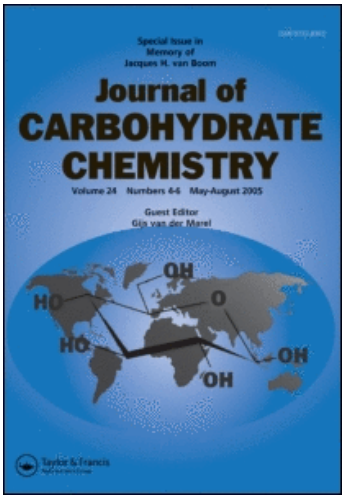

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COMMUNICATION

(5S)-HYDROXYMETHYL-δ-VALEROLACTONE : A USEFUL INTERMEDIATE FOR LEUCOTRIENES B SYNTHESIS

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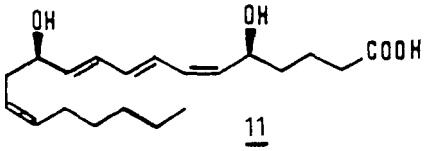
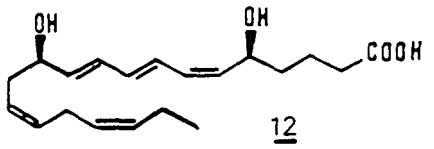
LTB_4 11, a member of the arachidonic acid cascade has been identified by Borgeat and Samuelsson[1]. LTB_4 is a potent chemotactic factor and it is now considered as the chemical mediator implicated in inflammatory processes.[2]



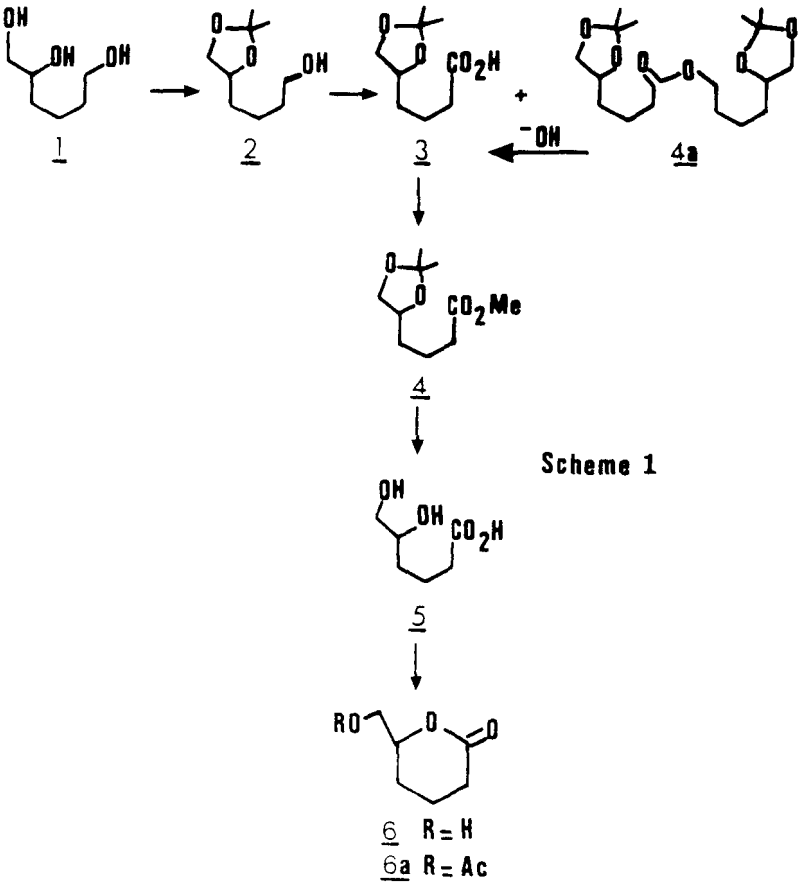
11



12

LTB_5 12, the analogue of 11 which originates from eicosapentaenoic acid rather than arachidonic acid, is of interest in connection with understanding the basis for the cardiovascular protective effect of dietary fish lipids.[3]

(5S)-Hydroxymethyl-δ-valerolactone 6 proved to be an important intermediate[4] for the synthesis of LTB_5 and was first prepared from rather expensive commercial tri-O-acetyl-D-glucal. We have

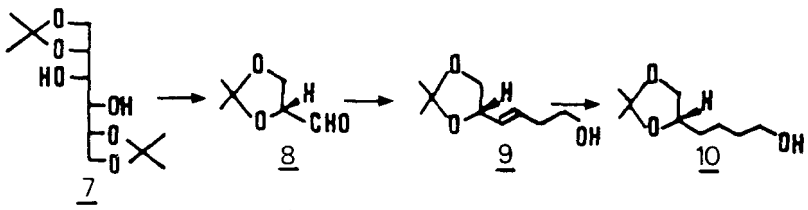


Scheme 1

now prepared the lactone 6 from a cheaper starting material ; namely D-Mannitol.

In a first attempt, 5,6-dihydroxyhexanoic acid 5, the precursor of lactone 6, was made from commercially available racemic 1,2,6-trihydroxyhexane 1 (Scheme I).

Racemic triol 1 was converted into the acetonide 2[5] which was oxidized to the carboxylic acid 3 (PDC[6], DMF, rt or $KMnO_4$, AcOH[7]).[8] No matter which method was used, oxidation yielded a by-product which was identified as 4a. Formation of this intermolecular ester resulted from the reaction of the primary alcohol 2 with the intermediary aldehyde, the resulting hemiacetal being overoxidized by the reagent. Compounds 3 and 4a were separated on one occasion by flash chromatography and isolated in 65 % and 35 % yield, respectively.



Scheme 2

From a practical point of view, the mixture of products resulting from oxidation was first saponified (1N aqueous KOH, rt) then acidified (Amberlite IR-120 ion-exchange resin) and finally esterified (CH_2N_2, MeOH). The methyl ester 4 was isolated in 83 % yield after separation from the alcohol 2 by flash chromatography. Saponification of the pure ester 4 followed by hydrolysis of the acetonide (AcOH-H_2O, 4:1, rt) gave the carboxylic acid 5 (80 %). Surprisingly, lactonization of the dihydroxyacid 5 did not occur spontaneously. The racemic lactone 6 could only be obtained after bulb to bulb vacuum distillation of the crude acid 5.

Enantiomerically pure lactone 6 was obtained starting from the readily available 1,2-5,6-di-O-isopropylidene-D-mannitol 7[9] (Scheme II).

Lead tetraacetate oxidation of compound 7 [$(Pb(OAc)_4$, CH_2Cl_2, 2eq.Na_2CO_3, rt)] yielded the 1,2-O-isopropylidene-D-glyceraldehyde 8 (95 %) after distillation. Wittig olefination ($Ph_3P^+(CH_2)_3OH$, Br^- [10], THF, 2eq.n-BuLi, - 78°C) of the chiral aldehyde 8 afforded the unsaturated derivative 9 in 80 % yield, the E-isomer being the major product formed. β-Alkoxy and δ-alkoxy phosphoranes [11] are known to afford the E-olefin during a Wittig reaction. This E-selectivity has been explained in terms of an internal Schlosser reaction[12] although at the present time this mechanism is really controversial.[13]

Hydrogenation of compound 9 (Raney Ni, EtOH) gave the saturated alcohol 10 in 92 % yield. Removal of the acetonide, followed by lactonization, as described before gave the chiral lactone 6 in a

45 % overall yield[14] ; $[\alpha]_D^{20}$ = + 42° (c, 1.00, $CHCl_3$), lit[4], $[\alpha]_D^{20}$ = + 35° (c, 1.30, $CHCl_3$) lactoné 6 was also fully characterized as its acetate. 6a. [15]

The availability of chiral lactone 6 from inexpensive D-mannitol and rather cheap reagents is of interest since this chiral material can be a useful intermediate for the leukotrienes B synthesis.

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8. All new compounds exhibited satisfactory NMR, IR and mass spectra as well as elemental (C, H) analyses.

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14. Lactone 6 : bp 130-140°C/0.5 mm Hg ; IR (neat) 3700-3100 (broad, OH), 1730 cm^{-1} (OCO) ; ^1H NMR. (300 MHz, $CDCl_3$) 4.42 (1H, m, $J_{5,4} = J_{5,4'} = 7.5$ Hz, $J_{5,6} = 6.0$ Hz, $J_{5,6'} = 3.5$ Hz, H5), 3.81 (1H, dd, $J_{6,6'} = 12.0$Hz, H_6), 3.69 (1H, dd, $H_{6'}$), 2.70-2.30 (2H, m, H_2 and $H_{2'}$), 2.10-1.60 (4H, m, H_4, $H_{4'}$, H_3 and $H_{3'}$) ; MS (CI NH_3, $C_6H_{10}O_3$, MW = 130) : 131 (M+1), 148 (M + NH_4^+).

15. Acetylated lactone 7 : $[\alpha]_D^{20} = +30°$ (c, 0.98, CCl_4) ; IR (neat) 1760-1740 cm^{-1} (broad, OCO) ; ^1H NMR (300 MHz, $CDCl_3$) 4.58 (1H, m, $J_{5,4} = J_{5,4'} = 7.5$ Hz, $J_{5,6} = 6.0$ Hz, $J_{5,6'} = 3.5$ Hz, H_5), 4.26 (1H, dd, $J_{6,6'} = 12.0$ Hz, H_6), 4.20 (1H, dd, $H_{6'}$), 2.70-2.50 (2H, m, H_2 and $H_{2'}$), 2.10-1.90 and 1.80-1.60 (2x2H, m, H_3, $H_{3'}$, H_4 and $H_{4'}$) ; ^{13}C NMR ($CDCl_3$) 170.6 (C_1 and C_7), 77.6 (C_5), 65.7 (C_6), 21.5 (C_2), 24.4 (C_3), 20.8 (C_8) and 18.4 (C_4) ; MS (CI NH_3, $C_8H_{12}O_4$, MW = 172) : 173 (M+1), 190 (M + NH_4^+).