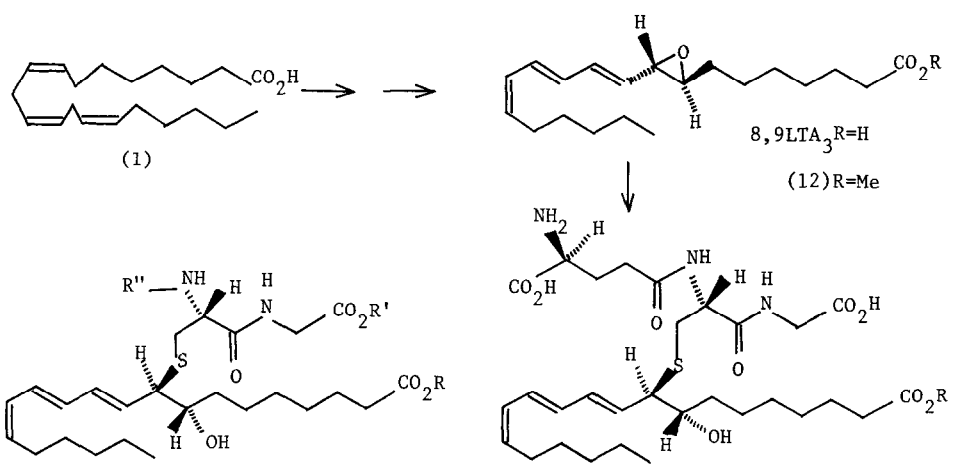
Tetrahedron Letters,Vol.24,No.41,pp 4469-4472,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

SYNTHESIS OF 8,9-LEUKOTRIENE C_3 AND D_3

S. Richard Baker*, John R. Boot, Sarah E. Morgan,
David J. Osborne, William J. Ross and Patricia R. Shrubsall
Lilly Research Centre Limited,
Erl Wood Manor, Windlesham, Surrey GU20 6PH.

Summary:
An asymmetric epoxidation provides a short convenient synthesis of 8,9-leukotrienes C_3 and D_3.

The arachidonic acid metabolites, leukotrienes C_4, D_4 and E_4 are thought to be responsible for many of the symptoms of immediate hypersensitivity[1]. It has recently been reported[2] that dihomo-γ-linolenic acid (1) can undergo similar metabolism to produce 8,9-leukotriene C_3 (8,9-LTC_3) (2) when incubated with ionophore stimulated murine mastocytoma cells. 8,9-LTC_3 is also reported[3] to have spasmogenic activity comparable to its positional isomer leukotriene C_3. Although the stereochemistry of 8,9-LTC_3 was not determined it seems probable, by analogy with arachidonic acid metabolism in the same cell system[4,5], that it has the 8S,9R,10,12E,14Z stereochemistry. We now wish to report the total synthesis of 8,9-LTC_3 (2) and its possible metabolite 8,9-LTD_3 (3).



8,9-LTD_3(3)R,R',R''=H
(14)R,R'=Me R''=$COCF_3$

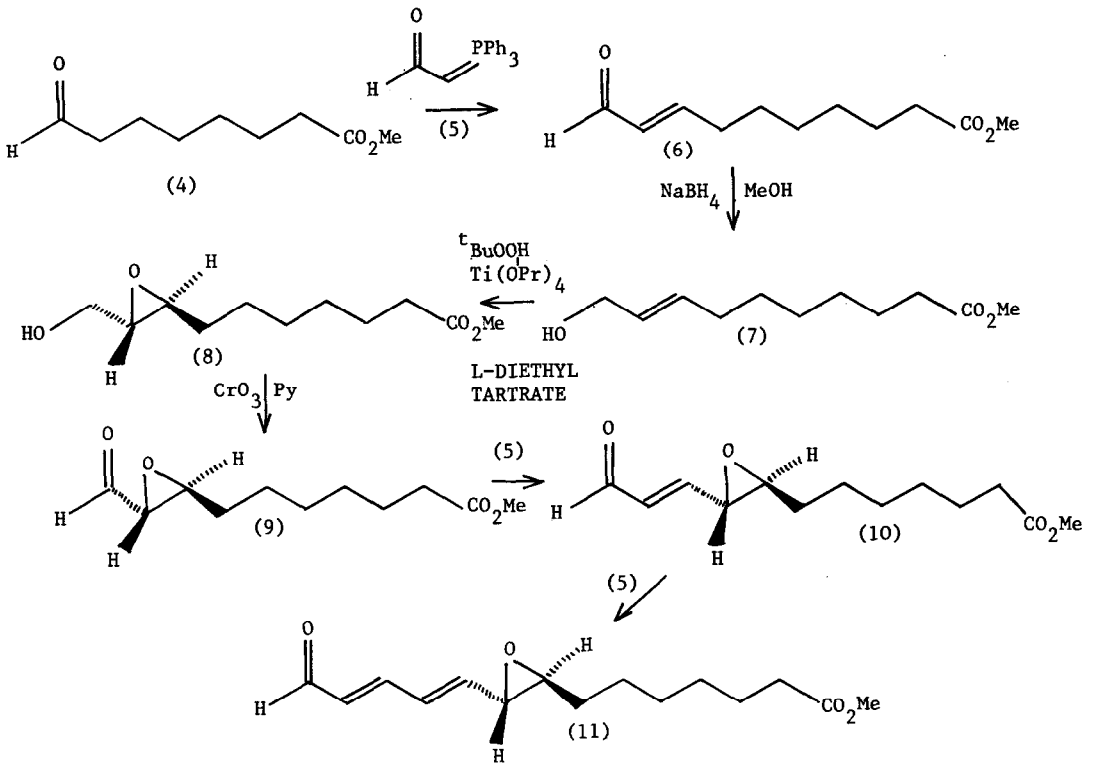
8,9-LTC_3(2)R=H
(13)R=Me

Methyl-8-oxo-octanoate[6] (4) was reacted with the phosphorane (5) in refluxing toluene to give exclusively the E isomer of the α,β unsaturated aldehyde (6) in 51% yield. Sodium borohydride reduction of (6) in methanol led to a 94% yield of the allylic alcohol (7) which was then epoxidised in the presence of L(+)-diethyl tartrate using the procedure of Katsuki and Sharpless[7].

The required 8S,9S-epoxy alcohol (8) $[\alpha]_D^{20}$-15.5° (C 0.5 $CHCl_3$)[8] was isolated in 69% yield and then oxidized with chromium trioxide/pyridine in dichloromethane to give the epoxy aldehyde (9). This crude product was then reacted with 1eq. of the phosporane (5) in benzene at 21°C to give the E-enal epoxide (10) (mp 32-35°C) in 34% yield from (8). Reaction of (10) with a further equivalent of phosphorane (5) in refluxing toluene gave the E,E-dienal epoxide (11) (mp 57-60°C) in 66% yield. The final Z double bond was formed by reacting (11) with the ylide produced from n-hexyl phosphonium bromide and n-butyl lithium at -78°C in THF. On examination by HPLC[9] the crude product from this reaction was found to be 90% of the required 8,10,12E,14Z-isomer (12) as determined by 360MHz H^1 NMR[10] plus approximately equal amounts of two isomeric impurities[11]. The HPLC purified 8,9-LTA_3 methyl ester (12) obtained in 30% yield from (11) was reacted with glutathione in methanol/triethylamine and the resultant mono methyl ester of 8,9-LTC_3 (13) (90% yield) purified by HPLC[12]. Hydrolysis of (13) with 0.1M aq. K_2CO_3 in methanol (3:1) gave 8,9-LTC_3 (2) (λmax MeOH 269, 280 and 291nm) in 95% yield after HPLC[11]. It was found that if (13) was not purified by HPLC prior to hydrolysis an additional less polar product was formed having λmax MeOH 268, 277 and 289nm. This compound is believed to be the 14E-isomer of 8,9-LTC_3 (2) arising by RS$^\cdot$ catalysed isomerization of the 14,15-double bond[13].

Reaction of 8,9-LTA_3 methyl ester (12) with N-trifluoroacetyl-L-cysteinylglycine methyl ester in methanol/triethylamine produced the 8,9-LTD_3 derivative (14) in 85% yield after HPLC[12]. Hydrolysis in aq 0.1M K_2CO_3 in methanol (3:1) for 16 hours at 21°C gave 8,9-LTD_3 (3) (91% yield) λmax 270, 280 and 291nm after HPLC[12].

In order to determine the optical purity of the 8,9-LTA_3 methyl ester (12) the γ,β-unsaturated aldehyde (6) was epoxidised directly with alkaline hydrogen peroxide to racemic aldehyde epoxide (8) which was then converted to racemic 8,9-LTA_3 methyl ester using the above procedure. The reaction of this racemic material with N-trifluoroacetyl-L-cysteinylglycine methyl ester gave rise to two HPLC[14] separable products in a 1:1 ratio, the more polar of which co-eluted with (14), the less polar co-eluting with a 7% impurity in the crude chiral material. Thus the chiral epoxidation gave rise to a 93% enantiomeric excess[15].



This type of approach has been used for a key intermediate in the synthesis of the 5,6-leukotrienes but it was found necessary to modify the isolation procedure[16]. The original technique apparently caused Lewis acid catalysed cyclization of the product to a diol lactone[16]. Such a reaction was considered unlikely in the case of a 8,9-epoxy ester and it was found that the addition of 10% aqueous tartaric acid to the reaction mixture followed by extraction with dichloromethane yielded a crude product suitable for chromatography (SiO_2/Et_2O).

The relative contractile effects of 8,9-LTC_3 (2), and their isomers were examined and compared with those of leukotriene D_4 (LTD_4) on isolated guinea pig ileum. Preliminary studies indicated that 8,9-LTC_3 (2) possess approximately 0.1% of the contractile activity of LTD_4 and it is at least ten times more potent that its 14E isomer. Both 8,9-LTD_3 (3) and its 8R, 9S-isomer possess <0.1% the activity of LTD_4.

1) For review see P. Borgeat and P. Sirois,
J. Med. Chem. 24, 121, (1981)

2) S. Hammarström,
J. Biol. Chem. 256, 7712, (1981).

3) S. Dahlen, P. Hedquist and S. Hammarström
European J. Pharmacol 86, 207, (1983).

4) R.C. Murphy, S. Hammarström and B. Samuelsson
Proc. Natl. Acad. Sci. U.S.A. 76, 4275, (1979).

5) E.J. Corey, D.A. Clark, G. Goto, A. Marfat, C. Mioskowski,
B. Samuelsson and S. Hammarström.
J. Am. Chem. Soc. 102, 1436, (1980).

6) F.C. Pennington, W.D. Celmer, W.M. McLamore, V.V. Bogert and
I.A. Solomons
J. Am. Chem. Soc. 75, 109, (1953).

7) T. Katsuki and K.B. Sharpless
J. Am. Chem. Soc. 102, 5974, (1980).

8) Reference 5 reports the $[\alpha]_D^{24}-37.4^{\circ}$ (C 0.27 $CHCl_3$) for the analogous ethyl 5(S),6(S) oxido-7-hydroxyheptanoate.

9) 50cm x 8.0mm i.d. Spherisorb S5W column, eluted with diethyl ether: hexane: triethylamine, (5:95:0.5).

10) $J_{10,11} = J_{12,13} = 15.3Hz$ $J_{14,15} = 11.0Hz$. We thank Mr. J.W. Paschel (Lilly Research Laboratories, Indianapolis) for providing this data, λmax cyclohexane 269, 280 and 291.5nm.

11) The stereochemistry of these impurities has not as yet been determined.

12) 12.5cm x 4.9mm i.d. Nucleosil 5 C_{18} column eluted with methanol: water: acetic acid (70:30:0.06).

13) An analogous process has been reported for leukotriene C_4.
E.J. Corey, D.A. Clark, A. Marfat and G. Goto
Tetrahedron Letters, 21, 3143, (1980).

14) 50cm x 8.0mm i.d. Spherisorb S5NH column eluted with dichloromethane: methanol (100:0.5).

15) All reactions were conducted under an atmosphere of nitrogen. Satisfactory mass spectra, PMR and where applicable u.v. spectra were obtained on all stable intermediates.

16) B.E. Rossiter, T. Katsuki and K.B. Sharpless
J. Am. Chem. Soc. 103, 464, (1981).

17) This work was presented in part at the
'Progress in Natural Product Chemistry' Symposium, Nottingham, July 1982.

(Received in UK 15 July 1983)