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A practical, stereospecific route to 18-, 19-, and 20-hydroxyeicosa-5(*Z*),8(*Z*),11(*Z*),14(*Z*)-tetraenoic acids (18-, 19-, and 20-HETEs)

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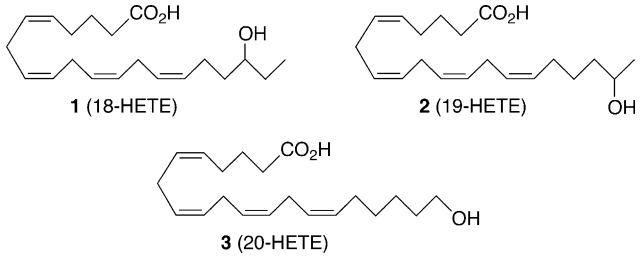
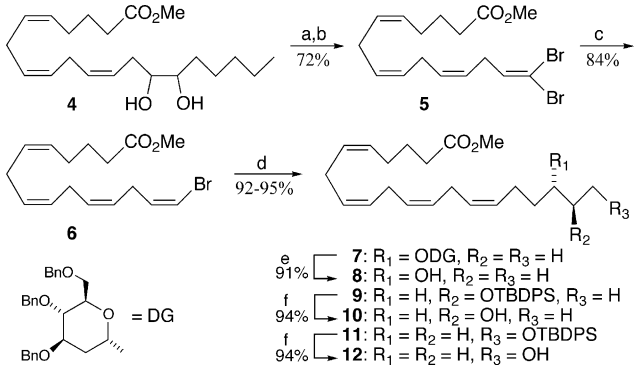
Abstract—Suzuki–Miyaura cross-coupling of *cis*-vinylbromide **6**, obtained in three steps from diol **4**, with functionalized boranes provides a practical, stereospecific route to the title CYP P450 eicosanoids.

Recent investigations have demonstrated that 18-, 19-, and 20-hydroxyeicosa-5(*Z*),8(*Z*),11(*Z*),14(*Z*)-tetraenoic acids (**1**–**3**, respectively), metabolites of the cytochrome P450 branch of the arachidonic acid cascade,[1] are powerful mediators of ion transport[2] and vascular reactivity.[3] Since **1**–**3** are available from natural sources in only minute amounts, several asymmetric total syntheses have been published.[4,5] Notably, all of these approaches utilize a Wittig condensation to generate the critical $\Delta^{14,15}$-olefin. This often affords poor yields and invariably results in mixtures of *cis*/*trans*-isomers that require tedious chromatographic separation. Herein, we describe a convenient, stereocontrolled route to **1**–**3** based on the Suzuki–Miyaura cross-coupling of a readily available *cis*-vinylbromide with suitably functionalized boranes. Our strategy is amenable to large scale operations as well as the preparation of stable- or radio-isotopically labeled products using commercial precursors.



Low temperature cleavage of diol **4**[4a,6] using lead tetraacetate generated a somewhat labile β,γ-unsaturated aldehyde[4g,6] that was subjected to Corey–Fuchs olefination without delay (Scheme 1).[7] Tin hydride reduction[8] of the resultant dibromide **5**[9] provided *cis*-vinylbromide **6** in good overall yield. None of the isomeric *trans*-olefin could be detected by NMR analysis. Subsequent Suzuki–Miyaura cross-coupling[10] of **6** at room temperature with the boranes arising from addition of 9-BBN to olefins **15**, **19**, and **20** smoothly led to adducts **7**, **9**, and **11**, respectively. Mild acidic hydrolysis of **7** afforded methyl 18(*R*)-hydroxyeicosa-5(*Z*),8(*Z*),11(*Z*),14(*Z*)-tetraenoate[4d,f] (**8**) whereas fluoride mediated desilylation of



Scheme 1. Reagents and conditions: (a) $Pb(OAc)_4$, CH_2Cl_2, −20 °C, 40 min; (b) PPh_3, CBr_4, CH_2Cl_2, 0 °C, 2 h; (c) *n*-Bu_3SnH, C_6H_6, $Pd(PPh_3)_4$, 23 °C, 14 h; (d) **15/19/20** (1.5 equiv), 9-BBN-H, THF, 23 °C, 3 h; Cs_2CO_3 (1.5 equiv), Ph_3As (10 mol%), $Pd(dppf)Cl_2$ (15 mol%), THF/DMF/H_2O (1:3.5:0.8), 23 °C, 6 h; (e) PTSA (cat.), MeOH, 65 °C, 6 h; (f) *n*-Bu_4NF (2 equiv), THF, 23 °C, 12 h.

Keywords: Eicosanoids; Suzuki reactions; Lipids; Biologically active compounds.
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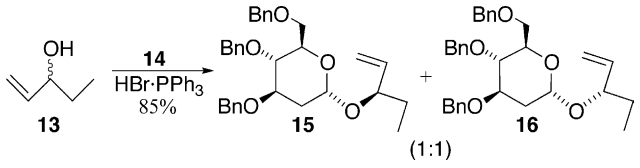
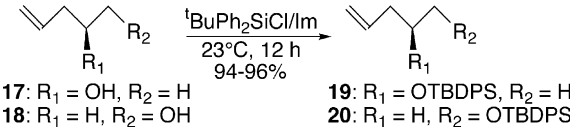
9 and **11** furnished methyl 19(*R*)-hydroxyeicosa-5(*Z*),8(*Z*),11(*Z*),14(*Z*)-tetraenoate[4c] (**10**) and methyl 20-hydroxyeicosa-5(*Z*),8(*Z*),11(*Z*),14(*Z*)-tetraenoate[4g] (**12**), respectively. Saponification (NaOH, THF/H_2O, 23 °C, 6–8 h, 94–98%) of the foregoing esters and extractive isolation gave free acids (*R*)-**1**, (*R*)-**2**, and **3** as colorless oils identical in all respects with authentic material.[4]

2-Deoxy-α-D-glucosides **15** and **16** (Eq. 1) were conveniently accessed via $Ph_3P{\cdot}HBr$ catalyzed[11] addition of (±)-1-penten-3-ol (**13**) to commercial 3,4,6-tri-*O*-benzyl-D-glucal (**14**) and chromatographic separation of the diastereomers over silica gel [EtOAc/hexane (15:85), $R_f \approx 0.53$ and 0.46, respectively].



(1)

Olefins **19** and **20** were prepared in excellent yields by silylation of commercial (*R*)-(−)-4-penten-2-ol (**17**, Aldrich Chem. Co.) and 4-penten-1-ol (**18**), respectively, using standard reaction conditions (Eq. 2).



(2)

Enantiomers (*S*)-**1** and (*S*)-**2** were obtained analogously and in comparable yields from **16** and (S)-(+)-4-penten-2-ol (Aldrich Chem. Co.), respectively.

Acknowledgements

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9. Physical and spectral data for **5**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.36 (t, 1H, $J = 7.3$ Hz), 5.54–5.30 (m, 6H), 3.67 (s, 3H), 2.92–2.78 (m, 6H), 2.32 (t, 2H, $J = 7.3$ Hz), 2.18–2.06 (m, 2H), 1.71 (quintet, 2H, $J = 7.3$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.11, 136.68, 130.45, 129.19, 128.82, 128.76, 127.63, 124.31, 89.50, 51.62, 33.55, 31.54, 26.71, 25.92, 25.78, 24.89. **6**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.17 (dt, $J = 1.5$, 7.0 Hz, 1H) 6.07 (ddd, $J = 7.0$, 7.0, 7.0 Hz, 1H), 5.50–5.32 (m, 6H), 3.66 (s, 3H), 2.98 (t, $J = 6.4$ Hz, 2H), 2.86 (t, $J = 6.1$ Hz, 2H), 2.81 (t, $J = 5.4$ Hz, 2H), 2.32 (t, $J = 7.3$ Hz, 2H), 2.18–2.06 (m, 2H), 1.70 (quintet, $J = 7.3$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.96, 133.02, 129.75, 129.09, 128.85, 128.48, 127.83, 125.54, 108.05, 51.49, 33.46, 28.38, 26.63, 25.84, 25.70, 24.83. **7**: $[\alpha]_D^{23}$ +45.44 (*c* 1.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35–7.25 (m, 13H), 7.18–7.16 (m, 2H), 5.40–5.30 (m, 8H), 5.04 (d, $J = 3.0$ Hz, 1H), 4.88 (d, $J = 10.9$ Hz, 1H), 4.69–4.62 (m, 3H), 4.50 (dd, $J = 10.6$, 5.8 Hz, 2H), 4.01–3.95 (m, 1H), 3.86 (br d, $J = 9.4$ Hz, 1H), 3.79 (dd, $J = 10.3$, 3.6 Hz, 1H), 3.65 (s, 3H), 3.64–3.51 (m, 3H), 2.84–2.70 (m, 6H), 2.31 (t, $J = 7.6$ Hz, 2H), 2.24 (dd, $J = 12.8$, 4.9 Hz, 1H), 2.12–2.04 (m, 4H), 1.76–1.66 (m, 3H), 1.57–1.49 (m, 4H), 0.87 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.14, 138.90, 138.67, 138.32, 130.01, 129.10, 128.94, 128.48, 128.44, 128.32, 128.25, 128.18, 128.12, 127.98, 127.71, 127.63, 96.60, 78.58, 78.27, 77.93, 75.12, 73.58, 71.90, 71.15, 69.05, 51.60, 36.16, 33.54, 32.72, 30.51, 27.45, 26.66, 25.75, 24.89, 22.95, 10.04. Adduct of **6** with **16**: $[\alpha]_D^{23}$ +57.1(*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38–7.22 (m, 13H), 7.20–7.14 (m, 2H), 5.46–5.27 (m, 8H), 5.08 (d, $J = 2.7$ Hz, 1H), 4.89 (d, $J = 10.6$ Hz, 1H), 4.61–4.71 (m, 3H), 4.50 (dd, $J = 10.3$, 8.8 Hz, 2H), 4.04–3.94 (m, 1H), 3.88–3.83 (m,1H), 3.80 (dd, $J = 10.3$, 3.6 Hz, 1H), 3.66 (s, 3H), 3.65–3.55 (m, 3H), 2.88–2.72 (m, 6H), 2.32 (t, $J = 7.6$ Hz, 2H), 2.24 (dd, $J = 12.8$, 4.9 Hz, 1H), 2.18–2.02 (m, 4H), 1.76–1.66 (m, 3H), 1.62–1.44 (m, 4H), 0.87 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.13, 138.89, 138.69, 138.29, 130.01, 129.05, 128.96, 128.51, 128.47, 128.42, 128.33, 128.26, 128.12, 128.04, 128.03, 127.98, 127.70, 127.68, 127.65, 127.61, 95.98, 78.54, 77.93, 77.34, 75.06, 73.56, 71.90, 71.22, 69.01, 51.59, 36.06, 34.10, 33.52, 32.17, 26.65, 26.35, 25.71, 25.47, 24.88, 23.52, 22.12, 9.18. **9**: $[\alpha]_D^{23}$ +16.5 (*c* 1.25 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68–7.66 (m, 4H), 7.43–7.34 (m, 6H), 5.40–5.30 (m, 8H), 3.84 (sextet, $J = 5.8$ Hz, 1H), 3.66 (s, 3H),

2.83–2.74 (m, 6H), 2.31 (t, $J = 7.7$ Hz, 2H), 2.10 (q, $J = 6.4$ Hz, 2H), 1.95 (q, $J = 5.5$ Hz, 2H), 1.70 (quintet, $J = 7.3$ Hz, 2H), 1.50–1.30 (m, 4H), 1.06–1.05 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) d 174.25, 136.08, 135.10, 134.76, 130.45, 129.65, 129.57, 129.14, 129.06, 128.72, 128.39, 128.09, 127.92, 127.66, 127.58, 69.67, 51.68, 39.20, 33.63, 27.39, 27.24, 26.75, 25.81, 25.40, 24.97, 23.42, 19.47. **10**: $[\alpha]_D^{23}$ −2.96 (*c* 1.55, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.43–5.33 (m, 8H), 3.80 (sextet, $J = 5.8$ Hz, 1H), 3.66 (s, 3H), 2.84–2.79 (m, 6H), 2.32 (t, $J = 7.4$ Hz, 2H), 2.10 (quintet, $J = 7.3$ Hz, 4H), 1.70 (quintet, $J = 7.6$ Hz, 2H), 1.50–1.38 (m, 4H), 1.19 (d, $J = 6.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.30, 130.15, 129.12, 129.04, 128.59, 128.37, 128.32, 128.20, 128.15, 68.18, 51.70, 39.06, 33.62, 27.32 26.73, 25.93, 25.83, 25.81, 25.79, 24.95, 23.70. **11**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.67–7.65 (m, 4H), 7.44–7.35 (m, 6H), 5.41–5.30 (m, 8H), 3.66–3.63 (m, 5H), 2.84–2.77 (m, 6H), 2.31 (t, $J = 7.3$ Hz, 2H), 2.12–2.02 (m, 4H), 1.69 (quintet, $J = 7.6$ Hz, 2H), 1.58–1.53 (m, 2H), 1.40–1.31 (m, 4H), 1.04 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.18, 135.73, 134.29, 133.88, 130.47, 129.66, 129.09, 129.03, 128.82, 128.71, 128.61, 128.34, 128.07, 127.82, 127.74, 64.07, 51.63, 33.58, 32.66, 29.88, 29.56, 27.40, 27.04, 26.71, 25.80, 25.78, 25.65, 24.94, 19.28. **15**: $[\alpha]_D^{23}$ +71.35 (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37–7.15 (m, 15H), 5.63–5.47 (m, 1H), 5.20–5.16 (m, 2H), 5.02 (d, $J = 3.3$ Hz, 1H), 4.88 (d, $J = 10.9$ Hz, 1H), 4.69–4.62 (m, 3H), 4.53–4.49 (m, 2H), 4.04–3.89 (m, 2H), 3.85–3.77 (m, 2H), 3.70–3.59 (m, 2H), 2.33 (dd, $J = 12.8$, 4.8 Hz, 1H), 1.73 (td, $J = 12.8$, 3.9 Hz, 1H), 1.63 (m, 2H), 0.88 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.96, 138.72, 137.90, 128.52, 128.47, 128.16, 127.99, 127.75, 127.73, 127.65, 118.13, 94.08, 78.65, 78.09, 78.05, 75.18, 73.58, 71.92, 71.12, 69.13, 35.14, 28.49, 10.09. **16**: $[\alpha]_D^{23}$ +92.3 (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37–7.25 (m, 13H), 7.18–7.16 (m, 2H), 5.80–5.72 (m, 1H), 5.18–5.04 (m, 3H), 4.89 (d, $J = 10.7$ Hz, 1H), 4.74–4.64 (m, 3H), 4.50 (t, $J = 10.9$ Hz, 2H), 4.04–3.91 (m, 2H), 3.84–3.77 (m, 2H), 3.67–3.59 (m, 2H), 2.29 (dd, $J = 12.8$, 4.9 Hz, 1H), 1.74 (td, 1H, $J = 12.5$, 3.7 Hz, 1H), 1.63–1.47 (m, 2H), 0.86 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) d 139.06, 138.97, 138.73, 128.54, 128.49, 128.47, 128.17, 128.05, 127.76, 127.67,115.58, 96.55, 79.41, 78.55, 77.97, 75.19, 73.58, 71.98, 71.00, 68.80, 35.93, 27.23, 9.45. **19**: $[\alpha]_D^{23}$ +9.18 (*c* 0.35, acetone); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.69–7.61 (m, 4H), 7.42–7.34 (m, 6H), 5.81–5.71 (m, 1H), 4.99–4.93 (m, 2H), 3.88 (sextet, $J = 6.0$ Hz, 1H), 2.25–2.15 (m, 2H), 1.06 (t, 3H, $J = 7.3$ Hz), 1.05 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.10, 136.08, 135.33, 134.94, 134.66, 129.73, 129.66, 127.71, 127.65, 117.00, 69.41, 44.16, 27.23, 23.05, 19.47. **20**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.75–7.67 (m, 4H), 7.50–7.35 (m, 6H), 5.88–5.78 (m, 1H), 5.10–4.90 (m, 2H), 3.70 (t, 2H, $J = 7.3$ Hz), 2.14–2.12 (m, 2H), 1.72–1.62 (m, 2H), 1.08 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.70, 135.78, 134.25, 129.74, 127.82, 114.77, 63.47, 32.03, 30.28, 27.09, 19.44.

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