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A Linchpin Approach to Unsaturated Fatty Acids: 11,12-Epoxyeicosatrienoic Acid and 11*S*,12*S*-Dihydroxyeicosatrienoic Acid Ethyl Esters

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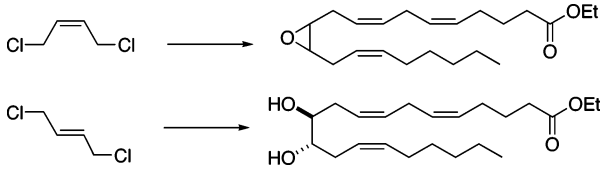
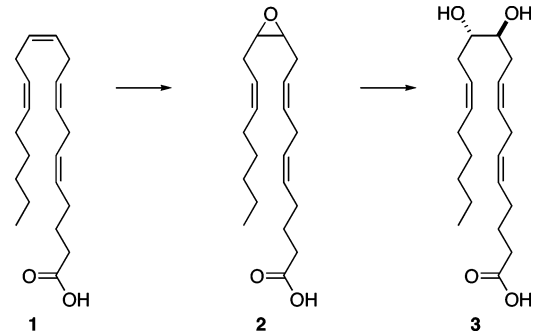


A "linchpin" coupling strategy is described for the construction of long-chain fatty acid metabolites. This strategy led to a short synthesis of the ethyl esters of both 11,12-epoxyeicosatrienoic acid (EET) and 11*S*,12*S*-dihydroxyeicosatrienoic acid (DHET).

Introduction

The monooxidation of arachidonic acid **1** (Scheme 1) effected[1] by cytochrome P_{450} generates the four regioisomeric epoxyeicosatrienoic acids[2] (EETs, represented by **2**), which are rapidly converted by cytosolic epoxide hydrolases to the corresponding dihydroxyeicosatrienoic acids[3] (DHETs, represented by **3**). The biological activities of the EETs are well documented.[4] In particular, 11,12-epoxyeiscosatrienoic acid **2** has potent antiinflammatory properties.[5] Further, 11,12-dihydroxyeicosatrienoic acid **3** was found to potently activate conductance Ca^{2+}-activated K^+ (BK) channels, with an EC_{50} of 1.87 ± 0.57 nM.[6]

Over the past two decades, several different pathways have been reported toward the synthesis of EETs[7] and DHETs.[8] In addition to partial syntheses[7a,b] of EETs, the total synthesis was carried out from malic acid[7c] and from 1-heptyne.[7d] The reported total syntheses of the DHETs[8a,b] have started from carbohydrate precursors, requiring more than 10 steps from commercial materials. To pursue studies of the physiological role of these metabolites, it is important to have a more practical synthesis. To this end, we describe (Scheme 1) a succinct assembly of the ethyl esters of both 11,12-epoxyeiscosatrienoic acid **2** and 11,12-dihydroxyeicosatrienoic acid **3** using a "linchpin" coupling strategy.



Results and Discussion

Synthesis of 11,12-Epoxyeiscosatrienoic Acid Ethyl Ester 8. Starting from 1-heptyne **10** (Scheme 2), the

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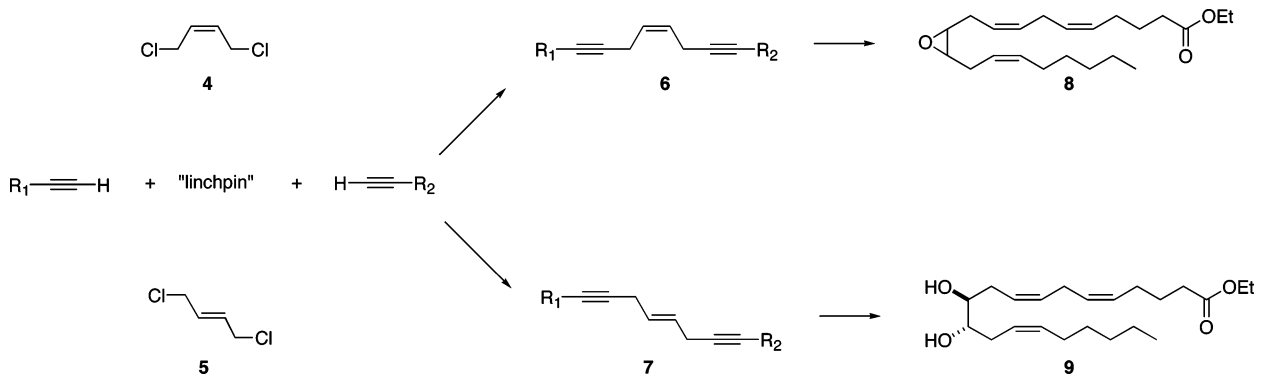
SCHEME 1



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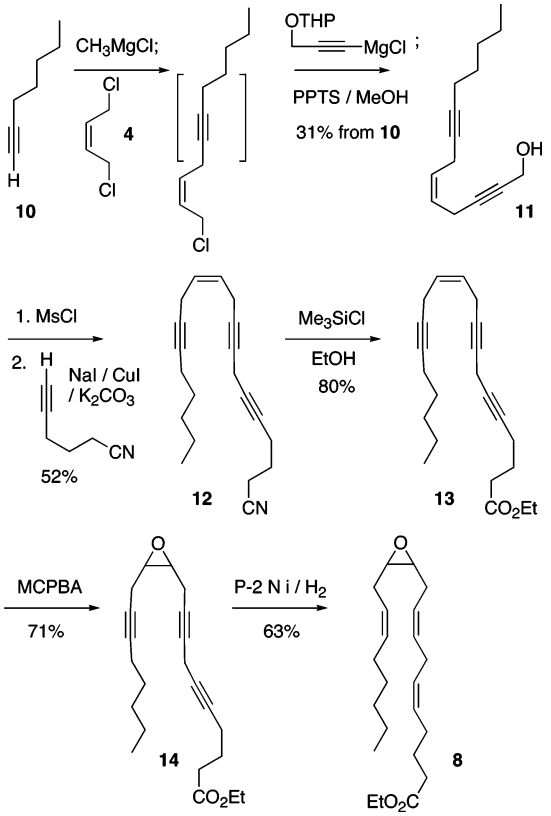
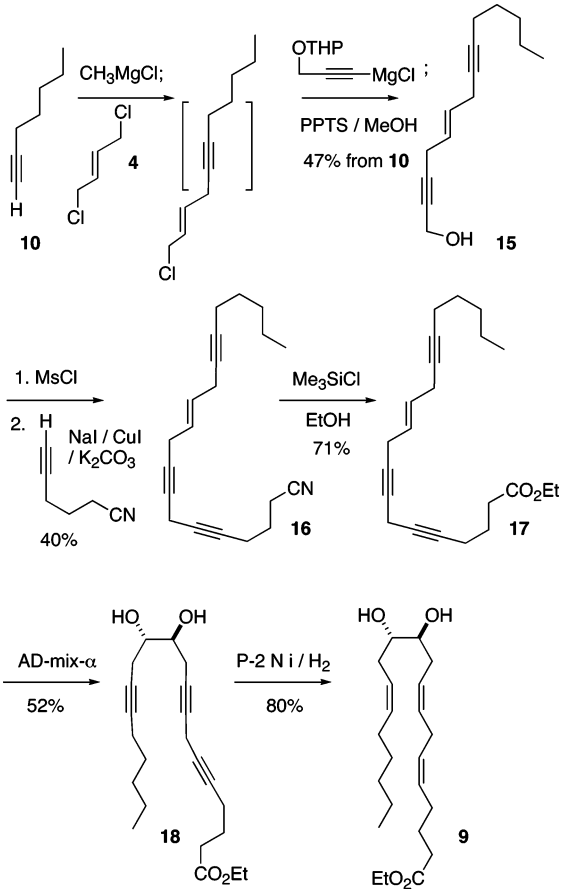


SCHEME 3



linchpin approach was effected by first coupling with an excess of *cis*-1,4-dichloro-2-butene **4**,[9] which gave a mixture of the S_N2 and S_N2' products.[9a] Without purification, the mixture was reacted with an excess of the Grignard reagent derived from THP-protected propargyl alcohol. We found that by adding the allylic chloride to the Grignard reagent at 50−60 °C, the ratio between S_N2 and S_N2' coupling was > 20:1. Without purification, the mixture was hydrolyzed with PPTS in EtOH,[10] leading to the alcohol **11**. Mesylation followed by a Cu(I)-mediated coupling reaction with 5-hexynenitrile yielded **12**, which was converted to the ethyl ester **13** with TMSCl and ethanol.[11]

Peracid oxidation of **13** yielded the epoxide **14**. The final step was partial hydrogenation[12] using P-2 Ni catalyst to afforded the desired product **8**. The usual workup conditions for the P-2 Ni catalyst, filtration of the reaction mixture through a short silica gel column, led to a low recovery of the product. A more conventional aqueous workup of the reaction mixture before chromatography gave much better material recovery.

Synthesis of (11*S*,12*S*)-Dihydroxyeiscosatrienoic Acid Ethyl Ester 9. A similar coupling reaction (Scheme 3) was carried out, except that *trans*-1,4-dichloro-2-butene **5** was used as the linchpin. PPTS deprotection gave **15**, which on mesylation followed by Cu(I)-mediated

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coupling with 5-hexynenitrile yielded **16**. Hydrolysis with TMSCl and ethanol gave the ethyl ester **17**, which was further treated with AD-Mix-α to introduce the 11*S* and 12*S* hydroxy groups. Partial hydrogenation of **18** using P-2 Ni catalyst then afforded the desired product **9**. We converted a portion of **9** to the corresponding methyl ester. This was found to be identical (^{1}H, ^{13}C NMR, $[\alpha]_D$) to the reported synthetic material.[8b]

Conclusion

We have established an efficient synthetic approach to the ethyl esters of 11,12-epoxyeiscosatrienoic acid and of 11*S*,12*S*-dihydroxyeicosatrienoic acid, using a very short linchpin coupling strategy. We expect that this strategy will also be useful for the preparation of other biologically important long-chain fatty acid metabolites.

Experimental Section

***cis*-Enyne Alcohol (11).** To a solution of 1-heptyne **10** (3.84 g, 40.0 mmol) in THF (40 mL) was added a solution of CH_3-MgCl (2.0 M solution in THF, 20.0 mL, 40.0 mmol) at 50−60 °C under N_2. After addition, the reaction mixture was stirred at 50−60 °C for 2 h and then cannula transferred to a solution of *cis*-1,4-dichloro-2-butene **4** (10.0 g, 80.0 mmol) and CuCl (1.60 g, 16.0 mmol) in THF (40 mL) at 50−60 °C under N_2. The resulting mixture was heated to reflux for 4 h. After being cooled to rt, the reaction mixture was partitioned between saturated aqueous NH_4Cl and ether. The combined organic extracts were dried (Na_2SO_4) and concentrated. Without purification, the residue was added over 10 min to a solution of ClMgC≡CCH_2OTHP (160.0 mmol, made from tetrahydro-2-(2-propynyloxyl)-2*H*-pyran (160.0 mmol) and CH_3MgCl (160.0 mmol)) and CuCl (1.60 g, 16.0 mmol) in THF (160 mL) at 50−60 °C under N_2. The resulting mixture was heated to reflux for 4 h. After being cooled to rt, the reaction mixture was partitioned between saturated aqueous NH_4Cl and ether. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was diluted with EtOH (100 mL), and PPTS (1.0 g) was added. The reaction mixture was stirred at 50 °C for 5 h and then concentrated. The residue was chromatographed to give the *cis*-enyne alcohol **11** as a colorless oil (2.53 g, 12.4 mmol, 31% yield from 1-heptyne): TLC R_f (MTBE/petroleum ether = 1:4) = 0.45; ^{1}H NMR δ 0.87 (t, J = 6.8 Hz, 3H), 1.30−1.33 (m, 4H), 1.44−1.47 (m, 2H), 2.12 (t, J = 7.2 Hz, 2H), 2.92 (br s, 2H), 2.99 (br s, 2H), 4.23 (s, 2H), 5.48−5.52 (m, 2H); ^{13}C NMR δ u 17.1, 17.2, 18.6, 22.2, 28.6, 31.0, 77.2, 78.4, 80.7, 83.9; d 13.9, 125.2, 127.2; IR (cm^{-1}); MS *m/z* 203 (M − H, 15), 91 (100); HRMS calcd for $C_{14}H_{21}O$ (M + H) 205.1592, obsd 205.1591.

***cis*-Triyne (12).** To a solution of **11** (1.0 g, 4.90 mmol) in CH_2Cl_2 (50 mL) were added Et_3N (990 mg, 9.80 mmol) and MsCl (674 mg, 5.88 mmol) at 0 °C under N_2. The reaction mixture was stirred at 0 °C for 20 min and then partitioned between brine and ether. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was diluted with acetone (20 mL), and 5-hexynenitrile (547 mg, 5.88 mmol) was added, followed by anhydrous K_2CO_3 (811 mg, 5.88 mmol), NaI (882 mg, 5.88 mmol), and CuI (559 mg, 2.94 mmol). The mixture was stirred at rt for 2 days and then filtered. The solid was rinsed with MTBE. The filtrate was concentrated and chromatographed to give the *cis*-triyne **12** as a colorless oil (711 mg, 2.55 mmol, 52% yield from **11**): TLC R_f (MTBE/petroleum ether = 1:10) = 0.35; ^{1}H NMR δ 0.86 (t, J = 6.9 Hz, 3H), 1.30−1.33 (m, 4H), 1.43−1.46 (m, 2H), 1.78−1.85 (m, 2H), 2.07−2.12 (m, 2H), 2.29−2.34 (m, 2H), 2.46 (t, J = 7.2 Hz, 2H), 2.88−2.93 (m, 4H), 3.07−3.11 (m, 2H), 5.42−5.49 (m, 2H); ^{13}C NMR δ u 9.7, 16.1, 17.1, 17.2, 17.8, 18.7, 22.2, 24.5, 28.6, 31.0, 74.1, 76.4, 77.3, 77.6, 78.2, 80.6, 119.2; d 14.0, 125.5, 127.0; IR (cm^{-1}) 3400, 2932, 2860; MS *m/z* 279 (M$^+$, 70), 222 (45); HRMS calcd for $C_{20}H_{25}NNa$ (M + Na) 302.1885, obsd 302.1881.

***cis*-Ester (13).** To a solution of the *cis*-triyne **12** (432 mg, 1.55 mmol) in EtOH (1.00 mL) was added TMSCl (680 mg, 6.26 mmol) under N_2 at rt. The mixture was stirred at 60 °C overnight. Water (56 mg, 3.10 mmol) was added to quench the reaction. The mixture was diluted with CH_2Cl_2. Na_2CO_3 (975 mg, 9.20 mmol) was added, and the mixture was stirred at rt for 10 min, then dried (Na_2SO_4), and filtered. The filtrate was concentrated, and the residue was chromatographed to give **13** as a colorless oil (404 mg, 1.24 mmol, 80% yield from **12**): TLC R_f (MTBE/petroleum ether = 1:10) = 0.45; ^{1}H NMR δ 0.87 (t, J = 7.1 Hz, 3H), 1.23 (t, J = 7.1 Hz, 3H), 1.30−1.33 (m, 4H), 1.41−1.46 (m, 2H), 1.75−1.82 (m, 2H), 2.08−2.12 (m, 2H), 2.19−2.23 (m, 2H), 2.39 (t, J = 7.2 Hz, 2H), 2.88−2.93 (m, 4H), 3.07−3.11 (m, 2H), 4.11 (q, J = 7.1 Hz, 2H), 5.44−5.49 (m, 2H); ^{13}C NMR δ u 9.7, 17.1, 17.2, 18.2, 18.7, 22.2, 23.9, 28.6, 31.0, 33.1, 60.3, 74.5, 75.1, 77.4, 78.0, 79.3, 80.6, 173.2; d 14.0, 14.2, 125.7, 126.8; IR (cm^{-1}) 2931, 1734, 1159; MS *m/z* 326 (M$^+$, 15), 167 (100); HRMS calcd for $C_{22}H_{31}O_2$ (M + H) 327.2324, obsd 327.2308.

Epoxide (14). To a solution of *cis*-ester **13** (126 mg, 0.38 mmol) in CH_2Cl_2 (10 mL) was added *m*-CPBA (77% 130 mg, 0.58 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 10 h and then partitioned between satd $NaHCO_3$ and CH_2-Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to give epoxide **14** as a colorless oil (92 mg, 0.27 mmol, 71% yield): TLC R_f (MTBE/petroleum ether = 1:10) = 0.35; ^{1}H NMR δ 0.88 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H), 1.30−1.35 (m, 4H), 1.43−1.50 (m, 2H), 1.75−1.82 (m, 2H), 2.11−2.15 (m, 2H), 2.20−2.23 (m, 2H), 2.28−2.35 (m, 2H), 2.39 (t, J = 7.5 Hz, 2H), 2.49−2.55 (m, 2H), 3.11−3.16 (m, 4H), 4.11 (q, J = 7.1 Hz, 2H); ^{13}C NMR δ u 9.8, 18.2, 18.6, 18.7 (×2), 22.2, 23.9, 28.5, 31.0, 33.1, 60.3, 74.3, 74.8, 75.2, 79.5, 82.8, 173.2; d 14.0, 14.2, 54.9, 55.3; IR (cm^{-1}) 2932, 1732, 1159; MS *m/z* 342 (M$^+$, 15), 167 (100); HRMS calcd for $C_{22}H_{30}O_3Na$ (M + Na) 365.2093, obsd 365.2092.

Triene (8). To a solution of $Ni(OAc)_2 \cdot 4H_2O$ (30 mg, 0.12 mmol) in ethanol (0.5 mL) was add a solution of $NaBH_4$ (1 M solution in ethanol, 0.10 mL, 0.10 mmol). The black mixture was evacuated and backfilled with H_2 three times. Ethylenediamine (9 mg, 0.15 mmol, 0.01 mL) was added, followed by a solution of epoxide **14** (11 mg, 0.03 mmol) in ethanol (0.1 mL). The flask was evacuated and backfilled with H_2 three times. The reaction mixture was stirred at rt for 10 h under H_2. The solvent was removed under reduced pressure, and the residue was partitioned between water and CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to give the triene **8** as a colorless oil (7 mg, 0.02 mmol, 63% yield): TLC R_f (MTBE/petroleum ether = 1:10) = 0.36; ^{1}H NMR δ 0.88 (t, J = 7.1 Hz, 3H), 1.28 (t, J = 7.1 Hz, 3H), 1.30−1.35 (m, 4H), 1.43−1.50 (m, 2H), 1.72−1.76 (m, 2H), 2.08−2.14 (m, 4H), 2.28−2.35 (m, 2H), 2.39 (t, J = 7.5 Hz, 2H), 2.49−2.55 (m, 2H), 2.85 (m, 2H), 3.00 (m, 2H), 4.16 (q, J = 7.1 Hz, 2H), 5.41−5.53 (m, 6H); ^{13}C NMR δ u 22.6, 24.8, 25.8, 26.1, 26.2, 26.6, 27.4, 29.2, 31.5, 33.7, 60.3, 173.6; d 14.1, 14.3, 56.4, 56.5, 123.6, 124.3, 128.4, 129.3, 130.6, 132.9; IR (cm^{-1}); 2927, 1736, 1159; MS *m/z* 349 (M$^+$ + H, 50), 242 (40); HRMS calcd for $C_{22}H_{36}O_3Na$ (M + Na) 371.2586, obsd 371.2571.

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Supporting Information Available: General experimental procedures, details for all intermediates in the trans series, and ^{1}H and ^{13}C NMR spectra for all new compounds and for the methyl ester of **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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