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STEREOSELECTIVE SYNTHESIS OF SOME ACETYLENIC ANALOGUES OF LEUKOTRIENES A AND D[1]

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Summary: The stereocontrolled synthesis of methyl 5(E)-epoxyeicosa-7-ynoate (7) and its conversion to a 7,8-acetyleno-LTD analog is described. Chiral acetyleno-LTA analogs are prepared following a novel and versatile "one pot" procedure from 5(S)-benzoyloxy-5-formylpentanoate (3).

There has been considerable ongoing interest in exploring the structural requirements for bioactivity of the important biological mediators, the leukotrienes, particularly with respect to the degree and stereochemistry of unsaturation in the polyenic backbone. Researchers have prepared leukotriene analogues lacking some[2] or all[3] of the double bonds, while others have incorporated acetylenes in place of selected double bonds[4] in the polyenic system. Recent studies have suggested that leukotrienes with three or even five double bonds (i.e. LTC_5) may exist in nature.[5] It is notable that LTC_5[5] and olefin isomers of the leukotrienes (such as 11-trans LTC_4)[6] as well as analogues of LTD_4 lacking up to three of the double bonds have been reported to be biologically very active,[2a,g] while positional isomers (e.g. having the S-peptide at C-12)[7] or the 6-epi-isomers,[8] were found to be considerably less active than the natural products.

In particular, the 7,8-double bond seems to be very important in conferring biological activity to these series.[2a,g,3]

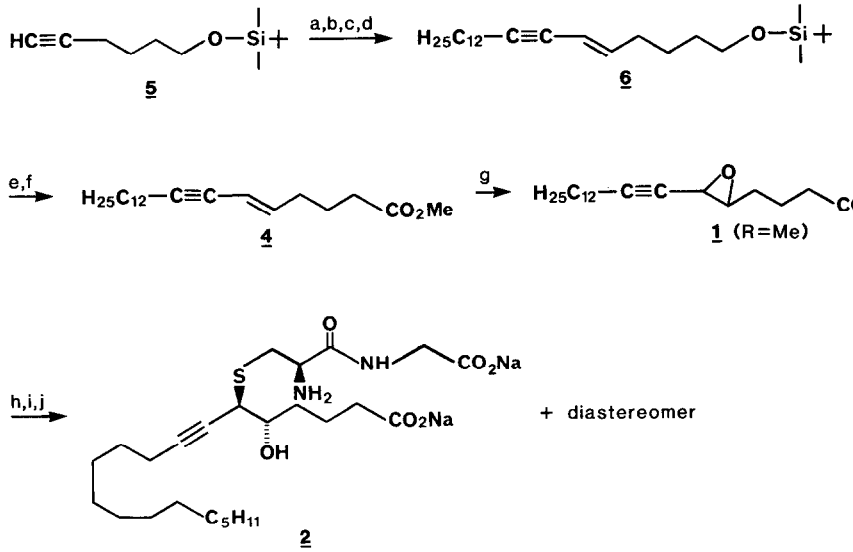
In spite of the perceived importance of the C7-C8 unsaturation in the leukotrienes, no leukotriene analogues have been reported where this key 7,8-double bond has been replaced with a triple bond. It is apparent that the standard synthetic approaches to leukotriene analogues (e.g. reaction of Wittig reagents with 6-formyl-5,6-epoxyhexanoates) are not readily applicable to the synthesis of such 7,8-acetyleno-analogues.

In this report we will discuss two approaches to the synthesis of such leukotriene analogues.

The racemic approach: Considering that methyl eicosa-5(E)-en-7-ynoate (4) would be a logical precursor of 1, our initial efforts were directed to the stereoselective preparation of this synthon. Of the many possible synthetic approaches examined, the most straightforward approach seemed to be the oxidative coupling of an appropriate alkylacetylene with a

terminally substituted derivative which could itself be derived from an acetylenic procursor.

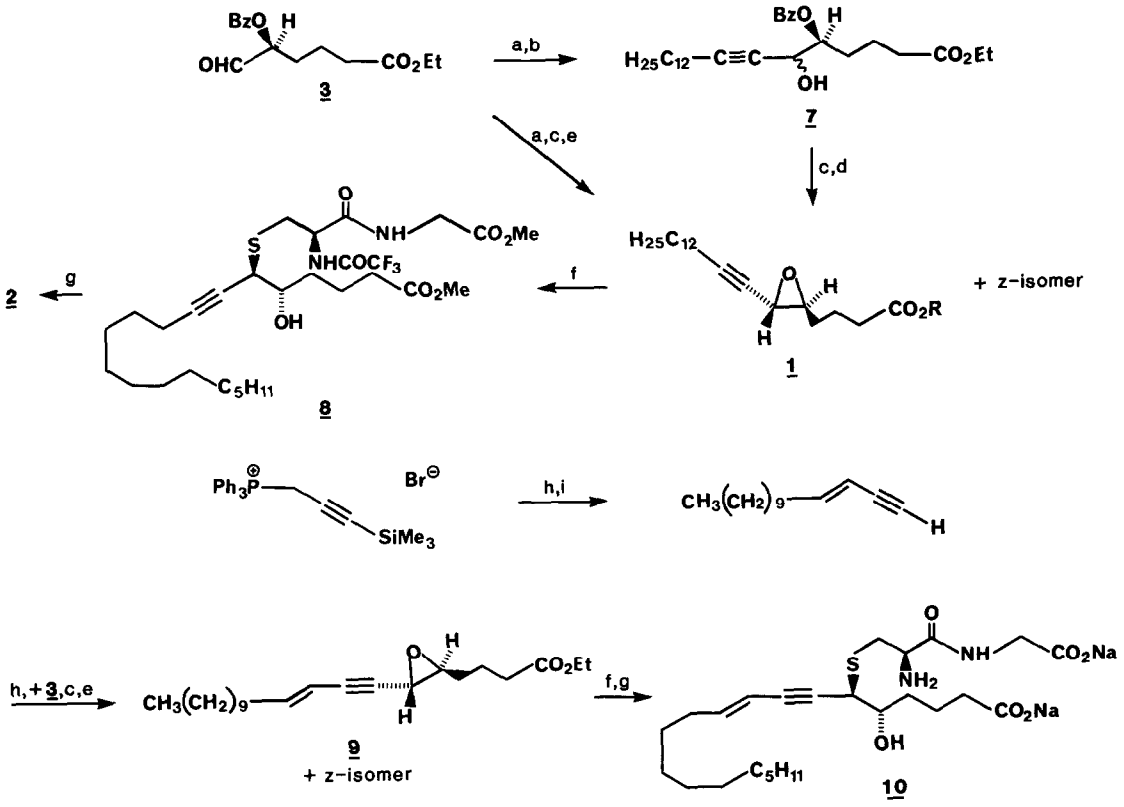
We were initially tempted to utilize Negishi's[9] palladium catalyzed coupling of a E-vinyl halide and an alkynylzinc derivative but stereoselective preparation of the requisite vinyl halide proved to be problematic, either due to low yields (via hydroalumination)[10] or lack of complete stereoselectivity (via halogenation of the catecholborane adduct)[11]. In the end the desired enyne was readily obtained (Scheme 1) by reaction of 6-(dimethyl-t-butylsilyloxy)-1-hexyne (5) with disiamylborane followed by reaction with 1-tetradecynyllithium, and oxidative coupling (1)I_2; OH^-;2)OH^-,H_2O_2) to provide 6[12] (73% yield) followed by desilylation and oxidation (Jones conditions) and subsequent esterification (CH_2N_2) to give 4 (56% yield). Selective epoxidation (mCPBA) gave the racemic LTA analogue (1) which reacted readily with methyl N-trifluoroacetylcysteinyl- glycinate to give the 7,8-acetyleno-LTD_4 analogue (2) after separation of the resulting diastereomers (HPLC) and alkaline hydrolysis. Final assignment of natural stereochemistry was made by comparison with the same compound obtained in the following stereoselective synthesis.



SCHEME 1

CONDITIONS: a) $HBSia_2$, THF, 0°C; b) $H_{25}C_{12}$-C≡C-Li, THF-HEXANE, -50°C; c) I_2, THF, -78° to 20°C, NaOH; d) 3N NaOH, H_2O_2; e) Jones oxidation; f) CH_2N_2; g) mCPBA, $CHCl_3$, 0°C; $Ca(OH)_2$, RT, h) $HSCH_2CH(NHCOCF_3)CONHCH_2CO_2Me$, Et_3N, MeOH; i) separate isomers; j) Na_2CO_3, MeOH, H_2O

The Chiral Approach: We envisaged that the LTB_4 synthon, ethyl 5(S)-benzoyloxy-5-formylpentanoate (3)[13] would be an excellent and versatile intermediate for the preparation of chiral acetyleno-analogues of LTA_4. Thus reaction of the formyl group with a carbon anion (such as an acetylene anion) would provide a 6-alkynyl-6-hydroxy-5(S)-benzoyloxy-pentanoate intermediate (i.e. 7). Conversion of the 6-hydroxy group to a leaving group followed by base treatment to liberate the 5-alkoxide anion would be expected to provide the desired epoxide (i.e. 1).



SCHEME 2

CONDITIONS: a) $H_{25}C_{12}$-C≡C-Li, THF, -78°; b) NH_4OAc, pH7; c) MsCl, Et_3N, -78 to 0°C; d) NaOMe, MeOH; e) NaOEt, EtOH; f) $HSCH_2CH(NHCOCF_3)CONHCH_2CO_2Me$, Et_3N, MeOH; g) Na_2CO_3, MeOH, H_2O; h) nBuLi, THF, -78°; $C_{10}H_{21}CHO$ i) $KF \cdot 2H_2O$, DMF

Some questions remained as to the strict stereochemical integrity of such a sequence as potential side reactions (e.g. benzoate transfer) could give enantiomeric impurities leading to partial racemization. In the event 3 was reacted with the 1-tetradecynyllithium (-78°C - 0°, aqueous workup; MsCl, Et_3N, -78° to 0°C; NaOMe, MeOH, 0°C) to provide a mixture of E and Z epoxides (30% yield) (1;R = Me) (ca 4:1). The E-epoxide reacted with methyl N-trifluoracetylcysteinylglycine to give the protected leukotriene analogue (8) (ca 50%) which by HPLC analysis was contaminated with about 30% of the unnatural (5R, 6S)-isomer. Thus it was apparent that in the initial addition of the acetylene anion some benzoate scrambling occurred. When the sequence was repeated but with trapping of the initially formed alkoxide anion with mesyl chloride, at -78°C, prior to workup and subsequent treatment of the resulting mesylates with sodium ethoxide, the resulting epoxides (30% yield) (E/Z ratio: 4:1) were chirally pure ((5S,6R)-2; $[\alpha]_D$ = -8.7° (C = 3.2, $CHCl_3$)) as evidenced by the conversion of 1 exclusively to the protected (5S, 6R)-leukotriene D analogue (8) (<2% diastereomer detected by HPLC). Subsequent hydrolysis (Na_2CO_3, MeOH, H_2O) provided disodium (5S, 6R)-5-hydroxy-6-(S)-cysteinylglycyleicosa-7-ynoic acid (2).

The versatility of the method was further demonstrated by repeating the sequence using

1-tetradec-1-yn-3(E)-enyllithium (prepared from triphenyl-(3-trimethylsilylprop-2ynyl) phosphonium ylid[14] and undecanal) to provide ethyl (5S, 6R)-5,6-epoxyeicosa-7-yn-9(E)-enoate (9) ($[\alpha]_D$ = -8.9° (C = 1.2, $CHCl_3$)) (14% overall yield) and thence disodium (5S, 6R)-5-hydroxy-6(S)-cysteinylglycyleicosa-7-yn-9(E)-enoate (10) (57% from 9).(Scheme 2)

These compounds were tested in comparison with LTD_4 on guinea pig tracheal tissue. Compounds 2 and 10 are weak contractile agonists and gave pD_2 values of 5.13 and 5.33 respectively, while the unnatural (5R, 6S) isomer of 2 gave pD_2 value of 4.76 (relative to LTD_4 at 8.2) These compounds are much less active relative to LTD_4 (1/700 - 1/2000) than has been reported for the corresponding 7(Z)-hexahydro LTD analogue.[2a,g] It thus appears that a triple bond cannot substitute for a double bond in this position.

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