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Total Synthesis of the Ethanol Inducible, Proinflammatory Autacoid 3(S)-Hydroxy-Leukotriene B_4 (3-OH-LTB_4) and Analogues

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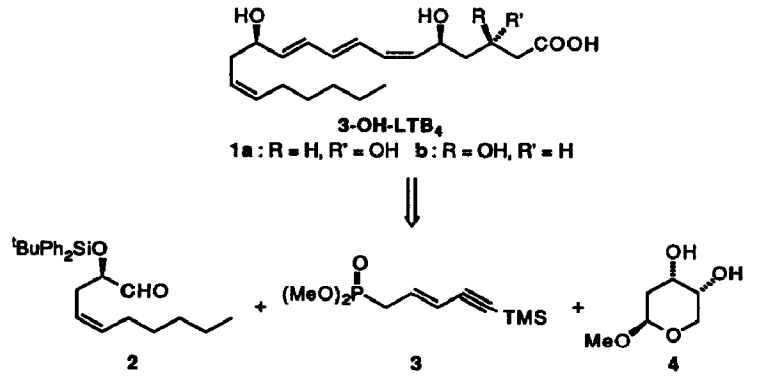
Abstract: 3(S)-Hydroxy-Leukotriene B_4 (**1a**), its 3(R)-epimer **1b**, and a 14,15-acetylenic analogue were efficiently prepared via chelation-controlled reduction of ketone **12**, obtained by acetylide addition to chiral ß-hydroxylactones **7/9**.

Leukotriene B_4 (LTB_4) is an important lipid mediator in inflammatory and immunologic responses.[1] In recent years, considerable attention has been devoted to elucidating its metabolic fate,[2] especially by catabolic processes that result in inactivation.[3] However, Shirley and Murphy[4] observed that low levels of ethanol interfere substantially with the normal ß-oxidation of LTB_4 by hepatocytes *in vitro*, resulting in the accumulation of a new metabolite identified by mass spectroscopy as 3-hydroxy-leukotriene B_4 (3-OH-LTB_4). It is important to note that such doses of ethanol are encountered by even casual consumers of alcoholic beverages. More significantly, 3-OH-LTB_4 retains or transcends the biological profile of the parent autacoid and, thus, may represent the long-sought ethanol inducible chemotactic agent associated with fibrotic and cirrhotic liver degeneration.[5]

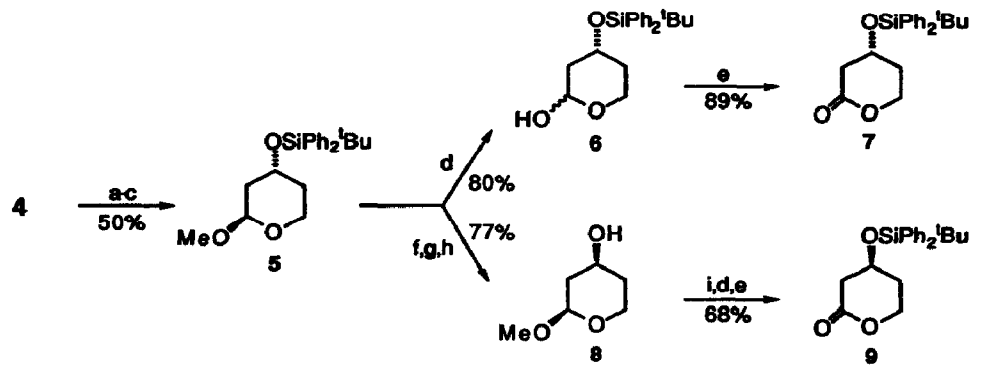
Scheme I



To expedite pharmacologic evaluations of this unique, bioactive secondary metabolite, we describe herein the asymmetric total synthesis of 3(S)-OH-LTB_4 (**1a**), its 3(R)-epimer (**1b**), and a 14,15-acetylenic analogue.[6]

Our approach (Scheme I) was based on a versatile, convergent strategy utilizing the readily accessible precursors **2**, **3**, and **4** which correspond to C(11)-C(20), C(6)-C(10), and C(1)-C(5), respectively.

Scheme II



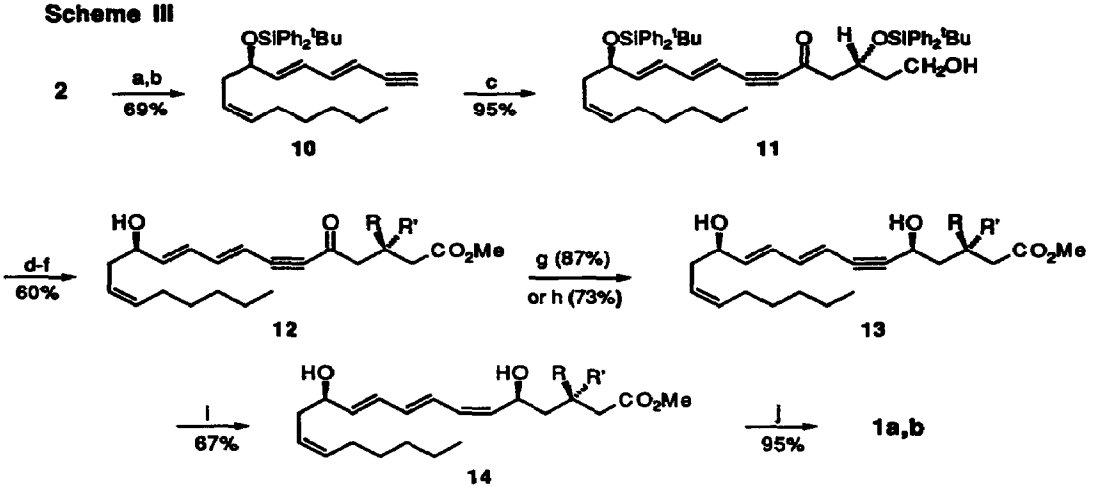
[a] *t*-BuPh$_2$SiCl, AgNO$_3$, C$_5$H$_5$N (5 equiv), CH$_2$Cl$_2$, 23°C, 3 h. [b] Tf$_2$O, C$_5$H$_5$N/CH$_2$Cl$_2$, 0°C, 2 h; DBU (10 equiv), 23°C, 10 h. [c] 10% Pd/C, H$_2$ (1 atm), EtOAc, 23°C, 10 h. [d] HOAc/THF/H$_2$O (1:1:1), 70°C, 14 h. [e] PCC (3 equiv), Al$_2$O$_3$, CH$_2$Cl$_2$, 23°C, 8 h. [f] ^{t}Bu$_4$NF, THF, 23°C, 3 h. [g] PhCO$_2$H/DEAD/Ph$_3$P (2 equiv each), THF, 23°C, 0.5h. [h] NaOMe, MeOH/THF, 23°C, 3 h. [i] *t*-BuPh$_2$SiCl, imidazole, DMAP, DMF, 50°C, 3 h.

Methyl ß-2-deoxy-D-ribopyranoside (**4**)[7] was converted to the pivotal methyl lactol **5**[8] by regioselective silylation[9] of the C(3)-alcohol (Scheme II). Minor amounts (~5-8%) of contaminatory C(4)-silyl ether were easily removed chromatographically after dehydration of the remaining free alcohol and catalytic hydrogenation. Mild acidic hydrolysis afforded lactol **6** from which lactone **7**[10] was obtained by pyridinium chlorochromate (PCC) oxidation. The epimer of **7** was acquired from **5** by desilylation, routine Mitsunobu inversion using benzoic acid, and saponification. Protection of the resultant alcohol **8** followed by hydrolysis and PCC oxidation as described above furnished **9**.

Convergence of the three subunits into the complete carbon framework and final elaboration to 3-OH-LTB$_4$ are outlined in Scheme III. Horner-Emmons condensation of aldehyde **2**[11] with the ylide of **3**[12] at low temperature and selective deprotection of the terminal acetylene led to *trans,trans*-dienyne **10** accompanied by <8% of the *cis,trans*-isomer.[13] Incubation of **10** with *n*-BuLi generated the related acetylide anion that was almost quantitatively acylated with **7**. The resultant adduct, **11**, was oxidized in two-steps using PCC followed by Jones reagent. Esterification with excess diazomethane and subsequent fluoride mediated deprotection ultimately gave **12a**. Chelation controlled reduction of the ketone in **12a** according to Evans[14] afforded a 3:1 diastereomeric mixture[13] of *threo*-diol **13a** and its 5(R)-epimer in 87% combined yield.

Repetition of the foregoing sequence using lactone **9** proceeded analogously and with comparable yields to give **12b**. In this case, however, ketone reduction by the Narasaka protocol[15] was somewhat less stereospecific; *erythro*-diol **13b** and its 5(R)-isomer were isolated as an ~2:1 diastereomeric mixture[13] in 73% combined yield. Rieke zinc reduction[16] of **13a,b** proved highly *cis*-selective and provided convenient access to **14a,b**[13] from which free acids **1a,b** could be prepared by saponification.

Scheme III



a : R = H, R' = OH **b** : R = OH, R' = H

[a]3, $LiN(SiMe_3)_2$, THF, -78°C to -20°C, 1 h; add 2, -78°C to -40°C, THF, 2 h.[b] K_2CO_3, MeOH, 23°C, 3 h.[c] *n*-BuLi, THF, -78°C to -30°C, 1 h; 7, THF, -78°C, 0.5 h.[d] PCC (3 equiv)/Al_2O_3, CH_2Cl_2, 23°C, 2 h.[e] CrO_3/H_2SO_4, Me_2CO, -78°C, 0.5 h; CH_2N_2, 0°C, 0.5 h.[f] Bu_4NF (1 M in THF)/H_2O/HOAc (1:4:2), THF, 45°C, 16 h.[g] $Me_4NHB(OAc)_3$ (10 equiv), CH_3CN/HOAc (1:1), -40°C, 20 h.[h] Bu_3B (1.2 equiv), THF, 23°C, 2 h; $NaBH_4$ (1.2 equiv), THF, -100°C, 4 h; then -78°C, 8 h.[i] Zn(Rieke), THF/H_2O/MeOH (7:1:5), 65°C, 4 h.[j] LiOH, THF/H_2O (3:1), 23°C, 3 h; oxalic acid (pH 4.5).

Additionally, the 14,15-acetylene analog of **1a** was assembled as described above starting with the known[17] acetylenic version of **2**. As expected,[16] only the conjugated, propargylic acetylene underwent hydrogenation with Rieke zinc. By taking advantage of this differential reactivity, it should be possible to site-specifically introduce ^2H- or ^3H-isotope labels for quantitation and metabolism studies. Comparisons[18] of **1a,b** with natural material established the 3(S)-stereochemistry. Results of biological testing will be reported elsewhere.

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10. Spectral and physical data for **7**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.62-7.70 (m, 4H), 7.36-7.55 (m, 6H), 4.55-4.62 (m, 1H), 4.10-4.25 (m, 2H), 2.57 (d, J= 4.8 Hz, 2H) 1.72-1.95 (m, 2H), 1.07 (s, 9H); ^{13}C NMR: δ 169.69, 135.57, 133.05, 130.02, 127.83, 65.16, 64.96, 39.70, 31.50, 26.81, 19.30. $[\alpha]_D^{24}$ + 8.06 (c 2.04, $CHCl_3$). **10**: ^{1}H NMR δ 7.55-7.57 (m, 4H), 7.30-7.40 (m, 6H), 6.50 (dd, J=10.6, 15.6 Hz, 1H), 5.85 (dd, J=2.3, 15.7 Hz, 1H), 5.68 (dd, J=6.2, 15.2 Hz, 1H), 5.35 (dd, J=2.3, 15.7 Hz, 1H), 5.10-5.22 (m, 2H), 4.18-4.20 (m, 1H), 2.93 (d, J=2.3 Hz, 1H), 2.08-2.22 (m, 2H), 1.70-1.92 (m, 2H), 1.10-1.30 (m, 6H), 1.03 (s, 9H), 0.80 (t, J=6.4 Hz, 3H). **12a**: ^{1}H NMR δ 6.88 (dd, J=11.0, 15.6 Hz, 1H), 6.39 (dd, J=11.0, 15.1 Hz, 1H), 6.02 (dd, J=5.3, 15.1 Hz, 1H), 5.72 (d, J=15.6 Hz, 1H), 5.52-5.63 (m, 1H), 5.25-5.40 (m, 1H), 4.48-4.62 (m, 1H), 4.15-4.26 (m, 1H), 3.68 (s, 3H), 3.30 (d, J=3.3 Hz, OH), 2.88 (ddd, J=4.3, 7.2, 16.8 Hz, 2H), 2.54 (d, 6.2 Hz, 2H), 2.39 (t, J=6.8 Hz, 2H), 2.0-2.10 (m, 2H), 1.92 (br s, OH), 1.10-1.22 (m, 6H), 0.85 (t, J=6.6 Hz, 3H); ^{13}C NMR (C_6D_6) δ 184.99, 171.93, 147.96, 143.06, 133.69, 127.99, 124.49, 107.99, 90.95, 90.73, 71.14, 64.56, 51.49, 51.17, 40.59, 35.46, 31.78, 29.61, 27.69, 22.91, 14.25. **12b**: ^{1}H NMR δ 6.88 (dd, J=11.0, 15.6 Hz, 1H), 6.40 (dd, J=11.0, 15.2 Hz, 1H), 6.02 (dd, J=5.3, 15.2 Hz, 1H), 5.71 (d, J=15.6 Hz, 1H), 5.51-6.01 (m, 1H), 5.33-5.40 (m, 1H), 4.54-4.62 (m, 1H), 4.23-4.40 (m, 1H), 3.70 (s, 3H), 3.30 (br s, OH), 2.82 (ddd, J=6.8, 10.7, 15.7 Hz, 2H), 2.57 (d, J=6.3 Hz, 2H), 2.38 (t, J=6.5 Hz, 2H), 1.97-2.10 (m, 2H), 1.95 (br s, OH), 1.20-1.40 (m, 6H), 0.83 (t, J=6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 185.57, 172.34, 147.99, 142.61, 134.57, 128.27, 123.43, 107.89, 91.69, 89.99, 71.13, 64.20, 51.88, 50.99, 40.26, 35.09, 31.45, 29.21, 27.37, 22.51, 14.02. **14a**: ^{1}H NMR ($CDCl_3$) δ 6.50 (dd, J=11.7, 14.1 Hz, 1H), 6.30 (dd, J=10.6, 14.8 Hz, 1H), 6.19 (dd, J=10.7, 14.7 Hz, 1H), 6.05 (t, J=11.2 Hz, 1H), 5.80 (dd, J=6.5, 14.4 Hz, 1H), 5.45-5.66 (m, 2H), 5.30-5.42 (m, 1H), 4.85-4.94 (m, 1H), 4.30-4.40 (m, 1H), 4.17-4.28 (m, 1H), 3.71 (s, 3H), 3.43 (d, J=3.3 Hz, OH), 2.32 (dd, J=1.8, 7.1 Hz, 2H), 2.27 (d, J=4.2 Hz, OH), 2.24-2.40 (m, 2H), 1.95-2.16 (m, 2H), 1.62-1.80 (m, 2H+OH), 1.08-1.20 (m, 6H), 0.84 (t, J=6.6 Hz, 3H); ^{13}C NMR (C_6D_6) δ 172.93, 137.49, 134.78, 134.23, 133.00, 130.27, 129.99, 128.01, 125.63, 71.93, 65.42, 65.40, 51.17, 43.30, 41.50, 35.84, 31.79, 29.67, 27.75, 22.93, 14.26. **14b**: ^{1}H NMR ($CDCl_3$) δ 6.58 (dd, J=11.8, 13.6 Hz, 1H); 6.34 (ddd, J=1.1, 6.0, 10.6 Hz, 1H), 6.22 (dd, J=8.8, 10.6 Hz, 1H), 6.10 (t, J=10.8 Hz, 1H), 5.80 (dd, J=6.3, 14.6 Hz, 1H), 5.50-5.61 (m, 1H), 5.24-5.42 (m, 2H), 4.89 (ddd, J=3.7, 8.8, 12.4 Hz, 1H), 4.18-4.37 (m, 2H), 3.76 (s, 3H), 3.65 (br s, OH), 2.97 (br s, OH), 2.52 (dd, J=1.8, 7.1 Hz, 2H), 2.34-2.40 (m, 2H), 1.88-2.08 (m, 2H), 1.62-1.82 (m, 2H), 1.56 (br s, OH), 1.10-1.42 (m, 6H), 0.84 (t, J=6.6 Hz, 3H); ^{13}C NMR (C_6D_6) δ 172.34, 137.43, 134.71, 134.20, 133.18, 130.06, 129.81, 128.46, 125.60, 71.91, 65.48, 65.41, 51.25, 43.41, 41.58, 35.86, 31.82, 29.68, 27.71, 22.80, 14.02.
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