Tetrahedron Letters, Vol.22, No.37, pp 3657 - 3658, 1981
Printed in Great Britain

0040-4039/81/373657-02$02.00/0

5(S), 6(R)-5, 7-DIBENZOYLOXY-6-HYDROXYHEPTANOATE ESTER : IMPROVED SYNTHESIS OF A LEUKOTRIENE INTERMEDIATE

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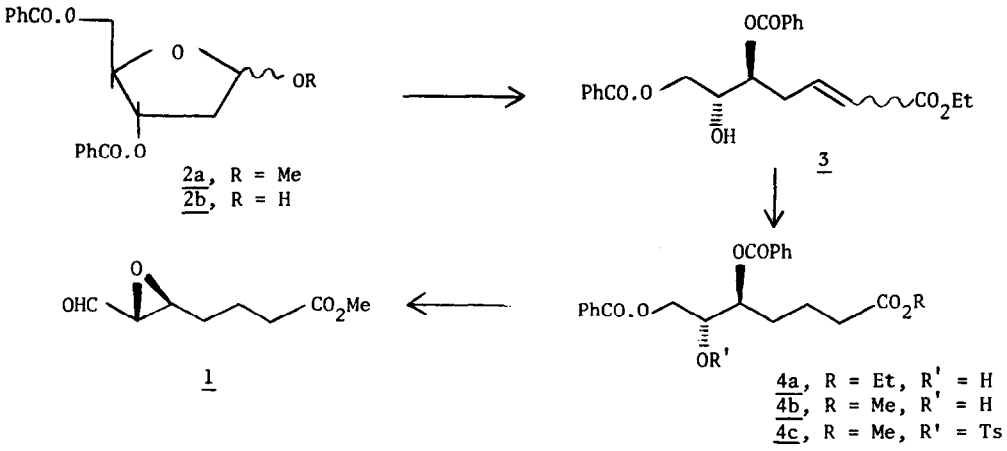
Summary The title compound, a key intermediate in the synthesis of leukotriene A_4, was prepared by a convenient procedure from 2-deoxy-D-ribose.

The possible biological importance of the family of "slow reacting substances" now known as leukotrienes C_4, D_4 and E_4, has been reflected in the number of papers devoted to their synthesis,[1] or to the preparation of their natural precursor, the epoxide LTA_4.[2] A key intermediate in the stereospecific syntheses of LTA_4 so far reported is enantiomer 1. As a ready source of chiral carbon atoms for the construction of the epoxide ring in 1, several different carbohydrate derivatives have been utilised, such as D-glyceraldehyde ketal derived from D-mannose,[2b] D-araboascorbic acid,[3] and in the initial crucial structural confirmation and stereochemical assignment of LTC_4, D-ribose.[1a] Recently in a different approach to 1, highly enantioselective epoxidation of the appropriate allylic alcohol was employed to construct the oxido-ring.[4]

The reported synthesis of 1 from D-ribose required reductive elimination by zinc amalgam of the unwanted hydroxyl group on carbon 2 of the original furanoside, necessitating a protection and deprotection step for what had been the ring oxygen at carbon 4. By starting from commercially available 2-deoxy-D-ribose we have greatly reduced the number of steps required to obtain 4b, a precursor of 1.



2a, R = Me
2b, R = H

3

1

4a, R = Et, R' = H
4b, R = Me, R' = H
4c, R = Me, R' = Ts

Thus, 2-deoxy-D-ribose was converted to the methyl 3,5-dibenzoyloxy-2-deoxy-D-erythropento-furanosides (2a),[5] which were demethylated by refluxing with dioxan, water, and concentrated HCl (25:10:1) for 45 minutes to give furanose 2b.[7] Without purification, 2b was refluxed in dimethoxyethane (N_2) with ethoxycarbonylmethylenetriphenylphosphorane (1.5 equiv.) and benzoic acid (0.3 equiv.) for 2.5 hours, and then evaporated. The residue was chromatographed to separate unchanged 2a, (silica gel; petroleum ether (bp 40 - 60°): ether 2:1) giving 3 as a mixture of geometrical isomers (E:Z 83:17 by ^{1}H NMR)[8] in 64% overall yield from 2-deoxy-D-ribose. Hydrogenation of 3 in ethanol (10% Pd/C)gave ethyl ester 4a quantitatively as a single product.[9] For comparison purposes 4a was treated with 0.05% dry HCl in methanol at 25° for 48 hr to give methyl ester 4b (quantitative), which was converted to the tosylate 4c (84%), mp 127 - 128°; $[\alpha]_D^{23}$ = + 34.1° (c 0.3, $CHCl_3$): reported, + 34.5° (c 1.72, $CHCl_3$).[1a]

Acknowledgement We wish to thank Professor E. J. Corey for making available to us experimental details relating to the preparation of 4b from D-ribose.

During the course of preparation of this manuscript we became aware of an alternative method of preparing 1 from 2-deoxy-D-ribose.[10]

References and Notes

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5. 1-Methylribofuranoside was prepared by the method of A. Rosenthal and C. M. Richards, Carbohydrate Res., 32, 67 (1974) with 0.05% methanolic HCl, but omitting treatment with silver carbonate. Unlike previous experience,[6] benzoylation then gave the anomeric mixture (2a) (70%) with no detectable pyranosides (HPLC). The anomers could be separated; silica gel, petroleum ether (40 - 60°) : ethyl acetate (5:1) : α-anomer, $[\alpha]_D^{23}$ = + 94.9° (c 0.66, $CHCl_3$); ^{1}HNMR ($CHCl_3$), δ 3.42 (s, OMe), 5.42 (m, H-1): β-anomer, $[\alpha]_D^{23}$ = -22.0° (c 0.73, $CHCl_3$); δ 3.35 (s, OMe), 5.60 (m, H-1).

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7. $[\alpha]_D^{23}$ = +35.5° (c 0.8, $CHCl_3$).

8. ($CHCl_3$): E isomer ; δ 7.02 (dt, 1H, J = 15, 7.5 Hz), 5.97 (d, 1H, J = 15 Hz), 5.37 (dt, 1H, J = 6, 6 Hz), 2.81 (t, 2H, J = 6 Hz). Z isomer ; 6.35 (m, 1H), 5.97 (d, 1H, J = 12 Hz), 5.42 (dt, 1H, J = 6,6 Hz), 3.3 (m, 2H).

9. $[\alpha]_D^{23}$ = + 17.2° (c 0.3, $CHCl_3$).

10. J. Rokach, C. K. Lau, R. Zamboni, Y. Girard, M. Larne and Y. Guindon, presented at the International Symposium on Leukotrienes and other Lipoxygenase Products, Florence, June 1981.

(Received in UK 22 June 1981)