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ASYMMETRIC TOTAL SYNTHESIS OF 14(R),15(S)-, 14(S),15(R)-, 14(R),15(R)-, AND 14(S),15(S)-EPOXYEICOSATRIENOIC ACIDS

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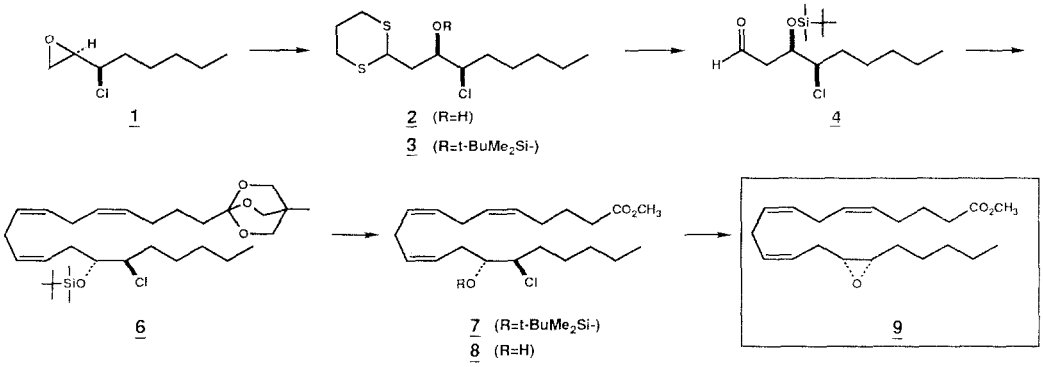
Abstract: The four chiral stereoisomers of 14,15-oxido-5Z,8Z,11Z-eicosatrienoic acid were synthesized. The absolute stereochemistry in each case was derived from an asymmetric epoxidation of E-2-octen-1-ol.

It is now widely recognized that in addition to the well-known cyclooxygenase and lipoxygenase pathways for eicosanoid production from arachidonic acid there exists an additional metabolic branch designated as the epoxygenase pathway.[1] Initiated by cytochrome P-450, this pathway produces four regioisomeric *cis*-epoxyeicosatrienoic acids.[2] Not only do each of these epoxides serve as pivotal intermediates for the generation of additional metabolites[3], but there is a growing body of evidence suggesting that these compounds possess significant physiological activity of their own.[4] It has been shown that epoxidation of arachidonic acid by purified rat liver microsomal cytochrome P-450 proceeds stereoselectively, favoring one enantiomeric epoxide by as much as 97%.[5] In conjunction with our interest in eicosanoid biochemistry and due to the limited availability of epoxygenase metabolites from biological sources, we initiated a program designed to synthesize the four stereoisomers of 14,15-epoxyeicosatrienoic acid (14,15-EET).

Outlined in Scheme I is our approach to the construction 14(R),15(S)-EET.[6] Alkylation of 2-lithio-1,3-dithiane with the epoxy-chloride **1** (THF, -30°C, 90%) gave the chlorohydrin **2**, which after alcohol protection and thioketal hydrolysis (CH_3I, $BaCO_3$, CH_3CN–H_2O, 55°C) afforded aldehyde **4** in 85% overall yield. Wittig olefination of **4** with the ylide derived from 1-(4-methyl-2,6,7-trioxabicyclo-[2.2.2]octyl)-deca-4Z,6Z-dienyltriphenylphosphonium iodide **5**[7] (THF, HMPA, -78° to 0°C) afforded the all-*cis* triene **6** in 70% yield after chromatography. Orthoester hydrolysis (Dowex 50W-X8 resin, CH_3OH, then K_2CO_3, 91%)gave the methyl ester **7**, which was treated with tetra-*n*-butylammonium fluoride in THF to give a mixture of alcohol **8** and the desired epoxide **9**. Dissolution of this mixture in methanol and brief treatment with K_2CO_3 completed the cyclization and produced 14(R),15(S)-EET methyl ester ($[\alpha]_D^{20}$ = -2.71°, c 0.885, $CHCl_3$) in 79% yield from **6**.

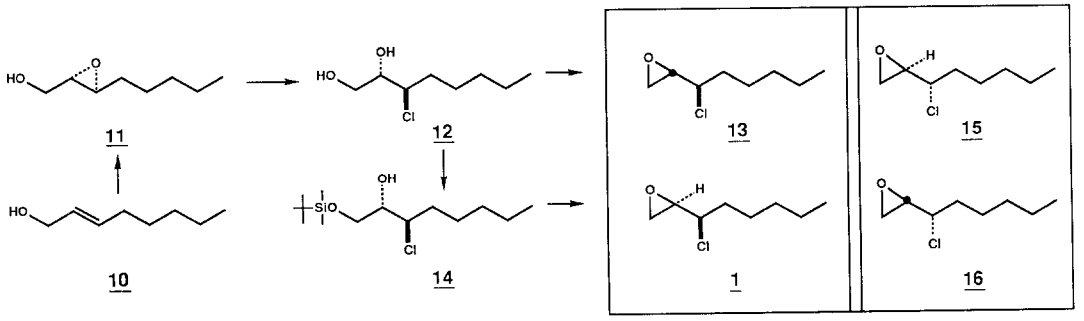
SCHEME I



Inherent in this synthetic sequence is the fact that the stereochemical disposition of the final epoxide product is clearly a reflection of the stereochemical disposition of the starting epoxy-chloride (e.g. **1**). Thus, in order to synthesize the four stereoisomers of 14,15-EET via the approach outlined in Scheme I, we needed a convenient route to the four corresponding epoxy-chlorides. Summarized in Scheme II is the methodology used to generate each of the four requisite 3-chloro-1,2-epoxyoctanes from the common intermediate E-2-octen-1-ol **10**. Sharpless epoxidation of **10** (t-butylhydroperoxide, $Ti(OPr)_4$, (+)-diethyl-L-tartrate, CH_2Cl_2)[8] efficiently affords the chiral epoxy-alcohol **11** (60%, $[\alpha]_D^{20}$ = -35.1°). Treatment of **11** with dichlorodiisopropoxytitanium in the presence of diethyl tartrate[9] (CH_2Cl_2, 88%) generates the chlorodiol **12** with only trace amounts of the undesired C-2 chloride regioisomer being detected. Tosylation of the primary hydroxyl of **12** (TsCl, pyr, 0°C) and subsequent base-induced ring closure (CH_3OH, K_2CO_3) gives the epoxychloride **13** in ~70% overall yield from **12**. Epoxy-chloride **1**, the diastereomer of **13**, is also produced from the chlorodiol **12** in three steps by silylation of the primary hydroxyl (t-butyldimethylchlorosilane, triethylamine, CH_2Cl_2), tosylation of the secondary hydroxyl (TsCl, DMAP, CH_2Cl_2), and desilylation with fluoride ion and concomitant ring closure (tetra-*n*-butylammonium fluoride, THF; CH_3OH, K_2CO_3) to finally afford **1** in 68% overall yield from **12**. In a completely analogous manner, the diastereomeric pair of epoxy-chlorides **15** and **16** were synthesized starting with the enantiomer of **11**, itself readily available from an asymmetric epoxidation of E-2-octen-1-ol using (-)-diethyl-D-tartrate. Unfortunately, all four of these epoxy-chlorides exhibited specific rotations of less than 1°, rendering comparisons of optical purity by rotations to be of limited value. However, excellent correlation of rotations of synthetic intermediates leading to and derived from these compounds provided compelling evidence of their stereochemical integrity.

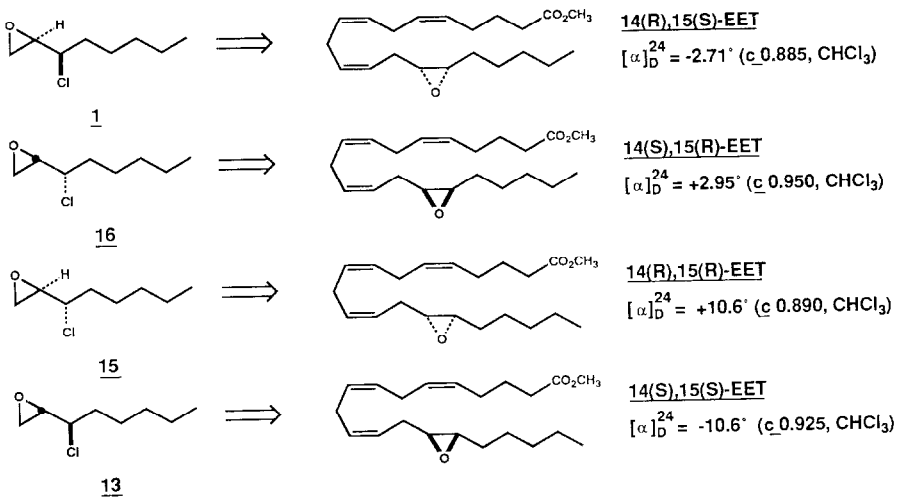
With each of the required epoxy-chlorides in hand, we were able to carry these compounds through the synthetic sequence shown in Scheme I and thus obtain all four of the desired 14,15 EET stereoisomers. In the Table is illustrated the relationship between the starting epoxy-chloride isomer and the ultimate epoxyeicosanoid product. It was gratifying to find that the specific rotation observed for the 14(R),15(S)-EET isomer was in excellent agreement with that reported by Falck, et.al. for this compound.[10]

SCHEME II



Hydrolysis of the methyl esters shown in the Table (LiOH, DME-H_2O) provided the free carboxylic acids suitable for biological evaluation.[11] Preliminary experiments have demonstrated that the 14(R),15(S)-EET stereoisomer is a potent inhibitor of the isolated cyclooxygenase enzyme (IC_{50} = 3-5μM). Interestingly, none of the other isomers, including the 14(S),15(R)- compound, exhibited any activity in this assay. However, all 14,15-EET stereoisomers were able to inhibit collagen-induced platelet aggregation, although the *cis*- compounds were nearly four times as potent as the *trans*-isomers. Full results of the biological evaluation of the 14,15-EET stereoisomers will be reported shortly.

TABLE: Relationship between epoxy-chlorides and 14,15-EET products



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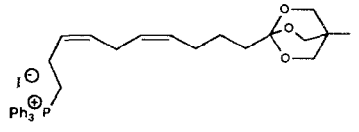
6. For all new and stable compounds satisfactory infrared, proton magnetic resonance, combustion analysis and/or mass spectral data were obtained.

7. Phosphonium salt **5** was prepared from 5-hexynoic acid OBO ester by 1) acetylene homologation with paraformaldehyde 2) Cu(I)-mediated displacement of the derived tosylate with the dianion of 3-butyn-1-ol 3) semihydrogenation to the Z,Z-diene 4) alcohol conversion to the iodide and subsequent displacement with triphenylphosphine.



5

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11. The biological evaluations reported herein were performed by Dr. F. A. Fitzpatrick. We are indebted to Dr. Fitzpatrick for providing to us these results for early communication.

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