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Chiral Acetals: Stereocontrolled Syntheses of 16-, 17-, and 18-Hydroxyeicosatetraenoic Acids, Cytochrome P-450 Arachidonate Metabolites

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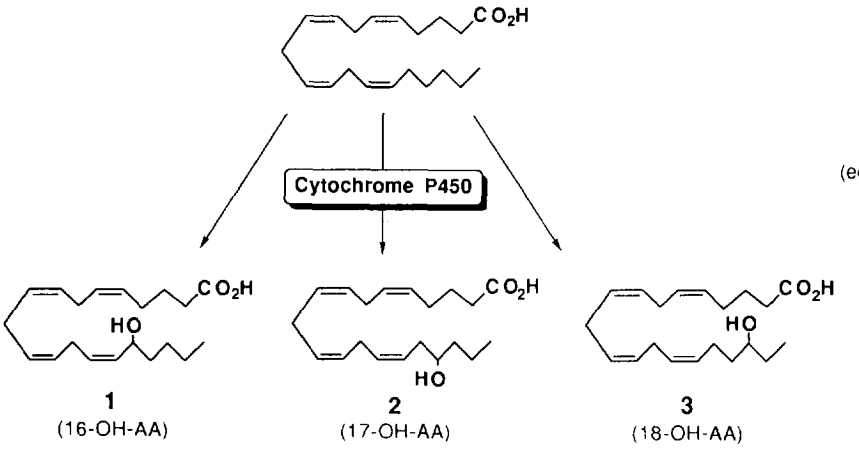
Abstract/ *Chiral adducts from Grignard or allylsilane additions to 1,3-dioxan/1,3-dioxolan-4-ones were exploited for the total synthesis of the* ***R****- and* ***S****-isomers of the title eicosanoids.*

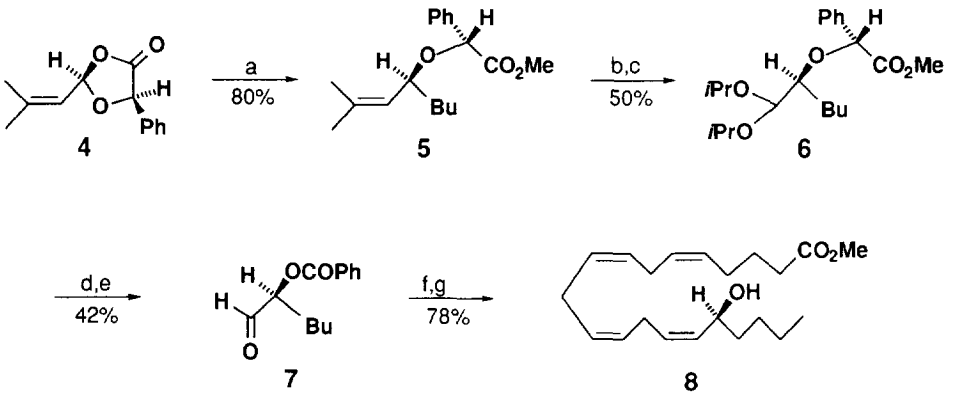
Extensive investigations by these and other laboratories have established a unique paradigm for eicosanoid biosynthesis via cytochrome P-450.[1] Most notably, the profile of metabolites and their absolute configurations are isozyme dependent and, thus, reflect the interplay amongst such factors as pathophysiology, gender, species, tissue, age, diet, and xenobiotic induction.[2] This often results in complex mixtures of closely related metabolites as recently observed[3] in the ω-oxidation pathway from which 16-,17-, and 18-hydroxyeicosatetraenoic acid (16-,17-,18-OH-AA) were isolated (eq 1). To expedite current stereochemical studies and pharmacological evaluations of this pathway, we describe herein the enantiospecific total syntheses of the three monooxygenase metabolites **1**-**3** by the strategic exploitation of chiral acetals.[4]



(eq 1)

Scheme 1 summarizes the route to 16-OH-AA. Nucleophilic S_N2 addition[5] of butyl magnesium bromide in Et_2O to the acetalic center of homochiral 1,3-dioxolan-4-one **4**,[6] prepared from 3-methyl-2-butenal and (**R**)-mandelic acid, followed by esterification with diazomethane readily afforded substituted O-allyl mandelate **5**.[7] Diisopropyl acetal **6** was obtained from **5** via low temperature ozonolysis with Me_2S workup and incubation of the resultant crude aldehyde with triisopropyl orthoformate in the presence of catalytic pyridinium *p*-toluenesulfonate (PPTS). Mild oxidative decarboxylation of **6** via an *in situ* generated dioxetanone as described by Heckmann et al.[8] led to the corresponding benzoate. Minor amounts of free alcohol released during this process were benzoylated and the combined degradation product was hydrolyzed using trifluoroacetic acid to furnish aldehyde **7**. Wittig condensation of **7** with 13-carbomethoxytrideca-3(Z),6(Z),9(Z)-trien-1-ylidene-triphenylphophorane[3a] (**9**) and methanolysis of the benzoate gave rise to methyl 16(S)-OH-AA(**8**), $[\alpha]_D^{23}$ = -5.4 (c 0.7, acetone).[9] Mitsunobu inversion[10] ($PhCO_2H$,Ph_3P,DEAD) of **8** and benzoate removal (NaOMe, MeOH, 24°C, 2h) yielded the 16(**R**)-isomer in 65-70% overall yield.

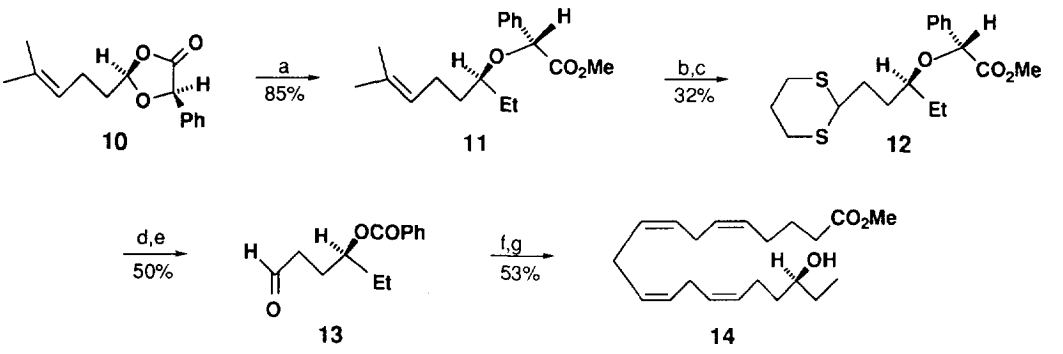
Scheme 1



[a]*n*-BuMgBr, Et_2O, -78→24°C, 12h; CH_2N_2. [b]O_3, MeOH, -78°C; Me_2S. [c]$(iPrO)_3CH$, PPTS, Et_2O, 12h. [d]*t*-BuOK, THF, O_2, 24°C, 10 min; PhCOCl, py. [e]CF_3CO_2H, CH_2Cl_2, 24°C, 10 min. [f]**9**, $NaN(TMS)_2$, THF/HMPA (5:1), -78°C, 1h. [g]NaOMe, MeOH, 24°C, 10h.

An analogous strategy utilizing **10**, the adduct[11] of (**R**)-mandelic acid with 5-methyl-4-hexenal, led to both antipodes of **3** (Scheme 2). In this instance, however, sequential copper catalyzed addition[5] of ethyl magnesium bromide to **10** and diazomethane esterification evolved **11** as a chromatographically separable [SiO_2:Et_2O/hexane(1:9)] diastereomeric mixture (92:8). Ozonolytic cleavage of the trisubstituted olefin and condensation of the product with propanedithiol gave rise to **12** which was converted to aldehyde **13** by oxidative degradation of the chiral auxiliary as described above and silver assisted thioacetal hydrolysis. Reaction of **13** with ylide **9** and methanolysis of the benzoate protecting group yielded methyl 18(S)-OH-AA (**14**), $[\alpha]_D^{23}$= +4 (c 0.35, acetone). As above, the **R**-isomer was secured without complication by Mitsunobu inversion.

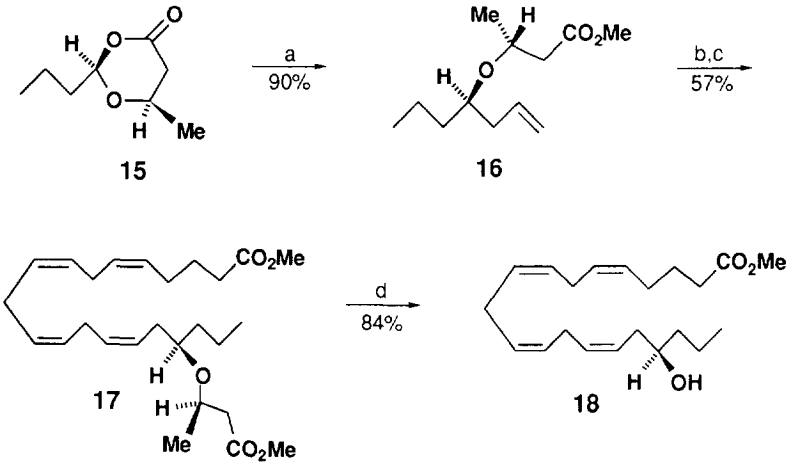
Scheme 2



[a]EtMgBr, CuI, Et_2O,-20°C, 12h; CH_2N_2. [b]O_3, MeOH, -78°C; Me_2S. [c]$HSCH_2CH_2CH_2SH$, $BF_3{\cdot}Et_2O$, Et_2O, -20→24°C, 24h. [d]*t*-BuOK, THF, O_2, 24°C, 10 min; PhCOCl, py. [e]$AgNO_3$, NCS, CH_3CN/H_2O, 24°C, 10 min. [f]**9**, $NaN(TMS)_2$, THF/HMPA (5:1), -78°C, 30 min. [g]NaOMe, MeOH, 24°C, 10h.

The six-membered 1,3-dioxan-4-one **15**, from butanal and 3(**R**)-hydroxybutyric acid,[12] reacted with allyltrimethylsilane in presence of isopropoxytitanium trichloride to form the ether **16** (Scheme 3). Olefination with ylide **9** of the aldehyde from ozonolysis of **16** afforded diester **17**. Based induced β-elimination of the chiral auxiliary liberated methyl 17(**R**)-OH-AA (**18**), $[\alpha]_D^{24}$ = +4 (c 1.4, acetone).[4] Transposition to the **S**-isomer relied on the standard Mitsunobu protocol.

Scheme 3



[a]$TMSCH_2CH{=}CH_2$, *i*-$PrOTiCl_3$, CH_2Cl_2, -78°C; CH_2N_2. [b]O_3, MeOH, -78°C; Me_2S. [c]**9**, $NaN(TMS)_2$, THF/HMPA (5:1), -78°C, 0.5h. [d]*t*-BuOK, THF, 0°C, 10 min.

Saponification of **8**, **14**, **18**, and their enantiomers provided the corresponding free acids which were identical by HPLC and GC/MS (as pentafluorobenzyl ester trimethylsilyl ethers) with their respective enzymatically derived counterparts.[4] These metabolites have been identified as endogenous constituents of kidney, aorta, and intestines where they display regio- and stereodependent vascular effects.[13] Details of current *in vivo* stereochemical studies of **1-3** and their physiological role have been reported elsewhere.[14]

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9. Physical data for **4**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.87 (m, 6H), 5.26 (d, J=1.2Hz, 1H), 5.44 (m, 1H), 6.32 (dd, J=7.8, 1.2Hz, 1H), 7.35-7.51 (m, 5H); mp 77-81°C (EtOAc/hexane); Anal. Calcd for $C_{13}H_{14}O_3$:C, 71.54, H, 6.47. Found C, 71.38, H, 6.68. **8**: ^{1}H NMR (200 MHz, C_6D_6) δ 0.87 (t, J=6.8Hz, 3H), 1.15-1.70 (m, 8H), 1.90-2.15 (m, 4H), 2.65-2.95 (m, 6H), 3.33 (s, 3H), 4.38 (dd, J=7,14Hz, 1H), 5.22-5.60 (m, 8H); TLC(SiO_2) EtOAc/hexane(1:2), R_f~0.39. **10**: ^{1}H NMR (200 MHz, $CDCl_3$), δ1.56 (s, 3H), 1.73 (s, 3H), 1.97 (m, 2H), 2.25 (m, 2H), 5.16 (tq, J=7.5, 1.0Hz, 1H), 5.25 (d, J=1.2Hz, 1H), 5.7 (td, J=5.1Hz, 1H), 7.3-7.5 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.66, 21.63, 25.64, 34.31, 76.70, 104.22, 122.17, 126.81, 128.72, 129.14, 133.34, 172.62; mp. 44-46°C; $[\alpha]_D$=-68 (c 1.8, $CHCl_3$). **15**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, J=7.2Hz, 3H), 1.22 (d, J=8.4Hz, 3H), 1.44 (m, 2H), 1.67 (m, 2H), 2.42 (ABX, δ_a=2.59, δ_b=2.29, J_{ab}=17.8, J_{ax}=4.4, J_{bx}=10.7Hz, 2H), 3.95 (m, 1H), 5.25 (t, J=4.9Hz, 1H); ^{13}C NMR (50 Mhz, $CDCl_3$) δ 13.51, 16.23, 20.97, 36.52, 37.49, 70.38, 103.02, 167.67. Esters **14** and **18** were identical with previously prepared standards.[4]

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