# ENANTIOSPECIFIC SYNTHESIS OF 14S,15S LEUKOTRIENE A₄ METHYL ESTER

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Abstract   A practical enantiospecific synthesis of methyl 14S,15S-oxido-5Z,8Z,10E,12E-eicosatetraenoate (14S,15S LTA₄ methyl ester) from D-glucose as chiral precursor has been described.

Since their discovery[1], leukotrienes have acquired prominence due to their pro hypersensitivity and inflammatory reactions. Sammuelsson has postulated[2] 14,15-oxido-5Z,8Z, 10E,12E-eicosatetraenoic acid (14,15 LTA₄) (1) as the hypothetical key precursor in conversion of 15-hydroperoxyeicosatetraenoic acid (15-HPETE) to 8, 15 LTB₄ (2) and 14, 15 LTB₄ (3). It is not known if 14, 15 LTA₄ has pharmacological role of its own. Due to its rapid chemical and biochemical conversion in vivo or in vitro the direct actions are difficult to study. However, studies by Sammuelsson et al[3] on 5, 6 LTA₄ stabilised by serum protein clearly establish LTA₄ as a circulating biochemical agent in its own right. This is a question that merits further investigation. Hence there arose an acute need to synthesize this scarce and unstable intermediate in order to probe its physiological role. The only total synthesis[4], reported so far, involved the use of an expensive starting material, 2-deoxy-D-ribose. We report herein an efficient enantiospecific approach towards 14S,15S LTA₄ methyl ester which could be adopted for large scale preparation.
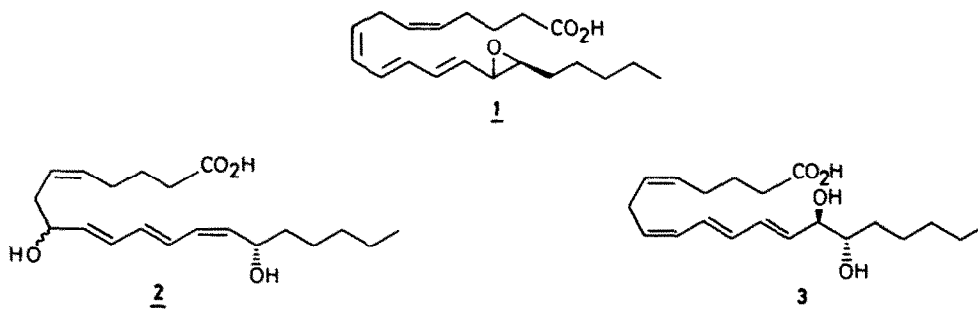

Retrosynthesis (Figure 1) indicated epoxyaldehyde (4) and phosphonium salt (5) as the key precursors.

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Oxidation of epoxyalcohol (13) to unstable epoxyaldehyde (14) followed by immediate coupling with 2 equivalents of formylmethylenetriphenylphosphorane, yielded a cis-trans mixture of unsaturated aldehyde (4). Isomerisation to the desired all-trans isomer was accomplished photochemically in the presence of a catalytic amount (1%) of iodine in dichloromethane. $[\alpha]_D$ -27.9° (c 1.2, $CHCl_3$). Reported[4] $[\alpha]_D$ -27.7° (c 1.0, $CHCl_3$).

The requisite phosphonium salt (5) was prepared from tetrahydropyranyl chloride 15 by a simple and efficient set of reactions as follows (Scheme 2): - Opening[8] of 15 gave acetylenic alcohol 16, which was subsequently protected as THP ether (17). For further chain extension, 17 was alkylated with ethylene oxide, to afford alcohol 18.[7] Partial hydrogenation[9] of acetylene to cis-olefin using P(II) nickel catalyst in equivalent amount, furnished olefin 19 in 85% yield. Treatment of alcohol 19 with $Ph_3P\text{-}CBr_4$ in the presence of anhydrous sodium bicarbonate, gave bromide 20 in 88% yield without any OTHP deprotection. Oxidation of the protected hydroxy with Jones reagent followed by diazomethane esterification, gave bromo ester (22)[7] in 80% yield. Finally, the required phosphonium salt (5) was prepared by treating bromo ester (22) with excess triphenylphosphine (1.5 equivalents) in refluxing acetonitrile under argon atmosphere, followed by column chromatographic purification.
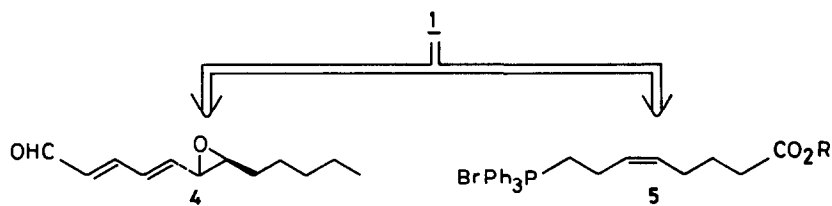
Scheme 2
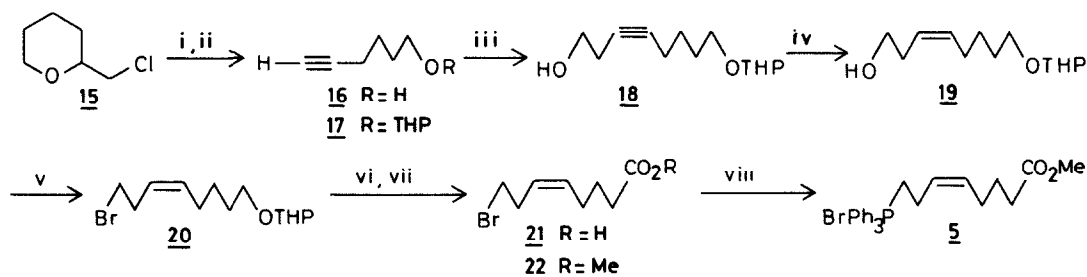
i) $NaNH_2$ (3 eq), liq. NH_3, -35°, 6 hr, 75%; ii) DHP, PTSA (cat), DCM, rt, 4 hr, 95%; iii) $LiNH_2$, liq. NH_3, ethylene oxide, -35°, 10 hr, 75%; iv) P(II)Ni; EtOH, 1 hr, 85%; v) Ph_3P, CBr_4, DCM, $NaHCO_3$, rt, 3 hr, 80%; vi) Jones reagent, acetone, 0°, 1 hr, 85%; vii) CH_2N_2, ether, 0°, 1 hr, 95%; viii) Ph_3P (1.5 eq), CH_3CN, 80°, 48 hr, 80%.

Having prepared both key units, i.e., epoxyaldehyde (4) and phosphonium salt (5), the stage was set for the final coupling reaction (Scheme 3). The coupling was successfully achieved using similar conditions as reported by Zamboni[4] et al, i.e., lithium-bis-(trimethyl silyl)-amide as the base for phosphorane generation and solvents THF-HMPA (4:1); to give a cis-trans (across C-8 to C-9) mixture of 14S, 15S LTA_4 methyl ester (23).[7] HPLC analysis (μ-porosil, 1% Et_3N-n-heptane) of the mixture revealed a ratio of cis:trans as 80:20. Since resolution of this mixture has already been achieved by Zamboni[4], this report constitutes

Figure 1

Epoxyaldehyde (**4**) was synthesized from D-glucose in the following manner (Scheme 1): - Tri-O-acetyl-D-glucal (**6**), prepared[5] from D-glucose, was subjected to hydrolytic cleavage[6] using Hg^{2+} and dilute sulfuric acid, to give α,β-unsaturated aldehyde (**8**) after acetylation. Two carbon homologation via Wittig olefination followed by hydrogenation afforded the requisite eight carbon skeleton **9**[7] in 75% overall yield. Deacetylation to triol **10** with subsequent selective primary hydroxyl protection furnished mesetylene sulfonate **11** in 75% yield. Treatment of **11** with 1.1 equivalents of sodium methoxide in methanol led to its rearrangement involving initial formation of an unisolable terminal epoxide **12** with subsequent internal displacement to give epoxyalcohol (**13**)[7] $[\alpha]_D$ -44.2° (c 1.3, $CHCl_3$). Reported[4] $[\alpha]_D$ -44.0° (c 1.0, $CHCl_3$).

Scheme 1
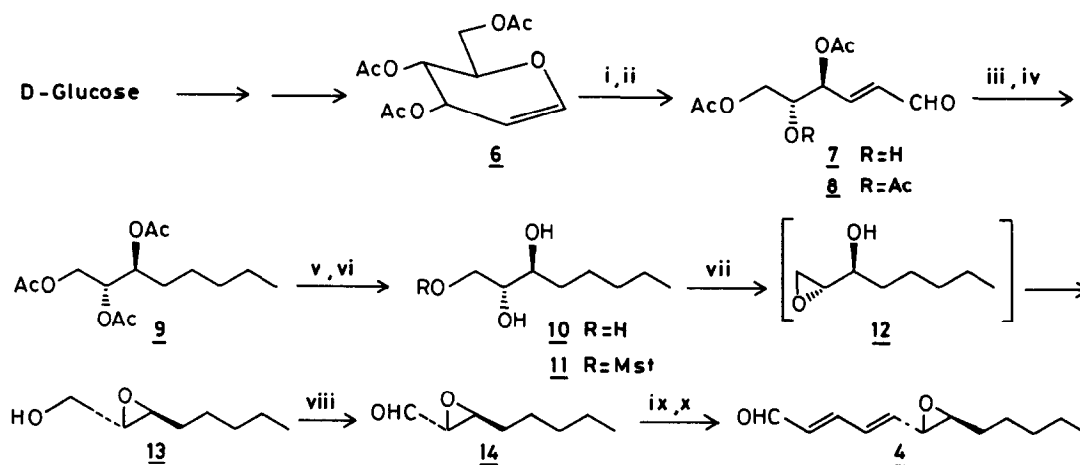
i) $HgSO_4$, H^+, Dioxane-H_2O, rt, 4 hr, 92%; ii) Ac_2O, Py, rt, 3 hr, 95%; iii) $Ph_3=CHCH_3$, THF-HMPA, -78° 0°, 1 hr, 78%; iv) H_2, Pd/C, EtOH, 2 hr, rt, 90%; v) NaOMe (0.5 eq), MeOH, rt, 1 hr, 90%; vi) Mesetylenesulfonylchloride (Mst-Cl), Py, 0°, 36 hr, 75%; vii) NaOMe (1.1 eq), MeOH, rt, 4 hr, 75%; viii) CrO_3-2Py, Celite, DCM, 0°, 1 hr, 85%; ix) $Ph_3PCHCHO$ (2.2 eq), Toluene, 80°, 3 hr, 70%; x) I_2 (0.1 eq), h, CH_2Cl_2, 2 hr, 95%.

Scheme 3
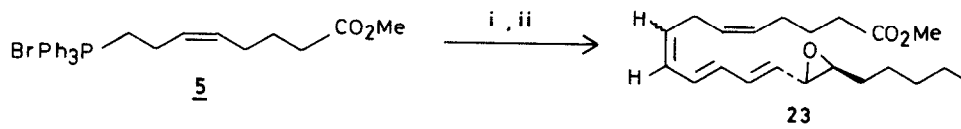
i) LHMDS, THF-HMPA (4:1), 0°, 30 min; ii) 5, -78°, 4 hr, 70%

an alternative and efficient approach to the synthesis of unsaturated aldehyde **4** and phosphonium salt **5** and to their coupling. Studies are underway to extend this approach to the synthesis of other lipoxygenase products.

References and Notes

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