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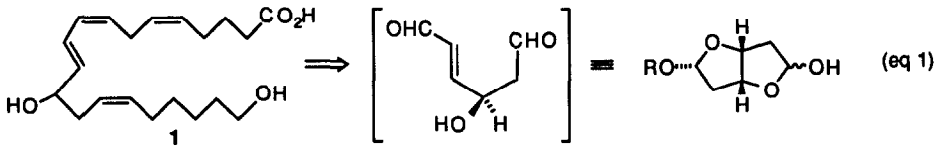
VASOACTIVE EICOSANOIDS: SYNTHESIS OF 12,20-DIHYDROXYEICOSA-5(Z),8(Z),10(E),14(Z)-TETRAENOIC ACID VIA A NOVEL CHIRAL BIS-LACTOL

J. R. Falck,*[1,2] Kamlesh Chauhan,[1] Mark Rosolowsky,[2] and William B. Campbell[2]

Departments of Molecular Genetics [1]and Pharmacology[2]
University of Texas Southwestern Medical Center
Dallas, Texas 75235

Abstract: The type IIB eicosanoids, 12(R),20- and 12(S),20-dihydroxyeicosatetraenoic acid (DiHETE), were conveniently synthesized utilizing a carbohydrate-derived bis-lactol as a differentiated 4–hydroxyhex-2(E)-enedial chiron. 12(S),20-DiHETE, but not the 12(R)-isomer, induced vasodilation in precontracted canine arteries.

The biogenesis of 12-hydroxyeicosatetraenoic acid (12-HETE) in mammals presents a unique paradigm, i.e., arachidonic acid is converted to either 12(S)-HETE by lipoxygenase[1,2] or to its R-antipode by cytochrome P450.[3] Depending on the tissue, both metabolic routes can function concurrently. The enantiomers display qualitatively and quantitatively different pharmacologic profiles,[4] yet both can be converted to 12,20-DiHETE[5] (1) via type IIB[6] transcellular metabolism. Compared to 12-HETE, relatively little is known about the physiological role(s) and the absolute configuration of endogenous **1**. Herein, we describe a convenient synthesis[7] of 12(S),20- and 12(R),20-DiHETE utilizing a carbohydrate-derived bis-lactol as a differentiated 4–hydroxyhex-2(E)-enedial chiron (eq 1) and describe the initial biological evaluation of both antipodes in canine coronary artery.

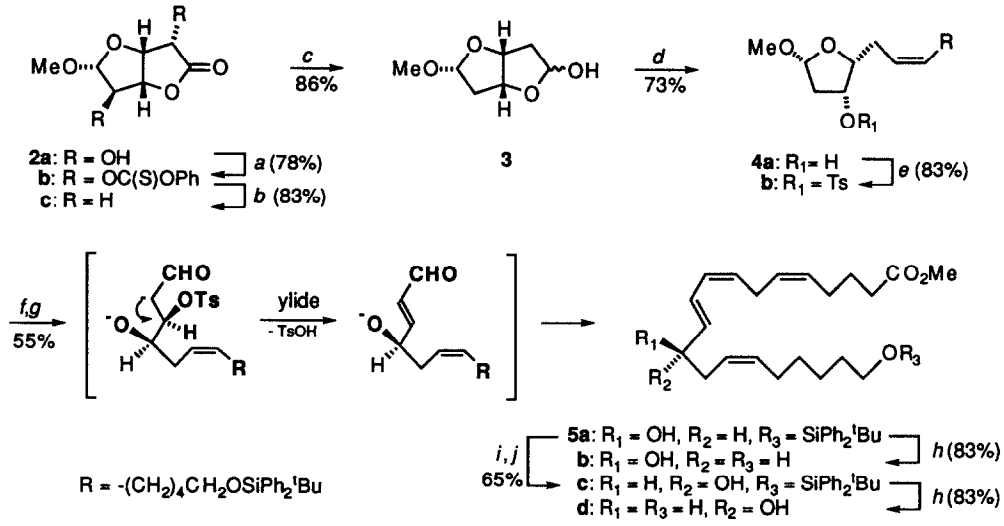


1
(12,20-DiHETE)

(eq 1)

Methyl β-furanoside **2a**, readily obtained[8] from commercial D-glucurono-6,3-lactone in 80% yield, was smoothly deoxygenated by way of its 2,5-bis(phenylthionocarbonate) **2b** (mp 164-66°C) using Bu_3SnH in toluene (Scheme 1).[9] Subsequent low temperature diisobutylaluminum hydride (DIBAL-H) reduction of the resultant lactone **2c**[10] (mp 103-4°C) gave rise to the strategic chiral bis-lactol **3**, whose implicit aldehydes were accessed individually. The first was homologated using 6-(*tert*-butyldiphenylsilyloxy)hexylidenetriphenylphosphorane[11] (**6**) leading to furanoside **4a**. Following tosylation of the newly exposed secondary alcohol, the remaining lactol was unlocked by mild acidic hydrolysis. Final elaboration to complete the eicosanoid carbon skeleton, thus furnishing mono-protected diol **5a**, exploited the rapid, ylide-induced elimination of tosylate from the open-chain tautomer of **4b**.[12] This generated a hydroxy-

Scheme 1



[a]PhOC(S)-Cl, N-hydroxysuccinimide (5 mol %), C_5H_5N/CH_3CN, 60°C, 5 h. [b]Bu_3SnH, AIBN, $PhCH_3$, 80°C, 3 h. [c]DIBAL-H, $PhCH_3$, -78 to 0°C, 2 h. [d]**6** (3 equiv), THF/HMPA/$PhCH_3$ (1:0.8:4), -78 to -20°C, 4 h. [e]TsCl, C_5H_5N/CH_2Cl_2 (1:1), 0 to 23°C, 8 h. [f]AcOH/THF/H_2O (2:1:1), 45°C, 13 h. [g]**7** (3.3 equiv), THF /HMPA (10:1), -20°C, 1 h. [h]Bu_4NF, THF, 23°C, 3h. [i]Ph_3P/DEAD/$PhCO_2H$, PhH, 23°C, 1 h. [j]25% NaOMe /MeOH, THF, 23°C, 0.5 h.

trans-enal intermediate which underwent facile *in situ* Wittig olefination with the remaining 7-carbomethoxyhepta-3(Z)-en-1-ylidenetriphenylphosphorane[12] (**7**). Fluoride mediated deprotection of **5a** afforded methyl 12(R),20-dihydroxyeicosatetraenoate **5b**. Its enantiomer **5d** was secured via **5c** by inversion of the C(12)-alcohol using the Mitsunobu procedure,[13] methanolysis of the derived benzoate, and desilylation as described above. Esters **5b,d** were converted to their free acids by saponification (NaOH, MeOH, 23°C, 4h), adjustment to pH 4.5, and extractive isolation.

Biological Evaluations

Canine polymorphonuclear leukocytes were incubated at 37°C with exogenous arachidonic acid and, following acidification, the incubate was extracted with EtOAc. Analysis of the organic soluble products by HPLC and GC/MS[14] revealed **1** was a major oxygenated metabolite. Natural and synthetic **1** were tested for vasoactivity in canine coronary arteries by monitoring isometric tension of arterial rings suspended in a muscle bath containing Krebs' solution. Both enzymatically-derived and synthetic 12(S)-**1** relaxed the coronary artery. The latter showed a concentration dependent relaxation between 5 x 10^{-9} and 5 x 10^{-6} M in vessels precontracted with U46619 (20 nM). 12(S)-**1** caused a 48±8% relaxation at 5 x 10^{-6} M ($p<0.01$). In contrast, 12(R),20-DiHETE and 12(S)-HETE were without effect whereas 20-HETE contracted coronary arteries under basal tone. These studies indicate that

ω–hydroxylation of 12(S)-HETE or 12–hydroxylation of 20-HETE results in the formation of a vasodilator or, in the latter case, the conversion of a vasoconstrictor into a vasodilator. It would be of interest, consequently, to examine the potential role of 12,20-DiHETE in leukocyte-mediated myocardial reperfusion injury.[15]

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10. Spectral and physical data for **2c**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.03-2.13 (ddd, J=14.5, 6.04 , and 4.88 Hz, 1H), 2.43 (d, J=14.5 Hz, 1H), 2.63 (dd, J=18.7 and 1.39 Hz, 1H), 2.81 (dd, J=18.7 and 7.4 Hz, 1H), 3.32 (s, 3H), 4.91 (br t, J=7.0 Hz, 1H), 5.09 (d, J=4.8 Hz, 1H), 5.11 (br t, J=5.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 37.49, 39.48, 55.35, 78.16, 82.40, 105.46, 175.19; TLC (SiO_2) EtOAc/hexane (3:7), $R_f \approx 0.17$; Anal. calcd for $C_7H_{10}O_4$: C, 53.16; H, 6.37; Found: C, 53.22; H, 6.47. **3** (as mixture of anomers): ^{1}H NMR δ 2.01-2.53 (m, 4H), 2.76 (br s, 1H), 3.38 and 3.49 (s, total of 3H) 4.72-5.03 (m, 2H), 5.08-5.13 (m, 1H), 5.45-5.56 and 5.71-5.79 (m, total of 1H). **4a**: ^{1}H NMR δ 1.05 (s, 9H), 1.28-1.41 (m, 4H), 1.44-1.62 (m, 2H), 1.92-2.18 (m, 4H), 2.30-2.58 (m, 2H), 2.78 (d, J=11.4 Hz, 1H), 3.32 (s, 3H), 3.62 (t, J=6.4 Hz, 2H), 3.88 (dt, J=3.7 and 7.4 Hz, 1H), 4.06-4.17 (m, 1H), 4.99 (d, J=3.8 Hz, 1H), 5.39-5.57 (m, 2H), 7.28-7.38 (m, 6H), 7.59-7.65 (m, 4H); ^{13}C NMR δ 19.22, 25.53, 26.86, 27.40, 28.89, 29.42, 32.50, 41.48, 54.69, 64.31, 71.25, 85.16, 105.32, 125.17, 127.56, 129.47, 132.23, 134.14, 135.56. **5b,d**: ^{1}H NMR δ 1.32-1.48 (m, 4H), 1.50-1.75 (m, 4H), 2.00-2.23

(m, 4H), 2.28-2.40 (m, 5H), 2.91 (br t, J=7.5 Hz, 2H), 3.58 (t, J=7.2 Hz, 2H) 3.62 (s, 3H), 4.00-4.34 (m, 1H), 5.33-5.62 (m, 5H) 5.72 (dd, J=15.1 and 5.3 Hz, 1H), 5.97 (br t, J=11.0 Hz, 1H), 6.62 (dd, J=15.1 and 11.0 Hz, 1H).

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