I. ALL CARBON INVERSE-ELECTRON-DEMAND DIELS-ALDER REACTIONS: EXPLORATION OF THE CHEMISTRY OF AN ELECTRON DEFICIENT DIENE

II. SYNTHESIS OF SOME 6,15-DISUBSTITUTED 2,11-DITHIA [3.3] METACYCLOPHANES

JONATHAN D. LANGILLE

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II. SYNTHESIS OF SOME 6,15-DISUBSTITUTED 2,11-DITHIA[3.3]METACYCLOPHANES

by

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Abstract

Dienes which bear electron withdrawing groups at the 1- and 3- positions are formal electronic complements of dienes such as Danishefsky's diene. Surprisingly, the inverse-electron-demand Diels-Alder (IEDDA) chemistry of these types of dienes has received little attention in the literature to date. The synthesis of (2*E*)-3-(1'-oxo-2'-cyclohexen-2'-yl)-1-phenyl-2-propen-1-one (**102**), a novel electron deficient diene substituted in the 1- and 3-positions with electron withdrawing groups, is discussed. This diene and, to a greater extent, its direct synthetic precursor acetal (**101**) are stable when stored under nitrogen at -20 °C, allowing them to be isolated and stored for later use. Like other electron deficient dienes prepared previously in our laboratory, the diene acetal (**101**) was observed to participate in a normal-electron-demand Diels-Alder reaction, while the deprotected diene (**102**) underwent IEDDA reactions with a variety of electron rich dienophiles, including ethyl vinyl ether, 2-(trimethylsilyl)oxy-3,4-dihydrofuran (**127**), and 1,1-diethoxyethene (**131**).

The use of enamines as dienophiles led to the formation of dihydronaphthalenones. A domino IEDDA-elimination-dehydrogenation reaction is postulated to account for the formation of these products. The dehydrogenation was proposed to be a result of hydrogen transfer to excess dienophile or other unsaturated species present during the reaction.

The chemistry of two additional dienes, 7-benzoyl-6-ethoxy- (**133**) and 7-benzoyl-6-hydroxy-3,4,4a,5-tetrahydro-1(*2H*)-naphthalenone (**167**), derived from the IEDDA adduct of diene **102** with **131**, was also examined. The ethoxy substituted diene (**133**) was observed to oxidize in the presence of a range of potential dienophiles, and the hydroxy substituted diene (**167**) was unreactive as a diene in an IEDDA cycloaddition under the conditions investigated.

As part of a cooperative effort within our group to study the solution state conformational preferences of substituted 2,11-dithia[3.3]metacyclophanes, 6,15-dibromo- (**198**) and 6,15-diiodo-2,11-dithia[3.3]metacyclophane (**199**), as well as 2,11-dithia[3.3]metacyclophane (**192**) have been synthesized. The 6,15-difluoro- (**196**) and 6,15-dichloro-2,11-dithia[3.3]metacyclophanes (**197**) were also targeted for synthesis, however the Na_2S/Al_2O_3 coupling technique used was unsuccessful for these compounds. The attempt to prepare the dichloro- substituted cyclophane (**197**) resulted in the isolation of the trimer, 6,15,24-trichloro-2,11,20-trithia[3.3.3]metacyclophane (**211**), in modest yield.

Acknowledgments

I would like to offer true thanks to everyone who had any involvement during the research and preparation that went into this thesis. Deepest gratitude goes to my supervisor Dr. Graham Bodwell, whose knowledge and unequaled enthusiasm were of tremendous benefit. To all the members of the Bod group over the past two and a half years, it has been a privilege to work with and share in an atmosphere contributed to by all of you.

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For funding, I owe appreciation to the School of Graduate Studies, the Department of Chemistry, and again, special thanks to Graham. Regards go to the Natural Sciences and Engineering Research Council (NSERC) of Canada, Petro-Canada, and the Xerox Research Centre of Canada who supply the funding to our group.

Finally, and most importantly, thanks goes to Rhea. I could never have made it through all this without you being there along with me. Thanks so much, I love you.

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List of Abbreviations and Symbols

Ac	acetyl (ethanoyl)
Ad	adamantyl
Anal.	elemental analysis
APT	attached proton test
BOC	*tert*-butyloxycarbonyl
CBz	carbobenzoxy
COSY	correlated spectroscopy
Cy	cyclohexyl
δ	chemical shift
d	doublet
D	Debyes
Δδ	change in chemical shift
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
dd	doublet of doublets
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
d.e.	diastereomeric excess
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
e.e.	enantiomeric excess

EDG	electron donating group
Et	ethyl
eV	electron volts
EWG	electron withdrawing group
FT	Fourier transform
FVT	flash vacuum thermolysis
g	gram(s)
GC	gas chromatography
H_{ax}	axial hydrogen
H_e	external hydrogen
H_{eq}	equatorial hydrogen
H_i	internal hydrogen
HETCORR	heteronuclear correlated spectroscopy
hfc	3-(heptafluoropropylhydroxymethylene)camphorate
HOMO	highest occupied molecular orbital
Hz	hertz
h	hour(s)
IEDDA	inverse-electron-demand Diels-Alder
IR	infrared (spectroscopy)
J	coupling constant (*J* value)
kcal	kilocalorie(s)
lit.	literature value

LUMO	lowest unoccupied molecular orbital
M	molar (moles per litre)
M^+	molecular ion (MS)
m	multiplet (NMR); medium (IR)
***m*-CPBA**	*meta*-chloroperoxybenzoic acid
Me	methyl
mg	milligram(s)
MHz	megahertz
min	minute(s)
mL	millilitre(s)
mmol	millimole(s)
mm Hg	millimetre(s) of mercury
mol	mole(s)
m.p.	melting point
MS	mass spectrometry
m/z	mass to charge ratio
Naph	naphthyl
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance (spectroscopy)
NOE-D	nuclear Overhauser effect by difference (spectroscopy)
NPM	*N*-phenylmaleimide
ppm	parts per million

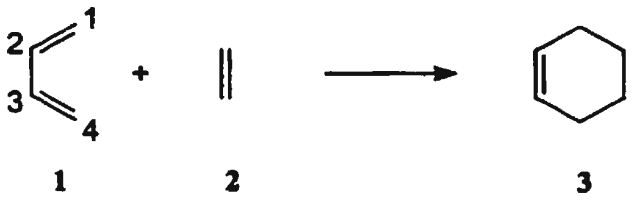
***p*-TSA**	***p*-toluenesulfonic acid**
R_f	**retention factor**
r.t.	**room temperature**
s	**singlet (NMR); strong (IR)**
t	**triplet**
TBS	***tert*-butyldimethylsilyl**
***t*-BuOK**	**potassium *tert*-butoxide**
td	**triplet of doublets**
Tf	**trifluoromethanesulfonoyl**
tfc	**3-(trifluoromethylhydroxymethylene)camphorate**
THF	**tetrahydrofuran**
TLC	**thin layer chromatography**
TMS	**trimethylsilyl**
ν	**wavenumbers (cm^{-1})**

I. ALL CARBON INVERSE-ELECTRON-DEMAND DIELS-ALDER REACTIONS: EXPLORATION OF THE CHEMISTRY OF AN ELECTRON DEFICIENT DIENE

1.0 Introduction

1.1 Diels-Alder Cycloadditions

The Diels-Alder reaction, first described in detail by Otto Diels and Kurt Alder,[1] has undoubtedly become one of the most versatile and powerful tools for the synthetic organic chemist and a great deal of knowledge has been accumulated regarding the factors controlling this reaction.[2] The Diels-Alder cycloaddition reaction is illustrated by the parent reaction of 1,3-butadiene (**1**) with ethylene (**2**) giving cyclohexene (**3**).



1 **2** **3**

Scheme 1.1: Diels-Alder cycloaddition.

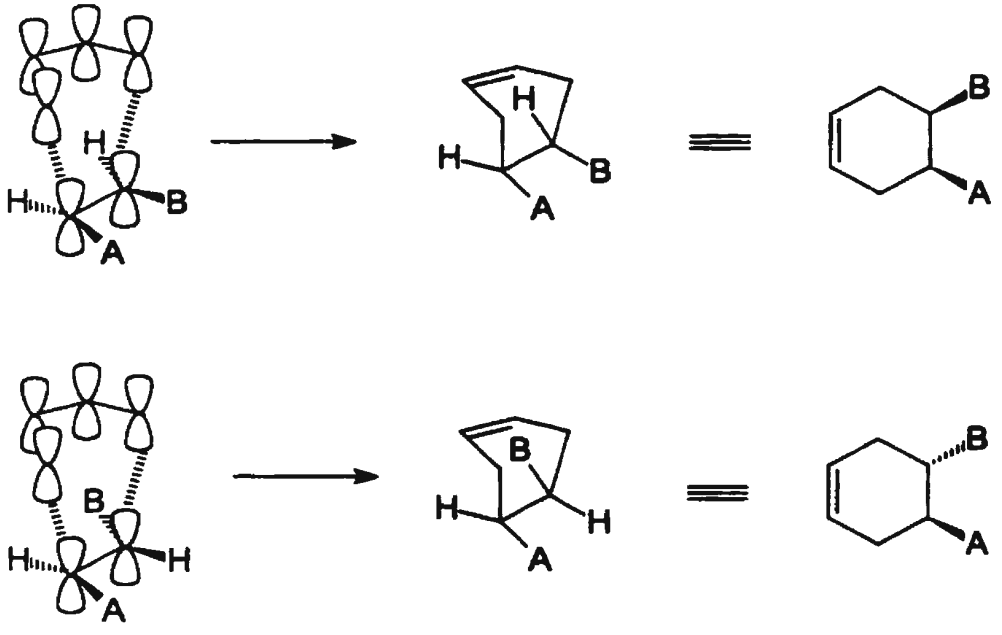
The Diels-Alder reaction is described as a [4π + 2π] pericyclic reaction, that is the reaction proceeds by simultaneous reorganization of the π-electrons between the reacting species, rather than bond formation and bond breaking that occurs in two or more steps.

---

[1] Diels, O.; Alder, K. *Justus Liebigs Ann. Chem.* **1928**, *460*, 98-122.

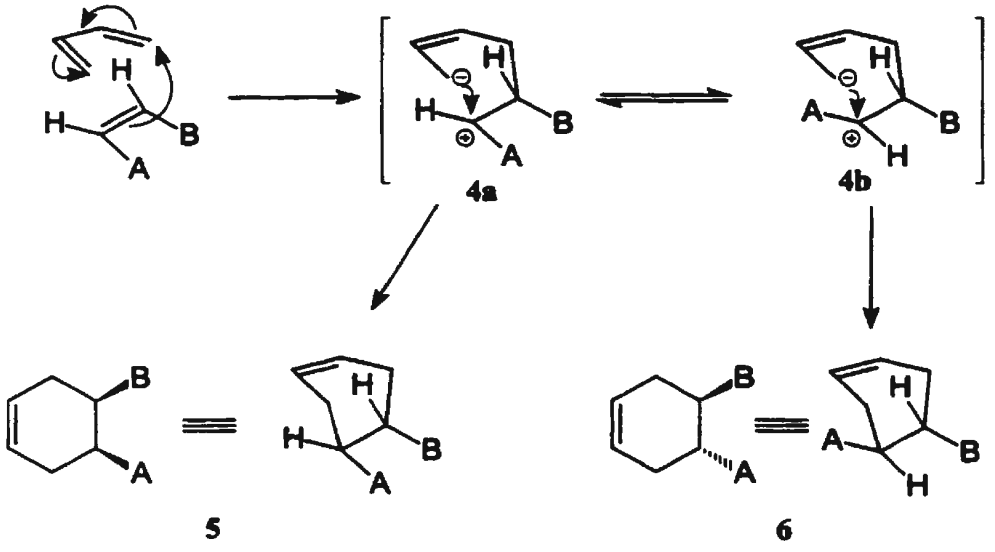
[2] Norton, J.A. *Chem. Rev.* **1942**, *31*, 319-523.; Martin, J.G.; Hill, R.K. *Chem. Rev.* **1961**, *61*, 537-562.; Sauer, J. *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 211-230.; Sauer, J. *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 16-33.; Kwart, H.; King, K. *Chem. Rev.* **1968**, *68*, 415-447.; Sauer, J.; Sustmann, R. *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 779-807.; Pancir, J. *J. Am. Chem. Soc.* **1982**, *104*, 7424-7430.; Gleiter, R.; Böhm, M.C. *Pure Appl. Chem.* **1983**, *55*, 237-244.

The reaction proceeds by suprafacial addition in both components. That is to say that the lobes of the interacting orbitals of the alkene, referred to as the dienophile, and those of the diene are on the same face of the respective π-systems. This arrangement is responsible for the stereochemical consequences of the Diels-Alder reaction, such as the preservation of the relative stereochemistry of the diene and dienophile.



Scheme 1.2: Suprafacial addition and conservation of relative stereochemistry.

The preservation of this relative stereochemistry is evidence that the Diels-Alder cycloaddition is a pericyclic, or concerted reaction. A stepwise mechanism might proceed through an intermediate such as **4a**. After the formation of **4a**, either ring closure or bond rotation to **4b** followed by ring closure could give rise to mixtures of diastereomers **5** and **6**.



Scheme 1.3: Stepwise mechanism with formation of a diastereomeric mixture.

In addition to the general consensus that the Diels-Alder reaction occurs via a concerted mechanism, is the notion that bond formation can be asynchronous.[3] Through a synchronous mechanism, the degree of bond breaking and bond formation at one terminus of the diene is essentially the same as the degree of bond breaking and bond formation at the other terminus of the diene. However, simultaneous bond breaking and bond formation can occur to differing degrees depending upon the nature and polarity of the reacting diene and dienophile. That is, the more polarized the reactants the more asynchronous the cycloaddition. Indeed, the concertedness of any particular Diels-Alder reaction can be considered as lying on a continuum between fully synchronous, with equal degrees of new σ-bond formation at the transition state, and stepwise. At some

[3] Woodward, R.B.; Katz, T.J. *Tetrahedron* **1959**, *5*, 70-89.; Dewar, M.J.S.; Pierini, A.B. *J. Am. Chem. Soc.* **1984**, *106*, 203-208.

point on this continuum, the reaction changes from asynchronous, with an unequal transition state, to stepwise, with the formation of a zwitterionic intermediate.

The reaction of 1,3-butadiene with ethylene is known,[4] but it requires harsh temperatures, high pressure, or both to proceed. The incorporation of electron donating and electron withdrawing substituents on the reacting species can greatly influence the course of the reaction. The reactivity between the diene and dienophile is often explained using frontier molecular orbital theory.[5] The electrons of the highest occupied molecular orbital (HOMO) of one component interact with the lowest unoccupied molecular orbital (LUMO) of the other component, and a pericyclic bond reorganization occurs, resulting in a cycloaddition product.

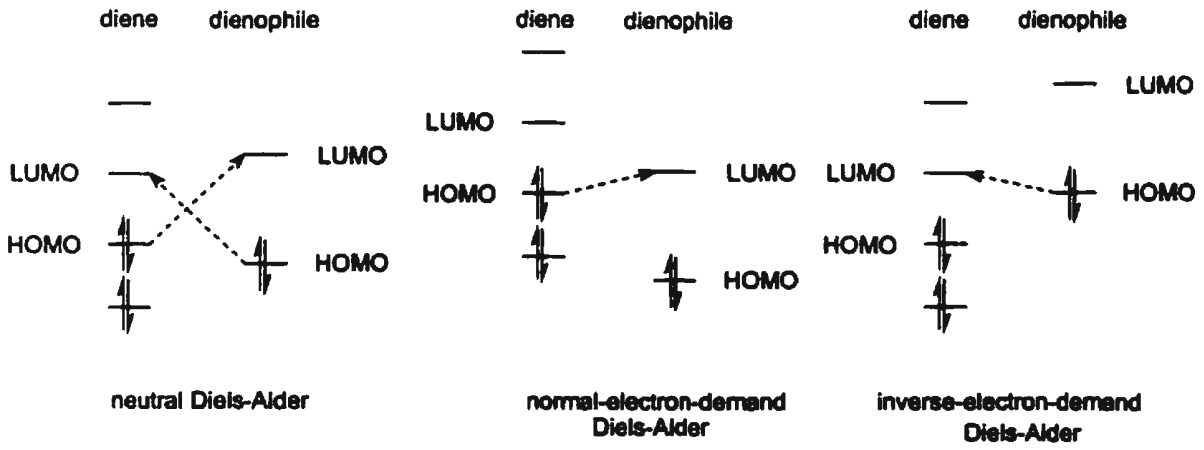


Figure 1.1: Frontier molecular orbital interactions in the Diels-Alder reaction.

[4] Joshel, L.M.; Butz, L.W. *J. Am. Chem. Soc.* **1941**, *63*, 3350-3351.; Houk, K.N.; Lin, Y.-T.; Brown, F.K. *J. Am. Chem. Soc.* **1986**, *108*, 554-556.

[5] Woodward, R.B.; Hoffmann, R. *J. Am. Chem. Soc.* **1965**, *87*, 395-397.; Sustmann, R.; Schubert, R. *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 840.; Houk, K.N. *J. Am. Chem. Soc.* **1973**, *95*, 4092-4094.; Houk, K.N. *Acc. Chem. Res.* **1975**, *8*, 361-369.

There are generally considered to be three categories of such systems. In the case of unsubstituted reactants, or reactants substituted with weakly electron donating or withdrawing groups, the energy difference between the HOMO of the diene and the LUMO of the dienophile is often similar to the energy difference between the HOMO of the dienophile and the LUMO of the diene. However, with the typically large energy differences between HOMO and LUMO orbitals, the neutral Diels-Alder reaction is usually very slow. Consequently, harsh conditions are typically required to force the reaction to proceed.

The inclusion of electron donating groups on the diene, the inclusion of electron withdrawing groups on the dienophile or, more commonly a combination of both, results in a marked rate acceleration of the cycloaddition reaction. Electronically biasing the reaction in this manner results in what is known as the normal-electron-demand Diels-Alder reaction. A π-donating substituent on the diene has the effect of raising the energy of the HOMO[6] compared to the parent system, thus lowering the energy difference for a $HOMO_{diene}$ - $LUMO_{dienophile}$ interaction. Similarly, by decreasing electron density of the dienophile, the energy of its LUMO is effectively decreased, again resulting in a lower energy barrier for a $HOMO_{diene}$ - $LUMO_{dienophile}$ interaction. The reduction of this energy barrier results in a substantial increase in the rate of the reaction and thus the normal Diels-Alder reaction can be carried out under far milder conditions than required for neutral Diels-Alder reactions.

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[6] For a discussion of the significance of the HOMO energy in cycloaddition reactions, see: Fukui, K.; Fujimoto, H. in *Mechanisms of Molecular Migrations*, Vol. 2., Thyagarajan, B.S. (Ed.), Wiley-Interscience: New York, 1968.

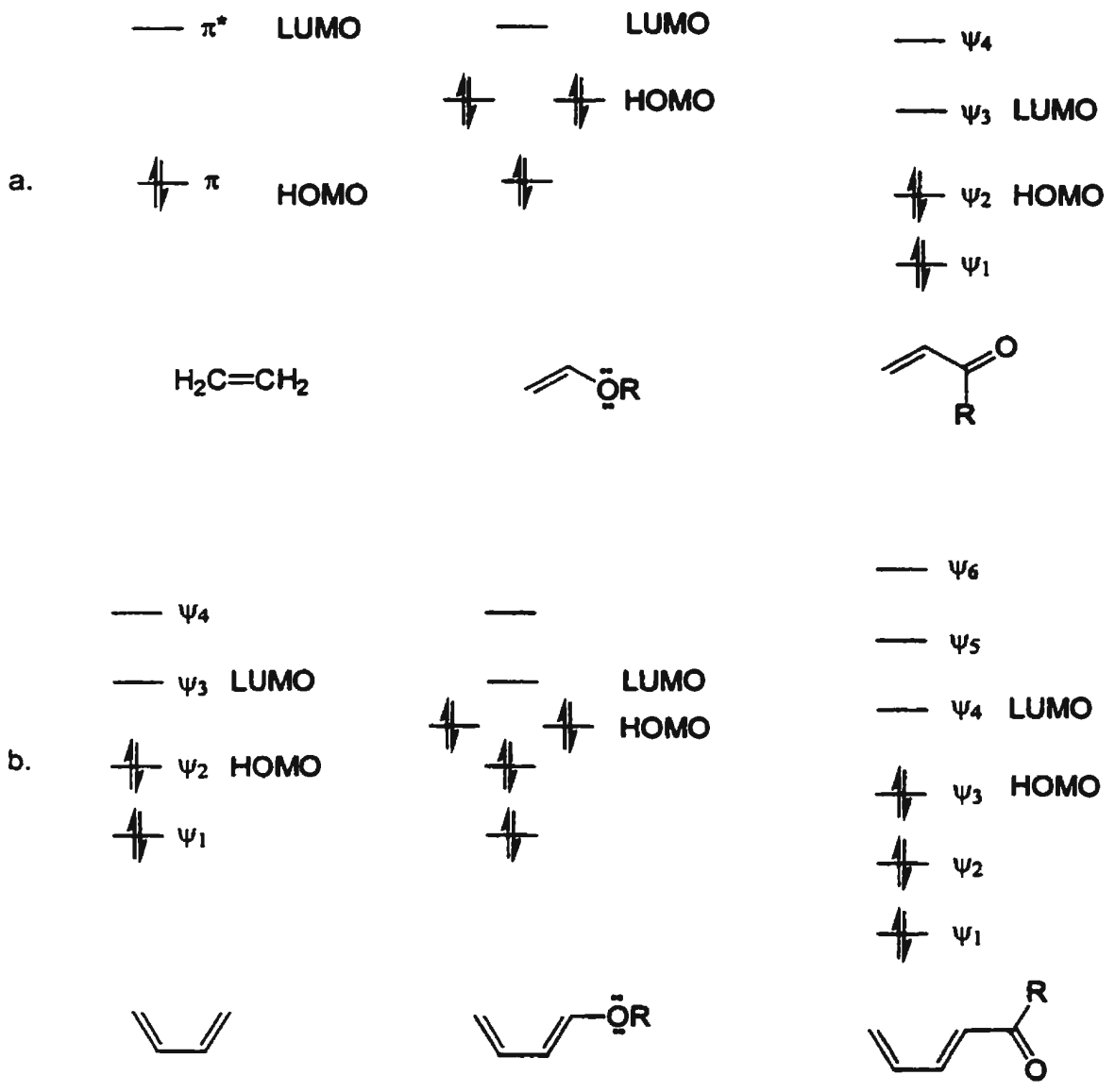

Figure 1.2: Qualitative representation of substituent effects on the HOMO and LUMO energies for, a. the dienophile and, b. the diene.

Complementary to the normal Diels-Alder system is the inverse-electron-demand Diels-Alder system. This is the case when the diene is substituted with electron withdrawing groups. This has the effect of lowering the energy levels of the molecular

orbitals of the diene compared to the parent (neutral) system. By using a dienophile substituted with electron donating groups, which will have molecular orbitals of higher energy than the parent system, the energy barrier for a $HOMO_{dienophile}$ - $LUMO_{diene}$ interaction should be decreased sufficiently to allow the Diels-Alder reaction to proceed as easily as in the case of the normal-electron-demand Diels-Alder reaction.

While frontier molecular orbital theory puts forward a convincing argument to explain the course of the Diels-Alder reaction, it does not stand alone in this objective. Another method for rationalizing the mechanism of the cycloaddition reaction is by the analysis of basis set orbitals, using symmetry correlation.[7] A plane of symmetry in the molecular orbitals of both the diene and dienophile is maintained throughout the Diels-Alder cycloaddition and exists in the product. The molecular orbitals of the diene, dienophile and the cyclohexene adduct can be classified as either symmetric (S) or antisymmetric (A) with respect to this plane.

An orbital correlation diagram[8] illustrates that all electrons in the product would be placed in bonding orbitals during the course of the reaction. As such, the concerted Diels-Alder cycloaddition is classified as a thermally allowed process. However, unlike with frontier molecular orbital considerations, analysis of orbital symmetries does not account for the effects of diene and dienophile substituents on the course of the [4 + 2] cycloaddition reaction.

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[7] Woodward, R.B.; Hoffmann, R. *The Conservation of Orbital Symmetry*, Academic Press, Inc.: New York, 1970.

[8] Hoffmann, R.; Woodward, R.B. *J. Am. Chem. Soc.* **1965**, *87*, 2046-2048.

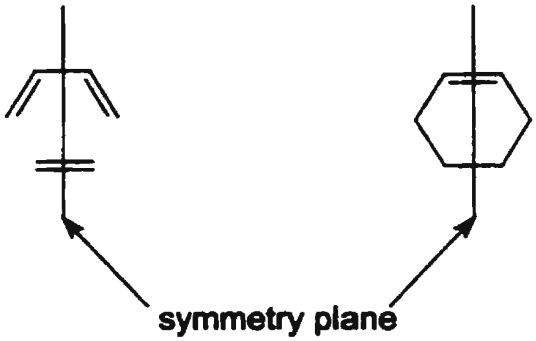


Figure 1.3: Orbital symmetry maintained during Diels-Alder reaction.

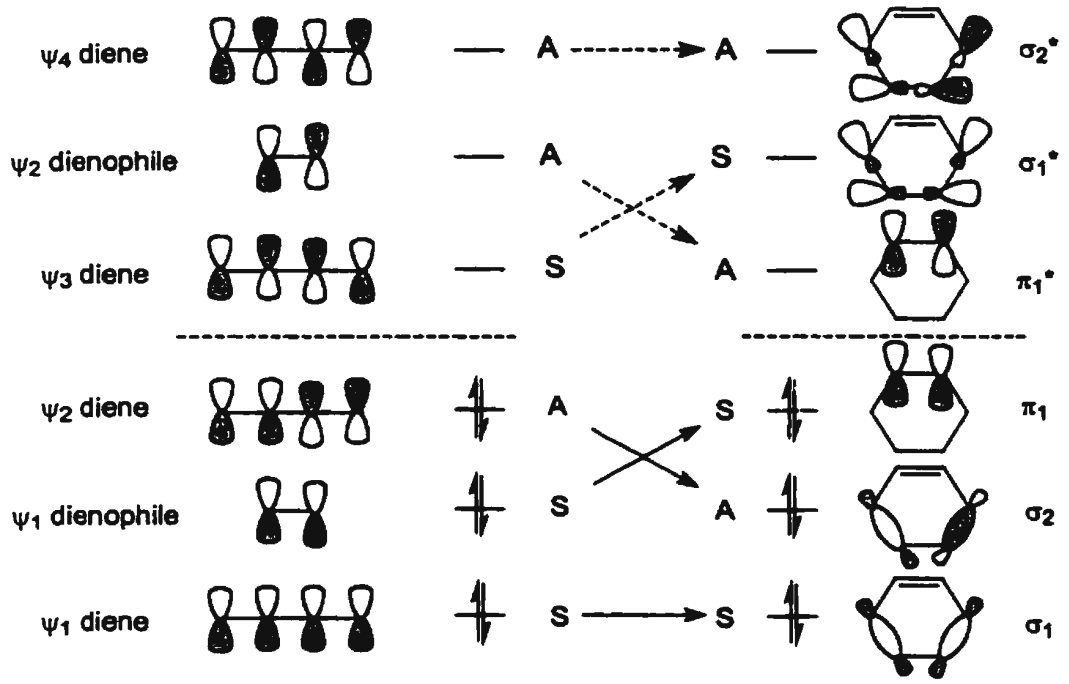


Figure 1.4: Correlation diagram for molecular orbital symmetries.

The synthetic utility of the Diels-Alder reaction arises from the high degrees of regiochemical and stereochemical control achievable in many cases, making the outcome predictable. The inherent regioselectivity observed can again be explained by frontier

molecular orbital theory. The presence of electron donating substituents in either the 1- or 2- position of the diene results in perturbation of the molecular orbitals, qualitatively represented by the size of the atomic orbital coefficient, increasing the electron density on C4 or C1 of the $HOMO_{diene}$, respectively.

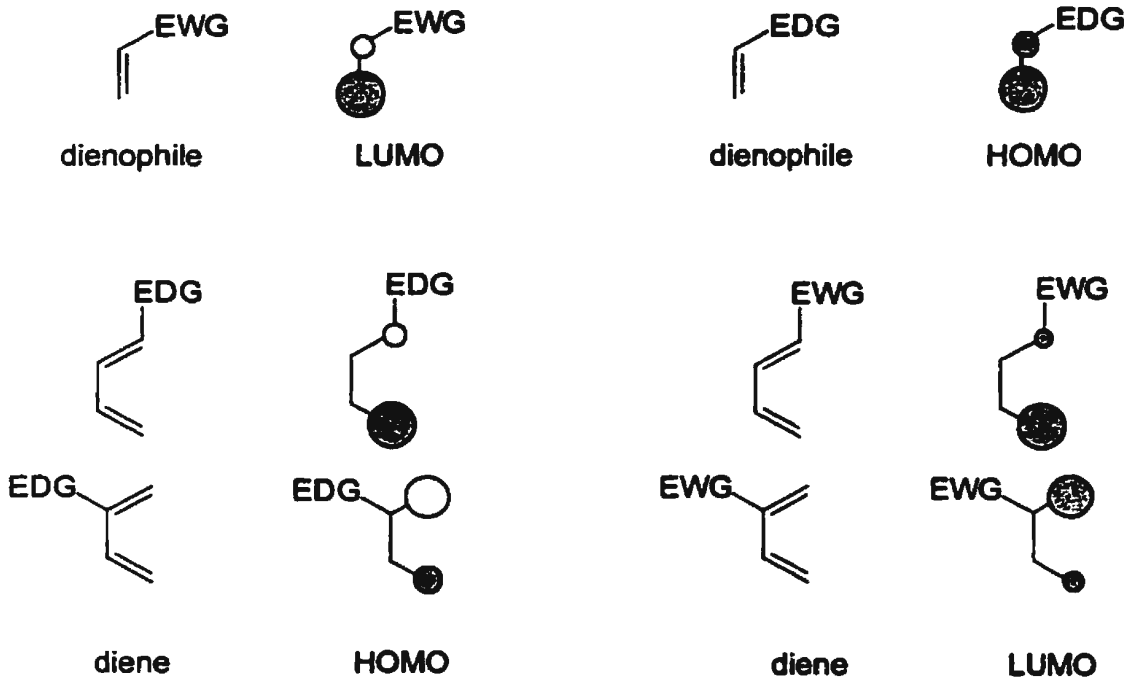
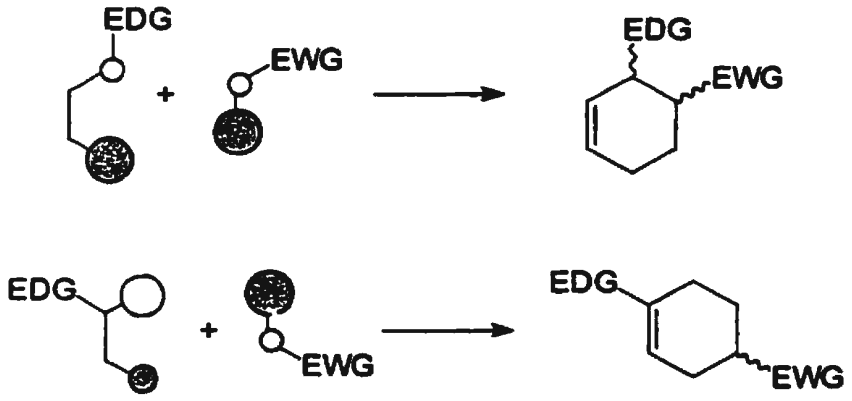


Figure 1.5: Atomic orbital perturbation predicted by frontier molecular orbital theory.

Similarly, dienophiles bearing electron withdrawing groups result in an increased atomic orbital coefficient in the $LUMO_{dienophile}$ at the position β to the electron withdrawing group, compared to the neutral case. In the Diels-Alder reaction, $HOMO_{diene}$ - $LUMO_{dienophile}$ interactions occur between the atomic orbitals with the largest coefficients. For example, the reaction of a 1-substituted electron rich diene with an electron-poor alkene results in a regioselective cycloaddition giving a 3,4-disubstituted

cyclohexene as the major product. For the same reason, 2-substituted dienes react to give predominately 1,4-disubstituted cyclohexenes.



Scheme 1.4: Orbital interactions and regioselectivity in the normal Diels-Alder reaction.

Regioselective addition is also observed in the inverse-electron-demand Diels-Alder reaction and, as with the normal Diels-Alder, frontier molecular orbital theory provides a reasonable explanation in many cases. In this instance, the orbital interactions occur between the $HOMO_{dienophile}$ and the $LUMO_{diene}$. Nevertheless, the reaction proceeds with association of the orbitals with the greatest orbital coefficients. As such, the same regiochemical outcomes are predicted.

As with the rate of reactivity, theories other than frontier molecular orbital theory also provide insight into the regioselective outcome of the Diels-Alder reaction. It can be argued that valence bond theory can quite simply account for the regioselectivity of the reaction. Examination of certain important resonance contributors of the reactants leads to the prediction of the observed regioselectivity. Regardless of the origin of the

regioselective outcome, the fact remains that this plays an essential role in the utility of the Diels-Alder reaction in organic synthesis.

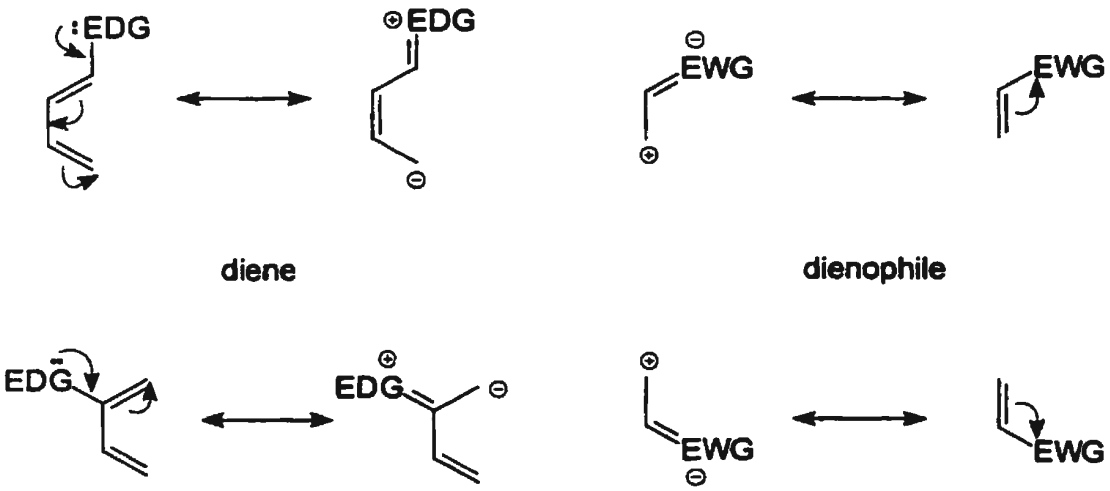


Figure 1.6: Resonance considerations of the Diels-Alder reaction.

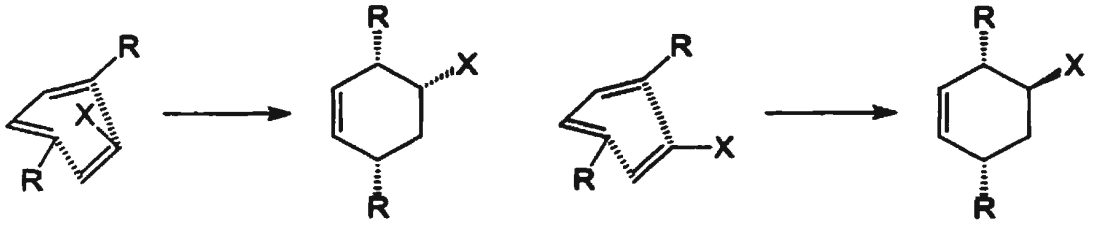
In many cases a high degree of control of the diastereoselective can also be achieved in the Diels-Alder reaction. In what has become known as the Alder rule, the Diels-Alder reaction often proceeds via an *endo* transition state.[9] That is, during the cycloadditon any substituent, and in particular, an unsaturated sunstituent, on the dienophile tend to be aligned such that they are under (or over[10]) the diene and nearest the newly forming alkene bond. This phenomenon has been extensively attributed to secondary orbital interactions,[11] which are the interactions between unsaturated groups in

[9] Alder, K.; Stein, G. *Angew. Chem.* **1937**, *50*, 510.

[10] Facial selectivity is an additional component to the utility of the Diels-Alder reaction, which can result in enantioselectivity. However, without additional considerations such as steric congestion, chiral induction or restrictive intramolecular conditions, facial selectivity is often minimal and racemic products result.

[11] Ginsburg, D. *Tetrahedron* **1983**, *39*, 2095-2135.

the dienophile and the incipient π-bond of the product. There is, however, little experimental support that these interactions actually play a significant role in the observed stereoselective outcomes.



Scheme 1.5: *Endo* and *exo* addition in the Diels-Alder reaction.

Alternate theories on the source of the *endo* preference involve σ/π orbital interactions in the ground state of an asymmetric diene,[12] as well as molecular orbital symmetry considerations.[13] Products arising from *endo* transition states are not exclusive in Diels-Alder reactions and there are many cases where no selectivity or even predominately *exo* selectivity is observed.[14,15]

[12] Paquette, L.A.; Schaefer, A.G.; Blount, J.F. *J. Am. Chem. Soc.* **1983**, *105*, 3642-3649.; Gleiter, R.; Paquette, L.A. *Acc. Chem. Res.* **1983**, *16*, 328-334.
[13] Hoffmann, R.; Woodward, R.B. *J. Am. Chem. Soc.* **1965**, *87*, 4388-4389.
[14] Alder, K.; Günzl, W. *Chem. Ber.* **1960**, *93*, 809-825.; Stockmann, H. *J. Org. Chem.* **1961**, *26*, 2025-2029.; Smith, J.R.L.; Norman, R.O.C.; Stillings, M.R. *Tetrahedron* **1978**, *34*, 1381-1383.
[15] Sodupe, M. *J. Am. Chem. Soc.* **1997**, *119*, 4232-4238.; Suarez, D.; Sordo, J.A. *Chem. Commun.* **1998**, 385-386.; Oikawa, H.; Kobayashi, T.; Katayama, K.; Suzuki, Y.; Ichihara, A. *J. Org. Chem.* **1998**, *63*, 8748-8756.

1.2 Inverse-Electron-Demand Diels-Alder Reactions

While much study has gone into the examination of nearly every aspect of the normal Diels-Alder reaction during the last seventy years, considerably less has been learned about the inverse-electron-demand Diels-Alder reaction. That is not to say that there has not been a great deal of exploration into this area. However the IEDDA reaction has received a significantly less comprehensive analysis. There have been several major areas of research that have evolved involving electron deficient dienes and their IEDDA reactivity. A brief overview of this area along with a few recent developments will be presented during the remainder of this chapter.

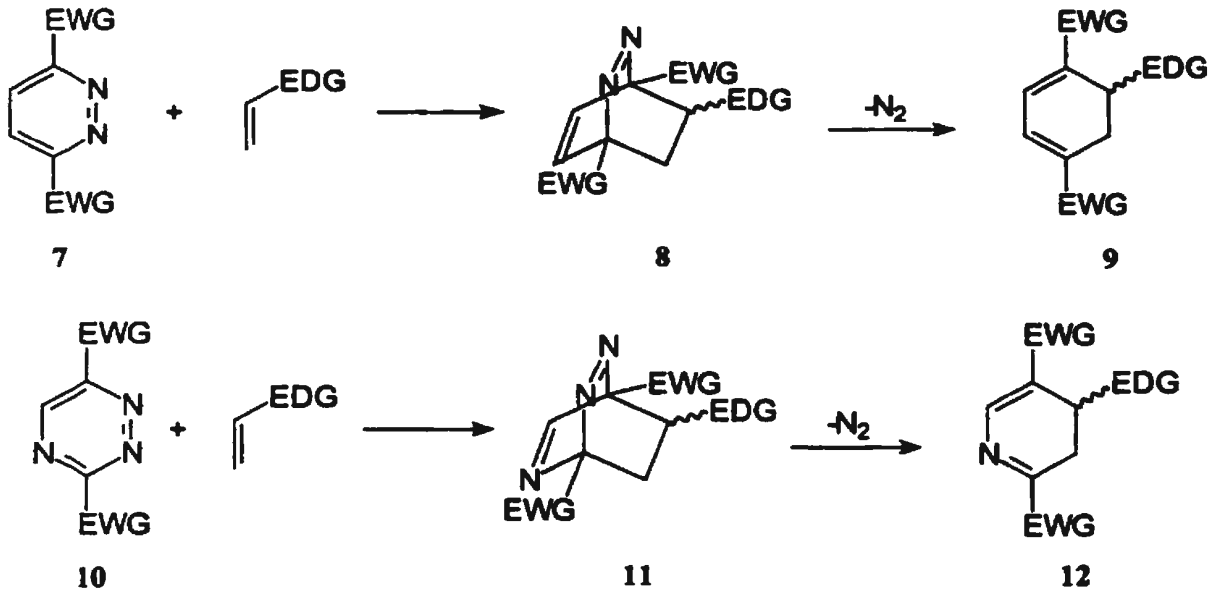
1.2.1 Azadienes and Nitrogen Substituted Dienes

Azadienes,[16] dienes which incorporate nitrogen atoms within the diene moiety, as well as nitrogen substituted dienes, have enjoyed widespread use in the IEDDA reaction, and have been applied broadly in the total synthesis of natural products.[17] Pyridazines (**7**) can react with electron rich dienophiles to give diazabicyclooctanes, such as **8**. These often undergo subsequent retro-Diels-Alder reactions, eliminating nitrogen, resulting in carbocycles (**9**).

---

[16] Boger, D.L.; Weinreb, S.M. *Hetero Diels-Alder Methodology in Organic Synthesis;* Academic Press, Inc.: San Diego, **1987**.; Fringuelli, F.; Taticchi, A. *Dienes In The Diels-Alder Reaction*; Wiley Interscience: New York, **1990**.; For reviews, see: Weinreb, S.M.; Staib, R.R. *Tetrahedron* **1982**, *38*, 3087-3128.; Boger, D.L. *Tetrahedron* **1983**, *39*, 2869-2939.

[17] Boger, D.L. *Chem. Rev.* **1986**, *86*, 781-793.



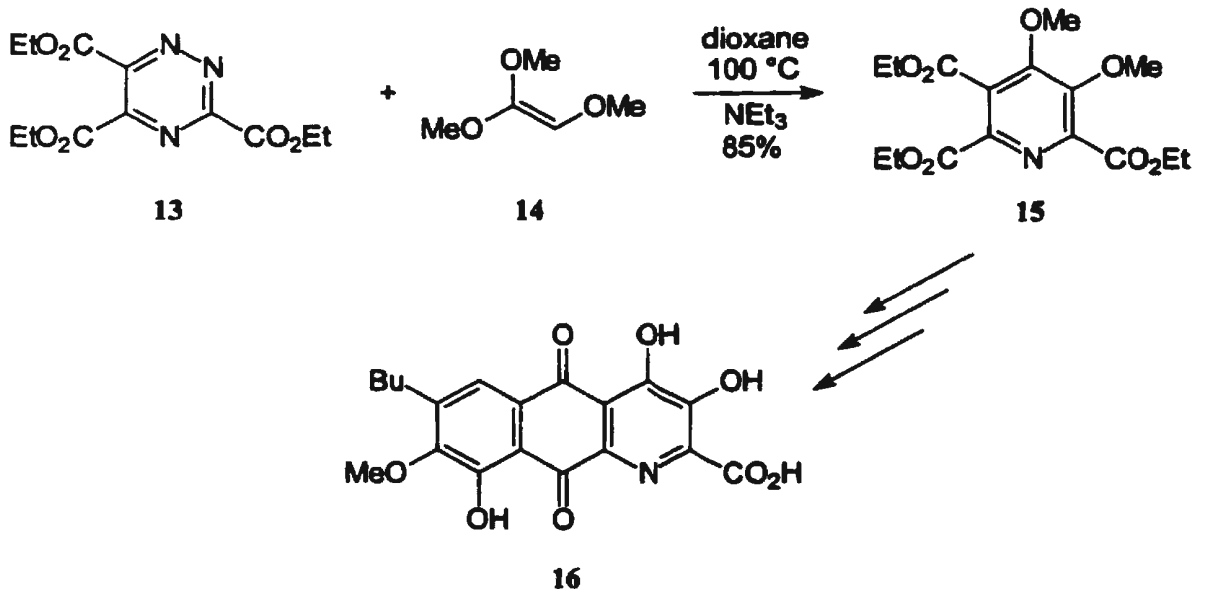
Scheme 1.6: Representative examples of IEDDA reactions of azadienes.

In an analogous manner, 1,2,4-triazines (**10**) can undergo IEDDA reaction with dienophiles containing electron donating substituents to yield bicyclic adducts (**11**), which also participate in a retro-Diels-Alder reaction, extruding nitrogen, to give heterodienes (**12**). The heterodienes obtained might take part in subsequent IEDDA reactions or undergo elimination or oxidation, to substituted pyridines.

A recent example of the use of a 1,2,4-triazine in an IEDDA reaction was in the total synthesis of phomazarin (**16**),[18] a structurally interesting, and previously unsynthesized, naturally occurring aza-anthraquinone. Electron deficient triazine **13** was reacted with trimethoxyethene (**14**) in refluxing dioxane, then treated with triethylamine to effect the elimination of methanol giving pyridine **15**. Having set up the precursors to

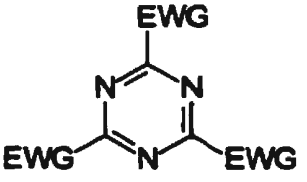
[18] Boger, D.L.; Hong, J.; Hikota, M.; Ishida, M. *J. Am. Chem. Soc.* **1999**, *121*, 2471-2477.

the required functionality on the pyridine ring, **15** was then converted in subsequent steps to the natural product.



13 **14** **15** **16**

Scheme 1.7: IEDDA reaction of triazine **13** in the synthesis of phomazarin (**16**).

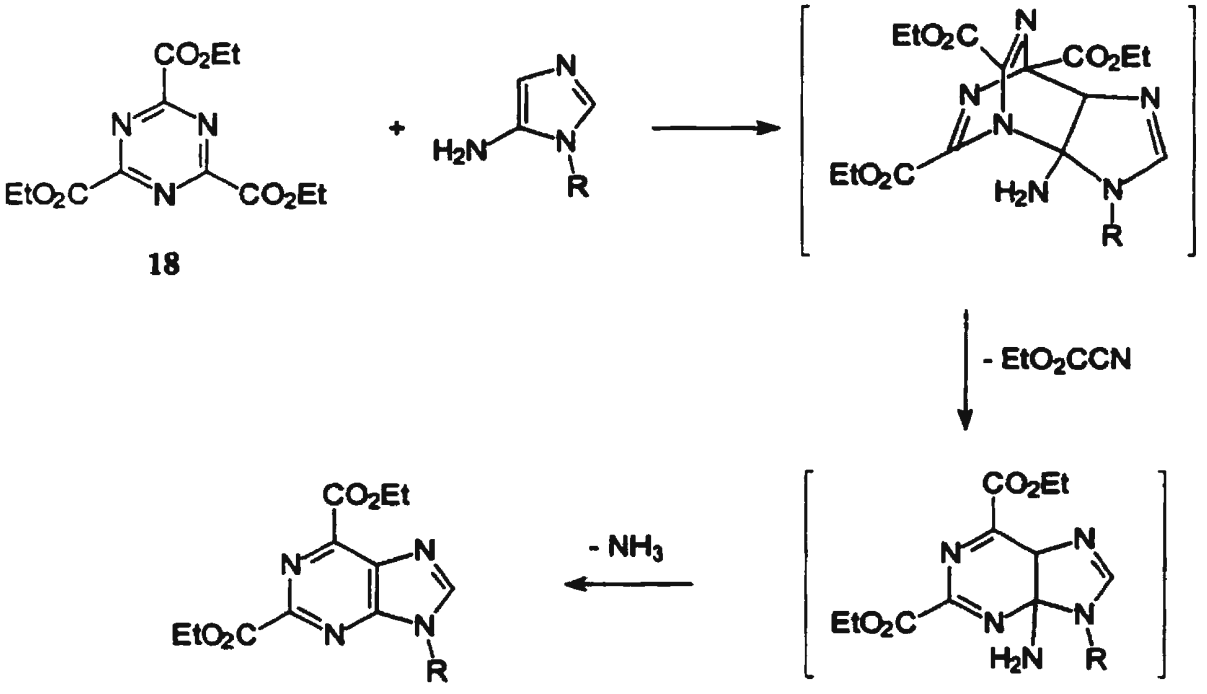


17

1,3,5-Triazines (**17**) have also been useful dienes in the inverse-electron-demand Diels-Alder reaction. For example, the synthesis of several purines and purine nucleosides have recently been reported[19] using an IEDDA reaction of triazine **18** with *N*-substituted 5-aminoimidazoles (generated *in situ* by decarboxylation of 4-

hydroxycarbonyl-5-aminoimidazoles due to their instability), followed by spontaneous loss of ethyl cyanoformate and ammonia.

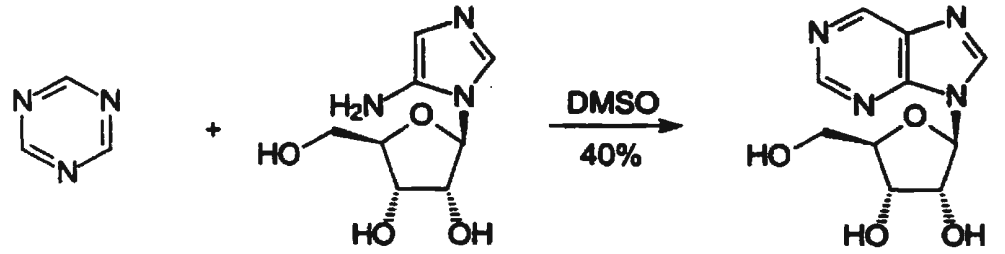
Several natural products, including the biologically active nebularine (20) were prepared by this method, but in one step, using the parent triazine 19. Not surprisingly, these required longer reaction times and proceeded with somewhat lower yields.



R = Bn, β-D-ribofuranosyl, or 2,3,5-tri-O-acetyl-β-D-ribofuranosyl

Scheme 1.8: Synthesis of purines and purine nucleosides by IEDDA reaction of 1,3,5-triazine 18.

[19] Dang, Q.; Liu, Y.; Erion, M.D. *J. Am. Chem. Soc.* **1999**, *121*, 5833-5834.



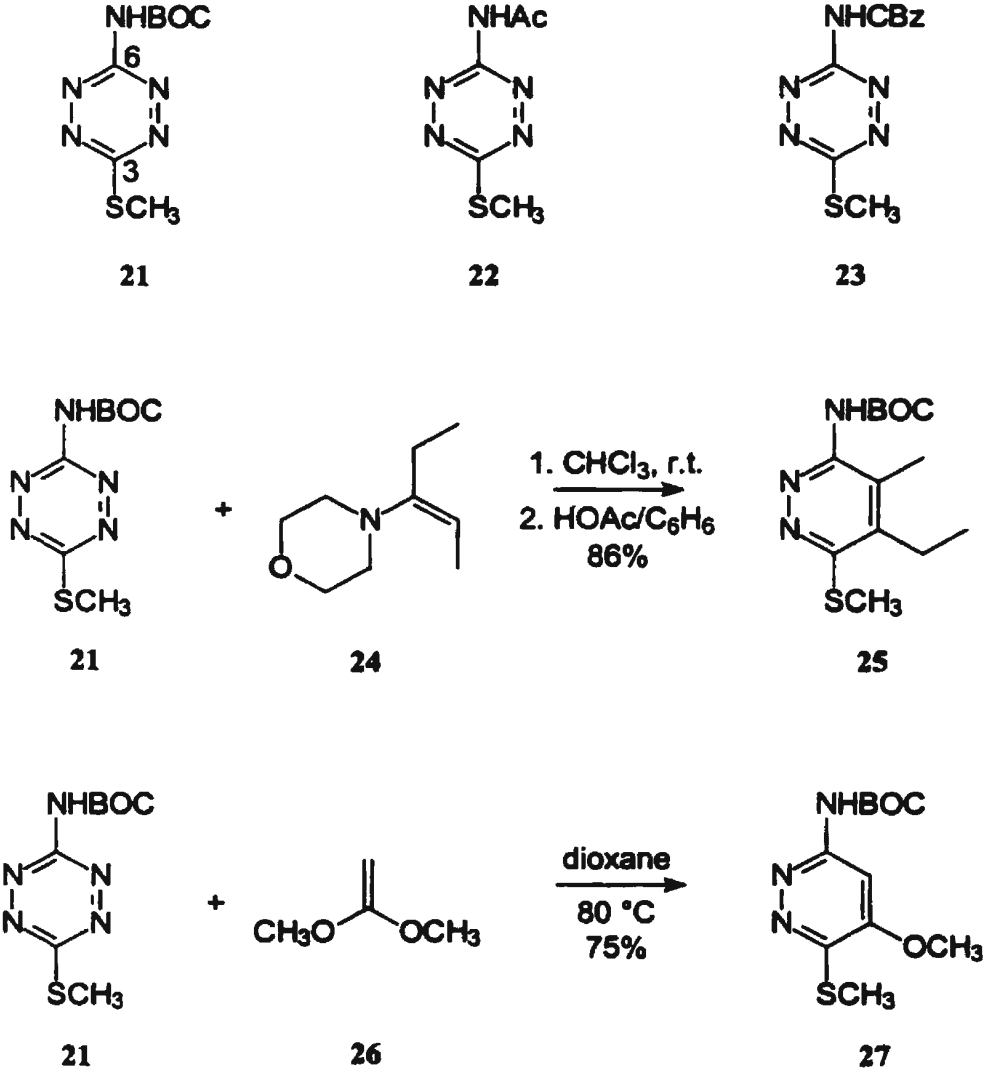
19 20

Scheme 1.9: One-pot synthesis of nebularine (20) by IEDDA reaction of 1,3,5-triazabenzene (19).

Just as pyridazines and triazines can participate in IEDDA reactions, so can 1,2,4,5-tetrazines, and indeed the cycloaddition reactions proceed more smoothly as more nitrogen atoms are incorporated into the aromatic ring. These reacted with dienophiles and often led ultimately to pyridazines by way of retro-Diels-Alder extrusion of nitrogen and a subsequent elimination reaction to the aromatic product. These pyridazines can then be used in a variety of ways, including subsequent inverse-electron-demand Diels-Alder reactions or reductive ring-contraction to pyrroles.[20] This methodology has been used for the synthesis of many alkaloid natural products.[16] A series of regiospecific IEDDA reactions of the unsymmetrically substituted 1,2,4,5-tetrazines **21**, **22** and **23** were recently reported.[21] The observed regioselectivities were consistent with expectations that the methylthio group would control the orientation of the dienophile by stabilizing a partial negative charge at C3 of the diene. As well, the ability of the acylamino group to stabilize a partial positive charge on C6 of the diene, in the transition

[20] Boger, D.L.; Coleman, R.S.; Panek, J.S.; Yohannes, D. *J. Org. Chem.* **1984**, *49*, 4405-4409.

state of the cycloaddition, was anticipated to assist in the highly regioselective reactions. These predictions were consistent with computational studies, where C6 was predicted to bear the largest LUMO orbital coefficient.



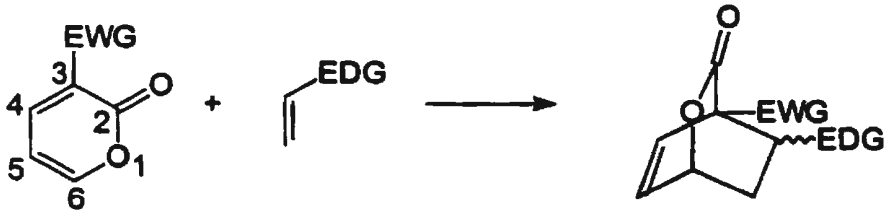
Scheme 1.10: Representative regioselective IEDDA reactions of tetrazine **21**.

[21] Boger, D.L.; Schaum, R.P.; Garbaccio, R.M. *J. Org. Chem.* **1998**, *63*, 6329-6337.

The *N-tert*-butyloxycarbonyl diene **21** reacted with the morpholine-derived enamine **24** at room temperature to give **25**, the product of an IEDDA reaction followed by the elimination of nitrogen and morpholine, in 86% yield. In addition, diene **21** reacted with the ketene acetal **26**, giving **27** in 75% yield.

1.2.2 2-Pyrones

A second field of IEDDA chemistry that has seen much exploration has been the reactivity of 2-pyrones.[22] Electron deficient pyrones, such as those substituted in the 3-position with an electron withdrawing group (**28**), can undergo IEDDA reactions with alkenes giving bicyclic lactones (**29**). In addition to electron rich alkenes, dienophiles successfully reacted with 2-pyrones in a Diels-Alder reaction have included alkynes,[23] as well as neutral,[24] and weakly electron rich alkenes.[25]



28 **29**

Scheme 1.11: IEDDA reaction of electron deficient 2-pyrones (**28**) to yield bicyclic lactones (**29**).

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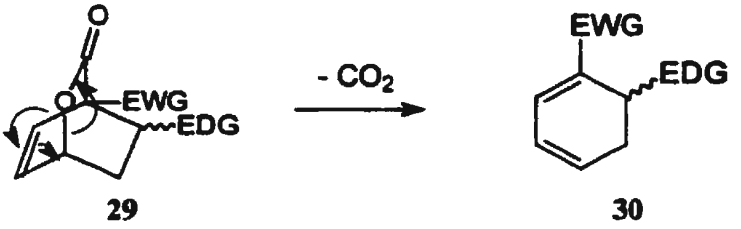
[22] For reviews, see: Posner, G.H.; Afarinkia, K.; Vinader, V.; Nelson, T.D. *Tetrahedron* **1992**, *48*, 9111-9171.; Kvita, V.; Fischer, W. *Chimia* **1993**, *47*, 3-18.; Kalinin, V.N.; Shilova, O.S. *Russ. Chem. Rev.* **1994**, *63*, 661-666.
[23] Gingrich, H.L.; Roush, D.M.; Van Saun, W.A. *J. Org. Chem.* **1983**, *48*, 4869-4873.
[24] Hatsui, T.; Hashiguchi, T.; Takeshita, H. *Chem. Lett.* **1994**, 1415-1416.
[25] Corey, E.J.; Watt, D.S. *J. Am. Chem. Soc.* **1973**, *95*, 2303-2311.



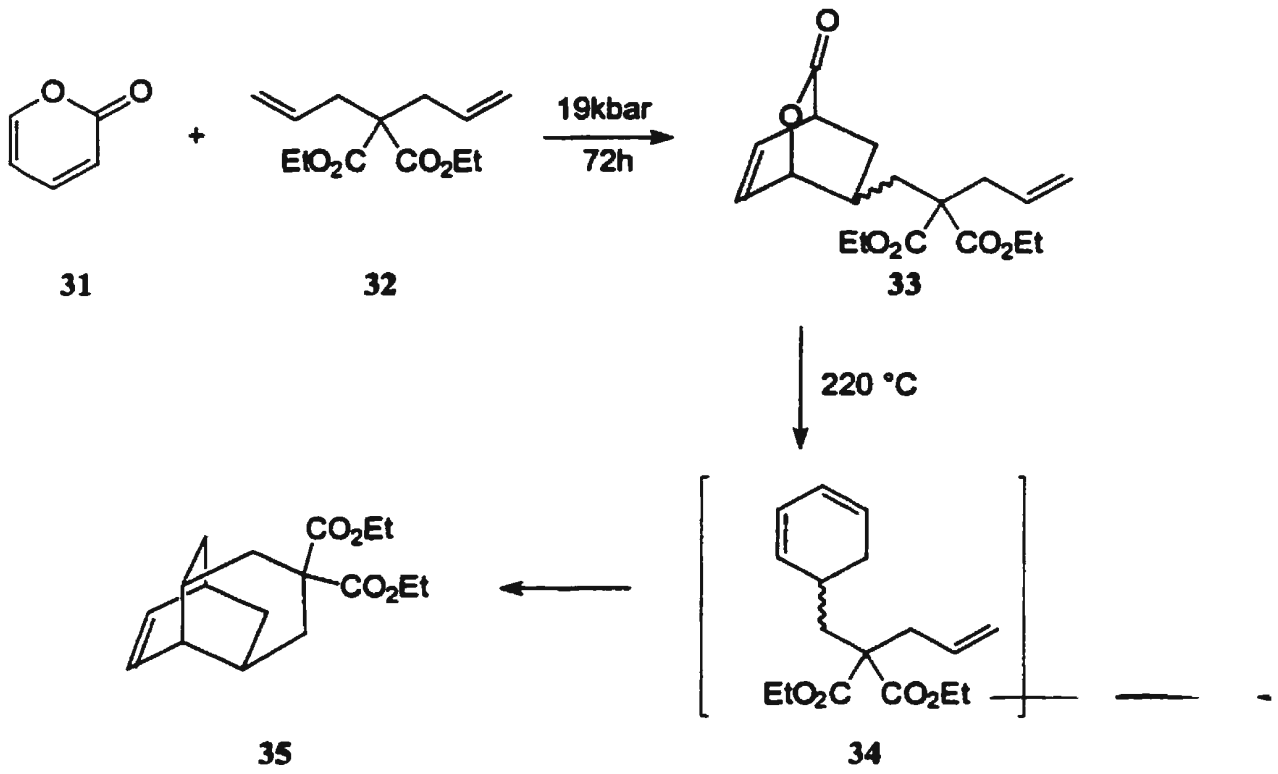
29 30

Scheme 1.12: Thermal extrusion of CO_2 from bicyclic lactones **29**.

When heated, the bicyclic lactones (**29**) generally result in the extrusion of CO_2 via a retro-Diels-Alder reaction leading to new unsaturated carbocyclic rings (**30**). Temperatures required for the thermolysis reaction are reactant dependent, but usually range from room temperature to around 200 °C.

These new dienes have been used in a range of transformations. The initial use of an α,ω-diene as the dienophile in the preliminary IEDDA reaction with a 2-pyrone allows, after the extrusion of CO_2, for the second, albeit neutral, Diels-Alder reaction to occur intramolecularly resulting in a fairly complex polycyclic system. Such a tandem IEDDA reaction is illustrated by the reaction of 2-pyrone (**31**) with malonate **32**, ultimately leading to the formation of **35** in 95% overall yield.[26] The initial Diels-Alder reactions of the unactivated substrates were slow to proceed and high pressure was required to induce the desired transformation. The bicyclic lactone intermediates (ex. **33**) were stable and could be isolated and stored if desired. Treatment at high temperatures (usually 200 - 220 °C) led smoothly to the extrusion of CO_2 (**34**) and the desired intramolecular Diels-Alder cycloaddition leading to **35**.

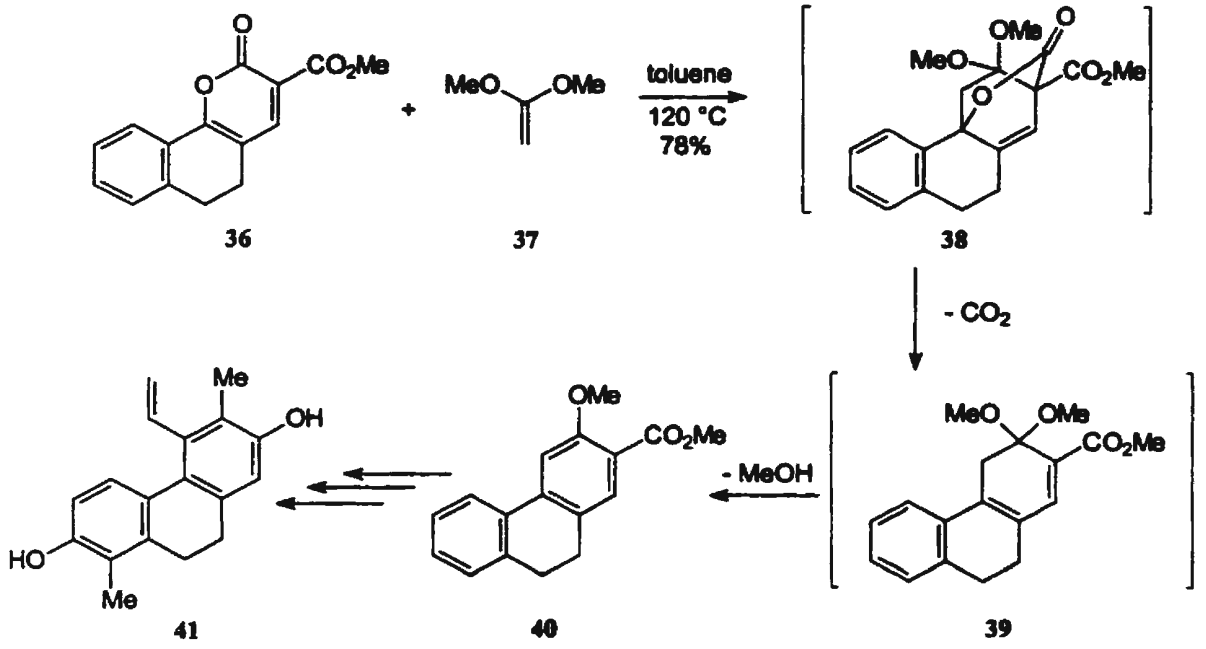
[26] Swarbrick, T.M.; Markó, I.E.; Kennard, L. *Tetrahedron Lett.* **1991**, *32*, 2549-2552.



Scheme 1.13: Tandem Diels-Alder reactions of 2-pyrone (**31**) with an α,ω-diene.

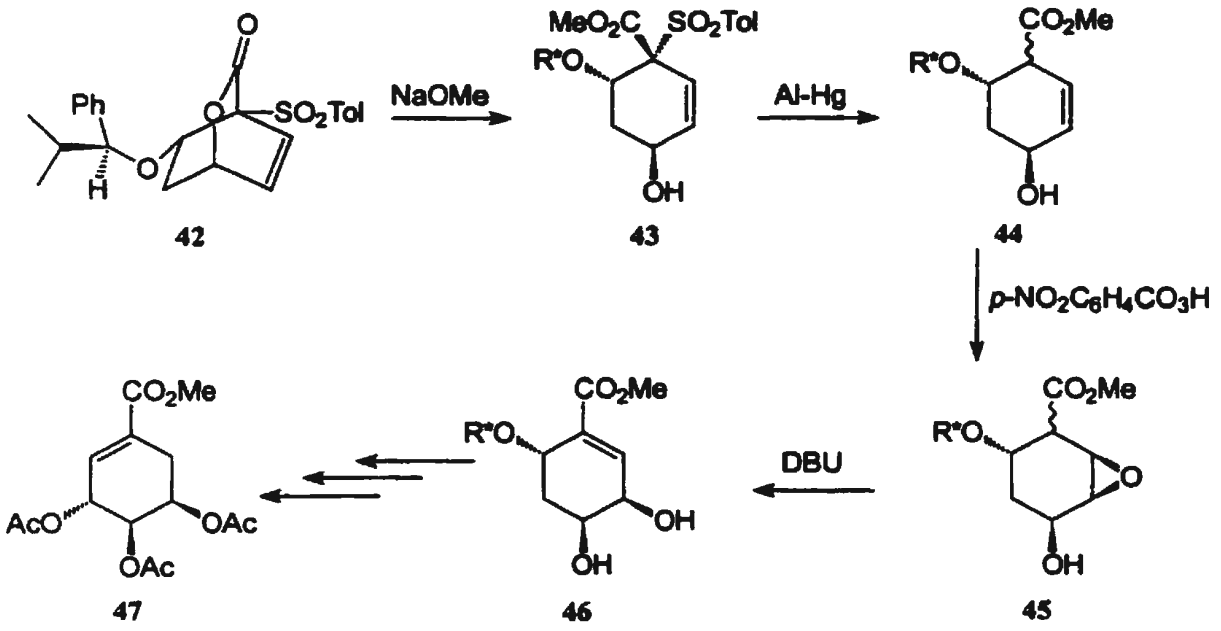
The use of an electron rich dienophile which, following IEDDA reaction and loss of CO_2, led to dienes that could then readily aromatize by elimination of a substituent introduced by the dienophile. The utility of such an aryl annulation process was demonstrated[27] in the conversion of pyrone **36** to dihydrophenanthrene **40** by IEDDA reaction with 1,1-dimethoxyethene (**37**), followed by retro-Diels-Alder extrusion of CO_2 from lactone **38** and aromitization by elimination of methanol from diene **39**. This sequence was then applied to the total synthesis of juncusol (**41**).[28]

[27] Boger, D.L.; Mullican, M.D. *Tetrahedron Lett.* **1982**, *23*, 4551-4554.
[28] Boger, D.L.; Mullican, M.D. *Tetrahedron Lett.* **1982**, *23*, 4555-4558.



Scheme 1.14: Aryl annulation by IEDDA reaction, loss of CO_2 and elimination in the total synthesis of juncusol (**41**).

The bicyclic lactones (e.g. **29**) were also synthetically useful intermediates for the preparation of more complex systems. They could be treated with nucleophiles leading to allylic alcohols which could then be used for the stereoselective introduction of further oxygen functionality. Such a sequence was employed in the asymmetric total synthesis of (-)-methyl triacetyl-4-epishikimate (**47**).[29] Methanolysis of lactone **42** gave allylic alcohol **43**. Following reductive cleavage of the sulfonyl group, allylic alcohol **44** was epoxidized with *p*-nitroperoxybenzoic acid, giving **45**. The crude epoxide was then treated with DBU to produce diol **46**. This diol was converted to the desired product (**47**) in a further ten steps and 23% yield overall from lactone **42**.



42 43 44 45 46 47

Scheme 1.15: Transformations of lactone **42** in the total synthesis of (-)-methyl triacetyl-4-epishikimate (**47**).

A further transformation of the lactones obtained from IEDDA reaction of 2-pyrones has been their stereospecific conversion to α,β-unsaturated esters with oxygen functionalities. These compounds have been explored as intermediates in the synthesis of a variety of vitamin D_3 analogs.[30] In one report, lactone **48** was selectively opened by treatment with lithium allyloxide giving mixed malonate **49**.

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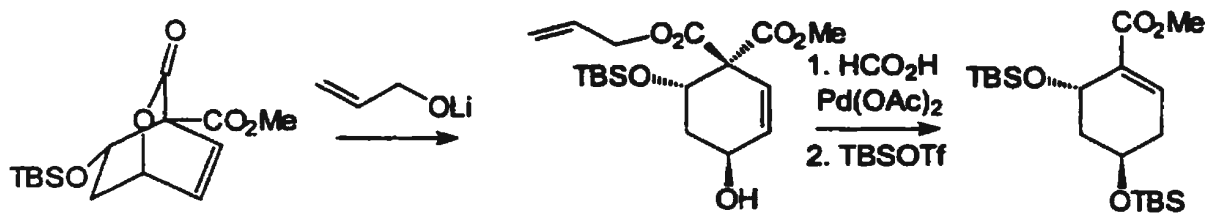
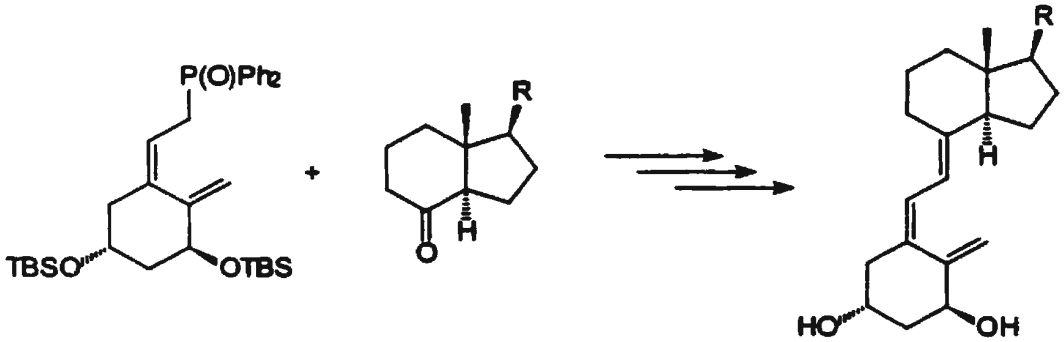
[29] Posner, G.H.; Wettlaufer, D.G. *J. Am. Chem. Soc.* **1986**, *108*, 7373-7377.

[30] a) Posner, G.H.; Nelson, T.D. *J. Org. Chem.* **1991**, *56*, 4339-4341.; b) Posner, G.H.; Carry, J.-C.; Anjeh, T.E.N.; French, A.N. *J. Org. Chem.* **1992**, *57*, 7012-7014.; c) Posner, G.H.; Eydoux, F.; Lee, J.K.; Bull, D.S. *Tetrahedron Lett.* **1994**, *35*, 7541-7544.; d) Cho, C.-G.; Posner, G.H. *Bull. Korean Chem. Soc.* **1998**, *19*, 957-961.



48 49 50

Scheme 1.16: Transformations of lactone **48** giving unsaturated ester **50**.



51 52 53

Scheme 1.17: Modified Wittig reaction leading to vitamin D_3 backbone **53**.

Subsequent deallylcarbonylation with formic acid and catalytic palladium acetate, followed by treatment with *tert*-butyldimethylsilyltriflate (TBSOTf) afforded ester **50** in 59% overall yield. Ester **50** had previously been shown[31] to be a precursor to phosphine oxide **51**, which could be employed in a modified Wittig olefination with ketones such as **52**, for construction of the vitamin D_3 backbone **53**.

Particularly synthetically useful developments in the use of 2-pyrones in the IEDDA reaction have provided methods by which the reaction can be performed with high degrees of stereoselectivity. At first, diastereoselectivities of up to 76% were

[31] Posner, G.H.; Kinter, C.M. *J. Org. Chem.* **1990**, *55*, 3967-3969.

achieved using sulphinyldienes.[32] These were then improved upon by the use of sulfonyldienes, leading to d.e.'s as high as 90%.[33] Respectable diastereoselectivities were also achieved in the IEDDA reaction of 2-pyrones with activated dienophiles using chiral Lewis acids, including (-)-$Pr(hfc)_3$,[30b] $Eu(hfc)_3$,[34] and ytterbium catalysts such as (+)-$Yb(tfc)_3$.[35] IEDDA reactions of 2-pyrones became even more synthetically attractive with the ability to obtain products as single enantiomers. Modest enantioselectivities were first reported with the use of homochiral titanium(IV) complexed Lewis acids.[36] Improved enantioselectivites, up to 98% e.e., were realized with $Yb(OTf)_3$ and Binol complexes[37], as well as titanium(IV) and Binol complexes.[30c]

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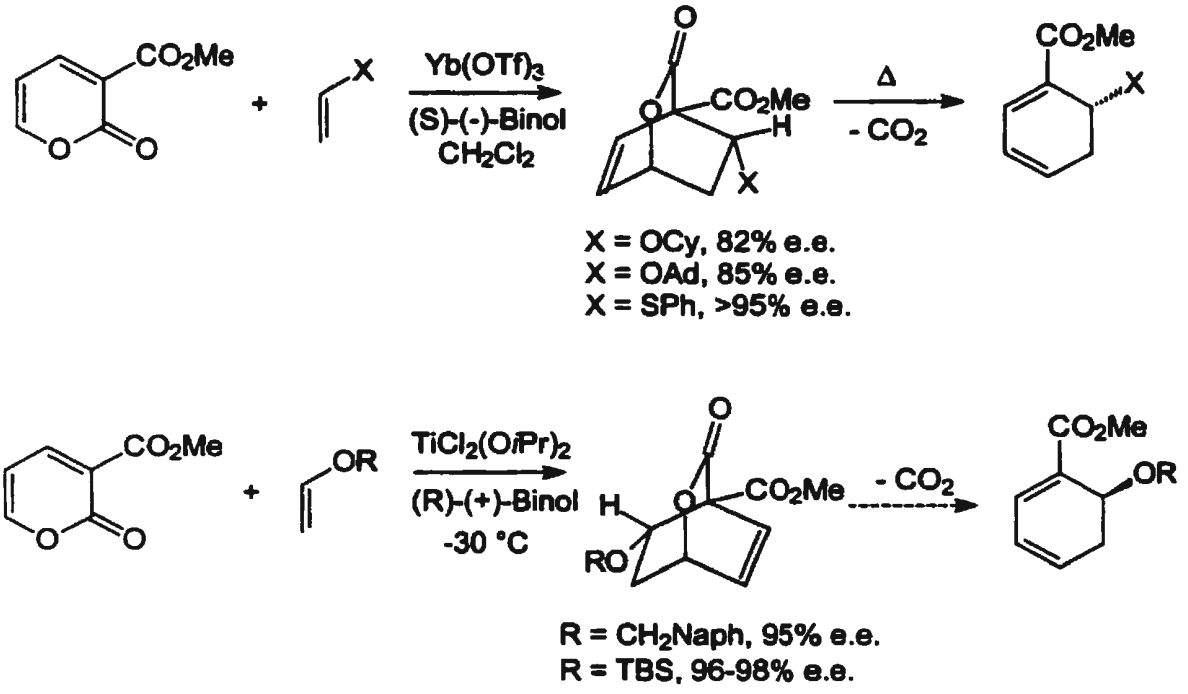
[32] Posner, G.H.; Harrison, W. *J. Chem. Soc., Chem. Commun.* **1985**, 1786-1787.
[33] Posner, G.H.; Wettlaufer, D.G. *Tetrahedron Lett.* **1986**, *27*, 667-670.
[34] Markó, I.E.; Evans, G.R. *Synlett* **1994**, 431-433.
[35] Posner, G.H.; Ishihara, Y. *Tetrahedron Lett.* **1994**, *35*, 7545-7548.
[36] Posner, G.H.; Carry, J.-C.; Lee, J.K.; Bull, D.S.; Dai, H. *Tetrahedron Lett.* **1994**, *35*, 1321-1324.
[37] Markó, I.E.; Evans, G.R. *Tetrahedron Lett.* **1994**, *35*, 2771-2774.; Markó, I.E.; Chellé-Regnaut, I.; Leroy, B.; Warriner, S.L. *Tetrahedron Lett.* **1997**, *38*, 4269-4272.



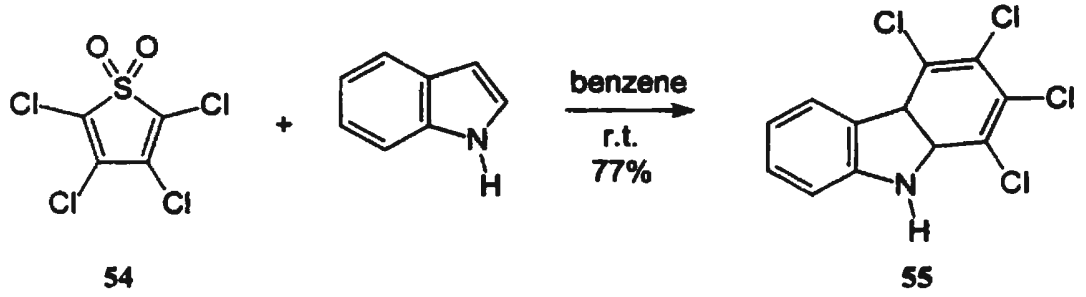
Scheme 1.18: Catalytic enantioselective IEDDA reactions of 2-pyrones.

1.2.3 Other Electron Deficient Dienes

A variety of other electron deficient dienes have seen use, albeit limited, in inverse-electron-demand Diels-Alder reactions. Thiophene-1,1-dioxides have been observed to participate in Diels-Alder reactions with a range of dienophiles, including neutral, electron poor and electron rich alkenes, as well as alkynes, indoles, enamides, pyrroles, and other thiophenes.[38] Diels-Alder cycloaddition followed by loss of SO_2 led

[38] Bluestone, H.; Bimber, R.; Berkey, R.; Mandel, Z. *J. Org. Chem.* **1961**, *26*, 346-351., Raasch, M.S. *J. Org. Chem.* **1980**, *45*, 856-867.

to aryl annulated products, a representative being the reaction of tetrachlorothiophene-1,1-dioxide **54** with indole giving **55**.

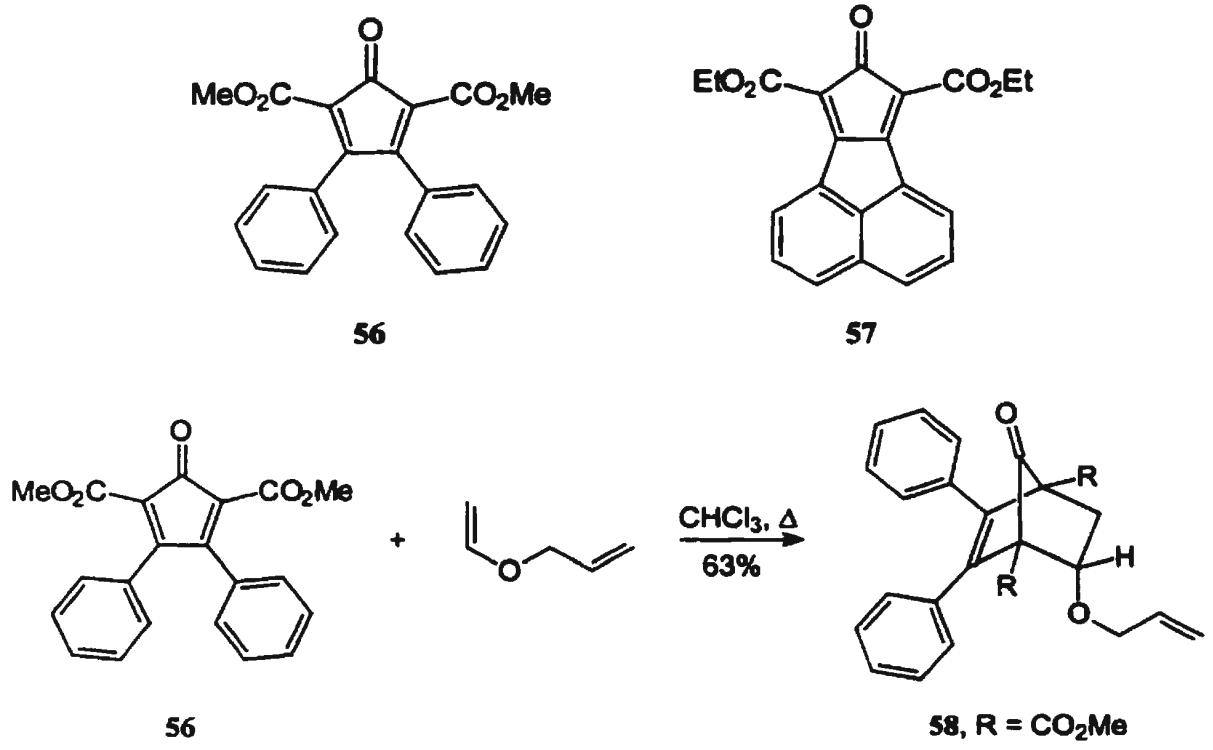


54 **55**

Scheme 1.19: IEDDA reaction of thiophene-1,1-dioxide **54** with indole.

IEDDA reactions of cyclopentadienones[39] have led to bicyclic ketones. The reaction of cyclopentadienone **56** with allyl vinyl ether gave bicyclic ketone **58** in 63% yield. However the instability of simple cyclopentadienones required the incorporation of numerous and bulky stabilizing substituents, such as in **56** or **57**,[40] leading to decreased synthetic utility. Loss of carbon monoxide led to new, albeit neutral, dienes which could conceivably participate in a second Diels-Alder cycloaddition, yielding polycyclic systems.

[39] Harano, K.; Yasuda, M.; Kanematsu, K. *J. Org. Chem.* **1982**, *47*, 3736-3743., Harano, K.; Uchida, K.; Izuma, M.; Aoki, T.; Eto, M.; Hisano, T. *Chem. Pharm. Bull.* **1988**, *36*, 2312-2322.
[40] Harano, K.; Yasuda, M.; Ban, T.; Kanematsu, K. *J. Org. Chem.* **1980**, *45*, 4455-4462.

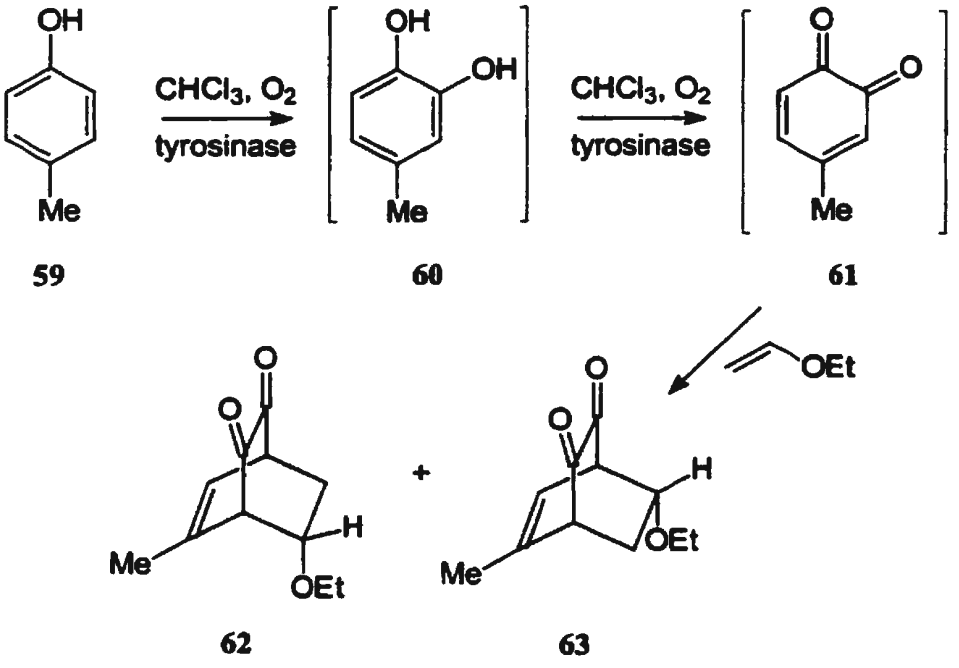


Scheme 1.20: IEDDA reactivity of cyclopentadienone **56**.

More recently, the inverse-electron-demand Diels-Alder reactions of *ortho*-quinones have been studied.[41] In a domino reaction, a variety of *o*-quinones, prepared *in situ* by enzyme initiated hydroxylation and oxidation of phenols, were reacted with electron rich dienophiles giving bicyclic 1,2-diketones, often in high yields over the three steps. 4-Methylphenol (**59**), when subjected to tyrosinase in the presence of oxygen, led to *o*-quinone **61** by way of catechol **60**. *o*-Quinone **61** then reacted with ethyl vinyl ether to give a 33:1 mixture of regioisomers **62** and **63** in 77% yield. This was the best regioselectivity realized under the reported conditions, and typical regioslectivities were

[41] Müller, G.H.; Lang, A.; Seithel, D.R.; Waldmann, H. *Chem. Eur. J.* **1998**, *4*, 2513-2522.

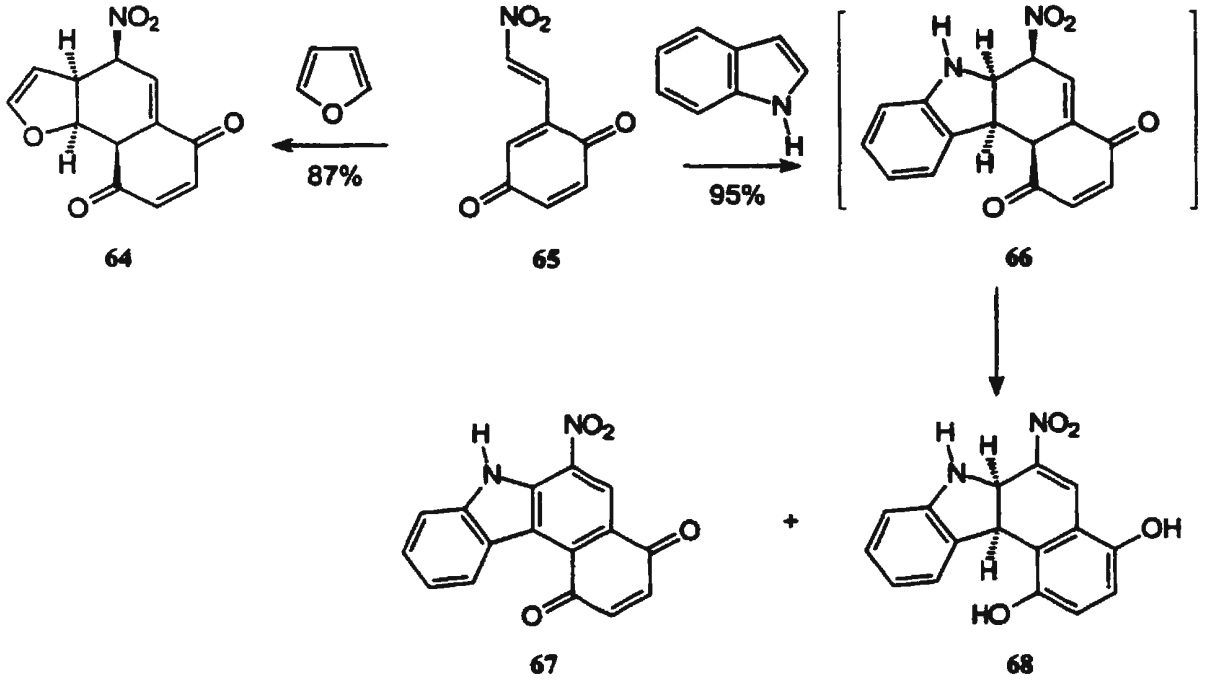
about 2 or 3:1, presumably due to the relatively low polarization of the diene moiety in the *o*-quinones. All products observed were those arising from an *endo* transition state.



Scheme 1.21: Enzyme initiated hydroxylation-oxidation IEDDA domino reaction.

The IEDDA reactions of nitrovinylquinones with dienophiles, including furans, indoles, and endocyclic enol ethers such as dihydropyran, have been described.[42] These reactions proceeded with high regioselectivity and the products could be transformed further to give fully aromatized systems. Quinone **65**, when reacted with neat furan, afforded **64** in 87% yield. Reaction of **65** with indole in benzene gave a 3.6:1 mixture of **68** and **67**, via IEDDA cycloadduct **66** and subsequent tautomerization to the dihydroquinone, which partially oxidized to the quinone.

[42] Noland, W.E.; Kedrowski, B.L. *J. Org. Chem.* **1999**, *64*, 596-603.

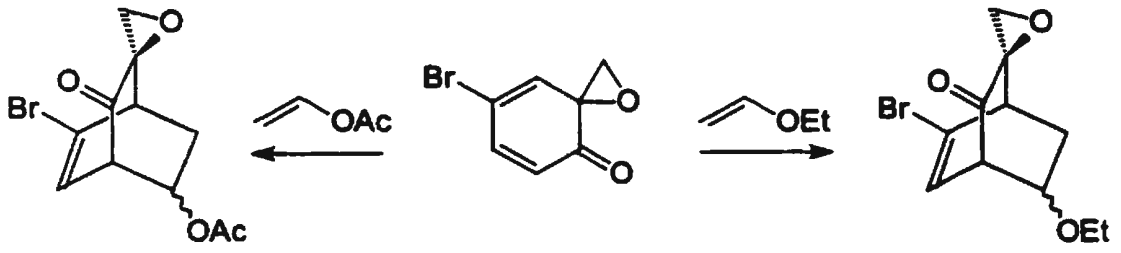


Scheme 1.22: Representative IEDDA reactions of nitrovinylquinone **65**.

4-Bromo-6-spiroepoxycyclohexa-2,4-dienone (**70**) has also recently been examined as an electron deficient diene in IEDDA reactions with electron rich dienophiles.[43] Diene **70** reacted with a range of dienophiles, giving bicyclic adducts regiospecifically, in good yields, and excellent facial selectivity with all dienophiles adding *syn* to the epoxide oxygen. The *endo*:*exo* selectivities varied from poor to excellent. For example, vinyl acetate reacted with diene **70** giving adduct **69** in 54% yield, with an *endo*:*exo* ratio of 1:2 while ethyl vinyl ether reacted to give **71** in 80% yield, with an *endo*:*exo* ratio of 19:1. The differences in selectivities were explained

[43] Bonnarme, V.; Bachmann, C.; Cousson, A.; Mondon, M.; Gesson, J.-P. *Tetrahedron* **1999**, *55*, 433-448.

based on the results of a computational study examining lowest energy conformations of the dienophile in the transition state.



69 70 71

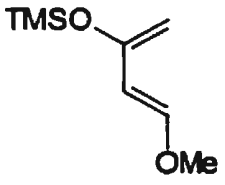
Scheme 1.23: Representative IEDDA reactions of spiroepoxydiene **70**.

1.3 Novel Electron Deficient Dienes

Electron deficient dienes bearing electron withdrawing groups in both the 1- and 3- positions, which would be formal electronic complements of well known normal demand dienes, such as Danishefsky's diene (**72**)[44] and more recently Rawal's diene **73**,[45] have received comparatively little attention in the literature. That the 1,3- arrangement of substituents on the diene has the cooperative effect of electronically biasing and increasing the reactivity of the diene is well known for the normal Diels-Alder reaction.[46] It was expected that the same effect would be observed in the IEDDA reaction, based on explanations that can be derived from frontier molecular orbital or valence bond theories. Such dienes should, in theory, undergo highly regioselective IEDDA reactions with electron rich dienophiles. In addition, the adducts obtained would be multifunctional,

[44] Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807-7808.
[45] Kozmin, S.A.; Janey, J.M.; Rawal, V.H. *J. Org. Chem.* **1999**, *64*, 3039-3052.

with plenty of opportunity for the introduction of further functionality. If as successful in Diels-Alder reactions as their normal demand counterparts, such electron deficient dienes could become just as synthetically useful in the preparation of complex cyclic natural products.



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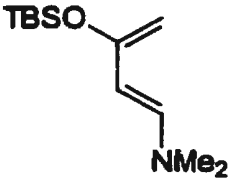
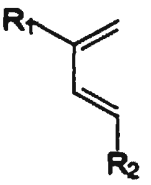


73

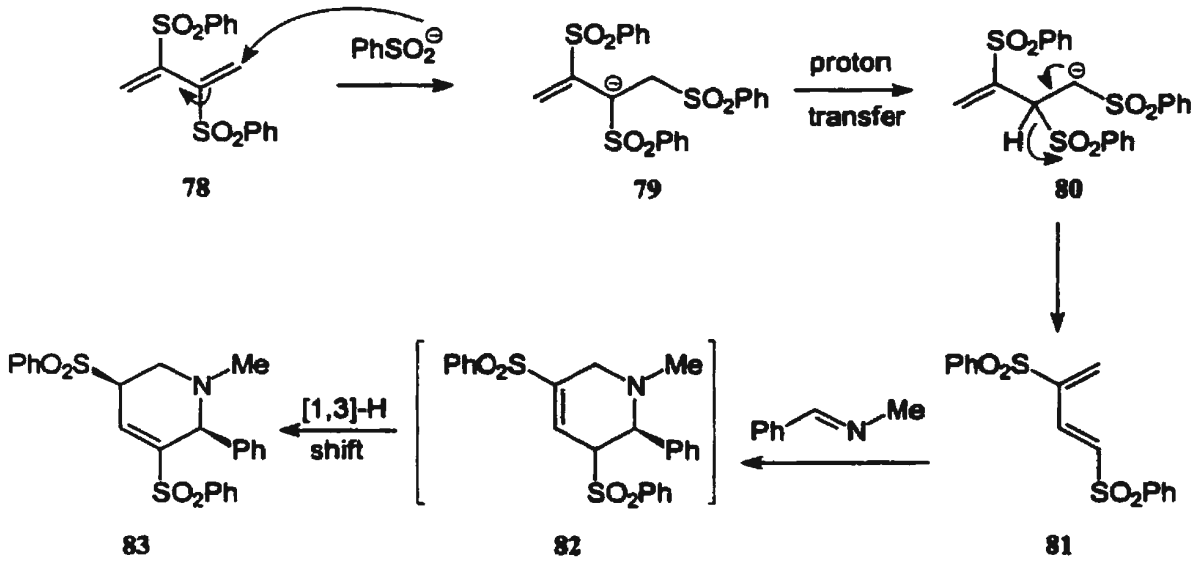


74: $R_1=R_2=CO_2Me$
75: $R_1=R_2=CN$
76: $R_1=CO_2Me$, $R_2=CN$
77: $R_1=CN$, $R_2=CO_2Me$

Dienes **74**, **75**, **76**, and **77** have been synthesized and were reported to readily polymerize in a 1,4-sense.[47] Their Diels-Alder reactivity was not examined. While a number of sulfonyl substituted 1,3-dienes have been studied,[48] the most promising lead in this area was the report of 1,3-bis(phenylsulfonyl)diene **81** by Padwa's group.[49] This diene readily dimerized when pure, but when generated *in situ* from 2,3-bis-(phenylsulfonyl)diene **78**, participated in IEDDA reactions with a variety of dienophiles including aryl imines,[50] enamines and ynamines.[51] Performing the reaction with *N*-

[46] Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400-406.; Grayson, J.I., Petrzilka, M. *Synthesis* **1981**, 753-786.; Hickmott, D.W. *Tetrahedron* **1984**, *40*, 2989-3051.
[47] Ahn, K.D.; Hall, H.K. *J. Polym. Sci., Polym. Chem.* **1981**, *19*, 629-644.
[48] Bäckvall, J.-E.; Chinchilla, R.; Nájera, C.; Yus, M. *Chem. Rev.* **1998**, *98*, 2291-2312.
[49] Padwa, A.; Harrison, B.; Norman, B.H. *Tetrahedron Lett.* **1989**, *30*, 3259-3262.
[50] Padwa, A.; Gareau, Y.; Harrison, B.; Norman, B.H. *J. Org. Chem.* **1991**, *56*, 2713-2720.
[51] Padwa, A.; Gareau, Y.; Harrison, B.; Rodriguez, A. *J. Org. Chem.* **1992**, *57*, 3540-3545.

benzylidenemethylamine led to the formation of the rearranged Diels-Alder cycloadduct **83** in 90% yield at room temperature.



Scheme 1.24: Proposed mechanism for *in situ* formation and IEDDA reaction of 1,3-bis(phenylsulfonyl)diene **81**.

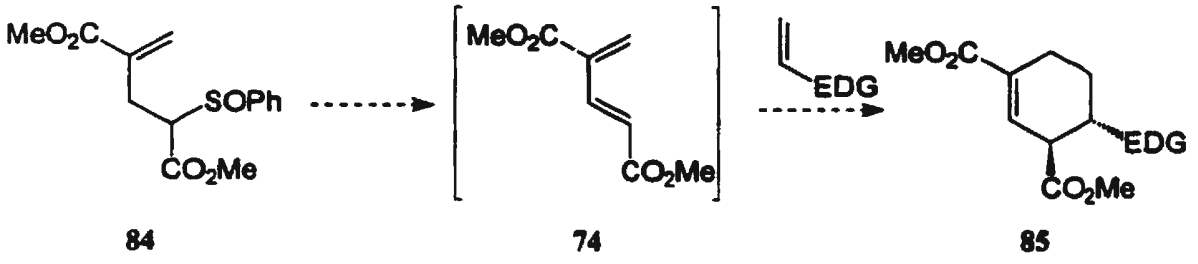
Conversion of **78** to the active diene **81** was attributed to the formation of the carbanion (**79**) by the presence of a trace quantity of aryl sulfinate anion, presumably remaining from the synthesis of **78**, followed by proton transfer to carbanion **80** and elimination of the neighboring aryl sulfinate group. Required reaction times were decreased upon addition of catalytic sodium benzenesulfinate. The unstable diene **81** was then trapped with the dienophile, leading to direct cycloadduct **82**, which then rearranged, reported via a [1,3]-hydride shift, giving **83** as the final product. None of the direct Diels-Alder adduct (**82**) was detected.

Based upon the promising results of Padwa's report in particular, on demonstrating the feasibility of preparing and reacting butadienes with electron withdrawing groups in the 1- and 3- positions, our group believed that this area of inverse-electron-demand Diels-Alder chemistry required more thorough exploration. The efforts taken to prepare some novel electron deficient 1,3-dienes and an examination of their inverse-electron-demand Diels-Alder chemistry are the focus of the following two chapters of this text.

2.0 Preparation of Electron Deficient Dienes

2.1 Previous Diene Syntheses

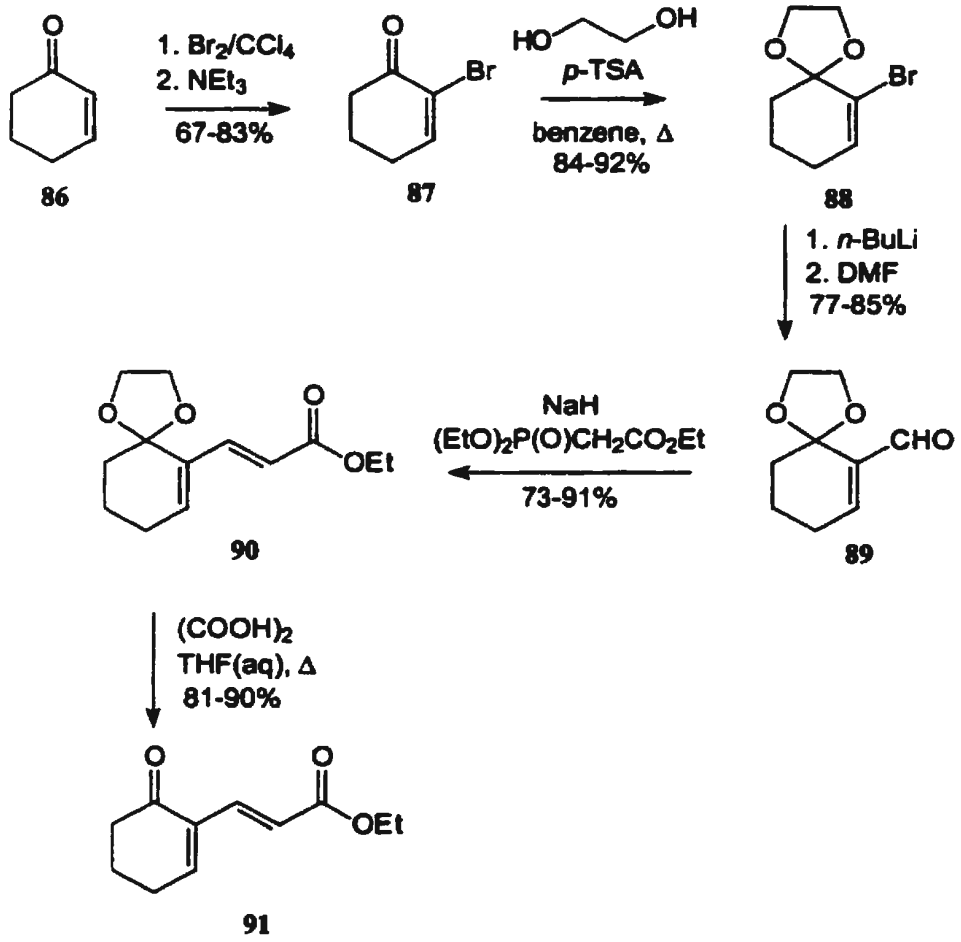
Efforts by our group to prepare reactive electron deficient dienes have been reasonably successful to date. In light of the report of dienes such as **74**, **75**, **76** and **77**,[47] some earlier work set out to examine the inverse-electron-demand Diels-Alder reactivity of diene **74**. Methods were explored[52] for a mild *in situ* generation of the diene in the presence of an activated dienophile that could react to give an inverse-electron-demand Diels-Alder adduct (**85**). Sulfoxide **84** was prepared, but a variety of methods to effect the thermal sulfoxide elimination to diene **74** enjoyed only limited success and no IEDDA adducts or follow-on products were detected in the presence of ethyl vinyl ether.



84 **74** **85**

Scheme 2.1: Attempted *in situ* preparation of diene **74** by sulfoxide elimination.

[52] Swinamer, A. *M.Sc. Thesis* **1997**, Memorial University of Newfoundland.

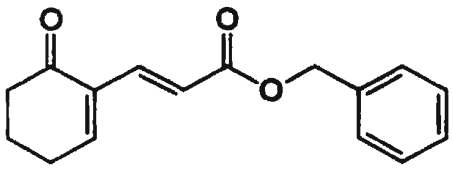


Scheme 2.2: Synthesis of electron deficient diene **91**.

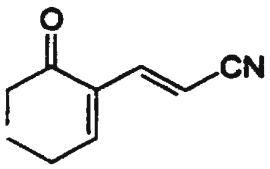
At the same time, a strategy of cycloalkane-annulating the diene in an effort to impart greater kinetic stability to the diene moiety was explored. Diene **91** was synthesized in five steps from 2-cyclohexen-1-one (**86**).[53] Bromination of **86** with Br_2 at 0 °C, followed by dehydrobromination with triethylamine, gave bromoenone **87** in up to 83% yield. This material, which was not stable, could easily be converted to the acetal **88** in 84-92% yield. Acetal **88** was a very stable species and could be stored indefinitely

at -20 °C under nitrogen. Treatment of **88** with *n*-butyllithium at -78 °C, followed by the addition of dry DMF, led to aldehyde **89** in 77-85% yield. Horner-Wadsworth-Emmons olefination gave diene **90** (73-91% yield) and deprotection by refluxing with oxalic acid in aqueous THF gave diene **91** in 81-90% yield. Diene **91** was found to be sufficiently stable to be isolated and characterized; it was stable for several weeks when stored under a nitrogen atmosphere at -20 °C. The direct synthetic precursor to **91**, acetal **90** was reported to be stable under the same conditions for several months.

Diene **91** did undergo IEDDA reactions with a variety of activated dienophiles, including ethyl vinyl ether, 1,1-diethoxyethene, styrene, and enamines.[54] While, by the same synthetic sequence dienes **92** and **93** were prepared, studies focused mainly on the IEDDA reactivity of diene **91**.

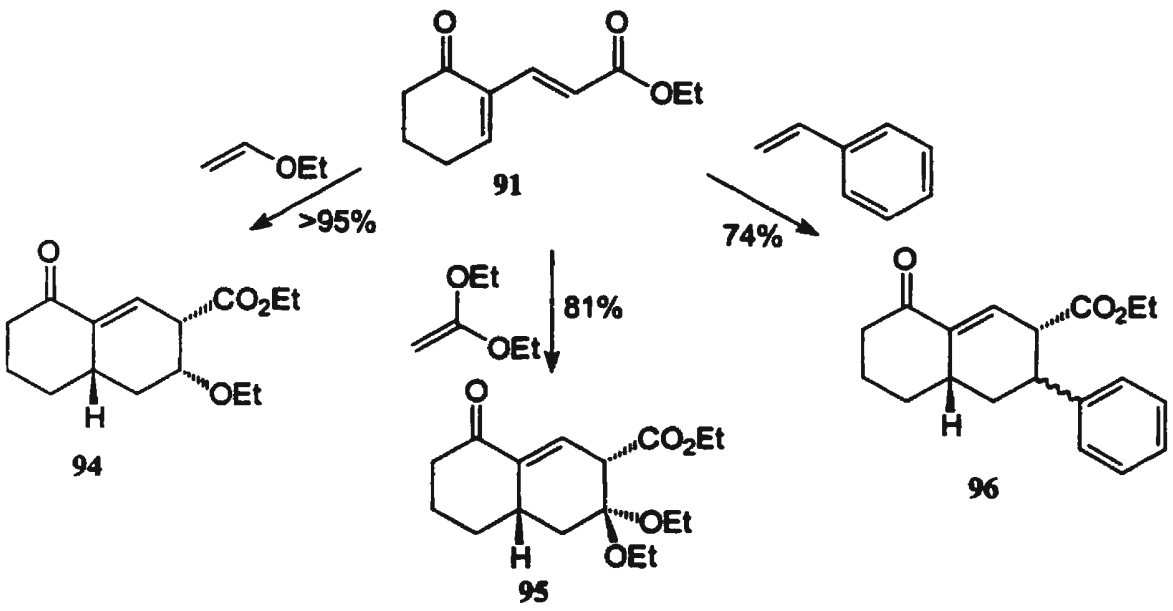


92



93

[53] Bodwell, G.J.; Pi, Z. *Tetrahedron Lett.* **1997**, *38*, 309-312.
[54] Bodwell, G.J.; Pi, Z.; Pottie, I.R. *Synlett* **1999**, 477-479.

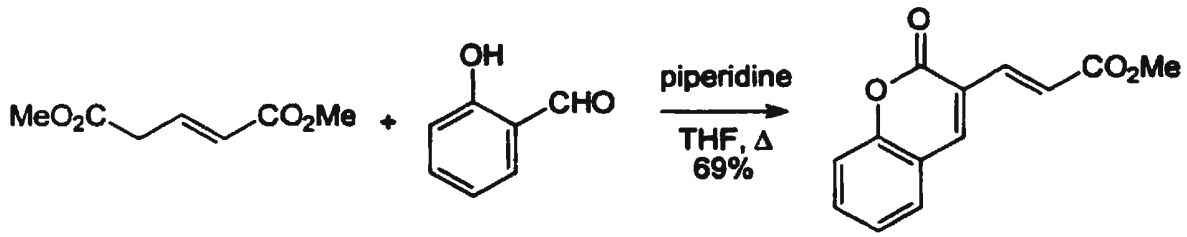


Scheme 2.3: Example IEDDA reactions of diene **91**.

In all cases, complete regioselectivities were observed, as were high, if not complete, *endo* selectivities when applicable. For cycloadditions giving rise to *cis*-substituted cyclohexene rings, such as **94** and **96**, epimerization at the carbon bearing the ethyl ester was observed during chromatography. This was presumably due to relief of steric strain imposed by the *cis*-relationship of the substituents.

Extension of this work, as well as the desire for more expedient syntheses of electron deficient dienes, led to the examination of the vinylogous Knoevevagel condensation. This permitted the preparation of diene **99** in one step from dimethyl glutaconate (**97**) and salicylaldehyde (**98**) in 69% yield.[54] This diene proved to be extremely stable, surviving indefinitely without significant decomposition, even in air at room temperature. The partial aromatic character of the 2-pyrone moiety most likely

contributed to this enhanced stability. However this also led to decreased IEDDA reactivity. For example, diene **99** does not react with ethyl vinyl ether, even at 140 °C for prolonged periods. IEDDA reactions of diene **99** do proceed with more reactive dienophiles, such as enamines.



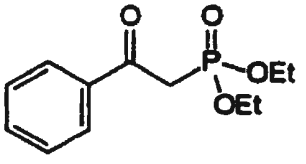
97 **98** **99**

Scheme 2.4: Synthesis of electron deficient diene **99**.

2.2 Novel Diene Synthesis: Results and Discussion

It was of interest to extend the work on diene **91** and to prepare a diene which would display improved kinetic stability relative to diene **91**, without significant compromise, or maybe even improvement, of the IEDDA reactivity. It was postulated that the desired results might be achieved by increasing the electron withdrawing nature of the substituents on the diene. For example, changing the electron withdrawing group at the 1- position of the diene unit from an ester to a ketone was expected to give a diene more reactive towards IEDDA cycloadditon. In addition, by simply adding bulky substituents such as a phenyl group, improved kinetic stability might be realized.

Thus, diene **102** was synthesized in a manner analogous to the synthesis of diene **91**. The bromination, dehydrobromination, conversion of the ketone to the acetal, and formylation to prepare aldehyde **89**, all proceeded smoothly with yields within the reported ranges.[53] Horner-Wadsworth-Emmons olefination[55] of aldehyde **89** with phosphonate **100**[56] gave diene acetal **101** in 76% yield. Phosphonate **100** was generated in 72% yield by Michaelis-Arbuzov reaction[57] of 2-bromoacetophenone with triethyl phosphite. The major product of the olefination reaction was determined to be the (*E*)-isomer by the 15.8 Hz coupling constant between C2-H and C3-H of the newly formed alkene. ^{1}H NMR detected no material consistent with the (*Z*)-isomer of the alkene. This material was initially isolated as a thick yellow oil, but continued efforts to further purify the material resulted in a low melting, bright yellow solid. Acetal **101** was stable indefinitely when stored under nitrogen at -20 °C. However, decomposition occurred when it was allowed to remain at room temperature for prolonged periods, even under a nitrogen atmosphere.

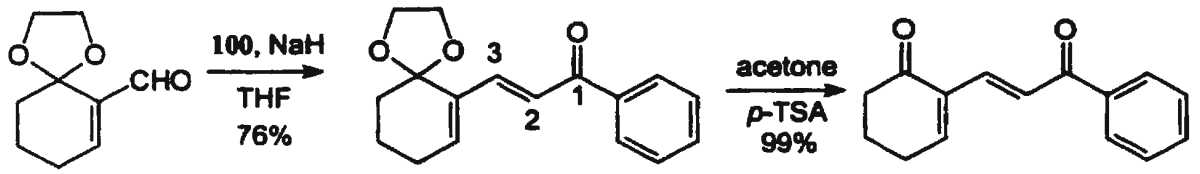


100

[55] For reviews of the Horner-Wadsworth-Emmons olefination, see: Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87-99.; Wadsworth, W.S. *Org. React.* **1977**, *25*, 73-253.; Groß, H.; Keitels, I. *Z. Chem.* **1982**, *22*, 117-126.

[56] Mathey, F.; Savignac, P. *Tetrahedron* **1978**, *34*, 649-654.

[57] For a review of the Michaelis-Arbuzov reaction, see: Bhattacharya, A.K.; Thyagarajan, G. *Chem. Rev.* **1981**, *81*, 415-430.



89 101 102

Scheme 2.5: Synthesis of electron deficient diene **102**.

In the original synthesis of diene **91**, treatment with oxalic acid in refluxing aqueous THF was used to remove the 1,3-dioxolane protecting group of diene **90**.[53] It was found that in the synthesis of **102**, an acetal exchange reaction[58] could be used for a more convenient removal of the protecting group from acetal **101**. Accordingly, **101** was treated with catalytic *p*-TSA in acetone[59] to give diene **102** in nearly quantitative yield in as little as one hour at room temperature. When the acetal exchange reaction was performed with distilled acetone and aqueous extraction solutions were prepared with deionized water, the crude product was sufficiently pure for use in subsequent reactions. For characterization purposes however, recrystallization from hexanes was performed. This often resulted in lower yields of product due to some oiling out of the material. Other lower boiling solvents such as diethyl ether and pentanes were less effective at dissolving the product.

Diene **102** was stable for several months when stored under nitrogen at -20 °C. However, like its acetal precursor, it slowly decomposed when allowed to stand at room temperature. As in the case of diene **91**, storing the diene as the acetal was very

[58] Bauduin, G.; Pietrasanta, Y.; Pucci, B. *Tetrahedron* **1977**, *33*, 3105-3110.; Bauduin, G.; Bondon, D.; Pietrasanta, Y.; Pucci, B. *Tetrahedron* **1978**, *34*, 3269-3274.

convenient and prevented excessive loss of material. Various attempts at identifying the decomposition products of diene **102** ended in limited success. ^{1}H NMR spectra of partially decomposed material consistently suggested complex mixtures. Stirring the diene at room temperature in ethyl acetate for two weeks resulted in partial conversion of the diene to at least two new products, as indicated by TLC. Isolation and attempted purification by flash chromatography afforded material that, while complex by ^{1}H NMR, gave a mass spectrum which implied that dimerization may be one process through which the diene was being consumed. Although no molecular ion was observed for a dimer (*m/z* 452), an ion was observed for the loss of a phenyl ketone from a dimer (*m/z* 347), and the presence of an ion that was consistent with a phenyl ketone (*m/z* 105) was unmistakable as the base peak in the mass spectrum. The observation during TLC analysis of the formation of two major new products may further support the process of dimerization of the diene; each new spot corresponding to the *endo* and *exo* adducts of a Diels-Alder cycloaddition. Regardless of the process of decomposition, ion peaks which are heavier than that of the diene (*m/z* 226) exist in the mass spectrum which suggests some type of self reaction is occurring.

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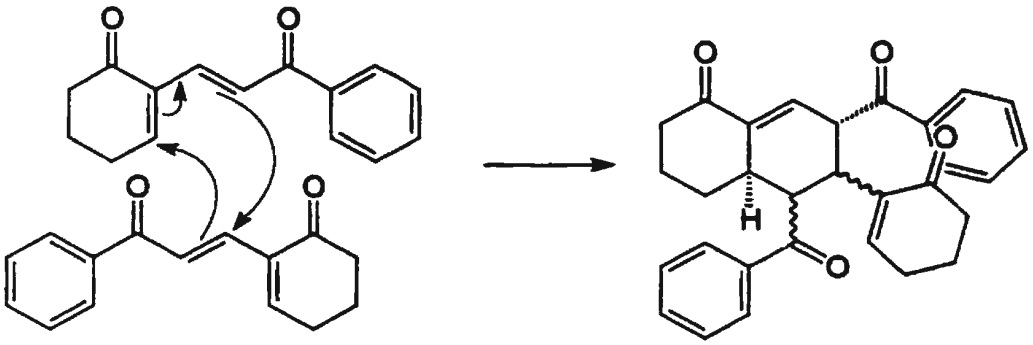
[59] Colvin, E.W.; Raphael, R.A., Roberts, J.S. *J. Chem. Soc., Chem. Commun.* **1971**, 858-859.



Scheme 2.6: One possible mechanism for dimerization of diene **102**.

2.3 Progress Toward Improved Diene Syntheses

Even though dienes such as **91** and **102** could be prepared fairly readily, each synthesis required five steps. Before inverse-electron-demand Diels-Alder reactions of such electron deficient dienes become more synthetically useful processes, more efficient modes of preparation are desirable.

The syntheses of a number of electron deficient dienes by palladium catalyzed cross coupling reactions have been explored recently.[60] Due to its apparently more direct route, it was the Heck reaction[61] that was initially examined as an improved synthesis of dienes related to **91**. Cursory attempts to react vinyl bromides **87** or **88** with ethyl acrylate in the presence of a Pd catalyst, either $Pd(PPh_3)_4$ or $Pd(OAc)_2$, did not yield the

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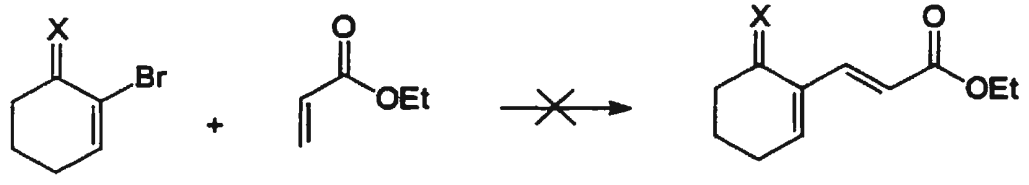
[60] Houpis, I.N.; DiMichele, L.; Molina, A. *Synlett* **1993**, 365-366.; Rossi, R.; Carpita, A.; Bellina, F.; Cossi, P. *J. Organometallic. Chem.* **1993**, *451*, 33-43.; Jeges, G.; Skoda-Földes, R.; Kollár, L.; Horváth, J.; Tuba, Z. *Tetrahedron* **1998**, *54*, 6767-6780.; Kim, H.-O.; Ogbu, C.O.; Nelson, S.; Kahn, M. *Synlett* **1998**, 1059-1060.

desired dienes, **91** or **90** respectively. Varying the nature of the base (triethylamine and DBU), the temperature (room temperature and refluxing in benzene), as well as the addition of CuI all did not lead to the formation of the desired product.

In all cases, the vinyl halide was nearly, if not completely, consumed, suggesting that the desired coupling reaction might have occurred, but that the product may have been too reactive under the reaction conditions. Dienes **90** and **91** are both known to decompose at elevated temperatures. In addition, dienes of this type have been observed to be unstable in the presence of amine bases, such as triethylamine and DBU. The use of high pressure[62] for these couplings was not explored.



87, X = O
88, X = OCH_2CH_2O

91, X = O
90, X = OCH_2CH_2O

Scheme 2.7: Reactants for attempted palladium catalyzed synthesis of electron deficient dienes.

Vinylic iodides are generally more reactive than bromides,[63] so vinyl iodide **103**[64] was prepared. Vinyl iodide **103** was reported to undergo Pd-catalyzed Suzuki coupling

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[61] Dieck, H.A.; Heck, R.F. *J. Am. Chem. Soc.* **1974**, *96*, 1133-1136.; Patel, B.A.; Heck, R.F. *J. Org. Chem.* 1978, *43*, 3898-3903.; For a review, see: de Meijere, A.; Meyer, F.E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379-2441.

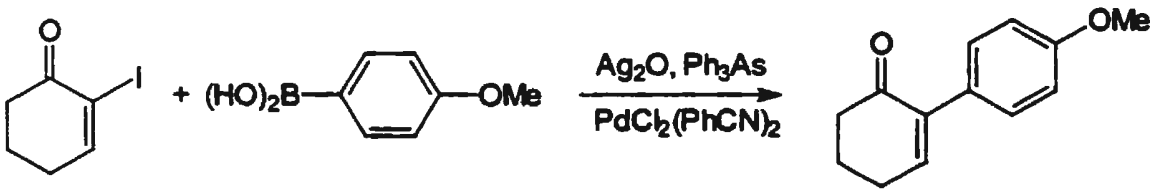
[62] Voigt, K.; Schick, U.; Meyer, F.E.; de Meijere, A. *Synlett* **1994**, 189-190.

[63] Dieck, H.A.; Heck, R.F. *J. Org. Chem.* **1975**, *40*, 1083-1090.; Kim, J.-I.I.; Patel, B.A.; Heck, R.F. *J. Org. Chem.* **1981**, *46*, 1067-1073.

[64] Ruel, F.S.; Braun, M.P.; Johnson, C.R. *Org. Synth.* **1997**, *75*, 69-77.

reactions, such as in the formation of **106** when treated with boronic acid **105**. However, when subjected to the Heck reaction conditions described above, none of the desired diene was obtained. As all **103** was consumed in these reactions, it was unclear whether the coupling reaction occurred, followed by decomposition of the resulting diene, or if the reportedly[64] unstable **103** did not survive under these reaction conditions. Attempts to prepared the 1,3-dioxolane **104**, from **103**, were also unsuccessful. Palladium catalyzed cross coupling reactions of this iodide could have led to diene precursors, such as acetal **90**.

103 **104**

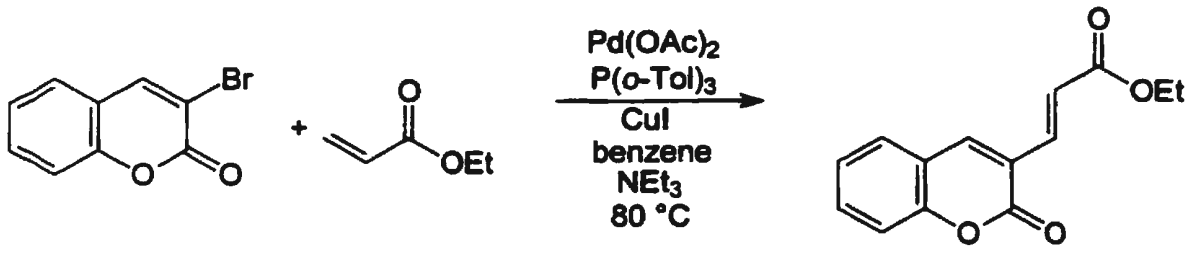


103 **105** **106**

Scheme 2.8: Sample Suzuki reaction of vinyl iodide **103**

Despite the disappointing results for the attempted palladium catalyzed cross coupling reactions, this system deserves further investigation, particularly in light of the successful Pd-catalyzed synthesis of some coumarin-fused dienes from 3-bromocoumarin

(107).[65] Diene **108** was prepared in as high as 85% yield by Heck reaction of **107** with ethyl acrylate.



107 **108**

Scheme 2.9: Preparation of coumarin-fused diene **108** via Heck reaction.

The titanium catalyzed synthesis of conjugated dienes, including electron deficient dienes, from alkynes, as discussed in a recent report, [66] was not explored for the synthesis of diene such as **91** or **102**.

2.4 Progress Towards Other Electron Deficient Dienes

Efforts to synthesize other interesting electron deficient dienes, particularly diene **109**, were undertaken. Previous efforts[67] to make a cyclopentenone based diene had limited success and were not pursued beyond an initial examination. In the formylation of **111**, the desired product was obtained in only 32% yield; it was suspected that aldehyde **112** was somewhat unstable.

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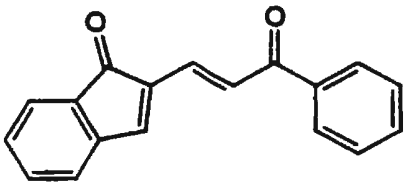
[65] Bodwell, G.J.; Lines, W. *Unpublished results.*
[66] Hamada, T.; Suzuki, D.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 7342-7344.
[67] Pi, Z. *M.Sc. Thesis* **1996**, Memorial University of Newfoundland.



109

110 111 112

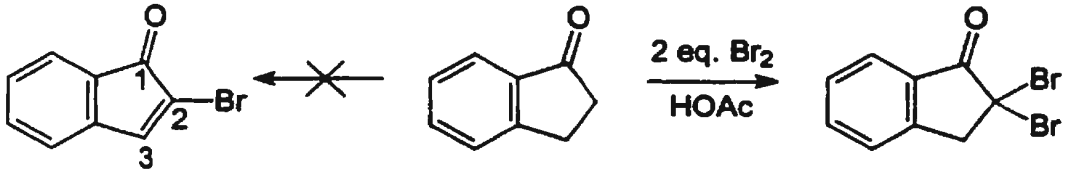
Scheme 2.10: Attempted synthesis of cyclopentanone based dienes.

Initially, it was speculated that the bromination of 1-indanone (**114**) with two equivalents of bromine in acetic acid[68], via dibromination and dehydrobromination under the acidic reaction conditions, might lead to enone **113**. This bromoenone could then be subjected to the standard reaction sequence for the preparation of the dienes **91** and **102**, to give diene **109**. However, under the reaction conditions, the dehydrobromination did not occur and dibromide **115**[69] was obtained in an excellent yield of 93%.

Treatment of **115** with a variety of bases, including triethylamine, pyridine and potassium *tert*-butoxide did not effect the desired dehydrobromination. Only in the case of triethylamine in refluxing CH_2Cl_2 was a small amount (<5 %), of what appeared to be the desired product (**113**), observed. No pure material was obtained, but a ^1H NMR spectrum of the crude material showed only aromatic signals, including a singlet

[68] Langley, W.D.; Clarke, H.T.; Boutwell, P.W. *Org. Synth., Coll. Vol. I* **1941**, 127-128.

integrating to one at δ = 7.59 ppm, which may have been the C3-H of **113**. While in all cases some starting material was recovered, large quantities of intractable material were also produced. This may have been due to the reported[70] instability of **113**; not entirely surprising given its partial antiaromatic character.



113 **114** **115**

Scheme 2.11: Attempted preparation of bromoenone **113**.

Attempted dehydrobromination of **115** using lithium bromide and lithium carbonate in hot DMF[71] resulted in the formation of one product. However, isolation was difficult and no pure material was obtained, again suggesting that the product may be unstable. Attempts to generate acetals **116** or **117** from the crude material, either by treatment with ethylene glycol or by acetal exchange using 2,2-dimethoxypropane, were also unsuccessful. Potentially milder, acid free methods of generating acetals, including a procedure which uses chlorotrimethylsilane,[72] were not explored for this system but may have a role in future investigations.

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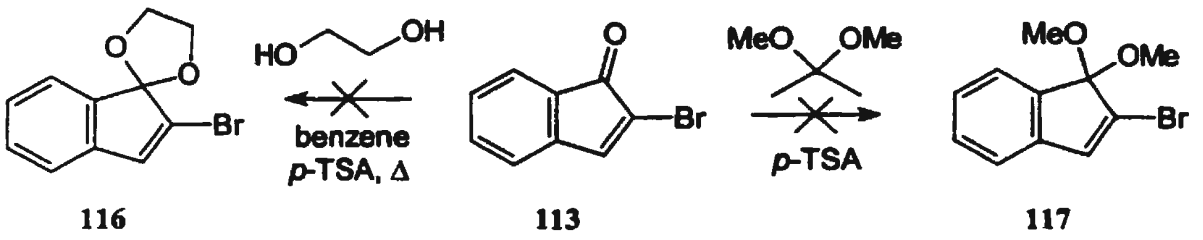
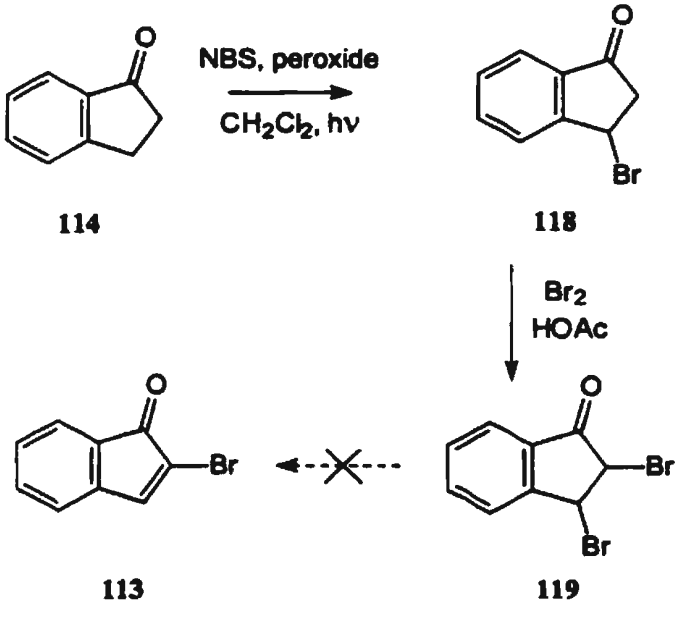
[69] Rutherford, K.G.; Stevens, C.L. *J. Am. Chem. Soc.* **1955**, *77*, 3278-3280.
[70] Marvel, C.S.; Hinman, C.W. *J. Am. Chem. Soc.* **1954**, *76*, 5435-5437.; Undheim, K.; Hansen, P.E. *Chemica Scripta* **1972**, *3*, 113-116.
[71] Holysz, R.P. *J. Am. Chem. Soc.* **1953**, *75*, 4432-4437.; Stotter, P.L.; Hill, K.A. *J. Org. Chem.* **1973**, *38*, 2576-2578.
[72] Chan, T.H.; Brook, M.A.; Chaly, T. *Synthesis* **1983**, 203-205.



116 113 117

Scheme 2.12: Unsuccessful acetal formation from crude 113.



114 118 113 119

Scheme 2.13: Proposed alternate route to bromoenone 113.

Another route, which could generate bromoenone **113** under milder conditions, compared to heating in basic DMF, was also explored. Dibromide **119**[70] was prepared by benzylic bromination of 1-indanone (**114**), giving **118**, followed by α-bromination with bromine in acetic acid. Disappointingly, attempted dehydrobromination of **119** with

triethylamine at 0 °C[73] led to a complex mixture of products. At this stage, pursuits toward the synthesis of diene **109** were abandoned and the study of the IEDDA chemistry of diene **102** was resumed.

2.5 Experimental for Diene Synthesis

2.5.1 General Experimental Procedures

All reactions were performed in air unless otherwise noted. Except where stated, commercial reagents and all solvents were used without further purification. Benzene, toluene, DMF and acetonitrile (CH_3CN) were distilled from calcium hydride and stored over 4Å molecular sieves under nitrogen. THF was distilled immediately prior to use from sodium/benzophenone. All recrystallizations were performed with distilled solvents. Melting points (mp) were measured with a Fisher-Johns melting point apparatus and are uncorrected.

Thin layer chromatography (TLC) was performed using Macherey-Nagel Polygram® SIL G/UV_{254} precoated silica plates. Flash chromatography was carried out using Silica Gel 60 (E. Merck, 230-400 mesh) with the mobile phase solvents indicated in the experimental sections.

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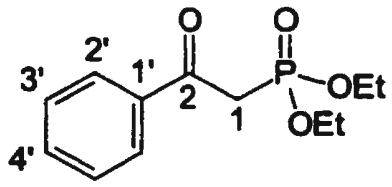
[73] Lie, R.; Undheim, K. *J. Chem. Soc., Perkin Trans. I* **1973**, 2049-2050.

Nuclear magnetic resonance (NMR) spectra were acquired on a General Electric GN-300NB spectrometer at 300.1 MHz for ^{1}H NMR and 75.5 MHz for ^{13}C NMR, using $CDCl_3$ as solvent, unless otherwise noted. Chemical shifts are reported in ppm measured relative to tetramethylsilane (δ = 0.0 ppm) for ^{1}H NMR and $CHCl_3$ (δ = 77.0 ppm) for ^{13}C NMR. Proton spectra are reported as chemical shift, number of hydrogens, multiplicity, coupling constant and signal assignment. Carbon spectra are reported as chemical shift, followed by the number of attached protons (either 0, 1, 2 or 3) and the signal assignment, when possible. Signal assignments and the number of attached protons are based on the results of ^{1}H-COSY, ^{13}C-APT, ^{1}H, ^{13}C-HETCORR, or NOE-D experiments.

Infrared (IR) spectra were collected on a Mattson Polaris FT-IR spectrophotometer. Samples were either neat or as Nujol® films, using NaCl cells. Low resolution mass spectroscopy (MS) was performed on a V.G. Micromass 7070Hs mass spectrometer operating at 70 eV. Elemental analyses were obtained from the MicroAnalytical Service Laboratory at the University of Alberta.

2.5.2 Experimental

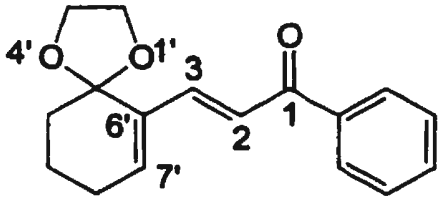
Diethyl (2-oxo-2-phenylethyl)phosphonate (100)



A magnetically stirred solution of 2-bromoacetophenone (25.1 g, 126 mmol) and triethyl phosphite (25 mL, 146 mmol) in a 50 mL round bottomed flask equipped with a distilling head and condenser, was slowly warmed to 160 °C under N_2. Once the desired temperature was reached, the reaction was maintained for 1 h, while bromoethane collected in the receiving flask. The crude product was cooled, and purified by flash chromatography (70% EtOAc/hexanes, R_f = 0.23) yielding phosphonate **100** as a clear, colourless liquid (23.4 g, 91.3 mmol, 72%). b.p.: 180-188 °C/5.5 mm Hg (lit. 150-155 °C/0.9 mm Hg[56]). IR (neat): ν_{max} 1682 (s), 1599 (m), 1448 (m), 1257 (s), 1027 (s), 968 (s), 786 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 8.02 (2H, dd, J = 8.4, 1.3 Hz, C2'-H), 7.60 (1H, tt, J = 7.4, 1.6 Hz, C4'-H), 7.48 (2H, td, J = 6.7, 1.5 Hz, C3'-H), 4.14 (4H, m -OCH_2CH_3), 3.64 (2H, d, J = 22.8 Hz, C1-H), 1.28 (6H, t, J = 7.0 Hz, -OCH_2CH_3). ^{13}C NMR ($CDCl_3$): δ = 191.9 (d, J_{CP} = 6.2 Hz, C2), 136.4 (C1'), 133.6 (C4'), 128.9 (C2'), 128.5 (C3'), 62.5 (d, J_{CP} = 6.5 Hz, -OCH_2CH_3), 38.4 (d, J_{CP} = 130 Hz, C1), 16.2 (-OCH_2CH_3). MS *m/z* (%): 256 (M^+, 4), 211 (2), 183 (1), 166 (2), 155 (16), 139 (13), 127 (11), 111 (27), 105 (100), 99 (23), 93 (21), 81 (28), 77 (35).

Note: Chromatography was superior to distillation under reduced pressure as less polar side-products were not completely removed during distillation. The following work-up procedure worked very well for the purification of phosphonate **100** on large scale. Approximately 31 g of crude product was dissolved into CH_2Cl_2 (250 mL) and extracted with 1M NaOH solution (4 × 250 mL). The aqueous layer was neutralized, then made slightly acidic with 3M HCl solution. The aqueous solution was then extracted with Et_2O (4 × 500 mL), dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure. This purification technique yielded product of comparable yield and purity to that obtained during chromatography.

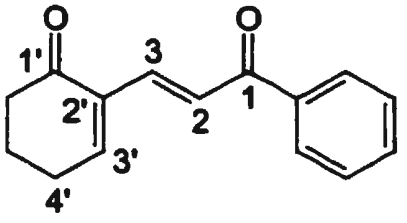
(2*E*)-3-(1',4'-Dioxaspiro[4,5]dec-6'-en-6'-yl)-1-phenyl-2-propen-1-one (101)



In a 100 mL three-neck round bottomed flask, equipped with a rubber septum, reflux condenser and addition funnel, was placed NaH (1.44 g, 36.1 mmol) and THF (25 mL). The flask was purged with nitrogen and cooled to about 0 °C (ice/salt water bath). A solution of phosphonate **100** (10.00 g, 39.0 mmol) in THF (50 mL) was added dropwise through the addition funnel. Following the addition, the mixture was warmed to r.t. for 30 min, then cooled again to 0 °C for the dropwise addition of 6-formyl-1,4-dioxospiro[4.5]dec-6-ene (**89**) (5.68 g, 33.8 mmol) in THF (25 mL). The reaction was

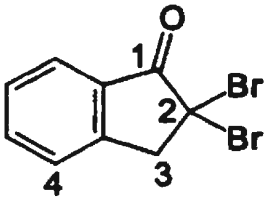
allowed to stir at 0 °C for 30 min, then at reflux for 2 h, before being cooled, quenched with saturated aqueous NH_4Cl solution (75 mL) and extracted with Et_2O (100 mL). The aqueous layer was washed with fresh Et_2O (3 × 25 mL) and the combined organic solutions were dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. Flash chromatography (50% EtOAc/hexanes, $R_f = 0.52$), followed by rigorous removal of solvent under reduced pressure, afforded pure **101** as a yellow solid (6.93 g, 25.7 mmol, 76%). m.p.: 52.0-53.0 °C (pentanes). IR (film): ν_{max} 2946 (s), 1662 (s), 1601 (s), 1447 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.94-7.91 (2H, m), 7.58-7.43 (3H, m), 7.39 (1H, dd, J = 15.7, 0.9 Hz, C3-H), 7.16 (1H, d, J = 15.8 Hz, C2-H), 6.61 (1H, t, J = 4.1 Hz, C7'-H), 4.17-4.06 (4H, AA'BB' system, C2'-H + C3'-H), 2.28-2.23 (2H, m, C8'-H), 1.87-1.75 (4H, m, C9'-H + C10'-H). ^{13}C NMR ($CDCl_3$): δ = 191.0 (0, C1), 142.7 (1, C3), 139.0 (1, C7'), 138.6 (0, C6'), 135.9 (0), 132.7 (1), 128.7 (1), 128.6 (1), 122.8 (1, C2), 106.9 (0, C5'), 65.1 (2, C2' + C3'), 33.5 (2, C10'), 26.4 (2, C8'), 20.3 (2, C9'). MS *m/z* (%): 270 (M^+, 14), 242 (4), 198 (7), 170 (100), 105 (36), 99 (36), 77 (67).

(2*E*)-3-(1'-Oxo-2'-cyclohexen-2'-yl)-1-phenyl-2-propen-1-one (102)



A solution of diene acetal **101** (570 mg, 2.11 mmol) and *p*-TSA·H_2O (59 mg, 0.31 mmol) in distilled acetone (10 mL) was magnetically stirred at r.t. for 1 h. The stir-bar was removed and the acetone was evaporated under reduced pressure. The concentrated product mixture was diluted with Et_2O (50 mL) and extracted with water (50 mL), saturated aqueous $NaHCO_3$ solution (50 mL), and water (50 mL). The organic solution was dried ($MgSO_4$), filtered and concentrated under reduced pressure, yielding pure **102** as a yellow solid (475 mg, 2.10 mmol, 99%). m.p.: 65.0-66.5 °C (hexanes). IR (film): ν_{max} 1689 (s), 1666 (m), 1607 (s) 1578 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 8.30-7.99 (2H, m), 7.92 (1H, d, *J* = 16.2 Hz, C3-H), 7.59-7.45 (3H, m), 7.36 (1H, d, *J* = 16.1 Hz, C2-H), 7.33 (1H, t, *J* = 4.3 Hz, C3'-H), 2.61-2.50 (4H, m, C4'-H + C6'-H), 2.11-2.03 (2H, m, C5'-H). ^{13}C NMR ($CDCl_3$): δ = 198.1 (0, C1'), 191.4 (0, C1), 155.1 (1, C3'), 139.7 (1, C2), 138.2 (0), 134.7 (0), 133.0 (1), 128.8 (1), 128.7 (1), 125.1 (1, C3), 39.4 (2, C6'), 27.3 (2, C4'), 22.5 (2, C5'). MS *m/z* (%): 226 (M^+, 2), 207 (14), 170 (9), 121 (62), 105 (100), 91 (11), 77 (65).

2,2-Dibromoindanone (115)



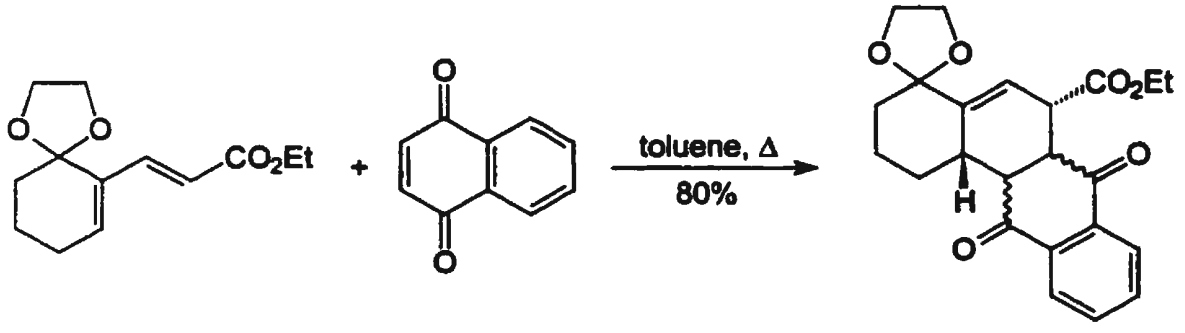
To a magnetically stirred solution of 1-indanone (**114**) (3.30 g, 25.0 mmol) in glacial acetic acid (10 mL), bromine (2.6 mL, 51.0 mmol) was added dropwise via a

syringe over 30 min. Following the bromine addition, the reaction was stirred at r.t. until a thick precipitate formed (approximately ten min). The mixture was cooled in an ice/water bath, then suction filtered to collect the solid, which was washed with cold 1:1 ethanol/water. The mother liquor was cooled in the ice bath and a second crop of precipitate was collected. The combined portions were dried under vacuum, yielding nearly pure **115** as an orange solid (6.75 g, 23.3 mmol, 93%). Pure **115** was obtained as a light yellow solid by recrystallization from ethanol. m.p.: 131-133 °C (ethanol; lit. 130-132 °C[69]). ^{1}H NMR ($CDCl_3$): δ = 7.95 (1H, d, J = 7.8 Hz, C7-H), 7.74 (1H, td, J = 7.5, 1.0 Hz, C5-H), 7.50 (1H, td, J = 7.6, 0.6 Hz, C6-H), 7.41 (1H, d, J = 7.7 Hz, C4-H), 4.29 (2H, s, C3-H). ^{13}C NMR ($CDCl_3$): δ = 192.9 (C1), 147.3 (C3a), 137.1, 129.2, 126.8, 126.2, 57.0 (C2), 52.5 (C3), C7a not observed. MS *m/z* (%): 292 (M+4, 34), 290 (M+2, 77), 288 (M^+, 38), 244 (23), 211 (81), 209 (79), 131 (73), 102 (100), 75 (41). Anal. calcd for $C_9H_6Br_2O$: C 37.28, H 2.09; found C 37.57, H 1.89.

3.0 Diels-Alder Reactions

3.1 Normal-Electron-Demand Diels-Alder Reactions

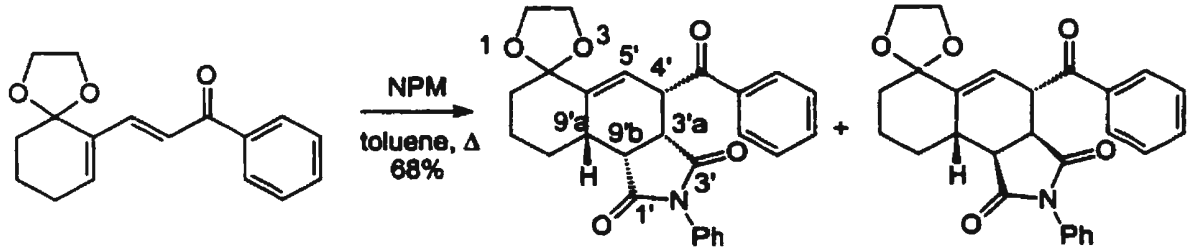
During the synthesis of the electron deficient diene **91**, there was a point at which the diene moiety had been constructed, but all of the electron withdrawing substituents had not yet been fully incorporated. The Diels-Alder reactivity of such a species, for example diene acetal **90**, was also of interest. In fact, it was reported that diene **90** participated in normal Diels-Alder reactions, with a variety of electron deficient dienophiles, including *N*-phenylmaleimide (NPM) and 1,4-naphthoquinone.[53] For example, 1,4-naphthoquinone (**120**) gave adducts *endo*-**121** and *exo*-**121** in 80% combined yield, in the ratio of 64:36. However, diene **90** did not participate in an inverse-electron-demand Diels-Alder reaction with 1,1-diethoxyethene, thus demonstrating the need for both electron withdrawing substituents on the dienophile.



90 **120** **121** (64:36)

Scheme 3.1: Normal Diels-Alder reaction of diene **90** with 1,4-naphthoquinone (**120**).

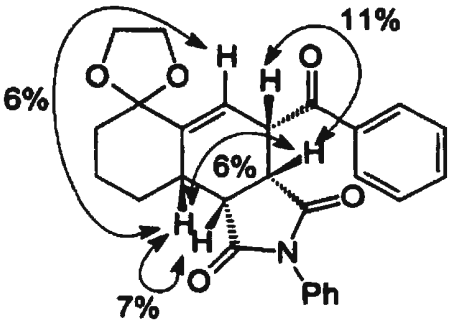
To determine whether diene **101** behaved similarly in normal-electron-demand Diels-Alder reactions, it was reacted with NPM in refluxing toluene. It was found that the normal Diels-Alder reaction did proceed, giving rise to an approximately 2:1 mixture of products as determined by analysis of the crude ^{1}H NMR spectrum. Chromatography gave the major and minor products in 45% and 23% isolated yield, respectively.



101 **122** **123**

Scheme 3.2: Normal Diels-Alder reaction of diene **101** with NPM

Adduct **122** was fully characterized, and assigned the structure of the *endo*-adduct using NOE-D experiments. Irradiation of the signal for C3'a-H gave an enhancement of 11% at C4'-H, and saturation of the signal at C9'a-H resulted in enhancements of 6% at C5-H, 7% for C9'b-H, and 6% for C3'a-H. In no Diels-Alder adducts were NOE effects observed across the cyclohexene ring, for example between C4'-H and C9'a-H in adduct **122**.



122

Figure 3.1: NOE-D enhancements observed for Diels-Alder adduct **122**.

Full characterization of the minor product was not achieved, but it was assigned the structure of *exo* adduct **123** based on the following reasoning. The ^{1}H NMR spectrum was clearly consistent with that of a Diels-Alder adduct. Key signals included a doublet at δ = 6.00 ppm for C5'-H, a doublet at 4.94 ppm for C4'-H, and a doublet of doublets at 3.25 ppm for C3'a-H. Obeying a trend consistently observed between *endo* and *exo* adducts during the normal Diels-Alder reactions of diene **90**,[67] the melting point of **123** (71-73 °C) was significantly lower than that of **122** (231-233 °C). Furthermore, as both compounds were obtained from column chromatography without contamination from the other, it was concluded that **123** was unlikely to have been the C4' epimer of **122**. Heating **122** in toluene for several days did not give any trace of **123** detectable by TLC analysis of the reaction mixture.

The Diels-Alder reaction of diene **90** with NPM was reported to give a mixture of *endo*:*exo* adducts with a ratio of 94:6. While the discrepancy between the *endo*:*exo* selectivities of dienes **90** and **101** were not readily apparent, steric factors in the transition

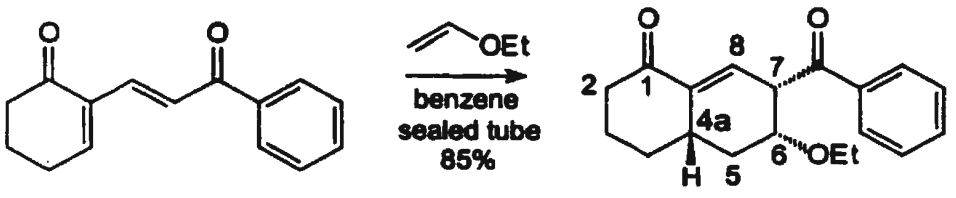
state may have played an important role. As previously described, Diels-Alder reaction of diene **90** with 1,4-naphthoquinone gave only a 64:36 ratio of *endo*:*exo* adducts.

No unreacted diene (**101**) was recovered from the reaction, suggesting that while its decomposition is slow at room temperature, this process may be accelerated at higher temperatures. While it was established that diene **101** could indeed undergo a normal-electron-demand Diels-Alder reaction, additional reactions with other electron deficient dienophiles were not pursued.

3.2 Inverse Electron Demand Diels-Alder Reactions

The primary objective of this area of research was to explore the inverse-electron-demand Diels-Alder chemistry of new electron deficient dienes. With diene **102** in hand, such reactions could now be examined. The remainder of this chapter is dedicated to the results of these Diels-Alder reactions with a range of electron rich dienophiles. Initial studies of the chemistry of one of the adducts obtained will also be described.

For the time being, the subsequent addition reactions will be referred to as inverse-electron-demand Diels-Alder reactions, and a concerted, asynchronous mechanism will be assumed. A more detailed discussion of the nature of the mechanisms that may be involved will be presented in Section 3.5.



102 **124**

Scheme 3.3: IEDDA reaction of diene **102** with ethyl vinyl ether.

Diene **102** reacted with ethyl vinyl ether in benzene at 80 °C in a sealed tube for 12 hours, giving the crude Diels-Alder adduct **124** in 85% yield. The results of all characterization experiments obtained on the crude product were consistent with an IEDDA adduct. A characteristic signal for adducts of this type was the C8-H signal in the ^{1}H NMR spectrum, which was observed as a doublet of doublets due to coupling with C7-H and C4a-H. For **124**, this signal appeared at $\delta = 6.45$.

NOE-D experiments on crude **124** gave enrichments of 9% at C6-H when irradiated at C7-H and 2% at C4a-H when irradiated at C6-H, suggesting that it was indeed the *endo*-adduct of the IEDDA cycloaddition. The mass spectrum of the material did not show a molecular ion (*m/z* 298), but an ion was present that corresponded to **126** (*m/z* 252), suggesting that ethanol was eliminated readily from the initial IEDDA adduct when heated.

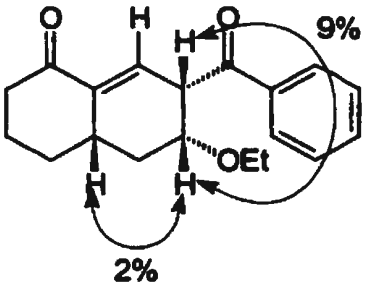
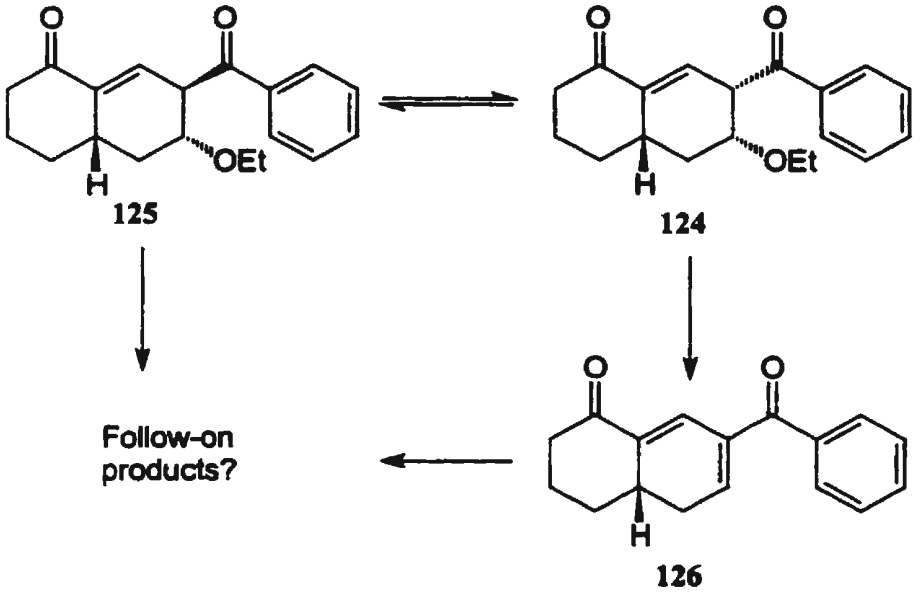


Figure 3.2: NOE-D enhancements observed for IEDDA adduct **124**.

Crude adduct **124** was obtained as a yellow oil and attempts at purification by chromatography consistently led to nearly complete conversion to a more complex product mixture. No pure product or follow-on products could be isolated. It was anticipated that epimerization at C7 may occur during chromatography, as reported in the IEDDA reaction of diene **91** with ethyl vinyl ether, leading to a mixture of **124** and **125**. However, the complexity of the mixture obtained after chromatography suggested that if epimerization was occurring, other processes must also have been involved in the consumption of the material. It is possible that elimination of ethanol occurred, giving diene **126**, however no pure material was obtained from chromatography to support this.

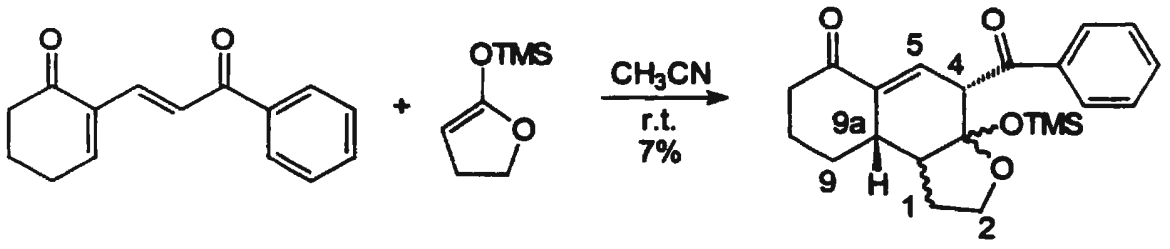


Scheme 3.4: Potential decomposition reactions of adduct **124** during chromatography.

Following the successful cycloaddition with ethyl vinyl ether, IEDDA reactions with more electron rich dienophiles were of interest. 2-(Trimethylsilyl)oxy-3,4-dihydrofuran (**127**), prepared from γ-butyrolactone,[74] was reacted with diene **102** in CH_3CN, giving the cycloaddition reaction at room temperature. TLC analysis showed that all of the diene had been consumed after just 30 minutes. However, the reaction had not proceeded cleanly and the product mixture was fairly complex. Attempted purification by chromatography, yielded a small amount (7%) of what appeared, by ^1H NMR spectroscopy, to be IEDDA adduct **128**. Signals characteristic for a Diels-Alder adduct included C5-H appearing as a doublet of doublets at δ = 7.18 and C4-H as a doublet of doublets at δ = 4.46 ppm. The relative stereochemistry of **128** could not be

[74] Rasmussen, J.K.; Hassner, A. *J. Org. Chem.* **1974**, *39*, 2558-2561.

confidently assigned owing to the low yield and difficulty of the purification. No other identifiable products deriving from **102** were obtained. Since **102** would not have been expected to decompose significantly under the reaction conditions, the low yield of adduct **128** was attributed to difficulties with purification of the potentially labile trimethylsilyl-protected hemiacetal.



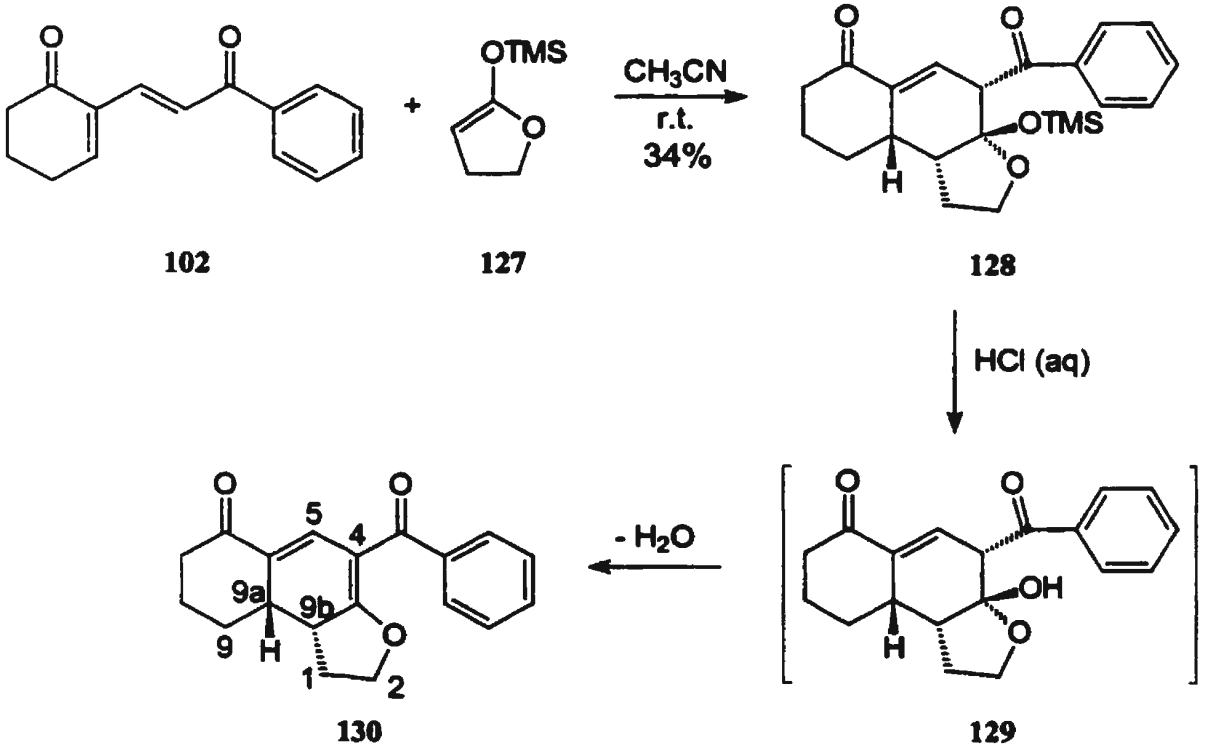
102 **127** **128**

Scheme 3.5: IEDDA reaction of diene **102** with silyl enol ether **127**.

In an effort to obtain a higher yield of material derived from the IEDDA cycloaddition, the reaction was modified. Following the reaction, but prior to chromatography, an acidic aqueous work-up was performed with the intention of hydrolyzing the TMS-protected hemiacetal to give a more easily isolated and robust set of products. The crude reaction mixture was washed with 0.5 M HCl solution,[75] and chromatography yielded **130** in 34% yield. Diene **130** presumably arose via IEDDA cycloaddition to give **128**, followed by hydrolysis of the TMS ether to afford hemi-acetal **129**, and finally dehydration. The spectroscopic properties of the product were consistent with the proposed structure of **130** and NOE-D experiments suggested that it was likely

[75] Galbraith, M.N.; Horn, D.H.S.; Middleton, E.J.; Hackney, R.J. *J. Chem. Soc., Chem. Commun.* **1968**, 466-467.

the *endo*[76] adduct, as irradiation at C9b-H gave an enhancement of 3% at C9a-H, it was tentatively assigned structure **130**. IEDDA reaction of **102** with **127** via an *exo* transition state would have expectedly led to C9a-H and C9b-H of the isolated product being in, or very close to, a *trans*-diaxial relationship, and no observable NOE-D enrichment would be expected. Several attempts at obtaining x-ray quality crystals were unsuccessful, and eventually the adduct decomposed to give an intractable material. As in the initial reaction of diene **102** with **127**, no other material, either diene, adducts or other follow-on products, could be isolated.



102 **127** **128**

130 **129**

Scheme 3.6: Reaction of diene **102** with silyl enol ether **127** with aqueous work-up.

[76] The *endo* adduct was arbitrarily assigned the one where the dihydrofuran ring of the dienophile was aligned *endo* to the diene.

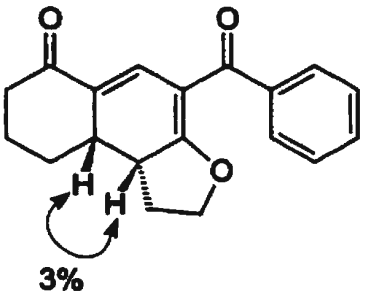
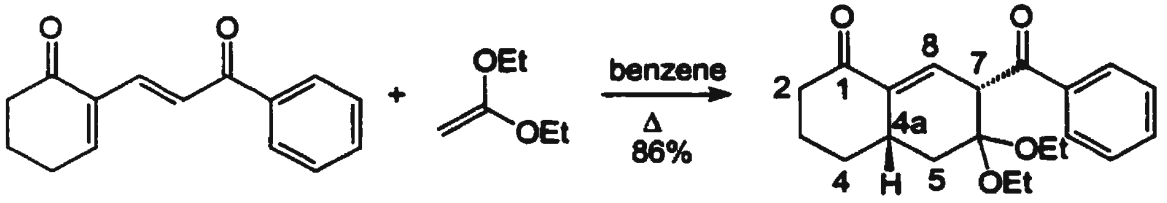


Figure 3.3: NOE-D enhancement observed for IEDDA adduct **130**.

Increasing the electron donating nature of the dienophile appeared to facilitate the IEDDA reaction of diene **102**. As such, other electron rich dienophiles were of interest. 1,1-Diethoxyethene[77] **(131)** was reacted with **102** in refluxing benzene, leading to complete consumption of the diene after three hours, and gave adduct **132** in 86% yield.

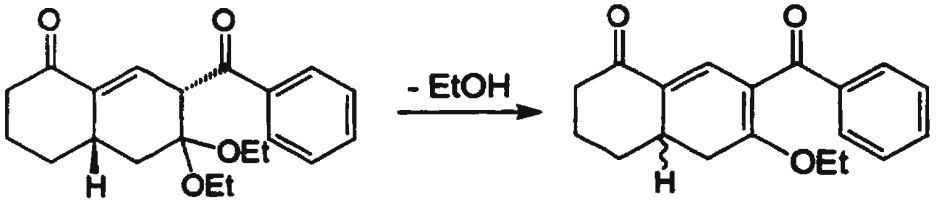


102 **131** **132**

Scheme 3.7: IEDDA reaction of diene **102** with 1,1-diethoxyethene **(131)**.

This product was easily purified by flash chromatography and was obtained as a racemic mixture of one diastereomer. The product was assigned structure **132**, the direct IEDDA adduct, on the basis of the following data. Characteristic signals for a Diels-Alder adduct of this type were present in the ^{1}H NMR spectrum. C8-H was observed as a doublet of doublets at $\delta = 6.38$. C7-H was a multiplet at 4.72 ppm, and C4a-H was also a

multiplet, overlapped by a C2-H signal, at 2.67-2.57 ppm. All other spectra agreed with the structure of **132** as the product from this reaction. As in the case with adduct **124**, MS analysis did not show a molecular ion (*m/z* 342), but instead an ion for the elimination of ethanol was observed (*m/z* 296), again suggesting that the elimination to give **133** occurs readily under the conditions of the mass spectrometer.



132 **133**

Scheme 3.8: Elimination of ethanol from IEDDA adduct **132**.

A variety of other electron rich alkenes, related to those already described, were also investigated as dienophiles for IEDDA reaction with diene **102**. These included vinyl acetate (**134**), ethyl 3,3-diethoxyacrylate (**135**), 2-methoxypropene (**136**), 3,4-dihydro-(*2H*)-pyran (**137**), phenyl vinyl sulfide (**138**) and styrene (**139**). Disappointingly, under a range of experimental conditions all of these reactions either returned the starting material or led to the formation of complex mixtures. These conditions included stirring at room temperature, heating to reflux either in solvent or in neat dienophile, and heating in a sealed tube. In only a few cases, ^{1}H NMR analysis of the crude product mixture indicated that trace amounts of IEDDA products or follow-on products might be present.

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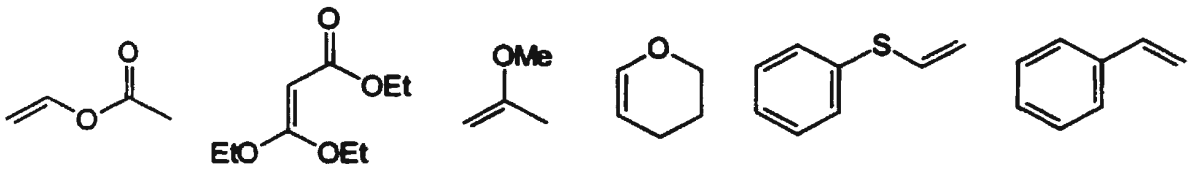
[77] McElvain, S.M.; Kundiger, D. *Org. Synth., Coll. Vol. III* **1955**, 506-508.

All attempts at improving the yields of these adducts or obtaining pure material ended in failure.



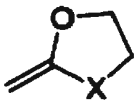
134 **135** **136** **137** **138** **139**

That no IEDDA reaction occurred between diene **102** and esters **134** or **135** was not entirely surprising. As dienophiles, they should have been less electron donating than ethyl vinyl ether, which required heating at 80 °C in a sealed tube to drive the IEDDA cycloadditon. As such, the necessity of even harsher conditions would be anticipated for the cycloaddition reaction of either **134** or **135** with diene **102**, conditions which the diene would probably not survive. Vinyl sulfide **138** may have been less reactive than ethyl vinyl ether because sulfur is a weaker π-electron donor than is oxygen.

Based on the conclusions of recent reports, which calculated the most likely IEDDA transition state geometries of several electron rich dienophiles,[43,78] it is not surprising that dihydropyran **137** did not react with diene **102**. Calculations have suggested that dienophiles such as enol ethers adopt an *s-trans* geometry in the transition state of the Diels-Alder reaction. That is, the transition state of the Diels-Alder reaction with the dienophile in the *s-trans* geometry is of lower energy than that with the *s-cis* geometry. As such, dienophiles which can more easily adopt the *s-trans* configuration would be more reactive in cycloaddition reactions. Being locked in the *s-cis*

conformation, **137** should be less reactive than ethyl vinyl ether. Also, based on the reactivity of diene **102** with ethyl vinyl ether, it was initially disappointing that vinyl ether **136** gave no IEDDA adducts when reacted with diene **102**. However, considering that the *s-cis* conformation of **136** may be slightly lower in energy than the *s-trans* conformation, the lack of reactivity (relative to ethyl vinyl ether) may be rationalized. If such considerations actually play a significant role, then the reaction of diene **102** with a dienophile locked in the *s-trans* conformation, such as **140a**, should occur very readily compared to those of dienophiles **136** or **137**. Similarly, cyclic ketene acetal **140b** should be even more reactive than 1,1-diethoxyethene (**131**). Such reactions were not performed in this study, but will be of great interest in the future.

s-trans *s-cis*

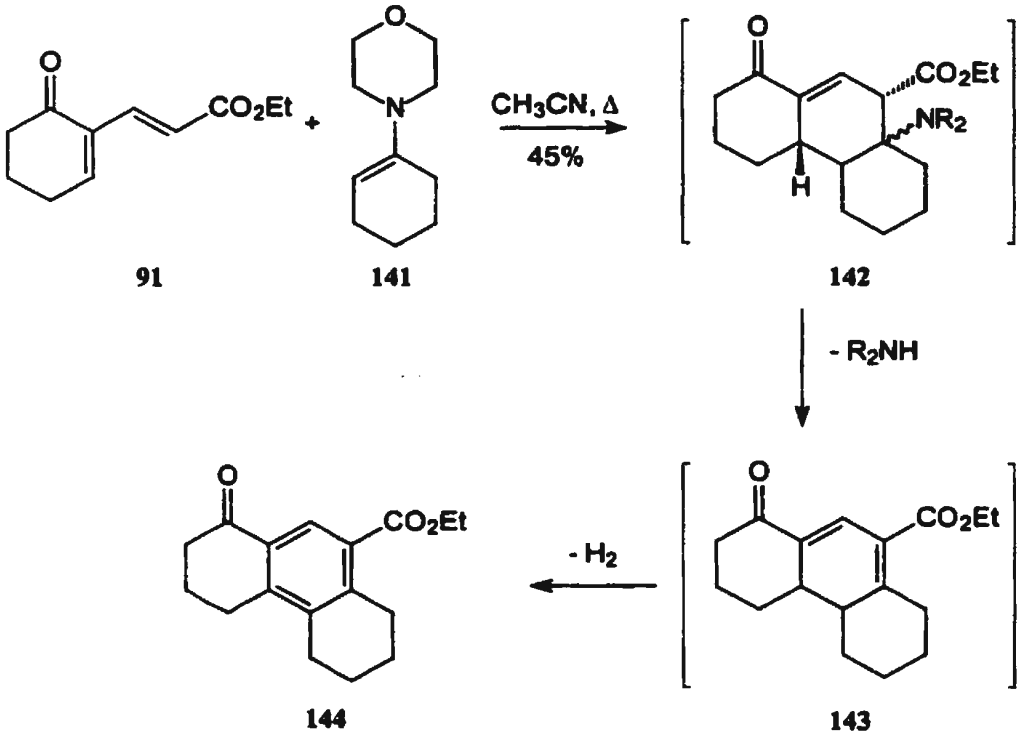


140a, X = CH_2
140b, X = O

[78] Liu, J.; Niwayama, S.; You, Y.; Houk, K.N. *J. Org. Chem.* **1998**, *63*, 1064-1073.

Enamines have been known for some time to react as dienophiles in the IEDDA reaction with electron deficient dienes.[79] More recently, diene **91** was reported to react with enamine **141** to give hexahydrophenanthrone derivative **144** in 45% yield.[54] Formation of this compound was attributed to the Diels-Alder cycloaddition, giving **142**, elimination of morpholine, to give diene **143**, and dehydrogenation. Product **144** was obtained in less than 50% yield, but no reduction products, or other identifiable materials derived from the diene, were either isolated or observed. As was concluded by Danishefsky in a related system,[80] this dehydrogenation was speculated to have occurred by a mechanism other than disproportionation of proposed intermediate **143**.

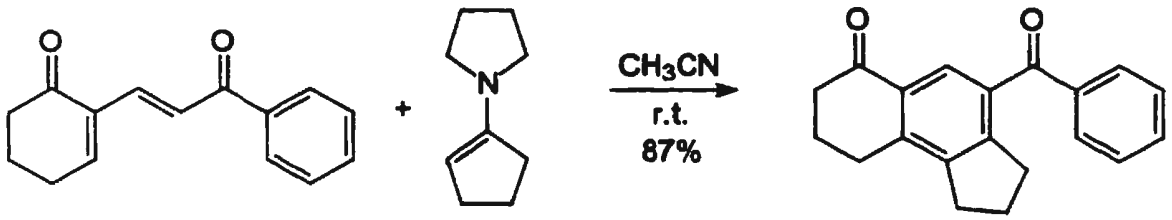
[79] Dyke, S.F. *The Chemistry of Enamines* Cambridge University Press: Mass., 1973, p.49.; Cook, A.G. *Enamines* (2nd Ed.) Marcel Dekker, Inc.: New York, 1988, pp.367-368.
[80] Danishefsky, S.; Cunningham, R. *J. Org. Chem.* **1965**, *30*, 3676-3679.



Scheme 3.9: IEDDA reaction of diene **91** with enamine **141**.

In this work, it was shown that diene **102** readily undergoes IEDDA reaction with a variety of enamines. These enamines were generated by the treatment of ketones with pyrrolidine, in the presence of catalytic acid, in refluxing benzene with azeotropic removal of water.[81] Reaction of **102** with five equivalents of enamine **145** in CH_3CN at room temperature led, presumably, to a domino IEDDA-elimination-dehydrogenation reaction, affording **146** in 87% yield. Monitored by TLC, consumption of diene **102** was observed to be complete after only ten minutes. Attempts to observe the formation of any intermediate products by TLC analysis were fruitless due to the rapidity with which the reaction proceeded. While not employed here, following the reaction by ^1H NMR at low

temperature may prove to be more useful in future work. The choice of solvent appeared to play at most a small role in this sequence of reactions as repeating the reaction in CH_2Cl_2 again led to **146**, this time in 85% yield after ten minutes. As in all the IEDDA reactions of diene **102** described thus far, no unreacted diene or other identifiable products derived from the diene were obtained.



102 **145** **146**

Scheme 3.10: IEDDA reaction of diene **102** with enamine **145**.

Treatment of diene **102** with five equivalents of cyclohexanone-derived enamine **147** in CH_3CN at room temperature, herein referred to as the standard conditions, led to **148** in 52% yield. All of the diene, as observed by TLC analysis, had reacted after 20 minutes. Repeated attempts at performing this reaction with longer reaction times did not lead to an improvement in the yield. Varying the reaction temperature was not explored. Purification of **148** was hampered by the formation of unidentifiable side-products of similar R_f during TLC, and ultimately no material sufficiently pure to satisfy elemental analysis was obtained. This seemed to suggest that the formation of alternate products, either from the IEDDA adduct or the product of amine-elimination, may be possible.

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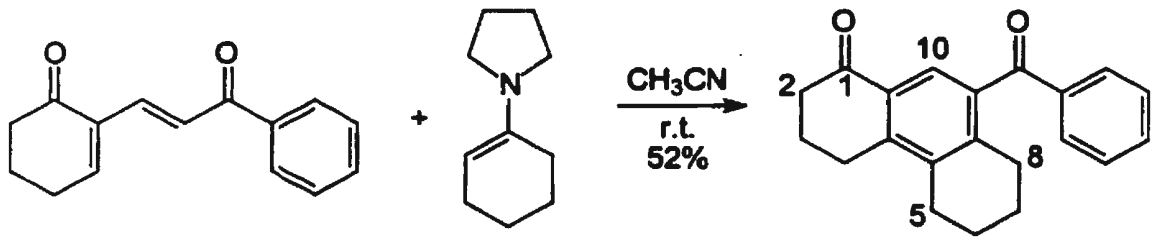
[81] Hüng, S.; Lücke, E.; Brenninger, W. *Org. Synth., Coll. Vol. V* **1973**, 808-809.

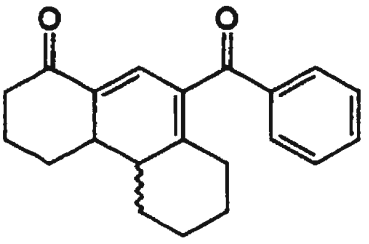
Despite this, no identifiable material other than the dehydrogenated product **148** was obtained.



102 **147** **148**

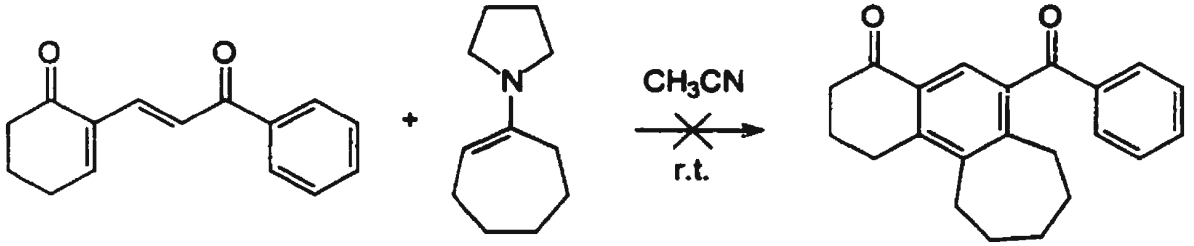
Scheme 3.11: IEDDA reaction of diene **102** with enamine **147**.

A particularly interesting result was obtained when the reaction was repeated, but allowed to react for only ten minutes. In this case, only 21% of **148** was obtained, along with a new material that was not observed in the product mixture when the reaction was allowed to react for longer periods. As purification proved even more difficult that in the previous experiment, no pure material was isolated. However, the ^{1}H NMR spectrum of the crude product resembled that of a Diels-Alder adduct, including a singlet at $\delta = 7.97$, which integrated to one proton (possibly C10-H), in addition to the easily identifiable signals of the phenyl ketone. This material was determined not to be intermediate **149**, the proposed precursor to **148**, as it was unreactive when subjected to the reaction conditions. Stirring at room temperature for 48 hours in CH_3CN in the presence of enamine **147** did not lead to the formation of **148** or any other new products.



149

Attempted reaction under the standard conditions of diene **102** with cycloheptanone-derived enamine **150** also resulted in the formation of a complex and inseparable mixture. The ^{1}H NMR spectrum of the product mixture did not indicate the presence of any of the desired product **154**.



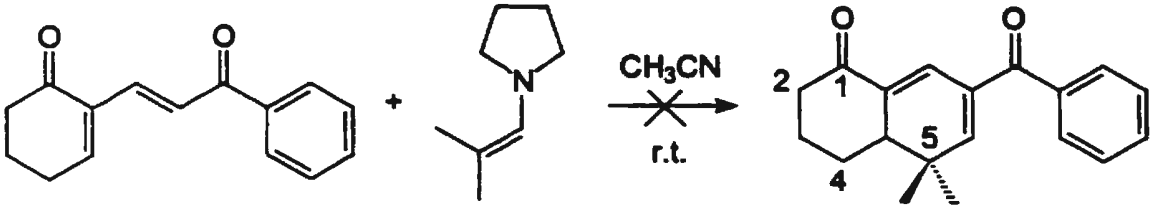
102 **150** **151**

Scheme 3.12: Attempted IEDDA reaction of diene **102** with enamine **150**.

The increasing ring size of the enamine dienophile clearly had a detrimental effect on the course of the domino IEDDA-elimination-dehydrogenation sequence. The yield of product varied from 87% for the cyclopentanone-derived enamine **145**, to 52% for cyclohexane-derived enamine **147**, and finally to 0% for the cycloheptanone-derived enamine **150**. It was believed that steric interactions must play an important role in the course of the reaction. These could arise either in the transition state of the IEDDA

reaction or by influencing the reactivity of the intermediates and preventing the formation of the dehydrogenated product.

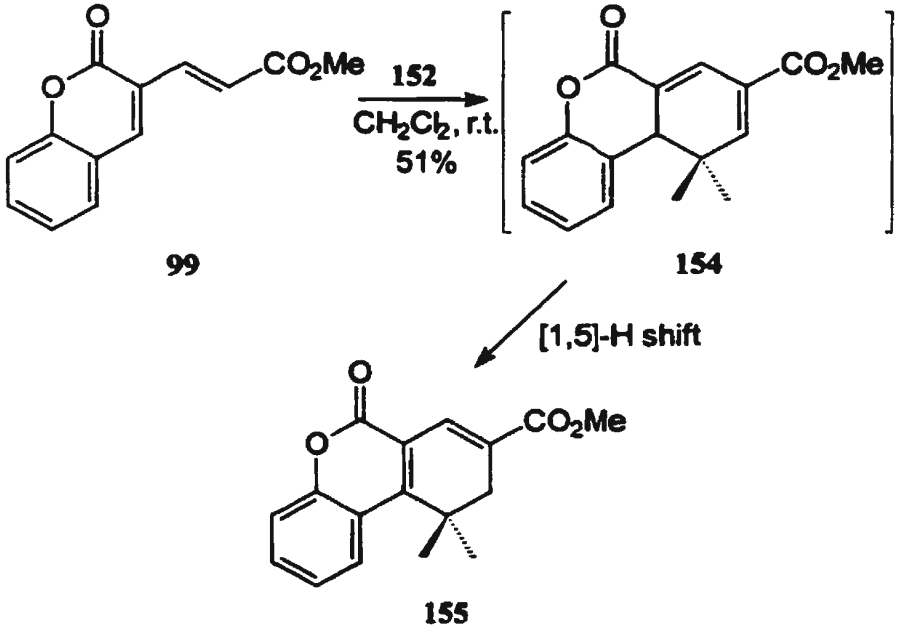
Possible alternate reaction pathways for the intermediates in the domino IEDDA-elimination-dehydrogenation reaction were of interest. While no specific side products had yet been isolated from these systems that suggested such reactions were progressing, the often complex nature of the side-products observed along with the frequently low yields of the dehydrogenated product allowed for this possibility of competing side reactions. As such, diene **102** was reacted with enamine **152**, which, if resulting in diene **153**, could not oxidize due to the presence of the *gem*-dimethyl at C5. Under the standard conditions, this resulted in the formation of a complex mixture of products that were inseparable by chromatography. No IEDDA adducts were identifiable in the ^{1}H NMR spectrum of this crude product mixture. Thus if the IEDDA reaction had occurred, the diene **153** must have been sufficiently reactive to undergo further transformations. Should this have been the case, it might shed some light on the fate of the diene intermediate in some of the other domino reactions, which resulted in low yield of the final products.



102 **152** **153**

Scheme 3.13: Attempted IEDDA reaction of diene **102** with enamine **152**.

Indeed, in a related system, IEDDA-elimination product **154** from the reaction of enamine **152** with diene **99** was observed to undergo a [1,5]-hydride shift, giving **155**.[54] This was speculated to have occurred due to the formation of more extended conjugation, regeneration of the partially aromatic 2-pyrone sub-unit, and less steric congestion in **155** compared to the direct IEDDA adduct **154**.



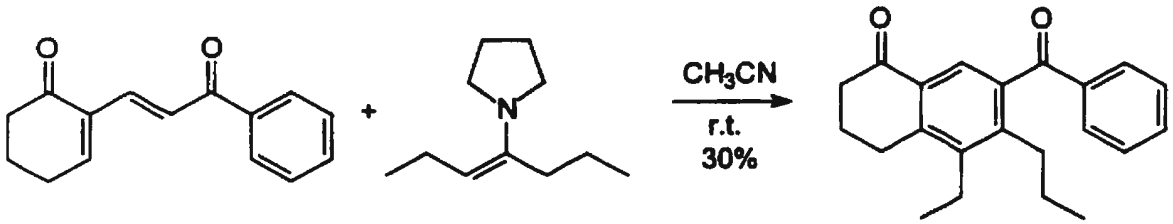
Scheme 3.14: [1,5]-Hydride shift observed for IEDDA adduct **154**.

In addition, diene **91** was observed to behave in a fashion similar to diene **102** with enamine **152**.[82] While diene **91** was consumed, no identifiable products were obtained.

The IEDDA reaction of diene **102** with the acyclic analogue of **150**, 4-heptanone-derived enamine **156**, did proceed under the standard conditions, affording **157** in 30%

[82] Bodwell, G.J.; Pi, Z. *Unpublished results*.

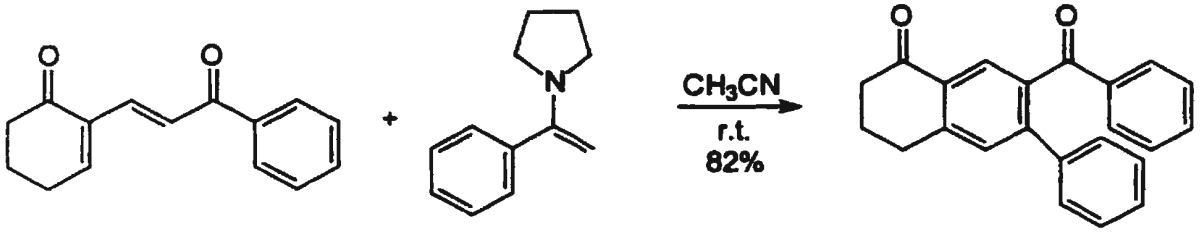
yield. All attempts to verify the regiochemistry of the addition, including NOE-D experiments, were inconclusive due to overlap of key signals in the ^{1}H NMR spectrum. Crystals suitable for x-ray crystallographic analysis could not be obtained. However, the structure of **157** was assigned based on the high degrees of regioselectivity observed in other IEDDA reactions of diene **102**.



102 **156** **157**

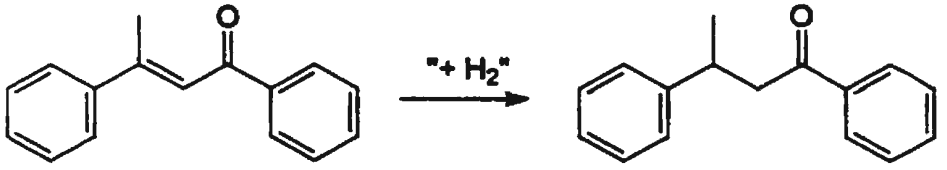
Scheme 3.15: IEDDA reaction of diene **102** with enamine **156**.

IEDDA reaction of diene **102** with acetophenone-derived enamine **158** under the standard conditions led to **159**, again presumably by the IEDDA cycloaddition-elimination-dehydrogenation reaction sequence, in 82% yield. As in a related system,[54] ketone **161** was also isolated from this reaction in 13% yield based on the amount of dienophile used. This is the hydrogenated self-condensation product of acetophenone. Despite being freshly distilled, the readiness with which enamine **158** underwent hydrolysis when exposed to moisture does not rule out the possibility of the presence of some residual acetophenone. Presumably two molecules of acetophenone participated in a base catalyzed self-condensation, forming enone **160**. This material, once formed, behaved as a hydrogen acceptor and resulted, at least in part, in the oxidation to **159**.



102 **158** **159**

Scheme 3.16: IEDDA reaction of diene **102** with enamine **158**.

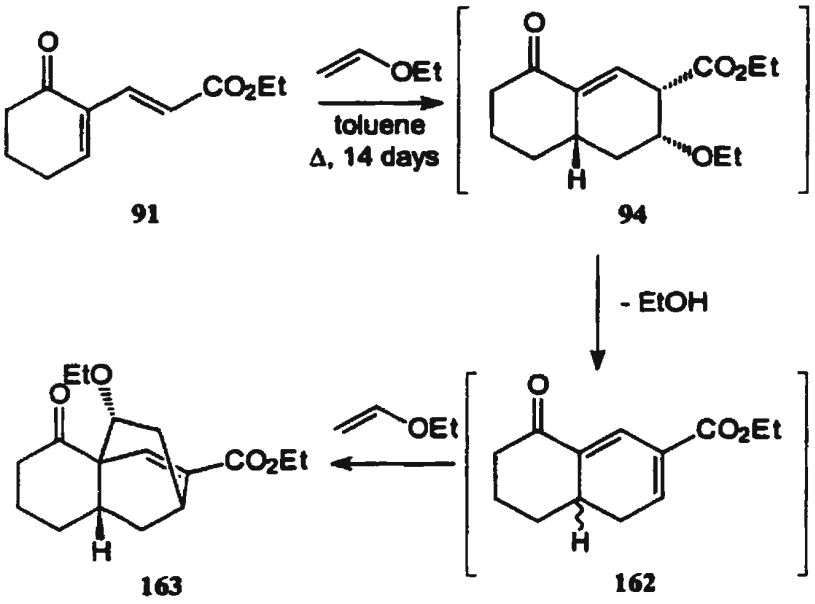


160 **161**

Scheme 3.17: Enone **160** behaves as a hydrogen acceptor, leading to ketone **161**.

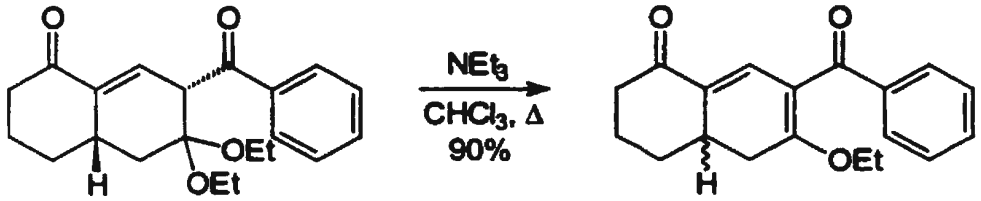
3.3 Chemistry of Inverse-Electron-Demand Diels-Alder Adducts

Another point of interest was the possibility of the IEDDA adducts undergoing elimination reactions, generating new dienes that could take part in subsequent Diels-Alder cycloadditions. This would provide a method for the rapid construction of highly functionalized bicyclic systems. Such a reaction was first observed during the reaction of diene **91** with excess ethyl vinyl ether where, after two weeks in refluxing toluene with periodic reintroduction of the dienophile, **163** was obtained in 21% yield.[67] It was postulated that **163** arose via successive IEDDA cycloaddition to give **94**, elimination of ethanol to generate the new electron deficient diene **162**, and finally a second IEDDA reaction. Particularly remarkable was the observation that the material obtained appeared to be the stereoisomer derived from complete *endo*-, regio-, and facial selecivity; this prompted a further investigation.



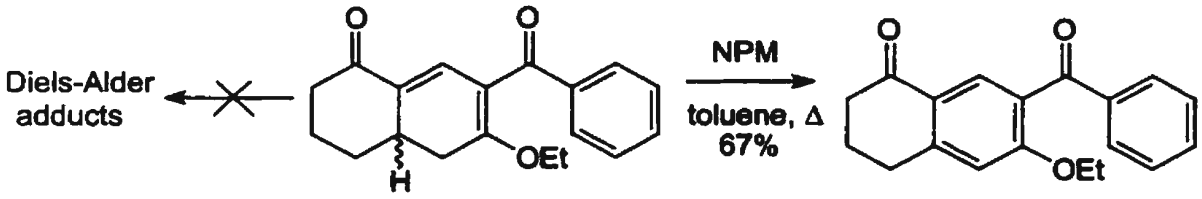
Scheme 3.18: Tandem IEDDA-elimination-IEDDA reaction of diene **91** with ethyl vinyl ether.

IEDDA adduct **132** was treated with triethylamine in refluxing dichloromethane and gave the desired elimination, yielding diene **133** in 82%, along with 10% yield of recovered **132**. The yield of **133** was improved to 90%, with no recovered **132**, by performing the reaction in refluxing chloroform. While this new diene was, like diene **102**, substituted in the 1- and 3- positions with electron withdrawing groups, it also contained an ethoxy substituent, which is strongly electron donating. As such, the question of whether diene **133** would take part in the normal or inverse-electron-demand Diels-Alder reaction needed to be addressed.



132 133

Scheme 3.19: Diene formation by elimination of ethanol from adduct **132**.



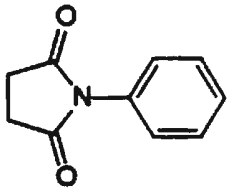
133 164

Scheme 3.20: Attempted normal Diels-Alder reaction of diene **133** with NPM.

Diene **133** was reacted with NPM in refluxing toluene until all diene had been consumed, as monitored by TLC (four days). Following purification by chromatography, it was surprising to learn that a Diels-Alder reaction had not occurred, but rather that **164**, the product of dehydrogenation, was obtained in 67% yield. Also isolated from this reaction was a portion of *N*-phenylsuccinimide (**165**). It appears NPM oxidized **133**, reminiscent of the well known reaction of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) with cyclohexadienes to give arenes.[83] However, the amount of **165** obtained accounted for only two thirds of the **164** obtained. No other products were isolated that could have accounted for the oxidation of the remaining portion of **133** that was

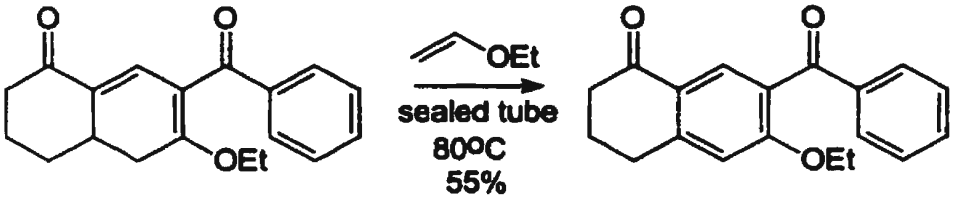
[83] Findlay, J.W.A.; Turner, A.B. *Org. Synth., Coll. Vol. V* **1973**, 428-431.

converted to **164**. NPM was used in excess (two equivalents) but only 0.8 equivalents were recovered from the reaction, suggesting that more **165** may have been produced during the reaction but was lost during purification. For completeness, **164** was prepared in 55% yield by treating diene **133** with DDQ.



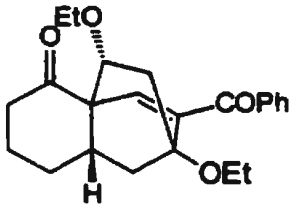
165

The inverse-electron-demand Diels-Alder reactivity of diene **133** was also investigated. Reaction with ethyl vinyl ether in benzene in a sealed tube at 80 °C for 20 hours, gave a mixture of starting material and one major new product according to TLC analysis. The ^{1}H NMR spectrum of this new material, which was isolated by column chromatography, indicated that it consisted of at least two products in a ratio of about 10:1. The major product was clearly that of oxidation product **164**, as obtained when **133** was treated with NPM or DDQ. The minor product could not convincingly be assigned the structure of expected IEDDA adduct **166**. Some ^{1}H NMR signals for the minor product suggested that it was derived from starting diene **133**, and no **133** was present following chromatography. No attempt was made to detect the presence of diethyl ether in the reaction mixture as the byproduct of oxidation of **133** by ethyl vinyl ether.

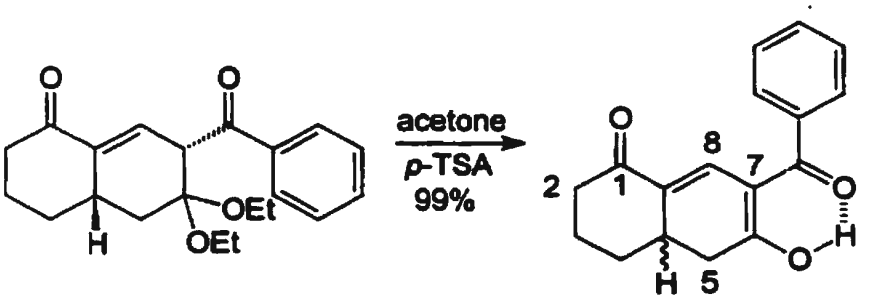


133 164

Scheme 3.21: Attempted IEDDA reaction of diene **133** with ethyl vinyl ether.



166



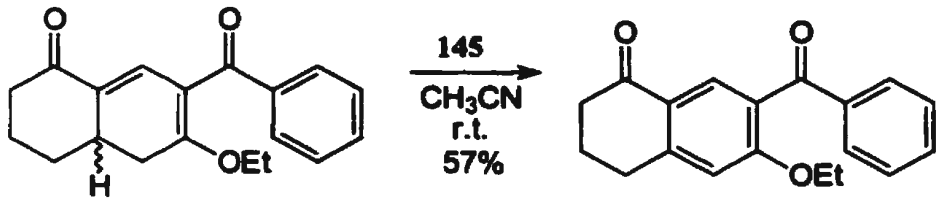
132 167

Scheme 3.22: Acetal hydrolysis of **132** giving enol **167**.

The diethyl acetal moiety of IEDDA adduct **132** was readily removed in near quantitative yield by treatment with catalytic *p*-TSA in acetone. The material obtained (**167**) was observed to be exclusively in the enol form as indicated by the ^{1}H NMR spectrum, which exhibited a strong, sharp singlet at $\delta = 16.51$. No signals attributed to the keto form of **167** were observed. This was not surprising as the C7-H proton of the keto form of **167** should have been sufficiently acidic for rapid enolization to occur. The

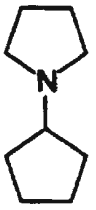
presence of the carbonyl α to the enol (at C7) allowed for a stable hydrogen-bonding arrangement, stabilizing the enol form of the equilibrium. The IEDDA reactivity of diene **167** will be presented later in this chapter.

A variety of enamines were shown to behave as dienophiles in these systems, having undergone successful inverse-electron-demand Diels-Alder reactions with diene **102**. The reactivity of enamines with dienes such as **133** and **167** was also of interest. As enamine **145** was shown to give the highest yield of product with diene **102**, it was chosen for the exploration of the enamine IEDDA chemistry of dienes **133** and **167**. Diene **133** had already been observed to preferentially oxidize, forming **164**, rather than participate in an IEDDA cycloaddition with ethyl vinyl ether. When reacted with five equivalents of enamine **145** under the standard conditions, diene **133** was once again converted to oxidized product **164** in 57% yield. No sign of amine **168** as the byproduct of oxidation by enamine **145** was detected by examination of the ^{1}H NMR spectrum of the crude product mixture or during chromatography, nor was any material resembling the product of the desired IEDDA reaction detected.



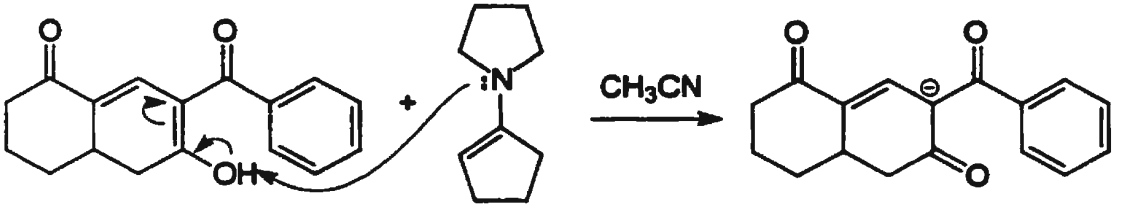
133 **164**

Scheme 3.23: Attempted IEDDA reaction of diene **133** with enamine **145**.



168

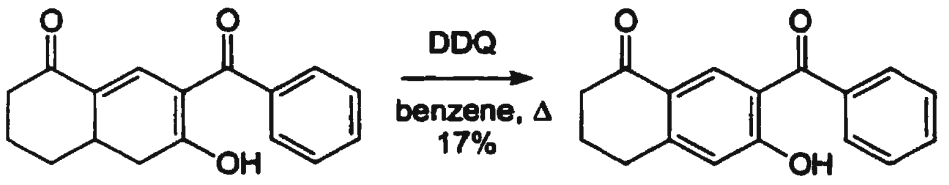
Interestingly, diene **167** did not react with enamine **145** to give an IEDDA adduct or the oxidized product, phenol **170**. After stirring at room temperature in CH_3CN for one hour, the diene (**167**) was recovered in nearly quantitative yield. The lack of IEDDA reactivity of diene **167** with an enamine was most likely due to the presence of the stabilized enol. As a weak base, enamine **145** would be expected to deprotonate the enol, rendering the diene unreactive toward an IEDDA cycloaddition. The resulting anion **169**, being α or γ to three ketone functionalities, would have been well stabilized. IEDDA reactions with less basic dienophiles, such as ethyl vinyl ether or 1,1-diethoxyethene, were not explored.



167 **145** **169**

Scheme 3.24: Proposed alternate pathway for the attempted IEDDA reaction of diene **167** with enamine **145**.

Unlike either diene **102** or **133**, which decompose to intractable materials unless participating in an IEDDA reaction, diene **167** was not sensitive to the reaction conditions. The low reactivity of **167** was further demonstrated by oxidation with DDQ. Phenol **170** was obtained in only 17% yield after refluxing in benzene for two hours.



167 **170**

Scheme 3.25: Generation of phenol **170** by DDQ oxidation of diene **167**.

3.4 Discussion of the Dehydogenation

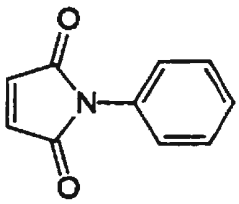
Despite the natures of the apparent dehydrogenation occurring in the domino IEDDA-elimination-dehydrogenation reactions of diene **102** and attempted Diels-Alder reactions of diene **133** initially being mysteries, some new insight has been gained. Clearly disproportionation could be ruled out as **146** was obtained in as high as 87% yield. Spontaneous loss of hydrogen is exceedingly rare at room temperature and was ruled out as a possibility in these cases. Oxidation by the presence of atmospheric oxygen to form the new aromatic ring also seemed unlikely based on the findings that dienes such as **133** and **167** were air stable and their isolation was performed without any oxidation whatsoever. Furthermore, the IEDDA reactions with enamines were performed

under nitrogen atmospheres. Aerial oxidation would have had to occur during work-up or purification.

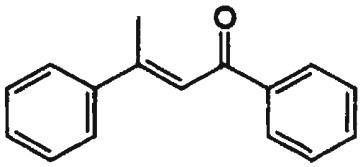
In light of the fact that diene **133** was at least partially oxidized to **164** by the dienophile, NPM, it is possible that a similar oxidation was occurring with the enamines. This did not seem unreasonable as an excess (five equivalents) of dienophile had been used in each case. However, in no reaction with enamines as dienophiles could a reduced enamine, for example amine **168**, be identified. Such amines may have been sufficiently volatile to be lost during purification, but none were ever observed as being present in the crude product mixtures by ^{1}H NMR analysis. Analysis by GC/MS might prove helpful in the future. Repeating the IEDDA reaction of diene **102** with less than two equivalents of enamine **145** did give **146**, but in reduced yield. Purification and determination of the exact yield in this case was difficult due to contamination by side-products which were not observed in the reaction with excess enamine. While ^{1}H NMR spectra suggested that some of these side-products may have been diene derived, none could be obtained sufficiently pure for speculation on their precise nature.

It is also of interest to note that in all the reactions where reduced species were isolated from the product mixtures, they were derived from electron deficient alkenes. *N*-Phenylsuccinimide (**165**) was isolated from the oxidation of diene **133** during the attempted Diels-Alder reaction with NPM. Ketone **161**, was isolated from the oxidation of the IEDDA cycloaddition-elimination product by enone **160** during the reaction of diene **102** with enamine **158**. The oxidations were also successful with DDQ, which also contains electron deficient alkenes. Enamines, which contain electron rich alkenes, may

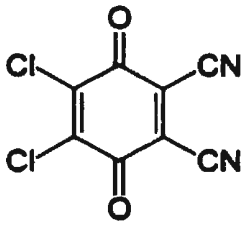
have effected the oxidation of the IEDDA cycloaddition-elimination intermediates by a different method than did the electron deficient alkenes. This may offer another explanation for the lack of reduced enamines, such as amine **168**, in the crude reaction mixtures.



NPM



160

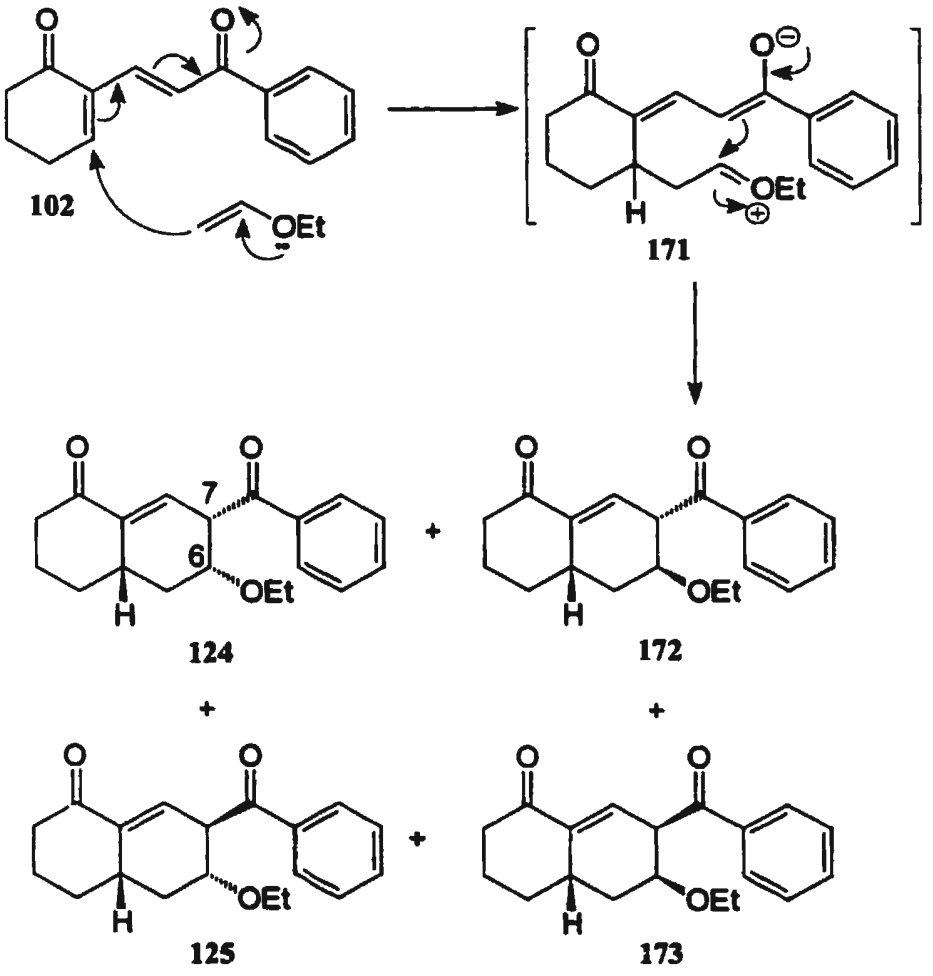


DDQ

3.5 Discussion of Mechanism

Intuitively, as well as by considering the high degrees of regioselectivity observed in the IEDDA reactions of dienes such as **102**, it could be deduced that the diene moiety must be highly polarized in nature. As such, it is conceivable that the cycloaddition reactions of **102** may occur via a stepwise process. Such a process would involve nucleophilic addition of the alkene to the diene, giving a zwitterionic imtermediate (**171**), followed by intramolecular ring closure. This process would result in adducts closely resembling those arising from a concerted cycloaddition, however they would be mixtures of up to four possible diastereomers **124**, **125**, **172**, and **173** due to free rotation in intermediate **171**.

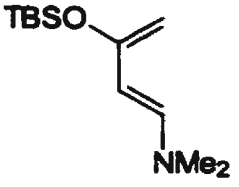
The formation of **124** as a single diastereomer in 85% yield was a particularly significant result as it is strong evidence that the cycloaddition reaction occurs via a concerted mechanism rather than a two step process through an intermediate such as **171**. With a *cis* relationship between the C6 and C7 substituents, adduct **124** would be a kinetic product from a step-wise mechanism and should have been obtained as part of a diastereomeric mixture had the reaction proceeded by conjugate addition of the alkene to the diene and subsequent ring closure. The relative stereochemistry of adduct **124** also suggested that the IEDDA reaction proceeds through an *endo* transition state. Adduct **132**, arising from the reaction of diene **102** with 1,1-diethoxyethene (**131**), was also obtained as a single diastereomer, adding further to the likelihood of a concerted cycloaddition reaction in these instances.



Scheme 3.26: Mechanism for cycloaddition of diene **102** with ethyl vinyl ether via a two step process leading to up to four diastereomers.

A more rigorous determination of activation parameters, including the temperature dependence of rate constants for the Diels-Alder reactions, may shed more light into the concertedness of the mechanism for the formation of the cycloaddition adducts, but such experiments were not performed during the course of this work.

Recently,[84] such a study concluded that the normal demand Diels-Alder reactions of the highly polarized diene **73** likely proceeded by a concerted mechanism. This conclusion was based on the experimentally determined large negative entropy of activation which suggests a highly ordered transition state, characteristic of the Diels-Alder reaction.



73

Less useful results were obtained when examining the enamines as dienophiles. In all cases, the only identifiable diene derived products were those of the cycloaddition-elimination-dehydrogenation reaction sequence, where all stereochemical information had been lost. As such, it was impossible to comment conclusively on the mechanism of the presumed cycloaddition reaction of diene **102** with enamines such as **145**. A recent report examined the effect of reactant polarity on the concertedness of the inverse-electron-demand Diels-Alder reaction, using computational methods. The authors concluded that the reaction with enamines likely proceeds by an asynchronous, concerted mechanism in which nucleophilic addition of the enamine on the electrophilic carbon of the diene is more advanced at the transition state than the concomitant ring closure.[85] The participation of zwitterionic intermediates was ruled out. Whether this was true for the reactions described here could only be speculated, but it would seem highly likely

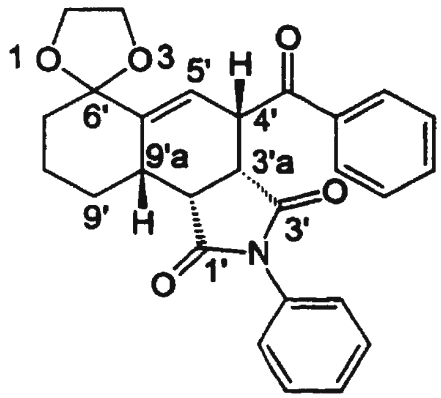
[84] Kozmin, S.A.; Green, M.T.; Rawal, V.H. *J. Org. Chem.* **1999**, *64*, 8045-8047.

that if the reactions were proceeding in a concerted fashion, they were highly asynchronous, likely much more so than were the reactions with dienophiles such as ethyl vinyl ether or 1,1-diethoxyethene.

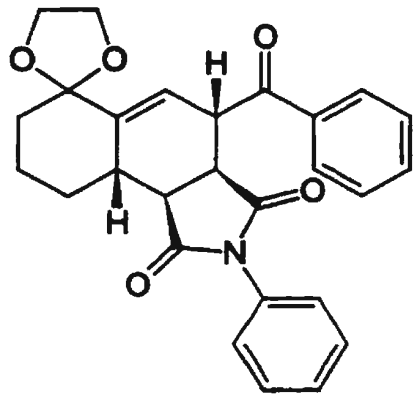
[85] Domingo, L.R.; Arnó, M.; Andrés, J. *J. Org. Chem.* **1999**, *64*, 5867-5875.

3.6 Experimental [86]

(3'aα,4'α,9'aα,9'bα)-4'-Benzoyl-3'a,4',7',8',9',9'a,9'b-heptahydro-2'-phenyl-spiro[1,3-dioxolane-2,6'-(*1H*)benz[*e*]isoindole]-1',3'-dione (122) and (3'aβ,4'α,9'aα,9'bβ)-4'-Benzoyl-3'a,4',7',8',9',9'a,9'b-heptahydro-2'-phenyl-spiro[1,3-dioxolane-2,6'-(*1H*)benz[*e*]isoindole]-1',3'-dione (123)



122



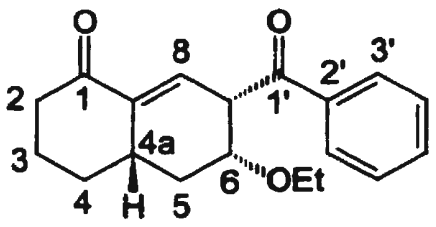
123

A solution of diene acetal **101** (460 mg, 1.70 mmol) and NPM (872 mg, 5.04 mmol) in toluene (10 mL) was heated at reflux under N_2 for 3.5 h. After cooling to r.t., the solvent was removed under reduced pressure. The products were purified by flash chromatography (30% EtOAc/hexanes), yielding **123** (R_f = 0.30, 176 mg, 0.40 mmol, 23%) and **122** (R_f = 0.09, 342 mg, 0.77 mmol, 45%). **122**: m.p.: 231-233 °C (ethanol/water). IR (film): ν_{max} 1710 (s), 1653 (m), 1496 (m), 1455 (m), 1372 (s), 1366

[86] For General Experimental Procedures, see Chapter 2, Section 2.5.1.

(s), 1245 (m), 1155 (m), 1097 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.83 (2H, dd, *J* = 7.0, 1.3 Hz), 7.60-7.29 (8H, m), 6.47 (1H, m, C5'-H), 4.50 (1H, ddd, *J* = 8.6, 2.5, 2.5 Hz, C4'-H), 4.00-3.86 (4H, m, C4-H + C5-H), 3.34 (1H, dd, *J* = 8.6, 5.6 Hz, C3'a-H), 2.90-2.81 (1H, m, C9'b-H), 2.55 (1H, s (br), C9'a-H), 1.85-1.80 (1H, m), 1.73-1.65 (2H, m), 1.61-1.43 (2H, m), 1.40-1.27 (1H, m). NOE-D ($CDCl_3$): δ = 6.47 (4.50, 0.7%), 3.34 (4.50, 11.4%), 2.90-2.81 (3.34, 6.5%; 2.55, 6.2%), 2.55 (6.47, 5.8%; 3.34, 5.7%; 2.90-2.81, 6.8%). ^{13}C NMR ($CDCl_3$): δ = 195.5(0, COPh), 176.9 (0), 174.9 (0), 139.3 (1, C5'), 137.1 (0), 134.1 (0), 133.0 (1), 131.8 (0), 130.0 (1), 129.3 (1), 128.73 (1), 128.66 (1), 126.3 (1), 109.4 (0, C6'), 64.84 (2), 64.76 (2), 45.0 (1, C9'a), 44.0 (1, C3'a), 39.7 (1, C4'), 34.4 (1, C9'b), 32.8 (2, C7'), 22.5 (2), 22.3 (2). MS *m/z* (%): 444 (7), 443 (M^+, 24), 439 (0.8), 398 (4), 371 (6), 343 (6), 338 (22), 296 (0.1), 266 (1), 250 (10), 235 (4), 208 (3), 196 (4), 141 (3), 105 (66), 99 (59), 91 (9), 86 (100), 77 (38). Anal. calcd for $C_{27}H_{25}NO_5$: C 73.31, H 5.68, N 3.16; found C 73.19, H 5.67, N 3.09. **123**: m.p.: 71-73 °C (hexanes). ^1H NMR ($CDCl_3$): δ = 8.08 (2H, d, J = 8.1 Hz), 7.66-7.26 (8H, m), 6.00 (1H, d, J = 5.4 Hz, C5'-H), 4.94 (1H, d, J = 4.7 Hz, C4'-H), 3.95-3.88 (2H, m), 3.74-3.66 (2H, m), 3.25 (1H, dd, J = 8.6, 5.1 Hz, C3'a-H), 2.64-2.59 (1H, m, C9'b-H), 2.32-2.27 (1H, m, C9'a-H), 1.83-1.74 (3H, m), 1.50-1.34 (3H, m).

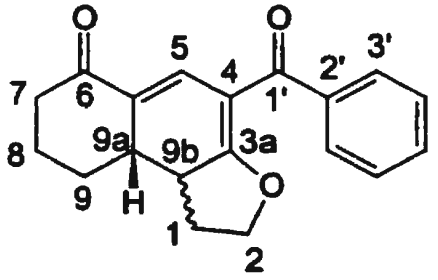
(4aα,6α,7α)-7-Benzoyl-6-ethoxy-3,4,4a,5,6,7-hexahydro-1(*2H*)-naphthalenone (124)



A solution of diene **102** (282 mg, 1.25 mmol) and distilled ethyl vinyl ether (1.2 mL, 12.5 mmol) in benzene (3 mL) in a degassed sealed tube was heated to 80 °C for 12 h. After the reaction mixture cooled to r.t., the solvent was removed under reduced pressure affording crude **124** as a yellow oil (377 mg). The crude product was approximately 85% pure by ^{1}H NMR and this material was used for structural identification without further purification. IR (film): ν_{max} 2930 (m), 1688 (s), 1621 (m), 1448 (m), 1214 (s), 1118 (s), 1110 (s). ^{1}H NMR ($CDCl_3$): δ = 7.99-7.97 (2H, m, C3'-H), 7.58-7.53 (1H, m, C5'-H), 7.48-7.43 (2H, m, C4'-H), 6.45 (1H, dd, *J* = 4.4, 2.7 Hz, C8-H), 4.75-4.71 (1H, m, C7-H), 3.81 (1H, ddd, *J* = 8.5, 7.4, 6.4 Hz, C6-H), 3.52 (1H, dq, *J* = 8.8, 7.0 Hz, -OC**H**$_2$CH$_3$), 3.34 (1H, dq, *J* = 8.9, 7.0 Hz, -OC**H**$_2$CH$_3$), 2.63-2.49 (2H, m, C2-H$_{eq}$ + C4a-H), 2.36 (1H, ddd, *J* = 17.0, 13.0, 6.5 Hz, C2-H$_{ax}$), 2.08-1.97 (4H, m, C3-H$_{eq}$ + C4-H$_{eq}$ + C5-H), 1.85-1.69 (1H, m, C3-H$_{ax}$), 1.65-1.53 (1H, m, C4-H$_{ax}$), 0.91 (3H, t, *J* = 7.0 Hz, -OCH$_2$C**H**$_3$). NOE-D ($CDCl_3$): δ = 4.75-4.71 (3.81, 9%), 3.81 (2.63-2.49, 2%). ^{13}C NMR ($CDCl_3$): δ = 200.8 (0), 198.8 (0), 142.6 (0), 138.4 (0), 132.9 (1, C5'), 129.6 (1, C8), 128.5 (1, C3'), 128.4 (1, C4'), 76.1 (1, C6), 64.5 (2, -OCH$_2$CH$_3$), 46.6 (1, C7), 40.6 (2, C2), 38.0 (1, C4a), 31.41 (2, C4), 31.37 (2, C5), 23.0 (2, C3), 15.1 (3, -

OCH_2CH_3). MS *m/z* (%): Molecular ion not observed, 252 (5), 250 (12), 222 (3), 208 (6), 196 (6), 173 (19), 147 (6), 105 (100), 91 (7), 77 (46).

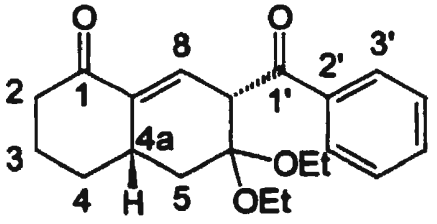
(9aα,9bα)-4-Benzoyl-1,2,8,9,9a,9b-hexahydronaphtho[2,1-*b*]furan-6(7*H*)-one (130)



To a stirred solution of diene **102** (227 mg, 1.00 mmol) in CH_3CN (5 mL) under N_2 was added silyl enol ether **127** in one portion via a syringe. The reaction was stirred at r.t. for 30 min, and then was diluted with CH_2Cl_2 (20 mL) and washed with 0.5 M HCl solution (2 × 25 mL). The aqueous solutions were back-extracted with CH_2Cl_2 (25 mL) and the combined organic solutions were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (75% EtOAc/hexanes, R_f = 0.33) afforded **130** as an orange solid (99 mg, 0.34 mmol, 34%). m.p.: 207-209 °C (ethanol). IR (film) ν_{max} 1660 (s), 1595 (s), 1535 (s), 1450 (m), 1413 (m), 1258 (s), 1225 (s), 933 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.69-7.65 (3H, m, C5-H + C3'-H), 7.53-7.47 (1H, m, C5'-H), 7.43-7.38 (2H, m, C4'-H), 4.71 (1H, dd, *J* = 8.8, 8.8 Hz, C2-H_{eq}), 4.36 (1H, ddd, *J* = 12.1, 9.0, 5.7 Hz, C2-H_{ax}), 2.98 (1H, ddd, *J* = 16.7, 11.8, 7.7 Hz, C9b-H), 2.70-2.55 (2H, m, C7-H_{eq} + C9a-H), 2.48 (1H, ddd, *J* = 12.7, 7.7, 5.7 Hz, C1-H_{eq}), 2.39-2.26 (1H, m, C7-H_{ax}), 2.19-2.03 (2H, m, C8-H_{eq} + C9-H_{eq}), 1.92 (1H,

dddd, J = 12.1, 12.0, 11.9, 8.8 Hz, C1-H_{ax}), 1.81-1.65 (1H, m, C8-H_{ax}), 1.54-1.40 (1H, m, C9-H_{ax}). NOE-D ($CDCl_3$): δ = 2.98 (2.70-2.55, 2.5%). ^{13}C NMR ($CDCl_3$): δ = 197.0 (0), 192.1 (0), 175.7 (0, C3a), 139.2 (0, C2'), 136.1 (1, C5), 132.1 (1, C5'), 129.1 (1, C3'), 128.3 (1, C4'), 126.4 (0, C5a), 107.0 (0, C4), 75.7 (2, C2), 48.6 (1, C9b), 40.5 (1, C9a), 39.2 (2, C7), 29.8 (2, C1), 28.8 (2, C9), 21.4 (2, C8). MS *m/z* (%): 295 (30), 294 (M^+, 100), 292 (12), 251 (19), 238 (19), 215 (18), 189 (95), 161 (3), 147 (5), 133 (5), 105 (86), 91 (9), 77 (82). Anal. calcd for $C_{19}H_{18}O_3$: C 77.53, H 6.16; found C 77.16, H 6.02.

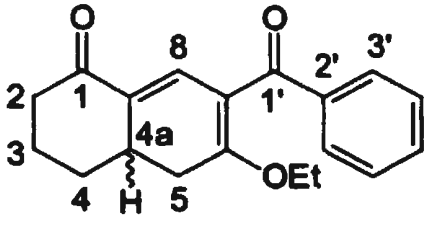
(4aα,7α)-7-Benzoyl-6,6-diethoxy-3,4,4a,5,7-pentahydro-1(*2H*)-naphthalenone (132)



A stirred solution of diene **102** (1.94 g, 8.56 mmol) and 1,1-diethoxyethene (**131**) (1.99g, 17.2 mmol) in benzene (50 mL) under N_2 was heated at reflux for 3 h. Once the solution was allowed to cool to r.t., the solvent was removed under reduced pressure. Flash chromatography (20% EtOAc/hexanes, R_f = 0.32) afforded **132** as a light yellow solid (2.52g, 7.35 mmol, 86%). Further purification by recrystallization from hexanes yielded a fine, white powder. m.p. : 123.0-124.5 °C (hexanes). IR (film): ν_{max} 2929 (s), 1662 (s), 1620 (s), 1446 (s), 1217 (s), 1123 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 8.02-7.98 (2H, m, C3'-H), 7.60-7.55 (1H, m, C5'-H), 7.51-7.45 (2H, m, C4'-H), 6.38 (1H, dd, J =

5.0, 2.8 Hz, C8-H), 4.73-4.71 (1H, m, C7-H), 3.69-3.54 (2H, m), 3.45 (1H, dq, J = 9.0, 7.0 Hz), 3.29 (1H, dq, J = 9.0, 7.1 Hz), 2.67-2.57 (2H, m, C2-H_{eq} + C4a-H), 2.36 (1H, ddd, J = 17.2, 13.2, 6.6 Hz, C2-H_{ax}), 2.20-1.95 (4H, m, C3-H_{eq} + C4-H_{eq} + C5-H), 1.89-1.73 (1H, m, C3-H_{ax}), 1.61-1.47 (1H, m, C4-H_{ax}), 1.20 (3H, t, J = 7.0 Hz), 0.92 (3H, t, J = 7.0 Hz). NOE-D ($CDCl_3$): δ =6.38 (4.73-4.71, 9.6%), 4.73-4.71 (8.02-7.98, 8.3%). ^{13}C NMR ($CDCl_3$): δ = 200.8 (0), 197.2 (0), 142.1 (0, C8a), 138.3 (0, C2'), 133.2 (1, C5'), 129.2 (1, C8), 128.7 (1, C3' + C4'), 100.5 (0, C6), 56.1 (2), 55.6 (2), 49.7 (1, C7), 40.8 (2, C2), 36.6 (1, C4a), 34.2 (2, C3), 31.0 (2, C4), 23.1 (2, C5), 15.5 (3), 15.1 (3). MS *m/z* (%): Molecular ion not observed, 297 (11), 296 (6), 239 (3), 192 (18), 164 (5), 136 (5), 116 (6), 105 (100), 77 (30). Anal. calcd for $C_{21}H_{26}O_4$: C 73.66, H 7.65; found C 73.44, H 7.78.

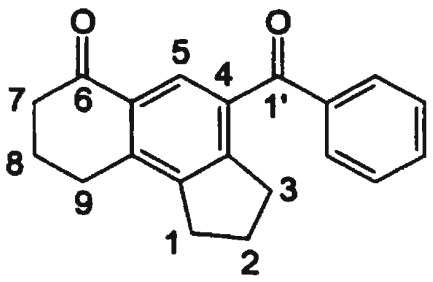
7-Benzoyl-6-ethoxy-3,4,4a,5-tetrahydro-1(*2H*)-naphthalenone (133)



To a solution of acetal **132** (684 mg, 2.00 mmol) in $CHCl_3$ (10 mL) in a 50 mL two-neck flask, equipped with a reflux condenser and rubber septum, under N_2 was added triethylamine (0.16 mL, 1.2 mmol) via a syringe. The reaction was heated to reflux for 24 h, cooled to r.t., and the solvent was removed under reduced pressure. The crude

mixture was purified by flash chromatography (50% EtOAc/hexanes, $R_f = 0.22$), yielding diene **133** (535 mg, 1.81 mmol, 90%). m.p.: 167-169 °C (hexanes). IR (film): ν_{max} 1663 (s), 1619 (s), 1588 (s), 1523 (s), 1246 (s), 1018 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.76-7.73 (2H, m, C3'-H), 7.53-7.46 (2H, m, C8-H + C5'-H), 7.43-7.38 (2H, m, C4'-H), 3.95-3.83 (2H, m, $-OCH_2CH_3$), 2.99-2.85 (1H, m, C4a-H), 2.70 (1H, dd, J = 17.0, 6.7 Hz, C5-H_{eq}), 2.62-2.53 (1H, m, C2-H_{eq}), 2.39-2.24 (2H, m, C2-H_{ax} + C5-H_{ax}), 2.14-2.01 (2H, m, C3-H_{eq} + C4-H_{eq}), 1.82-1.67 (1H, m, C3-H_{ax}), 1.53-1.41 (1H, m, C4-H_{ax}), 1.00 (3H, t, J = 7.0 Hz, $-OCH_2CH_3$). ^{13}C NMR ($CDCl_3$): δ = 197.3 (0), 194.5 (0), 168.5 (0, C6), 139.4 (0, C2'), 134.3 (1), 132.4 (1), 129.1 (1, C3'), 128.3 (1, C4'), 120.5 (0), 114.7 (0), 65.6 (2), 39.4 (2, C2), 35.0 (1, C4a), 33.1 (2, C5), 30.2 (2, C4), 21.8 (2, C3), 14.8 (3). MS *m/z* (%): 296 (M^+, 41), 294 (3), 268 (13), 240 (15), 239 (50), 225 (10), 212 (25), 191 (9), 189 (9), 163 (16), 134 (24), 105 (100), 77 (80).

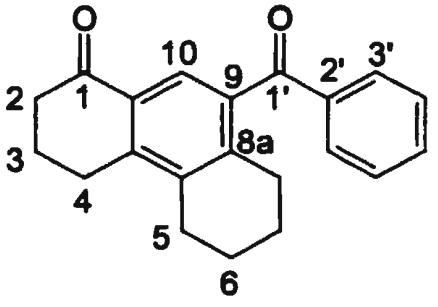
4-Benzoyl-2,3,8,9-tetrahydro-[1H]benz[*e*]inden-6(*7H*)-one (146)



To a stirred solution of diene **102** (205 mg, 0.91 mmol) in CH_3CN (5 mL) under N_2 was added enamine **145** (0.70 mL, 4.8 mmol) in one portion via a syringe. The reaction was stirred at r.t. for 10 min before the solvent was removed under reduced pressure. The residue was taken up into CH_2Cl_2 (25 mL) and extracted with water (2 × 25 mL). The organic solution was dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by flash chromatography (10% EtOAc/hexanes, $R_f = 0.21$) afforded **146** as a light brown solid (228 mg, 0.79 mmol, 87%). Recrystallization from hexanes yielded pure product as a white powder. m.p.: 92.5-94.5 °C (hexanes). IR (film): ν_{max} 1690 (s), 1662 (s), 1594 (m), 1223 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 8.07 (1H, s, C5-H), 7.79-7.76 (2H, m, C3'-H), 7.62-7.56 (1H, m, C5'-H), 7.49-7.44 (2H, m, C4'-H), 3.17 (2H, t, J = 7.6 Hz, C3-H), 2.92 (4H, t, J = 6.7 Hz, C1-H + C9-H), 2.67 (2H, dd, J = 7.7, 7.1 Hz, C7-H), 2.23-2.11 (4H, m, C2-H + C8-H). ^{13}C NMR ($CDCl_3$): δ = 198.0 (0), 197.1 (0), 150.9 (0), 144.8 (0), 143.5 (0), 137.9 (0), 133.0 (1, C5'), 132.6 (0), 130.8 (0), 130.2 (1, C3'), 128.6 (1, C4'), 127.9 (1, C5), 39.0 (2, C7), 33.6 (2, C3), 31.0 (2), 27.4 (2), 25.0 (2), 22.7 (2). MS *m/z* (%): 290 (M^+, 100), 289 (57), 275 (18), 234 (20), 205 (46),

149 (15), 128 (22), 105 (60), 77 (83). Anal. calcd for $C_{20}H_{18}O_2$: C 82.73, H 6.25; found C 82.78, H 6.08.

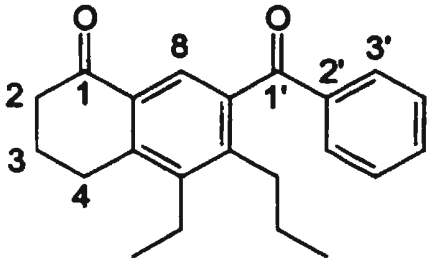
9-Benzoyl-3,4,5,6,7,8-hexahydro-1(*2H*)-phenanthrenone (148)



To a stirred solution of diene **102** (225 mg, 0.99 mmol) in CH_3CN (5 mL) under N_2 was added enamine **147** (0.80 mL, 5.0 mmol) in one portion via a syringe. The reaction stirred at r.t. for 20 min before the solvent was removed by evaporation under reduced pressure. The residue was dissolved into CH_2Cl_2 (25 mL) and washed with water (2 × 25 mL). The aqueous layer was back-extracted with CH_2Cl_2 (25 mL) and the combined organic solution was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. The resulting red oil was purified by flash chromatography (20% EtOAc/hexanes, $R_f = 0.37$), yielding **148** as a light yellow oil (157 mg, 0.52 mmol, 52%). ^{1}H NMR ($CDCl_3$): δ = 7.84 (1H, s, C10-H), 7.81-7.78 (2H, m, C3'-H), 7.61-7.55 (1H, m, C5'-H), 7.47-7.41 (2H, m, C4'-H), 2.87 (2H, t, J = 6.0 Hz, C4-H), 2.79 (2H, t, J = 6.2 Hz, C5-H), 2.73 (2H, t, J = 6.4 Hz, C8-H), 2.64 (2H, t, J = 6.6 Hz, C2-H), 2.17 (2H, tt, J = 6.6, 6.0 Hz, C3-H), 1.90-1.82 (2H, m, C7-H), 1.76 (2H, m, C6-H). ^{13}C NMR

($CDCl_3$): δ = 198.44 (0), 198.36 (0), 145.0 (0), 141.6 (0), 137.50 (0), 137.48 (0), 136.6 (0), 133.6 (1, C5'), 130.3 (1, C3'), 129.9 (0), 128.7 (1, C4'), 124.1 (1, C10), 38.6 (2, C2), 28.5 (2, C5), 27.2 (2, C8), 26.4 (2, C4), 22.7 (2, C3), 22.6 (2, C7), 22.2 (2, C6). MS *m/z* (%): 305 (16), 304 (M^+, 71), 303 (56), 289 (12), 286 (12), 248 (18), 143 (8), 128 (18), 115 (21), 105 (78), 98 (34), 84 (21), 77 (97), 55 (100).

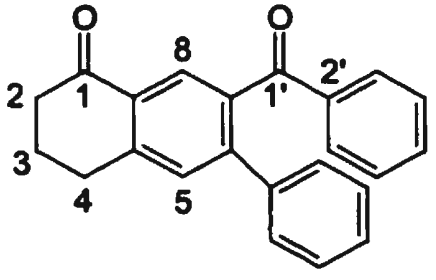
7-Benzoyl-5-ethyl-6-propyl-3,4-dihydro-1(*2H*)-naphthalenone (157)



To a stirred solution of diene **102** (226 mg, 1.00 mmol) in CH_3CN (5 mL) in a 25 mL flask under N_2 was added enamine **156** (816 mg, 4.88 mmol) in one portion via a syringe. The resulting orange solution was allowed to stir at r.t. for 25 min before the solvent was evaporated. The residue was diluted with CH_2Cl_2 (30 mL) and extracted with water (2 × 30 mL). The aqueous layer was back extracted with CH_2Cl_2 (30 mL) and the combined organic solution was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. Purification by flash chromatography (20% EtOAc/hexanes, R_f = 0.32) yielded nearly pure **157** as a yellow oil (97 mg, 0.30 mmol, 30%). A second purification by flash chromatography (*vide supra*) gave pure material as a white solid. m.p.: 111-114 °C (hexanes). IR (film): ν_{max} 1675 (s), 1664 (s), 1595 (m), 1584 (m), 1453

(s), 1291 (m), 1255 (m), 1176 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.84 (1H, s, C8-H), 7.81-7.77 (2H, m, C3'-H), 7.61-7.55 (1H, m, C5'-H), 7.47-7.41 (2H, m, C4'-H), 3.02 (2H, t, *J* = 6.0 Hz, C2-H), 2.78 (2H, q, *J* = 7.6 Hz), 2.72-2.62 (4H, m), 2.18 (2H, tt, *J* = 6.6, 6.0 Hz, C3-H), 1.72-1.45 (2H, m), 1.21 (3H, t, *J* = 7.5 Hz), 0.90 (3H, t, *J* = 7.3 Hz). NOE-D ($CDCl_3$) δ = 0.90 (7.61-7.55, 0.3 %), 1.21 (3.02, 0.9 %). ^{13}C NMR ($CDCl_3$): δ = 198.5 (0), 198.2 (0), 145.2 (0), 144.5 (0), 141.7 (0), 138.1 (0), 137.7 (0), 133.5 (1, C5'), 130.4 (1, C3'), 128.7 (1, C4'), 125.2 (1, C8), 125.1 (0), 38.7 (2), 32.5 (2), 26.8 (2, C2), 25.4 (2), 23.0 (2, C3), 22.0 (2), 14.8 (3), 14.6 (3). MS *m/z* (%): 321 (9), 320 (M^+, 40), 319 (11), 303 (3), 292 (23), 291 (100), 263 (22), 262 (40), 243 (27), 215 (6), 191 (7), 171 (5), 149 (10), 128 (13), 115 (15), 105 (95), 91 (19), 77 (86)

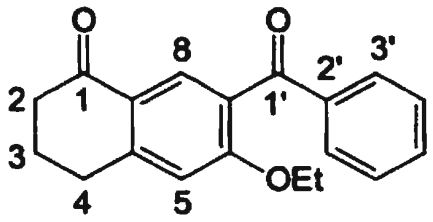
7-Benzoyl-6-phenyl-3,4-dihydro-1(*2H*)-naphthalenone (159)



To a stirred solution of diene **102** (230 mg, 1.02 mmol) in CH_3CN (5 mL) in a 25 mL flask under N_2 was added enamine **158** (899 mg, 5.19 mmol) in one portion via a syringe. The resulting orange solution was stirred at r.t. for 20 min. The solvent was removed, the residue taken up into CH_2Cl_2 (30 mL) and extracted with water (2 × 30 mL). The aqueous layer was back extracted with CH_2Cl_2 (30 mL) and the combined

organic solution was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. Purification by flash chromatography (20% EtOAc/hexanes) afforded ketone **161** (R_f = 0.54, 74 mg, 0.33 mmol, 13%) and **159** as a light brown solid (R_f = 0.21, 274 mg, 0.84 mmol, 82%). **159**: m.p.: 143.5-144.0 °C (hexanes). IR (film): ν_{max} 1692 (s), 1666 (m), 1601 (s), 1257 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 8.17 (1H, s, C8-H), 7.68-7.66 (2H, m, C3'-H), 7.47-7.42 (1H, m, C5'-H), 7.38 (1H, s, C5-H), 7.33-7.18 (7H, m), 3.08 (2H, t, *J* = 6.1 Hz, C4-H), 2.72 (2H, t, *J* = 6.5 Hz, C2-H), 2.22 (2H, m, C3-H). ^{13}C NMR ($CDCl_3$): δ = 197.6 (0), 197.5 (0), 146.5 (0), 146.2 (0), 139.5 (0), 137.8 (0), 137.3 (0), 133.3 (1, C5'), 131.2 (0), 130.9 (1, C5), 130.1 (1, C3'), 128.9 (1, C4'), 128.6 (1), 128.4 (1), 128.2 (1), 128.1 (1, C8), 39.3 (2, C2), 29.9 (2, C4), 23.3 (2, C3). MS *m/z* (%): 327 (21), 326 (M^+, 88), 325 (58), 298 (8), 270 (22), 249 (100), 221 (6), 193 (13), 178 (11), 165 (28), 135 (8), 105 (94), 77 (80), 51 (21). **161**: m.p.: 70.5-72.0 °C (hexanes). ^1H NMR ($CDCl_3$): δ = 7.91 (2H, dd, *J* = 8.3, 1.3 Hz), 7.57-7.47 (1H, m), 7.45-7.38 (2H, m), 7.35-7.25 (4H, m), 7.20-7.15 (1H, m), 3.50 (1H, ddq, *J* = 8.3, 6.9, 5.7 Hz), 3.29 (1H, dd, *J* = 16.5, 5.7 Hz), 3.16 (1H, dd, *J* = 16.5, 8.3 Hz), 1.33 (3H, d, *J* = 6.9 Hz). $^{13}CNMR$ ($CDCl_3$): δ = 199.3, 146.8, 137.4, 133.2, 128.8, 128.3, 127.1, 126.5, 47.3, 35.8, 22.1. MS *m/z* (%): 224 (M^+, 13), 209 (27), 131 (5), 120 (16), 105 (100), 91 (16), 77 (67).

7-Benzoyl-6-ethoxy-3,4-dihydro-1(*2H*)-naphthalenone (164)



A. Attempted Diels-Alder reaction with *N*-phenylmaleimide

A solution of diene **133** (200 mg, 0.67 mmol) and NPM (234 mg, 1.35 mmol) in toluene (5 mL) was heated to reflux, under N_2, for 4 days. After cooling to r.t. the solvent was removed under reduced pressure. The major products were purified by flash chromatography (50% EtOAc/hexanes), yielding **164** as a yellow solid (R_f = 0.36, 133 mg, 0.45 mmol, 67%), unreacted NPM (96 mg, 0.55 mmol), and *N*-phenylsuccinimide (**165**) as a yellow solid (53 mg, 0.30 mmol, 45%). Further purification by recrystallizing from hexanes gave **164** as a light brown solid. **164**: m.p.: 126.0-127.5 °C (hexanes). IR (film): ν_{max} 1677 (s), 1650 (s), 1601 (s), 1253 (s), 1122 (m), 1041 (m). ^{1}H NMR ($CDCl_3$): δ = 8.09 (1H, s, C8-H), 7.78-7.75 (2H, m, C3'-H), 7.57-7.52 (1H, m, C5'-H), 7.44-7.39 (2H, m, C4'-H), 6.77 (1H, s, C5-H), 4.03 (2H, q, J = 7.0 Hz, -OCH_2CH_3), 3.00 (2H, t, J = 6.0 Hz, C4-H), 2.64 (2H, t, J = 6.5 Hz, C2-H), 2.16 (2H, tt, J = 6.5, 6.1 Hz, C3-H), 1.15 (3H, t, J = 7.0 Hz, -OCH_2CH_3). ^{13}C NMR ($CDCl_3$): δ = 196.7 (0), 195.6 (0), 160.8 (0, C6), 149.4 (0, C4a), 138.0 (0, C2'), 133.1 (1, C5'), 129.8 (1, C8 + C3'), 128.4 (1, C4'), 125.9 (0, C8a), 120.5 (0, C7), 111.3 (1, C5), 64.6 (2), 39.0 (2, C2), 30.6 (2, C4), 23.4 (2, C3), 14.4 (3). MS *m/z* (%): 295 (9), 294 (M^+, 38), 276 (17), 265 (23), 249 (5),

238 (15), 217 (17), 194 (16), 189 (100), 160 (10), 132 (12), 105 (55), 77 (60). Anal. calcd for $C_{19}H_{18}O_3$: C 77.53, H 6.16; found C 77.39, H 6.06. **165**: m.p.: 147-152 °C (lit. 156 °C).[87] ^{1}H NMR ($CDCl_3$) δ = 7.51-7.37 (3H, m), 7.30-7.26 (2H, m), 2.89 (4H, s).

B. Attempted Diels-Alder reaction with ethyl vinyl ether

A degassed solution of diene **133** (80 mg, 0.27 mmol) and ethyl vinyl ether (0.3 mL, 3.1 mmol) in benzene (5 mL) was heated to 80 °C in a sealed tube for 20 h. After cooling, the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (50% EtOAc/hexanes, R_f = 0.40), affording **164** (47 mg, 0.16 mmol, 55%) which was identical to the material described above.

C. Attempted Diels-Alder reaction with enamine **145**

To a magnetically stirred solution of diene **133** (197 mg, 0.66 mmol) in CH_3CN (5 mL) at r.t., under N_2, was added enamine **145** (0.5 mL, 3.4 mmol) in one portion via a syringe. The solution was allowed to stir at r.t. for 30 min, before the solvent was evaporated. The resulting residue was taken up into CH_2Cl_2 (50 mL) and washed with water (2 × 25 mL). The organic solution was dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The product was purified by flash chromatography (50% EtOAc/hexanes, R_f = 0.36), yielding **164** as a yellow solid (111 mg, 0.38 mmol, 58%). All spectroscopic analyses of this material were consistent with those from the previously described experiments.

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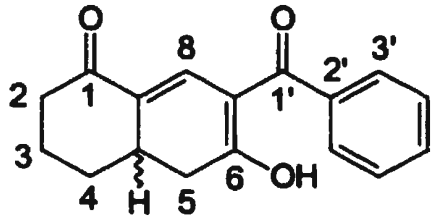
[87] Lide, D.R.(Ed.) *CRC Handbook of Chemistry and Physics*, 75th Ed., CRC Press: Boca Raton, FL, 1994,

D. Oxidation with DDQ

To a stirred solution of diene **133** (102 mg, 0.34 mmol) in benzene (3 mL), under N_2, was added a solution of DDQ (89 mg, 0.39 mmol) in benzene (3 mL). The reaction was heated at reflux for 20 min, during which time the dark coloured mixture turned light orange. The reaction mixture was cooled on ice, filtered and washed with a small portion of warm benzene. The filtrate was concentrated under reduced pressure and the crude product was purified by flash chromatography (50% EtOAc/hexanes, R_f = 0.36), affording **164** as a yellow solid (56 mg, 0.19 mmol, 55%).

7-Benzoyl-6-hydroxy-3,4,4a,5-tetrahydro-1(*2H*)-naphthalenone (167)



To a stirred solution of acetal **132** (466 mg, 1.36 mmol) in distilled acetone (7 mL) was added *p*-TSA·H_2O (50 mg, 0.26 mmol). Once the resulting bright yellow solution had stirred at r.t. for 30 min, the stir-bar was removed and the solvent was removed by evaporation under reduced pressure. The residue was dissolved into CH_2Cl_2 (50 mL) and extracted with saturated aqueous $NaHCO_3$ solution (50 mL) and water (50

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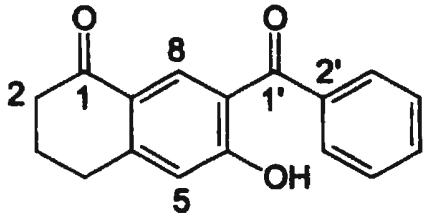
p.3-305.

mL). The aqueous layers were back-extracted with CH_2Cl_2 (50 mL), and the combined organic solution was dried ($MgSO_4$) and filtered. Removal of solvent under reduced pressure gave **167** as a yellow solid (364 mg, 1.36 mmol, 100%). m.p.: 134.0-135.5 °C (ethanol/water). IR (film): ν_{max} 3540 (m), 3500-3160 (m), 1677 (s), 1666 (s), 1581 (s), 1562 (s), 1552 (s), 1240 (s), 1169 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 16.51 (1H, m, C6-OH), 7.63-7.46 (6H, m, C3'-H + C4'-H + C5'-H + C8-H), 3.01-2.89 (1H, m, C4a-H), 2.72 (1H, dd, J = 16.8, 5.1 Hz, C5-H_{eq}), 2.64-2.55 (1H, m, C2-H_{eq}), 2.46 (1H, dd, J = 16.8, 7.4 Hz, C5-H_{ax}), 2.32 (1H, ddd, J = 18.6, 13.4, 6.2 Hz, C2-H_{ax}), 2.17-2.01 (2H, m, C3-H_{eq} + C4-H_{eq}), 1.86-1.70 (1H, m, C3-H_{ax}), 1.49-1.35 (1H, m, C4-H_{ax}). ^{13}C NMR ($CDCl_3$): δ = 203.1 (0), 197.7 (0), 181.9 (0, C6), 133.6 (0, C2'), 132.7 (1), 132.1 (1), 129.4 (1, C3'), 128.8 (1, C4'), 120.5 (0, C8a), 108.1 (0, C7), 43.1 (2, C5), 39.3 (1, C2), 34.3 (1, C4a), 30.3 (2, C4), 21.8 (2, C3). MS *m/z* (%): 269 (5), 268 (M^+, 26), 266 (5), 265 (5), 240 (8), 239 (29), 225 (5), 212 (18), 197 (8), 189 (3), 163 (10), 134 (28), 105 (77), 77 (100). Anal. calcd for $C_{17}H_{16}O_3$: C 76.10, H 6.01; found C 76.14, H 5.91.

7-Benzoyl-3,4-dihydro-6-hydroxy-1(*2H*)-naphthalenone (170)



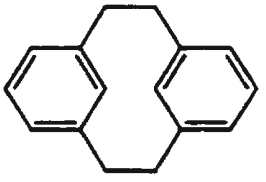
To a solution of diene **167** (183 mg, 0.68 mmol) in benzene (10 mL) was added DDQ (174 mg, 0.77 mmol). The resulting mixture was heated at reflux under N_2 for 2 h. After cooling on ice, the mixture was filtered through Celite, rinsing with a small portion of warm benzene. The solvent was removed from the filtrate under reduced pressure and the resulting material was purified by flash chromatography (80% CH_2Cl_2/hexanes, R_f = 0.33), yielding **170** as a yellow solid (31 mg, 0.12 mmol, 17%). m.p.: 150.0-153.5 °C (hexanes). ^{1}H NMR ($CDCl_3$): δ = 12.44 (1H, s, C6-OH), 8.39 (1H, s, C8-H), 7.70-7.50 (5H, m), 6.91 (1H, s, C5-H), 2.99 (2H, t, J = 6.0 Hz, C4-H), 2.63 (2H, t, J = 6.5 Hz, C2-H), 2.14 (2H, tt, J = 6.5, 6.0 Hz, C3-H). MS *m/z* (%): 267 (17), 266 (M^+, 95), 265 (100), 249 (3), 238 (34), 210 (5), 189 (37), 161 (4), 160 (16), 132 (17), 111 (9), 105 (64), 97 (17), 84 (28), 77 (62).

II. SYNTHESIS OF SOME 6,15-DISUBSTITUTED 2,11-DITHIA[3.3]METACYCLOPHANES

4.0 Solution Conformations of 2,11-Dithia[3.3]metacyclophanes

4.1 Introduction to Cyclophanes

Reports of cyclophanes can be traced back to at least 1899 and the preparation of [2.2]metacyclophane (**174**).[88] Extensive interest in this field didn't begin to grow until the late 1940's, and today the synthesis and study of cyclophanes have developed into a distinct sub-section of organic chemistry. Research into cyclophanes has had many appeals to scientists. These include their often unusual and aesthetically appealing structures. Despite often being simple molecules, they can pose a great synthetic challenge. Many cyclophanes display unique conformational behavior and unusual chemical and physical properties. As a result of these interesting properties, cyclophanes can often make useful model or test compounds in theoretical studies.



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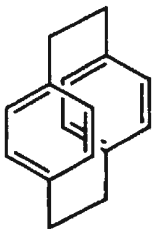
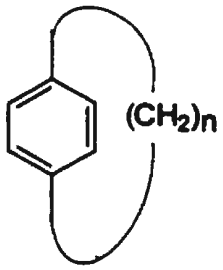
Cyclophanes are quite simply described by the phrase from which their name is derived: *cyclophe*nyl(ene) alk*ane*. That is, a cyclophane is a molecule consisting of one or more aromatic units linked by one or more bridges such that the aromatic units form

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

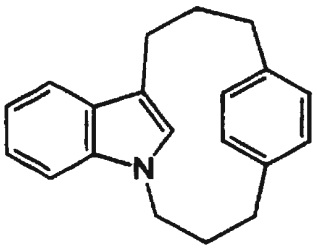
part of a cycle. A well defined, and accepted, system for the nomenclature of cyclophanes has been developed[89] and a vast array of cyclophanes has subsequently been described.[90] A small sample includes [*m.n*]cyclophanes, such as [2.2]metacyclophane (**174**) and [2.2]paracyclophane (**175**),[91] [*n*]cyclophanes such as **176**[92], as well as those containing different aromatic units, for example indolophane **177**.[93]



175



176



177

Our group is actively involved in the synthesis and study of a wide range of cyclophanes, including expanded cyclophanes such as **178**,[94] and cyclophanes containing non-planar aromatic rings, for instance **179**[95] and **180**.[96] Cyclophane **180** was determined

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[89] Vögtle, F.; Neumann, P. *Tetrahedron Lett.* **1969**, 5329-5334.; Vögtle, F.; Neumann, P. *Tetrahedron* **1970**, *26*, 5847-5873.

[90] For general overviews, see: *Cyclophanes*, Weber, E. (Ed.), Springer-Verlag: Berlin, **1994**.; *Cyclophanes II*, Vögtle, F. (Ed.), Springer-Verlag: Berlin, **1983**.; Bodwell, G.J. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2085-2088.

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

[92] Greenberg, A.; Liebman, J.F. *Strained Organic Molecules*, Academic Press: New York, **1978**, 153.; Bickelhaupt, F.; de Wolf, W.H. in *Advances in Strain in Organic Chemistry*, Vol. 3., Halton, B. (Ed.), JAI Press: Greenwich, CT, **1993**, 185.

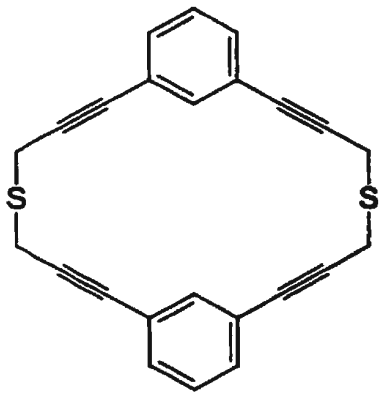
[93] Bodwell, G.J.; Li, J.; Miller, D.O. *Tetrahedron* **1999**, *55*, 12939-12956.

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

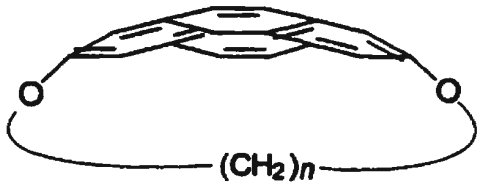
[95] Bodwell, G.J.; Bridson, J.N.; Houghton, T.J.; Kennedy, J.W.J.; Mannion, M.R. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1320-1321.

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

to contain a pyrene moiety bent by 109.2 ° between the two ends, which is more distorted from planarity than is the corresponding pyrene subunit of the equator of C_{70}.



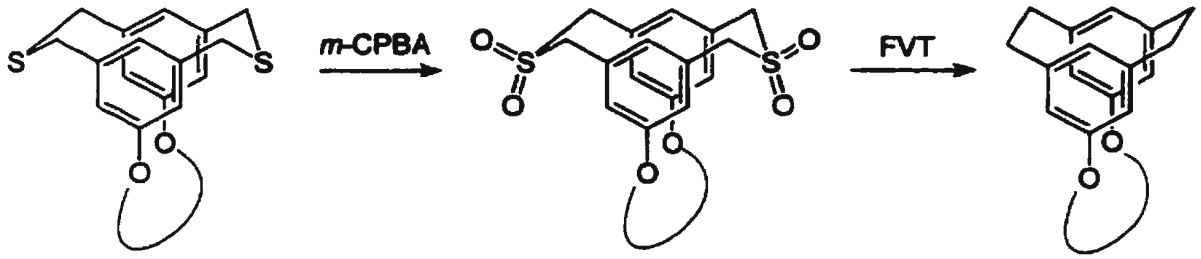
178



179, n = 6
180, n = 5

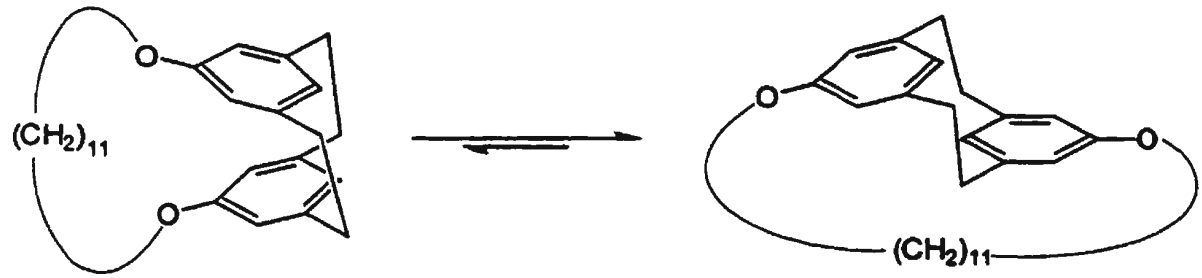
4.2 2,11-Dithia[3.3]metacyclophanes

2,11-dithia[3.3]cyclophanes are often versatile and easily prepared precursors to lower cyclophanes. Several ring contraction methods are available for their conversion into [2.2]cyclophanes. Dithia[3.3]metacyclophanes, such as **181**, can be converted to [2.2]metacyclophanes (**183**) through *m*-CPBA oxidation to the bis(sulfone) (**182**) and extrusion of SO_2 by flash vacuum thermolysis.[97] This reaction has led to the synthesis of compounds that behave as prototype molecular devices. [2.2]Metacyclophane **184**, containing a 13 atom tether, was observed to exist in an equilibrium between the *syn* and *anti* conformers at room temperature.



181 **182** **183**

Scheme 4.1: Conversion of tethered 2,11-dithia[3.3]metacyclophanes into tethered [2.2]metacyclophanes.



***syn*-184** ***anti*-184**

Scheme 4.2: *Syn-anti* equilibrium observed for tethered [2.2]metacyclophane **184**.

Dithia[3.3]metacyclophanes (**181**) can also be converted to [2.2]metacyclophane dienes (**187**) by way of methylation with Borch reagent, giving tetrafluoroborate salts (**185**), Stevens rearrangement to the bis(sulfide) (**186**), and Hofmann elimination. Such a sequence was employed for the preparation of cyclophane dienes which, after oxidation with DDQ, gave pyrenophanes **179** and **180**.[95,96]

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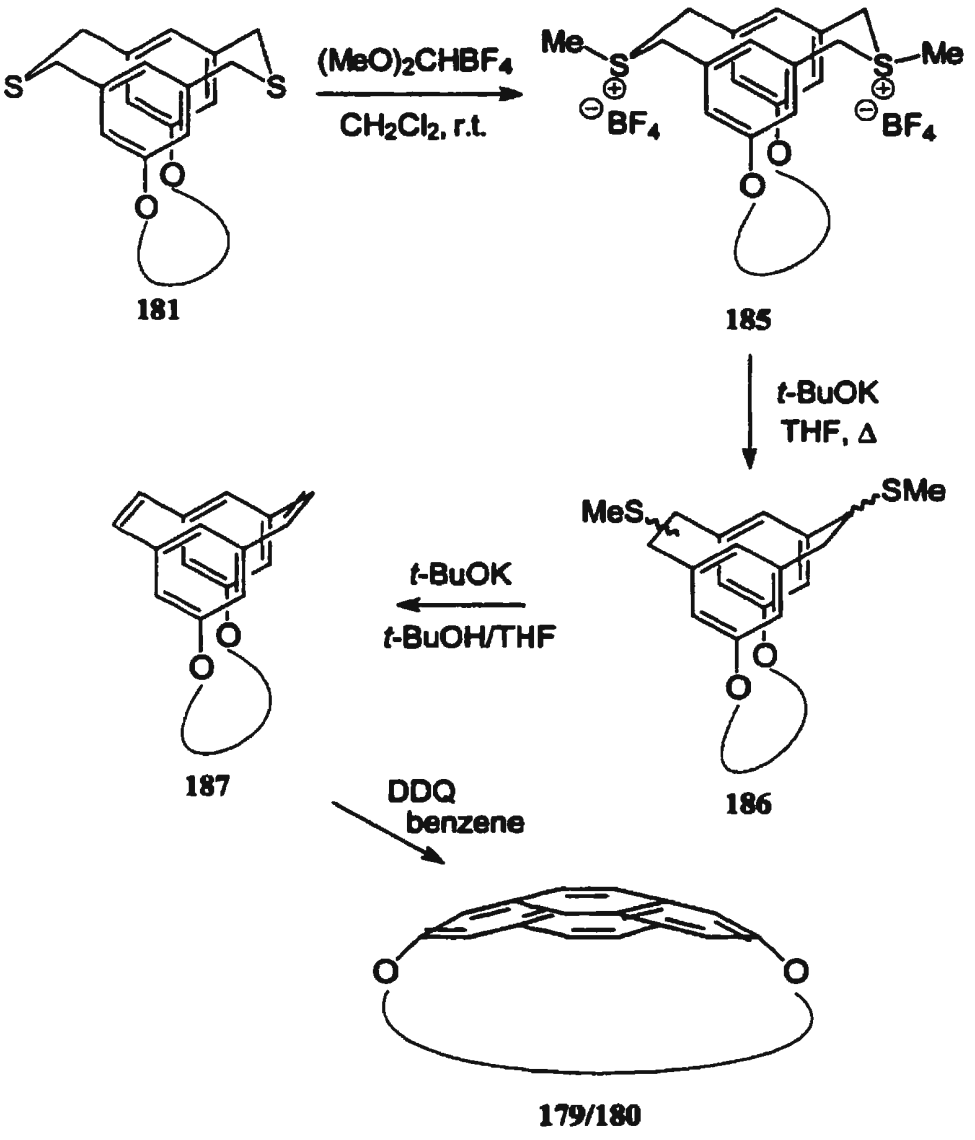
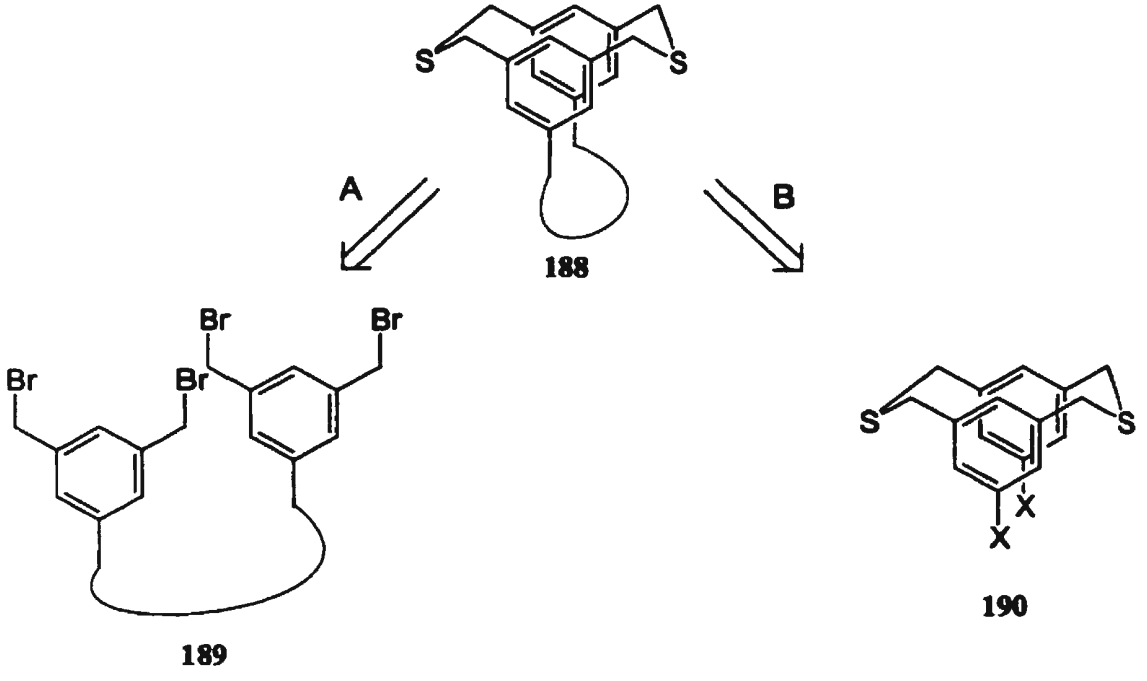
[97] Bodwell, G.J.; Houghton, T.J.; Kennedy, J.W.J.; Mannion, M.R. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2121-2123.



Scheme 4.3: Conversion of tethered 2,11-dithia[3.3]metacyclophanes into [*n*](2,7)pyrenophanes.

Throughout the course of each of the two projects mentioned, the tethered dithia[3.3]metacyclophanes (**181**) were required. Initial retrosynthetic analysis of **188**

(Scheme 4.4) led back to either tetrabromide **189** (path A), where a sulfide coupling reaction could be used form the cyclophane ring, or to the 6,15-disubstituted dithia[3.3]metacyclophane **190** (path B), where the tether could be introduced later.

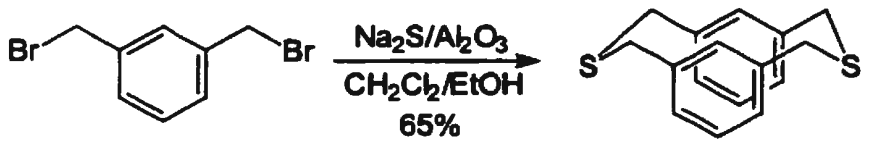


Scheme 4.4: Retrosynthetic analysis for the preparation of tethered dithia[3.3]metacyclophanes.

Path A was the first method to prove successful, aided greatly by the adaptation by our group of the Na_2S/Al_2O_3 reagent for the efficient conversion of dibromides (**191**) to dithia[3.3]metacyclophanes (**192**),[98] without the need for the preparation or isolation of

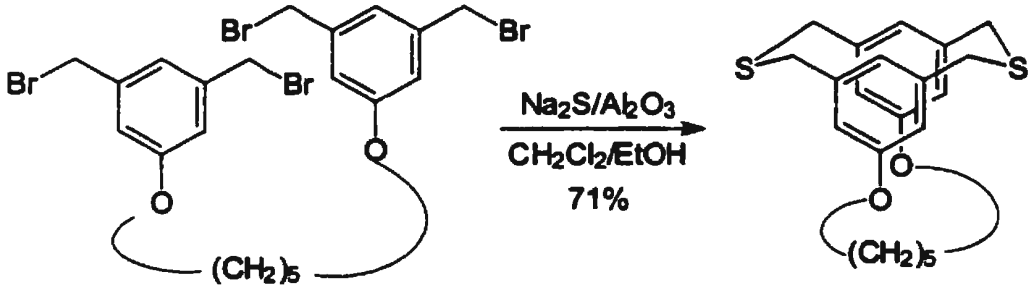
[98] Bodwell, G.J.; Houghton, T.J.; Koury, H.E.; Yarlagadda, B. *Synlett* **1995**, 751-752.

a dithiol. For example, intramolecular Na_2S/Al_2O_3 coupling of seven atom tethered tetrabromide **193** gave tethered dithia[3.3]metacyclophane **194** in 71% yield.[96]



191 **192**

Scheme 4.5: Na_2S/Al_2O_3 coupling of dibromide **191** giving dithia[3.3]-metacyclophane **192**.



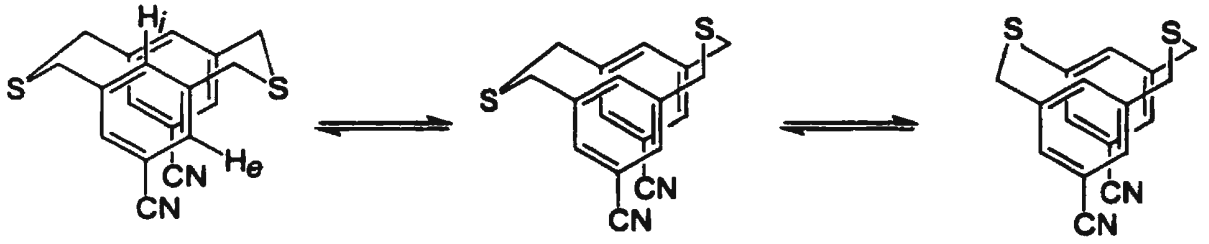
193 **194**

Scheme 4.6: Intramolecular coupling of tetrabromide **193** giving tethered dithia[3.3]metacyclophane **194**.

During the pursuit of path B, the 6,15-dicyano- substituted dithia[3.3]metacyclophane (**195**) was prepared. Unexpectedly, x-ray crystallographic analysis of this compound showed that it crystallized in the higher energy *pseudo-boat,pseudo-boat* configuration of the *syn* conformation (**195c**).[99] As the *pseudo-*

[99] Bodwell, G.J.; Bridson, J.N.; Houghton, T.J.; Yarlagadda, B. *Tetrahedron Lett.* **1997**, *38*, 7475-7478.

boat,pseudo-boat conformation was reported (calculated at the AM1 level) to be only 1.77 kcal/mol higher in energy than the *pseudo-chair,pseudo-chair* conformation (**195a**), the unexpected behavior was attributed to dipolar effects, either dipoles inherent in the molecule or the dipole component of the crystal packing forces. The *pseudo-boat,pseudo-boat* conformation was calculated to have a dipole effectively half that of the *pseudo-chair,pseudo-chair* conformation, 3.63 D and 7.30 D, respectively.



195a **195b** **195c**

Scheme 4.7: Conformational isomers for *syn* dithiacyclophane **195**.

Since crystal packing forces are not well understood, a method for measuring the equilibrium of the dithia[3.3]metacyclophanes was desired, preferably in solution. This led to the initiation of a study of the solution phase conformational preferences of a series of 6,15-disubstituted 2,11-dithia[3.3]metacyclophanes. Initially it was postulated that, by examining the solution behavior of a comprehensive series of 6,15-disubstituted 2,11-dithia[3.3]metacyclophanes, a trend may be recognized between the nature of the substituent and the position of the equilibrium between the three possible *syn* conformations.

It is known that the presence of sulfur substituents on the bridges of [2.2]cyclophanes results in steric deshielding of the aromatic protons.[100] Therefore, in dithia[3.3]metacyclophanes where the bridge is in the *pseudo-chair,pseudo-chair* conformation, it would be expected that the external aromatic protons (H_e, see cyclophane **195**) would be deshielded, relative to the corresponding protons in an appropriate aromatic model compound where the sulfur atoms are not present (such as the 5-halo-*m*-xylene). Similarly, the internal aromatic proton (H_i, see cyclophane **195**) would be expected to be deshielded relative to the corresponding proton in a model compound when the bridge is in the *pseudo-boat,pseudo-boat* conformation. It is of interest to determine if the size of the changes in chemical shift ($\Delta\delta$) for H_e and H_i could be correlated with some physical organic parameter such as σ_m (the Hammett parameter for the effect of *meta*-substituents on the reactivity or equilibrium position of benzene ring containing systems). Additional parameters that will be considered for comparison with the $\Delta\delta$ values include Pauling electronegativities and the carbon-substituent dipole moment.

Indeed, a very preliminary examination of the $\Delta\delta$ values for a few dithia[3.3]metacyclophanes revealed that such a relationship with σ_m might exist.[101] However, more compounds needed to be examined and, due to the potential for often small $\Delta\delta$ values, great care must be taken to eliminate errors arising from factors such as differing concentrations of the NMR samples. An extensive series of 6,15-disubstituted

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[100] Mitchell, R.H.; Boekelheide, V. *J. Am. Chem. Soc.* **1974**, *96*, 1547-1557; Mitchell, R.H.; Vinod, T.K.; Bushnell, G.W. *J. Am. Chem. Soc.* **1990**, *112*, 3487-3497.
[101] Bodwell, G.J.; Mannion, M.R.; Yarlagadda, B. *Unpublished results*.

2,11-dithia[3.3]metacyclophanes were targeted for synthesis as part of a cooperative effort within our group, and the work described herein focuses on the halogen substituted dithia[3.3]metacyclophanes.

4.3 Synthesis of 6,15-Dihalo-2,11dithia[3.3]metacyclophanes

The 6,15-disubstituted 2,11-dithia[3.3]metacyclophanes of interest for synthesis in this study included the unsubstitued (**192**), difluoro- (**196**), dichloro- (**197**), dibromo- (**198**), and diiodo- (**199**) compounds. Therefore, the model compounds chosen were the *m*-xylenes **200**, **201**, **202**, **203**, and **204**, respectively. In addition, α,α'-dibromo-*m*-xylenes **207**, **208**, **209** and **210** were envisioned as synthetic precursors to their respective dithia[3.3]metacyclophanes. *m*-Xylenes **202**[102] and **203**[103] were easily prepared by an appropriate Sandmeyer reaction of 3,5-dimethylaniline (**205**), while *m*-xylene **201** was prepared from **205** by the Schiemann reaction,[104] via the stable tetrafluoroborate salt (**206**). 5-Bromo-*m*-xylene (**203**) was commercially available.

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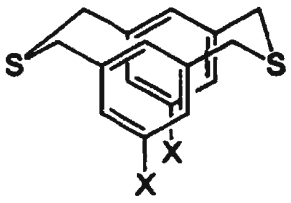
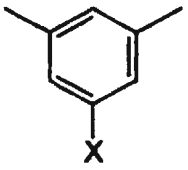
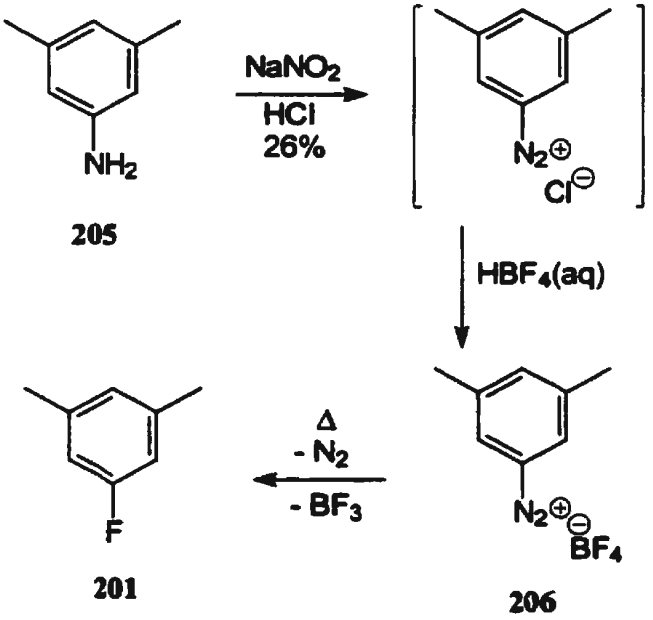
[102] Marvel, C.S.; McElvain, S.M. *Org. Synth. Coll. Vol. I*, **1932**, 170-172.
[103] Lucas, H.J.; Kennedy, E.R. *Org. Synth. Coll. Vol, II*, **1943**, 351-352.
[104] Schiemann, G.; Winkelmüller, W. *Org. Synth. Coll. Vol. II* **1943**, 188-190.; Schiemann, G.; Winkelmüller, W. *Org. Synth. Coll. Vol. II* **1943**, 299-301.



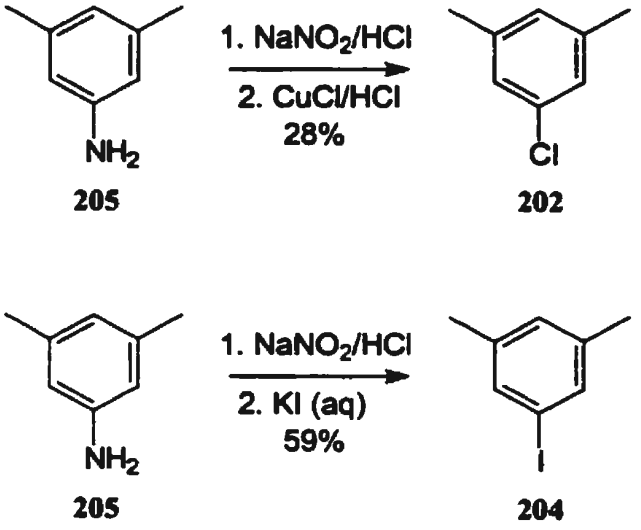
192, X = H
196, X = F
197, X = Cl
198, X = Br
199, X = I



200, X = H
201, X = F
202, X = Cl
203, X = Br
204, X = I



Scheme 4.8: Preparation of 5-fluoro-*m*-xylene (**201**) by the Schiemann reaction.

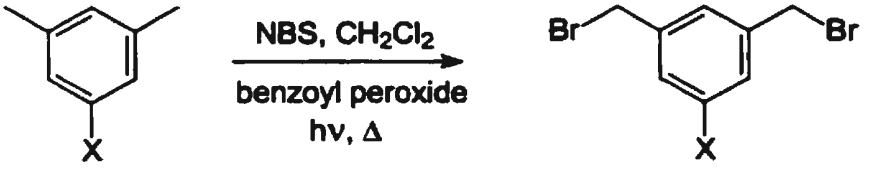


Scheme 4.9: Preparation of 5-chloro- (**202**) and 5-iodo-*m*-xylene (**204**) by the Sandmeyer reaction.

Benzylic bromination of the 5-halo-*m*-xylenes with NBS[105] afforded the α,α'-dibromo compounds **207, 208, 209** and **210** in low to modest yields. A range of conditions to effect the radical halogenation reaction was explored. These conditions included varying the solvent (benzene, carbon tetrachloride and dichloromethane were used), varying the source of radical initiator (peroxide, light and combinations of both were used), using the NBS as obtained commercially and freshly recrystallized, as well as adding the NBS in one portion and in several small portions as the reaction proceeded. Disappointingly, at this stage, improved yields were not obtained. In all cases, ^{1}H NMR analysis of the crude product mixtures suggested that the major side-products included mono-brominated, α,α-dibrominated, and α,α,α'-tribrominated products, however none

[105] Tashiro, M.; Yamato, T. *J. Org. Chem.* **1985**, *50*, 2939-2942.

of these undesired products were isolated. α,α'-Dibromo-*m*-xylene (**191**) was purchased commercially.



201, X = F
202, X = Cl
203, X = Br
204, X = I

191, X = H
207, X = F, 4%
208, X = Cl, 17%
209, X = Br, 19%
210, X = I, 22%

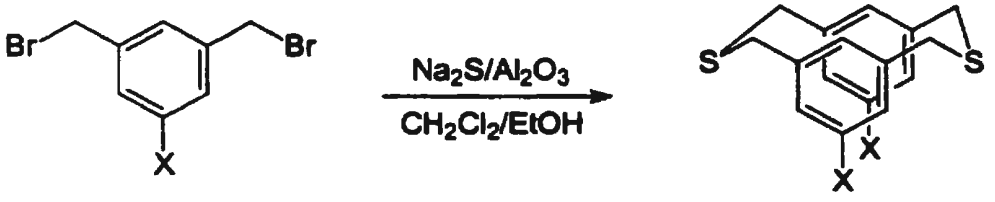
Scheme 4.10: Benzylic bromination of 5-halo-*m*-xylenes.

Following a literature procedure for the synthesis of **192**,[98] the NaS_2/Al_2O_3 coupling conditions were utilized for the preparation of the dihalo substituted dithia[3.3]metacyclophanes. Treatment of the dibromides with freshly prepared reagent[106] afforded dithia[3.3]metacyclophanes **198** and **199** in moderate yields of 37 % and 40 %, respectively. These yields were only somewhat lower than the reported optimized yield for the parent system (**191** to **192**) of up to 65%.[98] Analysis of reaction mixtures by TLC suggested that the dibromides were consumed after the standard reaction times (usually 1 to 1.5 hours after the addition of the final portion of Na_2S/Al_2O_3 reagent) leading to the formation of one major product spot. Following chromatography, no other products were isolated. Some loss of desired product may have occurred due to

[106] The NaS_2/Al_2O_3 reagent is reported to work best when used within 24 hours of preparation, as the presence of water in the reaction can have detrimental effect on the yield of diathiacyclophane obtained.

low solubility of the dithia[3.3]metacyclophanes in the chromatography solvent, usually 33% CH_2Cl_2 in hexanes.

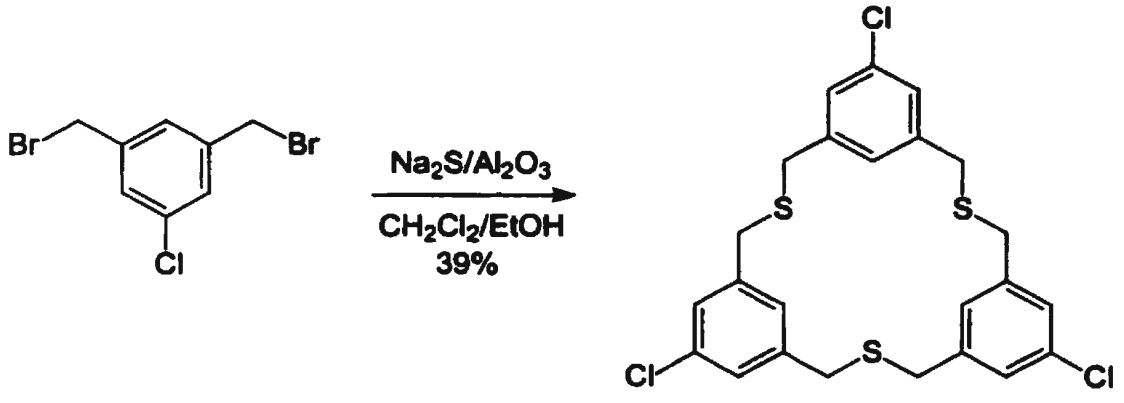
Under identical conditions, the coupling reactions of dibromides **207** and **208** each led to the formation of one major product, as suggested by TLC analysis. However, the solid material obtained after work-up displayed low solubility (even upon heating) in a number of solvents, including CH_2Cl_2, $CHCl_3$ and benzene. This made purification difficult, and pure samples of neither were obtained. ^1H NMR analysis of both crude materials resembled what would be expected for the desired dithia[3.3]metacyclophanes (**196** and **197**), but analysis of the product from the coupling reaction of **208** by mass spectrometry clearly identified it as the cyclic trimer **211** (*m/z* 510), arising from the cyclization of three molecules of the dibromide. This product was obtained in 39% yield, and none of the desired dimer (**197**) was eluted during chromatography.



191, X = H
209, X = Br
210, X = I

192, X = H
198, X = Br
199, X = I

Scheme 4.11: 2,11-Dithia[3.3]metacyclophanes by Na_2S/Al_2O_3 coupling.



208 **211**

Scheme 4.12: Formation of cyclic trimer **211** from Na_2S/Al_2O_3coupling of dibromide **208**.

The solubility of desired dithia[3.3]metacyclophanes **196** and **197** may have played a major role in the difficulty experienced with their syntheses by the Na_2S/Al_2O_3 coupling reaction. Other reaction conditions, including the standard dithiol-dibromide coupling reaction,[107] will be examined for their synthesis in the future.

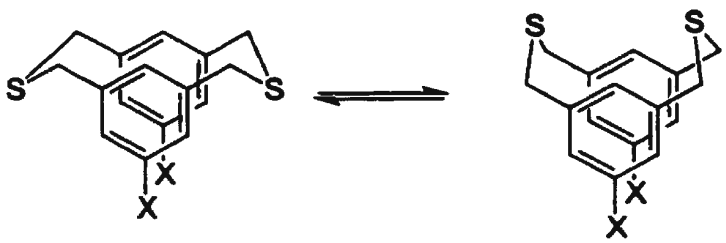
As the preference for dithia[3.3]metacyclophane **195** to crystallize in the *pseudo-boat,pseudo-boat* conformation (**195c**) was attributed to a dipolar effect,[99] the dipoles for each of the targeted cyclophanes were calculated[108] for both the *pseudo-chair,pseudo-chair* and *pseudo-boat,pseudo-boat* conformations. The energy differences between the two conformations were also calculated for each of the dithia[3.3]metacyclophanes **192**, **196**, **197**, **198**, and **199**.

[107] Vögtle, F. *Chem. And Ind.* **1972**, 346.

Compound	Calculated Dipole[a] (D)	Calculated Dipole[a] (D)	Energy[b] (kcal/mol)
	chair,chair	*boat,boat*	*boat,boat*
192	1.48 ↓	2.58 ↑	2.40
196	4.31 ↓	0.48 ↓	1.92
197	3.71 ↓	0.12 ↑	1.87
198	3.91 ↓	0.09 ↓	1.78
199	3.84 ↓	0.03 ↓	1.83

[a] dipole direction given relative to molecular orientation shown below
[b] relative to the *chair,chair* conformation (kcal/mol)

Figure 4.1: Calculated molecular dipoles and energies for several conformations of the *syn* dithia[3.3]metacyclophanes.



chair,chair *boat,boat*

Clearly, based on the calculation data for the dithia[3.3]metacyclophanes, the *pseudo-boat,pseudo-boat* conformations for all the 6,15-dihalo substituted analogues (**196**, **197**, **198**, and **199**) might be expected to be the favored conformations in non-polar solvents, as this conformation leads to the lowest molecular dipole. Conversely, unsubstituted dithia[3.3]metacyclophane **192** might be expected to favor the *pseudo-chair,pseudo-chair* conformation in non-polar solvents.

[108] Calculations were performed at the AM1 level using the Spartan software package.

For a preliminary analysis of the experimental data obtained up to this point in the study, the chemical shift obtained during characterization of the dithia[3.3]metacyclophanes will be used. The ^1H NMR data for the full study of the dithia[3.3]metacyclophanes will be aquired by a single operator at a future time. In addition, the samples will be run in several different NMR solvents in an attempt to learn more about the effect that the dielectric constant of the solvent plays on the position of the conformational equilibrium.

Compound	H_i (ppm)	H_e (ppm)
200	7.01	7.05
203	6.85	7.09
204	6.90	7.31
192	6.82	6.95
198	6.95	7.05
199	7.01	7.25

Figure 4.2: Chemical shifts for model compounds and dithia[3.3]metacyclophanes.

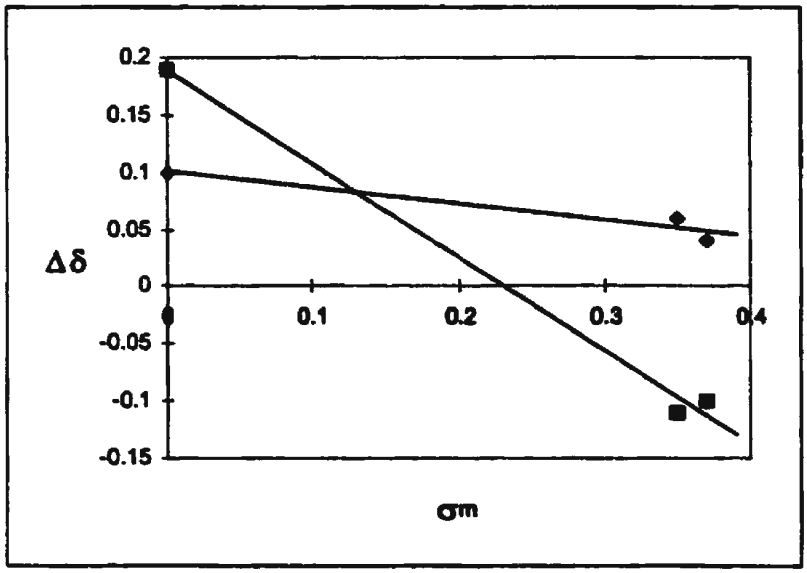


Figure 4.3: Δδ against σ_m for H_i (■) and H_e (◆) in dithia[3.3]metacyclophanes **192, 198, and 199.**

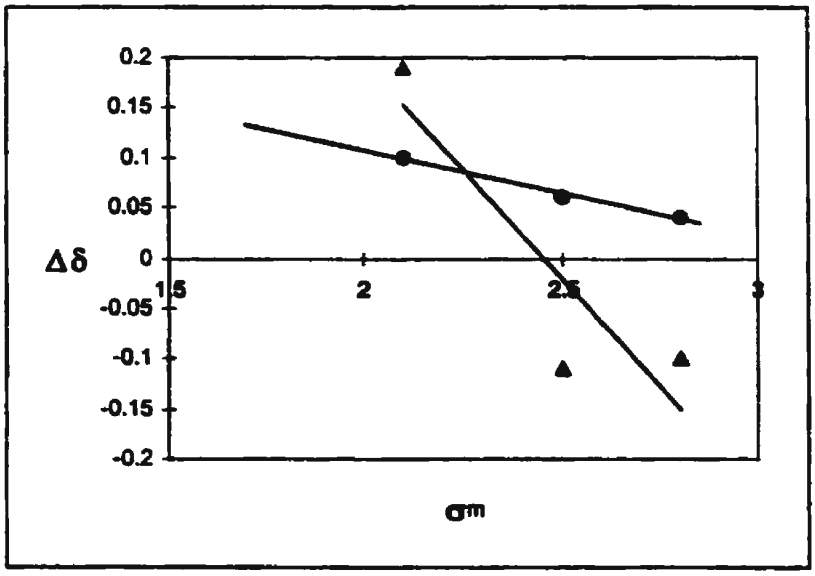


Figure 4.4: Δδ against Pauling electronegativities for H_i (▲) and H_e (●) in dithia[3.3]metacyclophanes **192, 198, and 199.**

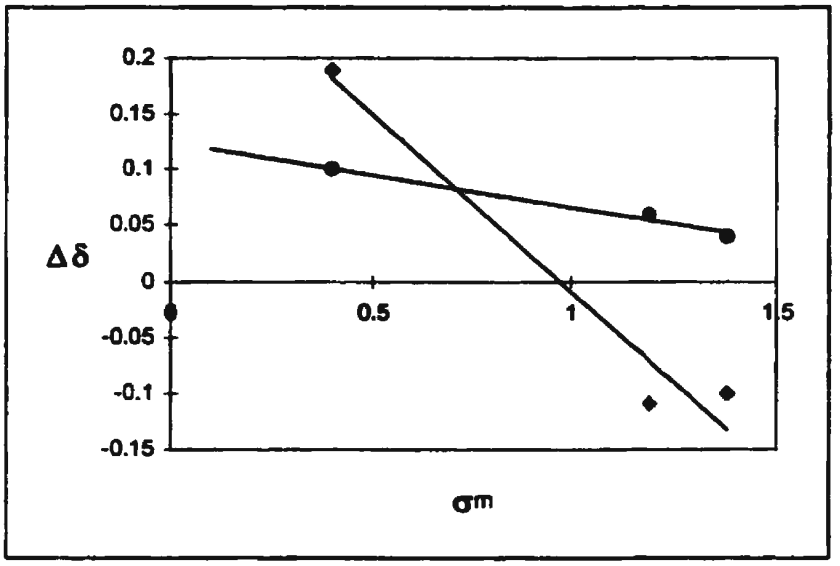
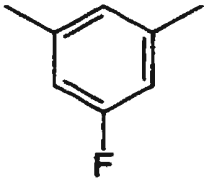


Figure 4.5: Δδ against bond dipole moments for H_i (◆) and H_e (●) in dithia[3.3]metacyclophanes **192**, **198**, and **199**.

Few conclusions could be drawn by a stand-alone examination of the Δδ values for the dithia[3.3]metacyclophanes **192**, **198** and **199**, particularly any comment on the linearity or non-linearity of the plots. This was due largely to the similarity of Δδ and the σ_m values for bromine and iodine, which are essentially constant, along with the very few data points currently available. However, it is anticipated that, when combined with the results from the remainder of 6,15-disubstituted 2,11-dithia[3.3]metacyclophanes synthesized as part of this study, a much more detailed picture describing the solution state behavior of this system will emerge.

4.4 Experimental

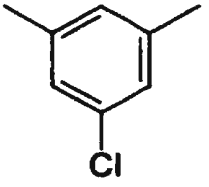
5-Fluoro-*m*-xylene (201)



A solution of water (40 mL) and concentrated HCl (60 mL) was added slowly over 30 min to a mechanically stirred solution of 3,5-dimethylaniline (**205**) (61.9 g, 0.51 mol) in a 1 L three necked flask. The mixture was cooled to about -10 °C (ice/salt water bath) and, with vigorous stirring throughout, a solution of $NaNO_2$ (38.0g, 0.55 mol) in water (80 mL) was added dropwise over 40 min, then HBF_4 (48-50 %, 90 mL) was added dropwise over 40 mins. Following the addition, the reaction was allowed to warm to r.t. and stirred for a further 30 min, before the precipitate was collected by suction filtration and washed with water, MeOH, and Et_2O. After air drying overnight, the tetrafluoroborate complex was decomposed by placing it in a 1 L three-necked flask equipped with three air condensers and gently warming with a heat gun. The resulting black oil was diluted with pentanes, slurried with silica, and poured onto a silica gel column eluted with pentanes. The fractions containing the least polar spot (R_f = 0.65) were combined, the pentanes were removed by distillation, then the product was distilled, yielding pure **201** as a colourless liquid (16.5 g, 0.13 mol, 26%). b.p.: 145 °C (760 mm Hg). IR (neat): ν_{max} 1623 (s), 1588 (s), 1470 (m), 1306 (s), 1129 (s), 841 (s) cm^{-1}. ^1H

NMR ($CDCl_3$): δ = 6.74 (1H, s, C2-H), 6.65 (2H, d, J = 9.7 Hz, C4-H + C6-H), 2.28 (6H, d, J = 0.5 Hz, -CH_3). ^{13}C NMR ($CDCl_3$): δ = 163.1 (d, J_{CF} = 244 Hz, C5), 140.1 (d, J_{CF} = 7.7 Hz, C1 + C3), 125.7 (d, J_{CF} = 1.4 Hz, C2), 113.1 (d, J_{CF} = 20.7 Hz, C4 + C6), 21.4 (-CH_3). MS *m/z* (%): 125 (5), 124 (M^+, 58), 123 (29), 109 (100), 97 (3), 95 (3). Anal. calcd for C_8H_9F: C 77.39, H 7.31; found C 77.45, H 7.37.

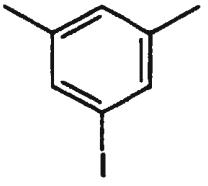
5-Chloro-*m*-xylene (202)



To distilled 3,5-dimethylaniline (**205**) (30.0 g, 0.25 mol) in a 1 L three necked flask equipped with a mechanical stirrer was slowly added concentrated HCl (90 mL). The mixture was cooled to below 0 °C (ice/salt water bath) and a solution of $NaNO_2$ (18.2 g, 0.26 mol) in water (65 mL) was added. A few pieces of crushed ice were periodically added directly into the reaction mixture. A pre-cooled solution of freshly prepared CuCl[102] (30.5 g, 0.31 mol) in concentrated HCl (100 mL) was then added slowly. The reaction was gradually warmed to r.t. and, once the evolution of N_2 had ceased (monitored with a bubbler), was diluted with pentanes (100 mL) and the layers separated. After re-extracting the aqueous layer with a small portion of fresh pentanes, the combined organic solutions were slurried with silica and poured onto a column eluted with pentanes. The fractions containing the least polar material (R_f = 0.53) were combined

and the pentanes removed by distillation. Purification by distillation under reduced pressure afforded pure **202** as a colourless liquid (9.60g, 0.068 mol, 28%). b.p.: 74-77 °C (18 mm Hg). IR (neat): ν_{max} 1607 (s), 1582 (s), 1462 (m), 1267 (m), 1258 (m), 1111 (m), 842 (s), 678 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 6.94 (2H, s, C4-H + C6-H), 6.83 (1H, s, C2-H), 2.25 (6H, s, $-CH_3$). ^{13}C NMR ($CDCl_3$): δ = 139.7 (C1 + C3), 133.9 (C5), 128.3 (C2), 126.3 (C4 + C6), 21.2 ($-CH_3$). MS *m/z* (%): 142 (6), 140 (M^+, 19), 105 (34), 77 (43), 63 (67), 62 (34), 51 (87), 50 (54), 39 (100). Anal. calcd for C_8H_9Cl: C 68.34, H 6.45; found C 68.12, H 6.34.

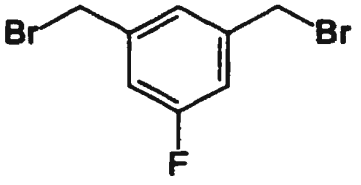
5-Iodo-*m*-xylene (204)



To distilled 3,5-dimethylaniline (**205**) (29.6 g, 0.24 mol) in a 1 L three necked flask equipped with a mechanical stirrer was slowly added concentrated HCl (90 mL). The mixture was cooled to below 0 °C (ice/salt water bath) and a solution of $NaNO_2$ (17.6 g, 0.26 mol) in water (65 mL) was added. A few pieces of crushed ice were periodically added directly into the reaction mixture. A pre-cooled solution of KI (52.4 g, 0.32 mol) in water (65 mL) was then added. The reaction was slowly warmed to r.t. and, once the evolution of N_2 had ceased (monitored with a bubbler), pentanes (100 mL) were added. A portion of $NaHSO_3$ was added and the aqueous layer removed. After re-extracting the

aqueous layer with a small portion of fresh pentanes, the combined organic solutions were slurried with silica and poured onto a column eluted with pentanes. The fractions containing the least polar material ($R_f = 0.50$) were combined and the pentanes removed by distillation. Purification by distillation under reduced pressure afforded pure **204** as a colourless liquid (33.3 g, 0.14 mol, 59%). b.p.: 108-114 °C (19 mm Hg). IR (neat): ν_{max} 1602 (s), 1563 (s), 1461 (m), 1252 (m), 838 (s), 788 (s), 677 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.31 (2H, s, C4-H + C6-H), 6.90 (1H, s, C2-H), 2.22 (6H, s, $-CH_3$). ^{13}C NMR ($CDCl_3$): δ = 140.0 (C1 + C3), 135.2 (C4 + C6), 129.5 (C2), 94.5 (C5), 21.1 ($-CH_3$). MS *m/z* (%): 233 (8), 232 (M^+, 100), 127 (5), 105 (67), 79 (36), 77 (30). Anal. calcd for C_8H_9I: C 41.41, H 3.91; found C 41.65, H 3.81.

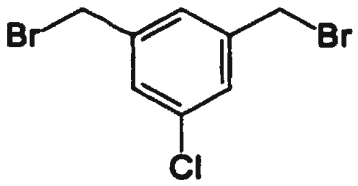
3,5-Bis(bromomethyl)fluorobenzene (207)



A solution of 5-fluoro-*m*-xylene (**201**) (4.97 g, 40.0 mmol), NBS (16.5 g, 92.6 mmol) and benzoyl peroxide (0.84 g, 3.5 mmol) in CCl_4 (100 mL) in a 250 mL round bottomed flask was heated at reflux, under irradiation by a 100 W sun lamp, for 12 h. After being allowed to cool to r.t., the mixture was filtered and the filtrate concentrated under reduced pressure. The resulting orange oil was purified by flash chromatography (pentanes, R_f = 0.15) giving, after further purification by recrystallizing from

ethanol/water, pure **207** as a white powder (504 mg, 1.79 mmol, 4%). m.p.: 45.5-47.0 °C (ethanol/water). IR (film): ν_{max} 1594 (m), 1310 (s), 1213 (s), 989 (m), 871 (m), 693 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.20 (1H, s, C4-H), 7.29 (2H, d, J = 9.0 Hz, C2-H + C6-H), 4.43 (4H, s, $-CH_2Br$). ^{13}C NMR ($CDCl_3$): δ = 162.8 (d, J = 248 Hz, C1), 140.7 (d, J = 8.0 Hz, C3 + C5), 125.4 (d, J = 2.9 Hz, C4), 116.3 (d, J = 22.2 Hz, C2 + C6), 31.9 ($-CH_2Br$). MS *m/z* (%): 284 (M + 4, 5), 282 (M + 2, 11), 280 (M^+, 7), 203 (95), 201 (100), 122 (95), 121 (20), 101 (18), 96 (17), 75 (12).

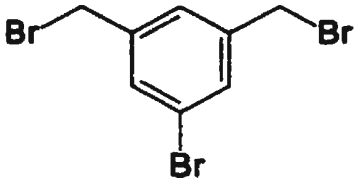
3,5-Bis(bromomethyl)chlorobenzene (208)



To a solution of 5-chloro-*m*-xylene (**202**) (5.63 g, 40.0 mmol) in CCl_4 (100 mL) at reflux in a 250 mL round bottomed flask was added NBS (16.8 g, 94.3 mmol) and benzoyl peroxide (1.07 g, 4.43 mmol) in three approximately equivalent portions at 60 min intervals. Following the final addition, the reaction was refluxed for another 1 h. After being allowed to cool to r.t., the mixture was filtered and the filtrate concentrated under reduced pressure. The resulting oil was placed in the freezer to induce crystallization. The resulting solid was rinsed with ethanol, cooled on ice and filtered, yielding a yellow powder. Recrystallization from ethanol/water gave pure **208** as thin, white needles (1.99 g, 6.66 mmol, 17%). m.p.: 87.5-89.0 °C (ethanol/water). IR (film):

ν_{max} 1581 (m), 1268 (m), 1211 (s), 974 (m), 873 (m), 691 (s), 608 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.32 (2H, s, C2-H + C6-H), 7.29 (1H, s, C4-H), 4.41 (4H, s, $-CH_2Br$). ^{13}C NMR ($CDCl_3$): δ = 140.3 (C3 + C5), 135.0 (C1), 129.3 (C2 + C6), 128.0 (C4), 31.8 ($-CH_2Br$). MS *m/z* (%): 302 (M + 6, 1), 300 (M + 4, 7), 298 (M + 2, 10), 296 (M^+, 4), 221 (24), 219 (100), 217 (75), 140 (17), 138 (53), 103 (26), 77 (18). Anal. calcd for $C_8H_7Br_2Cl$: C 32.20, H 2.36; found C 32.11, H 2.11.

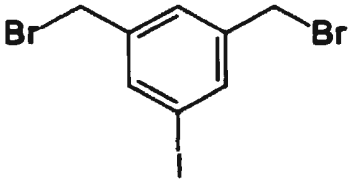
3,5-Bis(bromomethyl)bromobenzene (209)



A solution of commercially available 5-bromo-*m*-xylene (**203**) (2.7 mL, 19.9 mmol), NBS (8.46 g, 47.5 mmol) and benzoyl peroxide (204 mg, 0.84 mmol) in CCl_4 (80 mL) was heated at reflux for 12 h. After cooling, the insoluble material was removed by filtration and the filtrate was concentrated under reduced pressure, yielding an orange solid. Washing with ethanol and recrystallization from ethanol gave dibromide **209** as light yellow needles (1.32 g, 3.84 mmol, 19%). m.p.: 97-99 °C (ethanol). IR (film): ν_{max} 1572 (m), 1446 (s), 1262 (m), 1212 (s) 879 (m), 691 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.47 (2H, s, C2-H+ C6-H), 7.33 (1H, s, C4-H), 4.40 (4H, s, $-CH_2Br$). ^{13}C NMR ($CDCl_3$): δ = 140.4 (C3 + C5), 132.1 (C2 + C6), 128.4 (C4), 122.9 (C1), 31.7 ($-CH_2Br$). MS *m/z* (%): 346 (M + 6, 3), 344 (M + 4, 9), 342 (M + 2, 9), 340 (M^+, 3), 265 (47), 263 (100),

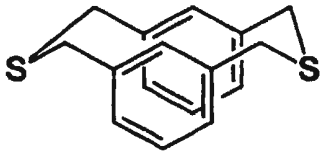
261 (51), 184 (31), 182 (32), 131 (2), 103 (31), 77 (33). Anal. calcd for $C_8H_7Br_3$: C 28.02, H 2.06; found C 28.10, H 1.78.

3,5-Bis(bromomethyl)iodobenzene (210)



To a solution of 5-iodo-*m*-xylene (**204**) (9.30 g, 40.1 mmol) in CCl_4 (100 mL) at reflux in a 250 mL round bottomed flask was added NBS (16.33 g, 91.7 mmol) and benzoyl peroxide (1.02 g, 4.19 mmol) in three approximately equivalent portions at 60 min intervals. Following the final addition, the reaction was refluxed for another 1 h. After cooling to r.t. the mixture was filtered and the filtrate concentrated under reduced pressure. The resulting solid was rinsed with ethanol, cooled on ice and filtered, yielding a light brown powder. Recrystallization from ethanol/water gave pure **210** as thin, white needles (3.40 g, 8.72 mmol, 22%). m.p.: 107-109 °C (ethanol/water). IR (film): ν_{max} 1566 (m), 1446 (s), 1435 (m), 1258 (m), 1210 (s), 971 (m), 879 (m), 691 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.66 (2H, s, C2-H + C6-H), 7.37 (1H, s, C4-H), 4.38 (4H, s, -CH_2Br). ^{13}C NMR ($CDCl_3$): δ = 140.4 (C3 + C5), 138.0 (C2 + C6), 129.2 (C4), 94.5 (C1), 31.5 (-CH_2Br). MS *m/z* (%): 392 (M + 4, 9), 390 (M + 2, 20), 388 (M^+, 10), 311 (100), 309 (100), 265 (3), 263 (6), 261 (3), 230 (53), 184 (5), 182 (5), 115 (20), 103 (44), 77 (48). Anal. calcd for $C_8H_7Br_2I$: C 24.65, H 1.81; found C 24.83, H 1.53.

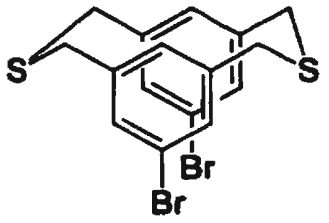
2,11-dithia[3.3]metacyclophane (192)



To a stirred solution of dibromide **191** (659 mg, 2.50 mmol) in CH_2Cl_2 (160 mL) and absolute ethanol (16 mL) under N_2 was added the Na_2S/Al_2O_3 reagent (2.57 mmol/g) (2.00 g, 5.14 mmol) in four approximately equal portions at 15 min intervals. Following the final addition, the reaction stirred at r.t. for a further 3 h. The mixture was filtered through Celite and the solvent removed under reduced pressure. Purification by flash chromatography (33% CH_2Cl_2/hexanes, $R_f = 0.24$) gave **192** as a white solid (40 mg, 0.15 mmol, 12%). m.p.: 113-115 °C (ethanol, lit. 155.5-156.5 °C[109]). ^1H NMR ($CDCl_3$): δ = 7.00-6.91 (6H, m, C5-H + C6-H + C7-H + C14-H + C15-H + C16-H), 6.82 (2H, s, C9-H, C18-H), 3.75 (8H, s, C1-H + C3-H + C10-H + C12-H). ^{13}C NMR ($CDCl_3$): δ = 137.2, 132.0, 128.7, 127.2, 38.0. MS *m/z* (%): 272 (M^+, 85), 167 (18), 137 (55), 136 (42), 135 (36), 105 (100), 91 (48), 78 (27), 77 (22).

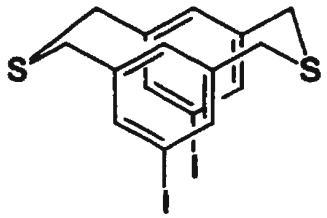
[109] Sato, T.; Wakabayashi, M.; Kainosho, M.; Hata, K. *Tetrahedron Lett.* **1968**, 4185-4189.

6,15-Dibromo-2,11-dithia[3.3]metacyclophane (198)



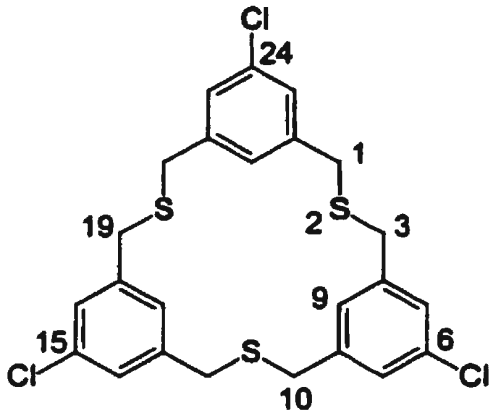
To a stirred solution of dibromide **209** (860 mg, 2.51 mmol) in CH_2Cl_2 (160 mL) and absolute ethanol (16 mL) under N_2 was added the Na_2S/Al_2O_3 reagent (2.51 mmol/g) (2.09 g, 5.25 mmol) in four approximately equal portions at 15 min intervals. Following the final addition, the reaction stirred at r.t. for a further 1.5 h. The mixture was filtered through Celite and the solvent removed under reduced pressure. Purification by flash chromatography (33% CH_2Cl_2/hexanes, R_f = 0.35) gave **198** as a white solid (197 mg, 0.46 mmol, 37%). m.p.: 186-188 °C (ethanol/water). ^1H NMR ($CDCl_3$): δ = 7.05 (4H, d, J = 1.4 Hz, C5-H + C7-H + C14-H + C16-H), 6.95 (2H, s (br), C9-H, C18-H), 3.73 (8H, s, C1-H + C3-H + C10-H + C12-H). ^{13}C NMR ($CDCl_3$): δ = 139.2 (C4 + C8 + C13 + C17), 130.4 (C5 + C7 + C14 + C16), 130.2 (C9 + C18), 122.6 (C6 + C15), 37.8 (C1 + C3 + C10 + C12). MS *m/z* (%): 432 (M + 4, 43), 430 (M + 2, 77), 428 (M^+, 37), 351 (13), 349 (12), 247 (22), 245 (20), 217 (52), 216 (56), 215 (70), 214 (52), 213 (20), 186 (81), 184 (100), 134 (64), 103 (69), 77 (74). Anal. calcd for $C_{16}H_{14}Br_2S_2$: C 44.67, H 3.28; found C 44.20, H 3.07.

6,15-Diiodo-2,11-dithia[3.3]metacyclophane (199)



To a stirred solution of dibromide **210** (781 mg, 2.00 mmol) in CH_2Cl_2 (130 mL) and absolute ethanol (13 mL) under N_2 was added the Na_2S/Al_2O_3 reagent (2.57 mmol/g) (2.16 g, 5.55 mmol) in four approximately equal portions at 15 min intervals. Following the final addition, the reaction stirred at r.t. for a further 1 h. The mixture was filtered through Celite and the solvent removed under reduced pressure. Purification by flash chromatography (33% CH_2Cl_2/hexanes, R_f = 0.34) gave **199** as a white solid (211 mg, 0.403 mmol, 40%). m.p.: 183-185 °C (ethanol). IR (film): ν_{max} 1712 (m), 1593 (s), 1563 (s), 1248 (m), 1231 (m), 1212 (m), 868 (s), 800 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.25 (4H, d, J = 1.5 Hz, C5-H + C7-H + C14-H + C16-H), 7.01 (2H, s (br), C9-H, C18-H), 3.71 (8H, s, C1-H + C3-H + C10-H + C12-H). ^{13}C NMR ($CDCl_3$): δ = 139.2 (C4 + C8 + C13 + C17), 136.3 (C5 + C7 + C14 + C16), 130.9 (C9 + C18), 94.4 (C6 + C15), 37.7 (C1 + C3 + C10 + C12). MS *m/z* (%): 525 (19), 524 (M^+, 100), 397 (45), 293 (14), 263 (33), 262 (38), 232 (58), 231 (68), 230 (21), 135 (47), 134 (43), 103 (40), 91 (40), 77 (66). Anal. calcd for $C_{16}H_{14}I_2S_2$: C 36.66, H 2.69; found C 36.99, H 2.51.

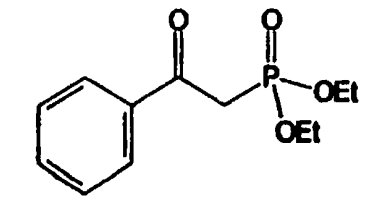
6,15,24-Trichloro-2,11,20-trithia[3.3.3]metacyclophane (211)



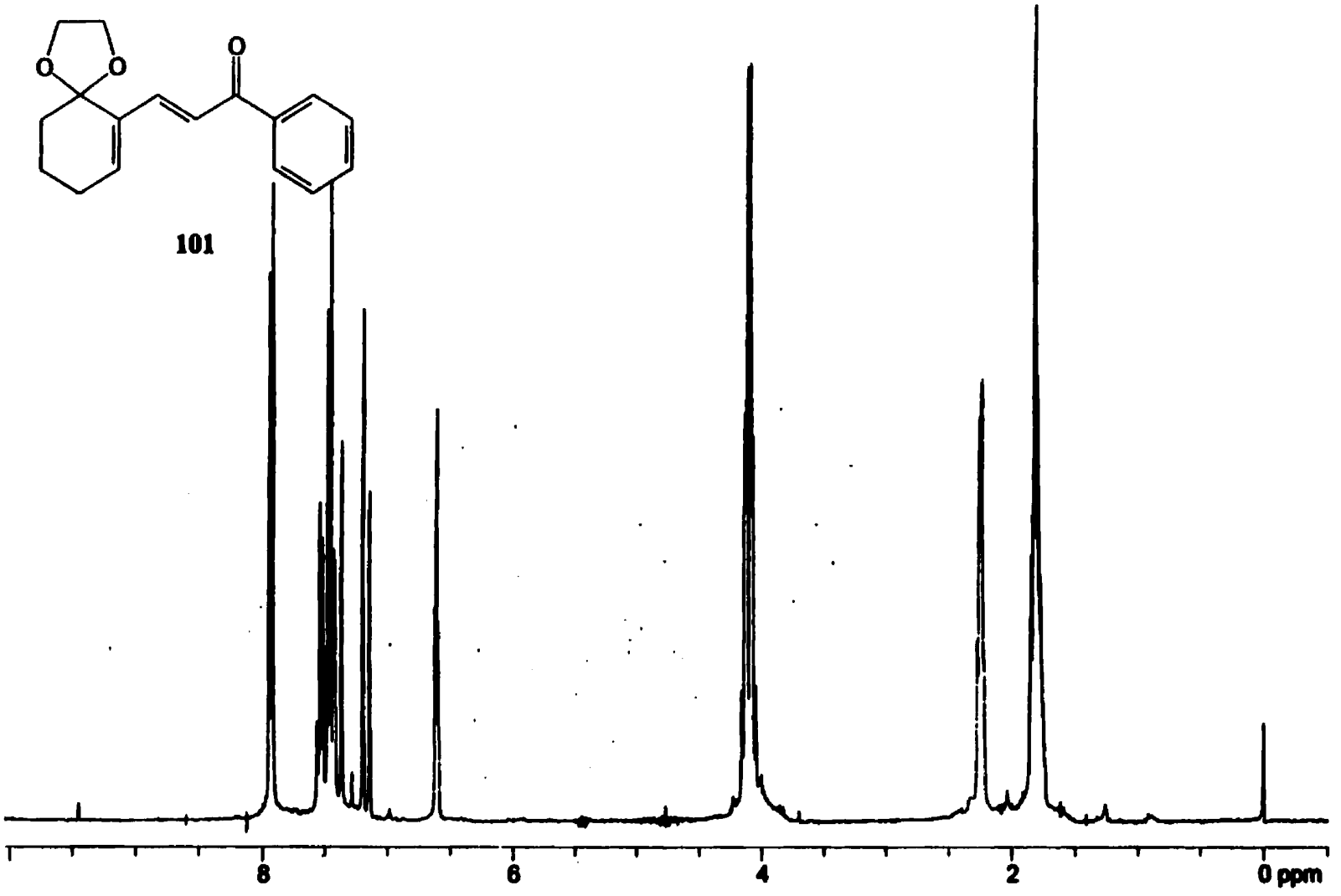
To a stirred solution of dibromide **208** (756 mg, 2.53 mmol) in CH_2Cl_2 (160 mL) and absolute ethanol (16 mL) under N_2 was added the Na_2S/Al_2O_3 reagent (2.57 mmol/g) (2.00 g, 5.15 mmol) in four approximately equal portions at 15 min intervals. Following the final addition, the reaction stirred at r.t. for a further 2 h. The mixture was filtered through Celite and the solvent removed under reduced pressure. Purification by flash chromatography (33% CH_2Cl_2/hexanes, R_f = 0.40) gave **211** as a white solid (168 mg, 0.33 mmol, 39%). m.p.: 206-210°C (ethanol). IR (film): ν_{max} 3603-3247 (m), 1712 (m), 1579 (w), 722 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.32 (6H, d, J = 1.4 Hz), 6.92 (3H, s (br)), 3.51 (12 H, s). ^{13}C NMR ($CDCl_3$): δ = 140.1, 135.4, 128.23, 128.17, 34.7. MS *m/z* (%): 516 (M + 6, 1), 514 (M + 4, 5), 512 (M + 2, 11), 510 M^+, 10), 373 (8), 371 (10), 341 (20), 339 (27), 309 (3), 307 (5), 275 (63), 273 (66), 239 (4), 201 (5), 171 (43), 169 (56), 139 (78), 134 (40), 125 (24), 103 (100), 91 (21), 89 (18), 77 (42).

Appendix

^{1}H NMR spectra for selected compounds appearing in the body of this text.



100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O
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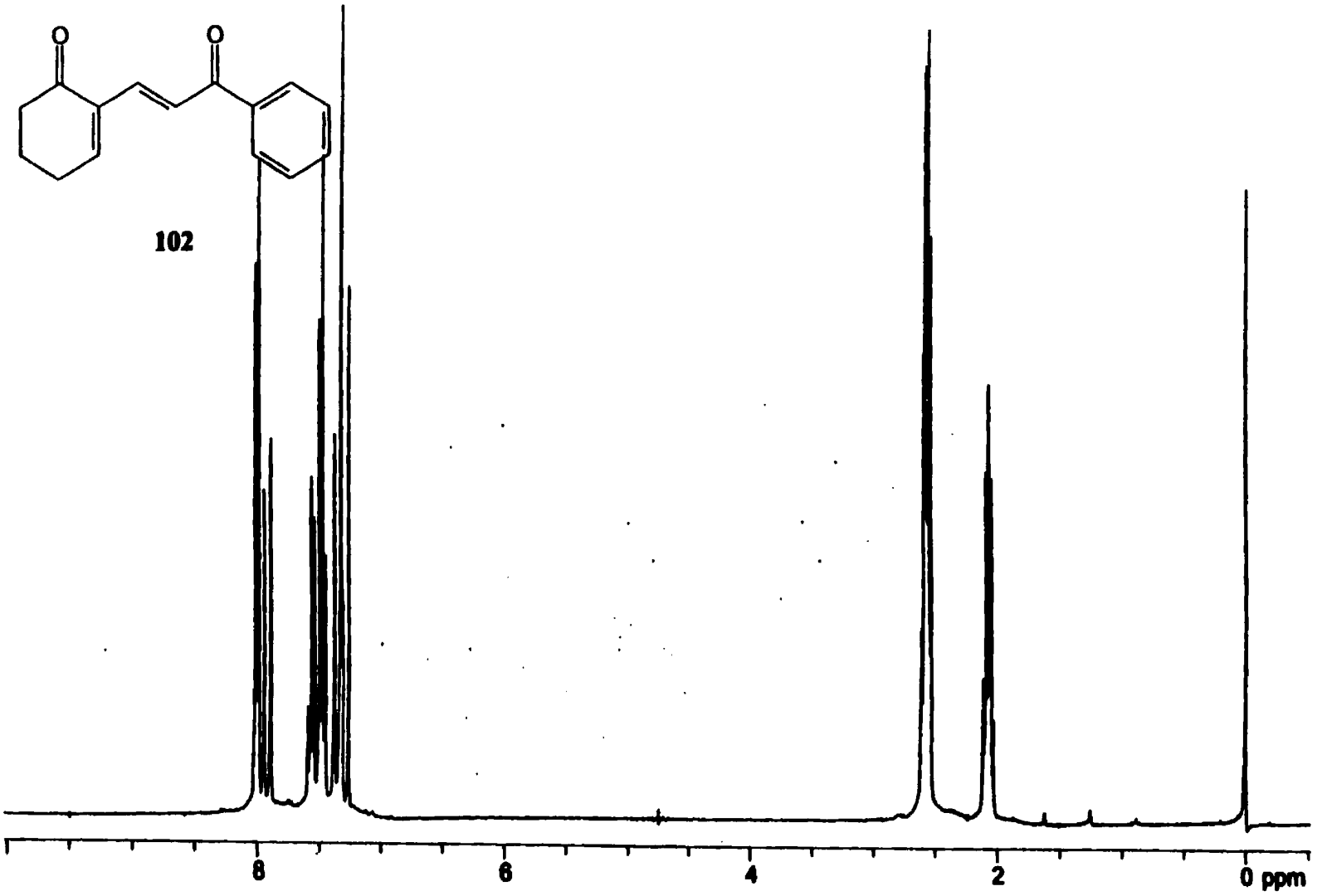
8
6
4
2
0 ppm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O
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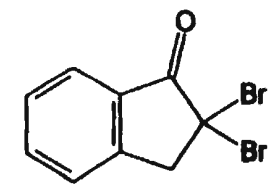
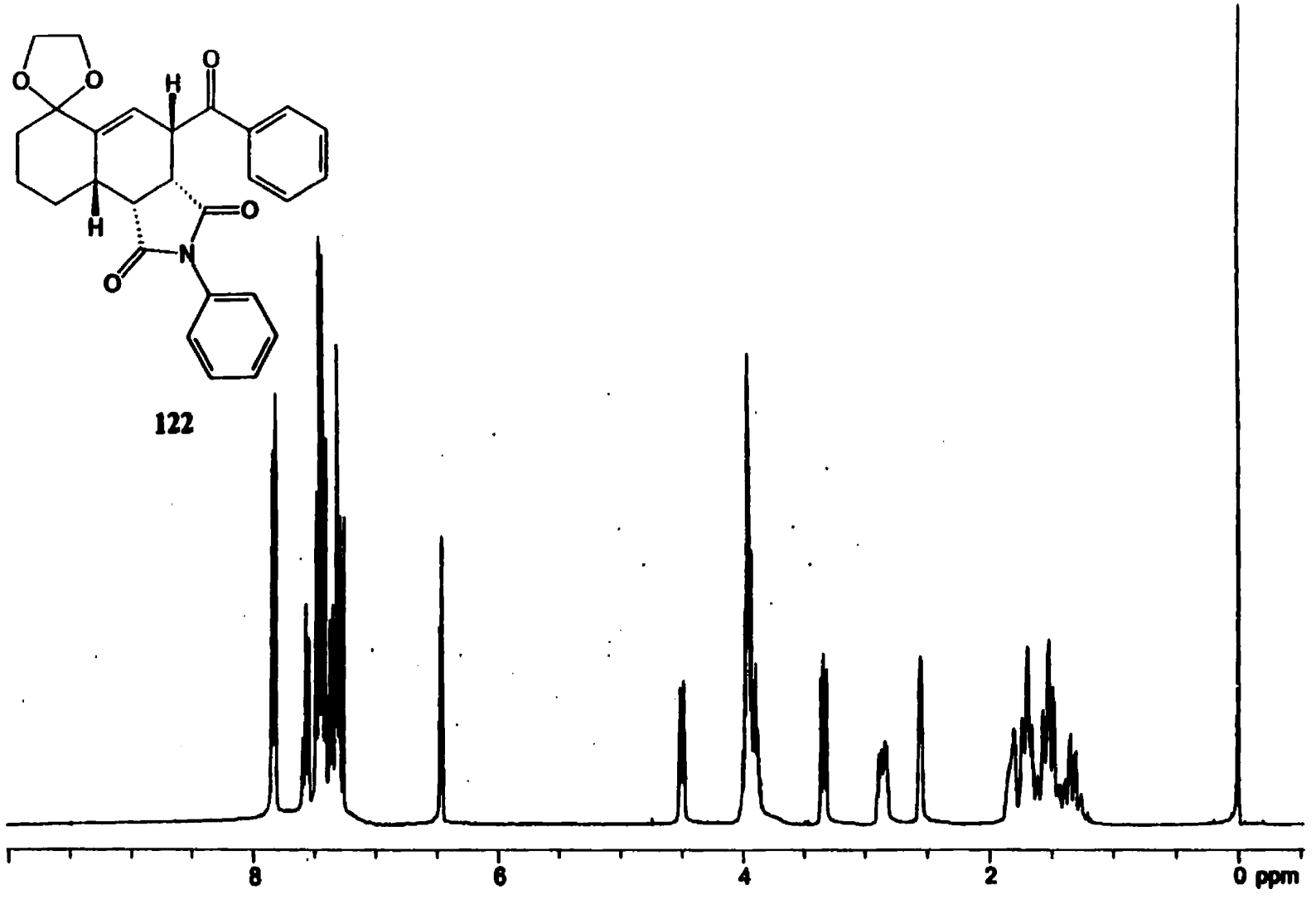
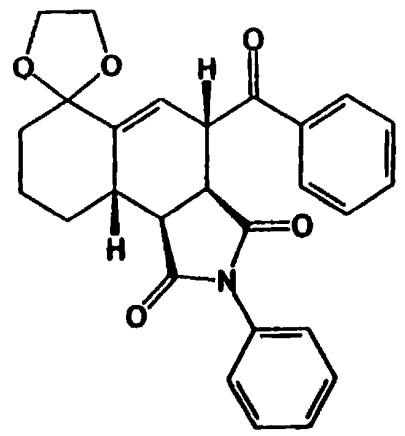
8
6
4
2
0 ppm



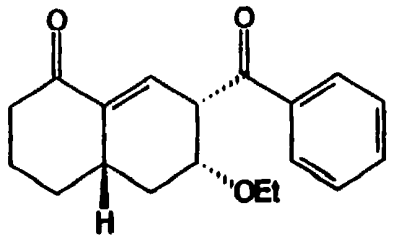
115



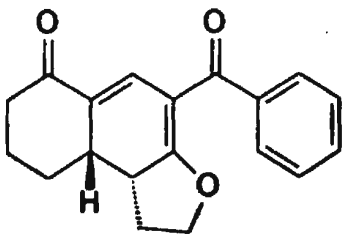
122



123



124



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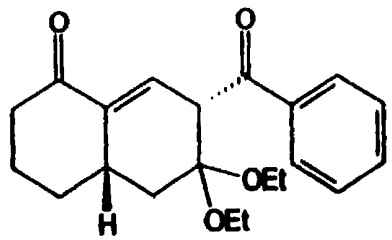

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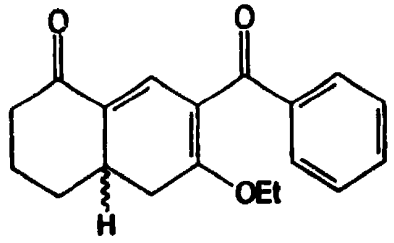

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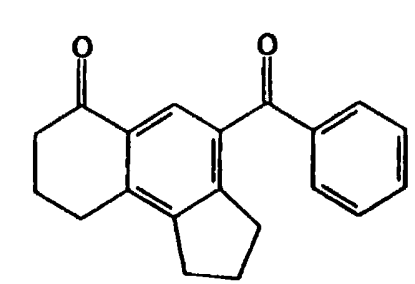

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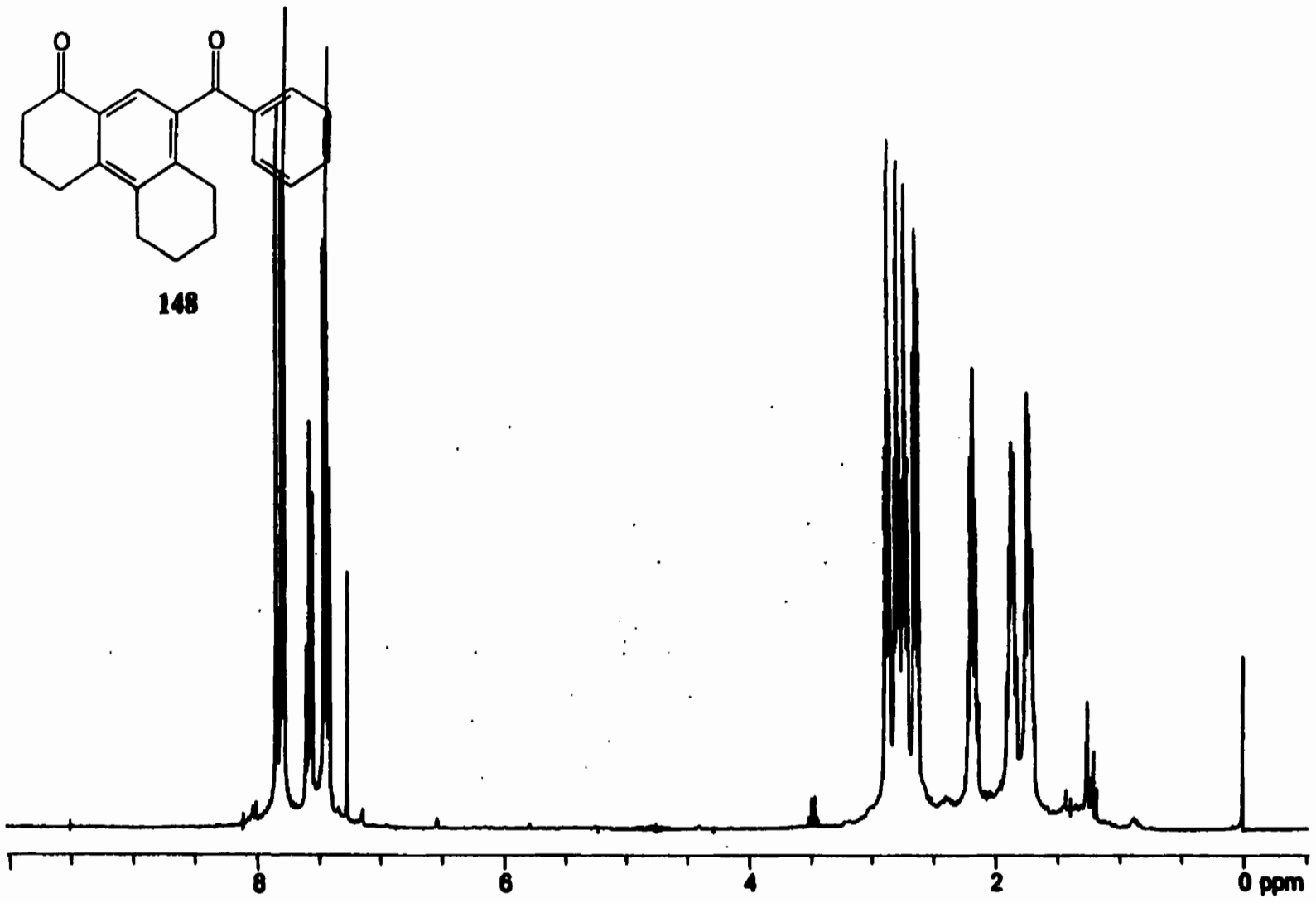
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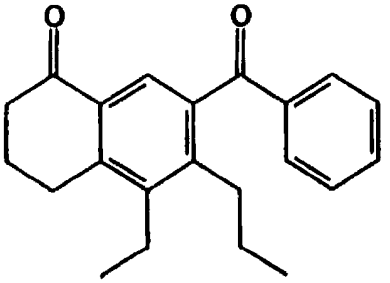

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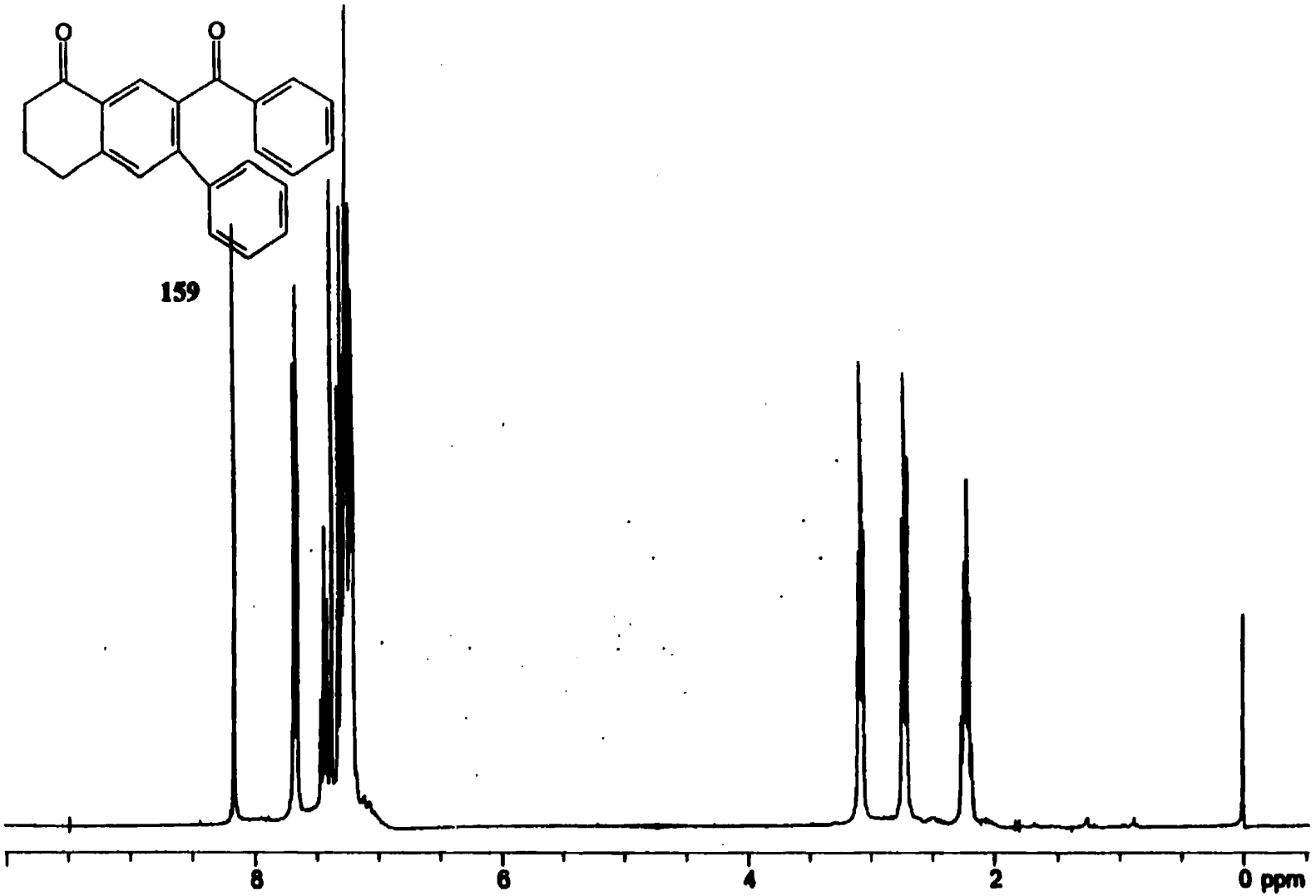
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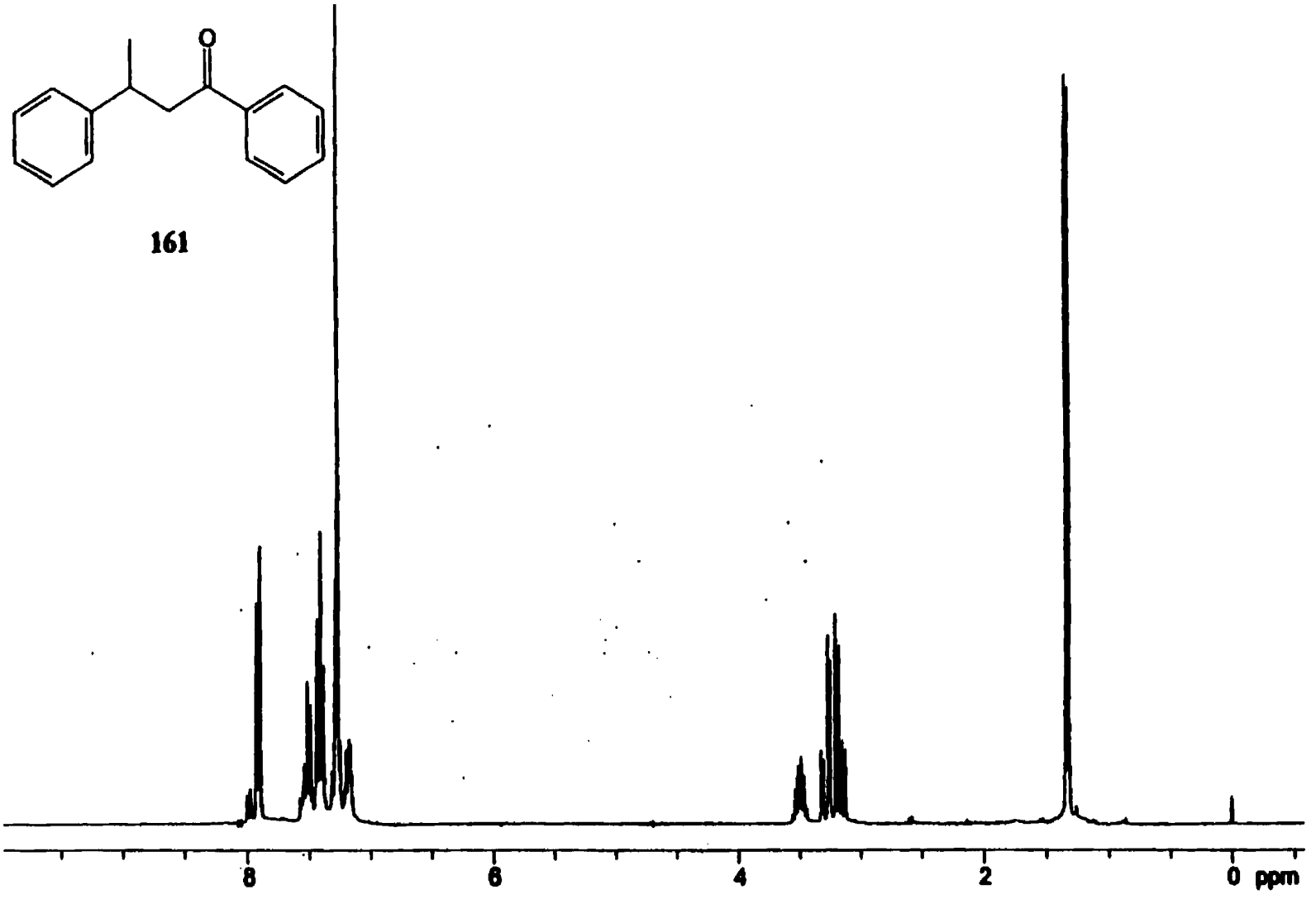

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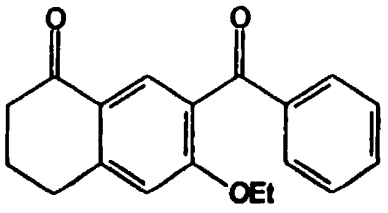

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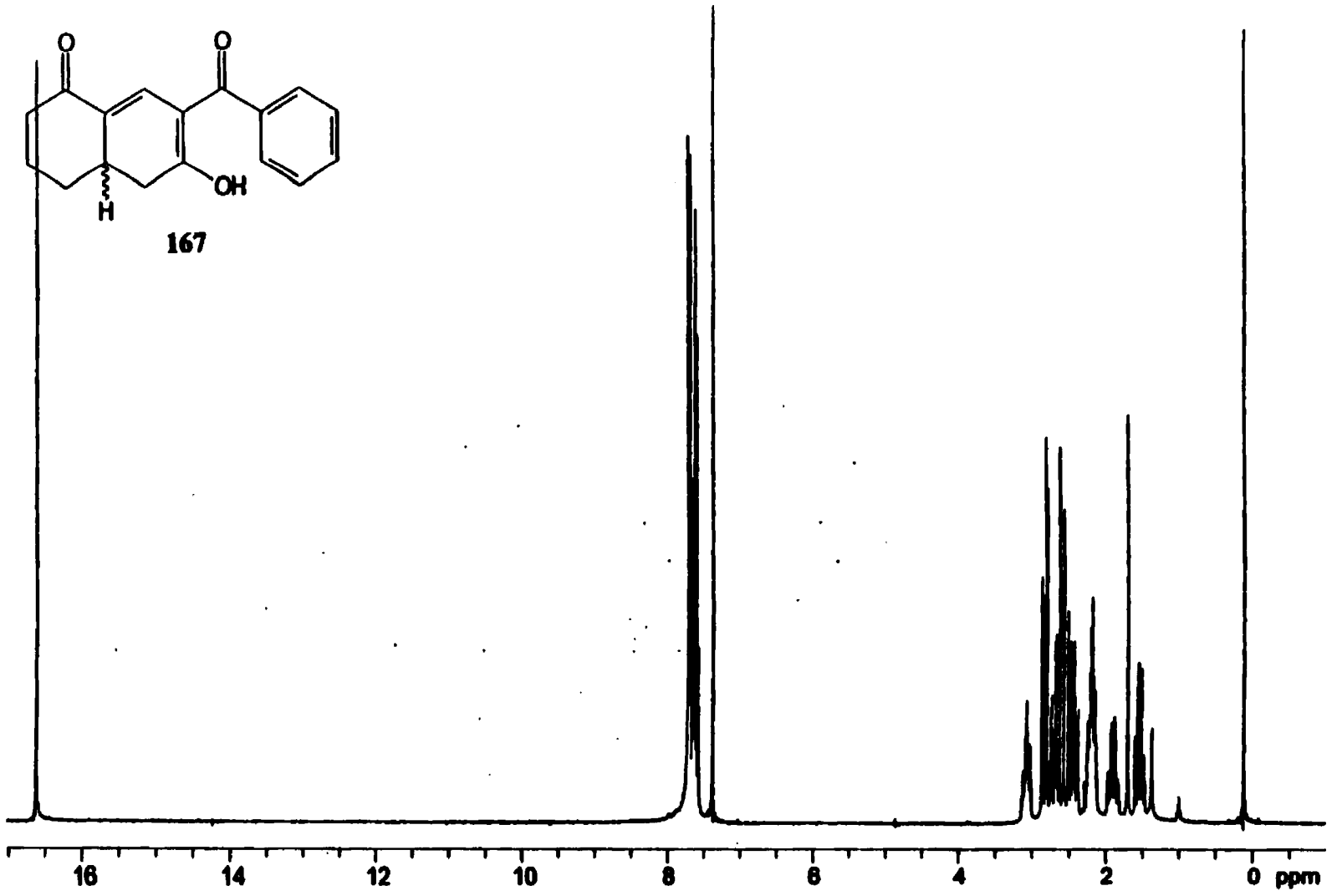

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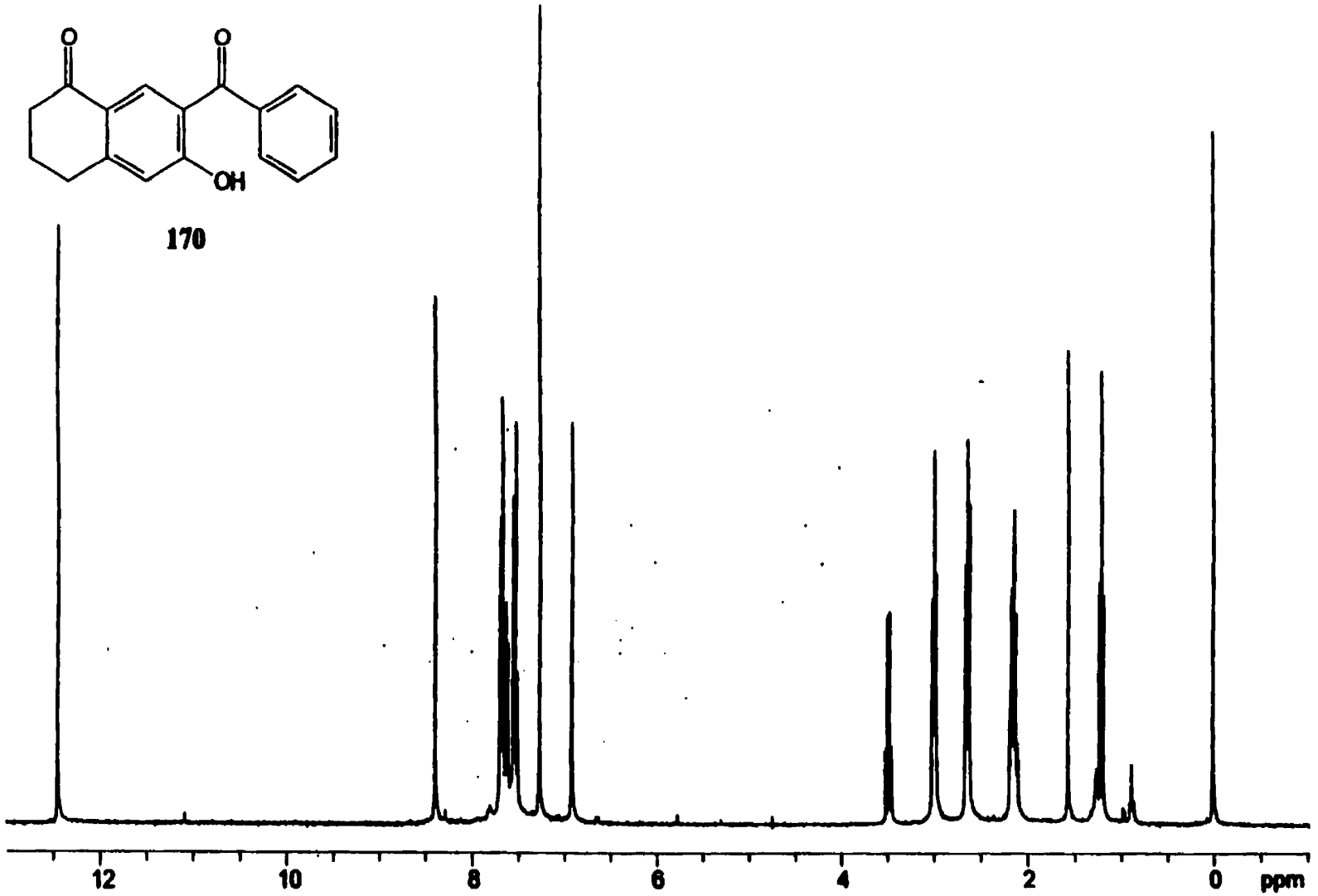

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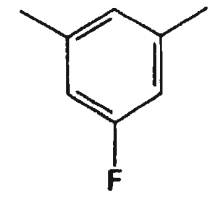

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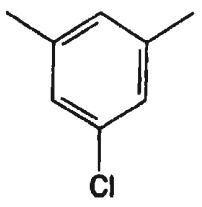

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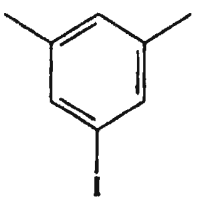

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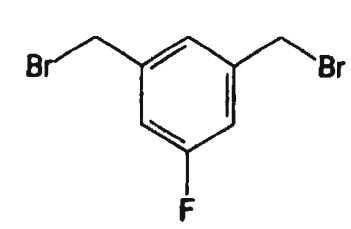

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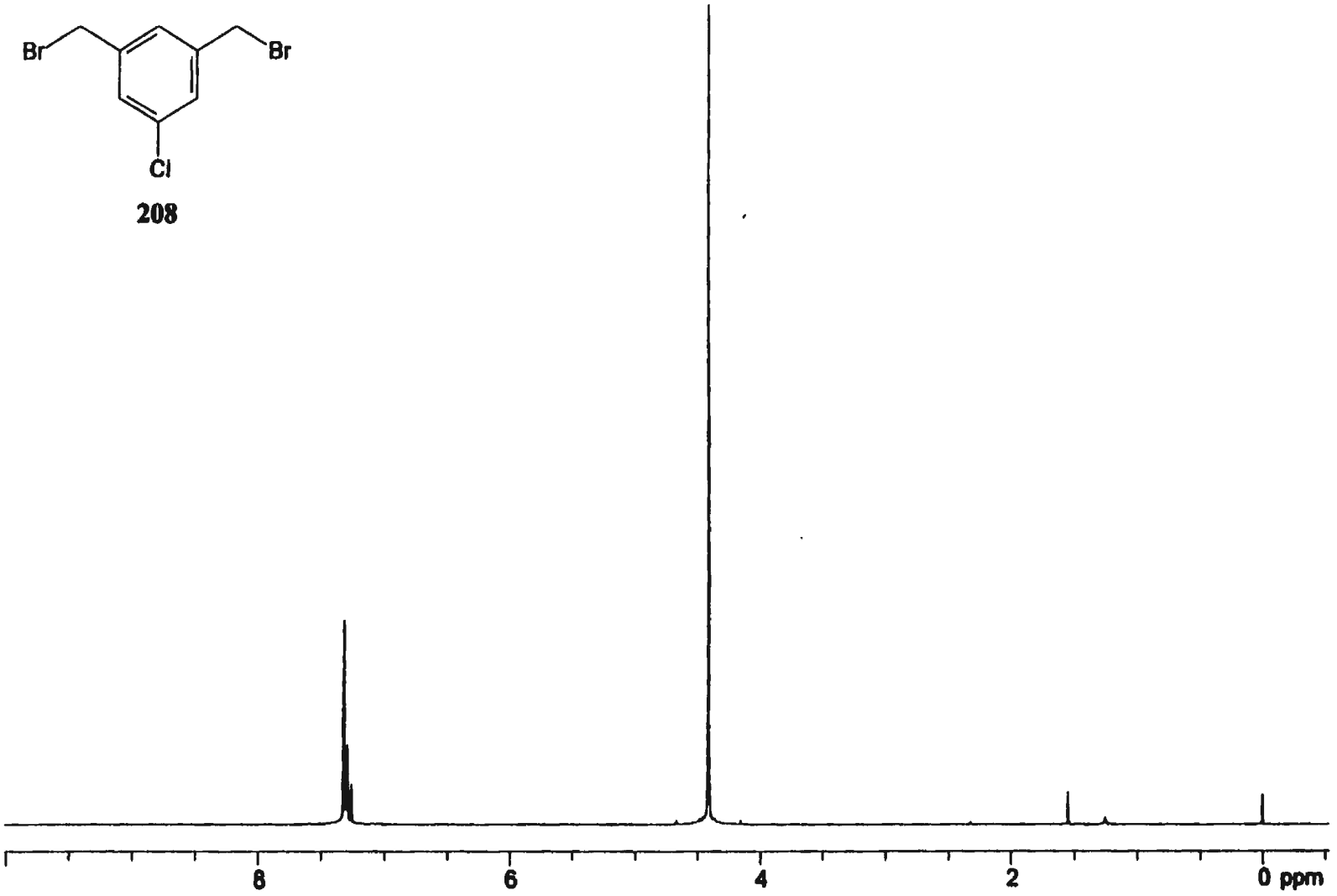

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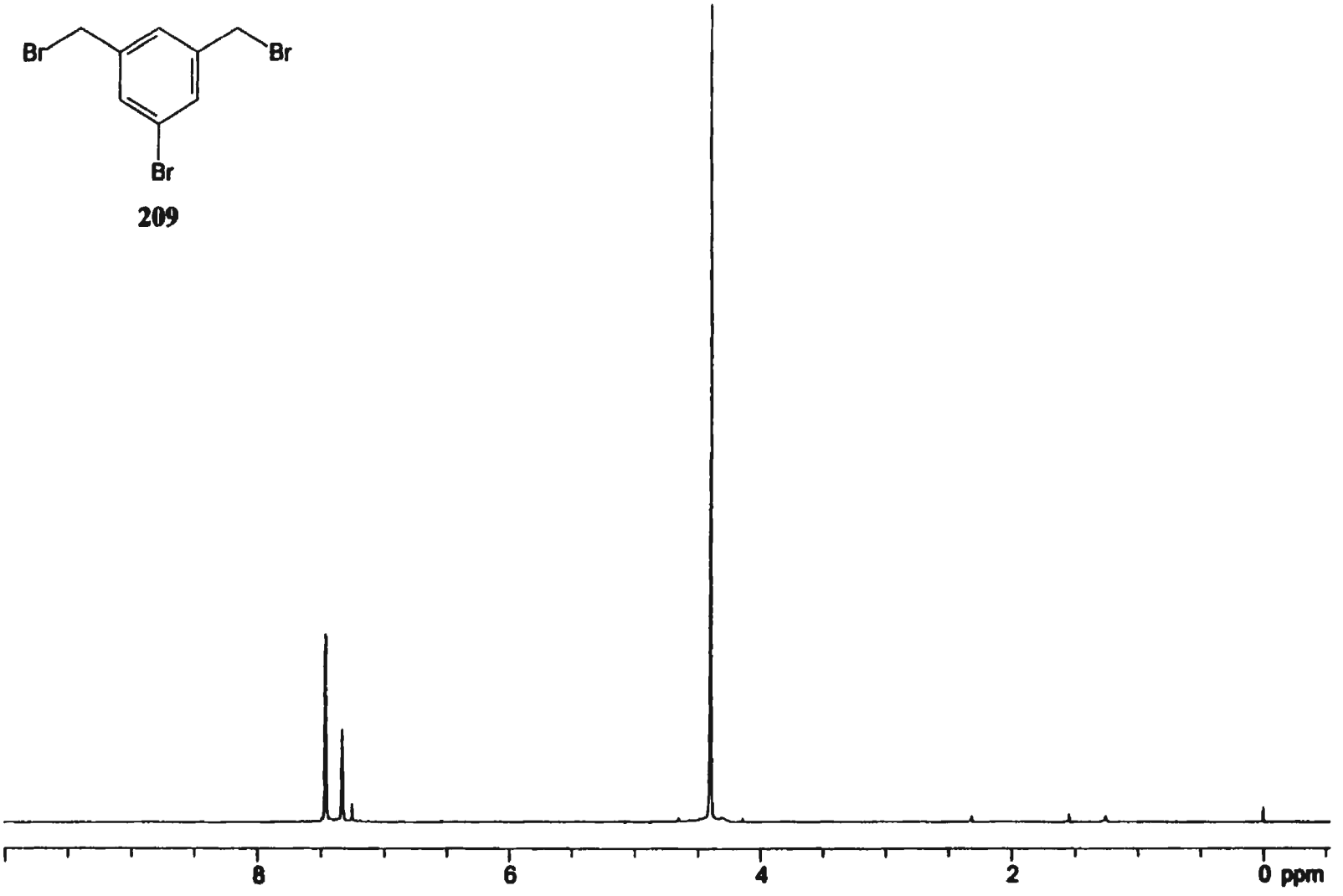

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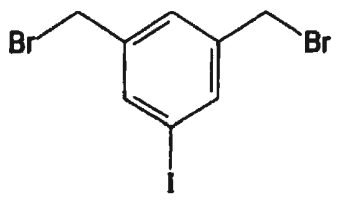

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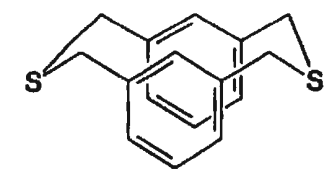

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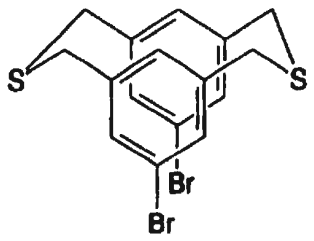

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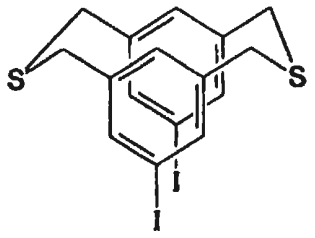

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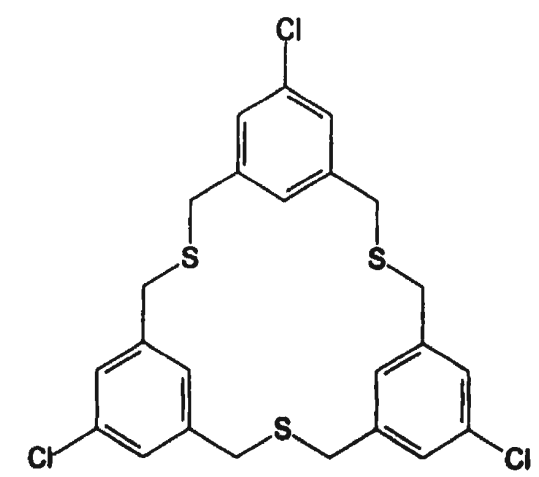

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