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STEREOSPECIFIC SYNTHESIS OF 5S-HETE, 5R-HETE AND THEIR TRANSFORMATION TO 5(±)HPETE

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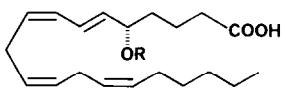
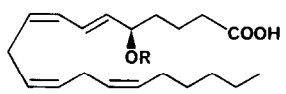
Summary: The stereospecific synthesis of 5S-HETE and 5R-HETE has been accomplished via intermediates 5 and 8 as chiral precursors and their transformation to the corresponding HPETES has been investigated.

The lipoxygenase pathway is the most recently discovered metabolic route of arachidonic acid.[1] Some of the most important metabolites identified so far include the leukotrienes, namely, LTB_4, C_4, D_4 and E_4. The detailed physiological role of these leukotrienes is being elucidated. It is already apparent that these mediators play an important role in respiratory diseases and inflammation. The primary step in the biosynthetic transformation of arachidonic acid (Scheme 1), which eventually leads to the leukotriene family, is the introduction of a hydroperoxy group in the 5-position by a 5-lipoxygenase enzyme to yield 5-HPETE 1. 5-HPETE is converted by a dehydrase to LTA_4 and independently by a reductase to 5-HETE 2.

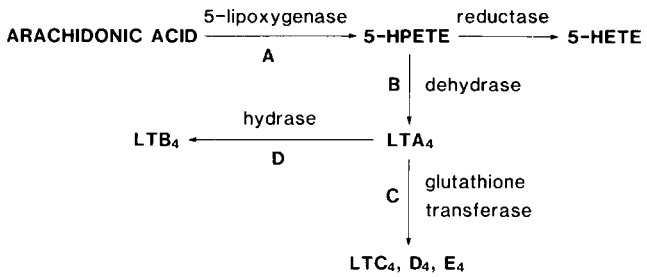


1 R=OH 5S-HPETE
2 R=H 5S-HETE



3 R=OH 5R-HPETE
4 R=H 5R-HETE

Scheme 1

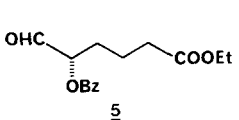


When one is confronted with the problem of studying inhibitors of this pathway, steps A, B, C or D could be considered. The study of steps C and D has been greatly facilitated by the ready availability of LTA_4, B_4, C_4, D_4, and E_4 through synthesis.[2] Study of step B, which could

be the most interesting one to inhibit since it prevents the formation of all leukotrienes, is still hampered by the supply problem of 5-HPETE and 5-HETE.

Due to the extreme scarcity of the biological materials we decided to undertake the synthesis of these mediators, and we describe here the first stereospecific synthesis of 5S-HETE and 5R-HETE and their transformation to (±)-HPETE.

A synthesis of racemic 5-HETE has been described previously[3] and this material has been resolved chemically.[4] Our plan was to use synthon 5 and synthon 8 as the source of the required chiral centers. The remaining carbons would be attached using two successive Wittig reactions. The synthesis of 5 from 2-deoxy-D-ribose[2e] has previously been described by us. The synthon 8 required for the synthesis of 5R-HETE and was easily prepared from 6, an intermediate used in our synthesis of 5-epi and 6-epi-LTA_4.[2C] Hydrolysis of the acetonide (EtOH/.5N HCl at 50° for 2 h) afforded diol 7 in 70% yield. Cleavage of the diol ($Pb(OAc)_4/Na_2CO_3$ in CH_2Cl_2, -40°) afforded aldehyde 8, $[\alpha]_D$ = +35°, (c=2.0, $CHCl_3$) in 50% yield.



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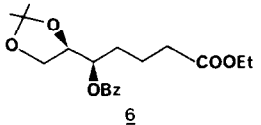

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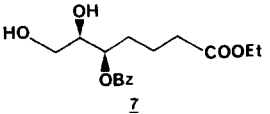

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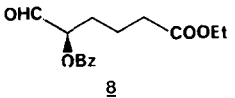

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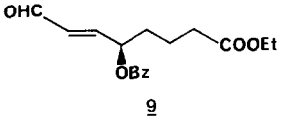

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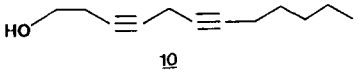

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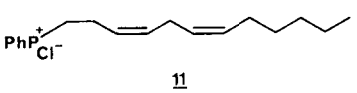

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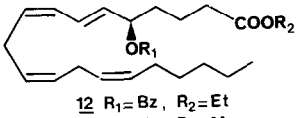
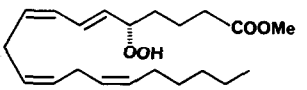


12 R_1=Bz, R_2=Et
13 R_1=H, R_2=Me



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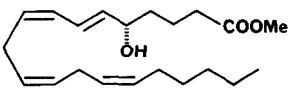

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The synthesis of 5R-HETE from 8 was completed as follows. Homologation of aldehyde 8 (1.2 eq Ph_3P=CH-CHO, toluene, +75°) afforded α,β unsaturated aldehyde 9 in >90% yield. The phosphonium salt 11 required for the final Wittig reaction was easily prepared from 10[5] (1. reduction with nickel boride,[6] 2. MsCl/Et_3N, 3. NaI/acetone, 4. Ph_3P/toluene, 5. AG 1-X8 anion exchange resin, chloride form/methanol) in 30% overall yield. Condensation of aldehyde 9 with 11 (nBuLi, THF/HMPA, -78°) afforded, after purification by HPLC, 12[7] in 46% yield. Removal of the benzoate (K_2CO_3/MeOH) afforded 13[8], $[\alpha]_D$ = -13.7°, (c=1.0, benzene) lit.[4] $[\alpha]_D$ = -13.5° in 95% yield. HPLC analysis (μ-porasil, 5% ethyl acetate/hexane) of the MTPA ester[11] of 13 indicated an enantiomeric purity of >95%. Hydrolysis of 12 (K_2CO_3/H_2O/MeOH) afforded 5R-HETE 4 (UV λ(MeOH) 230(sh), 236, 247(sh)nm) in 80% yield. Alcohol 13 was transformed to the expected hydroperoxide 1 using known methodology (1. MsCl/Et_3N/CH_2Cl_2, 2. H_2O_2, 3. LiOH/DME/H_2O)[3] in only 10-15% overall yield after purification by HPLC (Waters μ-porasil column at 0° using 2% isopropanol/hexane/.1% AcOH).[9,10] HPLC and NMR showed that the initial displacement of the mesylate with hydrogen peroxide afforded 3 compounds in a 1:2:1 ratio with the desired hydroperoxide as the major product. Because of the difficulty in separation of the three products it was found to be more convenient to purify after hydrolysis. In order to determine the enantiomeric purity, 1 was transformed to its methyl MTPA diester (1. $NaBH_4$/EtOH, 2. CH_2N_2, 3. DCC/DMAP/(+)-MTPA). HPLC analysis indicated that complete racemization had occurred during the treatment of mesylate 13 with H_2O_2! This displacement reaction probably occurred via an SN_1 type mechanism.

Repeating the above sequence, starting from 5, 15 was prepared $[\alpha]_D$ = +14.4°, (c=2.0, benzene), lit.[4] $[\alpha]_D$= +14.0°. HPLC analysis of the MPTA ester of 15 indicated an enantiomeric purity of >99%. Hydrolysis of 15 (K_2CO_3/MeOH/H_2O) afforded 2. Similarly, when the sequence (1. MsCl/Et_3N/CH_2Cl_2, 2. H_2O_2, 3. LiOH/DME/H_2O)[3] was performed on alcohol 15, a racemic mixture of 5S-HPETE 1 and 5R-HPETE 3 was obtained.

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7. Pmr (400MHz, $CDCl_3$) δ8.06 (t, 2H), 7.55 (t, 1H), 7.44 (t, 2H), 6.64 (dd, H_7, J_1 = 10Hz, J_2 = 15Hz), 5.99 (t, H_8, $J_1 = J_2$ = 10Hz), 5.68 (m, 1H, H_5), 5.72 (q, H_6, J_1 = 6Hz, J_2 = 15Hz), 5.3-5.5 (m, 5H, H_{11}, H_{12}, H_{14}, H_{15}, H_9), 4.1 (q, 2H, J = 7Hz, $CO_2\underline{CH_2}CH_3$), 2.96 (t, 2H, C=C-$\underline{CH_2}$-C=C), 2.79 (t, 2H, C=C-$\underline{CH_2}$-C=C), 2.37 (t, 2H, $\underline{CH_2}CO_2CH_2CH_3$), 2.04 (q, 2H, CH_2-C=C), 1.7-1.9 (m, 4H), 1.2-1.4 (m, 6H), 1.12 (t, 3H, J = 7Hz, $CO_2CH_2\underline{CH_3}$), .9 (t, 3H, $CH_2\underline{CH_3}$).
8. Pmr (400MHz, $CDCl_3$) δ6.55 (dd, H_7, J_1 = 10.7Hz, J_2 = 15Hz), 5.99 (t, H_8, $J_1 = J_2$ = 10.7Hz), 5.68 (dd, H_6, J_1 = 6.8Hz, J_2 = 15Hz), 5.30-5.45 (m, 5H, H_{11}, H_{12}, H_{14}, H_{15}, H_9), 4.20 (q, H_5, J ≈ 7Hz); 3.67 (s, 3H, OCH_3), 2.96 (t, 2H, C=C-$\underline{CH_2}$-C=C), 2.81 (t, 2H, C=C-$\underline{CH_2}$-C=C), 2.37 (t, 2H, $\underline{CH_2}CO_2CH_3$), 2.06 (q, 2H, $\underline{CH_2}$-C=C), 1.55-1.80 (m, 5H), 1.2-1.4 (m, 6H), .90 (t, 3H, $CH_2\underline{CH_3}$).
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10. In this solvent the hydroperoxide was found to be stable for >1 month at -70°.
11. Prepared by treatment of the alcohol with DCC/DMAP and (+) α-Methoxy-α-trifluoromethyl phenyl acetic acid ((+)-MPTA).

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