

Total Synthesis of 5(*S*),20- and 15(*S*),20-Dihydroxyeicosatetraenoic Acid and 5(*S*),6(*R*)-Epoxy-20-hydroxy- and 14(*R*),15(*S*)-Epoxy-20-hydroxyeicosatrienoic Acid

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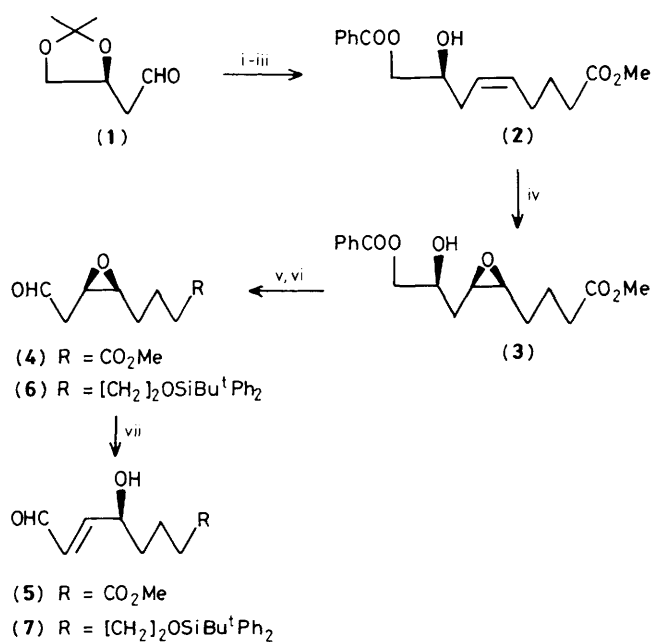
Aldehyde (**1**), derived from dimethyl *L*-malate, was exploited in a stereocontrolled total synthesis of the ω -hydroxylated eicosanoid metabolites 5(*S*),20- and 15(*S*),20-dihydroxyeicosatetraenoic acid as well as 5(*S*),6(*R*)-epoxy-20-hydroxy- and 14(*R*),15(*S*)-epoxy-20-hydroxyeicosatrienoic acid.

Cytochrome P-450 mediated ω -hydroxylation is a major pathway in the secondary metabolism of eicosanoids¹ and can dramatically alter biological activity.² Recent examples include the oxidation of 12(*S*)-hydroxyeicosatetraenoic acid (HETE)³ and several epoxygenase metabolites.⁴ *In vitro*, cytochrome P-450 is also able to ω -hydroxylate epoxyeicosatrienoic acids (EETs) in addition to other HETEs.[†] As part of our efforts⁵ to evaluate the pharmacological consequences of ω -hydroxylation and in anticipation of the isolation of new metabolites, a versatile and convergent enantiospecific approach to mono-oxygenase fatty acid metabolites was developed. The synthetic potential of this route is illustrated herein by total syntheses of 5(*S*),20- and 15(*S*),20-dihydroxyeicosatetraenoic acids as well as 5(*S*),6(*R*)-epoxy-20-hydroxy- and 14(*R*),15(*S*)-epoxy-20-hydroxyeicosatrienoic acids.

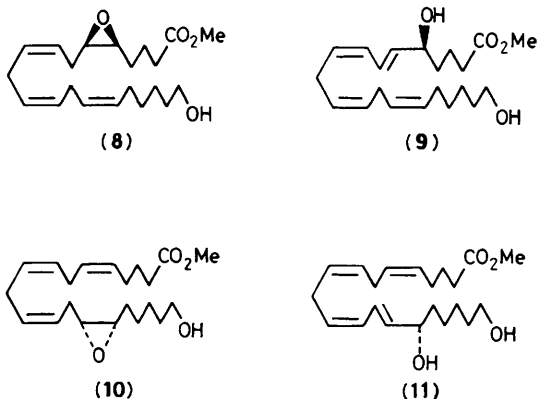
Aldehyde (**1**)⁶ was transformed into hydroxy-benzoate (**2**)[‡] (61%) by homologation with 4-methoxycarbonylbutylidene-triphenylphosphorane under *cis*-olefination conditions, selective acetonide hydrolysis, and benzylation of the primary alcohol (Scheme 1). Erythro-specific epoxidation⁷ furnished (**3**) (77%) which was converted into aldehyde (**4**) (88%) by exposure to methanolic KHCO₃ followed by periodate cleavage of the resultant diol. Stirring with an ethereal suspension of silica gel smoothly isomerized (**4**) to the *trans*-enal (**5**) (96%).

[†] The details of these experiments will be published elsewhere.

[‡] Satisfactory n.m.r., u.v., and mass spectral data were obtained for all new compounds using chromatographically homogeneous samples.



Scheme 1. Reagents: i, Ph₃PCH[CH₂]₃CO₂Me, tetrahydrofuran (THF)-hexamethylphosphoric triamide (HMPT) (4:1), -78 → 20°C, 3 h; ii, 1 M HCl-MeOH (1:5), 4°C, 12 h; iii, PhCOCN, 10 mol% Et₃N, CH₂Cl₂, 0°C, 0.5 h; iv, Bu^tOOH, VO(acac)₂ (Hacac = MeCOCH₂COMe), CH₂Cl₂, 0°C, 10 h; v, KHCO₃, MeOH, 20 h; vi, NaIO₄, MeOH-H₂O (3:1), Na₂HPO₄, 0°C, 40 min; vii, SiO₂, Et₂O, 1 h.



Wittig coupling of (4) with 12-(*t*-butyldiphenylsilyloxy)-dodeca-(*Z,Z*)-3,6-dien-1-ylidetriphenylphosphorane [generated at -78°C , tetrahydrofuran (THF), 45 min, $\text{NaN}(\text{SiMe}_3)_2$] in THF-toluene (1:4.6) at -100 to -15°C over 4 h and fluoride mediated desilylation afforded methyl 5(*S*),6(*R*)-epoxy-20-hydroxyeicosatrienoate (8) (59%).[§] Treatment of (5) with the same phosphorane (-78 to -15°C , 3 h) in THF-hexamethylphosphoric triamide (HMPT) (4:1) led to methyl 5(*S*),20-dihydroxyeicosatetraenoate (9) (58%).

When the adduct between aldehyde (1) and 6-(*t*-butyldiphenylsilyloxy)hexylidetriphenylphosphorane was

§ (8): ^1H n.m.r. (90 MHz, CDCl_3) δ 1.20–2.48 (16H, m), 2.66–3.02 (6H, m), 3.58 (2H, t, J 7 Hz), 3.62 (3H, s), 5.20–5.56 (6H, m); $[\alpha]_{\text{D}}^{23} -3.77^{\circ}$ (*c* 1.28, acetone). (9): ^1H n.m.r. (90 MHz, CDCl_3) δ 1.16–1.72 (10H, m), 1.90–2.44 (4H, m), 2.66–3.02 (4H, m), 3.57 (2H, t, J 7 Hz), 3.62 (3H, s), 4.00–4.24 (1H, m), 5.14–6.05 (7H, m), 6.46 (1H, dd, J 11 and 15 Hz); $[\alpha]_{\text{D}}^{23} 10.2^{\circ}$ (*c* 1.53, acetone). (10): $[\alpha]_{\text{D}}^{23} 4.66^{\circ}$ (*c* 1.01, acetone). (11): $[\alpha]_{\text{D}}^{23} 12.0^{\circ}$ (*c* 1.76, acetone). The ^1H n.m.r. spectra of (10) and (11) are virtually identical to those of (8) and (9), respectively.

carried through the sequence outlined in Scheme 1, aldehydes (6) and (7) were obtained in 44% and 42% overall yield, respectively. Condensation of (6) with 10-methoxycarbonyl-dodeca-(*Z,Z*)-3,6-dien-1-ylidetriphenylphosphorane according to the conditions described above and desilylation resulted in methyl 14(*R*),15(*S*)-epoxy-20-hydroxyeicosatrienoate (10) (54%) whereas (7) gave methyl 15(*S*),20-dihydroxyeicosatetraenoate (11) (68%). Esters (8)–(11) were converted into the corresponding acids using LiOH in MeOH- H_2O (3:1), acidification to pH 4.5, and extractive isolation.

Results from current investigations into the occurrence, enzymatic origin, and pharmacology of the above metabolites will be reported later.

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