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Efficient total synthesis of 5-oxo-6(*E*),8(*Z*),11(*Z*),14(*Z*)-eicosatetraenoic acid (5-oxo-ETE), a potent proinflammatory autacoid

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Abstract—The title eicosanoid was prepared in good overall yield via a convergent aldol strategy that obviates the need for HPLC separation of olefinic isomers.

Recent studies[1,2] have established 5-oxo-6(*E*),8(*Z*), 11(*Z*),14(*Z*)-eicosatetraenoic acid (5-oxo-ETE, **1**) as a potent proinflammatory autacoid.[3] It is derived from the 5-LO pathway metabolite 5(*S*)-hydroxyeicosatetraenoic acid [5(*S*)-HETE] by a stereospecific $NADP^+$-dependent dehydrogenase.[1] In neutrophils and eosinophils, **1** induces calcium mobilization,[4] degranulation,[5] actin polymerization,[6,7] superoxide generation,[6] chemotaxis,[4,8] L-selectin shedding,[9] and expression of adhesion molecules.[7] Many of these effects are associated with G protein-linked receptors.[4–6,10]

Although quite labile and prone to isomerization, **1** is the precursor to a variety of secondary metabolites[11] of considerable current interest (Fig. 1), including a novel, bioactive 1,4-glutathione adduct[12] (FOG_7) reminiscent of leukotriene C_4. To expedite continuing efforts to elucidate its pharmacology and metabolic fate, as well its involvement in chronic pathology,[1] e.g. asthma, we report herein an efficient, stereospecific total synthesis of **1**.[13] Our approach exploits a convergent aldol strategy that obviates the need for HPLC separation of olefinic isomers[13] and is amenable to the introduction of stable and/or radio-isotopes.[14]

The nucleophile for the aldol reaction, representing C(1)–C(6), was derived from commercial 4-acetylbutyric acid (**2**) (Scheme 1). This was transformed

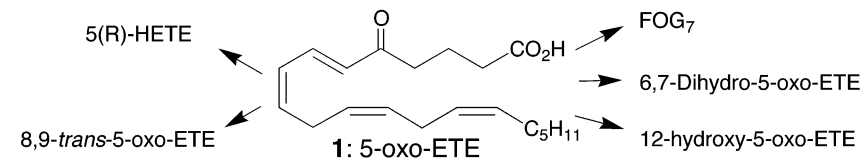
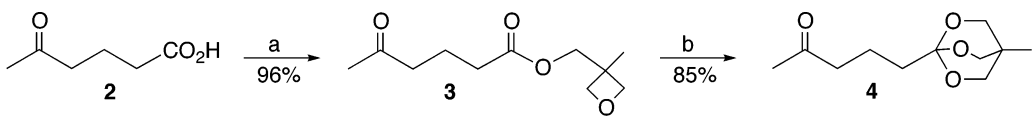


Figure 1. Metabolism of **1**.



Scheme 1. *Reaction conditions*: (a) DCC, DMAP, MOX-OH, CH_2Cl_2, 0°C, 12 h. (b) $BF_3{\cdot}Et_2O$ (0.3 equiv.), CH_2Cl_2, 23°C, 8 h.

Keywords: eicosanoids; aldol reactions; biologically active compounds; hydrogenation; metabolites.
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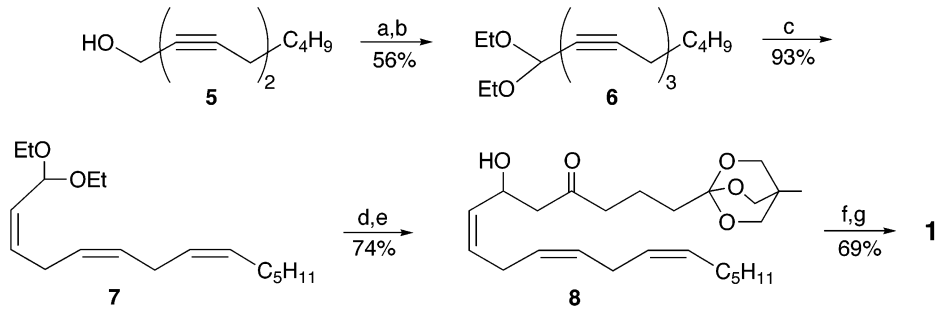

Scheme 2. *Reaction conditions*: (a) TsCl, py, CH_2Cl_2, 23°C, 12 h. (b) **9**, CuI, NaI, K_2CO_3, DMF, −40 to 23°C, 12 h. (c) Ni(P2), H_2, EtOH, 23°C, 2 h. (d) 4% oxalic acid, acetone/H_2O (1:1), 0°C, 1 h. (e) **4**, LDA, THF, −78°C, 2 h; product of step d, −78°C, 3 h. (f) 0.01% H_2SO_4, MeOH, 0°C, 0.5 h; K_2CO_3 (pH 10), 0°C, 1 h. (g) 1N LiOH, *i*-PrOH, 23°C, 12 h.

uneventfully into orthoester **4**[15] via methyloxetane (MOX) ester **3** according to Corey and Raju.[16]

The electrophilic aldol acceptor (Scheme 2) was fashioned from the readily available bis-acetylene **5**[17] by tosylation under conventional conditions and alkylation with propiolaldehyde diethyl acetal (**9**) in the presence of Cu(I).[17] The resultant tris-acetylene adduct **6** contains all of the remaining carbons of the eicosanoid backbone. Its partial hydrogenation utilizing P-2 nickel[18] reproducibly afforded all-*cis*-triene **7** over a wide scale (μmol–mmol) without the need for purification beyond filtration and evaporation of the solvent. Deuteration or tritiation could also be conveniently achieved during this procedure using isotopic gas. Carefully controlled acetal hydrolysis using 4% oxalic acid at 0°C gave rise to a labile *cis*-enal that was immediately condensed with the enolate of **4** in anhydrous THF at −78°C. The adduct **8** was converted to **1** by sequential acidic hydrolysis of the orthoester with 0.01% H_2SO_4, in situ transesterification to its methyl ester, taking care not to exceed 0°C and pH 10, and finally saponification in *i*-PrOH, as recommended by Kerdesky et al.[19] The use of MeOH or THF/H_2O as solvent induced significant, but variable, isomerization to 8,9-*trans*-5-oxo-ETE.

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15. **Orthoester 4**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.79 (s, 3H), 1.64–1.77 (m, 4H), 2.12 (s, 3H), 2.45 (t, 2H, J=7.0 Hz), 3.88 (s, 6H). **Acetal 7**: δ 0.89 (t, 2H, J=7.0 Hz), 1.22 (t, 6H, J=7.0 Hz), 1.26–1.46 (m, 6H), 2.05 (q, 2H, J=7.3 Hz), 2.80 (t, 2H, J=6.7 Hz), 2.93 (t, 2H, J=6.7 Hz), 3.48–3.55 (m, 2H), 3.61–3.69 (m, 2H), 5.24 (d, 1H, J=6.4 Hz), 5.30–5.43 (m, 4H), 5.47–5.52 (m, 1H), 5.56–5.63 (m, 1H). **Adduct 8**: δ 0.79 (s, 3H), 0.89 (t, 3H, J=6.7 Hz), 1.26–1.41 (m, 6H), 1.64–1.79 (m, 4H), 2.04 (q, 2H, J=7.3 Hz), 2.47 (t, 2H, J=7.3 Hz), 2.52–2.67 (m, 2H), 2.79 (t, 2H, J=6.7 Hz), 2.87 (q, 2H, J=7.9 Hz), 3.01 (d, 1H, J=3.3 Hz), 3.87 (s, 6H), 4.87–4.93 (m, 1H), 5.28–5.49 (m, 6H). Synthetic **1** was identical by NMR, MS, and HPLC with an authentic standard.
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