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CONVERGENT SYNTHESIS OF LEUKOTRIENE A METHYL ESTER

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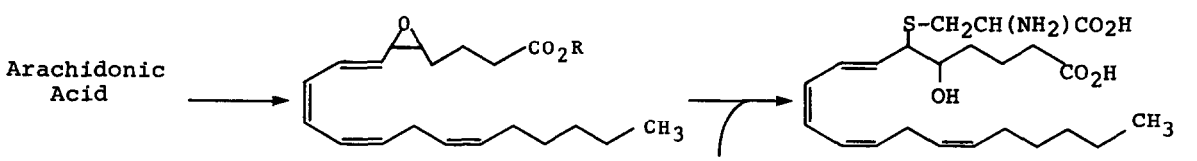
A convergent total synthesis of methyl 5,6-oxido-7,9,11,14-eicosapentaenoate from oct-2-yn-1-ol and methyl 4-formylbutyrate is described.

Leukotriene A (1) has been proposed by Samuelsson and his co-workers to be a shortlived intermediate in the arachidonic acid cascade in human and rabbit leukocytes[1]. This material is believed to play a central role in the conversion of arachidonic acid to leukotrienes, a novel series of 7, 9, 11, 14 eicosatetraenoic acids. Included in this group of metabolites is leukotriene C, suggested by Samuelsson[2] to be SRS (slow reacting substance), a potent bronchiospastic agent and mediator of anaphylaxis in human asthma[3]. Because of our interest in the possible role which these arachidonic acid



1, R=H, Leukotriene A
2, R= CH_3

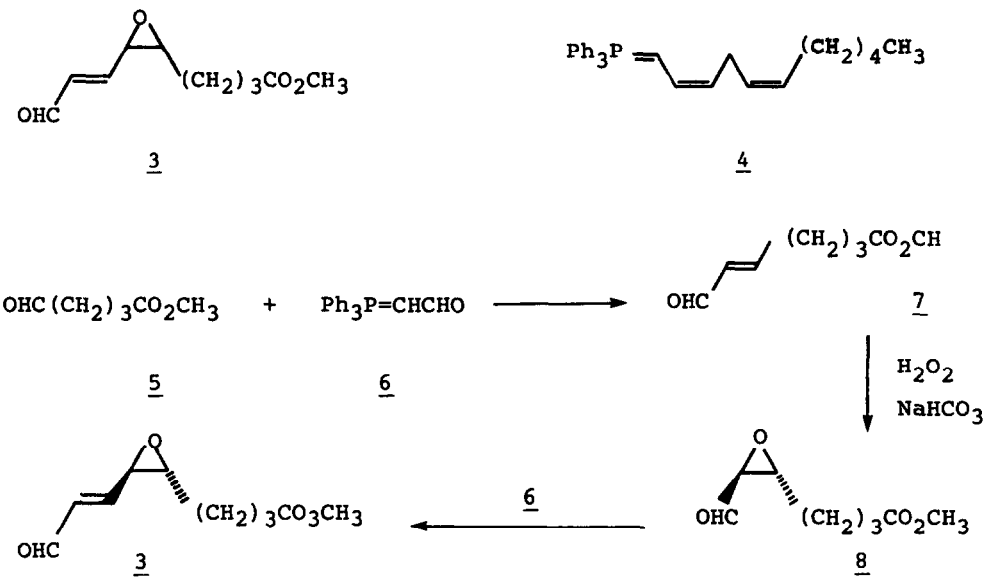
cysteine

Leukotriene C (SRS)

metabolites may play in respiratory diseases, we have developed a convergent synthesis of the methyl ester 2 of Leukotriene A. An alternate synthesis of 2 was described by Corey and his co-workers subsequent to the completion of this synthesis[4].

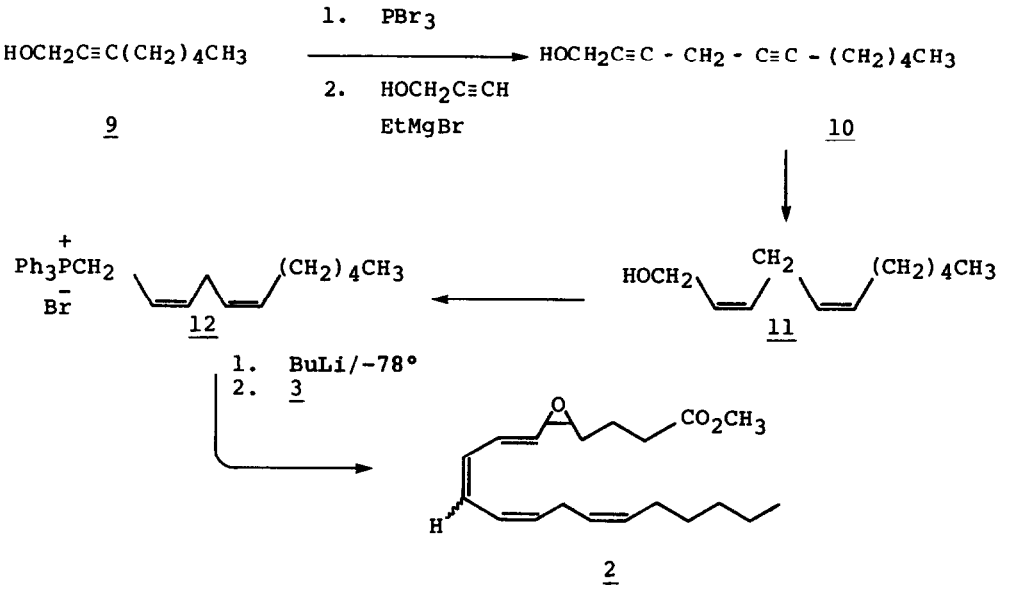
We envisioned the synthesis of 2 as proceeding via coupling of an γ-epoxy-α,β-unsaturated aldehyde 3 to a Z, Z-diene ylide 4. The

requisite aldehyde 3 was synthesized in three steps from methyl 4-formylbutyrate[5] (5), depicted[6]. Addition of ylide 6 to 5 in refluxing toluene afforded aldehyde 7 in 50% yield.



Epoxidation of 7 in basic media gave the trans-glycidaldehyde 8 which was used directly in a Wittig reaction with ylide 6 to afford methyl 9-oxo-5,6-trans-epoxynon-7(E)-enoate (3) in 22% yield from 5. The stereochemistry of 3 was determined by ^1H nmr ($J_{2,3}$=15.5 Hz, $J_{4,5}$=2 Hz) after simplification of the spectrum by addition of Eu(fod)$_3$.

The second requisite fragment, ylide 4, was prepared in the following manner. Oct-2-yne-1-ol 9 was brominated with PBr_3 and the resulting halide was coupled with the dimagnesium halide salt of propargyl alcohol to give the diynol 10. Catalytic reduction of 10 over Pd/$BaSO_4$ catalyst afforded exclusively Z, Z-diene 11 which was transformed via the allylic bromide to phosphonium salt 12 in 70% yield from the acetylenic alcohol 9. Although the vinyl region of the ^1H nmr spectrum of 11 was too complex to allow stereochemical assignments, the use of Eu(fod)$_3$ to separate the vinyl resonances allowed the assignment of all cis stereochemistry on the basis of 10.5 Hz coupling constant for both pairs of olefinic protons.



Generation of ylide 4 from the phosphonium salt 12 at low temperature and coupling with aldehyde 3 afforded the desired Leukotriene A methyl ester 2 as a pale yellow oil in 68% yield: uv(hexane) 270s, 280, 290s[7]; mass spectrum, m/e 332.2337 (calc'd for $C_{21}H_{32}O_3$,332.2351); ^{1}H nmr ($CDCl_3$) δ 0.9 (t, $C_4H_8C\underline{H}_3$), 1.3 (m, $(C\underline{H}_2)_3$ + $C\underline{H}_2CH_2CO_2Me$), 1.68 (m, $C\underline{H}_2$-CH-CH), ca. 2.0 (m, $C\underline{H}_2C$=), 2.35 (broad t, $C\underline{H}_2CO_2$), 2.8 (m, CH-CH-CH_2, =C-$C\underline{H}_2$-C=), 3.1 (m, CH-CH-CH_2), 3.66 (s, OCH_3), 5.45 (m, CH_2-HC=CH-CH_2), ca. 6.3 (-CH=CH-)$_3$; ^{13}C nmr ($CDCl_3$)ppm 14.0 (C_{20}), 21.4 (C_2), 22.5 (C_{19}), 26. (C_{17}), 27.3, 28.0 (C_{13}), 29.3 (C_{17}), 31.3, 31.5 (C_{18}, C_3), 33.6 (C_4), 51.5 (CH_3O), 58.3 (C_6), 60.5 (C_5), 174 (C_1), 124-135 (vinyl). The complexity of the vinyl region as well as the observation of doublets in the ^{13}C spectrum for both C_{13} and C_6 suggest that the final product was a ~2:1 mixture of E and Z

isomers about the C_9 double bond[8]. Further proof of structure was obtained upon catalytic reduction of 2 over palladium which afforded exclusively methyl 5-hydroxyarachidate, the silyl derivative of which was shown to be identical in the mass spectrum to that material obtained by Samuelsson from Raney Nickel reduction of Leukotriene C.

Unlike the free acid, Leukotriene A[1], the ester 2 appears to be a relatively stable compound in the absence of acid and may serve as a valuable precurser for the synthesis of other species related to the leukotrienes.

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2. R. C. Murphy, S. Hammarström and B. Samuelsson, Proc. Natl. Acad. Sci., USA, 76, 4275 (1979).
3. For a review, see K. Austin, J. Immunol. 121, 793 (1978); R. P. Orange, and K. F. Austin, Adv. Immunol., 10, 105 (1969).
4. E. J. Corey, Y. Arai and C. Mioskowski, J. Amer. Chem. Soc., 101, 6748 (1979).
5. A. Burgstahler, L. O. Weigel and C. G. Shaefer, Synthesis, 767 (1976).
6. Satisfactory spectral data (^1H nmr, ms, ir, and where appropriate ^{13}C nmr) were obtained for all intermediates.
7. For comparison, the uv spectrum of Leukotriene C has an absorbance maximum at 280 nm with shoulders at 270 and 292 nm (ref. 2).
8. The configuration of the C(9) double bond in Leukotrienes A and C have not definitively been assigned (references 1 and 2).

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