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AN EFFICIENT SYNTHESIS OF LEUKOTRIENE B_4

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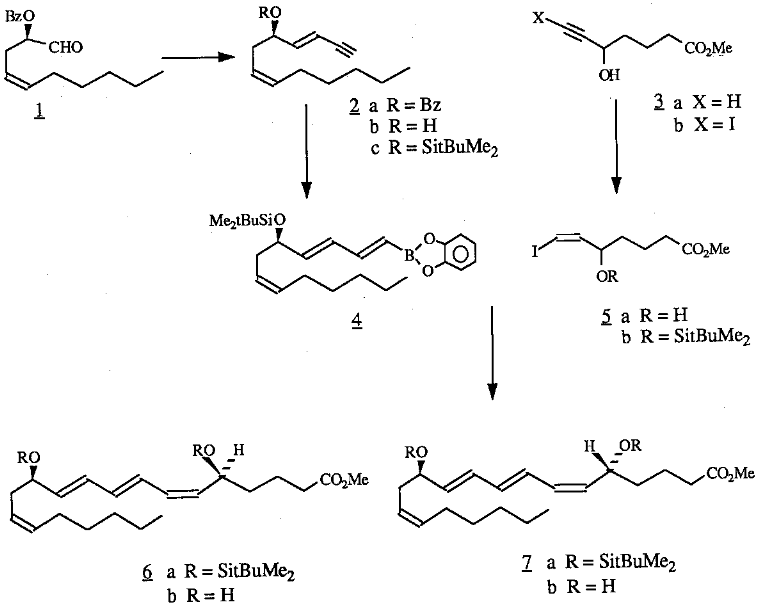
Leukotriene B_4 (5S,12R) and its epimer (5R,12R) have been prepared by coupling a chiral hydroxy vinyl borane with a racemic vinyl iodide, followed by the easy separation of the thus formed diastereomers.

Leukotriene B4 is an important metabolite of the 5-lipoxygenase arachidonic acid peroxidation pathway and several syntheses of this compound have appeared.[1] The key step is usually a Wittig reaction combining two chiral blocks. We reported a synthesis involving a Pd-Cu synthesis of a dienyne followed by reduction of the triple bond into a cis double bond.[2-4] However, the Pd-Cu coupling reaction occurred in moderate yield (33 %). We now report a more straightforward synthesis of LTB$_4$ based a) on a stereoselective coupling of a (E,E)-dienyl borane with a (Z)-vinyl iodide leading to the desired (Z,E,E) geometry b) on the easy separation by silica gel column chromatography of the two subsequent diastereomers 6b and 7b. This result allows the preparation of the leukotrienes B which have two chiral centres from one easily obtainable chiral source 1. Thus, reaction of



aldehyde 1[5,1] with the ylide generated from (3-trimethylsilyl-2-propynyl) triphenylphosphonium bromide and butyllithium in THF at -78°, followed by desilylation with tetrabutylammonium fluoride gave (70 %) a mixture (77:23) of (E) and (Z) isomers 2a ; the (E) isomer was purified by silica gel column chromatography (67 %). Saponification (92 %) with sodium methylate in methanol gave the (E) alcohol 2b. Silylation with chloro-t-butyldimethylsilane and hydroboration with 1,3,2-benzodioxaborole (1.2 equiv., 24h, 20°) afforded (90 %) the vinyl borane 4. On the other hand, methyl 5-hydroxy-6-heptynoate 3a was prepared by reaction of ethynyllithium with methyl 5-oxo-pentanoate in THF at -78° in 55 % yield. Treatment with N-iodo succinimide in THF for 1h gave (64 %) the alkynyl iodide 3b, reduction with diimide (81 %) and silylation with chloro-t-butyldimethylsilane led to the (Z) vinyl iodide 5b (95 %). This compound 5b was then coupled with the vinyl borane 4 under the Kishi conditions ($Pd(PPh_3)_4$, TlOH)[6] affording a mixture of diastereomers 6a and 7a in 62 % yield. Desilylation with tetrabutylammonium fluoride in THF, followed by treatment with diazomethane (to methylate the carboxylic acid formed) gave (90 %) a 1:1 mixture of LTB4 methyl esters (5S,12R) 6b and 7b which were easily separated by silica gel column chromatography (elution : dichloromethane/ethyl acetate 6:4 ; 6b : Rf = 0.37 ; 7b : Rf = 0.46).[7]

The above strategy to the leukotriene B not only provides the naturally occuring substance LTB4 but also makes available a number of potentially useful analogues.

Notes and References

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