An Entry to Chiral Cyclohexenes from Carbohydrates: A Short, Efficient, and Enantiospecific Synthesis of (−)-Shikimic Acid from D-Mannose

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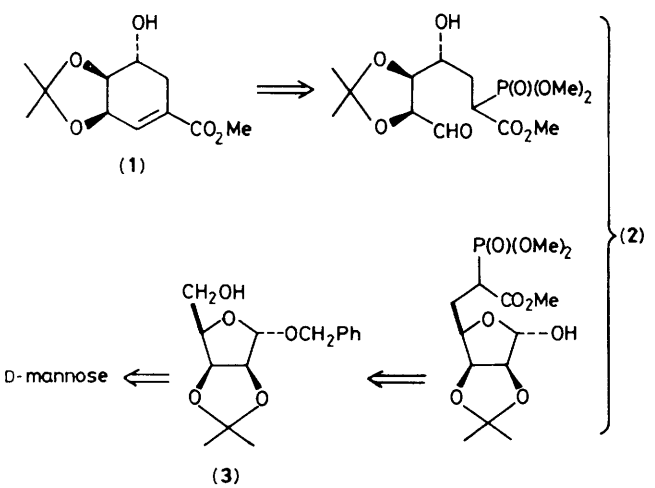
A short, efficient, and enantiospecific synthesis of (3*R*,4*S*,5*R*)-shikimic acid from benzyl 2,3-*O*-isopropylidene-α-D-lyxofuranoside (readily available from D-mannose) is described.

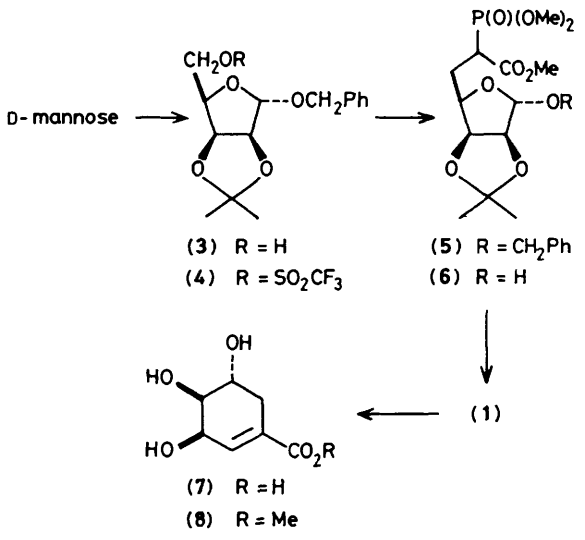
Of the successful syntheses of racemic shikimic acid (**7**),[1] an important intermediate in the biosynthesis of aromatic amino acids and other compounds of biological importance, the most recent is a seven-step synthesis from 1,4-dihydrobenzoic acid proceeding in an overall yield of 13%.[2] The only previously reported enantiospecific synthesis involves fifteen steps from D-arabinose and produces (−)-shikimic acid in an overall yield of 2%.[3]



Scheme 1

The strategy for the short enantiospecific synthesis of (−)-shikimic acid from D-mannose described in this paper is shown in Scheme 1; the key step is the formation of methyl *O*,*O*-isopropylideneshikimate (**1**) from the phosphonate (**2**) by an intramolecular Wadsworth–Emmons[4] olefination. The lactol form of the phosphonate (**2**) may be derived by a two-carbon chain extension of the suitably protected lyxofuranoside (**3**)[5] *via* nucleophilic substitution of a modified C-5 hydroxy-group by a phosphonate stabilised carbanion. D-Mannose was converted into 2,3 : 5,6-di-*O*-isopropylidene-α-D-mannofuranose[6] and subsequently, without isolation of any other intermediates, into crystalline benzyl 2,3-*O*-isopropylidene-α-D-lyxofuranoside (**3**)[5] in a 66% yield on a large scale (Scheme 2).

The lyxo alcohol (**3**) was esterified with trifluoromethanesulphonic anhydride[7] (1.3 equiv.) in methylene dichloride containing pyridine (2 equiv., −30 °C, 25 min) to give the trifluoromethanesulphonate (**4**), $[\alpha]_D^{20}$ +69.8°, (*c*, 2.0, $CHCl_3$) in quantitative yield. Alkylation of (**4**) with the sodium salt of trimethylphosphonoacetate (1.5 equiv.) in *N*,*N*-dimethylformamide (50 °C, 4 h) in the presence of 18-crown-6 afforded a mixture of diastereoisomeric phosphonates (**5**) (74% yield) in *ca.* 1 : 1 ratio as determined by ^1H n.m.r. (4 Me singlets at δ 1.30, 1.31, 1.45, and 1.46), $[\alpha]_D^{20}$ +57.0 (*c*, 0.5, $CHCl_3$). Palladium catalysed hydrogenolysis (H_2, MeOH, 10 h, room



Scheme 2

temp.) of the phosphonate benzyl furanosides (**5**) gave a mixture of lactols (**6**) which, without isolation, was treated with methanolic sodium methoxide (3 equiv., 2 h, room temp.) to form methyl *O,O*-isopropylideneshikimate (**1**) which was deacetonated under mild conditions (Dowex 50 W X-8 resin, H^+ form, methanol, room temp.) to give crystalline methyl shikimate (**8**), in 62% yield from (**5**), m.p. 115—116.5 °C (lit.[8] 113—114 °C), $[\alpha]_D^{20}$ −125° (*c*, 1.8, EtOH) {lit.[8] $[\alpha]_D^{20}$ −130° (*c*, 1.88, EtOH)}. Although the yields of the alkylation and cyclisation steps have not yet been optimised, the overall yield of pure methyl shikimate (**8**)† is 46% from benzyl 2,3-*O*-isopropylidene-α-D-lyxofuranoside (**3**) and 31% from D-mannose.

Methyl shikimate (**8**) can be hydrolysed under alkaline conditions[9] to shikimic acid (80%). Thus the overall yield of (3*R*,4*S*,5*R*)-shikimic acid from D-mannose is 25%; this procedure may be particularly suitable for the synthesis of isotopically labelled shikimic acid. There are still only a few examples of the synthesis of cyclohexene derivatives from carbohydrates; the application of intramolecular olefination reactions has considerable potential for the general enantiospecific synthesis of chiral cyclohexenes including other shikimic acid metabolites.

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† The synthetic sample was shown to be identical to an authentic sample prepared from (−)-shikimic acid (Aldrich).

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