

FACIAL SELECTIVITY IN THE DIELS-ALDER
REACTION OF PLANE-NONSYMMETRIC
CYCLOPENTADIENE DERIVATIVES

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MARK A. WELLMAN



**Facial Selectivity in the Diels-Alder
Reaction of Plane-Nonsymmetric
Cyclopentadiene Derivatives**

by

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Abstract

π -Facial selectivity in the Diels-Alder reaction of 1,3-cyclopentadienes substituted at C-5 with various halogens (Cl, Br, I) and alkyl groups (Me, Et, *n*-Bu, CH₂OCH₃) is detailed. It was found that *N*-phenylmaleimide, 4-phenyl-1,2,4-triazoline-3,5-dione and tetra-cyanoethylene gave markedly different diastereofacial outcomes with a given diene thus proving that the nature of the dienophile as well as the C-5 substituent on the diene imparts a significant influence on the reaction.

The results obtained were investigated by collaborators using high level 6-31G* theoretical calculations. The mechanism of facial selectivity is explained on the basis of a steric interaction between the diene and the dienophile that induces bending mainly in the diene. This bending translates into torsional strain in the diene in its *syn* transition state and the amount of distortion that occurs determines the diastereofacial outcome of the reaction. It was also found that the dienophiles studied imparted different steric effects on the substituted dienes thereby each affording different facial outcomes with a given diene. These results also disprove many popular theories that have recently been proposed involving the mechanism of π -facial selectivity in Diels-Alder reactions.

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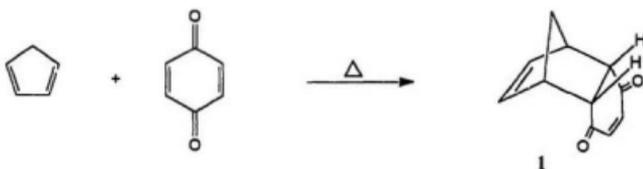
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Glossary of Abbreviations

DMAD	dimethyl acetylenedicarboxylate
FMO	frontier molecular orbital theory
FT	Fourier transform
HOMO	highest occupied molecular orbital
ir	infrared (spectroscopy)
LUMO	lowest unoccupied molecular orbital
MA	maleic anhydride
MO	molecular orbital
mp	melting point
ms	mass spectrometry
NMR	nuclear magnetic resonance (spectroscopy)
NOE	nuclear Overhauser effect
NPM	<i>N</i> -phenylmaleimide
PTAD	4-phenyl-1,2,4-triazoline-3,5-dione
rt	room temperature
TCNE	tetracyanoethylene
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
UV	ultraviolet

Introduction

It has been nearly 70 years since German researchers Otto Diels and Kurt Alder reported the reaction between *p*-benzoquinone and 1,3-cyclopentadiene and proposed the correct structure of the product as the bridged tricyclic compound **1** (Scheme 1).¹

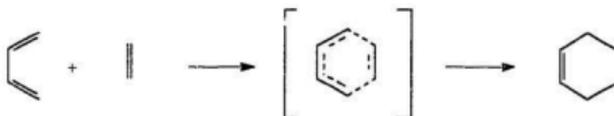


Scheme 1. The seminal discovery of Diels and Alder

They went on to demonstrate that reactions between 1,3-dienes and alkenes substituted with an α -electron-withdrawing group were of wide applicability, and for this discovery they were awarded the Nobel Prize in chemistry in 1950. Reactions of this sort have been named Diels-Alder reactions, and these reactions have become an indispensable part of the organic chemist's repertoire of synthetic methodology. The reason for the popularity of the Diels-Alder reaction becomes clear when one considers that, in a single predictable synthetic operation, two new σ -bonds are formed and up to four new contiguous stereogenic centers develop.

The mechanism by which the Diels-Alder reaction takes place has been the source of much debate.² Although stepwise mechanisms have been postulated, including the

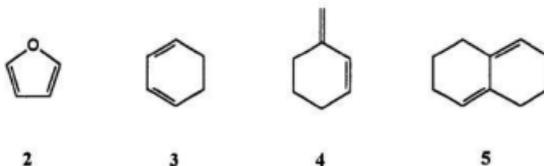
consideration of diradical¹ and zwitterionic^{4,3} intermediates, it is now generally accepted that the reaction takes place by a concerted, thermally allowed $4\pi, + 2\pi$, mechanism with the formation of the two new σ -bonds taking place simultaneously (Scheme 2).²



Scheme 2. Concerted mechanism for the Diels-Alder reaction

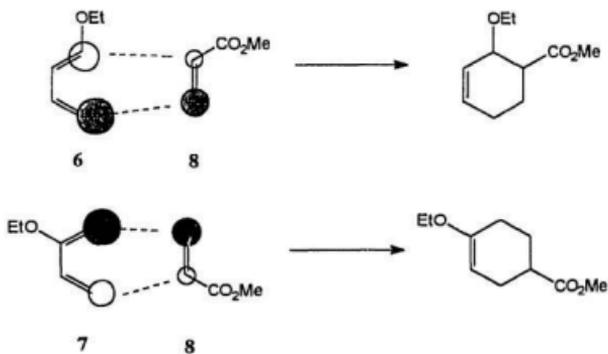
There are a number of features of the Diels-Alder reaction that determine the outcome: the conformation of the diene, the substitution patterns of the diene and the dienophile, and the manner in which the diene and dienophile approach each other. The diene in the Diels-Alder reaction can react when it is in an *s*-cis geometry but not in an *s*-trans geometry.⁶ Therefore, of the simple examples below, only **2** and **3** are reactive as Diels-Alder dienes, whereas **4** and **5** are not. The *s*-cis geometry is essential for the concerted overlap of the *p*-orbital components of both termini of the diene and dienophile.

The dienophile may contain a double or triple bond. Its reactivity is enhanced



significantly by an electron-withdrawing substituent. Furthermore, it has been shown that the placement of more than one withdrawing group in the allylic position further increases the reactivity of the dienophile dramatically.⁶

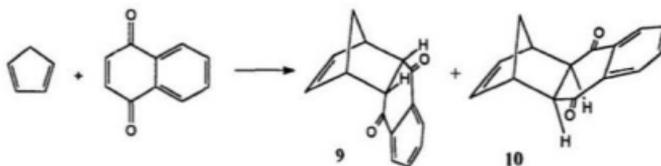
When the diene and the dienophile are unsymmetrically substituted, different regioisomers can be formed in the Diels-Alder reaction. Frontier molecular orbital (FMO) theory has been used to predict successfully the regiochemistry of many Diels-Alder reactions. One theory developed by Houk^{7,8} states that the Diels-Alder transition state will be stabilized by favourable interaction of components of the diene HOMO (highest occupied molecular orbital) and dienophile LUMO (lowest occupied molecular orbital). The orbital coefficients of the p-orbitals of the diene HOMO, when the diene is substituted by an electron-donating group at either the 1 or 2 position, are as in structures 6 and 7 (Scheme



Scheme 3. FMO rationalization of regiochemistry in the Diels-Alder reaction

3). For the dienophile, an electron-withdrawing group in the allylic position leads to the LUMO depicted in structure 8. There is a marked difference in the size of the coefficient of the wavefunction for each case. (A shaded circle indicates a positive component and an open circle represents a negative component; the relative size of the circle indicates the relative size of the coefficient.) Based on Houk's theory, the diene and the dienophile prefer to orient themselves in the manner that the terminal coefficients that are closer in energy will become bonded preferentially. Thus, an electron-donating group on the end of a diene gives mainly an "ortho-disubstituted" product, whereas a diene substituted by an electron-donating group in the 2-position yields the "para-disubstituted" product predominantly.

Different stereochemical outcomes are possible in the Diels-Alder reaction. Endo-addition occurs when the reference substituent on the dienophile is oriented towards the π -orbitals of the diene. Oppositely, exo-addition has the substituents on the diene and the dienophile pointing away from each other as the reacting partners come together. Endo-addition products predominate in most Diels-Alder reactions, and this also has been rationalized on the basis of FMO theory.⁸ For instance, with 1,3-cyclopentadiene and 1,4-naphthoquinone (Figure 1), the exo orientation can only exhibit primary interactions between the HOMO and LUMO at the centres of the new bond formation. However, the transition state for endo-addition is further stabilized by secondary orbital interactions between the double bonds of the diene and carbonyl components of the dienophile. The presence of this secondary effect serves to lower the activation energy for endo-addition. In fact, this reaction gives a mixture of **9**, the endo-addition product, and **10**, the exo-addition product, in a ratio of greater than 99 : 1, respectively (Scheme 4).



Scheme 4. The Diels-Alder reaction between 1,3-cyclopentadiene and 1,4-naphthoquinone

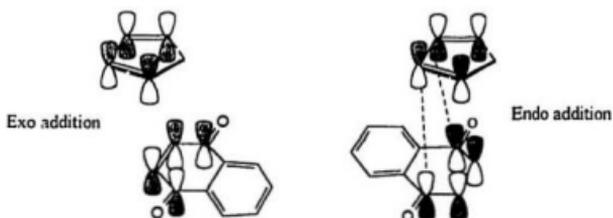


Figure 1. Simple FMO diagram for endo and exo transition states

Another stereochemical aspect of the Diels-Alder reaction becomes important when the two faces of the diene are not equivalent, i.e., the diene is plane-nonsymmetric. To illustrate this, consider a Diels-Alder addition involving 1,3-cyclopentadiene that has been substituted by a group (R) in the 5-position. Syn addition is defined in this thesis as the approach of the dienophile to the same side as this substituent group, and this gives generalized structure 11 as the product. Anti addition arises from the attack of the dienophile to the face opposite the substituent, giving generalized structure 12 (Figure 2).

It will be the primary focus of this thesis to address the factors governing π -facial diastereoselectivity. The ability to understand the factors controlling this phenomenon is of great interest to theoreticians and those concerned with synthesis because the presence of a stereogenic center can exert a significant influence on facial approach.^{9,10} Facial selectivity can also be influenced by blocking one face of the diene or the dienophile with a chiral auxiliary.¹¹ However, the demands of modern synthesis cannot always accommodate such features. It has been shown that the presence of a plane-nonsymmetric substituent in the allylic position of the diene can exert a surprisingly strong influence over facial selectivity. This effect has surfaced in Corey's prostaglandin synthesis,¹² wherein the

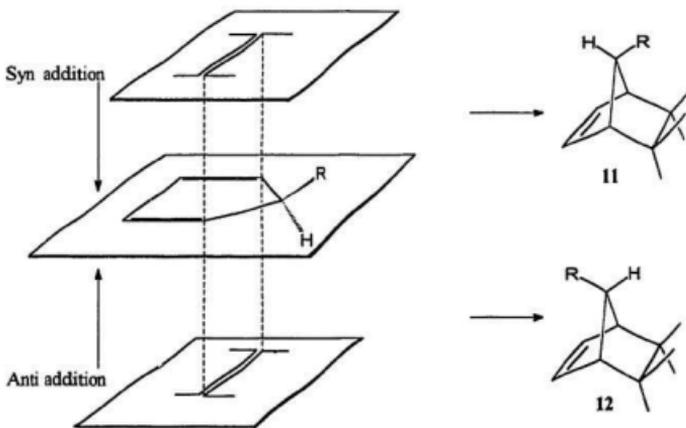
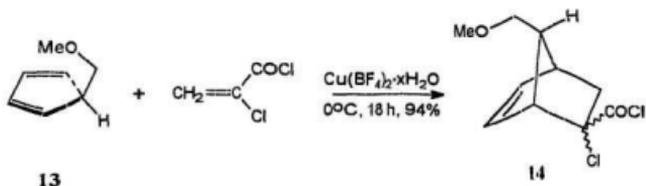


Figure 2. Syn and anti addition of a dienophile to a plane-nonsymmetric diene

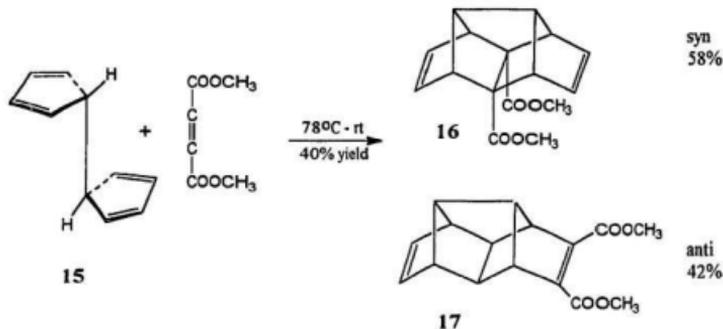
use of 5-methoxymethyl-1,3-cyclopentadiene **13** led to a reaction with complete diastereofacial control, affording only the anti adduct **14** (Scheme 5).



Scheme 5. π -Facial selectivity in Corey's prostaglandin synthesis¹²

In other instances, such as in Paquette's dodecahedrane synthesis,¹³ the placement of a relatively large cyclopentadiene group in the 5-position of 1,3-cyclopentadiene **15** showed a surprisingly small influence on facial selectivity. This reaction proceeded to give a mixture of **16** (syn) and **17** (anti) adducts in a ratio of 58 : 42, respectively (Scheme 6).

π -Facial selectivity has been rationalized in many ways, and the remainder of this introduction is an overview of the experimental data supporting each theory. Particular attention will be applied to cyclic dienes in which problems with conformation are much less contentious than with acyclic dienes. The three remaining factors that may be important in determining facial selectivity for cyclic dienes are steric, torsional and stereoelectronic effects. More than one of these factors may be operating, and there can be debate over which is playing the most prominent role in controlling the diastereofacial outcome of a reaction.



Scheme 6. π -Facial selectivity in Paquette's dodecahedrane synthesis ¹³

Steric Effects

Recent investigations in our laboratory by Burry *et al.*¹⁴ showed that facial selectivity with 1,2,3,4,5-pentachloro-5-methoxy-1,3-cyclopentadiene **18** is controlled mainly by steric and / or torsional effects. Dienophiles of various types were reacted with this diene (Scheme 7). Some reactions were expected to proceed via the inverse-electron-demand mode (entry 1), whereas others were of the normal electronic configuration (entry 2). However, the facial selectivity in every case was the same, i.e., 100% *syn* to the methoxy group, *despite* the electronic nature of the dienophile used. This ruled out any possibility that a stereoelectronic factor was controlling facial selectivity in this type of system.

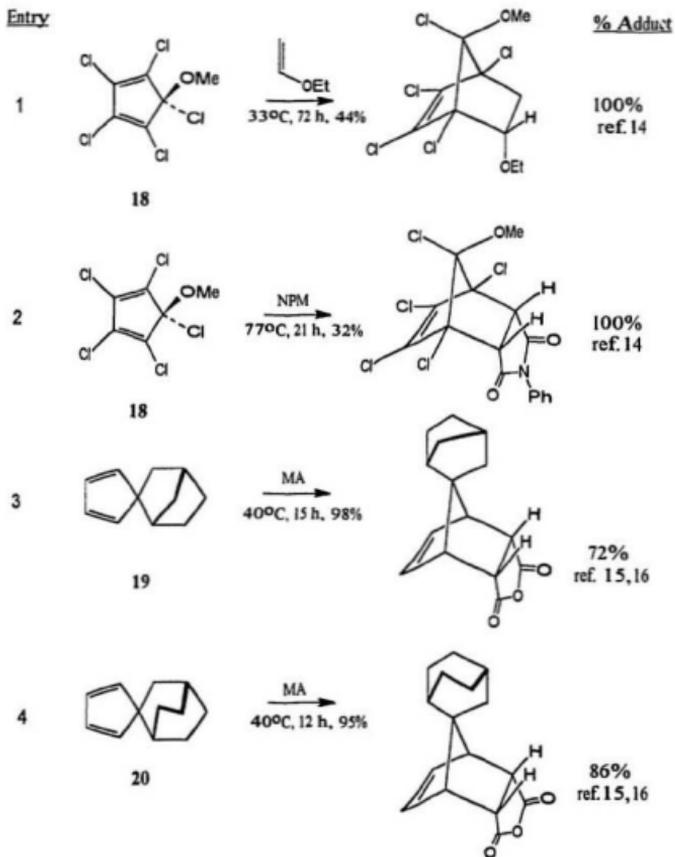
Another investigation by Valenta and Burnell^{15,16} also pointed towards a predominant steric effect in the determination of facial selectivity for the bridged-ring-substituted 1,3-cyclopentadienes **19** and **20**. The results shown in entries 3 and 4 of Scheme 7 indicate

that the methine hydrogen is more sterically demanding than the methylene hydrogens. The methine hydrogen is pointed directly towards the incoming dienophile, whereas the methylene hydrogens are oriented in such a manner that they are angled slightly away from the incoming dienophile (Figure 3). The facial selectivity was modelled successfully using steric factors as the basis of facial difference.¹⁶

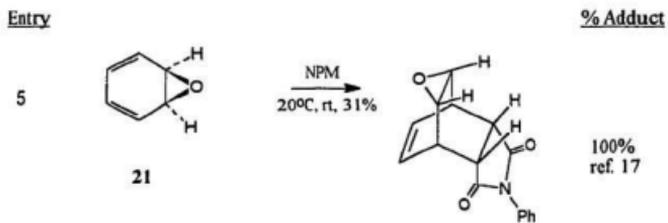
Another case of sterically controlled facial selectivity involves the reaction of benzene oxide **21** with *N*-phenylmaleimide which results in addition anti to the oxygen.¹⁷ This anti addition is in marked contrast to many examples of an allylic oxygen atom directing addition syn to itself. While it has been argued that electronic factors predominantly govern facial selectivity in allylic oxygen bearing dienes, it was suggested that a steric interaction between the allylic oxygen and the dienophile might be causing this anti result.¹⁷ Indeed, it was shown that the geometry of **21** is such that the oxygen is almost perpendicular to the plane of the diene moiety, whereas the allylic hydrogens lie roughly coplanar with the diene. This would cause a significant steric interaction between an incoming dienophile on the syn-face, leaving the anti face open for dienophile approach.

Electronic Effects

The first example of a C-5 heteroatom-substituted 1,3-cyclopentadiene was reported by Woodward *et al.*¹⁸ who reacted 5-acetoxy-1,3-cyclopentadiene **22** with ethylene (Scheme 8, entry 1). This was accomplished through the thermolysis of diacetoxydicyclopentadiene in the presence of ethylene. They reported a single adduct, arising from the attack of the dienophile onto the face of the diene syn to the acetoxy group. Clearly, this is a contrasteric



Scheme 7. Major adducts for sterically controlled Diels-Alder reactions (NPM = *N*-phenylmaleimide, MA = maleic anhydride)



Scheme 7. Continued
NPM = *N*-phenylmaleimide

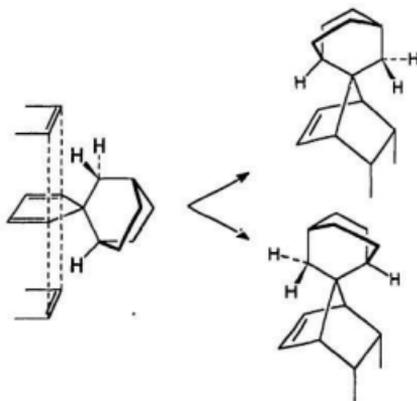
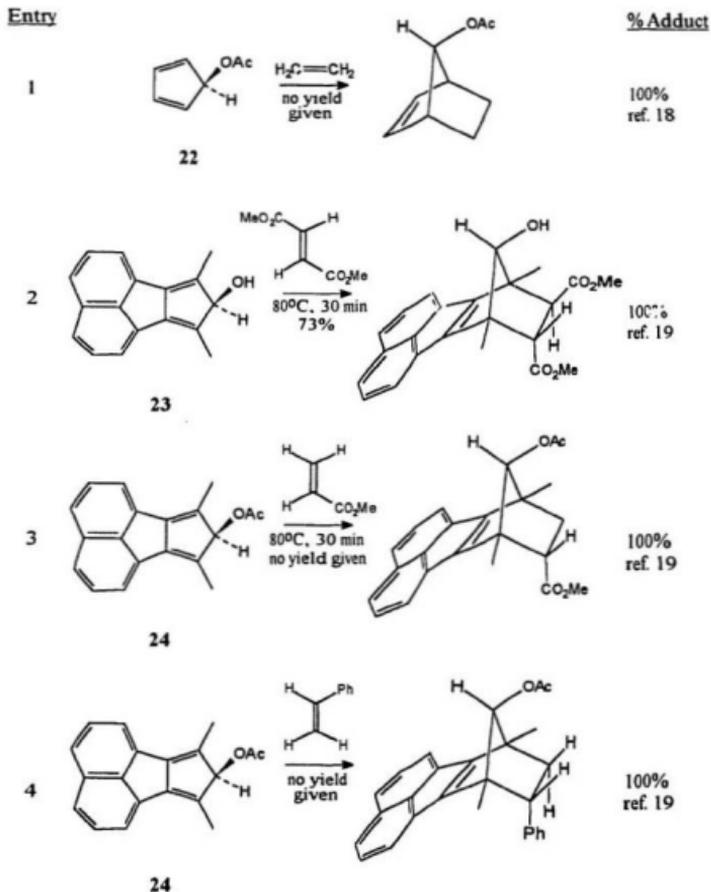


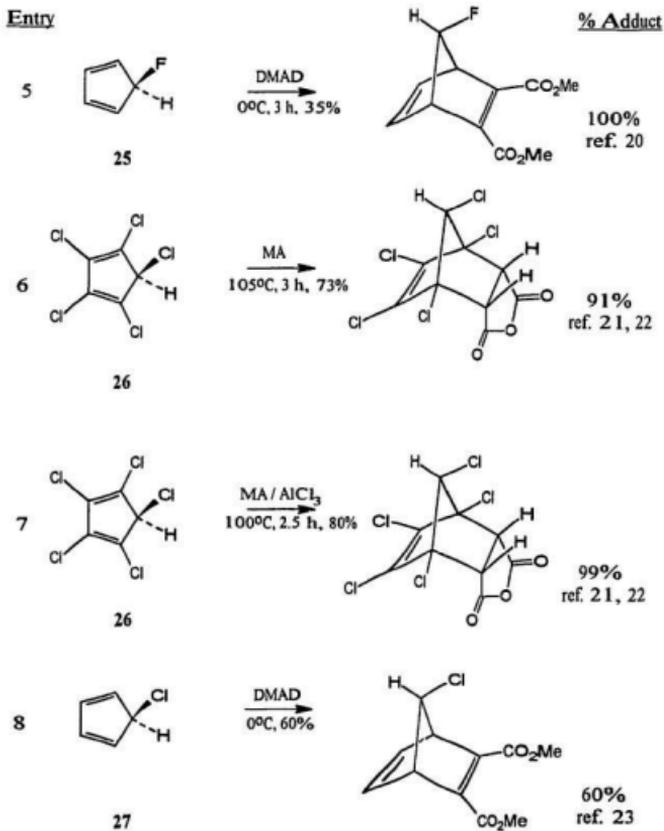
Figure 3. Facially distinct addition with a bridged-ring-substituted diene **20**

result, although with the conditions employed some argument can be made as to whether or not the observed product was derived through a kinetic process. Nevertheless, other investigations into the Diels-Alder reactions of 5-hydroxy- **23** and 5-acetoxy-1,3-cyclopenta-diene **24** derivatives also afforded exclusively the product of addition syn to oxygen.¹⁹ The stereochemistry of the adducts was not the consequence of hydrogen bonding between an allylic oxygen substituent and the dienophile since reaction of styrene with **24** also led to addition syn to hydroxyl (Scheme 8, entry 4). More recently, the fluorinated diene **25** was synthesised, and it displayed addition exclusively syn to the fluorine, also.²⁰ The pentachloro diene **26** displayed a preference for syn addition.^{21,22} Furthermore, the proportion of this syn adduct was shown to increase with the addition of a Lewis acid.²² These results, which should be disfavoured on steric grounds, were explained on the basis of an attractive interaction between the allylic substituent on the diene and the dienophile through dipole-dipole, dipole-induced-dipole or London dispersion forces. These interactions would be enhanced by complexing the dienophile with a Lewis acid and thereby increasing the preference for addition syn to chlorine. This was consistent with experimental results.

5-Chloro-1,3-cyclopentadiene **27** has also been synthesised,^{23,24} and it reacted in a Diels-Alder fashion with dimethyl acetylenedicarboxylate (DMAD) to give a mixture of syn and anti adducts, showing a slight preference for the latter. Interestingly, the reaction of 5-thiophenyl-1,3-cyclopentadiene **28** with maleic anhydride (MA) yielded the same facial diastereoselectivity as **27**.²⁵ However, 5-bromo-1,3-cyclopentadiene **29** afforded only the anti adduct on reaction with DMAD.²³ This result was echoed by the reaction of

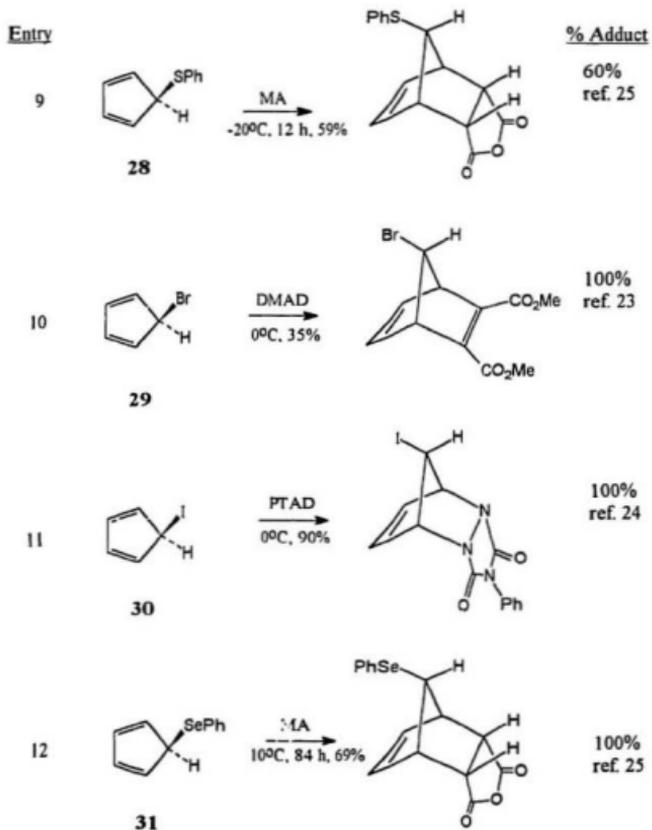


Scheme 8. Major Diels-Alder adducts with various 1,3-cyclopentadiene derivatives



Scheme 8. Continued

DMAD = dimethyl acetylenedicarboxylate, MA = maleic anhydride



Scheme 8. Continued

MA = maleic anhydride, DMAD = dimethyl acetylenedicarboxylate

PTAD = 4-phenyl-1,2,4-triazoline-3,5-dione

5-iodo-1,3-cyclopentadiene **30**, which furnished exclusively the anti Diels-Alder adduct on reaction with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD).²⁴ Furthermore, it was shown that the phenylselenyl derivative **31** also reacted with complete diastereofacial selectivity in which addition of the dienophile was anti to the heteroatom.²⁵

In Scheme 8 we see a *syn* (contrasteric) approach to the C-5 substituent when it is O or F, and a mixture of diastereomers when the substituent is Cl or S. Larger atoms like Br, I and Se direct addition towards the anti-face of the diene. While it may be argued that steric repulsion may dominate with the latter group of atoms, it has been suggested by Anh²⁶ that a beneficial interaction between the C-5 substituent and the incoming dienophile may play an important role in facial selectivity. The *syn* selectivity for atoms like oxygen was explained on the basis of an interaction between the C-5 substituent's lone pairs and the LUMO of the *syn*-adding dienophile. This "attraction" allows for better interaction between the symmetrical π -orbital of the diene and the vacant π^* orbital of the dienophile, and thus provides a net stabilization towards *syn* approach to the heteroatom (Figure 4). When the energy of this molecular orbital becomes significantly different from that of the dienophile's LUMO, this stabilizing interaction is diminished and steric hindrance controls the stereochemistry of the reaction. Although this theory can be successfully applied to a large number of experimental results, it cannot be extended in a straightforward manner to explain *syn* selectivity with substituents like F and Cl, whose symmetrical π -orbital is significantly different in energy to the π^* orbital of the dienophile and should therefore not be able to stabilize the *syn* approach by this mechanism.

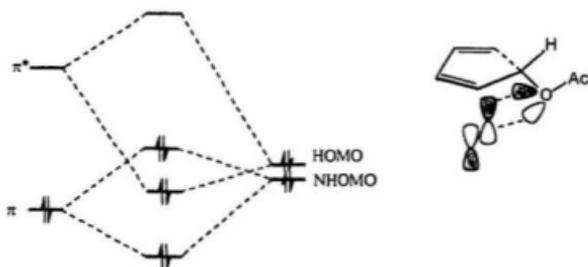


Figure 4. MO diagram for Anh's theory of facial selectivity with heteroatom substituents

The apparent contrasteric addition of 5-heterosubstituted cyclopentadienes has also been explained by an hypothesis offered by Fukui and coworkers.^{27,28,29} They suggested that orbital mixing between the lone pair electrons of the allylic heteroatom and the diene HOMO causes this HOMO to be biased towards the syn surface, thereby inducing kinetically controlled dienophile attack to this face. However, this theory cannot explain the preference for anti addition with atoms like chlorine and sulphur for which the n orbital energy for the heteroatom is close to the π -orbital energy of the diene. Significant n - π mixing should occur in the diene HOMO thereby promoting high facial selectivity. However, there is no agreement between the computational data and the experimental results for this case. Furthermore, this hypothesis has been discounted recently by Werstiuk and coworkers³⁰ who claimed that n - π orbital mixing cannot be the source of π -facial diastereoselectivity. They based this argument on *ab initio* / AM1 calculations and photoelectron spectroscopy, which showed no significant mixing of the lone pair orbitals of

the allylic substituent and the π -system. Furthermore, Poirier and Burnell³¹ showed that there is an insignificant difference in the hybridization of the 5-substituent in the syn or anti transition states and that the bond orders between the allylic heteroatom and C-1 or C-4 of the diene are negligible at the transition states.

Another hypothesis has been offered to explain the range of facial selectivities encountered for heteroatom substituents by Ishida, Aoyama and Kato.²⁵ They proposed that the syn attack towards many heteroatoms may be stabilized by favourable interactions of the π -electrons in the developing norbornene bond with the back lobe of the polarized carbon - heteroatom bond (Figure 5). Since the electronegativities of the heteroatoms decrease in the order of $F > O > S > Se$, the tendency to add syn to these atoms will tend to decrease in that order.

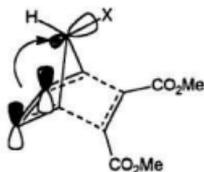
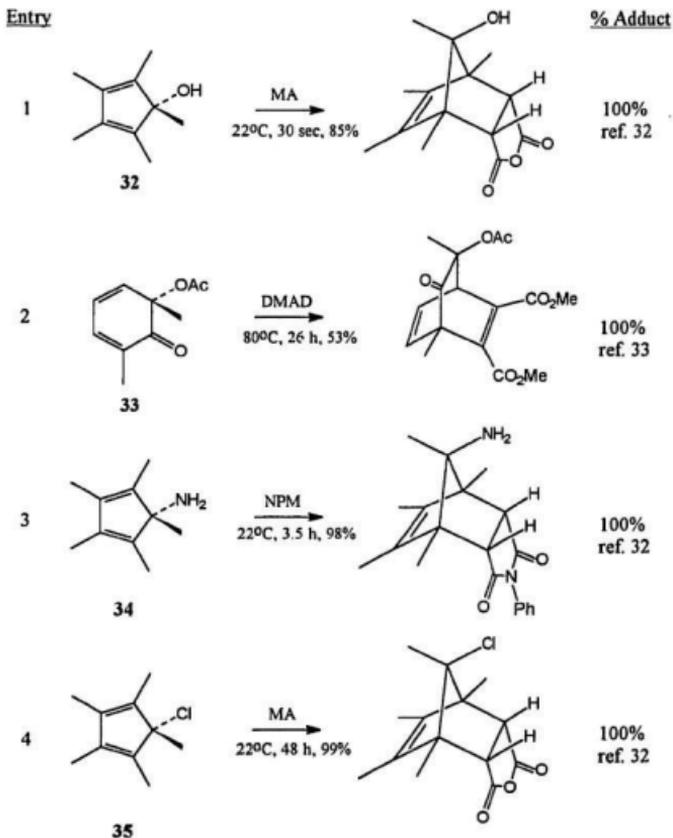


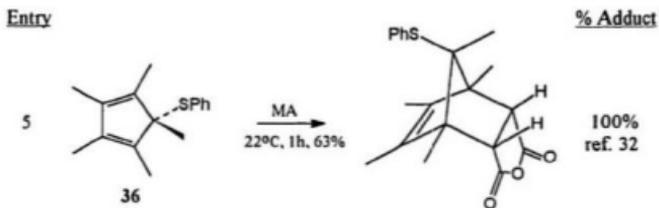
Figure 5. Depiction of Ishida's mechanism for stabilization in the syn transition state

Up to this point, we have only considered factors governing facial selectivity for the simplest of diene systems. In each case, facial selectivity was considered for an allylic substituent relative to a hydrogen. More complicated systems exist wherein the π -facial diastereoselectivity is relative to a substituent other than hydrogen. The most comprehensive databases of diastereofacial selectivities for this type of system have been acquired through investigations on 5-substituted-1,2,3,4,5-pentamethyl-1,3-cyclopentadienes and substituted cyclohexadiene systems (Scheme 9). As with many of the simple 5-substituted 1,3-cyclopentadiene systems, a facial preference for addition *syn* to oxygen in competition with a methyl group was observed. 5-Hydroxy-1,2,3,4,5-pentamethylcyclopentadiene **32** and the cyclohexadiene derivative **33** both gave addition *syn* to oxygen exclusively.^{12,33} Furthermore, this high level of selectivity can be extended towards nitrogen derivatives, as the amine **34** also afforded exclusively the *syn* diastereomer.¹² However, in marked contrast to the simple 1,3-cyclopentadiene derivative **27**, the chloro derivative of 1,2,3,4,5-pentamethylcyclopentadiene **35** provided exclusively the *syn* adduct whereas the thiophenyl derivative **36** exhibited almost exclusive diastereofacial selectivity for the *anti* adduct.¹²

The results for these cycloadditions established the strong preference for *syn* additions towards N, O, Cl and *anti* towards S. Previous explanations of facial selectivity have tended to focus on some ground state property of the allylic substituent that invoked the π -facial diastereoselectivity. Cieplak^{34,35} pioneered what would later be developed into an alternative analysis by investigating the mode of facial attack towards carbonyls. He observed that both thermal and photochemical additions occurred at the face *anti* to the α



Scheme 9. Major Diels-Alder adducts for various pentamethyl-1,3-cyclopentadiene derivatives and a cyclohexadiene derivative
 MA = maleic anhydride, DMAD = dimethyl acetylenedicarboxylate
 NPM = *N*-phenylmaleimide



Scheme 9: Continued
MA = maleic anhydride

substituent that was the better sigma donor. This would be favoured by mixing of the σ_{α}^* of the forming bond with the filled σ -orbital of the α C-X bond. For example, additions to the carbonyl of cyclohexanone favour axial attack because the α C-H bond is a better σ donor than the α C-C bond (Figure 6). This observation was extended by Fallis³⁶ to account for facial selectivity in Diels-Alder reactions. He proposed that, based on Cieplak's hypothesis, one should expect cycloaddition involving plane-nonsymmetric dienes to display a preference for addition anti to the antiperiplanar bond that is the better σ donor. A list in

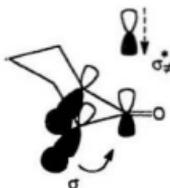


Figure 6. Cieplak's hypothesis for the axial attack on cyclohexanone

increasing order of σ -donating ability for common atoms is C-O < C-N < C-Cl < C-H < C-S.¹⁷ Therefore, when a diene is substituted with a C-S bond and a C-C bond, addition should occur anti to the C-S bond since it is the better σ donor (Figure 7).

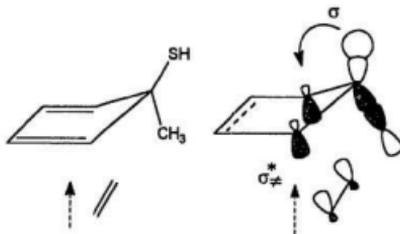


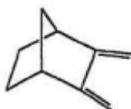
Figure 7. Depiction of σ donation from the anti substituent into the $\sigma_{\text{C-C}}^*$ orbital of the forming bond.

π - Facial selectivity with bridged-ring cyclopentadienes has also received considerable attention. Diels-Alder reactions with isodicyclopentadiene **37** (Scheme 10) proceeded exclusively anti to the methano bridge.³⁸ Dienes **38** and **39** behaved similarly, affording exclusively the products of addition anti to the methano moiety. The cause of this behaviour cannot be steric since additions occurred syn to the larger, ethano bridge. Paquette rationalized this facial selectivity by proposing that orbital mixing of the non-reactive portion of isodicyclopentadiene with the π , diene orbital is important.³⁹ This interaction causes an inward tilt of the diene orbitals resulting in a minimization of the antibonding interaction on the below-plane face of the diene, which in turn results in preferred addition to this side (Figure 8).

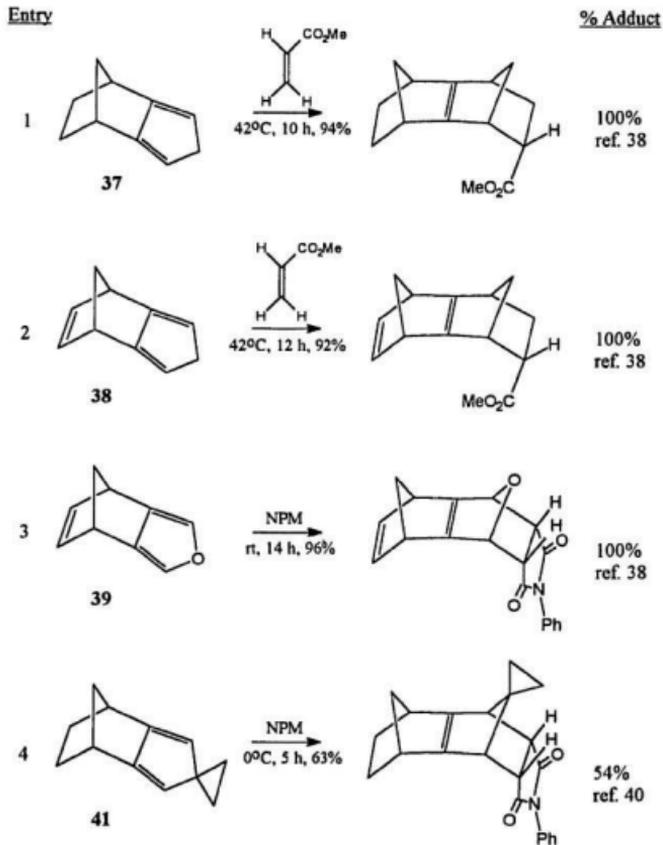


Figure 8. Depiction of rotation of the terminal p_{π} lobes for π_5 in **37**

This was supported by calculations on the simpler system **40**, which indicated that there is significant mixing between the lowest occupied π -orbital and high lying σ -orbitals. Significant differences in the frontier electron distribution on the above-plane and below-plane diene surfaces resulted in the rotation of the p_{π} orbital for the π_5 . It is this orbital tilting that was proposed to be responsible for the addition anti to the methano bridge. The different overlap between the dienophile and the rotated π orbital of the terminal carbon atoms of the diene causes the antibonding interactions between the π_5 of the diene fragment and the HOMO of the dienophile to be diminished for below-plane attack relative to above-plane attack (Figure 9). However, cycloadditions with **41** occurred predominantly from the above-plane face.⁴⁹ On the basis of the photoelectron spectra of **41** and extensive INDO (incomplete neglected differential overlap) calculations, it was suggested that the terminal π lobes of these dienes are rotated away from the methano bridge, in a manner



40



Scheme 10. Syn : anti ratios for various isodicyclopentadiene derivatives
 NPM = *N*-phenylmaleimide

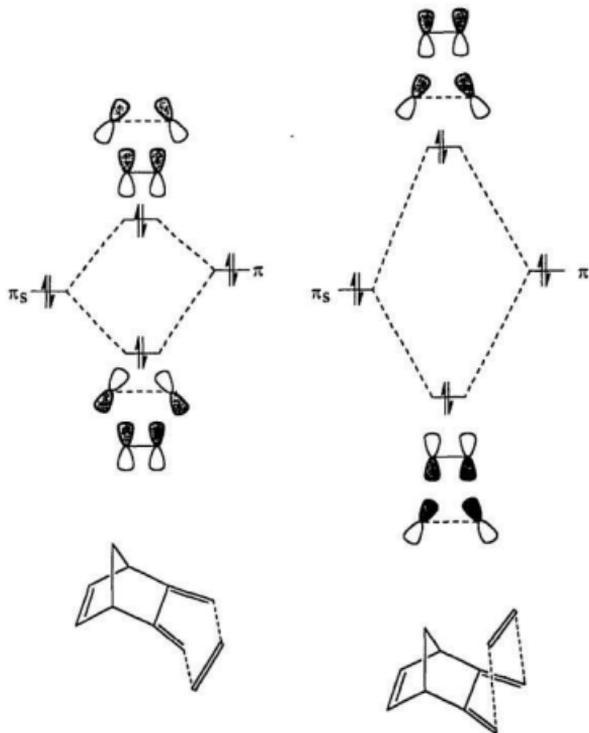
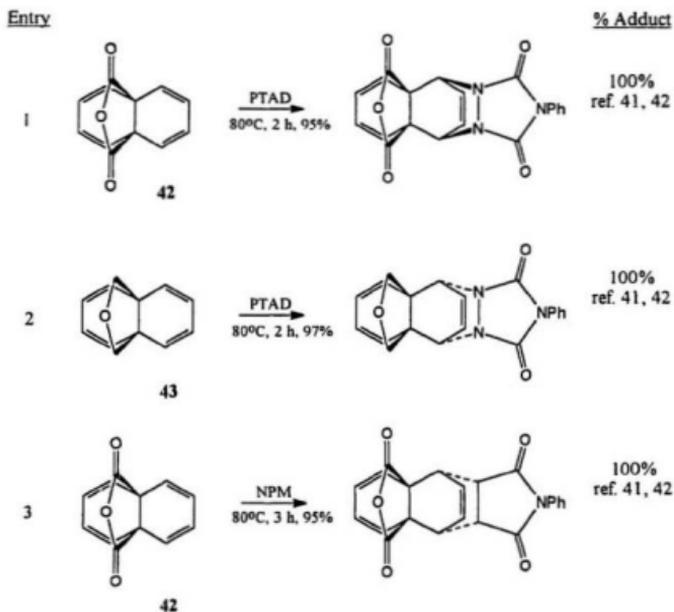


Figure 9. Qualitative diagram of the interaction between the π_S of the butadiene unit in 40 with ethylene. On the left, below-plane approach is depicted and, on the right, above-plane approach.

opposite to 37, 38, and 39 and thus addition occurs from the above-face.

Diels-Alder reactions with heterocyclic propellanes have received considerable attention. For example, the reaction between propellane 42 and PTAD afforded the syn adduct (Scheme 11).^{41,42} However, replacement of the carbonyls by methylenes as in 43, provided anti adducts exclusively. It was proposed that this crossover in facial selectivity was due to stabilization from secondary orbital overlap between the π components of the carbonyl carbons and the lone pair orbitals on the nitrogens of the dienophile (Figure 10). Clearly, no such overlap would be possible for additions of PTAD to 43, and hence the anti product predominates. Furthermore, addition of a carbon-based dienophile to 42 should provide the anti adduct because no secondary overlap would be possible.⁴³ Therefore, it can be concluded that for propelladienes, secondary orbital overlap favours syn addition when possible, otherwise steric effects dominate and the anti adduct is observed.

Halterman and co-workers⁴⁴ attempted to establish conclusively the importance of electronic interactions in determining the diastereoselective outcome in the Diels-Alder reaction. This was approached by the investigation of facial selectivity for 1,3-cyclopentadienes with sterically unbiased, yet electronically different substituents in the allylic position (Scheme 12). The Diels-Alder reaction of diene 44 with DMAD showed a preference for addition syn to the substituted phenyl group. However, diene 45 afforded more of the adduct from anti addition. It seemed apparent that addition occurred anti to the more electron-rich phenyl ring. These findings are consistent with Fallis' suggestion that dienophile additions should occur to the diene face opposite the better σ donor.³⁶



Scheme 11. Major Diels-Alder adducts for selected propelladienes
 PTAD = 4-phenyl-1,2,4-triazoline-3,5-dione, NPM = *N*-phenylmaleimide

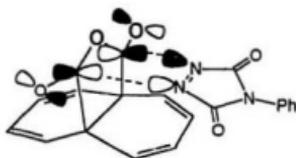
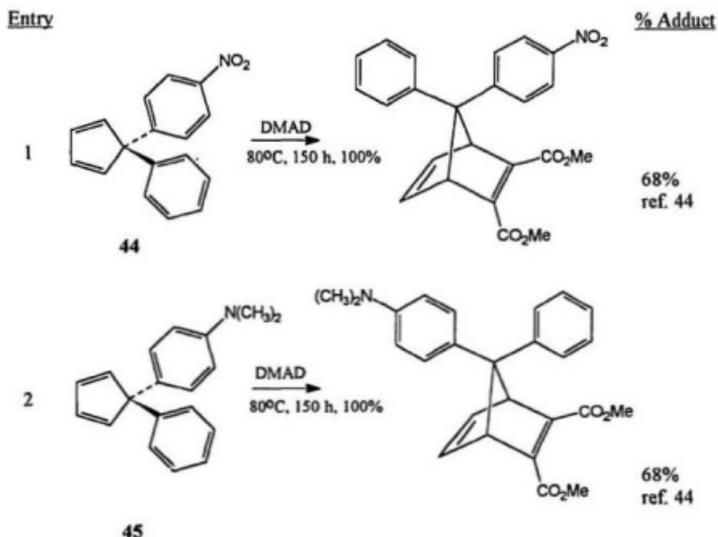


Figure 10. Secondary orbital overlap for the approach of a heteroatom-based dienophile to an anhydride-bridged propelladiene

Halterman's study supported the idea that in the absence of steric factors, diastereoselective control in the Diels-Alder reaction can be significantly altered by internal electronic parameters.

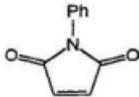
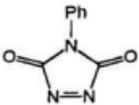
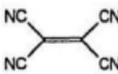
Inagaki has proposed that selectivity for Diels-Alder reactions is controlled by the reactivity of the dienophile.⁴³ He supported this theory on the basis of the diastereoselective



Scheme 12. Major Diels-Alder adducts for additions to sterically unbiased, yet electronically different dienes

outcome of the reactions of 5-thiophenyl-1,3-cyclopentadiene **28** with dienophiles of different reactivities (Table 1). The selectivity changed from a slight preference for anti attack with a less reactive dienophile to exclusive anti attack with a highly reactive dienophile. On the basis of these data, he concluded that selectivity should increase with the reactivity of the dienophile. This also suggested that if the reactivity of the dienophile is enhanced by a Lewis acid the selectivity should also increase. Currently there is very little

Table 1. π -Facial selectivities of Diels-Alder reactions between 5-thiophenyl 1,3-cyclopentadiene and dienophiles of different reactivities

Dienophile	Reactivity (L/mol-sec)	Syn / Anti	$\Delta \Delta G^\ddagger$ (Syn / Anti) (kcal/mol)
	55 600	40 : 60	0.22
	70 500	30 : 70	0.46
	16 000 000	14 : 86	1.00
	430 000 000	100% anti	3.8

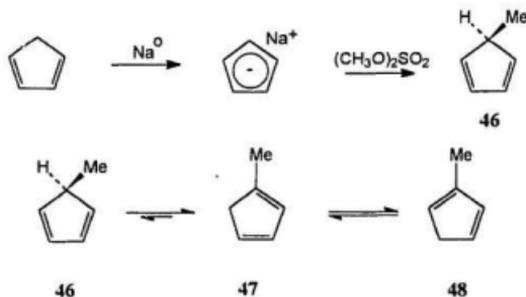
experimental evidence supporting this argument.^{15,16} Furthermore, there seems to be little correlation between the $\Delta\Delta G^\ddagger$ for the modes of facial approach (syn : anti ratio) and the reactivity of the dienophile.

This introduction has reviewed many antithetical theories regarding π -facial selectivity in the Diels-Alder reaction. A serious problem with the development of any unified theory explaining facial selectivity in Diels-Alder reactions is that carefully and systematically prepared data for the simplest of dienes are unavailable. Therefore, we sought to develop an efficient route towards the synthesis of 5-substituted-1,3-cyclopentadienes, which are among the most rudimentary class of cyclic plane-nonsymmetric dienes, and to react these with various dienophiles. The inherent simplicity of this type of diene should minimize secondary steric, torsional and electronic interactions between the diene and the dienophile. Furthermore, cyclic dienes obviate the conformational ambiguities that are inherent to acyclic systems, allowing the effects of the allylic substituent on π -facial selectivity to be studied unobtrusively. Reactions involving dienes of this size can also be studied computationally by using *ab initio* methods at a high level of theory. These synthetic studies and some aspects of the results of the theoretical studies are described in the remainder of this thesis.

Results

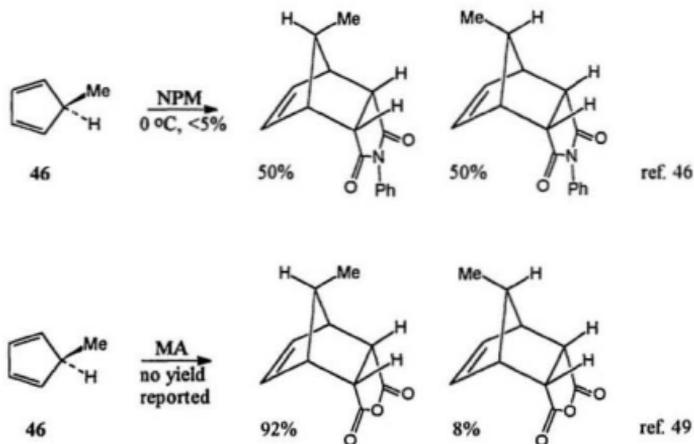
5-Alkyl-substituted cyclopentadienes

In the 1960's there were attempts, largely unsuccessful, at synthesizing 5-alkyl-substituted-1,3-cyclopentadienes. Nevertheless, McLean and Haynes⁴⁶ published the synthesis of 5-methyl-1,3-cyclopentadiene **46** by the reaction of sodium with cyclopentadiene, to give the cyclopentadienide anion, which was subsequently treated with dimethyl sulfate to provide **46** in extremely poor yield. This was due, in part, to the inherent lability of this compound, which can readily undergo a 1,5-hydrogen shift to give the regioisomers **47** and **48** (Scheme 13). Indeed, it was shown that the rearrangement of 5-methyl-1,3-cyclopentadiene (**46**) to give **47** and **48** follows first order kinetics with the $t_{1/2}$ for **46** being less than 30 minutes at 20°C.^{47,48} Furthermore, polymethylation products arising



Scheme 13. Synthesis and rearrangement of 5-methyl-1,3-cyclopentadiene

from the reaction of excess base with the methylated diene **47** and subsequent re-methylation accounted for a significant portion of side product. To avoid the problem associated with the rearrangement of **46**, the diene was trapped as a Diels-Alder adduct by reacting it with NPM, which gave a mixture of syn and anti diastereomers in equal amounts⁴⁶ (Scheme 14). However, at approximately the same time, Mironov and co-workers⁴⁹ reported a Diels-Alder addition of MA with **46**, which they claimed showed a strong preference for addition anti to the methyl group. These contradictory results involving the reactions of **46** with very similar dienophiles had yet to be resolved. Furthermore, assignment of the stereochemistry relied on different long range NMR



Scheme 14. Diels-Alder adducts for the reaction of 5-methyl-1,3-cyclopentadiene with NPM and MA.

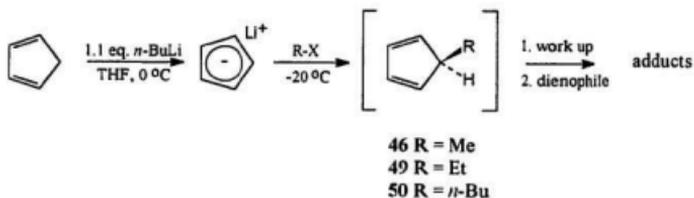
NPM = *N*-phenylmaleimide, MA = maleic anhydride

coupling patterns⁵⁰ of the protons on the newly generated double bond of the norbornene skeleton with the substituent at the apex of the methylene bridge. Today, assignments based on such data would be deemed unreliable in the absence of supporting NOE (nuclear Overhauser effect) or X-ray data.

It was in our interest to devise an efficient, general synthetic strategy to produce 5-alkyl-1,3-cyclopentadienes and to examine subsequently the effect of the alkyl substituents on π -facial selectivity in Diels-Alder reactions. From McLean's results we immediately realised that we would be required to take precautions to avoid the isomerization of the substituted dienes and the generation of polyalkylated side products.

Freshly cracked 1,3-cyclopentadiene (pKa 16)⁵¹ was treated with a slight excess of *n*-butyllithium in tetrahydrofuran (THF) to give a solution of the cyclopentadienide anion. The use of a base such as *n*-butyllithium ensured that nearly a stoichiometric amount of base was added and therefore minimized the generation of polyalkylated side products by the presence of an excess of base. Addition of this solution to an excess of an appropriate alkyl halide at -20°C afforded the desired 5-alkyl-1,3-cyclopentadienes **46**, **49**, and **50** (Scheme 15).

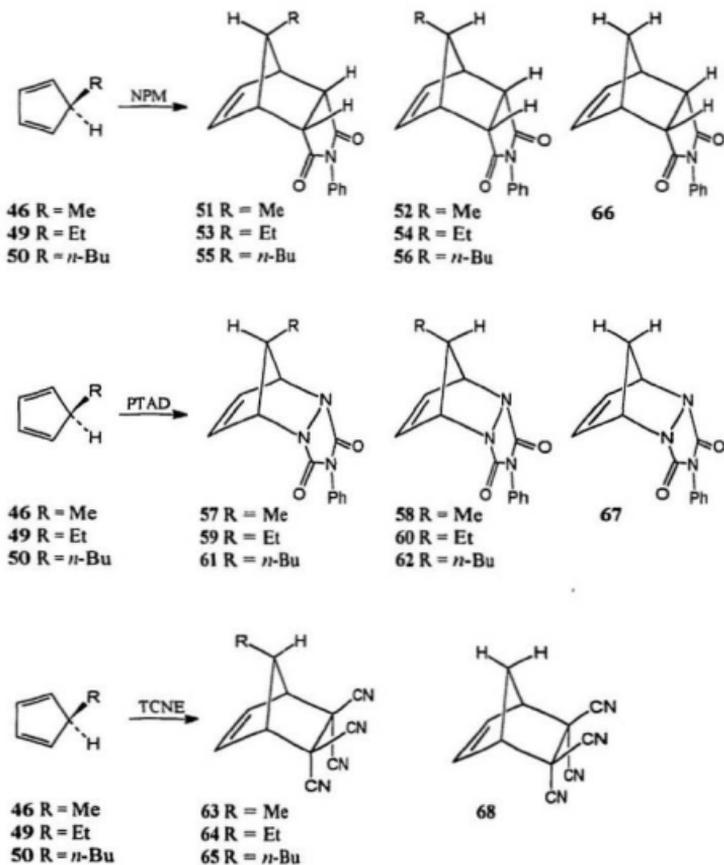
We found that rearrangement could be curtailed by performing the reaction at a low temperature (-20 °C) without adversely affecting the alkylation process. Since we were interested solely in the Diels-Alder adducts, isolation of the dienes was not attempted. The original idea was to react the dienes *in situ* with a suitable dienophile in order to generate the Diels-Alder adducts. However, direct addition of the dienophile to the reaction mixture resulted in the immediate generation of a thick black liquid, which after washing and



Scheme 15. General synthetic strategy towards 5-alkyl-1,3-cyclopentadienes

removal of the solvent, furnished a black tarry material that we were unable to identify by NMR. Since most dienophiles bear a double bond α to a carbonyl, it was suspected that some unreacted cyclopentadienide anion was attacking the dienophile by a 1,2- or 1,4-process to give undesired products. The diene was therefore quickly washed with a cold brine solution to quench any remaining organolithium species. Subsequent addition of dienophile afforded Diels-Alder adducts **51** - **65** in reasonable yields (Scheme 16). The product ratios are presented in Table 3 at the end of this section.

Separation and purification of the diastereomeric adducts was performed by flash chromatography and/or recrystallization, which provided each diastereomer in homogeneous form. Boiling solutions of each of the isolated diastereomers in benzene for extended periods showed no equilibration, which indicated that the adduct ratios were kinetically derived. The stereochemistry of each diastereomer was determined by NOE difference experiments in its ^1H NMR spectrum. For example, one adduct from the cycloaddition between 5-methyl-1,3-cyclopentadiene and NPM is shown in Figure 11. The structure of the syn adduct, **51**, was assigned based on the NOE enhancement of the signal



Scheme 16. Diels-Alder products generated from the alkyl-substituted dienes
 NPM = *N*-phenylmaleimide, PTAD = 4-phenyl-1,2,4-triazoline-3,5-dione,
 TCNE = tetracyanoethylene

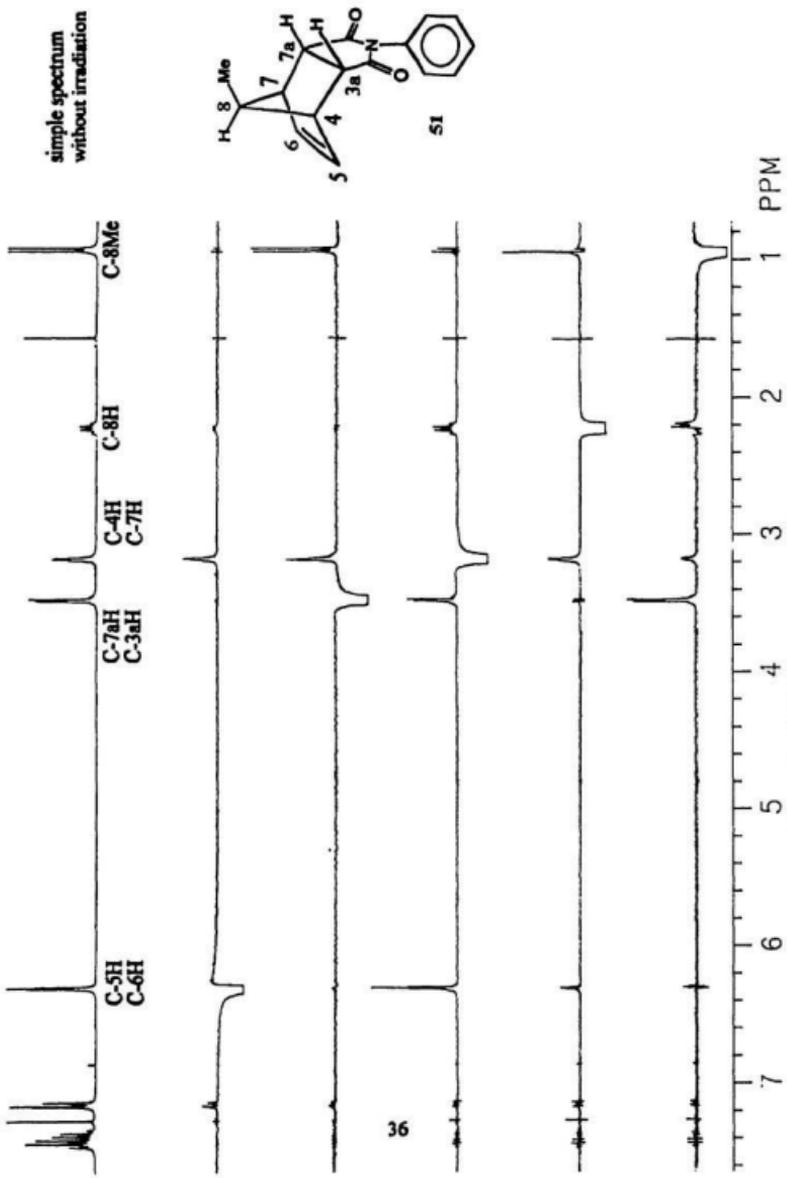


Figure 11. NOE difference spectra of 51

simple spectrum
without irradiation

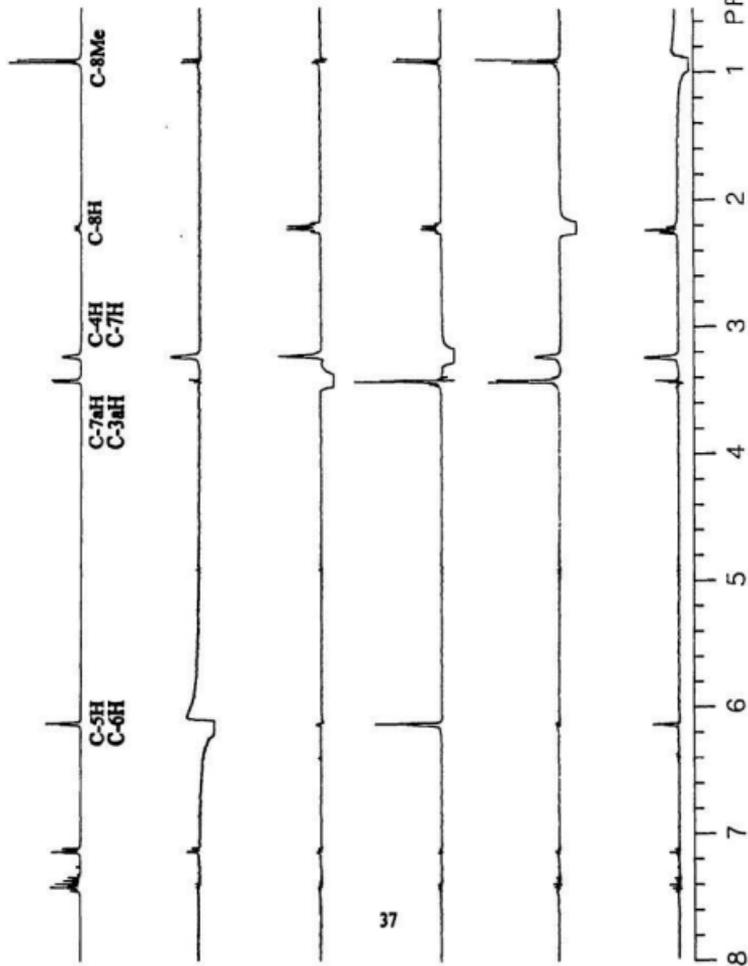


Figure 12. NOE difference spectra of 52

for the hydrogen on C-8 upon saturation of the signals for C-5H and C-6H. This result was confirmed by an NOE enhancement for C-5H and C-6H signal upon saturation of the C-8H signal. It can be noted that the NOE enhancements are uncharacteristically small in these cases due to the relatively large distance that separates the protons at C-5 and C-6 from the one at C-8. However, saturation of C-3aH and C-7aH provided a relatively large NOE enhancement of the C-8Me signal and *vice versa*. Based on these data, we could unambiguously assign **51** as the product of syn-addition. The stereochemistry of the anti-addition product **52** was also assigned by a similar argument based on NOE experiments (Figure 12). Thus, saturation of the C-3aH and C-7aH signals resulted in a significant NOE enhancement of the signal for C-8H. This stereochemistry was confirmed by the fact that saturation of C-8H led to an NOE enhancement of the C-3aH and C-7aH signals.

We found that the major impurities in the reactions of 5-substituted 1,3-cyclopentadienes were **66**, **67**, or **68**, which were obviously derived from unsubstituted 1,3-cyclopentadiene. We therefore looked into optimizing the alkylation step. The alkylation step was most effective when an alkyl iodide was used as the electrophile. While alkyl bromides would work, the yield of the substitution reaction was poor, and alkyl chlorides did not alkylate under the conditions employed. Table 2 reports the results of varying the reaction time for alkylation and the number of equivalents of alkylating agent. The alkylation products and unreacted 1,3-cyclopentadienes were trapped as Diels-Alder adducts with *N*-phenylmaleimide. From this study, the proportion of substituted adduct was increased to 93%, as measured from the NMR spectra of the crude adduct mixtures.

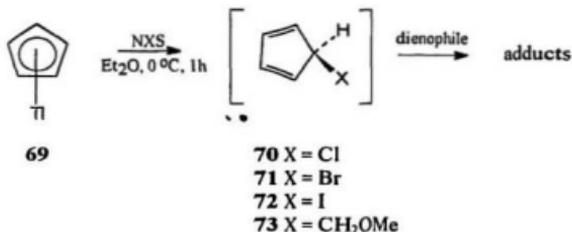
Table 2. Variation in the conditions of the alkylation step shown in Scheme 15

conditions	substituted : unsubstituted	total yield of adducts
30 min @ 1.5 eq. EtI	1.1 : 1	88%
60 min @ 1.5 eq. EtI	2.2 : 1	85%
120 min @ 2.3 eq. EtI	6.2 : 1	90%
180 min @ 1.5 eq. EtI	6.9 : 1	92%
30 min @ 7.5 eq. EtI	22 : 1	93%
60 min @ 5.0 eq. EtI	24 : 1	93%

5-Halogen-substituted cyclopentadienes and methoxymethyl-substituted cyclopentadienes

We also wanted to investigate the effect of an allylic heteroatom substituent on π -facial selectivity. It had been demonstrated that 5-halo-1,3-cyclopentadienes bearing an allylic heteroatom substituent, or a methoxymethyl substituent, could be efficiently synthesized through the reaction of cyclopentadienylthallium **69** with an *N*-halosuccinimide, or bromomethylmethyl ether.^{52,13} The inherent lability of these halogenated dienes is considerably lower than that of their alkyl-substituted counterparts. Breslow²⁴ reported that with a chlorine substituent (**70**), the time required for the "diene to equilibrate" with its regioisomers was two hours at 75°C. However, when the substituent was bromine (**71**) the time required for equilibration was found to be two hours at 100°C, whereas with iodine (**72**), six hours at 100°C were required to reach equilibrium. No equilibration studies have been reported for the methoxymethyl compound. We suspect that the increased stability associated with larger heteroatoms is in part due to the eclipsing interaction that the molecule would have to endure if the heteroatom were forced into either the 1 or 2 position.

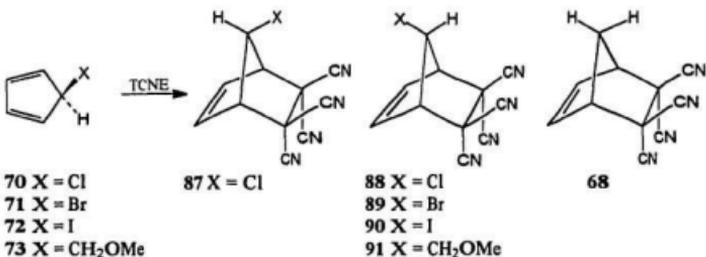
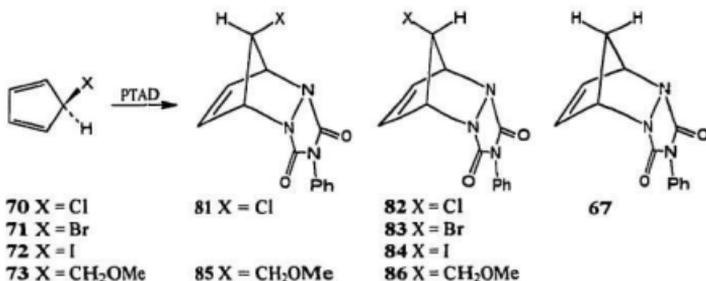
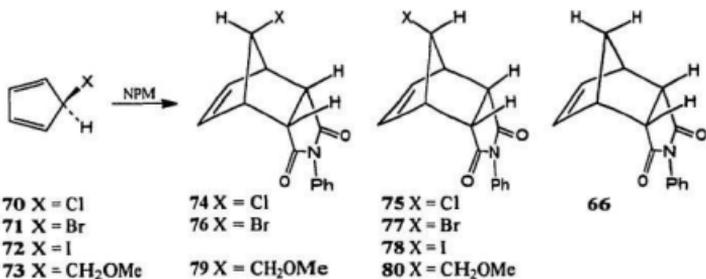
We used **69** to generate the 5-halo-1,3-cyclopentadienes or 5-methoxymethyl-1,3-cyclopentadienes **70 - 73** (Scheme 17). These were subsequently allowed to react *in situ* with a variety of dienophiles to give the Diels-Alder adducts **74 - 91** (Scheme 18).



Scheme 17. Synthesis of 5-halo-1,3-cyclopentadienes and 5-methoxymethyl 1,3-cyclopentadiene

Each adduct was again proven to be the kinetic product. Syn to anti ratios, isolation and characterisation of these adducts were performed by the same methods as described earlier. In some cases, NOE experiments were inconclusive and X-ray crystallography was used to assign unequivocally the stereochemistry of the product. For example, the Diels-Alder reaction of 5-iodo-1,3-cyclopentadiene and tetracyanoethylene (TCNE) afforded exclusively the anti diastereomer **90**, which could not be assigned by NOE. The X-ray crystal structure is shown in Figure 13.

We also attempted to synthesize various other 1,3-cyclopentadiene derivatives. These are summarized in Scheme 19. Generating a methyl ketone functionality in the 5-position of 1,3-cyclopentadiene (**92**) was unsuccessful by the reaction of lithium



Scheme 18. Diels-Alder products generated from halo and methoxymethyl substituted dienes

NPM = *N*-phenylmaleimide, PTAD = 4-phenyl-1,2,4-triazoline-3,5-dione, TCNE = tetracyanoethylene

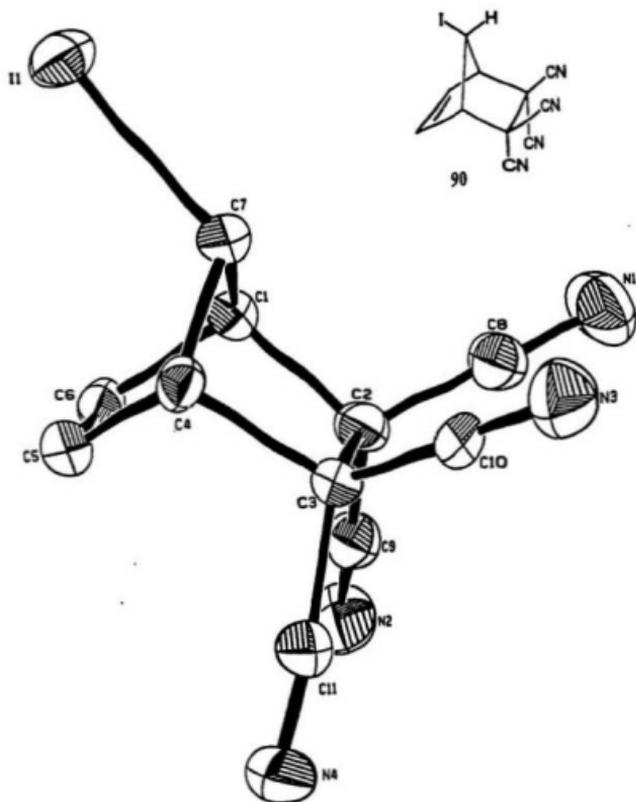


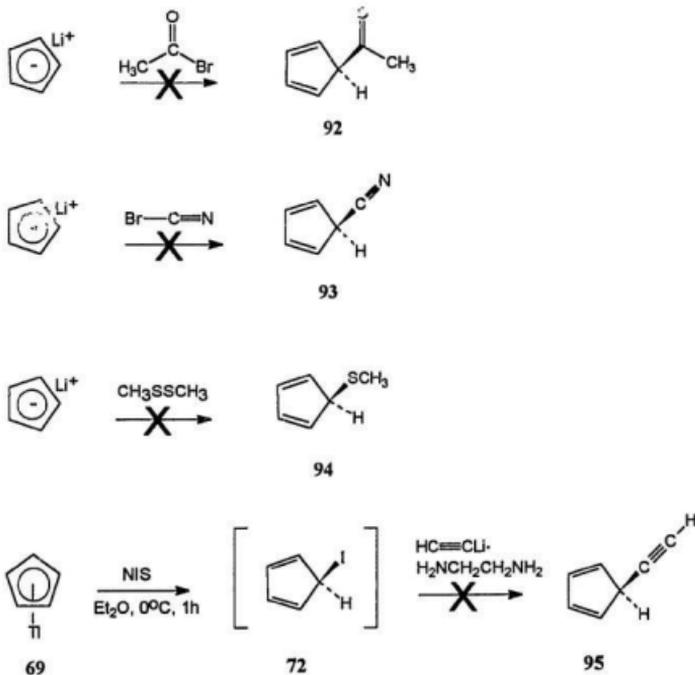
Figure 13. X-Ray structure of 90

cyclopentadienide with acetyl bromide. Cyanogen bromide did not exhibit any desired reactivity towards the cyclopentadienide anion in attempts to generate 5-cyano-1,3-cyclopentadiene **93**, instead an adduct of diene **71** was obtained. Reaction of dimethyl disulphide with the anion of cyclopentadiene also failed to generate any of the desired thiomethyl compound **94**. Attempts to place an acetylene group in the allylic position of 1,3-cyclopentadiene also were unsuccessful. This was attempted by displacement of the iodine in **95** with lithium acetylide ethylene diamine complex.

Adduct Ratios

Many dienophiles proved to be too unreactive towards the 5-substituted dienes under the cold conditions that were necessary to prevent isomerization of the diene. The dienophiles that were not useful were: dimethyl acetylenedicarboxylate, methyl acrylate, dimethyl fumarate, dimethyl maleate, *p*-benzoquinone and 1,4-naphthoquinone. Fortunately, three structurally different dienophiles did have reasonable reactivity under the cold conditions. These were the ethylene-based dienophile *N*-phenylmaleimide, the heteroatom-based dienophile 4-phenyl-1,2,4-triazoline-3,5-dione and the highly reactive, but more sterically demanding dienophile, tetracyanoethylene. The ratio of the syn to anti diastereomers was determined by careful integration of the NMR spectrum of the crude adduct mixture. The reactions of the synthesized dienes **46**, **49**, **50** and **70 - 73** with the previously mentioned dienophiles allowed us to generate the facial selectivities presented in Table 3.

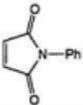
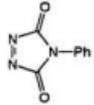
Williamson^{21,22} suggested, on the premise of his hypothesis regarding facial selectivity, that selectivity in the Diels-Alder reaction would be enhanced in the presence of a Lewis acid. We chose to investigate the effect of a Lewis acid catalyst on facial selectivity with dienes **46**, **70** and **71**. This was undertaken simply by the addition of a catalytic amount



Scheme 19. Unsuccessful attempts at generating 5-substituted-1,3-cyclopentadienes

(0.3 molar equivalents) of SnCl_4 to the dienophile before introducing the solution of the diene. The results of this investigation are also shown in Table 3. It was concluded that the catalyst had a negligible effect on the diastereofacial outcome of the reaction.

Table 3. Syn : anti facial selectivity for 5-substituted-1,3-cyclopentadienes with *N*-phenylmaleimide, 4-phenyl-1,2,4-triazoline-3,5-dione and tetracyanoethylene
 Bracketed ratios indicate reactions in the presence of SnCl₄

			
	3.7 : 1 (4.3 : 1)	1 : 1.4	1 : 2.2
	1 : 5.5 (1 : 5.9)	100% anti	100% anti
	100% anti	100% anti	100% anti
	1 : 1.5 (1 : 1.7)	3.8 : 1	100% anti
	1 : 2.2	2.3 : 1	100% anti
	1 : 2.8	1.9 : 1	100% anti
	5.2 : 1	5.1 : 1	100% anti

Discussion

A major problem with the facial selectivities reported in the literature on substituted 1,3-cyclopentadienes is centered around the fact that these results have been derived from isolated studies on single dienes using different dienophiles. Furthermore, there has only been a very limited number of substituted dienes studied. Thus, it has been very difficult to rely on these data as a basis of formulating any hypothesis for the mechanism of facial selectivity in the Diels-Alder reaction.

Table 3 is the most complete series of facial selectivities with substituted 1,3-cyclopentadienes in existence. We have demonstrated the effect, using different dienophiles, of increasing the size of an alkyl or halo group. The results clearly show that both the dienophile and the allylic substituent on the diene have pronounced effects on the diastereofacial outcome of the reaction.

Inagaki²⁷ recently proposed that the reactivity of the dienophile is directly proportional to the selectivity of the Diels-Alder cycloaddition (Table 1). Our results demonstrate that such a simplistic model cannot be a significant factor in determining facial selectivity: addition of 5-chloro-1,3-cyclopentadiene to NPM, PTAD, and TCNE resulted in syn : anti ratios of 3.7 : 1, 1 : 1.4, and 1 : 2.2, respectively. This clearly shows a decrease and a reversal of the facial selectivity with an increase in the reactivity of the dienophile. Other contradictions to this hypothesis are also prevalent in our investigations on additions with the alkyl-substituted 1,3-cyclopentadienes.

Other groups have linked facial selectivity to stereoelectronic effects in the diene. Such phenomena have been used to explain the preference for syn attack towards O, F and N, however they cannot be extended in a straightforward manner to explain facial selectivity towards larger groups. We postulate that this syn-driving phenomenon for atoms like O, F and N can be extended to include many other atoms, but for steric reasons many of the larger substituents give the anti product. Referring to Table 3, a slight preference for syn-addition to chlorine is observed with NPM. However, bromine, due to its increased size, affords more of the anti product, and iodine gives exclusively the anti diastereomer. This suggests that electronic factors may not play as large a role in influencing facial selectivity as has been previously claimed. Indeed, Halterman's⁴⁴ studies showed that a fairly large difference in the electronic nature of the allylic substituent resulted in only a very modest degree of facial selectivity in the Diels-Alder reaction (Scheme 12).

To investigate the presence of any correlation between facial selectivity and the electronic or steric properties of the allylic substituent, the difference in the Gibbs free energy for the syn : anti ratios in Table 3 was plotted against various electronic and physical properties of the substituent on the diene. Molar refractivities,⁵³ n -values and A -values⁵⁴ are included since they have been widely used for the estimation of the spatial requirements of various substituents. A list of van der Waals' radii⁵⁵ for the substituents under consideration also provides data of the effective "size" of the group, whereas the electronegativity⁵⁶ estimates an electronic property. Table 4 compares these values for cycloadditions with NPM. The molar refractivities of ethyl, *n*-butyl and methoxymethyl groups do not reflect conformational effects that would likely render the methyl and ethyl rather similar in

Table 4. Plotted data for additions to NPM

Atom or group	Ratio with NPM (syn : anti)	$\Delta\Delta G^\ddagger$ Anti = "+" Syn = "-" (kcal/mol)	MR* (cm ³ /mol)	Pauling's Electronegativity	n-value (kcal/mol)	A-value (kcal/mol)	van der Waal's radii (Å)
Cl	79 : 21	-0.73	5.8	3.03	8.1	0.43	1.75
Br	15 : 85	0.96	8.7	2.8	9.2	0.38	1.85
I	100% anti	3.8**	14	2.28	9.9	0.43	1.98
Me	40 : 60	0.22	5.7	2.3	8.5	1.7	2
Et	31 : 69	0.44	10.3	2.3	----	1.75	----
<i>n</i> -Bu	26 : 74	0.58	19.6	----	----	----	----
CH ₂ OCH ₃	84 : 16	-0.91	12.1	----	----	----	----

* MR = molar refractivity, **based on a 0.1 : 99.9 ratio

effective size. This conformational effect is seen in the practical identity of the methyl and ethyl A-values, but the A-values show no difference in "size" for the halogens due to the A-value being effected by the C-X bond length. Thus we have not plotted the data for ethyl, *n*-butyl and methoxymethyl substituents in Figures 14-17.

A plot of molar refractivity as well as the electronegativity as a function of the difference in the Gibbs free energy for the syn : anti ratios revealed a fairly linear relationship for the halogen substituents and the methyl group (Figures 14 and 16). However, a linear correlation was not observed when the electronegativity and van der Waals' radii were plotted versus the difference in Gibbs free energy for the reaction (Figures 15 and 17). (The A-values showed no correlation with the Gibbs free energy.)

These results readily suggest an hypothesis that, with a simple carbon based dienophile, a steric effect appears to be more important than an electronic one on governing

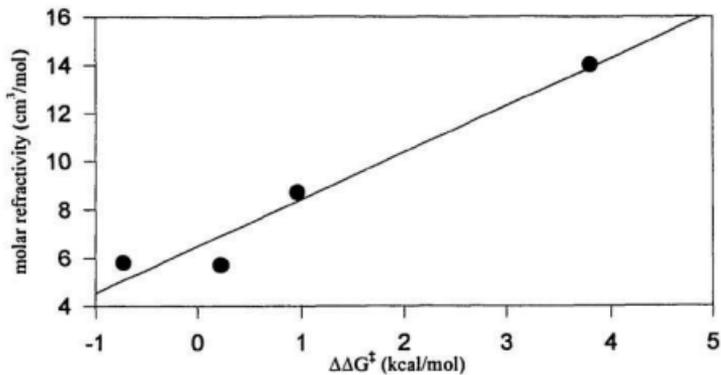


Figure 14. Plot of molar refractivities as a function of $\Delta\Delta G^\ddagger$ for syn : anti ratios with NPM

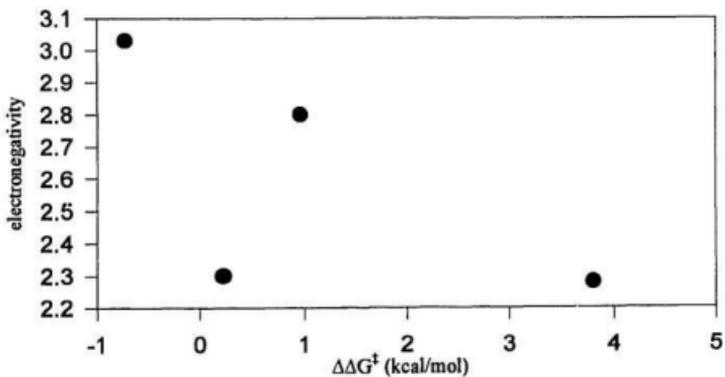


Figure 15. Plot of Pauling's electronegativities as a function of $\Delta\Delta G^\ddagger$ for syn : anti ratios with NPM

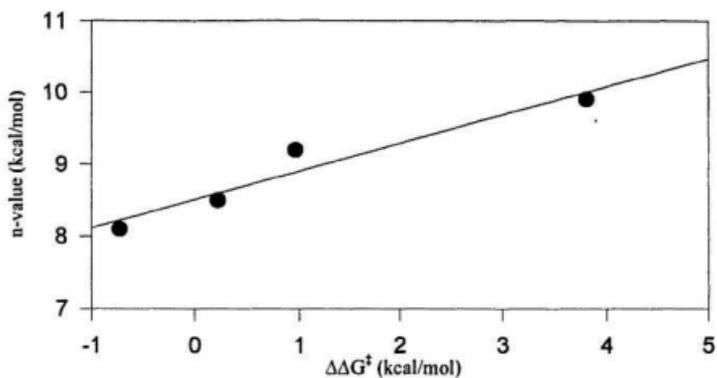


Figure 16. Plot of n -values as a function of $\Delta\Delta G^\ddagger$ for syn : anti ratios with NPM

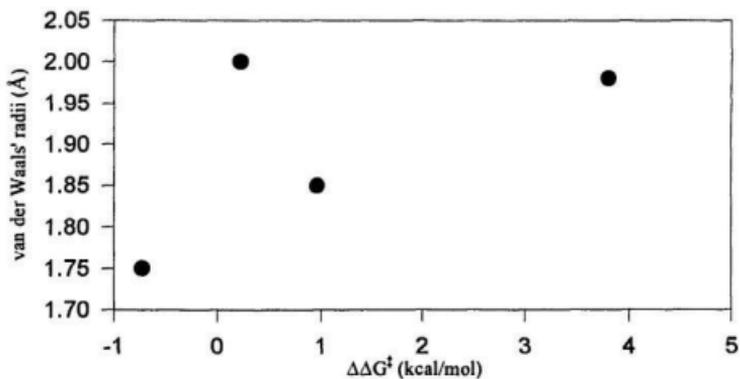


Figure 17. Plot of van der Waals' radii as a function of $\Delta\Delta G^\ddagger$ for syn : anti ratios with NPM

facial selectivity. Nevertheless, the steric factor is not a straightforward analogy to the axial - equatorial relationships in cyclohexanes (A-values) or on simple "size", because of the lack of correlation with van der Waals' radii. The importance of steric interactions is in agreement with the observation of Breslow²¹ that 70, 71, and 72 react with *N*-phenylmaleimide more slowly than does 1,3-cyclopentadiene itself.

The results obtained with PTAD and TCNE (Tables 5 and 6). showed no correlation between the properties of the allylic substituent and the difference in the Gibbs free energy for the *syn* : *anti* ratios of the resulting cycloadditions. This may be due to an added complexity with these dienes. PTAD bears lone pairs on the reacting moiety of the dienophile which might complicate the mechanism by an added electrostatic parameter, and TCNE imposes an overwhelming steric interaction as it comes in contact with a diene due to the larger size of the cyano groups compared to hydrogens.

A detailed investigation into the mechanistic pathway of the Diels-Alder reaction is underway through a comprehensive *ab initio* computational study being performed in our group by James Xidos in collaboration with Cory Pye and Dr. Ray Poirier.³¹ Many of the dienes in both the ground state and their *syn* and *anti* transition states (with ethylene as the dienophile) have been fully optimized with the 6-31G* basis set using gradient optimization methods. In spite of the rather simple model for the dienophile, the calculated facial selectivities are similar to the experimental data in Table 3, particularly for the carbon-based dienophile *N*-phenylmaleimide. In order to identify the factors responsible for facial selectivity, the amount of energy required to deform the diene and the dienophile from the ground state to their *syn* and *anti* transition state geometries was calculated. The total

Table 5. Plotted data for additions to PTAD

Atom or group	Ratio with PTAD (syn : anti)	$\Delta\Delta G^\ddagger$ Anti = "+" Syn = "-" (kcal/mol)	MR* (cm ³ /mol)	Pauling's Electro-negativity	n-value (kcal/mol)	A-value (kcal/mol)	van der Waal's radii (Å)
Cl	42 : 58	0.18	5.8	3.03	8.1	0.43	1.75
Br	100% anti	3.8**	8.7	2.8	9.2	0.38	1.85
I	100% anti	3.8**	14	2.28	9.9	0.43	1.98
Me	79 : 21	-0.73	5.7	2.3	8.5	1.7	2
Et	70 : 30	-0.47	10.3	2.3	----	1.75	----
<i>n</i> -Bu	66 : 34	-0.37	19.6	----	----	----	----
CH ₂ OMe	84 : 16	-0.91	12.1	----	----	----	----

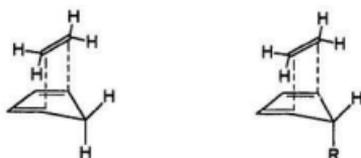
*MR = molar refractivity, ** based on a 0.1 : 99.9 ratio

Table 6. Plotted data for additions to TCNE

Atom or group	Ratio with TCNE (syn : anti)	$\Delta\Delta G^\ddagger$ Anti = "+" Syn = "-" (kcal/mol)	MR* (cm ³ /mol)	Pauling's Electro-negativity	n-value (kcal/mol)	A-value (kcal/mol)	van der Waal's radii (Å)
Cl	31 : 69	-0.73	5.8	3.03	8.1	0.43	1.75
Br	100% anti	3.8	8.7	2.8	9.2	0.38	1.85
I	100% anti	3.8	14	2.28	9.9	0.43	1.98
Me	100% anti	3.8	5.7	2.3	8.5	1.7	2
Et	100% anti	3.8	10.3	2.3	----	1.75	----
<i>n</i> -Bu	100% anti	3.8	19.6	----	----	----	----
CH ₂ OMe	100% anti	3.8	12.1	----	----	----	----

*MR = molar refractivity, ** based on a 0.1 : 99.9 ratio

activation energy for each reaction was then compared with the deformation energies of the diene and the dienophile. The dienophile underwent very little deformation at the transition state and consequently displayed only a small range of activation energies. However, the calculated deformation energies for the diene were in a range of 8.9 kJ/mol for the anti transition states. These values were in fact clustered around the activation energy for cyclopentadiene itself (Figure 18). Thus, addition towards the anti-face of an allylic-substituted cyclopentadiene is not that much different energetically than an addition to 1,3-cyclopentadiene (Scheme 20).



Scheme 20. Transition states for 1,3-cyclopentadiene and the anti transition state for a 5-substituted 1,3-cyclopentadiene.

The dienophile and the diene experience essentially the same environment in each case, and the anti substituent that is pointing away on the opposite side of the diene exerts little influence on the reaction. The range of activation energies for the syn transition state was significantly larger, exhibiting a range of 57.9 kJ/mol calculated for various allylic substituents (Figure 19). Furthermore, the diene deformation energies correlated very well with the computed activation energies. This reveals that it must largely be the deformation of the diene that accounts for the range of activation energies observed for the diene bearing

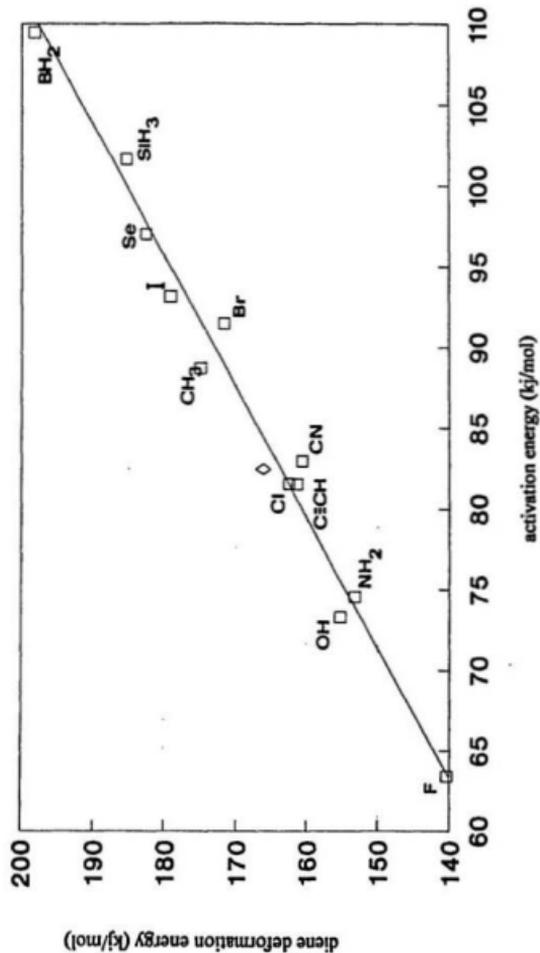


Figure 19. Diene deformation energies as a function of activation energy for syn transition states
 □syn, ◇ cyclopentadiene (1 cal = 4.184 J)

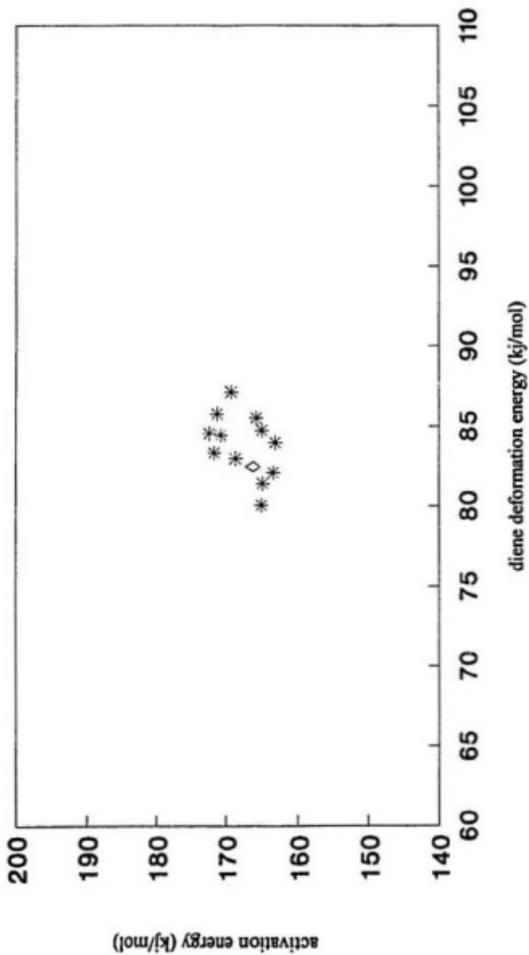


Figure 18. Diene deformation energies as a function of activation energy for anti transition states
 * anti, ◇ cyclopentadiene (1 cal = 4.184 J)

different substituents. Thus, it appears that direct interactions such as steric effects between the addends have already translated largely into deformation of the diene at the transition state.

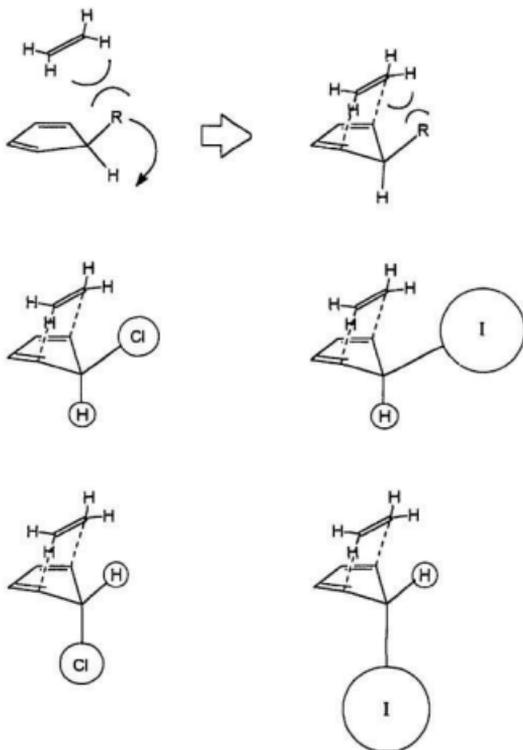
A closer look at the diene in its calculated *syn* transition state reveals that the diene adopts a geometry in which the *syn* substituent lies close to the plane of the diene moiety and the bond of the C-5 substituent that is *anti* is almost perpendicular to that plane. The *anti* bond is lengthened and the *syn* bond is shortened. The fact that diene deformation energies for *syn* additions to F, NH₂ and OH are significantly lower than that for 1,3-cyclopentadiene itself indicates that these dienes, deformed into their transition state geometries, are stabilized by these substituents. The mechanism of this stabilization is not clear. While it may be tempting to propose that stabilization could arise from interaction with the coplanar *syn* substituent, in every case that was studied there was an insignificant difference in hybridization of the allylic group in the *syn* and *anti* transition state. Furthermore, bond orders between the allylic substituent and C-1 or C-4 of the diene were found to be negligible. It has been speculated that *syn* stabilization may be effected by the fact it should be generally easier to compress the *syn* C-X bond over the *anti* C-H bond. However, any such stabilization is offset as the substituent atom becomes larger. More energy is associated with the *syn* transition state due to the large amount of deformation which the diene must endure to adopt the required transition state geometry. For example, when the substituent is SiH₃ there is a very large (30.9°) angular change about the C-2 - C-1 - C-5 bond angles for the *syn* transition state and hence *syn*-addition would be disfavoured.

For the favoured anti transition state the C-2 - C-1 - C-5 bond angles are only distorted by 4.5°.

We compared the computational results with the experimental data from Table 3. The experimental results of cycloadditions with NPM show a slight preference for syn-addition to chlorine whereas additions towards bromine and iodine afford the anti adduct. A slight preference for anti-addition is observed towards methyl which becomes more pronounced as the length of the alkyl chain is increased.

From our studies, we now offer the following hypothesis for the mechanism of facial selectivity in the Diels-Alder reaction: A *syn*-driving phenomenon, so far unknown in nature, predisposes the diene towards *syn*-addition, but then steric interactions between the diene and the dienophile induce bending in the diene, which translates into torsional energy mainly in the diene (Scheme 21). With smaller substituents such as chlorine there is not a large amount of steric repulsion between the diene and the dienophile and hence less deformation of the diene results. The *syn* product is therefore observed. However, if the diene is substituted with a larger group, greater steric interactions between the diene and the dienophile result. This translates into more deformation of the diene and addition anti to larger groups is therefore favoured.

The results for cycloadditions with NPM agree quite well with the computational predictions for facial selectivity calculated using ethylene as the dienophile. This may be because these two dienophiles closely resemble each other with respect to their reacting moieties. Since the simple dienophile that was used computationally is dissimilar to the structures of PTAD and TCNE, the computational predictions cannot be directly used to



Scheme 21. Syn and anti transition states for 1,3-cyclopentadienes substituted with a small and a large allylic substituent

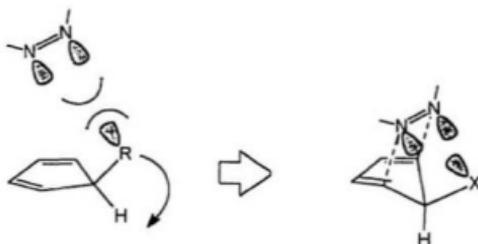
explain the facial selectivities obtained using these dienophiles.

The Diels-Alder additions with PTAD resulted in preferred addition anti to chlorine which increased to exclusively anti-addition with bromo- and iodo-substituted 1,3-cyclopentadienes. Furthermore, in marked contrast to the earlier results with NPM, a propensity for syn-addition was observed towards all alkyl groups which decreased in magnitude as the size of the alkyl chain increased.

The preferred addition anti to heteroatoms can be rationalized on the basis of closed-shell lone-pair lone-pair electrostatic repulsions between the nitrogens on the dienophile and the allylic heteroatom substituent (Scheme 22). This repulsion may result in a significant amount of deformation on the part of the diene in the syn transition state and as a result anti-addition could be expected. However, since the diene bears no substituent on the double bond it should exhibit a smaller steric interaction upon initial contact with an alkyl-substituted diene. This in turn will impart a significantly smaller amount of deformation in the syn transition state than did NPM, and therefore a preference for syn-addition occurs.

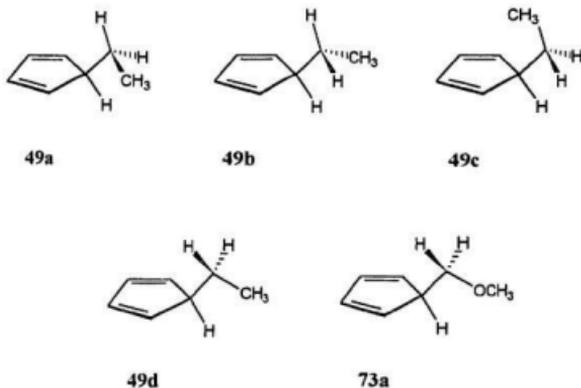
Anti-addition is almost exclusively favoured with TCNE. Cycloadditions with this dienophile should experience a significant amount of steric repulsions upon initial contact between the two addends. This is because in contrast to NPM and PTAD, TCNE bears larger cyano groups. As the reacting partners come together, larger steric repulsions between TCNE and the C-5 substituent of the diene force such a large amount of deformation in the diene that the anti pathway is always more favourable.

The addition syn to the methoxymethyl group with NPM has not yet been discussed. It is expected that the conformation of the substituent may be playing a prominent role in



Scheme 22. Disfavored syn transition state for additions of PTAD to 5-hetero-substituted 1,3-cyclopentadienes

determining facial selectivity for this diene. Burnell and Valenta^{15,16} illustrated the importance of this effect in studies on Diels-Alder additions towards bridged-ring cyclopentadienes wherein it was observed that a hydrogen pointing directly at the dienophile imparted a larger steric influence than two hydrogens staggered away from the incoming dienophile (Scheme 7, entries 3 and 4). On the basis of this we expect that the conformer of the allylic alkyl group may be significant. Therefore, for additions of 5-ethyl-1,3-cyclopentadiene to NPM (syn : anti 1 : 2.8) we expect the likely reacting conformers are 49a, 49b, or 49c but not 49d (Scheme 23). Extending this to the methoxymethyl group, we suggest that, in contrast to the likely reacting conformers for 49, the preferred reacting conformer for the methoxymethyl analogue must be 73a. Detailed computational investigations examining the effect of the conformation of the allylic substituent on facial selectivity are in progress. Preliminary results indicate that this phenomenon may influence facial selectivity significantly. The results described in this thesis demonstrate that there is



Scheme 23. Likely reacting conformers for 5-ethyl-1,3-cyclopentadiene and 5-methoxymethyl-1,3-cyclopentadiene.

also a need for the computational study to be expanded to include structurally different dienophiles. Work in this area is now being undertaken.

Many groups have postulated different mechanisms to account for facial selectivity in Diels-Alder reactions. Phenomena that have been implicated and covered in the introduction of this thesis are: a favourable admixture of the C-5 substituents' lone pair with the LUMO of the syn-adding dienophile, energetically different interactions of a dienophile with a π -system that is facially biased in terms of either electron density or nucleophilicity by a C-5 substituent, dienophile interactions with tilted p-components of the π -orbitals of a plane-nonsymmetric diene, and facially different dipole-dipole or electrostatic interactions.

Such phenomena should be evident at the transition state if they play a significant role in determining facial selectivity. However no evidence of such interactions has been found at the transition state. Furthermore, Fallis' proposal that facial selectivity is controlled by σ -donation from the anti-face can be discounted since this mechanism would predict a large range of activation energies for anti-addition.

In summary, π -facial selectivity for simple plane-nonsymmetric 1,3-cyclopentadiene derivatives is almost entirely the result of the difference in the energetics of distorting the addends, principally the diene. Computational studies into the effect of structurally different dienophiles and the conformation of the allylic substituent on the diene are ongoing.

Experimental

General:

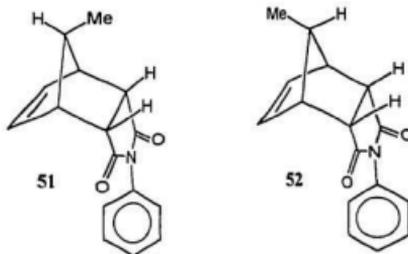
Reactions requiring nonaqueous conditions were performed in high temperature-dried glassware under a positive pressure of nitrogen. All solvents were purified by distillation. Tetrahydrofuran was distilled from sodium metal/benzophenone. Cyclopentadiene was fractionally distilled from dicyclopentadiene and dried over $MgSO_4$ just prior to use. Cyclopentadienylthallium was purified by sublimation of commercial material. All other reagents were used without purification. Reactions were monitored by thin layer chromatography using Baker-Flex silica gel plates which were visualized by UV fluorescence, or by spraying with a solution of phosphomolybdic acid, ceric sulphate and sulphuric acid followed by heating. Flash chromatography was performed on Merck type 60 silica gel, 230 - 400 mesh. Melting points were performed on a Fisher - Johns apparatus and are uncorrected. Infrared spectra were recorded on a Mattson Polaris FT instrument. Nuclear magnetic resonance spectra were obtained on a 300 MHz General Electric 300-NB instrument. The 1H NMR shifts were measured relative to tetramethylsilane internal standard. The ^{13}C NMR shifts were calibrated to the solvent resonance signal. The relative stereochemistry of products was determined from NOE data obtained from a set of interleaved 1H experiments (16K) of 8 transients cycled 16 to 32 times through the list of irradiated frequencies. The decoupler was gated on continuous-wave mode for 6 seconds with sufficient attenuation to give a 70-90% reduction in intensity of the irradiated signal. Frequency changes were preceded by a 60 second delay. Four scans were used to equilibrate spins before data acquisition but a relaxation was not applied between scans of

the same frequency. The NOE difference spectra were obtained by zero-filled 32K data tables to which a 1-2 Hz exponential line broadening was applied. The NOE results are reported in the following format: δ saturated signal: enhanced signal (% enhancement). Mass spectral data were obtained from a V.G. Micromass 7070 HS instrument. Gas chromatography - mass spectra data were acquired on a Hewlett-Packard system (model 5890 gas chromatograph equipped with a 12.5 m or 25 m fused silica capillary column with cross-linked dimethylsilicone coupled to a Hewlett-Packard model 5980 mass selective detector). X-ray crystallographic data was collected by using a Rigaku AFC6S diffractometer by Dr. J. N. Bridson. Elemental analyses was performed by Canadian Microanalytical Service Ltd., Vancouver, B.C.

Regarding Diels-Alder Reactions:

No diene was isolated because of the well-known tendency of 5-substituted 1,3-cyclopentadienes to undergo 1,5-sigmatropic rearrangement.⁴⁷ To the cold solution of a crude, freshly prepared diene was added a solution of the dienophile. After 12 - 14 hours the reaction mixture was washed, dried and concentrated under vacuo. The mass of the residue was always very similar to the sum of the expected mass of the diene and the dienophile. The adduct ratios were determined by careful integration of the NMR spectrum of the crude adduct mixture. In some instances, the adducts were the major component in the crude mixture, whereas in others there appeared to be considerable amounts of products of decomposition of the diene along with unreacted dienophile. Not all reactions were repeated, but in the instances that were carried out many times, e.g. the reactions of 49 and

70 with *N*-phenylmaleimide, the adduct ratios proved to be very similar. In many instances the assignment of the relative stereochemistry was carried out on adducts isolated by careful chromatography and crystallization. The emphasis was on obtaining homogeneous materials, so the isolated "yields" quoted below reflect not only the extent of adduct formation but also the ease of purification.



(3 α ,4 α ,7 α ,7 α ,8 r)-8-Methyl-3a,4,7,7a-tetrahydro-2-phenyl-4,7-methano-1H-isoindole-1,3-(2H)-dione (51)
and

(3 α ,4 α ,7 α ,7 α ,8 s)-8-Methyl-3a,4,7,7a-tetrahydro-2-phenyl-4,7-methano-1H-isoindole-1,3-(2H)-dione (52)

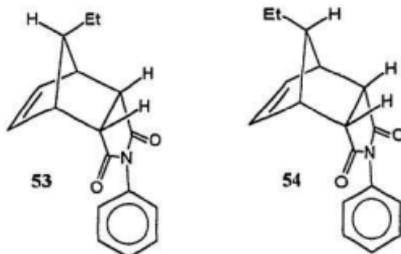
A solution of 1,3-cyclopentadiene (0.40 mL, 5.0 mmol) in THF (15 mL) under a nitrogen atmosphere was treated with *tert*-butyllithium (2.20 mL, 5.47 mmol) at 0°C and stirred for 10 min. The resulting cloudy solution was added dropwise over 20 min to a -20°C solution of iodomethane (1.54 mL, 24.9 mmol) in THF (10 mL) under nitrogen. The reaction mixture was stirred for an additional 1 h, transferred to a separatory funnel and quickly washed with cold brine (2 x 10 mL). *N*-Phenylmaleimide (0.861 g, 4.97 mmol) was added to the organic layer and the resulting solution was stirred at -20°C for 3 h, washed with water (2 x 10 mL) and dried over anhydrous MgSO₄. Rotary evaporation of the solvent furnished a pale yellow solid. ¹H NMR analysis indicated a 1.5 : 1 ratio for **52** to **51**. Flash chromatography afforded adducts **52** (0.288 g, 23%) and **51** (0.143 g, 11%) as

colorless solids, which were recrystallized from 5% dichloromethane / pentane to give materials homogeneous by NMR.

For **52**: mp 133 - 134.5 °C; ν_{max} : 2993, 2952, 1713, 1499, 1375, 1182 cm^{-1} ; ^1H NMR (CDCl_3) δ : 7.47-7.34 (3H, m, C-3'H, C-4'H, C-5'H), 7.15 (2H, br d, $J = 7.0$ Hz, C-2'H, C-6'H), 6.30 (2H, apparent t, $J = 2.0$ Hz, C-5H, C-6H), 3.48 (2H, dd, $J = 1.6, 2.9$ Hz, C-3aH, C-7aH), 3.18 (2H, m, C-4H, C-7H), 2.22 (1H, q, $J = 6.8$ Hz, C-8H), 0.94 (3H, d, $J = 6.8$ Hz, C-8Me); NOE results δ : 6.30: 3.18 (4%), 2.22 (1.2%), 3.48: 3.18 (6%), 0.94 (3%), 3.18: 6.30 (5%), 3.48 (4%), 2.22 (8%), 0.94 (0.8%), 2.22: 6.30 (0.7%), 3.18 (2%), 2.22 (5%); ^{13}C NMR (CDCl_3) δ : 177.4 (C-1, C-3), 136.3 (C-5, C-6), 131.9 (C-1'), 129.1 (C-3', C-5'), 128.5 (C-4'), 126.6 (C-2', C-6'), 59.1 (C-8), 49.3 (C-4, C-7), 44.0 (C-3a, C-7a), 13.7 (CH_3); ms m/z (%): 253 (M^+ , 21), 239, (1), 173 (31), 145 (2), 129 (6), 106 (8), 91 (2), 80 (100), 65 (6), 51 (5). Exact mass calcd. for $\text{C}_{18}\text{H}_{15}\text{NO}_2$: 253.1102, found: 253.1108.

For **51**: mp 129 - 130 °C; ν_{max} : 2991, 2907, 1713, 1497, 1380, 1176 cm^{-1} ; ^1H NMR (CDCl_3) δ : 7.45-7.33 (3H, m, C-3'H, C-4'H, C-5'H), 7.14 (2H, br d, $J = 7.0$ Hz, C-2'H, C-6'H), 6.13 (2H, apparent t, $J = 1.9$ Hz, C-5H, C-6H), 3.42 (2H, dd, $J = 1.4, 2.9$ Hz, C-3aH, C-7aH), 3.23 (2H, m, C-4H, C-7H), 2.22 (1H, q, $J = 6.3$ Hz, C-8H), 0.91 (3H, d, $J = 6.3$ Hz, C-8Me); NOE results: 6.13: 3.23 (2%), 0.91 (0.3%), 3.42: 3.23 (3%), 2.22 (7%), 3.23: 6.13 (3%), 3.42 (2%), 2.22 (4%), 0.91 (1.1%), 2.22: 3.42 (4%), 3.23 (2%), 0.91 (1.2%), 0.91: 6.13 (1.1%), 3.23 (3%), 2.22 (5%); ^{13}C NMR (CDCl_3) δ : 176.6 (C-1, C-3), 134.7 (C-1'), 131.7 (C-5, C-6), 128.9 (C-3', C-5'), 128.4 (C-4'), 126.5 (C-2', C-6'), 58.5 (C-8), 50.5 (C-4, C-7), 46.0 (C-3a, C-7a), 11.6 (CH_3); ms m/z (%): 253 (M^+ , 20), 239 (1),

173 (27), 145 (2), 129 (6), 106 (8), 91 (18), 80 (100), 65 (6), 51 (5). Exact mass calcd. for $C_{16}H_{17}NO_2$: 253.1102, found: 253.1110.



(3 α ,4 α ,7 α ,7 α ,8s)-8-Ethyl-3 α ,4,7,7 α -tetrahydro-2-phenyl-4,7-methano-1H-isoindole-1,3-(2H)-dione (53)
and

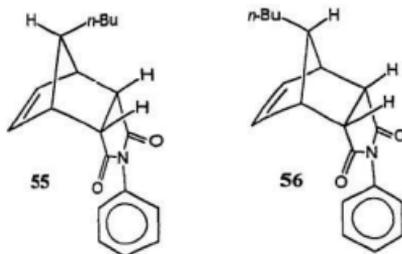
(3 α ,4 α ,7 α ,7 α ,8r)-8-Ethyl-3 α ,4,7,7 α -tetrahydro-2-phenyl-4,7-methano-1H-isoindole-1,3-(2H)-dione (54)

A solution of 1,3-cyclopentadiene (0.40 mL, 5.0 mmol) in THF (15 mL) under a nitrogen atmosphere was treated with *n*-butyllithium (2.20 mL, 5.47 mmol) at 0°C. The resulting cloudy solution was added dropwise over 20 min to a -20°C solution of iodoethane (0.60 mL, 7.46 mmol) in THF (10 mL) under nitrogen. The reaction mixture was stirred for an additional 10 min, transferred to a separatory funnel and quickly washed with cold brine (2 x 10 mL). *N*-Phenylmaleimide (0.861 g, 4.97 mmol) was added to the organic layer and the resulting solution was stirred at -20°C for 2 h, washed with water (2 x 10 mL) and dried over anhydrous $MgSO_4$. Rotary evaporation of the solvent afforded a yellow oil. 1H NMR analysis indicated a 1.8 : 1 ratio for 54 to 53. Flash chromatography afforded adducts 54 (0.298 g, 22%) and 53 (0.136 g, 10%) as colorless solids.

For **54**: mp 144 - 145 °C; ν_{max} : 2962, 1715, 1536, 1372, 1180 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ : 7.46 - 7.35 (3H, m, C-3'H, C-4'H, C-5'H), 7.13 (2H, br d, $J = 7.0$ Hz, C-2'H, C-6'H), 6.13 (2H, apparent t, $J = 1.7$ Hz, C-5'H, C-6'H), 3.42 (2H, dd, $J = 1.6, 3.0$ Hz, C-3aH, C-7aH), 3.34 (2H, m, C-4H, C-7H), 2.00 (1H, t, $J = 7.2$ Hz, C-8H), 1.34 (2H, apparent quintet, $J = 7.4$ Hz, C-8 Et), 0.83 (3H, t, $J = 7.5$ Hz, C-8 Et); NOE results δ : 6.13: 3.34 (2%), 1.34 (0.5%), 3.42: 6.13 (0.4%), 2.00 (7%), 3.34: 6.13 (3%), 2.00 (4%), 1.34 (1.0%), 0.83 (0.7%), 2.00: 3.42 (4%), 3.34 (2%), 1.34 (1.0%), 0.83 (0.9%), 1.34: 6.13 (1.0%), 3.34 (2%), 2.00 (2%), 0.83 (2%), 0.83: 6.13 (0.2%), 3.34 (2%), 2.00 (2%), 1.34 (2%); $^{13}\text{C NMR}$ (CDCl_3) δ : 176.7 (C-1, C-3), 134.1 (C-1'), 131.8 (C-5, C-6), 129.0 (C-3', C-5'), 128.5 (C-4'), 126.5 (C-2', C-6'), 66.4 (C-8), 48.6 (C-4, C-7), 45.9 (C-3aH, C-7aH), 19.1 (CH_2CH_3), 12.9 (CH_2CH_3); ms m/z (%): 267 (M^+ , 41), 252 (1), 173 (30), 119 (11), 94 (100), 79 (54), 65 (8), 51 (5). Exact mass calcd. for $\text{C}_{17}\text{H}_{17}\text{NO}_2$: 267.1258, found: 267.1253.

For **53**: mp 124.5 - 125 °C; ν_{max} : 2963, 1715, 1563, 1373, 1182 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ : 7.46 - 7.36 (3H, m, C-3'H, C-4'H, C-5'H), 7.15 (2H, br d, $J = 7.0$ Hz, C-2'H, C-6'H), 6.31 (2H, apparent t, $J = 1.9$ Hz, C-5'H, C-6'H), 3.42 (2H, dd, $J = 1.6, 2.7$ Hz, C-3aH, C-7aH), 3.28 (2H, m, C-4H, C-7H), 2.02 (1H, t, $J = 7.6$ Hz, C-8H), 1.26 (2H, apparent quintet, $J = 7.4$ Hz, C-8 Et), 0.91 (3H, t, $J = 7.4$ Hz, C-8 Et); NOE results δ : 6.31: 3.28 (3%), 2.02 (1.4%), 3.42: 3.28 (3%), 1.26 (5%), 3.28: 6.31 (4%), 3.42 (3%), 2.02 (6%), 1.26 (1.0%), 2.02: 6.31 (0.7%), 3.28 (3%), 2.02 (0.9%), 1.26: 3.42 (5%), 3.28 (1.2%), 2.02 (2%), 0.91 (1.2%), 0.91: 3.28 (2%), 2.02 (2%), 1.26 (1.4%); $^{13}\text{C NMR}$ (CDCl_3) δ : 177.3 (C-1, C-3), 136.1 (C-6, C-5), 131.9 (C-1'), 129.0 (C-3', C-5'), 128.5

(C-4'), 126.6 (C-2', C-6'), 66.9 (C-8), 47.4 (C-4, C-7), 44.1 (C-3aH, C-7aH), 21.2 (CH₂CH₃), 11.9 (CH₃CH₃); ms *m/z* (%): 267 (M⁺, 73), 252 (5), 213 (3), 173 (42), 119 (27), 94 (100), 79 (62), 65 (11), 51 (7). Exact mass calcd. for C₁₇H₁₇NO₂: 267.1258, found: 267.1256.



(3 α ,4 α ,7 α ,7 α ,8 r)-8-*n*-Butyl-3 a ,4,7,7 a -tetrahydro-2-phenyl-4,7-methano-1H-isindole-1,3-(2H)-dione (55)
and
(3 α ,4 α ,7 α ,7 α ,8 s)-8-*n*-Butyl-3 a ,4,7,7 a -tetrahydro-2-phenyl-4,7-methano-1H-isindole-1,3-(2H)-dione (56)

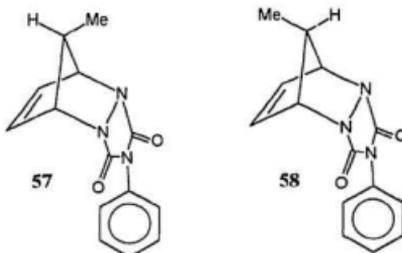
A solution of 1,3-cyclopentadiene (0.40 mL, 5.0 mmol) in THF (10 mL) under a nitrogen atmosphere was treated with *n*-butyllithium (2.20 mL, 5.47 mmol) at 0°C. The resulting cloudy solution was added dropwise over 15 min to a -20°C solution of 1-iodobutane (2.00 mL, 17.6 mmol) in THF (10 mL) under nitrogen. The reaction mixture was stirred for an additional 2 h, transferred to a separatory funnel and quickly washed with cold brine (2 x 10 mL). *N*-Phenylmaleimide (0.861 g, 4.97 mmol) was added to the organic layer and the resulting solution was stirred at -20°C overnight, then gradually warmed to rt. The resulting solution was washed with water (2 x 10 mL) and dried over anhydrous

MgSO₄. Rotary evaporation of the solvent afforded the product. ¹H NMR analysis indicated a 2.8 : 1 ratio for **56** to **55**. Flash chromatography afforded adducts **56** (0.356 g, 24%) and **55** (0.111 g, 8%) as colorless solids.

For **56**: mp 145 - 146 °C; ir ν_{max} : 2983, 2922, 2852, 1713, 1534, 1377, 1169 cm⁻¹; ¹H NMR (CDCl₃) δ : 7.45-7.35 (3H, m, C-3'H, C-4'H, C-5'H), 7.13 (2H, br d, J = 8.6 Hz, C-2'H, C-6'H), 6.13 (2H, apparent t, J = 1.7 Hz, C-5H, C-6H), 3.42 (2H, dd, J = 1.6, 2.9 Hz, C-3aH, C-7aH), 3.33 (2H, m, C-4H, C-7H), 2.07 (1H, t, J = 7.0 Hz, C-8H), 1.28 (6H, m, C-8 CH₂CH₂CH₂CH₃), 0.87 (3H, t, J = 7.1 Hz, C-8 CH₂CH₂CH₂CH₃); NOE results δ : 6.13: 3.33 (3%), 3.42: 2.07 (9%), 3.33: 6.13 (3%), 2.07 (4%), 1.28 (1.4%), 0.87 (2%), 2.07: 3.42 (5%), 3.33 (3%), 1.28 (1.2%), 0.87 (1.5%), 1.18: 6.13 (0.8%), 3.33 (2%), 2.07 (3%), 0.87 (2%); ¹³C NMR (CDCl₃) δ : 176.8 (C-1, C-3), 131.9 (C-5, C-6), 129.0 (C-3', C-5'), 128.5 (C-4'), 126.6 (C-2', C-6'), 64.7 (C-8), 48.9 (C-4, C-7), 45.9 (C-3a, C-7a), 30.0 (butyl), 25.8 (butyl), 22.7 (butyl), 14.0 (butyl); ms m/z (%): 295 (M⁺, 13), 239 (1), 173 (14), 122 (14), 119 (12), 91 (21), 80 (100), 65 (5). Exact mass calcd. for C₁₉H₂₁NO₂: 295.1571, found: 295.1565.

For **55**: mp 82 - 84 °C; ir ν_{max} : 2927, 2885, 1707, 1511, 1389, 1187 cm⁻¹; ¹H NMR (CDCl₃) δ : 7.45-7.36 (3H, m, C-3'H, C-4'H, C-5'H), 7.14 (2H, br d, J = 7.1 Hz, C-2'H, C-6'H), 6.31 (2H, apparent t, J = 2.0 Hz, C-5H, C-6H), 3.43 (2H, dd, J = 1.6, 2.8 Hz, C-3aH, C-7aH), 3.25 (2H, m, C-4H, C-7H), 2.07 (1H, t, J = 6.8 Hz, C-8H), 1.26 (6H, m, C-8 CH₂CH₂CH₂CH₃), 0.91 (3H, t, J = 6.9 Hz, C-8 CH₂CH₂CH₂CH₃); NOE results δ : 6.31: 3.25 (3%), 2.07 (1.0%), 3.43: 3.25 (4%), 1.26 (2%), 3.25: 6.31 (4%), 3.43 (2%), 2.07 (6%), 1.26 (1.0%), 2.07: 6.31 (1.1%), 3.25 (3%), 1.26 (0.9%), 1.26: 3.43 (3%), 3.25

(2%), 2.07 (3%), 0.91 (2%); ^{13}C NMR (CDCl_3) δ : 177.4 (C-1, C-3), 36.1 (C-6, C-5), 131.9 (C-1'), 129.1 (C-3', C-5'), 128.6 (C-4'), 126.6 (C-2', C-6'), 65.2 (C-8), 47.8 (C-4, C-7), 44.3 (C-3a, C-7a), 29.8 (butyl), 27.9 (butyl), 22.7 (butyl), 14.0 (butyl); ms m/z (%): 295 (M^+ , 30), 252 (3), 213 (2), 173 (19), 119 (19), 119 (23), 91 (33), 80 (100), 65 (8), 54 (5). Exact mass calcd. for $\text{C}_{19}\text{H}_{21}\text{NO}_2$: 295.1571, found: 295.1569.



(10r)-5,8-Dihydro-10-methyl-2-phenyl-5,8-methano-1H-[1,2,4]-triazolo[1,2-a]pyridazine-1,3-(2H)-dione (57)

and

(10s)-5,8-Dihydro-10-methyl-2-phenyl-5,8-methano-1H-[1,2,4]-triazolo[1,2-a]pyridazine-1,3-(2H)-dione (58)

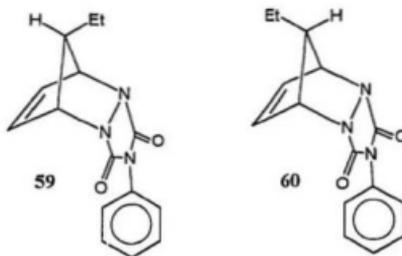
A solution of 1,3-cyclopentadiene (0.20 mL, 2.5 mmol) in THF (10 mL) under a nitrogen atmosphere was treated with *n*-butyllithium (1.10 mL, 2.73 mmol) at 0°C. The resulting cloudy solution was added dropwise over 20 min to a -20°C solution of iodomethane (0.73 mL, 12 mmol) in THF (7.0 mL) under nitrogen. The reaction mixture was stirred for an additional 2 h, transferred to a separatory funnel and quickly washed with cold brine (2 x 10 mL). 4-Phenyl-1,2,4-triazoline-3,5-dione (0.434 g, 2.48 mmol) was added to the organic layer, and the solution was stirred at -20°C overnight, then gradually

warmed to rt. The resulting solution was washed with water (2 x 10 mL) and dried over anhydrous MgSO₄. Rotary evaporation of the solvent afforded a beige solid. ¹H NMR analysis indicated a 3.8 : 1 ratio for **57** to **58**. Flash chromatography afforded adducts **57** (0.127 g, 20%) and **58** (0.057 g, 9%) as colorless solids.

For **57**: mp 140 - 141 °C; ir ν_{\max} : 3073, 1724, 1503, 1395, 1248, 1133 cm⁻¹; ¹H NMR (CDCl₃) δ : 7.47-7.33 (5H, m, C-2'H, C-3'H, C-4'H, C-5'H, C-6'H), 6.47 (2H, apparent t, J = 1.9 Hz, C-6H, C-7H), 4.77 (2H, dd, J = 1.5, 3.1 Hz, C-5H, C-8H), 2.36 (1H, q, J = 6.5 Hz, C-10H), 1.21 (3H, d, J = 6.5 Hz, C-10 CH₃); NOE results δ : 6.47: 4.77 (5%), 2.36 (2%), 4.77: 6.47 (5%), 2.36 (10%), 1.21 (1.4%), 2.36: 6.47 (2%), 4.77 (6%), 1.21 (0.9%), 1.21: 4.77 (2%), 2.36 (4%); ¹³C NMR (CDCl₃) δ : 159.1 (C-1, C-3), 132.9 (C-6, C-7), 131.4 (C-1'), 129.1 (C-3', C-5'), 128.3 (C-4'), 125.5 (C-2', C-6'), 68.3 (C-5, C-8), 55.9 (C-10), 12.8 (C-10 CH₃); ms m/z (%): 255 (M⁺, 21), 240 (1), 214 (2), 177 (5), 121 (15), 119 (55), 91 (24), 80 (100), 77 (21), 64 (15), 51 (13). Exact mass calcd. for C₁₄H₁₃N₁O₂: 255.1007, found: 255.1012.

For **58**: mp 126 -127.5 °C; ir ν_{\max} : 2989, 1725, 1491, 1397, 1235, 1129 cm⁻¹; ¹H NMR (CDCl₃) δ : 7.48-7.32 (5H, m, C-2'H, C-3'H, C-4'H, C-5'H, C-6'H), 6.37 (2H, apparent t, J = 1.8 Hz, C-6H, C-7H), 4.86 (2H, dd, J = 1.7, 3.2 Hz, C-5H, C-8H), 2.86 (1H, q, J = 6.5 Hz, C-10H), 0.96 (3H, d, J = 6.5 Hz, C-10 CH₃); NOE results δ : 6.37: 4.86 (4%), 0.96 (0.7%), 4.86: 6.37 (3%), 2.86 (7%), 0.96 (1.3%), 2.86: 4.86 (4%), 0.96 (2%), 0.96: 6.37 (2%), 4.86 (5%), 2.86 (11%); ¹³C NMR (CDCl₃) δ : 158.6 (C-1, C-3), 135.4 (C-6, C-7), 131.2 (C-1'), 129.1 (C-3', C-5'), 128.3 (C-4'), 125.5 (C-2', C-6'), 68.9 (C-5, C-8), 54.6 (C-10), 10.9 (C-10CH₃); ms m/z (%): 255 (M⁺, 8), 240 (1), 214 (1), 177 (9), 121 (18), 119

(52), 91 (24), 79 (100), 77 (26), 64 (16), 51 (14). Exact mass calcd. for $C_{14}H_{13}N_3O_2$:
255.1007, found: 255.0998.



(10r)-5,8-Dihydro-10-ethyl-2-phenyl-5,8-methano-1H-[1,2,4]triazolo[1,2-a]pyridazine-1,3-(2H)-dione (59)
and
(10s)-5,8-Dihydro-10-ethyl-2-phenyl-5,8-methano-1H-[1,2,4]triazolo[1,2-a]pyridazine-1,3-(2H)-dione (60)

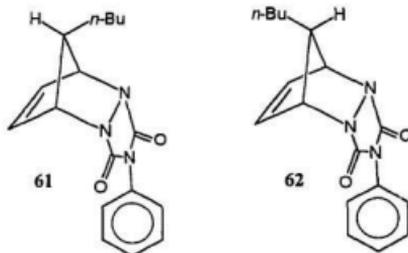
A solution of 1,3-cyclopentadiene (0.34 mL, 4.3 mmol) in THF (10 mL) under a nitrogen atmosphere was treated with *n*-butyllithium (1.89 mL, 4.71 mmol) at 0°C. The resulting cloudy solution was added dropwise over 20 min to a -20°C solution of iodoethane (1.71 mL, 21.4 mmol) in THF (7.0 mL) under nitrogen. The reaction mixture was stirred for an additional 40 min, transferred to a separatory funnel and quickly washed with cold brine (2 x 10 mL). 4-Phenyl-1,2,4-triazoline-3,5-dione (0.750 g, 4.28 mmol) was added to the organic layer, and the solution was stirred at -20°C overnight, then gradually warmed to rt. The resulting solution was washed with water (2 x 10 mL) and dried over anhydrous $MgSO_4$. Rotary evaporation of the solvent afforded a yellow oil. 1H NMR analysis indicated

a 2.3 : 1 ratio for **55** to **60**. Flash chromatography afforded adducts **59** (0.161 g, 14%) and **60** (0.053 g, 5%).

For **59**: mp 108.5 - 109 °C; ν_{max} : 2971, 1724, 1502, 1400, 1252, 1135 cm^{-1} ; ^1H NMR (CDCl_3) δ : 7.44-7.32 (5H, m, C-2'H, C-3'H, C-4'H, C-5'H, C-6'H), 6.44 (2H, apparent t, $J = 1.9$ Hz, C-6'H, C-7'H), 4.82 (2H, dd, $J = 1.5, 3.1$ Hz, C-5'H, C-8'H), 2.11 (1H, t, $J = 7.2$ Hz, C-10H), 1.57 (2H, m, C-10 CH_2CH_3), 0.95 (3H, t, $J = 7.3$ Hz, C-10 CH_2CH_3); NOE results δ : 6.44: 4.82 (6%), 2.11 (3%), 4.82: 6.44 (7%), 2.11 (13%), 1.57 (2%), 0.95 (1.4%), 2.11: 6.44 (1.4%), 4.82 (6%), 1.57 (2%), 1.57: 4.82 (3%), 2.11 (5%), 0.95 (2%), 0.95: 4.82 (3%), 2.11 (4%), 1.57 (3%); ^{13}C NMR (CDCl_3) δ : 158.7 (C-1, C-3), 132.4 (C-6, C-7), 131.1 (C-1'), 128.8 (C-3', C-5'), 128.0 (C-4'), 125.2 (C-2', C-6'), 66.3 (C-5, C-8), 63.0 (C-10), 20.0 (C-10 CH_2CH_3), 11.5 (C-10 CH_2CH_3); m/z (%): 269 (M^+ , 11), 240 (2), 214 (1), 177 (2), 120 (13), 119 (48), 94 (42), 79 (100), 77 (36), 65 (16), 51 (13). Exact mass calcd. for $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_2$: 269.1163, found: 269.1156.

For **60**: mp 105 - 106 °C; ν_{max} : 2963, 1725, 1501, 1395, 1232, 1130 cm^{-1} ; ^1H NMR (CDCl_3) δ : 7.46-7.32 (5H, m, C-2'H, C-3'H, C-4'H, C-5'H, C-6'H), 6.35 (2H, apparent t, $J = 1.6$ Hz, C-6'H, C-7'H), 4.92 (2H, dd, $J = 1.6, 3.2$ Hz, C-5'H, C-8'H), 2.68 (1H, t, $J = 7.6$ Hz, C-10H), 1.30 (2H, m, C-10 CH_2CH_3), 0.89 (3H, t, $J = 7.4$ Hz, C-10 CH_2CH_3); NOE results δ : 6.35: 4.92 (6%), 1.30 (0.8%), 4.92: 6.35 (6%), 2.68 (9%), 1.30 (2%), 0.89 (2%), 2.68: 4.92 (5%), 1.30 (2%), 0.89 (1.2%), 1.30: 6.35 (2%), 4.92 (3%), 2.68 (5%), 0.89 (1.3%), 0.89: 6.35 (0.8%), 4.92 (4%), 2.68 (5%), 1.30 (2%); ^{13}C NMR (CDCl_3) δ : 158.5 (C-1, C-3), 131.1 (C-1'), 129.2 (C-6, C-7), 129.0 (C-3', C-5'), 128.2 (C-4'), 125.4 (C-2', C-6'), 67.4 (C-5, C-8), 61.3 (C-10), 18.7 (C-10 CH_2CH_3), 12.2 (C-10 CH_2CH_3); m/z :

(%): 269 (M^+ , 5), 240 (2), 214 (1), 177 (5), 121 (21), 119 (34), 94 (41), 91 (26), 79 (100), 64 (11), 51 (9). Exact mass calcd. for $C_{15}H_{15}N_2O_2$: 269.1163, found: 269.1168.



(10*r*)-10-*n*-Butyl-5,8-dihydro-2-phenyl-5,8-methano-1*H*-[1,2,4]triazolo[1,2-*a*]pyridazine-1,3-(2*H*)-dione (**61**)
and
(10*s*)-10-*n*-Butyl-5,8-dihydro-2-phenyl-5,8-methano-1*H*-[1,2,4]triazolo[1,2-*a*]pyridazine-1,3-(2*H*)-dione (**62**)

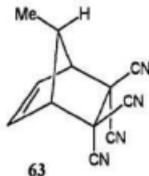
A solution of 1,3-cyclopentadiene (0.40 mL, 5.0 mmol) in THF (15 mL) under a nitrogen atmosphere was treated with *n*-butyllithium (2.20 mL, 5.47 mmol) at 0°C. The resulting cloudy solution was added dropwise over 20 min to a -20°C solution of 1-iodobutane (2.00 mL, 17.6 mmol) in THF (10 mL) under nitrogen. The reaction mixture was stirred for an additional 2 h, transferred to a separatory funnel and quickly washed with cold brine (2 x 10 mL). 4-Phenyl-1,2,4-triazoline-3,5-dione (0.871 g, 4.97 mmol) was added to the organic layer, and the solution was stirred at -20°C overnight, then gradually warmed to rt. The resulting solution was washed with water (2 x 10 mL) and dried over anhydrous $MgSO_4$. Rotary evaporation of the solvent afforded a yellow oil. 1H NMR analysis indicated a 2.0 : 1 ratio for **61** to **62**. Flash chromatography afforded adducts **61**

(0.461 g, 31%) and **62** (0.265 g, 18%), which were recrystallized from 20% dichloromethane / hexane to yield colorless crystals.

For **61**: mp 85.5 - 86 °C; ir ν_{max} : 2961, 2929, 1779, 1726, 1502, 1394, 1251, 1018 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ : 7.46-7.35 (5H, m, C-2'H, C-3'H, C-4'H, C-5'H, C-6'H), 6.48 (2H, apparent t, $J = 1.9$ Hz, C-6H, C-7H), 4.85 (2H, dd, $J = 1.8, 3.3$ Hz, C-5H, C-8H), 2.21 (1H, t, $J = 7.1$ Hz, C-10H), 1.59 (2H, m, C-10 $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.35 (4H, m, C-10 $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 0.93 (3H, t, $J = 6.8$ Hz, C-10 $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$); NOE results δ : 6.48: 4.85 (3%), 2.21 (0.3%), 4.85: 6.48 (5%), 2.21 (5%), 1.59 (0.7%), 1.35 (0.8%), 2.21: 6.48 (1.0%), 4.85 (4%), 1.59 (0.9%), 1.35 (0.5%), 1.59: 4.85 (2%), 2.21 (3%), 1.35 (0.6%), 1.35: 4.85 (2%), 2.21 (3%), 1.59 (1.2%), 0.93 (2%), 0.93: 1.35 (1.1%); $^{13}\text{C NMR}$ (CDCl_3) δ : 159.0 (C-1, C-3), 132.6 (C-6, C-7), 131.3 (C-1'), 129.0 (C-3', C-5'), 128.3 (C-4'), 125.5 (C-2', C-6'), 66.8 (C-10), 61.7 (C-5, C-8), 29.5 (butyl), 26.8 (butyl), 22.5 (butyl), 13.9 (butyl); ms m/z (%): 297 (M^+ , 8), 254 (3), 241 (2), 178 (2), 135 (4), 119 (47), 91 (33), 80 (100), 66 (19), 51 (11), 41 (11). Exact mass calcd. for $\text{C}_{17}\text{H}_{19}\text{N}_3\text{O}_2$: 297.1476, found: 297.1473.

For **62**: mp 74 - 75 °C; ir ν_{max} : 2959, 2931, 1775, 1725, 1502, 1234, 1017 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ : 7.46-7.34 (5H, m, C-2'H, C-3'H, C-4'H, C-5'H, C-6'H), 6.36 (2H, m, C-6H, C-7H), 4.92 (2H, dd, $J = 1.8, 3.5$ Hz, C-5H, C-8H), 2.75 (1H, m, C-10H), 1.27 (6H, m, C-10 $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 0.89 (3H, t, $J = 7.0$ Hz, C-10 $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$); NOE results δ : 6.36: 4.92 (3%), 1.27 (0.1%), 4.92: 6.31 (4%), 2.75 (5%), 1.27 (0.9%), 2.75: 4.92 (4%), 1.27 (1.0%), 1.27: 6.31 (3%), 4.92 (4%), 1.27 (1.0%), 1.27: 6.31 (3%), 4.92 (8%), 2.75 (11%), 0.89 (3%), 0.89: 1.27 (1.0%); $^{13}\text{C NMR}$ (CDCl_3) δ : 158.6 (C-1, C-3), 131.2 (C-1'),

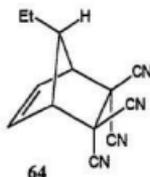
129.2 (C-6, C-7), 129.1 (C-3', C-5'), 128.3 (C-4'), 125.4 (C-2', C-6'), 67.8 (C-10), 59.8 (C-5, C-8), 30.1 (butyl), 25.3 (butyl), 22.5 (butyl), 13.8 (butyl); ms *m/z* (%): 297 (*M*⁺, 2), 254 (1), 240 (1), 135 (2), 119 (41), 93 (11), 79 (100), 66 (19), 51 (12), 41 (10). Exact mass calcd. for C₁₇H₁₉N₄O₂: 297.1476, found: 297.1489.



(7s)-7-Methyl-2,2,3,3-tetracyanobicyclo[2.2.1]hept-5-ene (63)

A solution of 1,3-cyclopentadiene (0.40 mL, 5.0 mmol) in THF (15 mL) under a nitrogen atmosphere was treated with *n*-butyllithium (2.20 mL, 5.47 mmol) at 0°C. The resulting cloudy solution was added dropwise over 20 min to a -20°C solution of iodomethane (1.54 mL, 24.9 mmol) in THF (10 mL) under nitrogen. The reaction mixture was stirred for an additional 40 min, transferred to a separatory funnel and quickly washed with cold brine (2 x 15 mL). Tetracyanoethylene (0.637 g, 4.97 mmol) was added to the organic layer, and the solution was stirred at -20°C overnight, then gradually warmed to rt. The resulting solution was washed with water (2 x 15 mL) and dried over anhydrous MgSO₄. Rotary evaporation of the solvent afforded a yellow, oily semi-solid. ¹H NMR analysis indicated 100% anti addition to give 63. Flash chromatography afforded adduct 63 (0.766 g, 74%) as a light grey solid, which was recrystallized from 40% dichloromethane / ethyl acetate to give 63 as a colorless solid, homogeneous by NMR: mp 193 - 194 °C; ir

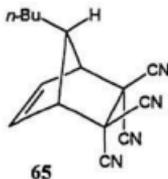
ν_{max} : 2933, 2968, 2252, 1581, 1452, 1336, 1259 cm^{-1} ; $^1\text{H NMR}$ (CD_3COCD_3) δ : 6.67 (2H, apparent t, $J = 1.9$ Hz, C-5H, C-6H), 4.16 (2H, dd, $J = 1.6, 3.3$ Hz, C-1H, C-4H), 2.80 (1H, m, C-7H), 1.12 (3H, d, $J = 6.3$ Hz, C-7 CH_3); NOE results δ : 6.67: 4.16 (5%), 2.80 (0.5%), 1.12 (0.5%), 4.16: 6.67 (5%), 2.80 (6%), 1.12 (1.1%), 2.80: 4.16 (3%), 1.12 (2%), 1.12: 6.67 (1.4%), 4.16 (4%), 2.80 (8%); $^{13}\text{C NMR}$ (CD_3COCD_3) δ : 136.8 (C-5, C-6), 114.3 (C-2CN, C-3CN), 113.3 (C-2CN, C-3CN), 61.5 (C-1, C-4), 54.8 (C-7), 11.9 (C-7 CH_3); *ms* m/z (%): no M^+ , 180 (5), 155 (2), 143 (3), 128 (41), 102 (5), 80 (100), 79 (70), 77 (22), 76 (46), 65 (8), 51 (12), 50 (11). Anal. calcd. for $\text{C}_{12}\text{H}_8\text{N}_4$: C 69.22, H 3.87, N 26.91; found: C 69.22, H 3.85, N 27.18.



(7s)-7-Ethyl-2,2,3,3-tetracyanobicyclo[2.2.1]hept-5-ene (64)

A solution of 1,3-cyclopentadiene (0.40 mL, 5.0 mmol) in THF (15 mL) under a nitrogen atmosphere was treated with *n*-butyllithium (2.20 mL, 5.47 mmol) at 0°C. The resulting cloudy solution was added dropwise over 20 min to a -20°C solution of iodoethane (1.98 mL, 24.9 mmol) in THF (10 mL) under nitrogen. The reaction mixture was stirred for an additional 40 min, transferred to a separatory funnel and quickly washed with cold brine (2 x 15 mL). Tetracyanoethylene (0.637 g, 4.97 mmol) was added to the organic layer and the solution was stirred at -20°C overnight, then gradually warmed to rt. The resulting

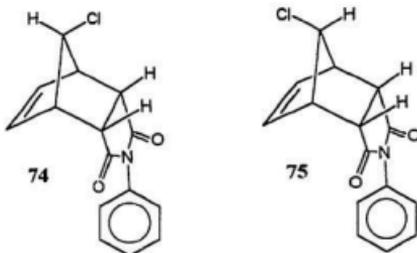
solution was washed with water (2 x 15 mL) and dried over anhydrous MgSO_4 . Rotary evaporation of the solvent afforded an oily semi-solid. ^1H NMR analysis indicated 100% anti addition to give **64**. The crude product was dissolved in hot methanol, filtered through a small portion of charcoal and recrystallized upon cooling to yield **64** (0.744 g, 67%) as colorless crystals upon cooling: mp 175.5 - 176 °C; ir_{max} : 3097, 2976, 2251, 1579, 1450, 1381, 1343, 1256, 1142 cm^{-1} ; ^1H NMR (CD_3COCD_3) δ : 6.68 (2H, apparent t, $J = 1.9$ Hz, C-5H, C-6H), 4.25 (2H, apparent s, C-1H, C-4H), 2.55 (1H, t, $J = 6.9$ Hz, C-7H), 2.05 (2H apparent quintet, $J = 7.3$ Hz, C-7 CH_2CH_3), 0.96 (3H, t, $J = 7.5$ Hz, C-7 CH_2CH_3); NOE results δ : 6.68: 4.25 (4%), 2.05 (0.4%), 4.25: 6.68 (5%), 2.55 (7%), 2.05 (1.3%), 0.96 (1.2%), 2.55: 4.25 (3%), 2.05 (2%), 0.96 (0.8%), 2.05: 6.68 (0.8%), 4.25 (2%), 2.55 (6%), 0.96: 4.25 (0.9%), 2.55 (3%); ^{13}C NMR (CD_3COCD_3) δ : 136.8 (C-5, C-6), 114.2 (C-2CN, C-3CN), 113.3 (C-2CN, C-3CN), 62.0 (C-7), 60.0 (C-1, C-4), 20.2 (C-7 CH_2CH_3), 13.3 (C-7 CH_2CH_3); $\text{ms } m/z$ (%): no M^+ , 194 (2), 180 (2), 167 (2), 140 (2), 128 (61), 102 (7), 94 (63), 93 (11), 91 (12), 79 (100), 77 (42), 76 (68), 65 (11), 51 (11), 50 (10). Anal. calcd. for $\text{C}_{13}\text{H}_{10}\text{N}_4$: C 70.26, H 4.54, N 25.21; found: C 70.02, H 4.48, N 25.12.



(7s)-7-*n*-Butyl-2,2,3,3,-tetracyanobicyclo[2.2.1]hept-5-ene (65)

A solution of 1,3-cyclopentadiene (0.40 mL, 5.0 mmol) in THF (15 mL) under a nitrogen atmosphere was treated with *n*-butyllithium (2.20 mL, 5.47 mmol) at 0°C. The resulting cloudy solution was added dropwise over 20 min to a -20°C solution of 1-iodobutane (1.98 mL, 24.9 mmol) in THF (10 mL) under nitrogen. The reaction mixture was stirred for an additional 40 min, transferred to a separatory funnel and quickly washed with cold brine (2 x 15 mL). Tetracyanoethylene (0.637 g, 4.97 mmol) was added to the organic layer, and the solution was stirred at -20°C overnight, then gradually warmed to rt. The resulting solution was washed with water (2 x 15 mL) and dried over anhydrous MgSO₄. Rotary evaporation of the solvent afforded a brown oily solid. ¹H NMR analysis indicated 100% anti addition to give **65**. The crude product was dissolved in hot dichloromethane / pentane, filtered through a small portion of charcoal and recrystallized upon cooling to yield **65** (0.742 g, 59%) as colorless crystals: mp 131 - 132.5 °C; *ir* ν_{\max} : 2964, 2923, 2861, 2250, 1451, 1340 cm⁻¹; ¹H NMR (CD₃COCD₃) δ : 6.68 (2H, m, C-5H, C-6H), 4.24 (2H, dd, *J* = 1.5, 3.2 Hz, C-1H, C-4H), 2.61 (1H, apparent t, *J* = 6.9 Hz, C-7H), 1.50 (2H, m, C-7CH₂CH₂CH₂CH₃), 1.32 (4H, m, C-7CH₂CH₂CH₂CH₃), 0.89 (3H, t, C-7CH₂CH₂CH₂CH₃); NOE results δ : 6.68: 4.24 (3%), 1.50 (0.5%), 4.24: 6.68 (3%), 2.61 (4%), 1.50 (1.2%), 1.32 (0.8%), 2.61: 4.24 (3%), 1.50 (2%), 1.32 (0.7%), 1.50: 6.68 (1.3%), 4.24 (4%), 2.61 (7%), 1.32: 6.68 (0.5%), 4.24 (4%), 2.61 (7%), 0.89 (2%), 0.89: 1.32 (1.3%); ¹³C NMR (CD₃COCD₃) δ : 136.4 (C-5, C-6), 113.8 (C-2CN, C-3CN), 112.8 (C-2CN, C-3CN), 59.8 (C-7), 59.7 (C-1, C-4), 47.9 (C-2, C-3), 31.0 (C-7 butyl), 26.0 (C-7 butyl), 23.1 (C-7 butyl), 14.2 (C-7 butyl); *ms* *m/z* (%): no M⁺, 129 (9), 128 (100), 102 (9),

76 (84), 64 (12), 50 (10). Anal. calcd. for $C_{11}H_{14}N_2$: C 71.98, H 5.64, N 22.38; found: C 71.69, H 5.44, N 22.38.



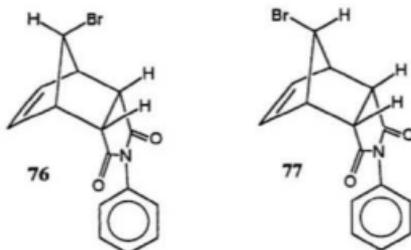
(3 α ,4 α ,7 α ,7 α ,8 s)-8-Chloro-3a,4,7,7a-tetrahydro-2-phenyl-4,7-methano-1H-isoindole-1,3-(2H)-dione (74)
and
(3 α ,4 α ,7 α ,7 α ,8 r)-8-Chloro-3a,4,7,7a-tetrahydro-2-phenyl-4,7-methano-1H-isoindole-1,3-(2H)-dione (75)

A solution of cyclopentadienylthallium (0.576 g, 2.14 mmol) and *N*-chlorosuccinimide (0.293 g, 2.14 mmol) in diethyl ether (20 mL) under nitrogen was immersed in an ice bath and stirred for 1 hour. The resulting suspension was filtered through a glass wool plug on sintered glass into a solution of *N*-phenylmaleimide (0.370 g, 2.14 mmol) in benzene (10 mL). The reaction mixture was returned to the ice bath and stirred overnight, then gradually warmed to rt. Rotary evaporation of the solvent gave a cream-colored solid. ^1H NMR analysis indicated a 3.7 : 1 ratio for 74 to 75. Flash chromatography afforded adducts 74 (0.216 g, 37%) and 75 (0.074 g, 13%) as colorless solids. The sample of adduct 74

contained a small amount of *N*-phenylmaleimide so it was recrystallized from 40% ethyl acetate / hexane to give an analytical sample that was homogenous by NMR.

For 74: mp 166 - 167.5 °C; ir ν_{max} : 3015, 3063, 1711, 1495, 1380, 1186 cm^{-1} ; ^1H NMR (CDCl_3) δ : 7.44 - 7.37 (3H, m, C-3'H, C-4'H, C-5'H), 7.14 (2H, br d, $J = 8.2$ Hz, C-2'H, C-6'H), 6.32 (2H, apparent t, $J = 2.1$ Hz, C-5'H, C-6'H), 4.07 (1H, m, C-8'H), 3.81 (2H, dd, $J = 1.6, 3.0$ Hz, C-3aH, C-7aH), 3.48 (2H, m, C-4H, C-7H); NOE results δ : 6.32: 4.07 (1.3%), 3.48 (3%), 4.07: 6.31 (0.7%), 3.48 (3%), 3.81: 3.48 (4%), 3.48: 6.32 (3%), 4.07 (7%), 3.81 (4%); ^{13}C NMR (CDCl_3) δ : 176.1 (C-1, C-3), 134.7 (C-5, C-6), 131.7 (C-1), 129.1 (C-3', C-5'), 128.7 (C-4'), 126.5 (C-2', C-6'), 70.7 (C-8), 50.3 (C-4, C-7), 43.7 (C-4a, C-7a); ms m/z (%): 273 (M^+ , 85), 238, (6), 210 (5), 173 (89), 145 (16), 129 (55), 119 (100), 103 (22), 91 (82), 65 (67), 54 (45), 50 (26). Exact mass calcd. for $\text{C}_{15}\text{H}_{12}^{35}\text{ClNO}_2$: 273.0556, found: 273.0547.

For 75: mp 169.5 - 171 °C; ir ν_{max} : 3071, 3003, 1719, 1562, 1498, 1375, 1266, 1179 cm^{-1} ; ^1H NMR (CDCl_3) δ : 7.47 - 7.38 (3H, m, C-3'H, C-4'H, C-5'H), 7.14 (2H, br d, $J = 6.9$ Hz, C-2'H, C-6'H), 6.26 (2H, m, C-5H, C-6H), 4.06 (1H, m, C-8H), 3.64 (2H, m, C-4H, C-7H), 3.49 (2H, dd, $J = 1.6, 3.0$ Hz, C-3aH, C-7aH); NOE results δ : 6.26: 3.64 (3%), 4.06: 3.64 (3%), 3.64 (4%), 3.64: 6.13 (3%), 4.06 (4%), 3.49 (1.3%), 3.49: 4.06 (10%), 3.64 (4%); ^{13}C NMR (CDCl_3) δ : 174.9 (C-1, C-3), 131.6 (C-5, C-6), 129.2 (C-3', C-5'), 128.8 (C-4'), 126.5 (C-2', C-6'), 72.5 (C-8), 51.5 (C-4, C-7), 42.8 (C-4a, C-7a); ms m/z (%): 273 (M^+ , 74), 238 (4), 210 (3), 173 (100), 145 (6), 129 (23), 119 (33), 100 (15), 77 (11), 65 (24), 54 (13). Exact mass calcd. for $\text{C}_{15}\text{H}_{12}^{31}\text{ClNO}_2$: 273.0556, found: 273.0549.



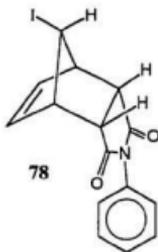
(3 α ,4 α ,7 α ,7 α ,8s)-8-Bromo-3 α ,4,7,7 α -tetrahydro-2-phenyl-4,7-methano-1*H*-isoindole-1,3-(2*H*)-dione (76)
and
(3 α ,4 α ,7 α ,7 α ,8r)-8-Bromo-3 α ,4,7,7 α -tetrahydro-2-phenyl-4,7-methano-1*H*-isoindole-1,3-(2*H*)-dione (77)

A solution of cyclopentadienylthallium (0.930 g, 3.45 mmol) and *N*-bromosuccinimide (0.614 g, 3.45 mmol) in diethyl ether (35 mL) under nitrogen was immersed in an ice bath and stirred for 1 h. The resulting mixture was filtered through a glass wool plug on sintered glass into a solution of *N*-phenylmaleimide (0.597 g, 3.45 mmol) in benzene (15 mL). The combined solutions were returned to the ice bath and stirred overnight, then gradually warmed to rt. Rotary evaporation of the solvent gave a pale yellow solid. ¹H NMR analysis indicated a 5.2 : 1 ratio for 77 to 76. Flash chromatography afforded adducts 77 (0.581 g, 53%) and 76 (0.024 g, 2%) as colorless solids, which were recrystallized from 17% dichloromethane / hexane to afford samples that were homogeneous by NMR.

For 76: mp 194.5 - 196 °C; ν_{\max} : 3063, 1714, 1594, 1497, 1377, 1185 cm⁻¹; ¹H NMR (CDCl₃) δ : 7.47 - 7.37 (3H, m, C-3'H, C-4'H, C-5'H), 7.14 (2H, br d, J = 7.0 Hz, C-2'H, C-6'H), 6.32 (2H, apparent t, J = 2.2 Hz, C-5H, C-6H), 4.15 (1H, s, C-8H), 3.88

(2H, dd, $J = 0.8, 2.5$ Hz, C-3aH, C-7aH), 3.53 (2H, m, C-4H, C-7H); NOE results δ : 6.32: 4.15 (1.5%), 3.53 (3%), 4.15: 6.32 (0.6%), 3.53 (3%), 3.88: 3.53 (4%), 3.53: 6.32 (3%), 4.15 (6%), 3.88 (4%); ^{13}C NMR (CDCl_3) δ : 176.2 (C-1, C-3), 135.2 (C-5, C-6), 131.6 (C-1'), 129.1 (C-3', C-5'), 128.8 (C-4'), 126.5 (C-2', C-6'), 61.4 (C-8), 50.7 (C-4, C-7), 44.0 (C-3a, C-7a); ms m/z (%): 319 (23) and 317 (24) both M^+ , 174 (23), 173 (100), 144 (7), 129 (16), 119 (11), 91 (33), 65 (32), 54 (10). Exact mass calcd. for $\text{C}_{15}\text{H}_{12}^{79}\text{BrNO}_2$ (M^+ - Br): 238.0867, found: 238.0862.

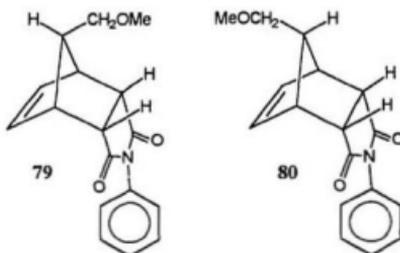
For 77: mp 188 - 189 °C; ir ν_{max} : 3063, 1716, 1594, 1548, 1497, 1377, 1185 cm^{-1} ; ^1H NMR (CDCl_3) δ : 7.47 - 7.37 (3H, m, C-3'H, C-4'H, C-5'H), 7.13 (2H, br d, $J = 7.0$ Hz, C-2'H, C-6'H), 6.26 (2H, apparent t, $J = 1.8$ Hz, C-5H, C-6H), 4.06 (1H, s, C-8H), 3.66 (2H, m, C-4H, C-7H), 3.47 (2H, dd, $J = 1.4, 2.9$ Hz, C-3aH, C-7aH); NOE results δ : 6.26: 3.66 (3%), 4.06: 3.66 (3%), 3.47 (5%), 3.66: 6.26 (4%), 4.06 (5%), 3.47 (3%), 3.47: 4.06 (9%), 3.66 (4%); ^{13}C NMR (CDCl_3) δ : 174.8 (C-1, C-3), 132.5 (C-5, C-6), 131.5 (C-1'), 129.2 (C-3', C-5'), 128.9 (C-4'), 126.4 (C-2', C-6'), 63.2 (C-8), 51.9 (C-4, C-7), 42.8 (C-3a, C-7a); ms m/z (%): 319 (63) and 317 (66) both M^+ , 239 (19), 173 (100), 146 (5), 129 (11), 91 (12), 65 (33), 54 (36), 51 (17). Exact mass calcd. for $\text{C}_{15}\text{H}_{12}^{79}\text{BrNO}_2$ (M^+ - Br): 238.0867, found: 238.0863.



(3 α ,4 α ,7 α ,7 α ,8 r)-3 α ,4,7,7 α -Tetrahydro-8-iodo-2-phenyl-4,7-methano-1*H*-isoindole-1,3-(2*H*)-dione (78)

A solution of cyclopentadienylthallium (0.200 g, 0.742 mmol) and *N*-iodosuccinimide (0.167 g, 2.04 mmol) in diethyl ether (15 mL) under nitrogen was immersed in an ice bath and stirred for 1 h. The resulting mixture was filtered through a glass wool plug on sintered glass into a solution of *N*-phenylmaleimide (0.129 g, 0.742 mmol) in benzene (10 mL). The combined solutions were returned to the ice bath and stirred overnight, then gradually warmed to rt. Rotary evaporation of the solvent gave a pale yellow solid. ¹H NMR analysis indicated 100% anti addition. (The structure was confirmed by X-ray analysis as 78.) Flash chromatography afforded adduct 78 (0.120 g, 41%) as a beige solid. Adduct 78 was recrystallized from 25% hexane/dichloromethane to give a colorless crystals: mp 211 - 212.5 °C; ν_{max} : 1707, 1377, 1177 cm⁻¹; ¹H NMR (CDCl₃) δ : 7.47 - 7.38 (3H, m, C-3'H, C-4'H, C-5'H), 7.11 (2H, br d, J = 6.9 Hz, C-2'H, C-6'H), 6.29 (2H, apparent t, J = 1.8 Hz, C-5H, C-6H), 4.03 (1H, br s, C-8H), 3.69 (2H, m, C-4H, C-7H), 3.57 (2H, dd, J = 1.5, 2.9 Hz, C-3aH, C-7aH); NOE results δ : 6.29: 3.69

(4%), 4.04: 3.69 (3%), 3.57 (6%), 3.69: 6.29 (4%), 4.03 (5%), 3.1: 7 (2%), 3.57: 4.03 (11%), 3.69 (5%); ^{13}C NMR (CDCl_3) δ : 174.6 (C-1, C-3), 134.3 (C-5, C-6), 131.4 (C-1'), 129.1 (C-3', C-5'), 128.8 (C-4'), 126.4 (C-2', C-6'), 53.1 (C-4, C-7), 42.6 (C-3a, C-7a), 41.0 (C-8); *ms m/z* (%): 365 (M^+ , 33), 238 (39), 210 (17), 192 (41), 173 (48), 145 (3), 129 (16), 119 (16), 95 (11), 91 (65), 77 (16), 69 (39), 65 (100), 57 (43). Exact mass calcd. for $\text{C}_{15}\text{H}_{12}\text{INO}_2$ (M^+): 238.0868, found: 238.0859.



(3 α ,4 α ,7 α ,7 α ,8s)-3 α ,4,7,7 α -Tetrahydro-8-methoxymethyl-2-phenyl-4,7-methano-1H-isoindole-1,3-(2H)-dione (79)
 and
(3 α ,4 α ,7 α ,7 α ,8r)-3 α ,4,7,7 α -Tetrahydro-8-methoxymethyl-2-phenyl-4,7-methano-1H-isoindole-1,3-(2H)-dione (80)

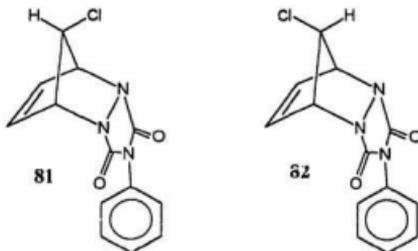
A suspension of cyclopentadienylthallium (0.750 g, 2.78 mmol) in THF (1.5 mL) at -20°C under nitrogen was treated with chloromethoxymethane (0.42 mL 5.56 mmol) and stirred for 5 h. The resulting mixture was filtered through a glass wool plug on sintered glass into a solution of *N*-phenylmaleimide (0.481 g, 2.78 mmol) in ethyl ether (5 mL). The combined solutions were stirred at -20°C overnight, then gradually warmed to rt. Rotary evaporation of the solvent gave a yellow solid. ^1H NMR analysis indicated a 5.0 : 1 ratio for

79 to 80. Flash chromatography afforded adducts 79 (0.197 g, 25%) and 80 (0.065 g, 9%) as colorless solids.

For 79: mp 113.5 - 114 °C; ir ν_{max} : 3014, 2893, 1714, 1496, 1376, 1183 cm^{-1} ; ^1H NMR (C_6D_6) δ : 7.37 - 7.14 (5H, m, C-2'H, C-3'H, C-4'H, C-5'H, C-6'H), 5.94 (2H, apparent t, $J = 1.9$ Hz, C-5H, C-6H), 3.01 (2H, m, C-4H, C-7H), 2.98 (3H, s, C-8 CH_2OCH_3), 2.66 (2H, dd, $J = 1.3, 2.8$ Hz, C-3aH, C-7aH), 2.59 (2H, d, $J = 7.4$ Hz, C-8 CH_2OCH_3), 2.04 (1H, t, $J = 7.4$ Hz, C-8H); NOE results δ : 5.94: 3.01 (5%), 2.04 (2%), 2.66: 3.01 (5%), 2.98 (2%), 2.04: 5.94 (1.3%), 3.01 (5%); ^{13}C NMR (C_6D_6) δ : 176.2 (C-1, C-3), 136.3 (C-5, C-6), 133.6 (phenyl), 129.2 (phenyl), 128.7 (phenyl), 127.2 (phenyl), 70.9 (C-4, C-7), 63.9 (C-3a, C-7a), 59.1 (C-8), 46.8 (C-8 CH_2OCH_3), 44.6 (C-8 CH_2OCH_3); ms m/z (%): 283 (M^+ , 17), 251 (3), 210 (1), 186 (4), 173 (28), 129 (10), 119 (11), 110 (22), 103 (10), 91 (29), 78 (21), 65 (16), 45 (100). Exact mass calcd. for $\text{C}_{17}\text{H}_{17}\text{NO}_3$: 283.1207, found: 283.1208.

For 80: mp 118.5 - 119 °C; ir ν_{max} : 2922, 1703, 1495, 1380, 1167 cm^{-1} ; ^1H NMR (C_6D_6) δ : 7.33 - 7.13 (5H, m, C-2'H, C-3'H, C-4'H, C-5'H, C-6'H), 5.78 (2H, apparent t, $J = 1.7$ Hz, C-5H, C-6H), 3.07 (2H, m, C-4H, C-7H), 2.96 (3H, s, C-8 CH_2OCH_3), 2.85 (2H, d, $J = 7.0$ Hz, C-8 CH_2OCH_3), 2.65 (2H, dd, $J = 1.2, 2.8$ Hz C-3a, C-7a), 1.80 (1H, t, $J = 7.0$ Hz, C-8H); NOE results δ : 5.78: 3.07 (8%), 2.85 (0.9%), 3.07: 5.78 (10%), 2.85 (2%), 2.65 (7%), 1.80 (7%), 2.96: 5.78 (0.8%), 2.65: 3.07 (10%), 1.80 (18%), 1.80: 3.07 (4%), 2.85 (2%), 2.65 (9%); ^{13}C NMR (C_6D_6) δ : 175.8 (C-1, C-3), 132.4 (C-5, C-6), 129.2 (phenyl), 128.7 (phenyl), 128.4 (phenyl), 127.2 (phenyl), 69.9 (C-4, C-7), 64.0 (C-3a, C-7a), 58.9 (C-8), 47.7 (C-8 CH_2OCH_3), 46.1 (C-8 CH_2OCH_3); ms m/z (%): 283 (M^+ , 14),

268 (2), 251 (5), 225 (2), 173 (24), 119 (11), 110 (21), 104 (19), 91 (22), 78 (32), 65 (16), 45 (100). Exact mass calcd. for $C_{17}H_{17}NO_3$: 283.1207, found: 283.1213.

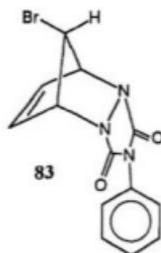


(10s)-10-Chloro-5,8-dihydro-2-phenyl-5,8-methano-1H-[1,2,4]triazolo[1,2-a]pyridine-1,3-(2H)-dione (81)
and
(10r)-10-Chloro-5,8-dihydro-2-phenyl-5,8-methano-1H-[1,2,4]triazolo[1,2-a]pyridine-1,3-(2H)-dione (82)

A solution of cyclopentadienylthallium (0.439 g, 1.63 mmol) and *N*-chlorosuccinimide (0.220 g, 1.63 mmol) in diethyl ether (20 mL) under nitrogen was immersed in an ice bath and stirred for 1 h. The resulting mixture was filtered through a glass wool plug on sintered glass into a solution of 4-phenyl-1,2,4-triazoline-3,5-dione (0.291 g, 1.63 mmol) in benzene (15 mL). The combined solutions were returned to the ice bath and stirred for 4 h. Rotary evaporation of the solvent furnished a pale orange product. ^1H NMR analysis of the crude product indicated a ratio of 1.4 : 1 for **82** to **81**. Flash chromatography afforded adducts **82** (0.177 g, 39%) and **81** (0.120 g, 27%) as colorless solids. Adduct **82** was recrystallized from 20% ethyl acetate / hexane to give colorless crystals.

For 82: mp 166.5 - 167.5 °C; ir ν_{\max} : 1719, 1408 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ : 7.47-7.34 (5H, m, C-2'H, C-3'H, C-4'H, C-5'H, C-6'H), 6.47 (2H, apparent t, $J = 1.9$ Hz, C-6H, C-7H), 5.11 (2H, dd, $J = 1.8, 3.6$ Hz, C-5H, C-8H), 4.56 (1H, t, $J = 1.1$ Hz, C-10H); $^{13}\text{C NMR}$ (CDCl_3) δ : 157.9 (C-1, C-3), 129.2 (C-6, C-7), 129.0 (C-1', C-3', C-5'), 128.7 (C-4'), 125.5 (C-2', C-6'), 78.5 (C-5, C-8), 66.4 (C-10); ms m/z (%): 275 (M^+ , 41), 240 (43), 214 (2), 156 (24), 119 (3), 100 (100), 91 (27), 78 (22), 65 (58), 51 (11). Exact mass calcd. for $\text{C}_{11}\text{H}_{10}^{35}\text{ClN}_3\text{O}_2$: 275.0461, found 275.0453. Anal. calcd. for $\text{C}_{11}\text{H}_{10}\text{ClN}_3\text{O}_2$: C 56.72, H 3.63, N 15.27; found: C 56.66, H 3.69, N 15.36.

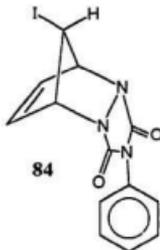
For 81: mp 175.5 - 176 °C; ir ν_{\max} : 2978, 1725, 1491 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ : 7.47-7.38 (5H, m, C-2'H, C-3'H, C-4'H, C-5'H, C-6'H), 6.56 (2H, apparent t, $J = 2.1$ Hz, C-6H, C-7H), 5.05 (2H, dd, $J = 2.0, 3.5$ Hz, C-5H, C-8H), 4.23 (1H, t, $J = 1.3$ Hz, C-10H); NOE results δ : 6.56: 5.05 (3%), 4.23 (1.4%), 4.23: 6.56 (0.5%), 5.05 (3%); $^{13}\text{C NMR}$ (CDCl_3) δ : 158.0 (C-1, C-3), 132.8 (C-6, C-7), 129.2 (C-1', C-3', C-5'), 128.6 (C-4'), 125.6 (C-2', C-6'), 67.8 (C-5, C-8), 65.6 (C-10); ms m/z (%): 275 (M^+ , 36), 240 (100), 214 (2), 156 (4), 119 (63), 100 (56), 91 (23), 78 (28), 65 (41), 51 (9). Exact mass calcd. for $\text{C}_{11}\text{H}_{10}^{35}\text{ClN}_3\text{O}_2$: 275.0461, found 275.0453. Anal. calcd. for $\text{C}_{11}\text{H}_{10}\text{ClN}_3\text{O}_2$: C 56.72, H 3.63, N 15.27; found: C 56.17, H 3.61, N 15.12.



(10r)-10-Bromo-5,8-dihydro-2-phenyl-5,8-methano-1H-[1,2,4]triazolo[1,2-a]pyridazine-1,3-(2H)-dione (83)

A solution of cyclopentadienylthallium (0.850 g, 3.15 mmol) and *N*-bromosuccinimide (0.561 g, 3.15 mmol) in diethyl ether (40 mL) under nitrogen was immersed in an ice bath and stirred for 1h. The resulting mixture was filtered through a glass wool plug on sintered glass into a solution of 4-phenyl-1,2,4-triazoline-3,5-dione (0.552 g, 3.15 mmol) in benzene (25 mL). The combined solutions were returned to the ice bath and stirred at -20°C for 22 h while gradually warmed to rt. Rotary evaporation of the solvent furnished a pale red product. ¹H NMR analysis of the crude product indicated 100% anti addition. (The structure of **83** was confirmed by X-ray analysis.) Flash chromatography afforded adduct **83** (0.552 g, 55%) as a colorless solid. Adduct **83** was recrystallized from 20% dichloromethane / hexane to give a colorless crystalline material: mp 170 - 170.5 °C; ν_{\max} : 2928, 1719, 1494, 1399, 1234, 1136 cm⁻¹; ¹H NMR (CDCl₃) δ : 7.45-7.34 (5H, m, C-2'H, C-3'H, C-4'H, C-5'H, C-6'H), 6.47 (2H, apparent t, J = 1.8 Hz, C-6'H, C-7'H), 5.15 (2H, dd, J = 1.9, 4.1 Hz, C-5'H, C-8'H), 4.51 (1H, t, J = 1.8 Hz, C-10'H); ¹³C NMR (CDCl₃) δ : 158.7 (C-1, C-3), 130.9 (C-1'), 129.6 (C-6, C-7), 128.7 (C-4'), 125.4 (C-2', C-6'), 68.9 (C-5,

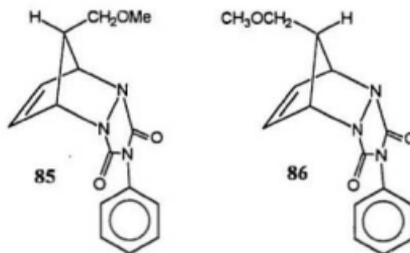
C-8), 55.2 (C-10); ms m/z (%): 321 (11), 319 (12) both M^+ , 240(28), 200 (6), 146 (62), 144 (64), 121 (20), 119 (50), 91 (19), 65 (100), 51 (8). Exact mass calcd. for: $C_{13}H_{10}N_3O_2$ (M^+ -Br): 240.0772, found 240.0757.



(10r)-5,8-Dihydro-10-iodo-2-phenyl-5,8-methano-1H-[1,2,4]triazolo[1,2-a]pyridazine-1,3(2H)-dione (84)

A solution of cyclopentadienylthallium (0.550 g, 2.04 mmol) and *N*-iodosuccinimide (0.460g, 2.04 mmol) in diethyl ether (25 mL) under nitrogen was immersed in an ice bath and stirred for 1 h. The resulting mixture was filtered through a glass wool plug on sintered glass into a solution of 4-phenyl-1,2,4-triazoline-3,5-dione (0.359 g, 2.04 mmol) in benzene (10 mL). The combined solutions were returned to the ice bath and stirred overnight in the absence of light while gradually warmed to rt. Rotary evaporation of the solvent gave a red solid. 1H NMR analysis indicated 100% anti addition. (The structure of was determined by X-ray analysis as **84**.) Flash chromatography afforded adduct **84** (0.260 g, 35%) as a beige solid, and crystallization from 30% ethyl acetate / hexane to gave **84** as colorless crystals: mp 133.0 - 134.0°C; ir ν_{max} : 1712, 1493, 1400 cm^{-1} ; 1H NMR ($CDCl_3$) δ : 7.44-7.34 (5H, m,

C-2'H, C-3'H, C-4'H, C-5'H, C-6'H), 6.47 (2H, apparent t, $J = 1.8$ Hz, C-6H, C-7H), 5.19 (2H, dd, $J = 1.7, 3.4$ Hz, C-5H, C-8H), 4.42 (1H, m, C-10H); ^{13}C NMR (CDCl_3) δ : 157.6 (C-1, C-3), 130.7 (C-6, C-7), 129.1 (C-1', C-3', C-5'), 128.6 (C-4'), 125.4 (C-2', C-6'), 70.2 (C-5, C-8), 30.0 (C-10); ms m/z (%): 367 (M^+ , 12), 24 (8), 240 (20), 192 (69), 177 (17), 151 (5), 119 (62), 91 (14), 65 (100). Exact mass calcd. for: $\text{C}_{13}\text{H}_{10}\text{N}_2\text{O}_2$; 366.9818, found 366.9799.



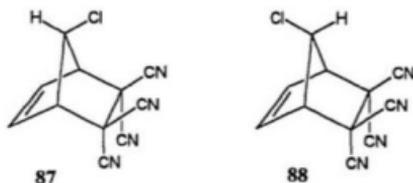
(10s)-5,8-Dihydro-10-methoxymethyl-2-phenyl-5,8-methano-1H-[1,2,4]-triazolo[1,2-a]pyridazine-1,3-(2H)-dione (85)
and
(10r)-5,8-Dihydro-10-methoxymethyl-2-phenyl-5,8-methano-1H-[1,2,4]-triazolo[1,2-a]pyridazine-1,3-(2H)-dione (86)

A solution of cyclopentadienylthallium (1.00 g, 3.71 mmol) and bromomethoxymethane (1.21 mL, 14.8 mmol) in diethyl ether (10 mL) under nitrogen was stirred for 5 h at -20°C . The resulting mixture was filtered through a glass wool plug on sintered glass into a solution of 4-phenyl-1,2,4-triazoline-3,5-dione (0.520 g, 2.04 mmol) in ethyl ether (10 mL). The combined solutions were stirred overnight at -20°C . Rotary evaporation of the solvent gave a pale yellow solid. ^1H NMR analysis indicated a ratio of 3.8 : 1 for **85** to **86** (

86 was not isolated). Flash chromatography afforded adduct **85** (0.511 g, 48%) as a white solid which contained a small amount of **86**, the minor anti diastereomer.

For **85**: mp 150 - 151.5 °C; ir ν_{\max} : 3085, 2929, 1713, 1493, 1396, 1244 cm^{-1} ; ^1H NMR (CDCl_3) δ : 7.47-7.36 (5H, m, C-2'H, C-3'H, C-4'H, C-5'H, C-6'H), 6.49 (2H, apparent t, $J = 1.9$ Hz, C-6H, C-7H), 4.98 (2H, dd, $J = 1.5, 3.3$ Hz, C-5H, C-8H), 3.52 (2H, d, $J = 6.7$ Hz, C-10 CH_2OCH_3), 3.38 (3H, s, C-10 CH_2OCH_3), 2.51 (1H, t, $J = 6.6$ Hz, C-10H); NOE results δ : 6.49: 4.98 (3%), 2.51 (2%), 4.98: 6.49 (3%), 3.52 (1.3%), 2.51 (6%), 3.52: 4.98 (2%), 2.51 (4%), 3.38: 4.98 (0.7%), 3.52 (1.0%), 2.51: 6.49 (0.8%), 4.98, (3%), 3.52 (1.3%); ^{13}C NMR (CDCl_3) δ : 158.7 (C-1, C-3), 132.3 (C-6, C-7), 131.2 (C-1'), 129.1 (C-3', C-5'), 128.4 (C-4'), 125.5 (C-2', C-6'), 69.2 (C-10 CH_2OCH_3), 65.6 (C-5, C-8), 60.4 (C-10 CH_2OCH_3), 59.2 (C-10); ms m/z (%): 285 (M^+ , 11), 255 (5), 253 (3), 177 (3), 119 (15), 91 (8), 78 (11), 45 (100). Exact mass calcd. for $\text{C}_{17}\text{H}_{15}\text{N}_3\text{O}_3$: 285.1112, found: 285.1102.

For **86**: (from mixture): ^1H NMR (CDCl_3) δ : 7.47 - 7.36 (5H, m, C-2'H, C-3'H, C-4'H, C-5'H, C-6'H), 6.38 (apparent t, $J = 1.8$ Hz, C-6H, C-7H), 5.01 (2H, dd, $J = 1.8, 3.6$ Hz, C-5H, C-8H), 3.30 (3H, s, C-10 CH_2OCH_3), 3.25 (2H, d, $J = 7.0$ Hz, C-10 CH_2OCH_3), 2.50 (1H, t, $J = 6.9$ Hz).

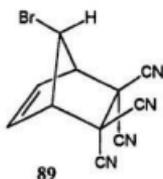


(7r)-7-Chloro-2,2,3,3,-tetracyanobicyclo[2.2.1]hept-5-ene (87)
and
(7s)-7-Chloro-2,2,3,3,-tetracyanobicyclo[2.2.1]hept-5-ene (88)

A solution of cyclopentadienylthallium (0.550 g, 2.05 mmol) and *N*-chlorosuccinimide (0.280 g, 2.04 mmol) in diethyl ether (20 mL) under nitrogen was immersed in an ice bath and stirred for 1 h. The resulting mixture was filtered through a glass wool plug on sintered glass into a solution of tetracyanoethylene (0.260 g, 2.04 mmol) in ethyl acetate (5.0 mL). The combined solutions were returned to the ice bath and stirred overnight, then gradually warmed to rt. Rotary evaporation of the solvent gave a brown solid. ¹H NMR analysis indicated a 2.3 : 1 ratio for **88** to **87**. Flash chromatography afforded adduct **88** (0.169 g, 36%) and **87** (0.80 g, 17%) as white solids. Adduct **88** was crystallized from 20% hexane / dichloromethane to give a colorless crystals: mp 206 - 207.5 °C; ir ν_{max} : 3029, 2982, 2255, 1338, 1271 cm⁻¹; ¹H NMR (CDCl₃) δ : 6.69 (2H, m, C-5H, C-6H), 4.44 (1H, apparent t, *J* = 0.9 Hz, C-7H), 4.09 (2H, dd, *J* = 2.0, 3.6 Hz, C-1H, C-4H); ¹³C NMR (CD₃COCD₃) δ : 136.2 (C-5, C-6), 112.7 (C-2CN, C-3CN), 111.9 (C-2CN, C-3CN), 68.1 (C-7), 60.8 (C-1, C-4), 46.0 (C-2, C-3); ms *m/z* (%): no M⁺, 193 (7), 166 (13), 102 (54),

101 (13), 100 (100), 76 (15), 65 (46), 64 (13), 63 (16), 51 (13), 50 (14). Exact mass calcd. for $C_{11}H_5^{35}ClN_4$ ($M^+ - Cl$): 193.0514, found 193.0514.

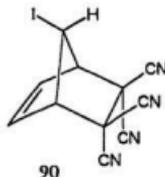
For **88**: mp 200 - 201 °C; ir ν_{max} : 3010, 2254, 1332, 1272 cm^{-1} ; 1H NMR ($CDCl_3$) δ : 6.79 (2H, apparent t, $J = 2.2$ Hz, C-5H, C-6H), 4.35 (1H, apparent t, $J = 1.5$ Hz, C-7H), 4.04 (2H, dd, $J = 1.9, 3.9$ Hz, C-1H, C-4H); ^{13}C NMR (CD_3COCD_3) δ : 140.0 (C-5, C-6), 113.0 (C-2CN, C-3CN), 111.8 (C-2CN, C-3CN), 66.2 (C-7), 59.6 (C-1, C-4), 46.3 (C-2, C-3); ms m/z (%): no M^+ , 193 (5), 166 (10), 139 (4), 128 (4), 102 (39), 101 (9), 100 (100), 76 (11), 65 (11), 63 (10), 50 (7). Exact mass calcd. for $C_{11}H_5N_4$ ($M^+ - Cl$): 193.0514, found 193.0506.



(7s)-7-Bromo-2,2,3,3-tetracyanobicyclo[2.2.1]hept-5-ene (89)

A solution of cyclopentadienylthallium (0.555 g, 2.06 mmol) and *N*-bromosuccinimide (0.367 g, 2.06 mmol) in diethyl ether (20 mL) under nitrogen was immersed in an ice bath and stirred for 1 h. The resulting mixture was filtered through a glass wool plug on sintered glass into a solution of tetracyanoethylene (0.263 g, 2.06 mmol) in ethyl acetate (10 mL). The combined solutions were returned to the ice bath and stirred overnight, then gradually warmed to rt. Rotary evaporation of the solvent gave a black solid. 1H NMR

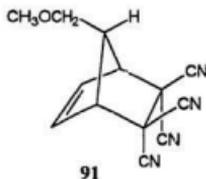
analysis indicated 100% anti addition. (The structure was confirmed by X-ray analysis as **89**.) Flash chromatography afforded adduct **89** (0.269 g, 48%) a white solid, which was crystallized from 15% hexane / dichloromethane to give colorless crystals: mp 215.5 - 217 °C; ν_{max} : 3104, 3025, 2984, 2254, 1336, 1268 cm^{-1} ; $^1\text{H NMR}$ (CD_3COCD_3) δ : 6.80 (2H, apparent t, $J = 2.0$ Hz, C-5H, C-6H), 4.48 (1H, s, C-7H), 4.13 (2H, dd, $J = 1.8, 3.5$ Hz, C-1H, C-4H); $^{13}\text{C NMR}$ (CD_3COCD_3) δ : 137.3 (C-5, C-6), 113.0 (C-2CN, C-3CN), 112.1 (C-2CN, C-3CN), 61.4 (C-1, C-4), 56.7 (C-7), 45.9 (C-2, C-3); $\text{ms } m/z$ (%): no M^+ , 193 (5), 166 (12), 146 (73), 144 (75), 128 (10), 102 (64), 76 (17), 75 (11), 65 (100), 50 (11). Exact mass calcd. for $\text{C}_{11}\text{H}_3\text{N}_4$ ($\text{M}^+ - \text{Br}$): 193.0514, found 193.0515.



(7s)-2,2,3,3-tetracyano-7-iodo-bicyclo[2.2.1]hept-5-ene (90)

A solution of cyclopentadienylthallium (0.500 g, 1.93 mmol) and *N*-iodosuccinimide (0.434 g, 1.93 mmol) in diethyl ether (20 mL) under nitrogen was immersed in an ice bath and stirred for 1 h. The resulting mixture was filtered through a glass wool plug on sintered glass into a solution of tetracyanoethylene (0.220 g, 1.71 mmol) in ethyl ether (10 mL). The combined solutions were returned to the ice bath and stirred overnight in the absence of light, then gradually warmed to rt. Rotary evaporation of the solvent gave a black solid. $^1\text{H NMR}$ analysis indicated 100% anti addition. Flash chromatography through a column

containing charcoal and SiO₂ afforded adduct **90** (0.260 g, 42%) as a white solid, which was crystallized from 15% hexane / dichloromethane to give colorless crystals: mp 186.0 - 188.5 °C; ir ν_{max} : 3092, 3018, 2252, 1333, 1254, 1205 cm⁻¹; ¹H NMR (CDCl₃) δ : 6.71 (2H, m, C-5H, C-6H), 4.44 (1H, apparent d, $J = 0.8$ Hz, C-7H), 4.11 (2H, dd, $J = 1.5, 3.2$ Hz, C-1H, C-4H); ¹³C NMR (CD₃COCD₃) δ : 139.1 (C-5, C-6), 113.4 (C-2CN, C-3CN), 112.2 (C-2CN, C-3CN), 63.2 (C-1, C-4), 44.9 (C-2, C-3), 30.3 (C-7); ms m/z (%): no M⁺, 320 (8), 193 (3), 192 (47), 166 (4), 128 (13), 102 (3), 76 (13), 65 (100). Exact mass calcd. for C₁₁H₇N₄ (M⁺ - 1): 193.0514, found 193.0515. Anal. calcd. for C₁₂H₉N₄: C 41.28, H 1.57, N 17.50; found: C 41.27, H 1.58, N 17.68.



(7s)-2,2,3,3-tetracyano-7-methoxymethyl-bicyclo[2.2.1]hept-5-ene (91)

A solution of cyclopentadienylthallium (0.450 g, 1.67 mmol) and bromomethoxymethane (0.54 mL, 6.68 mmol) in THF (10 mL) under nitrogen was stirred for 3.5 h at -20°C. The resulting mixture was filtered through a glass wool plug on sintered glass into a solution of tetracyanoethylene (0.214 g, 1.67 mmol) in ethyl ether (10 mL). The combined solutions were stirred for 1 h at -20°C. Rotary evaporation of the solvent afforded a pale red solid. ¹H NMR analysis indicated 100% anti addition as to give **91**. The crude material was

recrystallized from dichloromethane using charcoal to afford **91** (0.211 g, 53%) as colorless crystals: mp 143 - 144 °C; ir ν_{max} : 2924, 2267, 1547, 1331, 1107 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ : 6.61 (2H, m, C-5H, C-6H), 3.92 (2H, dd, $J = 1.7, 3.4$ Hz, C-1H, C-4H), 3.34 (2H, d, $J = 7.0$ Hz, C-7 CH_2OCH_3), 3.30 (3H, s, C-7 CH_2OCH_3), 2.92 (1H, t, $J = 6.9$ Hz, C-7H); NOE results δ : 6.61: 3.92 (3%), 3.34 (0.6%), 3.92: 6.61 (3%), 3.34 (1%), 2.92 (4%), 3.34: 6.61 (0.8%), 3.92 (2%), 2.92 (6%), 3.30: 6.61 (0.4%), 3.92 (0.9%), 2.92 (3%), 2.92: 3.92 (2%), 3.34 (0.8%); $^{13}\text{C NMR}$ (CD_3COCD_3) δ : 136.6 (C-5, C-6), 113.9 (C-2CN, C-3CN), 112.9 (C-2CN, C-3CN), 68.9 (C-7 CH_2OCH_3), 59.4 (C-1, C-4), 59.3 (C-7), 58.5 (C-7 CH_2OCH_3), 48.2 (C-2, C-3); ms m/z (%): no M^+ , 179 (15), 173 (39), 141 (20), 128 (42), 110 (100), 109 (73), 95 (32), 79 (56), 76 (51), 58 (23). Anal. calcd. for $\text{C}_{11}\text{H}_{10}\text{N}_4\text{O}$: C 65.54, H 4.23, N 23.52; found: C 65.22, H 4.19, N 23.55.

Attempts to prepare adducts of **92**, **93** and **94**

A solution of 1,3-cyclopentadiene in THF under a nitrogen atmosphere was treated with *n*-butyllithium (1.1 molar equivalents) at 0°C and stirred for 10 min. The resulting cloudy solution was added dropwise over 20 min to a -20°C solution of acetyl bromide, cyanogen bromide or dimethyldisulfide (2-5 molar equivalents) in THF under nitrogen. The reaction mixture was stirred for up to 30 h at -20°C, transferred to a separatory funnel and quickly washed with cold brine. *N*-Phenylmaleimide, tetracyanoethylene or 4-phenyl-1,2,4-triazoline-3,5-dione was added to the organic layer and the resulting solution was stirred at -20°C for up to 48 h, washed with water and dried over anhydrous MgSO_4 . Rotary

evaporation of the solvent furnished only starting materials and other materials unidentifiable by NMR.

Attempts to prepare adduct(s) of 95

A solution of cyclopentadienylthallium and *N*-iodosuccinimide (1 molar equivalent) in diethyl ether under nitrogen was immersed in an ice bath and stirred for 1 h. The resulting mixture was filtered through a glass wool plug on sintered glass into a solution of lithium acetylide, ethylenediamine complex (1.5 molar equivalents) in THF, and the reaction mixture was stirred at -20°C for up to 30 h. *N*-Phenylmaleimide, tetracyanoethylene or 4-phenyl-1,2,4-triazoline-3,5-dione (1 molar equivalent) was added to the reaction mixture and the resulting solution stirred for up to 48 h. Rotary evaporation of the solvent furnished only starting materials and other material unidentifiable by NMR.

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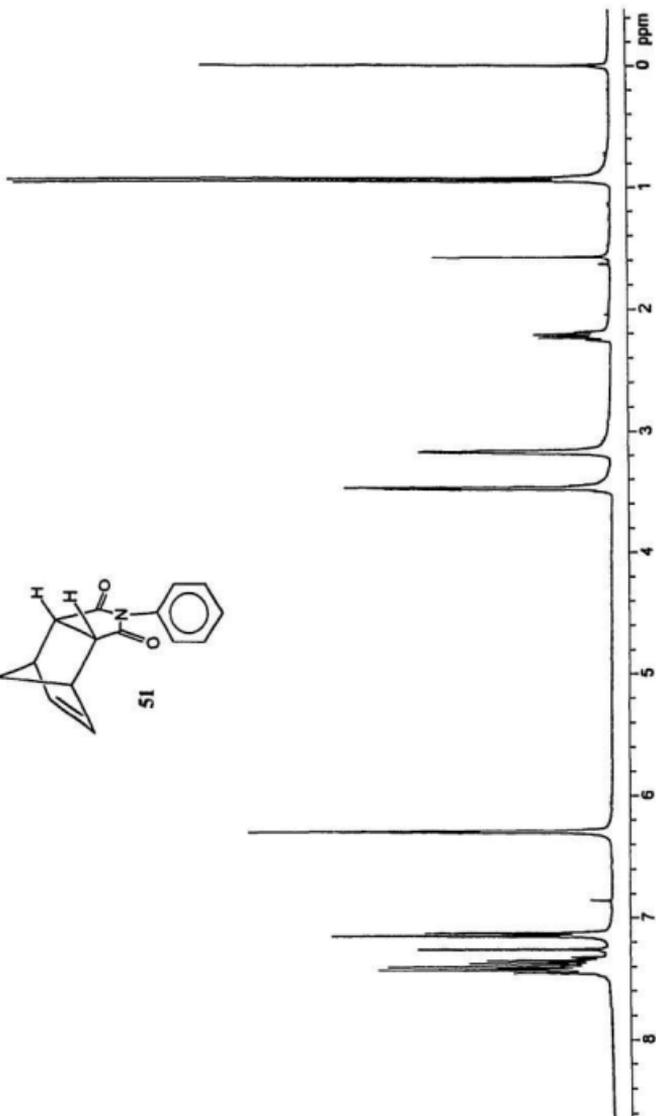
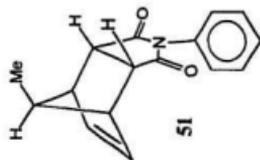
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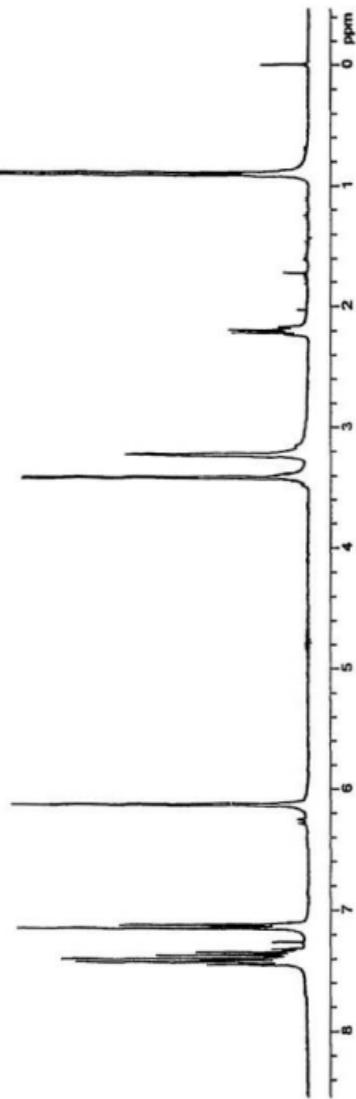
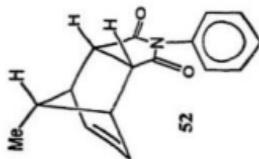
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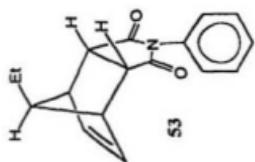
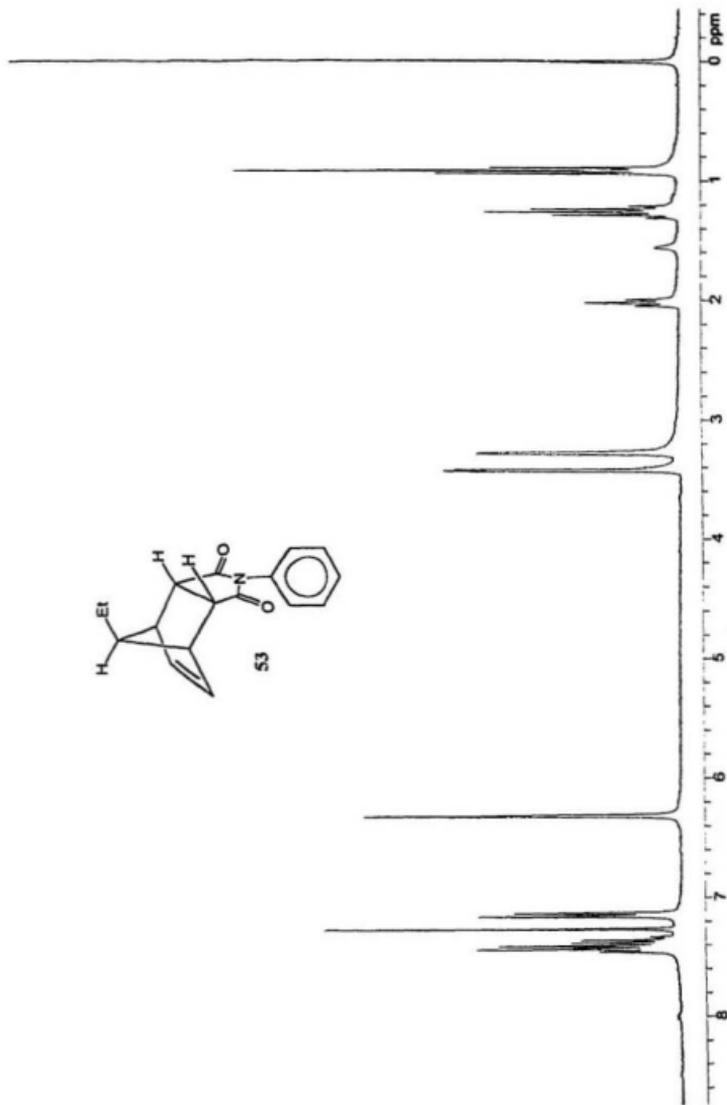
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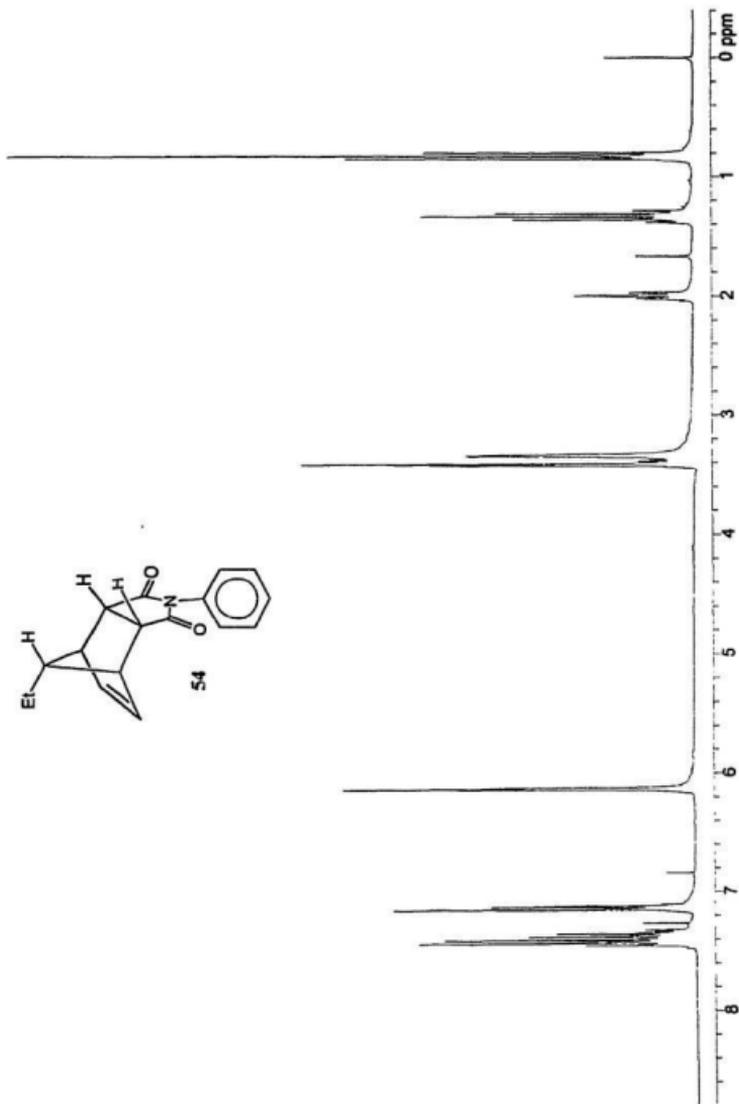
Appendix

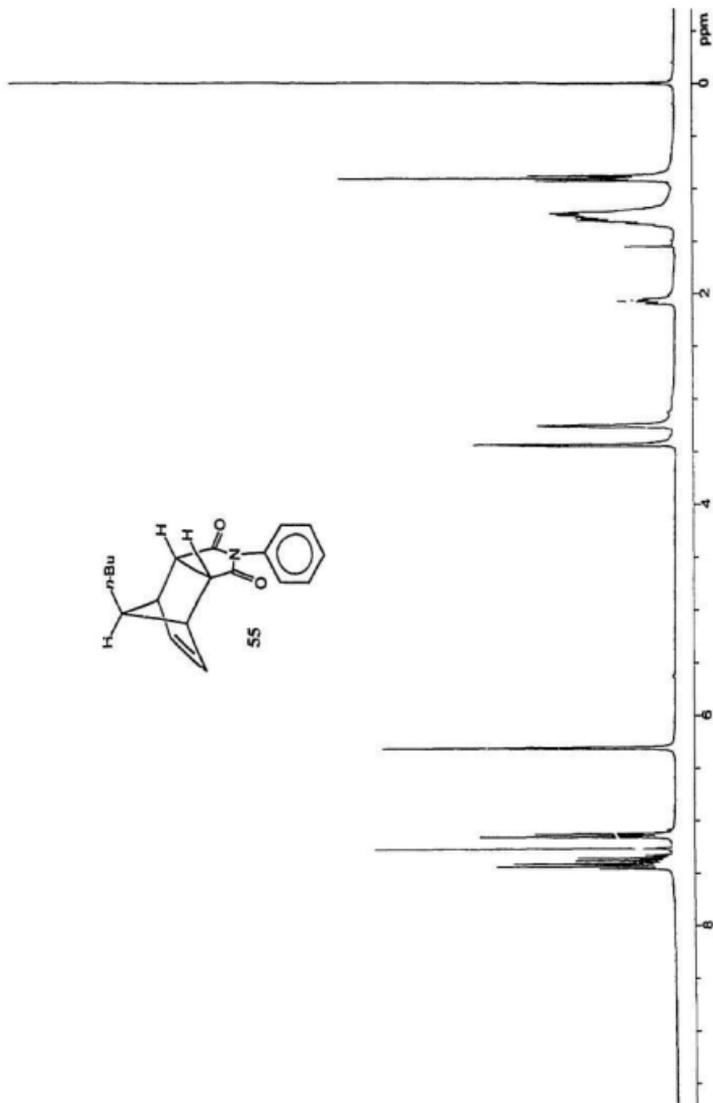
Selected ^1H NMR spectra of adducts are arranged in the order in which they appear in the text. For the instrument and conditions employed see Experimental - General.

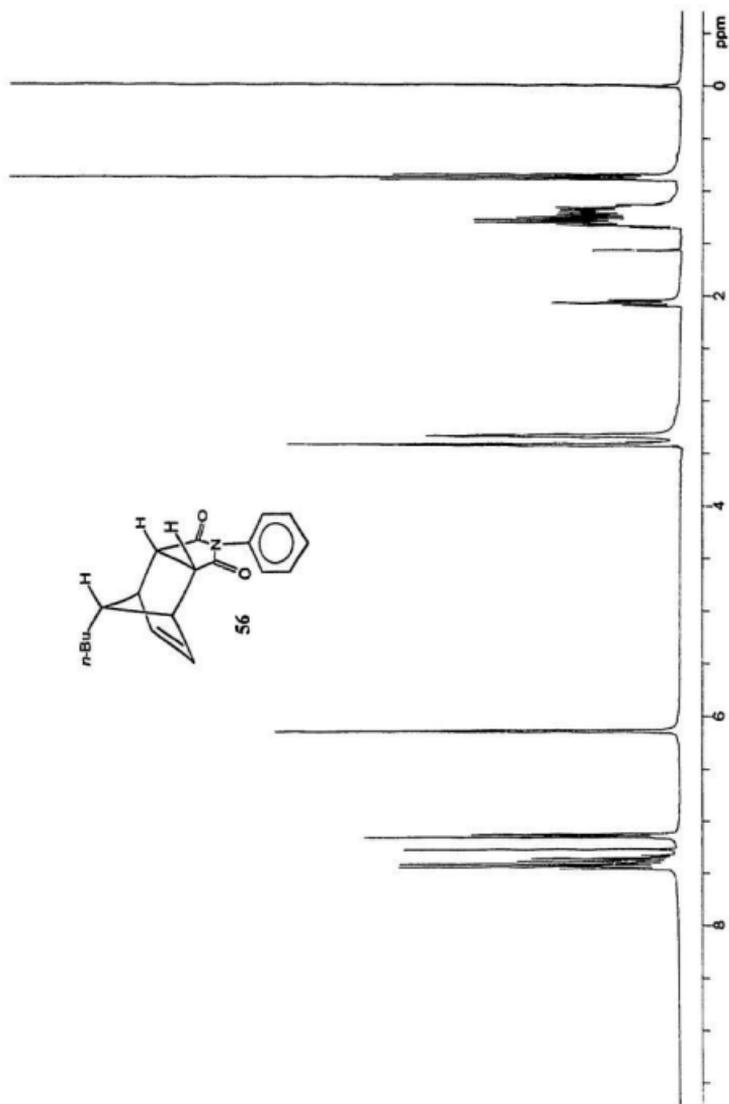


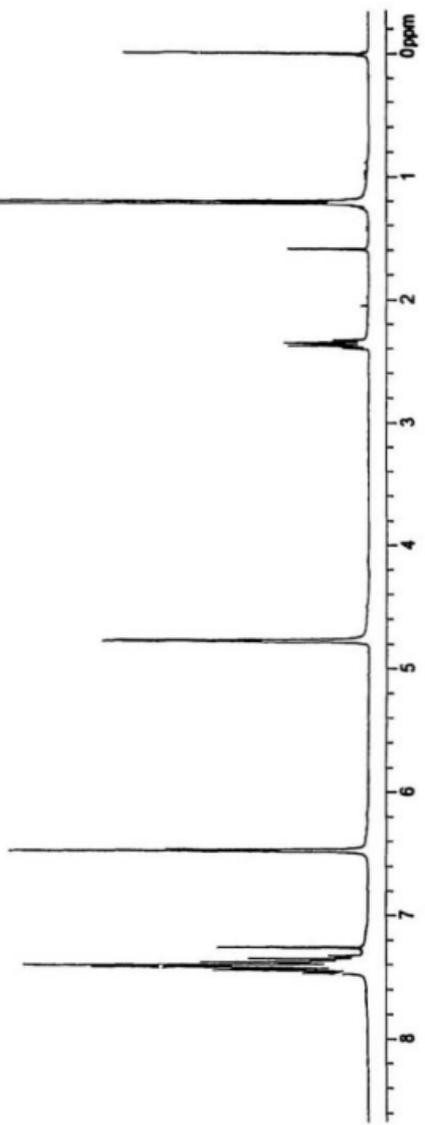
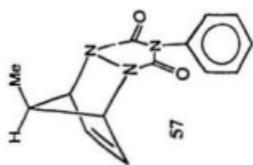


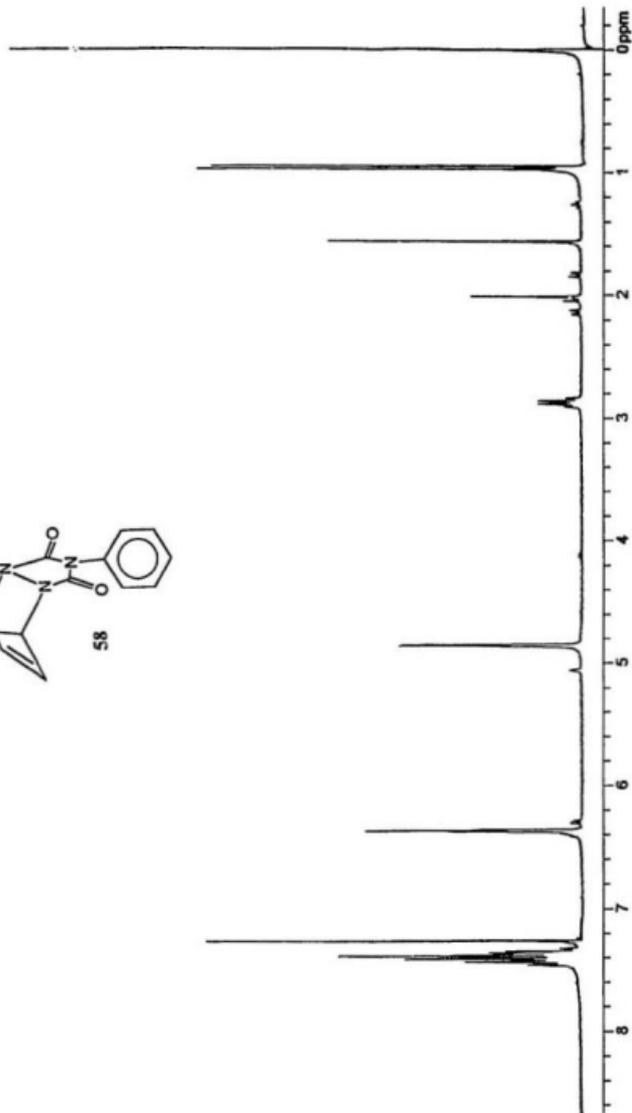
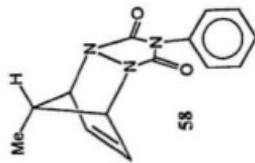


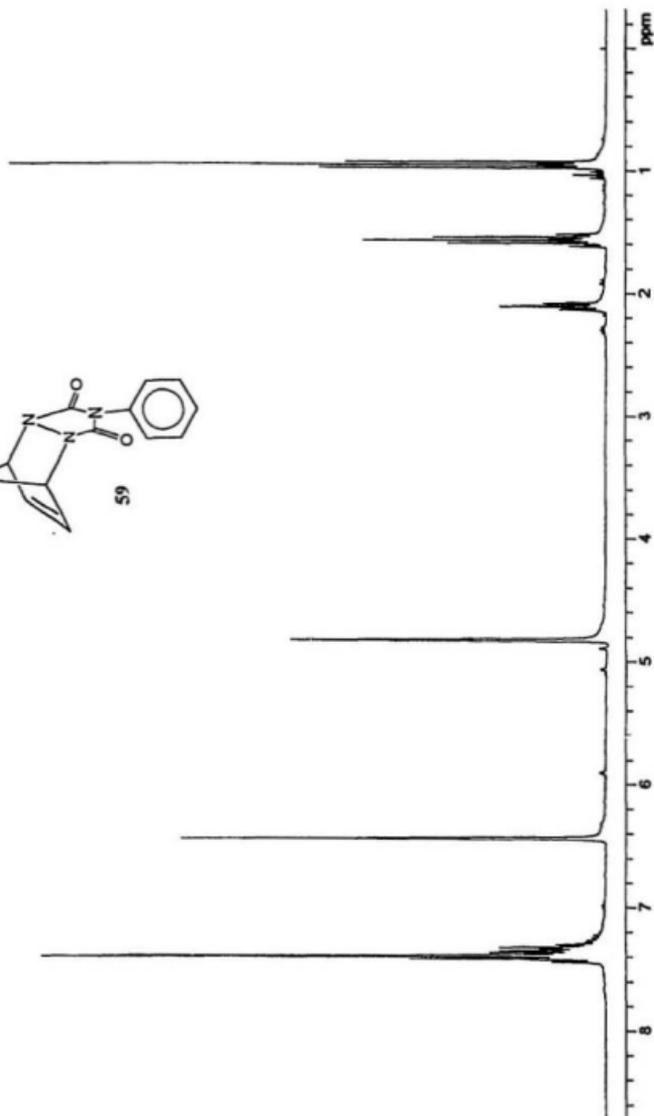
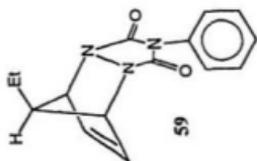


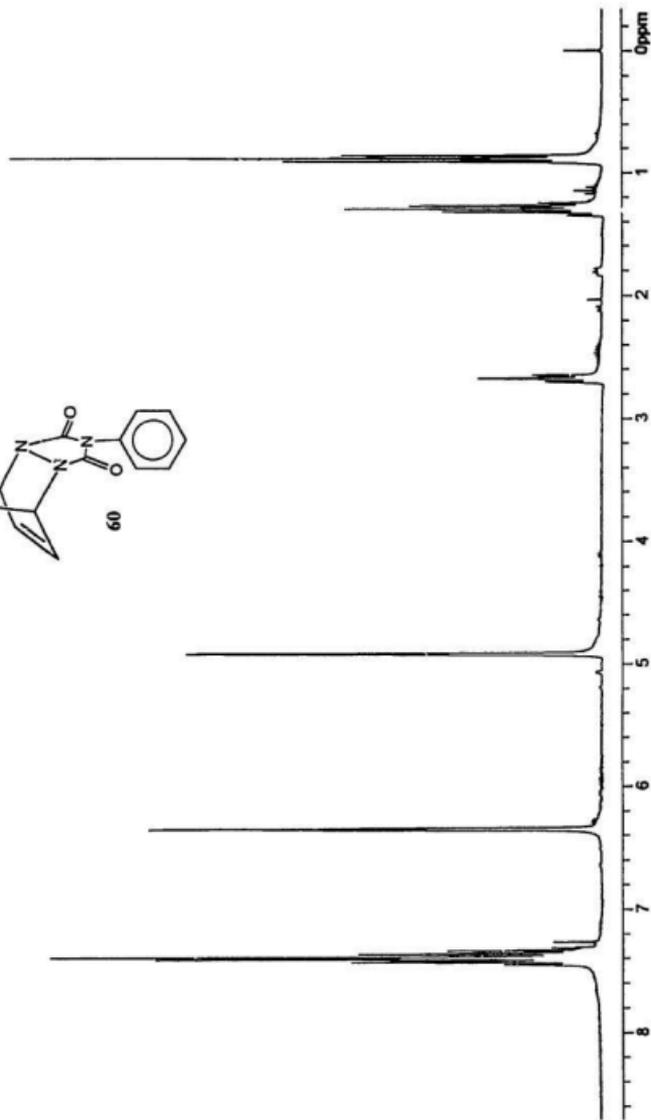
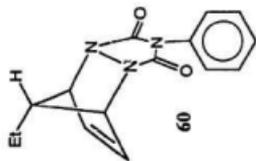


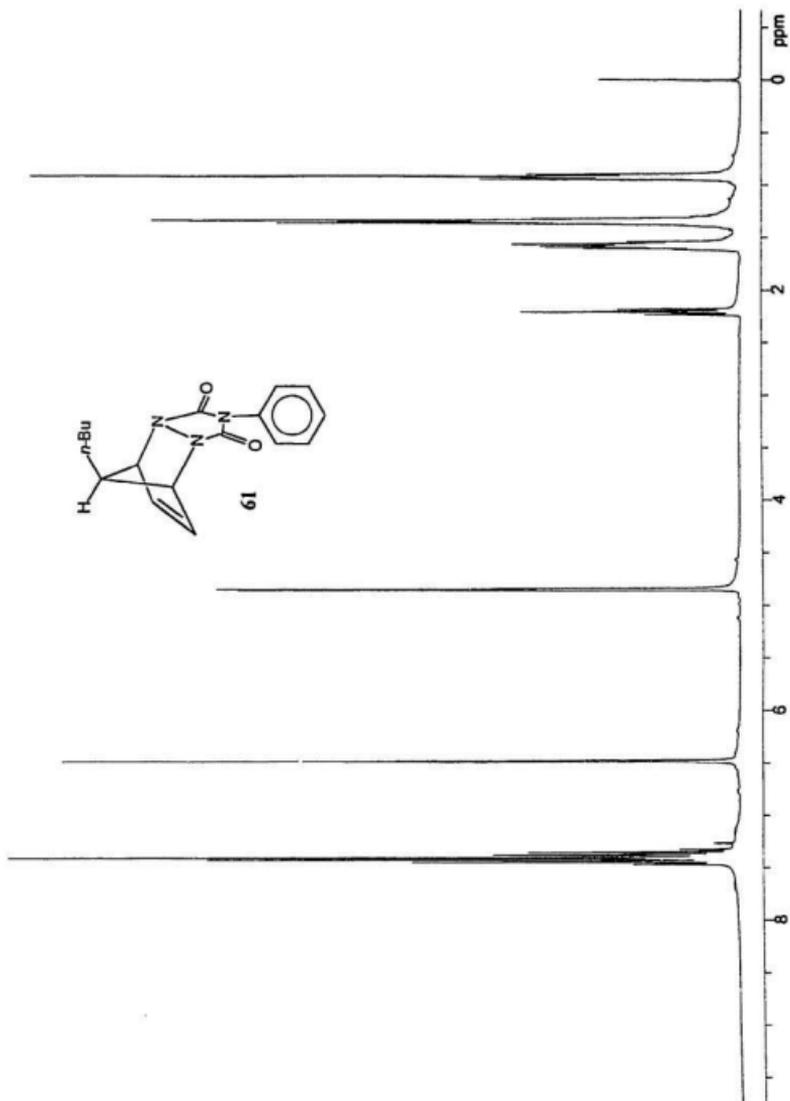


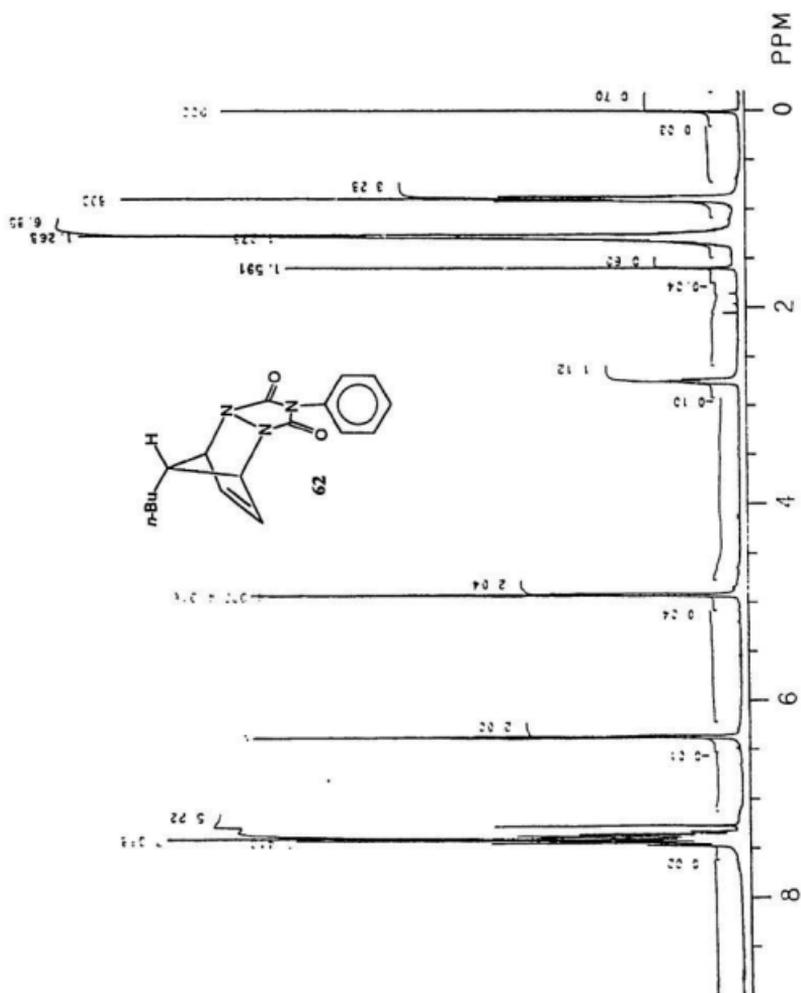


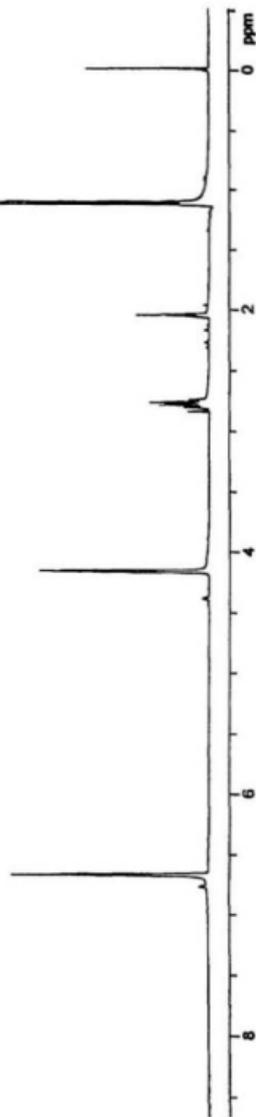
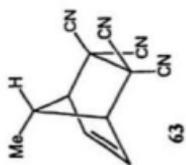


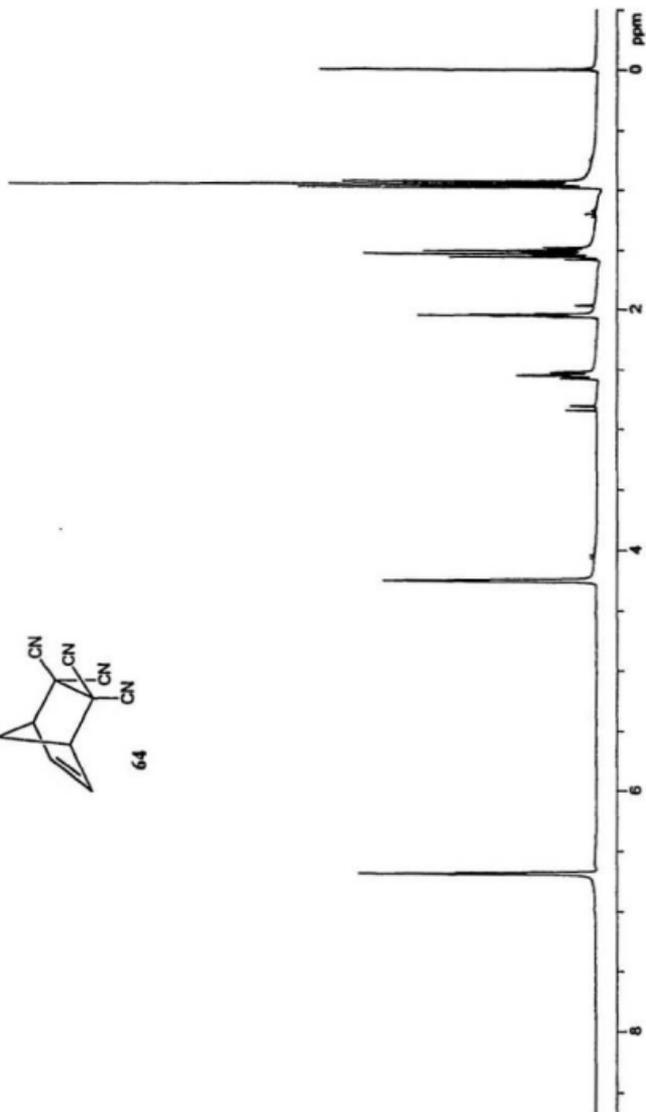
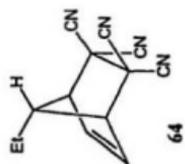


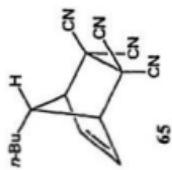
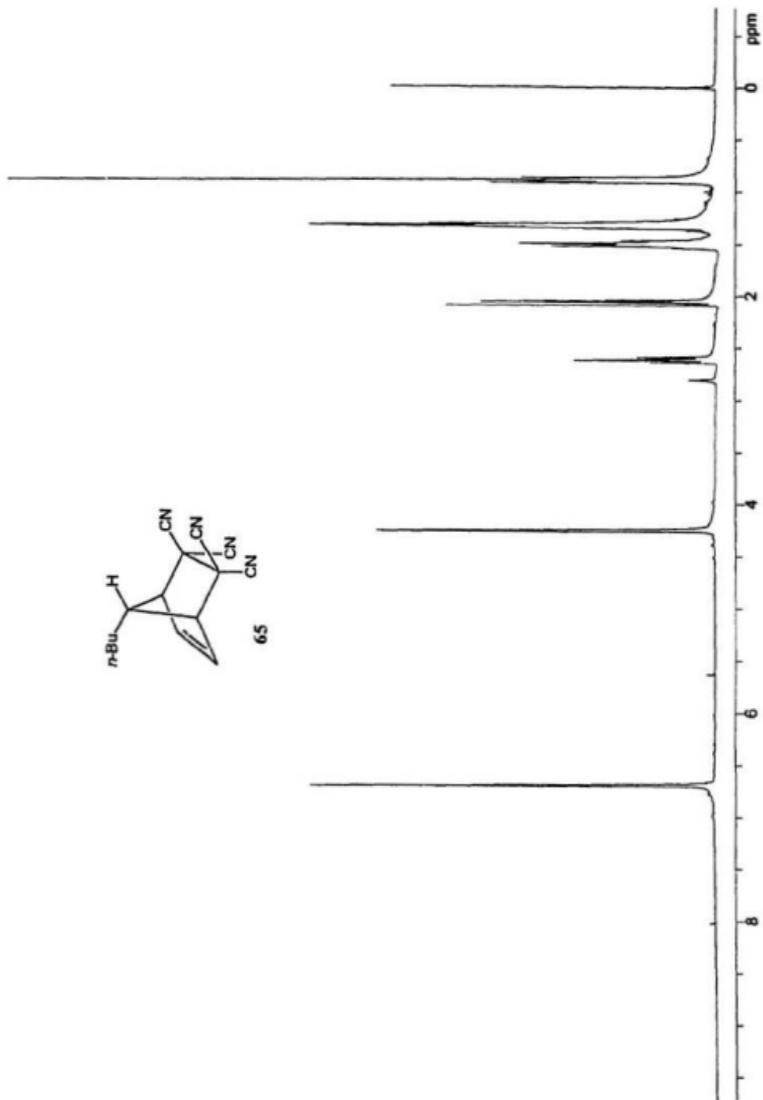


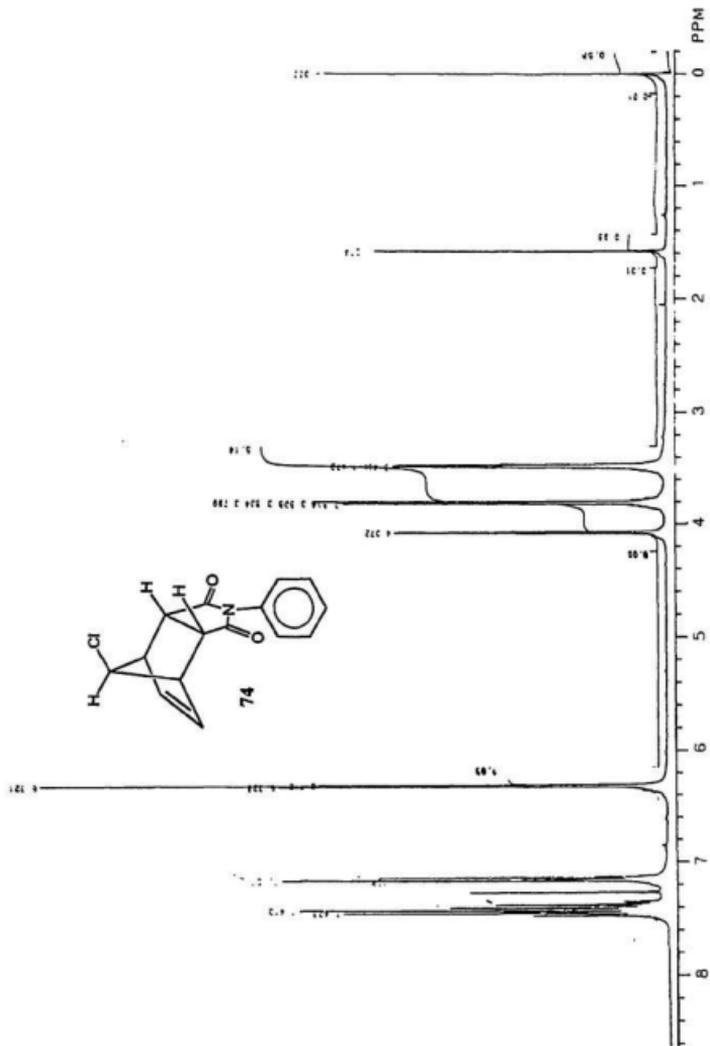


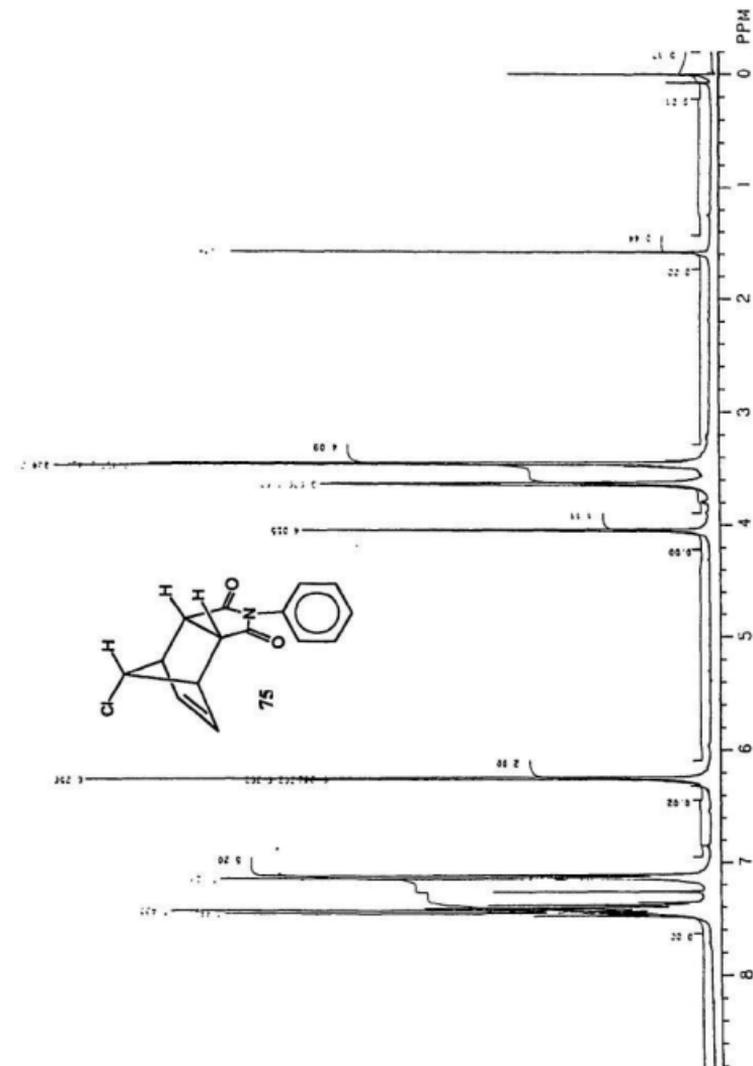


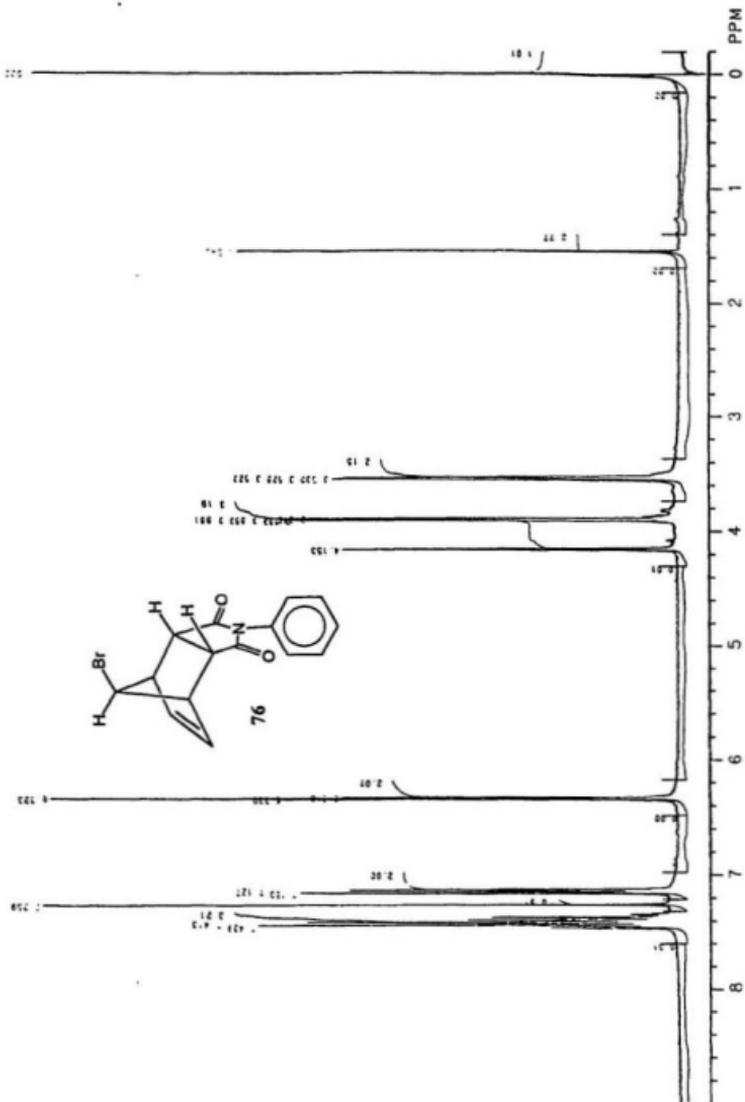


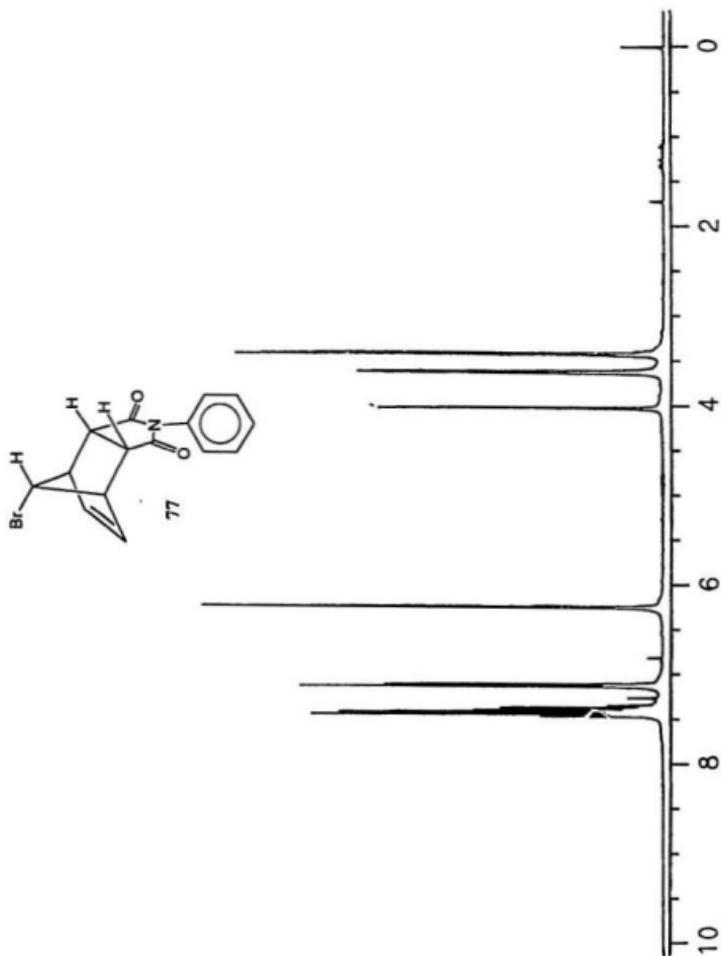


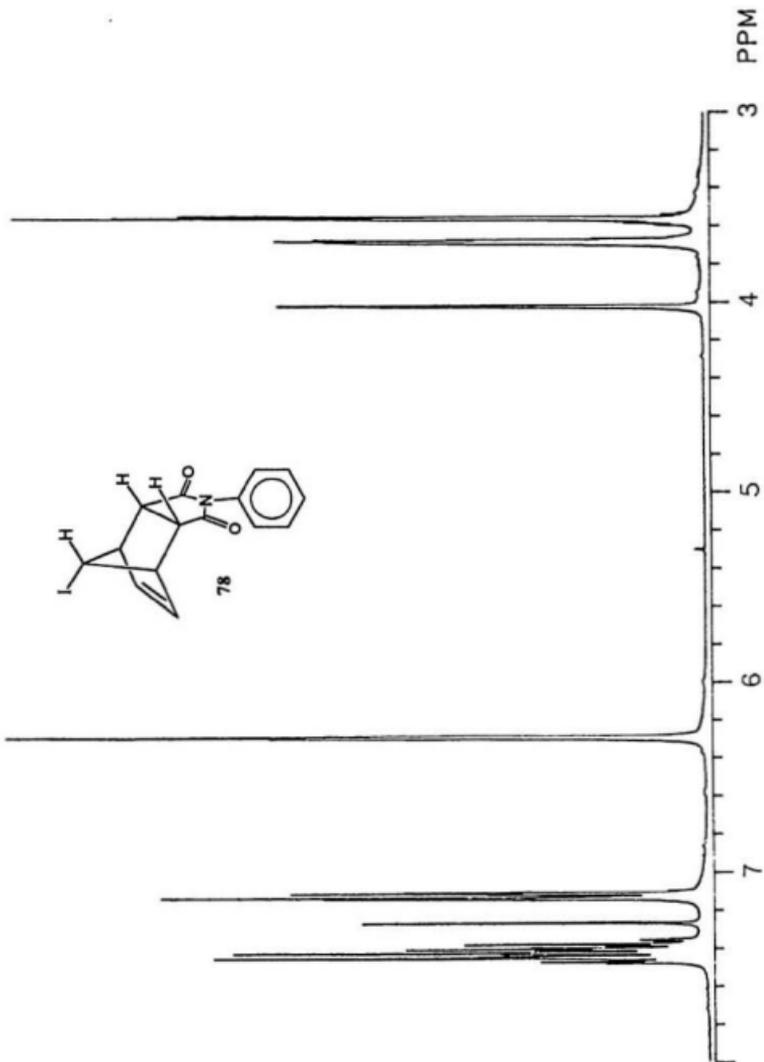


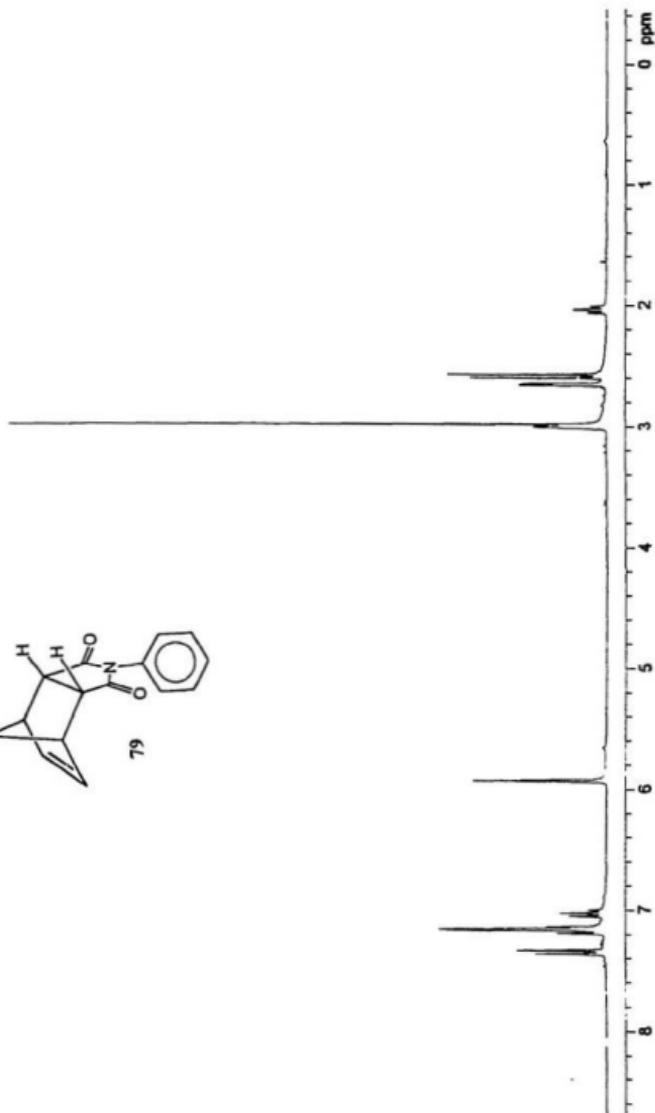
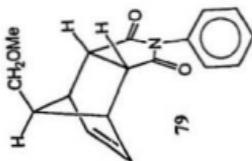


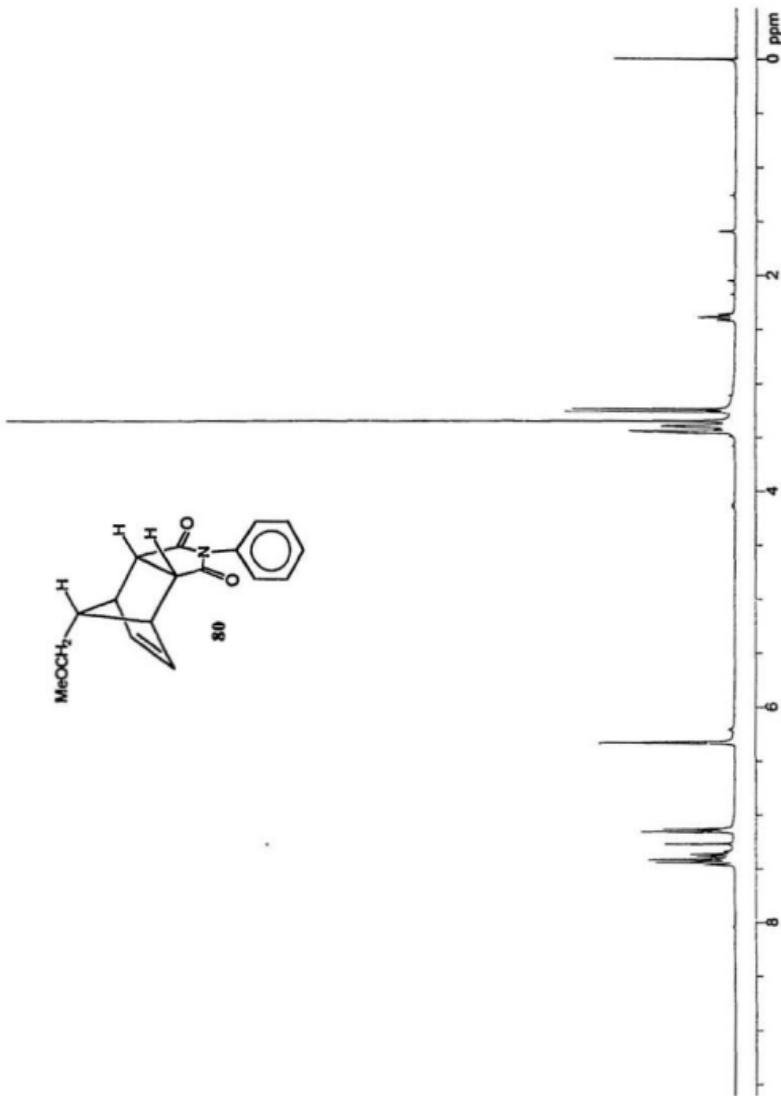


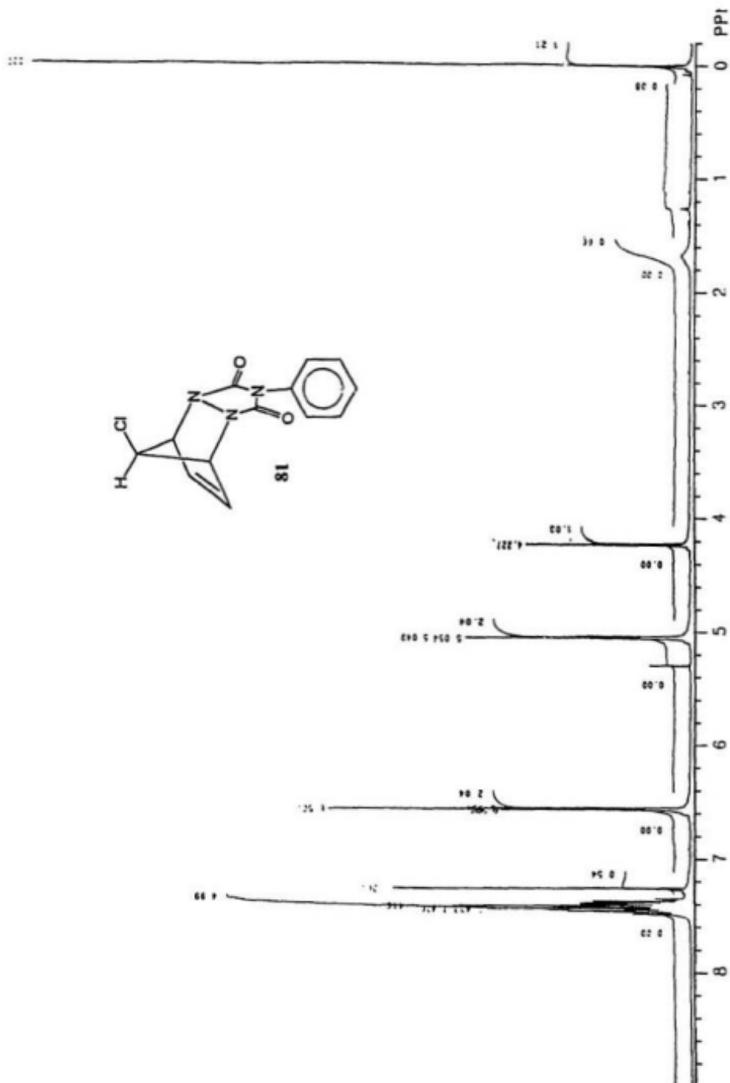


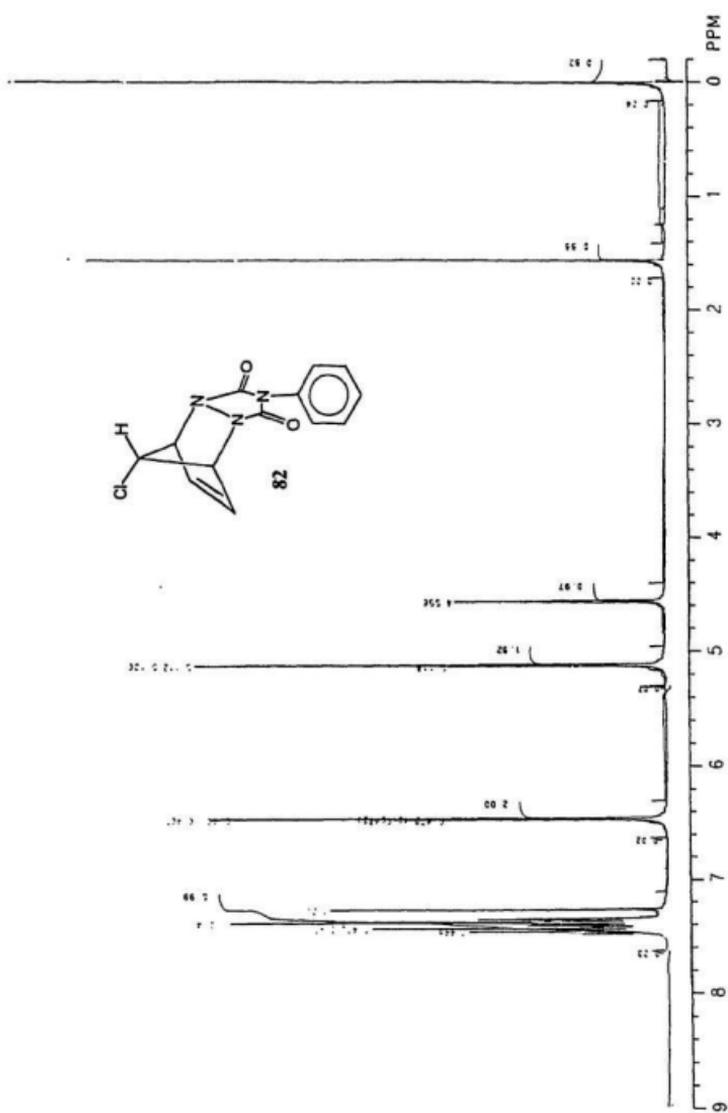


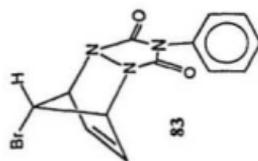












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