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A STEREOSPECIFIC SYNTHESIS OF A DIHYDROFURAN ANALOG OF LEUKOTRIENE A_4

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Summary: A stereospecific synthesis of a dihydrofuran analog of leukotriene A_4, **3**, starting from (+)-D-mannose (**4**) is described.

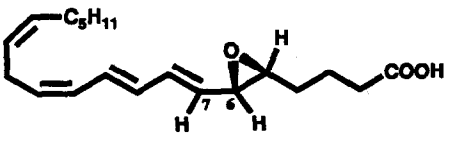
Leukotriene A_4 (LTA_4) (**1**), produced from arachidonic acid in human leukocytes through the action of combined 5-/12-lipoxygenase,[1] is converted enzymatically to leukotriene B_4 (LTB_4) (**2**) and the C(6) glutathione thiol conjugate leukotriene C_4 (LTC_4).[2] The transformation of LTA_4 to LTB_4 has not been duplicated chemically despite the facile epoxide cleavage and hydration of LTA_4, even under neutral conditions. Solvolysis of LTA_4 in various media containing water invariably produces a mixture of (5*S*,6*S*)- and (5*S*,6*R*)-diols and (5*S*,12*S*)- and (5*S*,12*R*)-diols with the *E*-6,8,10-triene arrangement being generated exclusively in the case of the 5,12-diol pair. No significant quantity of LTB_4 or its 12-epimer with the 6*Z*,8*E*,10*E*-triene geometry can be detected by HPLC analysis. It is evident that the enzymic conversion of LTA_4 to LTB_4 involves a reacting conformation of LTA_4 in which the hydrogens at C(6) and C(7) are s-*cis* to one another and that this conformation is unimportant in non-enzymatic hydrolysis of LTA_4, probably because of its higher free energy as compared to the H(6)/H(7) s-*trans* geometry. The dihydrofuran **3**, an isomer of LTA_4 was of interest because of the *s-cis*-like arrangement of H(6)/H(7) and the expected greater stability in aqueous media relative to LTA_4. These properties might enable **3** to function as a stable mimic of LTA_4 in biological systems or as an inhibitor of biosynthesis of LTB_4 from LTA_4. In this report we describe an efficient synthesis of dihydrofuran **3**.

Optically pure allylic alcohol **5** was readily prepared from (+)-D-mannose (**4**) as described by Tipson in 76% overall yield in three steps.[3,4] Conversion of **5** to the key intermediate, dihydrofuran methyl ester **6**,

was achieved in 55% overall yield by a stereospecific Claisen rearrangement[5] brought about by a one-flask reaction sequence in which **5** was treated sequentially in THF with: (1) *n*-butyllithium (1.0 equiv, -78°C, 15 min); (2) acetyl chloride (1.0 equiv, -78°C, 15 min then 0°C, 10 min); (3) lithium diisopropylamide (1.1 equiv, -78°C, 40 min); (4) chlorotrimethylsilane (1.6 equiv, -78°C, 15 min then 23°C, 2.5 h); (5) aqueous 1 *M* sodium hydroxide (3 equiv, 23°C, 1 h); and (6) diazomethane (excess in ether, 0°C, 1 h). Reduction of ester **6** with lithium aluminum hydride (1.5 equiv, THF, 23°C, 1 h) provided primary alcohol **7** in 95% yield. Treatment of **7** in acetonitrile-ether (1 : 3) at 23°C with triphenylphosphine, imidazole and iodine (1 : 1.2 : 1.2 equiv) gave the corresponding iodide **8** in 99% yield.[6] Alkylation of dimethyl sodiomalonate (1.2 equiv) with the iodide **8** in refluxing THF for 2 h yielded dimethyl ester **9** (95%). Decarbomethoxylation of **9** by treatment with sodium cyanide (3 equiv) in dimethylsulfoxide containing 10 equiv of water at 115°C for 2 h resulted in monoester **10** in 90% yield.[7] Hydrolysis of the acetonide **10** (3% HCl in methanol, 23°C, 10 h)[4] followed by oxidative cleavage with sodium periodate (3 equiv)[8] in methanol-pH 7 buffer (2 : 1) at 23°C gave rise to aldehyde **11** in 100% yield. Coupling of **11** with formylmethyltriphenylphosphorane[9] (1.1 equiv, benzene, 80°C, 2 h) produced the unsaturated aldehyde **12** in 81% yield after silica gel chromatographic purification. Treatment of **12** with the ylide generated from nona-3-enyl triphenylphosphonium iodide[10] (1.1 equiv) and *n*-butyllithium (1.1 equiv) in THF at -78°C to 0°C over 2.5 h, extractive workup and silica gel chromatography afforded tetraenic methyl ester **13** in 90% yield.[11] Saponification of **13** with 1 *M* lithium hydroxide (3 equiv) in THF-methanol-water (3 : 1 : 1) at 23°C for 12 h furnished the dihydrofuran derivative **3** in quantitative yield.

The activity of the dihydrofuran analog **3** as an inhibitor of the enzymic synthesis of LTB_4 from LTA_4 was evaluated using an enzyme preparation obtained from broken human leukocytes by (1) centrifugation, (2) precipitation with ammonium sulfate (at 80% of saturation), and (3) dissolution in buffer and dialysis.[12] Only weak inhibition of LTB_4 formation (*ca.* 7%) was observed at 10μM concentration of **3** using an HPLC assay and appropriate controls without **3**.[12,13] Compound **3** was found to be oxidized by soybean lipoxygenase to a 15-hydroperoxy-9,11,13-trienic acid, an interesting analog of pre-lipoxin A.

As expected, compound **3** is much more stable to hydrolysis than LTA_4. It remained unchanged after stirring at 23°C for 3 days in a 0.1 *M* hydrochloric acid solution. Hydrolysis of **3** in THF with 0.1 *M* aqueous perchloric acid at 23°C for 24 h led to formation of a mixture of diols among which LTB_4 could be detected by reversed-phase high performance liquid chromatographic analysis. Various attempts to produce **3** by isomerization of LTA_4 in solvents such as $CHCl_3$ were not fruitful.[14]



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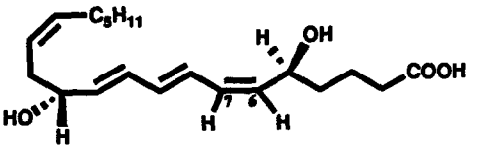

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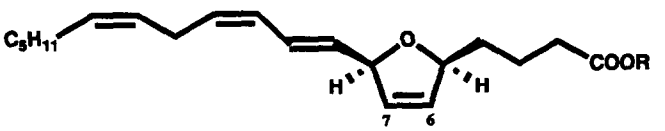
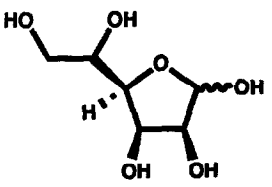


3 R = H

13 R = CH_3



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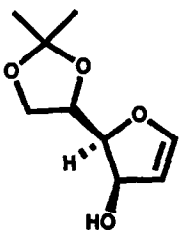

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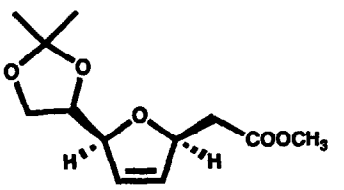

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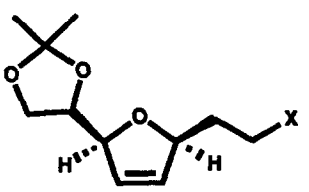
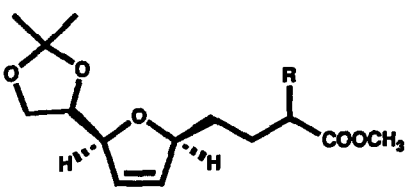


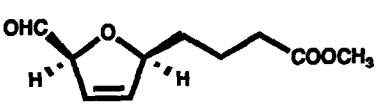
7 X = OH

8 X = I



9 R = $COOCH_3$

10 R = H



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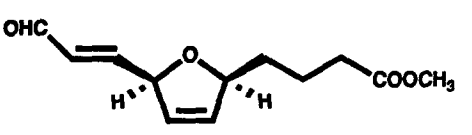

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11. Spectral data for the dihydrofuran methyl ester **13**: ^{1}H-NMR (270 MHz, $CDCl_3$): δ 6.53 (dd, J 15.2, 11.2 Hz, 1 H, H-10), 5.98 (t, J 11.2 Hz, 1 H, H-11), 5.82 (dt, J 5.3, 1.6 Hz, 1 H, H-7), 5.73 (dt, J 0.9, 1.6 Hz, 1 H, H-6), 5.58 (dd, J 15.2, 7.6 Hz, 1 H, H-9), 5.40 (m, 3 H, H-12, 14, 15), 5.20 (m, 1 H, H-8), 4.80 (m, 1 H, H-5), 3.64 (s, 3 H, -$COOCH_3$), 2.92 (t, J 6.9 Hz, 2 H, H-13), 2.36 (t, J 7.3 Hz, 2 H, H-2), 2.04 (m, 2 H, H-16), 1.72 (m, 2 H, H-3), 1.35 (m, 6 H, H-17, 18, 19), 0.89 (t, J 6.7 Hz, 3 H, H-20); ^{13}C-NMR (270 MHz, $CDCl_3$): δ 173.75 (C-1), 133.77, 131.12, 130.85, 130.31, 129.50, 127.72, 127.08, 126.32 (C-6, 7, 9, 10, 11, 12, 14, 15), 86.50 (C-8), 85.69 (C-5), 51.32 ($COOCH_3$), 36.10 (C-13), 34.00 (C-16), 31.51, 29.25, 27.25, 26.12, 22.50, 20.94 (C-2, 3, 4, 17, 18, 19), 13.97 (C-20); IR (neat): 1730 cm^{-1}; UV (methanol): λ max = 235 nm (ε = 22,000); EI-MS: 332 (M^+), 301 (M^+- OCH_3); $[\alpha]_D^{23}$ = -1.2° (c 1.15, chloroform).
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13. Additionally experiments by Prof. C. Serhan (Harvard Medical School) using A23187-stimulated intact PMN cells revealed only weak inhibition of LTB_4 synthesis by **3** at a concentration of 10μM.

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