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Practical, Asymmetric Synthesis of 16-Hydroxyeicosa-5(*Z*),8(*Z*), 11(*Z*),14(*Z*)-tetraenoic Acid (16-HETE), an Endogenous Inhibitor of Neutrophil Activity

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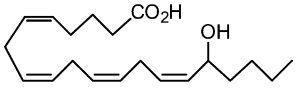
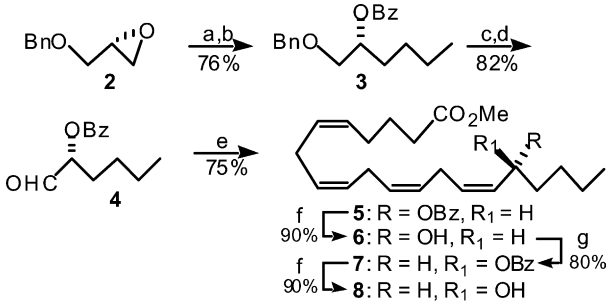
Abstract—An asymmetric synthesis of 16-HETE, an endogenous inhibitor of neutrophil activity, was achieved in six steps from *R*-(−)-glycidyl benzyl ether in 28% overall yield.

16-Hydroxyeicosa-5(*Z*),8(*Z*),11(*Z*),14(*Z*)-tetraenoic acid (16-HETE, **1**),[1] a metabolite of the cytochrome P450 branch of the arachidonate cascade,[2] has attracted considerable attention as a vasodilator[3] and as the first endogenous lipidic inhibitor of human neutrophil adhesion and aggregation.[4] The latter activity may be useful for therapeutic intervention in acute ischemic brain injury.[5] However, progress in exploring the pharmacology of **1** has been trammeled by its limited availability from natural sources[6] and its co-occurrence, in most instances,[7] with structurally similar regioisomers. Herein, we report a practical, asymmetric synthesis[8,9] of both enantiomers of **1**. Importantly, this strategy is amenable to escalation of scale and also provides access to stable- or radio-isotopically labeled **1** without altering the synthetic route.[10]



1 (16-HETE)

In a one pot procedure (Scheme 1), *n*-propyl Grignard was added under copper catalysis to commercial *R*-(−)-glycidyl benzyl ether (**2**) at low temperature and the newly generated alcoholate[11] was quenched with benzoyl chloride affording benzoate **3**.[12] Debenzylation via catalytic hydrogenation and Swern oxidation provided aldehyde **4**.[13] Condensation of **4** with 13-carboxytrideca-3(*Z*),6(*Z*),9(*Z*)-trien-1-ylidenetriphenylphosphorane[10] (**9**) and diazomethane esterification yielded methyl ester **5**.[9] Adduct **5** was most conveniently resolved chromatographically[14] from a minor amount of $\Delta^{14,15}$-*trans* isomer (~5%) following solvolytic conversion to methyl 16(*R*)-HETE (**6**).[8] The enantiomer, methyl 16(*S*)-HETE (**8**), was secured via Mitsunobu inversion of **6** and methanolysis of the resultant benzoate **7**. Saponification (NaOH, THF/H_2O, 23 °C, 6–10 h, 90–95%) of **5**–**8** and extractive isolation furnished the corresponding free acids as colorless oils.



Scheme 1. Reagents and conditions: (a) *n*-PrMgCl, 10 mol% CuCN, THF, −20 to 0 °C, 12 h; (b) PhC(O)Cl, 0–23 °C, 12 h; (c) 10% Pd/C, H_2 (1 atm), EtOAc, 23 °C, 4 h; (d) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, 1 h; Et_3N, −78 to 23 °C, 1 h; (e) **9**, $LiN(SiMe_3)_2$, THF/HMPA (4:1), −78 °C, 1.5 h; CH_2N_2, 1 h; (f) NaOMe, MeOH, 23 °C, 8 h; (g) $PhCO_2H$, DEAD, Ph_3P, THF, 23 °C, 4 h.

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12. ^{1}H NMR (400 MHz, $CDCl_3$) of **3**: δ 0.88 (t, $J=6.6$ Hz, 3H), 1.24–1.42 (m, 4H), 1.70–1.80 (m, 2H), 3.60–3.70 (m, 2H), 4.57 (ABq, $J=10.3$, 29.4 Hz, 2H), 5.32 (quintet, $J=4.4$ Hz, 1H), 7.24–7.34 (m, 5H), 7.45 (t, $J=7.5$ Hz, 2H), 7.56 (t, $J=7.5$ Hz, 1H), 8.06 (d, $J=7.5$ Hz, 2H).
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14. HPLC: microsorb silica (10×250 mm), 0.4% 2-propanol/hexane, 6 mL/min flow rate, UV detection at 206 nm, R_t ~34.5 min.