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Hepoxilins B_3: Synthesis of All Four Stereoisomers and a Glutathione Adduct

Yuri Y. Belosludtsev, R. Ominde Kollah, and J. R. Falck*

Departments of Molecular Genetics and Pharmacology
University of Texas Southwestern Medical Center
Dallas, Texas 75235

Jorge H. Capdevila

Departments of Medicine and Biochemistry
Vanderbilt University Medical School
Nashville, TN 37205

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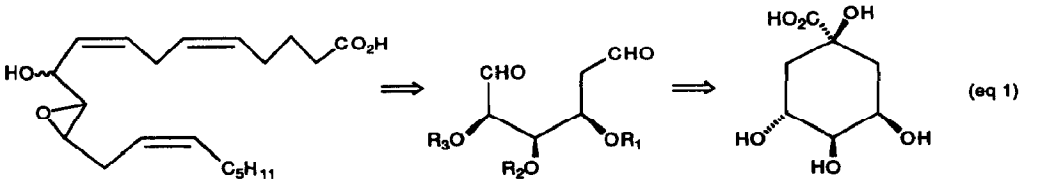
Abstract: Utilizing (-)-quinic acid as a differentiated bis-aldehyde chiron, both pairs of hepoxilin B_3 enantiomers and a glutathione adduct were synthesized by regiospecific functionalization of an acyclic *vic*-diol.

Since its initial isolation in 1979 by Walker et al.,[1] hepoxilin B_3 (HxB_3) (**1**) and related oxiranyl-carbinols have been identified in plants,[2] marine organisms,[3] and several animal species.[4] Generally, **1** occurs as a pair of C(10)-hydroxy diastereomers and, in the case of mammalian tissue, arises from 12(S)-hydroperoxyeicosatetraenoic acid [12(S)-HPETE] via enzymatic[5] and non-enzymatic intramolecular rearrangement.[6] The absolute configuration of **1** isolated from non-mammalian sources is for the most part unknown. *In vivo*, **1** is rapidly hydrated to the corresponding 10,11,12-triol, trioxilin B_3,[7] and is a substrate for glutathione S-transferases[8] in analogy with other fatty acid epoxides.[9]



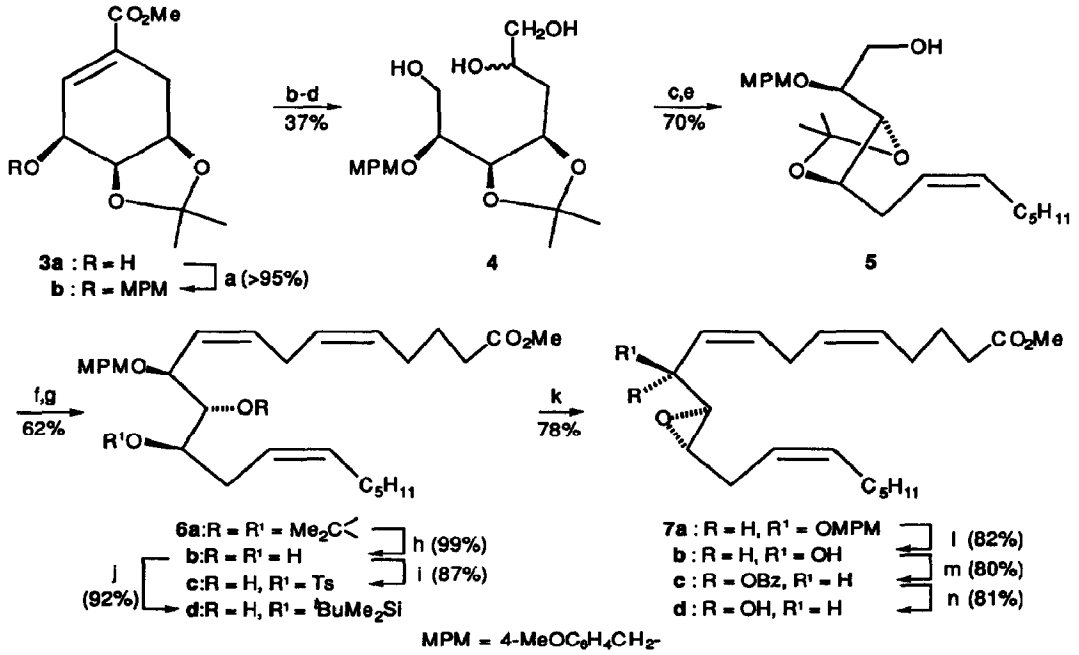
1 (HxB_3) ⟹ **2** [(-)-Quinic Acid] (eq 1)

Arachidonate metabolites from the hepoxilin/trioxilin pathway have garnered considerable attention recently as a consequence of their varied and potent biological effects.[10] As part of a comprehensive synthetic program[11] to expedite the physiologic evaluation and structural elucidation of novel eicosanoids, we report herein a stereocontrolled total synthesis of the four HxB_3 stereoisomers **7b,d** and **10b,c** as well as glutathione conjugate

9b.[12] Our strategy utilized (-)-quinic acid (**2**) as a convenient bis-aldehyde chiron and exploited a highly regiospecific derivatization of an acyclic diol as the key step (eq 1).

Alcohol **3a**, readily available[13] in 57% overall yield from commercial **2**, was protected by trityl cation promoted alkylation with 4-methoxybenzylchlorimidate[14] to give **3b** which was subjected to catalytic osmylation under standard conditions (Scheme 1). Lead tetracetate cleavage of the resultant *vic*-diol and hydride reduction was rewarded with acyclic triol **4**,[15] obtained as a mixture of diastereomers. In practice, the sequence from **3b** to **4** was performed without isolation of intermediates.

Scheme 1

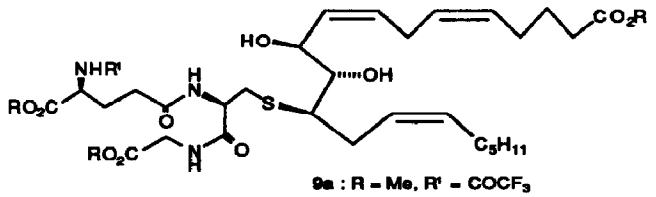


[a]MPMOC(CCl$_3$)=NH, Ph_3CBF_4 (3 mole %), Et_2O, 0°C, 1 h. [b]OsO_4, NMO, Me_2CO/H_2O (3:1), 23°C, 4 h. [c]$Pb(OAc)_4$, Na_2CO_3, CH_2Cl_2, -78°C, 0.25 h. [d]$LiAlH_4$, THF, 23°C, 3 h. [e]$Ph_3PCHC_5H_{11}$ (3 equiv), THF, -78°C, 0.5 h; then, 23°C, 12 h. [f]$(COCl)_2$/DMSO, CH_2Cl_2, -78°C, 1 h; Et_3N, -78° -> 23°C, 0.3 h. [g]**8** (1.1 equiv), THF/$PhCH_3$ (1:3), -78°C, 0.1 h; -40°C, 1 h; 0°C, 0.5 h. [h]0.5% HCl/MeOH, 23°C, 12 h. [i]TsCl (2 equiv), DMAP/Et_3N, CH_2Cl_2, -28°C, 48 h. [j]$Me_2{}^tBuSiCl$ (1.3 equiv), $AgNO_3$ (1.2 equiv), C_5H_5N (5 equiv), THF, -28°C, 4 d. [k]NaOMe, MeOH, 0°C, 3 h. [l]DDQ (1.4 equiv), CH_2Cl_2/H_2O (18:1), 23°C, 3 h. [m]DEAD/Ph_3P/BzOH (1.3 equiv each), PhH, 23°C, 2 h. [n]NaOMe, MeOH, 23°C, 1 h.

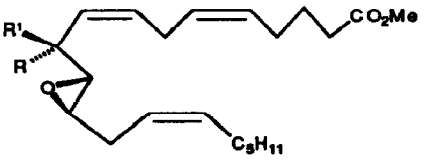
The bis-aldehyde functionality implicit in **4** was accessed sequentially by selective oxidation of the *vic*-diol with $Pb(OAc)_4$ and Wittig olefination using hexylidenetriphenylphosphorane. PTLC (SiO_2, 40% EtOAc/hexane, R_f~0.55) furnished **5**.[16] Swern oxidation of **5** gave rise to the second aldehyde that was homologated to give protected trioxilin **6a** by condensation with 7-carbomethoxyhepta-3(Z)-en-1-ylidenetriphenylphosphorane **8**.[17]

With the basic carbon skeleton complete, final functional group elaboration was initiated by acetonide hydrolysis with dilute acid. The liberated alcohols of **6b** were differentiated by low temperature tosylation affording **6c**. Notably, none of the C(11)-regioisomer was observed under these conditions. Tosylate **6c** was smoothly transformed to 10(S),11(S),12(S)-hepoxilin B_3 methyl ester (**7b**) via MPM ether **7a** by NaOMe induced ring closure and DDQ deprotection. Routine Mitsunobu inversion of **7b** secured the corresponding epimeric C(10)-benzoate **7c** that was solvolyzed to 10(R),11(S),12(S)-hepoxilin B_3 methyl ester (**7d**).

Interestingly, exposure of epoxide **7b** to N-trifluoroacetylglutathione dimethyl ester[18] [3.5 equiv (1.35 M), iPr$_2$NEt (10 equiv), MeOH, 35-40°C, 20h] gave regioisomer **9a** (67%) as the sole product after Sep-Pak® C_{18} isolation and PTLC purification (SiO_2, 8% MeOH/CH_2Cl_2, R_f~0.5). Standard hydrolysis [NaOH, EtOH/H_2O (1:1), 23°C, 16h] provided the unprotected conjugate **9b**.



9a : R = Me, R' = $COCF_3$
b : R = R' = H



10a : R = H, R' = OMPM
b : R = H, R' = OH
c : R = OH, R' = H

The hepoxilin isomers that would evolve from 12(R)-HPETE were also secured from **6b**, but in this instance, by exclusive C(12)-silylation resulting in **6d** (Scheme 1). Mesylation of the remaining C(11)-hydroxyl (MsCl,Et_3N,CH_2Cl_2,-20°C, 0.5h) and fluoride mediated desilylation with concomitant cyclization (Bu_4NF, THF, 23°C, 1h) led to **10a** (31% overall conversion from **6d**). Repetition of the MPM cleavage and C(10)-inversion sequence as described above and with comparable yields provided 10(S),11(R),12(R)- and 10(R),11(R),12(R)-hepoxilin B_3 methyl ester **10b** and **c**, respectively.

Esters **7b**, **7d**, **10b**, and **10c** were converted to their related free acids by saponification (NaOH, MeOH, 23°C, 4h), adjustment to pH 4.5, and extractive isolation.

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16. Spectral and physical data for **5**: ^1H NMR (250 MHz, $CDCl_3$) δ 0.88 (t,3H, J~6.7Hz), 1.25-1.32 (m,6H), 1.35 (s,3H), 1.45 (s,3H), 2.02 (dt, 2H, J~6.5, 7.2Hz), 2.28-2.38 (m,2H), 3.56-3.77 (m,2H), 3.80 (s,3H), 3.86-3.92 (m,2H), 4.16-4.23 (m,2H), 4.43 (d,1H, J~10.7Hz), 4.60 (d,1H, J~10.7Hz), 5.47-5.52 (m,2H), 6.88 (d,2H, J~8.7Hz), 7.25 (d,2H, J~8.7(Hz); ^{13}C NMR (62.5MHz, $CDCl_3$) δ 14.1, 22.6, 25.4, 27.5, 27.8, 27.9, 29.2, 31.6, 55.2, 61.4, 70.9, 76.8, 77.7, 108.1, 113.9, 125.5, 129.5, 129.7, 132.1, 159.4. **6b**: $[\alpha]_D^{23}$ + 16.5° (c 1.3, $CHCl_3$); ^1H NMR: δ 0.88 (t, 3H, J~6.7 Hz), 1.22-1.38 (m, 6H), 1.69 (pent, 2H, J~7.3Hz), 2.01-2.17 (m, 4H), 2.31 (t, 2H, J~7.5 Hz), 2.38-2.43 (m, 2H), 2.82-2.96 (m, 2H), 3.60-3.68 (m, 2H), 3.66 (s, 3H), 3.80 (s, 3H), 4.36 (dd, 1H, J~4.4, 9.5 Hz), 4.30 (d, 1H, J~11.2Hz), 4.55 (d, 1H, J~11.2Hz), 5.35-5.65 (m, 5H), 5.82 (dt, 1H, J~7.5, 11.7Hz), 6.87 (d, 2H, J~8.7Hz), 7.24 (d, 2H, J~8.7Hz);^{13}C NMR: δ 14.0, 22.5, 24.7, 26.3, 26.6, 27.4, 29.3, 31.0, 31.5, 33.3, 51.5, 55.2, 69.8, 72.0, 75.0, 113.8, 124.9, 126.5, 128.1, 129.4, 129.6, 130.1, 133.6, 134.9, 159.3, 174.0. **7b**: $[\alpha]_D^{23}$+72.0° (c1.26, $CHCl_3$); ^1H NMR: δ 0.88 (t, 3H, J~7Hz), 1.23-1.37 (m, 6H), 1.65-1.77 (m, 4H), 1.98-2.15 (m, 4H), 2.32 (t, 2H, J~7.6Hz), 2.20-2.45 (m, 2H), 2.82-2.92 (m,3H), 3.05 (dt, 1H, J~2.2, 5.4 Hz), 3.68 (s, 3H), 4.68 (dd, 1H, J~1.2, 4.2 Hz), 5.30-5.62 (m, 6H); ^{13}C NMR: δ 14.0, 22.5, 24.6, 26.2, 26.5, 27.3, 29.1, 29.2, 31.4, 33.3, 51.5, 54.2, 59.7, 65.0, 122.7, 127.4, 127.9, 129.6, 132.6, 133.3, 174.0. **7d**: $[\alpha]_D^{23}$ -62.3° (c 1.4, $CHCl_3$); ^1H NMR: δ 0.89 (t, 3H, J~6.8 Hz), 1.25-1.38 (m, 6H), 1.70 (pent, 2H, J~7.3Hz), 1.98-2.14 (m, 4H), 2.24-2.46 (m,2H), 2.32 (t, 2H, J~7.4Hz), 2.75-2.96 (m, 3H), 2.98 (dt, 1H, J~2.2, 5.4 Hz), 3.67 (s, 3H), 4.33 (dd, 1H, J~5.1, 7.7 Hz), 5.30-5.62 (m,6H); ^{13}C NMR: δ 14.0, 22.5, 24.6, 26.3, 26.5, 27.3, 29.2, 29.3, 31.4, 33.3, 51.5, 56.0, 60.8, 67.6, 122.7, 127.85, 127.9, 129.7, 132.2, 137.4, 174.0. **9a**: ^1H NMR δ 0.88 (t, 3H, J~6.5Hz), 1.23-1.40 (m, 8H), 1.70 (pent, 2H, J~7.3Hz), 2.04-2.25 (m, 6H), 2.33 (t, 2H, J~7.3 Hz), 2.35-2.42 (m, 2H), 2.60-3.20 (m, 4H), 3.67 (s, 3H), 3.76 (s, 3H), 3.79 (s, 3H), 3.98-4.06 (m, 2H), 4.57-4.60 (m, 3H), 5.38-5.60 (m, 6H), 6.96-7.04 (m, 1H), 7.15 (br s, 1H), 8.10-8.30 (br s, 1H); ^{13}C NMR: δ 14.0, 22.6, 24.6, 26.4, 26.5, 27.1, 27.5, 29.3, 29.7, 31.6, 31.7, 32.6, 33.3, 41.3, 48.9, 51.6, 52.4, 52.5, 52.8, 53.0, 68.2, 75.7, 126.8, 128.1, 129.0, 129.7, 132.6, 133.4, 169.8, 170.2, 170.8, 172.2, 172.6, 174.4; MS (FAB, glycerol) m/z (%): 782 (11, M^+), 764(17), 675(15), 647(16), 554(18), 465(25).
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