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Synthesis of Small Cyclophanes

Vinayak V. Kane*
Department of Chemistry, Vanderbilt University, Nashville, Tennessee 37235

Willem H. De Wolf and Friedrich Bickelhaupt,
Scheikundig Laboratorium, Vrije Universiteit, De Boelelaan 1083, 1081 HV Amsterdam

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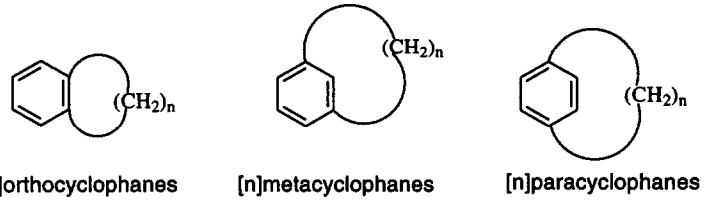
1 Introduction

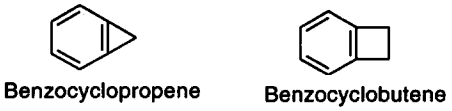
Strained organic compounds have attracted considerable attention from organic chemists during the last four decades. Synthetic chemists have accepted the challenge of designing and synthesizing strained molecules with exciting new properties to answer important fundamental questions.[1] Small [n]cyclophanes, especially, have received this attention. [n]Cyclophanes are bridged bicyclic systems containing a benzene ring, where n

symbolizes the number of methylene groups bridging the benzene ring. The three kinds of [n]cyclophanes[2] are illustrated in Scheme 1.



Scheme 1

The most highly strained [n]orthocyclophanes (also known as benzocycloalkenes, Scheme 2) are benzocyclopropene (n = 1) and benzocyclobutene (n = 2). Both of these classes of compounds have been reviewed in depth.[3,4]



Scheme 2

Excellent reviews on many aspects of the chemistry of cyclophanes are available.[5,6] However, despite the importance of [n]meta- and [n]paracyclophanes, only one review of limited scope on these subclasses has appeared.[7] Our aim in this review is to provide a comprehensive summary covering from 1961 through 1993 with special emphasis on methods for synthesis of [n]meta- and [n]paracyclophanes where $n \leq 8$. Related topics such as physical properties, geometries, and chemical reactivity of these unusual molecules will be discussed by us in a subsequent review. We regretfully omit any discussion of the larger [n]meta- and [n]paracyclophanes (where $n \geq 9$) for the sake of brevity.

2 Importance of Small Cyclophanes

Why are small [n]meta- and [n]paracyclophanes so intriguing to organic chemists? A simple answer is their geometry. Their properties are strongly dependent on the value of n.[5d,5e] As n decreases, the aromatic ring is increasingly distorted into a boat shape from its usual planar form and the usual favorable overlap of p-orbitals is diminished. Examination of molecular models and ultraviolet spectroscopy clearly show that this deformation takes place in metacyclophanes when n = 7 and in paracyclophanes when n = 8. It seemed reasonable that if the bridge length were decreased sufficiently a point would be reached where aromaticity of the benzene ring could completely collapse, and the ring might behave as 1,3,5-cyclohexatriene ie as a Kekule benzene. Bending has a considerable effect on the aromatic character of the benzene ring and causes a dramatic change in its chemical reactivity.[8] Consequently, a study of the small cyclophanes has a potential to contribute to a better understanding of the phenomenon of aromaticity.[8]

3 Aromaticity

Although aromaticity[8,9] is not directly observable, experiments so far have suggested its existence in cyclic conjugated systems, the first of which was benzene, a much studied molecule since its isolation by Michael Faraday in 1825. Understanding the structure of benzene was not trivial. The solution involved

experiments and imaginative speculation leading to Loschmidt's representation of the structure of benzene in 1861.[10] Benzene was shown to be a highly unsaturated hydrocarbon with a molecular formula C_6H_6 that did not possess the typical reactivity of a polyene. It was clear that there was something fundamentally different about benzene and its derivatives when compared to unsaturated cyclic compounds. Kekule in 1865 proposed benzene to be an equilibrating mixture of 1,3,5-cyclohexatrienes (Scheme 3).[10]

1,3,5-cyclohexatriene

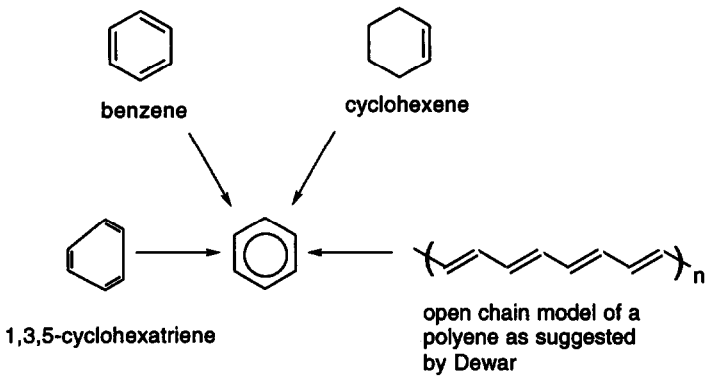
Scheme 3

In terms of chemical theory, the structure of benzene has puzzled prominent scientists, and discussions of its structure are not without controversy to this day. Everyone agrees that benzene is "aromatic", but what general criteria should be used for a compound to be ruled as an aromatic? The most wide-spread, and to a large extent acceptable, criteria are discussed below.

An understanding of the issue of aromaticity was greatly facilitated by the development of quantum mechanics. In 1931 Hückel with the use of π-electron molecular orbitals explained the theory of the aromatic sextet and described the famous (4n + 2) rule of aromaticity.[10d,e] Soon it was recognized that the extraordinary stability of benzene is due to its low ground state energy caused by π-electron delocalization. Although Hückel's rule is not perfect, it has certainly influenced current thinking about the problem of aromaticity. Numerous theoretical approaches have improved the Hückel rule and have resulted in various definitions for aromaticity.[11,12] The attribute of aromaticity currently accepted for a general class of compounds is that they must be cyclic π-electron systems and are stabilized by π-electron delocalization.

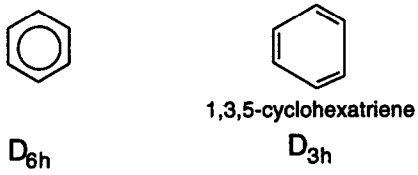
A puzzling aspect of benzene is the resonance energy gained by π-delocalization. A quantitative estimate of 36 kcal/mol for the resonance energy of benzene has been obtained by a comparison of its heats of hydrogenation to that of cyclohexene.[12] In order to obtain a more accurate value we would need to know the energy of localized 1,3,5-cyclohexatriene, a non-existent molecule.

To overcome some of these difficulties Dewar[13] has suggested an alternative way to estimate resonance energy (Scheme 4). His idea was to compare the heats of formation of benzene and open chain polyenes. He pointed out that a group increment value of an olefinic CH unit can be determined, so automatically $(CH)_6$ becomes the reference frame; and based on this consideration he derived for benzene a value of 20 kcal/mol resonance energy. This value is 16 kcal/mol lower than the one previously obtained from heats of hydrogenation. The reason for this lower energy is that there is already considerable stabilization due to conjugation in the reference acyclic polyene. Similar results have also been obtained by *ab initio* calculations.[14] In recent years the regular hexagonal structure[15] of benzene has been discussed. Several authors feel that the σ-system is responsible for the hexagonal structure and the π-system would prefer to be localized. If this theory proves correct then more emphasis will be given to the σ-electrons for aromatic stabilization, and the π-electrons will have to be considered to be of secondary importance for stability. Possibly the basic conceptual thinking about aromatic stability would have to be altered.



Scheme 4

A second criterion for aromaticity is based on X-ray crystal structures of several benzene derivatives. These derivatives have regular hexagonal planar structures with all carbon-carbon bonds of nearly equal length (usually 1.397 Å); slight observed differences in bond lengths were ascribed to substituent effects. Recently, some doubts have been expressed concerning the conclusions drawn from X-ray analysis of benzene itself. Ermer contends that within the experimental accuracy of the method used, a real choice can often not be made between a D_{6h} or a D_{3h} (1,3,5-cyclohexatriene) structure for benzene (Scheme 5).[16]



Scheme 5

The ^1H NMR spectrum of benzene exhibits a single resonance at δ 7.27, and this chemical shift provides a third criterion of aromaticity. This hydrogen resonance is at significantly lower field than that of an alkene hydrogen (for example cyclohexene, $\delta = 5.86$, cyclooctatetraene, $\delta = 5.69$). This deshielding effect has been attributed to a ring current[17] induced when benzene is in an externally applied magnetic field. The ring current produces its own opposing anisotropic magnetic field, with the result that hydrogens located in the plane of the benzene ring resonate at a lower field.[17]

The lack of reactivity of benzene has long been considered a characteristic of aromaticity. Under normal reaction conditions bromine adds to cyclic olefins, however, it does not add to benzene. However, in the presence of a Lewis acid benzene is attacked by bromine to give a substitution product, bromobenzene, indicating that ultimate rearomatization of any intermediate is thermodynamically favorable.[18] For a molecule with impaired aromaticity (for example a strained cyclophane) changes in the ground state and transition state energies will not be the same and would be difficult to predict quantitatively. Consequently reactivity criteria alone can not give precise information on the stability of a ground state.

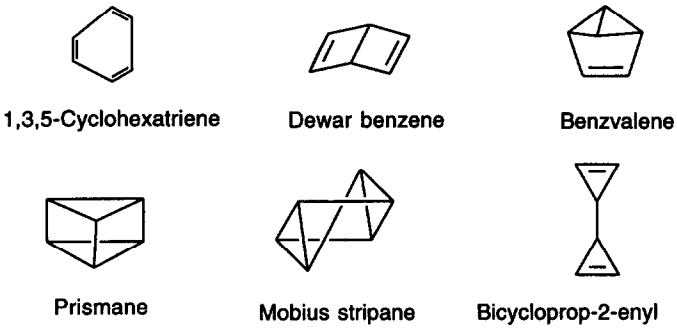
Similar objections can be raised against UV spectra as aromaticity indicators for small [n]cyclophanes. Since small cyclophanes are distorted, subtle (or small) unknown changes in the ground and electronically excited states make the applicability of such spectra problematic.

In 1986 Garratt put forth a critical overview of several criteria for aromaticity.[19] He prefers NMR criteria along with enthalpy arguments as unconditional prerequisites and defines aromatic compounds as "cyclic diatropic systems with a positive calculated Dewar resonance energy in which all the rings are involved in a single conjugated system."

4 Valence Isomers of Benzene

Valence isomerizations hold a very special position in organic chemistry. These are multicenter processes that take place synchronously by shift of σ- and/or π-electrons. The term valence isomerism was introduced by Grob and Schiess[20] and defined by Vogel in 1963.[21] These are relatively simple isomerizations that do not involve migration of atoms or groups, and also occur in ionic and free radical intermediates. These isomerizations are very sensitive to thermal and direct photochemical excitation but not to catalytic agents or to wide changes in solvent structure and polarity.

Interest in benzene valence isomers arose during the structure determination of benzene (C_6H_6) itself by 19th century chemists. However, in recent years when the empirical formula C_6H_6 was submitted to a computer, it came up with 217 possible structures that satisfy the rules of basic valency. When asked to adhere to $(CH)_6$ combinations, the computer provided only six possibilities (Scheme 6): 1,3,5-cyclohexatriene, Dewar benzene, benzvalene, prismane, Möbius stripane (Claus benzene) and bicycloprop-2-enyl, but not the real benzene. This structural group of $(CH)_6$ compounds compose the so-called valence isomers of benzene. During the past 27 years all the unsubstituted valence isomers with the exception of 1,3,5-cyclohexatriene and Möbius stripane (Claus benzene) have been synthesized and characterized.[22-25]



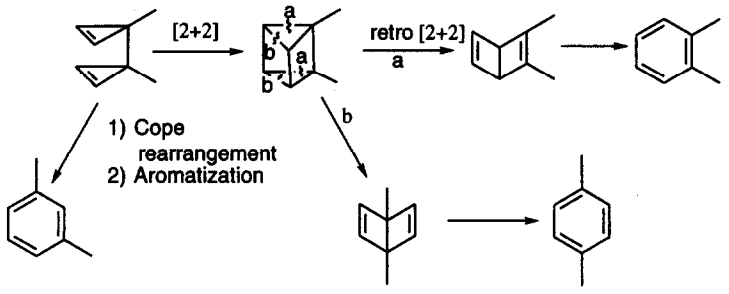
Scheme 6

All the valence isomers lie on the same multidimensional potential surface, and all except benzene possess the remarkable ability to store enormous amounts of potential energy in their highly strained aromatizable structures. The relative heats of formation of some of these isomers are given Table 1.[26]

Table 1. Relative Heats of Formation of $(CH)_6$ Isomers[26]

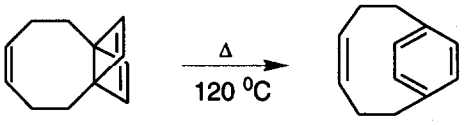
	$\Delta\Delta H^0_f$(kcal/mol)
Benzene	0
Dewar benzene	59.5
Benzvalene	65
Prismane	91.2
Bicycloprop-2-enyl	110-120

There was ample precedent from the excellent work of Breslow and his coworkers[27] and others[28] that these high energy molecules and their analogs were not only challenging targets by themselves but also could provide less strained valence isomers by thermal or photochemical processes (Scheme 7). These expectations have been confirmed experimentally.



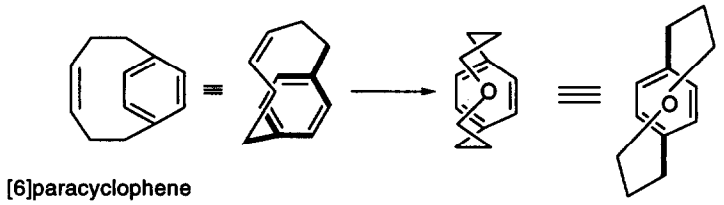
Scheme 7

The potential usefulness of valence isomerization in the synthesis of small [n]cyclophenes, e.g., as in Scheme 8, has now been realized. For other examples see Schemes 52, 53, and 55.



Scheme 8

Apart from the issue of aromaticity the small [n]cyclophanes may provide information on conformations of the bridge methylenes and on their dynamic processes .[29] In this connection spectroscopy, especially NMR, and thermochemical properties may provide a basis for refinement and revision of some of our ideas about strain energy and hindered rotation. Since small [n]cyclophanes are considerably deformed, they may also give insight regarding the transannular effects when the intramolecular cavity is considerably small. The unique features of [n]cyclophanes and [n] cyclophenes also make them attractive starting synthons for other molecules of fundamental interest, e.g., as in Scheme 9.



[6]paracyclophene

oxa [7]paracyclophane
(unknown compound)

Scheme 9

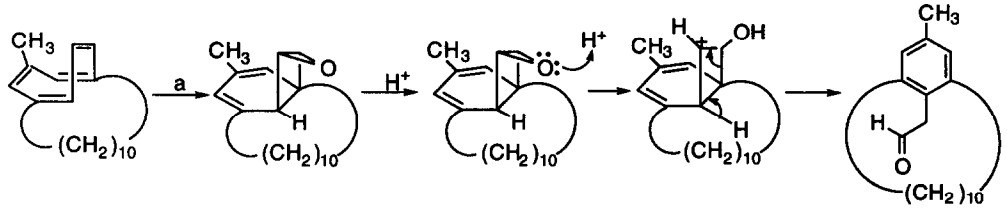
5 Synthesis of [n]Metacyclophanes

5.1 [n]Metacyclophanes

The purpose of this section is to demonstrate how synthetic strategy has led to the development of many useful methods as well as to the construction of [n]meta- and [n]paracyclophanes where $n \leq 8$. In comparison to the large amount of synthetic and theoretical work in the field of cyclophanes,[5] the [n]metacyclophanes have received considerably less attention, although a derivative was reported by von Braun as early as 1919.[30] A survey of the literature revealed several unsuccessful attempts at the preparation of [n]metacyclophanes where $n \leq 8$.[7a,31,32,33]

Before discussing the synthesis of [8]metacyclophane and lower analogs, we shall consider some of the recent methods for the synthesis of [9]- and [10]metacyclophanes. Such consideration is appropriate since the aforementioned syntheses may provide access to [n]metacyclophanes ($n \leq 8$).

In their studies on the chemical properties of [1,5]cyclooctatetraenophanes (**10.1**, Scheme 10), Paquette and coworkers[34] observed that on treatment of **10.1** with one equivalent of m-chloroperoxybenzoic acid at room temperature, rearrangement occurred to give 1,4-disubstituted [10]metacyclophane **10.3** as the major product. Evidently, the initially formed epoxide **10.2** undergoes acid-catalyzed rearrangement to the [10]metacyclophane derivative **10.3**. The driving force for the rearrangement is either relief of strain or gain of resonance energy in going from **10.2** to **10.3**, or a combination of the two.

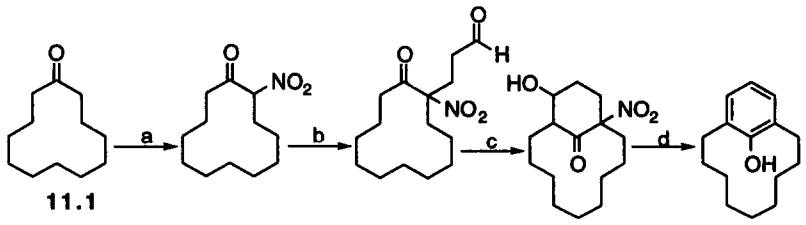


10.1 **10.2** **10.3**

a) MCPBA.

Scheme 10

A strategy for the synthesis of [n]metacyclophanes (n = 9) used by four research groups begins with macrocyclic ketone (**11.1**, Scheme 11) and fuses on to it a three carbon chain to form an aromatic ring.[35,36,37]

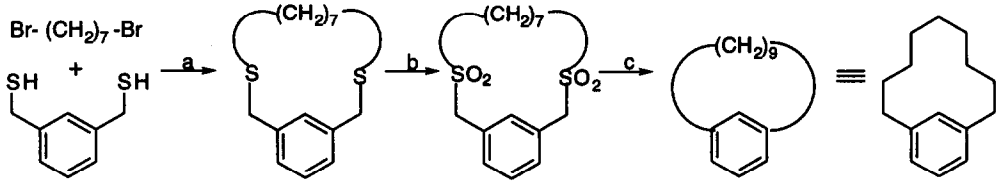


a) $RONO_2/KOBu^t$, b) CH_2=CHCHO/$(C_6H_5)_3P$, c) NaH, d) K_2CO_3/THF.

Scheme 11

Another alternative for the synthesis of cyclophanes starts from an aromatic precursor followed by the construction of an oligomethylene ring. Around 1970, several groups reported methods for preparing dithiacyclophanes. The facile conversion of these dithiacyclophanes to cyclophanes via sulfur extrusion offered a new, very general approach to the synthesis of various types of cyclophanes.[38] In this approach sulfur extrusion was best accomplished by conversion of dithiacyclophanes to the corresponding bis-sulfones followed by flash vacuum pyrolysis (FVP).[39]

A large number of cyclophanes has been synthesized[38,39] by the sulfur route, but only two reports exist on the application of this route to [n]metacyclophanes. Vögtle has employed this approach to prepare medium-sized [n]metacyclophanes, where n = 9-12.[40] An example is the synthesis of 2,10-dithia[11]metacyclophane **12.1** and its conversion into [9]metacyclophane (**12.2**, 53%, Scheme 12). (Otsubo and Misumi's analogous synthesis of [7]metacyclophane is discussed in Scheme 12 and shown later in Scheme 21).



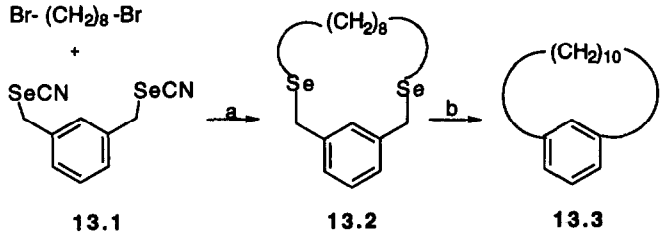
12.1 **12.2**

a) KOH/C_2H_5OH, b) MCPBA, c) Flash Vacuum Pyrolysis (FVP).

Scheme 12

In 1982, Higuchi and Misumi[41,42,43] discovered that benzyl selenocyanates (e.g., **13.1**) with dibromo-alkanes in the presence of sodium borohydride at high dilution gave diselenocyclophanes (e.g., **13.2**) in high yield (Scheme 13). These selenocyclophanes are smoothly converted to cyclophanes **13.3** by deselenation. Since C-Se bonds undergo fission thermally and photochemically more easily than do the corresponding C-S bonds, this method is superior to the conventional sulfur extrusion for the synthesis of cyclophanes.[43a] However, there are no reports of small [n]metacyclophanes prepared by this alternative strategy.

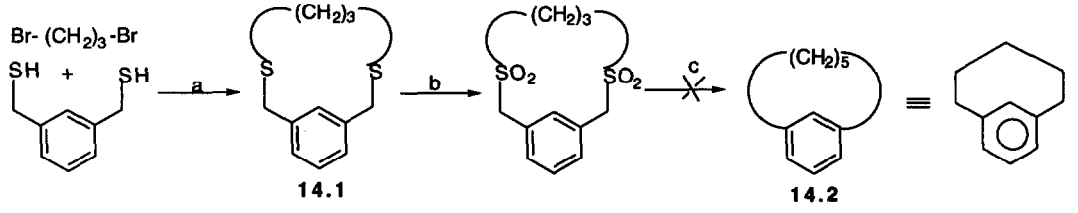
We in Amsterdam felt the ready availability of 2,6-dithia[7]metacyclophane **14.1** and 2,7-dithia-[8]metacyclophane would greatly enhance their usefulness in the synthesis of [5]metacyclophane **14.2**



a) $NaBH_4/C_2H_5OH/THF$, b) Benzyne-Stevens rearrangement

Scheme 13

(Scheme 14) and [6]metacyclophanes by the dithiacyclophane-sulfur extrusion route. However, experiments carried out in our laboratories in Amsterdam towards this goal were unsuccessful.[44]

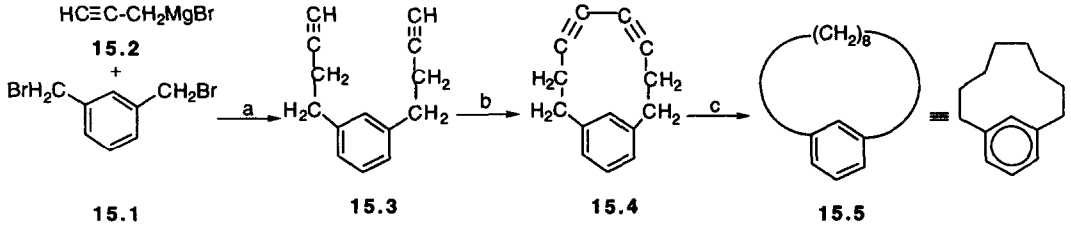


a)KOH / C_2H_5OH/high dilution, b) MCPBA , c)FVP.

Scheme 14

5.2 [8]Metacyclophanes

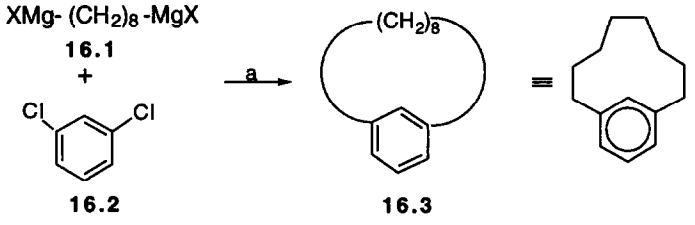
In the course of their work on the synthesis of macrocyclic rings containing diynes, Hubert and Dale isolated [8]metacyclophadiyne **15.4** (Scheme 15).[45] The required bisethynyl compound **15.3** was obtained by the reaction of α,α′-dibromo-m-xylene (**15.1**) with propargylmagnesium bromide (**15.2**). Intramolecular oxidative cyclization using Eglington oxidative coupling[46] (cupric acetate in pyridine) gave them [8]metacyclophadiyne (**15.4**, 10% yield), which on reduction gave [8]metacyclophane (**15.5**) as a colorless liquid, homogeneous by VPC. The UV spectrum for the [8]metacyclophane (**15.5**) in hexane showed λ_{max} 266 nm, log ε 3.00 in hexane. The absence of NMR data, not available to Dale and Hubert in 1963, made it difficult for them to judge the correct assignment of the [8]metacyclophane (**15.5**) structure by this route.



a) THF, b) $Cu(OAc)_2/C_5H_5N$, c) PtO_2/H_2.

Scheme 15

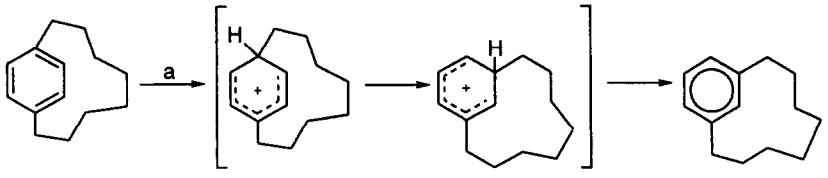
The use of the nickel-phosphine complex dichloro[1,3-bis-(diphenylphosphino)-propane]nickel(II) [Ni(dppp)Cl_2] in [8]metacyclophane (**16.3**) synthesis was well documented as early as 1975, due mainly to the efforts of Kumada and his coworkers[47] (Scheme 16). The key step was the addition of bis-Grignard reagent **16.1** (prepared from 1,8-dibromooctane) to an aromatic dihalide such as 1,3-dichlorobenzene (**16.2**) in the presence of catalytic amounts of the nickel-phosphine complex at 30-40 °C in THF. Furthermore, this group showed that this nickel-phosphine complex could also serve in the successful preparation of [6](2,6)pyridinophane and other larger pyridinophanes. Higher yields were obtained in the case of pyridinophanes than for metacyclophanes, an outcome that may be attributable primarily to the intrinsically higher reactivity of 2-halopyridines and to the smaller size of =N- than =CH-.



a) [Ni(dppp)Cl_2]/THF.

Scheme 16

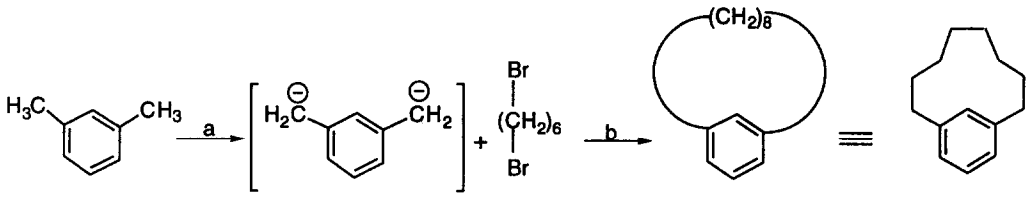
Hopf, Noble, and Ernst[48] achieved a synthesis of [n]metacyclophanes (n = 8 and 7) that involves an isomerization of [n]paracyclophane as a key step (Scheme 17). Under the influence of hydrogen chloride/aluminum trichloride at -10 °C, [8]paracyclophane (**17.1**) gave [8]metacyclophane (**17.2**) in 37% yield. Since [n]paracyclophanes can often be obtained in relatively large quantities, this method offers a very convenient one-step synthesis of [n]metacyclophanes in moderate yields. Although the principle of converting [n]paracyclophane to [n]metacyclophane where n = 10 had already been used by Blomquist,[49] it is difficult to predict a reaction pathway with smaller [n]paracyclophanes ($n \leq 8$) under these acidic conditions. In recent years this isomerization has been used by many others (see below), and credit is certainly due to Hopf for pointing out its considerable potential utility.



a) HCl/$AlCl_3$/CH_2Cl_2 at -10 °C.

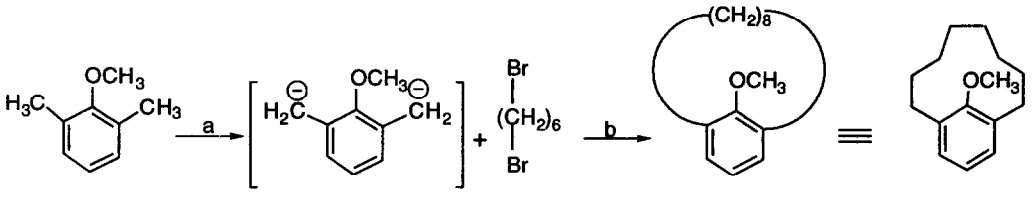
Scheme 17

That dianions can serve as suitable partners in organic synthesis is now well established. This concept has been used by Bates and coworkers for the past nine years to synthesize a variety of cyclophanes[50,51]. The method consists of the generation of stabilized dianions (-78 to 0 °C) from alkyl-substituted benzenes with Lochmann's base which is n-BuLi in hexane/KO-t-Bu (however most of the work reported here was carried out in Bates' group with heptane as a solvent) which on treatment with α,ω-dihalides provide cyclophanes. Two examples (Scheme 18) serve to illustrate this point.[52,53] The method constitutes a one-step synthesis of cyclophanes in low to moderate yields. Unfortunately it has limitations, e.g. no [n]metacyclophane derivatives could be formed where n < 7. Furthermore, this method was found to yield dimeric cyclophanes and also polymeric materials.



10% yield

a) n-BuLi/KO-t-Bu in heptane at 0 °C, b) THF was used as a solvent.



11% yield

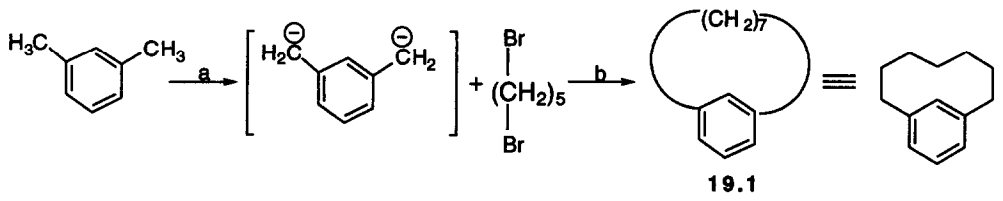
a) n-BuLi/KO-t-Bu in heptane at 0-20 °C, b) THF solvent. Also [n]metacyclophanes with n = 9-15 were synthesized by the outlined procedure.

Scheme 18

5.3 [7]Metacyclophane and its Derivatives

A [7]metacyclophane derivative was reported as early as 1962,[54] but a reevaluation of the assigned structure should be carried out with the benefit of instrumentation such as X-ray crystallography. The reaction that was attempted is thermodynamically feasible.[55]

Bates' group has used dianion chemistry to synthesize [7]metacyclophane (**19.1**) in 1% yield (Scheme 19).[52] The reaction is reproducible even though polymeric material was the main product.

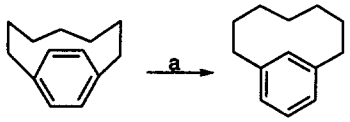


19.1

a) n-BuLi/KO-t-Bu in heptane at 0 °C, b) THF solvent.

Scheme 19

It is now evident from the above discussion (see Scheme 17) that the isomerization approach of Hopf offers a distinct advantage for the preparation of [n]metacyclophanes from [n]paracyclophanes. In connection with their studies of cycloaddition reactions with [n]metacyclophanes, Hopf and Jones[56] have developed a one-step synthesis of [7]metacyclophane (**20.2**) from now easily available (see below) [7]paracyclophane (**20.1**, Scheme 20).

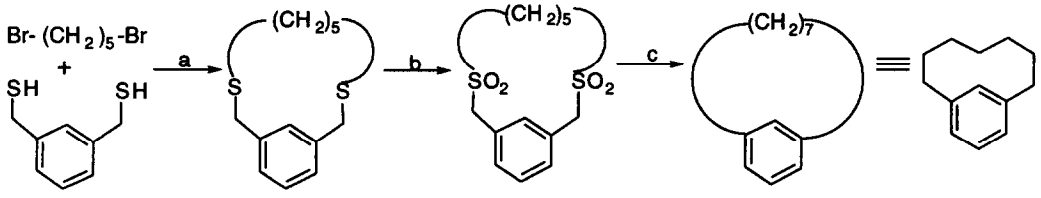


20.1 **20.2**

a) FSO_3H/ p-TsOH/ C_6H_6.

Scheme 20

The versatility of the dithiacyclophane method was further illustrated by Otsubo and Misumi[57] for the synthesis of [7]metacyclophane (**21.1**) in overall 30% yield from commercially available starting materials (Scheme 21).



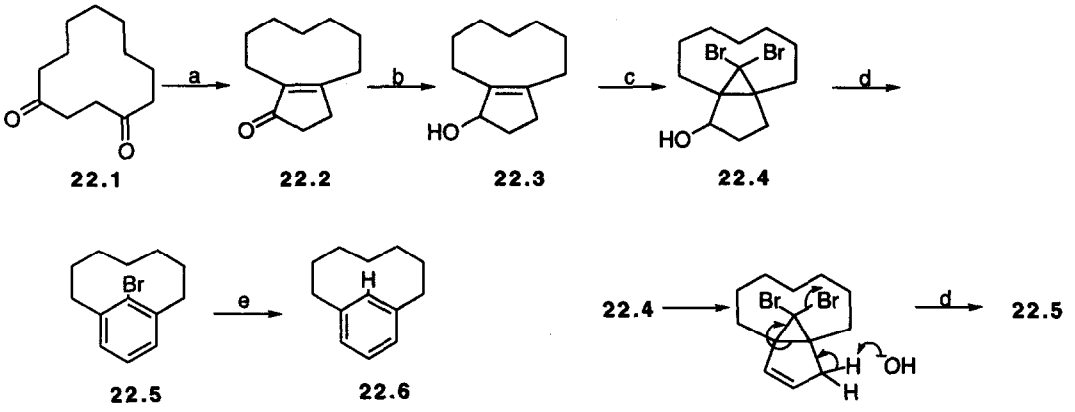
21.1

a) KOH/C_2H_5OH, b) MCPBA, c) FVP.

Scheme 21

A totally different approach to [7]metacyclophane and its derivatives was provided by Hirano, Nozaki and their associates (Scheme 22).[58] Intramolecular aldol condensation with methanolic sodium hydroxide of cyclododeca-1,4-dione (**22.1**) afforded bicyclic enone **22.2**, which was converted to bicyclic allylic alcohol **22.3** on reduction with $LiAlH_4$ in ether. Treatment of **22.3** with the carbene generated from $CHBr_3$ and potassium *t*-butoxide gave the propellane **22.4**. Flash vacuum pyrolysis (FVP) of **22.4** gave bromometacyclophane **22.5**, which on treatment with BuLi and subsequent hydrolysis furnished

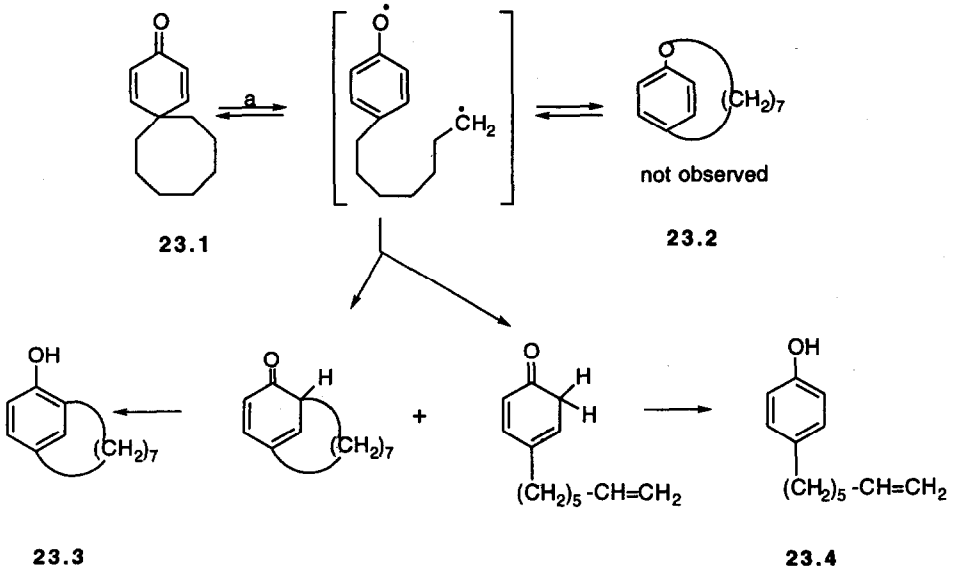
[7]metacyclophane (**22.6**) in overall 32% yield. An advantage of this method is that it permits the synthesis of benzene-substituted [n]metacyclophanes (n = 6, 7, 10). Mechanistically this reaction may be rationalized as shown.



a) NaOH/CH_3OH, b) $LiAlH_4$, c) $CHBr_3$/KO-t-Bu, d) heat, e) n-BuLi/H_2O.

Scheme 22

In connection with our own work in Amsterdam on the as yet unknown oxa[n]paracyclophanes **23.2**, the [7]metacyclophane derivative **23.3** was unexpectedly produced (Scheme 23).[59] The known spiro[5.7]trideca-1,4-dien-3-one **23.1**[60] on FVP did not result in the formation of oxa[8]paracyclophane **23.2** but instead gave 9-hydroxy[7]metacyclophane (**23.3**) in 29% yield together with 4-(6-heptenyl)phenol **23.4**.

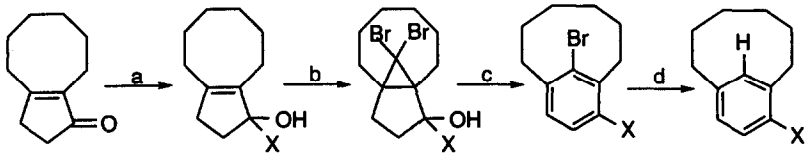


a) FVP at 520 °C.

Scheme 23

5.4 [6]Metacyclophane and its Derivatives

After their successful synthesis of [7]metacyclophane, Hirano and Nozaki[58,61,62] were interested in the applicability of the FVP approach to the synthesis of the lower [n]metacyclophanes. The crude propellane derivative **24.2** (Scheme 24) obtained by dibromocarbene addition to 9-hydroxybicyclo[6.3.0]- undec-1(8)-ene **24.1** gave on FVP 12-bromo[6]metacyclophane (**24.3**). Lithiation with BuLi proceeded smoothly and subsequent quenching with water gave [6]metacyclophane **24.4** in about 3% overall yield. This low yield is probably due to the use of a crude propellane precursor and also to the increase in the strain, indicating the limitation of this procedure for further use in [5]metacyclophane synthesis.



24.1 **24.2** **24.3** **24.4**

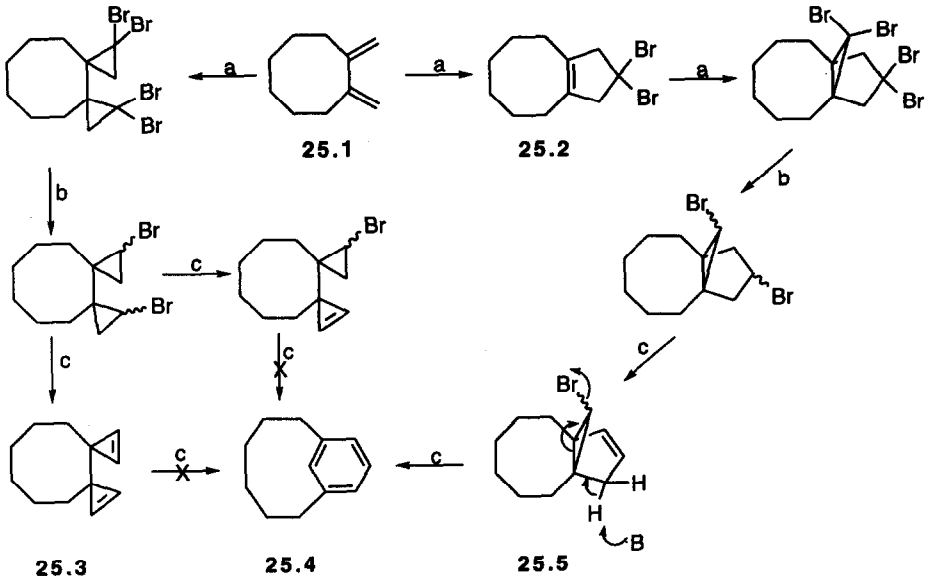
X = H and CH_3

a) $LiAlH_4$, b) $CHBr_3$/KO-t-Bu, c) heat, d) n-BuLi/H_2O.

Scheme 24

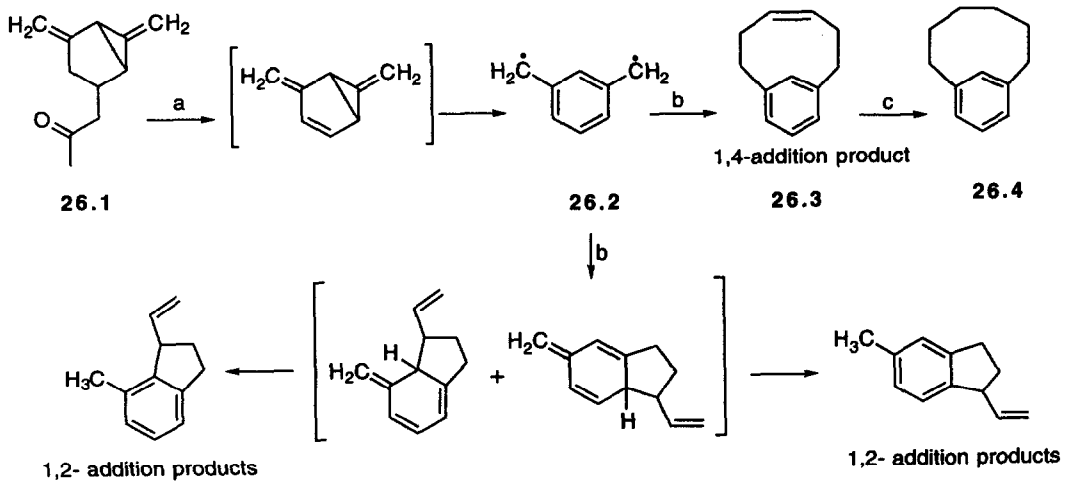
In connection with work on polymethylenebicyclopropenyls such as **25.3**, Van Straten observed the formation of [6]metacyclophane (**25.4**) in 2% yield.[63] This keen observation was exciting but puzzling. The route to this compound became clearer when the unsaturated propellane derivative **25.5** was isolated as a byproduct in the same reaction. A close investigation of the reaction revealed the course of events shown in Scheme 25. A rarely observed 1,4-addition of dihalocarbene to 1,2-dimethylenecycloalkanes[64] occurred as a side reaction[65] to give **25.2** as a byproduct; in subsequent steps the latter compound was carried along and transformed to **25.5** and then to [6]metacyclophane **25.4**. Jenneskens[66] utilized a similar method to prepare 9,12-dihalo[6]metacyclophane.

Goodman and Berson[67] in their mechanistic work on the 1,4 additions of dienes to the m-quinodimethane biradical (**26.2**) have observed the formation of [6]metacycloph-3-ene (**26.3**, Scheme 26). The structure was established by the usual analytical techniques and by diimide reduction to [6]metacyclophane (**26.4**). The potential of m-quinodimethane biradical **26.2** in [6]metacyclophane (**26.4**) synthesis has not been fully realized due to lack of a good preparative access to this intermediate. The severest limitation of this method is the multistep synthesis of substrate **26.1**.[67]



a) $CHBr_3$/KO-t-Bu, b) $(C_6H_5)_3SnH/Et_2O$, c) KO-t-Bu/DMSO.

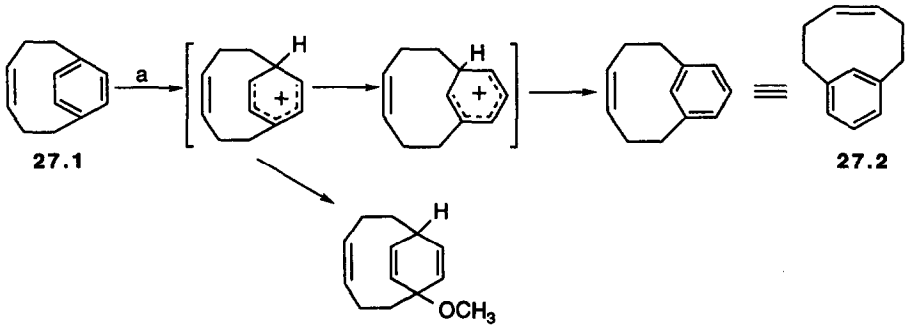
Scheme 25



a) hν/ pentane, b) CH_2=CH-CH=CH_2, c) N_2H_2.

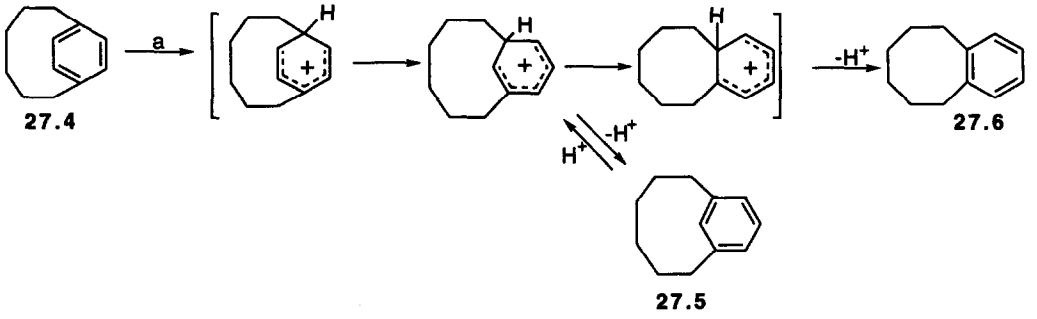
Scheme 26

The previously discussed acid-catalyzed isomerization[48,56] (see Schemes 17 and 20) has been utilized by Tobe to convert [6]paracycloph-3-ene (**27.1**) to [6]metacycloph-3-ene (**27.2**= **26.3**, 30%) and to the methanol 1,4-addition product **27.3** (47%, Scheme 27).[68] Similarly, acid-catalyzed isomerization of [6]paracyclophane (**27.4**) by use of trifluoroacetic acid produced [6]metacyclophane (**27.5**, 25%) and benzocyclooctene (**27.6**, 75%).[69] Even though **27.1** and **27.4** have to be prepared by multistep syntheses, the method employed by Tobe[68,69a] is by far the best for preparation of these elusive unsubstituted and substituted [6]metacyclophanes. However, in concentrated solutions, acid-catalyzed isomerization of **27.4** not only led to **27.5** and **27.6** but also gave dimers.[69b]



27.1 **27.2** **27.3**

a) CF_3COOH/CH_3OH; **27.2** /**27.3** = 33/66

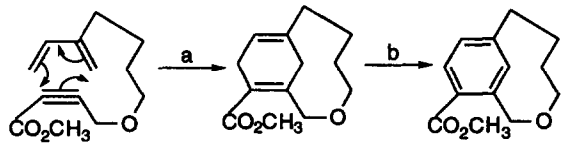


27.4 **27.5** **27.6**

a) $CF_3COOH/CHCl_3$; **27.5** /**27.6** = 33/66.

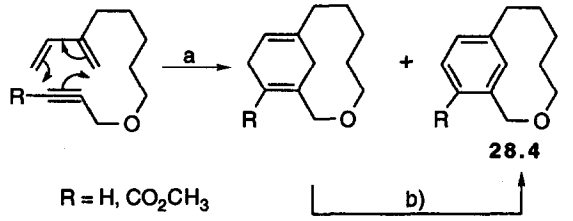
Scheme 27

A totally new entry into the field of [6]metacyclophane derivatives is due to Shea, Burke, and Doedens (Scheme 28).[70] Shea has been successful in preparing small ring bridgehead diene **28.2** from dienyne ether **28.1** using the intramolecular Diels-Alder reaction.[71] Thermal reaction of **28.1** as indicated in Scheme 28 gave **28.2.** Treatment of diene **28.2** with dichlorodicyanoquinone resulted in smooth oxidation to metacyclophane derivative **28.3**. Obvious extension of this method for the preparation of [7]metacyclophane derivatives **28.4** was also achieved.



28.1 **28.2** **28.3**

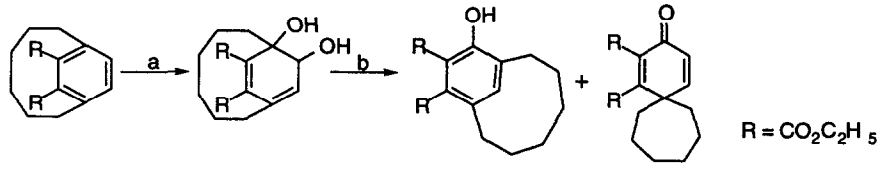
a) Xylene at 260 °C, b) DDQ in toluene at 25 °C.



a) Xylene at 260 °C, b) DDQ in toluene at 25 °C, or sealed tube, benzene at 260 °C.

Scheme 28

Tochtermann and his coworkers[72] discovered a route to [6]metacyclophane derivatives (Scheme 29). In analogy to higher paracyclophanes [48,49], they [72] and Tobe [68,69] found that acid-catalyzed isomerization of [6]paracyclophanes[48,56,68,69] could give [6]metacyclophanes under mild conditions and in high yields. Diol **29.2** obtained by osmium tetraoxide oxidation of paracyclophane derivative **29.1** serves as an appropriate substrate. Diol **29.2** on treatment with p-toluenesulfonic acid in benzene gives 92% yield of [6]metacyclophane derivative **29.3,** together with spirodienone **29.4** (7%).

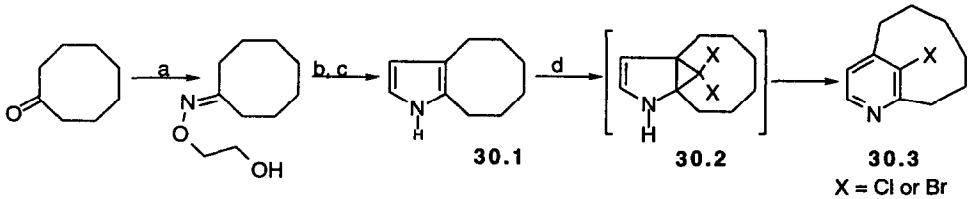


29.1 **29.2** **29.3** **29.4**

a) $OsO_4/C_5H_5N/Et_2O$, b) p-TsOH/C_6H_6.

Scheme 29

The synthesis of the pyridine analog **30.3** of [6]metacyclophane derivative was reported by Dhanak and Reese.[73] This involved the heat-promoted ring expansion of dihalocarbene adduct **30.2** (which was not isolated) of the pyrrole derivative **30.1** (Scheme 30) as shown below.



30.1 **30.2** **30.3**

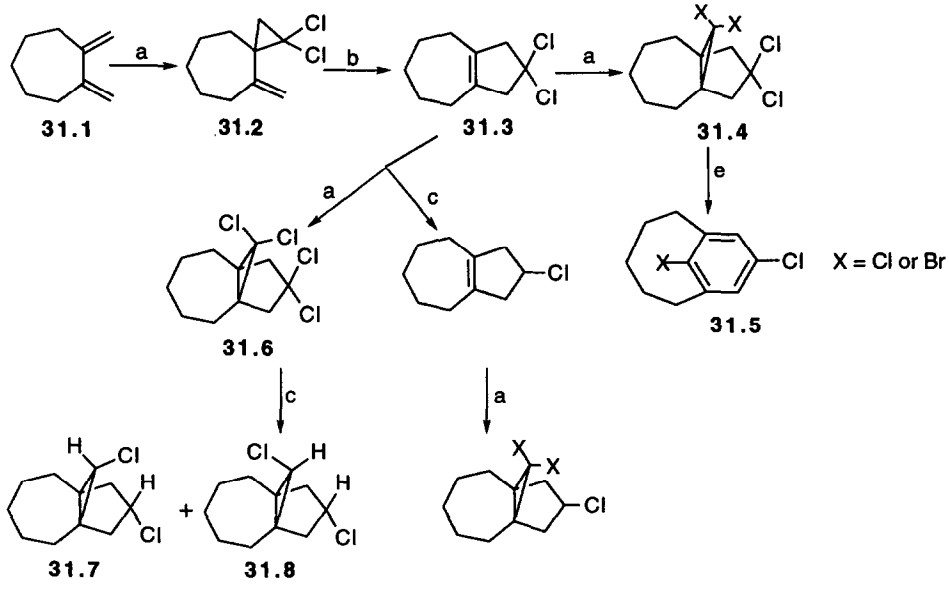
X = Cl or Br

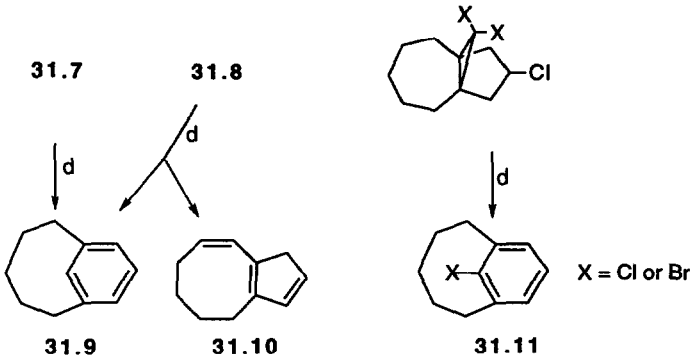
a) $H_2NO(CH_2)_2OH/CH_3CO_2H/C_5H_5N$, C_2H_5OH/reflux, b) $(C_6H_5O)_3P^+CH_3I^-/CH_3CN$,
c) KO-t-Bu/Bu^{t}OH, d), CCl_3CO_2Na in $CH_3OCH_2CH_2OCH_3$ or $C_6H_5HgCBr_3$ in C_6H_6.

5.5 [5]Metacyclophane and its Derivatives

Before going into the details of [5]metacyclophane synthesis, we feel obliged to point out that the principle of a ring expansion approach of converting propellanes to metacyclophanes was pioneered by Parham and his group[74] to prepare [6]metanaphthalenophane derivatives; and we have also discussed the thermal approach of Hirano and Nozaki.[58,61] However, both of these approaches are unsuitable for the synthesis of highly strained, heat sensitive [5]metacyclophanes.[75]

This situation led us to consider the use of milder methods (Scheme 31) that have resulted in the synthesis of [5]metacyclophane and its derivatives.[63,76-79] [6]Metacyclophanes and [5]metacyclophanes (**31.9**) were first detected as minor byproducts in the synthesis of 3,3-bridged bicyclopropenyls.[63,79] The crucial step for the formation of these compounds was the 1,4-addition of a dihalocarbene to 1,2-bismethylenecyclooctane and 1,2-bismethylenecycloheptane (**31.1**), respectively. However, because the yields of 1,4-addition range only from 2 to 20%, [64, 66] we considered an alternative versatile synthesis of di- and tetrahalo[n.3.1]propellanes and their conversion to [5]metacyclophane and its derivatives, Scheme 31. The crucial step in this general synthetic route is the thermal vinylcyclopropane rearrangement of the dihalocarbene monoadduct **31.2** to the bicyclic derivative **31.3** which is conveniently accomplished by FVP. This reaction proceeds well in the case of dichloro monoadducts, but extensive decomposition results in the case of the analogous mono or dibromo derivatives. Further addition of dichlorocarbene to **31.3** gave **31.6** in 95% yield. Reduction of **31.6** with triphenyltin hydride gave mainly dihalopropellane derivatives, which could be separated by preparative GLC into **31.7** and **31.8**. Treatment of **31.7** with KO-t-Bu in DMSO gave [5]metacyclophane **31.9**, whereas similar treatment of **31.8** gave [5]metacyclophane **31.9** (35%) along with **31.10** (21%). Silver perchlorate in lutidine was found to be more effective than KO-t-Bu/DMSO to convert **31.4**, the dihalocarbene adducts of **31.3**, to dihalo[5]metacyclophanes **31.5** (40 to 70% yield depending upon the substitution). Preparations of the monosubstituted [5]metacyclophanes (**31.11**) are also outlined in Scheme 31.

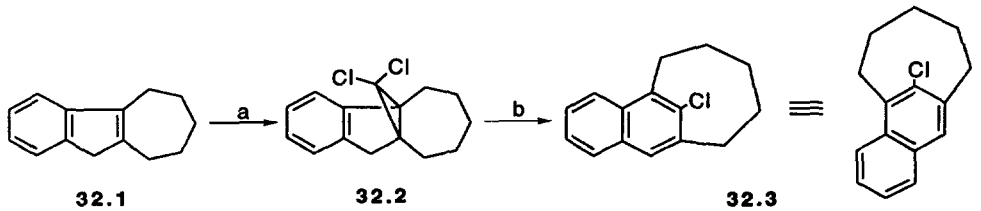




a) $CHCl_3$/KO-t-Bu or $CHBr_3$/KO-t-Bu, b) heat, c) $(C_6H_5)_3SnH/Et_2O$, d) KO-t-Bu/DMSO, e) $AgClO_4$/2,6-lutidine.

Scheme 31

In a related approach (Scheme 32), Reese and Grice[75, 80] have synthesized 7,8-benzo-11-chloro [5] - [metacyclophane (**32.3**) in over 50% yield.



a) $C_6H_5HgCCl_3$ in C_6H_6, b) $AgClO_4$/2, 6-lutidine.

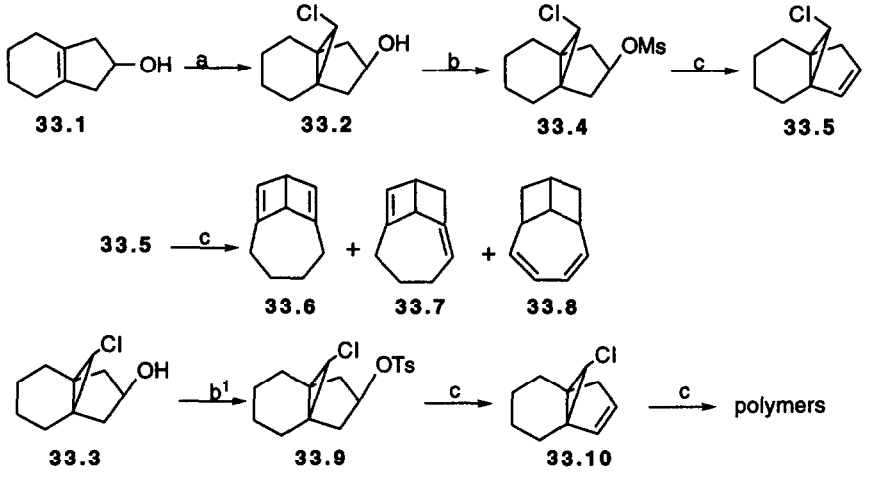
Scheme 32

5.6 [4]Metacyclophane

While our own attempts to synthesize [4]metacyclophane (**34.11**) have so far not met with success, its generation as an intermediate in two thermal processes has recently been clearly demonstrated. Furthermore, attempts to prepare [4]metacyclophane (**34.11**) have led to the unexpected isolation of strained Dewar benzenes (Schemes 33 and 34).

Before continuing with the route of choice (Scheme 34), we tried a route[81] (Scheme 33) similar to the general approach of Hirano, Nozaki, and coworkers to higher [n]metacyclophanes. Addition of chlorocarbene to the known bicyclic alcohol **33.1** gave a mixture of **33.2** and **33.3** in the ratio of 2:1. When the mixture of **33.2** and **33.3** was treated with two equivalents of tosyl chloride in pyridine, the minor component **33.3** gave tosylate **33.9**, while the major isomer **33.2** was hardly affected. Treatment of **33.9** with one equivalent of KO-t-Bu in DMSO afforded **33.10**, which upon further treatment with KO-t-Bu in DMSO at room temperature gave polymers. The anti isomer **33.2** could be smoothly converted into its mesylate **33.4**, which on treatment with KO-t-Bu in DMSO gave **33.5** in 70% yield. The reaction of **33.4** and **33.5** with excess KO-t-Bu in DMSO (3 to 5 equivalents) yielded an isomeric mixture of dienes **33.6-33.8**, which could be separated by GLC. The structures of these dienes were assigned on the basis of their spectral data and chemical properties.

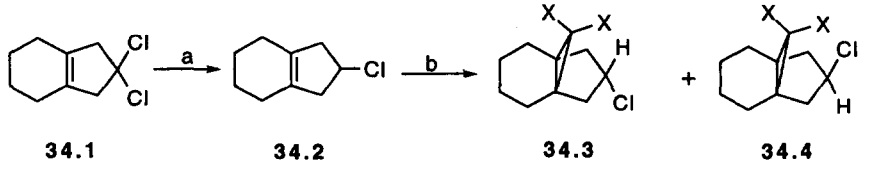
The formation of the Dewar benzene **33.6** is not yet clearly understood, but several reasonable mechanistic pathways are conceivable.[78, 81]

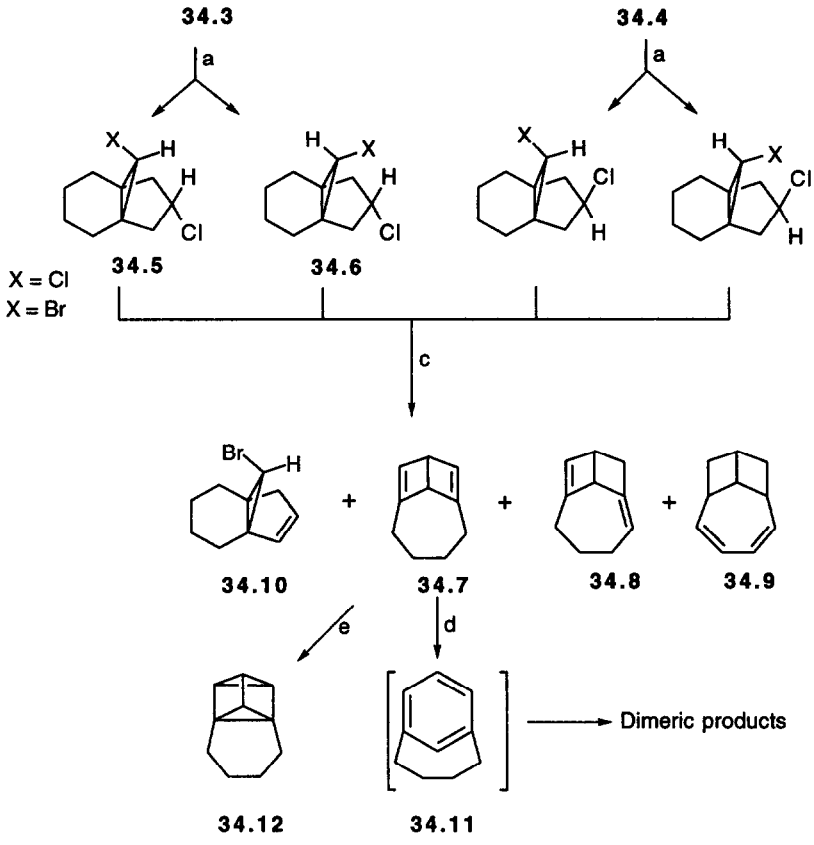


a) n-BuLi/CH_2Cl_2/Et_2O, b) MsCl/C_5H_5N, b[1]) p-TsCl/C_5H_5N, c) KO-t-Bu/DMSO.

Scheme 33

A more efficient route to the Dewar benzene **33.6** = **34.7**, which we feel may ultimately lead to the successful formation of [4]metacyclophane as an intermediate, is described[82a] in Scheme 34. The readily available dichloride **34.1**= **31.3** was treated with one equivalent of triphenyltin hydride at 90 °C to give **34.2** in 80% yield. Dibromocarbene addition to **34.2** resulted in a mixture of propellanes **34.3** and **34.4** in a ratio of 8:1. Separation of **34.3** and **34.4** was achieved by preparative GLC. Reduction with triphenyltin hydride of **34.3** (or a mixture **34.3** and **34.4**) in refluxing diethyl ether takes place selectively with dibromocyclopropane derivatives to give **34.5** and **34.6**, which could not be separated. Treatment of these halopropellanes with KO-t-Bu in DMSO at room temperature under reduced pressure gave Dewar benzene **34.7** with only minor (<10%) impurities, such as the rearranged isomers **34.8** and **34.9** and a mono elimination product **34.10**. This procedure afforded **34.7** as a pure colorless liquid in as high as 30% isolated yield. Attempts to obtain [4]metacyclophane **34.11** by photochemical irradiation of its Dewar isomer **34.7** furnished the prismane isomer **34.12**. Under thermolysis conditions, **34.7** yielded different product mixture (mainly dimers) of [4]metacyclophane **34.11**, clearly proving its intermediacy.[82b, 82c]





a) $(C_6H_5)_3SnH/Et_2O$, b) NaOH/$CHCl_3$ or $CHBr_3/CH_3(CH_2)_{15}N(CH_3)_3Br$, c) KO-t-Bu/DMSO, d) heat, d) heat, e)hv.

Scheme 34

6 Synthesis of [n]Paracyclophanes

Prior to 1950 eminent chemists including Ziegler, Lüttringhaus, Prelog, Cram, and others stimulated interest in the paracyclophanes with n >9; and routes to paracyclophanes have occupied an important place in synthetic chemistry since the announcement by Wiesner of a [9]paracyclophane synthesis in 1950 [83] and later of an [8]paracylophane by Cram .[84] Although several useful routes to small [n]paracyclophanes (n = 4-8) have since been devised, efforts continue by numerous teams to find more efficient synthetic methods particularly in view of the ongoing theoretical discussion regarding their aromaticity.[83, 85-88] Distortion of the benzene ring from planarity is achieved by linkage of the para positions by a short oligomethylene bridge or by introduction of bulky ortho groups.[26] Cram and Knox suggested, after studying the ultraviolet spectrum of [8]paracyclophane, that the benzene ring is severely bent from its normal planar structure, but that distortion is marginal for rings

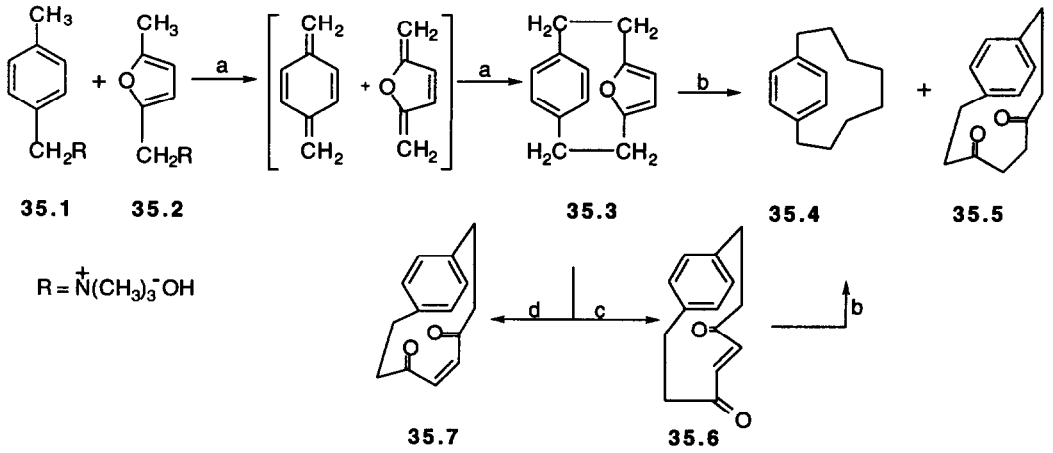
bigger than eight (8).[84] Also, from strain energy calculations it is clear that for the same bridge length a metacyclophane is less strained than is its para analog.[66, 82a]

Prior to 1961, [n]paracyclophane syntheses where n = 9-14 were conveniently carried out by intramolecular ring closures reactions, such as acyloin condensation, high dilution Friedel-Craft acylation, and intramolecular oxidative cyclization, all of which have been reviewed.[5d,m] These conventional approaches have not been successful for preparation of [n]paracyclophanes in which the distortion is significant (n = 7, 6) since intermolecular coupling dominates over the intramolecular process.

In addressing the synthesis of [n]paracyclophanes, n = 8-3, one must consider several formidable obstacles such as strain, instability, and rearrangements. Usually, an oligomethylene bridge is attached to high energy precursors (often valence isomers of benzene), which are then converted to an aromatic system in one of the final steps. This and other successful approaches used by us and by others to prepare strained [n]paracyclophanes are described below.

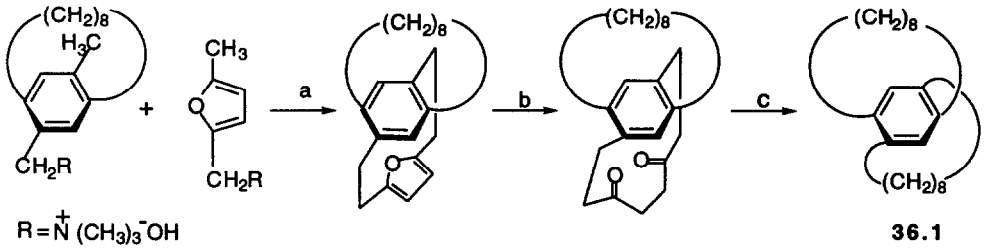
6.1 [8]Paracyclophane and Its Derivatives

The Hofmann type, 1,6-elimination of p-methylbenzyltrimethylammonium hydroxide and dimerization of the resulting p-xylylene is one of the most thoroughly studied thermal processes and has been applied to the synthesis of a wide variety of [2.2]paracyclophanes. Cram, Montgomery, and Knox prepared monofuran analog **35.3** of [2.2]paracyclophane in 23% yield by heating a mixture of salts **35.1** and its furan analog **35.2** (Scheme 35) indicated below.[89] When adduct **35.3** was subjected to Clemmensen reduction (Zn-Hg/HCl-CH_3COOH) [8]paracyclophane (**35.4**) was obtained (55%) along with 3,6-diketo[8]paracyclophane (**35.5**, 15%). When **35.3** was treated with bromine in CH_3OH at -30 °C (heterogeneous) and the mixture was added to 5% sulfuric acid, trans-enedione **35.6** was the product. When same reaction was worked up with water and sodium acetate, cis-enedione **35.7** was the product, the yield being 47% in both cases. Both **35.6** and **35.7** were reduced to give [8]paracyclophane in gram quantities for study its chemical behavior.[48] This process has also been employed for the preparation of specifically deuterium labeled [8]paracyclophane.[90,91]



a) Heat, b) Zn-Hg/HCl/CH_3COOH, c) $Br_2/CH_3COONa/CH_3OH/H^+$, d) $Br_2/CH_3COONa/CH_3OH/H_2O$.

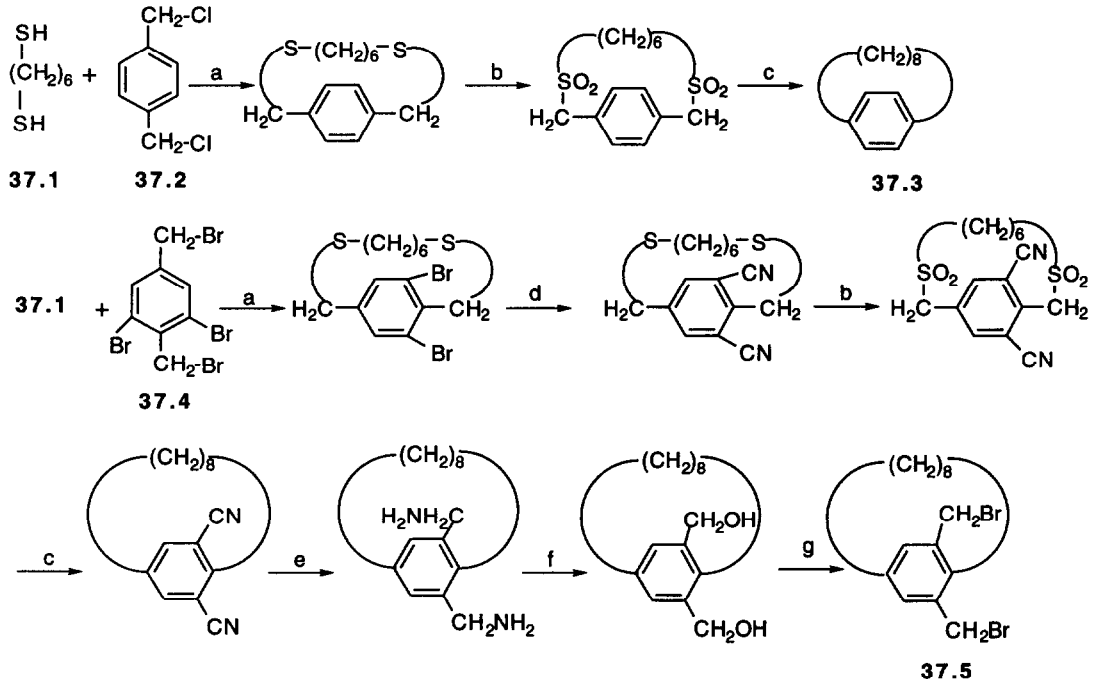
Nakazaki and coworkers have extensively studied this 1,6 to 1,6 cycloaddition and have used it to provide doubly bridged [8.8] and [8.10]paracyclophanes,[92,93] e.g., [8.8]paracyclophane (**36.1**) as outlined in Scheme 36.



a) Heat, b) CH_3COOH/10% H_2SO_4, c) BF_3/$HS(CH_2)_2SH$, Ra Ni/heat.

Scheme 36

The facile conversion of paradithiacyclophanes to paracyclophanes has been reported by Otsubo and Misumi[57] as a preparative method for synthesis of [8]paracyclophane (**37.3**, Scheme 37). The overall yield for the three-step conversion from the commercially available starting materials **37.1** and **37.2** was 40% . Misumi and coworkers[94] have studied in depth yet another application of this method to prepare tetrasubstituted [8]paracyclophane derivative **37.5**, in 15% overall yield starting with **37.1** and **37.4**.

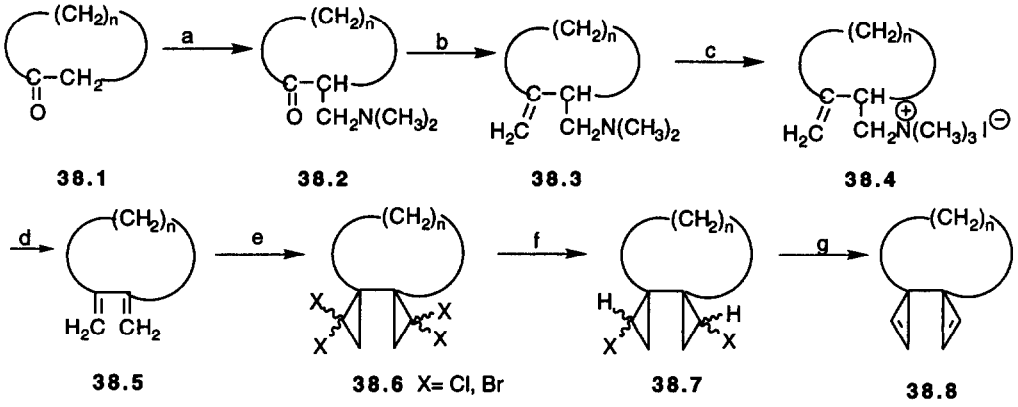


a) KOH/C_2H_5OH, b) MCPBA, c) heat, d) CuCN, e) $NaBH_4$/RaNi/NaOH, f) $NaNO_2$/CH_3COOH/KOH, g) PBr_3.

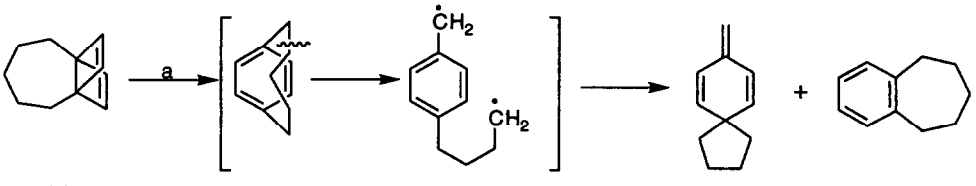
Scheme 37

The systematic investigation of the chemical properties of 3,3′-polymethylenebicyclopropenyls (**38.8**) with short and long bridges is of great interest.[7,95] In this connection our laboratory in Amsterdam has developed simple, efficient large-scale syntheses for these compounds (Scheme 38).[96] The Mannich bases **38.2** were prepared from the corresponding cyclic ketones **38.1** by reported methods.[97] Wittig reaction using the Corey method[98] gave **38.3**. Hofmann degradation of **38.3** via **38.4** gave the desired 1,2-dimethylenecycloalkanes **38.5** in 20-50% overall yield. The transformation of **38.5** to **38.6** was achieved by addition of dihalocarbenes, followed by triphenyltin hydride reduction, which gave **38.7**. Careful dehydrohalogenation with KO-t-Bu in dry DMSO gave the desired 3,3′-polymethylenebicyclopropenyls **38.8** in overall yields of 10-20%.

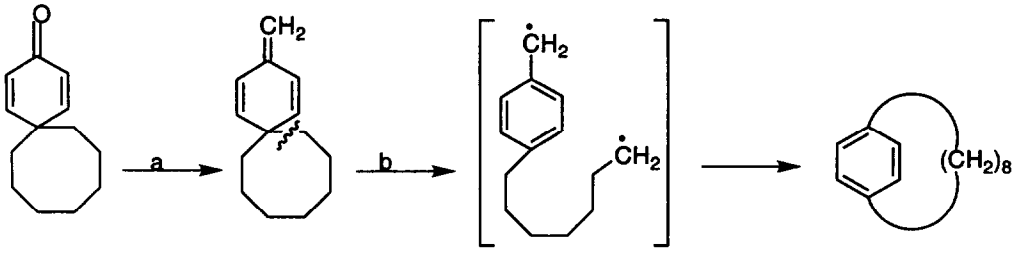
From FVP of 1,4-pentamethylene Dewar benzene (**38.9**)[99], obtained by silver ion catalyzed rearrangement of the corresponding 3,3′-pentamethylenebicyclopropenyl (**38.8**, n = 5),[100] van Straten observed benzocycloheptene **38.13** and 3-methylenespiro(4,5)deca-1,4-diene **38.12** in a ratio of 1:1.[99] The formation of **38.12** is interesting and can be explained most easily through the intermediacy of [5]paracyclophane (**38.10**) and diradical **38.11**. In an extension of these results, FVP of 3-methylene [5,7]trideca-1,4-diene **38.15** at 550 °C and 0.4 mbar gave 70% isolated yield of [8]paracyclophane (**38.16**).[101] The starting material (**38.15**) was conveniently prepared (70% yield)from the corresponding known dienone **38.14**[60] by a Wittig reaction with triphenylmethylenephosphorane. The general method developed for the synthesis 3,3'-polymethylenebicyclopropenyls, where n = 2-6, and 10 is outlined in Scheme 38.



a) $HCHO/NH(CH_3)_2.HCl$, b) $(C_6H_5)_3P^+CH_3I^-/NaH/DMSO$, c) CH_3I/Et_2O, d) Ag_2O/H_2O, heat, e) $CHCl_3$ or $CHBr_3$/50% $NaOH/CH_3(CH_2)_{15}N(CH_3)_3Br$, f) $(C_6H_5)_3SnH$, Et_2O, g) KO-t-Bu/DMSO.



a) FVP

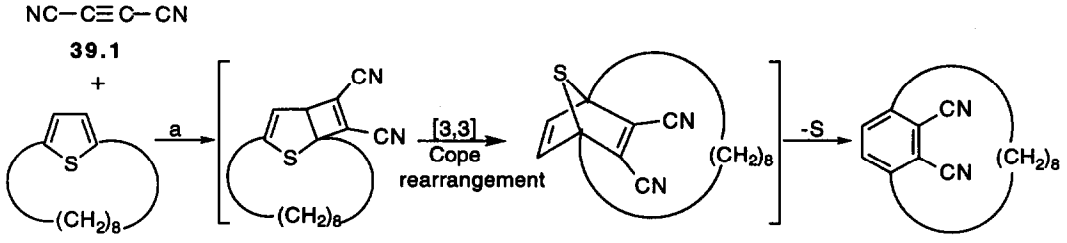


38.14 **38.15** **38.16**

a) $(C_6H_5)_3P^+CH_3I^-$/NaH/DMSO, b) FVP at 550 °C/0.4 mbar.

Scheme 38

Helder and Wynberg[102] devised a route to the [8]paracyclophane derivative **39.4** (Scheme 39) involving the Diels-Alder reaction of [8](2,5)thiophenophane (**39.2**) with dicyanoacetylene (**39.1**) to give a paddlane **39.3**, which loses elemental sulfur *in situ* and gives **39.4** in 6% yield.

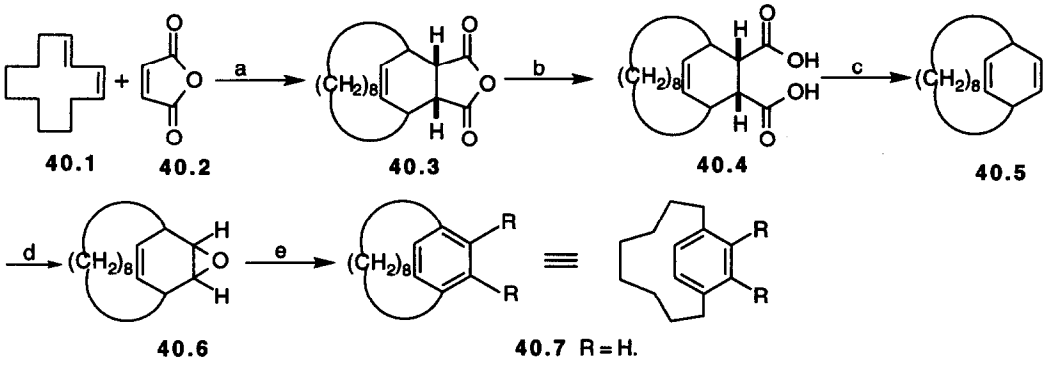


39.2 **39.3** **39.4**

a) Heat at 100 °C for 15h.

Scheme 39

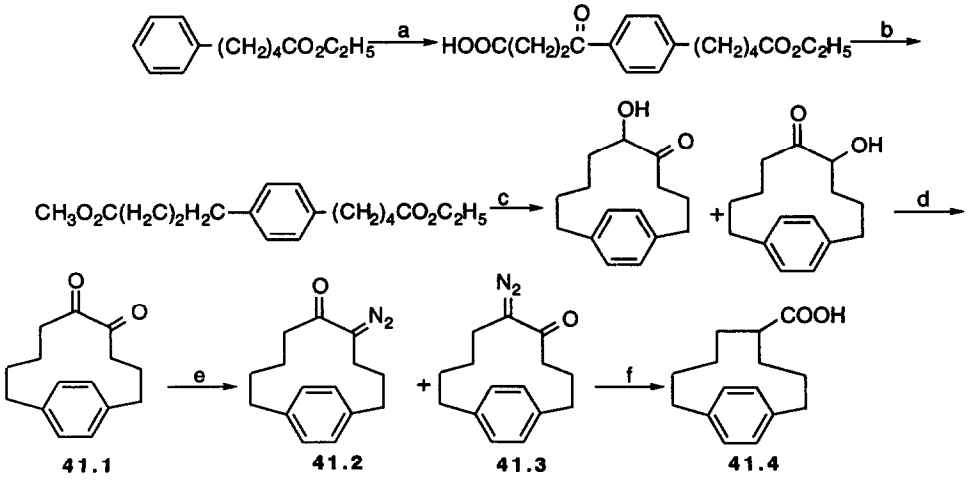
A convenient synthesis of substituted and unsubstituted [8]paracyclophanes[103] was developed by Gassman and coworkers during their investigation on inside-outside bicyclics (Scheme 40).[104] It was known that Diels-Alder addition of maleic anhydride (**40.2**) to cis,trans-1,3-cyclodecadiene (**40.1**) gave the Diels-Alder adduct **40.3** in 21% yield. Hydrolysis of **40.3** gave a quantitative yield of the dicarboxylic acid **40.4**, which was subjected to lead tetraacetate oxidation in C_5H_5N-toluene which gave **40.5** (22%). Electrochemical oxidation of **40.4** gave a higher yield of **40.5** (39%). Treatment with one equivalent of MCPBA gave 80% of the monoepoxide **40.6**. This epoxide was labile and underwent slow conversion to [8]paracyclophane (**40.7**). Exposure of **40.6** to HCl gave over 90% yield of **40.7**. Also, direct dehydrogenation of diene **40.5** with DDQ in toluene at 95 °C for 12 days afforded **40.7** in 79% yield. This synthetic procedure provides ready access to a variety of [8]paracyclophanes, e.g., **40.7**(R=CF_3). This approach was based on an earlier [9]paracyclophane synthesis by Wiesner,[83] but the modifications by Gassman and his group for the conversion of the Diels-Alder adducts in high yields to paracyclophanes are certainly valuable additions.

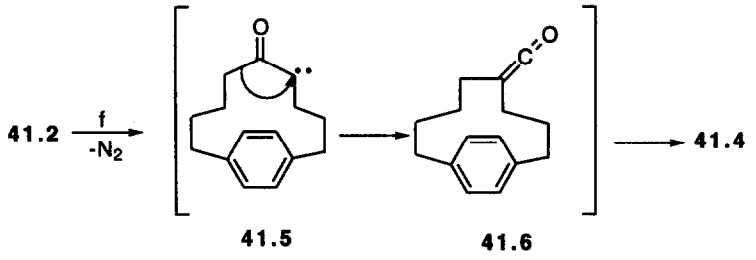


a) Heat, b) H_2O/THF, c) $Pb(OAc)_4$/toluene/C_5H_5N or electrochemical oxidation, d) MCPBA, e) HCl

Scheme 40

Allinger and his group developed a reproducible preparative route to the [8]paracyclophane ring system (Scheme 41).[105,106] They pointed out that although the method used was multistep and less imaginative than Cram's,[88] it did yield a crystalline carboxylic acid derivative suitable for X-ray crystal study and also as a starting material for the synthesis of a lower analog. The synthesis of 4-carboxy[8]paracyclophane (**41.4**) was achieved by ring contraction via the photolysis of the α-diazo ketones **41.2** and **41.3** prepared from the known 4,5-diketo[9]paracyclophane (**41.1**).[107] The formation of **41.4** can be regarded formally as going through a ketocarbene intermediate **41.5**.[108] A 1,2-shift of carbon produces ketene **41.6** which is trapped by nucleophilic attack of the solvent to yield acids (dioxane in H_2O), esters (alcohol) and amides (amines), respectively. Wolff rearrangement has been previously used for the synthesis of strained bicyclic acids, esters and amides.[109] This route then represents a high yield transformation of a ketone, in this case (1,2-diketone **41.1**) to a carbocyclic acid (**41.4**). This sequence accomplishes the loss of one carbon in an oligomethylene bridge under mild conditions.

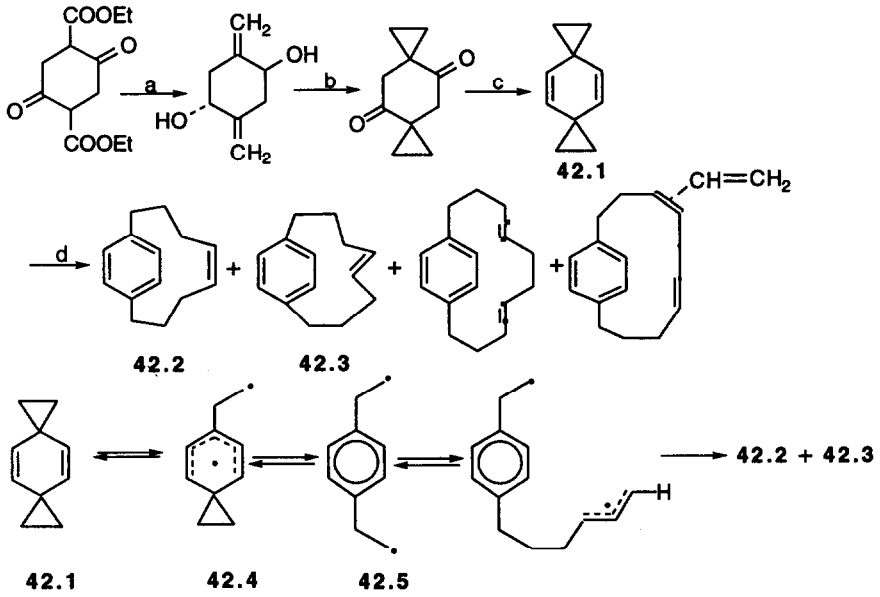




a)succinic anhydride/$AlCl_3$, b) $NH_2NH_2/CH_3OH/H^+$, c) Na/xylene, d) Bi_2O_3, e)NH_2NH_2/yellow HgO, f) hv/dioxane/H_2O.

Scheme 41

That thermal cycloadditions of cyclopropanes to activated olefins can rarely be accomplished is well documented. But Tsuji and Nishida have successfully shown (Scheme 42) that a cyclopropane-containing substrate such as **42.1** when heated in the presence of 1,3-dienes affords [8]paracycloph-4-enes **42.2** and **42.3** in over 65% yield.[110,40] They have used a variety of substituted dienes to yield variously substituted [8]paracyclophane derivatives. These authors[111] and Closs[112] have unequivocally demonstrated from CIDNP on **42.1** that the process **42.1** to **42.4** to **42.5** is reversible. Tsuji and Nishida have argued that 1,8-biradical **42.5** has a longer lifetime than does **42.4** and that **42.5,** once formed, is trapped intermolecularly by the diene faster than it recyclizes to **42.4**.



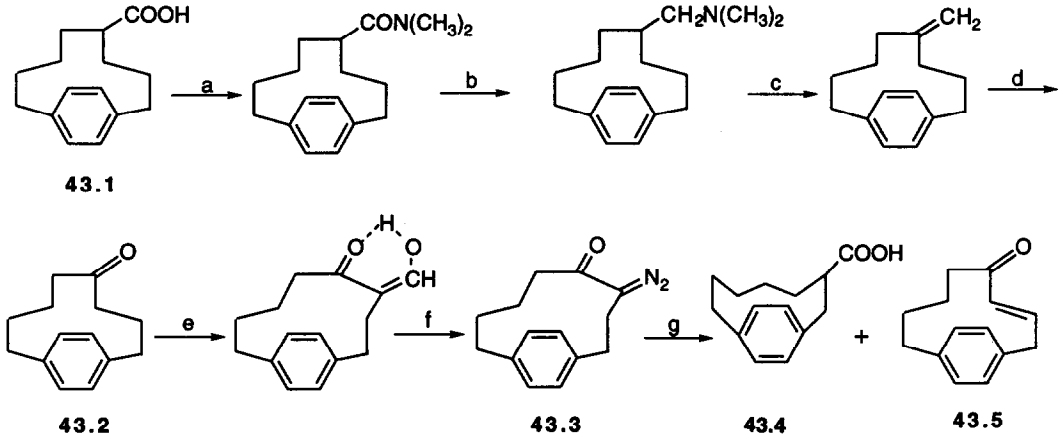
a) $LiAlH_4$/THF, b) Zn/Hg amalgam/CH_2I_2, Jones' reagent, c) $C_7H_7SO_2NHNH_2/CH_3Li$, d) CH_2=CH-CH=CH_2/C_6H_6/heat.

Scheme 42

6.2 [7]Paracyclophane and its Derivatives

Allinger reported a [8]paracyclophane synthesis in 1961.[105] Since then 11 more years elapsed before the first successful synthesis of a [7]paracyclophane derivative was achieved in 1972.[113] It became apparent that ring strain increases rapidly with diminished chain length, and some of the successful and general routes to [8]paracyclophane were totally unsuccessful for the synthesis of [7]paracyclophane. Older as well as more recent methods that have led [7]paracyclophane and its derivatives are summarized below.

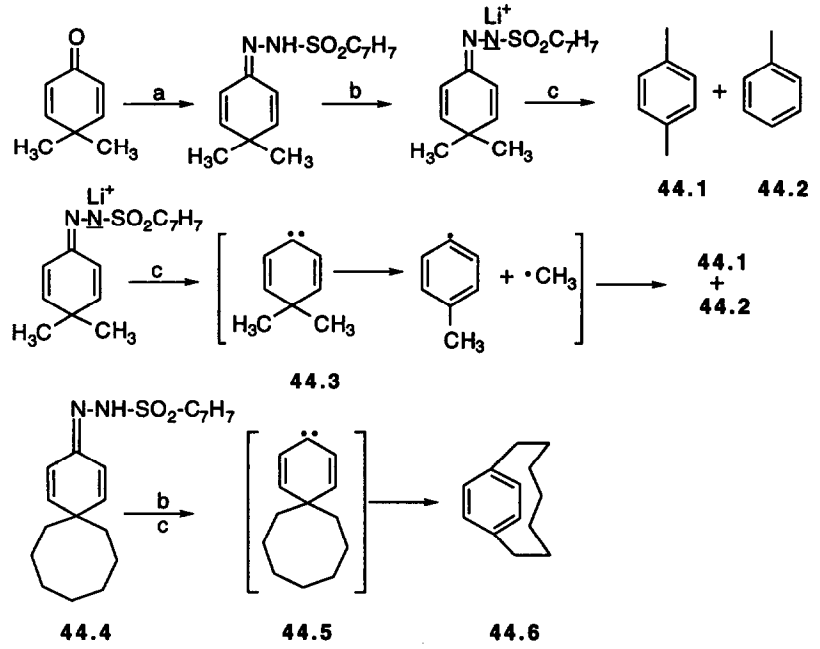
Allinger, Walter, and Newton[106] applied their diazo-ketone ring contraction route to the synthesis of a [7]paracyclophane derivative. Their first goal was to convert 4-carboxy[8]paracyclophane (**43.1=41.4**) to ketone **43.2** (Scheme 43). The successful four-step transformation to **43.2** was achieved in 65% overall yield, and **43.2** was converted in two steps to diazoketone **43.3**. Crude **43.3** was used directly in the photo-Wolff rearrangement to give 3-carboxy[7]paracyclophane (**43.4**, 50%) and 4-keto[8]paracycloph-2-ene (**43.5**, 25%).[114] The formation of **43.5** involved a 1,2-hydride shift in the initially generated ketocarbene. Although a Wolff rearrangement might be used to make a [6]paracyclophane derivative, the synthesis of 3-keto-4-diazo[7]paracyclophane proved to be an insurmountable task.[114]



a) $SOCl_2/HN(CH_3)_2$, b) $LiAlH_4$, c) H_2O_2/heat, d) $OsO_4/NaIO_4$, e) $NaH/HCO_2C_2H_5$, f) $TsN_3/N(CH_3)_3$, g) hv/dioxane/H_2O.

Scheme 43

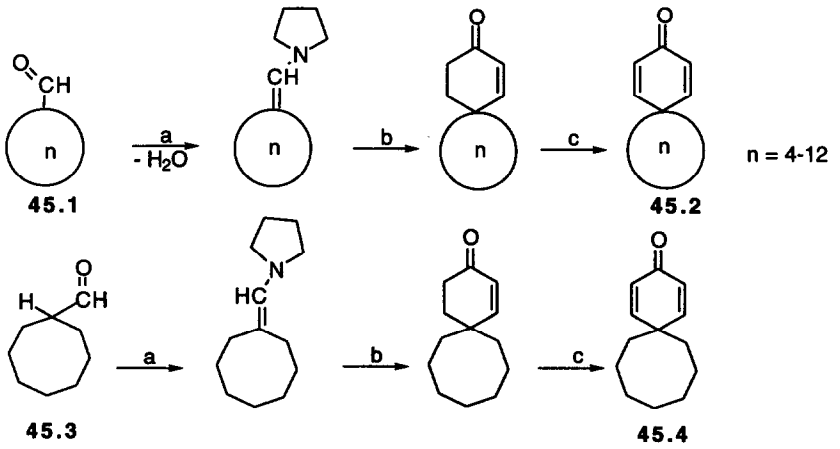
The first synthesis of unsubstituted [7]paracyclophane (**44.6**) was reported by Jones and coworkers in 1973 (Scheme 44).[115] Spirocyclohexadienone tosylhydrazone **44.4** with base gave the lithium salt, and FVP of the salt gave [7]paracyclophane (**44.6**). The beauty of the synthesis lies in its simplicity. The idea came from an experiment on the generation of **44.3** in the gas phase, which resulted in the isolation of only p-xylene **44.1** and toluene **44.2**.[116] The mechanism in Scheme 44 was supported by a crossover experiment.

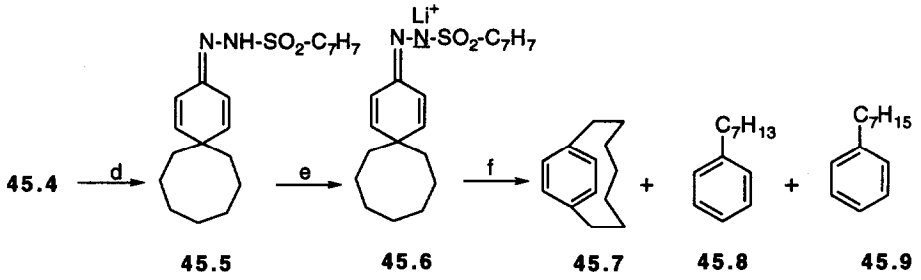


a) $C_7H_7SO_2NHNH_2/C_2H_5OH$, b) n-BuLi/THF, c) FVP.

Scheme 44

For access to [n]paracyclophanes by this route, a general very mild four-step route to spirocyclohexadieneones **45.2** from cyclic aldehydes **45.1** was developed (Scheme 45).[117] For example, spiro-dienone **45.4** was obtained from cyclooctanecarboxaldehyde **45.3** in 35% overall yield. On treatment with p-toluenesulfonylhydrazide **45.4** gave tosylhydrazone **45.5**, which on treatment with n-BuLi furnished crystalline lithium salt **45.6**. FVP of **45.6** led to [7]paracyclophane **45.7** (7-10% isolated yield) as well as to alkenyl- and alkylbenzene **45.8** and **45.9**, respectively. The overall yield was 2-3% from cyclooctanecarboxaldehyde **45.3**.

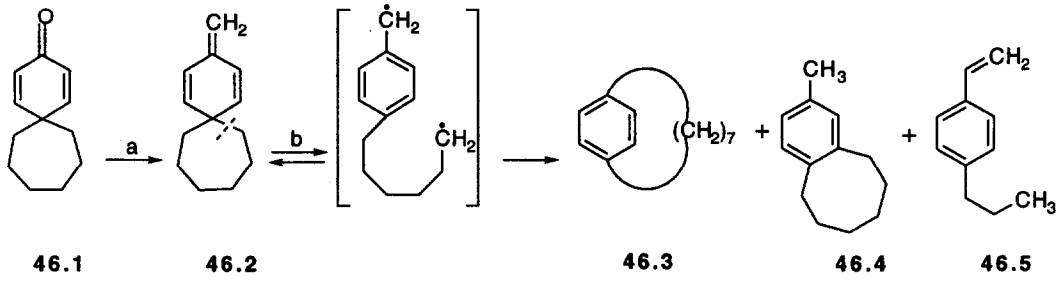




a) $C_4H_9N/C_7H_8/H^+$, b) $CH_2{=}CHCOCH_3/C_2H_5OH$, CH_3COONa/CH_3COOH, 5 h/NaOH/H_2O, c) DDQ/dioxane, d) $C_7H_7SO_2NHNH_2/C_2H_5OH$, e) n-BuLi/THF, f) FVP.

Scheme 45

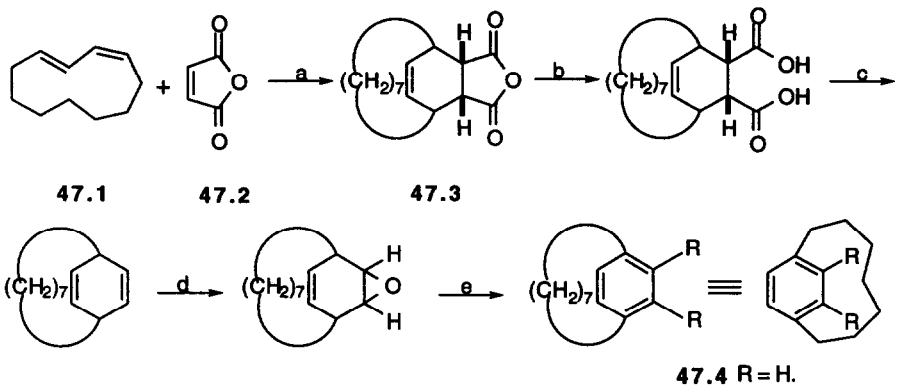
The most convenient route for the synthesis of [7]paracyclophane (**46.3=45.7**) is the FVP approach involving spirotriene **46.2** (Scheme 46).[99,101] Readily available 3-methylene-spiro[5.6]dodeca-1,4-diene (**46.2**) on FVP at 550 °C provides [7]paracyclophane (**46.3=45.7**) in 19% yield along with 14% starting material (**46.2**), 5,6,7,8,9,10-hexahydro-2-methylbenzocyclooctane **46.4** (19%) and p-propylstyrene **46.5** (8%). In Amsterdam we have studied the scope and limitations of this methodology. This is certainly the method of choice for the preparation of (8)paracyclophane (80%), and to a certain extent of (7)paracyclophane (19%). This technique is not suitable for the preparation of the lower analog [6]paracyclophane, which was too unstable to survive the conditions of its formation. The temperature dependent product formation gave useful information on the mechanism of formation and on reactions of [7]paracyclophane under FVP conditions.



a) $(C_6H_5)_3P^+CH_3I^-$/NaH/DMSO, b) FVP at 550 °C/0.4 mbar.

Scheme 46

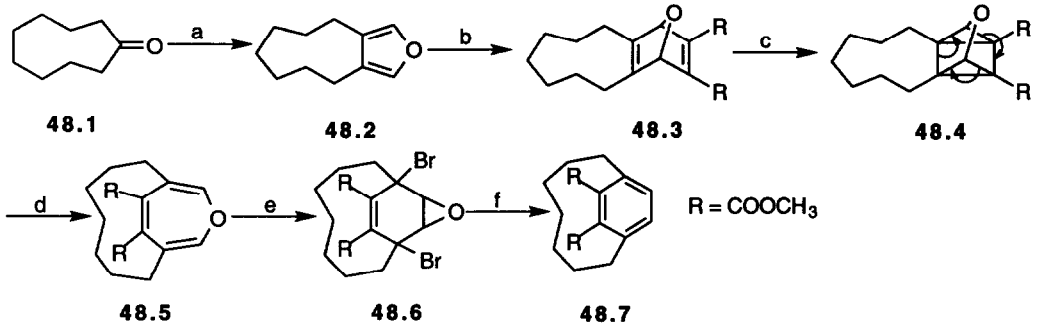
The versatility of Diels-Alder methodology was further illustrated by Gassman and coworkers[103,104] in the preparation of [7]paracyclophane (**47.4=45.7**) and its derivatives (Scheme 47). The initial adduct **47.3** was obtained from maleic anhydride **47.2** and cis, trans-cycloundeca-1,3-diene (**47.1**) in 23% yield; **47.3** was subsequently converted to [7]paracyclophane **47.4** as shown. This synthetic procedure also provides access in moderate yields to a variety of [7]paracyclophane derivatives such as **47.4** R=CF_3. The scope and limitation of this procedure have not yet been reported.



a) Heat, b) H_2O/THF, c) $Pb(OAc)_4$/toluene/C_5H_5N or electrochemical oxidation, d) MCPBA, e) HCl.

Scheme 47

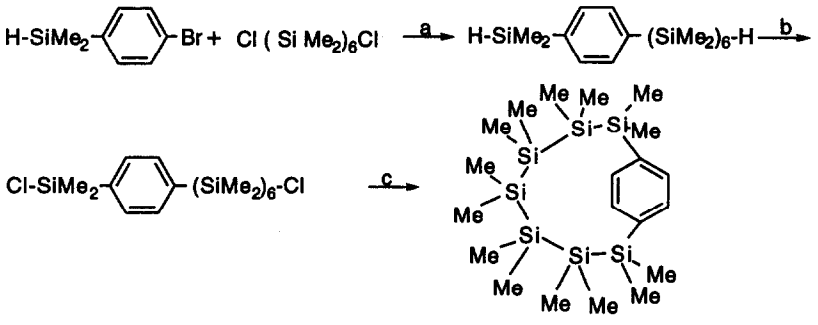
Tochtermann and his group developed a preparation of [7]paracyclophane diester **48.7** (Scheme 48).[118] The synthesis is based on an earlier strategy developed by him for [6]paracyclophanes. Cyclononanone (**48.1**) was converted to cyclonona[c]furan (**48.2**). Treatment of furan **48.2** with dimethylacetylene dicarboxylate (DMAD) yielded Diels-Alder adduct **48.3**, which was photolyzed in ether at -15 °C to give oxaquadricyclane **48.4**. Thermal isomerization of **48.4** in xylene at 140 °C resulted in oxepin derivative **48.5**. Bromination of **48.5** gave dibromoepoxide **48.6**. Dehydrobromination and deoxygenation with McMurry's reagent ($TiCl_3$ + $LiAlH_4$) gave the [7]paracyclophane derivative **48.7**.



a) $HCO_2C_2H_5$/NaH, n-$HS(CH_2)_3CH_3$/p-TsOH, NaH/DMSO/$(CH_3)_3S^+OI^-$, Ag_2O b) DMAD/heat, c) hv in Et_2O, d) heat in xylene, e) Br_2 in CH_2Cl_2, f) $TiCl_3$/$LiAlH_4$/THF.

Scheme 48

Recently, the [7]paracyclophane derivative heptasila[7]paracyclophane (**49.1**) was obtained by Ando, Tsumuraya, and Kabe (Scheme 49).[119] Although the yield in the critical step c (see Scheme 49) is low, one interesting feature of the approach is the use of the Wurtz reaction, the oldest method for cyclophane synthesis.



49.1

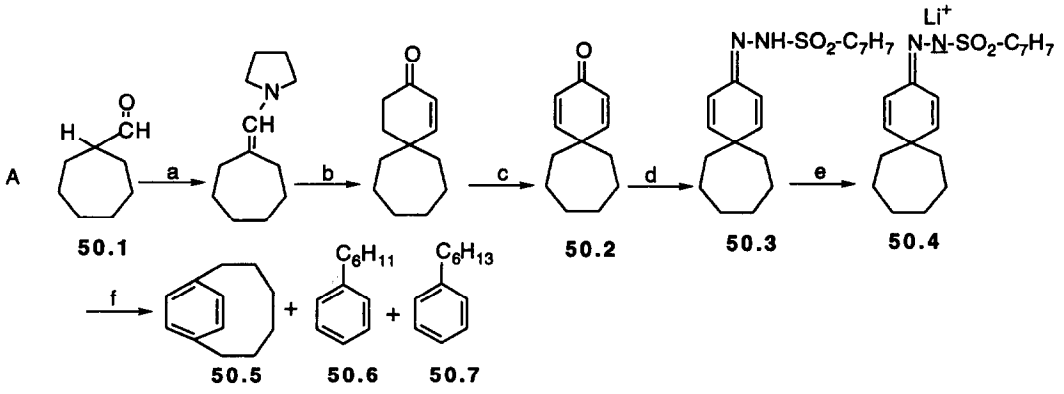
a) Mg/THF, $LiAlH_4$, b) CCl_4/BPO, c) Na/[18]crown-6/toluene/heat.

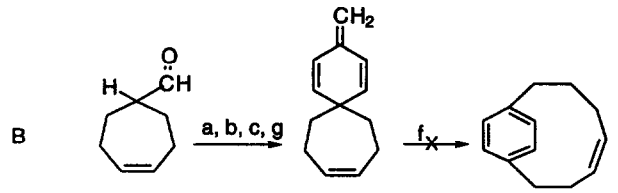
Scheme 49

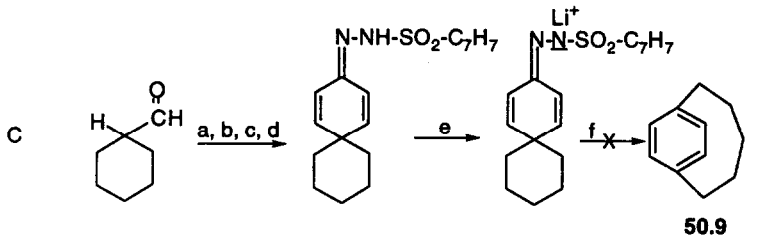
6.3 [6]Paracyclophane and its Derivatives

The isolation of [7]paracyclophane in 1973 paved the way for many ingenious subsequent total syntheses of that compound each in its own way reflecting to some extent the state of the art at that time. The question remained how many of these methods would allow access to the more strained [6]paracyclophane and its derivatives. The then available molecular mechanics calculations (MM2) had indicated increase in the strain energy by 10-12 kcal/mol when compared to [7]paracyclophane. Here we give a short summary of the successful syntheses of [6]paracyclophanes. They employ FVP, photochemistry, silver-ion-catalyzed rearrangement, and the principle of valence isomerization.

Jones' group[120] was the first to achieve the synthesis of [6]paracyclophane, using an extension of their method developed for [7]paracyclophane (Scheme 50 A). Dienone **50.2** was prepared from cyloheptanecarboxaldehyde (**50.1**) and methyl vinyl ketone and was converted to tosylhydrazone **50.3** and then to the lithio salt **50.4**. The salt on FVP at 250-400 °C led to [6]paracyclophane **50.5** along with alkenylbenzene **50.6** and alkylbenzene **50.7**. The isolated yield of **50.5** was 2%, but work up involved tedious gas chromatography. Two analogous approaches to [7]paracycloph-3-ene **50.8**[121] (Scheme 50 B) and [5]paracyclophane **50.9**[122] (Scheme 50 C) were attempted but both were unsuccessful, further indicating the limitation of this procedure.



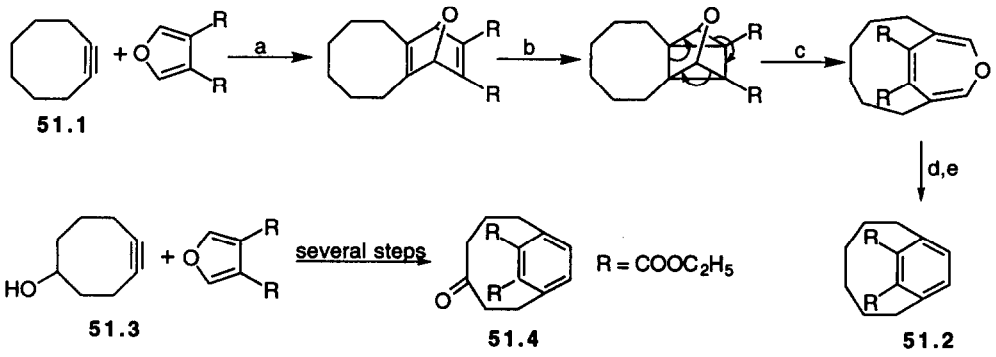




a)$C_4H_9N/C_7H_8/H^+$, b) CH_2=$CHCOCH_3/C_2H_5OH$, CH_3COONa/CH_3COOH, 5hr/NaOH/H_2O, c) DDQ/$C_4H_8O_2$, d) $C_7H_7SO_2NHNH_2/C_2H_5OH$, e) n-BuLi/ THF, f) FVP, g) $(C_6H_5)_3P^+CH_3Br$, n-BuLi/Et_2O/C_6H_6

Scheme 50

Tochtermann[72] described the synthesis of [6]paracyclophane diester **51.2** much earlier than that of its next higher homologue, [7]paracyclophane diester **48.7** using the same strategy (Scheme 51). Cyclooctyne (**51.1**) was converted to [6]paracyclophane diester **51.2** in only five steps with a relatively high yield of 15-20% overall. This efficient method provided Tochtermann and coworkers enough [6]paracyclophane diester **51.2** to study the chemical behavior of the [6]paracyclophane ring system. The method was extended by conversion of **51.3** to **51.4**.[123]

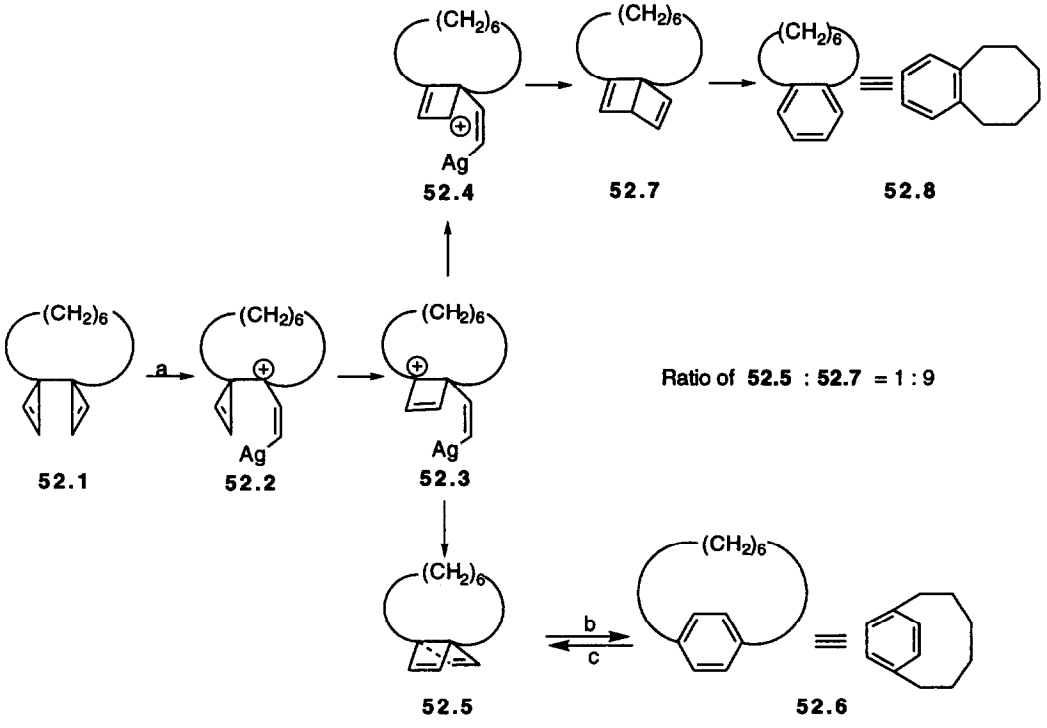


a) Heat, b) hν in Et_2O, c) heat in xylene, d) Br_2 in CH_2Cl_2, e) $TiCl_3/LiAlH_4$/THF.

Scheme 51

The route we developed to small [n]paracyclophanes involving silver-ion catalyzed rearrangement of 3,3′-disubstituted bicyclopropenyls (see Scheme 38 for synthesis) to Dewar benzenes, followed by their thermal

valence isomerization, was successful in the case of [6]paracyclophane **52.4** (Scheme 52).[100,124] More specifically, rearrangement[124] of the bicyclopropenyl **52.1** with silver tetrafluoroborate in anhydrous acetonitrile proceeds by a stepwise ionic mechanism (**52.1** → **52.2** → **52.3** → **52.4**) and gives isomeric Dewar benzenes **52.5** and **52.7**. Unfortunately, the ratio of the desired 1,4 isomer **52.5** to the unwanted 1,2 isomer **52.7** was 1:9. This ratio is very difficult to explain, since the desired 1,4 Dewar isomer was obtained in much higher yield in the case of bicyclopropenyls containing 3, 4, 5, and 10 bridge methylenes (Scheme 38, **38.8** where n = 3-5 and 10). Furthermore, these ratios were not strongly influenced by solvent (toluene, $CDCl_3$, CH_3OH) or by temperature (-25 to +25 °C) in the case of **52.1**. Separation by gas chromatography gave **52.5**, which when heated between 60-90 °C gave [6]paracyclophane (**52.6**). Although this route is by no means attractive, it involves a basic theme of converting Dewar benzenes into paracyclophanes. The conversion of Dewar benzene **52.5** to [6]paracyclophane (**52.6**) is reversible as demonstrated by photochemical conversion of **52.6** back to 1,4-hexamethylene Dewar benzene(**52.5**) in a photostationary equilibrium.

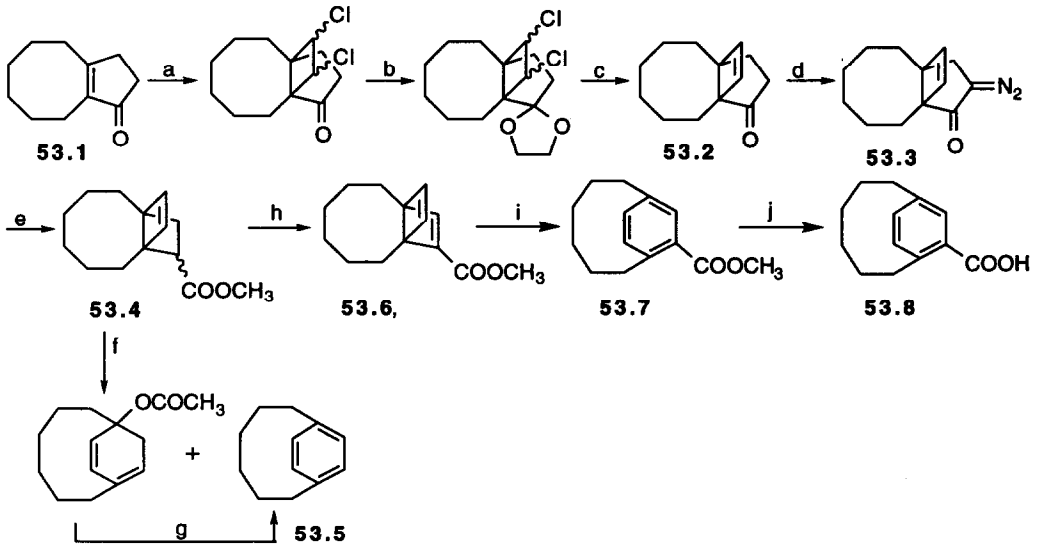


a) $AgBF_4/CH_3CN$, b) heat, >60 °C, c) hv/cyclohexane-d_{12}.

Scheme 52

Tobe and colleagues[125] developed a more efficient and convenient route to [6]paracyclophane (**53.5**) and its derivatives (**53.7**, **53.8**, Scheme 53) that also takes advantage of the thermal valence isomerization of 1,4-polymethylene Dewar benzenes derivatives to [6]paracyclophanes, a strategy used independently by Jones and by our group.[100,124] However Tobe's method for the synthesis of [6.2.2] propelladienes is superior. The

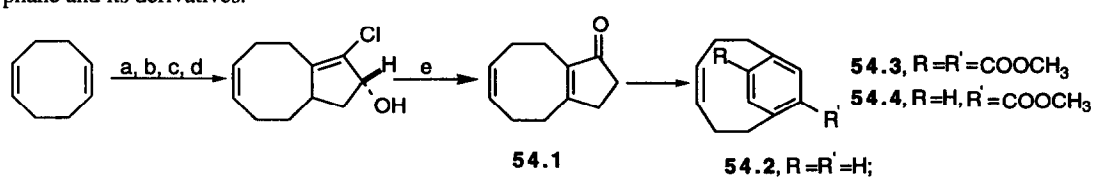
requisite propellanone **53.2** was synthesized by Tobe in three steps from the readily available bicyclic ketone **53.1**. The photo-Wolff rearrangement in methanol of α-diazoketone **53.3** (derived in two steps from **53.2**) gave a mixture of two epimeric methyl esters **53.4**. Standard functional group conversions (saponification, then oxidation with lead tetraacetate) gave [6]paracyclophane **53.5** = **52.6**. Treatment of **53.4** with LDA/-diphenyl diselenide at -70 °C afforded a mixture of two isomeric selenides, which on oxidation with H_2O_2 in CH_2Cl_2 gave [6.2.2]propelladiene **53.6**. Valence isomerization of **53.6** at 60 °C gave 8-carbomethoxy[6]-paracyclophane (**53.7**), which on hydrolysis with KOH in methanol yielded 8-carboxy[6]paracyclophane (**53.8**) as a crystalline solid of mp 123-125 °C in an overall yield of ~10%.



a) ClCH=CHCl/hv, b) $HOCH_2CH_2OH/H^+$, c) Na/NH_3, H^+, d) $HCOOC_2H_5$, $NaOC_2H_5)/TsN_3/N(C_2H_5)_3$ e) hv/CH_3OH, f) KOH/H_2O, $Pb(OAc)_4/Cu(OAc)_2/C_6H_6$, g) KO-t-Bu, h) $LDA/C_6H_5)_2Se_2/THF$,- H_2O_2/C_5H_5N, i) heat, j) KOH/H_2O.

Scheme 53

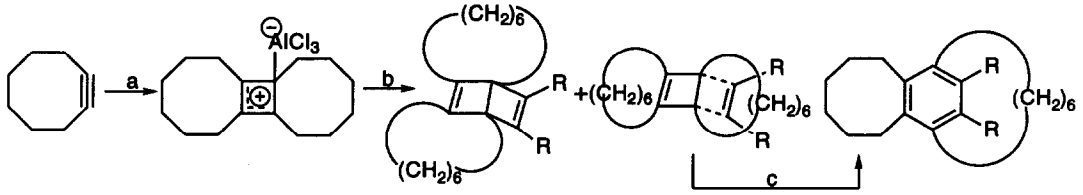
The scope of this procedure is expanded in Scheme 54.[126] The requisite starting material **54.1** for the synthesis of [6]paracycloph-3-ene **54.2** and its derivatives **54.3** and **54.4** was obtained by a method developed by Mehta and Rao.[127] This improvement allowed Tobe to study further the chemical reactions of [6]paracyclophane and its derivatives.



a) $Cl_2CHCOCl/N(C_2H_5)_3$, b) CH_2N_2/Et_2O, c) Li_2CO_3/DMF, d) $NaBH_4/CeCl_3/CH_3OH$, e) 80% HCOOH.

Scheme 54

The last method we discuss is that of Gleiter and Treptow[128], who describe a synthesis of the highly substituted [6]paracyclophane diester **55.5** (Scheme 55). They used the photochemical valence isomerization approach of opening Dewar benzene **55.4** to [6]paracyclophane diester **55.5**. The underlying strategy for a Dewar benzene skeleton was first published in 1971.[129] Since then the reaction has been thoroughly studied by Hogeveen and coworkers [130] for the general preparation of Dewar benzenes. Reaction of cyclooctyne with aluminum chloride gave complex **55.2**; subsequent addition of dimethyl sulfoxide followed by dimethyl acetylenedicarboxylate between 0-10 °C gave a mixture of isomeric Dewar benzenes **55.3** and **55.4**. Separation followed by irradiation at 250 nm gave the highly substituted [6]paracyclophane diester **55.5**. However, this method could not be used to prepare the corresponding, highly substituted [5]paracyclophane diester.



55.1 **55.2** **55.3** **55.4** **55.5** R =$COOCH_3$

a) $AlCl_3/CH_2Cl_2$/-50 °C , DMSO, b) DMAD, c) hν, 0 °C at < 280 nm.

Scheme 55

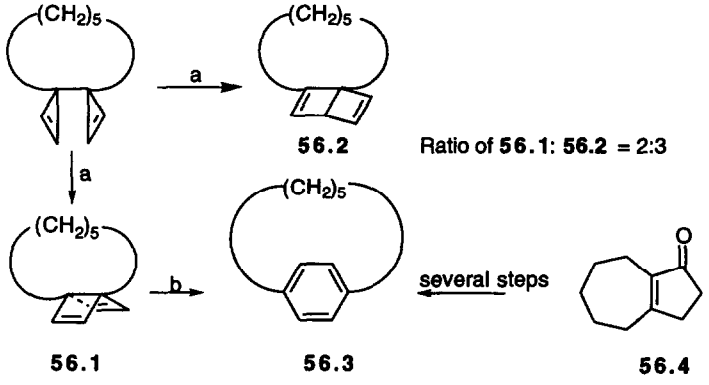
6.4 [5]Paracyclophane and Lower Analogs.

Recent calculations by our own group[66,82,131] on small [n]paracyclophanes, n = 3, 4 and 5 provided insight to the origin and magnitude of strain. Furthermore, the available experimental results seem to reveal that [n]paracyclophanes n = 3, 4 and 5 have much lower thermodynamic and kinetic stabilities than do [6]paracyclophanes. Recent success has been reported in spectroscopic characterization of [[5]paracyclophane,[132] which is stable at low temperatures in solution but not isolable; and more recently [4]paracyclophane has been proposed as a reactive intermediate.[133,134] The chemistry of these analogs are discussed below. No successful synthesis, nor the intermediacy, of [3]paracyclophane, even in a matrix system, has yet been reported.

6.5 [5]Paracyclophane and Its Derivatives

All the routes discussed so far to [6]paracyclophane failed for the synthesis of [5]paracyclophane **56.3** and its derivatives including the Tochtermann approach[72,123] and the thermal opening of the corresponding Dewar benzenes. However, a photochemical modification of the latter approach (Scheme 56) not only turned out to be the method of choice, but has proven to be the only successful one so far. Dewar benzene **56.1** has two properties that make it an ideal precursor for [5]paracyclophane **56.3**. The complete skeleton of **56.3** is already present in **56.1**, and the high energy content of the Dewar benzene **56.1** is available to compensate for the strain and instability in **56.3** that might tend to thwart the transformation. On purely thermodynamic

grounds this transformation appeared feasible since [5]paracyclophane **56.3** is calculated to be more stable than the Dewar benzene isomer **56.1**. (The stabilities are reversed in the case of [4]paracyclocyclophane).[131] Thermal conversion of **56.1** to **56.3** failed, however, due to the thermal instability of **56.3** at the temperature needed to generate it. At this point the photochemical method seemed promising, since the absorbed light energy may help to overcome the energy barrier ; and aromatization can be achieved at lower temperatures where sensitive products have a better chance of survival. Thus irradiation of **56.1** with a low pressure mercury lamp at -60 °C in THF-d_8 in a quartz tube gave **56.3** in 6-7% yield. A photostationary state was established with a ratio of **56.1**:**56.3** = 93:7. [5]Paracyclophane (**56.3**) was not isolated but was unequivocally characterized by its UV and ^{1}H NMR spectra.[132] This breakthrough in the chemistry of small paracyclophanes was achieved 11 years after the first synthesis of [6]paracyclophane by Jones and his group.[117]

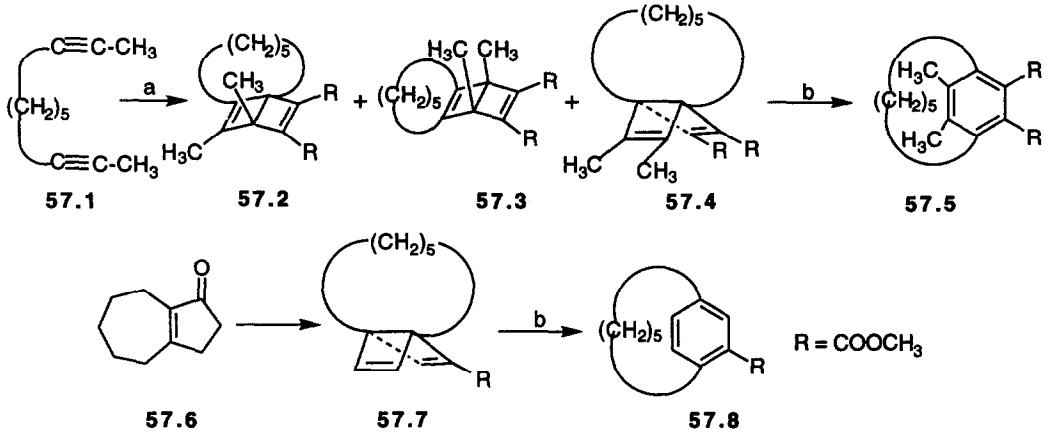


a) $AgBF_4/CH_3CN$, b) hν, THF-d_8 at -60 °C.

Scheme 56

Although the parent (unsubstituted) [5]paracyclophane (**56.3**) rapidly decomposes above 0 °C, two successful syntheses of substituted [5]paracyclophanes possessing higher thermal stability have been reported (Scheme 57).[135,136] Both syntheses use the photochemical conversion of the corresponding Dewar benzene (**57.4** and **57.7**) to the corresponding [5]paracyclophane derivative (**57.5** and **57.8**, respectively). The Dewar benzene **57.4** was prepared from undeca-2,9-diyne (**57.1**) by the method of Hogeveen,[130] which furnished a mixture of regioisomers **57.2**-**57.4** in a ratio of about 2:1:1. Compound **57.4** was obtained as colorless crystals of mp 50 °C. Irradiation of a degassed THF-d_8 solution of **57.4** at -50 °C for 30 minutes provided about 13% of **57.5**. The half life of **57.5** is several hours at room temperature, clearly illustrating the effect of the substituents. Attempts to separate **57.4** and **57.5** were unsuccessful.

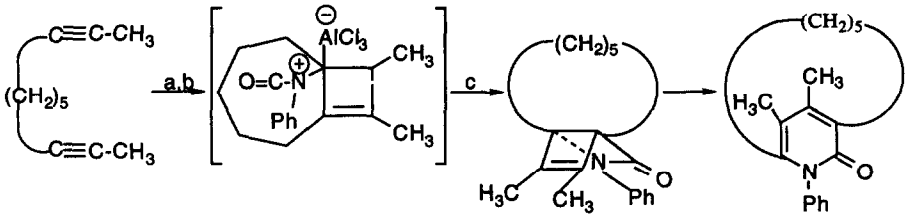
A comparable degree of stabilization for the 7-carbomethoxy derivative of [5]paracyclophane (**57.8**) was reported by Tobe.[136] The precursor **57.7** was prepared by a somewhat longer route from bicyclic enone **57.6**.



a) $AlCl_3/CH_2Cl_2$/-70 °C; DMAD, b) hv/THF, -50 °C.

Scheme 57

An attempted synthesis of a highly substituted pyridine analog of [5]paracyclophane[82b] by use of the Hogeveen method[130] is outlined in Scheme 58.



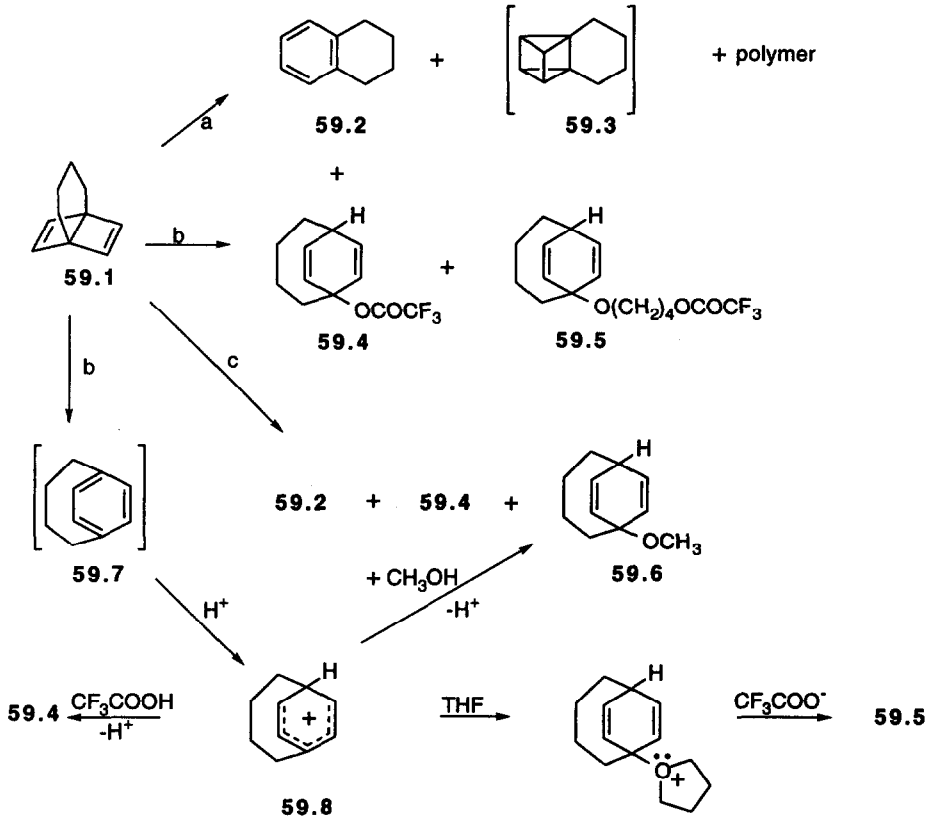
a) $AlCl_3/CH_2Cl_2$/-70 °C, b) C_6H_5NCO, c) hv/THF, -50 °C.

Scheme 58

6.6 [4]Paracyclophane and Its Derivatives

Recently, the intermediacy of unsubstituted and monosubstituted derivatives of [4]paracyclophane (**59.7**) was demonstrated on the basis of trapping experiments (Schemes 59 and 60).[133,134] A dramatic decrease in stability occurs for [4]paracyclophane (**59.7** = **60.4**), for which MNDO calculations indicate a strain energy of about 98 kcal/mol^{-1}, which by far exceeds the estimated resonance energy of benzene by approximately 20-40 kcal/mol^{-1}. The homologous [5]paracyclophane was stable only at -20 °C, so [4]paracyclophane (**59.8**) was expected to decompose well below this temperature. The photolytic approach that had proven successful in the case of [5]paracyclophane was tried for [4]paracyclophane (**59.7**). Irradiation of previously known **59.1** at -50 °C in THF-d_8 led to **59.2**, prismane **59.3**, and to polymer. The intermediacy of [4]paracyclophane **59.7** was unequivocally demonstrated by interception in acidic media to give 1,4-adducts **59.4**-**59.6** (reaction pathways b and c, Scheme 59).[133] A rationalization of the mechanistic pathway is as

follows. The easy protonation of [4]paracyclophane (**59.7**) at -20 °C is a consequence of the high strain, which is substantially relieved in the formation of the benzenium cation **59.8**. This cation is trapped by nucleophiles to give the 1,4-adducts **59.4-59.6**.

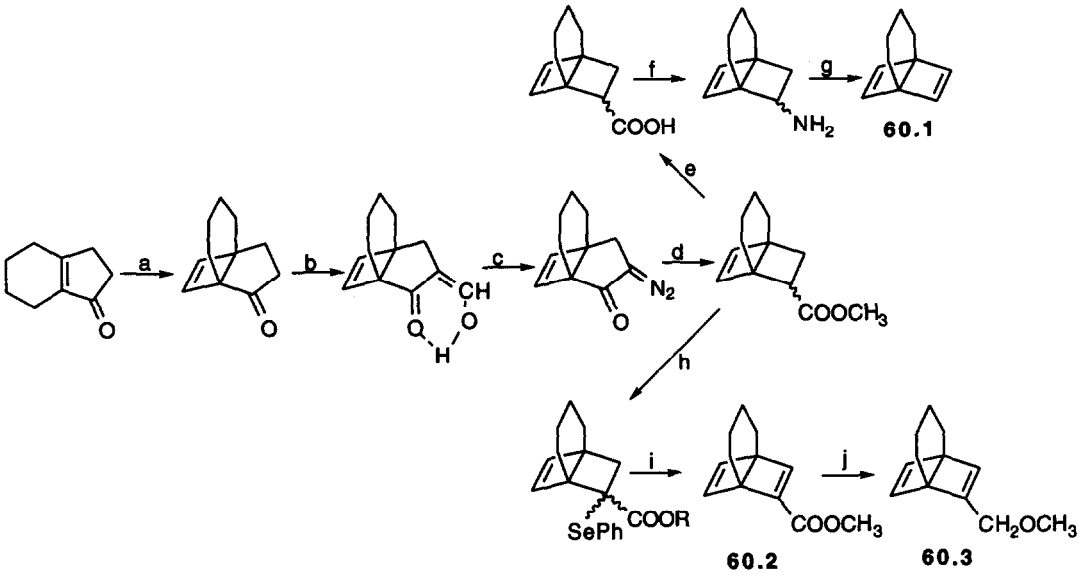


a) THF-d_8/-50 °C/hv, b) THF/-20 °C/5-30 eq. CF_3COOH/hv,

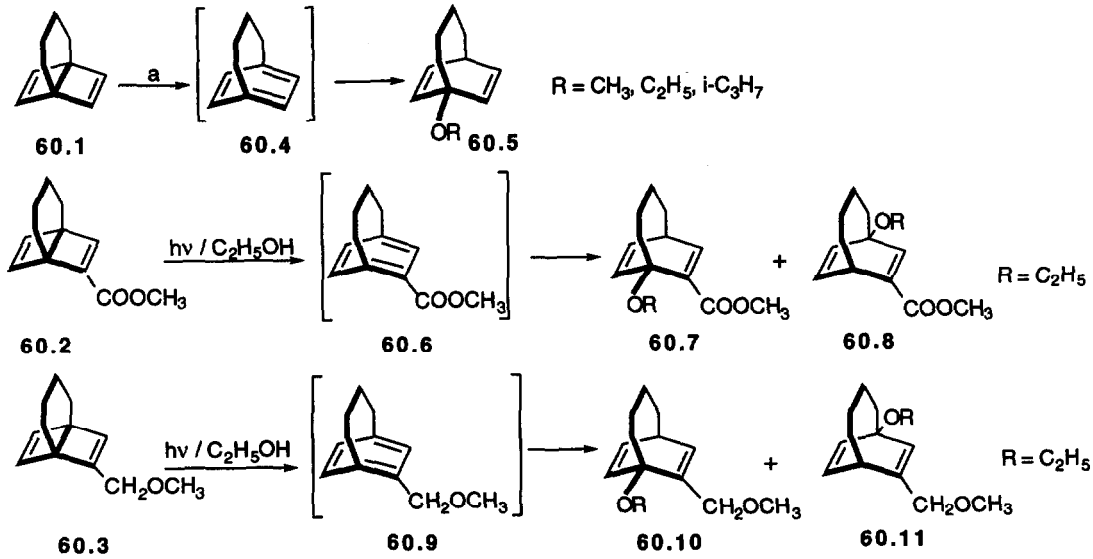
c) CH_3OH/-20 °C/5 eq. CF_3COOH/hv.

Scheme 59

A similar effort was carried out independently at practically the same time by Tsuji and Nishida (Scheme 60).[134] Their general approach to the Dewar benzenes **60.1-60.3** is shown. Irradiation of **60.1-60.3** in alcohols gave 1,4-addition products **60.5, 60.7, 60.8, 60.10**, and **60.11**. Additionally, these authors directly identified [4]paracyclophane (**60.4**) by UV spectroscopy. Irradiation of **60.1** in a matrix at 77 K gave an absorption maximum at 340 nm and an inflection at about 370 nm. These absorptions are in the range expected for [4]paracyclophane **60.4**.



a) acetylene(C_2H_2)/hv, b) $HCOOC_2H_5/NaOC_2H_5$, c) $TsN_3/N(C_2H_5)_3$, d) hv/CH_3OH, e) KOH/H_2O, f) $(C_6H_5O)_2P(O)N_3/C_6H_6/CH_3SCH_2CH_2OH/(CH_3)_2SO_4$, g)$CH_3I$/KO-t-Bu/heat h) LDA/$(C_6H_5)_2Se_2$/THF, i) H_2O_2/C_5H_5N, heat, j) i-Bu_2AlH/C_6H_{12}/NaH/CH_3I.



a) hv in CH_3OH, C_2H_5OH, or i-C_3H_7OH.

Scheme 60

7 Concluding Remarks

The last three decades have witnessed significant progress in the area of cyclophane chemistry, especially that of small [n]metacyclophanes and [n]paracyclophanes (n = 4-8). This report reviewed the synthetic strategies for the latter two subclasses. While the schemes included in this review show the high degree of ingenuity applied to the synthesis of these cyclophanes, there remains a need for improved methods and for shorter synthesis of these and other substituted small cyclophanes. The failure of efforts to make [4]paracyclophane by a bridged Dewar benzene valence isomerization route indicates that this route has probably reached its limit at n = 4. Valence isomerizations of prismane analogs to p-cyclophanes have not yet been exploited, but recent investigations of these compounds show that they hold considerable promise; this is just one example of many possibilities still open in the chemistry of these fascinating, highly strained unnatural products. Another fruitful area for future investigation would be to extend methodology for the synthesis of cyclophanes with unsaturations or with heteroatoms in the bridge. We hope that this review will stimulate interest in the small cyclophanes area in the years ahead.

Acknowledgments. In attempts to make this report as timely as possible, we may have inadvertently omitted some work that should have been included. For any such oversights that may have occurred, we extend our apologies. V.V.K. would like to thank the Council for International Exchange of Scholars (Fulbright Award to Thailand at Chulalongkorn University) and the Vrije Universiteit Amsterdam for financial support. W. H. de W. and F. B. thank the Netherlands Organization for Scientific Research (NWO) for financial support obtained through the Netherlands Foundation for Chemical Research (SON). Last but not least, V.V.K. thanks his wife Pauline for her forbearance when he disappeared to write and for her loving support when he resurfaced for encouragement.

References

1. For examples of unnatural products with strain see: (a) Nickon, A; Silversmith, E. F. *The Name Game*, Pergamon Press, 1987 and for synthetic approaches see (b) Cram, D. J.; Steinberg, H. J. *J. Am. Chem. Soc.* **1951**, *73*, 5691. (c) Sekine, Y.; Brown, M.; Boekelheide, V. *J. Am. Chem. Soc.* **1979**, *101*, 3126. (d) Sekine, Y.; Boekelheide, V. *J. Am. Chem. Soc.* **1981**, *103*, 1777. (e) Ternansky, R. J.; Balogh, D. W.; Paquette, L. A. *J. Am. Chem. Soc.* **1982**, *104*, 4503. (f) Paquette, L. A.; Ternansky, R. J.; Balogh, D. W.; Kentgen, G. *J. Am. Chem. Soc.* **1983**, *105*, 5446. (g) Fessner, W. D.; Prinzbach, H.; Rihs, G. *Tetrahedron Lett.* **1983**, *24*, 5857. (h) Maier, G. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 317. (i) Eaton, P. E.; Maggini, M. *J. Am. Chem. Soc.* **1988**, *110*, 7230. (j) Szeimies, G. *Reactive Intermediates*, Abramovitch, R. Ed.; **1983**, vol. 3, p. 299. (k) Wiberg, K. B. *Acc. Chem. Res.* **1984**, *17*, 379. (l) Wang, X. M.; Wang, R. J.; Mak, T. C. W.; Wong, H. N. C. *J. Am. Chem. Soc.* **1990**, *112*, 7790. (m) Gleiter, R. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 27. (n) Maier, H. *Advances in Strain in Organic Chemistry* (Ed.; B. Halton) JAI - Press, **1991**.

2. For nomenclature of phane systems: Vögtle, F.; Neumann, P. *Tetrahedron* **1970**, *26*, 5847.

3. For general reviews on benzocyclopropene see (a) Billups, W. E.; Rodin, W. A.; Haley, M. M. *Tetrahedron* **1988**, *44*, 1305. (b) Billups, W. E. *Acc. Chem. Res.* **1978**, *11*, 245. (c) Halton, B. *Chem. Rev.* **1973**, *73*, 113.
4. For a comprehensive review of quinodimethanes (benzocyclobutenes) in synthesis, see (a) Funk, R. L.; Vollhardt, K. P. C. *Chem. Soc. Rev.* **1980**, 41. (b) Thummel, R. P. *Acc. Chem. Res.* **1980**, *13*, 70. (c) Fallis, A. G. *J. Am. Chem. Soc.* **1984**, *62*, 143. (d) Quinkert, G.; Stark, H. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 637. (e) Kametani, T.; Fukumoto, K. *Med. Res. Rev.* **1981**, *1*, 23. (f) McCullough, J. J. *Acc. Chem.. Res.* **1980**, *13*, 270. (g) Kametani, T.; Nemoto, H. *Tetrahedron* **1981**, *37*, 3. (h) Oppolzer, W. *Heterocycles* **1980**, *14* , 1615. (i) Wong, N. C.; Lan, K-L; Tam, K. F. *Top. Curr. Chem.* (Edited by A. de Meijere) **1986**, *133*, 124. (j) For a later review, see Charlton J. L.; Alauddin, M. M. *Tetrahedron* **1987**, *43*, 2873.
5. (a) Cram, D. J.; Cram, J. M. *Acc. Chem. Res.* **1971**, *4*, 204. (b) Jones, M., Jr. *Acc. Chem. Res.* **1974**, *7*, 415. (c) Smith, B. H., *Bridged Aromatic Compounds*, Academic Press: New York, **1964**. (d) Vögtle, F.; Neumann, P. *Synthesis* **1973**, 85. (e) Vögtle, F.; Hohner, G. *Top. Curr. Chem.* **1974**, *4*, 204. (f) Vögtle, F.; Hohner, G. *Top. Curr. Chem.* **1978**, *74*, 1. (g) Misumi, S.; Otsubo, T. *Acc. Chem. Res.*. **1978**, *11*, 251. (h) Misumi, S., *Mem. Inst. Sci. Ind. Res. Osaka Univ.* **1976**, *33*, 53. (i) Boekelheide, V. *Acc. Chem. Res.* **1980**, *13*, 65. (j) Kleinschroth, J.; Hopf, H. *Angew. Chem. Int. Ed. Eng.* **1982**, *21*, 469. (k) Diederich, F. *Angew. Chem. Int. Ed. Eng.* **1988**, *27*, 36. (l) Keehn, P. M.; Rosenfeld, S. M. *Cyclophanes*, Academic Press: New York, **1983**.
6. (a) Fujita, S.; Nozaki, H. *J. Synth. Org. Chem., Jpn.* **1972**, *30*, 803. (b) Cram, D. J.; Cram, J. M. *Science* **1974**, *183*, 803.
7. Bickelhaupt, F.; de Wolf, W. H. *Recl. Trav. Chim. Pays-Bas* **1988**, *107*, 459.
8. For general reviews on aromaticity, see (a) Lewis, D.; Peters, D. *Facts and Theories of Aromaticity*, MacMillan: London, **1975**. (b) Maier, G. *Chemie in unserer Zeit* **1975**, *5*, 131.
9. (a) Bergmann, E. D.; Pullmann, B., Eds.; *Aromaticity, Pseudo-Aromaticity, Anti-Aromaticity*, Academic Press: New York, **1971**. (b) *Spec. Publ.-Chem. Soc.* **1967**, No. 21.
10. (a) Loschmidt, J. *Chemische Studien I*, Vienna, **1861**. (b) Noe, C. R.; Bader, A. *Chem. Br.* **1993**, 126 and references cited therein. (c) Wiswesser, W. J. *Aldrichimica Acta* **1989**, *22*, 17 and references cited therein. (d) Hückel, E. Z. *Physik* **1931**, *70*, 204. (e) Hückel, E. Z. *Physik* **1938**, *72*, 310. (f) Rocke, A. J. *Chem. Br.* **1993**, 401.
11. (a) Armit, J. W.; Robinson, R. *J. Chem. Soc.* **1925**, 1604. (b) Robinson, R. *Spec. Publ.-Chem. Soc.* **1967**, No. 21, 47.
12. (a) Pine, S. H. *Org. Chem.*, 5th ed., McGraw-Hill, **1987**, 203. (b) Dewar, M. J. S.; Longuet-Higgins, H. C. *Proc. R. Soc., London Ser. A* **1952**, *A214*, 482. (c) Wheland, C. W. *Resonance Theory in Organic Chemistry*, Wiley: New York, **1955**. (d) Wilcox, C. F. *Tetrahedron Lett.* **1968**, 795. (e) Herndon, W. C. *Tetrahedron* **1972**, *28*, 3675; **1973**, *29*, 3. (f) Graovac, I.; Gutmann, I.; Trinajstic, N.; Zivkovic, T. *Theor. Chim. Acta* **1972**, *26*, 67. (g) Kaneko, C. *Tetrahedron* **1972**, *28*, 4915. (h) Roth, W. R.; Adamczak, O.; Breuckmann, R.; Lennartz, H. W.; Boese, R. *Chem. Ber.* **1991**, *124*, 2499. In this publication resonance energy of benzene has been reported as 25.88 kcal/ mol.

13. (a) Dewar, M. J. S.; de Llano, C. *J. Am. Chem. Soc.* **1969**, *91*, 789. (b) Baird, N. C. *J. Chem. Educ.* **1971**, *48*, 509. (c) Kuwajima, S.; Soos, Z. G. *J. Am. Chem. Soc.* **1987**, *109*, 107 and references cited therein.
14. Hess, B. A.; Schaad, L. J. *J. Am. Chem. Soc.* **1983**, *105*, 7500. (b) Haddon, R. C.; Raghavachari, K. *J. Am. Chem. Soc.* **1985**, *107*, 289. (c) Ichikawa, H.; Ebisawa, Y. *J. Am. Chem. Soc.* **1985**, *107*, 161.
15. (a) Baird, N. C. *J. Org. Chem.* **1986**, *51*, 3907. (b) Hiberty, P. C.; Shaik, S. S.; Lefour, J. M.; Ohanessian, G. *J. Org. Chem.* **1985**, *50*, 4657. (c) Hiberty, P. C.; Shaik, S. S.; Ohanessian, G. *J. Org. Chem.* **1986**, *51*, 3908. (d) Hiberty, P. C.; Shaik, S. S. *J. Am. Chem. Soc.* **1987**, *109*, 363. (e) Janoschek, R. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1298. (f) Copper, D. L.; Garrett, J; Raomondi, M. *Nature* **1986**, *323*, 699. (g) Schultz, P. A.; Messner, R. P. *Phys. Rev. Lett.* **1987**, *58*, 2416. (h) Stanger, A.; Vollhardt, K. P. C. *J. Org. Chem.* **1988**, *53*, 4889. (i) Jug, K.; Köster, A. M. *J. Am. Chem. Soc.* **1990**, *112*, 6772.
16. Ermer, O. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 782.
17 Günther, H. in *NMR Spektroskopie*, Georg Thieme Verlag, Stuttgart, **1973.**
18. (a) See, e.g. Roberts, J. D.; Caserio, M. C. *Basic Principles of Organic Chemistry*, W. A. Benjamin, New York, **1965**, pp. 783-784. (b) For kinetic interpretation, see Dixon, W. T. *J. Chem. Soc., Chem. Commun.* **1969**, 599. (c) Bofill, J. M.; Castels, J.; Olivella, S.; Solé, A. *J. Org. Chem.* **1988**, *53*, 5148.
19. Garrat, P. J. *Aromaticity*, John Wiley: New York, **1986**.
20. Grob, C.; Schiess, P. *Angew. Chem.* **1958**, *70*, 502.
21. Vogel, E. *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 1.
22. (a) van Tamelen, E. E.; Pappas, S. P. *J. Am. Chem. Soc.* **1963**, *85*, 3297. (b) van Tamelen, E. E.; Pappas, S. P.; Kirk, K. L. *J. Am. Chem. Soc.* **1971**, *93*, 6092.
23. Benzvalene was isolated by (a) Wilzback, K. E.; Ritscher, J. S.; Kaplan, L. *J. Am. Chem. Soc.* **1967**, *89*, 1031. (b) Kaplan, L.; Wilzback, K. E. *J. Am. Chem. Soc.* **1968**, *90*, 3291. (c) Ward, H. R.; Wishnok, J. S. *J. Am. Chem. Soc.* **1968**, *90*, 1085. (d) Katz, T. J.; Wang, E. J.; Acton, N. *J. Am. Chem. Soc.* **1971**, *93*, 3782.
24. Katz, T. J.; Acton, N. *J. Am. Chem. Soc.* **1973**, *95*, 2738.
25. Billups, W. G.; Haley, M. M. *Angew. Chem. Int. Ed. Engl.* **1989**, 101, 1711.
26. See for instance: Greenberg, A.; Liebman, J. F. *Strained Organic Molecules*, Academic Press: New York, **1978**.
27. Breslow, R.; Gal, P.; Chang, H. W.; Altman, L. J . *J. Am. Chem. Soc.* **1965**, *87*, 5139.
28. (a) de Wolf, W. H.; Landheer, I. J.; Bickelhaupt, F. *Tetrahedron Lett.* **1975**, 179. (b) Weiss, R.; Köbl, H. *J. Am. Chem. Soc.* **1975**, *97*, 3222, 3224. (C) Dopper, J. H.; Greijdanus, B.; Wynberg, H. *J. Am. Chem. Soc.* **1975**, *97*, 216. (d) Turro, N. J.; Ramamurthy, V.; Katz, T. J. Nouv. J. Chim.**1977**, *1*, 363. For review articles on the valence bond isomers of benzene see (e) van Tamelen, E. E. *Acc. Chem. Res.* **1972**, *5*, 186. (f) Scott, L. T.; Jones, M., Jr. *Chem. Rev.* **1972**, *72*, 181.
29. Nakazaki, M.; Yamamoto, K.; Okamoto, S. *Tetrahedron Lett.* **1969**, 4957.

30. (a) von Braun, J.; Heider, K.; Wyczatkowsa, W. *Chem. Ber.* **1918**, *51*, 1215. (b) von Braun, J.; Newman, L. *Chem. Ber.* **1919**, *53*, 2015.
31. Griffin, R. W., Jr. *Chem. Rev.* **1963**, *63*, 45.
32. Prelog, V.; Wiesner, K. *Helv. Chim. Acta* **1947**, 30, 1465. Prelog in this paper has claimed the synthesis of 2,6-bridged p-nitrophenols, i.e. substituted [n]metacyclophanes where n = 5, 6, 7, 9, 10, 11, etc. The structure of [n]metacyclophane (n = 5) is based mainly on its UV spectrum, which showed a blue shift when compared to p-nitrophenol, which throws doubt on the correctness of this structure.[32]
33. In a subsequent paper (Prelog. V.; Wiesner, K.; Ingold, W.; Hafliger, O. *Helv. Chim. Acta* **1948**, *31*, 1325) a tautomeric structure was proposed for this substituted [5]metacyclophane. In the light of modern day instrumentation such as NMR and X-ray analysis, it would be appropriate to reinvestigate the structure of this compound. However, it is worthwhile to note that the idea of 3C + 3C annulation methodology for the synthesis of [n]metacyclophane occurred as early as 1947.
34. Paquette, L. A.; Trova, M. P.; Luo, J.; Clough, A. E.; Anderson, L. B. *J. Am. Chem. Soc.* **1990**, *112*, 228.
35. Marchesini, A.; Bradmante, S.; Fusco, R.; Pagani, G. *Tetrahedron Lett.* **1971**, 671.
36. Kang, G. J.; Chan, T. H. *J. Org. Chem.* **1985**, *50*, 452.
37. (a) Lorenzi-Riatsch, A.; Wälchli, R.; Hesse, M. *Helv. Chim. Acta* **1985**, *68*, 2177. (b) Nelson, P. H.; Nelson, J. T. *Synthesis* **1991**, 192.
38. For a comprehensive collection of methods for preparing dithiacyclophanes, and their conversion via *sulfur* extrusion to cyclophanes, see: Boekelheide, V. *Top. Curr. Chem.* **1983**, *113*, 87.
39. Vögtle, F.; Rossa, L. *Angew Chem. Int. Ed. Engl.* **1979**, *18*, 515.
40. Vögtle, F.; Koo, Tze Mew, P. *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 60.
41. Higuchi, H.; Misumi, S. *Tetrahedron Lett.* **1982**, *23*, 5571.
42. Higuchi, H.; Kugiyama, M.; Otsubo, T.; Sakata, Y.; Misumi, S. *Tetrahedron Lett.* **1983**, *24*, 2593.
43. (a) Higuchi, H.; Tani, K.; Otsubo, T.; Sakata, Y.; Misumi, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4027. (b) Breitenbach, J.; Ott, F.; Vögtle, F. *Angew. Chem. Int. Ed. Engl.* **1992**, *31* , 307.
44. Unpublished results of Dr. L. A. M. Turkenburg of Vrije Universiteit, Amsterdam, 1981.
45. Hubert, A. J.; Dale, J. *J. Chem. Soc.* **1963**, 86.
46. Eglington, G.; Galbraith, A. R. *J. Chem. Soc.* **1959**, 889.
47. Tamao, K; Kodama, S.; Nakatsuke, T.; Kiso, Y.; Kumada, M. *J. Am. Chem. Soc.* **1975**, *97*, 4405.
48. Noble, K. L.; Hopf, H.; Ernst, L. *Chem. Ber.* **1984**, *117*, 474.
49. Blomquist, A. T.; Stahl, R. E.; Meinwald, Y. C.; Smith, B. H. *J. Org. Chem.* **1961**, *26*, 1687.
50. Bates, R. B.; Camou, F. A.; Merbs, S. L.; Ortega, R. B.; White, J. J.; Kane, V. V.; Mishra, P. K. *Acta Crystallogr.* **1987**, *C43*, 517.
51. Bates, R. B.; Camou, F. A.; Kane, V. V.; Mishra, P. K.; Suvannachut, K.; White, J. J. *J. Org. Chem.* **1989**, *54*, 311.
52. Bates, R. B.; Ogle, C. A. *J. Org. Chem.* **1982**, *47*, 3949.
53. Bates, R. B.; Gangwar, S.; Kane, V. V.; Suvannachut, K.; Taylor, S. R. *J. Org. Chem.* **1991**, *56*, 1696.

54. (a) Mann, G. Thesis, Leipzig Universitet, Germany, 1962. (b) Mann, G. *J. Prakt. Chem.* **1963**, *20*, 210.
55. This feasibility has been tested by AM1 calculations; Kane, V. V.; van Baar, B. L. M., unpublished results.
56. Noble, K. L.; Hopf, H.; Jones, M., Jr.; Kammula, S. L. *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 602.
57. Otsubo, T.; Misumi, S. *Synth. Commun.* **1978**, *8*, 285.
58. Hirano, S.; Hara, S.; Hiyama, T.; Fuji, S.; Nozaki, H. *Tetrahedron* **1975**, *31*, 2219.
59. Jenneskens, L. W.; van Straten, J. W.; de Wolf, W. H.; Bickelhaupt, F. *Tetrahedron* **1984**, *40*, 3117.
60. Kane, V. V. *Synth. Commun.* **1976**, *6*, 237.
61. Hirano, S.; Hiyama, T.; Fujita, S.; Nozaki, H. *Chem. Lett.* **1972**, 707.
62. Fujita, S.; Hirano, S.; Nozaki, H. *Tetrahedron Lett.* **1972**, 403.
63. van Straten, J. W.; de Wolf, W. H.; Bickelhaupt, F. *Tetrahedron Lett.* **1977**, 4667.
64. Le, N. A.; Jones, M., Jr.; Bickelhaupt, F.; de Wolf, W. H. *J. Am. Chem. Soc.* **1989**, *111*, 8491.
65. Landheer, I. J. Thesis, Vrije Universiteit, Amsterdam, 1976.
66. (a) Jenneskens, L. W. Thesis, Vrije Universiteit, Amsterdam, 1986. (b) Jenneskens, L. W.; de Wolf, W. H.; Bickelhaupt, F. *Angew. Chem. Int. Ed. Engl.* **1985**, *24, 585.*.
67. Goodman, J. L.; Berson, J. A. *J. Am. Chem. Soc.* **1985**, *107*, 5409, 5424.
68. Tobe, Y.; Sorori, T.; Korio, K.; Kakiuchi, K.; Odaira, Y. *Tetrahedron Lett.* **1987**, *28*, 2861.
69. (a) Tobe, Y.; Ueda, K.; Kakiuchi, K.; Odaira, Y. *Chem. Lett.* **1983**, 1645. (b) Tobe, Y.; Takemura, A.; Jimbo, M.; Takahashi, T.; Kobiro, K.; Kakiuchi, K. *J. Am. Chem. Soc.* **1992**, *114*, 3479.
70. Shea, K. J.; Burke, L. D.; Doedens, R. J . *J. Am. Chem. Soc.* **1985**, *107*, 5305.
71. Shea, K. J. *Tetrahedron* **1980**, *36*, 1683.
72. Liebe, J.; Wolff, C.; Krieger, C.; Weiss, J.; Tochtermann, W. *Chem. Ber.* **1985**, *118*, 4144.
73. Dhanak, D.; Reese, C. B. *J. Chem. Soc., Perkins Trans. 1* **1987**, 2829.
74. (a) Parham, W. E.; Davenport, R. W.; Biasotti, J. B. *Tetrahedron Lett.* **1969**, 557. (b) Parham, W. E.; Rinehart, J. K. *J. Am. Chem. Soc.* ***1967***, *89*, 5668. (c) Parham, W. E.; Davenport, R. W.; Biasotti, J. B. *J. Org. Chem.* **1970**, *35*, 3775.
75. Grice, P.; Reese, C. B. *Tetrahedron Lett.* **1979**, 2563.
76. Turkenburg, L. A. M.; Block, P. L. M.; de Wolf, W. H.; Bickelhaupt, F. *Tetrahedron Lett.* **1981**, *22*, 3317.
77. Jenneskens, L. W.; De Kanter, F. J. J.; Turkenburg, L. A. M.; De Boer, H. J. R.; de Wolf, W. H.; Bicklehaupt, F. *Tetrahedron* **1984**, *21*, 4413.
78. Turkenburg, L. A. M. Thesis, Vrije Universiteit, Amsterdam, 1982.
79. van Straten, J. W. Thesis, Vrije Universiteit, Amsterdam, 1978.
80. Grice, P.; Reese, C. B. *J. Chem. Soc., Chem. Commun.* **1980**, 424.
81. Turkenburg, L. A. M.; van Straten. J. W.; de Wolf, W. H.; Bickelhaupt, F. *J. Am. Chem. Soc.* **1980**, *102*, 3256.
82. (a) Kostermans, G. B. M. Thesis, Vrije Universiteit, Amsterdam, 1989. (b) Kostermans, G. B. M.; Hogenbirk, M.; Turkenburg, L. A. M.; de Wolf, W. H.; Bickelhaupt, F. *J. Am. Chem. Soc.* **1987**, *109*, 2855.

(c) Kostermans, G. B. M.; van Dansik, P.; de Wolf; W. H.; Bickelhaupt, F. *J. Am. Chem. Soc.* **1987**, *109*, 7887. (d) Kostermans, G. B. M.; van Dansik, P.; de Wolf; W. H.; Bickelhaupt, F. *J. Org. Chem.* **1988**, *53*, 4531.

83. (a) Bartlett, M. F.; Figdor, S. K.; Wiesner, K. *Can. J. Chem.* **1952**, *30*, 291. (b) Wiesner, K.; McDonald, D. M.; Ingraham, R. B.; Kelley, R. B. *Can. J. Res., Sect. B.* **1950**, 28, 561.
84. Cram, D. J.; Knox, G. R. *J. Am. Chem. Soc.* **1961**, *83*, 2204.
85. Remington, R. B.; Lee, T. J.; Schaefer, H. F., III. *Chem. Phys. Lett.* **1986**, *124*, 199.
86. Rice, J. E.; Lee, T. J.; Remington, R. B.; Allen, W. D.; Schaefer, H. F., III. *J. Am. Chem. Soc.* **1987**, *109*, 2902.
87. Lee, T. J.; Rice, J. E.; Remington, R. B.; Allen, W. D.; Schaefer, H. F., III. *Chem. Phys.* **1988**, *123*, 1.
88. Lee, T. J.; Rice, J. E.; Remington, R. B.; Schaefer, H. F., III. *Chem. Phys. Lett.* **1988**, *150*, 63.
89. Cram, D. J.; Montgomery, C. S.; Knox, G. R. *J. Am. Chem. Soc.* **1966**, *88*, 515.
90. Cope, A. C.; Pawson, B. A. *J. Am. Chem. Soc.* **1968**, *90*, 636.
91. Whitesides, G. M.; Pawson, B. A.; Cope, A. C. *J. Am. Chem. Soc.* **1968**, *90*, 639.
92. Nakazaki, M.; Yamamoto, K.; Tanaka, S. *J. Org. Chem.* **1976**, *41*, 4081.
93. Nakazaki, M.; Yamamoto, K.; Ito, M.; Tanaka, S. *J. Org. Chem.* **1977**, *42*, 3468.
94. Higuchi, H; Kobayashi, E.; Otsubo, Y.; Sakata, Y.; Misumi, S. *Tetrahedron* **1986**, *42*, 1731.
95. de Wolf, W. H.; Bickelhaupt, F. *Recl. Trav. Chim. Pays-Bas* **1971**, *90*, 150.
96. van Straten, J. W.; van Norden, J. J.; van Schaik, T. A. M.; Franke, G. Th.; de Wolf, W. H.; Bickelhaupt, F. *Recl. Trav. Chim Pays-Bas* **1978**, *97*, 105.
97. (a) Treibs, W.; Mühlstädt, U. *Chem. Ber.* **1954**, *87*, 407. (b) Mannich, C. *Chem. Ber.* **1941**, *74*, 554.
98. Greenwald, R.; Chaykovsky, M.; Corey, E. J. *J. Org. Chem.* **1963**, *28*, 1128.
99. van Straten, J. W.; de Wolf, W. H.; Bickelhaupt, F. *Recl. Trav. Chim. Pays-Bas* **1977**, *96*, 88.
100. van Straten, J. W.; Landheer, I. J.; de Wolf, W. H.; Bickelhaupt, F. *Tetrahedron Lett.* **1975**, 4499.
101. Jenneskens, L. W.; de Wolf, W. H.; Bickelhaupt, F. *Tetrahedron* **1986**, *42*, 1571.
102. Helder, R. Thesis, Rijks Universiteit Groningen, The Netherlands, 1974.
103. Gassman, P. G.; Bailey, T. F.; Hoye, R. C. *J. Org. Chem.* **1980**, *45*, 2923.
104. (a) Gassman, P. G.; Korn, S. R.; Bailey, T. F.; Johnson, T. H.; Finer, J.; Clardy, J. *Tetrahedron Lett.* **1979**, 3401. (b) Gassman, P. G.; Thummel, R. P. *J. Am. Chem. Soc.* **1972**, *94*, 7183. (c) Gassman, P. G.; Korn, S. R.; Thummel, R. P. *J. Am. Chem. Soc.* **1974**, *96*, 6948.
105. Allinger, N. L.; Freiberg, L. A.; Hermann, R. B.; Miller, M. A. *J. Am. Chem. Soc.* **1963**, *85*, 1171.
106. Newton, G. M.; Walter, T.; Allinger, N. L. *J. Am. Chem. Soc.* **1973**, *95*, 5652.
107. Cram, D. J.; Ankar, M. F. *J. Am. Chem. Soc.* **1958**, *80*, 3103.
108. March, J. *Advanced Organic Chemistry: Reactions, Mechanisms and Structure*, John Wiley and Sons: New York, **1985**, p. 975.
109. (a) Horner, L.; Spetschka, E. *Chem. Ber.* **1954**, *88*, 934. (b) Meinwald, J.; Gassman, P. G. *J. Am. Chem. Soc.* **1960**, *82*, 2857. (c) Regitz, M. In *The Chemistry of Diazonium and Diazo Groups*, Patai, S. E.; Wiley: Chichester, **1975**, Chapter 17.

110. Tsuji, T.; Shibata, T.; Hienuki, Y.; Nishida, S. *J. Am. Chem. Soc.* **1978**, *100*, 1806.
111. Tsuji, T.; Nishida, S. *Acc. Chem. Res.* **1984**, *17*, 56, and references therein.
112. Closs, G. L.; Czeropski, M. S. *Chem. Phys. Lett.* **1977**, *45*, 115.
113. Allinger, N. L.; Walter, T. J. *J. Am. Chem. Soc.* **1972**, *94*, 9267.
114. Allinger, N. L.; Walter, T. J.; Newton, M. J. *J. Am. Chem. Soc.* **1974**, *96*, 4588.
115. Wolf, A. D.; Kane, V. V.; Levin, R. H.; Jones, M., Jr. *J. Am. Chem. Soc.* **1973**, *95*, 1680.
116. Berdick, T. E.; Levin, R. H.; Wolf, A. D.; Jones, M., Jr. *J. Am. Chem. Soc.* **1973**, *95*, 5087.
117. Kane, V. V.; Jones, M., Jr. *Org. Synth.* **1981**, *61*, 129.
118. Hünger, J.; Wolff, C.; Tochtermann, W.; Peters, E. M.; Peters, K.; von Schnering, H. G. *Chem. Ber.* **1986**, *119*, 2698.
119. Ando, W.; Tsumuraya, T.; Kabe, Y. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 778.
120. Kane, V. V.; Wolf, A. D.; Jones, M., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 2643.
121. Murray, D. F.; Baum, M. W.; Jones, M., Jr. *J. Org. Chem.* **1986**, *51*, 1.
122. R. H. Levin, Ph.D. Thesis, Princeton University, Princeton, N.J., 1970.
123. (a) Jessen, J. L.; Wolff, C.; Tochtermann, W. *Chem. Ber.* **1986**, *119*, 297. (b) Jenneskens, L. W.; Kostermans, G. B. M.; ten Brink, H. J.; de Wolf, W. H.; Bickelhaupt, F.*J. Chem. Soc., Perkin Trans. 1* **1987**, 2829.
124. (a) Kammula, S. L.; Iroff, L. D.; Jones, M., Jr.; van Straten, J. W.; de Wolf, W. H.; Bickelhaupt, F. *J. Am. Chem. Soc.* **1977**, *99*, 5815. (b) Weiss, R.; Schlierf, C. *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 811. (c) Weiss, R.; Andrae, S. *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 150, 152.
125. Tobe, Y.; Ueda, K.; Kikiuchi, K.; Odaira, Y.; Kai, Y.; Kasai, N. *Tetrahedron* **1986**, *42*, 1851, and references cited therein.
126. Tobe, Y.; Ueda, K.; Kameda, T.; Kakiuchi, K.; Odaira, Y.; Kasai, N. *J. Am. Chem. Soc.* **1987**, *109*, 1136, and references cited therein.
127. Mehta, G.; Rao, K. S. *Tetrahedron Lett.* **1984**, *25*, 1839.
128. (a) Gleiter, R.; Treptow, B. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1427. (b) Gleiter, R.; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 27
129. (a) Koster, J. B.; Timmermans, G. J.; van Bekkum, H. *Synthesis* **1971**, *139*. (b) Schäfer, W.; Hellman, H. *Angew. Chem. Int. Ed. Engl.* **1967**, 518.
130. (a) Hogeveen, H.; Kok, D. M. in *Chemistry of Triple Bonded Functional Groups, Supplement C*, Part 2 (Ed.; Patai, S.; Rappoport, Z.) Wiley: New York, p. 81 and references cited therein. (b) Driessen, P. B. J.; Hogeveen, H. *J. Am. Chem. Soc.* **1978**, *100*, 1193. (c) Driessen, P. B. J.; Hogeveen, H. *J. Organomet. Chem.* **1978**, *156*, 265.
131. Jenneskens, L. W.; Louwen, J. N.; de Wolf, W. H.; Bickelhaupt, F. *J. Phys. Org. Chem.* **1990**, *3*, 295.
132. Jenneskens, L. W.; de Kanter, F. J. J.; Kraakman, P. A.; Turkenburg, L. A. M.; Koolhaas, W. E.; de Wolf, W. H.; Bickelhaupt, F.; Tobe, Y.; Kakiuchi, K.; Odaira, Y. *J. Am. Chem. Soc.* **1985**, *107*, 3716.

133. Kostermans, G. B. M.; Bodeldijk, K. M.; de Wolf, W. H.; Bickelhaupt, F. *J. Am. Chem. Soc.* **1987**, *109*, 2471.

134. Tsuji, T.; Nishida, S. *J. Am. Chem. Soc.* **1988**, *110*, 1257.

135. (a) Kostermans, G. B. M.; de Wolf, W. H.; Bickelhaupt, F. *Tetrahedron Lett.* **1986**, *27*, 1095.
(b) Kostermans, G. B. M.; de Wolf, W. H.; Bickelhaupt, F. *Tetrahedron* **1987**, *43*, 2955.

136. Tobe, Y.; Kaneda, T.; Kakiuchi, K.; Odaira, Y. *Chem. Lett.* **1985**, 1301.

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