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"Religion blushing veils her sacred fires,
And unawares Morality expires.
Nor public flame nor private dares to shine;
Nor human spark is left, nor glimpse divine!
Lo! Thy dread empire Chaos is restor'd,
Light dies before thy uncreating word;
Thy hand, great Anarch, lets the curtain fall,
And universal darkness buries all."

—Alexander Pope (1688 - 1744)

For my grandfather, William A. Squires.

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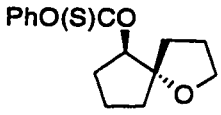
List of Abbreviations

Ac	acetyl
Anal. Calcd	elemental analysis calculated
AIBN	azobisisobutyronitrile
br	broad
t-BuLi	tertiary butyllithium
m-CPBA	*m*-chloroperoxybenzoic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DIBAL	diisobutylaluminum hydride
DMAD	dimethylacetylenedicarboxylate
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMS	dimethyl sulfide
Et	ethyl
eq.	equivalents
FVP	flash vacuum pyrolysis
g	grams
HMPA	hexamethylphosporamide
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	Hertz
IR	infrared spectroscopy
J	coupling constant
m	multiplet

MDEPA	methyl diethylphosphonoacetate
Me	methyl
mg	milligrams
MHz	megahertz
mmol	millimole
mol	mol
mp	melting point
MS	mass spectroscopy
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
NMTAD	*N*-methyl-1,2,4-triazoline-3,5-dione
NPTAD	*N*-phenyl-1,2,4-triazoline-3,5-dione
q	quartet
rt	room temperature
s	singlet
SET	single electron transfer
t	triplet
TBAF	tetra-*N*-butylammonium fluoride
TBS	*t*-butyldimethylsilyl
TCNE	tetracyanoethane
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N*, *N*, *N*', *N*'-tetramethylethylenediamine
TMG	1,1,3,3-tetramethylguanidine
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl
p-TSA	*p*-toluenesulfonic acid

Abstract (Part I)

The α-thionocarbonates of spiro tetrahydrofuran **42** and oxathiolanes **41** were prepared from the corresponding alcohols. Reflux in the presence of AIBN, allyltributyltin and benzene afforded no reaction with thionocarbonate **42**, however under the same conditions thionocarbonate **41** formed cyclopentenyl ether **44**. Barton ester **48** was prepared and photolysed in the presence of allyltributyltin at room temperature, also affording cyclopentenyl ether **44**.



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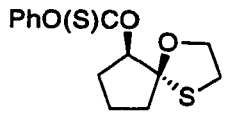

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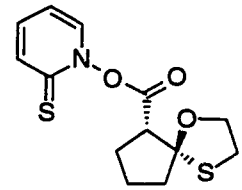

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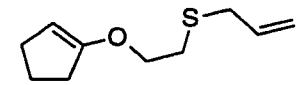


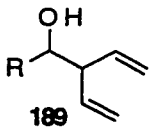
44

Abstract (Part II)

A series of alcohols **189**, obtained by the indium mediated coupling of 5-bromo-1,3-pentadiene and the corresponding aldehydes, were dehydrated with PPh_3/DEAD in benzene at 50 - 60 °C.

The novel 3-methylene substituted cross-conjugated triene **165** was reacted with a series of dienophiles in a diene-transmissive Diels-Alder study. The use of DMAD afforded adduct **171** as an inseparable mixture of diastereomers at a ratio of 2:1 (*trans:cis*) and dehydrogenated adduct **172**. In the case of cyclic dienophiles (NPTAD, 1,4-benzoquinone and *N*-phenylmaleimide) the resulting adducts (**168**, **166**, **167**) were obtained in very high diastereoselectivities; 91:9 in the case of NPTAD, and >95:5 in the cases of 1,4-benzoquinone and *N*-phenylmaleimide, (*trans:cis*).

A tandem diene-transmissive Diels-Alder and conventional Diels-Alder reaction was developed. In one-pot, cross-conjugated triene **165** was reacted with two equivalents of 1,4-benzoquinone, followed by two equivalents of cyclopentadiene. This resulted in a mixture of three diastereomers of bis-adduct **176b**, which contains 8 rings and 14 stereocenters, and one diastereomer of mono-adduct **177**, which contains 6 rings and 8 stereocenters. The tentative stereochemistry is as illustrated. The high complexity of the NMR data prevented the confirmation of the structure of bis-adduct **176b**, however its formation was likely in light of the verification of the structure of mono-adduct **177**.



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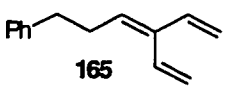

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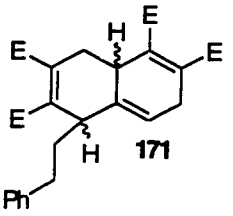

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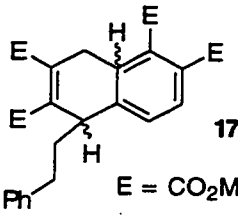

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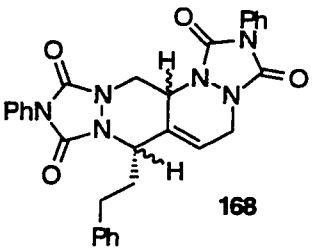
E = CO_2Me



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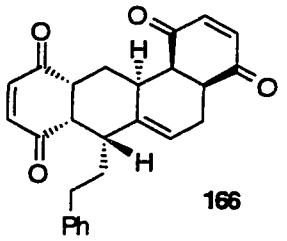

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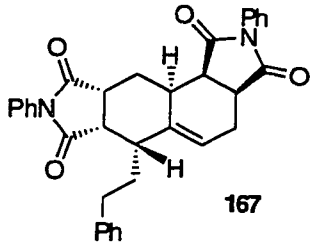

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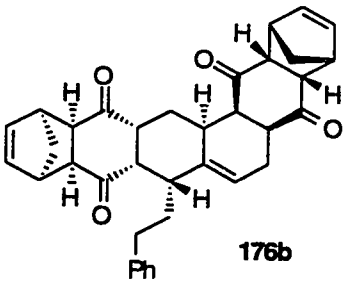
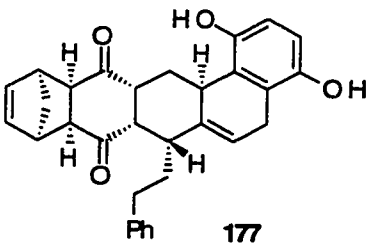


176b



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Last, but not least, my family. Mom, Dad, Nan, Brian, and Tiger, thanks for sending money when I was stuck, and paying a king's ransom in long distance, I love you.

Part I: The Chemistry of α-Oxathiolane Ketal Radicals

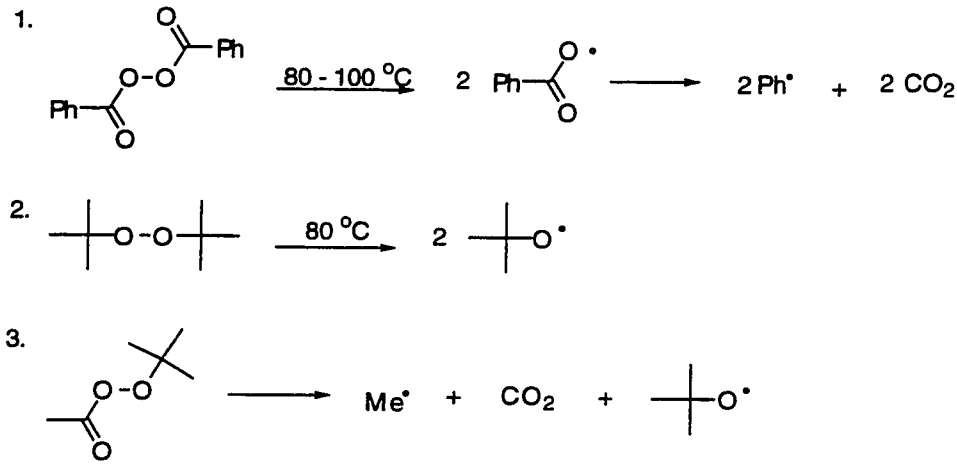
1 Introduction

1.1 Radical Chemistry

1.1.1 Sources of Free Radicals and Radical Precursors

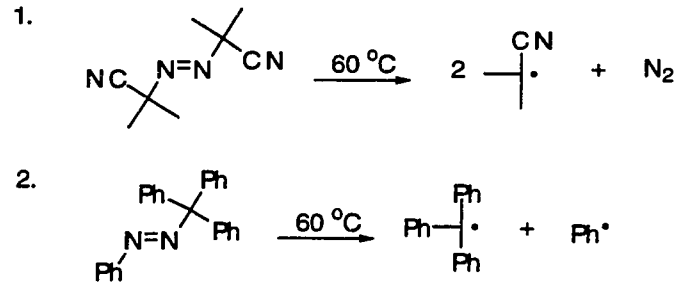
In order to initiate a radical process a source of radicals is required. All methods of free radical formation involve the decomposition of a molecule into two or more simpler radicals or molecules. The most common radical sources used in organic synthesis are aryoyl peroxides, dialkyl peroxides, peroxyesters, azo compounds, *N*-nitrosoanilides and Barton esters. All of these can be cleaved into radicals by heating at a relatively low temperature or by photolysis.[1]

The heating of an aroyl peroxide results in the formation of a carboxyl radical, which can decarboxylate to give an alkyl radical (reaction 1, Scheme 1). Dialkyl peroxides decompose to two alkoxylradicals (reaction 2, Scheme 1.). Peroxy esters decompose to an alkoxyradical and a carboxyl radical which can go on to form an alkyl radical (reaction 3, Scheme 1). [1]



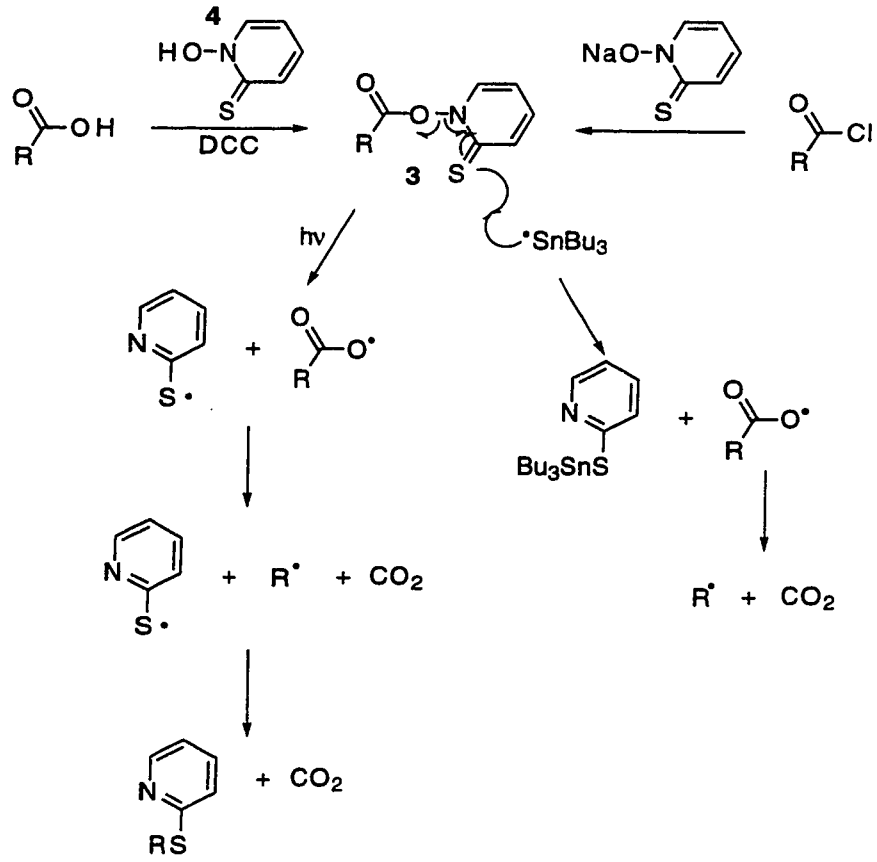
Scheme 1. Radical formation from peroxide species.

A second good source of radicals are azo compounds. Symmetrical and asymmetrical azo compounds can decompose either thermally or photochemically into two radicals and a molecule of nitrogen. The temperature at which azo compounds decompose thermally depends on the substituents. Azobisisobutyronitrile (AIBN) **1** decomposes at 60 °C (reaction 1, Scheme 2), however if phenyl radicals are required, then phenylazotriphenylmethane **2** must be used since azobenzene is thermally stable (reaction 2, Scheme 2).[1]



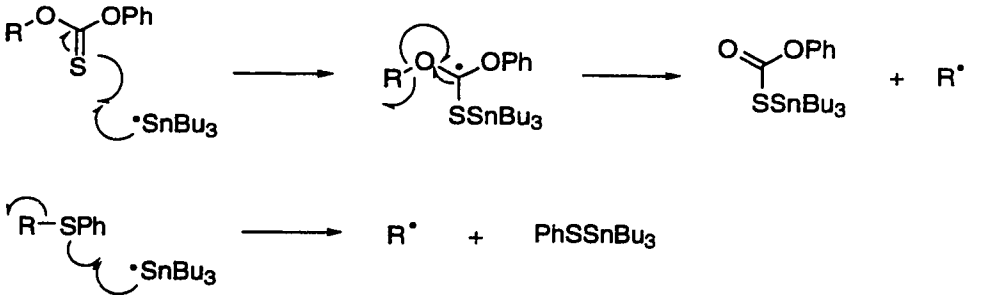
Scheme 2. Radicals from azo compounds.

Another good method to form radicals is using Barton esters. Barton esters **3** may be obtained through either the dicyclohexylcarbodiimide (DCC) mediated coupling between a carboxylic acid and mercaptopyridine-*N*-oxide **4**[2] or the reaction of an acid chloride with mercaptopyridine-*N*-oxide sodium salt. The Barton ester can be photolysed to give an thiopyridyl radical and a carboxyl radical which decomposes to give an alkyl radical (Scheme 3). Barton esters also behave as radical precursors. These arise from the reaction of tributyltin radical with the sulfur to generate a carbon centered radical.[3]



Scheme 3. Preparation of Barton esters and radical formation.

A group which propagates the radical chain reaction by forming an alkyl radical through the interaction with another radical is called a radical initiator. A number of functional groups may behave as radical precursors. Most commonly these are halides, thioethers, selenylethers, xanthates, thionocarbonates and Barton esters. This occurs through the pairing of an electron in the functional group with a free radical already present, and the cleavage of the carbon-functional group bond (Scheme 4). These new carbon centered radicals may go on to react with a radical acceptor and terminate the chain.[1,2,3]

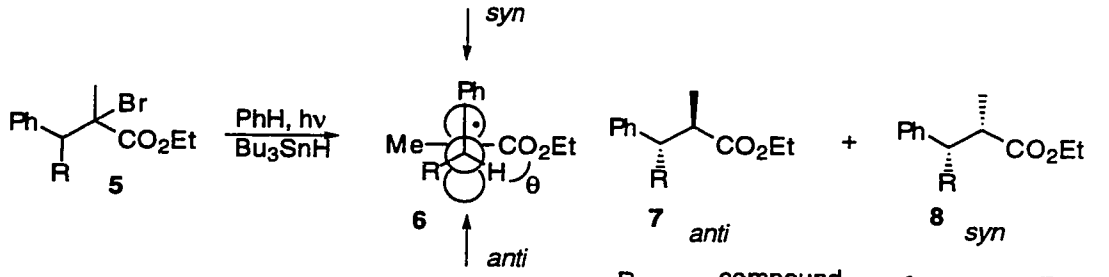


Scheme 4. Chain propagation involving thioethers and thionocarbonates.

1.1.2 Diastereoselective Intermolecular Radical Reactions

In terms of stereochemistry there are two general types of diastereoselective radical reactions. The radical center may be secondary or tertiary and become a chiral center once the reaction is complete or the radical acceptor may be secondary or tertiary and becomes chiral when the reaction is complete. Giese and coworkers studied hydride addition to a number of α,β substituted esters. A benzene solution of bromide **5** and tributyltin hydride was photoylised to give radical **6**. Hydride addition to radical **6** gave

varying diastereomeric ratios between **7** and **8**. The ratio significantly increased when the R group is switched with methyl to methoxy or fluro. Addition from the top of **6** gave the *syn* product, while addition from the bottom gave the *anti* product (Scheme 5). The rational for this was the more polar groups would repel the ester, increasing the angle θ, which in turn, would place the phenyl group at a position where it could sterically shield attack from the top, reducing the amount of *syn* product.[4]

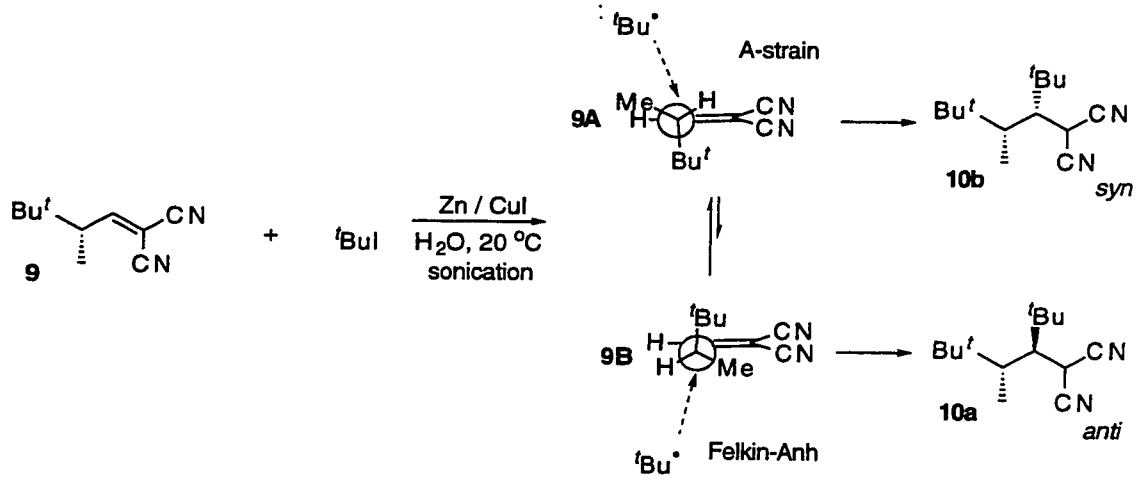


R	compound	θ	7 : 8
Me	**a**	4°	66 : 34
OMe	**b**	34°	97 : 3
F	**c**	31°	95 : 5

Scheme 5. Hydride addition to ester substituted radicals.

Giese and coworkers also studied the attack of a radical on alkene **9**. When an aqueous solution of alkene **9**, Zn, CuI, and *t*-butyliodide was sonicated, the attack of the resulting *t*-butyl radical on alkene **9** gave a ratio of 99:1 (**10a**:**10b**, *anti*:*syn*). **10b** Resulted from *syn* attack of conformer **9A** and **10a** resulted from attack *anti* of conformer **9B**. Conformer **9A** has the lower energy in terms of A-strain, as the smallest group (H) eclipses the alkene functionality. Conformer **9B**, predicted from the Felkin-Anh model,

has the largest group perpendicular to the plane of the alkene π system, and as such has the higher energy due to the eclipse of the methyl group with the alkene (Scheme 6).



Scheme 6. Intermolecular radical attack of alkenes.

Initially the *anti* to *syn* ratio is counterintuitive since one would expect the lower energy conformer to be the higher populated. The Curtin-Hammett principle states it is not the relative energy of the two conformers that determines the product ratio, but rather the energy of the two transition states involved in forming **10a** and **10b**. In this case conformer **9B** is more reactive (Figure 1).[5]

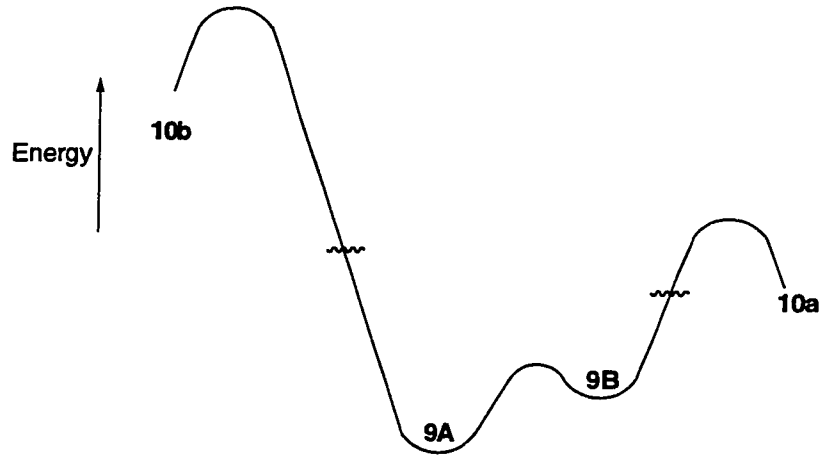
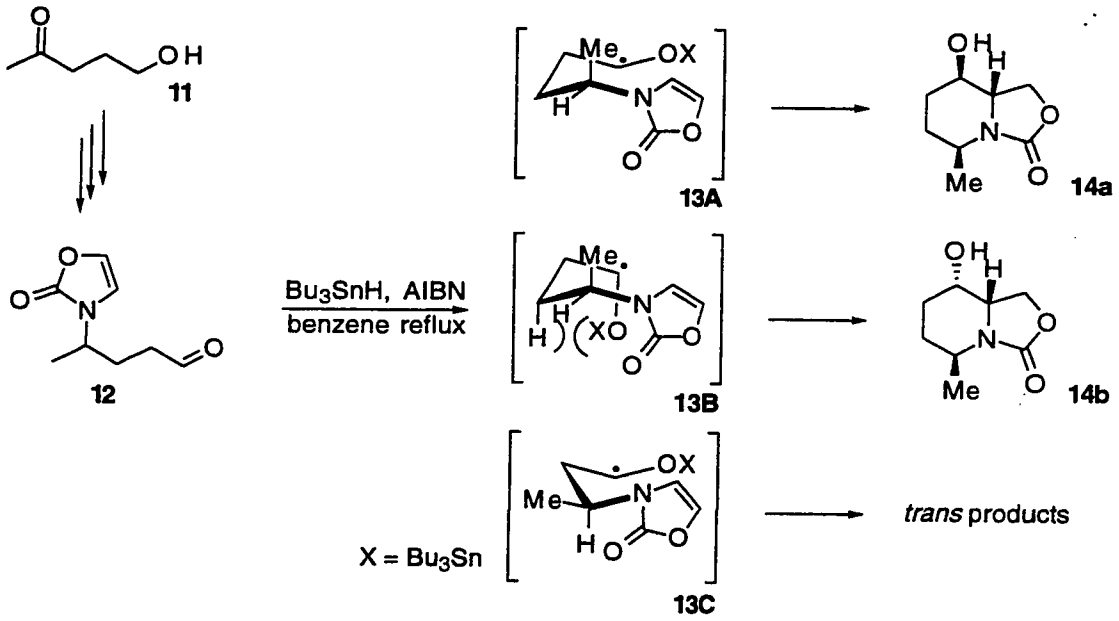


Figure 1. Energy profile for radical attack of alkene **9**, and the Curtin-Hammett principle.

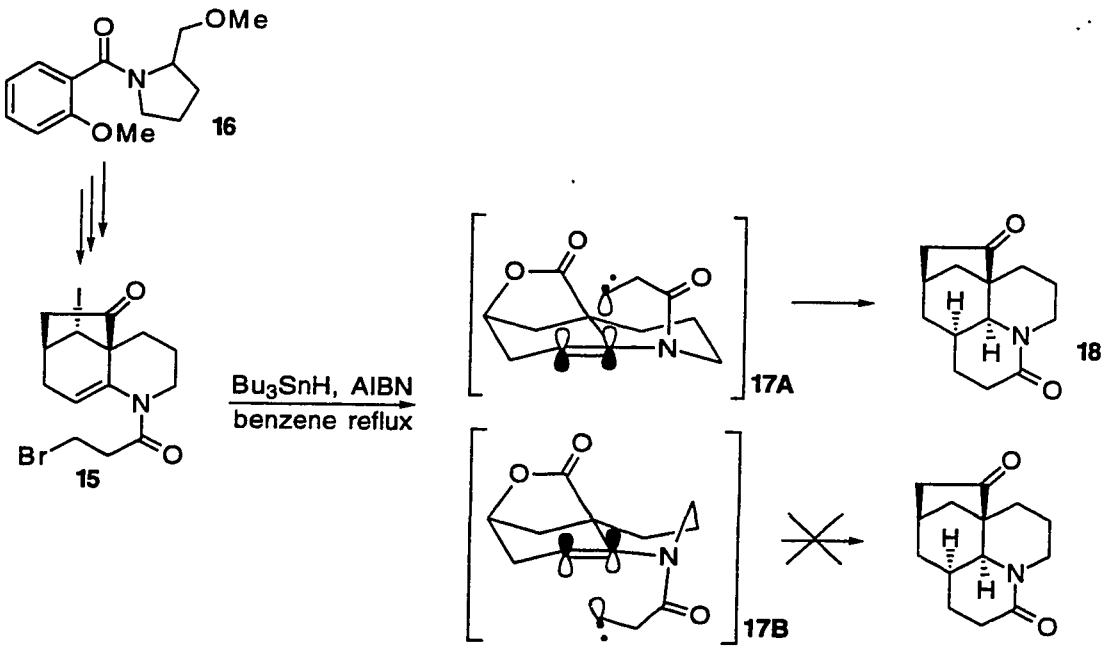
1.1.3 Diastereoselective Intramolecular Radical Reactions

Shibuya and coworkers used an intramolecular radical cyclisation in a route to 6-substituted 3-hydroxy-2-hydroxymethyl-piperidines. After a series of steps, 5-hydroxypentan-2-one **11** was converted into aldehyde **12**, which was treated with tributyltin hydride and AIBN in refluxing benzene, radical **13** resulted from attack of a tributyltin radical on the aldehyde. A 2: 1 mixture of compounds **14a** and **14b** was obtained with a slight *cis* selectivity with respect to the H and methyl group. This was explained using transition states **13A** and **13B**, which predominated over **13C**, due to the A-stain between the methyl group and the amide carbonyl. The slight predominance of **13A** over **13B** was due to the interaction between the axial hydrogen and the OX group (Scheme 7).[6]



Scheme 7. The intramolecular radical cyclisation of aldehyde **12**.

Shultz and coworkers, in a model study of the synthesis of hexahydrojulolidines and lycopodium alkaloids, obtained bromide **15** from amide **16** after a number of steps. Radical cyclisation of bromide **15** was carried out in the presence of AIBN and tributyltin hydride in benzene. It was found that radical **17** cyclised from the β face of the enamide, to give **18** in 80 % yield with *cis* stereochemistry. Calculation showed that there was a more favorable orbital overlap in transition state **17A**, which led to **18**, as compared to transition state **17B**. In addition the piperidine ring in transition state **17A** is in a chair conformation, while in **17B** it is in the less stable boat conformation (Scheme 8). Hydride addition from below to the resulting tertiary radical gave the final *cis* stereochemistry.[7]



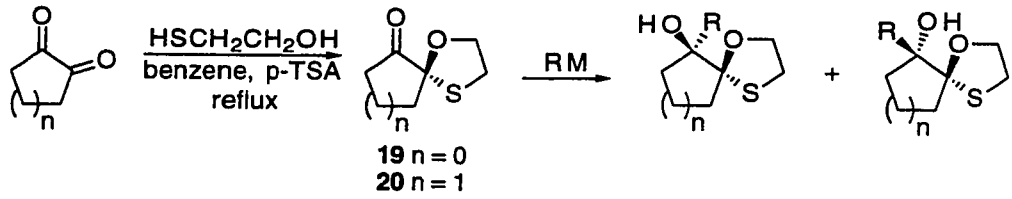
Scheme 8. Intramolecular radical cyclisation of bromide **15**.

1.2 π-Diastereofacial Selectivity of Cyclic Ketones Flanked by Oxygen and Sulfur

1.2.1 Cyclic Ketones with an α-Oxathiolane Ketal

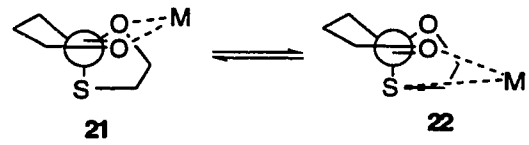
Fallis and coworkers prepared the α-oxathiolane ketals of cyclopentanone (**19**) and cyclohexanone (**20**) by refluxing a benzene solution of the corresponding α-diketones, 2-mercaptoethanol and a catalytic amount of p-TSA. A series of experiments were carried out testing the π-facial selectivity of nucleophilic reactions involving the ketones **19** and **20** using a number of methyl/metal reagents and hydrides. In nearly all the cases it was found that the nucleophile added *syn* to oxygen and *anti* to sulfur, with typical diastereoselectivities ranging from 96:4 to 70:30 (*anti*:*syn*) depending on the reagent and

reaction conditions. The only exception to this case was the addition of diisobutylaluminiun hydride (DIBAL) to ketone **19**, with a typical diastereoselectivity of 11:89 (*anti*:*syn*), depending on solvent (Scheme 9).



Scheme 9. Preparation of cyclic ketones **18** and **19**, and their nucleophilic additions. R = Me or H and M is a metal.

The selectivity was explained based on the Felkin-Ahn model, where the largest group adopts an antiperiplanar position to the new bond. Sulfur, being the best σ donor would then be *anti* to the nucleophile. A second explanation was offered based on the equilibrium between species **21** and **22** in Scheme 10. The type of complexation related to species **22** would leave the upper face free to attack by the nucelophile.[8, 9]

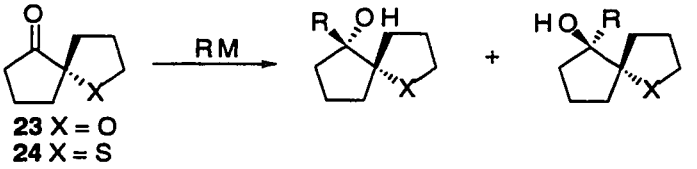


Scheme 10. The equilibrium between the two possible metal chelates involved in ketones with an α-oxathiolane ketal.

1.2.2 Spiro 2-Tetrahydrofuran and 2-Tetrahydrothiophene Ketones

In a similar study, Fallis and coworkers prepared spiro ketones **23** and **24**, and treated them with a series of hydride reagents and methyl/metal nucleophilies, varying the solvent and temperature. In nearly all the cases it was found that the nucleophile attacked

syn to carbon and *anti* to the heteroatom, with diastereoselectivies as high as >95:5 (*anti*:*syn*). The explanation offered for these results was based on an electrostatic interaction between the nucleophile and the heteroatom, where the nucleophile would avoid this electrostatic interaction and add *syn* to carbon (Scheme 11).[9,10]



23 X = O
24 X = S

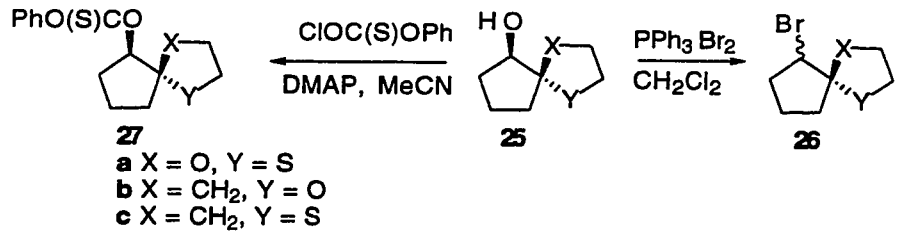
Scheme 11. The nucleophilic additions to spiro ketones **23** and **24**. R = Me or H and m is a metal.

1.3 Research Objectives

As outlined previously, hydride addition reactions involving α-oxathiolane ketals (**19, 20**), spiro 2-tetrahydrofurans (**23**), and spiro 2-tetrahydrothiophene ketones (**24**) are diastereoselective. Radical reactions involving such species could also show a diastereoselectivity. The absence of solvent effects in radical reactions may simplify the interpretation of facial behaviour.

1.3.1 Synthesis of a Viable Radical Precursor and its Radical Reaction

In work related to the α-oxathiolane ketals, 2-tetrahydrofuran, and 2-tetrahydrothiophene ketones, alcohols **25a-c** were prepared.[9] These alcohols could be used to prepare halides **26a-c**, or thionocarbonates **27a-c**, as radical precursors.



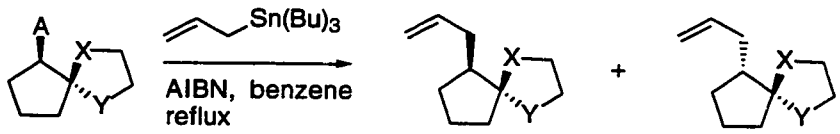
27
a X = O, Y = S
b X = CH_2, Y = O
c X = CH_2, Y = S

25

26

Scheme 12. Synthesis of radical precursors.

The secondary radicals of α-oxathiolane ketals, 2-tetrahydrofurans and 2-tetrahydrothiophenes being planar could display a π-facial selectivity similar to the nucleophilic additions to the corresponding ketones. Refluxing a solution of the radical precursor, AIBN and allyltributyltin, as the radical acceptor, would then give a mixture of diastereomers **28a-c, 29 a-c**.



26 A = Br or I
27 A = OC(S)OPh
a X = O, Y = S
b X = CH_2, Y = O
c X = CH_2, Y = S

28

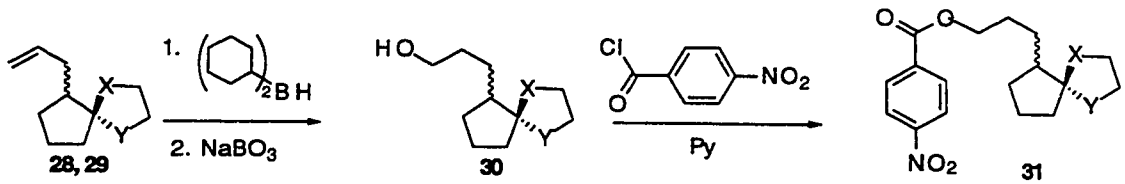
29

Scheme 13. Radical reaction of spiro α-oxathiolane ketals, tetrahydrofurans, and 2-tetrahydrothiophenes.

1.3.2 Evaluation of Diastereoselectivity

The numerical value of the diastereoselectivity can be determined by analytical procedures, however determining the relative stereochemistry may be problematic. nOe difference and NOESY studies could be used to determine relative stereochemistry of **28** and **29** but the conformational flexibility of the allyl group and the molecule in general

most likely would render the nOe studies futile. X-ray diffraction, can be used to determine the relative stereochemistry unambiguously. To accomplish this one would need to obtain crystals of the olefins. Reaction of the terminal olefin with dicyclohexanylborane followed by sodium perborate work-up would give primary alcohol **30a-c**, without removing the ketal. Then reaction with 4-nitrobenzoyl chloride, would give ester **31a-c**, which are usually crystalline.



28, 29
a X = O, Y = S
b X = CH_2, Y = O
c X = CH_2, Y = S

30 **31**

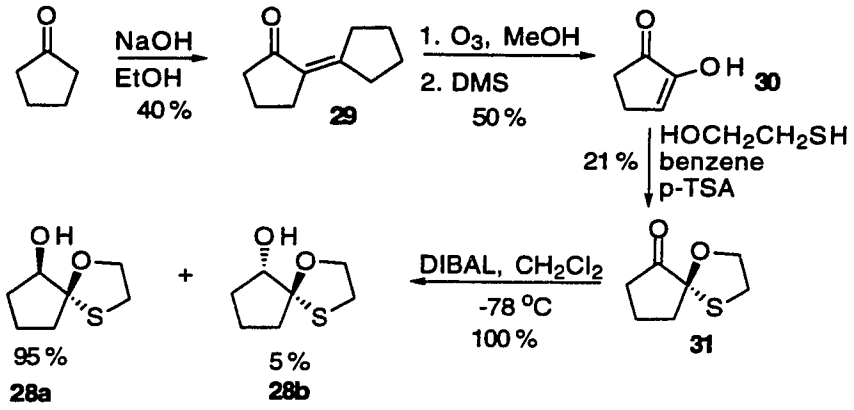
Scheme 14. Derivatives of olefins **28a-c** and, **29a-c**, based on the 4-nitrobenzoate.

2 Results and Discussion

2.1 Synthesis of Radical Precursors

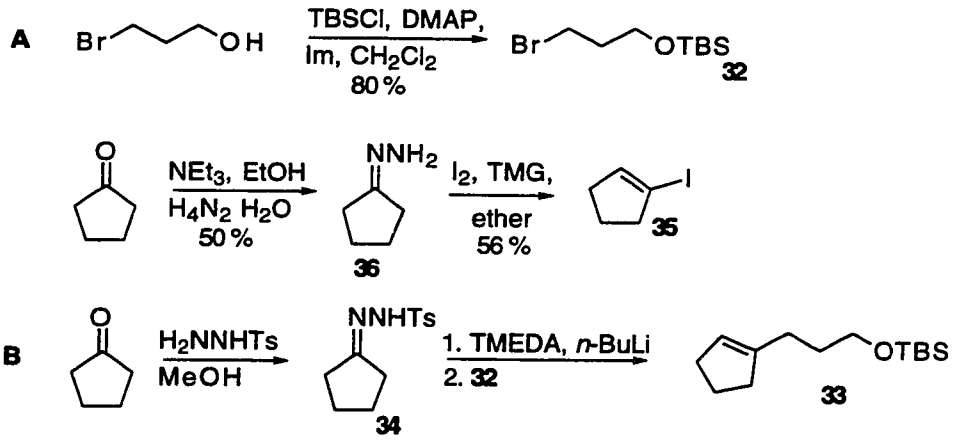
2.1.1 Preparation of Spiro Alcohols

Based on a procedure previously developed by the Fallis group spiro alcohols **28a** and **28b** were prepared (Scheme 15). α-Oxathiolane ketals were prepared by the route outlined in scheme 15. Self condensation of cyclopentanone was followed by ozonolysis and reductive dimethyl sulfide (DMS) work-up, gave the corresponding dione **30**. Reaction of the dione with 2-mercaptoethanol in the presence of p-TSA under Dean-Stark conditions afforded α-oxathiolane ketal **31**. Reduction of the ketone with diisobutylaluminiun hydride (DIBAL) afforded alcohol **28a,b**, with a diastereoselectivity of 95:5 (**28a**:**28b**). Yields for all the steps were comparable with the literature.[2,9]



Scheme 15. Preparation of (5*R**, 6*S**)-1-oxa-4-thiaspiro[4.4]nona-6-ol and of (5*R**, 6*R**)-1-oxa-4-thiaspiro[4.4]nona-6-ol.

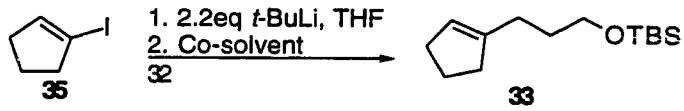
The spiro tetrahydrofurans were prepared through a 5-exo-tet cyclization involving the ring opening of an epoxide. Bromide **32** was prepared by *t*-butyldimethylsilyl (TBS) protection of the corresponding alcohol in 80% yield. In the literature procedure cyclopentene **33** was prepared via the Shapiro reaction involving hydrazine **34** and bromide **32**[9] , however difficulties were encountered in reproducing this reaction and a slightly different route was developed. 1-Iodocyclopentene **35** was prepared by the literature procedure of Barton[11] from hydrazine **36**, available from cyclopentanone.



Scheme 16. **A** Preparation of starting materials, to obtain cyclopentene **33**. **B** Literature procedure to cyclopentene **33**.

The reaction to produce cyclopentene **33** proved to be difficult. First, 1-iodocyclopentene underwent a halogen-metal exchange with *t*-BuLi, followed by attack of bromide **32** by the resulting anion in an SN2 displacement to give cyclopentene **33**. After stirring at room temperature overnight alkene **33** was isolated in a 14 % yield, along with starting material. Addition of either *N*, *N*, *N'*, *N'*-tetramethylethylenediamine (TMEDA) or hexamethylphosphoramide (HMPA) as co-solvents gave near complete reactions with

a significantly increased yield (typically 58%). HMPA gave the best results in terms of the amount of starting material **32** remaining in the reaction mixture (Table 1, entry 3). This was most probably due to the coordination of HMPA to the lithium cation, breaking up the dimers and trimers formed by the lithium species.[12]



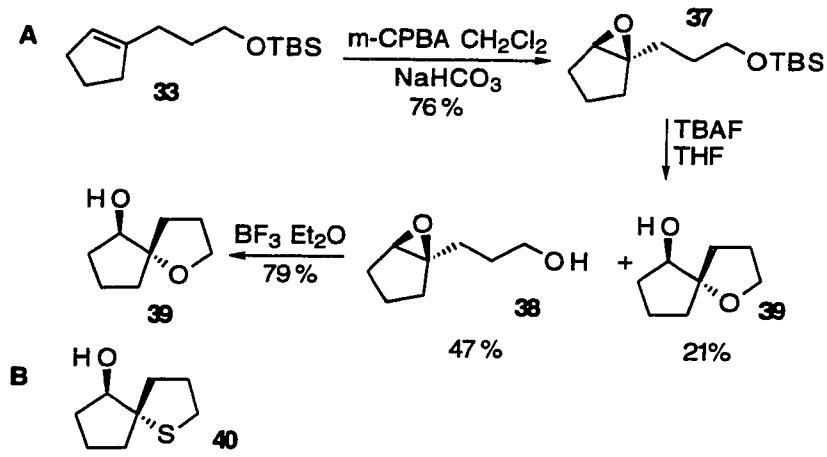
35 **32** **33**

Entry	Co-solvent[a]	**32:33**[b]	Time at 23 °C (hours)
1	HMPA	1:3.3	3
2	TMEDA	1:4.3	3.5
3	HMPA	1:41	17
4	TMEDA	1:18.7	17
5	None	1:1	18

Table 1. Preparation of cyclopentene **33**. (a) 1.1 eq. of co-solvent was used in each case. (b) Ratios were determined by GCMS analysis.

Cyclopentene **33** was converted to the spiro tetrahydrofuran by the literature route. Cyclopentene **33** was transformed into epoxide **37** with *m*-chloroperoxybenzoic acid (m-CPBA) in 76% yield. Deprotection with tetra-*N*-butylammonium fluoride (TBAF) gave alcohol **38** and spiro tetrahydrofuran **39** in 47% and 21% yields respectively. The formation of **39** was not noted in the literature procedure. The complete separation of this from the desired alcohol **38** proved difficult and a sample of pure **38** was not obtained. Fortunately **39** was the desired product in the next step and the mixture of alcohol **38** and tetrahydrofuran **39** were reacted with $BF_3 \cdot Et_2O$, giving

pure **39** in 79% yield. Attempts to prepare the spiro 2-tetrahydrothiophene **40**, were not carried out due to the poor purity of alcohol **38**.[2, 9]

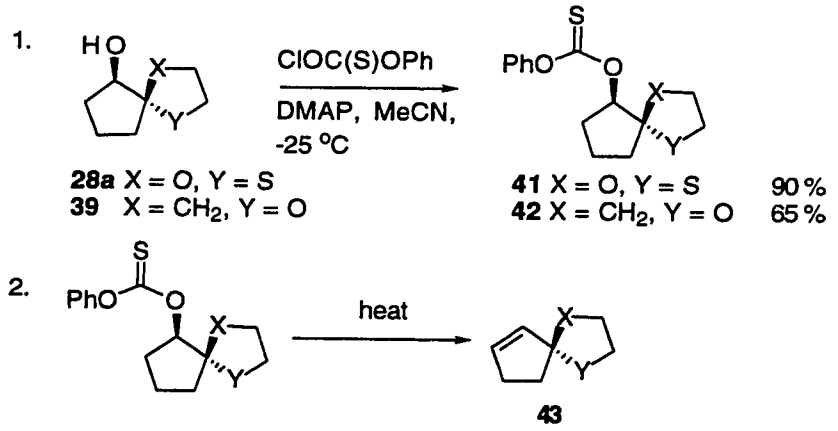


Scheme 17. **A** Preparation of spiro tetrahydrofuran **39**. **B** Spiro 2-tetrahydrothiophene **40**

2.1.2 Preparation of a Viable radical Precursor

Several attempts to prepare the corresponding bromide of spiro alcohols **28a** and **39** using PPh_3 Br_2 were carried out but complex reaction mixtures resulted. The tosylate of alcohol **28a** was prepared using 5 equivalents of tosyl chloride and stirring at room temperature for 3 weeks and 10 days at - 25 °C in 65% yield. The slow reaction was most likely due to the steric nature of the quaternary center α to the hydroxyl group. Attempts were made to form the corresponding iodide with NaI in acetone but no reaction occurred, most likely due to the quaternary center. Finally, thionocarbonates **41** and **42** were prepared by reacting alcohols **28a** and **39** with phenyl chlorothionocarbonate

and 4-dimethylaminopyridine (DMAP) in acetonitrile at -25 °C. The low temperature was necessary to prevent elimination of the thionocarbonate to the cyclopentene **43**. As a consequence, atypically long reaction times (2 weeks) were required, however the reactions were quite clean with reasonable yields.[13, 14, 15]



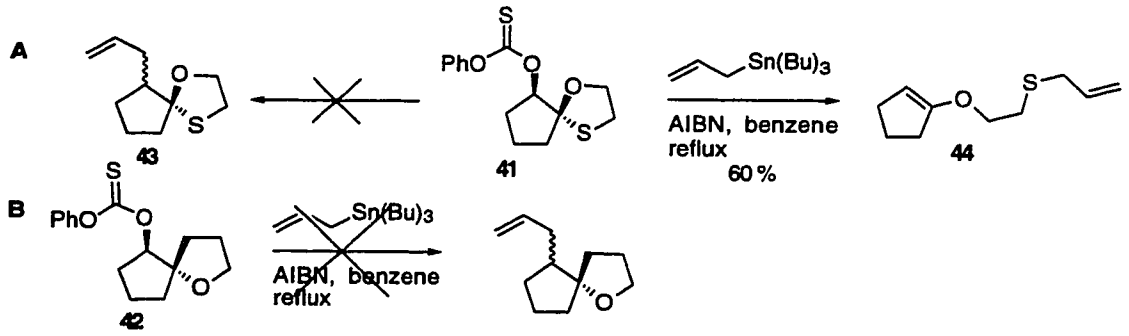
Scheme 18. Preparation of thionocarbonates **41**, and **42**.

2.2 Attempted Radical Reactions

2.2.1 The Radical Reactions

The key radical reactions were attempted on the thionocarbonates **41** and **42**. A solution of thionocarbonate **42**, 0.1 equivalents of AIBN and two equivalents of allyltributyltin in benzene was heated to reflux, in the absence of oxygen. This reaction proved to be very sluggish with the formation of no new significant spots on the TLC

plate (there is little doubt that the desired product would have had a significantly different polarity than the starting material). Even changing to a higher boiling solvent (toluene) gave the same result. The reaction with thiononcarbonate **41** gave a different result. Refluxing **41** in benzene, with 2 equivalents of allyltinbutyltin and 0.1 equivalents of AIBN gave complete reaction within 6 hours. Aside from excess allytibutyltin and tin side-products, a single product was isolated in 60% yield (based on **41**). On close inspection of the NMR data, particularly the COSY, it was determined that the product formed was not the desired product **44a** but the cyclopentenyl ether **44**.



Scheme 19. Radical reactions of the thionocarbonates **41** and **42**.

2.2.2 Characterization of Cyclopentenyl Ether 44

The NMR data did not fit what was expected for olefin **43**. The first obvious problem with the data was the fact that the peaks corresponding to the OCH_2 and SCH_2 were triplets. If **44** were chiral as the desired molecule would posses a complex splitting pattern, since the two centers are diastereotopic. Secondly, the chemical shift for the CH

associated with the cyclopentane (cyclopentene) ring was higher than would be expected - it was found above 4.0 ppm and would be expected near 2.0 ppm. The assignment as an olefinic proton would explain this result. Finally, the COSY interaction indicated by structure **C** in the following figure was not found, not even at a low intensity. Based on these observations and the COSY interactions indicated by structure **B**, figure 2, it was concluded that the isolated product was cyclopentenyl ether **44** (see also appended spectra).

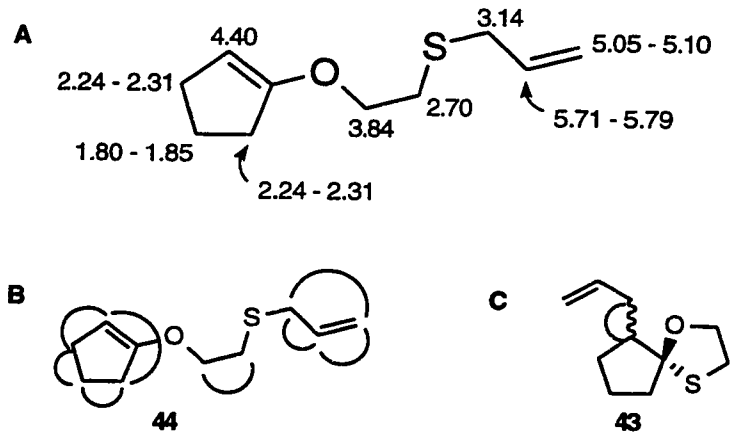
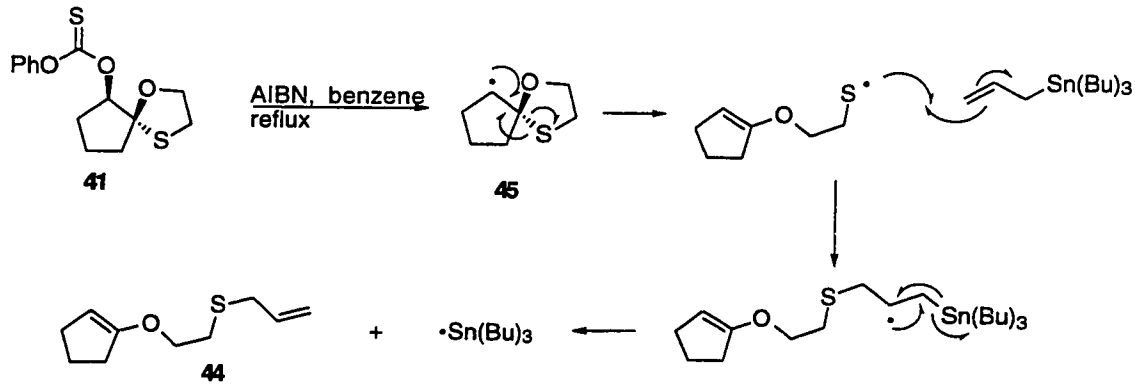


Figure 2. NMR data for cyclopentenyl ether **44**. **A:** ^{1}H NMR assignments for **44**. **B**: COSY interactions for **44**. **C**: COSY interaction for expected product **44a**.

Given a little thought, the formation of cyclopentenyl ether **44** was not a surprise - its formation can be explained by a simple mechanism (Scheme 20). Obviously a secondary radical **45** must have formed through the standard means.[2, 3] This was then followed by transfer of the electrons involved in the bond between S and the ring carbon, one to the S itself and the other pairing with the unpaired electron of the secondary

radical. This mechanism is facilitated by the formation of a sulfur centered radical which is more stable than that of carbon. Formation of an oxygen centered radical, although possible, is not as favorable. Lowering the temperature may reduce the ratio $S^{\bullet}:R_2HC^{\bullet}$, such that more of the carbon centered radical is trapped.



41 45 44

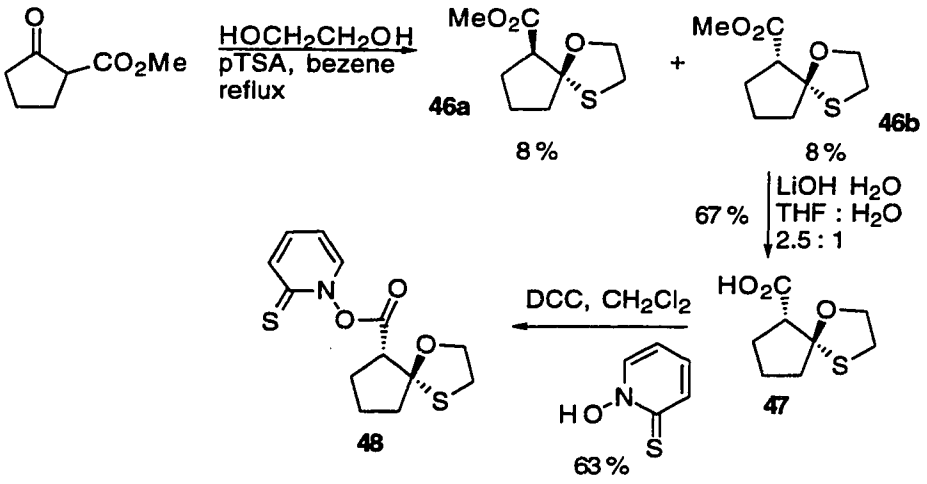
Scheme 20. Mechanism for the formation of cyclopentenyl ether **44**

2.3 A Barton Ester as the Radical Precursor

2.3.1 Synthesis of the Barton Ester

In order to obtain the required secondary radical, the carbonyl of the Barton Ester should be attached α to the oxathiolane ketal. Methyl 2-oxocyclopentane carboxylate was reacted with 2-mercaptoethanol and a catalytic amount of p-TSA giving methyl ester **46** as a 1:1 mixture of two diasteromers in 16% yield. Ester hydrolysis to the carboxylic

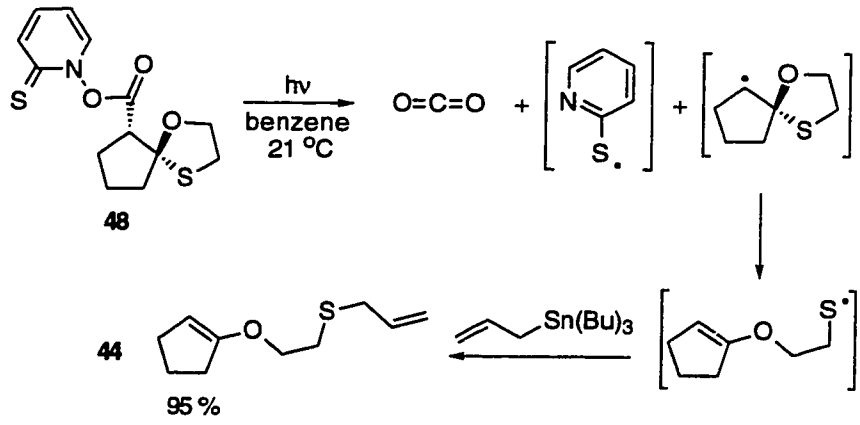
acid was carried out with KOH and ethanol. Problems isolating the product were encountered so **46b** was reacted with two equivalents of $LiOH{\cdot}H_2O$ in a 2.5:1 mixture of THF:water giving carboxylic acid **47** in 67% yield. Barton ester **48** was obtained by DCC coupling of carboxylic acid **47** and 2-mercaptopyridine-*N*-oxide in 63% yield.[2, 3, 14] Upon standing the Barton ester formed crystals and the X-ray structure was determined (Appendix I). From this the relative stereochemistry of Barton ester **48**, was unambiguously ascertained (scheme 21). The relative stereochemistry of **46** and **47** was assigned since none of the reactions performed so far involved that chiral center (scheme 21).



Scheme 21. Preparation of the required Barton ester.

2.3.2 Radical Reaction of the Barton Ester

A solution of Barton ester **48** and 2.5 equivalents of allyltributyltin in benzene was photoylized with a tungsten lamp, in the absence of oxygen,. The excess tin was used not only to facilitate faster reaction, but also to reduce the amount of coupling between the mercaptopyridine moiety and the secondary radical. Unfortunately, the only product isolated was cyclopentenyl ether **44** in 95% yield.[2,3]



Scheme 22. The radical reaction of the Barton ester.

3 Conclusions

The initial aim of this project was to determine the facial selectivity, of radicals flanked at the β position by oxygen or sulfur or both (re: spiro tetrahydrofurans, tetrahydrothiophenes and oxathiolane ketals). Thionocarbonates **41**, **42**, and Barton ester **48** were prepared as precursors to those radicals, but evaluation of the facial selectivity was not accomplished. In the cases of thionocarbonate **41** and Barton ester **48**, this was a consequence of the rapid rearrangement of the corresponding secondary radical to a sulfur centered radical, which was trapped with allyltributyltin, to give cyclopentene **44**. Lowering the reaction temperature (from 80 °C to room temperature), by using a Barton ester as the radical precursor, did not result in any of the desired carbon radical. A very low temperature is likely required to trap the secondary radical. The difference between thionocarbonate **41** and **42** could be attributed to the lack of sulfur, and any subsequent ring opening. This would give the secondary radical as the major radical species formed from thionocarbonate **42**. The secondary radical would then be β to the quaternary carbon, which may have offered sterric opposition to the coupling with allyltributyltin.

4 Experimental

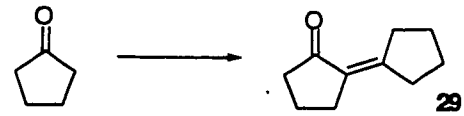
General Procedures

All starting materials were purchased from Aldrich Chemical Company and were used unpurified. In most cases reaction were carried out under inert conditions with an atmosphere of nitrogen in flasks with dry solvents and stirring. If it is stated a reaction was carried out under ambient conditions then the reaction was carried out at room temperature (21 °C), exposed to air and light. Solvents were dried by distillation from the appropriate drying agent (benzene, methylene chloride, and toluene from calcium hydride; diethyl ether, and tetrahydrofuran from sodium metal and benzophenone, acetonitrile was stored over molecular sieves for at least one day). Cyclopentadiene was distilled at 40 - 45 °C from dicyclopentadiene as needed, using a 30 cm vigreux column. Petroleum ether refers to a mixture of hydrocarbons with a boiling range of 30 - 60 °C. The solvent was first removed using a rotary evaporator, at either aspirator pressure or a PIAB lab vac (powered by an air line) and the residual solvent was removed under high vacuum. In most cases reactions were monitored using analytical thin layer chromatography using aluminum backed plates coated with silica gel 60 F_{254} (E. Merck). TLC plates were viewed with a UV lamp, developed in an iodine chamber, or the plate was treated with a stain consisting of 5% ammonium molybdate (w/v), and 10% sulfuric acid (w/v) in water, and heated on a hot plate. Flash chromatography was carried out with undistilled solvent and Merck silica gel 60 (35 - 75 μm).

Samples purified with preparative HPLC were conducted on an LC-908 recycling preparative HPLC (Japan Analytical Industry Co. LTD) with a 2 cm by 100 cm polystyrene column and Omni-solv chloroform as the eluting solvent. GCMS experiments were carried out on a Hewlett Packard 5890 series II gas chromatograph, with a Hewlwett Packard 5971 series mass selective detector.

Nuclear magnetic resonance experiments were carried out either on a Varian Gemini-200 instrument (^{1}H: 200 MHz, ^{13}C: 50MHz) or a Bruker AMX500 instrument (^{1}H: 500MHz, ^{13}C: 125MHz). The ^{1}H spectrum is reported as s = singlet, d = doublet, t = triplet, q = quartet, and p = pentet and the number of protons are in parentheses. Chemical shifts are reported in ppm downfield from tetramethylsilane, and in the case of $CDCl_3$, are referenced from the residual chloroform (^{1}H: δ ($CHCl_3$) = 7.26 ppm, ^{13}C: δ ($CHCl_3$) = 77.0ppm). Infrared experiments were carried out on a Bomen MB 100 FTIR spectrometer. Samples were mounted on sodium chloride disks neat (if a liquid), as a nujol mull, or in solution (if solid). Mass spectra were obtained using a Kratos Concept-IIA instrument, with an ionization energy of 70 eV. Melting points were determined on a Thomas - Hover capillary melting point apparatus, and are uncorrected. Samples for elemental analysis was performed at M-H-W Laboratories, Phoenix, Arizona.

2- Cyclopentylidenecyclopentanone 29



Under ambient conditions, 99% ethanol (58 mL) and cyclopentanone (89 mL, 1.24 mol) were added to a stirred solution of NaOH (4.14 g, 0.103 mol) in water (190 mL), in a round bottom flask (500mL). The solution turned a deep red once the addition was complete. over a period of 5 minutes The solution darkened to a red-brown, over a period of 5 minutes and after 15 minutes a suspension formed, to give an opaque mixture. The reaction mixture was diluted with water (450 mL), and extracted with diethyl ether (5 × 200 mL), after stirring for two days. The combined organic layers were washed with water (200 mL), dried over anhydrous magnesium sulfate, and filtered. The solvent was removed, to give 48.50 g of a deep red liquid, which was vacuum (0.1 Torr) distilled at 70 - 75 °C (lit[9] 142 - 144 °C, 20 Torr) , to give 37.50 g (40 %) of pure product. ^{1}H NMR (200 MHz, $CDCl_3$): 2.76 (m, 2H), 2.50 (m, 2H), 2.27 (m, 4H), 1.88 (m, J = 7.32 Hz, 2H), 1.67 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): 207.1, 158.4, 127.7, 39.6, 34.1, 32.4, 29.4, 26.8, 25.1, 19.9; IR (neat, cm^{-1}): 2909, 1707, 1639, 1415, 1252, 1166.

1,2-Cyclopentanedione 30

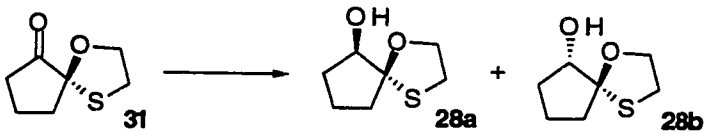
A solution of 2-cyclopentylidenecyclopentanone **29** (62.2 g, 0.414 mol) in methanol (500 mL) was purged with oxygen for 30 minutes at -78 °C, in a three-neck round-bottom flask (1L), equipped with a drying tube. Ozone was bubbled through the solution, causing the solution to turn a bright yellow and after 5 hours, the solution had turned blue-green. The ozone was turned off and the solution was purged with oxygen for 10 minutes, and DMS (300 mL) was added. The oxygen was turned off and the mixture was allowed to slowly warm to room temperature for 16 hours. The solvent was removed, to give 32.6 g of a yellow oil, which was purified by flash chromatography (2:1 petroleum ether/ethyl acetate) to give 20.5g (50 %) of a fluffy slightly yellow solid. mp: 47.5 - 49.5 °C (lit[9] liquid); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.39 - 2.51 (m, 4H), 6.54 - 6.57 (br s, 1H), 7.24 (t, J = 1.3 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.5, 33.0, 33.2, 131.7, 153.9, 205.5; IR (Neat, cm^{-1}) 3171, 1703, 1456, 1376.

(*RS*)-1-Oxa-thiaspiro[4.4]nonan-6-one 31

A solution of 1,2-cyclopentanedione **30** (20.5 g, 0.209 mol), mercaptoethanol (15.7g, 0.201 mol), *p*-toluenesulfonic acid (3.9 g, 0.0205 mol), in benzene (500 mL) was heated to reflux (reaction turned black), in a three-neck round bottom flask (1L), equipped with a Dean-Stark apparatus and condenser. After 2 hours, the solution turned very dark green and after 5 hours a large amount of black solid formed. The reaction mixture was

allowed to cool to room temperature and was washed with 10 % sodium hydroxide (200 mL). The aqueous layer was extracted with diethyl ether (2 × 150 mL), the combined organic layers were washed with water (200 mL), and brine (100 mL), dried over anhydrous magnesium sulfate and filtered. The solvent was removed, to give 14.5 g of a black - red oil, which was vacuum (0.1 Torr) distilled twice at 63 - 65 °C (lit[9] 80 - 100 °C, 0.2 Torr) , to give 6.7g (21 %)o f a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.55 - 2.46 (m, 6H), 3.05 - 3.24 (m, 2H), 4.10 - 4.24 (m, 1H), 4.38 - 4.50 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.4, 33.0, 33.8, 35.7, 72.7, 95.6, 212.0.

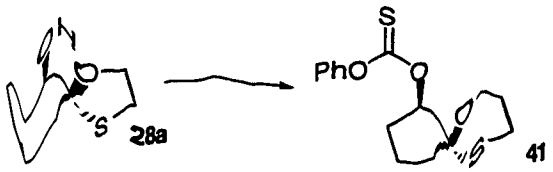
(5*R, 6*R**)-1-Oxa-4-thiaspiro[4.4]nonan-6-ol 28a** and **(5*R**, 6*S**)-1-Oxa-4-thiaspiro[4.4]nonan-6-ol 28b**



DIBAL (1.0M in toluene) (56.5 mL, 6.20 mmol) was added dropwise to a solution of ketone **31** (3.97 g, 25.3 mmol) in dichloromethane (400 mL) at -78 °C, in a two-neck round-bottom flask (1L). This was stirred for 1.5 hours to give a clear, colorless solution. Saturated aqueous potassium sodium tartrate (400 mL) was added dropwise at -78 °C, the mixture was allowed to warm to room temperature, and stirred overnight (16 hours). The layers were separated, the aqueous layer was extracted with dichloromethane (2 × 150 mL). The combined organic layers were washed with brine (150 mL), dried over anhydrous magnesium sulfate and filtered. The solvent was removed to give 4.36g of a

slightly yellow oil was purified by flash chromatography (3:1 petroleum ether/ethyl acetate) affording 3.89 g (95 %) of alcohol **28a** and 205 mg (5 %) of alcohol **28b**. **28a** ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.42 - 1.75 (m, 3H), 1.81 - 2.10 (m, 3H), 2.55 (br s, 1H), 2.80 - 2.98 (m, 2H), 3.65 (m, 1H), 3.92 (m, 2H), 4.04 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.8, 31.9, 33.9, 37.1, 71.1, 77.7, 105.7; **28b** ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.46 - 2.42 (m, 7H), 3.08 (m, 2H), 3.92 - 4.20 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.6, 34.2, 36.7, 71.4, 78.2, 101.3.[9]

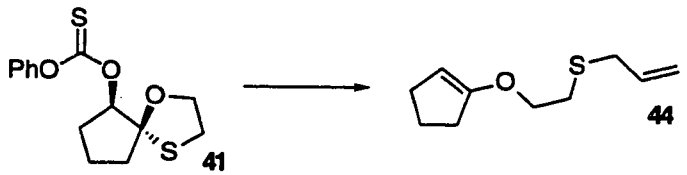
Phenyl (5*R, 6*S**)-1-oxa-7-thiaspiro[4.4]nona-6-thionocarbonate 41**



Phenyl chlorothionocarbonate (2.15 mL, 15.5 mmol) was added to a solution of alcohol **28a** (1.90 g, 12.9 mmol) and DMAP (4.09 g, 32.9 mmol) in acetonitrile (110 mL) at 0 °C, in a round bottom flask (250 mL). This afforded a lemon colored solution and after 5 minutes a precipitate. The reaction was stored in the freezer (-25 °C) for 12 days. The solvent was removed and the resulting yellow solid was mixed with ethyl acetate (500 mL). Some of the solid did not dissolve, and was filtered off. The organic solution was washed with water (3 x 50 mL), dried over anhydrous sodium sulfate, and filtered. The solvent was removed to give 5.686 g of a orange - brown oily solid, which was purified by flash chromatography (20:1 petroleum ether/ethyl acetate), affording 3.20 g

(90 %) of a slightly yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.80 - 1.86 (m, 2H), 1.95 - 2.01 (m, 1H), 2.07 - 2.17 (m, 2H), 2.25 - 2.32 (m, 1H), 2.97 - 3.01 (m, 1H), 3.04 - 3.08 (m, 1H), 4.03 - 4.08 (m, 1H), 4.19 - 4.23 (m 1H), 7.12 - 7.13 (m, 2H), 7.24 - 7.28 (m,1H), 7.38 - 7.41 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.0, 29.9, 33.7, 37.7, 70.9, 88.8, 101.4, 122.0, 126.4, 129.4, 153.4, 194.2; IR (Neat, cm^{-1}) 1592, 1489, 1434; MS m/z 296 (M^+, 2), 202(1), 159(2), 143(100), 115(18), 99(29), 94(46), 86(21), 83(31), 77(21), 55(55), 39(24), 32(24); HRMS: Calcd for $C_{14}H_{16}O_3S_2$, 296.0541; found, 296.0530; *Anal.* Calcd for $C_{14}H_{16}O_3S_2$: C, 56.73 %; H, 5.44 %; S, 21.64 %. found C, 56.92 %; H, 5.15 %; S, 21.38 %.

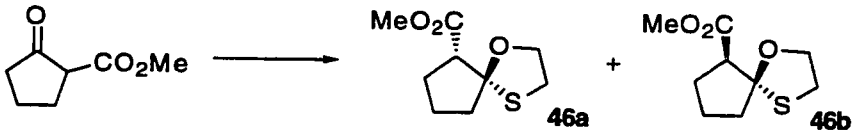
Cyclopentenyl 3-thia-5-hexenyl ether 44



A solution of thionocarbonate **41** (1.00g, 3.37 mmol), AIBN (84 mg, 0.52 mmol), and allyltributyltin (2.10 mL, 6.77 mmol) in benzene, which had been purged with argon for at least 30 minutes, was heated to reflux, in a three-neck round-bottom flask (100 mL). After 7 hours, a clear, colorless solution resulted. The solvent was removed and the resulting very slight yellow oil was diluted with petroleum ether (30 mL), and extracted with acetonitrile (10 × 10 mL). The combined acetonitrile layers were extracted with petroleum ether (3 × 100 mL). The solvent was removed from the acetonitrile solution,

to give 1.5 g of oil, which was purified by preparative TLC in 500 mg batches (20:1 petroleum ether/ethyl acetate). The resulting oil was heated in a Krugelrohr distillation apparatus to 50 °C, at atmospheric pressure. The remaining 374 mg of oil (60 %), proved to be the product. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.80 - 1.85 (m, 2H), 2.24 - 2.31 (m, 4H), 2.70 (t, J = 6.0 Hz, 2H), 3.14 (dt, J = 6.8 Hz, J = 0.9 Hz, 2H), 3.84 (t, J = 6.8 Hz, 2H), 4.40 (p, J = 2.0 Hz, 1H), 5.05 - 5.10 (m, 2H), 5.71 - 5.79 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.1, 28.9, 29.2, 21.8, 35.1, 68.6, 93.9, 117.1, 134.2, 159.4; MS m/z 184 (M^+, 1), 156(9), 143(19), 124(3), 101(91), 83(6), 73(100), 67(8), 55(30), 41(57), 27(19); HRMS: Calcd for $C_{10}H_{16}OS$, 184.0923; found, 184.0901.

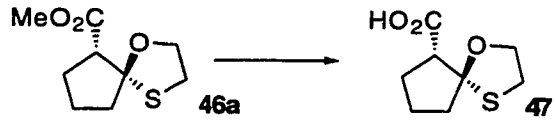
(5*R, 6*R**)-Methyl 1-oxa-4-thiaspiro[4.4]nona-6-carboxylate 46a (5*R**, 6*S**)-Methyl 1-oxa-4-thiaspiro[4.4]nona-6-carboxylate 46b**



A solution of *p*-toluenesulfonic acid (67 mg, 0.352 mmol), methyl-2-oxocyclopentane carboxylate (436 μL, 3.52 mmol), and 2-mercaptoethanol (271 μL, 3.87 mmol) in benzene (10 mL) was heated to reflux in a round-bottom flask (25 mL) equipped with a Dean-Stark trap. After 2 hours the resulting black reaction mixture was cooled to room temperature and washed with 10% aqueous sodium hydroxide (5 mL). The basic layer was extracted with diethyl ether (2 × 10 mL), the combined organic layers were washed with water (20 mL), and brine (20 mL), dried over anhydrous sodium sulfate and

filtered. The solvent was removed to give 710 mg of a yellow oil which was purified by flash chromatography (10:1 petroleum ether/ethyl acetate), affording 119 mg (16 %) of a colorless oil, at 16 % yield. A pure sample of **46b** could not be obtained, and data for **46b** was subtracted from that of **46a**. **46a** ^{1}H NMR (500MHz $CDCl_3$) δ 1.65-1.75 9 (m, 2H), 1.87-1.94 (m, 1H), 1.95-2.01 (m, 2H), 2.05-2.12 (m, 1H), 2.70-2.96(m, 3H), 3.60 (s, 3H), 3.95-4.02 (m, 2H); ^{13}C NMR (125MHz, $CDCl_3$) δ 23.1, 28.3, 33.2, 41.1, 51.4, 56.1, 69.8, 101.3, 173.7; IR (neat, cm^{-1}) 1730, 1448; MS m/z 202 (M^+, 35), 181(3), 171(19), 143(37), 129(10), 115(90), 100(6), 87(34), 83(12), 69(17), 60(100), 55(66), 45(17), 40(66); HRMS: Calcd for $C_9H_{14}O_3S$, 202.0664; found, 202.0620. **46b** ^{1}H NMR (500MHz $CDCl_3$) δ 1.55 - 1.63 (m, 1H), 1.82 - 1.91 (series m, 3H), 2.09 - 2.16 (m, 2H), 2.99 - 3.08 (m, 3H), 3.62 (s, 3H), 3.92 - 3.97 (m, 1H), 4.11 (dt, J = 10.7 Hz, J = 5.4 Hz, 1H); ^{13}C NMR (125MHz, $CDCl_3$) δ 22.2, 26.8, 33.6, 41.2, 52.0, 55.0, 71.3, 101.4, 172.4; IR (Neat, cm^{-1}) 1734, 1442; MS m/z 202 (M^+, 27), 171(15), 143(57), 129(15), 115(86), 99(9), 87(36), 60(100), 55(92), 45(25), 41(21); HRMS: Calcd for $C_9H_{14}O_3S$, 202.0664; found, 202.0670.

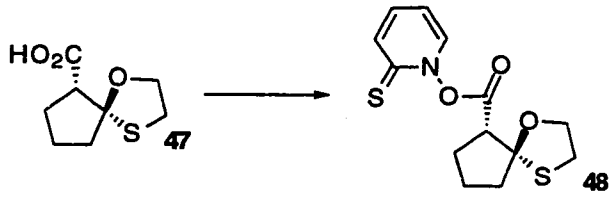
(5*R, 6*R**)-1-Oxa-4-thiaspiro[4.4]nonyl-6-carboxylic acid 47**



Under ambient conditions, ester **46a** (128 mg, 0.634 mmol), and lithium hydroxide monohydrate (72 mg, 1.27 mmol), were added to a 2.5:1 mixture of THF/water, in a

round-bottom flask (25 mL), to give a mixture of solid and solution. After 23 hours at room temperature, the resulting yellowish suspension was extracted with diethyl ether (3 × 10 mL). The aqueous layer was acidified with concentrated sulfuric acid (pH = 2, with paper), extracted with diethyl ether (4 × 20 mL), the combined organic layers were dried over sodium sulfate, and filtered. The solvent was removed to give 119 mg (67 %) of a slightly yellow solid. MP 72.0 - 74.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.66 - 1.83 (series m, 2H), 1.92 - 2.25 (series m, 4H), 2.98 - 3.03 (m, 3 H), 4.04 - 4.12 (m, 2H), 11.24 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.9, 28.4, 33.5, 41.2, 56.2, 70.1, 101.0, 179. 5; IR (Neat, cm^{-1}) 2900 (br), 1695, 1428; MS m/z 188 (M^+, 82), 159(11), 129(15), 115(100), 100(10), 73(7), 60(80), 55(28), 45(10); HRMS: Calcd for $C_8H_{12}O_3S$, 188.0507; found, 188.0479.

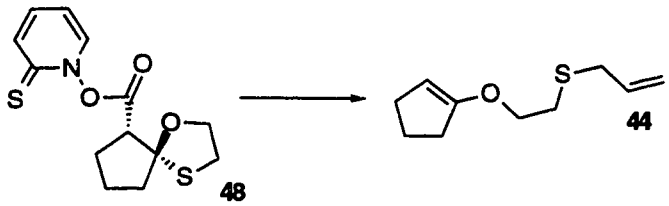
(5*R, 6*R**)-2-Mercaptopyridine-*N*-oxyl 1-oxa-4-thiaspiro[4.4]nonyl-6-carboxylate 48**



A solution of carboxylic acid **47** (58 mg, 0.31 mmol) in dichloromethane (0.5 mL), was added dropwise to a solution of 2-mercaptopyridine-*N*-oxide (41 mg, 0.32 mmol) and DCC (71 mg, 0.34 mmol) in dichloromethane (1 mL), in a round-bottom flask (10 mL), with protection from light, at 0 °C. After 5 minutes a bright yellow suspension had formed. The reaction mixture was protected from light, and stirred for 19 hours at room

temperature. The resulting gray-yellow mixture was filtered through a small plug of silica gel (0.5 cm × 2.5 cm), to give a yellow solution. The solvent was removed to give a yellow oil (79 mg), which was purified by flash chromatography (column wrapped in foil) (3:1 petroleum ether/ethyl acetate) affording 58 mg (63 %) of a bright yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.65 - 2.48 (series m, 6H), 3.07 - 3.25 (m, 2H), 3.07 - 3.25 (m, 2H), 3.51 - 3.58 (m, 1H), 4.02 - 4.13 (m, 1H), 4.25 - 4.35 (m, 1H), 6.56 - 6.63 (m, 1H), 7.12 - 7.26 (m, 1H), 7.58 (d, J = 7.0 Hz, 1H), 7.65 (d, J = 8.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.1, 27.0, 33.7, 40.9, 53.0, 71.5, 101.7, 112.6, 133.5, 137.2, 137.8, 167.7, 175.6; IR ($CHCl_3$, cm^{-1}) 1803, 1611, 1528; MS m/z 297 (M^+, 4), 224(38), 188(6), 171(20), 156(10), 143(33), 127(4), 111(38), 99(46), 83(15), 56(100), 41(25); HRMS: Calcd for $C_{13}H_{15}N_1O_3S_2$, 297.0494; found, 297.0510.

Photolysis of the Barton Ester



Allytributyltin (140 μL, 0.444 mmol) was added to a solution of Barton ester **48** (66 mg, 0.22 mmol), in benzene (2 mL), which had been purged with nitrogen for 45 minutes, in a round-bottom flask (10 mL), to give a yellow solution.. The reaction mixture was exposed to light (275 W tungsten lamp) at room temperature for 19 hours, to give a colorless solution. The solvent was removed, to give 196 mg of a lightly yellow oil,

which was purified by flash chromatography (27:1 petroleum ether/ethyl acetate), to afford 39 mg (95 %) of a slightly yellow oil. The isolated product proved to be ether **44**. See preparation of **44** for characterization data.

Cyclopentanone hydrazone 36

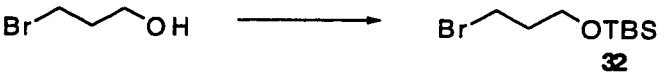
36

Hydrazine monohydrate (100 g, 2.00 mol), was added to a solution of cyclopentanone (5.0 g, 0.073 mol), triethylamine (20 mL) in 95 % ethanol (60 mL), in a round bottom flask (500 mL). The greenish solution was heated to reflux for 17 hours. The resulting clear solution was cooled to room temperature, diluted with water (150 mL), and was extracted with dichloromethane (3 × 75 mL), the combined organic layers were washed with water (100 mL), dried over anhydrous magnesium sulfate, and filtered. The solvent was removed under reduced pressure, to give a colorless liquid, which was distilled, using a Krugelrohr apparatus at 60 °C, (lit[11] not provided) affording 3.6 g (50 %) of a colorless liquid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.36 - 1.63 (m, 4H), 1.86 - 1.95 (m, 2H), 2.01 - 2.08 (m, 2H), 4.66 (br m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.9, 24.1, 24.9, 32.0, 159.6.

1-Iodocyclopentene 35

A solution of TMG (39.0 g, 0.339 mol) in dry diethyl ether (250 mL) was added dropwise over a period of 30 minutes to a solution of iodine (18.6 g, 0.0733 mmol) in diethyl ether (250 mL), in a three-neck round-bottom-flask (1 L), to give a dark brown - black solution. The reaction mixture was protected from light, and a solution of hydrazone **36** (3.3 g, 0.033 mol) in dry diethyl ether (50 mL) was added dropwise over a period of 10 minutes. During the addition each drop caused the formation of a white precipitate, which quickly decolorized back to dark brown, with the evolution of a. The diethyl ether was distilled off and The resulting brown - black oil was heated in a bath at 90 °C for 90 minutes, cooled and diluted with diethyl ether (500 mL), to give a dark brown - black solution. This was washed with water (150 mL), 1 M hydrochloric acid (2 × 130 mL), saturated sodium hydrogen sulfite (2 × 60 mL), saturated sodium bicarbonate (2 × 60 mL), brine (2 × 60 mL), dried over anhydrous sodium sulfate, and filtered. The solvent was removed to give a yellow liquid, which was distilled using a Krugelrohr apparatus, under aspirator pressure (15 Torr) at 50 - 60 °C (lit[11] 50 - 60 °C, 20 Torr) , to give 3.7 g (56 %) of a colorless liquid. The product was stored in the cold, in solution of known concentration with dry diethyl ether, or dry THF. ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.8, 33.9, 43.6, 92.6, 139.6.

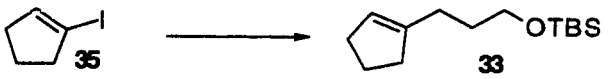
3-Bromo-1-*tert*-butyldimethylsiloxypropane 32



32

t-Butyldimethylsilyl chloride (40.7g, 0.270 mol) was added to a solution of 3-bromopropanol (41.2 g, 0.297 mol), DMAP (3.3 g, 0.0270 mol) and imidazole (21.1 g, 0.324 mol in dry dichloromethane (150 mL), in a three-neck round-bottom-flask (500 mL), at 0 °C. After 10 minutes the ice bath was removed to give a mixture consisting of a pale yellow solution and white precipitate, which was stirred at room temperature for 1 day and 19.5 hours. The reaction mixture was diluted with 200 mL of diethyl ether, washed with water (150 mL), saturated ammonium chloride (3 × 200 mL), dried over anhydrous magnesium sulfate, and filtered. The solvent was removed, to give a light brown oil, which was distilled at 40 - 45 °C, (0.1 Torr) (lit[a16] 70 - 80 °C, 0.2 Torr) , to give 55.2 g (80 %)of a colorless liquid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.86 (s, 9H), 1.99 (p, J = 6.4 Hz, 2H), 3.47 (t, J = 6.4 Hz, 2H), 3.68 (t, J = 3.5 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ -5.4, 18.2, 25.7, 30.5 , 35.5, 60.3.

1-(3-*tert*-Butyldimethylsiloxypropyl)cyclopentene 33

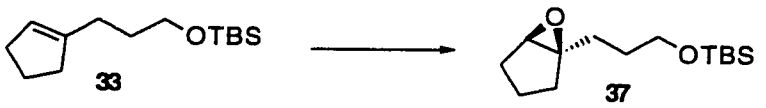


35 33

A 1.6 M solution of *t*-butyllithium in pentane (1.26 mL, 2.14 mmol) was added to a solution of 1.4 M 1-iodocyclopentene **35** in THF (0.75 mL, 1.03 mmol) diluted with THF (10 mL), in a round-bottom flask (50 mL), to give a yellow solution, which was

stirred at -78 °C for 45 minutes. HMPA (195 μL, 1.12 mmol) was added, the solution was stirred for 30 minutes, 3-bromo-1-*tert*-butyldimethylsiloxypropane **32** (276 mg, 1.09 mmol) was added and the yellow color faded. This was stirred for 30 minutes at -78 °C, and then for 18 hours at room temperature (reaction monitored by GCMS). Saturated ammonium chloride (10 mL) was added at 0 °C, the layers were separated. the aqueous layer was extracted with diethyl ether (2 × 15 mL), the combined organic layers were washed with water (2 × 10 mL), brine (10 mL), dried over anhydrous sodium sulfate and filtered. The solvent was removed, to give 222 mg of a yellow oil, which was purified by flash chromatography (petroleum ether). It was necessary to first monitor the fractions by TLC to determine which contained the product, which was the only material in the mixture visible by iodine, or any other method and then every 10 fractions was run through the GCMS to determine its purity. Once this was complete, 144 mg (58 %) of material were obtained. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.02 (s, 6H), 0.87 (s, 9H), 1.59 - 2.25 (series m, 10H), 3.59 (t, J = 6.3 Hz, 2H), 5.32 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ -5.3, 18.4, 23.5, 26.0, 27.4, 32.4, 35.2, 63.0, 123.2, 144.4.[9]

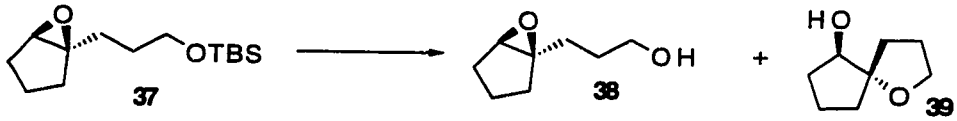
(1*R, 5*R**)-1-(3-*tert*-Butyldimethylsiloxypropyl)-6-oxabicyclo[3.1.0]hexane 37**



Under ambient conditions, sodium bicarbonate (124 mg, 1.47 mmol) and a mixture 50 % of 3-chloroperoxybenzoic acid with 3-chlorobenzoic acid (312 mg, 0.905 mmol)

were added to a solution of cyclopentene **33** (144 mg, 0.597 mmol) in dichloromethane (10 mL), in a round-bottom flask (25 mL), at 0 °C and was stirred at 0 °C for 2 hours. Saturated sodium sulfite (10 mL) was added, the layers were allowed to separate. the aqueous layer was extracted with diethyl ether (3 × 10 mL), the combined organic layers were dried over anhydrous sodium sulfate, and filtered. The solvent was removed, to give 138 mg of a colorless oil, which was purified by flash chromatography (30:1 petroleum ether/ethyl acetate), affording 116 mg (76 %) of a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ -0.01 (s, 6H), 0.84 (s, 9H), 1.20 - 1.98 (series m, 10 H), 3.20 (br s, 1H), 3.58 (t, J = 6.4 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ -5.4, 18.3, 19.5, 25.9, 27.5, 28.0, 28.9, 29.5, 62.5, 62.9, 67.6.[9]

(1*R, 5*R**)-1-(3-hydroxypropyl)-6-oxabicyclo[3.1.0]hexane 38** and **(5*R**, 6*S**)-1-oxaspiro[4.4]nonan-6-ol 39**



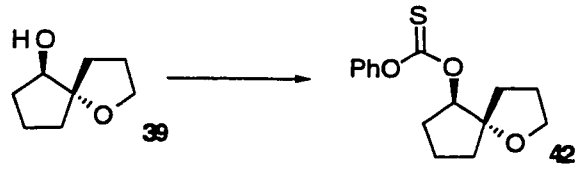
TBAF (713 mg, 2.26 mmol) was added to a solution of epoxide **37** (501 mg, 1.95 mmol) in THF (65 mL), in a round-bottom flask (100 mL), at 0 °C. This was stirred at 0 °C for 30 minutes, and then for 1 hour at room temperature. The yellow - brown reaction mixture was treated with water (40 mL), extracted with diethyl ether (3 × 100 mL), the combined organic layers were washed with sodium chloride (50 mL), dried over sodium sulfate, and filtered. The solvent was removed to give a slightly yellow oil which was

purified by flash chromatography (1:1 petroleum ether :diethyl ether). Two close running spot were found. A significant portion of the second spot could be separated from the first, but the first spot could not be obtained totally pure. The first spot proved to be compound **38**, at 130 mg (47 %) and the second, at 59 mg (21 %) **39**. **38**, ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.5, 27.5, 28.3, 28.6, 29.5, 29.7, 62.6, 63.0, 67.9.[9]

(5*R, 6*S**)-1-oxaspiro[4.4]nonan-6-ol 39**

Boron trifluoride etherate (0.20 mL, 1.58 mmol) was added dropwise to a solution of the mixture of epoxy alcohol **38** and alcohol **39** (130 mg, 0.912 mmol) in diethyl ether (57 mL), in a round-bottom flask (100 mL), at -78 °C, and was stirred for 1 hour. Saturated ammonium chloride (10 mL) was added, the layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried with anhydrous sodium sulfate, filtered and the solvent was removed, to give 145 mg of a colorless oil, which was purified by flash chromatography (1:1 petroleum ether/diethyl ether) to give 102 mg (79 %) of a colorless oil. ^1H NMR (200 MHz, $CDCl_3$) δ 3.20 (m, 1H), 3.74 (t, J = 6.6 Hz, 2H), 2.77 (br s, 1H), 2.17 - 1.36 (series of m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 92.2, 76.5, 67.1, 34.3, 31.5, 29.2, 25.6, 19.1.[9]

(5*R, 6*S**)-Phenyl 1-oxaspiro[4.4]nona-6-thionocarbonate 42**



Phenyl chlorothionocarbonate (320 μL, 2.31 mmol) was added to a solution of alcohol **39** (251 mg, 177 mmol), and DMAP (597 mg, 4.87 mmol) in acetonitrile (30 mL), in a round-bottom flask (50 mL), at 0 ^{0}C, to give a yellow solution, which formed a large amount of white precipitate after 5 minutes. This was stored in the freezer (-25 °C) for 13 days and 12 hours. The solvent was removed, and replaced with dichloromethane (20 mL), which was washed with water (3 × 20 mL), dried over anhydrous sodium sulfate, and filters. The solvent was removed to give 929 mg of a yellow oil which was purified by flash chromatography (19:1 petroleum ether/diethyl ether) affording 318 mg (65 %)of a slightly yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.72 - 1.95 (series m, 8H), 2.10 - 2.16 (m, 1H), 2.27 - 2.34 (m, 1H), 3.80 - 3.88 (m, 2H), 5.35 (dd, J = 2.4 Hz, J = 5.6 Hz), 7.08 - 7.09 (m, 2H), 7.24 - 7.28 (m, 1H), 7.38 - 7.41 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.5, 26.1, 30.0, 30.3,35.6, 67.8, 89.4, 91.5, 121.9, 126.4, 129.4, 153.3, 194.2; IR (Neat, cm^{-1}) 1593, 1490; MS (FAB) m+1/z 279(7), 125(100), 97(43), 95(14), 55(64); MS(FAB accurate mass): Calcd for $C_{15}H_{19}O_3S$, 279.1055; found, 279.0997; *Anal.* Calcd for $C_{15}H_{18}O_3S$: C, 64.72 %; H, 6.52 %; S, 11.52 %. Found: C, 64.50 %; H, 6.43 %; S, 11.50 %.

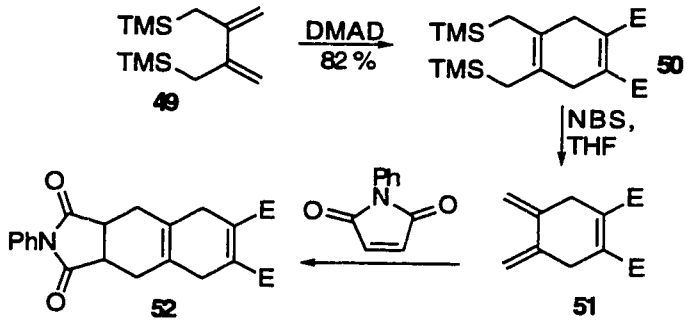
Part II: The Synthesis of Cross-conjugated Trienes Using Indium Chemistry, Their Diels-Alder Reactions, and a Tandem Diene-transmissive and Conventional Diels-Alder Reaction

5 Introduction

5.1 Diene-transmissive Diels-Alder Reactions

5.1.1 Multiple Diels-Alder Reactions

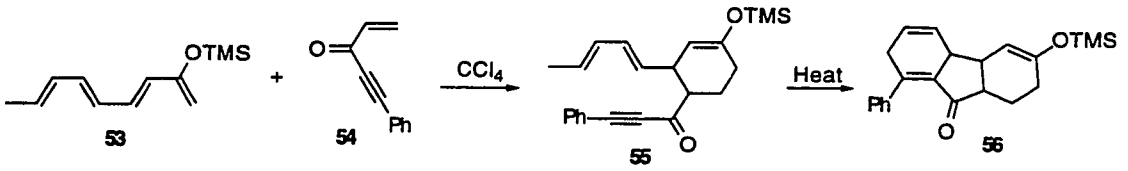
There are various types of multiple Diels-Alder reactions, including tandem, timed, and domino Diels-Alder reactions. A tandem Diels-Alder reaction is possible when the diene-dienophile combination from the first cycloaddition releases functionality for a second cycloaddition in one pot. Trost and coworkers prepared diene **49** and carried out a Diels-Alder reaction with dimethylacetylenedicarboxylate (DMAD) to give mono-adduct **50** in 82 % yield. Mono-adduct **50** was desilylated with *N*-bromosuccinimide (NBS) in THF to give diene **51** which was reacted with *N*-phenylmaleimide to provide bis adduct **52** (Scheme 23).[18]



Scheme 23. The tandem Diels-Alder reactions of diene **49**.

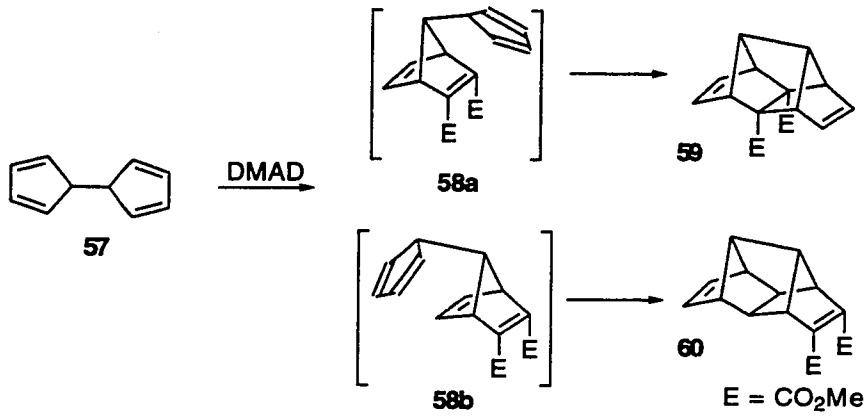
A similar type of multiple Diels-Alder reaction is the timed Diels-Alder reaction. In this case an intermolecular Diels-Alder reaction is followed by an intramolecular Diels-Alder reaction. Kraus and coworkers carried out a Diels-Alder reaction between bisdiene

53 and bis dienophile 54, to afford cyclopentene 55. Heating 55 gave adduct 56. In this case the reactivity of one dienophile for the diene outweighs that of the other dienophile so one Diels-Alder could occur selectively.[19]



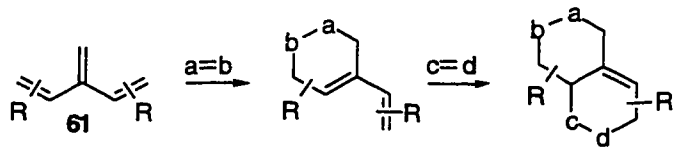
Scheme 24. The timed Diels-Alder reaction between bisdiene **54** and bisdienophile **54**.

The domino Diels-Alder reaction is slightly different than the aforementioned multiple Diels-Alder reactions. In a domino Diels-Alder reaction the initial Diels-Alder forms the dienophile which undergoes a second Diels-Alder reaction with a diene already present. Paquette and coworkers reacted 9,10-dihydrofulvalene (**57**) with one equivalent of DMAD. This gave intermediate diene **58a** or **58b** which underwent an intramolecular Diels-Alder reaction to give either cage compound **59** in 58 % yield or cage compound **60** in 42 % yield.[20,21]



Scheme 25. The domino Diels-Alder chemistry of 9,10-dihydrofulvalene.

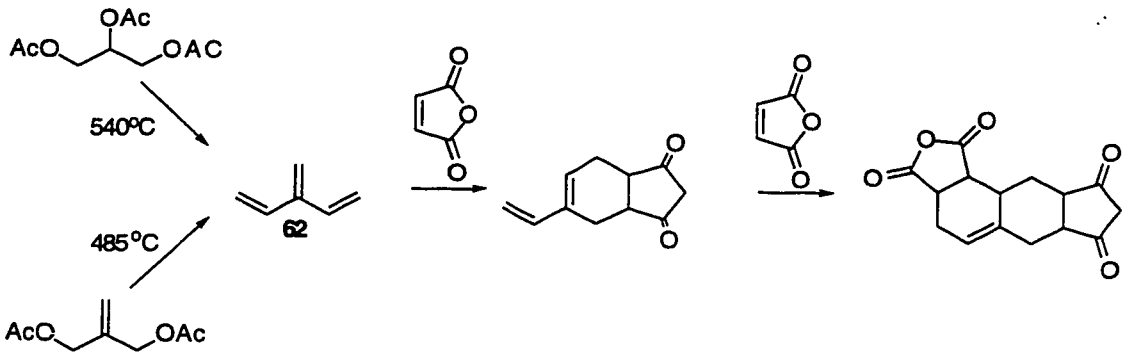
The diene-transmissive Diels-Alder reaction also offers an advantageous handle to numerous organic molecules. A Diels-Alder reaction with one equivalent of a dienophile and cross-conjugated triene **61**, places the newly formed double bond such that a new diene is formed. Thus reaction with a second equivalent of a dienophile gives a system consisting of two fused six-membered rings. The sequential reaction of two dienophiles with a triene, in this manner, is referred to as the diene-transmissive Diels-Alder reaction.[21, 22]



Scheme 26. The general diene-transmissive Diels-Alder reaction.

5.1.2 3-Methylene-1,4-pentadiene

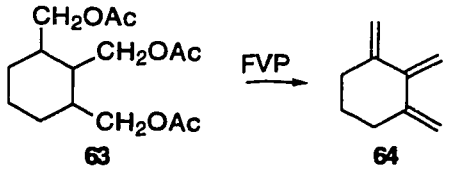
In 1955 Blomquist and Bailey prepared 3-methylene-1,4-pentadiene **62**, the first, and simplest cross-conjugated triene, through the pyrolysis of either 1,5-diactoxy-3-acetoxymethylpentane, or 3-methylene-1,5-pentanediol diacetate. Reactions with various dienophiles were carried out.[23, 24] Triene **62** was unstable, and polymerized even at -5 °C.[24] This reactivity limited its synthetic utility. The following sections deal with compounds related to triene **62** that overcome this problem and are more successful.



Scheme 27. 3-Methylene-1,4-pentadiene and its Diels-Alder chemistry.

5.1.3 Cyclic Derivatives of 3-Methylene-1,4-pentadiene

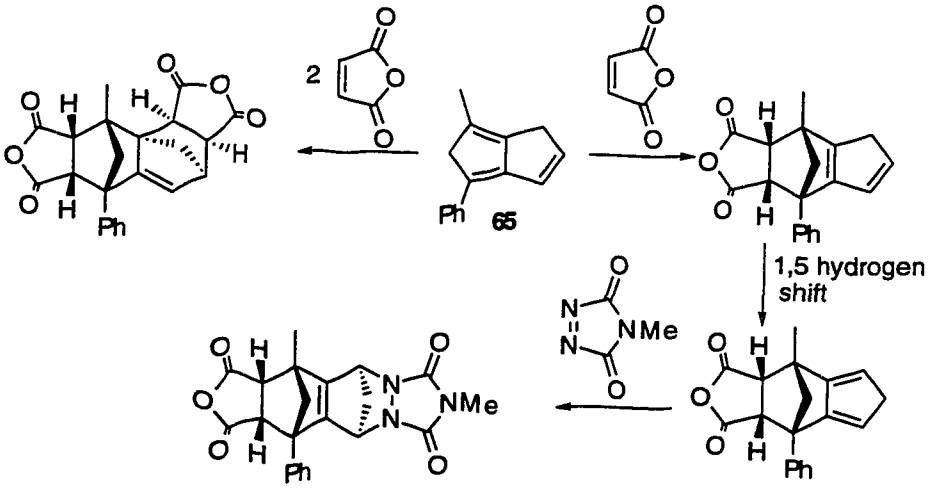
Trahanovsky employed the flash vacuum pyrolysis of 1,2,3-tri(acetoxymethyl)-cyclohexane **63**, to give 1,2,3-trimethylenecyclohexane **64**. This triene was more reactive than triene **62**, as it is locked in an *s-cis* conformation. The intermediate diene, however, is locked in the *s-trans* state after a single cycloaddition, which prevents any further Diels-Alder reaction.[25]



Scheme 28. The preparation of 1,2,3-tri(acetoxymethyl)cyclohexane.

Diels-Alder reactions have also been carried out on 1,5-dihydropentalene and its derivatives. Griesbeck and coworkers have reacted 6-methyl-4-phenyl-1,5-dihydropentalene **65** with *N*-methyl-1,2,4-triazoline-3,5-dione (NMTAD), DMAD, maleic anhydride, and *p*-benzoquinone. High concentrations of the dienophiles afforded bis-adducts after diene-transmissive Diels-Alder chemistry. Treatment of **65** with one

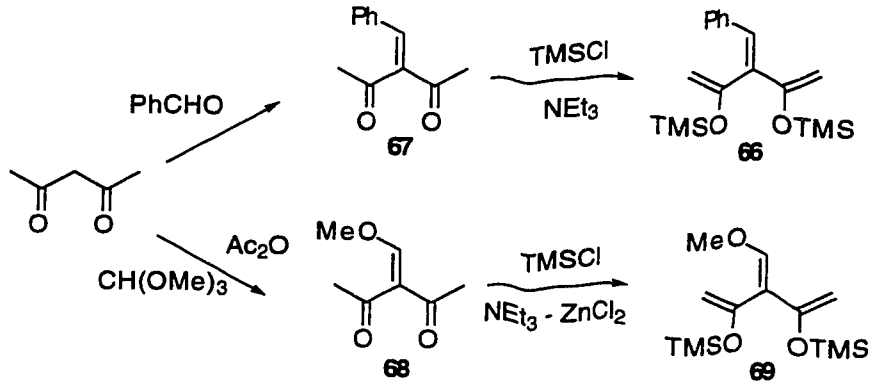
equivalent of a dienophile, followed by isomerization of the intermediate cyclopentadiene through a 1,5-hydrogen shift, and reaction with a second dienophile, led to crossed-bis-adducts.[26]



Scheme 29. The Diels-Alder chemistry of 6-methyl-4-phenyl-1,5-dihydropentalene.

5.1.4 Acyclic Derivatives of 3-Methylene-1,4-pentadiene

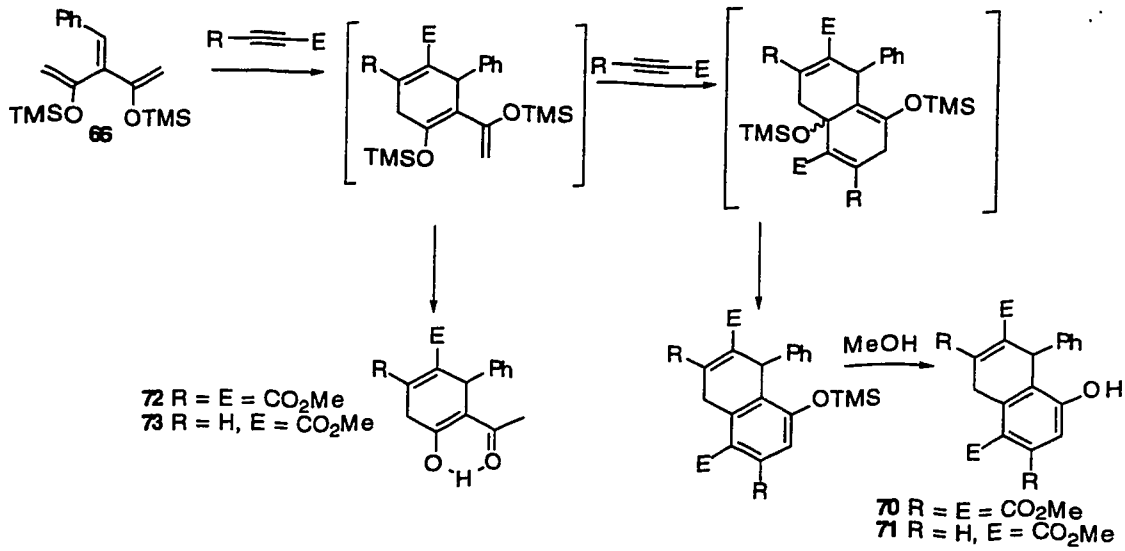
A variety of substituted cross-conjugated trienes have been synthesized and used in diene-transmissive Diels-Alder chemistry. In 1983, Tsuge and coworkers presented the first acyclic cross-conjugated triene which was sufficiently stable to be useful in organic synthesis. 3-Benzylidene-2,4-bis(trimethylsilyloxy)-1,4-pentadiene **66**, was prepared, first by the condensation of 2,4-pentanedione with benzaldehyde, to give 3-benzylidene-2,4-pentanedione **67**. Trimethylsilation of **67** with trimethylsilyl chloride (TMSCl) and NEt_3 gave triene **66**.[22] By changing the species involved in the condensation one can obtain a number of trienes.



Scheme 30. Preparation of the cross-conjugated trienes, 3-benzylidene-2,4-bis(trimethylsilyloxy)-1,4-pentadiene and 3-(methoxymethylene)-2,4-bis(trimethylsilyloxy)-1,4-pentadiene.

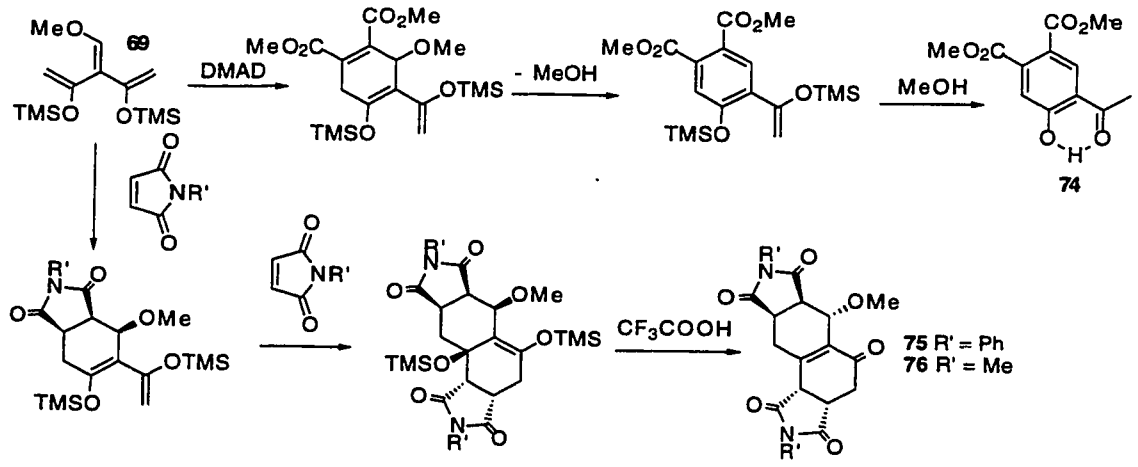
If the condensation between 2,4-pentanedione, and methyl orthoformate was employed, a second cross-conjugated triene was obtained through the trimethylsilation of methyoxymethylenepentanedione **68** to afford triene **69**. Tsuge and coworkers carried out several Diels-Alder reactions with these bis(trimethylsilyloxy) cross-conjugated trienes.

In the 3-benzylidene case, the reaction was carried out with DMAD, methyl propiolate, *N*-methylmaleimide, *N*-phenylmaleimide, and maleic anhydride. Reaction of triene **66** with excess DMAD and methyl propiolate afforded the adducts **70** and **71** in 51 % and 47 % yield, respectively, after elimination of TMSOH and de-trimethylsilylation with methanol. In the case of DMAD, the mono-adduct **72** was detected by NMR, but was not obtained in high enough yield to be isolated. In the methyl propiolate case, however, the mono-adduct **73** was isolated in a 2 % yield, and was found to exist primarily in the enol form.[22]



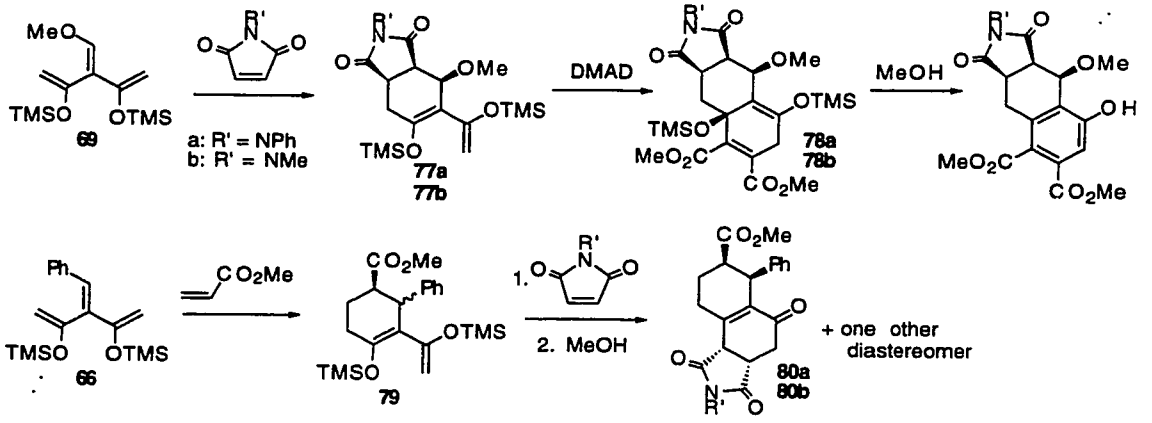
Scheme 31. The Diels-Alder reactions, and related chemistry, performed on 3-benzylidene-2,4-bis(trimethylsilyloxy)-1,4-pentadiene.

Similar work was conducted using 3-(methoxymethylene)-2,4-bis-(trimethylsilyloxy)-1,4-pentadiene **69**. Reaction with acetylenic dienophiles such as DMAD, gave exclusively the mono-adduct **74**, in yields varying from 7 - 57 %, unlike the reactions involving triene **66**. This was due to elimination of a molecule of methanol, which aromatizes the ring, preventing the second Diels-Alder reaction. Reaction with alkenic dienophiles, like *N*-phenylmaleimide, and *N*-methylmaleimide, overcame this problem, as elimination of methanol would not fully conjugate the ring. Consequently, the bis-adducts of *N*-phenylmaleimide, and *N*-methylmaleimide (**75**, **76**) were available in yields of 89 % and 90 % respectively, after de-silylation with CF_3COOH.[27]



Scheme 32. Reactions of **66** *with various dienophiles.*

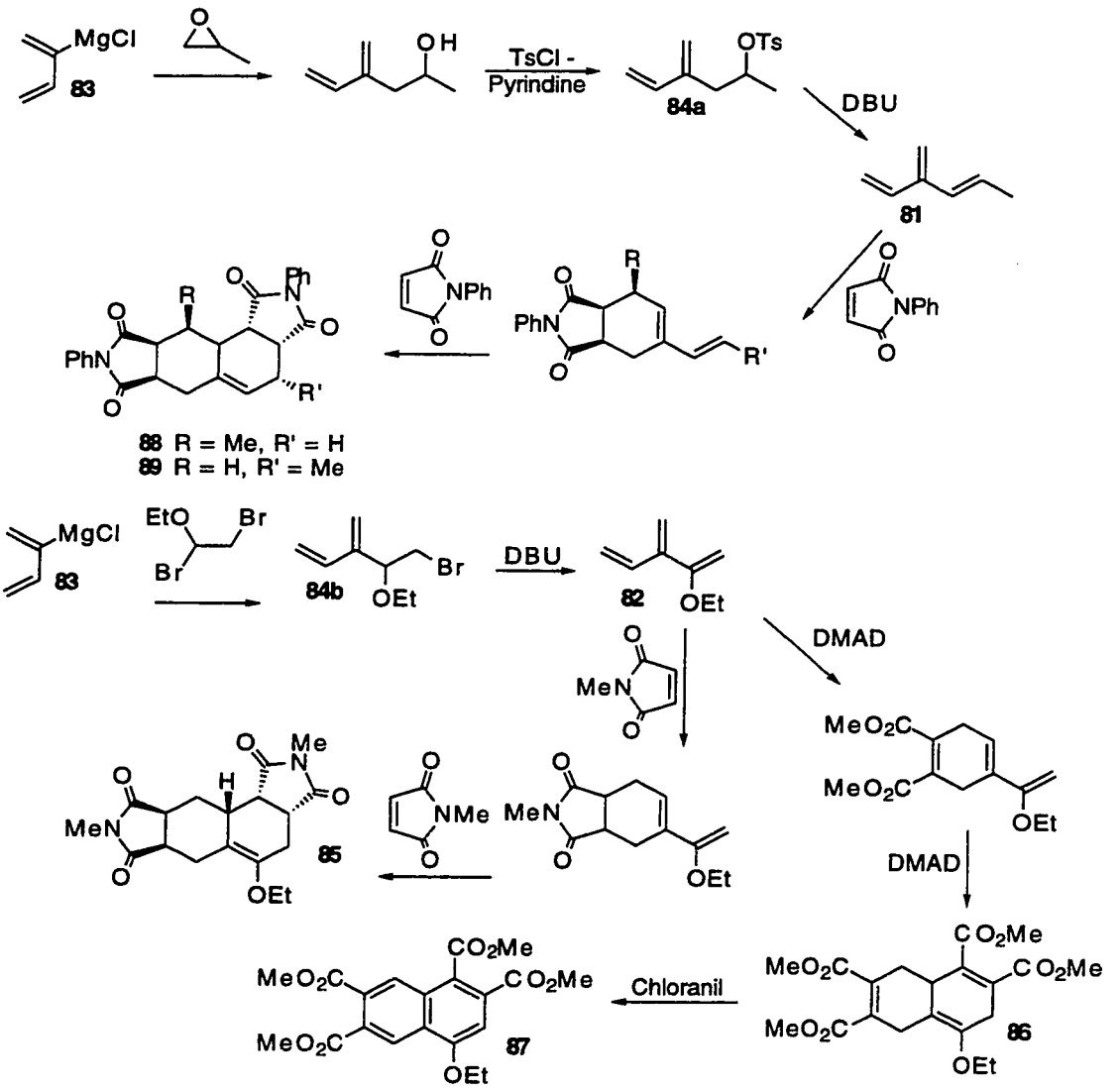
Tsuge also addressed the possibility of the reaction of mono-adducts with a dienophile different from the first, to give cross bis-adducts. Using the same trienes **66** and **69**, reactions were carried out with a variety of cyclic and acyclic dienophiles. In most cases, where the initial dienophile was cyclic (maleic anhydride, *N*-phenylmaleimide, or *N*-methylmaleimide), the second cycloaddition was highly diastereoselective. Reaction of **69** with either *N*-methylmaleimide or *N*-phenylmaleimide, gave mono-adducts **77a** and **77b**. A second reaction with DMAD, afforded adducts **78a** and **78b** as a single diastereomer (after elimination of TMSOH and de-silylation), in yields of 49 % and 41 %. In the cases where the first dienophile was acyclic, it was often found that the second addition, be it cyclic or acyclic, was not as diastereoselective. Triene **66** was reacted with methyl acrylate, adduct **79** was obtained, and was purified prior to further reaction. Adduct **79** was reacted with either *N*-methylmaleimide or *N*-phenylmaleimide followed by methanol to give adducts **80a** and **80b** respectively.[28]



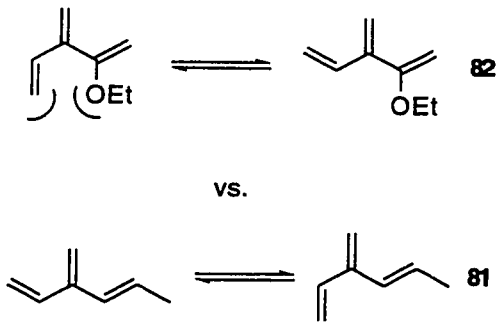
Scheme 33. Reactions of trienes **66** and **69**, to produce cross-adducts.

Tsuge did not limit his studies to bis(silyloxy) cross-conjugated trienes. Work was also carried out with *trans*-3-methylene-1,4-hexadiene **81** and 2-ethoxy-3-methylene-1,4-penadiene **82**. Reaction of (1-methylene-2-propenyl)magnesium chloride **83** with methyloxirane gave, after tosylation (TsCl, pyridine), 1-methyl-3-methylene-4-pentenyl tosylate **84a**. Elimination of the tosylate with DBU gave triene **81**. Similarly, reaction of **83** with 1,2-dibromo-1-ethoxy-ethane gave 2-(2-bromo-1-ethoxyethyl)-1,3-butandiene **84b**, which afforded triene **82**, on elimination with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Diels-Alder chemistry was carried out using these trienes with DMAD and *N*-methylmaleimide. Unlike the bis(silyloxy) trienes, trienes **81** and **82** are not symmetrical. As a consequence, two different isomers can result depending on which diene undergoes cycloadditon. Reaction of **82** with *N*-methylmaleimide gave adduct **85**, as a single isomer, in 66 % yield. Reaction with DMAD gave adduct **86**, also as one isomer, in a 63 % yield, which, upon reaction with chloranil, was dehydrogenated to naphthalene **87**, in 81 % yield. In contrast, when triene **81** was reacted with *N*-phenylmaleimide two isomers **88** and **89** were obtained. This was not the case for triene **82** and was a consequence of the

steric interaction between the ethoxy group of **82**, and the methylene group at the other end of the molecule (Scheme 35).[29]



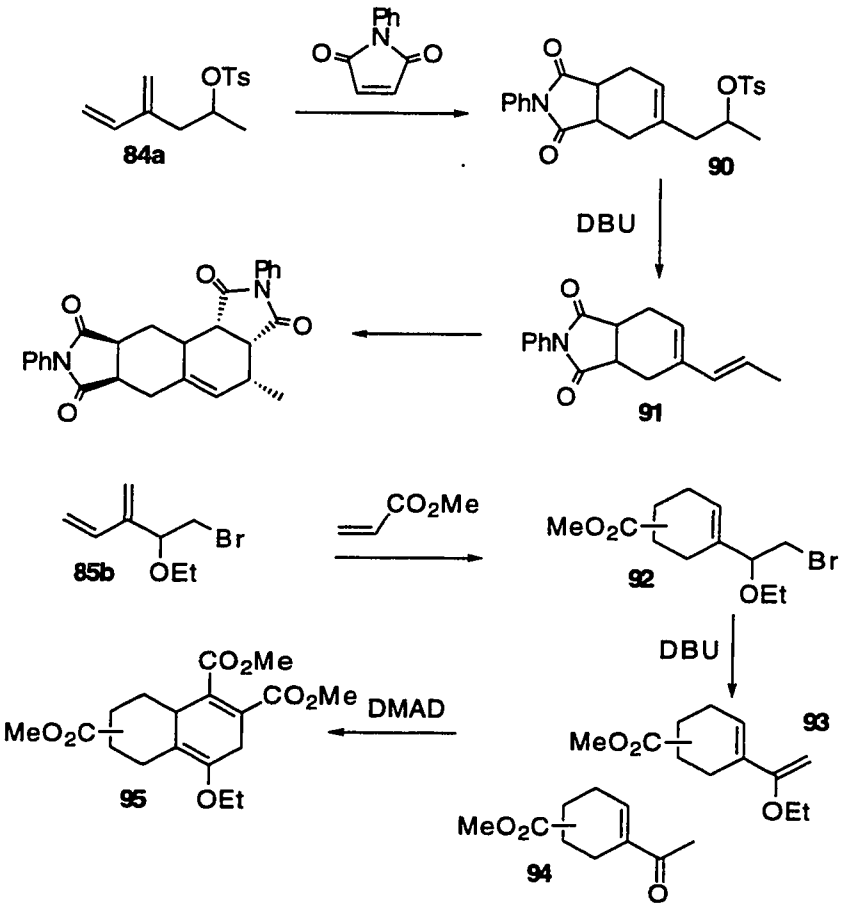
Scheme 34. The synthesis and Diels-Alder chemistry of trienes **81** and **82**.



Scheme 35. The sterics of trienes **81** and **82**.

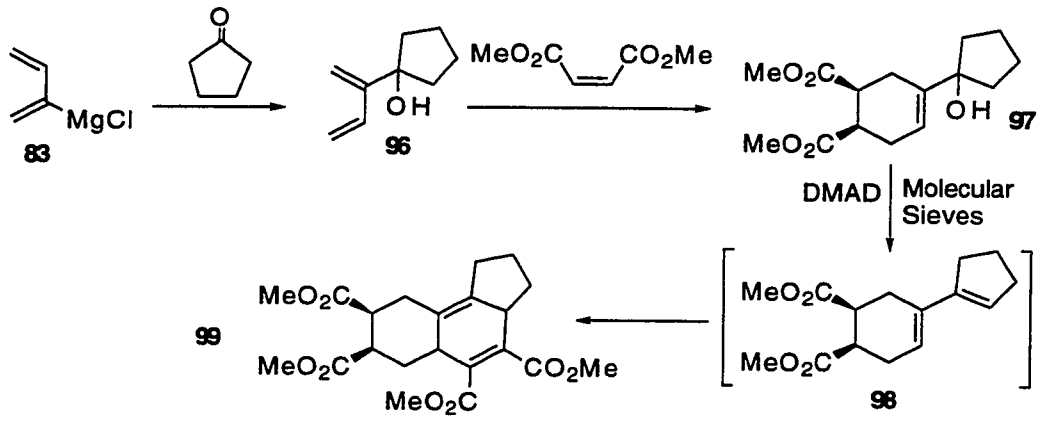
5.1.5 Synthetic Equivalents to Cross-conjugated Trienes

It should be noted a Diels-Alder reaction first, with dienes **84a** and **84b**, followed by the elimination, and subsequent reaction with a second dienophile is also possible. This makes **84a** and **84b** synthetic equivalents to the corresponding cross-conjugated trienes. Synthetic equivalents of cross-conjugated trienes offer a more selective route to adducts of unsymmetrical trienes, which normally are obtained with poor regioselectivity, and to crossed bis-adducts. Reaction of diene **84a** with *N*-phenylmaleimide gave adduct **90**, in 99 % yield, which upon elimination with DBU gave diene **91** in 91% yield. This was also carried out in one pot with an overall yield of 70 %. The subsequent reaction of diene **91** with *N*-phenylmaleimide gave the bis-adduct **89** in 78 % yield. Likewise, when diene **84b** was reacted with methyl acrylate adduct **92** was obtained in 80 % yield. Reaction of adduct **92** with DBU resulted in two products - the expected eliminated product **93** and unexpected ketone **94**. Reaction of diene **93** with DMAD gave the bis adduct **95** in a 67 % yield.[29]



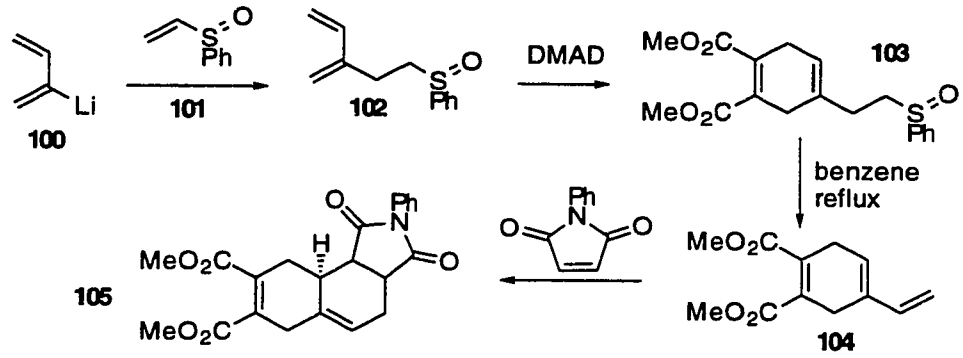
Scheme 36. Synthetic equivalents to cross-conjugated trienes.

In work related to the aforementioned, Tsuge reacted 2-(1,3-butadienyl) magnesium chloride with both cyclic and acyclic ketones. The tertiary alcohol that results could then be dehydrated in a later step after a cycloaddition. Cyclopentanone was reacted with **83**, and gave diene **96**, which was in turn reacted with dimethyl maleate, which afforded adduct **97** in 92 % yield. Dehydration of the tertiary alcohol with molecular sieves, gave a new diene **98**, which reacted with DMAD in one pot, affording bis-adduct **99** in 89 % yield.[30, 31]



Scheme 37. Tertiary alcohols as synthetic equivalents to cross-conjugated trienes.

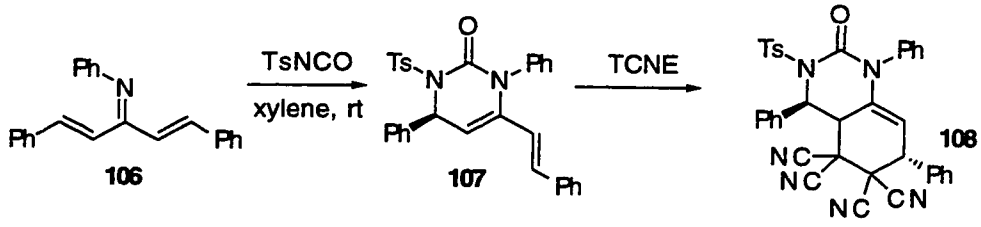
Groups other than alcohols can be eliminated, to provide the desired diene. A Michael addition was carried out between 2-lithio-1,3-butadiene **100** and phenylsulfinylethene **101**, which gave 3-methylene-5-phenylsulfinyl-1-pentene **102** in 38 % yield. Cycloaddition with DMAD gave adduct **103** in a 75 % yield. Reflux of a benzene solution of the mono-adduct caused the elimination of a benzenesulfinyl moiety, yielding diene **104**, which was trapped with *N*-phenylmaleimide, to afford bis-adduct **105** in 76 % yield.[32]



Scheme 38. Phenylsufinyl pentanes as synthetic equivalents to cross-conjugated trienes.

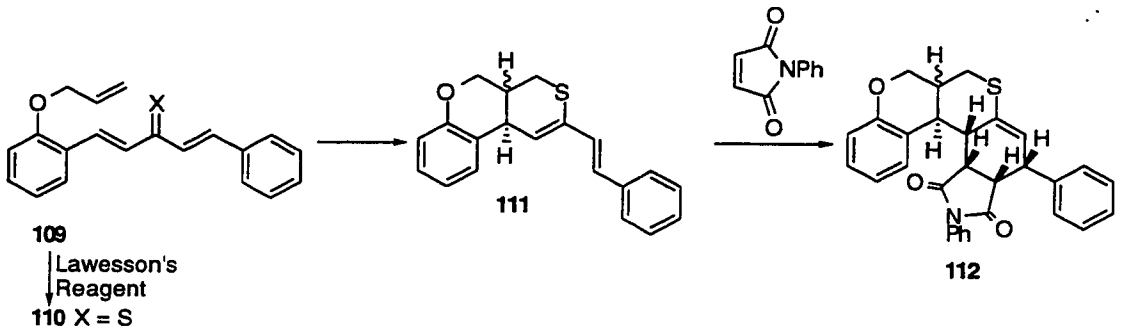
5.1.6 Diene-transmissive Hetero-Diels-Alder Chemistry

Like other Diels-Alder reactions, a heteroatom may be placed in the triene skeleton, such that a heterocycle would result. Saito and coworkers carried out work with cross-conjugated azatrienes. Reaction of azatriene **106** with tosyl isocyanate, resulted in the formation of heterocyclic diene **107**, in 90 % yield as one regioisomer. Reaction of this diene with tetracyanoethane (TCNE) then gave bis-adduct **108** in 99 % yield.



Scheme 39. The diene-transmissive hetero-Diels-Alder chemistry of azatrienes.

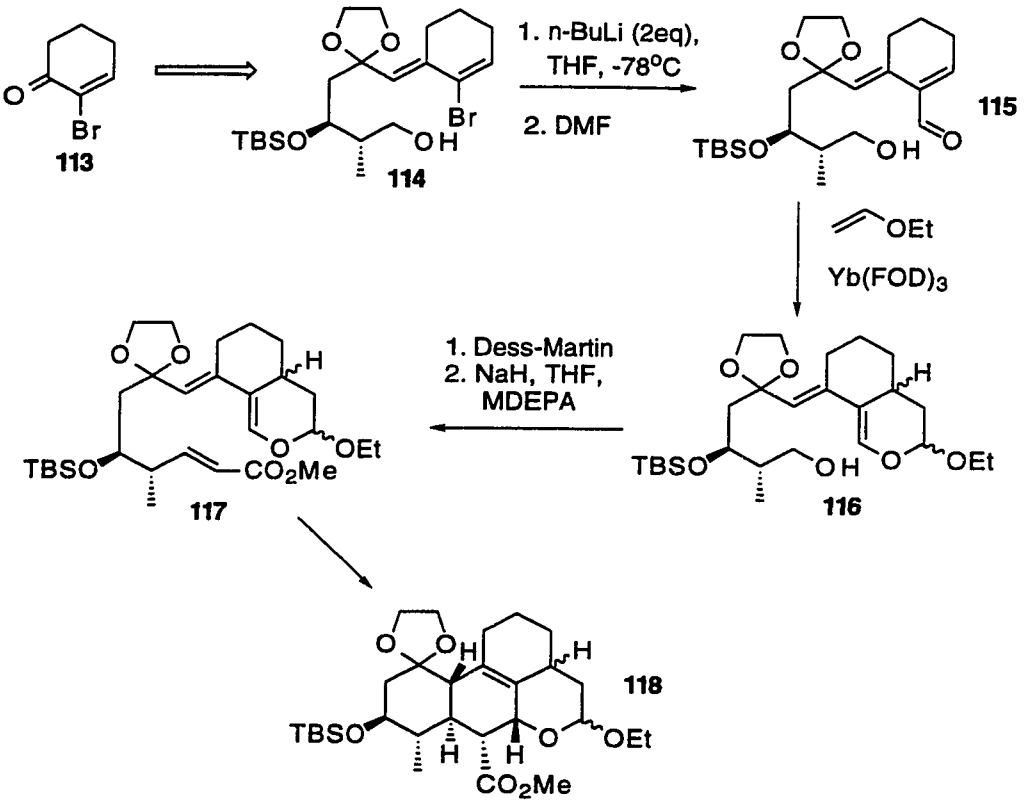
Saito also carried out hetero-Diels-Alder chemistry with thioketones. Starting with ketone **109**, possessing an (allyloxy)phenyl group, the corresponding thioketone **110** was prepared by treatment with Lawesson's reagent. The intramolecular diene-transmissive hetero-Diels-Alder reaction occurred immediately in the same pot, and afforded mono-adduct **111** in 85 % yield. The newly formed ring fusion was obtained in a ratio of 10:90 (*cis*:*trans*). Mono-adduct **111** was reacted with *N*-phenylmaleimide, to give bis-adduct **112** in quantitative yield, with the indicated stereochemistry (Scheme 40).[33, 34]



Scheme 40. The diene-transmissive hetero-Diels-Alder chemistry of thioketones.

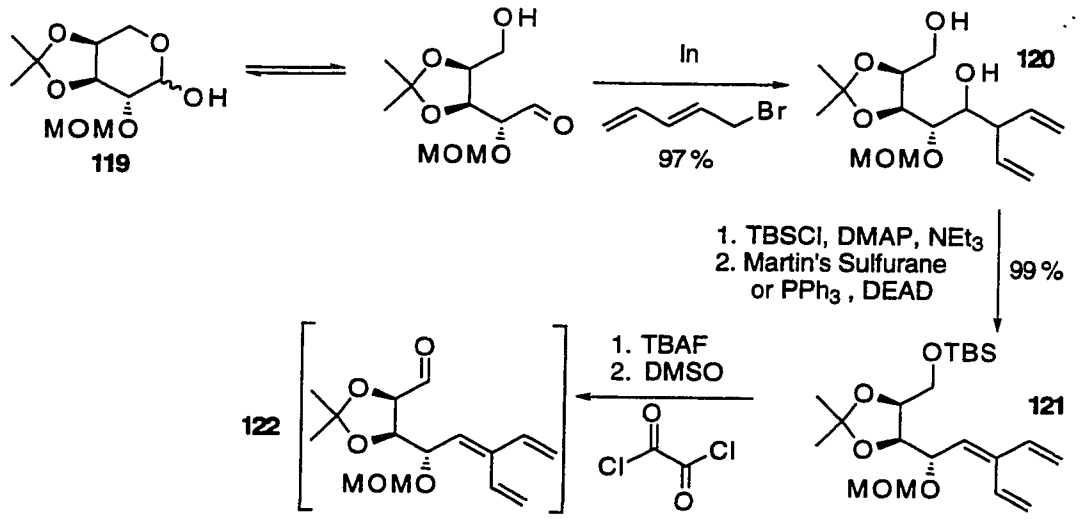
5.1.7 Diene-transmissive Diels-Alder Chemistry in Synthesis

The adaptability of the diene-transmissive Diels-Alder reaction has resulted in its used in the synthesis of natural product carbon skeletons. Spino and coworkers have used a hetero-diene-transmissive Diels-Alder approach to obtain the quassinoid framework. Bromide **113**, after several steps, was transformed into bromide **114**. Aldehyde **115** was then obtained in 80 % yield after reaction with 2 equivalents of n-BuLi and treatment of the resulting anion with *N,N*-dimethylformamide (DMF). A hetero-Diels-Alder reaction was carried out with the olefinic aldehyde and ethyl vinyl ether, under ytterbium catalysis, yielding diene **116** with good *endo* selectivity but as a 1:1 mixture of two diastereomers. Dess-Martin oxidation, followed by treatment with NaH and methyl diethylphosphonoacetate (MDEPA), gave unsaturated ester **117**. After isolation, **117** slowly underwent an intramolecular Diels-Alder reaction to the quassinoid skeleton **118**, in 89 % yield, as a mixture of diastereomers.[35, 36]



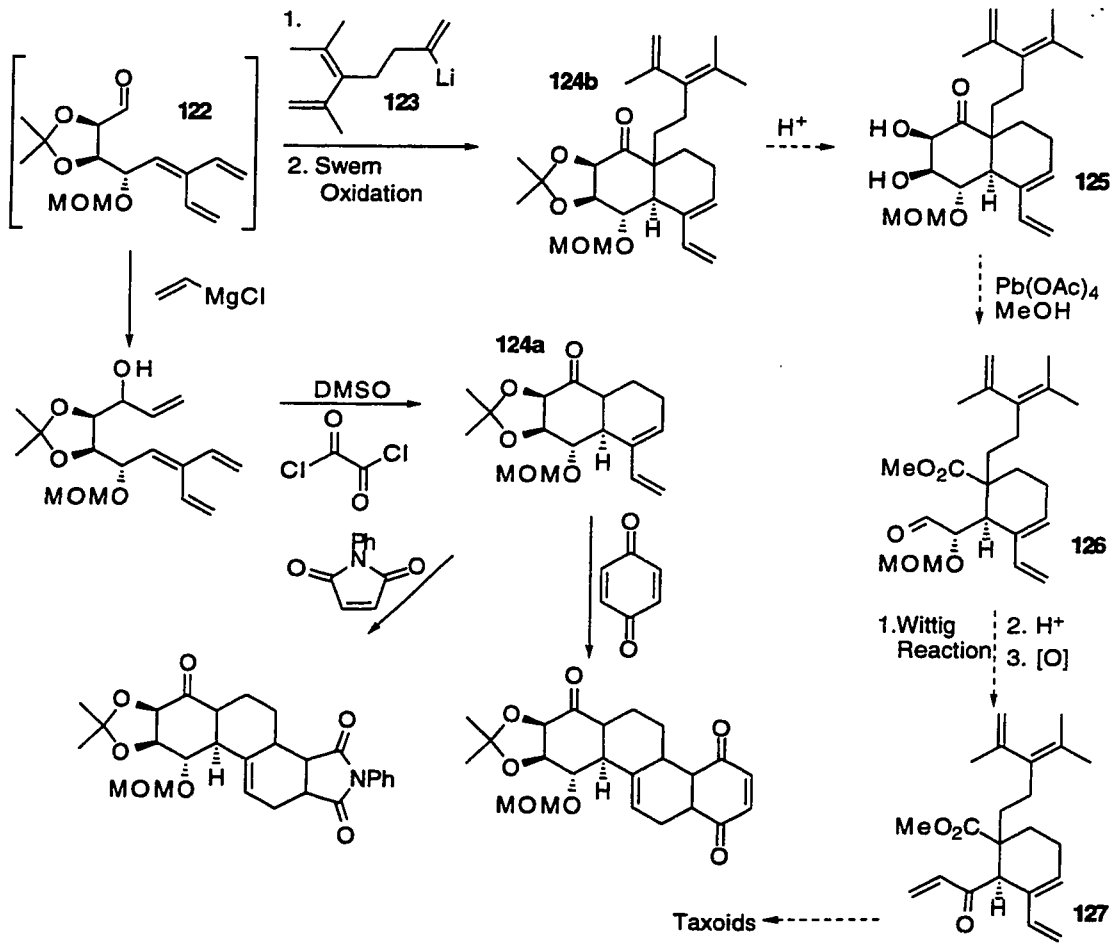
Scheme 41. Spino's approach to the quassinoid framework, using diene-transmissive hetero-Diels-Alder chemistry.

In unpublished work, Fallis and coworkers have studied the diene-transmissive Diels-Alder reaction on a route to the taxane and steroidal skeletons. Lactol **119** (in equilibrium with the hydoxy-aldehyde) was available through a series of steps from *L*-arabinose. Using an organoindium coupling reaction, secondary alcohol **120**, was obtained. Selective protection of the primary alcohol followed by dehydration of the tertiary alcohol with either Martin's sulfurane or PPh_3 / diethyl axodicarboxylate (DEAD) afforded cross-conjugated triene **121**. Deprotection of the primary alcohol with TBAF followed by Swern oxidation gave aldehyde **122**.



Scheme 42. The route to cross conjugated triene **122**.

At this point vinyl magnesium chloride was reacted with the aldehyde followed by Swern oxidation, in one pot to give steroid-like skeletons. As an alternative, side-chain **123** was installed, in a two step-procedure, if the taxane framework was desired. In either case, Swern oxidation of the resulting secondary alcohol to the ketone immediately induced Diels-Alder cycloaddition of the vinyl ketone with the cross-conjugated triene, in a manner that was so facile that the intermediate ketone could not be isolated. This resulted in either diene **124a** or **124b**. Diene **124a** was reacted with a variety of dienophiles, in particular 5-membered carbocycles, to furnish a highly functionalized steroidal-like skeleton. In conjunction, diene **124b** after several steps may afford the Taxane skeleton. Removal of the acetanide with acid would afford diol **125**, which upon reaction with two equivalents of $Pb(OAc)_4$, could give aldehyde **126**. After Wittig reaction and oxidative removal of the MOM group cyclization of **127** could give the taxane framework.



Scheme 43. Routes to steroidal-like systems and the taxane skeleton, utilizing diene-transmissive Diels-Alder chemistry and cross-conjugated trienes.

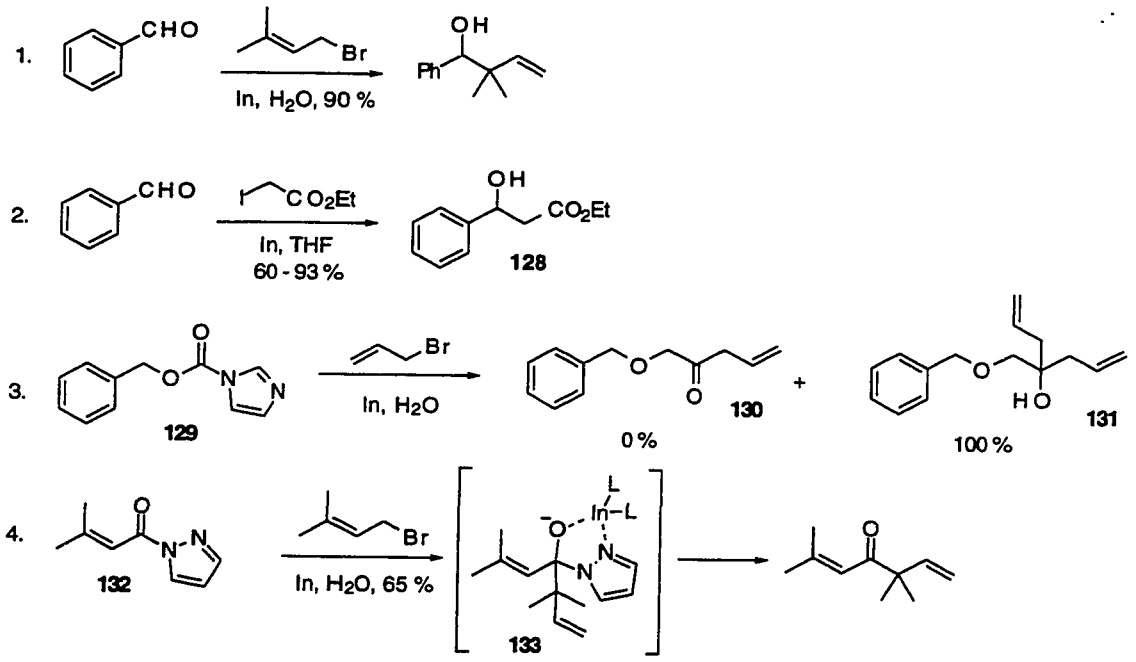
The synthesis of the steroidal skeleton provides an example of the preparation of cross-conjugated trienes employing indium mediated coupling and the subsequent study of their diene-transmissive Diels-Alder chemistry. The indium chemistry involved in the formation of carbon-carbon bonds is discussed in the next section.

5.2 Indium Mediated Chemistry

Organometallic reagents have been extensively used in organic chemistry. Particularly useful are those that are involved in carbon-carbon bond forming reactions. Metal based reagents known to effect carbon-carbon bond formation included magnesium, zinc and tin. One metal which, until recently, has been overlooked, is indium. It offers several advantages over most other metals in similar reactions. Indium can be also used in aqueous based reactions and thus there is no need to protect hydoxy groups elsewhere in the molecule.[37]

5.2.1 Reactions Mediated by Indium

Indium metal is a good mediator of several types of reaction, particularly where an addition is made to a carbonyl, or a related functional group. Indium can be used to mediate a reaction between allylic halides and an aldehyde or ketone (Scheme 44, reaction 1). It was found that under these conditions aldehydes are more reactive than ketones.[38] The allylation is not made at the carbon bearing the halide, but at the γ position through an addition elimination reaction.[39, 40, 41, 42]



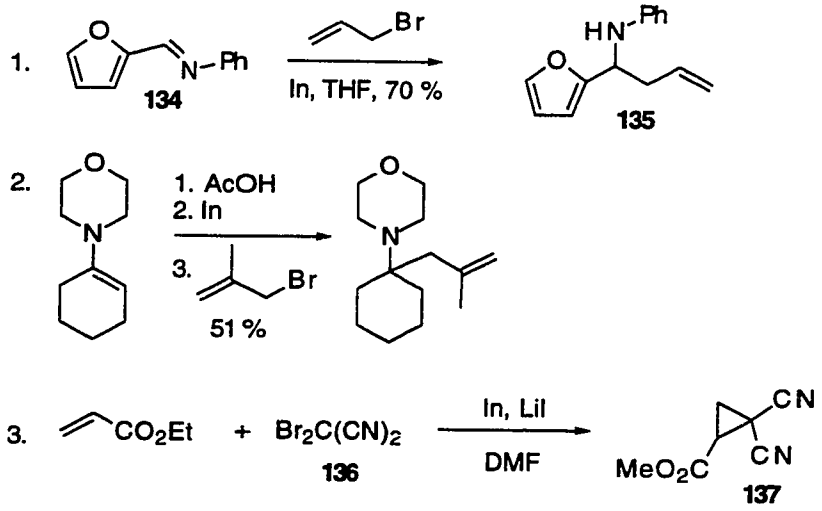
Scheme 44. Some reactions mediated by indium metal.

Indium has also been used to in a reaction similar to the Reformatsky reaction. Secondary or tertiary alcohols may be obtained when an α-haloester was treated with indium powder in the presence of an aldehyde or ketone. Ethyl iodoacetate in THF, was treated with indium powder in the presence of benzaldehyde, and the ester **128** was obtained in 60 - 93 % (reaction 2, Scheme 44).[43]

The allylation of acyloyl-imidazoles and pyrazoles has been effected using indium. An acyloyl-imidazole **129** was reacted with allyl bromide in the presence of indium gave either a symmetrical tertiary alcohol **131** (formed from an addition to the allylic ketone) or a mixture with the allylic ketone **130** (formed from a single addition to the carbonyl of the acyloyl-imidazole, followed by displacement of imidazole) (reaction 3, Scheme 44). In most cases the major product was a tertiary alcohol. If a acyloyl-

pyrazole **132** was used, however, the major product was the ketone (reaction 4, Scheme 44). This was due to the chelating ability of the second nitrogen in the pyrazole ring, as a stabilizing factor for intermediate **133**.[44]

Similarly, aldimines **134** have been efficiently allylated by indium to the secondary homoallylic amines **135**. Yields varied from 13 % to 91 % (reaction 1, Scheme 45). Low yields were found where there was an sp^3 carbon linked to the nitrogen, and high yields were obtained when there was an sp^2 carbon linked to the nitrogen.[45, 46]



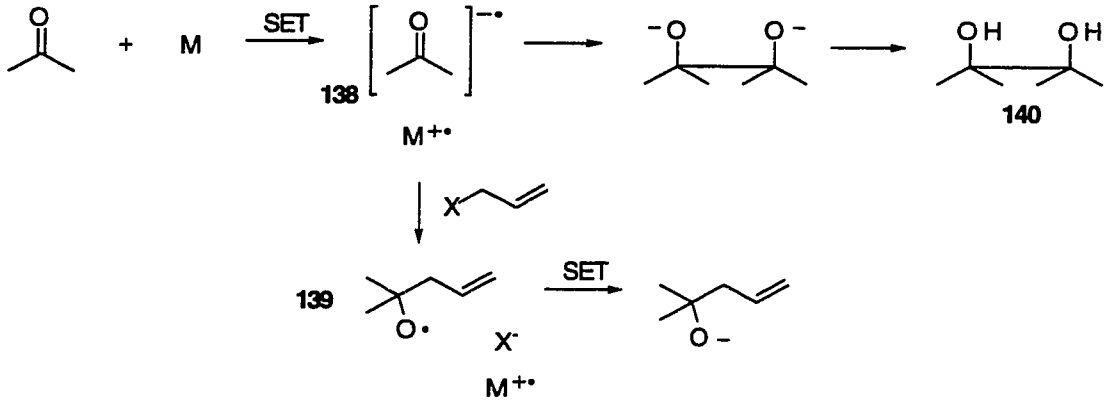
Scheme 45. Reaction of carbonyl derived species, mediated by indium.

Reaction of allyl halides with enamines have been mediated by indium. In the presence of acid an imine was formed, and further allylated by treatment with an allyl bromide and indium metal in THF. Allylation occurred at the position α to the nitrogen. In the absence of acid, the reaction reached completion in 20 hours. The addition of one equivalent of acetic acid, however, reduced the reaction time to 1 hour, with an increased

yield (reaction 2, Scheme 45).[47] Finally, indium metal was used in the formation of cyclopropanes. An alkene was treated with dibromodicyanomethane (**136**) indium metal and lithium iodide, in DMF, and cyclopropane **137** resulted, in 70 % yield (reaction 3, Scheme 45) .[48]

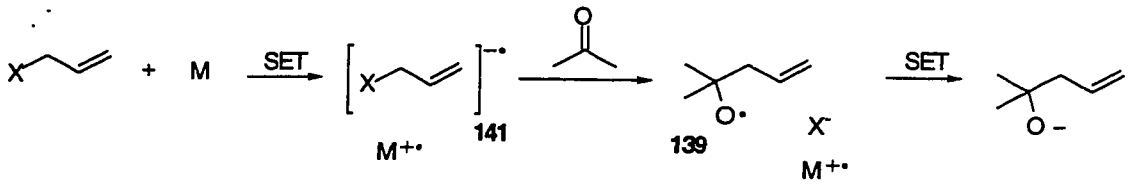
5.2.2 Mechanism of Indium Mediated Allylation

There has been considerable debate as to the exact nature of the mechanism and reactive species involved in the allylation. The first possible mechanism is that the metal reacts with the carbonyl species in a single electron transfer (SET) process to give radical anion **138**. This radical anion may then couple with the allyl bromide, to give alkoxy radical **139**. Reduction by the metal, in a second SET gives the alkoxy anion, which may then be protonated by water. This mechanism accounts for the formation of pinacol **140**, a side product of the reaction.



Scheme 46. Mechanism of allylation employing indium.

Another possible mechanism would be, first the allylic halide reacts with the metal in a SET process to give radical anion **141**, which may then couple with the carbonyl compound, to give alkoxy radical **139**. A second SET, followed by protonation, would then give the product. Neither one of these mechanisms require a reactive indium species, simply demanding that the reaction occurs on the surface of the metal.[37, 49]



Scheme 47. A second mechanism for allylation via indium.

Early papers suggested that the reactive species was R_2InX and $RInX_2$, as per the following reaction.

$$2In + 3RX \longrightarrow R_2InX + RInX_2$$

It has also been suggested the species is dimeric, with the structure of **142** ($R_4In_2X_2$). A structure similar to that of **142** is that of **143** ($R_3In_2X_3$).[37, 50, 51]

Figure 3. Two possible structures for the species involved in indium mediated allylation.

By assuming the indium center is tetravalent Paquette has proposed a transition state (Figure 4) for indium mediated allylation based on **142** and **143**. This explains why allyllation occurs at the γ position, and the diastereoselectivites he observed. Despite

this, however, there has been no evidence to fully support or dispute any of the mechanisms or species involved.[52, 53, 54, 55]

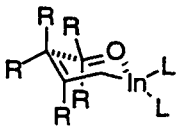
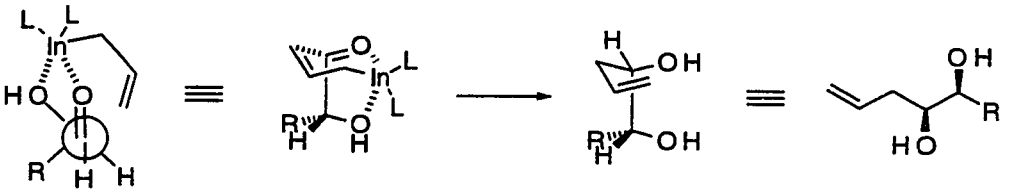


Figure 4. A general transition state for indium mediated allylation.

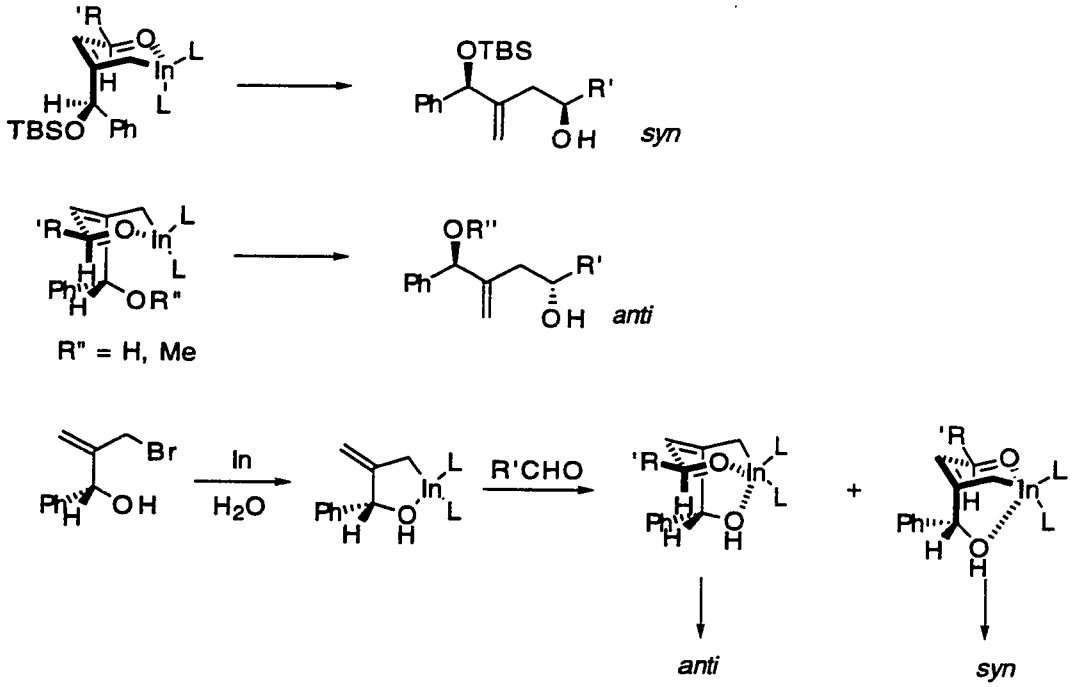
5.2.3 Stereochemical Considerations

If the product that results has more than one diastereomer, then one may discuss the proportions of the diastereomers in terms of the transition state. In general, which diastereomer results depends upon which face of the carbonyl is attacked by the indium species. A stereochemical bias may be imposed if one face of either carbonyl or allyl bromide is more sterically encumbered than the other in the lowest energy conformation. In Scheme 48 a substituted α-hydroxy-aldehyde is allylated by an allyl indium species. Chelation of both the carbonyl and hydroxyl group imposes a greater rigidity to the transition state and attack of the allyl group occurs on the less sterically hindered *re* face of the aldehyde. This results in a ratio (10.2 : 1) in favor of the *syn* diastereomer.



Scheme 48. Allylation of an α-hydroxy-aldehyde.

A β-hydroxyallylbromide was reacted with a series of aldehydes. If the hydroxyl group was protected as a TBS ether, there was a stereochemical bias for the *syn* stereoisomer (99 : 1). If a free hydroxyl group, or the methoxy group was used, there was chelation with the oxygen giving a more rigid transition state, resulting in the *anti* selectivity. This was due to the steric effect of the phenyl group.[52, 53]

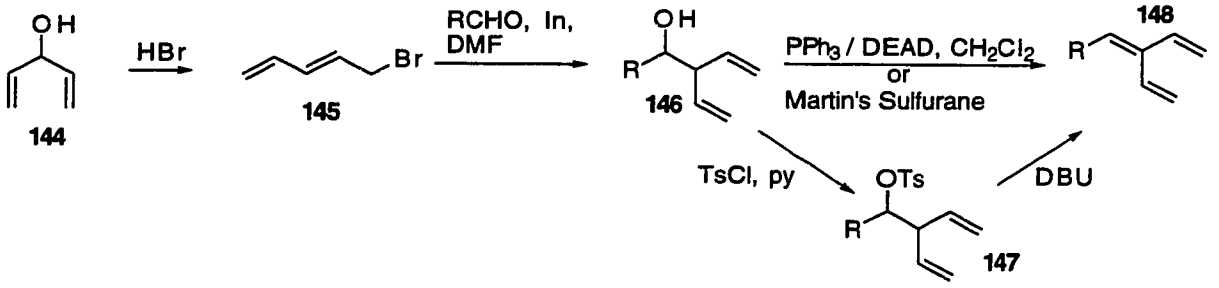


Scheme 49. Allylation with hydroxy-bromides, and derivatives thereof.

5.3 Research Objectives

5.3.1 Preparation of Cross-Conjugated Trienes

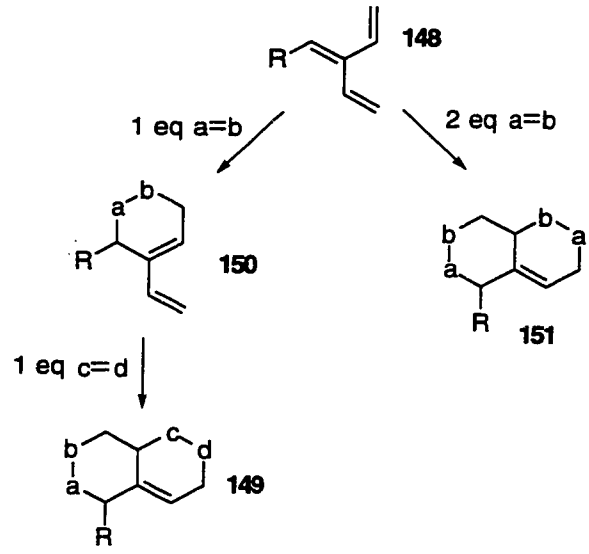
Synthesis of a series of cross-conjugated trienes could be accomplished utilizing indium chemistry in the first step, with an appropriately chosen allyl bromide and carbonyl species, followed by dehydration of the resulting secondary alcohol. If one were to react 5-bromo-1,3-pentadiene **144**, which is available from 1,4-pentadiene-3-ol **145** upon reaction with HBr, with a series of aldehydes a secondary alcohol would result. One should take care in choosing the reagent used to carry out the allylation. If one were to use *n*-butyl lithium, then addition would occur at the α position of the bromide. Indium metal, as outline previously, allylates exclusively at the γ position. The secondary alcohol **146** could be then preferentially eliminated into conjugation with the two existing double bonds. This elimination could be achieved in two steps, by first transforming the alcohol functionality into a better leaving group (a tosylate, or mesylate), and then eliminate tosylate **147** with a base such as DBU. This could also be accomplished in one step, using reagent systems like Martin's sulfurane or PPh_3/DEAD. This would provide a novel 3-methylene mono-substituted cross-conjugated triene **148**.



Scheme 50. Synthesis of 3-methylene-substituted cross-conjugated trienes.

5.3.2 Diene-transmissive Diels-Alder Study

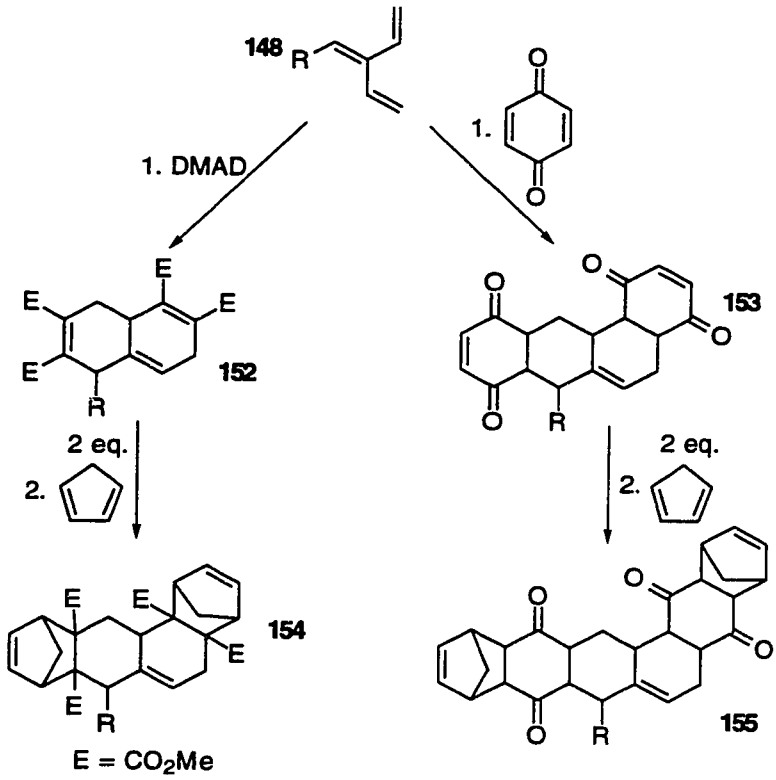
An appropriate cross-conjugated diene was selected in order to study its behavior in the diene-transmissive Diels-Alder reaction. Reaction with both cyclic *N*-phenyl-1,2,4-triazoline-3,5-dione (NPTAD), *N*-phenylmaleimide, 1,4-benzoquinone) and acyclic dienophiles (DMAD) were carried out, under various conditions. Reaction with two equivalents of a dienophile would afford bis-adducts **149**. Reaction with one equivalent of a dienophile could afford the mono-substituted adduct **150** which could be reacted further with another equivalent of the same dienophile, or a different dienophile, giving crossed bis-adducts **151**. An evaluation of both the diastereoselectivity and the determination of relative stereochemistry would then follow.



Scheme 51. Diene-transmissive Diels-Alder study of the cross-conjugated triene to be prepared.

5.3.3 Tandem Diene-Transmissive Diels-Alder and Conventional Diels-Alder Reactions

In the cases of DMAD and 1,4-benzoquinone, after the diene-transmissive Diels-Alder reaction has taken place, the resulting molecule (**C9**, **C10**) can behave as a dienophile itself. Reaction with two equivalents of a second diene, such as cyclopentadiene, would then provide molecules (**C11**, **C12**) with complicated fused and bridged ring systems. In principle, it is possible to carry out both the diene-transmissive Diels-Alder reaction and reaction of the resultant adduct (**C9**, **C10**) with the second diene in one pot, providing complex molecules from a simple triene more quickly.



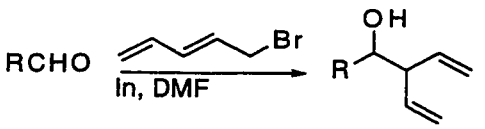
Scheme 52. Tandem diene-transmissive Diels-Alder and conventional Diels-Alder reactions.

6 Results and Discussion

6.1 The Synthesis of Cross-conjugated Trienes

6.1.1 Indium Mediated Allylations

In order to obtain the required cross-conjugated trienes, the corresponding secondary alcohols were prepared. This was accomplished through an indium mediated reaction between 5-bromo-1,3-pentadiene **156** and the aldehydes under study. First, 5-bromo-1,3-pentadiene **156** was prepared by the literature procedure of Prévost[56] from the reaction of 1,4-pentadiene-3-ol **157** with HBr. Then, indium metal 100 mesh was added to a stirring solution of the chosen aldehyde and bromide **156** in DMF giving a series of secondary alcohols. The reactions were usually complete overnight in adequate to good yields. These reactions proceeded with the usual reactivity of such indium mediated allylations, with the γ carbon bonded to the aldehyde (Table 2).[39]



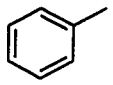
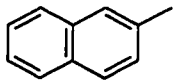
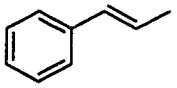
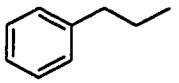
Entry	R	Product	Reaction Time (hours)	Yield (%)
1		**158**	16	51
2		**159**	17	72
3		**160**	21	90
4		**161**	13	63

Table 2. The indium mediated reaction between 5-bromo-1,3-pentadiene and a series of aldehydes

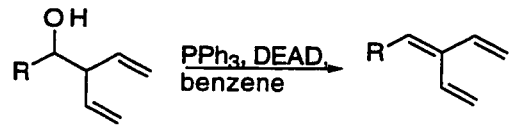
6.1.2 Dehydration of the Secondary Alcohols

There are a number of ways to dehydrate alcohols. For example, one could generate the tosylate, and eliminate with DBU, however a one-step method like Martin's Sulfurane, (carboxysulfamoyl)triethylammonium hydroxide inner salt methyl ester[57, 58] or PPh_3/DEAD would be preferred. The latter was chosen for its cost (compared to Martin's sulfurane), and ease of use. Consequently, secondary alcohol **158** was treated with PPh_3/DEAD and heated to 50-60 °C, but not enough of the desired cross-conjugated triene was isolated for characterization. There were three possible reasons for this result, the product could have been volatile and was lost during work-up, there was an inherent instability in the desired molecule and once formed it decomposed, or the set of reaction

conditions simply did not favor the desired product. The same set of dehydration conditions were carried out on secondary alcohol **159** and the desired product was isolated in only 13 % yield. This eliminated the first possibility, as triene **163** was solid. The mesylation and tosylation of alcohol **158** were attempted, but complex mixtures resulted. Dehydration was also attempted with (carboxysulfamoyl)triethylammonium hydroxide inner salt methyl ester, however none of the desired product was obtained. It was known by previous work done by the Fallis group that the dehydration product of alcohol **159** could be isolated by tosylation followed by elimination with DBU in 60 % yield for each step. Consequently, alcohol **161** was subjected to the PPh_3/DEAD dehydration conditions and the desired product was isolated in 42 % yield (Table 3). This yield, although modest, was comparable to the total yield of the tosylation procedure.

It was known that cross-conjugated trienes are subject to polymerization, but this would seem to be more prevalent for trienes **162** and **163**. The major difference between triene **165** and trienes **162** and **163** is that the triene unit is in conjugation with the aromatic ring. Synthesis of a triene that is similar to triene **165**, but is in conjugation with an aromatic ring may provide some insight. Alcohol **160** was treated with PPh_3/DEAD at 50-60 °C, however not enough product was isolated for characterization. This would seem to imply that cross-conjugated trienes which are brought in conjugation with an aromatic ring are unstable. It is known that styrene, and highly conjugated compounds in general,[59] polymerize on exposure to light, thus it is not surprising that cross-conjugated

trienes which are brought into further conjugation with an aromatic ring are also unstable. There was also the possibility that the tetraene **164**, if formed was unstable.



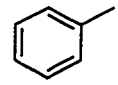
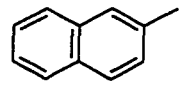
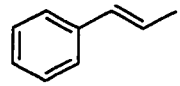
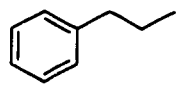
Entry	R	Product	Reaction Time (hours)	Yield (%)
1		**162**	17	0
2		**163**	19.5	13
3		**164**	16	0
4		**165**	17	42

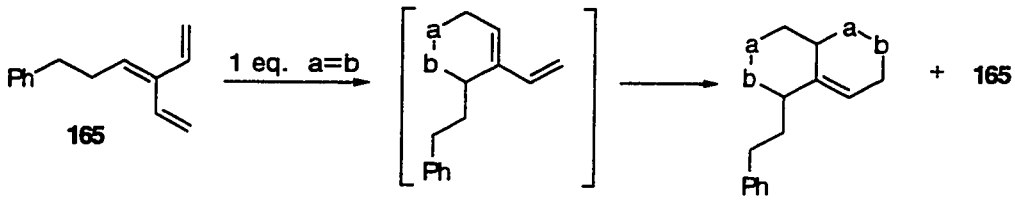
Table 3. Dehydration of the secondary alcohols.

Triene **165** was used in the Diels-Alder study since it was the compound most readily available, but it may offer some difficulty as the NMR spectra of its adducts would be more complicated than those of triene **162**.

6.2 The Diene-transmissive Diels-Alder Study

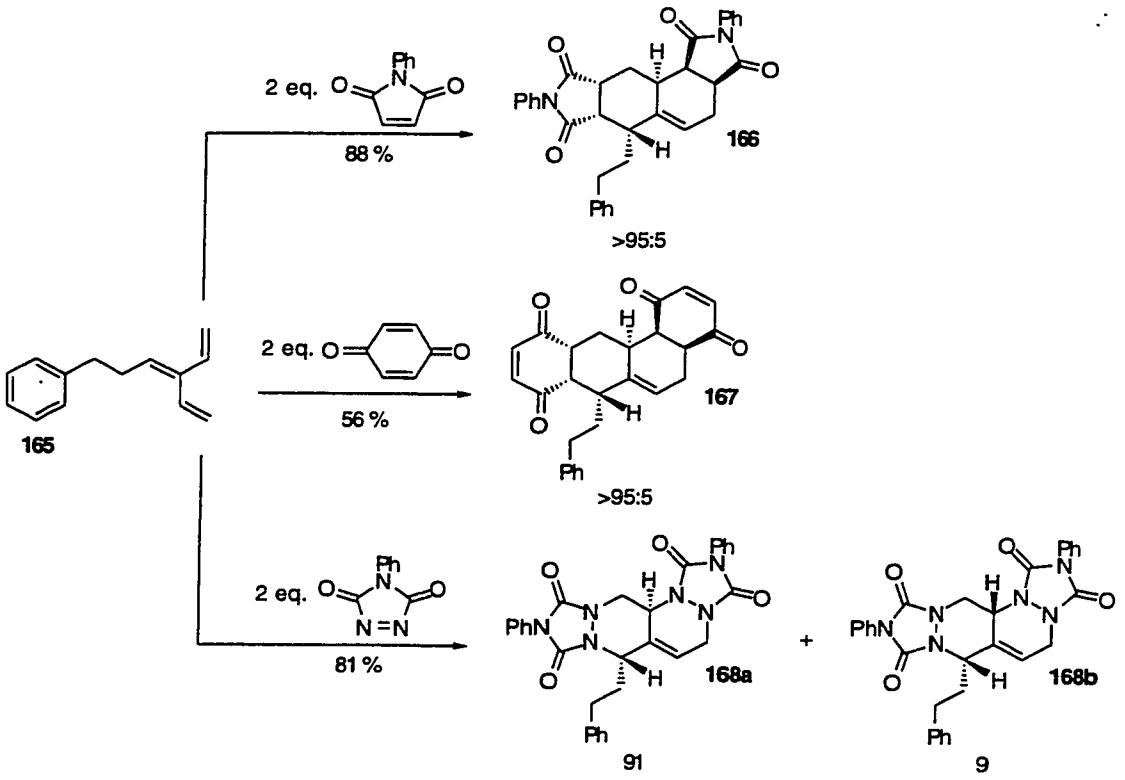
6.2.1 Reactions with Cyclic Dienophiles

Cross-conjugated triene **165** was reacted with a series of cyclic dienophiles, NPTAD, *N*-phenylmaleimide and 1,4-benzoquinone. In all cases the reaction with one equivalent of a dienophile resulted in a mixture of the bis-adduct and triene **165**, but no mono-adduct (Scheme 53). This implied that the reactivity of the mono-adducts is much higher than that of triene **165**. Nonetheless the study was continued by reacting triene **165** with two equivalents of the dienophiles.



Scheme 53. The reaction with one equivalent of a dienophile.

For *N*-phenylmaleimide and 1,4-benzoquinone, a benzene solution of triene **165** and two equivalents of the dienophile was stirred overnight. The resulting adducts **166** and **167** precipitated out of the reaction mixture with diastereoselectivities of >95:5, in 88 % and 56 % yield respectively. NPTAD was generated *in situ* by treating 2.2 equivalents of *N*-phenyl urazole with Dess-Martin periodinane in dichloromethane.[60] A dichloromethane solution of triene **165** was added, giving adduct **168** as a mixture of two diastereomers in a ratio of 91:9, in 30 minutes (Scheme 54).



Scheme 54. The diene-transmissive Diels-Alder reactions carried out.

6.2.2 Characterization of Adduct 167

NMR spectroscopy and X-ray crystallography confirmed the structure of adduct **167**. The relative stereochemistry of the system was established from the X-ray crystal structure (Figure 5, Appendix I). The ^1H NMR spectrum for the aliphatic region was well resolved and enabled assignment of nearly all the peaks. Using the HMQC[61] and DEPT[61] NMR protocols the protons of the four CH_2's were identified. Knowing that protons CH_2 11 and CH_2 12 were the only of the four which could couple with themselves, both CH_2 11 and CH_2 12 could be identified, and in turn H 1. From a COSY[61] experiment the remaining protons of the spin system were assigned. Using both

Shoolery's rules[61] and a COSY experiment, the protons of the aromatic ring were assigned. The remaining downfield protons belong to the enone systems. The ^{13}C NMR spectrum was then assigned using an HMQC experiment (Figure 6, Table 4). Due to the similar chemical environment of the enone carbons, one of them was missing in the ^{13}C NMR spectrum.

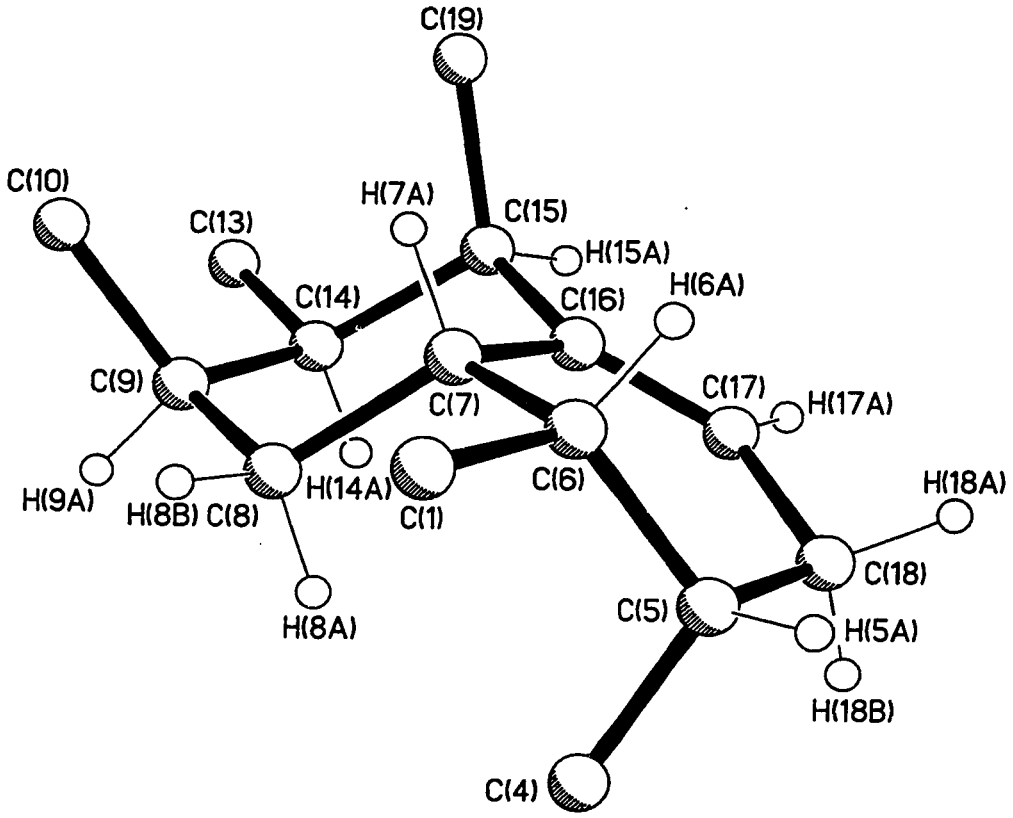


Figure 5. The abbreviated PLUTO view of adduct **167**. C19 is part of the phenethyl group, C1, C4, and C10, C13 are part of the diketone systems. H(5A), H(6A), and H(7A) are all *cis* to one another as are, H(9A), H(14A), and H(15A), and both sets are *trans* to each other.

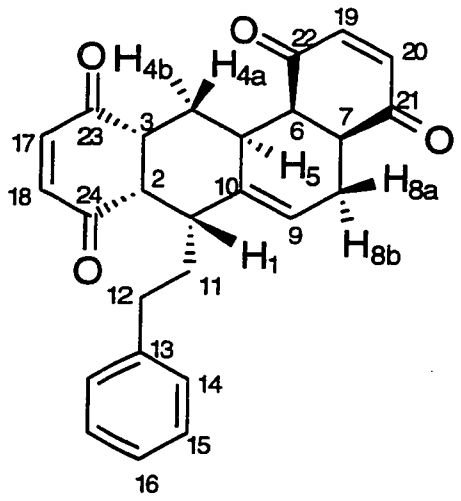


Figure 6. The numbering scheme for the NMR assignments of adduct **167**.

Number	^{1}H NMR assignment	^{13}C NMR Assignment	Number	^{1}H NMR assignment	^{13}C NMR Assignment
1	2.66-2.69	48.7	13		136.9
2	3.12-3.15	54.2	14	6.97	128.3
3	2.59-3.02	45.4	15	7.19-7.24	128.2
4	1.02, 2.12-2.14	29.2	16	7.10-7.13	125.9
5	2.56-2.65	30.7	(17/18 19/20) †	6.62-6.65 6.75-6.81	142.1,141.3 141.2
(6/7) †	3.21-3.26	43.9, 49.6			
8	2.05-2.10, 2.85	21.2			
9	5.56-5.57	120.7	(21/22 23/24) †	N/A	197.8, 198.7 199.8, 200.5
10	N/A	140.8			
11	1.22-1.30, 1.38-1.46	30.4			
12	2.20-2.26, 2.32-2.38	34.0			

Table 4. ^{1}H and ^{13}C NMR assignments for adduct **167**. † The assignments for these groups of protons was ambiguous.

6.2.3 Characterization of Adduct 166

The ^{1}H NMR spectrum for adduct **166** was not as cleanly resolved as that of adduct **167**, consequently all signals could not be assigned unambiguously. The partial assignments made follow (Figure 7, Table 5). As with adduct **167**, identification of the protons belonging to each CH_2 was made with an HMQC experiment and DEPT experiment. No concrete comment could be made as to the relative stereochemistry since all the CH's of the molecule were not resolved in the ^{1}H NMR spectrum. Based on the known structure of adduct **167**, a possible stereochemistry was proposed.

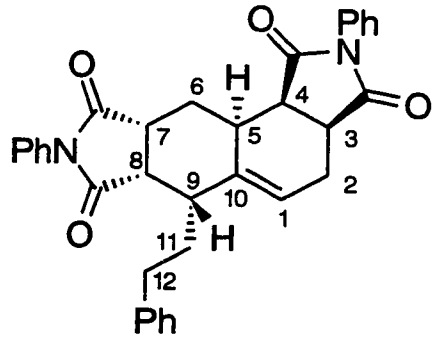


Figure 7. The numbering Scheme for the ^{1}H NMR assignments of adduct **166**.

^{1}H NMR Peak set	Possible ^{1}H NMR assignment
2.02-2.09	12
2.10-2.15	2
2.21-2.28	12
2.33-2.36	7 or 5
2.46-2.50	6
2.63-2.69	11 and (8 or 4)
2.83-2.94	2, 6 and 11
3.20-3.26	3 and (8 or 4)
3.34-3.42	9 and (7 or 5)
5.82-5.84	1
7.12-7.47	Ph

Table 5. The ^{1}H NMR assignments made for adduct **166**.

6.2.4 Characterization of Adduct 168

The NMR spectra of adduct **168** were considerably simpler than those of adducts **166** and **167** since adduct **168** contained four nitrogen atoms. As with the previous adducts the protons associated with the CH_2 's were identified. The hydrogens at H_1 and H_2 are the only CH_2 's which couple with each other. Thus, based on the chemical shift of H_7, and from a COSY experiment the aliphatic protons were assigned. From an HMQC experiment, the carbons associated with these protons were assigned. The aromatic region was quite cluttered, as the molecule has three phenyl groups, two of which are in very similar chemical environments, so the aromatic peaks could not be assigned with any certainty. The relative stereochemistry of this system was assigned in part, by the theory and the NOESY experiment[61]. Both diastereomers were isolated. The presence of a NOESY interaction between protons 3 and 5 in one diastereomer, and the lack of that interaction in the other diastereomer, helped establish the stereochemistry.

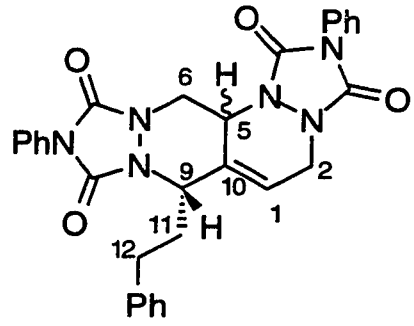


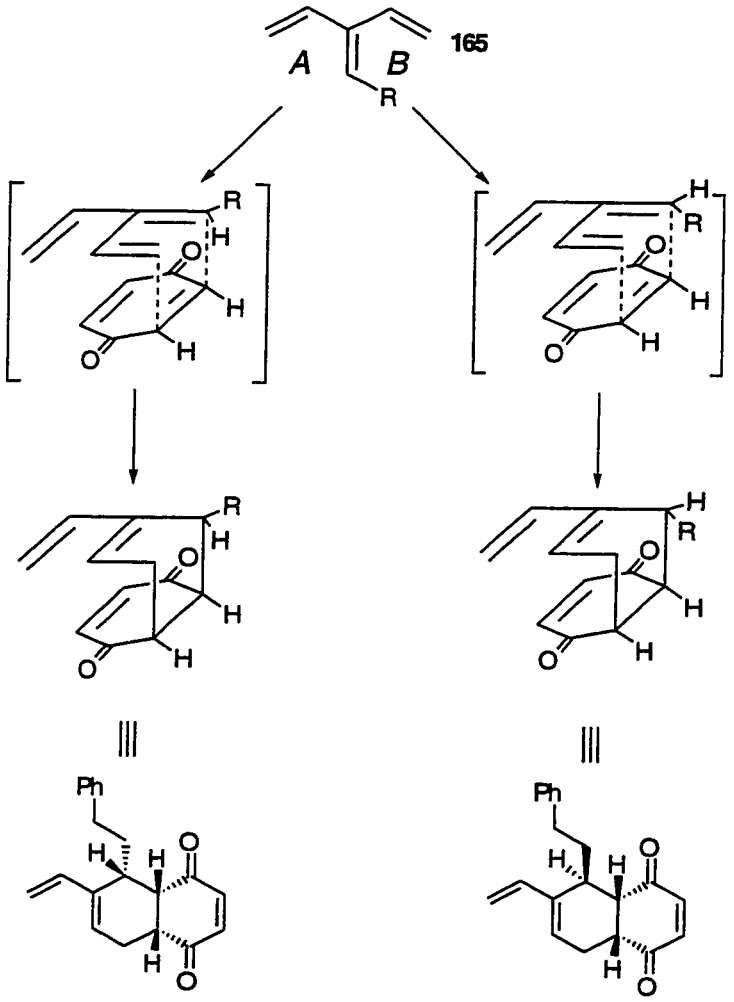
Figure 8. The numbering scheme for the ^1H and ^{13}C NMR assignments of adduct **168a** and **168b**.

Number or functional group	^{1}H NMR Assignment **168a**	^{13}C NMR Assignment **168a**	^{1}H NMR Assignment **168b**	^{13}C NMR Assignment **168b**
12	2.62-2.73	32.1	2.79-2.92	31.2
11	2.10-2.18, 2.23-2.30	30.7	2.52-2.58 ††	33.1
9	4.83	59.4	††	58.2
6	3.19, 5.08	47.4	3.41 ††	45.8
5	4.73-4.77	50.9	4.67-4.70	52.6
2	4.14-4.18, 4.28-4.33	42.9	††	43.4
1	6.12-6.13	121.3	6.13	119.0
10	N/A	140.4	N/A	141.2
C=O	N/A	151.1, 152.0, 152.6, 153.1	N/A	152.7, 151.1 ††
CPh NPh	7.20-7.23, 7.30-7.39 7.40-7.55	125.9-131.7 †	††	130.7, 126.6, 126.2 ††

Table 6. ^{1}H and ^{13}C NMR assignments for adducts **168a** and **168b**. † see the experimental section. †† Remainder buried under spectrum for **168a**.

6.2.5 Theoretical Aspects of the Stereochemical Outcome

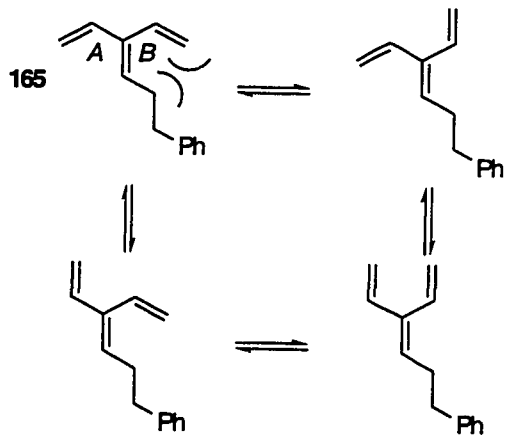
Considering the number of possible stereochemical outcomes the fact that only one diastereomer was observed seems quite astonishing. First, one should consider the initial Diels-Alder reaction that can occur. Triene **165** is composed of two dienes, *A* and *B* (Scheme 55), and a dienophile could react with either. Depending on which it reacts with first, two stereochemical outcomes are possible assuming preferential *endo* attack.[a38]



Scheme 55. The outcome of attack on diene *A* and *B* in triene **165** (R = CH_2CH_2Ph).

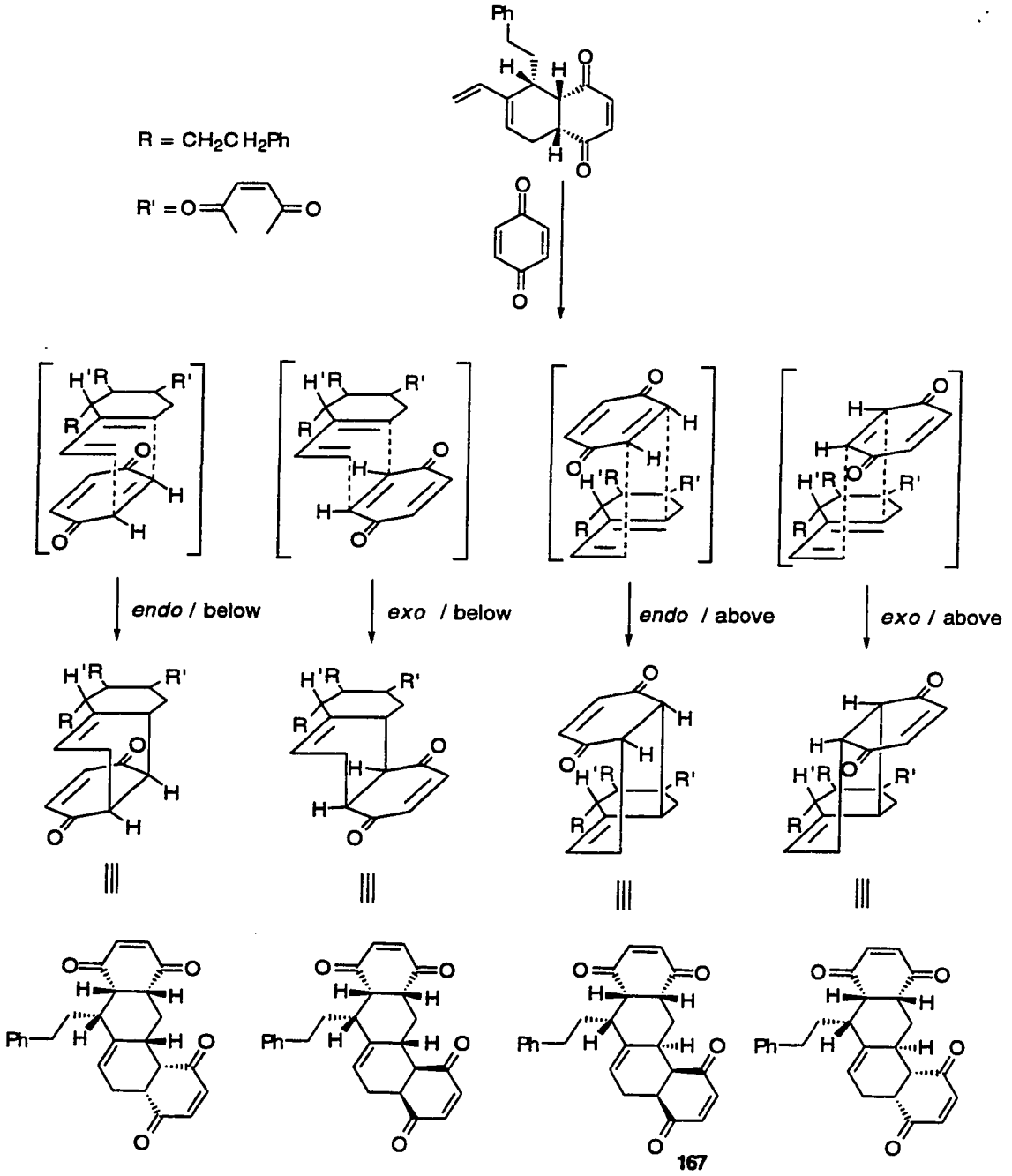
The outcome of attack on *A* has the stereochemistry in adduct **167**. There was a difference in the reactivity of the dienes *A* and *B*. Due to the steric interaction between the phenethyl group and the vinyl group *cis* to it, diene *B* is primarily in the *s-trans* state. Diene *A*, with no such interaction, would have its equilibrium shifted further toward the *s-cis* state, and would be more reactive (Scheme 56). This difference in reactivity could explain the observed stereochemistry of the ring junction initially formed in the product.

Since only one diastereomer was observed, this also means that the attack of the first diene equivalent occurred only in an *endo* fashion, which is quite unusual for a flexible open chain diene.



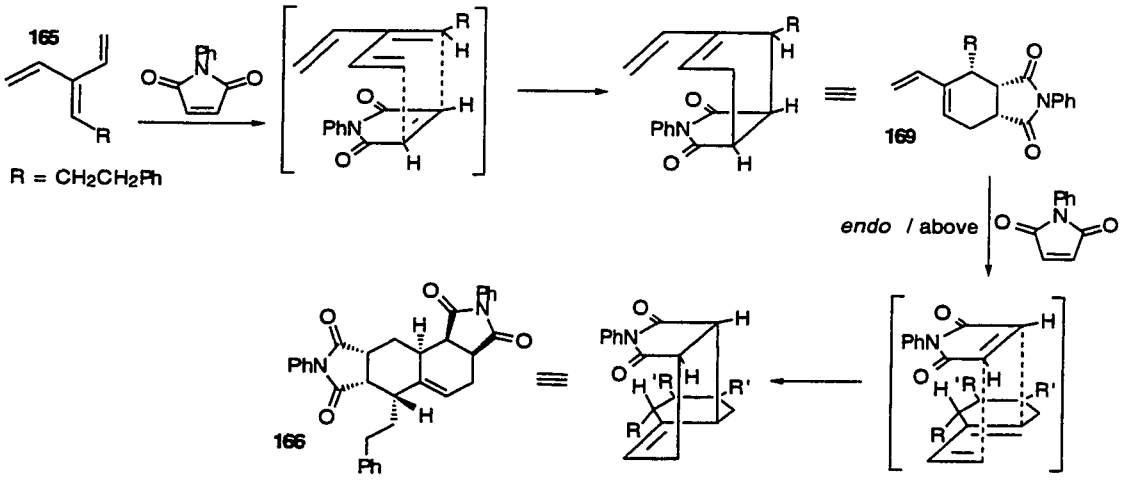
Scheme 56. The conformers of triene **165**.

The second diene equivalent may also attack in several ways (Scheme 57). There are two different faces of the diene which the dienophile can attack in either an *endo* or *exo* fashion. *Endo* attack from above results in adduct **167**. The high degree of facial selectivity can be accounted for on the basis of steric interactions. The phenethyl group and the quinone function, from the first Diels-Alder reaction are both down (below the plane of the paper). This imparts a high degree of steric bulk to that face of the diene, forcing attack from the opposite face. The phenethyl group does not have as much influence as the quinone function (evidence for this will follow).



Scheme 57. The possible stereochemical outcomes of attack on the intermediate diene.

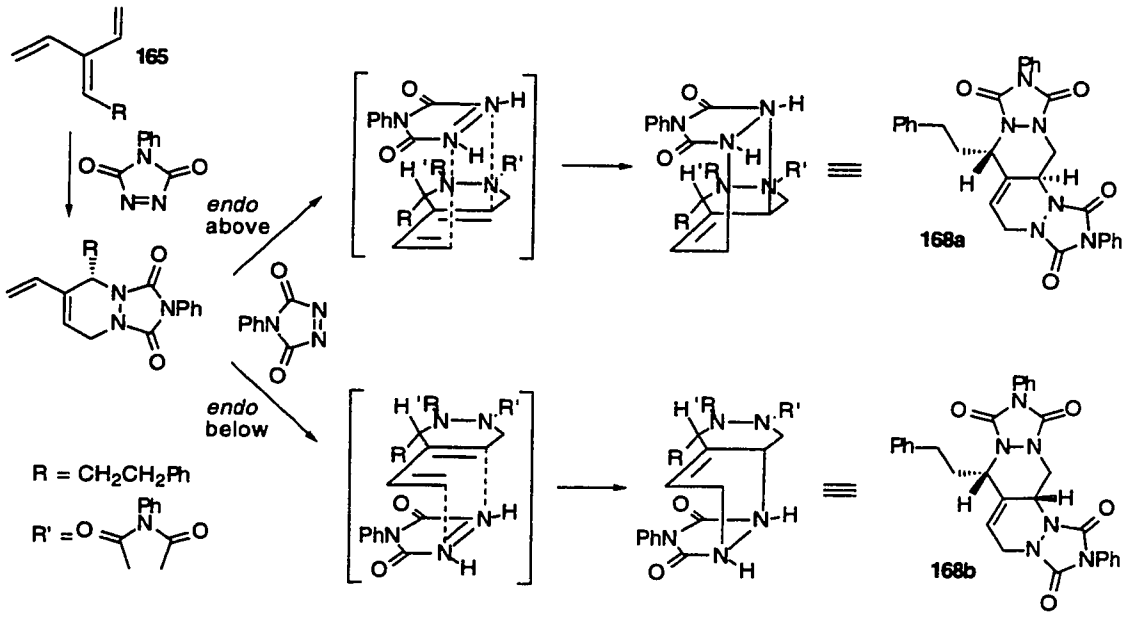
Using this argument, the stereochemical outcome for the Diels-Alder reaction between triene **165** and *N*-phenylmaleimide can be predicted, as *N*-phenylmaleimide and 1,4-benzoquinone are similar (both are cyclic, electron poor dienophiles). So *endo* attack of *N*-phenylmaleimide with triene **165** gives diene **169**. A second *endo* attack from the top face of diene **169** gives adduct **166** with the proposed stereochemistry (Scheme 58). The *N*-phenyl group would add to the steric bulk of the back face of diene **169** but in light of the results from adduct **167** it is of little consequence.



Scheme 58. The formation of adduct **166**, the transition states involved, and the proposed stereochemistry.

The selectivity of the adduct formed from cycloaddition of NPTAD with triene **165** was not as high as those of adducts **166** and **167**. When diene **169** forms, a set of diastereomers results as nitrogen has a pyramidal shape. Nitrogen, however, can invert allowing the diastereomers to interconvert, leaving the two CH's as the only two fixed chiral centers. The relative stereochemistry of the two CH's in adduct **168** was determined by the second cycloaddition, as attack of the first NPTAD molecule from

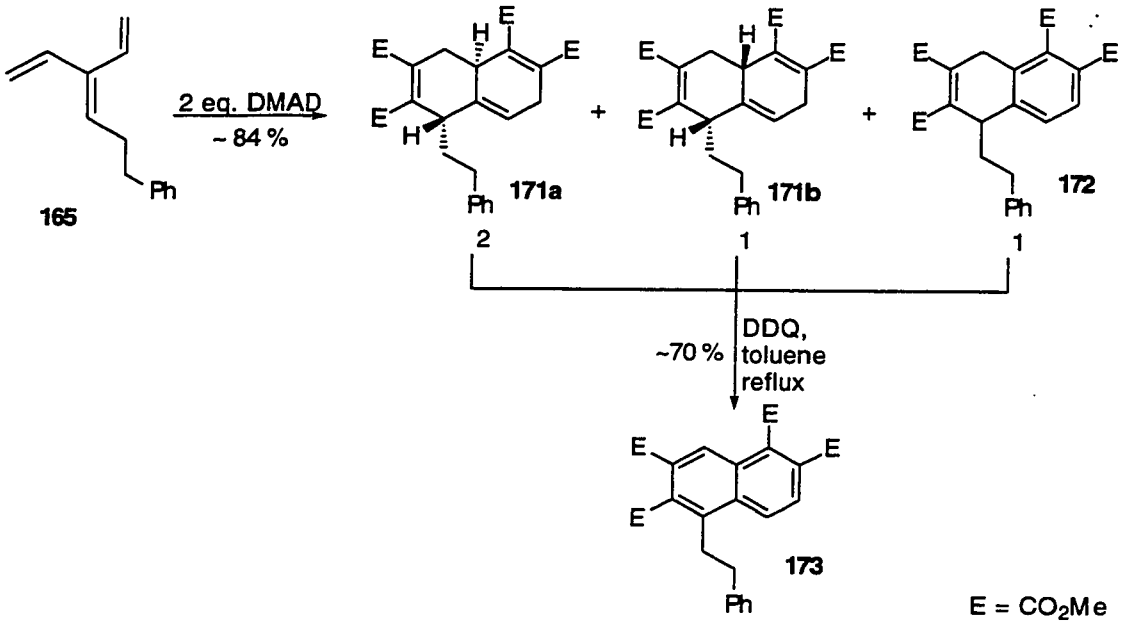
either face of triene **165**, in either *endo* or *exo* fashion could only give two configurations for the first CH. The junction formed in the first addition contains two nitrogen atoms, and would not be fixed in one configuration, unlike the analogous junctions in adducts **166** and **167**. As a result the *N*-phenyl urazole ring is not always on the back face of the diene (same side as the phenethyl group), but can also be on the top face. This, on average, reduces the amount of steric bulk on the back face of the diene compared to adducts **166** and **167**, giving the second NPTAD molecule a better opportunity to attack the back face resulting in the second diastereomer. The phenyl group however is fixed in place and still can protect the back face, so the diastereomeric ratio would be in favor of the *trans* diastereomer (Scheme 59).



Scheme 59. The formation of adduct **168**, the transition states involved, and the proposed stereochemistry.

6.2.6 The Reaction with an Acyclic Dienophile

Triene **165** was reacted with DMAD, in the hopes of developing a tandem reaction with cyclopentadiene, but this reaction was not quite as straight forward as those of the aforementioned dienophiles. Reaction with one equivalent of DMAD in refluxing benzene resulted in little of desired adduct **170**, and significant amounts of starting material were recovered. It was likely that none of the of the intermediate diene would be detected, considering the results in the previous section. Reaction of triene **165** with two equivalents DMAD in refluxing benzene still gave an incomplete reaction. Reaction by reflux of two equivalents of DMAD in refluxing toluene was quite sluggish. Finally, reaction of triene **165** with three equivalents of DMAD in refluxing toluene gave a complete reaction after 24 hours. It was concluded that adducts **171a**, and **171b**, along with singly aromatized adduct **172** were in the reaction mixture in a ratio of approximately 2:1:1 respectively. Discussion of the proposed stereochemistry will follow. The fractions containing **171a**, **171b** and **172** could not be further purified, even with recycling preparative HPLC. In order to prove that the carbon skeleton was in hand, and that the Diels-Alder reaction must have occurred, the product mixture was aromatized with DDQ. Reaction with one equivalent of DDQ in refluxing toluene afforded a mixture of the partially and fully aromatized adduct which could not be separated. When two equivalents of DDQ were used the completely aromatized adduct **173** was isolated in 70 % yield (Scheme 60).



Scheme 60. The reaction of triene **165** with DMAD, and aromatization of adduct **171**.

6.2.7 Characterizations Related to the Reaction of DMAD with Triene 165

Due to the complexity of the ^{1}H NMR spectrum the protons could not be fully assigned. The olefinic protons of both diastereomers could be easily assigned. The singlets associated with the methyl groups (~3.7-4.1 ppm), overlapped in both the proton and carbon spectrum. There were several multiplets associated with the phenyl groups. From the ^{13}C NMR and the DEPT, there were 7 CH_2's and 12 carbonyls in total. This in combination with the doublets at ~7.35 and ~7.90 ppm support the formation of **172** (Figure 9).

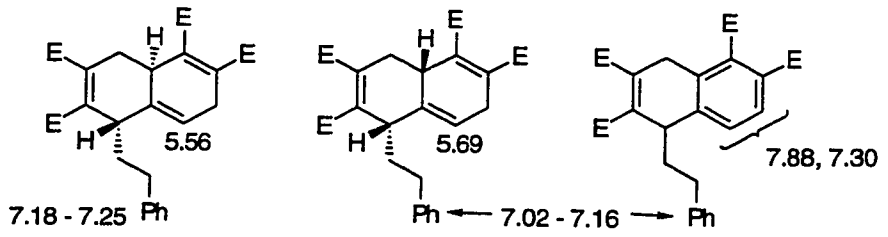


Figure 9. The partial ^{1}H NMR assignments for the reaction of DMAD with triene **165**, E = CO_2Me.

Dehydration with DDQ gave a substantial decrease in the complexity of the ^{1}H NMR spectra. Only 2 multiplets associated with the CH_2's (~2.9-3.3 ppm), 4 singlets (~4.0 ppm) that belonged to the methyl groups and the appropriate peaks associated with the aromatic rings were found. The spectra could not be assigned unambiguously due to similarities in chemical environment of the methyl groups and CH_2's (Figure 10).

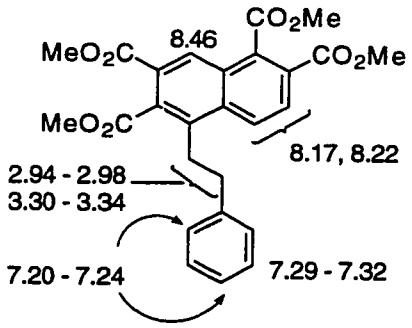
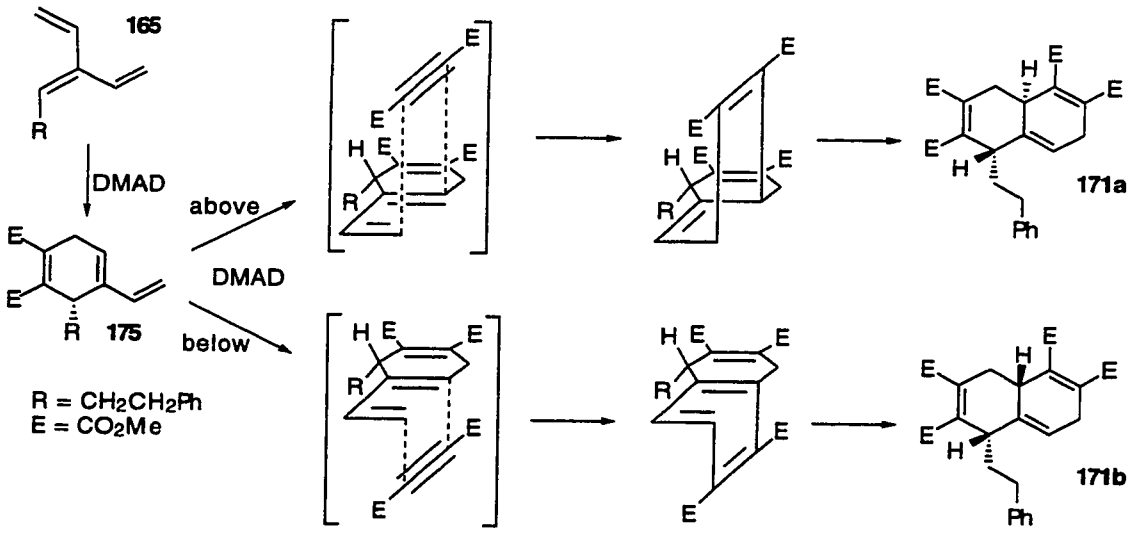


Figure 10. The ^{1}H NMR assignments for **172**. Methyl groups at 3.94, 3.96, 3.97, and 4.10 ppm.

6.2.8 Theoretical Considerations in the DMAD Reaction

Although diene *A* is more reactive than diene *B* (in **165**), the high temperature would have allowed reaction with diene *B*. Whichever diene DMAD reacted with first the only possible mono-adduct would have been **174**. Reaction of the second equivalent of DMAD must have occurred at either face of **175**, however the phenethyl group could

have provided some steric hindrance to one face of the diene causing a slight selectivity for the *trans* diastereomer. The selectivity in this reaction was much lower than that involving the cyclic dienophiles. This was due not only due to the high temperature, but also the high degree of planarity of **175**. This implied that the extra steric bulk provided to the back face of their mono-adducts by the cyclic dienophiles was crucial to the high diastereoselectivities.



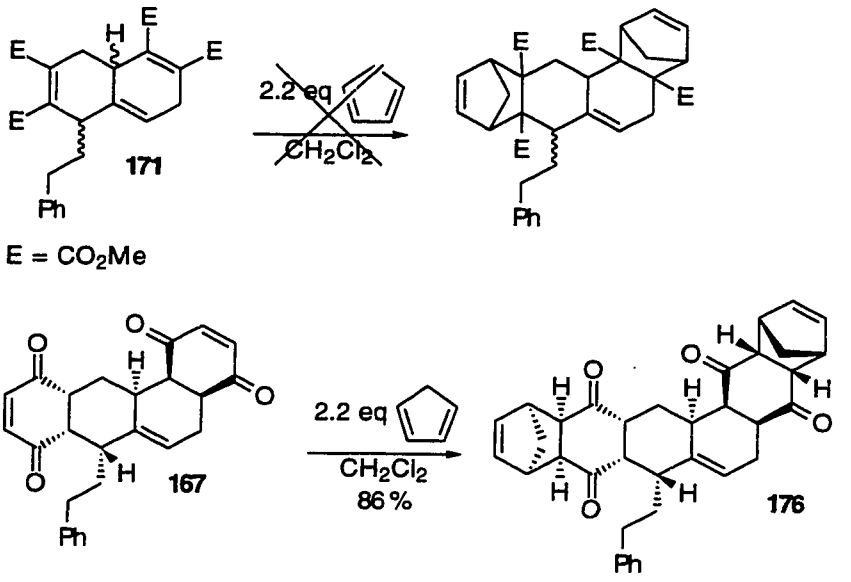
Scheme 61. Proposed intermediates and stereochemistry for the cycloaddition of DMAD to triene **165**.

The proposed singly aromatized adduct **172** would have formed through a dehydrogenation of the 1,4 hydrogens in the ring involved. Possible acceptors of these hydrogens may have been triene **165** or DMAD. The high temperature of the reaction (110 °C) and the excess DMAD may have promoted the dehydrogenation.

6.3 A Tandem Diene-transmissive Diels-Alder and Conventional Diels-Alder Reaction

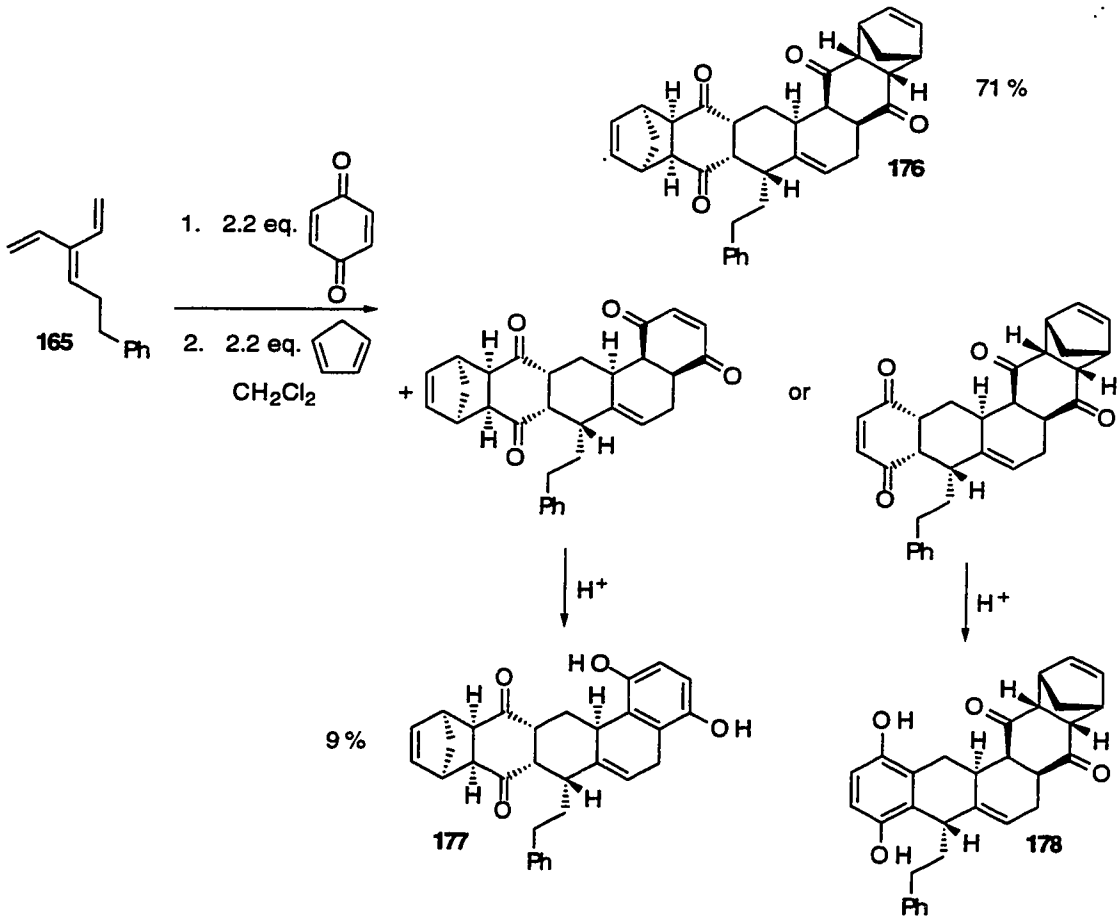
6.3.1 The Two Step and One-pot Procedures

Based on the progress with **165**, attempts were made with Diels-Alder reactions between adducts **167**, **171** and cyclopentadiene. The reaction of impure adduct **171** with freshly distilled cyclopentadiene was attempted under several conditions. Stirring adduct **171** and cyclopentadiene at room temperature, heating to 50 °C, heating to reflux in benzene, stirring with $AlEt_2Cl$ at room temperature in THF, and stirring with $AlEt_2Cl$ in refluxing THF all afforded only starting material and none of the desired adduct. The methyl esters were most likely impeding the attack of cyclopentadiene. Stirring adduct **167** and cyclopentadiene in dichloromethane at room temperature for 2 days gave complete reaction. After purification of the reaction mixture an inseparable mixture of compounds thought to consists of two major diastereomers, and one minor, of bis-adduct **176** in 86 % yield resulted. The mixture of compounds were run through a recycling preparative HPLC for 14 cycles, but no separation occurred. Three diastereomers were present since nearly triple the carbons required for bis-adduct **176** were observed in the ^{13}C NMR spectrum, and two large and one small peak, associated with the olefin formed in the Diels-Alder reaction. Due to the very high complexity of the NMR data the structure of **176** could not be confirmed. Considering the similar chemical environments of the carbonyls and the methene bridges, overlap was highly probable.



Scheme 62. Attempted reactions between adduct **171** and **167** and cyclopentadiene.

A one-pot procedure to produce bis-adduct **176** was carried out. Triene **165** and 1,4-benzoquinone were stirred in dichloromethane at room temperature for 16 hours. Two equivalents of freshly distilled cyclopentadiene were added and the mixture was allowed to stir for 3 days. After purification not only was bis-adduct **176** isolated but so was tautomerized mono-adduct **177** in 71 % and 9 % yield, respectively. Since adduct **167** possesses two electron poor double bonds the possibility existed that the isolated material was mono-adduct **178**. Evidence will follow to support the structure of adduct **177**. The acidity of the silca gel used in the purification was presumably the cause of the tautomerization



Scheme 63. The one-pot procedure providing bis-adduct **176** and mono-adduct **177**.

6.3.2 Characterization of Mono-adduct 177

The NMR data for adduct **177** were quite clean. Most of the peaks were resolved except for the ones related to the bridged ring system. Using a DEPT experiment and an HMQC experiment the protons of the 5 CH_2's were identified. Hydrogens H_5 and H_6 are the only two that couple to one another. Thus, the COSY experiment was used to identify protons H_5 and H_6, along with the remaining protons of that spin system. The protons of the bridged ring system were identified using the COSY experiment knowing

the chemical shift of H_{12} and H_{13}. The key to whether the mono-adduct isolated was **177** or **178** came from protons of C_{27}. If the product was **177**, then C_{27} would only couple with H_{28}. If it was **178** then it would couple with H_{28} and H_8. The protons of CH_2 27 were buried in the region of the C_5 protons, however from an HMQC experiment it had two sets of peaks at either end of the multiplet. From a COSY experiment there were no couplings to this part of the multiplet (3.20-3.40 ppm), so it was concluded that the isolated product was **177**. The stereochemistry could not be confidently assigned, but a possible relative stereochemistry has been proposed. With the structure of **177** confirmed, it was likely that the Diels-Alder reaction occurred with the second enone in adduct **167**.

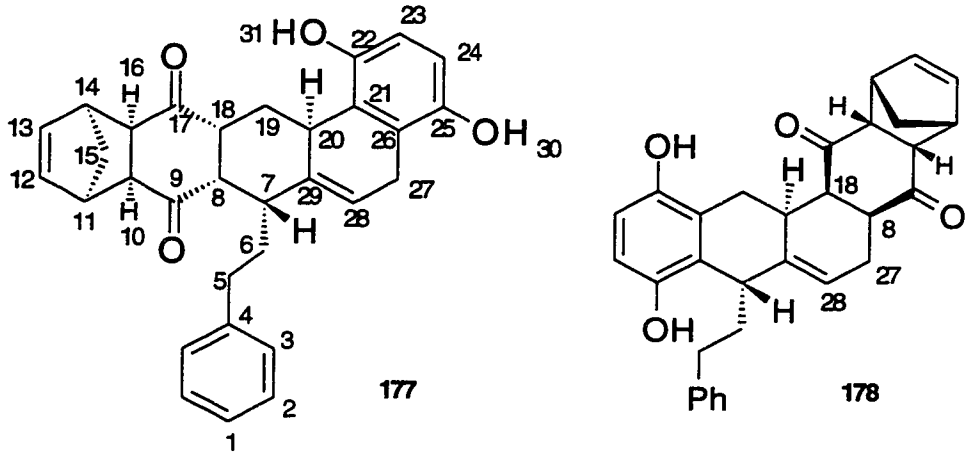


Figure 11. The numbering scheme used in the NMR assignments for **177**.

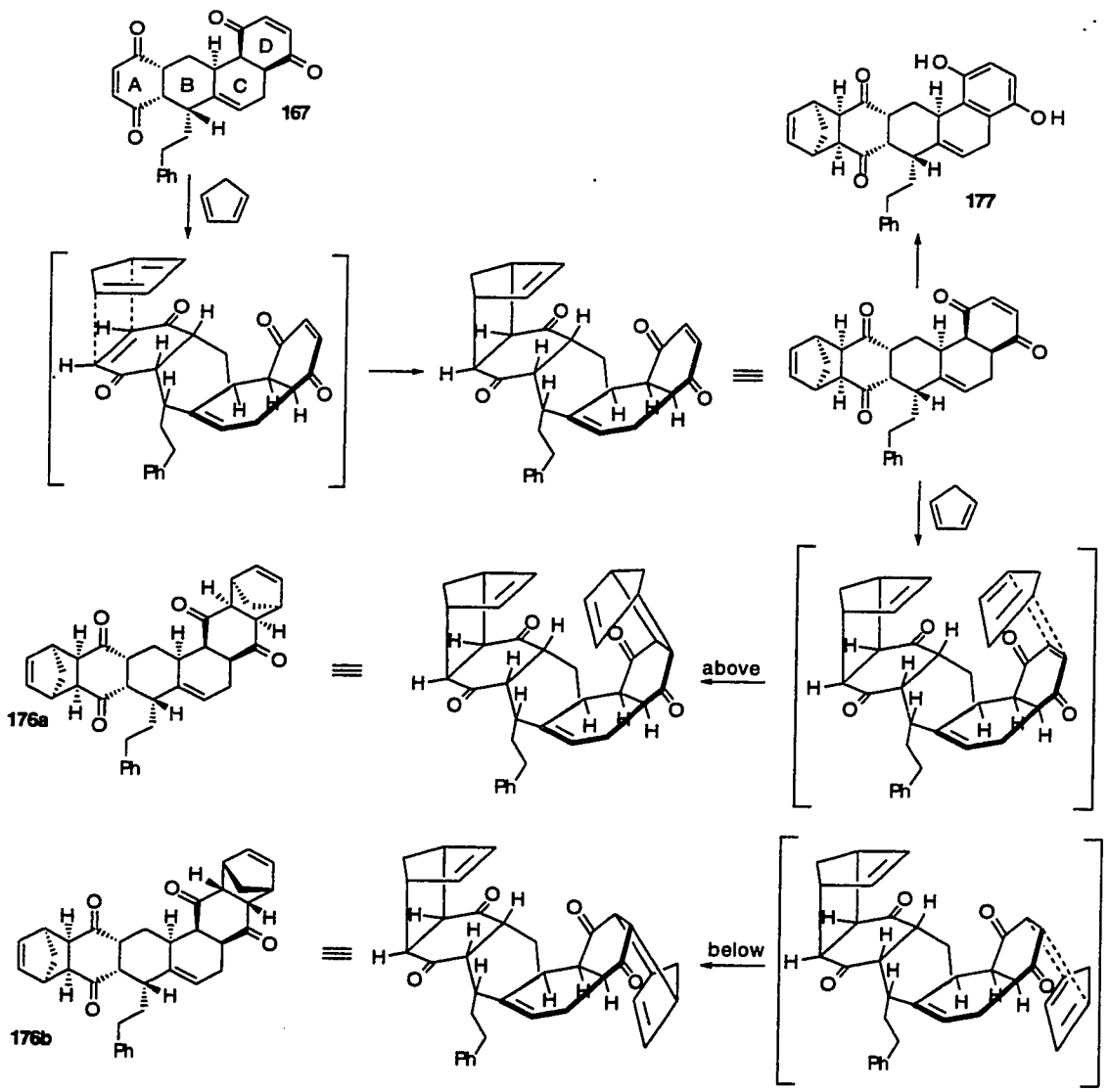
Number	^{1}H NMR Assignment	^{13}C NMR Assignment	Number	^{1}H NMR Assignment	^{13}C NMR Assignment
1	7.12	125.9	17	N/A	210.9 or 214.5
2	7.20	128.4	18	2.94 or 3.20-3.40	57.5 or 50.6(5)
3	7.00	128.3	19	2.64-2.67, 1.11-1.24	32.4
4	N/A	136.2	20	2.94 or 3.20-3.40	57.5 or 50.6(5)
5	2.23-2.29, 2.44-2.50	33.9	21	N/A	120.5 or 123.1
6	1.50-1.55, 1.67-1.75	29.8	22	N/A	146.2 or 148.2
7	2.70-2.75	47.2	(23/24) †	6.60, 6.72 †	113.5, 113.6 †
8	2.64-2.67	45.0			
9	N/A	210.9 or 214.5	25	N/A	146.2 or 148.2
10	3.13 or 3.20-3.40	50.5(6) or 54.8	26	N/A	120.5 or 123.1
11	3.62 or 3.20-3.40	49.3 or 50.4	27	3.20-3.40	24.8
(12/13) †	6.14, 6.32 †	135.3, 137.7 †	28	5.66	119.0
			29	N/A	140.9
14	3.20-3.40 or 3.62	49.3 or 50.4	(30/31) †	4.64, 5.99 †	N/A
15	1.41-1.43, 1.50-1.55	50.6(4)			
16	3.13 or 3.20-3.40	50.5(6) or 54.8			

Table 7. The NMR assignments for mono-adduct **177**. † The assignment for these groups could not be made unambiguously.

6.3.3 Theoretical Considerations in the Tandem Diels-Alder Reaction

A number of possible stereochemical outcomes are possible when adduct **167** behaves as a dienophile in a Diels-Alder reaction with cyclopentadiene. Adduct **167** contains two electron poor dienophiles, each with two different faces. Cyclopentadiene

may attack either face of both dienophiles in an *endo* or *exo* fashion giving 16 possible diastereomers. If *endo* attack is preferred[62], then there are 8 possible diastereomers. The conformation of adduct **167** is such that ring A (Scheme 64) and the phenethyl group are on one face of the molecule, which may offer some steric protection of the back face of that dienophile (ring A). Ring D is above the plane of the paper and cup towards the interior of the molecule. This could provide some protection to the top face of ring D, which would set adduct **176b** as the major diastereomer. These assumptions may explain why three diastereomers of bis-adduct **176** and why one diastereomer of mono-adduct **177** were isolated. The NMR of **176** and **177** were highly complex, and attempts at growing a crystal suitable for X-ray failed, so the stereochemistry could not be determined unambiguously.



Scheme 64. The reaction of adduct **167** with cyclopentadiene, the transition states involved, and the proposed stereochemistry of **176**.

7 Conclusions

7.1 Concluding Remarks

A series of aldehydes (cinnamaldehyde, hydrocinnamaldhyde, benzaldehyde and naphthaldehyde) were allylated with 5-bromo-1,3-pentadiene in the presence of indium. The resulting secondary alcohols were dehydrated with PPh_3 / DEAD, however the cross-conjugated triene was not obtained in all cases. It was found that cross-conjugated trienes conjugated with a phenyl ring substituent could not be isolated, which implied that these trienes were inherently unstable. Triene **165** was the only cross-conjugated triene obtained in a reasonable enough yield to carry out the Diels-Alder study.

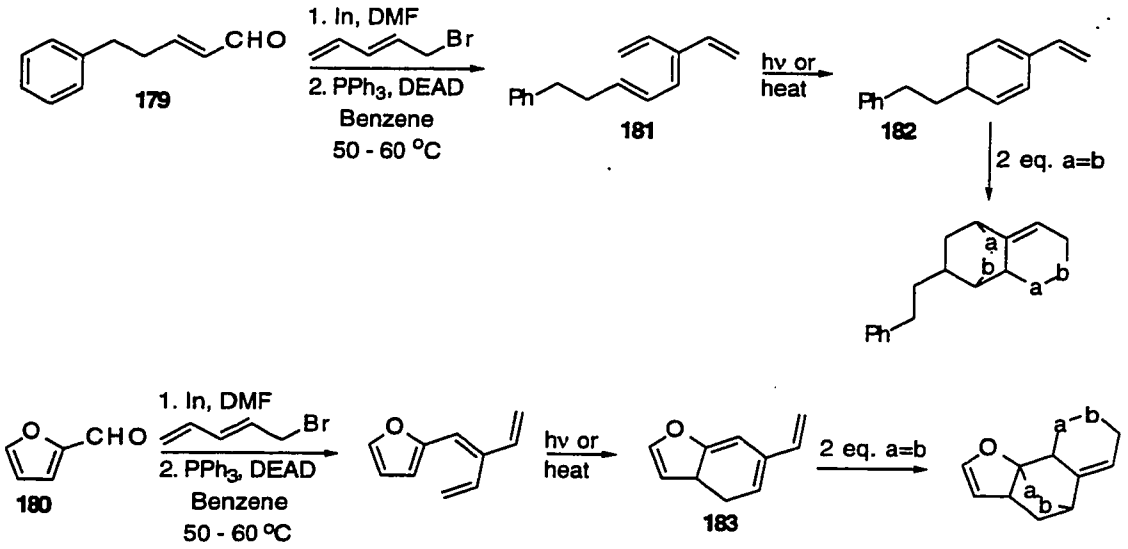
Diels-Alder reactions were carried out between triene **165** and a variety of dienophiles. Reaction with one equivalent of a dienophile afforded only bis-adducts and none of the mono-adducts. Reaction of two or more equivalents of a dienophile gave bis-adducts in moderate to good yields. If the dienophile was cyclic then high diastereoselectivities were observed, in ratios of >95:5 for 1,4-benzoquinone and *N*-phenylmaleimide, and 91:9 for NPTAD. DMAD, an acyclic dienophile gave a poor diastereoselectivity of 2:1. The difference between the diastereoselectivites was due to the steric bulk imparted to one face of the diene that resulted for mono addition of the cyclic dienophiles, which was not possible with DMAD.

A Diels-Alder reaction was carried out using adduct **167** as the dienophile, and cyclopentadiene and the diene, which gave a mixture of two major diastereomers, and one

minor isomer of **176**. This reaction was also carried out in tandem starting with triene **165** and 1,4-benzoquinone, to give adduct **176** and a mono-adduct **177**. This method afforded two highly complex molecules, one with 8 rings and 14 stereocenters **176** and another with 6 rings and 8 stereocenters, in one step staring from triene **165**.

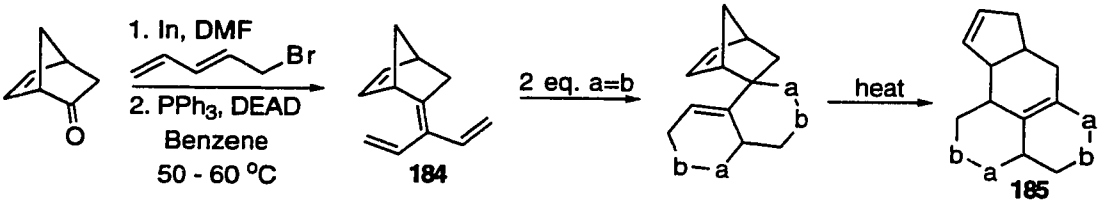
7.2 Future Work

Additional research may include indium mediated allylations with α,β unsaturated aldehydes, particularly **179** and **180**, followed by dehydration to give a series of cross-conjugated tetraenes. Preparation of tetraene **181** would impose a further test of the precept that cross-conjugated trienes in conjugation with a phenyl ring are unstable. The cross-conjugated tetraenes could undergo an electrocyclisation to another cross-conjugated triene **182**, with two endocyclic double bonds. The endocyclic diene should be more reactive as it is locked in an *s-cis* conformation, leading to bridged structures after diene-transmissive Diels-Alder chemistry. A similar procedure with 2-furaldehyde **180** would give triene **183**, which would offer a bridged system involving the ring junction and a quaternary carbon. In principle the electrocyclisation and the Diels-Alder reaction could be carried out in one pot.



Scheme 65. Cross-conjugated trienes with an endocyclic diene from cross conjugated tetraenes.

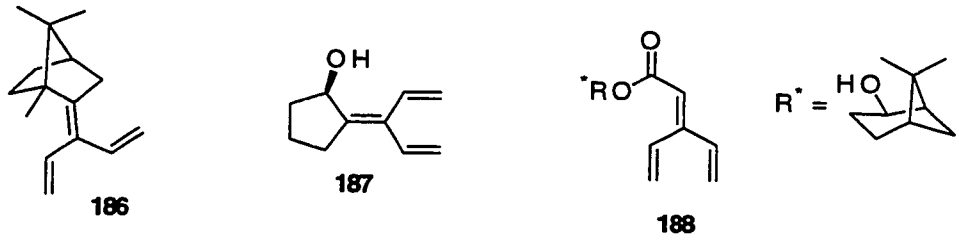
It is possible to carry out an indium mediated coupling with norbornenone and eliminate the tertiary alcohol that results to give cross-conjugated triene **184**. Once the diene-transmissive Diels-Alder reaction is carried out the two remaining double bonds would be in a 1,5 relationship and a Cope reaction could occur to give fused ring system **185**. These reactions could also be carried out in tandem.



Scheme 66. A tandem diene-transmissive Diels-Alder and Cope reaction.

Stereoselective diene-transmissive Diels-Alder reactions would be useful in asymmetric synthesis of natural products. If diene-transmissive Diels-Alder chemistry

were carried out on cross-conjugated trienes **186**, **187** and **188** the camphor, or alcohol group in **186** and **187** respectively, as well as using a pinene derivative as a chiral auxiliary in **188** could result in an excess of one enantiomer.



186 **187** **188**

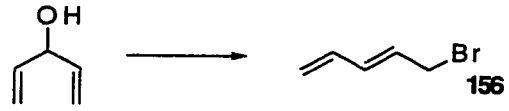
Figure 12. Cross-conjugated trienes which could be used in asymmetric synthesis.

8 Experimental

General Procedures

See the experimental section of part I for the general procedures.

5-Bromo-1,3-pentadiene 156



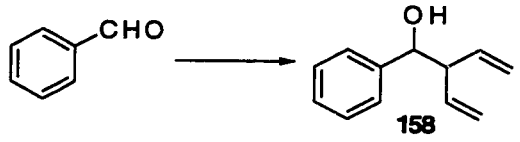
156

Under ambient conditions, 48% hydrobromic acid (37 mL, 328 mmol) was added dropwise to vigorously stirred 1,4-pentadiene-3-ol (25.0 g, 296 mmol), in a round-bottom flask (250 mL), at 0 °C. After the addition was one-half complete the mixture became cloudy, once the addition was complete (15 minutes) the mixture was stirred at room temperature for 2 hours. The layers were separated, the aqueous layer was extracted with diethyl ether (37 mL). The combined organic layers were washed with ice-cold water (3 × 37 mL), dried over anhydrous sodium sulfate, and filtered. The solvent was distilled off at room temperature under aspirator pressure (20 mbar) with the receiving flask at -78 °C. The remaining liquid was distilled at 35 - 38 °C (15 Torr) (lit[56]: 56 - 57 °C, at 38 Torr), to give a light yellow liquid (28.5 g, 66 %). ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.98 (d, 7.7 Hz, 2H), 5.10 - 5.28 (m, 2H), 5.77 - 5.88 (m, 1H), 6.18 - 6.39 (m, 2H).

The General Procedure for Indium Coupling Reactions

Indium metal, 100 mesh (1.3 eq, 9.75 mmol), was added in small portions (~75 mg) to a vigorously stirred solution of the aldehyde (1.0 eq, 7.5 mmol) and 5-bromo-1,3-pentadiene (2.0 eq, 15.0 mmol) in DMF (2 mL) at 0 °C. The addition required 15 minutes. The reaction mixture was stirred at room temperature until complete, at which point it was diluted with dichloromethane (20 mL). This solution was then added slowly to stirring diethyl ether (200 mL) and the resulting mixture was filtered though a pad of silica, which was washed with portions of ether (200 mL). The solvent was removed, and the resulting oil was purified by flash chromatography.

(*RS*)-1-Phenyl-2-vinyl-3-buten-1-ol 158

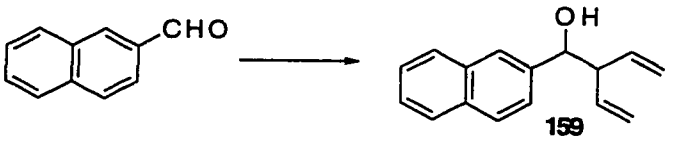


158

Following the general procedure, benzaldehyde (500 mg, 4.71 mmol), 5-bromo-1,3-pentadiene (1.380g, 9.42 mmol), DMF (0.8 mL), and indium metal, 100-mesh (703 mg, 6.13 mmol) were reacted. After 16 hours the dark olive green mixture was diluted with dichloromethane (8 mL), and added to diethyl ether (80 mL). This mixture was filtered through a plug of silica (2 cm × 5 cm) and the solvent was removed. This afforded 1.47 g of crude product, which was purified by flash chromatography (10:1 petroleum ether/ethyl acetate) to give 418 mg (51 %) of a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.78 (m, 1H), 3.11 (q, J = 7.2 Hz), 4.56 (d, J = 6.9 Hz, 1H), 5.01 - 5.23 (m,

4H), 5.68 - 5.90 (m, 2H), 7.27 - 7.36 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.9, 76.2, 116.9, 117.9, 126.9, 127.5, 128.1, 136.8(8), 136.9(3), 142.1; IR (Neat, cm^{-1}): 3409; MS: m/z 156(2), 141(3), 128(3), 115(3), 107(100), 79(61), 68(20), 51(13), 39(13), 27(5); HRMS: Calcd for $C_{12}H_{12}$, 156.0940; found, 156.0924.

(*RS*)-1-(2-Naphthyl)-2-vinyl-3-buten-1-ol 159

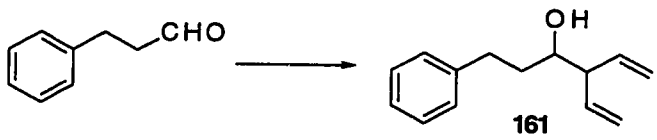


159

Following the general procedure, 2-naphthaldehyde (500 mg, 3.20 mmol), 5-bromo-1,3-pentadiene (941 mg, 6.40 mmol), DMF (0.35 mL), and indium metal, 100 mesh (478 mg, 4.16 mmol) were reacted. After 15 minutes the reaction mixture turned a dark olive-green and after 17 hours at room temperature, was rusty-brown. The mixture was diluted with dichloromethane (3.5 mL), added to 35 mL of diethyl ether, and filtered. The solvent was removed giving 1.060 g of a yellow oil which was purified by flash chromatography (10:1 petroleum ether/ethyl acetate) to afford 518 mg (72 %) of a very light yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 2.48 (br m, 1H), 3.22 (q, J = 7.2 Hz, 1H), 4.74 (d, J = 7.0 Hz, 1H), 5.01 - 5.18 (m, 2H), 5.21 - 5.28 (m, 2H), 5.69 - 5.79 (m, 1H), 5.86 - 5.93 (m, 1H), 7.45 - 7.51 (m, 3H), 7.75 (s, 1H), 7.81 - 7.84 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.9, 76.2, 117.0, 118.2, 124.7, 125.7(5), 125.7(9), 126.0, 127.6, 127.8, 128.0, 132.9(7), 133.0(3), 136.6, 139.3; IR (Neat, cm^{-1}) 3425; MS: m/z

206(1), 157(100), 129(84), 101(3), 77(5), 69(7), 51(4), 39(6), 28(22); HRMS: Calcd for $C_{16}H_{14}$, 206.1096; found, 206.1088.

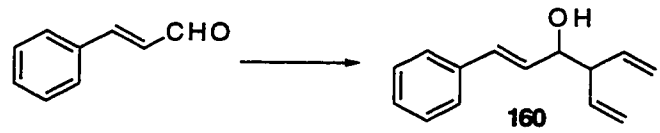
(*RS*)-1-Phenyl-4-vinyl-5-hexen-3-ol 161



161

Following the general procedure, 90% (tech) hydrocinnamaldehyde (14.4 g, 96.3 mmol) (12.9 g of hydrocinnamaldehyde), 5-bromo-1,3-pentadiene (28.3 g, 193 mmol), DMF (16.5 mL), and indium metal, 100 mesh (14.4g, 125 mmol), were reacted. After 13 hours at room temperature, the resulting red-brown suspension was diluted with dichloromethane (160 mL), added to diethyl ether (1.6 L), filtered and the solvent was removed. This gave 35g of a light yellowish oil, which was purified by flash chromatography (10:1 petroleum ether/ethyl acetate), to give 12.2 g (63 %) of a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.72 - 1.80 (m, 1H), 1.88 - 1.96 (m, 1H), 2.04 - 2.75 (br s, 1H), 2.70 - 2.75 (m, 1H), 2.76 -2.95 (m, 2H), 3.63 - 000 (m, 1H), 5.16 - 5.92 (m, 2H), 7.22 - 7.35 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 32.2, 36.1, 55.0, 72.6, 117.0, 117.6, 125.8, 128.4, 128.5, 137.0, 137.5, 142.2; IR (neat, cm^{-1}): 3421; MS: m/z 202(M^+, 1), 184(14), 169(4), 155(12), 134(63), 117(73), 105(67), 91(100), 89(16), 79(64), 77(74), 66(84), 68(66), 53(60), 41(94); HRMS: Calcd for $C_{14}H_{18}O$, 202.1358; found, 202.1344; *Anal.* Calcd for $C_{14}H_{18}O$: C, 83.31 %; H, 8.90 %. found: C, 83.13 %; H, 8.99 %.

(1*E*)-(*RS*)-1-Phenyl-4-vinyl-1,5-hexadien-3-ol 160



160

Following the general procedure, cinnamaldehyde (1.50 g, 11.0 mmol), 5-bromo-1,3-pentadiene (3.34 g, 22.7 mmol), DMF (1.9 mL), and indium metal, 100 mesh (1.69 g, 14.8 mmol) were reacted. After 21 hours at room temperature, the olive-green suspension was diluted with dichloromethane (1.9 mL), which was added to diethyl ether (190 mL). After filtration the solvent was removed, giving 4.24 g of a light yellow oil, which was purified by flash chromatography (10:1 petroleum ether/ethyl acetate), to afford 2.04 g (90 %) of a light yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.11 (br s, 1H), 3.01 (q, J = 6.7 Hz, 1H), 4.23 - 4.29 (m, 1H), 5.12 - 5.26 (m, 4H), 5.78 - 5.98 (m, 2H), 6.18 - 6.29 (m, 2H), 6.58 - 6.66 (m, 1H), 7.20 - 7.41 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 54.8, 74.3, 117.5, 117.8, 126.5, 127.6, 128.5, 129.5, 131.4, 136.5, 136.6; IR (Neat, cm^{-1}) 3400; MS: m/z 182(2), 167(4), 133(100), 115(89), 103(49), 91(52), 77(58), 67(21), 55(91), 51(23), 41(23), 39(33), 27(16); HRMS: Calcd for $C_{14}H_{14}$, 182.1096; found, 182.1088.

The General Procedure for Dehydration Reactions

DEAD (1.5 eq, 0.12 mmol), was added dropwise to a solution of the alcohol (1.0 eq, 0.08 mmol) and triphenylphosphine (1.5 eq, 0.12 mmol) in benzene (1 mL) at 5 - 10 °C. The initially yellow solution decolorized quickly, but once the addition was complete, remained yellow. This solution was heated in a bath at 50 - 60 °C, for the time

indicated, and the resulting solution, after cooling to room temperature, was diluted with petroleum ether (10 mL), forming an off-white precipitate. This mixture was filtered through a 1 cm pad of silica, and washed with petroleum ether (10 mL), giving a light pink solution. The solvent was removed, to afford a pink oil, which was purified by flash chromatography.

1-(2-Naphthyl)-2-vinyl-1,3-butadiene 163

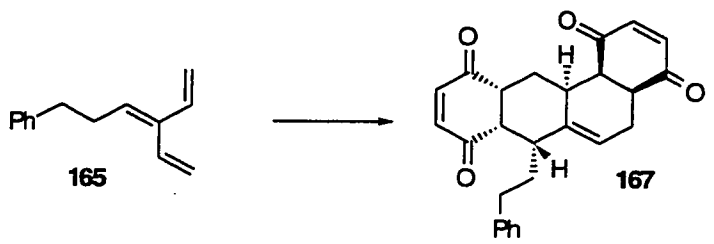
159 163

Following the general procedure, DEAD (220 μL, 235 mg, 1.35 mmol) was added to a solution of 1-(2-naphthyl)-2-vinyl-3-butene-1-ol **159** (107 mg, 0.477 mmol) and triphenylphosphine (357 mg, 1.36 mmol) in benzene (6 mL). After heating for 19.5 hours, and work-up, the 53 mg of crude material were purified by flash chromatography (10:1 petroleum ether/ethyl acetate), to afford 12 mg (13 %) of an off-white solid. mp 43.0 - 44.5 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.21 - 5.63 (m, 4H), 6.53 - 6.85 (m, 3H), 7.40 - 7.51 (m, 3H), 7.75 - 7.85 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 116.2, 118.6, 126.0, 126.2, 127.5, 127.6, 127.7, 128.0, 128.8, 129.6, 132.4, 133.2, 133.5, 133.6, 137.9, 138.2; MS: m/z 206(100), 203(25), 191(54), 178(52), 165(65), 152(14), 141(10), 115(7), 89(3), 69(7), 39(4); HRMS: Calcd for $C_{16}H_{14}$, 206.1096; found, 206.1101.

6-Phenyl-3-vinyl-1,3-hexadiene 165

Following the general procedure, DEAD (14.00 mL, 14.95g, 85.85 mmol) was added to a solution of 1-phenyl-4-vinyl-5-hexene-3-ol **161** (11.58 g, 57.24 mmol) and triphenylphosphine (22.52 g, 85.85 mmol) in benzene (700 mL). After heating for 17 hours, and work-up the 17.2 g of crude material were purified by flash chromatography (petroleum ether), to afford 4.38 g (42 %) of a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.55 (dq, J = 2.0 Hz, J = 8.0 Hz, 2H), 2.72 (dt, J = 1.8 Hz, J = 7.5 Hz, 2H), 5.03 - 5.29 (m, 4H), 5.67 (t, J = 7.2 Hz, 1H), 6.37 - 6.49 (m, 2H), 7.20 - 7.31 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 30.2, 35.8, 114.0, 117.4, 125.9, 128.3, 128.4, 131.4, 131.9, 137.5, 137.8, 141.7; MS: m/z 184 (M^+, 34), 169(17), 155(38), 128(8), 115(12), 104(25), 91(100), 77(83), 65(54), 53(12), 39(26); HRMS: Calcd for $C_{14}H_{16}$, 184.1253; found, 184.1248; *Anal.* Calcd for $C_{14}H_{16}$: C, 91.25 %; H, 8.75 %. Found: C, 91.21 %; H, 8.50 %.

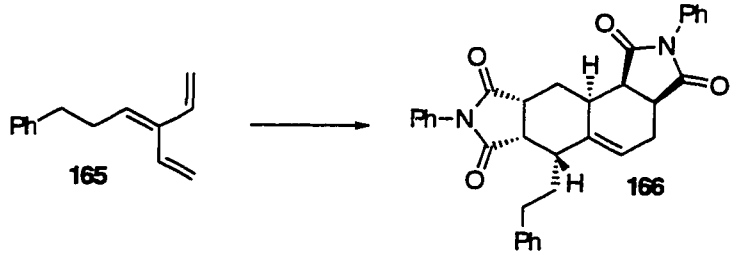
(4a*S, 7*R**, 7a*S**, 11a*R**, 12a*S**, 12b*R**)-1,4,4a,5,7,7a,11,11a,12,12a,12b-Dodecahydro-1,4,8,11-tetroxo-9-phenethylbenz[*a*]anthracene 167**



Under ambient conditions, triene **165** (100 mg, 0.543 mmol), and 1,4-benzoquinone (129 mg, 1.19 mmol) were dissolved in benzene (1.5 mL), giving a yellow solution, which was protected form light, and stirred at room temperature for 2 days, in a round-bottom flask (5 mL). The resulting gray precipitate was filtered from the yellow-green solution, giving 121 mg (56 %). If the precipitate was dissolved in dichloromethane and the solvent was removed, then a yellow solid resulted. Crystals suitable for X-ray crystallography were grown by slow evaporation of a dichloromethane solution at 5 °C in an NMR tube. mp 167.5 - 169.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02 (td, J = 12.94 Hz, J = 5.6 Hz, 1H), 1.22 - 1.30 (m, 1H), 1.38 - 1.46 (m, 1H), 2.05 - 2.10 (m, 1H), 2.12 - 2.14 (m, 1H), 2.20 - 2.26 (m, 1H), 2.32 - 2.38 (m, 1H), 2.56 - 2.65 (m, 1H), 2.66 - 2.69 (m, 1H), 2.85 (dd, J = 5.2 Hz, J = 18.6 Hz, 1H), 2.99 - 3.02 (m, 1H), 3.12 - 3.15 (m, 1H), 3.21 - 3.26 (m, 2H), 5.56 - 5.57 (m, 1H), 6.62 - 6.65 (m, 1H), 6.75 - 6.81 (m, 3H), 6.97 (d, J = 7.2 Hz, 2H), 7.10 - 7.13 (m, 1H), 7.19 - 7.24 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 29.2, 30.4, 30.7, 34.0, 43.9, 45.5, 48.7, 49.6, 54.2, 120.7, 125.9, 128.2, 128.3, 136.9, 140.8, 141.2, 141.3, 142.1, 197.8, 198.7, 199.8, 200.5; IR (Nujol, cm^{-1})

1676, 1599; MS: m/z 400 (M^+, 9), 291(2), 221(2), 185(5), 105(49), 91(100), 39(19); HRMS: Calcd for $C_{26}H_{24}O_4$, 400.1675; found, 400.1681; *Anal.* Calcd for $C_{26}H_{24}O_4$: C, 77.98 %; H, 6.04 %. found: C, 78.03 %; H, 5.94 %.

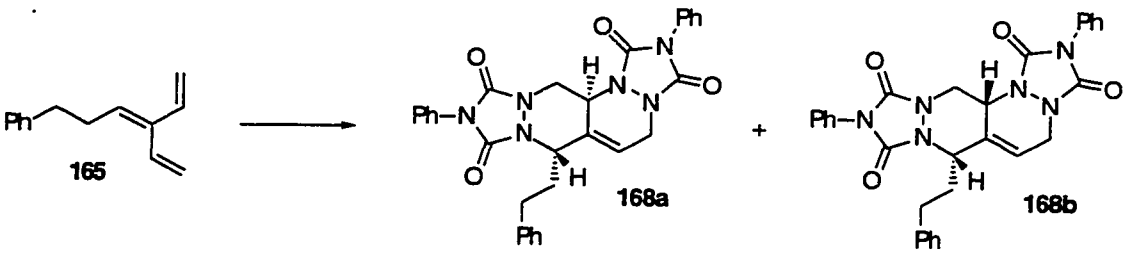
(1*R, 2*S**, 5*R**, 6*S**, 7*R**, 8a*S**)-*N*,*N*'-Diphenyl-1,2,3,5,6,7,8,8a-octahydro-5-phenethyl-1,2:6,7-naphthalene tetracarboximide 166**



Under ambient conditions, triene **165** (100 mg, 0.543 mmol) and *N*-phenylmaleimide (188 mg, 1.09 mmol) were dissolved in benzene (6 mL), in a round-bottom flask (10 mL). After 20 minutes of stirring, a white precipitate formed. After 20 hours the white solid was filtered off and washed with cold benzene (4 mL). Residual solvent was removed, giving 251 mg (88 %) of a white solid. mp 243.5 - 244.9 °C, at which point it darkens; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.02 - 2.09 (m, 1H), 2.10 - 2.15 (m, 1H), 2.21 - 2.28 (m, 1H), 2.33 - 2.36 (m, 1H), 2.46 - 2.50 (m, 1H0, 2.63 - 2.69 (m, 2H), 2.83 - 2.94 (m, 3H), 3.20 - 3.26 (m, 2H), 3.34 - 3.42 (m, 2H), 5.82 - 5.84 (m, 1H), 7.12 - 7.47 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.3, 25.3, 29.6, 33.4, 34.5, 37.5, 40.0, 40.1, 41.3, 43.2, 120.7, 126.0, 126.3, 126.4, 128.3, 128.5, 128.7(0), 128.7(3), 129.2, 131.7, 131.8, 141.0, 141.7, 176.5, 176.6, 178.3, 178.8; IR (Nujol, cm^{-1}) 1701, 1493, 1458; MS: m/z 530 (M^+, 100), 512(9), 439(69), 426(40), 344(5), 318(12), 292(16), 188(14),

174(72), 128(18), 119(24), 105(27), 91(70), 83(98), 78(47), 65(13), 47(29), 40(63); HRMS: Calcd for $C_{34}H_{30}N_2O_4$, 530.2206; found, 530.2223.

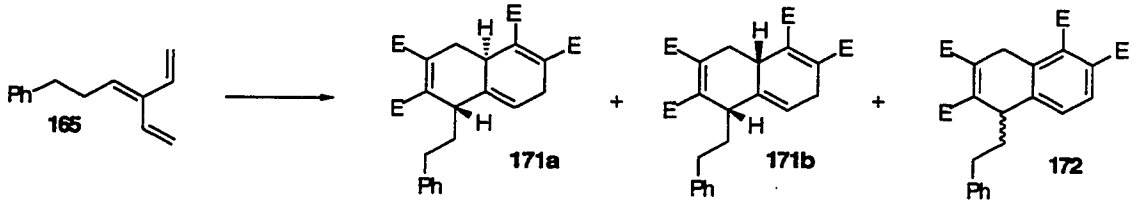
(5*S, 8a*R**)-*N,N'*-Diphenyl-1,2,3,5,6,7,8,8a-octahydro-5-phenethyl-1,2:6,7-pyridazino[3,4-*d*]pyridazine tetracarboximide 168a** and **(5*S**, 8a*S**)-*N,N'*-Diphenyl-1,2,3,5,6,7,8,8a-octahydro-5-phenethyl-1,2:6,7-pyridazino[3,4-*d*]pyridazine tetracarboximide 168b**



Sodium bicarbonate (100 mg, 1.19 mmol), followed by Dess-Martin periodinane (506 mg, 1.19 mmol), were added to a solution of *N*-phenyl urazole (192 mg, 1.09 mmol) in dichloromethane (4 mL), in a round-bottom-flask (10 mL). A bright pink mixture resulted after 5 minutes. A solution of triene **165** (100 mg, 0.543 mmol) in dichloromethane (1 mL) was added via canula, with dichloromethane washings (3 × 0.25 mL). After 5 seconds, the pink color had gone and the mixture was left to stir for 30 minutes. A solution consisting of a 1:1 mixture of saturated $NaHCO_3$ and Na_2SO_3 (5.6 mL) was added, and the mixture was left to stir for 30 minutes. The layers were separated, the aqueous layer was extracted with ethyl acetate (3 × 15 mL), the combined organic layers were dried over anhydrous sodium sulfate, and filtered. The solvent was removed, giving 352 mg of a crude mixture which was purified by flash chromatography (10:1 dichloromethane/ethyl acetate), to afford 234 mg (81 %) of an off-white solid, **168a**

and 19 mg (7 %) of an off-white solid (mix of **168a** and **168b**). **168a**: mp 225.5 - 226.5 °C; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 2.10 - 2.18 (m, 1H), 2.23 - 2.30 (m, 1H), 2.62 - 2.73 (m, 2H), 3.19 (t, J = 10.9, 1H), 4.14 - 4.18 (m, 1H), 4.28 - 4.33 (m, 1H), 4.73 - 4.77 (m, 1H), 4.83 (dd, J = 5.1 Hz, J = 10.3 Hz, 1H), 5.08 (dd, J = 5.6 Hz, J = 11.1 Hz, 1H), 6.12 - 6.13 (m, 1H), 7.20 - 7.23 (m, 3H), 7.30 - 7.39 (m, 2H), 7.40 - 7.55 (m, 10H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 30.7, 32.1, 42.9, 47.4, 50.9, 59.4, 121.3, 125.9, 126.0, 126.7, 128.6, 128.7, 128.8, 129.0, 129.4, 129.5, 131.4, 131.7, 140.4, 151.1, 152.0, 152.6, 153.1; IR (Nujol, cm^{-1}) 1769, 1707, 1500; MS: m/z 534 (M^+, 15), 429(33), 358(44), 310(12), 254(14), 205(8), 119(17), 83(100), 46(90); HRMS: Calcd for $C_{30}H_{26}N_6O_4$, 534.2016; found, 534.2042. **168b**: ^{1}H NMR (500 MHz, CD_2Cl_2) δ 2.52 - 2.58 (m, 1H), 2.79 - 2.92 (m, 2H), 3.41 (t, J = 11.1 Hz, 1H), 4.67 - 4.70 (m, 1H), 6.13 (br s, 1H), remainder buried in the spectrum of **168a**; ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.2, 33.1, 43.4, 45.8, 52.6, 58.2, 119.0, 126.2, 126.6, 130.7. 141.2, 152.7, 151.1, remainder buried in the spectrum of **168a**; IR ($CHCl_3$, cm^{-1}) 1775, 1700, 1502; MS(FAB): m+1/z 535(55), 429(21), 358(29), 346(14), 254(14), 191(26), 185(29), 178(15), 164(22), 154(32), 136(32), 133(46), 91(100); MS(FAB accurate mass): Calcd for $C_{30}H_{27}N_6O_4$, 535.2016; found, 535.2200.

(5*S, 8a*S**)-Tetramethyl 5-phenethyl-3,5,8,8a-tetrahydo-1,2,6,7-naphthalene tetracarboxylate 171a, (5*S**, 8a*R**)-Tetramethyl 5-phenethyl-3,5,8,8a-tetrahydo-1,2,6,7-naphthalene tetracarboxylate 171b and (*RS*)-Tetramethyl 5,8-dihydo-5-phenethyl-1,2,6,7-naphthalene tetracarboxylate 172**

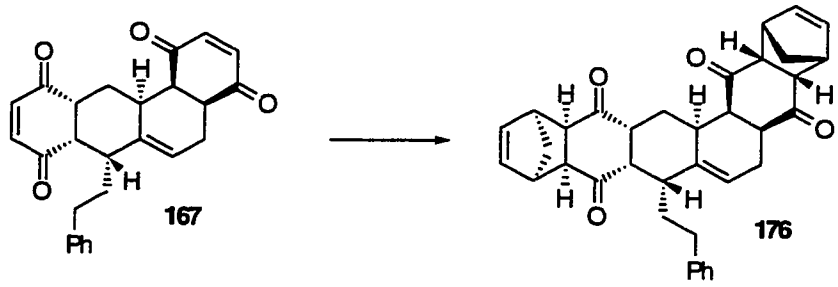


Under ambient conditions, a solution of triene **165** (200 mg, 1.09 mmol) and DMAD (660 μL, 770 mg, 5.43 mmol) in toluene (2 mL) was refluxed, in a round-bottom-flask (10 mL), for 24 hours. The solvent was removed, to give 1.357 g of a light yellow oil., which was purified by flash chromatography (2.75:1 petroleum ether/ethyl acetate), giving 426 mg (~ 84 %) of a syrupy oil, which was a mixture of **171a**, **171b**, and **172**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.62 - 1.76 (m), 1.88 (s), 1.91 - 1.99 (m), 2.00 - 2.11 (m), 2.17 (dd, J = 11.2 Hz, J = 18.0 Hz), 2.21 - 2.32 (m), 2.44 - 2.75 (series of m), 2.93 (dd, J = 5.7 Hz, J =18.2 Hz), 2.99 - 3.14 (m), 3.20 - 3.66 (series of m), 3.70 (s), 3.71 (s) 3.76 (s), 3.79 (s), 3.87 (s), 3.94 (s), 5.56 (s), 5.69 (s), 7.02 - 7.16 (m), 7.18 - 7.25 (m), 7.30 (d, J = 8.1 Hz), 7.88 (d, J = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.9, 28.0, 28.4, 30.4, 30.7, 31.4, 31.6, 32.0, 33.4, 33.6, 33.9, 33.3, 37.4, 41.8, 42.1, 44.0, 52.1(6), 52.2(2), 52.2(3), 52.3, 52.3(9), 52.4(4), 52.7, 77.2, 115.9, 118.0, 125.8(6), 125.9(4), 126.4, 128.0(5), 128.1(4), 128.2(6), 128.2(9), 128.3(3), 128.4, 128.5, 128.6, 128.7, 128.9, 130.3, 130.4, 131.5, 132.0, 132.3, 132.8, 133.0, 134.6, 135.6, 137.6, 139.1, 140.8, 141.0, 141.8(1), 141.8(6), 142.6, 165.8, 166.5, 167.1, 167.5, 167.6, 167.7(1), 167.7(4), 167.8,,

167.9, 168.0, 168.7, 169.0; IR (Neat, cm^{-1}) 1726, 1650, 1602; MS(FAB): m+1/z 469(25), 435(100), 403(28), 329(29), 271(18), 189(18), 185(20), 133(70), 91(61).

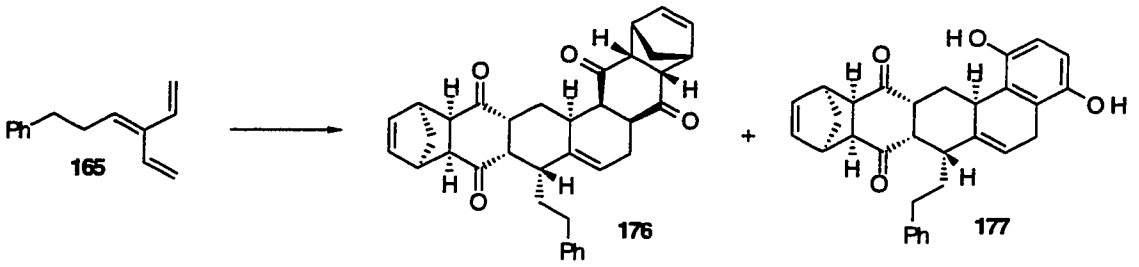
(1*S, 4*R**, 4a*S**, 5a*S**, 8*R**, 8a*S**, 9a*S**, 10*R**, 13*S**, 13a*R**, 14a*R**, 15a*S**, 15b*R**, 16a*R**)-1,4:10,13-Dimethano-1,4,4a,5,5a,6,8,8a,9,9a,10,13,13a,14,14a,15,15a,15b,16,16a-icosahydro-8-phenethyl-5,9,14,16-tetroxohexaphene 176** and **(7*R**, 7a*S**, 8a*S**, 9*R**, 12*S**, 12a*R**, 13a*R**, 14a*S**) 8,13-Dioxo-5,7,7a,8,8a,9,12,12a,13a,14,14a-dodecahydro-1,4-hydroxy-9,12-methano-7-phenethylbenz[*a*]naphthacene 177**

The Two Step Procedure



Under ambient conditions, a solution of tetraketone **165** (100 mg, 0.250 mmol) and cyclopentadiene (107 µL, 1.35 mmol) in dichloromethane (1 mL) was stirred at room temperature for 2 days, in a round-bottom-flask (5 mL). The solvent was removed, giving 154 mg of a yellowish solid, which was purified by flash chromatography (2:1 petroleum ether/ethyl acetate), to afford 101 mg (86 %) of an off-white solid. Further purification (and separation of any diastereomers) was attempted using preparative HPLC.

The One-Pot Procedure

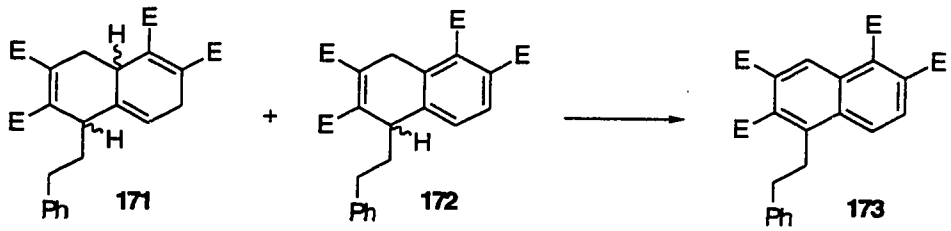


Under ambient conditions, a solution of triene **165** (100 mg, 0.543 mmol) and 1,4-benzoquinone (129 mg, 1.19 mmol) in dichloromethane (1 mL) was stirred at room temperature, with protection from light, for 16 hours, in a round-bottom flask (5 mL). Freshly distilled cyclopentadiene (107 μL, 1.35 mmol) was added to the resulting yellow solution, and was left to stir at room temperature for 3 days. The solvent was removed, giving 315 mg of a yellow solid, which was purified by flash chromatography (2:1 petroleum ether/ethyl acetate), to afford 241 mg of a yellowish solid. A spot ran close to the desired spot, so this was further purified using preparative HPLC, to give 206 mg (71 %) of a light yellow solid **176** and 23 mg (9 %) of a second light yellow solid **177**. **176**: mp 116.0 - 120.0 °C; ^{1}H NMR (500 MHz, C_6D_6) δ 0.70 (d, J = 8.3 Hz), 0.80 (d, J = 8.5 Hz), 0.86 (d, J = 8.3 Hz), 0.94 (d, J = 8.3 Hz), 1.03 - 1.07 (m), 1.10 (d, J = 7.9 Hz), 1.11 - 1.28 (m), 1.21 (d, J = 8.3 Hz), 1.30 - 1.74 (series m), 1.81 - 1.94 (m), 2.06 - 2.12 (m), 2.14 - 2.46 (series m), 2.49 - 2.58 (m), 2.59 - 2.77 (series m), 2.86 (dd, J = 3.8 Hz, J = 9.5 Hz), 2.94 - 3.01 (m), 3.04 - 3.06 (m), 3.22 (s), 3.26 (s), 3.30 (s), 3.33 (s), 3.36 (s), 3.41 (s), 5.17 - 5.18 (m), 5.24 (m), 5.31 - 5.32 (m), 5.72 - 5.75 (m), 5.98 - 6.05 (m), 6.44 - 6.45 (m), 6.92 (d, J = 7.6 Hz), 7.01 (t, J = 7.0 Hz), 7.06 - 7.20 (series m); ^{13}C NMR (125

MHz, C_6D_6) δ 21.7, 21.9, 25.0, 27.3, 28.4, 28.8, 29.3, 29.5, 29.7, 30.1, 30.3, 31.3, 31.5, 33.2, 34.2, 34.4, 34.5, 34.6, 41.7, 32.8, 43.2, 44.1, 44.2, 44.3, 44.5, 44.7, 44.8, 44.9, 45.1, 45.3, 46.87(6), 46.8(1), 47.1, 47.5, 47.6, 47.7, 47.8, 48.5, 48.9, 49.1, 49.3, 49.9(5), 49.9(7), 50.2, 50.3, 50.3(7), 50.4(3), 50.7, 51.1, 51.8, 52.0, 52.5, 52.6, 52.6(8), 52.7(1), 52.7(8), 52.8(4), 53.2, 53.4, 54.2, 54.3, 54.4, 54.6, 54.9, 55.1, 55.9, 57.0, 57.2, 58.4, 77.8, 120.6, 120.7, 120.9, 121.0, 126.2, 126.3, 127.8, 128.0, 128.2, 128.3, 128.5, 128.6(1), 128.6(4), 128.6(8), 128.7(3), 128.8, 135.2, 135.5, 135.6, 135.9, 136.0, 136.5, 136.8, 136.9, 137.2, 137.3, 137.5, 137.6, 137.7, 137.8, 139.4, 141.7, 142.3, 142.5, 208.3, 208.7, 208.8, 208.9(7), 209.0(1), 209.1, 209.2, 209.3, 209.8, 210.2, 210.9; IR ($CHCl_3$, cm^{-1}) 2948, 1697, 1176; MS (FAB) m+1/z 533(2), 467(4), 401(9), 187(2), 133(100), 105(10), 91(15), 55(13); (**177** mono-added) ^1H NMR (500 MHz, $CDCl_3$) δ 1.11 - 1.24 (m, 1H), 1.41 - 1.43 (m, 1H), 1.50 - 1.55 (m, 2H), 1.67 - 1.75 (m, 2H), 2.23 - 2.29 (m, 1H), 2.44 - 2.50 (m, 1H), 2.64 - 2.67 (m, 2H), 2.70 - 2.75 (m, 1H), 2.94 (t, J = 6.8 Hz, 1H), 3.13 (ddd, J = 0.9 Hz, J = 4.1 Hz, J = 9.2 Hz, 1H), 3.20 - 3.40 (series of m, 5H), 3.62 (s, 1H), 4.64 (br s, 1H), 5.66 (t, J = 3.3 Hz, 1H), 5.99 (br s, 1H), 6.14 (dd, J = 2.9 Hz, J = 5.6 Hz, 1H), 6.32 (dd, J = 2.9 Hz, J = 5.6 Hz, 1H), 6.60 (d, J = 8.6 Hz, 1H), 6.72 (d, J = 8.6 Hz, 1H), 7.00 (d, J = 7.1, 2H), 7.12 (t, J = 7.3 Hz, 1H), 7.20 (t, J = 7.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.8, 28.3, 29.8, 32.4, 33.9, 45.0, 47.2, 49.3, 50.4, 50.5(6), 50.6(4), 54.8, 57.5, 113.5, 113.6, 119.0, 120.5, 123.1, 125.9, 128.3, 128.4, 135.3, 136.2, 137.7, 140.9, 146.2, 148.2, 210.9, 214.5; IR ($CHCl_3$, cm^{-1}) 3500 (br), 1689; MS: (FAB) m+1/z

467 (M + 1, 2), 277(12), 241(8), 185(81), 149(14), 93(100), 75(36), 57(22); MS(FAB accurate mass): Calcd for $C_{31}H_{31}O_4$, 467.2222; found, 467.2196.

Tetramethyl 5-phenethyl-1,2,6,7-naphthalenetetracarboxylate (O)



A solution of the mixture of tetra-ester (**171a, 171b, 172**) (84 mg, 0.18 mmol) and DDQ (82 mg, 0.36 mmol) in toluene (1.5 mL) was refluxed in a round-bottom flask (5 mL). After 13 hours, the resulting brown - red solution with a tan precipitate was removed by suction filtration. The solvent was removed, giving 79 mg of a viscous brownish oil, which was purified by flash chromatography (2.75:1 petroleum ether/ethyl acetate), to afford 57 mg (70 %) of a light pink solid. mp 133.0 - 134.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.94 - 2.98 (m, 2H), 3.30 - 3.34 (m, 2H), 3.94 (s, 3H), 3.96(9) (s, 3H), 3.97(4) (s, 3H), 4.10 (s, 3H), 7.20 - 7.24 (m, 3H), 7.29 - 7.32 (m, 2H), 8.17 (1/2AB_q, J = 9.0, 1H), 8.22 (1/2AB_q, J = 9.0, 1H), 8.46 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 32.6, 37.2, 52.7, 52.8, 52.9, 53.2, 125.9, 126.2, 126.4, 126.7, 128.0, 128.2, 128.4, 128.6, 128.9, 133.2, 135.1, 136.6(0), 136.6(4), 141.0, 165.5, 165.6, 168.7, 169.4; IR ($CHCl_3$, cm^{-1}) 1729, 1439, 1276; MS: m/z 464 (M^+, 8) 432(100), 400(99), 374(54), 328(7), 281(20), 251(3), 226(3), 194(23), 162(8), 142(6), 90(97), 69(98); HRMS: Calcd for $C_{26}H_{24}O_8$,

464.1471; found, 464.1463; *Anal.* Calcd for $C_{26}H_{24}O_8$: C, 67.23 %; H, 5.21 %. found: C, 67.04 %; H, 5.13 %.

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Claims to Original Research

1. The synthesis of a novel 3-methylene substituted cross-conjugated trienes using indium mediated allylations.

2. A better understanding of the stability of cross-conjugated trienes.

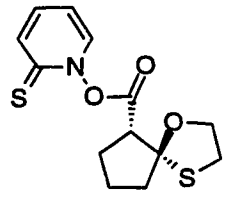
3. A better understanding of the diene-transmissive Diels-Alder chemistry of 3-methylene substituted cross-conjugated trienes, through the preparation of bis-adducts **166, 167, 168** and **171**.

4. The development of a tandem diene-transmissive Diels-Alder and conventional Diels-Alder reaction as a direct route to highly complex molecules, though the preparation of bis-adduct **176** and **177**.

Appendix I: X-ray Crystallographic Data

X-ray Crystallographic Data for

Barton Ester 48



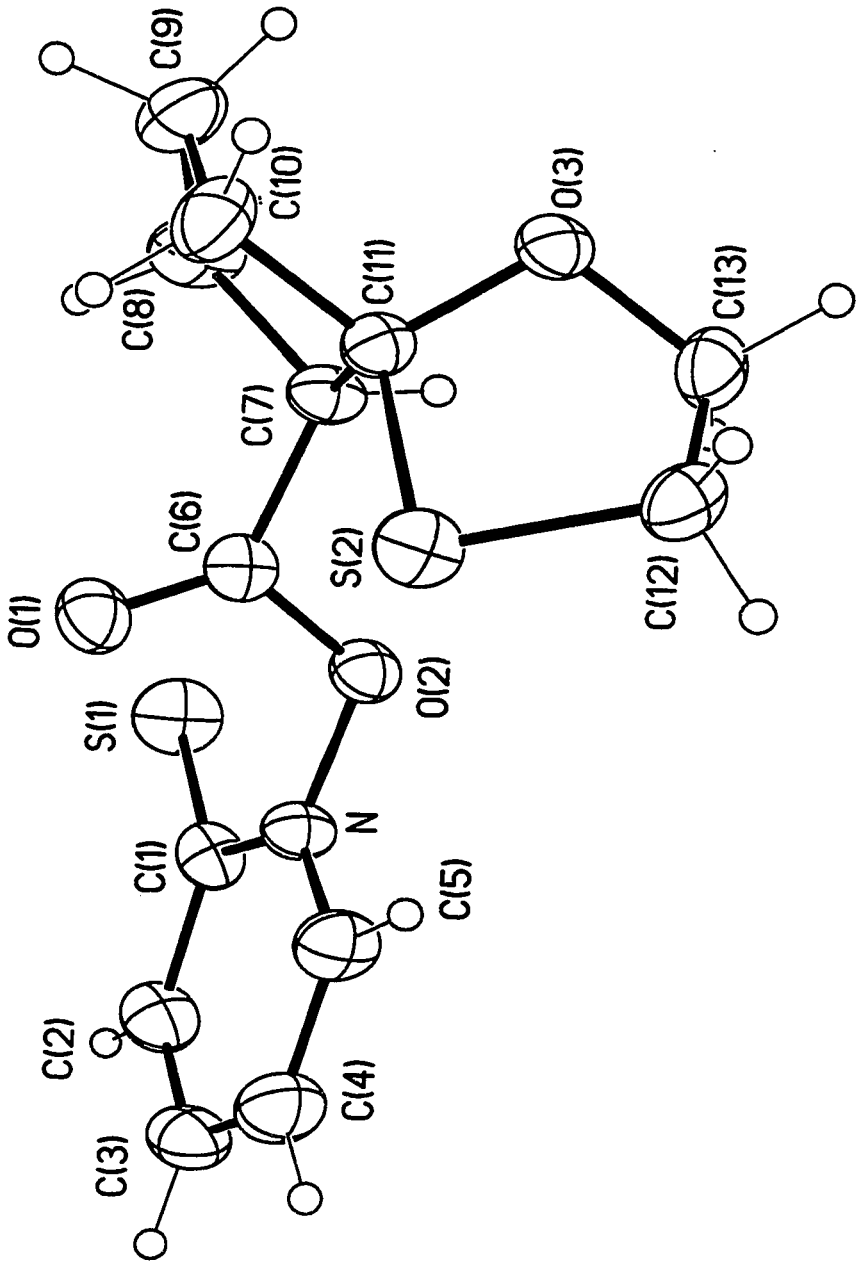


Figure A1. The ORTEP view of Barton ester **48**.

Table 1. Crystal data and structure refinement for af003.

Identification code	af003
Empirical formula	C13 H15 N O3 S2
Formula weight	297.38
Temperature	203(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P2(1)/n
Unit cell dimensions	a = 13.534(6) A alpha = 90 deg. b = 7.848(4) A beta = 104.496(8) deg. c = 13.628(6) A gamma = 90 deg.
Volume	1401.4(9) A^3
Z, Calculated density	4, 1.409 Mg/m^3
Absorption coefficient	0.382 mm^-1
F(000)	624
Crystal size	0.1 x 0.3 x 0.5 mm
Theta range for data collection	1.90 to 22.49 deg.
Limiting indices	-14<=h<=12, -8<=k<=8, -14<=l<=14
Reflections collected / unique	5600 / 1827 [R(int) = 0.0863]
Completeness to theta = 22.49	99.6 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1827 / 0 / 172
Goodness-of-fit on F^2	1.139
Final R indices [I>2sigma(I)]	R1 = 0.0748, wR2 = 0.1798
R indices (all data)	R1 = 0.0903, wR2 = 0.1918
Largest diff. peak and hole	0.510 and -0.698 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for af003.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
S(1)	2794(1)	4396(2)	871(1)	70(1)
S(2)	-815(1)	1506(1)	2474(1)	51(1)
N	1817(2)	1676(4)	1317(2)	44(1)
O(1)	149(2)	3387(3)	747(2)	55(1)
O(2)	1524(2)	2717(3)	2028(2)	47(1)
O(3)	-492(2)	4013(3)	3774(2)	49(1)
C(1)	2415(2)	2365(5)	758(3)	47(1)
C(2)	2684(3)	1138(6)	93(3)	60(1)
C(3)	2340(3)	-490(6)	27(3)	67(1)
C(4)	1714(3)	-1060(6)	628(4)	69(1)
C(5)	1464(3)	62(5)	1274(3)	59(1)
C(6)	601(2)	3554(4)	1602(3)	43(1)
C(7)	319(2)	4591(4)	2416(3)	44(1)
C(8)	-24(4)	6424(5)	2057(4)	73(1)
C(9)	-1072(3)	6669(6)	2253(4)	76(1)
C(10)	-1502(3)	4898(6)	2170(3)	65(1)
C(11)	-623(2)	3810(4)	2723(3)	41(1)
C(12)	-455(3)	1022(5)	3804(3)	55(1)
C(13)	58(3)	2603(5)	4297(3)	56(1)

Table 3. Bond lengths [A] and angles [deg] for af003.

S(1)-C(1)	1.669(4)
S(2)-C(12)	1.796(4)
S(2)-C(11)	1.846(4)
N-C(5)	1.349(5)
N-C(1)	1.356(5)
N-O(2)	1.398(4)
O(1)-C(6)	1.180(4)
O(2)-C(6)	1.402(4)
O(3)-C(11)	1.408(4)
O(3)-C(13)	1.422(5)
C(1)-C(2)	1.431(6)
C(2)-C(3)	1.355(6)
C(3)-C(4)	1.391(6)
C(4)-C(5)	1.348(6)
C(6)-C(7)	1.500(5)
C(7)-C(8)	1.552(5)
C(7)-C(11)	1.563(4)
C(8)-C(9)	1.519(6)
C(9)-C(10)	1.501(6)
C(10)-C(11)	1.505(5)
C(12)-C(13)	1.495(6)
C(12)-S(2)-C(11)	91.80(17)
C(5)-N-C(1)	127.2(3)
C(5)-N-O(2)	114.8(3)
C(1)-N-O(2)	118.0(3)
N-O(2)-C(6)	111.4(3)
C(11)-O(3)-C(13)	109.7(3)
N-C(1)-C(2)	111.7(3)
N-C(1)-S(1)	122.8(3)
C(2)-C(1)-S(1)	125.5(3)
C(3)-C(2)-C(1)	122.6(4)
C(2)-C(3)-C(4)	120.9(4)
C(5)-C(4)-C(3)	117.7(4)
C(4)-C(5)-N	119.8(4)
O(1)-C(6)-O(2)	123.0(3)
O(1)-C(6)-C(7)	128.7(3)
O(2)-C(6)-C(7)	108.3(3)
C(6)-C(7)-C(8)	112.4(3)
C(6)-C(7)-C(11)	111.1(3)
C(8)-C(7)-C(11)	104.4(3)
C(9)-C(8)-C(7)	106.3(3)
C(10)-C(9)-C(8)	103.4(3)
C(9)-C(10)-C(11)	104.1(3)
O(3)-C(11)-C(10)	109.1(3)
O(3)-C(11)-C(7)	108.9(3)
C(10)-C(11)-C(7)	103.9(3)
O(3)-C(11)-S(2)	105.9(2)
C(10)-C(11)-S(2)	114.0(3)
C(7)-C(11)-S(2)	115.0(2)
C(13)-C(12)-S(2)	104.8(3)
O(3)-C(13)-C(12)	107.2(3)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for af003. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

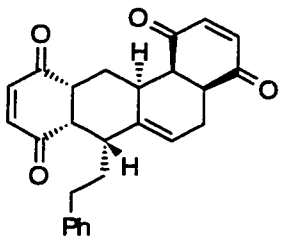
	U11	U22	U33	U23	U13	U12
S(1)	69(1)	61(1)	92(1)	2(1)	40(1)	-21(1)
S(2)	57(1)	43(1)	61(1)	1(1)	26(1)	-14(1)
N	47(2)	40(2)	52(2)	-3(1)	25(1)	-3(1)
O(1)	55(1)	66(2)	48(2)	1(1)	18(1)	2(1)
O(2)	50(1)	50(2)	46(2)	-1(1)	21(1)	0(1)
O(3)	62(1)	43(1)	51(2)	4(1)	31(1)	3(1)
C(1)	37(2)	61(3)	47(2)	-1(2)	16(2)	-4(2)
C(2)	45(2)	81(3)	60(3)	-6(2)	26(2)	8(2)
C(3)	57(2)	74(3)	67(3)	-19(2)	11(2)	18(2)
C(4)	80(3)	47(3)	80(3)	-5(3)	18(2)	-3(2)
C(5)	70(2)	45(2)	69(3)	1(2)	30(2)	-8(2)
C(6)	44(2)	41(2)	50(2)	4(2)	24(2)	-9(2)
C(7)	52(2)	37(2)	53(2)	-4(2)	29(2)	-5(2)
C(8)	115(3)	31(2)	87(3)	2(2)	53(3)	-9(2)
C(9)	99(3)	52(3)	82(3)	16(3)	32(2)	26(3)
C(10)	52(2)	73(3)	70(3)	17(3)	16(2)	15(2)
C(11)	42(2)	40(2)	45(2)	2(2)	19(1)	1(2)
C(12)	55(2)	46(2)	70(3)	14(2)	29(2)	5(2)
C(13)	59(2)	62(3)	51(2)	16(2)	21(2)	6(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for af003.

	x	y	z	U(eq)
H(2A)	3116	1474	-315	72
H(3A)	2527	-1245	-431	80
H(4A)	1474	-2188	584	83
H(5A)	1044	-278	1694	71
H(7A)	906	4647	3018	53
H(8A)	459	7265	2437	87
H(8B)	-60	6554	1333	87
H(9A)	-1017	7145	2929	91
H(9B)	-1495	7425	1745	91
H(10A)	-1738	4549	1459	78
H(10B)	-2074	4823	2489	78
H(12A)	-1057	755	4053	66
H(12B)	14	50	3941	66
H(13A)	50	2631	5013	68
H(13B)	769	2636	4251	68

X-ray Crystallographic Data

for Adduct 167



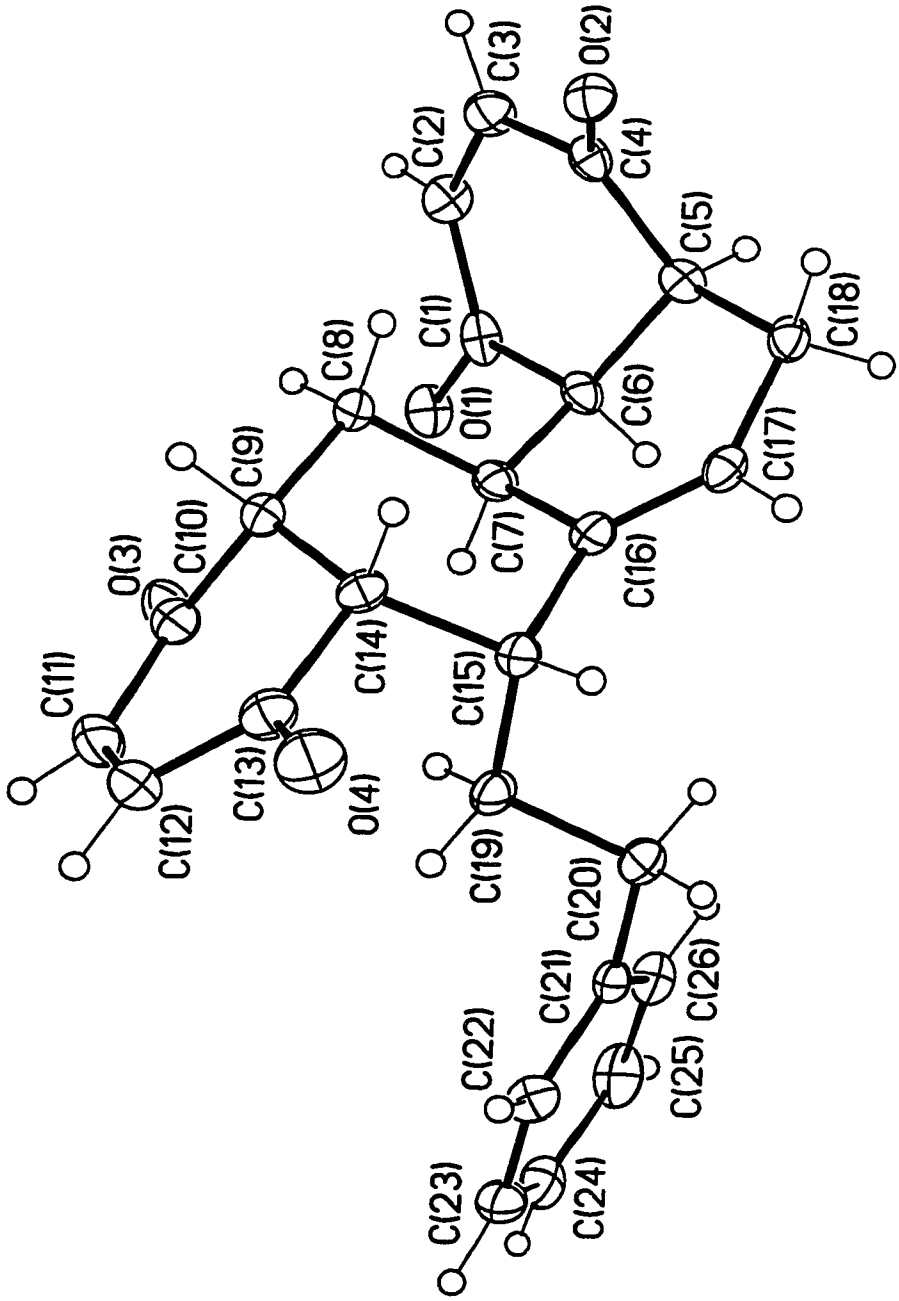


Figure A2. The ORTEP view of adduct **167**.

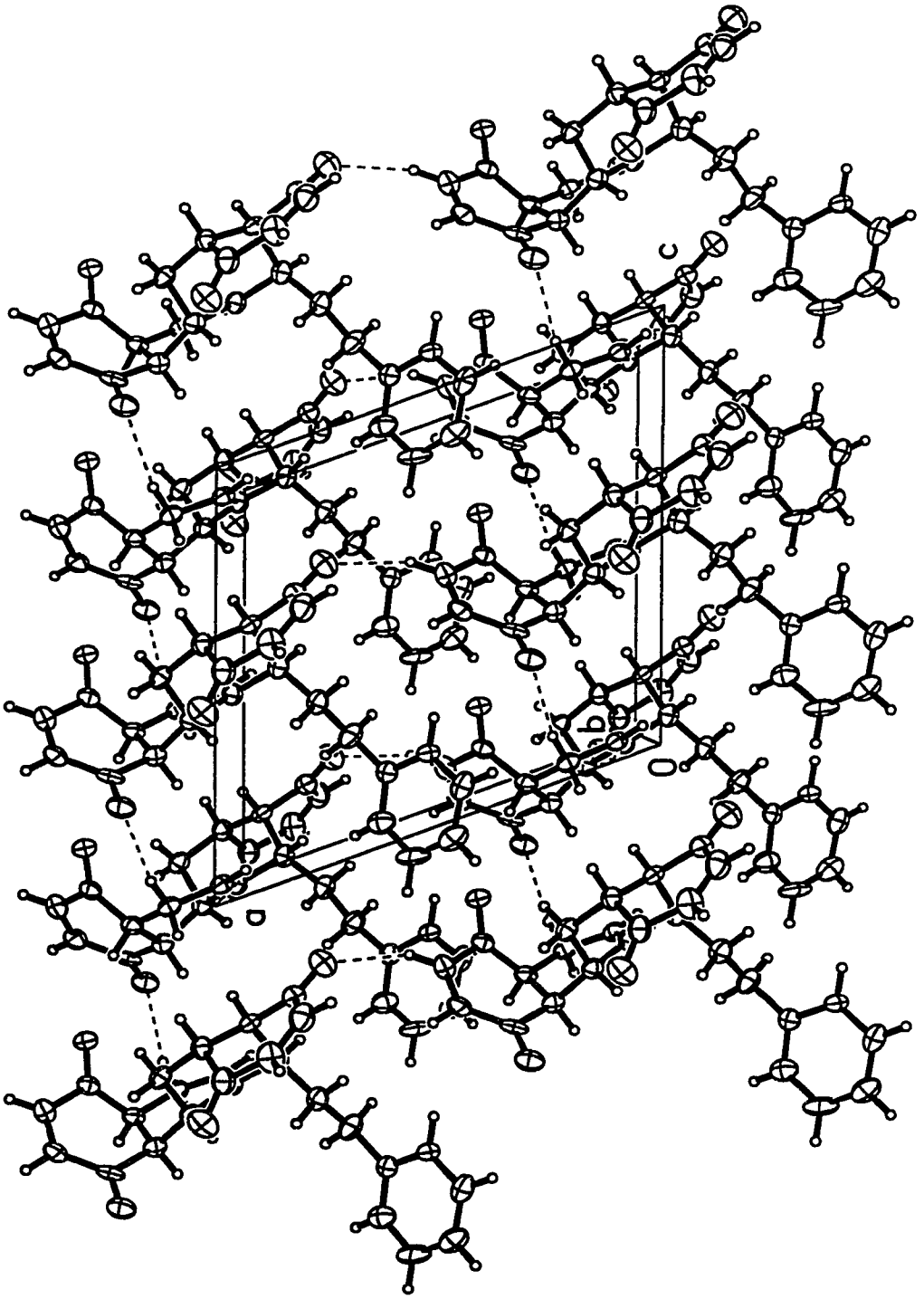


Table 1. Crystal data and structure refinement for af002a.

Identification code	af002a
Empirical formula	C26 H24 O4
Formula weight	400.45
Temperature	203(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, Pc
Unit cell dimensions	a = 10.658(2) A alpha = 90 deg. b = 9.479(3) A beta = 111.18(2) deg. c = 10.481(2) A gamma = 90 deg.
Volume	987.3(4) A^3
Z, Calculated density	2, 1.347 Mg/m^3
Absorption coefficient	0.090 mm^-1
F(000)	424
Crystal size	0.2 x 0.1 x 0.1 mm
Theta range for data collection	2.05 to 28.70 deg.
Limiting indices	-14<=h<=13, -12<=k<=12, -13<=l<=7
Reflections collected / unique	5824 / 3397 [R(int) = 0.1021]
Completeness to theta = 28.70	91.2 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3397 / 2 / 271
Goodness-of-fit on F^2	1.038
Final R indices [I>2sigma(I)]	R1 = 0.0738, wR2 = 0.1727
R indices (all data)	R1 = 0.1032, wR2 = 0.1975
Absolute structure parameter	0(3)
Largest diff. peak and hole	0.299 and -0.393 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for af002a.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	12778(4)	3213(4)	2957(4)	38(1)
O(2)	14018(4)	-131(4)	7206(4)	32(1)
O(3)	10610(4)	5372(4)	4586(5)	44(1)
O(4)	7894(4)	2703(5)	7245(5)	49(1)
C(1)	13141(6)	2285(5)	3823(6)	30(1)
C(2)	14507(6)	2202(6)	4836(7)	33(1)
C(3)	14878(6)	1321(6)	5893(7)	35(2)
C(4)	13904(5)	279(5)	6054(6)	27(1)
C(5)	12789(5)	-131(5)	4768(6)	27(1)
C(6)	12131(5)	1212(5)	3938(6)	27(1)
C(7)	11163(5)	1947(5)	4524(6)	27(1)
C(8)	11843(5)	2843(6)	5839(6)	30(1)
C(9)	10774(5)	3584(5)	6277(6)	29(1)
C(10)	10167(6)	4876(6)	5400(7)	36(2)
C(11)	9017(6)	5512(6)	5636(7)	44(2)
C(12)	8305(6)	4808(6)	6270(7)	43(2)
C(13)	8572(6)	3320(6)	6727(7)	34(1)
C(14)	9684(5)	2565(6)	6383(6)	28(1)
C(15)	9055(5)	1594(6)	5086(6)	29(1)
C(16)	10220(5)	904(6)	4812(6)	29(1)
C(17)	10506(5)	-448(5)	5000(6)	27(1)
C(18)	11754(6)	-1147(5)	4945(6)	28(1)
C(19)	8042(6)	2366(5)	3833(7)	31(1)
C(20)	7262(6)	1355(6)	2675(6)	37(2)
C(21)	6323(5)	2141(5)	1435(6)	26(1)
C(22)	5282(6)	2967(6)	1553(6)	32(1)
C(23)	4439(6)	3748(6)	447(7)	41(2)
C(24)	4661(7)	3754(6)	-762(7)	41(2)
C(25)	5654(7)	2922(7)	-903(7)	48(2)
C(26)	6462(7)	2124(6)	202(7)	37(2)

Table 3. Bond lengths [A] and angles [deg] for af002a.

O(1)-C(1)	1.222(7)
O(2)-C(4)	1.232(7)
O(3)-C(10)	1.210(7)
O(4)-C(13)	1.201(7)
C(1)-C(2)	1.461(9)
C(1)-C(6)	1.517(8)
C(2)-C(3)	1.329(8)
C(3)-C(4)	1.486(7)
C(4)-C(5)	1.491(8)
C(5)-C(18)	1.526(7)
C(5)-C(6)	1.558(7)
C(6)-C(7)	1.544(7)
C(7)-C(16)	1.516(7)
C(7)-C(8)	1.558(8)
C(8)-C(9)	1.542(7)
C(9)-C(10)	1.528(8)
C(9)-C(14)	1.545(7)
C(10)-C(11)	1.465(8)
C(11)-C(12)	1.353(8)
C(12)-C(13)	1.483(8)
C(13)-C(14)	1.535(8)
C(14)-C(15)	1.576(8)
C(15)-C(16)	1.520(7)
C(15)-C(19)	1.549(8)
C(16)-C(17)	1.315(7)
C(17)-C(18)	1.505(8)
C(19)-C(20)	1.534(8)
C(20)-C(21)	1.519(8)
C(21)-C(26)	1.353(8)
C(21)-C(22)	1.399(8)
C(22)-C(23)	1.394(8)
C(23)-C(24)	1.371(9)
C(24)-C(25)	1.370(9)
C(25)-C(26)	1.391(9)

O(1)-C(1)-C(2)	122.9(5)
O(1)-C(1)-C(6)	119.9(6)
C(2)-C(1)-C(6)	117.1(5)
C(3)-C(2)-C(1)	123.9(5)
C(2)-C(3)-C(4)	120.2(6)
O(2)-C(4)-C(3)	119.7(5)
O(2)-C(4)-C(5)	124.6(5)
C(3)-C(4)-C(5)	115.6(5)
C(4)-C(5)-C(18)	115.4(5)
C(4)-C(5)-C(6)	110.0(4)
C(18)-C(5)-C(6)	112.6(4)
C(1)-C(6)-C(7)	109.0(4)
C(1)-C(6)-C(5)	113.7(5)
C(7)-C(6)-C(5)	112.2(4)
C(16)-C(7)-C(6)	111.8(4)
C(16)-C(7)-C(8)	108.0(5)
C(6)-C(7)-C(8)	115.7(4)
C(9)-C(8)-C(7)	110.8(4)
C(10)-C(9)-C(8)	112.6(5)
C(10)-C(9)-C(14)	112.2(4)
C(8)-C(9)-C(14)	113.1(4)

O(3)-C(10)-C(11)	121.5(6)
O(3)-C(10)-C(9)	123.2(5)
C(11)-C(10)-C(9)	115.2(5)
C(12)-C(11)-C(10)	122.1(5)
C(11)-C(12)-C(13)	123.5(5)
O(4)-C(13)-C(12)	122.1(6)
O(4)-C(13)-C(14)	121.4(5)
C(12)-C(13)-C(14)	116.3(5)
C(13)-C(14)-C(9)	112.9(4)
C(13)-C(14)-C(15)	110.5(4)
C(9)-C(14)-C(15)	113.6(5)
C(16)-C(15)-C(19)	114.2(5)
C(16)-C(15)-C(14)	107.0(4)
C(19)-C(15)-C(14)	113.9(4)
C(17)-C(16)-C(7)	122.0(5)
C(17)-C(16)-C(15)	123.6(5)
C(7)-C(16)-C(15)	113.7(4)
C(16)-C(17)-C(18)	125.7(5)
C(17)-C(18)-C(5)	114.5(4)
C(20)-C(19)-C(15)	112.8(4)
C(21)-C(20)-C(19)	111.8(4)
C(26)-C(21)-C(22)	117.1(5)
C(26)-C(21)-C(20)	123.0(5)
C(22)-C(21)-C(20)	119.9(5)
C(23)-C(22)-C(21)	121.1(6)
C(24)-C(23)-C(22)	119.7(6)
C(23)-C(24)-C(25)	119.7(6)
C(24)-C(25)-C(26)	119.6(6)
C(21)-C(26)-C(25)	122.7(6)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for af002a. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
O(1)	50(2)	33(2)	37(3)	5(2)	23(2)	-3(2)
O(2)	38(2)	35(2)	23(2)	0(2)	10(2)	-1(2)
O(3)	51(3)	28(2)	61(4)	4(2)	30(3)	0(2)
O(4)	44(3)	55(3)	55(3)	2(2)	25(3)	-5(2)
C(1)	51(4)	24(3)	26(3)	1(3)	28(3)	-3(3)
C(2)	35(3)	35(3)	35(4)	5(3)	20(3)	-6(2)
C(3)	29(3)	36(3)	43(4)	2(3)	16(3)	-1(3)
C(4)	33(3)	24(3)	29(4)	-1(2)	16(3)	4(2)
C(5)	32(3)	27(3)	24(3)	4(2)	14(3)	3(2)
C(6)	34(3)	21(3)	27(4)	5(2)	10(3)	5(2)
C(7)	28(3)	25(3)	27(4)	5(2)	8(3)	2(2)
C(8)	30(3)	25(3)	28(4)	-5(2)	4(3)	1(2)
C(9)	26(3)	26(3)	33(4)	-4(2)	9(3)	-2(2)
C(10)	30(3)	31(3)	44(4)	-2(3)	11(3)	-2(2)
C(11)	40(3)	29(3)	61(5)	-1(3)	17(4)	2(3)
C(12)	35(3)	40(3)	49(5)	-9(3)	10(3)	7(3)
C(13)	32(3)	42(3)	29(4)	0(3)	10(3)	-3(3)
C(14)	27(3)	34(3)	18(3)	1(2)	3(3)	0(2)
C(15)	27(3)	23(3)	35(4)	0(2)	8(3)	-2(2)
C(16)	25(3)	27(3)	31(4)	-1(2)	8(3)	-4(2)
C(17)	31(3)	27(3)	22(3)	2(2)	6(3)	-8(2)
C(18)	34(3)	25(3)	24(3)	-2(2)	7(3)	-2(2)
C(19)	28(3)	25(3)	36(4)	3(3)	6(3)	-6(2)
C(20)	35(3)	35(3)	32(4)	-8(3)	1(3)	0(3)
C(21)	27(3)	20(3)	31(4)	-1(2)	9(3)	-5(2)
C(22)	34(3)	43(3)	21(4)	2(3)	10(3)	-2(3)
C(23)	31(3)	36(3)	44(5)	4(3)	1(3)	3(3)
C(24)	50(4)	29(3)	35(4)	6(3)	4(3)	-3(3)
C(25)	74(5)	51(4)	20(4)	-12(3)	19(4)	-8(4)
C(26)	47(4)	32(3)	32(4)	-3(3)	13(3)	-7(3)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for af002a.

	x	y	z	U(eq)
H(2A)	15162	2809	4733	40
H(3A)	15759	1356	6541	42
H(5A)	13218	-637	4206	32
H(6A)	11588	902	2998	33
H(7A)	10597	2598	3808	32
H(8A)	12399	2231	6582	36
H(8B)	12430	3553	5665	36
H(9A)	11256	3942	7215	34
H(11A)	8767	6441	5338	52
H(12A)	7603	5286	6430	51
H(14A)	10140	1927	7160	33
H(15A)	8554	834	5342	35
H(17A)	9877	-1028	5185	33
H(18A)	11489	-1820	4183	34
H(18B)	12179	-1684	5791	34
H(19A)	7401	2892	4125	37
H(19B)	8531	3047	3484	37
H(20A)	7901	798	2406	45
H(20B)	6737	701	3007	45
H(22A)	5148	2995	2391	39
H(23A)	3722	4268	531	49
H(24A)	4135	4327	-1491	49
H(25A)	5788	2891	-1741	57
H(26A)	7133	1549	88	45

Appendix II: Selected NMR Spectra From Part I

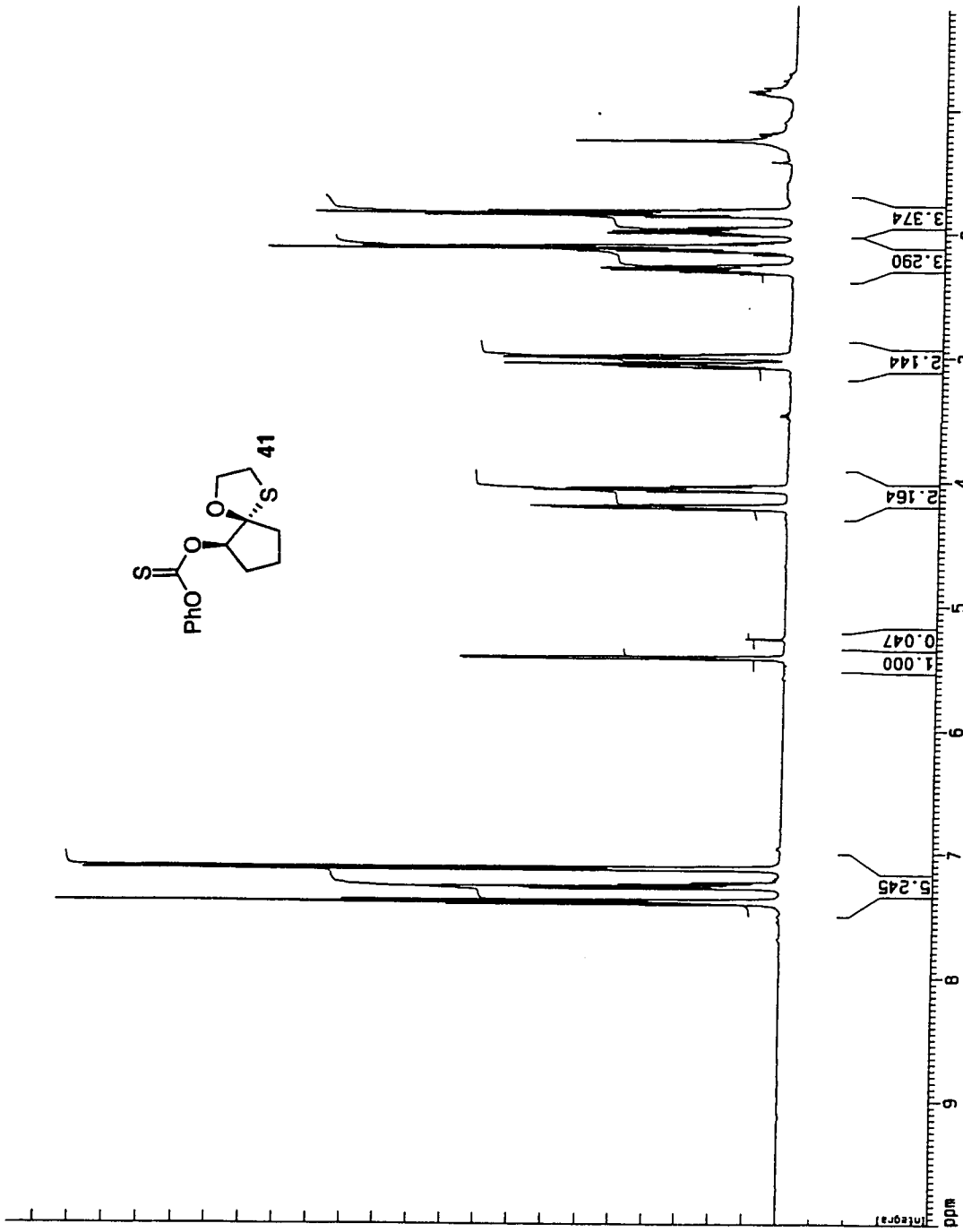


Figure A3. ^{1}H NMR (500 MHz) spectrum of thionocarbonate **41**.

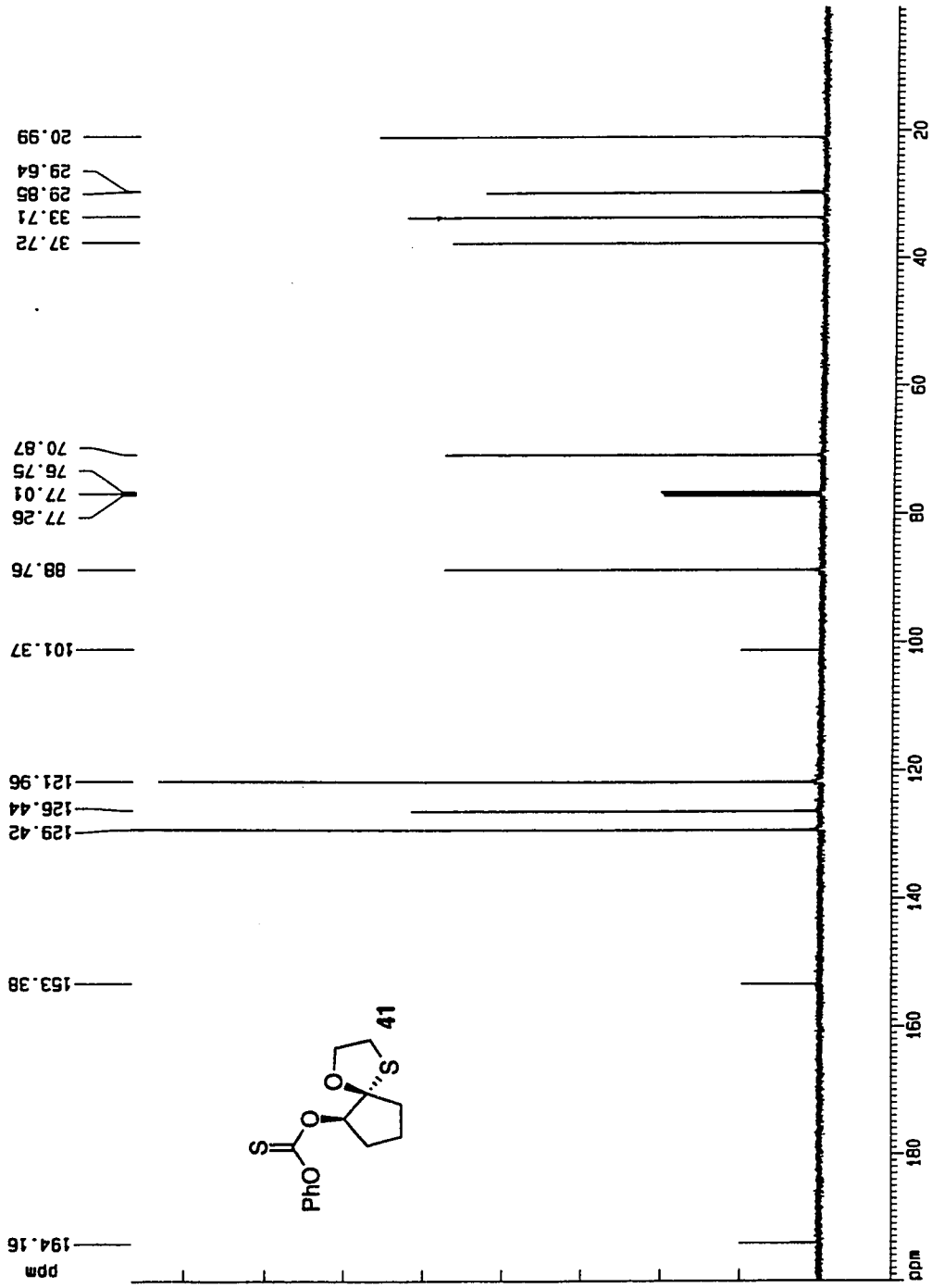


Figure A4. ^{13}C NMR (125 MHz) spectrum of thionocarbonate **41**.

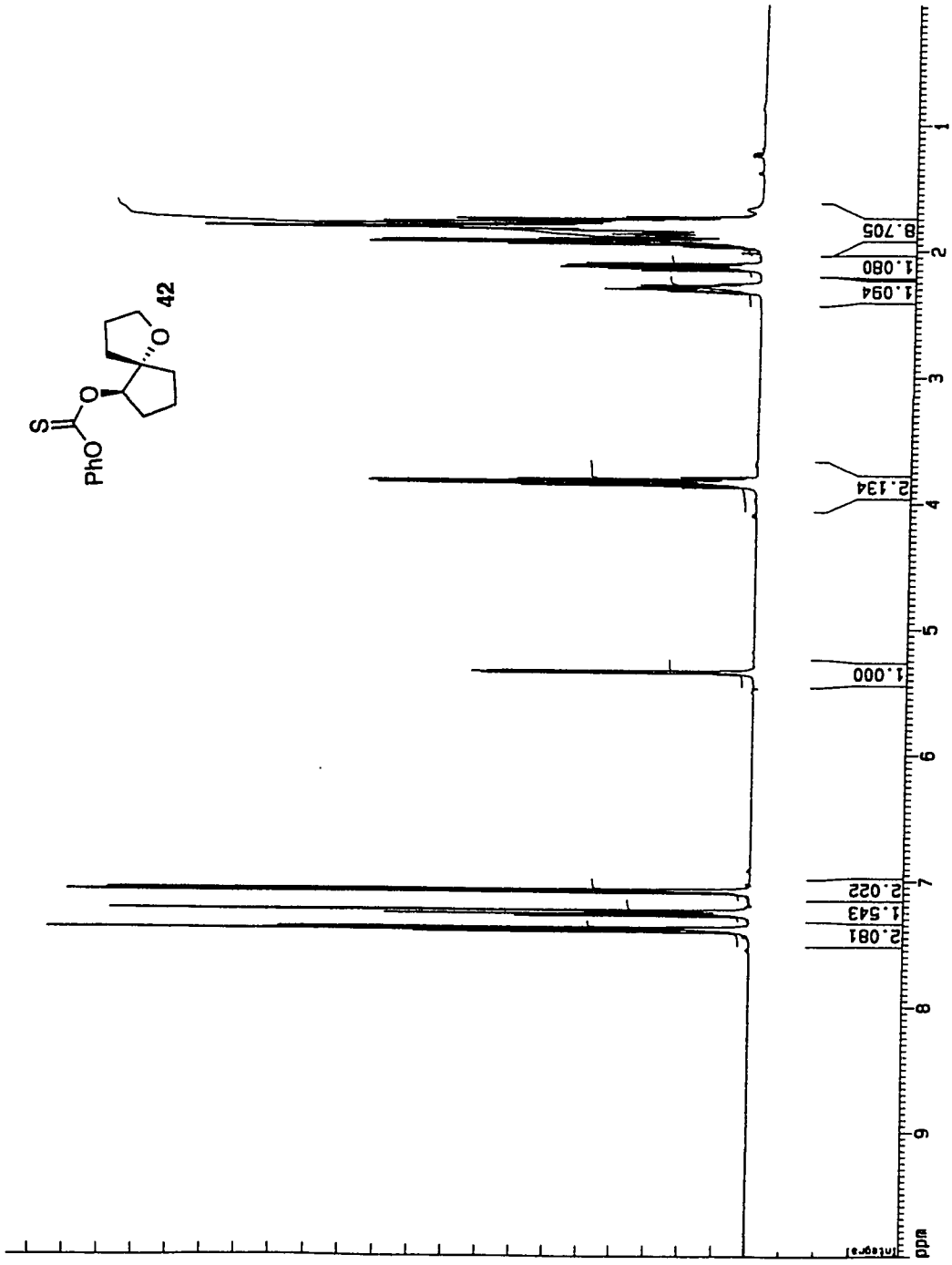


Figure A5. ^{1}H NMR (500 MHz) spectrum of thionocarbonate **42**.

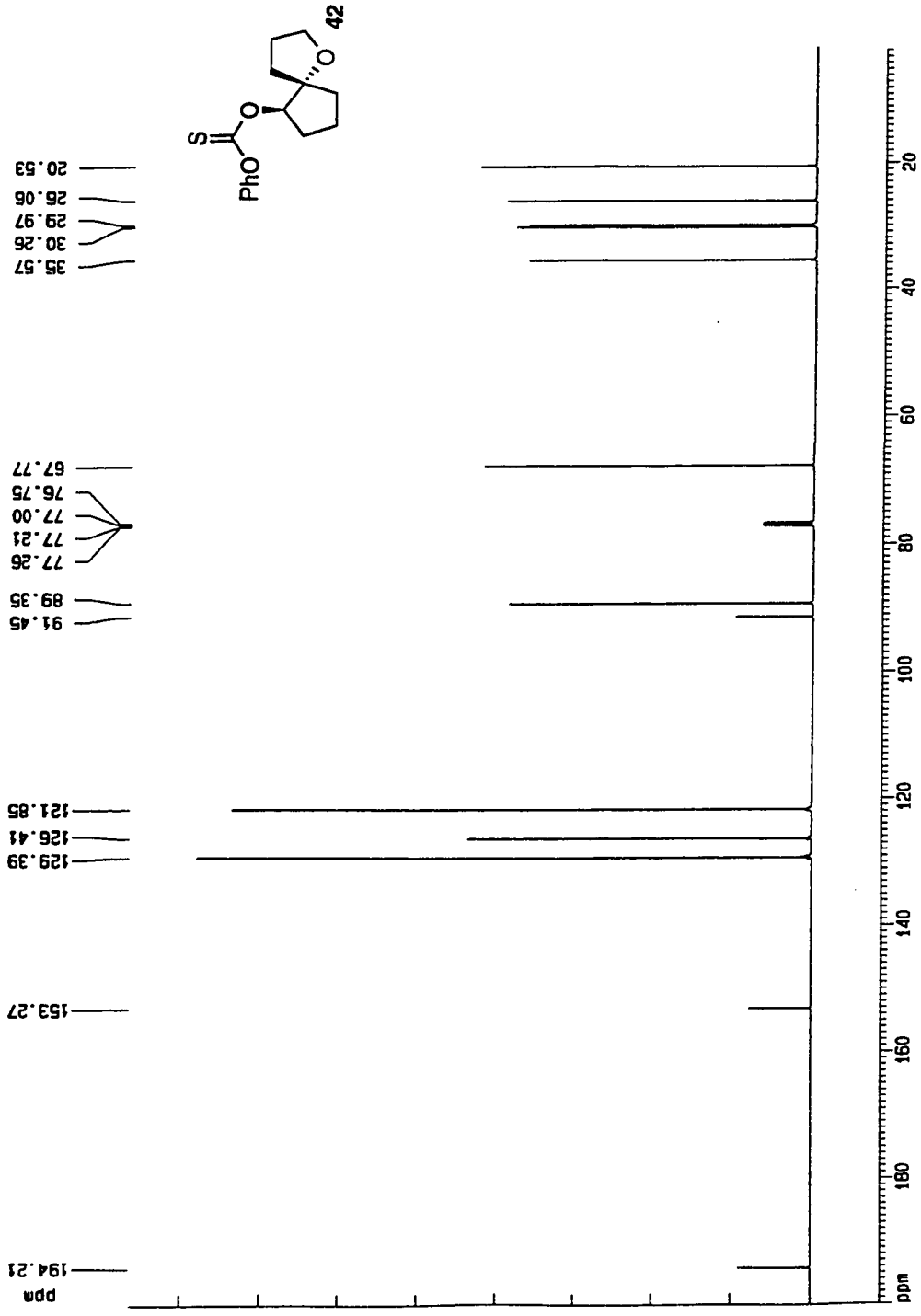


Figure A6. ^{13}C NMR (125 MHz) spectrum of thionocarbonate **42**.

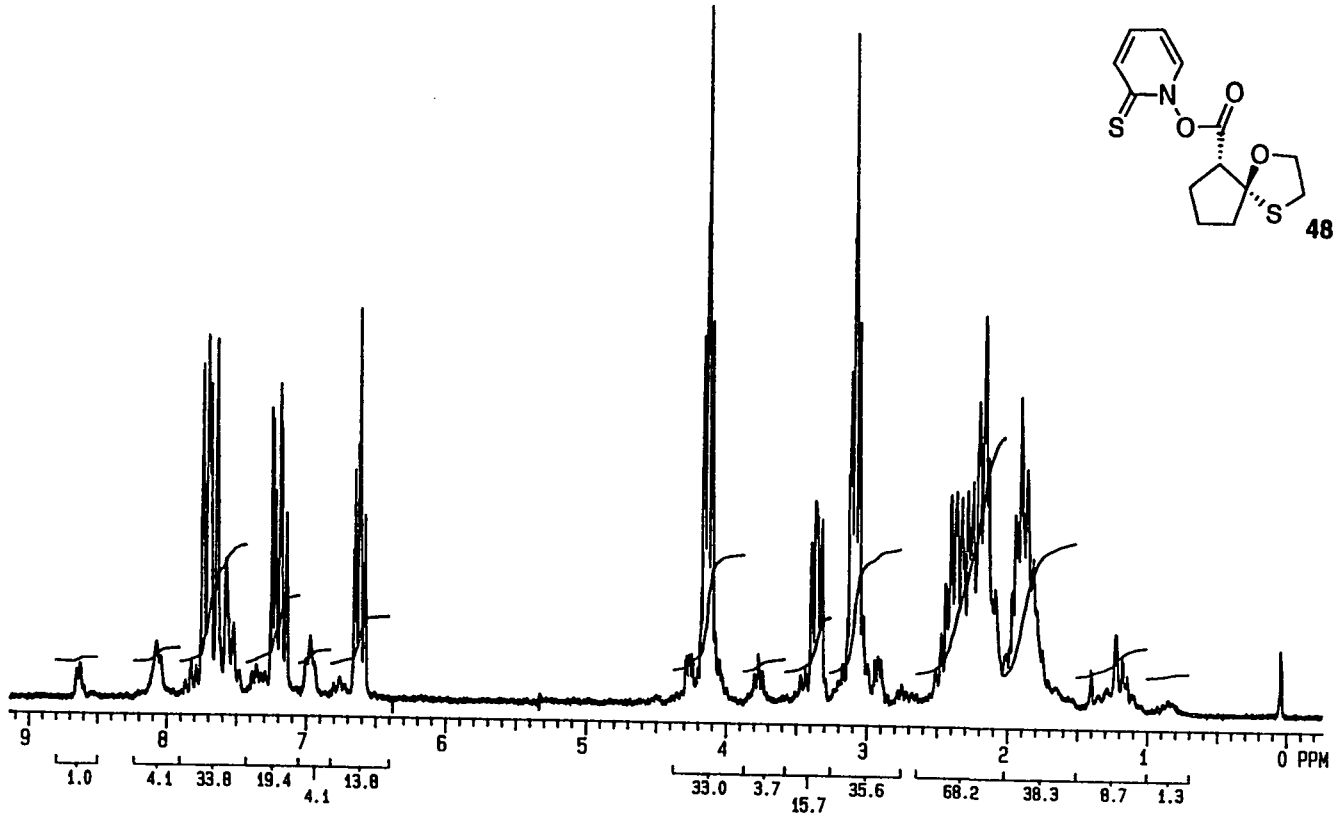


Figure A7. ^{1}H NMR (200 MHz) spectrum of Barton ester **48**.

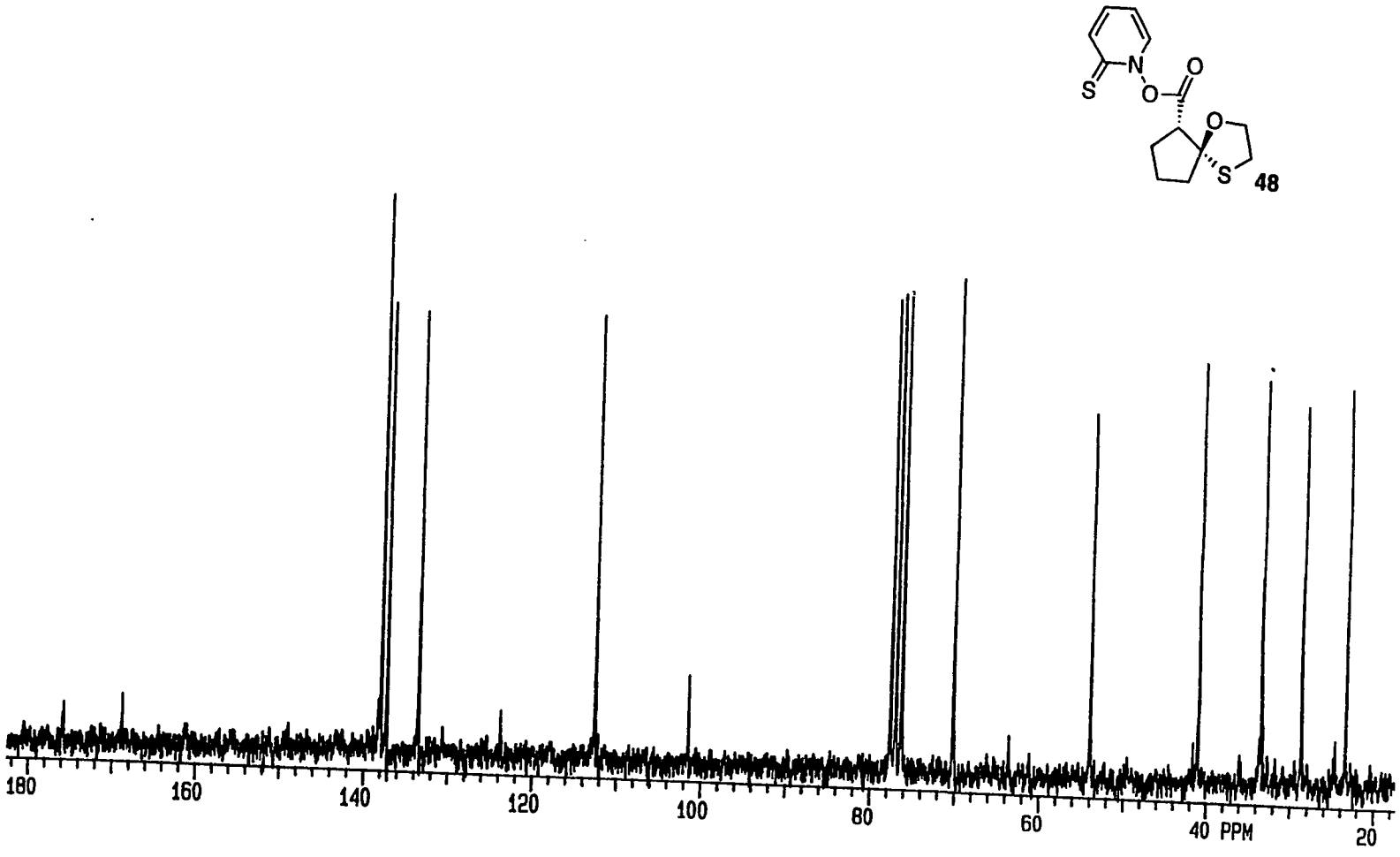


Figure A8. ^{13}C NMR (50 MHz) spectrum of Barton ester **48**.

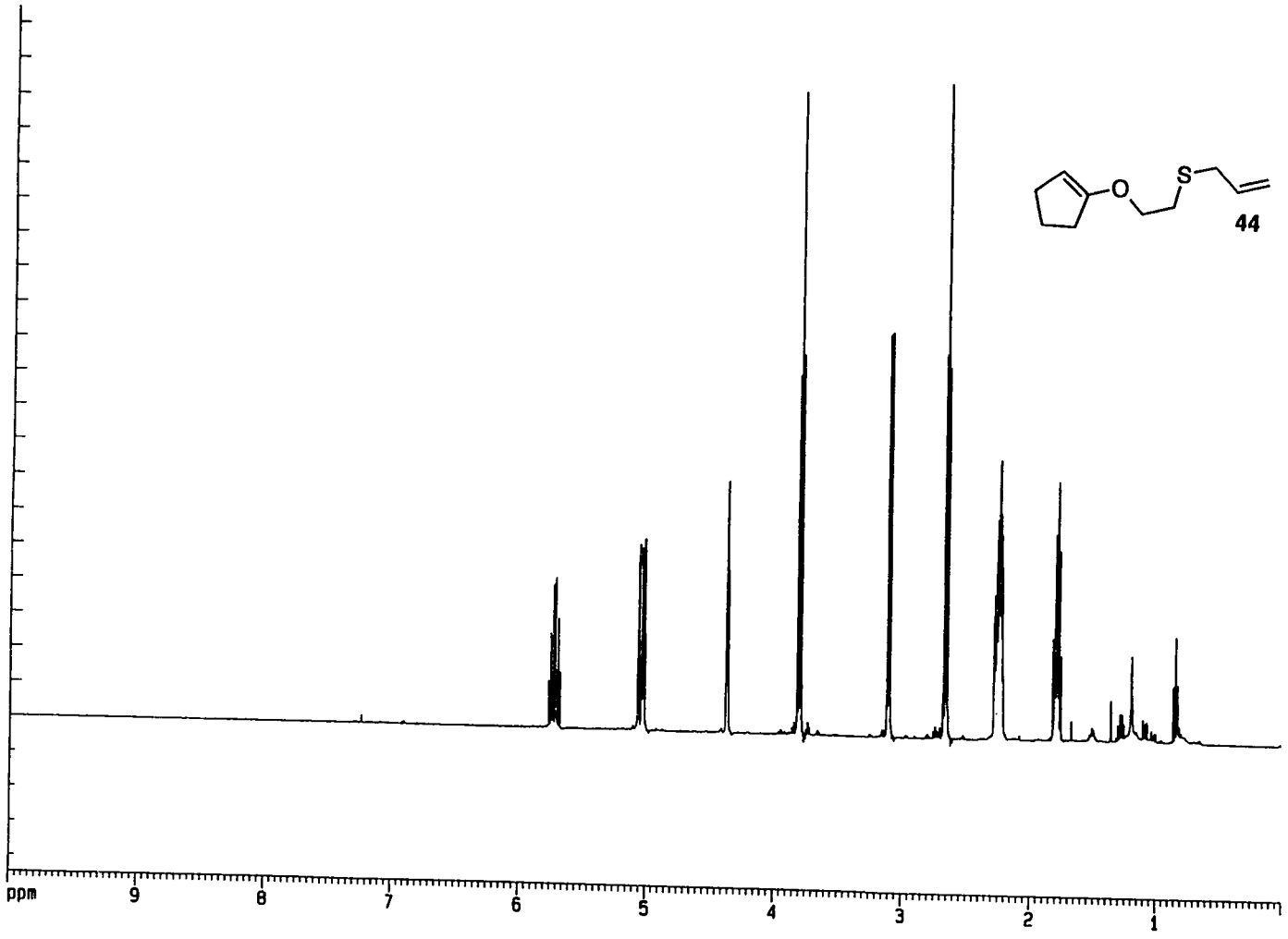


Figure A9. ^{1}H NMR (500 MHz) spectrum of cyclopentenyl ether **44**.

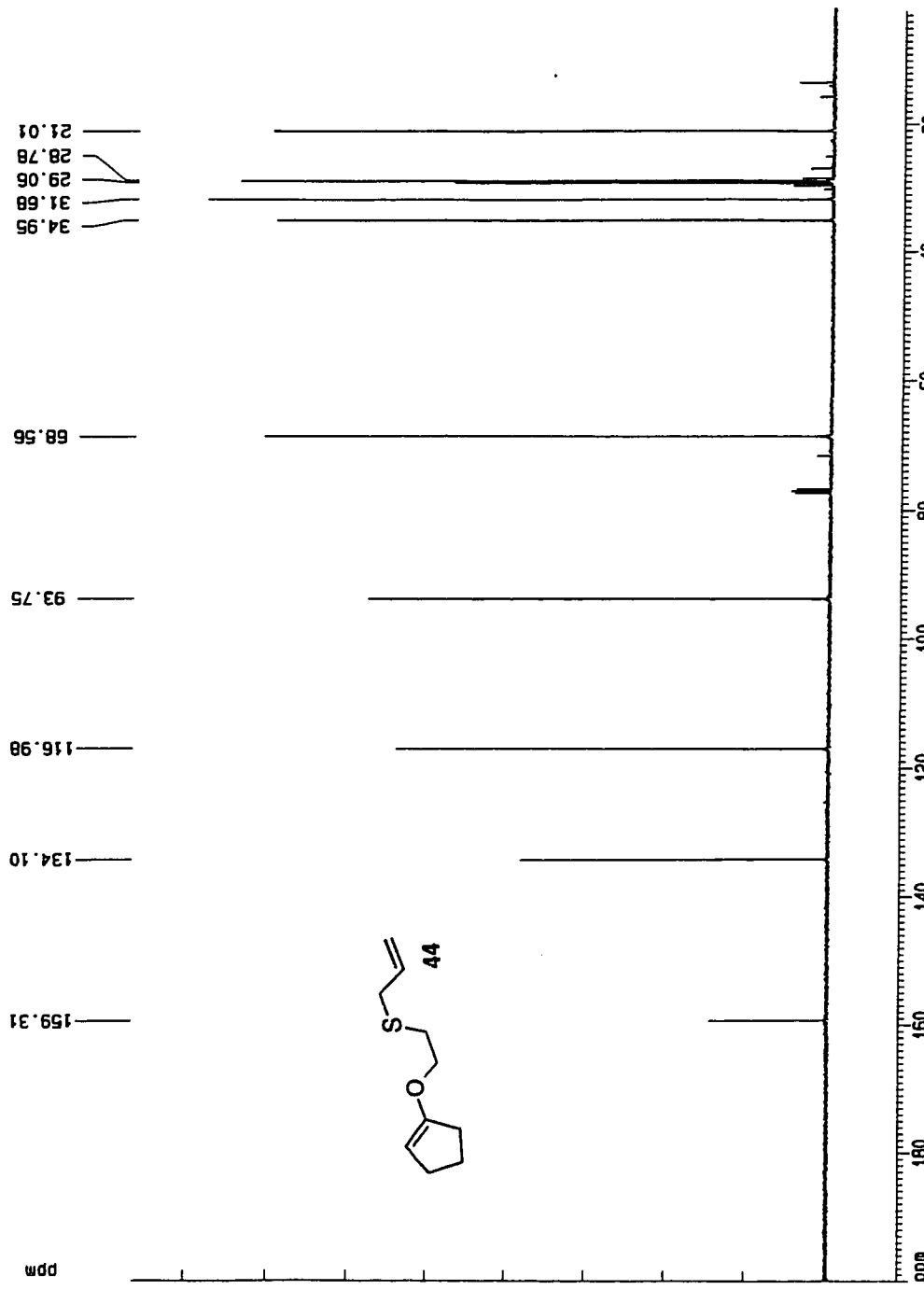


Figure A10. ^{13}C NMR (125 MHz) spectrum of cyclopentenyl ether **44**.

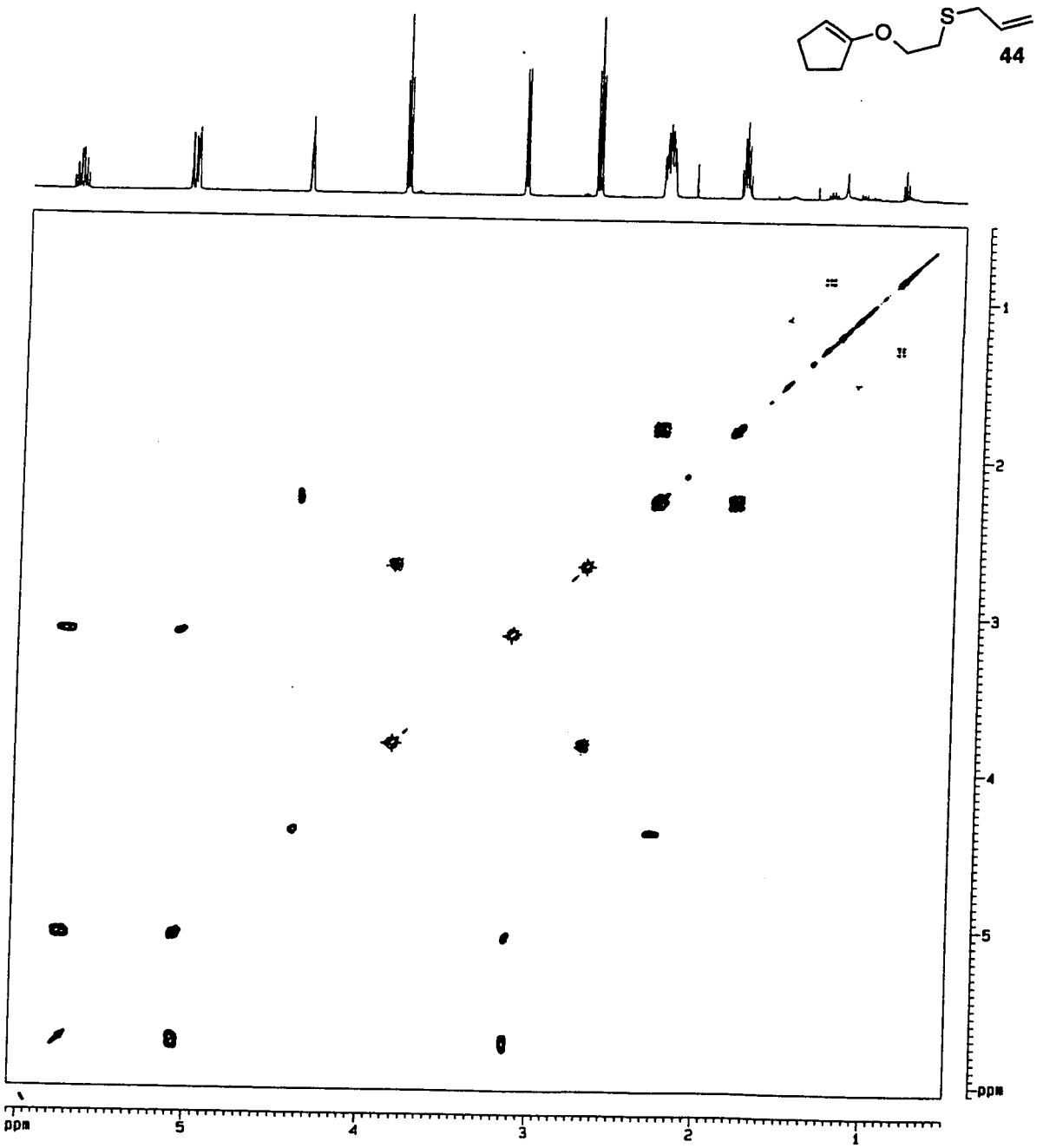


Figure A11. COSY (500 MHz) spectrum of cyclopentenyl ether **44**.

Appendix III: Selected NMR Spectra From Part II

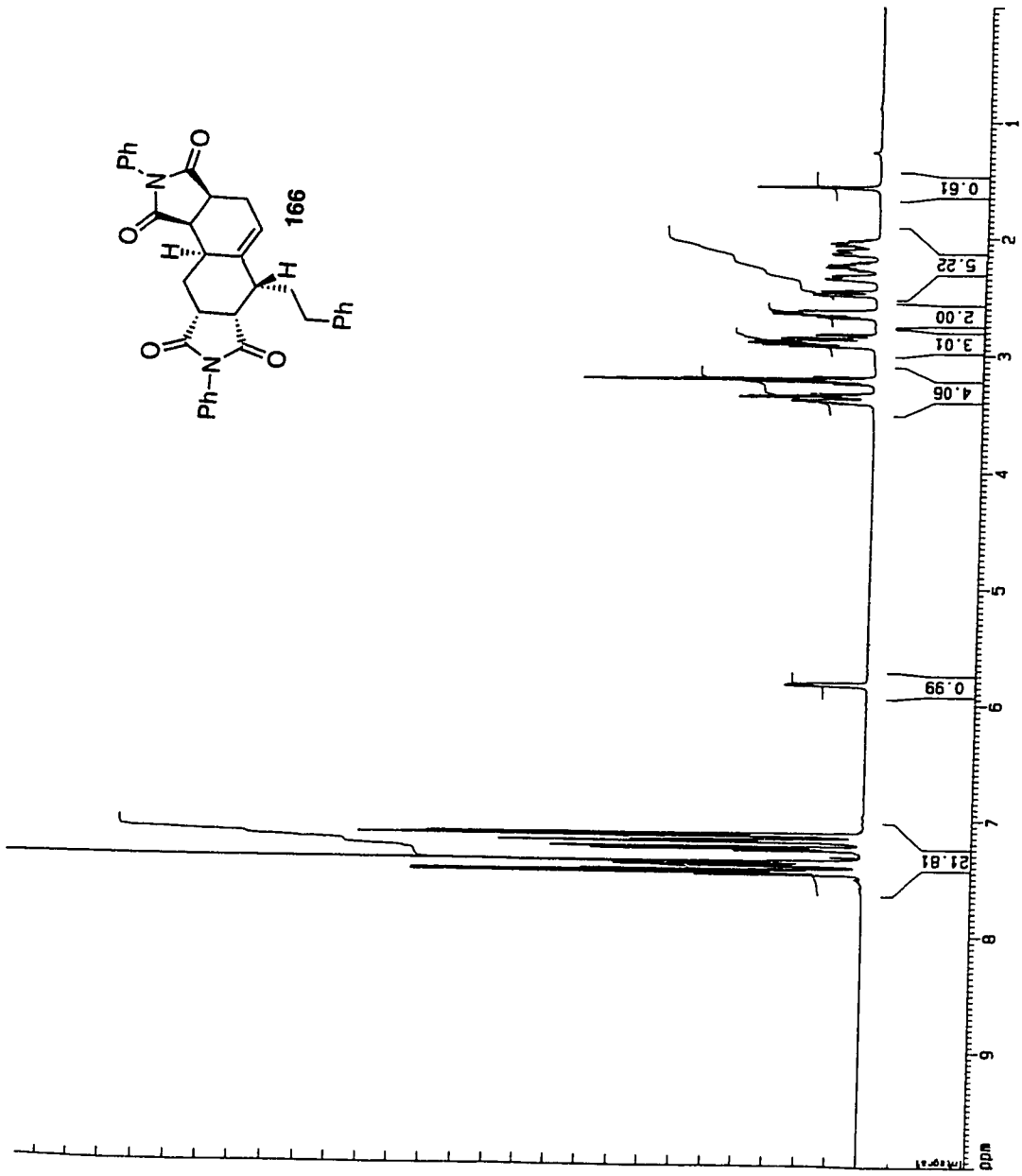


Figure A12. ^{1}H NMR (500 MHz) spectrum of adduct **166**.

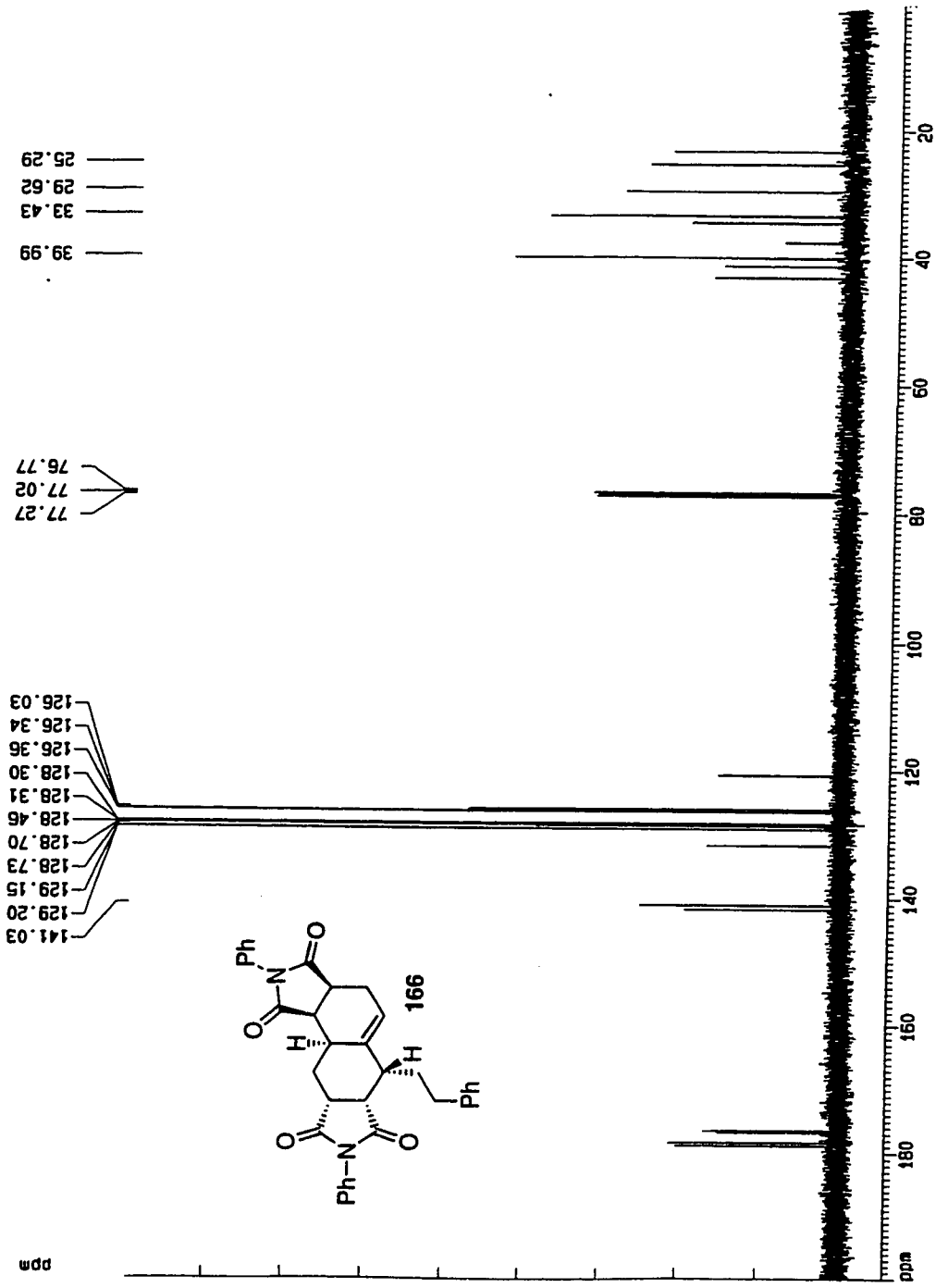


Figure A13. ^{13}C NMR (125 MHz) spectrum of adduct **166**.

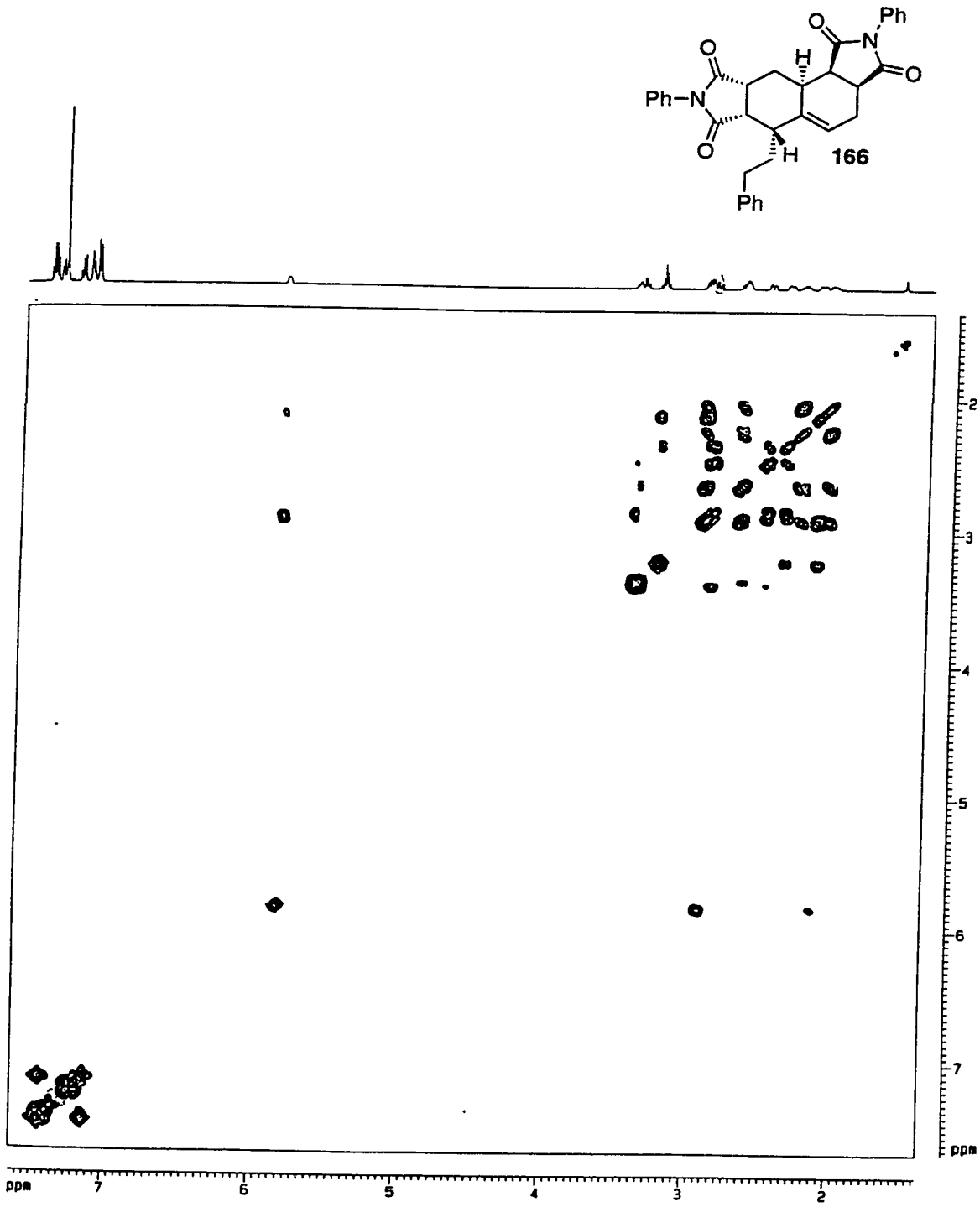


Figure A14. COSY (500 MHz) spectrum of adduct **166**.

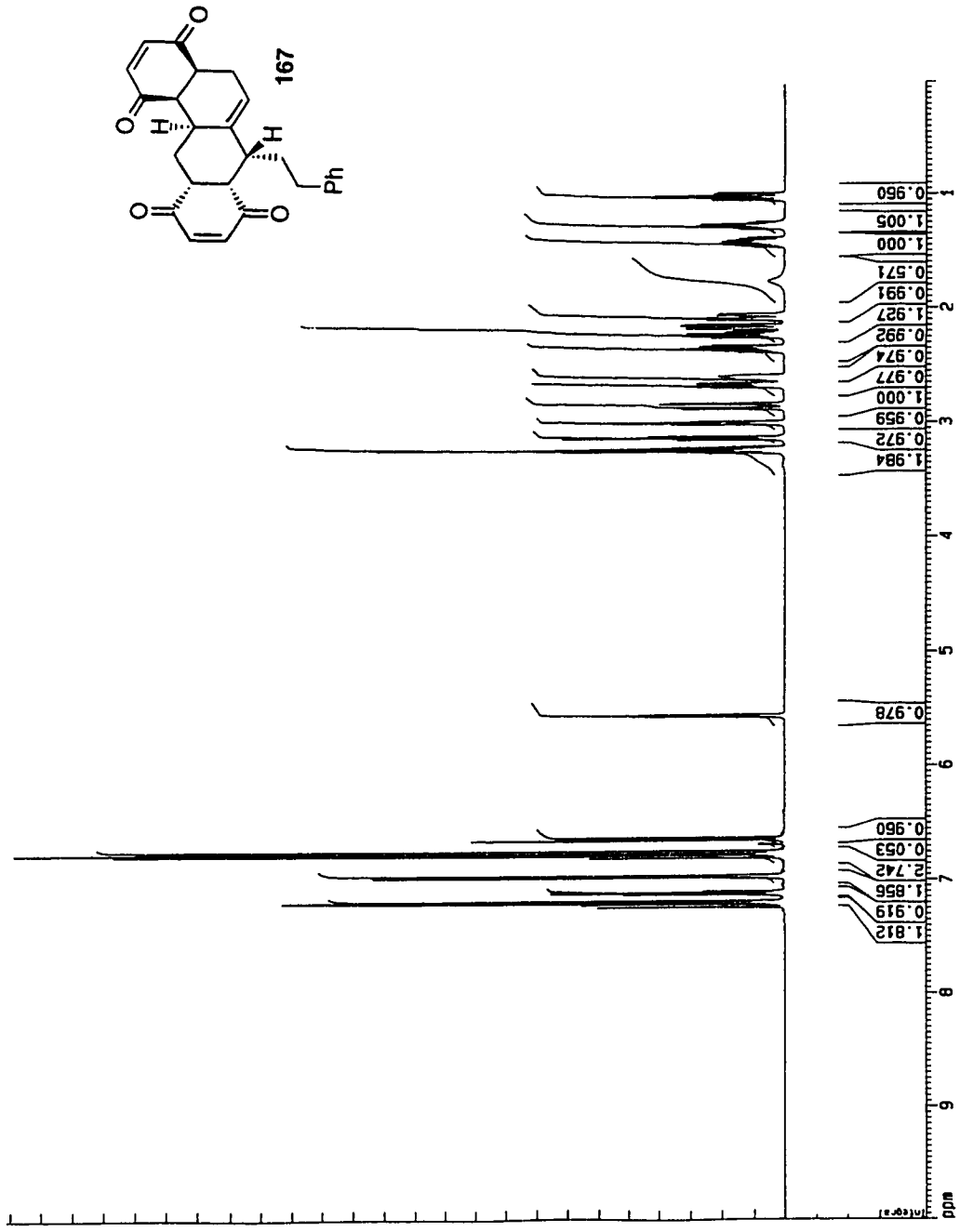


Figure A15. ^{1}H NMR (500 MHz) spectrum of adduct **167**.

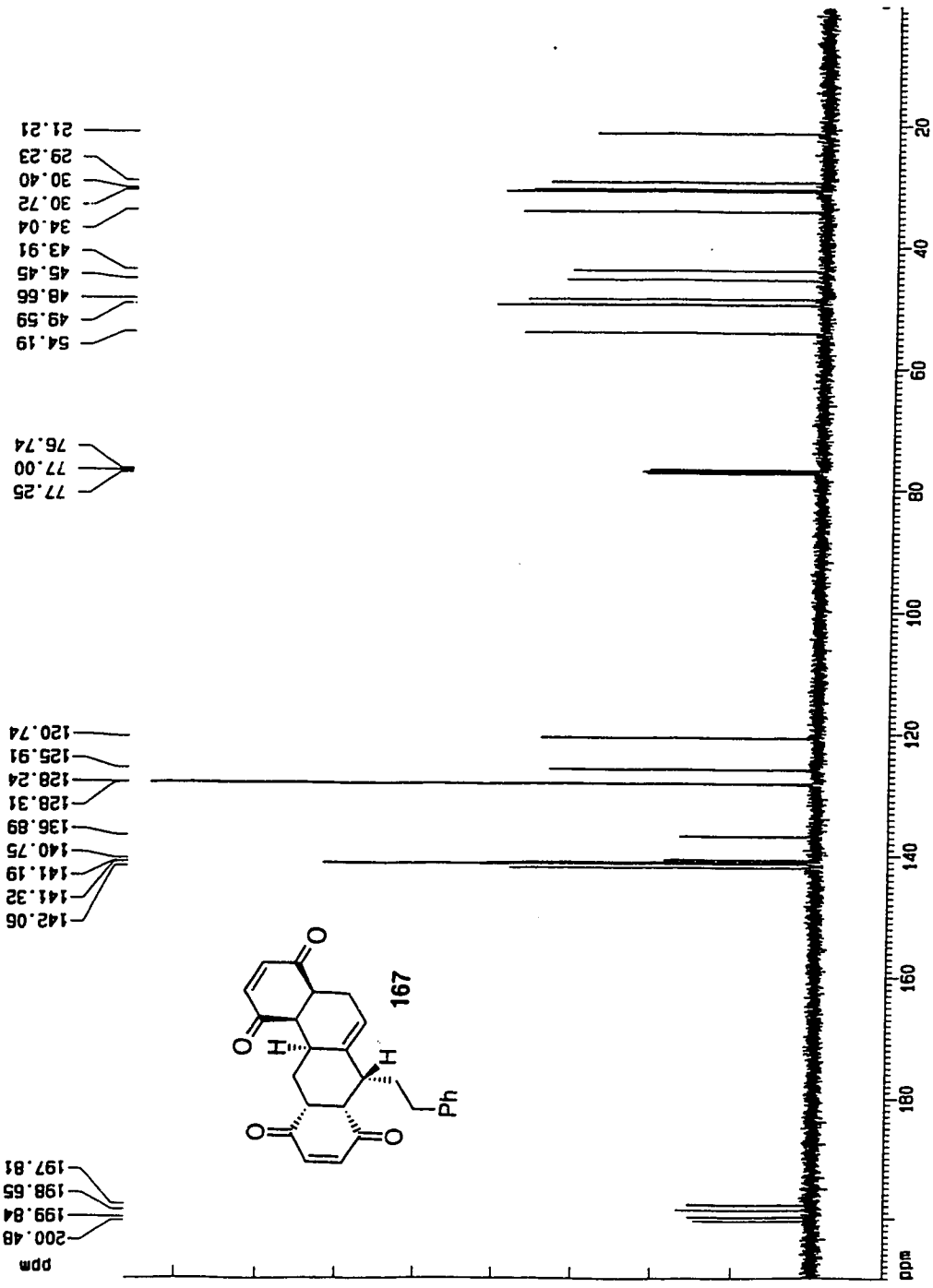


Figure A16. ^{13}C NMR (125 MHz) spectrum of adduct **167**.

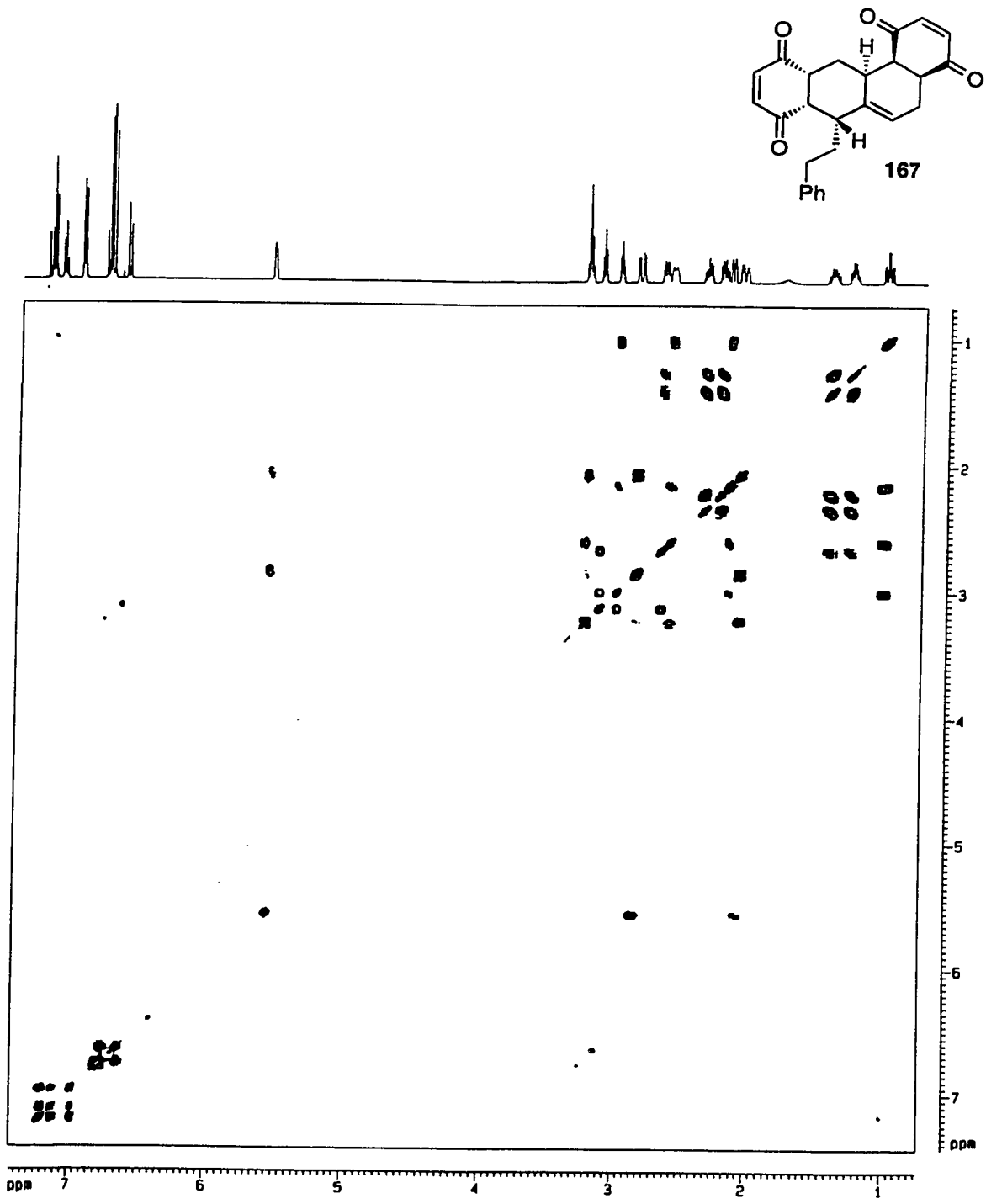


Figure A17. COSY (500 MHz) spectrum of adduct **167**.

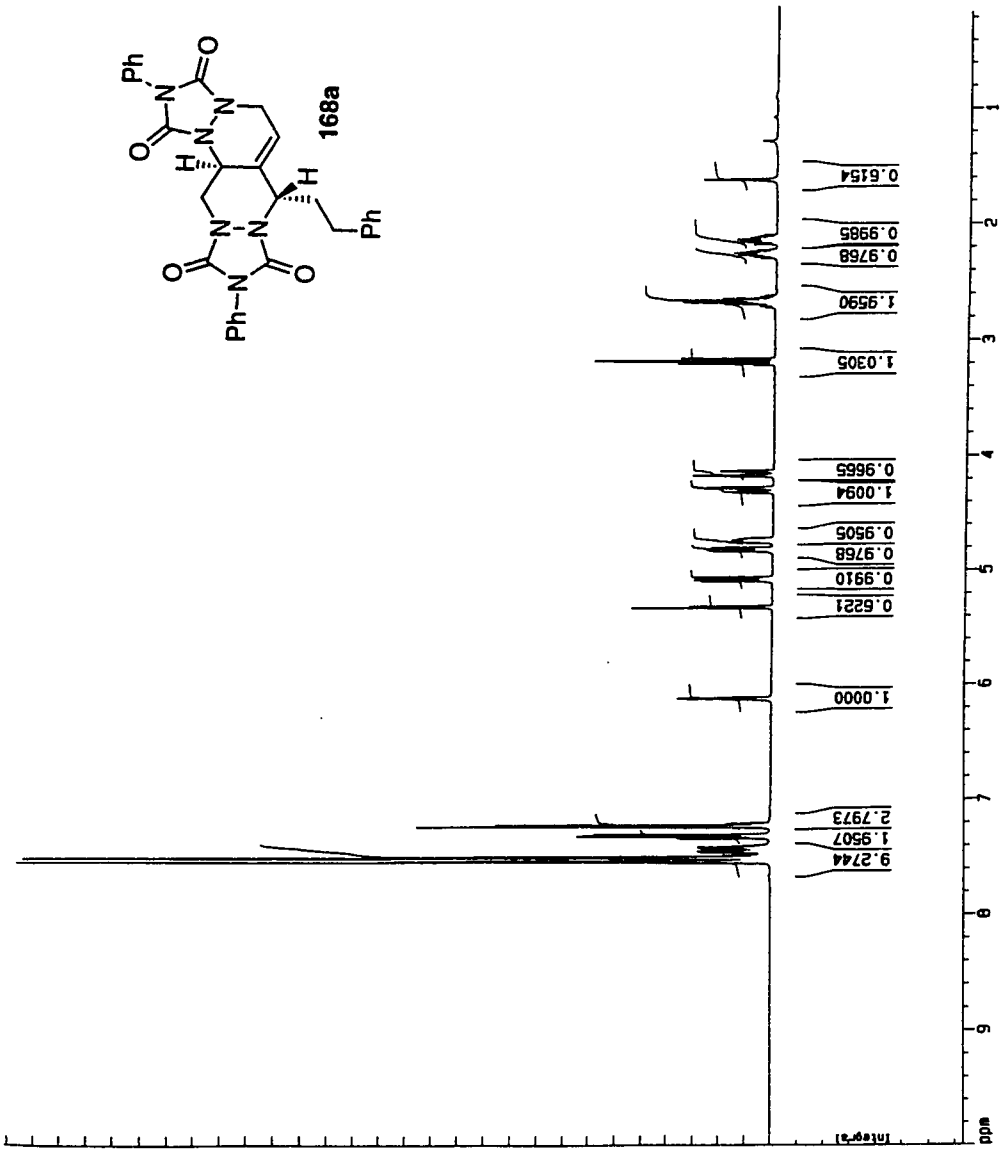


Figure A18. ^{1}H NMR (500 MHz) spectrum of adduct **168a**.

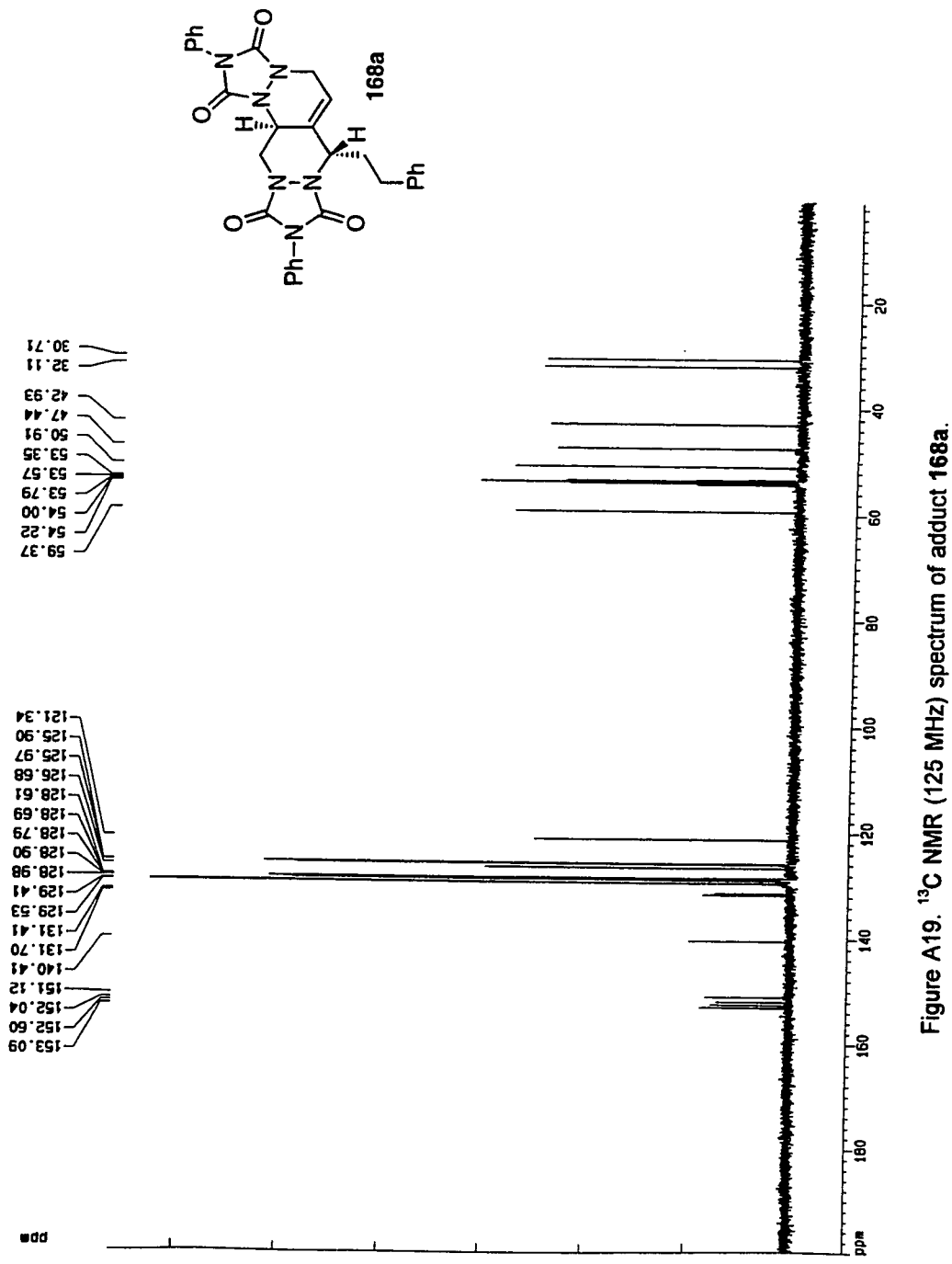


Figure A19. ^{13}C NMR (125 MHz) spectrum of adduct **168a**.

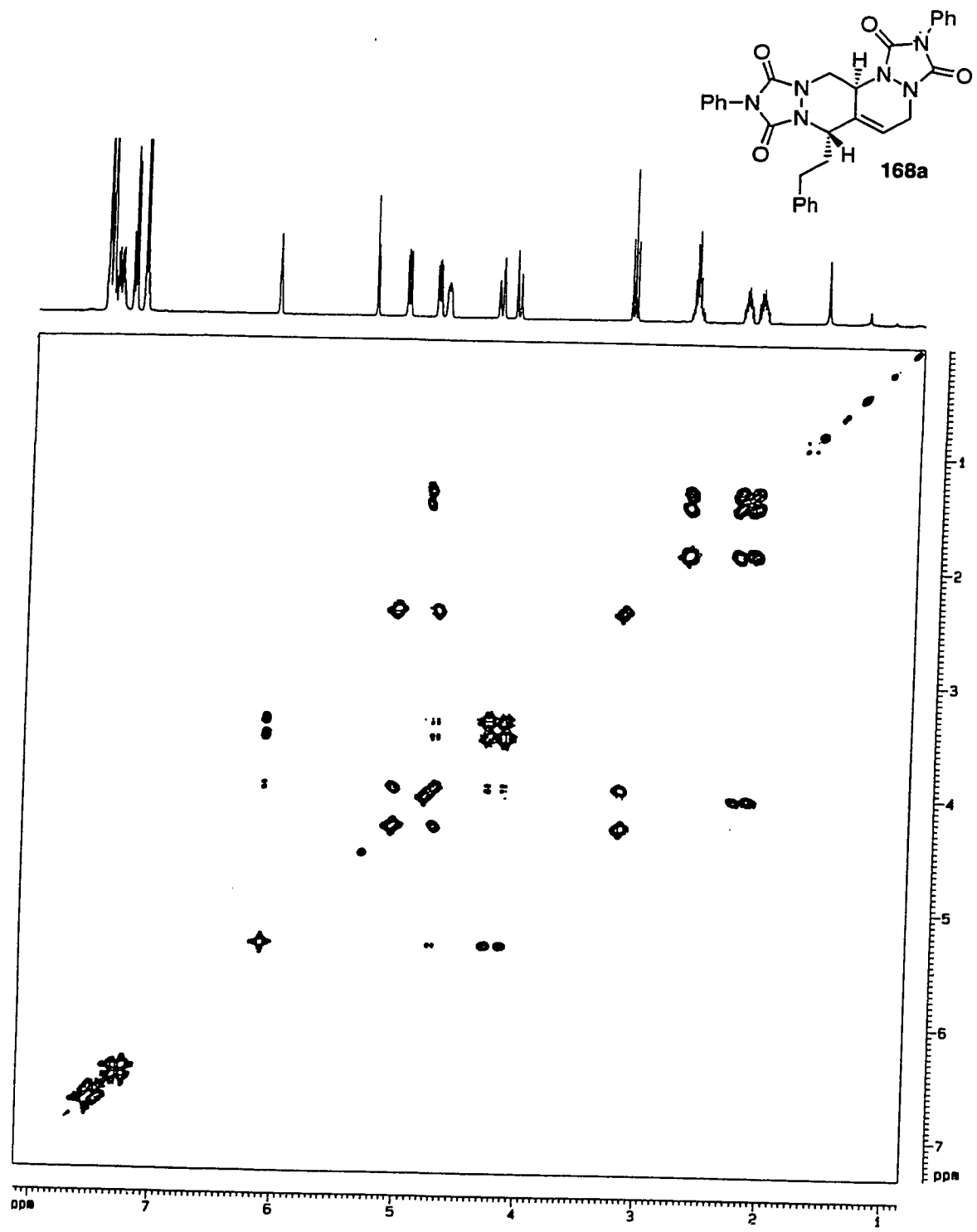


Figure A20. COSY (500 MHz) spectrum of adduct **168a**.

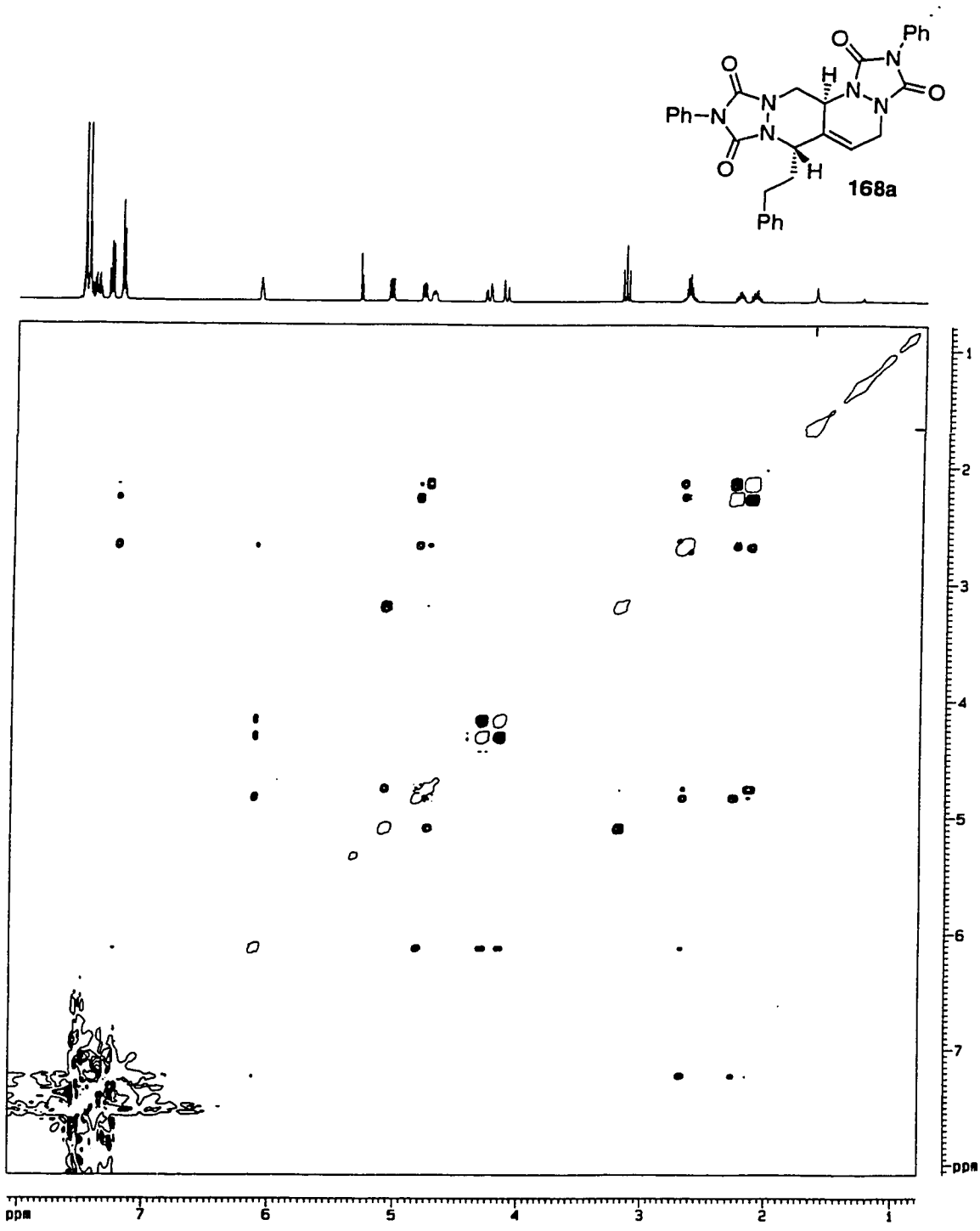


Figure A21. NOESY (500 MHz) spectrum of adduct **168a**.

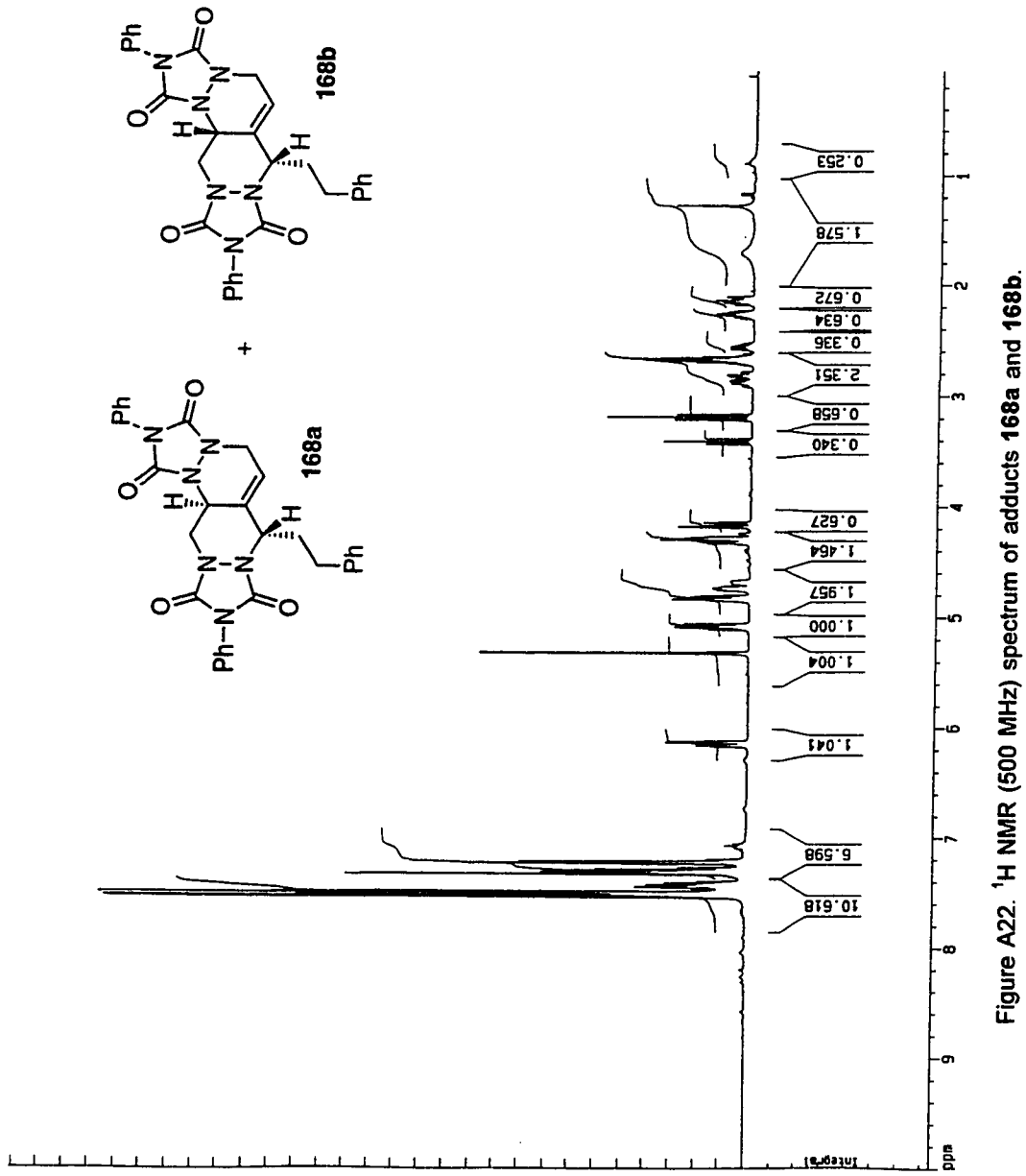


Figure A22. ^{1}H NMR (500 MHz) spectrum of adducts **168a** and **168b**.

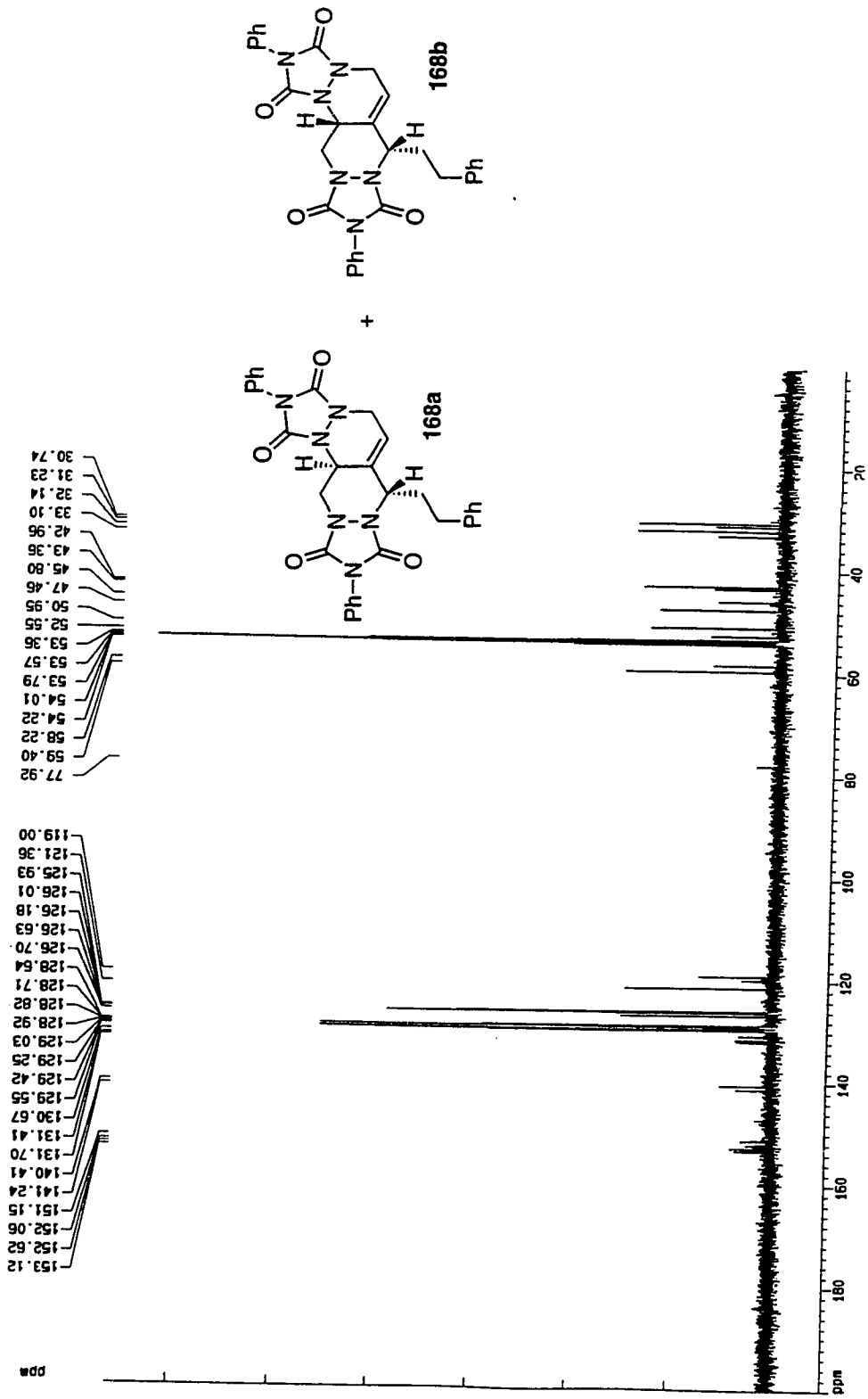


Figure A23. ^{13}C NMR (125 MHz) spectrum of adducts **168a** and **168b**.

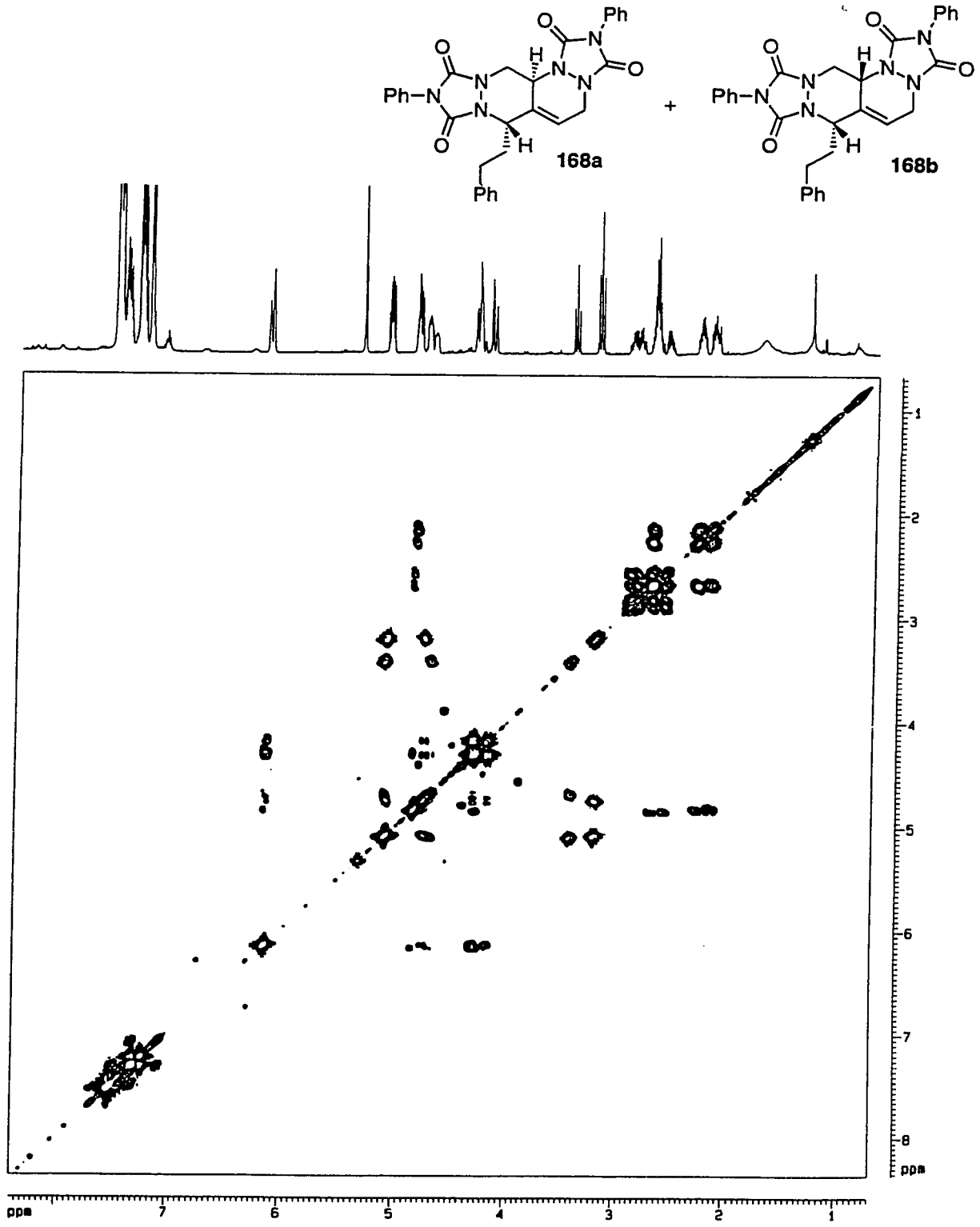


Figure A24. COSY (500 MHz) spectrum of adducts **168a** and **168b**.

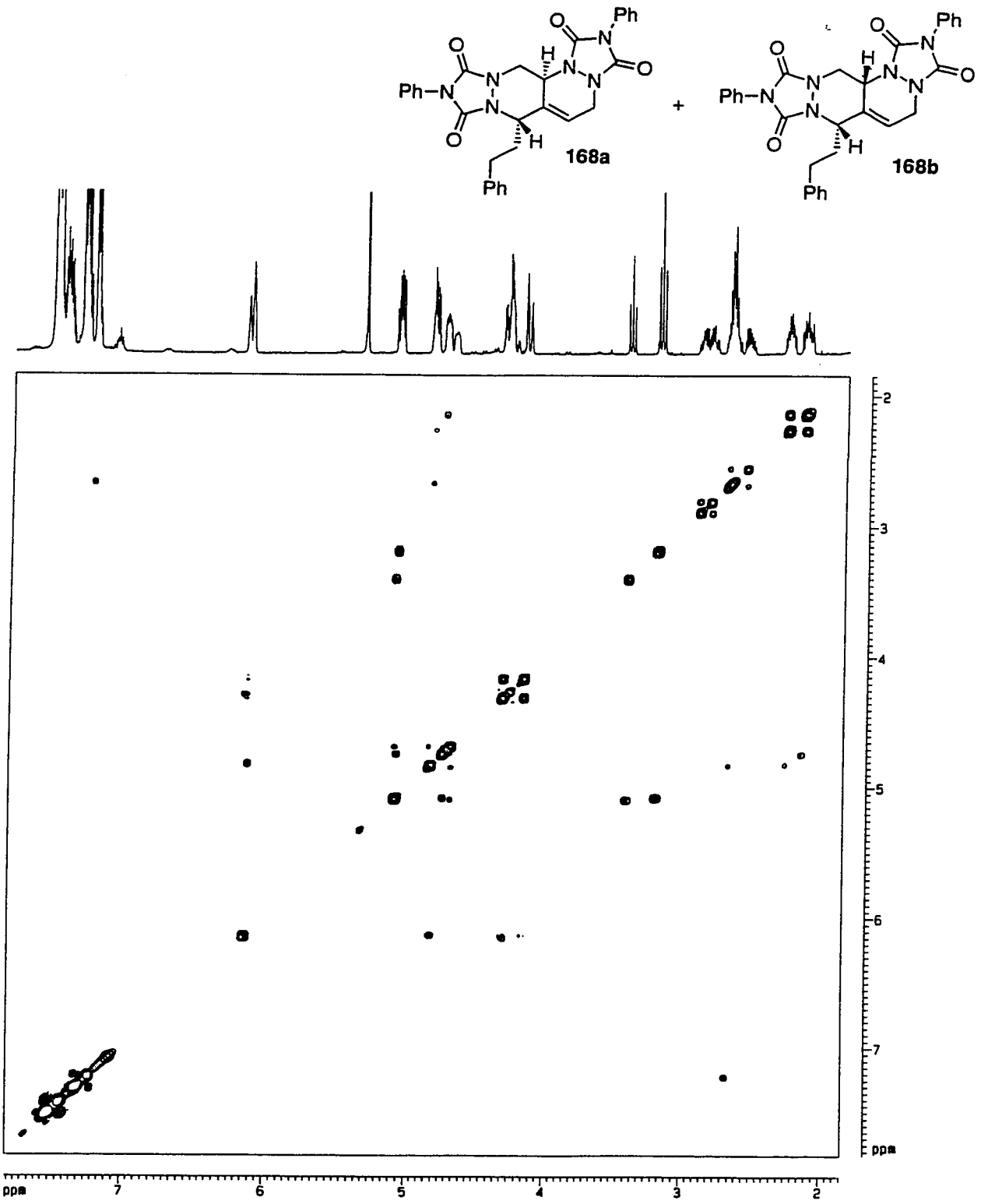


Figure A25. NOESY (500 MHz) spectrum of adduct **168a** and **168b**.

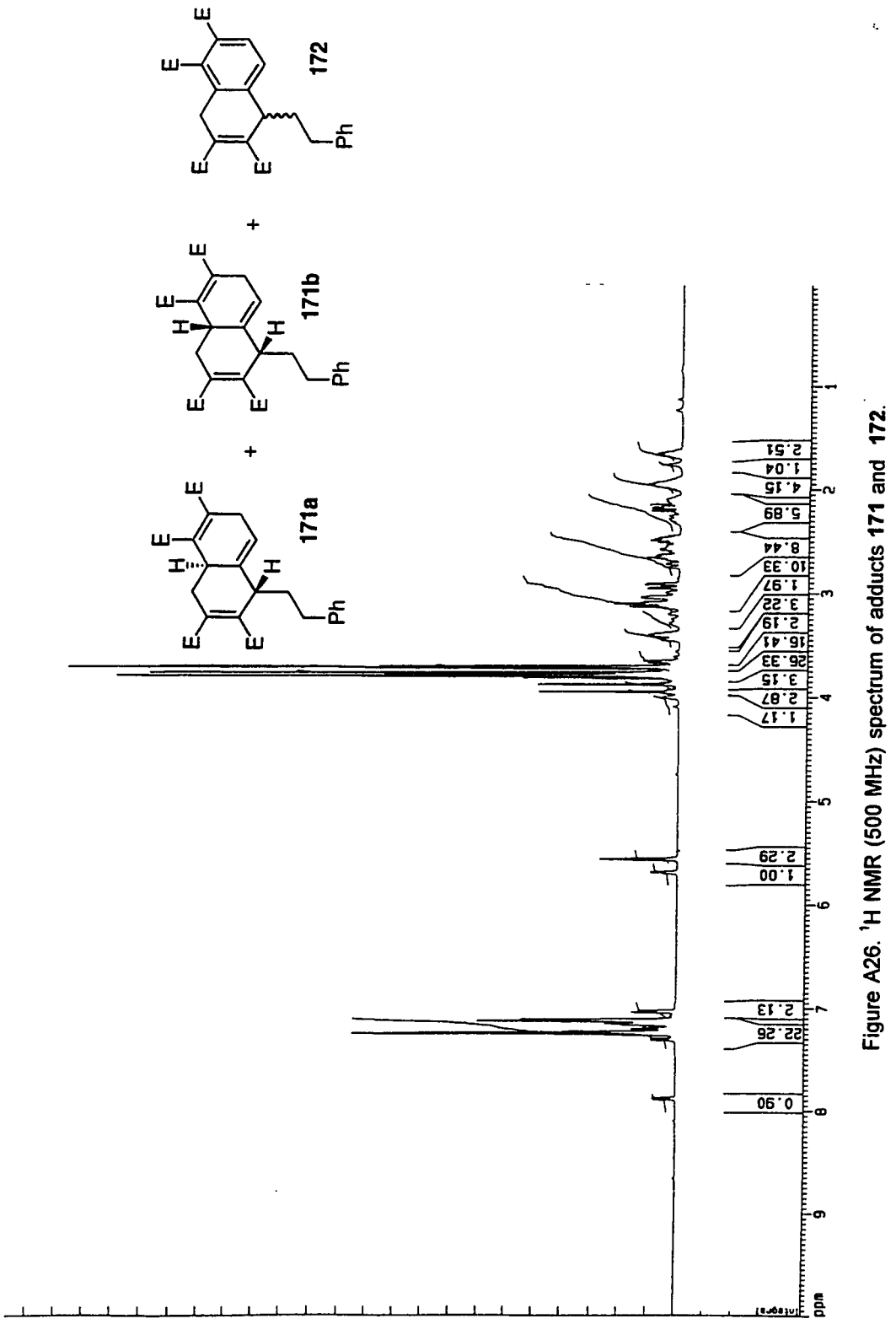


Figure A26. ^{1}H NMR (500 MHz) spectrum of adducts **171** and **172**.

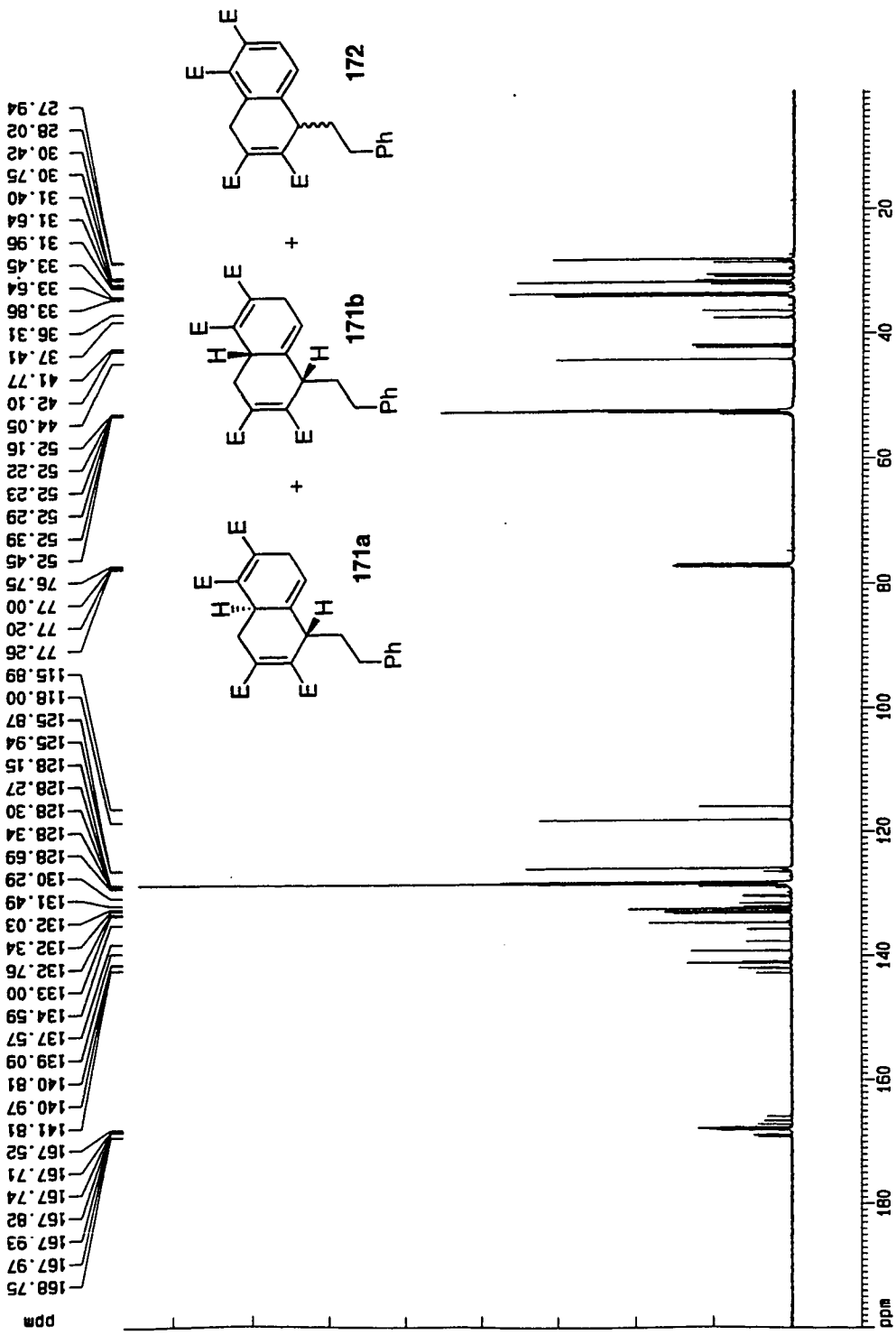


Figure A27. ^{13}C NMR (125 MHz) spectrum of adducts **171** and **172**.

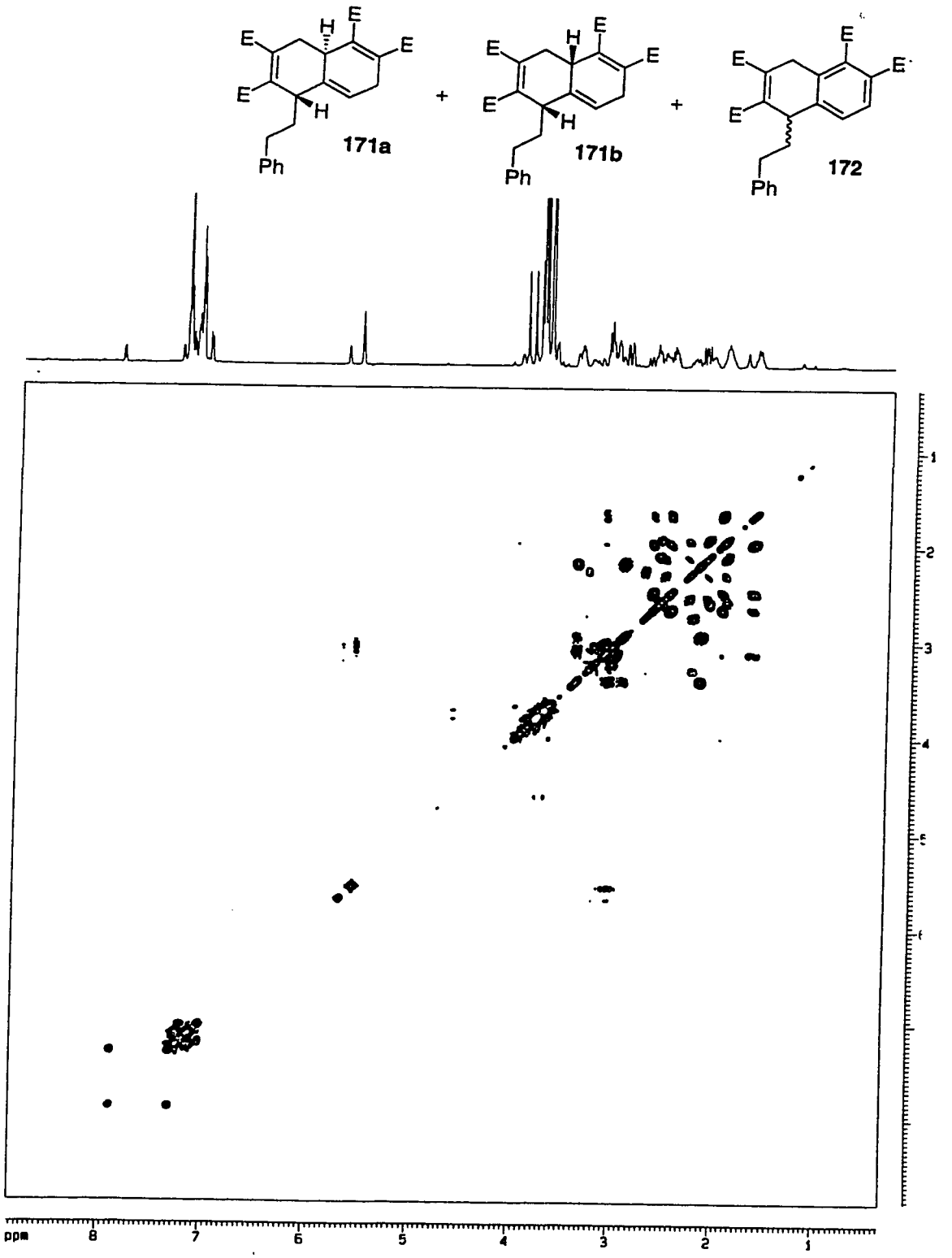


Figure A28. COSY (500 MHz) spectrum of adducts **171** and **172**.

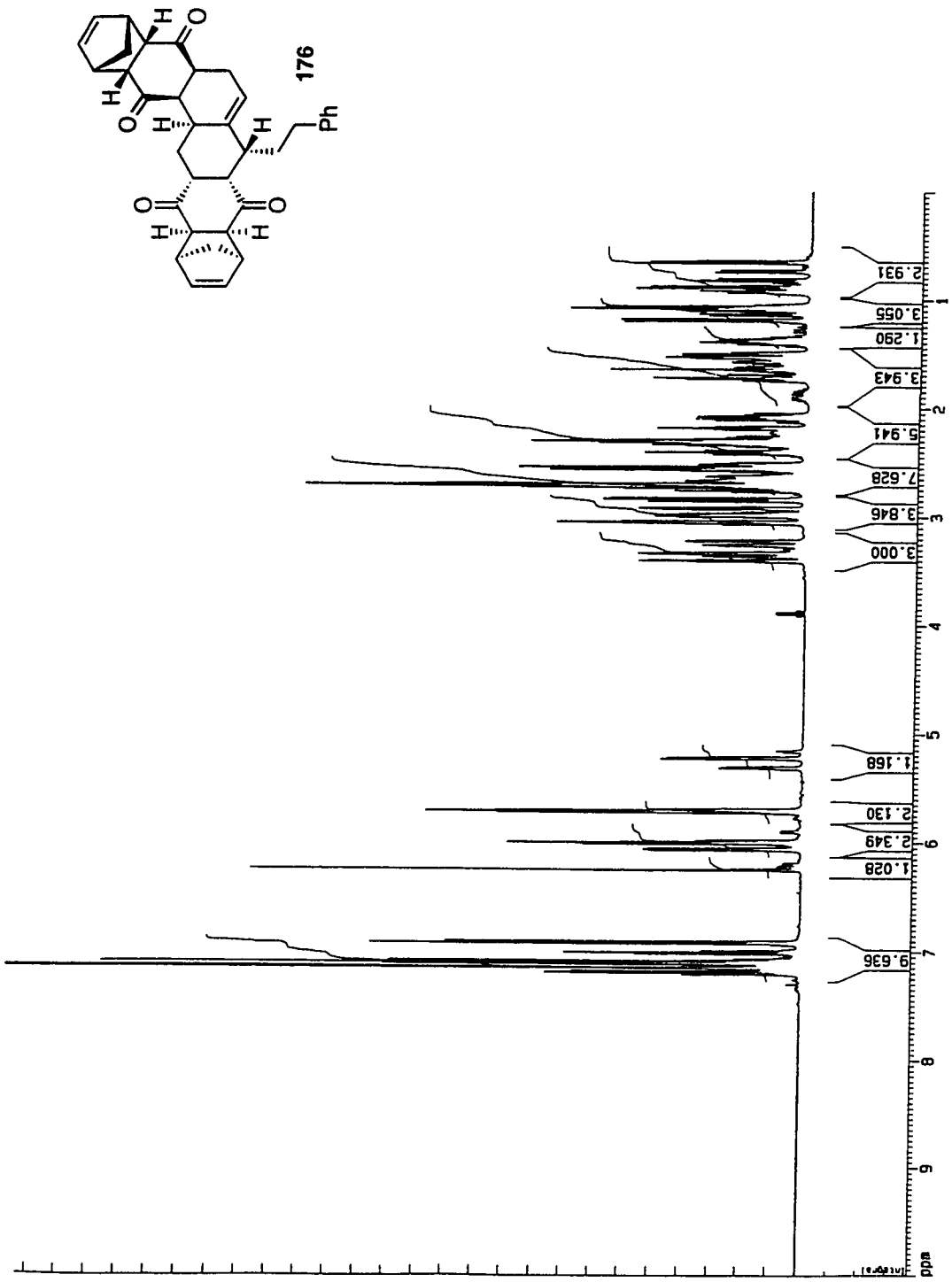


Figure A29. ^{1}H NMR (500 MHz) spectrum of adduct **176**.

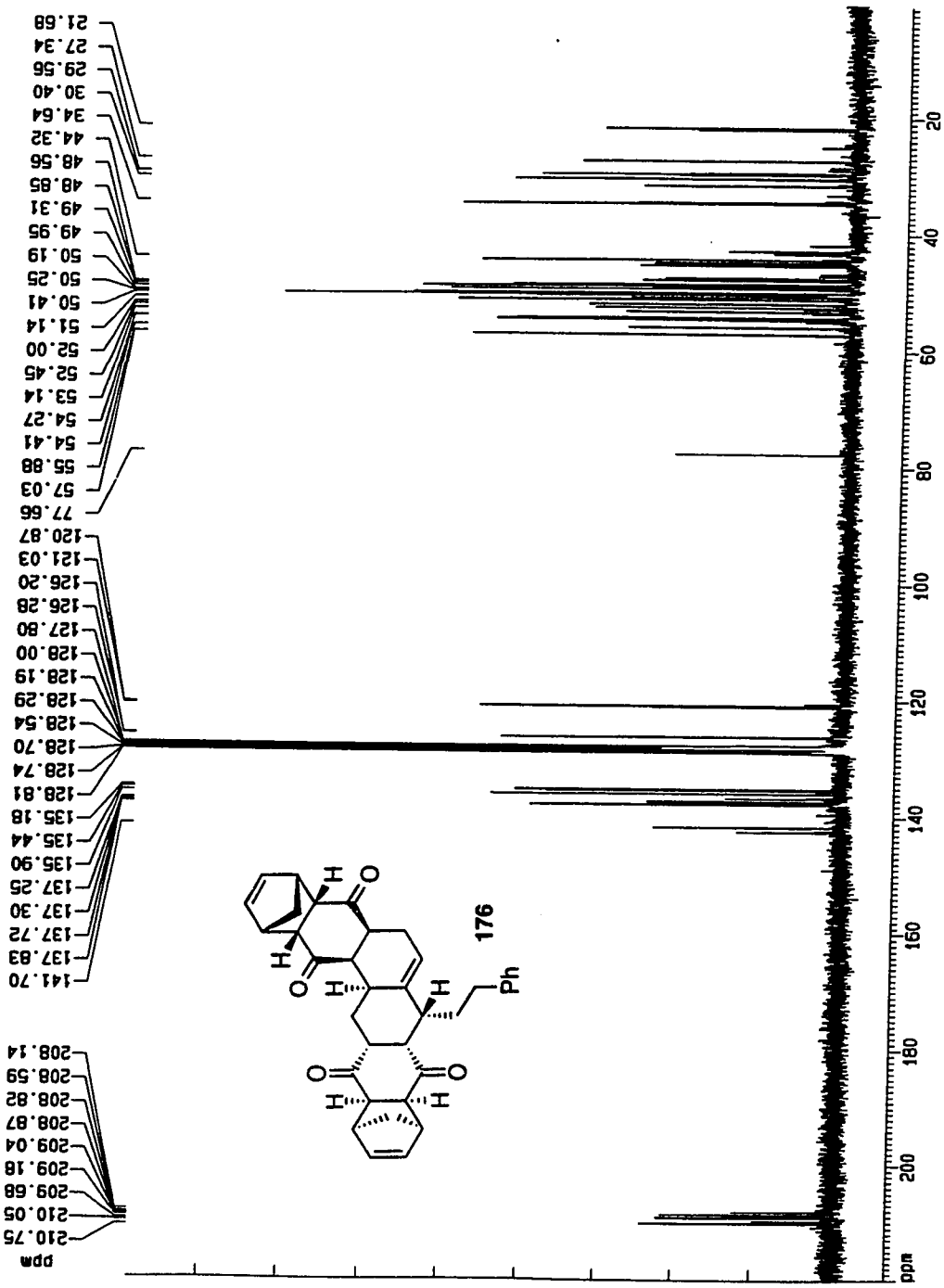


Figure A30. ^{13}C NMR (125 MHz) spectrum of adduct **176**.

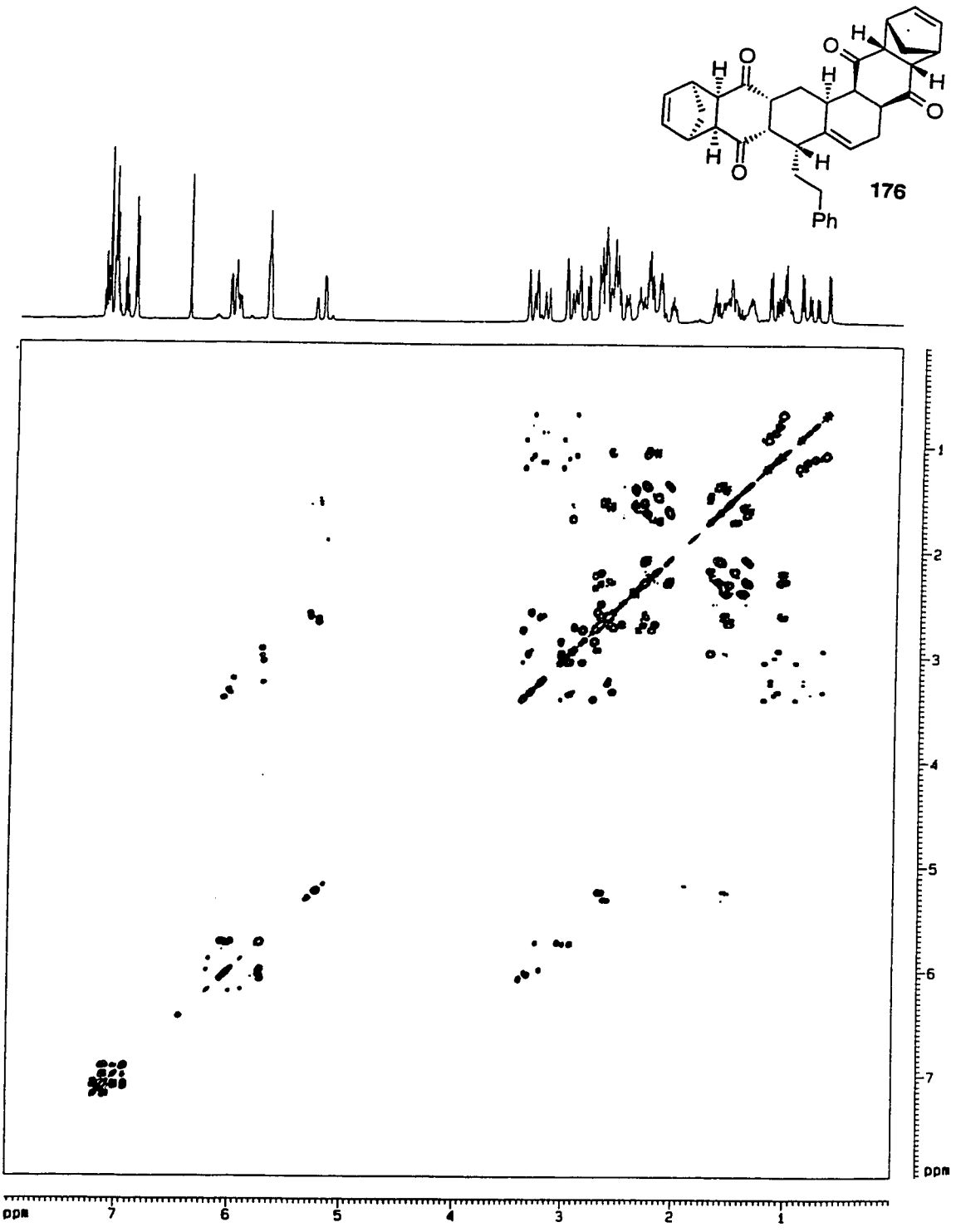


Figure A31. COSY (500 MHz) spectrum of adduct **176**.

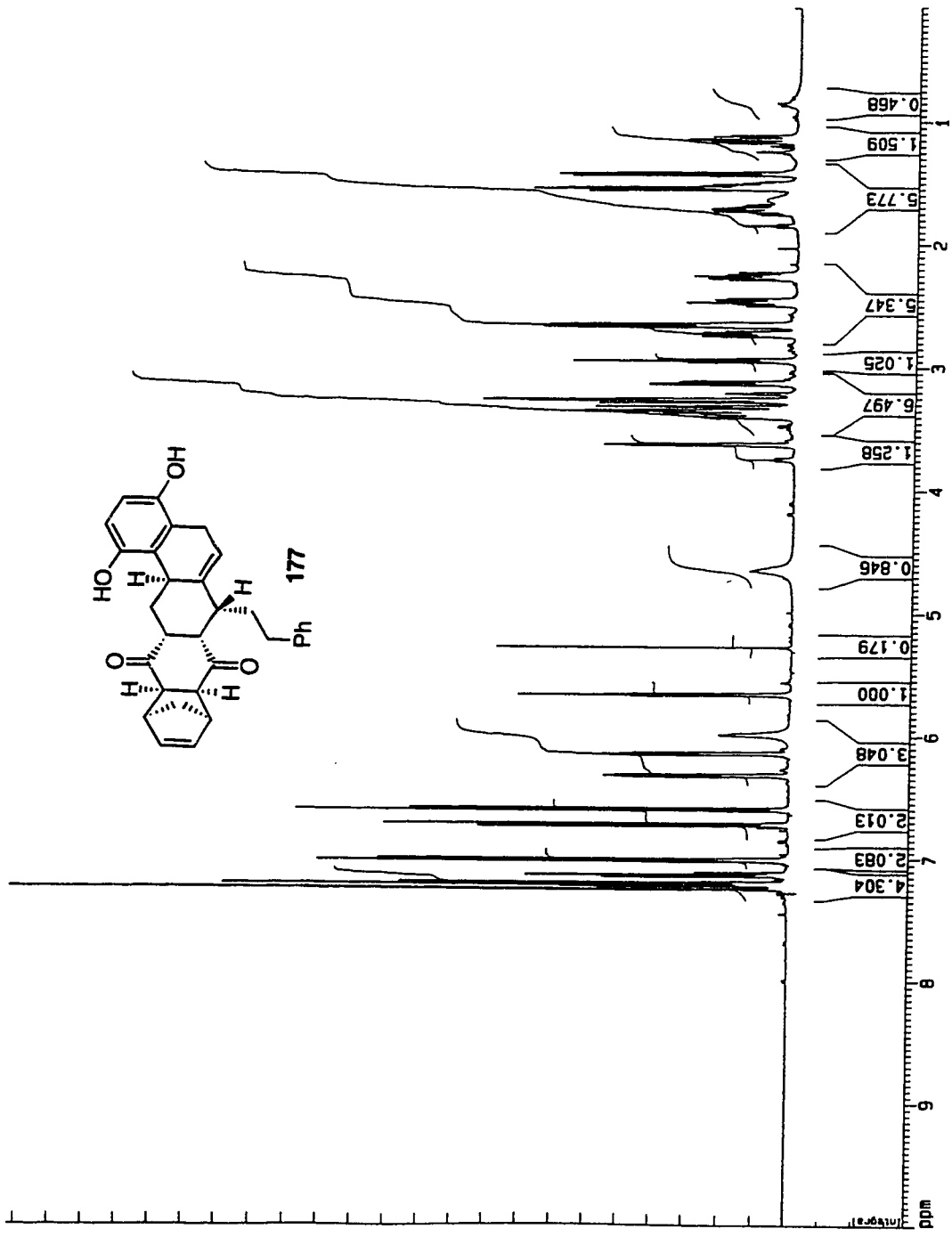


Figure A32. ^{1}H NMR (500 MHz) spectrum of adduct 177.

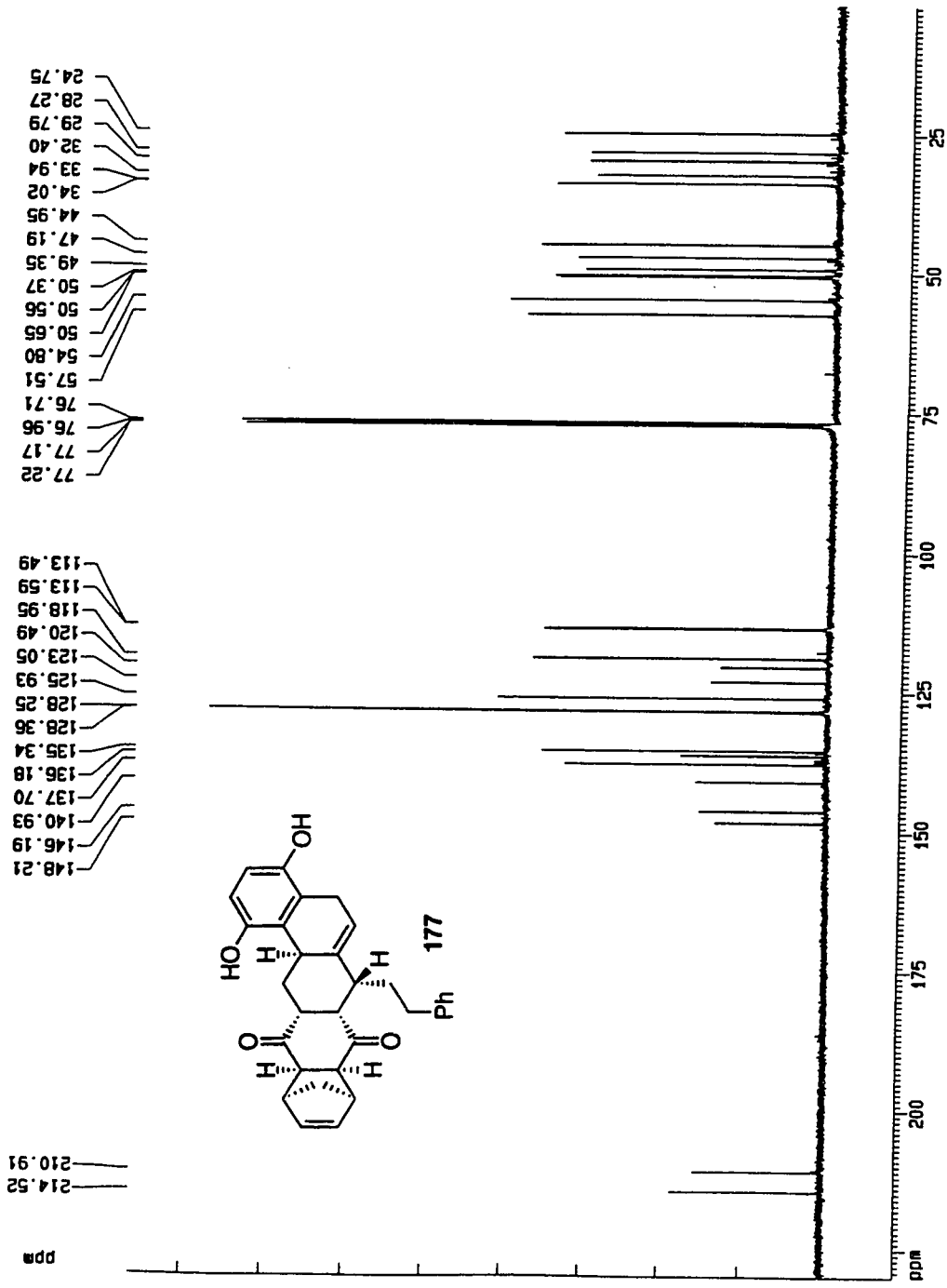


Figure A33. ^{13}C NMR (125 MHz) spectrum of adduct **177**.

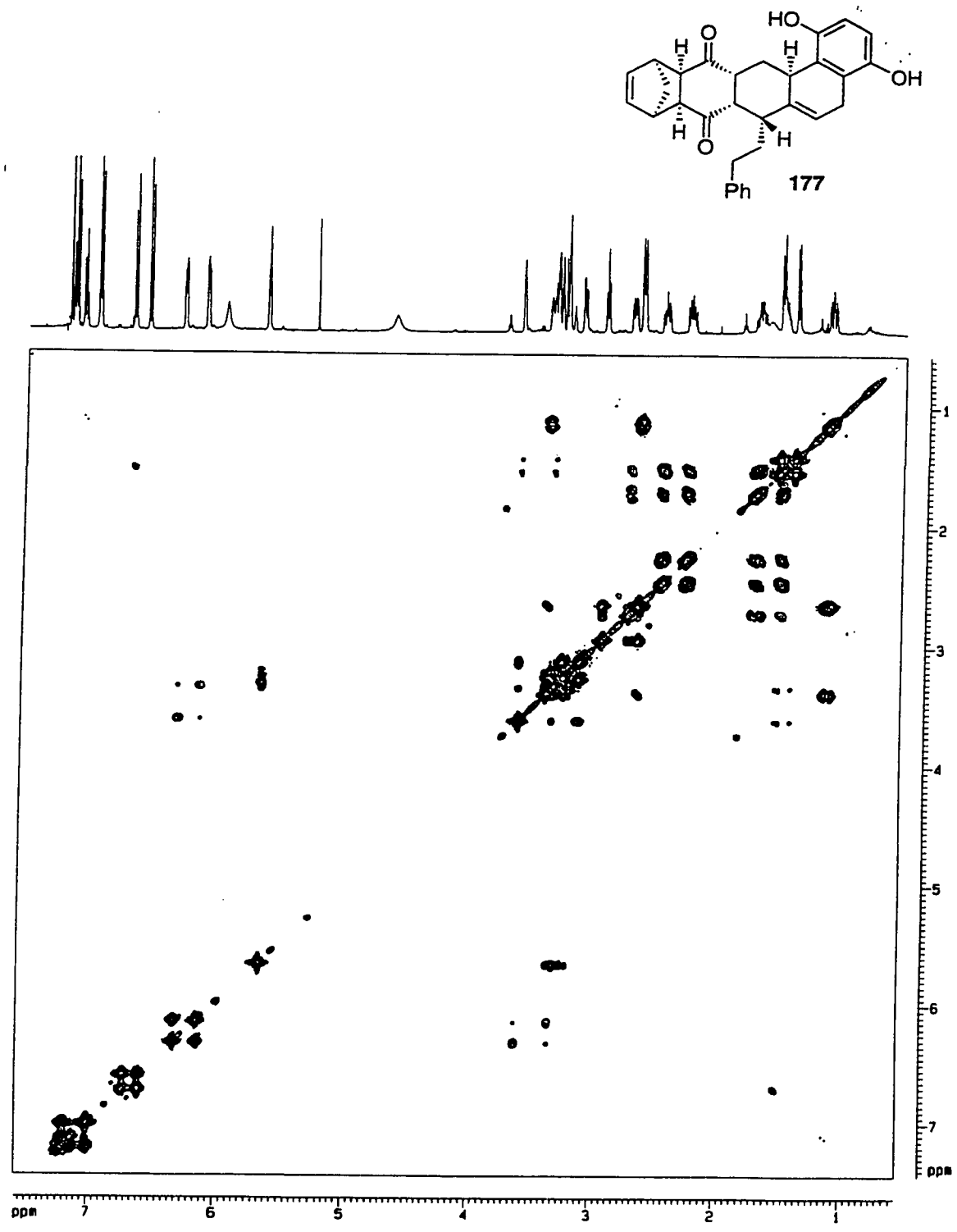


Figure A34. COSY (500 MHz) spectrum of adduct **177**.