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A C-GLYCOSIDE ROUTE TO LEUKOTRIENES

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Summary: The stereospecific syntheses of three isomers of 7-hydroxy-5,6-epoxy heptanoic acid methyl ester, 7, 12b and 19, have been achieved via a C-glycoside route.

As part of our continuing interest in the Leukotriene field, the synthesis of the four isomers of LTA_4 for biochemical studies was a matter of prime importance. Our stragegy was based on the use of a single commercially available precursor, 2-deoxy-D-ribose, 1, for the stereospecific synthesis of these compounds. From the outset we had planned a two-pronged approach using this same starting material and in the preceding communication[1] we have described a successful approach leading to the four possible isomers of LTA_4 (isomeric at positions 5 and 6) using chiral acyclic precursors derived from 1.

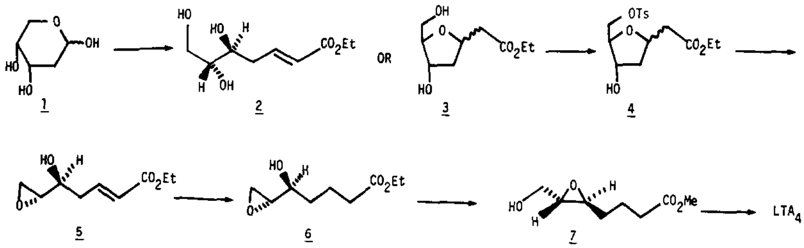
In this paper we present a second, or C-glycoside approach, also using 1 as starting material, which has led to the successful preparation of three critical intermediate epoxy alcohols, 7, 12 and 19, which have been transformed to LTA_4, 5-epi,6-epi-LTA_4 and 5-epi-LTA_4, respectively.

Wittig reactions with sugars have been described in the literature and depending on the reaction conditions, and the reagents employed, open chain[2] or C-glycoside[3] derivatives can be obtained. We have found that in the reaction of 1 with (carbethoxymethylene)triphenylphosphorane the conditions could easily be adjusted to give either 2 or 3 in excellent yields (Scheme 1). Hence, when 1 was refluxed with one equivalent of (carbethoxymethylene)triphenylphosphorane in THF for 6 h an 80% yield of 2 was obtained, whereas, using two equivalents of the Wittig reagent and refluxing the solution for 5 days an 80% yield of the C-glycoside 3 is produced. Alternatively, 3 can be obtained in greater than 95% yield by treating 2 with traces of sodium ethoxide in ethanol for 1 h.

The use of a cyclic chiral precursor such as 3 presents certain potential advantages such as a considerable degree of control of stereochemistry and as a method of selectively masking one of the hydroxyl groups until required.[4] In fact, the key reaction envisaged for the success of this C-glycoside approach was the generation of the anion alpha to the ester group followed by a β-elimination of the ring oxygen to form an alkoxide intermediate which was to go on to form an epoxide by displacement of a suitably located leaving group. Gratifyingly, this reaction proved successful in each case and led to the synthesis of the three key epoxy alcohols mentioned above.

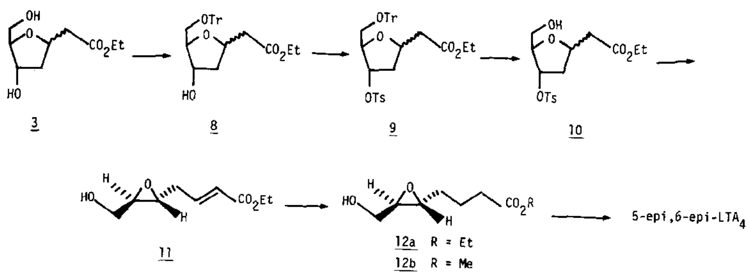
In order to obtain epoxy alcohol 7, which we had previously transformed to LTA_4,[1] the primary tosylate 4 was prepared in 95% yield by treatment of 3 with one equivalent of TsCl in pyridine at 0°C for 18 h. In our first test of the key ring opening reaction described above, tosylate 4 was then treated with two equivalents of LDA in dry THF (-78° 2 h, -10° 18 h) to give a 50% isolated yield of the unsaturated epoxy alcohol 5, $[\alpha]_D$ $CDCl_3$ +19.3° (c = 1.3, $CDCl_3$). Hydrogenation of 5 over 10% Pd/C in ethanol for 5 h gave a quantitative yield of the epoxy alcohol 6, $[\alpha]_D$ +18.3° (c = 1.9, $CDCl_3$), which upon treatment with 0.2 equivalents of sodium methoxide in methanol was smoothly transformed to the desired primary alcohol 7, $[\alpha]_D$ -36.5° (c = 0.5, $CDCl_3$), in 50% yield.

SCHEME 1



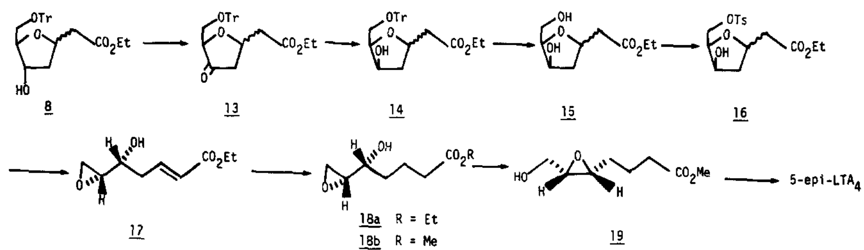
To prepare the enantiomer of 7, 12 (Scheme 2), the stereochemistry at C-5 of C-glycoside 3 has to be inverted. To achieve this, the primary alcohol of diol 3 was first selectively protected as the trityl ether 8 in 80% yield by treatment with one equivalent of trityl chloride in dry pyridine in the presence of catalytic amounts of 4-(N,N-dimethylamino)pyridine (DMAP). Tosylation of the secondary alcohol of 8 with five equivalents of TosCl and one equivalent of DMAP in dry pyridine at 55° for 20 h then afforded 9 in quantitative yield. Cleavage of the trityl group[4] was effected by hydrogenation over 10% Pd/C in ethanol-ethyl acetate to yield 10 (86%) which, when allowed to react with two equivalents of LDA in dry THF at -78°C, afforded 11, $[\alpha]_D$ +40.27° (c = 0.7, $CDCl_3$), in 26% yield along with 25% of recovered 10. Epoxide 11 was quantitatively hydrogenated to the desired epoxy alcohol 12a, $[\alpha]_D$ +33.6° (c = 0.5, $CDCl_3$), which has been previously transformed[1] to 5-epi,6-epi-LTA$_4$ methyl ester.

SCHEME 2



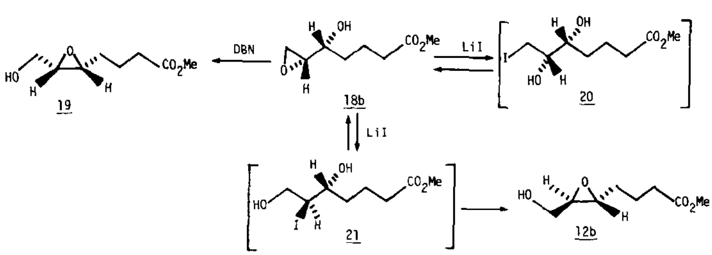
The synthesis of the third chiral epoxy alcohol, 19 (Scheme 3), required inversion of configuration at both C-5 and C-6 of the C-glycoside 3. To this end, trityl alcohol 8 was first oxidized (Collins reagent, 95% yield) to the ketone 13, which was then reduced in a highly stereoselective reaction with lithium perhydro-9B-boraphenalylhydride (PBPH) to give a 70% isolated yield of the pure C-5 epimeric alcohol 14. Hydrogenation (10% Pd/C in EtOH, 83% yield) to diol 15, followed by selective tosylation (one equiv. TosCl, pyridine, 0°C, 18 h), then gave the primary tosylate 16 in quantitative yield. Treatment of 16 with two equivalents of LDA in dry THF (-78° 2 h, -10° 18 h) afforded the epoxy alcohol 17, $[\alpha]_D$ +2.7° (c = 1.4, $CDCl_3$), in 40% yield. Hydrogenation over 10% Pd/C in ethanol for 4 h gave the terminal epoxide 18a, $[\alpha]_D$ -2.9° (c = 0.6, $CDCl_3$), in 95% yield. Treatment of 18a with sodium methoxide in methanol as described for the conversion of 6 to 7 gave only the methyl ester, 18b, instead of the expected 19. Clearly the rearrangement of 18 to 19 is much less favored than in the trans case. Molecular models indicate that the alignment of the hydroxyl group at C-5 in the orientation necessary to open the terminal epoxide gives rise to significant steric interference between the epoxide ring and the side chain bearing the ester group. In order to bring about this rearrangement, 18b was treated with 1.25 equivalents of DBN in MeOH at 90° giving 19, $[\alpha]_D$ -3.7° (c = 0.5, $CDCl_3$), in 20% yield.[5]

SCHEME 3



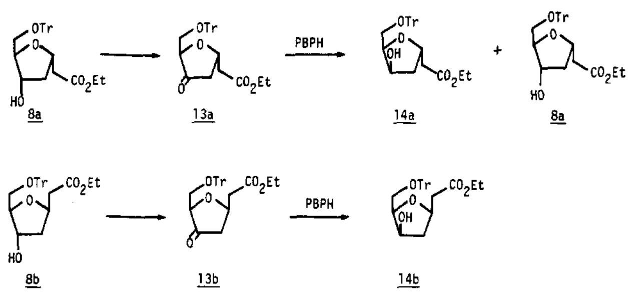
In another approach to effect the rearrangement of 18b to 19, the compound was heated with LiI (MeOH, 90°C, 20 h). However, to our surprise, the product isolated in 50% yield was the trans epoxy alcohol 12b (Scheme 4). An opening of the primary epoxide 18b to generate the halohydrins 20 or 21, which could either revert to 18b or go to the epoxide 12b, respectively, provides a reasonable explanation for this unexpected observation. The driving force of the reaction is presumably the formation of the thermodynamically more stable 12b. We thought of applying this unexpected finding to epoxide 6. If the same inversion at C-6 occured under the LiI conditions we would have had another route to 6-epi-LTA_4.[1] However, in this case only the normal rearrangement to 7 occured, indicating once again that the isomerization of 6 to 7 is indeed very facile.

SCHEME 4



We have investigated in some detail the stereospecific reduction of 13 to 14. Chromatographic separation afforded the pure α and β epimers, 8a, $[\alpha]_D$ +8.7° (c = 5.5, $CDCl_3$), and 8b, $[\alpha]_D$ +6.8° (c = 2.6, $CDCl_3$), each of which was oxidized to the corresponding ketones 13a and 13b (Scheme 5). Reduction of the α-isomer, 13a with $NaBH_4$ gave a 1:1 ratio of 14a, $[\alpha]_D$ -5.3° (c = 2.6, $CDCl_3$) and 8a , while the β-isomer, 13b gave a 3.5:1 ratio of 14b, $[\alpha]_D$ -3.4° (c = 9.0, $CDCl_3$), and 8b. In order to improve the ratio of the desired products (14a and 14b), the use of the highly hindered reducing agent PBPH was investigated. We were very pleased to find that the desired selectivity was thus achieved, with 13a giving a 10:1 ratio of 14a and 8a, while 13b was reduced exclusively from the α-face, giving an 87% isolated yield of pure 14b. From these results it is apparent that the trityl ether at C-6 is the major controlling factor in directing the stereochemistry of the reduction. On a preparative scale, as described earlier, the mixture of isomers of 13 was reduced without prior separation as the minor amount (ca. 5%) of 8a produced was readily removed by chromatography.

SCHEME 5



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5. When the tosylate 9 was treated with LDA, no trace of the expected compound was observed.
6. A more efficient synthesis of 19 is reported in the preceding paper.

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