A mixture of parasorbic acid (*1*) (5.6 g) methanol (50 ml), and CH_3ONa (100 mg) was kept at room temperature for 5 h. The solution was concentrated to half of its volume, diluted with water, and extracted several times with ether. After drying over sodium sulfate the solvent was removed to give a residue (5 g, 70 %), a mixture of the lactone *12* and the open ester *11* (1:4).

4 g of the above mixture was treated with 2 M HCl (24 ml) at room temperature for 30 to 45 min and extracted with ether which was dried over sodium sulfate and evaporated. The residue gave pure *12*, b.p. 101–103 °C/1.8 mmHg; yield: 3 g, 87 %. Found: C 58.14; H 8.25. Calc. for $C_7H_{12}O_3$: C 58.33; H 8.33. IR (film): 1740 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.38 (CH_3, d, J_{56} 6.5 Hz), 1.64 (H_{4a}, ddd, J_{4ae} 14.5 Hz, J_{4a3} 3.6 Hz, J_{4a5} 10.8 Hz), 2.10 (H_{4e}, dt, $J_{4e3} \sim J_{4e5} \sim 3.5$ Hz), 2.68 (H_{2ae}, d, J_{2ae3} 4.5 Hz), 3.34 (OCH_3, s), 3.80 (H_3, q), 4.68 (H_5, ddq).

2-Hydroxy-4-methoxy-6-methyltetrahydropyran (14). DIBAH (toluene solution, 20 %, 9 ml) was added to a cooled solution (−25 to −30 °C) of 4-methoxy-6-methyltetrahydropyran-2-one (*12*) (1.44 g, 0.01 mol) in dry THF (15 ml) under N_2 with stirring during 30 min. After stirring the reaction for 2½ h at −25 to −30 °C, the temperature was allowed to rise to 0 °C and the complex was decomposed by adding a mixture of $Na_2SO_4.10H_2O$ and celite. The temperature was not allowed to exceed 25 °C. After filtration the solid was washed several times with hot $CHCl_3$. The combined organic solution was dried over sodium sulfate and the solvent removed under reduced pressure. The residue was distilled and gave 2-hydroxy-4-methoxy-6-methyltetrahydropyran *14* as an anomeric mixture, *ca.* 1:1, b.p. 78–80 °C/1 mmHg, yield: 800 mg, 57 %. Found: C 57.3; H 9.59. Calc. for $C_7H_{14}O_3$: C 57.75; H 9.56. A slight elimination of methanol occurred during the distillation. ^{1}H NMR ($CDCl_3$): δ 3.33 and 3.40 (OCH_3, s, of equal intensity), 5.05 (H_{1a}, J_{1a2a} 10 Hz, J_{1a2e} 2 Hz), 5.13 (H_{1e}, br.s).

2,4-Dimethoxy-6-methyltetrahydropyran (15). 2-Hydroxy-4-methoxy-6-methyltetrahydropyran (*14*) (2 g) was kept in methanolic hydrogen chloride (15 ml, 2 %) at room temperature for 30 min. The solvent was removed under reduced pressure and the residue distilled to give the glucoside *15*, b.p. 68–69 °C/12 mmHg, yield: 47 %. Found: C 60.02, H 10.19. Calc. for $C_8H_{16}O_3$: C 59.97; H 10.07. ^{1}H NMR ($CDCl_3$): δ 1.20 (CH_3, d, J_{56} 6.2 Hz; weak d at δ 1.15, J 6.3 Hz), 1.2–2.2 (H_2, H_4, m), 3.33 and 3.47 (OCH_3, s; the former s stronger), 3.5–4.2 (H_3, H_5, m), 4.61 (H_1, dd, J_{1a2a} 9.5 Hz, J_{1a2e} 2.6 Hz), 4.8 (H_1, anomer, weak).

trans-*4-Aziridino-6-methyltetrahydropyran-2-one (13).* To parasorbic acid (*1*) (1.6 g, 0.00145 mol) and aziridine (0.8 g, 0.00145 mol) was added potassium *t*-butylate (50 mg) as catalyst.

The mixture became warm and addition is complete after 15 min. Distillation gave pure *13*, 85 % yield, b.p. 120 °C/0.5 mmHg. ^{1}H NMR ($CDCl_3$): δ 1.21 and 1.77 ($N(CH_2)_2$, m), 1.36 (CH_3, d, J_{56} 6.3 Hz), 1.6–2.2 (H_3 and H_4, m), 1.61 (H_2, d, J_{2ae3} 5.1 Hz), 4.86 (H_5, m).

Osmunda lactone (19) and its isomer (18). *m*-Chloroperbenzoic acid (4.4 g, 85 %) was added to *cis,trans*-sorbic acid (*17*) (2.4 g) in methylene chloride (40 ml) at 0 °C. After 4 days the reaction mixture was filtered and the filtrate evaporated. The residue was shaken with cold water (3 × 6 ml), filtered, and the combined filtrates were evaporated *in vacuum*. The remainder consisted of a mixture of *19* and *18* (1:3) which was used for further reactions without purifications. The crude yield was *ca.* 90 %. The ^{1}H NMR spectra of *18* and *19* were identical with those published earlier.[18]

Opening of the epoxide ring of 7 *and* 8 *with phenylselenide, preparation of* 10. Diphenyl diselenide (0.9 g) was reduced by solid sodium borohydride (0.28 g) in dimethoxyethane (15 ml). The light yellow solution turned colourless on addition of methanol (0.2 ml). Crude *7* (0.74 g) was added and the mixture was stirred overnight, then heated at 60 °C for *ca.* 1 h, hydrolyzed with water (20 ml) and extracted with methylene chloride. Evaporation of the solvent gave a yellow oil that was purified by preparative TLC ($CHCl_3$). *9* was obtained as an oil that slowly crystallized, 0.50 g, m.p. 82–84 °C from carbon tetrachloride. Mw. 329.0. Found: M^+ 330 (^{80}Se), 328 (^{78}Se). ^{1}H NMR ($CDCl_3$): δ 1.17 and 1.28 (iPr, d, J_{78} 6.1 Hz), 1.21 (H_6, d, J_{56} 6.4 Hz), 1.6–2.3 (H_4, m), 3.41 (H_3, q, $J_{2e3e} \sim J_{2e4ae} \sim 4.5$ Hz), 3.8 (H_2, m), 3.98 (H_7, sept., 6.1 Hz), 4.3 (H_5, m), 4.80 (H_1, d, 2.8 Hz), 7.2–7.7 (5H, m). ^{13}C NMR ($CDCl_3$): δ 20.35 (C_6), 21.22 and 23.17 (C_8 and C_9), 34.54 (C_4), 42.12 (C_3, $^1J_{CH}$ 145 Hz, $^1J_{CSe}$ 70.0 Hz), 62.89 (C_5, $^1J_{CH}$ 143 Hz), 69.00 (C_7), 70.21 (C_2, $^2J_{CSe}$ 14.7 Hz), 97.27 (C_1, $^1J_{CH}$ 165 Hz).

A second band with a slightly higher R_F value proved to consist of pure *8b*, oil, 0.15 g. Mw. 329.0; found: M^+ 330 (^{80}Se), 328 (^{78}Se). ^{1}H NMR ($CDCl_3$): δ 1.12 (CH_3, *J* 6.1 Hz), 1.20 (2 CH_3, *J* 6.1 Hz), 1.5–2.3 (H_4, m), 3.37 (H_2, br.s), 3.98 (H_7, sept., *J* 6.1 Hz), 4.1 (H_5, m), 5.28 (H_1, br.s), 7.2–7.7 (5H, m). ^{13}C NMR ($CDCl_3$): δ 21.20 (C_6 and C_8), 23.34 (C_9), 36.06 (C_4), 46.36 (C_3, $^1J_{CSe}$ 67 Hz), 60.02 (C_5, $^1J_{CH}$ 144 Hz), 68.82 (C_3), 69.72 (C_7), 98.93 (C_1, $^1J_{CH}$ 170 Hz).

Oxidation of *9* (0.25 g) with hydrogen peroxide (1 ml, 15 %) in methylene chloride (5 ml, two phase system) overnight gave the pyranoside *10* (35 mg) together with another major product of unknown structure, still containing the phenyl selenide function. No starting material was present. *10* showed the following ^{1}H NMR data ($CDCl_3$): δ 1.21, 1.23, 1.28 (3 CH_3, *J* 6.2 Hz), 2.2 (OH, s), 3.76 (H_2, m), 4.01 (H_7, sept., *J* 6.2 Hz), 4.37 (H_5, br.q., J_{56} 7 Hz), 4.93 (H_1, br.s), 5.87 (H_3, H_4, br.s). MS: M^+ missing; 113, ($M^+ - O - iPr$), 84.

cis-trans-*Sorbic acid (17)* was prepared according to the method of Eisner *et al.*[16] An excess of 50 % sodium was used. The crude product, *17*, was used for the further reactions. Use of lithium diisopropylamide[15] in HMPT as base did not improve the yield.

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