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A STEREOCONTROLLED AND EFFECTIVE SYNTHESIS OF LEUKOTRIENE B (1).

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Summary: An efficient synthesis of leukotriene B (1) is reported which renders this important substance accessible in quantity. The process is convergent and includes a novel method for stereospecific generation of the conjugated triene unit.

Leukotriene B, first obtained by incubation of arachidonic acid with polymorphonuclear leukocytes,[1] is formed by way of the intermediates 5-(S)-hydroperoxy-6-trans-8,11,14-cis-eicosatetraenoic acid (5-HPETE) and 5-(S)-trans-5,6-oxido-7,9-trans-11,14-cis-eicosatetraenoic acid (leukotriene A)[2,3] which are also precursors of the slow reacting substances (leukotrienes C, D, and E).[4] It has recently become clear that leukotriene B is of considerable medical interest since it is powerfully chemotactic for macrophages and neutrophils (at concentrations of ca. 1 ng/ml)[5] and therefore relevent to allergic and inflammatory states.[6] The detailed structure of leukotriene B (LTB) has been established as 1 by unambiguous synthesis[7] coupled with critical physical and biological comparisons of synthetic 1 with native LTB and various synthetically produced[7,8] stereoisomers of 1 differing in double bond geometry at Δ^6, Δ^8 and Δ^{10} linkages. Because of the importance of LTB we have carried out further investigations to provide an ample source of this compound which is available only in microgram amounts from biological sources. In this paper we report an especially simple and effective process for the synthesis of 1.

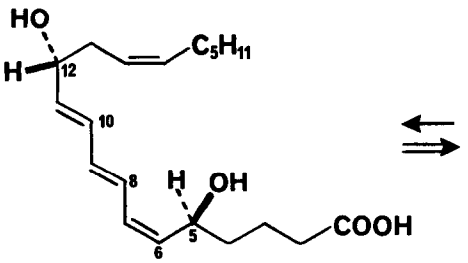
The key step of the synthesis outlined herein is a novel internally promoted elimination reaction of the epoxy acid derivative 2 which takes advantage of both the cis-Δ^6-olefinic linkage and the 5-hydroxy function of LTB to provide a low energy pathway for its formation.

2,3-Oxido-undeca-2-trans-5-cis-dien-1-ol, $[\alpha]_D^{20}$ +17.9° (c = 2.0 in $CHCl_3$), (3)[9] was oxidized to the corresponding aldehyde[10] by in situ generated CrO_3-2Pyr (excess) in methylene chloride at 23° for 15 min (90% yield). Reaction of the ylide prepared from the 2-methoxy-2-propyl ether of 3-hydroxypropyltriphenylphosphonium bromide[8,11,12] and n-butyllithium (in tetrahydrofuran (THF) at -78°/-78° to -20°) with this aldehyde in THF at -78° for 40 min and -78° to 0° over 80 min afforded the cis olefination product 4, X = $OC(CH_3)_2OCH_3$, in 92% yield.[13] Deprotection of this ether was accomplished by exposure to acetic acid (0.125 ml/g of olefinic ether) in 4:1

acetonitrile-water (pH ca. 4.6) at 23° for 2.5 hr to give after chromatography on silica gel the epoxy alcohol, 4, X = OH, (78%). This alcohol was converted via the corresponding tosylate and iodide into the phosphonium salt 4, X = $Ph_3P^+I^-$, (3 equiv of triphenylphosphine in acetonitrile at 60° for 12 hr, 94% overall).[14]

The second major fragment for the construction of 1, the aldehyde ester 7, was synthesized by a modification of the approach previously described.[7] Reaction of 2-deoxyribose with 1.2 equiv of methoxycarbonylmethylenetriphenylphosphorane and a trace of benzoic acid in dimethoxyethane at reflux for 5 hr provided in 82% yield the triol ester 5, m.p. 57-58°, $[\alpha]_D^{25}$ -17.6° (c = 0.5 in ethanol). Conversion of 5 to the epoxy diester 6 was accomplished in 67% overall yield by the sequence: (1) double bond reduction (1 atm. H_2), Pd-C, in ethanol at 25°; 97% yield; prod. m.p. 26-27°; $[\alpha]_D^{25}$ -12.5° (c = 0.8 in ethanol)); (2) monotosylation of the primary hydroxyl (1.1 equiv tosyl chloride-pyridine, 0°, 24 hr; 75% yield; prod. m.p. 60°, $[\alpha]_D^{25}$ +29.0° (c = 2.6 in $CHCl_3$)); (3) oxirane closure (2 equiv of K_2CO_3 in methanol at 25°; 96% yield); and (4) benzoylation using benzoyl chloride-pyridine at 25°, 1 hr, 96% yield). Hydrolytic ring opening of the oxirane ring was effected in 80% yield by exposure of 6 to 1:3:0.03 dimethyl carbonate-water-70% perchloric acid to form the corresponding 1,2-diol which upon cleavage with 1.05 equiv of lead tetraacetate in methylene chloride containing 2 equiv of powdered sodium carbonate at -40° for 10 min provided the aldehyde ester 7 in 77% overall yield.

The phosphonium salt 4, X = $Ph_3P^+I^-$, was converted to the corresponding ylide by reaction with 1 equiv of n-butyllithium in THF at -78° for 1 hr and the resulting Wittig reagent was treated sequentially at -78° with 15 equiv of hexamethylphosphorictriamide and the aldehyde ester 7. After 1 hr at -78° and 2.5 hr at -78° to 0°, extractive isolation and purification by column chromatography on silica gel, the all cis triene diester 8, $[\alpha]_D^{25}$ +53.1° (c = 3.3 in $CHCl_3$), was obtained as a colorless oil in 65% yield. Exposure of 8 (55°, 24 hr) to excess 1.5 M K_2CO_3 in methanol containing a trace of water and acidification to pH 5.5 with acetic acid produced leukotriene B (1) in 75% yield as determined by quantitative measurement of ultraviolet absorption (λ_{max} 260, 270.5 and 281 nm).[7] Extractive isolation furnished LTB of >95% purity as ascertained by reversed phase high performance liquid chromatography using a Waters associates C_{18} μ-Bondapak column with 3:1 methanol-water containing 0.01% acetic acid for elution.[7] No isomers of LTB could be detected.[7,8] The leukotriene B obtained in this way was identical in all respects with native LTB and synthetic LTB obtained by the process reported earlier.[7,15,16]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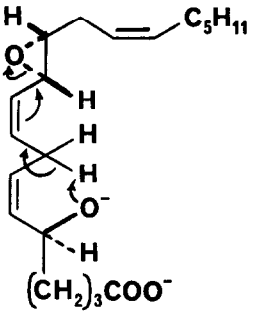
H
12
C_5H_{11}
10
8
H
OH
5
6
COOH

1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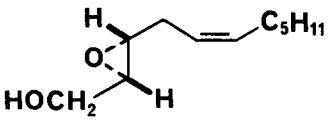
C_5H_{11}
H
H
H
O
H
$(CH_2)_3COO^-$

2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O
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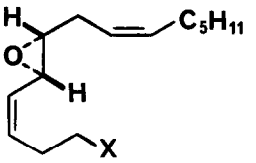
$HOCH_2$
H

3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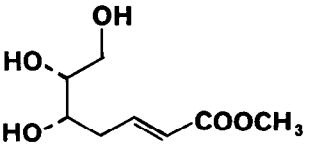
O
C_5H_{11}
H
X

4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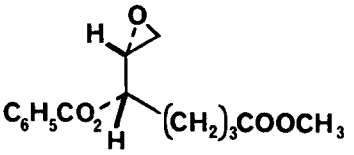
HO
HO
$COOCH_3$

5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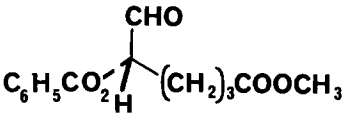
H
$C_6H_5CO_2$
H
$(CH_2)_3COOCH_3$

6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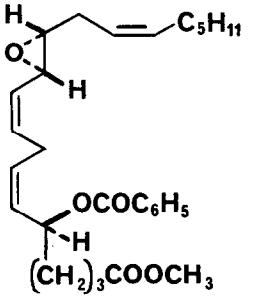
H
$(CH_2)_3COOCH_3$

7


H
O
C_5H_{11}
H
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H
$(CH_2)_3COOCH_3$

8

References and Notes

1. P. Borgeat and B. Samuelsson, J. Biol. Chem., 254, 2643 (1979).

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4. For nomenclature of leukotrienes see B. Samuelsson and S. Hammarström, Prostaglandins, 19, 645 (1980).

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6. (a) E. J. Goetzl, New Engl. J. Med., 303, 822 (1980); (b) R. A. Lewis, N. A. Soter, E. J. Corey and K. F. Austen, Clin. Res., in press.

7. E. J. Corey, A. Marfat, G. Goto and F. Brion, J. Am. Chem. Soc., 102, (Dec., 1980).

8. E. J. Corey, P. B. Hopkins, J. E. Munroe, A. Marfat and S. Hashimoto, ibid., 102, (Dec., 1980).

9. Previously synthesized in these laboratories (ref. 8) by enantioselective epoxidation (93% ee) of undeca-2,5-dien-1-ol.[10]

10. E. J. Corey, A. Marfat and G. Goto, J. Am. Chem. Soc., 102, 6607 (1980).

11. This phosphonium salt (m.p. 154-157° dec.) was prepared in >95% yield by stirring a fine suspension of 3-hydroxypropyltriphenylphosphonium bromide with a solution of 3 equiv. of 2-methoxypropene and 0.002 equiv. of pyridinium tosylate in 3:1 methylene chloride-2,2-dimethoxypropane (20 ml/g of the phosphonium salt) at -30° until the solid has dissolved (ca. 3 hr), quenching the reaction mixture with triethylamine (3 ml/g of phosphonium salt) and potassium carbonate (4 g/g of phosphonium salt), stirring at 0° for 15 min, filtration, concentration of the filtrate to a colorless solid which was washed with ether and dried.

12. Satisfactory spectroscopic data (^{1}H magnetic resonance, IR, UV and where possible mass) were obtained on a chromatographically homogeneous sample of each intermediate. All organometallic reactions were conducted under an argon atmosphere.

13. After removal of triphenylphosphine oxide by filtration of a hexane-ether soln. of the crude product through a plug of silica gel and removal of solvent.

14. Previous experience indicates that this salt contains at least 97% of the enantiomer required for the synthesis of 1. See, T. Katsuki and K. B. Sharpless, J. Am. Chem. Soc., 102, 5974 (1980), and E. J. Corey, S. Hashimoto and A. E. Barton, ibid., in press.

15. The extraordinary ease of the epoxide → allylic alcohol conversion, 8 → 2 → 1, which requires only the mildly basic potassium carbonate as reagent strongly indicates the operation of the internal rearrangement mechanism implied in expression 2.

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