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A concise synthesis of 12(*S*),20-dihydroxyeicosa-5(*Z*), 8(*Z*),10(*E*),14(*Z*)-tetraenoic acid, an endogenous vasoconstrictor

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Abstract—12(*S*),20-DiHETE, prepared by a combination of Evans–Crimmins asymmetric alkylation, Sonogashira alkynylation, and Suzuki–Miyaura cross-coupling, significantly sensitizes phenylephrine-induced vasoconstriction of rat renal interlobar arteries.

1. Introduction

Recent studies from these and other laboratories have documented the structure and biosynthesis of a variety of 'dual pathway metabolites' arising from secondary oxidation of a primary eicosanoid by cyclooxygenase, lipoxygenase, or cytochrome P450.[1] These novel biosynthetic paradigms significantly increase structural diversity and the range of biological activities.[2] A prominent example of this class of autacoids, 12(*S*),20-dihydroxyeicosa-5(*Z*),8(*Z*),10(*E*),14(*Z*)-tetraenoic acid (**1**), has attracted wide attention for its effects on vascular regulation and inflammation.[1a–f] To expedite continuing pharmacological investigations, we describe herein a concise, asymmetric synthesis[3] of **1** by a triply convergent strategy (Fig. 1). Additionally, **1** was evaluated for its ability to sensitize phenylephrine-induced vasoconstriction of rat renal interlobar arteries.[4]

Access to the central chiral retron (Fig. 1) was conveniently achieved by asymmetric alkylation of glycolate oxazolidinone **2**[5] with 1-chloro-3-iodoprop-1(*Z*)-ene **12**[6] at low temperature to give **3**[7] (Scheme 1). Suzuki–Miyaura cross-coupling of **3** with the alkylborane generated from 5-(*tert*-butyldiphenylsilyl-oxy)pent-1-ene[8] (**8**) via in situ addition of 9-BBN was best accomplished using Buchwald's catalytic system.[9] The resultant adduct, **4**, was converted to *E*-vinyl iodide **5** by sequential lithium borohydride reduction, Swern oxidation, and Takai iodoölefination.[10] Sonogashira[11] alkylation of **5** with methyl non-5(*Z*)-8-ynoate[12] (**9**) and semihydrogenation[13] over P-2 nickel smoothly evolved **6** and completed the synthesis of the carbon framework. Bis-desilylation generated methyl ester **7** from which **1** was obtained by saponification.

The somewhat labile allylic iodide **12** was prepared by modification of the procedures published by Wei and Taylor (Scheme 2).[14] Specifically, Michael addition of chloride anion to commercial ethyl propynoate (**10**) proceeded stereoselectively giving **11**, which was subsequently reduced with $LiAlH_4$. The newly generated alcohol was transformed into the corresponding iodide using a mixture of $KI/BF_3 \cdot Et_2O$.

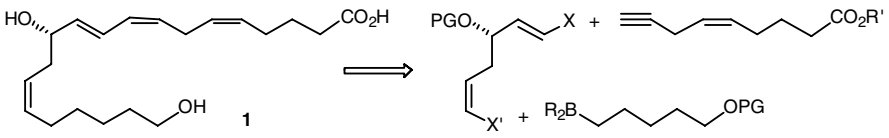

Figure 1. Retrosynthetic analysis.

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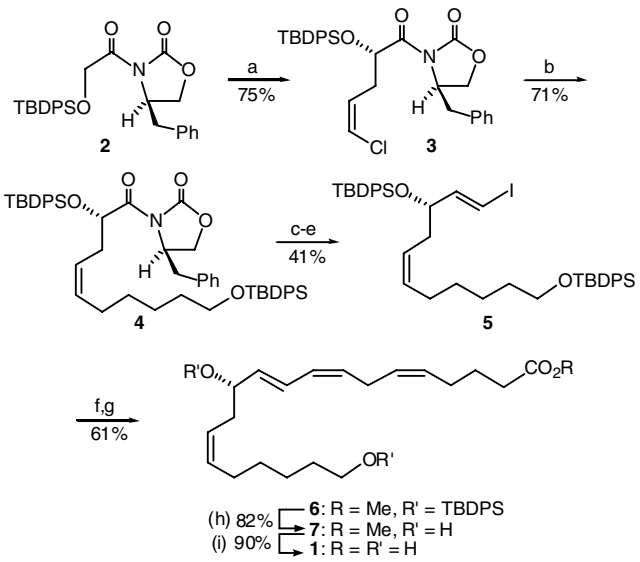
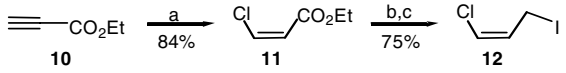


Scheme 1. Reagents and conditions: (a) $Na(TMS)_2N$, THF/$PhCH_3$ (2:1), −90 to −78 °C, 2 h; **12**, −90 to −78 °C, 6 h; (b) **8**, 9-BBN, THF, 23 °C, 2 h; $Pd(OAc)_2$ (1 mol%)/Buchwald ligand (2 mol%), K_3PO_4, THF, 65 °C, 18 h; (c) $LiBH_4$, Et_2O, 0 °C, 8 h, 83%; (d) $(COCl)_2$/DMSO/Et_3N, CH_2Cl_2, −78 to 0 °C, 6 h, 70%; (e) $CHI_3/CrCl_2$, THF, 23 °C, 6 h, 71%; (f) **9**, CuI/$Pd(Ph_3P)_4$/*n*-$BuNH_2$, C_6H_6, 23 °C, 5 h, 76%; (g) P-2 Ni/H_2 (1 atm), EtOH, 1.5 h, 80%; (h) *n*-Bu_4NF, THF, 0 °C, 8 h; (i) NaOH, THF/H_2O (3:1), 23 °C, 7 h.



Scheme 2. Reagents and conditions: (a) LiCl, AcOH/CH_3CN, 82 °C, 12 h; (b) $LiAlH_4$, Et_2O, 0 °C, 4 h, 84%; (c) $KI/BF_3 \cdot Et_2O$, dioxane, 23 °C, 5 h, 62%.

2. Bioassay

Ring segments of rat renal interlobar arteries bathed in Krebs' buffer were mounted on a wire-myograph. Phenylephrine elicited concentration dependent increases of isometric tension with an $EC_{50} = 0.49 \pm 0.04$ μmol/L ($R_{max} = 4.19 \pm 0.42$ mN/mm). Compound **1** (10 μmol/L) resulted in a significant ($P < 0.05$) sensitization of the arteries to phenylephrine ($EC_{50} = 0.16 \pm 0.07$ μmol/L) without changing R_{max}.

Acknowledgements

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7. Spectral and physical data for new compounds. Compound **2**: IR (neat) 1782, 1721, 1113 cm^{-1}; $[\alpha]_D^{23} - 46.4$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$ + TMS, 400 MHz) δ 7.22 (td, 4H, $J = 7.6$, 1.6 Hz), 7.46–7.36 (m, 6H), 7.32–7.24 (m, 3H), 7.12 (dd, 2H, $J = 6.1$, 1.6 Hz), 4.87 (q, 2H, $J = 9.5$ Hz), 4.64–4.57 (m, 1H), 4.18 (t, 1H, $J = 9.1$ Hz), 4.14 (dd, 1H, $J = 8.8$, 3.0 Hz), 3.19 (dd, 1H, $J = 13.4$, 3.0 Hz), 2.70 (dd, 1H, $J = 13.4$, 9.1 Hz), 1.13 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.18, 153.43, 135.90, 135.84, 135.07, 133.08, 130.09, 130.06, 129.60, 129.13, 127.96, 127.94, 127.55, 67.18, 64.74, 54.84, 37.72, 26.99, 19.55. Compound **3**: $[\alpha]_D^{23} - 74.9$ (*c* 1.09, $CHCl_3$); IR (neat) 1781, 1713, 1113, 701 cm^{-1}; ^1H NMR ($CDCl_3$ + TMS, 400 MHz) δ 7.71 (dd, 2H, $J = 7.6$, 1.2 Hz), 7.61 (dd, 2H, $J = 8.0$, 1.2 Hz), 7.44–7.32 (m, 6H), 7.31–7.22 (m, 3H), 7.16 (dd, 2H, $J = 6.7$, 1.2 Hz), 6.18 (app dt, 1H, $J = 7.0$ Hz), 6.12–6.05 (m, 1H), 5.51 (t, 1H, $J = 5.2$ Hz), 4.12–4.04 (m, 1H), 3.96 (dd, 1H, $J = 8.8$, 2.7 Hz), 3.79 (t, 1H, $J = 8.5$ Hz), 3.07 (dd, 1H, $J = 13.4$, 3.2 Hz), 2.94–2.83 (m, 1H), 2.78–2.68 (m, 1H), 2.56 (dd, 1H, $J = 13.4$, 9.7 Hz), 1.14 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.53, 152.68, 136.49, 136.09, 135.21, 133.45, 133.33, 130.04, 129.92, 129.60, 129.12, 127.82, 127.66, 127.52, 126.41, 120.66, 69.89, 66.59, 54.82, 37.77, 32.66, 27.15, 19.54. Compound **4**: $[\alpha]_D^{23} - 45.3$ (*c* 1.17, $CHCl_3$); IR (neat) 1782, 1712 cm^{-1}; ^1H NMR ($CDCl_3$ + TMS, 400 MHz) δ 7.74–7.60 (m, 8H), 7.42–7.20 (m, 15H), 7.09 (d, 2H, $J = 7.7$ Hz), 5.66–5.52 (m, 2H), 5.43 (t, 1H, $J = 5.1$ Hz), 4.06–3.80 (m, 1H), 3.95–3.89 (m, 1H), 3.73 (t, 1H, $J = 8.2$ Hz), 3.62 (t, 2H, $J = 6.6$ Hz), 3.03 (dd, 1H, $J = 13.3$, 2.9 Hz), 2.64–2.48 (m, 3H), 2.10–2.00 (m, 2H), 1.60–1.50 (m, 3H), 1.40–1.30 (m, 4H), 1.11 (s, 9H), 1.03 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.46, 152.58, 136.55, 136.22, 135.76, 135.25, 134.34, 133.76, 133.54, 133.38, 129.87, 129.77, 129.67, 129.59, 129.05, 127.77, 127.67, 127.57, 127.48, 123.95, 70.84, 66.37, 64.14, 54.76, 37.85, 33.11, 32.72, 29.59, 27.62, 27.18, 27.08, 25.74, 19.54, 19.41; MS (APCI) *m/z* 860 $(M + Na)^+$. Compound **5**: $[\alpha]_D^{23} - 26$ (*c* 0.5, $CHCl_3$); IR (neat) 2857, 1427, 1111, 700 cm^{-1}; ^1H

NMR ($CDCl_3$ + TMS, 400 MHz) δ 7.70–7.59 (m, 8H), 7.44–7.33 (m, 12H), 6.46 (dd, 1H, J = 14.3, 6.4 Hz), 5.96 (d, 1H, J = 14.3 Hz), 5.42–5.33 (m, 1H), 5.27–5.18 (m, 1H), 4.07 (q, 1H, J = 6.7 Hz), 3.63 (t, 2H, J = 6.4 Hz), 2.28–2.12 (m, 2H), 1.88–1.76 (m, 2H), 1.56–1.49 (m, 2H), 1.32–1.20 (m, 4H), 1.05 (s, 9H), 1.04 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.26, 136.29, 136.26, 135.98, 134.54, 134.20, 133.88, 133.06, 130.18, 130.15, 129.92, 128.00, 124.08, 77.86, 76.13, 64.36, 35.66, 32.92, 29.70, 27.73, 27.40, 27.31, 25.87, 19.73, 19.64. Compound **6**: $[\alpha]_D^{23}$ − 6.55 (c 0.9, $CHCl_3$); IR (neat) 1738, 1428, 1111 cm^1; ^{1}H NMR ($CDCl_3$ + TMS, 400 MHz) δ 7.70–7.62 (m, 8H), 7.44–7.30 (m, 12H), 6.23 (dd, 1H, J = 15.2, 10.3 Hz), 5.87 (t, 1H, J = 10.9 Hz), 5.62 (dd, 1H, J = 12.2, 6.7 Hz), 5.40–5.21 (m, 5H), 4.21 (q, 1H, J = 5.5 Hz), 3.64–3.60 (m, 5H), 2.76 (t, 2H, J = 6.1 Hz), 2.28 (t, 3H, J = 7.3 Hz), 2.23–2.14 (m, 1H), 2.10–2.00 (m, 2H), 1.81 (q, 2H, J = 7.0 Hz), 1.68 (q, 2H, J = 7.6 Hz), 1.66–1.48 (m, 2H), 1.32–1.18 (m, 4H), 1.06 (s, 9H), 1.04 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.25, 136.18, 136.14, 135.78, 134.56, 134.35, 134.29, 132.07, 129.77, 129.70, 129.57, 129.30, 128.80, 128.42, 127.79, 127.68, 127.59, 125.21, 124.87, 74.01, 64.16, 51.68, 36.23, 33.62, 32.72, 29.51, 27.54, 27.24, 27.09, 26.73, 26.17, 25.66, 24.95, 19.56, 19.43; MS (APCI) m/z 849 $(M + Na)^+$. Compound **7**: $[\alpha]_D^{23}$ − 2.5 (c 2.0, $CHCl_3$); IR (neat) 3392, 2930, 1727, 1437, 1216 cm^{-1}; ^{1}H NMR ($CDCl_3$ + TMS, 400 MHz) δ 6.60 (dd, 1H, J = 15.2, 10.9 Hz), 5.99 (t, 1H, J = 10.6 Hz), 5.72 (dd, 1H, J = 15.2, 6.1 Hz), 5.60–5.50 (m, 1H), 5.48–5.30 (m, 4H), 4.23 (q, 1H, J = 6.1 Hz), 3.67 (s, 3H), 3.63 (t, 2H, J = 6.4 Hz), 2.92 (t, 2H, J = 6.4 Hz), 2.40–2.26 (m, 4H), 2.16–2.02 (m, 4H), 1.90–1.65 (m, 4H), 1.62–1.52 (m, 2H), 1.46–1.32 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.41, 136.00, 133.38, 130.45, 129.46, 128.52, 128.07, 125.53, 124.87, 72.21, 63.10, 51.77, 35.55, 33.63, 32.80, 29.51, 27.53, 26.76, 26.30, 25.54, 24.92; MS (APCI) m/z 373 $(M + Na)^+$. Compound **11**: ^{1}H NMR ($CDCl_3$ + TMS,400 MHz) δ 6.70 (d, 1H, J = 8.2 Hz), 6.19 (d, 1H, J = 8.2 Hz), 4.24 (q, 2H, J = 7.4 Hz), 1.31 (t, 3H, J = 7.0 Hz). Compound **12**: ^{1}H NMR ($CDCl_3$ + TMS, 400 MHz) δ 6.13 (m, 2H), 4.00 (d, 2H, J = 7.7 Hz).

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