A CONVENIENT ROUTE TO 1,3-CYCLOOCTATETRAENOPHANES

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Summary: Three cyclooctatetraenes, bridged with methylene groups in a previously unknown 1,3-manner, have been prepared in racemic form by a route involving ultimate disrotatory opening of a suitably constructed bicyclo[4.2.0]octatriene precursor.

The capacity of the cyclooctatetraene (COT) nucleus for dynamic conformational change includes ring inversion (RI) and bond shifting (BS). While there is uniform agreement that RI proceeds by simple mechanical flexing of the ground state tub conformer, the precise reaction profile for BS has remained controversial. The transition state possibilities that have been considered include a planar-delocalized 4n species with equivalent C-C bond lengths,^{1,2} a nonplanar crown structure,³ and a flattened saddle conformation.⁴ The latter hypothetical reaction course can best be realized by pseudorotation about the trigonal carbons.⁵ If a resolution of this complicated mechanistic issue is eventually to be achieved, the likelihood is highest that properly annulated COT's will provide the necessary convincing evidence.

For this reason, synthetic effort has been mounted in this laboratory to prepare these previously unknown classes of molecules. A short time ago, the 1,4-bridged system 1 was reported and shown to be incapable of experiencing either BS or RI.⁶ Thus, 1 represents the extreme case where the relevant dynamic conformational mobility is totally arrested. While arrival at the 1,5-cyclooctatetraenophanes 2 (n = 5, 6 and 10) has also recently been accomplished,⁵ full analysis of the BS phenomenon would ultimately be better served by access as well to the 1,3-belted isomers (3). We describe here a general preparative route to 3 that





2

41

(CH2)

1

appears applicable to all but the most highly strained members of this series.

From the retrosynthetic perspective, the key step was viewed as involving disrotatory ring opening of a suitably constructed bicyclo[4.2.0]octatriene precursor. From among the several options available for positioning of the carbocyclic loop in this penultimate intermediate, the illustrated 1,3-arrangement was selected for investigation.



Accordingly, 2-cyclododecenone (4a)⁷ was converted quantitatively into 5a by straightforward Michael addition of acetoacetate and cyclizative decarboxylation⁸ (Scheme I). When this enone was irradiated (450W Hanovia lamp) in *trans*-1,2-dichloroethylene solution, a mixture of isomeric dichloroketones 6a resulted (73%).⁹ Direct ketalization, reductive dechlorination, and acid hydrolysis of 6a produced 7a (94% overall). The necessary cyclohexenone double bond was introduced by application of organoselenium chemistry (42%). Following reduction with L-Selectride in dichloromethane solution at -78 °C, the epimeric allylic alcohols 8a and 9a were produced efficiently (100%). Subsequent treatment of the mixture with 2,4-dinitrobenzenesulfenyl chloride and triethylamine in refluxing 1,2dichloroethane¹¹ provided 3a in 65% yield, thus completing the nine-step sequence.

Associated with implementation of the sulfenate \rightarrow sulfoxide [2,3] sigmatropic rearrangement is an important stereochemical issue. Thus, the orbital symmetry-mandated retention of configuration results in stereospecific formation of 10 and 11, respectively, from 8 and 9 (Scheme II). In 11, geometrical alignment between ArS(0)- and the neighboring cis methylene hydrogen remains quite respectable for a wide range of *n* values. Contrastingly, the sulfoxide group in 10 can hope to eclipse an adjacent C-H bond and enter into elimination only when *n* is sufficiently large to permit reasonable conformational mobility within the six-membered ring. This is possible when n = 9 as shown by the fact that pure 8a and 9a could independently be converted into 3a. The disparity in efficiency (60% versus 82%) could be a reflection of the subtle structural differences noted above.

The conversion of 2-cycloundecenone (3b) to 7b was similarly realized (49% overall).



L-Selectride reduction of the corresponding dienone gave 8b and 9b in a 1:2 ratio. Following chromatographic separation, these allylic alcohols were individually subjected to the Reich-Wollowitz procedure.¹¹ While 9b delivered 3b in 70% yield, 8b showed no signs of undergoing an analogous transformation. Therefore, a value of n = 8 appears adequate to curtail sulfoxide elimination within 10.

This latter phenomenon is, of course, exacerbated in 8c which has proven equally unresponsive to dehydration. Nonetheless, 9c was observed to produce 3c efficiently (70%). Since reduction of $7d^{12}$ leads stereospecifically to 8d and preliminary attempts to invert its hydroxyl configuration have proven unsuccessful, 3d is presently unavailable.

Like 2, 3a-c are chiral, having at most C_2 symmetry. Consequently, when n is even all methylene groups along the loop are constituted of a diastereotopic pair of protons. This



phenomenon applies as well to 3a and 3c with the exception of the central CH_2 link. One possible scheme for interconversion of the enantiomers involves passage of C-2 and its associated hydrogen atom through the loop, a process that should become progressively impeded as the value of n decreases. Determination of the rates of racemization requires optical resolution of 3a-c. The present synthetic achievements open the way for realizing this important aspect of cyclooctatetraene dynamics.¹³

References and Notes

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