Tetrahedron Letters,Vol.24,No.4,pp 331-334,1983 0040-4039/83/040331-04$03.00/0
Printed in Creat Britain

SYNTHESIS OF THE AZA ANALOG OF LTA_4

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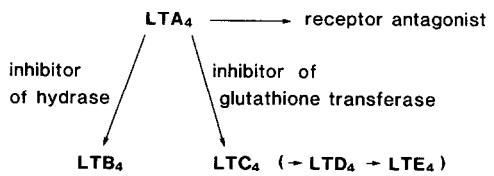
Summary: The stereospecific synthesis of trans-5S,6S-imino-7,9-trans-11,14-cis-eicosatetraenoic acid was accomplished from 5-epi,6-epi-LTA_4 by treatment with NaN_3 followed by cyclization with Ph_3P.

Several natural products derived from the arachidonic acid cascade via the lipoxygenase pathway are now available through synthesis.[1] Improved supply of the various mediators has allowed the establishment of an array of biochemical and pharmacological assays. As a result, attention is now turning toward the use of these biological assays for the discovery and study of receptor antagonists of such mediators or the biosynthetic inhibition of their production.

LTA_4 is a pivotal intermediate for the subsequent biotransformations leading to the lipoxygenase-derived mediators (Scheme 1). LTA_4 in a glutathione transferase mediated step undergoes a nucleophilic attack at position 6, resulting in the formation of LTC_4, a component of slow-reacting substance of anaphylaxis or SRS-A, which is thought to play an important role in the etiology of asthma. LTA_4 is also the substrate in another enzymatic step leading to LTB_4, which is a potent chemotactic factor most probably involved in the regulation of inflammatory processes. LTA_4, through interaction with a specific receptor, could also be involved in some pharmacological action of its own (not yet discovered).

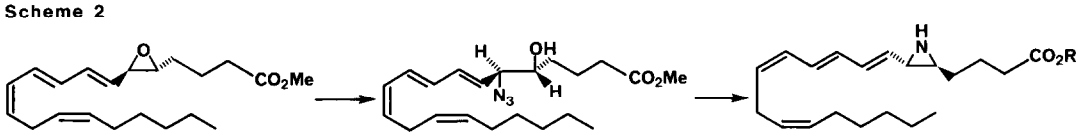
Scheme 1



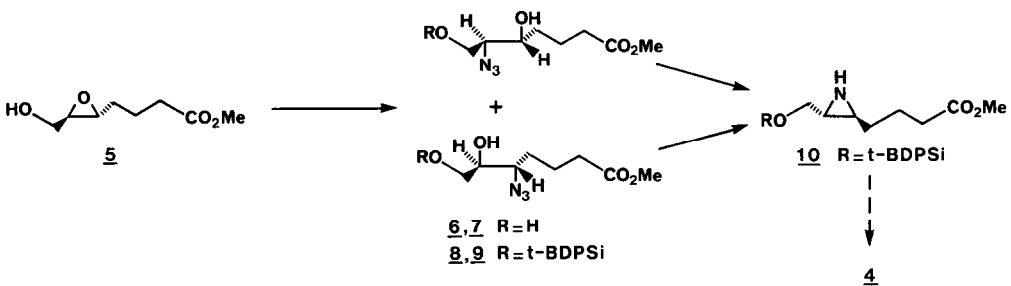
Since the two enzymes leading to formation of LTB_4 and LTC_4 recognize LTA_4, a molecule having all the features of LTA_4 could act as a reversible or irreversible inhibitor on one or both of these enzymes by occupying the LTA_4 cavity (Scheme 1). Furthermore, if LTA_4 has some physiological role by itself, it will likely act through a receptor. A molecule having most of the features of LTA_4 could compete for that receptor and provide a receptor antagonist to LTA_4.

One such molecule is trans-5S,6S-imino-7,9-trans-11,14-cis-eicosatetraenoic acid 4, the aza analog of LTA_4.[6] Such a close analog of LTA_4 could be an ideal tool to investigate the LTA_4 metabolic pathway as well as its receptor properties. We also thought that in order to avoid complication in the interpretation of the biological results, it was important to prepare an analog having natural stereochemistry 4.

Scheme 2



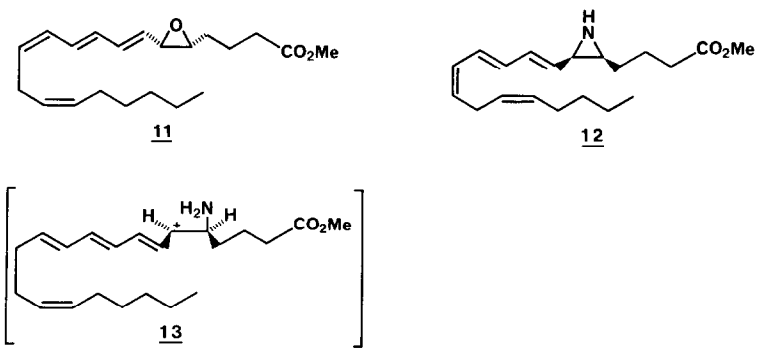
Scheme 3



We decided at the outset to prepare the aziridine ring from the corresponding oxirane using the 2 step procedure developed by Itah et al. (1. NaN_3, 2. Ph_3P).[2] Since it had been shown that the transformation occurs through an inversion at both centers of the epoxide, 5-epi,6-epi LTA_4 1 would be the logical starting material. We anticipated that the azide attack at position 6 resulting in the opening of the epoxide would present no big difficulties in analogy to the known nucleophilic attack on LTA_4 by sulphur nucleophiles.[1a,b] We were however less sure about the reductive ring closure step, which we anticipated to be less facile and possibly destructive to the sensitive molecule. For that reason we have considered as an alternate

strategy (Scheme 3) a synthesis using 5[1c] an available intermediate as our starting material. As anticipated 5-epi-6-epi LTA_4 1 reacted smoothly with NaN_3 to afford azido alcohol 2 in >90% yield. Unfortunately the azido alcohol under the reported reaction conditions (Ph_3P, reflux in ether)[2] failed to give any of the desired aziridine. At that stage we turned our attention to our alternate strategy (Scheme 3). Treatment of the epoxy alcohol with NaN_3/NH_4Cl[3] in ethanol at 60° afforded in nearly quantitative yield azido alcohols 6 and 7 as an unseparable mixture. Silylation (t-BDPSiCl/DMAP/Et_3N)[4] afforded the corresponding silyl ethers 8 and 9 in a 7:1 ratio which could easily be separated by flash chromatography. Again, no cyclization occurred using Ph_3P in ether but we found that either azido alcohol when heated in THF at 60-65° with 1.2 eq Ph_3P afforded cleanly in >80% yield the aziridine 10. The higher temperature was necessary for the cyclization. To our delight when we tried these conditions on azido alcohol 2 we obtained the desired aziridine 3 $[\alpha]_D$ = -64°, (c=.2, hexane) in 40-50% overall yield from the epoxide (see typical prodecure). Pmr (400 MHz) clearly showed that the triene stereochemistry had been preserved, and that the aziridine had trans stereochemistry ($J_{5,6}$ = 2.5Hz). Hydrolysis (NaOH/MeOH) afforded 4 (UV λ (MeOH) = 290,282,273 nm).

Scheme 4



When the sequence (1. NaN_3/MeOH, 2. Ph_3P/THF) was repeated on 5-epi LTA_4 11 there was obtained not only the desired cis aziridine[5] 12 ($J_{5,6}$ = 8Hz),$[\alpha]_D$ = -28°, (c=.2 hexane) in 20% yield but also what appeared to be trans-aziridine 3 (5-6%). Pmr (400MHz) showed that the trans-aziridine obtained as a byproduct (single peak by HPLC) was in fact a mixture of triene isomers (7,9,11-trans- and 7,9-trans-11-cis). This mixture of trans isomers presumably arose from isomerization of the cis aziridine via a carbonium ion 13. Indeed when a sample of pure cis-aziridine was kept in solution in the absence of Et_3N some trans-aziridine slowly formed (HPLC). Both trans and cis aziridines 3 and 12 were sensitive to the slightest traces of acid. Despite their instability they can be kept in hexane containing 2% Et_3N without decomposition for months at -78°.

Typical Producedure

To 100 mg (.3 mM) of the trans-epoxide 1 in 8 mL dry MeOH and 10 μL Et_3N was added NaN_3 (300 mg, 4.6 mM). The mixture was stirred 3 h at room temperature and hexane 10 mL was added. Filtration through a short silica gel column using 20% ethyl acetate/hexane/3% Et_3N afforded 100 mg crude azido alcohol 2 which was used without further purification. A solution of the azido alcohol 100 mg (.3 mM) and Ph_3P (100 mg, .38 mM) in 7 mL THF was heated at 60-65° for 3 h. The THF was evaporated. Flash chromatography of the residue using first 20% ethyl acetate/hexane/3% Et_3N then 40% ethyl acetate/hexane/3% Et_3N afforded 42 mg (42%) of the trans aziridine 3.

Pmr (400 MHz, $CDCl_3$), δ6.5 (q, H_{10}, J_1 = 11Hz, J_2 = 15Hz), 6.37 (q, H_8, J_1 = 11Hz, J_2 = 15Hz), 6.17 (q, H_9, J_1 = 11Hz, J_2 = 15 Hz), 6.02 (t, H_{11}, J_1 = J_2 = 11Hz), 5.3 - 5.5 (m, 3H, H_{12}, H_{14}, H_{15}), 5.25 (q, H_7, J_1 = 8Hz, J_2 = 15Hz), 3.68 (s, 3H, OCH_3), 2.95 (t, 2H, C=C-$\underline{CH_2}$-C=C), 2.28 (t, 2H, $\underline{CH_2}CO_2CH_3$), 2.23 (dd, H_6, J_1 = 2.8Hz, J_2 = 8.5Hz), 2.07 (q, 2H, $\underline{CH_2}$-C=C), 1.80 (dt, H_5, J_1 = 6Hz, J_2 = 2.5 Hz), 1.80 (m, 2H), 1.50 (q, 2H), 1.13-1.40 (m, 6H), 0.90 p.p.m. (t, 3H, $CH_2\underline{CH_3}$); UV λ (MeOH) 290,282 (ε = 48,000), 273 nm.

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5. pmr (400MHz, CD_3COCD_3, -20°) δ6.7 (q, H_{10}, J_1 = 11Hz, J_2 = 15Hz), 6.52 (q, H_8, J_1 = 11Hz, J_2 = 15Hz), 6.38 (q, H_9, J_1 = 11Hz, J_2 = 15Hz), 6.14 (t, H_{11}, J_1 = J_2 = 11Hz), 5.74 (q, H_7, J_1 = 8Hz, J_2 = 15Hz), 5.4 - 5.6 (m, H_{14}, H_{15}, H_{12}), 3.7 (s, 3H, OCH_3), 3.1 (t, 2H, C=C-$\underline{CH_2}$-C=C), 2.6 (t, H_6, J = 8Hz), 2.45 (t, 2H, $\underline{CH_2}CO_2CH_3$), 2.0-2.4 (m, 3H), 1.85 (m, 2H), 1.3-1.5 (m, 6H), 0.90 p.p.m. (t, 3H, $CH_2\underline{CH_3}$).
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(Received in USA 5 October 1982)