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Stereospecific synthesis of EET metabolites via Suzuki–Miyaura coupling

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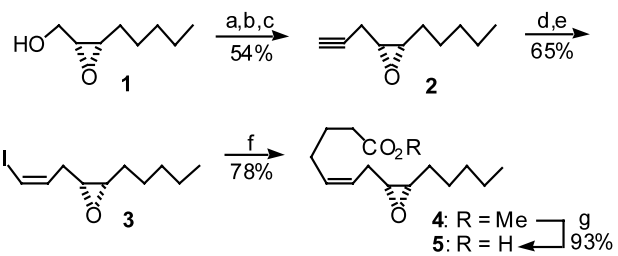
Abstract—Bioactive, chain-shortened EET metabolites, viz. 8,9-epoxytetradec-5(*Z*)-enoic acid and 9,10-epoxyoctadec-6(*Z*),12(*Z*)-dienoic acid, were prepared via Suzuki–Miyaura cross-couplings of *n*-alkylboronic acids with chiral vinyl iodides.

Epoxyeicosatrienoic acids (EETs) are amongst the most widely studied metabolites of the cytochrome P450 branch of the arachidonic acid cascade.[1] They help mediate numerous physiological functions, inter alia, vascular and bronchial smooth muscle tone,[2] cellular proliferation,[3] hormone secretion,[4] fluid and electrolyte transport,[5] and anti-inflammation.[6] Further metabolism by epoxide hydrolases,[7] acyl transferases,[8] and glutathione *S*-transferases[9] as well as additional oxidation by members of the cascade, i.e. cyclooxygenase,[10] lipoxidases, and cytochrome P450,[11] most often abolishes or attenuates biological activity. However, recent studies[12] have identified a novel pathway of secondary EET metabolism resulting in a family of chain-shortened (β-oxidized) metabolites, many of which are bioactive. To expedite their complete structure elucidation, stereochemical analysis, and pharmacological evaluation, we report herein the asymmetric total syntheses of two prominent representatives from this group, viz. 8,9-epoxytetradec-5(*Z*)-enoic acid (**5**) and 9,10-epoxyoctadec-6(*Z*),12(*Z*)-dienoic acid (**10**). Our approach exploited a practical modification of the Suzuki–Miyaura reaction for the efficient cross-couplings of *n*-alkylboronic acids with chiral vinyl iodides.[13]

The preparation of the 14,15-EET metabolite (**5**) commenced with the known[14] chiral epoxide **1** which was readily homologated to acetylene **2** by sequential alcohol to bromide interchange under standard conditions, alkylation with the lithium salt of (trimethylsilyl)acetylene, and KF mediated desilylation (Scheme 1). Iodination of the latter and selective reduction via diimide afforded *cis*-vinyliodide **3**[15] in good overall yield. Ag_2O-promoted[13] Suzuki–Miyaura cross-coupling of **3** with boronic acid **13a** smoothly evolved methyl ester **4**. Acid **5**, obtained by saponification, was identical by HPLC and MS with an authentic biological sample.

Access to the 11,12-EET metabolite **10** followed an almost identical route and in comparable overall yield starting from the known[16] chiral epoxy-alcohol **6** (Scheme 2). Suzuki–Miyaura cross-coupling, in this



Scheme 1. *Reagents and conditions*: (a) CBr_4, Ph_3P, CH_2Cl_2, 0°C, 1 h (80%); (b) TMS–C_2H, *n*-BuLi, THF, 0°C, 2 h; add epoxy-bromide, –40°C to rt, 6 h; (c) KF, MeOH, 60°C, 2 h (68% overall for steps b and c); (d) NIS, $AgNO_3$, Me_2CO, rt, 2 h (81%); (e) $KO_2CN{=}NCO_2K$/AcOH, THF, rt, 12 h (80%); (f) **13a**, Ag_2O (2.4 equiv.), Pd(dppf)Cl_2 (10 mol%), K_2CO_3 (2.4 equiv.), THF, 80°C, 8 h; (g) LiOH, THF/H_2O (4:1), rt, 12 h.

Keywords: eicosanoids; biologically active compounds; lipids; silver; Suzuki–Miyaura.

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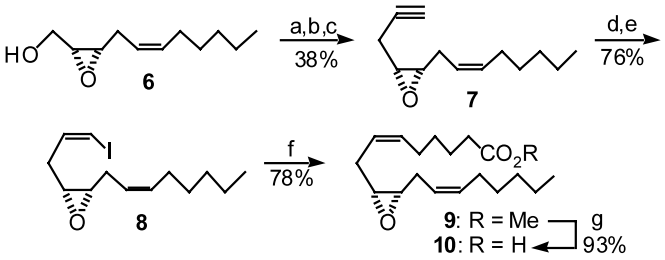
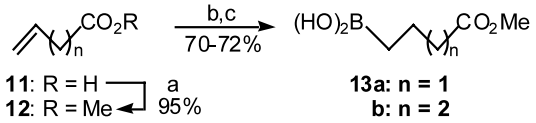


Scheme 2. *Reagents and conditions*: (a) CBr_4, Ph_3P, CH_2Cl_2, 0°C, 1 h (76%); (b) TMS–C_2H, *n*-BuLi, THF, 0°C, 2 h; add epoxy-bromide, –40°C to rt, 16 h (64%); (c) KF, MeOH, 60°C, 2 h (78%); (d) NIS, $AgNO_3$, Me_2CO, rt, 1 h (86%); (e) $KO_2CN{=}NCO_2K$/AcOH, THF, rt, 16 h (88%); (f) **13b**, Ag_2O (2.4 equiv.), Pd(dppf)Cl_2 (10 mol%), K_2CO_3 (2.4 equiv.), THF, 80°C, 8 h; (g) LiOH, THF/H_2O (4:1), rt, 12 h.



Scheme 3. *Reagents and conditions*: (a) MeI, K_2CO_3, Me_2CO, 60°C, 6 h (72%); (b) pinacolborane, $Rh(Ph_3P)_3Cl$, CH_2Cl_2, rt, 12 h; (c) NH_4OAc, $NaIO_4$, Me_2CO/H_2O (2:1), rt, 48 h.

instance, utilized boronic acid **13b**. The antipodes of **5** and **10** were prepared by a brief, stereoselective inversion sequence recently described by Falck et al.[17]

The key boronic acids **13a**,**b** were prepared from the corresponding commercial unsaturated carboxylic acids **11** by hydroboration of the methyl esters **12** with pinacolborane, and mild oxidative hydrolysis (Scheme 3).

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15. Spectral/physical data for **3**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.40 (dt, $J=1.5$, 7.0 Hz, 1H), 6.31 (apparent q, $J=7.0$ Hz, 1H), 3.01–3.07 (m, 1H), 2.91–2.98 (m, 1H), 2.39 (td, $J=7.9$, 1.5 Hz, 2H), 1.28–1.64 (m, 8H), 0.91 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.5, 84.9, 57.1, 54.8, 33.9, 31.7, 27.8, 26.3, 22.6, 14.1. Compound **6**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.44–5.56 (m, 2H), 2.90–2.98 (m, 2H), 2.30–2.40 (m, 3H), 2.15–2.25 (m, 1H), 2.08–2.15 (m, 2H), 1.72 (quintet, $J=7.6$ Hz, 2H), 1.30–1.60 (m, 10H), 0.91 (t, $J=6.7$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.2, 131.4, 125.4, 57.4, 56.7, 51.7, 33.6, 31.9, 27.9, 26.9, 26.4, 24.9, 22.8, 14.2. Compound **8**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.40 (dt, $J=1.5$, 7.0 Hz, 1H), 6.32 (apparent q, $J=7.0$ Hz, 1H), 5.51–5.60 (m, 1H), 5.36–5.47 (m, 1H), 3.01–3.09 (m, 1H), 2.92–3.01 (m, 1H), 2.36–2.50 (m, 1H), 2.20–2.39 (m, 1H), 2.06 (apparent q, $J=7.02$ Hz, 2H), 1.23–1.60 (m, 6H), 0.89 (t, $J=6.7$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.6, 133.3, 123.6, 85.2, 56.6, 55.0, 34.1, 31.7, 29.4, 27.6, 26.5, 22.7, 14.3. Compound **9**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.37–5.59 (m, 4H), 3.67 (s, 3H), 2.89–2.98 (m, 2H), 2.35–2.47 (m, 2H), 2.32 (t, $J=7.6$ Hz, 2H), 2.15–2.27 (m, 2H), 2.01–2.12 (m, 4H), 1.23–1.70 (m, 10H), 0.89 (t, $J=6.7$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.3, 133.1, 132.3, 124.6, 123.9, 56.7, 56.6, 51.7, 34.2, 31.7, 29.4, 29.2, 27.6, 27.3, 26.3, 24.7, 22.7, 14.3. Compound **13a**: ^{1}H NMR (400 MHz, $CDCl_3$+D_2O): δ 3.66 (s, 3H), 2.34 (t, $J=7.0$ Hz, 2H), 1.72 (quintet, $J=7.9$ Hz, 2H), 0.80 (t, $J=7.9$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.4, 51.5, 35.8, 18.9. Pinacol ester of **13b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.65 (s, 3H), 2.31 (t, $J=7.6$ Hz, 2H), 1.63 (quintet, $J=7.4$ Hz, 2H), 1.44 (quintet, $J=7.9$ Hz, 2H), 1.24 (s, 12H), 0.79 (t, $J=8.2$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.9, 82.8, 51.2, 33.8, 27.4, 24.7, 23.6.
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