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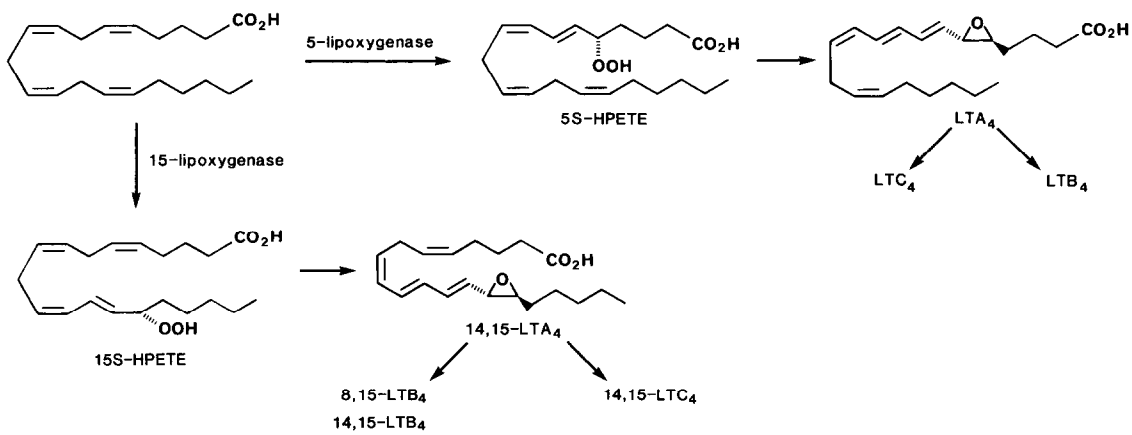
THE STEREOSPECIFIC SYNTHESIS OF 14S,15S-OXIDO 5Z,8Z,10E,12E-EICOSATETRAENOIC ACID

Robert Zamboni*, Suzanne Milette and Joshua Rokach
Merck Frosst Canada Inc., P.O. Box 1005, Pointe Claire-Dorval
Quebec, Canada H9R 4P8

Summary: The first total and stereospecific synthesis of 14S,15S-oxido 5Z,8Z,10E,12E-eicosatetraenoic acid from 2-deoxy-D-ribose has been achieved.

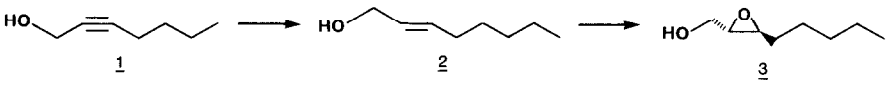
The recently discovered leukotrienes A_4, B_4, C_4, E_4 and F_4 are all derived from oxygenation of arachidonic acid at the 5 position by a lipoxygenase.[1] These compounds seem to play a role in immediate hypersensitivity reactions and also have pronounced pro-inflammatory effects. Human leucocytes contain, in addition to the 5-lipoxygenase, enzymes catalyzing the introduction of oxygen at C-15 (Scheme 1).

Scheme 1



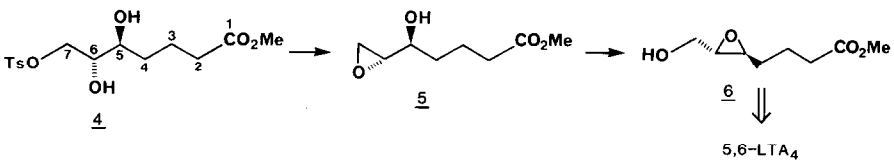
Initial findings indicate that a series of leukotrienes are derived from this pathway analogous to the well studied and biologically potent leukotrienes derived from oxidation at C-5. Samuelsson[1] has obtained strong evidence that 14,15-oxido 5Z,8Z,10E,12E-eicosatetraenoic acid (14,15-LTA_4) is formed and is a key intermediate in further biochemical transformations. As part of our continuing interest in leukotrienes we wished to study the biochemistry and possible biological properties of these new metabolites of arachidonic acid. Because of the unavailability of these unstable metabolites from natural sources, we have developed a totally stereospecific route to 14S,15S-LTA_4.[2]

We have first approached the synthesis of the necessary epoxy alcohol 3 via the chiral epoxidation of olefin 2. Reduction of acetylene 1 ($LiAlH_4$, rt, 24 h, THF) cleanly



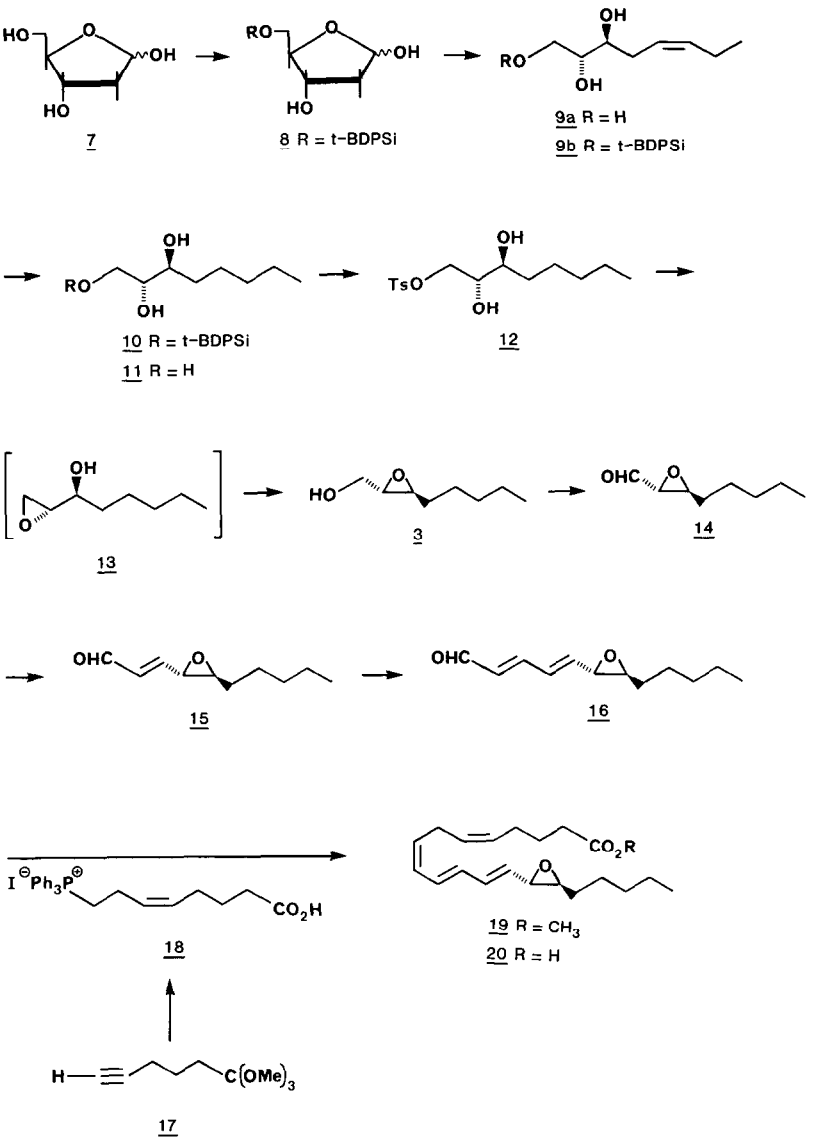
afforded olefin 2 in 75% yield. Chiral epoxidation of 2 [3] gave epoxy alcohol 3 in 56% yield. To our disappointment, 400 MHz p.m.r. analysis of the Mosher ester [4] of 3 in C_6D_6 gave an e.e. of only 80%. Since it has been our experience that even the presence of a few percent enantiomer in 20 could complicate biochemical studies we needed a totally stereospecific route to 3.

We have previously shown [5] that intermediates such as 4 can be converted efficiently



to the desired secondary epoxide 6. We have also shown that this transformation proceeded through the intermediacy of the primary epoxide 5. The net stereochemical result is the inversion of the configuration of carbon 6 and the retention at carbon 5. We decided to follow the same strategy in the construction of the desired epoxy alcohol 3, which required the synthesis of intermediate 12. Scheme 2 shows how this was accomplished, using 2-deoxy D-ribose 7 as our starting point. We have attempted at first to prepare the required 9a by a Wittig reaction on the unprotected 7. Unfortunately, treatment of 7 with excess propylidene triphenylphosphorane in THF/HMPA did not afford any olefin, presumably due to the insolubility of the tri-anion formed initially. We have found that the protection of the primary alcohol alone was sufficient to facilitate the Wittig reaction. Silylation of 7 (1.2 eq. t-BDPSiCl/pyridine) afforded 8 in 55% yield. Treatment of 8 with 6 eq. of propylidene triphenylphosphorane in THF/HMPA 4:1 afforded the desired olefin 9b in 40% yield. Catalytic hydrogenation (H_2/10% Pd/C) afforded 10. Removal of the silyl group (1.5 eq. $(nBu)_4NF$, 3 eq. AcOH, THF) gave triol 11 in 50% yield from 9b. Tosylation (1.1 eq. TsCl, py, 5°, 18h) gave tosylate 12 in 55% yield. Rearrangement of 12, via epoxide 13, with 1.3 eq. of NaOMe in MeOH proceeded smoothly and gave 3, $[\alpha]_D$ -44° (C=1.0 $CHCl_3$), in 50-60% yield. The epoxy alcohol 3 obtained this way was chirally pure, as no trace of the enantiomer could be detected in the 400 MHz p.m.r. of its Mosher ester. Oxidation of 3 (CrO_3/py, celite) afforded crude aldehyde 14 in 90-95% yield. [6] Homologation of 14 (1.2 eq. $\emptyset_3P{=}CH{-}CHO$, toluene, 70°) gave pure 15 in 60% overall yield from 3. 15 was transformed to 16, $[\alpha]_D$ -27.7° (C=1.0, $CHCl_3$), using the procedure described by Toda et al. [7] (1. $EtO{-}CH{=}CH{-}(nBu)_3Sn/nBuLi$, 2. $MsCl/Et_3N$ 3. $NaHCO_3$) in 60% yield. The phosphonium salt 18 needed to complete the synthesis was easily prepared from 17 [8] (1. Li/NH_3/ethylene oxide, 2. HCl, 3. Nickel boride/H_2, 4. $MsCl/Et_3N$, 5. NaI, 6. LiOH/THF, 7.$\emptyset_3P$) in 20% overall yield. Condensation [9] of 18 with 16 (2.2 eq. LiHMDS/THF -78°→0°) followed by the addition of excess dimethylsulphate/$NaHCO_3$ afforded 19 [10], $[\alpha]_D$ -27.4° (C=1.0, hexane), in 60% yield [11] after HPLC (μ-porasil, 2% Et_3N/hexane). Hydrolysis of 19 (1N NaOH/MeOH, 5°, 1h) afforded 14S,15S-LTA_4 20.

Scheme 2



The epoxy alcohol 3 prepared via the chiral epoxidation method was also converted to 20. Although this route cannot be used to prepare chirally pure 14,15-LTA_4 with high enough e.e. for our purposes; it is the most efficient route to prepare LTC_4 and LTD_4 analogues derived from 14,15-LTA_4. The 10% enantiomer can be removed when the epoxide is opened with the blocked peptide. The chiral epoxidation of alcohol 2 has produced 3 in lower e.e. than similar reported cases. We are at present collaborating with Professor Sharpless in order to determine if the e.e. for this particular allylic alcohol cannot be improved.

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9. To a solution of 18 (267 mg, .503 mmole) in 1 mL THF/.25 mL HMPA at 0° was added a solution of lithium hexamethyl disilizane (.862 mm) in 1mL THF + .25 mL HMPA. After stirring 1 h at 0° the solution was cooled to -78° and a solution of the aldehyde 16 (60 mg, .3 mmole) in 1 mL THF was added dropwise. The reaction mixture was stirred 30 min at -78° then 30-45 min at 0°. $NaHCO_3$ (100 mg) was added followed by 160 µL dimethylsulphate. After stirring 1h at 0° the reaction was poured into a mixture of 50 mL 25% NH_4OAc solution and 50 mL ether with 5% Et_3N. The organic layer was washed with saturated NaCl, dried and evaporated. Purification by flash chromatography (10% EtOAc/Hex, 1% Et_3N, column deactivated with 10% Et_3N/Hex) afforded 90 mg 19 (80%); purity by HPLC was > 90%. A pure sample was obtained by purification by HPLC (2% Et_3N/Hexane, µ-porasil) in 60% yield.

10. ϵ_{278}=50,000, p.m.r. 400 MHz, (CD_3COCD_3) δ 6.79 (q, H_{11}, J_1=11, J_2=15Hz), 6.66 (q, H_{10}, J_1=11Hz, J_2=15Hz), 6.38 (q, H_{12}, J_1=11Hz, J_2=15Hz), 6.16 (t, H_8, J=11Hz), 5.44-5.55 (m, H_7, H_{13}, H_5 + H_6), 3.37 (s, OCH_3), 3.25 (dd, H_{14}, J_1=2Hz, J_2=8Hz), 3.05 (bt, C=C-CH_2-C=C), 2.9 (m, H_{15}), 2.44 (t, $\underline{CH_2}CO_2CH_3$), 2.25 (C=C-$\underline{CH_2}$, bq), 1.4-1.8 (m, 10H), 1.0 p.p.m. (bt, CH_2-$\underline{CH_3}$).

11. All yields have not been optimized.

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