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BRIEF DIELS ALDER SYNTHESES OF (±)-METHYL 5-EPISHIKIMATE AND (±)-METHYL CIS-3,4-DIHYDRO-3,4-DIHYDROXYBENZOATE.

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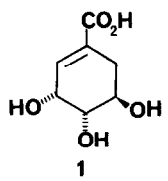
Summary Base-catalysed ring opening of the acetonide of cis-exo-2,3-dihydroxy-6-methoxycarbonyl-7-oxabicycloheptane affords a stereo-controlled route to (±)-methyl 5-epishikimate and thence, by an elimination process, to (±)-methyl -cis-3,4-dihydro-3,4-dihydroxybenzoate.

Shikimic acid (1) and chorismic acid (2) play fundamental roles in biosynthesis.[1,2] Synthetic interest in these compounds and structurally related systems is intense,[2,3] not only because of the stereochemical challenges presented in assembling them, but also because of the possibilities of producing chemical regulators of biological processes in plants and bacteria. Herein we describe a stereocontrolled and brief route to some structural variants. It has been shown that the difficult Diels Alder reaction between furan and methyl acrylate can be effected by zinc iodide catalysis,[4] to give endo- and exo- adducts (3). We observe that osmium tetroxide treatment[∓] of (3)[5] affords the exo-diols (4) (71%) which may then be converted into the acetonides (5) (94%). These products ring open on treatment with lithium hexamethyldisilazide to yield the acetonide of (±)-methyl 5-epishikimate (6) (36%, m.p. 78-79°, n.m.r. ^{1}H δ ($CDCl_3$) 1.35 (s, 6H, CMe_2), 2.60 (m, 2H, H-6), 2.96 (d, exch. D_2O, J = 7 Hz), 3.73 (s, 3H, CO_2Me), 3.97 (m, 1H, H-5), 4.44 (dd, 1H, J = 6.2 Hz, H-4), 4.75 (m, H-3), 6.73 (m, 1H, H-2) which was deprotected (50% aqueous acetic acid) to give (±)-methyl 5-epishikimate (7) (96%),[6] in 23% overall yield from the adducts (3).



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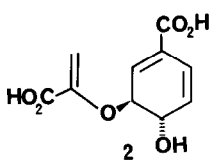

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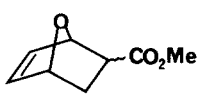

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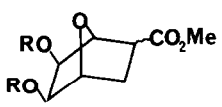
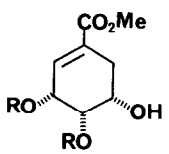


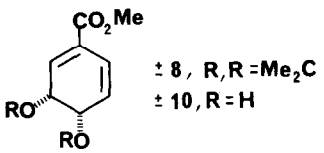
4, R = H
5, R,R = Me_2C



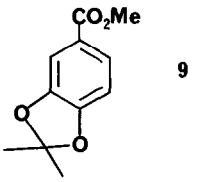
±6, R,R = Me_2C
±7, R = H

During our studies of the inversion of the 5-hydroxyl group in (6) an unexpected product was obtained. Reaction of (6) with triphenyl phosphine - diethyl azodicarboxylate gave 3-hydroxy methyl benzoate (47%) and, by an interesting dehydration, the diene (8) (39%), m.p. 47-49°; i.r. ($CHCl_3$) 1728, 1660, 1608 cm^{-1}, u.v. (hexane) 272 nm; n.m.r. ^1H δ ($CDCl_3$) 1.40 (s, 6H, CMe_2), 3.80 (s, 3H, CO_2Me), 4.62 (dd, 1H, J = 8, 3 Hz, H-4), 4.82 (dd, 1H, J = 8, 3 Hz, H-3), 6.02 (dd, 1H, J = 10, 3 Hz, H-5), 6.54 (d, 1H, J = 10 Hz, H-6), 6.86 (d, 1H, J = 3 Hz, H-2). Diene (8) readily aromatized in solution in the presence of air, giving the acetonide (9). Deprotection of (8) (50% aqueous acetic acid) gave the cis-diol (10), (48%), m.p. 84-86°; i.r. ($CHCl_3$) 3575, 1724, 1648, 1595 cm^{-1}; u.v. (CH_2Cl_2) 272 nm; n.m.r. ^1H δ (CD_3COCD_3) 3.73 (3H, s, CO_2Me), 4.20 (2H, m, H-3, H-4), 6.05 (1H, dd, J = 10, 5 Hz, H-5), 6.38 (1H, dd, J = 10, 2 Hz, H-6), 6.83 (1H, m, H-2). This cis-diol contrasts interestingly with the known trans-diol[7] (which is an oil), for it is surprisingly stable.

This route will therefore allow flexible access to a range of shikimic and chorismic types. Our further studies in this area will be reported in due course.



± 8, R,R = Me_2C
± 10, R = H



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∓ *This reaction was carried out on the mixture, although here as elsewhere, in the synthetic sequence, all mixtures were separated and the individual isomers fully characterised.*

Acknowledgements

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