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A PRACTICAL ENANTIOSELECTIVE SYNTHESIS OF 12-HYDROXYEICOSATETRAENOIC ACIDS

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Abstract

A practical enantioselective synthesis of 12(R)-HETE has been achieved from readily available starting materials. This process also constitutes a formal synthesis of Leukotriene B_4.

12-HETE is generated from arachidonic acid by a 12-lipoxygenase enzyme, found in platelets and skin keratinocytes. The 12(R)-HETE is of particular interest since it has been detected in high concentrations in psoriatic lesions and has been shown to possess potent human neutrophil chemotactic and chemokinetic properties.[1] As part of our program directed towards the synthesis of novel anti-inflammatory agents we required a versatile, enantioselective synthesis of 12(R)-HETE and its 12-substituted analogs for SAR studies.

Starting with the readily available 4-decynoic acid 1[2], we utilized Evans' innovation for the asymmetric oxidation of chiral imide enolates[3] to introduce the critical 12(R) stereochemistry inherent in the natural product. Carboxylic acid, 1 was reduced to the corresponding (Z)-olefin in 95% yield as shown in Scheme I and conversion to the chiral oxazolidinone proceeded uneventfully using Evans' conditions. Metallation and quenching of the enolate derived from 2 with Davis' reagent[4] afforded the α-hydroxy acyloxazolidinone 3, with a diasteroisomeric excess of ≥ 98:2 and chemical yield of 83%. tert-Butyldiphenylsilylation and subsequent reductive cleavage of the chiral auxiliary with lithium borohydride in the presence of excess cyclohexene gave enantiomerically pure alcohol which was

oxidized to the desired aldehyde 4[5] using the Swern procedure. Significantly, the yield of the borohydride reduction was found to be nearly 20% lower if cyclohexene was omitted from the reaction mixture while lithium aluminum hydride reduction afforded only complex mixtures of products. The aldehyde was converted into 12(R)-HETE using conditions previously reported by the Merck-Frosst group.[6] As the aldehyde 4 has also been converted into Leukotriene B_4[7] the approach outlined in this Letter also constitutes a formal total synthesis of this natural product.

Summarily, we have completed a concise, total synthesis of 12(R)-HETE in 11 steps from readily available starting materials in 29% overall yield. The construction of the key intermediate 4 for 12-hydroxy-eicosatetraenoic acid synthesis proceeded in 7 steps and in 63% overall yield from 4-decynoic acid. The advantages of this procedure over previous syntheses of 12(R)-HETE[8] are a) conciseness and high yield, b) versatility - this procedure provides for a general entry into the 12-HETE family and allows for the synthesis of previously unavailable analogs at the critical C-12 binding site with a high degree of stereogenic control.

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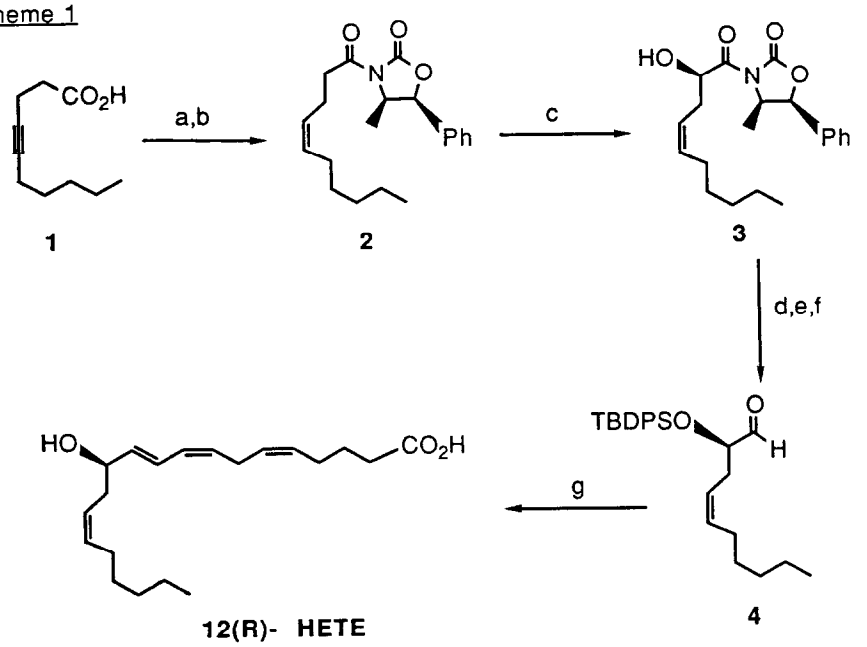
Scheme 1



Reagents

a)nickel boride, H_2, 98%, b) $(COCl)_2$, then n-BuLi/ (4R,5S)-(+)-4-Methyl-5-phenyl-2-oxazolidinone, THF,-78° to -10°C,99%, c)NaHMDS, Davis' reagent, THF,-78° to 0°C, 83%, d)t-butyldiphenylsilyl chloride, imidazole, DMF, 94%, e)$LiBH_4$,cyclohexene, Et_2O, 0°C, 87%, f)$(COCl)_2$,DMSO,Et_3N, 98%, g)see Ref. 6.

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