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SYNTHESIS OF RACEMIC 11,12-CYCLOPROPYL ANALOGS OF HEPOXILINS A_3 AND B_3

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Summary: Stable biologically active racemic 11,12-cyclopropyl analogs of hepoxilins A_3 and B_3 were prepared via polyacetylenic intermediates.

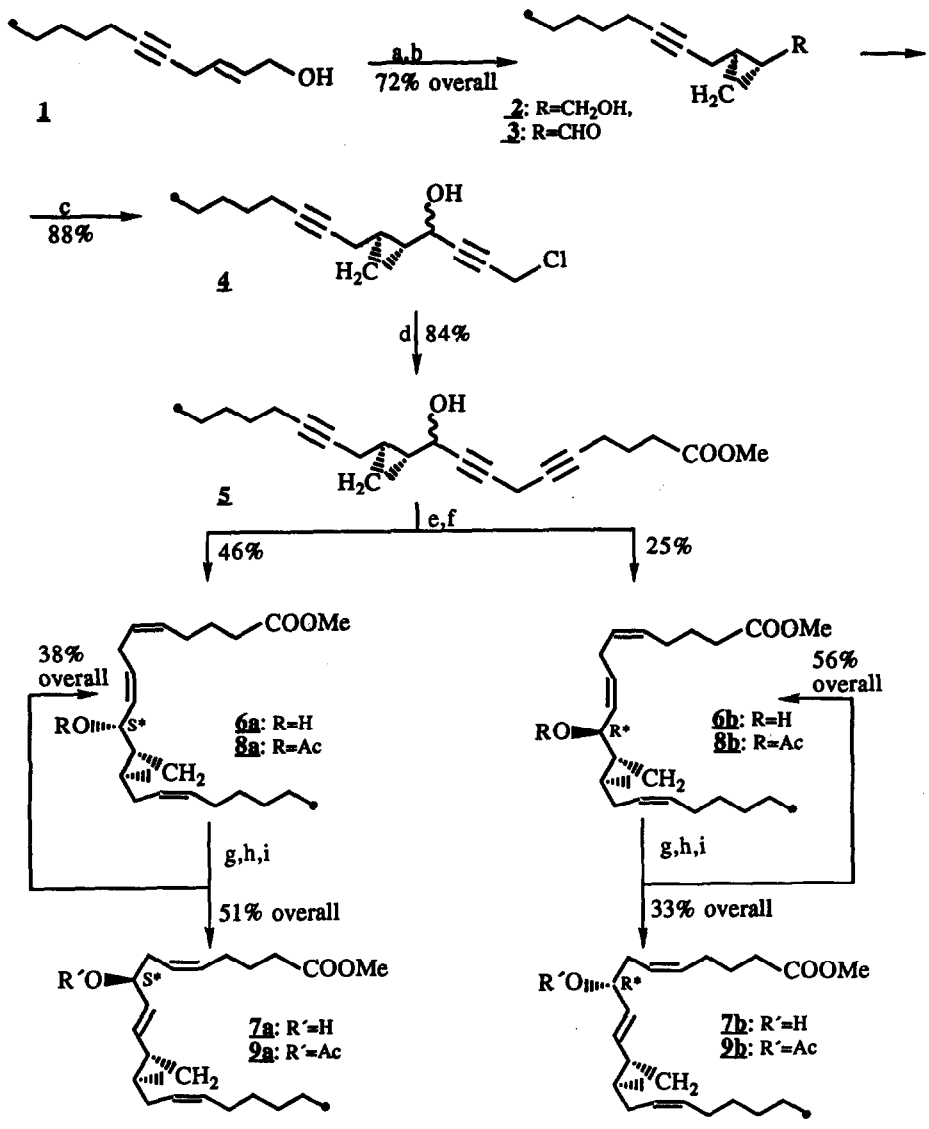
Hepoxilins (Hx) A_3 and B_3 are naturally occurring biologically active metabolites of 12(S)-HPETE.[1] They have been shown to stimulate insulin secretion,[2a,2b] Ca^{2+} transport across membranes[2c] and to mobilize Ca^{2+} from intracellular stores in human neutrophils.[2d] Additional studies have shown that HxA_3 increases vascular tone[2e,2f] and vascular permeability.[2g] HxA_3 appears to affect second messenger systems in the neutrophil releasing arachidonic acid and diacylglycerol.[2h] Hepoxilins have also been implicated in neurotransmission with actions on mammalian[2i] and Aplysia neurons.[2j] HxA_3 is relatively unstable biologically and chemically and can be metabolized into the corresponding trioxilins[3] or peptido-hepoxilins[4] by enzymatic mechanisms, the latter also possessing biological activity.[2k]

Total chemical synthesis of native hepoxilins has been reported by several laboratories,[5,6] which has afforded sufficient material for biological testing. In this connection, structural analogs of Hx which selectively modulate Hx actions may provide compounds through which the putative role of Hx may be investigated. Our approach has been to modify the unstable allylic epoxide group of HxA_3 through replacement with a cyclopropyl group to render it chemically and metabolically stable.

We describe herein the synthesis of stable racemic 11,12-cyclopropyl analogs of hepoxilins: methyl 8-hydroxy-11,12-cyclopropyl-5(Z),9(E),14(Z)-eicosatrienoate (ΔHxA_3) and methyl 10-hydroxy-11,12-cyclopropyl-5(Z),8(Z),14(Z)-eicosatrienoate (ΔHxB_3) based on the acetylenic approach to eicosanoids.[6b,7]

1-Hydroxyundeca-2(E)-en-5-yne **1**, which serves as key intermediate in the synthesis of native hepoxilin B series[6a,b] is employed herein to synthesize Hx analogs. It was prepared as described.[6b] **1** was treated with CH_2I_2 and Zn-Cu couple in dry ether giving racemic (2S*,3S*)-2,3-cyclopropylalcohol **2**; the latter was then oxidized to aldehyde **3** with pyridinium dichromate (see Scheme). Two subsequent condensations of aldehyde **3** with Li-derivative of propargyl chloride led to cyclopropylcarbinol **4**. ^{1}H-NMR spectrum showed a 7:3 ratio between two diastereomers. Chloride **4** was reacted with methyl hexynoate in the presence of equimolar amounts of CuI and NaI in DMF resulting in the triacetylenic analog of ΔHxB_3 **5** obtained as a unseparable mixture with the same epimeric ratio. Selective Lindlar hydrogenation of triacetylene **5** and separation by HPLC gave two C10-epimers of more and less polar ΔHxB_3 methyl esters

Scheme



[a] CH_2I_2, Zn(Cu), ether, 1h, reflux. [b] $Py_2H_2Cr_2O_7$, CH_2Cl_2, 30 min, 20°C. [c] $HC{\equiv}CCH_2Cl$, n-BuLi, ether, -78°C, 15 min, than H_2O. [d] $HC{\equiv}C(CH_2)_3COOMe$, CuI,NaI, K_2CO_3, DMF, 10 h, 20°C. [e] H_2, Pd/Pb/$CaCO_3$, C_6H_6, quinoline. [f] Ac_2O, Py, 10 h, 20°C. [g] $PdCl_2(MeCN)_2$, THF, 3 h, 20°C. [h] NaOH, MeOH/H_2O (2:1), 5 h, 20°C. [i] CH_2N_2, ether

6a,b in 7:3 ratio as a colorless oil. The same ratio between more and less polar epimers was obtained for native HxB_3 methyl esters when similar condensations of appropriate aldehyde with Li-derivative of terminal acetylene were used.[6b,7] On this basis we expected the same relative configuration for more and less polar ΔHxB_3 as for native HxB_3. This proposition was confirmed by the consideration of NMR spectra of individual ΔHxB_3 methyl esters **6a, 6b**. NMR spectra had shown larger coupling constant $J_{10,11}$ for more polar epimer (d, 7.8 Hz) than for less polar epimer (d, J 7.3 Hz).[8] These data were in agreement with those described for α,β-cyclopropylcarbinolic systems.[9] Also oxidation of both fully saturated ΔHxB (ΔHxB_0) epimer and native saturated HxB (HxB_0) by pyridinium dichromate into a corresponding ketone followed by treatment of the latter with sodium borohydride resulted in a mixture of initial α,β-cyclopropyl- and α,β-epoxycarbinols, respectively in 1.7:1 ratio between less and more polar epimers in both cases. This ratio was similar to that described for reduction of α,β-epoxyketones to α,β-epoxycarbinols by $NaBH_4$ with preference of *erythro*-epoxycarbinol.[10] On this basis, we concluded that the more polar ΔHxB_3 epimer **6a** has *threo* or *syn* or (10S*,11R*,12S*)-configuration and the less polar epimer of ΔHxB_3 **6b** has *erythro* or *anti* or (10R*,11R*,12S*)-configuration.[11]

To obtain the two C8-epimeric ΔHxA_3 methyl esters **7a,b** we used the stereo controlled rearrangement of allylic acetates catalyzed by Pd(II).[12] Treatment of individual ΔHxB_3 acetates **8a, 8b** obtained from **6a, 6b** with 0.1 eqv. of $PdCl_2(MeCN)_2$ in THF led to the mixtures of ΔHxB_3 and ΔHxA_3 acetates **8a, 9a** and **8b, 9b** in ca. 1:1 ratio in both cases which could be separated from each other by HPLC.[13] Following hydrolysis, two individual C8-epimers of ΔHxA_3 **7a, 7b** were obtained. On the basis of an S_N2' reaction mechanism[12] we refer to the more polar ΔHxA_3 (obtained from *anti* ΔHxB_3) as *syn* or (8R*,11S*,12S*)-epimer **7b**, and less polar ΔHxA_3 as *anti* or (8S*,11S*,12S*)-epimer **7a**, respectively. The chromatographic properties of ΔHxA_3 methyl esters **7a, 7b** were also similar to native HxA_3 methyl esters with known relative configuration.[14]

Preliminary biological testing has shown that the more polar isomers of ΔHxA_3 and ΔHxB_3 dose-dependently (0.05-0.5μg/ml) inhibit the rise in free intracellular Ca^{2+} in human neutrophils evoked by 3μg/ml of HxA_3.[15] Details of these studies will be reported fully at a later time.

References and Notes

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8. Chromatographic and spectral data for **6a**: R_f 0.39 (C_6H_6-Et_2O, 85:15, 3 developments). Mass-spectrum, t-BDMS-derivative (m/z, % of related intensity): 462 ([M]$^+$, 0.06), 431 ([M - OMe]$^+$, 0.80), 405 ([M - t-Bu]$^+$, 37), 324 ([C1-C11]$^+$, 20), 211 (12), 169 (12), 105 (21), 75 (100). **6b**: R_f 0.51 (C_6H_6-Et_2O, 85:15, 3 developments). Mass-spectrum, t-BDMS-derivative (m/z, % of related intensity): 462 (0.04), 431 (0.35), 405 (20), 334 (4.7), 324 (2.8), 215 (4.2), 211 (3.0), 169 (6.0), 105 (26), 75 (100). 1H-NMR spectra (500 MHz) show the difference in signals belong to protons at chiral groups as follows (δ, ppm): **6a**: 0.39 (dt, 1H, J 4.8 and 8.1 Hz, cyclopropyl-H), 0.53 (dt, 1H, J 4.8 and 8.5 Hz, cyclopropyl-H), 0.68 (m, 1H, H^{11}), 0.83 (m, 1H, H^{12}), 3.95 (ddd, 1H, J 1.0, 7.8 and 7.8 Hz, H^{10}). **6b**: 0.33 (dt, 1H, J 5.1 and 8.4 Hz, cyclopropyl-H), 0.43 (dt, 1H, J 5.1 and 8.4 Hz, cyclopropyl-H), 0.81 (m, 2H, H^{11} + H^{12}), 3.97 (ddd, 1H, J 3.0, 7.3, and 7.3 Hz, H^{10}).

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13. ^{1}H-NMR spectra for acetates **9a**,**9b** were identical to each other (500 MHz, δ, ppm): 0.57 (m, 2H, cyclopropyl-H), 0.80, 1.15 (m, 2H, H^{11} and H^{12}), 0.88 (t, 3H, J 6.91 Hz, H^{20}), 1.28-1.32 (m, 6H, H^{17} + H^{18} + H^{19}),1.69 (quintet, 2H, J 7.4 Hz, H^3), 1.99-2.07 (m, 6H, H^2 + H^4 + H^{16}), 2.01 (s, 3H, OAc), 2.32-2.37 (m, 4H, H^7 + H^{13}+$H^{13'}$), 3.67 (s, 3H, COOMe), 5.19 (dt, 1H, J 6.7 and 6.8 Hz, H^6), 5.29 (dd, 1H, J 8.7 and 15.5 Hz, H^{10}), 5.38 (m, 3H, H^5 + H^9+ H^{14} + H^{15}), 5.44 (m, 1H, H^8).

14. Chromatographic and spectral data for **7a**: R_f 0.46 (C_6H_6-Et_2O, 85:15, 3 developments), mass-spectrum, t-BDMS-derivative (m/z, % of related intensity): 431 ([M - OMe]$^+$, 0.18), 405 ([M - t-**Bu**]$^+$, 4.7), 351 ([C^1-C^{12}]$^+$, 0.18), 321 ([C^8-C^{20}]$^+$, 100), 197 (62), 189([C^8-C^{20}] - t-$BuMe_2SiOH$, 17], 171 (27), 75 (79), 73 (83). **7b**: R_f 0.50 (C_6H_6-Et_2O, 85:15, 3 developments), mass-spectrum, t-BDMS-derivative (m/z, % of related intensity): 431 (0.06), 405 (1.0), 351 (0.04), 321 (28), 197 (24), 189 (7.3), 171 (12), 75 (56), 73 (100).

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