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A FACILE ROUTE TO cis-HEXAHYDROFLUOREN-2,9-DIONE AND ITS 7-METHOXY ANALOG.

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In synthetic studies related to the gibberellins, e. g., gibberellic acid (1), it was found necessary to develop an efficient synthetic route to cis-hexahydrofluoren-2,9-dione[2] (6a) and its 7-methoxy analog 6b[3]. The approach entailed devising a stereospecific path to cis-5-oxo-2-phenyl cyclohexanecarboxylic acid (4a) which it was anticipated would readily cyclize to the diketone 6a under the appropriate conditions.

Condensation of phenyl pyruvic acid[4] with methyl vinyl ketone in aqueous methanolic sodium hydroxide afforded 1-hydroxy-5-oxo-2-phenylcyclohexanecarboxylic acid (2a)[5] as a single diastereomer of undefined stereochemistry. Thermal dehydration of the hydroxy acid at its melting point gave rise to 5-oxo-2-phenylcyclohex-1-enecarboxylic acid (3a). Subsequent reduction with zinc in aqueous acetic acid yielded the desired cis-acid 4a[6]. In the p-methoxyphenyl series, reduction of 3b with lithium in liquid ammonia afforded keto acid 4b, the same product as was derived by zinc-acetic acid reduction. This is in accord with the observation[7] that 3,4-diphenyl cyclohex-2-en-1-one affords cis-3,4-diphenylcyclohexanone, wherein the 3-phenyl group (in this case, the carboxylate anion) is capable of stabilizing the resultant anion from reduction. Under such circumstances protonation occurs at C-3 trans to the substituent at C-4. In addition, catalytic hydrogenation of 3b over 10% palladium-on-charcoal afforded not only keto acid 4b, but also allylic alcohol 5 as a single diastereomer. Oxidation of 5 with manganese dioxide in chloroform[8] regenerated 3b.

The proof of stereochemistry of keto acid 4a rests upon its conversion to the known cis-2-phenyl cyclohexanecarboxylic acid (8)[9] as outlined in the sequence 4a→7→8.

The requisite cyclization of 4a to 6a (lit.[2] m.p. 106-7°) was effected at 80° with polyphosphoric acid. The lower yield in the transformation 4b→6b is in keeping with the inability of β-(p-methoxyphenyl) propionic acid to undergo ready meta-cyclization.[10]

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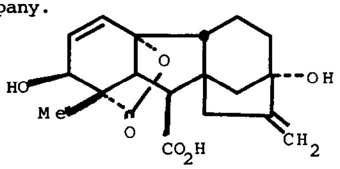

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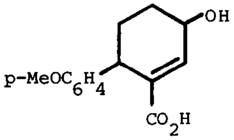

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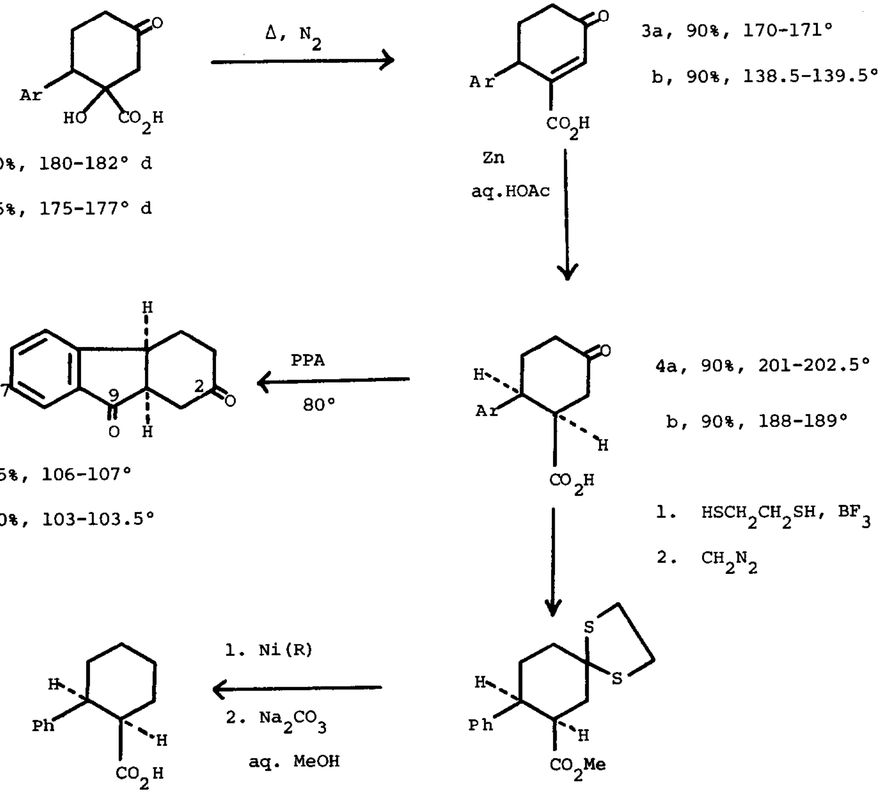

2a, 90%, 180-182° d

b, 85%, 175-177° d

3a, 90%, 170-171°

b, 90%, 138.5-139.5°

4a, 90%, 201-202.5°

b, 90%, 188-189°

6a, 85%, 106-107°

b, 50%, 103-103.5°

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3. The yields and melting points (corrected) for the phenyl series (a) and p-methoxyphenyl series (b) are listed under the appropriate structures.
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