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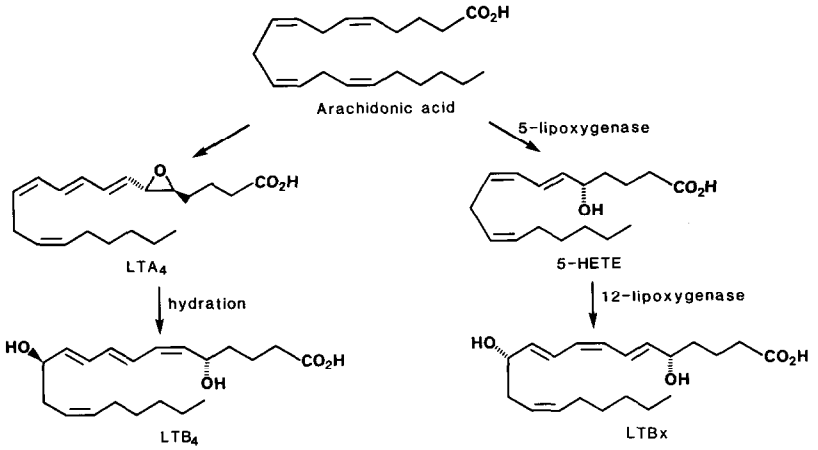
SYNTHESIS OF 5S,12S - diHETE (LTB_X)

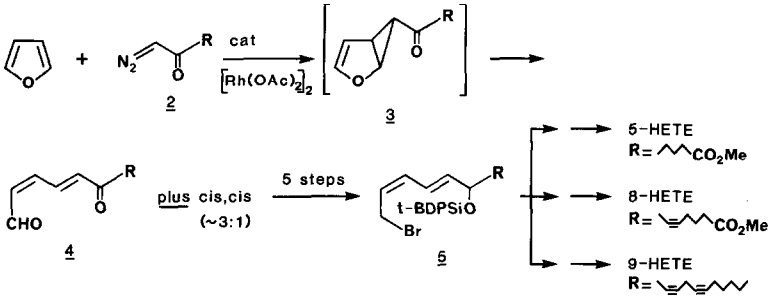
Julian Adams,* Yves Leblanc and Joshua Rokach
Merck Frosst Canada Inc.
P.O. Box 1005, Pointe Claire/Dorval, Quebec, Canada H9R 4P8

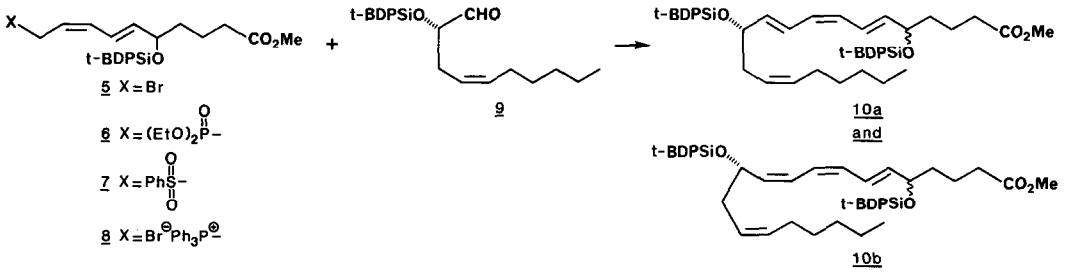
Summary: The total synthesis of 5S, 12S-diHETE (LTB_X) was completed. The Wittig reaction of phosphorane 8 and chiral aldehyde 9 provided the key step to from the C-20 chain.

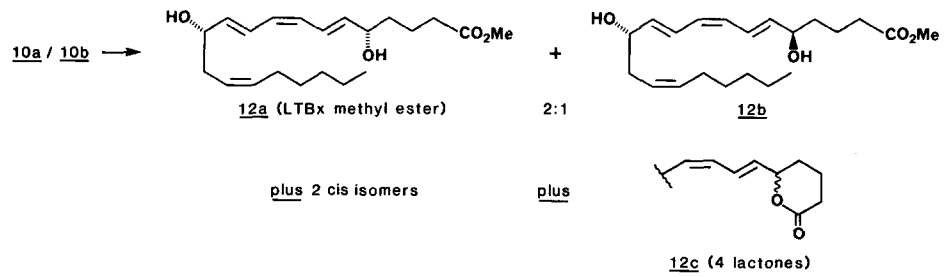
One of the many oxidative metabolites of arachadonic acid, 5S,12S-diHETE or LTB_X, was first described in the literature in 1981 by Borgeat and coworkers.[1,2] LTB_X is found in human leukoyctes and exhibits weak chemotactic activity,[1] however it is uncertain that this is its primary biological function. LTB_X is isomeric with the more abundant metabolite LTB_4, but its biosynthesis is markedly different. LTB_X is formed as a result of sequential oxidations by lipoxygenase enzymes, whereas LTB_4 is bio-synthesized by the stereospecific enzymatic hydration of LTA_4.

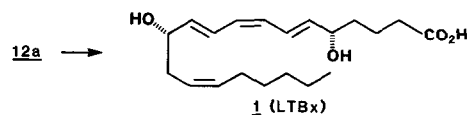


We have recently described a new method for the delivery of dienes of specifically cis-trans geometry, bearing a hydroxyl function allylic to the trans double bond.[3a,b] The addition of diazo-ketones to furan catalyzed by $[Rh(OAc)_2]_2$ furnishes this cis-trans dicarbonyl compound 4 via cyclopropyl furan adduct 3. We have applied this method to the synthesis of 5, 8 and 9-HETEs by varying the structure of the diazo-ketone. Two features of these syntheses include the convergent manner in which the synthons are used, the diazo-ketone being readily available from its corresponding carboxylic acid, and the control of the olefin geometry which produces the desired diene system. We now extend the scope of our approach to include the formation of trienes in the more complex dihydroxy metabolites. The natural product 5S,12S di-HETE was chosen as our target, as we require this material for biological evaluation and its rarity precludes sufficient supply from natural sources.


cat
[Rh(OAc)2]2
2
3
plus cis,cis
(~3:1)
5 steps
4
5
t-BDPSiO
Br
CHO
5-HETE
R=
8-HETE
R=
9-HETE
R=
CO2Me


X
t-BDPSiO
CO2Me
5 X=Br
6 X=(EtO)2P(O)-
7 X=PhS(O)2-
8 X=Br⊖Ph3P⊕
t-BDPSiO
CHO
9
10a
and
10b


10a / 10b
HO
OH
CO2Me
12a (LTBx methyl ester)
2:1
12b
plus 2 cis isomers
plus
12c (4 lactones)


12a
HO
OH
CO2H
1 (LTBx)

Since two chiral centers are present in LTR_x we chose a strategy employing a chiral synthon of known stereochemistry which would be coupled to a cis, trans diene bearing a racemic hydroxyl group at the C-5 carbon. The resolution provides the natural LTR_x and 5-epi-LTR_x. The biological profile of the unnatural product is also of interest in our overall program which is trying to elucidate the physiological role of lipoxygenase products.

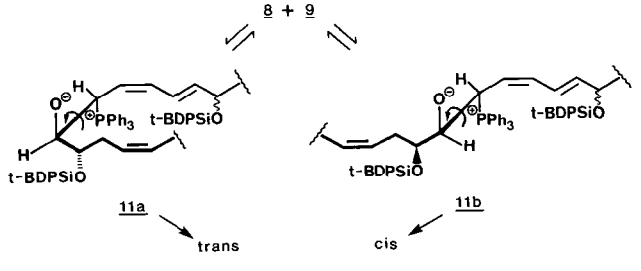
We recognized that C_1 to C_9 of LTR_x is identical C_1 to C_9 of previosuly synthesized 5-HETE and made use of the common intermediate 5. The diene dicarbonyl 4 (R=$(CH_2)_3$-CO_2Me) was converted to bromide 5 in 5 steps.[3a]

For the synthesis of LTR_x, we require that 5 be coupled with aldehyde 9 in a suitable manner to form a trans double bond at C-10. Chiral aldehyde 9, derived from D-arabinose, is readily available to us from our previous synthesis of LTB_4.[4]

Bromide 5 was converted to its corresponding phosphonate 6 (5 and $(EtO)_2PONa/THF$, 0°C)[5] in 85% yield. We feared that elimination of the siloxy group, and possible isomerization of the cis olefin at C-8 might pose problems. When 6 was deprotonated ($(Me_3Si)_2NLi/THF$, -78°C) and quenched with D_2O, deutero-6 was recovered with one exchanged proton α to the phosphonate, and the olefin geometry was retained. It is apparent that at low temperature, de-localization of the negative charge over the conjugated system is not occurring. Nevertheless, the expected Wittig reaction to give the trans coupled product resulted only in destruction of the aldehyde 9.

In an alternate approach, following the method of Kocienski and Lythgoe[6] bromide 5 was converted to its corresponding sulphone 7 (a) $\phi SH/K_2CO_3$, 4 h; b) oxone/MeOH-H_2O, 2 days) in 90% yeild. The anion of 7 did not provide any of the desired product and some elimination of O-siloxy was observed.

The phosphonium salt of 5 was formed (excess ϕ_3P/CH_3CN,RT, 4h) in 88% yield. The ylide was formed ($(Me_3Si)_2NLi$/toluene, -78°C) followed by addition of aldehyde 9 (-78°C, 1 h; 0°C, 1/2 h; RT, 1/2 h) and adducts 10a and 10b were obtained in 60% yield. We attribute the success of this reaction to the markedly lower basicity of the phosphorane as compared to the phosphonate anion or the sulphone anion. We were surprised but gratified to discover a 3:1 trans/cis ratio (10a/10b, determined by ^{1}HNMR). Normally Wittig reactions of allylic phosphoranes indicate a slight preference for cis olefins.[7] However we explain the preponderance of trans olefin by examining the betaine intermediates 11a and 11b.



Erthyro betaine 11b is kinetically favoured over threo betaine 11a, however the slow step is the collapse of the betaine to form the double bond. This requires a rotation of the newly formed C-C bond so that phosphorous and oxygen atoms are eclipsed. This creates serious steric compression in erthyro betaine 11b due to the bulky α-siloxy function. Alternatively 11b can revert to starting materials. Betaine 11a is more strained, for the same reason just mentioned, but rotation about the newly formed bond relieves strain and the reaction proceeds in the forward direction to give the thermodynamically favoured trans olefin.

The geometric isomers 10a/10b as well as the diastereomers 5S/5R, 12S could not be separated at this stage. Removal of the silyl protecting groups (n-Bu_4F/THF, 6h) gave a mixture of four diols in 40% yield and their corresponding lactones in 4% yield. HPLC analysis and separation (1% MeOH-CH_2Cl_2, Waters μ-porasil column) of the mixture produced a fascinating observation; not only are the desired trans geometric isomers the major ones (3:1 trans/cis), but there is also a diastereo-selection in favour of the natural product 5S,12S isomer 12a over the 5R,12S isomer 12b (2:1). Hydrolysis of the lactones 12c (K_2CO_3/MeOH/H_2O) and esterification (CH_2N_2/Et_2O) produces the same isomer distribution. Thus LTR_x-Me ester ($[\alpha]_D$= -10°, C=0.2, MeOH) is the major peak in the HPLC chromatogram. We are currently studying the Wittig reaction in greater detail in an effort to explain the observed results.

Finally, hydrolysis of isomer 12a (LiOH/DME-H_2O, 5:1, RT) gave the natural product quantitatively, and confirmation was obtained by comparison with a sample obtained from natural sources.[8] Similarly isomer 12b furnished the unknown 5R,12S diHETE or 5-epi LTR_x.

References

1. P. Borgeat, S. Picard, P. Vallerand and P. Sirois, Prostaglandins and Medicine, 6, 557 (1981).

2. For previous synthesis see: E.J. Corey, A. Marfat, P.C. Laguzza, Tetrahedron Letters 22, 3339 (1981).

3. a) J. Rokach, J. Adams and R. Perry, Tetrahedron Letters, 24, 5185 (1983).
   b) J. Adams and J. Rokach, Tetrahedron Letters. (in press)

4. Y. Guindon, R. Zamboni, C.K. Lau and J. Rokach, Tetrahedron Letters, 23, 739 (1982).

5. The Arbuzov reaction with $(EtO)_3P$ partially isomerizes the diene to give a 2:1 cis-trans/trans-trans mixture.

6. P.J. Kocienski, B. Lythgoe and S. Ruston, J.C.S. Perkin I, 829 (1978).

7. See review by I. Gosnez and A.G. Rowley in Organophosphorus Reagents in Organic Synthesis, pp. 66-70, Edited by J.I.G. Cadogan, Academic Press, 1979.

8. We kindly thank Dr. Pierre Borgeat for an authentic natural sample of LTR_x.

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