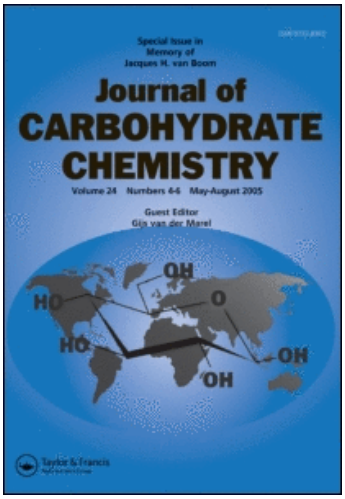

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Chiral Epoxides for Leukotriene Syntheses : A D-Xylose Approach

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Communication

CHIRAL EPOXIDES FOR LEUKOTRIENE SYNTHESES : A D-XYLOSE APPROACH

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Characterization of SRS-A, an important mediator of asthma and other hypersensitivity processes, was not achieved until 1979[1]. It has been proposed that leukotriene A_4 (LTA_4) is the short-lived key biochemical intermediate which can be either converted to LTB_4 by enzymatic hydration or to LTC_4, a precursor to LTD_4 and LTE_4, by glutathione transfer[2]. Therefore, in order to mimic the biosynthetic pathway, LTA_4 has been the prime synthetic target[3]. A survey of the various methods described in the literature clearly shows the pivotal status of the key-synthons, methyl 7-hydroxy-5,6-epoxyheptanoates (e.g. 4 and 6).

Having been involved in several chiral epoxide syntheses in the field of insect sex pheromones[4], we have developed a nine-step sequence from inexpensive D-xylose for the elaboration of chiral cis-epoxy-alcohols.

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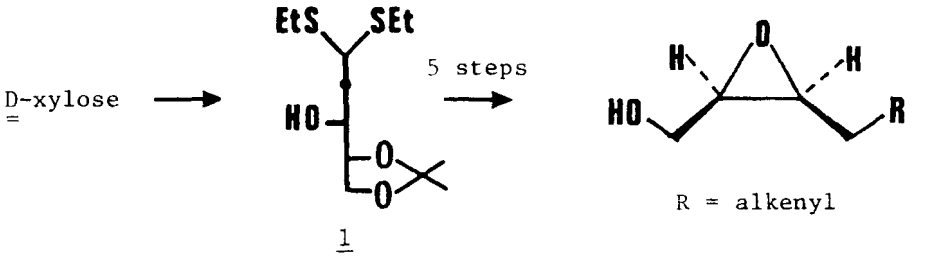


1

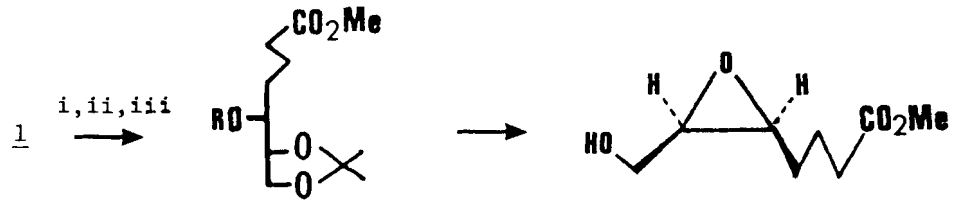
The synthesis of the (5S,6R)-diastereomer 4 has been carried out from intermediate 1[5] in a six-step sequence, as outlined in Scheme 1.

The saturated ester 2 was prepared in three steps from 1 with a 79% overall yield[6]. Mesylation of 2 to 3 (MsCl, NEt_3, CH_2Cl_2, -20°C, 90%) followed by hydrolysis of the ketal protecting group (1.3 eq. $TsOH.H_2O$ in CH_3OH, RT) then direct epoxidation (1.4 eq. CH_3ONa) led to 4, $\{\alpha\}_D$ + 2.3°(c=4.40, $CHCl_3$)[3e,3h] in 80% yield[7]. This diastereomer can be diverted to 6-epileukotrienes according to known procedures[3d,3e].

In order to obtain the (5R,6R)-diastereomer 6, the configuration of the chiral center at C-6 of 2 must remain unchanged, while that of C-5 must be inverted. This was achieved as shown in Scheme 2.

Tosylation of 2 with inversion of the configuration at C-5 occured upon treatment with zinc tosylate in benzene in the pre-

Scheme 1



2 R = H 3 R = Ms 8 R = Bz

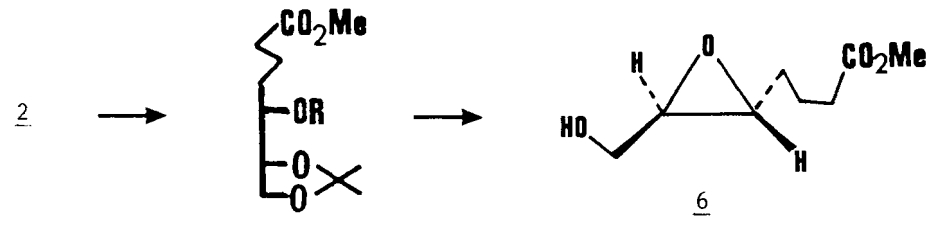
4

i) $HgO,BF_3.Et_2O,THF-H_2O$,RT. ii) Ph_3P=CHCOOMe,AcOEt,reflux.
iii) H_2,10% Pd/C,AcOEt.

sence of PPh_3 and DEAD[8], giving 5, $\{\alpha\}_D$ -1°(c=2.14, $CHCl_3$) in 52% yield. Hydrolysis of the ketal group and epoxidation were achieved as described above, thus leading to the (5R,6R)-epoxide 6, $\{\alpha\}_D$ + 31.5° (c=1.04, $CHCl_3$) in 80% yield. This diastereomer is a precursor to 5-epi-6-epi-LTA_4[3e]. In view of the known possible rearrangements of α,β-epoxyalcohols[9], spectroscopic data for compounds 4 and 6 were thoroughly studied to ascertain the secondary epoxide structures.

This D-xylose approach may find an extension to the synthesis of the other two diastereoisomeric epoxides (5S,6S) and (5R,6S) which can respectively be diverted to LTA_4 or to 5-epi-LTA_4[3a,3e,3h]. In that purpose, both the (5S)-benzoate 7, $\{\alpha\}_D$ + 0.5° (c=2.04, $CHCl_3$) and its (5R)-epimer 8, $\{\alpha\}_D$ + 23° (c=3.40, $CHCl_3$) can be obtained in one-step from 2 via either benzoyl-inversion ($Zn(OBz)_2$, PPh_3, DEAD, toluene, RT, 74% yield)[10] or conventional benzoylation (BzCl, pyridine, 84% yield). A five-step standard sequence[3e] (1. hydrolysis of the ketal group; 2.selective protection of the primary alcohol function; 3.mesylation of the secondary alcohol function; 4.MeONa-induced epoxidation; 5.deprotection of the primary alcohol function) would then lead to the expected epoxides.

Scheme 2



5 R = Ts 7 R = Bz

6

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