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THE STEREOSPECIFIC SYNTHESIS OF LEUKOTRIENE A_4 (LTA_4), 5-EPI-LTA_4, 6-EPI-LTA_4 and 5-EPI,6-EPI-LTA_4

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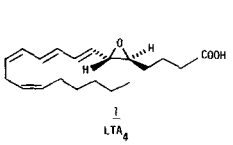
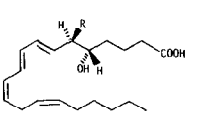
Summary: The stereospecific syntheses of the four isomers of 6-formyl-5,6-epoxy hexanoic acid methyl ester 8, 15, 23 and 30 from 2-deoxy-D-ribose have allowed the preparation of methyl esters of LTA_4, 1,and its three unnatural isomers.

The recent structure elucidation[1] of SRS-A has put to rest four decades of uncertainty concerning the nature of this important mediator of anaphylaxis. The final detailed geometrical and stereochemical assignment has been made possible by total synthesis[2] and subsequent comparison of synthetic and natural products.[3] It has been proposed that Leukotriene A_4 (LTA_4) is the key biochemical intermediate from which Leukotriene C_4 (LTC_4), one of the family of SRS-like compounds, is obtained by enzymatic opening of the epoxide ring with glutathione;[4] and in a series of enzymatic amino acid cleavages, Leukotriene D_4 (LTD_4) and Leukotriene E_4 (LTE_4) are produced.[5] It is not surprising therefore that in order to mimic the biochemical sequence, LTA_4 has been the prime synthetic target from which the other Leukotrienes have been made. Of the four possible isomers at the 5 and 6 positions in 1, the syntheses of only two have been reported, namely LTA_4[2] and 6-epi-LTA_4[6] which have the (5S,6S) and (5S,6R) configurations respectively. For complete biochemical and biological evalution and in order to guide the design of potentially useful antiallergic drugs, we required access to all the possible stereoisomers of LTA_4. Another factor which played an important role in the selection of our synthetic strategy, is the fact that the reported syntheses of LTA_4 and 6-epi-LTA_4 while elegant, are rather lengthy and we were eager to improve substantially on these and our own previous syntheses for the large-scale preparation of these compounds.

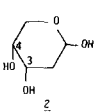
We report here a simple and short synthesis of 1 and its three unnatural isomers from a single commercially available starting material, 2-deoxy-D-ribose, 2, thus providing, with great economy of chirality, the first comprehensive stereospecific synthesis of these important compounds. The basic strategy of these syntheses involves appropriate manipulations of the chiral centers at C-3 and C-4 of 2 in such a way that these two centers eventually become the chiral centers C-5 and C-6 of the various leukotrienes. The overall stereochemical relationship between 2 and the various isomers of LTA_4 is summarized below:



1
LTA_4



LTC_4 R = Glutathione
LTD_4 R = Cys-gly
LTE_4 R = Cys



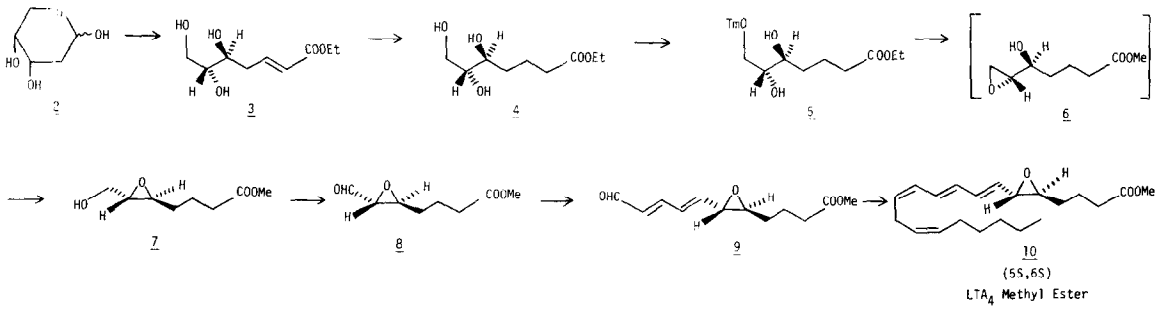
2

inversion at C_4 → LTA_4
inversion at C_3 → 5-epi-6-epi-LTA_4
double inversion at C_3 → 6-epi-LTA_4
inversion at C_3 & C_4 → 5-epi-LTA_4

The synthesis of natural LTA_4 methyl ester has been carried out in a total of 7 steps as outlined in Scheme 1. Reaction of 2 with one equivalent of (carbethoxymethylene)triphenylphosphorane[7] in refluxing THF for 6 hours gave the triol 3 in 80% yield. Hydrogenation of 3 over 10% Pd/C in ethanol gave the saturated compound 4, $[\alpha]_D$ -5.7° (c = 2.9, $CDCl_3$), in 80% yield from 3. The primary alcohol of 4 was selectively converted in 57% yield to the corresponding mesitylene sulfonate 5, $[\alpha]_D$ +1.9° (c = 2.5, $CDCl_3$), m.p. 98-100°C, on treatment with one equivalent of mesitylene sulfonyl chloride in pyridine at 0°C. Treatment of 5 with 1.1 equivalents of sodium methoxide in dry methanol at room temperature for 16 hours gave the primary epoxy alcohol 7, $[\alpha]_D$ -35° (c = 2.7, $CDCl_3$), in 60% yield. By monitoring the reaction we were able to show the intermediacy of the secondary epoxy alcohol 6.[8]

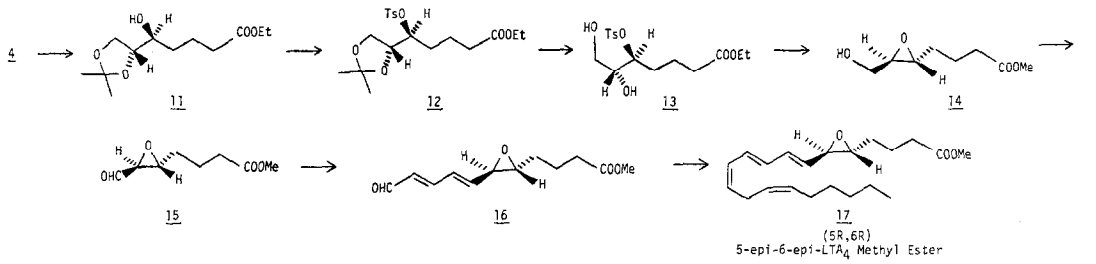
Collins oxidation of 7 gave the desired (5S,6R)-epoxy aldehyde 8, $[\alpha]_D$ +81° (c = 0.8, $CDCl_3$)[9], in 50% yield. Epoxy aldehyde 8 has been converted to LTA_4 methyl ester 10, $[\alpha]_D$ -27° (c = 0.8, C_6H_{12}), in 25% overall yield[2] by a Wittig reaction with two equivalents of formylmethylenetriphenylphosphorane to yield the diene aldehyde 9, $[\alpha]_D$ -25° (c = 0.3, $CDCl_3$), followed by a second Wittig reaction with triphenyl [(Z)-non-3-en-1-yl]phosphonium chloride.

SCHEME 1



To obtain the enantiomer of compound 8, the configuration of the chiral center at C-6 of the saturated triol 4 must remain unchanged, while that of C-5 must be inverted. This was achieved as shown in Scheme 2.

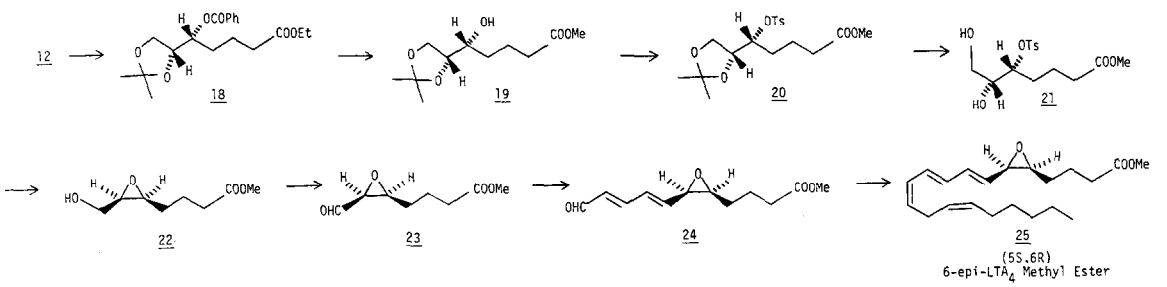
SCHEME 2



The vicinal diol unit at C-6 and C-7 of 4 was protected as the acetonide 11, $[\alpha]_D$ +9.4° (c = 4.6, $CDCl_3$), obtained in 55% yield by reacting triol 4 with dimethoxypropane in acetone in the presence of a catalytic amount of p-toluene sulfonic acid at 0°C. Treatment of 11 with five equivalents of TsCl in pyridine at 50°C for 24 hours gave the tosylate 12, $[\alpha]_D$ -1° (c = 1.9, $CDCl_3$), in 83% yield. Warming 12 with HCl in aqueous THF at 60°C gave the diol tosylate 13. On treatment with K_2CO_3 in methanol, displacement of tosylate with inversion of configuration at C-5 occured smoothly, yielding 14, $[\alpha]_D$ +35° (c = 2.4, $CDCl_3$), in 53% overall yield from 12. Oxidation of 14 as described above gave the methyl ester of 6-formyl-(5R,6S)-epoxy hexanoic acid 15, $[\alpha]_D$ -84° (c = 3.0, $CDCl_3$).[9] Compound 15 was transformed to 16, $[\alpha]_D$ +27° (c = 2.0, $CDCl_3$), then to the methyl ester 17 of the unknown (5R,6R) enantiomer of 1, $[\alpha]_D$ +28° (c = 1.0, C_6H_{12}), as already described.

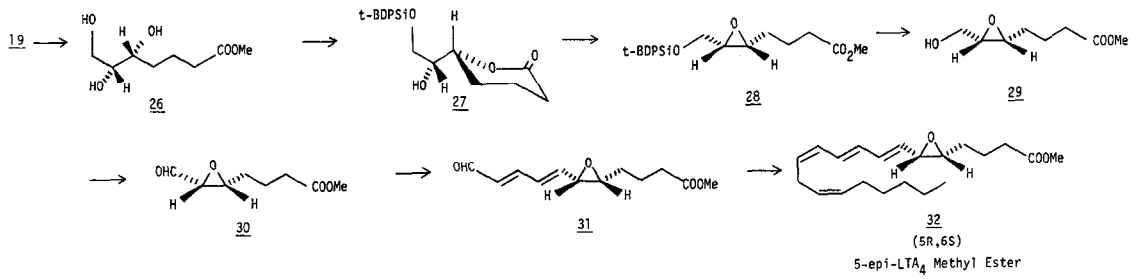
To obtain the 6-epi-LTA_4 (Scheme 3) the stereochemistry of C-5 and C-6 of triol 4 has to be preserved. Hence treatment of acetonide tosylate 12 with two equivalents of sodium benzoate in DMF gave a 42% yield of benzoate 18 (inversion at C-5), which upon exposure to sodium methoxide in methanol gave the alcohol 19, $[\alpha]_D$ -14° (c = 1.6, $CDCl_3$). Tosylation of 19 was effected as before to yield 20, $[\alpha]_D$ +11.3° (c = 2.2, $CDCl_3$). Cleavage of the acetonide, followed by treatment with sodium methoxide in dry methanol, gave epoxy alcohol 22, $[\alpha]_D$ +2.7° (c = 1.5, $CDCl_3$), in 37% yield via displacement of tosylate and inversion of configuration at C-5 (an overall double inversion at this center). The conversion of 22 to 23 $[\alpha]_D$ -142° (c = 0.7, $CDCl_3$),[9] 24 $[\alpha]_D$ -44.1° (c = 2.0, $CDCl_3$) and 6-epi-LTA_4 methyl ester (5S,6R isomer) 25, $[\alpha]_D$ -21.5° (c = 0.2, C_6H_{12}), was effected as already described.

SCHEME 3



The synthesis of 5-epi-LTA_4 is summarized in Scheme 4. Acetonide 19 was cleaved to the triol 26, $[\alpha]_D$ +11.9° (c = 2.7, $CDCl_3$), in the usual manner in 70% yield. Monosilylation[10] (tert-butyldiphenylsilylchloride, imidazole) of 26 followed by hydrolysis (NaOH, THF/H_2O) and lactonization (DCC) afforded silyl ether lactone 27, $[\alpha]_D$ -21.9° (c = 2.2, $CDCl_3$), in 63% yield from 26. Tosylation (TsCl, 4 equiv.) and treatment with NaOMe (2 equiv.) afforded silyl epoxide 28, $[\alpha]_D$ +1.7° (c = 0.8, $CDCl_3$), in 90% yield. Deprotection [$(n\text{-}Bu)_4NF$, THF/AcOH] cleanly afforded epoxy alcohol 29, $[\alpha]_D$ -2.3° (c = 1.5, $CDCl_3$), in 70% yield. Epoxy aldehyde 30, $[\alpha]_D$ +141° (c = 0.6, $CDCl_3$)[9], diene aldehyde 31, $[\alpha]_D$ +46° (c = 0.4, $CDCl_3$), and 5-epi-LTA_4 methyl ester (5R,6S) 32, $[\alpha]_D$ +18.1° (c = 0.5, C_6H_{12}), were then obtained as previously described.

SCHEME 4



The yields in these syntheses have not yet been optimized, but as they stand they provide both short and efficient routes to the two previously reported isomers of LTA_4 and the first synthesis of the remaining two possible isomers, 17 and 32.

The biological evaluation of the various Leukotrienes derived from these four isomers will be reported elsewhere.

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8. For the preparation of this epoxy alcohol see next paper.
9. The rotation of these epoxy aldehydes are variable (c.f. ref. 2) and is dependent upon the hydration of the aldehydic group. The rotation reported here is that of an extremely pure sample (non hydrate).
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