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# SYNTHESIS OF LEUKOTRIENES - NEW SYNTHESIS OF NATURAL LEUKOTRIENE $A_4$

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Summary: The acetonides of D- or L-glyceraldehyde are chiral synthons for an efficient and versatile synthesis of the natural leukotrienes $A_4$, $C_4$, $D_4$ and $E_4$ and equally can be used to prepare the corresponding unnatural analogues.

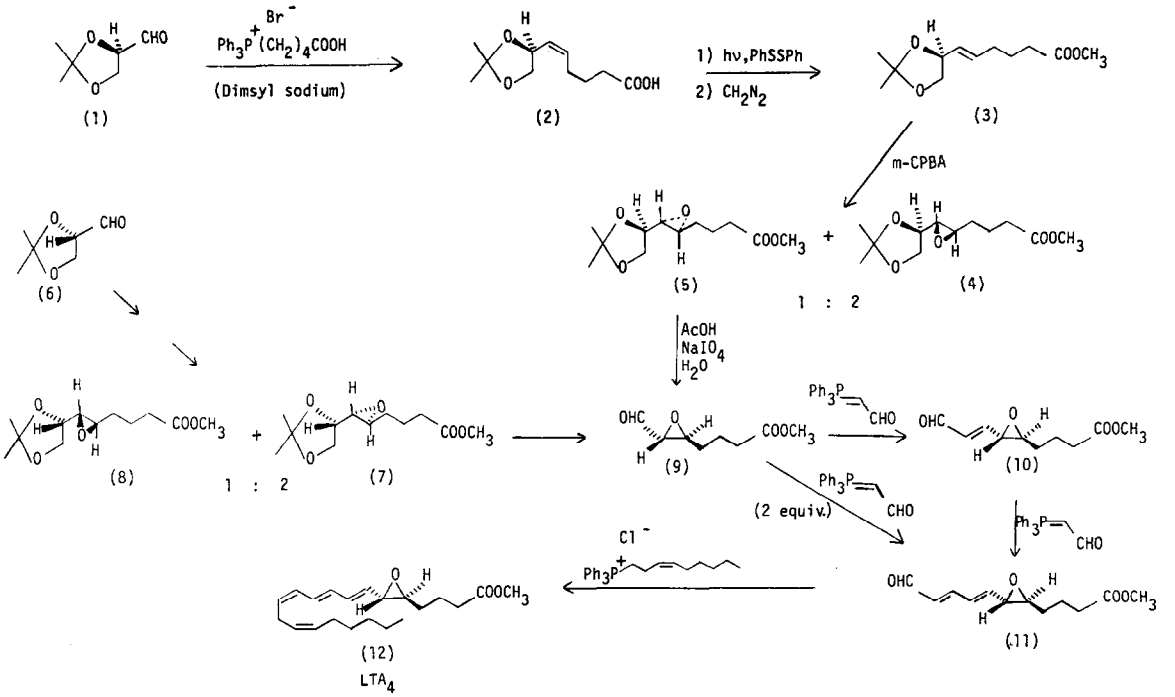
Since the pioneering work of Samuelsson et al.[1] on the structure elucidation of SRS-A, the synthesis of this important mediator of anaphylaxis has become the target of several laboratories around the world.[2] The final proof of structure of natural leukotrienes rested on the comparison with synthetic materials. This has been done in the case of leukotriene $C_4$[3] and for leukotriene $D_4$.[4] While working on our first synthesis of leukotrienes via racemic $LTA_4$ methyl ester, we also devised a strategy in which the segment $C_1$ to $C_7$ of leukotrienes could be constructed and then converted to the natural or, if desired, unnatural forms of $LTA_4$. In this communication, we describe: a short and versatile synthesis of the four enantiomerically pure stereoisomers of 6-formyl-5,6-epoxyhexanoic acid methyl ester; the efficient conversion of the 5S,6R isomer via a sequence of stereocontrolled Wittig reactions to natural $LTA_4$ methyl ester; and its further conversion to $LTC_4$, $LTD_4$ and $LTE_4$.

In the present approach we decided to introduce at the beginning of the synthesis a chiral center which would ultimately serve to resolve the desired enantiomers. This was achieved by the use of the acetonide of D-glyceraldehyde (1)[5] as the chiral precursor. Dimsyl sodium was found to be the base of choice for the subsequent Wittig reaction to obtain (2) ($[\alpha]_D$ +7.6°, $CHCl_3$) in 72% yield. The geometry of (2) obtained under several experimental conditions was almost exclusively cis. The isomerization of (2) to the trans isomer, was effected photochemically[6] in cyclohexane (4 hrs., 450W Hanovia H.P. lamp) in the presence of an equivalent amount of Ph-S-S-Ph in 70% yield (>95% trans)[7]. The trans olefinic ester (3) ($[\alpha]_D$ +27.6°, $CHCl_3$), on reaction with MCPBA in methylene chloride, yielded a mixture of the two epoxy esters (4) and (5). These two isomers separate readily on tlc, column chromatography and on prep. HPLC to provide pure (4) ($[\alpha]_D$ + 26.7°, $CHCl_3$) and (5) ($[\alpha]_D$ -11.9, $CHCl_3$) in 88% combined isolated yield. The methyl ester of the cis olefin acetonide (2), on treatment with MCPBA under the conditions described above, yielded the two expected cis epoxy esters which are equally easily separated by chromatographic techniques ($[\alpha]_D$ -15.0°, $CHCl_3$; and $[\alpha]_D$ +10.5°, $CHCl_3$).

At this point it is worth mentioning that the use of an acetonide ring bearing an asymmetric carbon is not fortuitous. It is obvious that the success of the synthesis and more importantly its practical application for gram scale preparation of intermediates and products rests upon the easy separation of the two pairs of epoxy acetonide diastereoisomers. Of the various asymmetric precursors we considered for the synthesis, we reasoned that a dioxolane ring system would introduce fewer degrees of freedom into the molecule with the possible result of better separation of the diastereoisomers. This was found to be the case[8].

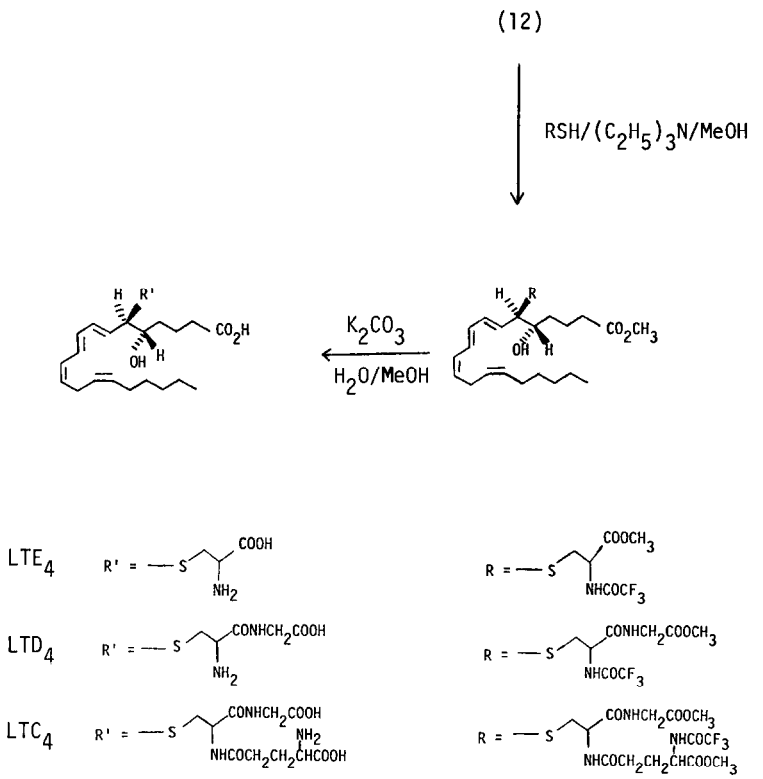
As can be noted in Scheme 1, there is an asymmetric induction in the epoxide forming step resulting in a 2:1 mixture in favor of isomer (4) which has the unnatural absolute stereochemistry at $C_5$ and $C_6$. In order to improve the efficiency of the synthesis of natural LTA we prepared the acetonide of L-glyceraldehyde (6) from L-arabinose[9], and carried out the same series of reactions described in Scheme 1 for the D-isomer. The epoxy acetonides (7) and (8) were obtained in a ratio of 2:1 in favor of the desired isomer (7), ($[\alpha]_D$ -24.7°, $CHCl_3$).

SCHEME 1



The hydrolytic cleavage of (5) (or (7)) with $NaIO_4/CH_3COOH$ afforded (9) ($[\alpha]_D$ +69.4°, $CHCl_3$; lit[2a] $[\alpha]_D$ +68.6°, $CHCl_3$) in 60% yield. The hydrolytic cleavage of (4) (or (8)) gave the enantiomer of (9) in 60% yield ($[\alpha]_D$ -72.3°, $CHCl_3$)[10]. The Wittig condensation of (9) with formylmethylenetriphenylphosphorane in refluxing benzene afforded (10) in 84% isolated yield. A second Wittig condensation of (10) with the same reagent in refluxing benzene afforded (11) in 34% isolated yield [45% based on recovered (10)]. The conversion of (9) into (11) in a one-step reaction with two equivalents of reagent has also been accomplished in 30% isolated yield; 40% of (10) is also isolated in the same reaction and can be recycled. The diene aldehyde (11) was converted into leukotriene $A_4$ methyl ester (12) by a Wittig condensation with triphenyl[(Z)-non-3-en-1-yl]phosphonium chloride[2b] in 56% yield. Compound (12), except for the optical rotation ($[\alpha]_D$ -21.4°, cyclohexane; lit[2a] $[\alpha]_D$ -21.9° cyclohexane) is identical in every respect to the racemic material we obtained in our first synthesis (IR, NMR, HPLC).

SCHEME 2



The leukotriene (12) has been converted to leukotrienes $C_4$, $D_4$ and $E_4$ as described in Scheme 2. The enantiomeric purity of (12) was confirmed by the fact that no detectable amount of the unnatural diastereoisomer was present (HPLC) in the resultant addition products. The biological activity, the chromatographic, and spectroscopic behavior of these compounds were identical to those obtained previously by us.

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7. On prolonged irradiation (12-24 hours) the yield was reduced due to formation of a by-product which has been identified as 8-hydroxy-7-oxo-5-phenylthiooctanoic acid.
8. Indeed, the corresponding diols isolated from the hydrolysis of (4) and (5) could not be separated by standard chromatographic techniques.
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10. The hydrolytic cleavage of the two cis epoxy acetonides ($[\alpha]_D$ -15° and $[\alpha]_D$ +10.5°) generated from the methyl ester of (2) yielded the corresponding cis epoxy aldehydes ($[\alpha]_D$ -101.3°, $CHCl_3$ and $[\alpha]_D$ +101.4°, $CHCl_3$ respectively). The yield however is lower than in the trans case (32%). The 5S,6S-6-formyl-5,6-epoxyhexanoic acid methyl ester has been reported ($[\alpha]_D$ -101.3°, $CHCl_3$) (E.J. Corey and G. Goto, Tetrahedron Lett., 21, 3463, (1980).

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