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REACTIVITY STUDIES IN THE SHIKIMIC ACID SERIES

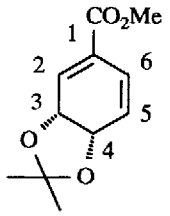
STEPHEN BOWLES, MALCOLM M. CAMPBELL*, AND MALCOLM SAINSBURY*
School of Chemistry, University of Bath, Claverton Down, Bath,
BA2 7AY, UK
and
GARETH M. DAVIES
ICI Pharmaceuticals, Mereside, Alderley Park, Macclesfield, Cheshire, SK10 4TG, U.K.

Summary: The regio- and stereo-selective epoxidation of methyl 3,4-dihydrobenzoate has been investigated and a synthesis of racemic methyl 6α-fluoroshikimate from the acetonide of methyl 3,4-dihydro-3α,4α-cyclohexenoate is described. This work has importance for the preparation of 6-substituted shikimic acid derivatives useful in the study of the biosynthesis of aromatic amino acids *via* the shikimic acid pathway.

A key step in the biosynthesis of aromatic acids in plants and microorganisms is the conversion of shikimic acid (2) into chorismic acid (3). The mechanism of this step is still uncertain, although it is known that the 6-*pro* R hydrogen atom of shikimic acid is lost during the conversion,[2] thus it became of interest to us to synthesise shikimic acids selectively fluorinated at C-6. Previously we noted the remarkable stability of the diene (1) which was prepared as an intermediate in a synthesis of shikimic acid (2).[1] From this diene we now describe the formation of the epoxide (4), and experiments to probe the regio- and stereo- selectivities of its ring opening. When the diene (1) was reacted with *m*-chloroperbenzoic acid (MCPBA)[3] a mixture of the two epoxides (4) and (5) [ratio 8:3] were formed in 89% yield, together with a trace of the isomer (6) . The same mixture of epoxides was formed when the reaction was repeated with either monoperphthalic acid, or vanadylacetylacetonate / ^{t}butyl hydroperoxide, in place of MCPBA. [4] In contrast, perbenzimidic acid[5] gave the epoxide (5) as the sole isolated product in 90% yield. It has been suggested that the epoxidation of a polar double bond by a weak peracid can be regarded as an intermediate case between a typical electrophilic epoxidation and the conjugate addition mode, which takes place between enones and hydrogen peroxide in basic media.[6] Perbenzimidic acid is a relatively weak acid and we suggest that two hydrogen bonding opportunities in the encounter complex (7) promote both the observed regio- and stereo-selectivities of the last epoxidation reaction.[7,8]

Similarly the diol (8), obtained from the diene ester (1) by treatment with aqueous acetic acid, reacts with MCPBA to give the two endo-epoxides (9) and (10) [52% yield, ratio 1:1].

Results of this type are well documented,[3] and signify reagent approach control. Rate enhancements are also observed, and we note that a reaction time of only 12h is required for our reaction, contrasting with three days under identical conditions which are necessary for the epoxidation of the diene (1) with the same reagent.



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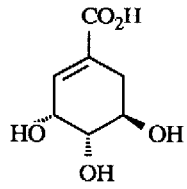

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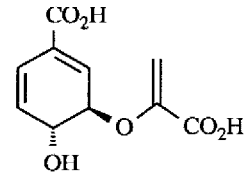

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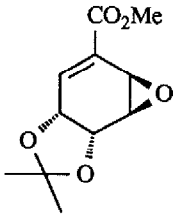

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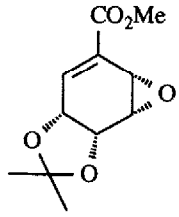

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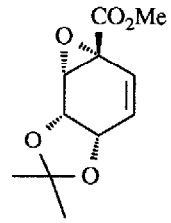

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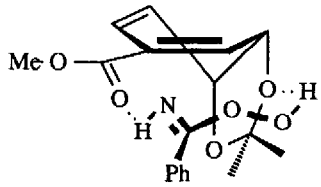


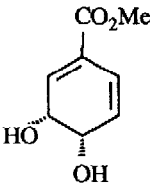
(7)

Hydrolysis of the diene ester (1) with pig-liver esterase affords the racemic acid (11) in 99% yield. Kinetic resolution of this and other esters in the series is under investigation.

Treatment of the acid with MCPBA gives only the epoxide (12) (90% yield), and this when reacted with one mol. equivalent of diazomethane forms the epoxy ester (4). With excess reagent the pyrazoline (13) is obtained.

When the epoxy ester (4) is treated with hydrogen fluoride in pyridine ring opening and removal of the acetonide protecting group occurs to afford methyl 6α-fluoroshikimate (14) in 49% yield, together with traces of the two fluoro-acetals (15) and (16). A similar regio- and stereo-chemical preference was observed when the epoxy ester was treated with trimethylsilylnitrile. Here only the

silyloxyisonitrile (17) was isolated.



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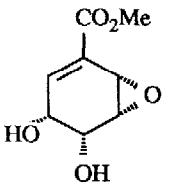

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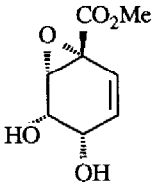

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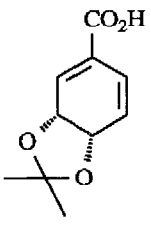

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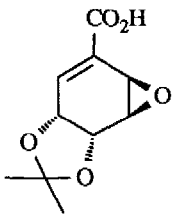

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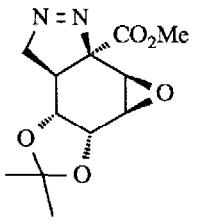

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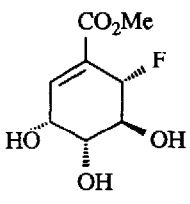

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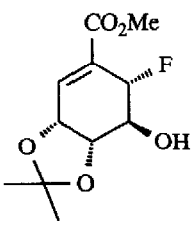

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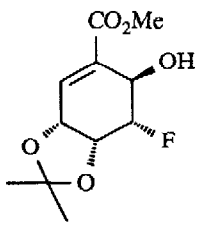

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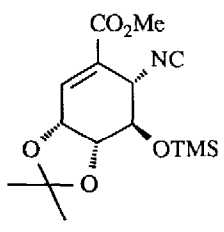

(17)

In this work we have demonstrated stereocontrol of the epoxidation of the double bond of the diene (1) and hence developed a stereoselective synthesis of shikimic and derivatives substituted at C-6.
All new compounds exhibit satisfactory elemental analyses and / or high resolution mass measurement on homogeneous samples. The structures and relative stereochemistry of these compounds are established by extensive ^{1}H, ^{13}C, and ^{19}F *n.m.r.* spectroscopy.

For example, the β- epoxide (4) has δ_H ($CDCl_3$) 1.38,1.39(2x3H, 2xs, 2xCMe_2), 3.65(1H,ddd, $J_{5,6}$=3.5Hz, $J_{5,4}$=2.0Hz, $J_{5,3}$= 0.5Hz, 5-H), 3.81(3H, s, OCH_3), 3.98(1H, ddd, $J_{6,5}$= 3.5Hz, $J_{6,2}$= 1.5Hz, $J_{6,4}$= 0.5Hz, 6-H), 4.56(1H, dd, $J_{3,4}$= 7.0Hz, $J_{3,2}$,= 2.5Hz, 3-H), 4.79(1H, m, $J_{4,3}$= 7.0Hz, $J_{4,5}$= 2.0Hz, $J_{4,2}$= 0.5Hz, $J_{4,6}$= 0.5Hz, 4-H), 6.81 (1H, ddd, $J_{2,3}$= 2.5Hz, $J_{2,6}$= 1.5Hz, $J_{2,4}$= 0.5Hz, 2-H).

NOEDS data

Signal irradiated (δ)	Observed n.O.e. (% enhancement)
5-H (3.65)	4-H (9), 6-H (10)
6-H (3.98)	5-H (7)
3-H (4.56)	2-H (9), 4-H (9)
4-H (4.79)	3-H 11), 5-H (7)

Methyl 6α-fluoroshikimate (14) exhibits: δ_H ($CDCl_3$) 2.70(3H, br.s, 3xOH), 3.69 (1H, dd, $J_{4,5}$= 9.0Hz, $J_{4,3}$= 4.0Hz, 4-H), 3.82 (3H, s, OCH_3), 4.23(1H, ddd, $J_{5H,6F}$= 17.0Hz, $J_{5,4}$= 9.0Hz, $J_{5,6}$= 6.0Hz, 5-H), 4.49 (1H, br.dd, $J_{3,2}$= 5.0Hz, $J_{3,4}$= 4.0Hz, 3-H), 5.23(1H, br.dd $J_{6H,6F}$= 48Hz, $J_{6,5}$= 6.0Hz, 6-H), 6.95 (1H, dd J_{23}=5.0Hz, $J_{2,6}$= 1.0Hz, 2-H), δ_C(CH_3OD) 53.0(q, $O\underline{C}H_3$), 66.7(dd, $J_{3,6F}$=2.0Hz, 3-C), 70.2(dd, $J_{4,6F}$= 7.7Hz, 4-C), 73.4 (dd, $J_{5,6F}$= 21.2Hz, 5-C), 90.15 (dd, $J_{2,6F}$= 173.2Hz, 6-C), 130.7(d, $J_{1,6F}$= 18.7Hz, 1-C), 142.2(dd, $J_{2,6F}$=5.5Hz, 2-C), 167.4(s, C=O).

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