

The structure-directed synthesis of cyclacene and polyacene derivatives

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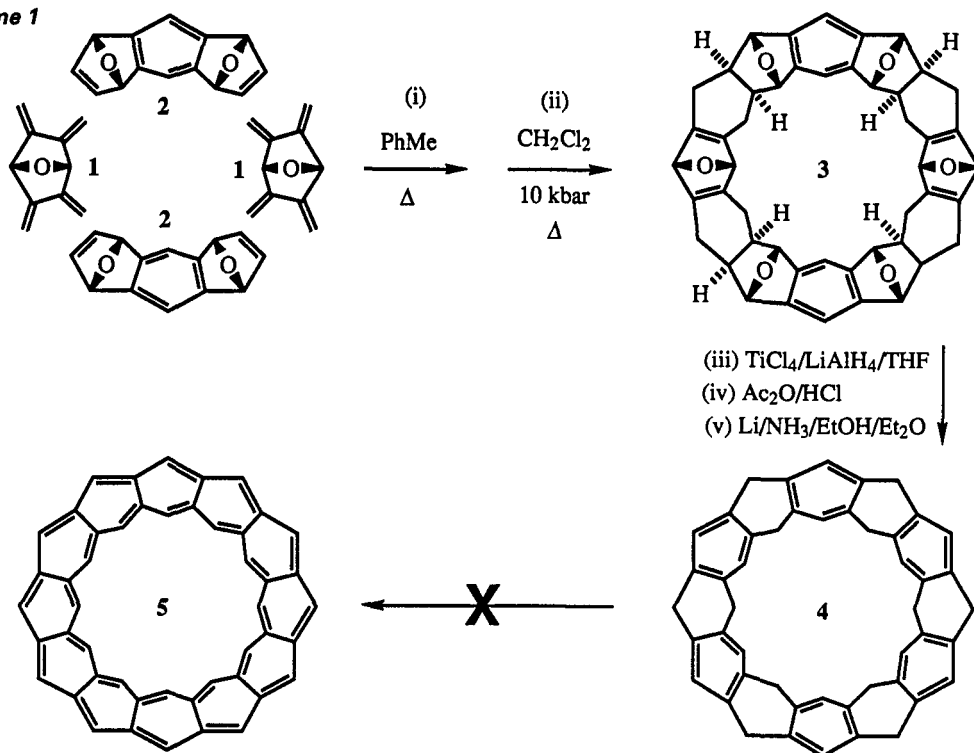
Abstract - The treble diastereoselectivities exhibited by Diels-Alder reactions which occur between diene and dienophilic components associated with bicyclic systems have been employed in the stepwise construction of compounds with molecular architectures that resemble cups and cages. These macropolycyclic compounds are potential synthetic precursors of novel hydrocarbons composed of [a,d]-fused and [a,c]-fused six-membered rings. The hydrocarbons themselves are of considerable importance in investigating the behaviour of π -electrons in highly-conjugated cyclic systems and in understanding the influence upon the aromaticity and antiaromaticity of benzenoid and fused benzenoid rings that are obliged to become bent.

INTRODUCTION

Following our recent structure-directed synthesis¹⁻⁹ of kohnkene (3) by means of repetitive Diels-Alder reactions starting from the bisdiene (1) and the bisdienophile (2), it was possible²⁻¹⁰ in three subsequent steps to effect its deoxygenation, dehydration, and reduction, affording (Scheme 1) the hydrocarbon, [12]-collarene (4), in which the alternating six-membered rings in this hydrocarbon containing twelve mutually [a,d]-fused six-membered rings are benzenoid in character. Next, we attempted^d to convert [12]-collarene (4) into [12]-cyclacene (5), employing various different dehydrogenating reagents (*e.g.* Pd/C, DDQ, chloranil) under a variety of different conditions. However, in all cases no [12]-cyclacene (5) was isolated from the reaction mixtures. These failed experiments obliged us to ask the obvious question as to whether compounds like 5 would be stable enough to be isolated and characterised by conventional laboratory techniques. In fact, it is well known¹¹ that the stabilities of linearly-annulated polycyclic saturated hydrocarbons decreases very rapidly with the number of [a,d]-fused rings. Although heptacene has been isolated,¹² it is quite unstable. In the case of [12]-cyclacene (5), such electronically-based instability is almost certainly augmented by the strain energy¹³ imposed upon the molecule by the six-membered rings being forced to adopt boat-like conformations. Moreover, a simple analysis of the structural formula of 5 indicates that it is not possible to identify a cyclic conjugated system containing $(4n+2)$ π electrons. Indeed, [12]-cyclacene (5) may be regarded (Fig. 1) as two [24]annulenes linked to each other by σ bonds attached to every other carbon atom around the macrorings. Thus, we argued that the incorporation of some [a,c]-fused rings into these molecular belt compounds might be beneficial towards helping us to isolate fully-unsaturated macropolycyclic hydrocarbons that have aromatic character to them.

^d It is interesting to note that the logo for the Seventh International Symposium on Novel Aromatic Compounds incorporates a space-filling representation of [18]-cyclacene.

Scheme 1



The structure-directed synthesis [(i) and (ii)] of kohnkene (3) and its transformation into [12]-collarene (4) by (iii) deoxygenation, (iv) dehydration, and subsequent (v) partial reduction.

The constitutional isomer 6 of [12]-cyclacene (5) is reproduced along with 5 in Fig. 1, which draws attention to the fact that the two macrorings comprising 6 contain 22 π and 26 π electrons, *i.e.* they both constitute $[4n + 2]$ annulenes, implying that this hydrocarbon might display some aromaticity.

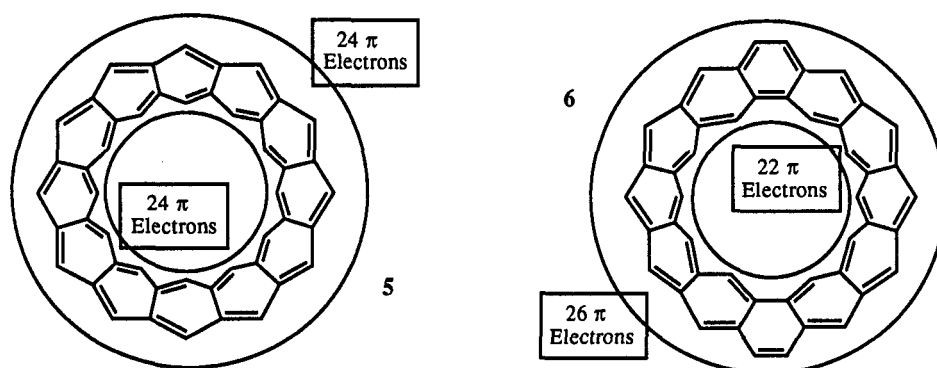
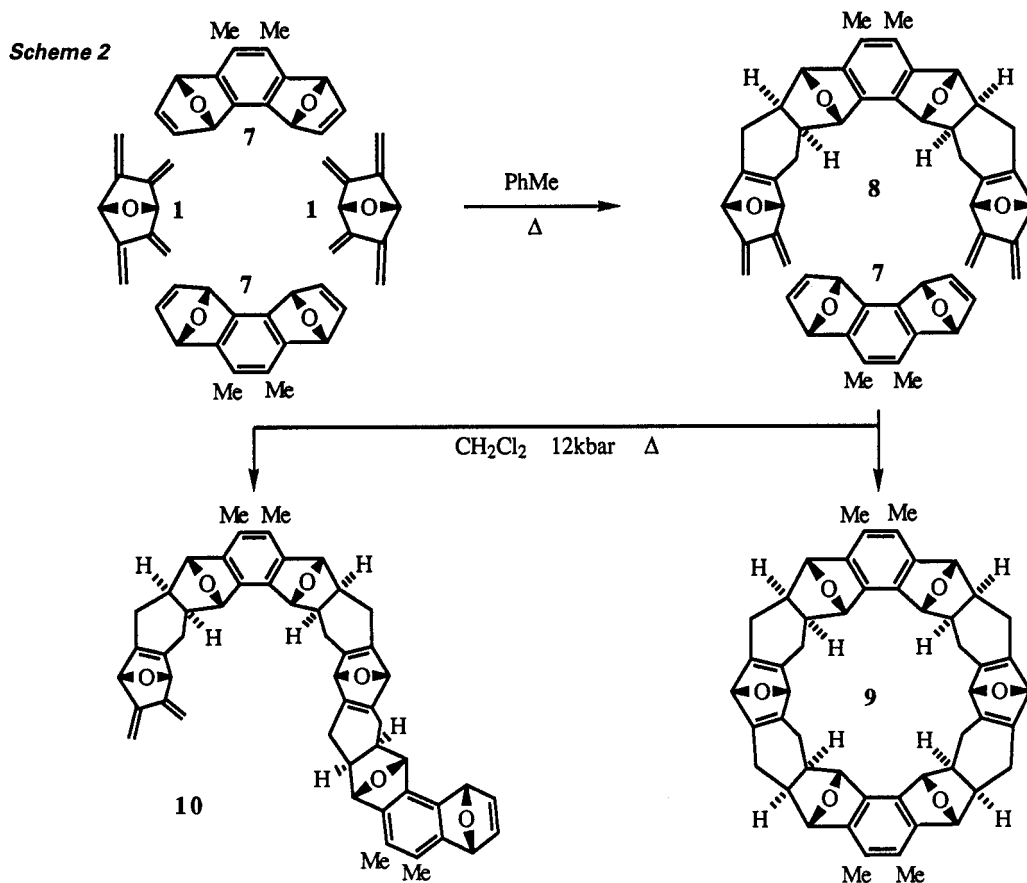


Fig. 1. Counting π -electrons in [12]-cyclacene (5) and in its constitutional isomer 6 which contains two [a,c]-fused rings.

ASSEMBLING AN ANGULAR MOLECULAR BELT COMPOUND

Taking the structure-directed synthesis¹⁻⁹ of kohnkene (3) as our cue, we identified⁸ the angular bisdienophile 7, along with the bisdiene 1, as suitable building blocks for the structure-directed assembly (Scheme 2) of the angular belt compound 9 containing two [a,c]-fused *o*-xylene rings. The bisdienophile 7 can be obtained (Scheme 3), together with its *anti*-isomer 7a, by trapping with furan the 1,3-bisaryne generated at low temperature on treatment of 4,5-dibromo-3,6-diiodo-*o*-xylene with *n*-butyl



The assembling of the angular belt compound **9** and the acyclic isomer **10** by reacting the bisdienophile **7** in a sequence of temperature and high pressure promoted cycloadditions. Note that in both **9** and **10** the newly-formed cyclohexene rings have the *syn/endo*-H configuration.

lithium. This reaction had been reported previously¹⁴ to give only one isomer whose stereochemistry had not been established. However, we were able to separate successfully the two isomers **7** and **7a** and to have (Fig. 2) their stereochemistries assigned by X-ray crystallography.^{15,16} These solid state structural studies indicated that, in both cases, the central benzenoid ring is distorted such that the carbon-carbon bonds associated with the two methyl substituents and the fused bicyclic rings are longer than the carbon-carbon bonds with which they alternate.

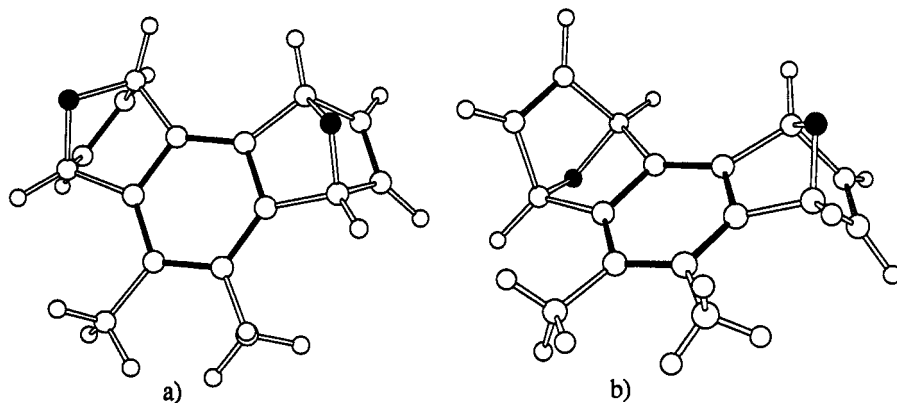
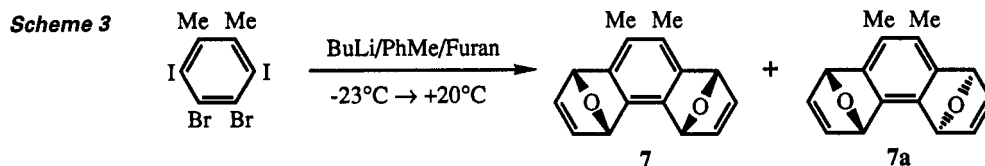


Fig. 2. The framework representations of a) the angular bisdienophile **7** and b) its *anti*-isomer **7a** in the solid state.

Although the two enantiomers of the *anti*-isomer **7a** can be separated analytically by chiral chromatography under high pressure, the single crystal which provided the X-ray diffraction data was found to be racemic, ruling out the opportunity to resolve **7a** by recrystallisation procedures. It has not escaped our attention that, if quantities of the *anti*-isomer **7a** could be obtained in its optically-pure forms, then the opportunity exists to construct chiral molecular ribbon-like polymers by carrying out repetitive Diels-Alder reactions on the chiral bisdienophiles with appropriate bisdienes.



The synthesis of the bisdienophile **7** and its *anti*-isomer **7a** by treatment of 4,5-dibromo-3,6-diiodo-*o*-xylene with *n*-butyl lithium and trapping the reaction intermediate(s) with furan.

When the angular bisdienophile **7** was reacted under reflux in toluene with 2.5 molar equivalents of the bisdiene **1**, the 2:1 adduct **8** was isolated (Scheme 2) in 90% yield. However, when this 2:1 adduct **8** was subjected to high-pressure promoted reaction with another 1 molar equivalent of the angular bisdienophile **7**, two constitutionally-isomeric compounds were obtained in almost equal amounts. Their ^1H and ^{13}C NMR spectroscopic characteristics were consistent with them having arisen from the two possible modes of reaction of the angular bisdienophile **7** with the 2:1 adduct **8**. In one case, the first [4+2] cycloaddition brings the reactive sites into a favourable disposition for the second [4+2] cycloaddition, leading to the angular belt compound **9**. In the other case, the angular bisdienophile **7** undergoes the first [4+2] cycloaddition with the 2:1 adduct **8** in the alternative constitutional sense, affording the acyclic compound **10**. This snake-like molecule is sufficiently rigid to keep the dienophilic end sufficiently far away from the diene end and so prevent macropolycyclisation occurring. The only possible further reaction pathways open to **10** are intermolecular [4+2] cycloadditions that would lead to oligomer and polymer formation under tight stereochemical control.¹⁷

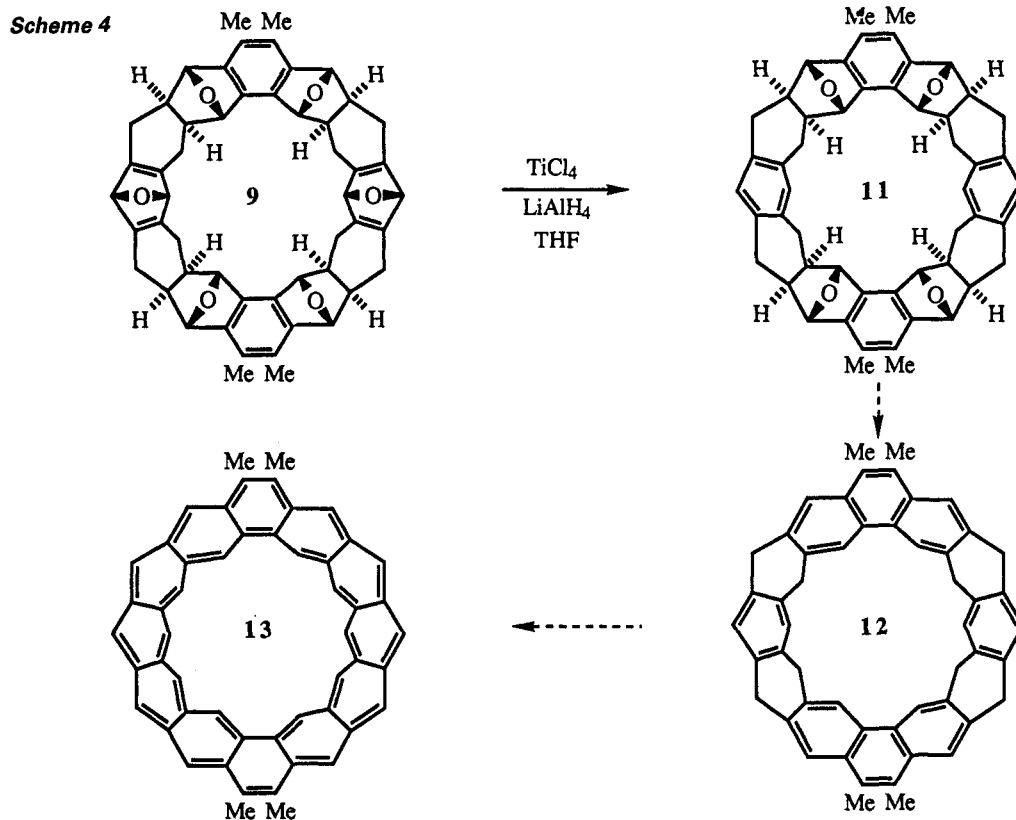
Although regiocontrol is lacking in the third [4+2] cycloaddition step in Scheme 2, the angular belt compound **9** must have been assembled from the bisdiene **1** and the angular bisdienophile **7** with complete treble diastereoselectivity operating at each successive Diels-Alder cycloaddition step along the reaction pathway, *i.e.* the stereochemical control which is exercised in the formation (Scheme 2) of the angular belt compound **9** is just as high as that already known¹⁻⁹ to operate during the formation (Scheme 1) of the linear belt compound, kohnkene (**3**). Although an X-ray crystal structure is not available for **9**, the structural assignment given to it in Scheme 2 is supported by all the NMR spectroscopic evidence. The ^1H NMR and the broad-band decoupled ^{13}C NMR spectra of **9** show, respectively, 11 signals for the heterotopic protons and 14 signals for the heterotopic carbon atoms expected on the basis of the C_{2v} symmetry of the angular belt compound. The fact that the bridgehead protons on the bicyclic rings next to the newly-formed cyclohexene rings resonate as singlets establishes the *syn/endo*-H stereochemistry¹⁻⁹ at the ring junction between these rings. Under comparable reaction conditions, we observed that the angular bisdienophile **7** is much more reactive than its linear isomer **2**.

We are inclined to speculate that, when the dienophilic carbon-carbon double bonds in **2** and **7** are transformed into single bonds, the distortion which leads to a lengthening of the carbon-carbon bonds in

the benzenoid ring associated with the fused bicyclic rings in **7** is relieved, allowing a more even distribution of bond orders to result within the benzenoid ring. The thermodynamic advantage gained by the angular bisdienophile **7** on undergoing a Diels-Alder reaction is thus greater than it is for the linear isomer **2**. It follows that **7** undergoes [4+2] cycloadditions faster than does **2**.

IN SEARCH OF NOVEL HYDROCARBONS

Although the angular belt compound **9** can be deoxygenated (Scheme 4) employing the conditions that proved successful¹⁰ in the deoxygenation of kohnkene (**3**), all attempts to effect the dehydration (*e.g.* using HCl/Ac₂O) of the dideoxy compound **11** and provide an entry into hydrocarbons such as **12** and **13** have so far failed. One of the difficulties that is encountered in this kind of reaction is the propensity for aromatic rings to migrate, under conditions of acid catalysis, around the macropolycyclic constitution. This problem was observed¹⁰ during the dehydration of dideoxykohnkene where the least symmetrical hydrocarbon, containing one benzene, two naphthalene, and one anthracene unit, was isolated. Molecular



The strategy for the synthesis of the hydrocarbon **13** by a sequence of transformations, starting from the angular belt compound **9**.

mechanics calculations suggest (Fig. 3) that the combination of two benzene and two phenanthrene units present in hydrocarbon **12** is not a particularly stable one. Indeed, in the case of the parent hydrocarbon **17**, its relative strain energy was calculated to be 23 kcal/mol less stable than hydrocarbon **14** which contains two benzene and two anthracene units. Hydrocarbons **15** - with one benzene, two naphthalene and one anthracene units - and hydrocarbon **16** - with four naphthalene units - are 10 and 13 kcal/mol less stable than hydrocarbon **14**. Thus, it would appear that a number of prototropic shifts will be encouraged to occur following the step-wise dehydration of compound **11**.

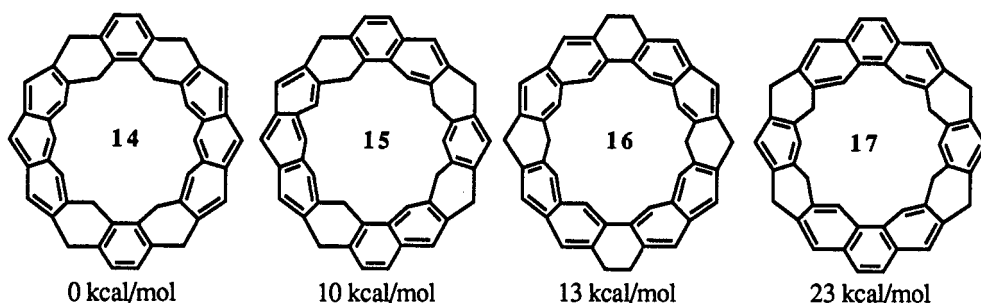
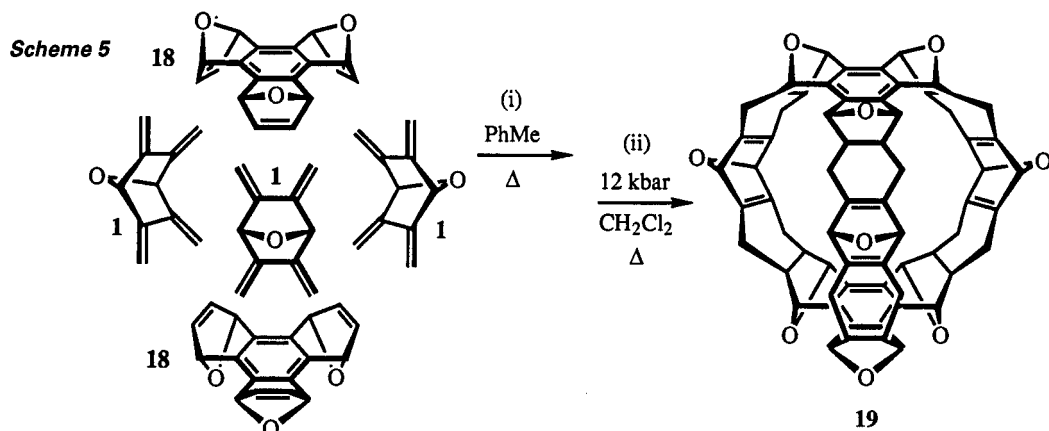


Fig. 3. The relative energies of some isomeric hydrocarbons related to compound 12. Calculations were performed on a Silicon Graphics Iris Indigo XS24 workstation using the CHARMM forcefield. The initial conformations were first refined using an Adopted-Basis Newton-Raphson approach, and then optimised to the minimum energy conformation using the Newton-Raphson method. The energy of each isomer was calculated using the empirical energy function of the CHARMM forcefield.

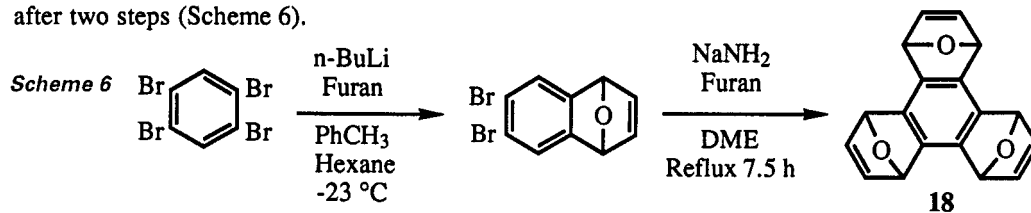
ASSEMBLING A MOLECULAR CAGE COMPOUND

So far, we have considered the structure-directed assembly of macropolycyclic compounds - *e.g.* 3 and 9 - which resemble molecular belts and cups. There is no reason, at least in principle, why molecular cages cannot be assembled in the same manner. Indeed, when the trisdienophile 18 is reacted with the bisdiene 1, in a sequence of Diels-Alder reactions promoted by heat and then subsequently by high pressure (Scheme 5), the molecular cage compound 19, which has been dubbed trinacrene, is obtained.¹⁸



The synthesis of the molecular cage compound 19, dubbed trinacrene, from the bisdiene 1 and the trisdienophile 18 in a sequence of thermally and high pressure promoted cycloadditions.

At present, a major impediment to further progress in elaborating this cage compound synthetically is the availability of the trisdienophile 18. Originally, it was obtained¹⁸ from 2,5-dibromoaniline in an overall yield of 0.4%. Recently, by employing 1,2,4,5-tetrabromobenzene in the generation of a trisaryne equivalent, we have isolated¹⁹ the trisdienophile as a mixture of *syn*- and *anti*-isomers in 7% yield overall after two steps (Scheme 6).



The improved synthesis of the trisdienophile 18 consists of a two step procedure starting from 1,2,4,5-tetrabromobenzene employing halogen-metal exchange and hydrogen-metal exchange reactions in the regioselective formation of the trisaryne equivalent.

REFLECTIONS AND ASPIRATIONS

We have established that derivatives of cyclacenes and polyacenes can be constructed stereoselectively from appropriate bisdienes and bisdienophiles using repetitive Diels-Alder reactions. These macropolycyclic derivatives should provide new synthetic entries into novel aromatic compounds in the future.

Acknowledgements

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