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

Sun Lumin,[a] Pendri Yadagiri,[a] J. R. Falck,*[a] Jorge Capdevila,[a] Paul Mosset,[b] and René Grée*[b]

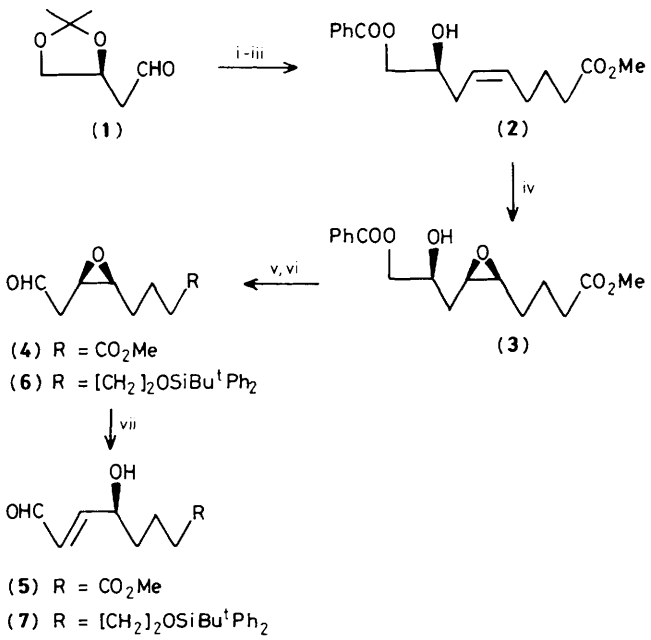
[a] *Departments of Molecular Genetics and Biochemistry, University of Texas Health Science Center, Dallas, Texas 75235, U.S.A.*

[b] *Groupe de Recherche de Physicochimie Structurale, U.A. C.N.R.S. No. 704, Universite de Rennes 1, 35042 Rennes Cedex, France*

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 eicosanoids[1] 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 efforts[5] 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.

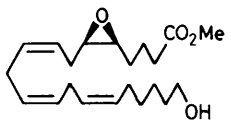
Aldehyde (**1**)[6] was transformed into hydroxy-benzoate (**2**)‡ (61%) by homologation with 4-methoxycarbonylbutylidenetriphenylphosphorane under *cis*-olefination conditions, selective acetonide hydrolysis, and benzoylation of the primary alcohol (Scheme 1). Erythrospecific epoxidation[7] furnished (**3**) (77%) which was converted into aldehyde (**4**) (88%) by exposure to methanolic $KHCO_3$ 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%).



Scheme 1. *Reagents:* i, $Ph_3PCH[CH_2]_3CO_2Me$, 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% Et_3N, CH_2Cl_2, 0 °C, 0.5 h; iv, Bu^tOOH, $VO(acac)_2$ (Hacac = $MeCOCH_2COMe$), CH_2Cl_2, 0 °C, 10 h; v, $KHCO_3$, MeOH, 20 h; vi, $NaIO_4$, MeOH–H_2O (3:1), Na_2HPO_4, 0 °C, 40 min; vii, SiO_2, Et_2O, 1 h.

† 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.



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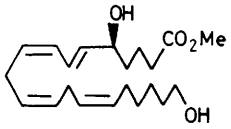

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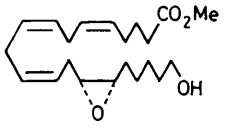

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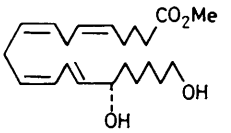

(11)

Wittig coupling of (**4**) with 12-(t-butyldiphenylsilyloxy)-dodeca-(*Z*,*Z*)-3,6-dien-1-ylidenetriphenylphosphorane [generated at −78 °C, tetrahydrofuran (THF), 45 min, $NaN(SiMe_3)_2$] 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)hexylidenetriphenylphosphorane was 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-deca-(*Z*,*Z*)-3,6-dien-1-ylidenetriphenylphosphorane 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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§ (**8**): ^{1}H 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); $[\alpha]_D^{23}$ −3.77° (*c* 1.28, acetone). (**9**): ^{1}H 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); $[\alpha]_D^{23}$ 10.2° (*c* 1.53, acetone). (**10**): $[\alpha]_D^{23}$ 4.66° (*c* 1.01, acetone). (**11**): $[\alpha]_D^{23}$ 12.0° (*c* 1.76, acetone). The ^{1}H n.m.r. spectra of (**10**) and (**11**) are virtually identical to those of (**8**) and (**9**), respectively.

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