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TOTAL SYNTHESIS OF SLOW REACTING SUBSTANCES (SRS's): 6-EPI-LEUKOTRIENE C AND 6-EPI-LEUKOTRIENE D

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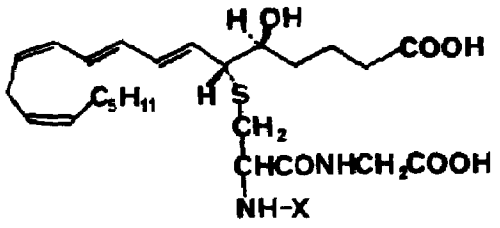
Summary: 6-Epi-leukotrienes C and D (3 and 4) have been synthesized unambiguously via the 5(S), 6(R)-epoxide (5,6-cis) which is isomeric with leukotriene A. These 6-epi-leukotrienes are less active (especially 4) than leukotrienes C and D (1 and 2) and have not been found in substantial quantity in natural SRS sources.

Previous papers from this laboratory have described for the first time the total synthesis of a number of naturally occurring slow reacting substances (SRS's)[1] including leukotrienes C (1) and D (LTC, LTD)[2,3]. As an integral part of this program we have simultaneously carried out unambiguous stereospecific syntheses of 6-epi-LTC (3) and 6-epi-LTD (4) in order to allow rigorous comparison with and proof of structure of the natural leukotrienes in all detail including stereochemistry. We describe herein the route of synthesis of 3 and 4, which is obviously also applicable to other 6-epi-LT's and their analogs. Comparison of the synthetic leukotrienes 1, 2, 3, and 4 (and natural SRS's) is straightforward since 1-4 are readily distinguished by reversed phase high performance liquid chromatography (RP-HPLC). The 6-epi-compounds 3 and 4 have not been detected thus far as naturally occurring SRS's. In principle 3 and 4 might be generated biosynthetically in a number of ways including (a) by 2 successive S_N2 displacements on LTA, (b) by S_N2 displacement on the 5(S), 6(R) isomer of leukotriene A (5,6-cis-LTA), or (c) from LTA by displacement of oxygen with retention (e.g. via a stabilized carbocation). Their absence in SRS sources such as hypersensitized human or guinea pig lung or peritoneal fluid from challanged rats therefore is especially noteworthy.

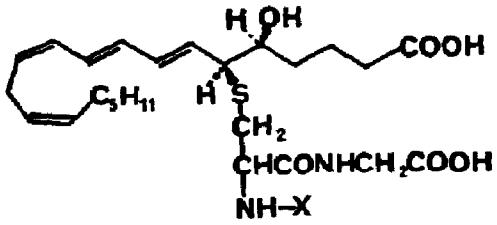
The starting point in the synthesis of 3 and 4 was the readily available bis-acetonide of D-(+)-mannose 5 which was converted to the glycal monoacetonide 6 (78% overall) by known procedure[4] and thence to the t-butyldimethylsilyl ether (7) in 98% yield using 2 equiv. of t-butyldimethylsilyl chloride and 2.5 equiv. of imidazole in dry dimethylformamide at 23° for 48 hr.[5,6] Hydration of 7 to give the corresponding cyclic hemiacetal was effected in one flask (95% yield) by the following process: (1) hydroxy mercuration using 1.1 equiv. of mercuric acetate in 4:1 tetrahydrofuran (THF)-water at 0° for 30 min., and (2) successive reaction of aqueous potassium iodide (5 equiv., 0°, 30 min.) and aqueous sodium borohydride (1 molar equiv., -10°, 5 min.), and the hemi-

acetal was converted in 96% yield to the α,β-unsaturated ester 8 (88:12 mixture of trans and cis) by reaction with 1.1 equiv. of methoxycarbonylmethylenetriphenylphosphorane in dimethoxyethane containing a trace of benzoic acid at 70° for 3 hr.[2b] Hydrogenation of the double bond in 8 (1 atm. hydrogen, platinum catalyst, 23°, 100% yield) followed by tetrahydropyranylation (dihydropyran and pyridinium tosylate in methylene chloride at 23° for 12 hr, 98% yield) and treatment with 2 equiv. of tetra-n-butylammonium fluoride[7] in THF at 23° for 2 hr formed an intermediate δ-lactone (99%) which upon stirring with methanolic triethylamine at 23° for 2 hr provided (99% yield) the hydroxy ester 9.[8] Reaction of 9 with 1.2 equiv. of tosyl chloride in pyridine at 23° for 12 hr gave the tosylate 10 (97%) which was depyranylated to 11 (92%), $[\alpha]_D^{25}$ -19.1° (c = 1.6 in $CHCl_3$), by exposure to a trace of $pyH^+ TsO^-$ in methanol at 23° for 3 hr. Benzoylation of 11 (1.3 equiv. of benzoyl chloride in pyridine at 23° for 4 hr) provided the benzoate tosylate 12, mp 78°, $[\alpha]_D^{25}$ +19.3° (c = 2.0 in $CHCl_3$) (98%). Treatment of 12 with 3% hydrogen chloride in methanol at 23° for 2 hr. cleaved the acetonide to form corresponding 1,2-diol (93%), mp 58°, $[\alpha]_D^{25}$ +12.6° (c = 2.0 in $CHCl_3$) which was reprotected[9] by reaction with 5 equiv. of methyl orthoacetate in methylene chloride containing a trace of tosic acid (23°, 30 min) to give 13 in 99% yield. The protected benzoate tosylate 13 was transformed into the cis-epoxy aldehyde 14 by the sequence (1) reaction with 3 equiv of potassium carbonate in methanol (2 hr., 23°, 96%) to form the cis-epoxide unit, (2) exposure to wet methylene chloride containing a trace of $pyH^+ TsO^-$ (5 min., 23°, 98%) to convert the cyclic orthoacetate to mono acetate (3) deacetylation by 1.1 equiv. of potassium carbonate in methanol (1 hr., 23°, 99%) to form 1,2-glycol, and (4) 1,2-glycol cleavage with 1.05 equiv. of lead tetraacetate in methylene chloride containing 10 equiv. of finely powdered sodium carbonate (-45°, 5 min 98% yield); the aldehyde 14 had $[\alpha]_D^{25}$ -101.3° (c = 1.5 in $CHCl_3$). Chain extension[10] of 14 as previously reported[2b] gave the trans,trans-dienal 15 (55%). Reaction of dienal 15 with an excess of the Wittig ylide 16[2b] in THF-hexamethylphosphoric triamide at -78° afforded in 66% yield the methyl ester of the 5(S), 6(R) isomer of leukotriene A (17), $[\alpha]_D^{25}$ -18.4° (c = 0.5 in cyclohexane), as a colorless oil, UV_{max} 269, 278 (ε = 40,000), 289 nm in CH_3OH.

The epoxy methyl ester 17 was converted to 6-epi-LTC (3)[2b] in two stages:[2b,3] (1) reaction with 2 equiv. of N-trifluoroacetylglutathione dimethyl ester and 3 equiv. of triethylamine in a minimum of methanol at 23° for 3 hr. under argon to give the N-trifluoroacetyl trimethyl ester of 3 (80%) and (2) deprotection with 25 equiv. of 0.05 M potassium carbonate in 4:1 dimethyoxyethane-water at 23° for 4 hr. to afford 3, UV_{max} 270, 281 (ε = 40,000), 290 nm in CH_3OH; RP-HPLC retention volume 7.8 (LTC = 6.4) using a Waters Associates C_{18} u-Bondapak column with 65:35:0.1 CH_3OH-H_2O-HOAc buffered



1 X = γ-glutamyl
2 X = H



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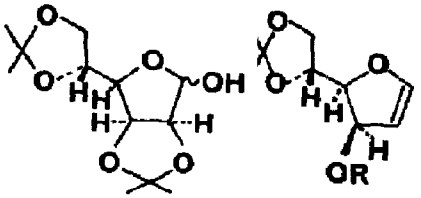
4 X = H



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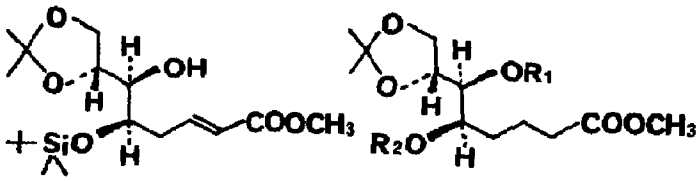
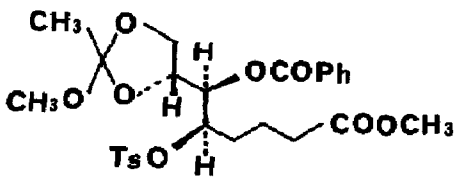
6 R = H
7 R = t-BuMe$_2$Si



8

9 R_1 = THP , R_2 = H
10 R_1 = THP , R_2 = Ts
11 R_1 = H , R_2 = Ts
12 R_1 = COPh , R_2 = Ts



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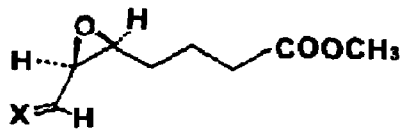
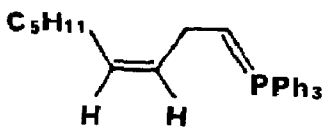


14 X = O
15 X = CH-CH=CHCHO



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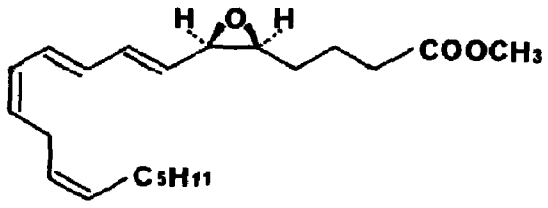

17

to pH 5.6 with 2 M ammonium hydroxide as eluent.

6-Epi-LTD (4) was prepared from 17 in a parallel way using N-trifluoroacetylcysteinylglycine methyl ester,[3] except that the deprotection step was carried out at 23° for 18 hr., for 4: UV_{max} 270, 281 (ε = 40,000), 290 nm in CH_3OH; RP-HPLC retention volume (conditions as for 3, above) 10. (LTD = 9.3).

The biological activity measured as contraction of pulmonary parenchymal strips (guinea pig) was as follows: 6-epi-LTC ca. 1/10 LTC, and 6-epi-LTD ca. 1/500 LTD.[11] Although the 6-epi-leukotrienes 3 and 4 possess SRS-like activity they are considerably less active than the isomers 1 and which are known to occur naturally. Further, no indication that 3 and 4 occur as substantial SRS components has as yet been obtained despite careful RP-HPLC analysis of the various known natural SRS sources.[12]

References and Notes

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