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STEREORATIONAL SYNTHESIS OF A CHIRAL D$_3$ TRIKETONE

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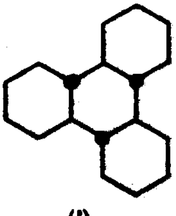
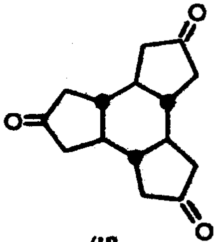
The D$_3$ symmetry group, typified by a three-bladed propeller, is represented in organic chemistry by only a handful of examples. While skew ethane, trimeric acetone peroxide,[1] cyclononane and some of its derivatives,[2] 1,5,9-*trans, trans, trans*-cyclododecatriene,[3] the trityl cation,[4] and trimesitylborane[5] possess D$_3$ symmetry in at least one conformation, to our knowledge the sole known organic molecule of D$_3$ symmetry which cannot equilibrate with achiral conformations is all-*trans* perhydrotriphenylene (I). Farina[6] obtained this hydrocarbon by high temperature isomerization of an isomer mixture prepared by hydrogenation of dodecahydrotriphenylene. Resolution by a circuitous method has been reported,[7] making (I) the organic molecule of highest symmetry to be resolved into optical antipodes.[8] It has the unusual property of forming inclusion compounds with a variety of guest molecules,[9] and Farina has observed that γ-ray irradiation of *trans*-piperylene as an inclusion compound in crystalline (–)-(I) produced an optically active isotactic polymer.[10]

Because of the striking properties of (I), we have undertaken the preparation of functionalized D$_3$ relatives by stereospecific routes. This paper reports the synthesis of the chiral triketone (II) by a stereospecific approach and the proof of its all-*trans* configuration by cmr spectroscopy.

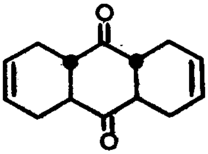
The readily available[11] diketone (III), containing four asymmetric centers of established configuration,[12] was chosen as starting material. The first objective was the conversion of the carbonyl groups to equatorial carboxymethyl sidechains, providing an intermediate (IV) with all the necessary carbons and six contiguous asymmetric centers in the correct configuration.



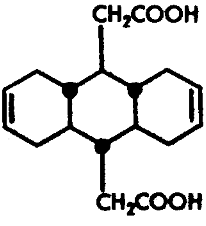
(I)



(II)

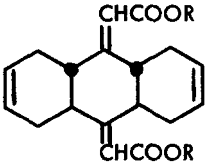


(III)

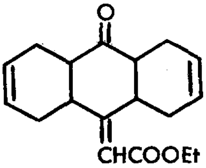


(IV)

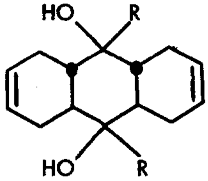
Initial efforts were directed toward diester (V). Wittig reaction of (III) with Ph_3P=CHCOOR failed, however, and the Wadsworth-Emmons procedure,[13] even with excess reagent, gave only the mono-ester (VI). Moreover, this was formed as an equilibratable mixture of two crystalline stereoisomers; apparently the trans-syn-trans backbone is no longer the most stable configuration in (VI) (in contrast to (III)) because of the 1,3-allylic strain[14] and at least one asymmetric center epimerizes, rendering this approach unsuitable for synthesis of (IV). Reformatsky reaction of (III) with ethyl bromoacetate, or better, the Rathke[15] procedure for addition of lithio ethyl acetate, gave diester (VII), and addition of ethoxyacetylene afforded (VIII) in good yield, but neither could be converted to (V), giving instead mixtures of endocyclic olefins, again presumably due to 1,3-allylic strain.



(V)



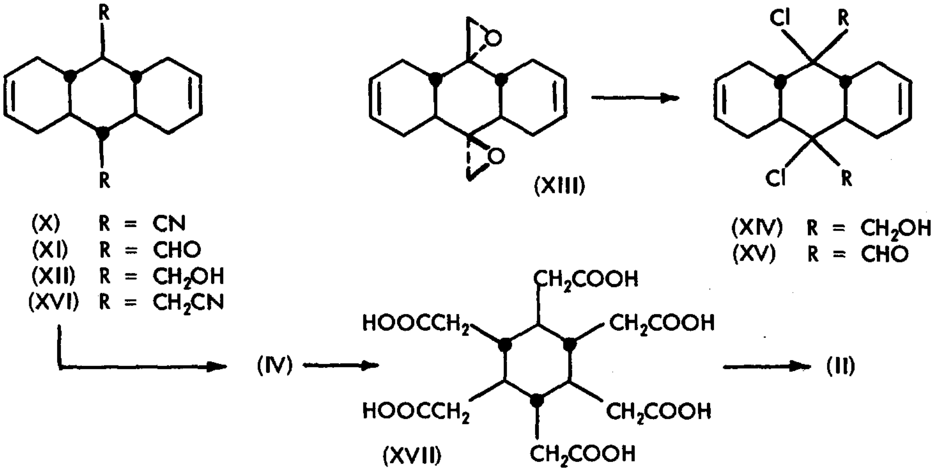
(VI)



(VII) R = CH_2COOEt
(VIII) R = C≡C-OEt
(IX) R = H

An alternate, somewhat longer, route to (IV) was successful. Sodium borohydride reduction of (III) gave a 4:4:1 mixture of the diequatorial, cis equatorial-axial, and diaxial diols (IX). The first two were identified by hydrogenation to the known[16] saturated diols, while the third must be the remaining trans-diaxial isomer.[17] The yield of this diaxial diol could be raised to 60 %by the use of potassium tri-sec-butyl borohydride, but attempted displacements with several nucleophiles on the diaxial bis-mesylate led primarily to elimination. Reaction of the mesylates of the mixed diols with KCN in DMF gave an excellent yield of stereoisomeric dinitriles of gross structure (X). Reduction with diisobutyl aluminum hydride gave dialdehyde (XI) as a 1:1 mixture of stereoisomers; brief equilibration with potassium t-butoxide changed the ratio to about 4:1. Separation was accomplished more easily after borohydride reduction to diols (XII). The cmr spectrum of the minor, more soluble, isomer showed two signals for olefinic carbons, showing it to have the cis-dihydroxy configuration, while the spectrum of the diacetate of the major stereoisomer displayed only seven signals, proving it to be one of the trans isomers. Since the diaxial dialdehyde can hardly be the predominant isomer after equilibration, the major product must be the desired diequatorial isomer (XII).

An alternative route to (XI) began with addition of trimethyloxosulfonium methylide to (III), affording the bis-epoxide (XIII). Treatment with gaseous HCl gave chlorohydrin (XIV) which was followed by Collins oxidation to the chloroaldehyde (XV). Zinc-acetic acid reduction led to the same 4:1 mixture of aldehydes (XI) as above, from which the pure trans diequatorial diol (XII) was obtained in 74 % yield after reduction.



With the substituents firmly fixed in equatorial positions, extension of the sidechains was straightforward. Displacement of the bis-mesylate of (XII) with KCN in DMF gave dinitrile (XVI), readily hydrolyzed to diacid (IV). The presence in (IV) of both a symmetry plane and a C_2 axis was confirmed by the cmr spectrum of the dimethyl ester, which showed only seven signals.

Ozonolysis of (IV) with oxidative workup gave the cyclohexane hexa-acetic acid (XVII). Proof of its all-trans configuration came from the cmr spectrum of its hexamethyl ester, which showed four signals: δ_{CDCl_3} 172.9 (C=O), 51.6 (OCH_3), 42.0 (methylene), and 35.8 (methine). Finally, pyrolysis of (XVII) with $Ba(OH)_2$ or, somewhat better, refluxing (XVII) with acetic anhydride, led directly to the crystalline triketone (II). The D_3 symmetry is confirmed by its cmr spectrum, which displays only three peaks: δ_{CDCl_3} 214.8 (C=O), 48.2 (methylene), and 43.5 (methine).

The success of this approach opens the way to a series of functionalized chiral D_3 compounds.

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17. The isolation of three stereoisomeric diols provides additional proof besides that cited in reference 12 that the stable diketone prepared by base-catalyzed isomerization of the bis-butadiene-benzoquinone adduct has the *trans-syn-trans* configuration (III) rather than the *trans-anti-trans* configuration.