NOVEL BIS(ISOBENZOFURAN)S AND THEIR UTILITY IN THE SYNTHESIS OF CYCLOPHANES

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Abstract

The synthesis of 1,2-bis(5-isobenzofuranyl)ethene by two routes is described. The first route involved generation of 1,2-bis(5-isobenzofuranyl)ethene from a bis(acetal) precursor under basic conditions. However, the synthesis was lengthy with low-yielding steps, which led to it being abandoned. The second route involved generation of 1,2-bis(5-isobenzofuranyl)ethene from a bis(oxabicyclic) precursor with 3,6-di(2'-pyridyl)-*s*-tetrazine.

Naphtho[1,2-*c*:5,6-*c*]difuran and 1,2-bis(5-isobenzofuranyl)ethene were used to construct novel cyclophanes by double Diels–Alder reactions with bis(maleimide)s. NMR, AM1 modeling, and X-ray studies of the cyclophanes are discussed.

Attempts to prepare phenanthro[2,3-*c*:6,7-*c*]difuran and its cyclophanes are discussed. None was successful, and investigations were hampered by the inability to obtain sufficient quantities of starting materials.

Finally, several suggestions are given for improving the syntheses of 1,2-bis(5-isobenzofuranyl)ethene, phenanthro[2,3-*c*:6,7-*c*]difuran, and their cyclophanes. Future directions, such as the functionalization of the double bond of 1,2-bis(5-isobenzofuranyl)ethene, aromatization of the oxabicyclic rings of the cyclophanes, and further X-ray studies are discussed.

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List of Abbreviations

Ac	acetyl
AM1	Austin Model 1 (a semi-empirical quantum mechanical theory)
b.p.	boiling point
br	broad
Bu	*n*-butyl
t-Bu	*tert*-butyl
Bz	benzoyl
Bz_2O_2	dibenzoyl peroxide
C	Celsius
COSY	Correlation Spectroscopy
*m*CPBA	*meta*-chloroperoxybenzoic acid
d	doublet (NMR)
d	day(s)
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
dec	decomposed (m.p.)
dipytet	3,6-di(2'-pyridyl)-*s*-tetrazine
DMAD	dimethyl acetylenedicarboxylate
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulphoxide
EI	electron impact
EPA	diethyl ether/isopentane/ethanol
Et	ethyl
eV	electronvolt(s)
g	gram(s)
h	hour(s)
HMQC	Heteronuclear Multiple-Quantum Coherence
Hz	Hertz
IR	infrared
IBF	isobenzofuran
K	Kelvin(s)
kcal	kilocalorie(s)
kJ	kilojoule(s)
LDA	lithium diisopropylamide
m	multiplet (NMR)
M	molarity
Me	methyl
mg	milligram(s)
MHz	megaHertz
mL	millilitre(s)
mm	millimetre(s)
mmol	millimole(s)
mol	mole(s)

m.p.	melting point
MS	mass spectroscopy
NBS	*N*-bromosuccinimide
NICS	nucleus-independent chemical shift
NMR	nuclear magnetic resonance
PCC	pyridinium chlorochromate
Ph	phenyl
ppm	parts per million
REPE	resonance energy per π-electron
RMS	root-mean-square
s	singlet (NMR)
s	second(s)
SC_P	structure count of the products
SC_R	structure count of the reactants
SC_{ratio}	structure count ratio
t	triplet (NMR)
THF	tetrahydrofuran
Ts	tosyl (*p*-toluenesulfonyl)

Introduction

Described in this thesis is the utility of novel bis(isobenzofuran)s in the synthesis of cyclophanes. The goal of this work is the eventual use of isobenzofurans and cyclophanes to make novel materials. The methodology developed for the synthesis of these cyclophanes could lead to the synthesis of designer catalysts, artificial enzymes, novel host molecules, and chiral ligands.

The thesis is laid out as described below. The literature on isobenzofuran is reviewed in Chapter 1. The structure, aromaticity, discovery, isolation, methods of generation, and reactivity of isobenzofuran and its benzologues are discussed. The synthesis of the novel difuran, 1,2-bis(5-isobenzofuranyl)ethene, by two routes is then described. The first route involved generation of 1,2-bis(5-isobenzofuranyl)ethene from a bis(acetal) precursor under basic conditions. However, the synthesis was lengthy with low-yielding steps, which led to it being abandoned. The second route involved generation of 1,2-bis(5-isobenzofuranyl)ethene from a bis(oxabicyclic) precursor with 3,6-di(2'-pyridyl)-*s*-tetrazine.

Cyclophanes are reviewed in Chapter 2, focusing on the syntheses of naphthalenophanes and stilbenophanes. Literature examples of the use of isobenzofurans in cyclophane chemistry are presented. The construction of cyclophanes from two difurans, naphtho[1,2-*c*:5,6-*c*]difuran and 1,2-bis(5-isobenzofuranyl)ethene, by double Diels–Alder reactions with bis(maleimide)s is then described. These cyclophanes have been characterized by NMR spectroscopy, IR spectroscopy, and mass spectrometry, and AM1 modeling studies have been conducted.

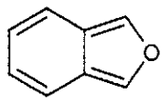
The synthesis of phenanthrenophanes and progress towards the preparation of phenanthro[2,3-*c*:6,7-*c*]difuran and its cyclophanes are described in Chapter 3. None of the attempts was successful, and investigations were hampered by the inability to obtain sufficient quantities of starting materials.

Finally, several suggestions for improving the syntheses of 1,2-bis(5-isobenzofuranyl)ethene, phenanthro[2,3-*c*:6,7-*c*]difuran, and their cyclophanes are given in Chapter 4. Future directions, such as the functionalization of the double bond of 1,2-bis(5-isobenzofuranyl)ethene, aromatization of the oxabicyclic rings of the cyclophanes, and further X-ray studies are discussed.

Chapter 1 Generation of Novel Bis(Isobenzofuran)s

1.1 Generation and Chemistry of Isobenzofuran

Isobenzofuran (IBF, 1, Figure 1.1) has been the subject of several reviews over the last twenty years.[1-6] Isobenzofurans are very reactive dienes in Diels–Alder reactions and have found great utility in the synthesis of natural products[2-5] and polycyclic aromatic hydrocarbons.[2-5,7-9] In fact, Rickborn has referred to IBF as "the most reactive isolable diene known."[4] More recently, isobenzofurans have been used in the synthesis of polymers,[10] polyacenequinones,[11] and cyclophanes (see Section 2.1.4).



1

Figure 1.1: Isobenzofuran

1.1.1 Structure and Aromaticity

Isobenzofuran has 10 π-electrons, which means that according to Hückel's rule, it should be aromatic. However, a resonance energy of 2.4 kcal/mol was calculated for IBF, indicating that it is almost nonaromatic.[12] For comparison's sake, the same authors calculated a resonance energy of 1.6 kcal/mol for furan,[12] and 0.869 eV (20.0 kcal/mol) for benzene.[13] In contrast, Palmer and Kennedy[14] obtained the more substantial values of 147 kJ/mol (35.1 kcal/mol) for isobenzofuran, 89 kJ/mol (21 kcal/mol) for furan, and 212 kJ/mol (50.7 kcal/mol) for benzene. However, there was a change in the definition of resonance energy between the two groups. Palmer and Kennedy used the original definition of resonance energy as the difference between the molecular total energy and

the sum of the non-interacting bonds, while Dewar *et al.* defined the reference non-aromatic structure with zero resonance energy as the corresponding acyclic polyolefin.

Trinajstic[15] calculated the resonance energy per π-electron (REPE) for several conjugated cyclic compounds and compared his results to earlier REPE calculations by Hess, Schaad, and Holyoke.[16] REPE's are calculated in units of β, which is defined as one-half the total π-electron energy of ethylene.[15] Both groups obtained a REPE of 0.007β for furan, making it nonaromatic (a compound is nonaromatic if $-0.01\beta \leq \text{REPE} \leq 0.01\beta$). Hess calculated a REPE of 0.002β for isobenzofuran, indicating that it is nonaromatic, while Trinajstic obtained a value of 0.011β, indicating that isobenzofuran is very weakly aromatic, though this value is so close to the upper limit for nonaromaticity that IBF may readily be considered nonaromatic. In comparison, Trinajstic and Hess calculated REPE's of 0.046β and 0.065β, respectively, for benzene.

The seemingly conflicting evidence led Chacko *et al.* to pose the question of whether the aromaticity extended over the entire 10π system or whether it resulted from only one ring.[17] Upon analysis of the NMR spectra of a series of heterocycles, they determined that isobenzofuran is best described by a structure wherein an aromatic heteroatom-containing ring is joined to a bond-fixated butadiene fragment (Figure 1.2). Therefore, the aromaticity of IBF is due mainly to the furan moiety, with a small contribution arising from fusion to butadiene.

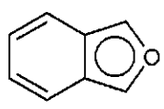


Figure 1.2: Another Representation of Isobenzofuran

More recently, Zhou and Parr used the concepts of absolute and relative hardness to determine the degree of aromaticity in a series of conjugated and heteroconjugated hydrocarbons.[18] Absolute hardness (η) was defined as one-half the HOMO-LUMO gap, while relative hardness (η_r) was defined as the absolute hardness of the molecule minus the absolute hardness of an acyclic reference structure. Relative hardness generally provides a better measure of the degree of aromaticity than absolute hardness since it accounts for the fact that all acyclic polyenes are nonaromatic and that some conjugated cyclic molecules are antiaromatic. A compound is predicted to be aromatic if $\eta_r > 0.08\beta$, nonaromatic if $-0.08\beta \leq \eta_r \leq 0.08\beta$, and antiaromatic if $\eta_r < 0.08\beta$. Values of 0.043β and 0.003β for η_r were obtained for furan and isobenzofuran, respectively, making them both nonaromatic (benzene's η_r was 0.482β). Both hardness indices correlated well with the previously calculated REPE's.

Schleyer has introduced the concept of the nucleus-independent chemical shift (NICS) as a method for calculating aromaticity.[19] Simply put, NICS is a measure of the absolute magnetic shielding computed at the ring centre. Negative NICS indicate aromaticity (a direct parallel to protons over a benzene ring exhibiting negative chemical shifts due to deshielding caused by the diatropic ring current), while positive NICS indicate antiaromaticity. The application of NICS calculations to isobenzofuran[20] led to the conclusion that the furan ring is strongly aromatic and the benzene ring weakly aromatic, mirroring Chacko's results. The advantage of a NICS calculation is that it assesses rings in polycyclic compounds separately, while a criterion such as resonance energy treats the molecule as a whole. The difference between the two approaches can lead to widely differing conclusions, as evidenced by this discussion of the aromaticity of

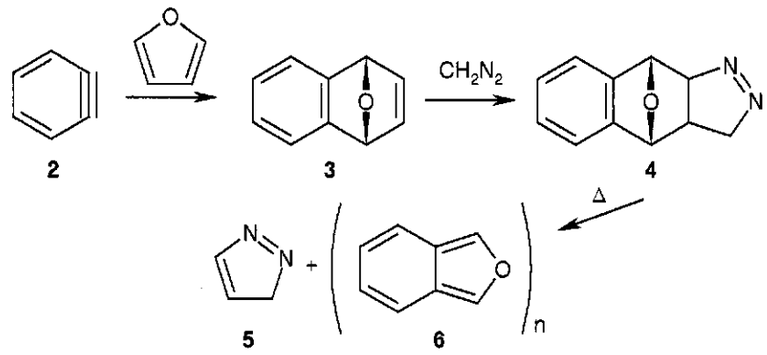
isobenzofuran. Schleyer further emphasizes that aromatic stabilization does not necessarily lead to greater thermodynamic stability, since stability is influenced by many factors.

In direct contrast to Schleyer's results, calculations by Martínez *et al.* led to the conclusion that the benzene ring of isobenzofuran is aromatic, and that the furan ring is only weakly aromatic.[21] Their calculations of the geometry of isobenzofuran can be represented by Figure 1.2. Unfortunately, the authors do not reference the above work by Schleyer, and thus there is no discussion of the contradictory NICS values.

An X-ray crystal structure of a substituted isobenzofuran also supports the representation of IBF as that in Figure 1.2.[22] Several recent calculations on the geometry of IBF also support the above representation.[6] Moreover, despite the range of values obtained for the resonance energy of IBF, it can be concluded that it is aromatic. There is clearly a diatropic ring current, since the furanoid protons resonate at 8.40 ppm (the same protons in furan itself are observed at 7.435 ppm).[23]

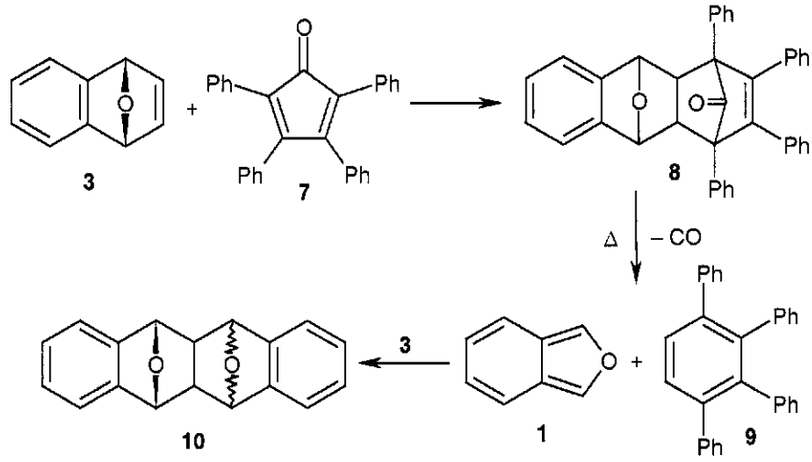
1.1.2 Discovery and Isolation

Wittig and Pohmer first postulated isobenzofuran as a reactive intermediate in 1956.[24] They trapped benzyne **2** with furan to generate 1,4-dihydro-1,4-epoxynaphthalene (**3**), which was then reacted with diazomethane to yield pyrazoline **4**. Upon heating, **4** decomposed to pyrazole **5** and a polymeric residue formulated as **6** (Scheme 1.1).

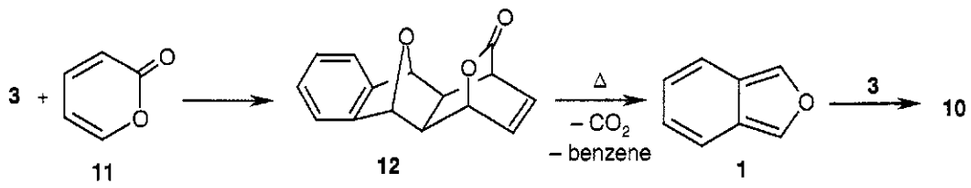


Scheme 1.1

Fieser and Haddadin[25] proved the existence of IBF as an intermediate in their study on tetraphenylcyclopentadienone (**7**). Reaction of **3** with **7** in refluxing benzene resulted in the isolation of **8**. Subsequent heating in the presence of more **3** led to the isolation of 1,2,3,4-tetraphenylbenzene (**9**), *exo-exo*-**10**, and *exo-endo*-**10**, with the latter two compounds clearly being formed from the Diels–Alder reaction of IBF with **3** (Scheme 1.2). They supported their results by reacting **3** with α-pyrone (**11**) to yield **12**, which was heated in the presence of more **3** to give **10** (Scheme 1.3).

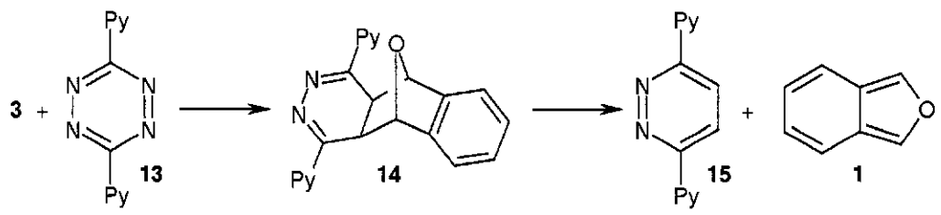


Scheme 1.2



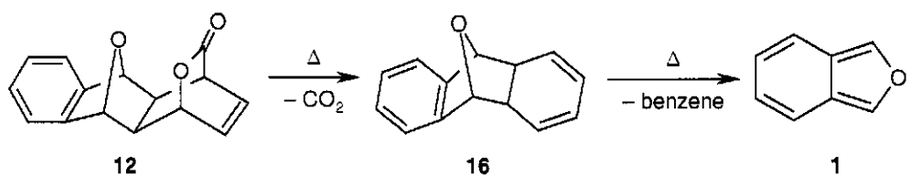
Scheme 1.3

IBF was finally isolated by three groups in the early 1970s. Warrener's communication[23] was the first to appear. His approach is outlined in Scheme 1.4. A suspension of 3,6-di(2'-pyridyl)-*s*-tetrazine (dipytet, **13**) in DMSO was stirred with **3** to give **14**, which rapidly decomposed at room temperature, yielding **15** and IBF. The presence of IBF was confirmed by trapping it as its *N*-methylmaleimide adduct. Pure IBF was obtained by vacuum pyrolysis of **14** and collection of IBF on a –80 °C cold finger as a colourless crystalline solid that melted at about 20 °C. The mass spectrum showed a parent peak at *m/e* 118, as well as peaks corresponding to loss of CO and H.



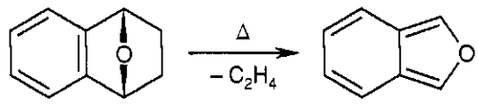
Scheme 1.4

Wege[26] followed shortly afterwards with his preparation of IBF (Scheme 1.5). Vacuum sublimation of **12** resulted in the collection of **16** in the tube and IBF in the cold trap. Wege found that dilute (10^{-4} M) solutions of IBF are stable to 70 °C, though polymerization occurred in more concentrated solutions at lower temperatures.



Scheme 1.5

Finally, Wiersum and Mijs[27] subjected 1,2,3,4-tetrahydro-1,4-epoxynaphthalene (**17**) to flash vacuum thermolysis (Scheme 1.6). Ethylene was expelled and IBF collected in a cold trap. The authors trapped IBF with maleic anhydride, *N*-phenylmaleimide, methyl vinyl ketone, styrene, and cyclohexene.

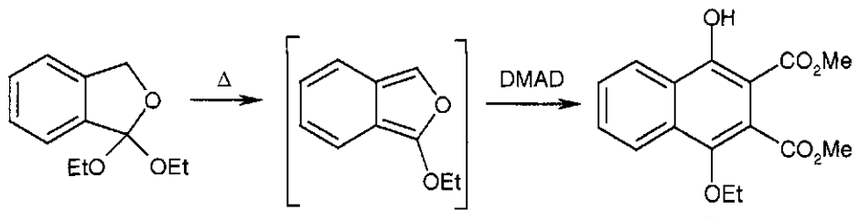


17 **1**

Scheme 1.6

1.1.3 Other Methods of Generating Isobenzofurans

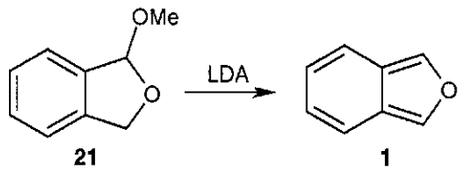
In addition to the above methods, several groups have developed other methods of generating isobenzofuran, its derivatives, and its benzologues. MacLean heated a chloroform solution of ortho ester **18** with DMAD in a sealed glass tube to generate polysubstituted naphthalenes (**20**, Scheme 1.7).[28] The intermediate was postulated to be 1-ethoxyisobenzofuran (**19**).



18 **19** **20**

Scheme 1.7

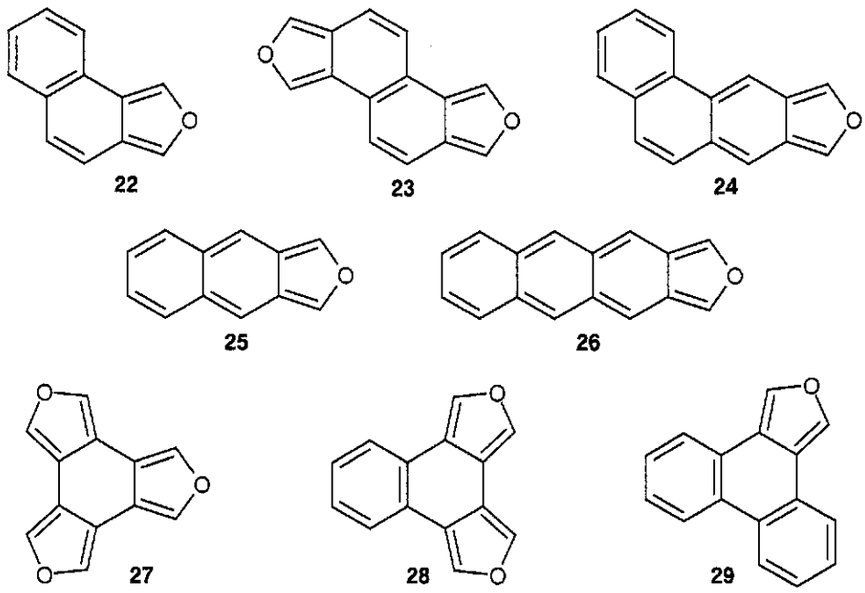
Rickborn[29] used the strong base LDA to induce a 1,4-elimination of methanol from the acetal precursor **21** to generate IBF (Scheme 1.8). This method has been used to generate naphtho[1,2-*c*]furan[30] (**22**), naphtho(1,2-*c*:5,6-*c*]difuran[31] (**23**), and phenanthro[2,3-*c*]furan[32] (**24**) (see Figure 1.3).



21 1

Scheme 1.8

Rodrigo[33] used acetic acid to generate 5,6-dimethoxyisobenzofuran from its acetal precursor. Acidic conditions have also been used for the syntheses of naphtho[1,2-*c*]furan (**22**),[34] naphtho[2,3-*c*]furan[34,35] (**25**), and anthra[2,3-*c*]furan[36] (**26**) (see Figure 1.3).



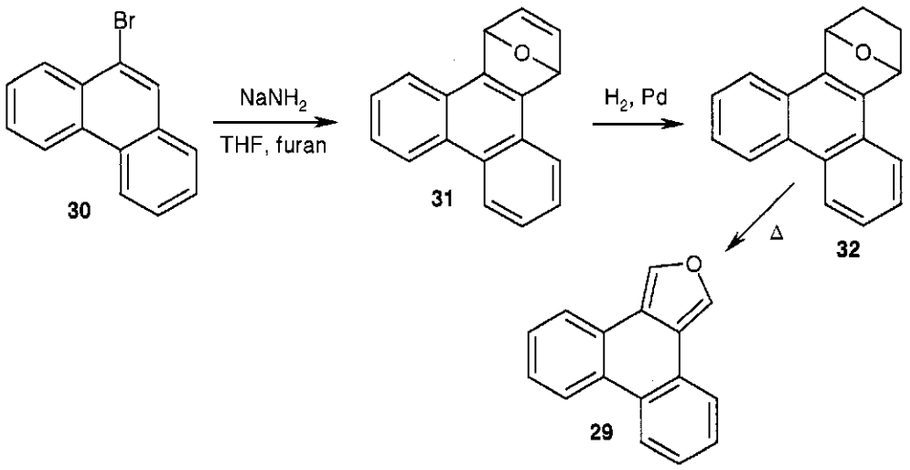
22 23 24

25 26

27 28 29

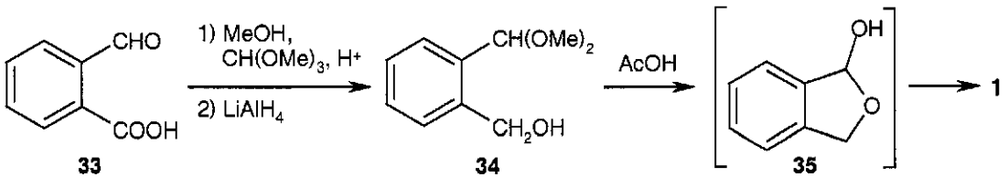
Figure 1.3: Several Benzannulated Isobenzofurans

Stringer and Wege used vacuum sublimation to prepare benzo[1,2-*c*:3,4-*c*':5,6-*c*"]trifuran (**27**), naphtho[1,2-*c*:3,4-*c*']difuran (**28**), and phenanthro[9,10-*c*]furan (**29**) (see Figure 1.3) from the appropriate epoxide precursors (see Scheme 1.9 for a representative procedure).[37]



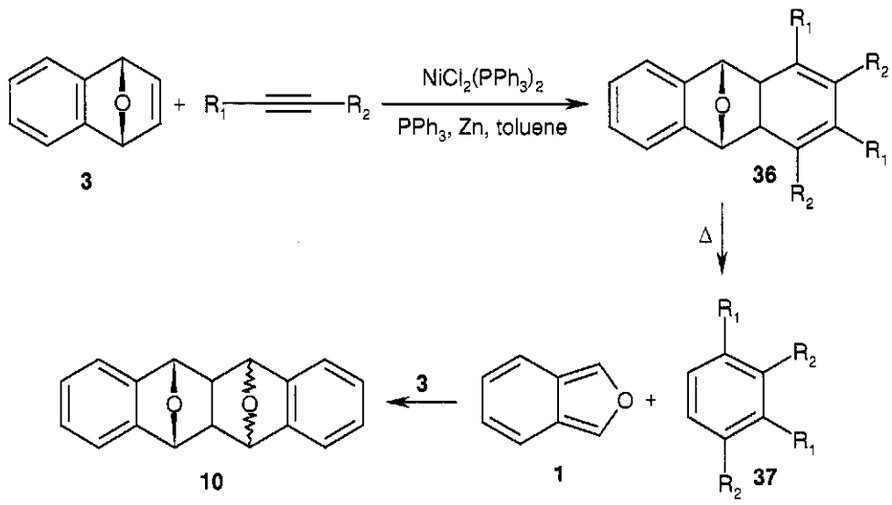
Scheme 1.9

In a variation on the usual acetal precursors to IBF, 2-(dimethoxymethyl)benzyl alcohol (**34**) was synthesized from 2-carboxybenzaldehyde (**33**), and refluxing acetic acid used to generate IBF *via* 1-hydroxyphthalan (**35**). IBF was subsequently trapped with several dienophiles (Scheme 1.10).[38]



Scheme 1.10

An attempted [2+2+2] cocyclotrimerization of **3** with various alkynes led only to *exo-exo*-**10** and *exo-endo*-**10**, regardless of the alkyne used.[39] It was determined that the cocyclotrimerization adduct **36** formed, then readily decomposed upon heating to yield the tetrasubstituted benzene **37** and IBF, which subsequently reacted with another molecule of **3** to give **10** (Scheme 1.11).



Scheme 1.11

Recently, isobenzofuran intermediates have been trapped in the coupling reaction of Fischer carbenes with *o*-alkynylbenzoyl derivatives.[40] Isobenzofurans have also been generated under neutral conditions using Pd(0) catalysts.[41]

1.1.4 Reactivity

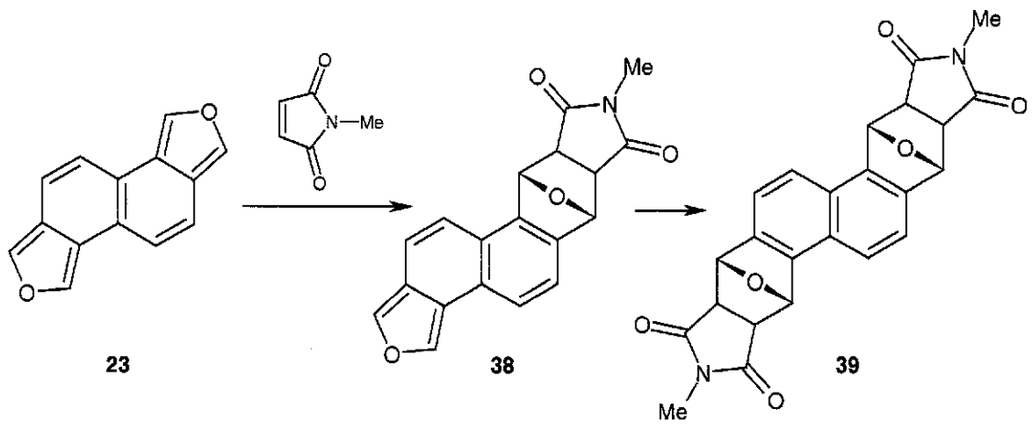
The Diels–Alder reactivity of 1,3-substituted IBF's with *N*-methylmaleimide has been studied.[42] Electron-donating substituents such as ethoxy, methyl, and *n*-butyl increase the rate of cycloadduct formation, while phenyl and trimethylsilyl decrease the rate, likely because of steric reasons. The results are similar to those obtained for substituted butadienes, despite the large reactivity difference between the two dienes. Substituents appear to have the same effect upon the rate of a Diels–Alder cycloaddition, regardless of the diene involved.

Herndon has developed a method of relating the reactivity of polycyclic aromatic hydrocarbons with maleic anhydride to the structure count ratio (SC_{ratio}). The SC_{ratio} is defined as $[(SC_R+SC_P)/SC_R]$, where SC_R and SC_P are the number of Kekulé structures for the reactant and product, respectively.[43-45] Moursounidis and Wege applied Herndon's

structure count theory to their study of the reaction rates of several benzannulated isobenzofurans with maleic anhydride and found that a plot of log SC_{ratio} against log k_2 was linear.[46] The most reactive example studied was IBF, though the authors made reference to naphtho[2,3-*c*]furan (**25**),[34,35] which was extrapolated to be 141 times more reactive than IBF. Another isobenzofuran benzologue, anthra[2,3-*c*]furan (**26**), was extrapolated to be 8000 times more reactive than IBF![36] More reactive than IBF but still isolable, the recently prepared phenanthro[2,3-*c*]furan (**24**), was found to be 15 times more reactive than IBF, taking from IBF the title of "the most reactive isolable Diels–Alder diene reported."[32] The conclusion to be drawn from this data is that linear benzannulation increases reactivity while angular benzannulation decreases reactivity.

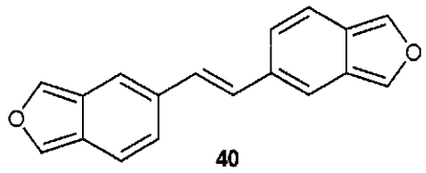
Herndon's SC_{ratio} methodology can also be applied to benzannulated difuran systems. Difuran systems are interesting because there is the possibility that the two furan rings will react at different rates in a Diels–Alder reaction. For example, naphtho(1,2-*c*:5,6-*c*]difuran (**23**)[31] is expected to be similar in reactivity to IBF, since it is essentially two IBF systems fused together. The SC_{ratio} for the addition of one equivalent of dienophile to **23** is 3, equivalent to the SC_{ratio} for IBF. Reaction with one equivalent of a dienophile leads to an intermediate, **38**, containing the naphtho[1,2-*c*]furan (**22**) substructure (Scheme 1.12). According to Wege's data, **22** is 40 times less reactive than IBF.[46] The SC_{ratio} for the addition of a second equivalent of dienophile is 2.5. Therefore, reaction of **38** with a second equivalent of dienophile to give **39** should proceed more slowly than the first reaction. When this hypothesis was tested by reacting one equivalent of *N*-methylmaleimide with **23**, it was found that the only product observed was intermediate **38**.[47] This result leads to the possibility that a difuran could be trapped with

two different dienophiles. Furthermore, a difuran can be trapped with bis(dienophile)s of suitable length to yield cyclophanes, as will be discussed in Chapter 2. The remainder of this chapter will discuss the synthesis of the novel difuran, 1,2-bis(5-isobenzofuranyl)ethene (**40**, Figure 1.4).



23 **38** **39**

Scheme 1.12



40

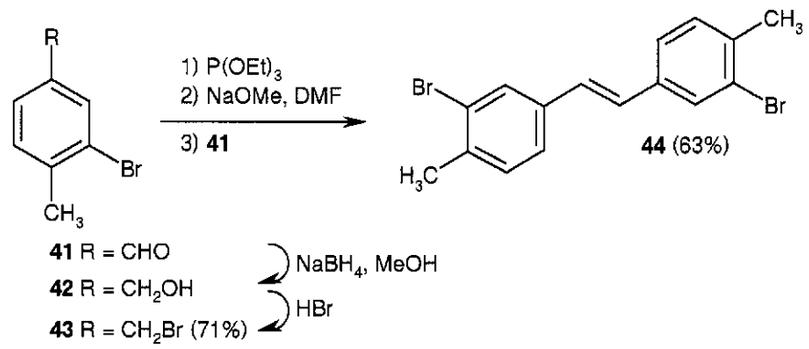
Figure 1.4: 1,2-Bis(5-isobenzofuranyl)ethene (40)

1.2 Results and Discussion

1.2.1 1,2-Bis(5-isobenzofuranyl)ethene *via* the Base-Induced Method

1,2-Bis(5-isobenzofuranyl)ethene (**40**) was initially prepared from its bis(acetal) precursor using Rickborn's base-induced method, as outlined in Scheme 1.13 and Scheme 1.14.[29] Aldehyde **41** was synthesized from *p*-tolualdehyde,[48] then reduced to afford 3-bromo-4-methylbenzyl alcohol (**42**) and brominated to give 3-bromo-4-methylbenzyl bromide (**43**). Stilbene **44** was constructed by an Arbuzov reaction of **43**

with triethyl phosphite, followed by a Wadsworth–Emmons reaction of the resultant phosphonate with **41**.[49] Due to the symmetrical nature of stilbene **44**, it was not possible to easily determine whether the double bond was in the *cis* or *trans* configuration. No coupling is observed in the ^{1}H NMR spectrum for the vinyl signal, and the IR spectrum has several peaks in the 1600 cm^{-1} region, making it difficult to choose one unequivocally as the vinyl stretch. Peaks at 703 and 969 cm^{-1} may correspond to C–H out-of-plane bends for *cis* and *trans* double bonds, respectively, but again it is difficult to establish with any certainty that this is the case. It is likely, however, that the double bond is predominantly *trans*, particularly in light of the fact that Wadsworth and Emmons reported *trans*-stilbene as the sole product from the reaction of diethyl benzylphosphonate with benzaldehyde. They postulated that both isomers initially formed, but that *cis*-stilbene readily isomerized to *trans*-stilbene under the basic conditions of the reaction.[50] Base-catalyzed *cis-trans* isomerization likely occurs by a nucleophilic attack upon the double bond by an alkoxide ion, followed by rotation about the C–C bond and folding in of a pair of electrons to regenerate the double bond and the alkoxide ion (Figure 1.5).[51]



Scheme 1.13

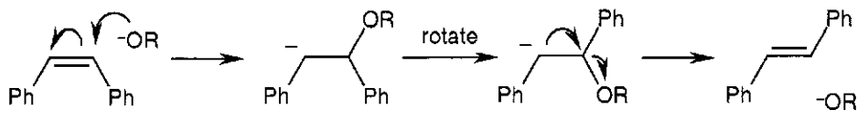
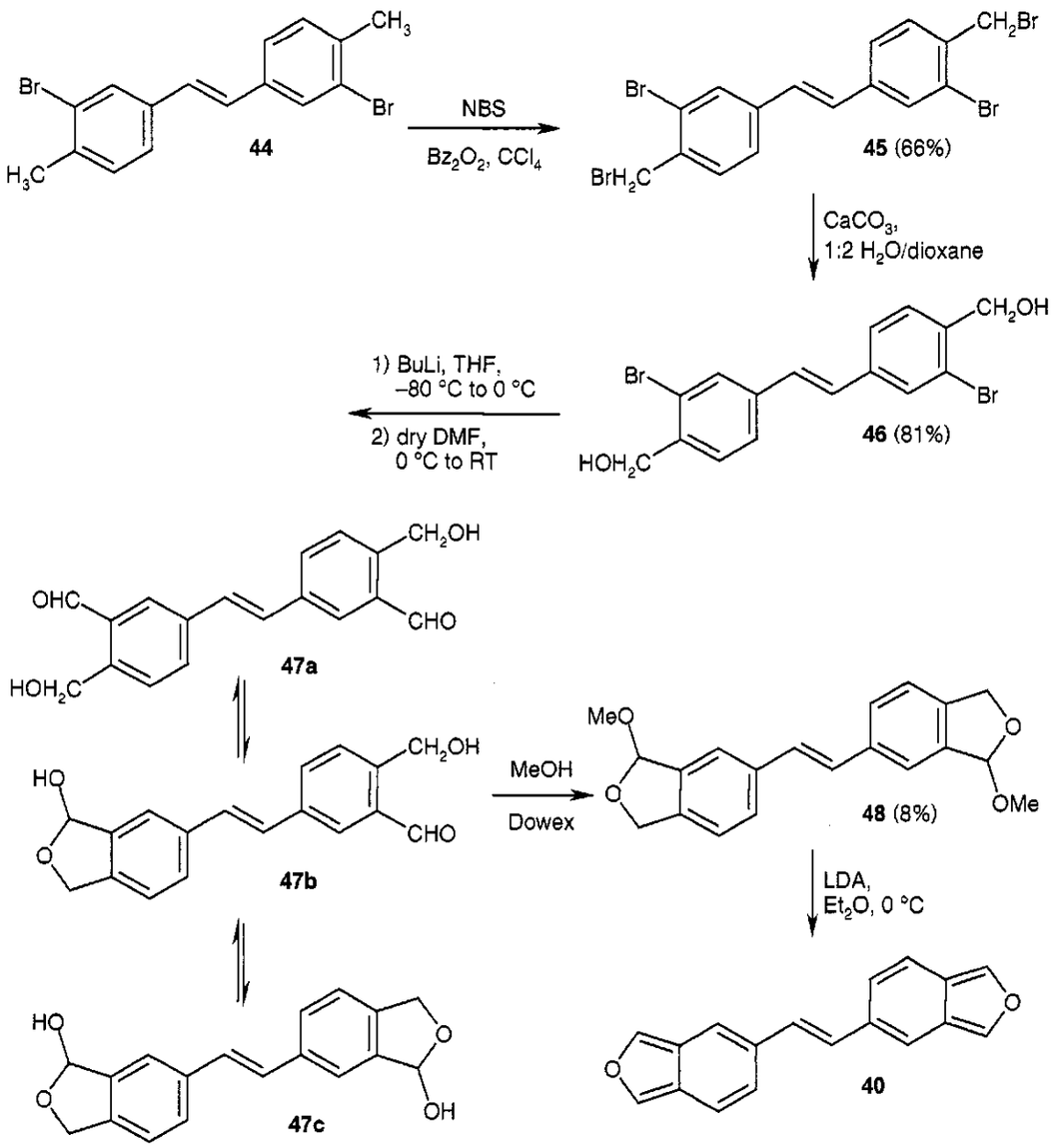


Figure 1.5: Mechanism of the Base-Catalyzed Isomerization of Stilbene

Radical bromination of **44** to give **45** and subsequent hydrolysis to afford **46** proceeded smoothly (Scheme 1.14). Metal-halogen exchange and formylation led to **47**, which existed in equilibrium as a mixture of tautomers **47a**, **47b**, and **47c**. The ^{1}H NMR spectrum was complex, not only because of the signals due to **47**, but also because the reaction did not appear to proceed cleanly. Rather than attempt a complete analysis, **47** was used directly in the next reaction. Thus, refluxing **47** with Dowex in MeOH gave bis(acetal) **48** cleanly but in low yield (based on diol **46**), most likely because of the poor results of the metalation reaction. The low yield may be due, in part, to the limited solubility of diol **46**, though one would expect that as some reacted, more would dissolve. Dibble *et al.* also found that decomposition appeared to be the only result of an attempted metalation of the dibromodiol precursor of naphtho(1,2-*c*:5,6-*c*]difuran.[31]



Scheme 1.14

To generate 1,2-bis(5-isobenzofuranyl)ethene (**40**), bis(acetal) **48** was stirred with a large excess of LDA, and a ^{1}H NMR spectrum (seen in Figure 1.6) immediately obtained. The furanoid protons, H_a and H_b, resonate at 7.99 and 8.03 ppm with a coupling constant of 1.5 Hz and slightly smaller long-range couplings of 1.3 Hz to H_c and H_e. The H_c–H_d coupling is 9.0 Hz, indicative of the polyenic nature of this bond. Difuran **40** begins to decompose within one hour, as evidenced by the small humps between 7.1 and

7.2 ppm, and 7.5 and 7.6 ppm. Two aldehyde peaks and a complex set of multiplets in the aromatic region were observed in an NMR sample that was stored at –20 °C over a weekend, indicating that hydrolysis and polymerization of **40** had occurred.

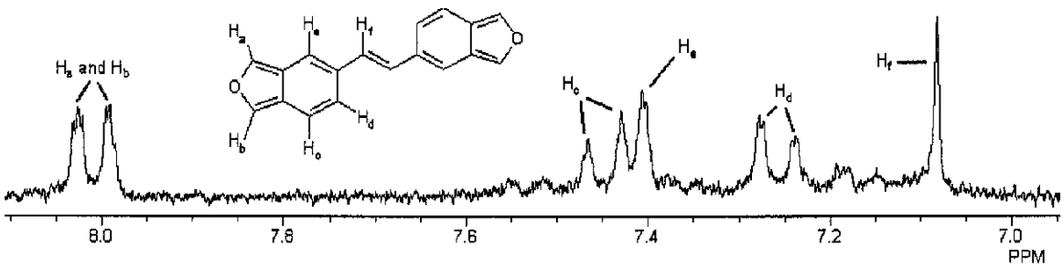


Figure 1.6: ^{1}H NMR Spectrum of 1,2-Bis(5-isobenzofuranyl)ethene (40) in CD_2Cl_2

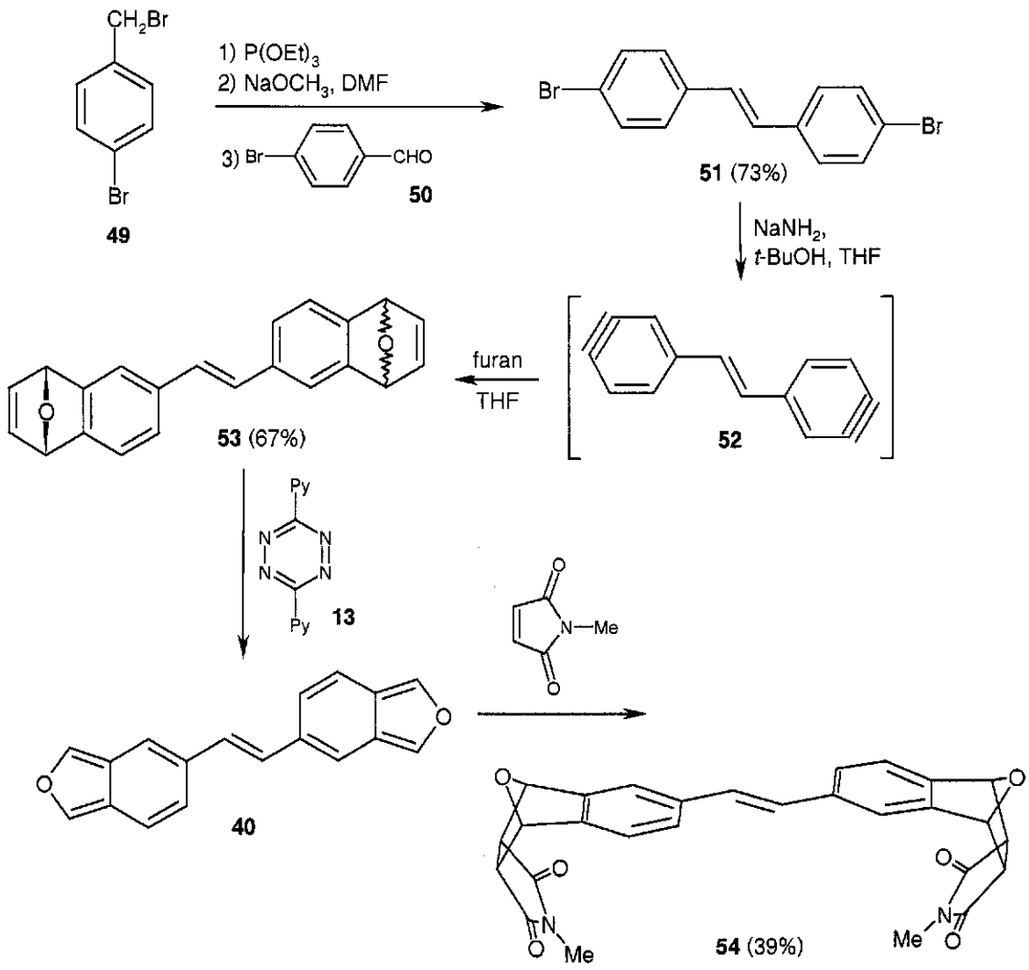
After the aliquot for ^{1}H NMR analysis was taken, an attempt was made to trap the remainder of the difuran with *N*-methylmaleimide. However, there may have been too much decomposition by this time, as no sign of adduct formation was observed.

Due to the lengthy nature of the synthesis and the low yield, in particular, of the metalation reaction, the development of an alternative synthesis of 1,2-bis(5-isobenzofuranyl)ethene was desired. The manufacture of sufficient quantities of precursor would enable the study of the utility of 1,2-bis(5-isobenzofuranyl)ethene in the synthesis of cyclophanes.

1.2.2 1,2-Bis(5-isobenzofuranyl)ethene *via* Dipytet

The alternative synthesis of 1,2-bis(5-isobenzofuranyl)ethene (**40**) is outlined in Scheme 1.15. Stilbene **51** was constructed by an Arbuzov reaction of *p*-bromobenzyl bromide (**49**) with triethyl phosphite, followed by a Wadsworth–Emmons reaction of the resultant phosphonate with *p*-bromobenzaldehyde (**50**). Dehydrobromination with Caubère's base[52] in the presence of furan[53] afforded the 1,2-bis(5-isobenzofuranyl)ethene precursor (**53**). The dehydrobromination of **51** and subsequent trapping with furan is certainly a stepwise process; however, **51** can be considered to act as the synthetic

equivalent to a bis(benzyne) intermediate (**52**). Precursor **53** could be stored with no special precautions and used as needed to generate difuran **40**.



Scheme 1.15

Two equivalents of dipytet (**13**)[23] were added to generate difuran **40**, which was subsequently trapped as its bis(*N*-methylmaleimide) adduct (**54**). Bis(adduct) **54** likely exists as a diastereomeric mixture of *syn* and *anti* bis(adduct)s; however, there is little to distinguish between the two bis(adduct)s spectroscopically. The ^{1}H NMR spectrum of **54** indicated that *endo*-addition had occurred, based on the ring junction–oxa-bridge coupling of 5.5 Hz (see Figure 1.7 for the labelling scheme). If *exo*-addition had

occurred, the dihedral angle would be about 90°, which means that little or no coupling would be observed between the ring junction and oxa-bridge protons. The ring junction protons are coincidentally chemical shift equivalent, and thus an AA'MM' pattern is approximated, rather than an ABMN pattern. The oxa-bridge protons should appear as two doublets; however, they instead appear as a broad multiplet because of second-order effects.

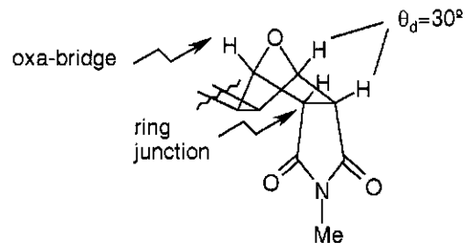


Figure 1.7: Labelling Scheme for the *endo* Adduct of Difuran 40

1.3 Summary

1,2-Bis(5-isobenzofuranyl)ethene (**40**) was prepared by two methods. The first method involved building the bis(acetal) precursor of difuran **40** from 1,2-bis(3-bromo-4-methylphenyl)ethene (stilbene **44**). The bis(acetal) was then subjected to base-induced 1,3-elimination of methanol to give difuran **40**. Difuran **40** was characterized by its ^{1}H NMR spectrum.

Due to the low yield of some intermediate steps of the above method, a more direct route was attempted. Thus, difuran precursor **53** was generated from 1,2-bis(4-bromophenyl)ethene and subsequently treated with dipytet to yield difuran **40**. Difuran **40** was trapped as its bis(*N*-methylmaleimide) adduct.

1.4 Experimental

Solvents were used without additional purification with the exception of diethyl ether and THF, both of which were distilled from sodium/benzophenone prior to use. DMF was dried by distilling it from P_2O_5 onto molecular sieves.[54,55] All organic starting materials were purchased from the Aldrich Chemical Co. unless otherwise noted. Melting points were performed in open capillaries and are uncorrected. NMR spectra were recorded on a Brüker AC-250/Tecmag Macspect NMR spectrometer at an ambient temperature of 298 K. ^{1}H NMR chemical shifts were referenced to TMS when in $CDCl_3$ or to the residual $CHDCl_2$ pentet at 5.32 ppm when in CD_2Cl_2. ^{13}C NMR chemical shifts were referenced to the $CDCl_3$ triplet at 77.23 ppm or to the CD_2Cl_2 pentet at 54.00 ppm. Infrared spectra were recorded on a Bomem MB-102 or Nicolet Avatar 360 spectrometer. Mass spectra were performed by the Mass Spectroscopy Lab, Department of Chemistry, University of Alberta. Elemental analyses were performed by M-H-W Laboratories, Phoenix, Arizona. Dipytet (**13**)[56] and aldehyde **41**[48] were synthesized according to the literature.

3-Bromo-4-methylbenzyl bromide (43): 16.32 g (0.0812 mol) of 3-bromo-4-methylbenzyl alcohol (**42**) was refluxed with 14.6 mL of concentrated HBr for 48 h. H_2O and $CHCl_3$ were added, the layers separated, and the aqueous layer washed three times with $CHCl_3$. The combined organic fractions were dried with $MgSO_4$, filtered, and the solvent removed using a rotary evaporator. Vacuum distillation yielded 15.26 g (71%) of bromide **43** as a colourless liquid. b.p. 68–69 °C (0.1 mm Hg).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.38 (s, 3H), 4.41 (s, 2H), 7.21 (m, 2H), 7.56 (d, J = 1.8 Hz, 1H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 22.8, 32.2, 125.2, 128.1, 131.3, 133.0, 137.4, 138.5.

IR (neat): 3051, 2972, 2921, 1701, 1491, 1223, 1041, 626 cm^{-1}.

Analysis calc'd for $C_8H_8Br_2$: C, 36.40; H, 3.06; found: C, 36.56; H, 3.07.

1,2-Bis(3-bromo-4-methylphenyl)ethene (44): 17.08 g (0.0647 mol) of 3-bromo-4-methylbenzyl bromide (**43**) was refluxed under nitrogen overnight with 11.2 mL (0.0653 mol) of $P(OEt)_3$. The phosphonate was allowed to cool, then added to a suspension of NaOMe (prepared by dissolving 1.74 g (0.0757 mol) of Na in MeOH and removing the excess MeOH) in 100 mL of DMF at 0 °C. 12.88 g (0.0647 mol) of 3-bromo-4-tolualdehyde (**41**) was added and the mixture stirred overnight, warming to room temperature. CH_2Cl_2 and H_2O were added, the layers separated, and the aqueous layer washed three times with CH_2Cl_2. The combined organic fractions were then washed three times with brine, dried with $MgSO_4$, filtered, and the solvent removed using a rotary evaporator. Recrystalization from EtOAc/hexanes yielded 14.93 g (63%) of **44** as fluffy white crystals. m.p. 150–152 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.40 (s, 6H), 6.95 (s, 2H), 7.21 (d, J = 8.0 Hz, 2H), 7.32 (dd, J = 8.0 Hz, J = 2.0 Hz, 2H), 7.58 (d, J = 2.0 Hz, 2H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 22.8, 125.6, 125.7, 127.9, 130.5, 131.2, 137.0, 137.6.

IR (KBr): 3060, 3003, 2978, 2949, 2919, 1653, 1598, 1541, 1495, 1448, 1392, 1251, 1228, 1036, 969, 948, 883, 820, 703, 678, 587, 441 cm^{-1}.

MS (EI) *m/e* calc'd for $C_{16}H_{14}Br_2$: 365.9442, found 365.9440; 369 (17), 368 (M^+ $^{81}Br_2$, 68), 367 (31), 366 (M^+ $^{81}Br^{79}Br$, 100), 365 (17), 364 (M^+ $^{79}Br_2$, 68), 272 (18), 270 (17), 207 (16), 206 (73), 205 (27), 202 (11), 191 (36), 190 (19), 189 (34), 115 (10), 103 (19), 102 (15), 89 (11).

Analysis calc'd for $C_{16}H_{14}Br_2$: C, 52.49; H, 3.85; found: C, 52.64; H, 4.00.

1,2-Bis(3-bromo-4-(bromomethyl)phenyl)ethene (45): 7.024 g (0.0192 mol) of stilbene **44**, 6.868 g (0.0386 mol) of NBS, a few crystals of benzoyl peroxide, and 100 mL of CCl_4 were refluxed for 2 d. After cooling, CH_2Cl_2 was added to dissolve the solid (heating necessary), and then the organic layer was washed three times with saturated aqueous $NaHCO_3$, dried with $MgSO_4$, filtered, and the solvent removed. Recrystalization from EtOAc/hexanes yielded 6.68 g (66%) of **45** as pale yellow fluffy needles. m.p. 213–216 °C.

^1H NMR (250 MHz, $CDCl_3$): δ = 4.62 (s, 4H), 7.02 (s, 2H), 7.41 and 7.45 (AB, J = 8.0 Hz, 4H), 7.72 (d, J = 1.5 Hz, 2H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 33.2, 125.2, 126.4, 128.9, 131.6, 131.8, 137.0, 139.2.

IR (KBr): 3047, 2976, 1596, 1494, 1214, 1196, 1037, 621, 560 cm^{-1}.

MS (EI) *m/e* calc'd for $C_{16}H_{12}Br_4$: 523.8900, found 523.7634; 528 (M^+ $^{81}Br_4$, 3), 526 (M^+ $^{81}Br_3{}^{79}Br$, 13), 524 (M^+ $^{81}Br_2{}^{79}Br_2$, 20), 522 (M^+ $^{81}Br^{79}Br_3$, 13), 520 (M^+ $^{79}Br_4$, 3), 447 (33), 446 (20), 445 (99), 444 (21), 443 (100), 441 (34), 367 (10), 366 (28), 365 (23), 364 (58), 363 (12), 362 (28), 204 (15), 203 (22), 202 (33), 189 (16), 101 (17), 82 (16), 80 (17).

Analysis calc'd for $C_{16}H_{12}Br_4$: C, 36.68; H, 2.31; found: C, 36.89; H, 2.29.

1,2-Bis(3-bromo-4-(hydroxymethyl)phenyl)ethene (46): 2.053 g (3.92 mmol) of tetrabromide **45**, 3.14 g (31.4 mmol) of $CaCO_3$, 30 mL of H_2O, and 60 mL of 1,4-dioxane were refluxed for 3 d. The dioxane was removed using a rotary evaporator, then EtOAc and 6 M HCl were added to dissolve the solid and the layers separated. The aqueous layer was washed three times with EtOAc, and then the combined organic fractions were washed three times with saturated aqueous $NaHCO_3$, dried with $MgSO_4$, filtered, and the EtOAc removed. Recrystalization from MeOH yielded 1.264 g (81%) of **46** as a pale yellow powder. m.p. 169–172 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.98 (br t, 2H), 4.77 (d, J = 5.8 Hz, 4H), 7.03 (s, 2H), 7.47 (d, J = 2.5 Hz, 4H), 7.71 (s, 2H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 65.2, 123.3, 126.2, 128.5, 129.4, 130.8, 138.5, 139.6.

IR (KBr): 3417, 2921, 1635, 1601, 1402, 1056, 1025, 964 cm^{-1}.

MS (EI) *m/e* calc'd for $C_{16}H_{14}Br_2O_2$: 398.0968, found 397.9338; 400 (M^+ $^{81}Br_2$, 47), 399 (18), 398 (M^+ $^{81}Br^{79}Br$, 100), 397 (12), 396 (M^+ $^{79}Br_2$, 61), 192 (16), 191 (23), 189 (14), 180 (28), 179 (18), 178 (29), 176 (11).

Analysis calc'd for $C_{16}H_{14}Br_2O_2$: C, 48.27; H, 3.55; found: C, 48.19; H, 3.72.

1,2-Bis(1,3-dihydro-3-hydroxy(5-isobenzofuranyl))ethene (47): 1.491 g (3.75 mmol) of diol **46** was dissolved in 60 mL of dry THF under nitrogen and then cooled to –80 °C. BuLi (12.0 mL of a 2.5 M solution in hexanes, 30.0 mmol) was added and the mixture stirred at –80 °C for 15 min, then warmed to 0 °C and stirred for another 30 min. Dry DMF (2.32 mL, 30.0 mmol) was added and the mixture warmed to room temperature

overnight. The reaction was quenched with brine, the layers separated, and the aqueous layer washed three times with THF. The combined organic extracts were then washed three times with brine, dried with $MgSO_4$, filtered, and the solvent and residual DMF removed to give a yellow solid. Bis(hemiacetal) **47** was used immediately without further purification.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.71 (s), 4.85 (s), 4.86 (s), 5.02 (s), 5.06 (s), 5.27 (d, J = 13.8 Hz), 6.01 (s), 6.51 (s), 6.98 (s), 7.10 to 7.73 (m), 9.37 (s), 10.14 (s).

1,2-Bis(1,3-dihydro-3-methoxy(5-isobenzofuranyl))ethene (48): Bis(hemiacetal) **47** and 687 mg Dowex 50WX8-100 ion-exchange resin were stirred in 100 mL MeOH and refluxed overnight. The mixture was filtered hot to remove the Dowex, then the solvent was removed and bis(acetal) **48** recrystalized from clean MeOH to yield 93 mg (8% from diol **46**) of yellow-orange crystals. m.p. 188–191 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.47 (s, 6H), 5.06 and 5.22 (AB, J = 13.0 Hz, 4H), 6.20 (d, J = 2.0 Hz, 2H), 7.16 (s, 2H), 7.26 (d, J = 7.8 Hz, 2H), 7.50 (d, J = 7.8 Hz, 2H), 7.56 (s, 2H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 54.5, 72.5, 107.8, 121.0, 121.6, 128.3, 128.9, 137.6, 138.7, 139.9.

IR (KBr): 3007, 2924, 2876, 2852, 1626, 1497, 1462, 1443, 1379, 1084, 1020, 1006, 966, 942, 817 cm^{-1}.

1,2-Bis(5-isobenzofuranyl)ethene (40): Acetal **48** (52 mg, 0.16 mmol) was dissolved in 40 mL of dry diethyl ether and cooled to 0 °C under nitrogen. LDA (0.80 mL of 2.0 M

solution in heptane/THF/ethylbenzene, 1.6 mmol) was added and the mixture stirred for 10 min. The reaction was quenched with water and the ether layer concentrated to leave a yellow solid that fluoresced blue under UV light.

^{1}H NMR (250 MHz, CD_2Cl_2): δ = 7.08 (s, 2H), 7.26 (dd, J = 9.0 Hz, J = 1.3 Hz, 2H), 7.40 (d, J = 1.3 Hz, 2H), 7.45 (dd, J = 9.0 Hz, J = 1.3 Hz, 2H), 7.99 (dd, J = 1.5 Hz, J = 1.3 Hz, 2H), 8.03 (dd, J = 1.5 Hz, J = 1.3 Hz, 2H).

1,2-Bis(4-bromophenyl)ethene (51): 2.065 g (8.26 mmol) of *p*-bromobenzyl bromide (**49**) and 1.50 mL (8.75 mmol) of $P(OEt)_3$ were refluxed under nitrogen for 1 h. The phosphonate was allowed to cool, then added to a suspension of NaOMe (prepared by dissolving 0.458 g (19.9 mmol) of Na in MeOH and removing the excess MeOH) in 50 mL of DMF at 0 °C. 1.566 g (8.46 mmol) of 4-bromobenzaldehyde (**50**) was added and the mixture stirred overnight, warming to room temperature. CH_2Cl_2 and H_2O were added, the layers separated, and the aqueous layer washed three times with CH_2Cl_2. The combined organic fractions were then washed twice with brine, dried with $MgSO_4$, filtered, and the solvent removed. Recrystalization from toluene yielded 2.049 g (73%) of stilbene **51** as white iridescent flakes. m.p. 211–213 °C. (lit. 215–216 °C).[57]

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.02 (s, 2H), 7.36 and 7.48 (AA'BB', J = 8.5 Hz, 8H).

1,2-Bis(5-isobenzofuranyl)ethene precursor (53): 7.50 mL (78 mmol) of *t*-BuOH was mixed with 10 mL of dry THF and added slowly via syringe to a suspension of 7.02 g (180 mmol) $NaNH_2$ in 10 mL dry THF. The mixture was stirred for 1 h at room temperature. Meanwhile, 2.094 g (6.19 mmol) of 1,2-bis(4-bromophenyl)ethene (**51**) was

dissolved in 20 mL furan and 100 mL THF. The dibromide mixture was added to the $NaNH_2$ mixture and stirred for 1.5 h. During this time, the colour changed from orange to brown. The mixture was poured slowly over ice water to quench it and the flask rinsed carefully with water. The layers were separated and the aqueous layer extracted several times with ether, and then the combined ether extracts were washed twice with brine, dried with $MgSO_4$, filtered, and the solvent removed. Recrystalization from toluene/hexanes yielded 1.291 g (67%) of **53** as a yellow powder. m.p. 163–165 °C (dec).

^1H NMR (250 MHz, $CDCl_3$): δ = 5.72 (d, J = 3.0 Hz, 4H), 7.02 (d, J = 3.0 Hz, 4H), 7.03 (s, 2H), 7.03 and 7.22 (AB, J = 7.0 Hz, 4H), 7.47 (s, 2H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 82.5, 82.6, 118.0, 120.6, 124.5, 128.6, 135.1, 143.0, 143.1, 148.6, 150.0.

IR (KBr): 3011, 2925, 1616, 1597, 1515, 1280, 988, 963, 869, 849, 835, 694 cm^{-1}.

MS (EI) *m/e* calc'd for $C_{22}H_{16}O_2$: 312.3716, found 312.1149; 313 (24), 312 (M^+, 100), 286 (38), 261 (17), 260 (20), 258 (21), 256 (10), 255 (14), 253 (16), 252 (18), 241 (10), 240 (15), 239 (24), 229 (22), 228 (15), 227 (15), 226 (16), 215 (19), 202 (17), 189 (10), 115 (15).

Analysis calc'd for $C_{22}H_{16}O_2$: C, 84.58; H, 5.17; found: C, 84.38; H, 5.45.

1,2-Bis(5-isobenzofuranyl)ethene, bis(*N*-methylmaleimide) adduct (54): 207 mg (0.663 mmol) of precursor **53** and 20 mL CH_2Cl_2 were stirred under nitrogen. 317 mg (1.34 mmol) of dipytet (**13**) was added and the mixture stirred for 1.5 h at room temperature. 151 mg (1.36 mmol) of *N*-methylmaleimide was added and the mixture stirred overnight. The reaction was washed repeatedly with 1 M HCl until the CH_2Cl_2

layer was orange, and then once with brine, dried with $MgSO_4$, filtered, and the CH_2Cl_2 removed. Recrystalization from EtOAc/hexanes yielded 124 mg (39%) of **54** as a yellow powder. m.p. dec > 192 °C.

^1H NMR (250 MHz, $CDCl_3$): δ = 2.32 (s, 6H), 3.78 (AB of ABMN, m, $^3J_{AB}$ = 8.0 Hz, $^3J_{AM} = {}^3J_{BN}$ = 5.5 Hz, 4H), 5.73 (MN of ABMN, m, 4H), 7.02 (s, 2H), 7.27 and 7.32 (AB, J = 10.3 Hz, 4H), 7.42 (s, 2H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 24.2, 49.0, 49.1, 80.6, 80.7, 118.6, 118.7, 121.4, 127.1, 127.2, 129.1, 129.2, 137.5, 137.6, 140.5, 140.6, 141.8, 174.4, 174.5, 174.6.

IR (KBr): 3020, 2954, 2925, 2856, 1773, 1700, 1434, 1382, 1288, 1131, 984, 858 cm^{-1}.

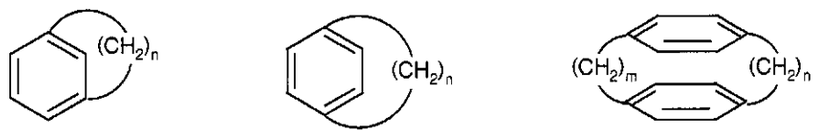
Analysis calc'd for $C_{28}H_{22}N_2O_6$: C, 69.69; H, 4.60; found: C, 69.54; H, 4.86.

Chapter 2 The Utility of Isobenzofurans in Cyclophane Formation

2.1 Cyclophane Syntheses: Naphthalenophanes, Stilbenophanes, and the Use of Isobenzofurans in Cyclophane Chemistry

2.1.1 A Brief Introduction to Cyclophanes

Cyclophanes are a very large class of molecules that incorporate an aromatic system bridged by an aliphatic subunit. The simplest cyclophanes are merely benzene rings tethered by a polymethylene chain at the *meta*- or *para*-positions (**55** and **56**, Figure 2.1). Heteroatoms can be incorporated in the tether or aromatic rings, as can other functional groups. Two benzene rings can be linked by two or more tethers, yielding multi-bridged cyclophanes. Several cyclophane units can also be linked to form multi-layered cyclophanes. There is a vast amount of interest in cyclophanes because of their non-planarity, anomalous bond lengths and angles, unique electronic properties, and stereochemistry. They are used as building blocks in more extended systems,[58] in host-guest chemistry,[59] and have recently been used for asymmetric catalysis[60] and natural product synthesis.[61]



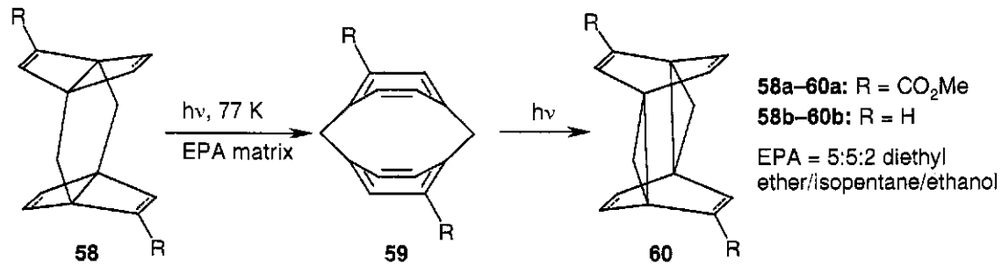
55 **56** **57**

Figure 2.1: [*n*]Meta- (55) and [*n*]Para- (56), and [*m.n*]Paracyclophane (57)

Cram established the modern field of cyclophane chemistry with his report of the synthesis of several [*m.n*]paracyclophanes (**57**) in 1951.[62] Much of his early work on the synthesis, structures, ring rotation, and reactions of [*m.n*]paracyclophanes is summarized in a review article he wrote twenty years later.[63] Along with the books by Hopf[58] and

Diederich,[59] several other reviews have been published that, taken together, provide a very comprehensive treatment of cyclophanes and their chemistry.[64-74] It is to these articles that the reader is referred for background on [*n*]cyclophanes and [*m.n*]cyclophanes, as only two recent examples will be discussed here.

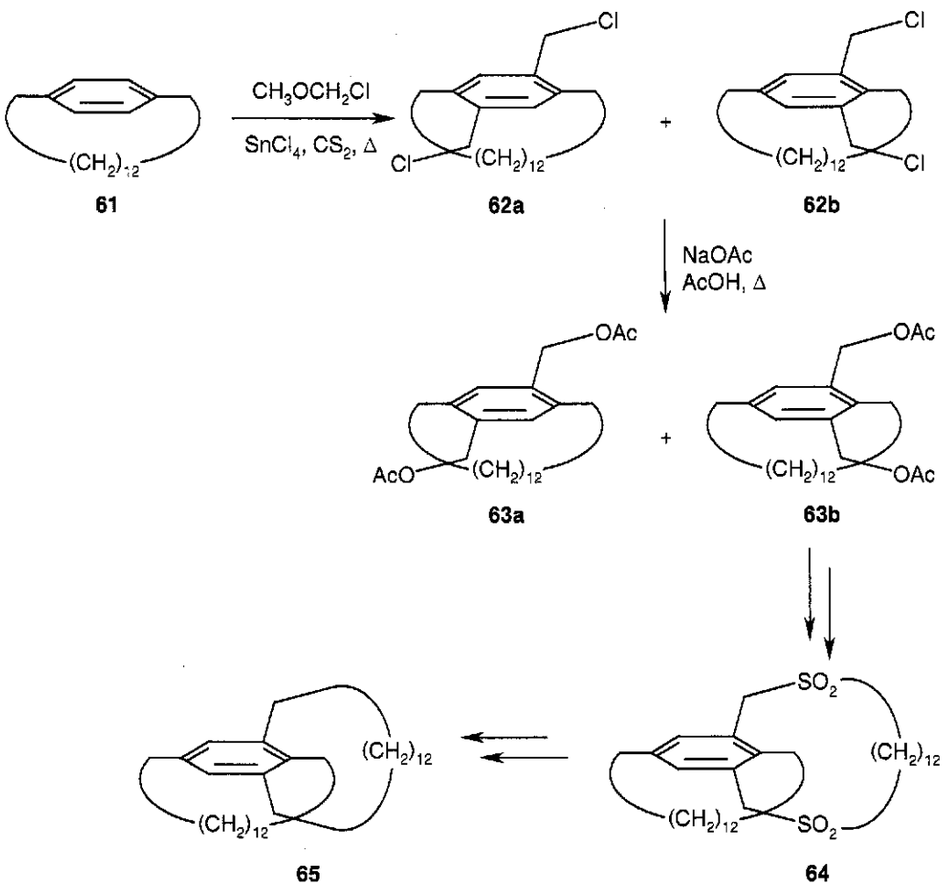
The synthesis of the bis(methoxycarbonyl) derivative of the most strained [*m.n*]paracyclophane, [1.1]paracyclophane has been reported.[75] Bis(Dewar benzene) **58a** was irradiated with 254 nm light to yield the unstable [1.1]paracyclophane derivative **59a** (see Scheme 2.1). Further irradiation with > 390 nm light gave **60a**. The authors succeeded a few years later in generating the parent [1.1]paracyclophane **59b** from the corresponding bis(Dewar benzene) **58b**.[76] Again, further irradiation with > 335 nm light led to **60b**. The [1.1]paracyclophanes were characterized by their UV/vis and ^{1}H NMR spectra at low temperatures, as they readily decomposed at room temperature. Calculations indicated that the benzene rings in **59** are bent into a boat formation and that the shortest transannular distance in [1.1]paracyclophane is 2.36–2.40 Å, 0.60 Å less than in [2.2]paracyclophane (3.09 Å),[62] and 1.0 Å shorter than the inter-layer distance in graphite (3.35 Å).



Scheme 2.1

Scheme 2.2 outlines the synthesis of the first example of an [*m*][*n*]metaparacyclophane, [14][14]metaparacyclophane (**65**).[77] The authors bis(chloromethylated) [14]paracyclophane (**61**), converted the dichlorides (**62a** and **62b**)

into diacetates (**63a** and **63b**), and separated the major *para-para* isomer (**63a**) from the minor *meta-para* isomer (**63b**). The *meta-para* isomer was elaborated to the disulphone (**64**), which was then subjected to sulphur dioxide extrusion to yield a 1,13-diene. Hydrogenation gave [14][14]metaparacyclophane (**65**).



Scheme 2.2

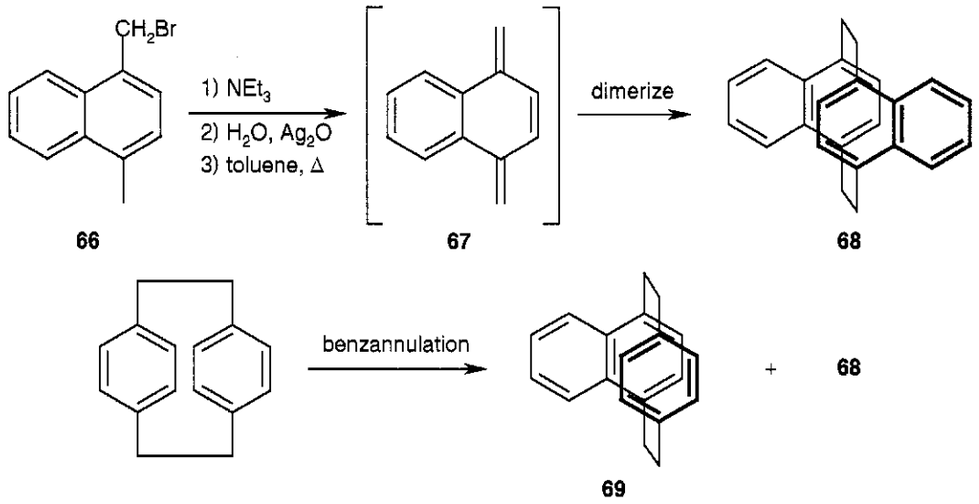
The above syntheses conclude a brief introduction to cyclophanes consisting only of benzene rings and one or more aliphatic bridges. The syntheses of naphthalenophanes and stilbenophanes, and a brief review of the use of isobenzofuran to generate cyclophanes will be discussed in the remainder of this section.

2.1.2 Naphthalenophanes

Naphthalenophanes can be bridged across one or both aromatic rings. The simple [*n*](1,3)- and [*n*](1,4)naphthalenophanes can be regarded as being merely benzannulated meta- and paracyclophanes and will not be discussed, as they have been adequately reviewed elsewhere.[65,66,69-71,73,74] This section will therefore focus on [*m.n*]naphthalenophanes. A discussion of [*m.n*](1,4)naphthalenophanes is included, but the bulk of this section will focus on those systems that are bridged across both rings. Additionally, the majority of naphthalenophanes synthesized have been [2.2]phanes, as the transannular electronic interactions are maximized in these systems. However, many of the synthetic methods developed are readily applicable to larger systems.

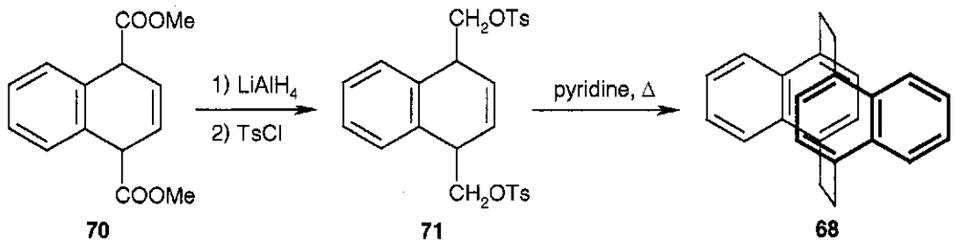
2.1.2.1 [*m.n*](1,4)Naphthalenophanes

Cram was the first to synthesize [2.2](1,4)naphthalenophane (**68**). He transformed 1-bromomethyl-4-methylnaphthalene (**66**) into its trimethylammonium salt and converted the counter-ion from Br^- to OH^- with Ag_2O. Subsequent heating in toluene formed the intermediate benzo-1,4-xylylene (**67**), which dimerized to give **68** (see Scheme 2.3) in 3% yield. To confirm that **68** had formed as its *anti* isomer, Cram benzannulated [2.2]paracyclophane, since the benzannulation procedure could only result in the formation of *anti*-**68**.[78] The benzannulation method resulted in a 0.07% yield of *anti*-**68**. [2]Paracyclo[2](1,4)naphthalenoparacyclophane (**69**) was also obtained as a by-product of the benzannulation.



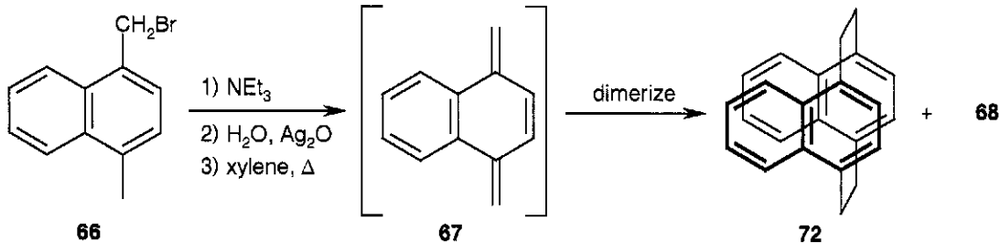
Scheme 2.3

Brown and Sondheimer improved the yield of **68** to 90% by reducing 1,4-dihydro-1,4-bis(methoxycarbonyl)naphthalene (**70**) and converting the diol to the tosylate (**71**). Solvolysis of **71** in pyridine yielded **68**, presumably *via* a xylylene intermediate (**67**) (Scheme 2.4).[79]



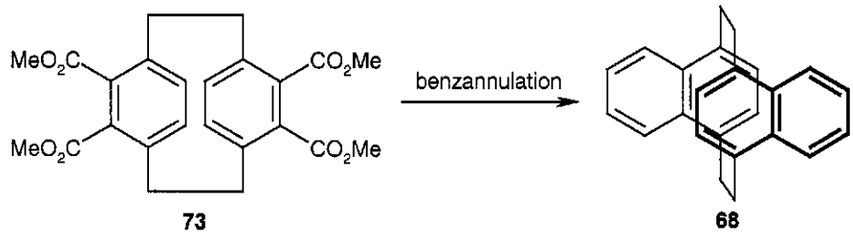
Scheme 2.4

Wasserman and Keehn succeeded in isolating *syn*-[2.2](1,4)naphthalenophane (**72**) in 4.1% yield a few years later. They also obtained a 41% yield of *anti*-[2.2](1,4)naphthalenophane (**68**). Cram's methodology[78] was employed, except xylene was used as the solvent instead of toluene (Scheme 2.5).[80] The authors found that the *syn* and *anti* isomers were interconvertible by thermal and photochemical means.



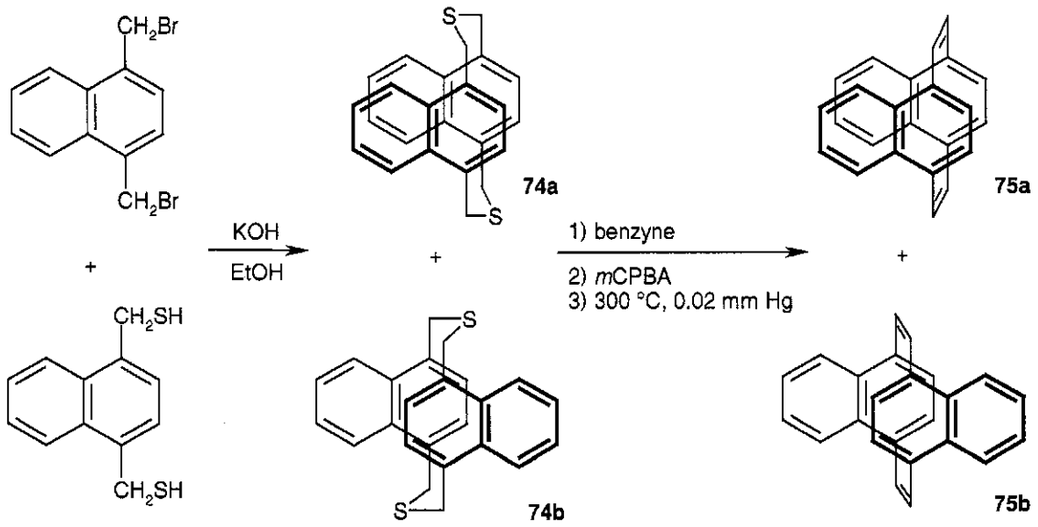
Scheme 2.5

Kleinschroth and Hopf also synthesized **68** from 4,5,12,13-tetrakis(methoxycarbonyl)[2.2]paracyclophane (**73**) by a lengthy benzannulation procedure (Scheme 2.6).[81]



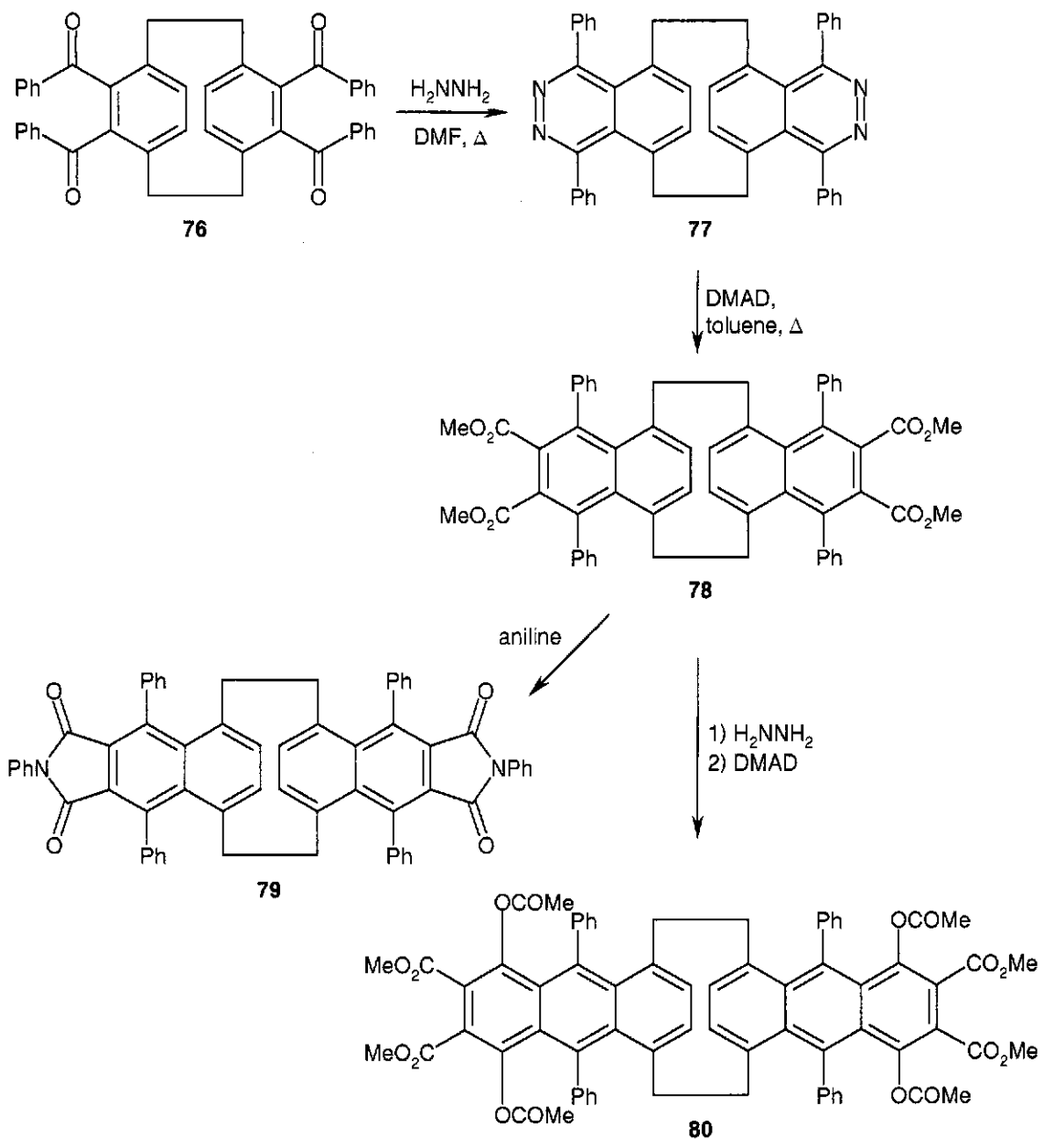
Scheme 2.6

[2.2]Paracyclophane dienes have been of interest because they are formally conjugated but orbitally unconjugated since the π-orbitals of the double bonds are orthogonal to the π-orbitals of the aromatic system.[82] Otsubo and Boekelheide synthesized *syn*- and *anti*-[2.2](1,4)naphthalenophane-1,13-diene (**75a** and **75b**, respectively), with the eventual goal of comparing the physical and chemical properties of *syn*- and *anti*-[2.2](1,4)naphthalenophane without the possibility of thermal interconversion.[83] They coupled together 1,4-bis(bromomethyl)naphthalene and 1,4-bis(thiomethyl)naphthalene to yield the *syn* and *anti* isomers of 2,13-dithia[3.3](1,4)naphthalenophane (**74a** and **74b**, respectively). Reaction of each isomer with benzyne in a benzyne–Stevens rearrangement, oxidation with *m*CPBA, and subsequent pyrolysis gave pure **75a** and **75b** (see Scheme 2.7).



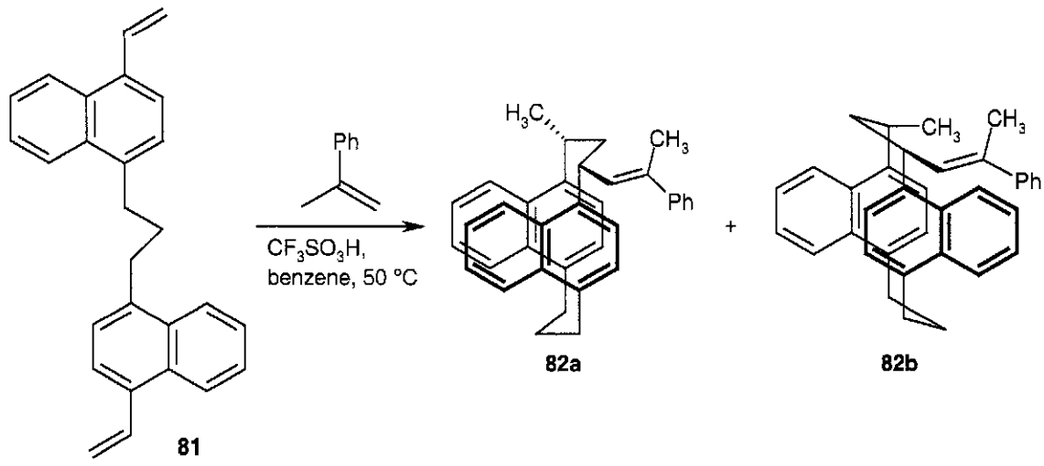
Scheme 2.7

A novel synthesis of (1,4)naphthalenophanes has appeared recently.[84] The synthesis of one of them, *syn*-5,6,15,16-tetrakis(methoxycarbonyl)-4,7,14,17-tetraphenyl[2.2](1,4)naphthalenophane (**78**) is outlined in Scheme 2.8. Tetra-substituted [2.2]paracyclophane (**76**) was heated with hydrazine to yield the [2.2]phthalazinophane **77**. Reaction of **77** with DMAD yielded **78**. Compound **78** could be further derivatized with aniline to give **79** or extended to an anthracenophanic system (**80**) by another reaction with hydrazine and DMAD.



Scheme 2.8

Larger [*m.n*]naphthalenophanes have been synthesized, as well. Nishimura employed cationic cyclocodimerization to generate derivatives of [3.3](1,4)naphthalenophane and [3]paracyclo[3](1,4)naphthalenophane, as outlined in Scheme 2.9.[85] For example, 1,3-bis(4-vinylnaphthyl)propane (**81**) was stirred with 2-phenylpropane in a CF_3SO_3H/benzene solution to yield substituted *syn*- and *anti*-[3.3](1,4)naphthalenophanes (**82a** and **82b**, respectively).

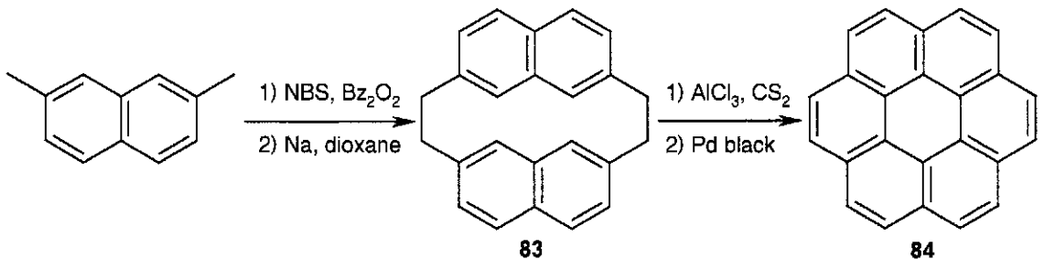


Scheme 2.9

2.1.2.2 [*m.n*]Naphthalenophanes Bridged at Positions Other than (1,4)

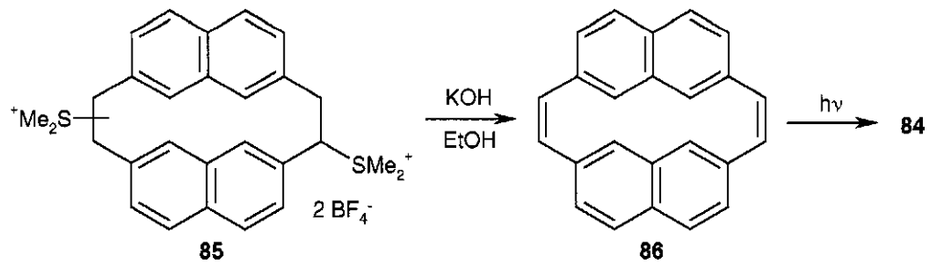
2.1.2.2.1 [2.2](2,7)Naphthalenophane

The first synthesis of [2.2](2,7)naphthalenophane (or of any naphthalenophane, for that matter) was reported in 1951 as part of a synthesis of coronene.[86] The procedure is outlined in Scheme 2.10. Bromination of 2,7-dimethylnaphthalene followed by Wurtz coupling gave [2.2](2,7)naphthalenophane (**83**) in 16.3% yield. Cyclodehydrogenation of **83** led to coronene (**84**). The yield of **83** was later improved to 20% by the use of phenyllithium instead of sodium metal.[87]



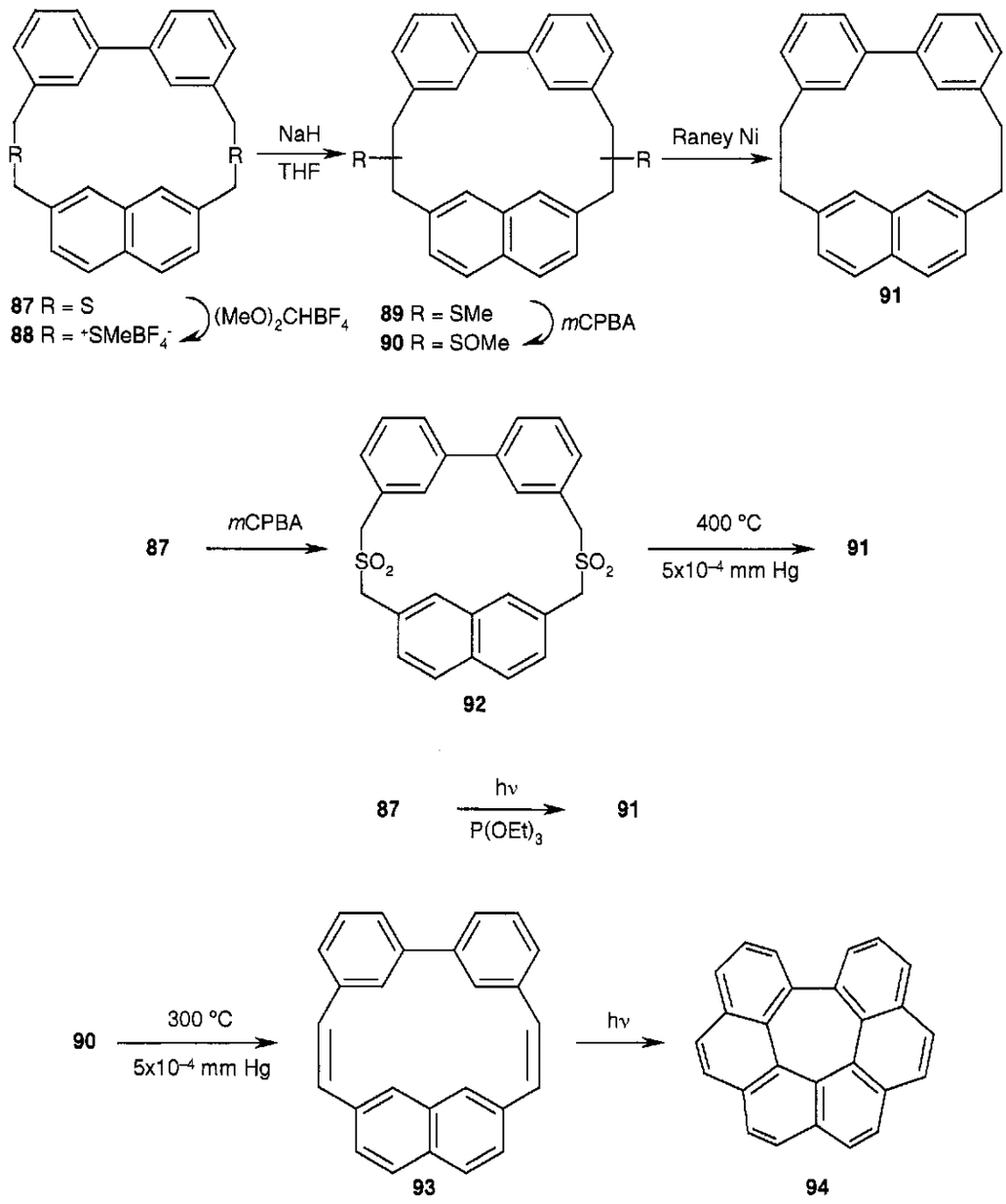
Scheme 2.10

The synthesis of [2.2](2,7)naphthalenophane-1,11-diene (**86**) is outlined in Scheme 2.11.[88,89] Base-induced elimination of dimethyl sulphide from **85** gave **86**, which yielded coronene (**84**) upon photocyclization.



Scheme 2.11

Two biphenyl naphthalenophanes, [2](3,3')biphenylo[2](2,7)naphthalenophane (**91**) and [2](3,3')biphenylo[2](2,7)naphthalenophane-1,11-diene (**93**), were synthesized by several methods.[90] Scheme 2.12 outlines those methods, and summarizes, in general, several commonly used procedures for generating cyclophanes. In the first synthesis of **91**, 2,13-dithia[3](3,3')biphenylo[3](2,7)naphthalenophane (**87**) was obtained by a base-induced coupling of 3,3'-bis(bromomethyl)biphenyl and 2,7-bis(thiomethyl)naphthalene. Reaction of **87** with Borch reagent gave **88**, which underwent a Stevens rearrangement upon reaction with NaH to afford **89**. Oxidation with *m*CPBA yielded **90**, which was subsequently hydrogenolyzed to [2](3,3')biphenylo[2](2,7)naphthalenophane (**91**) by Raney nickel. In the second synthesis, **87** was oxidized by *m*CPBA to the disulphone **92**, which was then vacuum pyrolysed to **91**. Finally, **87** could be subjected to photochemical extrusion of sulphur in triethyl phosphite to yield **91**.

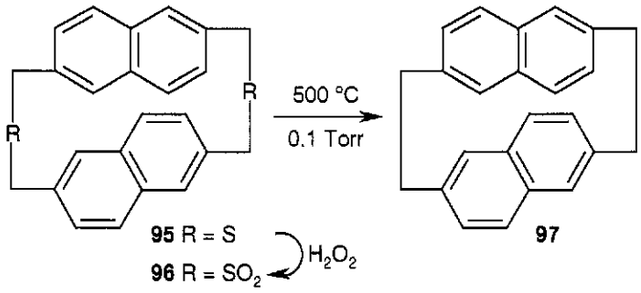


Scheme 2.12

[2](3,3')Biphenylo[2](2,7)naphthalenophane-1,11-diene (**93**) was obtained by vacuum pyrolysis of **90**. It was then photocyclized to hexa[7]circulene (**94**), illustrating the utility of cyclophanes in the synthesis of polycyclic aromatic hydrocarbons.

2.1.2.2.2 [2.2](2,6)Naphthalenophane

Haenel and Staab synthesized [2.2](2,6)naphthalenophane (**97**) through a coupling reaction of 2,6-bis(bromomethyl)naphthalene and 2,6-bis(thiomethyl)naphthalene, followed by oxidation of the dithia compound (**95**) to the disulphone (**96**) and then vacuum pyrolysis to give **97** (see Scheme 2.13).[91] The same authors also reported the synthesis of [2.2](2,6)naphthalenophane-1,11-diene (**98**, Figure 2.2) from **95** *via* the Stevens rearrangement, methylation, and subsequent base-induced elimination of dimethyl sulphide.[92] Naphthalenophane **97** and its diene **98** apparently form as their chiral twisted isomers (the point group for both is D_2), as the achiral symmetrical isomers (**99** and **100**, point group C_{2h}, Figure 2.2) were not observed.



Scheme 2.13

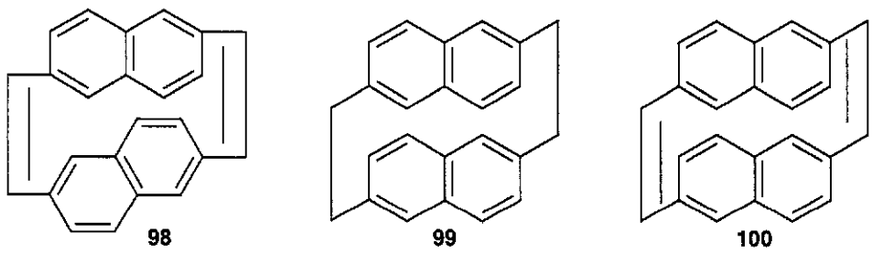
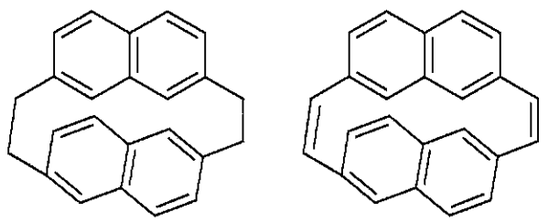


Figure 2.2: [2.2](2,6)Naphthalenophane-1,11-diene (98) and the Achiral Isomers of 97 and 98 (99 and 100, Respectively)

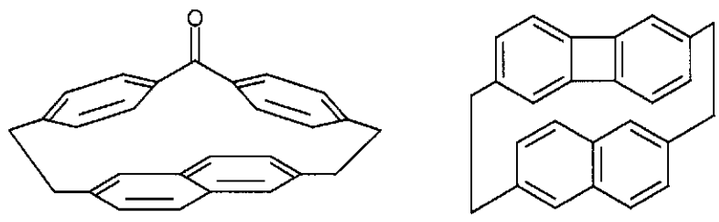
Syntheses of the mixed [2.2](2,6,2',7')naphthalenophane and its 1,11-diene (**101** and **102**, Figure 2.3) have been reported.[93,94] Both compounds undergo ring-flipping, with the diene having a much lower energy barrier than the saturated compound.



101 **102**

Figure 2.3: [2.2](2,6,2',7')Naphthalenophane and Its 1,11-Diene (101 and 102)

Other interesting mixed naphthalenophanes that have been synthesized include [2](4,4')benzophenono[2](2,6)naphthalenophane and [2](2,6)biphenyleno[2](2,6)naphthalenophane (**103** and **104**, Figure 2.4). Naphthalenophane **103** was synthesized from 2,6-bis(thiomethyl)naphthalene and 4,4'-bis(bromomethyl)benzophenone. The resultant [3.3]dithia cyclophane was oxidized to the disulphone and subjected to photochemical extrusion of SO_2 to give **103**.[95] Naphthalenophane **104** was synthesized from 2,6-bis(bromomethyl)biphenylene and 2,6-bis(thiomethyl)naphthalene. The resultant [3.3]dithia cyclophane was irradiated directly to give **104**.[96]

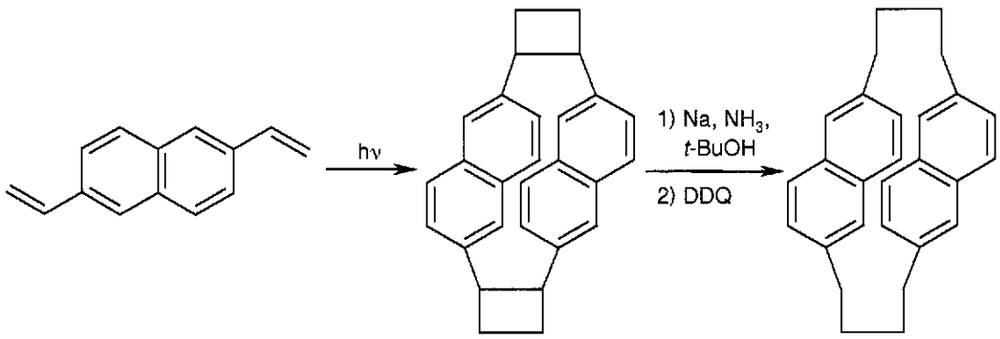


103 **104**

Figure 2.4: [2](4,4')Benzophenono[2](2,6)naphthalenophane (103) and [2](2,6)Biphenyleno[2](2,6)naphthalenophane (104)

2.1.2.2.3 Cyclobutane-fused [2.2]Naphthalenophanes

Nishimura's group has synthesized several cyclobutane-fused naphthalenophanes from [2+2] photocycloadditions of divinylnaphthalenes.[97] In all cases, only the *syn*-phanes were produced, in marked contrast to previously described methods that generally gave only the *anti*-phanes or mixtures of *syn*- and *anti*-phanes. Of particular interest is the dimerization of 2,6-divinylnaphthalene to the bis(cyclobutano)[2.2]naphthalenophane **105**, which was then subjected to Birch reduction and DDQ oxidation to yield [4.4](2,6)naphthalenophane (**106**, see Scheme 2.14).



105 **106**

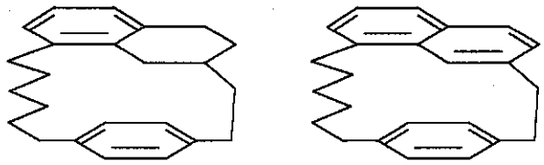
Scheme 2.14

When mixtures of divinylnaphthalenes (i.e. (1,6)- and (1,7)divinylnaphthalene, (2,6)- and (2,7)divinylnaphthalene, etc.) were irradiated, only homoadducts were formed. No reason was given for why cross-adducts were not observed.

The [2+2] photocycloaddition methodology has been applied to several other cyclophanic systems and is summarized in a recent review article.[98]

2.1.2.2.4 [*m.n*]Naphthalenoparacyclophanes

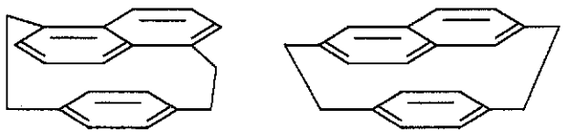
During the synthesis of [6.6]paracyclophane, Cram obtained a minor product that was identified as **107** (see Figure 2.5). The aromatic rings were hydrogenated and then dehydrogenated to give [6.2](1,7)naphthalenoparacyclophane (**108**).[99]



107 108

Figure 2.5: [6.2](1,7)Naphthalenoparacyclophane (108) and Its Precursor (107)

[2.2](1,5)Naphthalenoparacyclophane (**109**) and [2.2](2,6)naphthalenoparacyclophane (**110**) (Figure 2.6) were obtained from their [3.3]dithia cyclophane analogues by photochemical extrusion of the sulphur atoms in triethyl phosphite.[100] [2.2](2,6)Naphthalenoparacyclophane (**110**) was also obtained by vacuum pyrolysis of its [3.3]disulphone.



109 110

Figure 2.6: [2.2](1,5)Naphthalenoparacyclophane (109) and

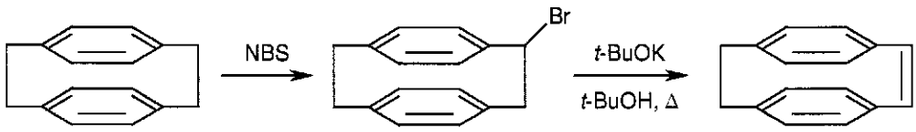
[2.2](2,6)Naphthalenoparacyclophane (110)

2.1.3 Stilbenophanes

It appears that stilbenophanes have not been a direct synthetic goal of many groups. Rather, mono- or di-olefinic cyclophanes (i.e., the cyclophane dienes) have been synthesized as part of larger studies on the interactions between the bridged aromatic rings. Some stilbenophanes have been synthesized in which the stilbene moiety is attached to the cyclophane as a substituent;[101] however, since it is not the stilbene unit that is being bridged, such examples will not be discussed. Nonetheless, there are a few isolated reports of stilbenophane-type compounds that are bridged across both rings.

The first stilbenophane synthesized was the mono-olefin of [2.2]paracyclophane (**112**).[82] NBS bromination of [2.2]paracyclophane gave 1-bromo[2.2]paracyclophane

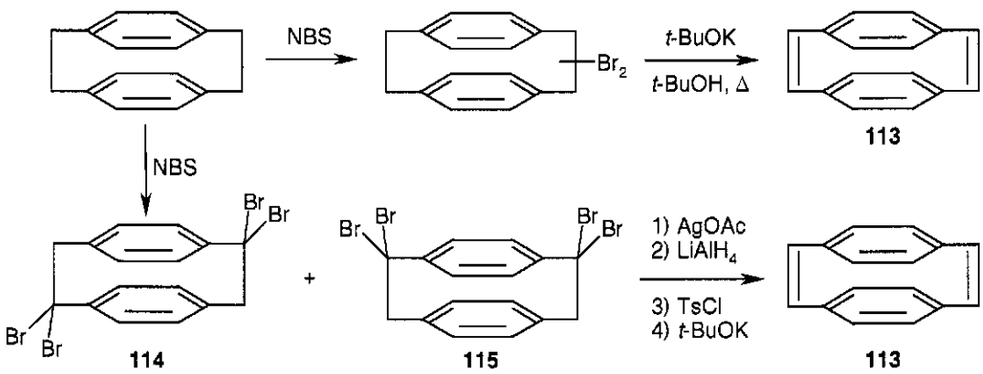
(**111**), which was subsequently dehydrobrominated to yield **112** (Scheme 2.15). The double bond in [2.2]paracyclophane-1-ene (**112**) readily underwent bromination, yet did not react with butadiene in a Diels–Alder reaction.



111 **112**

Scheme 2.15

The corresponding [2.2]paracyclophane-1,9-diene (**113**) was prepared by two routes (see Scheme 2.16).[82] The first route involved a bromination/dehydrobromination sequence analogous to that for **111**. The second route involved tetrabromination to **114** and **115**, followed by oxidation to the respective diketones, reduction to the diols, tosylation, and finally, dehydrotosylation to **113**. Cram also synthesized [2.2.2]paracyclophane triene (**116**) and several olefinic [4.4]paracyclophanes (**117–120**, Figure 2.7).[102]



114 **115** **113**

Scheme 2.16

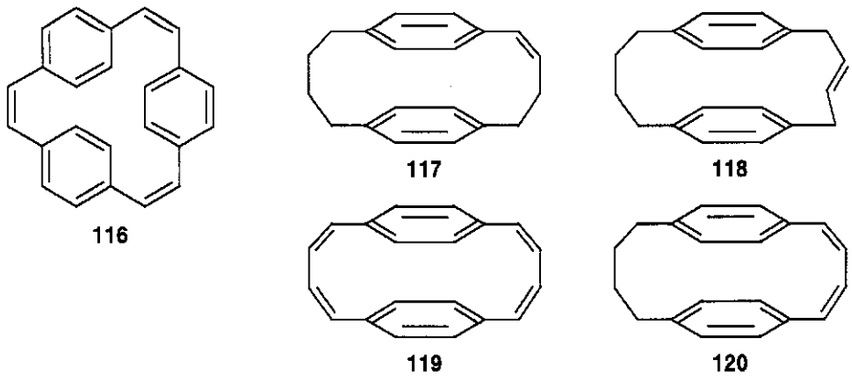
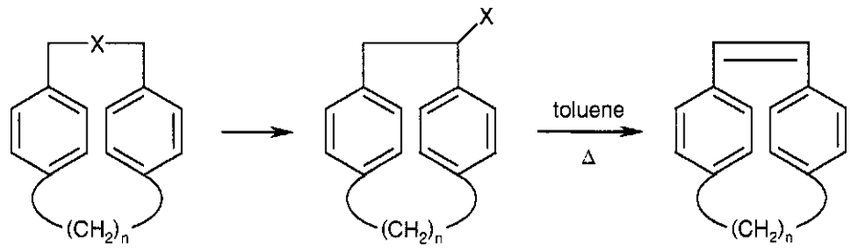


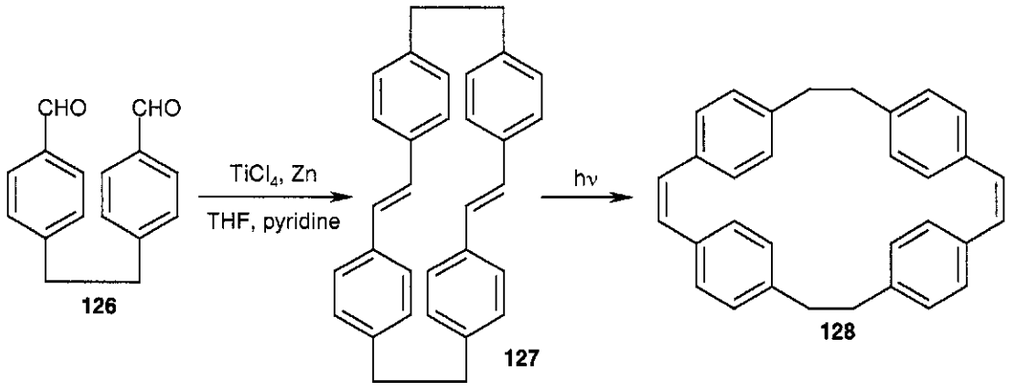
Figure 2.7: Several Stilbenophanes

Potter and Sutherland described the synthesis of a series of [*n*.2]paracyclophan-(*n*+7)-enes (**125**, *n* = 3–10) by several routes.[103] The most efficient synthesis is outlined in Scheme 2.17. The thia[*n*.3]paracyclophanes **121** were methylated (**122**) and subjected to the Stevens rearrangement (**123**). Formation of the *N*-toluene-*p*-sulphonylsulphilimine derivatives (**124**) and subsequent pyrolysis in toluene yielded the (*Z*)-stilbenophanes **125**. Bromine readily added to the double bond in all cases, and photocyclization of **125** (*n* = 7–10) gave the analogous series of (3,6)phenanthrenophanes.



Scheme 2.17

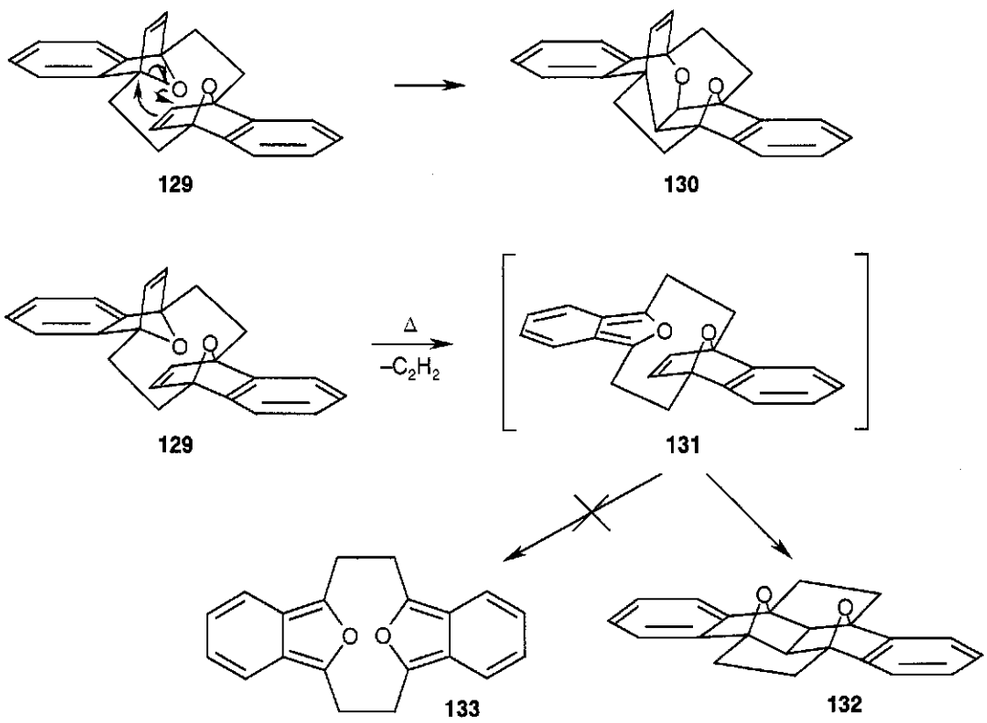
Tanner and Wennerström synthesized [2.2](*E*,*E*)-stilbenophane (**127**) from a coupling reaction of bibenzyl-4,4'-dicarbaldehyde (**126**, Scheme 2.18). Irradiation with 300 nm light led to an isomerization of **127** to (*Z*,*Z*)-stilbenophane (**128**), presumably *via* an (*E*,*Z*)-stilbenophane intermediate.[104]



Scheme 2.18

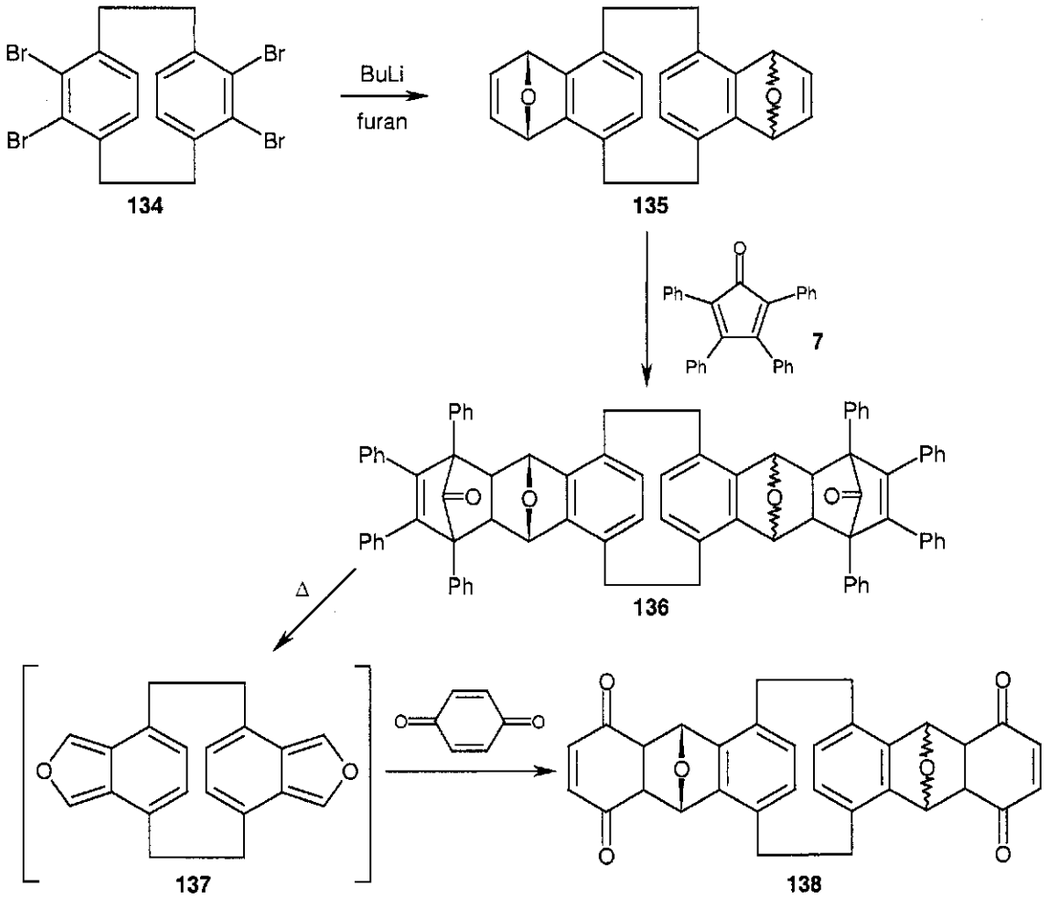
2.1.4 Isobenzofurans in Cyclophane Chemistry

The first report of an isobenzofuran intermediate in a cyclophane occurred in 1982.[105] Thermolysis of **129** in DMF or xylene led to the formation of two products, **131** and **132** (Scheme 2.19). There are severe non-bonded interactions between the oxygen atoms in **129**, so it is not surprising that it readily rearranges upon heating. Unsymmetrical **130** is the major product formed, indicating that the strain released by migration of an oxygen atom to the nearby olefin is quite substantial. Minor product **132** is formed when **129** loses a molecule of acetylene to give an intermediate (**131**) that contains an isobenzofuran moiety. A highly favoured transannular Diels–Alder reaction ensues to generate the relatively unstrained **132**, rather than a further loss of acetylene to give [2.2](1,3)isobenzofuranophane (**133**).



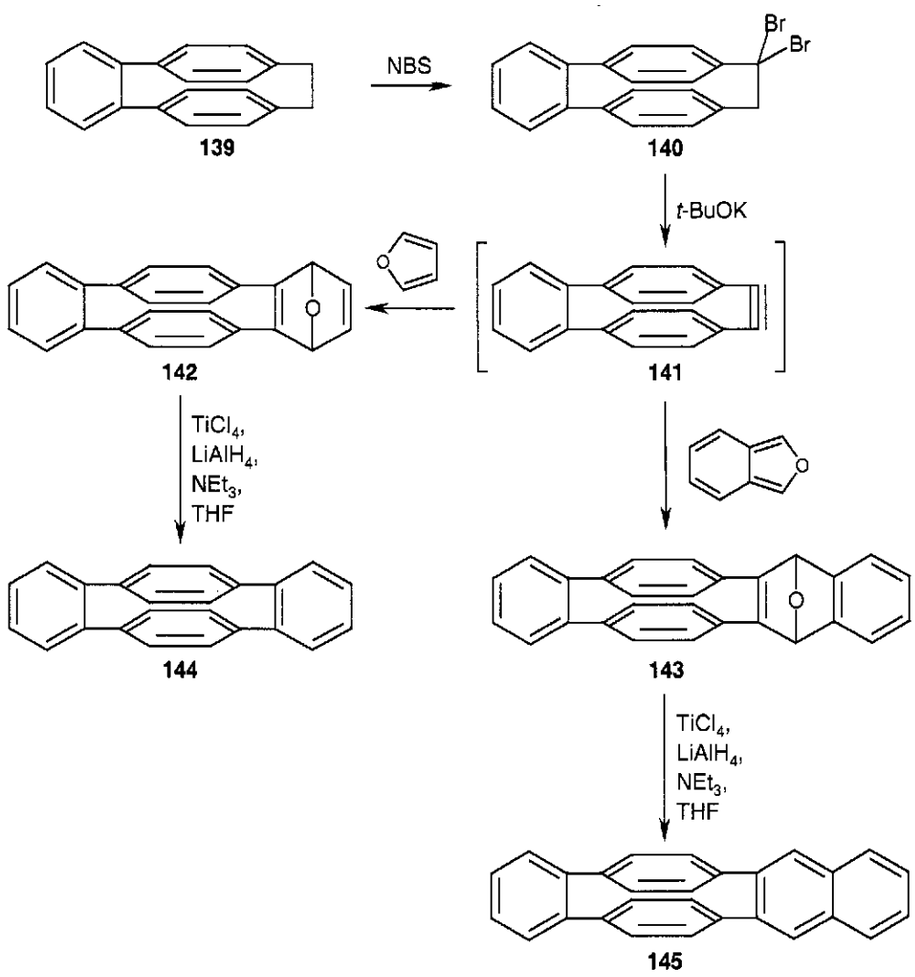
Scheme 2.19

The related [2.2](4,7)isobenzofuranophane (**137**) was generated as a reactive intermediate as outlined in Scheme 2.20.[106] 4,5,12,13-Tetrabromo[2.2]paracyclophane (**134**) was treated with BuLi in the presence of furan to give **135**. Reaction of **135** with tetraphenylcyclopentadienone (**7**) gave bis(adduct) **136**. Upon heating, **136** decomposed to generate **137**, which was then trapped as its bis(*p*-benzoquinone) adduct (**138**).



Scheme 2.20

Chan and Wong used furan and isobenzofuran to prepare two benzannulated [2.2]paracyclophanes.[107,108] 1,2-Benzo[2.2]paracyclophane (**139**) was treated with NBS to give the dibromide **140**. Dehydrobromination gave cyclophyne **141**, which was trapped with furan and isobenzofuran to give **142** and **143**, respectively. Deoxygenation with low-valent titanium[109] gave the respective hydrocarbons **144** and **145** (Scheme 2.21).

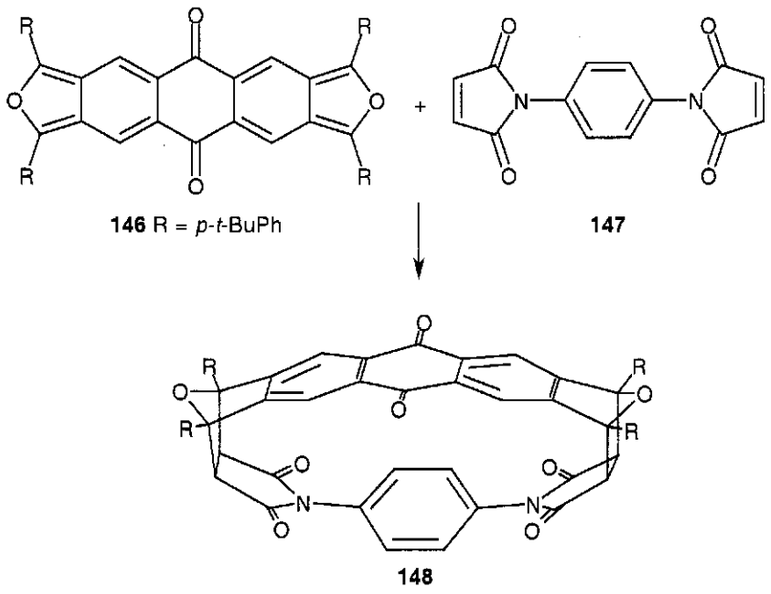


Scheme 2.21

Similarly, Tobe's group generated *peri*-substituted [6](1,4)naphthalenophanes and anthracenophanes[110] by dehydrobrominating 8-bromo[6]paracyclophane with Caubère's base,[52] trapping the aryne with a 1,3-substituted furan or isobenzofuran, and deoxygenating the adducts with low-valent titanium.

Mitchell has used isobenzofuran and naphtho(1,2-*c*:5,6-*c*]difuran (**23**) to generate photochromic switches based on the dimethyldihydropyrene-metacyclophanediene valence isomerization.[111]

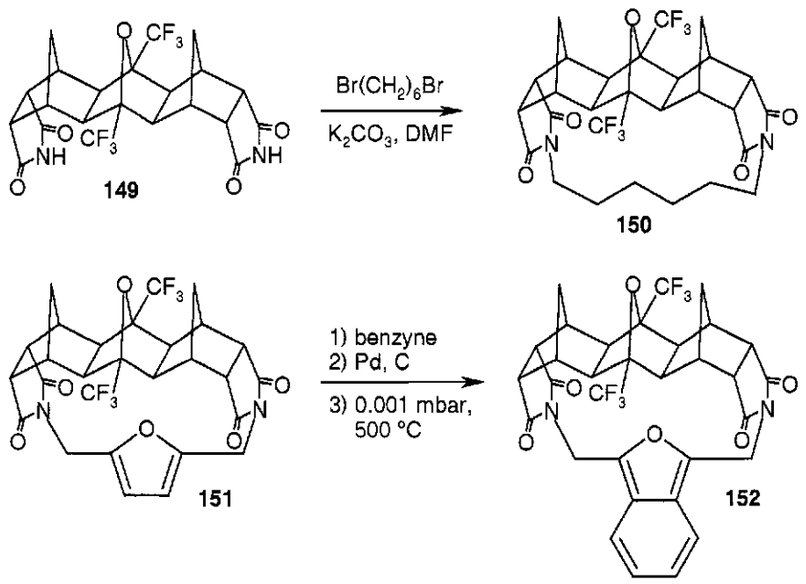
The above examples have used isobenzofuran or its derivatives mainly as benzannulation tools. The next example uses a double Diels–Alder reaction between a bis(isobenzofuran) and a bis(maleimide) to build a cyclophane. Thus, difuran **146** was added to dimaleimidobenzene (**147**) to generate cyclophane **148** (Scheme 2.22).[11] The authors were initially surprised by the result, as they expected an oligomeric rod to form. However, because of the high *endo* selectivity of maleimides in Diels–Alder reactions, once the first addition occurred, the diene and dienophile were perfectly lined up for the second addition.



Scheme 2.22

Finally, Butler *et al.* have recently reported the synthesis of alicyclophanes, or molecular racks, incorporating conformationally rigid fused bicyclic units instead of the usual aromatic rings (Scheme 2.23).[112] For example, polynorbornane **149** forms alicyclophane **150** when reacted with 1,6-dibromohexane in an S_N2 reaction. The same group later succeeded in isolating a stabilized isobenzofuran by mounting it on their alicyclophane backbone.[113] Benzannulation of rack-mounted furan (**151**) followed by

hydrogenation and flash vacuum thermolysis gave rack-mounted isobenzofuran (**152**). The isobenzofuran moiety was stable towards polymerization, yet was still reactive towards dienophiles.



Scheme 2.23

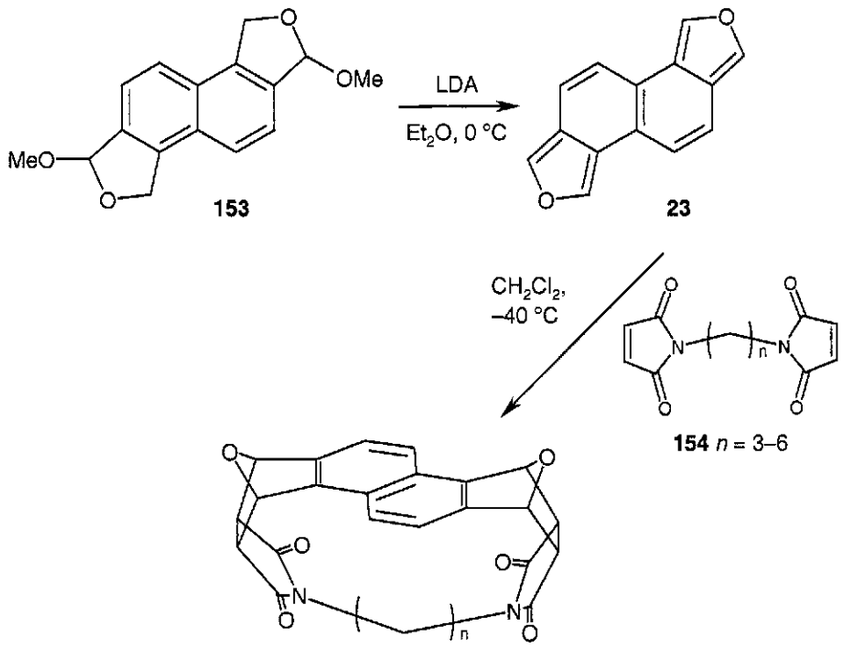
Somewhat related is the description by Cory of the synthesis of a macrocyclic belt by a double Diels–Alder cycloaddition between 1,4,5,8-anthradiquinone or **147** and 2,3,6,7-tetraheptylidene-1,2,3,4,5,6,7,8-octahydroanthracene.[114]

2.2 Results and Discussion

The previous examples led to the realization that similar cyclophanes could be constructed by bridging naphtho[1,2-*c*:5,6-*c*]difuran (**23**) and 1,2-bis(5-isobenzofuranyl)ethene (**40**) with bis(maleimide) tethers in double Diels–Alder reactions. The synthesis and characterization of these cyclophanes will be discussed in the remainder of this chapter.

2.2.1 Cyclophanes from Naphtho[1,2-*c*:5,6-*c*]difuran

The synthesis of a series of cyclophanes from naphtho[1,2-*c*:5,6-*c*]difuran (**23**) was straightforward. A large excess of LDA was used to generate the difuran from its bis(acetal) precursor (**153**),[31] then the difuran was trapped with a series of bis(maleimide) tethers (**154**, n = 3–6) to give a series of nC naphthodifuran-derived cyclophanes (**155**, Scheme 2.24). The double Diels–Alder cycloadditions were performed at low temperature and high dilution to minimize polymer formation.



Scheme 2.24

Table 2.1 compares the calculated N–N distances of the tethers (**154**), the cyclophanes (**155**), the *syn*-bis(maleimide) adduct of difuran **23**, and the yields of the cyclophanes. The tethers and cyclophanes were constrained to staggered conformations and C_2 symmetry, respectively. The yields of **155** ranged from 29% for the 3C cyclophane to a mere 1% for the 6C cyclophane. The range of yields can be rationalized

in terms of the N–N distances. The *syn*-bis(maleimide) adduct of **23** has an N–N distance of 5.60 Å, but the naphthalene ring is capable of curving outwards in the cyclophanes, which has the effect of bringing the nitrogen atoms closer together to accommodate shorter tethers. In fact, the calculated N–N distance of the 3C cyclophane (4.93 Å) is nearly identical to that of the 3C tether (4.96 Å). The N–N distance of the 4C cyclophane (5.31 Å) is slightly shorter than that of the bis(maleimide) adduct, and the 4C tether (6.23 Å) apparently has no problem finding a conformation that readily fits, as the yield of the 4C cyclophane is nearly as high as that of the 3C cyclophane. In the case of the 3C and 4C cyclophanes, once the first, intermolecular cycloaddition occurs, the other end of the intermediate monoadduct is well-aligned for the second, intramolecular cycloaddition. However, if the tether is too long, the yield dramatically decreases. A substantial amount of polymer is observed in the crude ^{1}H NMR spectra of the 5C and 6C cyclophanes despite the low temperature/high dilution conditions, indicating that the extra mobility afforded by the longer tethers leads to a greater chance of an intermolecular reaction rather than alignment for an intramolecular reaction. This, of course, is a reflection of the entropy of activation ($\Delta S^{\ddagger}$) of the reaction. Furthermore, the need to adopt an unfavourable, strained conformation in the transition state will also manifest itself in the enthalpy of activation ($\Delta H^{\ddagger}$).

Table 2.1: N–N Distances and Yields of the Naphthodifuran-derived Cyclophanes

n	N–N distance (Å)[1,2]		Yield of 155 (%)
	*n*C Tether (**154**)	*n*C Cyclophane (**155**)	
3	4.96	4.93	29
4	6.23	5.31	27
5	7.45	5.96	3
6	8.72	7.04	1

[1] Calculated at the AM1 level of theory.

[2] The N–N distance for the *syn*-bis(maleimide) adduct of difuran **23** is 5.60 Å.

AM1-calculated structures of the C_2-symmetric *n*C naphthodifuran-derived cyclophanes can be found in Figure 2.8. The aromatic ring curves slightly outward in the 3C cyclophane, is planar in the 4C cyclophane, and curves slightly inward in the 5C and 6C cyclophanes. The C_2 symmetry renders some or all of the methylene protons of the tether diastereotopic, depending on whether the tether has an odd or even number of carbons. The tether of the 3C cyclophane is labelled with its spin system to aid in the later discussion of its ^{1}H NMR spectrum.

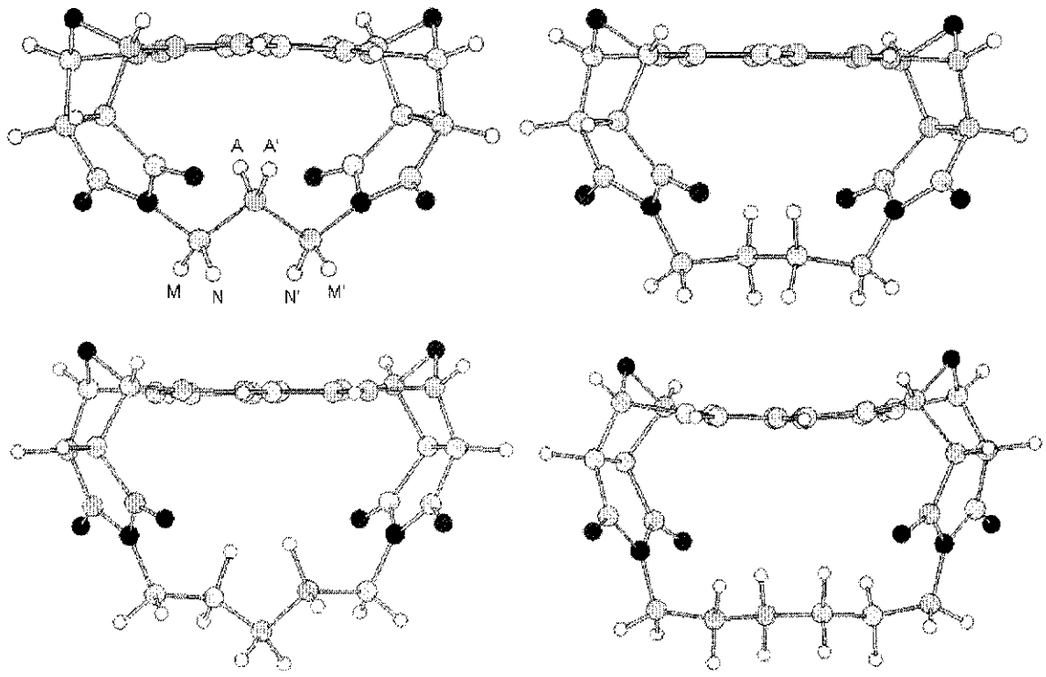


Figure 2.8: AM1-Calculated Structures of the Naphthodifuran-derived Cyclophanes

The ^{1}H NMR spectra of the naphthodifuran-derived cyclophanes display some interesting features, particularly those peaks corresponding to the tether protons. Table 2.2 summarizes the peak positions and topicity of the α, β, and γ (from nitrogen) tether protons for the series of naphthodifuran-derived cyclophanes. When compared with the β and γ methylene protons of the bis(maleimide) tethers (**154**), all of the cyclophanes display some degree of shielding of the β and γ tether protons due to the diamagnetic anisotropy of the naphthalene ring. For reference, the chemical shifts of the β and γ protons of **154** are 1.6–1.9 ppm and 1.3 ppm, respectively. Even the α protons of the series display a certain degree of shielding when compared with the α protons of the bis(maleimide)s; the α protons of the cyclophanes appear at or below 3.06 ppm, while the α protons of the bis(maleimide)s appear at about 3.5 ppm. The central methylene units are not always the most shielded, though that is obviously the only case possible for the

3C and 4C cyclophanes. For the 5C cyclophane, the β protons are actually more shielded than the γ protons, as they lie more fully under and are closer to the naphthalene ring. For the 6C cyclophane, the upper β and γ protons are the most shielded because they are closest to the ring, and the β protons are more shielded than the equivalent γ protons because they are more under the ring. Furthermore, only one signal is observed for the diastereotopic α protons of the 5C and 6C cyclophanes. This may be because the longer chains are more mobile and this averages the α proton chemical shifts, yet the other diastereotopic pairs are not averaged. The AM1-calculated structures show that the α protons point downwards and are fully under the bicyclic rings, and therefore, they may simply be coincidentally isochronous. COSY was used to substantiate the chemical shift assignments for the 3C and 4C cyclophanes. However, attempts to obtain COSY spectra of the 5C and 6C cyclophanes were hampered by the small quantities of these cyclophanes, and therefore, shift assignments for these cyclophanes were made based upon examination of the AM1-calculated structures and analogy with the smaller members of the series.

Table 2.2: ^{1}H Chemical Shifts and Topicity of the α, β, and γ Tether Protons of the *n*C Naphthodifuran-derived Cyclophanes

n	^{1}H Chemical Shift (ppm) and Topicity[1] of the Tether Protons					
	α	α (H/D)	β	β (H/D)	γ	γ (H/D)
3	2.59, 2.80	D	-1.41	H	—	—
4	2.71, 3.06	D	-0.14, 0.44	D	—	—
5	3.00	D	-0.70, 0.60	D	0.77	H
6	2.99	D	-0.09, 0.49	D	0.07, 1.11	D

[1] Homotopic (H) or Diastereotopic (D).

The signals for the tether protons of the cyclophanes are complex second-order multiplets because of the diastereotopic methylene groups. It was decided to fully analyze the spectrum of the tether protons for the 3C naphthodifuran-derived cyclophane since the fewest spins were involved.

The tether protons of the 3C cyclophane constitute an AA'MM'NN' spin system. The ^{1}H NMR spectrum did not lend itself to interpretation by inspection, and therefore, it was simulated using Mestre-C.[115] Mestre-C uses the inputted chemical shifts, coupling constants, and linewidth of the spins in question to calculate the transition energies and frequencies. In the case of the 3C cyclophane, the dihedral angles between tether protons were measured and the Karplus curve used for a first guess at the coupling constants. The chemical shifts and coupling constants were then varied until the simulated spectrum matched the experimental spectrum. The results of the simulation can be found in Figure 2.9. Some of the smaller peaks are lost in the noise in the experimental spectrum, but the chemical shifts and relative intensities of the peaks in the two spectra are nearly identical. Each of the diastereotopic methylene pairs (AA', MN, M'N') has a geminal coupling constant of –12.0 Hz. Vicinal coupling constants are 13.0 Hz for protons with a dihedral angle of approximately 180° (AN, AM', A'M, A'N') and 4.0 Hz for protons with a dihedral angle of about 60° (AM, AN', A'N, A'M').

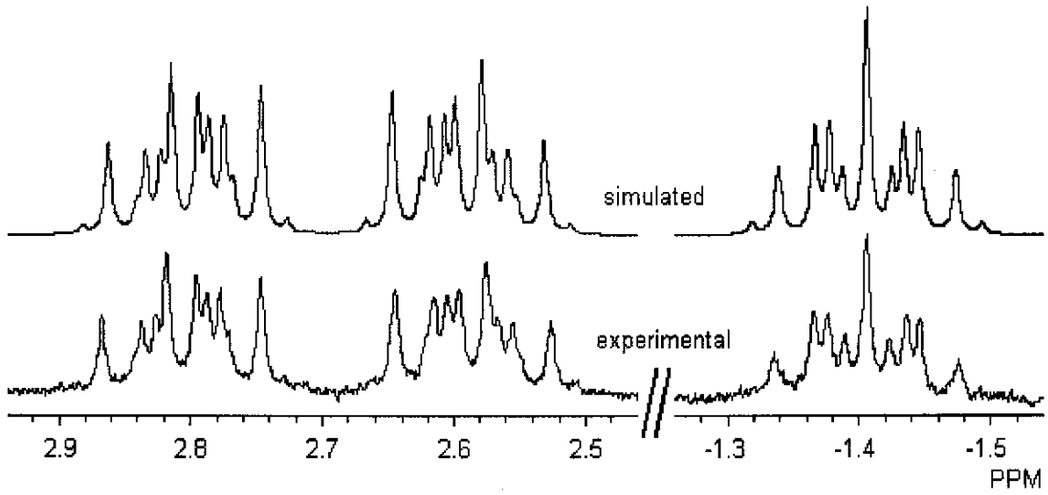


Figure 2.9: Experimental and Simulated ^{1}H NMR Spectra of the 3C Naphthodifuran-derived Cyclophane Tether Protons (250 MHz, $CDCl_3$)

Colourless, needle-like crystals of the 3C cyclophane were obtained by slow evaporation from CD_2Cl_2 and subjected to X-ray crystallographic analysis. Crystal data and structure refinement details can be found in Table 2.3, selected bond lengths and angles in Table 2.4, and the X-ray structure and atom-numbering scheme in Figure 2.10. The 3C cyclophane crystallizes as discrete molecules in the tetragonal space group $P4_2/n$. There are several short intermolecular contacts (less than the sum of the van der Walls radii of the elements involved) in the crystal. In fact, each molecule has forty short contacts between O and H, O and C, or C and H atoms to eleven other molecules. The closest contacts of each type are between O2 and H15 (2.356 Å), O5 and H18 (2.398 Å), O1 and C1 (2.964 Å), O1 and C2 (2.971 Å), and C17 and H20 (2.841 Å).

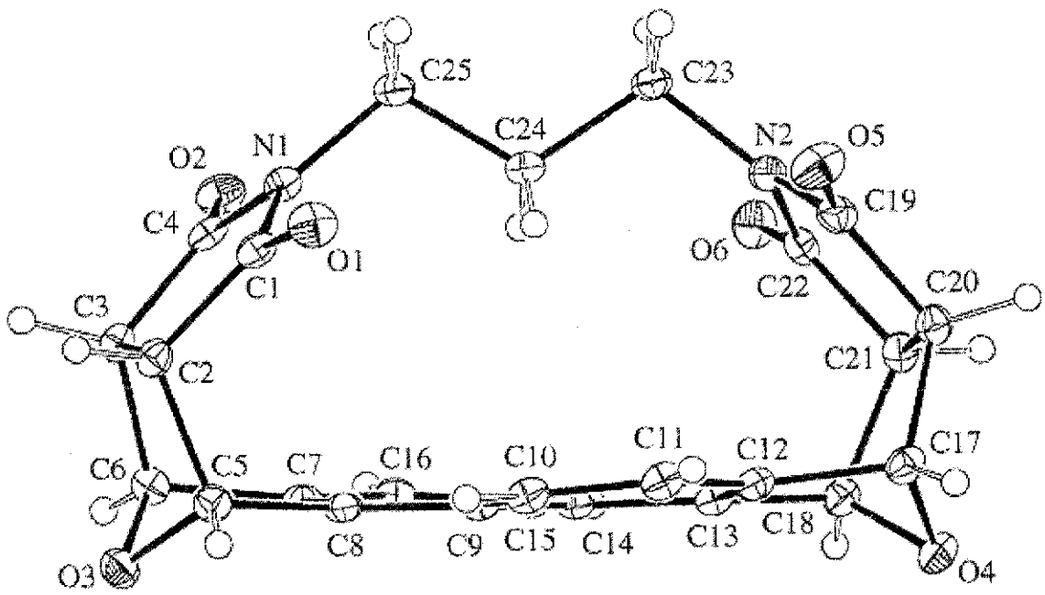


Figure 2.10: X-ray Structure of the 3C Naphthodifuran-derived Cyclophane

There is a small, but noticeable, outward curvature of the naphthalene ring, just as was predicted by the AM1 structure. The RMS deviation of the naphthalene carbons from a least-squares plane is 0.0685 Å, with C11 and C16 deviating the most. The measured N–N distance is 4.832 Å, 0.1 Å shorter than the calculated distance. The tether protons H24A and H24B point straight up into the naphthalene ring, consistent with their upfield ^{1}H NMR resonance of –1.41 ppm. The distance between these protons and C9 and C10 of the aromatic ring is about 2.7 Å. Finally, the C25–C24–C23 bond angle is stretched to 115.17(13)°, which leads to the C23–C24 and C24–C25 bond lengths being shortened to an average distance of 1.521 Å. The latter phenomenon has also been observed by Bodwell in his [*n*](2,7)pyrenophanes.[116,117]

Table 2.3: Crystal Data and Structure Refinement for 155 (n = 3)

Formula	$C_{25}H_{18}N_2O_6$
Molecular weight	442.41
Crystal size (mm)	0.35 × 0.12 × 0.12
Temperature (K)	173(2)
Wavelength (Å)	0.71073
Crystal system	Tetragonal
Space group	$P4_2/n$
Unit cell dimensions (Å)	a = 21.6349(9), c = 8.2624(2)
Volume (Å^3)	3867.4(2)
Z	8
Density$_{calc'd}$ (g cm^{-3})	1.520
Absorption coefficient (mm^{-1})	0.11
F(000)	1840
θ range for data collection (°)	1.3–27.5
Index ranges	$-27 \le h \le 28$, $-19 \le k \le 19$, $-9 \le l \le 10$
Reflections collected	7455
Independent reflections	4303 (R_{int} = 0.029)
Observed data [$I>2\sigma(I)$]	3077
Completeness to θ = 27.5º (%)	97.0
Absorption correction	Multi-scan method
Max. and min. transmission	0.987 and 0.962
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	4303/0/298
Goodness-of-fit on F^2	1.02
Final R indices [$I>2\sigma(I)$]	R_1 = 0.041, wR_2 = 0.095
R indices (all data)	R_1 = 0.069, wR_2 = 0.107
Weighting scheme	$w = 1/[\sigma^2F_o^2 + (0.0461P)^2 + 0.9086P]$, where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\theta)_{max}$	0.00
Largest diff. peak and hole (e Å^{-3})	0.19 and –0.19

Table 2.4: Selected Bond Lengths and Angles for 155 (n = 3)

Bond Lengths (Å)			
O(1)–C(1)	1.212(2)	C(7)–C(8)	1.376(2)
O(3)–C(5)	1.4523(19)	C(7)–C(16)	1.406(2)
N(1)–C(1)	1.386(2)	C(8)–C(9)	1.415(2)
N(1)–C(25)	1.465(2)	C(9)–C(10)	1.420(2)
C(1)–C(2)	1.503(2)	C(9)–C(14)	1.445(2)
C(2)–C(3)	1.544(2)	C(10)–C(11)	1.376(2)
C(2)–C(5)	1.563(2)	C(23)–C(24)	1.523(2)
C(5)–C(8)	1.525(2)		
Bond Angles (°)			
C(5)–O(3)–C(6)	96.84(11)	C(8)–C(5)–C(2)	109.09(13)
C(1)–N(1)–C(4)	113.15(13)	C(8)–C(7)–C(16)	122.16(15)
C(1)–N(1)–C(25)	122.21(13)	C(8)–C(7)–C(6)	105.20(13)
O(1)–C(1)–N(1)	123.81(16)	C(16)–C(7)–C(6)	132.46(15)
O(1)–C(1)–C(2)	127.59(15)	C(13)–C(14)–C(15)	122.96(14)
N(1)–C(1)–C(2)	108.52(13)	C(8)–C(9)–C(14)	116.05(14)
C(1)–C(2)–C(3)	105.10(13)	C(10)–C(9)–C(14)	119.89(15)
C(1)–C(2)–C(5)	114.57(13)	C(11)–C(10)–C(9)	121.64(15)
C(3)–C(2)–C(5)	101.47(12)	C(10)–C(11)–C(12)	118.22(15)
O(3)–C(5)–C(8)	101.09(12)	N(2)–C(23)–C(24)	108.10(13)
O(3)–C(5)–C(2)	99.32(12)	C(25)–C(24)–C(23)	115.17(13)

In general, the calculated structure predicted the crystal structure very well. Most of the calculated bond lengths were within 2.0% of the measured bond lengths, and half were actually within 1.0%. Greater deviations occurred for the four N–C bonds of the imide rings (2.0 to 2.5%), C7–C8 (2.1%), and C12–C13 (2.0%). Most of the calculated bond angles were also within 2.0% of the measured bond angles, with three-quarters within 1.0%. Greater deviations occurred for the angles C25–C24–C23 (2.3%), N1–C25–C24 (3.4%), and N2–C23–C24 (3.7%). These are all tether angles, and are the only instances in which the calculated structure differed substantially from the crystal structure. AM1 stretched all of these angles equally to 112°, when in actuality, the N–C–C angles average 108.31° and the C–C–C angle is 115.17°.

As mentioned above, the 3C cyclophane crystallizes in the $P4_2/n$ space group. This is an achiral space group, even though the 3C cyclophane is chiral by virtue of its C_2 symmetry. An examination of the packing diagram (Figure 2.11) reveals that the cyclophane crystallizes as a racemic mixture. There are four pairs of enantiomers in the unit cell, and each molecule is related to its enantiomer by a crystallographic centre of inversion.

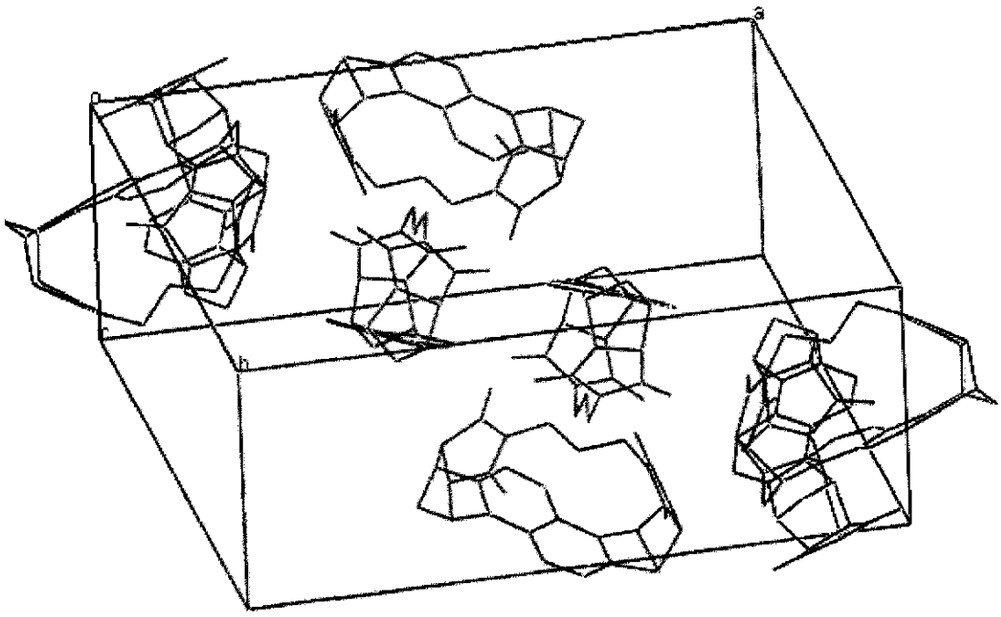
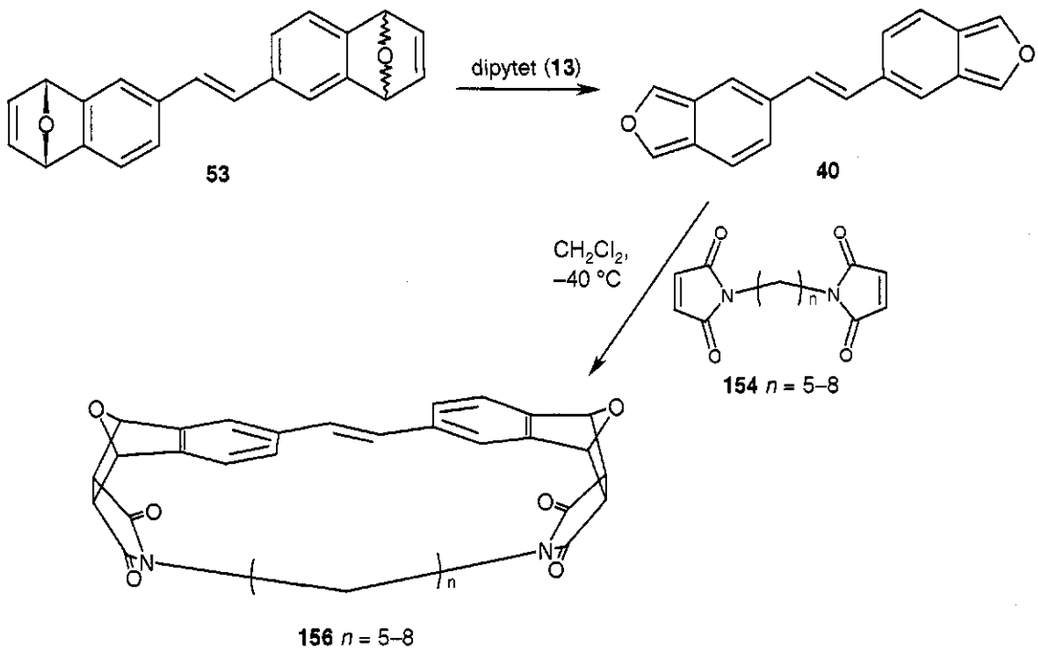


Figure 2.11: Packing Diagram of the 3C Naphthodifuran-derived Cyclophane

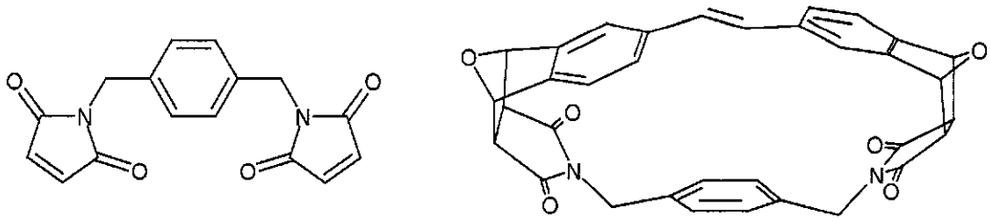
Attempts at growing crystals of the other naphthodifuran-derived cyclophanes were unsuccessful, likely because the increased mobility of the longer tethers makes it less probable that the larger cyclophanes will adopt relatively ordered conformations and form crystals. In the absence of crystal structures for these cyclophanes, one must resort to the AM1-calculated structures for structural information.

2.2.2 Cyclophanes from 1,2-Bis(5-isobenzofuranyl)ethene

Cyclophanes from 1,2-bis(5-isobenzofuranyl)ethene (or stilbenedifuran, **40**) were synthesized using dipytet. Stilbenedifuran **40** was generated from its precursor (**53**) and trapped with a series of bis(maleimide) tethers (**154**, n = 5–8) to give a series of nC stilbenedifuran-derived cyclophanes (**156**, Scheme 2.25). A p-xylyl stilbenedifuran-derived cyclophane (**158**) was also synthesized using a p-xylyl bis(maleimide) tether (**157**, Figure 2.12). As before, the double Diels–Alder cycloadditions were performed at low temperature and high dilution to minimize polymer formation.



Scheme 2.25



157 158

Figure 2.12: The *p*-Xylyl Bis(maleimide) Tether (157) and Stilbenedifuran-derived Cyclophane (158)

Table 2.5 summarizes the N–N distances and yields of the stilbenedifuran-derived cyclophanes. Clean samples were only obtained for $n = 5$ and $n = 6$. The stilbenedifuran-derived cyclophanes have about the same polarity as the bis(maleimide) tethers, and therefore, the cyclophanes do not separate well from the tethers, whether by column chromatography, recrystalization, or a combination of both. However, there is not a dramatic decrease in the yields as there was with the naphthodifuran-derived cyclophanes because the increased flexibility of the stilbene backbone allows a wider range of tethers to be incorporated. Nevertheless, the yields are overall quite low. The stilbenedifuran does not seem to form completely; the first fraction out of the column is usually the precursor, **53**. Varying the reaction time of **53** with dipytet before adding it to **154** did not seem to affect the yields of **156**. There is also the possibility that some monoadduct formed; there was some evidence of this in the crude ^{1}H NMR spectra, but it was far from conclusive.

Table 2.5: N–N Distances and Yields of the Stilbenedifuran-derived Cyclophanes

n	N–N distance (Å)[1,2]		Yield of 156 or 158 (%)	
	*n*C Tether (**154**)	*n*C Cyclophane (**156**)	Pure	Impure (Ratio)[3]
5	7.45	7.48	2.3	4.6 (1:4)
6	8.72	8.50	11	13 (1:4)
7	9.95	9.81	0	17 (0.8:4)
8	11.22	10.22	0	12 (1:4)
p-xylyl	6.99 (**157**)	7.64 (**158**)	0	13 (1.25:4)

[1] Calculated at the AM1 level of theory.

[2] The N–N distance for the *syn*-bis(maleimide) adduct of difuran **40** is 10.00 Å.

[3] Yield of tether-contaminated cyclophane and tether:cyclophane ratio.

AM1-calculated structures of the C_2-symmetric stilbenedifuran-derived cyclophanes can be found in Figure 2.13. AM1 calculations indicate that the stilbene backbone is curved in the 5C cyclophane, less curved in the 6C cyclophane, and planar, or very nearly so, in the 7C and 8C cyclophanes. The benzene rings are twisted with respect to one another in the 6C cyclophane. The *p*-xylyl cyclophane is curved to about the same degree as the 5C cyclophane, the benzene rings are twisted, and the *p*-xylyl group curves inwards, so that the two aromatic surfaces resemble nesting spoons. Bodwell also described an unusual spoon-like arrangement of pyrene and benzene rings in his preparation of [2]paracyclo[2](2,7)pyrenophane.[118] Normally, aromatic rings in small cyclophanes curve away from another in an attempt to reduce transannular π–π interactions.[65] Unfortunately, attempts to grow crystals of the stilbenedifuran-derived cyclophanes have failed.

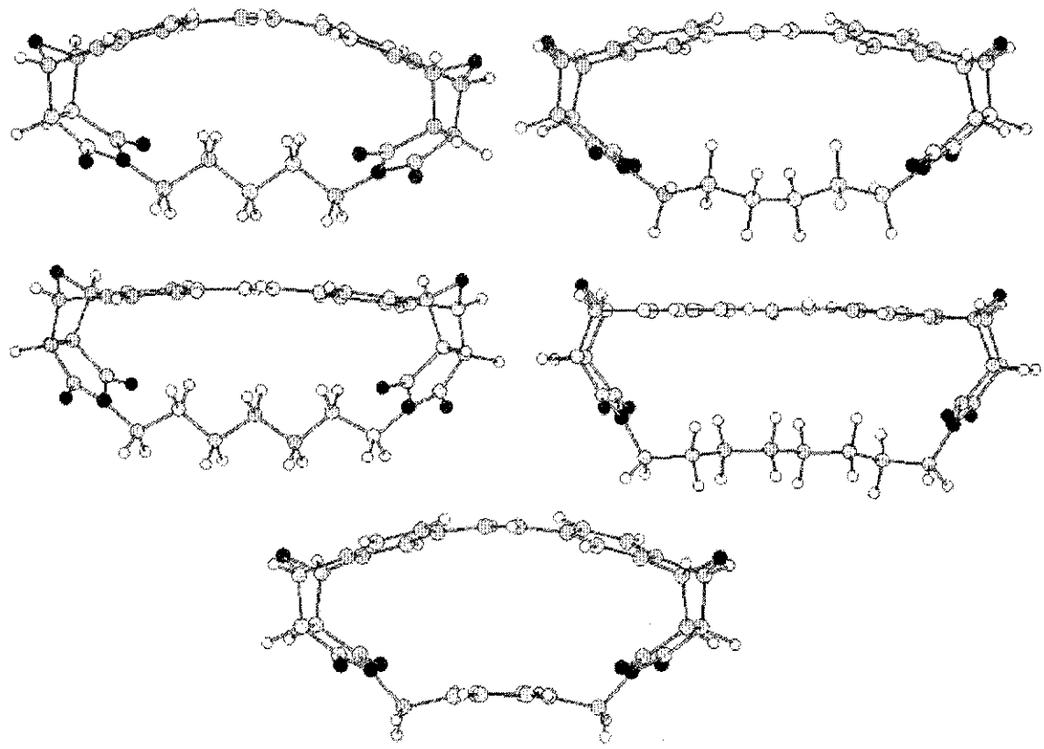
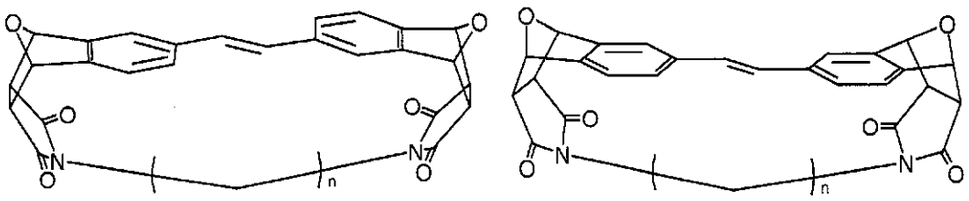


Figure 2.13: AM1-Calculated Structures of the Stilbenedifuran-derived Cyclophanes

Unlike the naphthodifuran-derived cyclophanes, the stilbenedifuran-derived cyclophanes can also adopt a C_1-symmetric conformation. A view of the C_2 and C_1 isomers can be found in Figure 2.14. The main difference between the two is the orientation of the benzene rings with respect to one another. The two isomers could conceivably be distinguished by their ^{1}H NMR spectra—the vinyl protons are equivalent in the C_2 isomer and inequivalent in the C_1 isomer. However, there is no evidence that any of the stilbenedifuran-derived cyclophanes formed as their C_1 isomers.



C_2 C_1

Figure 2.14: The Two Isomers of the Stilbenedifuran-derived Cyclophanes

The ^{1}H NMR spectra of the stilbenedifuran-derived cyclophanes exhibit many of the same features as those of the naphthodifuran-derived cyclophanes. Summarized in Table 2.6 are the chemical shifts and topicity of the tether protons of the *n*C stilbenedifuran-derived cyclophanes (the *p*-xylyl cyclophane will be discussed separately). All of the protons are shielded, though none to the same extent as in the naphthodifuran-derived series. The β protons are always the most shielded and give two signals because they are diastereotopic. The γ protons for the 6C stilbenedifuran-derived cyclophane also show two signals, though one overlaps with one of the β signals. The signals for the γ and δ protons of the 7C and 8C stilbenedifuran-derived cyclophanes overlap into one broad resonance at about 0.8 ppm. COSY and HMQC experiments were an invaluable aid in the interpretation of the ^{1}H NMR spectra of the stilbenedifuran-derived cyclophanes.

Table 2.6: ^{1}H Chemical Shift and Topicity of the α, β, γ, and δ Tether Protons of the *n*C Stilbenedifuran-derived Cyclophanes

n	^{1}H Chemical Shift (ppm) and Topicity[1] of the Tether Protons							
	α	α (H/D)	β	β (H/D)	γ	γ (H/D)	δ	δ (H/D)
5	2.66, 2.95	D	-0.13, 0.61	D	0.75	H	—	—
6	2.89	D	0.21, 0.56	D	0.56, 0.82	D	—	—
7	2.84, 2.96	D	-0.03, 0.26	D	0.84	D	0.84	H
8	2.86, 2.96	D	0.22, 0.34	D	0.85	D	0.85	D

[1] Homotopic (H) or Diastereotopic (D).

Unlike the naphthodifuran-derived cyclophanes, in which all of the tether proton resonances are complex multiplets, only the stilbenedifuran-derived cyclophane α protons are well-resolved. The remainder of the tether protons show considerable broadening. This is most likely due to a combination of second-order effects from the complex multiplets overlapping because of small chemical shift differences between them and averaging caused by the conformational mobility of the stilbene backbone and the longer tethers. Figure 2.15 shows the ^{1}H NMR spectrum of the 5C stilbenedifuran-derived tether protons. Unlike the larger stilbenedifuran-derived cyclophanes, some of the fine structure of the β and γ proton resonances is retained. The α protons appear as two triplets of doublets instead of second-order multiplets because the geminal coupling constant is coincidentally equal to one of the vicinal coupling constants.

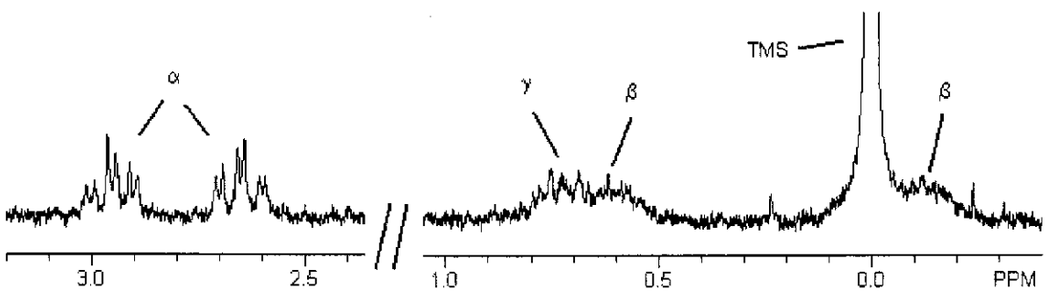


Figure 2.15: ^{1}H NMR Spectrum of the 5C Stilbenedifuran-derived Cyclophane Tether Protons (250 MHz, $CDCl_3$)

Just as the stilbene backbone shields the alkyl tethers, it can also shield the tether in the *p*-xylyl stilbenedifuran-derived cyclophane (**158**). The xylyl protons appear at 6.81 and 7.06 ppm, just upfield of their shift (7.29 ppm) in the *p*-xylyl tether (**157**). The signals for the stilbene protons are not affected by the presence of the benzene ring; they appear at their usual positions. The larger stilbene system is capable of shielding the xylyl protons, but the smaller benzene ring is not capable of perturbing the anisotropy of the larger stilbene system. The methylene protons are fully under the benzene rings of the stilbene unit and are thus expected to be shifted upfield relative to the corresponding protons in **157** (4.64 ppm). In the event, they appear at 4.03 and 4.46 ppm, despite the transannular distance of 4.8 Å, which is much larger than the aromatic–tether distance of the other naphthodifuran- and stilbenedifuran-derived cyclophanes (2.9–3.6 Å).

The low yields of the stilbenedifuran-derived cyclophanes coupled with the difficulty in obtaining clean samples precluded any substantial study of the chemistry of the double bond. Initial studies will be discussed in Chapter 4, as well as ideas for improving the synthesis of the stilbenedifuran-derived cyclophanes.

2.3 Summary

A series of cyclophanes (**155**) based on the naphtho[1,2-*c*:5,6-*c*]difuran backbone (**23**) were synthesized by double Diels–Alder cycloaddition reactions with bis(maleimide) tethers (**154**, n = 3–6). There is a dramatic decrease in yield between n = 4 and n = 5 because the rigid naphthalenic backbone makes it more difficult to incorporate a longer tether. ^{1}H NMR spectra of the **155** series indicate that all of the tether protons are shielded to some degree, with the β protons of the 3C naphthodifuran-derived cyclophane being the most shielded at –1.41 ppm. The spectrum of the 3C cyclophane tether protons was simulated to determine the coupling constants and chemical shifts. Too many spins were involved for the same procedure to be applied to the larger cyclophanes.

An X-ray structure of the 3C naphthodifuran-derived cyclophane was obtained and found to be nearly identical to the AM1-calculated structure. The cyclophane is chiral, yet it crystallizes in an achiral space group because it packs as a racemic mixture.

Cyclophanes (**156** and **158**) based on 1,2-bis(5-isobenzofuranyl)ethene (stilbenedifuran, **40**) were synthesized by double Diels–Alder cycloaddition reactions with bis(maleimide) tethers (**154**, n = 5–8, and **157**). The yields of the stilbenedifuran-derived series did not dramatically decrease; rather, they were uniformly low, and the cyclophanes were contaminated with unreacted **154**. The tether protons of the stilbenedifuran-derived cyclophanes were also shielded, though not to the same degree as the naphthodifuran-derived cyclophanes. Complex multiplets were expected, but second-order effects and conformational mobility led to broad, featureless peaks.

2.4 Experimental

Solvents were used without additional purification with the exception of diethyl ether and THF, both of which were distilled from sodium/benzophenone under a nitrogen atmosphere prior to use. All organic starting materials were purchased from the Aldrich Chemical Co. unless otherwise noted. Melting points were performed in open capillaries and are uncorrected. NMR spectra were recorded on a Brüker AC-250/Tecmag Macspect NMR spectrometer or a Varian INOVA-500 MHz NMR spectrometer at an ambient temperature of 298 K. ^{1}H NMR chemical shifts were referenced to TMS when in $CDCl_3$ or to the residual $CHDCl_2$ pentet at 5.32 ppm when in CD_2Cl_2. ^{13}C NMR chemical shifts were referenced to the $CDCl_3$ triplet at 77.23 ppm or to the CD_2Cl_2 pentet at 54.00 ppm. Infrared spectra were recorded on a Bomem MB-102 or Nicolet Avatar 360 spectrometer. Mass spectra were performed by the Mass Spectroscopy Lab, Department of Chemistry, University of Alberta. Elemental analyses were performed by M-H-W Laboratories, Phoenix, Arizona. Dipytet[56] (**13**) and the naphthodifuran bis(acetal)[31] (**153**) were synthesized according to the literature. AM1 calculations were performed using HyperChem.[119] Complex ^{1}H NMR splitting patterns were analyzed using Mestre-C.[115]

X-ray diffraction analysis of the 3C naphthodifuran-derived cyclophane (155, *n* = 3): X-ray crystallography was performed by Dr. Masood Parvez, University of Calgary. A colourless needle crystal of $C_{25}H_{18}N_2O_6$ was coated with Paratone 8277 oil (Exxon) and mounted on a glass fiber. All measurements were made on a Nonius KappaCCD diffractometer with graphite monochromated Mo-Kα radiation. Cell constants obtained from the refinement[120] of 3862 reflections in the range $1.0 < \theta < 27.5°$ corresponded to a

tetragonal cell, details of crystal data and structure refinement can be found in Table 2.3. The data were collected[121] at a temperature of 173(2) K using the ω and φ scans to a maximum θ value of 27.5°. The data were corrected for Lorentz and polarization effects and for absorption using a multi-scan method.[120] Since the crystal did not show any sign of decay during data collection, a decay correction was deemed unnecessary. The structure was solved by direct methods[122] and expanded using Fourier techniques.[123] The non-hydrogen atoms were refined anisotropically. The hydrogen atoms were included at geometrically idealized positions and were not refined. The final cycle of full-matrix least-squares refinement using SHELXL97[124] converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors, R = 0.041 and wR = 0.107 (all data), respectively, and goodness of fit, S = 1.02. The weighting scheme was based on counting statistics and the final difference map was essentially featureless. Additional crystallographic details can be found in Appendix I.

3C Naphthodifuran-derived cyclophane (155, n = 3): Bis(acetal) **153** (263 mg, 0.966 mmol) was dissolved in 40 mL of dry diethyl ether and cooled to 0 °C under nitrogen. LDA (5.0 mL of 2.0 M solution in heptane/THF/ethylbenzene, 10.0 mmol) was added *via* syringe and the mixture stirred for 30 min. The reaction was quenched with water and extracted several times with ether. The combined ether extracts were washed once with brine, dried with $MgSO_4$, and filtered. Meanwhile, a solution of 228 mg (0.973 mmol) of the bis(maleimide) tether **154** (n = 3) in ~250 mL of THF was cooled to –40 °C. The difuran solution was added dropwise to the bis(maleimide) solution at –40 °C and the reaction mixture stirred overnight, warming to room temperature. The solvent was

removed using a rotary evaporator, and the product passed through an alumina column with $CHCl_3$. The $CHCl_3$ was removed and the product recrystalized from $CHCl_3$/hexanes to yield 124 mg (29%) of **155** (n = 3) as a white powder. m.p. dec > 250 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = –1.41 (AA` of AA`MM`NN`, m, $^2J_{AA'}$ = –12.0 Hz, $^3J_{AM}$ = $^3J_{AN'}$ = $^3J_{A'M'}$ = $^3J_{A'N}$ = 4.0 Hz, $^3J_{AM'}$ = $^3J_{AN}$ = $^3J_{A'N'}$ = $^3J_{A'M}$ = 13.0 Hz, 2H), 2.59 and 2.80 (MM`NN` of AA`MM`NN`, m, $^2J_{MN}$ = $^2J_{M'N'}$ = –12.0 Hz, $^3J_{AM}$ = $^3J_{AN'}$ = $^3J_{A'M'}$ = $^3J_{A'N}$ = 4.0 Hz, $^3J_{AM'}$ = $^3J_{AN}$ = $^3J_{A'N'}$ = $^3J_{A'M}$ = 13.0 Hz, 4H), 3.82 and 3.90 (AB of ABMN, m, $^3J_{AB}$ = 8.0 Hz, $^3J_{AM}$ = $^3J_{BN}$ = 5.5 Hz, 4H), 5.90 (M of ABMN, d, $^3J_{AM}$ = 5.5 Hz, 2H), 6.21 (N of ABMN, d, $^3J_{BN}$ = 5.5 Hz, 2H), 7.55 and 7.74 (AB, J = 8.0 Hz, 4H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 25.7, 35.0, 46.7, 49.7, 80.5, 81.6, 120.5, 125.4, 128.3, 138.8, 141.3, 173.3, 173.3.

IR (KBr): 3005, 2949, 2852, 1776 and 1701 (C=O), 1458, 1396, 1344, 1220, 1128, 1040, 866, 635 cm^{-1}.

MS (EI) *m/e* calc'd for $C_{25}H_{18}N_2O_6$: 442.1165, found 442.1165; 442 (M^+, 17), 209 (18), 208 (100), 152 (5), 151 (5), 110 (5), 57 (7), 55 (5).

General procedure for the other naphthodifuran-derived cyclophanes: Bis(acetal) **153** (50 mg, 0.18 mmol) was dissolved in 20 mL of dry diethyl ether and cooled to 0 °C under nitrogen. LDA (0.92 mL of 2.0 M solution in heptane/THF/ethylbenzene, 1.8 mmol) was added *via* syringe and the mixture stirred for 30 min. The reaction was quenched with water and extracted several times with ether. The combined ether extracts were washed once with brine, dried with $MgSO_4$, and filtered. Meanwhile, a solution of one equivalent (0.18 mmol) of the bis(maleimide) tether **154** (n = 4–6) in about 250 mL

of THF was cooled to –40 °C. The difuran solution was added dropwise to the bis(dienophile) solution at –40 °C and the reaction mixture stirred overnight. The solvent was removed using a rotary evaporator, and the product passed through an alumina column with $CHCl_3$ (silica gel column with 5% EtOAc/$CHCl_3$ for **155** (n = 5 and 6)). The solvent was removed and the product recrystalized from $CHCl_3$/hexanes as a white powder.

4C Naphthodifuran-derived cyclophane (155, n = 4): Yield: 23 mg (27%). m.p. > 350 °C.

^{1}H NMR (500 MHz, CD_2Cl_2): δ = –0.14 (m, 2H), 0.44 (m, 2H), 2.71 (m, 2H), 3.06 (m, 2H), 3.90 and 3.94 (AB of ABMN, m, $^3J_{AB}$ = 8.0 Hz, $^3J_{AM}$ = $^3J_{BN}$ = 5.5 Hz, 4H), 5.90 (M of ABMN, d, $^3J_{AM}$ = 5.5 Hz, 2H), 6.20 (N of ABMN, d, $^3J_{BN}$ = 5.5 Hz, 2H), 7.60 and 7.80 (AB, J = 8.0 Hz, 4H).

^{13}C NMR (125 MHz, CD_2Cl_2): δ = 24.9, 38.7, 47.3, 49.4, 79.6, 81.0, 120.2, 124.8, 126.9, 139.0, 140.8, 173.9, 174.1.

IR (KBr): 3046, 2950, 2924, 2852, 1771 and 1698 (C=O), 1439, 1399, 1344, 1292, 1174, 864, 635 cm^{-1}.

MS (EI) *m/e* calc'd for $C_{26}H_{20}N_2O_6$: 456.1321, found 456.1327; 456 (M^+, 17), 209 (17), 208 (100), 151 (17), 110 (16), 97 (14), 85 (18), 83 (16), 71 (25), 69 (18), 57 (40), 55 (19).

5C Naphthodifuran-derived cyclophane (155, n = 5): Yield: 5 mg (3%). m.p. > 350 °C.

^{1}H NMR (500 MHz, CD_2Cl_2): δ = –0.70 (m, 2H), 0.60 (m, 2H), 0.77 (m, 2H), 3.00 (m, 4H), 3.94 and 3.96 (AB of ABMN, m, $^3J_{AB}$ = 8.0 Hz, $^3J_{AM}$ = $^3J_{BN}$ = 5.5 Hz, 4H), 5.87 (M of ABMN, d, $^3J_{AM}$ = 5.5 Hz, 2H), 6.18 (N of ABMN, d, $^3J_{BN}$ = 5.5 Hz, 2H), 7.62 and 7.83 (AB, J = 8.0 Hz, 4H).

IR (KBr): 3047, 2935, 2863, 1769 and 1701 (C=O), 1439, 1394, 1355, 1314, 1165, 1037, 855, 634 cm^{-1}.

6C Naphthodifuran-derived cyclophane (155, *n* = 6): Yield: 1 mg (1%). m.p. > 350 °C.

^{1}H NMR (500 MHz, CD_2Cl_2): δ = –0.09 (m, 2H), 0.07 (m, 2H), 0.49 (m, 2H), 1.11 (m, 2H), 2.99 (m, 4H), 3.95 and 4.02 (AB of ABMN, m, $^3J_{AB}$ = 8.0 Hz, $^3J_{AM}$ = $^3J_{BN}$ = 5.5 Hz, 4H), 5.82 (M of ABMN, d, $^3J_{AM}$ = 5.5 Hz, 2H), 6.12 (N of ABMN, d, $^3J_{BN}$ = 5.5 Hz, 2H), 7.64 and 7.83 (AB, J = 8.0 Hz, 4H).

IR (KBr): 3057, 2940, 2864, 1771 and 1701 (C=O), 1398, 1150, 1043, 865, 814 cm^{-1}.

MS (EI) *m/e* calc'd for $C_{28}H_{24}N_2O_6$: 484.1634, found 484.1630; 484 (M^+, 12), 209 (16), 208 (100), 152 (4), 110 (8), 55 (4).

General procedure for stilbenedifuran-derived cyclophanes: Approximately 200 mg (0.64 mmol) of stilbenedifuran precursor (**53**) and 20 mL CH_2Cl_2 were stirred under nitrogen. Two equivalents of dipytet (**13**) were added and the mixture stirred for 1 h at room temperature. Meanwhile, one equivalent of the bis(maleimide) tether (**154**, *n* = 5–8, or **157**) was dissolved in 200 mL CH_2Cl_2 and cooled to –40 °C. The dipytet solution was diluted to 50 mL, loaded into a syringe pump, and added to the bis(maleimide) at a rate of

50 mL/h. The reaction was warmed to room temperature overnight, then washed repeatedly with 1 M HCl until the CH_2Cl_2 layer was orange, then once with brine, dried with $MgSO_4$, filtered, and the CH_2Cl_2 removed.

5C Stilbenedifuran-derived cyclophane (156, *n* = 5): The product was passed through a silica gel column with $CHCl_3$. The product-containing fractions were combined and the solvent evaporated. Recrystalization from $CHCl_3$/hexanes yielded 8 mg (2%) of pure product as an ivory powder and 16 mg (5%) of dark yellow powder that was product contaminated with unreacted **154**. m.p. > 350 °C.

^{1}H NMR (500 MHz, CD_2Cl_2): δ = –0.13 (m, 2H), 0.61 (m, 2H), 0.75 (m, 2H), 2.66 (ddd, ^2J = –13.0 Hz, ^3J = 13.0 Hz, ^3J = 4.5 Hz, 2H), 2.95 (ddd, ^2J = –13.0 Hz, ^3J = 13.0 Hz, ^3J = 4.5 Hz, 2H), 3.67 and 3.76 (AB of ABMN, m, $^3J_{AB}$ = 8.0 Hz, $^3J_{AM}$ = $^3J_{BN}$ = 5.5 Hz, 4H), 5.73 (M of ABMN, d, $^3J_{AM}$ = 5.5 Hz, 2H), 5.76 (N of ABMN, d, $^3J_{BN}$ = 5.5 Hz, 2H), 7.02 (s, 2H), 7.29 and 7.42 (AB, J = 8.0 Hz, 4H), 7.43 (s, 2H).

^{13}C NMR (62.5 MHz, CD_2Cl_2): δ = 22.0, 24.8, 35.8, 45.2, 47.0, 77.7, 77.8, 115.7, 118.6, 124.3, 126.2, 135.5, 138.6, 138.8, 174.3, 175.5.

IR (KBr): 3014, 2972, 2942, 2866, 1772 and 1708 and 1690 (C=O), 1398, 1203, 1193, 1132, 862, 827, 626, 574 cm^{-1}.

6C Stilbenedifuran-derived cyclophane (156, *n* = 6): The product was passed through a silica gel column with $CHCl_3$. The product-containing fractions were combined and the solvent evaporated. Recrystalization from toluene/hexanes yielded 38 mg (11%) of pure

product as a pale yellow powder and 45 mg (13%) of yellow powder that was product contaminated with unreacted **154**. m.p. dec > 180 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.21 (br m, 2H), 0.56 (br m, 4H), 0.82 (br m, 2H), 2.89 (m, 4H), 3.72 (AB of ABMN, m, $^3J_{AB}$ = 8.0 Hz, $^3J_{AM}$ = $^3J_{BN}$ = 5.5 Hz, 4H), 5.71 (M of ABMN, d, $^3J_{AM}$ = 5.5 Hz, 2H), 5.75 (N of ABMN, d, $^3J_{BN}$ = 5.5 Hz, 2H), 6.97 (s, 2H), 7.17 and 7.34 (AB, J = 8.0 Hz, 4H), 7.41 (s, 2H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 26.5, 27.4, 38.5, 48.6, 49.2, 80.47, 80.51, 119.1, 121.4, 126.5, 129.3, 138.3, 140.9, 141.8, 174.1, 174.3.

IR (KBr): 3011, 2940, 2857, 1772 and 1701 (C=O), 1399, 1345, 1152, 859, 831 cm^{-1}.

7C Stilbenedifuran-derived cyclophane (156, *n* = 7): The product was loaded onto a silica gel column and 10% toluene/$CHCl_3$ passed through until the second yellow fraction eluted. ^{1}H NMR indicated that the first fraction was unreacted **53** and the second fraction unreacted tether (**154**) and a small amount of cyclophane (**156**). $CHCl_3$ was then passed through the column until the third yellow fraction eluted, which proved to be cyclophane (**156**) and a small amount of tether (**154**). The product-containing fractions were combined and the solvent evaporated. Recrystalization from toluene/hexanes yielded 62 mg (17%) of yellow powder that was product contaminated with unreacted **154**. m.p. dec > 180 °C.

^{1}H NMR (500 MHz, CD_2Cl_2): δ = –0.03 (m, 2H), 0.26 (m, 2H), 0.84 (br m, 6H), 2.84 (ddd, ^2J = –12.5 Hz, ^3J = 12.5 Hz, ^3J = 4.5 Hz, 2H), 2.96 (ddd, ^2J = –12.5 Hz, ^3J = 12.5 Hz, ^3J = 4.5 Hz, 2H), 3.75 and 3.80 (AB of ABMN, m, $^3J_{AB}$ = 8.0 Hz, $^3J_{AM}$ = $^3J_{BN}$ = 5.5 Hz, 4H), 5.72 (M of ABMN, d, $^3J_{AM}$ = 5.5 Hz, 2H), 5.73 (N of ABMN, d, $^3J_{BN}$ = 5.5 Hz,

2H), 7.11 (s, 2H), 7.32 (d, J = 7.5 Hz, 2H), 7.36 (br s, 2H), 7.54 (dd, ^{3}J = 7.5 Hz, ^{4}J = 1.5 Hz, 2H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 25.8, 28.7, 32.5, 38.2, 48.2, 49.0, 80.5, 80.7, 120.5, 121.6, 125.6, 128.5, 137.6, 141.5, 142.0, 174.1, 174.4.

IR (KBr): 3011, 2934, 2856, 1772 and 1700 (C=O), 1653, 1400, 1373, 1192, 860, 826, 624, 585 cm^{-1}.

8C Stilbenedifuran-derived cyclophane (156, *n* = 8): The product was loaded onto a silica gel column and toluene passed through until the first yellow fraction eluted. $CHCl_3$ was then passed through the column until the third yellow fraction eluted, which proved to be cyclophane (**156**) and a small amount of tether (**154**). The product-containing fractions were combined and the solvent evaporated. Recrystalization from toluene/hexanes yielded 45 mg (12%) of yellow powder that was product contaminated with unreacted **154**. m.p. dec > 145 °C.

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 0.22 (m, 2H), 0.34 (m, 2H), 0.85, (br m, 8H), 2.86 (ddd, ^{2}J = –12.0 Hz, ^{3}J = 12.0 Hz, ^{3}J = 5.0 Hz, 2H), 2.96 (ddd, ^{2}J = –12.0 Hz, ^{3}J = 12.0 Hz, ^{3}J = 5.0 Hz, 2H), 3.76 and 3.78 (AB of ABMN, m, $^3J_{AB}$ = 8.0 Hz, $^3J_{AM}$ = $^3J_{BN}$ = 5.5 Hz, 4H), 5.72 (M of ABMN, d, $^3J_{AM}$ = 5.5 Hz, 2H), 5.75 (N of ABMN, d, $^3J_{BN}$ = 5.5 Hz, 2H), 7.12 (s, 2H), 7.30 and 7.41 (AB, J = 8.0 Hz, 4H), 7.49 (s, 2H).

^{13}C NMR (125 MHz, CD_2Cl_2): δ = 25.8, 26.6, 29.0, 38.4, 48.6, 48.7, 80.4, 80.5, 119.1, 121.5, 126.6, 128.5, 137.4, 141.2, 142.4, 174.0, 174.2.

IR (KBr): 3022, 2933, 2855, 1772 and 1701 (C=O), 1653, 1399, 1363, 1149, 859, 829, 696, 621, 576 cm^{-1}.

***p*-Xylyl stilbenedifuran-derived cyclophane (158):** The product was passed through a silica gel column with $CHCl_3$. The product-containing fractions were combined and the solvent evaporated. Recrystalization from $CHCl_3$/hexanes yielded 48 mg (13%) of yellow powder that was **158** contaminated with unreacted **157**. m.p. 146–154 °C.

^1H NMR (250 MHz, $CDCl_3$): δ = 3.79 and 3.81 (AB of ABMN, m, $^3J_{AB}$ = 8.0 Hz, $^3J_{AM}$ = $^3J_{BN}$ = 5.5 Hz, 4H), 4.03 and 4.46 (AM, d, $^3J_{AM}$ = 6.3 Hz, 4H), 5.66 (M of ABMN, d, $^3J_{AM}$ = 5.5 Hz, 2H), 5.68 (N of ABMN, d, $^3J_{BN}$ = 5.5 Hz, 2H), 6.81 (d, J = 8.0 Hz, 2H), 6.99 (s, 2H), 7.06 (d, J = 8.0 Hz, 2H), 7.36 (s, 2H), 7.43 and 7.51 (AB, J = 8.8 Hz, 4H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 42.0, 49.1, 49.3, 80.6, 80.7, 118.5, 121.4, 127.6, 128.27, 128.31, 128.4, 128.7, 129.2, 129.5, 132.4, 174.29, 174.33.

IR (KBr): 3163, 3096, 3022, 2938, 1771 and 1706 (C=O), 1433, 1399, 1344, 1169, 858, 827, 695 cm^{-1}.

Chapter 3 Progress Towards the Syntheses of Phenanthro[2,3-*c*:6,7-*c*]difuran and Its Cyclophanes

3.1 Phenanthrenophane Syntheses

Phenanthrenophanes have been previously synthesized either by a coupling reaction of a dibromide and a dithiol, or by a photochemical reaction. Each method is reviewed briefly below.

3.1.1 Phenanthrenophanes from Coupling Reactions

Many of the same techniques used to synthesize naphthalenophanes have been used to synthesize phenanthrenophanes. For example, Haenel and Staab synthesized *syn*- and *anti*-[2.2](2,7)phenanthrenophane (**159** and **160**) from 5,6,17,18-tetrahydro[2.2](2,7)phenanthrenophane (**161**) by DDQ oxidation (see Figure 3.1). The tetrahydrophenanthrenophane **161** was itself synthesized by coupling 2,7-bis(bromomethyl)-9,10-dihydrophenanthrene and 2,7-bis(thiomethyl)-9,10-dihydrophenanthrene, oxidizing the resultant dithia cyclophane to the disulphone, and subjecting the disulphone to vacuum pyrolysis.[91,125] The synthesis of [2](4,4')biphenylo-[2](2,7)phenanthrenophane (**162**) was also reported.[125]

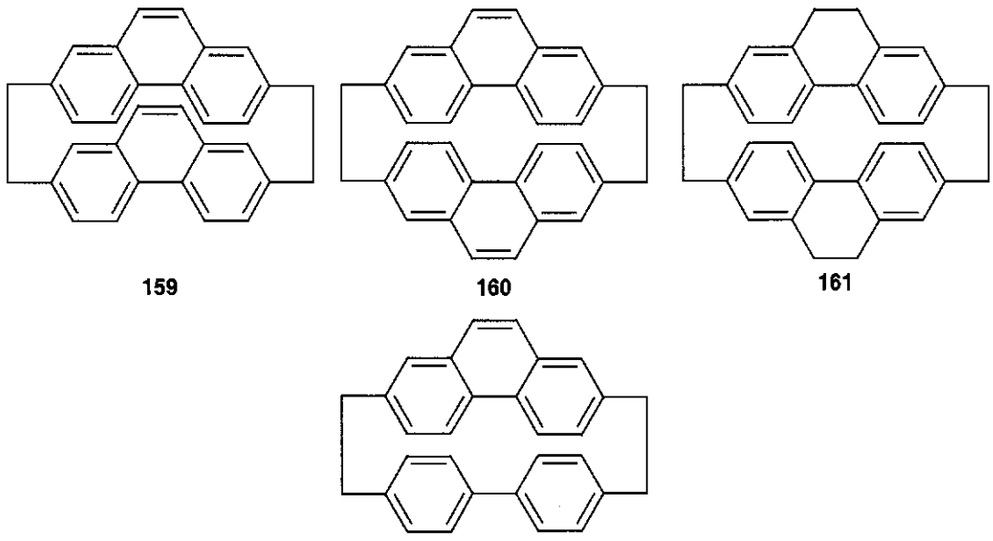
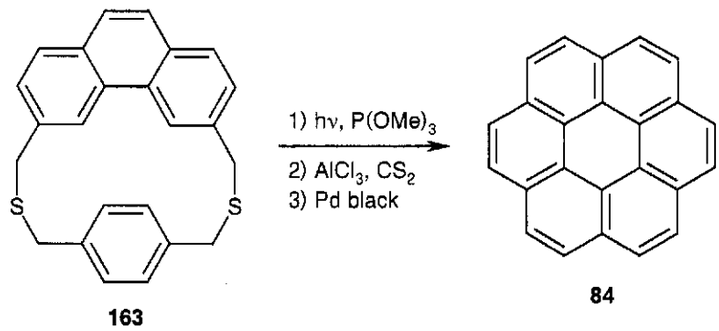


Figure 3.1: Haenel and Staab's Phenanthrenophanes

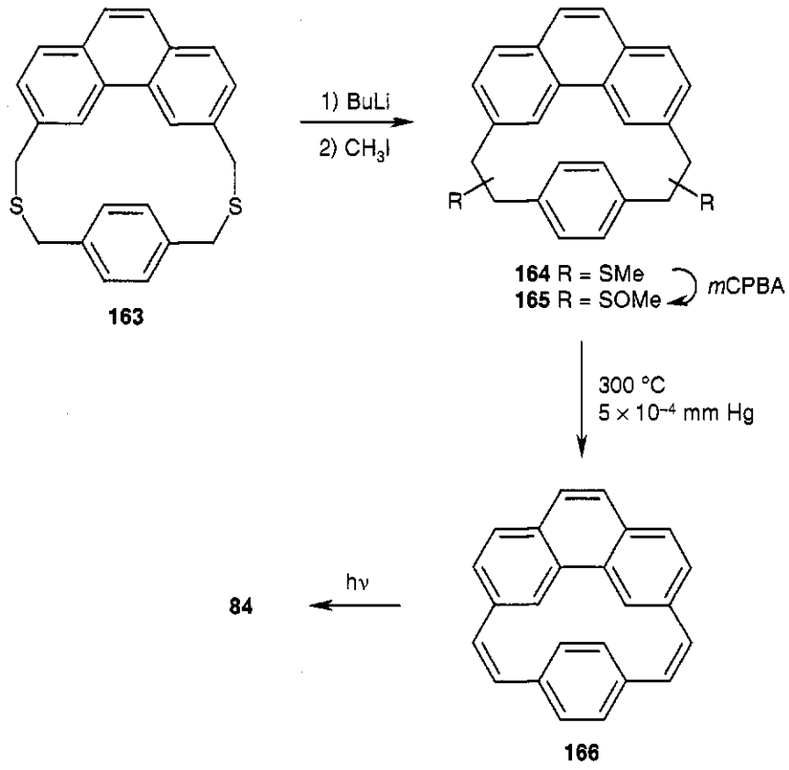
Phenanthrenophanes have proved useful in the synthesis of polycyclic aromatic hydrocarbons. 2,11-Dithia[3]paracyclo[3](3,6)phenanthrenophane (**163**) was prepared by coupling together 3,6-bis(bromomethyl)phenanthrene and 1,4-bis(thiomethyl)benzene. Photochemical extrusion of sulphur and cyclodehydrogenation gave coronene (**84**, Scheme 3.1).[126]



Scheme 3.1

Jessup and Reiss synthesized [2]paracyclo[2](3,6)phenanthrenophane-1,11-diene (**166**) from **163**.[127] The most efficient preparation involved a Wittig rearrangement of **163** and reaction with methyl iodide to give **164**, followed by oxidation to generate **165** and

subsequent vacuum pyrolysis to the diene (Scheme 3.2). Irradiation of the diene gave coronene. Jessup and Reiss also reported an attempted synthesis of [7]circulene from [2](3,6)phenanthro[2](2,7)naphthalenophane-1,11-diene.[128] Leach and Reiss reported an attempted synthesis of [8]circulene from [2](3,3')biphenylo[2](3,6)phenanthrenophane-1,15-diene.[129]



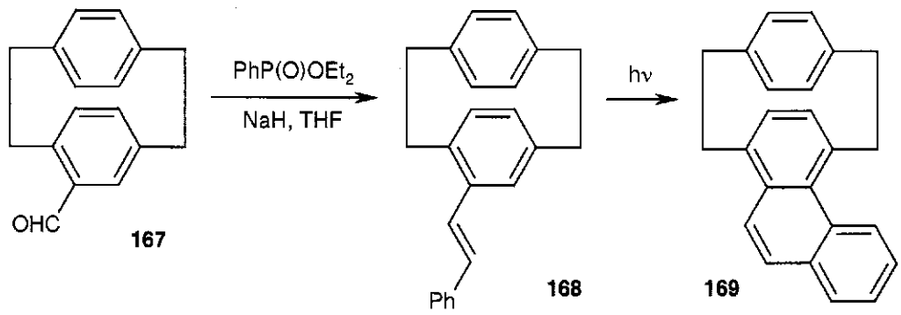
Scheme 3.2

3.1.2 Phenanthrenophanes by Photochemical Methods

The photocyclization of [*n*.2]paracyclophan-(*n*+7)-enes to [*n*](3,6)phenanthrenophanes (*n* = 7–10)[103] was previously described in Section 2.1.3.

Hopf's benzannulation approach to [2]paracyclo[2](1,4)phenanthrenophane (**169**) is outlined in Scheme 3.3. 4-Formyl[2.2]paracyclophane (**167**) was converted to a

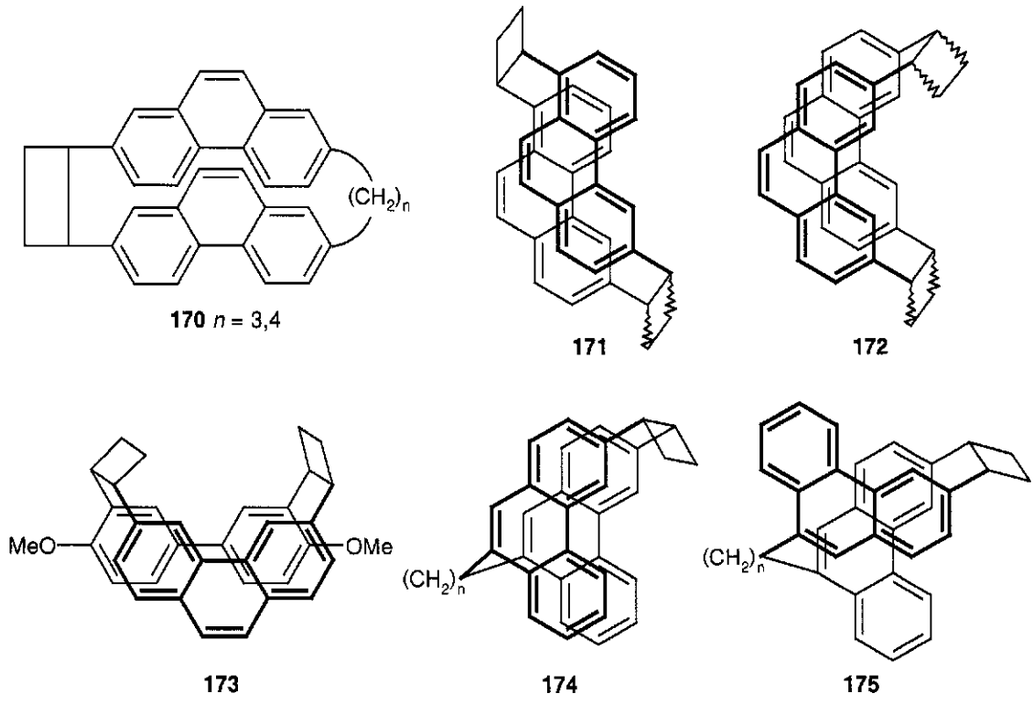
stilbene (**168**) by a Wadsworth–Emmons reaction, which was photocyclized to give **169**.[130]



167 **168** **169**

Scheme 3.3

Nishimura used his [2+2] photocycloaddition approach to isolate exclusively *syn*-cyclobutano[2.3]- and [2.4]phenanthrenophanes (**170**, Figure 3.2).[131] The synthesis of cyclobutano[2.2](1,6)- and [2.2](3,6)phenanthrenophanes was later reported (**171** and **172**, Figure 3.2).[132] The (3,6)phenanthrenophane (**172**) was subsequently converted to [4.4](3,6)phenanthrenophane by a Birch reduction and DDQ oxidation. Other phenanthrenophanes synthesized by this method include a [2](3,3')biphenylo[2](3,6)phenanthrenophane (**173**)[133] and *syn*- and *anti*-[*n*.2](3,9)phenanthrenophanes (*n* = 3,4; **174** and **175**).[134] This work has been summarized in a review article.[98]



170 n = 3,4 **171** **172**

173 **174** **175**

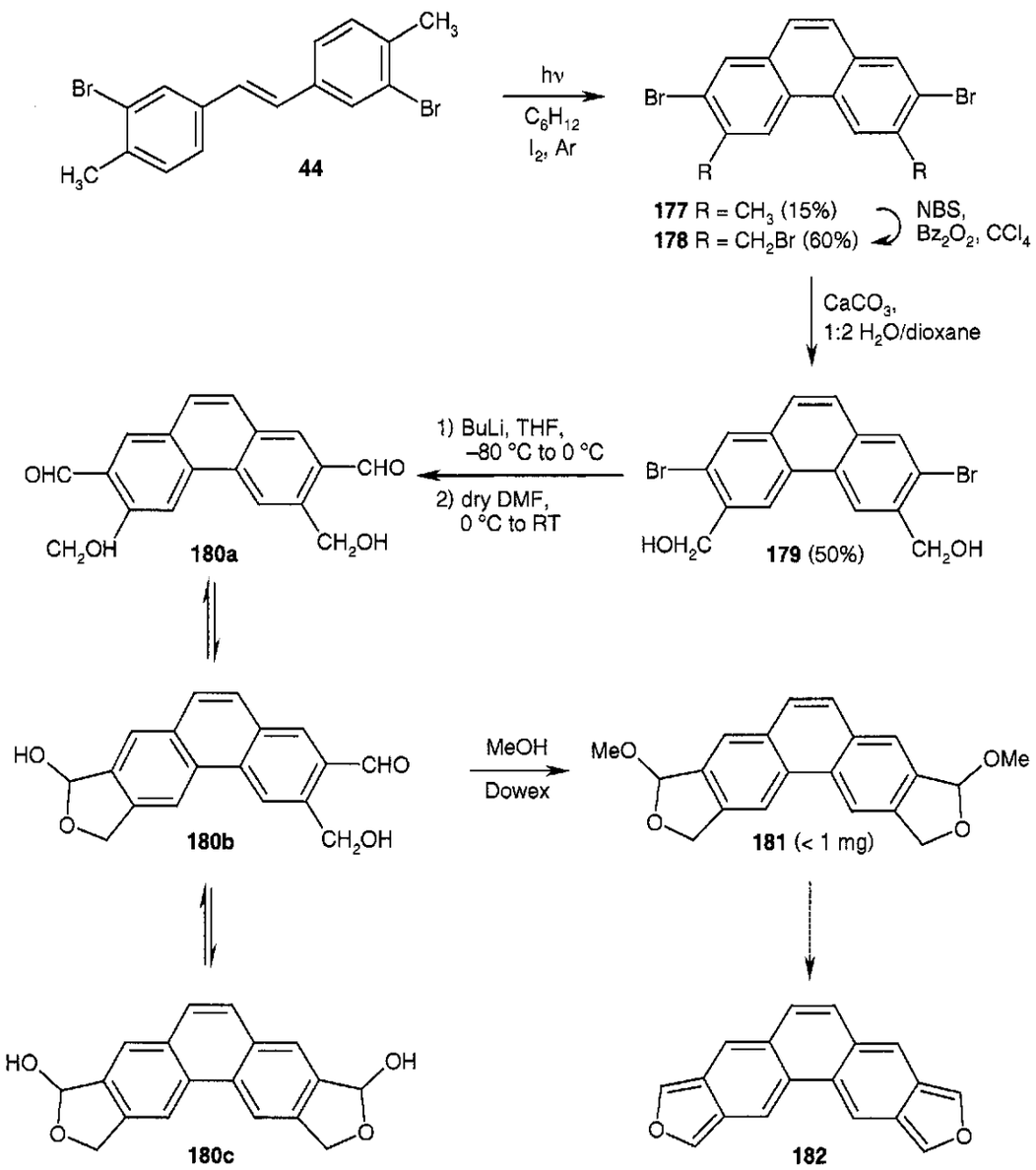
Figure 3.2: Nishimura's Cyclobutane-fused Phenanthrenophanes

3.2 Results and Discussion

Routes to phenanthro[2,3-*c*:6,7-*c*]difuran and (**182**) its cyclophanes were explored as part of the study on novel isobenzofuran systems and their use in the synthesis of cyclophanes. Generation of **182** from its bis(acetal) precursor by treatment with LDA, from the 1,2-bis(5-isobenzofuranyl)ethene precursor (**53**) by photocyclization, and from the bis(*N*-methylmaleimide) adduct of 1,2-bis(5-isobenzofuranyl)ethene (**54**) by photocyclization were all attempted. The bis(*N*-methylmaleimide) adduct was used as a model for the eventual generation of phenanthrodifuran cyclophanes from the corresponding stilbenedifuran-derived cyclophanes. If the adduct cyclized successfully, then it could be expected that the stilbenedifuran-derived cyclophanes would also cyclize.

3.2.1 Phenanthro[2,3-*c*:6,7-*c*]difuran *via* the Base-Induced Method

Outlined in Scheme 3.4 is the initial preparation of phenanthro[2,3-*c*:6,7-*c*]difuran (**182**) from its bis(acetal) by a sequence analogous to that used for the initial preparation of 1,2-bis(5-isobenzofuranyl)ethene (**40**). Photocyclization of stilbene **44** to 2,7-dibromo-3,6-dimethylphenanthrene (**177**) proceeded in low yield, with a substantial quantity of debrominated product (**183**, Figure 3.3) being isolated. Radical bromination of **177** to **178** and subsequent hydrolysis gave diol **179**. Metal-halogen exchange followed by formylation gave bis(hemiacetal) **180**, which existed in equilibrium as a mixture of tautomers **180a**, **180b**, and **180c**. As before, analysis of the ^{1}H NMR spectrum was complicated not only because of the tautomeric mixture, but also because the reaction did not appear to proceed cleanly. Bis(hemiacetal) **180** was converted directly to bis(acetal) **181** by stirring it in methanol with Dowex. Only a trace of **181** was isolated, most likely because of the poor results of the metalation reaction. Consequently, generation and trapping of difuran **182** was not attempted. The low yield of the photocyclization combined with the difficulty in cleanly forming the bis(hemiacetal) led to this strategy being abandoned.



Scheme 3.4

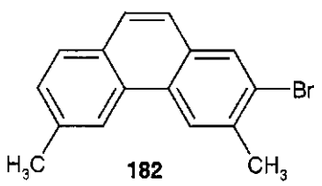
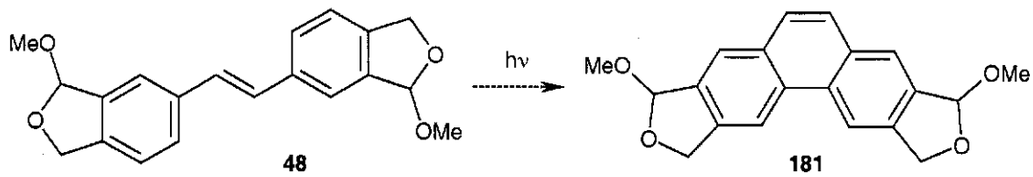


Figure 3.3: Debrominated Product from the Photocyclization of 44

3.2.2 Phenanthro[2,3-*c*:6,7-*c*]difuran *via* Photocyclization of 1,2-Bis(5-isobenzofuranyl)ethene Precursors or Adducts

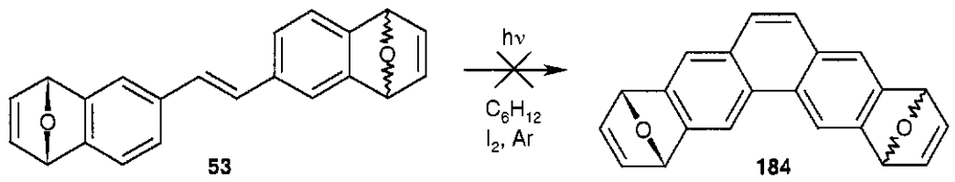
After it was found that the photocyclization of **44** proceeded with loss of bromine, the decision was made to attempt photocyclization of other 1,2-bis(5-isobenzofuranyl)ethene precursors to the analogous phenanthro[2,3-*c*:6,7-*c*]difuran precursors. The first candidate was bis(acetal) **48**, but because of the problems encountered in generating sufficient quantities of **48**, photocyclization to **181** (Scheme 3.5) was never attempted.



48 **181**

Scheme 3.5

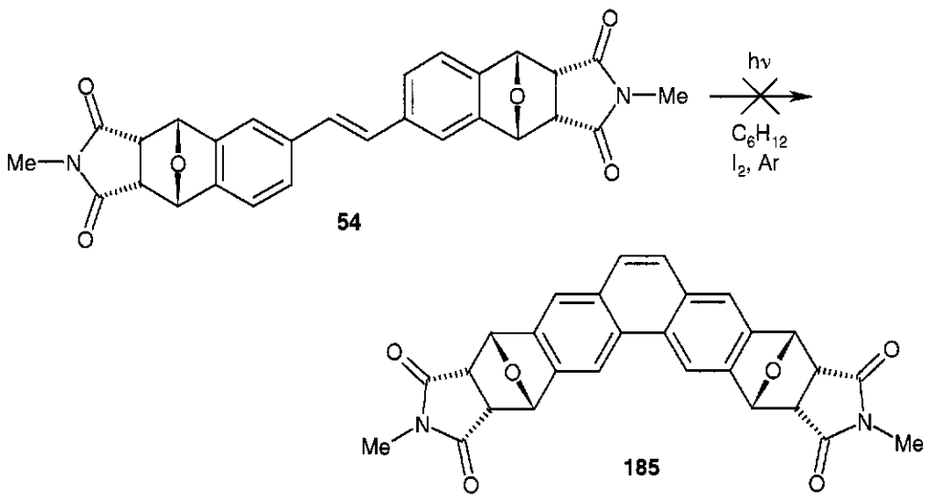
Photocyclization of **53** to **184** was attempted (Scheme 3.6). After two hours, the ^{1}H NMR signals due to the oxa-bridge protons had disappeared, indicating that cleavage of the C–O–C bonds had occurred. Work-up of the reaction mixture gave only an unidentifiable brown powder.



53 **184**

Scheme 3.6

The photocyclization of the bis(*N*-methylmaleimide) adduct (**54**) of 1,2-bis(5-isobenzofuranyl)ethene to **185** was also attempted (Scheme 3.7). Once again, the ^{1}H NMR spectrum indicated that cleavage of the C–O–C bonds had occurred, and work-up gave only an unidentifiable solid.



Scheme 3.7

In retrospect, photochemically-induced cleavage of the C–O–C bond is not surprising. Cossy *et al.* have reported that irradiation of 7-oxabicyclo[2.2.1]heptan-2-ones leads to the corresponding 3-hydroxycyclohexanones.[135,136] Furthermore, when iodine is used as the oxidant, HI is generated as a by-product.[137] A recent review article on oxabicyclo[2.2.1]heptanes indicates that HI can cleave oxabicyclic bridges.[138] The proton activates the oxa-bridge, and then the iodide anion acts as a nucleophile to displace the ethereal moiety. The net result is a substituted cyclohexanol ring.

In addition to the disappearance of signals due to the oxa-bridge protons, signals due to the vinyl protons of **53** and **54** disappeared and new aromatic signals appeared. However, none of the aromatic peaks was further downfield than 7.8 ppm; if **184** and **185** had formed, peaks due to the bay region protons should have been observed between 8.5 and 9.0 ppm.

Katz[139] reported that using a stoichiometric amount of I_2 and a large excess of propylene oxide (to consume the HI that is generated) for the photocyclization of

stilbenes led to better yields of phenanthrenes than I_2 alone. The photocyclization of **54** to **185** under these conditions was not successful.

3.3 Summary

Several synthetic pathways leading to phenanthro[2,3-*c*:6,7-*c*]difuran (**182**) or its cyclophanes were investigated, but none proved to be successful. The bis(acetal) route was hampered by low yields and the photocyclization of stilbene precursors led only to decomposition. Ideas for improving the synthesis of phenanthrodifuran and its cyclophanes will be presented in Chapter 4.

3.4 Experimental

Solvents were used without additional purification with the exception of diethyl ether and THF, both of which were distilled from sodium/benzophenone prior to use. Dry DMF was dried by distilling it from P_2O_5 onto molecular sieves.[54,55] All organic starting materials were purchased from the Aldrich Chemical Co. unless otherwise noted. Melting points were performed in open capillaries and are uncorrected. NMR spectra were recorded on a Brüker AC-250/Tecmag Macspect NMR spectrometer at an ambient temperature of 298 K. ^{1}H NMR chemical shifts in $CDCl_3$ were referenced to TMS. ^{13}C NMR chemical shifts were referenced to the $CDCl_3$ triplet at 77.23 ppm. Infrared spectra were recorded on a Bomem MB-102 or Nicolet Avatar 360 spectrometer. Mass spectra were performed by the Mass Spectroscopy Lab, Department of Chemistry, University of Alberta. Elemental analyses were performed by M-H-W Laboratories, Phoenix, Arizona.

2,7-Dibromo-3,6-dimethylphenanthrene (177): Stilbene **44** (9.22 g, 0.0252 mol) was photocyclized in three batches as follows: Approximately 3 g of **44**, a crystal of I_2, and 600 mL of cyclohexane were stirred in a photoreactor for 30 min while Ar was bubbled through. The mixture was then irradiated through a Vycor filter using a medium-pressure Hg lamp. The reaction was complete in 1–2 d. The three batches were combined and the cyclohexane evaporated. The solid was then dissolved in CH_2Cl_2, the solution washed three times with 10% $NaHSO_3$, dried with $MgSO_4$, filtered, and the CH_2Cl_2 removed using a rotary evaporator. The brown solid was passed through a silica gel column using cyclohexane as the eluent. A yellow band eluted that was a mixture of **177** and **183**. Recrystalization from EtOAc/petroleum ether yielded 1.33 g (15%) of pale yellow, fluffy crystals of **177**. m.p. 160–162 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.66 (s, 6H), 7.57 (s, 2H), 8.06 (s, 2H), 8.46 (s, 2H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 23.8, 124.4, 126.1, 128.8, 129.1, 131.9, 132.0, 136.5.

IR (KBr): 2946, 2911, 1613, 1596, 1491, 1449, 1433, 1377, 1052, 1005, 882, 874, 827, 719, 431 cm^{-1}.

MS (EI) *m/e* calc'd for $C_{16}H_{12}Br_2$: 364.0820, found 363.9285; 367 (12), 366 (M^+ $^{81}Br_2$, 66), 365 (26), 364 (M^+ $^{81}Br^{79}Br$, 100), 363 (18), 362 (M^+ $^{79}Br_2$, 67), 286 (22), 285 (32), 284 (23), 283 (30), 204 (17), 203 (33), 202 (44), 201 (11), 200 (12), 190 (10), 189 (49), 102 (11), 101 (33), 88 (12).

Analysis calc'd for $C_{16}H_{12}Br_2$: C, 52.78; H, 3.33; found: C, 53.00; H, 3.29.

2-Bromo-3,6-dimethylphenanthrene (183): The filtrate from the recrystalization of **177** was concentrated to yield 0.77 g (8%) of pale yellow powdery crystals of **183**. m.p. 109–111 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.62 (s, 3H), 2.66 (s, 3H), 7.44 (d, J = 8.5 Hz, 1H), 7.54 and 7.66 (AB, J = 8.8 Hz, 2H), 7.76 (d, J = 8.5 Hz, 1H), 8.05 (s, 1H), 8.41 (s, 1H), 8.50 (s, 1H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 22.3, 23.8, 122.6, 124.0, 124.6, 124.8, 126.1, 127.4, 128.8, 129.5, 130.1, 130.4, 131.7, 132.2, 135.9, 136.9.

IR (KBr): 3011, 2972, 2942, 2915, 2851, 1615, 1598, 1491, 1450, 1435, 888, 881, 837, 704, 543, 436 cm^{-1}.

MS (EI) *m/e* calc'd for $C_{16}H_{13}Br$: 285.1860, found 285.0202; 287 (12), 286 (M^+ ^{81}Br, 97), 285 (21), 284 (M^+ ^{79}Br, 100), 206 (13), 205 (31), 202 (12), 190 (14), 189 (31), 101 (13), 65 (11).

2,7-Dibromo-3,6-bis(bromomethyl)phenanthrene (178): 0.63 g (1.73 mmol) of **177**, 0.67 g (3.76 mmol) of NBS, and a few crystals of benzoyl peroxide were refluxed overnight in 40 mL CCl_4. Upon cooling, a white solid precipitated. The CCl_4 was removed using a rotary evaporator and EtOAc added to dissolve the solid. The organic layer was washed three times with saturated aqueous $NaHCO_3$ solution, dried with $MgSO_4$, filtered, and the EtOAc removed. Recrystalization from EtOAc/petroleum ether yielded 0.543 g (60%) of pale yellow fluffy crystals of **178**. m.p. 217–219 °C (dec).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.89 (s, 2H), 7.67 (s, 2H), 8.13 (s, 2H), 8.70 (s, 2H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 33.9, 123.3, 125.7, 127.2, 127.5, 133.2, 133.6, 136.0.

IR (KBr): 3006, 1731, 1603, 1432, 1210, 1054, 890, 874, 639 cm^{-1}.

MS (EI) *m/e* calc'd for $C_{16}H_{10}Br_4$: 521.8741 found 521.7475; 526 (M^+ $^{81}Br_4$, 5), 524 (M^+ $^{81}Br_3{}^{79}Br$, 18), 523 (20), 522 (M^+ $^{81}Br_2{}^{79}Br_2$, 27), 521 (28), 520 (M^+ $^{81}Br^{79}Br_3$, 19), 519 (18), 518 (M^+ $^{79}Br_4$, 5), 445 (34), 444 (34), 443 (96), 442 (32), 441 (100), 440 (19), 439 (35), 203 (13), 202 (57), 201 (33), 200 (43), 101 (25), 100 (13).

Analysis calc'd for $C_{16}H_{10}Br_4$: C, 36.82; H, 1.94; found: C, 36.68; H, 1.86.

2,7-Dibromo-3,6-bis(hydroxymethyl)phenanthrene (179): 0.370 g (0.709 mmol) of **178**, 0.292 g (2.92 mmol) of $CaCO_3$, 25 mL of H_2O, and 25 mL of 1,4-dioxane were refluxed for 3 d. The dioxane was removed using a rotary evaporator, EtOAc and 6 M HCl were added to dissolve the solids, and the layers separated. The aqueous layer was washed three times with EtOAc, then the combined organic fractions were washed three times with saturated aqueous $NaHCO_3$, dried with $MgSO_4$, filtered, and the EtOAc removed. Recrystalization from $CHCl_3$ yielded 0.141 g (50%) of **179** as a pale yellow powder. m.p. 237–239 °C.

^1H NMR (250 MHz, $CDCl_3$): δ = 2.15 (br s, 2H), 5.02 (s, 4H), 7.67 (s, 2H), 8.10 (s, 2H), 8.80 (s, 2H).

IR (KBr): 3417, 2858, 1674, 1606, 1426, 1048, 879, 429 cm^{-1}.

MS (EI) *m/e* calc'd for $C_{16}H_{12}Br_2O_2$: 396.0808 found 395.9178; 398 (M^+ $^{81}Br_2$, 36), 397 (14), 396 (M^+ $^{81}Br^{79}Br$, 73), 395 (10), 394 (M^+ $^{79}Br_2$, 47), 189 (30), 179 (35), 178 (100), 177 (19), 176 (38).

Bis(hemiacetal) precursor to phenanthro[2,3-*c*:6,7-*c*]difuran (180): 0.130 g (0.328 mmol) of diol **179** was dissolved in 20 mL of dry THF under nitrogen and then cooled to –80 °C. BuLi (1.20 mL of a 2.5 M solution in hexanes, 3.00 mmol) was added and the mixture stirred at –80 °C for 30 min, then warmed to 0 °C and stirred for another 15 min. Dry DMF (0.20 mL, 2.58 mmol) was added and the mixture warmed to room temperature overnight. The reaction was quenched with brine, the layers separated, and the aqueous layer washed three times with THF. The combined organic extracts were then washed twice with brine, dried with $MgSO_4$, filtered, and the solvent and residual DMF removed to give a yellow solid. Bis(hemiacetal) **180** was used immediately without further purification.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.98 (s), 5.02 (s), 5.10 (s), 5.12 (d, J = 11.0 Hz), 5.29 (m), 5.52 (m), 6.71 (d, J = 4.5 Hz), 6.98 (s), 7.62 to 7.98 (m), 8.41 to 8.83 (m), 10.25 (s), 10.26 (s), 10.31 (s).

Bis(acetal) precursor to phenanthro[2,3-*c*:6,7-*c*]difuran (181): Bis(hemiacetal) **180** and 129 mg Dowex 50WX8-100 ion-exchange resin were stirred in 50 mL MeOH and refluxed overnight. The mixture was filtered hot to remove the Dowex, the solvent removed, and bis(acetal) **181** recrystalized from MeOH to yield < 1 mg of yellow-orange powder.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.52 (s, 3H), 3.53 (s, 5H), 5.28 and 5.45 (AB, J = 13.3 Hz, 4H), 6.35 (s, 2H), 7.75 (s, 2H), 7.93 (s, 2H), 8.54 (s, 2H).

Attempted Photocyclization of 53 to 184: Stilbene **53** (0.192 g, 0.615 mmol), a crystal of I_2, and 600 mL of cyclohexane were stirred in a photoreactor for 30 min while Ar was bubbled through. The mixture was then irradiated through a Vycor filter using a medium-pressure Hg lamp for two h. The cyclohexane was removed using a rotary evaporator and the resultant solid dissolved in CH_2Cl_2. The solution was washed three times with 10% $NaHSO_3$, dried with $MgSO_4$, filtered, and the CH_2Cl_2 removed. Recrystalization from toluene/hexanes yielded an unidentifiable brown powder.

Attempted Photocyclization of 54 to 185, Method 1: Stilbene **54** (51 mg, 0.11 mmol), a crystal of I_2, and 350 mL of cyclohexane were stirred in a photoreactor for 15 min while Ar was bubbled through. The mixture was then irradiated through a Vycor filter using a medium-pressure Hg lamp for 12 h. The photoreactor was rinsed with MeOH, the solvents removed using a rotary evaporator, and the resultant solid dissolved in CH_2Cl_2. The solution was washed three times with 10% $NaHSO_3$, once with brine, dried with $MgSO_4$, filtered, and the CH_2Cl_2 removed. Recrystalization from toluene/hexanes yielded only 16 mg of starting material **54**. No identifiable material was obtained from the filtrate.

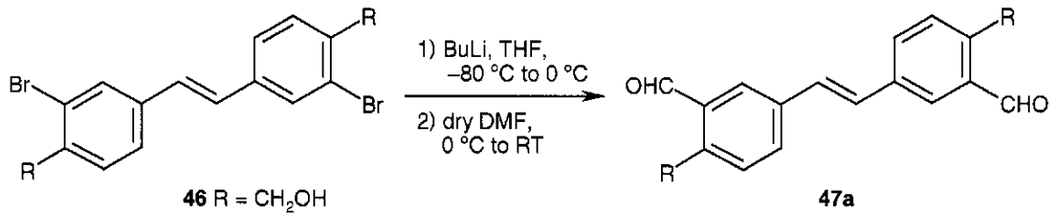
Attempted Photocyclization of 54 to 185, Method 2:[139] Stilbene **54** (53 mg, 0.11 mmol), 32 mg (0.13 mmol) of I_2, and 350 mL of cyclohexane were stirred in a photoreactor while Ar was bubbled through for 30 min. Propylene oxide (2.0 mL, 0.029 mol) was added and the mixture irradiated through a Vycor filter using a medium-pressure Hg lamp for 1 h. The ^1H NMR spectrum indicated that no reaction had occurred,

and therefore, a second addition of I_2 (35 mg, 0.14 mmol) and propylene oxide (1.5 mL, 0.021 mol) was made. The mixture was further irradiated for 4 h, with no change. A crystal of I_2 and 20 mL of toluene (to aid in dissolving the organics) were added and the mixture irradiated again for 4 h. The photoreactor was rinsed with MeOH, the solvents removed using a rotary evaporator, and the resultant solid dissolved in CH_2Cl_2. The solution was washed three times with 10% $NaHSO_3$, once with brine, dried with $MgSO_4$, filtered, and the CH_2Cl_2 removed. Recrystalization from toluene/hexanes yielded 20 mg of starting material **54**. The filtrate was concentrated and passed through a silica gel column with $CHCl_3$. No identifiable material was obtained.

Chapter 4 Future Directions

4.1 Synthesis of 1,2-Bis(5-isobenzofuranyl)ethene and Its Cyclophanes

As discussed in Chapter 1, the synthesis of 1,2-bis(5-isobenzofuranyl)ethene (**40**) worked well up to the generation of diol **46**, but the subsequent metal-halogen exchange and formylation to give **47** proceeded in low yield (Scheme 4.1), leading to this synthesis being abandoned. However, due to the difficulty in obtaining clean cyclophanic products when **40** was generated using dipytet, further examination of the bis(acetal) route is warranted. A preliminary study in which difuran **40** was generated from bis(acetal) **48** upon treatment with LDA and trapped with the bis(maleimide) tether (**154**, n = 7) gave the 7C stilbenedifuran-derived cyclophane in relatively good yield with very little unreacted bis(maleimide). If a better synthesis of difuran **40** could be devised, it would greatly facilitate the synthesis and characterization of its cyclophanes.

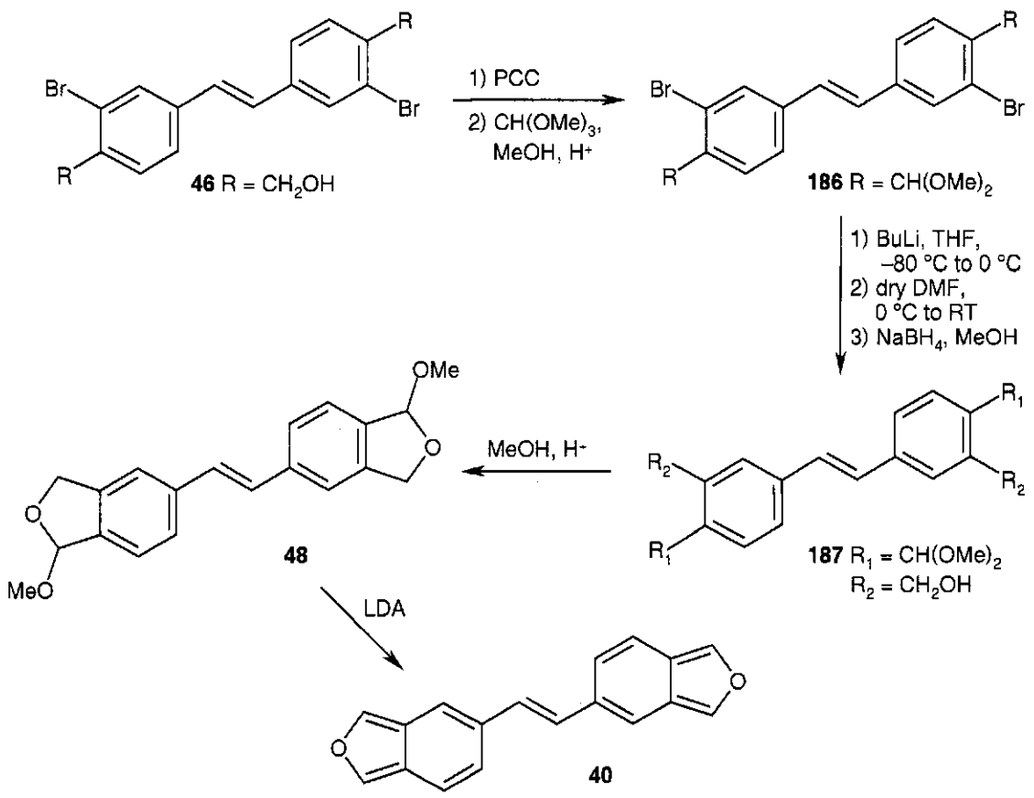


46 R = CH_2OH **47a**

Scheme 4.1

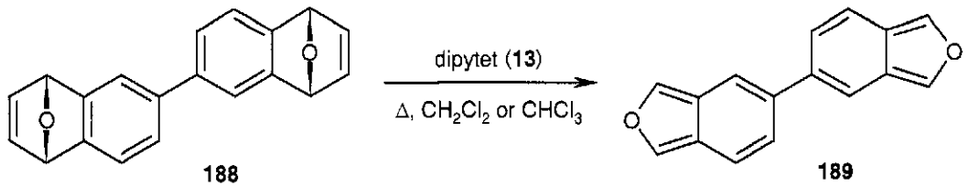
In earlier work with naphtho[1,2-*c*:5,6-*c*]difuran, attempts to generate its precursor bis(hemiacetal) from a dibromodiol analogous to **46** failed and thus a lengthier route involving oxidation and protection of the alcohols was developed.[47] Perhaps a similar strategy, such as that outlined in Scheme 4.2, would be successful for the synthesis of difuran **40**. Thus, diol **46** could be oxidized to a dialdehyde with PCC and the dialdehyde protected to give **186**. Metal-halogen exchange, formylation, and reduction

would give **187**, which could then be subjected to acid-catalyzed cyclization to give **48**. Difuran **40** could then be generated from the bis(acetal) in the usual manner.



Scheme 4.2

If the above synthesis proves not to be feasible, then experiments to optimize the dipytet procedure and its work-up should be conducted. A related study on the generation of 5,5'-bis(isobenzofuran) (**189**, Scheme 4.3) indicates that gently warming **188** with dipytet to generate **189** results in a higher yield of the subsequent bis(*N*-methylmaleimide) adduct than simply stirring the **188** and dipytet together at room temperature.[140] If the yields of the cyclophanes could be improved, then the products would be easier to purify and characterize. Having a larger quantity of clean product would also make it easier to grow X-ray quality crystals.



Scheme 4.3

4.2 Synthesis of Phenanthro[2,3-*c*:6,7-*c*]difuran and Its Cyclophanes

In general, the photocyclization procedure needs to be optimized. First, the current design of the photoreaction vessel, with a sidearm for the mechanical stirrer, does not lead to efficient mixing. A vessel without a sidearm would allow a magnetic stirrer to be used, which would lead to better mixing, which in turn would almost certainly lead to cleaner product.

Second, Mallory and Mallory state that quartz allows light of wavelengths above 200 nm to enter the reaction mixture, whereas Pyrex filters out light below 300 nm, resulting in the product being protected from photochemical degradation.[137] Vycor, the filter currently being used, is 96% SiO_2, and can thus be expected to behave similarly to quartz. Therefore, perhaps a Pyrex filter should be tried.

Third, the photocyclization needs to be more frequently monitored and the reaction stopped if substantial impurities become evident, regardless of whether starting material remains. As mentioned above, further irradiation could lead to degradation of the product. However, it may be likely that cleavage of the oxa-bridge of the stilbene precursors (**53** and **54**, Figure 4.1) will still occur.

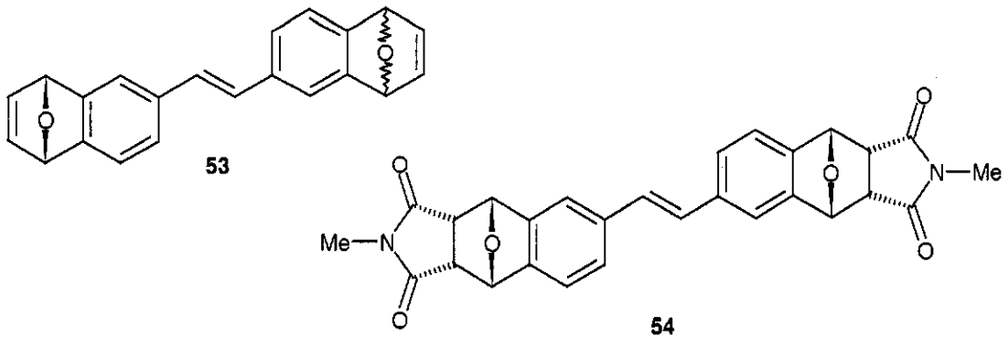
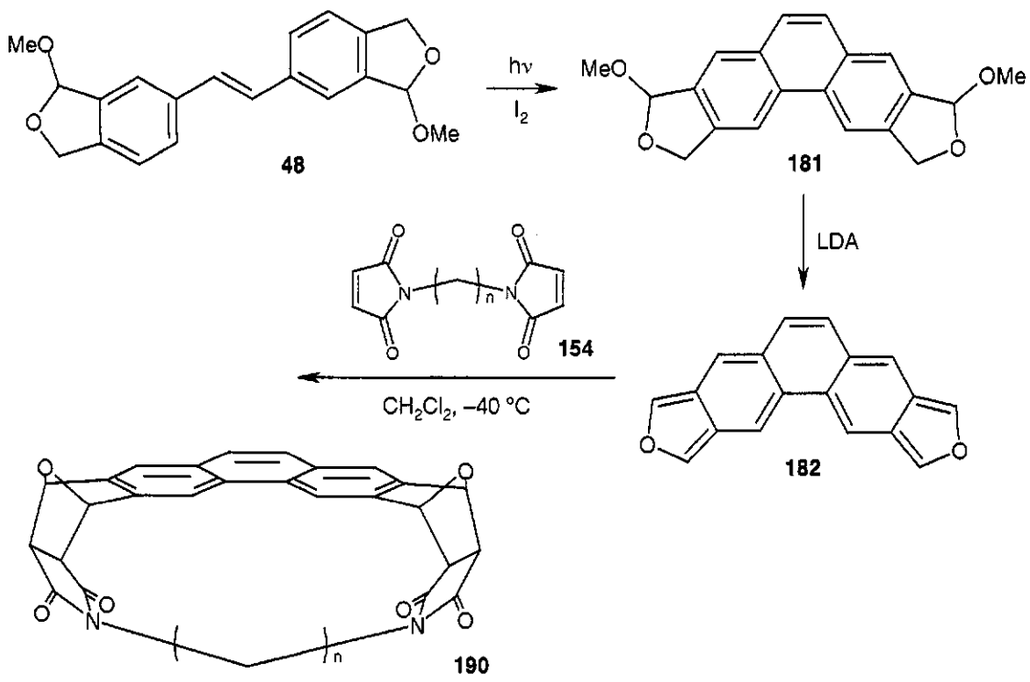


Figure 4.1: Attempted Stilbene Precursors for Photocyclization to Phenanthrodifuran

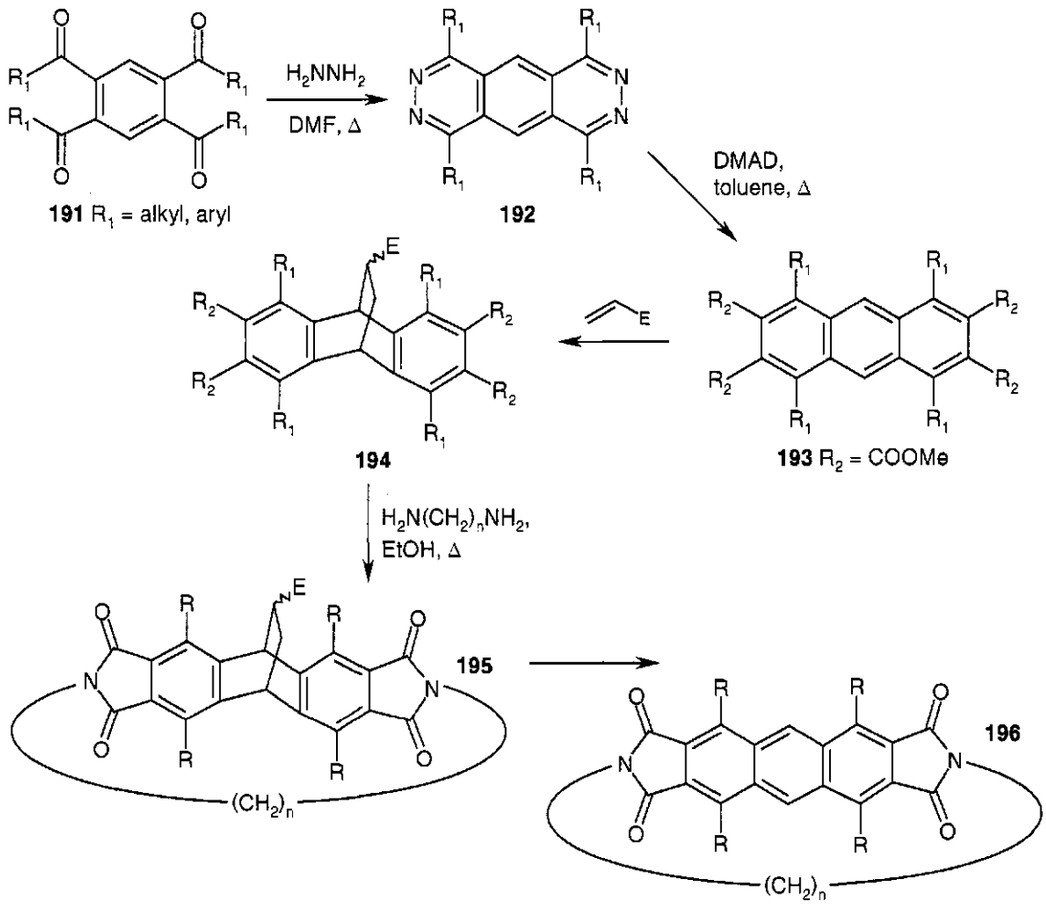
It may be likely that photocyclization of bis(acetal) **48** will be more successful than photocyclization of **53** and **54**. If the revised synthesis of bis(acetal) **48** is viable, then photocyclization of **48** to **181** can be attempted. Cyclophanes (**190**) from phenanthro[2,3-*c*:6,7-*c*]difuran could then be constructed by generating the difuran (**182**) and trapping it with a variety of bis(maleimide) tethers (**154**, see Scheme 4.4).



Scheme 4.4

4.3 Other Routes to Cyclophanes

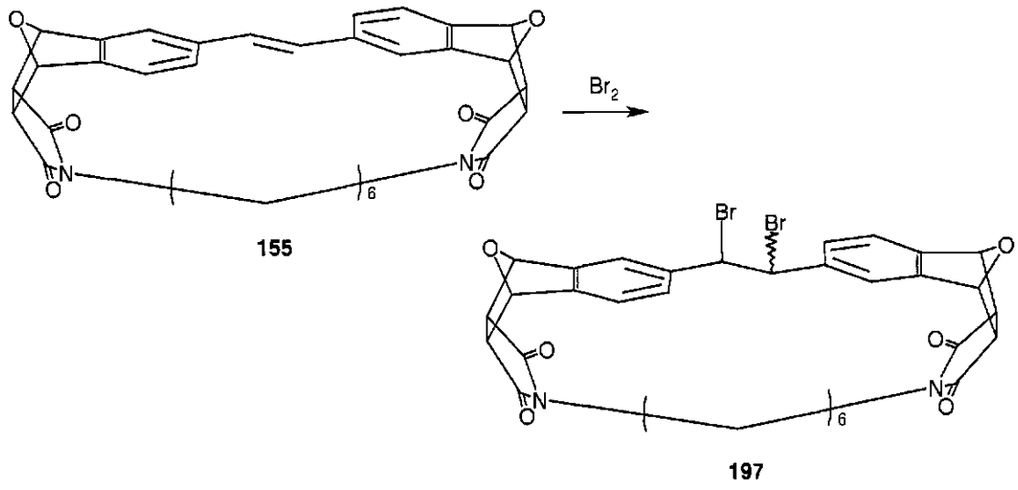
As discussed in Chapter 2, a novel approach to cyclophanes was described by Aly.[84] A similar strategy could be used to generate novel strained aromatics, as in Scheme 4.5. Thus, a tetrakis-substituted benzene (**191**) mixed with hydrazine would give bis(pyridazine) **192**. Subsequent reaction with DMAD would give **193**. A Diels–Alder reaction across the 9,10-positions would lead to a system with a curved backbone (**194**). A subsequent reaction with a 1,*n*-diamino-*n*-alkane would give cyclophane **195**. The 9,10-bridge could then be removed, to generate a strained aromatic (**196**).



Scheme 4.5

4.4 Functionalization, Aromatization, NMR, and X-ray Studies

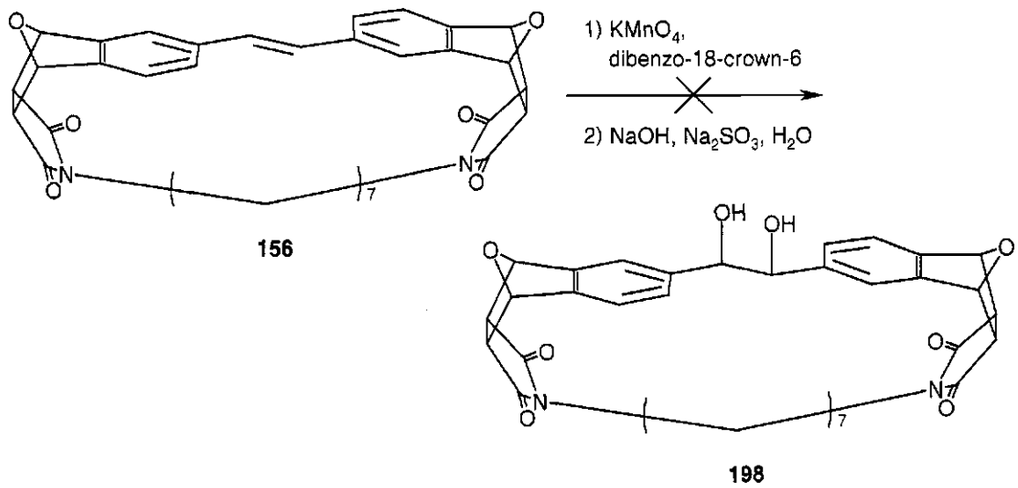
Preliminary studies on the functionalization of the double bond of the stilbenedifuran-derived cyclophanes have been conducted. Bromine readily added across the double bond of **156** (n = 6) to give **197** (Scheme 4.6), as evidenced by the disappearance of the vinyl signal at 7.0 ppm and the appearance of new signals around 5.5 ppm in the ^{1}H NMR spectrum. It is unclear whether the bromine atoms are *cis* or *trans*, because the difficulty in obtaining material of sufficient purity precluded a more detailed NMR or X-ray study. Determining the stereochemistry of the bromine addition would be of interest, as Potter and Sutherland found that bromination of the double bond of their stilbenophanes gave predominantly the *cis*-dibromide for the stilbenophanes with the shorter polymethylene chains, and that the proportion of *trans*-dibromide increased with the length of the tether.[103]



155 **197**

Scheme 4.6

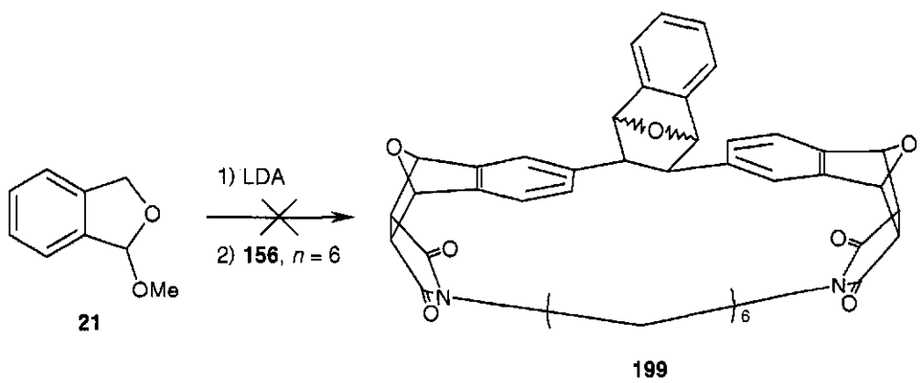
An attempted *cis*-hydroxylation of **156** (n = 7) gave none of the desired diol (**198**). A stoichiometric amount of $KMnO_4$ and dibenzo-18-crown-6 was used, as it was suggested that such a procedure gives higher yields of *cis*-diol than $KMnO_4$ alone.[141]



156 **198**

Scheme 4.7

A Diels–Alder reaction of **156** (n = 6) with isobenzofuran was attempted. Isobenzofuran was used because it was reasoned that if the double bond were a suitable dienophile, it would be sure to react with this very reactive diene to give **199**. However, no identifiable material was isolated.

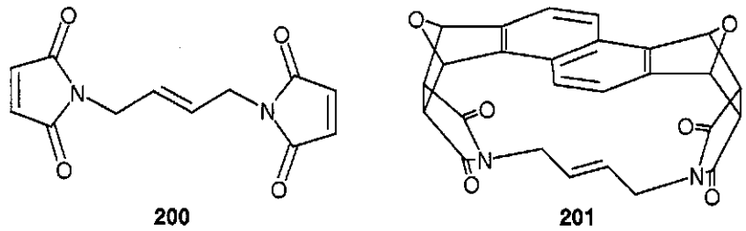


21 **199**

Scheme 4.8

The above investigations were all hampered by the inability to obtain sufficient quantities of clean stilbenedifuran-derived cyclophanes. A different strategy would be to

incorporate a tether with a double bond into the naphthodifuran-derived cyclophanes. For example, the 4C naphthodifuran-derived cyclophane forms cleanly in relatively good yield (27%). Therefore, a 2-butene-derived tether (**200**) could also be expected to form the corresponding naphthodifuran-derived cyclophane (**201**, Figure 4.2) in relatively good yield. Functionalization studies could then be followed more readily and more appropriate conditions found than those that were attempted.



200 **201**

Figure 4.2: The 2-Butene-derived Tether (200) and Naphthodifuran-derived Cyclophane (201)

Aromatization of the oxabicyclic rings should be tried. Figure 4.3 depicts the AM1-calculated structure of the aromatized 6C naphthodifuran-derived cyclophane. There is a substantial amount of curvature in the aromatic backbone, which will no doubt result in a degree of strain. It is likely that only the cyclophanes with the longer tethers will aromatize fully; the smaller cyclophanes might only aromatize partially, if at all.

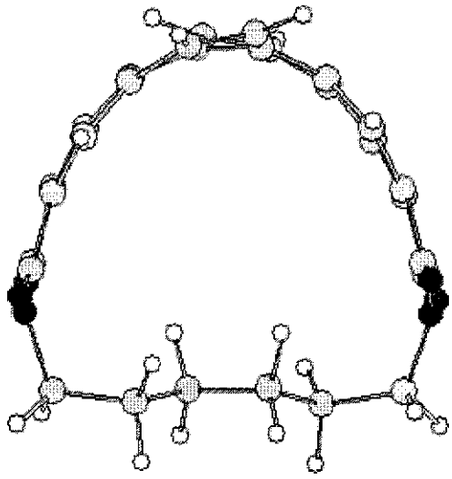


Figure 4.3: AM1-Calculated Structure of the Aromatized 6C Naphthodifuran-derived Cyclophane

It was mentioned in the discussion of the ^{1}H NMR spectra of the stilbenedifuran-derived cyclophane series that the tether protons showed considerable broadening because of second-order effects and conformational mobility. Variable-temperature NMR studies of these cyclophanes should be conducted, in order to obtain information on the energy barriers.

Finally, efforts need to be directed towards growing crystals suitable for X-ray analysis so that the calculated cyclophane structures may be substantiated.

4.5 Summary

Several suggestions have been given to improve the syntheses of 1,2-bis(5-isobenzofuranyl)ethene (**40**), phenanthro[2,3-*c*:6,7-*c*]difuran (**182**), and their cyclophanes (**156** and **190**, respectively). The bis(acetal) route to **40** should be re-examined or the dipytet procedure and work-up optimized. The photocyclization procedures leading to **182** need to be improved.

An approach to a novel anthracenophane involving benzannulation of a tetrakis-substituted benzene is described.

Initial studies on the bromination, *cis*-hydroxylation, and Diels–Alder reaction of the stilbenedifuran-derived cyclophanes were described. Improved yields and purities of the stilbenedifuran-derived cyclophanes (**156**) would greatly facilitate these studies. Alternatively, a naphthodifuran-derived cyclophane with an unsaturated tether could be made and functionalization of the double bond investigated in that way.

Aromatization of the oxabicyclic rings of the cyclophanes, variable-temperature NMR, and further X-ray studies should be undertaken.

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Appendix I Additional Crystallographic Details for $C_{25}H_{18}N_2O_6$ (155, n = 3)

Table I.1: Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for $C_{25}H_{18}N_2O_6$.
U(eq) is Defined as One-third of the Trace of the Orthogonalized U^{ij} Tensor.

Atom	x	y	z	U(eq)
O(1)	2225(1)	1374(1)	2324(2)	34(1)
O(2)	183(1)	1362(1)	3652(1)	31(1)
O(3)	1620(1)	1512(1)	7521(1)	27(1)
O(4)	1999(1)	–1981(1)	4046(1)	27(1)
O(5)	2250(1)	–749(1)	–273(2)	40(1)
O(6)	337(1)	–1002(1)	1906(2)	33(1)
N(1)	1173(1)	1332(1)	2649(2)	23(1)
N(2)	1252(1)	–767(1)	654(2)	24(1)
C(1)	1769(1)	1475(1)	3135(2)	24(1)
C(2)	1743(1)	1736(1)	4820(2)	24(1)
C(3)	1047(1)	1769(1)	5237(2)	24(1)
C(4)	728(1)	1477(1)	3805(2)	23(1)
C(5)	1987(1)	1293(1)	6167(2)	24(1)
C(6)	1019(1)	1375(1)	6827(2)	24(1)
C(7)	1102(1)	703(1)	6358(2)	21(1)
C(8)	1712(1)	651(1)	5908(2)	21(1)
C(9)	1946(1)	101(1)	5212(2)	20(1)
C(10)	2545(1)	47(1)	4521(2)	24(1)
C(11)	2729(1)	–480(1)	3725(2)	25(1)
C(12)	2321(1)	–985(1)	3688(2)	23(1)
C(13)	1747(1)	–960(1)	4404(2)	21(1)
C(14)	1522(1)	–414(1)	5135(2)	20(1)
C(15)	903(1)	–348(1)	5670(2)	21(1)
C(16)	685(1)	208(1)	6226(2)	22(1)
C(17)	2345(1)	–1613(1)	2891(2)	26(1)
C(18)	1456(1)	–1588(1)	4099(2)	24(1)
C(19)	1846(1)	–1006(1)	491(2)	27(1)
C(20)	1880(1)	–1609(1)	1424(2)	26(1)
C(21)	1250(1)	–1650(1)	2289(2)	25(1)
C(22)	874(1)	–1122(1)	1636(2)	25(1)
C(23)	1084(1)	–144(1)	124(2)	26(1)
C(24)	1184(1)	296(1)	1539(2)	28(1)
C(25)	1046(1)	970(1)	1186(2)	27(1)

Table I.2: Bond Lengths [Å] and Angles [°] for $C_{25}H_{18}N_2O_6$.

O(1)–C(1)	1.212(2)
O(2)–C(4)	1.2123(19)
O(3)–C(5)	1.4523(19)
O(3)–C(6)	1.4528(19)
O(4)–C(18)	1.4509(19)
O(4)–C(17)	1.4499(19)
O(5)–C(19)	1.212(2)
O(6)–C(22)	1.2126(19)
N(1)–C(1)	1.386(2)
N(1)–C(4)	1.392(2)
N(1)–C(25)	1.465(2)
N(2)–C(22)	1.384(2)
N(2)–C(19)	1.391(2)
N(2)–C(23)	1.461(2)
C(1)–C(2)	1.503(2)
C(2)–C(3)	1.544(2)
C(2)–C(5)	1.563(2)
C(3)–C(4)	1.508(2)
C(3)–C(6)	1.567(2)
C(5)–C(8)	1.525(2)
C(6)–C(7)	1.514(2)
C(7)–C(8)	1.376(2)
C(7)–C(16)	1.406(2)
C(8)–C(9)	1.415(2)
C(9)–C(10)	1.420(2)
C(9)–C(14)	1.445(2)
C(10)–C(11)	1.376(2)
C(11)–C(12)	1.404(2)
C(12)–C(13)	1.377(2)
C(12)–C(17)	1.512(2)
C(13)–C(14)	1.413(2)
C(13)–C(18)	1.518(2)
C(14)–C(15)	1.416(2)
C(15)–C(16)	1.371(2)
C(17)–C(20)	1.575(2)
C(18)–C(21)	1.567(2)
C(19)–C(20)	1.518(2)
C(20)–C(21)	1.541(2)
C(21)–C(22)	1.504(2)
C(23)–C(24)	1.523(2)
C(24)–C(25)	1.518(2)
C(5)–O(3)–C(6)	96.84(11)
C(18)–O(4)–C(17)	96.65(11)

C(1)–N(1)–C(4)	113.15(13)
C(1)–N(1)–C(25)	122.21(13)
C(4)–N(1)–C(25)	123.88(13)
C(22)–N(2)–C(19)	113.30(14)
C(22)–N(2)–C(23)	122.69(13)
C(19)–N(2)–C(23)	122.87(14)
O(1)–C(1)–N(1)	123.81(16)
O(1)–C(1)–C(2)	127.59(15)
N(1)–C(1)–C(2)	108.52(13)
C(1)–C(2)–C(3)	105.10(13)
C(1)–C(2)–C(5)	114.57(13)
C(3)–C(2)–C(5)	101.47(12)
C(4)–C(3)–C(2)	104.59(13)
C(4)–C(3)–C(6)	114.28(13)
C(2)–C(3)–C(6)	101.62(12)
O(2)–C(4)–N(1)	123.67(15)
O(2)–C(4)–C(3)	127.84(15)
N(1)–C(4)–C(3)	108.46(13)
O(3)–C(5)–C(8)	101.09(12)
O(3)–C(5)–C(2)	99.32(12)
C(8)–C(5)–C(2)	109.09(13)
O(3)–C(6)–C(7)	101.01(12)
O(3)–C(6)–C(3)	100.58(12)
C(7)–C(6)–C(3)	107.61(13)
C(8)–C(7)–C(16)	122.16(15)
C(8)–C(7)–C(6)	105.20(13)
C(16)–C(7)–C(6)	132.46(15)
C(7)–C(8)–C(9)	121.47(14)
C(7)–C(8)–C(5)	105.19(13)
C(9)–C(8)–C(5)	133.02(14)
C(8)–C(9)–C(10)	123.95(15)
C(8)–C(9)–C(14)	116.05(14)
C(10)–C(9)–C(14)	119.89(15)
C(11)–C(10)–C(9)	121.64(15)
C(10)–C(11)–C(12)	118.22(15)
C(13)–C(12)–C(11)	121.82(15)
C(13)–C(12)–C(17)	104.63(14)
C(11)–C(12)–C(17)	133.45(15)
C(12)–C(13)–C(14)	121.86(15)
C(12)–C(13)–C(18)	105.53(14)
C(14)–C(13)–C(18)	132.49(14)
C(13)–C(14)–C(15)	122.96(14)
C(13)–C(14)–C(9)	116.35(14)
C(15)–C(14)–C(9)	120.55(14)
C(16)–C(15)–C(14)	121.27(15)
C(15)–C(16)–C(7)	118.23(14)

O(4)–C(17)–C(12)	100.93(12)
O(4)–C(17)–C(20)	100.38(12)
C(12)–C(17)–C(20)	107.96(13)
O(4)–C(18)–C(13)	101.20(12)
O(4)–C(18)–C(21)	98.67(12)
C(13)–C(18)–C(21)	110.69(13)
O(5)–C(19)–N(2)	123.13(16)
O(5)–C(19)–C(20)	128.48(15)
N(2)–C(19)–C(20)	108.39(14)
C(19)–C(20)–C(21)	104.03(13)
C(19)–C(20)–C(17)	115.30(14)
C(21)–C(20)–C(17)	101.97(13)
C(22)–C(21)–C(20)	105.53(13)
C(22)–C(21)–C(18)	115.50(13)
C(20)–C(21)–C(18)	100.74(13)
O(6)–C(22)–N(2)	123.74(15)
O(6)–C(22)–C(21)	128.01(16)
N(2)–C(22)–C(21)	108.25(14)
N(2)–C(23)–C(24)	108.10(13)
C(25)–C(24)–C(23)	115.17(13)
N(1)–C(25)–C(24)	108.51(13)

Table I.3: Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for $C_{25}H_{18}N_2O_6$. The Anisotropic Displacement Factor Exponent Takes the Form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}]$

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	26(1)	42(1)	32(1)	4(1)	8(1)	0(1)
O(2)	23(1)	36(1)	33(1)	8(1)	–3(1)	0(1)
O(3)	30(1)	28(1)	24(1)	–3(1)	–2(1)	–2(1)
O(4)	27(1)	23(1)	31(1)	5(1)	3(1)	5(1)
O(5)	33(1)	47(1)	40(1)	14(1)	13(1)	9(1)
O(6)	24(1)	35(1)	39(1)	–2(1)	3(1)	4(1)
N(1)	23(1)	23(1)	23(1)	4(1)	0(1)	0(1)
N(2)	25(1)	27(1)	21(1)	0(1)	1(1)	5(1)
C(1)	24(1)	22(1)	27(1)	8(1)	1(1)	–1(1)
C(2)	23(1)	21(1)	27(1)	2(1)	0(1)	–2(1)
C(3)	24(1)	20(1)	26(1)	2(1)	1(1)	1(1)
C(4)	23(1)	20(1)	27(1)	9(1)	0(1)	3(1)
C(5)	23(1)	24(1)	25(1)	0(1)	–1(1)	0(1)
C(6)	23(1)	26(1)	23(1)	–1(1)	0(1)	–1(1)
C(7)	26(1)	25(1)	14(1)	4(1)	0(1)	1(1)
C(8)	22(1)	21(1)	18(1)	4(1)	–4(1)	–1(1)
C(9)	19(1)	23(1)	18(1)	5(1)	–3(1)	1(1)
C(10)	18(1)	26(1)	28(1)	6(1)	–2(1)	–2(1)
C(11)	19(1)	29(1)	28(1)	6(1)	2(1)	2(1)
C(12)	24(1)	24(1)	22(1)	5(1)	0(1)	4(1)
C(13)	21(1)	22(1)	20(1)	4(1)	–1(1)	1(1)
C(14)	21(1)	22(1)	16(1)	5(1)	–2(1)	–1(1)
C(15)	22(1)	23(1)	18(1)	4(1)	0(1)	–3(1)
C(16)	20(1)	27(1)	17(1)	3(1)	1(1)	–1(1)
C(17)	23(1)	27(1)	28(1)	4(1)	4(1)	6(1)
C(18)	25(1)	23(1)	25(1)	3(1)	2(1)	2(1)
C(19)	26(1)	33(1)	21(1)	–1(1)	3(1)	6(1)
C(20)	27(1)	25(1)	27(1)	–3(1)	3(1)	4(1)
C(21)	26(1)	22(1)	27(1)	–3(1)	0(1)	1(1)
C(22)	25(1)	27(1)	22(1)	–7(1)	–1(1)	1(1)
C(23)	28(1)	29(1)	21(1)	3(1)	–2(1)	6(1)
C(24)	34(1)	28(1)	21(1)	4(1)	–4(1)	4(1)
C(25)	31(1)	28(1)	21(1)	4(1)	–2(1)	2(1)

Table I.4: Hydrogen Coordinates ($\times 10^4$) and Isotropic Displacement Parameters ($Å^2 \times 10^3$) for $C_{25}H_{18}N_2O_6$.

Atom	x	y	z	U(eq)
H(2)	1943	2152	4882	28
H(3)	907	2203	5420	28
H(5)	2445	1302	6339	29
H(6)	657	1462	7546	29
H(10)	2825	384	4612	29
H(11)	3122	–502	3214	30
H(15)	635	–695	5644	25
H(16)	262	257	6513	26
H(17)	2769	–1769	2637	31
H(18)	1137	–1714	4910	29
H(20)	1949	–1969	688	32
H(21)	1045	–2056	2082	30
H(23A)	646	–134	–219	31
H(23B)	1344	–19	–805	31
H(24A)	920	160	2451	33
H(24B)	1620	261	1896	33
H(25A)	1308	1118	284	32
H(25B)	607	1019	868	32

Table I.5: Torsion Angles [°] for $C_{25}H_{18}N_2O_6$.

C(4)–N(1)–C(1)–O(1)	178.33(15)
C(25)–N(1)–C(1)–O(1)	7.9(2)
C(4)–N(1)–C(1)–C(2)	1.29(18)
C(25)–N(1)–C(1)–C(2)	–169.11(13)
O(1)–C(1)–C(2)–C(3)	179.59(16)
N(1)–C(1)–C(2)–C(3)	–3.51(16)
O(1)–C(1)–C(2)–C(5)	–69.9(2)
N(1)–C(1)–C(2)–C(5)	106.97(15)
C(1)–C(2)–C(3)–C(4)	4.25(16)
C(5)–C(2)–C(3)–C(4)	–115.36(13)
C(1)–C(2)–C(3)–C(6)	123.42(13)
C(5)–C(2)–C(3)–C(6)	3.80(15)
C(1)–N(1)–C(4)–O(2)	–176.40(14)
C(25)–N(1)–C(4)–O(2)	–6.2(2)
C(1)–N(1)–C(4)–C(3)	1.60(18)
C(25)–N(1)–C(4)–C(3)	171.81(13)
C(2)–C(3)–C(4)–O(2)	174.23(15)
C(6)–C(3)–C(4)–O(2)	64.0(2)
C(2)–C(3)–C(4)–N(1)	–3.66(16)
C(6)–C(3)–C(4)–N(1)	–113.89(14)
C(6)–O(3)–C(5)–C(8)	–50.90(13)
C(6)–O(3)–C(5)–C(2)	60.80(13)
C(1)–C(2)–C(5)–O(3)	–151.62(13)
C(3)–C(2)–C(5)–O(3)	–38.98(14)
C(1)–C(2)–C(5)–C(8)	–46.38(18)
C(3)–C(2)–C(5)–C(8)	66.26(15)
C(5)–O(3)–C(6)–C(7)	52.06(13)
C(5)–O(3)–C(6)–C(3)	–58.41(13)
C(4)–C(3)–C(6)–O(3)	144.55(13)
C(2)–C(3)–C(6)–O(3)	32.53(14)
C(4)–C(3)–C(6)–C(7)	39.30(18)
C(2)–C(3)–C(6)–C(7)	–72.71(15)
O(3)–C(6)–C(7)–C(8)	–33.94(15)
C(3)–C(6)–C(7)–C(8)	71.00(15)
O(3)–C(6)–C(7)–C(16)	150.96(16)
C(3)–C(6)–C(7)–C(16)	–104.09(18)
C(16)–C(7)–C(8)–C(9)	3.1(2)
C(6)–C(7)–C(8)–C(9)	–172.63(14)
C(16)–C(7)–C(8)–C(5)	177.36(13)
C(6)–C(7)–C(8)–C(5)	1.63(16)
O(3)–C(5)–C(8)–C(7)	31.17(15)
C(2)–C(5)–C(8)–C(7)	–72.85(15)
O(3)–C(5)–C(8)–C(9)	–155.52(16)
C(2)–C(5)–C(8)–C(9)	100.45(19)

C(7)–C(8)–C(9)–C(10)	170.97(14)
C(5)–C(8)–C(9)–C(10)	–1.5(3)
C(7)–C(8)–C(9)–C(14)	–5.2(2)
C(5)–C(8)–C(9)–C(14)	–177.62(15)
C(8)–C(9)–C(10)–C(11)	–173.83(15)
C(14)–C(9)–C(10)–C(11)	2.2(2)
C(9)–C(10)–C(11)–C(12)	–3.7(2)
C(10)–C(11)–C(12)–C(13)	0.8(2)
C(10)–C(11)–C(12)–C(17)	176.65(16)
C(11)–C(12)–C(13)–C(14)	3.6(2)
C(17)–C(12)–C(13)–C(14)	–173.23(14)
C(11)–C(12)–C(13)–C(18)	–179.96(14)
C(17)–C(12)–C(13)–C(18)	3.17(16)
C(12)–C(13)–C(14)–C(15)	170.65(15)
C(18)–C(13)–C(14)–C(15)	–4.6(3)
C(12)–C(13)–C(14)–C(9)	–5.0(2)
C(18)–C(13)–C(14)–C(9)	179.76(15)
C(8)–C(9)–C(14)–C(13)	178.42(13)
C(10)–C(9)–C(14)–C(13)	2.1(2)
C(8)–C(9)–C(14)–C(15)	2.7(2)
C(10)–C(9)–C(14)–C(15)	–173.62(14)
C(13)–C(14)–C(15)–C(16)	–173.38(15)
C(9)–C(14)–C(15)–C(16)	2.0(2)
C(14)–C(15)–C(16)–C(7)	–4.3(2)
C(8)–C(7)–C(16)–C(15)	1.8(2)
C(6)–C(7)–C(16)–C(15)	176.25(16)
C(18)–O(4)–C(17)–C(12)	52.79(14)
C(18)–O(4)–C(17)–C(20)	–57.98(13)
C(13)–C(12)–C(17)–O(4)	–35.42(15)
C(11)–C(12)–C(17)–O(4)	148.25(17)
C(13)–C(12)–C(17)–C(20)	69.39(16)
C(11)–C(12)–C(17)–C(20)	–106.94(19)
C(17)–O(4)–C(18)–C(13)	–50.62(13)
C(17)–O(4)–C(18)–C(21)	62.61(13)
C(12)–C(13)–C(18)–O(4)	30.01(15)
C(14)–C(13)–C(18)–O(4)	–154.14(16)
C(12)–C(13)–C(18)–C(21)	–73.82(16)
C(14)–C(13)–C(18)–C(21)	102.04(19)
C(22)–N(2)–C(19)–O(5)	–177.28(16)
C(23)–N(2)–C(19)–O(5)	–9.2(3)
C(22)–N(2)–C(19)–C(20)	2.06(18)
C(23)–N(2)–C(19)–C(20)	170.12(14)
O(5)–C(19)–C(20)–C(21)	173.59(18)
N(2)–C(19)–C(20)–C(21)	–5.71(17)
O(5)–C(19)–C(20)–C(17)	62.8(2)
N(2)–C(19)–C(20)–C(17)	–116.47(15)

O(4)–C(17)–C(20)–C(19)	142.32(13)
C(12)–C(17)–C(20)–C(19)	37.14(18)
O(4)–C(17)–C(20)–C(21)	30.35(14)
C(12)–C(17)–C(20)–C(21)	–74.84(15)
C(19)–C(20)–C(21)–C(22)	7.03(17)
C(17)–C(20)–C(21)–C(22)	127.24(13)
C(19)–C(20)–C(21)–C(18)	–113.47(14)
C(17)–C(20)–C(21)–C(18)	6.74(15)
O(4)–C(18)–C(21)–C(22)	–154.94(13)
C(13)–C(18)–C(21)–C(22)	–49.42(18)
O(4)–C(18)–C(21)–C(20)	–41.83(14)
C(13)–C(18)–C(21)–C(20)	63.69(15)
C(19)–N(2)–C(22)–O(6)	–178.31(15)
C(23)–N(2)–C(22)–O(6)	13.6(2)
C(19)–N(2)–C(22)–C(21)	2.70(19)
C(23)–N(2)–C(22)–C(21)	–165.38(13)
C(20)–C(21)–C(22)–O(6)	174.90(16)
C(18)–C(21)–C(22)–O(6)	–74.8(2)
C(20)–C(21)–C(22)–N(2)	–6.16(17)
C(18)–C(21)–C(22)–N(2)	104.13(16)
C(22)–N(2)–C(23)–C(24)	76.48(19)
C(19)–N(2)–C(23)–C(24)	–90.46(17)
N(2)–C(23)–C(24)–C(25)	178.61(14)
C(1)–N(1)–C(25)–C(24)	76.11(19)
C(4)–N(1)–C(25)–C(24)	–93.24(17)
C(23)–C(24)–C(25)–N(1)	–179.18(14)

Table I.6: Least-squares Plane (x,y,z in Crystal Coordinates) and Deviations of the Atoms from It (* Indicates Atom Used to Define Plane)

6.7994 (0.0074)x – 6.7744 (0.0083)y + 7.4044 (0.0011)z = 5.0352 (0.0012)

*	–0.0550 (0.0012)	C7
*	0.0621 (0.0012)	C8
*	0.0781 (0.0014)	C9
*	0.0109 (0.0013)	C10
*	–0.0960 (0.0012)	C11
*	–0.0587 (0.0012)	C12
*	0.0636 (0.0013)	C13
*	0.0824 (0.0013)	C14
*	0.0133 (0.0012)	C15
*	–0.1008 (0.0012)	C16

RMS deviation of fitted atoms = 0.0685