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COMPLEMENTARY SHORT SYNTHESES OF (±)-METHYL SHIKIMATE

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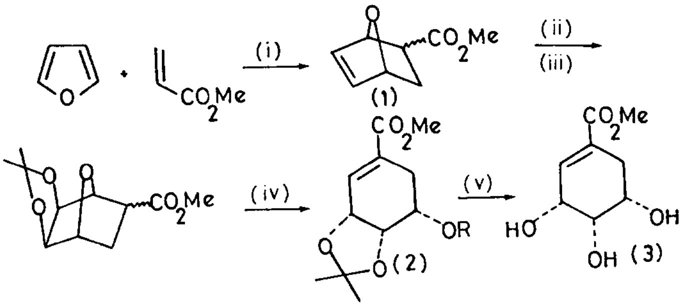
Summary Two syntheses of (±)-methyl shikimate from the adduct of furan and methyl acrylate are described. One requires the regioselective hydroxylation of (±)-5β,6β-dihydroxy-*O*,*O*-isopropylidene-2-methoxycarbonylcyclohexa-1,3-diene and the other *cis*-dihydroxylation of (±)-5-hydroxy-1-methoxycarbonylcyclohexa-1,3-diene.

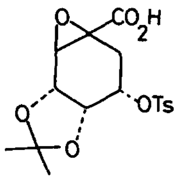
We recently reported the synthesis of (±)-methyl 5-epishikimate (3) by the route outlined in scheme 1,[1] but, so far, all attempts to invert the stereochemistry at C-5 in this product, or in several of its derivatives have failed. For example, reaction of the O-tosylate(2,R=Ts) and potassium superoxide affords the epoxide acid (4) as a mixture of diastereomers. In addition reduction of the unstable ketone (5) formed from the acetonide (2,R=H) by oxidation with pyridinium chlorochromate (PCC), leads to complex mixtures regardless of the reagents employed.

Scheme I



(i) ZnI_2, (ii) OsO_4/H_2O_2, (iii) Me_2CO/H^+, (iv) Li $(Me_3Si)_2N$, (v) HOAc

The desired inversion can however be achieved indirectly from the regioselective hydroxylation of the diene (6) by treatment with diborane and alkaline hydrogen peroxide. The yield of (±)-methyl shikimate (7) thus obtained is 45% and the starting diene is prepared by dehydration of the acetonide (2,R=H) by the action of diethyl azodicarboxylate and triphenylphosphine.[1]



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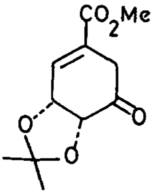

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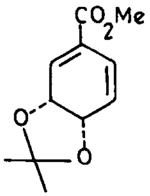

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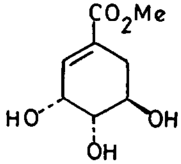

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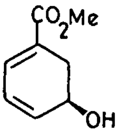
A second more direct route to (±)-methyl shikimate stems from the adducts (1) of furan and methyl acrylate. These with lithium hexamethylsilazane afford the diene (8),[2] which with osmium (IV) oxide gives (±)-methyl shikimate (7) and its epimer (3) in the ratio of 5:1, with an overall yield of 74%. The two epimers may be readily separated by 'flash' chromatography on silica eluting with ethyl acetate. Epoxidation of the adducts (1) with 3-chloroperbenzoic acid affords the epimeric epoxides (9,X=O), but treatment of these compounds with lithium hexamethylsilazane does not bring about ring-opening in the usual manner but gives instead the hydroxy ester (10,X=O). The carbon analogue (9,X=CH_2)[3] behaves similarly yielding the hydroxy ester (10,X=CH_2), but it is interesting that whereas this product is readily oxidised with PCC to the ketone (11) the oxa compound (10,X=O) is resistant to oxidation, except under very vigorous conditions which also cause extensive decomposition.



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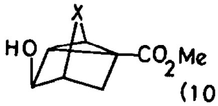

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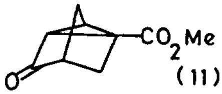

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