NEW ELECTRON DEFICIENT DIENES AND THEIR NORMAL AND INVERSE ELECTRON DEMAND DIELS-ALDER REACTIONS

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by

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Abstract

1,3-Butadienes bearing electron donating groups at their 1 and 3 positions (e.g. Danishefsky's diene **50**) are popular dienes for the normal Diels-Alder reaction due to their regiochemically predictable cycloaddition with a variety of electron deficient dienophiles and the multifunctional adducts they provide. However, their counterparts which bear electron withdrawing groups at their 1 and 3 positions, and their inverse electron demand Diels-Alder reactions are uncommon. Due to the instability of the few known parent dienes, e.g. dienes **56a-d** and **59**, the cycloalkane-annulated diene system **63d** was chosen for initial study.

The protected dienes (**68**, **70**, **72**) and the deprotected dienes (**69**, **71**, **73**) were prepared from the commercially available 2-cyclohexen-1-one in four and five steps, respectively. All these dienes were obtained as pure 2*E* isomers except **72**, which was obtained as a mixture of 2*E* and 2*Z* isomers (**72a** and **72b**). The synthetic methodology was also employed to prepare dienes such as **83-86**, which feature a five-membered ring.

The protected dienes **68** and **72** underwent cycloaddition with electron deficient dienophiles (TCNE, PTAD, DMAD, NPM, MA, NQ and BQ) to give *endo* adducts as the major products. The structures of the adducts **100**, **103**, **106**, **110**, **113** and **114** were determined by X-ray crystal structure analysis whereas the structures of other adducts were assigned by analogy. Epimerization was observed in the reactions of **68** with TCNE and with DMAD. Treatment of the protected diene **68** with an electron rich dienophile, 1,1-diethoxyethylene, in refluxing toluene resulted in no reaction.

The deprotected dienes **69**, **71** and **73** participated in cycloaddition with the electron rich dienophiles ethyl vinyl ether, 1,1-diethoxyethylene, 1-ethoxy-1-(trimethylsilyloxy)ethylene and styrene. Nothing less than 100% regioselectivity was

ever observed. The resulting adducts incorporated a variety of functionality and offer the potential to be elaborated in a number of ways.

Dienes **69** and **71** reacted with ethyl vinyl ether with 100% regioselectivity to give the *endo* adducts **118a** and **122**. Epimerization of **118a** to give **118c** was observed during chromatography.

The reactions of dienes **69** and **71** with 1,1-diethoxyethylene occurred with complete regioselectivity and in 81-86% yield. The structure of the adduct **123a** was assigned by X-ray crystallography. Reaction of **73** and the same dienophile resulted the formation of a new diene **125** by the elimination ethanol from the initially formed adduct.

Diene **69** underwent cycloaddition with styrene to provide the *endo* adduct **127** as the major product, as determined by X-ray crystallography. The minor product was assigned as the *exo* adduct **128** by comparing its nmr spectra with those of other adducts.

Dienes **69** and **73** reacted with enamines to give the aromatized compounds **132** and **138** by elimination of an amine from the initially formed adducts and subsequent dehydrogenation. Both **69** and **79** underwent cycloaddition with PTAD to give crystalline adducts **141** and **143**. Epimerization was observed during chromatographic purification of these adducts to give a mixture of them and their epimers **142** and **144**. Reaction of **69** with NPM followed by chromatography resulted in one major product in 90% yield, but a conclusive structural assignment of the adduct has not been made.

Acknowledgment

I would like to express my sincerest acknowledgment to my supervisor, Dr. G. Bodwell, for his stimulating supervision, continuous encouragement, great help and financial support throughout the course of this research. His assistance and patience in the preparation of this thesis are also greatly appreciated.

Many thanks are given to Mr. D. Miller, Ms. N. Brunet and Dr. C. R. Jablanski for excellent NMR spectroscopic experiments, to Ms. M. Baggs and Dr. B. Gregory for Mass Spectroscopy, and to Dr. J. Bridson and Mr. D. Miller for crystal structural determinations.

I would like to extend special thanks to Dr. D. J. Burnell and Dr. J. Bridson for proofreading and helpful discussions and suggestions.

I am deeply grateful to my fellow students for making the years in MUN enjoyable. I would like to thank the Chemistry Department and School of Graduate Studies of Memorial University of Newfoundland for their support.

Finally, I would like to thank my husband, Chunjian and my lovely daughter, Han Liu for their love, encouragement and support.

To my dear parents, my husband, Chunjian Liu,
and my daughter, Han Liu

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Glossary of abbreviations

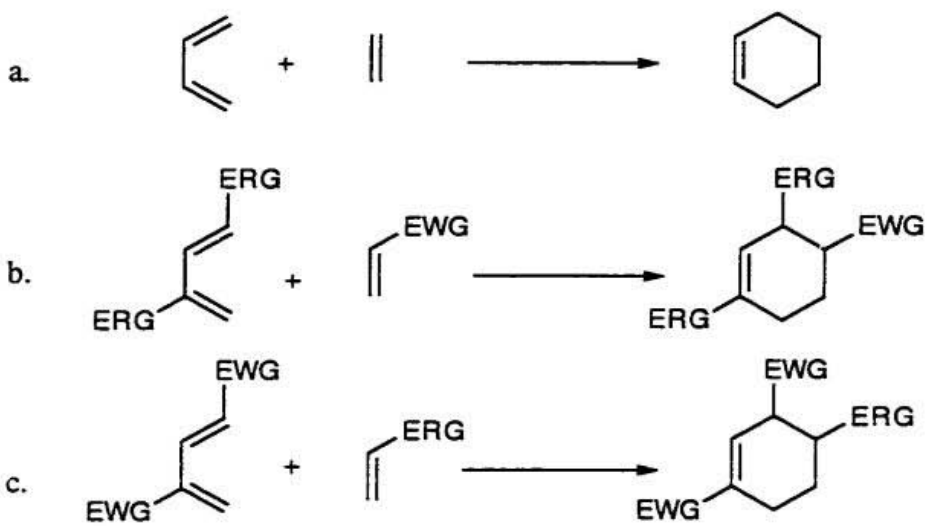
Ac	acetyl
APT	attached proton test
bp	boiling point
BQ	1,4-benzoquinone
Bu	*n*-butyl
Bn	benzyl (CH_2Ph)
COSY	^1H-^1H correlation spectroscopy
D-A	Diels-Alder
de	diastereomeric excess
DMAD	dimethyl acetylenedicarboxylate
DMF	*N,N*-dimethylformamide
ee	enantiomeric excess
ERG	electron releasing group
EWG	electron withdrawing group
Et	ethyl
fod	6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionate
HET-CORR	^{13}C-^1H heteronuclear correlation
hfc	3-(heptafluoropropylhydroxymethylene)-camphorate
HOMO	highest occupied molecular orbital
IED	inverse electron demand
IR	infrared spectroscopy
LDA	lithium diisopropylamide

LUMO	lowest unoccupied molecular orbital
MA	maleic anhydride
Me	methyl
mp	melting point
MS	Mass spectrometry
NMR	nuclear magnetic resonance spectroscopy
NOE	nuclear Overhauser effect
NPM	*N*-phenylmaleimide
NQ	1,4-naphthoquinone
Ph	phenyl
i-Pr	isopropyl
PTAD	4-phenyl-1, 2, 4-triazoline-3, 5-dione
tfc	3-(trifluoromethylhydroxymethylene)-camphorate
p-TsOH	*para*-toluenesulfonic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl

Chapter 1. Introduction

Since its initial report,[1] the Diels-Alder reaction (D-A) has been developed into one of the most common and elegant synthetic methods for the construction of six-membered and polycyclic systems.[2] Extensive studies[3,4] have defined the factors influencing the rate, stereoselectivity, regioselectivity, and enantioselectivity of the Diels-Alder reaction and have provided the basis for the classification of the Diels-Alder

Scheme 1



ERG - Electron Releasing Group; EWG - Electron Withdrawing Group
a. The neutral D-A reaction; b. The normal D-A reaction; c. The inverse electron demand D-A reaction

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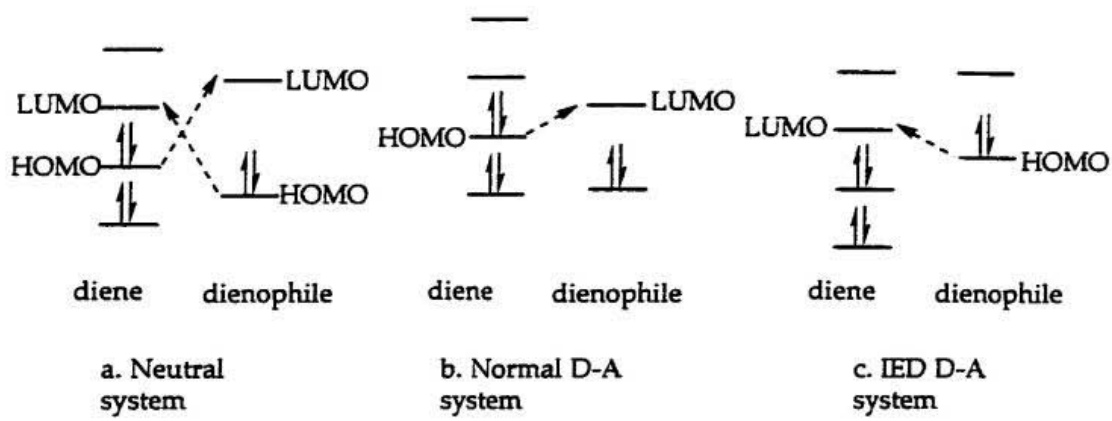
[1] Diels, O.; Alder, K. *Justus Liebigs Ann. Chem.* **1928**, *460*, 98.
[2] (a) Desimoni, G.; Tacconi, G.; Bario, A.; Pollini, G. P. In *Natural Product Synthesis through Pericyclic Reactions*. ACS Monograph; American Chemical Society, Washington D.C. **1984**. Ch. 5. (b) Helmchen, G.; Karge, R.; Weetman, J. In *Modern Synthetic Methods*. Scheffold. R., Ed., Springer Verlag: New York, **1986**, pp261. (c) Paquette, L. A.; In *Asymmetric Synthesis* Vol. 3, Morrison, J. D., Ed., Academic Press: New York, **1984**, Ch. 4.
[3] Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Academic Press: New York, **1970**.
[4] (a) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.*. **1984**, *23*, 876-889. (b) Sauer, J.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 779-807. (c) Houk, K. N. *J. Am. Chem. Soc.* **1973**, *95*, 4092-4094. (e) Burnier, J. S.; Jorgensen, W. L. *J. Org. Chem.* **1983**, *48*, 3923-3941.

cycloaddition into one of three processes: the neutral Diels-Alder reaction, the normal Diels-Alder reaction, and the inverse electron demand (IED) Diels-Alder reaction. The neutral Diels-Alder reaction is usually represented by the reaction of 1,3-butadiene with ethylene (a, Scheme 1). The normal Diels-Alder reaction (b, Scheme 1) usually involves electron rich dienes and electron deficient dienophiles whereas the IED Diels-Alder reaction (c, Scheme 1) proceeds with electron deficient dienes and electron rich dienophiles.

According to frontier molecular orbital (FMO) theory,[3] the rate of the Diels-Alder reaction is related to the magnitude of the lowest HOMO-LUMO energy separation achievable by the reacting diene/dienophile components: $HOMO_{diene}$-$LUMO_{dienophile}$ or $LUMO_{diene}$-$HOMO_{dienophile}$. Factors that affect the diene or/and the dienophile components of the reaction in a complementary manner reduce the magnitude of the HOMO-LUMO separation and result in an acceleration of the rate of cycloaddition.

Figure 1. Frontier orbital interactions in Diels-Alder reactions

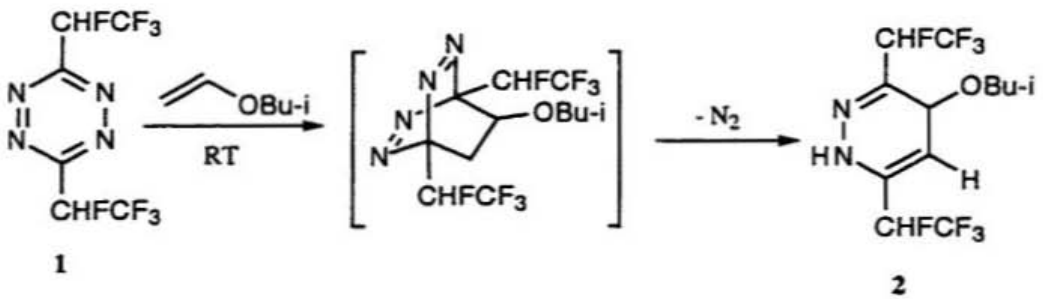


For the normal Diels-Alder reaction (b, Figure 1), the electron releasing groups on the diene unit raise the diene orbitals in energy relative to those of the neutral system,

whereas the electron withdrawing groups on the dienophile lower the dienophile orbitals. Therefore, a smaller energy gap between the HOMO of the diene and the LUMO of the dienophile results and the reaction is accordingly accelerated. On the other hand, in a IED Diels -Alder reaction (c, Figure 1), the electron withdrawing groups on the diene lower the diene orbitals and the electron releasing groups on the dienophile raise the dienophile orbitals. Consequently, a smaller energy difference and a stronger interaction between the LUMO of the diene and the HOMO of the dienophile is obtained. Therefore, the resulting Diels-Alder reaction is more efficient and rapid.

The complementary choice of diene/dienophile partners for the Diels-Alder reaction and the recognition of the origin of the resulting rate acceleration led to the development, predictive success, and application of the Diels-Alder reaction in synthesis.

Scheme 2



1 2

Aromatic azadienes such as 3,6-bis(1,2,2,2-tetrafluoroethyl)-1,2,4,5-tetrazine **1** (Scheme 2) were the first systems successfully applied in the IED Diels-Alder reaction.[5] In recent years, the IED Diels-Alder reaction employing electron deficient hetero dienes and miscellaneous dienophiles has enjoyed broad application in the synthesis of heterocyclic compounds.[6] The IED Diels-Alder reaction of substituted 1,2-diazines,[7] 1,2,4-triazines[8]

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[5] Carboni, R. A.; Lindsey, R. V., Jr. *J. Am. Chem. Soc.* **1959**, *81*, 4342-4346.

[6] For reviews of the inverse electron demand Diels-Alder reaction of hetero dienes: (a) Boger, D. L.

and 1,2,4,5-tetrazines[9] constitute the most thoroughly investigated and most widely used heteroaromatic azadiene systems capable of cycloaddition. The complementary addition of electron withdrawing groups to the azadiene systems generally increases their rate of participation in IED Diels-Alder cycloaddition, influences the mode of the cycloaddition and controls the regioselectivity.

Substituted 1,2,4-triazines such as 3,5,6-tricarbomethoxy-1,2,4-triazine **3** (Scheme 3) have been shown to react with enol ethers,[10] ketene acetals,[11] enamines[12] and many other electron rich dienophiles. The cycloaddition occurs exclusively across C3/C6 of the 1,2,4-triazine nucleus to give pyridine derivatives *via* the immediate release of nitrogen and subsequent aromatization of the initially formed adducts.

Tetrahedron **1983**, *39*, 2869-2939. (b) Boger, D. L. *Chem. Rev.* **1986**, *86*, 781-793. (c) Boger, D. L.; Weinreb, S. M. *Hetero Diels-Alder Methodology in Organic Synthesis*; Organic Chemistry Monograph Series, Vol. 47; Academic: New York, **1987**. (d) Kametani, T.; Hibino, S. In *Advances in Heterocyclic Chemistry;* Katritzky, A. R., Ed.; Academic: New York, **1987**; Vol. 42, pp 246-335. (e) Weinreb, S. M.; Staib, R. R. *Tetrahedron* **1982**, *38*, 3087-3128.

[7] For reviews of 1,2-diazine chemistry: (a) Tisler, M.; Stanovnik, B. In *Advances in Heterocyclic Chemistry;* Katritzky, A. R.; Boulton, A. J., Eds.; Academic: New York, **1979**; Vol. 24, pp 363-456. (b) Tisler, M.; Stanovnik, B. In *Comprehensive Heterocyclic Chemistry*; Boulton, A. J., McKillop, A., Eds.; Pergamon: Oxford, **1984;** Vol. 3, pp 1-56.

[8] For reviews of 1,2,4-triazine chemistry: (a) Neunhoeffer, H. *Chemistry of 1,2,3-Triazines and 1,2,4-Triazines, Tetrazines, and Pentazines*; The Chemistry of Heterocyclic Compounds Monograph Series, Vol. 33; Wiley-Interscience: New York, **1978**; pp 189-1072. (b) Neunhoeffer, H. In *Comprehensive Heterocyclic Chemistry;* Boulton, A. J., McKillop, A., Eds.; Pergamon: Oxford, **1984**; Vol. 3, pp 385-456.

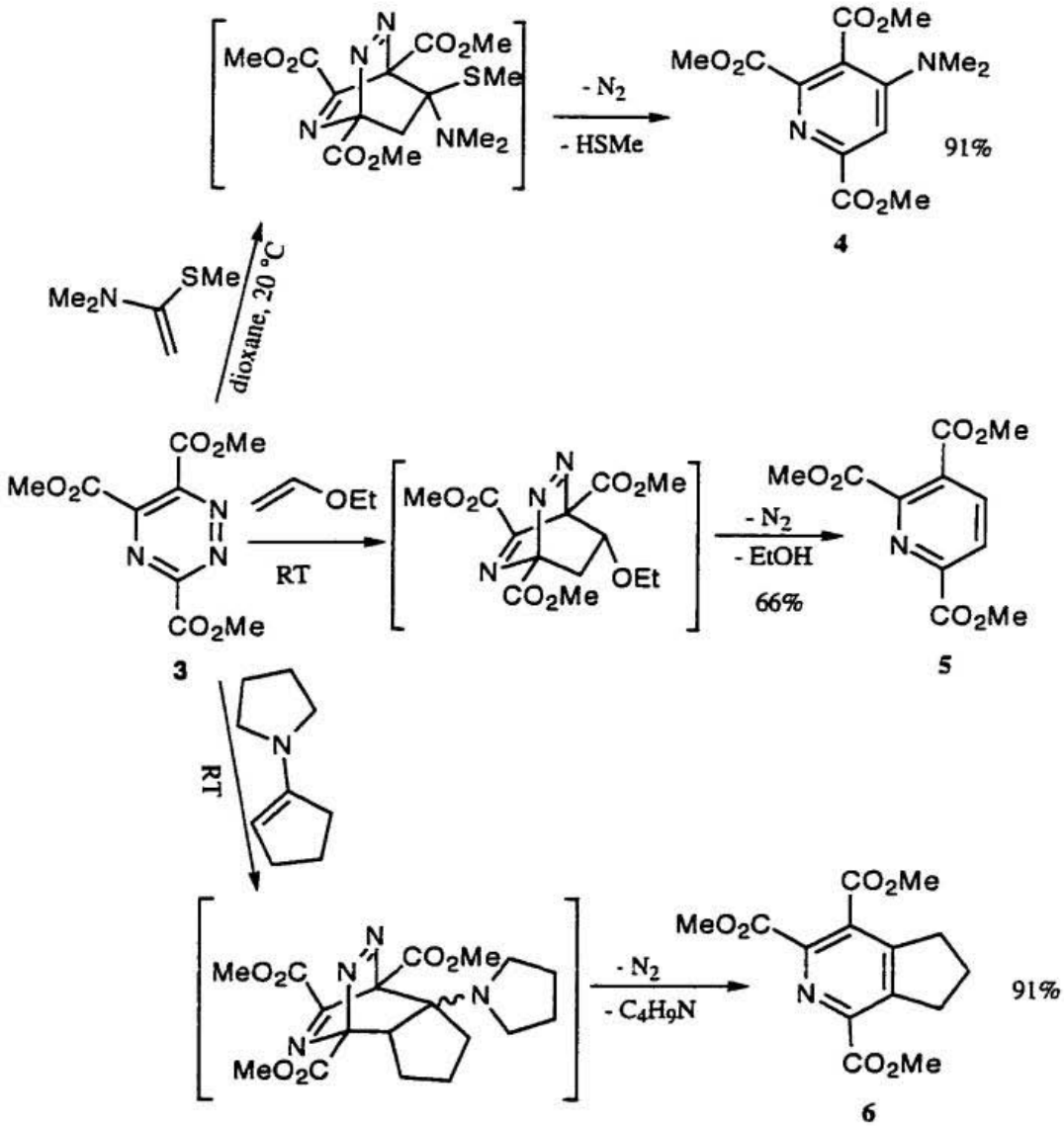
[9] For reviews of 1,2,4,5-tetrazine chemistry: (a) Neunhoeffer, H. *Comprehensive Heterocyclic Chemistry*; Pergamon: London, **1984**; Vol. 3, pp 550-555. (b) Neunhoeffer, H.; Wiley, P. F. *Chemistry of Heterocyclic Compounds*, Wiley: New York, **1978**, Vol. 33, pp 1095-1097.

[10] (a) Dittmar, W.; Sauer, J.; Steigel, A. *Tetrahedron Lett.* **1969**, *10*, 5171-5174. (b) Reim, H.; Steigel, A.; Sauer, J. *Tetrahedron Lett.* **1975**, *16*, 2901-2904.

[11] (a) Burg, B.; Dittmar, W.; Reim, H.; Steigel, A.; Sauer, J. *Tetrahedron Lett.* **1975**, *16*, 2897-2900. (b) Muller, K.; Sauer, J. *Tetrahedron Lett.* **1984**, *25*, 2541-2544.

[12] (a) Boger, D. L.; Panek, J. S. *J. Org. Chem.* **1981**, *46*, 2179-2182. (b) Boger, D. L.; Panek, J. S.; Meier, M. M. *ibid.* **1982**, *47*, 895-897.

Scheme 3

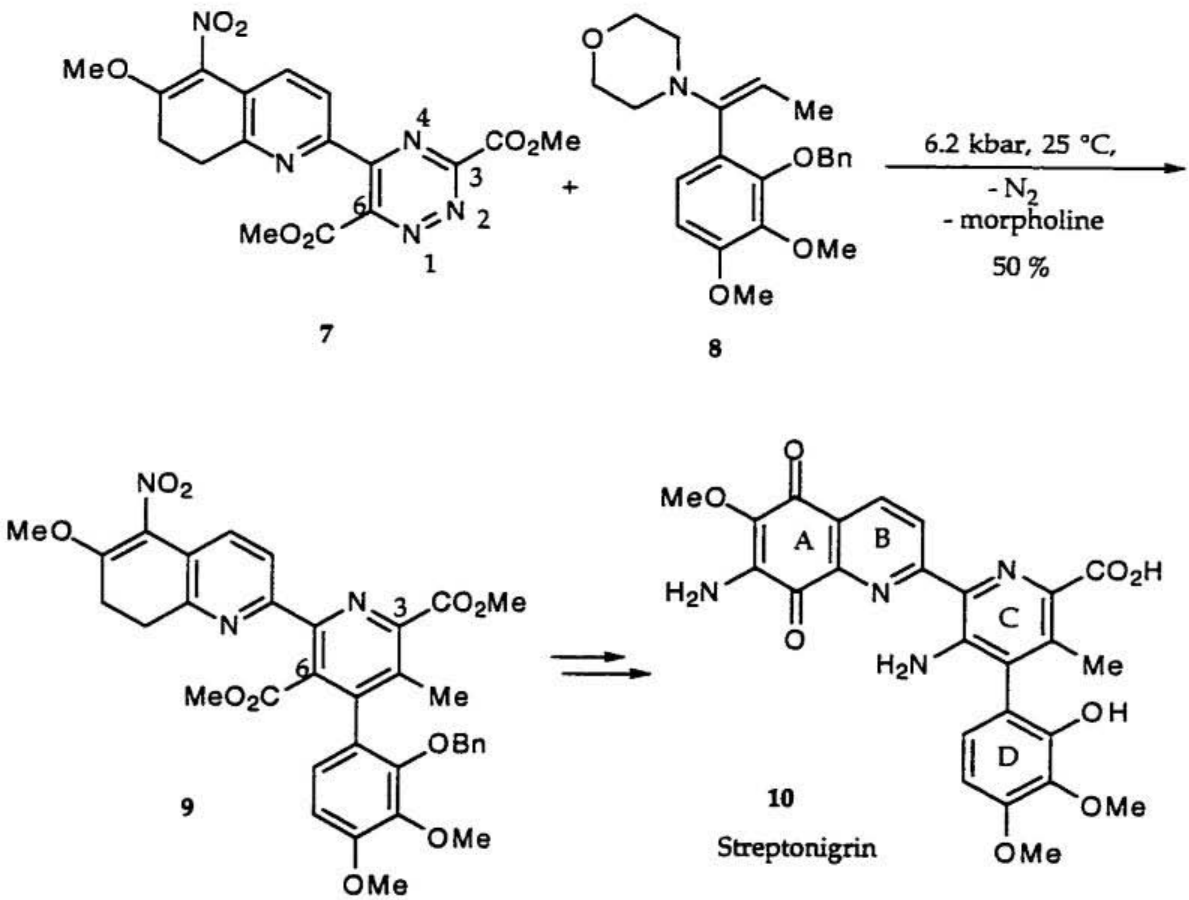


The IED Diels-Alder cycloaddition employing 1,2,4-triazines has become an important tool for the synthesis of biologically active natural and unnatural products. Boger *et al.* used this methodology in the synthesis of streptonigrin **10** (Scheme 4).[13] Triazine derivative **7**, upon treatment with enamine **8** at 6.2 kbar and 25 °C, afforded **9** by

[13] Boger, D. L.; Panek, J. S. *J. Am. Chem. Soc.* **1985**, *107*, 5745-5754.

cycloaddition across C3/C6 of the triazine nucleus followed by the release of nitrogen and the elimination of morpholine. Compound **9** was then elaborated into streptonigrin **10** in seven steps.

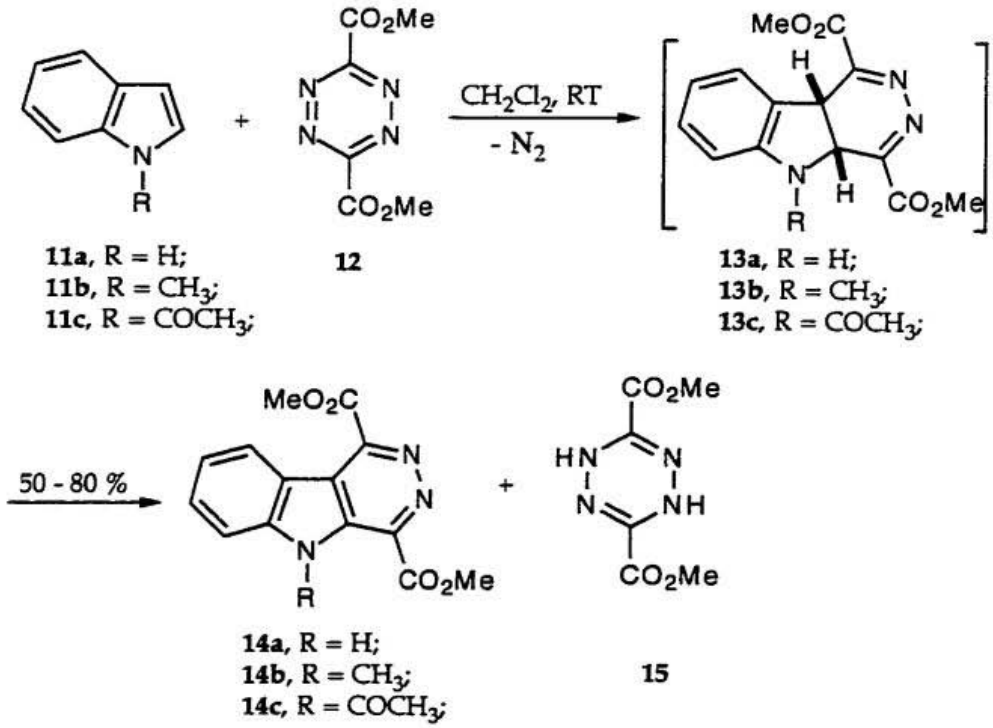
Scheme 4



Substituted 1,2,4,5-tetrazines have been shown to react with a wide range of dienophiles to provide 1,4-dihydropyridazines. Their cycloaddition reactions with indole derivatives have drawn the greatest amount of attention due to their potential utility in the synthesis of indole-based alkaloids. For instance, the reaction of indole or its derivatives **11a-c** with excess 3,6-dicarbomethoxy-1,2,4,5-tetrazine **12** (Scheme 5) at room temperature produced the adducts **13a-c** after expulsion of nitrogen. Dehydrogenation of

13a-c by excess tetrazine then gave the products **14a-c** and 1,4-dihydrotetrazine **15**. Compounds **14a-d** were obtained in 50-80% yields.[14]

Scheme 5



11a, R = H;
11b, R = CH_3;
11c, R = $COCH_3$;

12

13a, R = H;
13b, R = CH_3;
13c, R = $COCH_3$;

14a, R = H;
14b, R = CH_3;
14c, R = $COCH_3$;

15

The IED Diels-Alder reaction of α,β-unsaturated carbonyl compounds with alkyl vinyl ethers[15] affords various derivatives of 2-alkoxy-3,4-dihydro-*2H*-pyrans, useful in the synthesis of carbohydrates.[16] For example, α, β-unsaturated keto ester **16** reacted with ethyl vinyl ether (Scheme 6) to give a mixture of the *endo* adduct **17** and the *exo* adduct **18*** .[17] It was found that pressure and Lewis acids such as ethylaluminum chloride

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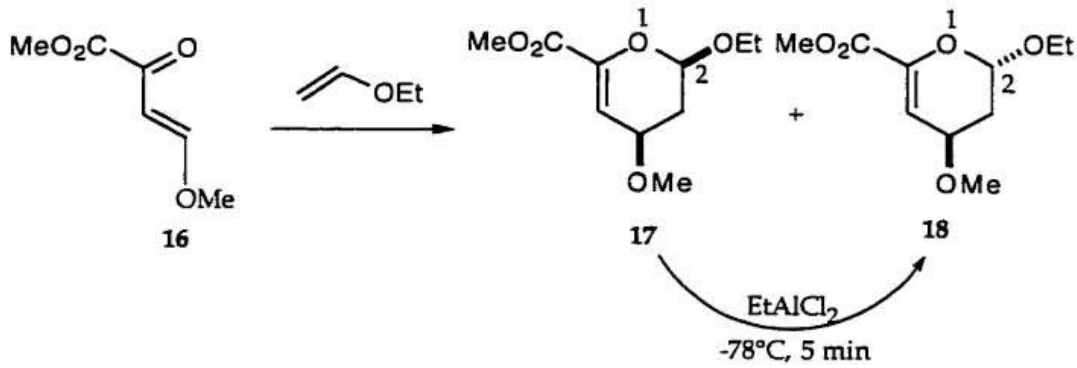
[14] (a) Benson, S. B.; Palabrica, C. A.; Snyder, J. K. *J. Org. Chem.* **1987**, *52*, 4610-4614. (b) Benson, S. B.; Gross, J. L.; Snyder, J. K. *J. Org. Chem.* **1990**, *55*, 3257-3269.

[15] For a review up to 1975: Desimoni, G.; Tacconi, G. *Chem. Rev.*, **1975**, *75*, 651-692.

[16] (a) For a review: Schmidt, R. R. *Pure Appl. Chem.* **1987**, *59*, 15-424. (b) Schmidt, R. R.; Apparao, S.; Maier, M. E. *Synthesis* **1987**, *10*, 900-904. (c) Maier, M. *Tetrahedron Lett.* **1985**, *26*, 2065-2068. (d) Tietze, L. F.; Voss, E. *Tetrahedron Lett.* **1986**, *27*, 6181-6184.

* The term "*endo* adduct" and "*exo* adduct" are used in this thesis to describe Diels-Alder adducts that on

Scheme 6



Conditions	Yield	**17 : 18**
a. neat, 13 kba, 24 °C, 65h	82%	(5.7 : 1.0)
b. toluene, 110 °C, 29h	48%	(1.8 : 1.0)
c. CH_2Cl_2, $EtAlCl_2$(0.1 eq), -78 °C	75%	(0.8 : 1.0)

increased the yield of the reaction, and as the reaction time, reaction temperature and amount of Lewis acid were increased, more *exo* adduct was obtained. It was also confirmed that at elevated temperatures or in the presence of Lewis acids, the *endo* adduct **17** epimerized to the more stable *exo* isomer **18**. The epimerization occurred at C2 of the *endo* adduct.

2-Pyrone **19** can function as the diene component to undergo cycloaddition with various alkenes and alkynes. Cycloaddition with alkynes generates the strained bicyclooctadienes **20** that readily undergo extrusion of CO_2 to form aromatic products **21** (Scheme 7). Cycloaddition with alkenes generates initially more stable and sometimes isolable bicyclooctenes **22**. Compounds such as **22** are also thermal labile. Extrusion of CO_2 and subsequent elimination can occur easily to provide the aromatic product **24**.

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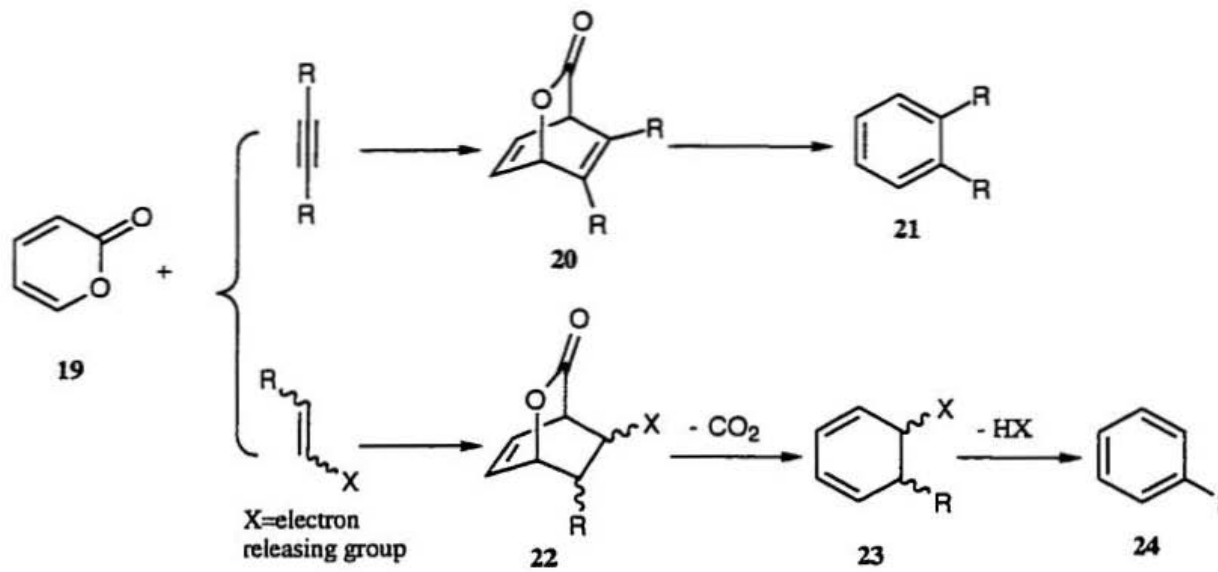
the surface, are the results of *endo* and *exo* Diels-Alder reactions, respectively. These terms are descriptive of the structures of the adducts and not of the mechanism of their formation.

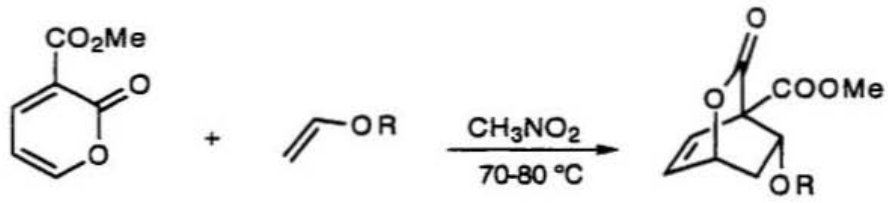
[17] Macdonald, S. J. F.; Huizinga, W.B.; McKenzie, T. C. *J. Org. Chem.* **1988**, *53*, 3373-3377.

Scheme 7



The IED Diels-Alder reaction of 2-pyrone **19** with electron rich alkenes proceeds under high pressure, but suitably substituted 2-pyrones do so under much milder

Scheme 8



25

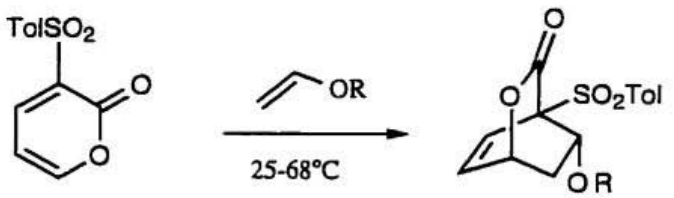
26a, R = OBn
26b, R = OBu

27a, R = OBn, 65%
27b, R = OBu, 95%

conditions. For example, 3-carbomethoxy-2-pyrone (3-CMP) **25** reacted smoothly with alkyl vinyl ethers **26a,b** giving the bicyclic lactones **27a,b** in good yields with complete *endo* selectivity (Scheme 8).[18]

3-(*p*-Tolylsulphonyl)-2-pyrone **28** was found to be a better electron deficient diene than 3-CMP **25** and reacted with a variety of alkyl vinyl ethers at 25-68°C to provide the *endo* bicycloadducts **29a-e** (Scheme 9).[19] When chiral alkyl vinyl ethers were employed as the dienophiles, high levels of diastereoselectivity were observed in the cycloaddition.

Scheme 9



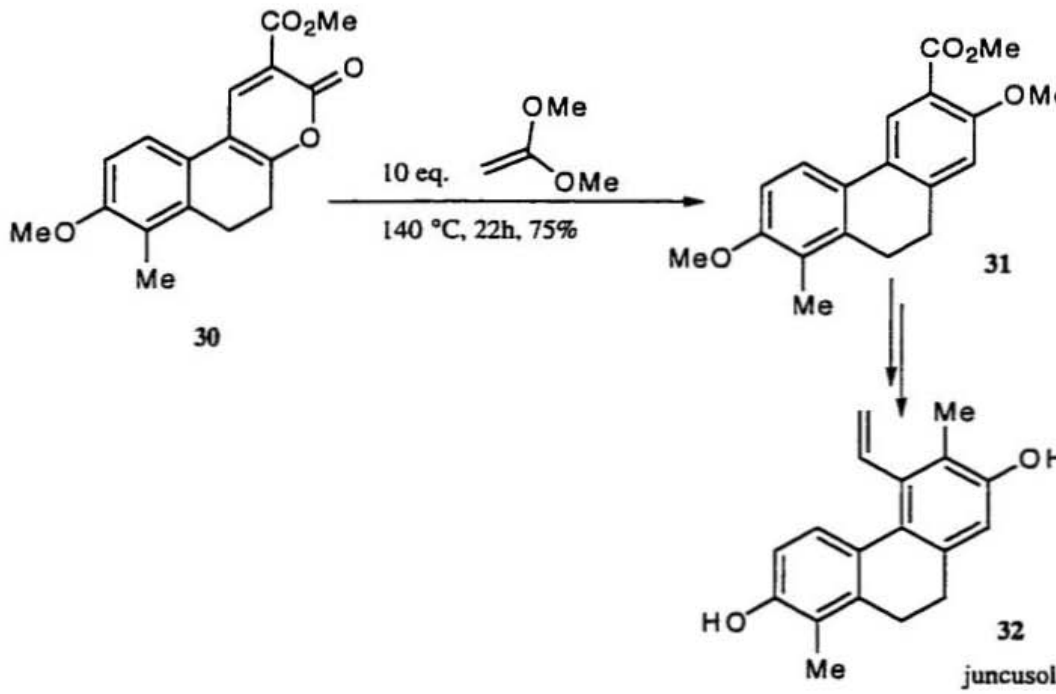
28 *endo*-**29**

29	**R**	**% yield**	**% de**
a	ethyl	95	–
b	2-octyl	>90	0
c	*endo*-2-bornyl	>90	5
d	menthyl	89	54
e	Ph(*i*-Pr)CH	94	84

[18] Prapansiri, V.; Thornton, E. R. *Tetrahedron Lett.* **1991**, *32*, 3147-3150.
[19] Posner, G. H..; Wettlaufer, D. G. *Tetrahedron Lett.* **1986**, *27*, 667-670.

Until the early 1970's, these cycloadditions were restricted almost exclusively to the synthesis of aromatic compounds. Boger *et al.* employed this methodology in the synthesis of natural products. For instance, substituted pyrone **30** readily reacted with 1,1-dimethoxyethylene (Scheme 10) at 140 °C to form the aromatized compound **31** in 75% yield *via* the extrusion of CO_2 and elimination of methanol from the initially formed adduct. Compound **31** was obtained as the sole regioisomer, and it was eventually converted into juncusol **32**.[20]

Scheme 10

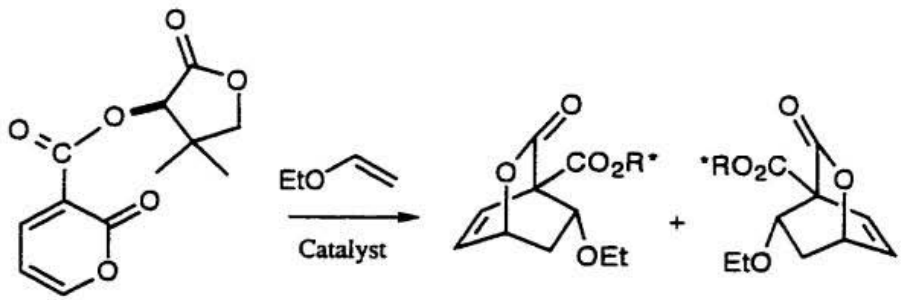


More recently, it was recognized that the initially formed bicycloadducts from the Diels-Alder cycloaddition of 2-pyrones and alkenes could serve as a valuable source of multifunctionalized compounds, formed with excellent control of the relative and

[20] Boger, D. L.; Mullican, M. D. *Tetrahedron Lett.* **1982**, *23*, 4555-4558. (b) Boger, D. L.; Mullican, M. D. *J. Org. Chem.* **1984**, *49*, 4045-4050.

absolute stereochemistry.[21] The groups of Posner and Markó have both made prolific contributions to the chiral IED Diels-Alder cycloadditions of 2-pyrone derivatives to form synthetically useful bicyclic lactone adducts that can be converted into various enantiopure and biologically active compounds. They have incorporated chiral auxiliaries separately into vinyl ethers and into the pyrone unit as well as into the Lewis acid.

Scheme 11



33 **34** **35**

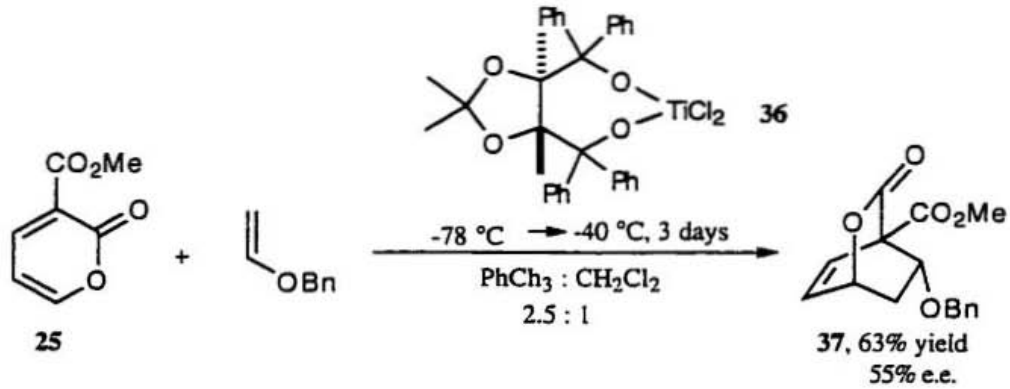
Entry	Catalyst	yield	de of **34**
1	(+)-Eu(hfc)$_3$	97%	>95%
2	Eu(fod)$_3$	94%	>95%
3	(-)-Eu(hfc)$_3$	91%	>95%

Markó *et al.* first reported their results on the lanthanide-catalysed diastereocontrolled cycloadditions of chiral 2-pyrone derivatives with various dienophiles.[22] For example, in the presence of a lanthanide shift reagent, chiral or not,

[21] For reviews on 2-pyrone chemistry: see (a) Afarinkia, K.; Vinader, V.; Nelson, T. D.; Posner, G. H. *Tetrahedron* **1992**, *48*, 9111-9171. (b) Kalinin, V. N.; Shilova, O. S. *Russ. Chem. Rev.* **1994**, *63*, 661-666.
[22] Markó, E. I.; Evans, G. R.; Declercq, J.-P. *Tetrahedron* **1994**, *50*, 4557-4574.

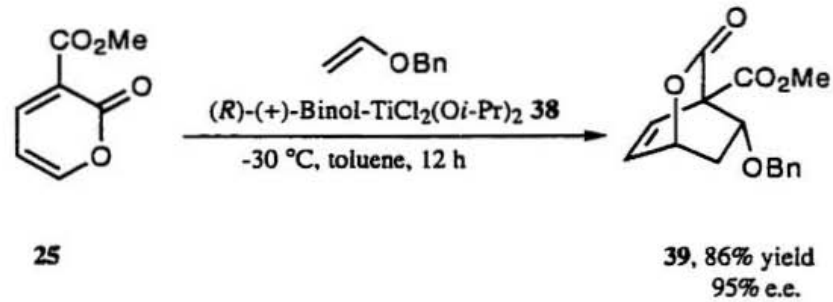
(+)-Eu(hfc)$_3$, Eu(fod)$_3$ or (-)-Eu(hfc)$_3$, diastereomerically pure bicyclic lactone **34** (Scheme 11) was obtained by using a pantolactone unit as the chiral auxilliary incorporated into the 2-pyrone diene **33**.

Scheme 12



Posner and coworkers found that the tartrate-derived TADDOL-complexed titanium IV species **36** (Scheme 12) catalyzed the cycloaddition of achiral 3-CMP **25** with benzyl vinyl ether under very mild conditions to produce the *endo* bicycloadduct **37** as a single diastereomer in 55% enantiomeric excess.[23]

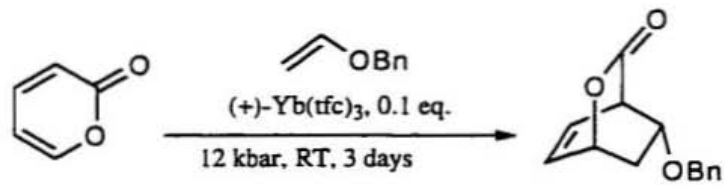
Scheme 13



[23] Posner, G. H; Carry, J.-C.; Lee, J. K.; Bull, D. S.; Dai, H. *Tetrahedron Lett.* **1994**, *35*, 1321-1324.

The (*R*)-(+)-1,1'-bi-2-naphthol-titanium Lewis acid complex **38** (Scheme 13) was also found to promote the cycloaddition of 3-CMP **25** and benzyl vinyl ether, with cycloadduct **39** being formed in 86% yield and in 95% ee.[24]

Scheme 14



19 **40**, 81% yield, 95% ee

The parent 2-pyrone **19** was reported (Scheme 14) to undergo ytterbium-promoted, high-pressure, regioselective, and stereoselective Diels-Alder cycloaddition with benzyl vinyl ether to form bicyclic lactone **40**.[25]

Markó *et al.* reported the cycloadditions between 3-CMP **25** (Scheme 15) and various vinyl ethers and vinyl sulfides **41**, catalyzed by the $Yb(OTf)_3$-Binol complex **42**, which afforded the bicyclic lactones **43** in moderate to excellent ee. It was found that vinyl sulphides always gave higher ee than the corresponding vinyl ethers.[26]

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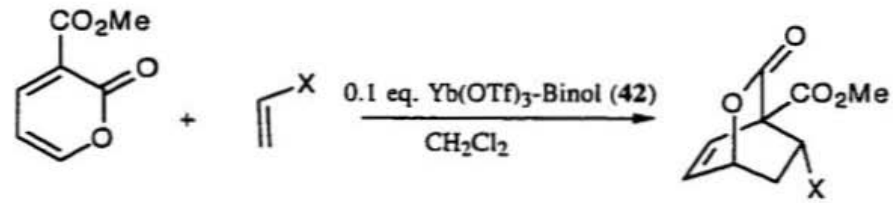
[24] (a) Posner, G. H.; Eydoux, F.; Lee, J. K; Bull, D. S. *Tetrahedron Lett.* **1994**, *35*, 7541-7544. (b) Posner, G. H.; Dai, H.; Lee, J. K.; Bull, D. S.; Eydoux, F.; Lee, J. K. *J. Org. Chem.* **1996**, *61*, 671-676.
[25] Posner, G. H.; Ishihara, Y. *Tetrahedron Lett.* **1994**, *35*, 7545-7548.
[26] Markó, I. E.; Evans, G. R. *Tetrahedron Lett.* **1994**, *35*, 2771-2774.

Scheme 15



25 **41** **43**

entry	substrate (**41**)	yield	ee of **43**
1	OEt	90%	27%
2	OAd	97%	85%
3	SCy	98%	86%
4	SPh	91%	>95%

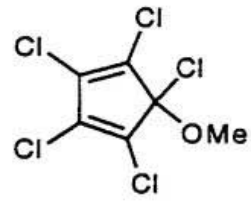
Ad = adamantyl; Cy = cyclohexyl

From a broad review of the literature, it can be seen that one of the major problems with the inverse type Diels-Alder reaction is that it is mainly restricted to heterodienes and/or heterodienophiles. Of the known all-carbon dienes, 2-pyrones appear to be the most useful. Derivatives of cyclopentadiene **44** (Scheme 16),[27] cyclopentadienone **45**,[28] and other isolated examples such as 2,3-dicarbomethoxy-1,3-butadiene **46**[29] and **47**[30] comprise the remainder of such dienes. Since none of these dienes can truly boast broad synthetic utility, it would be desirable to develop a family of electron deficient dienes that would offer wide scope in the synthesis of carbocyclic systems *via* the IED Diels-Alder reaction.

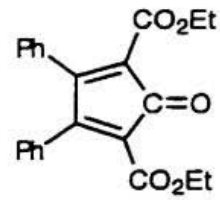
---

[27] Burry, L. C.; Bridson, J. N.; Burnell, D. J. *J. Org. Chem.* **1995**, *60*, 5931-5934.
[28] Harano, K.; Yasuda, M.; Kanematsu, K. *J. Org. Chem.* **1982**, *47*, 3736-3743.
[29] (a) Grundke, C.; Hoffmann, H. M. R. *Chem. Ber.* **1987**, *120*, 1461-1462. (b) Tarnchompoo, B.; Thebtaranonth, C.; Thebtaranonth, Y. *Tetrahedron Lett.* **1987**, *28*, 6671-6674.
[30] Prinzbach, H.; Auge, W.; Basbudak, M. *Helv. Chim. Acta*, **1971**, *54*, 759-764.

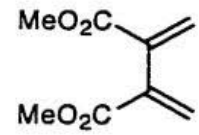
Scheme 16



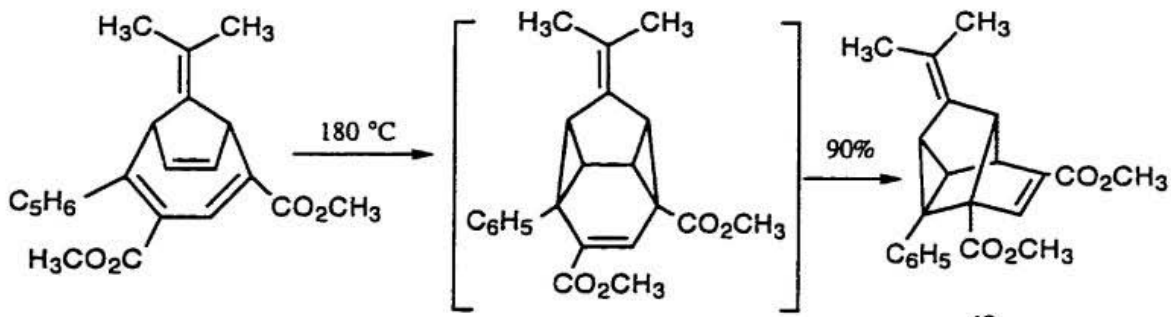
44



45



46



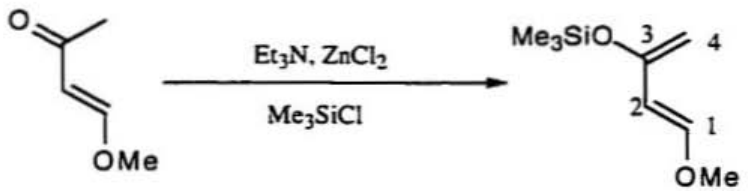
47 **48**

In deciding on what type of electron deficient dienes to focus on, a page was taken from the normal Diels-Alder reaction. Danishefsky's diene (1-methoxy-3-trimethylsilyloxy-1,3-butadiene) **50**, first reported in 1974, is one of the best dienes in the normal Diels-Alder reaction.[31] It is easily prepared from α,β-unsaturated ketone **49** (Scheme 17) and is commercially available. The electron donating groups at the 1 and 3 positions, which result in its markedly raised HOMO energy level, are responsible for its good reactivity toward a variety of dienophiles. The strongly electron donating substituents at the 1 and 3 positions work in concert to bias the two ends of the diene unit electronically and this results in excellent regiochemical control during reactions with electronically biased dienophiles. In addition, the functionality present in the Diels-Alder adducts can

[31] Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807-7808.

be manipulated in a number of ways to prepare more complex systems. As a result, Danishefsky's diene and its analogs have enjoyed wide application in the synthesis of natural poducts.[32]

Scheme 17



49 **50**

At the outset of this work, it was envisaged that one of the best chances for making a useful electron deficient diene would be to place the electron withdrawing groups at the 1 and 3 positions of a diene **51** (Figure 2). This might be expected to influence the nature of the diene unit in an opposite sense from Danishefsky's diene **50**.

Figure 2. Danishefsky's diene and 1,3-substituted electron deficient dienes

50 **51**

Danishefsky's diene 1,3-substituted electron deficient diene

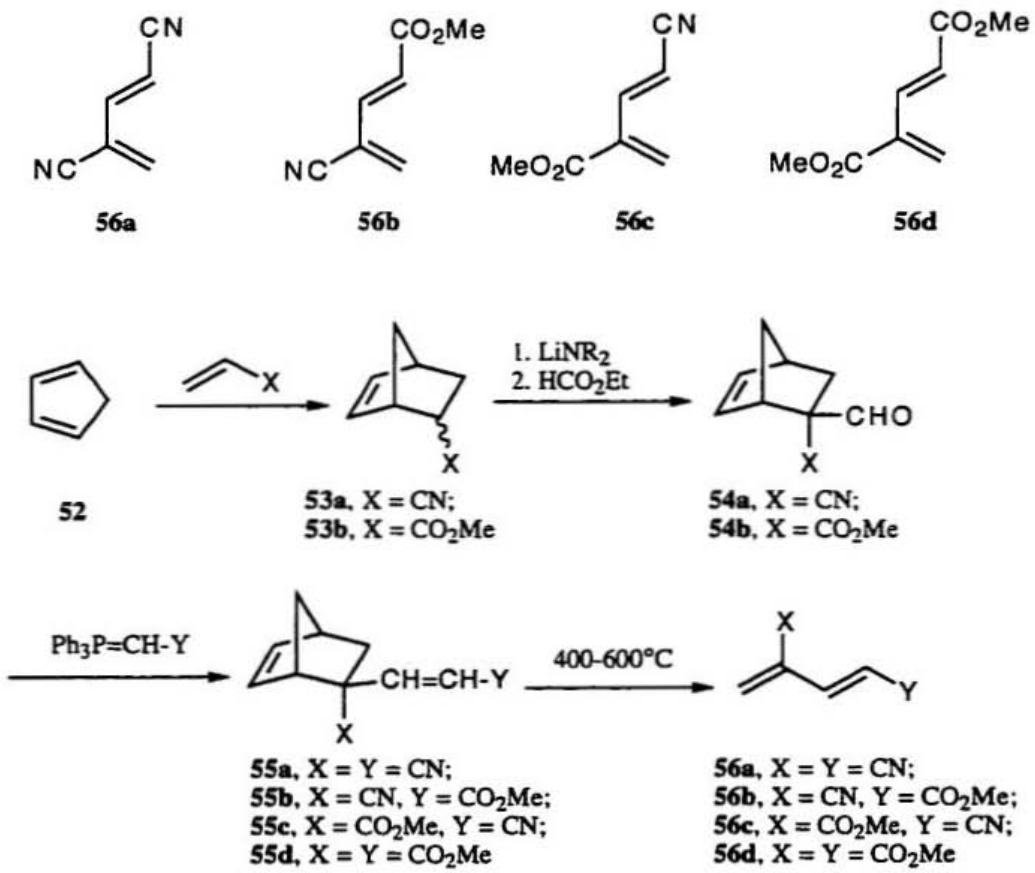
Not only would the two ends of the diene be electronically biased, but the LUMO energy of the diene would be expected to be very low. Thus, reactions with electronically biased

[32] Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400-406.

electron rich dienophiles would be predicted to occur readily and with high regiochemical control. Furthermore, the resultant cycloaddition products would incorporate a variety of functional groups which are all different from those present in adducts of Danishefsky's diene. These too could potentially be elaborated in a number of ways.

In the early '80s, Ahn and Hall[33] reported the synthesis of the four acyclic electron deficient dienes **56a-d** (Scheme 18). Diels-Alder reaction of cyclopentadiene **52** with

Scheme 18



acrylonitrile or methyl acrylate generated adducts **53a,b**, which were formylated with a lithium amide base and ethyl formate to give aldehydes **54a,b**. Wittig reaction of **54a,b**

---

[33] Ahn, K.-D.; Hall, H. K. *J. Polym. Sci. Polym. Chem. Ed.*, **1981**, *19*, 629-644.

with cyano- or carbomethoxymethylenephosphoranes provided **55a-d**. Thermolysis (retro-Diels-Alder reaction) of **55a-d** at 400-600 °C at 0.1-1 mm Hg led to the formation of cyclopentadiene and diene **56a-d**. Dienes **56a** and **56b** were obtained in more than 50% yield but they were found to polymerize readily. Dienes **56c** and **56d** could not be isolated under the reaction conditions. All of these dienes were made into polymers and, unfortunately, their Diels-Alder chemistry was not investigated.

In the late '80s and early '90s, Padwa reported the synthesis of 1,3-bis(phenylsulfonyl)butadiene **59** and its IED Diels-Alder cycloadditions with several dienophiles such as enamines, amidines and indole derivatives (Scheme 19).[34] Although diene **59** was first obtained accidentally from the isomerization of 2,3-bis(phenylsulfonyl)-butadiene,[35] its direct preparation involved the oxidation of 1,4-bis(phenylsulfonyl)-2-(phenylthio)-2-butene[36] **57** to give the corresponding trisulfone **58**. Elimination of benzenesulfinate by stirring **58** with Et_3N gave diene **59**, which dimerized readily in its pure form. In order to perform Diels-Alder reactions, it was generated *in situ* in the presence of various dienophiles. Its adducts with enamines, amidines and indole derivatives (Scheme 19) could not be isolated due to their further reactions such as eliminations and isomerizations.

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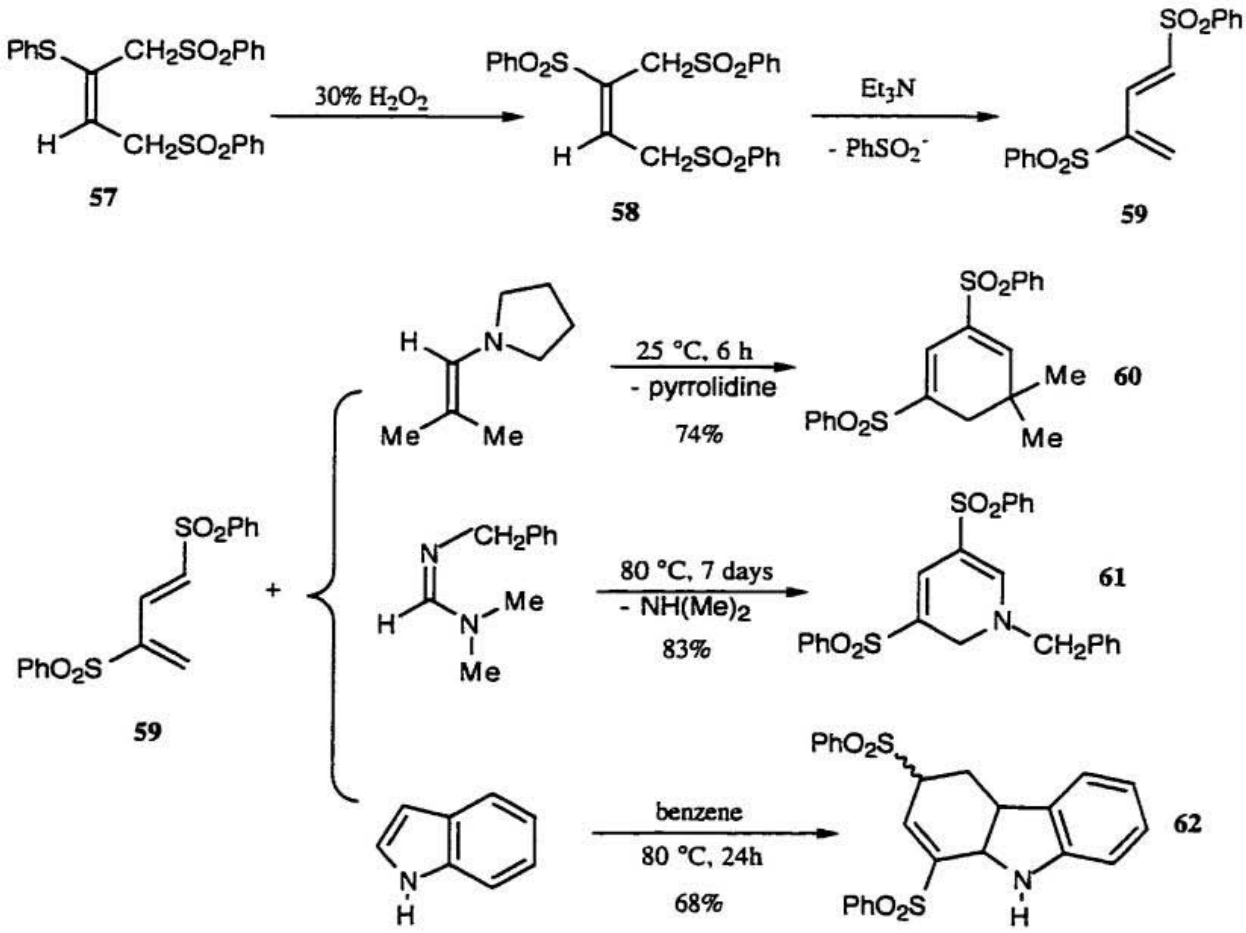
[34] Padwa, A.; Gareau, Y.; Harrison, B.; Rodriguez, A. *J. Org. Chem.* **1992**, *57*, 3540-3545.
[35] (a) Norman, B. H.; Gareau, Y.; Padwa, A. *J. Org. Chem.* **1991**, *56*, 2154-2161. (b) Padwa, A.; Harrison, B., Norman, B. H. *Tetrahedron Lett.* **1989**, *30*, 3259-3262. (c) Padwa, A.; Norman, B. H. *Tetrahedron Lett.* **1988**, *29*, 2417-2420.
[36] Maskyama, Y.; Sato, H.; Kurusu, Y. *Tetrahedron Lett.* **1985**, *26*, 67-68.

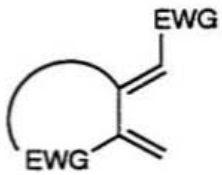
Scheme 19



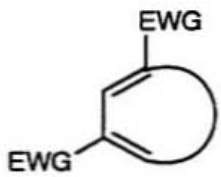
Because of the instability of the few known parent dienes, cycloalkane-annulated dienes were chosen for initial study. As shown in Figure 3, there are 4 modes **63a-d** of affixing a cycloalkane ring to the proposed electron deficient diene unit such that the *s-cis* conformer is still easily accessible. In the first two systems **63a,b**, the diene units are held rigidly in the *s-cis* conformation and, as such, may still be too reactive. Therefore, dienes belonging to system **63d** were chosen as the first targets. The general synthetic methodology and their normal and IED Diels-Alder reactions with a series of electron

rich and electron deficient dienophiles will be presented and discussed in the following chapters.

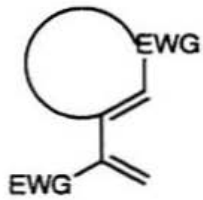
Figure 3. Cycloalkane-annulated systems of dienes



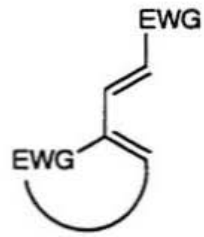
63a



63b



63c



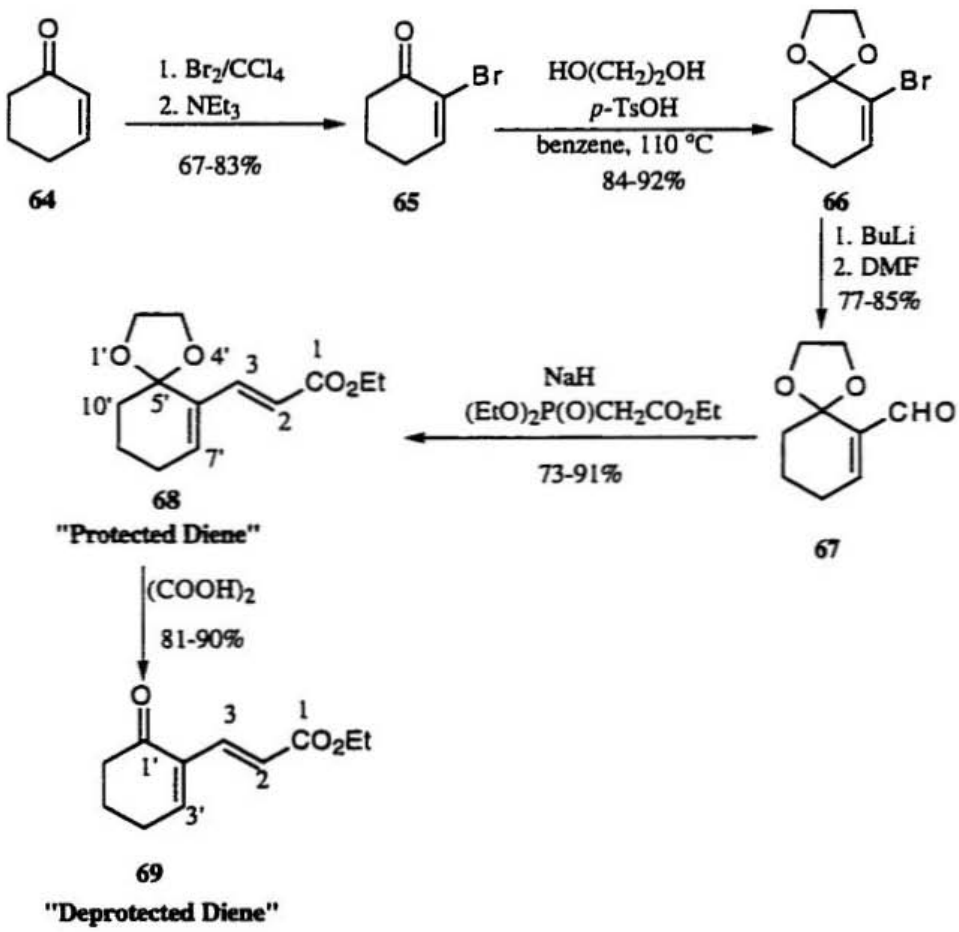
63d

Chapter 2. Synthesis of New Electron Deficient Dienes

2.1. Results and Discussion

The electron deficient dienes **68** and **69** were synthesized from 2-cyclohexen-1-one in four and five steps, respectively (Scheme 20). Bromination of 2-cyclohexen-1-one **64** followed by dehydrobromination with triethylamine gave 2-bromo-2-cyclohexen-1-

Scheme 20



64 → 65 → 66 → 67 → 68 "Protected Diene" → 69 "Deprotected Diene"

one **65** in 67-83% yield.[37,38] Protection of the ketone unit of **65** formed 6-bromo-1,4-dioxaspiro[4,5]dec-6-ene **66** in 84-92% yield.[38] Compound **66** could also be prepared in 52-59% overall yield from 2-cyclohexen-1-one without purifying **65**. Formylation[39] of **66** with butyllithium and DMF produced aldehyde **67** (77-85%). Horner-Wadsworth-Emmons reaction[40] of aldehyde **67** with ethyl diethylphosphonoacetate/sodium hydride resulted in diene **68** (73-91%). Diene **68** and its analogs (*vide infra*) will be refered to as "protected" dienes. The ^{1}H NMR spectrum of diene **68** showed a doublet of doublets at δ 7.28, a triplet at δ 6.46 and a doublet at δ 6.06. They were unambiguously assigned as C3-H, C7'-H and C2-H with the help of ^{13}C NMR, COSY, HET-CORR and APT experiments. The coupling constant between C2-H and C3-H was 16.0 Hz, suggesting that the newly formed double bond had the *E* configuration. There were no signals attributable to the *Z* isomer in the NMR spectra of the crude **68**. Diene **68** was transformed into diene **69** (81-90%) by heating with oxalic acid in a THF/water mixture. Without the presence of THF, the conversion of diene **68** to **69** proceeded in very low yield. Presumably, THF promoted the reaction by enhancing the solubility of diene **68** in aqueous oxalic acid. Diene **69** and related dienes will be refered to as "deprotected" dienes.

Dienes **70** and **71** were also prepared from aldehyde **66** (Scheme 21) employing similar methodology as for dienes **68** and **69**. Horner-Wadsworth-Emmons reaction of **67** with benzyl diethylphosphonoacetate/sodium hydride, which was prepared from benzyl bromoacetate and $(EtO)_3P$, gave **70** in 80% yield. Removal of the 1,3-dioxolane protecting group from **70** provided the deprotected diene **71** in 56% yield. This yield was not optimized. As before, the NMR spectra of **70** and **71** were consistent with the *E*

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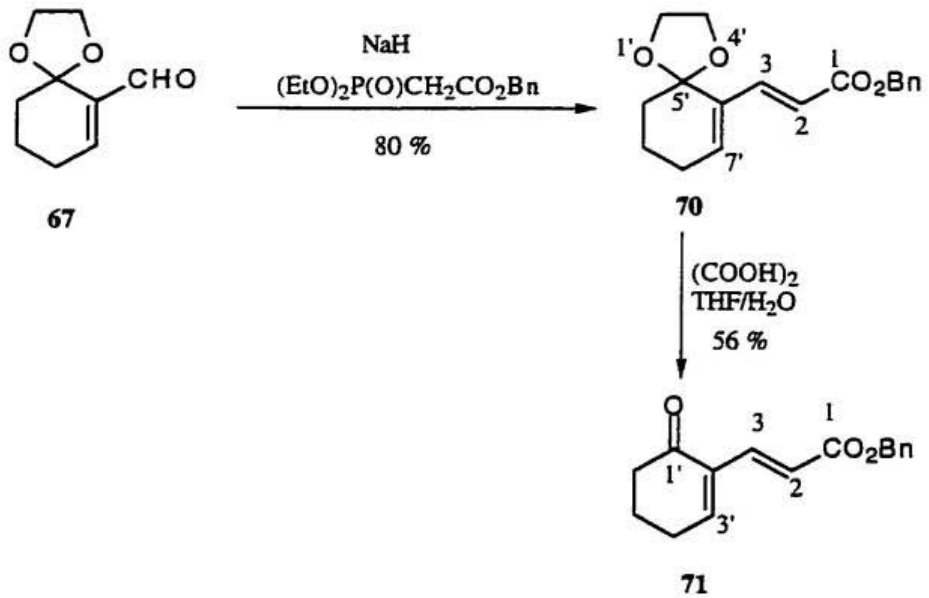
[37] Bordwell, F. C.; Wellmen, K. M. *J. Org. Chem.* **1963**, *28*, 2544-2550.
[38] Smith, A. B.; Branca, S. J.; Pilla, N. N.; Guaciaro, M. A. *J. Org. Chem.* **1982**, *47*, 1855-1869.
[39] Smith, J. G.; Dibble, P. W.; Sandborn, R. E.; *J. Org. Chem.* **1968**, *51*, 3762-3768.
[40] Jorgenson, M. J.; Thacher, A. F. *Org. Synth., Coll. Vol. V*, **1973**, 509-513. Wadsworth, W. S.; Emmons, W. D. *Org. Synth., Coll. Vol. V*, **1973**, 547-549.

configuration at the C2-C3 double bond, and no traces of the corresponding *Z* isomers were detected.

Scheme 21

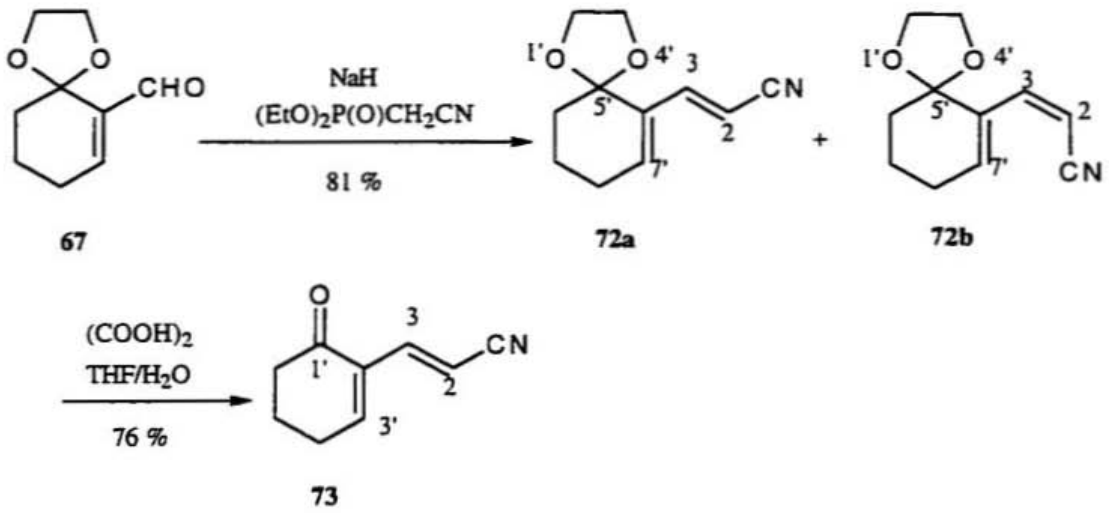


67 **70** **71**

Treatment of aldehyde **67** with the ylid derived from diethylphosphonoacetonitrile (prepared from $(EtO)_3P$ and bromoacetonitrile)[41] in THF under the same conditions as for diene **68** produced an inseparable mixture of dienes **72a** and **72b** (Scheme 22) in 81% total yield and in a ratio of 83 : 17, as determined by integration of C2-H signals in the ^1H NMR spectra of the mixture. The ^1H NMR spectrum of the major isomer **72a** included a doublet of doublets at δ 6.95 (C3-H), a triplet at δ 6.42 (C7'-H) and a doublet at δ 5.54 (C2-H). A 16.8 Hz coupling constant between C2-H and C3-H confirmed the *E* configuration of the new double bond. However, **72b** displayed a doublet of doublets at δ 6.94 (C7'-H), a doublet of doublets at δ 6.80 (C3-H) and a doublet at δ 5.30 (C2-H) and

[41] Naqta, W.; Wakabayashi, T.; Hayase, Y. *Org.* Synth., *Coll. Vol. VI*, **1988**, 448-450.

Scheme 22



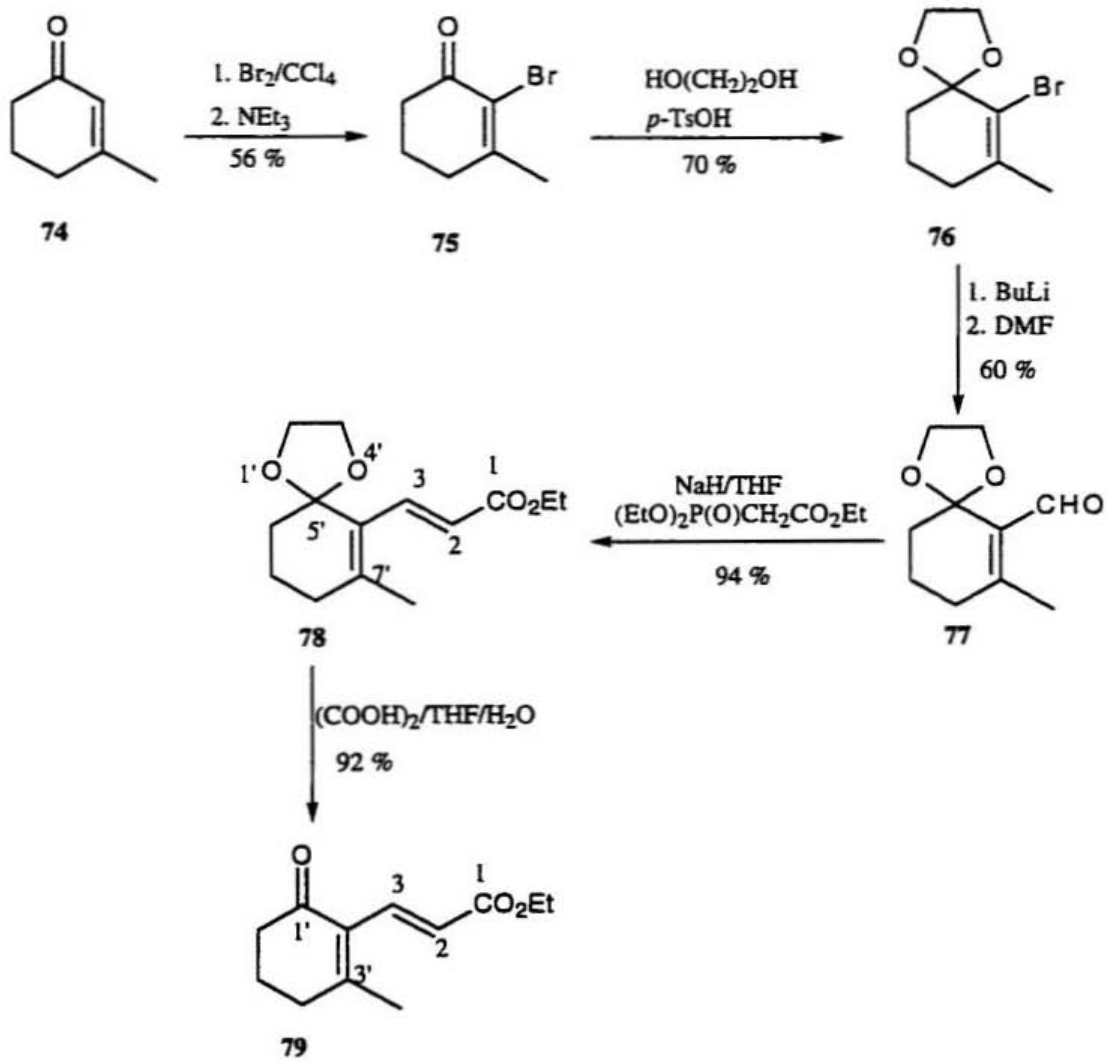
the coupling constant between C2-H and C3-H was 12.0 Hz, indicating the *Z* configuration of the C2, C3 double bond. That phosphonate anions stabilized by a cyano group are more disposed to the formation of isomeric mixtures than the corresponding ester-stabilized phosphonated anions has been documented.[42] Treatment of the mixture of **72a** and **72b** with aqueous oxalic acid provided the deprotected diene **73** in 76% yield. The ^{1}H NMR spectrum indicated that only the 2*E* isomer of **73** was obtained. No traces of **72b** or **72a** remained at the end of the reaction. Diene **73** could have resulted from the deprotection of both dienes **72a** and **72b** with the concomitant C2 double bond isomerization of **72b**. However, it is also possible that only **72a** was transformed into **73** while **72b** polymerized under the reaction conditions. Further experiments are required to determine whether both **72a** and **72b** were involved in the formation of diene **73**.

---

[42] (a) Jones, G; Maisey, R. F. *J. Chem. Soc., Chem. Commun.* **1968**, 543. (b) For reviews of the Horner-Wadsworth-Emmons reaction, see: Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87-99. (c) Wadsworth, W. S. In *Organic Reactions*; Baldwin, J. E. *et al.*, Eds.; John Wiley and Sons: New York, **1977**, *25*, pp 73-253.

A similar sequence of reactions was then employed in the preparation of dienes **78** and **79** (Scheme 23) from 3-methyl-2-cyclohexen-1-one, which was prepared according to a literature procedure.[43] By analyzing their NMR spectra (^{1}H, ^{13}C, COSY and HET-CORR), it was found that both **78** and **79** were obtained as pure 2*E* isomers. No *Z* isomers were observed.

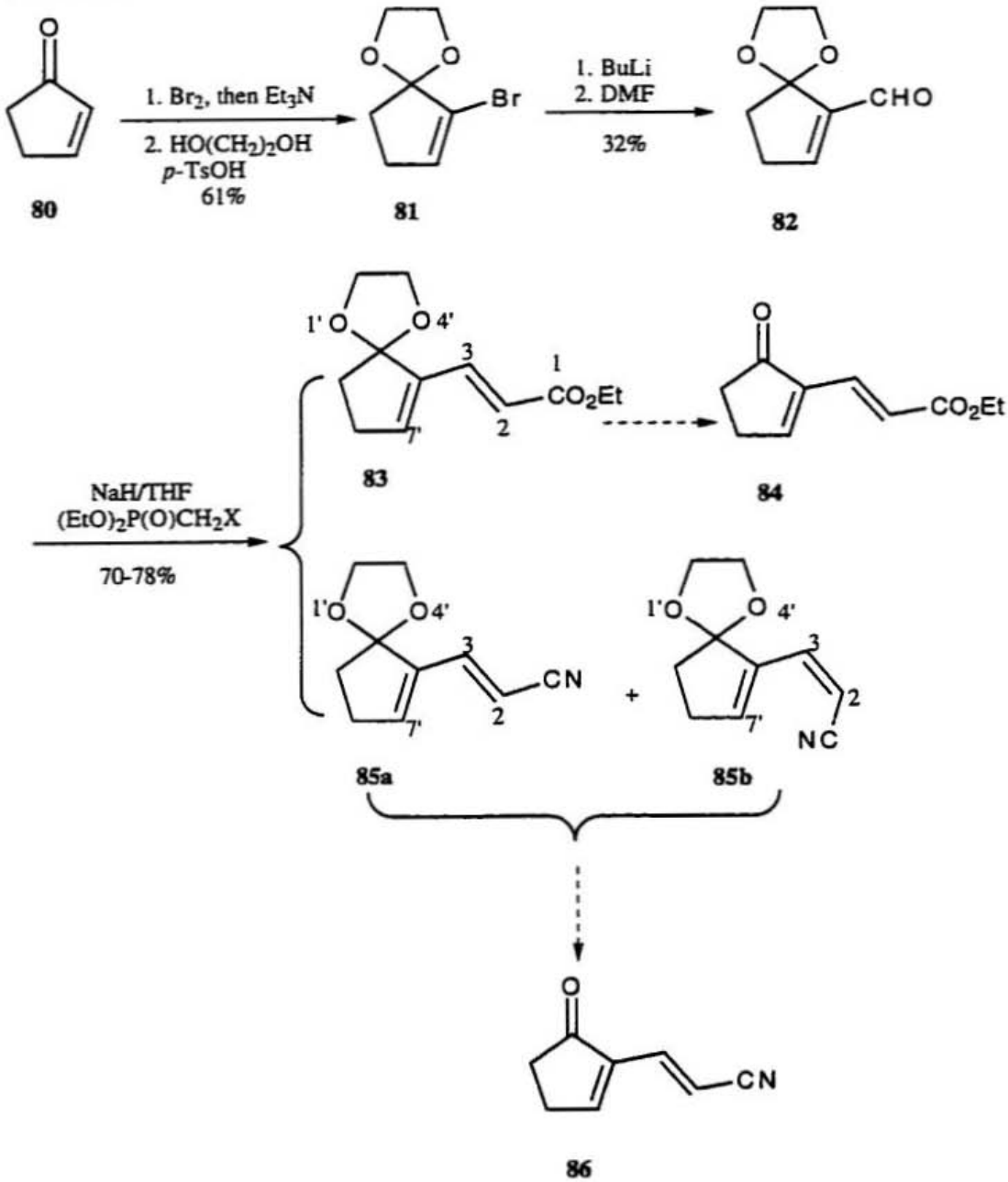
Scheme 23



[43] Gannon, W. F.; House, H. O. *Org. Synth., Coll. Vol. V*, **1973**, 539-541.

A similar approach was also attempted for the synthesis of the five-membered ring systems **83** and **85a** (Scheme 24) from 2-cyclopenten-1-one **80**, but this area has not been

Scheme 24



pursued to the same extent as the six-membered ring systems. Bromination of 2-cyclopenten-1-one **80** followed by dehydrobromination and subsequent protection of the resultant bromoketone gave **81** in 61% yield.[44] Unfortunately, the formylation of **81** to give **82**, proceeded in only 32% yield using the previously employed conditions. All attempts to improve the yield of this formylation led to failure. This is most likely due to inherent instability of aldehyde **82**. The protected diene **85a** was isolated as a mixture with its 2*Z* isomer **85b** in a ratio of 86 : 14, as determined by ^{1}H NMR spectroscopy. The ^{1}H NMR spectrum of **85a** included a doublet at δ 6.99 (C3-H), a triplet at δ 6.49 (C7'-H) and a doublet of doublets at δ 5.66 (C2-H). The coupling constant between C2-H and C3-H was 16.8 Hz, which suggested the *E* configuration. Protected diene **83** was obtained without any contamination by its 2*Z* isomer. The low yield of **82** largely limited further investigation of the 5-membered ring dienes. This approach will need to be modified if future studies of these systems are to be pursued (see Section 2.3).

Initial cursory attempts to prepare electron deficient dienes bearing more and/or stronger electron withdrawing groups by the methodology described above have been unsuccessful to date. For example, condensation of aldehyde **67** with nitromethane[45] (Scheme 25) in the presence of NaOH led to complete consumption of the starting material as established by TLC. The starting material's spot gave way to a new spot, which was presumed to be the nitrodiene **87**. However, only a baseline material was obtained after work-up. Future work in this system may have to focus on *in situ* preparations. A similar approach was applied to the synthesis of diene **88** (Scheme 25) from the condensation of aldehyde **67** and malononitrile.[46] The proton NMR spectrum of the crude product indicated that some diene **88** was formed but it decomposed during flash chromatography. These systems were not pursued further.

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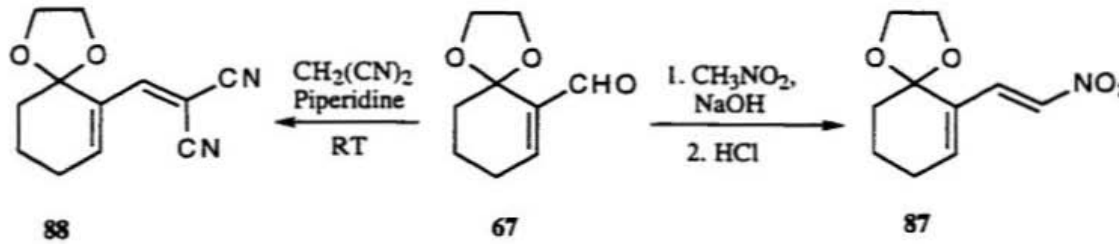
[44] Sato, K.; Inoue, S.; Kuranami, S.-I. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1666-1671.
[45] Worrall, D. E. *Org. Synth. Coll. Vol. VI* **1988**, 413-415.
[46] Hyatt, J. A. *J. Org. Chem.* **1983**, *48*, 129-131.

Scheme 25



88 **67** **87**

2.2. Proposed modifications of the methodology

An advantage of the methodology described above is that despite initially discouraging results, it might be applied to the synthesis of a variety of other electron deficient dienes, giving mainly *E* configured products (Scheme 26). However, a disadvantage of this methodogy is that it involves four and five steps to prepare the protected and deprotected dienes from commercially available materials. In addition, the aldehyde **82** employed in the 5-membered ring systems appears to be somewhat unstable, which limited further work in this area. An improved route to the dienes of interest could be based on the Heck reaction,[47] which involves the coupling of aryl or vinyl halides and alkenes in the presence of a palladium(0) catalyst. For example, coupling of 2-bromocyclohexen-1-one **65**, or its protected analog **66**, with methyl acrylate[48] would give the deprotected dienes **90** or the protected diene **91** (Scheme 27). Through the use of other vinyl halides and monosubstituted alkenes, a variety of electron deficient dienes might be accessible.

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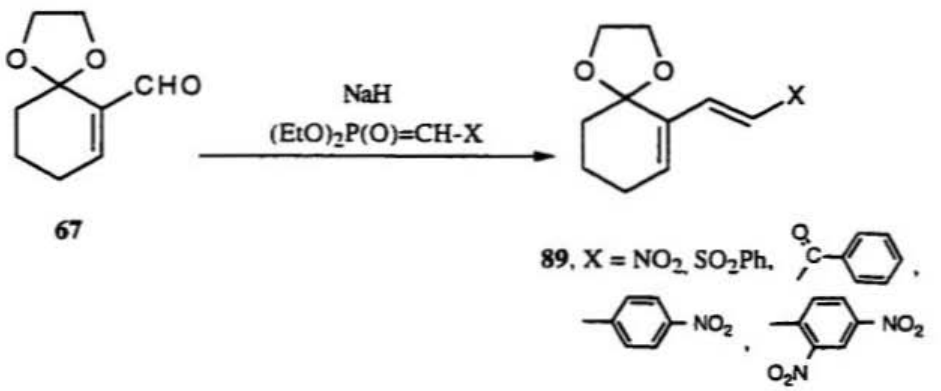
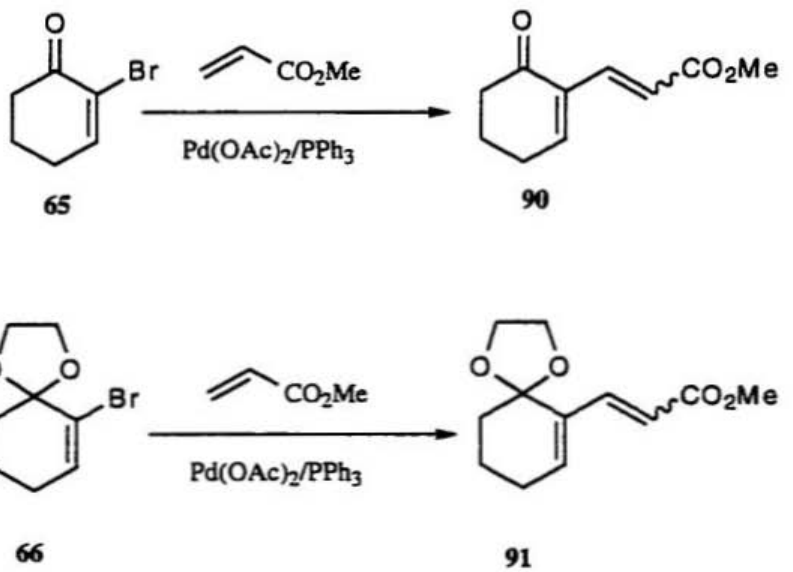
[47] For a review: (a) de Meijere, A.; Meyer, F. E. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2379-2441. (b) Mulzer, J.; Altenbach, H.-J.; Braun, M.; Krohn, K.; Reissig, H.-U. *Organic Synthesis Highlights*, VCH Publishers: New York, **1991**, pp 174-180.

[48] (a) Dieck, H. A.; Heck, R. F. *J. Am. Chem. Soc.* **1974**, *96*, 1133-1136. (b) Patel, B. A.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 3898-3903.

Scheme 26



Scheme 27

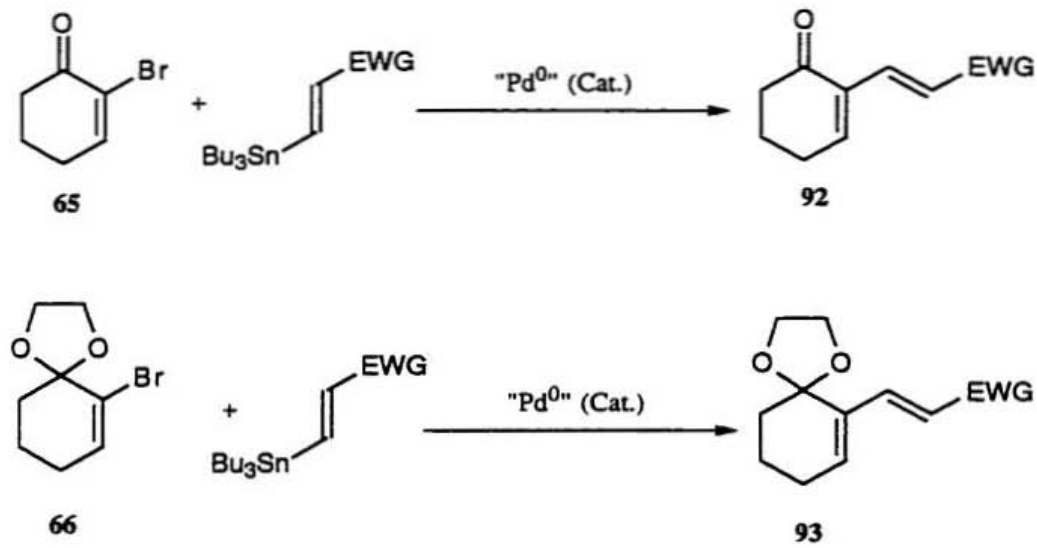


Alternatively, Stille couplings[49] might be employed to generate the diene unit (Scheme 28). An advantage of this particular reaction is that the double bond geometry can be controlled completely, as opposed to the Heck reaction which can lead to the

[49] (a) Stille, J. K. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508-631. (b) Mitchell, T. N. *Synthesis* **1992**, 803-815.

formation of mixture of isomers.[50] In both cases, however, the synthesis of electron deficient dienes would be considerably shorter.

Scheme 28



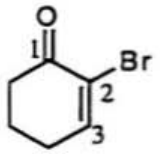
[50] Stille, J. K. *Pure & Appl. Chem.* **1985**, *57*, 1771-1780.

2.3. Experimental.

General procedures.

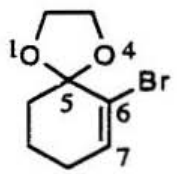
All reactions were performed under nitrogen. Unless otherwise noted, all commercial chemicals were used without further purification, and all solvents were distilled prior to use. Tetrahydrofuran was distilled over sodium/benzophenone. Toluene and benzene were distilled over calcium hydride and stored over 4Å Molecular sieves. Thin layer chromatography was performed on E. Merck 60 F_{254} precoated silica plates. Preparative thin layer chromatography (PTLC) plates were made from Aldrich silica gel (TLC standard grade, 2-25 μ) with 14% calcium sulfate. Column chromatography was carried out on silica gel 60 (E. Merck, 230-400 mesh) with the flash technique. Melting points (mp) were obtained on a Fisher-Johns apparatus and are uncorrected. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a GE GN-300NB spectrometer at 300 MHz and 75 MHz, respectively, usually in $CDCl_3$ solution unless otherwise specified. Chemical shifts are in ppm relative to internal standards: Me_4Si for ^{1}H and $CDCl_3$ (δ 77.0 ppm) for ^{13}C NMR. Individual peaks in the ^{1}H NMR spectra are reported as chemical shift, multiplicity (s=singlet, d=doublet, dd=double doublet, t=triplet, q=quartet, m=multiplet), number of hydrogens and coupling constant. Individual peaks in the 13C NMR spectra are reported as chemical shift and number of attached protons (3, 2, 1 or 0). The assignments were based on COSY, HET-CORR and APT. Infrared spectra (IR) were recorded on a Mattson Polaris FT instrument. Peaks are reported in cm^{-1} with the following intensities: s-strong, m-medium, w-weak. Low resolution and high resolution mass spectra (MS) were determined on a V. G. Micromass 7070HS instrument. MS data are reported as *m/z* and intensity. X-ray crystallography data were collected on a Rigaku AFC6S diffractometer at 298K.

2-Bromo-2-cyclohexen-1-one (65).[37,38]



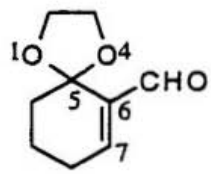
A solution of 2-cyclohexen-1-one (14.42 g, 150.0 mmol) in carbon tetrachloride (100 mL) was cooled to 0 °C (salt-ice bath) in a 500 mL, three-necked flask equipped with a mechanical stirrer, a thermometer and a dropping funnel. To the solution was added dropwise bromine (8.0 mL, 150 mmol) in carbon tetrachloride (20 mL) over 40 minutes followed by triethylamine (22.77 g, 225.0 mmol) in carbon tetrachloride (20 mL) over 35 minutes while keeping the internal temperature below 0 °C. The salt-ice bath was removed, and the mixture was stirred for an additional 2 h at room temperature. The resulting dark suspension was filtered with suction, and the filter-cake was washed with carbon tetrachloride. The filtrate and washings were combined and washed with 1 M HCl (2x100 mL), saturated $NaHCO_3$ solution (100 mL), water (100 mL) and brine (100 mL). The resultant solution was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by flash chromatography (20% ethyl acetate/hexane) gave **65** as colorless crystals (21.05 g, 120.0 mmol, 80%): mp 74.5-76 °C (lit.[37] mp 74 °C); ^1H NMR δ 7.44 (t, 1H, J = 4.4 Hz), 2.64 (t, 2H, J = 6.4 Hz) 2.49-2.44 (m, 2H), 2.13-2.04 (m, 2H); ^{13}C NMR δ 191.3, 151.2, 123.8, 38.3, 28.3, 22.6.

6-Bromo-1,4-dioxaspiro[4,5]dec-6-ene (66).[38]



A mixture of 2-bromo-2-cyclohexen-1-one **65** (6.56 g, 37.5 mmol), ethylene glycol (6.97 mL, 113 mmol), *p*-toluenesulfonic acid (66 mg) and benzene (230 mL) was refluxed in a 500 mL round-bottomed flask with azeotropic removal of water for 43 h. The mixture was cooled to room temperature and K_2CO_3 (4.0 g) was added. Filtration of the mixture through a cake of silica and $MgSO_4$ (1 : 1 mixture) with the aid of CH_2Cl_2, removal of the solvent under reduced pressure and column chromatography (20% ethyl acetate/hexane) gave **66** as a light yellow oil (7.00 g, 32.1 mmol, 85%).

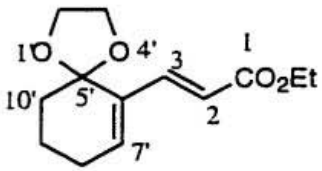
6-Formyl-1,4-dioxaspiro[4,5]dec-6-ene (67).[39]



A solution of 6-bromo-1, 4-dioxaspiro[4, 5]dec-6-ene **66** (3.29 g, 15.0 mmol), in anhydrous THF (45 mL) was cooled to -78 °C (Dry Ice/acetone) in a 100 mL round-bottomed flask. To the flask was added BuLi (2.5 M solution in hexane, 6.3 mL, 16 mmol) dropwise over 25 minutes. The mixture was stirred for another 1 h at -78 °C and then DMF (4.1 mL, 53 mmol) was introduced over 10 minutes. The resultant mixture was stirred for another 5 h at the same temperature. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution (40 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2x40 mL). The combined organic layers were then dried over $MgSO_4$. Filtration and evaporation of solvent under reduced pressure afforded the crude product as a yellow oil. Column chromatography (30% ethyl acetate/hexane) gave **67** as a light yellow oil (2.15 g, 12.8 mmol, 85%): ^{1}H NMR δ 9.46 (s, 1H, -CHO), 7.00 (t, 1H, J = 3.8 Hz, C7-H), 4.26-4.00 (AA'BB' system, 4H, C2-H + C3-H), 2.37-2.34 (m, 2H, C8-H), 1.82-1.80 (m, 4H, C9-H + C10-H); ^{13}C NMR δ 191.4

(1, CHO), 153.4 (1, C7), 140.0 (0, C6), 105.1(0, C5), 65.8 (2, C2+C3), 34.5 (2, C10), 26.3 (2, C8), 20.0 (2, C9); IR (film) υ 2940 (s), 1698 (s), 1631 (s), 952 (s) cm^{-1}; MS *m/z* (%) 168 (M^+, 8), 140 (100), 99 (52), 55 (44); Anal. calcd for $C_9H_{12}O_3$: C, 64.31; H, 7.19. found: C, 64.44; H, 7.20.

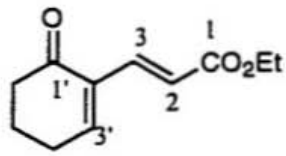
Ethyl (2*E*)-3-(1',4'-dioxaspiro[4',5']dec-6'-en-6'-yl)-2-propenoate (68)



To a 0°C slurry of 60% sodium hydride (0.629 g, 15.7 mmol) in anhydrous THF (20 mL) was added dropwise a solution of ethyl diethylphosphonoacetate[4] (3.55 g, 15.8 mmol) in THF (5 mL). The resulting clear yellow solution was stirred for additional 45 min at 0 °C, and then a solution of aldehyde **67** (2.07 g, 15.8 mmol) in dry THF (5 mL) was added dropwise over 15 min. The reaction mixture was stirred at 0 °C for 15 min and heated at reflux for another 1 h. After cooling, saturated aqueous NH_4Cl solution (20 mL) and CH_2Cl_2 (50 mL) were added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3x30 mL). The organic layer and the extracts were combined, washed with brine (3x20 mL) and dried over $MgSO_4$. Evaporation of solvent gave the crude product as a pale orange oil. Diene **68** was obtained as a light yellow oil (2.639 g, 11.07 mmol, 90%) after purification of the crude product by column chromatography (30% ethyl acetate/hexane): ^1H NMR δ 7.28 (dd, 1H, J = 16.0, 0.7 Hz), 6.46 (t, 1H, J = 4.1 Hz), 6.06 (d, 1H, J = 16.0 Hz), 4.20 (q, 2H, J = 7.2 Hz), 4.15-4.03 (AA'BB' system, 4H, C2'-H + C3'-H), 2.24-2.19 (m, 2H), 1.82-1.74 (m, 2H), 1.29 (t, 3H, J = 7.1 Hz); ^{13}C NMR 167.1 (0), 142.1 (1), 138.4 (1), 134.9 (0), 118.4 (1), 106.5 (0), 64.7 (2, 2C), 60.2 (2), 33.2 (2), 26.0 (2), 20.0 (2), 14.3 (3); IR (film) υ 2945 (s), 1711 (s), 1631 (s) cm^{-1}; MS

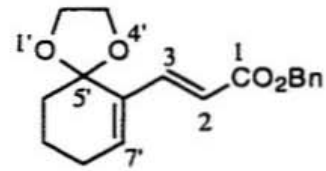
m/z 238 (M^+, 4), 193 (8), 137 (24), 99 (100), 55 (15); HRMS calcd for $C_{13}H_{18}O_4$ 238.1204, found 238.1216.

Ethyl (2*E*)-3-(1'-oxo-2'-cyclohexen-2'-yl)-2-propenoate (69).



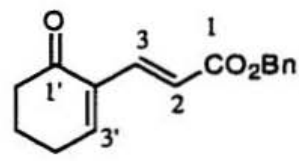
A mixture of **68** (1.20 g, 5.00 mmol), 15% aqueous oxalic acid solution (10 mL) and THF (20 mL) was heated at reflux for 1 h. The reaction mixture was cooled and CH_2Cl_2 (100 mL) was added. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (2x40 mL). The organic layer and the extracts were combined, washed with water (2x30 mL) and dried over $MgSO_4$. Evaporation of the solvent provided the crude product as a yellow oil. Purification of the crude product by flash chromatography (30% ethyl acetate/hexane) gave **69** (0.87 g, 4.4 mmol, 90%) as a light yellow oil: ^1H NMR δ 7.34 (dd, 1H, J = 16.1, 0.7 Hz, C3-H), 7.23 (t, 1H, J = 4.3 Hz, C3'-H), 6.63 (d, 1H, J = 16.1 Hz, C2H), 4.24 (q, 2H, J = 7.1 Hz), 2.57-2.49 (m, 4H, C4'-H + C6'-H), 2.08-2.02 (m, 2H, C5'-H), 1.30 (t, 3H J = 7.2 Hz); ^{13}C NMR δ 197.4 (0, C1'), 167.2 (0,C1), 152.4 (1, C3'), 139.1(1, C3), 134.2 (0, C2'), 120.9 (1, C2), 60.4 (2, OCH_2CH_3), 38.8 (2, C6'), 26.8 (2, C4'), 22.2 (2, C5'), 14.2 (3, CH_3); IR (film) υ 2940 (m), 1712 (s), 1682 (s), 1632 (s) 1174 (s), 1036 (m) cm^{-1}; MS *m/z* 194 (M^+, 43), 149 (36), 138 (36), 120 (100), 109 (29), 99 (20), 91 (19), 77 (19), 55 (27); HRMS calcd for $C_{11}H_{14}O_3$ 194.0942, found 194.0947.

Benzyl (2*E*)-3-(1',4'-dioxaspiro[4',5']dec-6'-en-6'-yl)-2-propenoate (70)



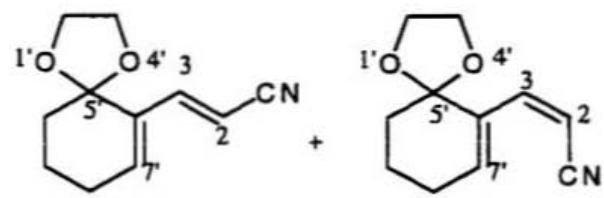
To a 0 °C solution of 60% sodium hydride (0.702 g, 17.5 mmol) in THF (20 mL) was added dropwise a solution of benzyl diethylphosphonoacetate (5.13 g, 17.7 mmol) in THF (10 mL) over 20 min. The resulting mixture was stirred at 0 °C for 1 h and a clear yellow solution was obtained. A solution of the aldehyde **67** (2.51 g, 14.9 mmol) in THF (10 mL) was added into the flask over 5 min. The reaction mixture was stirred for another 2 h at room temperature and was quenched by the addition of saturated NH_4Cl solution (30 mL). The organic layer was separated and the aqueous layer was extracted with ether (2x30 mL). The organic layer and the extracts were combined and washed with brine (3x50 mL) and dried over $MgSO_4$. Chromatography (2-5% Et_2O/CH_2Cl_2) gave **70** (3.59 g, 12.0 mmol, 80%) as a yellow liquid: ^1H NMR δ 7.37-7.27 (m, 6H), 6.46 (t, 1H, J = 4.0 Hz, C7'-H), 6.11 (d, 1H, J = 6.0 Hz, C2-H), 5.19 (s, 2H, -C**H**$_2$OBn), 4.12-3.98 (m, 4H, AA'BB' system, C2'-H + C3'-H), 2.23-2.18 (m, 2H, C9'-H), 1.80-1.68 (m, 4H, C8'-H + C10'-H); ^{13}C NMR δ 166.9 (0, **C**O$_2$-), 142.7 (1, C3), 138.8 (1, C7'), 136.2(0), 134.8 (0), 128.4 (1), 128.1 (1), 117.9 (1, C2), 66.0 (2), 64.7 (2, C2' + C3'), 33.1 (2, C8'), 26.0 (0, C6'), 19.9 (1, C7'); IR (film) υ 2946 (m), 2886 (m), 1712 (s), 1630 (s), 1163 (s) cm^{-1}; *m/z* (%) 300 (M$^+$, 2), 209 (40), 99 (100), 91 (62), 65 (10), 55 (10); Anal. calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. found: C, 71.91; H, 6.69.

Benzyl (2*E*)-3-(1'-oxo-2'-cyclohexen-2'-yl)-2-propenoate (71)



A solution of diene **70** (2.96 g, 9.87 mmol), 15% oxalic acid (20 mL) and THF (20 mL) was heated at reflux for 6 h under nitrogen. The reaction mixture was cooled and ether (200 mL) was added. The organic layer was separated and washed with H_2O (2x50 mL), saturated $NaHCO_3$ solution (50 mL) and brine (2x50 mL) and dried over $MgSO_4$. Removal of the solvent and purification of the residue by chromatography (30% ethyl acetate/hexane) afforded **71** (1.43 g, 5.58 mmol, 56%) as a pale yellow oil: ^1H NMR δ 7.40-7.30 (m, 6H, ArH + C3-H), 7.22 (t, 1H, J = 4.3 Hz, C3'-H), 6.70 (d, 1H, J = 16.0 Hz, C2-H), 5.20 (s, 2H, OCH_2Ph), 2.54-2.47 (m, 4H, C4'-H + C6'-H), 2.04-1.99 (m, 2H, C5'-H); ^{13}C NMR δ 197.3 (0, -CO-), 166.9 (0, $-CO_2-$), 152.9 (1), 139.7 (1), 136.0 (0), 134.0 (0), 128.1 (1), 128.4 (1), 120.5 (1), 66.1 (2, OCH_2Ph), 38.7 (2), 26.7 (2), 22.1 (2); IR (film) υ 2949 (m), 1714 (s), 1682 (s), 1630 (s), 1292 (s), 1162 (s) cm^{-1}; MS *m/z* (%) 256 (2, M^+), 150 (16), 121 (19), 91 (100), 65 (12); Anal. calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. found: C, 74.89; 6.34.

(2*E*) and (2*Z*)-3-(1',4'-Dioxaspiro[4',5']dec-6'-en-6'-yl)-2-propenonitrile (72a and 72b).

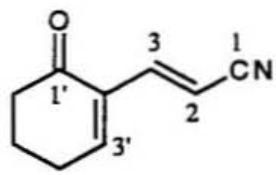


72a **72b**

An oven-dried 100 mL round-bottomed flask was charged with 60% sodium hydride (320 mg, 7.55 mmol) and THF (20 mL). The solution was cooled to 0 °C and a solution of diethyl phosphonoacetonitrile (1.36 g, 7.61 mmol), prepared by the reaction of $BrCH_2CN$ and $(EtO)_3P$) in THF (10 mL) was introduced dropwise over 15 min. The resulting mixture was stirred at 0 °C for an additional 1 h, and a solution of aldehyde **67** (1.02 g, 6.05 mmol) was added over 10 min. The ice-bath was removed after 30 min, and the

reaction mixture was stirred at room temperature for another 1.5 h. The reaction was quenched by the addition of saturated NH_4Cl solution (20 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2x20 mL). The organic layer and the extracts were combined, washed with water (3x20 mL) and dried over $MgSO_4$. Removal of the solvent afforded the crude product as a brown oil. Purification by flash chromatography (25% ethyl acetate/hexane) gave **72a** and **72b** (0.94g, 4.9 mmol, 81%) as light yellow liquid. ^1H NMR analysis of the product indicated that **72a** and **72b** were in a ratio of 87:13, respectively. ^1H NMR **72a:** δ 6.95 (dd, 1H, J = 16.8, 0.8 Hz), 6.42 (t, 1H, J = 1.5 Hz), 5.54 (d, 1H, J = 16.8 Hz), 4.01 (s, 4H), 2.28-2.21 (m, 2H), 1.82-1.71 (m, 4H); **72b:** δ 6.94 (dt, 1H, J = 4.1, 0.7 Hz), 6.80 (dd, 1H, J = 12.0, 1.1 Hz), 5.30 (d, 1H, J = 12.0 Hz), 4.07(s, 4H), 2.30-2.23 (m, 2H), 1.82-1.76 (m, 4H); ^{13}C NMR **72a:** δ 148.3, 139.7, 138.0, 118.5, 106.2, 96.6, 64.6, 32.8, 26.3, 19.7; **72b:** δ 146.0, 138.0, 133.8, 117.2, 106.2, 95.7, 64.9, 32.7, 26.0, 25.6, 19.9; IR (CCl_4) (**72a** + **72b**) υ 2948 (m), 2890 (m), 2215 (s), 1626 (s), 946 (s); MS *m/z* (**72a** + **72b**) 191 (M^+, 1), 119 (16), 99 (100), 91 (22), 55 (28); HRMS calcd for $C_{11}H_{13}NO_2$ (**72a** + **72b**) 191.0946, found 191.0933.

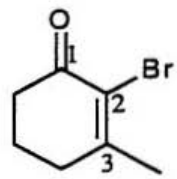
(2*E*)-3-(1'-Oxo-2'-cyclohexen-2'-yl)-2-propenonitrile (73).



According to the procedure employed for the preparation of diene **69**, diene **73** was synthesized from the mixture of **72a** and **72b** (0.628 g, 3.28 mmol), 15% aqueous oxalic acid (15 mL) and THF (15 mL). In this case, a few crystals of hydroquinone were added to the reaction mixture during reflux. Flash chromatography (30% ethyl acetate/hexane) of the crude product produced **73** (0.367 g, 2.49 mmol, 76%) as a light yellow solid: mp

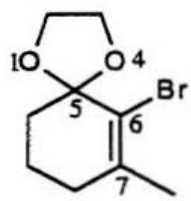
64-66 °C; ^{1}H NMR δ 7.19 (t, 1H, J = 4.4 Hz, C3'-H), 6.94 (d, 1H, J = 16.7 Hz, C3-H), 6.41 (d, 1H, J = 16.7 Hz, C2-H), 2.60-2.50 (m, 4H, C4'-H + C6'-H), 2.09-2.00 (m, 2H, C5'-H); ^{13}C NMR δ 197.3 (0, C1'), 154.8 (1, C3'), 145.6 (1, C3), 133.0 (0, C2'), 118.3 (0, C1), 100.2 (2, C2), 38.8 (2, C6'), 26.8 (2, C4'), 22.0 (2, C5'); IR (CCl_4) υ 2928 (s), 2855 (m), 2219 (m), 1692 (s), 1550 (vs) cm^{-1}; MS *m/z* 147 (100, M$^+$), 119 (70), 106 (72), 91 (81), 78 (48), 64 (30), 55 (97); HRMS calcd for C_9H_9NO 147.0684, found 147.0670.

2-Bromo-3-methyl-2-cyclohexen-1-one (75)



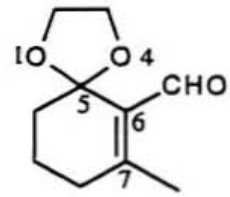
Bromocyclohexenone **75** was synthesized from 3-methyl-2-cyclohexen-1-one **74**[6](3.00 g, 27.2 mmol), bromine (1.5 mL, 28 mmol) and triethylamine (4.13 g, 4.08 mmol) using the same procedure described above for **64**. Purification by flash column chromatography (20% hexane/dichloromethane) gave **75** as an light yellow oil (2.87 g, 15.3 mmol, 56%) : ^{1}H NMR δ 2.59 (t, 2H, J = 6.3 Hz), 2.52 (t, 2H, J = 6.0 Hz), 2.18 (s, 3H), 2.05-1.97 (m, 2H); ^{13}C NMR δ 190.9 (0), 160.3 (0), 122.7 (0), 37.6 (2), 34.1 (2), 25.9 (2), 21.8 (3); MS *m/z* 190 (M$^+$, 55), 188 (M$^+$, 57), 162 (71), 160 (72), 82 (54), 53 (100); HRMS calcd for $C_7H_9{}^{79}BrO$ 187.9837, found 187.9831.

6-Bromo-7-methyl-1,4-dioxaspiro[4,5]dec-6-ene (76)



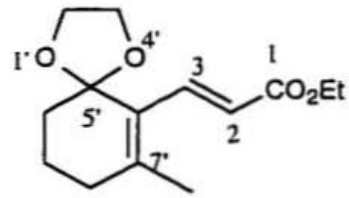
According to the procedure described for **66**, compound **76** was prepared from **75** (7.44 g, 39.4 mmol), ethylene glycol (7.33 g, 118 mmol), *p*- toluenesulfonic acid (90 mg) and benzene (120 mL). Chromatography (10% ethyl acetate/hexane) afforded **76** (6.37 g, 70%) as colorless crystals: mp 55-57 °C; ^{1}H NMR δ 4.23-3.96 (m, 4H, AA'BB' system), 2.15 (t, 2H, J = 6.0 Hz, C8-H), 1.92-1.90 (m, 2H, C10-H), 1.88 (s, 3H, -C**H**$_3$), 1.87-1.74 (m, 2H, C9-H); ^{13}C NMR δ141.2 (0, C7), 121.6 (0, C6), 106.7 (0, C5), 65.7 (2, 2C), 35.4 (2), 33.2 (2), 23.9 (3), 20.2 (2); IR (CCl_4) υ 2952 (m), 1549 (s), 1250 (s) cm^{-1}; MS *m/z* 234 (M^+, 17), 232 (M^+, 14), 206 (73), 204 9740, 153 (75), 125 (34), 99 (100), 55 (48), 53 (55); HRMS calcd for $C_9H_{13}{}^{79}BrO_2$ 232.0099, found 232.0109.

6-Formyl-7-methyl-1,4-dioxaspiro[4,5]dec-6-ene (77)



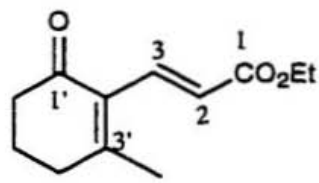
According to the procedure described for **67**, compound **77** was prepared from **76** (2.34 g, 10.1 mmol), butyllithium (7.5 mL, 12 mmol), DMF (2.61 g, 35.6 mmol) and THF (30 mL). Work-up and chromatography (30% ethyl acetate/hexane) gave **77** (1.08 g, 5.93 mmol, 59%) as a colorless oil: ^{1}H NMR δ 9.88 (s, 1H, -C**H**O), 4.19-4.02 (AA'BB' system, 4H, C2-H + C3-H), 2.24 (t, 2H, J = 5.3 Hz, C8-H), 2.16 (s, 3H, -C**H**$_3$), 1.79-1.72 (m, 4H); ^{13}C NMR δ 192.0 (1, -**C**HO), 158.2 (0, C7), 131.8 (0, C6), 107.0 (0, C5), 65.2 (2, 2C), 34.3 (2), 33.5 (2), 20.7 (3), 19.7 (2); IR (CCl_4) υ 2950 (m), 2880 (m), 1550 (vs), 1253 (s) cm^{-1}; MS *m/z* 182 (M^+, 4), 126 (51), 111 (100), 99 (32), 82 (54), 79 (36), 67 (28), 55 (45), 53 (41); HRMS calcd for $C_{10}H_{14}O_3$ 182.0942, found 182.0930.

Ethyl (2*E*)-3-(7'-methyl-1',4'-dioxaspiro[4',5']dec-6'-en-6'-yl)-2-propenoate (78).



According to the procedure described for **5**, diene **78** was synthesized from aldehyde **77** (0.92 g, 5.1 mmol), ethyl diethylphosphonoacetate (2.89 g, 12.9 mmol) and 60% sodium hydride (0.301g, 12.6 mmol). Purification of the crude product by column chromatography (20% ethyl acetate/hexane) provided **78** as a colorless liquid (1.20 g, 4.76 mmol, 94%): ^{1}H NMR δ 7.45 (d, 1H, J = 16.2 Hz, C3-H), 5.97 (d, 1H, J = 16.2 Hz, C2-H), 4.21 (q, 2H, J = 7.1 Hz, -OC**H**$_2$CH$_3$), 4.11-3.99 (AA'BB' system, 4H, C2'-H + C3'-H), 2.17 (t, 2H, J = 5.7 Hz, C8'-H), 1.90 (s, 3H, -C**H**$_3$), 1.80-1.69 (m, 4H), 1.29 (t, 3H, J = 7.1 Hz, -OCH$_2$C**H**$_3$); ^{13}C NMR δ 167.4 (0, C1), 146.5 (0, C7'), 140.0 (1, C3), 128.6 (0, C6'), 121.1 (1, C2), 107.7 (0, C5'), 64.5 (2, O**C**H$_2$CH$_3$), 60.1 (2, C2'+C3'), 33.3 (2, 2C), 21.3 (3) , 19.7 (2), 14.3 (3, -OCH$_2$C**H**$_3$); IR (CCl_4) υ 2949 (s), 1716 (s), 1551 (vs) cm^{-1}, MS *m/z* 252 (M^+, 2), 207 (5), 151 (18), 99 (100), 55 (14); HRMS calcd for $C_{14}H_{20}O_4$ 252.1360, found 252.1364.

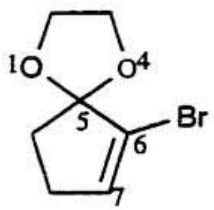
Ethyl (2*E*)-3-(3'-methyl-1'-oxo-2'-cyclohexen-2'-yl)-2-propenoate (79).



According to the procedure described for **69**, diene **79** was synthesized from **78** (1.01 g, 4.02 mmol) and oxalic acid (2.05 g, 32.0 mmol). The resulting **79** was obtained as a viscous oil (0.77 g, 3.7 mmol, 92%): ^{1}H NMR δ 7.49 (d, 1H, J = 6.1 Hz, C3-H), 6.61 (d, 1H, J = 6.1 Hz, C2-H), 4.22 (q, 2H, J = 7.1 Hz, -OC**H**$_2$CH$_3$), 2.53-2.45 (m, 4H, C4'-H +

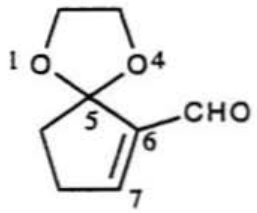
C6'-H), 2.14 (s, 3H, -CH_3), 2.03-1.94 (m, 2H, C5'-H), 1.30 (t, 3H, J = 7.1 Hz, -OCH_2CH_3); ^{13}C NMR δ 197.3 (0, C1'), 167.6 (0, C1), 163.0 (0, C3'), 136.5 (1, C3), 130.4 (0, C2'), 123.3 (1, C2), 60.3 (2, -OCH_2CH_3), 38.5 (2, C6'), 34.1 (2, C4'), 22.2 (3, -CH_3), 21.5 (2, C5'), 14.3 (3, OCH_2CH_3); IR (CCl_4) υ 2939 (m), 1713 (s), 1683 (s), 1551 (vs) cm^{-1}; MS *m/z* (%) 208 (M^+, 8), 163 (21), 135 (100), 91 (12), 79 (12), 55 (13); HRMS calcd for $C_{12}H_{16}O_3$ 208.1096, found 208.1094.

6-Bromo-1,4-dioxaspiro[4,4]non-6-ene (81).[44]



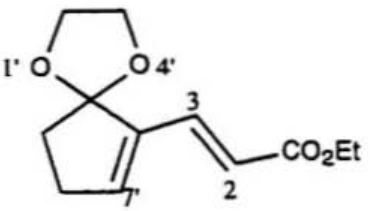
To a 0°C solution of cyclopentenone (4.16 g, 49.4 mmol) in CCl_4 was dropped bromine (2.6 mL, 52 mmol) in CCl_4 over 15 min. After 5 min, a solution of triethylamine (10.6 mL, 75.9 mmol) in CCl_4 (10 mL) was introduced slowly over 40 min, while keeping the internal temperature below 0°C (salt-ice bath). Removal of the solvent gave the crude 2-bromo-2-cyclopenten-1-one (5.89 g, 36.6 mmol) as yellow crystals. A solution of the crude 2-bromo-2-cyclopenten-1-one, ethylene glycol (6.2 mL, 111 mmol) benzene (350 mL) and *p*-TsOH (0.521 g, 13.0 mmol) was heated at reflux for 48 h. The solvent was removed and the residue was purified by column chromatography (16% ethyl acetate/hexane) to provide **81** (5.75 g, 29.8 mmol, 61% overall yield based on 2-cyclopenten-1-one) as a light yellow oil. ^{1}H NMR δ 6.18 (t, 1H, J = 2.6 Hz), 4.22-3.97 (AA'BB'system, 4H), 2.40-2.35 (m, 2H), 2.19-2.15 (m, 2H); ^{13}C NMR δ 136.6, 123.8, 117.5, 65.8 (2C), 34.3, 28.6.

6-Formyl-1,4-dioxaspiro[4,4]non-6-ene (82).



According to the procedure described for **67**, aldehyde **82** was prepared from **81** (1.01 g, 5.20 mmol), butyllithium (2.5 M in hexane, 2.1 mL, 5.2 mmol), DMF (1.4 mL, 5.2 mmol) and THF (20 mL). Removal of the solvent and flash chromatography (20% ethyl acetate/hexane) provided **82** (0.260 g, 1.69 mmol, 32%) as a yellow oil: ^{1}H NMR δ 9.75 (s, 1H, -C**H**O), 7.10 (t, 1H, J = 2.7 Hz, C7-H), 4.24-3.94 (AA'BB' system, 4H, C2-H + C3-H), 2.60-2.55 (m, 2H), 2.25(t, 2H, J = 6.5 Hz); ^{13}C NMR δ 188.1 (1, **C**HO), 156.7 (1), 145.5 (0), 117.1 (0), 66.1 (2, 2C), 37.1 (2), 28.7 (2); IR (CCl_4) υ 2978 (m), 2902 (m), 1697 (s), 1550 (s) cm^{-1}; MS *m/z* (%) 154 (73, M+), 125 (100), 99 (42), 82 (59), 55 (44); HRMS calcd for $C_8H_{10}O_3$ 154.0630, found 154.0634.

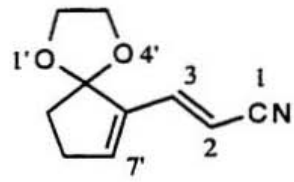
Ethyl 3-(1',4'-dioxaspiro[4',4']non-6'-en-6'-yl)-2-propenoate (83).



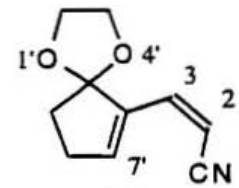
According to the procedure described for **68**, diene **83** was prepared from **82** (0.562 g, 3.63 mmol), 60% sodium hydride (0.188 g, 4.70 mmol) and ethyl diethylphosphonoacetate (1.07 g, 4.77 mmol) in THF (40 mL). Chromatography of the crude product (30% ethyl acetate/hexane) afforded **83** (0.638 g, 2.71 mmol, 78%) as a colorless liquid: ^{1}H NMR δ 7.28 (d, 1H, J = 16.3 Hz, C3-H), 6.48 (t, 1H, J = 2.8 Hz, C7'-H), 6.14 (d, 1H, J = 16.3 Hz, C2-H), 4.20 (q, 2H, J = 7.1 Hz), 4.14-3.98 (AA'BB' system,

4H, C2'-H + C3'-H), 2.50-2.45 (m, 2H), 2.11 (t, 2H, J = 6.4 Hz), 1.29 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ 167.0 (0, -CO_2-) 143.3 (1), 138.6 (0), 136.4 (1), 119.4 (1), 118.6 (0), 64.6 (2, 2C), 60.1 (2), 35.9 (2), 28.5 (2), 14.2 (3); MS *m/z* (%) 224 (21, M^+), 151 (100), 138 (63), 110 (42), 79 (27).

(2*E*) and (2*Z*)- 3-(1',4'-dioxaspiro[4',4']non-6'-en-6'-yl)-2-propenonitrile (85a and 85b).



85a



85b

According to the procedure described for **68**, diene **85a** was synthesized from **82** (0.355 g, 2.30 mmol), diethyl phosphono-acetonitrile (0.717 g, 3.20 mmol) and sodium hydride (60%, 0.128 g, 3.20 mmol) in THF (10 mL). Purification of the crude product by flash chromatography (25% ethyl acetate/hexane) provided a mixture of **85a** and **85b** (86 : 14 ratio, respectively) as a light yellow oil (0.285 g, 70%). ^{1}H NMR **85a:** δ 6.99 (d, 1H, J = 16.9 Hz, C3-H), 6.49 (t, 1H, J = 2.80 Hz, C7'-H), 5.66 (dd, 1H, J = 16.7, 0.6 Hz, C2-H), 4.07-4.01 (AA'BB' system, 4H, C2'-H + C3'-H), 2.52-2.47 (m, 2H), 2.10 (t, 2H, J = 6.4 Hz); **85b**: δ 7.16 (t, 1H, J = 2.4 Hz), 6.69 (dd, 1H, J = 12.0, 1.0 Hz), 5.38 (d, 1H, J = 12.0 Hz).

Chapter 3. Normal Diels-Alder Reaction of the Protected Dienes

3.1. Results and Discussion

The protected dienes described in the previous chapter were found to react with a series of electron deficient dienophiles whereas the deprotected dienes underwent cycloaddition with electron rich dienophiles (see Chapter 4). The results of the cycloadditions of the protected dienes with tetracyanoethylene (TCNE), dimethyl acetylenedicarboxylate (DMAD), 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD)[51], *N*-phenylmaleimide (NPM), maleic anhydride (MA), 1, 4-naphthoquinone (NQ), and 1,4-benzoquinone (BQ) will be presented in this chapter.

Diene **68** reacted with tetracyanoethylene (Scheme 29) in refluxing dichloromethane. Removal of the solvent under reduced pressure provided the crude product as a brown solid. The ^{1}H NMR spectrum of the crude product indicated that the starting materials had been completely consumed and that a single adduct had been generated. The crude yield was near quantitative. A signal at δ 6.18 (t, 1H, J = 2.1 Hz) in the ^{1}H NMR spectrum was assigned as the olefinic proton. The position of this resonance was consistent with a unconjugated double bond, which would result from cycloaddition. This, in combination with its other spectroscopic properties, led to its assignment to structure **94**. Recrystallization of the crude product from EtOAc/hexanes afforded **94** in 65% yield. It was noticed that the TLC of the crude product displayed two close spots, which suggested that the product underwent further reaction upon chromatography. In fact, purification of the crude product using column chromatography resulted a 87:13 mixture of the initially formed adduct and a second isomer, which gave an olefinic signal at δ 5.92 (d, 1H, J = 2.5 Hz). It was initially thought that the new

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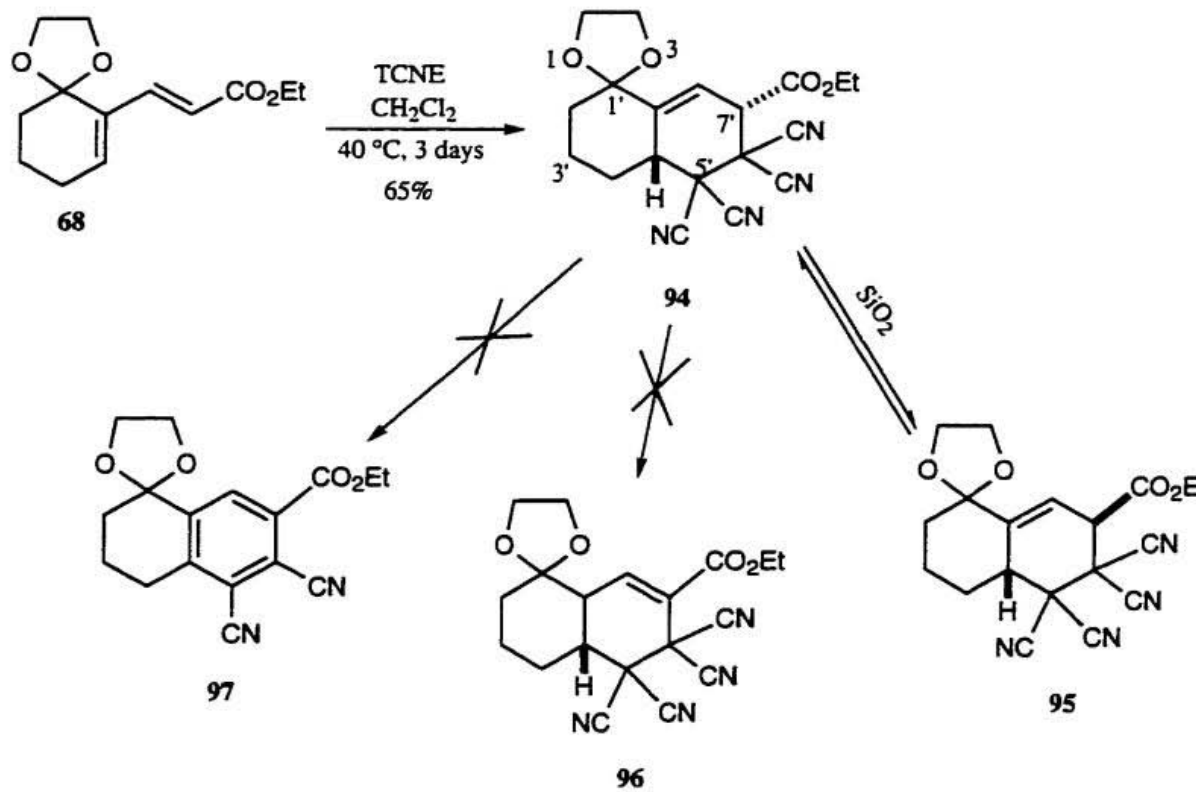
[51] (a) Cookson, R. C.; Gupte, S. S.; Stevens, I. D. R.; Watts, C. T. *Org. Synth., Coll. Vol. VI*, **1988**, 936-940. (b) Teeter, H. M.; Bell, E. W. *Org. Synth., Coll. IV*, **1963**, 125-127.

product could had arisen either by migration of the double bond in **94** into conjugation with the ester group

Scheme 29



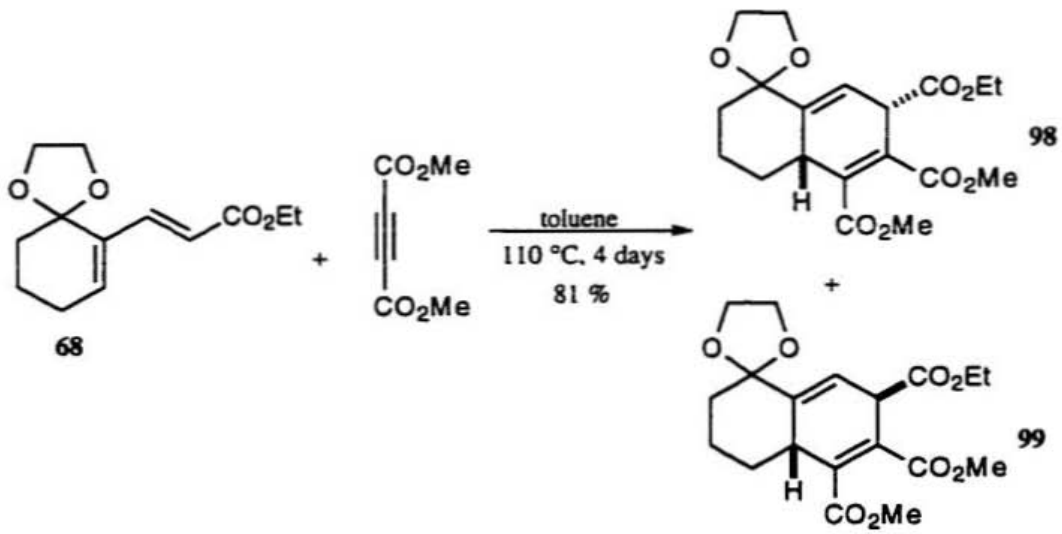
68 **94** **97** **96** **95**

to give **96** or epimerization of the ester group to give **95**. The chemical shift (δ 5.92) of the olefinic proton of the new isomer suggested that it was probably not **96**, and it was therefore assigned as the epimerized product **95**. Signals attributable to the aromatized product **97**, which would result from the elimination of 2 equivalents of HCN, were never observed. Performing this reaction in refluxing benzene or toluene also gave rise to some **94** along with at least two other minor products according to the ^1H NMR spectrum of the crude product, but the olefinic signal of **95** was not observed. Upon chromatography, a

mixture of **94** and **95** in the same ratio as before was isolated. None of the initially observed by-products were eluted and their exact structures remain unassigned.

Reaction of diene **68** with DMAD at 110 °C for 4 days followed by chromatography yielded two inseparable products in a ratio of 57 : 43 and in 81% total yield (Scheme 30). The adducts displayed olefinic proton signals at δ 5.85 (dd, J = 4.1, 1.0 Hz) and δ 5.92 (dd, J = 3.7, 1.8 Hz) in their ^{1}H NMR spectra. Since these chemical shifts were not consistent with aromatization or any double bond migration, one of the products was assigned as the cycloadduct **98**, and the other one as its epimer **99**. Unfortunately, we were unable to determine which was the major product by NMR techniques. That epimerization occurred much more easily than in the TCNE adduct **94** was reasonable because the proton α to the ethyl ester was now doubly allylic.

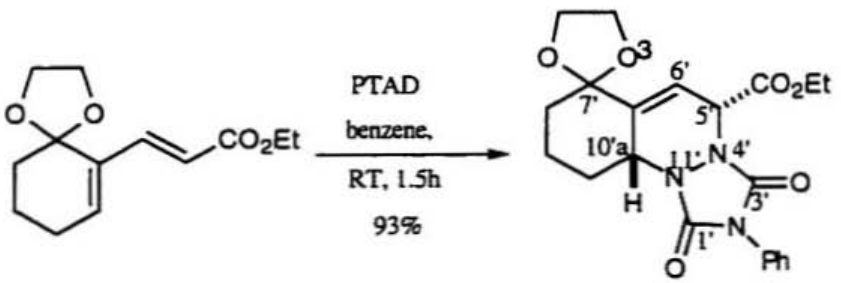
Scheme 30



Stirring diene **68** with PTAD (Scheme 31) at room temperature in benzene gave rise to a single product according to the ^{1}H NMR spectrum of the crude product.

Recrystallization of the crude mixture gave a single product **100**, the structure of which was unambiguously determined by X-ray crystallographic methods (Figure 4). This was the product of cycloaddition. Proton NMR spectroscopy indicated that epimerization of the adduct did not occur during chromatography.

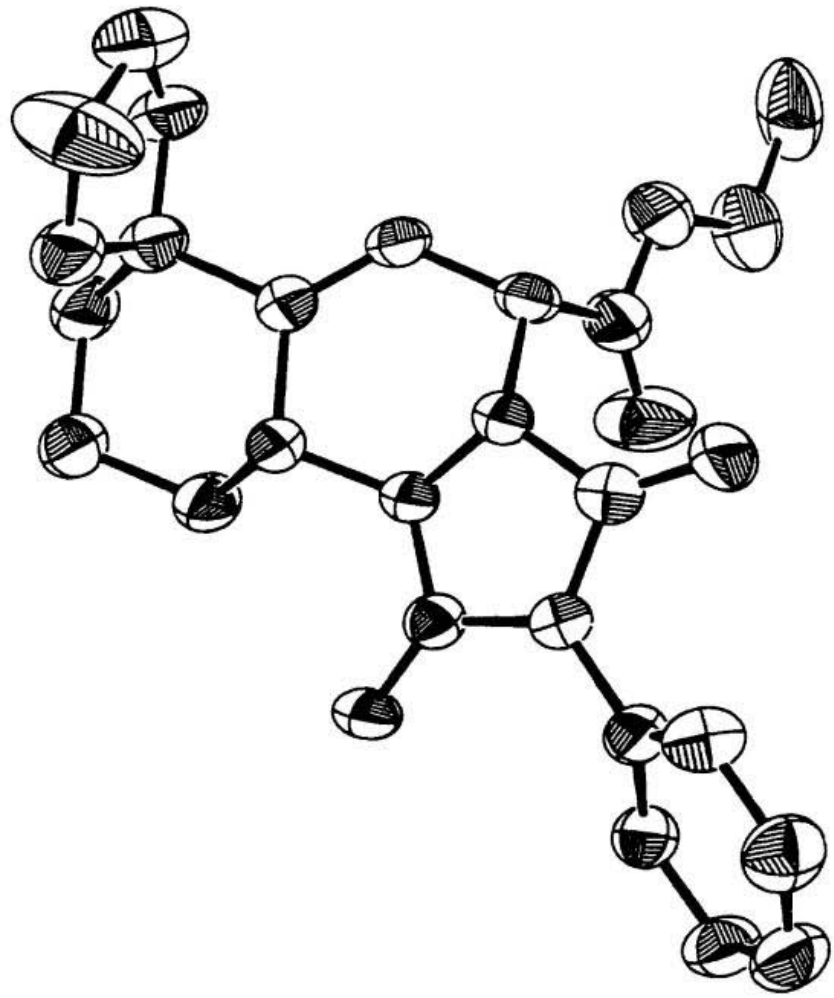
Scheme 31



68 **100**

Figure 4 **Two views (A and B) of X-ray crystal structure of 100***

(A)



(B)

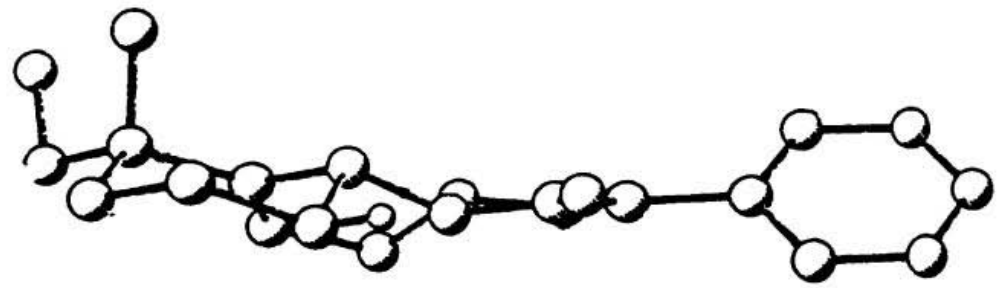
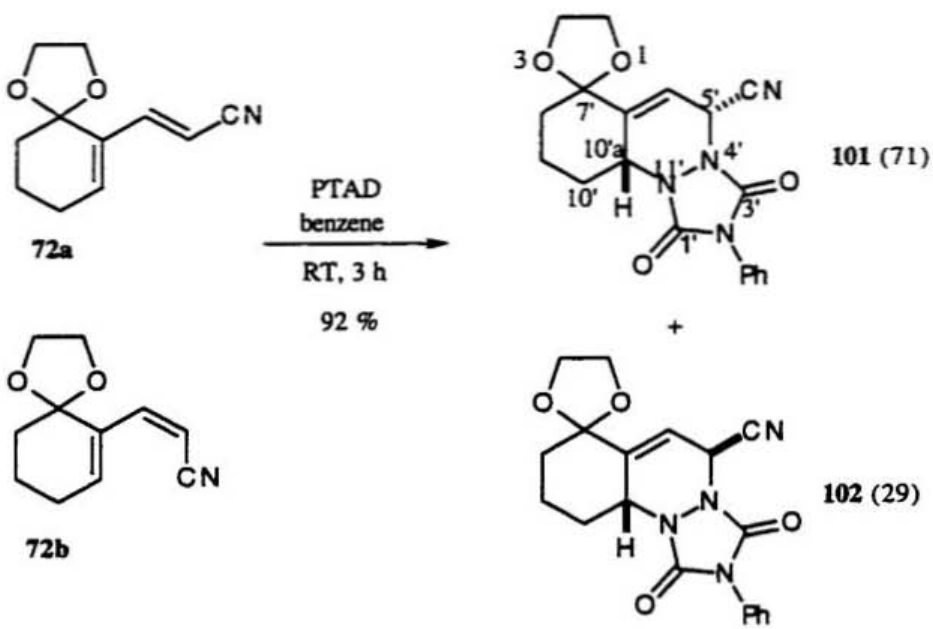


*Diagram B of the crystal structure of adduct **100** shows the co-planar arrangement of C10-Hb and the proximate C=O. Some atoms have been omitted for clarity.

Reaction of PTAD with an 83:17 mixture of **72a**:**72b** (Scheme 32) at room temperature resulted in complete consumption of the starting materials. Two chromatographically separable 1:1 adducts were formed, and these were isolated in 65% and 27% yields, respectively. This corresponded to a product ratio of 71:29 and a combined yield of 92%. Both products have been submitted for X-ray ccrystallographic structure determination.

As explained in the following paragraph, tentative assignments of the product structures had been made based on their ^{1}H NMR spectra. The major product was assigned structure **101**, the Diels-Alder adduct of the major diene **72a** and PTAD, and the minor product was assigned structure **102**. There were two possible pathways by which this latter compound could form: i) cycloaddition of the minor diene **72b** with PTAD and ii) epimerization of **101**. Since the isolated yield of **102** (27%) was greater than the theoretical ceiling of 17% for direct reaction of **72b** with PTAD, some **102** must have

Scheme 32



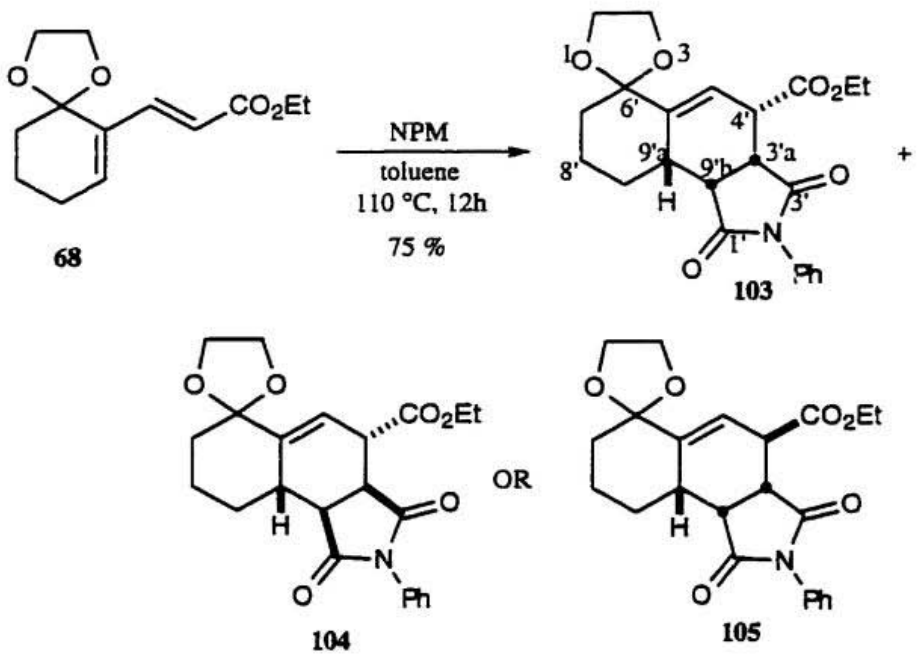
been generated by epimerization of **101**. In addition, the combined yield of the two adducts (92%) was greater than the percentage of **72a** in the starting diene mixture (83%), which means that some **102** must have come from direct cycloaddition of **72b**. Bearing in mind that the reaction rates of 72a and 72b towards the dienophiles are most likely different, the situation is most probably more complicated than the above treatment would suggest. Whatever the case, further experiments will be required to more fully understand this reaction. For a start, pure samples of 72a and 72b would be needed.

With the assistance of COSY and HET-CORR experiments, most of the signals in the ^{1}H NMR spectra of **100**, **101** and **102** were assigned. The very close similarity between the spectrum of **100**, the structure of which was unequivocally determined by X-ray methods, and that of **101** suggested that they were structurally alike. On the other hand, some marked chemical shift differences between the spectra of **100** and **102** pointed towards structural differences. Particularly diagnostic were the signals due to the equatorial C10'-Hß ("up" as drawn in Scheme 32). This proton was observed at δ 3.11 in **100** and at δ 3.04 in **101**, compared to δ 2.40 for **102**. The 0.64 ppm chemical shift difference between **101** and **102** was most likely due to the magnetic anisotropy of the proximal carbonyl group. The low field shifts observed for **100** and **101** were consistent with a (nearly) co-planar relationship between this carbonyl group and the equatorial C10'-Hß in solution. Examination of the crystal structure of **100** (see diagram B in Figure 4) revealed that this was indeed the case, at least in the solid state. Conformational changes in the bicyclic skeleton resulting from a change in configuration at C5', i.e., in **102**, could then result in movement of C10'-Hß out of the deshielding zone of the carbonyl group, thus accounting for the observed high field shift. As might be expected from this explanation, the chemical shift of C10'-Hα, which was more distant from the carbonyl group, was at similar field for all three compounds (δ(**100**) = 1.42, δ(**101**) = 1.56, δ(**102**) = 1.45). The bridgehead proton was also diagnostic. This was observed at δ

4.43 in **100**, δ 4.47 in **101** and δ 4.73 in **102**. Whether the low field shift observed for **102** was a result of the magnetic anisotropy of the neighboring carbonyl or a stereoelectronic effect was unclear at this time. The pending resultes of the X-ray crystal structure analysis of **102** may shed more light on this question.

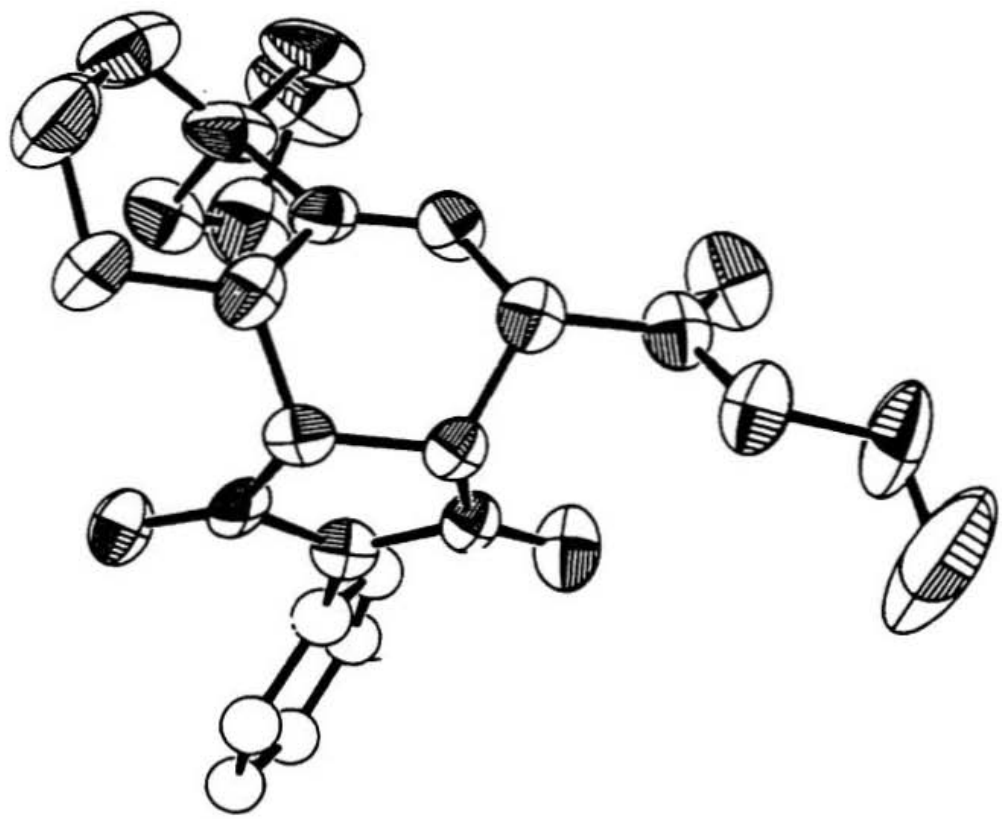
Reaction of diene **68** with 3 equivalents of *N*-phenylmaleimide (Scheme 33) in refluxing toluene for 6 h afforded two chromatographically separable products in a ratio of 94 : 6 and in 75 % total yield. The major product was isolated as a solid, and crystals suitable for X-ray crystal structure determination were obtained upon recrystallization from EtOAc/hexane. This analysis showed it to be the *endo* adduct **103** (Figure 5). The minor product was isolated as an oil. Its structure could not be definitely assigned on the basis of its ^{1}H and ^{13}C NMR spectra, but it was narrowed down to the *exo* adduct **104** or the epimerized product **105**. However, subjection of pure **103** to the original reaction

Scheme 33



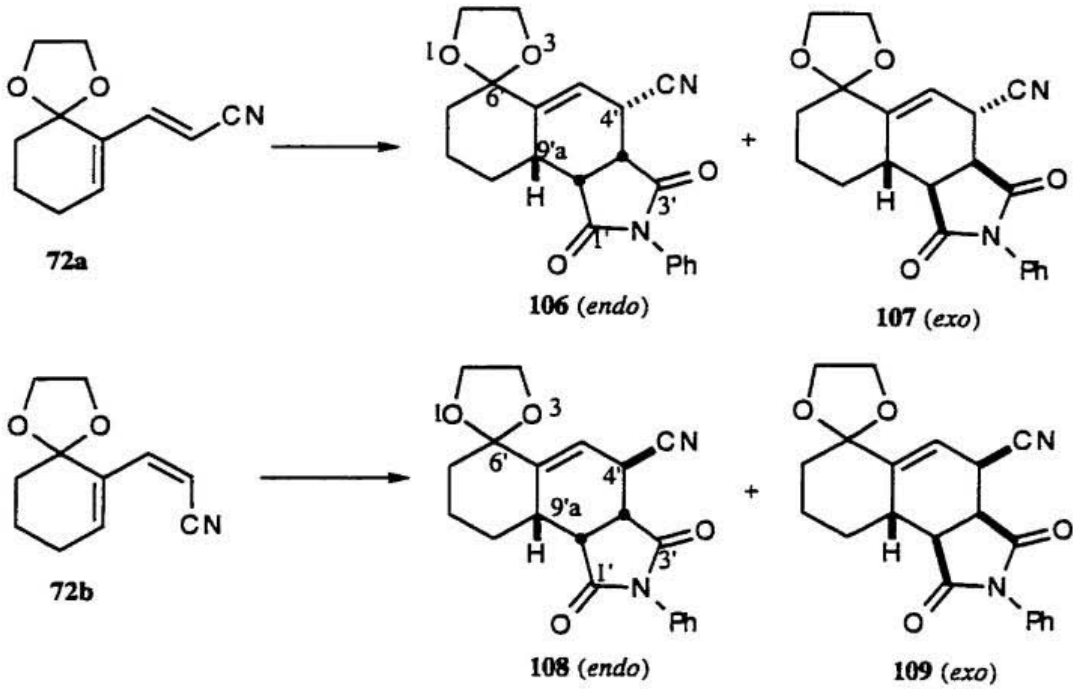
conditions for 4 days did not result in the formation of any of the minor product. This would suggest that the minor product was in fact the *exo* adduct **104**. Further evidence of this comes from comparison of the ^{1}H and ^{13}C NMR spectra of this compound to those of other adducts described later in this chapter, one of which, **114**, was shown to be an *exo* adduct by X-ray crystallography. A detailed discussion of this information appears in subsequent paragraphs. The reaction of **68** and NPM was repeated twice under the original conditions, but surprisingly, gave only **103** in 69-76% yield. No traces of the minor product were observed.

Figure 5 X-Ray crystal structure of 103



The reaction of NPM with diene mixture **72** proved to be more complicated due to the presence of two isomers (**72a**:**72b** = 83:17).[52] As shown in Scheme 34, there were four possible direct adducts: **106** (*endo* addition to **72a**), **107** (*exo* addition to **72a**), **108** (*endo* addition to **72b**) and **109** (*exo* addition to **72b**).

Scheme 34



After reaction of the addends in refluxing toluene, chromatographic separation of the crude mixture afforded a major product in 58% yield, a 1:1 mixture of two minor products in 28% combined yield and 3.6% of recovered **72b**. Diene **72a** was completely consumed. X-ray crystallographic analysis of the major product showed it to be adduct **106**. Worthy of note was that the ^{1}H and ^{13}C NMR spectra (see Tables 1 and 2) of **106**

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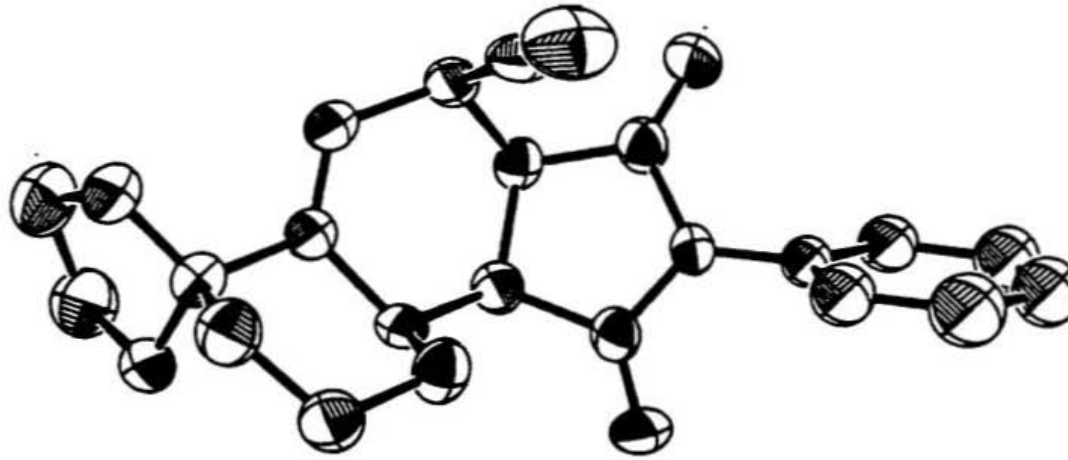
[52] The 83:17 ratio of **72a**:**72b** was determined by integration of ^{1}H nmr signals and is subject to an experimental error of ±5%.

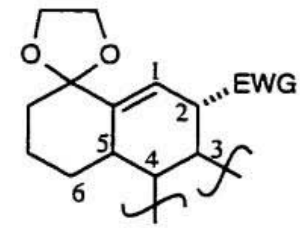
Figure 6 **X-ray crystal structure of 106**



closely resemble those of **103**. The ^{1}H NMR spectra of the two minor products were similar and several of their signals overlap. Nevertheless, there was a close correlation between the spectrum of the tentatively assigned *exo* adduct **104** (Scheme 33) and one of the minor compounds. Thus, one of the minor compounds was assigned as **107** by analogy. No concrete evidence to indicate whether the second minor product was **108** or **109** was forthcoming, but it seems intuitively more reasonable that it was the *endo* adduct **108**.

Assuming that these structural assignments were correct and that no epimerization occurred during the reaction or chromatography, the results indicate that **72a** reacted with NPM in 87% yield to give a 81:19 mixture of the *endo* and *exo* adducts **106** and **107**. Based on recovered starting material (3.6%), diene **72b** reacted with NPM in 97% yield to give only the *endo* adduct **108**. If epimerization was indeed a factor, then the situation becomes murkier. In addition, the individual yields of **72a** and **72b** were best viewed as reasonable approximations due to experimental error in determining their starting ratio by NMR spectroscopy.

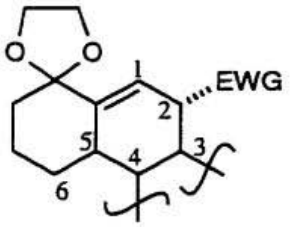
Table 1 **^{1}H NMR spectroscopic data of the adducts of protected dienes**[a,b,c]



Compound	H1	H2	H3	H4	H5	H6 β	H6 α
94[d]	6.08 (t, J = 2.1)[d]	4.11 (m)			3.35 (m)	2.32 (m)	1.68 (m)
95[d]	5.92 d, J = 2.5)						
98[d]	5.85 (dd, J = 4.1, 1.0)						
99[d]	5.92 (dd, J = 3.7, 1.8)						
100[d]	6.18 (dd, J = 5.6, 1.8)	5.11 (dd, J=5.6, 2.5)			4.43 (m)	3.11 (m)	1.45 (m)
101 (major)[d]	6.08 (dd, J = 5.2, 1.7)	5.28			4.47 (m)	3.03 (m)	1.52 (m)
102 (minor)[d]	6.03 (dd, J = 5.8, 1.8)	5.26 (d, J = 5.8)			4.73 (m)	2.39 (m)	1.39 (m)
103 (*endo*)[e]	6.32 (dd, J = 4.5, 2.0)	3.48	3.64 (dd, J = 9.4, 6.4)	3.40 (t, 9.4)	2.77 (m)	2.20 (m)	1.70 (m)
104 (*exo*)[d]	6.03 (dd, J = 6.4, 1.9)	3.67 (m)	3.67 (m)	3.01 (dd, J = 8.5, 5.5)	2.55 (m)	2.30 (m)	1.58 (m)
106 (*endo*)[e]	6.08 (dd, J = 5.0, 1.9)	3.74 (m)	3.42 (m)	3.42 (m)	2.85 (m)		
107 (*exo*)[d]	5.93 (t, J = 1.6)	4.16 (dd, J =5.0,1.6)	3.51 (m)	3.04 (dd, J = 8.6, 4.8)	2.64 (m)	2.29 (m)	1.29 (m)
108 (*epi-endo*)[d]	5.95 (t, J = 1.7)						
110 (*endo*)[e]	6.21 (m)	3.56 (m)	3.56 (m)	3.56 (m)	2.84 (m)	2.30 (m)	1.38 (m)
111 (*exo*)[d]	6.02 (dd, J = 5.5, 1.9)	3.7 (m)	3.70 (m)	3.07 (dd, J = 8.6, 6.2)	2.54 (m)	2.24 (m)	1.24 (m)
113 (*endo*)[e]	6.44 (s)	4.11 (m)	3.21 (m)	3.60 (dd, J = 7.6, 5.8)	2.90 (m)	1.08 (m)	0.68 (m)
114 (*exo*)[e]	6.06 dd, J = 5.4, 1.4)	4.06 (m)	3.88 (m)	3.15 (dd, J = 10.3, 5.1)	2.28 (m)	1.95 (m)	1.10 (m)

a. assignments were made with the aid of COSY, HET-CORR and APT experiments; b. chemical shift values refer to the center of multiplet; c. coupling constants are in Hz; d. proposed structure; e. structure determined by X-ray methods.

Table 2 **^{13}C NMR spectroscopic data of the adducts of the protected dienes**[a,b]



Compound	C1	C2	C3	C4	C5	C6
94[c]	111.8	46.6			42.8	30.0
100[c]	111.5	54.6			56.0	32.1
101 (major)[c]	109.4	42.7			56.7	31.7
102 (minor)[c]	108.7	43.5			54.3	29.1
103 (*endo*)[d]	117.1	61.4	64.6	64.1	35.5	26.0
104 (*exo*)[c]	114.2	38.0	39.7	43.0	35.2	35.4
106 (*endo*)[d]	113.5	26.0	41.5	40.3	34.9	
107 (*exo*)[c]	111.6 or 110.6	23.1	41.7 or 40.3	42.3 or 33.7	35.4	
108 (*epi-endo*)[c]	111.6 or 110.6	22.9	41.7 or 40.3	42.3 or 33.7		
110 (*endo*)[d]	114.9	39.3	41.2	41.0	33.5	27.9
111 (*exo*)[c]	113.8	37.8	40.7	43.2	34.4	34.7
113 (*endo*)[d]	115.4	47.3	39.6	51.1	37.0	31.4
114 (*exo*)[d]	116.2	38.7	47.3	51.8	35.2	36.2

a. assignments were made with the aid of COSY, HET-CORR and APT experiments; b. chemical shifts are in ppm; c. proposed structure; d. structure determined by X-ray methods.

Treatment of diene **68** with freshly sublimed maleic anhydride in refluxing toluene for 12 h resulted in two separable products (Scheme 35). The crude product ratio was estimated to be 63:35 by ^{1}H NMR spectrum, and the isolated product ratio was 70:30 after column chromatography. The combined isolated yield was 71%. The small

increase in the proportion of the major product may be due to a small amount of decomposition of the minor product during chromatography since performing the chromatographic separation slowly resulted in more pronounced loss of the minor product. The assignment of the major product as the *endo* adduct **110**, in which C3'a-H, C4'-H, C9'a-H and C9'b-H were all *cis* to each other, was consistent with the following ^{1}H NOE experiments. Saturation of the signal at δ 2.90 (C4'-H) gave NOE's at δ 2.71 (C3'a-H, 5%) and δ 2.27 (C9'a-H, 3%). When the signal at δ 2.71 (C3'a-H) was irradiated, NOE's at δ 2.90 (C4'-H, 4%) and δ 2.49 (C9'b-H, 3%) were observed. Saturation of the signal at δ 2.49 (C9'b-H) resulted in NOE's at δ 2.71 (C3'a-H, 4%) and δ 2.27 (C9'b-H, 3%). Saturation of the C9'a-H signal at δ 2.27 produced NOE's at δ 2.90 (C4'-H, 4%) and δ 2.49 (C9'b-H, 6%). The assignment of the structure of the major product was confirmed by X-ray crystallography (Figure 7). As in the case of the reaction of **68** with NPM, the second (minor) product could be either the *exo* adduct **111** or the epimer **112** of the *endo* adduct. Because of the overlap of the signals attributable to C3'a-H, C4'-H, C9'a-H and C9'b-H in the ^{1}H NMR ($CDCl_3$ or C_6D_6) spectrum of the minor product, the NOE experiments could not provide a conclusive assignment of the structure of the minor product. Fortunately, a few crystals of the low-melting (46-48 °C) minor product were obtained and had been submitted for X-ray crystal structure analysis. The ^{1}H and ^{13}C NMR spectra of **110** and the minor product bear a strong similarity to those of **103** and the tentatively assigned minor product **104** (see Tables 1 and 2). Once the crystal structure of the minor MA adduct has been unambiguously determined, the structure of **104** will be confirmed or reassigned by analogy.

Scheme 35

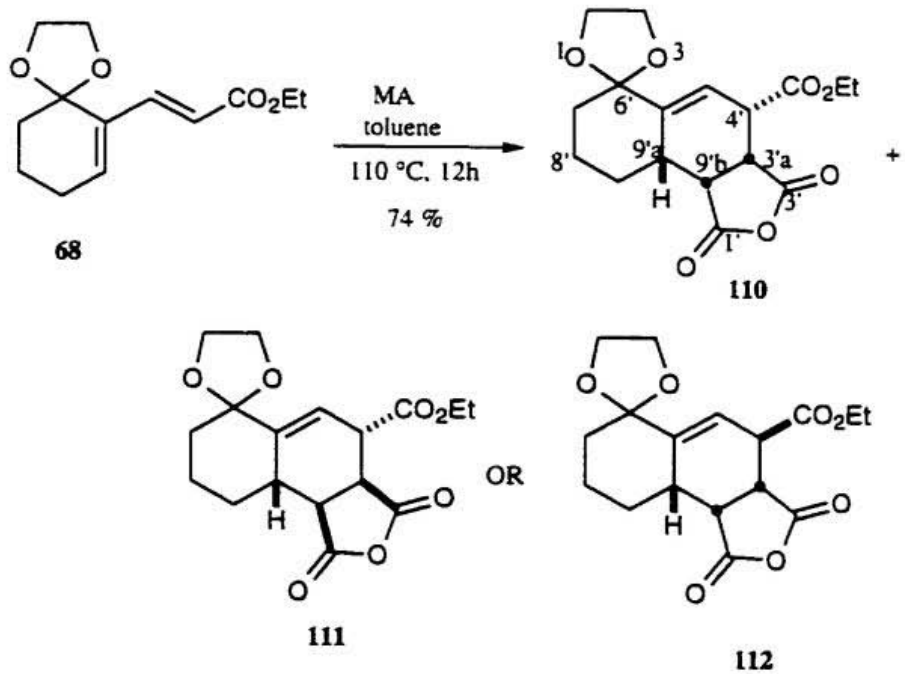
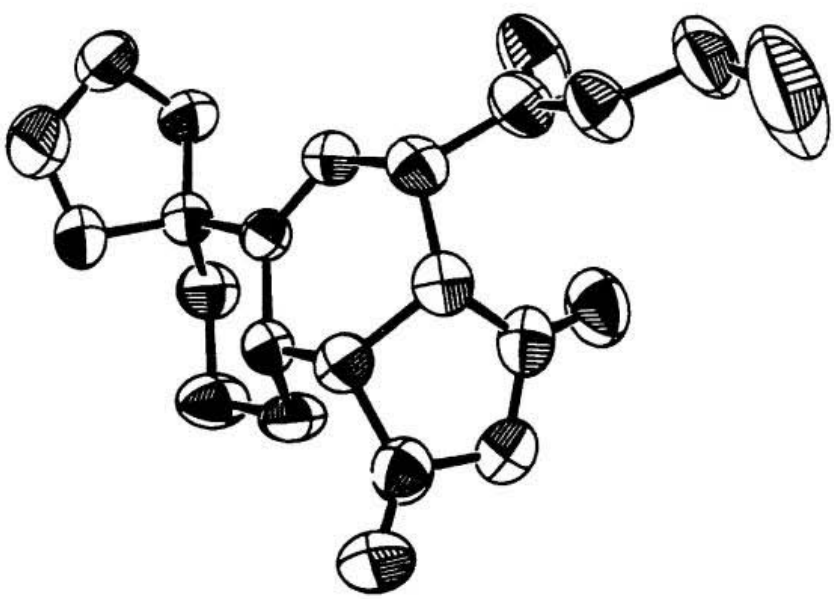
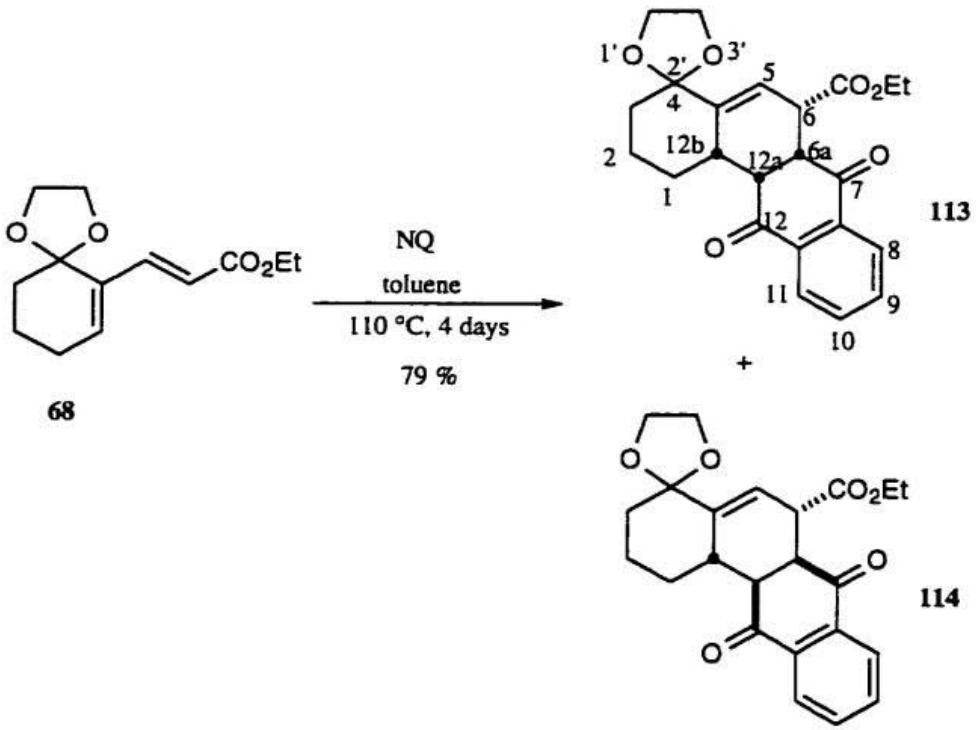


Figure 7 **X-ray crystal structure of 110**



Reaction of protected diene **68** with 1,4-naphthoquinone (Scheme 36) in refluxing toluene for four days also produced two products, this time in a crude ratio of 65:35. A 79% total yield was obtained, with the product ratio remaining virtually unchanged. Both of the products were isolated by flash chromatography and recrystallized from EtOAc/hexane as colorless crystals. Saturation of the signal at δ 4.11 (C6-H) in the ^{1}H NMR spectrum of the major product resulted in NOE's at δ 3.21 (C6a-H, 11%) and δ 3.60 (C12a-H, 8%). Saturation of the signal at δ 3.21 (C6a-H) produced NOE's at δ 4.11 (C6-H, 12%) and δ 3.60 (C12a-H, 5%). Saturation of signal at δ 3.60 (C12a-H) gave NOE's at δ 4.11 (C6-H, 8%), δ 3.21 (C6a-H, 5%) and δ 2.90 (C12b-H, 11%). When the signal at δ 2.90 (C12b-H) was irridiated, a 8% of NOE was obtained at δ 3.60 (C12a-H). These NOE data, particularly the 8% NOE enhancement between C6-H and C12a-H, are suggestive of an all-*cis* arrangement of the H atoms bonded to C6, C6a, C12a and C12b as in **113** and support the assignment of the major product as **113**, which resulted from *endo* addition. This assignment was confirmed by X-ray crystallography (Figure 8). However, in the minor product, the signals attributable to C6-H, C6a-H, C12a-H and C12b-H overlapped each other, and therefore, the NOE experiments could not provide conclusive assignment of its structure. It was determined as the *exo* adduct **114** by X-ray crystallography (Figure 9). In addition, the R_f value of major product **113** (0.13, 20% EtOAc/petroleum ether) was significantly smaller than that of the minor *exo* adduct **114** (0.35, 20% EtOAc/petroleum ether). This same trend was observed in all other reactions of the protected dienes. Another consistancy was that the major product had a significantly higher melting point (187-190 °C) than the minor product (138-140 °C).

Scheme 36



68

113

114

Figure 8 **X-ray crystal structure of 113**

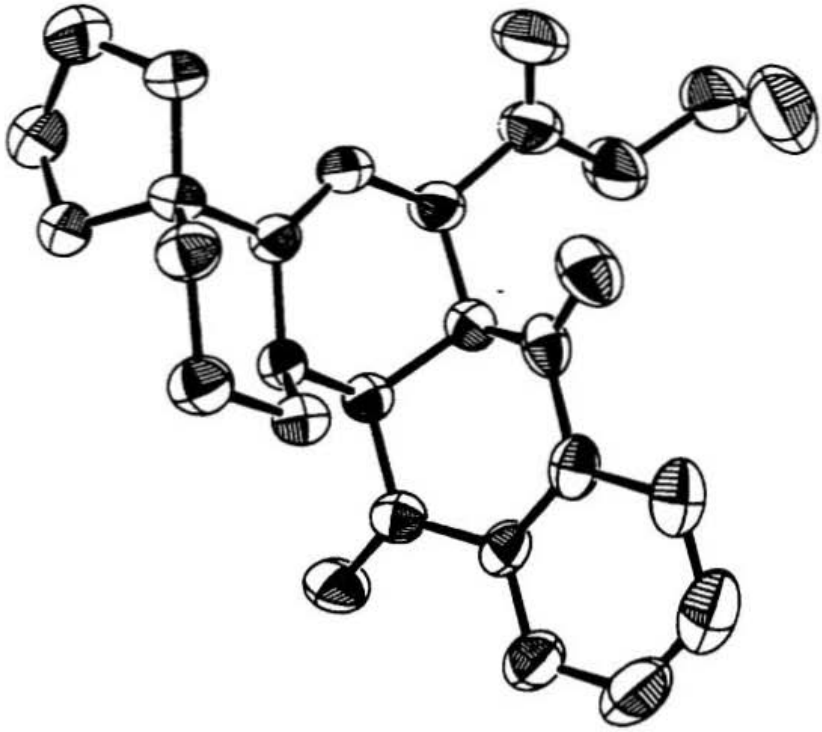
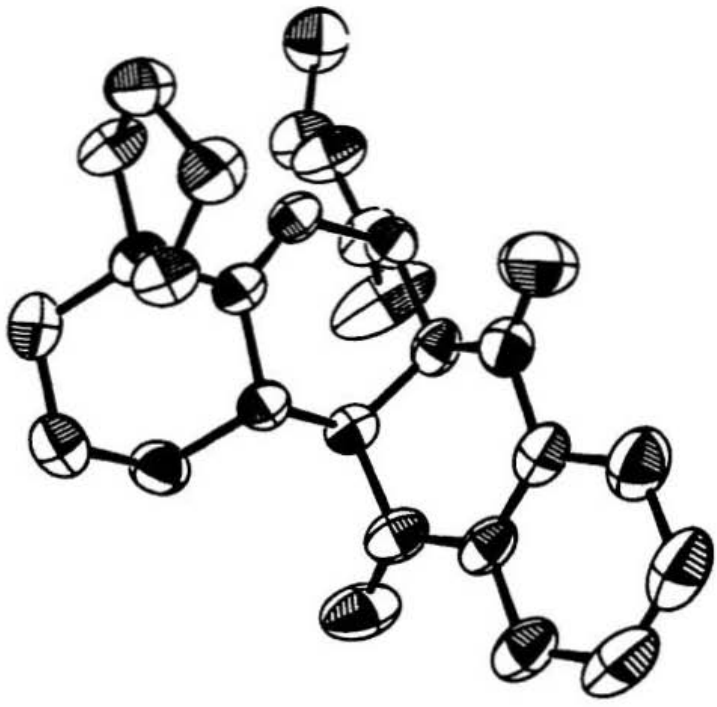
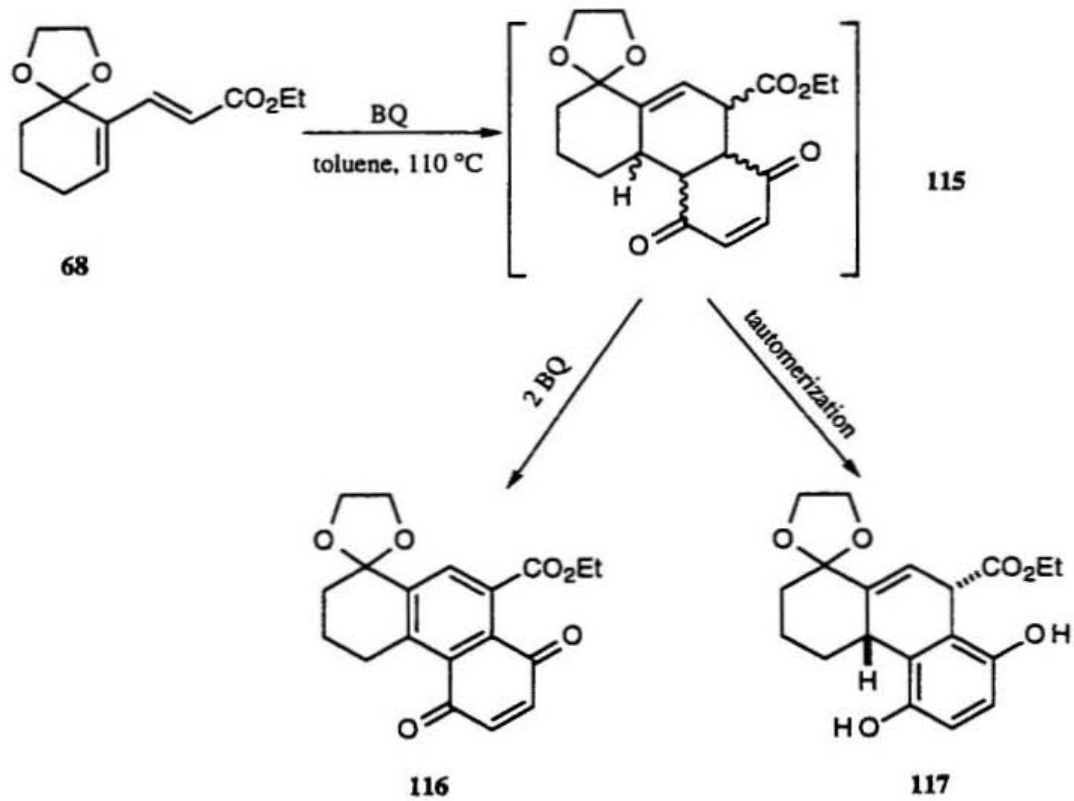


Figure 9 **X-ray crystal structure of 114**



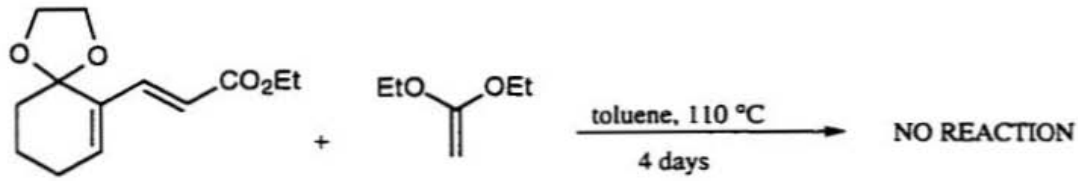
Surprisingly, the results of the reaction of diene **68** with 1,4-benzoquinone (Scheme 37) were different from those with 1,4-naphthoquinone. Refluxing **68** with three equivalents of freshly sublimed benzoquinone in toluene for 16 h followed by chromatography gave **116** as the only isolated product in 31% yield. Formation of this compound can be explained by aromatization of the initially formed adduct **115** by excess benzoquinone. However, when the reaction was carried out with 1.5 equivalents of benzoquinone, 26% of **117** as well as 15% of **116** were obtained. Hydroquinone **117** arises from two-fold tautomerization of the initially formed adduct **115**.

Scheme 37



Treatment of diene **68** with diethoxyethylene (Scheme 38) in refluxing toluene for 4 days gave no reaction. The starting diene was recovered quantitatively.

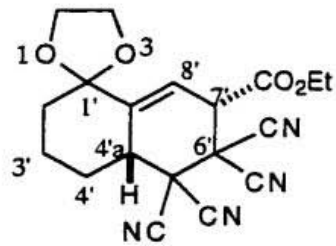
Scheme 38



68

3. 2. Experimental.*

(4'aα,7'α)-7'-Carboethoxy-3',4',4'a,5',6',7'-hexahydro-5',5',6',6'-tetracyanospiro[1,3-dioxolane-2,1'(2'*H*)-naphthalene (94).



A solution of diene **68** (200 mg, 0.84 mmol) and tetracyanoethylene (112 mg, 0.87 mmol) in dichloromethane (10 ml) was refluxed for 3 days. The solvent was removed under reduced pressure to provide the crude product as a brown solid. Recrystallization from EtOAc/hexane provided the adduct **94** as colorless crystals (168 mg, 0.46 mmol, 65%): mp 153-155 °C; ^{1}H NMR δ 6.18 (t, 1H, J = 2.1 Hz, C8'-H), 4.51-4.37 (AA'BB' system, 4H, C4-H + C5-H), 4.10-4.00 (m, 2H), 3.79 (m, 1H), 3.35 (m, 1H, C4'-H), 2.32 (m, 1H, C3'-H), 2.17-1.57 (m, 5H), 1.42 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ 165.1, 138.2, 111.8, 111.2, 109.9, 109.3, 106.8, 65.8, 64.1, 64.0, 46.6, 42.8, 36.2, 30.0, 22.2, 13.9; IR (Nujol) υ 1731 (s) cm^{-1}; MS *m/z* (%) 366 (M^+, 15), 293 (78), 241 (35), 165 (27), 139 (81), 99 (100), 86 (25); Anal. calcd for $C_{19}H_{18}N_4O_4$: C, 62.29; H, 4.95; N, 15.29. found: C, 62.37; H, 4.96.

(4'aα, 7'α)-7'-Carboethoxy-5',6'-dicarbomethoxy-3',4',4'a,7'-tetrahydrospiro[1,3-dioxolane-2,1'(2'*H*)-naphthalene] (98) and (4'aα, 7'β)-7'-carboethoxy-5',6'-dicarbomethoxy-3',4',4'a,7'-tetrahydrospiro[1,3-dioxolane-2,1'(2'*H*)-naphthalene] (99).

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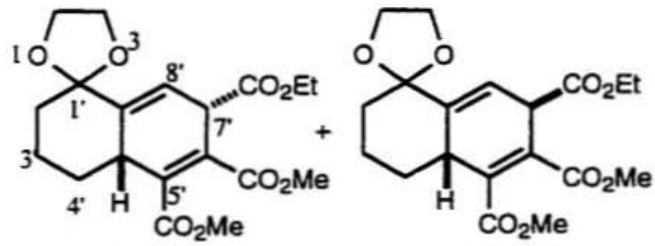
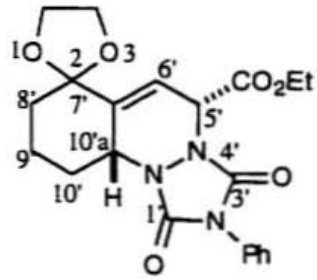
* For General Procedures, see Chapter 2, section 2.3.



98 **99**

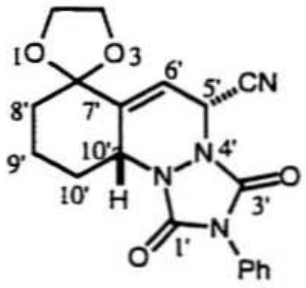
A solution of diene **68** (198 mg, 0.83 mmol), DMAD (235 mg, 1.64 mmol) in benzene (6.0 ml) was refluxed at 80 °C for 4 days. Removal of the solvent provided the crude product as a yellow oil. The ^{1}H NMR of the crude product indicated the presence of two products in a ratio of 57 : 43. Purification by chromatography (30% ethyl acetate/hexane) gave a mixture of **98** and **99** as a colorless oil (221 mg, 0.62 mmol, 48%). The ratio of the two products remained the same (57:43) after chromatography. The mixture was submitted for spectroscopic analysis. ^{1}H NMR (**98+99**): δ 5.85 (dd, 1H, J = 4.1, 1.0 Hz, C8'-H of the major product), 5.92 (dd, 1H, J = 3.7, 1.8 Hz, C8'-H of the minor product), 3.83 (s, 3H), 3.81 (s, 3H), 3.74 (s, 6H); ^{13}C NMR (mixture) δ 170.6, 169.3, 168.9, 165.7, 144.0, 143.3, 138.6, 137.4, 124.9, 124.4, 113.9, 113.8, 107.5, 107.3, 65.3, 65.1, 63.7, 63.5, 61.4, 61.3, 52.3, 52.2, 44.1, 43.8, 39.4, 38.1, 37.3, 36.9, 32.9, 31.8, 22.9, 22.6, 14.1; MS (mixture) *m/z* (%) 380 (M^+, 23), 348 (38), 321 (21), 307 (90), 275 (55), 263 (25), 231 (29), 221 (22), 161 (24), 103 (100), 99 (51), 86 (45), 59 (50); HRMS calcd for $C_{19}H_{24}O_8$ 380.1470, found (mixture) 380.1456.

(5'α,10'aα)-5-Carboethoxy-5',8',9',10',10'a-pentahydro-2'-phenyl-spiro[1,3-dioxolane-2,7'-[1*H*] [1,2,5]triazolo[1,2-*a*]cinnoline]-1',3'(2'*H*)-dione (100).

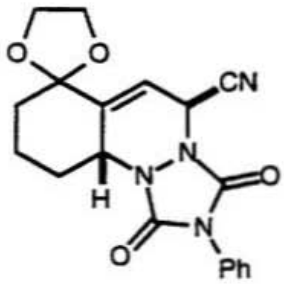


Diene **68** (101 mg, 0.43 mmol), PTAD (74 mg, 0.424 mmol) and benzene (6 ml) were combined and the resulting solution was stirred at room temperature for 1.5 h. Removal of the solvent under reduced pressure and column chromatography (10 % ethyl acetate/dichloromethane) afforded **100** as colorless crystals (163 mg, 0.39 mmol, 93 %): mp 163-165 °C; ^{1}H NMR δ 7.54-7.34 (m, 5H), 6.18 (dd, 1H, *J* = 5.6, 1.8 Hz, C6'-H), 5.11 (dd, 1H, *J* = 5.6, 2.5 Hz, C5'-H), 4.43 (m, 1H, C10'a-H), 4.31-4.18 (m, 2H), 4.08-3.97 (m, 3H), 3.82 (m, 1H), 3.11 (m, 1H, C10-H), 1.97-1.42 (m, 5H), 1.30 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR δ 166.7 (0, CO_2-), 152.4 (0), 151.8 (0), 138.5 (0), 131.1 (0), 129.0 (1), 128.1 (1), 125.7 (1), 111.5 (1, C6'), 106.9 (0, C7'), 65.5 (0), 63.8 (0), 62.3 (0), 56.0 (1, C10'a), 54.6 (1, C5'), 36.6 (2, C8'), 32.1 (2, C10'), 19.7 (2, C9'), 14.1 (3, -OCH_2CH_3); IR (CCl_4) υ 2982 (w), 2953 (w), 2887 (w), 1722 (s), 1549 (s), 1252 (s), 1217 (s) cm^{-1}; MS *m/z* (%) 413 (M^+, 12), 340 (100), 268 (50), 99 (25), 79 (10); HRMS calcd for $C_{21}H_{23}N_3O_6$ 413.1585, found 413.1587.

(5'α,10'aα)-5'-Cyano-2'-phenyl-5',8',9',10',10'a-pentahydrospiro[1,3-dioxolane-2,7'-[1*H*][1,2,5]triazolo[1,2-*a*]cinnoline]-1',3'(2'*H*)-dione (101) and (5'α,10'aβ)-5'-cyano-2'-phenyl-5',8',9',10',10'a-pentahydrospiro[1,3-dioxolane-2,7'-[1*H*][1,2,5]triazolo[1,2-*a*]cinnoline]-1',3'(2'*H*)-dione (102).



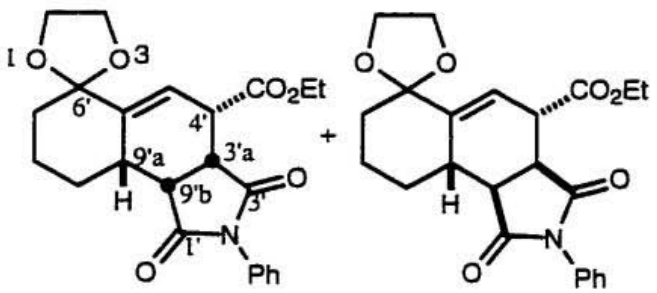
101



102

A mixture of diene **72a** and **72b** (402 mg, 2.10 mmol), PTAD (368 mg, 2.10 mmol) and benzene (20 ml) were combined and stirred at room temperature for 3 h. Removal of the solvent provided the crude product as a light pink solid. Two products were formed in a ratio of 71 : 29. Chromatography (40% ethyl acetate/hexane) afforded **101** (587 mg, 1.60 mmol) and **102** (193 mg, 0.52 mmol), both as colorless crystals. For **101:** mp 174-176 °C; ^{1}H NMR δ 7.52-7.39 (m, 5H), 6.08 (dd, 1H, J = 5.2, 1.7 Hz, C6'-H), 5.28 (m, 1H, C5'-H), 4.47 (m, 1H, C10'a-H), 4.04-3.95 (m, 3H), 3.79 (m, 1H), 3.03 (m, 1H, C10-H), 2.04-1.50 (m, 5H); ^{13}C NMR δ 152.5 (0), 151.1 (0), 141.8 (0), 130.4 (0), 129.2 (1), 128.6 (1), 125.5 (1), 113.7 (0), 109.4 (1, C6'), 106.6 (0), 65.6 (2), 64.0 (2), 56.7 (1, C10'a), 42.7 (1, C5'), 36.5 (2), 31.7 (2, C10'), 19.6 (2); IR (Nujol) υ 1722 (s) cm^{-1}; MS *m/z* (%) 366 (M^+, 61), 190 (18), 163 (69), 152 (40), 151 (95), 139 (40), 119 (49), 99 (100), 91 (37), 86 (25), 77 (18), 55 (27); HRMS calcd for $C_{19}H_{18}N_4O_4$ 366.1327, found 366.1329. For **102**: mp 216-219 °C; ^{1}H NMR δ 7.56-7.41 (m, 5H), 6.03 (dd, 1H, J = 5.8, 1.8 Hz, C6'-H), 5.26 (d, 1H, J = 5.7 Hz, C5'-H), 4.73 (m, 1H, C10'a-H), 4.09-4.00 (m, 3H), 3.92 (m, 1H), 2.39 (m, 1H, C10'-H), 1.98-1.39 (m, 5H); ^{13}C NMR δ 150.6 (0), 143.0 (0), 130.4 (0), 129.2 (1), 128.6 (1), 125.4 (1), 113.7 (0), 108.7 (1, C6'), 107.1 (0), 65.6 (2), 64.3 (2), 54.3 (1, C10'a), 43.5 (1, C5'), 37.3 (2), 29.1 (2, C10'), 20.1 (2); IR (Nujol) υ 1723 (s) cm^{-1}; MS *m/z* (%) 366 (M^+, 48), 190 (15), 162 (57), 152 (35), 151 (66), 139 (38), 119 (38), 99 (100), 86 (15), 55 (23); HRMS calcd for $C_{19}H_{18}N_4O_4$ 366.1327, found 366.1328.

(3'aα,4'α,9'aα,9'bα)-4'-Carboethoxy-3'a,4',7',8',9',9'a,9'b-heptahydro-2'-phenyl-spiro[1,3-dioxolane-2,6'-[1*H*]benz[*e*]isoindole]-1',3'(2'*H*)-dione (103) and (3'aα,4'β,9'aβ,9'bα)-4'-carboethoxy-3'a,4',7',8',9',9'a,9'b-heptahydro-2'-phenyl-spiro[1,3-dioxolane-2,6'-[1*H*]benz[*e*]isoindole]-1',3'(2'*H*)-dione (104)

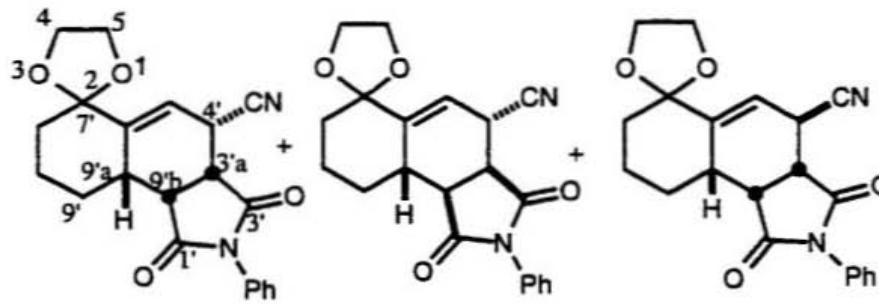


103 **104**

Diene **68** (402 mg, 1.69 mmol) and *N*-phenylmaleimide (876 mg, 5.06 mmol) were combined in 10 ml of toluene and heated to reflux for 6 h. The ^{1}H NMR of the crude product included signals from two products in the ratio of 94 : 6. Separation by flash chromatography (30 % ethyl acetate/hexane) gave **103** (487 mg, 1.18 mmol, 70%) as colorless crystals and **104** (33 mg, 0.08 mmol, 5%) as a colorless oil in 75% total yield. For **103**: mp 179-181°C, ^{1}H NMR δ 7.16-7.27 (m, 5H), 6.32 (dd, 1H, J = 4.5, 2.0 Hz, C5'-H), 4.27-4.19 (m, 2H), 3.96-3.88 (m, 3H), 3.76 (m, 1H), 3.64 (dd, 1H, J = 9.4, 6.4 Hz, C3'a-H), 3.48 (m, 1H, C4'-H), 3.40 (t, 1H, J = 9.4 Hz, C9'b-H), 2.77 (m, 1H, C9'a-H), 2.20 (m, 1H, C9-H), 1.93-1.82 (m, 2H), 1.78-1.60 (m, 3H), 1.28 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ 176.6 (0), 175.9 (0), 171.0 (0), 142.0 (0), 131.8 (0), 128.9 (1, 2C), 128.4 (1), 126.2 (1, 2C), 117.1 (1), 107.7 (0), 64.6 (2), 64.1 (2), 61.4 (2), 41.7 (1, C3'a), 41.4 (1), 40.0 (1, C9'b), 35.5 (1, C9'a), 35.2 (2), 26.0 (2), 21.4 (2), 14.1 (3); IR υ 1549 (s), 1252 (s), 1217 (s), 1004 (s), 979 (s) cm^{-1}; MS *m/z* (%) 411 (92), 366 (22), 365 (35), 339 (21), 338 (89), 337 (15), 191 (23), 165 (27), 151 (46), 147 (26), 119 (30), 99 (100), 91 (83), 77 (37), 55 (29), 29 (70), 28 (68); HRMS calcd for $C_{23}H_{25}NO_6$ 411.1680, found 411.1690.

For **104**: ^{1}H NMR δ 7.50-7.43 (m, 2H), 7.38 (m, 1H), 7.29-7.26 (m, 2H), 6.03 (dd, 1H, *J* = 6.4, 1.9 Hz, C5'-H), 4.28-4.15 (m, 2H), 4.00-3.87 (m, 4H), 3.71-3.64 (m, 2H, C3'a-H + C4'-H), 3.01 (dd, 1H, *J* = 8.5, 5.5 Hz, C9'b-H), 2.55 (m, 1H, C9'a-H), 2.30 (m, 1H, C9-H), 1.91-1.57 (m, 5H), 1.31 (t, 3H, *J* = 7.1 Hz, -OCH_2CH_3); ^{13}C NMR δ 178.2, 176.6, 172.0, 139.8, 134.2, 131.7, 129.1, 128.5, 126.1, 114.2, 107.7, 65.2, 63.5, 61.7, 43.0, 39.7, 38.0, 36.7, 35.4, 35.3, 22.4, 14.1; MS *m/z* (%) 411 (M^+, 14), 338 (43), 173 (23), 151 (26), 86 (63), 84 (100).

(3'aα,4'α,9'aα,9'bα)-4'-Cyano-3'a,4',7',8',9',9'a,9'b-heptahydro-2'-phenylspiro[1,3-dioxolane-2,6'-[1*H*]benz[*e*]isoindole]-1',3'-(2'*H*)-dione (106) and (3'aα,4'β,9'aβ,9'bα)-4'-cyano-3'a,4',7',8',9',9'a,9'b-heptahydro-2'-phenylspiro[1,3-dioxolane-2,6'-[1*H*]benz[*e*]isoindole]-1',3'-(2'*H*)-dione (107) and (3'aα,4'β,9'aα,9'bα)-4'-Cyano-3'a,4',7',8',9',9'a,9'b-heptahydro-2'-phenylspiro[1,3-dioxolane-2,6'-[1*H*]benz[*e*]isoindole]-1',3'-(2'*H*)-dione (108).

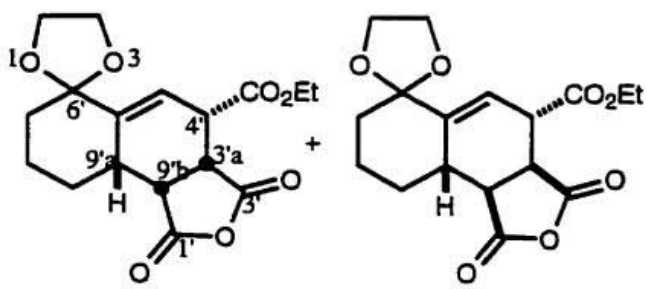


106 **107** **108**

A mixture of diene **72a** and **72b** (393 mg, 2.06 mmol), *N*-phenylmaleimide (709 mg, 4.09 mmol) and toluene (10 ml) was heated at reflux for 26.5 h. Removal of the solvent gave a thick yellow oil as the crude product. Chromatography provided **106** (436 mg, 1.20 mmol, 58%) as colorless crystals and a mixture of **107** and **108** (212 mg, 0.58 mmol, 28%) as colorless crystals. For **106**: mp 188-190 °C; ^{1}H NMR δ 7.51-7.30 (m, 5H), 6.08

(dd, 1H, J = 5.0, 1.9 Hz, C5'-H), 4.01-3.72 (m, 5H), 3.44-3.41 (m, 2H, C3'a-H + C9'b-H), 2.85 (m, 1H, C9'a-H), 2.34 (m, 1H, C7'-H), 1.98-1.58 (m, 4H); ^{13}C NMR δ 174.4 (0), 145.6 (0), 131.3 (0), 129.1 (1, 2C), 128.8 (1), 126.6 (1, 2C), 117.7 (0), 113.5 (1, C5'), 107.5 (0), 64.7 (2), 64.5 (2), 41.5 (1), 40.3 91), 35.7 (2), 34.9 (1, C9'a), 26.7 (2), 26.0 (1, C4'), 21.7 (2); IR (CH_2Cl_2) υ 2685 (s), 2410 (s), 2305 (s), 1719 (s) cm^{-1}; MS *m/z* (%) 364 (M^+, 69), 191 (44), 174 (59), 151 (100), 91 (88), 77 (81); HRMS calcd for $C_{21}H_{20}N_2O_4$ 364.1421, found 364.1448. For the mixture of **107** and **108**: ^{1}H NMR δ 5.95 (t, 1H, J = 1.7 Hz, C5'-H of **108**), 5.93 (t, J = 1.6 Hz, C5'-H of **107**); ^{13}C NMR δ 176.7 (0), 175.1 (0), 174.7 (0), 174.0 (0), 144.0 (0), 143.2 (0), 131.3 (0), 131.2 (0), 129.2 (1), 128.8 (1), 125.94 (1), 125.87 (1), 119.0 (0), 111.6 (1), 110.6 (1), 107.4 (0), 65.2 (2), 64.7 (2), 64.5 (2), 63.7 (2), 42.3 (1), 41.7 (1), 41.3 (1), 40.3 (1), 36.7 (2), 35.9 (2), 35.4 (1), 35.3 (2), 33.7 (1), 28.2 (2), 23.1 (1), 22.9 (1), 22.4 (2), 21.7 (2); IR (CH_2Cl_2) υ 2410 (s), 2306 (s), 1722 (s) cm^{-1}; MS *m/z* (%) 364 (M^+, 67), 191 (11), 174 (22), 151 (100), 139 (25), 119 (12), 99 (29), 86 (15); HRMS calcd for $C_{21}H_{20}N_2O_4$ 364.1422, found 364.1443.

(3'aα,4'α,9'aα,9bα)- 4'-Carboethoxy-3'a,4',7',8',9',9'a,9'b-heptahydrospiro[1,3-dioxolane-2, 6'-naphtho[1,2-*c*]furan]-1',3'-dione (110) and (3'aα,4'β,9'aβ,9'bα-)-4'-carboethoxy-3'a,4',7',8',9',9'a,9'b-heptahydrospiro[1,3-dioxolane-2,6'-naphtho[1,2-*c*]furan]-1',3'-dione (111).



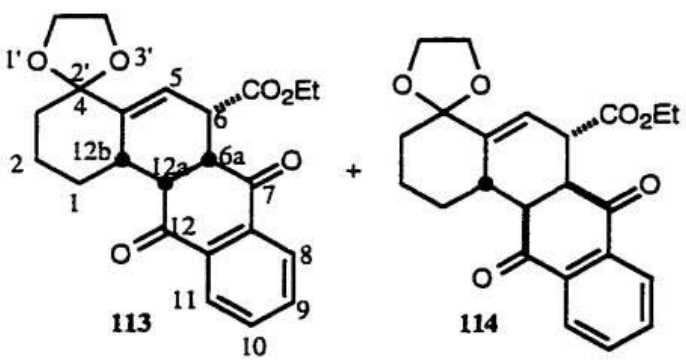
110 **111**

A mixture of diene **68** (417 mg, 1.75 mmol), freshly sublimed maleic anhydride (258 mg, 2.63 mmol) and toluene (10 ml) was heated at 110 °C for 12 h. The solvent was evaporated under reduced pressure and excess maleic anhydride was removed by sublimation. The crude product was obtained as a light yellow viscous oil. The ^{1}H NMR spectrum of the crude product displayed signals for two products in the ratio of 63 : 37. Flash chromatography (30 % ethyl acetate/hexane) gave **110** (292.7 mg, 0.87 mmol, 50%) and **111** (121 mg, 0.36 mmol, 21 %), both as colorless crystals. For **110**: mp 114-116 °C; ^{1}H NMR ($CDCl_3$) δ 6.21 (m, 1H, C5'-H), 4.21 (q, 1H, J = 7.1 Hz), 4.03-3.80 (AA'BB' system, 4H, C4-H + C5-H), 3.59-3.53 (m, 3H, C3'a-H + C4'-H + C9'b-H), 2.84 (m, 1H, C9'a-H), 2.30 (m, 1H, C9'-H), 1.93-1.76 (m, 2H), 1.74-1.56 (m, 2H), 1.38 (m, 1H), 1.27 (t, 3H, J = 7.2 Hz); ^{1}H NMR (C_6D_6) δ 6.32 (dd, 1H, J = 4.9, 1.9 Hz, C5'-H), 4.05-3.89 (m, 2H), 3.50-3.26 (AA'BB' system, 4H, C4-H + C5-H), 2.90 (m, 1H, C4'-H), 2.71 (dd, 1H, J = 10.0, 6.4 Hz, C3'a-H), 2.49 (t, 1H, J = 9.8 Hz, C9'b-H), 2.27 (m, 1H, C9'a-H), 2.06 (m, 1H, C9'-H), 1.77 (m, 1H), 1.66-1.32 (m, 4H), 0.95 (t, 3H, J = 7.1 Hz); NOE data (C_6D_6) δ 2.90 (2.71, 5%; 2.27, 3%), 2.71 (2.90, 4%; 2.49, 3%), 2.49 (2.71, 4%; 2.27, 3%), 2.27 (2.90, 4%; 2.49, 6%); ^{13}C NMR ($CDCl_3$) δ 171.7 (0), 170.4 (0), 170.3 (0), 142.2 (0), 114.9 (1, C5'), 107.8 (0), 64.6 (2), 64.3 (2), 61.9 (2), 41.2 (1), 41.0 (1), 39.3 (1), 36.3 (2), 33.5 (1, C9'a), 27.9 (2, C9'), 22.1 (2), 14.0 (3); ^{13}C NMR (C_6D_6) δ 172.3, 170.6, 142.6, 116.4 (C5'), 108.2, 64.8(2C), 62.0, 42.1 (C3'a + C9'b), 39.8 (C4'), 36.4, 34.7 (C9'a), 27.8 (C9'), 22.3, 14.1; IR (CCl_4) υ 2981 (w), 2950 (w), 2885 (w), 1786 (m), 1550 (s), 1252 (s), 1217 (s) cm^{-1}; MS *m/z* (%) 336 (M^+, 4), 335 (17), 263 (92), 237 (27), 235 (27), 151 (61), 108 (52), 99 (100), 73 (34); HRMS calcd for $C_{17}H_{20}O_7$ 336.1208, found 336.1198.

For **111**: mp 46-48 °C; ^{1}H NMR ($CDCl_3$) δ 6.02 (dd, 1H, J = 5.5, 1.9 Hz, C5'-H), 4.30-4.10 (m, 2H), 4.02-3.90 (m, 3H), 3.82-3.64 (m, 3H), 3.07 (dd, 1H, J = 8.6, 6.2 Hz, C9'b-H), 2.54 (m, 1H, C9'a-H), 2.24 (m, 1H, C9'-H), 1.92-1.66 (m, 3H), 1.56 (m, 1H), 1.30 (t,

3H, J = 7.1 Hz), 1.24 (m, 1H); ^{1}H NMR (C_6D_6) δ 5.74 (dd, 1H, J = 5.2, 1.5 Hz), 3.63-3.44 (m, 2H), 3.31 (m, 1H), 3.12-2.96 (m, 3H), 2.86-2.78 (m, 2H), 2.34-2.24 (m, 2H), 1.60 (m, 1H), 1.48-0.97 (m, 4H), 0.65 (m, 1H), 0.57 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 172.1 (0), 171.7 (0), 171.1 (0), 139.5 (0), 113.8 (1, C5'), 107.4 (0), 65.4 (2), 63.5 (2), 62.0 (2), 43.2 (1, C9'b), 40.7 (1), 37.8 (1), 36.6 (2), 34.7 (2, C9'), 34.4 (1, C9a'), 22.2 (2), 14.1 (3); ^{13}C NMR (C_6D_6), δ 172.6, 172.4, 171.4, 140.8, 114.5, 107.9, 65.6, 63.8, 62.0, 43.9, 40.4, 38.8, 37.4, 35.3, 35.0, 22.8, 14.3; IR υ 1851 (m), 1782 (s), 1549 (s), 1252 (s) cm^{-1}; MS *m/z* (%), 336 (M^+, 21), 263 (100), 191 (28), 151 (70), 99 (56), 91 (57); HRMS calcd for $C_{17}H_{20}O_7$ 336.1208, found 336.1220.

(6α,6aα,12aα,12bα)-6-Carboethoxy-1,2,6,6a,12a,12b-hexahydrospiro[benz[*a*]anthracene-4(3*H*),2'-[1,3]dioxolane]-7,12-dione (113) and (6α,6aβ,12aβ,12bβ)-6-carboethoxy-1,2,6,6a,12a,12b-hexahydrospiro[benz[*a*]anthracene-4(3*H*),2'-[1,3]dioxolane]-7,12-dione (114).

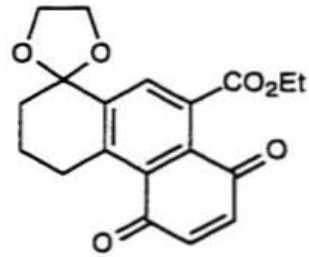


A mixture of diene **68** (501 mg, 2.10 mmol) and naphthoquinone (950 mg, 6.01 mmol) in toluene (10 ml) was heated at reflux for 4 days. Removal of the solvent provided the crude product as a brown solid. The ^{1}H NMR spectrum of the crude product indicated that **113** and **114** were obtained in a ratio of 65 : 35. Flash chromatography (20 % ethyl acetate/hexane) afforded **113** (420 mg, 1.06 mmol, 50%) and **114** (241 mg, 0.61 mmol,

29%), both as colorless crystals. For **113**: mp 187-190 °C; ^{1}H NMR δ 8.11 (m, 1H), 7.93 (m, 1H), 7.79-7.71 (m, 2H), 6.44 (s, 1H, C5-H), 4.35-4.20 (m, 2H), 4.11 (m, 1H, C6-H), 4.04-3.89 (m, 3H), 3.80 (dd, 1H, J = 14.1, 6.6 Hz), 3.6 (dd, 1H, J = 7.6, 5.8 Hz, C12a-H), 3.21 (m, 1H, C6a-H), 2.90 (m, 1H, C12b-H), 1.76 (m, 1H), 1.56-1.44 (m, 3H), 1.28 (t, 3H, J = 7.1 Hz), 1.08 (m, 1H), 0.68 (m, 1H); NOE data ($CDCl_3$) δ 4.11 (3.21, 11%; 3.60, 8%); 3.21 (4.11, 12%; 3.60, 5%); 3.60 (4.11, 8%; 3.21, 5%; 2.90, 11%); 2.90 (3.60, 8%); ^{13}C NMR δ 197.9 (0), 195.6 (0), 171.3 (0), 138.3 (0), 136.3 (0), 135.2 (0), 134.5 (1), 134.0 (1), 126.6 (1), 126.1 (1), 115.4 (1, C5), 107.9 (0, C4), 65.1 (2), 63.6 (2), 60.9 (2), 51.1 (1, C12a), 47.3 (1, C6), 39.6 (1, C6a), 37.0 (C12b), 36.9 (2, C3), 31.4 (2, C1), 23.3 (2, C2), 14.1 (3); IR υ 1740 (s), 1696 (s), 1255 (m), 1186 (m) cm^{-1}; MS *m/z* (%) 396 (M^+, 52), 321 (30), 237 (100), 165 (71), 152 (52), 151 (47), 43 (69); HRMS calcd for $C_{23}H_{24}O_6$ 396.1571, found 396.1577.

For **114**: mp 138-140 °C; ^{1}H NMR δ 8.08 (m, 1H), 7.98 (m, 1H), 7.80-7.71 (m, 2H), 6.06 (dd, 1H, J = 5.4, 1.4 Hz, C5-H), 4.26-4.13 (m, 2H), 4.11-4.00 (m, 2H), 3.93-3.83 (m, 3H), 3.55 (m, 1H), 3.15 (dd, 1H, J = 10.3, 5.1 Hz, C12a-H), 2.28 (m, 1H, C12b-H), 1.97 (m, 1H), 1.86-1.44 (m, 4H), 1.29 (t, 3H, J = 7.1 Hz), 1.11 (m, 1H); ^{13}C NMR δ 197.0 (0), 195.1 (0), 171.8 (0), 138.6 (0), 134.4 (1), 134.2 (1), 133.6 (0), 127.3 (1), 126.4 (1), 116.2 (1, C5), 107.4 (0), 65.4 (2), 62.9 (2), 61.2 (2), 51.8 (1, C12a), 47.3 (1, C6a), 38.7 (1, C6), 36.2 (2, C1), 35.2 (1, C12b), 31.6 (2), 21.8 (2), 14.1 (3); IR υ 1713 (s), 1695 (s), 1594 (m), 1294 (m) cm^{-1}; MS *m/z* (%), 396 (M^+, 32), 351 (26), 350 (100), 323 (43), 165 (25), 151 (37), 55 (30); HRMS calcd for $C_{23}H_{24}O_6$ 396.1571, found 396.1572.

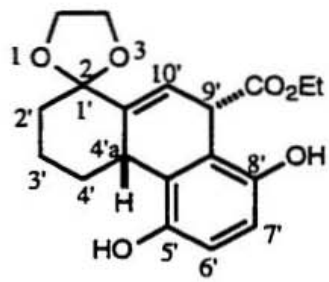
9'-Carboethoxy-3',4'-dihydrospiro-[1,3-dioxolane-2,1'(2'*H*)-phenanthrene]-5',8'-dione (116).



116

A solution of diene **68** (403 mg, 1.70 mmol) and benzoquinone (544 mg, 5.04 mmol) in toluene (10 ml) was heated at reflux for 16 h during which time a large amount of dark greed solid was produced. The green solid was removed by filtration, and then the solvent was removed under reduced pressure to provide the crude product as green solid. Chromatography (20 % ethyl acetate/hexane) yielded **115** (180 mg, 0.52 mmol, 31%) as yellow crystals: mp : 156-159 °C; ^{1}H NMR δ 7.83 (s, 1H), 6.89 (s, 2H), 4.44 (q, 2H, J = 7.2 Hz), 4.25-4.10 (m, 4H), 3.30 (t, 2H, J = 5.7 Hz), 2.05-1.93 (m, 4H), 1.38 (t, 3H, J = 7.2 Hz); ^{13}C NMR δ 186.4, 184.2, 169.4, 144.7, 143.4, 140.3, 136.3, 132.6, 130.5, 129.3, 105.9, 65.2, 61.8, 31.9, 28.1, 19.8, 13.8; MS *m/z* (%) 342 (M^+, 52), 273 (51), 242 (48), 241 (47), 115 (29), 99 (100), 55 (44).

(4'aα,9'α)-9'-Carboethoxy-5',8'-dihydroxy-3',4',4'a,9'-tetrahydrospiro[1,3-dioxolane-2,1'(2'*H*)-phenanthrene] (117).



A mixture of **68** (303 mg, 1.27 mmol) and 1,4-benzoquinone (206 mg, 1.91 mmol) was heated at reflux in toluene (10 ml) for 48 h followed by chromatography to gave **116** (114

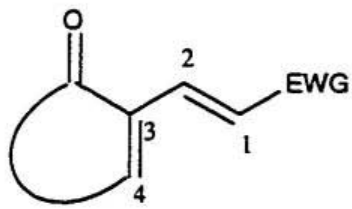
mg, 0.33 mmol, 26%) as colorless crystals and **117** (68 mg, 0.20 mmol, 15%). For **117**: mp 197-199 °C; ^{1}H NMR (CD_3COCD_3) δ 7.83 (s, 1H, C10'-H), 6.89 (s, 2H), 4.44 (q, 2H), 4.25-4.10 (AA'BB' system, 4H, C4-H + C5-H), 3.31, (t, 2H, J = 5.7 Hz), 2.00-1.93 (m, 4H), 1.38 (t, J = 7.2 Hz); ^{13}C NMR δ 173.5 (0), 148.9 (0), 143.1 (0), 127.5(0), 121.7 (0), 115.3 (1), 115.0 (1), 113.5 (1), 109.5 (0), 65.9 (2), 64.9 (2), 61.5 (2), 44.2 (1), 39.8 (2), 37.3 (1), 36.0 (2), 24.7 (2), 15.0 (3); IR (Nujol) υ 3428 (m), 1708 (s), 1287 (m), 1203 (m) cm^{-1}; MS *m/z* (%) 346 (M^+, 26), 273 (100), 173 (18), 99 (67); HRMS calcd for $C_{19}H_{22}O_6$ 346.1416, found 346.1431.

Chapter 4. Inverse Electron Demand Diels-Alder Reactions of Deprotected Dienes

4.1 Results and Discussion

The deprotected dienes contain a 1,3-butadiene unit bearing electron withdrawing groups at the 1 and 3 positions (Figure 10). Their inverse electron demand Diels-Alder reactions with a series of electron rich dienophiles will be discussed in this chapter.

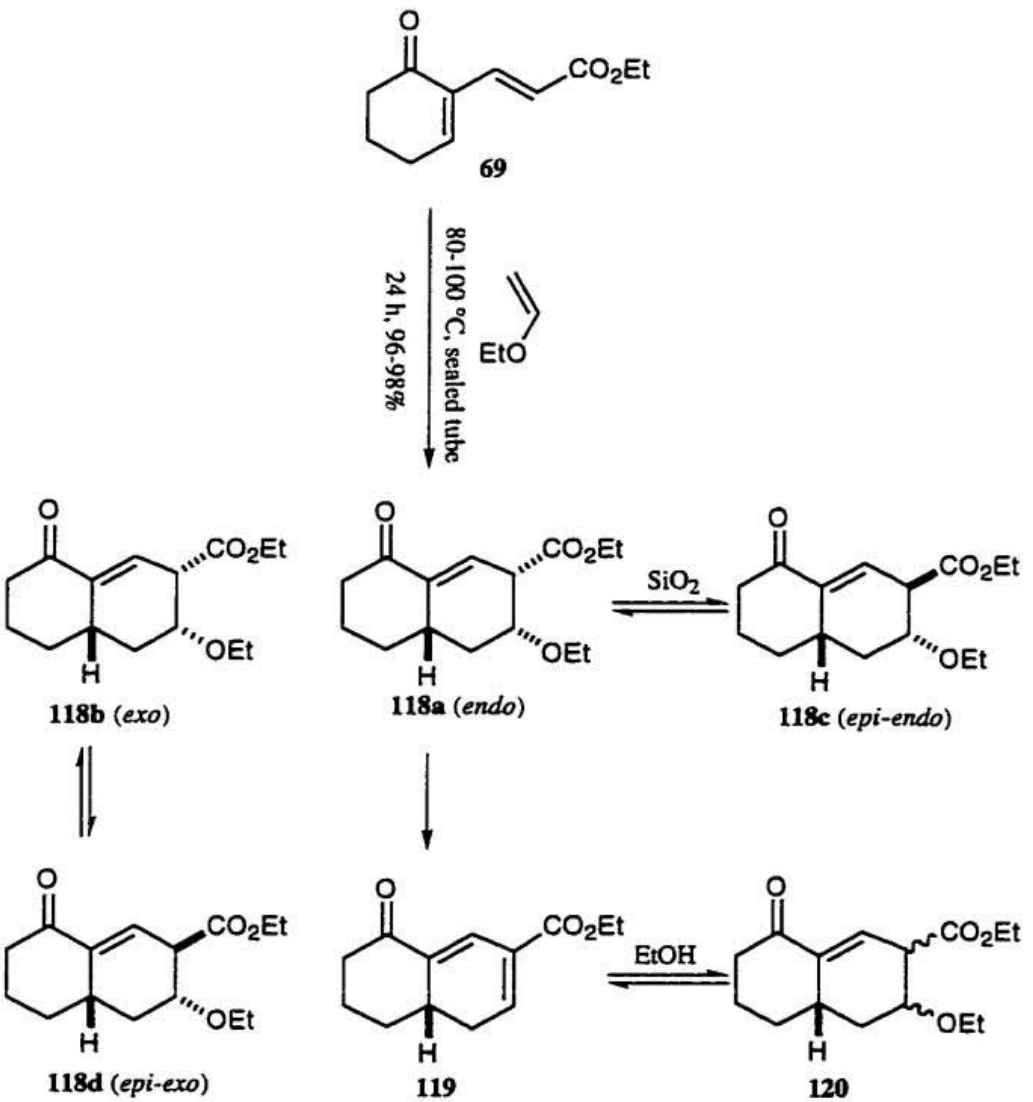
Figure 10. Deprotected dienes



deprotected dienes (EWG = CO_2R, CN)

Cycloaddition of the deprotected diene with ethyl vinyl ether proceeded readily. A mixture of diene **69** and ten equivalents of ethyl vinyl ether (Scheme 39) in benzene was heated in a sealed tube at 80-90 °C for 24 h. The crude yield was nearly quantitative. Its ^1H NMR spectrum indicated that the diene had been completely consumed and that one product predominated (>90% purity, conservatively). Some small signals from other products were observed, but these have not yet been identified. The TLC of the crude product showed one intense spot along with a few other very faint ones. Further NMR experiments (^{13}C, COSY, HET-CORR, APT) indicated that the major product was a 1:1 adduct with the expected regiochemistry shown in Scheme 1. However, the relative stereochemistry of the major product could not be unequivocally determined. Upon

Scheme 39



preparative thin layer chromatography (PTLC), a 13:87 mixture of the major product with a new isomer was obtained with 55% combined recovery. When the reaction was performed at 120-130 °C, the crude ^{1}H NMR spectrum indicated that 11% of the same new isomer was also generated along with the initially formed adduct in near quantitative combined crude yield. Since epimerization was observed in the adducts **35** and **39** of the protected dienes, it seemed very likely that this was the process being observed here. In

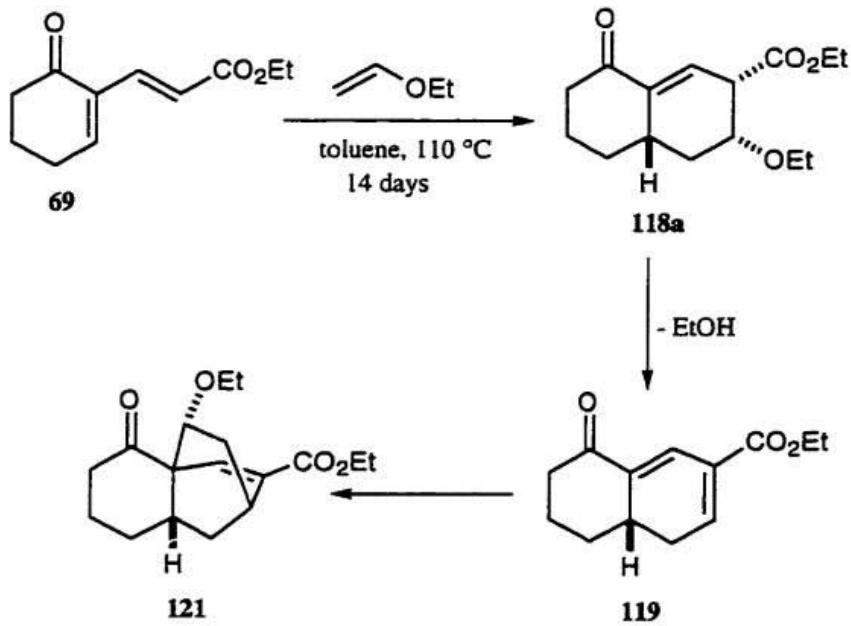
this case, the ester group was part of a vinylogous acetoacetate system, which was expected to be considerably more prone to enolization than **35** and **39**. The other possibility was that the ethoxy group was epimerizing. A possible mechanism (Scheme 1) involves the elimination of ethanol from the initially formed adduct to give the diene **119** followed by readdition of ethanol. However, this process could conceivably lead to the formation of every possible stereoisomer at C6 and C7. Since it seems quite unlikely that one of these isomers could be >4 kcal/mol lower in energy than all others, this dissociative mechanism had been discarded in favor of epimerization of the ester group.

Taking epimerization of the ester group into account, there were four possible products in this reaction: *endo* adduct **118a**, *exo* adduct **118b**, epimerized *endo* adduct **118c** and epimerized *exo* adduct **118d**. Based on the following structural analysis of **118a-d**, the initially formed adduct had been assigned as the *endo* adduct **118a**, and the new isomer produced at raised temperatures or during chromatography had been assigned as the epimerized isomer **118c**. It can be seen that in the *endo* adduct **118a**, the ethoxy group and the ester group were *cis* to each other and, therefore, upon chromatography, epimerization gives the more stable (presumably) *trans* isomer **118c**. However, if the initially formed adduct were **118b**, in which the ethoxy group and the ester group were already *trans* to one another, epimerization would provide the less stable *cis* isomer **118d**. If the observed ratio of **118a**:**118c** was an equilibrium ratio, the free energy difference between them was 1.3 kcal/mol.

An interesting result was obtained when **69** was reacted with ethyl vinyl ether in refluxing toluene. Fourteen days were required for the starting material to be completely consumed. Due to the low boiling point (33 °C) of the dienophile, fresh portions were added at two points (4 d and 7 d) during the reaction. A single product was isolated after chromatography of the crude reaction mixture. The mass spectrum (m/z = 292, M^+) showed that this was not a 1:1 adduct. The ^1H and ^{13}C NMR spectra suggested the

presence of an α,β-unsaturated ester and an isolated ketone. In conjunction with the remainder of these spectra, this was consistent with structure **121**, which was the result of Diels-Alder reaction between ethyl vinyl ether and diene **119**, which could be generated by the loss of EtOH from **118a** (Scheme 40).

Scheme 40

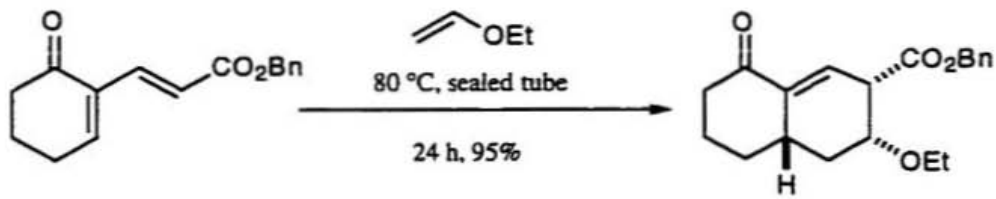


Like the starting material **69**, diene **119** contains a butadiene moiety with electron withdrawing groups at the 1 and 3 positions. As such, a Diels-Alder reaction with excess ethyl vinyl ether does not seem unreasonable. However, there were eight possible product isomers due to a combination of regio-, *endo/exo*- and facial selectivity in this reaction. The regiochemistry and the *endo* selectivity were assigned by analogy to the sealed tube reaction of **69** and ethyl vinyl ether and the facial selectivity was assigned as occurring from the convex face of diene **119** as was observed in a normal electron

demand Diels-Alder reaction of a structurally similar compound.[53] The product was thus assigned to structure **121**. The isolated yield of **121** was only 21%, but it demonstrates the potential for sequential Diels-Alder reactions in the systems under study. The multifunctional tricyclic molecule **121** was prepared in just 6 steps from 2-cyclohexen-1-one.

Since **118a** (Scheme 40) was obtained as an oil, diene **71** was prepared (see Chapter 2) and its reaction with ethyl vinyl ether (Scheme 41) was tried in order to obtain a crystalline adduct. Although compound **122** was also obtained as an oil (95%), the ^{1}H NMR spectrum of the crude product showed that the reaction was much cleaner than with **69**. Only the slightest traces of any other products could be observed. The purity of **122** was estimated to be >97%. The crude sample was submitted for NMR analysis without purification. The very close similarities between the ^{1}H and ^{13}C NMR spectra (see Tables 3 and 4) of **122** and those of **118a** suggest that they possess the same relative stereochemistry.

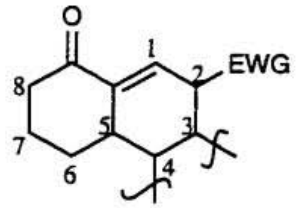
Scheme 41



71 **122**

[53] van Tamelen, R. E.; Zawacky, S. R. *Tetrahedron Lett.* **1985**, *26*, 2833-2836.

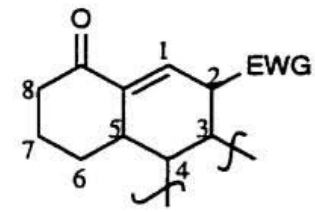
Table 3 ^{1}H NMR spectroscopic data of the adducts of deprotected dienes[a,b,c]



compound	H1	H2	H3	H4	H5	H6β	H6α	H8β	H8α
118a[d]	6.45 (dd, J = 4.4, 2.7)	3.64	3.64	1.97 (2H)	2.44	1.97	1.49	2.60	2.53
118c[d]	6.51 (t J = 2.9)								
122[d]	6.46 (dd, J = 4.3, 2.1)	3.68	3.64	2.01 (2H)	2.46	2.01	1.50	2.60	2.33
123a[e]	6.41 (dd, J = 5.1, 2.7	3.60		2.09	2.53	1.98	1.46	2.61	2.34
123b[d]	6.42 (dd, J = 5.1, 2.8)	3.67		2.06	2.53	1.97	1.44	2.60	2.32
126a[d,f]	6.41 (dd, J = 5.0, 2.8)								
126b[d,f]	6.37 (t, J = 2.7)								
127[e]	6.61 (dd, J = 4.9, 2.6)	3.56	3.11	2.38 + 2.04	2.55	2.38	1.55	2.65	2.38
128[d]	6.92 (t, J = 3.4)	3.55	3.50	2.47	2.08	1.69	1.41	2.60	2.33
141[d]	6.86 (dd, J = 5.1, 2.4)	5.24 (dd, J = 5.1, 3.1)			4.46	3.42	1.85	2.72	2.40
142[d] (*epi*)	6.67 (dd, J = 5.0, 2.3)								
143[d]	6.62 (d, J = 5.0)	5.22 (d, J = 5.0)				3.25	2.13	2.70	2.41
144[d] (*epi*)	6.48 (d, J = 5.5)	5.16 (d, J = 5.7)							

a. assignments were made with the aid of COSY, HET-CORR and APT experiments; b. chemical shifts were in ppmwhereas coupling constants were in Hz; c. center of multiplet; d. proposed structure; e. structure determined by X-ray methods; f. assignments were made without the aid of COSY, HET-CORR and APT.

Table 4 ^{13}C NMR spectroscopic data of the adducts of the deprotected dienes[a,b]



compound	C1	C2	C3	C4	C5	C6	C8
118a[c]	128.4	45.9	74.1		37.9	31.3	40.5
122[c]	128.4-128.1	46.0	74.5	31.9	38.0	31.3	40.6
123a[d]	128.4	49.9	99.1	33.8	36.2	30.6	40.4
123b[c]	128.4-128.0	49.9	99.1	33.9	36.2	30.6	40.5
127 (*endo*)[d]	130.4	48.5	41.0	30.3	39.2	31.3	40.6
128 (*exo*)[c]	130.7	45.8	38.3	34.7	33.0	34.7	40.4
141[c]	125.0	55.9			58.4	28.3	39.5
143[c]	122.7	55.8				33.9	39.7

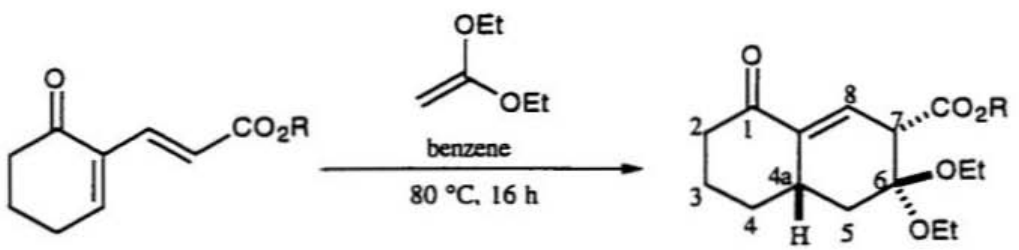
a. assignments were made with the aid of COSY, HET-CORR and APT experiments; b. chemical shifts were in ppm and coupling constants were in Hz; c. proposed structure; d. structure determined by X-ray methods.

Diene **69** was heated with 3.7 equivalents of 1,1-diethoxyethylene in benzene at reflux (Scheme 42) for 17 h. The ^1H NMR spectrum of the crude product indicated that a single product was formed, purification of which by flash chromatography provided **123a** in 81% yield. It was unequivocally assigned as the direct adduct **123a** by X-ray crystallographic methods (Figure 11). Again, complete regioselectivity was observed. Epimerization of the adduct occurred neither during the reaction nor upon chromatography. When reaction of diene **69** with 1.2 equivalents of 1,1-diethoxyethylene was carried out in a sealed tube at 80 °C for 17h, the ^1H NMR spectrum of the crude

product showed that only one product **123a** was generated but the diene had not been completely consumed. Purification of the crude product gave 67% of **123a** and 12% recovery of diene **69**. More dienophile was thus required for a higher yield.

Diene **71** was heated with 1.2 equivalents of 1,1-diethoxyethylene in benzene in a sealed tube at 80 °C for 17 h. Contrary to the previous result, the ^{1}H NMR spectrum of the crude product confirmed the entire consumption of the diene and the formation of a single product. Chromatographic purification provided the adduct in 86% yield. This may suggest that self-reaction of the diene competes with the IED Diels-Alder reaction. The bulkier ester in **71**, as compared to **69**, may serve to inhibit self-reaction. The adduct **123b** displayed spectroscopic properties very similar to those of **123a** (see Tables 3 and 4) and therefore it was assigned as the direct adduct **123b** by analogy.

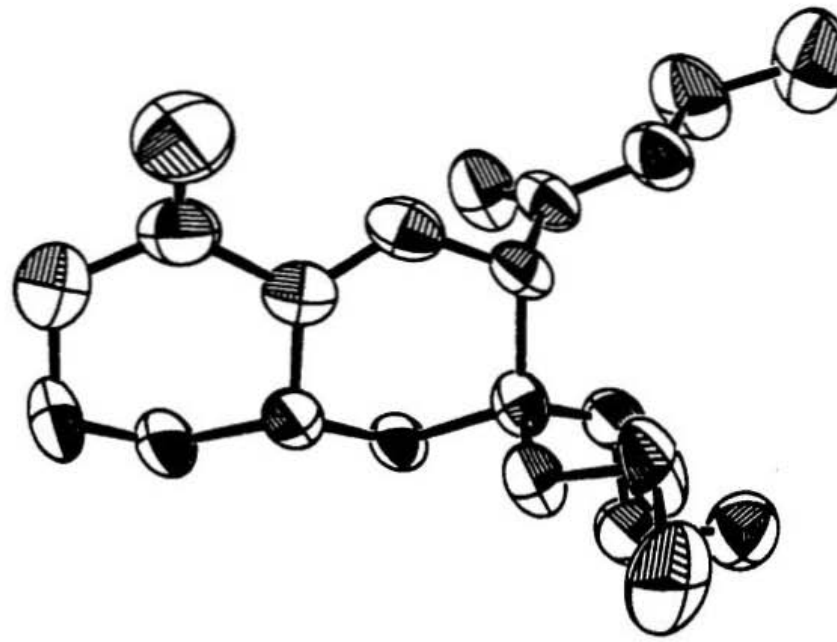
Scheme 42



69, R = Et
71, R = Bn

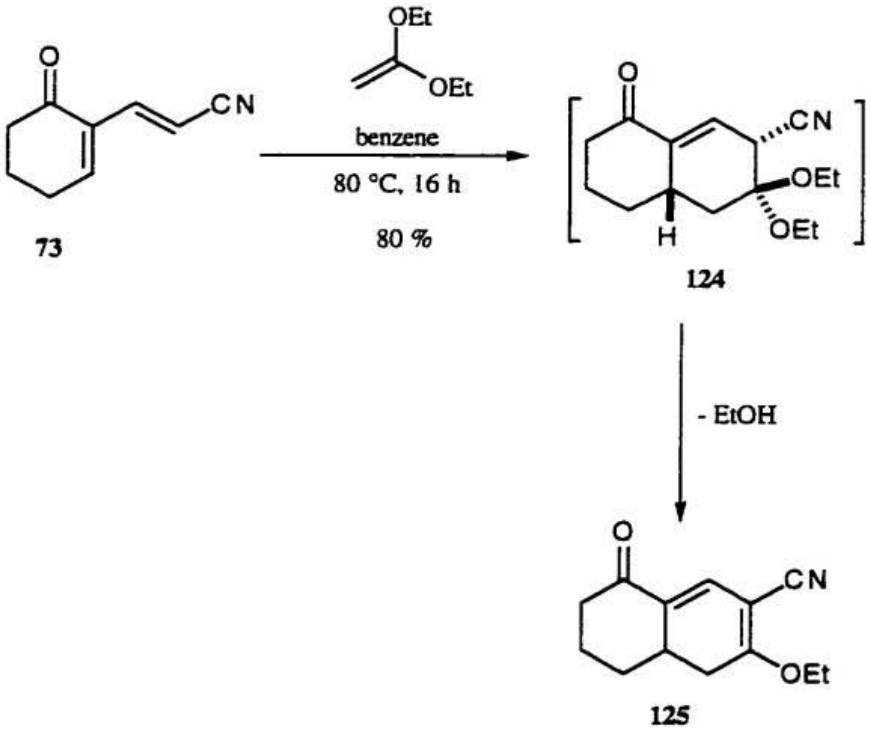
123a: R = Et
123b: R = Bn

Figure 11 X-ray crystal structure of adduct 123a



Compounds **123a** and **123b** (Scheme 42) contain a 6,6-fused ring system with two stereogenic centers and several functional groups including a conjugated ketone, a protected ketone and an ester group, which allow for many potential functional group transformations. It should therefore be possible to functionalize nearly every position of the molecule. For example, C-8 and C8a could be functionalized by Michael addition and/or tandem Michael addition. Substituents could conceivably be introduced at C2/C8a and C7 by deprotonation and alkylation. The same was true for C5 after deprotection of the C6 ketone. Functionalization of C-2, C-3, C-4, C-4a and C-5 could be achieved by employing substituted dienes in the Diels-Alder reaction or by introducing unsaturation at C2/C3 and/or C4a/C5. Adducts **123a**, **123b** and their analogs appear to be promising intermediates in organic synthesis.

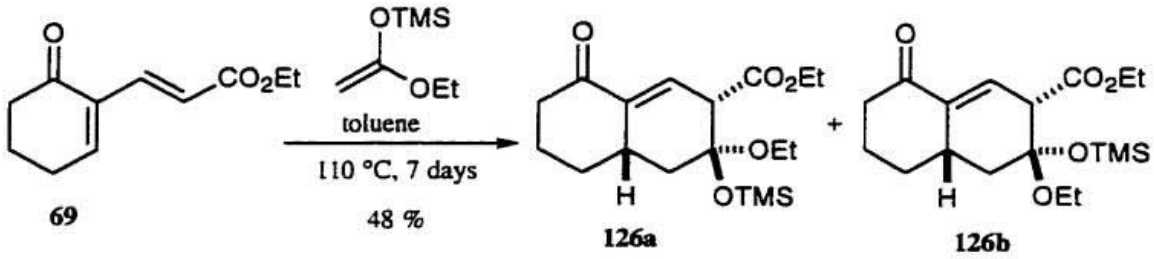
Scheme 43



Cycloaddition of diene **73** with 1,1-diethoxyethylene (Scheme 43) in refluxing benzene for 16 h yielded a new diene **125** in 80% isolated yield by the elimination of ethanol from the initially formed adduct **124**. The presence of **124** during the reaction was indicated by TLC analysis, but it had completely disappeared after 16 h. As in the case of **119**, the newly formed **125** contains electron withdrawing groups at the 1 and 3 positions, and its IED Diels-Alder chemistry will be investigated in the future. Bicyclo[2.2.2]octane derivatives related to **121** should be accessible using this starting material.

Two inseparable products were afforded in the reaction of diene **69** with 1-ethoxy-1-trimethylsilyloxyethylene in refluxing toluene (Scheme 44). The ratio of the two

Scheme 44



compounds was 50:50 based on the ^{1}H NMR spectrum of the crude product. One displayed a doublet of doublets at δ 6.41 (1H, J = 5.0, 2.8 Hz) while the other corresponded to a triplet at δ 6.37 (1H, J = 2.7 Hz) in the ^{1}H NMR spectrum of the mixture. However, the two products could be neither separated nor distinguished from each other. Purification of the crude mixture gave a 48% recovery of the 50:50 mixture. Since no epimerization was observed in the reaction of **69** with 1,1-diethoxyethylene, the products were assigned as **126a** and **126b**. The lack of any *endo/exo* selectivity was not surprising. This reaction was repeated with a 1:1.5 ratio of diene:dienophile in a sealed tube at 90 °C for 16.5 h and the ^{1}H NMR spectrum of the crude product indicated that the same 50:50 mixture was formed in near quantitative yield. This suggested that the products might have partly decomposed during flash chromatography.

Reaction of diene **69** with styrene in refluxing toluene for 3 days generated a mixture of two products (Scheme 45) in a ratio of 28 : 72 as determined from the ^{1}H NMR spectrum of the crude product. Upon chromatography, the minor product (R_f = 0.51, 20% EtOAc/petroleum ether) was isolated cleanly as a viscous oil, but the major product (R_f = 0.43, 20% EtOAc/petroleum ether) could not be isolated in pure form. The ^{1}H NMR spectrum of the major component was even more complicated than that of the crude product, and it included the initially formed major adduct and a new compound that was not the minor product. This new isomer may have resulted from the epimerization of

Scheme 45

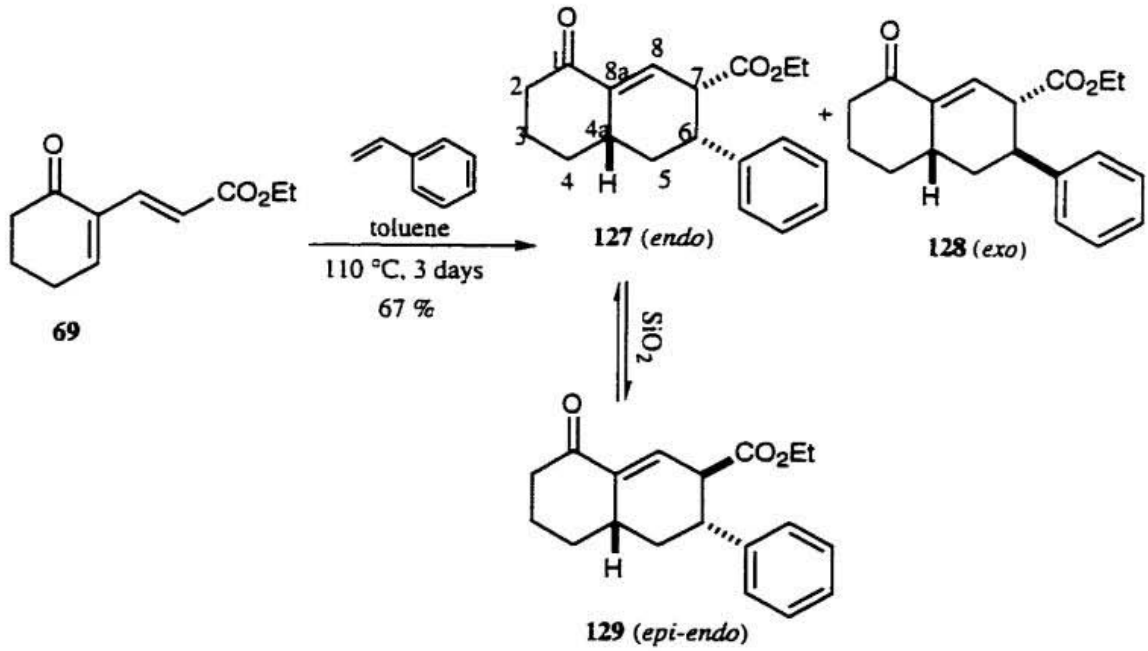
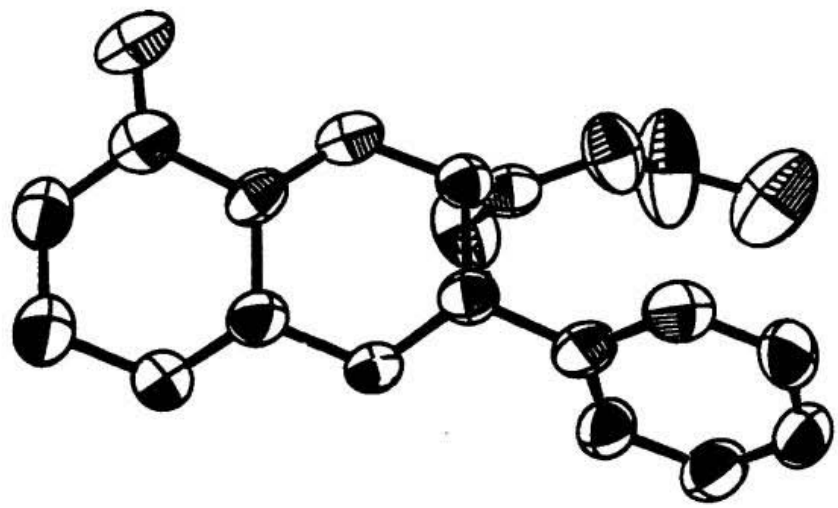


Figure 12 **X-ray crystal structure of adduct 127**



the ester group of the major product during chromatography. A clean sample of the major product was obtained by recrystallization of the crude reaction mixture. When the signal of C7-H at δ 3.56 was saturated, an NOE at δ 3.11 (C6-H, 7%) was observed. Saturation of the signal at 3.11 (C6-H) resulted in an NOE at δ 3.56 (C7-H, 8%). The 7-8% NOE's between C6-H and C7-H suggested that the major product must have come from the *endo* addition, which places the protons in question *cis* to one another. A *trans* arrangement of these two protons would almost certainly be diaxial and no NOE would be expected. An X-ray crystal structure determination (Figure 3) proved that it was the *endo* adduct **127**. In **127**, the phenyl group and the ester group were *cis* to each other and, therefore, epimerization would provide the more stable *trans* isomer **129**. These results were in agreement with the assignment of the *endo* structure to **118a**. The NMR spectrum of the minor product clearly indicated that the regiochemistry was the same as that of **127**. Since it displayed different spectroscopic properties from **129**, it had been assigned as **128**, which results from *exo* addition of styrene to **69**. The observation that **128** did not epimerize to **129** during chromatography was consistent with the *trans* relationship of the adjacent substituents. NOE experiments could not definitely assign the structure of the minor product.

Enamines have often been used as dienophiles in the IED Diels-Alder reaction.[29a,54] Thus, the reaction of **69** with the enamine derived from cyclohexanone and morpholine[55] was investigated. Using 1.5 equivalents of the enamine in refluxing benzene or acetonitrile for 3 h, a 37-45% yield of the hexahydrophenanthrene derivative **132** was obtained. The formation of **132** can be explained by cycloaddition of the two starting materials to gave adduct **130** followed by the elimination of morpholine to give

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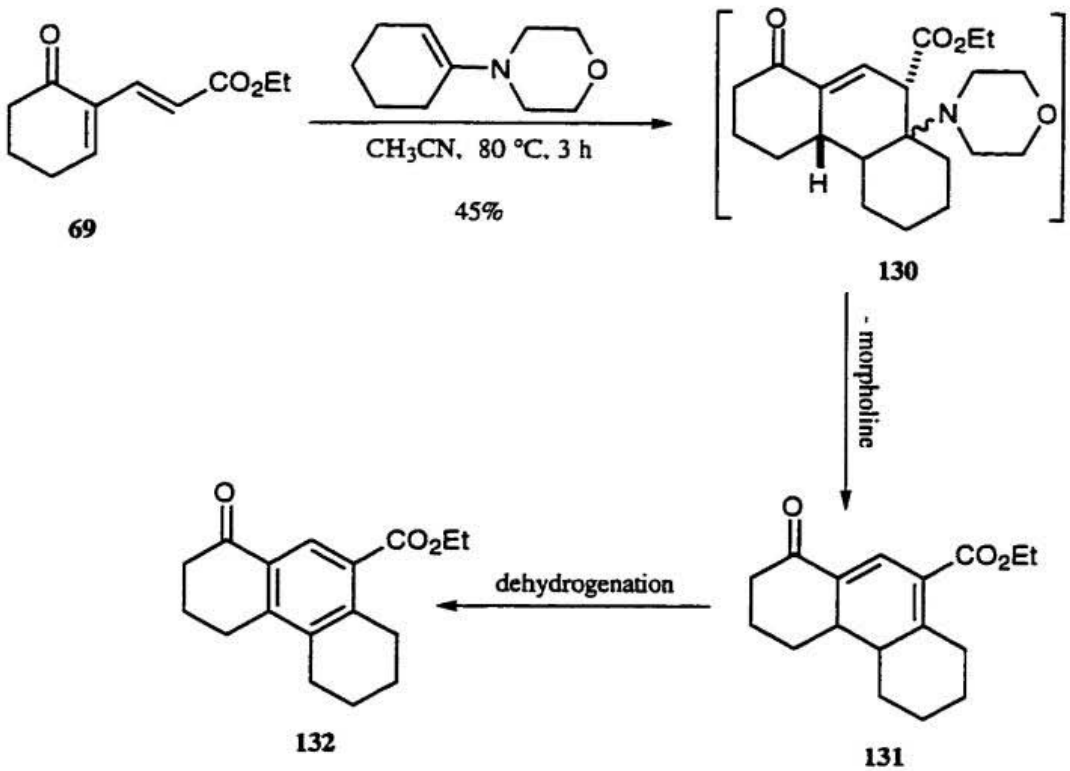
[54] (a)Danishefsky, S.; Cunningham, R. *J. Am. Chem. Soc.* **1965**, *30*, 3676-3678. (b) Berchtold, G. A.; Clabattoni, J.; Tunick, A. A. *J. Am. Chem. Soc.* **1965**, *30*, 3679-3682. (c) Abdel-Rahman, M. A. *Sohag Pure & Appl. Sci. Bull., Fac. Sci.*, Egypt, **1991**, *7*, 30-40.
[55] Hünig, S.; Lücke, E.; Brenninger, W. *Org. Synth., Coll. Vol. V*, **1973**, 808-809.

diene **131** and then loss of H_2 (Scheme 46). A Michael-type addition followed by a Mannich-type ring closure would also lead to **130**, but without knowing the relative

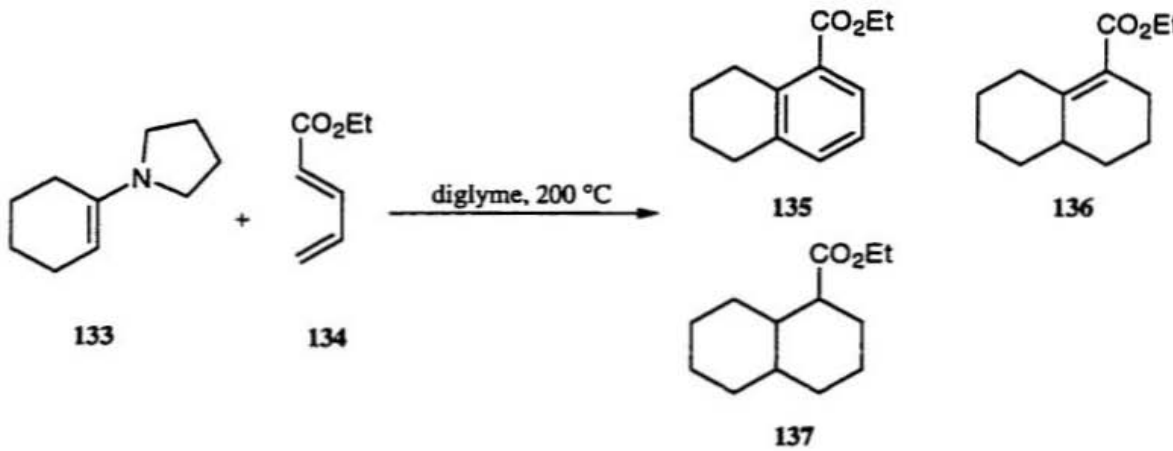
Scheme 46



stereochemistry of **130**, no comment can be made about which of these mechanisms was actually in effect. Monitoring the reaction by TLC revealed the presence of a compound more polar (R_f = 0.47, 40% EtOAc/hexane) than **132** (R_f = 0.51, 40% EtOAc/hexane), which may be **130**. The crude NMR spectrum was dominated by signals due to **132**, but a small signal at δ 6.57 (t, J = 2.8 Hz) was also observed. This could have been due to the olefinic proton of either **130** or **131**. However, column chromatography afforded only **132**. No other compounds were eluted.

That aromatization occurred in this reaction was somewhat puzzling, since no oxidizing agent was present (O_2 was excluded). If the spontaneous loss of molecular hydrogen can be discarded as unreasonable, then two other explanations were possible. The first of these was that oxidation of **131** occurs very rapidly when it exposed to air during work-up. On the other hand, disproportionation could take place. This would be consistent with the failure to achieve a yield in excess of 50%. However, no traces of the corresponding reduced products were observed, despite efforts to do so. These results were reminiscent of those reported by Danishefsky about the related reaction shown in Scheme 47.[54a]

Scheme 47

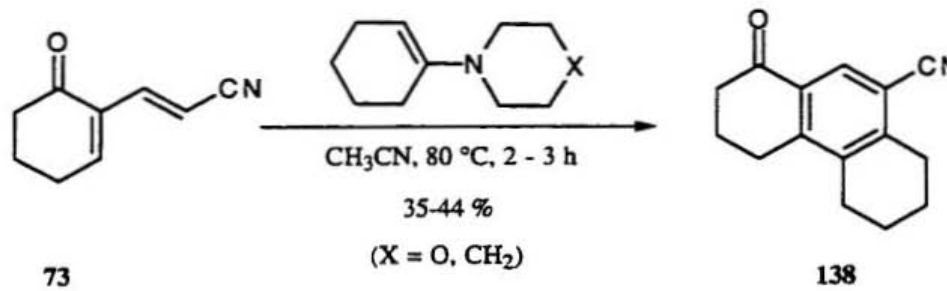


Reaction of enamine **133** with **134** in diglyme at 200 °C under pressure gave 58% of the aromatic ester **135**, contaminated by up to 7% of non-aromatic material, which was tentatively assigned as a mixture of **136** and **137**. He concluded that either **136** or **137** did not survive the reaction conditions "or, more likely, the aromatization also occurs by a process other than disproportionation." Under milder conditions (refluxing THF), intermediates corresponding to **130** and **136** were isolated. In a simultaneous report by Berchtold *et al.*,[54b] these products were the only ones described from the reactions of a

series of enamines with methyl *trans*-2,4-pentadienoate. The yields were highly variable (18-91%) and no mention was made of any aromatized products. That elimination of R_2NH from **130** should occur more readily than in the systems of Danishefsky and Berchtold seems reasonable owing to the greater acidity of the proton α to the ester group. In any event, the circumstances surrounding the loss of H_2 remain unclear.

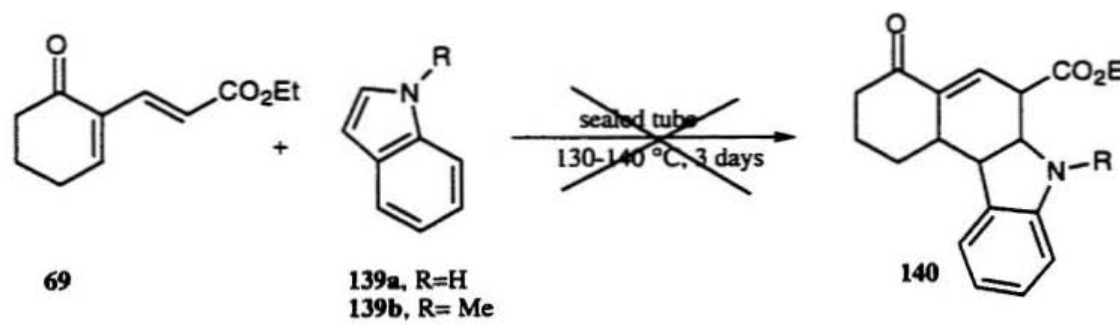
Diene **73** behaved in a similar fashion to **69**. Its reactions with 4-(1-cyclohexenyl)morpholine and 1-(cyclohexenyl)piperidine afforded 35-44% of compound **138** (Scheme 48).

Scheme 48



73 **138**

Scheme 49

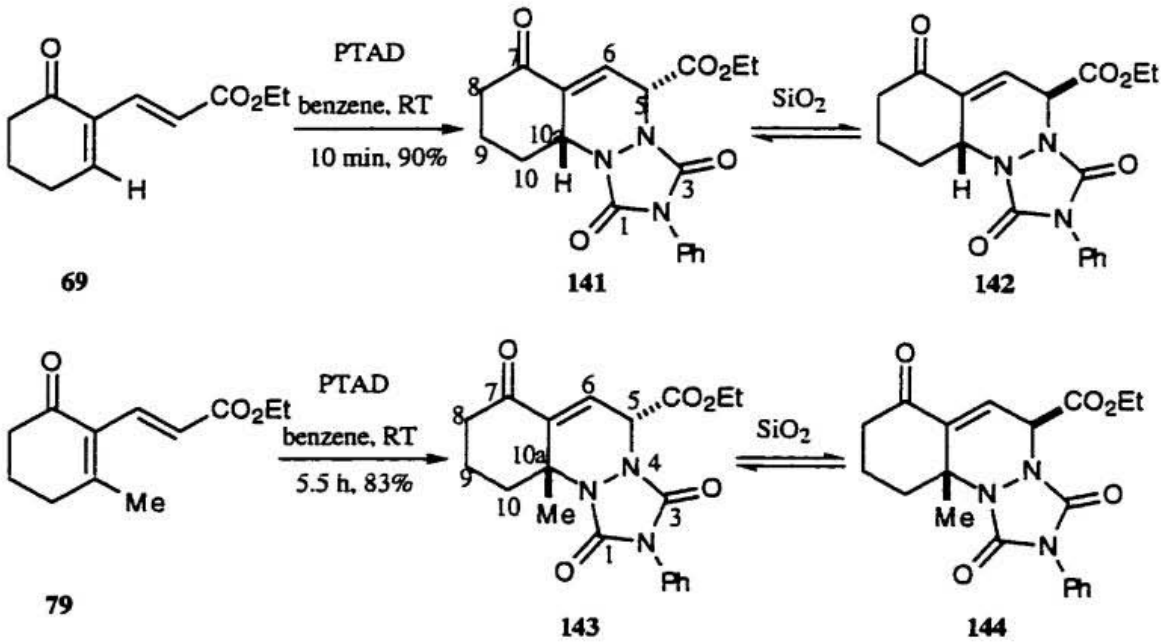


69 **139a**, R=H
139b, R= Me **140**

Somewhat surprisingly, treatment of the deprotected diene **69** with indole **139a** or 1-methylindole **139b** (Scheme 49) in a sealed tube at 130-140 °C for 3 days did not lead significant consumption of the starting material. No adducts of their follow-on products could be identified.

For completeness, the reactivity of the deprotected dienes towards electron deficient dienophiles was investigated. Dienes **69** and **79** both underwent cycloaddition with PTAD (Scheme 50) at room temperature. The crude ^{1}H NMR spectrum of the

Scheme 50

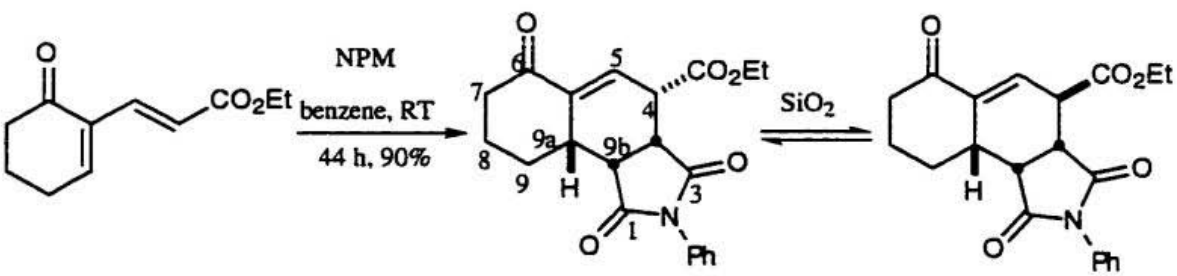


reaction of **69** with PTAD showed that a single product was produced, but upon chromatography a 67:33 mixture of the initially formed adduct **141** and the epimerized isomer **142** was obtained in a 95% combined isolated yield. No attempt was made to establish whether this was an equilibrium ratio. Recrystallization of the crude product from EtOAc/hexane gave **141** in 90% yield. Confirmation of this assignment of **141** will come from a pending X-ray structure determination.

Reaction of diene **79** with PTAD also provided a single product, assigned as **143** upon the examination of the ^{1}H NMR spectrum of the crude product and comparison to related examples. The presence of the extra methyl group resulted in a considerable reduction of the rate of the reaction (5.5 h required compared to 10 min for **69**). In this case, purification of the crude product by chromatography provided a 93:7 mixture of the initially formed adduct and, presumably, the epimerized product **144**. A 2% NOE was observed between the C10a-CH_3 and C5-H of the initially formed adduct, which suggested that the methyl group on C10a and the proton on C5 are *cis* to each other as in **141**. Crystals suitable for X-ray structure determination were obtained from this mixture and have been submitted for analysis.

One attempt was made to react **69** with NPM in refluxing toluene (Scheme 51). One major product of about 90% purity was obtained in 77% yield after chromatography. Based on the previous results, this may be either the *endo* adduct **145** or its epimer **146**, but conclusive assignment will have to wait for a re-investigation of this reaction.

Scheme 51



69 **145** **146**

The use of Lewis acid catalysts to accelerate the rate of the Diels-Alder reactions is well documented.[55] Cursory attempts to do so in the reaction of **69** with ethyl vinyl

[55] Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.* **1993**, *93*, 741-761.

ether using $ZnBr_2$ and $TiCl_4$ were made. However, addition of the Lewis acids resulted in rapid decomposition of the diene.

4.2 Future work

The deprotected dienes **69**, **71** and **73** undergo inverse electron demand Diels-Alder cycloaddition with alkyl vinyl ethers, ketene acetals, styrenes and enamines to provide multifunctional adducts with excellent regioselectivity. The resultant adducts were not only different from those resulting from the cycloaddition of derivatives of Danishefsky's diene but also offer the potential to be elaborated in a number of ways. This methodology promises access to a wide range of valuable synthetic intermediates. Future work to develop this methodology includes completion of the study of the basic methodology, chiral induction into the cycloaddition, further fuctionalization of the adducts and application of the methodology in total synthesis of biologically important compounds.

4.2.1 Development of the basic methodology

Besides the modifications to the synthesis of dienes discussed earlier (see Ch 2, section 2.3), the scope and limitations of the basic methodology should be further probed through the use of a wider variety of dienophiles. Dienophiles such as alkyl vinyl sulfides,[56] ketene O,S-acetals, ketene S,S-acetals, ketene O,N-acetals[57] and ynamines are prime candidates for future investigations. These dienophiles have been shown to react with azadienes.[6] The incorporation of other electron withdrawing groups into the diene unit also merits further study. Other ring sizes and other modes of annulating the reactive

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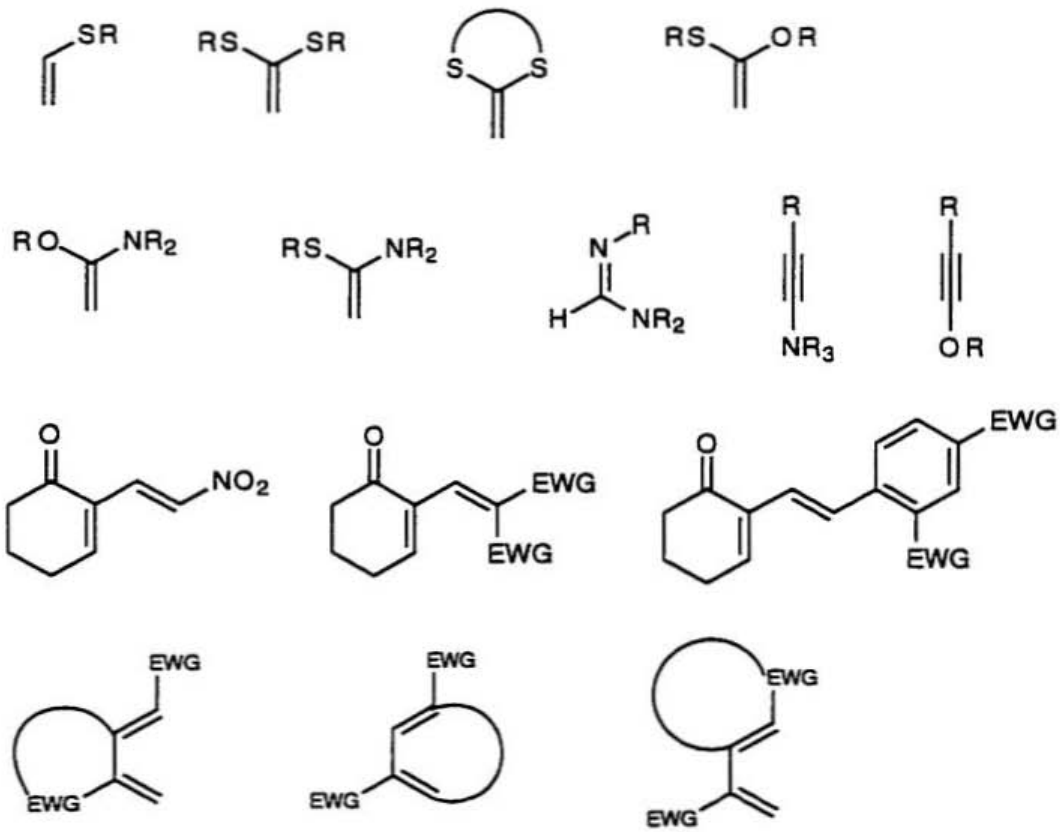
[56] (a) Kaya, R.; Beller, N. R. *J. Org. Chem.* **1981**, *46*, 196-197. (b) Kaya, R.; Beller, N. R. *Synthesis*, **1981**, *10*, 814-816.
[57] Bredereck, H.; Effenberger, F.; Beyerlin, H. P. *Chem. Ber.* **1964**, *97*, 3081-3091.

diene unit also present attractive targets. Representative examples are shown in Figure 13.

Figure 13 Representative systems of dienes and dienophiles



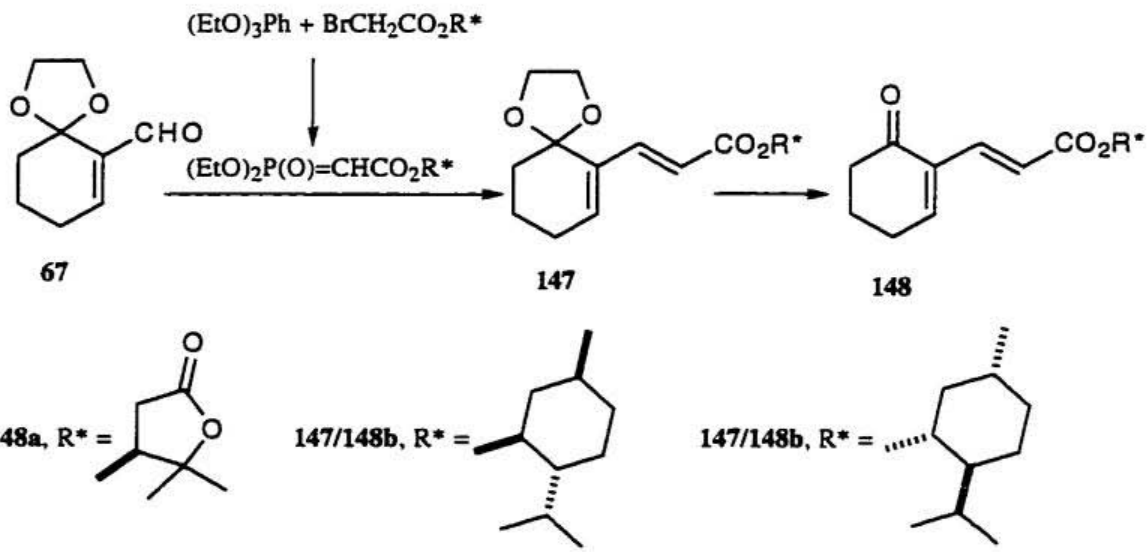
The cycloaddition of indole or its derivatives with the deprotected dienes may ultimately provide an elegant route to indole-based alkaloids. In spite of the negative initial results, cycloadditions employing high pressure and/or Lewis acid catalysts have not been investigated fully to date and should be included in the future work. Lewis acid catalysis in general, particularly by the soft lanthanides, will receive attention.

4.2.2. Enantioselective inverse electron demand Diels-Alder reactions

Chiral induction into the cycloadditions of the deprotected dienes would be a distinct advantage from a synthetic point of view. Enantioselectivity could be achieved by incorporating a chiral auxiliary into one or more of the diene, the dienophile and a Lewis acid catalyst.

Chiral auxiliaries such as pantolactone[22] and menthol could be easily incorporated into the diene systems (Scheme 52). It remains to be seen if the chiral centers will be close enough to exert good control in the cycloaddition.

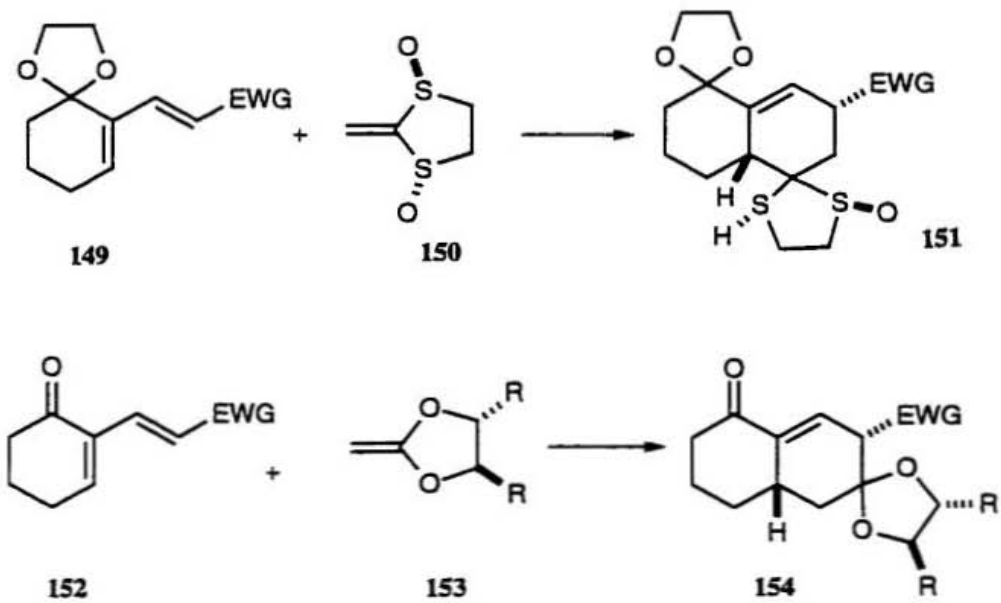
Scheme 52



The combination of chiral 2-pyrone derivatives and shift reagents, chiral or not, had given excellent enantioselectivity.[22] Thus the use of a chiral diene and a shift reagent such as (+)- or (-)-Eu(hfc)$_3$ and Eu(fod)$_3$ may result in good stereoselectivity in our systems. A chiral catalyst on its own (e.g. the tartrate-derived TADDOL-complexed titanium (IV) **36**,[23] (*R*)-(+)-1,1'-bi-2-naphthol-titanium complex **38**[24] and (*R*)-(+)-or (*R*)-(-)-1,1'-bi-2-naphthol-Yb(OTf)$_3$ complex **42**[26] will also be investigated.

The use of the enantiomerically pure dienophiles may also prove to be effective. The chiral sulfoxide **150**[58] was recently reported to give high ee's in normal Diels-Alder reactions and would be expected to do so with protected dienes **149** (Scheme 15). Ketene acetals **153** derived from enantiomerically pure 1,2-diol would appear to be suitable reaction partners for deprotected dienes **152**.

Scheme 53



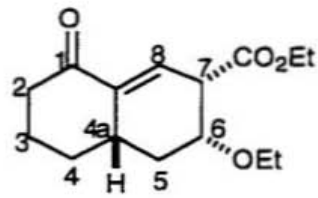
149 **150** **151**

152 **153** **154**

[58] Aggarwal, V. K.; Drabowicz, J.; Grainger, R. S.; Gültekin, Z.; Lightowler, M.; Spargo, P. L.; *J. Org. Chem.* **1995**, *60*, 4962-4963.

Experimental.*

(4aα,6α,7α)-7-Carboethoxy-6-ethoxy-3,4,4a,5,6,7-hexahydro-1(2*H*)-naphthalenone (118a)



A solution of diene **69** (499 mg, 2.57 mmol), and ethyl vinyl ether (2.5 mL, 26 mmol) in benzene (6.0 mL) was heated at 80 °C in a sealed tube (oil bath) for 24 h. Removal of the solvent under reduced pressure provided the crude product as a colorless oil (660 mg, 2.48 mmol, 96%). The ^{1}H NMR spectrum of the crude product indicated that **118a** was the predominant product. The crude product was submitted for the following spectroscopic analyses: ^{1}H NMR δ 6.45 (dd, 1H, J = 4.4, 2.7 Hz, C8-H), 4.20-4.07 (AB system, 2H), 3.70-3.57 (m, 3H), 3.48 (m, 1H), 2.60 (m, 1H), 2.53 (m, 1H), 2.44 (m, 1H), 2.31 (m, 1H), 2.05-1.89 (m, 4H), 1.72 (m, 1H), 1.49 (m, 1H), 1.24 (t, 3H, J = 7.1 Hz), 1.14 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ 200.8 (0, -CO-), 170.3 (0, -CO_2-), 142.3 (0), 128.4 (1, C8), 74.4 (1, C6), 64.2 (2), 60.8 (0), 45.9 (1, C7), 40.5 (2, C2), 37.9 (1, C4a), 31.9 (2), 31.3 (2, C4), 22.8 (2), 15.2 (3), 14.1 (3); IR (film) υ 2975 (s), 2935 (s), 2868 (s), 1731 (s), 1692 (s) cm^{-1}; MS *m/z* (%) ; Anal. calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.32. found: C, 67.80; H, 8.39.

(2*R,4a*R**,8a*S**,9*R**)-3-Carboethoxy-9-ethoxy-1,6,7,8a-tetrahydro-2*H*-2,4a-ethanonaphthalen-5(8*H*)-one (121).#**

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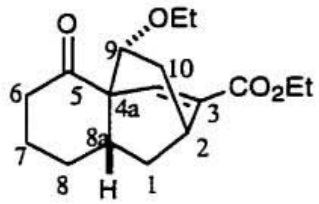
* For general procedures, see Chapter 2, section 2.4.

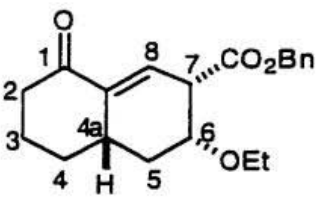
The ^{1}H and ^{13}C data were tentatively reported due to the absence of ^{1}H,^{1}H-COSY, HETCOR and APT.



121

A mixture of diene **69** (100 mg, 0.51 mmol) and ethyl vinyl ether (187 mg, 2.6 mmol) was refluxed in toluene (10 mL) for 14 days. A fresh portion (2 mL) of ethyl vinyl ether was added on the 4th and 7th days of the reaction. Chromatography of the crude product gave **121** as a colorless oil (32 mg, 0.11 mmol, 21%): ^{1}H NMR δ 7.21 (s, 1H), 4.23 (q, 2H, J = 7.1 Hz), 3.85 (m, 1H), 3.56-3.44 (m, 2H), 3.26 (m, 1H), 2.80 (m, 1H), 2.38 (m, 1H), 2.01 (m, 1H), 1.84 (m, 1H), 1.72-1.54 (m, 2H), 1.33 (t, 3H, J = 7.1 Hz), 1.09 (t, 3H, J = 7.0 Hz); ^{13}C δ 211.8, 164.5, 139.7, 137.2, 76.9, 64.5, 60.6, 42.9, 40.6, 36.1, 33.6, 32.3, 29.7, 28.2, 15.5, 14.2; MS *m/z* (%) 292 (4), 246 (27), 219 (41), 191 (23), 177 (29), 176 (100), 91 (29), 29 (33); HRMS calcd for $C_{17}H_{24}O_4$ 292.1673, found 292.1667.

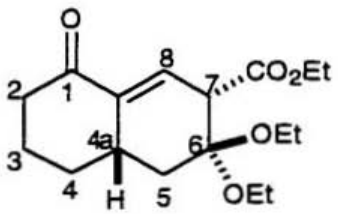
(4aα,6α,7α)-7-Carbobenzyloxy-6-ethoxy-3,4,4a,5,6,7-hexahydro-1(2*H*)-naphthalenone (122)



A solution of diene **71** (601 mg, 2.34 mmol) and ethyl vinyl ether (1.9 mL, 23 mmol) and benzene (6.0 mL) was heated in a sealed tube at 90 °C for 24 h. Removal of the solvent under reduced pressure provided 733 mg (2.24 mmol, 95%) of **122** as a colorless oil: ^{1}H NMR δ 7.36-7.30 (m, 5H), 6.46 (dd, 1H, J = 4.3, 2.07 Hz, C8-H), 5.19 (A of AB system, 1H), 5.13 (B of AB system, 1H), 3.70-3.47 (m, 4H), 2.60 (m, 1H), 2.46 (m, 1H), 2.33 (m,

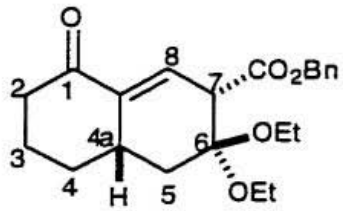
1H), 2.07-1.94 (m, 4H), 1.75 (m, 1H), 1.50 (m, 1H), 1.14-1.08 (m, 3H); ^{13}C NMR δ 200.8 (0, -CO-), 170.3 (0, -CO_2-), 142.5 (0), 135.7 (0), 128.4 (1), 128.2 (1), 128.1 (1), 74.5 (1, C6), 66.7 (2), 64.4 (2), 46.0 (1, C7), 40.6 (2, C2), 38.0 (1, C4a), 31.9 (2, C5), 31.3 (2, C4), 22.9 (2), 15.2 (3); IR (film) υ 2936 (s), 2867 (s), 1731 (s), 1691 (s), 1624 (s), 1454 (s) cm^{-1}; MS *m/z* (%) 328 (M^+, 0.4), 282 (1.5), 237 (2), 175 (4), 91 (100), 65 (6); Anal. calcd for $C_{20}H_{24}O_4$ 328.1673: C, 72.59; H: 7.05. found: C, 72.63; H, 7.08.

(4aα,7α)-7-Carbobenzyloxy-6,6-diethoxy-3,4,4a,5,7-pentahydro-1(2*H*)-naphthalenone (123a)



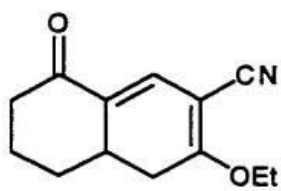
A solution of diene **69** (121 mg, 0.62 mmol), 1,1-diethoxyethylene (268 mg, 2.31 mmol) and benzene (5.0 mL) was refluxed for 17 h. Removal of the solvent and purification of the residue by flash chromatography (silica, 20 % ethyl acetate/hexane) afforded **123a** (154 mg, 0.50 mmol, 81%) as colorless crystals: mp 58-60 °C; ^{1}H NMR δ 6.41 (dd, 1H, *J* =5.1, 2.7 Hz, C8-H), 4.15 (q, 2H, *J* =7.1 Hz), 3.61-3.42 (m, 5H), 2.64-2.53 (m, 2H), 2.34 (m, 1H), 2.10-1.92 (m, 4H), 1.80 (m, 1H), 1.46 (m, 1H), 1.27 (t, 3H, *J* = 7.1 Hz), 1.16-1.11 (m, 6H); ^{13}C NMR δ 200.1 (0, -CO-), 169.8 (0, -CO_2), 141.4 (0), 128.4 (1, C8), 99.1 (0, C6), 61.0 (2), 55.9 (2), 55.3 (2), 49.9 (1, C7), 40.4 (2, C2), 36.2 (1, C4a), 33.8 (2, C5), 30.6 (2, C4), 22.7 (2), 15.0 (3, 2C), 14.0 (2); IR (CCl_4) υ 2979 (m), 2932 (m), 1738 (s), 1551 (s) cm^{-1}; MS *m/z* (%) 310 (M^+, 5), 265 (19), 191 (37), 149 (23), 116 (100), 89 (40), 43 (32), 29 (31); HRMS calcd for $C_{17}H_{26}O_5$ 310.1779, found 310.1792.

(4aα,7α)-7-Carboethoxy-6,6-diethoxy-3,4,4a,5,7-pentahydro-1(2*H*)-naphthalenone (123b)



A mixture of **71** (100 mg, 0.39 mmol), 1,1-diethoxyethylene (54 mg, 0.47 mmol) and benzene (2.0 mL) was heated at 80 °C for 17 h. Removal of the solvent and purification of the residue by chromatography (silica, 30% ethyl acetate/petroleum ether) gave **123b** (125 mg, 0.34 mmol, 86%) as a colorless liquid: ^{1}H NMR δ 7.36-7.31 (m, 5H), 6.42 (dd, 1H, J = 5.1, 2.8 Hz, C8-H), 5.15 (1H, A of AB system), 5.12 (1H, B of AB system), 3.67 (m, 1H, C7-H), 3.55-3.40 (m, 4H), 2.65-2.48 (m, 2H), 2.32 (m, 1H,), 2.13-1.89 (m, 4H), 1.78 (m, 1H), 1.44 (m, 1H), 1.12 (t, 3H, J = 7.1 Hz), 1.05 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ 200.2 (0, -CO-), 169.7 (0, -CO_2-), 141.6 (0), 135.6 (0), 128.4 (1), 128.1 (1), 128.0 (1), 99.1 (0, C6), 66.8 (2), 55.9 (2), 55.4 (2), 49.9 (1, C7), 40.5 (2, C2), 36.2 (1, C4a), 33.9 (2, C5), 30.6 (2, C4), 22.7 (2), 15.0 (3); IR υ 1728 (s), 1692 (s), 1626 (s) cm^{-1}; MS *m/z* (%) 326 (M^+-46, 0.9), 191 (7), 116 (40), 91 (100), 89 (16), 65 (11), 43 (14), 29 (17); Anal. calcd for $C_{22}H_{28}O_5$: C, 70.94; H: 7.58. found: C, 70.90; H, 7.60.

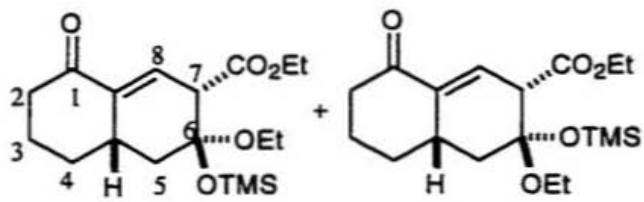
7-Cyano-6-ethoxy-3,4,4a,5-tetrahydro-1(2*H*)-naphthalenone (125)



125

A mixture of deprotected diene **69** (81 mg, 0.55 mmol), 1,1-diethoxyethylene (175 mg, 1.51 mmol) and benzene (6.0 mL) was refluxed for 16 h. Removal of the solvent and flash chromatography (silica, 40 % ethyl acetate/hexane) of the crude product gave **125** as light yellow crystals (96 mg, 0.44 mmol, 80%): mp 132-135 °C; ^{1}H NMR δ 7.10 (d, 1H, *J* =3.0 Hz, C8-H), 4.47-4.35 (m, 2H), 2.85 (m, 1H), 2.65-2.53 (m, 2H), 2.37-2.23 (m, 2H), 2.10-2.00 (m, 2H), 1.70 (m, 1H), 1.42 (t, 3H, *J* =7.0 Hz); ^{13}C NMR δ 196.2 (0, -CO-), 174.4 (0, -CO_2-), 131.4 (1), 128.2 (0), 116.8 (0), 85.1 (0), 66.7 (2), 39.0 (2), 34.2 (1), 34.1 (2), 29.7 (2), 21.3 (2), 15.0 (3); IR υ 2216 (m), 1680 (s), 1548 (s) cm^{-1}; MS *m/z* (%) 217 (M^+, 45), 189 (21), 146 (57), 145 (100), 133 (89), 132 (36), 77 (21), 28 (80), 27 (31); HRMS calcd for $C_{13}H_{15}NO_2$ 217.1102, found 217.1105.

(4aα,6α,7α)-7-Carboethoxy-6-ethoxy-3,4,4a,5,7-pentahydro-6-trimethylsilyloxy-1(2*H*)-naphthalenone (126a) and (4aα,6β,7α)-7-carboethoxy-6-ethoxy-3,4,4a,5,7-pentahydro-6-trimethylsilyloxy-1(2*H*)-naphthalenone (126b).

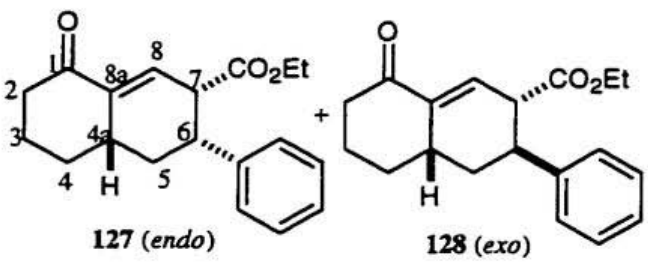


126a **126b**

A mixture of **69** (252 mg, 1.30 mmol), 1-ethoxy-1-trimethylsilyloxyethylene (1.039 g, 6.48 mmol) and toluene (10 mL) was heated at reflux for 7 days. Removal of the solvent and excess dienophile under reduced pressure provided a 50 : 50 mixture of two inseparable products as a light yellow oil (391 mg, 1.11 mmol, 85%). Column chromatography (silica, 20% ethyl acetate/hexane) could not separate the two products but gave a 48% (221 mg, 0.62 mmol) recovery of the mixture. The ratio of the two products remained the same after chromatography. The mixture was submitted for NMR

experiments. ^{1}H-NMR δ 6.41 (dd, 1H, J = 5.0, 2.9 Hz), 6.37 (dd, 1H, J = 4.8, 2.7 Hz), 1.27 (t, 3H, J = 7.1 Hz), 1.24 (t, 3H, J = 7.0 Hz), 1.11 (t, 3H, J = 7.1 Hz), 1.10 (t, 3H, J = 7.0 Hz), 0.15 (s, 9H), 0.14 (s, 9H); ^{13}C NMR δ 200.5, 200.3, 170.3, 170.1, 141.5, 141.3, 128.5, 128.5, 98.6, 98.2, 60.9, 56.3, 55.7, 54.4, 50.7, 40.6, 38.6, 36.8, 36.7, 36.4, 30.7, 30.6, 22.8, 22.8, 15.2, 15.2, 14.2, 14.1; IR (film) υ 2978 (m), 2933 (m), 1737 (s), 1696 (s), 1629 (s) cm^{-1}; MS *m/z* (%) 354 (M^+, 5), 267 (42), 149 (30), 117 (92), 116 (48), 75 (47), 73 (100); HRMS calcd for $C_{18}H_{30}O_5Si$ 354.1861, found 354.1857.

(4aα,6α,7α)-7-Carboethoxy-3,4,4a,5,6,7-hexahydro-6-phenyl-1(2*H*)-naphthalenone (127) and (4aα,6β,7α)-7-carboethoxy-3,4,4a,5,6,7-hexahydro-6-phenyl-1(2*H*)-naphthalenone (128)



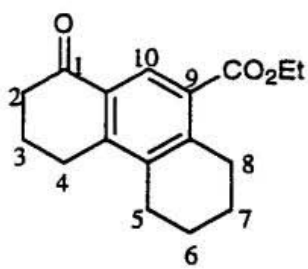
127 (*endo*) **128** (*exo*)

A solution of diene **69** (459 mg, 2.36 mmol) and styrene (1.4 mL, 11.8 mmol) in toluene (10 mL) was heated at reflux for 3 days. Removal of the solvent gave the crude product as a viscous yellow oil. ^{1}H NMR analysis of the crude product indicated that adducts **127** and **128** were produced in a ratio of 72:28. Chromatography (silica, 40 % ethyl acetate) provided **128** (119 mg, 0.40 mmol, 17%) and a mixture of **127** with a slight amount of **128** (399 mg). A pure sample of **127** was obtained by recrystallization of the mixture from ethyl acetate/hexane/chloroform (354 mg, 1.19 mmol, 50%): mp 102-104 °C; ^{1}H NMR δ 7.34-7.18 (m, 5H), 6.61 (dd, 1H, J =4.9, 2.6 Hz, C8-H), 3.86-3.67 (m, 2H), 3.56 (m, 1H, C7-H), 3.11 (m, 1H, C6-H), 2.70-2.50 (m, 2H), 2.46-2.31 (m, 2H), 2.13-1.96 (m, 3H), 1.80 (m, 1H), 1.55 (m, 1H), 0.87 (t, 3H, J =7.1 Hz); NOE data ($CDCl_3$) δ 3.56

(3.11, 7%), 3.11 (3.56, 8%); ^{13}C NMR δ 201.0 (0, CO), 171.0 (0, -CO_2-), 142.7 (0), 141.9 (0), 130.4 (1, C8), 128.2 (1), 127.4 (1), 126.7 (1), 60.5 (2), 48.5 (1, C7), 41.0 (1, C6), 40.6 (2, C2), 39.2 (1, C4a), 31.3 (2, C4), 30.3 (2, C5), 22.7 (2, C3), 13.7 (3); IR υ 1551 (s), 1249 (s) cm^{-1}; MS *m/z* (%) 298 (2, M$^+$), 252 (15), 225 (23), 104(26), 84 (100), 47 (20), 29 (20), 28 (58), Anal. calcd for $C_{19}H_{22}O_3$: C, 76.48; H: 7.43. found: C, 76.60; H, 7.49.

For **128**: ^{1}H NMR δ 7.32-7.10 (m, 5H), 6.92 (t, 1H, *J* =3.4 Hz, C8-H), 4.22-4.07 (m, 2H), 3.58-3.44 (m, 2H, C6-H+ C7-H), 2.60 (m, 1H), 2.33 (m, 1H), 2.05-1.60 (m, 6H, C4a-H), 1.41 (m, 1H), 1.24 (t, 3H, *J* =7.1 Hz); ^{13}C NMR δ 200.5 (0, CO), 172.3 (0, CO_2-), 143.6 (0), 142.3 (0), 130.7 (1, C8), 128.5 (1), 127.1 (1), 126.4 (1), 61.2 (2), 45.8 (1, C7), 40.4 (2, C2), 38.3 (1, C6), 34.7 (2, C5), 33.0 (1, C4a), 30.5 (2, C4), 22.4 (2, C3), 14.1 (3); IR (film) υ 2981 (s), 2934 (s), 1735 (s), 1693 (s) 1550 (s) cm^{-1}; MS *m/z* (%) 298 (11, M$^+$), 252 (18), 225 (65), 104 (100), 91 (33), 86(27), 84 (43); Anal. calcd for $C_{19}H_{22}O_3$: C, 76.48; H: 7.43. found: C, 76.54; H, 7.50.

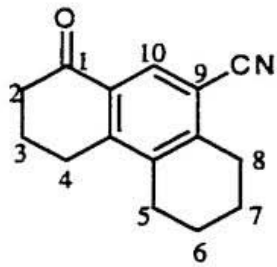
9-Carboethoxy-3,4,5,6,7,8-hexahydro-1(2*H*)-phenanthrenone (132)



A solution of diene **69** (190 mg, 0.98 mmol), 4-(1-cyclohexenyl)-morpholine (257 mg, 1.46 mmol) and a few crystals of hydroquinone in acetonitrile (20 mL) was heated at reflux for 3 h. Removal of the solvent and chromatography of the crude product (15% ethyl acetate/hexane) provided **132** as light yellow crystals (119 mg, 0.45 mmol, 45%): mp 70-72 °C; ^{1}H NMR δ 8.35 (s, 1H), 4.34 (t, *J* = 7.2 Hz), 3.10 (t, 1H, *J* = 6.1 Hz), 2.83

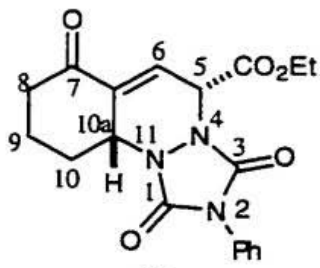
(t, 1H, J = 6.1 Hz), 2.70-2.61 (m, 2H), 2.14 (m, 1H), 1.88-1.72 (m, 2H), 1.38 (t, 3H, J = 7.2); ^{13}C NMR δ 197.9 (0), 167.6 (0), 146.1 (0), 143.7 (0), 136.5 (0), 130.0 (0), 129.4 (0), 126.3 (1), 60.9 (2), 38.3 (2), 28.8 (2), 27.3 (2), 26.3 (2), 22.4 (2), 22.3 (2), 22.2 (2), 14.3 (3); IR (CCl_4) υ 2941 (s), 2867 (s), 1720 (s), 1692 (s), 1551 (s) cm^{-1}; MS *m/z* (%) 272 (M^+, 48), 243 (64), 226 (100), 199 (28), 143 (36), 141 (35), 129 (35), 128 (46), 115 (42), 29 (26); Anal. calcd for $C_{17}H_{20}O_3$: C, 74.97; H: 7.40. found: C, 74.95; H, 7.49.

9-Cyano-3,4,5,6,7,8-hexahydro-1(2*H*)-phenanthrenone (138)

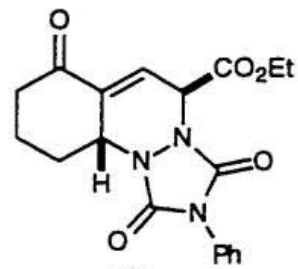


A solution of diene **73** (57 mg, 0.38 mmol), 4-(1-cyclohexenyl)-morpholine (150 mg, 0.90 mmol) and acetonitrile (8.0 mL) was refluxed at 80 °C for 3.5 h. Removal of the solvent followed by chromatography (20% EtOAc/hexane) gave **138** as a yellow solid (38 mg, 0.17 mmol, 44%) in 95% purity estimated by its ^{1}H NMR spectrum: mp 147-150 °C; ^{1}H NMR δ 8.18 (s, 1H), 2.99 (t, 2H, J = 5.5 Hz), 2.85 (t, 2H, J = 6.1 Hz), 2.69-2.62 (m, 4H), 2.20-2.11 (m, 2H), 1.91-1.81 (m, 4H); ^{13}C NMR δ 196.6 (0), 147.5 (, 145.0, 137.0, 130.8, 117.5, 129.2, 61.2, 38.0, 29.1, 26.7, 26.3, 22.3, 22.0, 21.5; IR (CH_2Cl_2) υ 2685 (s), 2305 (s), 2226 (s), 1688 (s), 1691 (s) cm^{-1}; MS *m/z* (%) 225 (M^+, 100), 210 (21), 197 (85), 169 (57), 154 (40), 55 (16), 28 (39); Anal. calcd for $C_{15}H_{15}NO$: C, 79.97; H: 6.71; N: 6.22. found: C, 79.99; H, 6.76.

(5α,10aα)-5-Carboethoxy-2-phenyl-5,8,9,10,10a-pentahydro-[1*H*][1,2,4]triazolo[1,2-*a*]cinnoline-1,3,7-(2*H*)-trione (141) and (5α,10aβ)-6-Carboethoxy-2-phenyl-5,8,9,10,10a-pentahydro-[1*H*][1,2,4]triazolo[1,2-*a*]cinnoline-1,3,7-(2*H*)-trione (142)



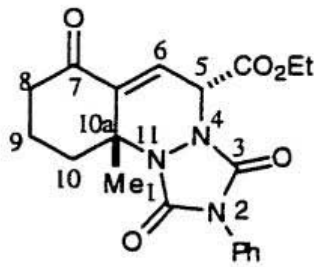
141



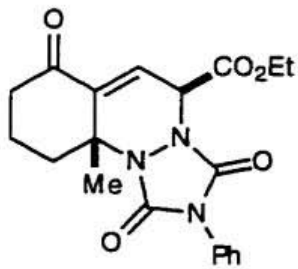
142

A benzene solution of **69** (192 mg, 0.99 mmol), and PTAD (174 mg, 0.99 mmol) was allowed stand stirring for 10 min under nitrogen. Removal of solvent under reduced pressure provided the crude product as a light pink solid. The ^{1}H NMR spectrum of this crude product contained a single adduct **141**. Recrystallization of the crude product gave the analytical sample of **141** as colorless crystals (328 mg, 0.89 mmol, 90%). However, purification of the crude product resulted in a 67:33 mixture of **141** and the epimerized product **142**. For **141**: ^{1}H NMR δ 7.54-7.37 (m, 5H), 6.86 (dd, 1H, *J* =5.1, 2.4 Hz, C6-H), 5.24 (dd, 1H, *J* =5.1, 3.1 Hz, C5-H), 4.46 (m, 1H, C10a-H), 4.33-4.21 (m, 2H), 3.42 (m, 1H), 2.72 (m, 1H), 2.40 (m, 1H), 2.15 (m, 1H), 1.89-1.80 (m, 2H), 1.31 (t, 3H, *J* =7.1 Hz); ^{13}C NMR δ 196.9 (0, -CO-), 165.7 (0, CO_2-), 152.3 (0), 137.6 (0), 130.8 (0), 129.2 (1), 128.5 (1), 125.9 (1), 125.0 (1,C6), 63.0 (2), 58.4 (1, C10a), 55.9 (1, C5), 39.5 (2, C8), 28.3 (2, C10), 19.2 (2, C9), 14.1 (3); IR (Nujol) υ 1700 (s) cm^{-1}; MS *m/z* (%) 369 (M^+, 13), 297 (19), 296 (100), 177 (66), 134 (18), 121 (43), 119 (38), 91 (32), 77 (32); Anal. calcd for $C_{19}H_{19}N_3O_5$: C, 61.78; H: 5.18; N: 21.66. found: C, 61.71; H, 5.18. For **142**: ^{1}H NMR δ 6.67 (dd, 1H, *J* = 2.3 Hz), 2.70 (m, 1H), 1.21 (t, 3H, *J* = 7.0 Hz).

(5α,10aα)-6-Carboethoxy-10a-methyl-2-phenyl-5,8,9,10,10a-pentahydro-[1*H*][1,2,4]triazolo[1,2-*a*]cinnoline-1,3,7-(2*H*)-trione (143) and (5α,10aβ)-6-Carboethoxy-10a-methyl-2-phenyl-5,8,9,10,10a-pentahydro-[1*H*][1,2,4]triazolo[1,2-*a*]cinnoline-1,3,7-(2*H*)-trione (144)



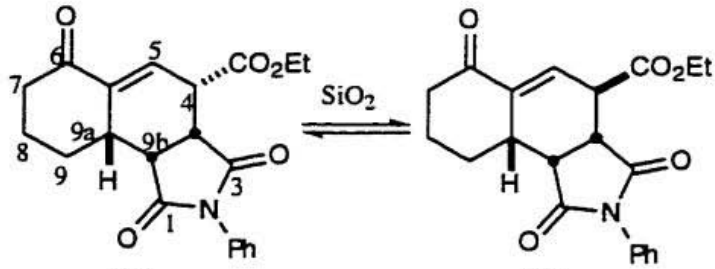
143



144

A solution of **73** (96 mg, 0.46 mmol), and PTAD (97 mg, 0.55 mmol) in benzene (6 mL) was stirred at room temperature for 5.5 h. The solvent was removed under reduced pressure keeping the temperature below 40 °C. The ^{1}H spectrum of the residue indicated that **143** obtained as a single adduct. Flash chromatography (silica, 30% EtOAc/hexane) gave 147 mg (0.38 mmol, 83%) of **143** with 7% of **144**, which was epimerized from the straight adduct **143** during chromatography. Recrystallization from ethyl acetate/hexane gave the analytical sample of **143** as colorless crystals: mp 160-162 °C; ^{1}H NMR δ 7.55-7.36 (m, 5H), 6.62 (d, 1H, *J* =5.0 Hz, C6-H), 5.22 (d, 1H, *J* =5.0 Hz, C5-H), 4.32-4.19 (m, 2H, -OC**H**$_2$CH$_3$), 3.25 (m, 1H), 2.70 (m, 1H), 2.41 (m, 1H), 2.19-2.06 (m, 2H), 1.93 (m, 1H), 1.50 (s, 3H), 1.30 (t, 3H, *J* =7.2 Hz); ^{13}C NMR δ 198.3 (0, -CO-), 165.7 (0, -**C**O$_2$-), 152.9 (0), 152.7 (0), 143.0 (0), 130.9 (0), 129.2(1), 128.4 (1), 125.8 (1), 122.7 (1, C6), 63.0 (2), 55.8 (1, C5), 39.7 (2, C8), 33.9 (2, C10), 20.8 (3), 18.6 (2, C9), 14.1 (3); IR (Nujol) υ 1713 (s), 1634 (m) cm^{-1}; MS *m/z* (%) 383 (M$^+$, 15), 310 (100), 191 (26), 149 (100), 71 (29), 57 (46); HRMS calcd for $C_{20}H_{21}N_3O_5$ 383.1480, found 383.1462. For **144**: ^{1}H NMR δ 6.48 (d, 1H, *J* = 5.6), 5.16 (d, 1H, *J* = 5.6).

(3aα,4α,9aα,9bα)-4-Carboethoxy-3a,4,7,8,9,9a,9b-heptahydro-2-phenyl-1*H*-benz[*e*]isoindole-1,3,6(2*H*)-trione (145) or **(3aα,4β,9aα,9bα)-4-Carboethoxy-3a,4,7,8,9,9a,9b-heptahydro-2-phenyl-1*H*-benz[*e*]isoindole-1,3,6(2*H*)-trione (146)**

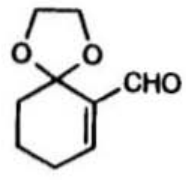


145 **146**

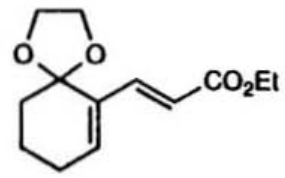
A solution of diene **69** (93 mg, 0.48 mmol) and NPM (257 mg, 1.48 mmol) in toluene (5 mL) was heated at reflux for 44 h. Removal of the solvent and chromatography of the crude product provided either the adduct **145** or the epimerized adduct **146** as colorless crystals (135 mg, 0.37 mmol, 77%): mp 164-166 °C; ^{1}H NMR δ 7.67 (s, 1H), 7.47-7.21 (m, 5H), 4.41 (m, 1H), 4.30 (q, 2H, J = 7.2 Hz), 3.44 (dd, 1H, J = 8.7, 5.3 Hz), 2.88 (d, 1H, J = 12.4 Hz), 2.70-2.32 (m, 3H), 2.25-2.12 (m, 2H), 1.87 (m, 1H), 1.61 (m, 1H), 1.34 (t, 3H, J = 7.2 Hz); NOE data ($CDCl_3$) δ 1.50 (5.22, 2%); ^{13}C NMR δ 205.7, 175.6, 173.5, 165.4, 137.1, 131.4, 129.1, 128.7, 127.7, 126.3, 61.4, 47.4, 43.1, 42.0, 41.1, 40.8, 27.8, 25.8, 14.1; IR (Nujol) υ 1720 (s) cm^{-1}; MS *m/z* (%) 367 (M^+, 12), 293 (10), 176 (12), 91 (19); HRMS calcd for $C_{21}H_{21}NO_5$ 367.1418, found 367.1424.

Appendix

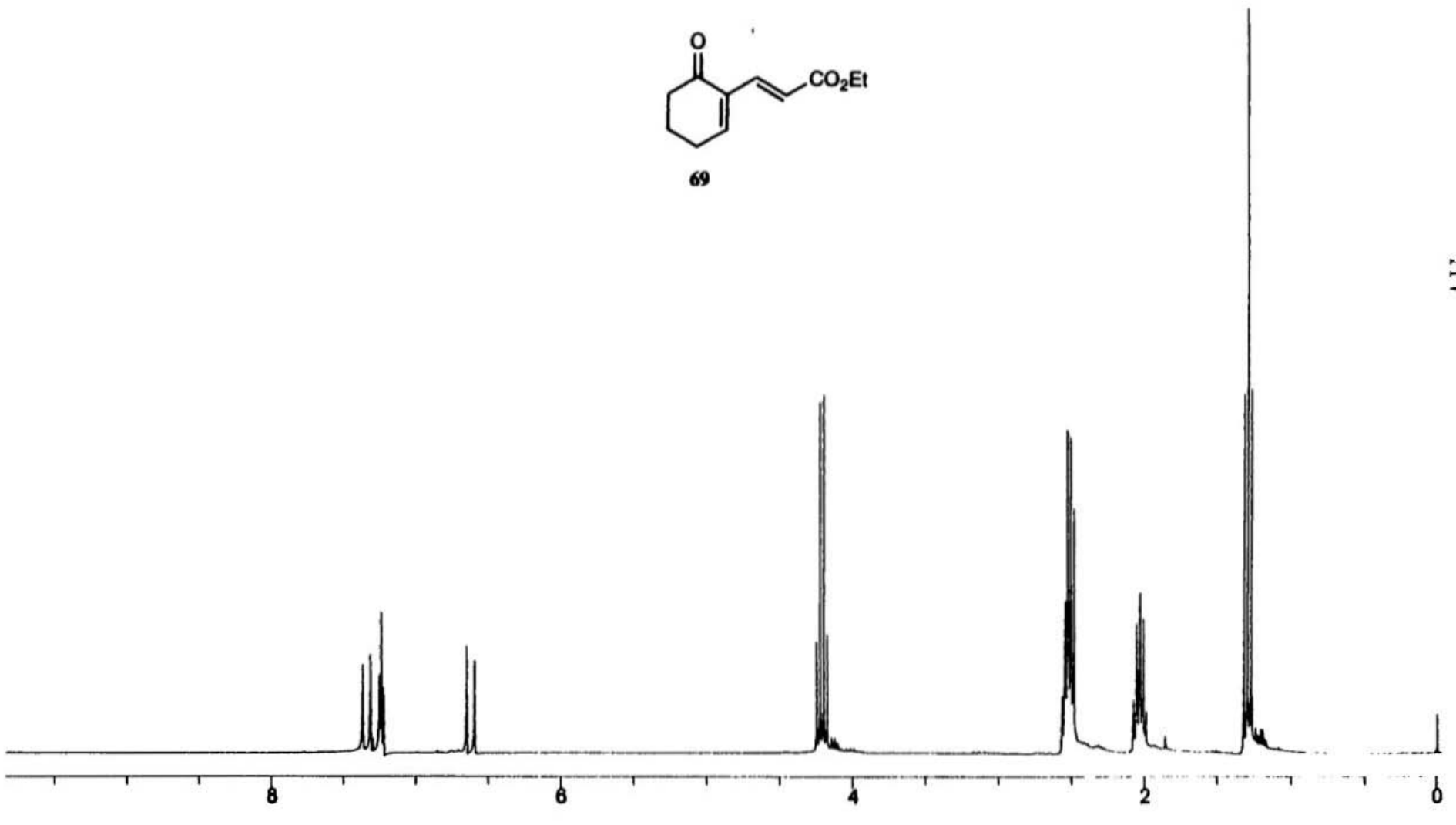
The selected ^{1}H spectra of the synthetic examples were arranged according to the order in which they appeared in the text. For the instruments, see **General Procedures** in Chapter 2, section 2.3.



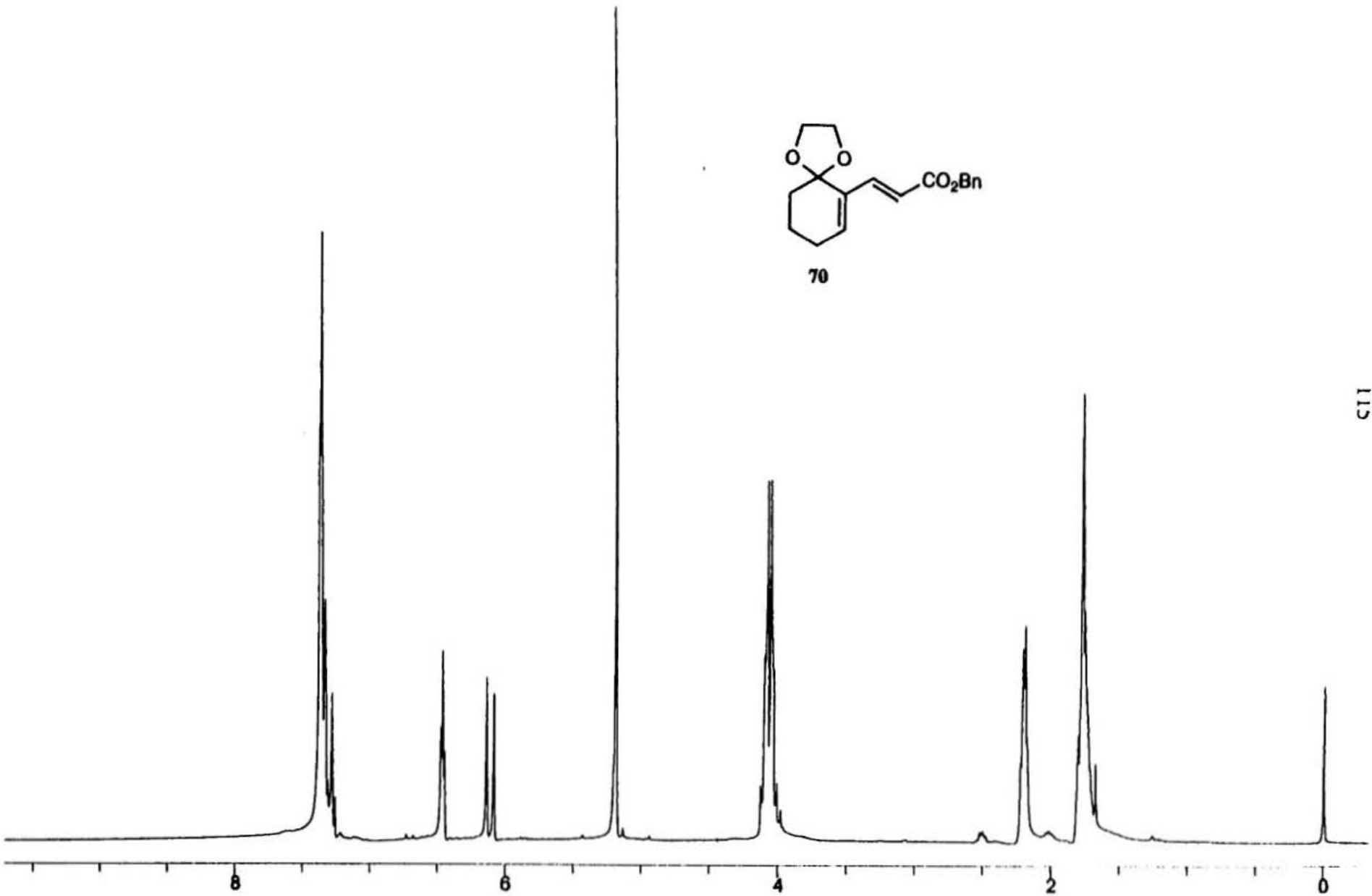
67



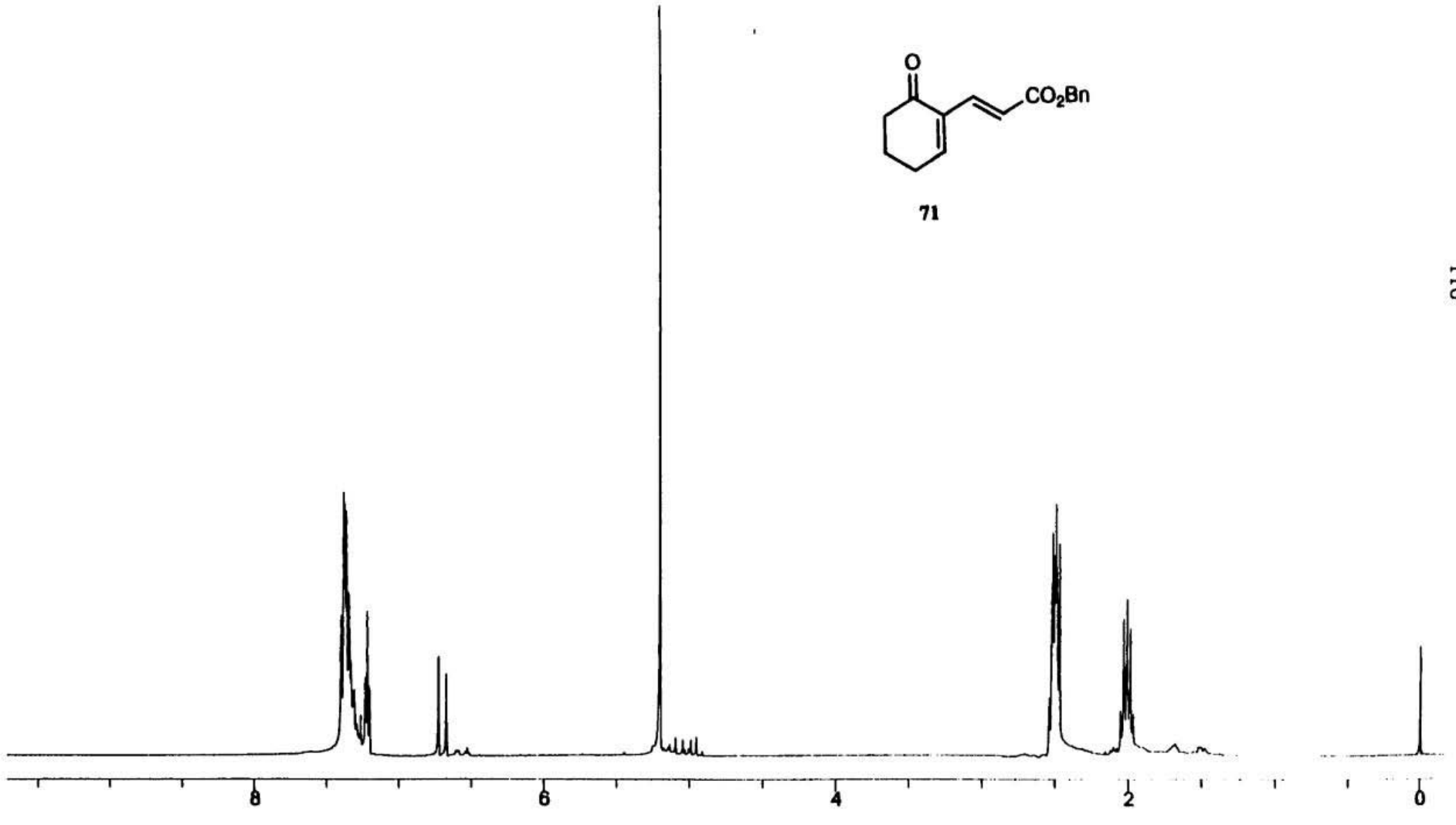
68



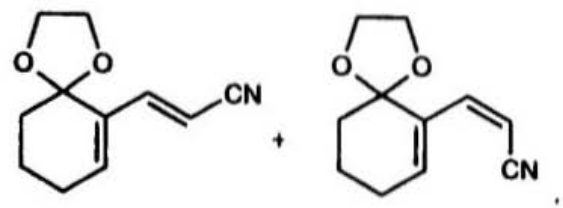
69



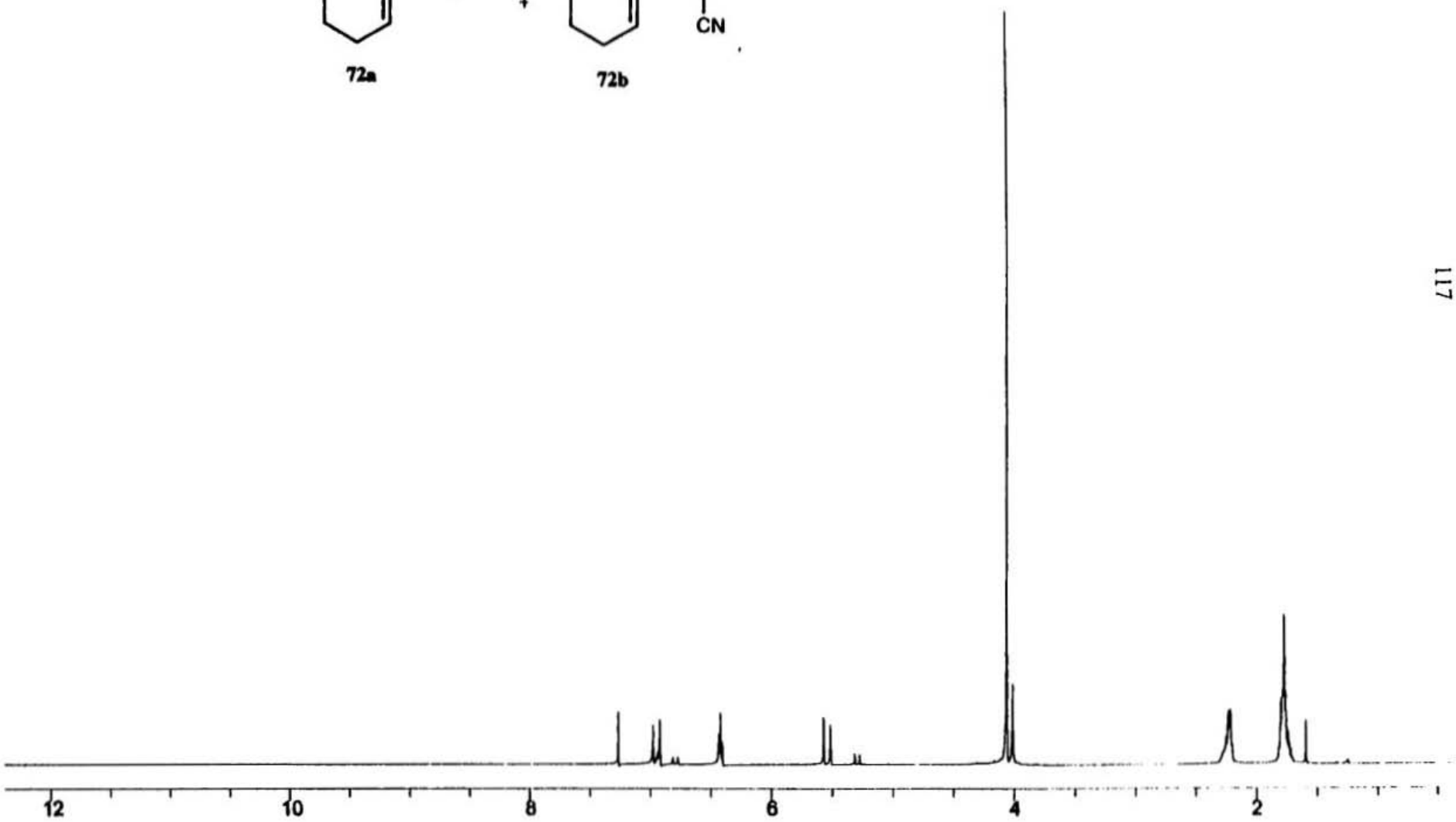
70

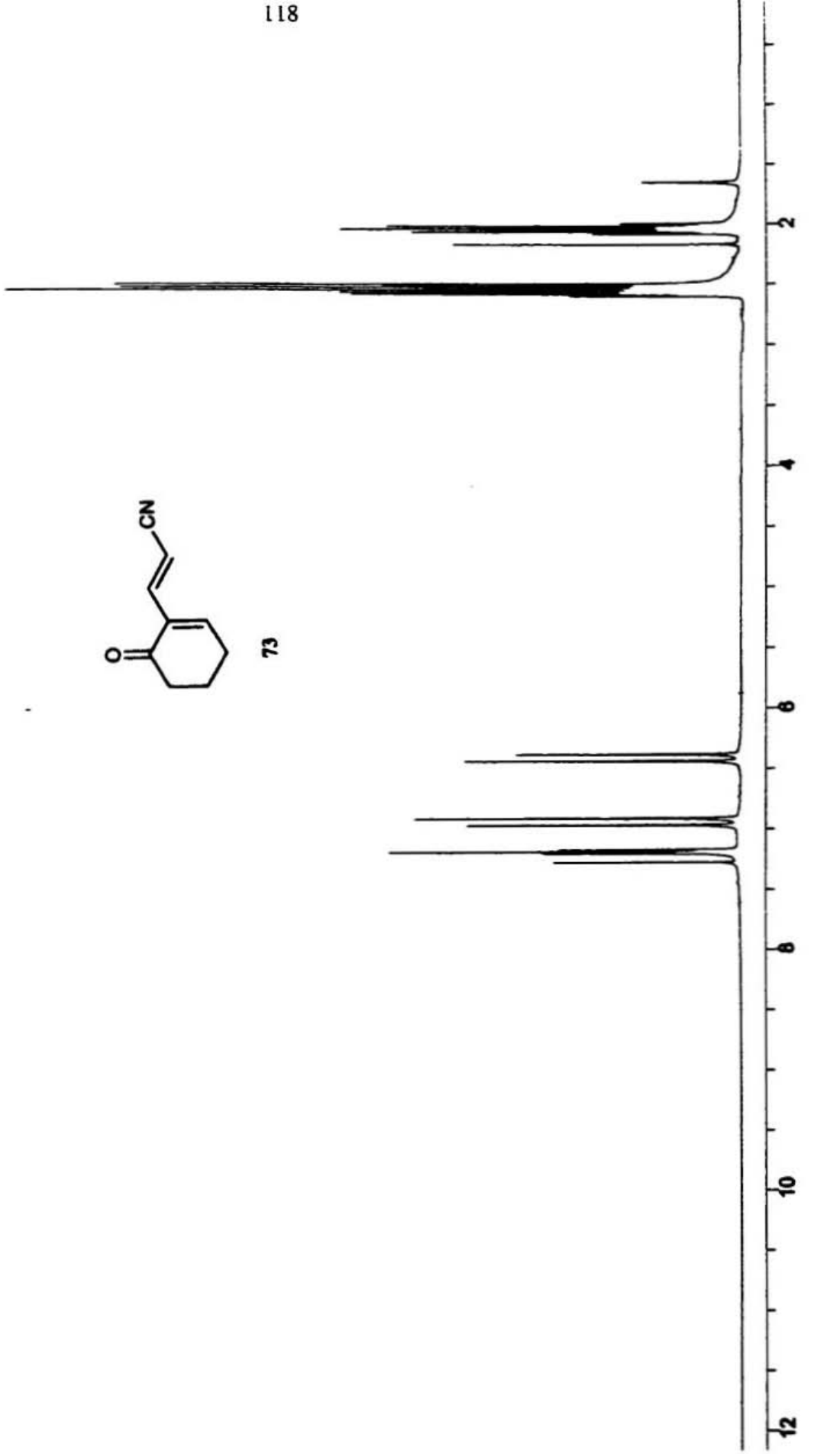


71



72a 72b




CN
O
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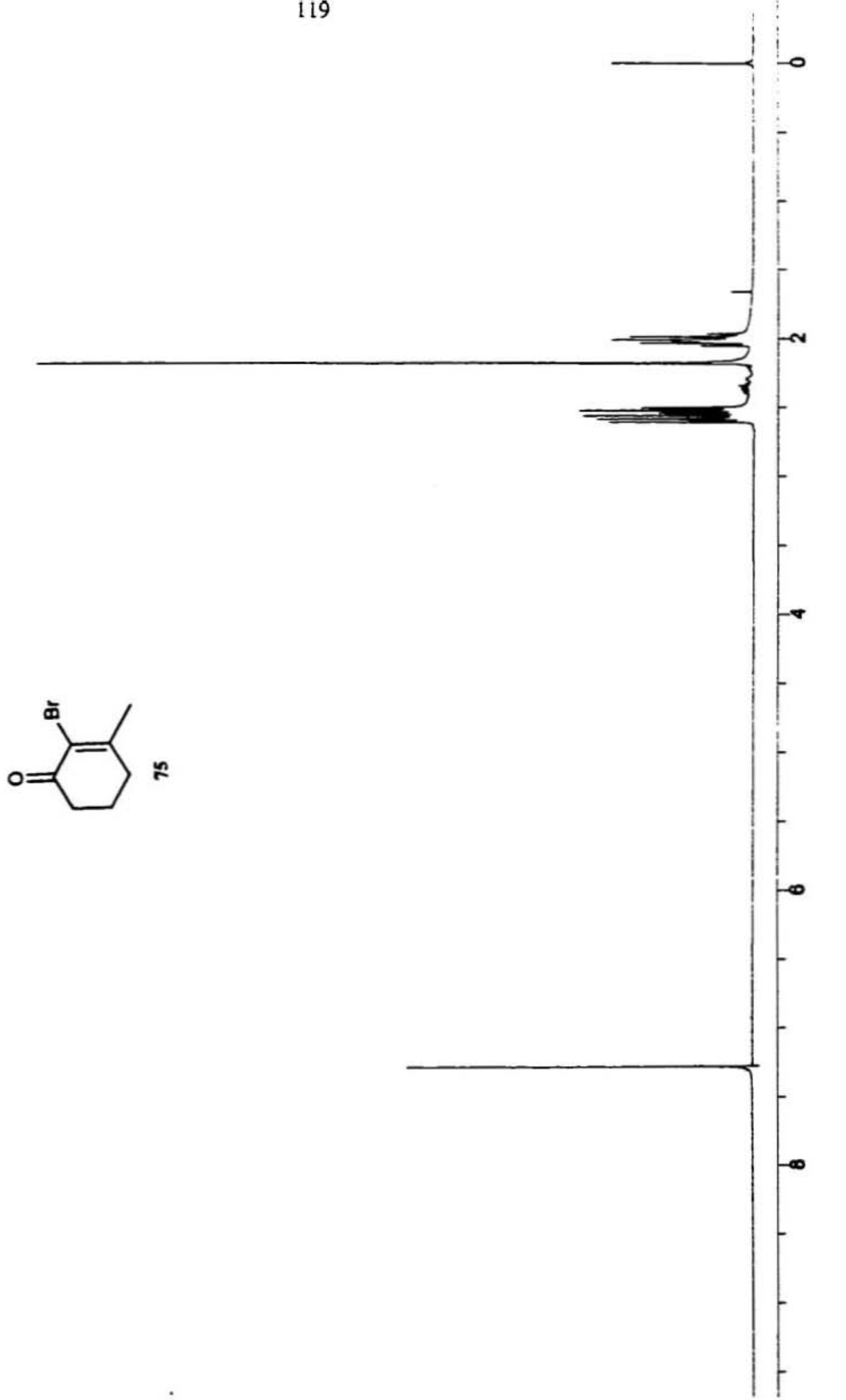
6
8
10
12


Br
O
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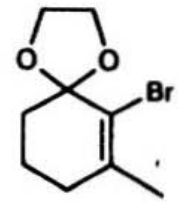
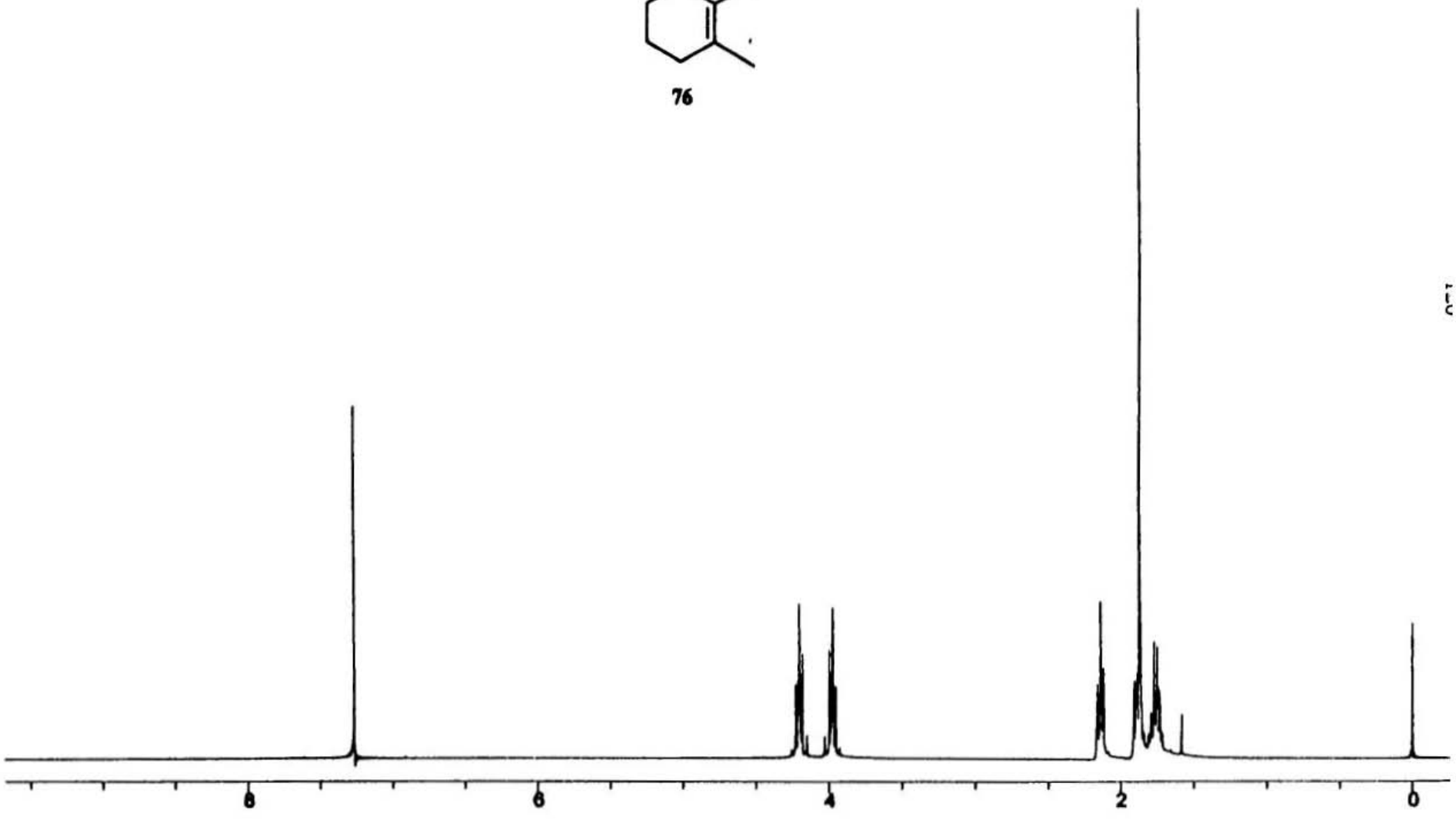
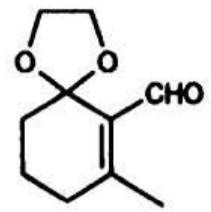
2
4
6
8



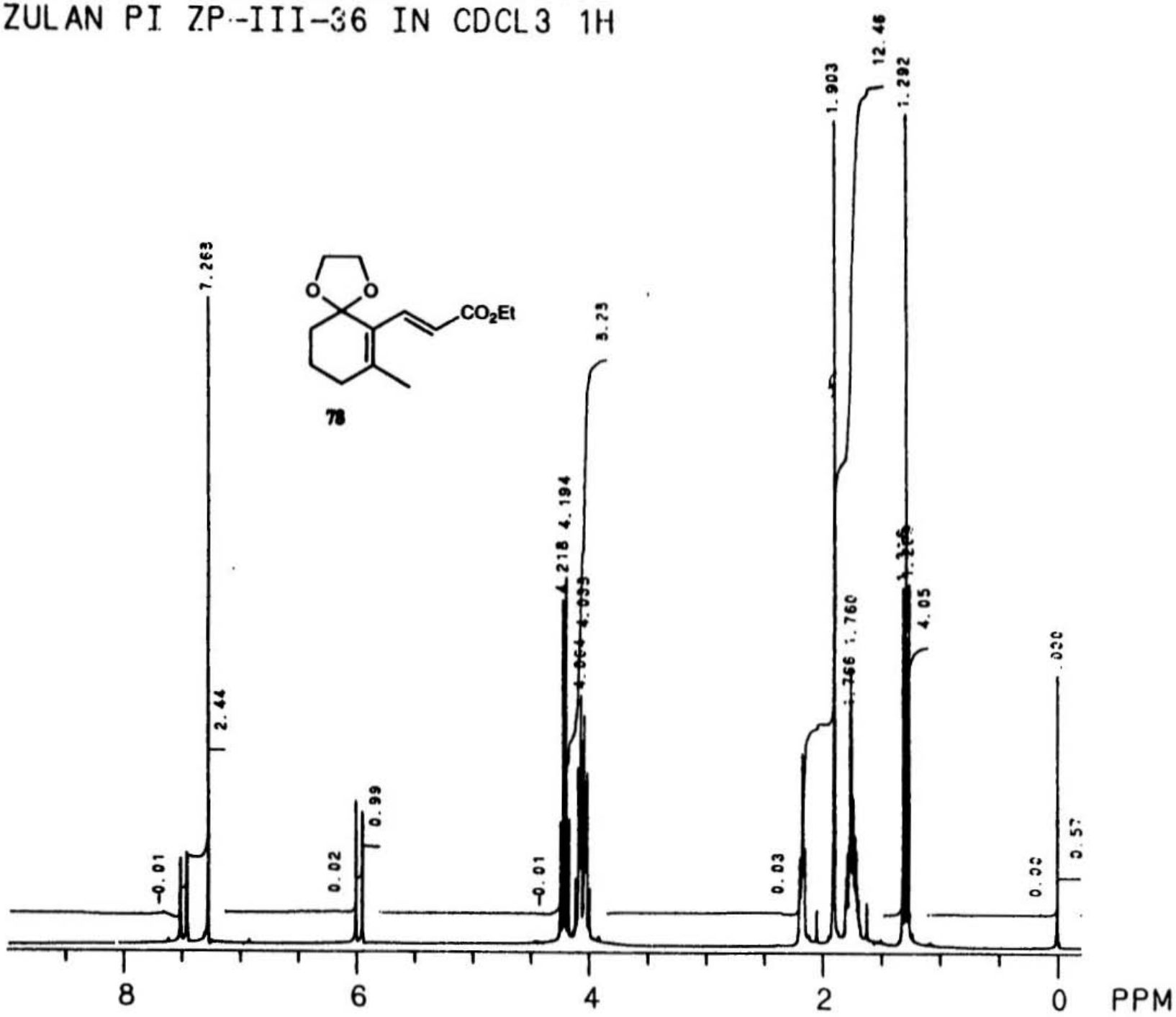
76



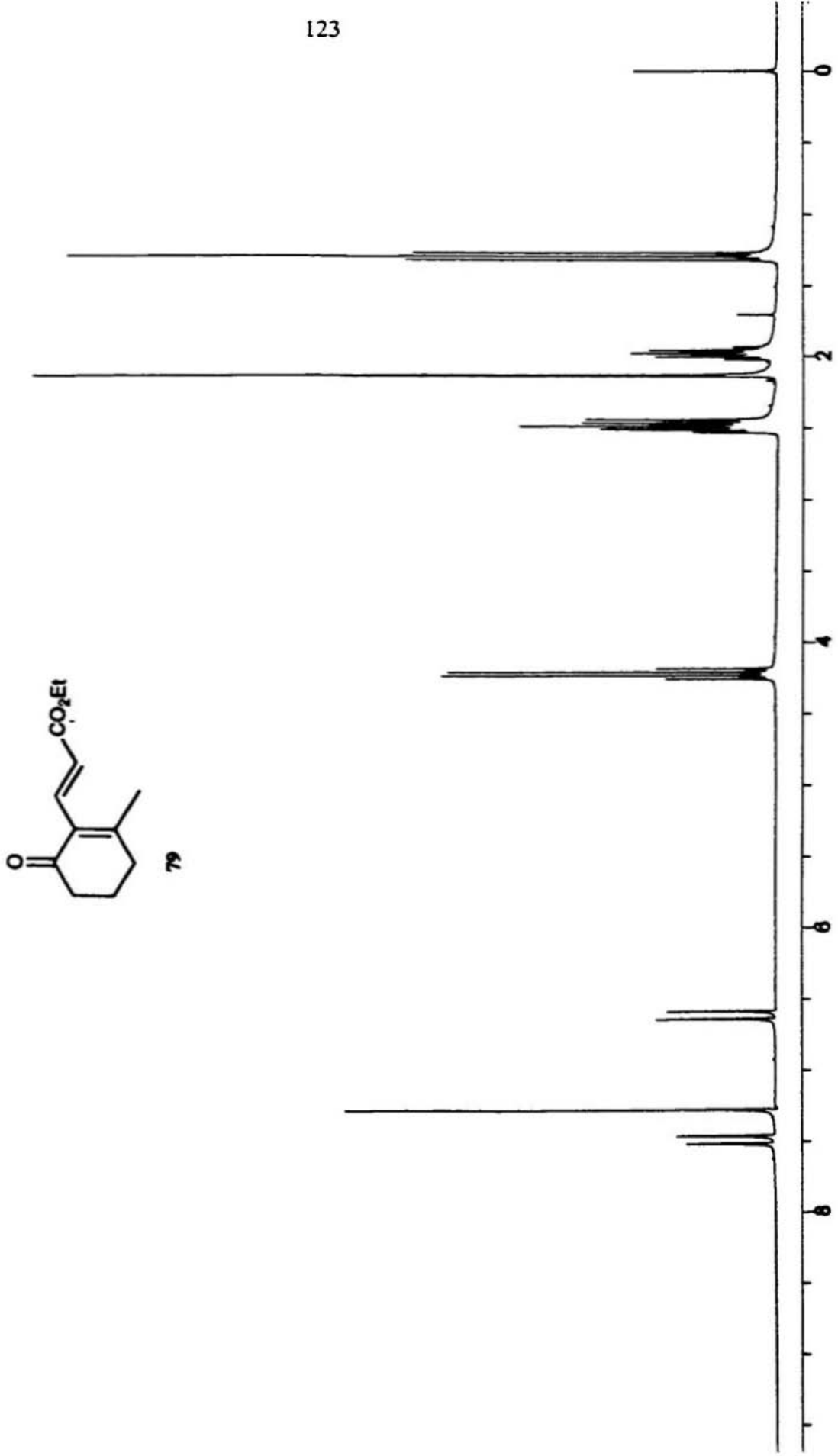


77

ZULAN PI ZP-III-36 IN CDCL3 1H



78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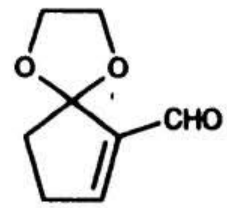
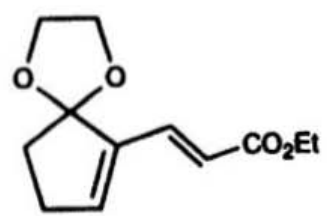
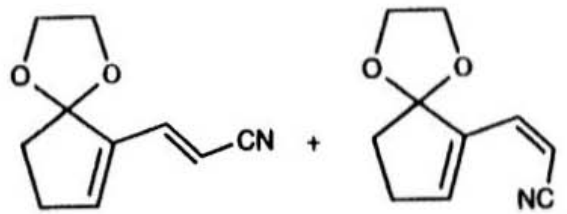
4
6
8



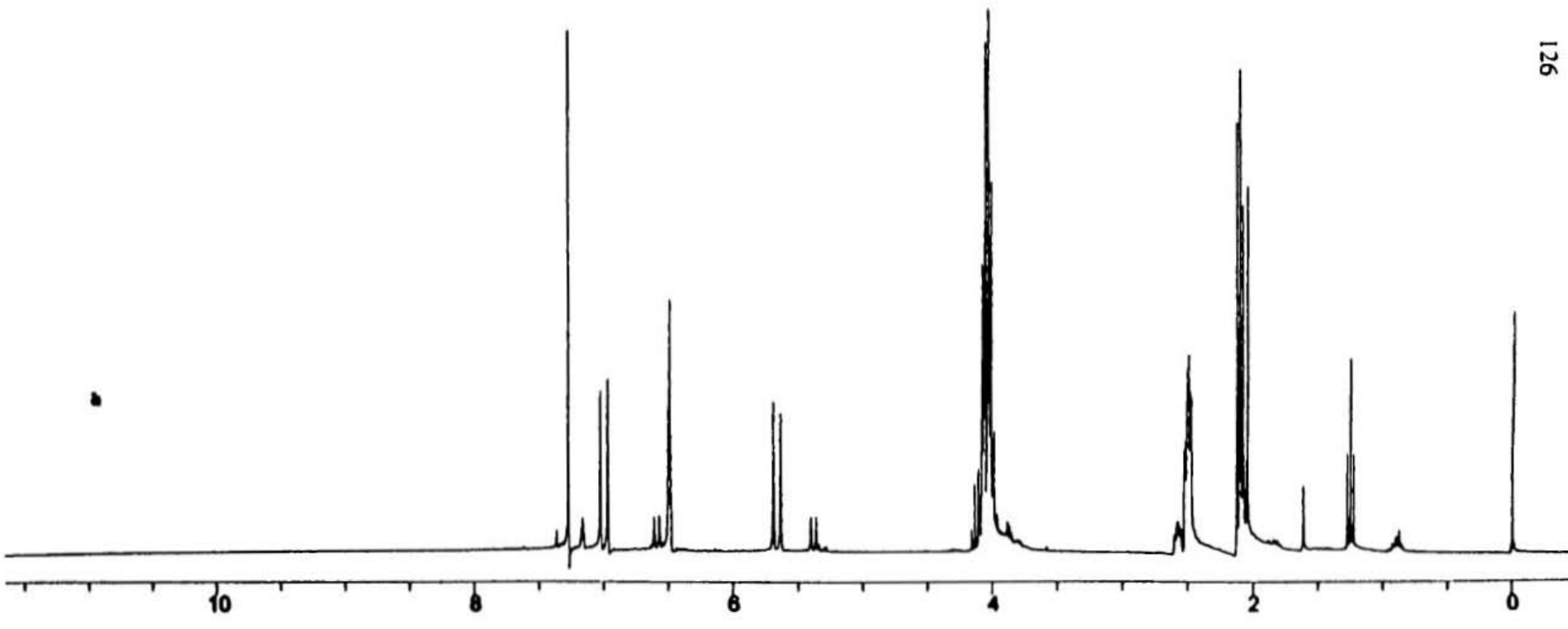
82

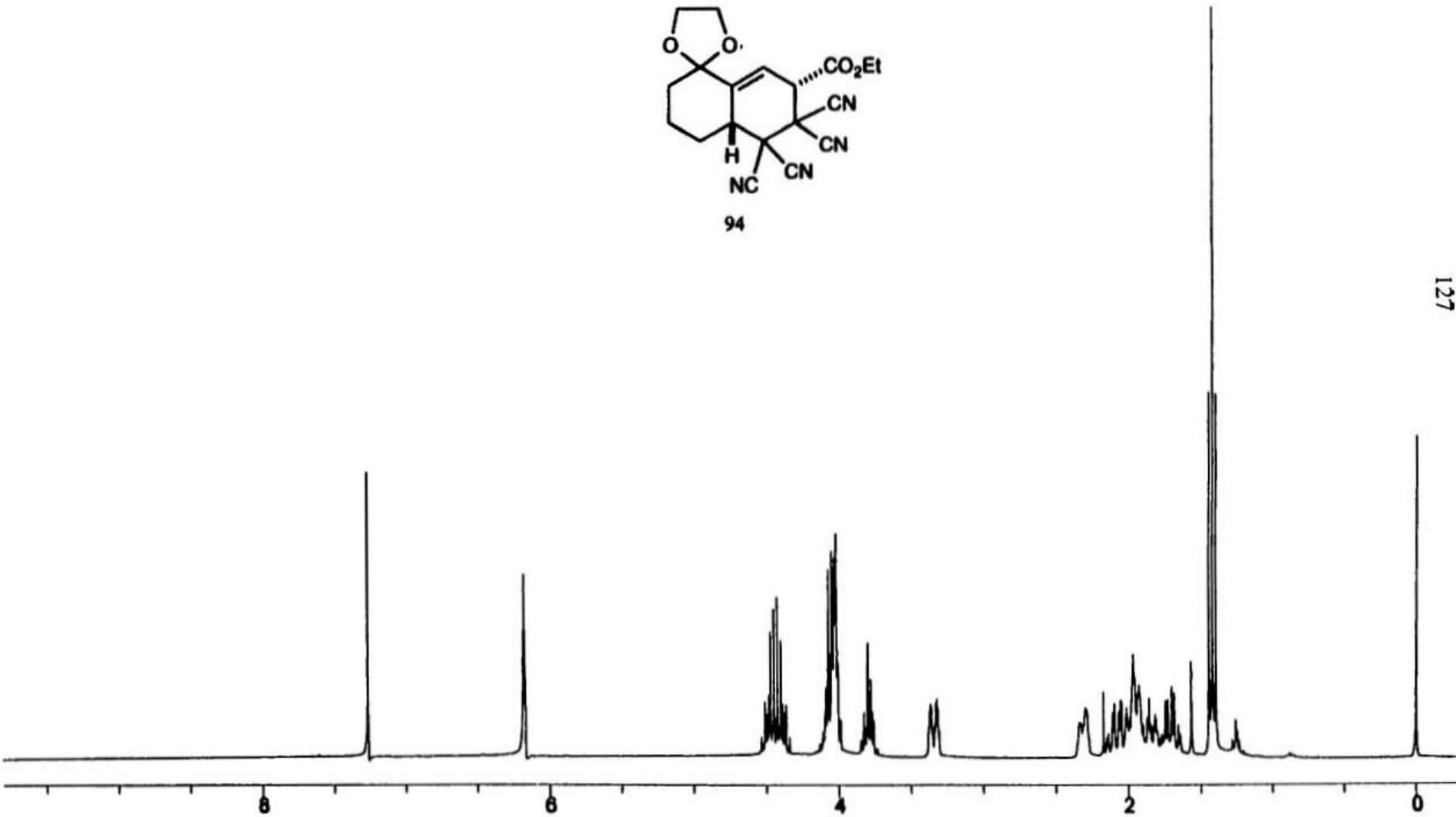


83

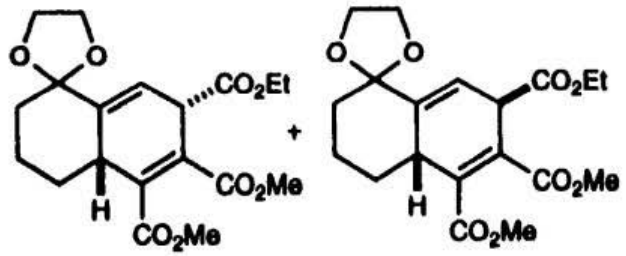


85a 85b

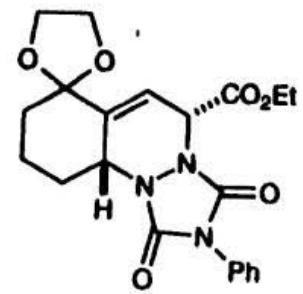




94



98 99



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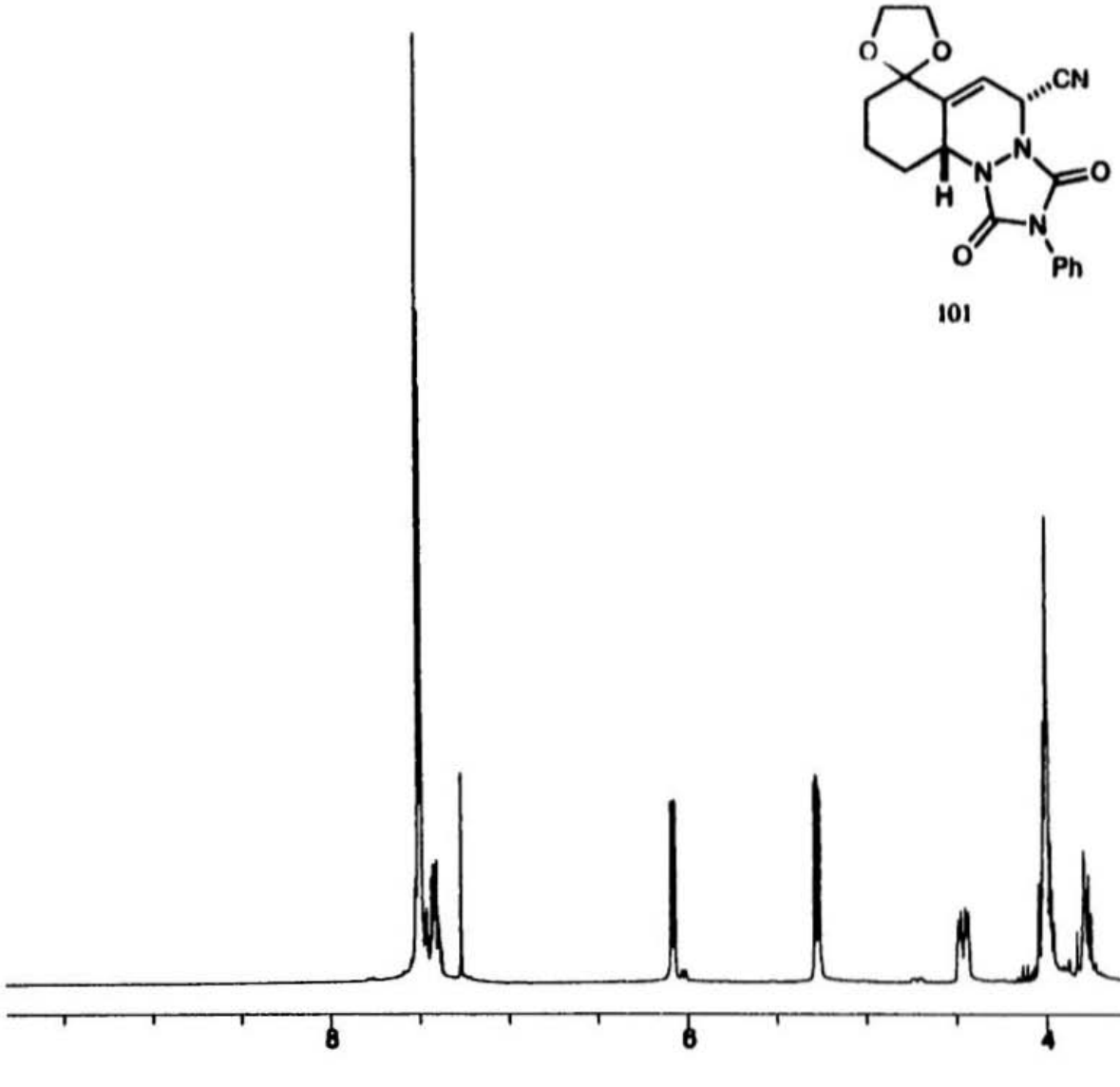
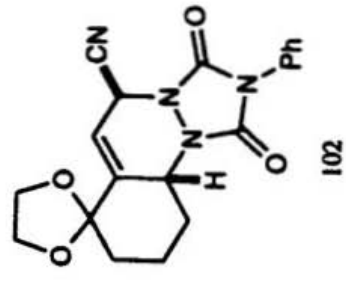
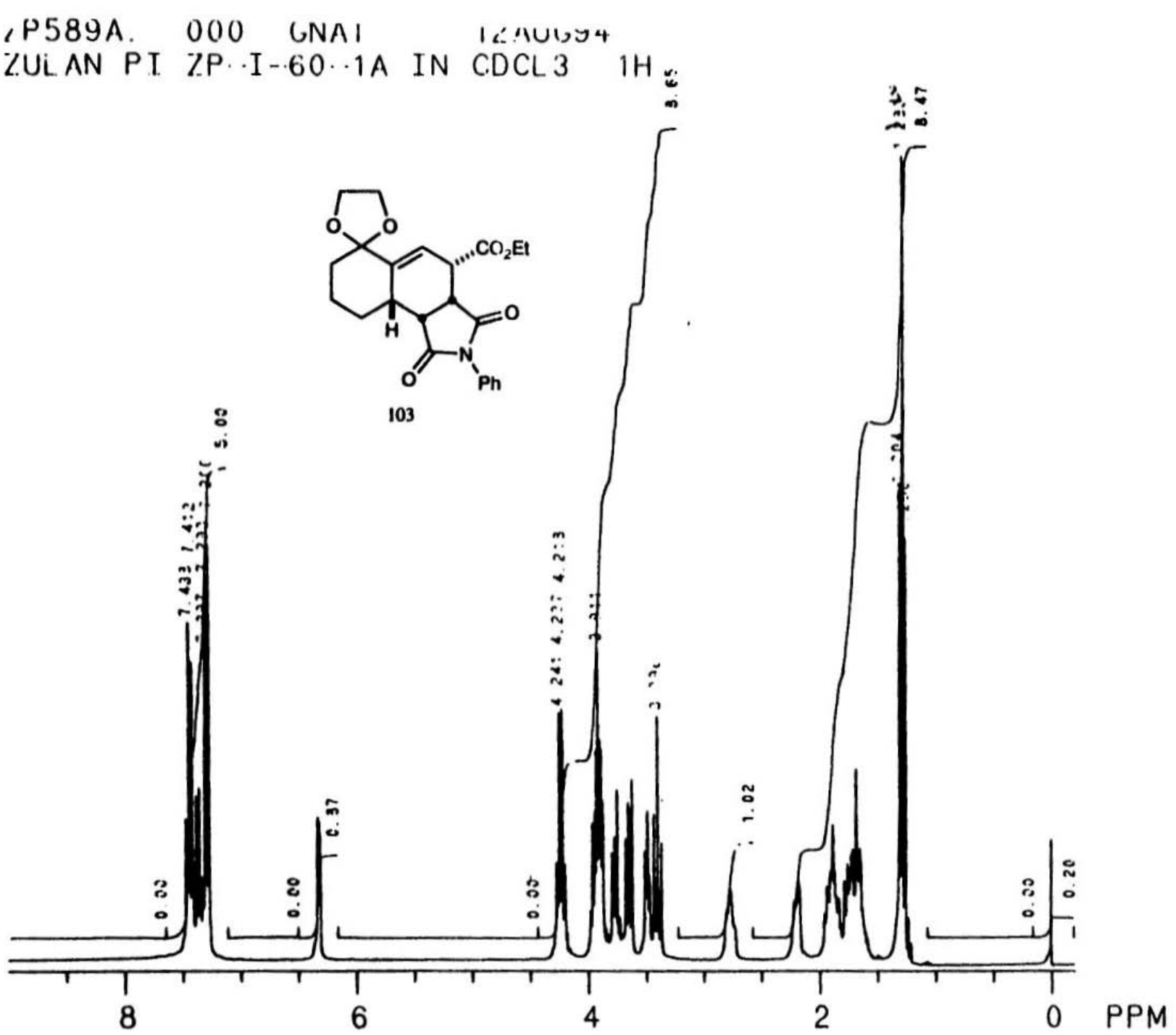
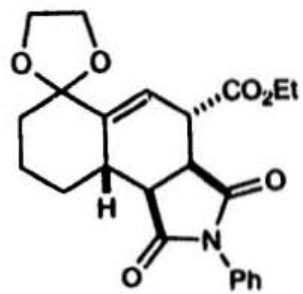


101

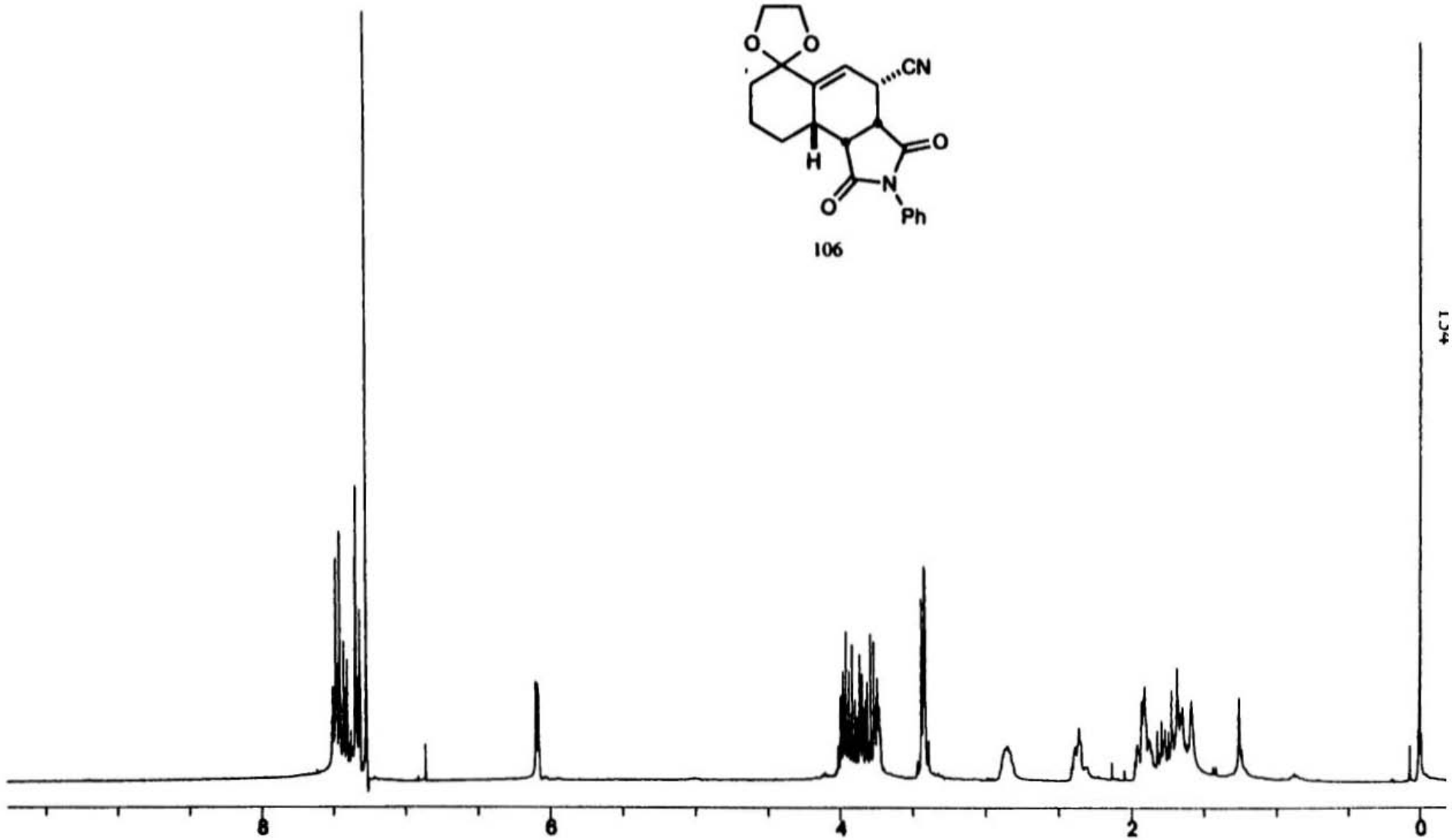


102

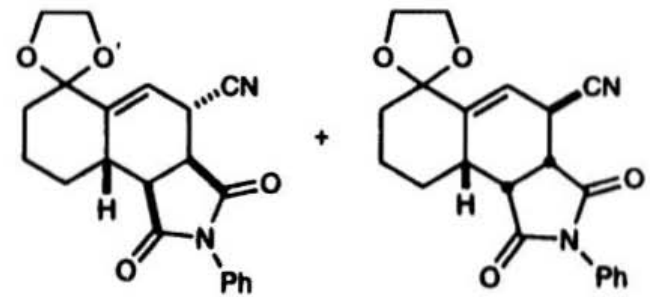

ZP589A. 000 GNAT
ZULAN PI ZP--I-60--1A IN CDCL3 1H
CO2Et
O
O
O
H
N
Ph
O
103
8.47
7.433
1.02
0.37
0.20
8
6
4
2
0
PPM



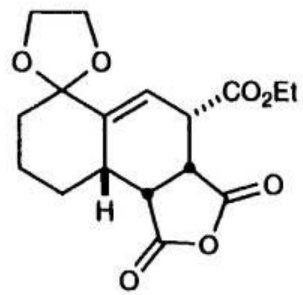
104



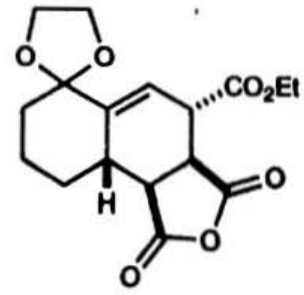
106



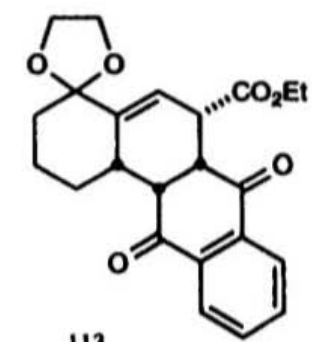
107 + 108



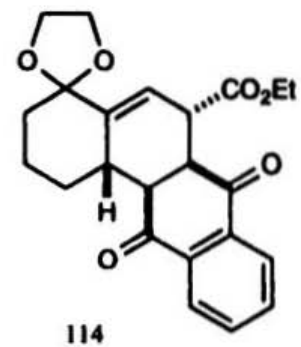
110



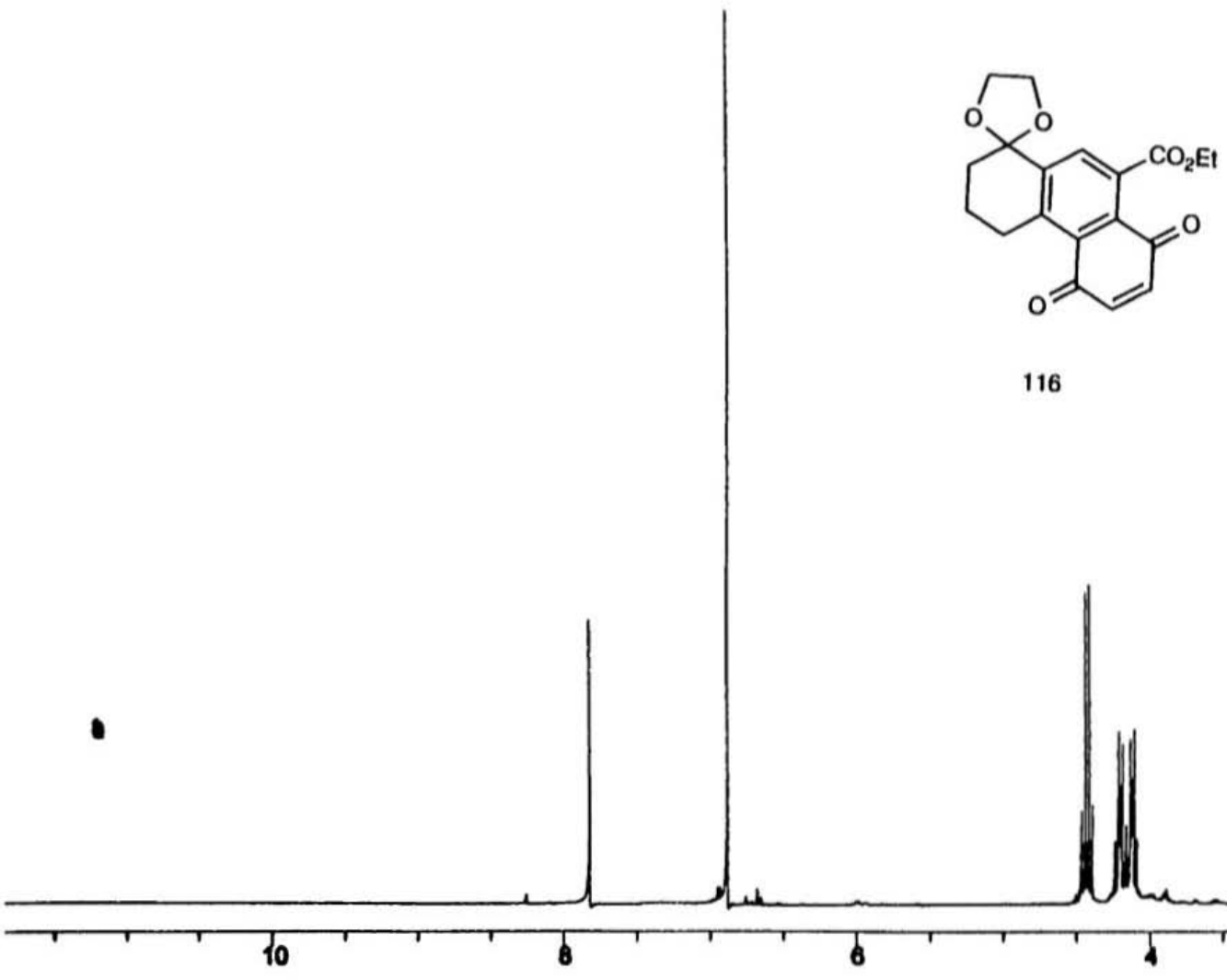
III



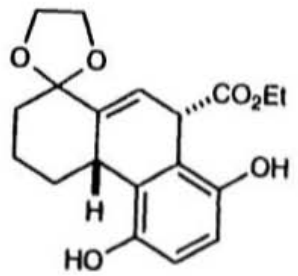
113



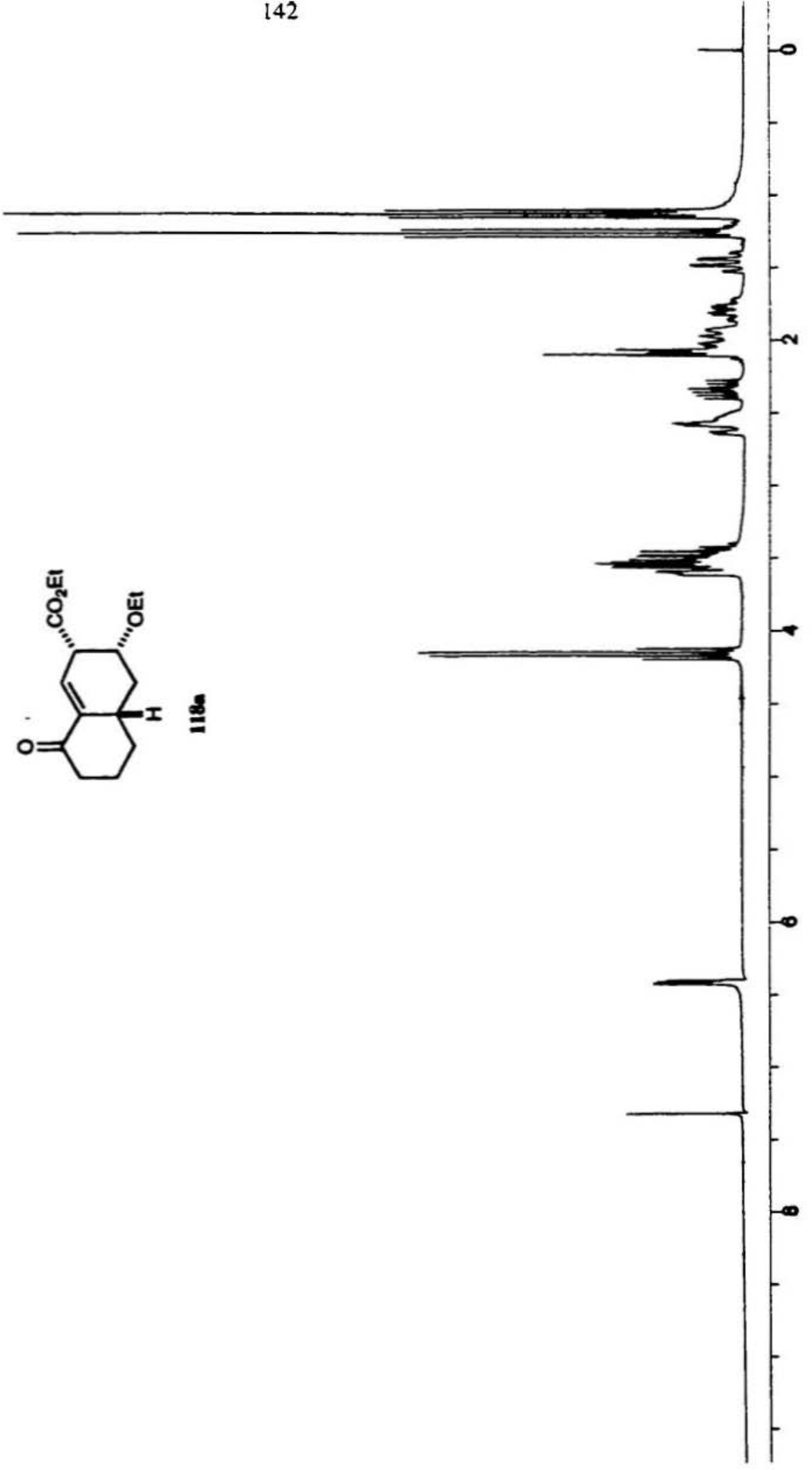
114

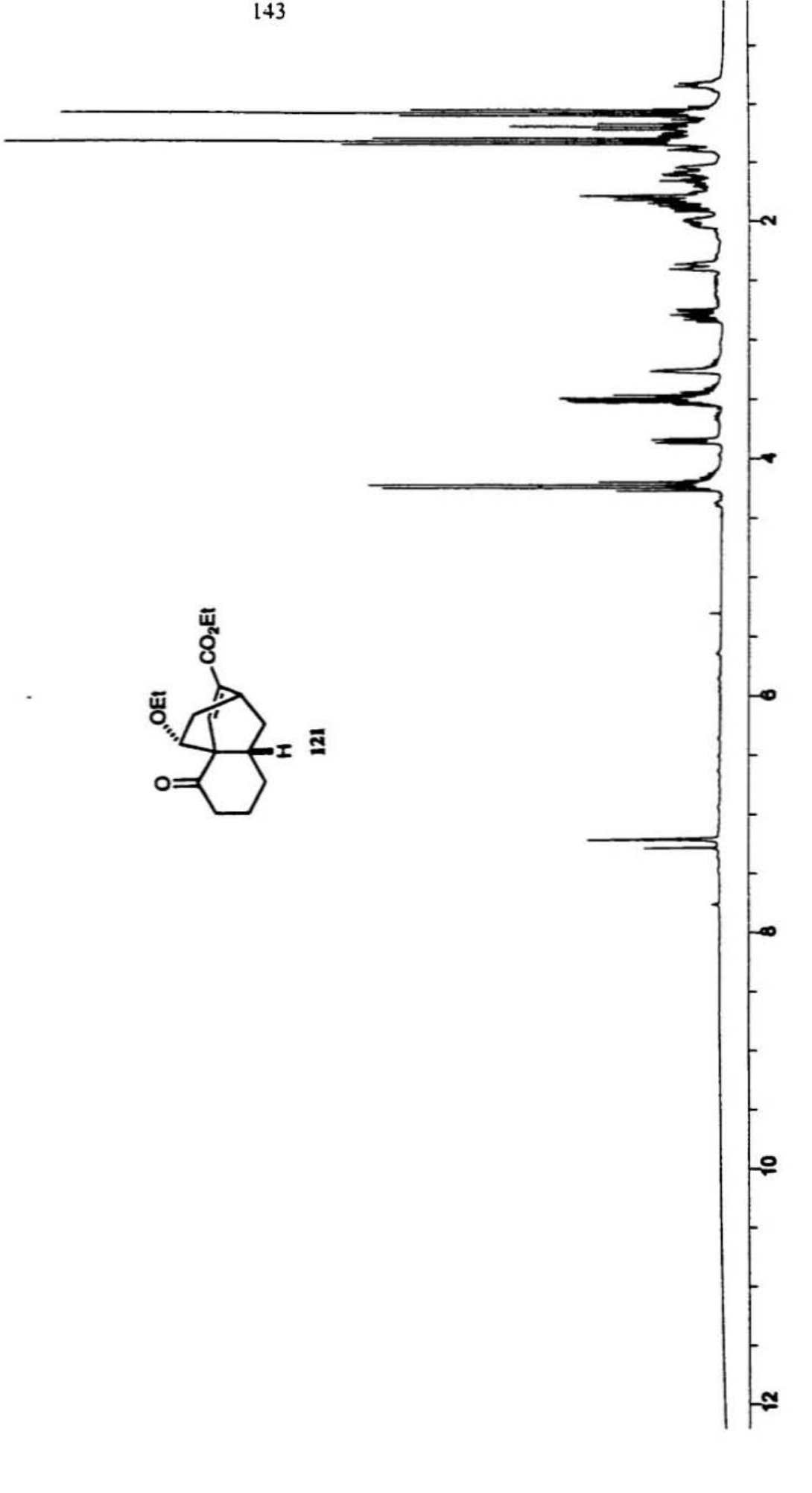


116



117


CO2Et
OEt
H
O
118a
8
6
4
2
0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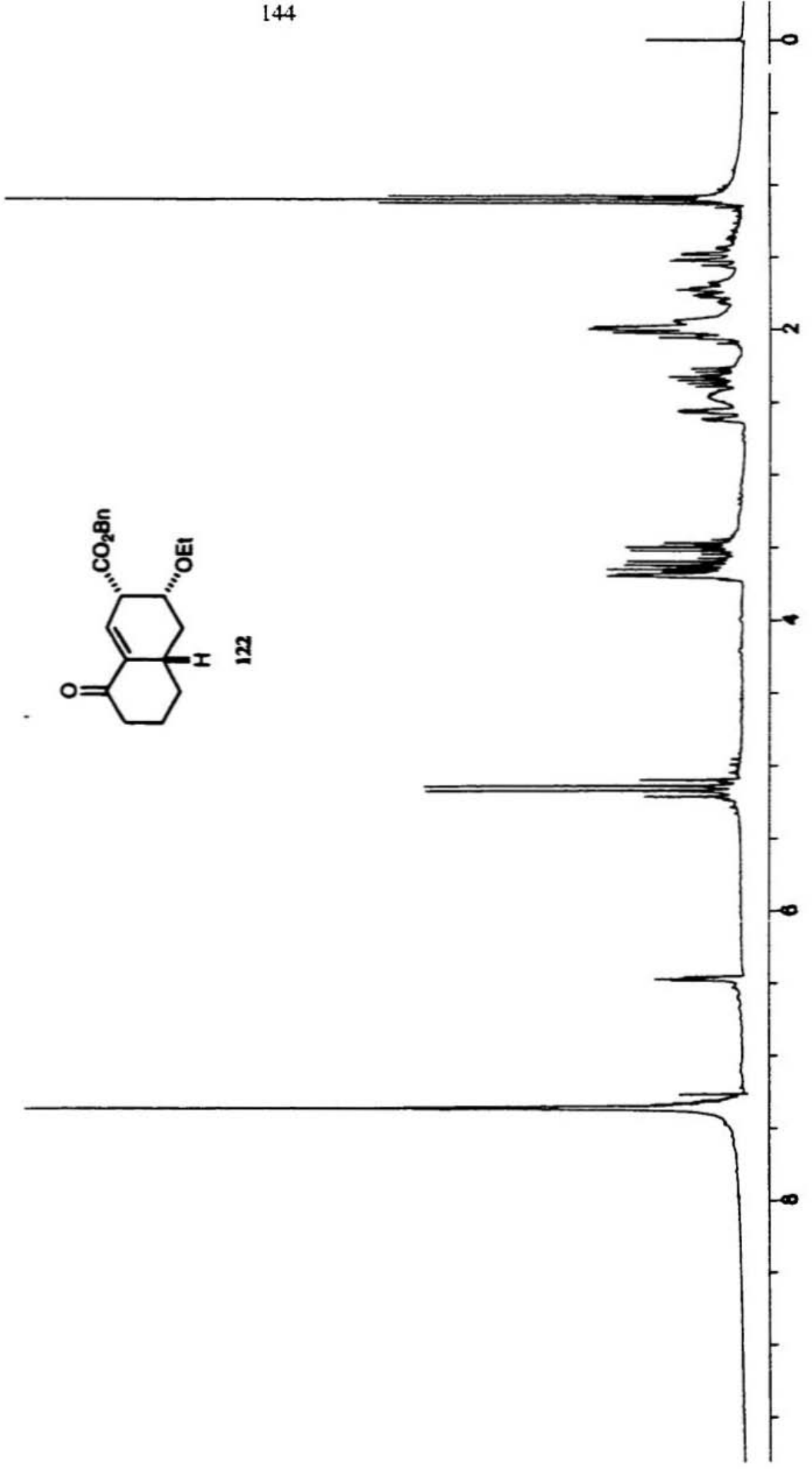
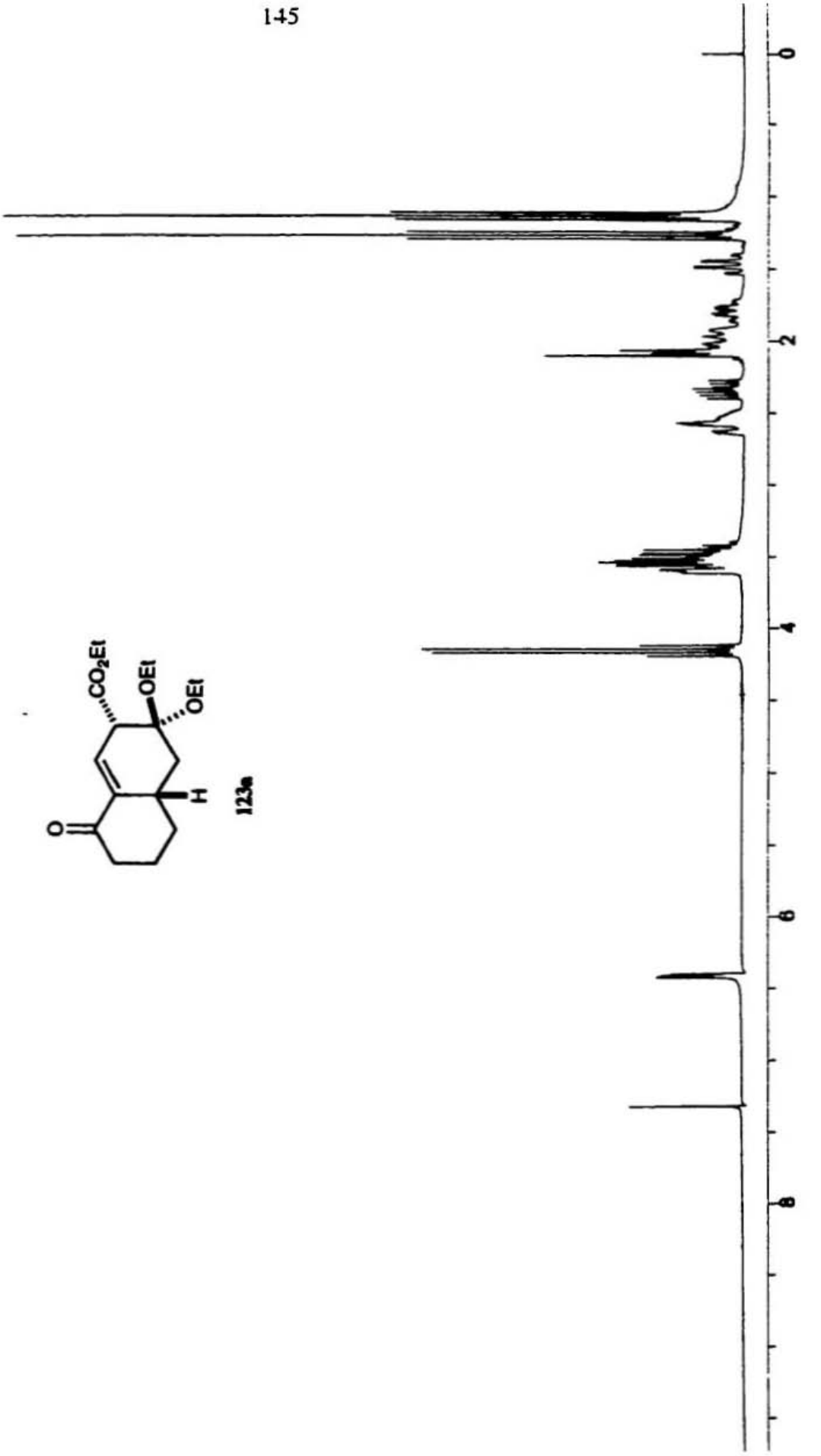
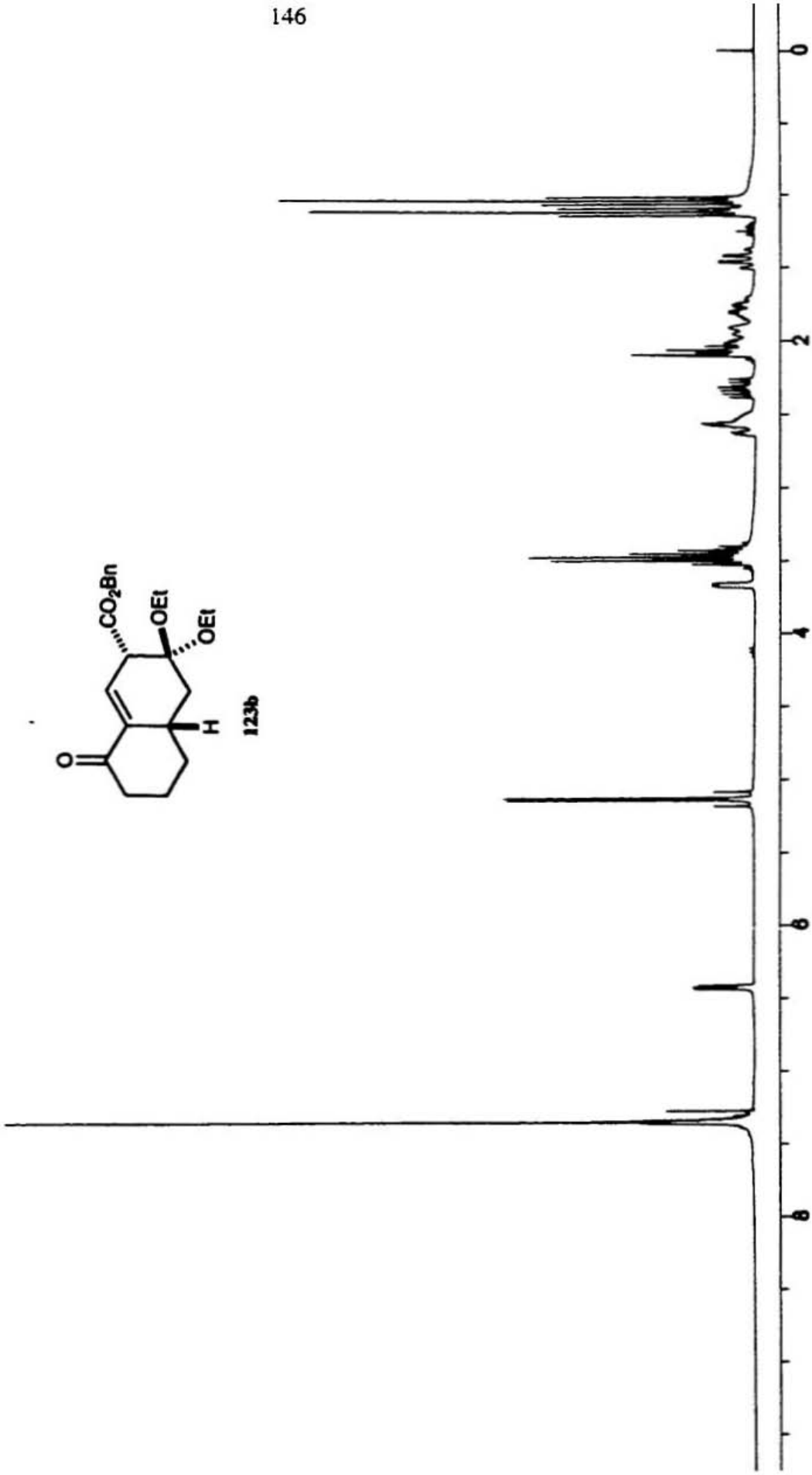
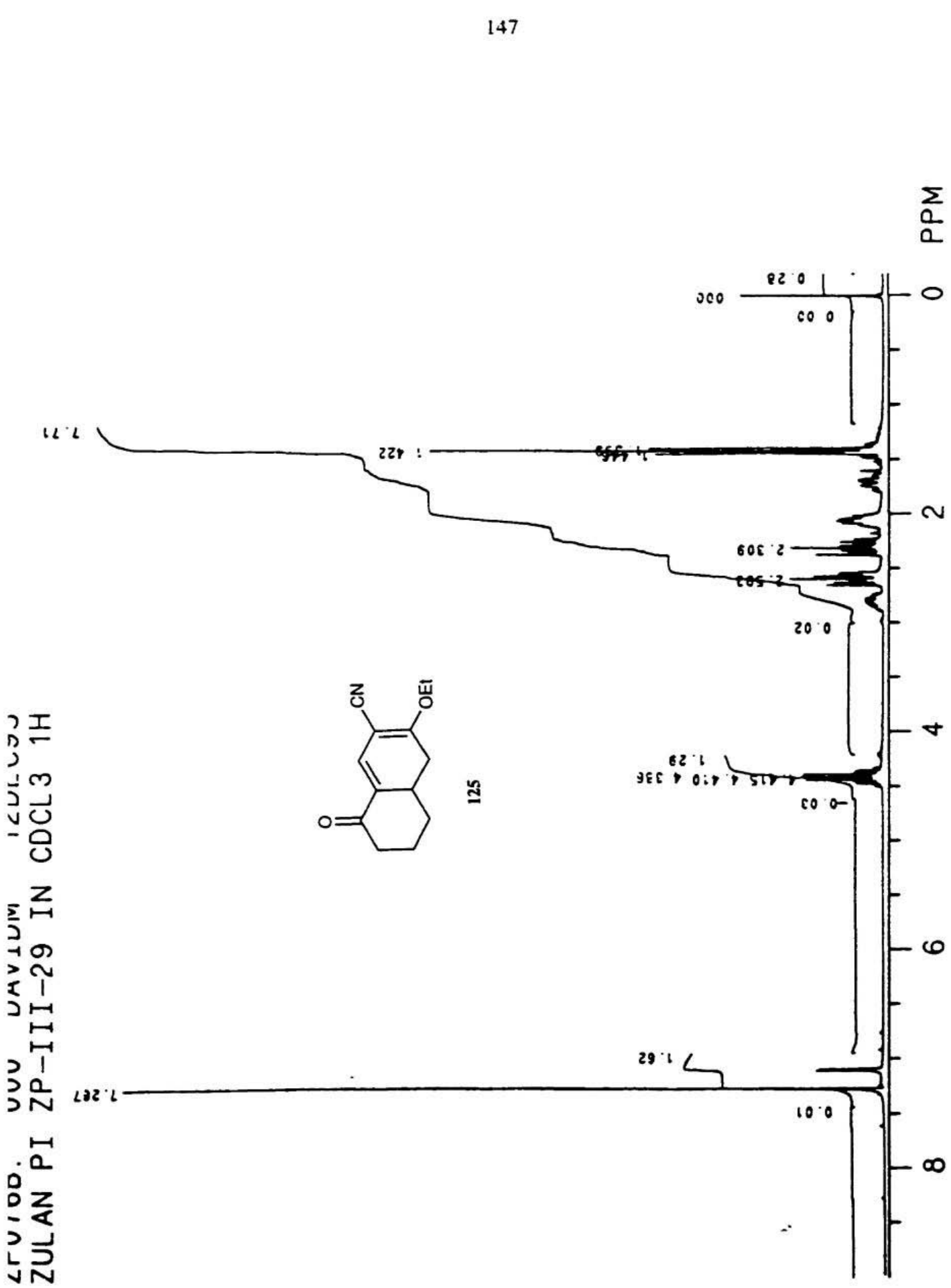
OEt
H
O
121
2
4
6
8
10
12

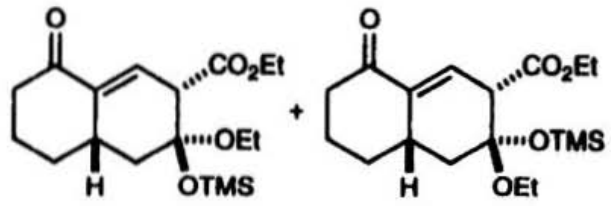

CO2Bn
OEt
H
O
122
0
2
4
6
8


CO2Et
OEt
OEt
H
O
123a
0
2
4
6
8


CO2Bn
OEt
OEt
H
O
123b
8
6
4
2
0


ZULAN PI ZP-III-29 IN CDCL3 1H
CN
OEt
O
125
PPM
0
2
4
6
8

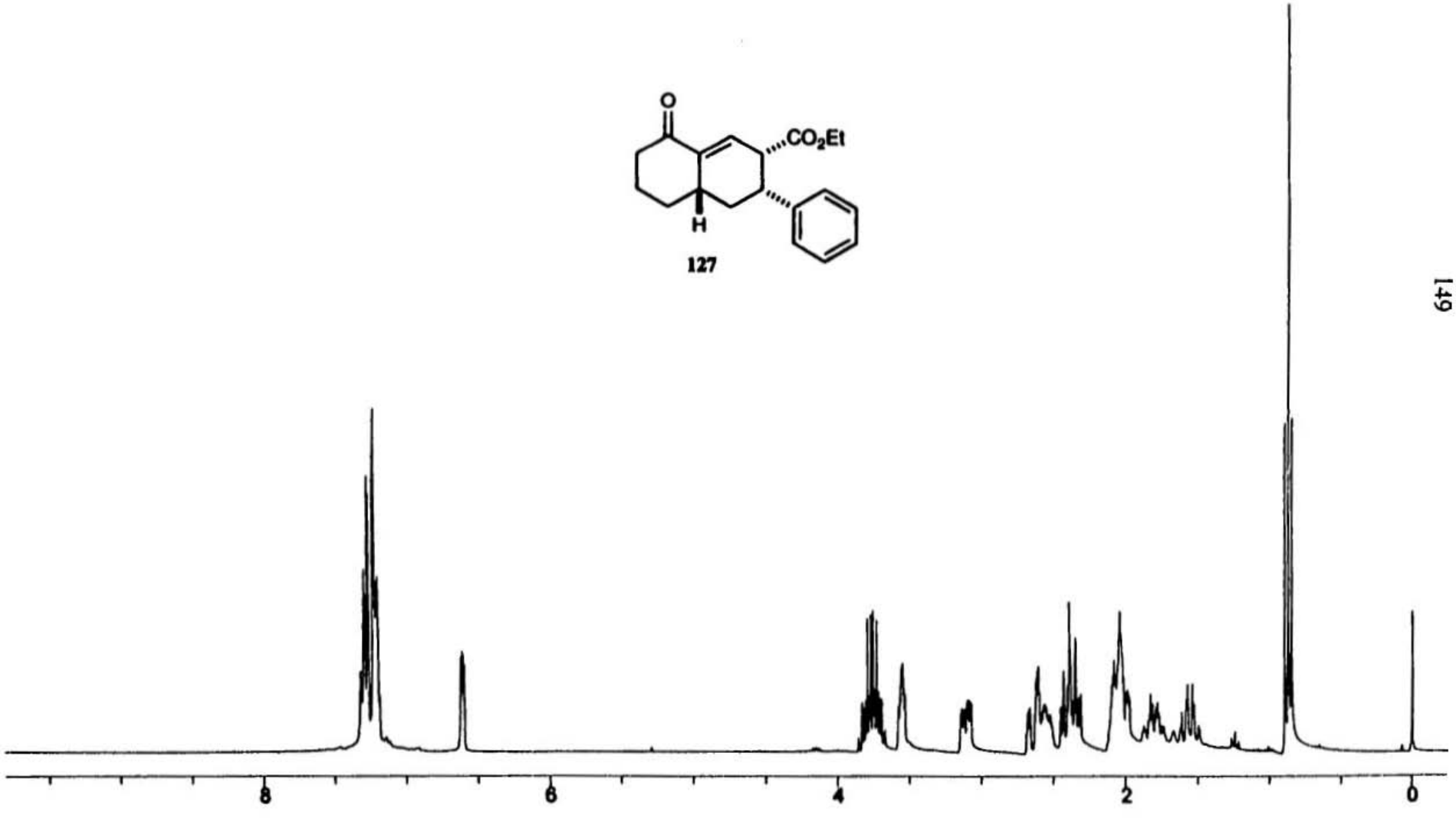
126a +



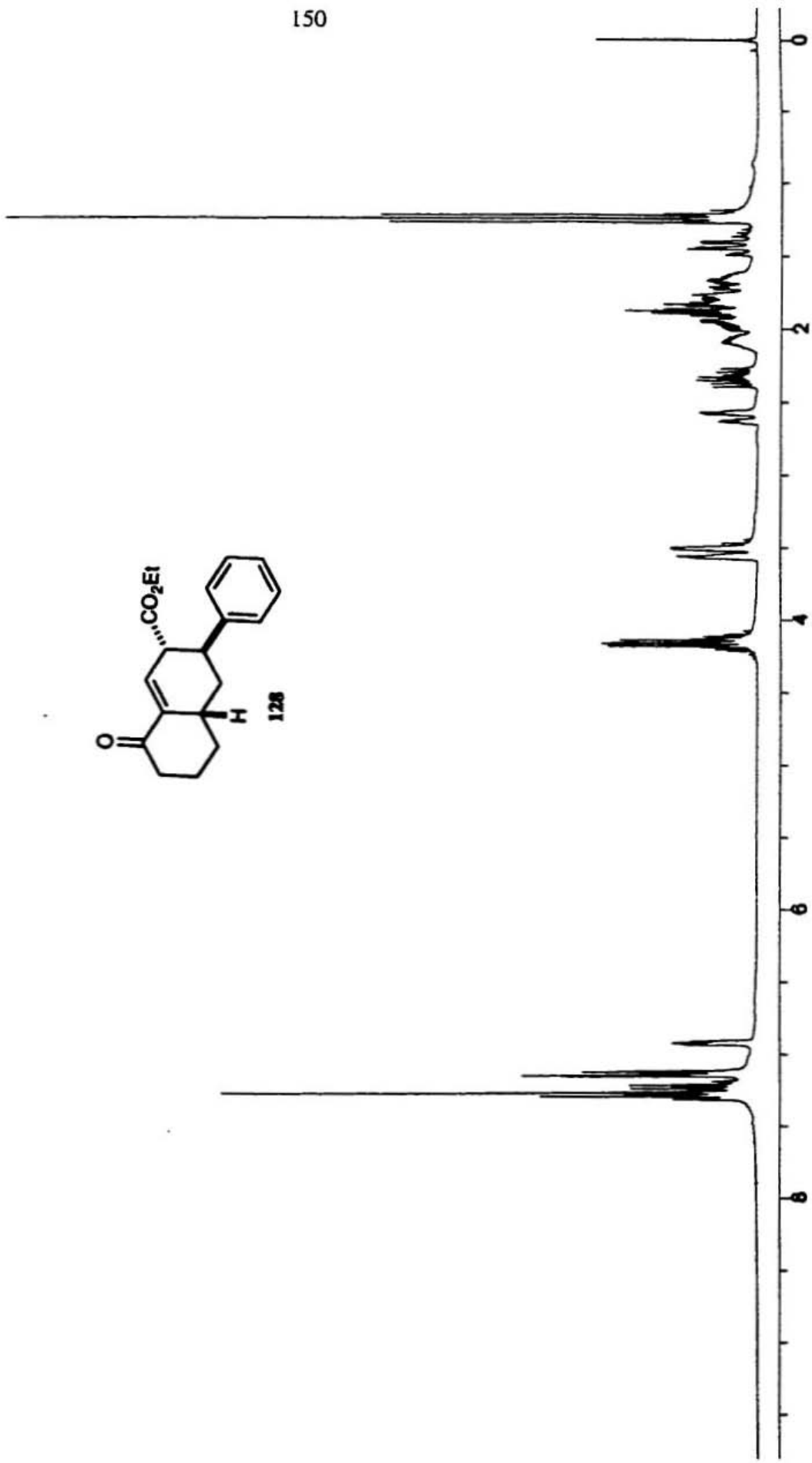
126a 126b

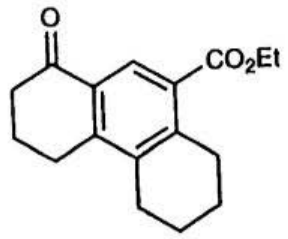
148

8 6 4 2 0

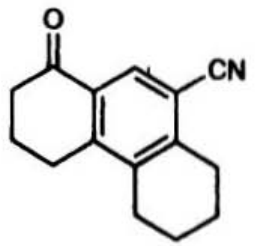


127

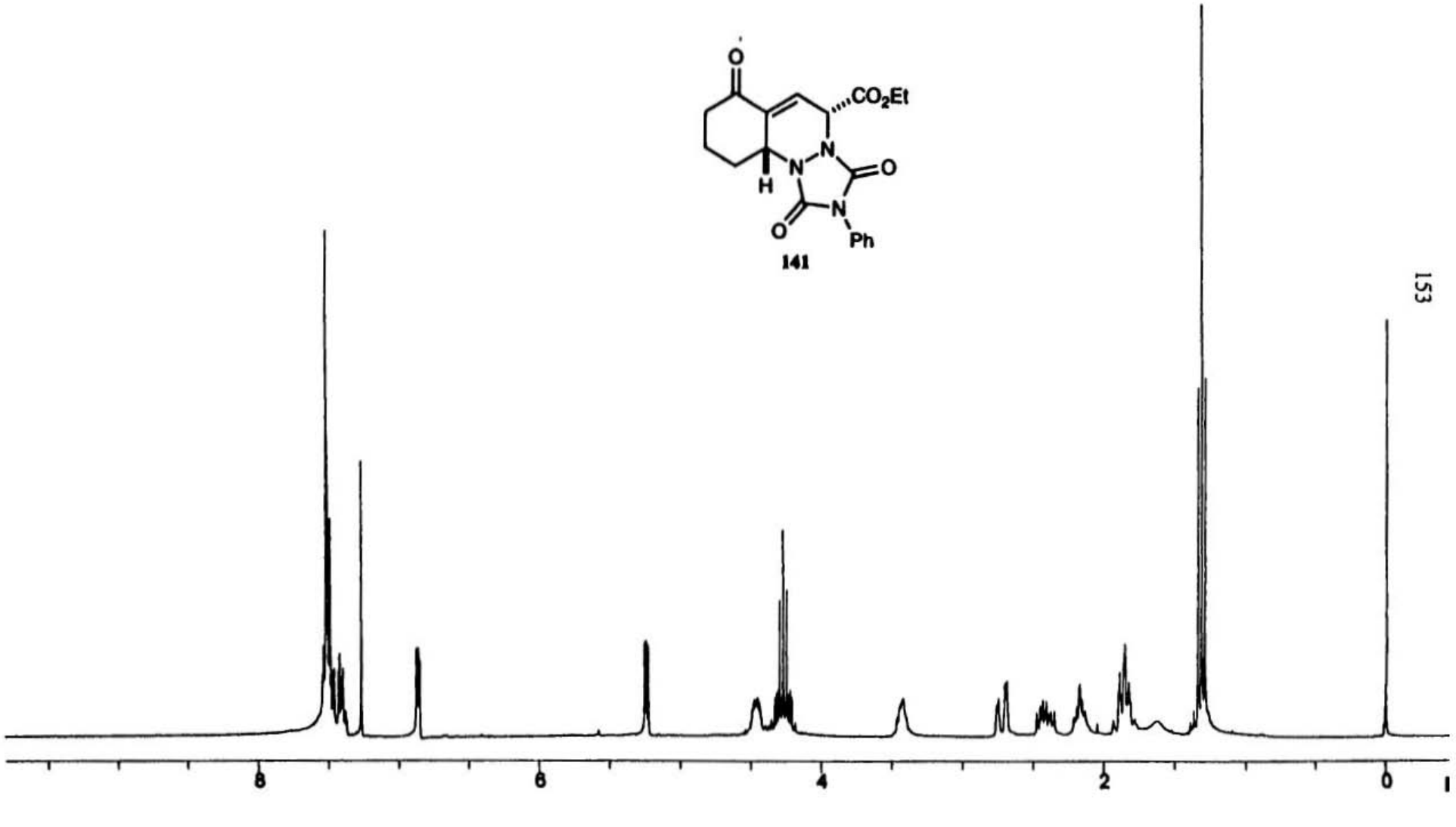

CO2Et
H
O
128
8
6
4
2
0

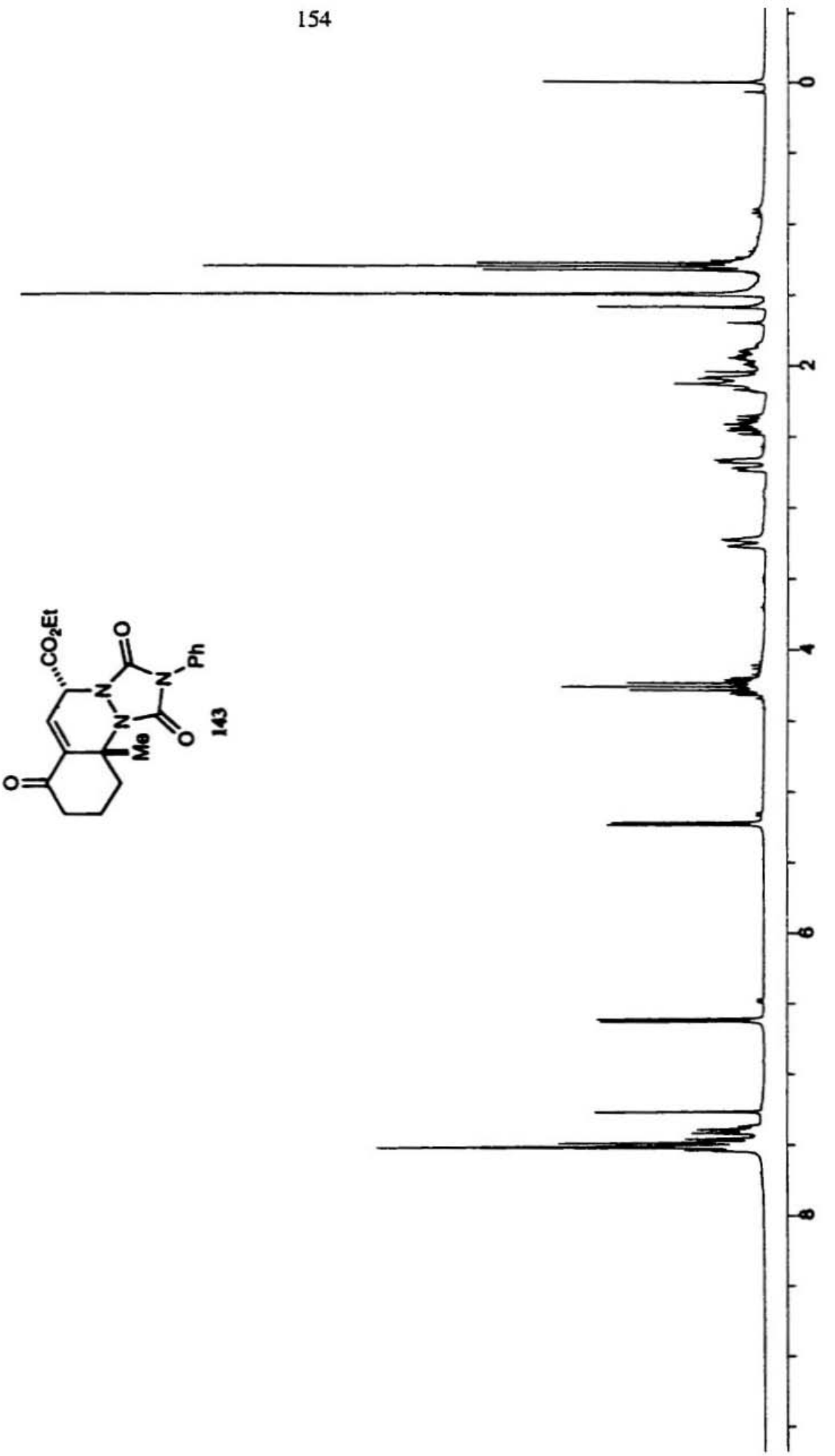


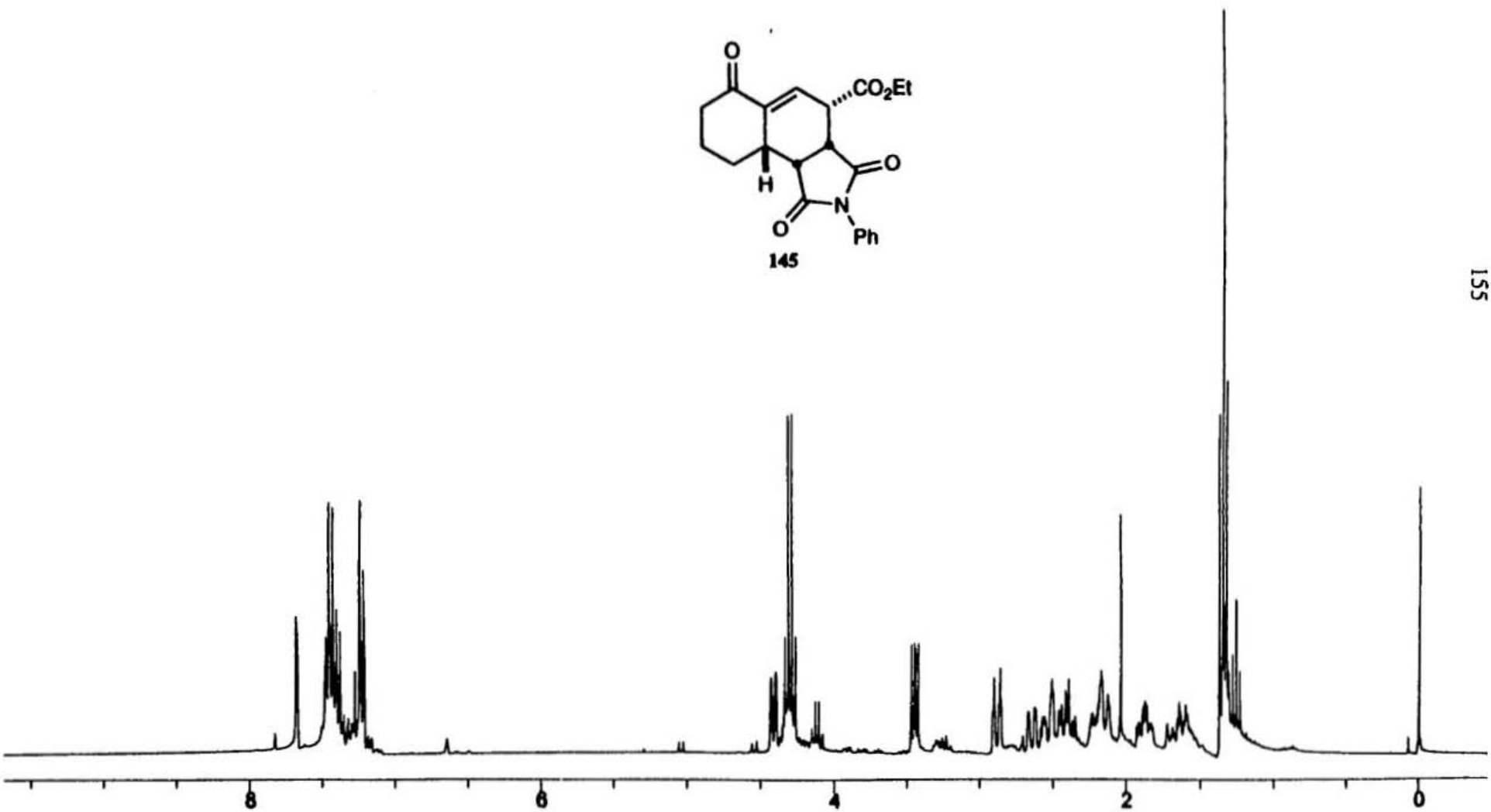
132



138


O
CO2Et
N
N
O
H
O
N
Ph
141
153
8
6
4
2
0


CO2Et
Ph
Me
143
8
6
4
2
0



145