

THE CONFIGURATION OF INTERMEDIATES IN THE TOTAL
SYNTHESIS OF D(-)-SHIKIMIC ACID

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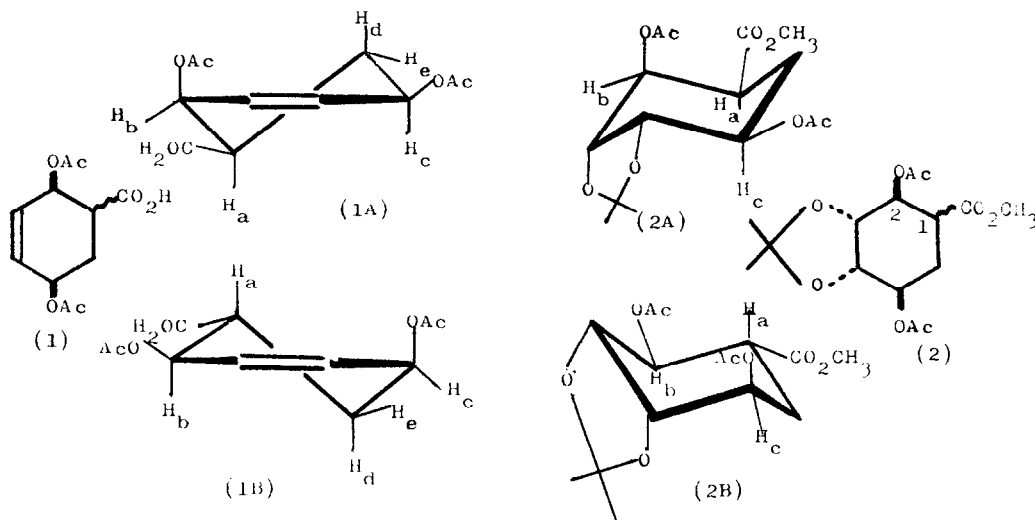
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In 1960 we reported¹ a total synthesis of D(-)-shikimic acid via the Diels-Alder adduct from trans-trans-1,4-diacetoxy-butadiene and acrylic acid. A synthesis by an essentially identical route had been independently reported in preliminary form² by Smissman and his colleagues. In their full paper³ these authors assigned the configuration at C-1 in the intermediates (1) and (2) as opposite to that proposed by us. Since the question at issue has been raised in the recently published monumental compendium "Reagents for Organic Synthesis" by L.F. and M. Fieser,⁴ and the configurational assignment by the American group is there accepted, we feel impelled here to record our recent p.m.r. studies with the intermediates (1) and (2) which unequivocally support our original assignment.

An examination of the p.m.r. spectrum* of the unsaturated acid (1) with single and double resonance afforded a convincing distinction between our and Smissman's formulations in their respective preferred conformations (1A) and (1B).

The relevant assignments are as follows: H_a double triplet (J = 12, 3, 3 Hz) centred at τ 7.16. Double irradiation at τ 8.00, leaves H_a as a single triplet (J = 3 Hz), removing the only major coupling (aa coupling with H_d). Formulation (1B) would under these conditions retain a major coupling (aa with H_b). [Irradiation at H_b, τ 4.43, leaves a double doublet (J = 12, 3 Hz) which does not distinguish between (1A) and (1B)].

* p.m.r. spectra taken in CDCl₃ (internal TMS) with a Varian HA 100 spectrometer.



H_b Triplet ($J = 5, 3$ Hz) centred at τ 4.46. This disallows (1B) in which H_b should show a major (> 10 Hz) aa coupling. [Irradiation at H_a (τ 7.12) leaves a doublet ($J = 5$ Hz)].

H_c Multiplet ($W^{\frac{1}{2}} \sim 25$ Hz), centred at τ 4.64. Irradiation at H_d (τ 8.03) removes the major coupling, leaving a multiplet, $W^{\frac{1}{2}} \sim 12$ Hz. Irradiation at H_e (τ 7.60) leaves a diffuse doublet ($J = 10$ Hz) which arises principally from the H_c H_d aa coupling. Irradiation simultaneously of both vinyl protons (τ 4.02) collapses H_c to a double doublet ($J = 10, 6$ Hz) [and H_b to a doublet ($J = 3$ Hz)]. These results clearly support (1A) against (1B).

Examination of the p.m.r. spectrum of the intermediate (2) again distinguishes between our and Smismann's formulation in their preferred conformations (2A) and (2B) respectively. The partial conformation of C-1, C-2, C-5 and C-6 in (2A) and (2B) approximate to the corresponding fragments in (1A) and (1B).

Proton H_a appears at τ 7.02 as a double triplet ($J = 12, 4, 3$ Hz), very similar in appearance to the corresponding signals in the acid (1), so that the same arguments favour (2A) over (2B), although the conditions for first-order analysis do not strictly obtain here. This accords with one aa and two ae couplings as in (2A) and not with two aa and one ae coupling required by (2B).

The resonance of H_b is an unresolved quartet centred at τ 4.37, $W^{\frac{1}{2}} \sim 8$ Hz. This again accords with the situation in (1A) [one ee, one ae coupling] but not (1B) [two aa couplings].

The proton H_c at τ 5.06 is a broadened quintuplet ($W^{\frac{1}{2}} = 26$ Hz) which conceals at least one coupling of more than 10 Hz, allowed by (1A) but disallowed by (1B).

Smisssman and his colleagues inverted our configurational assignment at C-1 in the triester (2) from β -CO₂Me to α -CO₂Me, assuming from their experimental conditions that the elimination of acetic acid in the transformation of (2) to (1) must involve pyrolytic cis elimination from conformation (2B). We do not feel that a firm prediction of either cis or trans elimination can be made on the basis of Smisssman's or our own experimental conditions, but presumably a cis elimination mechanism could operate even with the β -CO₂Me configuration in a suitable conformation (either distorted chair or boat). However the p.m.r. data which we now submit constitute clearcut and independent evidence that our original attribution of the configurations (1A) and (2A), made on the basis of the Alder rules, is correct.

References

1. R. McCrindle, K.H. Overton and R.A. Raphael, J. Chem. Soc., 1960, 1560.
2. E.E. Smisssman, J.T. Suh, M. Oxman and R. Daniels, J. Amer. Chem. Soc., 1959, 81, 2910.
3. E.E. Smisssman, J.T. Suh, M. Oxman and R. Daniels, J. Amer. Chem. Soc., 1962, 84, 1040.
4. L.F. and M. Fieser, "Reagents for Organic Synthesis", John Wiley, New York, 1967, p. 184.