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Asymmetric synthesis of the stereoisomers of 11,12,15(*S*)-trihydroxyeicosa-5(*Z*),8(*Z*),13(*E*)-trienoic acid, a potent endothelium-derived vasodilator

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Abstract—The four stereoisomers of the endothelial-derived vasorelaxant 11,12,15(*S*)-trihydroxyeicosatrienoic acid [**1**, 11,12,15(*S*)-THETA] were prepared by a triply convergent, asymmetric route that exploited the stereospecific, copper mediated cross-coupling of α,β-dialkoxystannanes with organic electrophiles and the utility of dialkylthionocarbamates as orthogonal alcohol protective groups. Only 11(*R*),12(*S*),15(*S*)-THETA was comparable to natural material by HPLC, GC/MS, and in vitro bioassay.

The endothelial lining of mammalian blood vessels generates[1] a variety of vasoactive substances, for example, prostacyclin (PGI_2),[2] nitric oxide,[3] epoxyeicosatrienoic acids,[4] and endothelin.[5] As a part of the intense search for additional endogenous vasomodulators,[6] our laboratories reported the isolation of triol **1**, which is generated by rabbit aortic endothelium from arachidonic acid via the 15(*S*)-lipoxygenase pathway.[7] The structure of **1** was assigned as 11,12,15(*S*)-trihydroxyeicosatrienoic acid [11,12,15(*S*)-THETA] based upon a combination of spectral and biochemical studies; however, the minute amounts available from natural sources precluded a complete stereochemical assignment.[8] In the rabbit aorta, **1** mediates acetylcholine-induced vasodilation[9] and its production is stimulated by interleukin-13 treatment.[10] To unambiguously establish the absolute configuration of **1** as well as expedite additional pharmacological evaluations, we herein report a concise, asymmetric synthesis of all four stereoisomers of 11,12,15(*S*)-THETA (**1**) and their comparisons with natural material. Our triply convergent strategy is summarized in Figure 1 and highlights two synthetic procedures recently introduced by our laboratories,

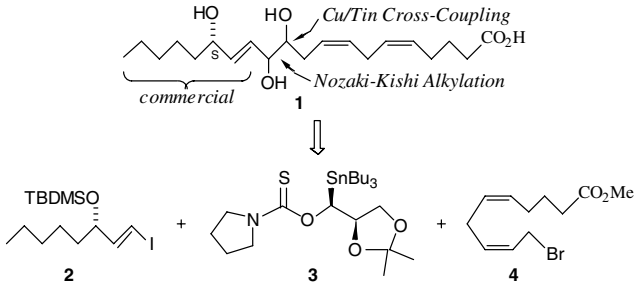

Figure 1. Retrosynthetic analysis.

viz., (i) the preparation and stereospecific, copper mediated cross-coupling of chiral α,β-dialkoxystannanes[11] with organic electrophiles and (ii) the utility of dialkylthionocarbamates as orthogonal protecting groups.[12]

Retron **3**[13] was conveniently accessed via diastereoselective addition[11] of zinc bis-(*n*-tributylstannane) to prochiral aldehyde (*R*)-2,3-*O*-isopropylidene-D-glyceraldehyde[14] (**5**) (Scheme 1). Thionocarbamoylation[12] of the resultant *anti*-adduct **6** evolved **3** in good overall yield. The *syn*-adduct **8** was obtained from **6** by a conventional Mitsunobu inversion/saponification sequence via benzoate **7**.

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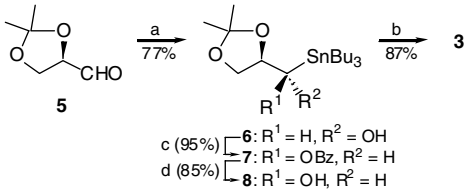
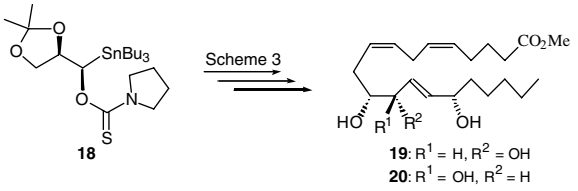


Scheme 1. Reagents and conditions: (a) $Zn(Bu_3Sn)_2$, THF, −78 °C, 4 h; (b) 1,1′-$Im_2C(S)$, DMAP, then pyrrolidine, CH_2Cl_2, 23 °C, 8 h; (c) DIAD, Ph_3P, $PhCO_2H$, C_6H_6, 23 °C, 24 h; (d) K_2CO_3, MeOH, 45 °C, 6 h.



Scheme 4. Synthesis of triols **19** and **20**.

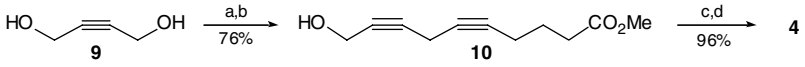
Bromo-ester **4** was readily prepared (Scheme 2) from 2-butyn-1,4-diol (**9**) via mono-tosylation and copper-catalyzed alkynylation[15] with commercial methyl 5-hexynoate (**11**). Semi-hydrogenation of the resultant diyne **10**[16] over P-2[17] Ni/H_2 and exchange of the alcohol for bromide using PBr_3 completed the synthesis of the C(1)–C(10) moiety.

Copper mediated cross-coupling[11] of chiral stannane **3** with bromide **4** smoothly generated ester **12** with retention of configuration at the C(11)-stereocenter (Scheme 3). Mild acidic hydrolysis of the acetonide and low temperature sodium periodate cleavage of the liberated diol transformed **12** into aldehyde **13**. Subsequent Nozaki-Kishi addition[18] of vinyl iodide **2**[19] provided a mixture (7:3) of diastereomeric triols **14** and **16**, which was most conveniently separated chromatographically at a later stage.[20] Concomitant cleavage of the thionocarbamate,[12] silyl ether, and methyl ester protecting groups by basic hydrogen peroxide and re-esterification with diazomethane afforded the methyl esters of 11(*S*), 12(*R*),15(*S*)-THETA (**15**) and 11(*S*),12(*S*),15(*S*)-THETA (**17**), respectively, in good yield. The relative stereochemistries of **15** and **17** were confirmed as *erythro* and *threo*, respectively, by $^1H/^{13}C$ analysis of the corresponding 11,12-acetonides.[21]

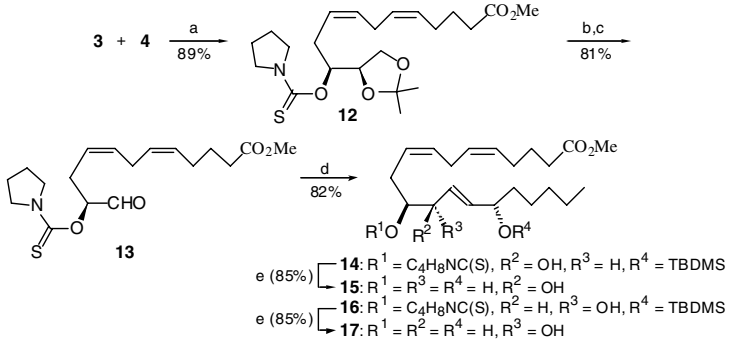
Thionocarbamoylation[12] of **8** furnished chiral stannane **18**, the C(1)-epimer of **3**, which was then carried through the sequence in Scheme 3 in comparable yields to give methyl 11(*R*),12(*S*),15(*S*)-THETA (**19**) and 11(*R*),12(*R*), 15(*S*)-THETA (**20**) (Scheme 4).[20]

Saponification (LiOH, THF/H_2O, 23 °C, 6–10 h, 90–95%) of **15**, **17**, **19**, and **20** and extractive isolation furnished the corresponding free acids as colorless oils. Of the four stereoisomers, only 11(*R*),12(*S*),15(*S*)-THETA (**19**) was identical with natural material by normal and reverse-phase HPLC, GC/MS, and in vitro bioassay.[8]

In conclusion, we describe the first synthesis of all four stereoisomers of **1** and validate novel methodology for creating carbon–carbon bonds at heteroatom-substituted chiral centers and for the orthogonal protection/deprotection of alcohols using thionocarbamate protective groups. The results of ongoing studies of the physiological significance of this new class of vasorelaxants will be reported elsewhere.



Scheme 2. Reagents and conditions: (a) TsCl, Py, CH_2Cl_2, 1 h, 0 °C, 85%; (b) **11**, NaI, CuI, K_2CO_3, DMF, −20 °C, 2 h; 23 °C, 12 h, 89%; (c) Ni (P-2), H_2 (1 atm), EtOH, 23 °C, 12 h, 98%; (d) PBr_3, Et_2O, 0 °C, 1 h, 95%.



Scheme 3. Reagents and conditions: (a) CuCN (7 mol%), THF, 50 °C, 4 h; (b) 80% aq HOAc, 23 °C, 12 h, 95%; (c) $NaIO_4$, THF/H_2O (3:1), −10 °C, 1 h, 85%; (d) **2**, $NiCl_2$ (cat)/$CrCl_2$, DMF, 23 °C, 12 h, 82%; (e) H_2O_2, NaOH, MeOH, 23 °C, 10 h; CH_2N_2, 85%.

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13. Spectral and physical data for **3**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.80–1.00 (m, 15H), 1.27–1.35 (m, 9H), 1.42 (s, 3H), 1.48–1.56 (m, 6H), 1.90–2.01 (m, 4H), 3.47–3.64 (m, 2H), 3.70–3.74 (m, 3H), 3.90–3.94 (m, 1H), 4.38–4.42 (m, 1H), 5.73–5.79 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.87, 13.78, 24.66, 25.20, 25.84, 26.64, 27.52, 29.10, 47.77, 52.13, 65.08, 76.65, 79.10, 108.13, 185.51; HRMS (CI, CH_4) calcd for $C_{19}H_{37}NO_3SSn$: 479.1516 $(M+H-Bu)^+$, found 479.1512. **4**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.60–1.77 (m, 2H), 2.02–2.18 (m, 2H), 2.34 (t, 2H, J = 7.8 Hz), 2.88 (apparent t, 2H, J = 6.4 Hz), 3.67 (s, 3H), 4.02 (d, 2H, J = 9.0 Hz), 5.40–5.82 (m, 4H); Anal. Calcd for $C_{11}H_{17}BrO_2$: C, 50.59; H, 6.56. Found: C, 50.68; H, 6.62. **6**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87–0.96 (m, 15H), 1.28–1.35 (m, 6H), 1.39 (s, 3H), 1.43 (s, 3H), 1.48–1.54 (m, 6H), 1.99–2.01 (m, 1H), 3.83–3.88 (m, 1H), 3.92–3.97 (m, 1H), 4.19–4.21 (m, 1H), 4.30–4.36 (m, 1H); $[\alpha]_D^{23}$ 11.9 (c 1.65, $CHCl_3$). **7**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.85–0.98 (m, 15H), 1.21–1.62 (m, 18H), 3.77 (t, 1H, J = 7.9 Hz), 3.97 (t, 1H, J = 6.4 Hz), 4.41–4.49 (m, 1H), 5.12–5.21 (m, 1H), 7.40–7.58 (m, 3H), 8.04 (d, 2H, J = 7.6 Hz); Anal. Calcd for $C_{25}H_{42}O_4Sn$: C, 57.16; H, 8.06. Found: C, 57.30; H, 8.29. **8**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.89–0.97 (m, 15H), 1.30–1.36 (m, 6H), 1.37 (s, 3H), 1.44 (s, 3H), 1.48–1.55 (m, 6H), 1.82 (d, 1H, J = 6.7 Hz), 3.75 (t, 1H, J = 7.30 Hz), 3.91–3.96 (m, 2H), 4.39 (q, 1H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.11, 13.84, 25.82, 26.55, 27.59, 29.26, 65.36, 65.58, 81.18, 108.89. **12**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.36 (s, 3H), 1.46 (s, 3H), 1.61–1.73 (m, 2H), 1.90–1.98 (m, 4H), 2.05–2.12 (m, 2H), 2.28–2.34 (m, 2H), 2.38–2.61 (m, 2H), 2.79 (apparent t, 2H, J = 6.4 Hz), 3.49–3.63 (m, 2H), 3.62 (s, 3H), 3.66–3.67 (m, 3H), 3.70–3.75 (m, 2H), 3.90–4.20 (m, 2H), 4.26–4.36 (m, 1H), 5.01–5.15 (m, 1H), 5.34–5.50 (m, 2H), 5.60–5.72 (m, 1H), 5.81–5.83 (m, 1H); Anal. Calcd for $C_{22}H_{35}NO_5S$: C, 62.09; H, 8.29. Found: C, 62.16; H, 8.10. **13**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.60–1.70 (m, 2H), 1.84–2.00 (m, 4H), 2.01–2.10 (m, 2H), 2.20–2.32 (m, 2H), 2.50–2.65 (m, 2H), 2.78 (apparent t, 2H, J = 6.4 Hz), 3.47 (t, 2H, J = 6.9 Hz), 3.55–3.62 (m, 2H), 3.81 (s, 3H), 4.04 (m, 1H), 5.33–5.55 (m, 4H), 9.67 (d, 1H, J = 1.5 Hz); HRMS (CI, CH_4) calcd for $C_{18}H_{28}NO_4S$: 354.1739 $(M+H)^+$, found 354.1734. **15**: TLC: R_f~0.25 (80% EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.89 (t, 3H, J = 6.0 Hz), 1.20–1.42 (m, 6H), 1.43–1.60 (m, 2H), 1.61–1.80 (m, 2H), 2.00–2.40 (m, 6H), 2.70–2.90 (m, 2H), 3.61 (s, 3H), 3.62–3.70 (m, 1H), 4.05–4.14 (m, 2H), 5.26–5.42 (m, 3H), 5.43–5.52 (m, 1H), 5.77 (dd, J = 6, 16 Hz, 1H), 5.85 (dd, J = 4.8, 16 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.25, 22,81, 24.92, 25.36, 26.03, 26.78, 31.79, 31.94, 33.61, 37.38, 51.82, 72.59, 74.16, 74.70, 125.50, 128.52, 128.75, 129.30, 131.37, 136.86, 174.56; $[\alpha]_D^{23}$ 2.66 (c 0.45, $CHCl_3$); HRMS (CI, CH_4) calcd for $C_{21}H_{37}O_5$: 369.2641 $(M+H)^+$, found 369.2639. **17**: TLC: R_f~0.27 (80% EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.89 (t, 3H, J = 8.8 Hz), 1.20–1.42 (m, 6H), 1.43–1.60 (m, 2H), 1.61–1.80 (m, 2H), 2.00–2.18 (m, 2H), 2.20–2.40 (m, 4H), 2.80 (apparent t, 2H, J = 6.4 Hz), 3.53 (br s, 1H), 3.67 (s, 3H), 4.02 (br s, 1H), 4.10–4.20 (m, 1H), 5.30–5.60 (m, 4H), 5.73 (dd, J = 6, 16 Hz, 1H), 5.85 (dd, J = 6, 16 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.25, 22.81, 24.91, 25.30, 26.01, 26.03, 31.42, 31.95, 33.60, 37.43, 51.81, 72.32, 74.32, 74.79, 125.25, 128.78, 129.33, 129.67, 131.56, 136.71, 175.89; $[\alpha]_D^{23}$ −8.5 (c 0.2, $CHCl_3$); HRMS (CI, CH_4) calcd for $C_{21}H_{37}O_5$ $(M+H)^+$ m/z 369.2641, found 369.2641. **18**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.80–1.00 (m, 15H), 1.27–1.35 (m, 9H), 1.42 (s, 3H), 1.48–1.56 (m, 6H), 1.90–2.01 (m, 4H), 3.47–3.64 (m, 2H), 3.70–3.74 (m, 3H), 3.90–3.94 (m, 1H), 4.38–4.42 (m, 1H), 5.73–5.79 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.87, 13.78, 24.66, 25.20, 25.84, 26.64, 27.52, 29.10, 47.77, 52.13, 65.08, 76.65, 79.10, 108.13, 185.51; HRMS (CI, CH_4) calcd for $C_{19}H_{37}NO_3SSn$: 479.1516 $(M+H-Bu)^+$, found 479.1520. **19**: TLC: R_f~0.20 (80% EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.89 (t, 3H, J = 6.3 Hz), 1.21–1.41 (m, 4H), 1.45–1.60 (m, 2H), 1.62–1.78 (m, 2H), 2.02–2.18 (m, 2H), 2.20–2.40 (m, 6H), 2.72–2.85 (m, 2H), 3.68 (s, 3H), 3.69–3.74 (m, 1H), 4.12–4.20 (m, 2H), 5.32–5.60 (m, 4H), 5.74 (dd, J = 5.6, 16 Hz, 1H), 5.82 (dd, J = 5.2, 16 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.23, 22,79, 24.89, 25.33, 26.00, 26.73, 30.39, 31.95, 33.57, 37.35, 51.80, 72.18, 74.28, 74.84, 126.62, 128.26, 128.81, 129.23, 131.11, 136.79, 174.57; $[\alpha]_D^{23}$ 7.24 (c 1.68, $CHCl_3$); HRMS (CI, CH_4) calcd for $C_{21}H_{37}O_5$: 369.2641 $(M+H)^+$, found 369.2643. **20**: TLC: R_f~0.23 (80% EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.89 (t, 3H, J = 8.80 Hz), 1.20–1.41 (m, 6H), 1.42–1.60 (m, 2H), 1.61–1.80 (m, 2H), 2.02–2.18 (m, 2H), 2.23–2.40 (m, 4H), 2.80 (t, 2H, J = 6.4 Hz), 3.55 (m, 1H), 3.68 (s, 3H), 4.02 (br s, 1H), 4.10–4.20 (m, 1H), 5.32–5.60 (m, 4H), 5.73 (dd, J = 6,

16 Hz, 1H), 5.85 (dd, J = 6, 16 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.25, 22,81, 24.93, 25.34, 25.99, 26.77, 31.37, 31.94, 33.61, 37.31, 51.81, 72.59, 74.22, 74.57, 125.33, 128.80, 129.28, 130.40, 131.36, 136.39, 174.54; $[\alpha]_D^{23}$ 21.9 (c 0.8, $CHCl_3$); HRMS (CI, CH_4) calcd for $C_{21}H_{37}O_5$: 369.2641 $(M+H)^+$, found 369.2643.

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20. In practice, the Nozaki-Kishi adducts were most conveniently separated after removal of the alcohol protecting groups by NP-HPLC using Microsorb silica (10 × 250 mm), 6% *i* PrOH/0.1% HOAc/hexane, UV 215 nm: R_f of **15** = 17 min, R_f of **17** = 19 min, R_f of **19** = 25 min, R_f of **20** = 27 min.
21. The spectral values for the acetonide of **15** (^{1}H NMR: $J_{11,12}$ = 6.0 Hz, ^{13}C NMR: δ 78.4, 79.0) and the acetonide of **17** (^{1}H NMR: $J_{11,12}$ = 7.9 Hz, ^{13}C NMR: δ 80.7, 81.6) are consistent with literature *erythro*- and *threo*-diol data, respectively. See: Kato, T.; Hirukawa, T.; Yano, M. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 839–842.