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SYNTHESIS OF LEUKOTRIENE A_4 METHYL ESTER FROM D-GLUCOSE

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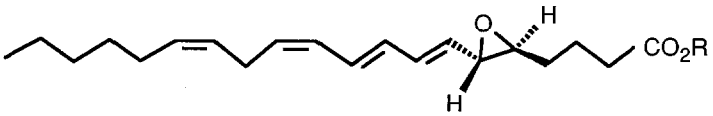
SUMMARY: A high yielding synthesis of leukotriene A_4 methyl ester is described which uses D-glucose as starting material

The peptido-leukotrienes C_4, D_4 and E_4 are very powerful bronchoconstrictor substances which probably have an important role in many human diseases including asthma[2]. The unsaturated epoxide leukotriene A_4 (LTA_4) (1) is both a biosynthetic precursor and, as its methyl ester (2), a convenient chemical precursor for all of the peptido-leukotrienes. LTA_4 methyl ester (2) has been prepared by a variety of methods[3], the majority of which use a sugar as a chiral starting material.

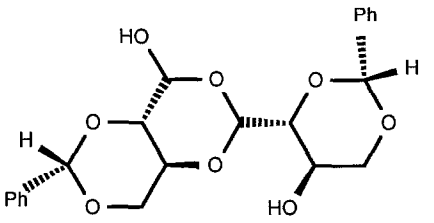


(1) R = H

(2) R = Me

We now wish to describe a new, high-yielding synthesis from D-glucose which overcomes previously reported difficulties[4]. The choice of sugar was made on the grounds of cost and availability. The strategy was to carry out a periodate cleavage on protected glucose to give a tetrose derivative which could be homologated to give the key seven carbon unit (3). Benzaldehyde dimethylacetal was reacted in DMF with 2 equivalents of D-glucose (4), using p-toluenesulphonic acid as catalyst, to generate 4,6-O-benzylidene-D-glucopyranose (5) (mp 178-181°C[5], lit[6] mp 186-187°C) in 71% yield. Pyranose (5) was reacted at room temperature with sodium periodate in the presence of sodium bicarbonate in a bi-phasic mixture of dichloromethane and water (2:1) to give the aldehyde (6), mp 134-136°C, in 72% yield. The use of a

two-phase reaction mixture and a short reaction time, 30 minutes, minimised the formation of the unwanted hemi-acetal (7). Interestingly, in the absence of sodium bicarbonate the synthetically useful formate ester (8) was formed in high yield. Aldehyde (6) was then reacted at -5°C with the ylide formed from triphenyl (2-carboxyethyl)phosphonium chloride and 3.9 eq. of n-butyllithium in THF:DMSO (4:1)[7]. The previously published conditions for this type of reaction[8], sodium hydride in THF:DMSO (1:1) at 0°C, proved unsatisfactory as there was considerable elimination of triphenylphosphine from the ylide. The carboxylic acid (3), obtained in 69% yield after chromatography, mp 116-117°C, was found to be exclusively the E-isomer, presumably the result of the β-alkoxide group affecting the normal stereochemical outcome of the Wittig reaction.

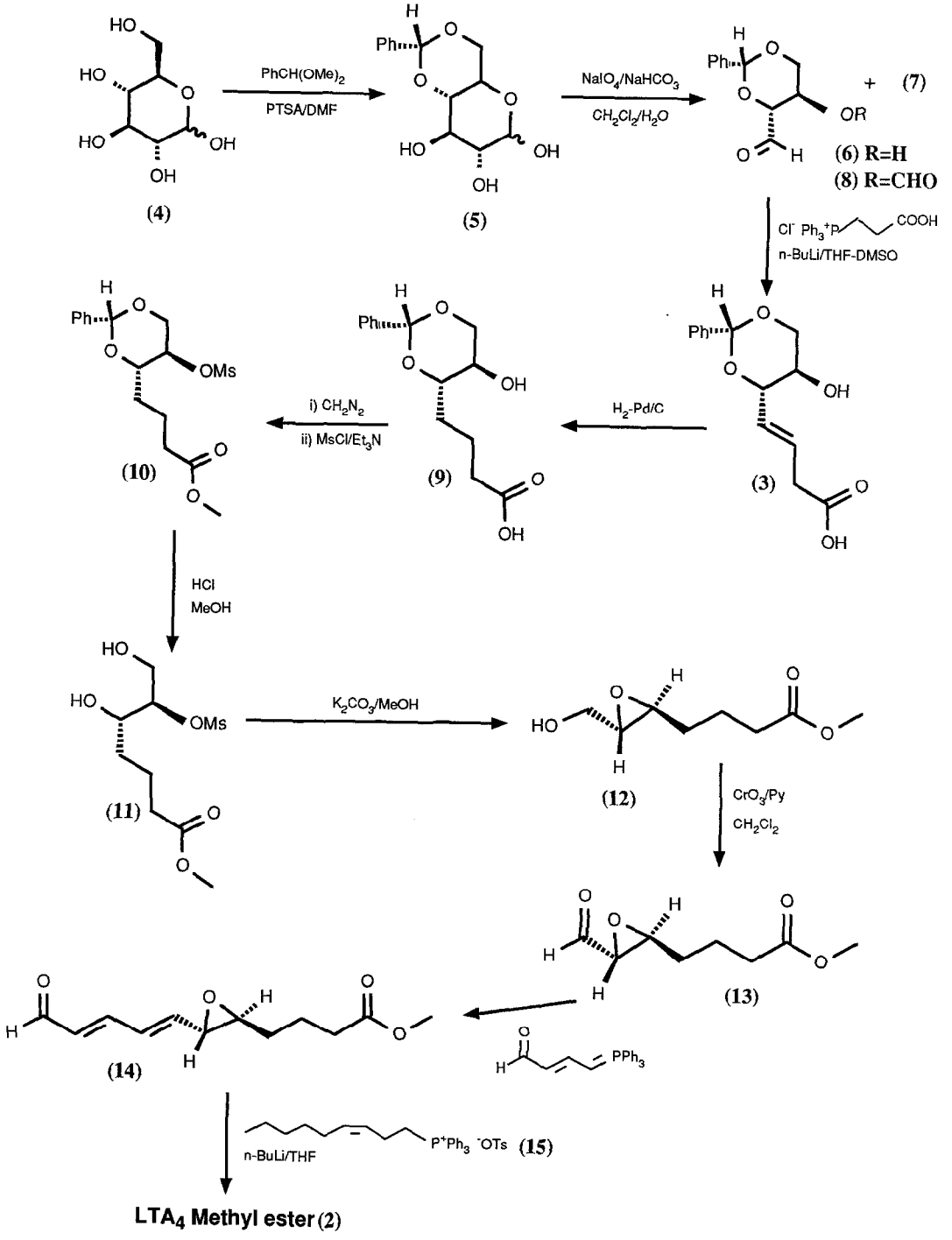


(7)

The double bond was then removed by hydrogenation using palladium on charcoal catalyst in THF, and the saturated acid (9), mp 110-111°C, esterified with ethereal diazomethane. Reaction with mesyl chloride and triethylamine in dichloromethane gave the mesylate (10), mp 89-90°C, in 65% overall yield from (3). Removal of the benzylidene group was achieved using anhydrous hydrogen chloride in methanol, and the resulting diol (11) then cyclised *in situ* to the epoxide (12) in 76% yield, by the addition of potassium carbonate. In this reaction the possibility exists that the alternative terminal epoxide might be formed which could then undergo a Payne rearrangement to give the 5S, 6R-isomer of epoxide (12). Careful NMR analysis of the epoxide (12) [$[\alpha]_D^{20}$ -35.2° (2.72, $CHCl_3$); lit[9] $[\alpha]_D$ -35° (2.7, $CDCl_3$)] failed to reveal either the terminal epoxide or the 5S, 6R-isomer.

Epoxy alcohol (12) was then oxidised with Collins reagent to give the aldehyde (13) in 63% yield, which was in turn converted to the dienal (14) in 70% yield using the procedure of Ernest[10]. Finally, the dienal (14) was reacted at -78°C with the ylide formed from the phosphonium salt[10] (15) and n-butyllithium to give LTA_4 methyl ester in 90% yield after chromatography. HPLC[11] and 300 MHz NMR analysis of LTA_4 methyl ester showed that there was less than 2% of the 11E-isomer present, and no other geometric isomer was detected.

Reaction with N-trifluoroacetyl cysteinylglycine methyl ester and HPLC[12] analysis of the resulting product indicated the presence of less than 1% of the 5R, 6S-isomer. It is therefore concluded that the LTA_4 methyl ester contained less than 1% of the 5R, 6R-isomer. The overall yield from D-glucose was 8%. We consider this synthesis to be a considerable improvement on the previous one from D-glucose[4] and to rival those from more expensive sugars in terms of yield and simplicity.


PhCH(OMe)2
PTSA/DMF
NaIO4/NaHCO3
CH2Cl2/H2O
(6) R=H
(8) R=CHO
(7)
(4)
(5)
n-BuLi/THF-DMSO
H2-Pd/C
i) CH2N2
ii) MsCl/Et3N
(3)
(9)
(10)
HCl
MeOH
K2CO3/MeOH
(11)
(12)
CrO3/Py
CH2Cl2
(13)
(14)
n-BuLi/THF
(15)
LTA4 Methyl ester (2)

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