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ENANTIOSELECTIVE TOTAL SYNTHESIS AND PHARMACOLOGIC PROFILE OF 12-DEOXY-12(S)-METHYL LEUKOTRIENE B_4

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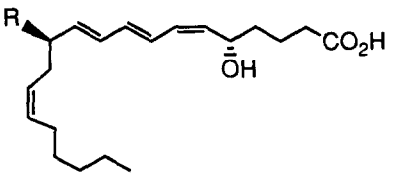
Abstract

An enantioselective synthesis of a unique analogue of the pro-inflammatory eicosanoid Leukotriene B_4 has been achieved in a convergent manner, from readily available starting materials. This analogue, 12-deoxy-12(S)-methyl LTB_4, provides convincing evidence that the 12(R)-hydroxy group present in the natural ligand is essential for its chemoattractant properties towards inflammatory cells, such as neutrophils.

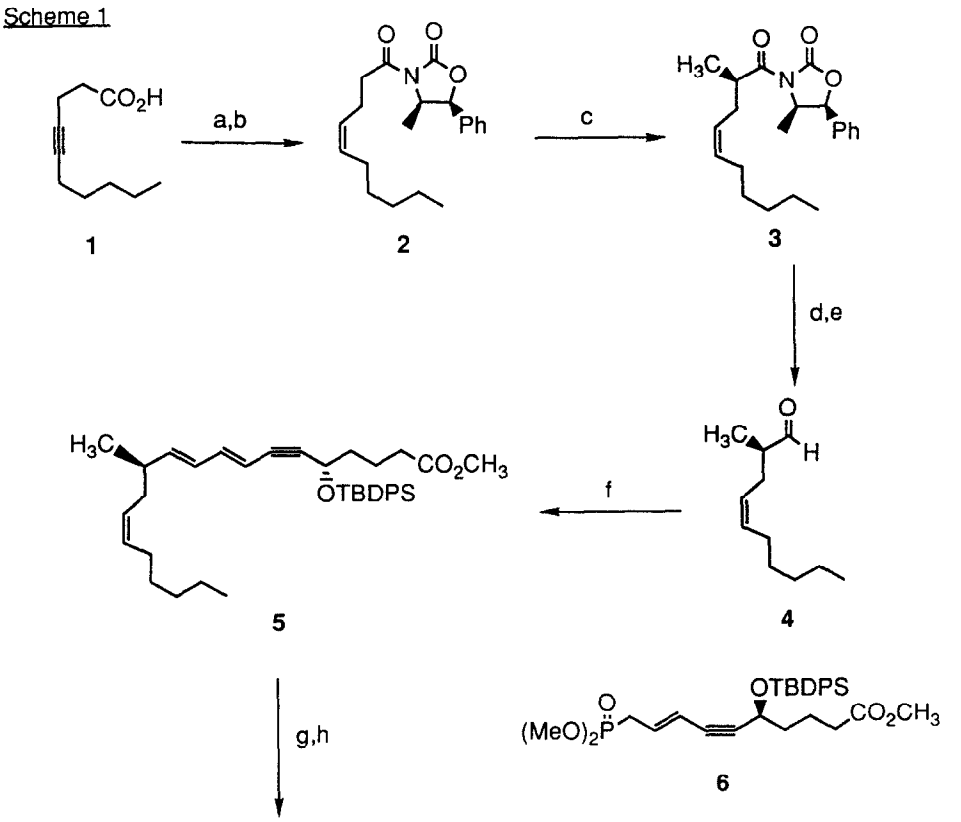
Leukotriene B_4 [(5S,12R) dihydroxy-6,14-cis, 8,10-trans-eicosatetraenoic acid] (LTB_4),[1] has been shown to stimulate the aggregation and degranulation of human neutrophils, promote chemotaxis and chemokinesis of leukocytes and is a mediator of lysosomal enzyme release and superoxide generation.[2] It has been postulated to be a major inflammatory mediator in a number of disease states such as psoriasis and inflammatory bowel disease (IBD).[3]

As part of our studies directed towards the identification of LTB_4 antagonists *based on the structure of the natural ligand itself* [4] we chose 12-deoxy-12(S)-methyl LTB_4 as an attractive target in light of our belief that the 12-hydroxy group of the natural ligand was critical for receptor mediated signal transduction via a guanine nucleotide-binding protein.[5]



Leukotriene B_4 R=OH
12-Deoxy-12(S)-methyl LTB_4 R=CH_3

Scheme 1



12-Deoxy-12(S)-methyl Leukotriene B_4

Reagents

a) nickel boride, H_2, 90% b) $(COCl)_2$, then n-BuLi/(4R,5S)-(+)-4-Methyl-5-phenyl-2-oxazolidinone, THF, -78% to -10°C, 99%, C)NaHMDS, CH_3I, -78°C to 0°C, 80%, d) $LiBH_4/H_2O$ (1:1), Et_2O, 85%, e) $(COCl)_2$, DMSO, Et_3N, f) 6, LiHMDS, THF, -25°C, 88%, g) H_2, Lindlar, 99%, h) n-Bu_4NF, THF, RT

The synthesis of the desired target was accomplished as in Scheme I. Starting with the readily available 4-decynoic acid 1,[6] we utilized Evans' innovation for the asymmetric alkylation of chiral imide enolates[7] to introduce the key 12(S) stereochemistry required in the natural product analog. Carboxylic acid, 1 was reduced to the corresponding (Z)-olefin in 90% yield and then converted uneventfully to the chiral acyloxazolidinone using Evans' conditions. Metallation and quenching of the enolate derived from 2 with methyl iodide afforded the α-methyl acyloxazolidinone 3 with diastereoisomeric excess of ≥ 97% and chemical yield of 80%. Reductive cleavage of the chiral auxiliary with lithium borohydride/water, in the manner recently described by us,[8] followed by Swern oxidation produced enantiomerically pure aldehyde 4. This material was coupled with the Wadsworth-Emmons reagent 6 according to the procedure of Nicolaou et al[8] in 88% yield after chromatographic purification. Lindlar reduction (99% yield) followed by desilylation with tetra n-butylammonium fluoride in THF and concomitant ester hydrolysis furnished 12-deoxy-12(S)-methyl LTB_4.[10] This synthesis once again demonstrates the considerable utility of Evans' acyloxazolidinone chemistry in the synthesis of LTB_4 or 12-hydroxy eicosatetraenoic acid analogs,[11] and that the lithium borohydride/H_2O reagent system is a very effective agent for the non-destructive reductive removal of sterically encumbered acyloxazolidinone auxiliaries.

12-Deoxy-12(S)-methyl-LTB_4 was evaluated in a series of pharmacologic assays designed to establish its ability to function as an antagonist of the natural ligand itself.[12] Although the compound demonstrated an IC_{50} of 3.8 μM in a LTB_4 human neutrophil receptor binding assay, it was devoid of either agonist or antagonist properties in a modified Boyden chamber chemotaxis assay at doses ranging from 10^{-5} to 10^{-8}M. Interestingly enough, however, it displayed a dose related inhibition of human neutrophil degranulation induced by LTB_4 with an IC_{50} of 3.4 μM.

This observation lends strong support to the current hypothesis that there are two functionally or even structurally different, high and low affinity LTB_4 receptors on human neutrophils; a high affinity site associated with the chemotactic response and a low affinity site associated with enzyme secretion and degranulation and suggests that these sites can be differentially regulated by pharmacologic agents such as 12-deoxy-12(S)-methyl LTB_4.[13]

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