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The Use of 10b,10c-Dimethyldihydropyrene (DHP) as a Probe to Study the Mills-Nixon Effect

by

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A Dissertation Submitted in Partial Fulfillment of the
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ABSTRACT

The syntheses of many cycloalkene and cycloalkeneone annelated DHPs have been achieved. A late ring formation approach was used to synthesize the dicycloalkeneone annelated DHP **63** (Scheme 4) and the unsymmetrical dicycloalkeneone annelated DHPs **70a** and **70b** (Scheme 5). To synthesize the other ring annelated DHPs, a more versatile early ring approach was employed. Through an asymmetrical coupling followed by a series of standard transformations, the cyclopentene-, cyclohexene-, cyclopentenone- and cyclohexenone-annelated DHPs **64**, **118**, **130**, **131** were synthesized (Schemes 13 and 15). Similarily, the dicycloalkene and dicycloalkenone annelated DHPs such as **41**, **42**, **123**, **124** and **136** were obtained by a symmetrical coupling followed by a series of standard transformations (Schemes 12, 14 and 16).

Other than the cycloalkene or cycloalkenone annelated DHPs, the acyclic tetra-substituted DHPs **142** and **143** (Scheme 17) were also synthesized as model compounds. As well, the asymmetrical DHPs **148** and **149** (Scheme 18), having a benzene and a cyclopentene annelation or with a benzene and a cyclopentenone annelation, were also synthesized to test the annelation effect with a combination of a benzene and a five-membered ring.

In the cycloalkene and cycloalkenone annelated DHP series, it was demonstrated that the π-bond fixation effect could be indirectly probed by the internal methyl proton chemical shifts. These are based on the ring current of DHP and the magnitude of bond fixation depends on the annelating ring size, the coplanarity of the carbonyl group with the π-system of DHP (for the cycloalkenone annelated DHPs) and the relative arrangement of the annelated rings (*cisoid* versus *transoid* for the diannelated

compounds). Thus, when the ring size varied from four to seven in the cycloalkene- and dicycloalkenene annelated DHP series, the cyclohexene ring has the strongest bond fixation effect. When the ring size varied from five to seven in the cycloalkenone- and the dicycloalkenone-annelated DHP series, the cyclopentenone annelated DHPs have the strongest bond fixation effect. In the mono-cycloalkenone annelated DHP series (ring size =5 to 7), the Kekulé structures of the cycloalkenone annelated DHPs were determined by the vicinal coupling constant ($^3J_{HH}$) to adopt an endocyclic structure (the double bond appears at the ring junction between the DHP and the annelating ring). For the diannelated DHP derivatives, the *cisoid* arrangement of ring annelation always has a stronger bond fixation effect compared to that of a *transoid* arrangement in almost all cases.

In this thesis work, the use of DHP as a sensitive NMR probe was successfully demonstrated in that its internal methyl proton chemical shift responds to a change of ring current caused by different ring annelations. It is so sensitive, that even the very small perturbation on ring annelation (by cycloalkanes) can be sensed. DHP is a better NMR probe molecule than benzene because the chemical shifts of the internal methyl protons of DHP are less seriously affected by any effects such as geometrical distortion, rehybridization, steric compression, hyperconjugation and through space effects as probed by the ^1H and ^{13}C-NMR spectroscopies in benzocycloalkenes. The ring annelation effect probed by DHP is closer to a pure π-effect due to a change in ring current which is different from benzene, which is a mixture of both σ- and π-effects.

In order to study a Mills-Nixon type bond fixation effect in the bridged [14]annulene, *trans*-10b,10c-dimethyldihydropyrene **9**, a series of annelated dihydropyrenes were prepared where the annelating rings were cyclopentene, cyclopentenone, cyclohexene, cyclohexenone, cycloheptene as well as some bis-annelated

and mixed annelated derivatives. Some tetra-substituted acyclic dihydropyrenes were also synthesized and used as model compounds to study the bis-ring annelation effect. Specifically, *p*-tolualdehyde in seven steps gave the intermediate dithiol, 6-methyl-7-sulfanylmethyl-2,3-dihydro-1H-5-indenylmethanethiol **86**, (Scheme 7); tolulene in five steps gave the intermediate dithiol 7-methyl-8-sulfanylmethyl-1,2,3,4-tetrahydro-6-napthalenylmethanethiol **93**, (Scheme 8); *p*-tolualdehyde in seven steps gave the intermediate dithiol 3-methyl-4-sulfanylmethyl-6,7,8,9-tetrahydro-5H-benzo[a]cyclo-hepten-2yl-methanethiol **101**, (Scheme 9). From these 5, 6 and 7-membered ring annelated dithiols, on reaction with the analogous dibromides, the dicycloalkene-annelated dihydropyrenes, *trans*-10c,10d-dimethyl-1,2,3,8,9,10,10c,10d-octahydrodicyclopenta-[a,i]pyrene **41a** and *trans*-11b,11c-dimethyl-1,2,3,7,8,9,11b,11c-octahydrodicyclopenta-[a,h]pyrene **41b** (Scheme 12); *trans*-12c,12d-dimethyl-1,2,3,4,9,10,11,12,12c,12d-decahydrobenzo[rst]pentaphene **123a** and *trans*-13b,13c-dimethyl-1,2,3,4,8,9,10,11,13b,13c-decahydrodibenzo-[b,def]chrysene **123b** (Scheme 14) and *trans*-14c,14d-dimethyl-1,2,3,4,5,10,11,12,13,14,14c,14d-dodecahydrodicyclo-hepta[a,i]pyrene **136a** and *trans*-15b,15c-dimethyl-1,2,3,4,5,9,10,11,12,13,15b,15c-dodecahydrodicyclohepta-[a,h]pyrene **136b** (Scheme 16) were obtained. Among the above three di-annelated dihydropyrenes, **41**, **123** and **136**, **41** and **123** could be oxidized to the corresponding dicycloalkenone-annelated dihydropyrene derivatives, *trans*-10c,10d-dimethyl-1,2,3,8,9,10,10c,10d-octahydrodicyclopenta[a,i]pyrene-3,8-dione **42a** and *trans*-11b,11c-dimethyl-1,2,3,7,8,9,11b,11c-octahydrodicyclopenta[a,h]pyrene-1,7-dione **42b**; *trans*-12c,12d-dimethyl-1,2,3,4,9,10,11,12,12c,12d-decahydrobenzo[rst]-pentaphene-4,9-dione **124a** and *trans*-13b,13c-dimethyl-1,2,3,4,8,9,10,11,13b,13c-decahydro-dibenzo[b,def]chrysene-1,8-dione **124b**. The cycloalkene annelated dihydropyrenes *trans*-11b,11c-dimethyl-8,9,11b,11c-tetrahydro-7H-cyclopenta[a]pyrene **64** and *trans*-12b,12c-dimethyl-7,8,9,10,12b,12c-hexahydrobenzo[def]chrysene **130**

were synthesized by an unsymmetical coupling of the dibromide **85** and **92** with the known dithiol **74**, followed by a Steven's rearrangement and a Hofmann elimination. When **64** and **130** were oxidized by pyridinium dichromate (PDC) , the corresponding cyclopentenone and cyclohexenone annelated dihydropyrenes, *trans*-11b,11c-dimethyl-8,9,11b,11c-tetrahydro-7H-cyclopenta[a]pyren-7-one **118** and *trans*-12b,12c-dimethyl-7,8,9,10,12b,12c-hexa-hydrobenzo[def]chrysen-7-one **131** were synthesized (Scheme 13 and 15).

To synthesize the acyclic dihydropyrenes with a substitution pattern similar to the dicycloalkene and the dicycloalkenone annelated dihydropyrene series, *trans*-1,2,7,8,10b,10c-hexamethyl-10b,10c-dihydropyrene **142a** and *trans*-1,2,6,7,10b,10c-hexamethyl-10b,10c-dihydropyrene **142b** were synthesized via a symmetrical coupling between the known dibromide **137** and its analogous dithiol and then followed by a Wittig rearrangement and a Hofmann elimination (See Scheme 17). After oxidation of **142** by PDC, the 2,7-diformyldihydropyrenes, *trans*-1,8,10b,10c-tetramethyl-10b,10c-dihydro-2,7-pyrene dicarboxaldehyde **143a** and *trans*-1,6,10b,10c-tetramethyl-10b,10c-dihydro-2,7-pyrene dicarboxaldehyde **143b** were obtained. Both the acyclic tetra-substituted dihydropyrenes **142** and **143** could be used as model compounds to study the ring strain effect.

To synthesize the unsymmetical diannelated dihydropyrenes *trans*-11b,11d-dimethyl-2,3,11c,11d-tetrahydro-1H-benzo[def]cyclopenta[a]chrysene **148a** and *trans*-12b,12c-dimethyl-2,3,12b,12c-tetrahydro-1H-benzo[def]cyclopenta[b]chrysene **148b**, the dithiol **86** was coupled with the known dibromide **144** to afford a mixture of thiacyclophanes **145** (Scheme 18). The thiacyclophane **145** was then subjected to a Wittig rearrangement followed by a Hofmann elimination to give the dihydropyrenes **148**, with a cyclopentene ring and a benzene ring. *trans*-11b,11d-dimethyl-2,3,11c,11d-tetrahydro-1H-benzo[def]cyclopenta[a]chrysen-1-one **149a** and *trans*-12b,12c-dimethyl-

2,3,12b,12c-tetrahydro-1H-benzo[def]cyclopenta[b]chrysen-1-one **149b** were then obtained from PDC oxidation of **148**.

To prepare for the dicyclopentadiene-annelated dihydropyrene ligands, dicyclopentenone annelated dihydropyrenes with their ketone groups positioned differently around the five-membered ring were synthesized. Specifically, diketone *trans*-10c,10d-dimethyl-1,2,3,8,9,10,10c,10d-octahydrodicyclopenta[a,i]pyrene-1,10-dione **63** was obtained by a bis-Friedel Crafts cyclization reaction (Scheme 4). Diketones *trans*-10c,10d-dimethyl-1,2,3,8,9,10,10c,10d-octahydrodicyclopenta[a,i]pyren-1,8-dione **70a** and *trans*-11b,11c-dimethyl-1,2,3,7,8,9,11b,11c-octahydrodicyclopenta[a,h]pyren-1,9-dione **70b** were obtained in six steps from the cyclopentene[a]annelated dihydropyrene **64** via a Friedel-Crafts cyclization followed by PDC oxidation (Scheme 5). Diketones **42a** and **42b** were obained by a bis-oxidation using PDC. All five diketones could be reduced smoothly to their dialcohols. However, only the dialcohols generated from diketones **70a** and **70b** could be eliminated successfully to afford the dicyclopentadienyl annelated dihydropyrenes **40a** and **40b** (Scheme 19). Attempts to convert the ligands *trans*-10c,10d-dimethyl-1,8,10c,10d-tetrahydrodicyclopenta[a,i]pyrene **40a** and *trans*-10c,10d-dimethyl-1,9,10c,10d-tetrahydrodicyclopenta[a,i]pyrene **40b** to their dianion using MeLi gave an orange solution in which the dicyclopentadienide annelated dihydropyrenes **37a** and **37b** might present. However, attempts to convert the dianion to a metal complex failed.

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Ar, Arom	Aromatic ring
Ar-H	aromatic proton
Ring-H	ring proton
bp	boiling point
mp	melting point
LDA	lithium diisopropylamide
HCl	hydrochloric acid
HBr	hydrobromic acid
n-BuLi	*n*-butyllithium
PDC	pyridinium dichromate
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
MTPI	methyl triphenoxylphosphonium iodide
t-Bu	*t*-Butyl
$CDCl_3$	chloroform-d
HMPT	hexamethylphosphoric triamide
DMF	N,N-dimethylformamide
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
MeOH	methanol
CH_2Cl_2	dichloromethane (methylene chloride)
$CHCl_3$	chloroform
PE	petroleum ether (b.p. 30 - 60 °C)
THF	tetrahydrofuran

^{1}H-NMR	proton nuclear magnetic resonance spectrum
^{13}C-NMR	carbon-13 nuclear magnetic resonance spectrum
IR	Infrared spectrum
UV	ultraviolet spectrum
MS	mass spectrum
EI-HRMS	electron impact - high resolution mass spectrum
CI	chemical ionisation
EI	electron impact
FAB	fast atomic bombardment
NMR	nuclear magnetic resonance
s	singlet
d	doublet
t	triplet
dd	doublet of doublets
m	multiplet
ppm	parts per million
decomp.	decomposed
DHP	*trans*-10b,10c-Dimethyldihydropyrene
Me	methyl
RE	Resonance Energy
REPE	Resonance Energy per π-Electron
HOMA	Harmonic Oscillator Model of Aromaticity

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To
the two
supervisors in my life,
who guided me through
the hurdles,
who encouraged me
when I am defeated,
who showed me the target I should aim at,
and taught me
how to
fight
against the odds
in my life.

Chapter 1 Introduction

A. The history of aromaticity

The history of "aromaticity" began with the work of Michael Faraday, who isolated benzene from the liquid residue that formed during the production of lamp gas in 1825[1]. It was Kekulé who first used the term "aromatic compounds" as a name for describing benzene and its derivatives because of their odour. Due to the continuing controversy on aromaticity, there has been a rapid development in both the theoretical and the experimental aspects of aromatic chemistry. The idea of aromaticity has developed so dramatically that its original meaning has been completely lost. Despite being one of the most common concepts used by chemists, aromaticity has not been precisely defined so far. This arises because no directly measurable physical and/or chemical property can be attributed uniquely to aromaticity. Aromaticity has many facets, to name a few, these include high thermal stability, high resonance stabilization energy, low reactivity, sustained induced ring current and diamagnetic susceptibility. But none of the above properties alone defines aromaticity precisely. Most chemists would accept the qualitative statement that aromaticity of a conjugated molecule is the set of properties associated with cyclic arrays of delocalized electrons with favorable symmetry. In contrast, the unfavorable properties of antiaromatic systems lead to localized rather than to delocalized electronic structures. The "delocalized electron" arrays are not restricted to π, but may be σ or mixed in character.[2,3] The latter is a fine subjective definition, but surely a quantitative measurement is needed. The search for a suitable quantitative measurement of aromaticity makes aromaticity difficult to define, because rather many points of view have arisen.

Some milestones concerning definitions or criteria for characterizing aromaticity are listed in chronological order as follows:[2]

before	1825	distinctive "aromatic" smell (Faraday)
before	1865	high carbon-hydrogen ratios - stable despite considerable unsaturation
	1865	benzene structure (Kekulé)
	1866	substitution is more favorable than addition (Erlenmeyer)
	1910	aromatic compounds have exalted diamagnetic susceptibilities (Pascal)
	1925	electron sextet and heteroaromaticity (Armit-Robinson)
	1931	theory of cyclic (4n+2) π systems (Hückel)
	1936	London diamagnetism - π electron current contribution to magnetic susceptibility
	1956	ring currents effects on NMR chemical shifts (Pople)
	1969	modern study of diamagnetic susceptibility exaltation (Dauben)
	1970	magnetic susceptibility anisotropy (Flygare)
	1980	IGLO quantum chemical calculation of magnetic properties: chemical shifts, magnetic susceptibilities and magnetic susceptibility anisotropies (Kutzelnigg)

B. Aromatic character

A wide variety of criteria have been proposed for the assessment of aromaticity ranging from the purely qualitative to the virtually quantitative[4] but this has not

been a trivial task. Aromaticity is a multidimensional phenomenon[5] and it is impossible to estimate aromaticity based on just a few parameters. To make it more complicated, the classical aromaticity of most heterocycles, and of some carbocycles such as azulene, increases with the polarity of the medium as shown by experimental and calculated bond lengths, aromaticity indices and dipole moments. In other words, aromaticity also varies with molecular environment.[6] Although it is difficult to define aromaticity well based on a single parameter, Krygowski et al. has demonstrated that the Harmonic Oscillator Model of Aromaticity (HOMA) may be separated into energetic and geometric contributions to the aromaticity of π-electron systems.[7,8]

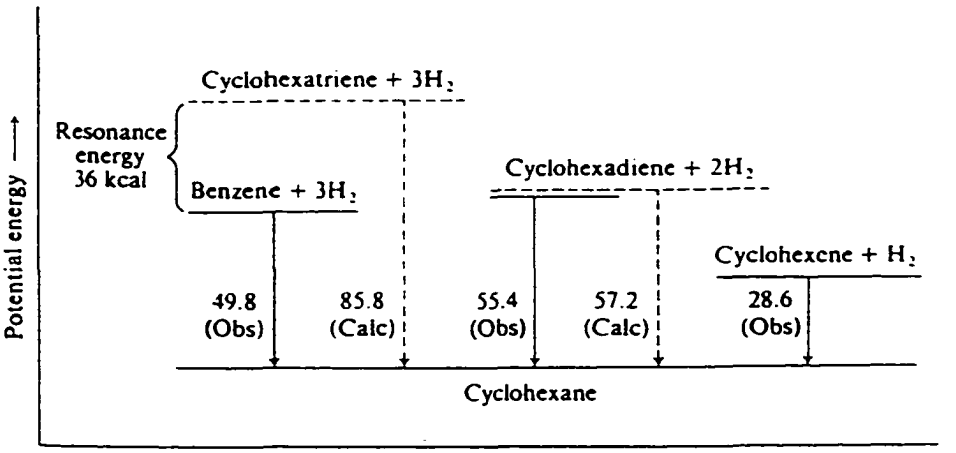
Among numerous criteria to define aromaticity, thermal stability, kinetic stability, a structural (geometric) criterion such as the bond length equalization, and a magnetic criterion such as the ring current effect are usually used:

1. Thermal stability:

Aromaticity can be interpreted as *the extra stabilization of cyclic unsaturated molecules arising from cyclic conjugation of π-electrons.* The extra stabilization energy is estimated with reference to the π-electron energy of a hypothetical reference molecule formed by "localized" π bonds. It is termed the Resonance Energy (RE).[9] As an example, there is quantitative data to show how much more stable benzene is when compared with the hypothetical reference, cyclohexatriene, based on the heat of hydrogenation:[10] Cyclohexene has a heat of hydrogenation of 28.6 kcal/mol and cyclohexadiene has one about twice that (55.4 kcal/mol). Thus, we might reasonably expect cyclohexatriene to

have a heat of hydrogenation about three times as large as cyclohexene, that is, about 85.8 kcal/mol. Actually, the value for benzene (49.8 kcal/mol) is 36 kcal/mol less than this expected amount. In other words, benzene is more stable by 36 kcal/mole than we would be expected for cyclohexatriene and this stabilization energy is called the Resonance Energy (RE). (Figure 1)[10]

Figure 1[10] Heats of hydrogenation and stability: benzene, cyclohexadiene and cyclohexene.



One should be aware that estimates of this extra stability depend on the compound taken as reference. For example, the resonance energy of benzene according to isodesmic equations varies from 35.2 to 64.2 kcal/mole (equation 1 to 3)[2]

3 cyclohexene = benzene + 2 cyclohexane	ΔH = -35.2 kcal/mol	Eq. 1
3 ethylene + 3 ethane = benzene + 6 methane	RE = -64.2 kcal/mol	Eq.2
3 ethylene + cyclohexane = benzene + 3 ethane	RE = -48.9 kcal/mol	Eq.3

Delocalization energy is a kind of Resonance Energy which results from the delocalization of π electrons, originally constrained to isolated double bonds in a Kekulé structure. It has been found that almost all compounds, even the ones that are unstable, have calculated delocalization energies which were not in the experimental order of stability.[11] To overcome these faults, Dewar Resonance Energy (DRE), which is defined as the difference in energy between a given aromatic compound and a corresponding localized structure (eg. benzene and 1,3,5-cyclohexatriene), was proposed in 1969 by Dewar and de Llano.[11] The "polyene" bond energies, which are found to be essentially constant from molecule to molecule, are

$$E_{C\text{-}C} = 4.3499\text{eV} \; ; \qquad E_{C=C} = 5.5378\text{eV}$$

There is a good correlation between DRE and experimental stability for many compounds:

$$DRE = E_a - (n_1E_{C\text{-}C} + n_2E_{C=C} + n_3E_{C\text{-}H})$$

where E_a is the heat of atomization of the conjugated molecule concerned, $E_{C\text{-}H} = 4.4375$ eV is the bond energy of the C-H bond, and n_1, n_2, n_3 are respectively the numbers of C-C bonds, C=C bonds, and C-H bonds.

Thus, for benzene[12], the DRE is:

$$DRE = 57.157-[3(4.3499) + 3(5.5378) + 6(4.4375)] = 0.8689eV$$
$$= 20 \text{ kcal/mol}$$

Although cyclic delocalization of (4n+2) π-electrons provides an important contribution to the overall stability of conjugated cyclic array, strain effects and other contributing factors may sometimes counterbalance or override the influence of aromaticity.[13] Thus, it is quite difficult to apply the energy criterion to a strained system.

2. Kinetic stability - Chemical behaviour which prefers electrophilic substitution over addition reactions

Reactivities toward substitution, or addition or both, have been used to measure the aromaticity of a molecule.[14] The competition between substitution and addition has been claimed to be a much better criterion of aromaticity than any other reactivity index. The result of the competition can not only be observed experimentally by determining the products of the competing reactions but also theoretically by computing the relative rates. However, not all aromatic systems react like benzene. For example bromine adds to phenanthrene, and anthracene serves as a diene in Diels-Alder reactions. Fullerenes are aromatic, but they undergo addition rather than substitution reactions.[15]

3. Structural criterion - bond length equalization

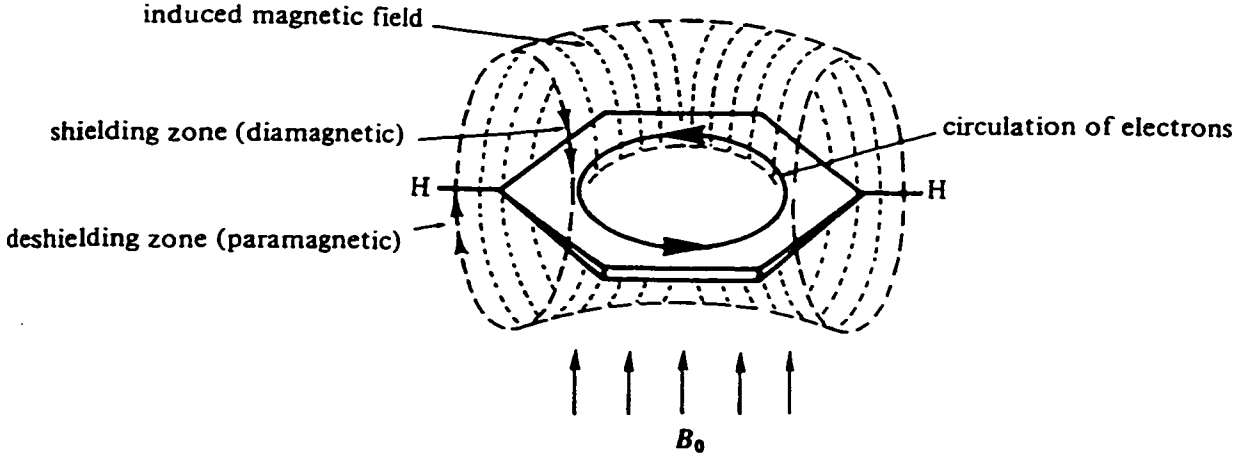
If a conjugated molecule is aromatic, this results in bond length equalization so long as the π-electrons involved are of favorable symmetry. Theorists are still debating whether bond length equalization is the result of a π-effect, σ-effect, or both.[3] Nonetheless, the direct determination of bond lengths provide valuable information on the extent of electron delocalization in molecules. For example, the C-C bond length of benzene, a perfectly delocalized system, is 1.396 Å. In contrast, cyclobutadiene has been computed to have alternating single (1.565 Å) and double (1.344 Å) bonds in the singlet state.[2] However, equal bond lengths is not a sufficient criterion. For example, borazine, which was found by magnetic susceptibility exaltation not to be aromatic, has equalized bond lengths. Some heteroaromatic compounds such as furan and pyrrole, which have unequal bond length, are still regarded as aromatic compounds.

4. Magnetic - "ring current" effects

It is preferable that some simple and easily determined experimental parameters could be used to define aromaticity. To determine aromaticity based on energetic properties is not trivial. Errors may arise in determining the stabilization energy, steric interactions or angle strain, and in some molecules these errors could cast doubts on the results. Bond length analyses are based on experimental (for example, from X-ray analyses) or theoretical structures. X-ray crystallography suffers from the drawbacks that suitable crystals are difficult to obtain and a lengthy procedure is generally involved to resolve the structure. More importantly, the bond length method is not suitable for hetero-aromatic molecules such as furan and pyridine since they have unequal peripheral bonds,

but there is no doubt that they are aromatic compounds. The accuracy of theoretical bond length calculations depends very much on the basis sets chosen and can vary considerably between different types of calculations. *^1H chemical shifts are perhaps the most often used criteria for characterizing aromatic and antiaromatic compounds.*[15a] Diamagnetic ring currents indicate aromatic while paramagnetic ring currents indicate antiaromatic compounds. The NMR experiment is routine and only a small sample size is required. Thus, for an aromatic compound with $(4n+2)\pi$ electrons, such as benzene, when an external magnetic field is applied, the cyclic π-array produces an induced ring current. This induced ring current generates an anisotropic diamagnetic field H_i which has opposite direction inside and outside of the ring. Therefore, a high field has to be applied for inner protons (which therefore appear shielded) and a lower field for external protons (which therefore appear deshielded) in order to bring them to resonance. (See Figure 2)[16] For $4n\pi$ rings systems, the induced ring current is paramagnetic. The chemical shifts appear

Figure 2[16] Anisotropic shielding and deshielding associated with the aromatic ring current. The molecules are constantly tumbling, but a net effect is still present. Protons attached to the ring have high δ values.



downfield for inner protons and upfield for other protons, which is opposite to the case of the aromatic system. Conventionally, a compound which has the ability to substain an induced diamagnetic ring current is called *diatropic* and a compound which sustains a paramagnetic ring current is called *paratopic*.

For example, in the aromatic [18]annulene **14** (See Table 1), ^{1}H-NMR chemical shifts of δ 9.28 (outer protons) and δ -2.99 (inner protons) are in sharp constrast to the values found for the antiaromatic [18]-annulene dianion, δ -1.13 ppm (outer protons) and δ 28.1, 29.5 (inner protons).[17] The difference between aromaticity and anitaromaticity is dramatic. However, a paramagnetic ring current may not always easily be observed, as it can be partly quenched by the localization and non-planarity of π-electrons which avoid the unfavorable energetics of antiaromaticity.

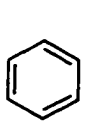
An "annulene" is a monocarbocyclic conjugated polyene, where the ring size is indicated by a number in brackets. Depending on the number of π-electrons, the π-electron delocalization and the planarity of the conjugated system, an annulene can exhibit diatropicity , paratropicity or not show any magnetic property at all.

In Table 1, selected examples of proton chemical shifts for a number of (4n+2)- and (4n)-π annulenes are shown:

Table 1: Proton chemical shifts[18] (δ) of (4n+2)-π and (4n)-π annulenes. δ in ppm

Annulene	compound no.	Outer protons δ	Inner protons δ	Ref.
[6]	**1**	7.27 (H)	NA	18a
[8]	**2**	5.70 (H)	NA	18b
[10]	**3**	5.66 (H)	NA	18c,18d
[10]	**4**	7.27-6.95 (H)	-0.52 (CH_2)	18c,18d
[12]	**5**	5.5-5.2 (H)	6.06 (H)	20
[12]	**6**	5.5-5.2 (H)	6.06 (CH_2)	18e
[14]	**7**	7.6 (H)	0.0 (H)	20
[14]	**8**	7.9-7.6 (H)	-0.6, -1.2 (CH_2, CH)	19
[14]	**9**	8.67-7.98 (H)	-4.25 (CH_3)	18f
[14]	**10**	8.74-7.50 (H)	-2.06 (CH_3)	18g
[16]	**11**	5.09-4.77 (H)	5.68, 8.30 (CH_2)	18h
[16]	**12**	9.6 (H)	-5.5 (H)	18i
[16]	**13**	9.6 (H)	-4.4 (H)	18j
[18]	**14**	9.28 (H)	-2.99 (H)	18k
[20]	**15**	9.35-7.15 (H)	4.52(CH_2)	18l
[22]	**16**	9.65-8.50 (H)	-0.40, -1.20 (H)	18m
[24]	**17**	8.62-8.36 (H)	4.04 (CH_2)	18l

Compound **1** to **17** for Table 1



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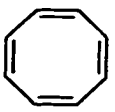

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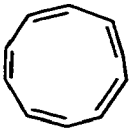

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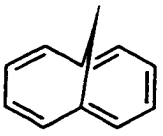

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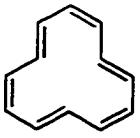

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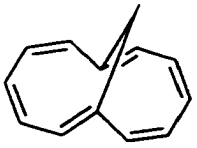

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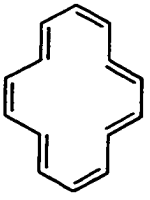

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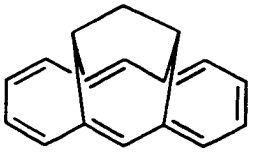

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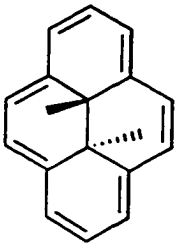

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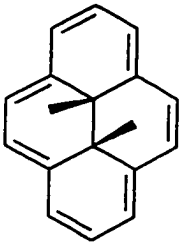

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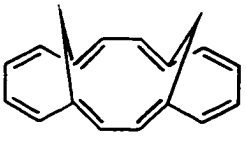

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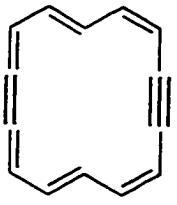

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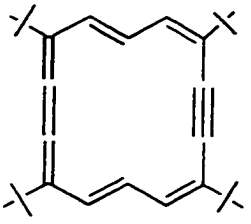

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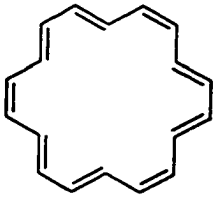

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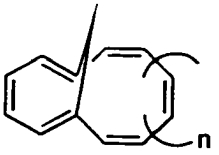
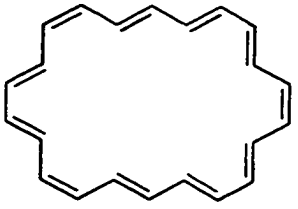


n = 5, **15**
n = 7, **17**



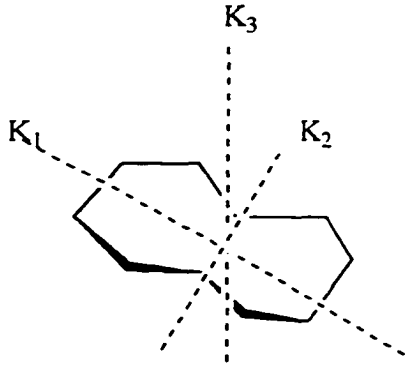
16

Because some annulenes are conformationally mobile, they show very little diatropicity or paratropicity. To increase the rigidity of annulenes, bridging systems were introduced as in Vogel's annulenes[19] such as **4** and **8** and Boekelheide's [14]annulenes[19] **9** and **10**. As well, acetylene units or the *tert*-butyl group were also introduced as in Sondheimer's[20] and Nakagawa's[21] annulene systems such as **12** and **13**.

It should be noted that diatropicity or paratropicity is not the only magnetic property of a conjugated system that has been related to aromaticity. Magnetic susceptibility anisotropy[22], has also been advocated as a criterion of aromaticity. The tensor normal to the aromatic ring is much larger than the average of the other tensors. Take naphthalene as an example, the susceptibility (K_3) measured normal to the plane of the molecule is considerably greater than those in the plane (K_1 and K_2 are approximately equal). (Figure 3) The magnetic susceptibility anisotropy (χ_{aniso}) is defined as:

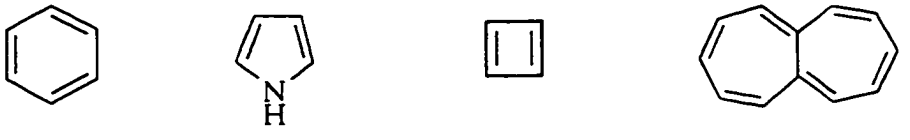
$$\chi_{aniso} = \Delta\chi = \chi_z - 1/2\,(\chi_x + \chi_y)$$

Figure 3 Magnetic susceptibility of naphthalene along x, y and z directions



Aromatic compounds such as benzene, **1**, and pyrrole, **18**, have quite large negative χ_{aniso}. In constrast, antiaromatic compounds, such as cyclobutadiene, **19**, and heptalene, **20**, have positive χ_{aniso} (See Figure 4)[2]. It is noteworthy that χ_{aniso} is only applicable for planar or nearly planar aromatic molecules and is useless for spherical systems, where χ_{aniso} vanishes.[15]

Figure 4 Magnetic susceptibility anisotropy (χ_{aniso}) for some selected compounds



	1	**18**	**19**	**20**
χ_{aniso} [10^{-6} erg/(G^2.mol)]	-62.9	-41.8	+28.7	+168.3

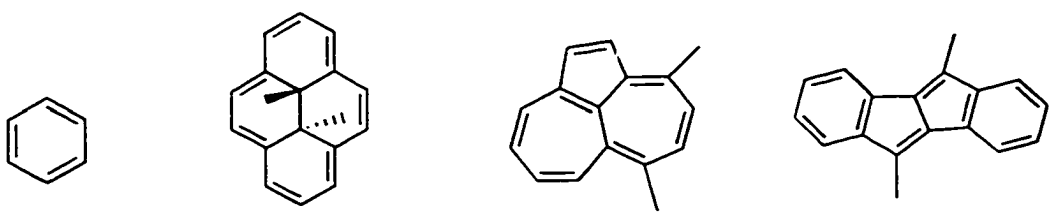
Another physical parameter, diamagnetic susceptibility exhaltation, DSE (Λ), was introduced by Dauben et al[23] to define aromaticity:

$$DSE\ (\Lambda) = \chi_m - \chi_m\cdot$$

where χ_m is the experimental determined molar susceptability of a compound and $\chi_m\cdot$ is the susceptabiltiy estimated for a cyclopolyene of that structure.

The values of DSE offer a direct method for determining aromaticity. A value of zero means that the compound is non-aromatic. Aromatic compounds should exhibit $\Lambda > 0$ while antiaromatic compounds should have $\Lambda < 0$. Examples are included in Figure 5:

Figure 5 Diamagnetic susceptibility exhaltation, DSE (Λ), for some selected compounds

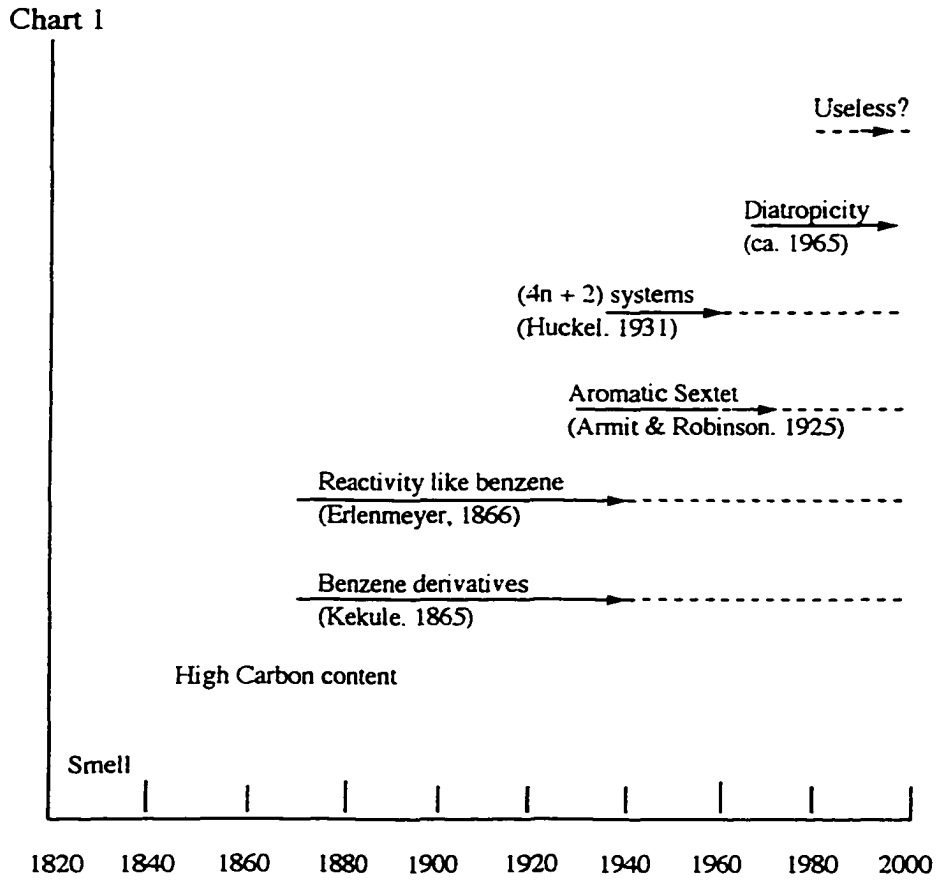


	1	**9**	**21**	**22**
DSE (Λ): (10^{-6} $cm^3.mol^{-1}$)	+13.7	+81	0.0	-14

5. Concluding remarks on the term "aromaticity"

To define the terms "aromatic" and "aromaticity" is not easy. Instead of giving aromaticity a very narrow definition, the chart illustrating the changes of meaning and interpretation which have been associated with the terms aromatic and aromaticity is quoted from Maier's review (See Chart 1).[24] He concluded the review by asking the question "Is the expression aromatic actually useless?" The article is written in German, and the answer supplied is "jein" (Yes and No).

Chart 1 The changes of meaning and interpretation which have been associated with the terms aromatic and aromaticity[24]



The very uncertainty involved in the concept of aromatic and aromaticity provides a stimulus and excitement in this research area. Through many intellectual debates and, perhaps even more important, through the amount of chemistry, especially practical but also theoretical, which has been or will be done in a desire to give aromaticity a definition, it is almost certain that many new aspects and discoveries will appear in the near future.

C. Dimethyldihydropyrene (DHP), **9**, and its derivatives

trans-10b,10c-Dimethyldihydropyrene (DHP, **9**)[25], is an aromatic compound judged by its proton NMR spectrum. It has a strong diamagnetic ring current which shields its internal methyl protons to δ -4.25 and deshields its external protons to δ 7.89 - 8.67.[26]

The X-ray structure of **9** has been reported (See Figure 6).[18] Bond alternation is absent in the periphery of the molecule, with bond lengths ranging from 1.377-1.396 Å. The largest torsional angle around the perimeter (C_{21}-C_{22}-C_{23}-C_{24} in Figure 6b) is only 4° and therefore the π-periphery of **9** is virtually planar. A diamagnetic susceptibility exhaltation (DSE) value of 81 x 10^{-6} cm^3/mol is also reported[23] for compound **9**. Based on the above observations, DHP, **9**, is truly an aromatic compound.

In the X-ray structure of **9**, the internal methyl groups are in the centre, above and below the plane, of the 14 π-cavity. It has been shown that the ^1H chemical shift of internal methyl group of **9** is very sensitive to the ring current reduction effects caused by bond fixation introduced by annelation of **9** with aromatic rings. Thus DHP, **9**,

was used as a probe molecule to measure the relative aromaticity of an annelating aromatic ring compared to a benzene ring and the relative aromaticity of many aromatic systems can be measured experimentally in this way by fusing the aromatic system in question on DHP.

Figure 6a: ORTEP drawing of **9** (first molecule)

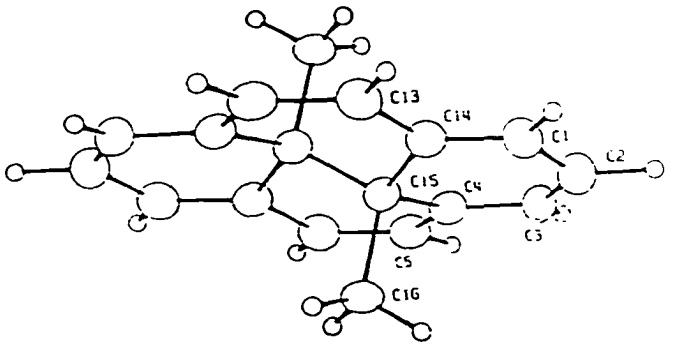
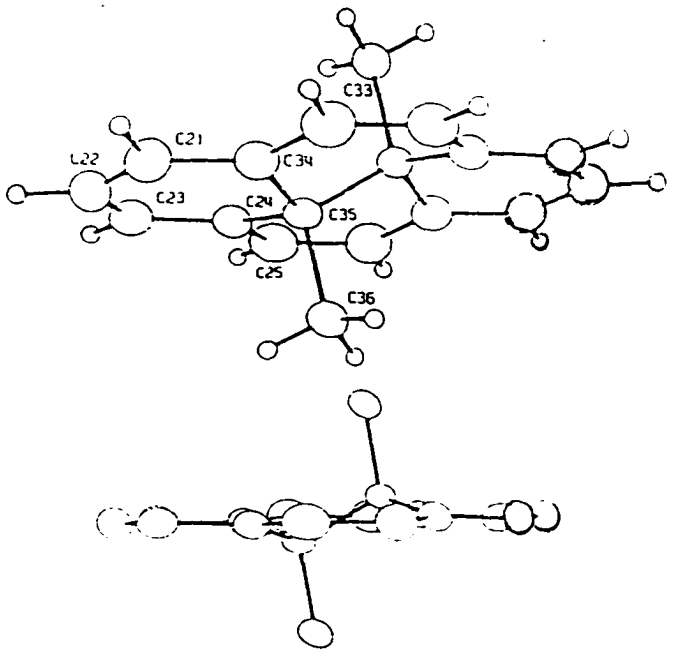
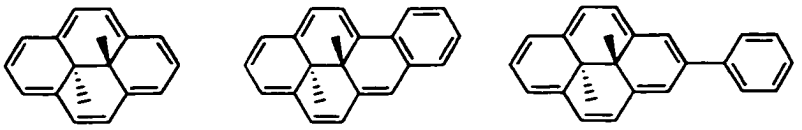


Figure 6a: ORTEP drawing of **9** (second molecule)



Although the ring current of DHP, **9**, is very sensitive to the fusion of an aromatic ring, it is much less sensitive to substitution effects. Thus benzannelation of DHP in the [a]-position to give **23** shows a large effect on the internal methyl proton chemical shift ($\Delta\delta$(Me) = 2.6 ppm) while substitution of a phenyl group to give **24** shows a small effect ($\Delta\delta$(Me) = 0.2 ppm), when their internal methyl proton chemical shifts were compared with that of the parent compound **9** (δ(Me) -4.25). (Figure 7)

Figure 7 Comparison of annelation and substitution effects of DHPs

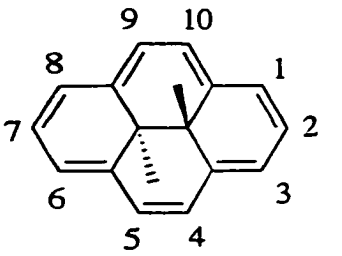


9 **23** **24**

Int. Me, δ(Me)	: -4.25	-1.62	-4.02
$\Delta\delta(Me) = \delta(Me)_X - \delta(Me)_9$	: 0	2.6	0.2

To illustrate further that chemical shift of the internal methyl group is relatively insensitive to substitution effects, the chemical shifts, δ(Me), of many substituted DHPs are listed in Table 2:

Table 2 : Internal methyl proton chemical shifts δ(Me) for some selected substituted derivatives of DHP (Note: δ(Me) for DHP **9** = -4.25)

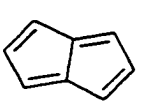


DHP 9

Substituents	Position	Int Me (δ, ppm)	Reference
Br	2	-4.07, -4.08	26
NO_2	2	-4.03	27
$NHCOCH_3$	2	-4.11, -4.14	27
CPh_3	2	-3.92, -4.03	27
Ph	2	-4.03, -4.00	28
DHP	2	-3.68, -3.77	28
OCH_2CH_3	2	-3.97	31
Br	2,7	-4.02	27
CH_3	2,7	-4.09	29
CHO	2,7	-3.60	29
CHO, CH_2OH	2,7	-3.80	29
$COOCH_3$	2,7	-3.92	29
$OCOCH_3$	2,7	-4.03	31
t-Bu	2,7	-4.06	30
$NHCOCH_3$, CHO	2,7	-3.68, -3.73	27

D. DHP, **9**, as a probe to study aromaticity

DHP is a [14]annulene. When a benzenoid such as benzene, naphthalene or phenanthrene is fused to DHP, an annulenoannulene results. Annulenoannulenes need not necessarily have an even number of carbon atoms in each of the fused rings. Hence, a classification into alternant annulenoannulenes and non-alternant annulenoannulenes may be appropriate.[32] The latter are made up of two fused odd-numbered ring such as pentalene, **25**, which has two fused five-membered rings. The alternant annulenoannulenes are the compounds upon which our group has mostly focused. The Benzo[a] fused DHP **23**,[33] is such an example which can be regarded as derivative of [6]annuleno[14]annulene.



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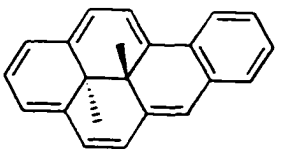
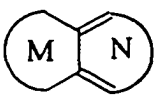


23

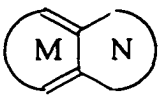
The alternant annulenoannulenes have three Kekulé resonance structures while the nonalternant annulenoannulenes have only two Kekulé structures as shown in Figure 8.

Figure 8 Kekulé structures for an alternant and nonalternant annulenoannulene

26a

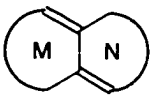


26b

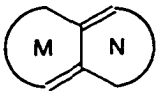


26c

Kekulé structures for an alternant annulenoannulene



27a

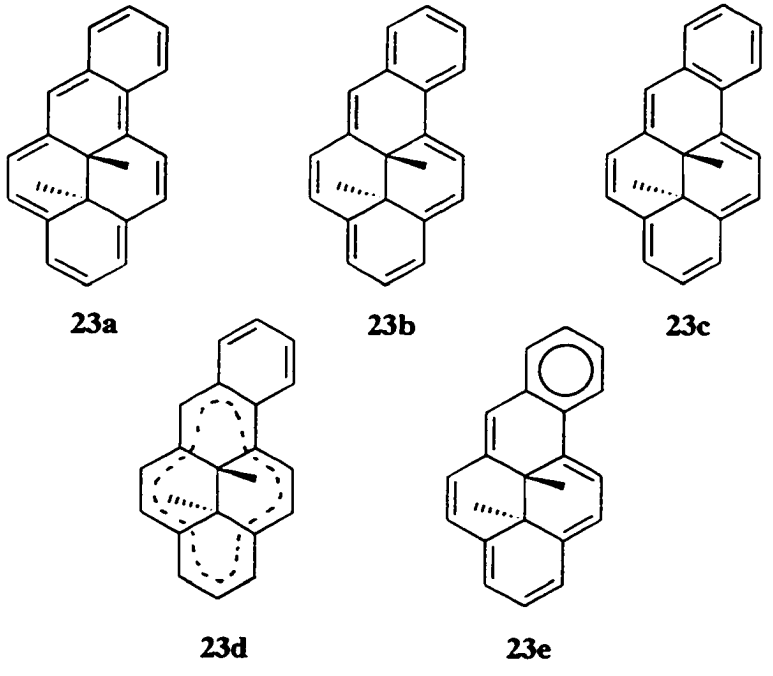


27b

Kekulé structures for an nonalternant annulenoannulene

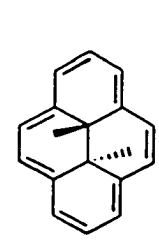
We have found that by fusing a benzenoid such as benzene onto DHP as in the benzo[a] fused DHP **23**, the benzenoid and the DHP π-systems compete for delocalization. This competition can be visualized if the Kekulé structures of **23** are considered. There are altogether three Kekulé structures for **23** (**23a**, **23b** and **23c**). Kekulé structures **23a** and **23c** represent a bond delocalized DHP with a bond fixed benzene, while Kekulé structures **23b** and **23c** represent the bond delocalized benzene fused to a bond fixed DHP. These can be represented by structures **23d** and **23e** respectively (See Figure 9). Mitchell has commented on this kind of competition for the delocalization between the annelated benzenoid and the DHP system and in 1982, the first

Figure 9 Kekulé structures of compound **23**



23d: Combination of Kekulé structures **23a** and **23c**
23e: Combination of Kekulé structures **23b** and **23c**

empirical formula was derived[33] to predict the internal methyl group chemical shift δ(Me) on annelation of DHP with another aromatic system. An empirical linear relationship was found between the chemical shift shielding of the internal protons for the series of benzannelated DHPs, **9**, **23**, **28**, **29**, **30**, and the average deviation of π-SCF bond order of the macrocyclic ring from that found (0.642) in a Hückel [14]annulene. A plot of chemical shift shielding of the internal methyl protons (Δδ) versus average bond order deviation from 0.642 (Δr) for annulenes **9**, **23**, **28-30** gave a reasonably good straight line (Figure 10 and equation 4) with a coefficient ρ= 0.9902.



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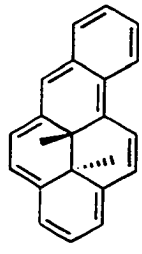
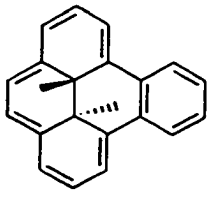


23



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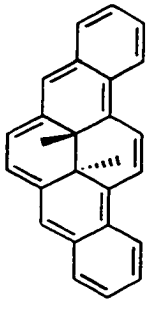

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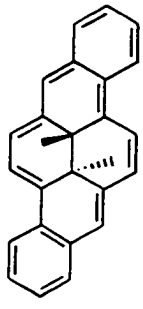

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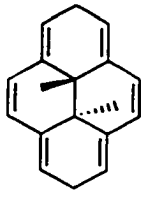
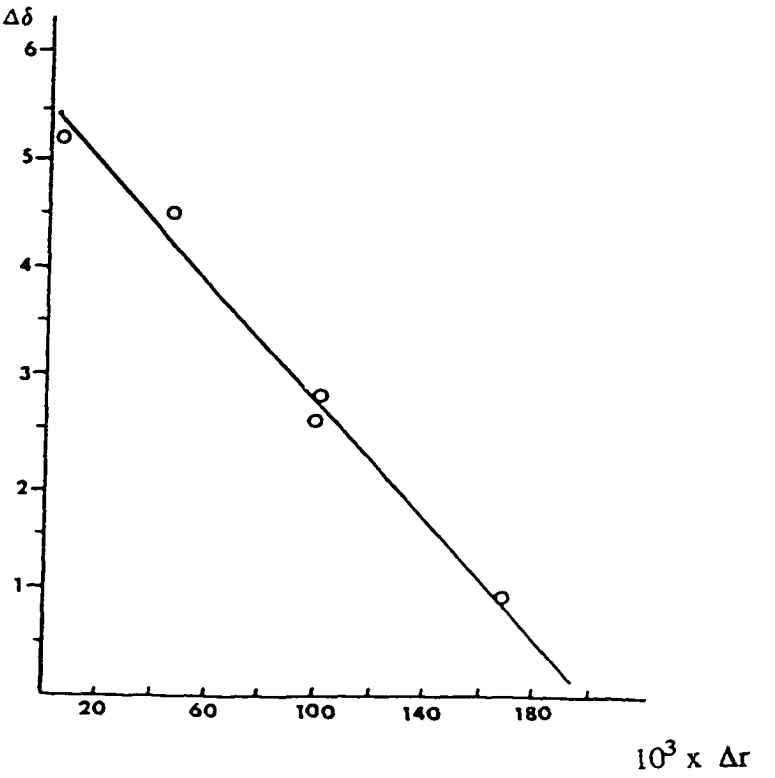


31

Figure 10 Plot of chemical shift shielding ($\Delta\delta$) vs. average bond order deviation (Δr) for annulenes **9**, **23**, **28**, **29**, **30**



$$\Delta\delta = 5.533 - 27.52\ \Delta r \qquad \text{(equation 4)}$$

$$\Delta\delta = \delta(Me)_{31} - \delta(Me)_{\text{annulene}} = 0.97 - \delta(Me)_{\text{annulene}}$$

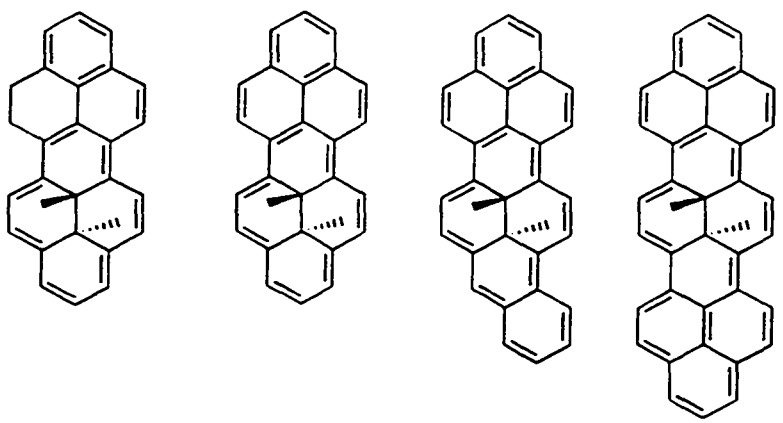
$$\Delta r = P_u / m \text{ where } P_u = \sum_m |(P_u - 0.642)| \qquad \text{(equation 5)}$$

(m = number of bonds of the macroring minus the benzannelating ring fused bond and 0.642 is the standard bond order for a [14]annulene)

It is worth noting that the bond order difference Δr is related to the bond order P_{uv} which can be derived both theoretically from a π-SCF calculation (equation 5) and experimentally from the $^3J_{HH}$ coupling constant (equation 6).[34]

$$P_{uv}\,(SCF) = 0.104\,{}^3J_{uv} - 0.120 \qquad \text{(equation 6)}$$

Then equation 4 was used to predict 18 known and 29 unknown chemical shifts of other benzannelated annulenes,[33] and most of the known shifts agree with those calculated to within 0.5 ppm. For example, the calculated chemical shift shieldings ($\Delta\delta$) for the compounds **32**, **33**, **34**, **35** were 3.72, 4.94, 2.70 and 3.96 ppm while those



32 **33** **34** **35**

found experimentally were 3.75, 5.20, 2.3 and 4.2 ppm. It is impressive that the equation has the predictive power that it does, considering the simplicity of the assumptions. After more than two decade's work and much accumunated experimental data, Mitchell has proven that the chemical shifts of DHP correlate with what is generally recognized to be the aromatic character of DHP.[35] The assumption is based on the observation that the chemical shift measured for the internal protons of DHP reflects the delocalization around the macrocyclic ring, at least as estimated from bond order calculations. The best experimental data for such a correlation should come from bond lengths determined by X-ray structure. Unfortunately, it is not always possible to obtain a suitable crystal of annelated DHP derivatives for X-ray structural determination. However, in the absence of suitable X-ray C-C bond length data, the $^3J_{cis}$ values are the best experimental indicator of bond lengths in aromatic systems, as pointed out by Cremer and Günther.[34] Therefore, Mitchell has correlated the $^3J_{cis}$ coupling constants with the chemical shifts of the internal methyl protons of DHP δ(Me) and they have the reasonably linear relationship shown in equation 7: [35]

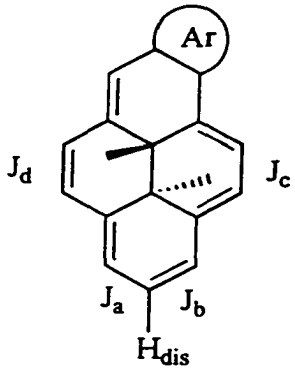
$$\delta(Me) = 7.99 (J_b / J_a) - 12.29 \qquad \text{(equation 7)}$$

Coupling constants, J_b and J_a (See Figure 11), are used in equation 7 because they are furthest away from the annelating system and are subject to the least steric effects. If it is not possible to determine J_b and J_a, then J_c and J_d can be used, using the relationship[35]:

$$J_b / J_a = 1.769 (J_d / J_c) - 1.023 \qquad \text{(equation 8)}$$

to substitute in equation 7.

Figure 11 Coupling constants and proton chemical shift used in equation 7, 8 & 9



(if $J_b / J_a = 1$, eg. in DHP, **9**, δ(Me) = -4.25)

Also the chemical shift of the most distant proton, $\delta(H_{dis})$ is related to δ(Me) by equation 9.[35] Comparison of $\delta(Me)^{exp}$ and $\delta(Me)^{calc}$ (calculated using equation 9 from $\delta(H_{dis})$) gives a check on the consistency of the results.

$$\delta(Me) = 17.515 - 2.685\ \delta(H_{dis}) \qquad \text{(equation 9)}$$

All of these linear correlations in the DHP system were then used to obtain a relationship between the Relative Aromaticity (RA) of benzene and the fused ring in question. Thus the Relative Aromaticity (RA) can be derived by calculating the ratio in the change in internal methyl group chemical shift of benzo[a] annelated DHP relative to that of the benzenoid in question when compared with the δ(Me) of the parent DHP:

$$\text{Relative Aromaticity (RA)} = [\delta(Me)_x - (-4.25)] / [\ \delta(Me)_{23} - (-4.25)]$$

For example, the RA of naphthalene can be calculated in this way:

δ(Me) for naphtho[a]-annelated DHP = - 0.44

δ(Me) for benzo[a]-annelated DHP **23** = -1.62

Therefore, Relative Aromaticity of naphthalene = [-0.44-(-4.25)] / [-1.62-(-4.25)]

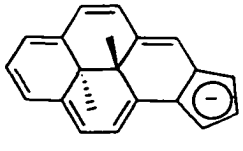
= 1.45

In fact, the relative aromaticities of naphthalene to benzene, as calculated by the ratio of Dewar Resonance Energies is 1.46,[35] is in surprisingly good agreement with the NMR derived results. Other examples are given in reference 35.

E. Background of the project

Many different benzenoid annelated DHP compounds have been synthesized; however, there are very few examples of diannelated DHPs probably due to the synthetic challenge involved. This is unfortunate since diannelated systems should be able to be complexed with metals and hence lead to interesting oligomeric or macrocyclic compounds.

At the start of this thesis project the [a,h]- and [a,i]-dibenzannelated DHPs **29, 30** were known[36] and Khalifa had prepared the mono-cyclopentadienide annelated DHP **36**[18] and shown that preparation of some metal complexes were feasible. Thus, the initial targets for this project were the bis-cyclopentadienide annelated DHPs **37a** and **37b**.



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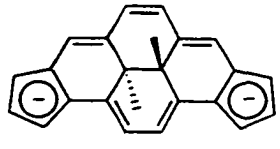
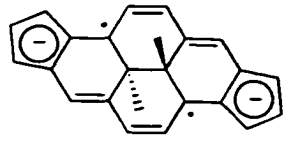
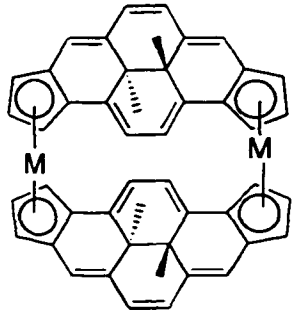


37a

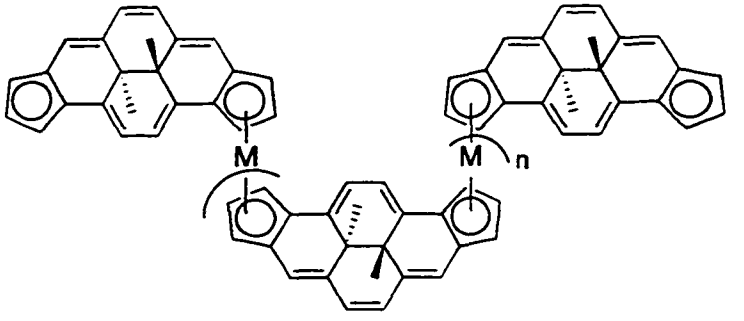


37b

We planned to investigate their metal complex formation, to give species such as the sandwich type compound **38** and the oligomer **39**. As it turns out, the dicyclopentadienes **40** could only be made in minute amounts, using a long multi-step synthesis. The anions are unfortunately rather unstable compounds, and together these prevented investigation of metal complexes. However, during the course of the synthetic work to **40**, we synthesized several dicyclopentene and dicyclopentenone annelated DHPs, **41**, **42**, as intermediates, which we noticed had unusual chemical shifts. This discovery turned out to be perhaps more important than our original goal since it led us into an extensive investigation of the Mills-Nixon effect in a [14]annulene system. Before this, nearly all the literature on the Mills-Nixon effect involved only benzenoid compounds.[89]



38



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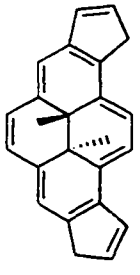
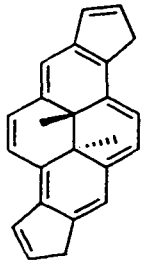
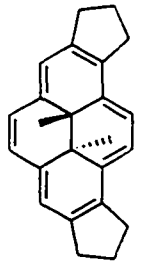


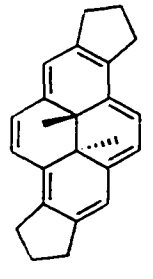
40a



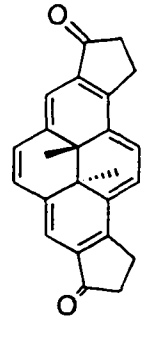
40b



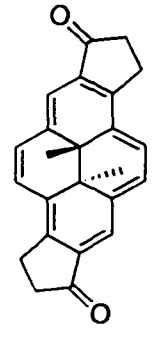
41a



41b

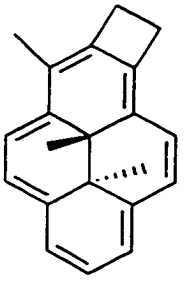


42a

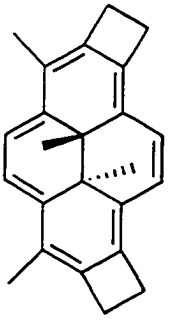


42b

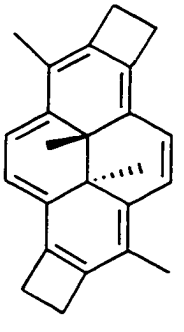
In 1983, Mitchell and coworkers synthesized some mono- and di-cyclobutene annelated DHPs,[37] **43**, **44a** and **44b**. Although the DHP was annelated with highly strained 4-membered ring(s), the internal methyl proton chemical shifts δ(Me) of **43** and **44** were not much affected. For **43**, δ(Me) is at δ -4.23 while for **44a** and **44b**, the internal methyl proton chemical shifts δ(Me) are at δ -4.09 and -4.21, respectively. Thus, from the observed chemical shift difference of 0.12 ppm for the internal methyl protons δ(Me) between **38a** and **38b**, the maximum average bond-order deviation from that of DHP was calculated to be 0.0044 between **44a** and **44b**.[37] The authors concluded that there was no significant π-bond localizing Mills-Nixon effect for the cyclobutene annelated DHP system.



43



44a



44b

When we synthesized the dicyclopentene- and the dicyclopentenone-annelated DHPs **41** and **42**,[38] which are precursors to synthesize the dicyclopentadienide

annelated DHPs **37**, we noticed that they had very different NMR properties. For the dicyclopentene-annelated DHPs **41**, the difference in δ(Me) between the *cisoid* and *transoid* isomers was only 0.03 ppm, which agreed with the results for the dicyclobutene-annelated DHPs and thus **41** showed almost no bond fixation effect. However, when the two cyclopentene rings were oxidized so that the DHP was annelated with two cyclopentenones as in **42**, there was a startling difference in chemical shift of 0.9 ppm between the *cisoid* and *transoid* isomer δ(Me) values for **42a** and **42b**.

In compounds **42a** and **42b**, both structures have a similar conjugation path and substituent effects. The only differences between the isomers are the orientation of the annelated five-membered ring and the carbonyl group. A question is raised - Is this a ring strain effect ? It is very tempting to explain it in terms of the long debated Mills-Nixon effect which was proposed in 1930 and discussed the chemistry of some indanols.[39] More details about the Mills-Nixon effect will be discussed in a later chapter.

Excited by the startling difference in internal methyl proton chemical shifts of the *cisoid* and the *transoid* dicyclopentenone annelated DHPs, we decided to look into the "Mills-Nixon type, bond fixation effect" in more detail. Although in the cycloalkene and cycloalkenone annelated benzene systems, the Mills-Nixon effect was reported to be insignificant, in this thesis we probe the Mills-Nixon effect again, using our DHP system as the probe. We hoped we would be able to observe the Mills-Nixon effect more readily using DHP as it is more susceptible to bond fixation effects according to the research data in hand. Thus, a series of cycloalkene and cycloalkenone annelated DHPs were synthesized and the effect of ring strain contribution to the Mills-Nixon effect in a 14π-annulene, dimethyldihydropyrene, was investigated.

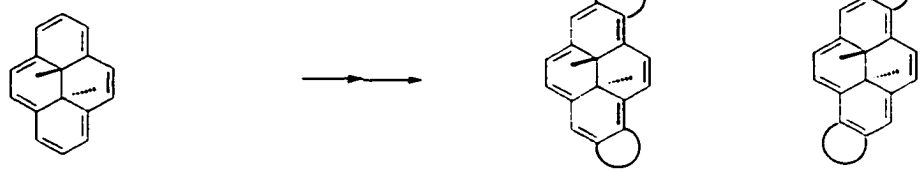
Chapter 2 Syntheses

A. Introduction

To synthesize the ring annelated DHP systems for studying the Mills-Nixon effect, two general approaches, namely the late ring formation approach and the early ring formation approach, have been developed. In the former approach, the ring system is built up after the dihydropyrene stage while the latter approach requires the ring system to be incorporated before the thiacyclophane stage. (Scheme 1)

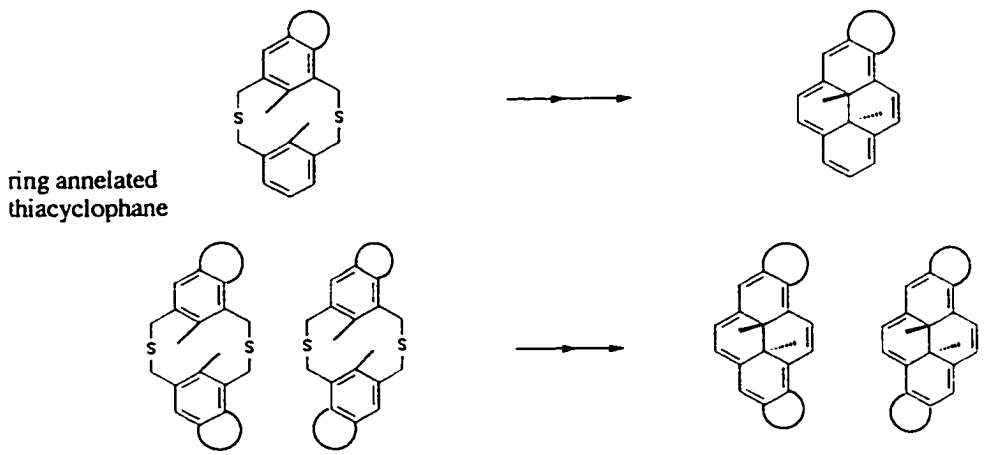
Scheme 1

Late ring formation approach



dimethyldihydropyrene
or its derivatives

Early ring formation approach



ring annelated
thiacyclophane

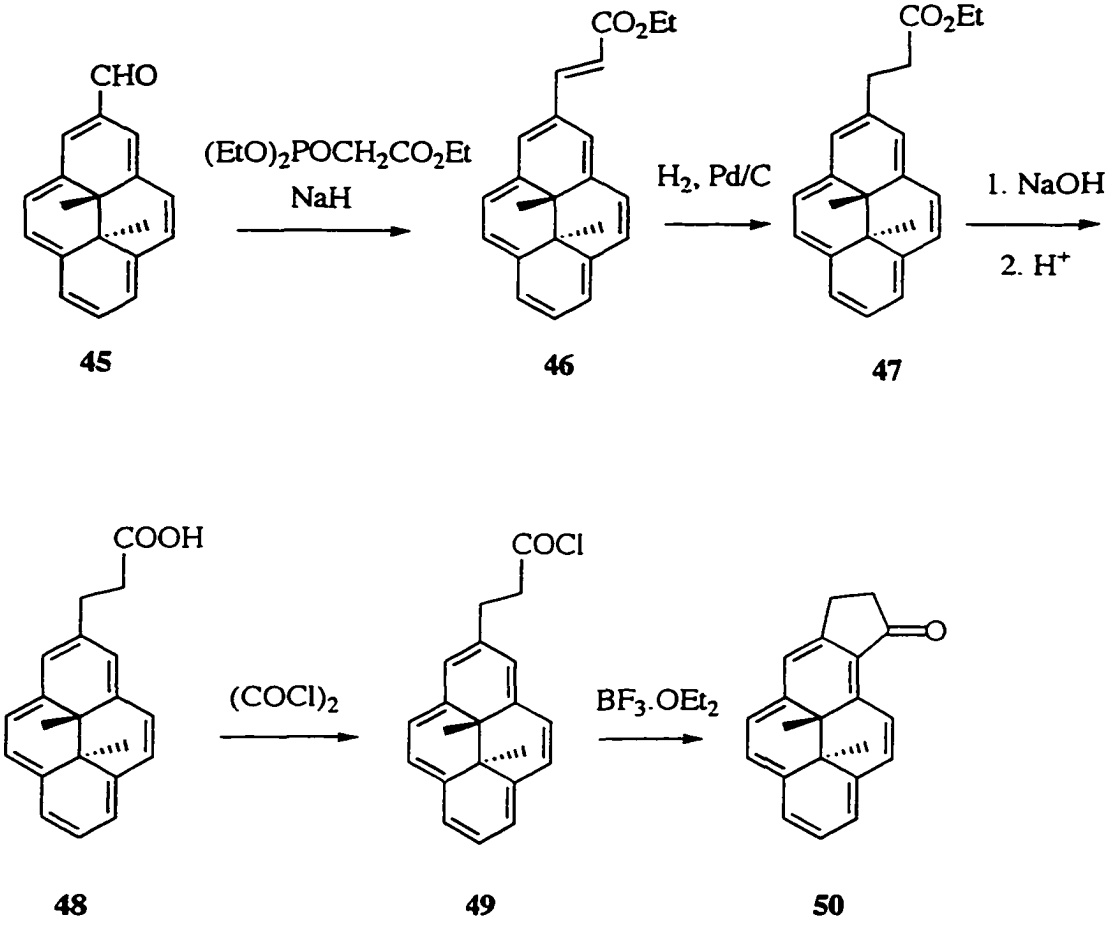
There are pros and cons for both approaches. For example, one can use a single intermediate to synthesize many different products when using the late ring formation approach approach. However, it suffers from the drawback that many DHP intermediates involved are unstable and there may be problem in the regioselectivity in some reactions. On the other hand, the early ring formation approach shortens the number of steps involved to synthesize our DHP targets but each target requires an individual route to build up the ring system. Nevertheless, both approaches are equally important as they are complementary to each other. Some ring annelated DHP targets have only been able to be synthesized by one of these approaches.

B. The synthesis of ring annelated DHPs using a late ring formation approach

Among the known substituted DHP derivatives in the literature, the formylated DHP[25a] is a good candidate to build up ring systems, as it can be chain-elongated using the Wittig reaction. Khalifa used 2-formyl DHP, **45**, to synthesize **50** as shown in Scheme 2[40]. Using a similar approach and a Wittig reagent with differing numbers of carbon atoms, different ring systems should be able to be built up. In this way, the cycloheptenone annelated DHP **56** was synthesized by Miyazawa (See Scheme 3):[41]

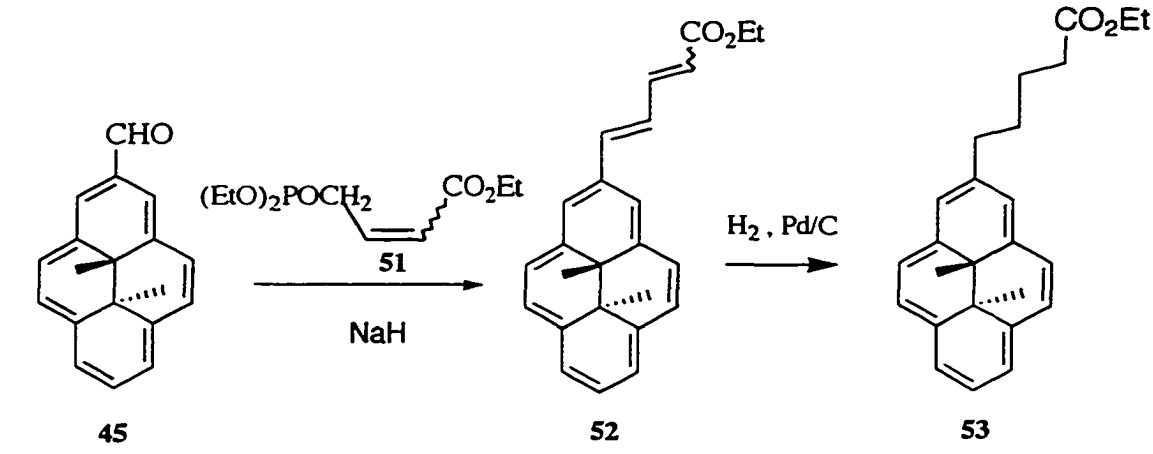
Scheme 2

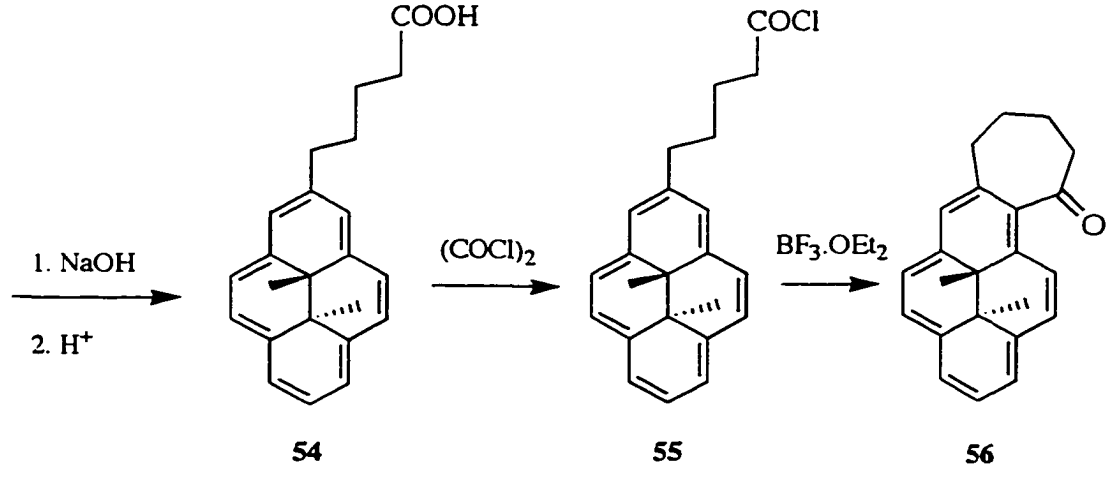
Synthetic route to cyclopentenone[a]annelated DHP **50**



Scheme 3

Synthetic route to cycloheptenone annelated DHP



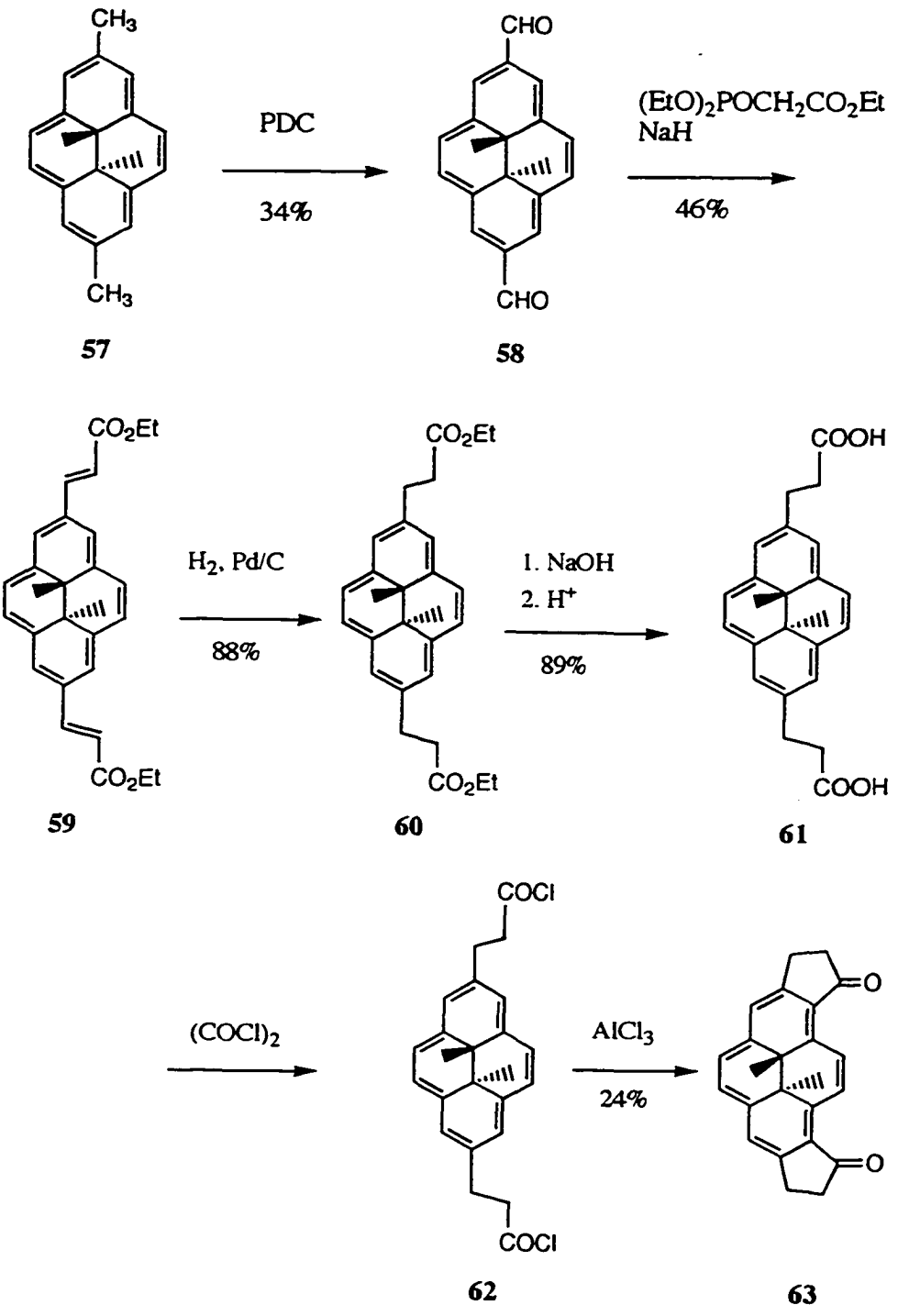


Chain-elongation of 2-formyl DHP, **45**, with triethyl 4-phosphono-crotonate,[42] **51**, gave a mixture of the unsaturated ester **52** (the stereochemistry of the double bonds were not well defined) (CI MS *m/z* 357(MH+)). The double bonds of alkene **52** were catalytically hydrogenated to give the saturated ester **53**. (CI MS *m/z* 361(MH+)). Base hydrolysis of the ester **53** proceeded smoothly and gave the acid **54** (CI MS *m/z* 333(MH+)) which was then converted to the acid chloride **55** using oxalyl chloride. The acid chloride **55** was then cyclized in situ using BF_3-etherate as Lewis acid to give the cycloheptenone[a]-annelated DHP **56** (CI MS *m/z* 315(MH+)).

To synthesize the diannelated DHP systems, a similar approach could also be used with 2,7-diformyl DHP, **58**,[43] instead of **45** as a starting material. However, it turned out that the last bis-Friedel-Crafts cyclization reaction was highly regioselective, giving exclusively the dicyclopentenone[a,i]-annelated DHP **63** (*cisoid*) (See Scheme 4).

Scheme 4 describes the synthesis of the dicyclopentenone annelated DHP **63**. Pyridinium dichromate (PDC) oxidation[44] (34% yield) of the known 2,7,10b,10c-tetramethyldihydropyrene, **57**,[27] was a more direct route to the known 2,7-diformyl dihydropyrene **58**[43] (CI MS *m/z* 289(MH+)). In its ^{13}C-NMR, the carbonyl group signal was found at δ 193.1 and its IR absorption was found at 1685cm^{-1}. Wittig reaction of the dialdehyde **58** with triethyl phosphonoacetate[42] gave the bis-unsaturated ester **59** in 46 % yield (CI MS *m/z* 429(MH+)). According to the coupling constant of the vinylic protons (J=16Hz), the double bonds were exclusively in an E configuration. In the IR spectrum of **59**, the carbonyl group stretch was at 1700 cm^{-1}. Hydrogenation of the purple unsaturated ester **59** gave the unstable green saturated ester **60** in 88% yield (CI MS *m/z* 433(MH+)). This was then saponified immediately to give the diacid **61** in 89% yield (CI MS *m/z*

Scheme 4



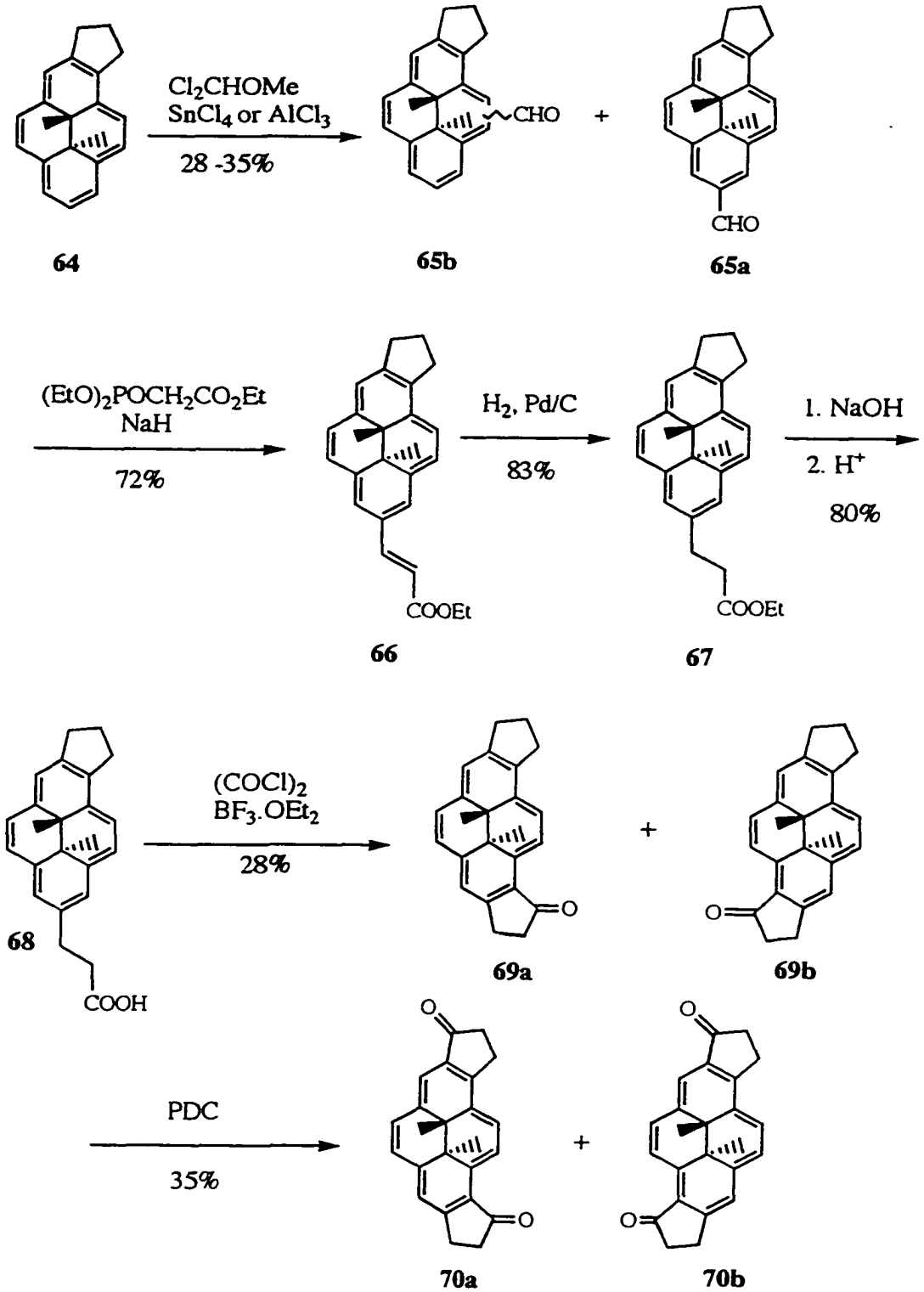
57 **58** **59** **60** **61** **62** **63**

377(MH+)). The carbonyl group of **61** appeared at 1702 cm^{-1} in its IR spectrum. The diacid **61** was then converted to its diacylchloride **62**, and bis-Friedel-Crafts cyclization of **62** using aluminum chloride gave the dicyclopentenone[a,i]-annelated DHP **63** (*cisoid*) as the sole product in 24 % yield (CI MS *m/z* 341(MH+)). In the ^{1}HNMR spectrum of **63**, the internal methyl protons appeared at δ -2.92 and in the ^{13}C-NMR, the carbonyl group appeared at δ 173.8 and in the IR spectrum the C=O stretch appeared at 1658 cm^{-1}. The overall yield from the DHP **57** to the diketone **63** was 3%. This reaction sequence proved that the dialdehyde **58** was a useful intermediate to form a dicycloalkenone-annelated system. The Friedel-Crafts bis-cyclization reaction appeared highly regioselective and favors the formation of the *cisoid* cyclized product.

In order to synthesize the unsymmetrical diketone **70**, an approach using the cyclopentene annelated DHP **64** as starting material was also investigated. The reaction sequence (See Scheme 5) involved the formylation of the cyclopentene annelated DHP **64**,[45] followed by chain-elongation and then Friedel-Crafts cyclization to gave the *cisoid* and *transoid* monoketone **69**. PDC oxidation[44] took place regioselectively at the benzylic position of the five membered ring, which was electron rich (the five membered ring without a carbonyl group).

In Scheme 5, the red 2-formyl-DHP **65a** was obtained in 28 to 35% yield (CI MS *m/z* 301(MH+)), depending on whether tin tetrachloride ($SnCl_4$) or aluminum chloride ($AlCl_3$) was used as Lewis acid in the formylation reaction of **64**. When aluminum chloride was used as Lewis acid, a cleaner reaction resulted compared to that using tin tetrachloride. The carbonyl group of the aldehyde **65a** appeared at 1674 cm^{-1} in

Scheme 5


Cl2CHOMe
SnCl4 or AlCl3
28 -35%
CHO
CHO
64
65b
65a
(EtO)2POCH2CO2Et
NaH
72%
H2, Pd/C
83%
1. NaOH
2. H+
80%
COOEt
COOEt
66
67
(COCl)2
BF3.OEt2
28%
68
COOH
69a
69b
PDC
35%
70a
70b

its IR spectrum. The two most deshielded singlets at δ 8.98 and 8.96 in its ^{1}H-NMR correspond to the aromatic protons adjacent to the aldehyde. 2-Formyl- or 2-keto-compounds are red in color whereas 1-derivatives are green. During this formylation reaction, the regioselectivity was not as good as that of the parent DHP. Also formed was a mixture of green DHPs **65b** (CI MS *m/z* 301(MH+)) with aldehyde protons at δ 11.47, 11.22, 11.21, 11.65, 11.14, 11.10, 11.09, 10.92 and 10.87 in their ^{1}H-NMR spectrum; that of **65a** is at δ 10.53. (Note: Theoretically, seven formylated isomers could be formed excluding the 2-formyl DHP **65a**; the extra aldehyde protons may be due to contamination by *cis*-methyl isomers) This accounts for 13 to 23% yield of the products. Annelation of a cyclopentene ring at the [a]-position of DHP reduces its reactivity towards Friedel-Crafts type formylation significantly; we could not push the reaction to completion no matter how we varied the reaction time, reaction temperature and Lewis acid. The formylated DHP **65a** obtained, was about 95% pure with the remaining 5% being isomers **65b**. We then converted this to the unsaturated ester **66** in 72% yield (CI MS *m/z* 371(MH+)). The alkene was in an E configuration judging by the coupling constant of the two vinylic protons (J=16Hz). The IR stretch of the carbonyl group of **66** appeared at 1703 cm^{-1}. The unsaturated ester **66** was next hydrogenated to the unstable green ester **67** in 83% yield (CI MS *m/z* 373(MH+)) which in its IR spectrum showed the carbonyl group at 1733 cm^{-1}. Immediately saponification of **67** gave the acid **68** in 80% yield (CI MS *m/z* 345(MH+)), of which the carbonyl group absorbed at 1685 cm^{-1} in its IR spectrum. The acid **68** was then converted to the acid chloride by oxalyl chloride and cyclized using BF_3-etherate to give the mono-ketone mixture **69a** and **69b** in 28% yield (CI MS *m/z*

327(MH+)). The ^{13}C-NMR of **69** showed two carbonyl absorptions at δ 209.1 and 209.0 and its IR showed a strong C=O absorption at 1624 cm^{-1}. Oxidation of the mono-ketone mixture **69** gave the expected unsymmetrical diketone mixture **70a** and **70b** in 35% yield (CI MS *m/z* 341(MH+)) which was a mixture of *trans, cisoid* and *trans, transoid* isomers. The internal methyl protons of **70a** and **70b** appeared at δ -2.89 and -3.80 in its ^{1}H-NMR spectrum. In the ^{13}C NMR spectrum, **70** showed four carbonyl signals in its at δ 208.4, 208.0, 207.7 and 207.4, and in the IR spectrum, the carbonyl group absorbed at 1670 cm^{-1}.

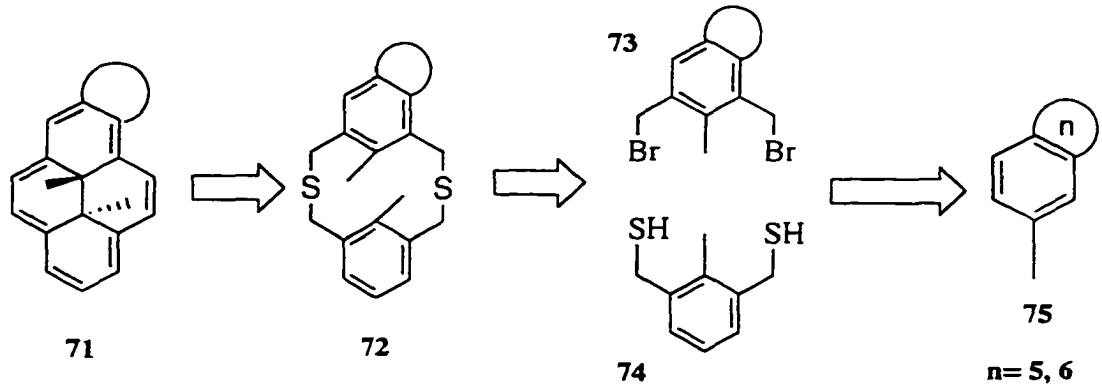
Although the late ring formation approach has the convenience that different ring systems could be constructed through one common intermediate, it suffered from the fact that some of the DHP intermediates involved are highly unstable and the overall yield for such an approach tends to be low because of the long multi-step synthesis involved. Apart from that, there are also some regioselectivity problems in some reactions. Therefore, an alternate approach was also studied.

C. The synthesis of ring annelated DHP systems using the early ring formation approach

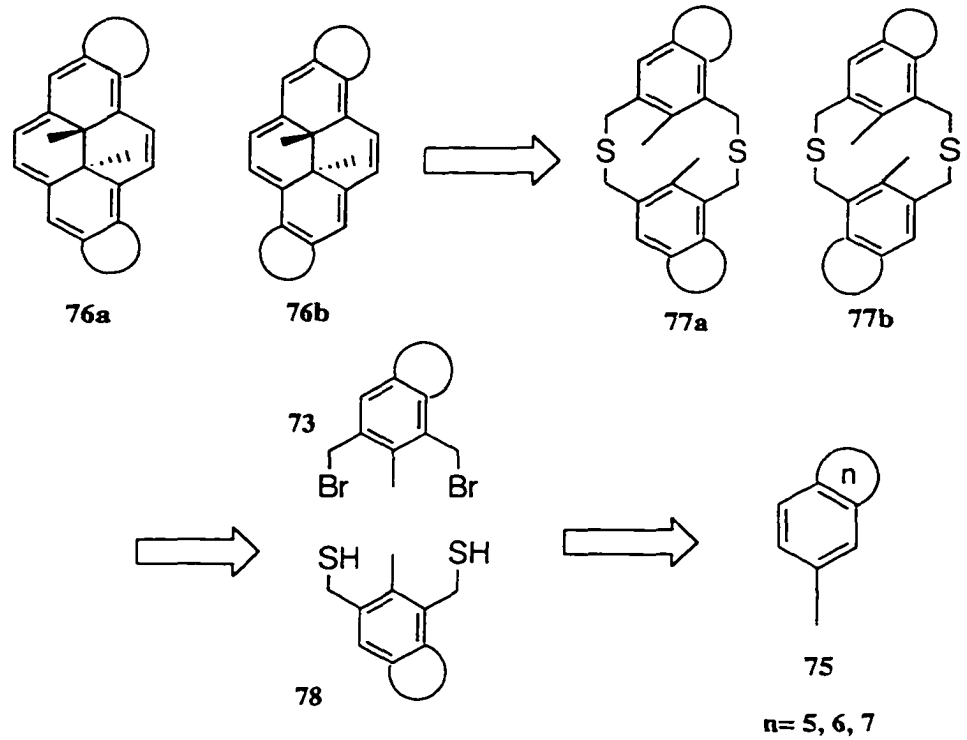
Using a disconnection approach, the ring-annelated thiacyclophanes should be synthesized from the dibromide **73** and the known dimercaptan **74** or the dibromide **73** and the dimercaptan **78**, which can in turn should be synthesized from the cycloalkene annelated toluenes **75** (See Scheme 6)

Scheme 6

Disconnection approach to synthesize mono-cycloalkene annelated dimethyldihydropyrene



Disconnection approach to synthesize di-cycloalkene annelated dimethyldihydropyrene



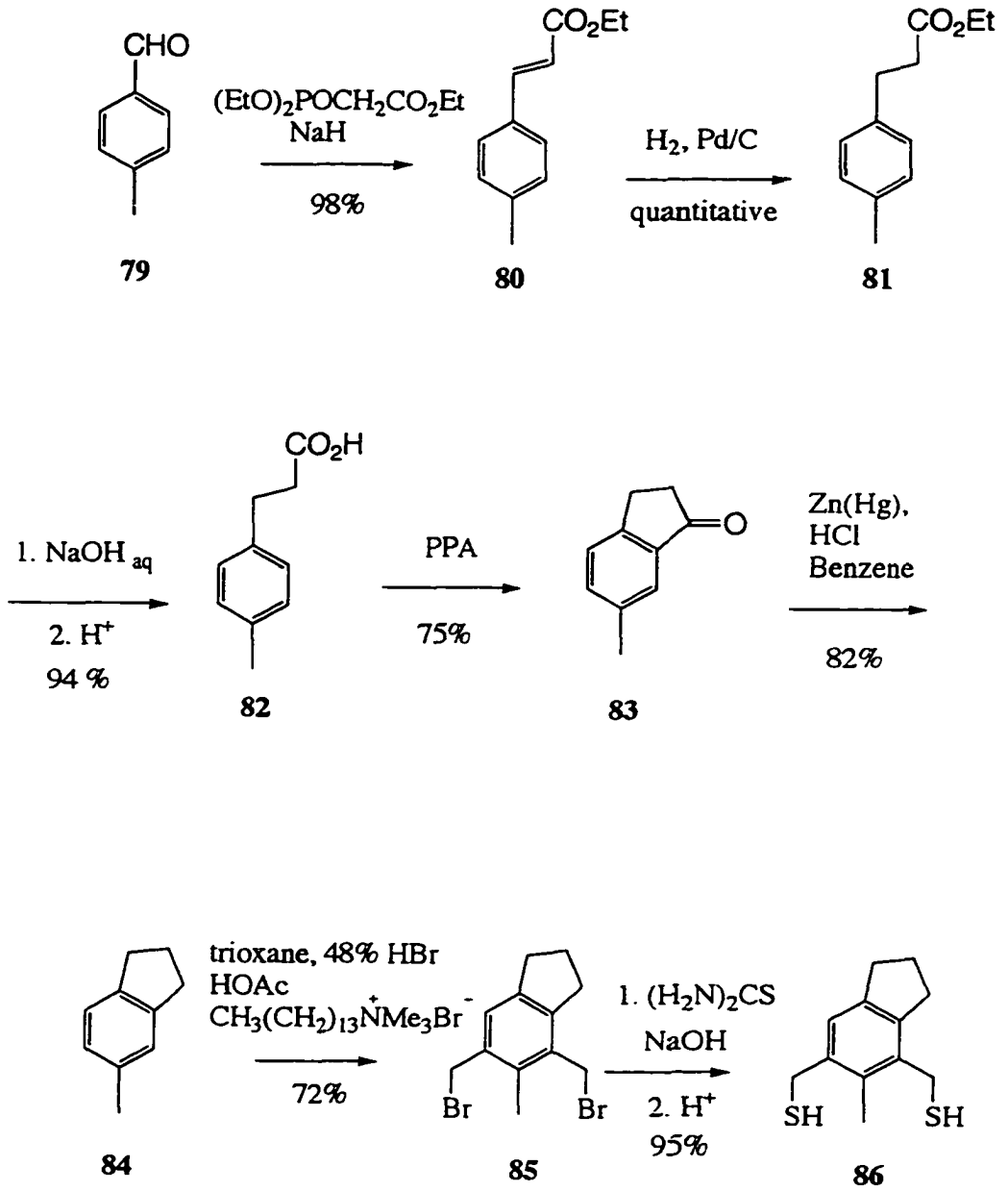
To synthesize the benzocycloalkenes, the ring annelated dibromides and the dimercaptans, the following Schemes were followed:

1. Syntheses of the methylindane **84**, the dibromide **85** and the dimercaptan **86** (Scheme 7):

To synthesize **84**, the reaction sequence of Collins et al[46] was followed. *p*-Tolualdehyde **79** was chain elongated by the Wittig-Horner reaction[47] with triethylphosphonoacetate[44] to give the unsaturated ester **80**. (CI MS *m/z* 191(MH+)). On a larger scale (>10g), ester **80** could be synthesized more economically by condensation of *p*-tolualdehyde with malonic acid followed by an acid catalyzed esterification reaction. Both chain elongation reactions gave exclusively the E-ester **80** indicated by the coupling constant of the vinylic protons (J=16Hz). The ester **80** was hydrogenated to give the saturated ester **81** (CI MS *m/z* 193(MH+)). Saponification of the ester **81** gave the acid **82** (CI MS *m/z* 165(MH+)) which was then cyclized using polyphosphoric acid (PPA)[48] to give the indanone **83** (CI MS *m/z* 147(MH+)). The carbonyl group of **83** was then removed by Clemmensen reduction[49] to afford the known 5-methylindane **84** (CI MS *m/z* 133(MH+)).

The indane **84** was next bis-bromomethylated using the method of Mitchell et al[50] to obtain the dibromide **85** in 72% yield (CI MS *m/z* 317, 319, 321(MH+)). It was characterized by the singlet aromatic proton at δ 7.16 and the two bromomethyl groups at δ 4.53, 4.52 in its ^{1}H-NMR spectrum. The dibromide **85** was then converted to the dimercaptan **86** in 95% yield (CI MS *m/z* 225(MH+)) which in its ^{1}H-NMR spectrum showed two overlapping triplets at δ 1.59 and 1.65 for the SH protons.

Scheme 7

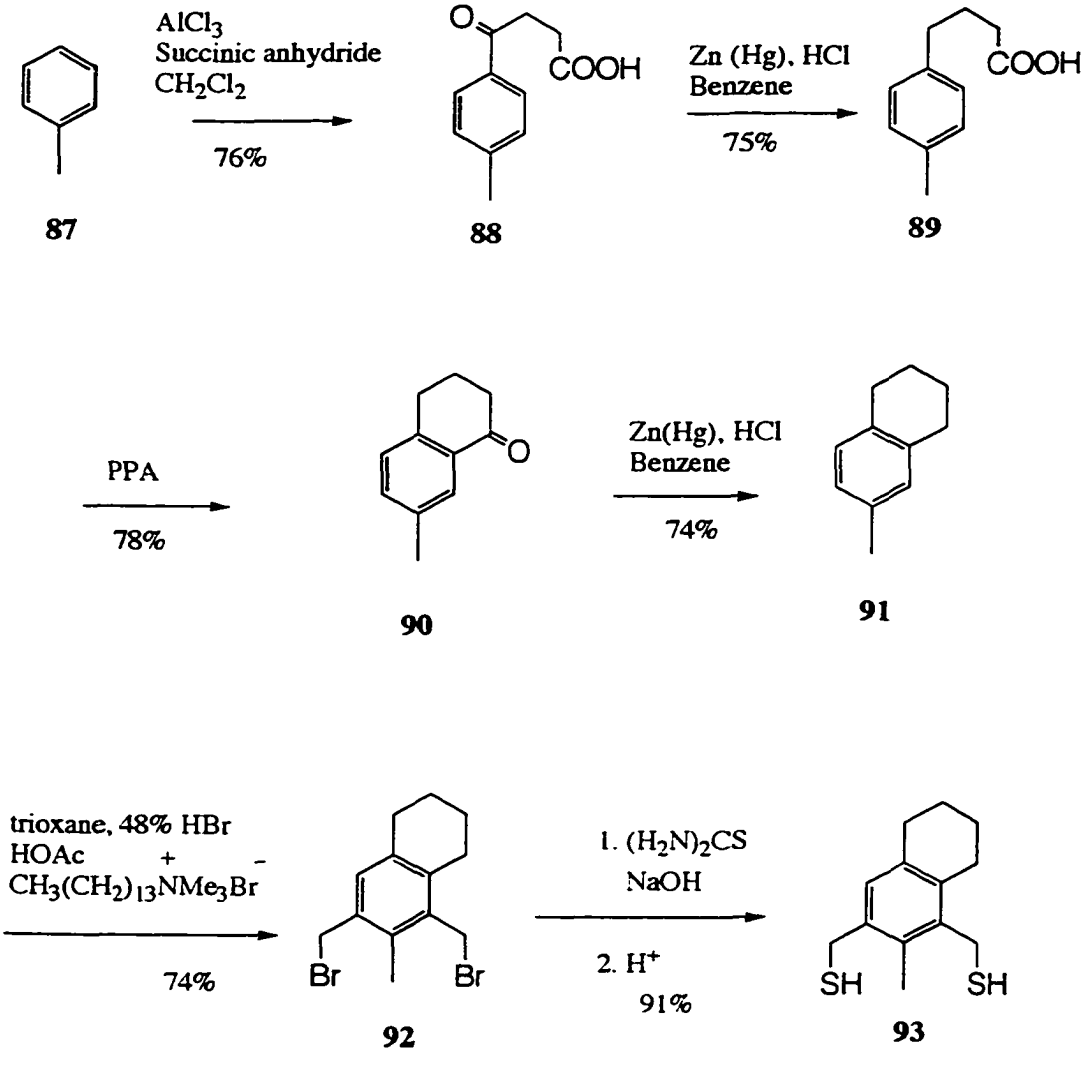

CHO
(EtO)2POCH2CO2Et
NaH
98%
CO2Et
H2, Pd/C
quantitative
CO2Et
79
80
81
1. NaOH aq
2. H+
94 %
CO2H
PPA
75%
O
Zn(Hg),
HCl
Benzene
82%
82
83
trioxane, 48% HBr
HOAc
CH3(CH2)13NMe3Br-
72%
Br
Br
1. (H2N)2CS
NaOH
2. H+
95%
SH
SH
84
85
86

2. Syntheses of the tetralin **91**, the dibromide **92** and the dimercaptan **93** (Scheme 8):

To synthesize **91**, the reaction sequence of Collins et al[46] was followed. Friedel-Crafts acylation of toluene with succinic anhydride using aluminum chloride as Lewis acid gave the keto-acid **88** in 76% yield (CI MS *m/z* 193(MH+)). The ketone group of **88** was then removed by Clemmensen reduction[49] to give the acid **89** in 75% yield (CI MS *m/z* 179(MH+)) which was then cyclized by PPA[48] to the tetralone **90** in 78% yield (CI MS *m/z* 161(MH+)). The ketone group of **90** was removed by Clemmensen reduction[49] again to afford the known tetralin **91** in 74% yield (CI MS *m/z* 147(MH+)).

The tetralin **91** was next bis-bromomethylated to the dibromide **92** in 74% yield (CI MS *m/z* 331, 333 and 335(MH+)). It was characterized by the singlet for the aromatic proton at δ 7.01 and the two bromomethyl groups appeared at δ 4.54 and 4.48 in its ^{1}H-NMR spectrum. The dibromide **92** was then converted to the dimercaptan **93** in 91% yield (CI MS *m/z* 239(MH+)) which was characterized by the two triplets (thiol protons) at δ 1.59 and 1.66 in its ^{1}H-NMR spectrum.

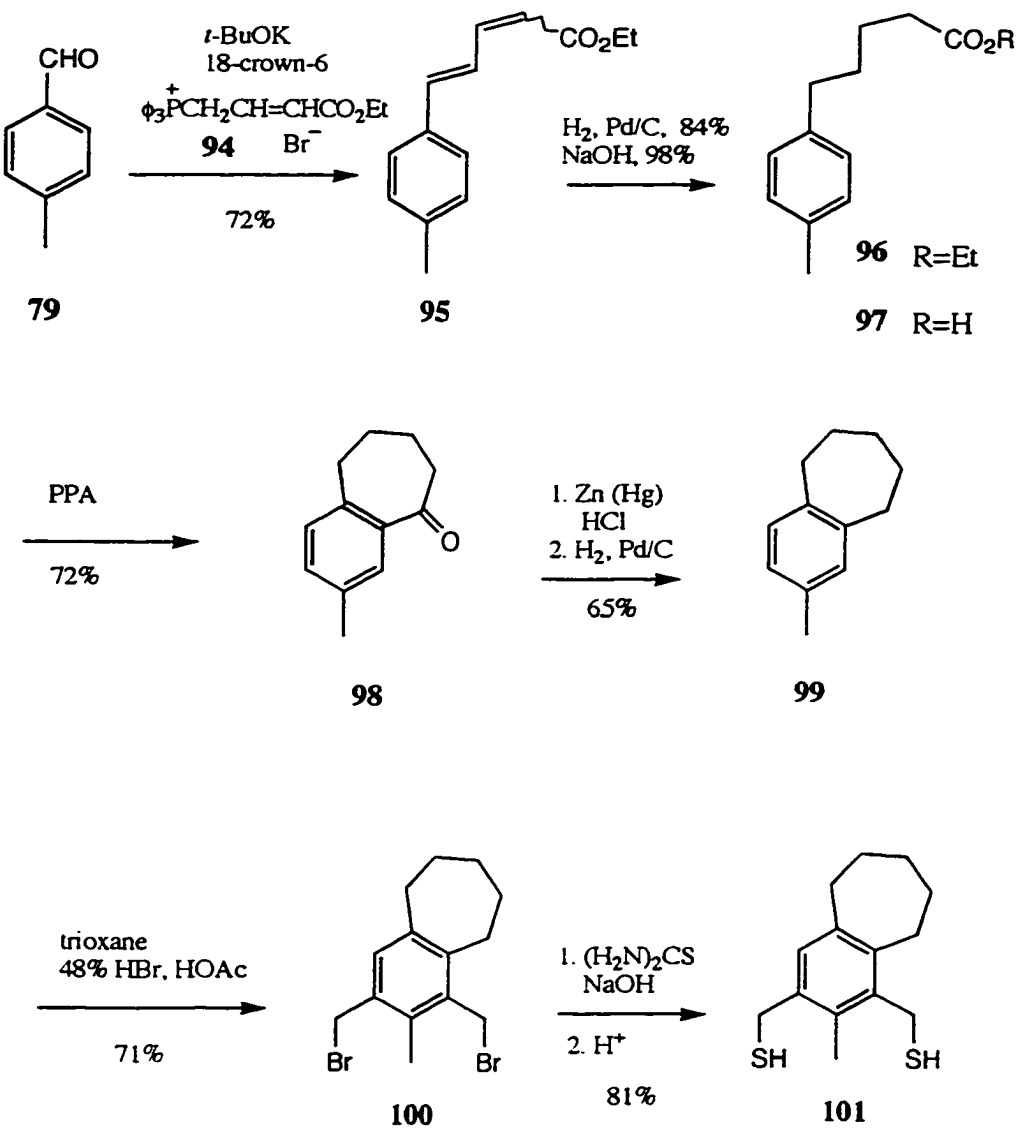
Scheme 8


AlCl3
Succinic anhydride
CH2Cl2
76%
COOH
Zn (Hg), HCl
Benzene
75%
COOH
87
88
89
PPA
78%
O
Zn(Hg), HCl
Benzene
74%
90
91
trioxane, 48% HBr
HOAc
CH3(CH2)13NMe3Br
74%
Br
Br
1. (H2N)2CS
NaOH
2. H+
91%
SH
SH
92
93

3. Syntheses of the cycloheptene annelated toluene **99**, the dibromide **100** and the dimercaptan **101** (Scheme 9):

To synthesize the cycloheptene annelated compounds for the coupling reaction, *p*-tolualdehyde was used as starting material. It was first condensed with the Wittig reagent **94**[51] to form the unsaturated ester **95** in 72% yield (CI MS *m/z* 217(MH+)), which was a mixture of E and Z isomers. The ester **95** was then hydrogenated with palladium on charcoal to give the saturated ester **96** in 84% yield (CI MS *m/z* 221(MH+)). Saponification of **96** gave the acid **97** in 98% yield (CI MS *m/z* 193(MH+)) which was then cyclized by PPA[48] to give the cycloheptenone annelated toluene **98** in 72% yield (CI MS *m/z* 175(MH+)). The carbonyl group of **98** absorbed strongly at 1679 cm^{-1} in its IR spectrum. Clemmensen reduction[49] of ketone **98** gave a mixture of **99** and the cycloheptadiene annelated toluene products, presumably generated from the hydride transfer reaction initiated by the zinc carbene. The mixture of products were subjected to a hydrogenation reaction to give **99** in 65 % yield (CI MS *m/z* 161(MH+)). The ^{1}H-NMR spectrum of **99** showed an AB and a singlet in the aromatic region which supported the assigned substitution pattern. Bis-bromomethylation of **99** gave the dibromide **100** in 71% yield (CI MS *m/z* 345, 347, 349 (MH+)). In its ^{1}H-NMR spectrum, the only aromatic proton appeared as a singlet at δ 7.04 and the two bromomethyl groups were observed at δ 4.46 and 4.48. Conversion of the dibromide **100** with thiourea followed by base hydrolysis gave the dimercaptan **101** in 81% yield (CI MS *m/z* 253(MH+)). The two triplets for the thiol protons appeared at δ 1.66 and 1.54 in its ^{1}H-NMR spectrum.

Scheme 9

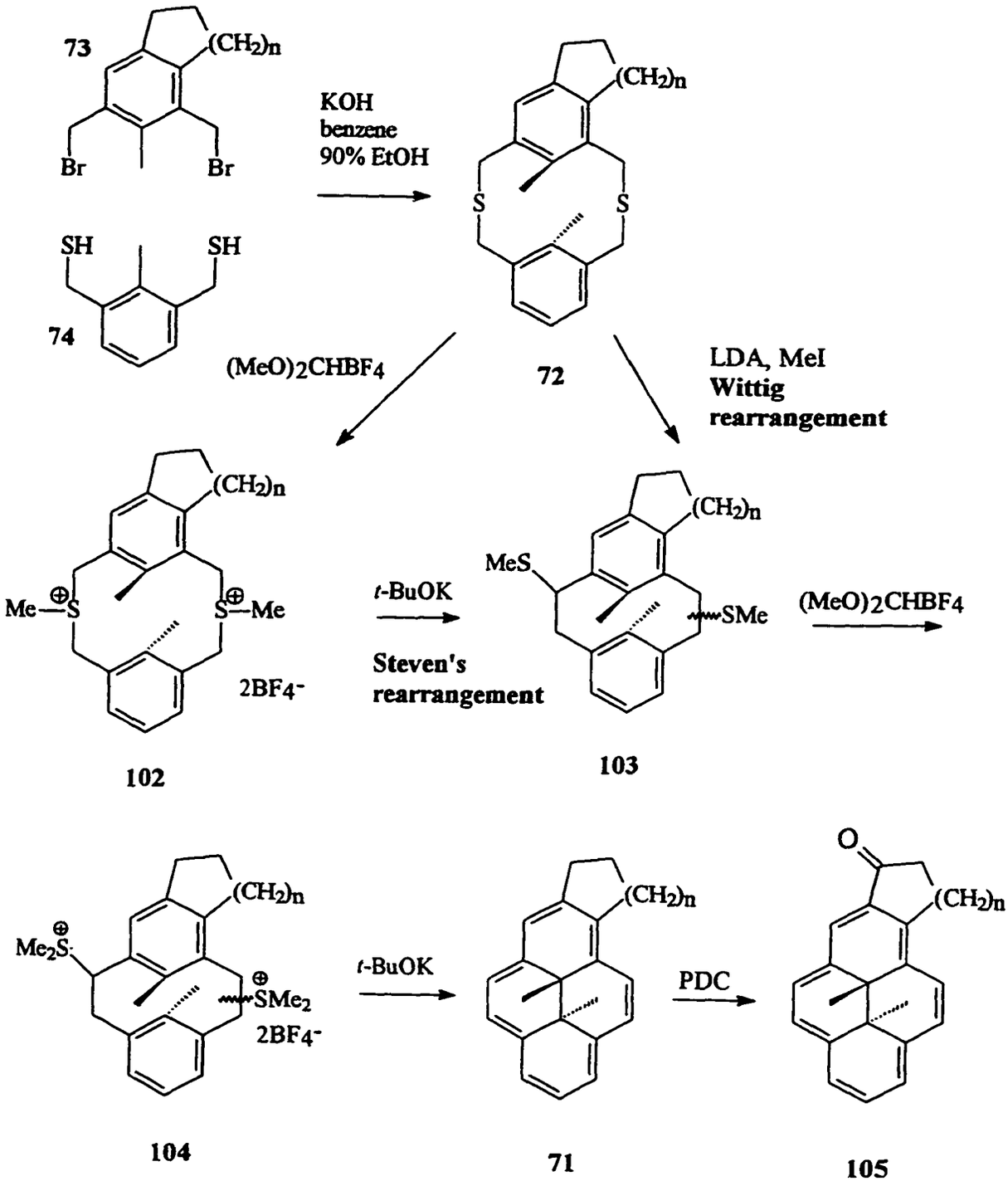

CHO
t-BuOK
18-crown-6
$\phi_3\overset{+}{P}CH_2CH{=}CHCO_2Et$
94 Br^-
72%
CO_2Et
H_2, Pd/C, 84%
NaOH, 98%
CO_2R
96 R=Et
97 R=H
79
95
PPA
72%
O
1. Zn (Hg)
HCl
2. H_2, Pd/C
65%
98
99
trioxane
48% HBr, HOAc
71%
Br
Br
1. $(H_2N)_2CS$
NaOH
2. H^+
81%
SH
SH
100
101

4. Synthetic route to cycloalkene and cycloalkenone annelated DHPs

To synthesize the cycloalkene annelated DHPs, either an unsymmetrical coupling of the dibromide **73** with the known dimercaptan **74** or a symmetical coupling of the dibromide **73** with the dimercaptan **78** was performed to give the mono- or dicycloalkene-annelated thiacyclophanes **72** and **77** (See Schemes 10 and 11). The standard reaction sequence developed by Mitchell and Boekeiheide[52] was followed to convert the thiacyclophanes to the DHPs **71** or **76**. The thiacyclophanes **72** or **77** were subjected to either Stevens or Wittig rearrangement to give the bis-thiomethyl ethers **103** and **107**. These were always obtained as a mixture of stereoisomers, and the Stevens products were always purer than the Wittig rearrangement products. During the synthesis of the parent DHP, it was found that the Wittig rearrangement converted all the *cis*-isomer to the *trans*-isomer whereas the Stevens rearrangement retained some of the *cis*-isomer. However, this was **NOT** the case in the rearrangement of our cycloalkene-annelated thiacyclophanes. We noticed that both the Wittig and Stevens rearrangement followed by Hofmann elimination gave a mixture of *cis*- and *trans*-DHPs and the Stevens rearrangement route always gave more *trans*-DHPs compared to the Wittig rearrangement route. Once the mono- or dicycloalkene-annelated DHPs were obtained, they were oxidized to cycloalkenone annelated DHPs **105** and **109** by PDC. (Scheme 10 and 11)

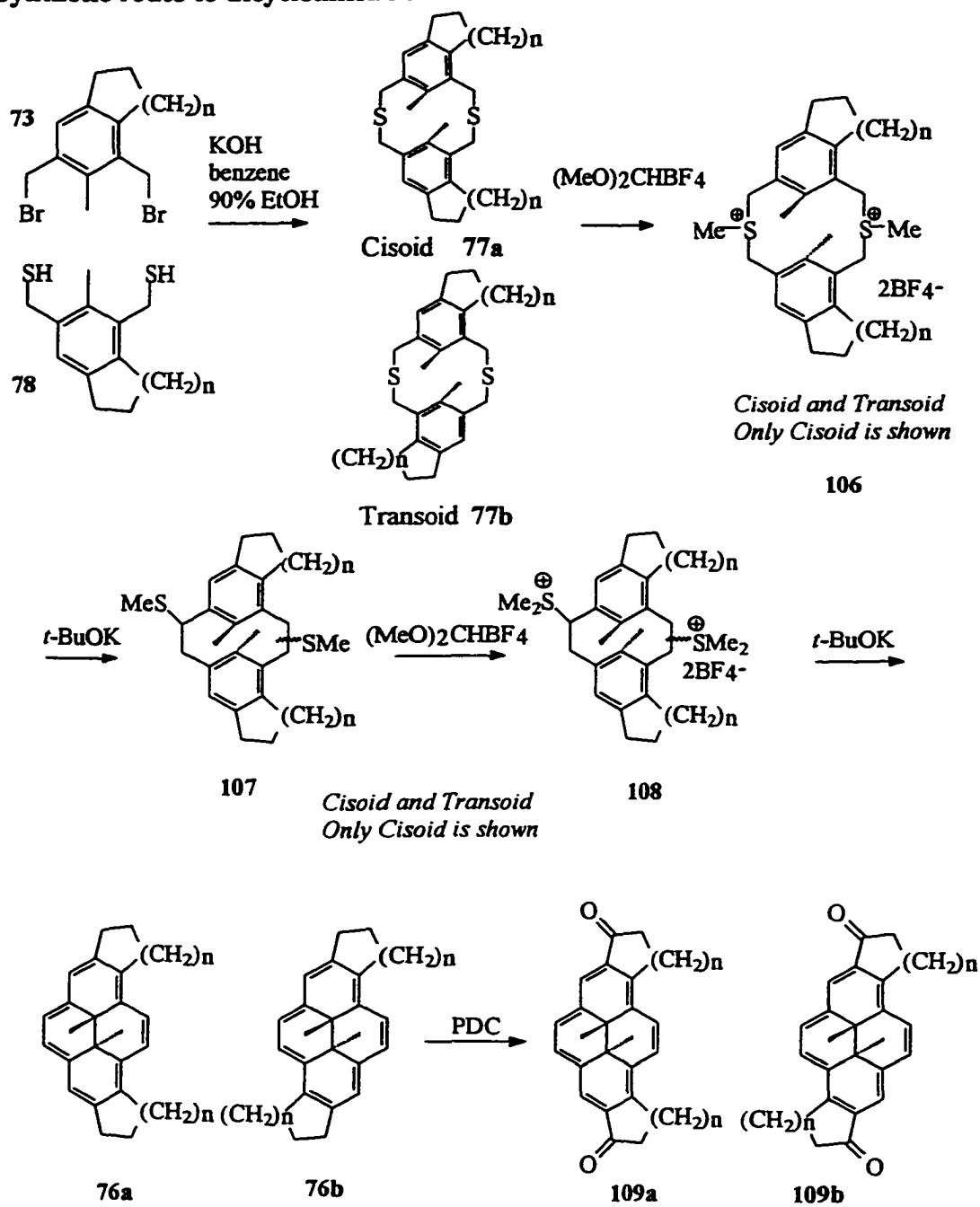
Scheme 10

Synthetic route to cycloalkene and cycloalkenone annelated DHPs



Scheme 11

Synthetic route to dicycloalkene annelated DHPs



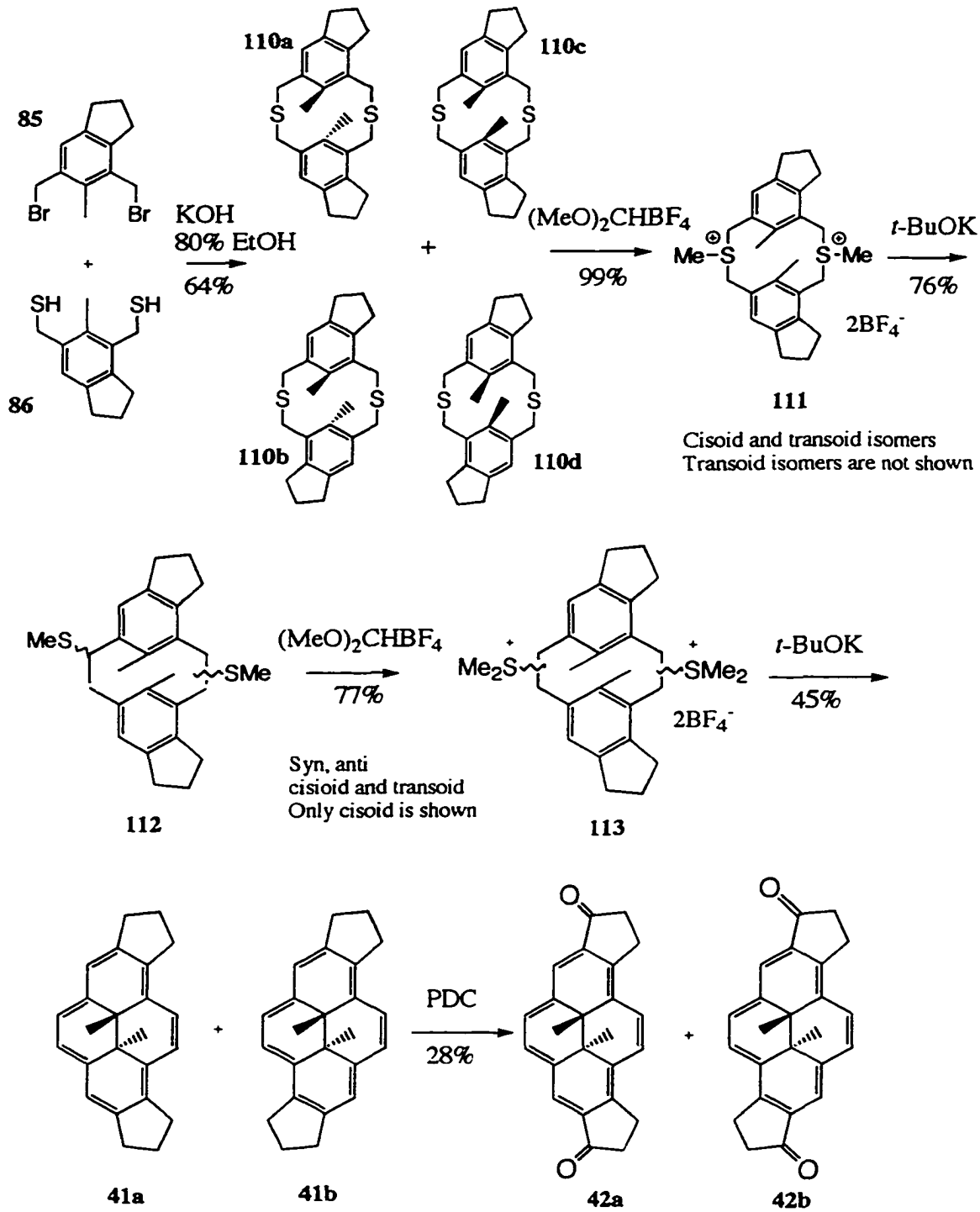
Experimentally, the early ring formation approach approach proved to be a versatile approach to synthesize a number of ring annelated DHP systems. The results are summarized in the following Schemes (Scheme 12 to Scheme 18):

Scheme 12:

Synthetic Scheme 12 describes the route to the dicyclopentene and the dicyclopentenone annelated DHPs **41** and **42**:

Coupling of the dibromide **85** with the dimercaptan **86** gave a mixture of the thiacyclophanes **110 a, b, c** and **d** which were a mixture of *syn-* and *anti-* isomers with the five-membered rings arranged *cisoid* or *transoid* with respect to each other. The yield for the coupling reaction was 64% (CI MS *m/z* 381(MH^+)) and the internal methyl protons for the four thiacyclophanes were observed in its ^{1}H-NMR spectrum at δ 1.24, 1.35 (*anti-* isomers) and 2.56, 2.53 (*syn*-isomers). Although the complete separation of the individual isomers proved to be difficult, one of the least soluble isomers, the *anti,transoid* **110b**, could be separated by repeated fractional crystallization of the thiacyclophane mixture from CH_2Cl_2-PE. In its ^{1}H-NMR spectrum, the aromatic proton and its internal methyl protons appeared as singlets at δ 7.34 and 1.24 respectively. The mixture of thiacyclophanes **110** was then methylated to give the salt **111** in 99% yield which was characterized by the broad strong IR absorption at 1056 cm^{-1}. Steven's rearrangement of **111** gave the foul smelling bis-thiomethyl ether **112** with a CI MS *m/z* 313(MH^+) which also showed elimination of two MeSH groups to form the DHP **41** (M-MeSH+1= 361, M-2xMeSH+1 = 313). The bis-thiomethyl ether **112** was re-methylated to afford the brown salt **113** in 77% yield which was characterized by the strong IR absorption at 1053 cm^{-1}. A Hofmann

Scheme 12

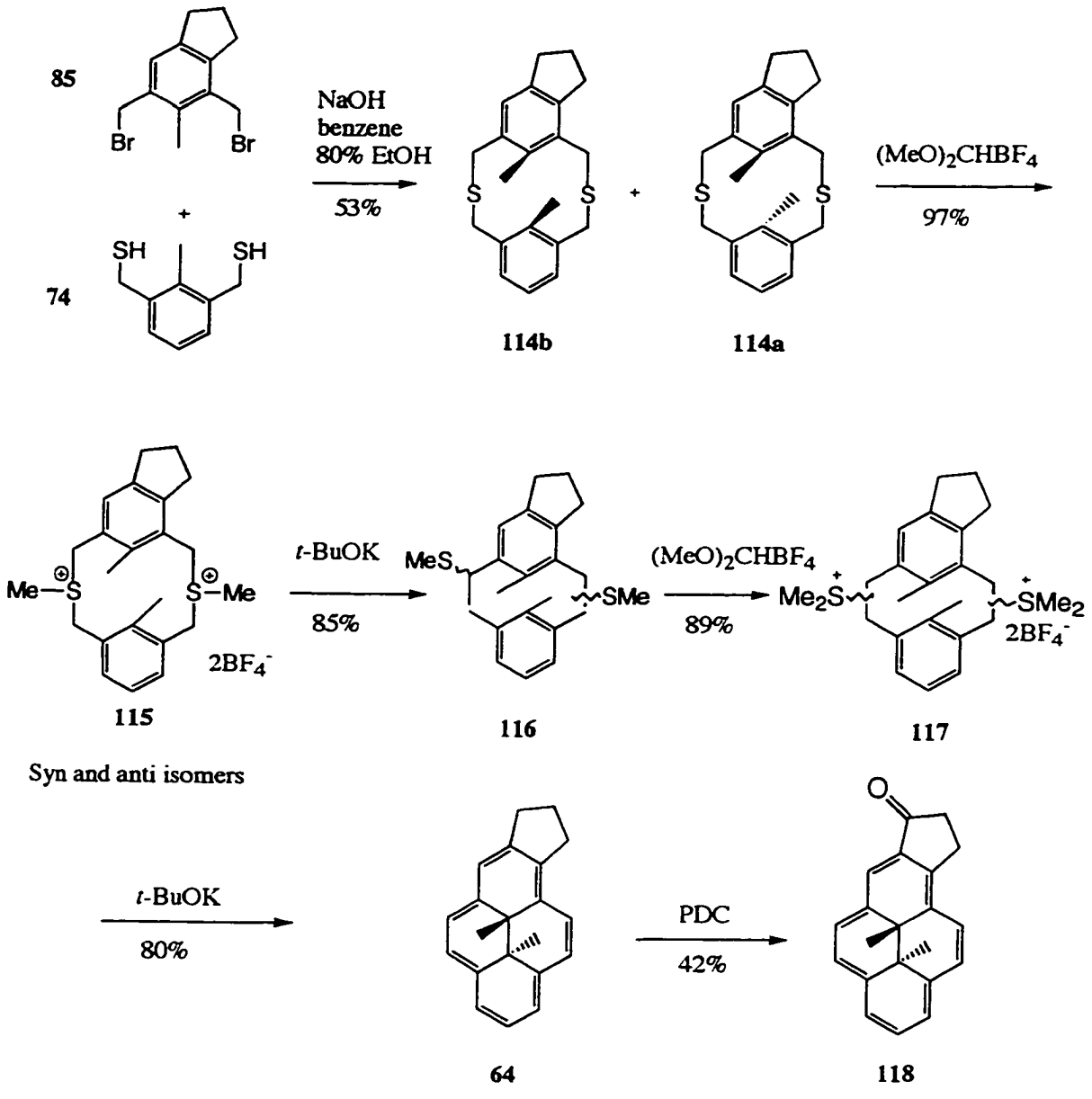

85
Br
Br
+
SH
SH
86
KOH
80% EtOH
64%
110a
110b
110c
110d
+
(MeO)2CHBF4
99%
Me-S
S-Me
2BF4-
t-BuOK
76%
111
Cisoid and transoid isomers
Transoid isomers are not shown
MeS
SMe
112
(MeO)2CHBF4
77%
Syn, anti
cisioid and transoid
Only cisoid is shown
Me2S
SMe2
2BF4-
113
t-BuOK
45%
41a
41b
PDC
28%
42a
42b

elimination on the salt **113** gave the green DHPs **41** in 45% yield (CI MS *m/z* 313(MH+)) which were mixed with about 4% of the syn isomers. The internal methyl protons of the *trans, transoid* isomer **41b** and the *trans, cisoid* isomer **41a** appeared at δ -4.15 and -4.12 respectively in their ^{1}H-NMR spectrum. Five fractional crystallizations of the DHP mixture **41** from MeOH-PE gave 93% pure *trans,transoid* DHP **41b**. The mixture of DHPs **41** was then oxidized by PDC regioselectively at the 2 and 7 positions to give a mixture of *trans, cisoid* and *trans, transoid* diketones **42a** and **42b** in 28% yield (CI MS *m/z* 341(MH+)). The internal methyl protons of **42a** and **42b** appeared at δ -2.91 and-3.83 respectively in the ^{1}H-NMR spectrum of the mixture. A combination of fractional crystallization and column chromatography gave enriched samples of **42a** (red in color, IR (C=O): 1697cm^{-1}) and **42b** (purple in color, IR (C=O): 1684 cm^{-1}).

Scheme 13:

Synthetic Scheme 13 describes the route to the cyclopentene and cyclopentenone annelated DHPs **64** and **118**. Coupling of the dibromide **85** with the known dimercaptan **74** gave a mixture of *syn*- and *anti*-thiacyclophanes **114b** and **114a** (CI MS *m/z* 341(MH+)). The ratio of the *anti* : *syn* isomers based on the internal methyl protons (δ 1.31, 1.19 for *anti* isomers **110a**; δ 2.52, 2.49 for *syn* isomer **110b**) was determined by ^{1}H-NMR to be 3:1. Fractional crystallization of the thiacyclophane mixture **114** twice from CH_2Cl_2-PE (1:3) gave the *anti*-isomer **114a**. The mixture of thiacyclophanes **114** was methylated by Borsch reagent[53] to give the salt **115** in 97% yield. Steven's rearrangement of **115** gave the thiomethyl ether **116** in 85%

Scheme 13


85
Br
Br
+
74
SH
SH
NaOH
benzene
80% EtOH
53%
114b
114a
(MeO)2CHBF4
97%
Me
S
S
Me
2BF4-
115
t-BuOK
85%
MeS
SMe
116
(MeO)2CHBF4
89%
Me2S
SMe2
2BF4-
117
Syn and anti isomers
t-BuOK
80%
64
PDC
42%
O
118

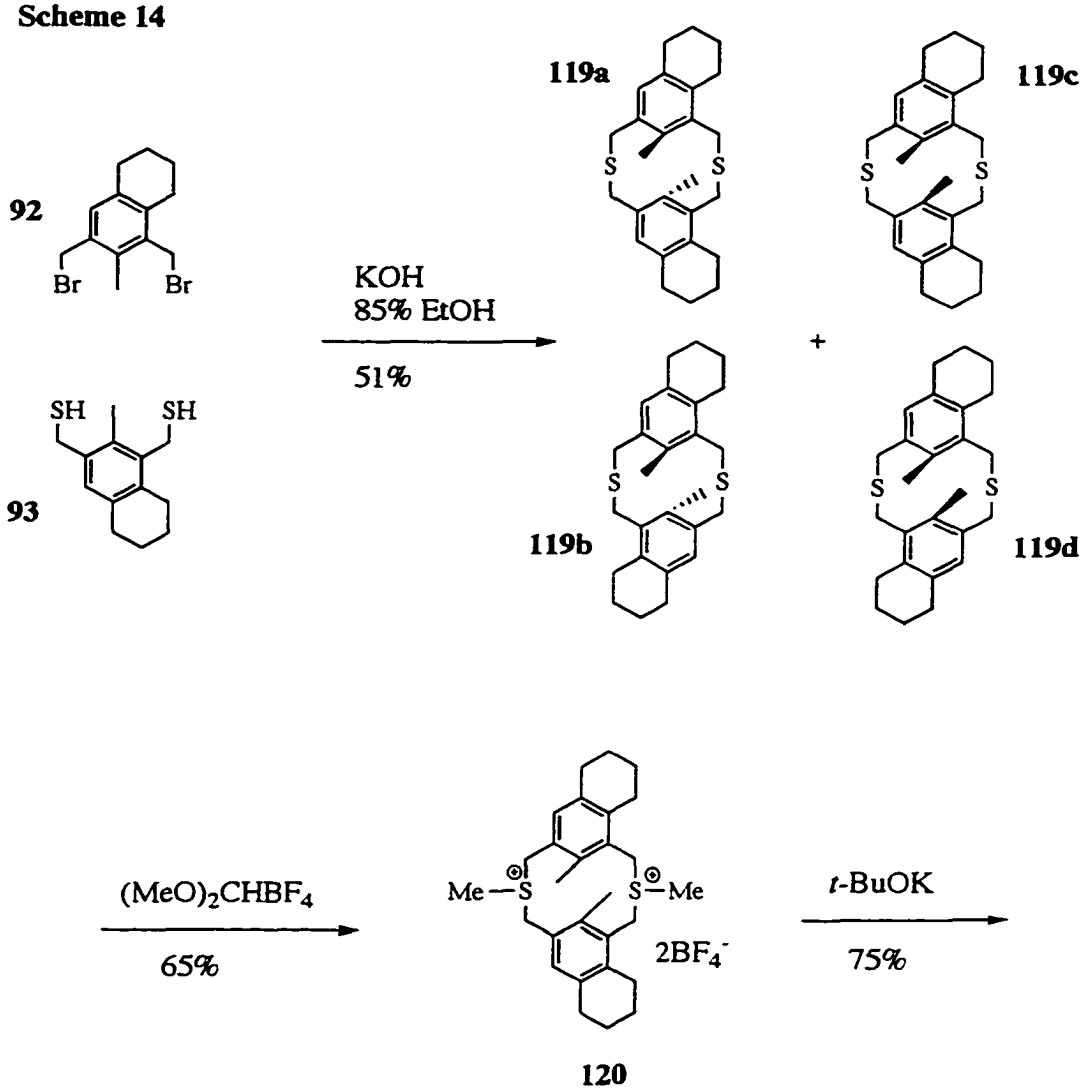
yield which showed successive fragmentation of the MeSH group (CI MS *m/z* 369(MH^+), M-MeSH+1 = 321; M-2xMeSH+1 = 273). The bis-thiomethyl ether **116** was then re-methylated to give a brown salt **117** in 89% yield which was followed by Hofmann elimination to give the green *trans*-DHP **64** in 80% yield, characterized by its internal methyl protons at δ -4.20 and -4.22 in its ^{1}H-NMR spectrum. The DHP **64** was then oxidized by PDC to the red cyclopentenone-fused DHP **118** in 42% yield (CI MS *m/z* 287(MH^+)). The internal methyl protons of **118** absorbed at δ -3.69 and -3.70 in its ^{1}H-NMR spectrum and in the IR spectrum, the C=O group of **118** absorbed at 1680 cm^{-1}.

Scheme 14:

Synthetic Scheme 14 describes the synthesis of dicyclohexene and the dicyclohexenone annelated DHPs **123** and **124**:

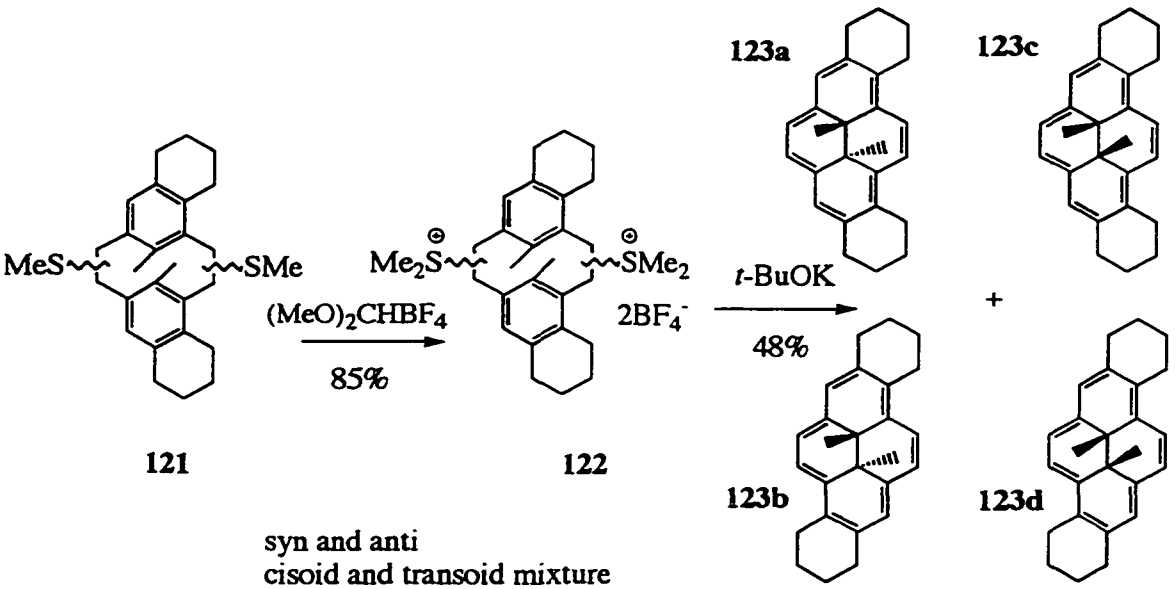
The dibromide **92** and dimercaptan **93** were coupled to give a mixture of four thiacyclophanes **119 a**, **b**, **c** and **d** in 51% yield (CI MS *m/z* 409(MH^+)). The ratio of syn : anti thiacyclophanes was determined by ^{1}H-NMR to be 1:5. The less soluble *anti,transoid* isomer **119b** was separated by fractional crystallization of the thiacyclophane mixtures from CH_2Cl_2-PE (1:3). In its ^{1}H-NMR spectrum, the aromatic proton and the internal methyl protons of **119b** appeared as singlets at δ 7.24 and 1.33 respectively. The thiacyclophane mixture **119** was then methylated by Borsch reagent[53] to give the salt **120** in 65% yield, which was characterized by the strong and broad IR absorption at 1057 cm^{-1}. Steven's rearrangement of **120** gave the foul smelling bis-thiomethyl ether **121** in 75% yield. CI MS *m/z* of **121** showed MH^+ = 437, M-MeSH+1 = 389 and M-2xMeSH+1 =

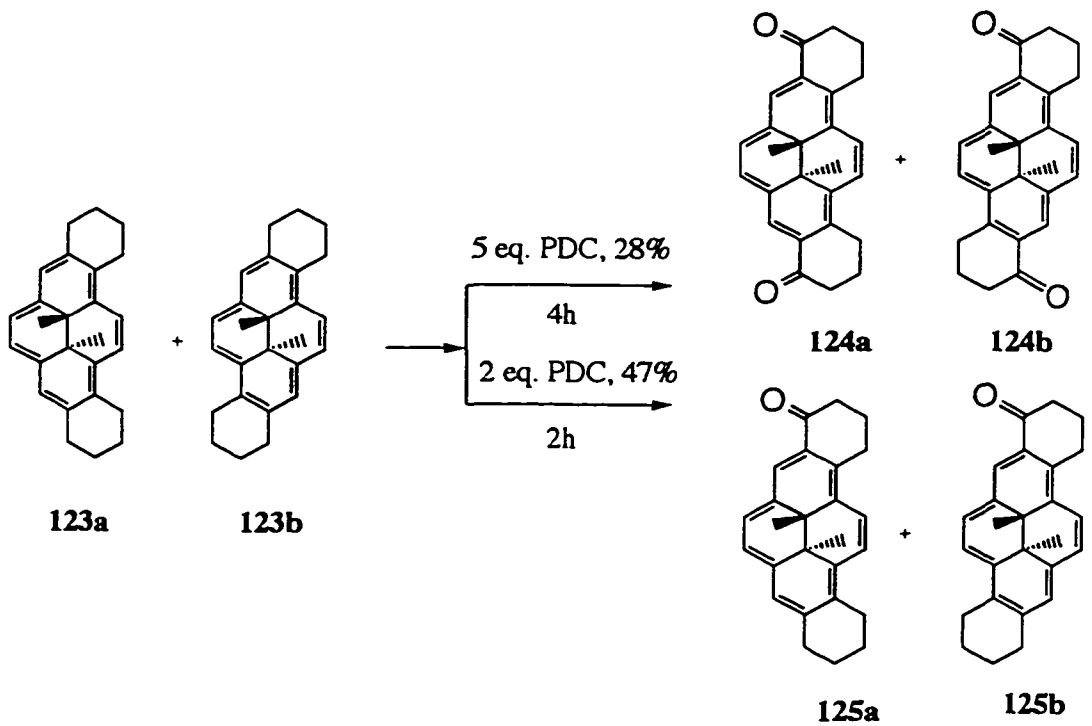
Scheme 14



Syn and anti, cisoid and transoid isomers
Only cisoid isomers are shown

Scheme 14


MeS
SMe
$(MeO)_2CHBF_4$
85%
$Me_2S^{\oplus}$
$^{\oplus}SMe_2$
$2BF_4^-$
t-BuOK
48%
123a
123c
123b
123d
121
122
syn and anti
cisoid and transoid mixture
Only cisoid is shown


5 eq. PDC, 28%
4h
2 eq. PDC, 47%
2h
123a
123b
124a
124b
125a
125b

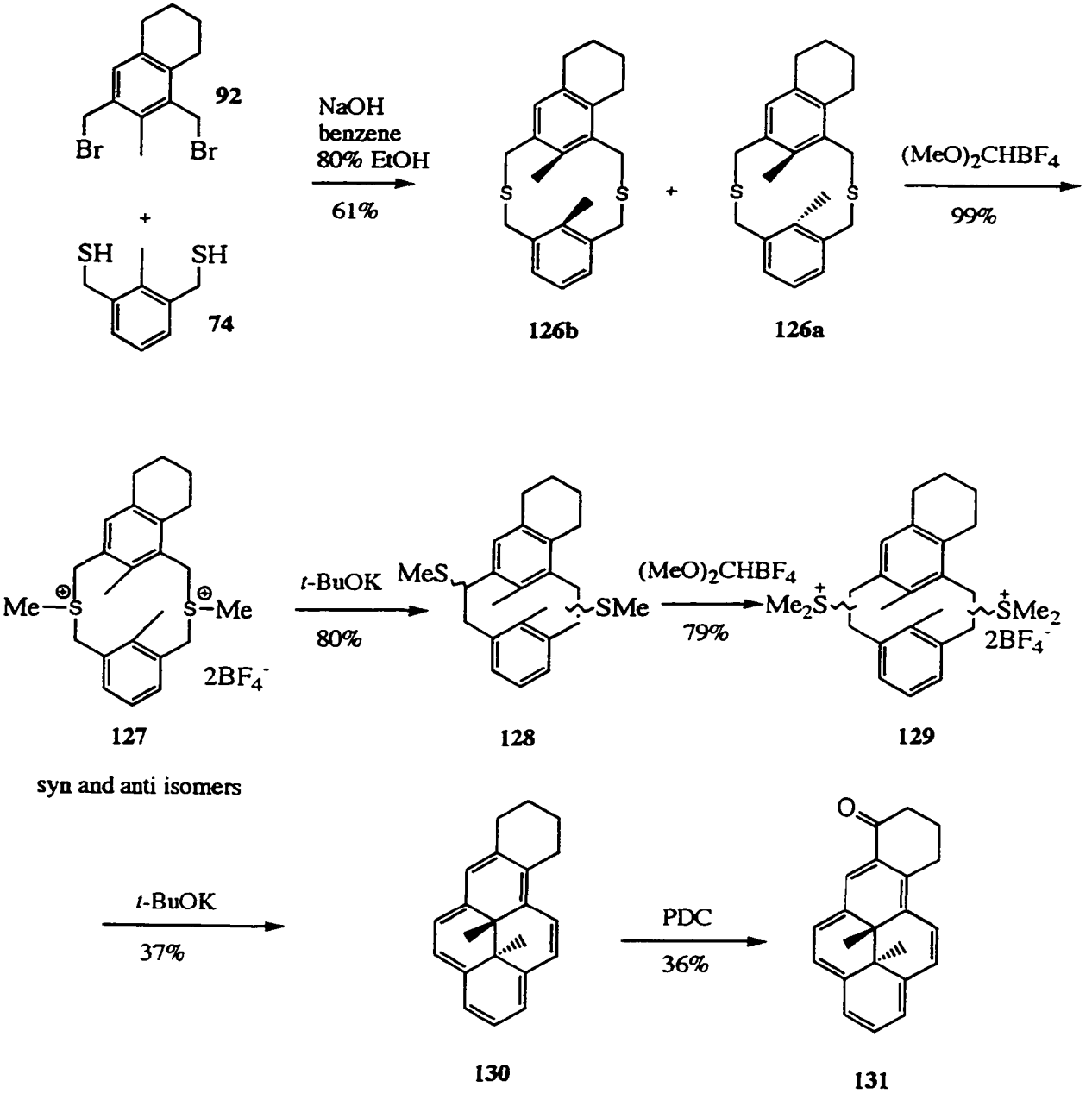
341. The thiomethyl ether **121** was then re-methylated to give the salt **122** in 85% yield which was characterized by the broad IR absorption at 1061 cm^{-1}. A Hofmann elimination of the bis-salt **122** afforded the green mixture of *cis*- and *trans* -dicyclohexene annelated DHPs **123 a**, **b**, **c** and **d** in 48% yield (CI MS *m/z* 341(MH^+)) with internal methyl protons at δ -3.40, -3.98, -1.60 and -1.93 respectively in its ^{1}H-NMR spectrum. PDC oxidation[44] of **123** gave the regioselective oxidation products **124** and **125** depending on the amount of PDC and the reaction time. With only 2 equivalents of PDC and a shorter reaction time (2h), the mono-ketone mixture **125a** and **125b** were obtained in 47% yield (CI MS *m/z* 355(MH^+)). The internal methyl protons of **125a** and **125b** appeared at δ -3.25, -3.27 and -3.81, -3.82, respectively. The carbonyl group of **125** absorbed at 1654 cm^{-1} in its IR spectrum. With 5 equivalents of PDC and a longer reaction time (4h), the diketone mixture **124a** and **124b** was obtained in 28% yield (CI MS *m/z* 369(MH^+)). The internal methyl protons of **124a** and **124b** appeared at δ -3.05 and -3.67 while their carbonyl group appeared at 1666cm^{-1} in the IR spectrum. During the oxidation of **123** to **124** and **125**, the *cis* DHPs **123c** and **123d** decomposed.

Scheme 15:

Synthetic Scheme 15 describes the synthesis of cyclohexene and cyclohexenone annelated DHPs **130** and **131**:

Coupling of the dibromide **92** with the known dimercaptan **74** gave a mixture of *syn* - and *anti*-thiacyclophanes **126b** and **126a** (CI MS *m/z* 355(MH^+)). The ratio of the *anti* : *syn* isomers based on internal methyl protons (δ 1.20, 1.38 for *anti*-

Scheme 15

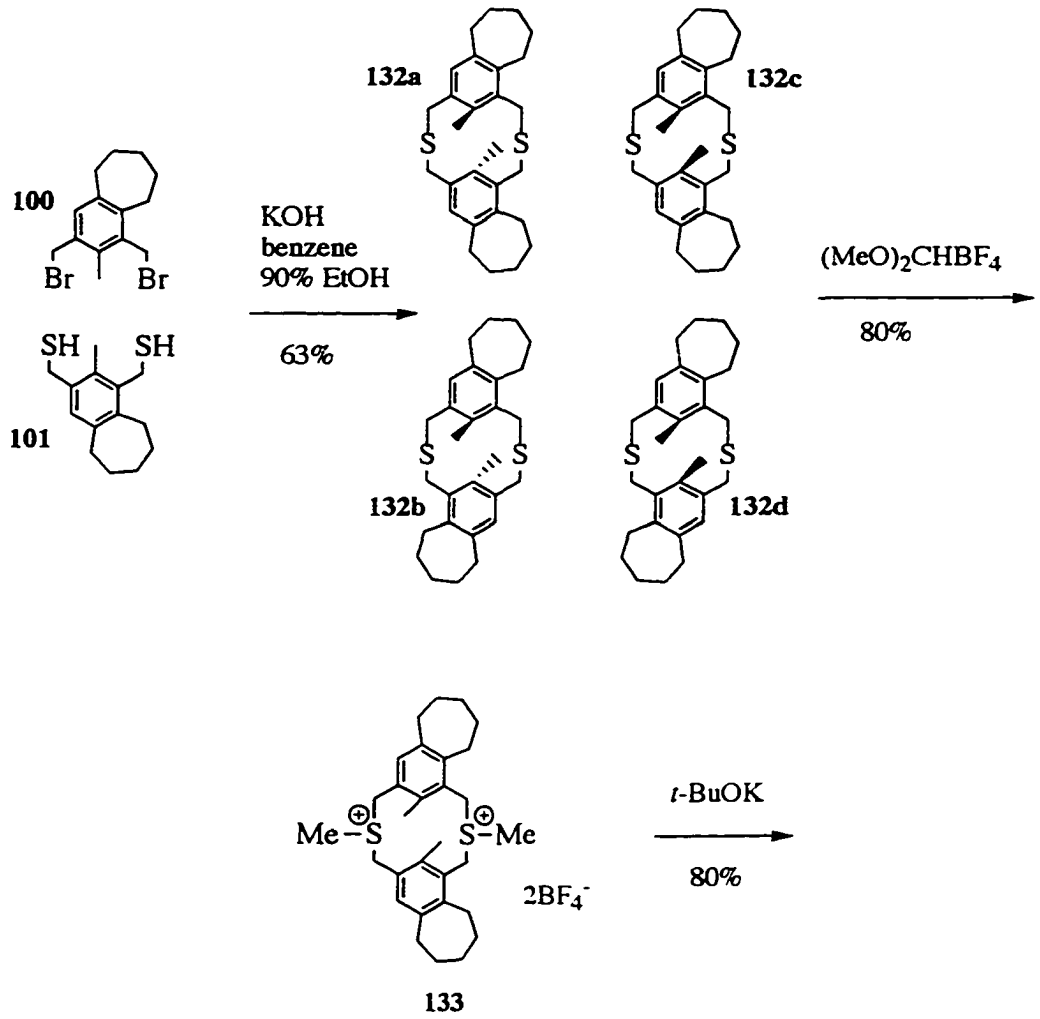

92
Br
Br
+
SH
SH
74
NaOH
benzene
80% EtOH
61%
126b
126a
(MeO)2CHBF4
99%
Me
S
S
Me
2BF4-
127
syn and anti isomers
t-BuOK
80%
MeS
SMe
128
(MeO)2CHBF4
79%
Me2S
SMe2
2BF4-
129
t-BuOK
37%
130
PDC
36%
O
131

isomers **126a**; δ 2.47, 2.52 for *syn*-isomer **126b**) was determined by ^{1}H-NMR to be 5:1. Fractional crystallization twice from CH_2Cl_2-PE (1:3) gave the *anti*-isomer **126a**. The mixture of thiacyclophanes **126** was methylated by Borsch reagent[53] to give the salt **127** in 99% yield. Steven's rearrangement of **127** gave the bis-thiomethyl ether **128** in 80% yield (CI MS *m/z* 383(MH+), M-MeSH+1 = 335; M-2xMeSH+1 = 287). The bis-thiomethyl ether **128** was then re-methylated to give a brown salt **129** in 79% yield which was followed by Hofmann elimination to give the green *trans*-DHP **130** in 37% yield, characterized by its internal methyl protons at δ -3.95 and -3.99 in its ^{1}H-NMR spectrum. The DHP **130** was then oxidized by PDC to the red cyclohexenone-fused DHP **131** in 36% yield (CI MS *m/z* 301 (MH+)). The internal methyl protons of **131** appeared at δ -3.75 and the C=O of **131** appeared at 1645 cm^{-1} in its IR spectrum.

Scheme 16:

Synthetic Scheme 16 describes the synthesis of dicycloheptene-annelated DHP **136**. High dilution coupling of **100** and **101** gave a mixture of *syn* - and *anti*-thiacyclophanes **132** in 63% yield (CI MS *m/z* 437(MH+)). The less soluble *anti, transoid* isomer **132b** was separated by fractional crystallization of the thiacyclophane mixture from CH_2Cl_2-PE. In its ^{1}H-NMR spectrum, the aromatic proton and its internal methyl protons appeared as singlets at δ 7.16 and 1.29 respectively. The thiacyclophane mixture **132** was then methylated by Borsch reagent[53] to give the salt **133** in 80% yield which was characterized by the strong and broad IR absorption at 1057 cm^{-1}. Steven's rearrangement of **133** gave the bis-thiomethylether **134** in 80% yield. CI MS *m/z* of **134** showed

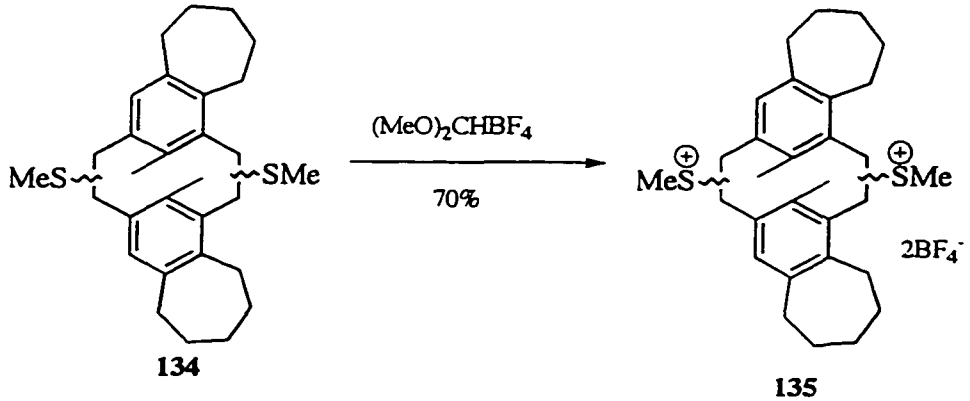
Scheme 16



133

syn and anti; cisoid and transoid isomers.
Only the cisoid isomers are shown

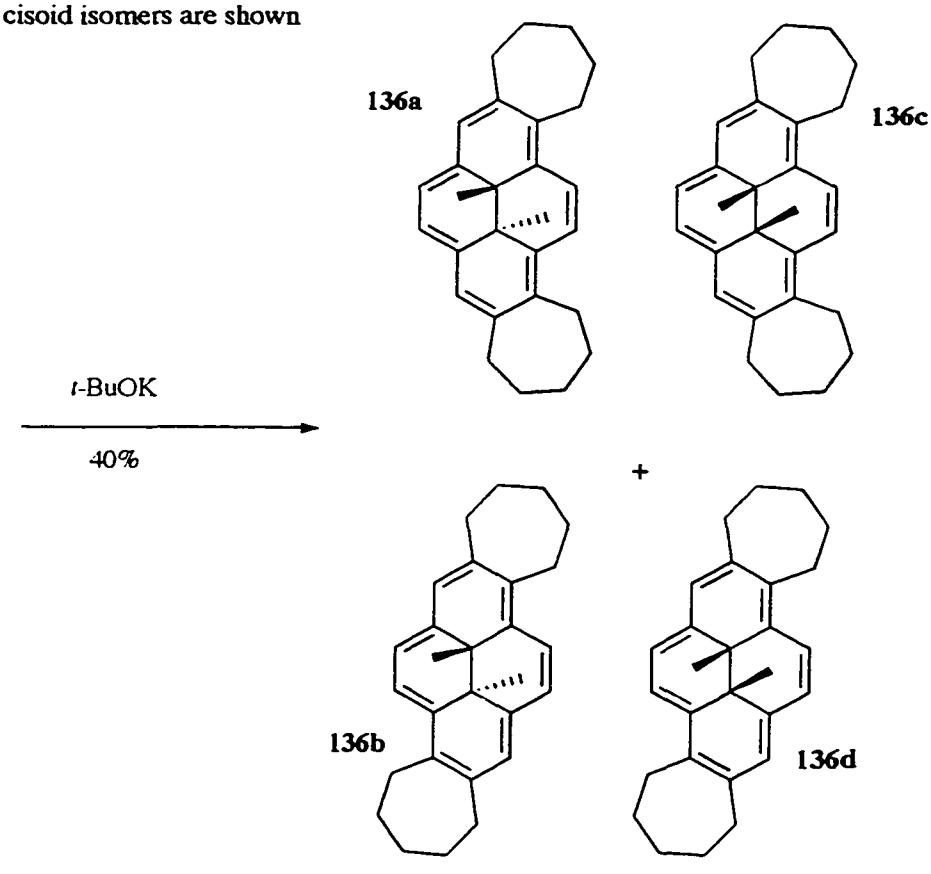
Scheme 16



134 **135**

syn and anti; cisoid and transoid isomers

Only cisoid isomers are shown



MH+ = 465, M-MeSH+1 = 417 and M-2xMeSH+1 = 369. The thiomethyl ether **134** was then re-methylated to give the salt **135** in 70% yield which was characterized by the broad IR absorption at 1057 cm-1. A Hofmann elimination of the bis-salt **135** then afforded the green mixture of *cis*- and *trans*-dicycloheptene annelated DHPs **136 a, b, c** and **d** in 40% yield (CI MS *m/z* 369(MH+)), the internal methyl protons of which appeared at δ -4.13, -4.15, -2.02 and -2.03 respectively in its ^{1}H-NMR spectrum. Attempts to oxidize **136** by PDC did not yield any products which could be identified.

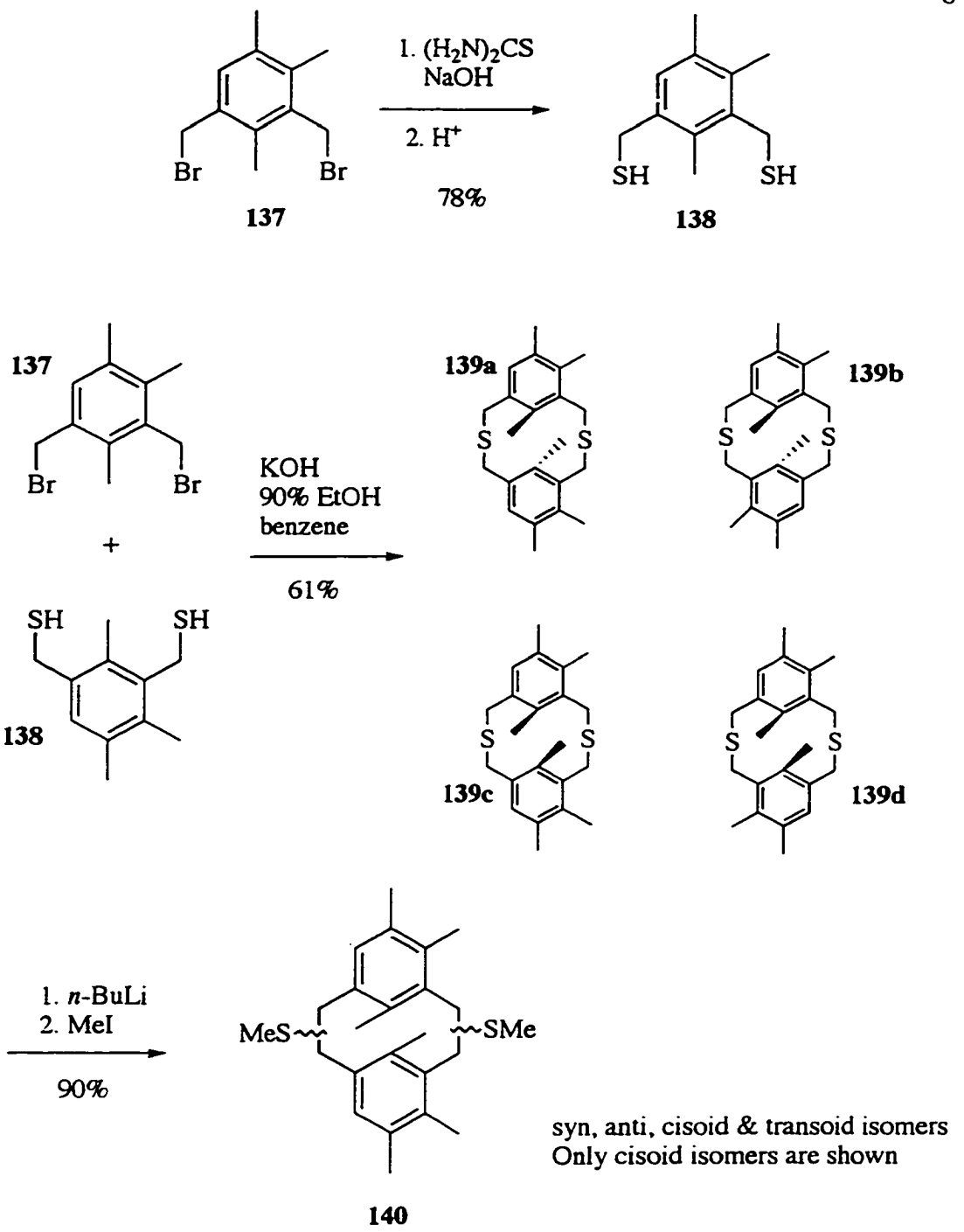
2.3e Synthetic route to acyclic tetra-substituted DHPs

Scheme 17:

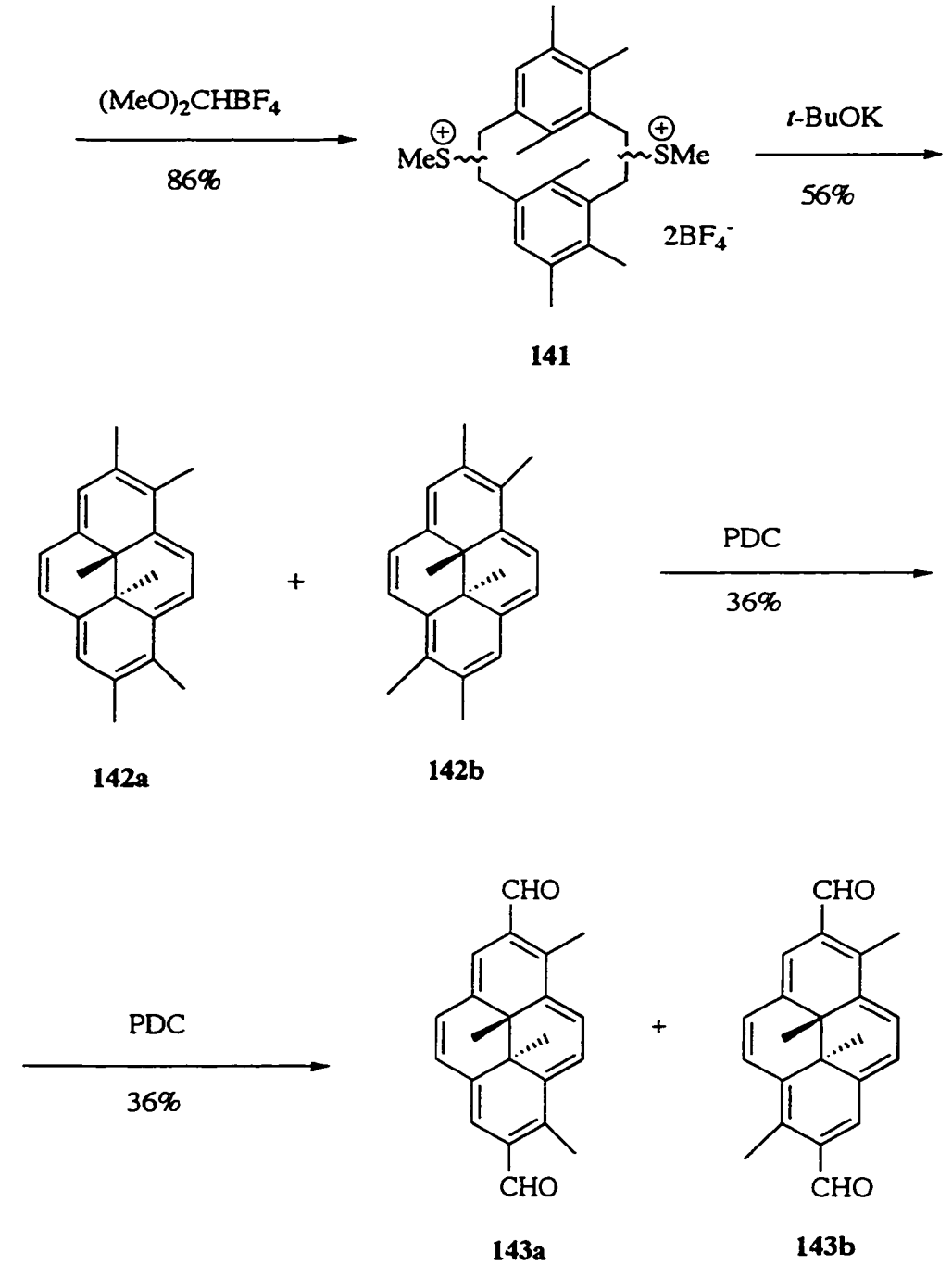
To study the steric compression in a non-annelated system for comparison with the annelated DHP system, the hexamethyldihydropyrene **142** and diformyl DHP **143** were synthesized. The syntheses were described in Scheme 17:

The known dibromide **137**[50] was first converted to the dimercaptan **138** in 78% yield (CI MS *m/z* 213(MH+)). The two thiol protons of **138** appeared as two triplets at δ 1.65 and 1.57 in its ^{1}H-NMR spectrum. The dimercaptan **138** was then coupled with the dibromide **137** to give a mixture of four thiacyclophanes **139a, b, c** and **d** in 61% yield (CI MS *m/z* 357(MH+)). The less soluble *anti, transoid* and *anti,cisoid* isomers **139a** and **139b** could be separated by frational crystallization of the mixture from CH_2Cl_2-hexane (1:2) and their internal methyl protons appeared at δ 1.27 and 1.18 in its ^{1}H-NMR spectrum. Wittig rearrangement of the thiacyclophane mixture **139** gave the

Scheme 17


1. $(H_2N)_2CS$
NaOH
2. H^+
78%
Br
Br
137
SH
SH
138
KOH
90% EtOH
benzene
61%
139a
139b
139c
139d
1. *n*-BuLi
2. MeI
90%
MeS
SMe
140
syn, anti, cisoid & transoid isomers
Only cisoid isomers are shown

Scheme 17


(MeO)2CHBF4
86%
MeS
SMe
2BF4-
t-BuOK
56%
141
142a
142b
PDC
36%
PDC
36%
CHO
CHO
CHO
CHO
143a
143b

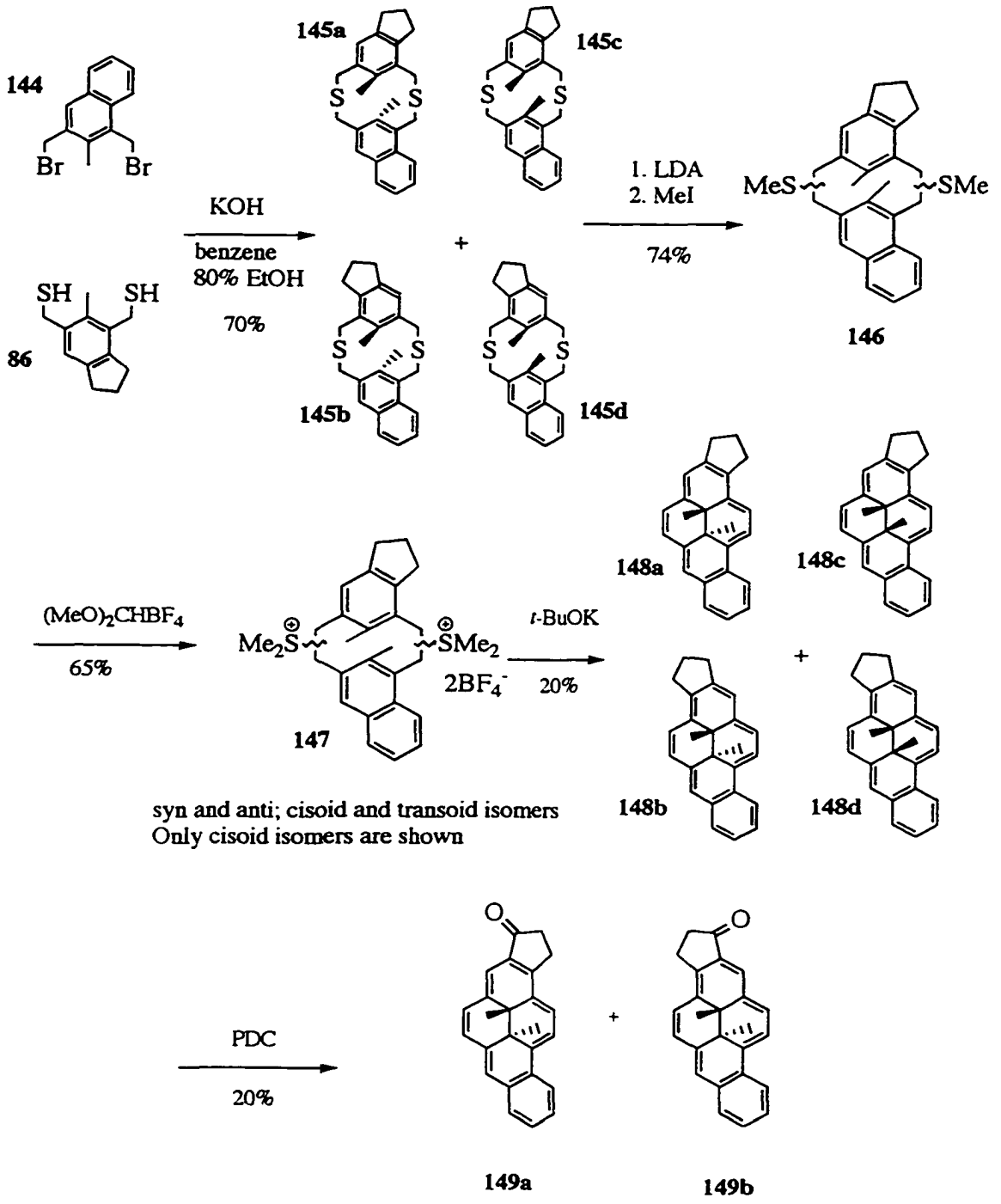
bis-thiomethyl ether **140** in 90% yield. CI MS of **140** showed MH+ *m/z* at 385, M-MeSH+1 at 337 and M-2xMeSH+1 at 289. Re-methylation of **140** gave the bis-salt **141** in 86% yield which has a characteristic broad absorption at 1067 cm^{-1} in its IR spectrum. A Hofmann elimination of **141** gave the DHP mixture **142a** and **142b** in 56% yield (CI MS *m/z* 289(MH+)). The internal methyl protons of **142a** and **142b** appeared at δ -4.03 and -4.06 respectively in its ^{1}H-NMR spectrum. The DHP mixture **142** was then subjected to PDC oxidation[44] to give the corresponding 2,7-bis-oxidation products **143a** and **143b** in 36% yield (CI MS *m/z* 317(MH+)). The internal methyl protons of **143a** and **143b** appeared at δ -3.29 and -3.49 in the ^{1}H-NMR spectrum. The ^{13}C-NMR of the carbonyl groups in **143a** and **143b** appeared at δ 193.5 and 193.0 and their carbonyl stretch appeared at 1663, 1638 and 1616 cm^{-1} in its IR spectrum.

Synthetic route to unsymmetrical ring fused DHPs

Scheme 18:

In the above Schemes 12, 14 and 16, we have symmetrically fused five, six and seven membered rings on to DHP. We were interested to see the effect of unsymmetrical fusion of a benzene and a five membered ring on to DHP. The synthesis is described in Scheme 18. Coupling of the known dibromide **144**[36] with the dimercaptan **86** gave the thiacyclophanes **145** in 70% yield (CI MS *m/z* 391(MH+)). Both the *anti*- and *syn*-isomers had very low solubility and they could not be separated from each other by either column chromatography or fractional crystallization. Wittig rearrangement of **145** by LDA gave the bis-thiomethyl ether **146** in 74% yield (EI MS *m/z* 418(MH+)) which was a complicated mixture of isomers. Other than the M^+ observed at 418, the fragments M-MeSH = 370 and M-2xMeSH = 322 were also observed in MS (EI). This was not a clean rearrangement and some side products were observed. This was judged by the fact that there were some other peaks at 561, 410, 386, 368 in the MS which could not be the fragments of **146**. Due to the similarity in polarity, the unwanted side products could not be removed and the impure mixture of **146** was methylated to give the salt **147** in 65% yield. The presence of the bis-salt **147** was confirmed by the broad IR absorption at 1042 cm^{-1}. A Hofmann elimination on **147** gave the deep orange red DHP **148** in 20% yield (CI MS *m/z* 323(MH+)) which is a mixture of four isomers. The internal methyl protons of **148a**, **b**, **c** and **d** appeared at δ -1.73, -1.74; -1.61; -0.38, -0.46 and -0.26, -0.36 in its ^{1}H-NMR spectrum. The mixture of DHP isomers **148** were then oxidized by PDC to give the mono-ketone mixture **149a** and **149b** in 20% yield (CI MS *m/z* 337MH+)). During the oxidation, the *cis*-DHP isomers **148c** and **148d** decomposed.

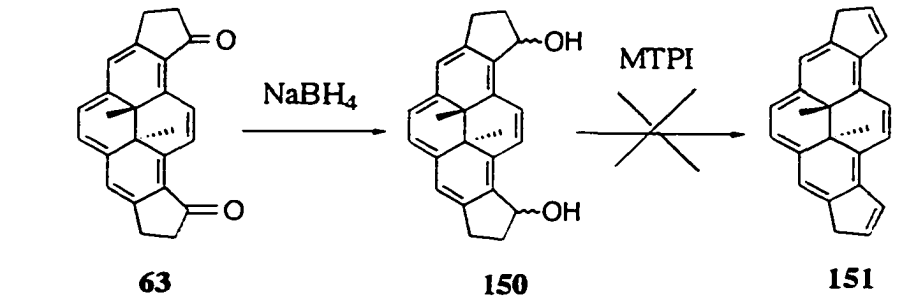
Scheme 18


144
Br
Br
145a
145c
KOH
benzene
80% EtOH
70%
1. LDA
2. MeI
74%
MeS
SMe
146
SH
SH
86
145b
145d
(MeO)2CHBF4
65%
Me2S
SMe2
2BF4-
147
t-BuOK
20%
148a
148c
148b
148d
syn and anti; cisoid and transoid isomers
Only cisoid isomers are shown
PDC
20%
O
O
149a
149b

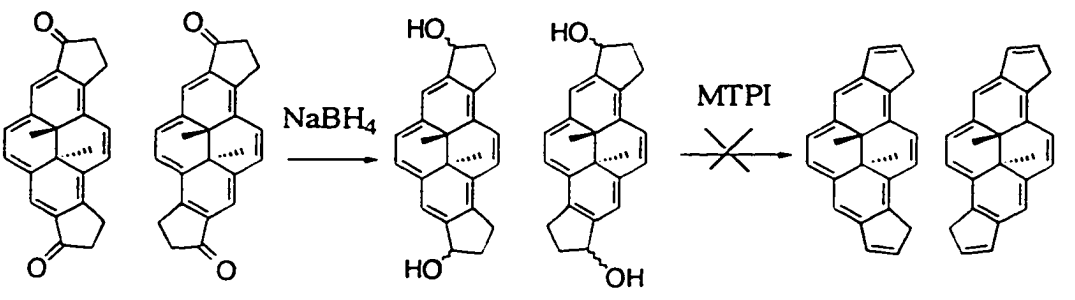
The mixture of **149a** and **149b** could be partially separated by a combination of column chromatography and fractional crystallization. The assignment of individual isomers was based on the ^{1}H-NMR absorption pattern of the ring protons (See experimental section). The internal methyl protons of the red *trans, cisoid* isomer **149a** appeared at δ -1.14 and -1.16 while that of the purple *trans, transoid* isomer **149b** appeared at δ -2.20 in its ^{1}H-NMR spectrum. The carbonyl stretch of **149a** appeared at 1683 cm^{-1} while that of **149b** appeared at 1698 cm^{-1} in their IR spectra.

In Schemes 4, 5 and 12, we have used different approaches to synthesize the dicyclopentenone annelated DHPs **63**, **70** and **42**. Compound **63** was obtained as a single isomer by a Friedel-Crafts bis-cyclization reaction. Compound **70** was obtained as two isomers from the cyclopentene-annelated DHP via a chain-elongation followed by Friedel-Crafts cyclization and then oxidation reaction. Compound **42** was obtained from the bis-oxidation of the dicyclopentene-annelated DHP as two isomers. As mentioned in the introduction, those diketones should be the precursors to the dicyclopentadienyl annelated DHPs and therefore we attempted the synthesis of dicyclopentadienyl annelated DHP as shown in Scheme 19:

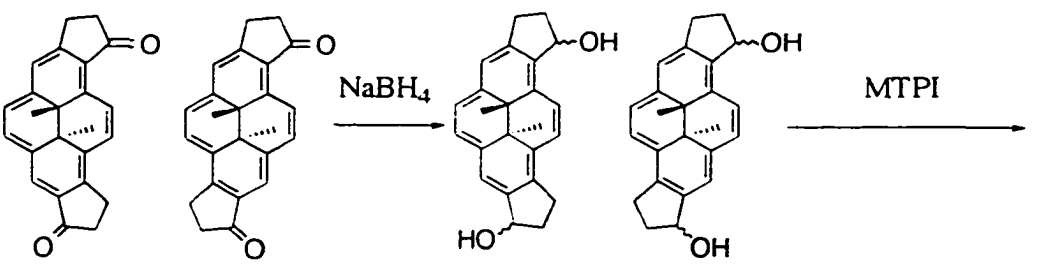
Scheme 19



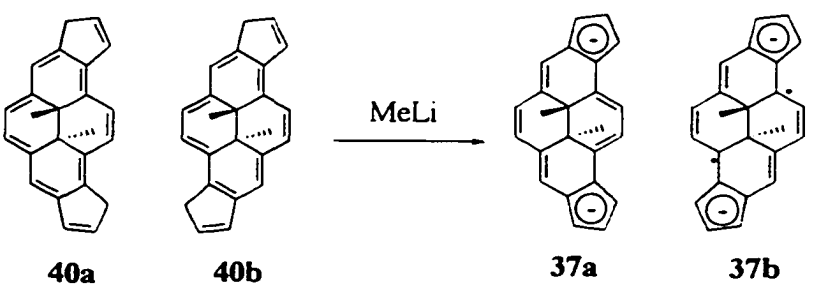
63 **150** **151**



42a **42b** **153** **154**



70a **70b** **152**



40a **40b** **37a** **37b**

Although the diketones **63**, **42** and **70** could be reduced to the corresponding dialcohols **150**, **153** and **152**, the elimination reactions of **150**, **152** and **153** proved most frustrating and our many attempts are described below.

In the literature, there are numerous methods to convert an alcohol to an alkene. For example, direct elimination can be achieved using copper (II) sulfate ($CuSO_4$)[54], $CuSO_4$ on silica gel,[55] ferric chloride ($FeCl_3$) on Silica gel,[56] tosyl sulphonic acid (TsOH) / benzene,[57] boron trifluoride etherate ($BF_3.OEt_2$),[58] potassium hydroxide (KOH),[59] potassium hydrogen sulfate ($KHSO_4$),[60] aluminum chloride ($AlCl_3$) / lithium aluminum hydride ($LiAlH_4$),[61] alumina (Al_2O_3) acidic or neutral or basic,[62] hexamethylphosphoric triamide (HMPT)[63] and dimethyl sulfoxide (DMSO).[64] Indirect elimination can be achieved by firstly converting the alcohol to a better leaving group and then followed by a elimination reaction. Examples of this kind are methanesulfonyl chloride / triethyl amine (MsCl / Et_3N); thionyl chloride / triethyl amine ($SOCl_2$ / NEt_3);[65] triphenylphosphine / carbon tetrachloride / diethyl amine (Ph_3P / CCl_4 / $NHEt_2$);[66] *o*-nitrophenylselenocyanate / tributylphosphine (Bu_3P)/ hydrogen peroxide (H_2O_2)[67] and methyl triphenoxyphosphonium iodide[68] (MTPI), $(PhO)_3P^+MeI^-$. In the above elimination methods, elimination using MTPI is the mildest and it has the advantage that the elimination is carried out at room temperature under almost neutral conditions.

Many of the above mentioned reagents were tried on alcohol **153** but failed. MTPI was the only reagent that successfully carried out the elimination of dialcohol **152** to the corresponding diene **40**.

The green diketone **63** was reduced by $NaBH_4$ to the green dialcohol **150** which was a complicated mixture of diastereomers. It is worth noting that once the

diketone **63** was reduced to its dialcohol, **150**, its internal methyl proton chemical shift changed signifcantly from δ -2.92 (a singlet) to eleven singlets between δ -3.98 to -4.25 in its ^{1}H-NMR spectrum. Attempts to affect the elimination of alcohol **150** using methyl triphenoxyphosphonium iodide[68], $(PhO)_3P^+MeI^-$ or 18% HCl failed and no product could be identified.

Reduction of the diketone mixture **42a** and **42b** gave the green dialcohol mixture **153** characterized by the broad IR absorption at 3300cm^{-1} and the internal methyl protons which appeared as many singlets between δ -4.03 to -4.22 in its ^{1}H-NMR spectrum. Attempted elimination of **153** with 18% HCl, methyl triphenoxyphosphonium iodide (MTPI)[68] and many other of the elimination reagents mentioned above also failed and led to serious decomposition with only a trace amount of the diketones **42a** and **42b** could be recovered.

The red diketone mixture of **70** was reduced by $NaBH_4$ to the green dialcohol mixture **152**. It is worth noting that once the diketone mixture **70** was reduced to their dialcohols, their internal methyl proton chemical shifts changed from δ -2.89 (*cisoid* **70a**) and δ -3.80 (*transoid* **70b**) to a narrow absorption range between δ -3.99 to -4.20. In this case however, the dialcohol mixture **152** could be eliminated by methyl triphenoxyphosphonium iodide (MTPI)[68] and gave an unstable reddish-green bis-alkene mixture **40** in 19% yield (CI MS *m/z* 309(MH^+)). It was a mixture of the *cisoid* **40a** and the *transoid* **40b**, the internal methyl protons of which appeared at δ -4.02 and -4.03 respectively in its ^{1}H-NMR spectrum.

The failure using compounds **150** and **153** to generate the dicyclopentadienyl annelated DHPs deserves some explanation. Compounds **63** and **42** could be reduced to their corresponding dialcohols smoothly. However, the elimination step caused the problem. Elimination of both dialcohols **150** and **153** resulted in serious decomposition . This may be explained by the structures of the dialcohols (See Figure 12), in which we indicate a 1,ω-type elimination is possible leading to unstable polyene type products which decompose. After failing in so many different kinds of elimination reaction, we were convinced that we were unlikely to alter the mode of reaction from a 1,ω-type elimination to a β-elimination by changing the reagents. We then focused our effort to modify the structure of the starting material. In alcohols **150** and **153** (See Figure 12), the way the alcohol groups are positioned allows not only the normal type of β-elimination but also the 1,ω-type elimination which may cause the observed decomposition. The 1,ω-type elimination pathway is possible whenever there is an odd number of bonds between the two alcohol groups (The two alcohol groups in **150** are 7 bonds apart while those of **153** are 9 bonds apart). In principle, one can synthesize dialcohols, which have an even number of bonds between the two alcohol groups, as in **152a** and **152b** (See Figure 12). 1,ω-type elimination is not possible for dialcohols **152** and a normal mode of β-elimination gave the expected dicyclopentadienyl-annelated DHPs **40a** and **40b** (See Scheme 19).

Having the diene ligand **40** in hand, the next step was to react it with base to generate the dicyclopentadienide dianion **37**. When methyl lithium (MeLi) was added,

the colour changed from green to orange. The internal methyl protons of **40** shifted from δ -4.02 and -4.03 to -3.8 and -4.2, presumably due to formation of the dianions **37a** and

Figure 12 β-elimination versus 1,ω-type elimination

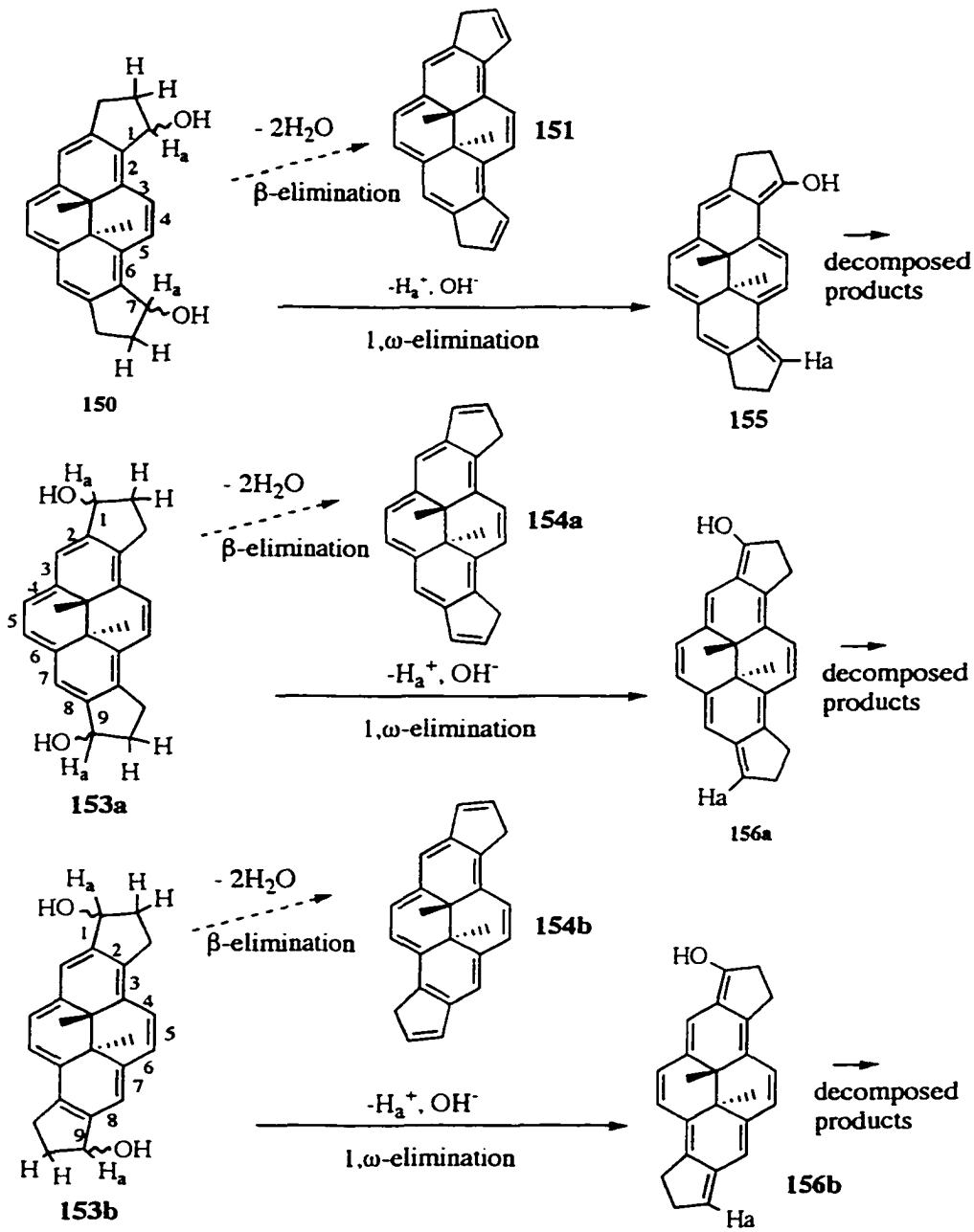
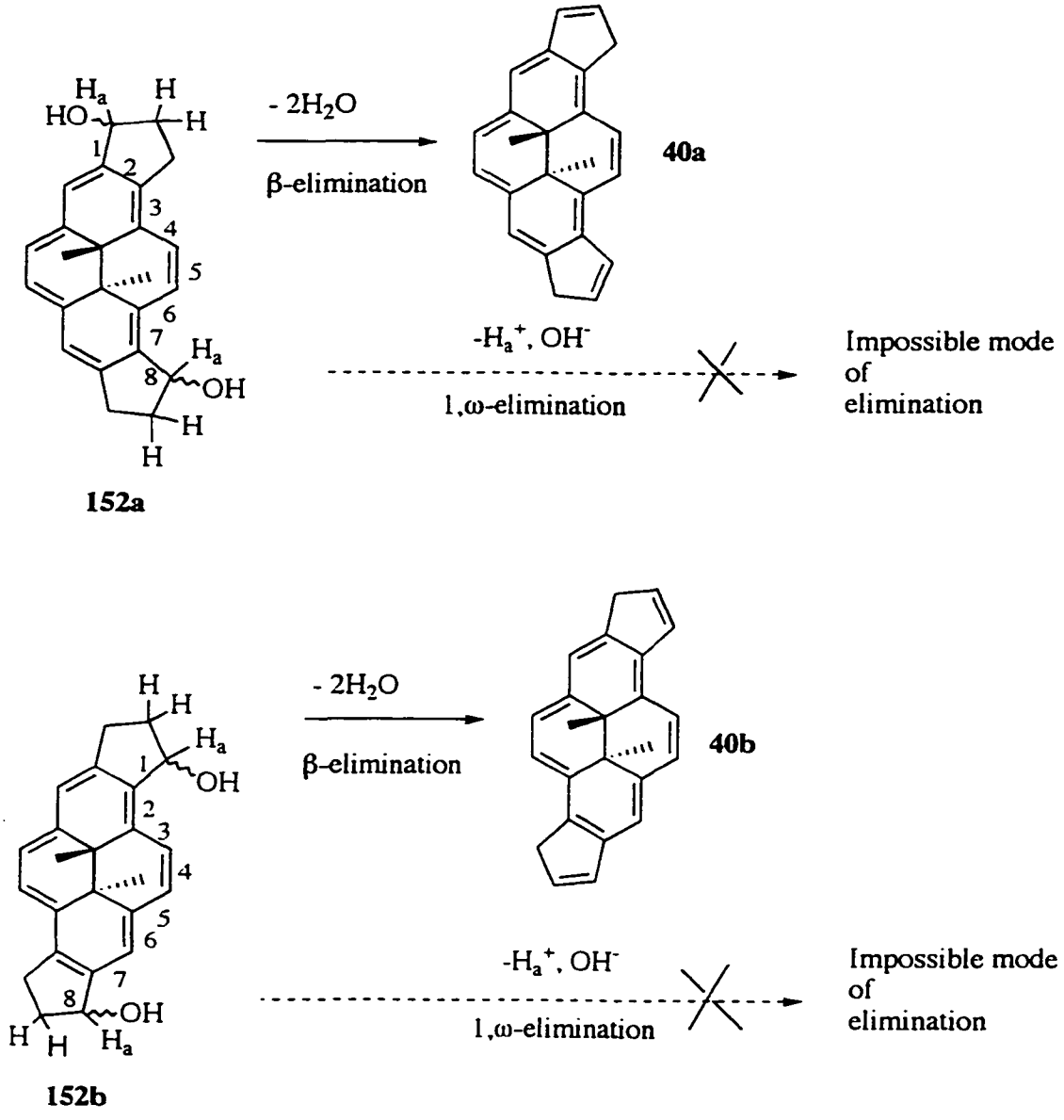


Figure 12 .....continued

Elimination of unsymmetrical dialcohols **148**



37b. However, the dianions could not be fully characterized due to serious decomposition and attempts to synthesize the ruthenium Cp* complex in situ also failed.

Apart from trying to obtain the dicyclopentadienyl annelated DHP from the dialcohols, we also tried the direct dehydrogenation of the dicyclopentene-annelated DHPs **41** to the dicyclopentadienyl annelated DHPs **154** using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ),[69] which also failed. As well the reductive elimination reaction of the dicyclopentenone-annelated DHPs **42** using either chlorotrimethylsilane (Me_3SiCl)/Zinc[70] or tosylhydrazine ($TsNHNH_2$) followed by methyllithium (MeLi)[71] was tried, which should also have given diene **154**, but these also failed.

D. Summary

In summary, the syntheses of cycloalkene and cycloalkenone annelated DHPs were achieved using two approaches. Both approaches were complementary to each other and it was demonstrated that the one involving early ring formation was more versatile in the sense that different compounds could be prepared through a symmetrical or unsymmetrical coupling. Other than the cycloalkene and cycloalkenone DHPs, we also synthesized some acyclic tetra-substituted DHPs and DHPs which were annelated with a benzene ring and a five-membered ring. This gave a whole series of DHP derivatives which allows us in the next chapter to comment on the long debated Mills-Nixon effect.

The effort to synthesize the dicyclopentadienyl annelated DHP ligand, its dicyclopentadienide dianion and its metal complex was also discussed. Although the dicyclopentadienyl annelated DHP **40** was successfully synthesized, due to its instability and its minute amount after a lengthy multi-step synthesis, the derived dianion could not be fully characterized and identified, and an attempt to form a metal complex from this failed.

Chapter 3 The long debated Mills-Nixon effect

A. What is the Mills-Nixon effect ?

In 1930, Mills and Nixon explained some electrophilic substitution data on some cyclopentene- and cyclohexene-annelated benzenes in terms of the effect of ring size on the Kekulé structures.[39] They mentioned that small ring annelation on benzene would induce bond fixation (bond alternation) by trapping out one of the Kekulé valence isomers.[39] Based on the classical success of van't Hoff's proof of tetrahedral carbon, Mills and Nixon's hypothesis was that benzene could be represented by two rapidly equilibrating Kekulé isomers constructed of van't Hoff tetrahedra (See Figure 13). When applying van't Hoff tetrahedra to benzene[72], the external CCH angles were either 109° or 125°, depending upon whether they pointed toward or away from a single bond. Hence, Mills and Nixon reasoned that in a molecule like indane **157** (See Figure 14), with an internal angle of 108° in a flat five-membered ring, the complementarity of angles would favor a single tautomer where the double bonds would be exocyclic to the five-membered ring. In contrast, a molecule such as tetralin **158**, with an internal angle of 120° in a flat

Figure 13 The Kekulé oscillation hypothesis of two rapidly equilibrating benzene isomers constructed of van't Hoff tetrahedra used by Mills and Nixon[89]

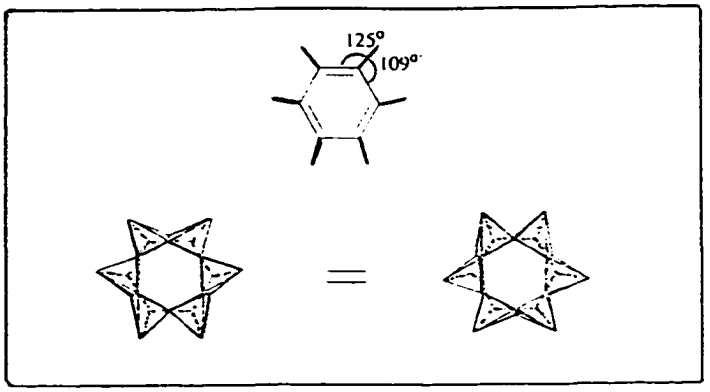
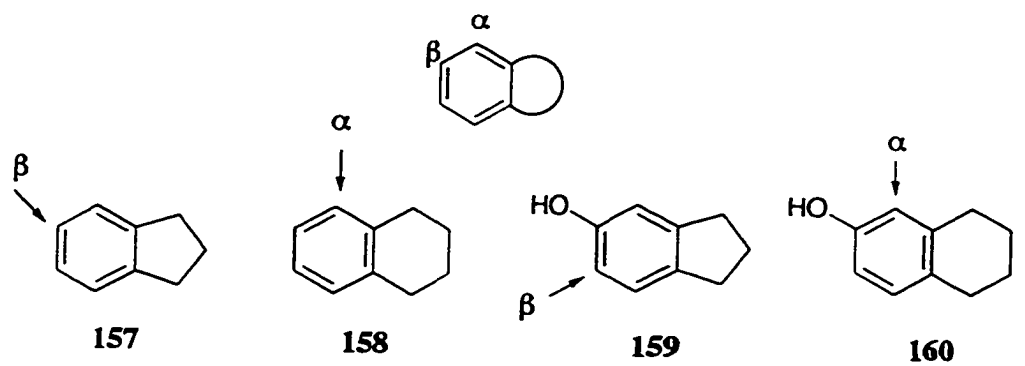


Figure 14 Selectivity of electrophilic aromatic substitution for some indane and tetralin derivatives



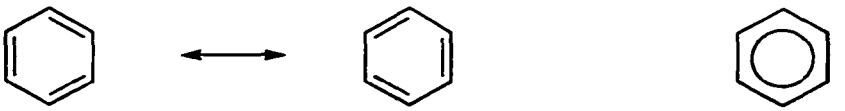
157 **158** **159** **160**

six membered ring, would prefer the valence isomer with a double bond at the ring junction. Siegel[89] has stated that due to the lack of a direct method for analyzing molecular structure in the 1930's, postulates of that time were often supported by product distributions. An experimental observable such as product selectivity or isomer count was correlated to an unobservable molecular structure. Mills and Nixon concluded that bond fixation was a direct result of small ring annelation on benzene because of the enol reactivity displayed β to the ring junction in 5-hydroxyindan **159** and α to the ring in 6-hydroxytetralin **160** during substitution by reactions of bromine and diazonium salt[39] and because of the known selectivity in the electrophilic aromatic chemistry[73] for indane **157** and tetralin **158** (β-selectivity for indane and α-selectivity for tetralin). (See Figure 14)

This older view of benzene being an equilibrium of two structures with a D_{3h} symmetry has been surpassed by the Pauling model of resonance hybrids[74] in which benzene has a single symmetrical form with a D_{6h} symmetry, not a time average between two Kekulé forms[75] (See Figure 15). Even though the modern theory of benzene is the

one with a single structure, the effect often referred to as "The Mills-Nixon Effect" that a small ring could perturb this structure is still useful in the sense that a non-bond equal benzene could be produced, in the same way that in naphthalene **161** (Figure 16) one benzene strongly perturbs the other to give bond alternation around the periphery.

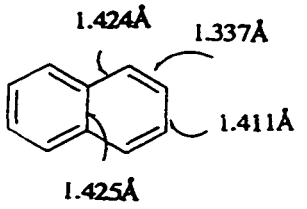
Figure 15 The older view of D_{3h} benzene vs Pauling's D_{6h} benzene



Kekulé structure of benzene
D_{3h} symmetry

Pauling's resonance hybrid
D_{6h} symmetry

Figure 16 Bond lengths of naphthalene **161**

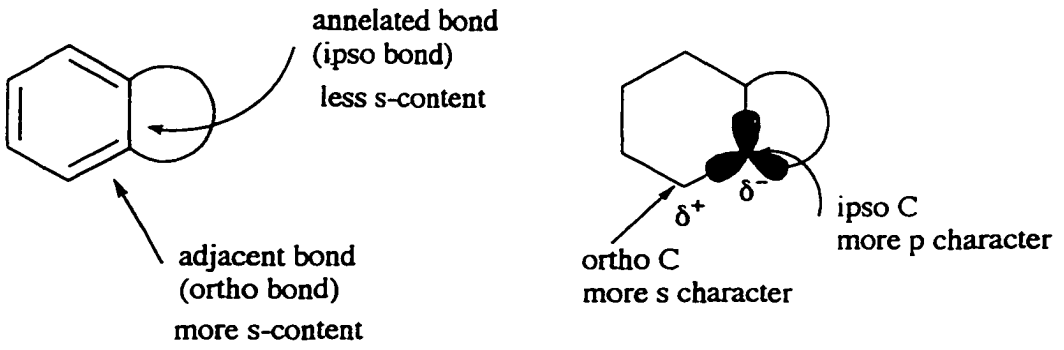


Naphthalene **161**

Although the premise of the Mills-Nixon effect has been proven wrong by the Pauling-Hückel model of benzene, two chemically important research goals[66,89] have emerged. The first and most obvious is to provide direct structural evidence to prove or disprove the bond fixation effect in annelated benzenes. The other is to account for the general selectivity of β versus α attack in the benzocycloalkenes having ring size smaller than cyclohexane. Through these two goals, there has been impact on the development in the research of chemical structure elucidation, the chemical dynamics and the synthetic methodologies towards strained molecules and theorectical calculations.

Even though the Mills-Nixon effect was based on a wrong premise, it has for several decades been used to denote nonequivalence of bonds in benzene resulting from annelation. More generally speaking, the Mills-Nixon effect can be defined as a perturbation of an aromatic moiety by an annelating ring(s). This perturbation has some structural and electronic consequences. As a result of annelation, the annelated (ipso) bond (See Figure 17) is longer than the predetermined standard bond, whereas, the adjacent (ortho) bond is shorter. Due to strain induced rehybridization[76], the p-content increased in the ipso bonds and decreased in the ortho bonds in response to the structural changes. This type of deformation and electron density redistribution corresponds to the ordinary Mills-Nixon effect.

Figure 17 Electron redistribution on small ring annelation for benzocycloalkene



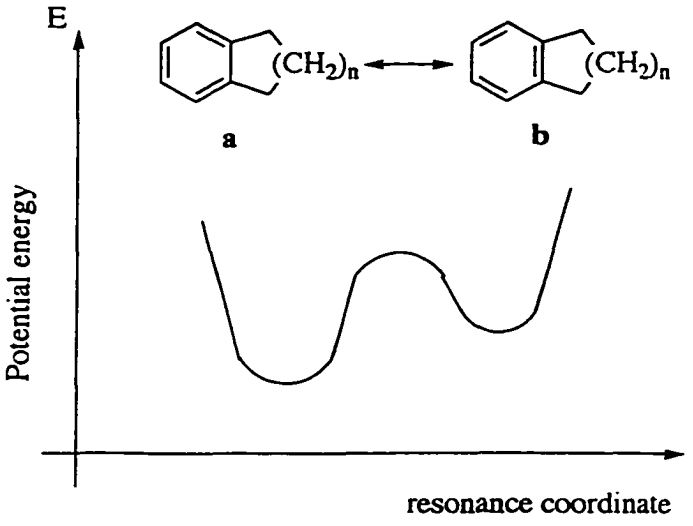
There are two approaches to explain non bond equal benzenes. One is based on resonance theory in which the real structure is closer to one "Kekulé structure" than the other. The other is based on rehybridization theory in which the structure of benzene is adjusted by using non-classical (ie. not sp^2) hybrids.

B. Resonance theory versus rehybridization theory in the explanation of the Mills-Nixon effect

1. Resonance theory:

The Mills-Nixon effect appears attractive from the empirical point of view of resonance theory. In structures a and b, Figure 18, the low energy resonance form should make a greater contribution to the resonance hybrid and the properties of this hybrid should more closely resemble this lower energy form.

Figure 18 A double-well potential energy curve for annelated benzene



If this is the case, the perturbation caused by annelation will alter the average structure to a species described by a double-well instead of, a single well potential.[77,78] The average position in a double-well structure is defined by the relative population of the two wells. A small energy change in either well leads to a large change in population and therefore a large shift in the average structure is expected. The double-well equilibrium fails to explain why the average position is not so sensitive to such

perturbation. The average position in a single-well potential, however, is related to the anharmonicity of the well, which is normally less sensitive to such perturbations.[78] Nevertheless, it is possible to vary several factors which may enhance the chances for a perceptible change in the weighting of the resonance forms. These factors are:

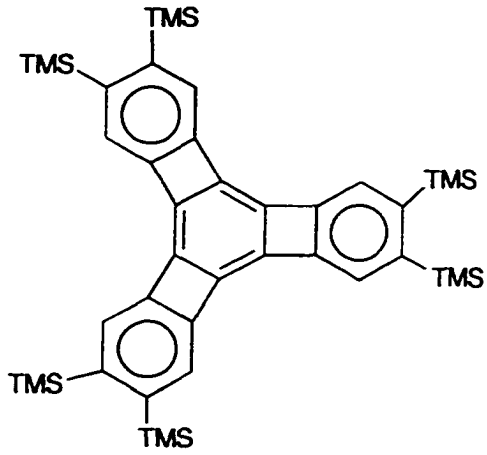
a. The size of the annelated ring[79,80]

b. The electronic effect of the annelated ring[81,82]

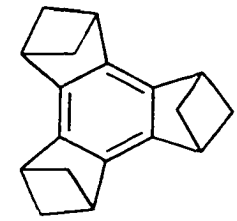
c. The orientation and number of rings annelated to a single aromatic nucleus[83]

d. The nature of the aromatic nucleus itself[84]

What causes the aromaticity of benzene has long been debated. Whether the driving force is due to the highly symmetrical σ-framework or the π-delocalization energy remains unknown.[85] On the whole, the strain induced in the benzene nucleus by annelation of a small ring causes the lengthening of the annelated bond and the shortening of adjacent bonds.[80] The annelated bond becomes longer as rehybridization takes place to accomodate the strain induced. Both the local atomic rehybridization and π electon redistribution caused by hyperconjugative perturbation arising from the CH_2 groups of the fused carbocycles (σ and π electrons) act in the same direction resulting in moderate Mills-Nixon distortions. Theoretically, it is of interest to answer the question "how much strain on the σ-framework will result in the π-system giving up its resonance stablization and hence aromaticity.[102] It is not until recently, when Vollhardt and Siegel synthesized compounds **162**[86] and **163**[87], that light has been shed on to this question.[88]



162



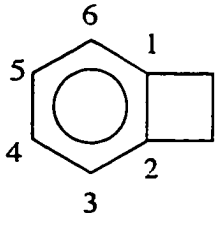
163

2. Rehybridization theory:

Much NMR data[89] and many X-ray structures[90] suggest that when benzene is annelated, it undergoes structural changes that are concentrated in the vicinity of the fused ring. According to simple resonance theory, strain induced double bond alternation should affect all positions of the benzene ring to an approximately equal extent. Hence a rehybridization theory has been set forth by Streitweiser[91] and also by Finnegan[92]. Their assumption, which is supported by a recent MO calculation[93], states that in order to relieve angle strain in the small ring, the aromatic (ipso) carbon atoms at the points of fusion rehybridize away from sp^2 to place more p-character in the bonds subtending the strained angle, and hence more s character in the bond to the ortho position. (See Figure 17) This ipso-ortho bond will therefore be polarised with a partial negative charge on the ipso carbon and a positive charge on the ortho carbon.[76]

For instance, in the benzocyclobutene **164** (Figure 19), four-membered ring fusion leads to some redistribution of p-character along the C-C bonds. The ipso bond (1-2) shows higher calculated percentage p-character than the ortho bonds (1-6), where bond 1-2 = $sp^{2.21}$, and bond 1-6 = $sp^{1.58}$. The unsubstituted carbons use hybids ranging from $sp^{1.85}$ to $sp^{1.92}$ for the 3-4, 4-5 and 5-6 bonds essentially identical to those of benzene $(sp^{1.88})$[94]. This indicates that the amount of ring strain transmitted along the σ framework is negligible. Such observation was also supported by the X-ray structure[95] and Electron Densities Difference (EDD) map[90] which indicates that the deformation in **164** is concentrated in the half of the benzene which has the four membered ring fusion. More examples of such uneven distortion based on the EDD map can be found in Boese's recent publication.[90]

Figure 19 Hybridization of benzocyclobutene



Compound **164**

C_1-C_2 : $sp^{2.21}$

C_1-C_6 : $sp^{1.58}$

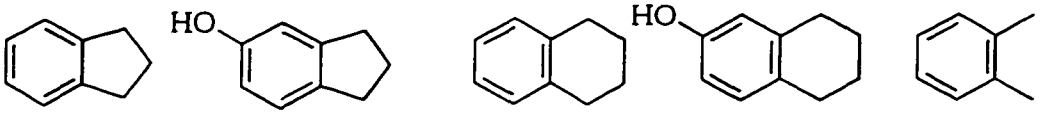
C_5-C_6 : $sp^{1.85}$ - $sp^{1.92}$

C. On the way to bond fix benzene

The molecules originally considered by Mills and Nixon in their bond fixation hypothesis were indane **157**, 5-hydroxyindan **159**, tetralin **158**,

6-hydroxytetralin **160** and *o*-xylene **165** (See Figure 20).[39] Soon this work was extended to benzocyclopropenes **166** and benzocyclobutenes **164** (Figure 21)[95a,95b,95c,95d]. However, most of the early work was limited to kinetic studies, regioselectivity studies in electrophilic aromatic substitution and spectroscopic studies such as UV and Photoelectron spectroscopy.[89] With the later development of NMR techniques and improving X-ray resolution power, these two techniques are now most used for research into the Mills-Nixon effect.

Figure 20 Original molecules considered by Mills and Nixon in their bond fixation hypothesis



157 **159** **158** **160** **165**

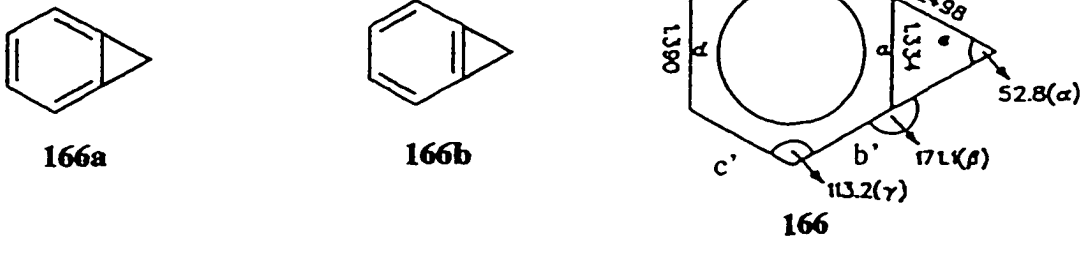
Figure 21 Molecules which were extensively studied as the debate of the Mills-Nixon effect goes by

166 **164**

In the benzocycloalkene series, one would expect that the benzocyclopropene **166** plays a central role in the bond fixation hypothesis. It is the most strained of the benzocycloalkene series and if the bond localization effect cannot be observed in this

compound, there will be an implication that the bond fixation is unimportant also in other (particularly less strained) annelated aromatics. Before 1988, the structure of **166** remained unknown, but through calculation, P.C. Hiberty, G. Ohanessian and F. Delbecq had computed the weights of the Kekulé[96] (**166a**, **166b**) and other structures of **166**, and found strong bond fixation favoring structure **166a**. However, when Boese resolved the X-ray structure of **166** in 1988[90], he demonstrated that there was no bond localization in the sense of the Kekulè resonance structures **166a** or **166b**, but rather a reduction in the symmetry with retention of the aromatic π-electron delocalization in the benzene nucleus as in Figure 22, **166**.[90] Thus the innercyclic angle α at the C(sp^3) atom is 52.8° and has a deviation from the tetrahedral angle of 56.7°. The exocyclic angle β at the adjacent C(sp^2) atoms are 171.1°, which is a deviation of 51.1° from the ideal trigonal planar angle of 120°.

Figure 22 Kekulé structures (**166a** , **166b**) and X-ray structure (**166**) of benzocyclopropene

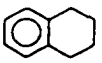


166a **166b** **166**

The strain at the two bridgehead atoms can only be released by a decrease of angle β at the expense of the innercyclic angle α at the C(sp^3) atom. This causes a shift of the bridgehead atoms towards the center of the benzene ring, thereby shortening the adjacent bonds b and b' and decreasing the angle γ to 113.2°. As shown in Figure 22, the distances b and b' in

166 are longer than a, but shorter than c and c'. *An alternation of atomic distances corresponding to bond-fixation in the benzene ring of **166**, according to the Mills-Nixon's hypothesis, is not observed.*[106] It seems that this molecule has an almost undistorted half at bonds c, d and c' with distances close to those of benzene and angles of 120°, and a distorted side at the bonds b, a and b'.[90] The NMR properties of benzocycloalkenes were well studied.[97] Their NMR data for the benzene ring carbon and protons is summarized in Table 3:

Table 3 Chemical shifts and coupling constants for the aromatic ring atoms in benzocycloalkenes [a]

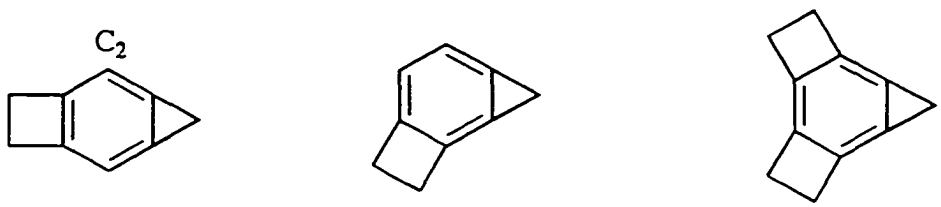
	Chemical Shifts [b]					Coupling Constants [c]				
	C(1)	C(2)	C(3)	H(2)	H(3)	C(2)-H	C(3)-H	C(2)-C(1)	H(2)-H(3)	H(3)-H(4)
	125.4	114.7	128.8	7.15	7.19	168.5	159	87.1	6.04	7.63
	145.2	122.1	126.5	6.76	6.91	162	157.5	59.8	7.36	7.79
	143.3	124.0	125.8	7.07	6.99	155.5	157	59.8	7.59	7.20
	136.4	128.8	125.2	7.01	6.93	155	159	58.6		

a. Taken from Reference 97. b. In ppm downfield from Me_4Si. c. In Hz

In Table 3, the largest variations are associated with carbon (1) and (2) and hydrogen (2) as compared with carbon (3) and hydrogen (3). This general observation implies that structural changes in the benzene ring occur to a greater extent in the vicinity of ring fused carbon (1). Strain-induced double bond alternation should affect all positions of the benzene ring to an approximately equal extent according to simple resonance theory. NMR data in Table 3 suggests that a rehybridization at the site of ring fusion takes place as proposed by Streitweiser[91] and also by Finnegan[92]. For the small ring fused benzocycloalkenes, the bridgehead carbons rehybridize to use orbitals of higher p-character in bonding to the small ring. This rehybridization leaves an orbital of higher s-character to bond to the ortho-carbon which results in an inductive polarization of the ortho-aromatic C-H bond, which results in the higher field shift of C_2 and the increase of $J_{C2\text{-}H}$ and $J_{C2\text{-}Cl}$ with increasing strain. Such polarization should result in an increase in the acidity of the ortho-aromatic proton (H_2) and this phenomenon has been observed chemically.[92,97]

To further strain the benzene nucleus, research shifted to the synthesis of the di-cycloalkene annelated systems where the two rings can adopt either linear [a,d] fusion as in dicyclopropa[a]cyclobuta[d]benzene **167** (Figure 23), or angular [a,c] fusion as in cyclopropa[a]-cyclobuta[c]benzene **168**. Incorporating two strained rings in a linear

Figure 23 Different annelations of benzene



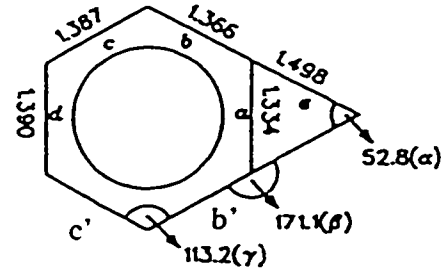
167 [a,d]-fusion

168 [a,c]-fusion

169 [a,c,e]-fusion

fusion resulted in structures which reflect a summation of the distortions found in each of the parent systems. The linear [a,d] annelation does not allow the two effects to influence one another significantly; only the bond angle at C_2 was altered noticeably. However, introducing more than one strained-ring in an angular [a,c] fusion should result in a cumulative effect of the strain. To maximize the effect of strain, the [a,c,e]-tricyclobenzoalkenes were synthesized.[89,93a,93b] Among which, the most strained cycloalkene-annulated benzene known todate is the cyclopropa[a]dicyclobuta[c,e]benzene **169**. The Berkeley and Rice groups (W.E. Billups, M.M. Haley, D.L Mohler, and K.P.C. Vollhardt) have prepared many of the benzocycloalkenes mentioned above[83], and in a collaboration with R. Boese, D. Bläser and A.H. Maulitz, many X-ray diffraction studies and Electron Density Difference (EDD) maps of the fore-mentioned compounds were determined.[90] Some selected X-ray diffraction data[90] for the above compounds are listed in Figure 24:

In Figure 24, it is clear that upon small ring annelation, there is distortion of the σ-framework of benzene. The bond at the site of ring fusion tends to elongate while the bond next to the annelated ring tends to contract. Although some effect in bond fixation was observed based on X-ray data, bond alteration is quite minor (< 0.056 Å) and appears to be chemically insignificant; this should not be taken as support for Mills-Nixon arguments. Besides, the bond alternation pattern as predicted by the original Mills-Nixon effect that one of the Kekulé structure being trapped out is not observed. It is important to realize that the concept of bond fixation concerned with localization of electrons in the π-framework, while the geometry is determined by both σ- and π-effects. However, many arguments for bond fixation are still based only on geometry change. This may be due to



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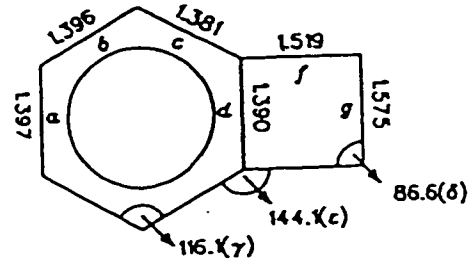

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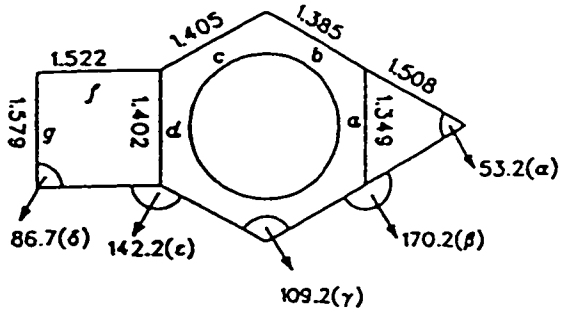

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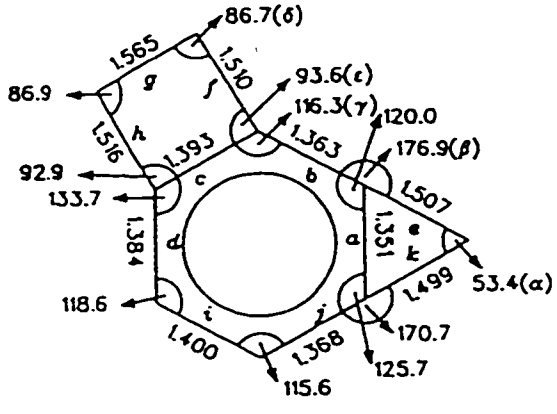
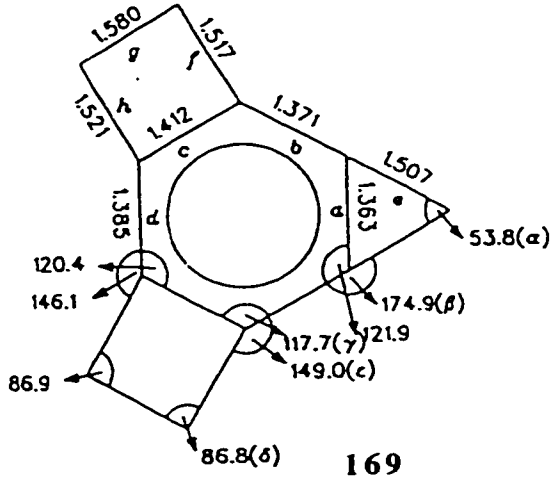


168

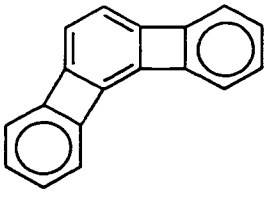


169

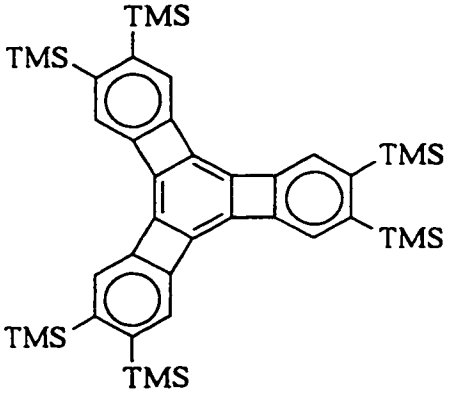
Figure 24 Distance (Å) and angles (in degrees) of the determined cyclopropa- and cyclobuta-annelated benzene molecules[90]

the difficulty to estimate experimentally the degree of bond fixation. As concluded by Apeloig,[98] the bond lengths of **166** do not reflect the degree of bond fixation of the π-electrons. Thus, in these series of benzocycloalkenes, a firm conclusion as to whether the Mills-Nixon effect exists or not still can not be made.

For more than 10 years, Vollhardt has been synthesizing phenylenes through cobalt-catalyzed chemistry[99] that combines *o*-diethynylarenes with alkynes to furnish biphenylenes. By using that methodology, a number of compounds like angular [3]phenylene **170**[100] and triangular [4]phenylene **162**[86] were synthesized. By juxtaposing aromatic benzene [(4n+2)π electrons] with antiaromatic cyclobutadiene (4nπ electrons), systems like **170** and **162** show significant bond fixation in the central benzene ring in order to avoid antiaromatic cyclobutadiene contributions.



170



162

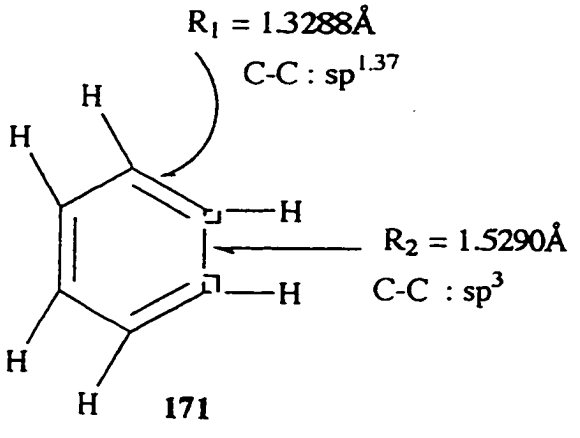
Those molecules serve to demonstrate that π-effect is much more dominant than ring strain effect in the bond fixation of benzene. As the central benzene ring in

compound **162** was obviously bond fixed, it was not surprising that it underwent addition reactions, as expected for a cyclohexatriene but not for a benzene. For example, **162** undergoes hydrogenation, epoxidation and cyclopropanation reactions[101].

Although the starphenylene **162** clearly demonstrated bond fixation in the central benzene ring by both X-ray structure and chemical reactions, it appears that avoidance of an anti-aromatic cyclobutadienoid circuit (π effect) is the major contributing factor rather than a ring strain (σ effect).[86]

Based on the results for the mono-, di- and tri-benzocycloalkenes, one might conclude that strain-induced bond alternation in a benzenoid compound is just too small to observe a Mills-Nixon effect. Although there is geometry distortion due to ring annelation of a benzene, the π-bond fixation in the sense of trapping out one of the Kekulé structures has never been observed. Stanger[102] reasoned that it may due to the formation of banana bonds which alleviate any strain imposed on benzene . Stanger and Vollhardt also examined an artifically strained benzene model where they constrained the HCC bond angles to be 90° in pair as shown in Figure 25. Their calculation at HF/6-31G* level

Figure 25 Stanger's highly deformed benzene



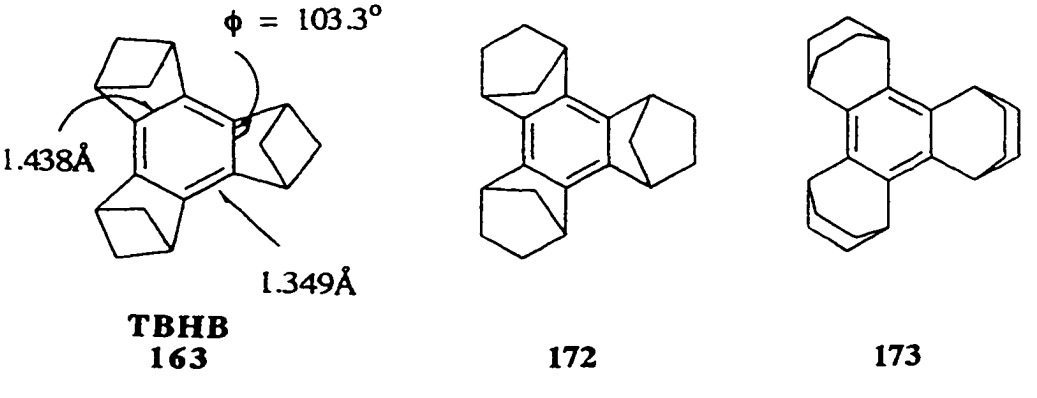
171

For compound **171**
$R = R_2 - R_1 = 0.2002$Å
cf. For benzene: R = 0 Å
$R_1 = R_2 = 1.395$Å

revealed the highly strained benzene structure exhibited significant CC bond alternation. The endo bond length in the distorted benzene is 1.5290 Å while the exo bond length is 1.3288 Å [Δ (long bond - short bond) = 0.2002 Å, which is comparable to a standard C_{sp^2}-C_{sp^2} single and double bond, Δ_d = 1.50 - 1.33 = 0.17 Å[103]]. Their analysis also revealed that the D_{3h} π component of **171** is stabilized relative to that of the symmetric D_{6h} structure.

Model compound **171** is good in a way that the strain induced benzene bonds cannot be released through banana bonding and therefore, more significant bond fixation results compared to the cycloalkene annelated analogs are calculated. Unfortunately, **171** is not a real molecule. In order to synthesize strained molecules in which the strain cannot be easily released through banana bonding, Siegel investigated bicyclic annelation. Before this work, Siegel has been collaborating with Baldridge to obtain calculations on many strained molecules. Baldridge had calculated that the trisbicyclo[2.1.1]hexabenzene (TBHB) **163** should show alternating bonds[80] even though synthetically it was unknown. In fact, in the series of bicyclic annelated compounds (See Figure 26), **163**[87], **172**[104] and **173**[105], **163** turned out to be the most strained of all.

Figure 26 Trisbicyclic annelated benzenes of different ring size



TBHB
163

172

173

This was discussed in terms of a bond fixing power of each bicyclic ring.[87] The bond alternation in **163**, **172** and **173** is 8.9, 3.8 and 1.5 pm respectively (This is defined as the average bond length difference between long and short bonds). The X-ray structure of **163**[87] indicated that the C-C bond length differs by 0.089 Å, between long bonds (1.438 Å) and short bonds (1.349 Å). The bicyclic annelation strongly constricts the C_{arom}-C_{arom} -$C_{methine}$ angle, ϕ, down to 103.3(2)° and this angle distortion is presumed to be correlated to the manifestation of bond alternation.

D. Techniques available to study the Mills-Nixon effect:

In the literature, a number of experimental techniques have been used to study the Mills-Nixon effect. Of these, low temperature high-accuracy X-ray crystallography and NMR studies are the most popular to probe the Mills-Nixon effect. However it is not easy to find a technique that only probes π-delocalization.

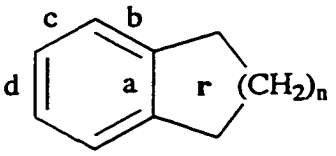
a. X-ray studies:

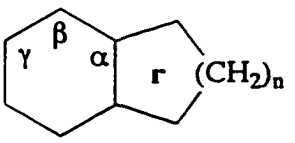
X-rays are diffracted by electrons. Experimentally, it has the drawback that the position of hydrogen atoms can be determined only with a low precision and the bond length obtained is temperature dependant.[90] Suitable single crystals are often not easy to obtain and sometimes due to defects in the crystals, precision X-ray data cannot be obtained. From the X-ray diffraction pattern, one can derive the complete electron distribution. If the electron density distribution of the core electrons of each atom is substracted from the total electon density, the remaining electron density should represent those electrons involved in the "chemical bonds" between the atoms and the lone pairs.[90] The information obtained is the so called X-X Electron Density Difference (EDD) map.

To prove any bond fixation related to the Mills-Nixon effect, X-ray and EDD studies can be used as direct evidence. In the early years when the Mills-Nixon hypothesis was proposed, most studies were limited to electophilic substitution studies in cycloalkene annelated systems. Nowadays, due to the fast growth of X-ray techniques, there are growing numbers of high precision X-ray structures available to comment on the bonding in strained cycloalkene annelated systems. However, when considering the precision X-ray data, not only should the standard deviations of bond lengths and angles (or the R-values) be examined, but also additional criteria concerning the quality of the data must be assessed.[90] Thus the displacement parameter (also named temperature parameter), which give evidence for the extent of thermal vibration in the molecule, must be examined, as any statistical disorder of the molecules may be hidden in these parameters. This reduces the reliability of the given geometrical data.

A variety of mean geometries for benzocycloalkenes with fused-ring sizes (r) = 3 - 6 are collected in Table 4, which have been obtained[106] from the Cambridge Crystallographic Database. The tabulations show no significant variations in aromatic bond lengths. The results of small ring annelation is reflected in lengthening of bonds *a* and *c*, shortening of *b*, contraction of angle β and opening up of angle α and γ.

Table 4. Mean geometries for benzocycloalkenes (r = fused-ring size)





r = ring size
= 3, 4, 5, 6

Ring size, r	**3**	**4**	**5**	**6**
a (Å)	1.342	1.383	1.391	1.399
b (Å)	1.394	1.391	1.384	1.393
c (Å)	1.407	1.395	1.387	1.384
d (Å)	1.390	1.392	1.385	1.383
α (°)	126.0	122.6	121.1	119.6
β (°)	109.2	115.1	117.8	120.1
γ (°)	124.5	122.3	121.1	117.2

b. NMR investigation of the Mills-Nixon effect

For more than 60 years, the Mills-Nixon effect has been probed using benzene and some other 6π-heterocyclic compounds. Commonly, benzocycloalkenes are used. For example, the ^{1}H- and ^{13}C-NMR spectra of a series of benzocycloalkenes (ring

size = 3 to 6) were studied and the results were tabulated and discussed (See Table 3).[97] Based on the data in Table 3, it is demonstrated that on ring annelation of benzene, the rehybridization effect in general is more important than the ring current effect affecting the ^{1}H- and ^{13}C-NMR chemical shifts. The chemical shifts for the aryl protons in benzocyclopropene and benzocyclobutene also deserve some comment. It has been suggested that the constant shift to higher ppm for the cyclopropanated system has been taken as evidence for an aromatic sigma ring current in cyclopropane.[107] In contrast, the shift to lower ppm values for the cyclobutanated systems has been taken as evidence for an antiaromatic sigma ring current in cyclobutane.[108]

For the ^{13}C-chemical shift of benzocycloalkenes, the changes in the benzocycloalkene series parallel the changes to the alkenyl carbon chemical shifts in simple cycloalkenes. This indicates that the aromatic ring has no special effect on the chemical shift. The ^{13}C-chemical shift data shows a significant change at $C_{1,2}$ but almost no change at $C_{3,4}$ (See Table 3) and this is consistent with the common picture of rehybridization.

In the literature,[46,109,110] it has been shown that the orthobenzylic coupling constant, $^{4}J_{ob}$ [$^{4}J(CH_3\text{-}C_1{=}C_2\text{-}H)$], correlates well with the square of the Self-Consistent Field (SCF) molecular orbital bond orders and the Pauling (VB) bond order, having correlation coefficients of 0.98 and 0.99 respectively. In fact, the standard deviation in the correlation of the $^{4}J_{ob}$ with the Pauling bond (VB) orders is almost within the experimental error of the measurement (0.06Hz)[107]. Thus, $^{4}J_{ob}$ is a useful tool to investigate π-bond orders in conjugated systems. For example, in our methyl substituted compound **57**, the aromatic proton region is composed of two singlets. The fact that no ortho benzylic coupling $^{4}J_{ob}$ was observed suggests that **57** is a delocalized compound. On the other

hand, a difference in $^4J_{ob}$ of 0.23 Hz implied some degree of bond fixation for 5-methylindan-1-one, with the difference between the highest and lowest bond orders being about 6 %[46]. In the cycloalkene annelated DHP series, we were not able to observe any ortho benzylic coupling. Maybe a freely rotating methyl group is essential for the observation of such a coupling.

An extensive NMR study of methyl benzocycloalkenes and their methyl benzocycloalkenone derivatives using $^4J_{ob}$ was performed by Collins et al.[46] It was shown that the difference in $^4J_{ob}$ values obtained for the methyl benzocycloalkenes are very close to the value obtained for the non-strained model. As expected, the methyl benzocyclopropene had the most abnormal difference in $^4J_{ob}$ values of 0.03 Hz[46], but even in this extreme case, the author suggested that the Mills-Nixon effect could not be considered as established.

For the methyl benzocycloalkenones, bond fixation was evident in tetralone and indanone derivatives. For example, the difference in $^4J_{ob}$ values in 5-methylindan-1-one was 0.23 Hz[46]. This was explained in terms of steric constraints which depended on the fixed coplanar geometry of the carbonyl group in the fused molecules.

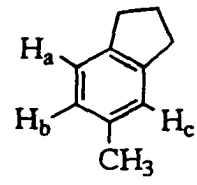
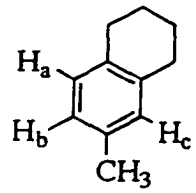
Although the $^4J_{ob}$ method has been shown to give a very good correlation with bond order and is insensitive to other effects[109], it is limited since an appropriately substituted methyl group is required on the aromatic nucleus. Therefore, more commonly, vicinal coupling constants ($^3J_{HH}$) are used[111] to indicate bond fixation. But one should be aware that $^3J_{HH}$ values can be affected by steric effects, the H-C=C-H bond angle and the electronegativity of attached groups[111]. **For simple annelated benzenes, the results as a whole do not suggest that there is any significant bond fixation.**

However, NMR results do provide information on bond orders through coupling constant analysis and hence indirect proof for the rehybridization at the ring junction.

Recently, Siegel[112,113] has commented in his review that the ring current in benzene is large and is relatively difficult to perturb, and that perphaps the 14π-electron system of DHP is a better choice as it responds more readily to changes in molecular structure.[37]

It is essential when comparing chemical shift data that the samples are run under similar conditions or better are mixed together to eliminate any solvent or concentration effects. On our way to prepare the cycloalkene annelated DHPs, we have made some benzocycloalkene intermediates. Their NMR data allows us to comment on the bond fixation of benzocycloalkenes on ring annelation. For the methylbenzocycloalkene compounds (ring size = 5,6,7), compound **84**, **91** and **99**, H_a, H_b and H_c protons are deshielded when the ring strain increases (See Table 5, ring strain increases in the order of ring size 5 ~ 7 > 6). Thus, the order of deshielding of H_a, H_b and H_c in terms of ring size is 5 > 7 ~ 6. The methyl protons and the aromatic protons of **84** (cyclopentene-annelated) are most deshielded (affected by strain rather than ring current; a reduction in the latter should shield rather than deshield the methyl and aromatic protons). The overall picture of methyl benzocycloalkenes suggests that their ^1H and ^{13}C-chemical shifts respond more to rehybridization rather than change in ring current on ring annelation.

Table 5 Selected chemical shifts for cycloalkene-annelated toluenes **84, 91 & 99**

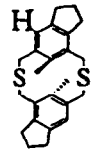
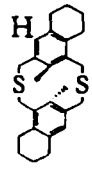
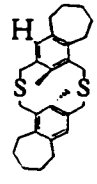
Compound	H_a (δ,ppm)	C_a (δ,ppm)	H_b (δ,ppm)	H_c (δ,ppm)	Ar-CH_3 (δ,ppm)	$C(CH_3)$ (δ,ppm)
84 	7.15	128.38	6.97	6.99	2.35	21.25
91 	6.98	129.67	6.91	6.90	2.28	20.92
99 	7.09	129.92	6.89	6.92	2.29	20.91

In the literature,[46,97,110,111] the ring current deshielding in benzocycloalkenes has never been demonstrated properly, presumably due to the small ring current in benzene and the proximity between the annelated ring and the aryl protons. For simple aromatics like benzene and naphthalene, the aromatic proton chemical shifts of their

annelated derivatives all cluster between 6.5 to 7.5 ppm.[89] Most of the chemical shifts changes of benzocycloalkenes are due to a rehybridization rather than a change in ring current. During our syntheses of cycloalkene annelated DHPs, we managed to isolate three dicycloalkene-annelated *anti,transoid* thiacyclophanes **110b**, **119b** and **132b**.

Based on the PCMODEL calculations, the relative geometry of the core in the three thiacyclophanes, *anti*-9,18-dimethyl-2,11-dithia[3,3]metacyclophane, remains almost not disturbed on ring annelation. The chemical shifts of the internal methyl protons are affected by the ring currents of their own and the opposite benzene rings and by any anisotropic effects of neighbouring atoms. In Table 6, the internal methyl proton chemical shifts, δ(Me), for the thiacyclo-phanes **110b**, **119b** and **132b** in the deshielding order based on ring size is 6 > 7 > 5, with the five-membered ring diannelated thiacyclophane **110b** being the least deshielded. The fact that the aryl proton of **110b** is the most deshielded suggested that rehybridization and steric compression deshielding might also be at play. Thus, with a combination of ring current and rehybridization effect which act opposite to each other, the aryl proton of the three [3,3]thiacyclophanes in the order of deshielding in terms of the ring size is 5 > 6 > 7.

Table 6 : Selective chemical shifts data* for the thiacyclophanes **110b, 119b & 132b**

Compound	Int. Me (H) δ(Me), ppm	Ar-CH_3 (δ, ppm)	C_{Ar}-H (δ, ppm)	Ar-H (δ, ppm)
110b 	1.24	14.46	125.93	7.33
119b 	1.32	14.80	131.00	7.26
132b 	1.29	15.44	130.98	7.16

* Chemical shifts in ppm was taken by dissolving the three thiacyclophanes together in $CDCl_3$ so as to minimize solvent effect

The above examples demonstrate how difficult and complicated it is to use benzene as an NMR probe to interpret the Mills-Nixon effect. The NMR data for the benzocycloalkene series are affected not only by ring current but also by rehybridization and other factors which make the results complicated and difficult to interpret. The ^1H and ^{13}C chemical shifts and coupling constant data in benzocycloalkenes are affected by both σ-effects (due to ring annelation, hyperconjugation, rehybridization and polarization due to

ring strain) and π-effects (due to ring current of benzene) and other effects such as non-bonding interactions.[115] It is almost impossible to separate all these effects from the π-effect; however, the internal methyl proton chemical shift of DHP depends mostly on the ring current caused by the delocalization of its 14π electrons, and less on other factors, and this makes DHP a better NMR probe molecule compared to benzene for studying ring current effects and hence bond fixation effects. The chemical shifts of the external benzene protons on carbocycloalkene-annelation differ at most by 1 ppm, whereas in DHP, the methyl protons have potentially 5.2 ppm of ring current effect to be perturbed.

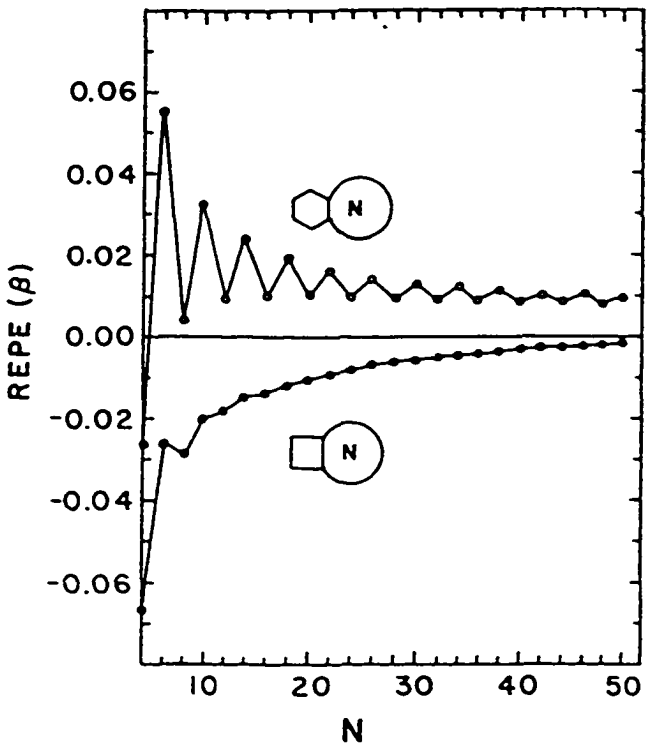
E. DHP as a probe to study the Mills-Nixon effect

In a broad sense, the Mills-Nixon effect can be redefined as a perturbation of the aromatic nucleus induced by fused small rings. Although we do observe a decrease in symmetry (eg.bond lengths) of the aromatic fragment and electronic density redistribution owing to small ring annelation, the bond fixation effect of such perturbations on benzene is by no means significant. This is understandable as benzene has the highest Resonance Energy per π Electron (REPE) in the 4n + 2 family.[116] The cost of bond fixation results in a serious loss of resonance stabilization energy and this is why for many sorts of structural distortion, the benzene nucleus tends to remain aromatic and bond delocalized.

When we examine the plot of Resonance Energy per π Electron (REPE) versus n (no. of π-electrons) (See Figure 27), one striking feature is that as n increases, the difference in REPE between the 4n and 4n + 2 systems approaches zero. In the 4n + 2

family for the [n]-annulenes, REPE constantly decreases as n increases. In other words, it is easier to observe bond fixation in an annulene higher than benzene.

Figure 27 Resonance energy per π electron of [4]annuleno[N]annulenes and [6]annuleno[N]annulenes



Experimentally both benzene and DHP are found to be fully bond delocalized aromatic systems. Because DHP has a smaller REPE it is easier to bond fix than benzene.

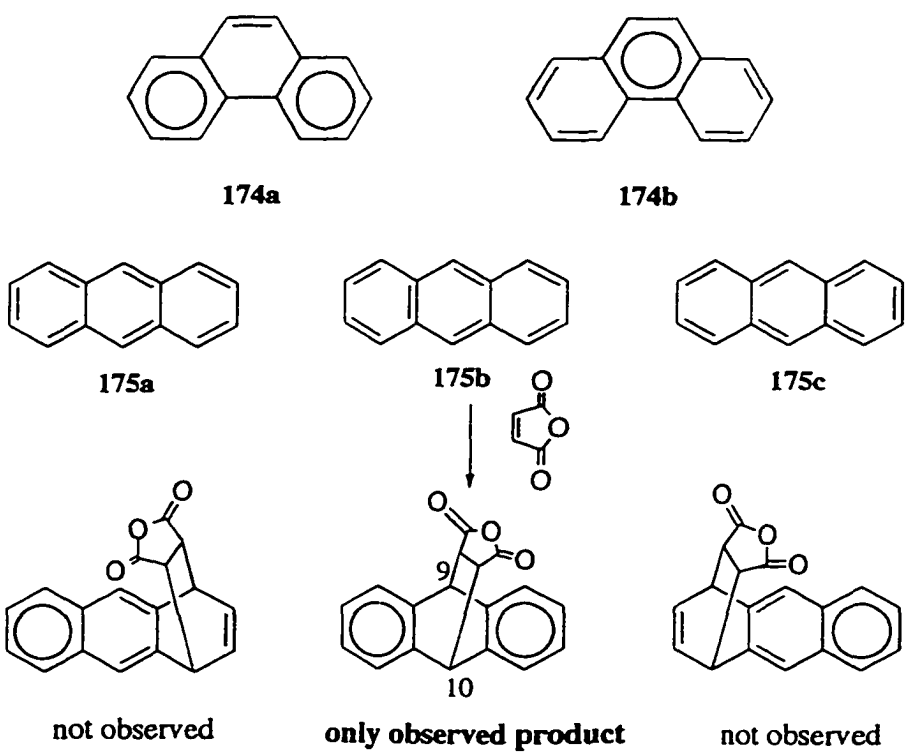
When one annulene is fused to another annulene, an annulenoannulene results. Randic's method of conjugated circults[117] predicts that the aromaticity of all annulenoannulenes is determined by the nature of the fused rings rather than by the size of the periphery. This is also supported by Clar[118] who illustrated two criteria which evidently enhance aromaticity:

I. The greater the *concentration* of aromatic sextets the more important a Clar structure is and the more aromatic is the molecular structure;

II. The greater the *sextet mobility* (of the more important Clar structures, eg., as measured by their number) the more aromaticity is enhanced.

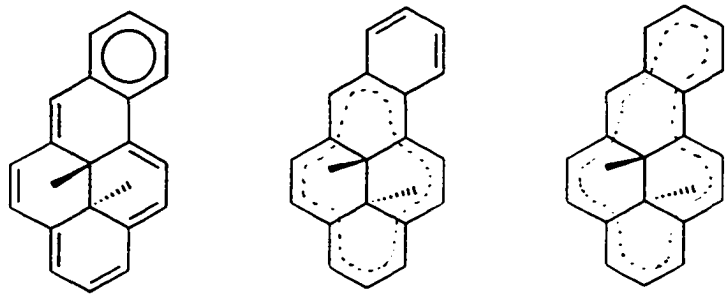
As an example, phenanthrene **174** has two Clar structures **174a** and **174b** (See Figure 28). By rule I, the Clar structure **174a** with a localized double bond in the central ring has more important contribution as it has two aromatic sextets compared to **174b** which has only one. By applying rule II to anthracene **175**, it is also easy to understand why addition reactions of **175** occurs at the central 9,10-positions. Because this gives the maximum number of aromatic sextets.

Figure 28 Clar structures of phenanthrene, anthracene and its cycloaddition adducts



Clar's argument is based on a large mass of empirical data on chemical reacitivitives as well as optical / UV and NMR spectra and states that a 6π-circult is more important than a 10π- or even higher circults.[118] If we examine the Clar structures of the benzo[a]DHP **23a**, **23b** and **23c** (Figure 29), then **23a** with a bond delocalized benzene fused to a bond fixed DHP, should have the biggest contribution, and **20c** should have the smallest contribution.

Figure 29 Clar structures of benzo[a]DHP **23**



23a **23b** **23c**

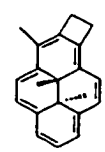
DHP, **9**, is a 14π-annulene, with a virtually planar structure and bond lengths running between 1.38 - 1.40 Å. The chemical shift of its internal methyl protons, δ -4.25, is relatively insensitive to simple substituent effects, but is very sensitive to anything that disturbs the cyclic delocalization of its π-electrons. Compared with its 6π analog, benzene, DHP, **9**, is particularly useful as the chemical shift of its internal methyl protons is a very useful NMR probe and thus might be useful to study the Mills-Nixon effect. Although the cycloalkene annelated benzene derivatives rely heavily on X-ray crystallography to prove the existence of bond fixation, cycloalkene-annelated DHP derivatives can pinpoint any bond fixation simply by the chemical shifts of their internal methyl protons.

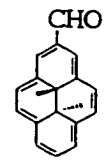
DHP has a larger area and more π-electrons than benzene and thus has a larger ring current. The ring current of benzene deshields its external aryl protons from the acyclic of value 6.14 to 7.24, whereas, that of DHP deshields its external protons from 6.14 to 8.11.[35] More importantly, DHP has an extra internal methyl proton probe, which are shielded by 5.2 ppm by its ring current. It has been demonstrated by Zhou[35,119] that the sensitivity of the internal methyl protons of DHP are 2.7 times more sensitive than the external aryl protons to the ring current.

In order to study the bond fixation effect of cycloalkene and cycloalkenone annelated DHP derivatives, four series of annelated DHP systems were synthesized. They are cycloalkene and cycloalkenone annelated DHPs, dicycloalkene and dicycloalkenone annelated DHPs. Their internal methyl proton chemical shifts, δ(Me), are shown in Tables 7 and 8. For the ease of data comparison, the chemical shift data of some other related DHP derivatives are also listed in Tables 7 and 8. Discussion of this data is in the next chapter, Chapter 4.

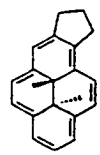
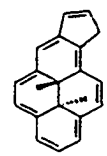
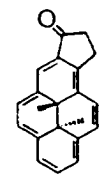
Table 7

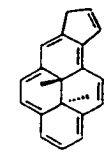
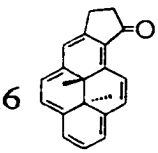
Internal Me proton chemical shifts, δ(Me), of some mono-annelated DHP derivatives


-4.23

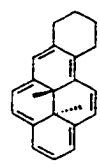
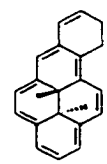
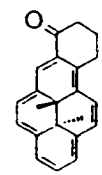
-4.25


-3.93

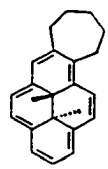
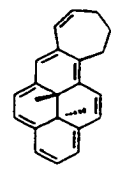
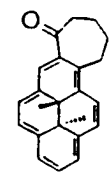

-4.19

-4.07


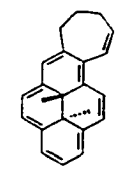
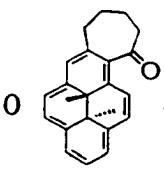
-3.70

-4.16


-3.73


-3.97

-3.91


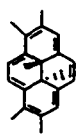
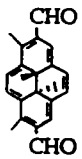
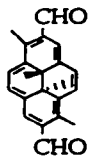
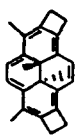
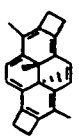
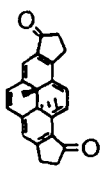
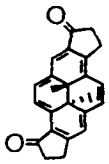
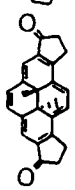
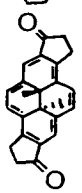
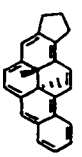
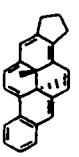
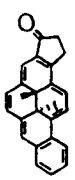
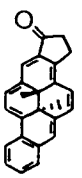
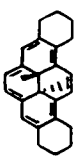
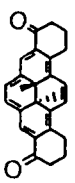
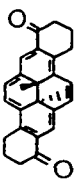
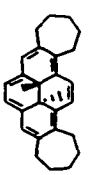
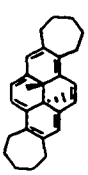
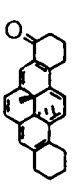
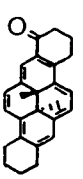
-3.75


-4.21

-4.02


-4.00

-4.10


-4.10

Table 8 : Chemical shifts of dicycloalkene and dicycloalkenone-annelated DHPs

Int. Me, δ(Me) *Cisoid*		Int. Me, δ(Me) *Transoid*		Δδ(Me)	Int. Me, δ(Me) *Cisoid*		Int. Me, δ(Me) *Transoid*		Δδ(Me)
	-4.09					-3.61			
	-4.03		-4.06	0.03		-3.29		-3.49	0.20
	-4.09		-4.21	0.12		-2.89		-3.80	0.91
	-4.12		-4.15	0.03		-2.91		-3.83	0.92
	-1.61		-1.74	0.13		-1.15		-2.20	1.05
	-3.40		-3.98	0.58		-3.05		-3.67	0.62
	-4.13		-4.15	0.02		-3.27		-3.82	0.55

F. Concluding Remarks:

The original Mills-Nixon hypothesis, in a narrow sense, was related to electrophilic substitution reactions at the aryl (Ar) fragment. As the experimental results were interpreted in terms of valence bond (VB) structures, the Mills-Nixon effect has been understood as the preference for one Kekulé structure over the other, and hence some researchers identify the Mills-Nixon effect as π-bond fixation. However, this perturbation has some structural and electronic consequences. In particular, the annelated (ipso) bond is longer whereas the adjacent (ortho) bond is shorter than the predetermined standard.[97] Concomitantly, π-density and the hybridization s-content are shifted from ipso to ortho bonds in harmony with the structural changes.[76] Consequently, **one could define the Mills-Nixon effect in a broad sense as a perturbation of the aromatic nucleus induced by fused small rings.** Results of such perturbation are usually a decrease in symmetry of the aromatic fragment and in electron density redistribution (distortion) leading to structural deformation. For the carbocyclic-annelated benzenoids, ambiguous results were obtained showing distortion but not so obvious that one Kekulé structure was indicated. Our goal is to show that one can detect bond fixation more easily in DHP (a 14π-annulene) than in benzene (a 6π-annulene) and shed some light on this long debated effect.

Chapter 4 Theoretical calculations and experimental results for the annelated DHP compounds

A. Theoretical calculations

The molecular mechanics (MM) or force field method has been shown to be a very reliable, fast, and efficient way of deriving molecular structures, energies and other properties for a wide variety of localized molecules, but unfortunately not so well for annulenes.[120] Since we now have data that can give us bond order values which can be compared with theoretical results, it is interesting to see if theoretical calculations agree with experimental results.

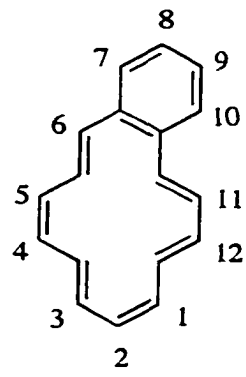
Our group has carried out many theoretical calculations on the DHP system and these are described below with their references. In many cases, the theoretical calculations agree with the experimental results. In some cases, even though the experimental and theoretical results do not agree very well, the trends can still provide us with some useful information. Some successful calculation examples are given below:

1. π-SCF bond order calculations of bond order in some DHPs were calculated and used to derive an empirical equation which describes the relationship between the chemical shift shielding of the internal methyl protons ($\Delta\delta$) and the average deviation of bond order (Δr):

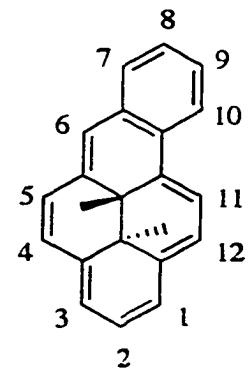
$$\Delta\delta = 5.533 - 27.52\ \Delta r \qquad \text{(Equation 4)}$$

Equation 4 can be used to predict the chemical shifts of benz-annelated DHPs, and generally good agreement is obtained. (< 0.5ppm experimental values).[33]

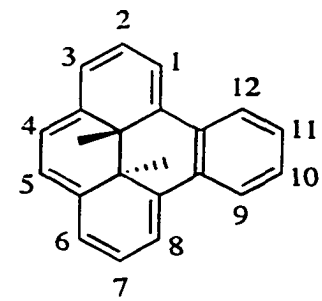
This π-SCF bond order calculation which use Pariser-Parr-Pople (PPP) π-electron theory[121] was also used to predict the chemical shift of a benzo[14]annulene **176** and hence the benzo[a]DHP **23**. Although the calculated $^3J_{uv}$ values (corrected for steric effect) and the experimental $^3J_{uv}$ values are not in excellent agreement, the effect of bond alternation and the localization of the double bond is clearly seen. The bond order (P_{uv}) and the coupling constants ($^3J_{uv}$) data for the benzo[e]DHP **28** are also listed for comparison. (See Table 9)



176



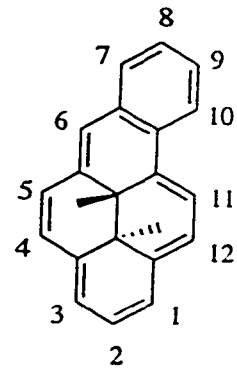
23



28

Table 9 Comparision of the calulated $^3J_{uv}$ and experimental $^3J_{uv}$ values for **23** and **28**

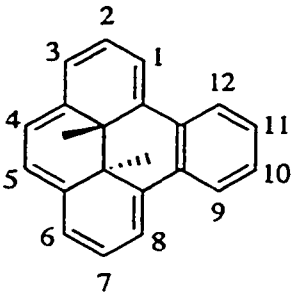
Compound **23**[122]



23

u,v	P_{uv}	$^3J_{uv}$ (calcd.)[a] (Hz)	$^3J_{uv}$ (calcd.) corr. for steric effect (Hz)	$^3J_{uv}$ (exptal) (Hz)
9,10	0.711	7.99	8.29	Not resolved
8,9	0.612	7.04	7.04	Not resolved
7,8	0.713	8.01	8.09	Not resolved
5,4	0.731	8.18	8.27-8.35	8.83
12,11	0.552	6.46	6.76-6.84	6.58
3,2	0.573	6.66	6.74	6.52
2,1	0.717	8.05	8.13	8.85

Compound **28**[123]



28

u,v	P_{uv}	$^3J_{uv}$ (calcd.)[a] (Hz)	$^3J_{uv}$ (calcd.) corr. for steric effect (Hz)	$^3J_{uv}$ (exptal)[b] (Hz)
12,11	0.707	7.95	8.25	8.3
3,2	0.729	8.16	8.24	9.0
2,1	0.550	6.44	6.74	6.8
10,11	0.617	7.09	7.09	6.9

a. $P_{uv}(SCF) = 0.104\ (^3J_{uv}) - 0.120$

b. Because of the limited number of data points, probably ± 0.4 Hz.

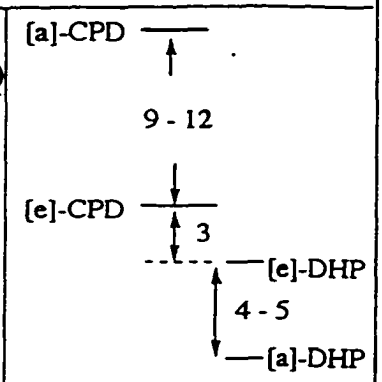
2. During a study on the photoisomerism between the DHPs **23**, **28**, **179**, **181** and the cyclophanedienes **177**, **178**, **180**, **182**, several AM1 and MM2 + pi calculations were made.[122] It has been shown that the DHPs in the [a]-series (**23**, **179**) were more stable than the [e]-series (**28**, **181**) by 4-5 kcal/mole, whereas in the cyclophanedienes, the [a]-series (**177**, **180**) is less stable than the [e]-series (**178**, **182**)

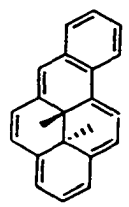
by 9-12 kcal/mole (See Figure 30). After calculation of the relative energies of the [a]- and [e]-series of DHPs, a better understanding of the photoswitchable properties of the [e]-annelated DHPs compared to the [a]-annelated DHPs was obtained.[122] Generally because the [e]-DHPs are close in energy to the [e]-CPDs, they switch more readily.

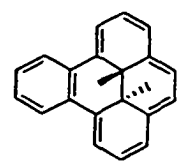
Figure 30 Schematic to show the relative energies of the DHPs and CPDs

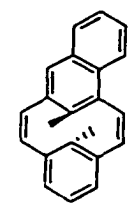
π-SCF/MM2 Values of ΔH_f, ΔSE (strain energy) and ΔπE(Pople π-energy)[122] for the [a]- and [e]-Fused Cyclophanedienes (CPD)s and Dihydropyrenes (DHPs)

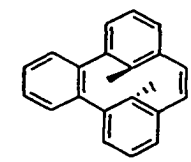
series	compd	ΔH_f (kcal/mol)	ΔSE (kcal/mol)	ΔπE (kcal/mol)
		DHPs		
benzo{[e] - [a]}	**28-23**	+5.34	+3.93	+1.81
naphtho{[e] - [a]}	**181-179**	+4.11	+3.57	+0.56
		CPDs		
benzo{[e] - [a]}	**178-177**	-8.94	-0.19	-9.21
naphtho{[e] - [a]}	**182-180**	-12.42	-0.25	-13.09

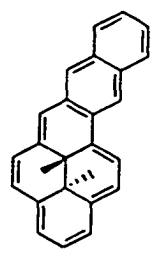


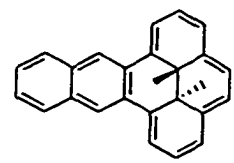

[a]-DHP **23**

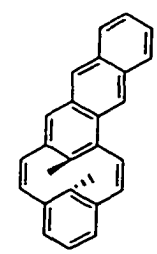

[e]-DHP **28**

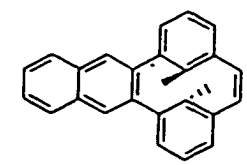

[a]-CPD **177**


[e]-CPD **178**


[a]-DHP **179**

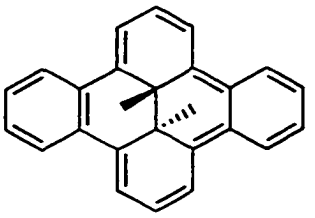

[e]-DHP **181**


[a]-CPD **180**


[e]-CPD **182**

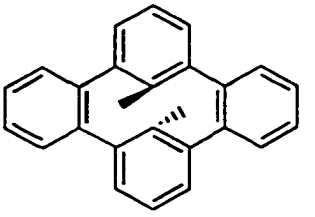
The AM1 calculation also indicated that the H_f value for **183** was 149 kcal/mole and for **184** was 131 kcal/mole (See Figure 31) and thus predicted that in this case, the cyclophanediene **184** should be the more stable isomer. This is consistent with recently published experimental results.[125]

Figure 31 AM1 calculation of the H_f values for **183** and **184**



AM1 (H_f): 149 kcal/mol

183

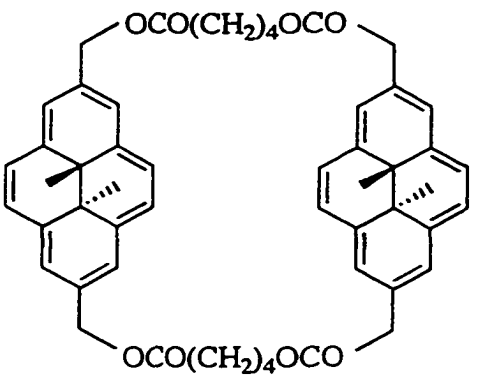


AM1 (H_f): 131 kcal/mol

184

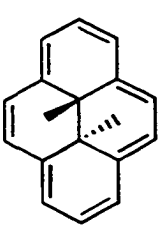
An AM1 calulation based on the relative stability order of the intermediate cations also showed the correct regioselectivity for the electrophilic aromatic substitution of NO_2^+ on DHP, **9**, having a substitution preference order of position 2 > 4 > 3 (H_f =280.2, 286.2, 293.3 kcal/mol, respectively).[124]

3. In order to predict the dynamic conformation of a cyclophane containing two bridged annulene units, compound **185**[126], MM calculations have been carried out. Based on the PCMODEL acquired conformation, the distance between the internal methyl protons of one DHP unit and the edge protons of the other was about 3.8 Å and this demonstrated that the two DHP units could rotate past each other which agreed with the weak NOESY interaction between the aromatic protons of one unit and the internal methyl protons of the other unit.

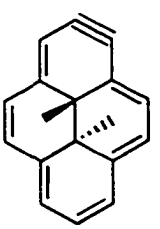


185

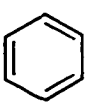
4. An MM calculation on **186** indicated that it is higher in energy than DHP, **9**, by about 80 kcal/mole, (ΔH_f), of which about 30 kcal/mole is strain energy.[127] These values are similar for those of benzyne **187** and benzene, **1**: 87 and 28 kcal/mole, respectively. This consistency was used to suggest a similarity in reactivity between **186** and benzyne **187**.



9



186



1

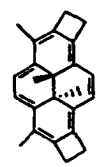
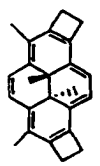
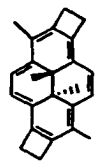
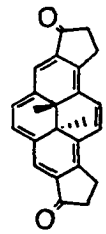
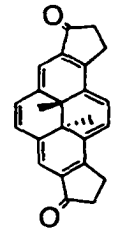
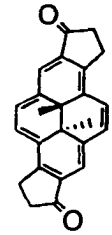
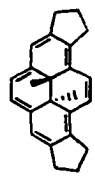
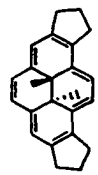
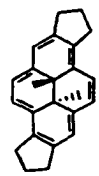
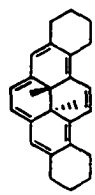
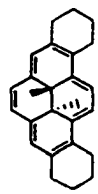
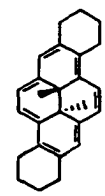
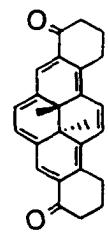
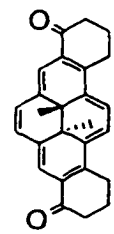
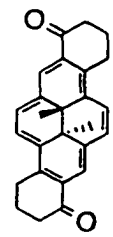
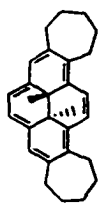
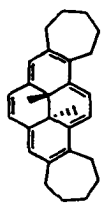
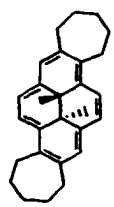
187

Being encouraged by these previous calculational results on DHP systems, we decided to perform PCMODEL and AM1 calculations on our ring annelated DHP systems and compare them with the experimental results. The PCMODEL (MM + π) and

AM1 calculations (ΔH_f and Δ(HOMO-LUMO)) results for some selected ring annelated compounds are tabulated in Tables 10 and 11. PCMODEL generally gives bond delocalized geometries when an MM + π calculation is carried out, unlike AM1, which even for the parent, DHP, **9**, gives a bond localized geometry. Thus for AM1 calculations two starting structures were used with a double bond in the annelated and out of the annelated rings. PCMODEL calculations gave the same geometry starting from either case. For the transoid structures, there is of course only one case due to the symmetry of the molecule.

Based on AM1 calculations of the dicycloalkene annelated DHPs (ring size = 4,5,6,7) (See Table 10), it was noticed that the *cisoid* dicyclobutene- and the dicyclopentene-annelated DHPs gave minima with the "exocyclic" structure while the *cisoid* dicyclohexene- and the dicycloheptene-annelated DHPs showed minima for the "endocyclic" structures. That is similar to results predicted by the Mills-Nixon effect in the benzocycloalkene system.[128] In general, the *transoid* dicycloalkene-annelated DHPs had heats of formation (H_f) and Δ(HOMO-LUMO) values in between those of the two *cisoid* valence isomers, except for the *transoid* dicycloheptene-annelated DHP, which has an H_f value larger than its two *cisoid* isomers. Thus on *cisoid* cycloalkene annelation, there is a preference for one of the Kekulé structures, and whether this is the exocyclic or an endocyclic Kekulé structure *depended on the ring size*. The *transoid* isomers only have two identical Kekulé structures, which have one endocyclic and two exocyclic double bonds.

Table 10 PCMODEL & AM1 calculations of some dicycloalkene- and dicycloalkenone-annelated DHPs

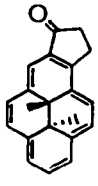
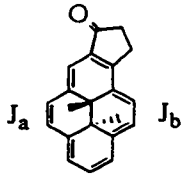
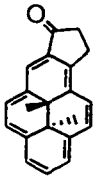
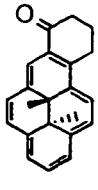
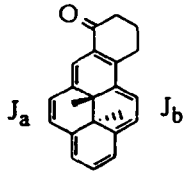
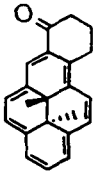
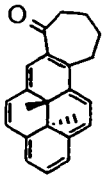
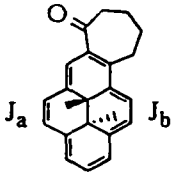
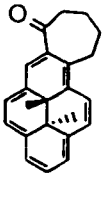
1. H_f (AM1) 2. MM + Pi (PCMODEL) 3. Δ(HOMO - LUMO) (AM1)			1. H_f (AM1) 2. MM + Pi (PCMODEL) 3. Δ(HOMO - LUMO) (AM1)		
					
1. 149.45 2. 92.90 3. 7.333	164.97 93.12 6.708	157.42 92.50 6.858	1. 32.43 2. 52.27 3. 6.967	37.78 52.27 6.745	35.07 52.11 6.816
					
1. 80.60 2. 40.93 3. 7.145	82.92 40.56 6.901	83.23 40.56 6.981			
					
1. 65.94 2. 37.11 3. 7.057	62.41 37.03 7.091	63.42 37.79 7.063	1. 15.76 2. 48.86 3. 6.879	15.01 48.99 6.881	15.30 48.67 6.877
					
1. 60.03 2. 50.22 3. 7.073	59.52 49.99 7.113	63.91 49.46 7.100			

However, when the MM +Pi energy from PCMODEL calculations were used to examine the same series of dicycloalkene annelated DHPs, there was only an insignificant difference in energy between the Kekulé structures of the *cisoid* and the *transoid* isomers. This suggested that **the AM1 calculation may over-emphasize, while the PCMODEL calculation may underestimate the bond alternation effect.** Unfortunately, X-ray structures of the dicycloalkene annelated DHPs were not readily available, and coupling constants did not give us any information on bond fixation, due to the symmetry of the molecules, so we could not comment further.

For the dicycloalkenone-annelated DHPs (ring size = 5,6), the AM1 calculation (Table 10) also indicated that there was a preference for one of the two *cisoid* Kekulé structures. Thus, for the *cisoid* isomer, the exocyclic structure of the dicyclopentenone-annelated DHP has lower energy than the corresponding endocyclic structure, whereas the endocyclic dicyclohexenone-annelated DHP is energetically more favored based on the AM1 H_f values than its exocyclic valence isomer. The H_f and the Δ(HOMO-LUMO) energy for the *transoid* isomers are in between the energy for those of the two *cisoid* Kekulé structures, similar to that observed in the dicycloalkene-annelated DHP series.

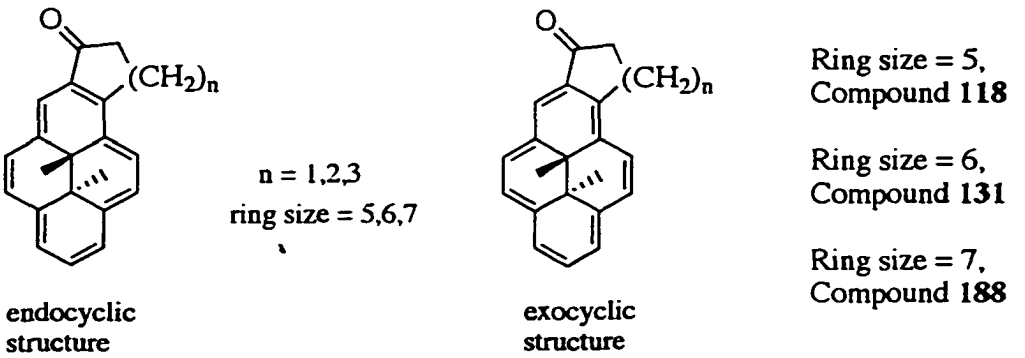
In order to probe the validity of the calculations, the mono-cycloalkenone annelated DHP derivatives, with ring size from 5 to 7, were studied such that the experimental coupling constants could be correlated with the predicted locations of the double bonds. (See Table 11)

Table 11 Theoretical calculations and experimental coupling constants of mono-cyclo-alkenone annelated DHPs **118, 131 and 188**

Starting Structure	PCMODEL (MM + Pi) MMXE	AM1 (H_f)	PCMODEL Δ(HOMO-LUMO)	AM1 Δ(HOMO-LUMO)	Structure suggested by coupling constant
	39.883	70.76	7.157	6.882	 **118**
	39.887	68.14	7.204	7.031	J_a = 8.29 Hz $J_{a(corr)}$ = 8.21 Hz J_b = 7.21 Hz $J_{b(corr)}$ = 6.91 Hz
	38.055	59.19	7.193	6.988	 **131**
	38.065	59.65	7.210	6.996	J_a = 8.15 Hz $J_{a(corr)}$ = 8.07 Hz J_b = 7.73 Hz $J_{b(corr)}$ = 7.43 Hz
	44.357	58.11	7.223	7.083	 **188**
	44.764	57.48	7.103	7.109	J_a = 7.83 Hz $J_{a(corr)}$ =7.75 Hz J_b = 8.03 Hz $J_{b(corr)}$ = 7.73 Hz

When the DHP is mono-cycloalkenone annelated, there are just two Kekulé structures for each ring size. These are referred to as the "endocyclic" and the "exocyclic" structures. (See Figure 32). As shown in Table 11, the PCMODEL calculations (MM + Pi) gave only a single delocalized structure with essentially no difference for the MMX energies or Δ(HOMO-LUMO) energies calculated starting with the endocyclic and exocyclic Kekulé structures of various cycloalkenone annelated DHPs (ring size = 5 ,6, 7). However, the AM1 calculation for the cyclopentenone and cycloheptenone annelated DHPs (**118**, **188**) predicts the exocyclic structure based on the H_f values and the endocyclic structure for cyclohexenone annelated DHP (**131**). There were very small difference in H_f values and Δ(HOMO-LUMO) values based on the AM1 and PCMODEL calculations. Coupling constants, determined experimentally by ^{1}H-NMR, indicated a preference for the endocyclic Kekulé structure (See Table 11) in the three cycloalkenone annelated DHPs **118**, **131** and **188** . Thus, it seems that for the cycloalkeneone annelated DHPs, AM1 calculations gave unclear results, whereas PCMODEL calculations did give the correct Kekulé structures, but this might just come out by chance as there was very little difference in MM + Pi energy between each pair of endocyclic and exocyclic Kekulé structures.

Figure 32 Endocyclic and exocyclic structures of cycloalkenone-annelated DHPs



It is worth emphasizing that although the MM calculations sometimes predict the results or trend correctly, it is dangerous to trust the results completely.

A handicap of the molecular mechanics method lies in the fact that it is an empirical method and, hence, a great amount of accurate data must be available for a given class of compounds before an appropriate force field can be developed. Calculations for the conjugated systems are more challenging than that for the localized system since the former cannot be represented by a single Kekulé form and it is easy to get inaccurate results if a bad data set was chosen. It is also evident that there are systems for which the current MM methods do not work well by simply adding new parameters. These unsatisfactory force field results may be due to special orbital interactions, which may not be described well by a simple π-electron theory.[129] A conjugated delocalized large annulene is a difficult system to paramatize since relatively few accurate results are known. Simple π-electron theory neglects configuration interaction and this can be important in conjugated systems. Thus, AM1 and PCMODEL calculations on DHPs only give us a guide to estimate the geometry and the relative stablilty of any individual structure. There are many factors which may affect the reliabilty of the calculations and therefore, one should be very careful interpreting such data. Based on our experience,[130] for more reliable calculation results for the DHP system, one has to go to ab Initio computations at a higher level such as Density Functional Theory (DFT) or MP2 methods which are not handled well for large molecules by our personal computers at this time.

B. Experimental results on annelated DHP compounds

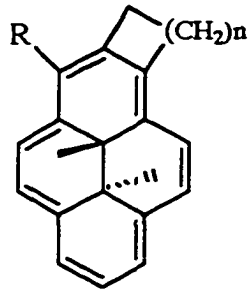
As discussed in Chapter 2, the cycloalkene and cycloalkeneone annelated DHPs were synthesized in order to observe the effect of cycloannelation on the ring current of the DHP, which can indirectly be probed by its internal methyl proton chemical shift. As an NMR probe, DHP should be much better than benzene because the π-system is larger and because the ring current is larger and has an equal effect on all the ring protons, even those distant from the site of annelation which are not perturbed by a geometry change or a local strain effect. In benzene, the probe hydrogens are close to the site of fusion. As well, in the case of DHP, we have the internal methyl protons, which being in the centre of the ring current are strongly shielded and show a large response to delocalization changes, and are empirically less affected by minor geometry changes, and possibly give better indication of the ring current or bond fixation effects.

For the ease of data comparison, the annelated DHP derivatives were separated into four groups. They are mono-cycloalkene annelated DHPs, dicycloalkene-annelated DHPs, mono-cycloalkenone annelated DHPs, and dicycloalkenone-annelated DHPs. Their internal methyl proton chemical shifts δ(Me) are tabulated in Tables 12,13,14 and 16 and are compared below. The data for some acyclic DHP derivatives are also included to demonstrate the ring annelation effect.

For the cycloalkene-annelated DHP series (Table 12), the ring size varies from 4 to 7. Theoretically, it is expected that the four-membered ring which is the most strained should show the strongest bond fixation effect, whereas the six-membered ring is almost strain free and is expected to have the least bond fixation effect. Experimentally, to our surprise, it is observed that the six-membered ring has the strongest π-bond alternation

Table 12 Internal methyl proton chemical shifts for some cycloalkene-annelated DHPs

Compound	$\delta(Me)_X$	$\Delta\delta(Me) = \delta(Me)_X - \delta(Me)_{DHP}$ = deshielding effect of ring (ppm)
DHP, **9**	-4.25	0
4DHP, **43**	-4.23	0.02
5DHP, **64**	-4.19	0.06
6DHP, **130**	-3.97	0.28
7DHP, **189**	-4.21	0.04



R=Me, n=1 compound **43**
R=H, n=2 compound **64**
R=H, n=3 compound **130**
R=H, n=4 compound **189**

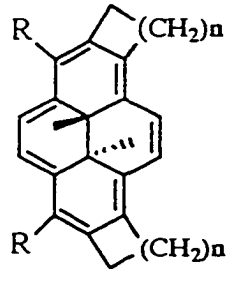
effect on DHP ($\Delta\delta$(Me) for **130** = 0.28 ppm) and the four-membered ring has the smallest bond fixation effect ($\Delta\delta$(Me) for **43** = 0.02 ppm). This suggests that ring strain is not the most important factor in bond fixation in the DHP system.

For the dicycloalkene-annelated DHP series (Table 13), the ring size varies from 4 to 7. It is expected that the [a,h]-diannelated (*transoid*) compounds should have their ring-strain effects counteract each other, whereas the [a,i]-diannelated (*cisoid*) compounds should experience an amplified ring-strain effect. In this series of dicycloalkene-annelated DHPs, the *cisoid* and *transoid* dicyclobutene-annelated DHPs **44a** and **44b** were reported in 1984 by Mitchell[37] and he demonstrated that the four-membered rings had negligible bond fixation effect on DHP. This was supported by a very small difference in internal methyl proton chemical shift Δδ(Me) between the *cisoid* and the *transoid* isomers of 0.12 ppm which corresponded to a maximum average bond-order deviation of 0.0044 from those of DHP. When the ring size changes from five to four to six, there is an increase in the chemical shift difference Δδ(Me) between the *cisoid* and the *transoid* isomers from 0.03 to 0.12 and then 0.58 ppm. The *cisoid* and *transoid* dicyclohexene-annelated DHPs **123a** and **123b** have the biggest difference in Δδ(Me) of 0.58 ppm. This is consistent with the mono-cycloalkene annelated DHP results which demonstrates that *the cyclohexene ring, when fused to DHP, has the strongest bond fixation effect*. When the ring size was further increased from a six to a seven-membered ring, as in the *cisoid* and *transoid* dicycloheptene-annelated DHPs **136a** and **136b**, the Δδ(Me) value drops significantly to 0.02 ppm, which implies that the cycloheptene ring has the weakest bond fixation effect in this series and both of its cisoid an transoid isomers are close to bond delocalized. Another interpretation is that only the six-membered ring has any effect and the ring strain effect is once again confirmed **NOT** to be the major factor in bond fixation.

Table 13 Internal methyl proton chemical shifts for some dicycloalkene-annelated DHPs

Compound[a]	δ(Me)x cisoid	Compound[a]	δ(Me)x transoid	Δδ(Me) between cisoid and transoid (ppm)
DHP, **9**	-4.25	DHP, **9**	-4.25	N.A.
c Me_4DHP, **142a**	-4.03	t Me_4DHP, **142b**	-4.06	0.03
c 44DHP, **44a**	-4.09	t 44DHP, **44b**	-4.21	0.12
c 55DHP, **41a**	-4.12	t 55DHP, **41b**	-4.15	0.03
c 5benzDHP,**148a**	-1.61	t 5benzDHP,**148b**	-1.74	0.13
c 66DHP, **123a**	-3.40	t 66DHP, **123b**	-3.98	0.58
c 77DHP, **136a**	-4.13	t 77DHP, **136b**	-4.15	0.02

a Apart from the ordinary numbering of compounds, code (c,t,a number,Me,benz) placed in front of DHP were used for the ease of identifying the compounds.
c = cisoid; t = transoid; the number in front of DHP stands for the size of the annelated ring; Me stands for a methyl group on DHP and benz stands for a benzene ring.



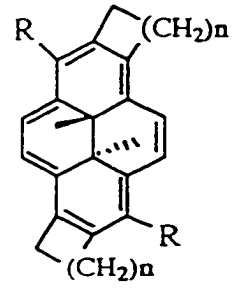
Cisoid dicycloalkene-annelated DHP

R=Me, n=1 compound **44a**

R=H, n=2 compound **41a**

R=H, n=3 compound **123a**

R=H, n=4 compound **136a**



Transoid dicycloalkene-annelated DHP

R=Me, n=1 compound **44b**

R=H, n=2 compound **41b**

R=H, n=3 compound **123b**

R=H, n=4 compound **136b**

In order to estimate the substitution effect in the dicycloalkene-annelated DHPs, the acyclic tetra-substituted DHPs **142a** and **142b** were synthesized. It was observed that the steric effect when the four methyl groups of **142** were arranged in a *cisoid* or *transoid* manner caused only a small difference in δ(Me) (0.03 ppm). This steric effect is comparable with the ring strain effect induced by a five and a seven-membered ring. On the basis of the results of the mono-cycloalkene and the dicycloalkene annelated DHPs, we observe that when the ring size varies from 4 to 7, *only the six-membered ring has any significant bond fixation effect on DHP.*

For the mono-cycloalkenone annelated DHPs, with ring size varying from 5 to 7 (See Table 14 and 15), it is noted that the degree of bond fixation (reflected by δ(Me) and $J_a - J_b$ (See Table 11)) decreases as ring size increases. Thus, the cyclopentenone-annelated DHP **118** has the strongest bond fixation effect (Δδ(Me) = 0.55ppm, J_a-J_b =1.08Hz; J_a-$J_{b(corr.)}$ = 1.30Hz), whereas, the cycloheptenone annelated DHP **188** is close to bond delocalized (Δδ(Me)=0.25ppm, J_a-J_b=0.2Hz; J_a-$J_{b(corr.)}$ = 0.02Hz). In this series of compounds, the coupling constants along the DHP periphery were able to be determined and it was shown that an "endocyclic" Kekulé structure was preferred in all cases (See Table 11). The experimental coupling constants may require correction for a steric effect of a naphthalene type for J_a and phenanthrene type for J_b, and these data are also shown in Table 15.

Table 14 Internal methyl proton chemical shifts for some cycloalkenone-annelated DHPs

Compound [a]	δ(Me)x	Deshielding effect of ring and ketone group (ppm) [b]	deshielding effect of ketone group [c]	dihedral angle between the C=O group and DHP (From PCMODEL)
DHP	-4.25	N.A.	N.A.	N.A.
5ketoDHP, **118**	-3.70	0.55	0.49	2.2°
6ketoDHP, **131**	-3.75	0.50	0.22	11.8°
7ketoDHP, **188**	-4.00	0.25	0.21	64.8°
2formDHP, **45**	-3.92	N.A.	0.33	N.A.
2acetDHP, **190**	-4.03	N.A.	0.22	N.A.

[a] codes (a number, keto, form & acet) placed in front of DHP were used for the ease of identifying the compounds: the number in front of DHP stands for the size of the annelated ring; keto stands for carbonyl group in the ring, form stands for a formyl group and acet stands for an acetyl group

[b] Deshielding effect of ring and ketone group: $\Delta\delta(Me) = \delta(Me)_X - \delta(Me)_{DHP}$

[c] Deshielding effect of ketone group = Δδ(Me) - deshielding effect of the annelated ring (From Table 12)

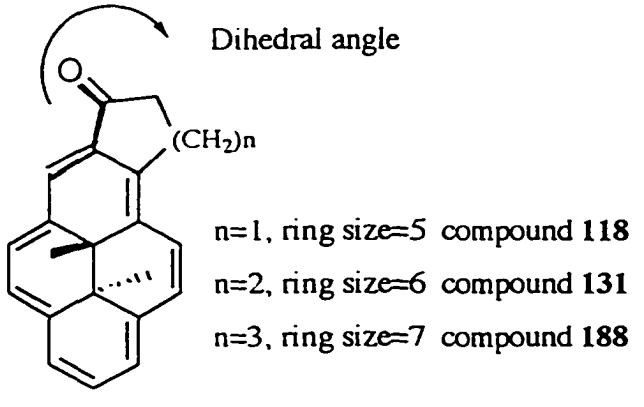
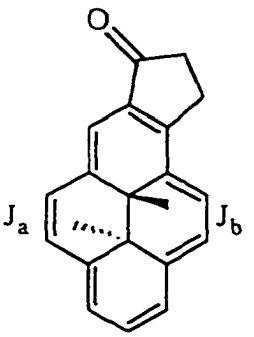
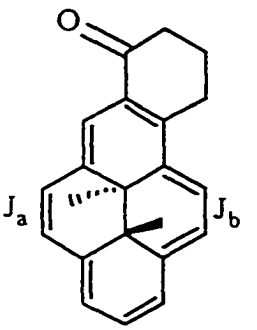


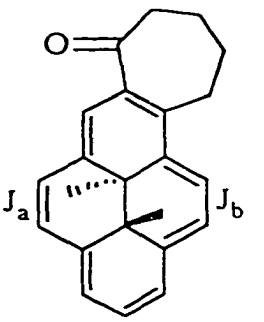
Table 15 Chemical shifts and coupling constants for compound **118**, **131** & **188**



118



131



188

Compound	$\delta_{Me}(x)$ (ppm)	$\Delta\delta_{Me}$ (ppm)	J_a (Hz)	J_b (Hz)	$J_a - J_b$ (Hz)	J_a (corr)[1] (Hz)	J_b (corr)[2] (Hz)	$J_a - J_{b(corr)}$ (Hz)
118, r = 5	-3.70	0.55	8.29	7.21	1.08	8.21	6.91	1.30
131, r = 6	-3.75	0.50	8.15	7.73	0.42	8.07	7.43	0.64
188, r = 7	-4.00	0.25	7.83	8.03	0.20	7.75	7.73	0.02

1. J_a needs a naphthalene type correction: J_a (corr) = J_a - 0.08 Hz

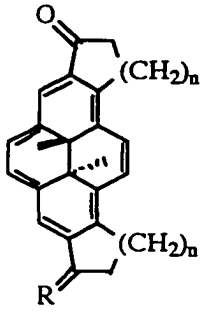
2. J_b needs a phenanthrene type correction: J_b (corr) = J_b - 0.30 Hz

In Table 16, the small difference in $\Delta\delta$(Me) for **143a** and **143b** (0.20ppm) compared with that of compounds **42**, **124** and **125** also demonstrated the unique role of the effects of the ring and the carbonyl group on bond fixation. For the

Table 16 Internal methyl proton chemical shifts for some dicycloalkenone-annelated DHPs

Compound [a]	$\delta(Me)_X$ cisoid	Compound	$\delta(Me)_X$ transoid	$\Delta\delta_{Me}$ between cisoid and transoid (ppm)
DHP, **9**	-4.25	DHP, **9**	-4.25	N.A.
c Me_2form_2DHP, **143a**	-3.29	t Me_2CHO_2DHP, **143b**	-3.49	0.20
c 55diketoDHP, **42a**	-2.91	t 55diketoDHP, **42b**	-3.83	0.92
c 5keto,benzDHP, **149a**	-1.15	t 5keto,benzDHP, **149b**	-2.20	1.05
c 66monoketoDHP, **125a**	-3.27	t 66monoketoDHP, **125b**	-3.82	0.55
c 66diketoDHP, **124a**	-3.05	t 66diketoDHP, **124b**	-3.67	0.62

a Apart from the ordinary numbering of compounds, codes (c,t,a number,Me,keto,benz, Form) placed in front of DHP were used for the ease of identifying the compounds. c = cisoid; t = transoid; the number in front of DHP stands for the size of the annelated ring; keto stands for carbonyl group in the ring; Me stands for a methyl group on DHP and benz stands for a benzene ring; form stands for CHO group on DHP.

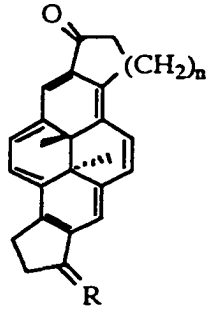


Cisoid dicycloalkenone-annelated DHP

n=1, R=O compound **42a**

n=2, R=O compound **124a**

n=2, R=H_2 compound **125a**



Transoid dicycloalkenone-annelated DHP

n=1, R=O compound **42b**

n=2, R=O compound **124b**

n=2, R=H_2 compound **125b**

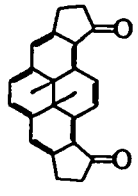
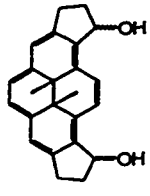
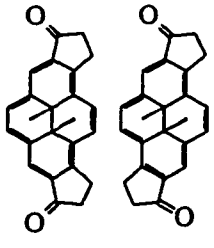
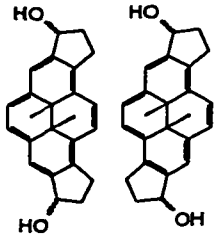
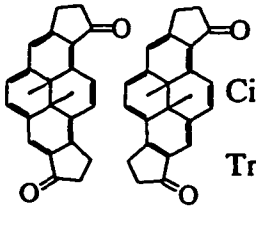
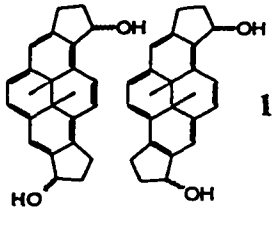
dicycloalkenone annelated DHPs, with ring size varying from 5 to 6 (Table 16), it is found that there is a bigger difference in internal methyl proton chemical shifts between the *cisoid* and *transoid* isomers for the dicyclopentenone-annelated DHPs **42a** and **42b** than that of the dicyclohexenone-annelated DHPs **124a** and **124b**. This result is also in good agreement with that of the mono-cycloalkenone annelated DHP series which implies that *the coplanarity of the carbonyl group has an effect on bond fixation.*

To confirm the unique role of the carbonyl group in bond fixation, the diketones **63**, **42** and **70** were reduced to their dialcohols. In the ketones, there was a large difference in $\Delta\delta$(Me) between the *cisoid* and the *transoid* diketones ($\Delta\delta$(Me) ~0.9 ppm); whereas, after reduction to the alcohols, the difference in $\Delta\delta$(Me) between the *cisoid* and *transoid* dialcohols was substantially reduced (See Table 17). The dialcohols **150**, **152** and **153** have their internal methyl proton chemical shifts δ(Me) all clustered between δ -3.98 to -4.25 which indicates almost no bond fixation when compared to that of DHP **9**, at δ -4.25.

The bond fixation effect of a carbonyl group in the ring is considerably larger than that of the ring strain effect alone. Attempts have been made to separate the bond fixation effect of a carbonyl group and the ring strain effect (See Table 14). It seems that the bond fixation effect of the carbonyl group depends on the coplanarity of it with the π-system of DHP. Thus, the five-membered ring ketone **118**, which has the smallest average dihedral angle between the carbonyl group and the DHP, shows the strongest bond fixation effect (0.49 ppm), whereas, the six and seven-membered ring ketones **131** and **188**, which have larger dihedral angles, show much smaller bond fixation effects

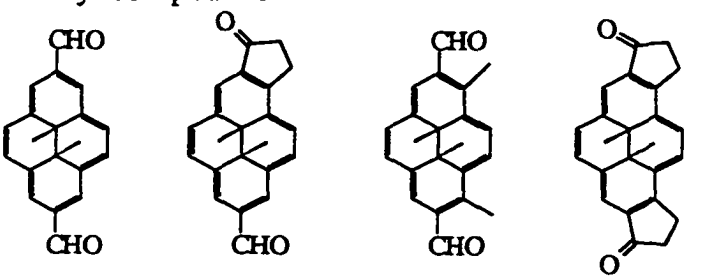
(0.22 and 0.21 ppm).

Table 17 Internal methyl proton chemical shifts, δ(Me), for some selected diketones and dialcohols

Diketone	Int. Me δ(Me), ppm	Dialcohol	Int. Me δ(Me), ppm
 Cisoid **62**	-2.92	 **150**	-3.98 to -4.25
 Cisoid **42a** Transoid **42b**	-2.91 -3.83	 **153**	-4.03 to -4.22
 Cisoid **70a** Transoid **70b**	-2.89 -3.80	 **152**	-3.99 to -4.20

To illustrate further the effect of the coplanarity of the carbonyl group on the bond fixation, the internal methyl proton chemical shifts of several carbonyl compounds are compared in Figure 33. The dialdehyde **58**[43], with its aldehyde freely rotating, has the least bond fixation effect as indicated by its most shielded internal methyl protons (δ -3.61). When one of the carbonyl groups is locked in a five membered ring, as in **191**, its internal methyl protons become less shielded (δ -3.37) due to the conjugation of the ketone group and the π-system of DHP. Relative to **58**, the coplanarity of the carbonyl group is changed in **143a** and **42a**, where the internal methyl protons become even less shielded probably due to better conjugation. Compound **42a**, with both five membered rings holding the two carbonyl groups in a planar position with the π-system, exhibits the strongest bond fixation effect due to extended conjugation.

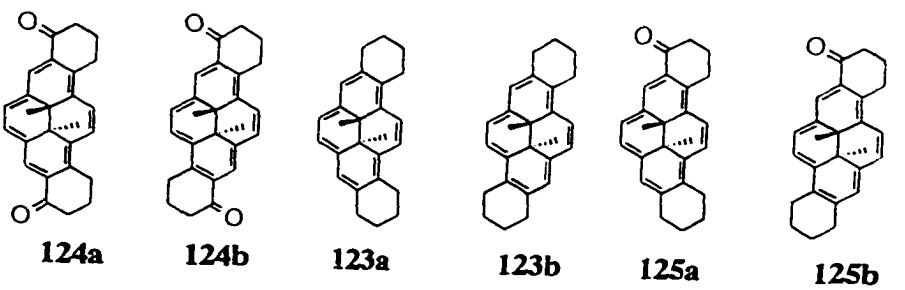
Figure 33 Internal methyl proton chemical shifts, δ(Me), for some selected carbonyl compounds



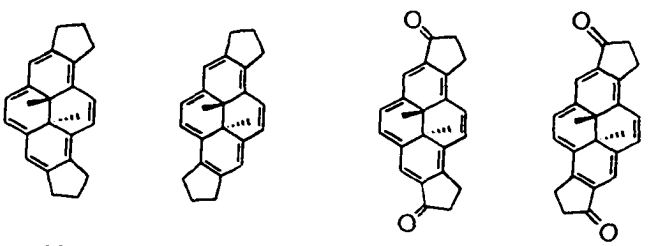
Int. Me δ(Me), ppm	**58** -3.61	**191** -3.37	**143a** -3.29	**42a** -2.91

For the diannelated DHPs (See Tables 13 and 16), it is also worth noting that the difference in internal methyl proton chemical shifts between the *cisoid* and the *transoid* isomers of the dicyclohexenone-annelated DHPs **124** and the dicyclohexene-

annelated DHPs **123** have very similar values (0.62 and 0.58 respectively). The difference in internal methyl proton chemical shifts between the *cisoid* and *transoid* isomers of the mono-ketone **125** and the diketone **124** also have a similar value of $\Delta\delta$(Me), δ 0.62 for **124** and δ 0.55 for **125**. One can conclude that in six-membered ring annelated DHPs, with or without an α-ketone, the bond fixation effect does not depend much on the carbonyl group but instead on the six-membered ring itself. In contrast, in the five membered ring series, the ketone containing annelated derivatives **42** show the strongest bond fixation effect ($\Delta\delta$(Me)=0.92ppm), indicates that *for the five-membered ring annelated DHPs, the coplanarity of the carbonyl group with the DHP ring is one of the major factors which causes bond fixation.*



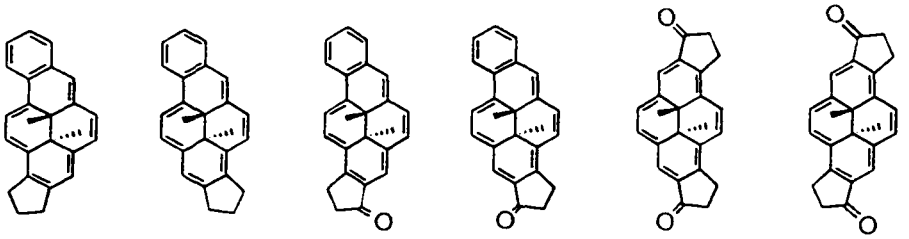
124a **124b** **123a** **123b** **125a** **125b**



41a **41b** **42a** **42b**

C. Effect of unsymmetrical fusion of a benzene and a five-membered ring on DHP

During our synthesis of diannelated DHPs, we were interested to see the effect of unsymmetrical fusion of a benzene and a five-membered ring on DHP. It turns out that the fusion of a five membered ring does not enhance the bond fixation effect of a benzene ring. The difference in internal methyl proton chemical shifts, Δδ(Me), is 0.13 ppm for *cisoid* **148a** and *transoid* **148b** (See Table 13). This is just slightly larger than the Δδ(Me) value for **41a** and **41b** (0.03 ppm) . When **148** was oxidized to the monoketone **149**, the Δδ(Me) between the *cisoid* **149a** and *transoid* **149b** was much enhanced as compared with that of compound **148** (See Table 16). The difference in chemical shifts for the *cisoid* **149a** and *transoid* **149b** is almost the same as that between *cisoid* **42a** and *transoid* **42b**.

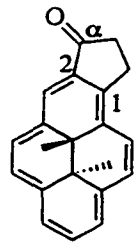
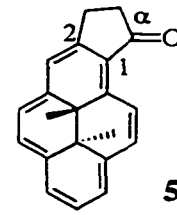
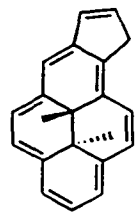
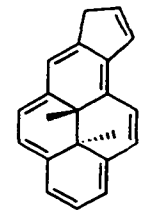
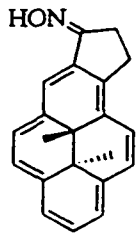
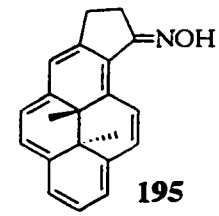
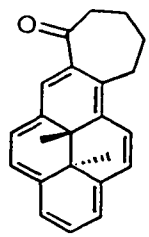
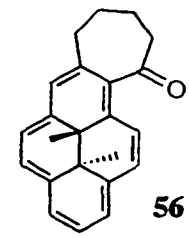
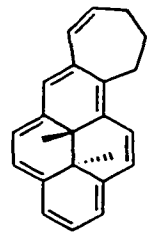
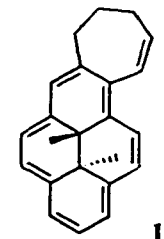


148a **148b** **149a** **149b** **42a** **42b**

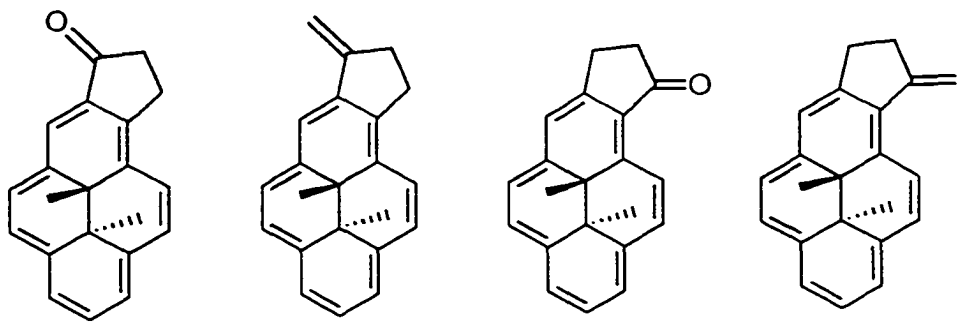
D. Effect of the position of functional group on the chemical shift of DHP

In the mono-annelated DHPs, a series of compounds with functional groups positioned at the benzylic positions of DHP was prepared. Those functional groups include a carbonyl group , an alkene and an oxime and are shown in Table 18. In general, it can be seen from Table 18 that the functional group located α to the 2-position of DHP is slightly more deshielding than that located α to the 1-position of DHP. The carbonyl group has a stronger deshielding effect than an oxime and this is in turn more deshielding than an alkene. The coplanarity of the carbonyl group with the π-electrons of the DHP has a fairly significant effect on the internal methyl proton chemical shifts. Thus, the more coplanar cyclopentenone annelated dihydropyrenes **118** and **50** are more deshielded than that of the less coplanar cycloheptenone annelated dihydropyrenes **188** and **56**. In Stanger's paper[102], he mentioned that small ring annelated system such as benzocyclopropene and benzocyclobutene compensate the imposed strain by forming "banana" bonds and in order to observed bond fixation in benzene, one had to incorporate sp^2 carbons at the strained positions. These, however, might participate in the π-conjugation, and thus a conjugation effect could not be ruled out. Therefore, one needs an experimental system that has sp^2 carbons at strained conjugated positions that do not participate in the π-conjugation.[102] Realistically, such a system is difficult to find. For all the mono-annelated DHP derivatives (See Table 18), there is at least one sp^2 center in the strained annelated ring. However, it seems that only those sp^2 centers that form a carbonyl group or an oxime group can induce bond fixation whereas the sp^2 center of the alkene has no strong

Table 18 Effect of the regiochemistry of the functional group on the internal methyl proton chemical shifts δ(Me) of some selected DHPs

	δ(Me), (ppm)		δ(Me), (ppm)
 **118**	-3.70	 **50**	-3.73
 **192**	-4.07	 **193**	-4.16
 **194**	-3.79	 **195**	-3.86
 **188**	-4.00	 **56**	-4.10
 **196**	-4.02	 **197**	-4.10

perturbation on the aromatic π-delocalization. Therefore, Stanger's speculation about enhanced bond fixation by incorporation of sp^2 carbons at strained ring is not totally correct. Possibly the strain effect of a sp^2 center can only be observed when it is located at the exocyclic rather than endocyclic position of the ring. However, this statement cannot be proved correct or wrong until the synthesis of compound **198** and **199**, which has a methylene group replacing the carbonyl group in compound **118** and **50**. We attempted the synthesis of both **198** and **199** but failed.



118 **198** **50** **199**

E. Can the Mills-Nixon effect be observed in the DHP (a 14-π annulene) system?

Before making any conclusions as to whether or not the Mills-Nixon effect can be observed in the DHP system, it is necessary to re-address the definition of the Mills-Nixon effect. In our opinion, we think that it is suitable to define the Mills-Nixon effect in a broad sense as **any non 4n or 4n+2 π ring annelation effect which causes geometry distortion and π-bond fixation (alternation) of the aromatic perphery or its π-system.** Traditionally, only carboalkene and carboalkenone

annelations were involved in discussions of the Mills-Nixon effect. As there are now growing numbers of examples of other ring annelation effect which demonstrate bond fixation, those ring annelation effects should also be considered as Mills-Nixon effects. Examples of such ring annelations include bicyclic systems such as norbornane and 7-oxanorbornane and heterocycles. However, Siegel considers that none of these should be called Mills-Nixon effects, rather bond localization effects.[87]

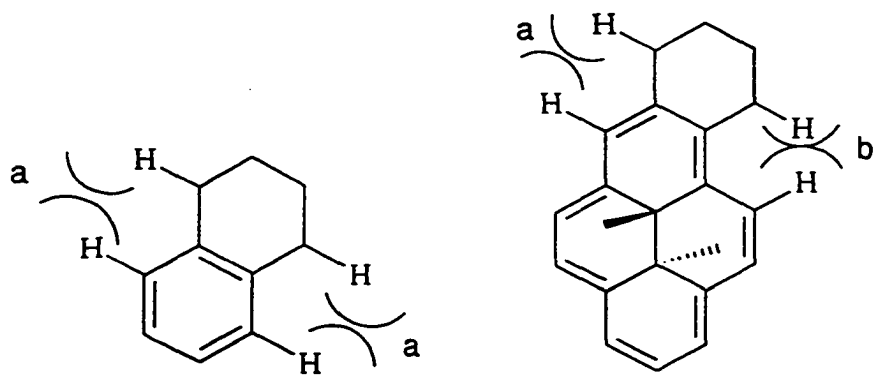
Our studies on the annelation of the DHP system revealed that the bond fixation effect in the mono-cycloalkene series is based on ring size and is 6 > 5 ~ 7 ~ 4 while that for the dicycloalkene annelation is 6 > 4 > 5 ~ 7 (See Tables 12 and 13). For both types of annelation, it is obvious that **the six-membered ring has the strongest bond fixation effect**. As the dicycloalkene annelation should amplify the effect of bond fixation when compared with mono-cycloalkene annelation, the bond fixation effect from the dicycloalkene annelation should be more reliable and hence *the bond fixation effect of cycloalkene annelation on DHP based on ring size is therefore in the order* 6 > 4 > 5 ~ 7.

From the chemical shift data of mono- and dicycloalkenone annelated DHPs (Tables 14 and 16), the bond fixation effect based on ring size was established as 5 > 6 > 7. It is worth mentioning that for the cycloalkenone annelated DHPs, the bond fixation effect is not only due to the ring size but also due to the coplanarity of the carbonyl group with the aromatic π-system and the position of the carbonyl group.

Results obtained for benzoalkenes are different from those for cycloalkene-annelated DHPs. In the benzocycloalkene series, the benzocyclopropene has the most significant effect on the geometry change at the ring junction and the chemical shift of the protons and carbons in benzene. On the contrary, the cyclohexene-annelated DHPs have the most significant bond fixation effect observed in the cycloalkene-annelated DHP series.

The choice of the aromatic compound to study bond fixation effects is important. DHP with its smaller REPE compared to benzene appears from our results to bond fix more readily and this is a better choice for the study. Thus, **the Mills-Nixon effect does not only depend on the size of the annelating ring but also depends on the nature of the aromatic compound.** Geometrically, there is a big difference between benzene and DHP. Benzene is a monocyclic molecule while DHP is a polycyclic molecule. On ring annelation, they have different modes of ring proton and aromatic proton interaction. For benzocycloalkenes, there is only one type of ring proton and aromatic proton interaction, which is called the naphthalene type interaction. (See Figure 34). On the other hand, when DHP is cycloalkene-annelated, on top of the weaker naphthalene type interaction, there are also much stronger phenanthrene type interaction. The phenanthrene type interaction may induce greater distortion and affect the π-orbital overlap more. The ring system may change its conformation such that a stronger hyperconjugation between the σ bond of the annelated ring and the aromatic π-system results.[131a,b]

Figure 34 Ring-H and Ar-H interaction for benzocycloalkenes and cycloalkene-annelated DHPs



Different modes of aromatic proton and ring proton interaction
a. Naphthalene type interaction
b. Phenanthrene type interaction

In conclusion, our "Mills-Nixon effect" is not only a ring strain effect. In our study on the annelated DHP compounds, the "Mills-Nixon effect" is a complicated effect which depends on the ring size, the coplanarity between the carbonyl group and the aromatic π-system (for the cycloalkenone annelated aromatics) and the nature of the aromatic ring. The ring size alone needs further explanation. The Mills-Nixon effect does not simpily depend on the ring size, which induces angle strain and then bond fixation. The conformation of the ring, the bond length distortion, the bond angle distortion, the torsional strain, the ring proton and aromatic proton interaction (non-bonded interaction), the energy changes due to a rehybridization and the hyperconjugation between the σ-bond of the annelated ring and the π-electron of the aromatic system should all be taken into consideration when the Mills-Nixon effect is being discussed.

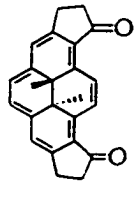
Chapter 5 Conclusions and future work

A. Conclusions

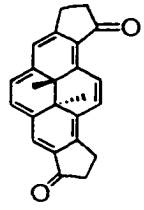
1. Probing the Mills-Nixon effect using DHP (See next page for structures)

The syntheses of many cycloalkene and cycloalkeneone annelated DHPs have been achieved. A late ring formation approach was used to synthesize the dicycloalkeneone annelated DHP **63** (Scheme 4) and the unsymmetrical dicycloalkeneone annelated DHPs **70a** and **70b** (Scheme 5). To synthesize the other ring annelated DHPs, a more versatile early ring approach was employed. Through an asymmetrical coupling followed by a series of standard transformations, the cyclopentene-, cyclohexene-, cyclopentenone- and cyclohexenone-annelated DHPs **64**, **118**, **130**, **131** were synthesized (Schemes 13 and 15). Similarily, the dicycloalkene and dicycloalkenone annelated DHPs such as **41**, **42**, **123**, **124** and **136** were obtained by a symmetrical coupling followed by a series of standard transformations (Schemes 12, 14 and 16).

Other than the cycloalkene or cycloalkenone annelated DHPs, the acyclic tetra-substituted DHPs **142** and **143** (Scheme 17) were also synthesized as model compounds. As well, the asymmetrical DHPs **148** and **149** (Scheme 18), having a benzene and a cyclopentene annelation or with a benzene and a cyclopentenone annelation, were also synthesized to test the annelation effect with a combination of a benzene and a five-membered ring.



63



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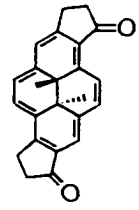
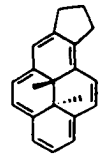


70b



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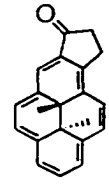

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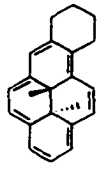

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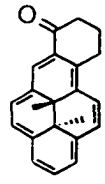

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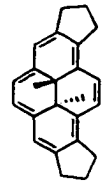

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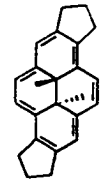

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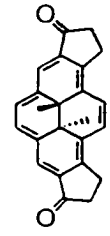

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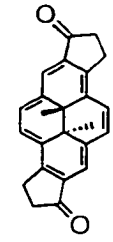

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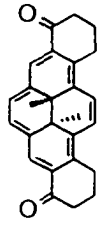

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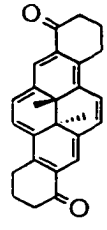

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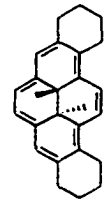

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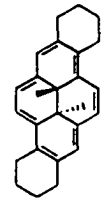

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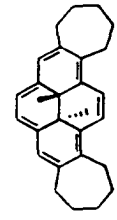

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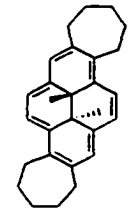

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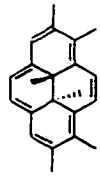

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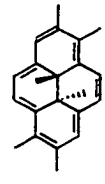

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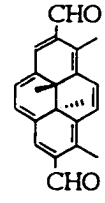

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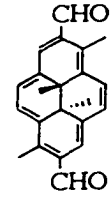

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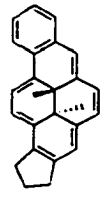

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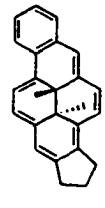

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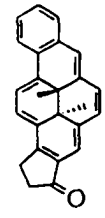

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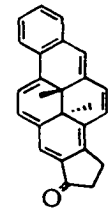


149b

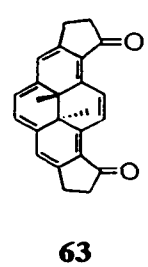
In the cycloalkene and cycloalkenone annelated DHP series, it was demonstrated that the π-bond fixation effect could be indirectly probed by the internal methyl proton chemical shifts. These are based on the ring current of DHP and the magnitude of bond fixation depends on the annelating ring size, the coplanarity of the carbonyl group with the π-system of DHP (for the cycloalkenone annelated DHPs) and the relative arrangement of the annelated rings (*cisoid* versus *transoid* for the diannelated compounds). Thus, when the ring size varied from four to seven in the cycloalkene- and dicycloalkenene annelated DHP series, the cyclohexene ring has the strongest bond fixation effect. When the ring size varied from five to seven in the cycloalkenone- and the dicycloalkenone-annelated DHP series, the cyclopentenone annelated DHPs have the strongest bond fixation effect. In the mono-cycloalkenone annelated DHP series (ring size =5 to 7), the Kekulé structures of the cycloalkenone annelated DHPs were determined by the vicinal coupling constant ($^3J_{HH}$) to adopt an endocyclic structure (the double bond appears at the ring junction between the DHP and the annelating ring). For the diannelated DHP derivatives, the *cisoid* arrangement of ring annelation always has a stronger bond fixation effect compared to that of a *transoid* arrangement in almost all cases.

In this thesis work, the use of DHP as a sensitive NMR probe was successfully demonstrated in that its internal methyl proton chemical shift responds to a change of ring current caused by different ring annelations. It is so sensitive, that even the very small perturbation on ring annelation (by cycloalkanes) can be sensed. DHP is a better NMR probe molecule than benzene because the chemical shifts of the internal methyl protons of DHP are less seriously affected by any effects such as geometrical distortion, rehybridization, steric compression, hyperconjugation and through space effects as probed

by the ^{1}H and ^{13}C-NMR spectroscopies in benzocycloalkenes. The ring annelation effect probed by DHP is closer to a pure π-effect due to a change in ring current which is different from benzene, which is a mixture of both σ- and π-effects.

2. Synthesis of dicyclopentadiene dianions and their metal complexes

In this work, different dicyclopentenone-annelated DHPs **63**, **42** and **70**, were synthesized and attempts had been tried to convert them to the dicyclopentadienyl-annelated DHP **40** or its isomers. Among the five diketones prepared, only the asymmetrical diketones **70a** and **70b** could both be reduced and eliminated to the neutral dicyclopentadienyl annelated DHP ligands **40a** and **40b.** The synthesis of diketones **70** required six steps in 1.6% overall yield. However, due to the instability of the ligand and the minute amount of it obtained after a lengthy multi-step synthesis, the dianion **37** could not be fully characterized nor have any of its corresponding metal complexes been made.



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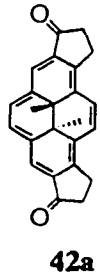

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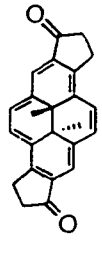

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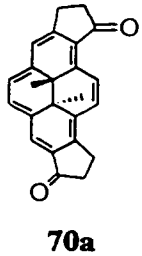
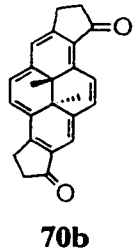
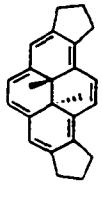


70a



70b



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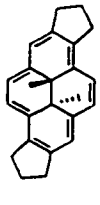

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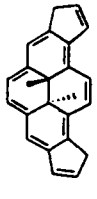
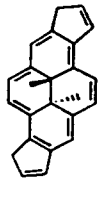


40a



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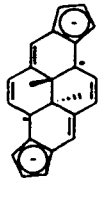
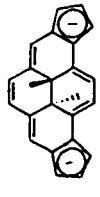


37a



37b

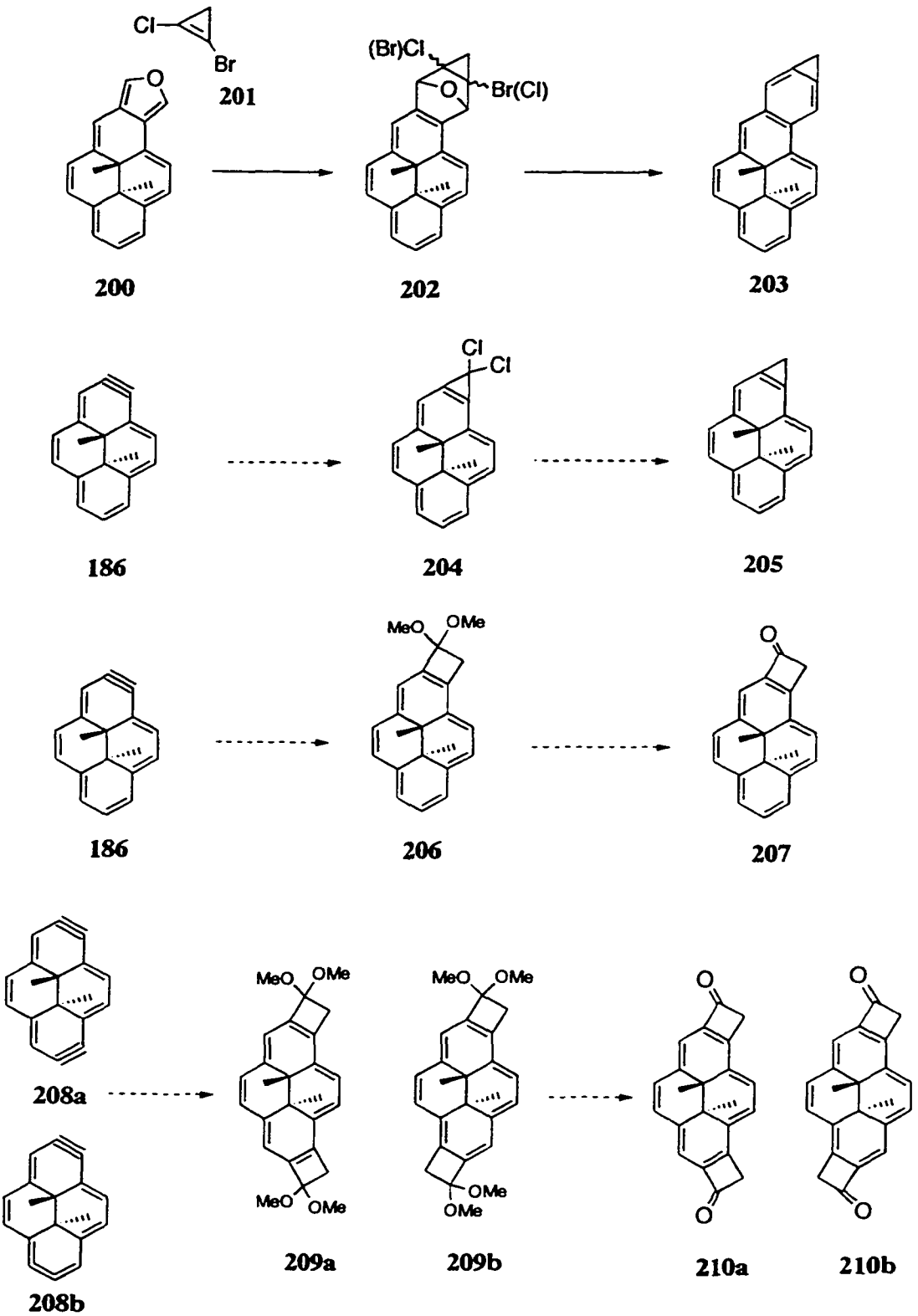
B. Expansions of this work

1. Synthesis of other annelated DHPs

a. Synthesis of cyclopropene-, cyclobutenone[a]-annelated DHPs and dicylobutene-one[a,h]-, [a,i]-annelated DHPs:

We have demonstrated in this thesis that DHP is a very sensitive NMR probe molecule for the determination of π-bond fixation effects of annelated rings. In this work, we have a series of cycloalkene-annelated DHP derivatives of which the ring size varies from four to seven. We also have another series of cycloalkenone annelated DHP derivatives in which the ring size varies from five to seven. However, having the cyclopropene-, cyclobutenone- and dicyclobutenone-annelated DHPs would complete our series of annelated DHP compounds to better describe the Mills-Nixon effect. Synthetically, it is challenging to make such small ring annelated compounds, but the synthesis of them should not be impossible. For example, Iyer has reported[132] that the oxa[17]annulene **200** underwent a Diels-Alder reaction with the unstable cyclopropene **201** to form the cycloadducts **202** in 60% yield as a mixture of isomers (See Scheme 20). Reaction of the adducts with the "green titanium" species generated from $TiCl_4$-Zn gave a mixture of products in which the cyclopropabenzo[a]-annelated DHP **203** was present. The reaction mixture was claimed to be unstable and full characterization was not attempted. Hopefully, by modification of the synthetic conditions and the purification procedure, the pure cyclopropabenzo-[a]-annelated DHP **203** could be isolated and characterized.

Scheme 20


Cl
Br
201
O
200
(Br)Cl
Br(Cl)
O
202
203
186
Cl
Cl
204
205
186
MeO
OMe
206
O
207
208a
208b
MeO
OMe
MeO
OMe
209a
MeO
OMe
OMe
OMe
209b
O
O
210a
O
O
210b

In the literature, the aryne **186** has been reported[125] by Mitchell and Zhou as an active intermediate to synthesize many benzenoid annelated DHPs. However, the potential use of aryne **186** to synthesize some other adducts is not fully investigated. For example, the aryne might react with α,α-dichlorocarbene to give the interesting dichlorocyclopropa[a]DHP **204** which then could be reduced to the cyclopropa[a]DHP **205** (See Scheme 20). Analysis of the NMR spectrum of **205** would allow comment on the electronic and ring strain effect of a three-membered ring on the bond fixation of DHP. The aryne might also react with 1,1-dimethoxyethene to give the four- membered ring adduct **205** which might be converted to the cyclobutenone[a]annelated DHP **207**. Similarily, the bis-arynes **208a** and **208b** may also be generated in situ and be used to trap the 1,1-dimethoxyethene to give the dicyclobutene-annelated DHP **209**. After acid hydrolysis of **209**, the *cisoid* and *transoid* dicyclobutenone annelated DHPs **210** should be obtained.

b. Synthesis of cycloalkene- and cycloalkenone[e]-annelated DHPs and some of their related derivatives:

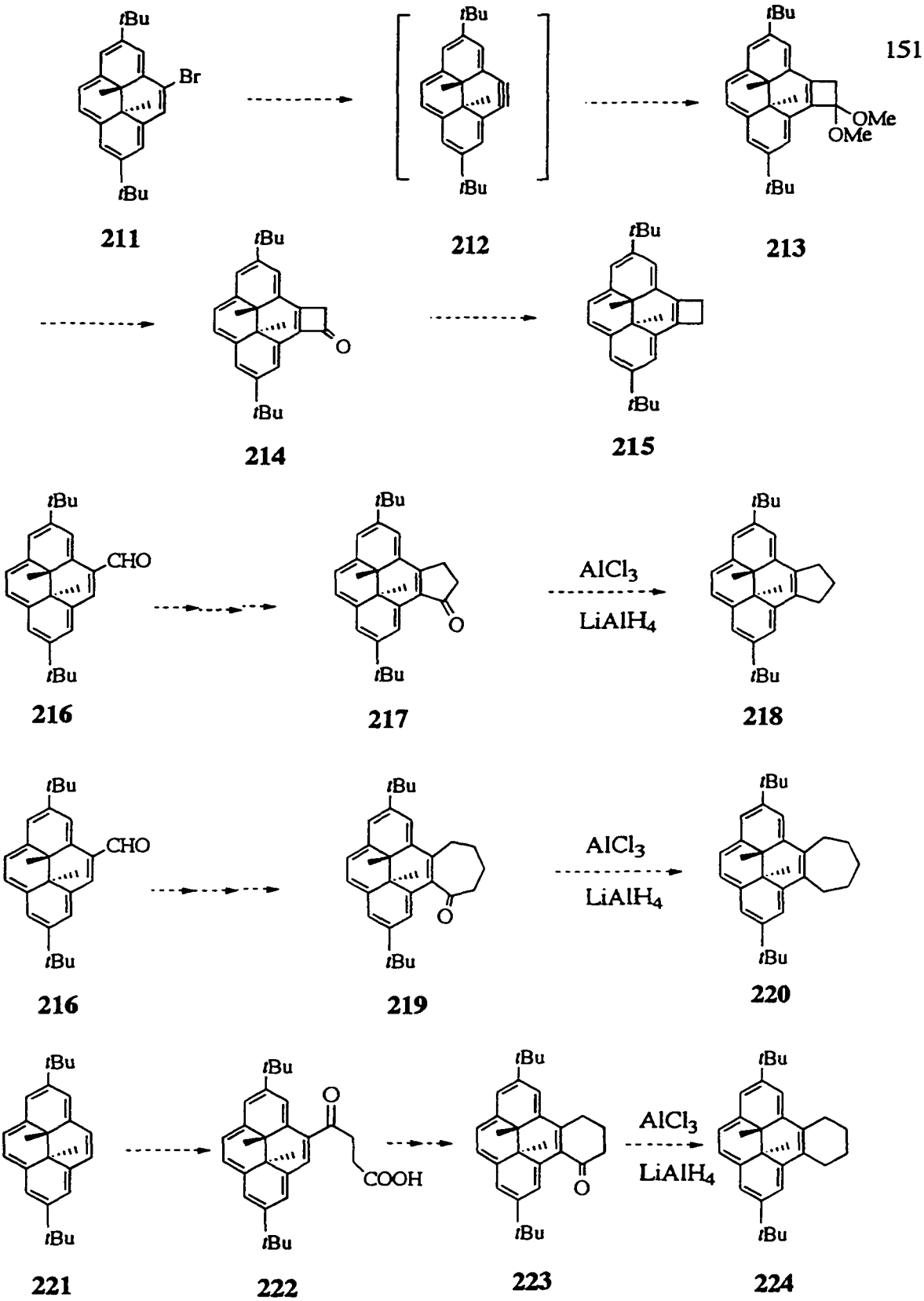
The [a]-, [a,h]- and [a,i]-annelated DHPs have been synthesized to probe the Mills-Nixon effect. The results prove that DHP is a very sensitive NMR probe although the effect of ring annelation on the π-electron is small. To confirm the Mills-Nixon effect determined by the above ring annelated DHP derivatives, the [e]-annelated DHP compounds should also be synthesized. Both [a]- and [e]-annelated DHPs have non-bonding interactions between their ring protons and aromatic protons. In the [a]-series there are naphthalene type and phenanthrene type proton interactions, whereas, in the [e]-series a stronger non-bondings interaction which is composed of two phenanthrene type proton interaction is expected. The [e]-annelated DHP derivatives should allow us to comment on how important the non-bonding interaction is on the Mills-Nixon effect.

To synthesized the four-membered ring [e]-annelated DHPs, the aryne route might also be used:

It has reported that 4-bromo-DHP **211** could be dehydrobrominated to give the aryne **212**[123]. This might then be trapped by 1,1-dimethoxyethene which should give the cyclobutenone[e]-annelated DHP **214** after hydrolysis. Removal of the carbonyl group should give the cyclobutene[e]-annelated DHP **215** (See Scheme 21).

To synthesize the five and seven-membered ring [e]-annelated DHPs, the Wittig reaction approach similar to the synthesis of [a]-annelated DHP could be used (See Scheme 21). Starting from the known 4-formyl DHP **216**, reaction with Wittig reagent with different chain length should give the corresponding unsaturated ester which after hydrogenation, saponification and cyclization should give the corresponding cyclopentenone- and cycloheptenone[e]-annelated DHPs, **217** and **219** respectively.

Scheme 21

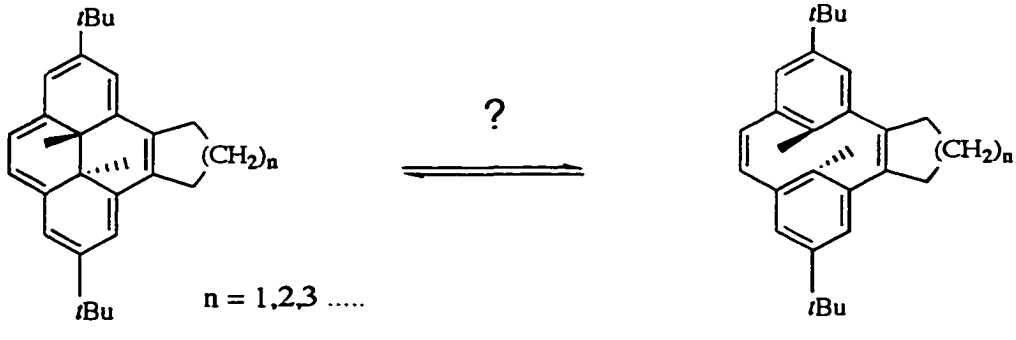

tBu
Br
tBu
211
tBu
tBu
212
tBu
OMe
OMe
tBu
213
tBu
O
tBu
214
tBu
tBu
215
tBu
CHO
tBu
216
tBu
O
tBu
217
AlCl3
LiAlH4
tBu
tBu
218
tBu
CHO
tBu
216
tBu
O
tBu
219
AlCl3
LiAlH4
tBu
220
tBu
tBu
221
tBu
O
COOH
tBu
222
tBu
O
tBu
223
AlCl3
LiAlH4
tBu
224

Removal of the carbonyl groups in **217** and **219** using a mixture of aluminum chloride and lithium aluminum hydride ($LiAlH_4$) should give the cyclopentene- and cycloheptene[e]-annelated DHPs **218** and **220**.

To synthesize the six-membered ring [e]-annelated DHPs, a similar approach to that used to synthesize the cylohexane[a]-annelated DHP could also be used. (See Scheme 21)

Starting from the known 2,7 di-*t*Bu-DHP **221**, the keto-acid **222** should be obtained by a Friedel-Crafts acylation reaction of **221** with succinic anhydride. After removal of the ketone group and then cyclization, compound **222** should be converted to the cyclohexenone[e]annelated DHP **223**. Removal of the carbonyl group in **223** should then give the cyclohexene[e]-annelated DHP **224**.

The importance of having [e]-annelated DHPs is not only limited to an intensive study of the Mills-Nixon effect but also because the data may shed light on how the equilibrium position between the cyclophane diene **225a** and the DHP **225b** may be

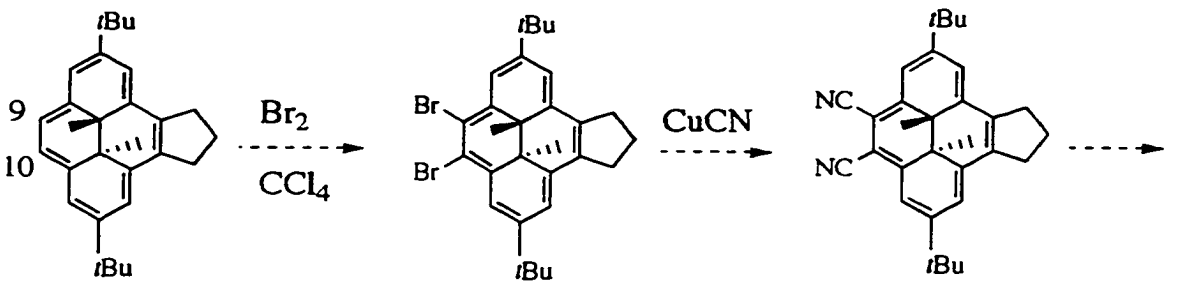


225a **225b**

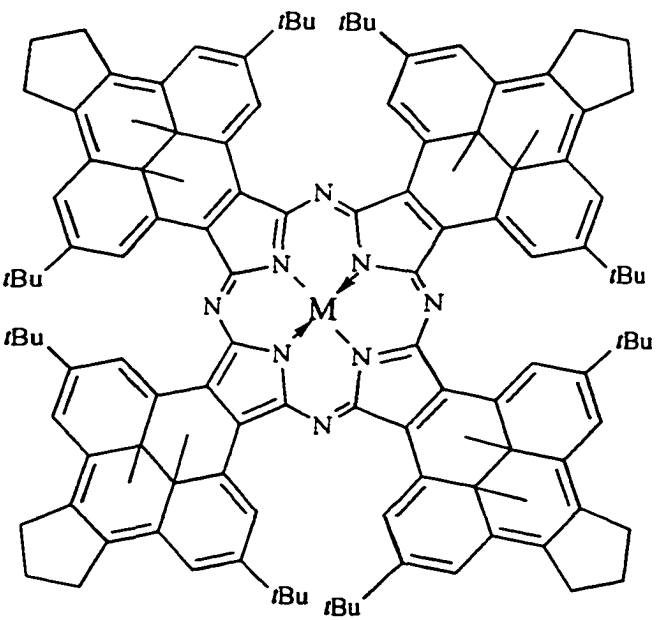
fine-tuned. This is particularly important as such information might allow us to modify DHP as a photoswitch. As well, an [e]-annelated of DHP, e.g. compound **218**, may

function as a blocking group which allows us to brominate the 9,10-positions to synthesize the dibromide **226** (Scheme 22). Dibromide **226** should then undergo a cyanation reaction to give the dicyanide **227** which after a base condensation reaction may give the novel annulenoannulene **228** which has a phthalocyanine core. DHP annelated phthalocyanine compounds are a future target for our group. It might be a useful dye or a component of conducting material[133] which shows unusual properties.

Scheme 22



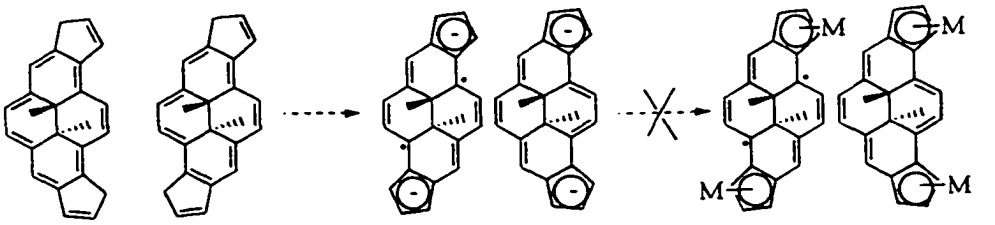
218 **226** **227**



228

2. How to tackle the failure in the formation of dicyclopentadiene dianion and its metal complexes

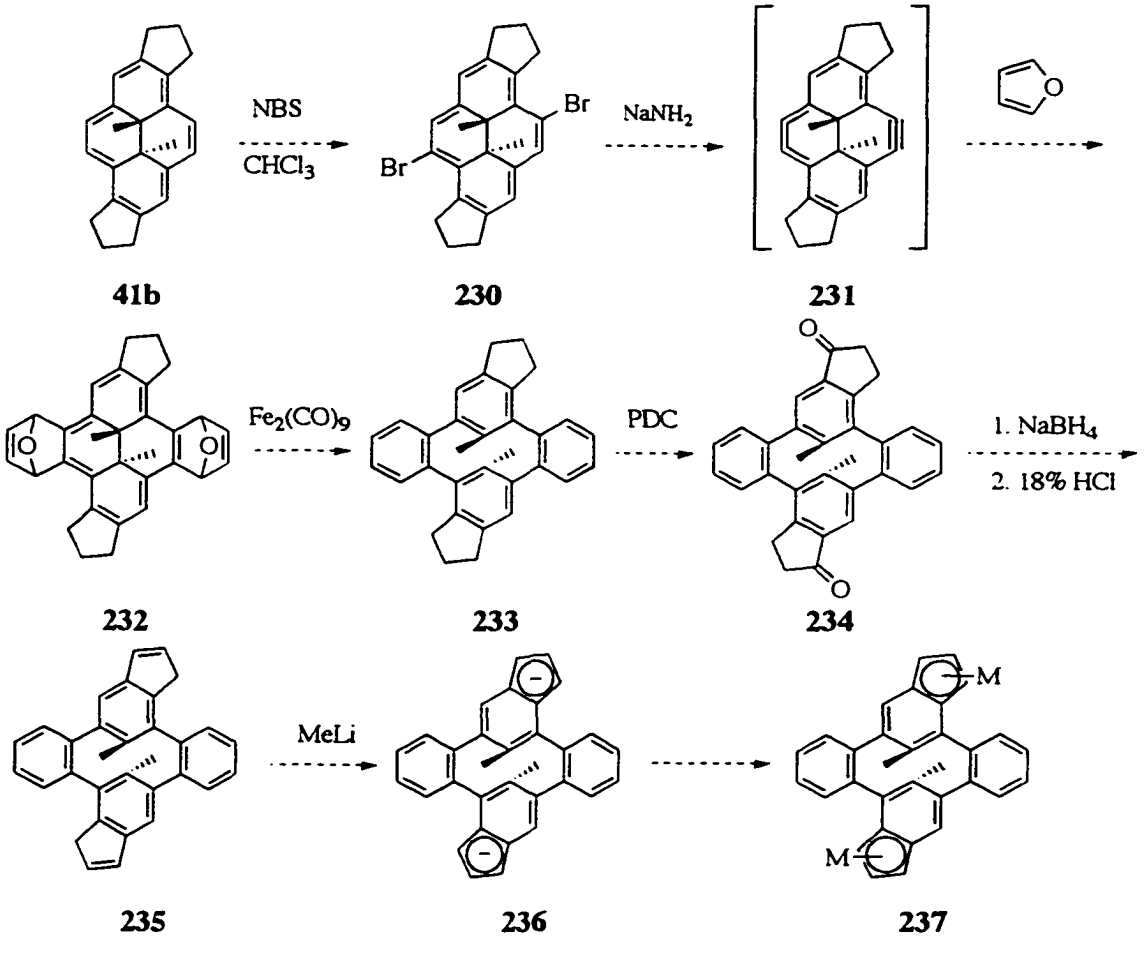
In this thesis work, although the dicyclopentadienyl[a,i]- and [a,h]annelated DHPs **40** (*cisoid* **40a** and *transoid* **40b**) were synthesized, the corresponding dianion **37** has not been fully characterized due to the minute amount of compound available and its instability. The formation of bis-metal complexes **229** also failed. Learning from the lesson that the stability of the intermediate is very important and knowing that on benzo[e]annelation, the equilibrium will favor the chemically more stable cyclophane diene valence isomer, we propose the synthesis of the even more theorectically interesting metal complex **236** as shown in Scheme 23. The known dicyclopentene[a,h]annelated DHP **41b** (For simplicity, only one isomer is shown though the reaction should be able to carry out with a mixture of *cisoid* and *transoid* isomers) should be able to be dibrominated by N-bromosuccimide to give the dibromide **230**. By generating the bis-aryne **231** in situ and trapping with furan, the bis-furan adduct **232** should be obtained. A standard deoxygenation reaction using $Fe_2(CO)_9$ should give the dibenzo[e,l]annelated DHP which should isomerize spontaneously to its cyclophane diene valence isomer **233**. **233** should be more stable and easier to handle compared with its DHP valence isomer. Benzylic oxidation of **233** should give the diketone **234** which should be able to undergo a reduction and elimination reaction to give the dicyclopentadienyl-annelated DHP ligand



40a **40b** **37a** **37b** **229b** **229a**

235. Deprotonation of **235** with MeLi should give the dianion **236** which may react with metal complex to form the bis-metal complex **237**. Compound **237** is much more interesting than **229** as it allows us to study the effect of forming metal complexes on the equilibrium between the DHP and the cyclophane diene. Besides, the benzene rings at the [e,l] position are also capable of forming metal complexes. The two potential different metal complex formation sites of cyclopentadienide and benzene as in ligand **235** might allow us to study the formation of mixed metal complexes which are rarely found in the literature.

Scheme 23



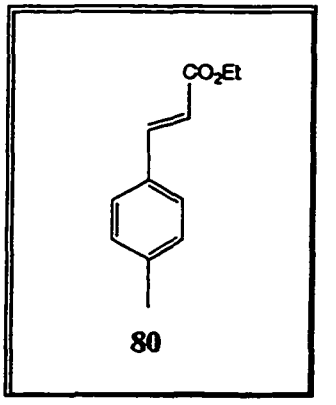
Chapter 6 Experimental

Instrumentation

Melting points were determined on a Reichert 7905 melting point apparatus integrated to an Omega Engineering Model 199 Chromel-alumel themocouple. Infrared spectra, were recorded on a Bruker IFS25 FTIR spectrometer and only the major bands are reported. UV-Visible spectra were recorded on a Cary 5 UV-VIS-NIR spectrometer using cyclohexane as solvent. Proton magnetic resonance spectra of solution in chloroform-d (unless otherwise specified) were recorded on a Bruker 300 MHz spectrometer or a Bruker AMX 360 (360 MHz), using the chloroform peak at 7.24 ppm for calibration. Carbon nuclear magnetic resonance spectra were recorded at 90.6 MHz, using solutions in chloroform-d, and the solvent peak at 77.0 ppm was the calibrant. Mass spectra were recorded on a Finnigan 3300 gas chromatography-mass spectroscopy system using methane as a carrier gas for chemical ionisation. Exact mass measurements were done on a Kratos Concept-H instrument using perfluorokerosene as the standard. Elemental analyses were performed by Canadian Microanayltical Service Ltd., Vancouver, B.C. All the solvents used in the reactions were purified and distilled according to standard procedure.[134] All evaporations were carried under reduced pressure on rotary evaporator. SiGel refers to silica gel, mesh 70 -210.

Experimental Procedures

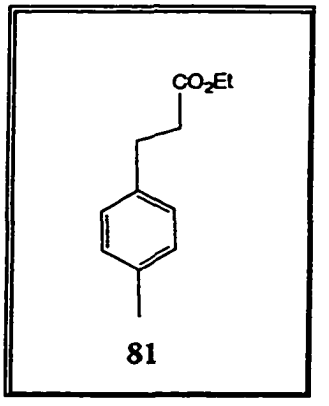
Ethyl (E)-3-(4-methylphenyl)-2-propenoate 80[46]



80

Triethylphosphonoacetate[42], $(EtO)_2POCH_2CO_2Et$ (25.2 mL, 0.13 mole) was added dropwise to a suspension of sodium hydride, 60% in mineral oil (5.7 g, 0.14 mole) in 450 mL dry THF at 0°C under nitrogen. After hydrogen gas evolution had subsided, *p*-tolualdehyde **79** (15 mL, 0.13 mole) in 200 mL dry THF was added dropwise. The reaction mixture was allowed to warm to 20°C and was subsequently refluxed for an hour. Saturated ammonium chloride solution (200 mL) was added and the product was extracted with Et_2O (3 x 300 mL). The organic layer was washed, dried and evaporated to give a yellow oil, which was chromatographed over SiGel with EtOAc-PE (1: 8) as eluant to give pure **80** as a colorless oil, 24.2 g, 98%. ^1H NMR (360 MHz): δ 7.64 (d, 1H, J=16.0Hz, H3'), 7.39 (AB, 2H, J=8.0Hz, Ar-H), 7.16 (AB, 2H, J=8.0Hz, Ar-H), 6.37 (d, 1H, J=16.0Hz, H2'), 4.24 (q, 2H, J=7.1 Hz, $-C\mathbf{H}_2CH_3$), 2.34 (s, 3H, Ar-Me), 1.32 (t, 3H, J=7.1Hz, $-CH_2C\mathbf{H}_3$); ^{13}C NMR (90.6 MHz): 167.1 (C=O), 144.5, 140.5, 131.6, 129.5, 128.0, 117.1, 60.3, 21.4, 14.3; IR (neat, major bands cm^{-1}): 2971, 2924, 1714 (C=O), 1643, 1171, 975; MS (CI), *m/z* 191 (MH^+).

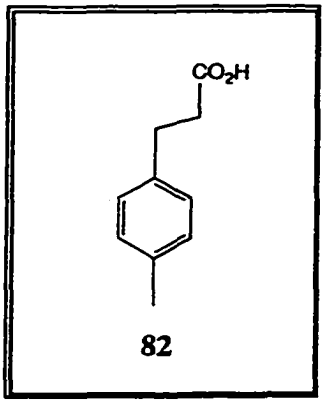
Ethyl 3-(4-methylphenyl)propanoate 81[46]



81

Palladium on activated charcoal, 10 % (0.5g) was added to the unsaturated ester **80** (30g, 0.16 mole) dissolved in EtOAc (20 mL). The reaction mixture was shaken under hydrogen (20psi) until one equivalent of hydrogen was consumed. The mixture was then suction filtered over a bed of celite and washed with Et_2O. The solvent was evaporated to give a colorless oil, 26 g, 85 %. ^1H NMR (360 MHz): δ 7.10, 7.09 (2s, 4H, Ar-H), 4.13 (q, 2H, J=7.1Hz, -CH_2CH_3), 2.91 (t, 2H, J=7.8Hz, Ar-CH_2-), 2.60 (t, 2H, J=7.8Hz, -CH_2-CO_2Et), 2.31 (s, 3H, Ar-Me), 1.24 (t, 3H, J=7.1Hz, -CH_2CH_3) ; ^{13}C NMR (90.6 MHz): 172.9 (C=O), 137.4, 135.6, 129.1, 128.1, 60.3, 36.0, 30.5, 20.9, 14.1; IR (neat, major bands cm^{-1}): 2983, 2912, 1725 (C=O), 1513, 1453,1039, 802; MS (CI), *m/z* 193 (MH^+).

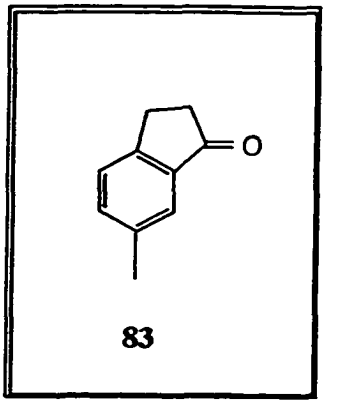
3-(4-Methylphenyl)propanoic acid 82[46]



82

The saturated ester **81** (10 g, 0.052 mole) was refluxed in 2M aqueous sodium hydroxide (50 mL) for 24 h. The solution was then cooled to room temperature and added dropwise with stirring to a mixture of concentrated sulfuric acid (10 mL) in crushed ice (400 g). The crude acid was suction filtered, washed and then dried with phosphorus pentoxide under vacuum until a constant weight was obtained, 8 g, 94 %. A sample was crystallized from water, mp 116 - 118°C (lit.[46] 117 - 118°C) ^{1}H NMR (300 MHz): δ 7.09 (s, 4H, Ar-H), 2.91 (t, 2H, J=8.1Hz, Ar-C**H**$_2$-), 2.65 (t, 2H, J=8.1Hz, -C**H**$_2$-COOH), 2.31 (s, 3H, Ar-Me); ^{13}C NMR (90.6 MHz): 179.1 (C=O), 134.1, 135.9, 129.2, 128.1, 35.7, 30.2, 21.0; MS (CI), *m/z* 165 (MH^+).

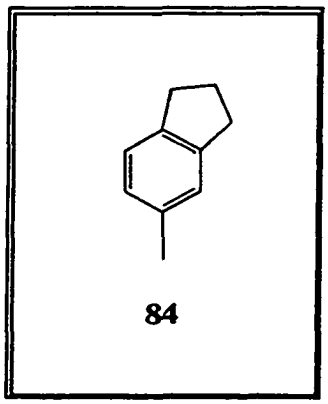
6-Methyl-1-indanone 83[46]



83

The acid **82** (10 g, 0.061 mole) was added in one portion to polyphosphoric acid (PPA) (40 g) which was degassed and preheated to 110°C. After the acid had melted, the resulting gel was mechanically stirred for 20 min. and the temperature was controlled carefully between 100°C to 120°C. Then crushed ice (500 g) was added to decompose the excess PPA. The crude cyclized product was suction filtered. It was then dissolved in CH_2Cl_2 (500 mL), washed, dried and evaporated to give a yellow oil. The yellow oil was then subjected to Kugelrohr distillation (98 - 115 °C, 0.6 mmHg) to give a colorless oil (6.7 g, 75 %) which solidified on standing at room temperature. A sample was crystallized from hexanes, mp. 62 - 63°C (lit.[46] 63°C) ^{1}H NMR (300 MHz): δ 7.49 (s, 1H, H-7), 7.33 (AB, 2H, J=8.2Hz, H-4,5), 3.04 (t, 2H, J=5.9Hz, H-2), 2.62 (m, 2H, H-3), 2.35 (s, 3H, Ar-Me); ^{13}C NMR (90.6 MHz): 207.2 (C=O), 152.5, 137.2, 137.1, 135.8, 126.3, 123.6, 36.5, 25.4 (C-2,3), 21.0 (Ar-Me); IR (neat, major bands cm^{-1}): 2920, 2924, 1707 (C=O), 1439, 1281, 828; MS (CI), *m/z* 147 (MH^+).

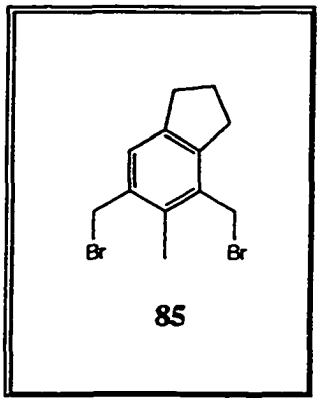
5-Methylindane 84[46]



84

Zinc dust (100 g, 1.53 mole), mercury (II) chloride (10 g, 0.036 mole), concentrated HCl (4 mL) and water (160 mL) were mixed together and stirred for 5 min. The aqueous layer was decanted. Ketone **83** (23 g, 0.16 mole) in benzene (120 mL) was added, followed by concentrated HCl (141 mL) and water (63 mL). The mixture was refluxed for 24 h. After cooling, water (200 mL) was added and the resulting mixture was extracted with Et_2O (3 x 300 mL). The combined organic extracts were washed, dried and evaporated to give a yellow oil. The crude oil was purified by Kugelrohr distillation (50 - 60°C, 0.5 mmHg) to give a colorless oil, 17.3 g, 82 %. ^1H NMR (300 MHz): δ 7.09 (s, 1H, H-4), 7.15, 6.98 (AB, 2H, J=7.4Hz, H-6,7), 2.90 (t, 4H, J=7.4Hz, H-1,3), 2.35 (s, 3H, Ar-Me), 2.14-2.03 (m, 2H, H-2); ^{13}C NMR (90.6 MHz): δ 144.4, 141.1, 135.6, 126.8, 125.1, 124.1, 32.8, 32.5, 25.6, 21.3; IR (neat, major bands cm^{-1}): 2937, 2853, 1613, 1488, 1437, 860, 810; MS (CI), *m/z* 133 (MH^+).

4,6-bis(Bromomethyl)-5-methylindane 85



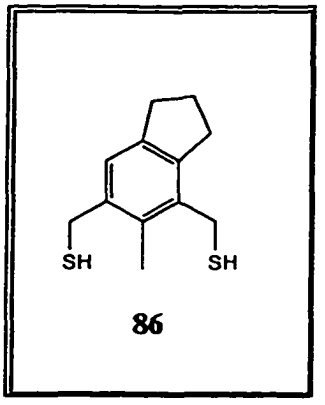
85

A mixture of 5-methyl indane **84** (10 g, 0.076 mole), 1,3,5-trioxane (5.22 g, 0.057 mole), 48% hydrobromic acid (45 mL), glacial acetic acid (11 mL) and tetradecyltrimethylammonium chloride (0.43 g) were heated at 90-100°C for 36 h. Then the reaction mixture was allowed to cool to 20°C and stirred overnight. The precipitate was suction filtered and washed with water. It was then dissolved in CH_2Cl_2 (300 mL), washed, dried and evaporated to give a yellow oil. PE (80 mL) was added and the dibromide was precipitated out on standing as white crystals, 17.4 g, 72 %. A sample was crystallized from hexanes, mp. 92 - 94 °C. ^{1}H NMR (360 MHz): δ 7.16 (s, 1H, H-7), 4.53, 4.52 (2s, 4H,-C**H**$_2$Br), 2.95 (t, J=7.5Hz, 2H, H-3), 2.89 (t, J=7.5Hz, 2H, H-1), 2.40 (s, 3H, Ar-Me), 2.11 (m, 2H, H-2) ; ^{13}C NMR (90.6 MHz): 145.3, 142.4, 134.6, 134.1, 132.5, 126.6, 33.6, 32.7, 31.3, 29.6, 24.6, 13.9; IR (KBr, major bands cm^{-1}): 2964, 2838, 1456, 1130, 600, 543; MS (CI), *m/z* 317, 319, 321 (MH+).

Anal. Calculated for $C_{12}H_{14}Br_2$: % C: 45.85 % H: 4.44

Found % C: 44.85 % H: 4.42

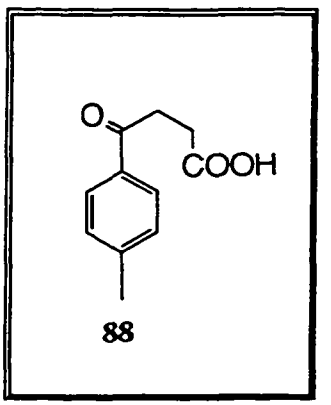
6-Methyl-7-sulfanylmethyl-2,3-dihydro-1H-5-indenylmethanethiol 86



86

Thiourea (4.6 g, 0.06 mole) was added to 100 % ethanol (20 mL) and the solution was warmed to about 60°C. Then the dibromide **85** (8 g, 0.025 mole) was added in five portions. After complete addition, the reaction mixture was refluxed for 30 min. The solvent was evaporated and degassed aqueous sodium hydroxide solution (5.4 g NaOH in 200 mL water) was added. The system was flushed with argon and refluxed under argon atmosphere for 6 h. Then 2M iced cooled hydrochloric acid was added to neutralize the reaction mixture and the thiol was extracted with Et_2O (3 x 200 mL). The combined organic extracts were washed, dried and evaporated to give a cloudy oil. It was chromatographed over SiGel using Et_2O-PE (1:9) as eluant to give the dimercaptan **86** as a colorless oil, 5.3 g, 95%. ^1H NMR (360 MHz): δ 7.02 (s, 1H, H-4), 3.73 (d, 2H, J=6.9Hz, -C**H**$_2$SH), 3.72 (d, 2H, J=7.1Hz, -C**H**$_2$SH), 2.91 (t, 2H, J=7.5Hz, H-1), 2.87 (t, 2H, J=7.7Hz, H-3), 2.37 (s, 3H, Ar-Me), 2.07 (m, 2H, H-2), 1.65 (t, 1H, J=7.1Hz, SH), 1.59 (t, J=6.9Hz, 1H, SH) ; ^{13}C NMR (90.6 MHz): 142.3, 142.0, 138.0, 135.6, 131.0, 123.9, 33.8, 31.4, 27.8, 24.8, 24.1, 14.2; IR (neat, major bands cm^{-1}): 2920, 1450, 1425, 1235, 865; MS (CI), *m/z* 225 (MH^+); EI-HRMS calculated for $C_{12}H_{16}S_2$: 224.0693, found: 224.0692.

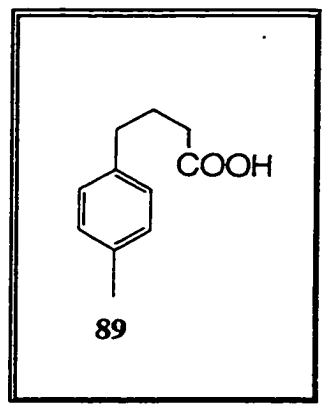
4-(4-Methylphenyl)-4-oxobutanoic acid 88



88

Succinic anhydride (41.3 g, 0.409 mole) and aluminum trichloride (58.0 g, 0.435 mole) in CH_2Cl_2 (400 mL) were mechanically stirred at 25°C under nitrogen for 15 min. Then toluene (40 mL, 0.376 mole) in CH_2Cl_2 (60mL) was added slowly and the resulting mixture was stirred for 2 h at 25°C. The solution was then poured into ice-water (600 mL) and 2M HCl (200 mL) was added until the solution became acidic. The product was extracted with CH_2Cl_2 (3 x 300 mL) and the combined organic extracts were washed, dried and evaporated. Then PE (200 mL) was added and the product was collected. Recrystallization from CH_2Cl_2-hexane (1:4) gave white needles, 53 g, 76%, mp 118-120°C (lit.[46] mp 120°C). ^{1}H NMR (300 MHz): δ 7.86, 7.24 (AB, 4H, J=8.09Hz, Ar-H), 3.27 (t, 2H, J=6.62Hz, -C**H**$_2$COOH), 2.78 (t, 2H, J=6.62Hz, Ar-COC**H**$_2$-), 2.39 (s, 3H, Ar-Me); ^{13}C NMR (90.6MHz) δ 197.5 (C=O), 178.9 (COOH), 144.2, 133.9, 129.3, 128.2, 33.0, 28.1, 21.7; IR (KBr, major bands cm^{-1}): 2926, 1680 (C=O), 1230, 808; MS(CI), *m/z* 193 (MH+).

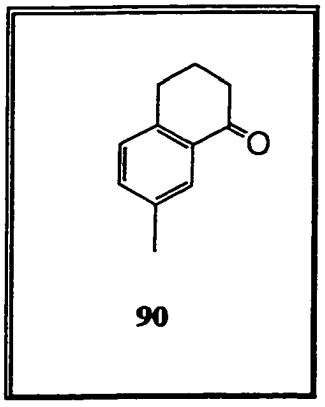
4-(4-Methylphenyl)butanoic acid 89



89

Zinc dust (128.0 g, 1.96 mole), mercury (II) chloride (12.8 g, 0.0471 mole), concentrated HCl (6.4 mL) and water (209 mL) were mixed together with stirring for 5 min. The aqueous layer was decanted. Ketone **88** (53.0 g, 0.276 mole) in benzene (140 mL) was added, followed by concentrated HCl (182 mL) and water (79 mL). The mixture was refluxed for 24 h. After cooling, water (200 mL) was added and the resulting mixture was extracted with Et_2O (3 x 300 mL). The combined organic extracts were washed, dried and evaporated to give the product as a white solid, 37.0 g, 75%. A sample was crystallized from hexane, mp 60-61°C (lit.[46] 61-62°C). ^1H NMR (300 MHz) δ 7.09, 7,06 (AB, J=8.5Hz, 4H, Ar-H), 2.63 (t, 2H, J=7.7Hz, CH_2), 2.36 (t, 2H, J=7.7Hz, CH_2), 2.31 (s, 3H, Ar-Me), 1.94 (quintet, 2H, J=7.5Hz, CH_2); ^{13}C NMR (90.6MHz) δ 179.9 (C=O), 138.1, 131.5, 129.3, 128.4, 34.5, 33.3, 26.3, 21.0; IR (KBr, major bands cm^{-1}): 2940, 1692 (C=O), 1516, 1461, 1408, 1285, 1198, 916, 809, 755; MS(CI), *m/z* 179 (MH^+).

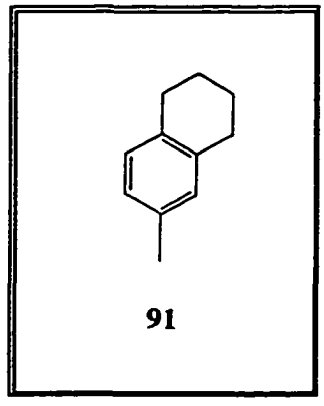
7-Methyl-1,2,3,4-tetrahydro-1-naphthalenone, 90



90

The acid **89** (10.0 g, 0.0562 mole) was added to polyphosphoric acid (PPA) (50 g) preheated in a water bath at 75 - 80°C. This was then stirred vigorously in a steam bath for 5 min. The reaction mixture was further stirred at 50 -60°C for 4 min. and crushed ice was added to decompose the excess PPA. The product was extracted with CH_2Cl_2 (3 x 250 mL), washed, dried and evaporated to give a yellow oil which solidified on standing. The crude tetralone was further purified by Kugelrohr distillation (90-105°C, 0.5 mmHg) to give a colorless liquid (7.0 g, 78 %) which solidified on standing. A sample was crystallized from hexane, mp 34-36°C (lit.[46] 33-35°C). ^1H NMR (360 MHz) δ 7.82 (d, J=1.3Hz, 1H, H-8), 7.27 (dd, 1H, J=7.8Hz, 1.95Hz, H-6), 7.13 (d, 1H, J=7.8Hz, H-5), 2.90 (t, 2H, J=6.1Hz, ring H), 2.62 (t, 2H, J=6.6Hz, ring H), 2.34 (s, 3H, Ar-Me), 2.09 (quintet, 2H, J=6.3Hz, ring H); ^{13}C NMR (90.6MHz) δ 198.7 (C=O), 141.6, 136.3, 134.3, 132.3, 128.7, 127.2, 39.2, 29.3, 23.4, 20.9; IR (KBr, major bands cm^{-1}): 2900, 1660 (C=O), 1595, 1475, 1390, 1265, 1150, 890, 795; MS(CI), *m/z* 161 (MH^+).

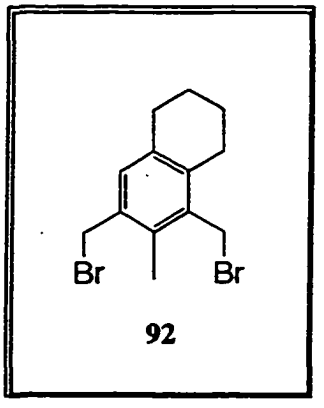
6-Methyl-1,2,3,4-tetrahydronaphthalene, 91[46]



91

Zinc dust (58.0 g, 0.0887 mole), mercury (II) chloride (5.8 g, 0.0214 mole), concentrated HCl (3 mL) and water (96 mL) were mixed together with stirring for 5 min. The aqueous layer was decanted. Ketone **90** (20.0 g, 0.125 mole) in benzene (65 mL) was added, followed by concentrated HCl (83 mL) and water (36 mL). The mixture was refluxed for 24 h. After cooling, water (200mL) was added and the resulting mixture was extracted with Et_2O (3 x 300 mL). The combined organic extracts were washed, dried and evaporated to give a yellow oil which was further purified by Kugelrohr distillation (50 - 65°C, 0.5 mmHg) to afford a colorless oil, 13.5 g, 74 %. ^1H NMR (360 MHz) δ 6.91, 6.97 (AB, J=7.8Hz, 2H, H-7,8), 6.9 (s, 1H, H-5), 2.7 (m, 4H, ring H), 2.28 (s, 3H, Ar-Me), 1.75-1.81 (m, 4H, ring H); ^{13}C NMR (90.6MHz): δ 136.9, 134.8, 134.0, 129.7, 129.0, 126.2, 29.3, 29.0, 23.4, 23.3, 20.9; IR (KBr, major bands cm^{-1}): 2986, 2923, 2860, 1504, 1442, 802, 663; MS(CI), *m/z* 147 (MH^+).

5,7-bis(Bromomethyl)-6-methyl-1,2,3,4-tetrahydronaphthalene, 92

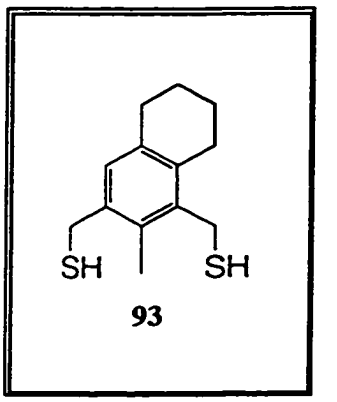


92

The tetralin **91**, (10.0 g, 0.0685 mole), 1,3,5-trioxane (4.7 g, 0.052 mole), tetradecyltrimethylammonium chloride (0.38 g), glacial acetic acid (10 mL) and 48 % HBr (41 mL) were heated at 90-100°C under nitrogen for 30 h. Then ice water (100 mL) was added and the reaction mixture was stirred for an hour. The precipitated dibromide was filtered and washed with water (2 x 200 mL). It was then dissolved in CH_2Cl_2 (100 mL), dried and evaporated to give a yellow oil. PE (50 mL) was added to precipitate the dibromide. After standing overnight, the dibromide was collected by suction filtration, 16.8 g, 74 %, mp 103-105°C. ^1H NMR (360 MHz): δ 7.01 (s, 1H, Ar-H), 4.54, 4.48 (2s, 4H, $-CH_2Br$), 2.80 (t, 2H, J=6.2Hz, ring H), 2.71 (t, 2H, J=6.4Hz, ring H), 2.39 (s, 3H, Ar-Me), 1.87-1.80 (m, 2H, ring H), 1.70-1.77 (m, 2H, ring H); ^{13}C NMR (90.6MHz) δ 137.4, 135.8, 134.9, 134.2, 133.5, 131.6, 33.2, 29.6, 29.0, 26.1, 23.1, 22.4, 14.3; IR (KBr, major bands cm^{-1}): 2930, 2857, 1449, 1204, 988, 958, 737; MS(CI), *m/z* 331, 333, 335 (MH^+).

Anal.	Calculated for $C_{13}H_{16}Br_2$	% C: 47.02	% H: 4.86
	Found	% C: 46.63	% H: 4.42

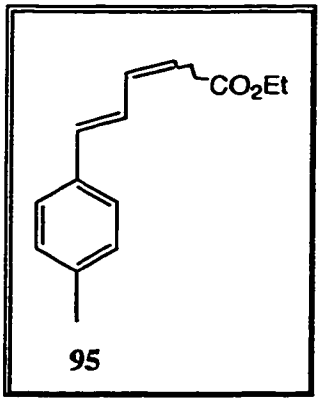
7-Methyl-8-sulfanylmethyl-1,2,3,4-tetrahydro-6-napthalenylmethanethiol, 93



93

The dibromide **92** (3.97 g, 0.012 mole) in four portions was added to a solution of thiourea (1.19 g, 0.025 mole) in 100 % ethanol (30 mL) at 60°C. After complete addition, the reaction mixture was refluxed for 30 min. The solvent was evaporated and degassed aqueous sodium hydroxide solution (2.6 g NaOH in 200 mL water) was added. The system was flushed with argon and refluxed under argon for 6 h. Then 2M iced cooled hydrochloric acid was added to neutralize the reaction mixture and the thiol was extracted with Et_2O (3 x 200 mL). The combined organic extracts were washed, dried and evaporated to give a cloudy oil. It was chromatographed over SiGel using Et_2O-PE (1:9) as eluant to give the dimercaptan as a colorless oil, 2.59 g, 91%. ^1H NMR (300 MHz) δ 6.89 (s, 1H, Ar-H), 3.75 (d, J=7.4Hz, 2H, $-CH_2SH$), 3.70 (d, J=6.6Hz, 2H, $-CH_2SH$), 2.81 (t, J=6.6Hz, 2H, ring H), 2.72 (t, J=5.9Hz, 2H, ring H), 2.39 (s, 3H, Ar-Me), 1.87-1.72 (m, 4H, ring H), 1.66 (t, J=7.4Hz, 1H, -SH), 1.59 (t, J=6.6Hz, 1H, -SH); ^{13}C NMR (90.6MHz) δ 138.0, 136.9, 135.6, 134.2, 131.1, 128.9, 29.9, 27.6, 26.3, 23.4, 22.7, 22.6, 14.5; IR (KBr, major bands cm^{-1}): 2927, 1453, 1373, 880; MS(CI), *m/z* 239 (MH^+); EI-HRMS calculated for $C_{13}H_{18}S_2$: 238.0850, found: 238.0848.

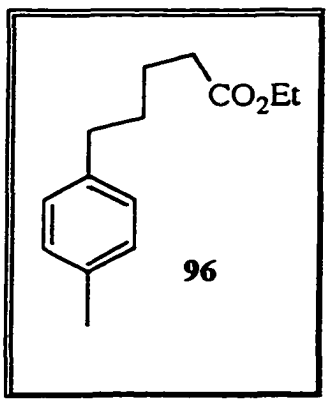
Ethyl(2E;4E)-5-(4-methylphenyl)-2,4-pentadienoate and Ethyl(2Z;4E)-5-(4-methylphenyl)-2,4-pentadienoate 95



95

Potassium *t*-butoxide (17 g, 0.14 mole) was added into a slurry of Wittig reagent **94**[51], $\phi_3P^+CH_2CH{=}CHCO_2Et$, Br^- (63 g, 0.14 mole) and 18-crown-6 (0.38g, 1.43 mmole) in CH_2Cl_2 (300 mL) at 0°C under argon. After stirring for 5 min, *p*-tolualdehyde (14 mL, 0.12 mole) in CH_2Cl_2 (30 mL) was added dropwise. The reaction mixture was then allowed to warm to 50°C and stirred for 24 h. Saturated ammonium chloride solution (200 mL) was added and the product was extracted with Et_2O (3 x 300 mL). The organic layer was washed, dried and evaporated to give a yellow oil, which was chromatographed over SiGel with EtOAc-PE (1: 8) as eluant to give pure **95** as a yellow oil, 17.9 g, 72%. ^1H NMR (300 MHz): δ 7.38-7.42 (m, 1H,vinylic H), 7.24 (AB, 4H, J=8.1Hz, Ar-H), 6.75-6.88 (m, 2H, vinylic H), 5.94 (d, J=15.4Hz, 1H, vinylic H), 4.2 (q, 2H, J=7.4Hz, $-OC\mathbf{H}_2CH_3$), 2.4 (s, 3H, Ar-Me), 1.30 (t, 3H, J=7.35Hz, $-OCH_2C\mathbf{H}_3$); ^{13}C NMR (90.6 MHz): 167.1 (C=O), 144.8, 140.4, 139.2, 133.3, 129.5, 127.2, 125.3, 120.7, 60.3, 21.4, 14.3; IR (neat, major peaks cm^{-1}): 2980, 1708, 1629, 1000, 847, 807, 738; MS (CI), *m/z* 217 (MH^+); EI HRMS calculated for $C_{14}H_{16}O_2$: 216.1150, found: 216.1155.

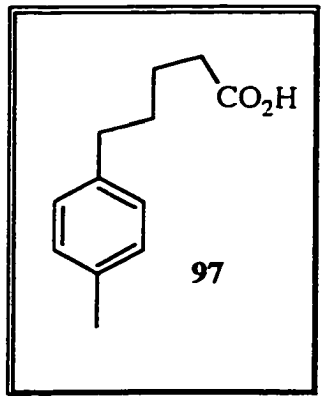
Ethyl 5-(4-methylphenyl)pentanoate 96



Palladium on activated charcoal, 10 % (0.4 g) was added to the unsaturated ester **95** (10 g, 0.046 mole) in EtOAc (20 mL). The reaction mixture was shaken under hydrogen (20 psi) until two equivalents of H_2 were consumed. The mixture was then suction filtered over a bed of celite and washed with Et_2O. The solvent was evaporated to give a colorless oil, 8.7 g, 84%, which is pure enough for the next reaction. ^1H NMR (300 MHz): δ 7.07 (AB, 4H, J=8.5Hz, Ar-H), 4.11 (q, 2H, J=7.1Hz, -OC**H**$_2$CH$_3$), 2.58 (t, 2H, J=7.0Hz, CH_2), 2.31 (t, 2H, 7.0Hz, CH_2), 2.31 (s, 3H, Ar-H), 1.66 (m, 4H, CH_2), 1.24 (t, 3H, J=7.4Hz, CH_2**C**H$_3$); ^{13}C NMR (90.6 MHz): 173.7 (C=O), 139.1, 135.2, 129.0, 128.3, 60.2, 35.1, 34.2, 31.0, 24.6, 21.0, 14.3; IR (neat, major peaks cm^{-1}): 3000, 2982, 1769 (C=O), 1264, 1052, 786; MS (CI), *m/z* 221 (MH^+).

Anal.	Calculated for $C_{14}H_{20}O_2$	% C: 76.33	% H: 9.15
	Found	% C: 76.32	% H: 8.91

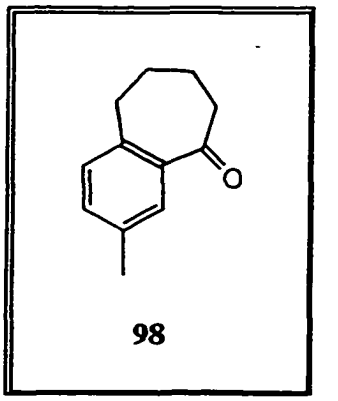
5-(4-Methylphenyl)pentanoic acid 97



The saturated ester **96** (36 g, 0.16 mole) was refluxed in 3.5 M aqueous sodium hydroxide (100 mL) and EtOH (50 mL) for 24 h. The solution was then cooled to room temperature and was added dropwise to a mixture of concentrated sulfuric acid (10 mL) in crushed ice (400 g) with stirring. The crude acid was suction filtered, washed with water (2 x 200mL) and dried with phosphorus pentoxide under vacuum until a constant weight was obtained, 31 g, 98%. A sample of the crude acid was crystallized from hexanes, mp. 72 - 73°C. ^{1}H NMR (300 MHz): δ 7.03-7.10 (AB, 4H, Ar-H), 2.58 (t, 2H, J=6.9Hz, CH_2), 2.36 (t, 2H, J=8.5Hz, CH_2), 2.30 (s, 3H, Ar-Me), 1.63-1.71 (m, 4H, CH_2); ^{13}C NMR (90.6 MHz): 179.9 (C=O), 138.9, 135.2, 129.0, 128.3, 35.1, 33.9, 30.9, 24.3, 21.0; IR (KBr, major peaks cm^{-1}): 2938, 1716 (C=O), 909, 728; MS (CI), *m/z* 193 (MH^+).

Anal.	Calculated for $C_{12}H_{16}O_2$	% C: 74.97	% H: 8.39
	Found	% C: 75.19	% H: 8.62

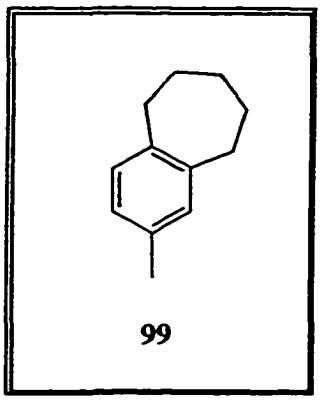
3-Methyl-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-5-one, 98



98

The acid **97** (20 g, 0.12 mole) was added in one portion to approximately 40 g of polyphosphoric acid (PPA)[48] which was degassed and preheated to 120°C. After the acid had melted, the resulting gel was mechanically stirred for 20 min. and the temperature was controlled carefully between 100°C to 120°C. Then crushed ice (300 g) was added to decompose the excess PPA. The crude cyclized product was extracted with CH_2Cl_2 (3 x 300 mL) and then washed, dried and evaporated to give a yellow oil. It was then subjected to Kugelrohr distillation (90 - 95°C, 0.5 mmHg) to give a colorless oil, 4.9 g, 72 %. ^{1}H NMR (300 MHz): δ 7.50 (d, 1H, J=1.4Hz, H-4), 7.19 (dd, 1H, J=7.3Hz, 1.5Hz, H-1), 7.04 (d, 1H, J=7.4Hz, H-2), 2.85 (t, 2H, J=6.3Hz, ring H), 2.69 (t, 2H, J=5.9Hz, ring H), 2.31 (s, 3H, Ar-Me), 1.79 (m, 4H, ring H); ^{13}C NMR (90.6 MHz): 206.3 (C=O), 138.6, 138.4, 136.2, 132.9, 129.7, 128.9, 40.9, 32.0, 25.3, 20.9, 20.8; IR (neat, major peaks cm^{-1}): 2938, 2857, 1679 (C=O), 1268, 1170, 830, 741; MS (CI), *m/z* 175 (MH^+); EI-HRMS calculated for $C_{12}H_{14}O$: 174.1045, found: 174.1043.

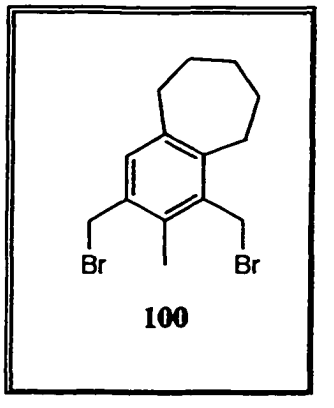
2-Methyl-6,7,8,9-tetrahydro-5H-benzo[a]cycloheptene, 99



99

Zinc dust (60 g, 0.92 mole), mercury (II) chloride (6 g, 0.022 mole), concentrated HCl (3.6 mL) and water (28 mL) were stirred for 5 min. The aqueous layer was decanted. Ketone **98** (20 g, 0.11 mole) in benzene (150 mL) was added, followed by concentrated HCl (86 mL) and water (38 mL). The mixture was refluxed for 24 h. After cooling, water (200 mL) was added and the resulting mixture was extracted with Et_2O (3 x 300 mL). The organic extract was washed, dried and evaporated to give a yellow oil. The crude oil was then dissolved in EtOAc (20 mL) and 10% of palladium on charcoal (0.4 g) was added and the reaction mixture was stirred under an atmosphere of hydrogen for 3 h. It was then suction filtered over a bed of celite and concentrated to give a yellow oil. The oil was further purified by Kugelrohr distillation (55 - 60°C, 0.5 mmHg) to give a colorless oil , 12 g, 65 %. ^1H NMR (300 MHz) δ 6.94 (AB, 2H, J=7.7Hz, H-3,4), 6.92 (s, 1H, H-1), 2.75 (m, 4H, ring H), 2.29 (s, 3H, Ar-Me), 1.82 (m, 2H, ring H), 1.62 (m, 4H, ring H); ^{13}C NMR (90.6 MHz): 143.3, 141.4, 135.3, 129.9, 129.0, 126.4, 36.7, 36.2, 32.8, 28.5, 28.4, 20.9; IR (neat, major peaks cm^{-1}): 2920, 2840, 1500, 1450, 810; MS (CI), *m/z* 161 (MH^+); EI-HRMS calculated for $C_{12}H_{16}$: 160.1252, found: 160.1250.

1,3-Bis(bromomethyl)-2-methyl-6,7,8,9-tetrahydro-5H-benzo[a]cycloheptene, 100

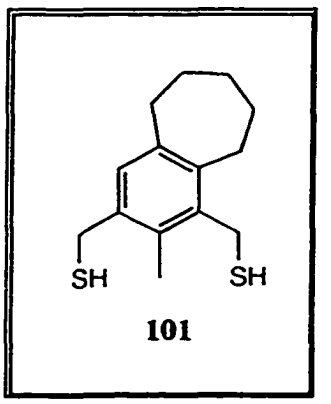


100

A mixture of **99** (11 g, 0.069 mole) , 1,3,5-trioxane (4.16 g, 0.046 mole), 48% hydrobromic acid (33 mL), glacial acetic acid (8.7 mL) and tetradecyltrimethylammonium chloride (0.35 g) were heated at 100-105°C for 36 h. Then the reaction mixture was allowed to cool to room temperature and stirred overnight. The precipitate was suction filtered and washed with water (2 x 200 mL). It was then dissolved in CH_2Cl_2 (400 mL) , washed, dried and evaporated to give a yellow oil. PE (50 mL) was added and the dibromide was precipitated out as white crystals on standing. The crude dibromide was suction filtered to give 16.9 g, 71 % of the crude product. A sample was crystallized from pentane. mp. 158 -159°C. ^{1}H NMR (300 MHz): δ 7.04 (s, 1H, Ar-H), 4.46, 4.48 (2s, 4H, CH_2Br), 2.89-2.86 (m, 2H, ring H), 2.77-70 (m, 2H, ring H), 2.40 (s, 3H, Ar-Me), 1.85-1.76 (m, 2H, ring H), 1.68-1.53 (m, 4H, ring H); ^{13}C NMR (90.6 MHz): 144.3, 142.3, 134.4, 133.9, 133.5, 131.4, 36.0, 33.3, 32.2, 30.2, 29.7, 28.0, 27.0, 14.8; IR (KBr, major peaks cm^{-1}): 2919, 2846, 1447, 1212, 976, 913; MS (CI), *m/z* 345, 347, 349 (MH+).

Anal.	Calculated for $C_{14}H_{18}Br_2$	% C: 48.58	% H: 5.24
	Found	% C: 48.23	% H: 5.11

3-Methyl-4-sulfanylmethyl-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-2yl-methanethiol, 101

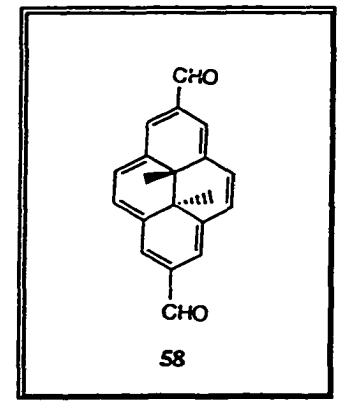


101

Thiourea (1.8 g, 0.024 mole) was added into 100% EtOH (30 mL) and the solution was warmed to about 60°C. Then the dibromide **100** (4.1 g, 0.012 mole) was added in 4 portions. After complete addition, the reaction mixture was refluxed for 30 min. The solvent was evaporated and degassed aqueous sodium hydroxide solution (2.43 g NaOH in 70 mL water) was added. The system was flushed with argon and refluxed under argon atmosphere for 6 h. Then 2M HCl was added to neutralize the reaction mixture and the thiol was extracted with Et_2O (3 x 200mL). The organic extract was washed dried and evaporated to give a cloudy oil. It was then chromatographed over SiGel using Et_2O-PE (1:9) as eluant to give the dimercaptan **101** as a white solid, 2.4 g, 81 %, mp. 70 - 72°C. ^1H NMR (300 MHz): δ 6.91 (s, 1H, Ar-H), 3.79 (d, 2H, J=6.6Hz, C**H**$_2$SH), 3.69 (d, 2H, J=5.1Hz, C**H**$_2$SH), 2.85 (m, 2H, ring H), 2.74 (m, 2H, ring H), 2.39 (s, 3H, Ar-Me), 1.81 (m, 2H, ring H), 1.62 (m, 4H, ring H), 1.66 (m, 1H, CH_2S**H**), 1.54 (t, 1H, J=6.6Hz, CH_2S**H**); ^{13}C NMR (90.6 MHz): 142.2, 140.9, 137.0, 136.8, 131.3, 128.9, 36.2, 32.3, 30.0, 28.4,

27.7, 23.5, 15.0; IR (KBr, major peaks cm^{-1}): 2917, 2852, 1458, 1255, 972, 889; MS (CI), *m/z* 253 (MH^+). EI-HRMS calculated for $C_{14}H_{20}S_2$: 252.1006, found: 252.1003.

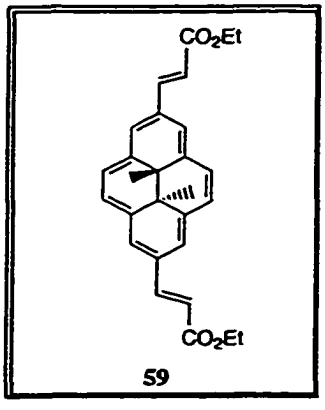
Pyridinium dichromate (PDC) oxidation of the *trans*-2,7,10b,10c-tetramethyldihydro-pyrene 57 to dialdehyde 58.
2,7-Diformyl-*trans*-10b,10c-dimethyl-10b,10c-dihydropyrene 58



58

PDC[44] (14.4 g, 38 mmole) was added in one portion to the DHP **57**[27] (1.11 g, 4.27 mmole) in dried CH_2Cl_2 (150 mL). The resulting mixture was then stirred at 20°C under argon for 6 h. The reaction mixture was then suction filtered througth a bed of celite and the filter cake was washed thoroughly with CH_2Cl_2. The filtrate was then preadsorbed onto SiGel and was chromatograhed over SiGel with CH_2Cl_2 as eluant. After evaporation of solvent, the crude black solid was crystallized from CH_2Cl_2 and hexane 1:5 (10 mL) to give **58** as dark purple crystals, 0.42 g, 34 %. mp 187-189°C (lit.[43] 187-190°C); ^{1}H NMR (300 MHz): δ 10.58 (s, 2H, CHO), 8.96 (s, 4H, H-1,3,6,8), 8.77 (s, 4H, H-4,5,9,10), -3.61 (s, 6H, Int Me); ^{13}C NMR (90.6MHz) δ 193.1 (C=O), 139.5 (C-2,7), 131.4 (C-3a,5a,8a,10a), 128.8 (C-1,3,4,8), 125.0 (C-4,5,9,10), 32.4 (C-10b,10c) 15.8 (Int Me C); IR (KBr, major bands cm^{-1}): 3000, 2935, 2837, 1685 (C=O), 1129, 965, 886, 663; MS(CI), *m/z* 289 (MH^+); EI-HRMS calculated for $C_{20}H_{16}O_2$: 288.1150, found: 288.1163.

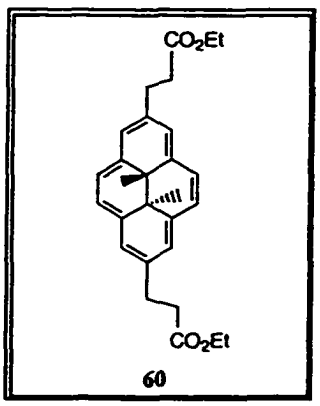
Ethyl *trans*-3-(2,7-*trans*-10b,10c-dimethyl-10b,10c-dihydropyrenyl)-propenoate 59



59

Triethylphosphonoacetate[44] (0.37 mL, 1.8 mmole) was added to a suspension of 60% sodium hydride (74 mg, 1.8 mmole) in dry THF (15 mL) at 0°C under argon. After hydrogen gas evolution had subsided, the dialdehyde, **64** (0.106 g, 0.37 mmole) dissolved in dry THF (20 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature and was subsequently warmed at 40°C for an hour. Saturated ammonium chloride solution (50 mL) was then added and the solution was extracted with CH_2Cl_2 (4 x 60 mL). The organic layer was washed, dried and evaporated to give a purple oil, which was chromatographed over SiGel with CH_2Cl_2-PE (1:5) as eluant to give pure **59** as a purple oil, 73 mg, 46 %. ^1H NMR (300 MHz): δ 8.54 (s, 4H, H-1,3,6,8), 8.46 (s, 4H, H-4,5,9,10), 8.22 (d, 2H, J=16.1Hz, H-3'), 6.88 (d, 2H, J=16.1Hz, H-2'), 4.34 (q, 4H, J=7.2Hz, $-OCH_2$), 1.39 (t, 6H, J=7.2Hz, $-CH_2CH_3$), -3.49 (s, 6H, Int Me); ^{13}C NMR (90.6MHz): δ 167.0 (C=O), 145.5, 138.4, 129.9, 126.3 (C-1,3,4,8), 123.9 (C-4,5,9,10), 118.7, 60.4, 31.4, 29.6, 14.3; IR (KBr, major bands cm^{-1}): 2967, 2918, 1700 (C=O), 1618, 1177, 1150, 892, 732; UV ($CHCl_3$) λ_{max} nm (log ε): 338 (4.78), 335 (4.94), 395 (4.37), 420 (4.55), 573 (4.62), 630 (3.14); MS(CI), *m/z* 429 (MH^+); EI-HRMS calculated for $C_{28}H_{28}O_4$: 428.1987, found: 428.1955.

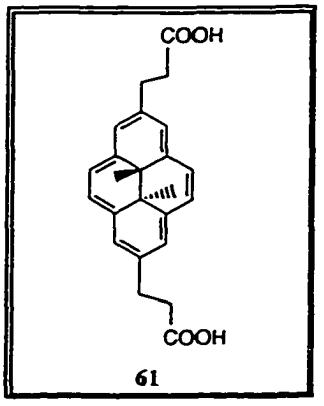
Ethyl *trans*-3-(2,7-*trans*-10b,10c-dimethyl-10b,10c-dihydropyrenyl)-propanoate 60



60

Palladium on activated charcoal, 10% (20 mg) was added to the unsaturated ester **59** (60 mg, 0.14 mole) in EtOAc (30 mL). The reaction mixture was stirred under hydrogen (atmospheric pressure) for approxiately 2.5 h. The mixture was then suction filtered through a bed of celite, washed with CH_2Cl_2 and then evaporated. The product was chromatographed over SiGel with CH_2Cl_2-PE (1:10) to give an unstable green oil, 53 mg, 88 %, which was used immediately for the next reaction. ^1H NMR (300 MHz): δ 8.49 (s, 4H, H-1,3,6,8), 8.39 (s, 4H, H-4,5,9,10), 4.13 (q, 4H, J=7.4Hz, -OC**H**$_2$CH$_3$), 3.62 (t, 4H, J=7.7Hz, -CH_2C**H**$_2$-), 2.98 (t, 4H, J=7.7Hz, -CH_2C**H**$_2$-), 1.19 (t, 6H, J=7.4Hz, -CH_2C**H**$_3$), -3.89 (s, 6H, Int Me); ; MS(CI), *m/z* 433(MH+); EI-HRMS calculated for $C_{28}H_{32}O_4$: 432.2275, found: 432.2291.

3-(2,7-*trans*-10b,10c-Dimethyl-10b,10c-dihydropyrenyl)-propionic acid 61

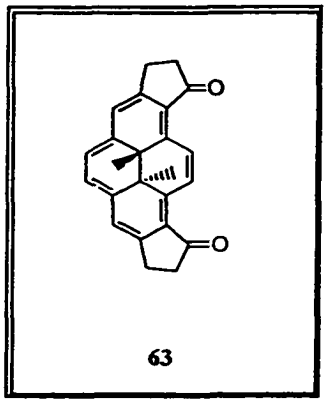


61

The saturated ester **60** (53 mg, 0.12 mmole) was refluxed in 2M sodium hydroxide solution (50 mL) for 16 h. The solution was then cooled to room temperature, acidified with 2M hydrochloric acid and then extracted with CH_2Cl_2 (3 x 80 mL). The organic layer was dried and evaporated. It was then chromatographed over SiGel with CH_2Cl_2-MeOH (9:1) to give the diacid 67 as a green solid, 40 mg, 89 %, mp 213-215°C. ^1H NMR (360 MHz): δ 12.18 (s, 2H, COOH), 8.54 (s, 4H, H-1,3,6,8), 8.48 (s, 4H, H-4,5,9,10), 3.50 (t, 4H, J=7.6Hz, -CH_2CH_2-), 2.89 (t, 4H, J=7.6Hz, -CH_2CH_2-), -4.30 (s, 6H, Int Me); ^{13}C NMR (90.6MHz): δ 173.8 (C=O), 135.7, 123.6, 122.5, 36.1, 32.3, 28.8, 13.7 (Int Me C); IR (KBr, major bands cm^{-1}): 3025, 3000, 2930, 1702 (C=O), 1218, 886, 667; UV ($CHCl_3$) λ_{max} nm (log ε): 240 (3.21), 346 (3.98), 384 (3.63), 328 (3.52), 477 (2.86); MS(CI), *m/z* 377 (MH^+); EI-HRMS calculated for $C_{24}H_{24}O_4$: 376.1675, found: 376.1695

trans-10c,10d-Dimethyl-1,2,3,8,9,10,10c,10d-octahydrodicyclopenta-[a,i]pyrene-1,10-dione 63

Oxalyl chloride (0.08 mL, 0.9 mmole) was added to the acid **61** (40 mg, 0.11 mmole) dissolved in CH_2Cl_2 (15 mL). The solution was stirred at 20°C for 6 h, after which the solvent was evaporated and the brown oil was dried under vacuum for about an hour to get rid of the excess chlorinating reagent. The crude di-acid chloride **62** was used immediately for the next step.

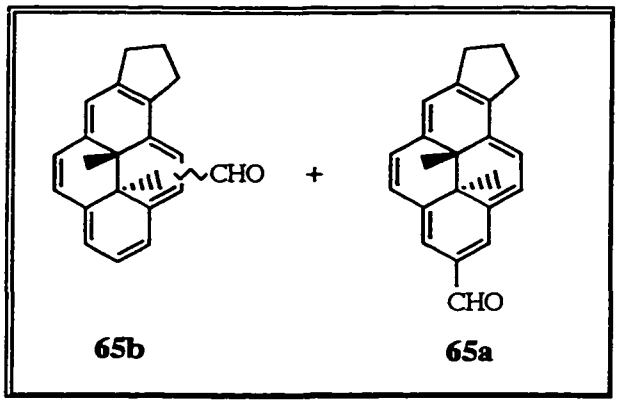


63

The brown oily residue was taken up in dry CH_2Cl_2 (80 mL) and aluminum chloride (42 mg, 0.31 mmole) was added into the mixture under argon. The solution was then allowed to stir for 8 h at 20°C. Iced water (40 mL) was added and the solution was extracted with CH_2Cl_2 (3 x 80 mL). The organic layer was washed, dried and evaporated to give a green solid. It was then chromatographed over SiGel with CH_2Cl_2. Eluted first was the green diketone **63**, 9 mg, 24 %, mp 239°C (decomp.). ^1H NMR (360 MHz): δ 9.27 (s, 2H, H-11,12), 8.31 (s, 2H, H-5,6), 8.20 (s, 2H, H-4,7), 3.65-3.44 (m, 4H, H-3,8), 3.04-2.89 (m, 4H, H-2,9), -2.92 (s, 6H, Int Me); ^{13}C NMR (90.6MHz): δ 208.3 (C=O), 156.0, 154.2, 143.4, 129.2 (quarternary C), 122.0 (C-11,12), 123.3 (C-4,7), 128.1 (C-5,6), 37.0 (C-2,9), 34.1 (C-12b,12c), 27.4 (C-3,8), 15.8 (Int Me-C); IR (KBr, major bands cm^{-1}): 2887, 1658 (C=O), 1437, 1154, 886, 715; UV ($CHCl_3$) λ_{max} nm (log ε): 229 (3.60), 368 (3.98), 391 (3.95), 454 (3.56), 720 (2.67); MS(CI), *m/z* 341 (MH^+); EI-HRMS calculated for $C_{24}H_{20}O_2$: 340.1463, found: 340.1450. Eluted next with CH_2Cl_2-MeOH (8:1) gave the unreacted diacid **61**, 3 mg, 7%.

trans-11b,11c-Dimethyl-8,9,11b,11c-tetrahydro-7H-cyclopenta[a]pyrene-2-carboxaldehyde 65a

Method 1: Using $TiCl_4$ as Lewis acid



α,α-Dichloromethyl methyl ether (0.05 mL, 0.6 mmole) was added to a solution of cyclopentene-[a]-annelated cyclopentene [a]-annelated DHP **64** (103 mg, 0.4 mmole) in dry CH_2Cl_2 (30 mL) at 0°C. Then Tin (IV) chloride, $SnCl_4$ (0.07 mL, 0.6 mmole) was added dropwise under N_2 and the resulting greenish-blue solution was stirred at 20°C for 4 h, after which it was slowly added to ice-cooled water (100 mL). Some black intactable precipitate formed and was filtered before extraction. The filtrate was extracted with CH_2Cl_2 (4 x 50 mL) and the combined organic extracts were washed, dried and evaporated to give a deep red gum, which was chromatographed over SiGel. The first green fraction eluted with hexanes was identified as the unreacted DHP **64** (30 mg, 27%). The second fraction eluted with hexanes-CH_2Cl_2 (1:1) gave a brown solution which was discarded. The third fraction gave a pale green oil (16 mg, 13 %). This fraction was identified as a mixture of formylated DHPs **65b** other than 2-formyl-DHP **65a**. ^1H NMR (300 MHz) δ 11.47, 11.22, 11.21, 11.65, 11.14, 11.10, 11.09, 10.92, 10.87 (9s, CHO), 9.83-7.96 (m, Ar-H), 4.03-3.50 (m, ring H), 2.58-2.43 (m, ring H), -3.91 to -4.08 (6s, Int Me); ^{13}C NMR: δ 193.8, 193.5, 192.7 (C=O), 144.7-119.3 (35 peaks, aromatic C), 35.0-13.6 (20 peaks, aliphatic C); MS(CI), *m/z* 300 (MH^+); EI-HRMS calculated for $C_{22}H_{20}O$: 300.1514, found: 300.1514. The last

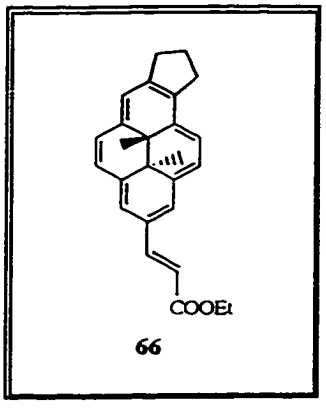
fraction eluted with CH_2Cl_2 gave a red gummy solid and was identified as 2-formyl-DHP **65a** (34 mg, 28 %). ^1H NMR (360 MHz) δ 10.53 (s, 1H, CHO), 8.98, 8.96 (2s, 2H, H-1,3), 8.78, 8.77 (2d, 2H, J=7.6Hz, 7.9Hz, H-10,4), 8.48-8.43 (m, 3H, H-5,6,11), 3.87-3.49 (m, 4H, H-7,9), 2.58-2.38 (m, 2H, H-8), -3.88,-3.90 (2s, 6H, Int Me); ^{13}C NMR (90.6MHz) δ 193.5 (C=O), 146.5, 143.1, 138.2, 136.4, 134.6, 134.2, 129.0, 128.7, 127.9, 125.6, 124.1, 123.0, 120.8, 119.8, 35.4, 33.2, 31.6, 31.4, 25.3, 16.5, 14.3 (Int Me C); IR (KBr, major bands cm^{-1}): 1674 (C=O), 1541, 1138, 1120, 882, 868, 666. 662; UV (CH_2Cl_2) λ_{max} (nm) log(ε): 224 (3.98), 358 (4.44), 378 (3.93), 409 (4.09), 528 (4.06), 600 (3.494), 664 (2.84); MS(CI), *m/z* 301 (MH^+); EI-HRMS calculated for $C_{22}H_{20}O$: 300.1514, found: 300.1518.

Method 2: Using $AlCl_3$ as Lewis acid

Aluminum chloride (190 mg, 1.5 mmole) was added under N_2 to a solution of DHP **64** (200 mg, 0.74 mmole) in dry CH_2Cl_2 (30 mL) at 0°C. The resulting greenish blue solution was stirred for 10 min. before the addition of α,α-dichloromethyl methyl ether (0.14 mL, 1.5 mmole) The resulting solution was stirred at 40°C for 4 h, after which it was slowly added to ice-cooled water (100 mL). The filtrated was extracted with CH_2Cl_2 (4 x 50 mL) and the combined organic extracts were washed, dried and evaporated to yield a deep red gum, which was chromatographed over SiGel. The first green fraction eluted with hexanes was identified as DHP **64** (30 mg, 14%). The second fraction eluted with hexanes-CH_2Cl_2 (1:1) gave a brown solution which was discarded. The third fraction afforded a pale green oil (52 mg, 23%). This fraction was identified as a mixture of formylated DHPs other than 2-formyl-DHP. The last fraction was eluted with CH_2Cl_2 to

give a red gummy solid which was identified as 2-formyl-DHP **65a**, 78 mg, 35 %. ^1H and ^{13}C NMR was identical to that synthesized by using $SnCl_4$ as Lewis acid.

Ethyl-(E)-3[11b,11c-dimethyl-8,9,11b,11c-*trans*-dimethyl-8,9,11b,11c-tetrahydro-7H-cyclopenta[a]pyren-2yl]-2-propenoate 66

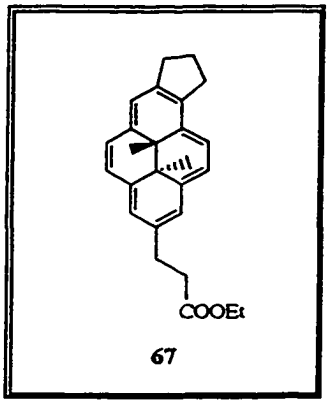


66

Triethylphosphonoacetate[44] (0.062 mL, 0.3 mmole) was added to a suspension of 60% sodium hydride (120 mg, 3 mmole) in dry THF (10 mL) at 0°C under N_2. After hydrogen gas evolution had subsided, 2-formyl-DHP **65a** (~95 % pure, mixed with some other formylated DHPs) (47 mg, 0.2 mmole) dissolving in dry THF (20 mL) was added dropwise. The reaction mixture was allowed to warm to 20°C and was further stirred for an hour. Then saturated ammonium chloride solution (30 mL) was added and the solution was extracted with CH_2Cl_2 (4 x 40 mL). The organic extract was washed, dried and preadsorbed onto SiGel. Then it was chromatographed over SiGel with CH_2Cl_2-hexanes (1:1) as eluant to give **66** as a red gum, 42 mg, 72 %. ^1H NMR (300 MHz): δ 8.62 (s, 2H, H-1,3), 8.55 (d, 2H, J=7.2Hz, H-4,11), 8.35-8.40 (m, 3H, H-6,5,10), 8.27 (d, 1H, J=16.1Hz, H-3'), 6.87 (d, 1H, J=16.1Hz, H-2'), 4.33 (q, J=7.2Hz, 2H, -C**H**$_2$CH$_3$), 3.44-3.91 (m, 4H, H-7,9), 2.34-2.50 (m, 2H, H-8), 1.40 (t, J=7.2Hz, 3H, -CH$_2$C**H**$_3$), -3.81, -3.84 (2s, 6H, Int Me); ^{13}C NMR (90.6MHz) δ 167.5 (C=O), 146.5, 143.8, 140.8, 138.2, 135.6, 135.3, 133.9, 127.1, 126.0, 125.5, 124.3, 123.4, 123.0, 120.6, 119.8, 116.9, 60.4, 35.2, 31.8, 31.4, 30.7, 25.3, 15.9, 14.5, 14.4;

IR (KBr, major bands cm^{-1}): 2972, 2917, 1703 (C=O), 1625, 1282, 1180, 1167, 1046, 981; UV (CH_2Cl_2) λ_{max} (nm) log(ε): 318 (5.23), 385 (5.02), 408 (4.88), 526 (4.24), 671 (2.84); MS(CI), *m/z* 371 (MH^+); EI-HRMS calculated for $C_{26}H_{26}O_2$: 370.1933, found: 370.1921.

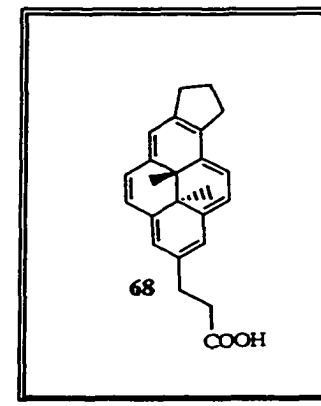
Ethyl-3[*trans*-11b,11c-dimethyl-8,9,11b,11c-tetrahydro-7H-cyclopenta-[a]pyren-2yl]-propanoate 67



67

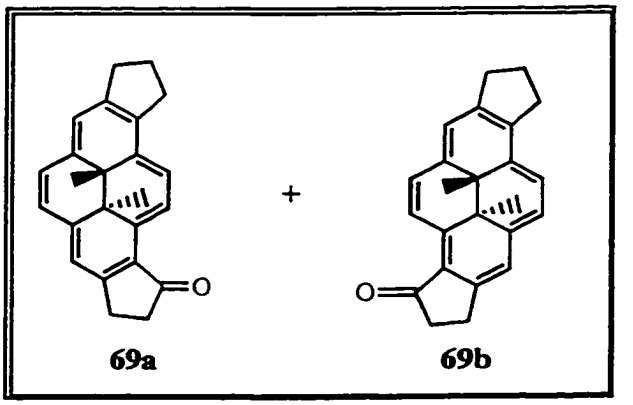
Palladium on activated charcoal, 10% (50 mg) was added to the unsaturated ester **66** (42 mg, 0.1 mmole) in EtOAc (20 mL). The reaction mixture was stirred under hydrogen (atmospheric pressure) for approximately 2.5 h during which the color of solution changed from red to green. The mixture was then suction filtered through a bed of celite, washed with CH_2Cl_2 and the solvent was evaporated to give an unstable dark green oil. It was flash chromatographed over deactivated SiGel using PE-CH_2Cl_2 (2:1) as eluant to gave the unstable saturated ester **67**, 35 mg, 83 %. ^1H NMR (300 MHz) δ 8.49-8.31 (m, 7H, Ar-H), 4.10 (m, 2H, CH_2CH_3), 3.82-3.65 (m, 4H, H-7,9), 3.59 (t, J=8.0Hz, 2H, H3'), 2.96 (t, J=8.0Hz, 2H, H2'), 2.53-2.43 (m, 2H, H-8), 1.17 (t, J=7.2Hz, 3H, CH_2CH_3), -4.16, -4.17 (2s, 6H, Int Me); IR (neat, major bands cm^{-1}): 2924, 1733 (C=O), 1174, 1041, 884, 668; MS(CI), *m/z* 373 (MH^+); EI-HRMS calculated for $C_{26}H_{28}O_2$: 372.2089, found: 372.2086.

3-[*trans*-11b,11c-Dimethyl-8,9,11b,11c-tetrahydro-7H-cyclopenta[a]pyren-2yl]-propanoic acid 68



The saturated ester **67** (40 mg, 0.1 mmole) in THF (10 mL) was refluxed in 2M aqueous sodium hydroxide (30 mL) for 10 h. The solution was then cooled to room temperature and neutralized with 2M HCl. The product was extracted with CH_2Cl_2 (3 x 40 mL), dried and evaporated. The dry solid was chromatographed over SiGel with CH_2Cl_2 as eluant to give 29 mg, 80 % of the acid **68**. mp 186°C (decomp.) ^{1}H NMR(300 MHz) δ 8.53-8.40 (m, 5H Ar-H), 8.37, 8.36 (2s, 2H, Ar-H), 3.88-3.48 (m, 6H, H-7,9,3'), 3.05 (m, 2H, H-2') , 2.54-2.37 (m, 2H, H-8), -4.14, -4.15 (2s, 6H, Int Me); ^{13}C NMR (90.6MHz) δ 179.2 (C=O), 140.9, 137.9, 137.4, 136.4, 136.0, 134.0, 131.0, 123.2, 123.0, 122.8, 122.6, 121.9, 120.0, 119.4, 36.5, 35.1, 32.6, 31.6, 30.6, 30.1, 25.4, 14.6, 13.9 (Int Me C); IR (KBr, major bands cm^{-1}): 2926, 1685 (C=O), 1319, 1032, 894, 685; UV (CH_2Cl_2) λ_{max} (nm) log(ε): 230 (3.56), 349 (4.27), 390 (3.85), 476 (3.64), 646 (2.70); MS(CI), *m/z* 345 (MH^+); EI-HRMS calculated for $C_{24}H_{24}O_2$: 344.1776, found: 344.1785.

trans-10c,10d-Dimethyl-1,2,3,8,9,10,10c,10d-octahydro-dicyclopenta[a,i]pyren-1-one (_cisoid_ monoketone) 69a
trans-11b,11c-Dimethyl-1,2,3,7,8,9,11b,11c-octahydro-dicyclopent[a,h]pyren-3-one (_transoid_ monoketone) 69b



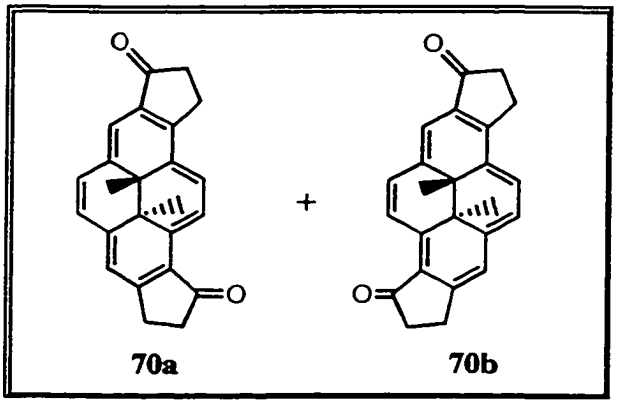
Oxalyl chloride (0.075 mL, 0.9 mmole) was added to the acid **68** (98 mg, 0.3 mmole) in dry CH_2Cl_2 (30 mL). The solution was stirred at 20°C for 6 h, after which the solvent was evaporated and the brown oily residue was dried under vacuum for about one hour to get rid of the excess chlorinating reagent.

The oily residue was taken up in dry CH_2Cl_2 (50 mL) and $BF_3.Et_2O$ (0.07 mL, 0.6 mmole) was added to the mixture. The solution was then allowed to stir for approximately 12 h, after which ice water was added and the solution was extracted with CH_2Cl_2 (3 x 80 mL). The combined organic extracts were dried and evaporated. The residue was then chromatographed over SiGel using CH_2Cl_2 as eluant. Elution first was the green monoketone **69**, 26 mg, 28 %, mp 210°C (decomp.). ^1H NMR (360 MHz) for **69**, mixture of two isomers, **69a & 69b** : δ 9.64 (d, J=7.4Hz, H-4, *transoid*), 9.57 (d, J=7.3Hz, H-12, *cisoid*), 8.57 (d, J=8.2Hz, Ar-H), 8.48 (d, J=8.3Hz, Ar-H), 8.43-8.36 (m, Ar-H), 8.32 (d, J=7.2Hz, Ar-H), 3.82-3.43 (m, ring H), 3.11-2.93 (m, ring H), 2.53-2.15 (m, ring H), -3.69, -3.70 (2s, Int Me), -3.83, -3.84 (2s, Int Me); ^{13}C NMR (90.6MHz) δ 209.1, 209.0 (C=O), 152.9, 152.0, 142.3, 141.8, 141.4, 141.0, 140.9, 140.1, 138.4, 138.3, 132.8, 130.3, 129.2, 128.6, 127.2, 125.8, 125.5, 124.6, 123.9,

123.6, 123.5, 122.8, 122.3, 121.4, 119.9, 119.9, 119.7, 119.4, 37.4, 37.3, 35.1, 34.5, 32.7, 32.4, 31.8, 31.7, 31.5, 31.2, 27.4, 27.3, 25.7, 24.8, 15.2, 14.8, 14.2, 14.4; IR (KBr, major bands cm^{-1}): 2930, 1698, 1624 (C=O), 1448, 1256, 1174, 1023, 721; UV (CH_2Cl_2) λ_{max} (nm) log(ε): 230 (3.11), 368 (3.82), 437 (4.05), 457 (4.10), 564 (2.02), 621 (2.18), 687 (2.62); MS(CI), *m/z* 327 (MH^+); EI-HRMS calculated for $C_{24}H_{22}O$:326.1671, found: 326.1682. Eluted next with MeOH-CH_2Cl_2 give the green unreacted acid **68**, 12 mg, 12%.

Oxidation of the monoketone 69 to the diketone 70a and 70b.

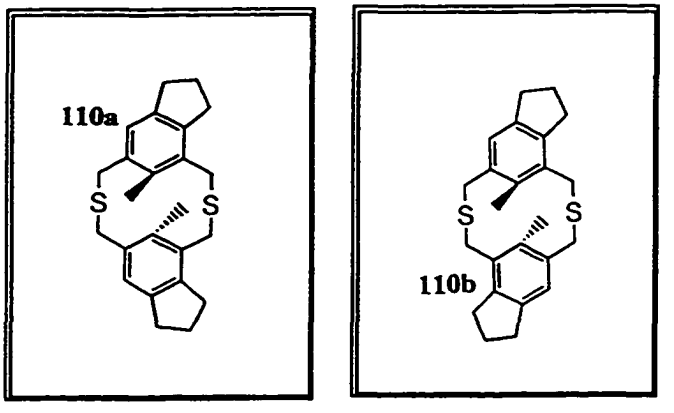
***trans*-10c,10d-Dimethyl-1,2,3,8,9,10,10c,10d-octahydro-dicyclopenta[a,i]pyren-1,8-dione (*cisoid* diketone) 70a**
***trans*-11b,11c-Dimethyl-1,2,3,7,8,9,11b,11c-octahydro-dicyclopent[a,h]pyren-1,9-dione (*transoid* diketone) 70b**



The green monoketone **69** (26 mg, 0.08 mmole) in CH_2Cl_2 (30mL) was added dropwise to a slurry of PDC in CH_2Cl_2 (25mL). After about 4 h, the reaction mixture was suction filtered through a bed of celite and eluted with CH_2Cl_2. The filtrate was then preadsorbed onto SiGel. It was then chromatographed over SiGel using CH_2Cl_2 as eluant to gave the mixture of diketone **70**, 9 mg, 35 % yield, mp 176°C (decomp.). ^1H NMR (360 MHz), mixture of two isomers, absorptions due to each individual isomer was resolved by COSY, NOESY and NOE experiments. ***Transoid* 70b**: δ 9.85 (d,

J=8.03Hz, H-12), 8.96 (s, H-10), 8.95 (d, J=6.79Hz, H-11), 8.90 (d, J=7.76Hz, H-6), 8.56 (s, H-4), 8.53 (d, J=7.76Hz, H-5), 4.08-3.45 (m, ring-H), 3.19-2.87 (m, ring-H), -3.80 (s, Int Me); ***Cisoid* 70a**: δ 9.25 (d, J=7.03Hz, H-12), 8.46-8.42 (m, H-6,7,11), 8.21 (d, J=8.58Hz, H-5), 8.13 (s, H-4), 4.08-3.45 (m, ring-H), 3.19-2.87 (m, ring-H), -2.89 (s, Int Me); ^{13}C NMR (90.6MHz) δ 208.4, 208.0, 207.7, 207.4 (C=O), 159.1, 154.9, 153.1, 149.4, 146.3, 144.2, 137.3, 136.8, 136.1, 134.6, 134.1, 132.2, 131.3, 130.5, 129.9, 126.8, 126.1, 125.9, 125.6, 125.1, 122.2, 121.2, 121.1, 120.9, 120.8, 118.8, 118.7, 37.4, 36.9, 36.8, 36.3, 35.2, 34.1, 33.2, 32.2, 27.7, 27.4, 24.9, 24.8, 16.8, 16.0, 15.7, 14.6; IR (KBr, major bands cm^{-1}): 2890, 1670 (C=O), 1520, 1425, 1275, 1145, 1120; UV (CH_2Cl_2) λ_{max} (nm) log(ε): 385 (4.93), 428 (4.19), 517 (3.70), 629 (2.34), 673 (2.39), 692 (2.42); MS(CI), *m/z* 341 (MH+); EI-HRMS calculated for $C_{24}H_{20}O_2$: 340.1463, found: 340.1457.

anti-9,18-Dimethyl-5,6;15,16-bis(trimethylene)-2,11-dithia-[3,3]metacyclophane, (_cisoid_ 110a)
anti-9,18-Dimethyl-5,6;14,15-bis(trimethylene)-2,11-dithia-[3,3]metacyclophane, (_transoid_ 110b)



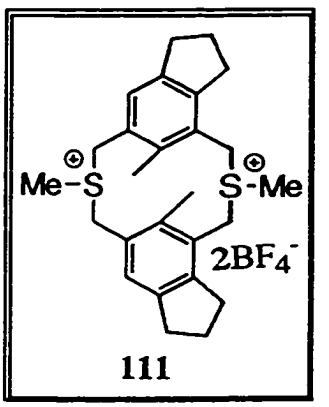
A solution of the dibromide **85** (2.348 g, 7.38 mmole) and the dimercaptan **86** (1.656 g, 7.38 mmole) in nitrogen purged benzene (600 mL) was added dropwise via a precision addition funnel to a well stirred solution of KOH (1.5 g, 0.023 mole) in nitrogen purged 90% EtOH (2.5 L) at 20°C under nitrogen. The addition took about 24 h. After the addition, the mixture was further stirred for an additional 6 h after which the bulk of solvent was removed under reduced pressure. Water (500 mL) was added and the product was extracted with CH_2Cl_2 (3 x 300 mL). The organic extract was washed, dried and preadsorbed onto SiGel (20 g). It was then chromatographed over SiGel using CH_2Cl_2 as eluant to give a white powder, 1.8 g, 64 %, which is a mixture of thiacyclophane isomers. The ratio of syn:anti isomers based on the NMR integration of the internal methyl groups (δ 2.56, 2.53 for *syn* isomers; δ 1.35, 1.24 for *anti* isomers) was determined to be 1:3. A sample was recrystallized three times from benzene to give the *anti,transoid* thiacyclophane **110b**, mp 230-233°C. ^{1}H NMR (360 MHz): δ 7.33 (s, 2H, Ar-H), 3.84-3.75 (m, 4H, bridge CH_2), 3.45 (s, 4H, bridge CH_2), 3.14-3.06 (m, 2H, ring CH_2), 2.90-2.80 (m, 6H, Ring CH_2), 2.19-2.07 (m, 4H, ring CH_2), 1.24 (s, 6H, Int Me); ^{13}C NMR (90.6 MHz): 142.8, 141.0, 136.0, 135.3, 128.8, 125.9, 32.7, 32.1,

30.7, 29.3, 25.2, 14.5; IR (KBr, major bands cm^{-1}): 2898, 1440, 1196, 872, 755; MS (CI), *m/z* 381 (MH^+).

Anal. Calculated for $C_{24}H_{28}S_2$: % C: 75.74 % H: 7.42

Found % C: 75.69 % H: 7.55

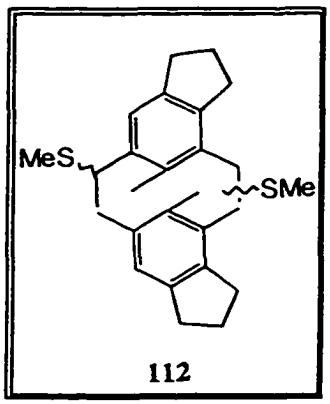
Bis-sulphonium salt 111



111

A solution of the dithiacyclophane **110** (0.64 g, 1.68 mmole) in CH_2Cl_2 (30 mL) was added to a stirred suspension of $(MeO)_2CHBF_4$[53], 80% as oil, (0.67 mL) in CH_2Cl_2 (20 mL) at 0°C under argon. After the addition, the mixture was allowed to warm to 20°C and stirred for an additional 6 h. Then EtOAc (100 mL) was added to dissolve any excess methylating reagent present and the mixture was stirred overnight. The white bis-sulfonium salt was suction filtered, washed with EtOAc and dried under vacuum to give **111**, 0.97 g, 99 %. IR (KBr, major bands cm^{-1}): 2958, 1462, 1422, 1056, 521.

Steven's rearrangement of salt 111 to give bis-thiomethyl ether 112

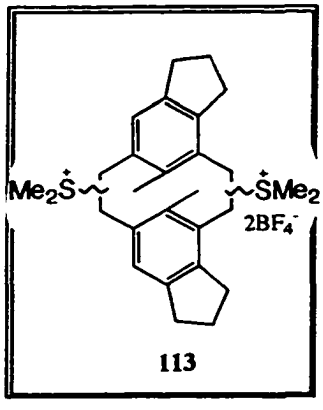


112

The salt **111**, (5.9 g, 0.010 mole) was suspended in degassed dry THF (175 mL) at 0°C under argon and potassium *t*-butoxide (2.7 g, 22 mmol) was added. The reaction mixture was stirred at 20°C for 30 min. Then saturated ammonium acetate (100 mL) was added and the solution was extracted with CH_2Cl_2 (3 x 250 mL). The organic layers were combined, washed, dried and evaporated to yield the crude product. This was chromatographed on SiGel, using 7:3 PE : CH_2Cl_2 as eluant, to give the bis-thiomethyl ether **112** as a mixture of many isomers, 3.1 g, 76 %. ^1H NMR (360 MHz): δ 7.64-6.94 (m, Ar-H), 4.24-3.73 (m), 3.31-2.30 (m), 2.30-2.10 (m, -SMe), 0.46-0.90 (m, Int Me) ; ^{13}C NMR (90.6 MHz): 142.4-120.6 (34 peaks, aromatic C), 50.4-14.9 (17 peaks, aliphatic C); IR (neat, major bands cm^{-1}): 2946, 1445, 1309, 909, 727; MS (CI), *m/z* 409 (MH^+); EI-HRMS calculated for $C_{26}H_{32}S_2$: 408.1945, found: 408.1946.

The bis-salt 113

$(MeO)_2CHBF_4$[53] (2.3 mL, 80% oil) was added to a solution of mixed Stevens isomers **112** (3.1 g, 7.59 mmole) in CH_2Cl_2 (150 mL) at 0°C under argon. The solution was then stirred at 20°C for 3 h before the addition of EtOAc (150 mL). After stirring overnight, the brown salt 12 was suction filtered and washed thoroughly with EtOAc, to give 3.57 g, 77 %. IR (KBr, major bands cm^{-1}): 3412, 2948, 1442, 1053, 513.

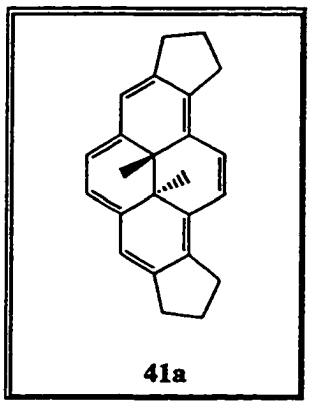


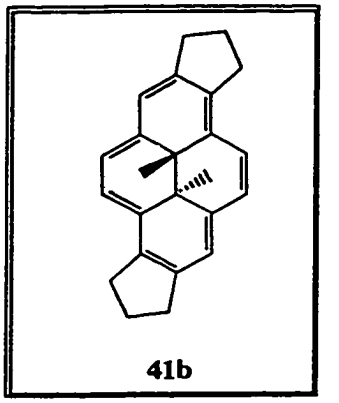
113

Hofmann elimination of bis-salt 113 to give DHP 41.

***trans*-10c-10d-Dimethyl-1,2,3,8,9,10,10c,10d-octahydro-dicyclopenta[a,i]pyrene, (*Cisoid* 41a)**

***trans*-11b,11c-Dimethyl-1,2,3,7,8,9,11b,11c-octahydro-dicyclopenta[a,h]pyrene, (*Transoid* 41b)**



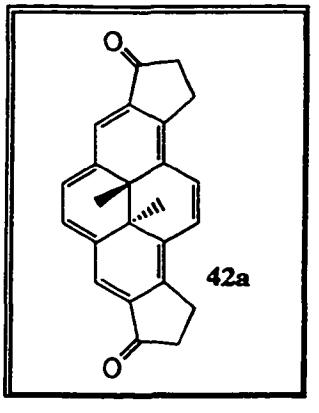


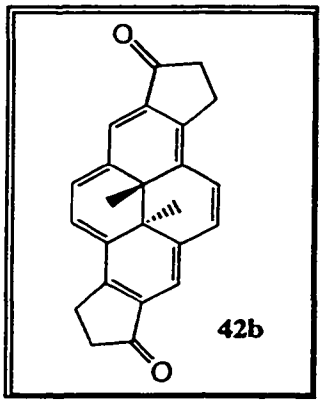
The salt **113** (3.57 g, 5.83 mmole) was suspended in degassed dry THF (200 mL) under argon and potassium *t*-butoxide (1.96 g, 16.6 mmole) was added. This was stirred at 20°C for 2.5 h. Then water was added and the solution was extracted with CH_2Cl_2 (3 x 200 mL). The organic layers were combined, washed, dried and concentrated to leave a green residue. This was chromatographed twice rapidly on deactivated SiGel using CH_2Cl_2-hexane (1:8) as eluant to give the DHP **41** as a green oil, 0.82 g, 45%. A sample was rechromatographed and crystallized from MeOH-hexane (8:1) to afford a green powder which is a mixture of *anti, cisoid* and *anti, transoid* isomers. ^1H NMR (300 MHz) *Cisoid* and *transoid* was resolved based on symmetry and fractional crystallization which enriched one isomer: ***trans, transoid* 41b**: δ 8.48-8.46 (m, Ar-H), 3.90-3.95 (m, CH_2), 2.58-2.38 (m, CH_2), 2.58-2.38 (m, CH_2), -4.15 (s, Int Me); ***trans, cisoid* 41a**: δ 8.45, 8.41, 8.40 (3s, Ar-H), 3.90-3.95 (m, CH_2), 2.58-2.38 (m, CH_2), 2.58-2.38 (m, CH_2), -4.12 (s, Int Me); ^{13}C NMR (90.6 MHz): 140.2, 139.9, 137.6, 137.4, 136.8, 136.7, 130.6, 130.4, 122.3, 121.4, 119.5, 119.4, 119.2, 118.3, 35.1, 35.0, 31.6, 31.0, 30.9, 25.5, 25.3, 14.4, 14.3; IR (KBr, major bands cm^{-1}): 2915, 1437,

886, 813; UV (CH_2Cl_2) λ_{max}(nm) (log ε): 230 (4.21), 353 (5.26), 386 (4.79), 474 (4.06), 533 (2.21), 646 (3.21); MS (CI), *m/z* 313 (MH^+); EI-HRMS calculated for $C_{24}H_{24}$: 312.1878, found: 312.1869.

Pyridinium dichromate (PDC) oxidation of the DHP 41 to diketone 42.

***trans*-10c,10d-Dimethyl-1,2,3,8,9,10,10c,10d-octahydro-dicyclopenta[a,i]pyrene-3,8-dione, (*Cisoid* 42a)**
***trans*-11b,11c-Dimethyl-1,2,3,7,8,9,11b,11c-octahydro-dicyclopenta[a,h]pyrene-1,7-dione, (*Transoid* 42b)**

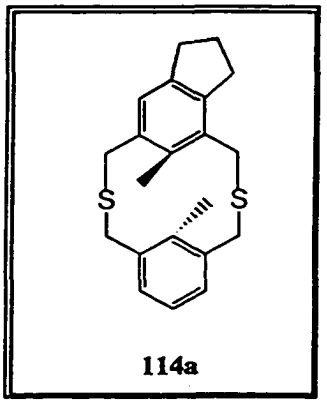




PDC[44] (9.05 g, 32.5 mmole) was added in one portion to the DHP **41** (1 g, 3.2 mmole) in dried CH_2Cl_2 (100 mL). Then the solution was stirred at 20°C under argon for 5 h. The reaction mixture was then suction filtered througth a bed of celite and the filter cake waswashed thoroughly with CH_2Cl_2.The filtrate was then preadsorbed onto SiGel and was chromatograhed over SiGel with MeOH-CH_2Cl_2 (1:9) as eluant. After evaporation of solvent, the crude black solid was crystallized in CH_2Cl_2 and hexane 1:5 (3 mL) to give a brown solid which contained a mixture of *cisoid* and *transoid* diketones **42a** and **42b**, 0.31 g, 28%. ^1H NMR (360 MHz), mixture of two isomers. The absorption due to individual isomers was resolved by COSY, NOESY and NOE experiments. ***Transoid* 42b**: δ 8.92 (s, H-6,12), 8.87, 8.83 (AB, J=7.90Hz, H-

4,5,10,11), 3.88-4.11 (m, H-1,7), 2.96-3.22 (m, H-2,8), -3.83 (s, Int Me) ; ***Cisoid* 42a**: δ 8.39 (s, H-11,12), 8.38 (s, H-4,7), 8.35 (s, H-5,6), 3.80-3.76 (m, H-1,10), 2.96-3.22 (m, H-2,9), -2.91 (s, Int Me); ^{13}C NMR (90.6MHz) δ 208.3, 207.6 (C=O), 152.2, 146.1, 140.7, 140.5, 136.9, 134.1, 133.3, 132.7, 128.9, 122.0, 116.0, 128.5, 123.1, 118.7, 36.9, 36.4, 35.0, 33.2, 24.8, 24.6, 17.0, 15.8; IR (KBr, major bands cm^{-1}): 2925, 1697, 1684 (C=O), 1443, 1300, 1198, 1028, 816; UV (CH_2Cl_2) λ_{max}(nm) (log ε): 242 (3.73), 360 (4.45), 385 (4.00), 410 (4.09), 539 (3.86), 702 (3.01); MS (CI), *m/z* 341 (MH^+); EI-HRMS calculated for $C_{24}H_{20}O_2$: 340.1463, found: 340.1453.

anti-9,18-Dimethyl-5,6-trimethylene-2,11-dithia[3,3]metacyclophane 114a



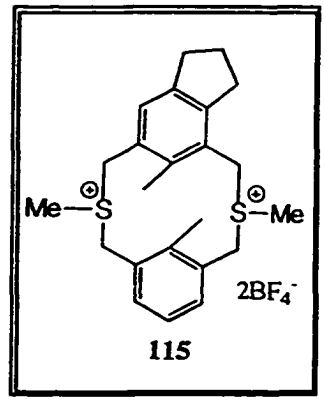
114a

A solution of the dibromide **85** (3.50 g, 0.011 mole) and the dimercaptan **74** (2.03 g, 0.011 mole) in nitrogen purged benzene (800 mL) was added via a precision addition funnel dropwise to a well stirred solution of KOH (2.18 g) in nitrogen purged 80 % EtOH (3 L) at 20°C under nitrogen. The addition took about 36 h. After the addition, the mixture was further stirred for an additional 5 h after which the bulk of solvent was removed under reduced pressure. Then water (300 mL) was added and the product was extracted with CH_2Cl_2 (3 x 250 mL). The organic extract was washed, dried and preadsorbed onto SiGel (20 g) and filtered through a column of SiGel using CH_2Cl_2-PE (1:2) as eluant to yield the sticky white solid dithiacyclophane **114**, as a mixture of *syn* and *anti* isomers, 2.0 g, 53 %. The ratio of the isomers based on internal methyl protons (δ 1.31, 1.19 for *anti* isomer; δ 2.52, 2.49 for *syn* isomer) was determined by NMR to be 3:1, *anti* : *syn*. A sample was crystallized twice from CH_2Cl_2-PE (1:3) to give the *anti* isomer **114a**, mp. 133 - 135°C. ^{1}H NMR (360 MHz): δ 7.38 (d, 1H, J=7.5Hz, H-14(16)), 7.22 (d, 1H, J=7.5Hz, H-16(14)), 7.25

(s, 1H, H-7), 7.07 (t, 1H, J=7.6Hz, H-15), 3.48-3.80 (m, 8H, H-1,3,10,12), 3.10-3.20 (m, 1H, ring-H), 2.99-2.78 (m, 3H, ring-H), 1.94-2.20 (m, 2H, ring-H), 1.31 (s, 3H, Int Me), 1.20 (s, 3H, Int Me); ^{13}C NMR (90.6 MHz): 143.1, 141.0, 138.7, 136.7, 136.1, 134.5, 134.2, 129.4, 129.8, 129.7, 126.3, 125.4, 32.7, 32.2, 32.1, 31.2, 30.8, 29.2, 25.2, 14.8, 14.2; IR (KBr, major peaks cm^{-1}): 2991, 2924, 1459, 726; MS (CI), *m/z* 341 (MH^+); EI-HRMS calculated for $C_{21}H_{24}S_2$: 340.1319, found: 340.1318.

Anal.	Calculated for $C_{21}H_{24}S_2$:	% C: 74.07	% H: 7.10
	Found	% C: 73.94	% H: 7.04

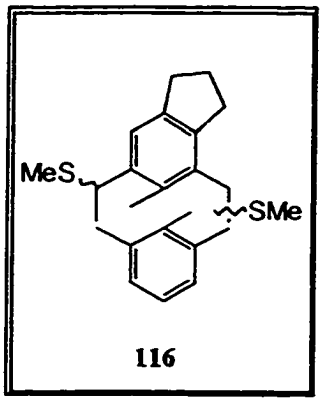
Methylation of the dithiacyclophane 114 to give the bis-salt 115



115

A solution of the dithiacyclophane **114** (2.0 g, 5.88 mmole) in CH_2Cl_2 (100 mL) was added to a stirred suspension of $(MeO)_2CHBF_4$[53] (2.36 mL, 80 % as oil) in CH_2Cl_2 (20 mL) at 0°C under Argon. After the addition, the mixture was allowed to warm to 20°C and stirred for an additional 6 h. Then EtOAc (100 mL) was added to dissolve any excess methylating reagent present and the mixture was stirred overnight. The white powder, the bis-sulfonium salt **115**, was suction filtered, washed with EtOAc and dried under vacuum to give 3.1 g, 97 %.

Stevens rearrangement of the bis-salt 115 to the bis-thiomethyl ether 116

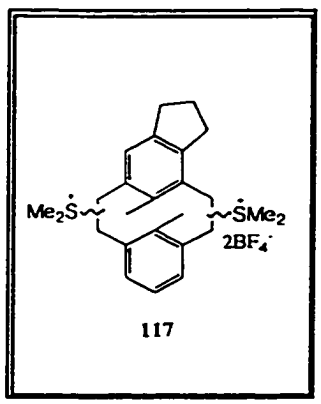


116

The salt **115** (6.76 g, 0.012 mol) was suspended in degassed dry THF (75 mL) under argon and potassium*t*-butoxide (3.5 g, 0.031 mol) was added. The reaction mixture was stirred at 20°C for 2 h. Then water (50 mL) was added and the solution was extracted with CH_2Cl_2 (3 x 200 mL). The organic layers were combined, washed, dried and evaporated to yield the crude product. This was chromatographed on SiGel, using 7:3 PE : CH_2Cl_2 as eluant, to give **116** as a mixture of many isomers, 3.75 g, 85 %. ^{1}H NMR (300 MHz) δ 7.84-6.84 (m, Ar-H), 4.67-3.89 (m, methine H), 3.44-2.45 (m, ring-H), 2.10-2.22 (~19s, -SMe), 0.96-0.46 (~29s, Int Me); ^{13}C NMR (90.6 MHz): 143.2-120.7 (33 peaks, aromatic C), 14.2-68.0 (37 peaks, aliphatic C); IR (neat, major bands in cm^{-1}): 2915, 1454, 785, 723, 585; MS (CI), *m/z* 369 (MH+); EI-HRMS calculated for $C_{23}H_{28}S_2$: 368.1632, found: 368.1644.

Methylation of 116 to give the bis-salt 117

$(MeO)_2CHBF_4$[53] (3.5 mL, 80 % oil) was added to a solution of mixed Stevens isomers of **116** (3.75 g, 0.010 mole) in CH_2Cl_2 (80 mL) at 0°C under argon. The solution was then stirred at 20°C for 3 h before the addition of EtOAc (90 mL). After stirring overnight, the brown salt **117** was suction filtered and washed thoroughly with EtOAc, 5.12 g, 89 %.

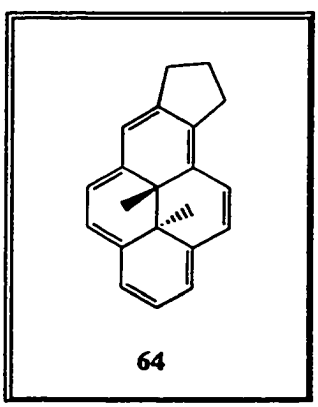


117

Hofmann elimination of 117 to give the DHP 64.

***trans*-11b,11c-Dimethyl-8,9,11b,11c-tetrahydro-7H-cyclopenta[a]pyrene 64**

The salt **117** (5.08 g, 8.89 mmole) was suspended in degassed dry THF (100 mL) under argon and potassium *t*-butoxide (2.3 g, 0.019 mole) was added. This was stirred at 20°C for 4 h under argon. Then water was added and the solution was extracted with CH_2Cl_2 (4 x 150 mL). The organic layers were combined, washed, dried and concentrated to leave a green residue.

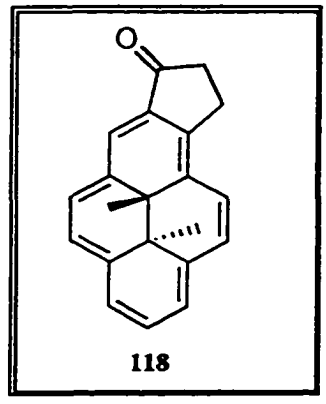

64

This was chromatographed rapidly twice over deactivated SiGel, eluting with PE under argon to give the cyclopentene annelated DHP **64** as a green oil. A sample was crystallized from MeOH-hexane (10:1) to give a green solid, mp. 88 - 89°C, 1.93 g, 80%. ^{1}H NMR (360 MHz): δ 8.47-8.60 (m, 7H, Ar-H), 8.00 (t, 1H, J=7.59Hz, H-2), 3.53-3.90 (m, 4H, H-7,9), 2.40-2.59 (m, 2H, H-8), -4.20, -4.22 (2s, 6H, Int Me); ^{13}C NMR (90.6 MHz): 141.4, 138.3, 137.1, 135.9, 135.7, 131.4, 123.6, 123.3, 122.9, 122.8, 122.1, 121.8, 119.8, 119.0, 35.1, 31.6, 30.5, 30.3, 25.4, 14.7, 13.6; IR (KBr, major bands cm^{-1}): 2920, 1434, 1366, 886, 821, 667; UV (cyclohexane) λ_{max} (nm) log (ε): 388 (4.10), 448 (3.73), 471 (3.78), 531 (2.22), 582 (2.36), 631 (2.69), 643 (2.91); MS (CI), *m/z* 273 (MH^+).

Anal.	Calculated for $C_{21}H_{20}$:	% C: 92.60	% H: 7.40
	Found	% C: 92.02	% H: 7.34

Pyridinium dichromate (PDC) oxidation of the cyclopentene annelated DHP 64 to ketone 118.

***trans*-11b,11c-Dimethyl-8,9,11b,11c-tetrahydro-7H-cyclopenta[a]-pyren-7-one 118**

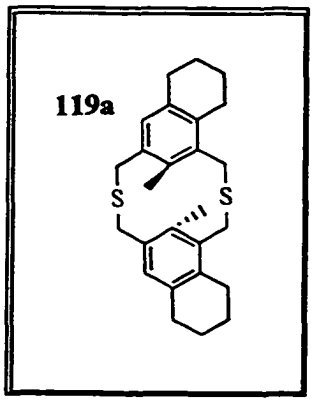


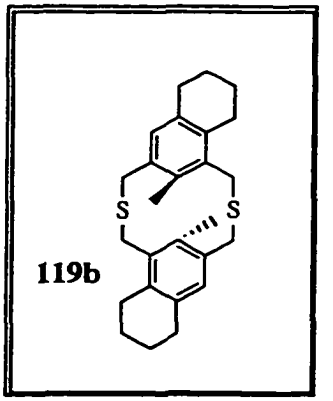
118

PDC[44] (0.17 g, 0.45 mmole) was added in one portion to the DHP **64** (25 mg, 0.092 mmole) in dried CH_2Cl_2 (30 mL). The reaction mixture was then stirred at 20°C under argon for 5 h. Then the reaction mixture was suction filtered througth a bed of celite and the filter cake was washed thoroughly with CH_2Cl_2. The filtrate was then preadsorbed onto SiGel and was chromatographed over SiGel with CH_2Cl_2 as eluant. After evaporation of solvent, the crude black solid was crystallized from CH_2Cl_2 and hexane 1:6 (2 mL) to give a deep red solid, 11 mg, 42 %, mp 140°C (decomp.). ^1H NMR (360 MHz) δ 8.72 (s, 1H, H-6), 8.70 (d, 1H, J=7.13Hz, H-10), 8.68 (d, 1H, J=6.99Hz, H-5), 8.50 (d, 1H, J=8.29Hz, H-4), 8.43 (d, 1H, J=8.25Hz, H-1), 8.38 (d, 1H, J=7.29Hz, H-11), 8.37 (d, 1H, J=7.21Hz, H-3), 8.05 (t, 1H, J=7.73Hz, H-2), 3.82-3.95 (m, 2H, H-8), 2.96-3.18 (m, 2H, H-9), -3.69, -3.70 (2s, 6H, Int Me); ^{13}C NMR (90.6 MHz): 208.2 (C=O),149.9, 142.0, 140.5, 137.3, 131.0, 130.5, 128.8, 126.4, 125.2, 124.8, 123.3, 123.1, 122.0, 116.5, 36.7, 32.4, 32.2, 24.8, 15.8, 15.1; IR (KBr, major bands cm^{-1}): 2955, 2900, 1680 (C=O), 1520, 1430, 1315, 1290, 1200, 1170, 810, 825, 660; UV (cyclohexane) λ_{max} (nm) log (ε): 351 (5.20), 373 (4.62), 397 (4.87), 507 (4.39), 593 (2.87), 657 (3.07); MS (CI), *m/z* 287 (MH^+).

Anal.	Calculated for $C_{21}H_{18}O$:	% C: 88.08	% H: 6.34
	Found	% C: 87.91	% H: 6.39

***anti*-9,18-Dimethyl-5,6;15,16-bis(tetramethylene)-2,11-dithia[3,3]metacyclophane, *cisoid* 119a**
***anti*-9,18-Dimethyl-5,6;14,15-bis(tetramethylene)-2,11-dithia[3,3]metacyclophane, *transoid* 119b**



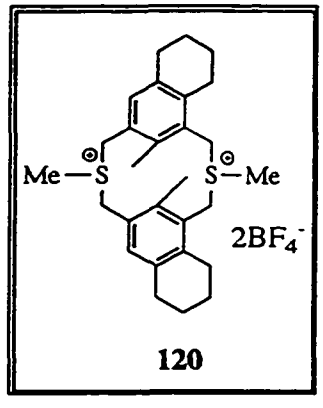


A solution of the dibromide **92** (3.018 g, 9.10 mmol) and the dimercaptan **93** (2.165 g, 9.10 mmole) in nitrogen purged benzene (800 mL) was added dropwise via a precision addition funnel to a well stirred solution of KOH (3.6 g) in nitrogen purged 85 % EtOH (3 L) at 20°C under nitrogen. The addition took about 30 h. After the addition, the mixture was further stirred for an additional 5 h after which the bulk of solvent was removed under reduced pressure. Then water (300 mL) was added and the product was extracted with CH_2Cl_2 (4 x 200 mL). The organic extracts were washed, dried, preadsorbed onto SiGel (15 g) and then were filtered through a column of SiGel using CH_2Cl_2-PE (1:2) as eluant to yield the thiacyclophane **119** as a sticky white solid. The crude product was then re-chromatographed to afford a white solid, 1.9 g, 51%. The ratio of the isomers based on internal methyl protons chemical shift (δ 1.25, 1.34 for *anti* isomer; δ 2.41 for *syn* isomer) was determined by NMR to be 5:1, *anti* : *syn*. A sample was crystallized twice from CH_2Cl_2-PE (1:3) to give the *anti, transoid* isomer **119b**, mp 225-227°C. ^{1}H NMR (300 MHz): δ 7.27 (s, 1H, Ar-H), 3.81 (q, J=11.8Hz, 4H, bridge CH_2), 3.30-3.42 (m, 4H, bridge CH_2), 2.64-2.99 (m, 8H, ring H), 1.67-1.95 (m, 8H, ring H), 1.33 (s, 6H, Int Me); ^{13}C NMR (90.6MHz) δ 135.9, 134.9, 134.6, 134.2,

131.0, 130.6, 29.9, 29.8, 27.8, 27.0, 23.7, 22.9, 14.8; IR (neat, major bands cm^{-1}): 2929, 1452, 1220, 760; MS(CI), *m/z* 409 (MH^+); EI-HRMS calculated for $C_{26}H_{32}S_2$: 408.1945, found: 408.1948.

Anal.	Calculated for $C_{26}H_{32}S_2$	% C: 76.40	% H: 7.89
	Found	% C: 75.07	% H: 7.91

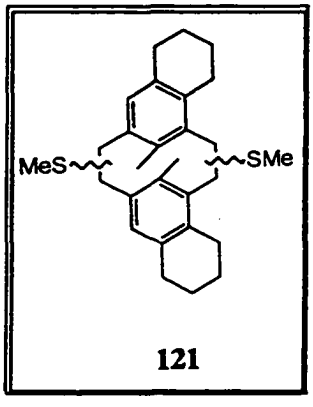
Bis-salt 120



120

A solution of the mixed dithiacyclophane **119** (0.88 g, 2.16 mmole) in CH_2Cl_2 (20 ml) was added to a stirred suspension of $(MeO)_2CHBF_4$[53] (0.9 mL, 6.7 mmole , 80% as oil) in CH_2Cl_2 (20 mL) at 0°C under argon. After the addition, the mixture was allowed to warm to 20°C and stirred for an additional 4 h. Then EtOAc (60 mL) was added to dissolve any excess methylating reagent present and the mixture was stirred overnight. The white powder of the bis-sulfonium salt **120** was suction filtered, washed with EtOAc and dried under vacuum, 0.86 g, 65 %. IR (KBr, major peaks cm^{-1}): 2935, 1433, 1057, 521.

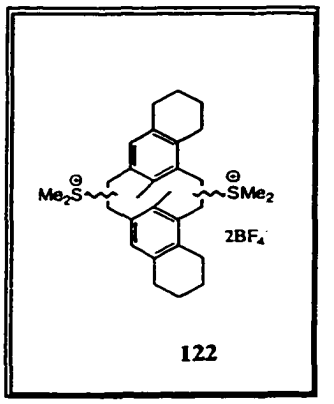
Stevens rearrangement of the bis-salt 120 to the thiomethyl ether 121



121

The salt **120**, (0.86 g, 1.41 mmole) was suspended in degassed dry THF (50 mL) under argon and potassium *t*-butoxide (0.5 g, 4.2 mmol) was added. The reaction mixture was stirred at 20°C for an hour. Then water (50 mL) was added and the solution was extracted with CH_2Cl_2 (3 x 50 mL). The organic layers were combined, washed, dried and evaporated to yield the crude product. This was chromatographed on SiGel, using 7:3 PE : CH_2Cl_2 as eluant, to give **121** as a mixture of many isomers (0.46 g, 75 %) ^{1}H NMR (300 MHz) δ 7.49-6.78 (m, Ar-H),4.94-4.82 (m), 3.92-1.66 (m), 0.91-0.48 (m, Int Me); ^{13}C NMR (90.6MHz) δ 140.5-124.9 (13 peaks), 50.3-15.0 (27 peaks); IR (neat, major bands cm^{-1}): 2926, 2870, 1461, 1426, 1269, 1097, 741; MS(CI), *m/z* 437 (MH^+); EI-HRMS calculated for $C_{28}H_{36}S_2$: 436.2258, found: 436.2256.

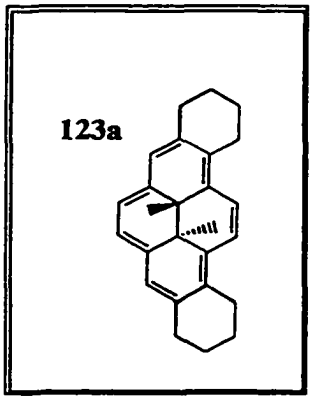
Bis-sulfonium salt 122

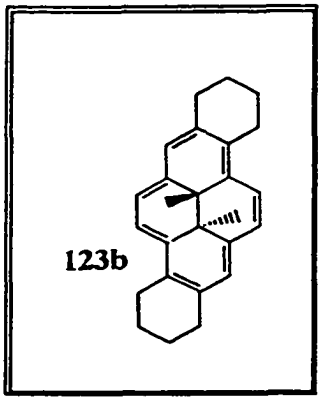


122

$(MeO)_2CHBF_4$[53] (0.4 mL, 3.0 mmol) was added to a stirred solution of the bis-thiomethyl ether 32 (0.46 g, 1.06 mmole) in CH_2Cl_2 (40 mL) under argon at -30°C. After the addition, the cooling bath was removed and the solution was allowed to warm to 20°C and further stirred for 3 h. EtOAc (50 mL) was added and the stirring was continued for another 24 h. A brown crystalline precipitate was formed and it was suction filtered, washed with dry EtOAc (10 mL) and air-dried, 0.58 g, 85%. The salt was used immediately in the next step. IR (KBr, major bands cm^{-1}): 3433, 2944, 1439, 1061, 533.

***trans*-12c,12d-Dimethyl-1,2,3,4,9,10,11,12,12c,12d-decahydrobenzo-[rst]pentaphene, (*cisoid* 123a)**
***trans*-13b,13c-Dimethyl-1,2,3,4,8,9,10,11,13b,13c-decahydrodibenzo-[b,def]chrysene, (*transoid* 123b)**


123a


123b

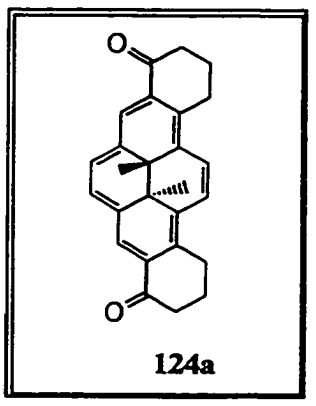
The salt **122** (0.58 g, 0.91 mmol) was suspended in degassed dry THF (50 mL) under argon and potassium *t*-butoxide (0.43 g, 3.64 mmol) was added. This was stirred at 25°C for 4 h. Then water was added and the solution was extracted with CH_2Cl_2 (3 x 100 mL). The organic layers were combined, washed, dried

and evaporated to leave a green residue. The residue was chromatographed twice rapidly on deactivated SiGel eluting with PE under argon to give the dicyclohexene-annelated DHP as a green oil, which is a mixture of 4 inseparable isomers, 0.15 g, 48 %. ^{1}H NMR (300 MHz): Assignment of the individual isomers was based on symmetry, COSY and NOESY experiments: ***trans, transoid*** **123b**: δ 8.57, 8.37 (AB, J=8.03Hz, 4H, H-6,7,13,14), 8.24 (s, 2H, H-5,12), -3.98 (s, 6H, Int Me); ***trans, cisoid*** **123a**: δ 8.17 (s, 2H, H-13,14), 8.15 (s, 2H, H-6,7), 7.91 (s, 2H, H-5,8), -3.40 (s, 6H, Int Me); ***cis, transoid*** **123d**: δ 8.74, 8.55 (AB, J=8.03Hz, 4H, H-6,7,13,14), 7.92 (s, 2H, H-5,12), -1.93 (s, 6H, Int Me); ***cis, cisoid*** **123c**: δ 8.43 (s, 2H, H-13,14), 8.36 (s, 2H, H-6,7), 7.62 (s, 2H, H-5,8), -1.60 (s, 6H, Int Me); 3.90-3.20 (m, ring H), 2.25-2.00 (m, ring H), remain unresolved for individual isomer. ^{13}C NMR (90.6MHz) δ 136.7-115.9 (24 peaks), 41.0-14.6 (28 Peaks); IR (neat, major bands cm^{-1}): 2934, 2868, 1453, 1245, 868, 736, 679; UV (CH_2Cl_2) λ_{max}(nm) (log ε): 228 (4.59), 356 (5.26), 390 (4.76), 436 (4.13), 461 (4.25), 480 (4.29), 647 (2.95), 656 (2.98); MS(CI), *m/z* 341 (MH+); EI-HRMS calculated for $C_{26}H_{28}$: 340.2191, found: 340.2209.

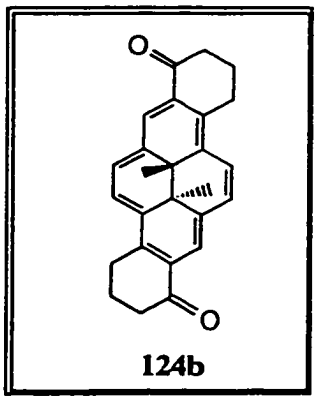
PDC oxidation of the dicyclohexene annelated DHP 123 to diketone 124.

***trans*-12c, 12d-Dimethyl-1,2,3,4,9,10,11,12,12c,12d-decahydro-benzo[rst]pentaphene-4,9-dione, (*cisoid* 124a)**

***trans*-13b,13c-Dimethyl-1,2,3,4,8,9,10,11,13b,13c-decahydro-dibenzo[b,def]chrysene-1,8-dione, (*transoid* 124b)**



124a



124b

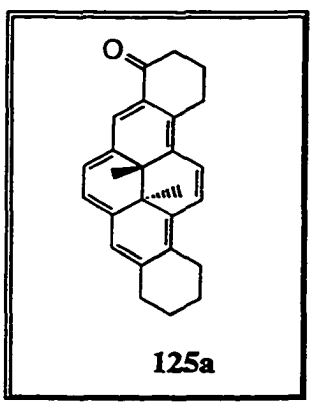
PDC[44] (0.67 g, 1.75 mmol) was added to the DHP **123** (120 mg, 0.35 mmol) in dried CH_2Cl_2 (30 mL). Then the resulting mixture was stirred at 20°C under argon for 4 h. The reaction mixture was suction filtered througth a bed of celite and the filter cake was washed thoroughly with CH_2Cl_2. The filtrate was then preadsorbed onto SiGel and was chromatograhed over SiGel with CH_2Cl_2: MeOH (10:1) as eluant. After evaporation of solvent, the deep red solid was crystallized in CH_2Cl_2:hexane (1:6) (5 mL) to give a reddish brown solid, 36 mg, 28 % ^1H NMR (360 MHz): Assignment of the individual isomers was based on symmetry, COSY and NOESY experiments: ***Cisoid* 124a:** δ 8.78 (s, 2H, H-5,8), 8.49 (s, 2H, H-13,14), 8.37 (s, 2H, H-6,7), 4.00-3.60 (m, ring H), 3.10-2.80 (m, ring H), 2.60-2,35 (m, ring H), -3.05 (s, 6H, Int Me); ***Transoid* 124b**: δ 9.22 (s, 2H, H-5,12), 8.81, 8.69 (AB, J=8.03Hz, 4H, H-6,7,13,14), 4.00-3.60 (m, ring H), 3.10-2.80 (m, ring H), 2.60-2.35 (m, ring H), 3.1-2.8 (m, ring H), 2.3-2.6 (m, ring H), -3.67 (s, 6H, Int Me); ^{13}C NMR (90.6MHz) δ 199.8, 199.4 (C=O), 138.9, 138.4, 138.2, 135.9, 135.6, 128.3, 128.2, 128.1, 127.9,

123.7, 123.6, 123.0, 122.5, 119.5, 39.4, 39.0, 33.1, 31.9, 26.4, 26.0, 23.2, 23.1, 16.9, 16.0; IR (KBr, major bands cm^{-1}): 2935, 1666 (C=O), 1355, 1330, 1290, 1179, 1018, 915; UV (CH_2Cl_2) λ_{max}(nm) (log ε): 251 (3.86), 360 (4.61), 389 (3.96), 414 (4.15), 549 (3.89), 716 (2.87), 645 (2.06); MS(CI), *m/z* 369 (MH^+); EI-HRMS calculated for $C_{26}H_{24}O_2$: 368.1776, found: 368.1792.

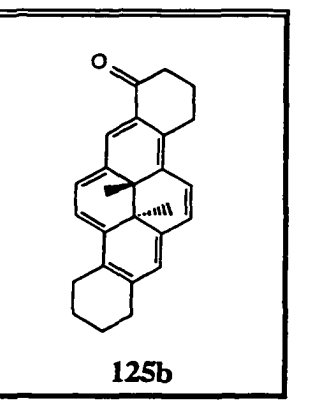
Oxidation of the dicyclohexene annelated DHP 123 monoketone 125.

***trans*-12c, 12d-Dimethyl-1,2,3,4,9,10,11,12,12c,12d-decahydro-benzo[rst]pentaphen-4-one, (*cisoid* 125a)**

***trans*-13b,13c-Dimethyl-1,2,3,4,8,9,10,11,13b,13c-decahydro-dibenzo[b,def]chrysene-1-one, (*transoid* 125b)**



125a

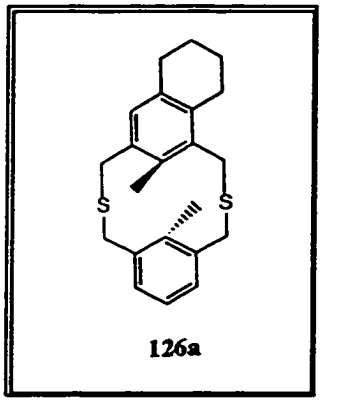


125b

PDC (2 eq.) was added to the DHP **123** (40 mg, 0.12 mmole) dissolved in dried CH_2Cl_2 (30 mL). Then and the resulted mixture was stirred at 20°C under argon for 2 h. The reaction mixture was suction filtered througth a bed of celite and the filter cake was washed thoroughly with CH_2Cl_2. The filtrate was then preadsorbed onto SiGel and was chromatograhed over SiGel with CH_2Cl_2:hexanes 1:4 as eluant. Eluted first was the unreacted green DHP **123**, 12 mg. Elution with CH_2Cl_2 : MeOH (10: 1) gave the red monoketone **125**, 20 mg, 47 %. ^1H NMR (360 MHz): Assignment of the the individual isomers was based on symmetry, COSY and NOESY experiments: ***Cisoid* 125a**: δ 8.84 (s, 1H, H-5), 8.54, 8.17 (AB, 2H, J=8.03Hz, H-14,13), 8.41, 8.15 (AB,

2H, J=8.59Hz, H-6,7), 7.91 (s, 1H, H-8), 4.00-2.00 (m, ring H), -3.27, -3.26 (2s, 6H, Int Me); ***Transoid* 125b**: δ 9.24 (s, 1H, H-14), 8.83, 8.35 (AB, 2H, J=7.95Hz, H-6,5), 8.70, 8.57 (AB, 2H, J=8.03Hz, H-12,13), 8.24 (s, 1H, H-7), 4.00-2.00 (m, ring H), -3.81, -3.82 (2s, 6H, Int Me); IR (KBr, major bands cm^{-1}): 1654 (C=O); MS(CI), *m/z* 355 (MH^+); EI-HRMS calculated for $C_{26}H_{26}O$: 354.1984, found: 354.1983.

syn and _anti_-9,18-Dimethyl-5,6-tetramethylene-2,11-dithia[3,3]metacyclophane 126



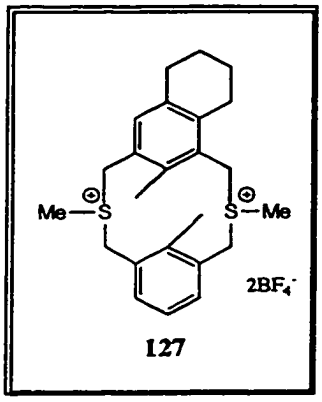
126a

A solution of the dibromide **92** (7.38 g, 22.2 mmol) and the dimercaptan **74** (4.10 g, 22.2 mmole) in nitrogen purged benzene (800 mL) was added dropwise via a precision addition funnel to a well stirred solution of KOH (11.7 g) in nitrogen purged 85 % EtOH (3 L) at 20°C under nitrogen. The addition took about 30 h. After the addition, the mixture was further stirred for an additional 5 h after which the bulk of solvent was removed under reduced pressure. Then water (300 mL) was added and the product was extracted with CH_2Cl_2 (5 x 200 mL). The organic extracts were washed, dried, preadsorbed onto SiGel (10 g) and filtered through a column of SiGel using CH_2Cl_2-PE (1:3) as eluant to yield sticky white solid of the dithiacyclophane **126**. The crude product was then re-chromatographed to afford 4.78 g, 61% of white solid. The ratio of the isomers based on internal methyl protons chemical shift (δ 2.47, 2.52 for *syn* isomer; δ 1.20, 1.38 for *anti* isomer) was determined by NMR to be 5:1, *anti* : *syn*.. A sample was crystallized twice from CH_2Cl_2:PE (1:3) to give the *anti* isomer **126a**, mp 130-132°C. ^{1}H NMR (360 MHz): δ 7.52 (dd, J=7.5Hz, 1.3Hz, 1H, H-14(16)), 7.11-7.14 (m, 2H, H-16(14), H-7), 7.06 (t, J=7.5Hz, 1H, H-15), 3.47-3.88 (m, 6H, bridge-H), 3.43 (s, 2H, bridge-H), 2.6-3.1 (m, 4H, ring H), 1.65-1.90 (m, 4H, ring H), 1.20, 1.38 (2s, 6H, Int Me); ^{13}C NMR (90.6 MHz): 138.9, 137.7, 136.1, 135.1, 134.2, 134.1, 133.6, 131.6, 130.6, 129.8, 129.4, 125.3, 33.4, 30.2, 30.1, 29.7, 27.7, 26.8, 23.6, 22.9, 15.0, 14.3; IR (KBr, major bands cm^{-1}): 2900, 1445, 1420, 1195, 860, 775, 735,

715; MS(CI), *m/z* 355 (MH^+); EI-HRMS calculated for $C_{22}H_{26}S_2$: 354.1476, found: 354.1475.

Anal.	Calculated for $C_{22}H_{26}S_2$	% C: 74.52	% H: 7.35
	Found	% C: 74.19	% H: 7.30

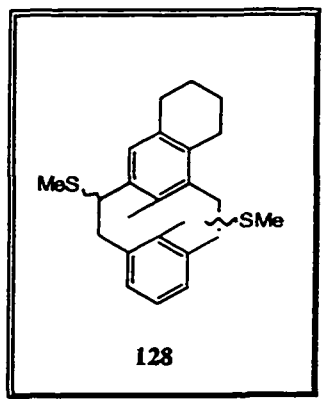
Methylation of 126 to the bis-salt 127



127

A solution of the mixed dithiacyclophane **126** (4.03 g, 11.4 mmole) in CH_2Cl_2 (20 mL) was added to a stirred suspension of $(MeO)_2CHBF_4$[53] (3.6 mL, 42 mmole , 80% as oil) in CH_2Cl_2 (20 mL) at 0°C under argon. After the addition, the mixture was allowed to warm to 20°C and stirred for an additional 4 h. Then EtOAc (40 mL) was added to dissolve any excess methylating reagent present and the mixture was stirred overnight. The white powder of the bis-sulfonium salt **127** was suction filtered, washed with EtOAc and dried under vacuum, 6.3 g, 99 %. IR (KBr, major bands cm^{-1}): 2900, 1450, 1410, 1100, 720.

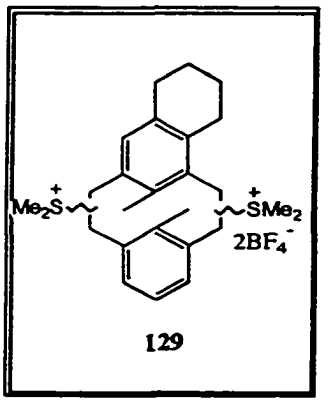
Steven's rearrangement of 127 to give the bis-thiomethyl ether 128



128

The salt **127**, (3.0 g, 5.4 mmole) was suspended in degassed dry THF (75 mL) under argon and potassium *t*-butoxide, *t*-BuOK (1.33 g, 12.5 mmol) was added. The reaction mixture was stirred at 20°C for an hour. Then water (50 mL) was added and the solution was extracted with CH_2Cl_2. The organic layers were combined, washed, dried and evaporated to yield the crude product. This was chromatographed on SiGel, using PE-CH_2Cl_2 (7:3) as eluant, to give **128** as a mixture of many isomers (1.65 g, 80 %). ^{1}H NMR (300 MHz): δ 7.78-6.80 (m, Ar-H), 1.60-4.10 (m, ring H and bridge H), 2.10-2.30 (m, -SMe) 0.47-0.93 (m, Int Me); ^{13}C NMR (90.6 MHz): 124.7-145.0 (>15 peaks), 14.9-52.4 (16 peaks); IR (neat, major bands cm^{-1}): 2906, 1453, 1070, 789, 734, 606; MS(CI), *m/z* 383 (MH^+); EI-HRMS calculated for $C_{24}H_{30}S_2$: 382.1789, found: 382.1795.

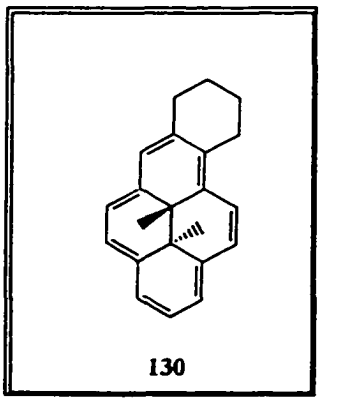
Methylation of 128 to give the bis-sulfonium salt 129



129

$(MeO)_2CHBF_4$[53] (1.6 mL, 11.9 mmol) was added to a stirred solution of the bis-thiomethylether **129** (2.06 g, 5.38 mmole) in CH_2Cl_2 (40 mL) under argon at -30°C. After the addition, the cooling bath was removed and the solution was allowed to warm to 20°C and further stirred for 3 h. EtOAc (30 mL) was added and the stirring was continued for another 24 h. A brown crystalline precipitate was formed and it was suction filtered, washed with dry EtOAc (10 mL) and air-dried, 2.5 g, 79%. The salt was used immediately in the next step. IR (KBr, major bands cm^{-1}): 2900, 1410, 1150, 755.

***trans*-12b,12c-Dimethyl-7,8,9,10,12b,12c-hexahydrobenzo[def]chrysene 130**

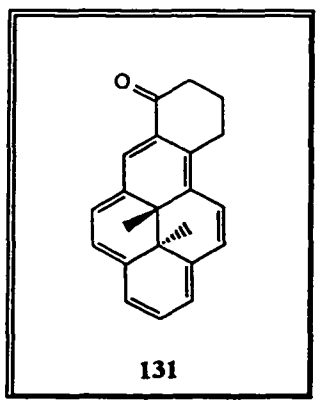

130

The salt **129** (2.50 g, 4.26 mmol) was suspended in degassed dry THF (100 mL) under argon and potassium *t*-butoxide (1.50g, 12.7 mmol) was added. This was stirred at 25°C for 4 h. Then water was added and the solution was extracted with CH_2Cl_2 (3 x 100 mL). The organic layers were combined, washed, dried and evaporated to leave a green residue. The residue was chromatographed twice rapidly on deactivated SiGel eluting with PE under argon to give the cyclohexene annelated DHP **130** as a green oil, 0.45 g, 37%. ^1H NMR (360 MHz): δ 8.50 (d, J=7.77Hz, 2H, H-11,5),

8.40-8.43 (m, 3H, H-4,12,3 (1)), 8.37 (d, J=7.35Hz, 1H, H-1(3)), 8.25 (s, 1H, H-6), 7.90 (t, J=7.71Hz, 1H, H-2), 3.38-3.83 (m, 4H, ring H), 2.05-2.22 (m, 4H, ring H), -3.95, -3.99 (2s, 6H, Int Me); ^{13}C NMR (90.6 MHz): 136.5, 136.2, 135.8, 134.9, 133.7, 129.2, 124.8, 124.1, 123.7, 122.6, 122.5, 122.4, 122.0, 117.0, 32.5, 30.7, 30.6, 26.5, 23.7, 23.6, 15.2, 13.9; IR ($CHCl_3$, major bands cm^{-1}): 3005, 1500, 1410, 915; UV ($CHCl_3$) λ_{max} (nm) (log ε): 241 (4.03), 349 (4.91), 385 (4.53), 476 (3.93), 584 (2.38), 645 (2.69); MS(CI), *m/z* 287 (MH^+); EI-HRMS calculated for $C_{22}H_{22}$: 286.1722, found: 286.1744.

Pyridinium dichromate (PDC) oxidation of the cyclohexene annelated DHP, 131.

***trans*-12b,12c-Dimethyl-7,8,9,10,12b,12c-hexahydrobenzo[def]chrysen-7-one, 131**



131

PDC[44] (2.11g, 5.50 mmol) was added to the DHP **130** (0.40 g, 1.40 mmol) in dried CH_2Cl_2 (40 mL) and the resulted mixture was stirred at 20°C under argon for 4 h. The reaction mixture was then suction filtered througth a bed of celite and the filter cake was washed thoroughly with CH_2Cl_2. Then the filtrate was preadsorbed onto SiGel and was chromatograhed over SiGel with CH_2Cl_2-MeOH (10:1) as eluant. After evaporation of solvent, the deep red solid was crystallized in CH_2Cl_2 : hexane 1:6 (5 mL) to give **131** as a reddish brown solid, 0.15 g, 36%, mp 141 - 142°C. ^1H NMR (360 MHz): δ 9.19 (s, 1H, H-6), 8.81, 8.41 (AB, J=7.71Hz, 2H, H-11,12), 8.69, 8.48 (AB, J=8.14Hz, 2H, H-5,4), 8.41 (d, J=8.00Hz, 1H, H-1), 8.36 (d, J=7.33Hz, 1H, H-3), 8.03 (t, J=7.78Hz,

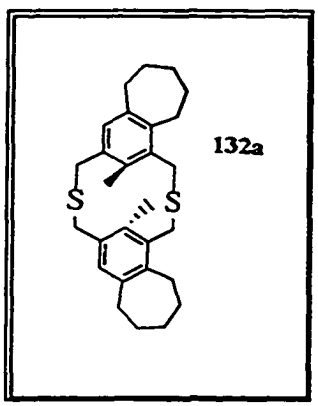
1H, H-2), 3.80-4.00 (m, 2H, ring H), 2.90-3.05 (m, 2H, ring H), 2.40-2.56 (m, 2H, ring H), -3.73, -3.77 (2*s*, 6H, Int Me); ^{13}C NMR (90.6 MHz): 199.9 (C=O), 141.3, 140.6, 137.6, 135.1, 132.7, 128.7, 126.4, 125.7, 124.5, 124.1, 123.9, 123.1, 122.4, 120.8, 39.3, 32.0, 30.7, 26.4, 23.5, 15.6, 15.1; IR (KBr, major bands cm^{-1}): 3100, 2910, 2900, 1645 (C=O), 1530, 1445, 1320, 1285, 1165, 895, 810, 645; UV (cyclohexane) λ_{max} (nm) (log ε): 236 (3.97), 254 (3.89), 332 (4.51), 350 (4.90), 377 (4.16), 402 (4.39), 511 (3.98), 601 (2.51), 666 (2.73); MS(CI), *m/z* 301 (MH^+); EI-HRMS calculated for $C_{22}H_{20}O$: 300.1514, found: 300.1521.

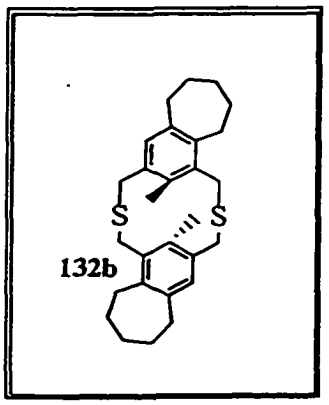
Anal.	Calculated for $C_{22}H_{20}O$	% C: 87.96	% H: 6.71
	Found	% C: 87.55	% H: 6.65

***anti*-9,18-Dimethyl-5,6;15,16-bis(pentamethylene)-2,11-dithia[3,3]metacyclophane, (*cisoid* 132a)**

***anti*-9,18-Dimethyl-5,6;14,15-bis(pentamethylene)-2,11-dithia[3,3]metacyclophane, (*transoid* 132b)**

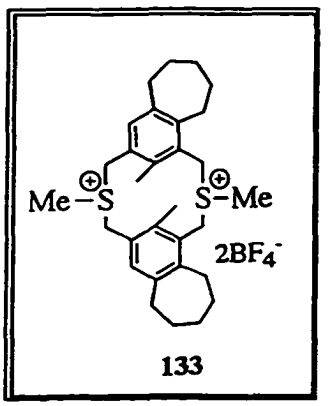
A solution of the dibromide **100** (3.152 g, 9.115 mmol) and the dimercaptan **101** (2.297 g, 9.115 mmole) in nitrogen purged benzene (800 mL) was added dropwise via a precision addition funnel to a well stirred solution of KOH (3 g) in nitrogen purged 90 % EtOH (2.5 L) at 20°C under nitrogen. The addition took about 30 h. After the addition, the mixture was further stirred for an additional 5 h after which the bulk of solvent was removed under reduced pressure. Then water (300 mL) was added and the product was extracted with CH_2Cl_2 (4 x 200 mL). The organic extracts were washed, dried, preadsorbed onto SiGel (15 g) and filtered through a column of SiGel using CH_2Cl_2-PE (1:3) as eluant to yield sticky white solid of the dithiacyclophane **132**. A sample was crystallized twice from CH_2Cl_2-PE (1:3) to give the *anti, transoid* isomer **132b**, mp 221 - 223°C. ^{1}H NMR (300 MHz): δ 7.16 (s, 1H, Ar-H), 3.80 (m, 4H, bridge CH_2), 3.54 (m, 4H, bridge CH_2), 2.97-2.68 (m, 8H, ring H), 1.87-1.58 (m, 12H, ring H), 1.29 (s, 6H, Int Me); ^{13}C NMR : 141.8, 140.9, 136.5, 133.2, 131.6, 131.0, 36.4, 32.6, 31.4, 30.7, 28.3, 27.7, 15.4; IR (KBr, major peaks cm^{-1}): 2919, 2840, 1435, 1201, 956, 722; MS (CI), *m/z* 437 (MH^+). EI-HRMS calculated for $C_{28}H_{36}S_2$: 436.2258, found: 436.2261.





Anal.	Calculated for $C_{28}H_{36}S_2$	% C: 77.01	% H: 8.31
	Found	% C: 76.34	% H: 8.31

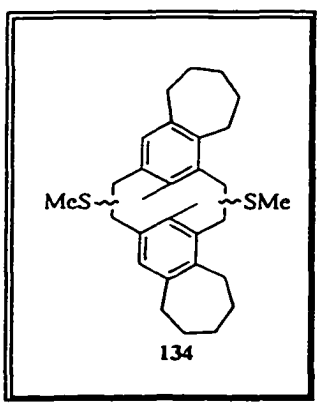
Bis-salt, 133



133

A solution of the mixed dithiacyclophane **132** (1.467 g, 3.36 mmole) in CH_2Cl_2 (20 mL) was added to a stirred suspension of $(MeO)_2CHBF_4$[53] (1.4 mL, 10.4 mmole , 80% as oil) in CH_2Cl_2 (20 mL) at 0°C under argon. After the addition, the mixture was allowed to warm to 20°C and stirred for an additional 4 h. Then EtOAc (40 mL) was added to dissolve any excess methylating reagent present and the mixture was stirred overnight. The white powder of the bis-sulfonium salt **133** was suction filtered, washed with EtOAc and dried under vacuum to give 1.72 g, 80 %. IR (KBr, major peaks cm^{-1}): 2930, 2859, 1449, 1057.

Stevens rearrangement of 133 to give the bis-thiomethyl ether, 134



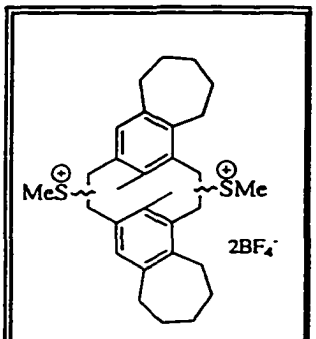
134

The salt **133**, (1.72 g, 2.69 mmole) was suspended in degassed dry THF (55 mL) under argon and potassium *t*-butoxide (1.2 g, 10.7 mmol) was added. The reaction mixture was stirred at 20°C for an hour. Then water (50 mL) was added and the solution was extracted with CH_2Cl_2 (3 x 70 mL). The organic layers were combined, washed, dried and evaporated to yield the crude product. This was chromatographed on SiGel, using 7:3 PE : CH_2Cl_2 as eluant, to give **134** as a mixture of many isomers, 1.65 g, 80 %. ^1H NMR (300 MHz) δ 7.53-6.66 (m, Ar-H), 4.00-1.62 (m, aliphatic H), 1.32-0.70 (m, Int Me); ^{13}C NMR: 142.4-125.3 (24 peaks, aromatic H),

50.0-11.5 (32 peaks, aliphatic H); IR (KBr, major peaks cm^{-1}): 2924, 2846 1449, 1205, 961; MS (CI), *m/z* 465 (MH+), EI-HRMS calculated for $C_{30}H_{40}S_2$: 464.2572, found: 464.2570.

Bis-sulfonium salt, 135

$(MeO)_2CHBF_4$[53] (1.6 mL, 11.9 mmol) was added to a stirred solution of the bis-thiomethylether, **134** (0.87 g, 1.87 mmole) in CH_2Cl_2 (40 mL) under argon at -30°C. After the addition, the cooling bath was removed and the solution was allowed to warm to 20°C and further stirred for 3 h. EtOAc (50 mL) was added and the stirring was continued for another 24 h. A brown crystalline precipitate was formed and was collected by suction filtration, washed with dry EtOAc (10 mL) and air-dried, 1.0 g, 70 %. The salt was used immediately in the next step. IR (KBr, major peaks cm^{-1}): 2917, 2847, 1441, 1057.

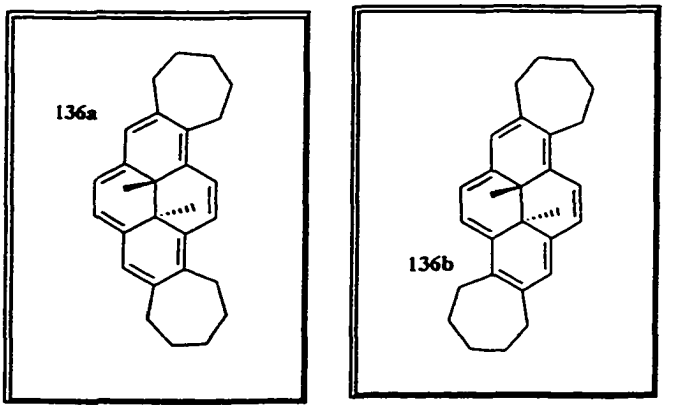


135

Dicycloheptene annelated DHP 136.

***trans*-14c,14d-Dimethyl-1,2,3,4,5,10,11,12,13,14,14c,14d-dodeca-hydrodicyclohepta[a,i]pyrene, (*cisoid* 136a)**

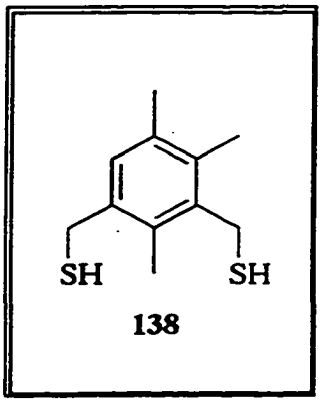
***trans*-15b,15c-Dimethyl-1,2,3,4,5,9,10,11,12,13,15b,15c-dodeca-hydrodicyclohepta[a,h]pyrene, (*transoid* 136b)**



The salt **135** (1.0 g, 1.5 mmole) was suspended in degassed dry THF (100 mL) under argon and potassium *t*-butoxide (0.6 g, 5.1 mmol) was added. This was stirred at 25°C for 2 h. Then water was added and the solution was extracted with CH_2Cl_2 (3 x 100 mL). The organic layers were combined, washed, dried and evaporated to leave a green residue. The residue was chromatographed twice rapidly on deactivated SiGel eluting with PE under argon to give the green dicycloheptene annelated DHP **136** as a mixture of 4 isomers, 0.22 g, 40 %. ^{1}H NMR (360 MHz): assignment of the individual isomers was based on symmetry and NMR integration. ***trans, transoid* 136b**: δ 8.75, 8.47 (AB, 4H, J=8.03Hz, H-6,7,14,15), 8.36 (s, 1H, H-8,16), 3.20-3.90 (m, ring H), 1.84-1.99 (m, ring H), -4.13 (s, 6H, Int Me); ***trans, cisoid* 136a**: δ 8.79 (s, 2H, H-15,16), 8.40 (s, 2H, H-6,9) 8.35 (s, 2H, H-7,8), 3.20-3.90 (m, ring H), 1.84-1.99 (m, ring H), -4.11 (s, 6H, Int Me); ***cis, cisoid* and *transoid* 136c and 136d**: δ 8.93, 8.91, 8.60, 8.57, 8.03, 8.00 (Ar-H), 3.20-

3.90 (m, ring H), 1.84-1.99 (m, ring H), -2.02 (Int Me of **136c**), -2.03 (Int Me of **136d**); ^{13}C NMR (90.6MHz) δ 139.1-118.2 (29 peaks, aromatic C), 37.9-14.3 (26 peaks, aliphatic C); IR (KBr, major bands cm^{-1}): 3055, 2919, 2850, 1425, 1201, 878, 722, 644; UV (CH_2Cl_2) λ_{max} (nm) log(ε): 353 (5.01), 389 (4.48), 396 (3.94), 437 (3.80), 457 (3.94), 480 (3.96), 648 (2.83); MS(CI), *m/z* 369 (MH^+); EI-HRMS calculated for $C_{28}H_{32}$: 368.2504, found: 368.2499.

2,4,5-Trimethyl-3-sulfanylmethylphenylmethanethiol 138

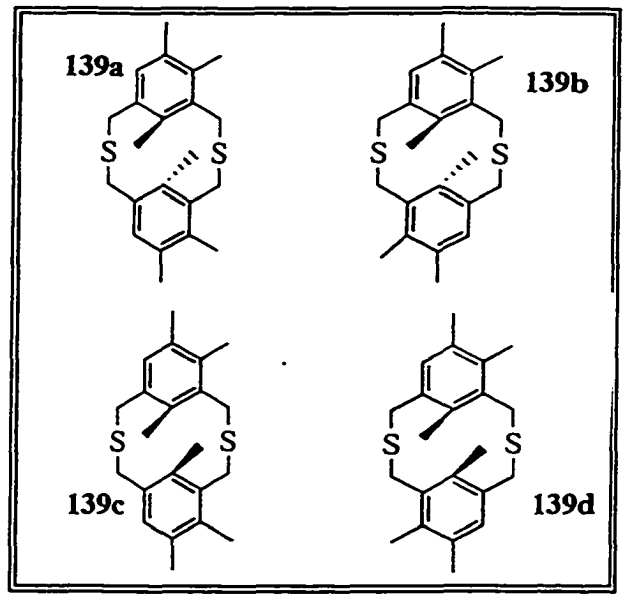


138

Thiourea (3.5 g, 0.046 mole) was added to 100 % EtOH (35 mL) and the solution was warmed to about 60°C. Then the dibromide **137**[50] (7.0 g, 0.023 mole) was added in four portions. After complete addition, the reaction mixture was refluxed for 30 min. The solvent was evaporated and degassed aqueous sodium hydroxide solution (4.7 g NaOH in 200 mL water) was added. The system was flushed with argon and refluxed under argon for 6 h. Then 2M ice cooled hydrochloric acid was added to acidify the reaction mixture and the thiol was extracted with Et_2O (3 x 200 mL). The combined organic extracts were washed, dried and evaporated to give a cloudy oil. This was chromatographed over SiGel using Et_2O-PE (1:9) as eluant to give the dimercaptan **138** as white solid, 3.78 g, 78 %, mp 34 - 35°C. ^{1}H NMR (300 MHz) δ 6.95 (s, 1H, H-6), 3.79 (d, 2H, J=6.6Hz, Ar-CH_2-), 3.71 (d, 2H, J=6.6Hz, Ar-CH_2-), 2.39 (s, 3H, 2-Me), 2.28 (s, 3H, 4-Me), 2.24 (s, 3H, 5-Me), 1.65 (t, J=6.6Hz, 1H,-SH), 1.57 (t, J=6.6Hz, 1H, -SH); ^{13}C NMR (90.6MHz) δ 138.2, 136.9, 134.8, 133.8, 131.2, 129.6 (C-6), 27.6, 23.7, 20.6, 15.5, 14.8; IR (KBr, major bands cm^{-1}): 2998, 2908, 1452, 1249, 1209, 1007, 875, 754, 683, 552; MS(CI), *m/z* 213 (MH+); EI-HRMS calculated for $C_{11}H_{16}S_2$: 212.0693, found: 212.0708.

syn and _anti_ -5,6,9,15,16,18-Hexamethyl-2,11-dithia[3,3]metacyclophane 139 a,c

syn and _anti_ -5,6,9,14,15,18-Hexamethyl-2,11-dithia[3,3]metacyclophane 139 b,d

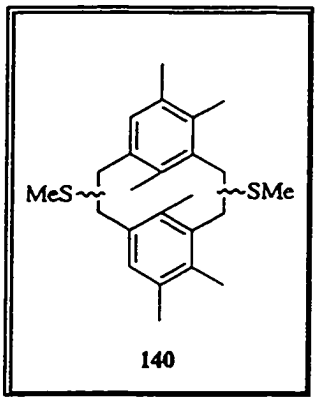


A solution of the dibromide **137** (3.03 g, 9.91 mmole) and the dimercaptan **138** (2.10 g, 9.91 mmole) in nitrogen purged benzene (600 mL) was added dropwise via a precision addition funnel to a well stirred solution of KOH (2.6 g, 39 mmole) in nitrogen purged 90% EtOH (3 L) at 20°C under nitrogen. The addition took about 24 h. After the addition, the mixture was further stirred for an additional 6 h after which the bulk of solvent was removed under reduced pressure. Water (500 mL) was added and the product was extracted with CH_2Cl_2 (3 x 300 mL). The organic extract was washed, dried and preadsorbed onto SiGel (20 g). It was then chromatographed over SiGel using CH_2Cl_2 as eluant to give a white powder, 2.15 g, 61%. A sample was recrystallized three times from CH_2Cl_2:hexanes 1:2 to give a mixture of *anti,cisoid* and *anti,transoid* thiacyclophanes **139a** and **139b**. ^1H NMR (300 MHz) δ 7.27 (s, Ar-H), 7.08 (s, Ar-H), 3.88-3.64 (m, bridge-H), 3.43 (s, bridge-H), 2.36, 2.33, 2.26, 2.25 (4s, Ar-Me), 1.27, 1.18 (2s, Int Me); ^{13}C NMR (90.6MHz): δ 136.5, 136.2, 135.4, 134.5, 134.0, 133.7, 133.5, 132.1, 131.8, 131.7, 131.6, 31.8,

30.6, 28.9, 28.6, 20.6, 20.4, 20.3, 16.5, 16.0, 15.0, 14.7; IR (KBr, major bands cm^{-1}): 2972, 2906, 1462, 1217, 1009, 877; MS(CI), *m/z* 357 (MH^+).

Anal.	Calculated for $C_{22}H_{28}S_2$:	% C: 74.52	% H: 7.92
	Found	% C: 74.28	% H: 8.00

Wittig rearrangement of 139 to give the bis-thiomethyl ether 140

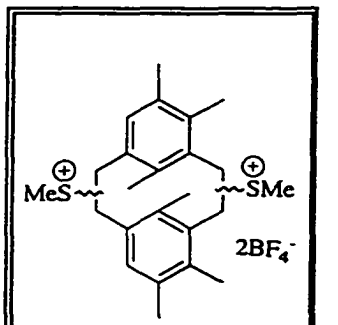


140

n-BuLi (2.5 M, 1.93 mL) was added to a solution of the dithiacyclophane **139** mixture (0.781 g, 2.19 mmole) in THF (20 mL) at 0°C under argon. After the addition, the mixture was allowed to warm to 20°C and stirred for an hour. Then MeI (0.7 mL) was added and the solution was further stirred for 0.5 h. Ice water (50 mL) was then added and the solution was extracted with CH_2Cl_2 (3 x 60 mL). The organic extract was washed, dried and evaporated to afford a yellow oil. This was then chromatographed over SiGel using EtOAc: hexanes 1:4 as eluant to afford the thiomethyl ether **140** as a mixture of isomers, 0.76 g, 90 %. ^1H NMR (300 MHz): 7.58-7.49 (m, Ar-H), 7.17-6.64 (m, Ar-H), 5.06-3.85 (m, bridge-H), 3.82-3.65 (m, bridge-H), 3.60-1.80 (m, Ar-Me), 0.99-0.48 (m, Int Me); ^{13}C NMR (90.6MHz): 140.5-125.1 (30 peaks, aromatic C); 53.9-115.0, (32 peaks, Aliphatic C); IR (KBr, major bands cm^{-1}): 2915, 1457, 1377, 910, 735, 651; MS(CI), *m/z* 385 (MH^+); EI-HRMS calculated for $C_{24}H_{32}S_2$: 384.1945, found: 384.1946.

Methylation of 140 to give the bis-salt 141

$(MeO)_2CHBF_4$[53] , 80% as oil (1 mL, 8 mmole) was added to a solution of the mixture of Wittig isomers, **140** (0.99 g, 2.58 mmole) in CH_2Cl_2 (60 mL) at 0°C under argon. The solution was then stirred at 20°C for 3 h before the addition of EtOAc (80 mL). After stirring overnight, the brown salt was suction filtered and washed thoroughly with EtOAc, 1.3 g, 86%. IR (KBr, major bands cm^{-1}): 2960, 1430, 1067, 535; It was then used immediately for the next reaction.

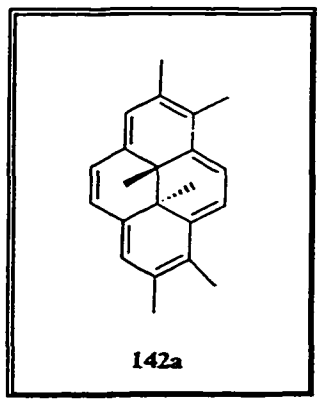


141

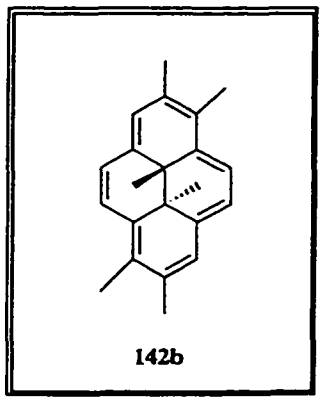
Hofmann elimination of the bis-salt 141 to give the DHP 142

***trans*-1,2,7,8,10b,10c-Hexamethyl-10b,10c-dihydropyrene, (*cisoid* 142a)**

***trans*-1,2,6,7,10b,10c-Hexamethyl-10b,10c-dihydropyrene,(*transoid* 142b)**



142a

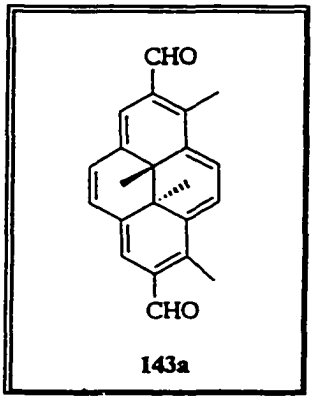


142b

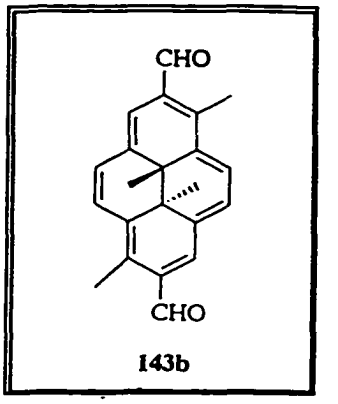
The salt **141** (1.3 g, 2.21 mmole) was suspended in degassed dry THF (80 mL) under argon and potassium *t*-butoxide (0.74 g, 6.26 mmole) was added. This was stirred at 20°C for 2.5 h. Then water was added and the solution was extracted with CH_2Cl_2 (3 x 100 mL). The organic layers were combined, washed, dried and evaporated to leave a green residue. This was chromatographed twice rapidly on deactivated SiGel using CH_2Cl_2-hexane (1:8) as eluant to give the DHP **142** as a green oil, 0.36 g, 56 %. A sample was rechromatographed and crystallized from MeOH-hexane (8:1) to afford green crystals which is an inseparable mixture of *trans, cisoid* and *trans, transoid* isomers **142a** and **142b**, mp 172°C (decomp.); ^{1}H NMR (360 MHz): Assignment of the individual isomers was based on symmetry, COSY and NOESY experiment. ***trans, cisoid* 142a:** δ 8.61 (s, 2H, H-9,10), 8.36 (s, 2H, H-4,5), 8.30 (s, 2H, H-3,6), 3.09, 2.96 (2s, 6H, Ar-Me), -4.03 (s, 6H, Int Me); ***trans, transoid* 142b:** δ 8.63 (d, J=7.85Hz, 2H, H-5,10), 8.40 (d, J=7.83Hz, 2H, H-4,9), 8.34 (s, 2H, H-3,8), 3.08, 2.97 (2s, 6H, Ar-Me), -4.06 (s, 6H, Int Me); ^{13}C NMR (90.6MHz): Mixture of **142a** and **142b**: δ 135.8, 135.4, 133.8, 133.7, 131.9, 131.6, 128.6, 128.5, 125.2,

125.1, 122.0, 121.3, 118.7, 118.1, 30.7, 30.6, 22.7, 22.5, 15.3, 15.2, 14.5, 14.4 (Int Me C); IR (KBr, major bands cm^{-1}): 2968, 2919, 1435, 1376, 1347, 878, 791, 673; UV (CH_2Cl_2) λ_{max} (nm) log (ε): 231 (3.20), 352 (5.21), 387 (4.78), 398 (4.09), 475 (4.13), 478 (4.14), 538 (2.42), 651 (3.19); MS(CI), *m/z* 289 (MH^+); EI-HRMS calculated for $C_{22}H_{24}$: 288.1878, found: 288.1867.

Pyridinium dichromate (PDC) oxidation of DHP 142 to dialdehyde 143. *trans*-1,8,10b,10c-Tetramethyl-10b,10c-dihydro-2,7-pyrene-dicarboxaldehyde, (*cisoid* 143a) & *trans*-1,6,10b,10c-Tetramethyl-10b,10c-dihydro-2,7-pyrene-dicarboxaldehyde (*transoid* 143b)



143a



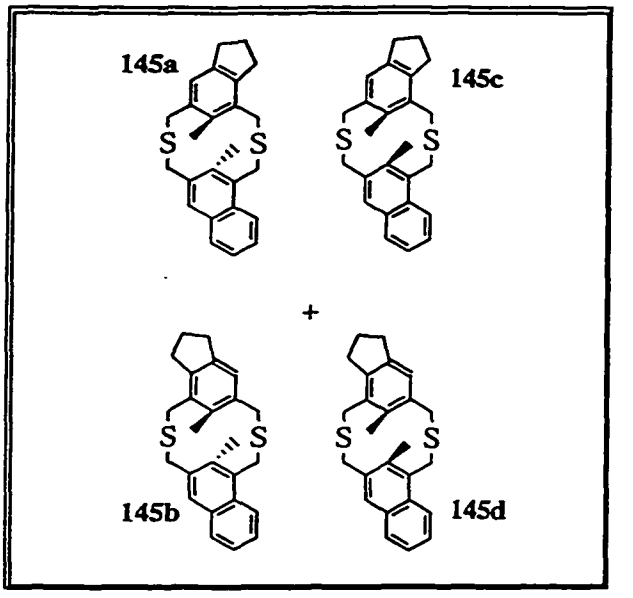
143b

PDC[44] (3.4 g, 9 mmole) was added in one portion to the DHP **77** (0.30 g, 1.0 mmole) in dried CH_2Cl_2 (100 mL). Then the resulted mixture was stirred at 20°C under argon for 5 h. The reaction mixture was then suction filtered througth a bed of celite and the filter cake was washed thoroughly with CH_2Cl_2. The filtrate was then preadsorbed onto SiGel and was chromatograhed over SiGel with methanol-CH_2Cl_2 (1:9) as eluant. After evaporation of solvent, the crude black solid was crystallized from CH_2Cl_2 and hexane 1:5 (10 mL) to give a brown solid which contained a mixture of *cisoid* and *transoid* dialdehyde **78**, 0.12 g, 36 %. ^1H NMR (300 MHz): Assignment of the individual isomers was based on symmetry, COSY, NOESY and NOE experiments. *Cisoid* **143a** δ 10.99 (s, 2H, CHO), 8.80 (s, 2H, H-9,10), 8.77 (s, 2H, H-3,6), 8.52 (s, 2H, H-4,5), 3.41 (s, 6H, Ar-Me), -3.29 (s, 6H, Int Me); *Transoid* **143b**: δ 10.96 (s, 2H, CHO), 8.92 (s, 2H, H-3,8) 8.90 (d, J=8.17Hz, 2H, H-5,10), 8.65 (d, J=8.10Hz, 2H, H-4,9), 3.43 (s, 6H, Ar-Me), -3.49 (s, 6H, Int Me); ^{13}C NMR

(90.6MHz) δ 193.5, 193.0 (C=O), 139.7, 139.1, 138.4, 138.3, 138.0, 134.7, 132.3, 129.9, 129.4, 128.4, 128.2, 125.7, 124.4, 124.1, 122.7, 33.0, 32.6 (Ar-Me) 16.6, 16.3, 14.4, 13.8 (Int Me C); IR (KBr, major bands cm^{-1}): 2972, 2924, 2923, 1663 (C=O), 1638 (C=O), 1430, 1362, 1049, 893; UV (CH_2Cl_2) λ_{max} (nm) log (ε): 358 (4.12), 391 (3.52), 416 (3.68), 553 (3.55), 658 (2.20), 725 (2.66); MS(CI), *m/z* 317 (MH^+); EI-HRMS calculated for $C_{22}H_{20}O_2$: 316.1463, found: 316.1444.

13, 22-Dimethyl-19,20(trimethylene)-2, 15-dithia-1,3-naphthalenophane 145a,c

13, 22-Dimethyl-18,19(trimethylene)-2, 15-dithia-1,3-naphthalenophane 145b,d



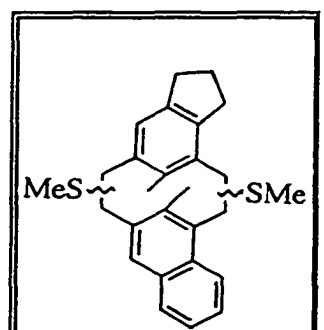
A solution of the dibromide **144**[50] (2.334 g, 7.34 mmole) and the dimercaptan **86** (1.717g, 7.34 mmole) in nitrogen purged benzene (2 L) was added dropwise via a precision addition funnel to a well stirred solution of KOH (2.9 g, 0.044 mole) in nitrogen purged 80% EtOH (2.5 L) at 20°C under nitrogen. The addition took about 24 h. After the addition, the mixture was further stirred for an additional 6 h after which the bulk of solvent was removed under reduced pressure. Water (500 mL) was added and the product was extracted with CH_2Cl_2 (4 x 250 mL). The organic extract was washed, dried and preadsorbed onto SiGel (20 g). It was then chromatographed over SiGel using CH_2Cl_2 as eluant to give a white powder, 2.0 g, 70 % ,which is a mixture of thiacyclophane isomers. A sample was recrystallized three times from benzene to give the *anti,cisoid* **145a** and

anti,transoid **145b** mixture of thiacyclophanes. ^{1}H NMR (300 MHz): δ 8.06-6.90 (m, Ar-H), 4.07-3.55 (m, bridge-H), 2.83-1.96 (m, ring-H), 0.76-0.81 (4s, Int Me); ^{13}C NMR (90.6MHz): δ 143.3-123.3 (33 signals, aromatic-C), 37.6-14.6 (32 signals, aliphatic-C); IR (KBr, major bands cm^{-1}): 3024, 2915, 1427, 1210, 1177, 670; MS(CI), *m/z* 390 (MH^+); EI-HRMS calculated for $C_{25}H_{26}S_2$: 390.1476, found: 390.1472.

Anal.	Calculated for $C_{25}H_{26}S_2$:	% C: 76.89	% H: 6.72
	Found:	% C: 76.50	% H: 6.69

Wittig rearrangement of the thiacyclophane 145 to give bis-thiomethyl ether 146

The thiacyclophane mixture **145**, (0.367 g, 0.94 mmole) was suspended in degassed dry THF (50 mL) at 0°C under argon and 1.52 M LDA (1.3 mL, 2 mmol) was added. The reaction mixture was stirred at 20°C for 30 min. Then MeI (0.3 mL) was added and the solution was further stirred for an hour. The solution was then extracted with CH_2Cl_2 (3 x 70 mL). The organic layers were combined, washed, dried and evaporated to yield the crude product. This was

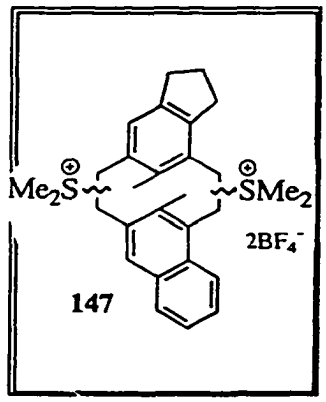


146

chromatographed over SiGel, using PE : CH_2Cl_2 (7:3) as eluant, to give the bis-thiomethyl ether **146** as a mixture of many isomers, 0.29 g, 74 %. ^1H NMR (300 MHz): δ 8.25-6.5 (m, Ar-H), 5.95-3.70 (m, bridge-H), 3.00-2.00 (m, ring-H), 1.27-0.54 (m, Int Me); ^{13}C NMR (90.6MHz) δ 142.3-120.7 (28 signals, aromatic-H), 53.8-14.1 (37 peaks, aliphalic-C); IR (Neat, major bands cm^{-1}): 2913, 2845, 2238, 1452, 1433, 905, 734; MS(EI), *m/z* 418 (M^+); EI-HRMS calculated for $C_{27}H_{30}S_2$: 418.1789, found: 418.1791.

Methylation of 146 to give the bis-salt 147

$(MeO)_2CHBF_4$[53], 80% oil (0.28 mL, 2.1 mmole) was added to a solution of mixed **146** (0.29 g, 0.69 mmole) in CH_2Cl_2 (40 mL) at 0°C under argon. The solution was then stirred at 20°C for 3 h before the addition of EtOAc (100 mL). After stirring overnight, the brown salt **147** was suction filtered and washed thoroughly with EtOAc, 0.28 g, 65 %. IR (KBr, major bands cm^{-1}): 3413, 2925, 1430, 1042, 759, 519.



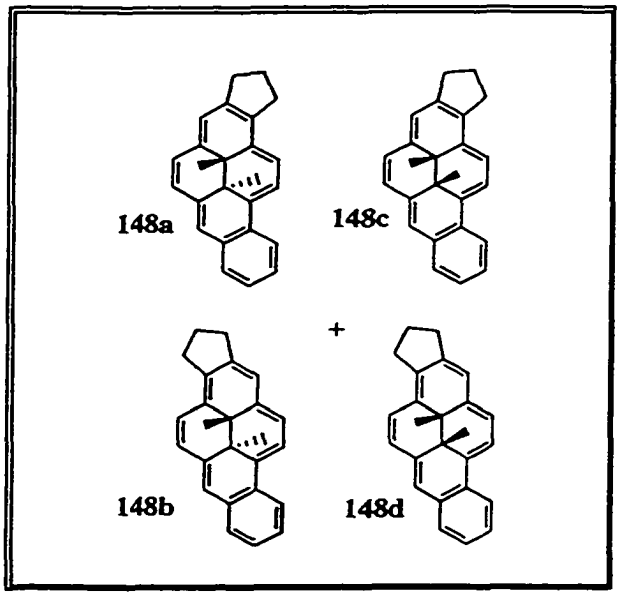
147

Hofmann Elimination of Bis-salt 147 to give the DHP 148.

***trans*-11c,11d-Dimethyl-2,3,11c,11d-tetrahydro-1H-benzo[def]-cyclopenta[a]chrysrene, *cisoid* 148a**

***trans*-12b,12c-Dimethyl-2,3,12b,12c-tetrahydro-1H-benzo[def]-cyclopenta[b]chryrene, *transoid* 148b**

The salt **147** (1.3 g, 2.1 mmole) was suspended in degassed dry THF (60 mL) under argon and potassium *t*-butoxide (0.59 g, 5 mmole) was added. This was stirred at 20°C for 2.5 h. Then water was added and the solution was extracted with CH_2Cl_2 (3 x 200 mL).



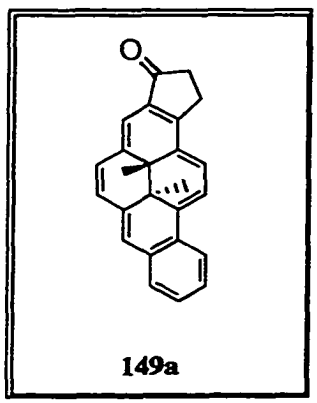
The organic layers were combined, washed, dried and concentrated to leave a brown residue. This was chromatographed twice rapidly on deactivated SiGel using CH_2Cl_2-hexane (1:8) as eluant to give the DHP **148** as a brown oil, 0.14 g, 20 %, which is a mixture of *trans, cisoid* **148a**; *trans, transoid* **148b**; *cis, cisoid* **148c** and *cis, transoid*

148d isomers. ^{1}H NMR (300 MHz): δ 8.96-7.10 (m, aromatic-H), 3.26-2.00 (m, ring-H), -0.26, -0.36 (2s, syn, cisoid, Int Me), -0.38, -0.46 (2s, *cis, transoid*, Int Me), -1.61 (s, *trans, cisoid*, Int Me), -1.73, -1.74 (2s, *trans, transoid*, Int Me); ^{13}C NMR (90.6MHz) δ 139.5-116.3 (29 signals, aromatic-C), 35.9-16.8 (21 signals, aliphatic-C); IR (neat, major bands cm^{-1}): 2890, 1410, 865, 715; UV (CH_2Cl_2): λ_{max} nm (log ε_{max}): 229 (4.18), 357 (4.39), 382 (3.74), 394 (3.75), 457 (3.37), 484 (3.37); MS(CI), *m/z* 323 (MH^+); EI-HRMS calculated for $C_{25}H_{22}$: 322.1721, found: 322.1713.

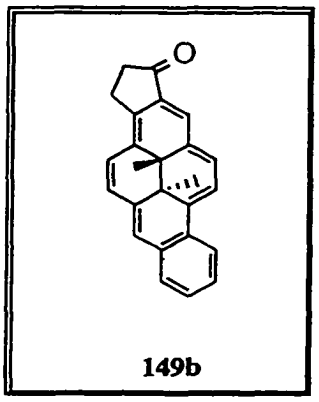
Pyridinium dichromate (PDC) oxidation of the DHP 148 to mono-ketone 149.

***trans*-11c,11d-Dimethyl-2,3,11c,11d-tetrahydro-1H-benzo[def]-cyclopenta[a]chrysen-1-one, *cisoid* 149a**

***trans*-12b,12c-Dimethyl-2,3,12b,12c-tetrahydro-1H-benzo[def]-cyclopenta[b]chrysen-1-one, *transoid* 149b**



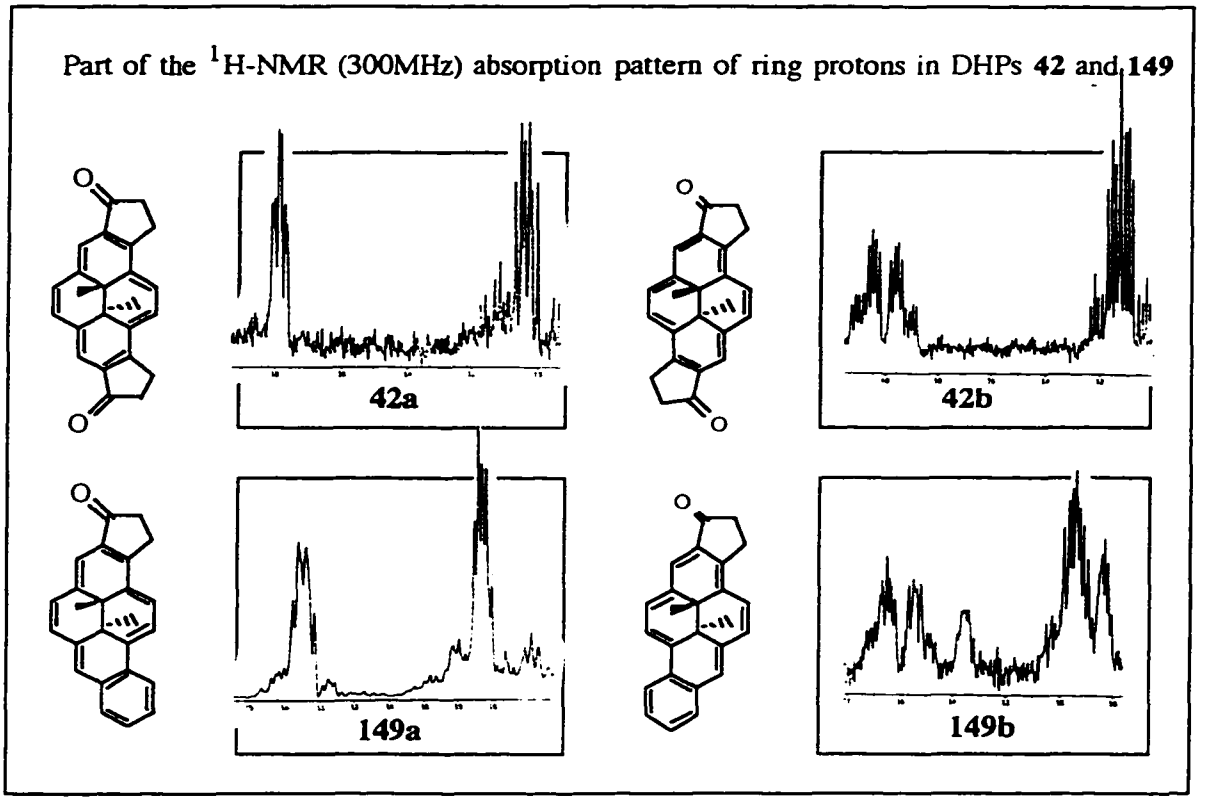
149a



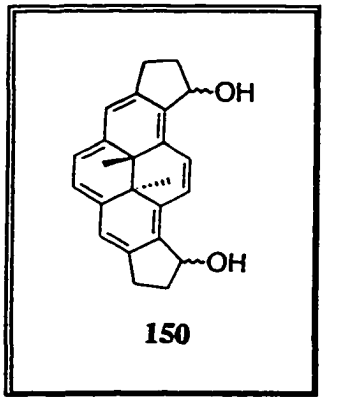
149b

The DHP **148** (0.14 g, 0.43 mmole) was dissolved in dried CH_2Cl_2 (30 mL). Then PDC[44] (0.81 g, 2.2 mmole) was added in one portion and the resulting mixture was stirred at 20°C under argon for 5 h. The reaction mixture was then suction filtered througth a bed of celite and the filter cake was washed thoroughly with CH_2Cl_2. The filtrate was then preadsorbed onto SiGel and was chromatograhed over SiGel with MeOH-CH_2Cl_2 (1:9) as eluant to give a brown oil, 25 mg, 20%. Combined column chromatograph and fractional crystallization, 5 times each was done to give enrich samples of the ***trans, cisoid* 149a** and ***trans, transoid* 149b** isomers, ^1H NMR (300 MHz): **149a** (red in color) δ 8.58 (d, J=7.23Hz, H-11), 7.89 (d, J=6.43Hz, Ar-H), 7.85-7.43

(m, Ar-H), 3.43-2.67(m, ring-H), -1.14, -1.16 (2s, Int Me); IR (KBr, major bands cm^{-1}): 1683 (C=O); UV (CH_2Cl_2) λ_{max} nm : 490, 412, 360, 230; **149b** (purple in color) δ 8.94 (d, J=8.84Hz, H-12), 8.48 (d, J=7.23Hz, Ar-H), 8.31(s, H-4) , 8.21 (s, H-7), 8.14-7.99 (m, Ar-H), 7.83-7.75 (m, Ar-H), 3.67-2.82 (m, ring-H), -2.20 (s, Int Me); IR (KBr, major bands cm^{-1}): 1698 (C=O); UV (CH_2Cl_2) λ_{max} nm: 630, 522, 413, 390, 364, 230; ^{13}C NMR (90.6MHz): **149a** and **149b**, δ 206.8, 204.2 (C=O), 184.2-114.6 (46 signals, aromatic-C), 49.3-17.1 (17 signals, aliphatic-C); MS(CI), *m/z* 337 (MH^+); EI-HRMS calculated for $C_{25}H_{20}O$: 336.1514, found: 336.1513. The assignment of the *cisoid* and *transoid* isomers was based on the ^1H-NMR absorption patten of the five-membered ring protons using the diketones **42a** and **42b** as standard.


Part of the ^{1}H-NMR (300MHz) absorption pattern of ring protons in DHPs **42** and **149**
42a
42b
149a
149b

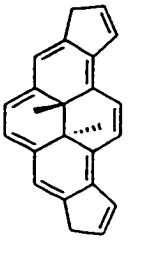
Reduction of the diketone 63 to the 1,10-dialcohol 150



150

Sodium borohydride, $NaBH_4$ (11 mg, 0.3 mmole) was added to a solution of the diketones **63** (100 mg, 0.3 mmole) in MeOH-THF (1:1), (20 mL) at 0°C under argon. Then the solution was further stirred at 20°C for an hour. Degassed ice water was added and the solution was extracted with CH_2Cl_2 (4 x 30 mL), dried with anhydrous sodium sulfate and evaporated to give the unstable dialcohol **150** as a mixture of many isomers. ^1H NMR (300 MHz): δ 8.87-8.38 (m, Ar-H), 7.90-8.10 (m), 6.43-6.28 (m, -C**H**-OH), 5.76-5.53 (m, -C**H**-OH), 4.00-2.00 (m, ring H), -3.98 to -4.25 (15 s, Int Me); MS(CI), *m/z* 309 (M-36+1).

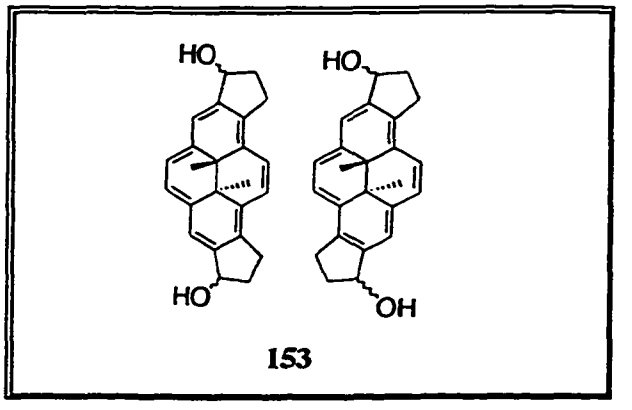
Attempted synthesis of dicyclopentadienyl DHP 151.
***trans*-10c,10d-Dimethyl-3,8,10c,10d-tetrahydrodicyclopenta[a,i]pyrene 151**



151

The mixture of di-alcohol **150** (30 mg, 0.087 mmole) was dissolved in HMPT (1 mL). Then methyl triphenoxy-phosphonium iodide[68], $(PhO)_3P^+MeI^-$ (0.24 g, 6 eq.) was added and the reaction mixture was stirred under argon for an hour. Degassed ice water was then added and the reaction mixture was extracted with CH_2Cl_2 (3 x 50 mL). The organic extract was washed, dried and evaporated. The residue was chromatographed over deactivated SiGel with PE followed by increasing portions of CH_2Cl_2. Neither the expected product nor any starting material could be recovered.

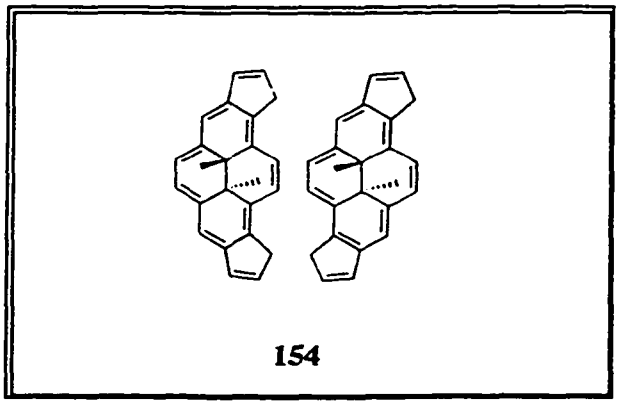
Reduction of the diketones 42 to the dialcohol 153



153

Sodium borohydride, $NaBH_4$ (11 mg, 0.3 mmole) was added to a solution of the diketones **42** (100 mg, 0.3 mmole) in MeOH-THF (1:1), (20 mL) at 0°C under argon. Then the solution was further stirred at 20°C for an hour during which the solution turned color from deep red to green. Degassed ice water was added and the solution was extracted with CH_2Cl_2 (4 x 30 mL), dried with anhydrous sodium sulfate and evaporated to give the unstable dialcohol **153** as a mixture of many isomers.

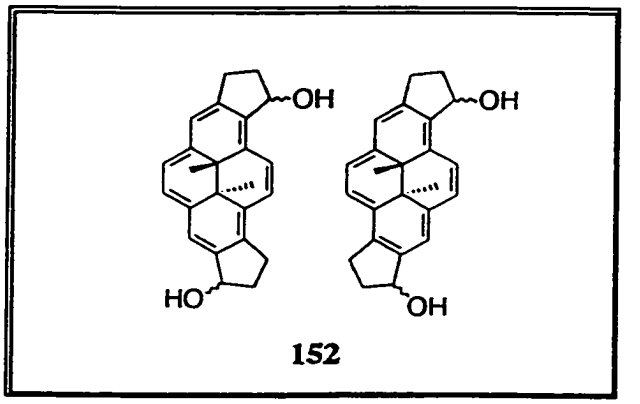
Attempted synthesis of dicyclopentadienyl DHP 154



154

The mixture of dialcohol (30 mg, 0.087 mmole) was dissolved in HMPT (1 mL). Then methyl triphenoxyphosphonium iodide[68], $(PhO)_3P^+MeI^-$ (0.24 g, 6 eq) was added and the reaction mixture was stirred under argon for an hour. Degassed ice water was added and the reaction mixture was extracted with CH_2Cl_2 (3 x 50 mL). The organic extract was washed, dried and evaporated. The residue was chromatographed over deactivated SiGel with hexane followed by increasing portion of CH_2Cl_2. Only trace amount of the diketone (identified by NMR and MS) was recovered.

Reduction of the diketone 70 to the dialcohol 152



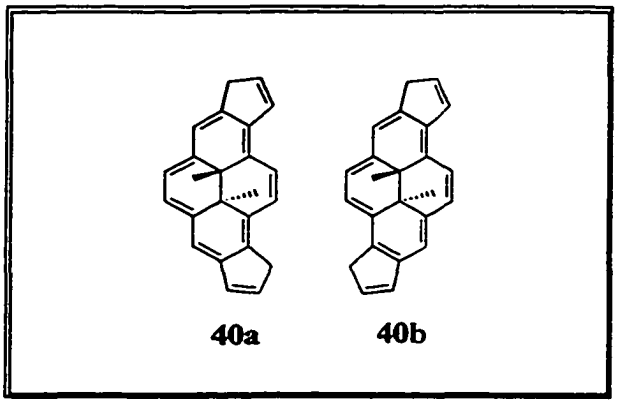
152

The mixture of diketone **70** (46 mg, 1.4 mmole) was dissolved in a solvent mixture of MeOH-THF (1:1) (15 mL) and sodium borohydride, $NaBH_4$ (1.7 mg, 0.04 mmole) was added in one portion at 0°C under N_2. Then the solution was further stirred at room temperature for an hour during which the solution turned color from deep red to green. Water (20mL) was added and the solution was extracted with CH_2Cl_2 (4 x 30 mL), dried and evaporated to give the crude unstable green dialcohol mixture which was used without purification for the next step, 46 mg, 100%. ^1H NMR (300 MHz): δ 8.82-8.37 (m, Ar-H), 6.29 (t, J=6.4Hz, -C**H**-OH), 5.94 (m, -C**H**-OH), 5.82 (t, J=5.6Hz, -C**H**-OH), 5.55-5.41 (m, -C**H**-OH), 3.30-4.00 (m, ring-H), 2.10-3.00 (m, ring-H), -3.99 to -4.20 (15s, Int Me).

Elimination of the dialcohol 152 to the diene 40.

***trans*-10c,10d-Dimethyl-1,8,10c,10d-tetrahydrodicyclopenta[a,i]pyrene (*cisoid* 40a)**

***trans*-10c,10d-Dimethyl-1,9,10c,10d-tetrahydrodicyclopenta[a,h]pyrene (*transoid* 40b)**



The mixture of dialcohol **152** (46 mg, 1.3 mmole) was dissolved in HMPT (1 mL). Then methyl triphenoxyphosphonium iodide[68], $(PhO)_3P^+MeI^-$ (0.24 g, 6 eq.) was added and the reaction mixture was stirred under argon for an hour. Degassed ice water was added and the reaction mixture was extracted with CH_2Cl_2 (3 x 50 mL). The organic extract was washed, dried and evaporated. The residue was chromatographed over deactivated SiGel with PE to give the unstable orange-green bis-alkenes, 8 mg, 19 %, which is a mixture of the *trans, cisoid* and *trans, transoid* isomers **40a** and **40b**. ^1H NMR (300 MHz): δ 8.80-8.44 (m, 6H, aromatic-H), 7.94 (m, 1H, vinylic-H), 7.38 (m, 1H, vinylic-H), 6.94 (m, 1H, vinylic-H), 6.89 (m, 1H, vinylic-H), 4.31-3.88 (m, 4H, ring CH_2), -4.02, -4.03 (2s, 6H, Int Me); MS(CI), *m/z* 309 (MH^+); EI-HRMS calculated for $C_{24}H_{20}$: 308.1565, found: 308.1573.

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IMAGE EVALUATION
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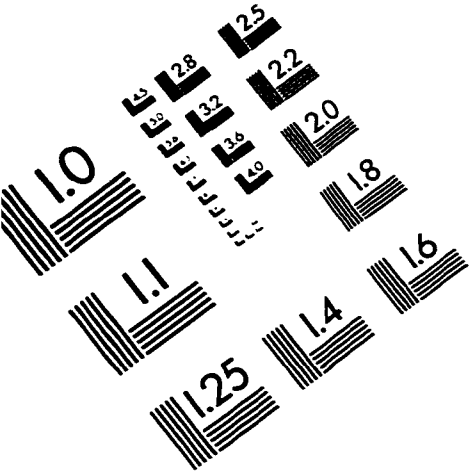

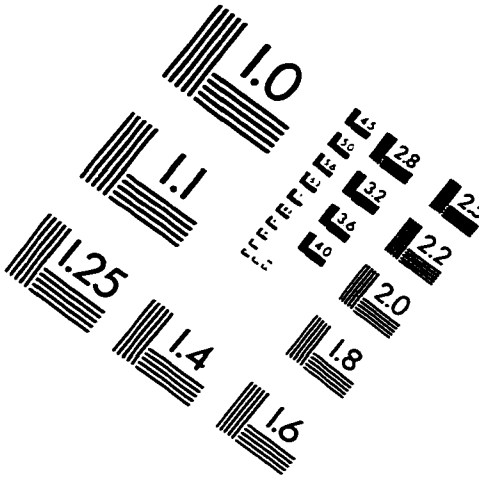

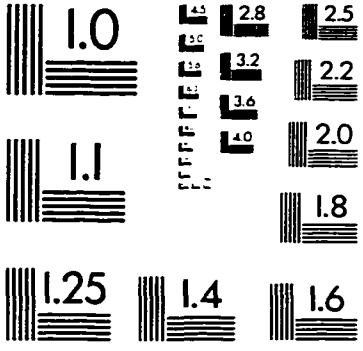

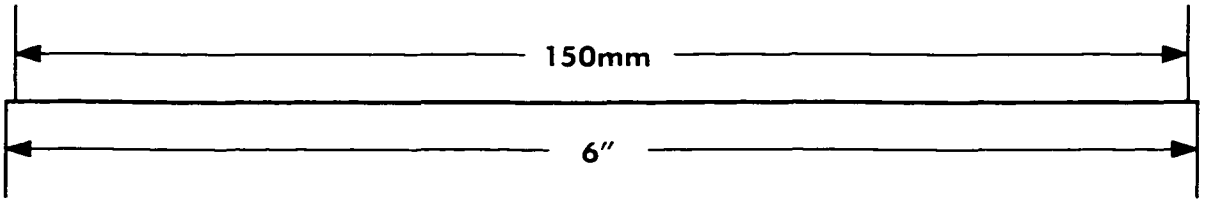

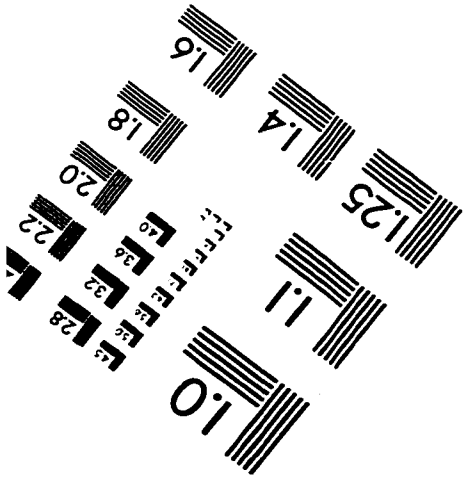

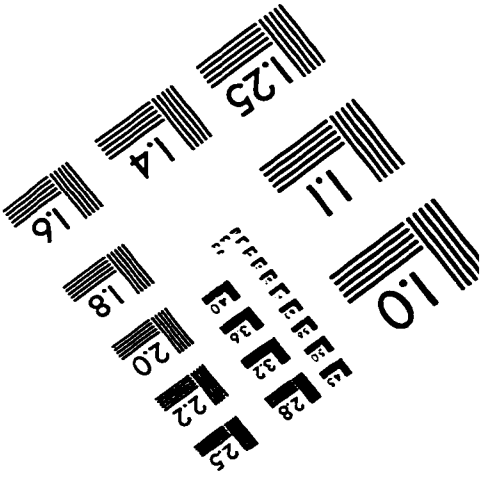

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