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vic-Diol Chirons: Enantiospecific Synthesis of 11,12- and 14,15-Dihydroxyeicosatrienoic Acids

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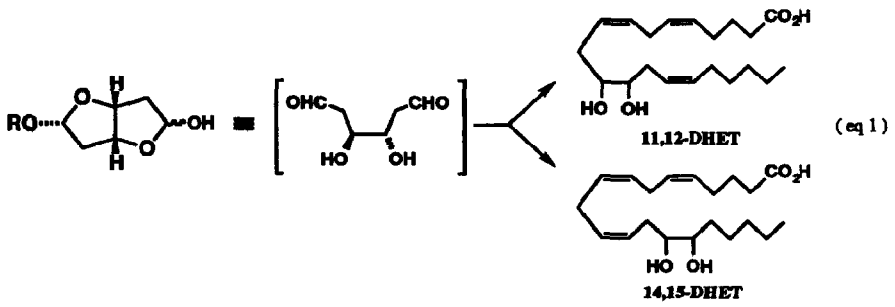
Abstract: A differentiated, six-carbon *vicinal*-diol chiron was prepared from D-glucurono-6,3-lactone and exploited in the asymmetric synthesis of the *erythro/threo*-isomers of the title eicosanoids.

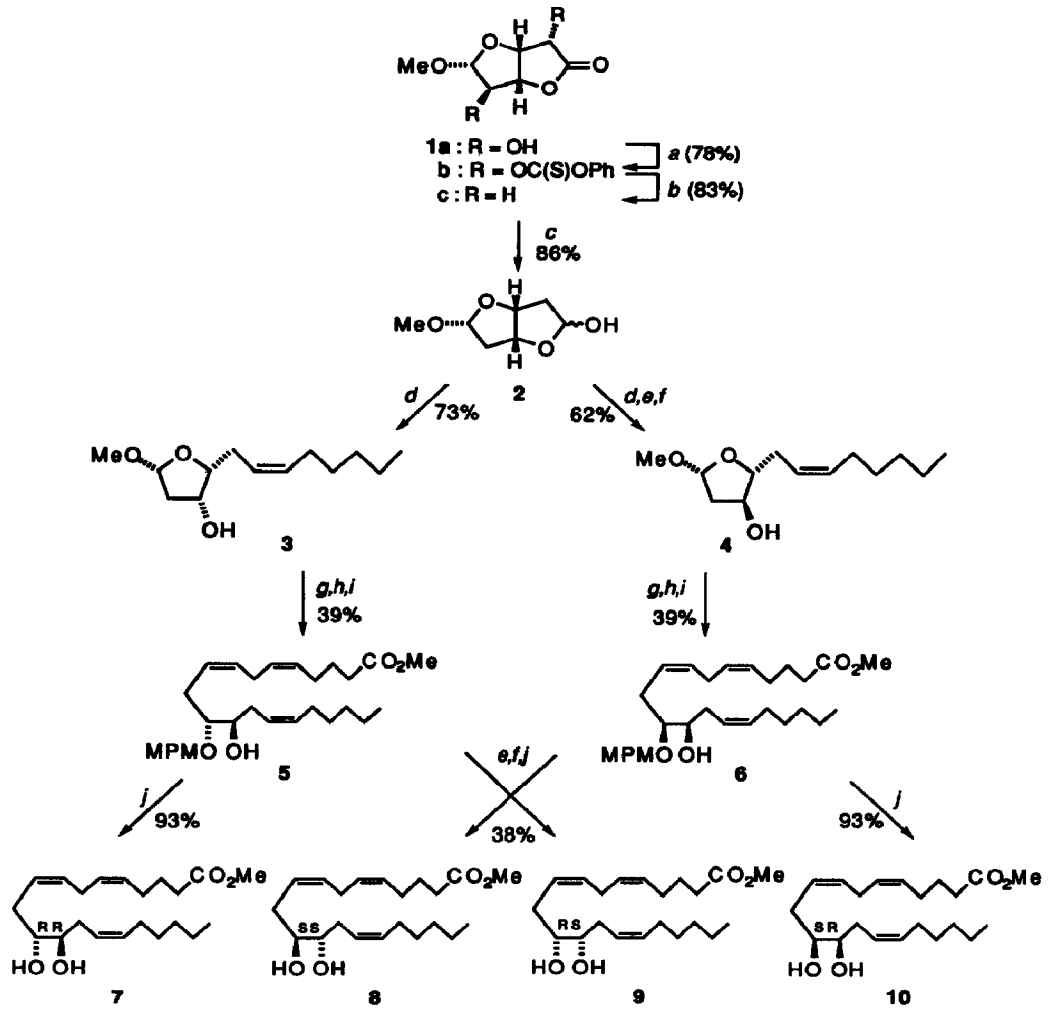
Cytochrome P450 mediated[1] oxidation of arachidonic acid generates, *inter alia*, four regioisomeric epoxyeicosatrienoic acids (EETs) which are rapidly hydrated by cytosolic epoxide hydrolases[2] to the corresponding *vic*-dihydroxyeicosatrienoic acids (DHETs). Compared to their antecedents, the EETs, relatively little is known regarding the physiological role(s) and metabolic fate of the DHETs. They do, however, display potent *in vitro* biological activities[3] and since their levels *in vivo* are dramatically elevated during preeclampsia[4] and salt loading,[5] the DHETs may be relevant to the etiology of hypertension. As part of current studies to elucidate the absolute configurations[6] of the endogenous DHETs as well as to facilitate SAR studies, we describe herein the preparation of a differentiated, chiral bis-lactol from a readily available carbohydrate. The utility of this chiron for the preparation of optically active *vic*-diols was demonstrated during syntheses of the *erythro*- and *threo*-isomers of 11,12- and 14,15-DHET (eq 1).[7,8]



(eq 1)

Methyl ß-furanoside (**1a**),[9] obtained in 80% yield from commercial D-glucurono-6,3-lactone, was smoothly deoxygenated by way of its 2,5-bis(phenylthionocarbonate) **1b** (mp 164-66°C) using the Barton stannyl hydride procedure[10] (Scheme 1). Subsequent low-temperature diisobutylaluminum hydride (DIBAL-H) reduction of the resultant lactone **1c**[11] (mp 103-4°C) produced the strategic chiral bis-lactol **2**. Of the two aldehydes implicit

Scheme 1

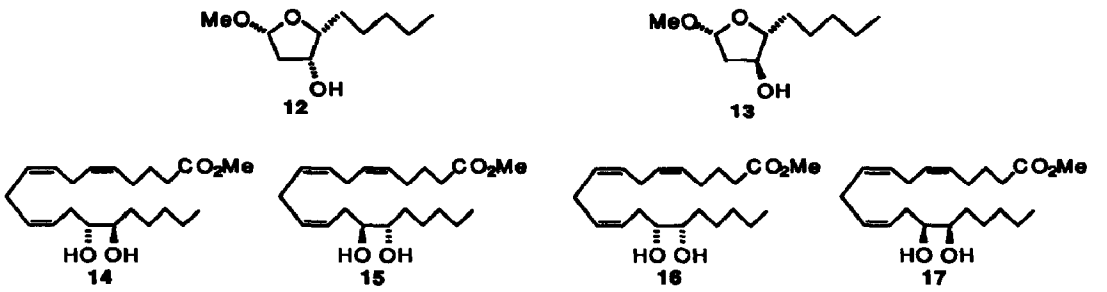


[a]PhOC(S)-Cl, *N*-hydroxysuccinimide (5 mol %), C_5H_5N/CH_3CN, 60°C, 5 h. [b]Bu_3SnH, AIBN, $PhCH_3$, 80°C, 3 h. [c]DIBAL-H, $PhCH_3$, -78° to 0°C, 2 h. [d]$C_5H_{11}CH{=}PPh_3$, THF/HMPA/$PhCH_3$ (1 : 0.6 : 4), -78° to -20°C, 2 h. [e]DEAD/Ph_3P, 4-$(NO_2)C_6H_4CO_2H$, C_6H_6, 23°C, 12 h. [f]NaOMe, MeOH/THF, 23°C, 0.5 h. [g]4-$(MeO)C_6H_4CH_2Cl$/KH, THF, 0° to 23°C, 1 h. [h]THF/H_2O/HOAc (1 : 2 : 2), 60°C, 4 h. [i]11, THF/$PhCH_3$ (1 : 3), -78° to 0°C, 2 h. [j]15% HCl/MeOH, 0° to 23°C, 2 h.

in 2, only one was available for Wittig *cis*-olefination using hexylidenetriphenylphosphorane to give furanoside 3. Final elaboration to complete the basic carbon skeleton required protection of the free secondary alcohol in 3 as a 4-methoxybenzyl (MPM) ether and mild acidic hydrolysis of the methyl lactol. Repetition of the Wittig coupling, this time with 7-carbomethoxyhepta-(3Z)-en-1-ylidenetriphenylphosphorane (**11**),[12] afforded the mono-protected

threo-diol **5**. The isomeric *erythro*-diol **6** was prepared, also from **2**, by sequential Mitsunobu[13] inversion of **3**, saponification of the epimeric benzoate to give furanoside **4**, and olefination after lactol hydrolysis as described for **5**.

Direct deprotection of **5** and **6** using methanolic HCl gave rise to (11R),(12R)- and (11S),(12R)-DHET methyl esters, **7** and **10**, respectively. Their enantiomers **8** and **9**, respectively, were secured by inversion of the C-12 alcohol using the Mitsunobu procedure, methanolysis of the derived benzoate, and MPM ether cleavage.



Minor modification of the above strategy allowed ready access to the other regioisomeric DHETs. For instance, elaboration of **2** with propylidenetriphenylphosphorane followed by catalytic hydrogenation (H_2, Pd/C, MeOH, 2.5 h; 90%) gave rise to furanosides **12** and **13**. Their further transformation to **14-17**, the four *erythro*/*threo*-isomers of 14,15-DHET methyl ester, similarly paralleled the protocols in Scheme 1, except the final Wittig reaction was conducted with 10-carbomethoxydeca-(3Z),(6Z)-dien-1-yltriphenylphosphorane.[14]

Esters **7-10** and **14-17** were converted to their free acids by saponification (NaOH, MeOH, 23°C, 4 h), adjustment to pH 4.5, and extractive isolation.[15]

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11. Spectral and physical data for **1c**: ^{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=0.17. Anal. calcd for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 53.22; H 6.47. **2** (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). **3**: ^{1}H NMR δ 0.89 (t, J=6.6 Hz, 3H), 1.22-1.45 (m, 6H), 1.93-2.23 (m, 4H), 2.35-2.51 (m, 2H), 2.82 (d, J=1.4 Hz, 1H), 3.31 (s, 3H), 3.91 (dt, J=3.6 and 7.3 Hz, 1H), 4.12 (dt, J=12.8 and 7.03 Hz, 1H). 5.00 (d, J=3.80 Hz, 1H), 5.39-5.63 (m, 2H); ^{13}C NMR δ 13.4, 21.9, 26.7, 28.3, 28.7, 30.9, 40.9, 54.2, 70.9, 84.3, 104.0, 124.4, 131.8; $[\alpha]^{23}_D$-102.3° (c 2.05, $CHCl_3$). **4**: ^{1}H NMR δ 0.89 (t, J=6.58 Hz, 3H), 1.22-1.47 (m, 6H), 1.69 (d, J=4.9 Hz, 1H), 2.03-2.23 (m, 4H), 2.38-2.50 (m, 2H), 3.36 (s, 3H), 3.85 (dt, J=4.1 and 7.0 Hz, 1H), 4.28 (dt, J=10.1 and 5.85 Hz, 1H), 5.39-5.55 (m, 2H); ^{13}C NMR δ 13.3, 21.9, 26.5, 28.4, 28.7, 30.9, 40.9, 55.3, 70.1, 87.3, 101.3, 124.4, 131.3; $[\alpha]^{23}_D$ -51° (c 2.3, $CHCl_3$). **7**: ^{1}H NMR δ 0.85 (t, J=6.7 Hz, 3H), 1.22-1.42 (m, 6H), 1.73 (dt, J=14.6 and 7.7 Hz, 2H), 2.03-2.20 (m, 6H), 2.35 (t, J=4.4 Hz, 2H), 2.33-2.41 (m, 4H), 2.81 (br t, J=5.8 Hz, 2H), 3.46-3.58 (m, 2H), 3.71 (s, 3H), 5.30-5.76 (m, 6H); $[\alpha]^{23}_D$+6.3° (c 0.97, $CHCl_3$). **10**: ^{1}H NMR δ 0.88 (t, J=6.6 Hz, 3H), 1.28-1.41 (m, 6H), 1.50-1.62 (m, 2H), 1.70 (dt, J=14.9 and 7.4 Hz, 2H), 1.95-2.16 (m, 6H), 2.20-2.51 (m, 4H), 2.31 (t, J=7.5 Hz, 2H), 2.85 (br t, J=5.5 Hz, 2H), 3.68 (s, 3H), 3.68-3.71 (m, 2H), 5.32-5.69 (m, 6H); $[\alpha]^{23}_D$+2.1° (c 0.57, $CHCl_3$). The isomers **8** and **9** were identical in all respects to their enantiomers **7** and **10**, respectively, except for having opposite sign of rotation. **12**: ^{1}H NMR δ 0.88 (t, J=7 Hz, 3H), 1.25-1.50 (m, 6H), 1.65 (dt, J=8.5 and 6.4 Hz, 2H), 2.01-2.18 (m, 2H), 2.73 (d, J=10.5 Hz, 1H), 3.37 (s, 3H), 3.92 (dt, J=3.7 and 6.9 Hz, 1H), 4.10 (dt, J=11.6 and 3.9 Hz, 1H); 5.00 (d, J=3.97 Hz, 1H); ^{13}C NMR δ 14.04, 22.59, 25.87, 30.62, 31.96, 41.57, 54.52, 71.55, 85.15, 104.38; $[\alpha]^{23}_D$ -124.7° (c 1.9, $CHCl_3$). **13**: ^{1}H NMR δ 0.83 (t, J=7.1 Hz, 3H), 1.21-1.48 (m, 6H), 1.65 (dt, J=8.3 and 6.4 Hz, 2H), 2.00-2.29 (m, 2H), 3.45 (s, 3H), 3.83 (dt, J=3.9 and 6.3 Hz, 1H), 4.31 (br t, J=4.8 Hz, 1H), 5.08 (dd, J=2.5 and 3.0 Hz, 1H); ^{13}C NMR δ 13.99, 22.55, 25.75, 31.72, 34.89, 42.00, 54.99, 75.69, 86.59, 104.36; $[\alpha]^{23}_D$ -60.2° (c 0.7, $CHCl_3$).

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15. The *threo*-diols **7**, **8**, **14**, and **15** were identical by chiral HPLC analysis[6], i. e., co-injection on a Chiralcel OC column, with the methyl esters of enzymatically derived 11,12- and 14,15-DHETs. The erythro-DHETs, which resolve from the *threo*-isomers under these chromatographic condtions, are not generated from the EETs by cytosolic epoxide hydrolases.[6]

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