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THE USE OF L-TARTARIC ACID IN THE SYNTHESIS OF ENANTIOMERICALLY PURE COMPOUNDS: SYNTHESIS OF 4-O-BENZYL-2,3-DIDEOXI-L- THREO-HEX-2-ENO NO-1,5-LACTONE.

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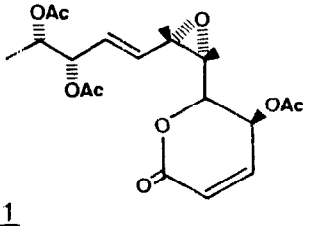
SUMMARY. The title compound was obtained through a seven steps sequence and using dimethyl L-tartrate as the starting material (30% overall yield).
The system 2,3-dideoxy-L-threo-hex-2-enono-1,5-lactone is present in several natural compounds.

In connection with our planned synthesis of olguine[1,2] 1 the preparation of 2,3 -dideoxy-L-threo-hex-2-enono-1,5-lactone was required. This system is also present in other natural compounds such as anamarine[3], asperlin[4] and analogous products[5]. It could also be an entry for the synthesis of biologically important[6] L-sugars.



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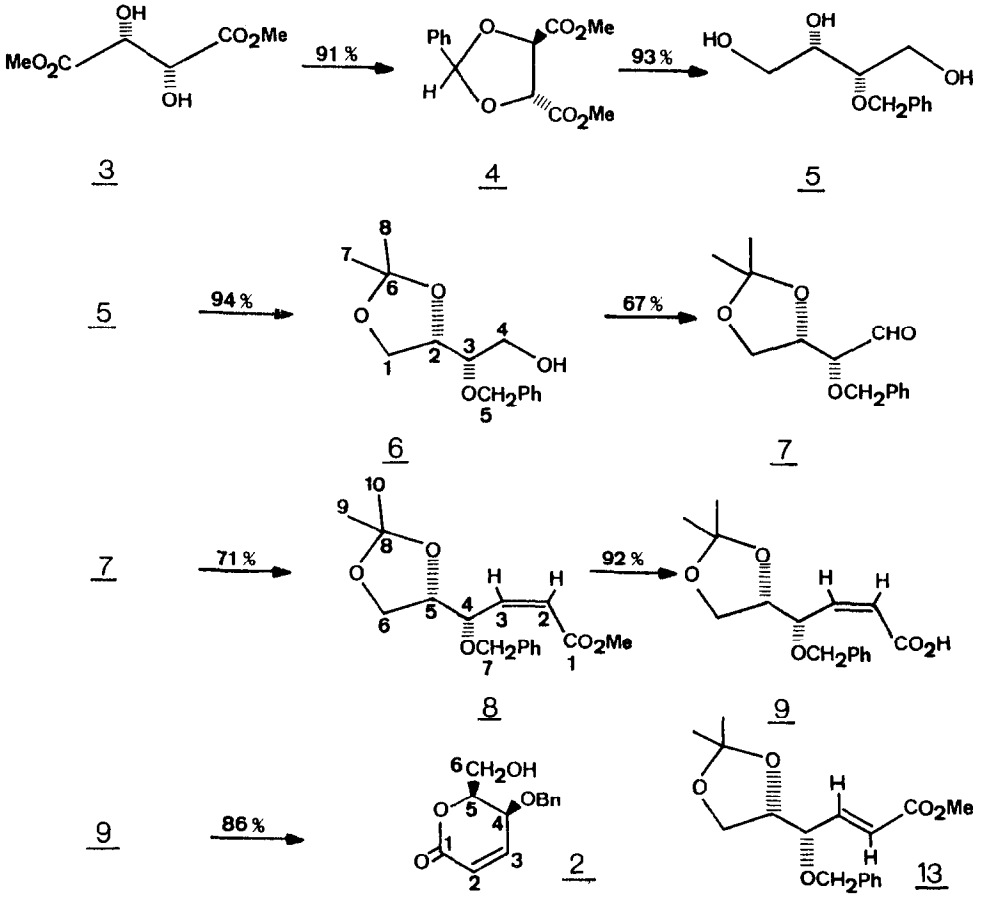
In the present communication we describe the synthesis of 4-O-benzyl-2,3-dideoxy-L-threo-hex-2-enono-1,5-lactone 2 starting with dimethyl L-tartrate 3.

The known[7] benzylidene acetal of 3 (4) was prepared (see Scheme) by reacting dimethyl L-tartrate with benzaldehyde, in benzene as solvent, and p-toluensulfonic acid as a catalyst. Water was removed azeotropically. Reduction of 4 with $LiAlH_4/AlCl_3$ using the conditions described by Seebach and Hungerbühler[8] provided (S,S)-2-benzyloxy-butan-1,3,4-triol 5 ($(\alpha)_D$ +14.7º (c=0.136, EtOH); lit[8] +15.5 (EtOH); m.p. 75-77º; lit[8] 75.5-76.5) in 93% yield. Reaction of 5 with acetone in the presence of p-toluensulfonic acid[9] gave the isopropylidene derivative[10] 6 in 94% yield[11].

Compound 6 was subjected to oxidation with PCC[12] in the presence of molecular sieves[13] affording aldehyde 7 (67% yield)[10]. This product was used in the following step without further purification. The compound tends to hydrate rather easily, a be-

haviour which has been previously reported[14] for aldehydes of analogous structures. Normal column chromatography on silica gel of 7 led to the isolation of a new compound to which we tentatively assigned[15] structure 12. Collins oxidation[16] of 6 gave compound 7 in 27% yield only.

The reaction of aldehyde 7 with methoxycarbonyltriphenylphosphorane[17] in methanol was stereoselective[18] yielding a mixture of the two possible olefins 8 (Z, 71%) and 13 (E, 6%). The stereochemistry was assigned considering the coupling constants of the olefinic protons[10].



Hydrolysis of methyl ester 8 with aqueous 0.5N LiOH (8 equiv) in THF/MeOH (2:1) provided[10] the acid 9 (92% yield). The acid was dissolved in aqueous trifluoroacetic acid (9:1) at 0º, and the mixture was allowed to reach room temperature. Stirring of the reaction mixture for five hours was followed by addition of solid anhydrous K_2CO_3. Extraction with CH_2Cl_2 and subsequent purification by flash chromatography (hexane:EtOAc, 2:3) gave lactone 2 (86%). An analytical sample[19] was obtained by crystallization from hexane: EtOAc, m.p. 83º, $(\alpha)_D$ +284º (c 0.18, $CHCl_3$).

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10. Spectral data for 6: $(\alpha)_D$ = -16.4º (c=0.180, $CHCl_3$) (lit[21] -14.1º). ^1H NMR (300MHz): δ 7.36-7.25 (5H, m, aromatic), 4.77 (1H, d, J= 11.7 Hz, H-5), 4.68 (1H, d, J= 11.7 Hz, H-5), 4.30 (1H, ddd, J= 6.6, 6.6 and 6.6 Hz, H-2), 4.02 (1H, dd, J= 6.6 and 8.4 Hz, H-1), 3.80 (1H, dd, J= 6.6 and 8.4 Hz, H-1) 3.72 (1H, m, H-4), - 3.57 (2H, m, H-3 and H-4), 2.25 (1H, s, -OH), 1.44 (3H, s, H-7 or H-8), - 1.37 (3H, s, H-8 or H-7); ^{13}C NMR: δ 138.4, 128.5 and 127.9 (aromatic), - 109.4 (s, C-6), 79.5 (d, C-2), 76.7 (d, C-3), 72.9 (t, C-5), 65.7 (t, C-1), 61.8 (t, C-4), 26.4, 25.4 (q, C-7, C-8).

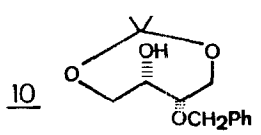
7: (purified by flash chromatography); ^1H NMR: δ 9.65 (1H, s, CHO), 7.2 (5H, s, aromatic), 4.6 (2H, s, OCH_2Ph), 4.4 - 3.6 (4H, m), 1.3 (3H, s, CH_3), 1.2 (3H, s, CH_3).

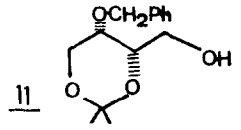
8: ^1H NMR: δ 7.3 (5H, s, aromatic), 6.2 (1H, dd, J= 11.0 and 4.0 Hz, - H-3), 5.9 (1H, d, J= 11.0 Hz, H-2), 5.2 (1H, dd, J= 4.0 and 8.0 Hz, H-4), 4.65 (1H, d, J= 12 Hz, H-7), 4.5 (1H, d, J= 12 Hz, H-7), 4.3 (1H, m, H-5), 3.95 (2H, d, J= 6 Hz, H-6), 3.7 (3H, s, H-11), 1.4 (3H, s, H-9 or H-10), 1.3 (3H, s, H-10 or H-9). ^{13}C NMR: δ 166.1 (s, C-1), 146.2 (d, C-3), 138.1 (s) and 128.3, 127,8, 127.6 (d) (aromatic carbon atoms), 123.1 (d, C-2), 109.8 (s, C-8). 77.7 (d, C-4), 74.4 (d, C-5), 71.5 (t, C-7), 65.3 (t, C-6) 51.5 (q, C-11), 26.2 and 25.6 (q, C-9 and C-10).

The E-isomer of 8 (13) showed the following properties: ^1H NMR: δ 7.3 (5H, s, aromatic), 6.85 (1H, dd, J= 6 and 15 Hz, H-3), 6.1 (1H, d, J= 15 Hz, H-2), 4.7 - 3.9 (6H, m), 3.7 (3H, s, H-11), 1.3 (3H, s, H-9 or H-10), 1.2 (3H, s, H-10 or H-9).

9: ^1H NMR: δ 8.8 (1H, b.s, COOH), 7.3 (5H, s, aromatic), 6.3 (1H, dd, J= 11 and 2 Hz, H-3), 5.95 (1H, d, J= 11 Hz, H-2), 5.15 (1H, dd, J= 2 and 6 Hz, H-4), 4.65 (1H, d, J= 12 Hz, H-7), 4.5 (1H, d, J= 12 Hz, H-7), 4.25 (1H, m, H-5), 3.95 (2H, d, J= 6 Hz, H-6), 1.3 (3H, s, H-9 or H-10), 1.2 (3H, s, H-10 or H-9).

11. Reaction of 5 with 2,2-dimethoxypropane (J. A. Musich and H. Rapoport, J. Am. Chem. Soc., 100, 4865 (1978)) or with 2-methoxypropene in DMF and p-toluensulfonic acid yields, besides 6, variable amounts of 10 and 11 - (^{13}C NMR evidence)[22] depending on experimental conditions.





Using the latter reagents the three acetals (6, 10 and 11) were obtained almost in equal amounts (total yield 92%).

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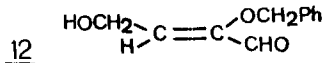
15. The product eluting from the column was assigned structure 12:



(no stereochemistry implied), according with its ^{1}H NMR spectrum: δ 9.25 (1H, s, CHO), 7.3 (5H, s, aromatic), 6.1 (1H, t, J= 5 Hz, olefinic), 5.05 (2H, s, OCH_2Ph), 4.3 (2H, d, J= 5.0 Hz, CH_2OH), 2.3 (1H, b. singlet, -OH).

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19. Spectral data (see refs [20]) for compound 2: IR (KBr): 3250, 2950, 2920, 2870, 1740, 1730, 1630, 1455, 1260, 1110, 1065, 820 and 700 cm^{-1}. ^{1}H NMR: δ 7.3 (5H, s, aromatic), 6.85 (1H, dd, J= 11.0 and 6.0 Hz, H-3), 6.1 (1H, d, J= 11.0 Hz, H-2), 4.6 (2H, s, $-O-CH_2Ph$), 4.45 (1H, dt, J= 3.0 and 6.0 Hz, H-5), 4.1 (1H, dd, J= 6.0 and 3.0 Hz, H-4), 3.9 (2H, m, H-6), 2.55 (1H, b. singlet, -OH). ^{13}C NMR (300 MHz): δ 162.9 (s, C-1), 142.6 (d, C-3), 137.2 (s, aromatic), 128.6, 128.3, 127.9 (d, aromatic), 123.8 (d, C-2), 80.4 (d, C-5), 71.6 (t, OCH_2Ph, 66.2 (d, C-4), 61.0 (t, C-6). MS: m/z= 234 (M^+).

20. See for example: J. MIEZKOWSKI, J. JURCZAK, M. CHIMIELEWSKI AND A. ZAMOJSKI, Carbohydr. Res. 56, 180 (1977) and ref. 4, for spectral data of analogous lactones.

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