SYNTHESIS AND STUDY OF SOME NOVEL AND INTERESTING CYCLOPHANES

TOM J. HOUGHTON

Synthesis and Study of Some Novel and Interesting Cyclophanes

by

Tom J. Houghton

B.A., Hons., Worcester College, Oxford, 1988

A thesis submitted to the School of Graduate Studies

in partial fulfillment of the requirements for

the degree of Doctor of Philosophy

Department of Chemistry

Memorial University of Newfoundland

St. John's, Newfoundland, Canada

September 1999

Abstract

The somewhat vague title of this thesis is due to the fact that several fairly loosely-connected projects were investigated, the common thread being the classification of all the targets as "cyclophanes". [For a definition of this term see Chapter 1.] This approach has naturally had its disadvantages, but it has allowed the author the opportunity to explore some fascinating concepts and methodologies.

The idea of a tethered-cyclophane-based molecular switch was investigated in Chapter 2. This work led to a new thiacyclophane-forming methodology, and ultimately to the observation of the desired *syn-anti* equilibrium process sought at the outset. This process was studied by dynamic NMR, and the thermodynamic data for the process, including the transition state, calculated.

The previous project was expanded to the study of cyclophanes and pyrenophanes bridged by crown ether tethers. Two tethers were used, corresponding to 15-crown-5 and 18-crown-6. The target compounds were successfully synthesised and their conformational properties predicted by computational studies and observed by NMR.

Two C_2-symmetric chiral tetra-functionalised [2.2]paracyclophanes were synthesised, paving the way for the synthesis of some interesting chiral ligands. In the course of this study a much-simplified and very economical apparatus for flash vacuum thermolysis was developed.

A dithiatetraynophane, a tetraynophane and an enediynophane were synthesised.

Finally, a new class of "esterophane" was synthesised. The structural features of one example were studied by X-ray crystallography, and a computational analysis performed.

Acknowledgements

I would like to thank my supervisor Dr. Graham Bodwell for his constant enthusiasm and encouragement throughout the course of my studies here. I would thank him for some great ideas, for fostering a creative atmosphere and for allowing me to explore some ideas of my own. Along with Graham I would like to thank especially Dr. Jean Burnell as well as Dr. Chet Jablonski and Dr. Brian Gregory for the excellent teaching I have received here, and for their availability to discuss difficulties I have had with course work.

I am grateful to Dave Miller, Nathalie Brunet and Chet Jablonski for assistance with NMR spectra; to Marion Baggs and Brian Gregory for mass spectral analyses; and to Dr. John Bridson and Dave Miller for X-ray crystallography.

I would like to acknowledge the considerable contribution of Dr. Earle Ralph in explaining the principles and helping me with the thermodynamic calculations of Chapter 2 of this thesis, and to thank Dr. Peter Golding for his helpful discussions on this subject. I would also like to thank Dr. James Xidos for enabling me to perform the computational analyses of Chapter 3 and for helping me to grasp their true significance.

Thanks are due to Graham Bodwell and Brian Gregory for help with preparation of this thesis. Financial support from the School of Graduate Studies and Memorial University of Newfoundland is gratefully acknowledged. The friendly, positive atmosphere of the Bodwell group, as well as that of the department as a whole, has been greatly appreciated.

Table of Contents

List of Figures

List of Schemes

Glossary of Abbreviations

Å	Angstroms
Ac	acetyl
AM	Austin Model
Boc	*t*-butoxycarbonyl
BOM	benzyloxymethyl
BOP-Cl	*N,N*-bis[2-oxo-3-oxazolidinyl]phosphorodiamidic chloride
BOP reagent	benzotriazolyl *N*-oxytrisdimethylaminophosphonium hexafluorophosphate
Borch reagent	dimethoxycarbonium tetrafluoroborate
Bu	butyl
Bzl	benzyl
ca.	*circa*
cat.	catalytic
CIDNP	chemically induced dynamic polarisation
CSA	camphorsulphonic acid
δ	chemical shift in ppm downfield from tetramethylsilane
D	Debye (measurement of dipole moment)
Δ	heat
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N*-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
Dess-Martin reagent	1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one
DIBAL	diisobutylaluminium hydride

DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMP	2,2-dimethoxypropane
DMSO	dimethyl sulphoxide
DNA	deoxyribonucleic acid
e.e.	enantiomeric excess
Et	ethyl
eV	electron volts
FVT	flash vacuum thermolysis
GC	gas chromatography
Gly	glycine
HMPA	hexamethylphosphoric triamide
HRMS	high-resolution mass spectrum
hv	light
IR	infrared
K_a	association constant
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazane
lit.	literature
Lys	lysine
m-CPBA	*m*-chloroperoxybenzoic acid

Me	methyl
MM	molecular mechanics
MO	molecular orbital
MOM	methoxymethyl
mp	melting point
MS	mass spectrometry
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
Nu	nucleophile
Ph	phenyl
PMA	phosphomolybdic acid
ppm	parts per million (in NMR)
Pr	propyl
p-TSA	*p*-toluenesulphonic acid
pyr	pyridine
R_f	retention factor (in chromatography)
RT	room temperature
Ser	serine
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMS	trimethylsilyl
TPE	tetraphenylethene

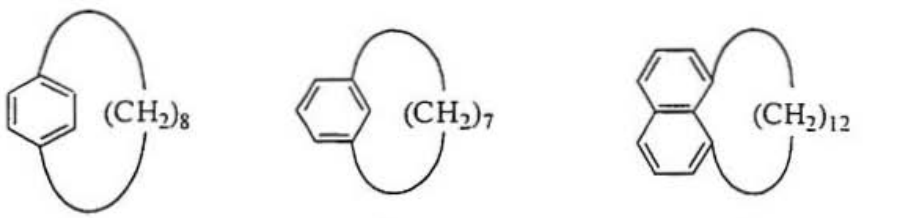
Tyr	tyrosine
UV	ultraviolet
XS	excess
Z	benzyloxycarbonyl

Cyclophanes – a General Introduction

1.1 A Working Definition

The term "cyclophane" was coined by the great Donald Cram[1] as an easily remembered trivial name for a loosely defined class of compounds. The word can be broken down into three sections:

1. Cyclo- The compound must possess at least one ring connecting an aromatic ring to itself, or to any number of other aromatic rings. A conceptually simple example would be [8]paracylophane **1** (Figure 1.1), a benzene ring with an eight carbon alkyl bridge connecting carbons with a para relationship. "Para" indicates the relationship of the carbons linked by the alkyl ring, [8] clearly defines the number of atoms in the bridge. Compounds **2** and **3** below serve to further illustrate the basic naming scheme. In the case of **3** the second bracket, (1,8), clearly identifies the carbons of the aromatic ring which are bridged.



1 [8]Paracyclophane

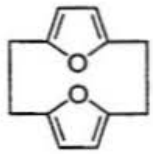
2 [7]Metacyclophane

3 [12](1,8)Naphthalenophane

Figure 1.1 Simple Examples of Cyclophanes

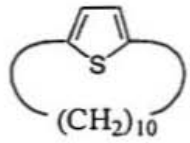
2. -ph- The "ph" stands for phenyl, and the compound must contain at least one aromatic ring. Heteroaromatic rings and non-benzenoid aromatic rings are also possible, as shown

in Figure 1.2. In the case of compound **4**, [2.2] indicates that there are two bridges, each containing two atoms.



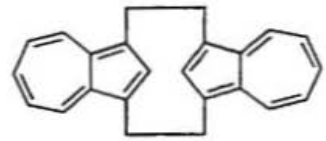
4

[2.2](2,5)Furanophane



5

[10](2,5)Thiophenophane

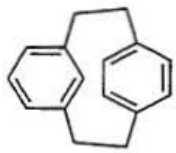


6

[2.2](1,3)Azulenophane

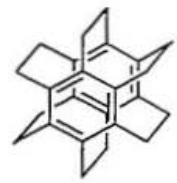
Figure 1.2 Cyclophanes Possessing Non-Benzenoid Aromatic Rings

3. -ane The compound is at heart an alkane. In fact most of the interest in cyclophanes stems not from their functional groups but from their geometry. For example, [2.2]metaparacyclophane **7**, and "superphane" **8** are examples of cyclophanes with no functional groups which are nevertheless of great interest due to their geometric properties. In the case of the latter molecule the prefix $[2_6]$ is shorthand for [2.2.2.2.2.2], and hence indicates six two-atom bridges.



7

[2.2]Metaparacyclophane

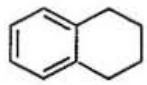


8

$[2_6]$(1,2,3,4,5,6)Cyclophane ("superphane")

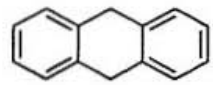
Figure 1.3 Structurally Interesting Cyclophanes Possessing no Functional Groups

As mentioned above, the set of definitions is not strict and is loosely applied. Compounds are generally included in the classification because they exhibit peculiar qualities such as unusual ring strain and bent benzene rings, or special reactivity such as intraannular effects. Molecules such as tetralin (1,2,3,4-tetrahydronaphthalene) **9** and 9,10-dihydroanthracene **10** which lack these characteristics are generally not referred to as cyclophanes, despite the fact that they fit the definition above. [2.2]Orthocyclophane, **11**, is sometimes described as dibenzocycloocta-1,5-diene, the choice of name generally depending on the context.



9

Tetralin



10

9,10-Dihydroanthracene

11

[2.2]Orthocyclophane
(Dibenzocycloocta-1,5-diene)

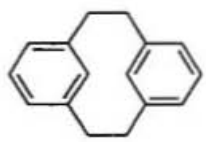
Figure 1.4 Compounds Illustrating the Borderlines of the Definition of a Cyclophane

1.2 Nomenclature and Numbering Schemes

The examples of Section 1.1 were intended to give some insight into the naming scheme used for cyclophanes. As was mentioned, the names are essentially trivial in nature, although some attempt has been made among chemists working in this area to standardise the naming process. A very thorough paper has been published by Vögtle which clearly defines the accepted usage of nomenclature for cyclophanes.[2,3] For the purposes of this thesis the basic ideas from Section 1.1 should suffice, and the introductions of the main chapters will explain further ideas such as *syn-anti* isomerism as appropriate.

1.3 A Brief Summary of the History of Cyclophane Synthesis

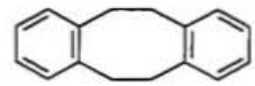
The first cyclophane to have been deliberately synthesised appears to have been [2.2]metacyclophane **12** (Figure 1.5), prepared by Wurtz coupling of α,α′-dibromo-*m*-xylene by Pellegrin in 1899.[4] The second cyclophane synthesis was not reported for almost another fifty years. In this case the more easily accessible (less strained) [2.2]orthocyclophane **11** was made, again through Wurtz coupling of the appropriate dibromide, by Baker, Banks, Lyon and Mann in 1945.[5] The third cyclophane was discovered rather than made and was reported in 1949 by Brown and Farthing of the ICI company.[6] The great crystallinity of [2.2]paracyclophane **13** allowed its separation from a complicated mixture of impurities produced by the industrial polymerisation of *p*-xylene. This compound was characterised solely on the basis of an unrefined crystal structure. By the time of publication of this fortuitous discovery Cram's worker Steinberg had already prepared [2.2]paracyclophane by a designed synthesis.[7] Cram was not the first to have pondered the possibilities of compounds with "face to face" benzene rings, as Reichstein and Oppenauer had already reported their unsuccessful attempts to prepare [*m.n*]paracyclophanes as early as 1933.[8]



12

[2.2]Metacyclophane

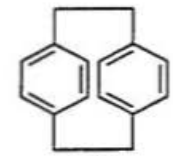
1899[4]



11

[2.2]Orthocyclophane

1945[5]



13

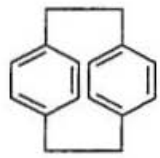
[2.2]Paracyclophane

1949[6]

Figure 1.5 The Chronological Order of Discovery of the Common [2.2]Cyclophanes

1.4 Strain Considerations

The 2.1% yield of Cram's designed synthesis of [2.2]paracyclophane[7] (see Chapter 4 for details), in which only one intramolecular Wurtz coupling was required, demonstrates very clearly the main synthetic problem and the greatest fascination of the cyclophanes - the strain present in the molecules. Below are shown three of the simpler cyclophanes, their experimental heats of formation, and their calculated strain energies. [The data in Figure 1.6 have all been taken from the same article,[9] but the original references have been given for the reader's convenience.] It should be noted that in the case of most other cyclophanes experimental heats of formation have not been obtained due to lack of sufficient material. Three different sets of calculated strain energies have been quoted, and despite quite large differences in the values obtained by the different methods, the order of the strain energies is the same in each case.



13

[2.2]Paracyclophane

$\triangle H_f$ 57.6 kcal.mol^{-1}

SE_1 32[a] kcal.mol^{-1}

SE_2 28 kcal.mol^{-1}

SE_3 32 kcal.mol^{-1}

7

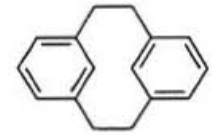
[2.2]Metaparacyclophane

$\triangle H_f$ 52.2 kcal.mol^{-1}

SE_1 24 kcal.mol^{-1}

SE_2 22 kcal.mol^{-1}

SE_3 27 kcal.mol^{-1}



12

[2.2]Metacyclophane

$\triangle H_f$ 40.8 kcal.mol^{-1}

SE_1 12 kcal.mol^{-1}

SE_2 15 kcal.mol^{-1}

SE_3 17 kcal.mol^{-1}

All the heats of formation above were determined experimentally. The strain energies SE_1,[10] SE_2[11] and SE_3[11] were calculated according to the respective references except for *a* which is the average of the molecular mechanical calculations of Shieh[10] and Boyd.[12]

Figure 1.6 Strain Energies of Some [2.2]Cyclophanes[9]

Clearly the strain energy is significant in each case, but that of [2.2]paracyclophane is the highest due to the pronounced boat-distortion of the benzene rings and to a strong electrostatic repulsion between the π-electron clouds.

As the reader is no doubt becoming aware, the interest in cyclophanes pertains almost entirely to their three-dimensional structures, and two-dimensional representations do not convey the true character of these molecules. Later chapters will attempt to elucidate in detail the interesting features of several cyclophane ring systems.

1.5 Unusual Physical Properties

As has been pointed out, calorimetric tests on these molecules have been few and far between. However, physical analysis of the unusual properties of the cyclophanes has been conducted by almost every imaginable method known to science, and very frequently the cyclophanes, especially the smaller more strained members of the genre, show results divergent from the norm.

Nuclear magnetic resonance spectrometry (NMR) has been extensively used to probe the structures of the cyclophanes. Before the advent of readily available X-ray crystallography it represented by far the most powerful tool for the job. Particularly interesting have been the so-called "internal protons" of *anti*-metacyclophanes, which often appear at very high field for aromatic protons due to the shielding effect of a proximal benzene ring. [This will be discussed in much greater depth in Chapter 2.] Much of what we know about the fluxional movements of various cyclophanes has been gleaned from careful NMR work, sometimes through running experiments at different

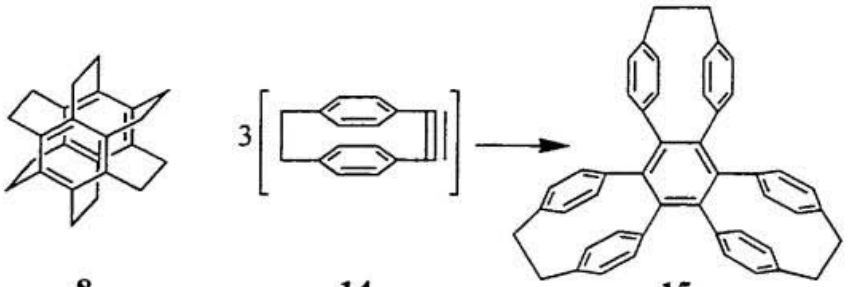
temperatures to measure coalescence points. Mitchell has provided a major review of work in this area.[13]

The best evidence for the solid state structure of the cyclophanes comes, of course, from X-ray crystallography. A huge bank of data has accumulated over the years, and strongly bears out what had been expected from all the previous NMR studies and theoretical studies with regard to the degree of distortion of the benzene rings due to strain and electrostatic repulsion. As has been mentioned earlier, X-ray analysis gave the first structural "picture" of paracyclophane, revealing its now famous boat-shaped benzene rings, and its use in cyclophane chemistry has been growing ever since. Keehn has published a major review of the X-ray data from the cyclophane literature.[14]

Among the many other techniques used to analyse cyclophanes one which may not be immediately obvious is UV spectrometry. This has been used to investigate π-stacking interactions between aromatic rings in paracyclophanes. Misumi's group was successful in synthesising a six-layered paracyclophane (see Chapter 4 for details), and comparison of its UV spectrum with those of two, three and four-layered cyclophanes showed that the bathochromic effect increased with the number of layers.[15] [The bathochromic effect is a measure of the transannular electronic interaction between the benzene rings.]

1.6 Famous Cyclophanes from the Literature

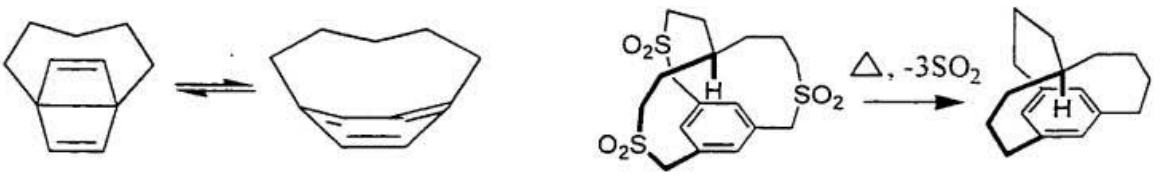
There is a huge volume of chemical literature devoted to the cyclophanes. Any summary of the most interesting examples is doomed to exclude some worthy candidates,



8 **14** **15** **16**

1979 1982 1983

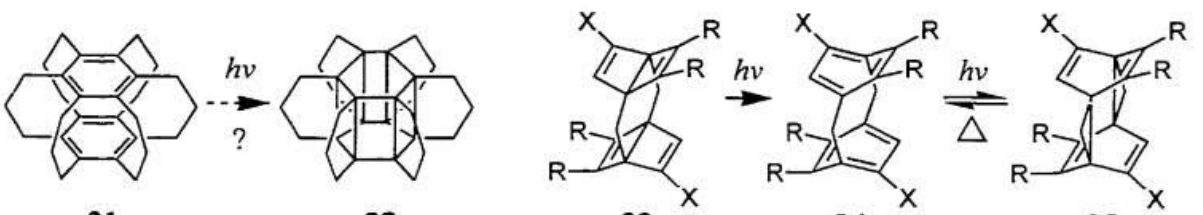
Boekelheide Hopf Miyahara



17 **18** **19** **20**

1985 1987

Bickelhaupt and Odaira Pascal Jr.



21 **22** **23** **24** **25**

1996 1998

Shinmyozu Tsuji

X = $CONMe_2$
R = CH_2SiMe_3

Figure 1.7 Some Interesting Cyclophanes from the Literature

so shown above are some of the compounds I feel best exemplify this area of research. [Compounds illustrated in later chapters have been omitted from this section.]

No discussion of important cyclophanes would be complete without mention of superphane, **8**. From the discovery of paracyclophane onwards, chemists were fascinated by the idea of adding more ethano bridges between the benzene rings to ultimately produce this structure. Superphane has D_{6h} symmetry, as demonstrated by X-ray crystallography, and its benzene rings are planar hexagons, most unlike the boat-shaped rings of [2.2]paracyclophane. The ultimate synthesis of superphane was the culmination of years of work. Friendly competition in this area between the Hopf and Boekelheide groups even included a bet between the two supervisors. Boekelheide finally succeeded in synthesising **8** in 1979,[16] and in a full paper in 1981 described its physical and chemical properties.[17] The synthetic route developed by Boekelheide is remarkable in that it is amenable to the production of **8** in multigram quantities, a level of practicality rarely seen in this field of chemistry. While **8** possesses the highest strain energy of any [2_n]cyclophane, the strain is spread over a large number of bonds, resulting in thermal stability. The extremely high symmetry leads to a melting point of over 300 °C for this $C_{24}H_{24}$ unfunctionalised hydrocarbon, and low solubility in common solvents.

Compound **15**, named trifoliaphane by Hopf due to its structural similarity to a three-leafed clover, is an intriguing molecule in many ways.[18] An obvious comparison to be made is between this compound and hexaphenylbenzene. In the case of the latter the "external" benzene rings adopt a propeller shape, with a pitch of 65°. The ethano bridges of **15** should cause all the external benzene rings to be parallel and perpendicular to the central ring. This could give rise to an unusual interaction between the orthogonal π-

systems of the external and central benzene rings. Furthermore, the issue of bond-fixation, not mentioned in Hopf's paper, should be considered. The double bonds of the central ring would be expected to favour the positions as drawn in Figure 1.7, since this arrangement avoids the resonance form in which each paracyclophane unit is forced to accommodate one etheno bridge. [Vollhardt demonstrated complete bond-fixation in the case of tris(benzocyclobutadieno)benzene by X-ray analysis.][19] An X-ray crystal structure of **15** is eagerly awaited. One further point of interest is that **15** is apparently formed through the trimerisation of [2.2]paracyclophyne **14** - the paracyclophane possessing one ethano and one ethyno bridge. [The byproducts from the reaction are consistent with this assumption.] Not surprisingly, this intermediate has not been isolated.

Miyahara reported the successful synthesis of [1_4]paracyclophane **16** in 1983.[20] This compound was synthesised by a unique methodology, whereby the final benzene ring was created by a Diels-Alder reaction. The compound was targeted due to its expected rigidity, and was hoped to be of use for selective inclusion complex formation. Another interesting idea mentioned was that the perhydro derivatives of **16**, and to a greater extent the bigger [1_n]paracyclophanes, might resemble cyclodextrins. [1_4]Paracyclophane is expected to have a rigid, exactly square cavity, with the four benzene rings fixed in a "face" conformation.[21] Similar to **8**, **16** was found to be very insoluble and high melting (340-341 °C), but unfortunately no X-ray crystal structure has yet appeared to confirm its solid-state structure.

Bickelhaupt has had a long fascination with [n]cyclophanes, and has attempted to find the limiting structures for both the meta[22,23] and para series. This search has led to the situation where the bridged Dewar benzenes are actually thermodynamically more stable

than the corresponding cyclophanes. This is indeed the case with [5]paracyclophane, **18**, which has not been obtained pure. It has been observed by NMR by mercury lamp irradiation of a solution of the Dewar isomer **17** at -60 °C, the estimated yield being 6-7%.[24] [5]Paracyclophane apparently decomposes at room temperature.

Compound **20** was synthesised by Pascal's group in 1987.[25] Like most highly-strained cyclophanes in the recent literature (and most in this thesis), **20** was prepared by extrusion of additional atoms from the bridges. In this case three molecules of SO_2 were thermally removed from the corresponding trisulphone **19**, for which X-ray crystallographic data were obtained. The X-ray structure of **19** showed the methine proton to be only 2.21 Å from the benzene ring below it. Unfortunately only 2.2 mg **20** was obtained, and X-ray analysis was not possible. However, MM2 calculations indicated that the methine proton of **20** should be only 1.78 Å from the phenyl ring. The resulting shielding effect of the π-electron cloud is seen in the NMR spectrum where the methine proton appears at δ -4.03 - an enormous upfield shift.

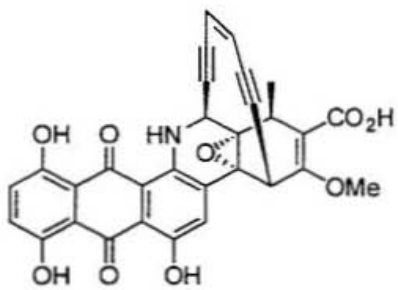
Similar to chemists' interest in the synthesis of superphane has been their interest in the prismanes. While some success has been achieved in this area, hexaprismane remains elusive. Compound **21** had been predicted,[26] based on semiempirical MO calculations, to photo-isomerise to the propella[3_6]prismane **22**.[27] Moreover, similar calculations also predicted a solution phase correlated inversion of the six propano bridges, similar to the inversion of a pinwheel or water mill. The successful synthesis of this homologated superphane was finally reported in 1996 after much effort.[28] While the NMR spectrum of **21** was consistent with the aforementioned inversion, successful execution of the desired photo-isomerisation reaction has not yet been achieved.

The last of my selections from the literature is the truly astounding recent achievement of Tsuji in synthesising a substituted [1.1]paracyclophane.[29] Not only did the Tsuji group successfully synthesise compound **24**, they isolated it and obtained crystallographic data. [It should be noted that the preparation of [1.1]metacyclophane has not been achieved, although Bickelhaupt's attempts suggest that an internally dichlorinated derivative has been produced as a fleeting intermediate.[30] It appears that the general rule of a paracyclophane being less stable than the corresponding metacyclophane may be reversed for the [1.1] compounds, since in [1.1]metacyclophane the internal atoms are by necessity practically on top of each other.] Tsuji's ultimate success was the culmination of much work in this area, and was due to the understanding that the instability of his previously observed [1.1]paracyclophanes (unstable above -20 °C even in dilute solution) could be overcome by sterically shielding all four bridgehead sites.[31] Hence in compound **24** attack on a bridgehead position is sterically impossible, and a dilute solution could be heated to 50 °C for two hours in the absence of air and light with no apparent decomposition. The synthesis of **24** proceeds by irradiation of Dewar benzene **23**. Only a very low yield (5% at 80% conversion) of **24** is obtained directly, along with a 66% yield of **25**, resulting from a second transannular [4+4] addition within **24**. The [1.1]paracyclophane is obtained in quantitative yield by heating a benzene solution of **25** at 45 °C.

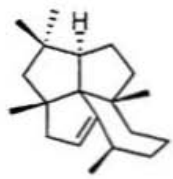
1.7 Naturally Occurring Cyclophanes

The cyclophanes have always been thought of as most "unnatural" products. This has been due to their bent, twisted and strained aromatic rings and unfeasible-looking

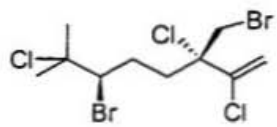
carbon skeletons; but perhaps more so to the fact that they were conceived by human imagination before their discovery in nature. It is nevertheless true that some natural products are, by our prestated definition, cyclophanes. This can hardly be seen as surprising when one peruses the bizarre natural products that have appeared in the recent chemical literature. The increase in throughput of screening programs searching for biologically active compounds has led to the discovery of some unexpectedly complex molecules. They have been found purely because they have biological activity. It seems that chemists have the idea that the structures targeted by cyclophane chemists, often inspired by mathematical thinking, are somehow inaccessible to Nature. It should not be forgotten that several enediynes (for example dynemicin A **26**, Figure 1.8)[32] are naturally occurring compounds, as is the fenestrane laurenene **27**.[33] The pentahaloalkene halomon **28** (an antitumour agent) is another example of a molecule which most chemists might not have expected to find in Nature.[34]



26 Dynemicin A



27 Laurenene

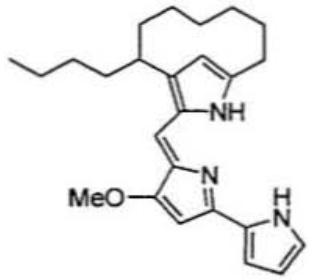


28 Halomon

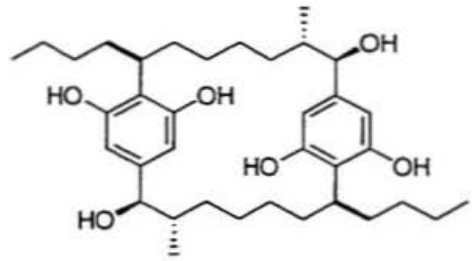
Figure 1.8 Three of Many Surprising Natural Products

There may be naturally occurring [2.2]paracyclophanes, possibly even [1.1]paracyclophanes, but unless they are biologically active (like **26** and **28** above), or

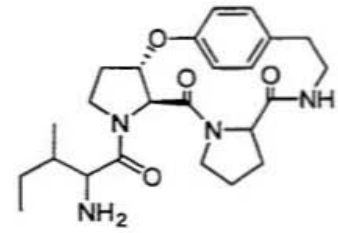
are present in high concentrations (like **27** above), they may not be found. Below (Figure 1.9) are shown some of the naturally-occurring cyclophanes which have been identified.



29 Streptorubin B



30 Cylindrocyclophane A

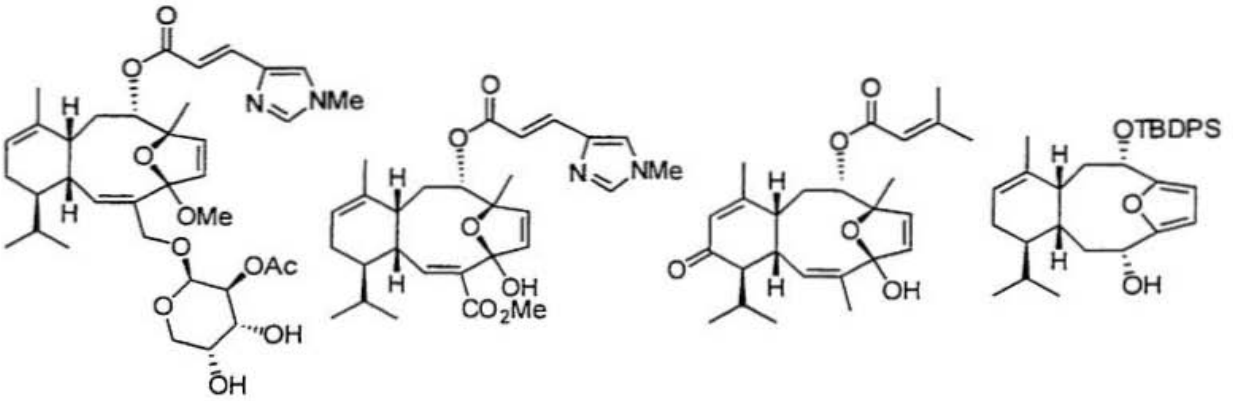


31 Dihydrozizyphin G

Figure 1.9 Cyclophane Natural Products

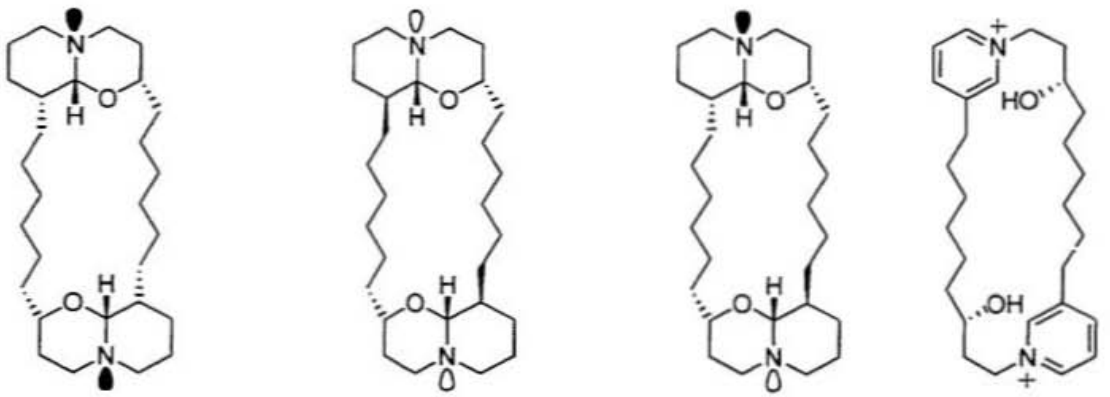
Streptorubin B **29** is a member of the prodiginine family of antibiotics. Both **29** and another cyclophane member of this family, metacycloprodigiosin, exhibit promising immunomodulating properties, and a deep red coloration due to the pyrrolylpyrromethene chromophore. They are produced by some eubacteria and actinomycetes. Fürstner has effected particularly elegant formal syntheses of both of these compounds.[35] The cylindrocyclophanes (including **30** above) and the structurally-similar nostocyclophanes are produced by blue-green algae.[36] They possess fascinating C_2-symmetric chiral [7.7]paracyclophane skeletons, and show some cytotoxicity. Syntheses of these molecules have not yet been published. Dihydrozizyphin G **31** has been isolated from plant material,[37] and is an example of a [10]paracyclophane. The synthesis of this molecule has been achieved by Häusler.[38]

It should also be mentioned that Danishefsky's recently published convergent route which gives access to all the "eleuthesides" (eleutherobin, sarcodyctin and valdivone A, **32-34** respectively) features the cyclophane intermediate **35** (Figure 1.10).[39]



32 Eleutherobin **33** Sarcodyctin **34** Valdivone A **35**

Danishefsky's cyclophane intermediate **35** in his route to the eleuthesides **32-34**



36 (+)-Araguspongine B **37** (-)-Xestospongin A **38** (+)-Xestospongin C **39**

Baldwin's cyclophane intermediate **39** in his route to marine sponge alkaloids **36-38**

Figure 1.10 Cyclophane Intermediates in Natural Product Syntheses

Likewise, Baldwin's synthesis of (-)-Xestospongin A **37** (and its diastereomers (+)-Araguspongine B **36** and (+)-Xestospongin C **38**) features a cyclophane intermediate **39** (Figure 1.10).[40] In this paper Baldwin even proposes **39** to be the intermediate for the biosyntheses of these compounds. [He had previously suggested the biosynthetic intermediate might be the corresponding dihydropyridinium dimer.][41]

No cyclophane natural product has yet proved to be very important biologically, but when that time comes the ensuing synthetic race between the traditional natural product research groups and the cyclophane research groups will be fascinating.

1.8 References

[1] Cram, D.J.; Steinberg, H. *J. Am. Chem. Soc.* **1951**, *73*, 5691-5704.

[2] Vögtle, F.; Neumann, P. *Tetrahedron* **1970**, *26*, 5847-5873.

[3] For a preliminary paper on cyclophane nomenclature, see Vögtle, F.; Neumann, P. *Tetrahedron Lett.* **1969**, *10*, 5329-5334.

[4] Pellegrin, M.M. *Recl. Trav. Chim. Pays-Bas* **1899**, *18*, 457-465.

[5] Baker, W.; Banks, R.; Lyon, D.R.; Mann, F.G. *J. Chem. Soc.* **1945**, 27-30.

[6] Brown, C.J.; Farthing, A.C. *Nature (London)* **1949**, *164*, 915-916.

[7] Cram, D.J.; Steinberg, H. *J. Am. Chem. Soc.* **1951**, *73*, 5691-5704.

[8] Reichstein, T.; Oppenauer, R. *Helv. Chim. Acta* **1933**, *16*, 1373-1380.

[9] Liebman, J.F. in *Organic Chemistry, A series of monographs*, Volume 45, "Cyclophanes", Wasserman, H.H., Ed.; Academic Press: New York, 1983; Chapter 2.

[10] Shieh, C.-F.; McNally, D.; Boyd, R.H. *Tetrahedron* **1969**, *25*, 3653-3665.

[11] Lindner, H.J. *Tetrahedron* **1976**, *32*, 753-757.

[12] Boyd, R.H. *Tetrahedron* **1966**, *22*, 119-122.

[13] Mitchell, R.H. in *Organic Chemistry, A series of monographs*, Volume 45, "Cyclophanes", Wasserman, H.H., Ed.; Academic Press: New York, 1983; Chapter 4.

[14] Keehn, P.M. in *Organic Chemistry, A series of monographs*, Volume 45, "Cyclophanes", Wasserman, H.H., Ed.; Academic Press: New York, 1983; Chapter 3.

[15] Otsubo, T.; Tozuka, Z.; Mizogami, S.; Sakata, Y.; Misumi, S. *Tetrahedron Lett.* **1972**, *13*, 2927-2930.

[16] Sekine, Y.; Brown, M.; Boekelheide, V. *J. Am. Chem. Soc.* **1979**, *101*, 3126-3127.

[17] Sekine, Y.; Boekelheide, V. *J. Am. Chem. Soc.* **1981**, *103*, 1777-1785.

[18] Psiorz, M.; Hopf, H. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 623-624.

[19] Diercks, R.; Vollhardt, K.P.C. *J. Am. Chem. Soc.* **1986**, *108*, 3150-3152.

[20] Miyahara, Y.; Inazu, T.; Yoshino, T. *Tetrahedron Lett.* **1983**, *24*, 5277-5280.

[21] Tabushi, I.; Yamada, H.; Kuroda, Y. *J. Org. Chem.* **1975**, *40*, 1946-1949.

[22] For the preparation of [5]metacyclophane see Van Straten, J.W.; De Wolf, W.H.; Bickelhaupt, F. *Tetrahedron Lett.* **1977**, *18*, 4667-4670. For analogous compounds with even shorter tether lengths see Van Es, D.S.; Egberts, A.; Nkrumah, S.; De Nijs, H.; De Wolf, W.H.; Bickelhaupt, F. *J. Am. Chem. Soc.* **1997**, *119*, 615-616; Van Eis, M.J.; De Kanter, F.J.J.; De Wolf, W.H.; Bickelhaupt, F. *J. Am. Chem. Soc.* **1998**, *120*, 3371-3375.

[23] For the preparation of the Dewar isomer of [4]metacyclophane see Turkenberg, L.A.M.; Van Straten, J.W.; De Wolf, W.H.; Bickelhaupt, F. *J. Am. Chem. Soc.* **1980**, *102*, 3256-3257.

[24] Jenneskens, L.W.; De Kanter, F.J.J.; Kraakman, P.A.; Turkenburg, L.A.M.; Koolhaas, W.E.; De Wolf, W.H.; Bickelhaupt, F.; Tobe, Y.; Kakiuchi, K.; Odaira, Y. *J. Am. Chem. Soc.* **1985**, *107*, 3716-3717.

[25] Pascal, R.A., Jr.; Grossman, R.B.; Van Engen, D. *J. Am. Chem. Soc.* **1987**, *109*, 6878-6880.

[26] For both photoisomerisation and inversion predictions see Shinmyozu, T.; Kusumoto. S.; Nomura, S.; Kawase, H.; Inazu, T. *Chem. Ber.* **1993**, *126*, 1815-1818 and the references within.

[27] Gleiter has synthesised two of the lower homologues of **22**, propella[3_4]prismane (Gleiter, R.; Karcher, M. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 840-841) and *S*4-symmetric propella[4_4]prismane (Brand, S.; Gleiter, R. *Tetrahedron Lett.* **1997**, *38*, 2939-2942).

[28] Sakamoto, Y.; Miyoshi, N.; Shinmyozu, T. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 549-550. For the synthesis of [3_5](1,2,3,4,5)cyclophane see Shimyozu, T.; Hirakida, M.; Kusumoto, S.; Tomonou, M.; Inazu, T.; Rudzinski, J.M. *Chem. Lett.* **1994**, 669-672.

[29] Kawai, H.; Suzuki, T.; Ohkita, M.; Tsuji, T. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 817-819.

[30] Van Eis, M.J.; De Kanter, F.J.J.; De Wolf, W.H.; Bickelhaupt, F. *J. Org. Chem.* **1997**, *62*, 7090-7091.

[31] For Tsuji's previous work on [1.1]paracyclophanes and other highly-strained paracyclophanes see Tsuji, T.; Ohkita, M.; Nishida, S. *J. Am. Chem. Soc.* **1993**, *115*, 5284-5285; Okuyama, M.; Ohkita, M.; Tsuji, T. *J. Chem. Soc., Chem. Commun.* **1997**,

1277-1278; Okuyama, M.; Tsuji, T. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1085-1087; Tsuji, T.; Ohkita, M.; Konno, T.; Nishida, S. *J. Am. Chem. Soc.* **1997**, *119*, 8425-8431.

[32] Konishi, M.; Ohkuma, H.; Matsumoto, K.; Tsuno, T.; Kamei, H.; Miyaki, T.; Oki, T.; Kawaguchi, H.; VanDuyne, G.D.; Clardy, J. *J. Antibiot.* **1989**, *42*, 1449-1452; Konishi, M.; Ohkuma, H.; Tsuno, T.; Oki, T.; VanDuyne, G.D.; Clardy, J. *J. Am. Chem. Soc.* **1990**, *112*, 3715-3716.

[33] Corbett, R.E.; Lauren, D.R.; Weavers, R.T. *J. Chem. Soc. Perkin Trans. 1*, **1979**, 1774-1790; Corbett, R.E.; Couldwell, C.M.; Lauren, D.R.; Weavers, R.T. *J. Chem. Soc. Perkin Trans. 1*, **1979**, 1791-1794.

[34] Fuller, R.W.; Cardellina, J.H.; Kato, Y.; Brinen, L.S.; Clardy, J.; Snader, K.M.; Boyd, M.R. *J. Med. Chem.* **1992**, *35*, 3007-3011; Fuller, R.W.; Cardellina, J.H.; Jurek, J.; Scheuer, P.J.; Alvarado-Lindner, B.; McGuire, M.; Gray, G.N.; Steiner, J.R.; Clardy, J.; Menez, E.; Shoemaker, R.H.; Newman, D.J.; Snader, K.M.; Boyd, M.R. *J. Med. Chem.* **1994**, *37*, 4407-4411.

[35] Fürstner, A.; Szillat, H.; Gabor, B.; Mynott, R. *J. Am. Chem. Soc.* **1998**, *120*, 8305-8314.

[36] Moore, B.S.; Chen, J.-L.; Patterson, G.M.L.; Moore, R.E. *J. Am. Chem. Soc.* **1990**, *112*, 4061-4063; Chen, J.-L.; Moore, R.E.; Patterson, G.M.L *J. Org. Chem.* **1991**, *56*, 4360-4364; Moore, B.S.; Chen, J.-L.; Patterson, G.M.L.; Moore, R.E. *Tetrahedron* **1992**, *48*, 3001-3006.

[37] Tsesche, R.; Khokar, I.; Spilles, Ch.; Eckhardt, G.; Cassels B.K. *Tetrahedron Lett.* **1974**, *15*, 2941-2944.

[38] Schmidt, U.; Lieberknecht, A.; Griesser, H.; Haeusler, J. *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 281-282.

[39] Chen, X.-T.; Gutteridge, C.E.; Bhattacharya, S.K.; Zhou, B.; Pettus, T.R.R.; Hascall, T.; Danishefsky, S.J. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 185-187.

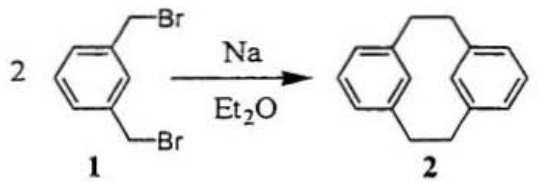
[40] Baldwin, J.E.; Melman, A.; Lee, V.; Firkin, C.R.; Whitehead, R.C. . *J. Am. Chem. Soc.* **1998**, *120*, 8559-8560. For interesting syntheses of cyclophane natural products structurally very similar to **39** using the Zincke reaction, see Kaiser, A.; Billot, X.; Gateau-Olesker, A.; Marazano, C.; Das, B.C. *J. Am. Chem. Soc.* **1998**, *120*, 8026-8034.

[41] Baldwin, J.E.; Whitehead, R.C. *Tetrahedron Lett.* **1992**, *33*, 2059-2062.

Synthesis and Study of Tethered Metacyclophanes Capable of Acting as Molecular Switches

2.1 Introduction

[2.2]Metacyclophane **2** was the first of the [2.2]cyclophanes to be discovered.[1] It was successfully synthesised in 1899 by Pellegrin, who used a Wurtz coupling reaction on the corresponding α,α′-dibromoxylene **1** (Figure 2.1). The yield of this reaction was low, as is to be expected for the formation of a strained medium-size ring, but Pellegrin's melting point of 131.5 °C (lit. 134.5-135 °C)[2] and cryoscopic molar mass determination of 205.2-205.7 g mol^{-1} (theoretical molar mass 208.31 g mol^{-1}) both strongly suggest that he did indeed obtain some pure **2**.

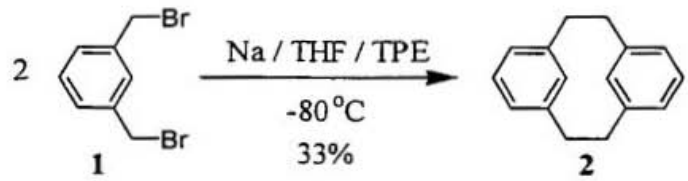


Scheme 2.1 Pellegrin's Successful Wurtz Coupling[1]

At that time the structural geometry of the molecule could not be adequately ascertained. However, NMR spectroscopy and X-ray crystallography have since shown that the lower energy form of this molecule is the *anti* isomer. [A painstaking experimental and chromatographic procedure was employed by Mitchell to eventually obtain the *syn* isomer in 1985.[3,4] This remarkable feat is discussed later in this chapter.]

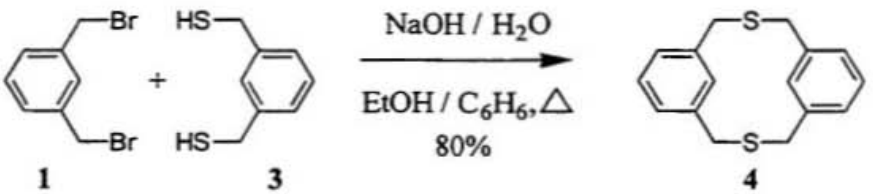
2.1.1 Synthetic Methods for *anti*-[2.2]Metacyclophane Synthesis

Improved methods have been developed for the synthesis of the *anti*-[2.2]metacyclophanes. The original Wurtz coupling approach has been successfully modified using the procedure shown below:



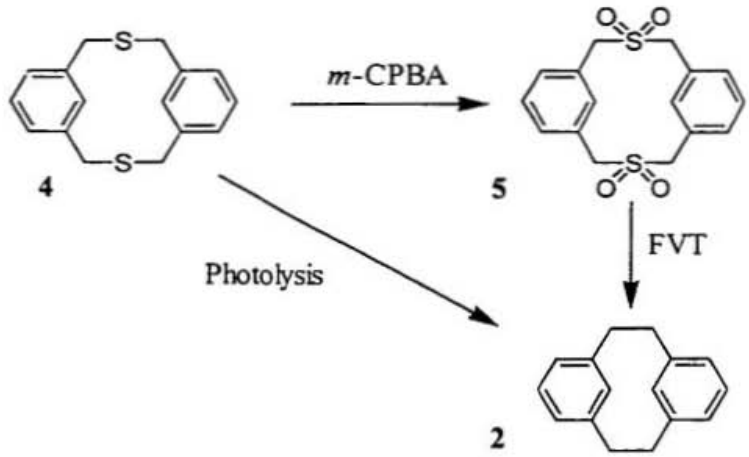
Scheme 2.2 Müller and Röscheisen's Modification[5]

Müller and Röscheisen modified the standard Wurtz coupling by using THF as the solvent at –80 °C and by adding tetraphenylethylene (TPE).[5] The rationale presented for the improved yields was that the sodium partially dissolves under the reaction conditions, while when the traditional Wurtz conditions are used the reaction proceeds on the metal surface. Thus the effective dilution of the reaction increases dramatically, while the lower temperature promotes a more selective reaction pathway, possibly favouring the second, intramolecular Wurtz reaction over oligomerisation. The reaction mixture turns a dark red colour, reminiscent of the purple sodium benzophenone ketyl formed in the drying of THF. Efficient mixing is essential, and a vibration mixer has often been used. The procedure has since been used to great effect by several chemists, the highest yield ever claimed for [2.2]metacyclophane being 77% for the intramolecular closure of 1,2-bis[3-(bromomethyl)phenyl]ethane (**9** → **2**, see also Scheme 2.6 below) obtained by Boekelheide using this method.[6]



Scheme 2.3 Boekelheide's Thiacyclophane Synthesis[7]

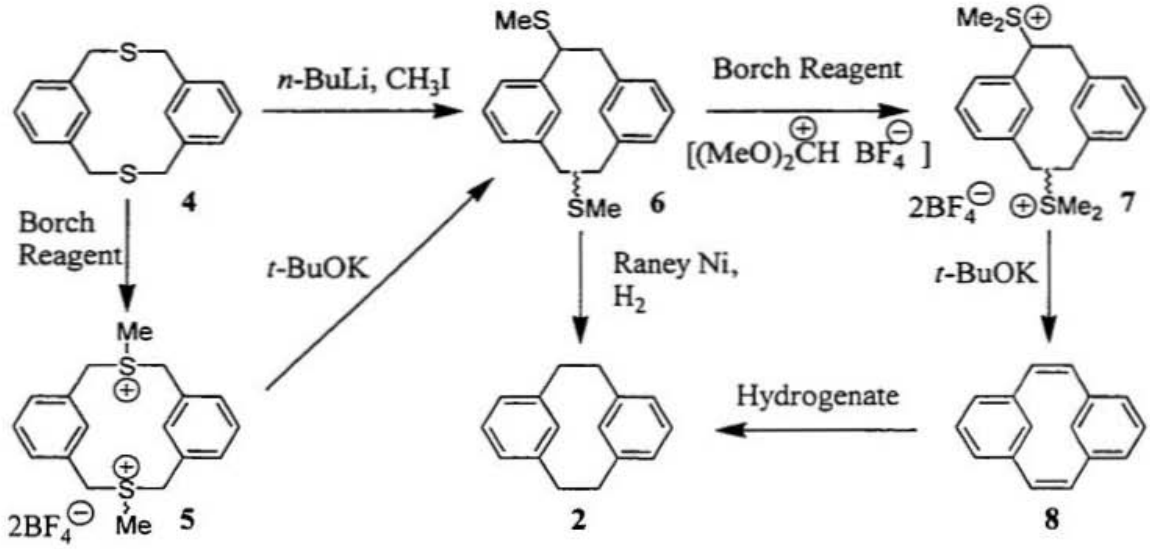
At present by far the most commonly used methodology involves formation of the intermediate dithiacyclophane (e.g. **4**) from a high dilution 1:1 mixture of a dibromide and a dithiol. [The dithiol is generally readily obtained from the dibromide.] This procedure, described by Boekelheide in 1974,[7] usually allows relatively high yields of the 2,11-dithia[3.3]metacyclophanes. These have been widely studied and have some interesting properties themselves. Part of the philosophy behind this approach is that the closure of the dithiacyclophane ring is far less sterically demanding than the Wurtz ring-closure above due to the reduced strain energy of the larger ring system. To obtain the cyclophanes from the dithiacyclophanes it is necessary to extrude the sulphur atoms. At least four methods are commonly used to accomplish this. Conceptually simplest, and most direct, is photolysis in an appropriate thiophilic solvent ($P(OMe)_3$ or $P(OEt)_3$ are most common).[8] Mercury lamp irradiation is performed using a quartz tube to allow efficient passage of light. A radical mechanism is invoked.[9] Alternatively the sulphide link can be oxidised to the sulphone level, at which stage the sulphur is removed as SO_2 gas using flash-vacuum thermolysis (FVT), provided the correct conditions of temperature and pressure can be found.[10,11] Again, a radical process is thought to be involved. [The mechanism of this process is discussed in reference 9.]



Scheme 2.4 Common Sulphur Extrusion Methods[8,10]

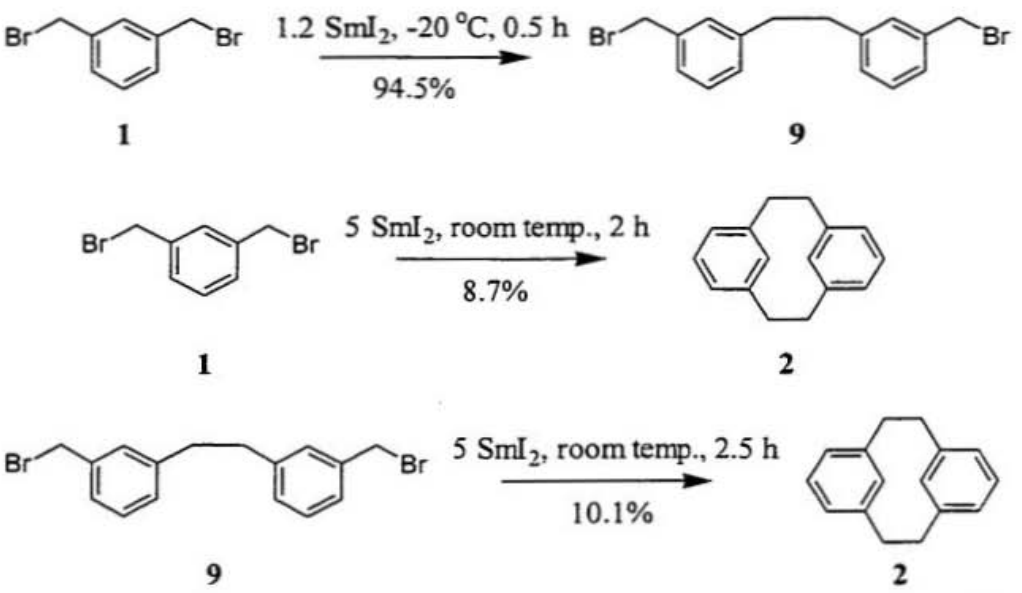
The weaknesses of this methodology are the expensive apparatus generally deemed necessary and the extra (generally high-yielding) oxidation step. An alternative method in which the disulphones are photolysed has also been reported, but seems inferior to both of those mentioned above due to low conversion rates and byproduct formation.[12]

The other two methods depend upon base-induced rearrangements and are shown below. It will be noted that both proceed via the same synthetic intermediates **6**,**7** and **8**. Some thiacyclophanes can be directly converted to analogues of **6** by the Wittig rearrangement,[13,14] while in other cases the less direct method employing intermediates analogous to **5** and the Stevens rearrangement using *t*-BuOK gives higher yields.[7] Due to the number of steps required, and the instability of many cyclophanedienes, the photolytic and pyrolytic methods are generally preferred. Another method of sulphur removal after ring contraction is the treatment of intermediates such as **6** with Raney Ni.[7]



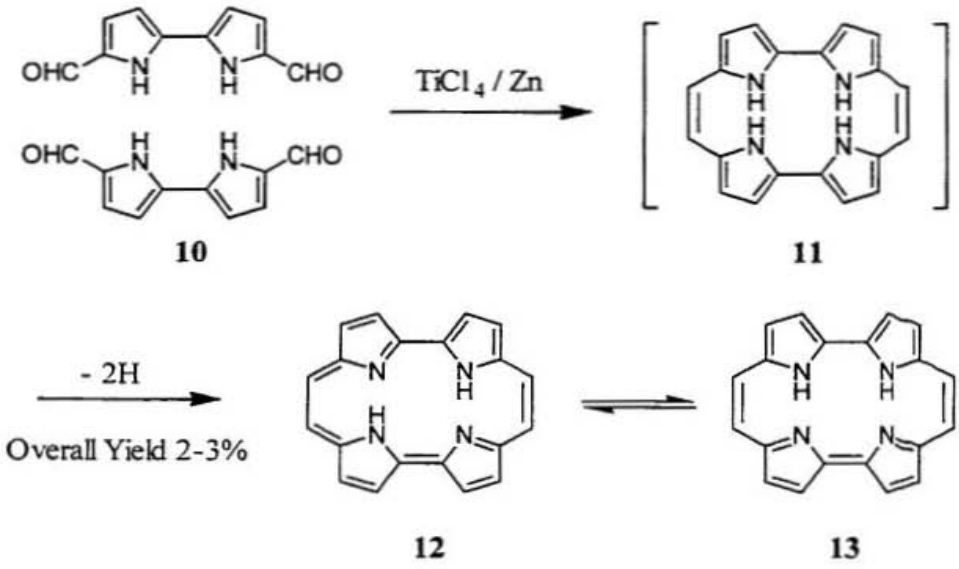
Scheme 2.5 Sulphur Extrusion via Base-Induced Rearrangement[7.13.14]

There have been several recent attempts to improve upon the existing methods in the literature. Samarium (II) iodide has seen much use as a ring-closing agent,[15] and has been investigated as an alternative to sodium in the reaction of α,α'-dibromoxylenes (Scheme 2.6).[16] While the initial intermolecular reaction can be achieved in spectacularly high yields, the subsequent intramolecular closure is unsatisfactory. A best yield of 8.7% was obtained for the direct production of **2** by this method. Interestingly the two step approach following isolation of the intermediate **9** was not much more successful. This work and the previous work of Müller and Röscheisen strongly suggest that a hybrid approach using SmI_2 for the first coupling and Na / TPE for the second could be very useful for the production of many symmetrical [2.2]metacyclophanes.



Scheme 2.6 Mori's Investigation of SmI_2 as a Cyclophane-Closing Reagent[16]

A new version of the Ramberg-Bäcklund reaction has been introduced by Chan, and this has facilitated the production of many higher cyclophanes.[17] Unfortunately this method fails to produce [2.2]cyclophanes, apparently due to the strain energy of the latter. Several attempts, ours included,[18] to use two consecutive McMurry type reactions to close cyclophane rings have proved to be rather disappointing, although this methodology has been used to obtain low yields of the interesting compounds porphycene **12** and tetraoxaporphycene.[19,20] The synthesis of the former compound is shown below (Scheme 2.7).[19] Considering the achievements previously obtained using this methodology in closing strained rings (see references 21-23 for examples) the poor yields are rather surprising, and perhaps just serve to reaffirm the fact that cyclophanes are particularly difficult to make.[21,22,23,24] Approaches based on the Wittig reaction and its variants have long been known to give generally just tetramers and bigger oligomers.[25]

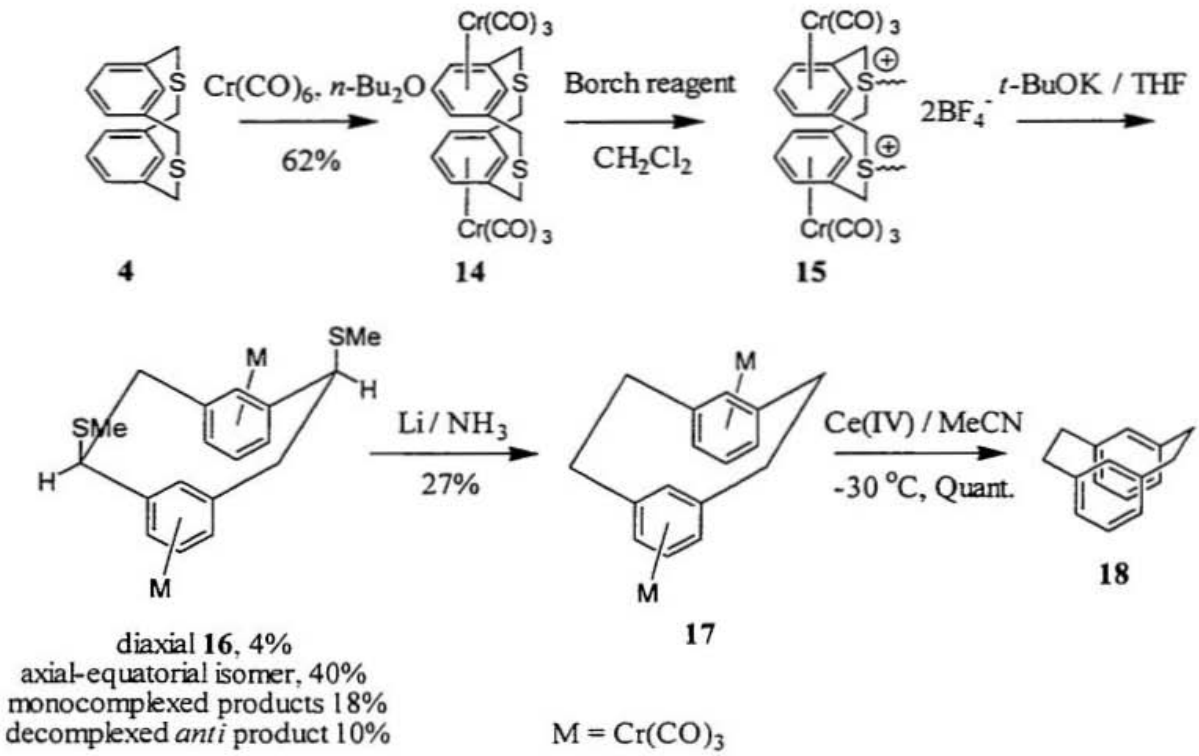


10 **11** **12** **13**

Scheme 2.7 Vogel's McMurry Reaction-Based Porphycene Synthesis[19]

2.1.2 Mitchell's Synthesis of *syn*-[2.2]Metacyclophane

Mitchell reported the successful preparation and isolation of *syn*-[2.2]metacyclophane in 1984, with the full paper following in 1990.[3,4] This achievement should not to be underestimated, as there were several challenging problems to be overcome, and some interesting methodology had to be developed to prevent exclusive production of the thermodynamically more favoured *anti* isomer. [Mitchell's methodology below is an adaptation of a standard cyclophane synthetic route employing the Stevens rearrangement. However, as is readily seen, this standard route had to be modified substantially to enable isolation of the desired product.] The well-known dithiacyclophane **4**, which was shown previously by Mitchell to be predominantly *syn*,[26,27] was first complexed using chromium hexacarbonyl in di-*n*-butyl ether.



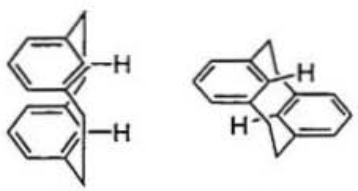
Scheme 2.8 Mitchell's Successful Synthesis of *syn*[2.2]Metacyclophane **18**[3,4]

The purpose of this step was to provide a large steric encumbrance to prevent subsequent *syn-anti* conformational switching during or after ring contraction. The following steps are common to several cyclophane syntheses. *S*-Methylation was followed by Stevens rearrangement. As usual, a mixture of isomers resulted from this procedure. Unfortunately, Mitchell discovered that the only isomer which could lead to the desired **17** was **16**, in which both -SMe groups occupy axial positions. [In most cyclophane syntheses all isomers ultimately lead to the same product.] Partial arene decomplexation was also a problem. Hence the desired isomer was only a minor component obtained in 4% overall yield from **14**. Compound **16** was reduced under Birch conditions for 20

seconds, allowing a 27% yield of the desulphurised, non-Birch reduced product **17**. The final step required removal of the "steric protecting groups" and purification to be conducted at low temperature to prevent isomerisation. Both the reaction and chromatography were conducted at ≤ -30 °C, and the elusive *syn* isomer **18** was finally observed by NMR, which conclusively confirmed its structure and showed its conversion to **2** at 0 °C.

2.1.3 Geometrical Properties

The most obvious point is the possibility of *syn-anti* isomerism alluded to earlier. The two conformers are illustrated below (Figure 2.1):

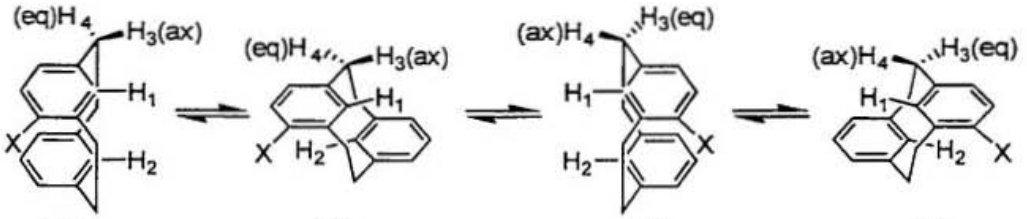


18 *syn* **2** *anti*

Figure 2.1 The *syn* and *anti* Forms of [2.2]Metacyclophane

The observed (X-ray) shape of the *anti* isomer is unusual in that the benzene rings have a pronounced bend and are hence boat shaped. The hydrogen atoms illustrated in Figure 2.1 are referred to as the "internal protons". They have unique NMR properties due to the fact that in the *anti* isomer they are positioned directly above an aromatic π cloud. The shielding effect due to this causes the internal protons of **2** to appear at δ 4.2.[28] In the case of **18** the internal protons appear at δ 6.6. While this value also represents a small upfield

shift relative to *m*-xylene (δ 7.0), there is obviously a huge difference in the magnetic environment of the internal protons of **2** and **18**. The bridge protons of the cyclophane unit are also of some interest. In both isomers they are non-equivalent, resulting in an AA'XX' system in the NMR spectrum. It is interesting to consider the consequences of an *anti-anti'* conformational interconversion, and also the possibility of a reversible *syn-anti* equilibrium (Scheme 2.9). The question of chirality also arises in the sense that planar chirality is possible with this skeleton.

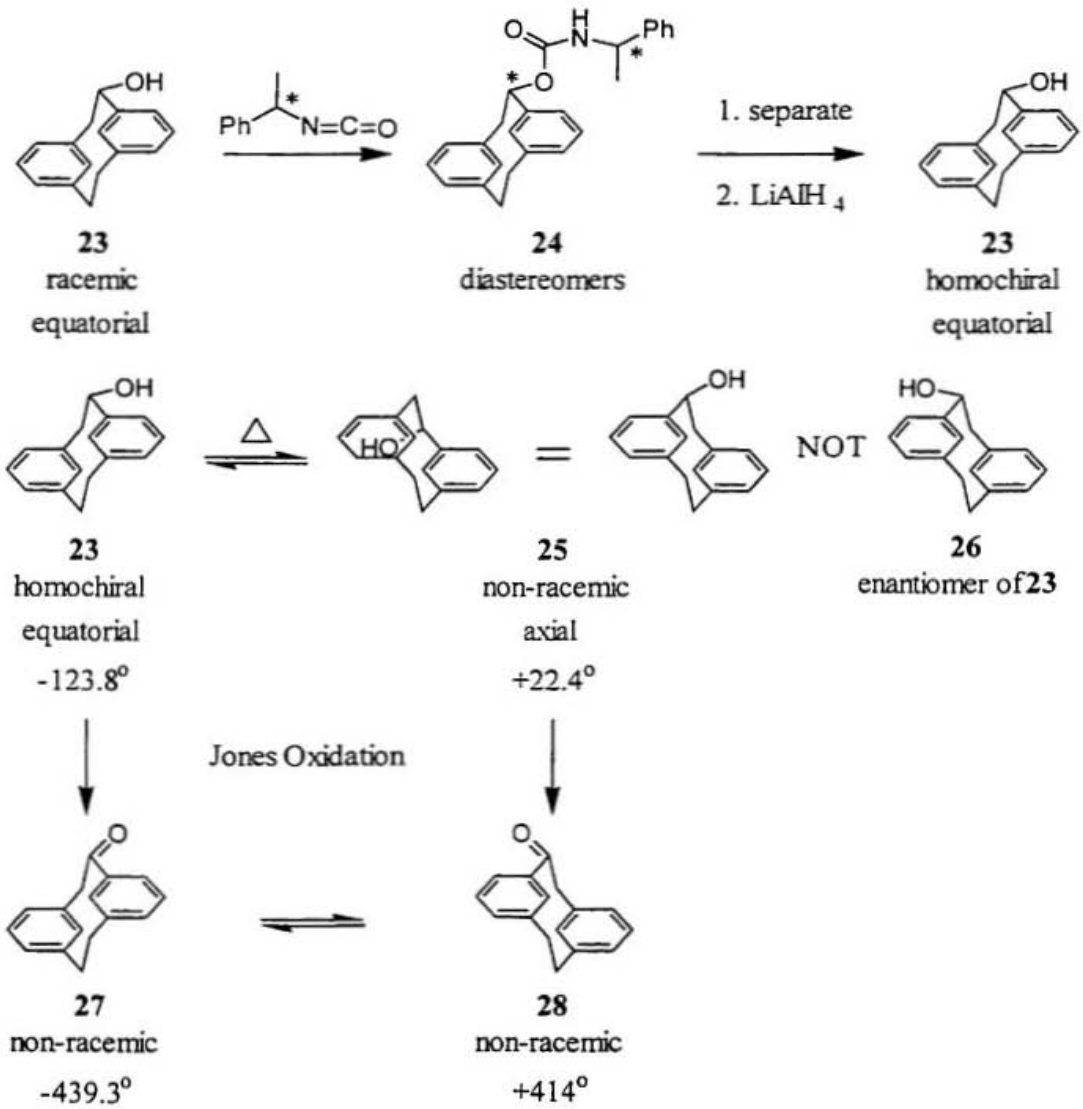


19 *syn* **20** *anti* **21** *syn'* **22** *anti'*

Scheme 2.9 Possible Conformational Interconversions of [2.2]Metacyclophanes

Scheme 2.9 serves to illustrate a series of possible equilibrium processes which would enable racemisation of planar-chiral **19** or **20**, and also the *anti-anti'* flip. It also shows the consequences of a flip for the bridge protons. [To best understand these diagrams the use of a model kit is strongly recommended.] The equatorial positions are defined as those which lie closest to the plane of the proximal benzene ring. From this scheme it is clear that both *syn* and *anti* forms of [2.2]metacyclophane can possess planar chirality if appropriately substituted. Careful examination of the diagrams and preferably the corresponding models reveals the fact that H_3 in *anti* conformer **20**, which occupies an axial position, is moved to an equatorial position in *anti* conformer **22** by the proposed

process. The fact that an AA'XX' system is seen in the NMR spectrum of unsubstituted [2.2]metacyclophane **2** demonstrates that this process does not occur rapidly on the NMR time scale. It should be noted at this point that there is no evidence to support the idea that the *anti-anti'* flip occurs via the *syn* conformer, although use of a model kit strongly suggests that any such flip must involve a *syn*-like intermediate.



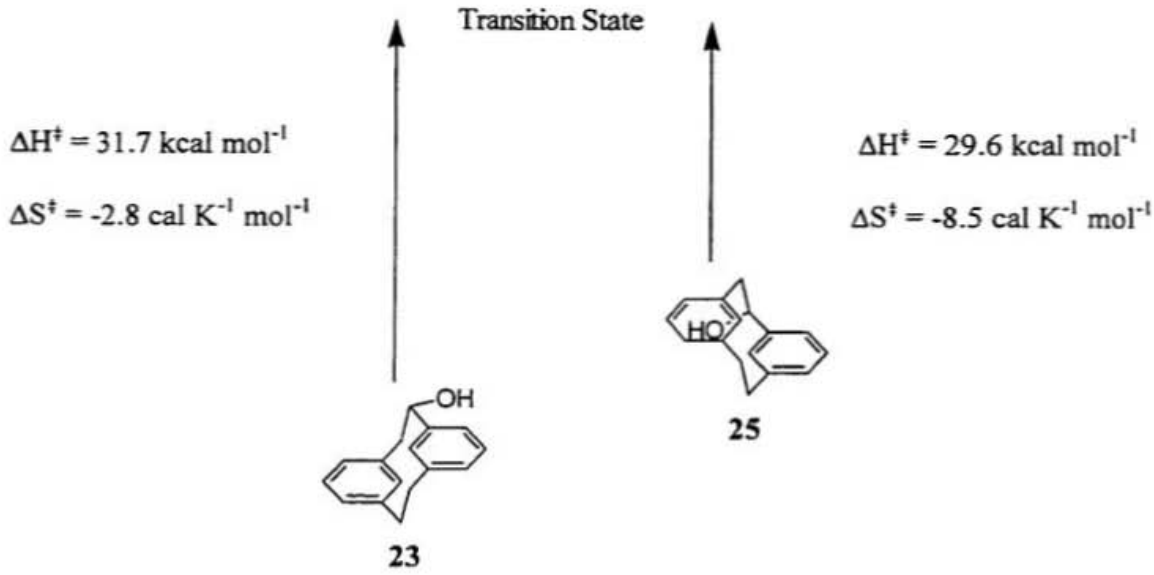
Scheme 2.10 Gschwend's Investigation of Ring-Flipping in [2.2]Metacyclophanes[29]

Gschwend (Scheme 2.10 above) performed a very interesting study on a bridge-substituted metacyclophane, which casts some light on the *anti-anti'* flip process.[29] He successfully resolved carbamate **24** and reduced this with LAH to give homochiral equatorial alcohol **23**. Compound **23** contains two elements of chirality, the inherent dissymmetry due to the skeleton as well as the asymmetric carbinol carbon. It is hence a very useful model for investigating the *anti-anti'* flip. It was found that heating **23** at 185 °C for 2 hours was sufficient for **23** and its bridge-flipped diastereomer **25** to reach their equilibrium ratio of 61:39. [The equatorial alcohol **23** was thermodynamically favoured.] During this process no diradicals could be detected by chemically induced dynamic nuclear polarisation (CIDNP).[30] The new alcohol **25** was demonstrated to be non-racemic, possessing an optical rotation of +22.4° compared to the value of –123.8° for **23**. The NMR spectrum of **25** was consistent with it being the axial diastereomer shown. Oxidation of **25** produced ketone **28** with a rotation of +414°, while oxidation of **23** led to ketone **27** for which $[\alpha]_D$ = -439.3°. The NMR spectra of **27** and **28** were identical. Gschwend's results lead to the following conclusions:

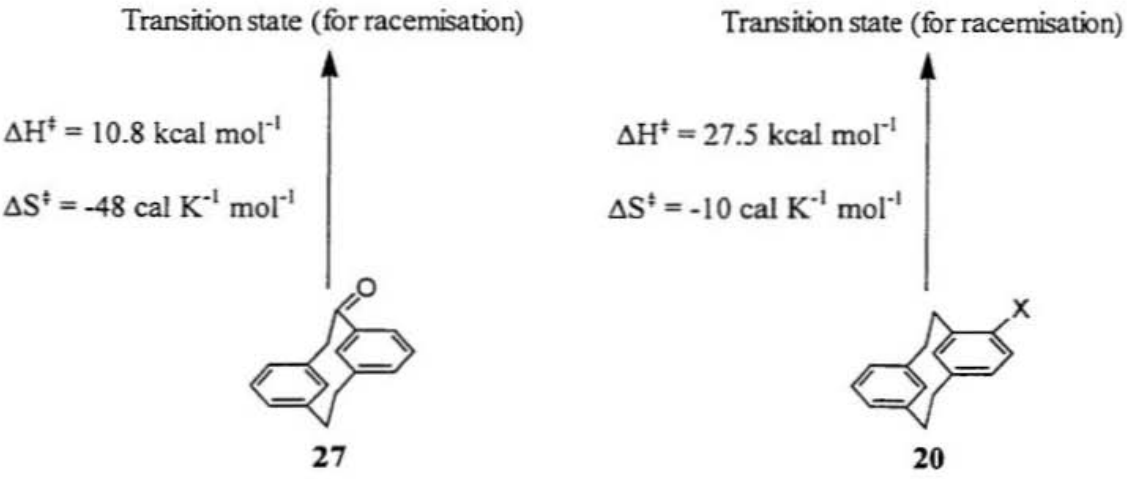
1. Heating **23** led to its equilibration with its thermodynamically less favourable diastereomer **25**. The fact that no diradicals were detected does not prove that none were present, however the fact that oxidation of **25** led to ketone **28** whose optical rotation was reduced in magnitude by less than 6% relative to the maximal rotation found for **27** strongly suggests that the mechanism for the equilibration did not involve ring-opened intermediates. This is in direct contrast with the mechanism of racemisation of chiral [2.2]paracyclophanes, which racemise via open diradicals at about 200 °C.[31] Hence an *anti-anti'* flip appears to be responsible for the observed results.

2. The ring-flip caused inversion of the planar chirality of **23** but retention of the chirality at the carbinol centre, which would be defined as *S* in both alcohols. When this chiral centre was later destroyed by oxidation of the alcohols to the respective ketones the rotations were almost equal and opposite. Gschwend also investigated the racemisation of the ketones and found this process to occur even at room temperature (60% racemisation over 60 h at 25 °C). It is hence possible that this was the reason for the slightly lower rotation of **28** relative to **27**. In any case the loss of optical activity due to the isomerisation was very small.

Gschwend's experiments were obviously very important, and show that the [2.2]metacyclophanes differ fundamentally from the [2.2]paracyclophanes in their conformational behaviour. It is sterically impossible for ring flipping to occur in the latter in the absence of a bond-breaking process. Returning briefly to Scheme 2.9, it is seen that the process operating in Gschwend's experiment would allow racemisation of an appropriately ring-substituted [2.2]metacyclophane such as **20**, and the cases where X=CO_2H, CO_2CH_3, $COCH_3$, $NHCO_2Bz$ have been carefully investigated by Schlögl.[32] Both authors calculated the thermodynamic data for the ring inversion and there was good agreement between the findings of the two (Schemes 2.11 and 2.12). The strong correlation between the data gleaned by these two groups is encouraging and gives the impression that the bridge substitution of **23** above had very little impact on the inversion barrier, while the change of hybridisation of a bridge carbon in **27** seemed to have a much greater impact.



Scheme 2.11 Thermodynamic Data for Gschwend's Ring-Flip Experiment[29]



Scheme 2.12 Thermodynamic Data for the Racemisation of Gschwend's Ketone **27** and Schlögl's 4-Substituted Metacyclophanes **20**[32]

Since an inversion clearly occurs, it is interesting to consider whether or not the *syn* isomer is an intermediate. If Mitchell's transiently observed *syn*-metacyclophane rapidly changes to *anti* above 0 °C, then according to the principle of microscopic reversibility the *anti* form must be able to lead to the *syn* via the same pathway, given enough energy. As has been mentioned, it is very hard to manipulate a model of an *anti*-[2.2]metacyclophane to the corresponding *anti'* form without passing through a *syn*-like intermediate. However, there is no evidence that the data for the transition states gleaned by Gschwend and Schlögl can be assumed to apply to the elusive *syn* forms.

2.2 This Work

2.2.1 Introduction

Our interest in this area of research was in the possibility of constructing a molecular switch, ideally capable of reversibly switching between *syn* and *anti* forms with no decomposition. Such a switch might find use in a high-tech application requiring such a binary device. From a purely academic point of view, the compounds we proposed to make would be useful test beds for investigating the transition from *syn* to *anti*, as observed by Mitchell, and may even show other interesting molecular motions (see below). Finally, other derivatives may later provide the means for studying the exact pathways for the transitions via chirality.

The initial aim of this work was to synthesise and study a series of tethered metacyclophanes in search of one which may exhibit an equilibrium between the *syn* and *anti* forms. [See Scheme 2.13 below.]

28 **29**

Scheme 2.13 Our Goal: A Tunable Reversible Molecular Switch

The following points should be made concerning the scheme above:

1. The chemical composition of the tether was considered to be a variable capable of fine-tuning, and so is not defined above.

2. When the tether is very short, there is obviously no possibility of an *anti* conformer.

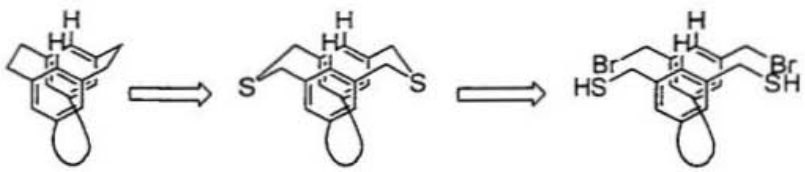
3. When the tether is long, it was expected that the molecule would behave as if no tether were present, so that the metacyclophane structure would adopt its thermodynamically more favourable *anti* conformation.

4. At some point between these extremes it was hoped that there would exist an appropriate tether length capable of supporting an equilibrium between the two forms. Of course, there was no guarantee of this. The remote possibility also existed that there would be more than one tether length which would allow an equilibrium.

At the time this project commenced *syn* metacyclophanes were rare in the literature, and so from that point of view the shorter tethered members of the series were intrinsically interesting as they were all found, as expected, to be *syn*. The project was started by Jason Kennedy, an Honours student in the group.[33] However, the search for the elusive first *anti* metacyclophane in the series was longer than expected, and despite his determined efforts could not be completed during Jason's tenure. Hence I was lucky

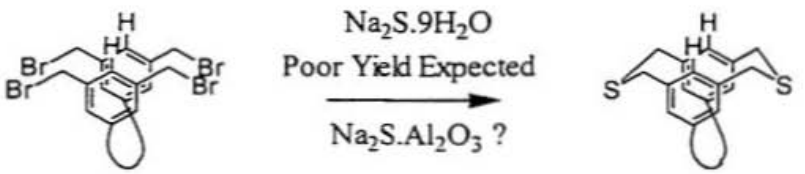
enough to take over the project at a critical stage. The work described below was all performed by this researcher, although it should be stated that Jason had previously synthesised compound **54**, albeit on a very small scale and by a different route. At that stage there was a clear need to develop a more reliable method of generating the cyclophanes. I would like to acknowledge the contributions of both Jason and Mike Mannion of the Bodwell group towards the development of the optimised routes to the thiacyclophanes discussed below.

As was discussed above, the most widely used method of preparation of dithiametacyclophanes is the high-dilution coupling of dithiols with dibromides. Examination of Scheme 2.14 reveals a significant synthetic problem to be overcome.



30 **31** **32**

Conventional Retrosynthetic Route

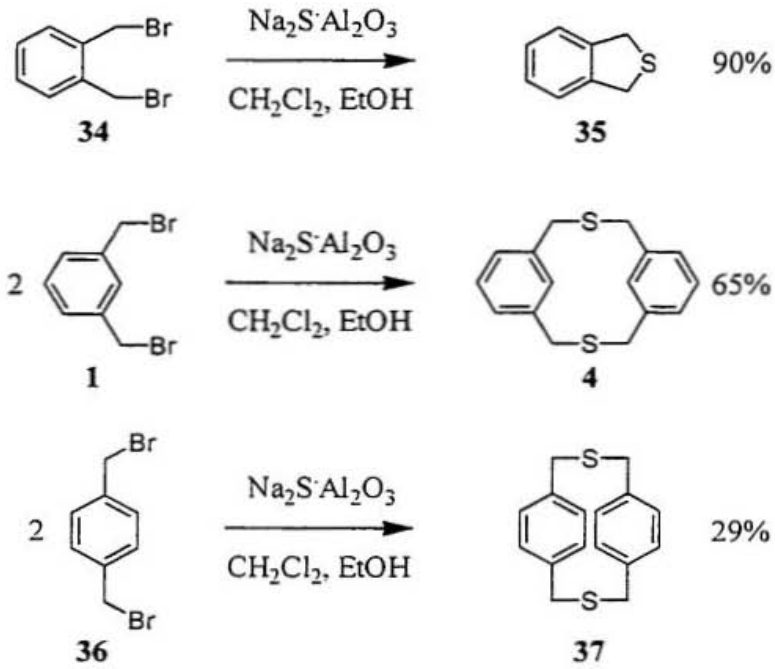


33 Other Possibility **31**

Scheme 2.14 A Synthetic Problem

Production of intermediate **32** would not be straightforward since, as was previously stated, the thiol functionality is generally generated from the bromide. Prospects for the

sodium sulphide closure of an intermediate such as **33** were not good either, since literature yields of couplings using $Na_2S{\cdot}9H_2O$ were consistently low.[34] Since reasonably large quantities of a series of dithiacyclophanes were required, an alternative coupling employing the $Na_2S{\cdot}Al_2O_3$ reagent was investigated.[35] Preliminary results obtained for the α,α'-dibromoxylenes are shown below:[36]



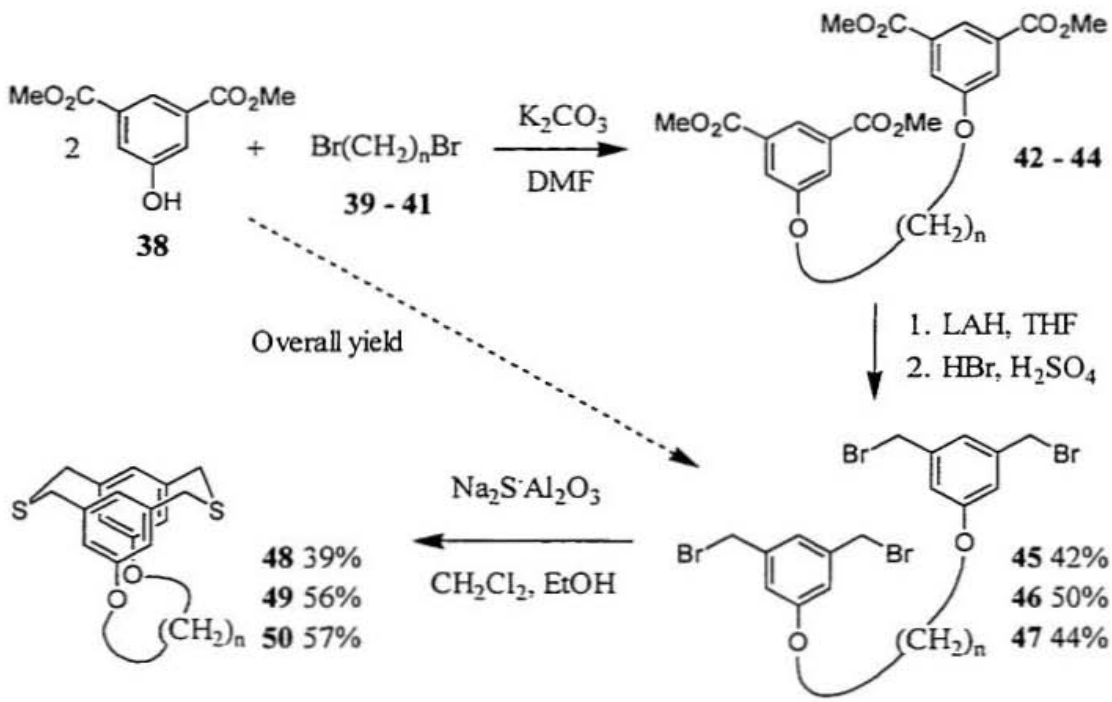
Scheme 2.15 Reactions of the α,α'-Dibromoxylenes with $Na_2S{\cdot}Al_2O_3$

We had previously shown that the $Na_2S{\cdot}Al_2O_3$ reagent was very useful for the intermolecular closure of [3.3]dithiametacyclophanes as shown above. As will be demonstrated below, this reagent also proved to be very effective in effecting the desired intramolecular reactions required for this project, the only necessary change being an increase in dilution.

2.2.2 Synthesis

The starting material for all the metacyclophanes in this section was diester **38**, prepared in close to quantitative yield by Fischer esterification of the corresponding very cheap commercially-available diacid. Diester **38** could be alkylated to create the tether in high yield following either of two protocols developed in our group. [In practice, the K_2CO_3-promoted alkylation was generally used, although the alternative using NaH was equally effective.] This type of tether was chosen purely due to the ease of its formation; had we not succeeded in obtaining a switch, other types of tether would have been investigated. Reduction of the ester groups using a large excess of LAH at room temperature was found to be more reliable than performing the reaction in refluxing THF.[37] Several sets of conditions were investigated for the bromination of the intractable tetraols, the most generally useful being evaporation of the crude alcohol on to the aluminium salts from the reduction, and subsequent treatment of this material with a mixture of concentrated hydrobromic and sulphuric acids. This very expedient protocol led to high yields of the tetrabromides on a roughly 10 g scale. That the phenolic ether linkages do not cleave to any significant degree may be due to the fact that the aluminium salts buffer the reaction to some extent. Since the LAH reaction is quenched only with ethyl acetate the actual substrate in this reaction is apparently an aluminium alkoxide. Following this step the tetrabromide thus formed was easily purified by column chromatography. For preparative purposes the intermediates were not purified prior to this stage as it was unnecessary and in the case of the tetraols rather difficult. The tetrabromides were easily obtained pure despite the build up of byproducts *en route*, and their purity was absolutely necessary in order to obtain a high yield in the following

sodium sulphide coupling. The sodium sulphide coupling procedure used has already been referred to above. At least 2 equivalents of Na_2S were necessary, and it was found best to use freshly prepared reagent. A 10:1 ratio of CH_2Cl_2 to absolute ethanol was used - experiments showed that no reaction occurs in the absence of ethanol.

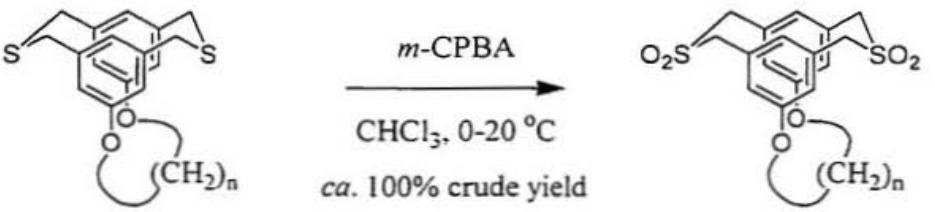


Scheme 2.16 The Synthesis of the Tethered Dithiacyclophanes **48-50**

The scheme above shows that the production of the tetrabromides is very efficient. The bromides can be obtained pure in around 50% overall yield from diester **38** on a 5-10 g scale. Only one chromatographic separation is necessary (following the bromination). Since this series of reactions represents 10 individual steps for the dibromide (**39-41**), the yield per step (assuming all to be equal) is 93%. The thiacyclophane closure is also a

reliable reaction, and does not require especially high dilution or an inert atmosphere. Other results from the Bodwell group have shown that the yield of the closure is higher in cases where the tether is shorter, favouring the intramolecular reaction.[33,38]

At this point the three desired dithiacyclophanes were all readily accessible on a gram scale. However, extrusion of the sulphur atoms proved to be non-trivial, and several early approaches, including photolysis, gave very low and inconsistent yields. The proper equipment for FVT reaction of the corresponding disulphones was not available; however since that reaction appeared the most viable remaining method for sulphur extrusion an adaptation using simpler apparatus was attempted.



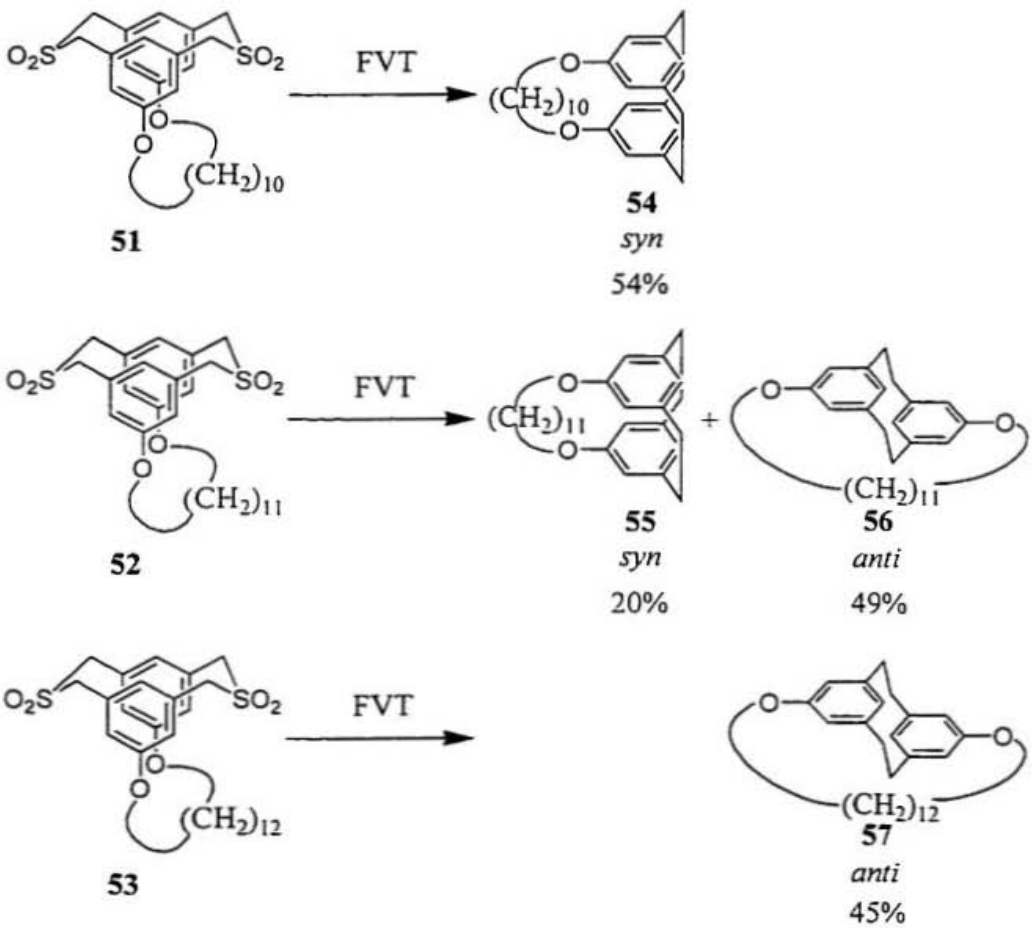
48 - 50 **51-53**

n = 10 -12, lowest-numbered of each diagram refers to shortest tether

Scheme 2.17 Oxidation of the Dithiacyclophanes

Oxidation of the dithiacyclophanes to the disulphones proceeded in close to quantitative yield, although purification of the latter was very difficult owing to the impossibility of chromatography and problems in their crystallisation. [It seemed that the impurity was from the *m*-CPBA used in the oxidation, but purification of *m*-CPBA is known to be dangerous.] In practice the crude material was used directly in the modified FVT procedure which is described in detail in the experimental section. Use of too strong

a vacuum or an insufficiently hot flame led to sublimation of the unchanged starting material, while the use of too weak a vacuum leads to destruction of the product before it can sublime to the safety of the cold-finger. Another example of a "first principles approach" to the FVT reaction has been reported by Pascal Jr.[39] The generally rather intimidating FVT apparatus can be demystified thus: it is a setup which allows for the achievement of a particular temperature and pressure. If these conditions can be achieved by a much simpler piece of equipment, then the reaction will still work.



Scheme 2.18 The Flash Vacuum Thermolysis of the Disulphones

Compound **54**, with a 12 atom tether, was found like all the shorter-tethered compounds to be purely *syn*. Compound **57**, with a 14 atom tether, showed initially only the *anti* form (see below for a more thorough analysis). The NMR spectra of both of these compounds showed all the typical features. However, the case of the intermediate 13 atom tether length was much more interesting. The FVT reaction led to two product spots of R_f 0.25 and 0.40 in 1:1 CH_2Cl_2:hexanes showing the fairly distinctive development behaviour of this group of compounds. The spots developed spontaneously on dipping in phosphomolybdic acid (PMA) solution, without heating, and developed to a very bright colour. The large R_f difference facilitated separation of the components. Chromatography was conducted as quickly as possible and evaporation of solvents was done using a cold water bath. Under these conditions it was found possible to separate the *syn* and *anti* conformers **55** and **56** and to obtain each in a pure state.

The realisation of the goal of this project was naturally a very exciting moment. Initially, however, our success was obscured by the fact that the NMR samples of **55** and **56** were allowed to stand in solution for several hours before the spectra were run. Under such circumstances the conformers equilibrate, and both NMR spectra showed a similar mixture of peaks. After a little thought this phenomenon was understood, and later dynamic NMR experiments were run in an effort to determine the thermodynamics of this equilibration process. The NMR spectra of the cyclophanes **54-57** are shown below to illustrate their key features. Of particular interest are the following points:

1. The *syn* conformers possess two planes of symmetry, and hence have simpler NMR spectra than the *anti*, which have one.

2. The so-called "internal" aromatic protons of the *anti* conformers have unusual NMR properties. These are non-equivalent, as the "inside" internal proton (H_2 in Figure 2.3 below) is by necessity pushed further into the shielding cone of the opposing aromatic ring than the other. Both internal protons are heavily shielded, and they are labelled in the spectra below. Of particular interest is the more-shielded inside internal proton H_2 of **56** which appears at δ 3.04. This was hoped to have been a record shift for a benzenoid aromatic proton, but Siegel has since produced compound **58** (Figure 2.2) which has an astounding shift of δ 1.89 ppm.[40]

3. Among *anti* conformers the difference between the shifts of the two internal protons decreases as the tether is increased in length. As the tether length increases the aromatic rings are able to achieve a more nearly parallel orientation, such that each internal proton is shielded by approximately the same amount. [For further discussion of this point see Chapter 3.]

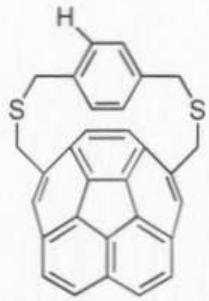
4. Some of the protons of the alkyl tether of the *anti* conformers are heavily shielded by the aromatic rings, and appear at much higher field than those of the *syn* conformers.

5. Cyclophane **57** was later synthesised on a bigger scale. A minor, less-polar spot was obtained almost pure (7.5 mg, 4%) which exhibited a proton NMR spectrum very strongly suggesting that it was the previously unknown *syn* isomer **59** (see Figure 2.4). A sample of **57** was analysed by NMR at 150 °C (DMSO-d_6). Careful examination revealed the emergence of some new peaks consistent with the generation of a very small amount of *syn* isomer **59**. At the very high temperature of the FVT reaction, the equilibrium concentration of **59** would be expected to be higher than at room temperature. Hence immediate rapid chromatography, possibly at reduced temperature (to slow down

equilibration in solution), may allow the future isolation of sufficient **59** for proper characterisation of this isomer. Another contrasting approach would be optimisation of the photolysis reaction of the thiacyclophane precursor at low temperature, as the thiacyclophane itself is *syn* as discussed above.

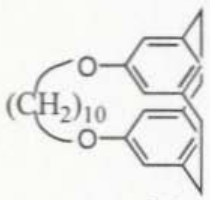
6. The possibility of obtaining the *anti* form, **60** (see Figure 2.4), of the 12 atom tethered cyclophane **54** has not been ruled out. This may yet be achieved by conducting the FVT experiment on a bigger scale, immediately followed by rapid, cold chromatography.

δ for the proton shown = 1.89 ppm

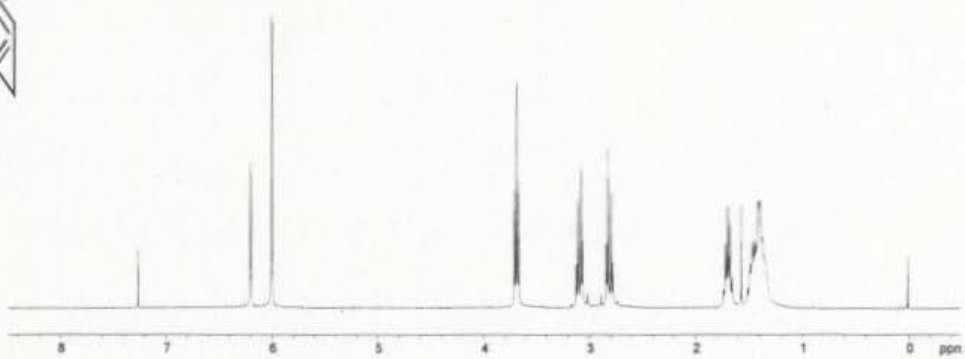


58

Figure 2.2 Siegel's Record-Setting Corannulene Cyclophane **58**



54
syn



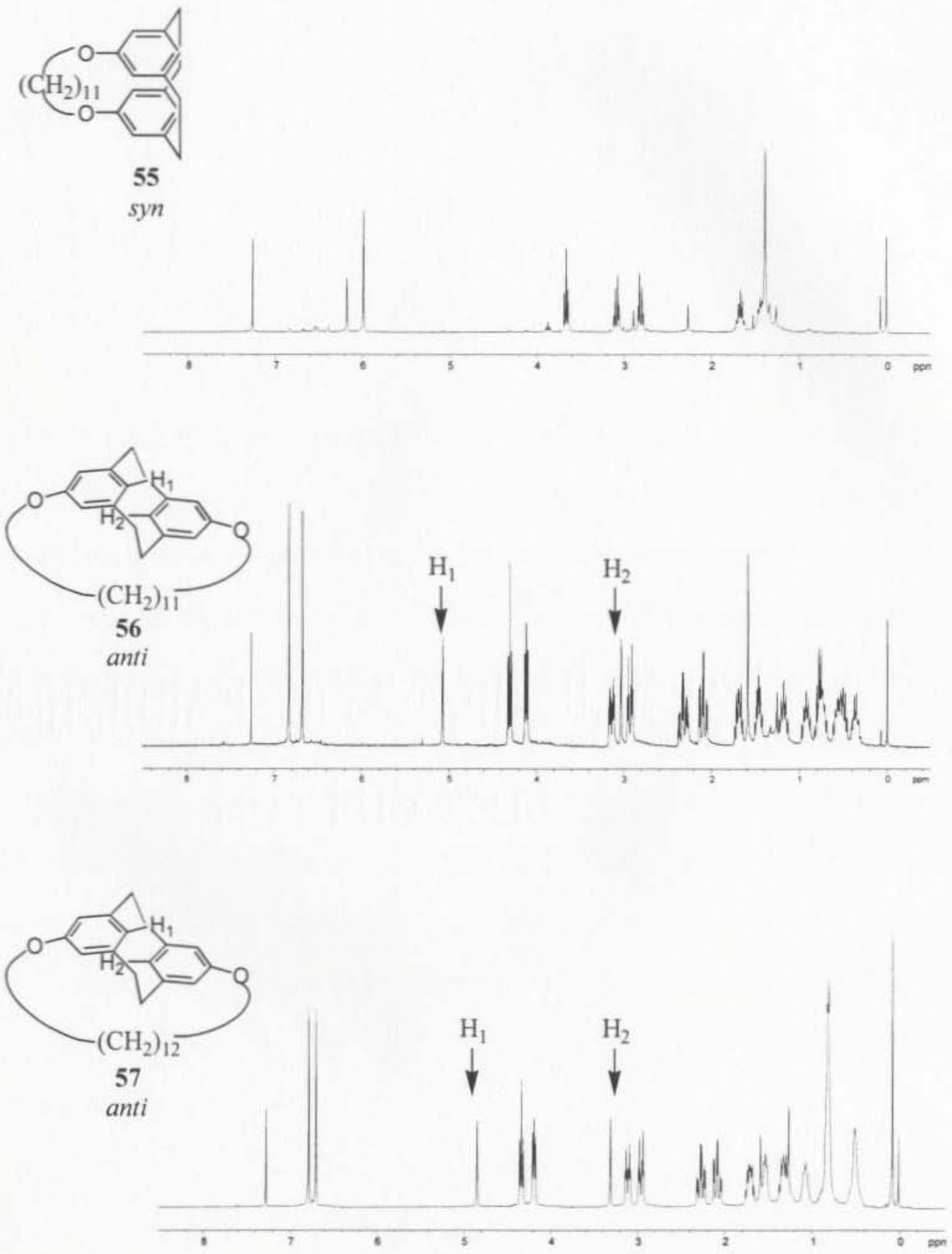
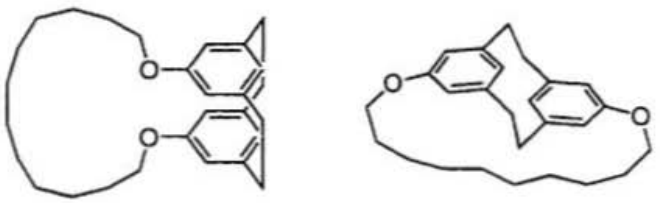


Figure 2.3 The NMR Spectra of the Tethered Metacyclophanes **54-57**



59 **60**

Figure 2.4 Possible Limiting Cases of the Present Project

2.2.3 Dynamic NMR Experiments

We were understandably eager to investigate the properties of the "switch" system further. It was soon realised that following the equilibration reaction of the conformers by NMR could reveal all of the thermodynamic data for the conformational flip. Not only this, but running the same NMR experiment at several different temperatures would also allow the determination of the data concerning the normally elusive transition state for the reaction (so long as the reaction proceeds via a single transition state). As stated earlier, the transition state for the forward reaction is the same as for the backward one, hence the law of microscopic reversibility. If all the data obtained for the transition state (obtained from both directions) were to prove self-consistent this would strongly support the notion that there is only one transition state involved in the reaction, casting some light on the reaction mechanism itself.

The dynamic NMR experiment was run from both directions, (*anti* → equilibrium, *syn* → equilibrium), and at three different temperatures. Analysis of the results was performed by comparison of the ratios of the integrals of well-separated, chemically similar protons, following the reaction until the ratio no longer fluctuated within

experimental limits or as long as was feasible. Every effort was made to try to treat all spectra in the same way, however it should be noted from the outset that NMR integration is not a preferred method for quantitative analysis, and is generally used only for reasons of convenience. In the present case no other more accurate method of monitoring the equilibrium presents itself. [Obviously, use of GC would be inappropriate since heating the sample would dramatically change the very ratio being measured.]

The equations derived below explain the graphs which follow, and which ultimately allow the calculation of the thermodynamic data for the equilibrium. Many trivial steps have been included in the hope that the reader will be readily able to follow the derivation of each equation from first principles.

1. $\mathbf{A} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathbf{B} \equiv \textit{anti} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \textit{syn}$

A_0, B_0 initial concentrations

A_e, B_e equilibrium concentrations

2. $\mathbf{dA/dt = -k_1A + k_{-1}B}$

This follows from simple consideration of equilibrium **1.**

From the stoichiometry of **1.** above it is clear that A + B = constant.

Thus $A_0 + B_0 = A + B$; and

3. $\mathbf{A_0 + B_0 - A = B}$

Substituting for B in equation **2.** gives: $dA/dt = -k_1A + k_{-1}(A_0 + B_0 - A)$

$$= -k_1A - k_{-1}A + k_{-1}A_0 + k_1B_0$$

$$= -(k_1 + k_{-1})A + k_{-1}(A_0 + B_0)$$

4. $\mathbf{-dA / [(k_1 + k_{-1})A - k_{-1}(A_0 + B_0)] = dt}$

Integration of **4.** by standard methods gives:

$[-1/(k_1 + k_{-1})]$. ln $[(k_1 + k_{-1})A - k_{-1}(A_0 + B_0)] = t + c$ [c is a constant of integration]

Multiplying both sides by $-(k_1 + k_{-1})$ gives **5.** below, where C is just a different constant:

5. $\ln [(k_1 + k_{-1})A - k_{-1}(A_0 + B_0)] = -(k_1 + k_{-1})t + C$

By definition, at equilibrium $k_1A_e = k_{-1}B_e$. Using equation **3.** to substitute for B_e gives:

$k_1A_e = k_{-1}(A_0 + B_0 - A_e)$

Rearranging: $A_e(k_1 + k_{-1}) = k_{-1}(B_0 + A_0)$

Substituting for $k_{-1}(B_0 + A_0)$ in **5.** above:

$\ln [(k_1 + k_{-1})A - A_e(k_1 + k_{-1})] = -(k_1 + k_{-1})t + C$

6. $\ln [(k_1 + k_{-1})(A - A_e)] = -(k_1 + k_{-1})t + C$

At $t = 0$, $A = A_0$. by definition. Substituting into **6.** above gives:

$\ln [(k_1 + k_{-1})(A_0 - A_e)] = C$ Substituting for C in **6.** produces the expression below:

$\ln [(k_1 + k_{-1})(A - A_e)] = -(k_1 + k_{-1})t + \ln [(k_1 + k_{-1})(A_0 - A_e)]$

$\ln [(k_1 + k_{-1})(A - A_e)] - \ln [(k_1 + k_{-1})(A_0 - A_e)] = -(k_1 + k_{-1})t$

Hence $\ln \{[(k_1 + k_{-1})(A - A_e)] / [(k_1 + k_{-1})(A_0 - A_e)]\} = -(k_1 + k_{-1})t$

$\ln [(A - A_e) / (A_0 - A_e)] = -(k_1 + k_{-1})t$

$\ln [(A_0 - A_e) / (A - A_e)] = (k_1 + k_{-1})t$

7. $\ln [(A_e - A_0) / (A_e - A)] = (k_1 + k_{-1})t$

From the stoichiometry of the equilibrium, $A_e + B_e = A + B$, therefore $A_e - A = B - B_e$

Also, $A_0 + B_0 = A_e + B_e$, so $A_e - A_0 = B_0 - B_e$

8. $\ln [(B_0 - B_e) / (B - B_e)] = (k_1 + k_{-1})t$

One of the reasons for going through this derivation from first principles is to demonstrate that no approximations have been made up to this point. What should be clear is that a graph of:

$\ln \{[anti]_{eqm} - [anti]_0\} / \{[anti]_{eqm} - [anti]\}$ vs time

should give a straight line of gradient $(k_1 + k_{-1})$. The equilibrium constant $K = k_1 / k_{-1}$ is readily found from the infinity values of [*syn*] and [*anti*], enabling the calculation of k_1 and k_{-1} at a given temperature from a series of NMR spectra. It should also be clear that a similar graph could be plotted for the reaction beginning from either conformer (see equations **7.** and **8.**), and that it is not actually necessary for the starting conformer to be 100% pure. That is. in a *syn* → equilibrium run it is not essential that the initial concentration of *anti*, $[anti]_0$, be zero. [Of course the expression plotted is simplified in this ideal case, and the amount of useful data from an overnight dynamic NMR run is also maximised.]

In practice the following dynamic NMR runs were performed:

1. [*anti*] → equilibrium at 50 °C.
2. [*anti*] → equilibrium at 40 °C.
3. [*anti*] → equilibrium at 30 °C.
4. [*syn*] → equilibrium at 30 °C.

In the first two cases the reaction went to completion during the time period of the experiment. In the last two the actual infinity values were found by maintaining the NMR solution at 30 °C for a prolonged period until the ratio of the conformers became constant. A point should be made concerning the "best fit" lines drawn on the graphs. The lines were plotted using a proper error analysis rather than a simple least squares approach.

Hence points known with less certainty, typically those near the end of the run, have been given their proper weighting so that they influence the line of best fit considerably less than the more reliable points nearer the beginning of the run. The graphs below show that the data is consistent with equations **7.** and **8.** above.

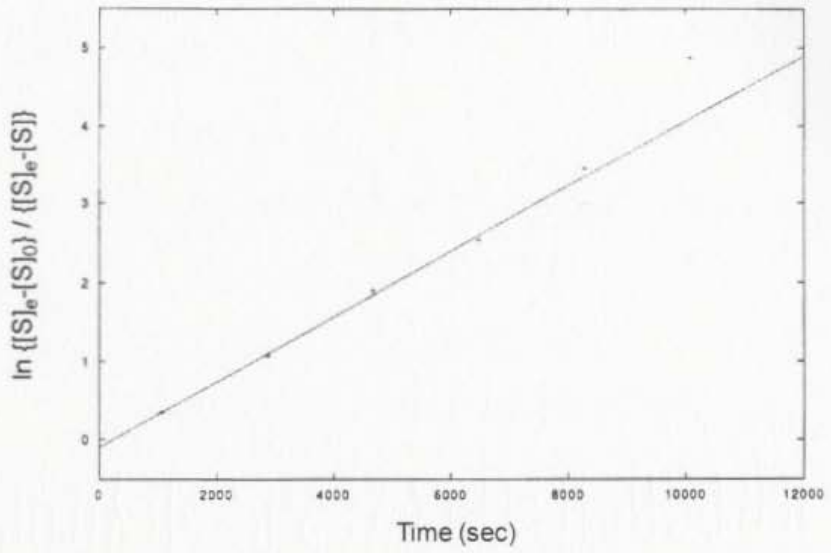


Figure 2.5 Graph of Data from Dynamic NMR Run 1.

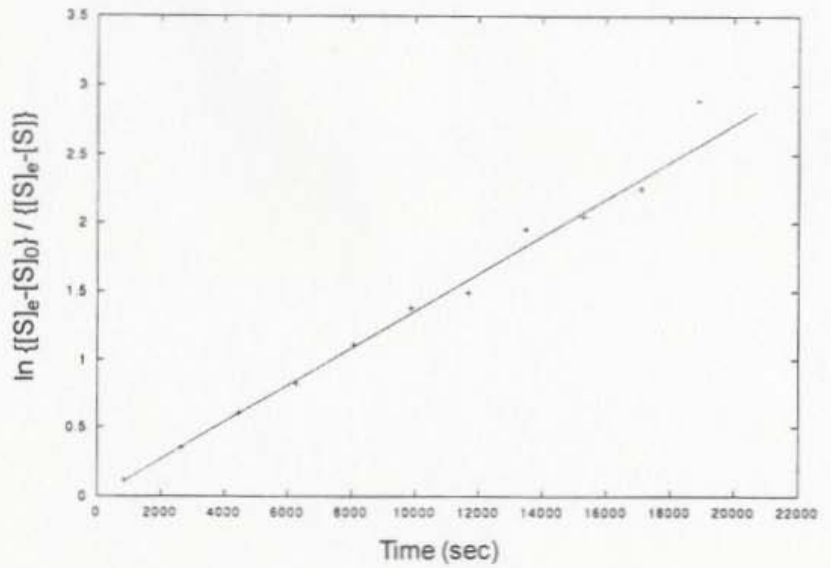


Figure 2.6 Graph of Data from Dynamic NMR Run 2.

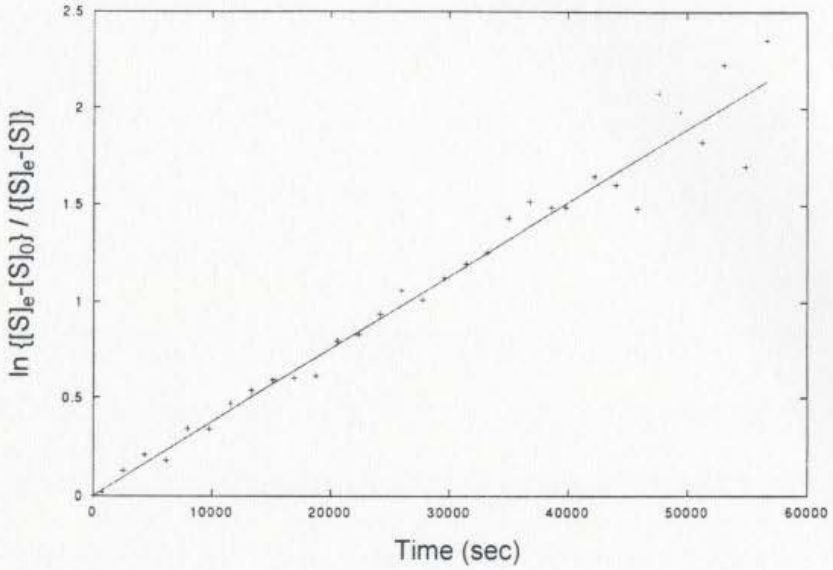


Figure 2.7 Graph of Data from Dynamic NMR Run 3.

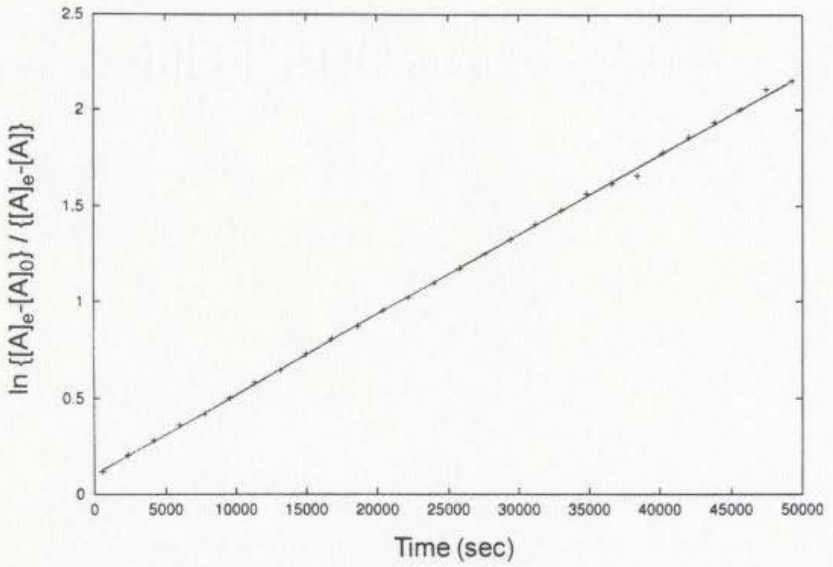


Figure 2.8 Graph of Data from Dynamic NMR Run 4.

The next step in investigating the thermodynamics of the equilibrium is explained below:

$K = k_1 / k_{-1}$, readily obtained from the NMR data.

9. $\Delta G^{\theta} = \Delta H^{\theta} - T\Delta S^{\theta} = -RT\ln K$

10. $\ln K = \Delta S^{\theta} / R - \Delta H^{\theta} / RT$

From equation **10.** it is apparent that a plot of lnK vs. 1/T should give a straight line of slope $- \Delta H^{\theta} / R$ and intercept $\Delta S^{\theta} / R$. Thus all of the thermodynamic data for the overall forward reaction *anti* → *syn* may be obtained from this one simple graph. Dynamic NMR runs were performed at only three temperatures. However, to improve the data for this particular graph K was determined at the additional temperature of 60 °C. [A dynamic run at this temperature was not feasible since equilibrium would have been reached too rapidly.] As is seen from the graph below, the data was again consistent with the equations.

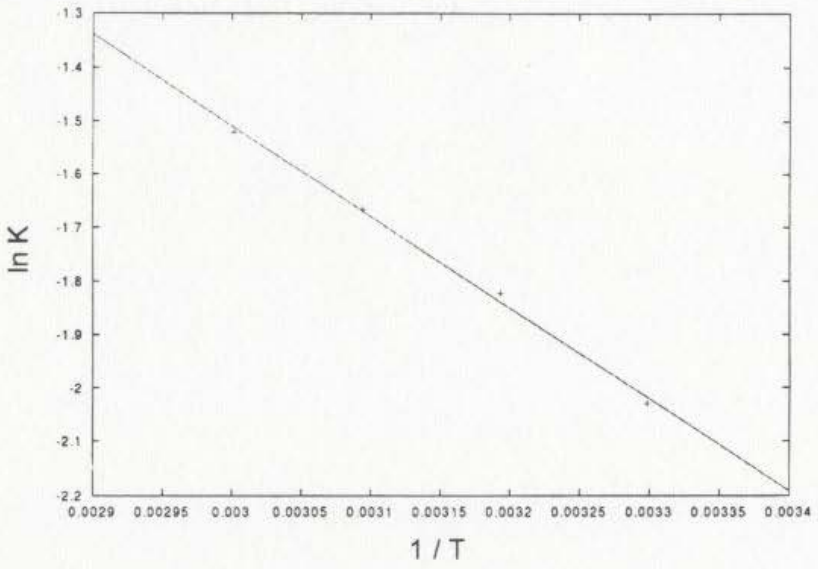


Figure 2.9 Graph to Determine Thermodynamic Data for the Reaction *anti* → *syn*

Finally, it was possible to obtain thermodynamic information about the transition state for the reaction (assuming there is only one) using the equations below:

According to transition state theory, for a reaction such as this

11. $\mathbf{k_1 = [k_B T / h].e^{-\Delta H/RT}.e^{\Delta S/R}}$, where k_B is Boltzman's constant and $\Delta H \equiv \Delta H^{\theta\ddagger}$, $\Delta S \equiv \Delta S^{\theta\ddagger}$.

Dividing by T and taking the natural logarithm of both sides:

12. $\mathbf{\ln(k_1 / T) = \ln(k_B / h) - \Delta H^{\theta\ddagger} / RT + \Delta S^{\theta\ddagger} / R}$

Hence a graph of $\ln(k_1 / T)$ vs 1/T should give a straight line of slope $-\Delta H^{\theta\ddagger} / R$ and intercept $\Delta S^{\theta\ddagger} / R$. [The values of k_1 used to plot this graph were obtained from the previous graphs.]

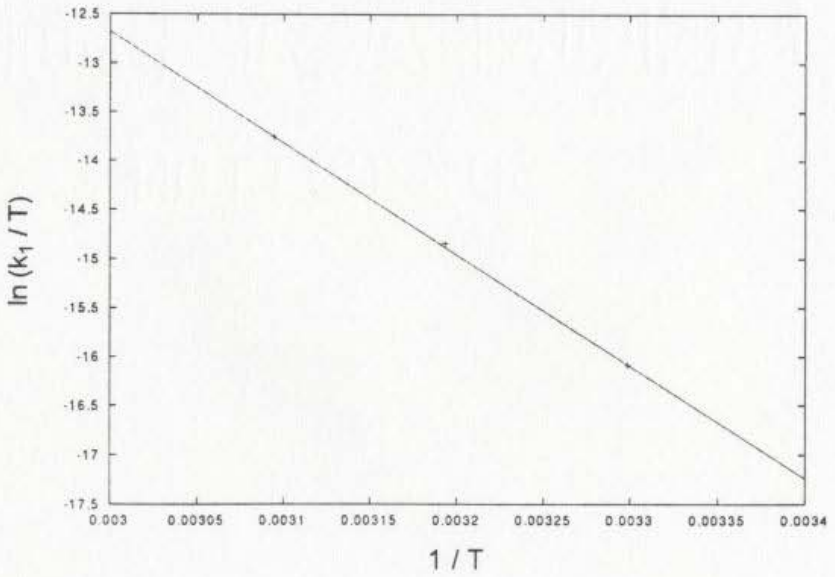
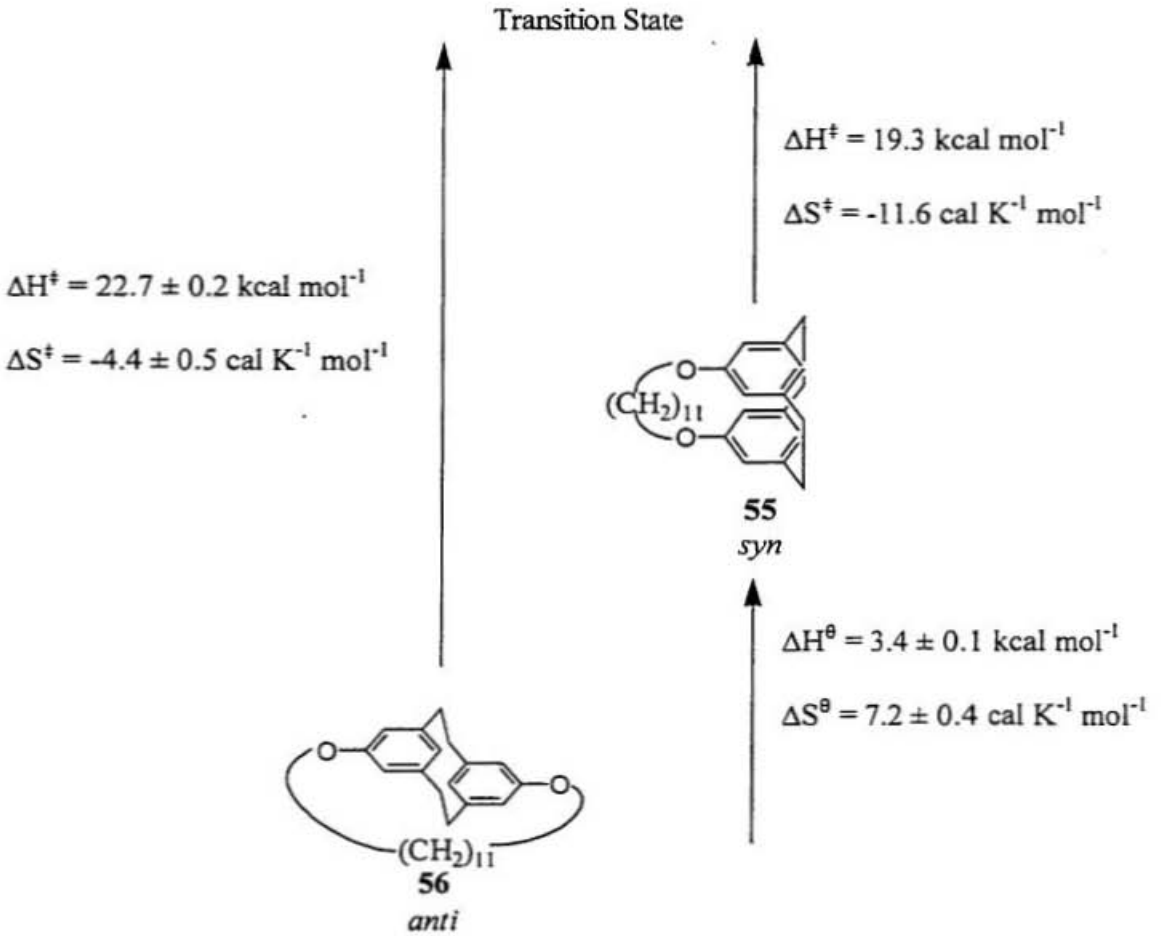


Figure 2.10 Graph to Determine Thermodynamic Data for the Transition State for the *anti-syn* Equilibrium

Unfortunately only three points could be plotted for this graph, but the correlation to a straight line was once again very good, suggesting that the equilibrium does have a reaction mechanism with just one transition state. If this is indeed the case then the energy diagram (Scheme 2.19) below is valid for the *syn* and *anti* states and the transition state.



Scheme 2.19 Energy Diagram for the *syn* and *anti* Conformers and the Transition State

The following points can be safely made concerning the data in Scheme 2.19:

1. The molar entropy is larger for the *syn* conformer **55** than the *anti* **56**. This is not surprising, as the tether would be expected to be much more flexible in **55**.

2. The entropy of activation from the *anti* conformer is negative (-4.4 cal K^{-1} mol^{-1}), suggesting that the transition state is a very rigid structure.

3. Comparison of the data with that obtained by Gschwend and Schlögl in ring-flip experiments indicates that the activation energy for the *anti-syn* equilibrium discussed here is significantly lower than that for the *anti-anti'* flip of an untetherered [2.2]metacyclophane. [No-one has yet reported a study of the *anti-anti'* flip of a tethered metacyclophane, and it is to be expected that the tether would lower the activation energy of this process.]

What is not clear, and would be interesting to find out, is whether or not the same transition state is involved in both the *anti-syn* equilibrium and the *anti-anti'* flip. It is hoped that further work within this research group will cast more light on this.

2.2.4 Experimental

General Procedures

All reactions were performed under N_2. Unless otherwise noted, all commercial chemicals including solvents were used without further purification. Tetrahydrofuran (THF) was distilled over Na / benzophenone. Thin layer chromatography (TLC) was performed on E. Merck 60 F_{254} precoated silica plates. Column chromatography (chromatography) was carried out on silica gel 60 (E. Merck, 230-400 mesh). Melting points (mp) were obtained on a Fisher-Johns apparatus and are uncorrected. ^{1}H and ^{13}C

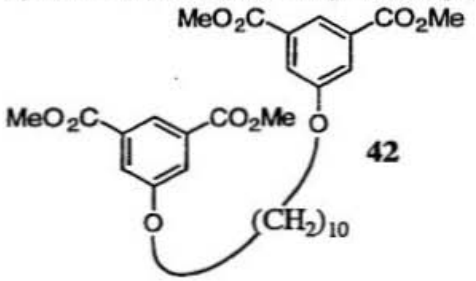
nuclear magnetic resonance (NMR) spectra were recorded on a GE GN-300NB spectrometer at 300 MHz and 75 MHz respectively. NMRs were run in $CDCl_3$ solution unless otherwise specified. Chemical shifts are in ppm relative to internal standards: Me_4Si (δ 0.0) for ^1H and $CDCl_3$ (δ 77.0) for ^{13}C NMR. Individual peaks in the ^1H NMR spectra are reported as chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet), number of hydrogens and coupling constant. Reported multiplicities are apparent. Individual peaks in the ^{13}C spectra are reported as chemical shift. Low and high resolution mass spectra (MS) were determined on a V.G. Micromass 7070HS instrument. Electron impact spectra were obtained at 70 eV with a source temperature of 200 °C; samples were introduced via a direct probe inlet. MS data are reported as *m/z* and intensity. X-ray crystallographic data were collected on a Rigaku AFC6S diffractometer at 298 K. Elemental analyses were performed by the microanalytical service of the University of Alberta.

General Procedure for Preparation of Tetraesters **42-44**

K_2CO_3 was added to a solution of dimethyl 5-hydroxyisophthalate **38** in DMF (100 mL) in a 250 mL round-bottomed flask (RBF). The magnetically stirred suspension was heated to 70 °C. After 30 min the dibromide (**39-41**) was added. After 19 h further K_2CO_3 was added. After a total of 48 h heating the cooled reaction mixture was added to a mixture of diethyl ether (800 mL) and 10% H_2SO_4 solution (200 mL). After separation the ether layer was washed with 10% H_2SO_4 solution (3x100 mL) and water (100 mL). The resultant solution was dried over $MgSO_4$, filtered and the solvent removed under reduced

pressure. A small sample was purified by chromatography (ethyl acetate / hexane) and recrystallisation (heptane).

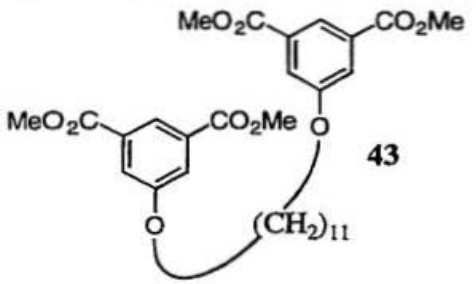
1,10-Bis(3,5-bis(methoxycarbonyl)phenoxy)decane (42)



42

K_2CO_3 (6.91 g, 50.0 mmol), dimethyl 5-hydroxyisophthalate **38** (10.51 g, 50.0 mmol) and 1,10-dibromodecane **39** (7.50 g, 25.0 mmol) were used. After 19 h further K_2CO_3 (3.46 g, 25.0 mmol) was added. Following the general procedure above a yield of 12.55 g (90%) was obtained. The analytical sample had the following properties: mp 104-104.5 °C; ^{1}H NMR δ 8.26 (s, 2H), 7.74 (s, 4H), 4.04 (t, 4H, J = 6.2 Hz), 3.94 (s, 12H), 1.84-1.79 (m, 4H), 1.48-1.34 (m, 12H); ^{13}C NMR δ 166.2, 159.2, 131.6, 122.7, 119.8, 68.6, 52.4, 29.4, 29.3, 29.1, 25.9; MS *m/z* (%) 558 (M^+, 11), 527 (5), 317 (4), 223 (3), 211 (37), 210 (36), 193 (5), 179 (43), 151 (43), 138 (14), 110 (6), 109 (9), 55 (100). Anal. Calcd for $C_{30}H_{38}O_{10}$: C, 64.50; H, 6.86. Found: C, 64.30; H, 6.97.

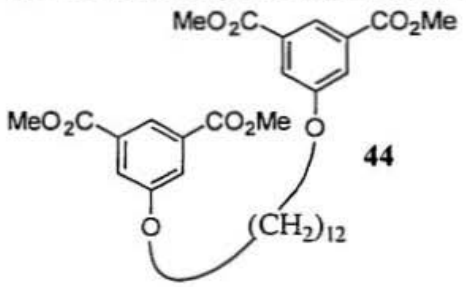
1,11-Bis(3,5-bis(methoxycarbonyl)phenoxy)undecane (43)



43

K_2CO_3 (6.61 g, 47.8 mmol), dimethyl 5-hydroxyisophthalate **38** (10.05 g, 47.8 mmol) and 1,11-dibromoundecane **40** (7.15 g, 22.8 mmol) were used. After 19 h further K_2CO_3 (3.30 g, 23.9 mmol) was added. Following the general procedure above a yield of 12.68 g (97%) was obtained. A small sample was isolated as above as colourless crystals: mp 70-72 °C; ^{1}H NMR δ 8.26 (s, 2H), 7.74 (s, 4H), 4.03 (t, 4H, J = 6.4 Hz), 3.94 (s, 12H), 1.83-1.76 (m, 4H), 1.47-1.27 (m, 14H); ^{13}C NMR δ 166.2, 159.2, 131.6, 122.7, 119.8, 68.6, 52.4, 29.5 (2C), 29.3, 29.1, 25.9; MS *m/z* (%) 572 (M^+, 38), 541 (8), 508 (2), 330 (3), 211 (47), 210 (47), 179 (54), 152 (14), 151 (13), 55 (100); HRMS calcd for $C_{31}H_{40}O_{10}$ (M^+) 572.2619, found 572.2613.

1,12-Bis(3,5-bis(methoxycarbonyl)phenoxy)dodecane (44)



44

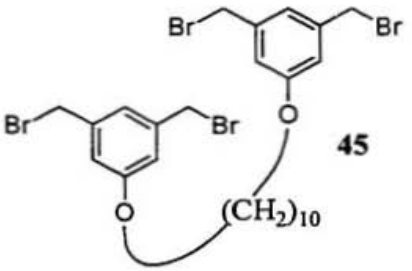
K_2CO_3 (6.91 g, 50.0 mmol), dimethyl 5-hydroxyisophthalate **38** (10.51 g, 50.0 mmol) and 1,12-dibromododecane **41** (8.20 g, 25.0 mmol) were used. After 19 h further K_2CO_3 (3.46 g, 25.0 mmol) was added. The only deviation from the general procedure was in the extractive work-up, when it was found necessary to add ethyl acetate (300 mL) to the diethyl ether used (800 mL) to help solubilise the product. The yield was 13.32 g (91%). A small sample was purified as above as colourless crystals: mp 97-99 °C; ^{1}H NMR δ 8.26 (s, 2H), 7.74 (s, 4H), 4.03 (t, 4H, J = 6.5 Hz) 3.94 (s, 12H), 1.83-1.78 (m, 4H), 1.47-1.31 (m, 16H); ^{13}C NMR δ 166.2, 159.2, 131.6, 122.7, 119.8, 68.6, 52.4, 29.5 (2C), 29.3,

29.1, 26.0; MS *m/z* (%) 586 (M^+, 34), 555 (8), 522 (2), 345 (9), 344 (5), 211 (58), 210 (57), 179 (50), 151 (12), 138 (4), 111 (18), 110 (10) 109 (13), 55 (100); HRMS calcd for $C_{32}H_{42}O_{10}$ (M^+) 586.2775, found 586.2761.

General Procedure for Preparation of Tetrabromides **45-47**

The crude tetraester (**42-44**) as prepared above was dissolved in dry THF (200 mL). This solution was added dropwise to a stirred slurry of LAH in dry THF (200 mL) in a 1L 3 neck round-bottomed flask. [A mild exotherm was observed.] The reaction mixture was stirred for 40 h, then cooled in an ice bath and quenched with ethyl acetate (65 mL) added dropwise. The solvent was then removed under reduced pressure. To the well-stirred crude residue was added 4:1 48% HBr:H_2SO_4 (180 mL). [A powerful exotherm occurs when the acids are mixed, another occurs upon addition of the acid mixture to the substrate.] After 5 min further H_2SO_4 (100 mL) was added. When the reaction mixture had cooled to close to room temperature water (300 mL) was added. When the resultant exotherm abated CH_2Cl_2 (300 mL) was added. After separation the aqueous phase was extracted with CH_2Cl_2 (200 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (300 mL), then brine (300 mL) and then dried over $MgSO_4$. The crude product was evaporated onto silica gel and chromatographed eluting with hexanes / CH_2Cl_2. An analytical sample was obtained by recrystallisation of the colourless solid obtained from heptane.

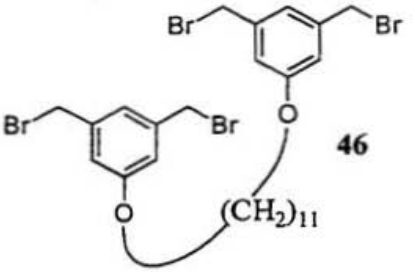
1,10-Bis(3,5-bis(bromomethyl)phenoxy)decane (45)



45

Crude tetraester **42** (max. 22.5 mmol) and LAH (10.9 g, 287 mmol) were used in the reduction step. Following bromination and work-up as above the crude product was evaporated onto silica gel and chromatographed (2:1 hexanes:CH_2Cl_2). The product obtained following chromatography was found to be impure. Recrystallisation from heptane afforded almost pure **45** (7.26 g, 42% overall from diester **38**). An analytical sample was obtained by further recrystallisation from heptane: mp 122-123 °C; ^{1}H NMR δ 6.99 (s, 2H), 6.86 (s, 4H), 4.44 (s, 8H), 3.96 (t, 4H, J = 6.7 Hz), 1.81-1.74 (m, 4H), 1.49-1.35 (m, 12H); ^{13}C NMR δ 159.5, 139.5, 121.6, 115.2, 68.1, 32.9, 29.5, 29.3, 29.2, 26.0; MS *m/z* (%) 698 (M^+, 2x^{79}Br, 2x^{81}Br, 3), 337 (2), 278 (2), 269 (7), 257 (4), 201 (32), 199 (32), 121 (27), 120 (30), 55 (100). Anal. Calcd for $C_{26}H_{34}Br_4O_2$: C, 44.73; H, 4.91. Found: C, 44.89; H, 4.89.

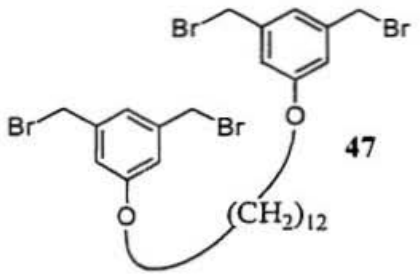
1,11-Bis(3,5-bis(bromomethyl)phenoxy)undecane (46)



46

Crude tetraester **43** (max. 22.1 mmol) and LAH (10.9 g, 287 mmol) were used in the reduction step. Following bromination and work-up as above the crude product was evaporated onto silica gel and chromatographed (2:1 hexanes:CH_2Cl_2 then 1:1 hexanes:CH_2Cl_2). The mixed fractions were recrystallised from heptane and combined with the pure material from the column to give pure **46** (total yield 8.19 g, 50% overall based on dibromide **40**). An analytical sample was obtained by further recrystallisation from heptane: mp 89-90 °C; ^{1}H NMR δ 6.99 (s, 2H), 6.86 (s, 4H), 4.43 (s, 8H), 3.96 (t, 4H, J = 6.5 Hz), 1.81-1.76 (m, 4H), 1.46-1.33 (m, 14H); ^{13}C NMR δ 159.5, 139.5, 121.6, 115.2, 68.1, 32.9, 29.5 (2C), 29.4, 29.3, 29.2, 26.0; MS *m/z* (%) 714 (13), 712 (M^+, $2x^{79}Br$, $2x^{81}Br$, 18), 710 (12), 633 (5) 631 (5), 353 (5), 351 (5), 276 (11), 201 (32), 199 (32), 121 (23), 120 (25), 109 (19), 55 (100). Anal. Calcd for $C_{27}H_{36}Br_4O_2$: C, 45.53; H, 5.09. Found: C, 45.25; H, 4.94.

1,12-Bis(3,5-bis(bromomethyl)phenoxy)dodecane (47)



47

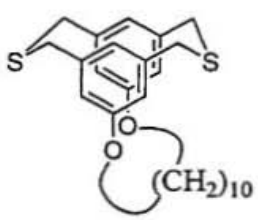
Crude tetraester **44** (max. 22.7 mmol) and LAH (10.3 g, 271 mmol) were used in the reduction step. Following bromination and work-up as above the crude product was evaporated onto silica gel and chromatographed (3:1 hexanes:CH_2Cl_2 then 2:1 hexanes:CH_2Cl_2) to give pure **47** (total yield 7.95 g, 44% overall from diester **38**). An analytical sample was obtained by recrystallisation from heptane: mp 88-89 °C; ^{1}H NMR

δ 6.98 (s, 2H), 6.85 (s, 4H), 4.43 (s, 8H), 3.96 (t, 4H, J = 6.3 Hz), 1.80-1.75 (m, 4H), 1.47-1.31 (m, 16H); ^{13}C NMR δ 159.5, 139.5, 121.6, 115.2, 68.2, 32.9, 29.5 (2C), 29.3, 29.2, 26.0; MS *m/z* (%) 730 (12), 728 (M^+, 2x^{79}Br, 2x^{81}Br, 16), 726 (11), 647 (5) 565 (2), 446 (2), 365 (5), 285 (7), 201 (34), 199 (33), 121 (27), 120 (23), 109 (23), 55 (100). Anal. Calcd for $C_{28}H_{38}Br_4O_2$: C, 46.31; H, 5.27. Found: C, 46.33; H, 5.30.

General Procedure for Preparation of Dithiacyclophanes **48-50**

The tetrabromide (**45-47**) as prepared above was dissolved in a 9:1 CH_2Cl_2:EtOH mixture (roughly 350 mL per mmol). This solution was stirred very vigorously, and freshly prepared $Na_2S{\cdot}Al_2O_3$ (roughly 2.5 mmol Na_2S g^{-1})[41] added in one portion. The reaction mixture was stirred for roughly 24 h, adding further $Na_2S{\cdot}Al_2O_3$ to ensure the reaction went to completion. [Two equivalents of $Na_2S{\cdot}Al_2O_3$ were used initially.] When TLC indicated completion of the reaction the mixture was filtered, evaporated onto silica gel and chromatographed eluting with hexanes / CH_2Cl_2.

1,12-Dioxa-20,29-dithia[12.3.3](1,3,5)cyclophane (48)

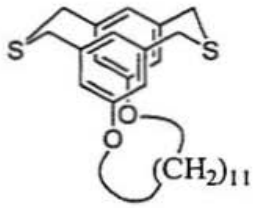


48

Tetrabromide **45** (3.99 g, 5.72 mmol) and $Na_2S{\cdot}Al_2O_3$ (12.5 mmol Na_2S) were initially combined in 2000 mL 9:1 CH_2Cl_2:EtOH. After 12 h further $Na_2S{\cdot}Al_2O_3$ was added (12.5 mmol). After a total of 22 h the reaction was worked up. Chromatography (2:1 hexanes:

CH_2Cl_2) gave analytically pure **48** (0.99 g, 39%): mp 127-128 °C; ^{1}H NMR δ 6.83 (s, 2H), 6.37 (s, 4H), 3.83-3.71 (m, 12H), 1.77-1.68 (m, 4H), 1.53-1.38 (m, 12H); ^{13}C NMR δ 159.1, 138.3, 124.1, 113.0, 67.1, 38.8, 28.6, 26.6 (2C), 24.4; MS *m/z* (%) 444 (11), 443 (25), 442 (M^+, 84), 409 (13), 378 (13), 290 (7), 271 (6), 165 (8), 153 (11), 152 (12), 151 (17), 122 (75), 121 (37), 120 (14), 55 (92), 41 (100). Anal. Calcd for $C_{26}H_{34}O_2S_2$: C, 70.55; H, 7.74. Found: C, 70.18; H, 7.70.

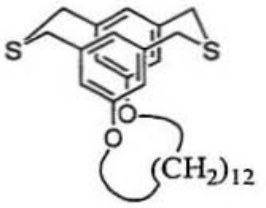
1,13-Dioxa-21,30-dithia[13.3.3](1,3,5)cyclophane (49)



49

Tetrabromide **46** (4.00 g, 5.62 mmol) and $Na_2S{\cdot}Al_2O_3$ (12.5 mmol Na_2S) were initially combined in 2000 mL 9:1 CH_2Cl_2:EtOH. After 25 h further $Na_2S{\cdot}Al_2O_3$ was added (12.5 mmol). After a total of 35 h the reaction was worked up. Chromatography (2:1 hexanes:CH_2Cl_2, then 1:1 hexanes:CH_2Cl_2) gave analytically pure **49** (1.44 g, 56%): mp 149-150 °C; ^{1}H NMR δ 6.81 (s, 2H), 6.37 (s, 4H), 3.83-3.70 (m, 12H), 1.73-1.69 (m, 4H), 1.48-1.40 (m, 14H); ^{13}C NMR δ 159.0, 138.4, 124.1, 113.1, 68.0, 38.8, 28.5, 26.6, 26.0, 24.9, 23.8; MS *m/z* (%) 458 (11), 457 (25), 456 (M^+, 76), 423 (13), 392 (11), 304 (9), 165 (8), 153 (11), 152 (11), 151 (16), 122 (68), 121 (36), 120 (13), 55 (88), 41 (100). Anal. Calcd for $C_{27}H_{36}O_2S_2$: C, 71.01; H, 7.94. Found: C, 70.86; H, 8.19.

1,14-Dioxa-22,31-dithia[14.3.3](1,3,5)cyclophane (50)



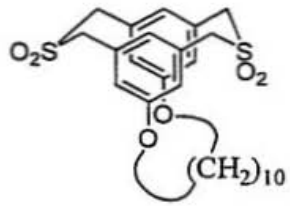
50

Tetrabromide **47** (1.27 g, 1.75 mmol) and $Na_2S{\cdot}Al_2O_3$ (7.02 mmol Na_2S) were initially combined in 640 mL 9:1 CH_2Cl_2:EtOH. After 7 h further $Na_2S{\cdot}Al_2O_3$ was added (1.89 mmol). After a total of 23 h the reaction was worked up. Chromatography (2:1 hexanes:CH_2Cl_2, then 1:1 hexanes:CH_2Cl_2) gave analytically pure **50** (0.47 g, 57%): mp 144-145 °C; ^{1}H NMR δ 6.82 (s, 2H), 6.37 (s, 4H), 3.84-3.72 (m, 12H), 1.74-1.70 (m, 4H), 1.49-1.39 (m, 16H); ^{13}C NMR δ 159.0, 138.4, 124.1, 113.3, 68.1, 38.8, 29.1, 27.6, 26.6 (2C), 24.7; MS *m/z* (%) 471 (31), 470 (M^+, 100), 437 (15), 406 (13), 318 (11), 151 (11), 122 (60), 121 (31), 120 (10), 55 (58), 41 (52). Anal. Calcd for $C_{28}H_{38}S_2O_2$: C, 71.44; H, 8.14. Found: C, 71.29; H, 8.33.

General Procedure for Preparation of Disulphones **51-53**

The dithiacyclophane (**48-50**) as prepared above was dissolved in $CHCl_3$ and cooled to 0 °C. 50-60% *m*-CPBA was added (4 eq. based on 50% purity of *m*-CPBA). The reaction was allowed to warm to room temperature over roughly 24 h. The reaction mixture was washed with 2M K_2CO_3, then dried over $MgSO_4$ and evaporated. Purification of the disulphones was not achieved, hence analyses were not obtained.

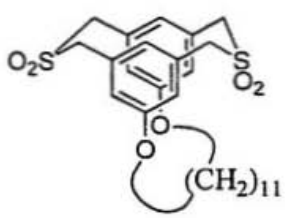
1,12-Dioxa-20,20,29,29-tetraoxo-20,29-dithia[12.3.3](1,3,5)cyclophane (51)



51

Dithiacyclophane **48** (0.430 g, 0.971 mmol), 50-60% *m*-CPBA (1.341 g, 3.884 mmol) and $CHCl_3$ (140 mL) were used. The reaction was stirred for 36 h. The solution was then washed with 2x50 mL 2M K_2CO_3, dried and evaporated to give disulphone **51** (0.484 g, 98%): mp > 300 °C; ^{1}H NMR (DMSO-d_6) δ 7.16 (s, 2H), 6.64 (s, 4H), 4.84 (AX half spectrum, J_{AX} = 14.0 Hz, 4H), 4.23 (AX half spectrum, J_{AX} = 14.0 Hz, 4H), 3.76 (t, J = 5.8 Hz, 4H), 1.69-1.65 (m, 4H), 1.5-1.2 (m, 12H); ^{13}C NMR (d_6-DMSO) δ 157.1, 129.6, 128.0, 116.5, 66.6, 60.0, 27.9, 26.7, 26.0, 24.3; MS *m/z* (%) 507 (2), 506 (M^+, 5), 505 (11), 378 (18), 377 (36), 240 (15), 239 (42), 238 (43), 223 (18), 222 (34), 210 (23), 121 (22), 120 (13), 55 (96), 41 (100).

1,13-Dioxa-21,21,30,30-tetraoxo-21,30-dithia[13.3.3](1,3,5)cyclophane (52)

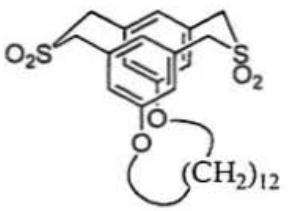


52

Dithiacyclophane **49** (0.700 g, 1.533 mmol), 50-60% *m*-CPBA (2.120 g, 6.131 mmol) and $CHCl_3$ (220 mL) were used. The reaction was stirred for 29 h. The solution was then washed with 2x50 mL 2M K_2CO_3, dried and evaporated to give disulphone **52** (0.840 g,

quantitative): mp > 300 °C; ^{1}H NMR (DMSO-d_6) δ 7.15 (s, 2H), 6.65 (s, 4H), 4.85 (AX half spectrum, J_{AX} = 13.8 Hz, 4H), 4.27 (AX half spectrum, J_{AX} = 13.8 Hz, 4H), 3.73 (t, J = 6.8 Hz, 4H), 1.67-1.63 (m, 4H), 1.36 (br s, 14H); ^{13}C NMR (DMSO-d_6) δ 157.1, 129.7, 128.0, 116.4, 67.4, 60.0, 27.5, 26.3, 25.8, 25.3, 23.5; MS *m/z* (%) 520 (M^+, 7), 519 (7), 392 (34), 239 (40), 238 (39), 223 (19), 222 (38), 210 (20), 121 (23), 120 (14), 55 (100), 41 (100).

1,14-Dioxa-22,22,31,31-tetraoxo-22,31-dithia[14.3.3](1,3,5)cyclophane (53)



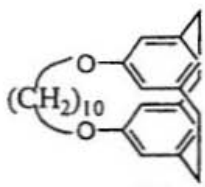
53

Dithiacyclophane **50** (0.500 g, 1.062 mmol), 50-60% *m*-CPBA (1.467 g, 4.250 mmol) and $CHCl_3$ (150 mL) were used. The reaction was stirred for 35 h. The solution was then washed with 2x50 mL 2M K_2CO_3, dried and evaporated to give disulphone **53** (0.583 g, quantitative): mp > 300 °C; ^{1}H NMR (DMSO-d_6) δ 7.16 (s, 2H), 6.64 (s, 4H), 4.84 (AX half spectrum, J_{AX} = 13.8 Hz, 4H), 4.24 (AX half spectrum, J_{AX} = 13.8 Hz, 4H), 3.74 (t, J = 6.5 Hz, 4H), 1.68-1.63 (m, 4H), 1.42-1.34 (m, 16H); ^{13}C NMR (DMSO-d_6) δ 157.1, 129.7, 128.0, 116.6, 67.3, 60.0, 27.9, 27.2, 26.5, 26.3, 24.5; MS *m/z* (%) 534 (M^+, 2), 533 (10), 406 (26), 240 (12), 239 (35), 238 (36), 223 (18), 222 (39), 221 (10), 211 (11), 210 (17), 121 (23), 120 (13), 55 (99), 41 (100).

General Procedure for Preparation of Cyclophanes **54-57**

The disulphone (**51-53**) (roughly 250 mg) as prepared above was dissolved in CH_2Cl_2 and evaporated onto the surface of a 100 mL or 250 mL round-bottomed flask to produce a thin film. The flask was fitted with a sublimation cold-finger and placed under partial vacuum using a vacuum pump and a N_2 bleed. The flask was then heated using a strong Bunsen flame so as to instigate the flash vacuum thermolysis reaction. When activity in the flask appeared to have ceased and most material had sublimed onto the cold finger the heating was ceased and after cooling the cold-finger was washed into the flask with CH_2Cl_2. The washings were evaporated once more onto the surface of the flask and the FVT reaction repeated. The cold-finger was again washed into the flask with CH_2Cl_2, and the contents of the flask evaporated onto silica. Chromatography was then performed eluting with hexanes / CH_2Cl_2.

***syn*-1,12-Dioxa [12.2.2](1,3,5)cyclophane (54)**

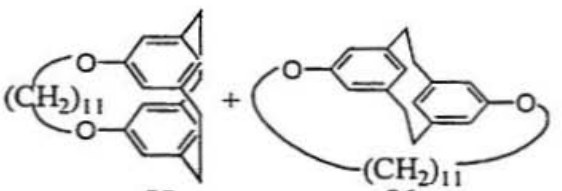


54
syn

Disulphone **51** (0.160 g, 0.316 mmol) was used. Chromatography (2:1 hexanes:CH_2Cl_2) provided pure **54** (0.065 g, 54%): mp 152-153 °C; ^{1}H NMR δ 6.20 (s, 2H), 6.00 (s, 4H), 3.69 (t, 4H, J = 5.9 Hz), 3.13-3.02 (m, 4H), 2.89-2.78 (m, 4H), 1.74-1.66 (m, 4H), 1.51-1.33 (m, 12H); ^{13}C NMR δ 159.3, 139.0, 131.3, 112.8, 66.7, 35.6, 28.8, 27.0, 26.3, 24.7;

MS *m/z* (%) 379 (28), 378 (M^+, 100), 377 (7), 239 (31), 238 (35), 223 (14), 222 (26), 210 (17), 55 (52); HRMS calcd for $C_{26}H_{34}O_2$ (M^+) 378.2557, found 378.2532.

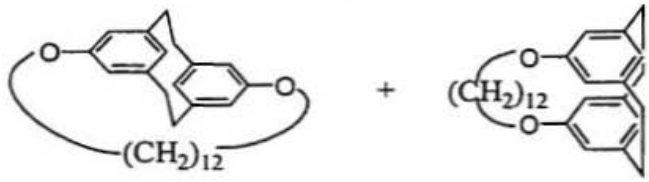
1,13-Dioxa [13.2.2](1,3,5)cyclophane (*syn*- 55 and *anti*- 56)



55 *syn* **56** *anti*

Disulphone **52** (0.195 g, max. 0.357 mmol) was used. Chromatography (2:1 hexanes:CH_2Cl_2, then 1:1 hexanes:CH_2Cl_2) provided pure **55** (0.028 g, 20%): mp 91-92 °C; ^{1}H NMR δ 6.18 (s, 2H), 5.99 (s, 4H), 3.67 (t, 4H, J = 6.5 Hz), 3.12-3.06 (m, 4H), 2.84-2.78 (m, 4H), 1.70-1.63 (m, 4H), 1.47-1.27 (m, 14H); ^{13}C NMR δ 159.1, 139.0, 131.3, 112.8, 67.5, 35.6, 28.5, 26.7, 26.4, 25.9, 24.4; MS *m/z* (%) 394 (12), 393 (29), 392 (M^+, 100), 391 (14), 239 (31), 238 (35), 223 (12), 222 (28), 210 (13), 55 (30). Anal. Calcd for $C_{27}H_{36}O_2$: C, 82.61; H, 9.24. Found: C, 82.25; H, 9.25. The second major component was pure **56** (0.069 g, 49%): mp 109-110 °C; ^{1}H NMR δ 6.84 (s, 2H), 6.68 (s, 2H), 5.08 (s, 1H), 4.31 (t, 2H, J = 6.2 Hz), 4.12 (t, 2H, J = 5.5 Hz), 3.18-3.11 (m, 2H), 3.04 (s, 1H), 2.97-2.90 (m, 2H), 2.38-2.28 (m, 2H), 2.14-2.05 (m, 2H), 1.74-1.65 (m, 2H), 1.51-1.43 (m, 2H), 1.24-1.14 (m, 2H), 0.98-0.33 (m, 12H); ^{13}C NMR δ 160.6, 157.5, 143.8, 136.2, 134.6, 129.0, 117.7, 117.3, 72.2, 70.0, 41.5, 39.4, 30.3, 29.9, 29.7, 29.5, 29.0, 28.0, 27.6, 26.2, 25.9; MS *m/z* (%) 393 (29), 392 (M^+, 100), 391 (13), 240 (13), 239 (34), 238 (41), 223 (14), 222 (33), 210 (15), 55 (23). Anal. Calcd for $C_{27}H_{36}O_2$: C, 82.61; H, 9.24. Found: C, 82.51; H, 9.41.

1,14-Dioxa [14.2.2](1,3,5)cyclophane (57)



57 + **59**

anti *syn*

Disulphone **53** (0.250 g, max. 0.454 mmol) was used. Chromatography (2:1 hexanes:CH_2Cl_2, then 1:1 hexanes:CH_2Cl_2) provided first an almost pure fraction which appeared to be **59** (0.0075 g, 4%): ^{1}H NMR δ 6.18 (s, 2H), 5.98 (s, 4H), 3.65 (t, 4H, J = 6.9 Hz), 3.11-3.05 (m, 4H), 2.83-2.77 (m, 4H), 1.69-1.64 (m, 4H), 1.45-1.25 (m, 16H); followed by pure **57** (0.072 g, 39%): mp 143-143.5 °C; ^{1}H NMR δ 6.79 (s, 2H), 6.71 (s, 2H), 4.85 (s, 1H), 4.34 (t, 2H, J = 5.7 Hz), 4.20 (t, 2H, J = 5.1 Hz), 3.32 (s, 1H), 3.15-3.08 (m, 2H), 3.00-2.93 (m, 2H), 2.32-2.23 (m, 2H), 2.13-2.04 (m, 2H), 1.75-0.52 (m, 20H); ^{13}C NMR δ 159.5, 158.9, 143.0, 137.1, 133.4, 129.3, 116.5, 115.9, 70.7, 68.5, 41.6, 39.9, 30.3 (2C), 29.9, 29.8, 29.7, 29.0, 28.2 (2C), 26.1, 24.9; MS *m/z* (%) 407 (30), 406 (M^+, 100), 405 (17), 240 (15), 239 (41), 238 (50), 223 (15), 222 (36), 210 (18), 69 (15), 55 (35). Anal. Calcd for $C_{28}H_{38}O_2$: C, 82.71; H, 9.42. Found: C, 82.46; H, 9.62. [In a previous experiment run on a smaller scale (55 mg **53**) a yield of 45% was obtained for **57**.]

2.3 References

[1] Pellegrin, M.M. *Recl. Trav. Chim. Pays-Bas* **1899**, *18*, 457-465.

[2] Burri, K.; Jenny, W. *Helv. Chim. Acta* **1967**, *50*, 1978-1993.

[3] Mitchell, R.H.; Vinod, T.K.; Bushnell, G.W. *J. Am. Chem. Soc.* **1985**, *107*, 3340-3341.

[4] Mitchell, R.H.; Vinod, T.K.; Bushnell, G.W. *J. Am. Chem. Soc.* **1990**, *112*, 3487-3497.

[5] Müller, E.; Röscheisen, G. *Chem. Ber.* **1957**, *90*, 543-553.

[6] Lindsay, W.S.; Stokes, P.; Humber, L.G.; Boekelheide, V. *J. Am. Chem. Soc.* **1961**, *83*, 943-949.

[7] Mitchell, R.H.; Boekelheide, V. *J. Am. Chem. Soc.* **1974**, *96*, 1547-1557.

[8] Boekelheide, V.; Reingold, I.D.; Tuttle, M *J. Chem. Soc., Chem. Commun.* **1973**, 406-407.

[9] See Corey's original paper on this type of sulphur extrusion: Corey, E.J.; Block, E. *J. Org. Chem.* **1969**, *34*, 1233-1240.

[10] For a review of the flash vacuum thermolysis of disulphones see Vögtle, F.; Rossa, L. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 515-529.

[11] For a general review of extrusion reactions of organochalcogen compounds see Guziec, F.S. Jr.; Sanfilippo, L.J. *Tetrahedron* **1988**, *44*, 6241-6285.

[12] Givens, R.S.; Olsen, R.J. *J. Org. Chem.* **1979**, *44*, 1608-1613.

[13] Mitchell, R.H. *Heterocycles* **1978**, *11*, 563-586.

[14] Mitchell, R.H.; Otsubo, T.; Boekelheide, V. *Tetrahedron Lett.* **1975**, *16*, 219-222.

[15] Molander, G.A.; Harris, C.R. *Tetrahedron* **1998**, *54*, 3321-3354.

[16] Takahashi, S.; Mori, N. *J.C.S. Perkin Trans. 1* **1991**, 2029-2034.

[17] "Directed Synthesis of [2^n]Cyclophanes", Cao, X.-P.; Lou, W.; Lee, H.-F.; Atkins, J.A.; Chan, T.-L. *216th A.C.S. National Meeting* **1998**, Abstr. 009.

[18] The results of this briefly investigated project are not included in this thesis.

[19] Vogel, E.; Köcher, M.; Schmickler, H.; Lex, J. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 257-259.

[20] Vogel, E.; Sicken, M.; Röhrig, P.; Schmickler, H.; Lex, J.; Ermer, O. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 411-414.

[21] Lenoir, D. *Synthesis* **1989**, 883-897.

[22] McMurry, J.E. *Chem. Rev.* **1989**, *89*, 1513-1524.

[23] Fürstner, A.; Bogdanovic. B. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2443-2469.

[24] For an example of a surprisingly high yield of a tetrahydroxy[2.2]metacylophane from an aluminium-mediated pinacol coupling of an aromatic dialdehyde see Sahade, D.A.; Mataka, S.; Sawada, T.; Tsukinoki, T.; Tashiro, M. *Tetrahedron Lett.* **1997**, *38*, 3745-3746.

[25] See for example Reiss, J.A. in *Organic Chemistry, A series of monographs*, Volume 45, "Cyclophanes", Wasserman, H.H., Ed.; Academic Press: New York, 1983; Chapter 7.

[26] Anker, W.; Bushnell, G.W.; Mitchell, R.H. *Can. J. Chem.* **1979**, *57*, 3080-3087.

[27] For a recent discussion of isomerism in dithiametacyclophanes see Bodwell, G.J.; Bridson, J.N.; Houghton, T.J.; Yarlagadda, B. *Tetrahedron Lett.* **1997**, *38*, 7475-7478.

[28] See for example Mitchell, R.H. in *Organic Chemistry, A series of monographs*, Volume 45, "Cyclophanes", Wasserman, H.H., Ed.; Academic Press: New York, 1983; Chapter 4.

[29] Gschwend, H.W. *J. Am. Chem. Soc.* **1972**, *94*, 8430-8437.

[30] Ward, H.R. *Acc. Chem. Res.* **1972**, *5*, 18-24; Lawler, R.G. *Acc. Chem. Res.* **1972**, *5*, 25-33.

[31] Reich, H.J.; Cram, D.J. *J. Am. Chem. Soc.* **1969**, *91*, 3517-3526.

[32] Glotzmann, C.; Langer, E.; Lehner, H.; Schlögl, K. *Monatsh. Chem.* **1974**, *105*, 907-916.

[33] Kennedy, J.W.J., Honours Dissertation, Memorial University of Newfoundland, 1995.

[34] For example see Boekelheide, V.; Lawson, J.A. *J. Chem. Soc., Chem. Commun.* **1970**, 1558-1560.

[35] The paper which brought this reagent to our attention was Nicolaou, K.C.; Zuccarello, G.; Riemer, C.; Estevez, V.A.; Dai, W.-M. *J. Am. Chem. Soc.* **1992**, *114*, 7360-7371.

[36] Bodwell, G.J.; Houghton, T.J.; Koury, H.E.; Yarlagadda, B. *Synlett*, **1995**, 751-752; Bodwell, G.J.; Houghton, T.J.; Koury, H.E. unpublished results.

[37] Y.-H. Lai, private correspondence.

[38] Bodwell, G.J.; Bridson, J.N.; Houghton, T.J.; Kennedy, J.W.J.; Mannion, M.R. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1320-1321.

[39] Pascal, R.A., Jr; Grossman, R.B.; Van Engen, D. *J. Am. Chem. Soc.* **1987**, *109*, 6878-6880.

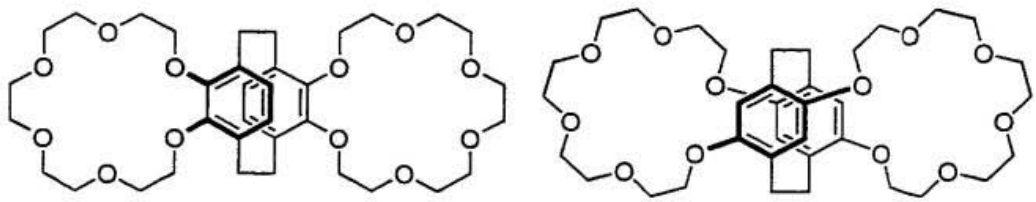
[40] Seiders, T.J.; Baldridge, K.K.; Siegel, J.S. *J. Am. Chem. Soc.* **1996**, *118*, 2754-2755.

[41] The reagent was prepared as described in reference 35 above.

Synthesis and Study of Two Crown Ether Tethered Metacyclophanes and the Related Pyrenophanes

3.1 Introduction

Crown ether molecules containing aromatic rings have been extensively studied. Some intriguing examples from the literature are shown below in chronological order:

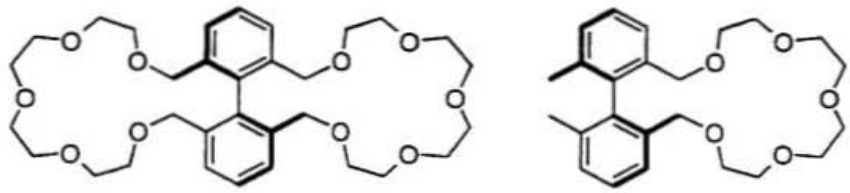


1 **2**

Figure 3.1 Cram's Crown Ether Cyclophanes, 1977[1]

The paper from which the above structures are taken marked a significant turning point in Cram's illustrious career. He was, of course, the great pioneer of cyclophane chemistry before moving on to crown ethers and eventually the more sophisticated cryptands and spherands designed to imitate the properties of enzymes. It was for this later work that Cram won the Nobel Prize in 1987, sharing the award with Jean-Marie Lehn and Charles Pedersen. Crown ether paracyclophanes **1** and **2** were obviously designed to complex cations. They are structural isomers, achiral compound **1** having C_{2h} symmetry, while **2** is D_2-symmetric and chiral. Compound **1** was further described as being "sided", while **2** is not. When **2** was treated with one equivalent of an alkylammonium salt, the same complex was formed when complexation occurred from any of the four possible faces. When **1** was mono-complexed there were two possible products, depending on whether the cation approached from the "outside" or "inside". Several other related compounds

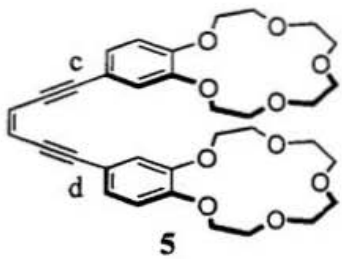
were also synthesised, and their complexation behaviour was compared and contrasted. The most striking feature of the results aside from the interesting geometrical properties of the cyclophanes was that **1** exhibited much higher K_a values than **2** for all cations tested, presumably due to the greater distortion of the "18-crown-6" rings in **2**.



3 **4**

Figure 3.2 Rebek's Biphenyl-Based Crown Ethers, 1981[2]

Cyclic polyethers **3** and **4** were synthesised in order to investigate binding cooperativity. The best known example of this phenomenon is the binding of oxygen to haemoglobin.[3] The idea in the present case was that as one of the crown ether moieties of **3** organised to complex a metal ion this might set up the other crown ether perfectly to complex a second ion. In the study it was found that the receptivity of **3** towards a second Hg^{2+} ion was enhanced 10-fold by the binding of the first. The first association constant was in good agreement with that found for the monocyclic ether **4**.



5

Figure 3.3 König's Enediyne-Based Crown Ether, 1994[4]

Compound **5** contains the enediyne moiety in addition to two crown ether groups.

Enediynes are well known to be susceptible to the Bergman reaction, a measure of their expected reactivity being the so-called cd distance between the termini of the alkyne units.[5] When **5** was treated with an excess of $NaPF_6$ two sodium ions were coordinated. If KPF_6 was used instead only one ion was complexed, giving rise to a sandwich-type structure. Subsequent differential scanning calorimetry experiments suggested that the latter complex underwent the Bergman reaction at a lower temperature than the former, supporting the idea that the sandwiched potassium ion helped to pull the crown ether units closer together, concomitantly decreasing the cd distance, and thus increasing the reactivity of the substrate.

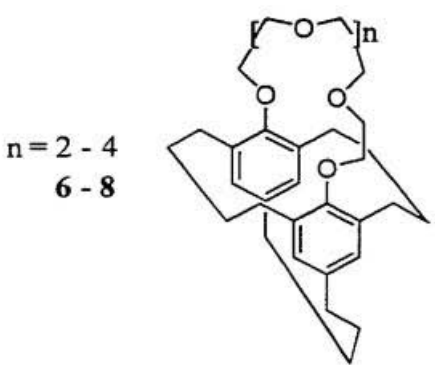


Figure 3.4 Nishimura's Crown Ether Cyclophanes, 1995[6]

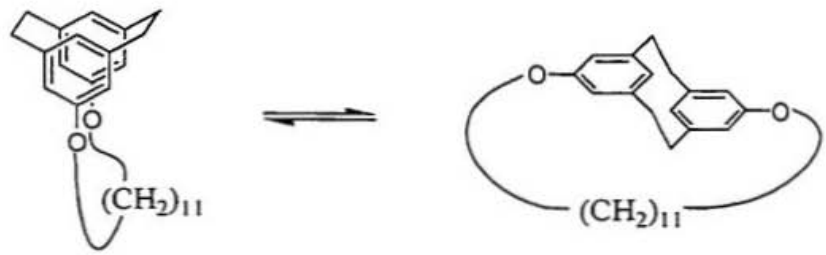
The series of cyclophanes **6-8** was synthesised with crown ether tethers of various lengths. The abilities of these ionophores to extract alkali metal picrates from water into dichloromethane were studied. Compound **6,** analogous to 15-crown-5, was found to be very ineffective at transporting any alkali metal ions. Compound **7** showed the properties expected for a slightly enlarged relative of 18-crown-6, and was efficient at extracting potassium, and even more so at extracting rubidium and cesium. Compound **8**, roughly corresponding to a 21-crown-7 molecule, showed a gradual improvement in transport

efficiency from sodium up to cesium, although it was still less competent than **7** in each case. The significance of these results, apart from the predictable correlation between ligand and cation size, was the unexpected failure of the 15-crown-5-type molecule **6** to extract any of the alkali metal ions. This brings to mind again Cram's results, and shows that a slight distortion of the crown ether moiety can bring about a big change in its binding ability.

3.2 This Work

3.2.1 Introduction

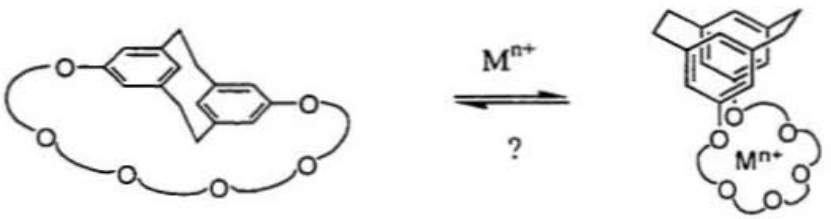
Our own foray into this area of research was prompted by the recent discovery of a prototype molecular switch (see previous chapter). A series of tethered [2.2]metacyclophanes had been investigated, and eventually a case was found where the *syn* and *anti* isomers of the cyclophane were close enough in energy to be in equilibrium.[7]



9 *syn* **10** *anti*

Scheme 3.1 *syn-anti* Tethered Metacyclophane Equilibrium

Following on from these results, it was speculated that with the incorporation of a crown ether tether it might be possible for a thermodynamically favoured *anti* isomer to be switched to *syn* by the presence of an appropriate metal ion.

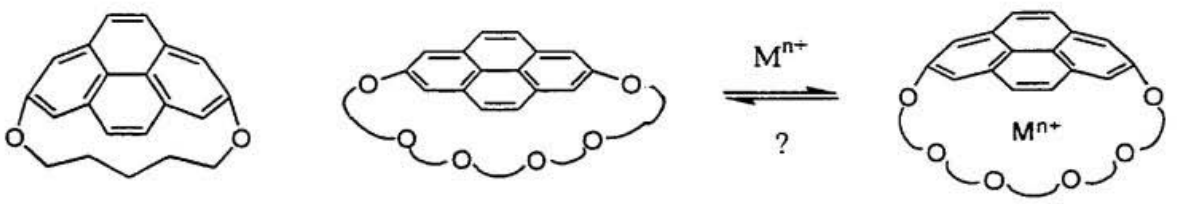


11 *anti* **12** *syn*

Scheme 3.2 Prototype Crown Ether Tethered Metacyclophane-Based Molecular Switch

Clearly, the *anti* conformer **11** is incapable of coordination to a metal ion in the usual crown ether manner, as its tether is fully extended and there is effectively no cavity present. However, in the *syn* conformer a cavity analogous to 18-crown-6 appears to be present. If the two conformers exist in equilibrium in solution it may be possible that the addition of the appropriate metal ion may dramatically shift the equilibrium to the right. due to the favourable enthalpy of coordination. It had previously been found that the *anti* metacyclophane **10** had a significantly lower R_f than the *syn* compound **9**. This observation suggested that the oxygen lone pairs of the *anti* conformer may be "externalised", whereas those of the *syn* conformer might be directed towards the interior of the cavity. This augured well for the planned investigation.

Our group's work with highly strained pyrenophanes[8] suggested another possibility. Perhaps it would be possible to observe a metal ion-induced increase in the bend of a crown ether pyrenophane (Scheme 3.3 below). At present the shortest tether length achieved for an [n](2,7)pyrenophane is seven atoms.[9] Despite a high strain energy and the pronounced curvature imposed on the aromatic portion of the molecule, 1,7-dioxa[7](2,7)pyrenophane **13** is a reasonably stable molecule.



13 **14** **15**

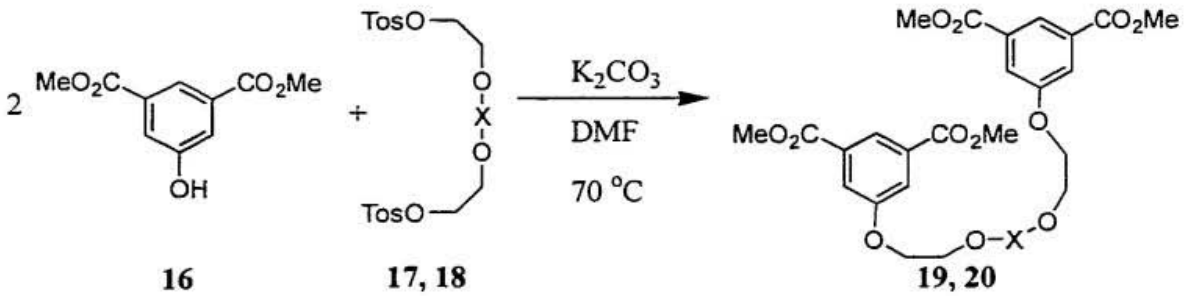
Scheme 3.3 Possible Cation-Driven Distortion of a Crown Ether Tethered Pyrenophane

The proposal here was to synthesise much less strained pyrenophanes containing long crown ether tethers, and to then treat these with metal ions in the hope that they may be capable of distorting in their presence to encapsulate a cation in their cavities. Assuming X-ray crystal structures of both the complexed and uncomplexed pyrenophanes could be obtained, this would provide an empirical method of estimating the increase in strain energy in going from a flat to a bent pyrene unit. [The energy of coordination of a metal ion to a crown ether has been established for several examples in the literature.][10] An obvious shortcoming of this whole plan is that the crown ether part of the pyrenophane is massively distorted from the ideals of 18-crown-6 or 15-crown-5, and the examples cited from the literature seem to suggest that this might be a big problem. On the other hand, a factor which may work in favour of this project is the fact that certain metal ions, notably silver, are capable of complexing with not only the crown ether functionality, but also the large aromatic pyrenophane unit.[11] Hence, while this project may be considered a long shot, it had some justification. At the very least, it would lead to the synthesis of the longest [n](2,7)pyrenophanes yet produced, and hence perhaps determine the point at which the pyrene unit is able to return to its familiar flat state.

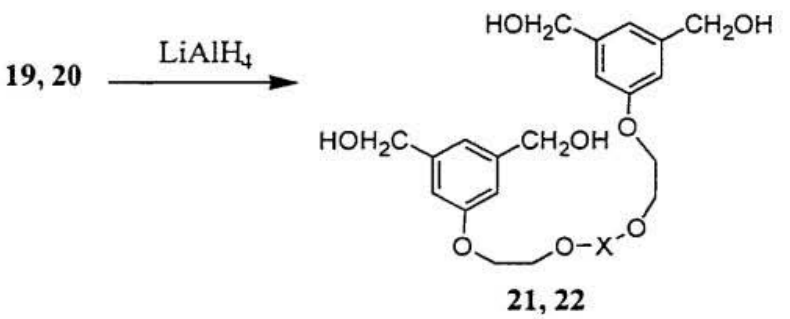
3.2.2 Preparation of the Dithiacyclophanes

Having previously found that a 13 atom tether could give a *syn-anti* equilibrium, the two linker units selected for the present project were those leading to the 13 atom 5-oxygen and the 16 atom 6-oxygen tethers. The synthetic routes were similar to the previously reported protocols (see Chapter 2). The synthesis of dithiacyclophane **25** commenced with the alkylation of diester **16** using commercially available ditosylate **17**. The crude tetraester **19**, obtained as a pale yellow oil in quantitative yield, was directly reduced using 12 equivalents of LAH at room temperature. At this point there was a divergence from the usual procedure, and an extractive work-up was performed, providing the corresponding tetraol **21** as a pink syrupy oil. This intermediate, again obtained in quantitative yield in the crude state, was treated with a small excess of PBr_3 in CH_2Cl_2 to afford the tetrabromide **23**. Chromatography provided pure **23** as a white solid. The overall yield of **23** was 54% from the ditosylate **17**. Since this series of transformations represents 10 individual steps, the yield per step was 94%. It is also noteworthy that the reactions were all amenable to relatively large scale, and over 6 g of **23** was produced in one run. In the final step the dithiacyclophane **25** was accessed using the $Na_2S{\cdot}Al_2O_3$ reagent.[12] A remarkably high yield of 89% was obtained, suggesting the existence of a favourable template effect.[13] [The yields for the dioxa tethered dithiacyclophanes are usually in the 50-75% range.] Dithiacyclophane **26** was obtained in a generally analogous fashion to **25**. Ditosylate **18** was readily prepared in 89% yield following a literature procedure.[14] Alkylation of **16** proceeded in the usual manner. The crude **20**, obtained in quantitative yield, was then reduced as before, however the previous

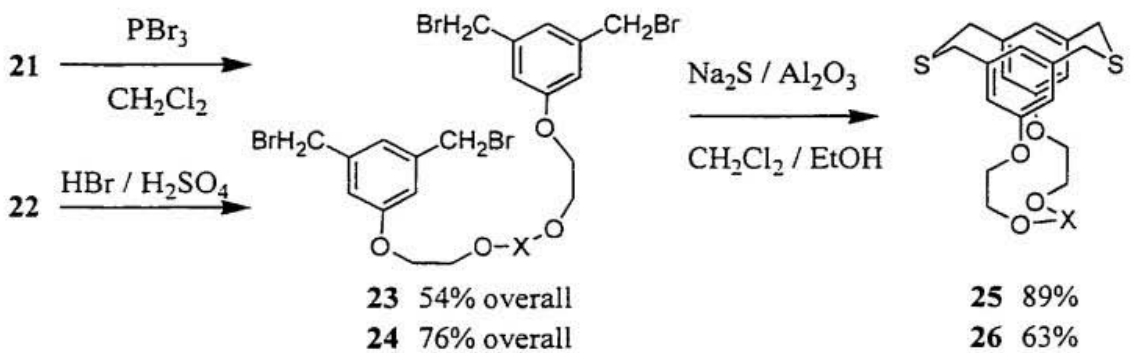
work-up protocol (see Chapter 2) of evaporating the crude tetraol **22** onto the aluminium salts at the end of the reduction was employed.



16 **17, 18** **19, 20**



21, 22



23 54% overall
24 76% overall

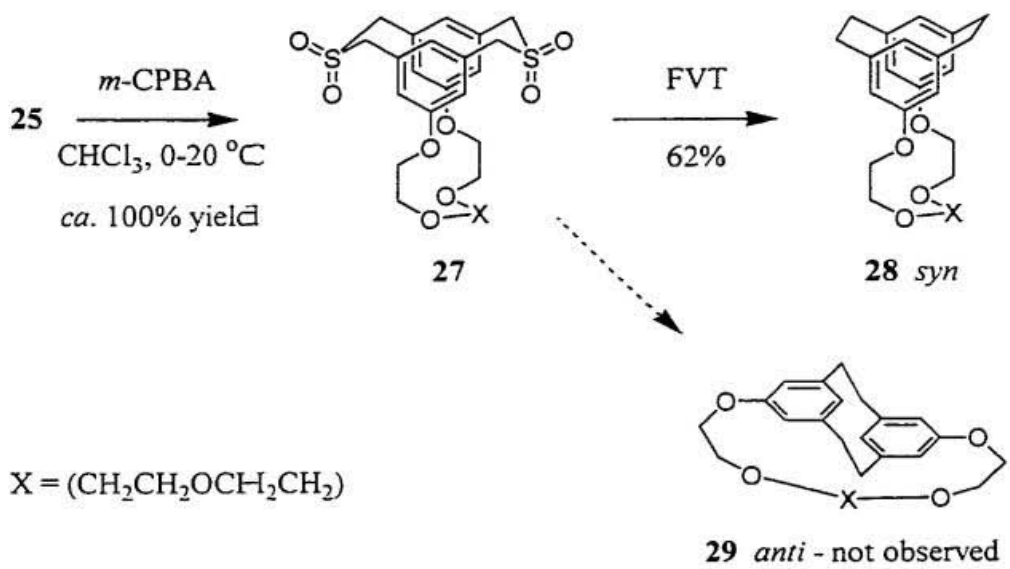
25 89%
26 63%

X = $CH_2CH_2OCH_2CH_2$ for the lower-numbered and $CH_2CH_2OCH_2CH_2OCH_2CH_2$ for the higher-numbered of each pair of like molecules.

Scheme 3.4 Synthesis of the Crown Ether Tethered Dithiametacyclophanes

Treatment of this residue with a mixture of concentrated HBr and H_2SO_4, followed by chromatography, gave almost pure **24** in 76% overall yield from the ditosylate. This material was treated with $Na_2S{\cdot}Al_2O_3$ to produce compound **26** in 63% yield. In this case it was observed that the dithiacyclophane was unstable to storage under air. The reason for this instability is not known. The dithiacyclophanes **25** and **26** are versatile intermediates, providing easy access to the desired cyclophanes and pyrenophanes.

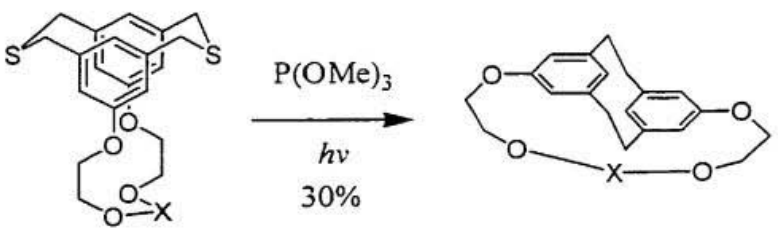
3.2.3 The Route to the Cyclophanes



Scheme 3.5 Synthesis of the Crown Ether Tethered Cyclophane **28** Using FVT

In the case of thiacyclophane **25**, *m*-CPBA oxidation to the disulphone was essentially quantitative. Flash vacuum thermolysis (FVT) using the very simple procedure outlined in Chapter 2 produced one main product in a yield of 62%. The symmetry

revealed by the NMR spectrum clearly identified the product to be the *syn* conformer **28**. [See Section 3.4 for a discussion of computational studies designed to predict the favoured conformer.] The 16 atom-tethered metacyclophane **11** has not yet been satisfactorily synthesised using the pyrolytic route. The failure of FVT in this instance is thought to have been due to the expected low volatilities of cyclophane **11** and its precursor disulphone preventing successful sublimation of the product prior to decomposition at the temperatures used. [Use of a stronger vacuum may facilitate this transformation.] However, photolysis of a solution of **26** in $P(OMe)_3$[15] did succeed, giving an unoptimised yield of 30%.



26 **11**

X = $(CH_2CH_2OCH_2CH_2OCH_2CH_2)$

Scheme 3.6 Synthesis of the Crown Ether Tethered Cyclophane **11** Using Photolysis

Only the *anti* isomer **11** was to be expected in this case, since the tether is so long that the cyclophane unit should be essentially free to adopt its most favourable conformation. The NMR spectrum of the product proved to be quite fascinating. While confirming the product to be the *anti* conformer **11**, the spectrum was quite different from the spectra previously obtained for shorter-tethered *anti* metacyclophanes synthesised in Chapter 2 (Figure 3.5).

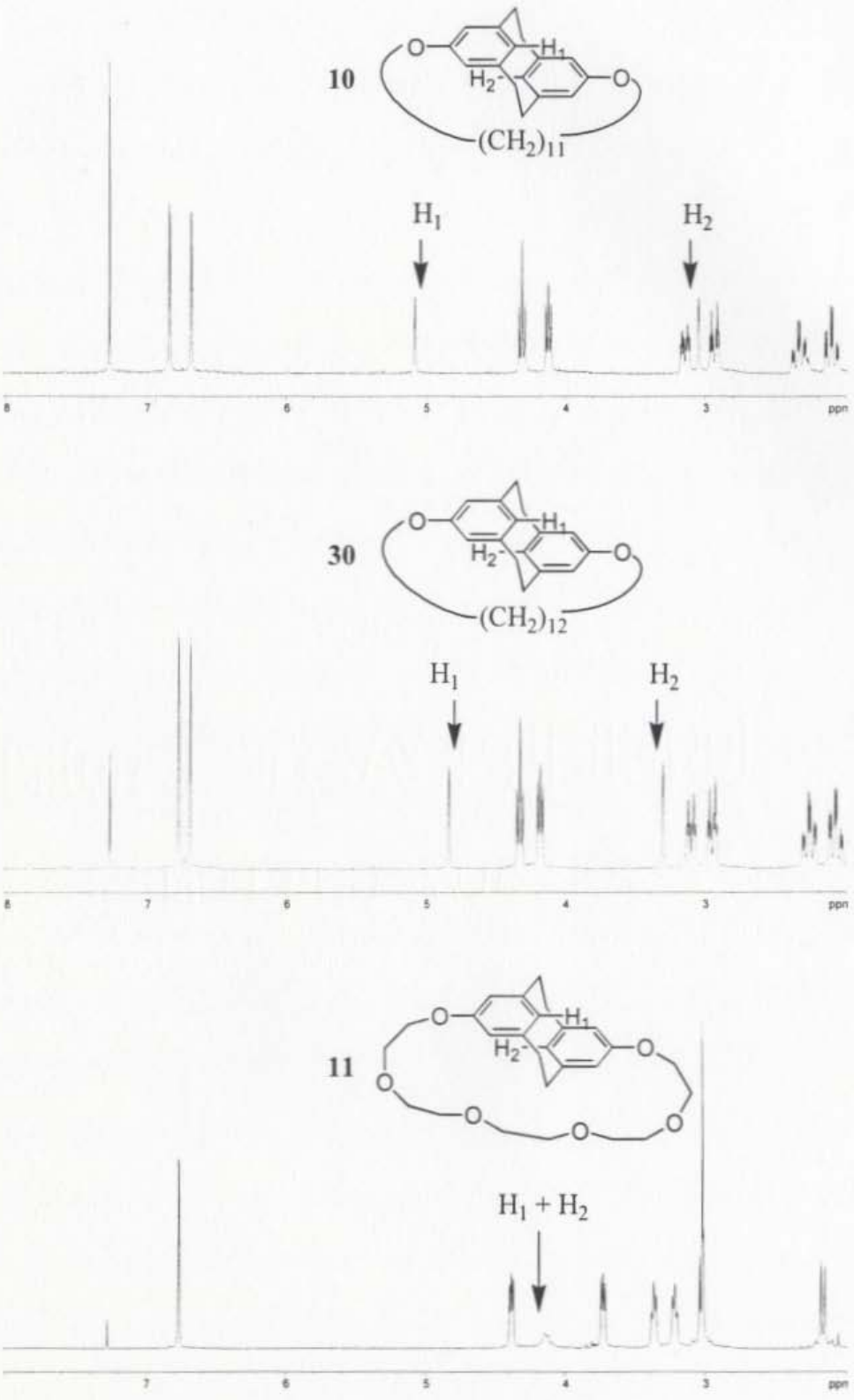
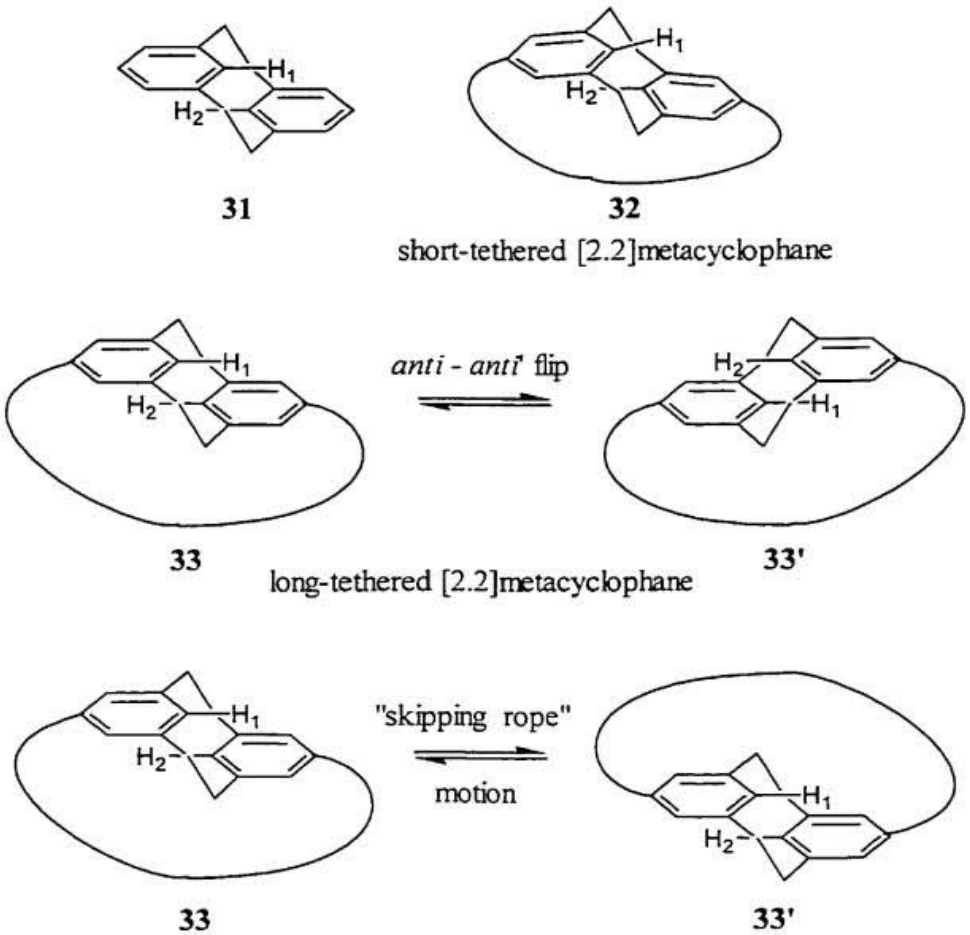


Figure 3.5 Contrasting NMR Data of *anti* Tethered Metacyclophanes

The obvious difference between the spectrum of **11** and those of **10** and **30** is in its simplicity. It is apparent that the two aromatic rings have become equivalent on the NMR time scale, and the signals belonging to the tether protons show the two ends of the tether to be equivalent. This is thought to be due to a molecular motion which interconverts the aromatic rings. The fact that the internal protons appear as a very broad singlet gives the impression that they are close to their coalescence point, and that use of low temperature NMR may enable their resolution as separate signals by preventing any interconversion process. The nature of the process is not known, and could be an *anti-anti'* flip or a spin by which the tether and the aromatic core would move relative to one another with a net result as if the tether circled the core like a skipping rope (Scheme 3.7). The former might seem more likely, as similar flips have been observed in other systems (see for example the results of Gschwend and Schlögl, Chapter 2, pp. 31-34). It is noteworthy, however, that the *anti-anti'* flip has never before been observed to occur so rapidly at room temperature. This could be explained by the idea that the tether helps set up the molecule for the flip by tilting the rings towards the transition state, reducing the activation energy. If this were true, though, it would be expected that this flip would be observed in the shorter-tethered molecules **10** and **30** too. Since this is not the case the latter skipping rope motion may be the correct explanation. From models it appears that **11** is the first tethered metacyclophane synthesised possessing a large enough cavity for the aromatic core to spin freely within the tether. The only other possible explanation of the NMR spectrum of **11** is accidental chemical shift equivalence. The tether in **11** is so far removed from the aromatic core that it may be possible that the two do not interact with each other to any significant degree. In this case the benzene rings become identical and

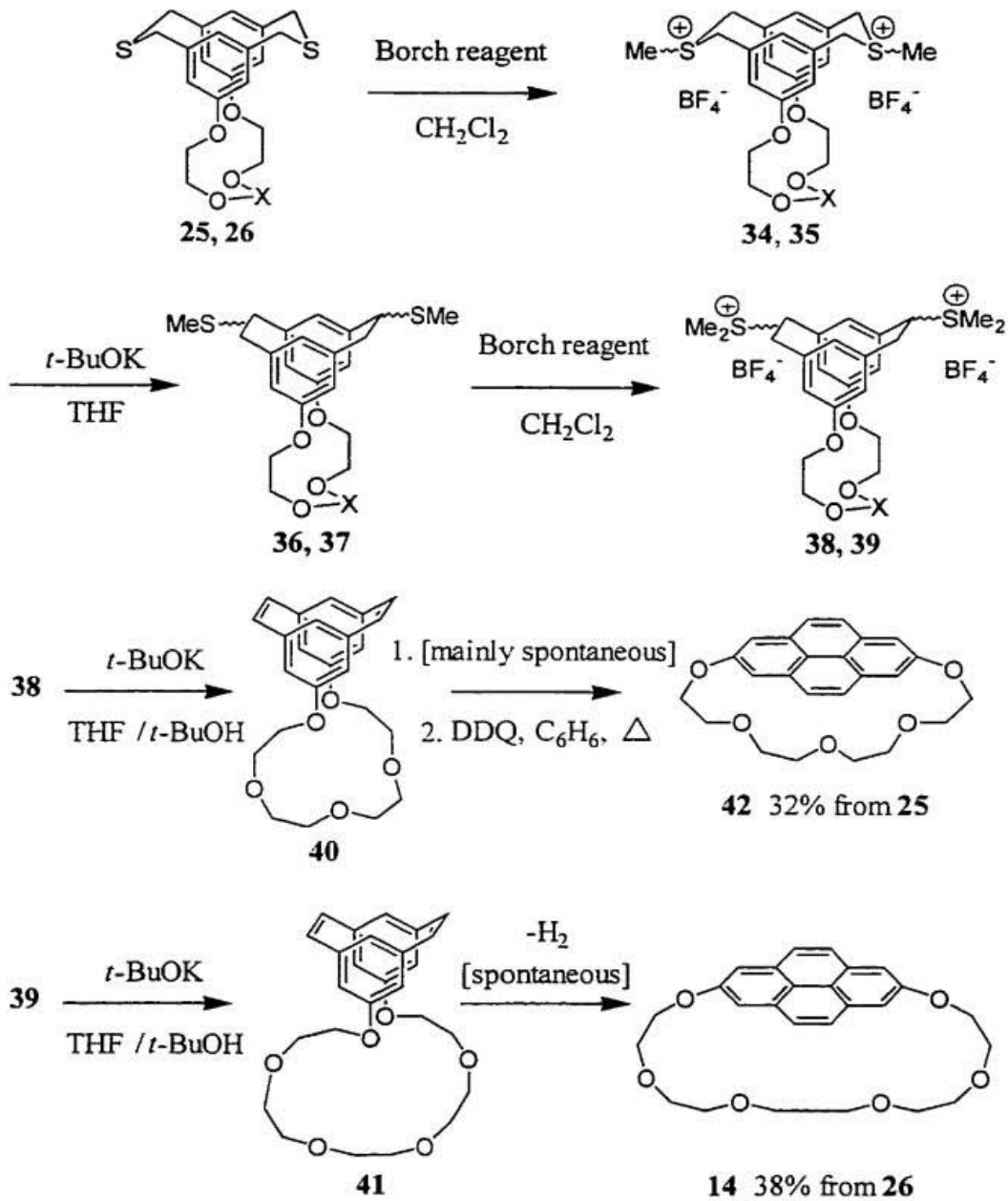
the tether possesses a centre of symmetry. This argument does not explain the broadening of the internal protons. The subject is certainly worthy of further investigation, and future work will no doubt clarify the situation. Scheme 3.7 summarises the possibilities.



In **31**, δ H_1 = δ H_2 = 4.2 ppm. In **32** δ H_1 can be as high as 5.1, δ H_2 as low as 3.0 ppm. This is due to the fact that the tether positions H_2 of **32** where it is strongly shielded by the neighbouring π-electron cloud. H_1 is concomitantly less shielded in **32** than in **31**. In compound **11** the shifts of the internal protons are equal, δ = 4.1, suggesting either a molecular motion or an accidental equivalence. [**11** is an example of **33** above.]

Scheme 3.7 Possible Explanations of the NMR Spectra of the *anti* Tethered [2.2]Metacyclophanes

3.2.4 The Pyrenophanes

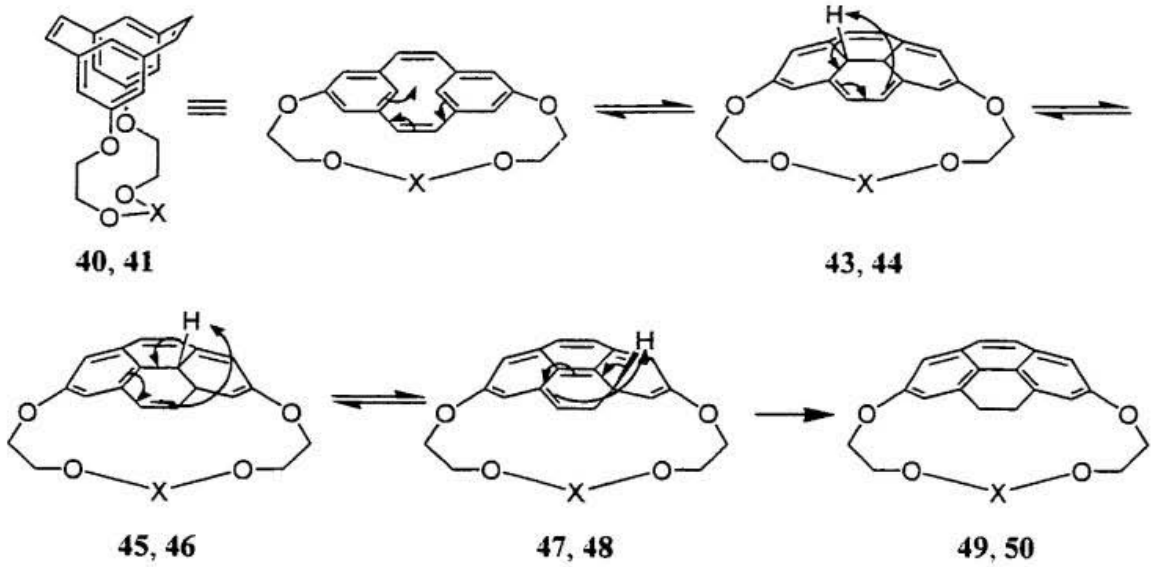


X = $CH_2CH_2OCH_2CH_2$ for the lower-numbered and $CH_2CH_2OCH_2CH_2OCH_2CH_2$ for the higher-numbered of each pair of like molecules.

Scheme 3.8 Synthesis of the Crown Ether Tethered Pyrenophanes **42** and **14**

The pyrenophanes were prepared using the usual methodology (Scheme 3.8). *S*-Methylation of the dithiacyclophanes **25** and **26** was followed by Stevens rearrangement.[16] The crude mixture of bis-thioethers was then subjected to a second methylation step. The crude salts **38** and **39** were treated with *t*-butoxide eliminating dimethyl sulphide. In each case the products obtained from the latter reaction were the desired pyrenophane (**42** from **38**, **14** from **39**) along with a byproduct whose NMR spectrum was consistent with a dihydropyrene structure (**49**, **50**). Such byproducts had been observed before,[17] and the scheme shown below accounts for all the observed products. It is thought that the intermediate cyclophanedienes formed from the initial elimination reaction initially undergo an electrocyclic ring closure to give *cis*-dihydropyrenes **43** and **44**. Spontaneous loss of hydrogen can then occur leading to the observed pyrenophanes. However, **43** and **44** may also react via a series of three sigmatropic [1,5]-hydrogen shifts to give the most thermodynamically stable dihydropyrene isomers **49** and **50**. This is rationalised by the idea that the intermediates are all in equilibrium, and could each irreversibly lose H_2 leading to the pyrenophane or undergo another 1,5 shift. [Presumably **49** and **50** are stable enough that they do not spontaneously lose H_2.] After chromatography **14** was obtained in 38% overall yield from the corresponding dithiacyclophane **26**. Pyrenophane **42** was obtained contaminated with a small amount of a byproduct presumed to be dihydropyrene **49** by analogy with previous work. The mixture was heated with DDQ to complete the dehydrogenation affording pure **42** in 32% yield from **25**. The more facile and higher yielding production of **14** is rationalised by the idea that the strain energy of the longer-tethered pyrenophane is less, meaning that spontaneous loss of hydrogen from its precursor is more favourable.

Indeed, it has been observed in the dioxa-tethered series that with tether lengths of 7 carbons (9 atoms) some pyrenophane is spontaneously formed, while with shorter tethers the cyclophanedienes are isolable.



X = $CH_2CH_2OCH_2CH_2$ for the lower-numbered and $CH_2CH_2OCH_2CH_2OCH_2CH_2$ for the higher-numbered of each pair of like molecules. Intermediates **43-48** can all lose H_2 to produce the corresponding pyrenophane **42** or **14**.

Scheme 3.9 A Possible Mechanism Accounting for Byproducts **49** and **50**

3.3 Computational Studies

Prior to the successful preparation of the target cyclophanes and pyrenophanes some computational studies were conducted in an attempt to predict their most favourable conformations. The more interesting study was the case of the cyclophanes. As previously mentioned, it seemed certain from the outset that the longer-tethered 18-crown-6 cyclophane would adopt the *anti* conformation **11**. However, the geometry of the shorter-tethered 15-crown-5 cyclophane (*syn* **28** or *anti* **29**) was not so easily predicted. The

corresponding dioxa-tethered cyclophane had proved to be a molecular switch, with *syn* and *anti* forms in equilibrium. The fact that this equilibrium favoured *anti* over *syn* by a ratio of about 8:1 at room temperature suggested that *anti* **29** may predominate, while the shortening of the tether due to the substitution of six slightly shorter C-O bonds in place of C-C bonds might be expected to change this situation in favour of the *syn* conformer. While *anti* conformer **11** was anticipated in isolation, it was hoped that it and/or **29** could be cajoled into a conformational change to *syn* on exposure to the appropriate metal ion. Reliable computational data for the *syn* and *anti* forms of both cyclophanes would give an indication of the energy difference in each case, and hence if an *anti-syn* change could be induced an estimate of the minimum value of the enthalpy of coordination of the metal ion could be obtained.

The ideal scenario would certainly have been to use *ab initio* calculations, especially as the geometrical properties of these molecules were expected to be anomalous. However, the size of the molecules and the flexibility of the long tethers forced the use of the empirical MM2 level of calculation due to time and financial constraints. This put obvious limitations on the usefulness of the data generated. All calculations were performed using the Spartan 4.1.1 software package produced by Wavefunction Inc., Irvine, California.

The first stage of the experiment was geometry optimisation of the *syn* and *anti* structures for both cyclophanes. This optimisation provided a starting point for the more advanced surface scan. Geometry optimisation generates a structure that represents an energy minimum on the potential energy surface close to the structure initially drawn on the computer, but which is unlikely to be the global minimum. Following this step, a

surface scan was performed using the Osawa method. This method is specific for exploring ring conformations in an attempt to find the global minimum for the structure. It should be noted that no solvent effects are included in this calculation, and that the global minimum defined by this program is valid only for an isolated molecule in the gas phase.

Geometry optimisations were performed on both **11** and its analogous *syn* form. The surface scan experiment was then run in an attempt to determine the global minima for these molecules. Both scans predicted that the *anti* conformer (Figure 3.6) was preferred. The strain energy was determined to be 46 kcal mol^{-1}.[18] Among the 50 lowest energy conformers reported by each scan not a single *syn* form was found. Apparently the program was rigorous enough to detect the possibility of the *syn-anti* flip and hence the conformer initially entered had practically no impact on the final calculation. While this result was pleasing in that it showed the power of the Osawa surface scan, it did not produce a properly optimised conformer for the *syn* isomer of **11** for comparison. Hence the lowest energy *syn* conformer generated was from the original geometry optimisation, which gave a strain energy of 60 kcal mol^{-1}. While a lower energy *syn* form probably exists, the *anti-syn* energy gap is obviously large for cyclophane **11**, and is of the order of 14 kcal mol^{-1}.

As expected, the case of the 15-crown-5 tethered cyclophane was more interesting. Separate surface scans were again run on the structures obtained from geometry optimisation of the *syn* and *anti* conformers. In this case, however, the gap between *syn* and *anti* was small enough that separate global minima could be obtained for each conformer (Figures 3.7 and 3.8).

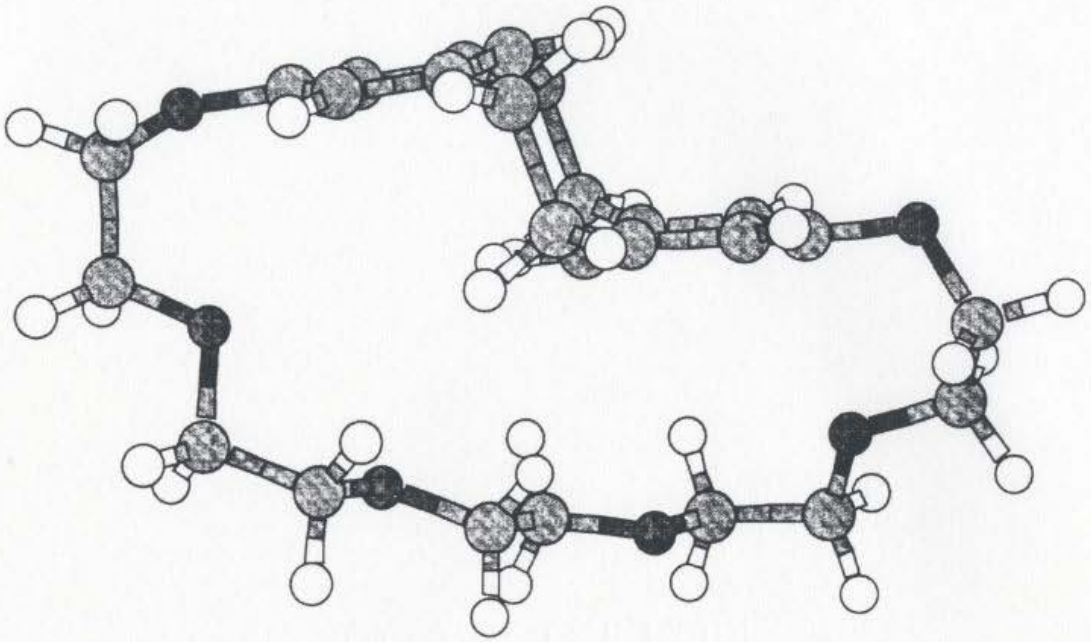


Figure 3.6 Optimised *anti* Conformer of 18-Crown-6 Tethered **11**

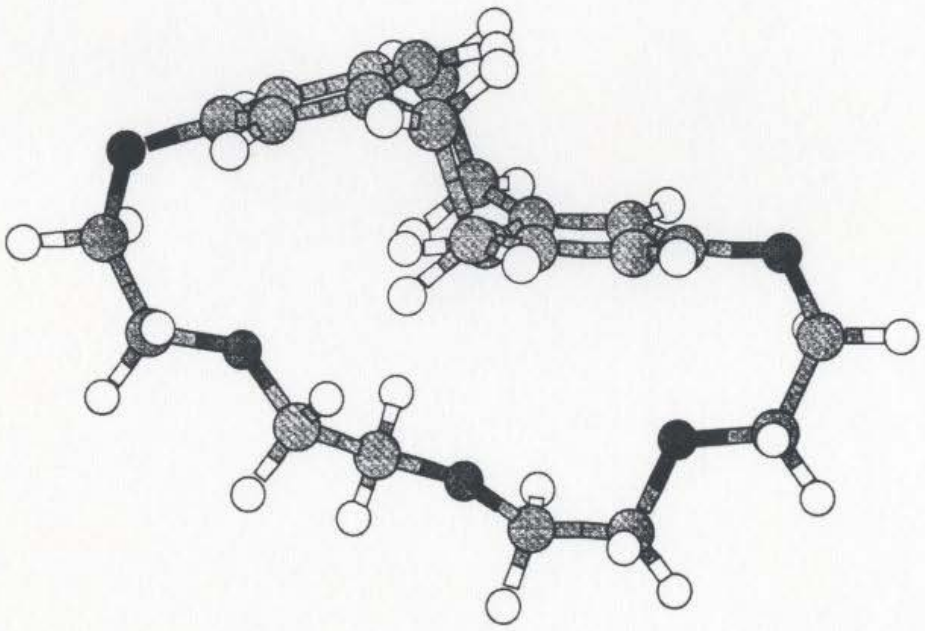


Figure 3.7 Optimised *anti* Conformer of 15-Crown-5 Tethered **29**

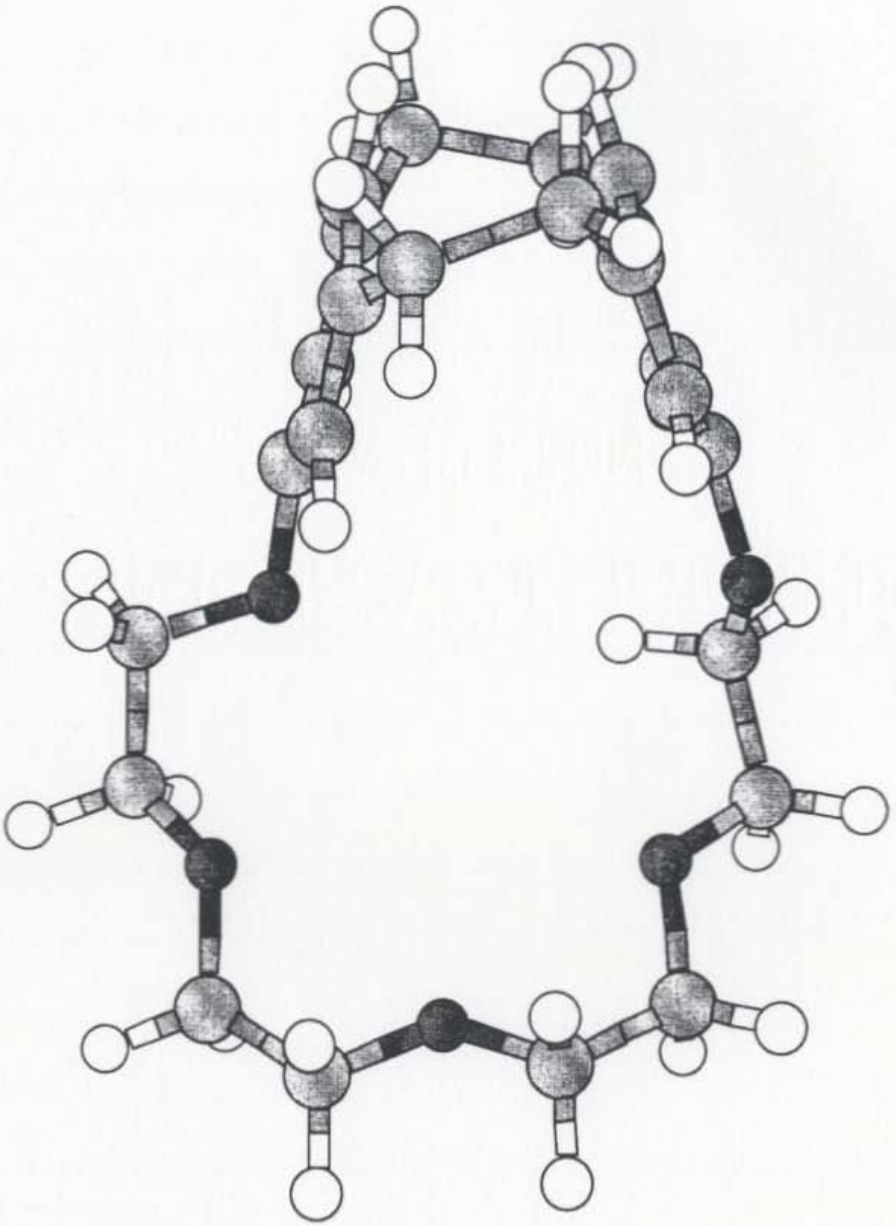


Figure 3.8 Optimised *syn* Conformer of 15-Crown-5 Tethered **28**

The lowest energy *anti* form (Figure 3.7) had a strain energy of 49 kcal mol^{-1}, while the lowest energy *syn* form (Figure 3.8) had a strain energy of 51 kcal mol^{-1}. Clearly these figures suggested that the *anti* form **29** should predominate. As was discussed earlier in this chapter, it was actually found that the *syn* conformer **28** predominates, and the *anti* form was not detected. There are several explanations for this discrepancy, two of which have already been mentioned above:

1. *ab initio* methods could not be used due to the size and large number of degrees of freedom of the molecules concerned. The MM2 program used is parametrised based on the properties of other molecules, which may result in an inaccurate calculation in the present case.

2. It is uncertain whether or not the Osawa method found the true global minimum. Finding the true global minimum is not guaranteed, as is evident above. In the case of **11** the program was able to make the *syn-anti* flip to generate an *anti* global minimum from an optimised *syn* structure, while a surface scan from an optimised *syn* conformer of **28** failed to generate an *anti* global minimum despite the fact that a lower-energy *anti* form existed. Hence it appears that some conformers were not found.

3. The data generated are valid only for an isolated molecule in the gas phase. Hence any solvent effects or crystal packing forces are ignored. Since the conformation of the compound in the gas phase has not been investigated, it is possible that the *anti* conformer is favoured in the gas phase.

4. The errors for these calculations have not been discussed, and may exceed the small difference in energy between the global minima of the two conformers. In the case of **11** it was found that although starting the surface scan from either *syn* or *anti* gave an

optimised *anti* conformer there was a difference in the calculated strain energy of about 1 kcal mol^{-1} between the two calculations. This is perhaps to be expected due to the very large number of degrees of freedom of the molecule.

A further computational study that was planned initially was to add metal ions to the cyclophane and see if the predicted conformation changed markedly. Unfortunately the computational resources were not available to do this. Such a study might be possible using *ab initio* methods or density functional theory, but both of these techniques were beyond the scope of this investigation.

3.4 X-Ray Crystallographic Analysis

Unfortunately, X-ray crystallography on the cyclophanes and pyrenophanes has been largely unsuccessful as yet. However, it should be noted that a partial X-ray crystal structure was obtained for pyrenophane **14**, which showed that the pyrene unit itself had indeed returned to total planarity at this tether length. Unfortunately, the 16 atom tether was also responsible for disorder within the crystal, rendering the structure unpublishable. Initial attempts to co-crystallise the compounds with metal salts have also failed to produce good data. It is hoped that crystal structures showing metal coordination in the solid state will be obtained in the future.

3.5 NMR Experiments Using Metal Ions

Some rather naive initial attempts were made to study the possible interactions of the crown ether cyclophanes and pyrenophanes with metal ions using NMR spectroscopy. As yet, these have proved to be unsuccessful. An important consideration for future work

in this area is that the NMR solvent used should not be strongly solvating. [In early experiments deuterated methanol was used as it was found to be a good solvent for some alkali metal salts. It was pointed out to the author at a conference that a less-strongly solvating solvent such as deuterated acetonitrile may better facilitate complexation of metal ions by the crown ether moieties. It is hoped that this will be investigated in the future.]

3.6 Experimental

General Procedures

For general procedures please refer to the section in Chapter 2.

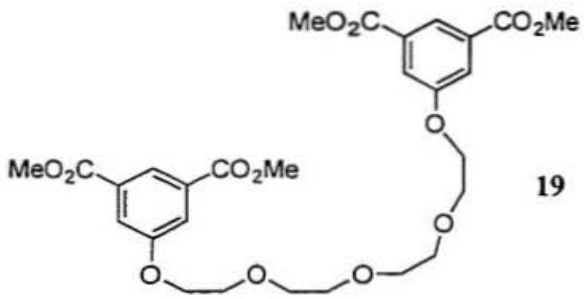
Pentaethylene glycol di-*p*-tosylate (18)

$Tos(OCH_2CH_2)_5OTos$ **18**

To a stirred solution of *p*-toluenesulphonyl chloride (24.29 g, 127 mmol) in pyridine (75 mL) cooled to -10 °C was added dropwise over 10 min a solution of pentaethylene glycol (10.00 g, 42.0 mmol) in pyridine (75 mL). The reaction was allowed to warm gradually to room temperature and after 17.5 h was poured into ice / water (300 mL) with stirring. After 5 min the mixture was extracted with CH_2Cl_2 (2x100 mL), the combined organics washed with ice cold 5M HCl (3x100 mL) and ice cold saturated NH_4Cl solution (150 mL). Drying ($MgSO_4$) and evaporation provided known compound **18** (20.45 g, 89%) sufficiently pure for further experiments.[14] An analytical sample was obtained by chromatography (2:1 ethyl acetate:hexanes) and this clear oil showed ^1H NMR spectral data consistent with the literature: ^1H NMR δ 7.80 (AX half spectrum, J_{AX} = 8.3 Hz, 4H),

7.34 (AX half spectrum, J_{AX} = 8.3, 4H), 4.15 (t, J = 4.9 Hz, 4H), 3.68 (t, J = 4.8 Hz, 4H), 3.61-3.58 (m, 12H), 2.45 (s, 6H).

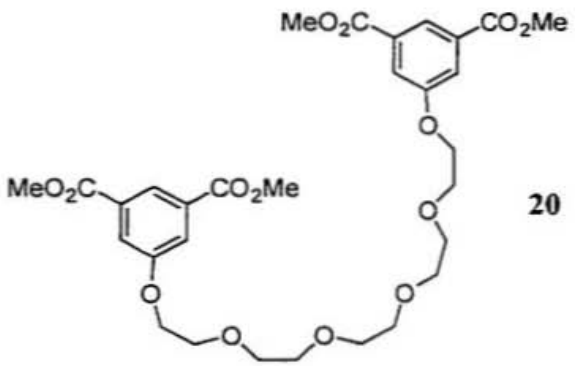
1,11-Bis(3,5-bis(methoxycarbonyl)phenoxy)(3,6,9-trioxa)undecane (19)



19

K_2CO_3 (7.00 g, 50.6 mmol) was added to a solution of dimethyl 5-hydroxyisophthalate **16** (7.01 g, 33.4 mmol) and tetraethylene glycol di-*p*-tosylate **17** (8.39 g, 16.7 mmol) in DMF (100 mL). The magnetically stirred suspension was heated to 70 °C for 23 h, and then cooled before being poured into a mixture of diethyl ether (500 mL) and 15% citric acid (500 mL). After stirring for 10 min the mixture was separated and the ether layer washed with 15% citric acid (2x250 mL) and water (250 mL). Drying ($MgSO_4$) and evaporation provided **19** (10.21 g, 106%) sufficiently pure for further experiments. An analytical sample was obtained by chromatography (2:1 ethyl acetate:hexanes): mp 73-74 °C, ^{1}H NMR δ 8.29 (s, 2H), 7.78 (s, 4H), 4.23 (t, 4H, J = 4.6 Hz), 3.95 (s, 12H), 3.91 (t, 4H, J = 4.6 Hz), 3.77-3.73 (m, 8H); ^{13}C NMR δ 166.1, 158.8, 131.7, 123.1, 119.9, 70.9, 70.7, 69.5, 68.0, 52.4; MS *m/z* (%) 578 (M^+, 1), 281 (16), 237 (57), 236 (58), 205 (48), 193 (46), 179 (21), 178 (16), 177 (20), 161 (21), 147 (27), 134 (23), 133 (20), 59 (97), 45 (100). Anal. Calcd for $C_{28}H_{34}O_{13}$: C, 58.13; H, 5.92. Found: C, 57.71; H, 5.96.

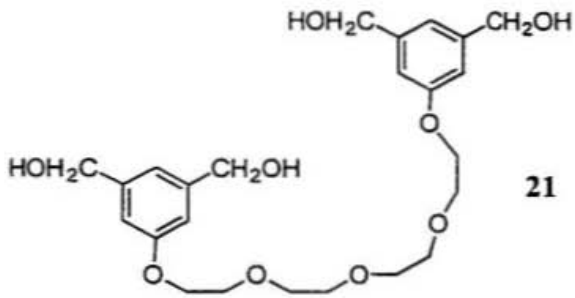
1,14-Bis(3,5-bis(methoxycarbonyl)phenoxy)(3,6,9,12-tetraoxa)tetradecane (20)



20

K_2CO_3 (6.82 g, 49.3 mmol) was added to a solution of dimethyl 5-hydroxyisophthalate **16** (7.01 g, 33.4 mmol) and pentaethylene glycol di-*p*-tosylate **18** (9.00 g, 16.5 mmol) in DMF (100 mL). The magnetically stirred suspension was heated to 70 °C for 25 h, and then cooled before being poured into a mixture of ethyl acetate (250 mL) and 15% citric acid (250 mL). After stirring for 30 min the mixture was separated and the organic layer dried ($MgSO_4$) and evaporated to give **20** (12.12 g, 118%) sufficiently pure for further experiments. An analytical sample was obtained by chromatography (4:1 ethyl acetate:hexanes): mp 39-40 °C, ^{1}H NMR δ 8.27 (s, 2H), 7.76 (s, 4H), 4.21 (t, 4H, J = 4.7 Hz), 3.93 (s, 12H), 3.88 (t, 4H, J = 4.9 Hz), 3.74-3.67 (m, 12H); ^{13}C NMR δ 166.0, 158.8, 131.7, 123.1, 119.9, 70.9, 70.6, 69.5, 68.0, 52.4; MS *m/z* (%) (M^+ not found), 281 (28), 280 (19), 254 (16), 237 (94), 236 (100), 205 (65), 193 (60), 179 (23), 178 (20), 177 (23), 161 (26), 147 (30), 134 (24), 133 (20), 59 (90), 45 (93). Anal. Calcd for $C_{30}H_{38}O_{14}$: C, 57.87; H, 6.15. Found: C, 57.96; H, 6.22.

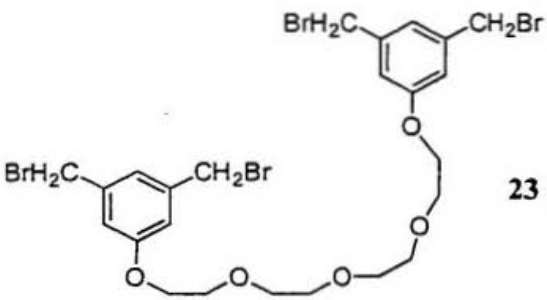
1,11-Bis(3,5-bis(hydroxymethyl)phenoxy)(3,6,9-trioxa)undecane (21)



21

Crude tetraester **19** (max. 16.0 mmol) was dissolved in anhydrous THF (200 mL). This solution was added dropwise over 45 min to a stirred slurry of LAH (7.30 g, 192 mmol) in dry THF (200 mL) in a 1L 3 neck round-bottomed flask. [A mild exotherm was observed.] The reaction mixture was stirred for 24 h then cooled in an ice bath and quenched with ethyl acetate (40 mL) added dropwise. This slurry was then added to ice water (3L), acidified (H_2SO_4) and the aqueous layer saturated with NaCl. Extraction with ethyl acetate (3x600 mL) and evaporation gave crude **21** (8.64 g, 116%) as a pink syrupy oil used directly to make **23**. [The high polarity and non-crystallinity of this compound precluded its isolation.]

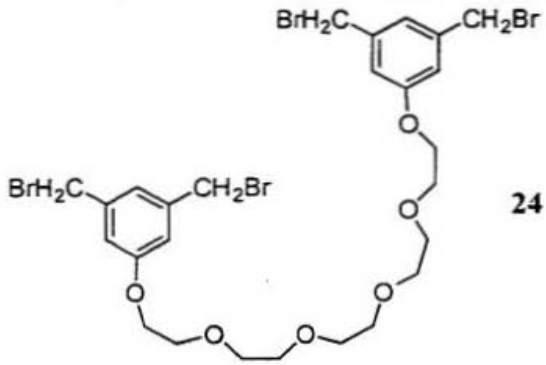
1,11-Bis(3,5-bis(bromomethyl)phenoxy)(3,6,9-trioxa)undecane (23)



23

Crude tetraol **21** (max. 16.0 mmol) was slurried in CH_2Cl_2 (250 mL) and cooled to 0 °C with stirring. To this suspension was added PBr_3 (2.5 mL, 26.3 mmol). The resulting mixture was allowed to warm to room temperature over 36 h, before pouring into ice water (250 mL). Stirring for 10 min was followed by separation, washing the organic layer with water (2x250 mL), brine (200 mL), and drying ($MgSO_4$). Evaporation and chromatography (2:1 hexanes:ethyl acetate, then 2:1 hexanes:ethyl acetate) produced pure **23** (6.18 g, 54% overall from ditosylate **17**) as a white solid. An analytical sample was obtained by recrystallisation from heptane / ethyl acetate: mp 45-47 °C; ^{1}H NMR δ 6.99 (s, 2H), 6.88 (s, 4H), 4.41 (s, 8H), 4.13 (t, J = 4.8 Hz), 3.85 (t, J = 4.9 Hz), 3.73-3.69 (m, 8H); ^{13}C NMR δ 159.2, 139.5, 122.0, 115.3, 70.9, 70.7, 69.6, 67.6, 32.8; MS *m/z* (%) 718 (M^+, 2x^{79}Br, 2x^{81}Br, 4), 307 (18), 227 (38), 225 (35), 201 (15), 199 (21), 184 (16), 182 (15), 147 (71), 146 (21), 145 (35), 120 (21), 119 (27), 109 (20), 107 (20), 105 (20), 104 (25), 103 (52), 102 (16), 45 (100). Anal. Calcd for $C_{24}H_{30}Br_4O_5$: C, 40.14; H, 4.21. Found: C, 40.05; H, 4.12.

1,14-Bis(3,5-bis(bromomethyl)phenoxy)(3,6,9,12-tetraoxa)tetradecane (24)

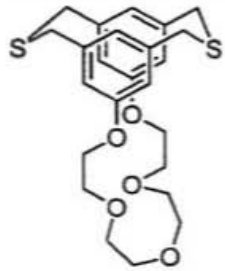


24

Crude tetraester **20** (max. 15.8 mmol) was dissolved in dry THF (200 mL). This solution was added dropwise over 40 min to a stirred slurry of LAH (7.19 g, 189 mmol) in

anhydrous THF (200 mL) in a 1L 3 neck round-bottomed flask. [A mild exotherm was observed.] The reaction mixture was stirred for 27.5 h then cooled in an ice bath and quenched with ethyl acetate (40 mL) added dropwise. The solvent was then removed under reduced pressure. To the well-stirred crude residue was added 4:1 48% HBr:H_2SO_4 (120 mL). [A powerful exotherm occurs when the acids are mixed, another upon addition of the acid mixture to the substrate.] After 5 min further H_2SO_4 (66 mL) was added. After 2 h the reaction mixture had set to a solid mass and had cooled close to room temperature. Water (200 mL) and CH_2Cl_2 (400 mL) were added and the mixture stirred until all the solids dissolved. After separation the aqueous layer was extracted with CH_2Cl_2 (200 mL), the combined organics diluted with further CH_2Cl_2 (200 mL) and washed with saturated $NaHCO_3$ solution (200 mL) and brine (200 mL). Drying ($MgSO_4$), evaporation and chromatography (1:1 ethyl acetate:hexanes) provided almost pure **24** as a colourless oil (9.12 g, 76% from ditosylate **18**) used without further purification to make **26**. An analytical sample was obtained by further chromatography (2:1 ethyl acetate:hexanes): ^{1}H NMR δ 6.99 (s, 2H), 6.88 (s, 4H), 4.42 (s, 8H), 4.13 (t, J = 5.0 Hz, 4H), 3.85 (t, J = 4.8 Hz, 4H), 3.74-3.67 (m, 12H); ^{13}C NMR δ 159.1, 139.5, 121.9, 115.3, 70.8, 70.6 (2C), 69.6, 67.6, 32.8; MS *m/z* (%) (M^+ not found), 227 (19), 225 (16), 147 (39), 145 (15), 109 (19), 107 (19), 103 (22), 45 (100). Anal. Calcd for $C_{26}H_{34}Br_4O_6$: C, 40.97; H, 4.50. Found: C, 40.69; H, 4.19.

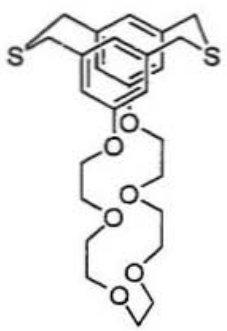
1,4,7,10,13-Pentaoxa-21,30-dithia[13.3.3](1,3,5)cyclophane (25)



25

Tetrabromide **23** (5.65 g, 7.87 mmol) and $Na_2S{\cdot}Al_2O_3$[12] (17.4 mmol Na_2S) were initially combined in 2800 mL 9:1 CH_2Cl_2:EtOH. After 15.5 h further $Na_2S{\cdot}Al_2O_3$ (2.95 mmol Na_2S) was added. After a total of 19.5 h the reaction mixture was filtered, evaporated and purified by chromatography (1:1 ethyl acetate:hexanes, then 2:1 ethyl acetate:hexanes) providing **25** (3.23 g, 89%) as a colourless solid. An analytical sample was obtained by crystallisation from EtOH: mp 150-151 °C; ^{1}H NMR δ 6.80 (s, 2H), 6.38 (s, 4H), 3.95-3.70 (m, 24H); ^{13}C NMR δ 158.5, 138.4, 124.3, 113.4, 70.8, 70.2, 69.6, 67.5, 38.6; MS *m/z* (%) 463 (20), 462 (M^+, 71), 148 (19), 147 (31), 145 (17), 134 (18), 122 (27), 121 (20), 45 (100). Anal. Calcd for $C_{24}H_{30}O_5S_2$: C, 62.31; H, 6.54. Found: C, 62.12; H, 6.52.

1,4,7,10,13,16-Hexaoxa-24,33-dithia[16.3.3](1,3,5)cyclophane (26)

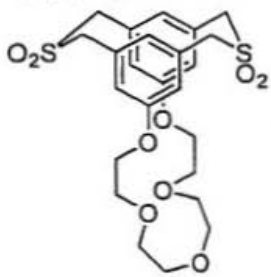


26

Tetrabromide **24** (8.80 g, 11.5 mmol) and $Na_2S{\cdot}Al_2O_3$[12] (25.4 mmol Na_2S) were initially combined in 4180 mL 9:1 CH_2Cl_2:EtOH. After 3.5 h further $Na_2S{\cdot}Al_2O_3$ (5.96 mmol

Na_2S) was added. After a total of 19 h the reaction mixture was filtered, evaporated and purified by chromatography (4:1 ethyl acetate:hexanes) providing **26** (3.66 g, 63%) as a pale yellow solid. This material proved to be unstable to prolonged storage under air. An analytical sample was obtained by crystallisation from heptane / ethyl acetate: mp 109-111 °C; ^{1}H NMR δ 6.80 (s, 2H), 6.38 (s, 4H), 3.93-3.71 (m, 28H); ^{13}C NMR δ 158.2, 138.4, 124.4, 113.7, 71.4, 70.8, 70.7, 70.0, 67.9, 38.6; MS *m/z* (%) 507 (16), 506 (M^+, 49), 147 (20), 122 (19), 45 (100). Anal. Calcd for $C_{26}H_{34}O_6S_2$: C, 61.63; H, 6.76. Found: C, 60.32; H, 6.63.

1,4,7,10,13-Pentaoxa-21,21,30,30-tetraoxo-dithia[13.3.3](1,3,5)cyclophane (27)

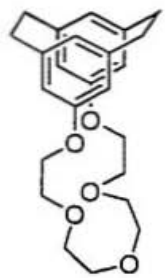


27

Dithiacyclophane **25** (0.750 g, 1.62 mmol) was dissolved in $CHCl_3$ (140 mL) and cooled to 0 °C. To this stirred solution was added 50-60% *m*-CPBA (2.24 g, 6.48 mmol). The reaction mixture was allowed to warm to room temperature over 20 h. The solution was then washed with 2M K_2CO_3 (100 mL) and brine (50 mL), dried ($MgSO_4$) and evaporated to give the crude disulphone **27** (0.862 g, 101%). On this occasion the disulphone was purified by heating with boiling methanol (50 mL) for 5 min, cooling in the refrigerator for 15 min, filtration and washing of the white solid with MeOH (25 mL) to give pure **27** (0.708 g, 83%): mp >300 °C; ^{1}H NMR (DMSO-d_6) δ 7.15 (s, 2H), 6.67 (s, 4H), 4.85 (AX half spectrum, J_{AX} = 14.1 Hz, 4H), 4.29 (AX half spectrum, J_{AX} = 14.1 Hz, 4H), 3.86 (br

s, 4H), 3.70 (br s, 4H), 3.59 (br s, 8H); ^{13}C NMR (DMSO-d_6) δ 156.8, 129.8, 128.1, 116.3, 69.7, 69.6, 68.4, 67.2, 59.9; MS *m/z* (%) (M^+ not found), 238 (8), 91 (10), 83 (14), 28 (100).

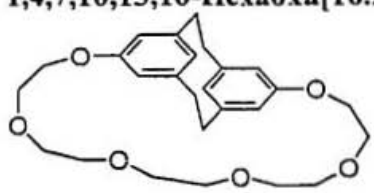
1,4,7,10,13-Pentaoxa[13.2.2](1,3,5)cyclophane (28)



28

Disulphone **27** (0.250 g, 0.475 mmol) was dissolved in CH_2Cl_2 and evaporated onto the surface of a 100 mL round-bottomed flask. The FVT experiment was performed as described in the experimental section of Chapter 2. One pass was sufficient in this case for complete conversion. Chromatography (1:1 ethyl acetate:hexanes) provided pure 28 as a white crystalline solid (0.093 g, 62%): mp 109-110 °C; ^{1}H NMR δ 6.16 (s, 2H), 6.02 (s, 4H), 3.89-3.72 (m, 16H), 3.11-3.05 (m, 4H), 2.84-2.81 (m, 4H); ^{13}C NMR δ 158.8, 139.3, 131.6, 113.2, 70.7, 70.4, 69.6, 67.4, 35.5; MS *m/z* (%) 399 (12), 398 (M^+, 47), 238 (34), 237 (16), 45 (100). Anal. Calcd for $C_{24}H_{30}O_5$: C, 72.34; H, 7.59. Found: C, 72.14; H, 7.78.

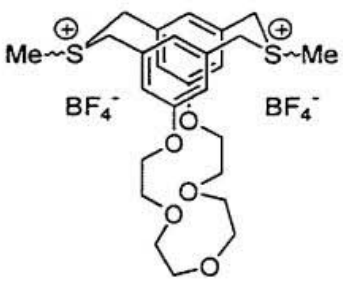
1,4,7,10,13,16-Hexaoxa[16.2.2](1,3,5)cyclophane (11)



11

Dithiacyclophane **26** (0.1046 g, 0.206 mmol) was dissolved in $P(OMe)_3$ (5 mL) in a freshly cleaned (base bath) quartz tube. The solution was degassed and stirred in a Rayonet photoreactor for 18 h. The reaction mixture was poured into 50 mL ice cold 5M HCl, stirred 10 min then extracted with ethyl acetate (2x50 mL), dried ($MgSO_4$) and purified by chromatography (1:1 ethyl acetate:hexanes) to give **11** as a white solid (0.0290g, 32%): mp 92-95 °C; ^{1}H NMR δ 6.75 (s, 4H), 4.37 (t, J = 3.8 Hz, 4H), 4.12 (br s, 2H), 3.72 (t, J = 3.7 Hz, 4H), 3.37-3.01 (m, 16H), 2.17-2.05 (m, 4H); ^{13}C NMR δ 159.7, 140.0, 130.8, 114.6, 71.9, 70.9, 70.0, 69.0, 68.4, 41.0; MS *m/z* (%) 443 (17), 442 (M^+, 59), 238 (35), 237 (15), 45 (100). Anal. Calcd for $C_{26}H_{34}O_6$: C, 70.56; H, 7.74. Found: C, 70.22; H, 7.90.

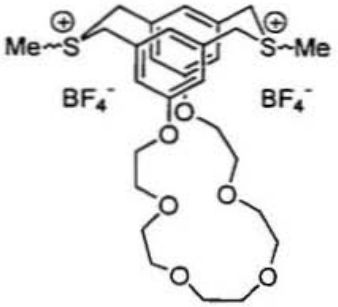
Bis(methylsulphonium tetrafluoroborate) salt of 25 (34)



34

Dithiacyclophane **25** (2.05 g, 4.43 mmol) was dissolved in dry CH_2Cl_2 (200 mL). Borch reagent (dimethoxycarbonium tetrafluoroborate), (1.8 mL, 14.9 mmol) was added via syringe, and the mixture allowed to stir 24 h. The solvent was evaporated and the residue triturated with ethyl acetate (20 mL) in diethyl ether (40 mL). Crude **34** was filtered off and washed with diethyl ether (2x50 mL). This material was used directly in the preparation of **36**.

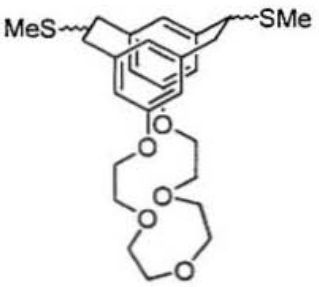
Bis(methylsulphonium tetrafluoroborate) salt of 26 (35)



35

Dithiacyclophane **26** (2.00 g, 3.95 mmol) was dissolved in dry CH_2Cl_2 (200 mL). Borch reagent (1.5 mL, 12.4 mmol) was added via syringe, and the mixture allowed to stir 3 h. The solvent was evaporated and the residue triturated with ethyl acetate (20 mL) in diethyl ether (40 mL). Crude **35** was filtered off and washed with diethyl ether (2x50 mL). This material was used directly in the preparation of **37**.

(20,27/28)Bis(methylthio)-1,4,7,10,13-pentaoxa-[13.2.2](1,3,5)cyclophane (36)

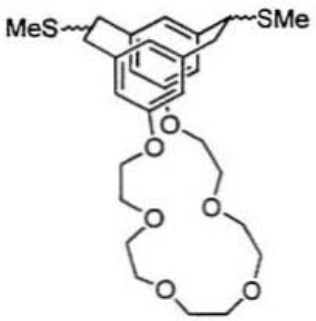


36

Crude salt **34** prepared above (max. 4.43 mmol) was suspended in anhydrous THF (100 mL). To this stirred mixture was added *t*-BuOK (2.49 g, 22.2 mmol). After 4 h the reaction was quenched by the addition of saturated NH_4Cl solution (50 mL), the solvent evaporated and the residues taken up in CH_2Cl_2 (200 mL) and water (100 mL). The layers were separated and the aqueous extracted with CH_2Cl_2 (200 mL). The combined organics

were dried ($MgSO_4$) and evaporated to give crude **36** as a foam (2.03 g, 93%). The crude material was passed through a silica column eluting with ethyl acetate to remove baseline material. The mixture of isomers **36** thus obtained (1.77g, 3.61 mmol) was used directly in the preparation of **38**.

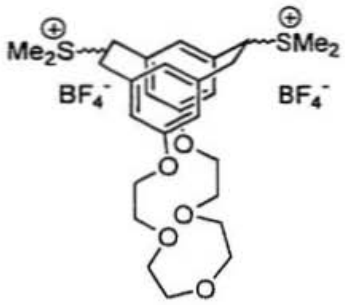
(23,30/31)Bis(methylthio)-1,4,7,10,13,16-hexaoxa-[16.2.2](1,3,5)cyclophane (37)



37

Crude salt **35** prepared above (max. 3.95 mmol) was suspended in anhydrous THF (100 mL). To this stirred mixture was added *t*-BuOK (2.25 g, 20.0 mmol). After 17 h the reaction was quenched by the addition of saturated NH_4Cl solution (50 mL), the solvent evaporated and the residues taken up in CH_2Cl_2 (200 mL) and water (100 mL). The layers were separated and the aqueous extracted with CH_2Cl_2 (200 mL). The combined organics were washed with brine (100 mL), dried ($MgSO_4$) and evaporated to give crude **37** as an orange oil which was used directly in the preparation of **39**.

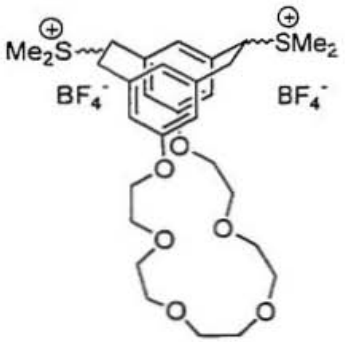
Bis(methylsulphonium tetrafluoroborate) salt of 36 (38)



38

Bis(thioether) **36** (1.77 g, max. 3.61 mmol) was dissolved in dry CH_2Cl_2 (300 mL). Borch reagent (1.5 mL, 12.4 mmol) was added via syringe, and the mixture allowed to stir 15 h. The solvent was evaporated and the residue triturated with ethyl acetate (20 mL) in diethyl ether (100 mL). Crude **38** was filtered off and washed with diethyl ether (2x50 mL) to give a fine beige powder. This material was used directly in the preparation of **42**.

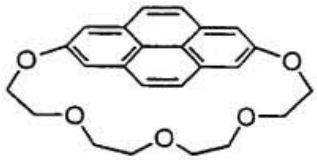
Bis(methylsulphonium tetrafluoroborate) salt of 37 (39)



39

Bis(thioether) **37** (max. 3.95 mmol) was dissolved in dry CH_2Cl_2 (300 mL). Borch reagent (2.5 mL, 20.7 mmol) was added via syringe, and the mixture allowed to stir 18 h. The solvent was evaporated and the residue triturated with ethyl acetate (20 mL) in diethyl ether (100 mL). Crude **39** was filtered off and washed with diethyl ether (2x50 mL) to give a fine beige powder. This material was used directly in the preparation of **14**.

1,4,7,10,13-Pentaoxa[13](2.7)pyrenophane (42)

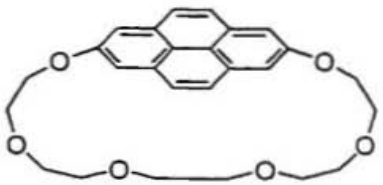


42

Crude salt **38** prepared above (max. 3.61 mmol) was suspended in a mixture of anhydrous THF (40 mL) and anhydrous *t*-BuOH (40 mL). To this stirred mixture cooled in a cold water bath was added *t*-BuOK (2.03 g, 18.1 mmol). After 5 min the cooling bath was removed and after 3 h the reaction was quenched by the addition of saturated NH_4Cl solution (50 mL) and then water (100 mL). The Me_2S produced by the reaction was removed by purging with N_2 in the hood. The organic solvents were evaporated and the aqueous residue extracted with ethyl acetate (2x100 mL), the combined organics dried ($MgSO_4$), and evaporated. Chromatography (1:1 ethyl acetate:hexanes) gave **42** (0.668 g, 38% from dithiacyclophane **25**) as a white solid, pure by TLC. NMR analysis revealed the presence of a small amount of an impurity thought to be a dihydropyrenophane. Chromatographed **42** (0.542 g, max. 1.38 mmol) and DDQ (0.330g, 1.47 mmol) were dissolved in benzene (50 mL) and heated to reflux for 2 h. The solvent was evaporated and the residue taken up in CH_2Cl_2 (100 mL) and 2M K_2CO_3 (100 mL). After separation the aqueous layer was extracted with CH_2Cl_2 (100 mL) and the combined organics dried ($MgSO_4$), evaporated and chromatographed (1:1 ethyl acetate:hexanes) to give pure **42** (0.452 g, 32% from dithiacyclophane **25**) as a white solid: mp 200-202 °C; ^{1}H NMR δ 7.98 (s, 4H), 7.89 (s, 4H), 4.46-4.44 (m, 4H), 3.55-3.53 (m, 4H), 2.16-2.11 (m, 4H), 1.61-1.56 (m, 4H); ^{13}C NMR δ 156.3, 131.7, 127.3, 118.2, 72.8, 71.9, 69.1, 67.6; MS *m/z* (%) 394 (34), 393 (27), 392 (M^+, 100), 234 (61), 232 (31), 206 (34), 205 (15), 200 (18), 189

(36), 188 (44), 187 (15), 176 (36), 116 (22). Anal. Calcd for $C_{24}H_{24}O_5$: C, 73.45; H, 6.16. Found: C, 72.87; H, 6.14.

1,4,7,10,13,16-Hexaoxa[16](2.7)pyrenophane (14)



14

Crude salt **39** prepared above (max. 3.95 mmol) was suspended in a mixture of anhydrous THF (40 mL) and anhydrous *t*-BuOH (40 mL). To this stirred mixture cooled in a cold water bath was added *t*-BuOK (2.22 g, 18.1 mmol). After 5 min the cooling bath was removed and after 25 min the reaction was quenched by the addition of saturated NH_4Cl solution (50 mL) and then water (100 mL). The Me_2S produced by the reaction was removed by purging with N_2 in the hood. The organic solvents were evaporated and the aqueous residue extracted with CH_2Cl_2 (200 mL, then 2x100mL), the combined organics dried ($MgSO_4$), and evaporated. Chromatography (1:1 ethyl acetate:hexanes, then 2:1 ethyl acetate:hexanes, then neat ethyl acetate) gave **14** (0.654 g, 38% from dithiacyclophane **26**) as a colourless solid. An analytical sample was obtained by recrystallisation from heptane / ethyl acetate: mp 169-170 °C; ^{1}H NMR δ 7.97 (s, 4H), 7.86 (s, 4H), 4.63-4.61 (m, 4H), 3.78-3.76 (m, 4H), 3.12-3.09 (m, 4H), 2.60-2.57 (m, 4H), 1.76 (s, 4H); ^{13}C NMR δ 157.0, 131.4, 127.4, 115.1, 72.4, 70.0 (2C), 69.4, 68.5; MS *m/z* (%) 438 (17), 437 (29), 436 (M^+, 100), 235 (16), 234 (83), 232 (16), 206 (24), 200 (16), 189 (19), 188 (28), 176 (22), 116 (18). Anal. Calcd for $C_{26}H_{28}O_6$: C, 71.54; H, 6.47. Found: C, 71.41; H, 6.52.

3.7 References

[1] Helgeson, R.C.; Tarnowski,T.L.; Timko, J.M.; Cram, D.J. *J. Am. Chem. Soc.* **1977**, *99*, 6411-6418.

[2] Rebek, J. Jr.; Wattley, R.V.; Costello, T.; Gadwood, R.; Marshall, L. *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 605-606.

[3] For a discussion of allosteric effects in the binding of oxygen to haemoglobin see Dickerson, R.E.; Geis, I. *Hemoglobin*; The Benjamin/Cummings Publishing Company, Inc.: Menlo Park, California, 1983; 47-49.

[4] König, B.; Rütters, H. *Tetrahedron Lett.* **1994,** *35*, 3501-3504.

[5] See for example Nicolaou, K.C.; Zuccarello, G.; Riemer, C.; Estevez, V.A.; Dai, W.-M. *J. Am. Chem. Soc.* **1992,** *114*, 7360-7371.

[6] Inokuma, S; Gao, S.-R.; Nishimura, J. *Chem. Lett.* **1995**, 689-690.

[7] Bodwell, G.J.; Houghton, T.J.; Kennedy, J.W.J.; Mannion, M.R. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2121-2123.

[8] Bodwell, G.J.; Bridson, J.N.; Houghton, T.J.; Kennedy, J.W.J.; Mannion, M.R. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1320-1321.

[9] Bodwell, G.J.; Bridson, J.N.; Houghton, T.J.; Kennedy, J.W.J.; Mannion, M.R. *Chem. Eur. J.* **1999**, *5*, 1823-1827.

[10] For some examples of free energies of complexation of cations with crown ethers see Cram, D.J.; Cram, J.M. *Container Molecules and their Guests*; The Royal Society of Chemistry: Cambridge, England, 1994; 43. See also More, M.B.; Ray, D.; Armentrout, P.B. *J. Am. Chem. Soc.* **1999,** *121*, 417-423.

[11] For examples of silver ion complexation with aromatic hydrocarbons see Munakata, M.; Wu, L.P.; Kuroda-Sowa, T.; Maekawa, M.; Suenaga, Y.; Ning, G.L.; Kojima, T. *J. Am. Chem. Soc.* **1998,** *120*, 8610-8618; Gross, J.; Harder, G.; Vögtle, F.; Stephan, H.; Gloe, K. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 481-484; Kang, H.C.; Hanson, A.W.; Eaton, B.; Boekelheide, V. *J. Am. Chem. Soc.* **1985**, *107*, 1979-1985.

[12] Bodwell, G.J.; Houghton, T.J.; Koury, H.E.; Yarlagadda, B. *Synlett*, **1995**, 751-752.

[13] For several examples of templated cyclisations see *Macrocycle Synthesis*; Parker, D. Ed.; Oxford University Press: Oxford, 1996.

[14] For the procedure used see van Klink, G.P.M., Ph.D. Dissertation, Vrije Universiteit te Amsterdam, 1998, 207. For an alternative, possibly more convenient methodology see Amabiliano, D.B.; Preece, J.A.; Stoddart, J.F. in *Macrocycle Synthesis*; Parker, D. Ed.; Oxford University Press: Oxford, 1996; 84-85.

[15] Boekelheide, V.; Reingold, I.D.; Tuttle, M. *J. Chem. Soc. Chem. Commun.* **1973**, 406-407.

[16] Mitchell, R.H.; Boekelheide, V. *J. Am. Chem. Soc.* **1974**, *96*, 1547-1557.

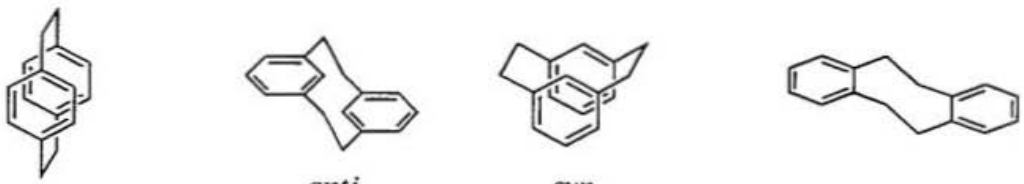
[17] Bodwell, G.J.; Mannion, M.R. unpublished results.

[18] For a discussion of various definitions of the term "strain energy" see Burkert, U.; Allinger, N.L. *Molecular Mechanics, ACS Monograph 177*; American Chemical Society: Washington, D.C., 1982; 184-194.

Approaches to New C_2-Symmetric Tetra-Functionalised Chiral Ligands Based on the Paracyclophane Skeleton

4.1 Introduction

Paracyclophane **1** was the third of the [2.2]cyclophanes to be reported (1949)[1] following *anti*-[2.2]metacyclophane **2** (1899)[2] and [2.2]orthocyclophane **4** (1945)[3].



anti *syn*

1 **2** **3** **4**

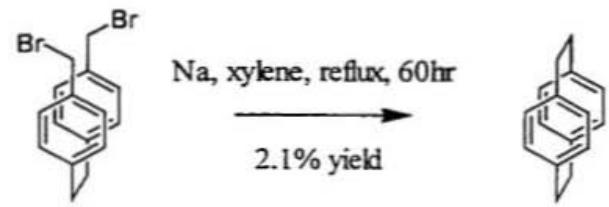
[2.2]Paracyclophane [2.2]Metacyclophane [2.2]Orthocyclophane

Figure 4.1 The Simple [2.2]Cyclophanes

The structure of **1** was, as stated in the general introduction, initially proved by X-ray crystallography.[1] This was most unusual at that time, and actually remarkably appropriate, since **1** is extremely crystalline (melting point 285-287 °C) and features boat-shaped benzene rings which would have eluded discovery without X-ray. The crystallinity of **1** enabled its isolation in the first place from a mixture of byproducts in the industrial polymerisation of *p*-xylene.[1] [An interesting study has subsequently been published on the polymerisation of the intermediate *p*-xylylene under various conditions of temperature and concentration.][4]

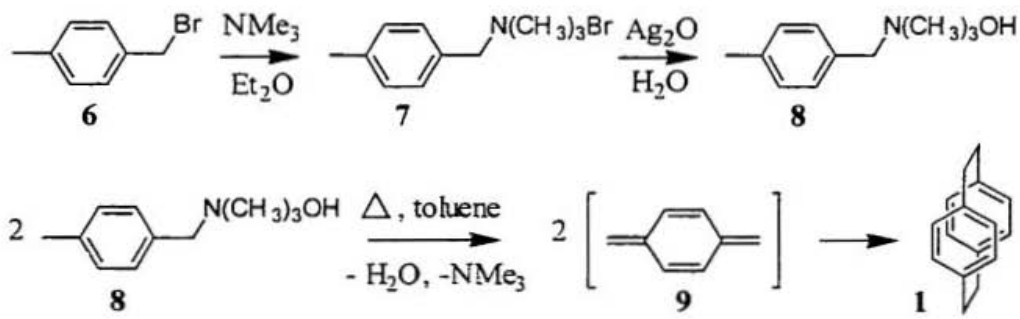
[2.2]Paracyclophanes are difficult to make in the laboratory due to the energetically unfavourable distortion of the benzene rings mentioned above. Indeed the final step of Cram's first designed synthesis required high dilution, a 60 hour reaction

period, boiling xylene as solvent, and molten sodium stirred at 7000 rpm.[5] The yield of 2.1% is especially poor given that this is a one-step intramolecular reaction.



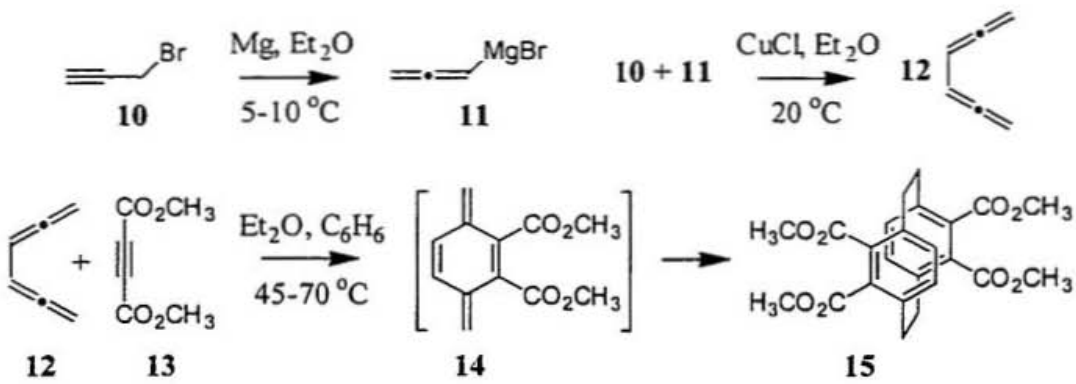
5 **1**

Scheme 4.1 Cram's First Designed Synthesis of [2.2]Paracyclophane[5]



10% overall yield

Scheme 4.2 Winberg and Fawcett's [2.2]Paracyclophane Synthesis[6]



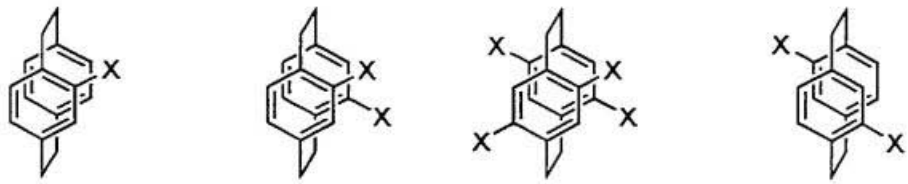
15% overall yield

Scheme 4.3 Hopf, Bohm and Kleinschroth's Synthesis of Substituted Paracyclophanes[7]

Even the Organic Syntheses preparations (outlined above) involve somewhat esoteric procedures and give low yields.[6,7] Winberg and Fawcett's [2.2]paracyclophane synthesis (Scheme 4.2) proceeds via the dimerisation of *p*-xylylene **9**. This species is created *in situ* by the Hofmann elimination of intermediate quaternary ammonium hydroxide **8**. As would be expected, much material is wasted through the formation of oligomeric byproducts. Hopf's synthesis of substituted paracyclophanes (Scheme 4.3) also proceeds via the dimerisation of a *p*-xylylene intermediate, but in this case the intermediate is generated using an unusual Diels-Alder reaction. It is impressive to note that this procedure could be used to produce as much as 60 g **15** in one run.

The high melting points of [2.2]paracyclophane and its derivatives are attributed to the rigidity and symmetry of the skeleton, which presumably manifest themselves in the crystal packing forces. Despite the inherent strain of the system, the unfunctionalised bridges remain intact up to around 200 °C, at which point one will break to yield two benzyl radicals, which may or may not then rejoin to give back the paracyclophane skeleton, depending on the circumstances. It is important to note at this point that the two benzene rings are conformationally locked relative to one another until radical formation occurs, meaning that appropriately substituted [2.2]paracyclophanes possess planar chirality,[8] and do not racemise below 200 °C (see Figure 4.2 and Scheme 4.4).[9]

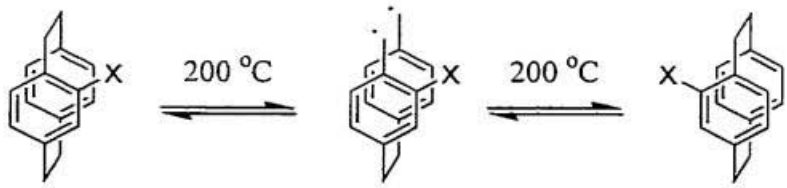
Cram went so far as to determine the critical bridge length for planar chirality in paracyclophanes, and the results serve to emphasise the resistance to rotation of the benzene rings relative to one another (see Figure 4.3).[10,11,12,13]



16 **17** **18** **19**

Chiral C_2-Symmetric and Chiral Achiral

Figure 4.2 The Geometrical Properties of [2.2]Paracyclophanes



16 **20** **21**

Scheme 4.4 Racemisation of Chiral [2.2]Paracyclophanes

22 $m = n = 2$
23 $m = n = 3$
24 $m = 3, n = 4$
25 $m = n = 4$

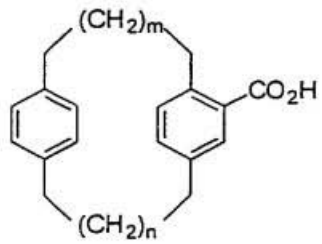
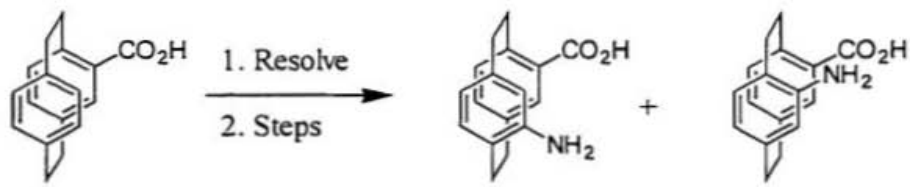


Figure 4.3 Cram's Investigation of the Barrier to Rotation in Chiral Paracyclophanes[10-13]

It was found that compounds **22**, **23** and **24** could all be resolved into their enantiomers, whereas **25** could not. Hence, at the temperatures employed for the resolutions, the aromatic rings of compounds **22** to **24** could not rotate relative to one another, while those of **25** could. This was in line with expectations from molecular models. Unfortunately this work predated NMR, precluding NMR study of the rotational process in **25**.

4.2 Previous Work on Chiral [2.2]Paracyclophanes

Figure 4.2 above demonstrates the potential of the paracyclophane skeleton as a scaffold to build chiral reagents, ligands and catalysts. The chemical inertness of the framework to most common reagents is appealing, and the temperature limitation (less than 200 °C) is unlikely to pose many problems. To exploit this system all that is required is a functional group amenable to resolution. One might expect that in the long period between Cram's chirality studies and the present day there would have been a concerted effort to capitalise on the opportunities offered by the paracyclophane skeleton. That few papers have appeared in the literature until very recently perhaps reflects the difficulties in synthesising and then resolving chiral paracyclophanes. It is also the case that for those working in the field of asymmetric organic synthesis there already exists a beguiling bounty of readily available chiral pool materials, and economically the idea of using a designed chiral auxiliary has little appeal. Two interesting examples are, however, outlined below.

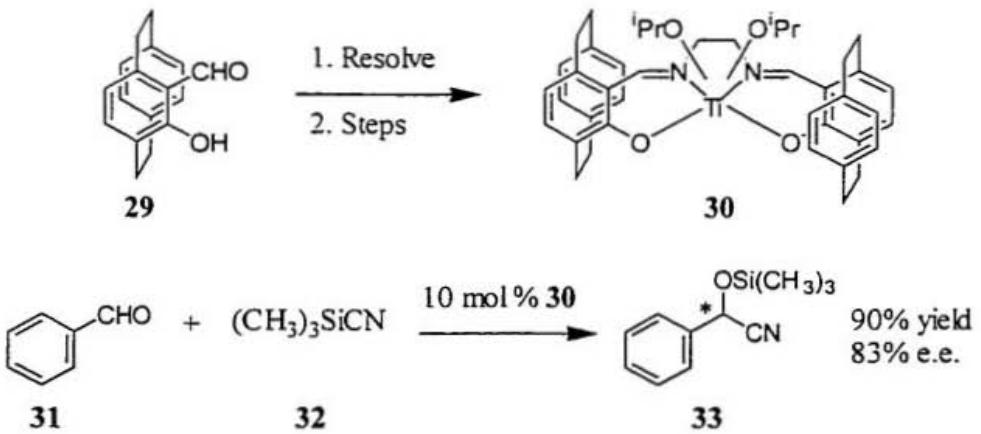


26 **27** **28**

Scheme 4.5 Pelter's Homochiral [2.2]Paracyclophane-Derived Amino Acids[14,15]

Amino acids, both naturally occurring and synthetic, are of course of great interest to the pharmaceutical industry. Peptide chemists are constantly seeking methods to control the steric and electronic relationships of portions of peptide chains. The ß-turn is a

common structural motif in peptides, and many attempts have been made to replace this with a more rigid template. Pelter's idea was that compounds **27** and **28** may be capable of providing this useful constraint in a fully predictable way, while being impervious to enzymatic degradation or racemisation. The compounds have been successfully obtained homochiral, however the hypothesis remains as yet untested.



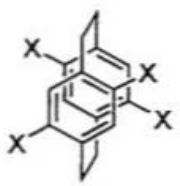
Scheme 4.6 Belokon's [2.2]Paracyclophane-Based Chiral Salen Ligand[16,17]

Belokon' previously succeeded in synthesising and resolving the hydroxy-formylparacyclophane **29**, and in using it as a chiral auxiliary for the asymmetric synthesis of amino acids.[16] In the later work depicted in Scheme 4.6 the complex **30** was generated by treatment of the salen from **29** with $Ti(O^iPr)_4$, and used as a chiral catalyst for the asymmetric trimethylsilylcyanation of benzaldehyde. The yield and e.e. of this process were good, and the catalyst could be recovered and reused.

4.3 This Work

Due to the expected difficulties in obtaining large quantities of any chiral paracyclophane, the most promising plan appeared to be to make a chemical capable of being part of a chiral-catalytic system. Thus it could be used sparingly and subsequently recycled. It seemed both sensible and most aesthetically pleasing to pursue a C_2-symmetric tetra-substituted target. Although it could be anticipated that the intermediates may be more difficult to handle, the final product would make the best possible use of the chiral skeleton (four possible reaction / coordination sites, excellent atom-efficiency),[18] and it would be expected that a single resolution could furnish all four sites homochiral. Moreover, it has been stated in the literature that the presence of a C_2-symmetry axis within a chiral auxiliary can dramatically reduce the number of possible competing diastereomeric transition states.[19] [One need not spend long in the chemical literature to uncover a host of bifunctional C_2-symmetric chiral compounds in common use.]

The following compounds were selected as likely to be of most interest:

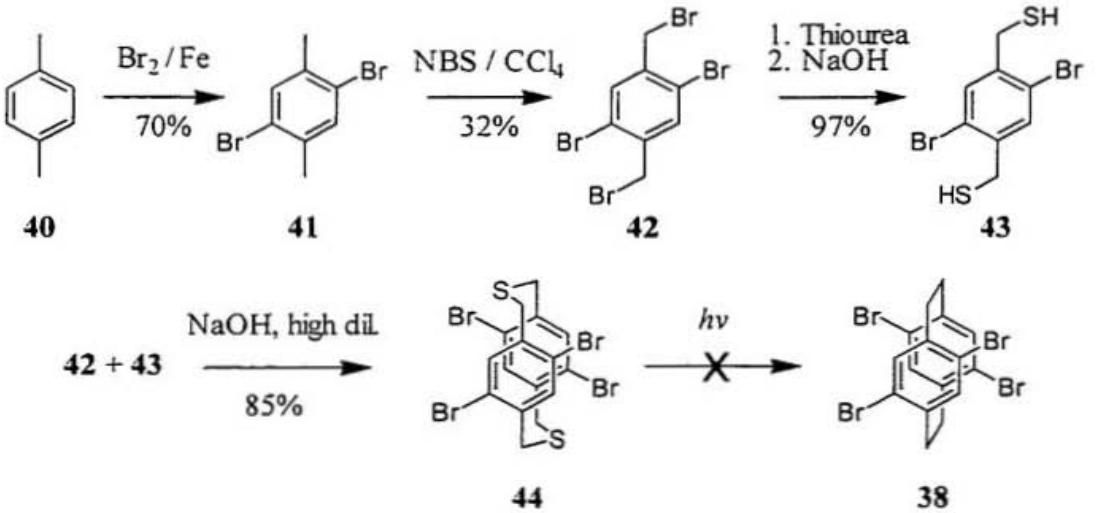


34 X = -CO_2H
35 X = -CH_2NH_2
36 X = -CH_2OH
37 X = -PPh_2
38 X = -Br
39 X = -CN

Figure 4.4 Target Molecules

It was initially hoped that all of the compounds **34-37** could be accessed from the common precursor, tetrabromide **38**,[20] the route to **34**, **35** and **36** requiring the common intermediate **39**, which might itself have some applications.[21]

The synthesis began with the treatment of *p*-xylene **40** with bromine in the presence of iron filings to give the doubly ring-brominated product **41** in 70% yield after crystallisation. Benzylic bromination of **41** under standard free radical conditions provided a 32% yield of **42**. Dithiol **43** was produced in the customary fashion via the bis(isothiouronium) salt intermediate.[22] The dibromide and dithiol were then coupled at high dilution in the presence of base to produce dithiacyclophane **44**.



Scheme 4.7 Attempted Synthesis of Tetrabromide **38** via Photolysis

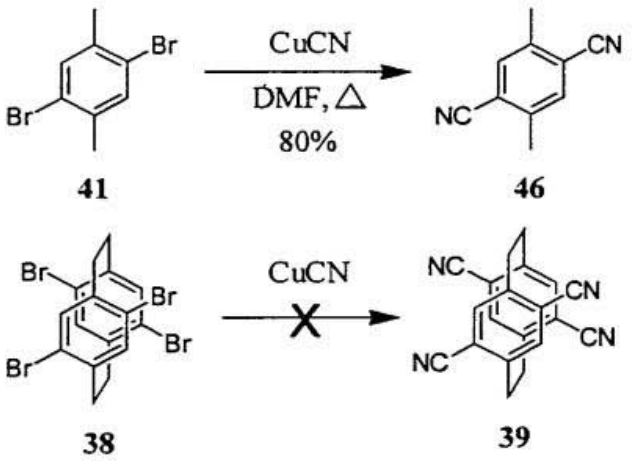
In the initial, larger-scale preparation of **44** the yield of this compound could not be ascertained due to solubility problems. The low solubility and low polarity of **44** cause difficulties with column chromatography, while crystallisation is also problematic – the compound being extremely slow to dissolve in any amount of the common solvents, and then very reluctant to crystallise. These properties are not fully understood and are partly attributed to the high symmetry of the molecule. Photolytic removal of sulphur from **44** in trimethyl phosphite failed, delaying progress for some time.[23,24] This was disappointing,

since we had earlier produced the parent molecule **1** in 65% yield by a directly analogous reaction. It was eventually found that the disulphone **45**, easily obtained by *m*-CPBA oxidation of **44** (Scheme 4.8), could be converted to cyclophane **38** by an FVT reaction using the simplified apparatus described in Chapter 2.[25,26] As usual, the oxidation step was roughly quantitative. The FVT experiment was not amenable to the scale we required, necessitating that it be run eight times. The crude material from these runs was combined and chromatographed together, showing that the relatively high yield of 55% was indeed reproducible.

44 **45** **38**

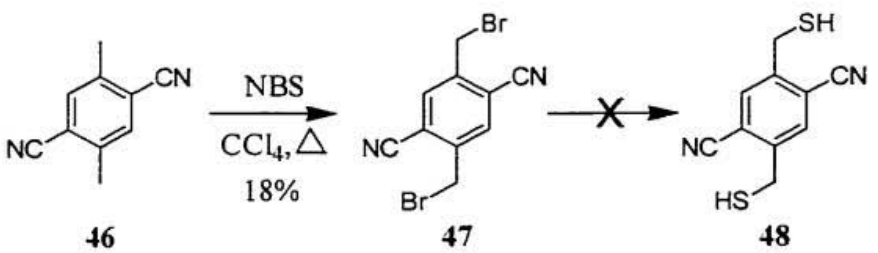
Scheme 4.8 Successful Synthesis of Tetrabromide **38** Using FVT

As mentioned earlier, compounds **34-36** were expected to be obtained via the tetracyano compound **39**. The Rosenmund von Braun reaction had already proved to be very successful on the open model compound **41**, yields of 80% being obtained on a 20 g scale with CuCN in DMF (see Scheme 4.9).[27] However, in the case of the cyclophane **38** the reaction was totally unsuccessful, even when higher-boiling solvents were used. [Cram had used CuCN in quinoline at 225 °C to effect some stubborn transformations, however there is no description of an attempted cyanation of **38**, which was first synthesised in the same paper.][20]



Scheme 4.9 Contrasting Rosenmund von Braun Reactions of **41** and **38**

Another avenue explored was preparation of **39** by a more direct method from **46** itself, which was readily available as shown in Scheme 4.9.

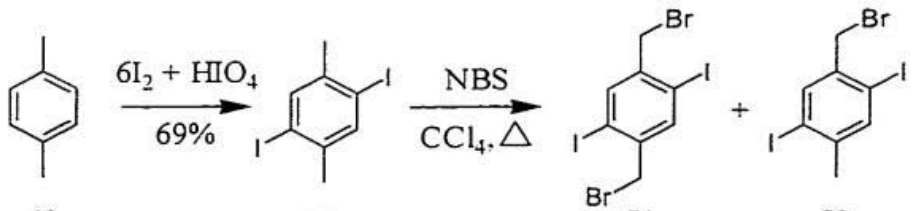


Scheme 4.10 Attempted Preparation of the Dicyanodithiol **48**

The yield in the NBS bromination reaction of **46** was poor (Scheme 4.10), partly due to difficulties in separating the desired product **47** from impurities, and no conditions could be found which would enable transformation of this dibromide to the desired dithiol **48**. The prospects for successfully conducting the required subsequent high-dilution coupling were not good either, due to the likely incompatibility of the nitrile groups with the proximal thiolate anions which would be generated, so this course of investigation was

abandoned. Cursory attempts to employ the $Na_2S{\cdot}Al_2O_3$ coupling[28] to *p*-di(bromomethyl)benzenes analogous to **47** were also unsuccessful. It seems so far that this useful methodology is limited to the less sterically demanding metacyclophanes.

For these reasons the focus shifted to the preparation of the tetraiodoparacyclophane **49** (Scheme 4.13). It was reasoned that the iodine atoms would be more easily substituted than the bromine atoms of **38** using a Rosenmund von Braun reaction,[26] a Heck-type reaction[29] or a lithiation.[30] Once again the starting material was the cheap and readily available *p*-xylene **40**. Diiodination using the Organic Syntheses procedure[31] was easily conducted, purification being readily achieved by crystallisation from acetone to give a 69% yield on a 20 g scale. However, the NBS reaction of **50** turned out to be unexpectedly problematic.

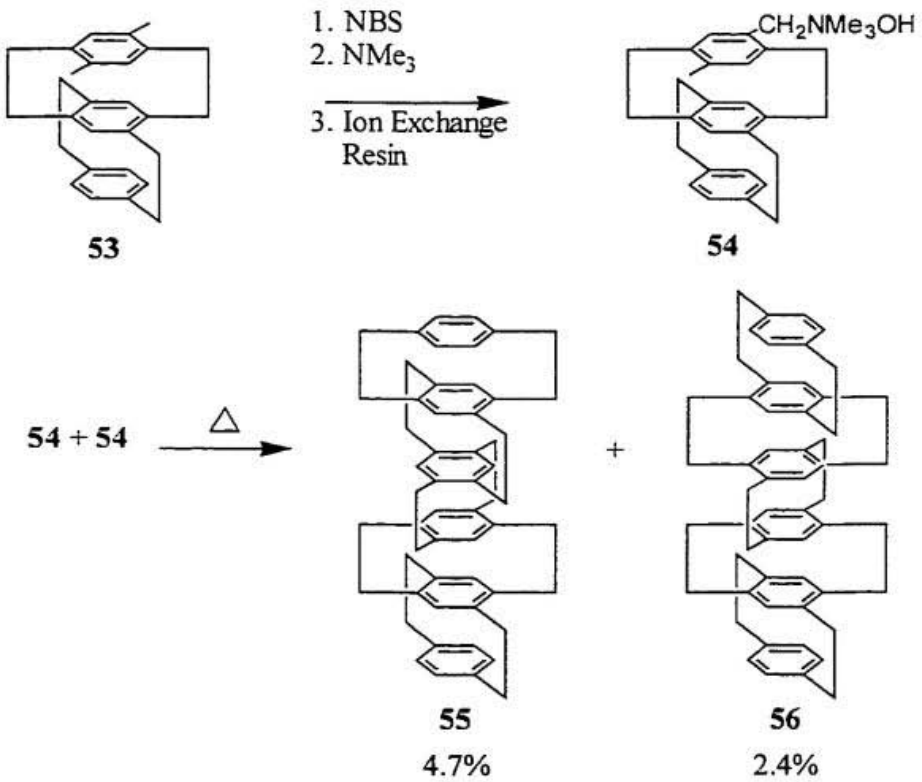


40 **50** **51** 6% **52** 49%

Scheme 4.11 Preparation of Monobromomethyl Intermediate **52**

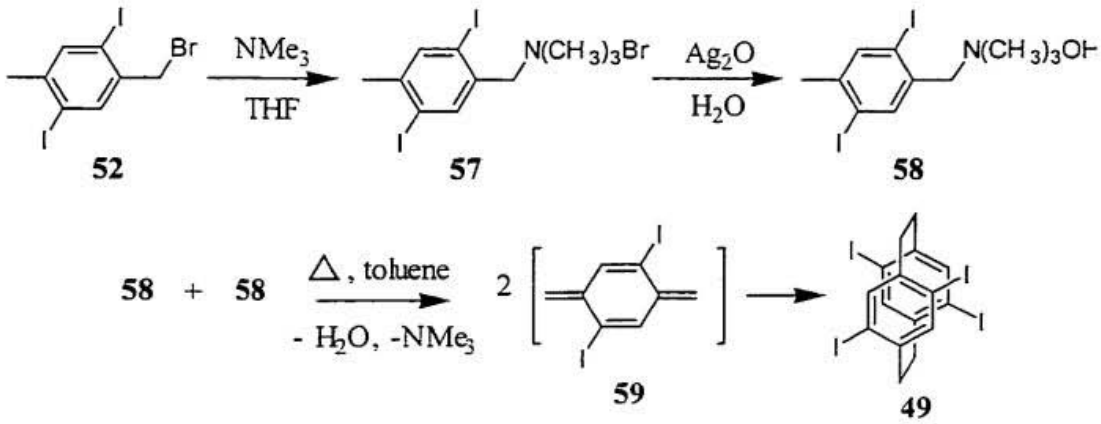
The yield of the desired *p*-di(bromomethyl)benzene **51** was very poor, and neither modifying the solvent nor changing the brominating agent solved this problem. It is not clear exactly why no more **51** is formed in this reaction. After fruitless attempts to find an alternative route to **51** a different approach to the cyclophane was envisaged, which required not the troublesome dibromo compound **51** but the monobromo compound **52**. In

fact **52** was the major product from the NBS bromination of **50**, and could be obtained almost pure by crystallisation. Total purification of **52** was actually quite problematic, as will be mentioned below. The new strategy used the methodology of the Organic Syntheses preparation of paracyclophane (**1**) (see above).[6] Hopf's elegant method for producing tetrasubstituted paracyclophanes was unfortunately not amenable to the substitution pattern we required.[7] Although the tetraiodocyclophane we had targeted would be significantly more sterically hindered than **1**, the same Hofmann elimination strategy has been successfully applied by Misumi to the synthesis of some impressive multi-layer paracyclophanes with the same substitution pattern (Scheme 4.12).[32,33]



Scheme 4.12 Misumi's Sixfold-Layered Cyclophanes[32,33]

Scheme 4.12 above shows two of the spectacular sixfold-layered cyclophanes made using this approach. Using the same methodology Misumi has apparently achieved a yield of 27% for the Hofmann elimination forming the tetramethylparacyclophane with the same substitution pattern as our own.[33] Thus the synthesis of cyclophane **49** progressed parallel to the Winberg and Fawcett Organic Syntheses procedure (Scheme 4.2)[6] as shown in Scheme 4.13.



13% overall yield

Scheme 4.13 Successful Preparation of Tetraiodoparacyclophane **49**

Quaternary ammonium salt **57** was obtained by treatment of **52** with NMe_3 in THF. [This solvent was used due to the low solubility of **57** in diethyl ether.] Treatment of the crude product with freshly prepared Ag_2O[6] afforded the quaternary ammonium hydroxide **58**. This compound was expected to be sensitive to CO_2, and was hence used immediately. It was found that **58** was much less water-soluble than **8** used by Winberg and Fawcett, meaning that the final Hofmann elimination / dimerisation had to be conducted at much higher dilution. The series of reactions shown in Scheme 4.13 was carried out twice, once on a 10 g scale using slightly impure **52** obtained from a crystallisation of the crude

product from the NBS reaction (Scheme 4.11), and once using analytically pure **52**. A much higher overall yield of 26% (after chromatography) was obtained from the former series of reactions, but NMR revealed the presence of at least one impurity with the same R_f as the product. Crystallisation from several different solvents failed to effectively purify this sample of **49**. The second run was conducted on a considerably smaller scale, and the Hofmann elimination / dimerisation was carried out at higher dilution in the hope that this would discourage the competing oligomerisation reaction. In the event a reduced yield of 13% was obtained, although in this case purification of **49** was possible. While it is gratifying that this yield is in fact greater than that obtained in Winberg and Fawcett's Organic Syntheses paper, it seems possible that a higher yield may be possible for the series above, perhaps by finding the optimal concentration for the final reaction.

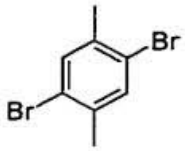
Unfortunately it has not been possible to finish this project. Useable routes have been developed to cyclophanes **38** and **49**, but successful substitution of the halogen atoms by other functional groups and resolution of the resulting products has not been achieved. It is anticipated that **49** will prove to be a better substrate for substitution reactions than **38**, and it is hoped that optimisation of the route may significantly increase the overall yield of **49**.

4.4 Experimental

General Procedures

For general procedures please refer to the section in Chapter 2.

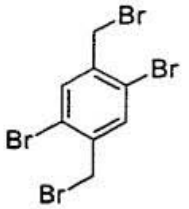
2,5-Dibromo-*p*-xylene (41)



41

Neat *p*-xylene (106.17 g, 1.00 mol) and iron filings (2.00 g, catalytic) were placed in a three-necked 1L round bottomed flask equipped with a mechanical stirrer and cooled in an ice bath. Bromine (112.8 mL, 2.20 mol) was added dropwise over a period of 1 h. Stirring was continued for a further 0.5 h with stoppers removed to aid evaporation of excess bromine and HBr. Dichloromethane (350 mL) was added to dissolve the product, and the resulting solution was washed with saturated sodium metabisulphite (2x150 mL), dried ($MgSO_4$) and evaporated to give crude **41** (247.65 g, 94%). Recrystallisation from ethanol gave pure **41** (183.67 g, 70%). The colourless crystals obtained (mp 73-74 °C, lit.[34] mp 73-74 °C) showed ^{1}H NMR spectral data consistent with the literature.[34]

1,4-Dibromo-2,5-bis(bromomethyl)benzene (42)

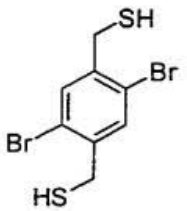


42

Compound **41** (33.37 g, 126.4 mmol) and NBS (47.48 g, 266.8 mmol) were combined in carbon tetrachloride (1 L) and the suspension heated to reflux. A spatula tip of dibenzoyl peroxide was then added and a bright light shone on the flask to promote radical formation. Heating was continued for a period of 2 h. Evaporation of the solvent and

chromatography (neat hexanes) followed by crystallisation from heptane produced pure **42** (17.14 g, 32%). The colourless crystals obtained (mp 160-161 °C, lit.[35] mp 161-162 °C) showed ^{1}H NMR spectral data consistent with the literature[35] δ 7.66 (s, 2H), 4.51 (s, 4H).

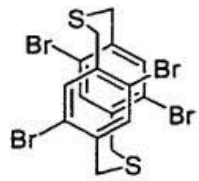
1,4-Dibromo-2,5-bis(thiomethyl)benzene (43)



43

Compound **42** (8.57 g, 20.3 mmol) and thiourea (3.17 g, 41.6 mmol) were dissolved in 95% ethanol (500 mL) and the solution refluxed for 5.5 h. The solvent was evaporated and the crude bis(isothiouronium) salt thus formed dissolved in degassed water (500 mL), NaOH added (4.06 g, 101.5 mmol) and the mixture refluxed for 2h. The solution was acidified to pH 2 with H_2SO_4, extracted with dichloromethane (1x200 mL, 2x100 mL), dried (Na_2SO_4) and evaporated to give pure **43** (6.47 g, 97%). An analytical sample was obtained by chromatography (4:1 hexanes:dichloromethane): mp 112-113 °C; ^{1}H NMR δ 7.57 (s, 2H), 3.76 (d, J = 7.8 Hz, 4H), 1.99 (t, J = 8.5 Hz, 2H); ^{13}C NMR δ 141.1, 134.0, 122.6, 28.8; MS *m/z* (%) 330 (18), 328 (M^+, 1x^{79}Br, 1x^{81}Br, 34), 326 (16), 297 (52), 295 (100), 293 (52), 264 (24), 262 (48), 260 (25), 134 (27), 102 (55). Anal. Calcd for $C_8H_8Br_2S_2$: C, 29.29; H, 2.46. Found: C, 28.99; H, 2.37.

5,8,14,17-Tetrabromo-2,11-dithia[3.3]paracyclophane (44)



44

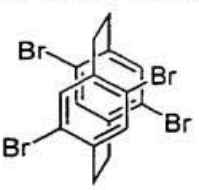
Dithiol **43** (0.547 g, 1.67 mmol) and dibromide **42** (0.703 g, 1.67 mmol) were dissolved in benzene (100 mL). This mixture was added dropwise to a mechanically-stirred solution of NaOH (0.333 g, 8.33 mmol) in a mixture of 95% ethanol (840 mL) and water (160 mL) over a period of 5 h. The reaction mixture was allowed to stir for a further 16 h, then the solvents were evaporated and the residue taken up in chloroform (200 mL) and saturated ammonium chloride solution (100 mL). After separation the aqueous layer was extracted with chloroform (50 mL) and the combined organics dried ($MgSO_4$), evaporated and chromatographed (4:1 hexanes:dichloromethane, then 3:1 hexanes:dichloromethane and finally neat dichloromethane) to give almost pure **44** (0.836 g, 85%). An analytical sample was obtained by further chromatography of a small sample eluting with 4:1 hexanes:dichloromethane: mp 255-258 °C; ^{1}H NMR δ 7.47 (s, 4H), 3.95 (AB half spectrum, J_{AB} = 15.3 Hz, 4H), 3.69 (AB half spectrum, J_{AB} = 15.3 Hz, 4H); ^{13}C NMR δ 136.3, 134.2, 123.6, 37.0; MS *m/z* (%) 590 (32), 588 (M^+, 2x^{79}Br, 2x^{81}Br, 45), 586 (32), 509 (41), 507 (43), 263 (49), 215 (35), 213 (32), 171 (35), 169 (39), 166 (49), 134 (57), 102 (92), 45 (100). Anal. Calcd for $C_{16}H_{12}Br_4S_2$: C, 32.68; H, 2.06. Found: C, 32.39; H, 1.84.

5,8,14,17-Tetrabromo-2,2,11,11-tetraoxo-2,11-dithia[3.3]paracyclophane (45)

45

To a stirred solution of dithiacyclophane **44** (0.408 g, 0.694 mmol) in chloroform (160 mL) was added 50-60% *m*-CPBA (0.960 g, 2.78 mmol based on 50%). The reaction was allowed to stir for 3 d, when further *m*-CPBA (0.250 g, 0.724 mmol based on 50%) was added. After 3 d the reaction mixture was washed with 2M potassium carbonate solution, the aqueous extracted with chloroform (2x50 mL), the combined organics washed with brine (100 mL), dried ($MgSO_4$) and evaporated to give crude **45** (0.440 g, 97%) as a white powder: mp >300 °C; ^{1}H NMR (DMSO-d_6) δ 8.05 (s, 4H), 4.85 (AB half spectrum, J_{AB} = 14.7 Hz, 4H), 4.71 (AB half spectrum, J_{AB} = 14.7 Hz, 4H); ^{13}C NMR (DMSO-d_6) δ 134.5, 131.7, 123.7, 59.4; MS *m/z* (%) (M^+ not found), 524 (M - $2SO_2$, 2x^{79}Br, 2x^{81}Br, 9), 264 (39), 262 (71), 260 (40), 200 (31), 102 (100). As usual, further purification of the disulphone was impractical, and the crude material was used directly. It should be noted that subsequent work has shown that the prolonged stirring and second addition of *m*-CPBA is unnecessary.

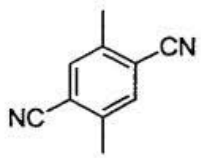
4,7,12,15-Tetrabromo[2.2]paracyclophane (38)



38

Disulphone **45** (2.452 g, 3.76 mmol) was subjected to our simplified FVT procedure as described in Chapter 2. The material was divided into eight portions and each portion subjected to two iterations of the FVT process. The crude material obtained from the FVT reactions was combined and chromatographed (4:1 hexanes:dichloromethane) to give pure **38** (1.082 g, 55%). An analytical sample was obtained by recrystallisation from ethanol. The white crystals obtained (mp 167-169 °C, lit.[20] mp 165.5-167.5 °C) showed ^{1}H NMR spectral data consistent with the literature[20] δ 7.20 (s, 4H), 3.29-3.18 (AA'BB' half spectrum, 4H), 3.04-2.93 (AA'BB' half spectrum, 4H).

2,5-Dicyano-*p*-xylene (46)

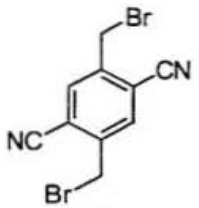


46

Compound **41** (40.0 g, 152 mmol) was dissolved in DMF (600 mL) and CuCN (32.0 g, 357 mmol) was added. The stirred mixture was heated to 160 °C for 17 h, cooled, and added to 0.88 ammonia (1.5L). To the resulting mixture was added $FeCl_3$ (58 g, 358 mmol) in water (400 mL) and stirring was continued for 1 h. Dichloromethane was then added and after 20 min further stirring the mixture was subjected to Buchner filtration, washing the residue through with dichloromethane (3x250 mL). After separation the aqueous layer was further extracted with dichloromethane (1x500 mL, 1x250 mL) and the combined organic layers washed with water (500 mL) and 1M HCl (3x330 mL), dried (Na_2SO_4) and evaporated. The crude material so obtained (48.6 g, 205%) was obviously still contaminated with a large amount of DMF. Recrystallisation from ethanol provided

pure **46** (16.6 g, 70%). Further material was obtained by chromatography and crystallisation of the residue affording an additional 2.6 g **46** (11%) for a total yield of 81%. The white crystals obtained (mp 203-205 °C, lit.[36] mp 213-215 °C) showed ^{1}H NMR spectral data consistent with the literature[36] δ 7.56 (s, 2H), 2.55 (s, 6H).

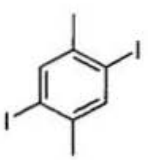
2,5-Bis(bromomethyl)-1,4-dicyanobenzene (47)



47

Compound **46** (15.57 g, 100 mmol) and NBS (35.49 g, 200 mmol) were combined in carbon tetrachloride (250 mL) and the suspension heated to reflux. A spatula tip of dibenzoyl peroxide was then added and a bright light shone on the flask to promote radical formation. Heating was continued for a period of 1.5 h. The boiling suspension was filtered and the product allowed to crystallise. A second crystallisation produced pure **47** (5.50 g, 18%). The white crystals obtained (mp 156-158 °C, lit.[37] mp 164 °C) showed ^{1}H NMR spectral data consistent with structure **47** δ 7.87 (s, 2H), 4.62 (s, 4H).

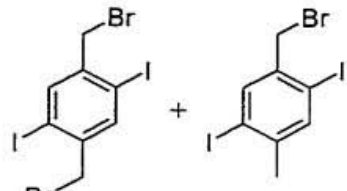
2,5-Diiodo-*p*-xylene (50)



50

A mixture of *p*-xylene (10.00g, 94.2 mmol), $HIO_4 2H_2O$ (8.95 g, 39.3 mmol), iodine (19.05 g, 75.1 mmol), water (37.5 mL), H_2SO_4 (5.5 mL) and CH_3CO_2H (185 mL) was heated with stirring (bath temperature 80-100 °C) for 3.5 h. Water (250 mL) was then added and the flask cooled in ice water to promote crystallisation of the product. The crude material was filtered off, washed with water (2x200 mL, 1x100 mL) and recrystallised from acetone to give pure **50** (23.33 g, 69%). The white crystals obtained (mp 103-104 °C, lit.[38] 102-103 °C) showed ^{1}H NMR spectral data consistent with structure **50** δ 7.64 (s, 2H), 2.33 (s, 6H).

2,5-Bis(bromomethyl)-1,4-diiodobenzene (51) and 2-(bromomethyl)-5-methyl-1,4-diiodobenzene (52)

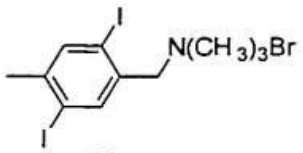


51 **52**

Compound **50** (3.73 g, 10.4 mmol) and NBS (3.89 g, 21.9 mmol) were combined in carbon tetrachloride (150 mL) and the suspension heated to reflux. A spatula tip of dibenzoyl peroxide was then added and a bright light shone on the flask to promote radical formation. Heating was continued for a period of 8 h. Evaporation of the solvent and chromatography (neat hexanes) produced **52** (2.24 g, 49%). Further elution (2:1 hexanes:dichloromethane) gave compound **51** (0.32 g, 6%). An analytical sample of **52** was obtained by further chromatography (hexanes) and two crystallisations from ethanol: mp 160-161 °C; ^{1}H NMR δ 7.86 (s, 1H), 7.70 (s, 1H), 4.49 (s, 2H), 2.37 (s, 3H); ^{13}C

NMR δ 143.8, 140.3, 139.9, 139.4, 100.8, 99.4, 37.1, 27.2; MS *m/z* (%) 438 (M^+, ^{79}Br, 8), 436 (8), 358 (11), 357 (100), 230 (18), 103 (19). Anal. Calcd for C_8H_7BrI: C, 22.00; H, 1.62. Found: C, 21.71; H, 1.40. An analytical sample of **51** was obtained by two crystallisations from chloroform: mp 230-231 °C (lit.[39] mp 217-223 °C); ^1H NMR (DMSO-d_6) δ 8.11 (s, 2H), 4.67 (s, 4H); ^{13}C NMR (DMSO-d_6) δ 142.4, 140.9, 100.9, 37.7; MS *m/z* (%) 516 (M^+, $1x^{79}Br$, $1x^{81}Br$, 13), 437 (72), 435 (73), 178 (15), 127 (22), 102 (100). Anal. Calcd for $C_8H_6BrI_2$: C, 18.63; H, 1.17. Found: C, 18.43; H, 0.93.

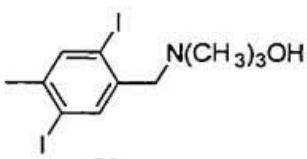
[(2,5-Diiodo-4-methylphenyl)methyl]trimethylammonium bromide (57)



57

Compound **52** (2.50 g, 5.72 mmol) was dissolved in anhydrous THF (100 mL) and cooled with mechanical stirring in an ice salt bath. A solution of trimethylamine (3.2 g, 54.1 mmol) in anhydrous THF (50 mL) was added via cannula over a period of 5 min. The reaction was allowed to warm slowly to room temperature and was stirred for 27 h, at which point the solvent and excess trimethylamine were evaporated to give crude salt **57**. A small sample (50 mg) was removed, the remainder used directly in the next step.

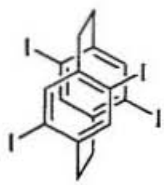
[(2,5-Diiodo-4-methylphenyl)methyl]trimethylammonium hydroxide (58)



58

Crude salt **57** (max. 5.62 mmol) was dissolved in hot water (100 mL) which had previously been distilled under N_2. The mechanically stirred solution was cooled in a cold water bath and freshly prepared Ag_2O (max. 5.71 mmol) was added in one portion. The reaction was stirred 1.5 h filtered through a sinter funnel. The residue was washed with water (3x17 mL), and the resulting solution of crude **58** used directly in the next step.

4,7,12,15-Tetraiodo[2.2]paracyclophane (49)



49

To the solution of crude **58** in water (150 mL) produced above (max. 5.62 mmol) was added toluene (150 mL) and phenothiazine (a polymerisation inhibitor) (75 mg). The mixture was refluxed with mechanical stirring under Dean-Stark conditions. After 2 h 100 mL water had been removed, and additional toluene (100 mL) was added. Azeotropic removal of water was complete after 1 h further heating, and the reaction was refluxed for a further 14 h to ensure it proceeded to completion. The hot reaction mixture was then filtered and the residue extracted with boiling toluene (2x100 mL). The solvent was evaporated, and the residue chromatographed (hexanes) to give pure **49** (0.266 g, 13%) mp 215-217 °C; ^{1}H NMR δ 7.44 (s, 4H), 3.11-3.08 (m, 8H); ^{13}C NMR δ 143.5, 139.0, 102.7, 35.7; MS *m/z* (%) (M+ not found), 357 (11), 356 (M^+ / 2, 100), 202 (11), 102 (80). Anal. Calcd for $C_{16}H_{12}I_4$: C, 27.00; H, 1.70. Found: C, 26.85; H, 1.51.

4.5 References

[1] Brown, C.J.; Farthing, A.C. *Nature (London)* **1949**, *164*, 915-916.

[2] Pellegrin, M.M. *Recl. Trav. Chim. Pays-Bas* **1899**, *18*, 457-465.

[3] Baker, W.; Banks, R.; Lyon, D.R.; Mann, F.G. *J. Chem. Soc.* **1945**, 27-30.

[4] Errede, L.A.; Gregorian, R.S.; Hoyt, J.M. *J. Am. Chem. Soc.* **1960**, *82*, 5218-5223.

[5] Cram, D.J.; Steinberg, H. *J. Am. Chem. Soc.* **1951**, *73*, 5691-5704.

[6] Winberg, H.E.; Fawcett, F.S. *Organic Syntheses*; Wiley: New York, 1973, Collect. Vol. V, 883-886.

[7] Hopf, H.; Bohm, I; Kleinschroth, J. *Organic Syntheses*; Wiley: New York, 1990, Collect. Vol. VII, 485-490.

[8] For a review of planar chirality, see Wilen, E.L.; Wilen, S.H. (Eds.) *Stereochemistry of Organic Compounds (Wiley, New York)* **1994**, 1166-1170.

[9] Reich, H.J.; Cram, D.J. *J. Am. Chem. Soc.* **1969**, *91*, 3517-3526.

[10] Cram, D.J.; Allinger, A.L. *J. Am. Chem. Soc.* **1955**, *77*, 6289-6294.

[11] Sheehan, M.; Cram, D.J. *J. Am. Chem. Soc.* **1969**, *91*, 3544-3552.

[12] Cram, D.J.; Wechter, W.J.; Kierstead, R.W. *J. Am. Chem. Soc.* **1958**, *80*, 3126-3133.

[13] Cram, D.J.; Kierstead, R.W. *J. Am. Chem. Soc.* **1955**, *77*, 1186-1190.

[14] Synthesis and resolution of acid **26**: Falk, H.; Reich-Rohrwig, P.; Schlögl, K. *Tetrahedron* **1970**, *26*, 511-527.

[15] Pelter, A.; Crump, R.A.N.C.; Kidwell, H. *Tetrahedron: Asymmetry* **1997**, *8*, 3873-3880.

[16] Rozenberg, V.; Kharatinov, V.; Antonov, D.; Sergeeva, E.; Aleshkin, A.; Ikonnikov, N.; Orlova, S.; Belokon', Yu. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 91-92; Antonov, D.; Belokon', Yu.; Ikonnikov, N.; Orlova, S.; Pisarevsky, A.; Raevsky, N.; Rozenberg, V.; Sergeeva, E.; Sruchkov, Yu.; Tararov, V.; Vorotsov, E. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1873-1879.

[17] Belokon', Yu.; Moscalenko, M.; Ikonnikov, N.; Yashkina, L.; Antonov, D.; Vorontsov, E.; Rozenberg, V. *Tetrahedron: Asymmetry*, **1997**, *8*, 3245-3250.

[18] This term was used as the framework of only 16 carbon atoms can provide 4 chiral sites. Trost's "atom economy" term cannot be strictly applied in this context. [Trost, B.M. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259-281.]

[19] Whitesell, J.K. *Chem. Rev.* **1989**, *89*, 1581-1590.

[20] Reich, H.J.; Cram, D.J. *J. Am. Chem. Soc.* **1969**, *91*, 3527-3533.

[21] Aromatic nitriles have been found to form interesting complexes with silver ions. See Wu, H.-P.; Janiak, C.; Rheinwald, G.; Lang, H. *J. Chem. Soc., Dalton Trans.*, **1999**, 183-190 and references within; Suenaga, Y.; Kuroda-Sowa, T.; Munakata, M.; Maekawa, M. *Polyhedron*, **1998**, *18*, 191-195.

[22] Urquhart, G.G.; Gates, J.W., Jr.; Connor, R. *Organic Syntheses*; Wiley: New York, 1955, Collect. Vol. III, 363-365.

[23] For the first report of the photochemical extrusion of sulphur in the presence of trivalent phosphorus compounds see Corey, E.J.; Block, E. *J. Org. Chem.* **1969**, *34*, 1233-1240.

[24] For the first use of this useful transformation in the cyclophane context see Boekelheide, V.; Reingold, I.D.; Tuttle, M *J. Chem. Soc., Chem. Commun.* **1973**, 406-407.

[25] For a review of the flash vacuum thermolysis of disulphones see Vögtle, F.; Rossa, L. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 515-529.

[26] For a general review of extrusion reactions of organochalcogen compounds see Guziec, F.S. Jr.; Sanfilippo, L.J. *Tetrahedron* **1988**, *44*, 6241-6285.

[27] Friedman, L.; Schechter, H. *J. Org. Chem.* **1961**, *26*, 2522-2524. See also Ellis, G.P.; Romney-Alexander, T.M. *Chem. Rev.* **1987**, *87*, 779-794.

[28] Bodwell, G.J.; Houghton, T.J.; Koury, H.E.; Yarlagadda, B. *Synlett* **1995**, 751-752.

[29] For a recent review of the Heck reaction see de Meijere, A.; Meyer, F.E. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2379-2411.

[30] For an example of a successful perlithiation of a compound containing four brominated aromatic rings, see Vögtle, F.; Eisen, N.; Franken, S.; Büllesbach, P.; Puff, H. *J. Org. Chem.* **1987**, *52*, 5560-5564. For the preparation of 1,3,5-trilithiobenzene see Rot, N.; Bickelhaupt, F. *Organometallics* **1997**, *16*, 5027-5031.

[31] Suzuki, H. *Organic Syntheses*; Wiley: New York, 1988, Collect. Vol. VI, 700-704.

[32] Otsubo, T.; Tozuka, Z.; Mizogami, S.; Sakata, Y.; Misumi, S. *Tetrahedron Lett.* **1972**, *13*, 2927-2930.

[33] The yields here are taken from *Organic Chemistry. A series of monographs*, Volume 45, "Cyclophanes", Wasserman, H.H., Ed.; Academic Press: New York, 1983; Chapter

10. Misumi successfully increased the yield of the Hofmann elimination subsequent to his first synthesis of these compounds.

[34] Aldrich catalogue.

[35] McCoy, R.K.; Karasz, F.E.; Sarker, A.; Lahti, P.M. *Chem. Mater.* **1991**, *3*, 941-947.

[36] Suzuki, H.; Hanafusa, T. *Synthesis* **1974**, 53-55.

[37] Staab, H.A.; Taglieber, V. *Chem. Ber.* **1977**, *110*, 3366-3376.

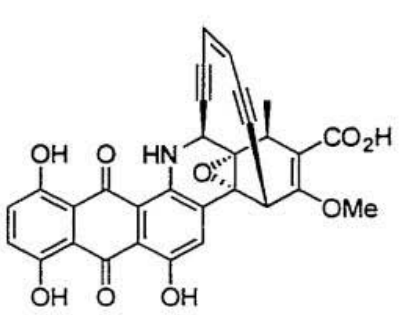
[38] Merkushev, E.B.; Simakhina, N.D.; Koveshnikova, G.M. *Synthesis* **1980**, 486-487.

[39] Wheland, R.C.; Martin, E.L. *J. Org. Chem.* **1975**, 3101-3109.

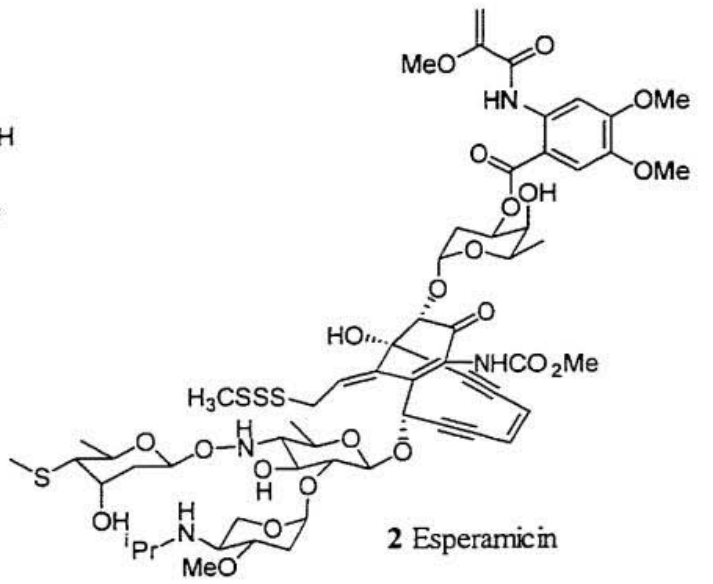
Synthesis and Study of Novel Alkyne- and Enediyne-Containing Cyclophanes

5.1 Introduction

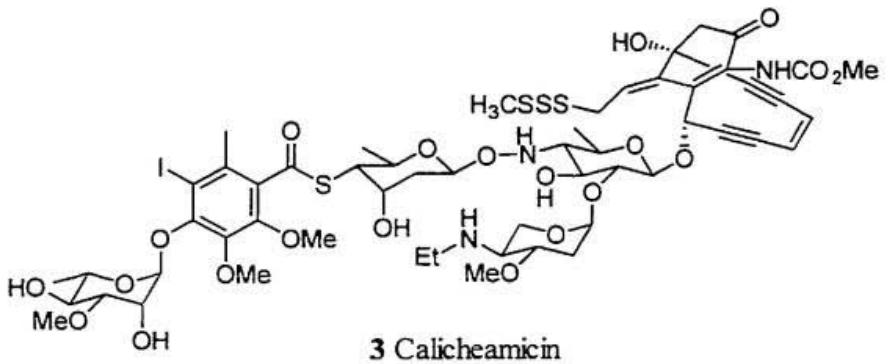
A huge volume of literature has been generated over the last few years in the areas of enediyne and general alkyne chemistry.[1] The discovery of various enediyne-containing natural products possessing very interesting biological properties has prompted an immense effort from some of organic chemistry's strongest research groups towards not only the synthesis, but also the fuller understanding of these fascinating compounds.[2]



1 Dynemicin



2 Esperamicin



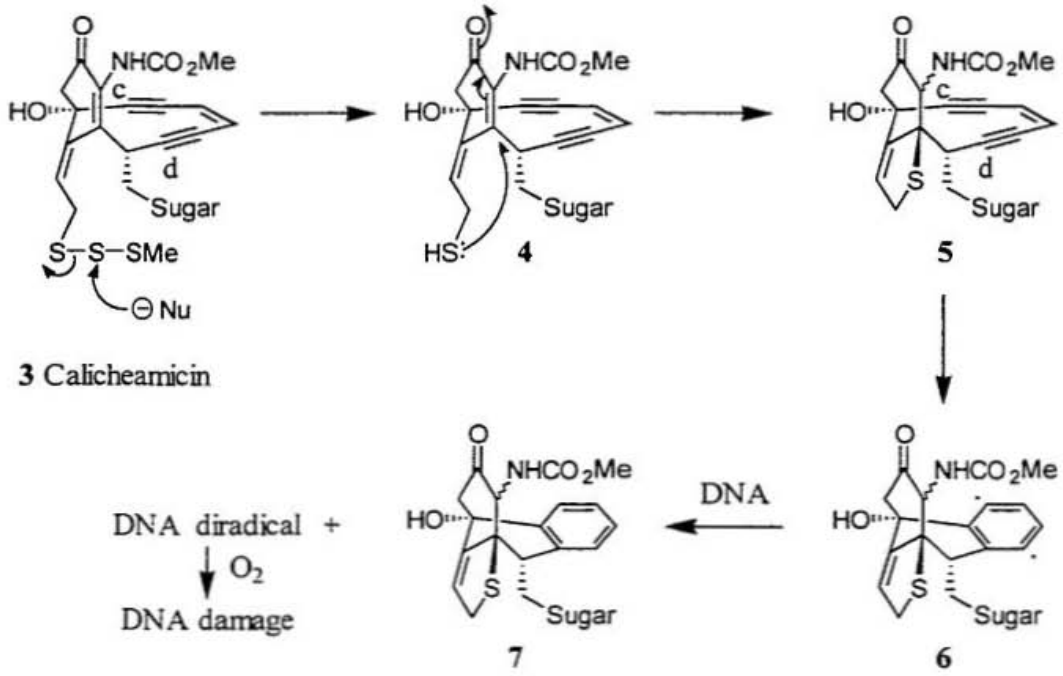
3 Calicheamicin

Figure 5.1 The Most Famous Enediyne Natural Products

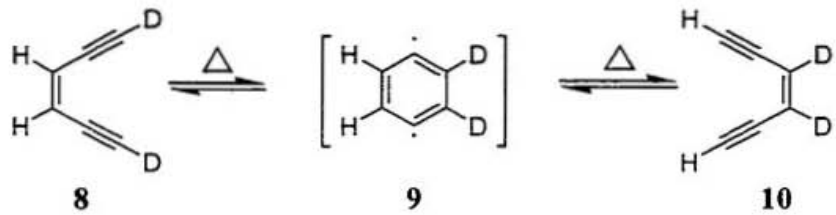
Among the compounds which were first to attract the chemical community's attention were **1** dynemycin A,[3] **2** esperamycin A_1[4] and **3** calicheamicin γ_1^I.[5] [The phrase "natural products" above is used loosely, as calicheamicin γ_1^I is an artificially engineered, more active form of the true natural product.[6] The latter contains a bromine atom in place of the iodine of **3**.] All three were very thoroughly studied due to both natural curiosity at their interesting and almost unprecedented molecular architecture, and to their powerful cytotoxic activity which presented the possibility of an anti-cancer drug. [Cytotoxins, by definition, kill cells, however they sometimes show selectivity such that the more rapidly reproducing cancer cells are killed more rapidly.[7] In the case of calicheamicin in particular, it was thought that particularly good selectivity might be possible through coordination of one or more functional groups with the DNA.]

Scheme 5.1 below shows the presumed mode of action of calicheamicin.[8] The key step, **5** → **6**, is a Bergman reaction (see Scheme 5.2).[9] This transformation, which had long languished in relative obscurity, has proved to be responsible for the mode of action of a whole series of biologically active, naturally-occurring compounds. The mechanism of this reaction was postulated by Bergman in 1973 to account for the gas phase thermal equilibration of enediynes **8** and **10**. The biradical nature of the intermediate was later supported by CIDNP.[10] Study of a wide range of enediynes led to the conclusion that the activation energy of this reaction is largely determined by the distance between the termini of the enediyne unit, shown here as c and d.[11] The shorter the cd distance, the lower the activation energy.[12] It has been calculated (MM2-level calculations using W.C. Still's Macromodel) that the cd distance in **3** is 3.35Å, while in the so-called "triggered

enediyne" **5** it is 3.16Å.[8] It is postulated that a nucleophilic species attacks the middle sulphur of the unusual trisulphide group, creating a thiol or thiolate functionality perfectly set up for an intramolecular Michael reaction. This reaction gives rise to the triggered enediyne **5**, which readily undergoes the Bergman reaction to give the benzenoid diradical **6** which itself goes on to cause DNA damage.



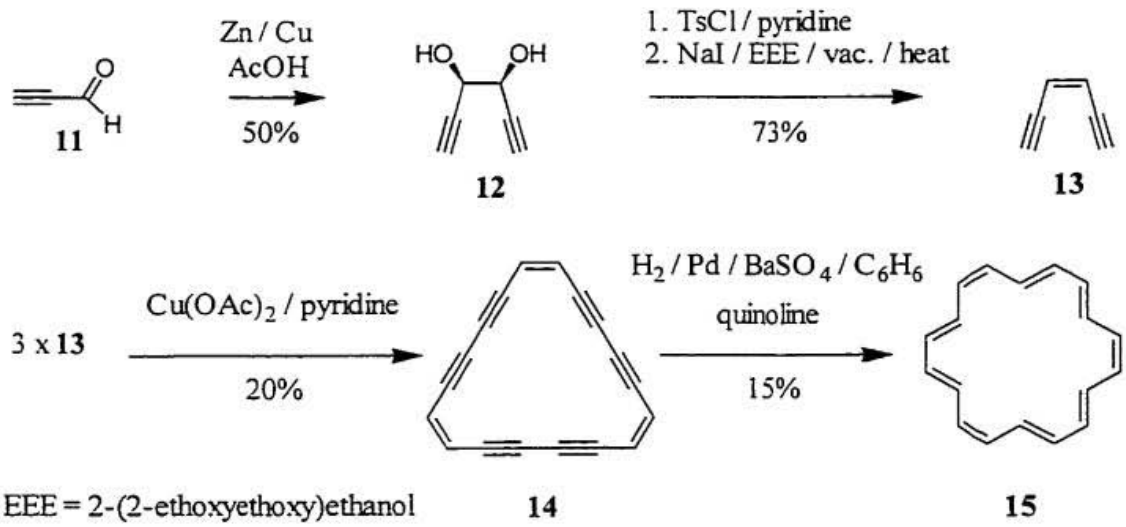
Scheme 5.1 The Presumed Mode of Action of Calicheamicin



Scheme 5.2 The Mechanism of the Bergman Reaction

Nicolaou[13] and Danishefsky[14] both conducted a series of biochemical experiments on calicheamicin demonstrating its sequence-selective cleavage of DNA. Nicolaou also synthesised an interesting series of enediynes in order to establish a pattern of reactivity, apparently vindicating his early assertion that the cd distance determined the reactivity of the endiyne unit.[12]

The sudden great interest in the enediyne area spawned new synthetic methodologies. Before their discovery in nature, interest in enediynes had been very limited, confined to Bergman's studies and those of annulene chemists such as Sondheimer and Figeys. Sondheimer was the first to make the theoretically very important compound [18]annulene (**15**), using 1,5-hexadiyne as a key intermediate.[15] In 1970 Figeys' synthesis of this same compound was published, which utilised instead the simplest *cis*-enediyne, **13**,[16] and featured a stereospecific synthesis of this compound.[17]



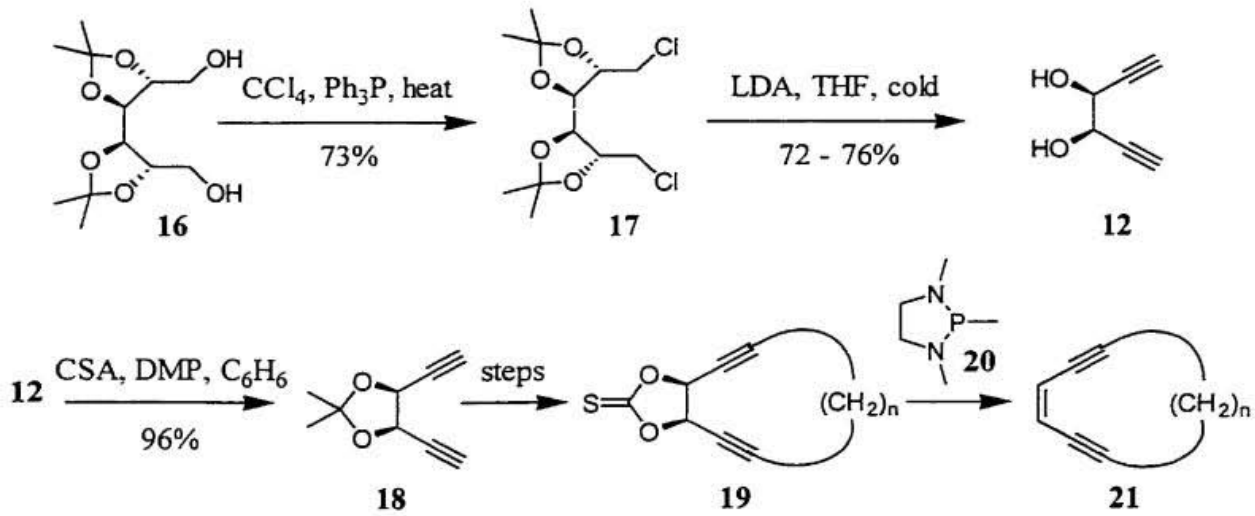
Scheme 5.3 Figeys' [18]Annulene Synthesis Featuring Stereospecific Generation of **13**

In the context of enediyne chemistry this paper was an important contribution. Indeed, the reaction **11** → **12** (referred to by Figeys as an "electrodimerisation") represents a stereoselective pinacol reaction which predates even Mukaiyama's work,[18] let alone McMurry's.[19] Unfortunately the transformation **12** → **13** was problematic, requiring 62 hours over which period the product is collected in liquid N_2 cooled traps.

5.2 Syntheses of the Enediyne Unit

Due to the newness of the enediyne moiety as a structural unit, several different general approaches to it were developed around the same time. The most direct idea is to construct the enediyne unit in its entirety and build the rest of the molecule from this core. An obvious advantage of such a strategy is that it allows a convergent approach where the losses due to *trans* double bond formation are confined to the synthesis of the enediyne unit itself. An obvious disadvantage is that differentiation between the two ends of **13** or a synthetic equivalent will be required at some stage, and this may well be expected to lead to large losses. At least three general methodologies have been investigated with the ultimate goal of inserting the whole enediyne unit as one piece. Amongst the chief protagonists have been Danishefsky, Vollhardt, Semmelhack and the relative newcomer G.B. Jones. Semmelhack's approach has much in common with Figeys' above, and is hence discussed first.[20]

Semmelhack's basic idea was to develop a masked form of **13** (**18** below) and to use this in coupling reactions. Subsequent conversion of the acetonide to the thionocarbonate would provide the necessary substrate for the Corey-Winter reaction,[21] which would ultimately reveal the enediyne moiety.

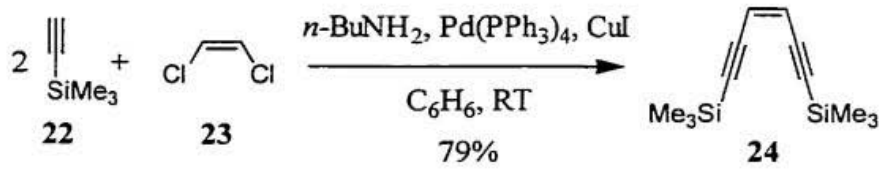


Scheme 5.4 Semmelhack's Corey-Winter Approach to Enediynes

Starting material **16** was easily prepared from the readily available sugar dulcitol, and the synthesis of **18** could be conducted on a 100 g scale. However, as might be expected, the required alkylation of the dianion of **18** with diiodoalkanes proceeded in only around 50% yield in the examples reported. Subsequent deprotection and thionocarbonate formation led to further losses. Finally the desired Corey-Winter reaction required the use of the rather esoteric electron-rich phosphine **20**. The reason for this choice was to allow the enediyne synthesis to occur at below -5 °C so compounds of marginal stability could be isolated without spontaneously undergoing the Bergman reaction first. The weak points of the above methodology are the number of steps and the lack of control over the alkylation step. The very practical synthesis of **12** has much to commend it, however, and this building block can be expected to see much further use.

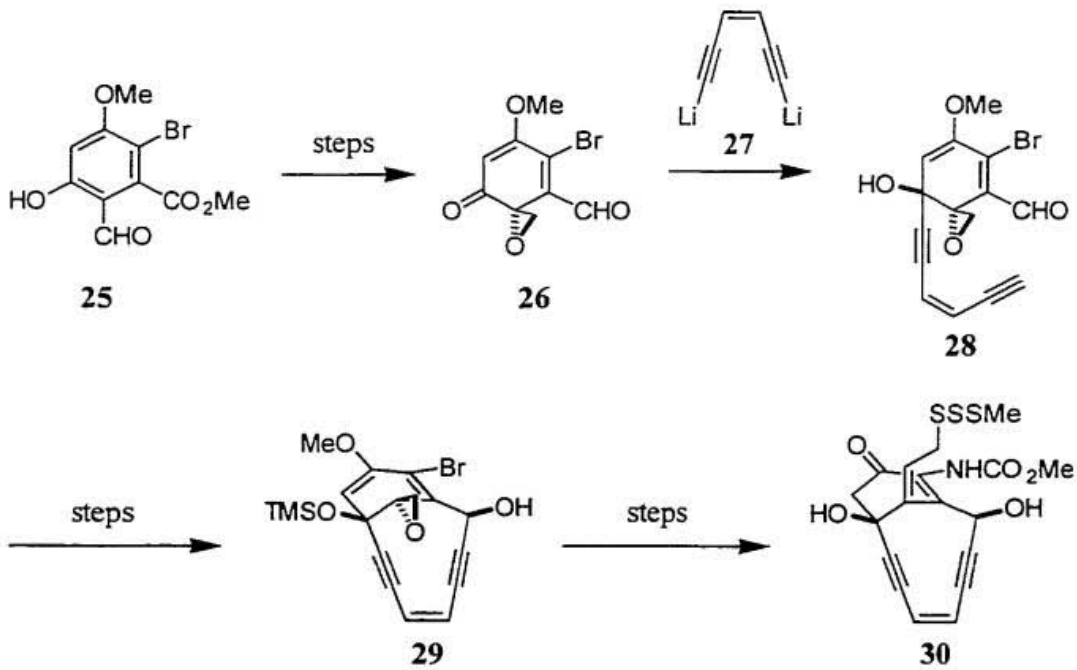
Vollhardt developed a very simple and effective small-scale preparation of the key enediyne **13**. Starting from the commercially available (though expensive) *cis*-1,2-

dichloroethene **23** and the similarly expensive trimethylsilyl acetylene **22** he was able to produce TMS-protected **24** stereospecifically in one step via the Heck reaction.[22] [See Scheme 5.5 below.]



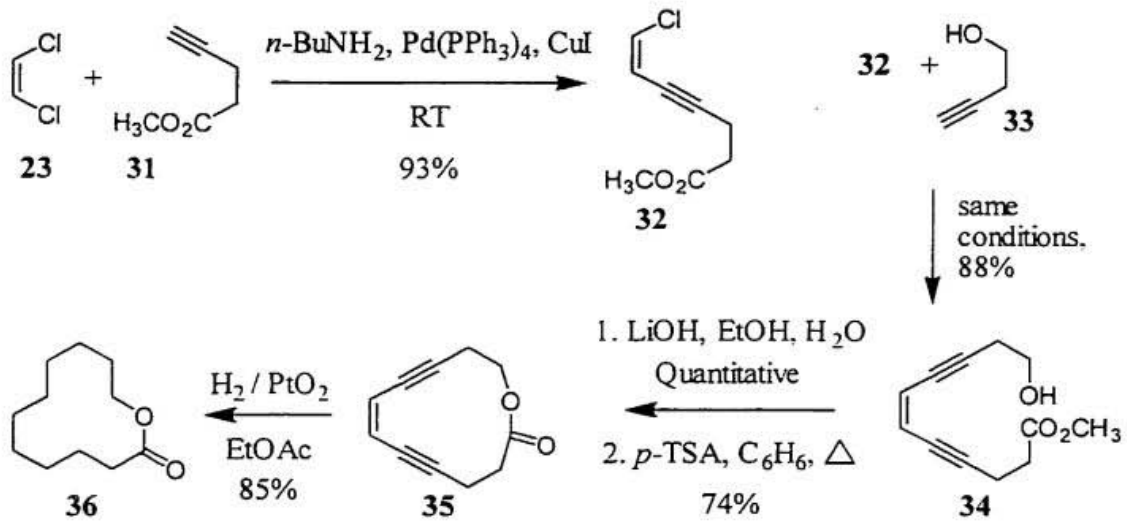
Scheme 5.5 Vollhardt's Stereospecific Synthesis of TMS-Protected *cis*-Enediyne **24**

Deprotection of **24** could be accomplished very easily using LiOH. Thus **13** was rendered much more readily accessible, and Danishefsky was among the first to capitalise on this with his very elegant synthesis of calicheamicinone **30**, the aglycon of calicheamicin (Scheme 5.6)[23]



Scheme 5.6 Danishefsky's Synthesis of Calicheamicinone

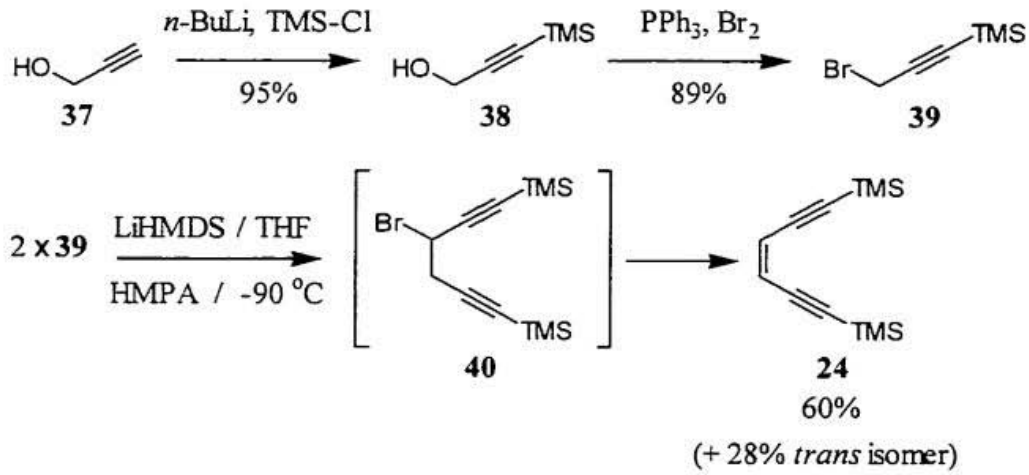
Other groups, led by Linstrumelle, later demonstrated that the two ends of the enediyne could be differentiated at an early stage by performing two separate Heck reactions on **23**. A particularly attractive example is Linstrumelle's synthesis of 11-undecanolide **36** via an enediyne precursor (Scheme 5.7).[24] A common tactic later adopted by many groups was to use the easily deprotected TMS acetylene at one end and a more robustly protected alkyne group at the other.[25] This refinement proved very successful, and the only weakness of this whole approach is the cost of the reagents and the catalyst required.



Scheme 5.7 Linstrumelle's 11-Undecanolide Synthesis

Jones' approach (Scheme 5.8) attempted to overcome this last problem. The problem of economy is by no means trivial to the pharmaceutical industry, and with the promise shown by the enediynes as potential anti-cancer drugs it was necessary to solve it. Jones' synthesis of **24** uses inexpensive reagents, intermediate **39** can be made on a one mole scale, and the key step proceeds in 60% yield, the only impurity being the

corresponding *trans* compound.[26] The reaction is believed to proceed via a carbenoid intermediate. Addition of HMPA had a beneficial effect on the yield, presumably since this destabilises the intermediate and favours product formation.[27] This methodology appears to be of potentially great use to industry, and Jones anticipated its use to prepare libraries of compounds in the search for a drug candidate.[28]

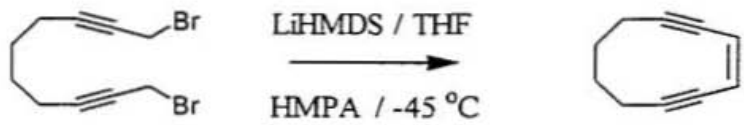


Scheme 5.8 Jones' Enediyne Synthesis

5.3 Late-Stage Enediyne Formation

The other general strategy is to form the enediyne moiety from two separate functional groups in advanced intermediates. As was stated earlier, the risk here is that a low yield may result at a late stage in the synthesis, most probably due to the possibility of formation of a *trans* double bond rather than the desired *cis*.[29] If the enediyne-forming step could be contrived to be intramolecular this disadvantage could be minimised. Several groups have synthesised enediynes using a late-stage ring closure. The most

obvious example is Jones' intramolecular carbenoid coupling.[30] Based on his procedure shown in Scheme 5.8 above, this methodology allowed 9, 10 and 11-membered enediyne rings to be closed in high yield, and on a 100 g scale. An advantage of this intramolecular reaction is of course the fact that the formation of the *trans* compound is suppressed due to strain considerations.

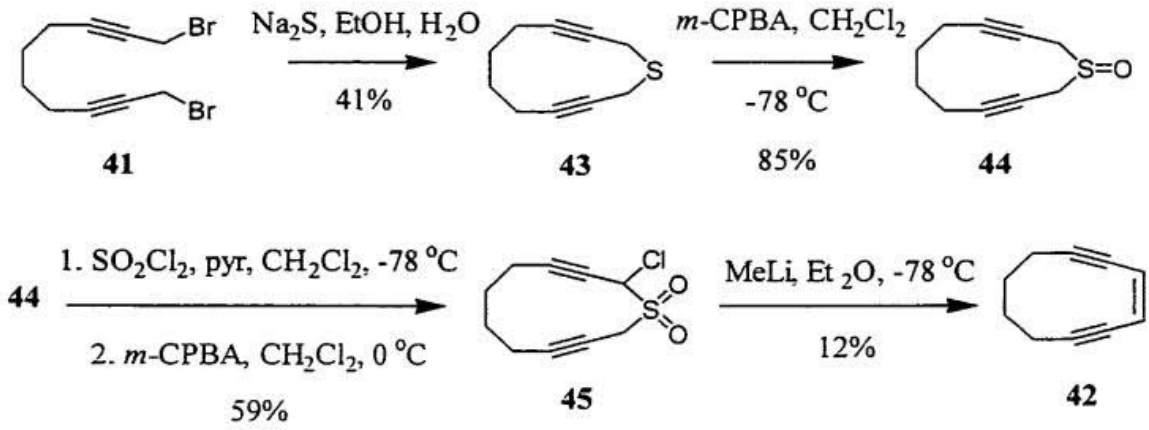


41 95% **42**

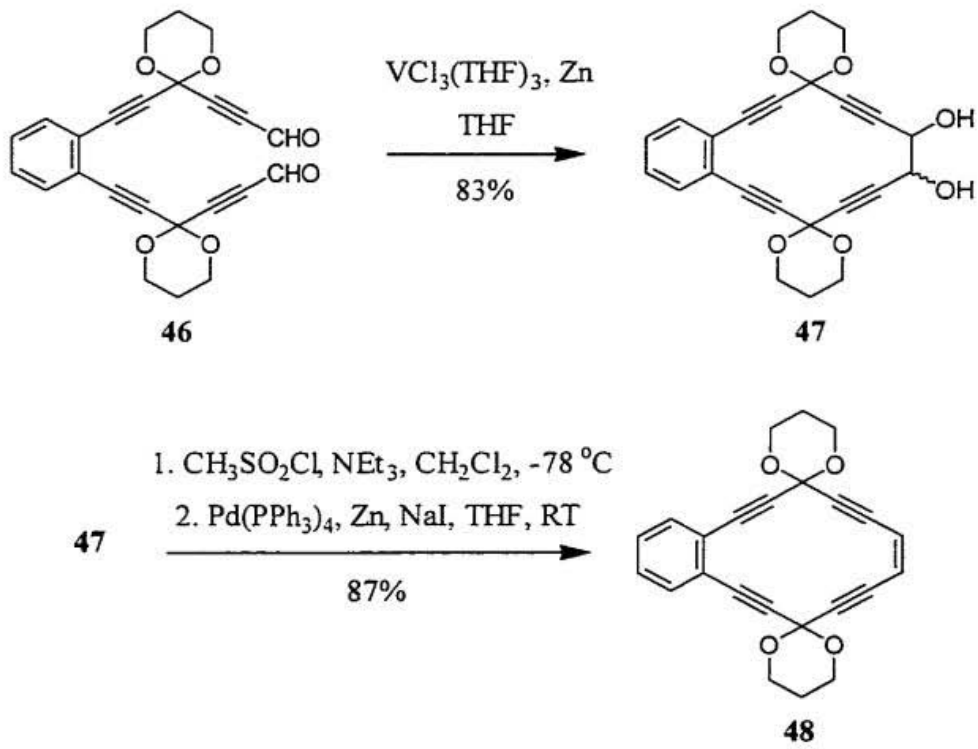
Scheme 5.9 Jones' Intramolecular Enediyne Closure

Similar in spirit to this approach was Nicolaou's use of the Ramberg-Bäcklund reaction (Scheme 5.10).[12] Treatment of α,ω-dipropargyldibromides with Na_2S gave the intermediate cyclic sulphides. Oxidation to the sulphoxide, α-chlorination, further oxidation to the sulphone and finally elimination gave access to the enediyne, albeit laboriously and in low overall yield. [Cyclophane chemists have known for some time that the Ramberg-Bäcklund reaction gives poor yields when employed in the contraction of medium-sized rings.] Nicolaou's results serve to re-emphasise the efficiency of Jones' methodology.

Another enediyne closure reaction was pioneered by Kuwatani (Scheme 5.11).[31] He utilised a modified form of the McMurry reaction, due to Pederson, as the key step.[32] Interestingly the conventional McMurry reaction failed to work despite the possible close proximity of the aldehydes and the fact that it was intramolecular.



Scheme 5.10 Nicolaou's Ramberg-Bäcklund-Based Approach



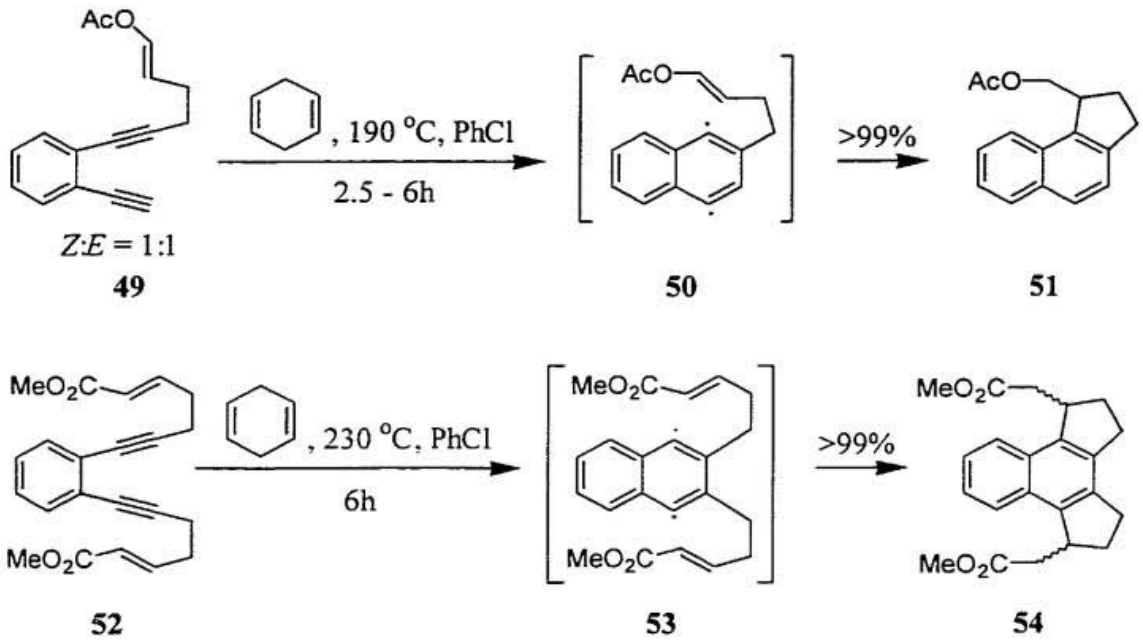
Scheme 5.11 Kuwatani's Dialdehyde Closure

As pointed out by Kuwatani, there are similarities between the intermediate diol here and the work of Semmelhack referred to earlier.[20] In this case mesylation of the alcohols followed by reductive elimination reveals the central double bond in good yield.

5.4 Synthetic Possibilities of the Bergman Reaction

The Bergman reaction has been a fairly unpredictable one until quite recently. Several groups expended a large amount of effort in producing their desired natural product and then proceeded to destroy it under Bergman conditions. The products of the reaction were merely used to support the idea that the reaction actually occurred, and frequently the major product accounted for only around 50% of the material. With the huge improvement of the enediyne-forming methodologies over the last few years the possibility presented itself that enediynes could eventually be used as intermediates in the synthesis of benzene rings. In order for this idea to be realised, however, it would be necessary to "tame" the Bergman reaction so that a high yield of the desired product would be produced. We were very excited to read of Grissom's pioneering work in this area, which was reported after the commencement of this project.[33] Despite the fact that the "disconnection" of a benzene ring to an enediyne is intuitively obvious, no one had previously achieved high yields of aromatics using the forward reaction, and the Bergman reaction had been more of a test of a system's reactivity than a synthetic step. Scheme 5.12 below shows two of Grissom's best results. In these examples the instability of the benzenoid diradical intermediate does not result in a variety of byproducts, due presumably to the availability of a single low-energy pathway to a stable product. The proximity of an alkene double bond to one or both benzenoid radicals allows at least one

immediate cyclisation to a thermodynamically and kinetically favourable 5-membered ring. In addition to this strategic advantage, Grissom found optimal reagents and conditions for the reaction to allow the very high yields seen here.



Scheme 5.12 Grissom's Use of the Bergman Reaction in Synthesis

5.5 Novel Alkyne-Containing Hydrocarbons

The remarkable growth in the synthetic approaches to such chemicals, which had previously been seen as mainly curiosities, fuelled much research in the area of novel hydrocarbons. Indeed, some remarkable alkyne-containing cyclophanes have been reported over the last few years. Some of the most interesting examples are shown below (Figure 5.2). Compound **55** is an example of several "medium-sized metacyclophanediynes" synthesised and studied by Gleiter.[34] Cyclophane **56** is a representative of Fallis' "revolveneynes".[35] [Fallis was also responsible for the invention

of the "taxamycin" enediyne family, in which part of the basic taxane skeleton was replaced with an enediyne group.][36] Kuwatani produced the novel hydrocarbon **57** from an enediyne-containing intermediate.[31] [See previous section.]

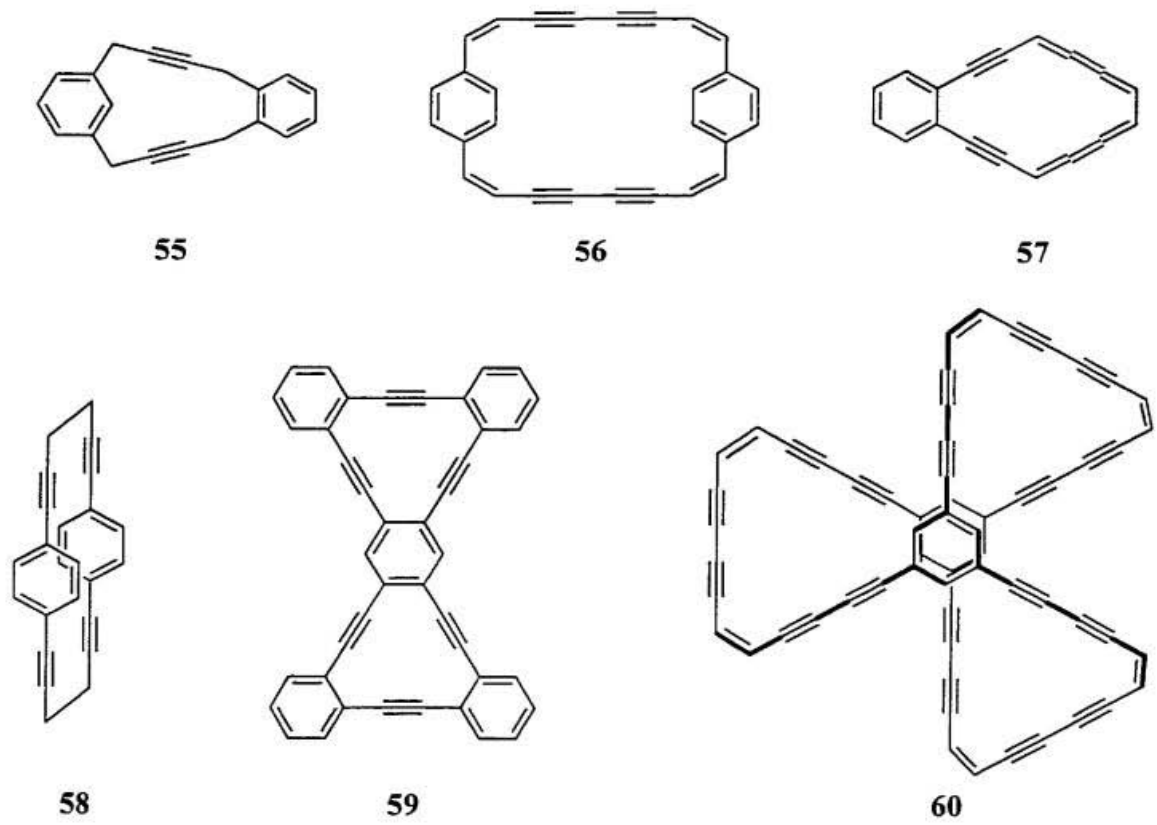


Figure 5.2 Interesting Alkynophanes from the Literature

This compound is very unstable, and could be obtained only in dilute solution. It is a rare example of a Sworski-type dehydroannulene.[37] Paracyclophane **58**, prepared by Hopf, was of special interest to us due to its similarity to the compounds we had in mind.[38] Compound **59** was prepared by Haley[39] in his pursuit of graphyne,[40] and is one of the largest graphyne fragments yet prepared. Finally compound **60** was made by Rubin.[41]

Since this remarkable structure has the formula $C_{60}H_{18}$, it was hoped that it might rearrange to C_{60} Buckminster fullerene in the gas phase. Unfortunately mass spectrometry has failed to detect this transformation.

5.6 This Work

5.6.1 Introduction

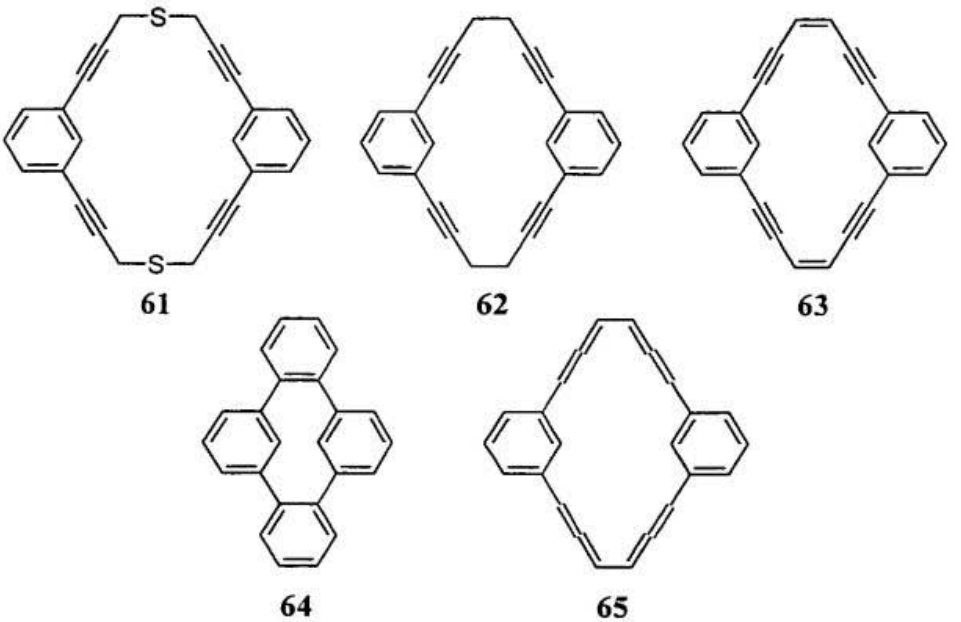
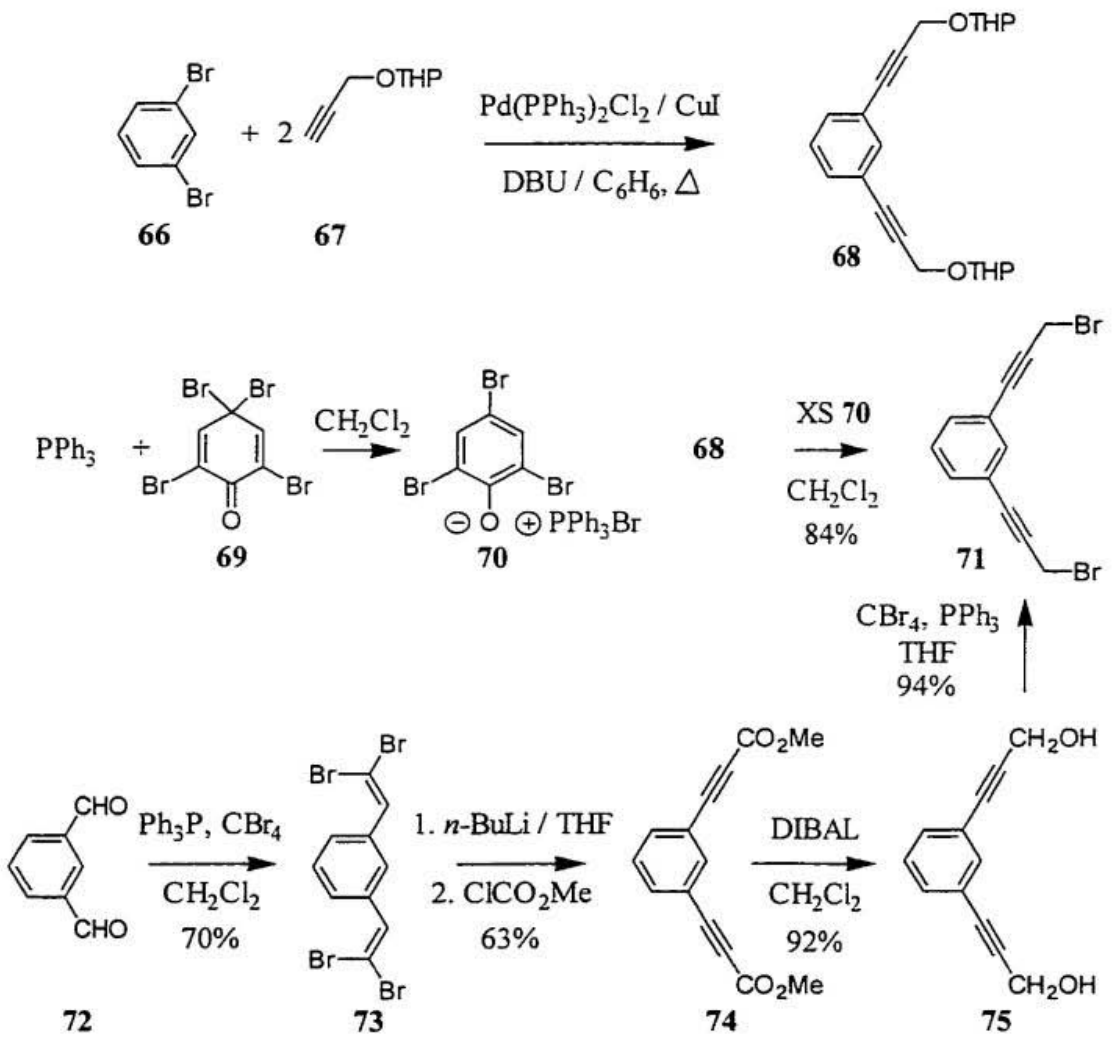


Figure 5.3 Synthetic Targets of This Work

This project was already underway when many of the above papers were published, and all these developments were followed with much interest. In particular the synthetic advances made by other groups enabled us to formulate several new possible routes to our various alkyne-containing targets. The primary targets (Figure 5.3) were thiacyclophane **61**, alkynophane **62** and enediynophane **63**. Contingent on the successful achievement of these goals, it was hoped that dibenzocyclophanediene **64** and

allenophane **65** could also be made: the former by double Bergman reaction of **63**, the latter by base-catalysed isomerisation of **62**. Especially attractive to us was Jacobs' methodology whereby this isomerisation might be achieved by chromatography of the alkynophane on alumina impregnated with KOH.[42]

5.6.2 Preparation of the Dithiacyclophane 61



Scheme 5.13 Syntheses of the Dibromide **71**

It was originally hoped that thiacyclophane **61** could serve as a common intermediate for all the desired products, and that this could be made from dibromide **71** (Scheme 5.13) using the $Na_2S{\cdot}Al_2O_3$ reagent.[43] However, it was not clear whether a good yield could be obtained from such a Na_2S-induced coupling reaction as the Ensley group had trouble with a remarkably similar, though more demanding, transformation (Scheme 5.15 below).[44] It was also not known whether the sulphur atoms of **61** could be successfully extruded by any of the conventional means (as described in previous chapters). Hence several alternative methodologies were formulated, as will be explained below.

In the event it was found possible to prepare thiacyclophane **61** by a slight refinement of our usual $Na_2S{\cdot}Al_2O_3$ method (Scheme 5.14). The yield (41%) compared very favourably with that obtained by Ensley (see Scheme 5.15 and reference 44). Dibromide **71** was prepared by a very concise and efficient route employing some recently published techniques (Scheme 5.13). Heck reaction of 1,3-dibromobenzene was found to be much more reliable with THP-protected propargyl alcohol than with the alcohol itself.[45] In practice the best synthesis of **71** used direct bromination of the crude intermediate **68** using a very useful protocol developed by Tanaka.[46] This method obviated deprotection or purification of the diacetal, allowing **71** to be obtained in just two steps from 1,3-dibromobenzene in an overall yield of 84%. The effective brominating agent is the salt **70** formed when hexadienone **69**[47] is mixed with PPh_3 in CH_2Cl_2 solution. [Stepwise deprotection of **68** followed by bromination gave a lower yield.]

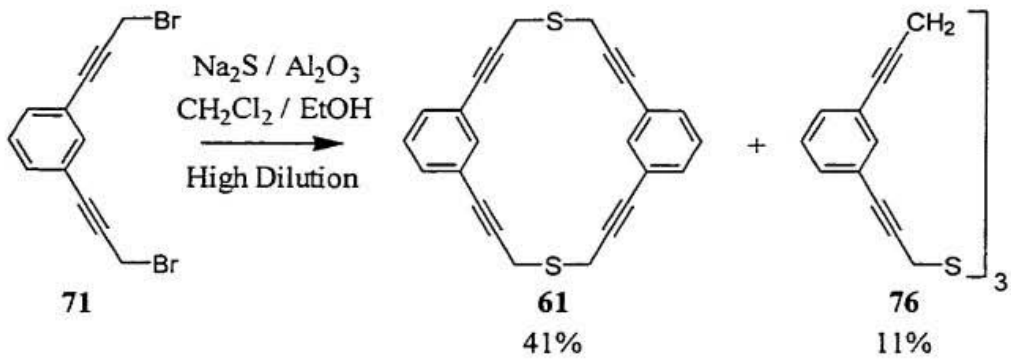
An alternative series of reactions mirroring Nicolaou's work was also investigated (Scheme 5.13).[12] In this case the dialdehyde **72** was prepared by a literature method,[48] and

then subjected to the Corey-Fuchs procedure to produce tetrabromodiene **73** in 70% yield.[49] Lithiation and acylation with methyl chloroformate led to diester **74** which was readily selectively reduced to diol **75** in 58% overall yield using DIBAL. Use of freshly generated dry gaseous formaldehyde to allow direct formation of **75** from the dianion generated from **73** was also successful, though in only 28% yield. Despite the fact that bromination of **75** could be achieved in 94% yield, the use of the Heck reaction followed by Tanaka's procedure was clearly a far more efficient process.

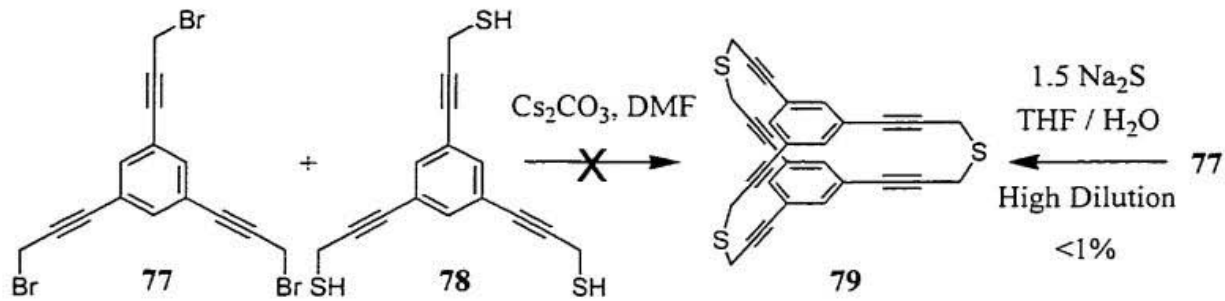
The sodium sulphide coupling was carried out in a similar fashion to our previously published intermolecular coupling[43] but at one eighth the concentration and with a more gradual addition of the $Na_2S{\cdot}Al_2O_3$ reagent.[50] This procedure appeared to be necessary in order to favour the second, intramolecular reaction over oligomerisation. This was not at all surprising since a 20-membered ring was being closed. Preliminary work showed that separation of the desired dimer from the trimer was problematic. The final conditions employed allowed us to obtain an isolated yield of 41% of the dimer **61** after careful chromatography. Another compound presumed to be the trimer **76** was also isolated in 11% yield.[51]

As shown below, Ensley encountered serious difficulties in synthesising the trithiacyclophane **79**.[44] It was found that the trithiol **78** was not stable in the conditions required to affect coupling with tribromide **77**, and also that high dilution coupling using Na_2S in H_2O / THF solution was extremely inefficient. He was eventually successful in his endeavours using a more sophisticated, multi-stepped route. Admittedly **79** is a more demanding target than **61**, but Ensley's problems highlight the simplicity and versatility

of our $Na_2S{\cdot}Al_2O_3$ methodology. It would be interesting to see what yield of **79** could be obtained from **77** using the $Na_2S{\cdot}Al_2O_3$ protocol.[52]



Scheme 5.14 The Successful Synthesis of Dithiacyclophane **61**

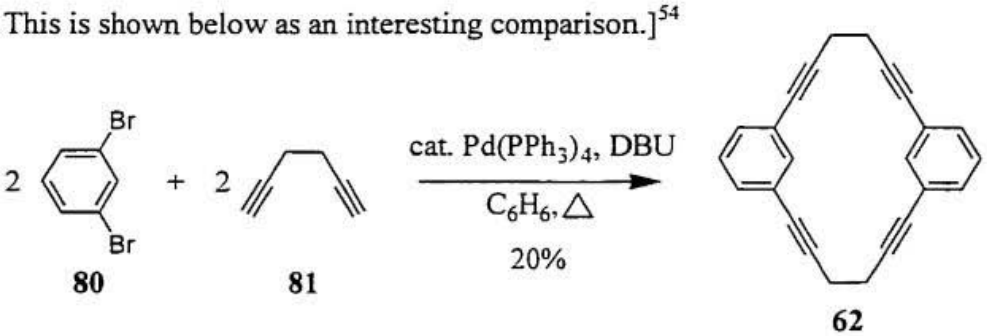


Scheme 5.15 Ensley's Problems in the Synthesis of Trithiacyclophane **79**

5.6.3 Preparation of the Tetraynophane 62

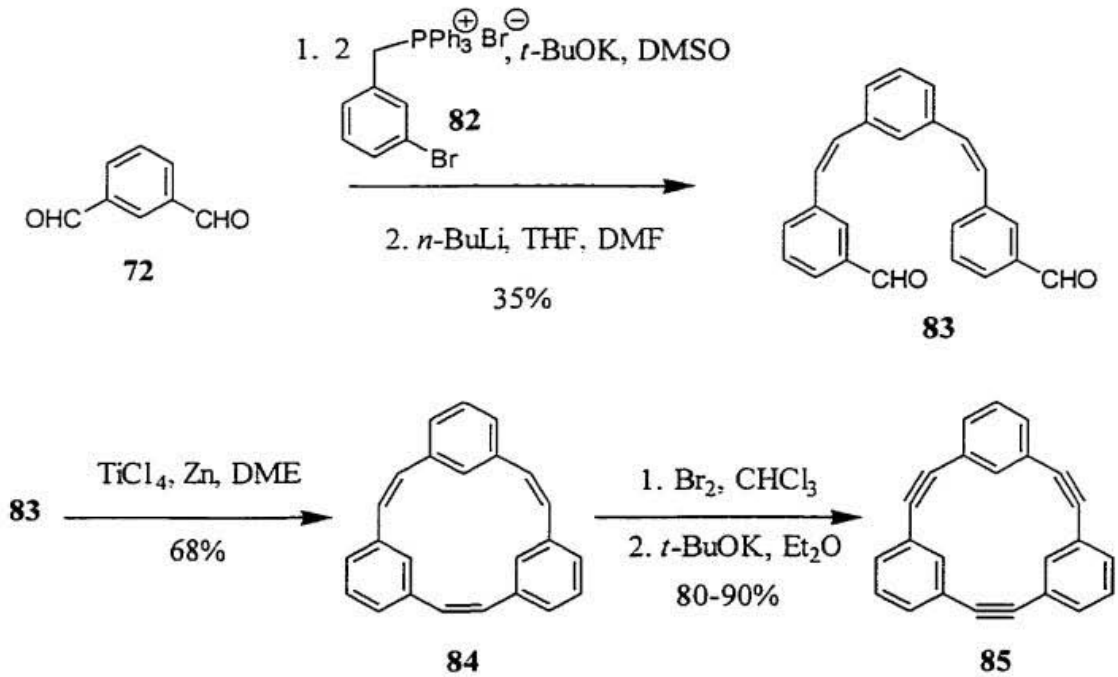
Although the original plan had been to use **61** as a key intermediate in making our other primary targets the tetraynophane **62** and the dienetetraynophane **63**, there were doubts about whether it would be possible to extrude the sulphur atoms without destroying the target molecule. The great efficiency of the Heck reaction in the syntheses above prompted a change of strategy.[53] It was postulated that **62** may be accessible in one step from the commercially available 1,3-dibromobenzene **80** and 1,5-hexadiyne **81**. [The

latter is apparently no longer available from the Aldrich Chemical Company.] This seemed a very attractive idea, since if successful it would be both expedient and elegant. In the event conditions were found which allowed synthesis of **62** in a yield of about 20%. While the yield is obviously low, the directness of this method is very attractive, especially when compared to most cyclophane syntheses in the literature. [Oda's recent 5-step synthesis of [2.2.2]metacyclophane-1,9,17-triyne **85** also proceeded in 20% overall yield. This is shown below as an interesting comparison.][54]



80 **81** **62**

Scheme 5.16 The Synthesis of Tetraynophane **62** Using a Four-Fold Heck Reaction



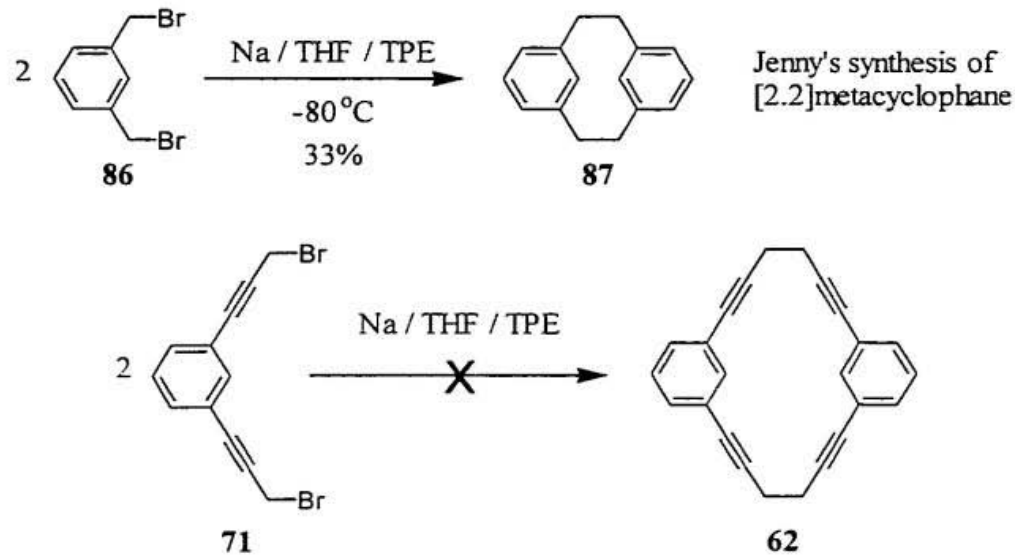
72 **82** **83** **84** **85**

Scheme 5.17 Oda's Synthesis of Cyclophane **85**[54]

Several attempts were made to improve the yield of **62** from the Heck reaction. Literature precedent suggested that the corresponding diiodobenzene would be a more reactive substrate, perhaps allowing the use of milder reaction conditions and allowing greater selectivity for the desired dimer. Unfortunately the use of 1,3-diiodobenzene[55] gave only lower yields than **80**. Other unsuccessful modifications were the use of the cuprous acetylide from **81**,[56] different Pd catalysts,[57] and different solvents.[58] In each case no improvement in the yield was obtained. One possible explanation for the low yield was that **62** was unstable to chromatography on SiO_2. [A similar stability problem was noted by Oda with compound **85**.] Indeed, rapid dry flash chromatography allowed a 38% yield of impure material on one occasion, but the exact purity was not determined.[59] As might be expected, separation of **62** from the byproducts of the reaction is not trivial, and proper chromatography is necessary to achieve this.

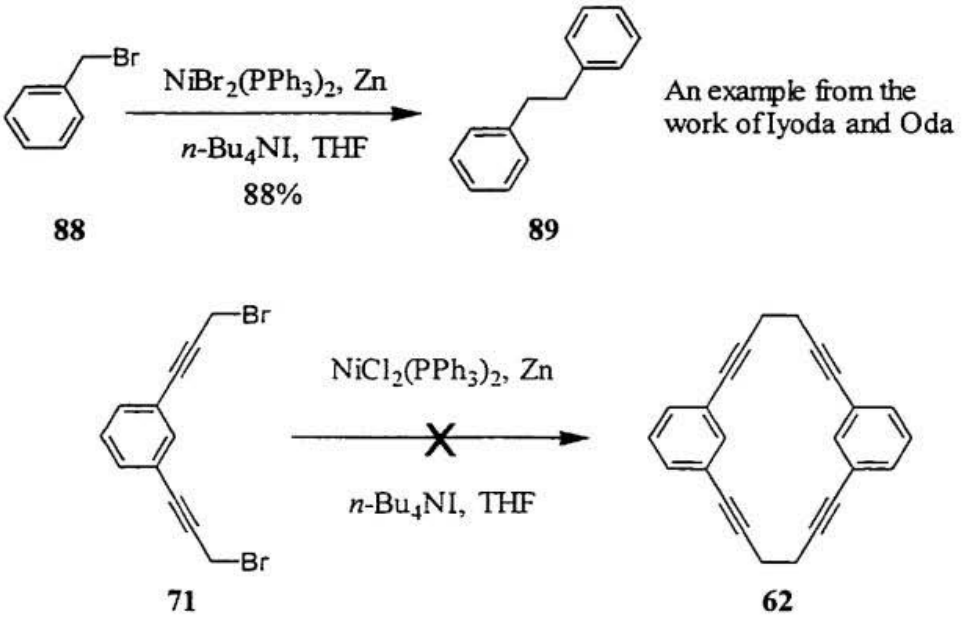
Despite the qualified success of the above method, a higher yielding synthesis of **62** amenable to larger scale would still be desirable. Sulphur extrusion from **61** may yet prove possible, although this has been only briefly investigated. Two other ideas were considered, both of which would require just one step from the readily available dibromide **71**. As has been discussed in a previous chapter, the Müller-Röscheisen variation of the Wurtz reaction has often been used to synthesise [2.2]metacyclophanes.[60] Since the $Na_2S{\cdot}Al_2O_3$ cyclisation had been shown to be effective in closing the corresponding dithiacyclophane, it was hoped that the modified Wurtz reaction could be employed to close this "expanded cyclophane". [It was considered that these compounds might be thought of as carbomers of the more usual [3.3]dithiametacyclophanes and [2.2]metacyclophanes according to Chauvin's concept.][61] Unfortunately the application of

this reaction to the synthesis of **62** failed to produce the desired product, presumably due to competing oligomerisation reactions (Scheme 5.18).



Scheme 5.18 Attempted Application of the Müller-Röscheisen Variation of the Wurtz Reaction[60]

Similarly, an attempt to utilise Iyoda and Oda's Ni(0) catalysed reductive coupling failed (Scheme 5.19).[62] This reaction had previously been used to produce a large number of bibenzyls, but has not yet, to our knowledge, been successfully used in cyclophane synthesis. This failure was again disappointing, but it should be taken into account that our group had no prior experience of these rather specialised reactions, and their further investigation may be worthwhile. In both of these speculative attempts it was thought likely that the reactivity of 1,3-bis(3-bromo-1-propynyl)benzene (**71**) would be similar to that of a benzyl halide, which may not be a valid assumption.

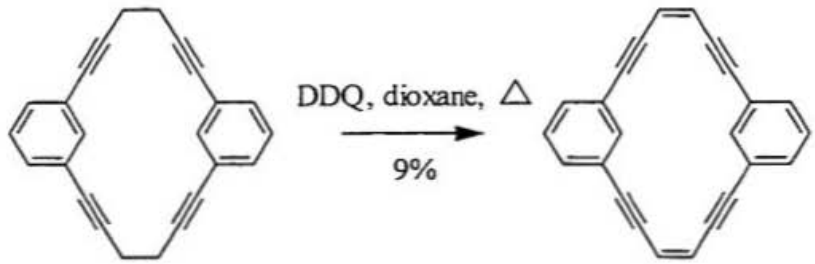


Scheme 5.19 Attempted Application of Iyoda and Oda's Ni(0) Catalysed Reductive Coupling Reaction[62]

5.6.4 Preparation of the Enediynophane 63 by Dehydrogenation of 62

The third target molecule, the dienetetraynophane **63**, was the next goal of the project. Due to the massive interest in the enediynophanes in the literature, more plausible strategies presented themselves for this synthesis than for the less sophisticated **62**. Since we had a route to **62**, the conceptually simplest route was dehydrogenation of **62**. It was reasoned that there would be a strong thermodynamic driving force for such a transformation due to the concomitant increase in delocalisation energy. The dehydrogenation of 1,2-bis(4-methoxyphenyl)ethane using DDQ is an Organic Syntheses procedure, and it was hoped that a directly analogous approach would be successful here.[63] [Further reading revealed that the exact composition of the compound to be dehydrogenated could have a big impact on the effectiveness of the reaction, and that 1,2-

bis(4-methylphenyl)ethane gives a much lower yield of the corresponding stilbene.][64] The dehydrogenation reaction was attempted in both benzene and dioxane, with varying degrees of success. The stoichiometry, duration and concentration of the reaction were varied in an attempt to find optimal conditions. The reaction was particularly easy to follow by TLC due to the strong fluorescence of the product. Unfortunately conditions could not be found which would consistently give a yield higher than 9%. [An unreliable yield of 30% was obtained once but on a very small scale.] Once again part of the reason for the losses appeared to be partial decomposition of the product during chromatography on silica. Despite the fact that the reaction successfully delivered compound **63**, the yield was unsatisfactory and the conditions seemed too harsh. Hence milder dehydrogenating agents were sought.

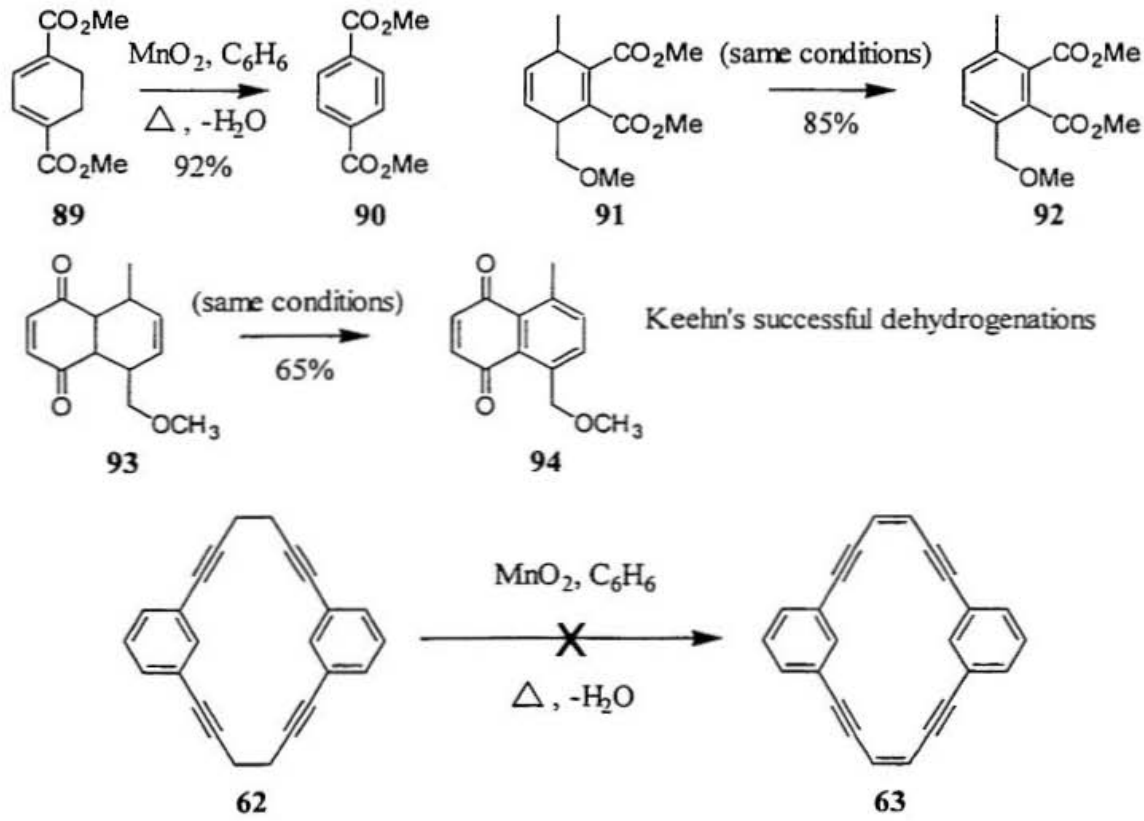


62 **63**

Scheme 5.20 The Dehydrogenation of Tetraynophane **62**

From the literature two less reactive quinones presented themselves, namely *o*- and *p*-chloranil.[65] The former is the more reactive of the two due to dipole moment considerations. Both avoid some potential side reactions of DDQ due to their relative inertness. While *p*-chloranil is commercially available and inexpensive, *o*-chloranil was synthesised following a literature procedure.[66] Unfortunately neither of these reagents proved powerful enough to dehydrogenate **62**, which was unchanged by TLC.

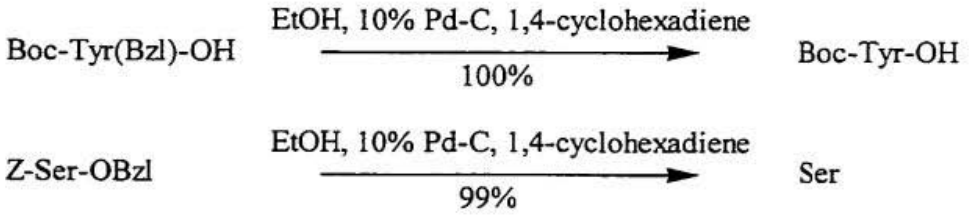
There were, of course, many other possible dehydrogenation reactions, and several of these were investigated. One of the most attractive possibilities was the use of activated MnO_2, since this reagent is both mild and easily separable from the product.[67] An interesting paper from Keehn clearly indicated the efficacy of this methodology even when other dehydrogenations failed (Scheme 5.21).[68] Active MnO_2 was prepared according to a simple literature procedure,[69] and dehydrogenation of **62** was attempted according to Keehn's protocol. No reaction was observed by TLC. It is possible that a more active form of MnO_2 may be able to achieve this transformation, and further work on this reaction is warranted.



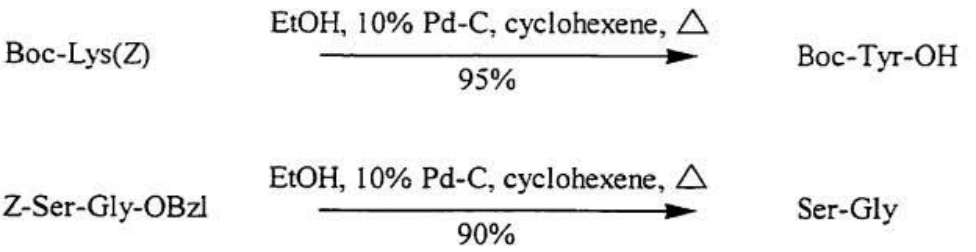
Scheme 5.21 Attempted Application of Keehn's MnO_2 Dehydrogenation Conditions[69]

Another appealing methodology for dehydrogenation was heterogeneous catalytic dehydrogenation. If successful this would also avoid troublesome chromatography. The particular procedure investigated was catalytic transfer hydrogenation. Transfer hydrogenation is commonly used to remove several common peptide protecting groups, the most easily removed being the *N*-benzyloxycarbonyl and benzyl ester groups. The commonly used hydrogen donor is 1,4-cyclohexadiene,[70] although it has been found that under certain circumstances the less reactive and much cheaper cyclohexene can be used instead.[71] These facts led us to believe that it might be possible for tetraynophane **62** to act as the hydrogen donor in this reaction (Scheme 5.22). It was realised from the outset that this idea was rather speculative, but it was hoped that an improvement on the 9% yield in the DDQ reaction (Scheme 5.20) might be obtained. It should be noted that in typical catalytic transfer hydrogenation reactions a large excess of the hydrogen donor is used. Our idea was to use a large excess of the easily hydrogenolysed benzyl acetate **95** instead. It was thought that the driving force for the first dehydrogenation of **62** should be greater than in the case of cyclohexene, and that the driving force for the second reaction would be greater than that for the first.

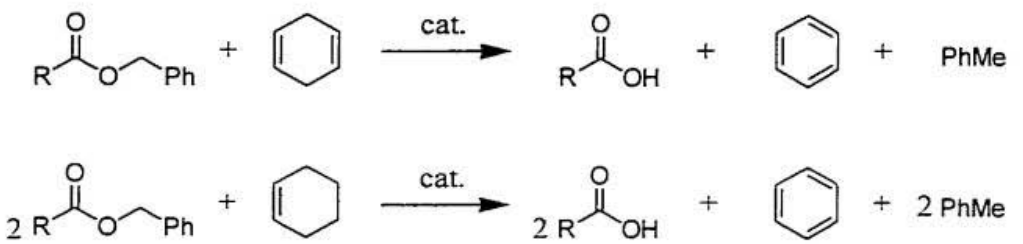
The somewhat variable nature of the commonly used catalysts led us to first seek a system in which cyclohexene could act as the hydrogen donor in the hydrogenolysis of **95**. This was duly achieved using 5% Pd-C in ethanol solution (Scheme 5.23). In this case a large excess of cyclohexene was used, as in the usual cases in the literature. The next step was to find conditions whereby **95** could effectively be used to dehydrogenate a hydroaromatic molecule, similar to our planned dehydrogenation of **62**.



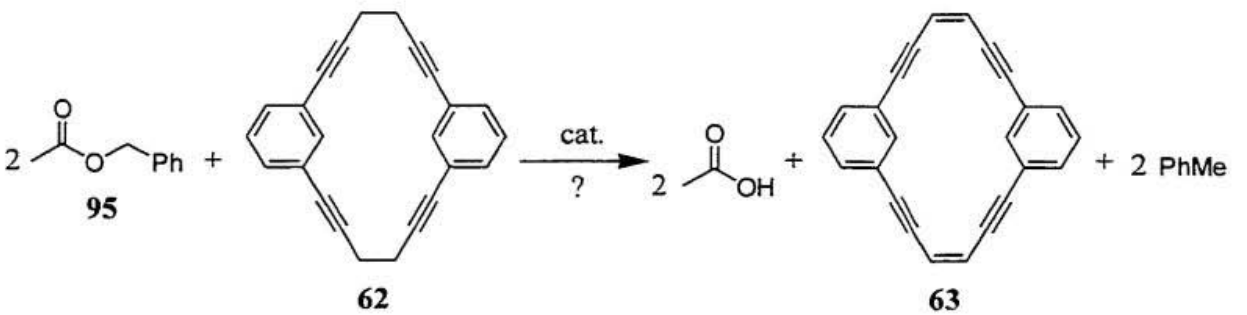
Felix's deprotection results using transfer hydrogenation [70]



Sivanandaiah's deprotection results using transfer hydrogenation [71]

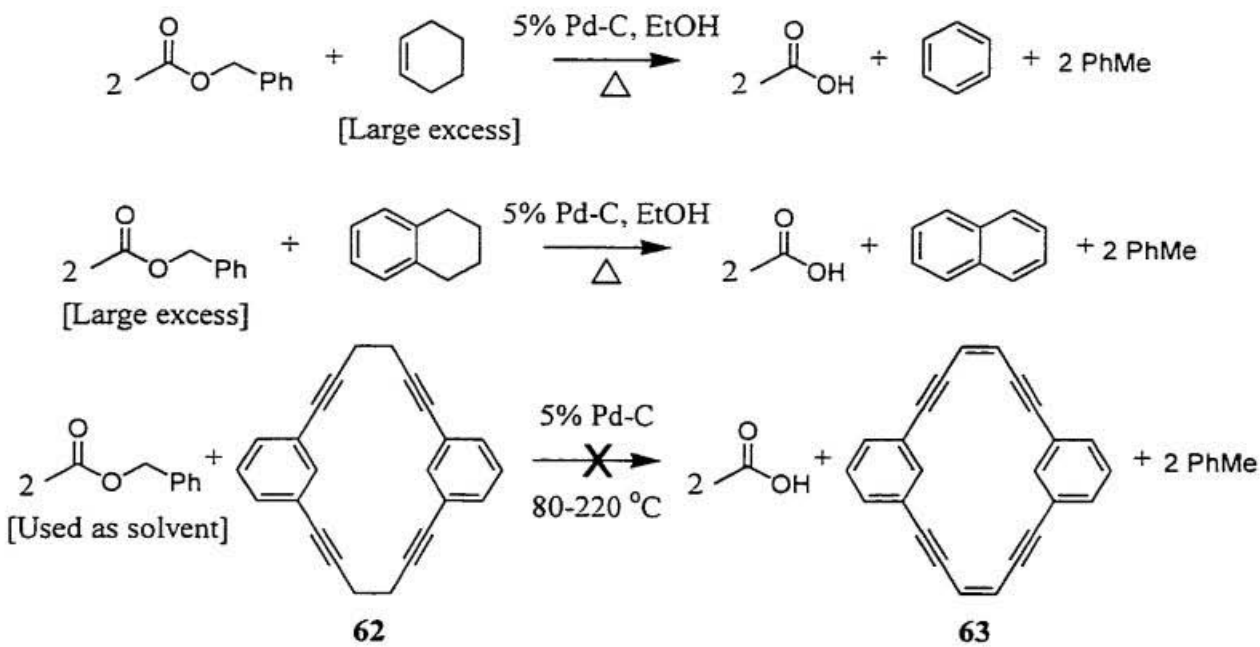


The basic catalytic transfer hydrogenation reaction using 1,4-cyclohexadiene or cyclohexene



Scheme 5.22 The Catalytic Transfer Hydrogenation Reaction

The model compound chosen for this purpose was tetralin, since it was regarded as being somewhat similar to the case of **62**. Using a large excess of **95** in refluxing ethanol with the same catalyst apparently (TLC evidence) caused almost total conversion of the tetralin to naphthalene. An attempt to apply similar conditions to the dehydrogenation of **62** proved unsuccessful, and work on this project was curtailed by other priorities. In retrospect this idea seems worthy of further investigation. One potential improvement would be the use of freshly prepared palladium black, a very reactive catalyst advocated by Sivanandaiah for use in difficult cases.[71] It is perhaps also possible that the use of ethanol as a solvent somehow promotes the reaction. This was omitted in the attempted dehydrogenation of **62** in order to allow a higher reaction temperature.

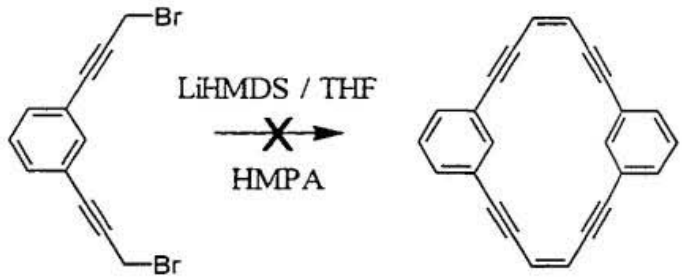


Results suggested by TLC only

Scheme 5.23 Preliminary Results of Catalytic Transfer Hydrogenation Studies

5.6.5 Attempted Preparation of the Enediynophane 63 by Other Methods

As previously mentioned, a tremendous volume of work has been published in the last few years on the synthesis of enediynes. Four of these methodologies were cursorily investigated in the hope that an expedient direct route to **63** could be found, avoiding the (so far) low-yielding dehydrogenation of the tetraynophane **62**. The chosen strategies are shown in Schemes 5.24-5.27 below.



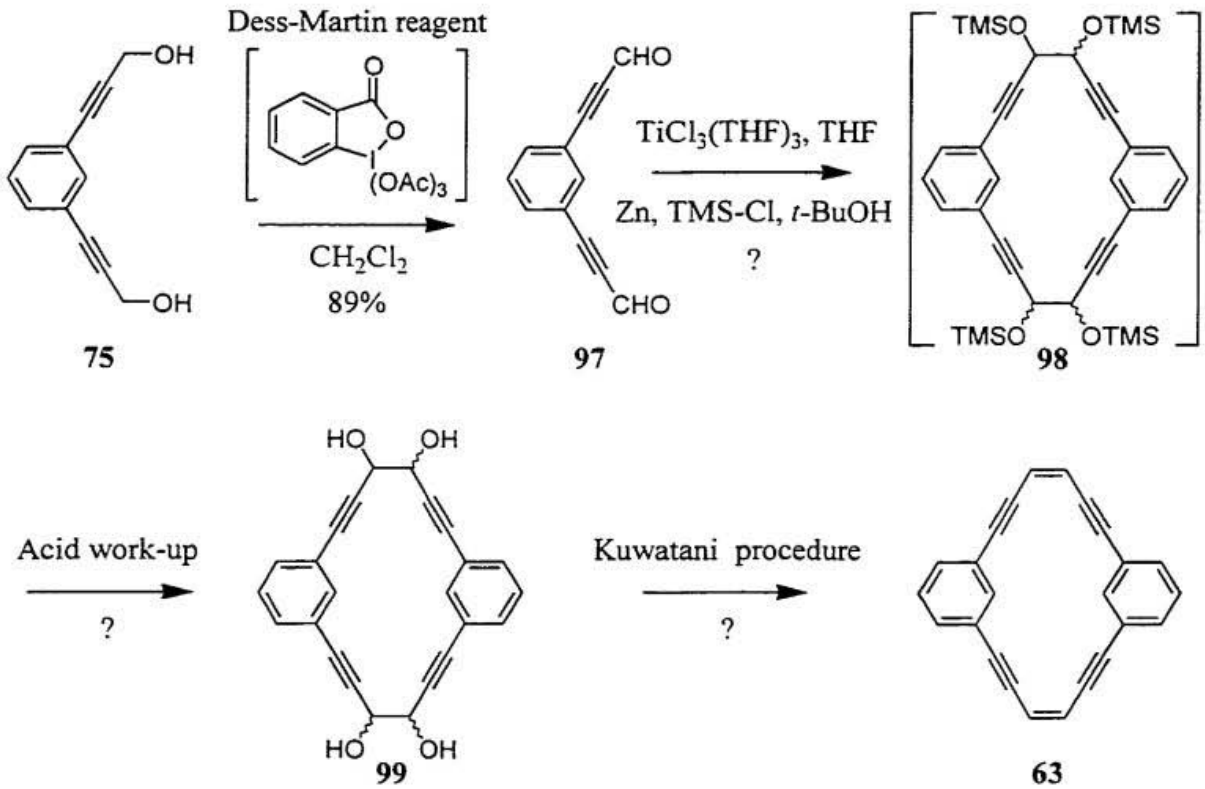
71 **63**

Scheme 5.24 Attempted Use of Jones' Methodology (See also Schemes 5.8 and 5.9)

The previously described methodology of G.B. Jones was very attractive, since compound **71** was available on a large scale and in high yield (Scheme 5.13). Despite the fact that we were able to repeat his synthesis of enediyne **24** (Scheme 5.8),[26] albeit in lower yield and with lower *Z*:*E* selectivity (37% *Z*, 25% *E*),[72] conditions were not found which would allow conversion of **71** to **63**. It is thought that the use of a syringe pump for the slow addition of the base to **71** may help, and further study of this reaction including finding the optimal temperature may be worthwhile.

Another approach looked into due to the ready availability of the essential starting material was a special kind of McMurry reaction, pioneered by Nelson, followed by an adaptation of Kuwatani's reaction sequence (Scheme 5.11).[73,31] Nelson's protocol traps

the diol initially formed with TMS-Cl. The ethers formed do not eliminate, unlike the diols, under the reaction conditions. This point was thought to be critical to the successful synthesis of **63**, since elimination frequently leads to *E*/*Z* mixtures. Clearly, if it is possible for an *E* double bond to be formed before the second ring-closing McMurry reaction can occur the desired second reaction will become impossible and oligomerisation will occur instead.

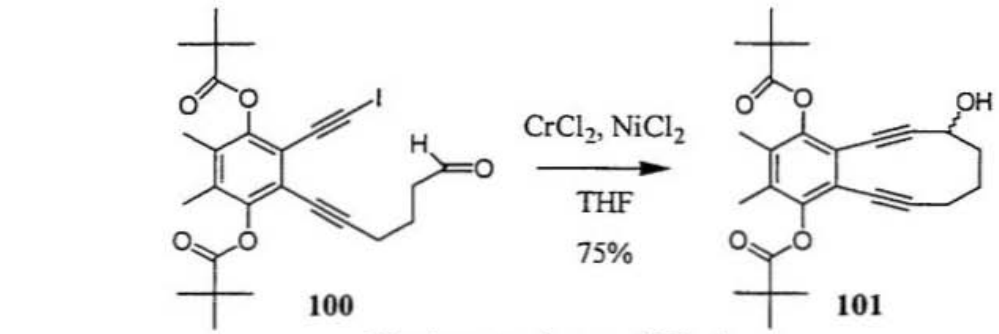


Scheme 5.25 Attempted Use of Nelson's McMurry Protocol

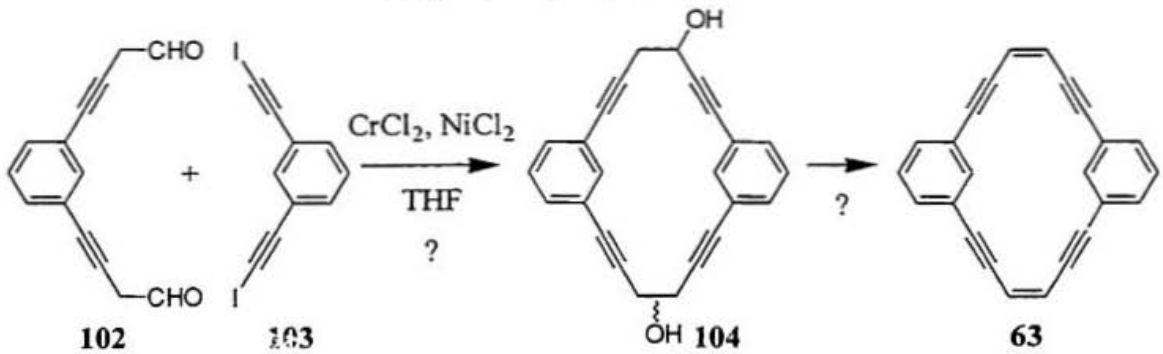
Diol **75** was readily available by trivial deprotection of the THP-ether **68**. Oxidation using the Dess-Martin reagent[74] proceeded in 89% yield to give the required dialdehyde **97**. Inconclusive results were obtained in the McMurry reaction, although on one run a spot

corresponding to **63** was observed by TLC following the Kuwatani procedure, and lack of time prevented thorough investigation of this interesting strategy. An alternative to the use of Kuwatani's reaction sequence would have been exposure of tetraol **99** to the usual McMurry reagents, at elevated temperature if necessary, to bring about the expected elimination to give **63**. It was not proved whether or not intermediate **98** was actually formed in the McMurry reaction. If it was, then merely adding fluoride ion to the reaction and heating the mixture may have directly afforded enediynophane **63**.

The final two methodologies given some consideration were based on strategies from the Nicolaou group. The first of these was the use of the Nozaki-Kishi reaction to close an enediyne-containing ring.[75]



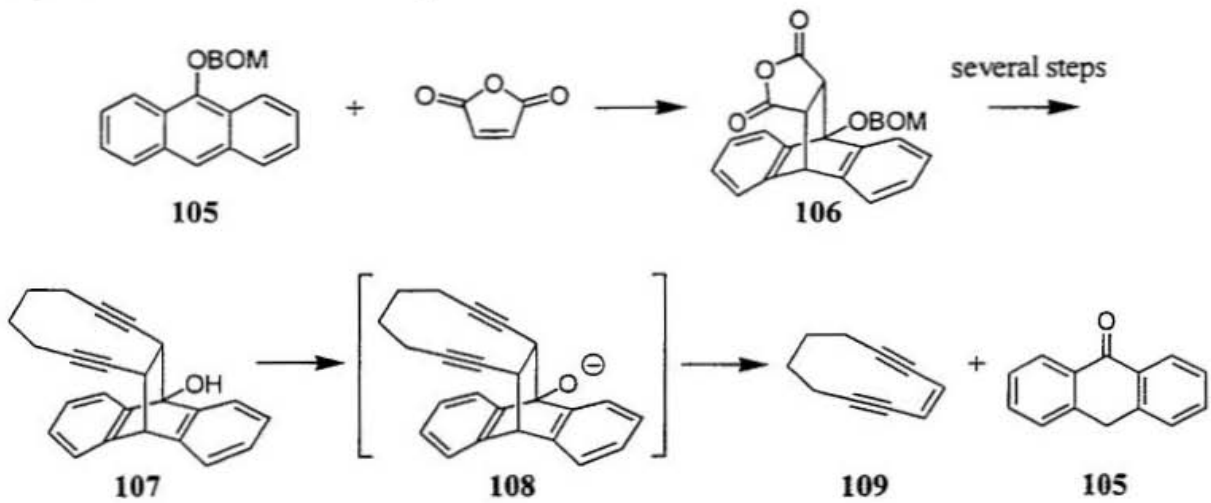
The key step in one of Nicolaou's designed endiyne syntheses



Scheme 5.26 The Planned Use of the Nozaki-Kishi Reaction to Form Compound **63**

Routes were found which led to a diiodoalkyne analogous to **103** and to the alcohol precursor of **102**. However, no method could be found which would produce the desired homopropargyl dialdehyde **102**. This unexpected setback put an end to this strategy.

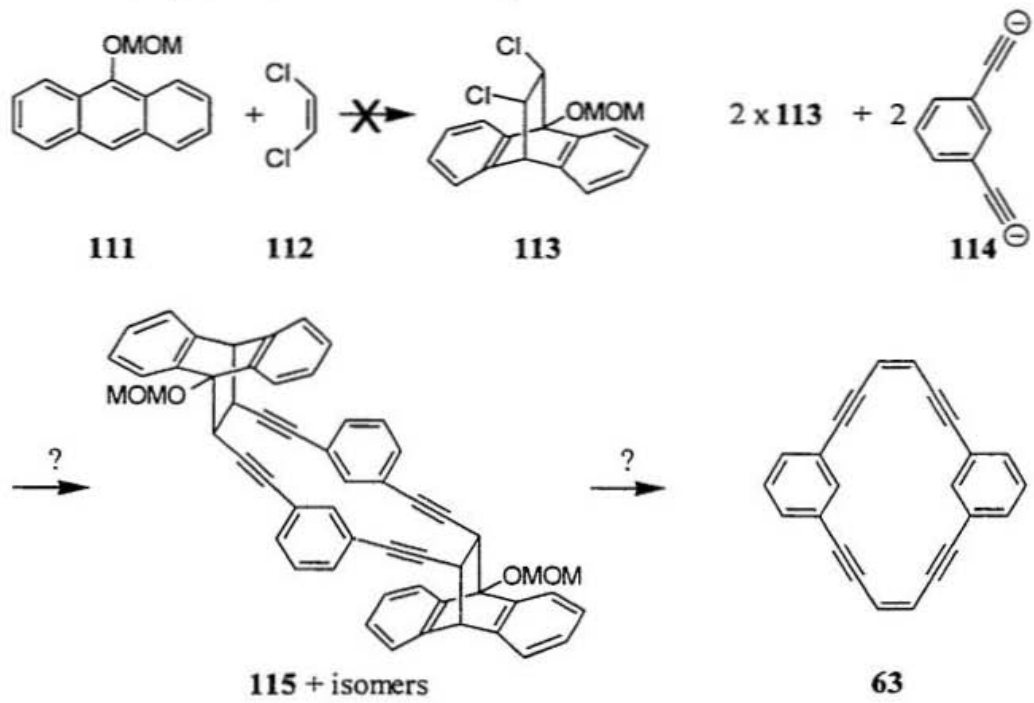
The last attempt to find an elegant and high-yielding synthesis of **63** was inspired by Nicolaou's unusual and fascinating synthesis of the very unstable cyclodecenediyne **109**.[76] This synthesis depended on an anionic retro-Diels-Alder reaction which could be conducted at room temperature as the final step. The mildness of this reaction enabled the ultimate isolation of **109**, despite the fact that it is unstable with respect to Bergman cycloaromatisation at room temperature.



Scheme 5.27 Nicolaou's Synthesis of the Unstable Enediyne **109** Using a Diels-Alder-Anionic-Retro-Diels-Alder Strategy

Our planned adaptation of Nicolaou's general strategy to target molecule **63** required the Diels-Alder reaction of **105**, or a similar compound, with commercially available *Z*-1,2-dichloroethene **112**. While this molecule has not been commonly employed as a

dienophile, it was hoped that the electron-withdrawing chlorine atoms and lack of steric hindrance would provide sufficient reactivity.



Scheme 5.28 Attempted Adaptation of Nicolaou's Anionic-Retro-Diels-Alder Strategy to the Synthesis of **63**

In the event MOM-ether **111** was synthesised from anthrone using a standard procedure, and its Diels-Alder reaction with compound **112** investigated. Nicolaou had found that BOM-ether **105** reacted with maleic anhydride in quantitative yield at reflux in benzene. Unfortunately **111** and **112** showed no signs of any reaction under these conditions. Hence a benzene solution of the substrates was heated for 16 hours at 130 °C in a sealed tube. Once again, no reaction was observed. The failure of this reaction was rather disappointing, since compound **112** had seemed likely to be a good dienophile. [The difference in reactivity between the MOM-ether used in our reaction and Nicolaou's

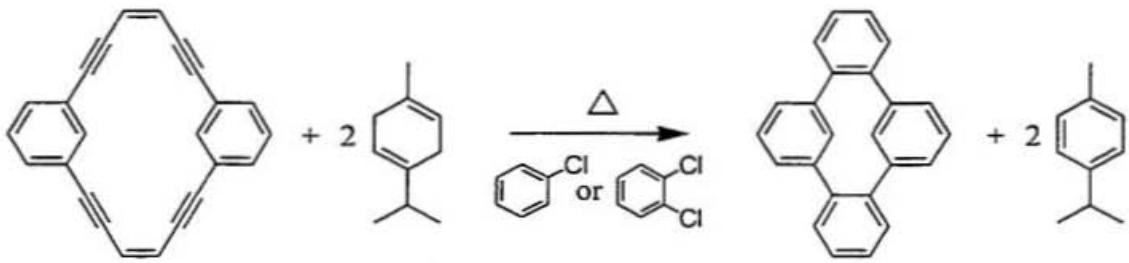
BOM-ether was thought to be insignificant.] Our attention turned to attempted syntheses of more reactive anthracenes such as 9,10-dimethoxyanthracene generated from anthraquinone, but such compounds were found to be much harder to make. Had we successfully generated compound **113**, its reaction with **114** might well have been problematic, since the S_N2 reactions of **113** appear quite sterically hindered.

As yet the only successful route to enediynophane **63** is a very low yielding two step procedure consisting of a quadruple Heck reaction and a double dehydrogenation using DDQ. Several intriguing and promising methodologies have been investigated to varying degrees, and it may well be possible that one of these alternatives will eventually allow a greatly improved overall yield, hence also providing sufficient **63** for some more probing study of its chemistry and physical properties. Alternative synthetic possibilities not investigated here which might allow the more efficient generation of **63** from **62** include the use of elemental sulphur as a dehydrogenating agent, and the use of bromination-dehydrobromination.

5.6.6 Attempted Controlled Bergman Reaction of Enediynophane 63 to Produce 64

Grissom's success in particular gave us hope that it might be possible to perform a double Bergman reaction on enediynophane **63** to produce the last two benzene rings of highly strained bridge difunctionalised [2.2]metacyclophane **64**. This common motif in cyclophane chemistry of forming a more favourable ring system and then contracting it to the desired but more highly-strained product had never before utilised the Bergman reaction, and the likelihood of a successful outcome was hard to predict. Unfortunately the low yields incurred in the synthesis of enediynophane **63** limited the scale of this key

reaction to 20 mg. Following the protocols of Grissom, **63** was combined with 20 equivalents of γ-terpinene per reaction, dissolved in chlorobenzene and heated at 170-230 °C in a sealed tube for 4.5 hours.

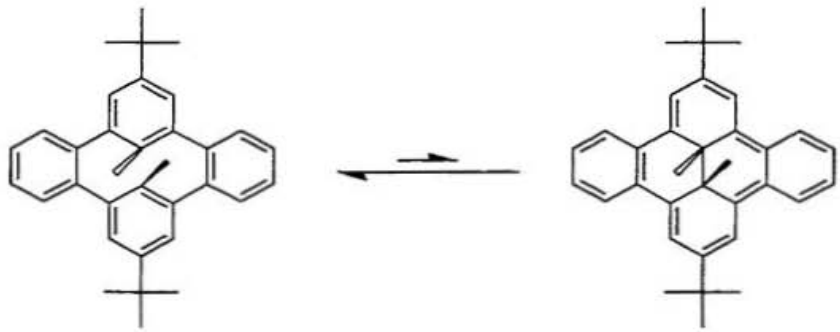


63 **115** **64** **116**

Scheme 5.29 Attempted Double-Bergman Reaction of Enediynophane **63**

It was found that no reaction occurred under these circumstances. Hence the solvent was removed and the experiment repeated using 1,2-dichlorobenzene and heating to 300 °C in a furnace for 4 hours. Thin layer chromatography of the reaction mixture now revealed no spot corresponding to starting material, but a large number of spots of similar intensity. Hence it was clear that compound **63** undergoes some sort of reaction at 300 °C, but separation of the desired product was not attempted due to the small scale of the reaction and large number of close-running products observed by TLC. Clearly, repetition of this experiment on a larger scale and isolation of product **64** would be highly desirable, although it is possible that the stability of **64** is insufficient under the reaction conditions to allow its successful synthesis by this route. Specifically, the proximity of the so-called internal protons in **64** may be problematic, and internally substituted derivatives may be more easily generated by this route.[77] Mitchell recently published a very interesting synthesis of the internally methylated derivative **117**, including a study of its equilibrium

with the valence-isomerised dihydropyrene **118** (Scheme 5.30).[78] It must also be remembered that the excellent results obtained by Grissom were with substrates in which the intermediate 1,4-diradical could undergo at least one intramolecular reaction, while in our case the intermediates would each have to react with neighbouring γ-terpinene molecules.



117 **118**

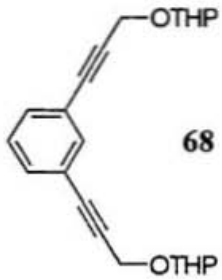
Scheme 5.30 Mitchell's Photo-Switch

5.7 Experimental

General Procedures

For general procedures please refer to the section in Chapter 2.

1,3-Bis[3-(2-tetrahydropyranyloxy)-1-propynyl]benzene (68)

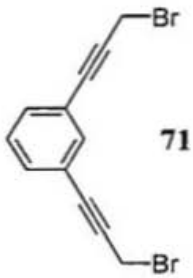


68

A mixture of **66** (4.72 g, 20.0 mmol), **67** (5.61 g, 40.0 mmol), DBU (9.13 g, 60.0 mmol), $Pd(PPh_3)_2Cl_2$ (0.24 g, 0.34 mmol) and CuI (0.25 g, 1.31 mmol) was refluxed in benzene

(40 mL). After 2h further **67** (2.80 g, 20.0 mmol) was added. The reaction was cooled after a total reflux time of 6 h, diluted with pet. ether (200 mL), stirred for 2 h and filtered. The filter cake was washed with further pet. ether (50 mL) and the combined organics washed with saturated ammonium chloride (2x50 mL), water (50 mL) and brine (50 mL), and dried ($MgSO_4$). After evaporation of the solvent a crude yield of 10.4 g was obtained (147%). This material was used directly in the preparation of **71**.

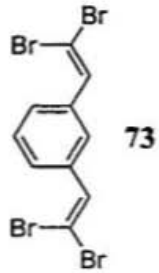
1,3-Bis(3-bromo-1-propynyl)benzene (71)



71

To a stirred solution of PPh_3 (2.62 g, 9.99 mmol) in dry dichloromethane (20 mL) cooled in an ice bath was added **69** (4.10 g, 10.0 mmol). When the yellow colour due to **69** abated crude **68** (1.04 g, max. 2.00 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirring continued overnight. The mixture was then evaporated onto silica gel and chromatographed (5:1 pet. ether:CH_2Cl_2). A second column (neat pet ether) was required to produce pure **71** as a white crystalline solid (0.525 g, 84% from **66**): mp 64-65 °C; ^{1}H NMR δ 7.53-7.25 (m, 4H), 4.14 (s, 4H); ^{13}C NMR δ 135.0, 132.1, 128.4, 122.5, 85.5, 85.0, 14.8; MS *m/z* (%) 312 (M^+, 1x^{79}Br, 1x^{81}Br, 14), 233 (94), 231 (96), 152 (100), 150 (23). Anal. Calcd for $C_{12}H_8Br_2$: C, 46.20; H, 2.58. Found: C, 46.08; H, 2.32.

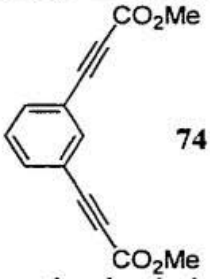
1,3-Bis(2,2-dibromoethenyl)benzene (73)



73

To a stirred solution of PPh_3 (54.75 g, 209 mmol) in dichloromethane (200 mL) cooled in an ice bath was added CBr_4 (34.62 g, 104 mmol) in portions. To this red mixture was added dropwise a solution of **72** (7.00 g, 52.2 mmol) in dichloromethane (100 mL). After 15 min the cooling bath was removed and the reaction allowed to continue stirring 40 h. [Other experiments suggest the reaction to be complete after roughly one hour if sufficient reagents are used initially.] A mixture of PPh_3 (10.95 g, 41.7 mmol) and CBr_4 (6.92 g, 20.9 mmol) in dichloromethane (50 mL) was then added dropwise to ensure completion. After 0.5 h the mixture was evaporated, and the residue extracted with 1:1 diethyl ether:pet. ether (6x300 mL). The combined extracts were chromatographed eluting with neat pet ether to give pure **73** as a pale yellow solid (16.36 g, 70%). An analytical sample was obtained by recrystallisation from ethanol: mp 69-70 °C, lit.[79] (no mp was reported); ^{1}H NMR δ 7.73 (s, 1H), 7.49-7.34 (m, 5H); ^{13}C NMR δ 136.2, 135.5, 128.5 (2C), 128.0, 90.6; MS *m/z* (%) 450 (15), 448 (59), 446 (M^+, 2x^{79}Br, 2x^{81}Br, 94), 444 (60), 442 (17), 288 (25), 286 (54), 284 (26), 126 (100), 103 (16).

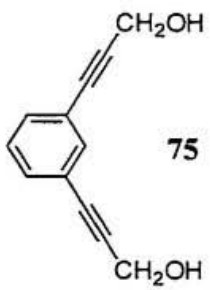
1,3-Bis(2-methoxycarbonyl-1-ethynyl)benzene (74)



74

To a stirred solution of **73** (3.37 g, 7.58 mmol) in THF (40 mL) cooled to -78 °C was added 1.3M *n*-BuLi (25 mL, 32.5 mmol) via syringe over 10 min. After 1.25 h the resulting solution was added via cannula to an ice cooled solution of methyl chloroformate (6.0 mL, 77.7 mmol) in THF (30 mL). After stirring 1 h at 0 °C this mixture was added via cannula to a stirred saturated solution of ammonium chloride (20 mL). The THF was evaporated and the aqueous residue extracted with dichloromethane (1x100 mL, 1x25 mL). The combined organics were dried ($MgSO_4$) and evaporated to give crude **74** (2.27 g, 124%). This material was recrystallised from heptane to give almost pure **74** (1.24 g, 63%) used directly in the alternative preparation of **75** (see below). An analytical sample was obtained by chromatography (5:1 hexanes:ethyl acetate: mp 79-81 °C (lit.[80] mp 94 °C); ^{1}H NMR spectral data consistent with the literature[80] ^{1}H NMR δ 7.78-7.39 (m, 4H), 3.85 (s, 6H).

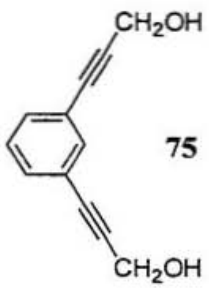
1,3-Bis(3-hydroxy-1-propynyl)benzene (75)



75

The most practical synthesis of this molecule was the one pot procedure from **66** via **68**. A mixture of **66** (2.91 g, 12.3 mmol), **67** (4.50 g, 32.1 mmol), DBU (5.64 g, 37.0 mmol), $Pd(PPh_3)_2Cl_2$ (0.15 g, 0.21 mmol) and CuI (0.15 g, 0.79 mmol) was refluxed in benzene (50 mL). After 3h the reaction was cooled, methanol (40 mL) added and the reaction mixture acidified by addition of *p*-TSA (3 g). The reaction was stirred for a further 3 h, then poured into a mixture of water (100 mL) and ethyl acetate (100 mL). After separation the aqueous layer was extracted with ethyl acetate (100 mL) and the combined organic extracts washed with water (100 mL), saturated sodium bicarbonate (100 mL) and brine (100 mL). The solution was dried ($MgSO_4$) and evaporated and the residue chromatographed (3:2 hexanes:ethyl acetate then 1:1 hexanes:ethyl acetate) to give **75** as a pale orange oil (2.14 g, 93%). This material was used directly in the synthesis of **97**. An analytical sample (colourless solid) was obtained from a previous experiment: mp 51.5-52.5 °C; ^{1}H NMR δ 7.50-7.23 (m, 4H). 4.49 (d, J = 6.1 Hz, 4H), 1.91 (t, J = 6.1 Hz, 2H); ^{13}C NMR δ 134.7, 131.6, 128.4, 122.8. 87.8, 84.7, 51.6; MS *m/z* (%) 186 (M^+, 100), 185 (45), 157 (34), 139 (47), 129 (56), 128 (66), 127 (41), 115 (47). Anal. Calcd for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41. Found: C, 77.30; H, 5.32.

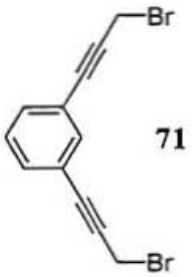
1,3-Bis(3-hydroxy-1-propynyl)benzene (75) [alternative preparation]



75

To a stirred solution of **74** (0.500 g, 2.06 mmol) in dichloromethane (50 mL) cooled to -78 °C was added 1.0M DIBAL in toluene (9.5 mL, 9.5 mmol). The reaction mixture was allowed to warm to -15 °C over a period of 3 h, at which point TLC revealed the reaction to be essentially complete. After reducing the temperature to -20 °C the reaction was quenched with methanol (1 mL) and then saturated sodium potassium tartrate (10 mL). The mixture was allowed to warm to room temperature, added to dichloromethane (50 mL) and water (50 mL) and stirred for 10 min. Following separation the aqueous was extracted with dichloromethane (50 mL) and the combined organics washed with brine (50 mL). The brine was back-extracted with further dichloromethane (50 mL). The combined extracts were dried ($MgSO_4$) and evaporated to give essentially pure **75** (0.354 g, 92%).

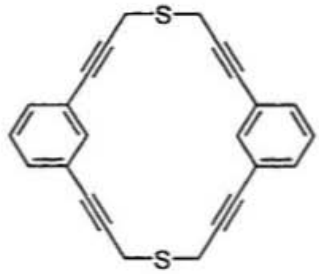
1,3-Bis(3-bromo-1-propynyl)benzene (71) [alternative preparation]



71

To a mixture of **75** (0.500g, 2.69 mmol) and CBr_4 (1.96 g, 5.91 mmol) in THF (30 mL) at 0 °C was added a solution of PPh_3 (1.76 g, 6.71 mmol) in THF (20 mL). The reaction mixture was allowed to gradually warm to room temperature, and after 9 h further PPh_3 (0.88 g, 3.4 mmol) was added to ensure completion. After a further 14 h the reaction mixture was evaporated onto silica and chromatographed using the dry flash technique (1:3 dichloromethane:pet. ether) to give pure **71** (0.786 g, 94%).

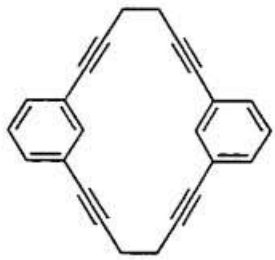
4,17-Dithia[7.7]metacyclophane-1,6,14,19-tetrayne (61)



61

To a stirred solution of **71** (0.600 g, 1.92 mmol) in a mixture of dichloromethane (1000 mL) and ethanol (100 mL) was added $Na_2S{\cdot}Al_2O_3$ (1.603 g, 4.23 mmol) in eight portions, one every 30 min. Stirring was continued overnight. The reaction mixture was filtered, evaporated and chromatographed (3:2 pet. ether:dichloromethane) to give pure **61** as a colourless solid (0.147 g, 41%): mp 224-226 °C; ^{1}H NMR δ 7.61-7.60 (m, 2H), 7.31-7.14 (m, 6H), 3.70 (s, 8H); ^{13}C NMR δ 135.8, 131.0, 128.2, 123.3, 85.7, 83.2, 21.1; MS *m/z* (%) 368 (M^+, 36), 333 (23), 320 (17), 308 (17), 302 (15), 300 (15), 289 (23), 277 (20), 276 (25), 264 (21), 252 (18), 171 (15), 152 (35), 151 (41), 150 (29), 140 (22), 139 (100), 127 (18), 126 (29), 114 (17), 113 (17). Anal. Calcd for $C_{24}H_{16}S_2$: C, 78.22; H, 4.38. Found: C, 78.33; H, 4.28. A second fraction was also isolated as a colourless solid believed to be the corresponding trimer **76** (0.040 g, 11%): mp 158-161 °C; ^{1}H NMR δ 7.60 (s, 3H), 7.39-7.22 (m, 9H), 3.70 (s, 12H); ^{13}C NMR δ 135.3, 131.4, 128.3, 123.1, 85.2, 82.5, 19.9; MS *m/z* (%) (M^+ not found). Good MS data for this compound could not be obtained. This is thought to be due either to its low volatility or to a stability problem. Anal. Calcd for $C_{36}H_{24}S_3$: C, 78.22; H, 4.38. Found: C, 77.95; H, 4.39.

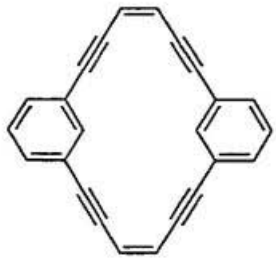
[6.6]Metacyclophane-1,5,13,17-tetrayne (62)



62

A stirred mixture of **66** (1.18 g, 5.00 mmol), **81** (50% in pentane, 0.801 g, 5.13 mmol), DBU (1.68 g, 11.0 mmol) and $Pd(PPh_3)_4$ (0.251 g, 0.22 mmol) in benzene (200 mL) was heated to reflux. After 2 h further $Pd(PPh_3)_4$ (0.140 g, 0.12 mmol) was added, and the reaction allowed to reflux overnight. To the cooled mixture was added pet. ether (200 mL). After stirring 15 min the mixture was filtered. The filtrate was washed with saturated ammonium chloride (50 mL) then brine (2x50 mL), dried ($MgSO_4$), evaporated and chromatographed (15:1 pet. ether:diethyl ether) to give almost pure **62** (0.128 g, 17%) along with some mixed fractions. Two recrystallisations of the almost pure material (dichloromethane / heptane, then chloroform) gave an analytical sample: mp 193-194 °C; ^{1}H NMR δ 7.84 (s, 2H), 7.33-7.20 (m, 6H), 2.69 (s, 8H); ^{13}C NMR δ 136.9, 129.9, 128.3, 124.0, 88.8, 81.6, 19.4; MS *m/z* (%) 305 (25), 304 (M^+, 100), 303 (22), 302 (31), 301 (25), 300 (24), 287 (16), 276 (22), 152 (38), 151 (27), 150 (17), 126 (19). Anal. Calcd for $C_{24}H_{16}$: C, 94.70; H, 5.30. Found: C, 93.54; H, 5.25. The mixed fractions were chromatographed a second time (20:1 pet. ether:diethyl ether) to give further **62** (0.027 g, 4%). [The true yield of this reaction was 15-20%, and in other runs a yield higher than 17% has never been obtained.]

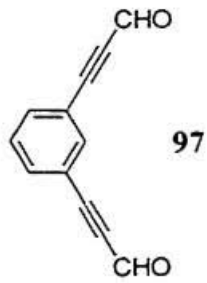
(*Z*,*Z*)-[6.6]Metacyclophane-3,15-diene-1,5,13,17-tetrayne (63)



63

A stirred mixture of **62** (0.232 g, 0.761 mmol) and DDQ (0.863 g, 3.80 mmol) in dioxane (20 mL) was heated at reflux for 10 h. Further DDQ (0.345 g, 1.52 mmol) was then added and the mixture refluxed for 2 h more. After cooling, hydroquinone (0.431 g, 3.91 mmol) was added in order to break up any complexes of the product. The reaction mixture was then evaporated onto silica and chromatographed to give **63** as a colourless solid (0.0195 g, 9%): ^{1}H NMR δ 7.89 (s, 2H), 7.46-7.31 (m, 6H), 6.12 (s, 4H).

1,3-Bis(3-oxo-1-propynyl)benzene (97)

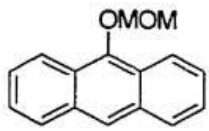


97

To a stirred solution of **75** (2.14 g, 11.5 mmol) in dichloromethane (200 mL) was added a solution of the Dess-Martin reagent (11.22 g, 26.5 mmol) in dichloromethane (65 mL). After 1.5 h further reagent (1.50 g, 3.5 mmol) was added, the reaction stirred for 30 min, diluted with diethyl ether (600 mL), and saturated sodium bicarbonate (200 mL) and $Na_2S_2O_3$ (40 g) added. The mixture was stirred for a further 15 min, water added (400 mL), the layers separated, and the upper organic layer washed with saturated sodium

bicarbonate (250 mL) and water (250 mL). The solution was dried ($MgSO_4$) and evaporated to give **97** as a yellow solid (1.862 g, 89%). An analytical sample was obtained by chromatography (5:1 hexanes:ethyl acetate): mp 57-58 °C; ^{1}H NMR δ 9.44 (s, 2H), 7.83 (s, 1H), 7.72-7.46 (m, 4H); ^{13}C NMR δ 176.3, 137.2, 135.3, 129.3, 120.5, 92.2, 88.7; MS *m/z* (%) 183 (19), 182 (M^+, 100), 181 (81), 154 (26), 153 (82), 126 (76). Anal. Calcd for $C_{12}H_6O_2$: C, 79.12; H, 3.32. Found: C, 78.82; H, 3.17.

9-(Methoxymethoxy)anthracene (111)



111

To a stirred solution of anthrone (5.40 g, 27.8 mmol) in THF (100 mL) cooled to just above 0 °C (to avoid precipitation of the anthrone) was added NaH (60% dispersion, 1.33 g, 33.4 mmol). [The initially dark red solution changed to orange-red.] The solution was cooled to 0 °C and after 15 min chloromethyl methyl ether was added (2.6 mL, 34.2 mmol). The reaction was removed from the ice bath, stirred 2 h at room temperature and then quenched with water (3 mL). Excess chloromethyl methyl ether was removed by purging the solution with N_2 in the hood. The solvent was then evaporated and the residue taken up in water (100 mL) and benzene (200 mL). After separation the organic layer was washed with 2M sodium hydroxide (2x100 mL) and brine (50 mL), dried ($MgSO_4$) and evaporated to give **111** as a pale orange solid (5.76 g, 87%). An analytical sample (colourless solid) was obtained by chromatography (2:1 hexanes:dichloromethane): mp 77-78 °C; ^{1}H NMR δ 8.34-7.44 (m, 9H), 5.38 (s, 2H), 3.76 (s, 3H); ^{13}C NMR δ 132.3,

128.3, 125.5, 125.4, 125.0, 122.8, 122.6, 122.5, 101.2, 58.1; MS *m/z* (%) 238 (M^+, 17), 193 (50), 165 (23), 45 (100). Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.58; H, 5.89.

5.8 References

[1] For a good recent text book on alkyne chemistry see *Modern Acetylene Chemistry*; Stang, P.J.; Diederich, F. Eds.; VCH: New York, 1995.

[2] Nicolaou, K.C.; Dai, W.-M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1387-1530.

[3] Konishi, M.; Ohkuma, H.; Matsumoto, K.; Tsuno, T.; Kamei, H.; Miyaki, T.; Oki, T.; Kawaguchi, H.; Van Duyne, G.D.; Clardy, J. *J. Antibiot.* **1989**, *42*, 1449-1452.

[4] Golik, J.; Dubay, G.; Groenweld, G.; Kawaguchi, M.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.; Doyle, T.W. *J. Am. Chem. Soc.* **1987**, *109*, 3462-3464.

[5] Lee, M.D.; Dunne, T.S.; Siegel, M.M.; Chang, C.C.; Morton, G.O.; Borders, D.B. *J. Am. Chem. Soc.* **1987**, *109*, 3464-3466.

[6] Lee, M.D.; Ellestad, G.A.; Borders, D.B. *Acc. Chem. Res.* **1991**, *24*, 235-243.

[7] See for example Nicolaou, K.C.; Stabila, P.; Esmaeli-Ezad, B.; Wrasidlo, W.; Hiatt, A. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 3142-3146.

[8] Nicolaou, K.C.; Smith, A.L. *Acc. Chem. Res.* **1992**, *25*, 497-503; Groneberg, R.D.; Miyazaki, T.; Stylianides, N.A.; Schulze, T.J.; Stahl, W.; Schreiner, E.P.; Suzuki, T.; Iwabuchi, Y.; Smith, A.L.; Nicolaou, K.C. *J. Am. Chem. Soc.* **1993**, *115*, 7593-7611.

[9] (a) Jones, R.R.; Bergman, R.G. *J. Am. Chem. Soc.* **1972**, *94*, 660-661; (b) Bergman, R.G. *Acc. Chem. Res.* **1973**, *6*, 25-31; (c) Lockhart, T.P.; Comita, P.B.; Bergman, R.G. *J.*

Am. Chem. Soc. **1981**, *103*, 4082-4090; (d) Lockhart, T.P.; Bergman, R.G. *J. Am. Chem. Soc.* **1981**, *103*, 4091-4096.

[10] Ward, H.R. *Acc. Chem. Res.* **1972**, *5*, 18-24; Lawler, R.G. *Acc. Chem. Res.* **1972**, *5*, 25-33.

[11] This idea is due to Nicolaou. An alternative explanation has been offered by Magnus, namely that the relative stability of **3** towards Bergman reaction is due to the anti-Bredt strain energy which would be present in the putative product. See Magnus, P.; Fortt, S.; Pitterna, T.; Snyder, J.P. *J. Am. Chem. Soc.* **1990**, *112*, 4986-4987; Snyder, J.P. *J. Am. Chem. Soc.* **1990**, *112*, 5367-5369. Although this is also a compelling argument, subsequent results suggest Nicolaou's simpler explanation to be sufficient.

[12] Nicolaou, K.C.; Zuccarello, G.; Riemer, C.; Estevez, V.A.; Dai, W.-M. *J. Am. Chem. Soc.* **1992**, *114*, 7360-7371.

[13] Nicolaou, K.C.; Tsay, S.-C.; Suzuki, T.; Joyce, G.F. *J. Am. Chem. Soc.* **1992**, *114*, 7555-7557.

[14] Aiyar, J.; Danishefsky, S.J.; Crothers, D.M. *J. Am. Chem. Soc.* **1992**, *114*, 7552-7554.

[15] (a) Sondheimer, F.; Wolovsky, R. *Tetrahedron Lett.* **1959**, *3*, 3-6; (b) Sondheimer, F.; Wolovsky, R.; Amiel, Y. *J. Am. Chem. Soc.* **1962**, *84*, 274-284.

[16] Figeys, H.P.; Gelbcke, M. *Tetrahedron Lett.* **1970**, *11*, 5139-5142.

[17] Sondheimer's previous synthesis of **13** produced a mixture of *cis* and *trans* isomers which required glpc separation. Okamura, W.H.; Sondheimer, F. *J. Am. Chem. Soc.* **1967**, *89*, 5991-5992.

[18] Mukaiyama, T.; Sato, T.; Hanna, J. *Chem. Lett.* **1973**, 1041-1044.

[19] McMurry, J.E.; Fleming, M.P. *J. Am. Chem. Soc.* **1974**, *96*, 4708-4709.

[20] Semmelhack, M.F.; Gallagher, J. *Tetrahedron Lett.* **1993**, *34*, 4121-4124.

[21] Corey, E.J.; Winter, R.A.E. *J. Am. Chem. Soc.* **1963**, *85*, 2677-2678.

[22] Vollhardt, K.P.C.; Winn, L.S. *Tetrahedron Lett.* **1985**, *26*, 709-712.

[23] Danishefsky, S.J.; Yamashita, D.S.; Mantlo, N.B. *Tetrahedron Lett.* **1988**, *29*, 4681-4684.

[24] Guillerm, D.; Linstrumelle, G. *Tetrahedron Lett.* **1985**, *26*, 3811-3812.

[25] See for example reference 36 or 41.

[26] Huber, R.S.; Jones, G.B. *Tetrahedron Lett.* **1994**, *35*, 2655-2658.

[27] Tarhouni, R.; Kirschleger, B.; Rambaud, M.; Villieras, J. *Tetrahedron Lett.* **1984**, *25*, 835-838.

[28] Borman, S. *C. & E. News* **1995**, *August 28*, pp. 28-30.

[29] The possibility of converting *trans* enediynes to *cis* has been addressed. See reference 9(c) and König, B.; Schofield, E.; Bubenitschek, P. *J. Org. Chem.* **1994**, *59*, 7142-7143.

[30] Jones, G.B.; Huber, R.S.; Mathews, J.E. *J. Chem. Soc., Chem. Commun.* **1995**, 1791-1792.

[31] Kuwatani, Y.; Ueda, I. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1892-1894.

[32] Raw, A.S.; Pederson, S.F. *J. Org. Chem.* **1991**, *56*, 830-833.

[33] Grissom, J.W.; Calkins, T.L.; Egan, M. *J. Am. Chem. Soc.* **1993**, *115*, 11744-11752.

[34] Ramming, M.; Gleiter, R. *J. Org. Chem.* **1997**, *62*, 5821-5829.

[35] Romero, M.A.; Fallis, A.G. *Tetrahedron Lett.* **1994**, *35*, 4711-4714.

[36] Lu, Y.-F.; Harwig, C.W.; Fallis, A.G. *Can. J. Chem.* **1995**, *73*, 2253-2262.

[37] Sworski, T.J. *J. Chem. Phys.* **1948**, *16*, 550.

[38] Hopf, H.; Jones, P.G.; Bubenitschek, P.; Werner, C. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2367-2368.

[39] Haley, M. *Synlett* **1998**, 557-565.

[40] Baughman, R.H.; Eckhardt, H.; Kertesz, M. *J. Chem. Phys.* **1987**, *87*, 6687-6699.

[41] Rubin, Y.; Parker, T.C.; Khan, S.I.; Holliman, C.L.; McElvany, S.W. *J. Am. Chem. Soc.* **1996**, *118*, 5308-5309.

[42] Jacobs, T.L.; Singer, S. *J. Org. Chem.* **1952**, *17*, 475-481; Jacobs, T.L.; Dankner, D. *J. Org. Chem.* **1957**, *22*, 1424-1427; Jacobs, T.L.; Dankner, D.; Singer, S. *Tetrahedron* **1964**, *20*, 2177-2180.

[43] Bodwell, G.J.; Houghton, T.J.; Koury, H.E.; Yarlagadda, B. *Synlett* **1995**, 751-752.

[44] Ensley, H.E.; Mahadevan, S.; Mague, J. *Tetrahedron Lett.* **1996**, *37*, 6255-6258.

[45] Hopf,[38] obtained a 93% yield for the double Heck reaction of propargyl alcohol with 1,4-dibromobenzene but only 47% for the 1,2 isomer. Ensley,[45] obtained a 96% yield for the triple Heck reaction of 1,3,5-tribromobenzene using the THP protected alcohol. We achieved a maximum yield of 67% with the unprotected alcohol in the double Heck reaction of 1,3-dibromobenzene.

[46] Tanaka, A.; Oritani, T. *Tetrahedron Lett.* **1997**, *38*, 1955-1956.

[47] Tsubota, M.; Iso, M.; Suzuki, K. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1252-1253.

[48] Ackerman, J.H.; Surrey, A.R. *Organic Syntheses*; Wiley: New York, 1973, Collect. Vol. V, 668-669.

[49] Corey, E.J.; Fuchs, P.L. *Tetrahedron Lett.* **1972**, *23*, 3769-3772.

[50] Bodwell, G.J.; Houghton, T.J.; Miller, D. *Tetrahedron Lett.* **1998**, *39*, 2231-2234.

[51] Unfortunately mass spectroscopy failed to give a molecular ion for this material, which TLC, NMR and elemental analysis suggested to be the trimer.

[52] For other recent examples of alkyne-bridged dithiacyclophanes see Cao, D.; Kolshorn, H.; Meier, H. *Tetrahedron Lett.* **1995**, *36*, 7069-7072; Cao, D.; Kolshorn, H.; Meier, H. *Tetrahedron Lett.* **1996**, *37*, 4487-4490.

[53] For a good recent review of the Heck reaction see de Meijere, A.; Meyer, F.E. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2379-2411.

[54] Kawase, T.; Ueda, N.; Oda, M. *Tetrahedron Lett.* **1997**, *38*, 6681-6684.

[55] Prepared from **80** according to the method of Suzuki, H.; Kondo, A.; Ogawa, T. *Chem. Lett.* **1985**, 411-412.

[56] Owsley, D.C.; Castro, C.E. *Organic Syntheses*; Wiley: New York, 1988, Collect. Vol. VI, 916-918.

[57] The combinations $Pd(PPh_3)_2Cl_2$ / CuI, and $Pd(PPh_2CH_2CH_2CH_2PPh_2)Cl_2$ / CuI both proved to give worse results than $Pd(PPh_3)_4$.

[58] Pyrrolidine has been reported to give good results for some reactions, but gave only lower yields in our hands.

[59] For an introduction to the use of dry flash chromatography see Harwood, L.M.; Moody, C.J. *Experimental Organic Chemistry*, Blackwell Scientific Publications: Oxford, 1989; 185-188.

[60] For example, see Burri, K.; Jenny, W. *Helv. Chim. Acta* **1967**, *50*, 1978-1993.

[61] Chauvin, R. *Tetrahedron Lett.* **1995**, *36*, 397-400.

[62] Iyoda, N.; Sakaitani, M.; Otsuka, H.; Oda, M. *Chem. Lett.* **1985**, 127-130.

[63] Findlay, J.W.A.; Turner, A.B. *Organic Syntheses*; Wiley: New York, 1973, Collect. Vol. V, 428-431.

[64] This reference could not be found.

[65] Fu, P.P.; Harvey, R.G. *Chem. Rev.* **1978**, *78*, 317-361.

[66] Chang, W.-H. *J. Org. Chem.* **1962**, *27*, 2921-2923.

[67] For reviews of the scope of this reagent see Fatiadi, A.J. *Synthesis* **1976**, 65-104, 133-167.

[68] Mashraqui, S.; Keehn, P. *Synth. Commun.* **1982**, *12*, 637-645.

[69] Harwood, L.M.; Moody, C.J. *Experimental Organic Chemistry*, Blackwell Scientific Publications: Oxford, 1989; 524.

[70] Felix, A.M.; Heimer, E.P.; Lambros, T.J.; Tzougraki, C.; Meienhofer, J. *J. Am. Chem. Soc.* **1978**, *43*, 4194-4196.

[71] Anantharamaiah, G.M.; Sivandaiah, K.M. *J. Chem. Soc. Perkin Trans. 1*, **1977**, 490-491.

[72] At least one other group has reported difficulty in repeating Jones' yield and selectivity for this reaction.

[73] Lipski, T.A.; Hilfiker, M.A.; Nelson, S.G. *J. Org. Chem.* **1997**, *62*, 4566-4567.

[74] The reagent was prepared by the method of Ireland, R.E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

[75] Nicolaou, K.C.; Liu, A.; Zeng, Z.; McComb, S. *J. Am. Chem. Soc.* **1992**, *114*, 9279-9282.

[76] Bunnage, M.E.; Nicolaou, K.C. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1110-1112. Nicolaou had previously synthesised **109** in 12% yield using a Ramberg-Bäcklund reaction.[12]

[77] For an early study of similar compounds substituted at the internal positions, see Mitchell, R.H.; Ananda Weerawarna, S. *Tetrahedron Lett.* **1986**, *27*, 453-456.

[78] Mitchell, R.H.; Chen, Y. *Tetrahedron Lett.* **1996**, *37*, 5239-5242.

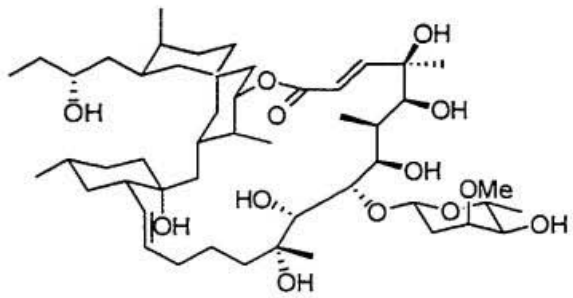
[79] Bestmann, H.J.; Frey, H. *Liebigs Ann. Chem.* **1980**, 2061-2071.

[80] Kumar, U.; Neenan, T.X. *Macromolecules* **1995**, *28*, 124-130.

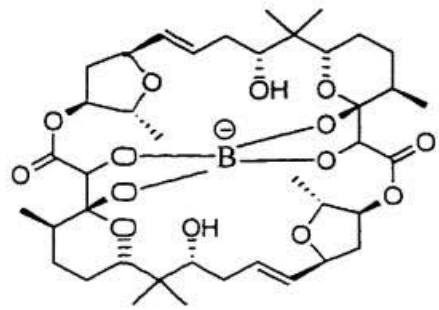
Synthesis and Study of Novel Macrolide Cyclophanes, and Their Participation in the Fries Rearrangement

6.1 Introduction

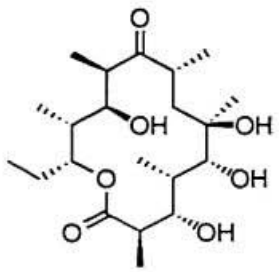
Macrolides have been the subject of a great deal of research. Prominent examples from the literature include Evans' synthesis of **1** cytovaricin,[1] Corey's syntheses of **2** aplasmomycin[2] and **3** erythronolide B,[3] and Boger's synthesis of the cyclophane **4** combretastasin D-2.[4] Also of interest is Scherkenbeck's synthesis of **5** cyclooctadepsipeptide PF1022A, in which the relative merits of macrolactamisation and macrolactonisation were compared.[5]



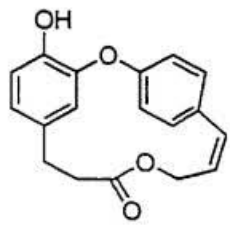
1 Cytovaricin



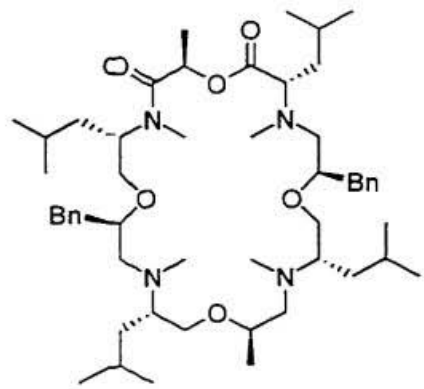
2 Aplasmomycin



3 Erythronolide B



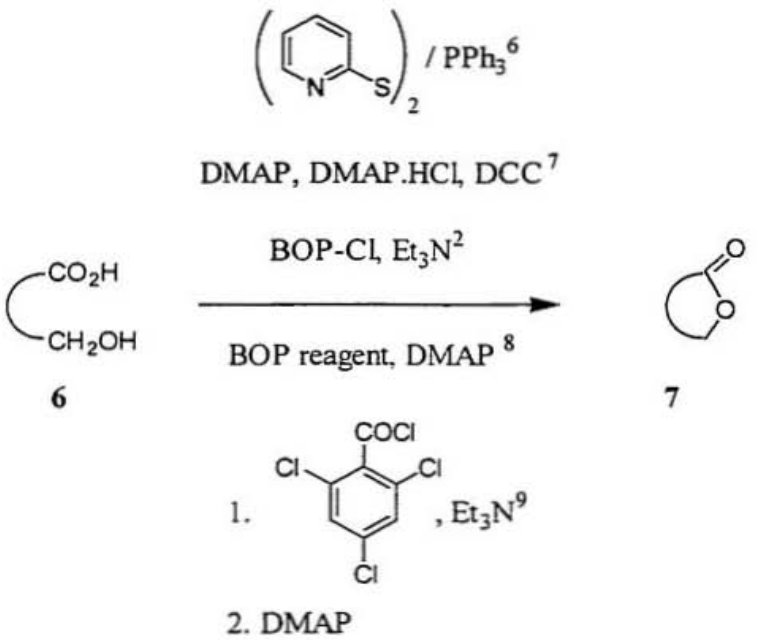
4 Combretastatin D-2



5 Cyclooctadepsipeptide PF1022A

Figure 6.1 Selected Macrolides from the Literature

Macrolides occur widely in nature, including a host of compounds with interesting biological activity, and methodologies for the macrolactonisation reaction itself have been optimised by many groups (Scheme 6.1).[6,7,8,9] Until the very recent advent of the Grubbs ring-closing metathesis,[10] the lactone functionality was almost always the first disconnection in a macrolide synthesis.[11]



Scheme 6.1 Commonly Used Methodologies for the Closure of Macrolide Rings

Each of the methodologies shown above has been used very successfully in closing lactones. Several of them have also been applied to acyclic ester formation, and several to lactam closure. As a general principle, each protocol works by activating the carbonyl group towards nucleophilic attack in the presence of a weak base. The final case above is Yamaguchi's two-step method in which the first step generates an activated mixed

anhydride. The macrolide is subsequently closed using the powerful nucleophilic catalyst DMAP.[9,12] All the other methods are one step procedures.

6.2 Ideas Behind This Work

The driving force for this project was the idea that the ester linkages of a lactone intermediate could be easily converted to ketone linkages using the venerable Fries rearrangement.[13] This rearrangement would concomitantly lead to contraction of the bridges between the rings, a recurring motif in cyclophane chemistry. With such a multiplicity of possible reactions to close the proposed "esterophanes" it seemed very likely that a satisfactory synthetic method could be found.

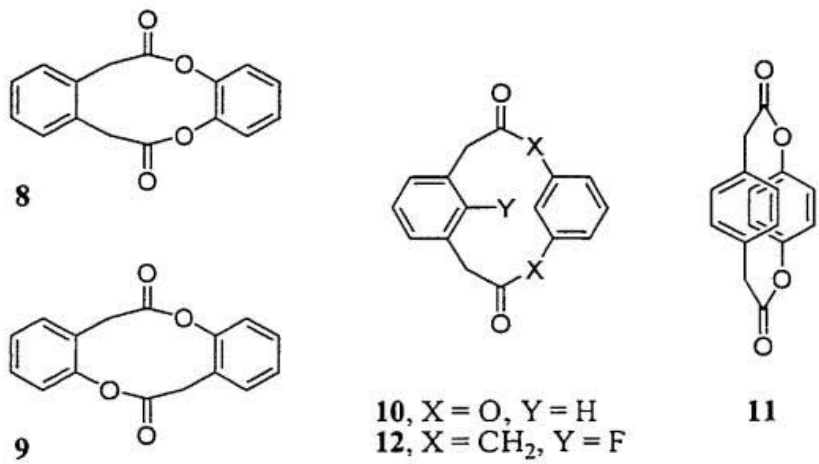
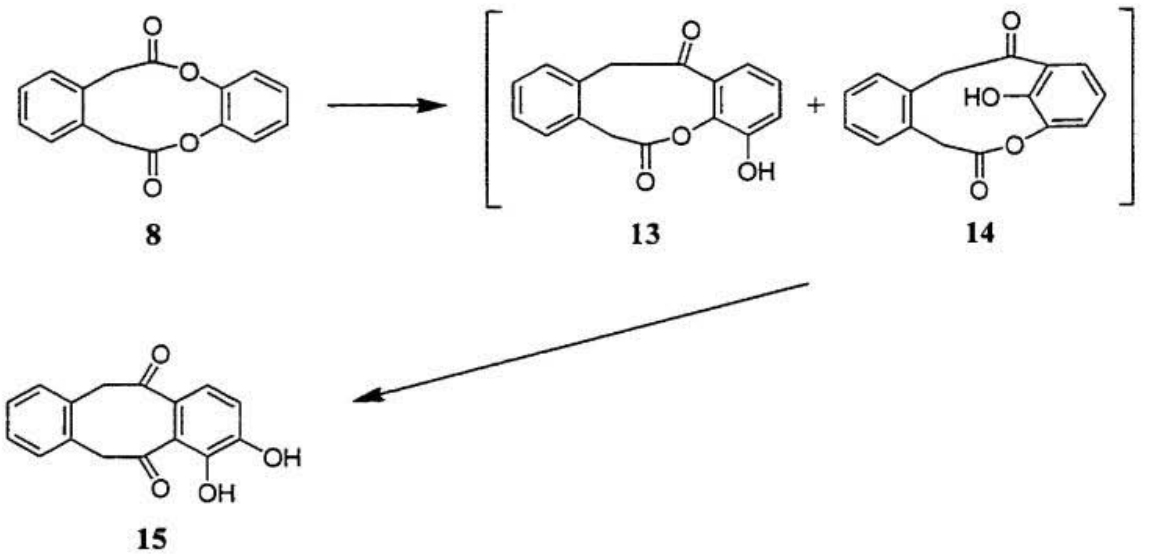


Figure 6.2 Esterophanes Considered as Synthetic Targets

The structures above were all considered as possible targets. It was hoped that they might possess interesting properties themselves, such as unusual conformational behaviour, as well as participating in the proposed Fries rearrangement. Compounds **8** and **9** represent

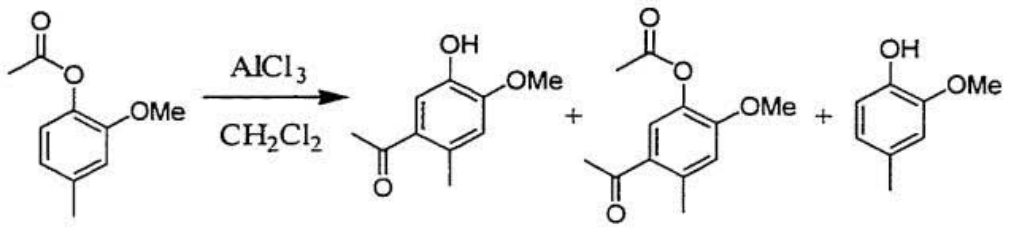
two contrasting strategies, and corresponding alternatives for **10** and **11** were also considered. Compound **8** would be synthesised by the coupling of two different partners, **9** by a simple dimerisation. Although the latter strategy has the benefit of requiring only one starting material, the former was preferred since it would allow access to a wider variety of products. [Formation of **9** would also be problematic since the monomer would be expected to undergo an intramolecular closure to give the five-membered lactone.] Compounds **10** and **11** were not expected to pose very difficult synthetic problems since the corresponding [3.3]thiacyclophanes are routinely available.[14] [The hybridisation of the central bridging atom is different in the thiacyclophane case, but the diketone **12** corresponding to **10** has been synthesised, with a yield of 68% for the ring-forming reaction.][15] Indeed, all of the above structures would be very interesting to compare with the corresponding thiacyclophanes, which have already been thoroughly studied, and it was anticipated that the X-ray crystal structures might be easily obtained due to their expected high degree of crystallinity.



8 **13** **14** **15**

Scheme 6.2 Possible Sequence of Fries Rearrangements of **8**

For all the esterophanes above it was hoped that consecutive Fries reactions might be induced to occur in a manner similar to that shown for compound **8** (Scheme 6.2). The idea was that Fries rearrangement of **8** could lead to compounds **13** and **14**, both of which would be likely to react further under the same conditions to produce the same product, diphenol **15**. Chemists have long argued over whether the Fries rearrangement is intra- or intermolecular. In the case shown below (Scheme 6.3), Munavalli showed that the mechanism of the reaction was dependent on temperature.[16] Low temperatures (0 °C) strongly favoured the production of the expected product **17**, presumably through an intramolecular pathway. At room temperature, however, compounds **18** and **19** were observed, which could have been produced only by intermolecular reaction. Hence in this case the two mechanisms compete with one another.



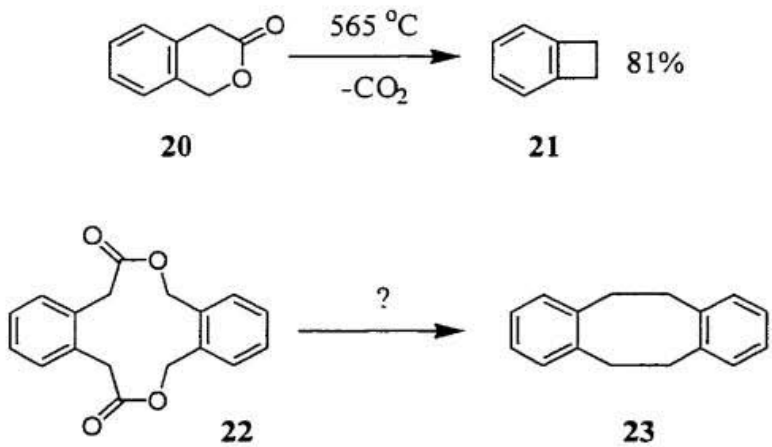
16 **17** **18** **19**

Scheme 6.3 Munavalli's Experiment[16]

The rationale for the intramolecular case is rather interesting, since the intermediate is thought to be a complex rather than a bonded species. In the case we propose there is expected to be an increase in strain energy associated with the ring contractions, but the intermediates are held together by a tether as well as any favourable complexation energy, and these factors should favour the intramolecular reactions. The substrate **8** for the

experiment we were proposing should be nearly as reactive as **16**, having two phenolic ester moieties on the ring to be acylated.

Apart from the Fries rearrangement, another possibility presented itself. The work of Spangler had previously shown that under certain circumstances FVT could lead to a useful ring contraction in similar compounds, suggesting that if an appropriate esterophane were subjected to the correct FVT conditions the corresponding [2.2]cyclophane might be produced.[17] [It should be noted that investigation of this idea would require a different group of esterophanes (Scheme 6.4).] While this idea was not pursued at this point, it is definitely worthy of future consideration, and the requisite esterophanes should be accessible via a similar route.



Scheme 6.4 Spangler's Methodology: a Possible Extension of the Esterophane Project

Esterophane **22** and the corresponding [4.4]*meta* and [4.4]*para* derivatives should be readily available, as well as the compounds with different substitution patterns in the two benzene rings. Hence a wide range of [2.2]cyclophanes could theoretically be accessed. The beauty of cyclophane syntheses based on Spangler's methodology would be that two

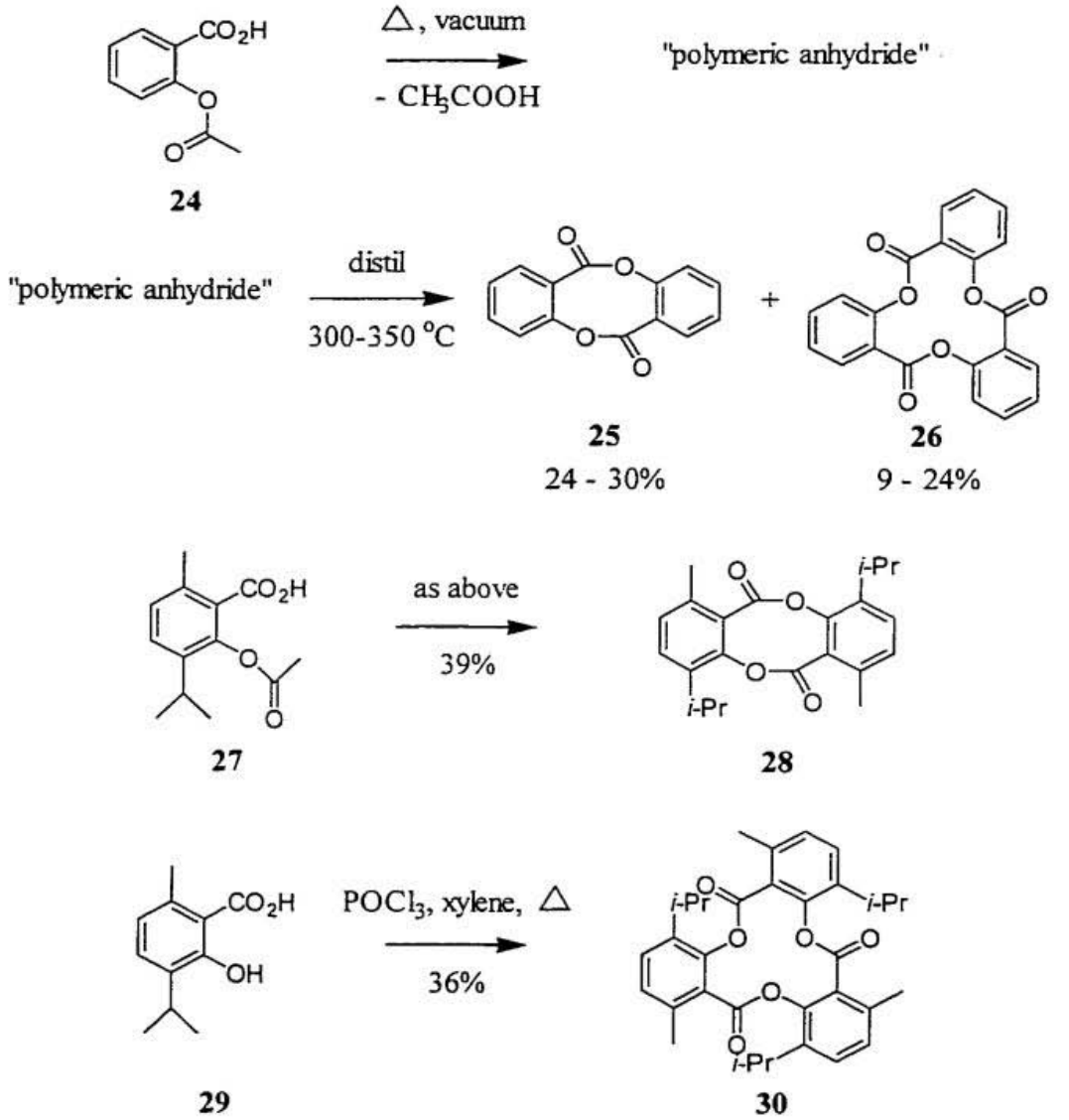
bridging atoms are expelled in each step. Thus the starting [4.4]esterophanes such as **22** are expected to be less strained than the corresponding [3.3]dithiacyclophanes. A potential drawback is the fact that the two "ends" which must then rejoin following the first CO_2 extrusion are further apart than in the corresponding SO_2 (FVT) or S (photo) extrusions. The final ring-closing reaction is presumably identical to that in the thiacyclophane route.

Another possibility not yet pursued was to synthesise the whole series of corresponding "amidophanes". From previous studies (e.g. reference 5) it is well known that the lactam closure is more easily achieved than the corresponding lactone closure. The amidophanes might be readily reduced to the corresponding aminophanes. Once again, these compounds might be expected to have interesting physical properties, and could also be powerful chelating ligands.[18]

6.3 The Salicylides and Thymotides

Although the exact esterophane structures we intended to synthesise were unprecedented in the literature, some examples of similar compounds already existed. When *O*-acetylsalicylic acid **24** is heated under reduced pressure, acetic acid is removed leaving a residue believed to be a polymeric anhydride. After distillation at 300-350 °C both a dimer (disalicylide **25**) and a trimer (trisalicylide **26**) could be isolated by crystallisation (Scheme 6.5).[19] These products are well known, and their stereochemical properties have been studied by dipole measurements,[20] and later by variable temperature NMR.[21] The dimer **25** can be compared to [2.2]orthocyclophane **23**, whose

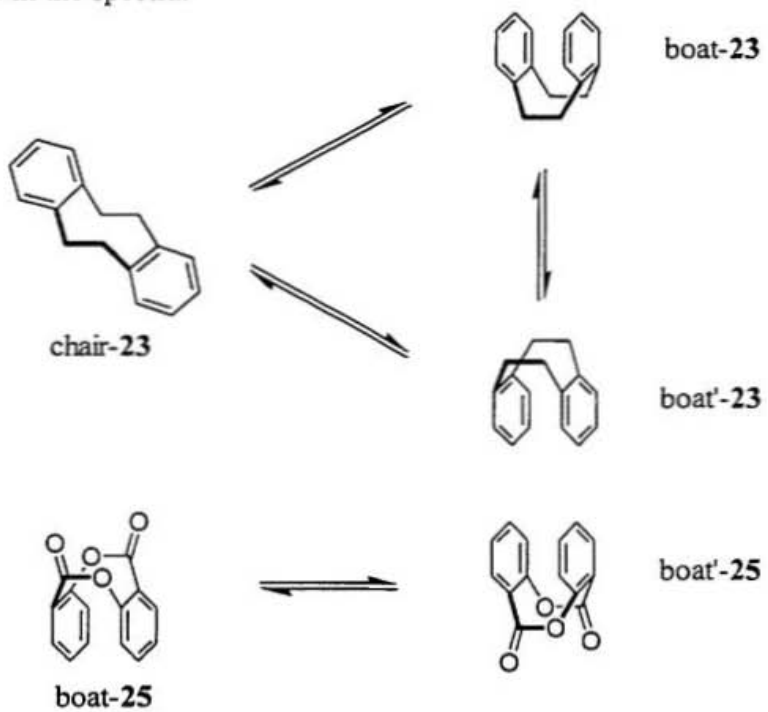
conformational properties have also been extensively studied by variable temperature NMR (see Scheme 6.6).[22]



Scheme 6.5 Dimerisation and Trimerisation of Salicylic and *o*-Thymotic Acids[19,23]

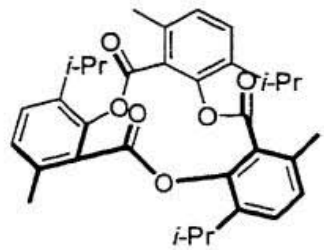
An early crystal structure of **23** showed the 8-membered ring to exist in a chair (*trans*) conformation in the solid state.[24] However, the later NMR studies suggested that

in solution a rapidly inverting boat (*cis*) form was favoured over the chair at low temperatures (< -100 °C), while at room temperature both conformations are roughly equally populated. In the case of **25** it was initially believed that both of these forms had been isolated, but more careful measurement of the molecular masses of the two compounds actually obtained revealed the supposed *trans* form to be trimer **26**. Compound **25** was initially believed to favour the *cis* conformation in solution on the basis of its high dipole moment (6.26 D). [The *trans* conformer would be expected to have a dipole moment of approximately zero.] Subsequent NMR studies on ring-substituted disalicylides suggested that, similar to **23**, two twist boat (*cis*) forms of **25** interconvert at room temperature. No mention was made of the chair form, suggesting it is not observed in the spectra.[21]



Scheme 6.6 The Presumed Conformational Behaviour of [2.2]Orthocylophane **23** and Disalicylide **25**

The ring-substituted derivative *O*-acetyl-*o*-thymotic acid **27** can be similarly condensed with itself to give *cis*-di-*o*-thymotide **28**, and the parent acid **29**, when heated with $POCl_3$, produces the trimer tri-*o*-thymotide **30** (Scheme 6.5).[23] The latter is a fascinating molecule which has been the subject of much study, primarily for its very unusual geometrical properties.[25] This compound possesses neither a chiral centre nor any inherent planar chirality. However, the presence of three ester functionalities creates the possibility of chirality through steric crowding. [The molecule may be thought of as propeller shaped, its chirality dictated by the "screw" of the propeller (Figure 6.3).]

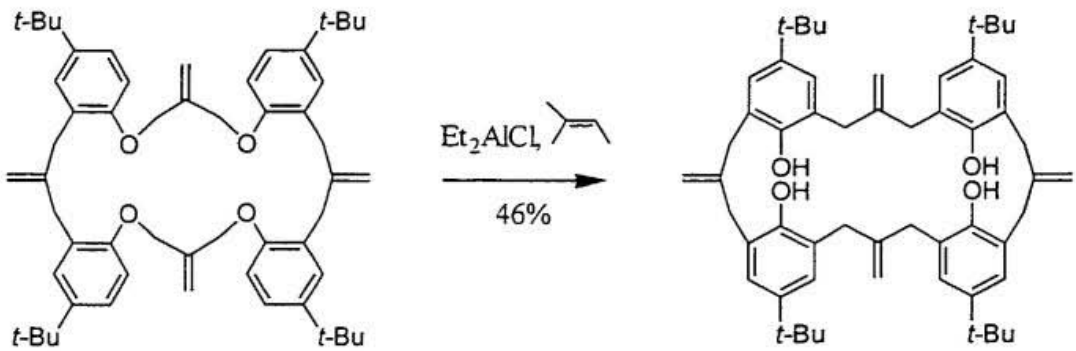


30

Figure 6.3 The Propeller Conformation of **30** Responsible for its Chirality

As **30** crystallises from a non-polar solvent, the crystals formed consist of just one of the two enantiomeric forms, the absolute chirality apparently depending on that of the first crystal.[26] Indeed, a single crystal taken from one batch of trithymotide can be used to seed another crystallisation so that the same enantiomer is produced in a separate crystallisation. This behaviour allows the possibility of obtaining every molecule of a given sample with the same absolute chirality. Clearly, this is more powerful than any type of resolution, where, by necessity, half of the molecules are wasted. The corollary of this is that such a crystallisation could not occur without racemisation in solution,

allowing all of one enantiomer to be inverted at the point of crystallisation.[27,28] Attempts have been made to harness the unique properties of trithymotide, although these ended rather early, perhaps due to the expense of the material itself and the starting material in its synthesis. One of the ideas touted close to the time of its discovery was that the compound might be particularly helpful in the resolution of small hydrocarbons containing only unresolvable functional groups such as halogens.[29] This idea stemmed from another interesting aspect of the behaviour of **30**, its ability to encapsulate solvent molecules of a certain size within its homochiral crystals. It was thought, correctly, that the crystallisation process might preferentially cause encapsulation of one enantiomer of the hydrocarbon over the other. Despite the favourable early results obtained interest in trithymotide has declined. However, its interesting geometrical properties augured well for the present project.



31 **32**

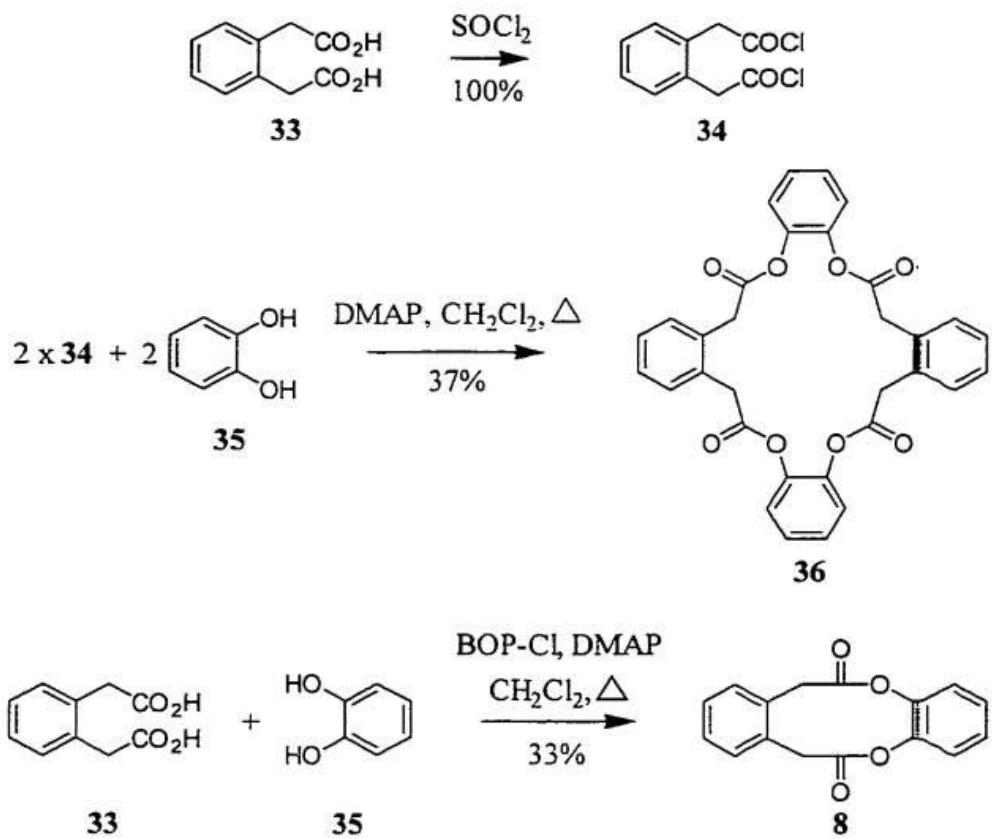
Scheme 6.7 Hiratani's Tandem Claisen Rearrangement[30]

After this project's inception a paper appeared from Hiratani's group which to a great degree mirrored our intentions with the Fries reaction (Scheme 6.7).[30] Hiratani used a Lewis acid catalysed tandem Claisen rearrangement to effect a ring contraction

remarkably similar to the ones we planned. The success of this approach, albeit in a system expected to have less strain energy than our dimeric substrates, was very encouraging.

6.4 This Work[31]

Two basic concepts were considered to achieve our goal. The first involved the condensation of an appropriate diacyl chloride with a diphenol, the other treatment of a mixture of a diphenol and a diacid with a coupling agent (Scheme 6.8).

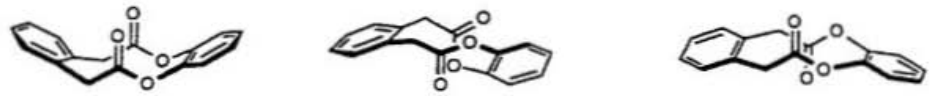


Scheme 6.8 The Successful Synthesis of Esterophanes **36** and **8**

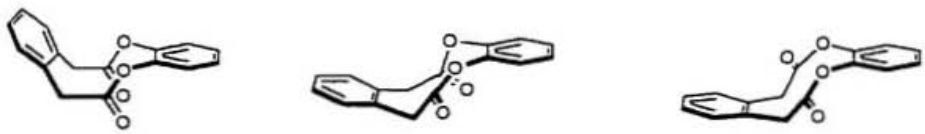
The possibilities were approached with an open mind, as neither possibility seemed intrinsically more likely to give a better yield of "dimer". [The word dimer will be used to describe products formed from the union of one molecule of each starting material.] In the event it was found possible to synthesise bis(acyl chloride) **34** in 100% yield from commercially available diacid **33**. Reaction of this material at high dilution with catechol **35**, using DMAP as the base produced a 37% yield of a material which was subsequently shown to be the "tetramer" **36**. Analysis of the crude reaction mixture by TLC revealed the existence of a weak spot corresponding to the dimer **8**, but after work-up this spot disappeared. Hence it appeared that this strategy was not capable of producing significant quantities of the desired dimeric structure **8**, and the second possibility was then investigated. Of the many possible coupling agents (see above), BOP-Cl was chosen due to its ease of preparation and use,[32] and due to its reliability.[33] The reagent was prepared according to Palomo-Coll's procedure,[32] but the reaction conditions were modified slightly in an attempt to favour the dimer over higher oligomers. Hence a dichloromethane solution of the diacid, the diphenol and DMAP was added dropwise to a vigorously stirred slurry of BOP-Cl in refluxing dichloromethane. When TLC indicated that all the starting material had reacted the mixture was concentrated and purified by silica gel chromatography. An idea not thoroughly considered at the outset was the possible instability of the lactone products. It was found absolutely critical to oven dry the silica before use. Even then, it was suspected that, in the case of the dimer **8**, the low yield of 33% was to some extent due to cleavage during chromatography.

X-ray crystallography and an AM1 level conformer search were both performed on dimer **8**, in order to establish the solid-state conformation and the predicted lowest

energy conformation. The calculations, performed using the Spartan software package,[34] suggested that the six lowest energy conformers are those shown below (Figure 6.4).



8A 0.00 kcal mol^{-1} **8B** 0.32 kcal mol^{-1} **8C** 1.85 kcal mol^{-1}



8D 1.97 kcal mol^{-1} **8E** 4.85 kcal mol^{-1} **8F** 5.02 kcal mol^{-1}

37 X = CH_2
38 X = S
39 X = Se
40 X = O

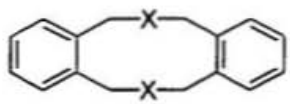


Figure 6.4 Calculated Low Energy Conformers of **8**

Previous studies have been published on the analogous compounds **37-40**.[35] Fukazawa's work in particular has revealed some interesting facets of their behaviour.[36] X-ray crystallography has shown the solid state conformations of all four compounds to be *anti* chair structures, most similar to **8E** and **8F** above. In the case of **40**, as previously noted for [2.2]orthocyclophane, the most populous conformer in solution does not correspond to that favoured in the solid state. While the X-ray structure closely approximates the C_{2h} form predicted by MM2 calculations, the NMR spectrum is inconsistent with this conformation. Fukazawa took the most plausible structures generated by his MMRS program,[37] and calculated the expected shift values for the methylene protons in each case using the ring current method. The only low energy conformation consistent with the

observed NMR conformation was directly analogous to our calculated lowest energy conformer, **8A**.

It is readily observed that the identity of the atoms in the bridges can have a major effect on the most favourable conformation, and in this case two conformers without precedent in the previous examples of [3.3]orthocyclophanes are the second and third lowest in their predicted energies. This may be due either to the sp^2-hybridisation of the central carbon atoms or to dipole moment considerations. [Conformers **8A** and **8D** would be expected to have high dipole moments, while in **8B** and **8C** the dipoles oppose one another.] The closeness of the calculated energies gives no certainty as to the most stable conformer in solution, and indeed suggests that structures **8A-8D** may all be present. Variable temperature NMR was undertaken to further probe this question. In the event no significant line broadening was observed for the benzylic protons (observed as a singlet) down to -90 °C, indicating that any species present interconvert rapidly even at that temperature.

8A **8A'**

Scheme 6.9 Possible Process Accounting for Interconversion of Benzylic Protons

Interconversion of the four lowest energy forms of the molecule is possible through rotation of the bridge bonds, but this does not account for the observed NMR data since these rotations do not interconvert the benzylic protons, which are diastereotopic in each

conformer. Hence it is necessary that, besides any interconversion of conformers, an inversion similar to that shown in Scheme 6.9 must be taking place. The NMR data show that the activation energy for the process concerned is < 9.5 kcal.mol^{-1}, assuming a very small Δv value of 10 Hz.

X-ray crystallography revealed a structure similar to the unprecedented predicted second lowest energy conformer **8B** (Figure 6.5). The structure is best described as a twisted *anti* conformation. It possesses C_1-symmetry, and is hence chiral. [It is not known whether or not individual crystals consist of a single enantiomer, as in the case of trithymotide **30**.] The aromatic rings show no significant deviations from planarity, and the torsion angle of C(3)-C(4)-C(9)-C(10) is, within experimental error, 0°. The torsion angle of O(1)-C(18)-C(13)-O(12) is 6.4(8)°. As mentioned above, a possible reason for the molecule favouring this conformer might be that it allows the dipoles to oppose one another. At this stage it is not known whether this is the predominant conformer in solution, but an inversion of **8B** analogous to that shown for **8A** in Scheme 6.9 can be easily envisaged.

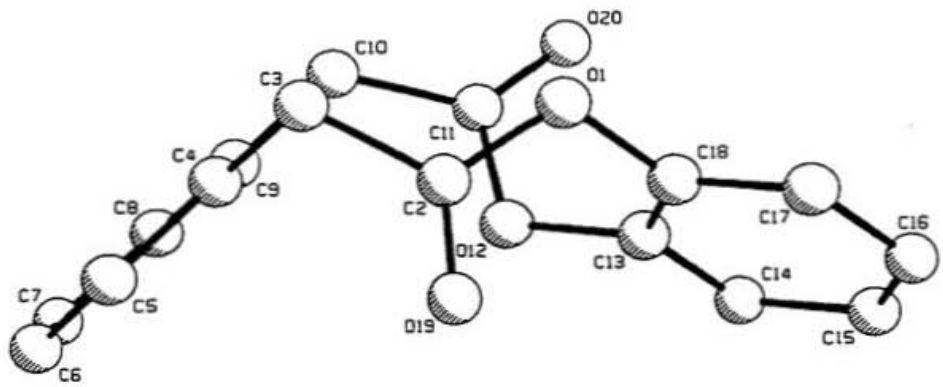
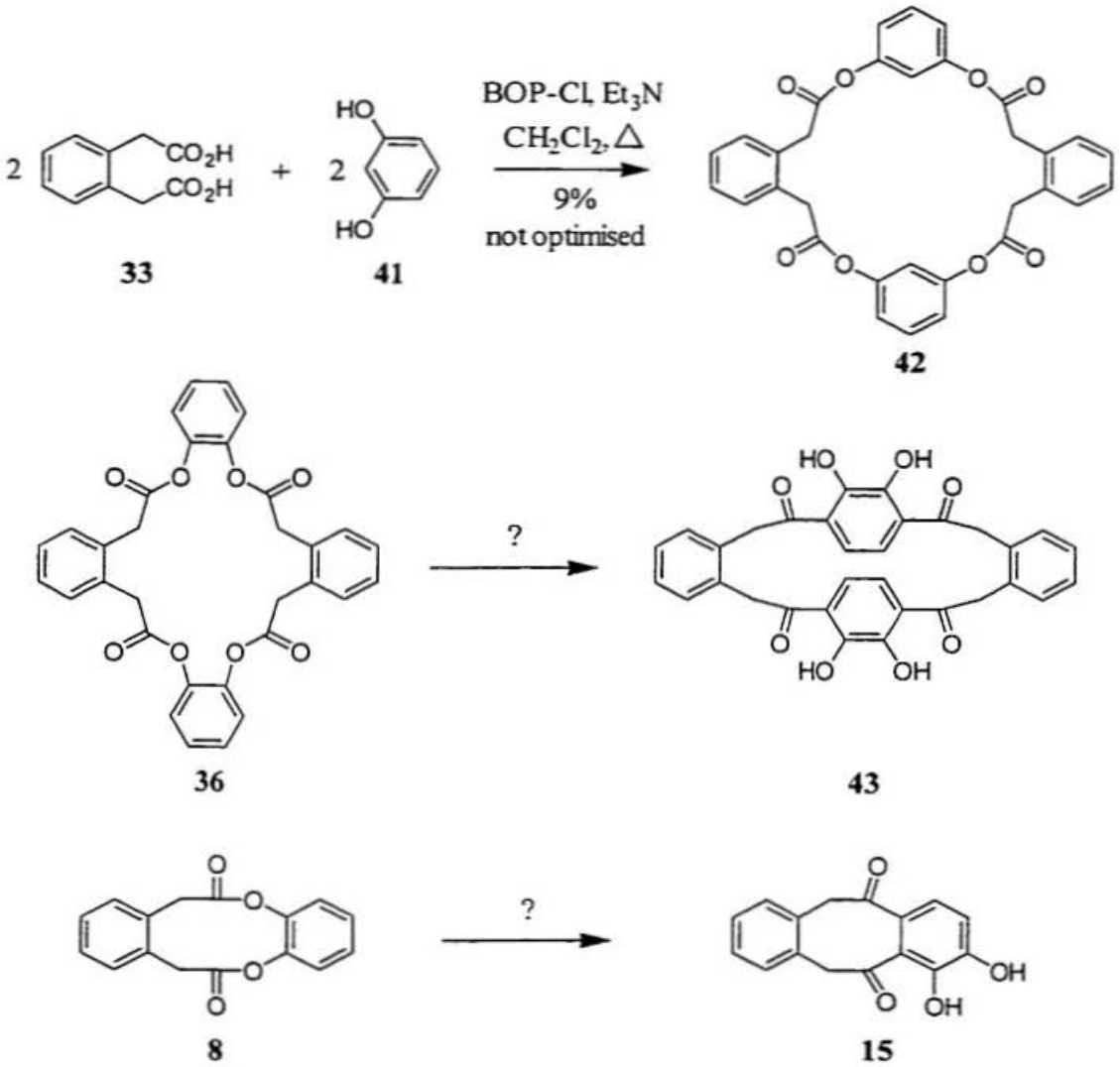


Figure 6.5 Molecular Structure of **8** in the Solid State



Scheme 6.10 Some of the Unfinished Business of this Chapter

Having demonstrated the feasibility of both the diacyl chloride and BOP-Cl methodologies it was unfortunate that there was not more time to spend on this project. The synthesis of only one other "esterophane" was attempted, and this was done before the improved methodologies described above had been established (Scheme 6.8). In this

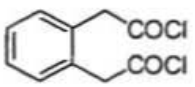
case only the tetramer **42** was isolated, and the yield obtained was just 9%. One attempt was made to conduct the much-anticipated Fries rearrangement, but the result was inconclusive. No effort has yet been made to synthesise any of the esterophanes required to investigate the adaptation of Spangler's methodology (Scheme 6.4), but they are expected to be more easily accessible than **8** due to their lower expected strain energies. There seem to be very many possibilities left to explore, and it appears likely that the most interesting results are yet to be obtained.

6.5 Experimental

General Procedures

For general procedures please refer to the section in Chapter 2.

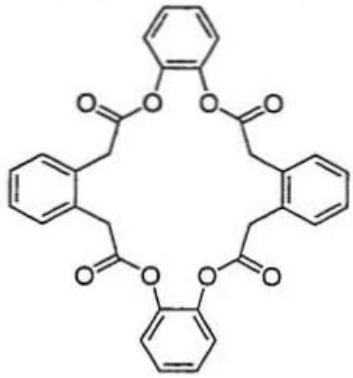
o-Phenylenediacetyl chloride 34



34

A stirred mixture of **33** (5.00 g, 25.7 mmol) and thionyl chloride (15 mL, 206 mmol) was heated at gentle reflux until dissolution was complete. The excess thionyl chloride was then removed by rotary evaporation, heptane added (40 mL) and the latter also removed by rotary evaporation to give, after thorough drying, **34** as an orange solid (5.94 g, 100%): mp 30-31 °C (heptane), lit.[38] (no mp was reported) ^{1}H NMR δ 7.39-7.29 (m, 4H), 4.20 (s, 4H); ^{13}C NMR δ 171.5, 131.6, 130.7, 129.2, 50.6; MS *m/z* (%) 230 (M^{+}, 2), 195 (24), 167 (29), 158 (41), 141 (35), 139 (100), 104 (35), 103 (24).

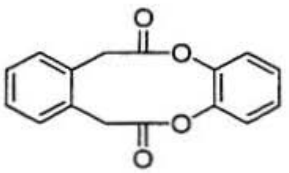
1,12,19,30-Tetraoxa-2,11,20,29-tetraoxo[3.3.3.3]orthocyclophane 36



36

To a stirred refluxing solution of DMAP (1.06 g, 8.66 mmol) in dichloromethane (150 mL) was added dropwise over 13 h a solution of **34** (0.500 g, 2.16 mmol) and catechol (0.238 g, 2.16 mmol) in dichloromethane (200 mL). After 2 h further heating the cooled solution was filtered through a plug of silica, washed with ice cold 5% citric acid (2x50 mL), ice cold 5% sodium bicarbonate (2x50 mL) and ice cold brine (50 mL), dried ($MgSO_4$) and filtered through a second plug of silica. After evaporation the solid obtained (0.340 g, 68%) was found by NMR to be contaminated with grease. The product was washed with several portions of pet ether giving pure **36** (0.213 g, 37%): mp 252-255 °C, ^{1}H NMR δ 7.40-7.33 (m, 8H), 7.20 (m, 8H), 3.98 (s, 8H); ^{13}C NMR δ 168.8, 141.8, 132.6, 130.9, 128.2, 126.6, 123.3, 38.5; MS *m/z* (%) 536 (M^+, 4), 269 (32), 241 (16), 233 (36), 205 (17), 159 (33), 158 (32), 131 (79), 110 (29), 104 (72), 103 (100), 102 (15). Anal. Calcd for $C_{32}H_{24}O_8$: C, 71.64; H, 4.51. Found: C, 71.63; H, 4.39.

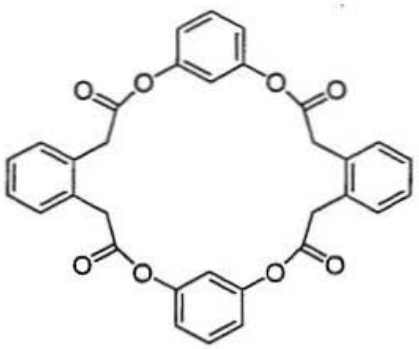
1,12-Dioxa-2,11-dioxo[3.3]orthocyclophane 8



8

To a stirred suspension of BOP-Cl (2.00 g, 7.86 mmol) in refluxing dry dichloromethane (200 mL) was added dropwise over 9 h a solution of **33** (0.529 g, 2.72 mmol), catechol (0.300 g, 2.72 mmol) and DMAP (2.00 g, 16.4 mmol) in dry dichloromethane (300 mL). When the addition was complete the reaction mixture was cooled, concentrated to about 100 mL and filtered through a plug of oven dried silica eluting with dry dichloromethane. The crude product was then chromatographed (dry dichloromethane) on oven dried silica to give pure **8** as a colourless solid (0.244 g, 33%): mp 191-193 °C, ^{1}H NMR δ 7.35 (m, 4H), 7.21 (m, 4H), 3.98 (s, 4H); ^{13}C NMR δ 170.3, 144.1, 132.9, 132.2, 128.6, 126.7, 122.6, 40.6; MS *m/z* (%) 268 (M^{+}, 7), 159 (26), 158 (46), 131 (41), 110 (51), 104 (59), 103 (100); HRMS calcd for $C_{16}H_{12}O_4$ (M^{+}) 268.0735, found 268.0735.

1,12,19,30-Tetraoxa-2,11,20,29-tetraoxo[3.3.3.3]orthometaorthometacyclophane 42



42

To a solution of resorcinol (0.297 g, 2.70 mmol), **33** (0.524 g, 2.70 mmol) and triethylamine (1.6 mL, 11.5 mmol) in dichloromethane (150 mL) was added BOP-Cl (1.39 g, 7.58 mmol). The reaction mixture was stirred for 10.5 h at room temperature, washed with ice-water (100 mL), then brine (50 mL), evaporated and chromatographed (dichloromethane then 2:1 pet ether:ethyl acetate). The first spot eluted was pure **42** (0.063 g, 9%). An analytical sample was obtained by recrystallisation from heptane / ethyl acetate: mp 211-212 °C, ^{1}H NMR δ 7.39-7.31 (m, 8H), 7.20-6.82 (m, 8H), 3.92 (s, 8H); ^{13}C NMR δ 168.8, 150.8, 132.3, 131.7, 129.1, 128.1, 118.4, 115.1, 39.3; MS *m/z* (%) 536 (M^{+}, 8), 269 (19), 268 (15), 241 (21), 213 (43), 159 (20), 158 (96), 131 (82), 110 (24), 104 (39), 103 (100), 102 (23). Anal. Calcd for $C_{32}H_{28}O_8$: C, 71.11; H, 5.22. Found: C, 69.58; H, 4.30.

6.6 References

[1] Evans, D.A.; Kaldor, S.W.; Jones, T.K.; Clardy, J.; Stout, T.J. *J. Am. Chem. Soc.* **1990**, *112*, 7001-7031.

[2] Corey, E.J.; Hua, D.H.; Pan, B.-C.; Seitz, S.P. *J. Am. Chem. Soc.* **1982**, *104*, 6818-6820.

[3] (a) Corey, E.J.; Trybulski, E.J.; Melvin, L.S. Jr.; Nicolaou, K.C.; Secrist, J.A.; Lett, R.; Sheldrake, P.W.; Falck, J.R.; Brunelle, D.J.; Haslanger, M.F.; Kim, S.; Yoo, S. *J. Am. Chem. Soc.* **1978**, *100*, 4618-4620.

(b) Corey, E.J.; Kim, S.; Yoo, S.; Nicolaou, K.C.; Melvin, L.S. Jr.; Brunelle, D.J.; Falck, J.R.; Trybulski, E.J.; Lett, R.; Sheldrake, P.W. *J. Am. Chem. Soc.* **1978**, *100*, 4620-4622.

[4] Boger, D.L.; Sakya, S.M.; Yohannes, D. *J. Org. Chem.* **1991**, *56*, 4204-4207.

[5] Scherkenbeck, J.; Plant, A.; Harder, A.; Mencke, N. *Tetrahedron* **1995**, *51*, 8459-8470.

[6] Corey, E.J.; Nicolaou, K.C.; Melvin, L.S. Jr. *J. Am. Chem. Soc.* **1975**, *97*, 654-655.

[7] Boden, E.P.; Keck, G.E. *J. Org. Chem.* **1985**, *50*, 2394-2395.

[8] Castro, B.; Dormay, J.R.; Evin, G.; Selve, C. *Tetrahedron Lett.* **1975**, *16*, 1219-1222.

[9] Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989-1993.

[10] For a major recent review of the olefin metathesis reaction see Grubbs, R.H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413-4450.

[11] An exception to this rule among the macrolides of Figure 6.1 is **4**, combretastatin D-2. Apparently the 15-membered ring could not be formed by conventional macrolactonisation. The ring-forming reaction eventually used was an Ullmann macrocyclisation.[4]

[12] For discussion of DMAP's role as a nucleophilic catalyst see Hofle, G.; Steglich, W.; Vorbruggen, H. *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 569-583; Scriven, E.F.V. *Chem. Soc. Rev.* **1983**, *12*, 129-161.

[13] For a major review of the Fries rearrangement see Martin, R. *Org. Prep. Proc. Int.* **1992**, *24*, 369-435. For further references on the photo-Fries reaction, which appeared a less viable option, see Kobsa, H. *J. Org. Chem.* **1962**, *27*, 2293-2298; Finnegan, R.A.; Mattice, J.J. *Tetrahedron* **1965**, *21*, 1015-1026; Belluš, D.; Hrdlovič, P. *Chem. Rev.* **1967**, *67*, 599-609; Syamala, M.S.; Nageswer Rao, B.; Ramamurthy, V. *Tetrahedron* **1988**, *44*, 7234-7242.

[14] Mitchell, R.H.; Boekelheide, V. *J. Am. Chem. Soc.* **1974**, *96*, 1547-1557.

[15] Osada, S.; Miyahara, Y.; Shimizu, N.; Inazu, T. *Chem. Lett.* **1995**, 1103-1104.

[16] Munavalli, S. *Chem. Ind. (London)* **1972**, 293-294.

[17] (a) Spangler, R.J.; Kim, J.H. *Synthesis*, **1973**, 107-108; (b) Spangler, R.J.; Beckmann, B.G. *Tetrahedron Lett.* **1976**, *17*, 2517-2518; (c) Spangler, R.J.; Beckmann, B.G.; Kim, J.H. *J. Org. Chem.* **1977**, *42*, 2989-2996.

[18] For an example of such an aminophane, see Zolotov, Yu. A.; Larikova, G.A. ; Bodnya, V.A.; Efremova, O.A.; Davydova, S.L.; Yatsimirskii, K.B.; Kolchinski, A.G. *Doklady Chem.* **1981**, *258*, 235-237.

[19] Baker, W.; Ollis, W.D.; Zealley, T.S. *J. Chem. Soc.* **1951**, 201-208.

[20] Edgerley, P.G.; Sutton, L.E. *J. Chem. Soc.* **1951**, 1069-1074.

[21] Ollis, W.D.; Stoddart, J.F. *J. Chem. Soc., Chem. Commun.* **1973**, 571-572.

[22] Allinger, N.L.; Sprague, J.T. *Tetrahedron* **1975**, *31*, 21-23; Ollis, W.D.; Stoddart, J.F.; Sutherland, I.O. *Tetrahedron* **1974**, *30*, 1903-1921; Montecalvo, D.; St-Jacques, M.; Wasylishen, R. *J. Am. Chem. Soc.* **1973**, *95*, 2023-2024; Crossley, R.; Downing, A.P.; Nógrádi, M.; Braga de Oliveira, A.; Ollis, W.D.; Sutherland, I.O. *J. Chem. Soc., Perkin Trans. 1* **1973**, 205-217.

[23] Baker, W.; Gilbert, B.; Ollis, W.D. *J. Chem. Soc.* **1951**, 1443-1446.

[24] Baker, W.; Banks, R.; Lyon, D.R.; Mann, F.G. *J. Chem. Soc.* **1945**, 27-30.

[25] For further interesting papers discussing tri-*o*-thymotide not referenced below see Downing, A.P.; Ollis, W.D.; Sutherland, I.O.; Mason (née Banus), J.; Mason, S.F. *J. Chem. Soc., Chem. Commun.* **1968**, 329-332; Williams, D.J.; Lawton, D. *Tetrahedron Lett.* **1975**, *16*, 111-114; Ripmeester, J.A.; Burlinson, N.E. *J. Am. Chem. Soc.* **1985**, *107*, 3713-3714.

[26] Newman, A.C.D.; Powell, H.M. *J. Chem. Soc.* **1952**, 3747-3751.

[27] For an NMR study of the ring inversion of tri-*o*-thymotide, see Ollis, W.D.; Sutherland, I.O. *J. Chem. Soc., Chem. Commun.* **1966**, 402-404.

[28] The activation energy for racemisation was estimated as 16 kcal mol^{-1}, based on optical rotation measurements (reference 22). This value was later recalculated from the same data as 21.2 kcal mol^{-1}. The value obtained from the NMR study of reference 23 was 22.2 kcal mol^{-1}.

[29] Powell, H.M. *Nature*, **1952**, *170*, 155.

[30] Uzawa, H.; Hiratani, K.; Minoura, N.; Takahashi, T. *Chem. Lett.* **1998**, 307-308.

[31] Bodwell, G.J.; Houghton, T.J.; Miller, D. *Tetrahedron Lett.* **1997**, *38*, 1469-1472.

[32] Diago-Meseguer, J.; Palomo-Coll, A.L.; Fernandez-Lizarbe, J.R., Zugaza-Bilbao, A. *Synthesis*, **1980**, 547-551.

[33] For a comparison of many of the common lactonisation and lactamisation protocols see Bartra, M.; Vilarassa, J. *J. Org. Chem.* **1991**, *56*, 5132-5138.

[34] Spartan 4.1.1 software package produced by Wavefunction Inc., Irvine, California.

[35] Lai initially reported that **38** was observed to adopt a *syn* conformation in solution, in accord with his MM2 calculations (Lai, Y-H.; Nakamura, M. *J. Org. Chem.* **1988**, *53*, 2360-2362), but Fukuzawa's argument (reference 36(a)) appears to refute this. See also Bodwell, G.; Ernst, L.; Hopf, H.; Jones, P.G. *Tetrahedron Lett.* **1989**, *30*, 6005-6008.

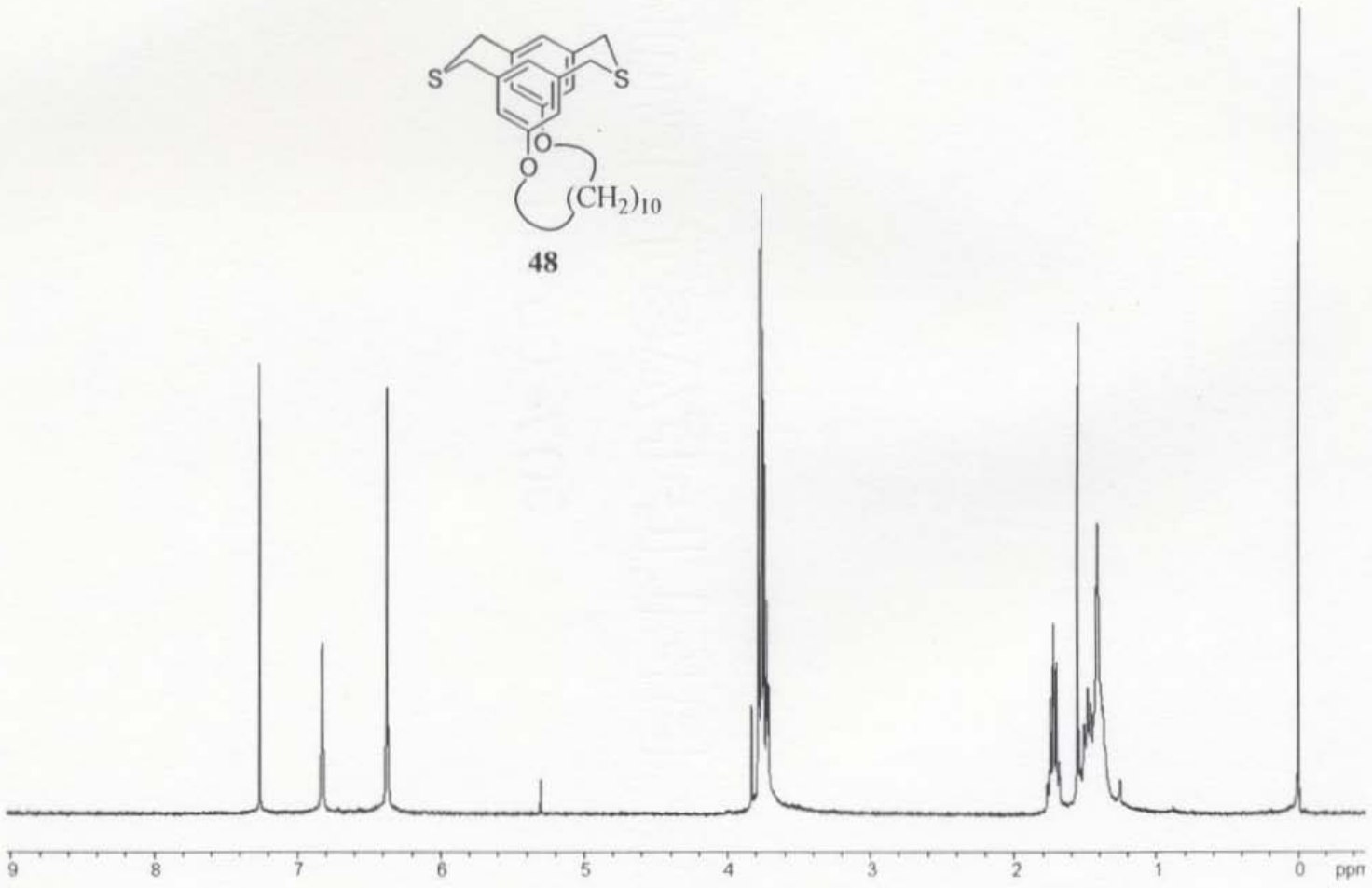
[36] (a) Okajima, T.; Wang, Z.-H.; Fukazawa, Y. *Tetrahedron Lett.* **1989**, *30*, 1469-1472; (b) Okajima, T.; Wang, Z.-H.; Fukazawa, Y. *Chem. Lett.* **1991**, 37-40; (c) Wang, Z.-H.; Usui, S.; Fukazawa, Y. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1239-1243.

[37] Fukazawa, Y.; Usui, S.; Uchio, Y.; Shiobara, Y.; Kodama, M. *Tetrahedron Lett.* **1986**, *27*, 1825-1828.

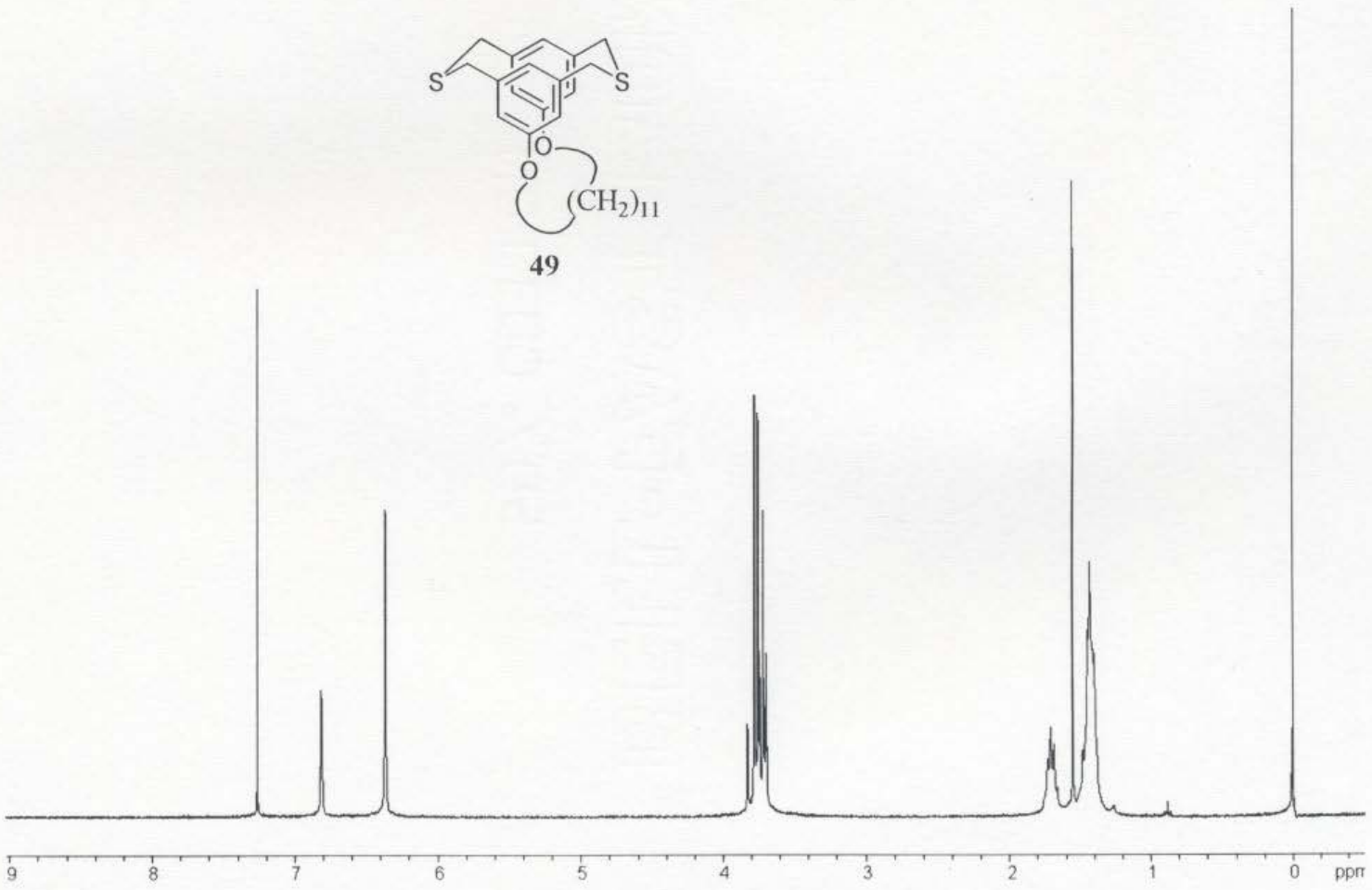
[38] Oku, A.; Urano, S.-I.; Nakaji, T.; Qing, G.; Abe, M. *J. Org. Chem.* **1992**, *57*, 2263-2266.

Appendix

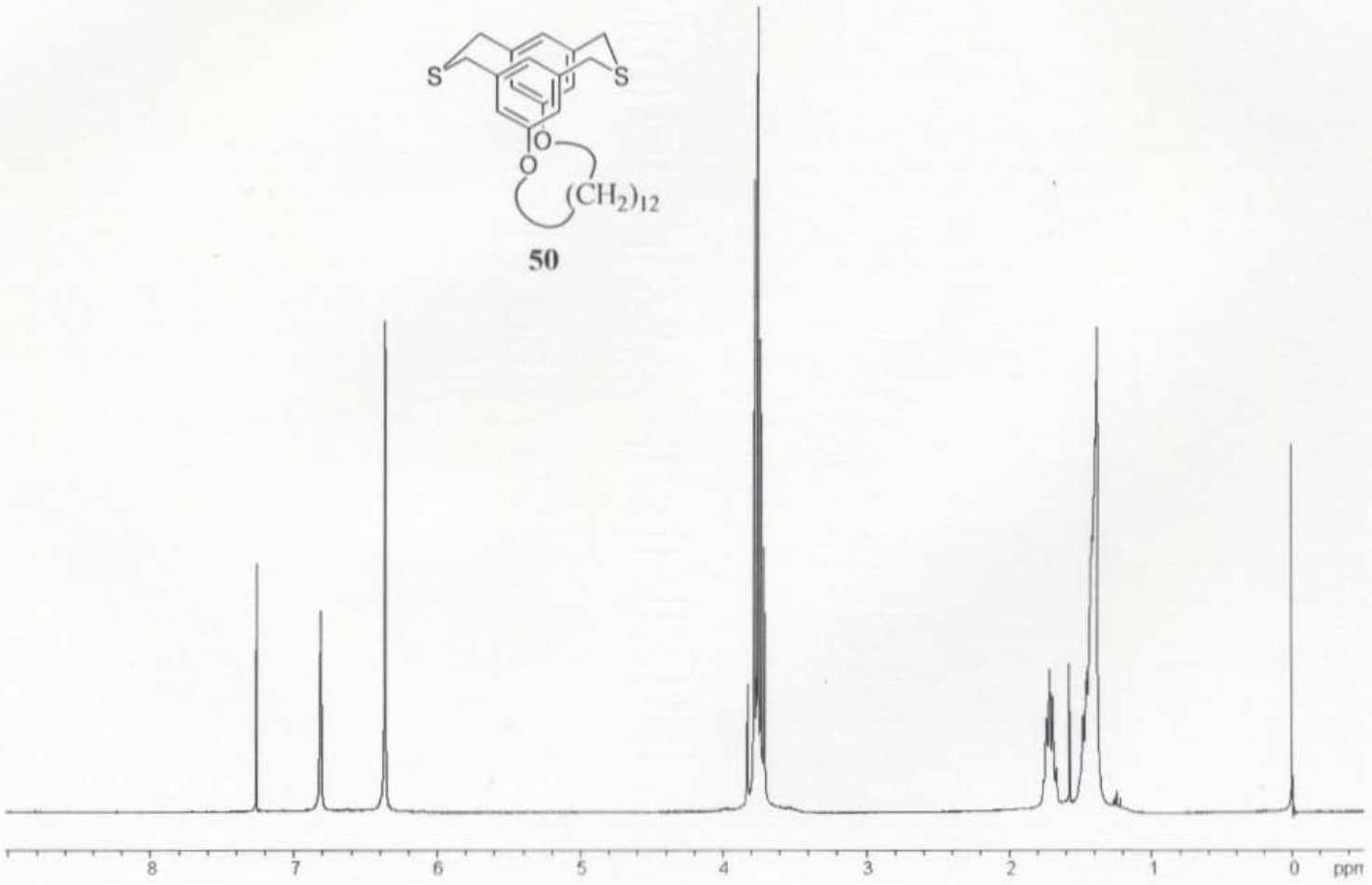
Selected ^{1}H NMR spectra are arranged according to the order in which the compounds appear in the text.



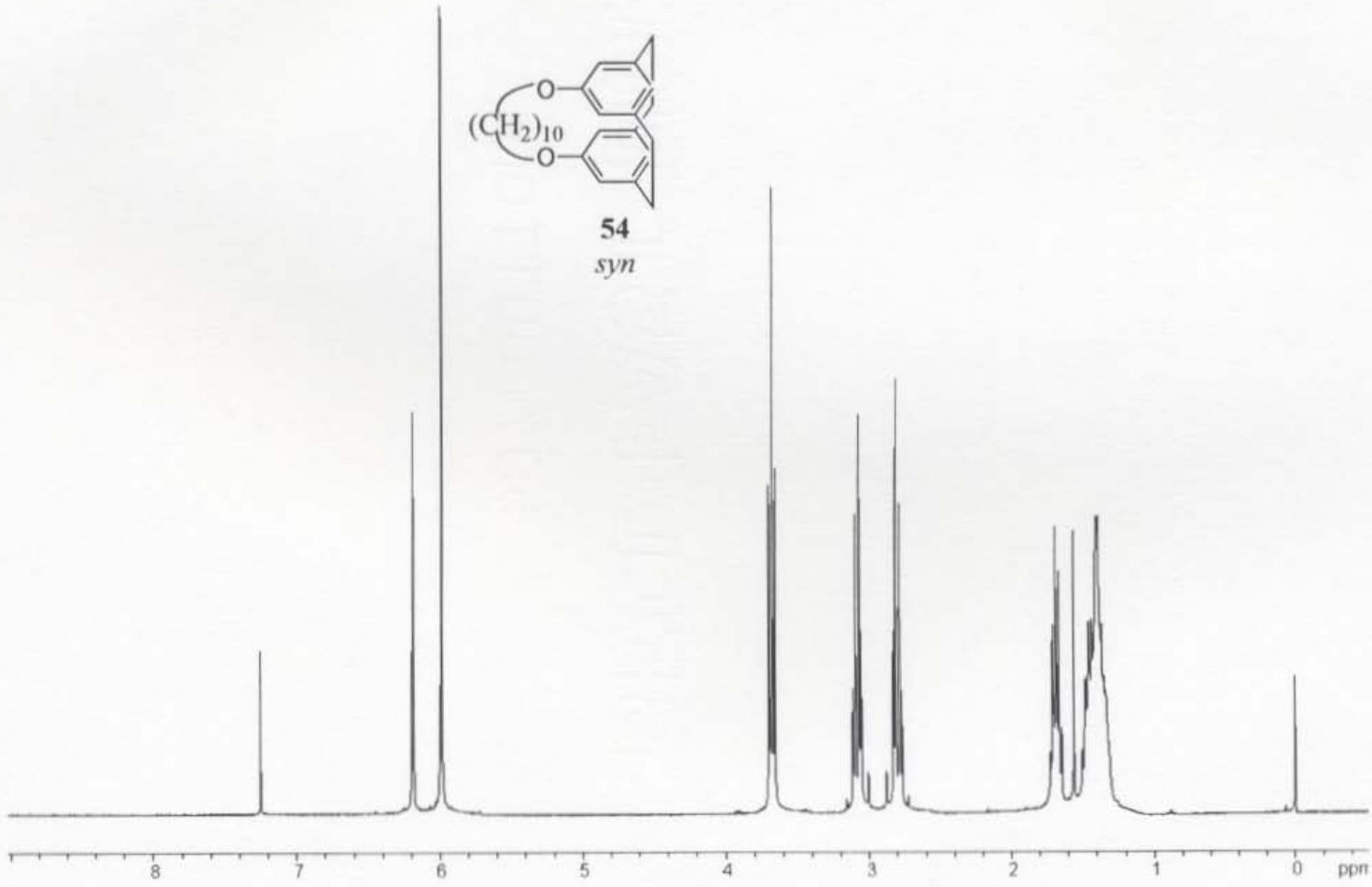
48



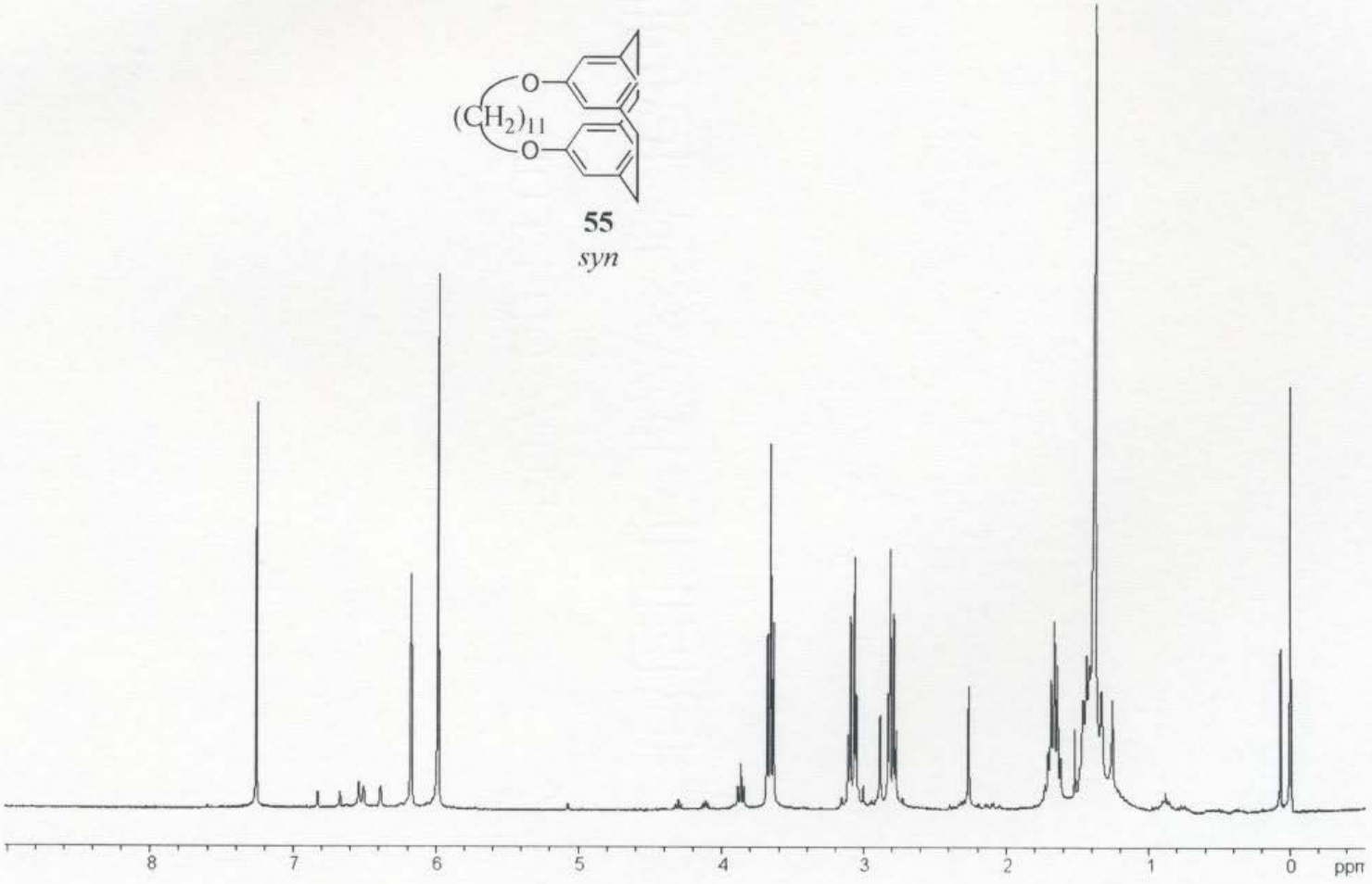
49



50

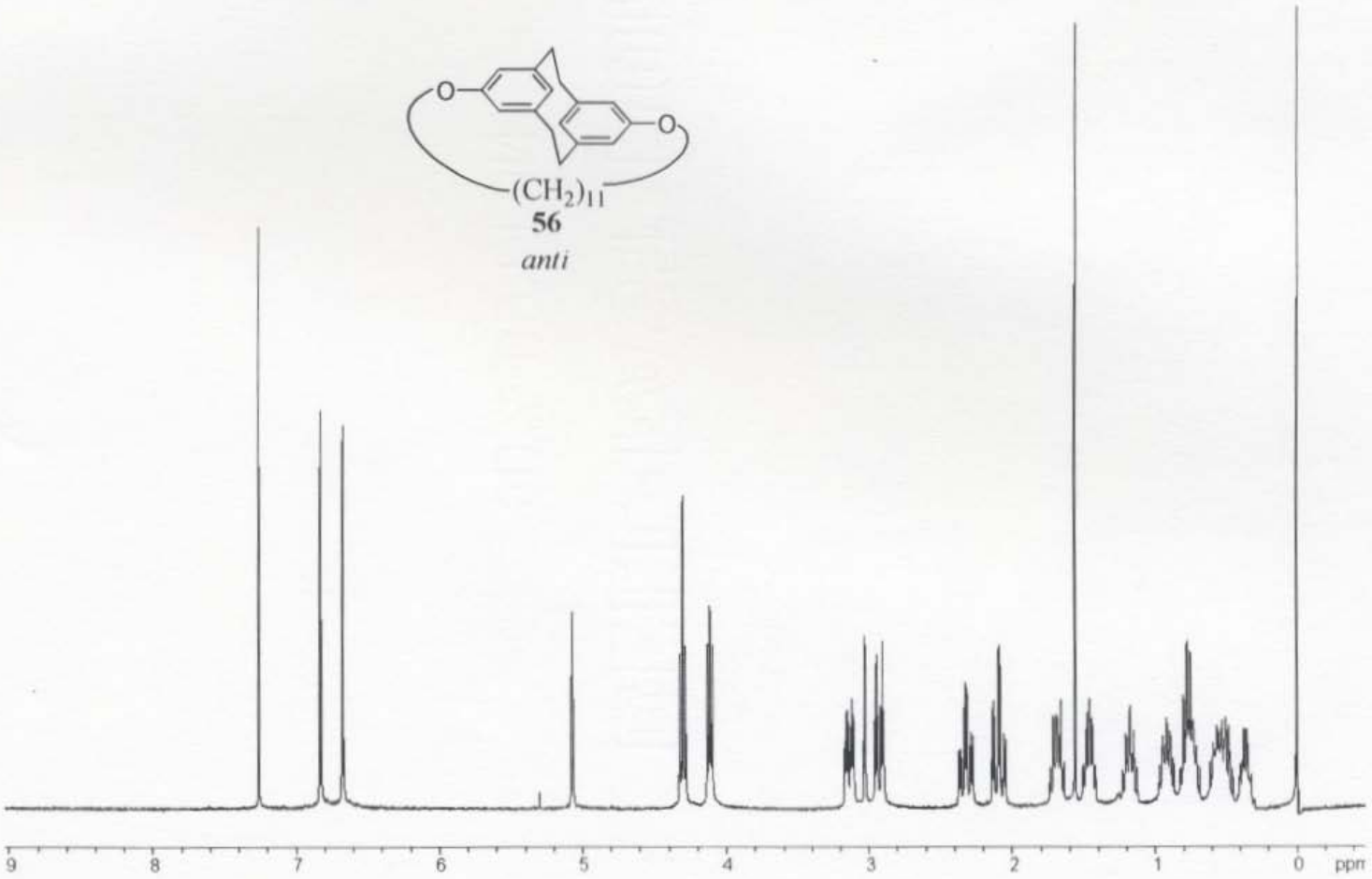


54
syn



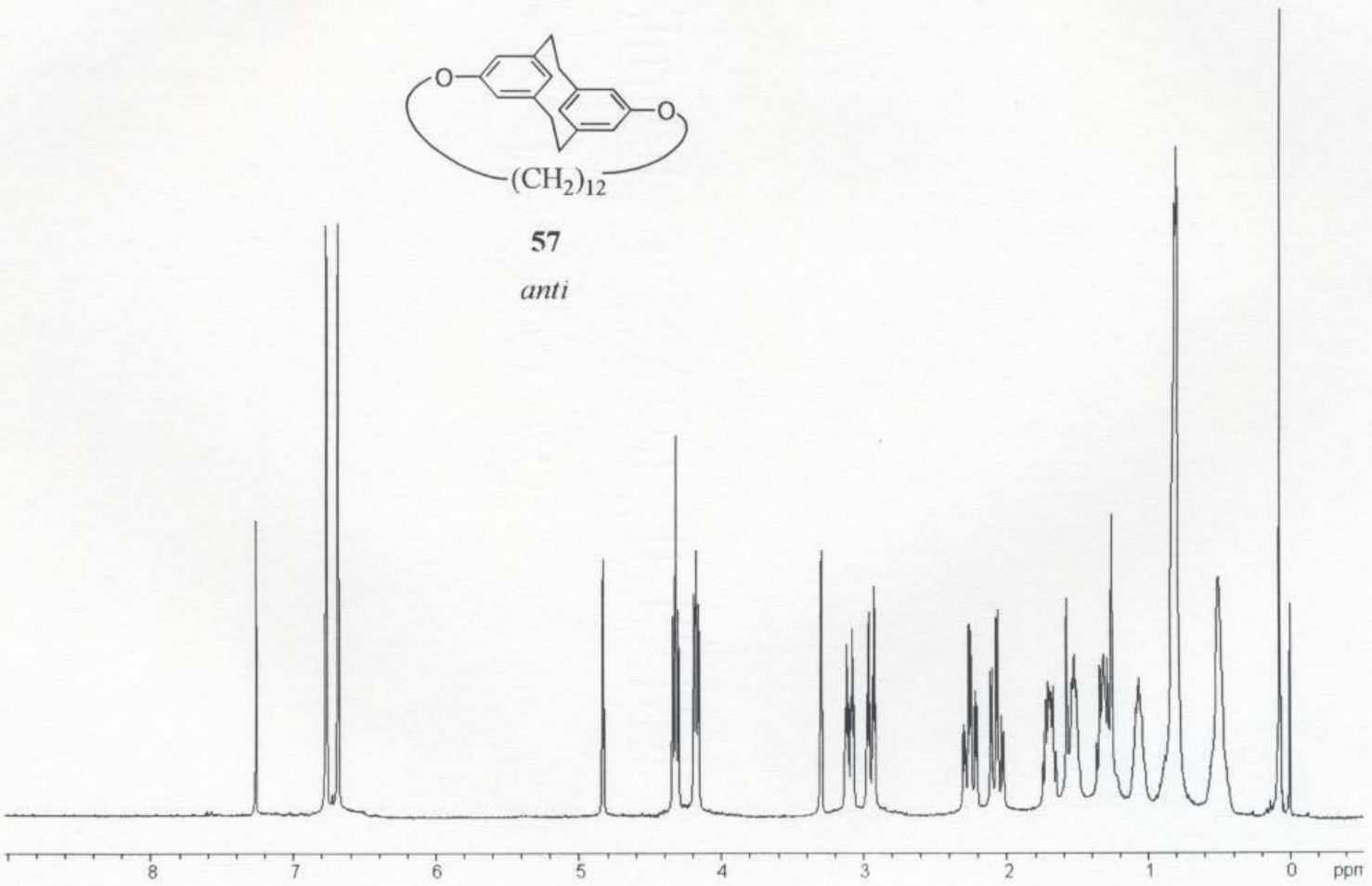
55

syn



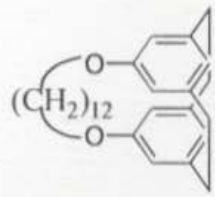
56

anti



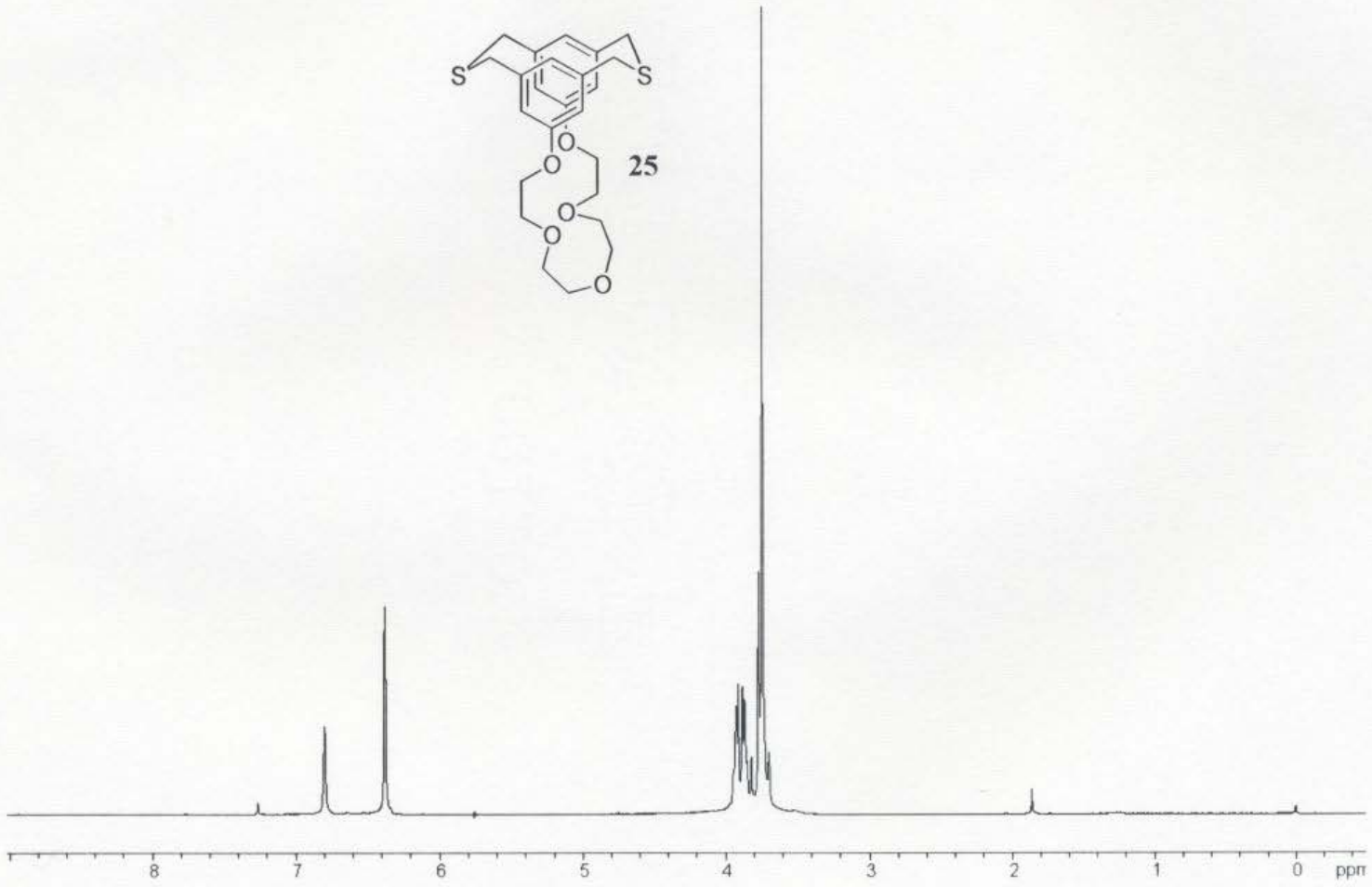
57

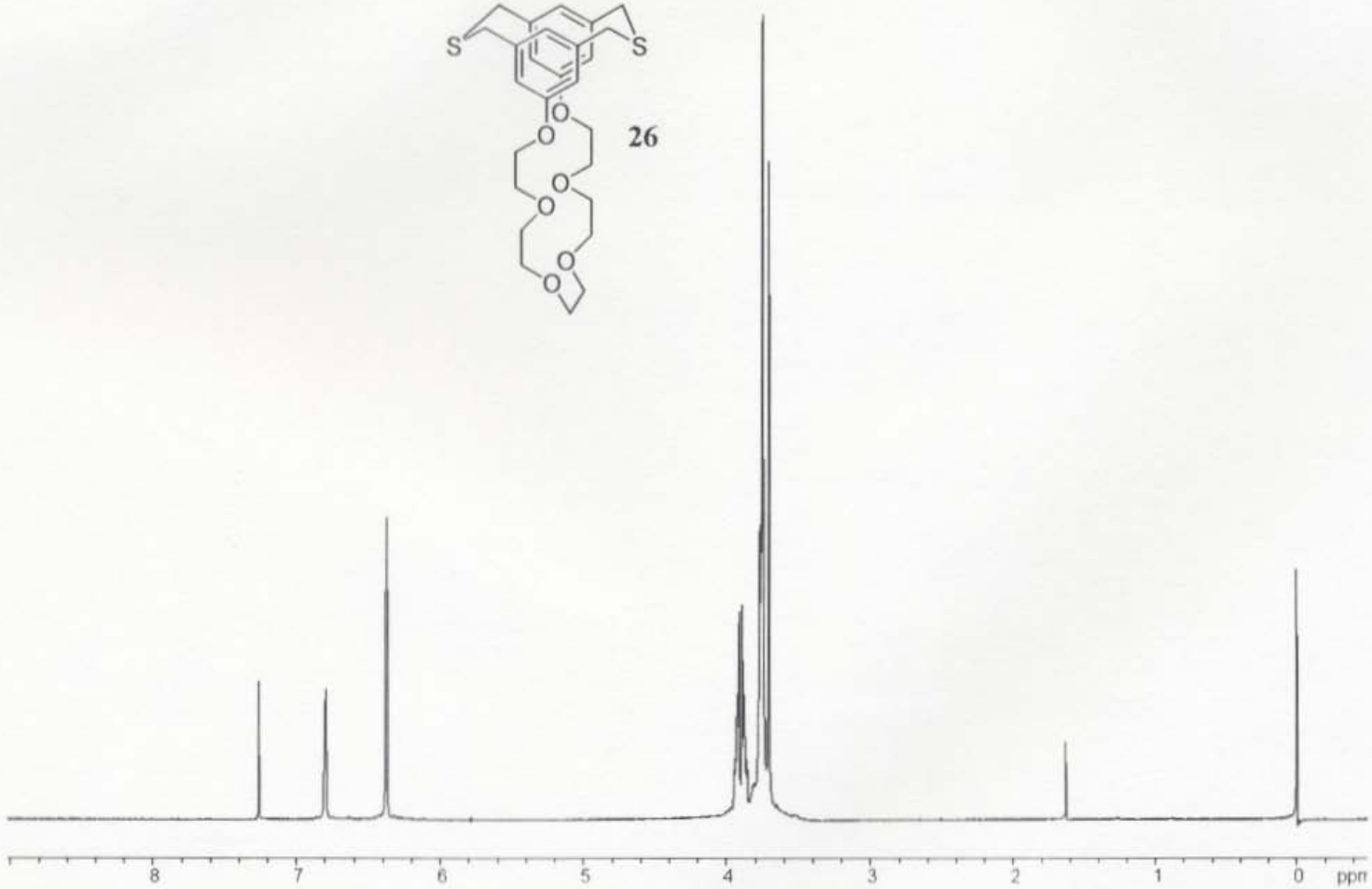
anti

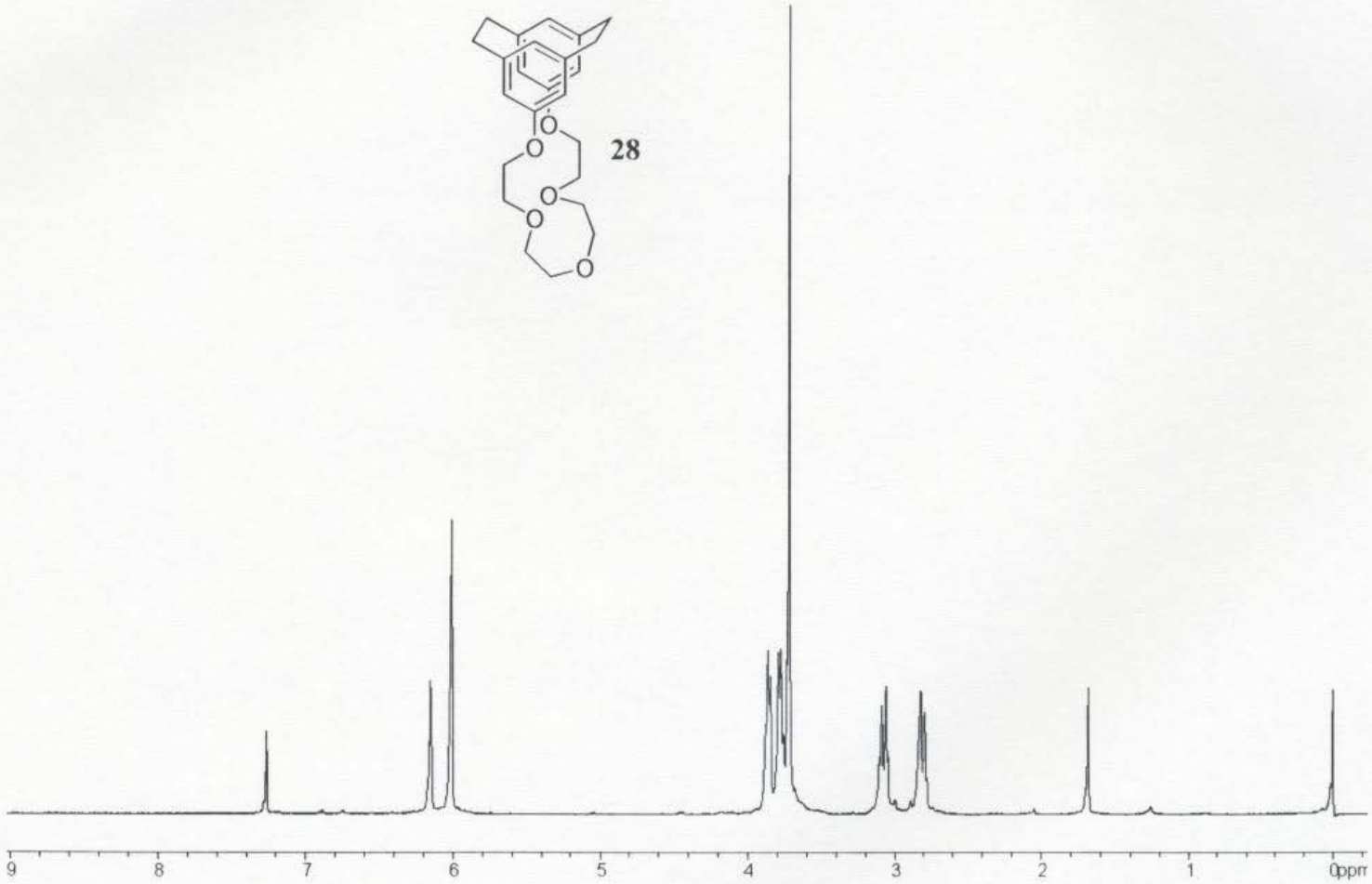


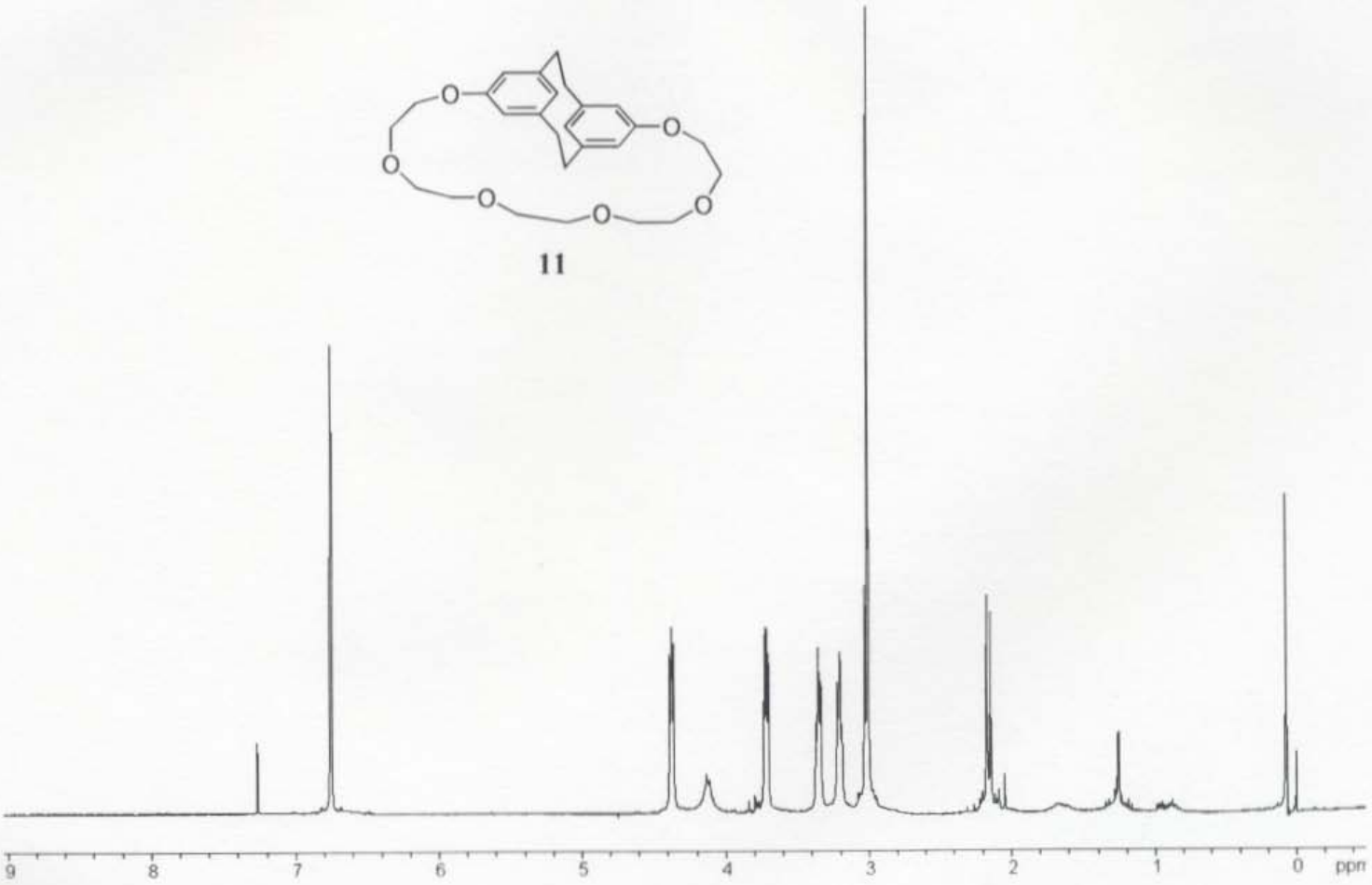
59

syn

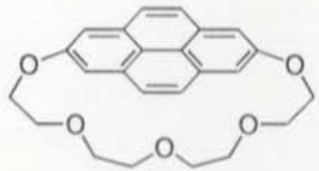

S
S
O
O
O
O
O
25
8
7
6
5
4
3
2
1
0
ppm


S
S
O
O
O
O
O
O
O
O
26
8
7
6
5
4
3
2
1
0
ppm

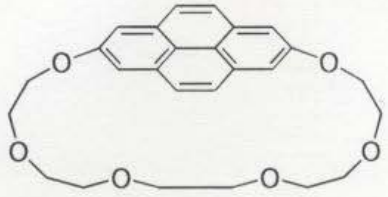

28
9
8
7
6
5
4
3
2
1
0ppm



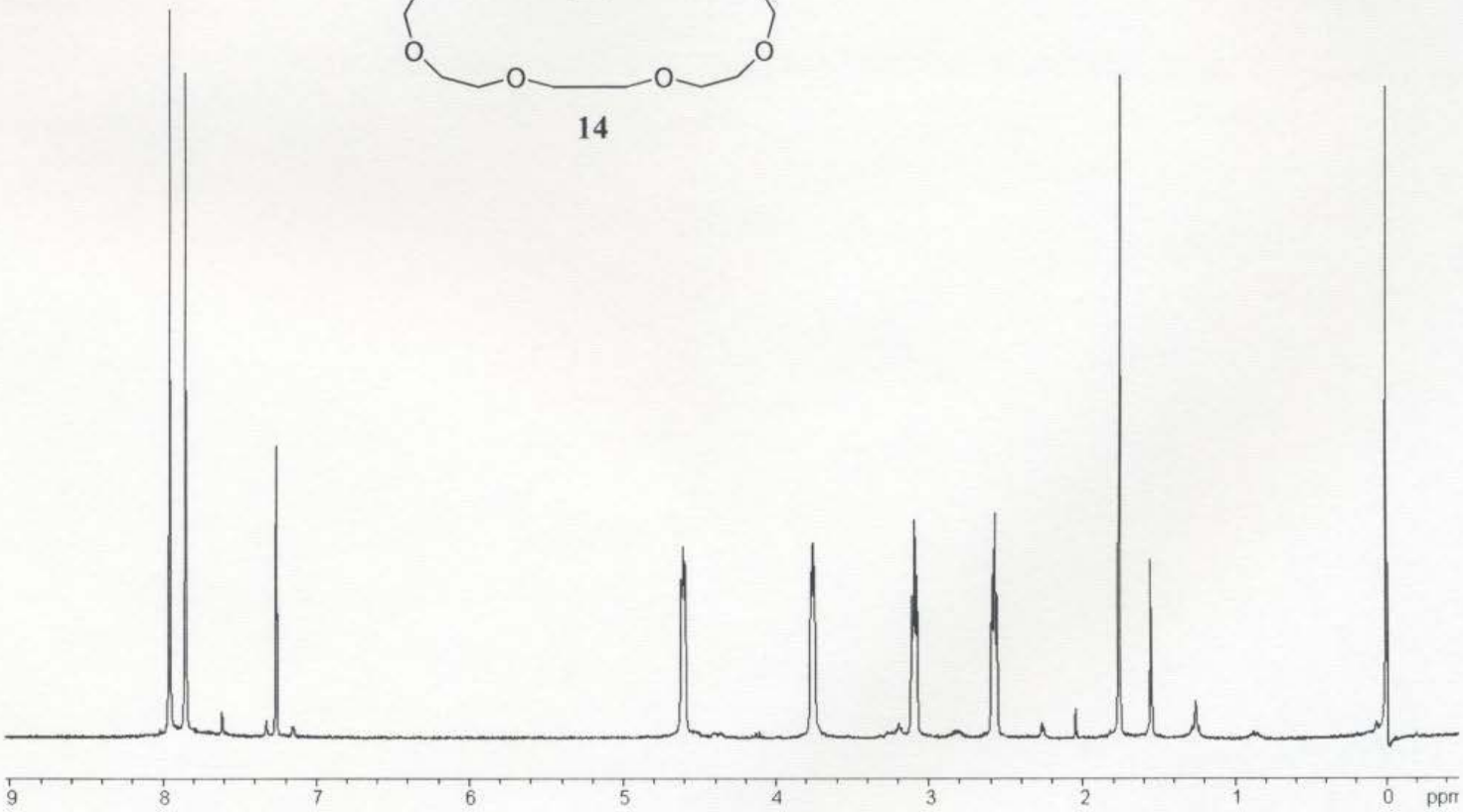
11



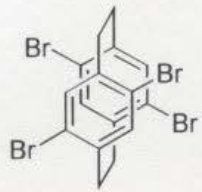
42



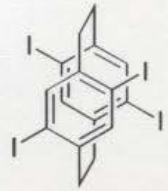
14



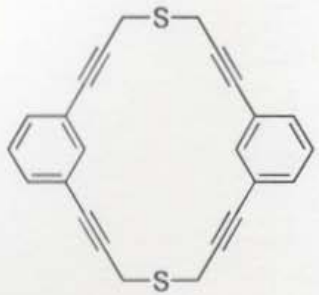
44



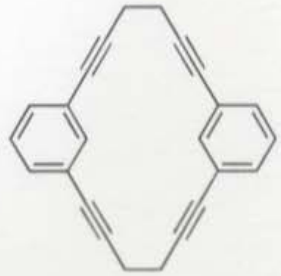
38



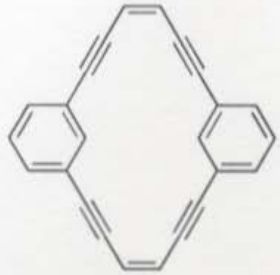
49



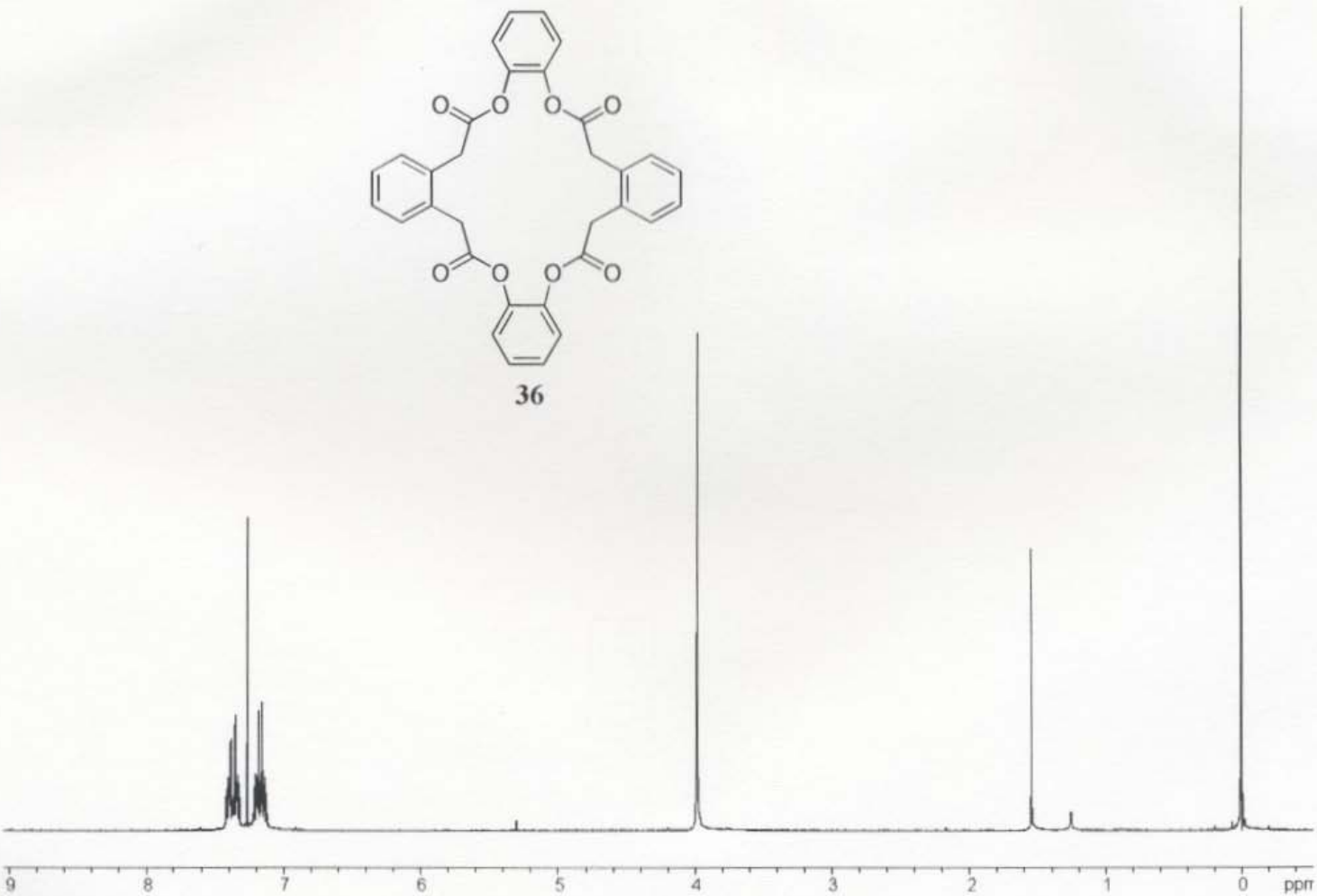
61



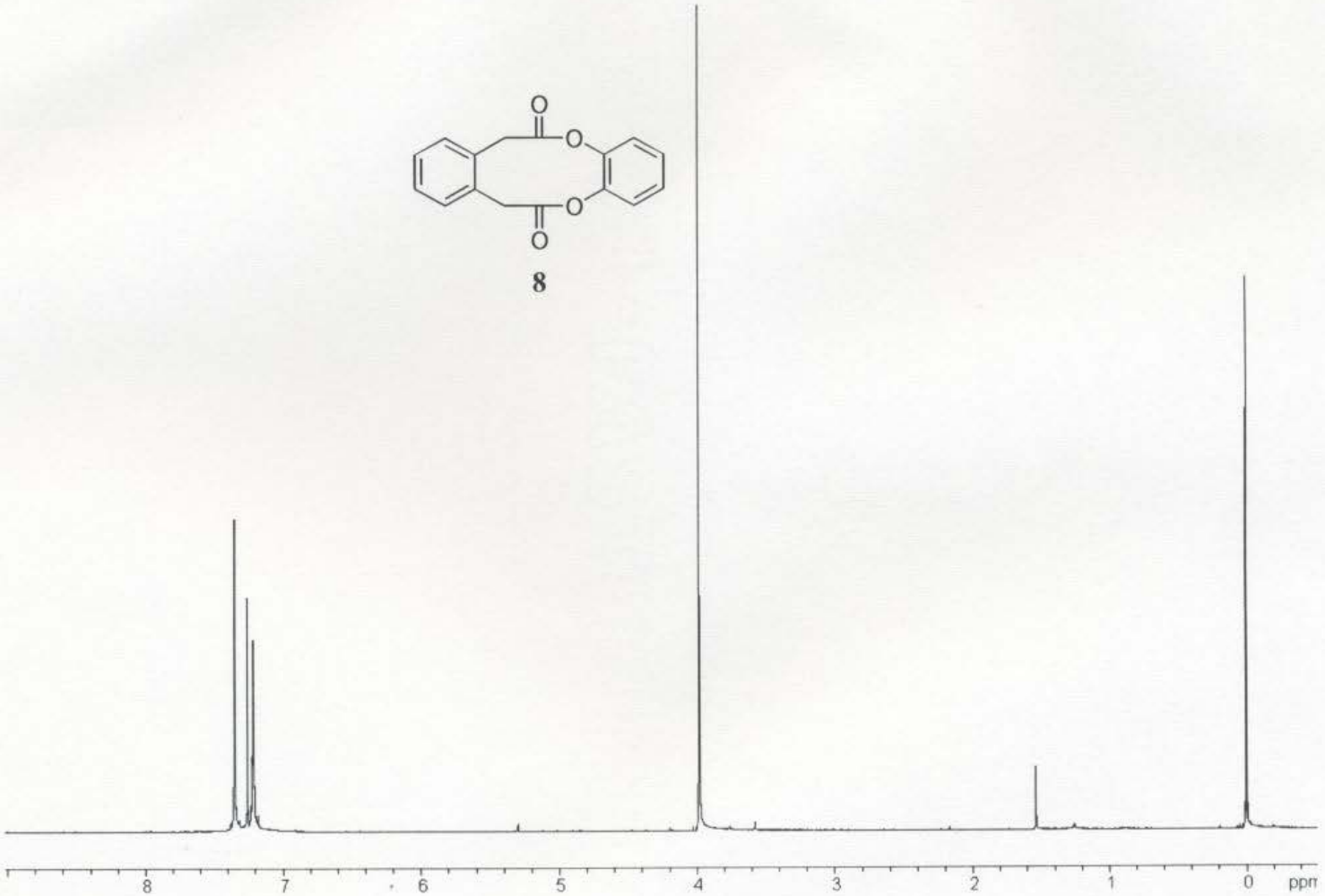
62



63



36


O
O
O
O
8
8
7
6
5
4
3
2
1
0
ppm

42