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A Short Catalytic Enantioselective Synthesis of the Vascular Antiinflammatory Eicosanoid (11*R*,12*S*)-Oxidoarachidonic Acid

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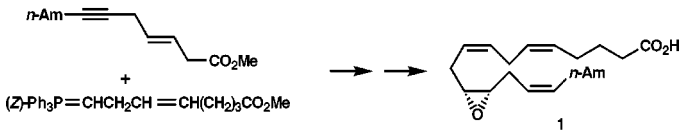
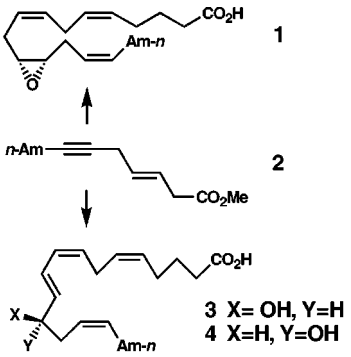
ABSTRACT



An effective pathway is described for the synthesis of (11*R*,12*S*)-oxidoarachidonic acid (1) from the achiral precursors shown.

Disregulation and malfunction of cells in the vasculature leading to inflammation are important components of cardiovascular disease that contribute significantly to atherosclerosis, heart attack, and stroke.[1,2] Although the biochemical basis for these inflammatory processes remains unclear, remarkable progress has been made recently on the involvement of the TNF-α[3,4] and NF-κB[5−7] signaling pathways in vascular inflammation and on the regulatory role of eicosanoids, especially (11*R*,12*S*)-oxidoarachidonic acid (**1**) [(11*R*,12*S*)-EET].[8−11] Epoxide **1** appears to be formed by



the action of the cytochrome P450 isoform CYP2J2 on arachidonic acid in endothelial cells and to inhibit the degradation of IκB, thereby blocking the activation (release) of NF-κB and its migration into the nucleus where it functions as a proinflammatory transcription factor.[8] Stimulation of bovine endothelial cells with TNF-α increased IκB kinase activity, which was strongly inhibited by **1** with an IC_{50} of 20 nM.[8] It is clear that (11*R*,12*S*)-EET (**1**) is a potent endogenous antiinflammatory eicosanoid which may be the forerunner of a new class of cardiovascular therapeutic agents.[12]

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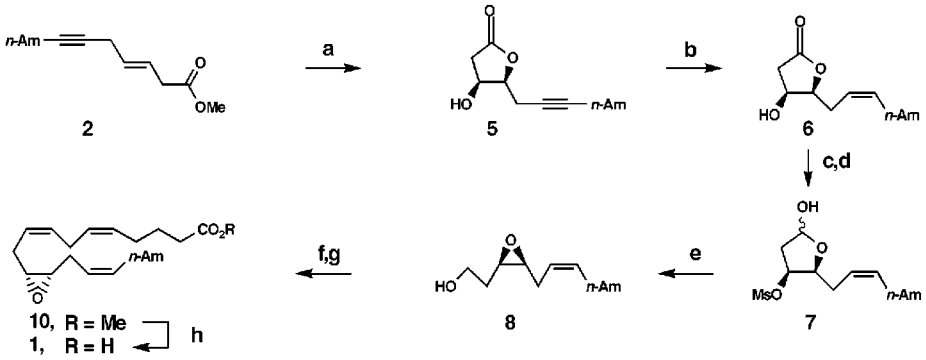
Scheme 1



(a) AD-mix-α, 1 eq $CH_3SO_2NH_2$, 1:1 *t*-BuOH-H_2O, 36 h at 0 °C. (b) 1 atm H_2, Pd-$CaCO_3$-Pb, THF, 0 °C, 45 min. (c) 1.4 eq CH_3SO_2Cl, 1.4 eq NEt_3, CH_2Cl_2, 0 °C, 1 h. (d) 1.2 eq *i*-Bu_2AlH, C_7H_8, -78 °C, 1h. (e) 2 eq $NaBH_4$, CH_3OH, 0 °C, 1.5 h then 3 eq K_2CO_3, 3 h at 23 °C. (f) 1.3 eq Dess-Martin periodinane, CH_2Cl_2, 50 min at 23 °C. (g) (*Z*)-$Ph_3P{=}CHCH_2CH{=}CH(CH_2)_3CO_2Me$ (**9**), 5:1 C_7H_8-THF, -94 °C to -15 °C, 3 h. (h) 10 eq LiOH, DME-H_2O, 23 °C for 15 h.

Since the first chemical synthesis of (±)-(11,12)-EET in these laboratories two decades ago,[13] there have been described the nonposition selective peroxy acid conversion of arachidonic acid to a mixture of four racemic EET's,[14] an adaptation of the original method[13] to the synthesis of (11*S*,12*R*)-EET,[15] and a synthesis of (11*S*,12*R*)- and (11*R*,-12*S*)-EET's from *R* or *S* malic acid.[16] In this paper we report an efficient, catalytic enantioselective synthesis of the biologically more active (11*R*,12*S*)-EET using the same achiral intermediate **2** that served as a precursor of (12*R*)- and (12*S*)-HETE (**3** and **4**).[17]

The eneyne ester **2** was subjected to enantioselective Sharpless dihydroxylation[18] with AD-mix-α, $CH_3SO_2NH_2$ (1 equiv), in 1:1 *t*-BuOH−H_2O (0.1 M in **2**) at 0 °C for 36 h to form directly the hydroxy lactone **5** of 88% ee (70% yield) (Scheme 1). Recrystallization of this product gave **5** of 94% ee in 86% yield. Catalytic reduction of **5** with 1 equiv of H_2 (1 atm) using Lindlar catalyst (10% Pd−$CaCO_3$−Pb) in THF at 0 °C (with careful monitoring of the reaction with $AgNO_3$-impregnated TLC plates and 1:2 EtOAc/CH_2Cl_2) gave after 45 min the *Z*-unsaturated lactone **6** in 99% yield. Treatment of **6** with 1.4 equiv of CH_3SO_2Cl and 1.4 equiv of Et_3N in CH_2Cl_2 at −20 to 0 °C over 1 h afforded cleanly the corresponding mesylate which, without purification, was reduced by 1.2 equiv of *i*-Bu_2AlH in toluene at −78 °C for 1 h to afford the lactol mesylate **7** cleanly. Reduction of unpurified **7** with 2 equiv of $NaBH_4$ in MeOH at 0 °C for 1.5 h and subsequent treatment in the same flask with 3 equiv of K_2CO_3 furnished the *Z*-epoxy alcohol **8** in 80% overall yield from **6** after flash column chromatography on silica gel.

Oxidation of **8** using 1.3 equiv of Dess−Martin periodinane reagent in CH_2Cl_2 at 23 °C for 50 min produced the corresponding epoxy aldehyde which was treated with (*Z*)-$Ph_3P{=}CHCH_2CH{=}CH(CH_2)_3CO_2Me$ (**9**)[19] in 5:1 toluene−tetrahydrofuran at −94 to −15 °C over 3 h to form (11*R*,12*S*)-EET methyl ester **10** in 71% overall yield from **8**. The optical rotation of **10** was found to be $[\alpha]^{23}_D$ +5.38 (*c* 1.3, acetone) as compared to the reported value of $[\alpha]^{23}_D$ +4.94 (*c* 1.6, acetone).[16] Saponification of **10** with 10 equiv of LiOH in 2.5:1 dimethoxyethane−H_2O at 23 °C for 15 h, as previously described, provides (11*R*,12*S*)-EET (**1**).

Synthetic **1** is conveniently prepared in gram amounts by the process outlined above which should expedite biological research. This biologically intriguing eicosanoid, produced by chemical synthesis many years before the recognition of its biomedical importance, its enantiomer, or the enantiomeric 12-HETE's[17] can all be synthesized from the achiral precursors **2** and **9**.

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Supporting Information Available: Full experimental procedures for the synthesis of **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) In contrast 5,6-, 8,9-, and 14,15-EET's were much less active in blocking IκB degradation.

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