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STEREOSPECIFIC SYNTHESIS OF 11S, 12S-OXIDO 5Z,7E,9E,14Z-EICOSATETRAENOIC ACID

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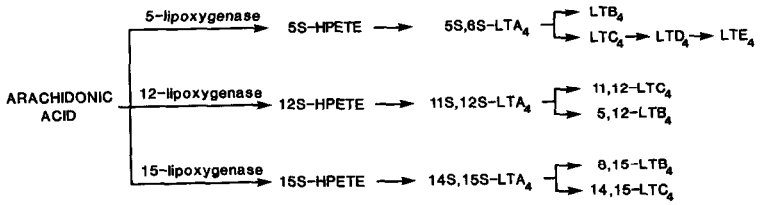
Summary: The first stereospecific synthesis of 11S,12S-oxido 5Z,7E,9E,14Z-eicosatetraenoic acid has been achieved from 2-deoxy-D-ribose using either a Horner-Emmons or Wittig condensation to form the 9,10-trans or the 5,6-cis-double bond respectively.

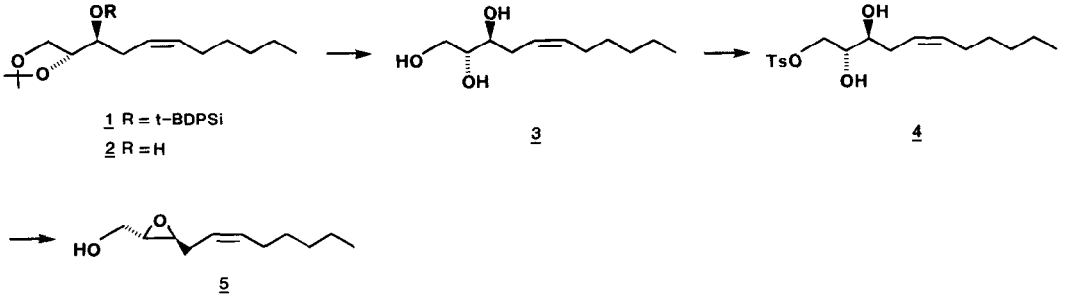
Lipoxygenases in leucocytes are known to oxygenate positions 5, 12 and 15 of arachidonic acid (Scheme 1). Oxidation at the 5 position leads to the biologically potent leukotrienes LTB_4, LTC_4, LTD_4 and LTE_4. Oxygenation at the 12 and 15 positions has been recently shown to lead to an analogous series of leukotrienes, whose function is at present unknown.[1] In order to study these pathways, adequate supplies of 11S,12S-LTA_4, and 14S,15S,-LTA_4, the key intermediates in both pathways, are required. We have recently described a stereospecific synthesis of 14S,15S-LTA_4.[2] We wish to now describe the stereospecific synthesis of 11S,12S-LTA_4[3], which will allow the study of this natural product and the unambiguous assignment of the chemical and enzymatic metabolites derived from this molecule.

Scheme 1



Our first approach (Scheme 2) to the necessary epoxy alcohol 5 started from 1 which we had successfully used in our synthesis of 12-epi-LTB_4.[4] Deprotection of 1 ($(nBu)_4NF$, 0°→r.t., 6h) afforded 2. Removal of the acetonide group (TFA/THF/H_2O) gave triol 3 in 50% overall yield from 1. Tosylation (1 eq. TsCl/Py, 5°, 24 h) afforded tosylate 4 in 50-55% yield.

Scheme 2



1 R = t-BDPSi
2 R = H

3

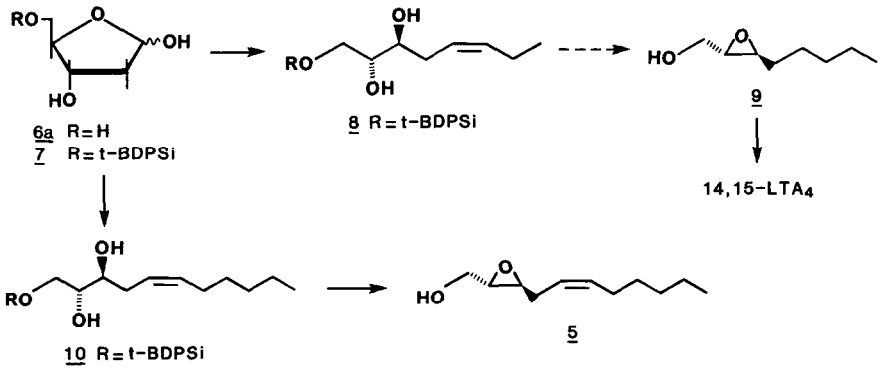
4

5

Rearrangement of 4 (1.2 eq. NaOMe/MeOH, 24 h) afforded epoxy alcohol 5, $[\alpha]_D$ = -20° (C=1.0, $CHCl_3$) in 50% yield. 400 MHz p.m.r. of the Mosher ester[5a,b] of 5 clearly showed that the sequence leading to 5 was entirely stereospecific. Although this approach gave the desired epoxy alcohol from intermediate 1, of which we had a good supply, the synthesis was too lengthy, if the preparation of 1 (11 steps from D-arabinose) is included.

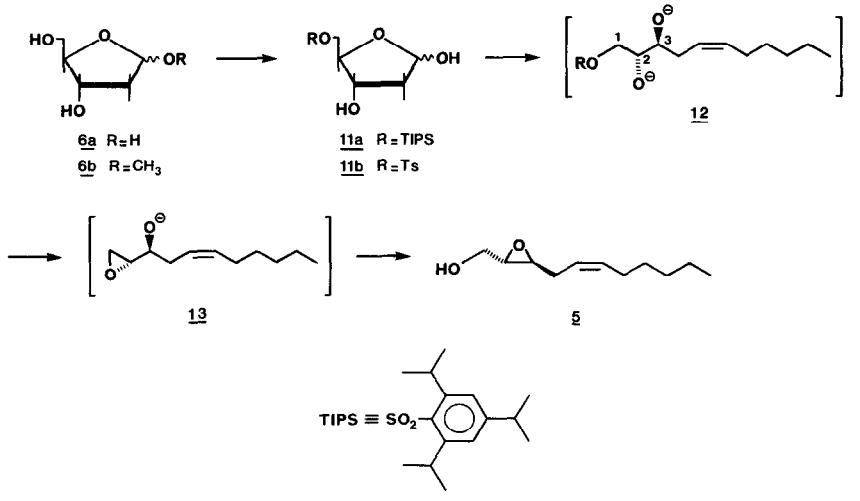
A more efficient and direct route (Scheme 3) was found to lie in an approach similar to the one described in our synthesis of 14,15-LTA_4. The key to this more efficient route was the realisation that whereas the Wittig reaction of unprotected 2-deoxy-D-ribose 6a did not afford

Scheme 3



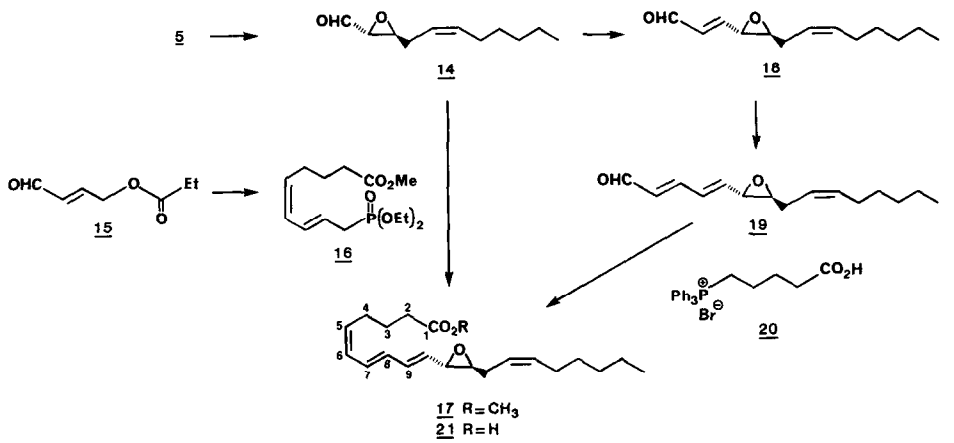
any condensation product, the monoprotected derivative 7 led to a successful coupling reaction to afford 8 which has been transformed to epoxy alcohol 9, the key intermediate in our approach to 14,15-LTA_4. The required epoxy alcohol 5 was obtained from 2-deoxy-D-ribose derivative 7[2] by using the appropriate phosphonium salt. Hence treatment of 7 with 6 eq. of hexylidene triphenyl-phosphorane in THF/HMPA (-78°→r.t.) afforded 10 in 50% yield.[6] Removal of the silyl group [$(nBu)_4NF$, THF, 0°C→ r.t., 3 eq. AcOH] afforded 3 in 60% yield, which was transformed as described above to 5. We thought that we might be able to shorten the synthesis even more by not protecting the primary alcohol with a silyl group but by preparing the sulphonyl

Scheme 4



derivative 11a directly (Scheme 4). We reasoned that Wittig reaction on 11a should give 12 which should in situ rearrange via 13 to 5. Unfortunately, we were unable to prepare pure 11a. Treatment of 6a with TIPSCl/pyridine gave a mixture of Triisopropyl benzene sulfonates. Nevertheless, we wished to determine if the sequence was feasible. Tosylate 11b was easily prepared in 50% yield from methyl furanoside 6b.[7] (1 TsCl/Py, 2 HCl/dioxane). Treatment of 6b with 7 eq of hexylidene triphenylphosphorane in 4:1 THF/HMPA cleanly afforded epoxy alcohol 13 in 70% yield. $[\alpha]_D$ = +27°, which did not rearrange under the reaction conditions. Alcohol 13 on treatment with NaOMe afforded 5 $[\alpha]_D$ = -20°. Mosher analysis clearly showed that the alcohol was chirally pure. We are presently investigating a procedure to prepare a 2-deoxy D-ribose derivative containing a leaving group on the primary OH in one step. This would allow the preparation of chiral epoxy alcohols in 3 steps from 2-deoxy D-ribose.

Scheme 5



Oxidation of 5 (pyridine / CrO_3, CH_2Cl_2) afforded 14 in 80% yield. From 14 we have completed the synthesis of 11,12-LTA_4 in two ways (Scheme 5). The first approach involved formation of the 9,10-trans double bond last via a Horner-Emmons phosphonate condensation. We first tried the phosphonate route since it avoided the problem of handling the 11,12-LTA_4 carboxylic acid salt. The necessary phosphonate 16 was prepared uneventfully from 15.[8] (1. ϕ_3P=CH-$(CH_2)_3CO_2Li$/HMPA, 2. CH_2N_2, 3. K_2CO_3/MeOH, 4. CBr_4/ϕ_3P, 5. $(EtO)_3P/\Delta$) in ≈20% overall yield. Condensation of 16 with 14 (NaH/15-crown-5, r.t.)[8] afforded a low yield (22%) of 11,12-LTA_4 estermethyl 17 after purification by flash chromatography. The difficulty in preparing 16 coupled with the low yield of the Horner-Wittig condensation step makes this route unattractive. Our second approach involved formation of the 5,6-cis double bond last via a Wittig reaction. Homologation of 14 (1.2 eq. ϕ_3P=CH-CHO, benzene, 60°, 2 h) afforded 18 which was transformed to 19 $[\alpha]_D$ = -17.4 (C=2.0, $CHCl_3$) in 30-35% overall yield from 5 using the procedure of Toda et al.[9] (1. EtO-CH=CH-$(nBu)_3Sn$/nBuLi, 2. MsCl/Et_3N, 3. $NaHCO_3$). Condensation of 19 with phosphonium salt 20 (2.2 eq. LiHMDS, THF/HMPA (4:1), -78°→0°)[10] afforded 11S, 12S-LTA_4 methyl ester 17 $[\alpha]_D$ = -14.6° (C = 4, hexane) in 70% yield after flash chromatography

(purity 90%). A pure sample was obtained by HPLC (1% Et_3N/hexane, μ-porasil), but recovery was low ≈50%.[11] In fact the 11,12-LTA_4 proved to be more unstable than the corresponding 5,6 and 14,15 LTA_4. Hydrolysis of 17 (1N NaOH/MeOH, 5°, 1 h) afforded 11S,12S-LTA_4 21.

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5a. Prepared by treatment of the alcohol with Mosher acid chloride in THF with Et_3N/DMAP.

5b. The antipode of alcohol 5 has been described. E.J. Corey, P.B. Hopkins, J.E. Munroe, A. Marfat, and S. Hashimoto, J. Am. Chem. Soc. 102, 7986 (1980) and Y.K. Yee, 14th Northeast Regional Meeting ACS June 10 - 13, 1984.

6. The use of such a large excess of phosphorane is necessary to obtain a reasonable yield.
7. R.E. Deriaz, W.G. Overend, M. Stacey, and L.F. Wiggins, J. Chem. Soc., 2836 (1949).
8. J. Buck, F. Ellis and P.C. North, Tetrahedron Lett., 23, 416 (1982).
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10. For detailed procedure see ref. 3.
11. ε_{278}=50,000, p.m.r. 400 MHz ($CDCl_3$). δ 6.48 (m, H_7+H_8) 6.17 (dd, H_9, J_1=11Hz, J_2=15 Hz), 6.03 (t, H_6, J=11Hz), 5.3-5.6 (m, 4H, H_5, H_{10}, H_{14}, H_{15}), 3.7 (s, 3H, OMe), 3.15 (dd, H_{11}, J_1=2Hz, J_2=8Hz), 2.90 (dt, J_1=2Hz, J_2=8Hz) 2.45 (m, 1H), 2.35 (t, $\underline{CH_2}CO_2Me$), 2.25 (m, 1H) 2.15 (m, $\underline{CH_2}$-C=C), 1.75 (m, 2H), 1.2-1.4 (m,6H), .95 (t, 3H).

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