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STEREOSPECIFIC TOTAL SYNTHESIS OF 12-(R)- AND 12-(S)-FORMS OF 6-TRANS LEUKOTRIENE B

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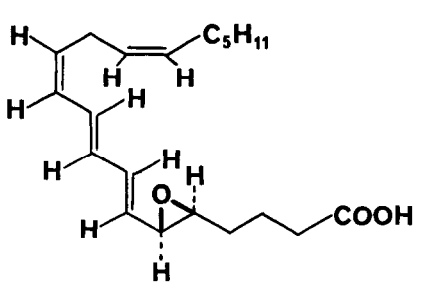
Summary: Non enzymatic hydration of leukotriene A (1), the biogenetic precursor of leukotriene B (2) affords among other products two diastereomeric 6-trans-isomers of 2, the first stereospecific and efficient syntheses of which are recorded herein.

Enzymatic reactions of leukotriene A (1) give rise to the "slow reacting substances"[1] and also to the biologically important neutrophil chemotactic factor leukotriene B (2) (LTB).[2] In contrast, non-enzymatic hydration of 1 in neutral or acidic aqueous media generates no significant amount of LTB (2) but mainly a mixture of two 6-trans-isomers of 2 which are diastereomeric at C(12) and two diastereomeric 5,6-diols formed by direct displacement at C(6).[2] In order to confirm the structures of the two diastereomeric 5,12-diols and to provide ample amounts of these compounds 12-(S)- and 12-(R)-3 for biological study efficient stereospecific syntheses have been developed as outlined herein. Key features of the twin routes to 12-(S)- and 12-(R)-3 include the use of a common intermediate for one segment of the final structure and enantiomeric, chirally synthesized units for the other, and also a stereospecific (to trans C=C) coupling of the two segments via a β-oxido ylide. A practical synthesis of the versatile chiral intermediate (R)-(+)-dimethyl malate (unnatural form) from (R,R)-(+)-dimethyl tartrate (natural form) is also described.



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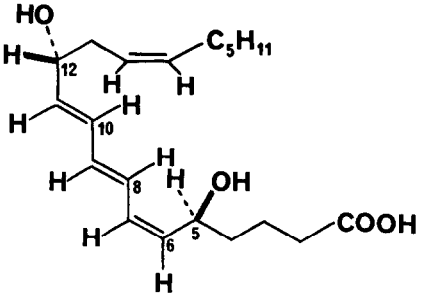

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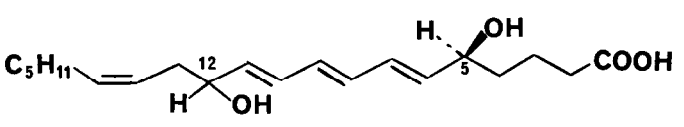
The construction of 12-(S)-3 was accomplished from the intermediates 4 and 5, the former of which had been made earlier by chiral synthesis from natural (S)-(-)-malic acid and applied to the synthesis of 12-(S)-HETE.[3] The dienal 5 was prepared from the ester aldehyde 6[2b] by reaction as previously described[1c] with 1-lithio-4-ethoxybutadiene.[4] The phosphonium salt 4 was

transformed into the corresponding β-oxido ylide[3,5] by treatment in THF at -78° with 2 equiv. of n-butyllithium for 1 hr and then treated with 10 equiv. of hexamethylphosphoric triamide and 1.0 equiv. of the dienal 5. The reaction mixture was allowed to warm to -30° over 1.5 hr, kept at -30° for 1 hr, warmed to 0° and quenched with water-ether. Extractive isolation and chromatography afforded the methyl ester of the 5-benzoate of 12-(S)-3 (25%), uv max at 270.4 nm with shoulders at 261.5 and 281.5 nm (CH_3OH), R_f = 0.34 (silica gel plates 2:1 hexane-Et_2O containing 1% triethylamine); no isomers of this major product could be detected by HPLC analysis, all byproducts being relatively very polar. Saponification was effected by exposure to excess potassium carbonate in methanol (7.5 hr at 23°) followed by addition of excess aqueous lithium hydroxide and reaction at 23° for a further hr. to give cleanly 12-(S)-3, homogeneous by reversed phase HPLC anlaysis (Waters Associates C_{18}-column using 75:25 CH_3OH-H_2O containing 0.01% HOAc),[6] uv max 259, 269, and 280 nm (in CH_3OH). Synthetic 12-(S)-3 produced in this way was identical by uv and HPLC comparison with one of the diastereomeric 5,12-diols produced by acid-catalyzed hydrolysis of LTA (1).

The synthesis of 12-(R)-3 by a parallel route necessitated the preparation of the enantiomer of phosphonium salt 4 which in turn required the use of the unnatural form of malic acid [(R)-(+)-isomer]. Reaction of (R,R)-(+)-dimethyl tartrate (natural form) with 4 equiv. of sat. HBr in acetic acid at 25° for 4 hr afforded the acetoxy bromide 7[7] after extractive workup (76% crude yield) which was used directly in the next step without purification. A cooled (ice bath) ethanolic solution of 7 (1 M), 0.02 equiv. of trimethyltin chloride, and 0.008 equiv. of azobisisobutyronitrile was treated with 1.03 equiv. of 1 M sodium borohydride in ethanol at such a rate so as to maintain the reaction temperature below 10° to effect replacement of bromine by hydrogen (via Me_3SnH).[8] The crude dimethyl acetylmalate so obtained was deacetylated by exposure to 3% HCl in methanol at reflux for 1 hr. to afford after concentration, treatment with Et_2O-$NaHCO_3$, filtration and distillation (R)-(+)-dimethyl malate (8), $[\alpha]_D^{21}$ +6.89° (neat, l = 1 dm), b.p. 75-78° at 0.07 nm.[10] The overall yield of 8 from (+)-dimethyl tartrate was 56% on a 0.2 mole scale. The synthesis of 9 was then carried out from 8 essentially as reported earlier.[3] Further using the β-oxido ylide from 9 and the dienal 5, the 12-(R)-isomer of 3 was synthesized as described above for the diastereomer. The 12-(R) isomer of 3 showed uv max at 258, 268 and 280 nm in CH_3OH and was indistinguishable from 6-trans-LTB

[12-(R)-3] [6] which had been synthesized earlier [2b] by a non-stereoselective route.

In order to illustrate further the utility of the enantiomeric β-oxido ylides 4 and 9 in the synthesis of optically active all trans trienols, sorbaldehyde (10) was studied as substrate. Reaction of 10 with the ylide from 9 essentially as described above produced the tetraenol 11 in 78% yield and >95% purity (HPLC analysis) after simple chromatographic isolation using a silica gel column. [11]



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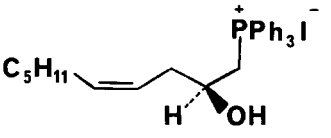

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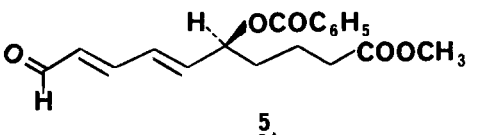

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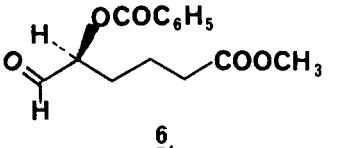

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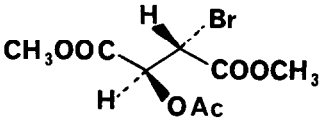

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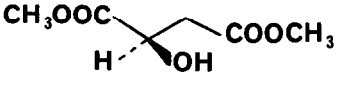

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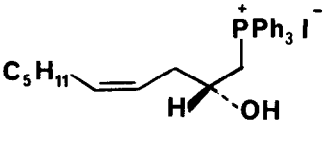

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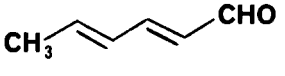

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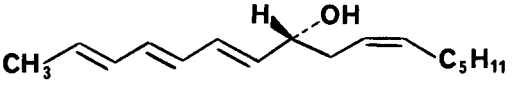

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References and Notes

1. (a) R. C. Murphy, S. Hammarström and B. Samuelsson, Proc. Natl. Acad. Sci. USA, 76, 4275 (1979(; (b) S. Hammarström, B. Samuelsson, D. A. Clark, G. Goto, A. Marfat, C. Mioskowski, and E. J. Corey, Biochem. Biophys. Res. Commun., 92, 946 (1980); (c) E. J. Corey, D. A. Clark, G. Goto, A. Marfat, C. Mioskowski, B. Samuelsson, and S. Hammarström, J. Am. Chem. Soc., 102, 1436, 3663 (1980); (d) for nomenclature see, B. Samuelsson and S. Hammarström, Prostaglandins, 19, 645 (1980).

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3. E. J. Corey, H. Niwa and J. Knolle, J. Am. Chem. Soc., 100, 1943 (1978).

4. See R. H. Wollenberg, Tetrahedron Letters, 717 (1978). 1-Lithio-4-ethoxybutadiene (1 equiv) in tetrahydrofuran (THF) was added gradually to the ester aldehyde 6 in THF at -78° and the mixture was maintained at -78° until reaction was complete (2 hrs.). Triethylamine (10 equiv) and methanesulfonyl chloride (5 equiv) in methylene chloride (vol equal to THF solution) were added at -78° and after 1 hr at -78°, 3 hr at -40° and 1 hr at -20°, the mixture was quenched with pH 7 phosphate buffer to afford pure 5 in 50% yield after isolation and chromatography on silica gel. Structural assignment of 5 was confirmed by pmr, infrared and uv spectra (uv max 266 nm in CH_3OH). Rf 0.54 on silica gel plates using 6:1 $CH_2Cl_2 \cdot Et_2O$ containing 1% triethylamine).[3] All reactions described herein were conducted under an argon atmosphere.

5. See, E. J. Corey, P. Ulrich and A. Venkateswarlu, Tetrahedron Letters, 3231 (1977) and references therein cited.

6. Under these HPLC conditions the following retention volumes were observed: LTB, 3.70; 12-(S)-3, 3.40; 12-(R)-3, 3.15.

7. K. Mori and H. Iwasawa, Tetrahedron, 36, 87 (1980).

8. E. J. Corey and J. W. Suggs, J. Org. Chem., 40, 2554 (1975).

9. For (S)-(-)-dimethyl malate $\alpha_D^{20} = -8.41°$; $[\alpha]_D^{20} = -6.84°$ (neat, l = 1 dm.); see, P. Frankland and F. M. Wharton, J. Chem. Soc., 75, 337 (1899).

10. An enantiomeric purity of >98% was indicated by HPLC analysis of the 3,5-dinitrobenzoate of 8 using a chiral stationary phase of the type described by W. H. Pirkle and D. W. House, J. Org. Chem., 44, 1957 (1979). We thank Dr. Pirkle for the use of the column.

11. This work was supported by the National Institutes of Health.

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