

CONFIGURATION OF INTERMEDIATES IN THE TOTAL SYNTHESIS OF SHIKIMIC ACID

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Several years ago the total synthesis of shikimic acid (III) was reported by two groups (1,2) of investigators, who both used the Diels-Alder adduct (I) of trans, trans-1,4-diacetoxybutadiene with acrylic acid (2) or its methyl ester (1) as the starting point. Smitsman *et al* (1) assigned (I) the configuration with $-CO_2R$ trans to $-OAc$, arguing that the pyrolytic elimination of acetic acid from (II) was a cis elimination of the C_1 proton and the C_2 acetate; this assignment has been accepted in a recent monograph (3). Raphael and coworkers (2) chose the alternate all cis configuration for (I) on the basis of the Alder rules (4), an assignment consistent with their failure to effect thermal elimination of acetic acid from (II) in the absence of base.

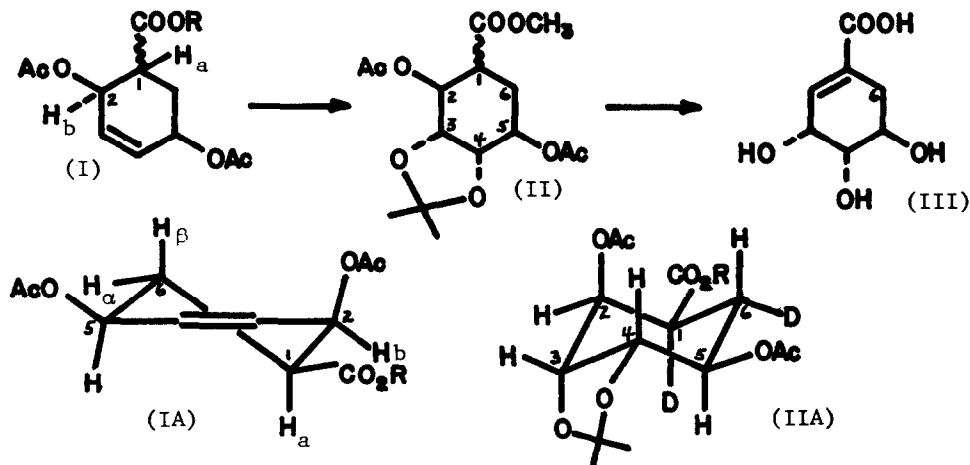
This stereochemical question became of critical importance to us in designing syntheses of (III) stereospecifically deuterated at C_6 by this route. We present unequivocal evidence here from the nmr spectra of (I), (II), and their deuterated analogs that the cis configuration at C_1 and C_2 was assigned correctly by the Glasgow group (2).

1. The nmr spectra of the crystalline adduct (I, $R = H$) and the ester (I, $R = CH_3$) prepared from it with diazomethane show H_a as a pair of triplets ($J = 13, 4, 3$ Hz) centered at τ 7.14 and H_b as a triplet at τ 4.45 with two small coupling constants ($J \sim 4, 4$ Hz). The H_b triplet in these spectra is identical in appearance with that in the spectrum of the known (5) cis adduct of acrylic acid and 1-acetoxybutadiene. The coupling constants show clearly that H_a must be axial and H_b pseudoequatorial, as shown in conformation (IA) of the cis adduct.

2. Dideuterated (I, $R = CH_3$) prepared from the Diels-Alder reaction with cis- α,β -dideuterio methyl acrylate (6) shows H_6 as a doublet at τ 8.17 ($J_{5,6} = 11$ Hz). This large coupling is consistent only with trans diaxial protons at C_5 and C_6 , which again requires conformation (IA, H_a and $H_\alpha = D$).

3. In the series of deuterated intermediates beginning with cis- α,β -dideuterio methyl acrylate, the dideuterio acetonide (II), m.p. 143-144°, and its precursor diol diacetate both exhibit simple nmr spectra amenable to first analysis and consistent only with conformation (IIA):

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H ₂ : τ 4.56, doublet, J = 4 Hz	Coupling: ee
H ₃ : τ 5.88, doublet of doublets, J = 4, 4 Hz	ee, ea
H ₄ : τ 6.22, doublet of doublets, J = 10, 4 Hz	aa, ae
H ₅ : τ 4.93, doublet of doublets, J = 10, 12 Hz	aa, aa
H ₆ : τ 8.1, doublet, J = 12 Hz	aa

4. In another deuterated series starting with β-deuterio methyl acrylate (D *cis* to CO₂CH₃), the nmr spectrum of (II) shows H₂ as a doublet of doublets with two small coupling constants, (J = 3, 4 Hz), while H₅ is coupled with its neighbors by only one large coupling constant (J = 10, 6 Hz), again explicable only on the basis of configuration (IIA).

5. The nmr spectrum of the liquid methyl acrylate adduct (1) (I, R = CH₃) showed it to be a mixture, approximately 73:27, of stereoisomers. The spectrum differs from that of the pure ester prepared by methylation of the crystalline acid (2) in having an additional -COOCH₃ singlet 1.2 cycles downfield and an additional -COOCH₃ singlet 1.2 cycles upfield from the low-field acetate. The major isomer is identical with (I, R = CH₃) from Raphael's acid (2) and all subsequent crystalline intermediates are identical whether formed from the acid or ester adduct. In agreement with the Glasgow group (2) and others (7) we find that the elimination of acetic acid from (II) is best accomplished by heating with a basic catalyst (calcium oxide) at 310-320°.

The metabolism of 6α- and 6β-deuterioshikimic acids in bacterial mutants will be the subject of a separate paper.

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