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STEREOCHEMICAL FACTORS IN THE INTRAMOLECULAR KETO-CARBENE ADDITION TO SUBSTITUTED CYCLOHEXENES

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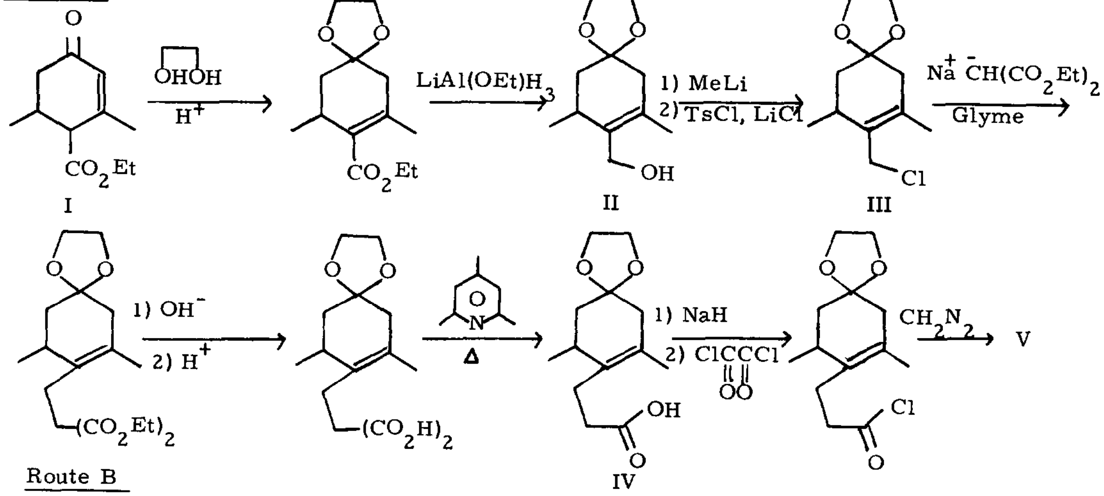
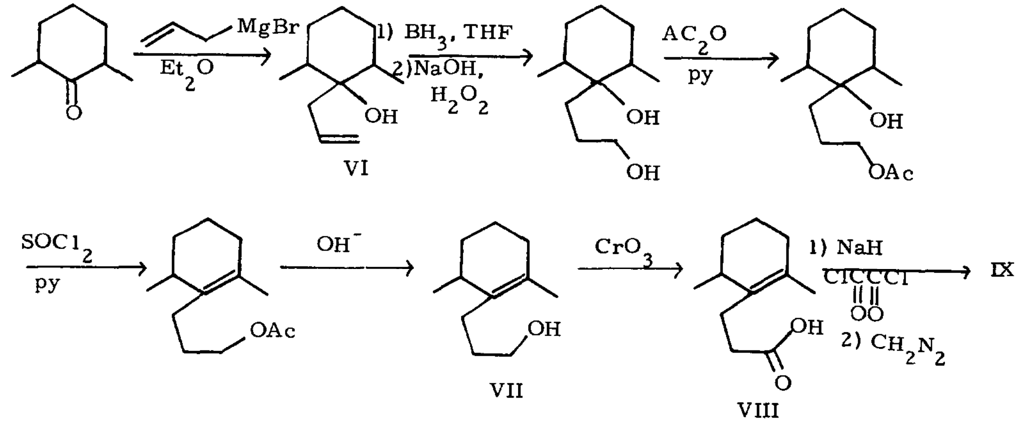
The intramolecular ketocarbene insertion reaction was discovered in these laboratories (1) and has recently been applied here in a synthesis of sirenin (2). Within the broader context of addition reactions to substituted cyclohexenes (3), and as a route to spiro [4.5] decanes, we have investigated the copper catalyzed decomposition of two unsaturated diazoketones V and IX, prepared by the following routes A and B respectively.

Route A



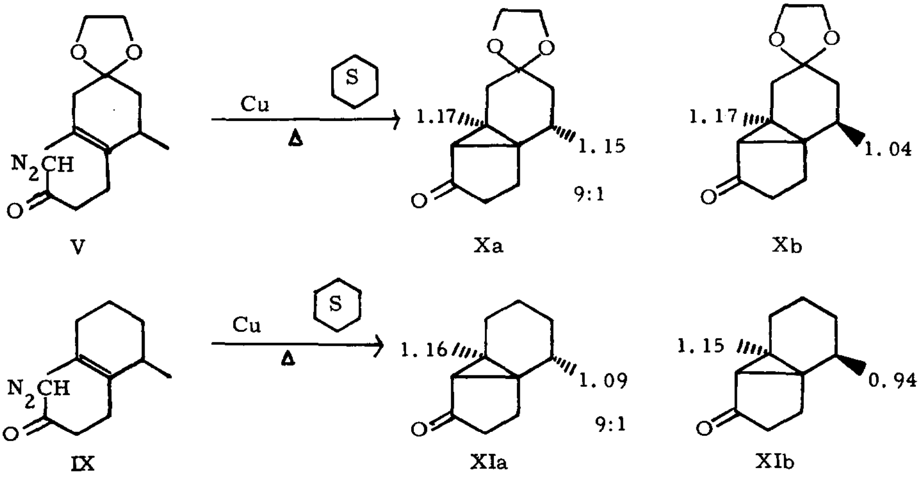
Route B



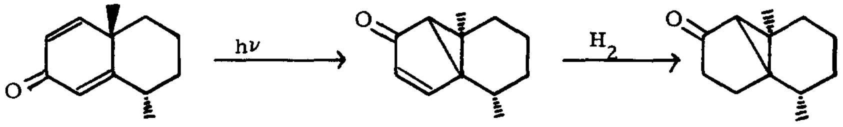
In route A (4) the known compound I (5), was ketalized and then reduced, with lithium monoethoxyaluminumhydride (6), to afford the unsaturated alcohol II, in 50% yield, b.p, 110-115° / 0.1mm. The unstable vinylogous β-chloroketal, III, prepared by the method of Stork, et. al. (7), was submitted to a malonic ester synthesis. The unsaturated ketal acid IV, obtained in 80% yield from II, was then converted to the diazoketone V, via treatment of the acid chloride with an excess of diazomethane.

In route B, the Grignard reaction of allylmagnesiumbromide and 2,6-dimethylcyclohexanone afforded the tertiary carbinol VI in 90% yield, b.p. 60-63° / 0.5mm. Conversion of VI to the isomeric primary alcohol VII, b.p. 76-78° / 0.15mm, by the sequence shown, proceeded in 80% overall yield. Jones oxidation of VII yielded the unsaturated acid VIII, which was converted to the diazoketone IX.

The intramolecular ketocarbene insertion of both V and IX (8) produced a 90:10 mixture of cyclopropylketones in 31 and 44% yield, respectively, from the corresponding acids IV and VIII.



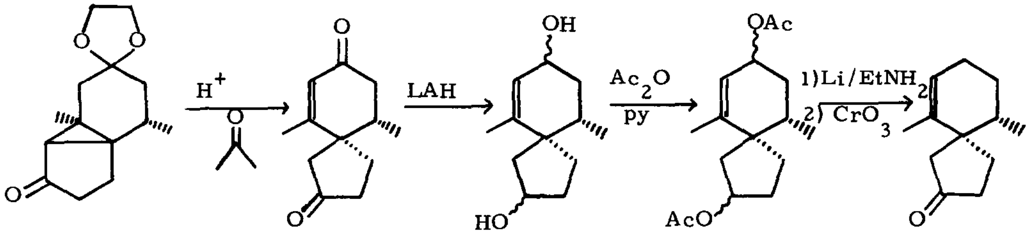
The structure of the major product from IX, i.e., XIa, was proved by direct comparison with a sample of authentic XIa, which had been previously synthesized by Kropp (9), via the following sequence.



XIa

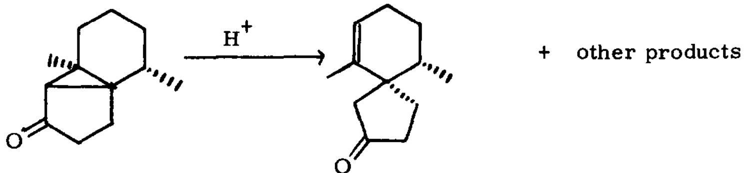
We observed that in both Xb and XIb, the secondary methyl group resonances appeared at higher field (0.11-0.15 ppm) than in the corresponding epimeric compounds. This is probably due to the well documented (10) shielding effect of the cyclopropane ring.

The structure of Xa was elucidated by its conversion to XIII, an intermediate in Marshall's synthesis of β-vetivone (11).



Xa XII XIII

Cleavage of the cyclopropylketone to the crystalline (m.p. 94-97°) enedione XII proceeded in 97% yield. This material was reduced to the enediol, and converted to the corresponding diacetate. Henbest reduction (12) of the allylic acetate and Jones oxidation of the cyclopentanol afforded XIII. The ir, nmr, and melting point of the DNP of XIII were identical with those of authenic XIII (13).



XIa XIII

Attempts to cleave XIa to XIII under a variety of conditions gave very complex mixtures (14), which contained varying amounts of XIII.

The intramolecular insertion reaction of the carbenoid species derived from diazoketones, has been shown to be a very stereoselective reaction, and this result should prove to be useful in further synthetic studies.

The experimental details of all work reported herein can be found in the author's thesis (15).

Acknowledgments:

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