INVESTIGATIONS ON THE MECHANISM OF THE DIELS-ALDER REACTION AND SYNTHETIC STUDIES ON THE PREZIZAENE SESQUITERPENES

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by

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Abstract

Spiro(bicyclo[2.2.1]heptane-2,1'-3-cyclopentene-2,5-dione) (**69**) which was obtained from norcamphor in three steps underwent cycloaddition with cyclopentadiene to give all of four possible adducts in a 50 : 22 : 24 : 4 ratio. The π-facial stereoselectivity in the *endo* region (72 : 28) was consistent with that of the complementary diene spiro(bicyclo[2.2.1]heptane-2,1'-[2,4]-cyclopenadiene) (**58**) with Z-ethylenic dienophiles (70 : 30). Likewise, the π-facial stereoselectivity of the cycloaddition of symmetrical dienophile spiro(bicyclo[2.2.2]octane-2,1'-3-cyclopentene-2,5-dione) (**70**) with cyclopentadiene is similar to that of the corresponding diene sipro(bicyclo[2.2.2]octane-2,1'-[2,4]cyclopentadiene) (**59**) in the Diels-Alder reaction with Z-ethylenic dienophiles. These results suggest very strongly that the steric interactions are responsible for the observed π-facial stereoselectivity in these spiro-addends.

The relatively large proportions of *exo* addition products in the cycloadditions of spiro(bicyclo[2.2.1]heptane-2,1'-3-cyclopentene-2,5-dione) (**69**) and spiro(bicyclo[2.2.2]octane-2,1'-3-cyclopentene-2,5-dione) (**70**) with cyclopentadiene stimulated the reevaluation of the *endo-exo* selectivity observed with simple dienophiles 4-cyclopentene-1,3-dione (**118**), spiro[4.5]dec-2-ene-1,4-dione (**104**), and 2,2-dimethyl-4-cyclopentene-1,3-dione (**107**). The results are discussed based on frontier molecular orbital theory.

Comparison experiments of dienes 2-(trimethylsiloxy)-1,3-cyclohexadiene (**145a**), 6,6-dimethyl-2-(trimethylsiloxy)-1,3-cyclohexadiene (**145b**), and 5,5-dimethyl-2-(trimethylsiloxy)-1,3-cyclohexadiene (**145c**) with both symmetrical and unsymmetrical dienophiles were conducted. The cycloadditions of diene 6,6-dimethyl-2-(trimethylsiloxy)-1,3-cyclohexadiene (**145b**) with symmetrical dienophiles proceeded at roughly the same rates as those of diene 5,5-dimethyl-2-(trimethylsiloxy)-1,3-cyclohexadiene (**145c**), which suggested that the reaction was not merely concerted but also synchronous.

2-Methyltricyclo[6.2.1.$0^{1,5}$]undecan-7-one (**278**) could serve as a precursor to the prezizaene sesquiterpenes. The synthesis of 2-methyltricyclo[6.2.1.$0^{1,5}$]undecan-7-one (**278**) was started with 1,4-dioxaspiro[4.5]decane-8-one (**294**), which was treated with methyllithium to give 8-methyl-1,4-dioxaspiro[4.5]decan-8-ol (**295**). The spiro-annulation of this ketal alcohol with 1,2-bis(trimethylsiloxy)cyclobutene (**77**) proceeded smoothly to produce 8-methylspiro[4.5]dec-7-ene-1,4-dione (**281**). Addition of methyllithium and ozonolysis, followed by intramolecular aldol cyclization afforded a 1 : 1 mixture of two double bond isomers 7-acetyl-4-methylenespiro[4.4]non-7-en-1-one (**299**) and 7-acetyl-4-methylspiro[4.4]nona-3,7-dien-1-one (**280**). Hydrogenation and base-induced aldol condensation of this mixture gave 2-methylspiro[6.2.1.$0^{1,5}$]undecan-7-one (**278** and **304**).

During the synthetic studies of prezizaene sesquiterpenes we found that the addition of methyllithium to 8-methylspiro[4.5]dec-7-ene-1,4-dione (**281**) is stereoselective. Similar diketones were treated with both methyllithium and sodium borohydride. In all the cases the nucleophiles prefer to approach the spiro-diketones at the same face as the double bond of cyclohexene ring. The observed facial selectivity is consistent with the predictions based on the Cieplak model.

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To my dear husband Yong-jin Wu

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Glossary of abbreviations

Ac	Acetyl
APT	Attached proton test
bp	Boiling point
Bu	Butyl
Bzl	Benzyl (CH_2Ph)
COSY	^1H-^1H Correlation spectrum
DASYN	Degree of asynchronicity
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl azodicarboxylate
DMAD	Dimethyl azodicarboxylate
DIBAL	Diisobutylaluminum hydride
DIPHOS-4	1,4-Bis(diphenylphosphino)butane
DMAP	4-(Dimethylamino)pyridine
DME	Dimethoxyethane
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulfoxide
Et	Ethyl
GC-MS	Gas chromatography-mass spectrometry
HMPA	Hexamethylphosphoric triamide
hν	Ultraviolet irradiation
*i*Pr	*iso*-Propyl
IR	Infrared spectroscopy

LDA	Lithium diisopropylamide
Me	Methyl
MOM	Methoxymethyl
mp	Melting point
Ms	Mesyl = methanesulphonyl
MS	Mass spectrometry
*m*CPBA	*meta*-Chloroperoxybenzoic acid
NBA	*N*-Bromoacetamide
NBD	Norbornadiene
NBS	*N*-Bromosuccinimide
NMR	Nuclear magnetic resonance spectroscopy
NOE	Nuclear Overhauser enhancement
Nu	Nucleophile
PCC	Pyridinium chlorochromate
Ph	Phenyl
*p*TSA	*para*-Toluenesulphonic acid
TBDMSCl	*tert*-Butylchlorodimethylsilane
THF	Tetrahydrofuran
TFA	Trifluoroacetic acid
TLC	Thin layer chromatography
TMSCl	Chlorortimethylsilane
Ts	Tosyl = *para*-toluenesulphonyl

Chapter 1

ENDO-EXO AND π-FACIAL STEREOSELECTIVITY IN THE DIELS-ALDER REACTIONS OF 2,2-DISUBSTITUTED CYCLOPENT-4-ENE-1,3-DIONE DERIVATIVES

I. Introduction

Since its discovery in 1928 by Diels and Alder,[1] the Diels-Alder reaction has been refined to become one of the most powerful tools in modern organic synthesis.[2] It presents a very convenient and highly stereospecific route to the ubiquitous six-membered ring involving the elaboration of as many as four contiguous stereogenic centers in a single operation. Woodward and Hoffman's[3] pericyclic theory successfully predicted an allowed [$\pi_{4S} + \pi_{2S}$] process and indeed agreed with the known facts with respect to the mechanism. It was this theory that correlated many experimental results which had been thought to be unrelated, and it was thus rapidly accepted by chemists around the world. According to their theory, Diels-Alder reactions of alkenes to 1,3-dienes, are controlled by the in-phase relationships of both frontier-orbital pairs [HOMO(diene) - LUMO(dienophile)] and [HOMO(dienophile) - LUMO(diene)].* These strongly favored in-phase relationships are first-order orbital interactions which play a vital role in the control of the stereospecificity of the reaction.

Although Diels-Alder reactions occur in some unsubstituted cases, the most successful reactions involve dienes and dienophiles bearing substituents of complementary electronic influence. Very often there is an electron-donating group on the diene and an

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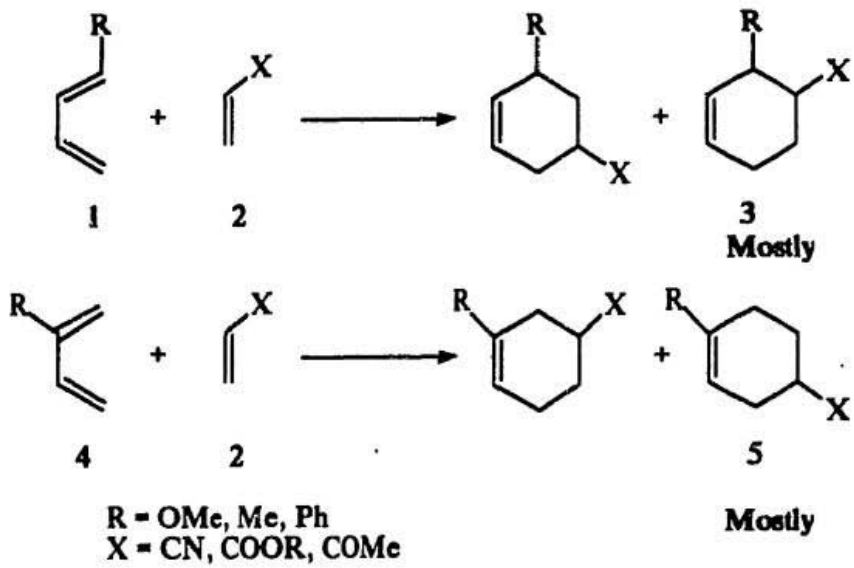
* HOMO: Highest Occupied Molecular Orbital; LUMO: Lowest Unoccupied Molecular Orbital.

electron-withdrawing group attached to the dienophile. Nevertheless, there are few examples involving "inverse-electron-demand", *i.e.*, an electron-withdrawing group on the diene and an electron-donating group connected to the dienophile.[4,5]

Scheme 1



There are three important stereochemical features pertaining to the Diels-Alder reaction, *i.e.*, regiochemistry, topography (*endo* or *exo*), and π-facial diastereoselectivity. The regiochemistry may be controlled by choosing the appropriate substituents on the addends. For example, the formation of *ortho* and *para* products **3** and **5**, respectively, is strongly favored for electron-rich substrates such as **1** and **4** (Scheme 1).[3] This regioselectivity may be explained in terms of frontier orbital interactions.[4] Figure 1a shows the π energy levels of butadiene and ethylene, with HOMO-LUMO interactions as indicated. In Figure 1b an electron-donating group R on the diene will raise the diene HOMO and an electron-withdrawing group X on the dienophile will lower the dienophile LUMO, which results in the stronger dominant interaction as depicted. Figure 1c shows orbital energies, and the resulting orbital interaction in the case of inverse-electron-demand. With respect

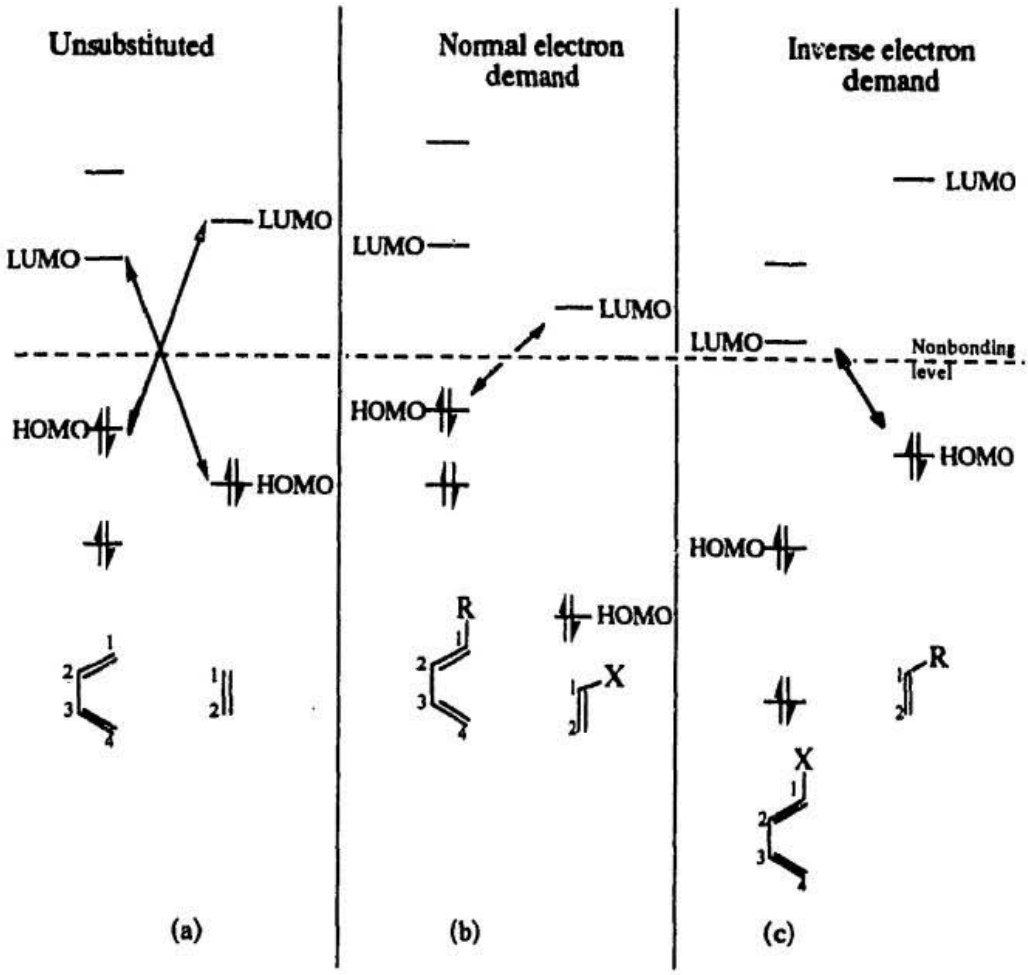


Figure 1. Frontier orbital interactions in the Diels-Alder reaction. In the unsubstituted case, butadiene + ethylene (a), both HOMO-LUMO interactions are equally important. Substituting an electron donor R on the diene and an acceptor X on the dienophile leads to the energy-level pattern (b) characteristic of normal electron demand. The interaction diene HOMO-dienophile LUMO now is strong and dominates the interaction. Inverse-electron-demand occurs for the substitution pattern shown in (c).

to the usual electronic situation shown in Figure 1b, the important orbitals involved are the diene HOMO and dienophile LUMO. The electron-donating group R on C-1 results in a large difference in the HOMO orbital coefficients at C-1 and C-4 of the diene, as indicated in **6** (Figure 2), in which the shaded circles represent a positive sign and the

unshadowed circles represent a negative sign and the relative sizes of the circles represent the relative contributions of the respective p orbitals to the HOMO. Obviously, the C-4 coefficient is much larger than the C-1 coefficient in **6**. However, if the donor substituent R is at C-2, then the coefficient at C-1 is much larger than that at C-4, as shown in **8**. Similarly, the electron-withdrawing group X on the dienophile leads to a larger coefficient at C-2 than at C-1. On the basis of the concept that the stabilization energy is maximized when the larger coefficients overlap each other, the strongest interaction of diene **1** with dienophile **2** is between C-4 in **1** and C-2 in **2** (see **6** and **7** in Figure 2), thereby leading to *ortho* product **3** as the major product. Likewise, C-1 in diene **4** interacts very strongly with C-2 in dienophile **2** (see **7** and **8** in Figure 2) and the *para* product **5** is formed as the predominant adduct.[6]

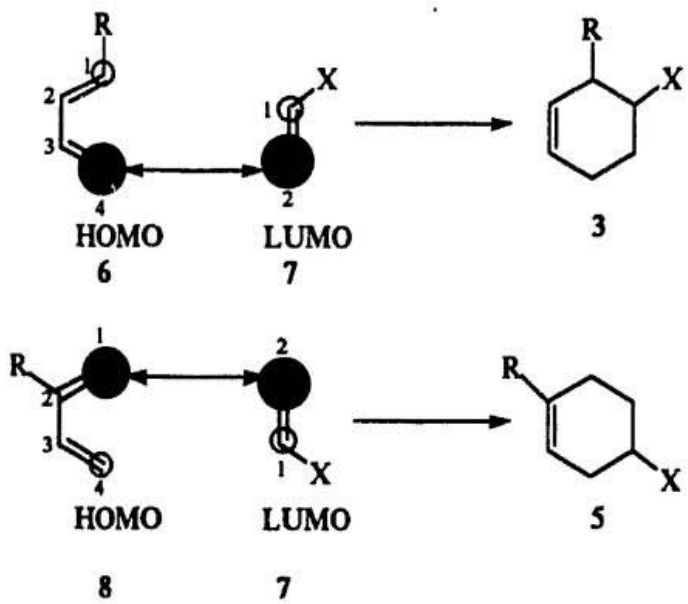
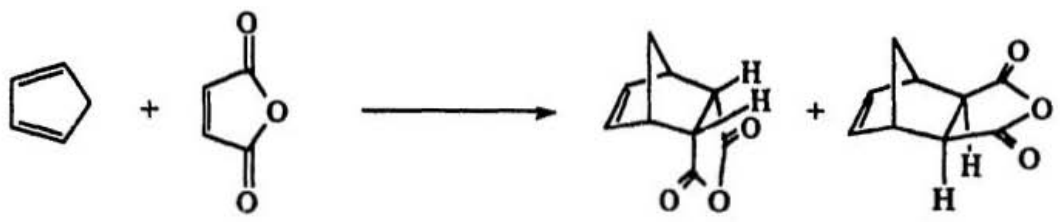


Figure 2. Regiochemical control of the Diels-Alder reaction

When both diene and dienophile are substituted, *endo* addition is frequently very much predominant over *exo* addition, a fact attributed to secondary orbital interactions.[3] For example, the cycloaddition of cyclopentadiene to maleic anhydride produces a 99 : 1

mixture of *endo* (**9**) and *exo* (**10**) adducts. The *endo* principle can also be rationalized on the basis of frontier orbital theory. Figure 3 shows the HOMO of cyclopentadiene and the LUMO of maleic anhydride when these molecules are oriented in the *endo* and *exo* transition states. In addition to the primary interaction as indicated by solid lines, there is also a stabilizing secondary orbital interaction (dotted lines) in the *endo* transition state. Clearly, this secondary orbital interaction is absent in the *exo* orientation. Hence, the *endo* addition is favored.

Scheme 2



9 **10**

endo *exo*

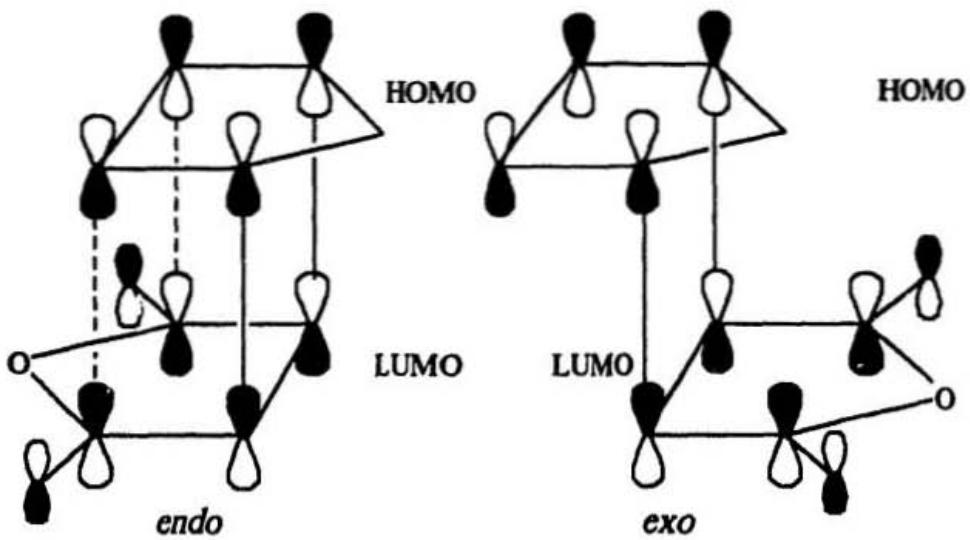


Figure 3. Frontier molecular orbital diagram of both endo and exo transition states in the Diels-Alder reaction of cyclopentadiene with maleic anhydride

The third stereochemical feature is π-facial diastereoselectivity, which arises when the addends possess two different reactive faces. In general, the *syn* or *anti* addition are relatively designated. As shown in Figure 4, an incoming dienophile can approach the diene *syn* to R substituent from the top face of the diene or *anti* to R substituent from the bottom face of the diene. Likewise, a diene can add to the plane-nonsymmetrical dienophile *syn* to R_1 substituent or *anti* to R_1 substituent. This is important for both the understanding of the reaction mechanism and the design of natural product synthesis. Indeed, π-facial (*syn-anti*) stereoselectivity in Diels-Alder reactions involving plane-nonsymmetric dienes has been widely studied in recent years. The cyclic dienes have been frequently chosen in studies of π-facial selectivity simply due to their rigid conformation. In many instances, the cycloaddition occurs on the less sterically hindered face of the diene. Table 1 shows some examples of addition *anti* to a more sterically hindered substituent. For example, the CHX_2 (X = Br, Cl) group in **16** is bulkier than the methyl group, thereby resulting in exclusive addition *anti* to CHX_2 (Entry 6).[12] The predominant addition *anti* to the hydroxymethyl group in **15** (Entry 5) can be attributed mainly to steric factors since the hydroxymethyl group is somewhat more sterically encumbering than a methyl group.[11].

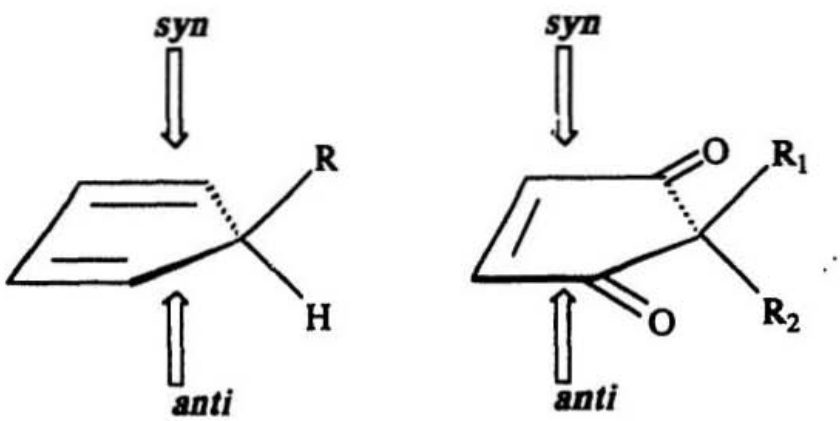


Figure 4. syn/anti additions of plane-nonsymmetrical dienes and dienophiles

Table 1. Facial selectivity of cyclic dienes

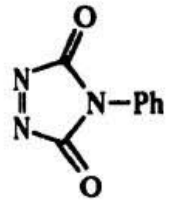
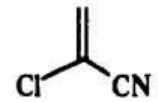
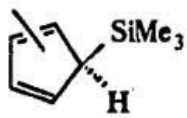
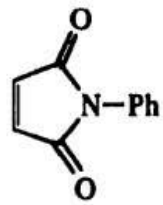
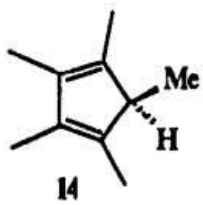
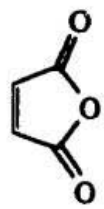
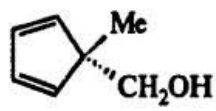
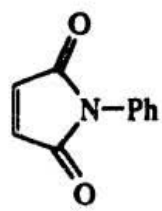
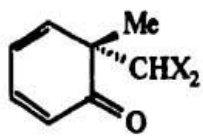
Entry	Diene	Dienophile	% of *anti*	Ref.
1	 **11** X = Br, I		100	7
2	 **12** X=Me, Bn, CH_2CCl_3		100	8
3	 **13**		100	9
4	 **14**		80	10
5	 **15**		87	11
6	 **16** X = Br, Cl		100	12

Table 2. Facial selectivity of hetero-substituted cyclopentadienes

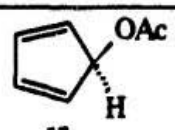
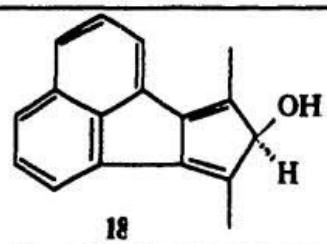
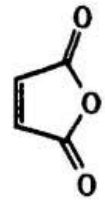
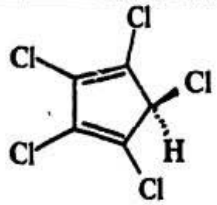
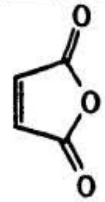
Entry	Diene	Dienophile	% of *syn*	Ref.
1	 **17**		100	13
2	 **18**		100	14
3	 **19**		90	15

Table 3. Facial selectivity of hetero-substituted dienes

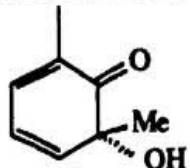
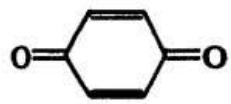
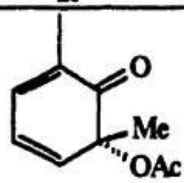
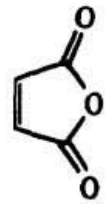
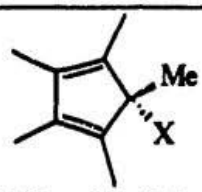
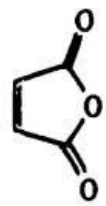
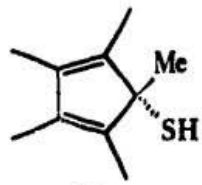
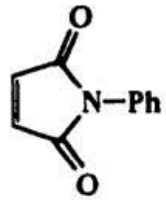
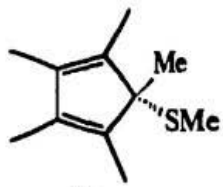
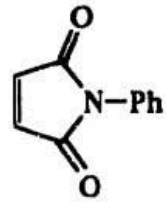
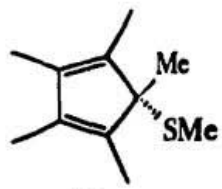
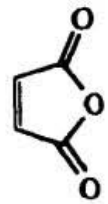
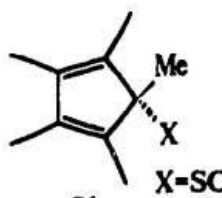
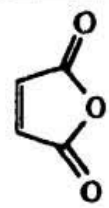
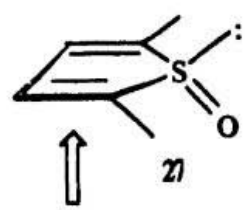
Entry	Diene	Dienophile	% of *syn*	Ref.
1	 **20**		100	19
2	 **21**		100	19
3	 **22** X = OH, OMe, NH_2, NHAc		100	20

Table 4. Facial selectivity of 5,5-disubstituted cyclopentadienes

Entry	Diene	Dienophile	% of *anti*	Ref.
1	 23		45	20
2	 24		92	20
3	 25		97	20
4	 X=SOMe, SO_2Me 26		100	20


27

There are some Diels-Alder reactions in which the facial selectivity is controlled by what might be loosely called "electronic" effects. Table 2 shows three contrasteric additions of 5-heterosubstituted cyclopentadienes. These results were rationalized by Fukui and coworkers[16] in the following way. The orbital mixing between the lone-pair electrons of the heteroatom directly attached to cyclopentadiene and the diene HOMO causes the HOMO to be biased toward the *syn* surface, thereby inducing kinetically controlled dienophile attack from that direction. Alternatively, Anh[17] proposed that a beneficial interaction of an antisymmetric oxygen orbital with the diene LUMO is mainly responsible for the contrasteric addition. More recently, Kahn and Hehre[18] proposed that cycloadditions involving electron-rich dienes and electron-poor dienophiles should occur preferentially onto the diene face which is more nucleophilic and onto the face of the dienophile which exhibits the greater electrophilicity. Indeed, this idea is in agreement with the *syn* additions as presented in Table 2.

As summarized in Table 3, the cycloadditions of dienes **20**, **21** and **22** (X = OH, OMe, NH_2, NHAc) occur exclusively from the face *syn* to the heteroatoms directly attached to the cyclohexanediene or cyclopentanediene rings. This may be rationalized in terms of a combination of steric, van der Waals-London and secondary orbital overlap factors. The simple electrostatic model proposed by Kahn and Hehre[18] can be suitable in these cases.

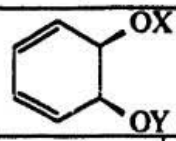
In contrast to the reactions of dienes **22** (X = OH, OMe, NH_2, NHAc), dienes **24**, **25**, and **26** displayed the reversed facial selectivities as shown in Table 4.[20] In these cases, steric effects may play a more important role in the control of facial selectivity than electronic factors. The larger size of the sulfur substituents -SX (X ≠ H) may cause the dienophile to approach *anti*, so that the cycloaddition occurs from the sterically less encumbered methyl face. The reversed facial selectivity can be attributed to the fact that the sulfur substituents -SX (X ≠ H) are somewhat larger than the oxygen analogues -OX. The reduced π-facial selectivity of diene **23** (Entry 1) may result from the relatively small

size of the thiol group SH.

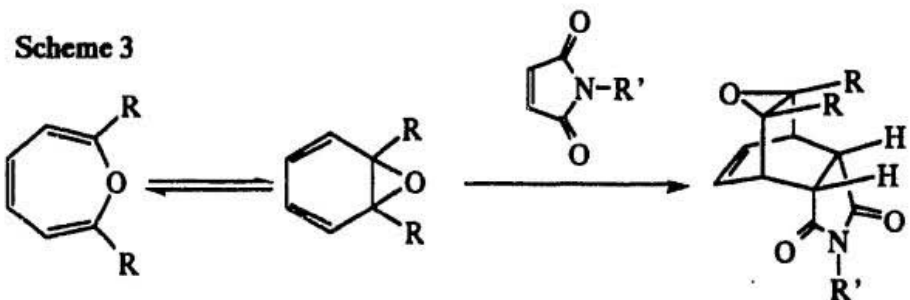
It should be pointed out that in the case of the sulfur systems illustrated in Table 4 the simple electrostatic model can no longer be applicable in a straightforward fashion. The Cieplak model,[21] based on σ-donor ability of the *anti* plane-nonsymmetric atom has been applied to the cycloadditions by Macaulay and Fallis.[20] They concluded that the cycloadditions of cyclopentadienes prefer *anti* addition to the antiperiplanar σ bond that is the better σ donor on the basis of hyperconjugation and the beneficial interaction with the incipient bond. The common atom combinations are listed in order of increasing σ donor ability: $\sigma_{CO} < \sigma_{CN} < \sigma_{CCl} < \sigma_{CC} < \sigma_{CH} < \sigma_{CS}$.[22] Thus, when the competition is between a CC and CS σ bond, the cycloaddition should take place by *anti* addition to the better donor (the CS σ bond), as is observed (except with **23**). Similarly, when the choice is between a CC σ bond or a CO σ bond-bearing face, the preferential addition should occur *anti* to the better donor (the CC σ bond) and thus *syn* to the CO σ bond, as is found. The preferred *syn* addition to other heteroatoms such as chlorine and nitrogen (Table 2 and 3) can be interpreted in the same fashion. The Cieplak model has been successfully applied to the 2,5-dimethylthiophene oxide system **27**. For thiophene oxide, in which the competition is between a lone pair and a sulfoxide oxygen, the cycloaddition should prefer to proceed *anti* to the better donor (the lone pair) and hence *syn* to C-O. In fact, the exclusively contrasteric *syn* addition to oxygen was observed with several dienophiles.[23]

Recently, in our laboratories Gillard[24] studied the facial selectivity of cycloadditions of *cis*-cyclohexa-3,5-diene-1,2-diol and its derivatives with *N*-phenylmaleimide. As summarized in Table 5, the cycloadditions occurred preferentially to the face of the diene *syn* to the oxygen substituents, but the facial selectivity was less pronounced in the more reactive, cyclic derivatives. These contrasteric *syn* additions might be rationalized on the basis of either orbital mixing, or for electrostatic reasons, or by invoking Cieplak's model. The reduced facial selectivity in the case of the cyclic derivatives **31** and **32** may

Table 5. Facial selectivity of 3,5-cyclohexadiene-1,2-diol derivatives with *N*-phenylmaleimide

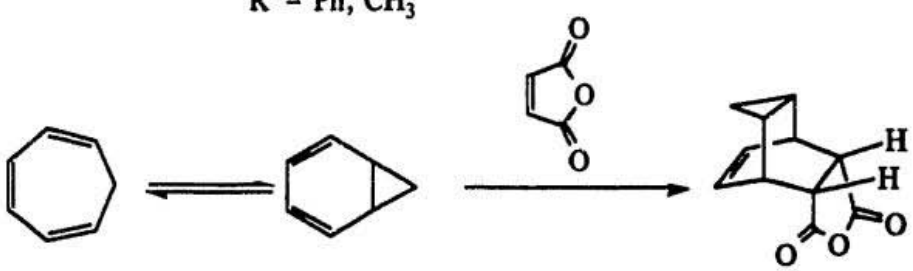
Entry				% of *syn*
	X	Y	Diene	
1	H	H	28	94
2	Ac	Ac	29	88
3	TMS	TMS	30	100
4	—$SiMe_2$—		31	65
5	— CMe_2 —		32	60

Scheme 3

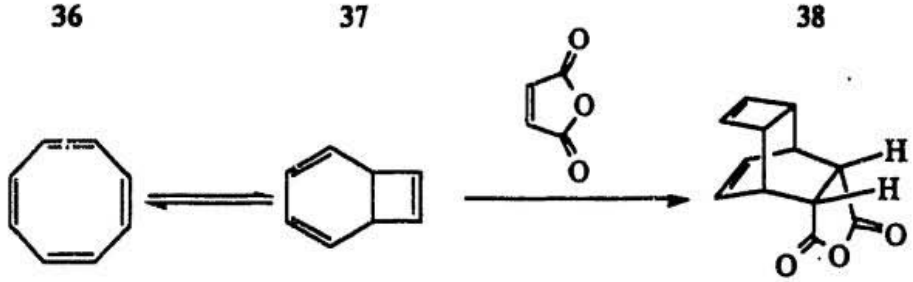


33 34 35

R = H, Me, -$(CH_2)_3$-
R' = Ph, CH_3



36 37 38



39 40 41

be attributed to steric interactions.

The Diels-Alder reactions of *N*-phenyl or *N*-methylmaleimide with benzene oxide **34** (R = H) (oxepin-1,3,5-cyclohexatriene 1,2-oxide, **33** ⥱ **34**) and its more substituted derivatives (R = Me, $-CH_2CH_2CH_2-$) have also been investigated in detail (Scheme 3).[25] In all the cases examined, the dienophile approached the diene **34** exclusively *anti* to the plane-nonsymmetrical oxygen leading to a single adduct **35**. Clearly, Kahn and Hehre's idea that dienophiles should add to the more nucleophilic face (*i.e. syn* to the oxygen in this case) cannot be operative here. In addition, the conclusion put forward by Fallis and Macaulay that the cycloaddition should prefer *anti* addition to the antiperiplanar σ bond that is the better donor (C-H or C-C in this case) cannot be extended in a straightforward manner to the benzene oxide system. The observed facial selectivity can be rationalized in terms of the steric and the electronically repulsive interactions between the oxygen and the incoming dienophile. This repulsion might be somewhat related to that encountered in the cycloaddition of maleic anhydride to cycloheptatriene (**36** ⥱ **37**)[26] or cyclooctatetraene (**39** ⥱ **40**),[27] in which only the *anti* products **38** and **41** were obtained (Scheme 3).

The π-facial selectivity in the cycloadditions of several propellane substrates has been examined by Ginsburg and his coworkers[28,29] as summarized in Table 6. The exclusive *anti* addition in the case of dienes **42** and **43** (Entries 1 and 2) can be explained

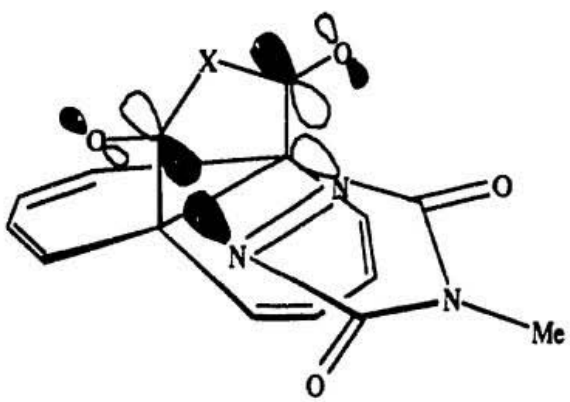
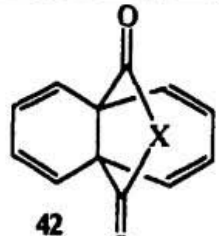
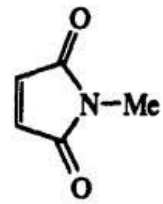
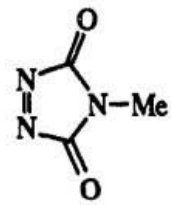
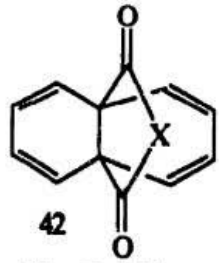
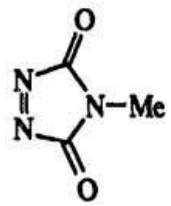
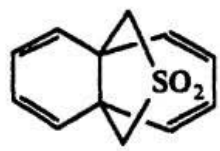
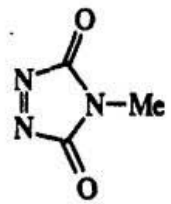


Figure 5. Secondary orbital overlap in the approach of an azo dienophile *syn* to an anhydride bridged propellane

Table 6. Facial selectivity of propellanes

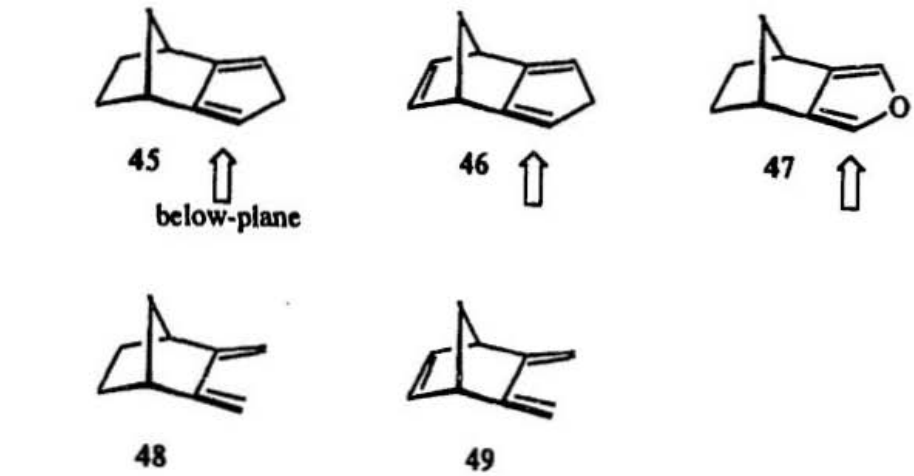
Entry	Diene	Dienophile	% of *anti*	Ref.
1	 **42** X = O, NMe		100	28
2	 **43** x = CH_2, O, NH_2, S		100	29
3	 **42** X = O, NMe		0	29
4	 **44**		5	29

on the basis of repulsive steric interactions between the five-membered ring system and the *syn*-approaching dienophile. It is very interesting to note that the facial selectivity of diene **42** is completely reversed (Entry 3) upon changing the dienophile. This has been rationalized in terms of secondary orbital interactions. The attractive interaction between the π system of the anhydride moiety (with X = O) with the lone-pair orbitals on the nitrogens of the dienophile greatly stabilizes the *syn* transition state for dienophile (*N*-methyltriazolinedione) attack at the cyclohexadiene face as depicted in Figure 5, resulting in exclusive *syn* addition. The contrasteric *syn* addition of diene **44** with *N*-methyltriazolinedione cannot be justified by secondary orbital interactions. The reason for *syn* addition might be attributed to a stabilizing Coulombic attraction between the strongly electron-deficient sulfur atom in the SO_2 group and the electron-rich -N=N- group in the dienophile.

The π-facial selectivity of the cycloadditions to exocyclic dienes such as **45-47**[30-33] has been examined in considerable detail. Cycloadditions of the diene **45** proceeded exclusively from the "below-plane" with all dienophiles except maleic anhydride and singlet oxygen. Dienes **46** and **47** behaved very similarly. Since the primary reacting carbons of the cyclopentadiene rings are remote from either bridge, steric factors cannot be responsible for the overwhelming kinetic preference for below-plane attack of dienophiles on **45**, **46** and **47**. The rationalization invoked by Paquette and coworkers[31] involved σ orbital mixing with the π_s diene orbital. Such interactions should cause a tilt of the diene orbitals in a disrotatory manner as shown in Figure 6a, resulting in minimization of the level of antibonding interaction on the below-plane face of **45**, **46** and **47** as compared with the above-plane face.

Calculations on the simple model systems **48** and **49** indicated strong mixing between the lowest occupied π orbital (π_s) and high-lying σ orbitals of proper symmetry, which was supported by the photoelectron (PE) spectra of **48** and **49**.[34] The rotation of the terminal p_π lobes for π_s in **48** results in significant differences in the frontier electron

distribution on the *exo* and *endo* diene surfaces. It is this orbital tilting that is responsible for the preferred addition of a dienophile *anti* to the methano bridge. Because of the different overlap between the dienophile and the rotated $2p_{\pi}$ orbitals at the terminal carbon atoms of the diene moiety, the antibonding interaction between the π_s of the butadiene fragment and the HOMO of the dienophile in the case of *anti* attack is smaller than that of *syn* approach (Figure 7).



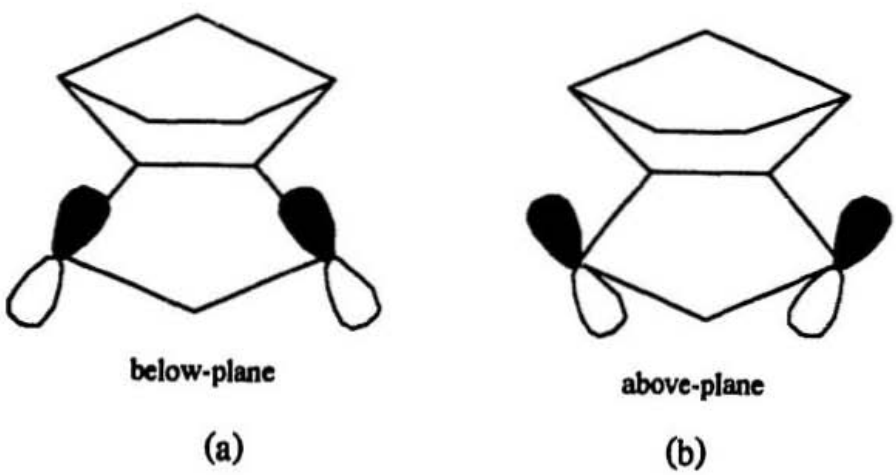
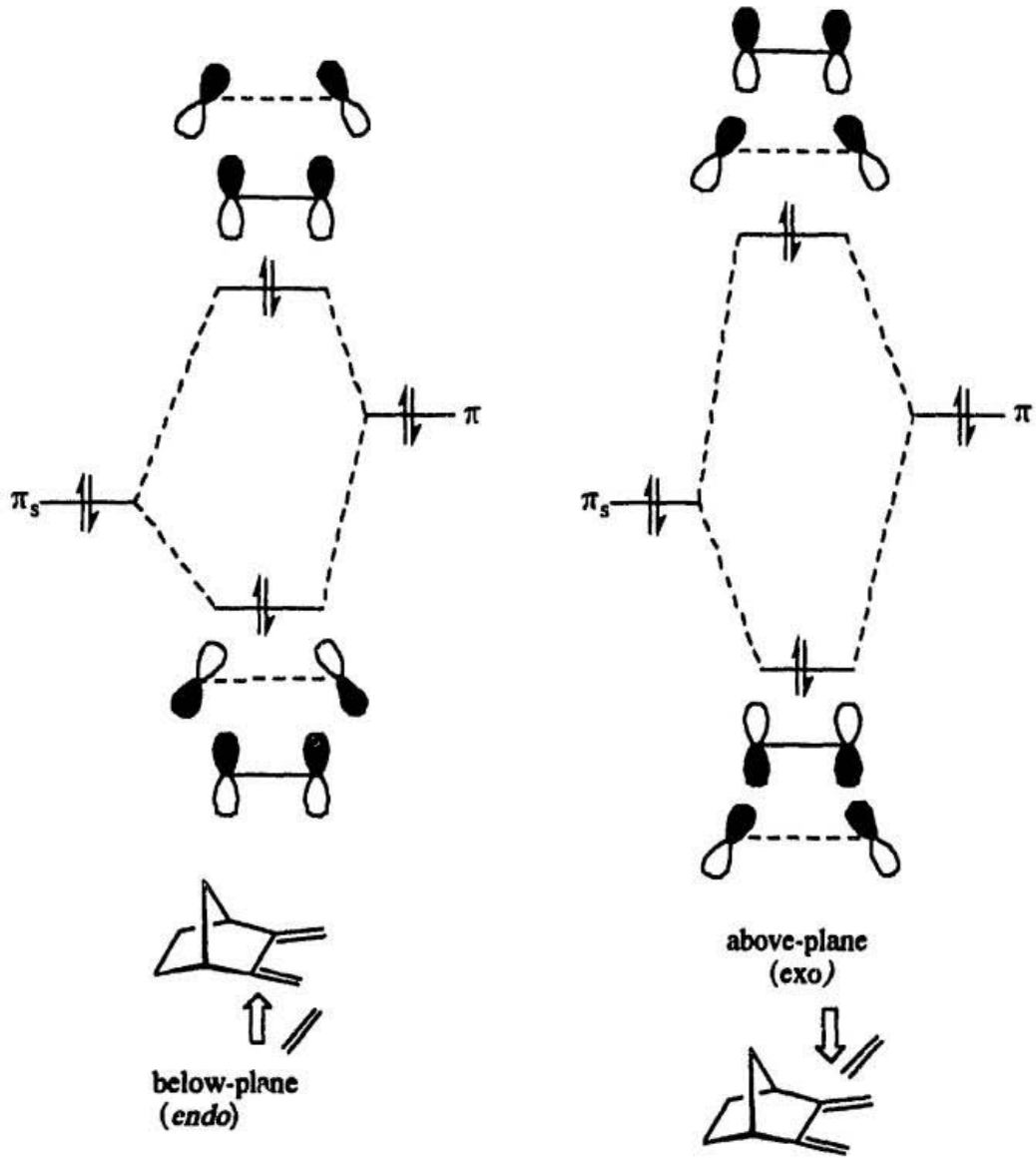
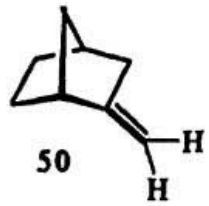


Figure 6. Disrotatory rotation of the terminal p_{π} lobes for π_s in **45, 46, 47** *etc.* (a) and **56, 57** *etc.* (b).

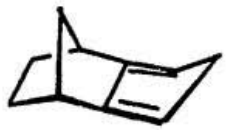


(a) below-plane approach (b) above-plane approach

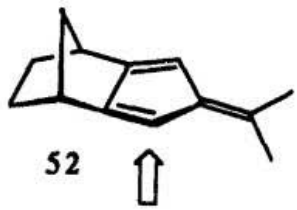
Figure7. Qualitative diagram of the interaction between the butadiene unit in **48** and **49** with a π bond.



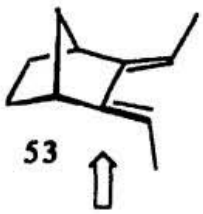
50



51



52



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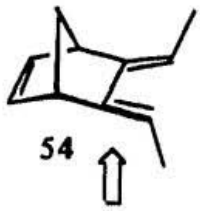
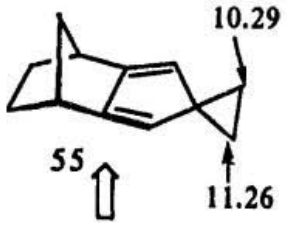


54



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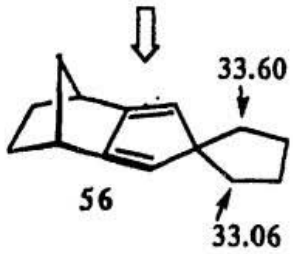

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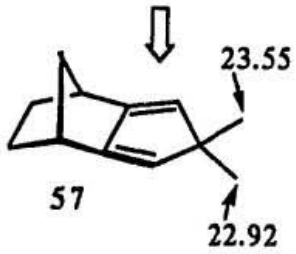


57

Based on his extensive calculations, Houk[35] has shown that the exocyclic double bond in 2-methylidenenorbornane (**50**) is pyramidalized so as to bend the terminal hydrogens in the *exo* direction. The analogous pyramidalization of **45** (see **51**) might be considered as an alternative rationalization for preferential attack of the dienophile from below-plane. However, as shown by Paquette and coworkers,[36] the Diels-Alder additions of the planar norbornyl-fused dimethylfulvene **52** occurred exclusively from the below-plane, which ruled out Houk's πorbital distortion arguments.

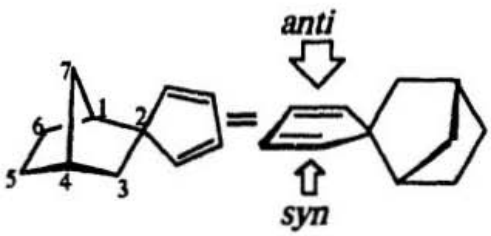
Vogel[33b] suggested that the π-facial selectivity observed in the cycloaddition reactions of *iso*dicyclopentadiene systems is controlled by the relative stabilities of the isomeric adducts. However, Diels-Alder reactions are not generally thermodynamically controlled. Furthermore, Paquette *et al.*[37] demonstrated that the [4 + 2] additions of dienes **53** and **54** to a variety of dienophiles occurred exclusively from below-plane. It should be noted that the adducts of **53** (or **54**) are not sesquinorbornene derivatives, and consequently their thermodynamic stabilities should be roughly the same.

The spirocyclopropane system **55** was found to have a preference for below-plane attack by a variety of dienophiles.[38] In contrast, the [4 + 2] cycloadditions of systems **56** and **57** occurred exclusively from above-plane to provide *anti*-sesquinorbornene derivatives, except with dimethyl azodicarboxylate (DMAD).[38] On the basis of the PE spectra of **55**, **56** and **57** and extensive calculations, Gleiter and Paquette[34] argued that the terminal π lobes of **56** and **57** in their individual π_s MO's are rotated *away from* the methano bridges as indicated in Figure 6b. Note that this rotation is different from that of **45**, **46**, **47** and **55** and hence results in different π-facial selectivity (Figure 6). The spirocyclopropane **55** exhibited the π-facial selectivity opposite to **56** and **57** simply due to spiroconjugation. The π orbital tilting in these spiro systems was supported by the ^{13}C NMR data: the carbon shielding effects present in **56** and **57** are *reversed* relative to those in **55**.

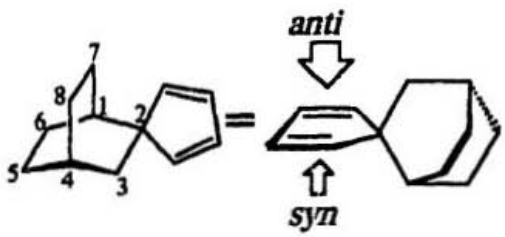
The σ/π interactions have been quite successfully applied to *iso*dicyclopentadiene systems, but they cannot explain, for example, why DMAD attacked **56** from below-plane, while all other dienophiles reacted from above-plane.[38] The σ/π model ignores interactions between the diene and dienophile, and it does not consider the nature of the transition state of the cycloaddition. Consequently, the model cannot rationalize the different π-facial selectivity for a given diene when different dienophiles were employed.

Burnell and Valenta[39] reported that dienes **58** and **59**, which are also rigid hydrocarbons, react predominantly by *anti* attack with a variety of Z-ethylenic dienophiles. This π-facial selectivity was ascribed to steric interactions in the transition states, and this

π-facial selectivity was ascribed to steric interactions in the transition states, and this argument was supported by a computational study performed by Houk *et al.*[35,40] It should be pointed out that certain resonances in the ^{13}C NMR spectra of **58** and **59** are significantly upfield of their expected positions (in $CDCl_3$, **58**: δ 44.1 for C-1 and δ 33.9 for C-3; **59**: δ 31.4 for C-1 and δ 28.9 for C-3), which may be symptomatic of appreciable mixing of the bicyclic σ orbital framework with diene π_s orbital. At present, it is still uncertain whether hyperconjugative effects present in **58** and **59** are major contributory factors in the π-facial selectivity control of these diene systems.



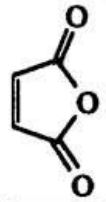
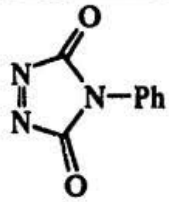
58



59

Recently, Coxon and coworkers[41] investigated the π-facial selectivity in the Diels-Alder reactions of dissymmetric 1,3-cyclohexadienes. Reactions of **60a-c** with maleic anhydride and benzoquinone show strong preference for addition to the "carbonyl" face of the diene. For dimethyl acetylenedicarboxylate, attack from this face decreases with successive methylidene substitution while for *N*-phenyl-1,2,4-triazolinedione the reverse occurs. The sensitivity in the selectivity of **60a-c** with dimethyl acetylenedicarboxylate was ascribed to unfavorable orbital interaction of the closed shells of the carbonyl(s) and methylene(s) *syn* to the incoming orthogonal π orbital of dimethyl acetylenedicarboxylate.

Table 7. Product ratios for the Diels-Alder reaction of **60**

Entry	Dienophile	% Reaction at the carbonyl face		
		2a	2b	2c
1		100	100	85
2		100	100	100
3		55	25	10
4		64	78	93

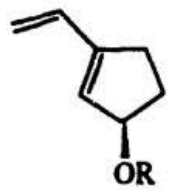
60

a: X = Y = O
b: X = O, Y = CH_2
c: X = Y = CH_2

The facial selectivity of Diels-Alder reactions of acyclic unsymmetric dienes is relatively unexplored. Recently, Overman and coworkers[42] reported that ether substituents have no *syn* directing effect in cycloadditions of allylically-oxygenated dienes of general structure **61**. In striking contrast to the *syn* addition of 5-oxygenated cyclopentadienes (see Table 2), dienes **61** were found to exhibit moderate (R = H) to excellent (R = Me, TMDMS) *anti* facial selectivity as summarized in Table 8. The sulfinyl group was shown to be a powerful *anti* director as evidenced by the exclusive *anti* addition of sulfinyl dienes **62**, **63** and **64** with *N*-phenylmaleimide (see Table 9). Clearly, the π-facial

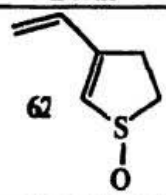
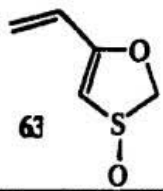
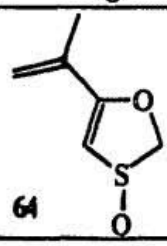
Table 8. Facial selectivity of acyclic unsymmetric dienes **61**

Entry	R	Solvent	% of *anti*
1	H	toluene	36
2	H	THF	64
3	H	MeOH	80
4	Me	toluene	97
5	Me	THF	97
6	Me	MeOH	96
7	$Si(Me)_2Bu^t$	toluene	100



61

Table 9. Facial selectivity of sulfinyl dienes

Entry	Diene	% of *anti*
1	 **62**	100
2	 **63**	100
3	 **64**	100

selectivity of acyclic dienes containing (*E*)-allylic substituents is different from that of 5-heterosubstituted 1,3-cyclopentadienes, which can be attributed to the absence of destabilizing steric and electrostatic interactions between the dienophile and the 5-substituent of 1,3-cyclopentadiene systems (see, for instance Figure 8a). The high *anti* facial selectivity observed in the [4 + 2] cycloadditions of acyclic dienes containing allylic sulfoxide or ether substitutions results from destablizing steric and electrostatic interactions between the allylic heteroatom and the dienophile in the *syn* transition state (see, for instance the destabilizing interaction of R_{syn} and O in Figure 8b).

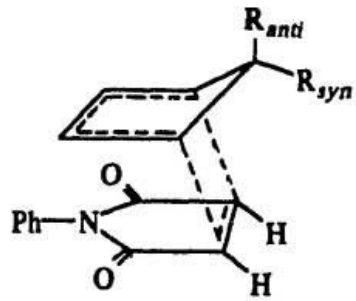


Figure 8a. The transition state of the cycloaddition of 5,5-disubstituted cyclopentadiene with *N*-phenylmaleimide

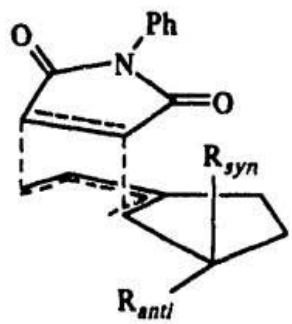
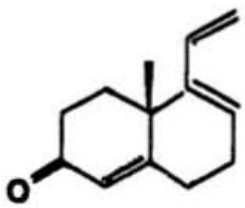
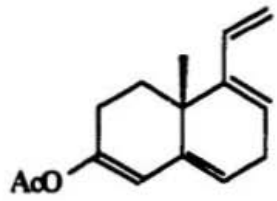


Figure 8b. The transition state of the cycloaddition of sulfinyl diene with *N*-phenylmaleimide

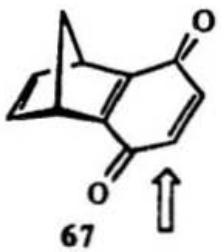
Valenta and coworkers[43,44] demonstrated that addition of a dienophile to acyclic diene **65** was predominantly *syn* to the methyl group, while addition to **66** was mainly *anti* to the methyl group. This difference could be explained largely on the basis of steric effects. Indeed, it was this difference in π-facial selectivity that Valenta [43,44] had taken advantage of to accomplish elegant syntheses of some steroids.



65



66



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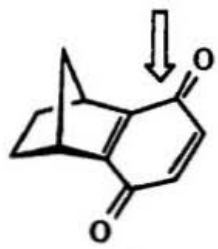

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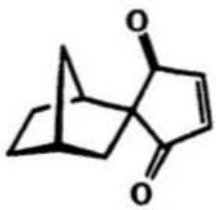
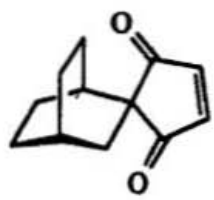


69



70

Recently, Mehta and coworkers[45] reported the stereochemistry of the Diels-Alder cycloaddition of several dienes to the plane-nonsymmetrical dienophiles **67** and **68** that complement Paquette's work with **45** and **46**. 2,3-Norbornenobenzoquinone (**67**) was found to exhibit preference for addition to several dienes from the below-plane. In

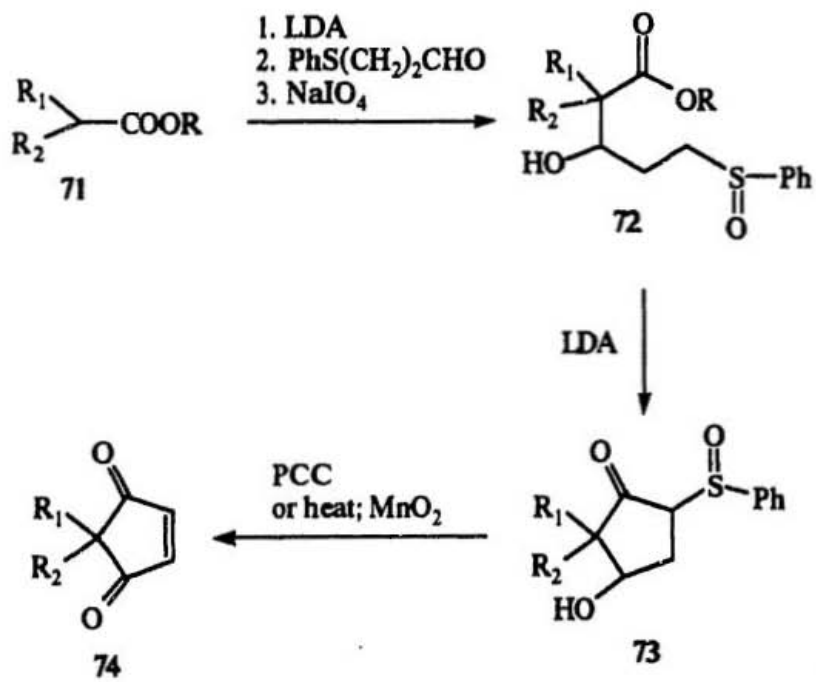
contrast, the stereochemical outcome was reversed in the case of **68**. The observed stereoselectivities were believed to arise from steric interactions in the transition states instead of from electronic control, and some calculations provided support for this interpretation.

Although the stereoselectivity exhibited by facially perturbed dienes in Diels-Alder reactions has been studied extensively in recent years, complementary investigations involving plane-nonsymmetrical dienophiles have not received matching attention. As described earlier, the π-facial stereoselectivity of the Diels-Alder reactions of dienes **58** and **59** was ascribed, but not unequivocally, to steric factors. Analysis of the chemical shifts in the ^{13}C NMR spectra of **58** and **59** indicated that electronic factors might play an important role in controlling the facial stereoselectivity of **58** and **59**, just as Gleiter and Paquette suggested for *iso*dicyclopentadiene and related systems. Examination of the plane-nonsymmetrical dienophiles **69** and **70**, which are complementary to dienes **58** and **59**, might shed light on whether steric or electronic factors are the controlling elements in the π-facial stereoselectivities of cycloadditions involving of spiro dienes such as **58** and **59**. The facially distinct steric interactions in the Diels-Alder reactions of **58** and **59** should be closely mimicked by the reactions of **69** and **70** with a simple diene. The following sections describe the preparation of the 2,2-disubstituted cyclopent-4-ene-1,3-dione derivatives, including **69** and **70**, and the results of their Diels-Alder reactions with cyclopentadiene.

II. Preparation of the dienophiles

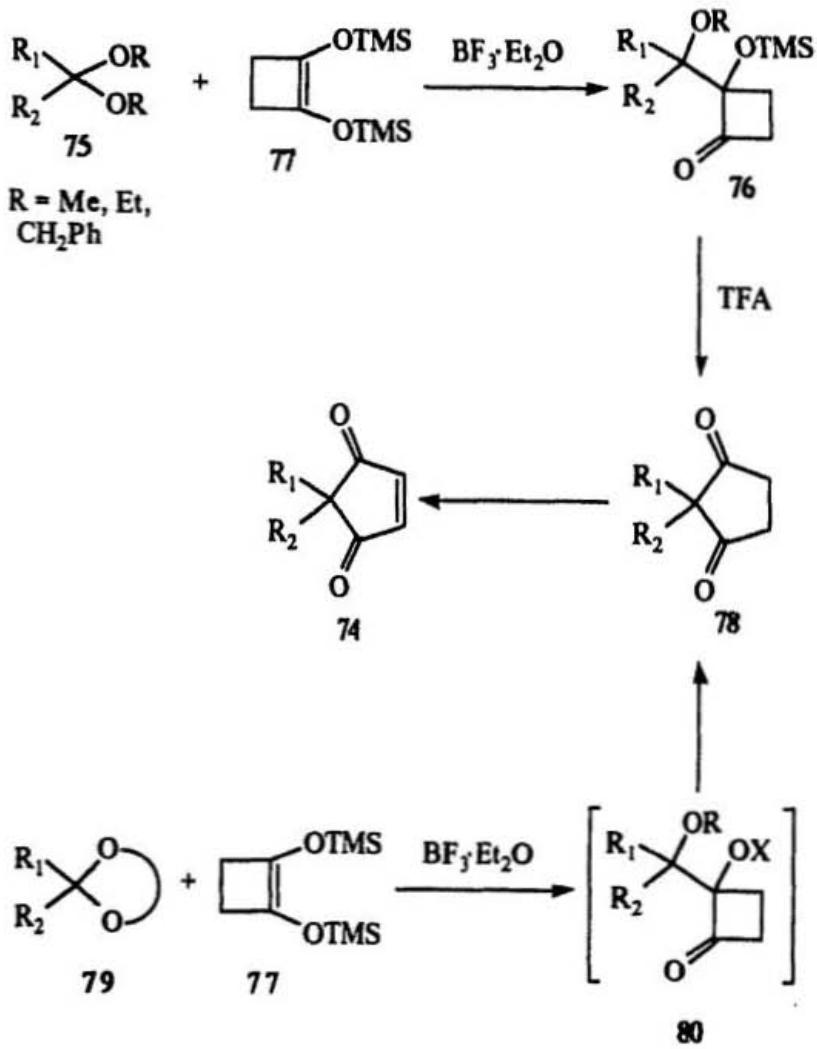
In order to conduct this investigation into the facial (*syn-anti*) stereoselectivity convenient supplies of 2,2-disubstituted cyclopent-4-ene-1,3-dione derivatives **74** were required. To the best of our knowledge, few general approaches to **74** have been reported. Recently, Pohmakotr and coworkers[46] developed a general route to **74** by means of intramolecular acylation of an α-sulfinyl carbanion as outlined in Scheme 4. Thus, treatment of the ester enolate anion derived from the corresponding ester **71** and lithium diisopropylamide (LDA) with 3-phenylthiopropanal followed by oxidation of the resulting hydroxy sulfide with $NaIO_4$ provided the desired sulfoxide ester **72** in good yield. The sulfoxide ester **72** underwent cyclization upon treatment with LDA to afford the sulfoxide

Scheme 4



73, which was converted into **74** in moderate yield by oxidation with pyridinium chlorochromate (PCC). This synthetic sequence could probably have been used to prepare the dienophiles **69** and **70** for our study. Unfortunately, the starting esters **71** required for the syntheses of **69** and **70** were not commercially available.

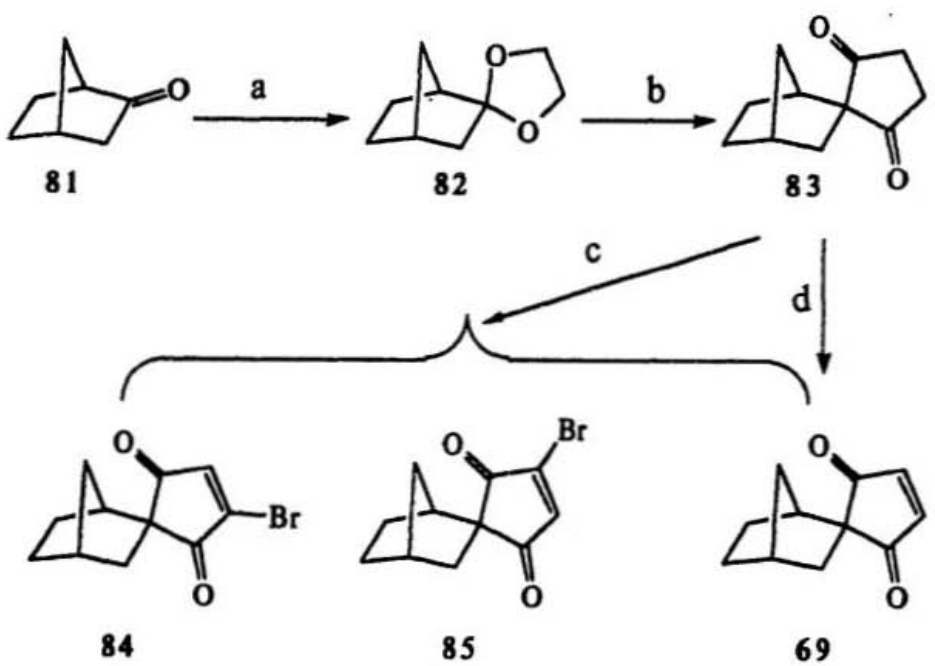
Scheme 5



It was thought that **74** could instead be prepared from the 2,2-disubstituted cyclopentane-1,3-dione **78** *via* dehydrogenation (Scheme 5). It is well known that *C*-alkylation of cyclic β-diketones can be a poor reaction due to the formation of the

undesired *O*-alkylation products as well as ring cleavage.[47] However Kuwajima and coworkers[48] reported that the Lewis acid-catalyzed reaction of a dimethyl, or diethyl, or dibenzyl ketal **75** with 1,2-bis(trimethylsilyloxy)cyclobutene (**77**) followed by rearrangement of the resulting cyclobutanone derivative **76** with trifluoroacetic acid (TFA) can produce a 2,2-disubstituted cyclopentane-1,3-dione **78** in reasonable yield. In our laboratories Wu[49] examined a variety of ketals including the cyclic ones **79**, and discovered that the use of a large excess of $BF_3{\cdot}Et_2O$ and a longer reaction time afforded **78** *directly* and in a better yield. Thus, our strategy for the preparation of **74** was to form the cyclopentane-1,3-dione moiety by a geminal acylation reaction, then to dehydrogenate.

Scheme 6

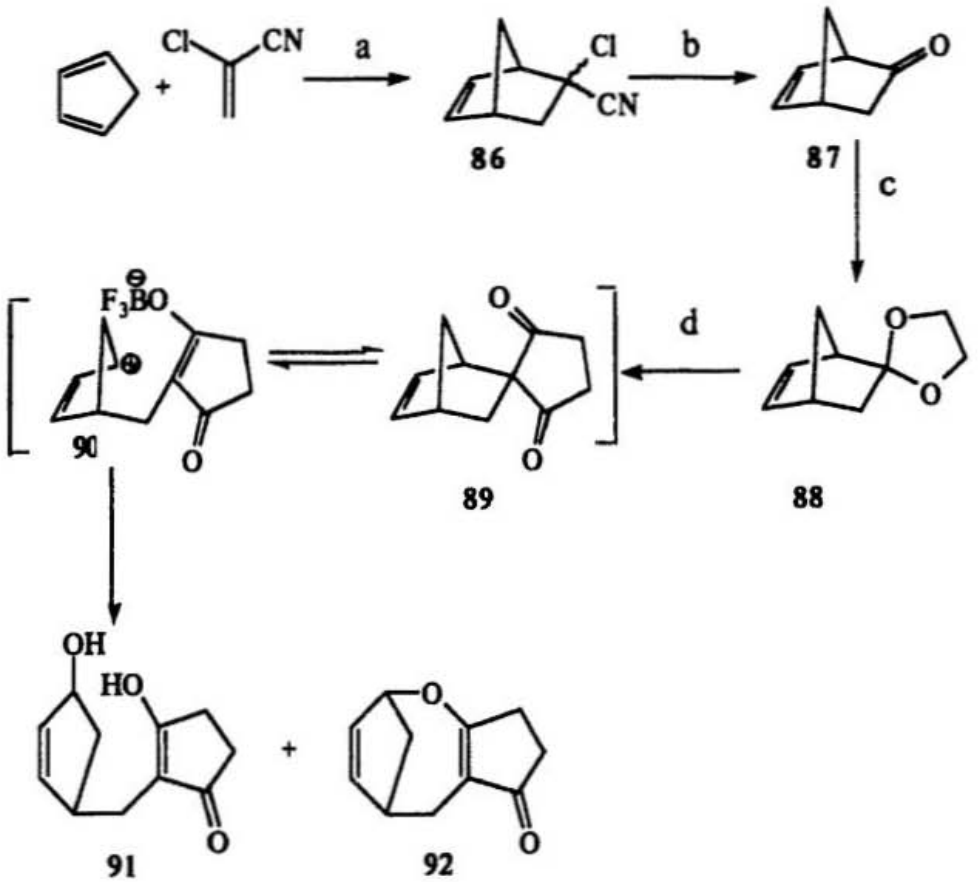


Reagents: (a) ethylene glycol, *p*TSA; (b) $BF_3{\cdot}Et_2O$, 77; (c) NBS, CCl_4, heat; (d) *p*TSA, DDQ, C_6H_6, reflux or $(PhSeO)_2O$, chlorobenzene, 110°C.

The preparation of **69** is outlined in Scheme 6. Ketalization of norcamphor (**81**) with ethylene glycol and a catalytic amount of *p*TSA in benzene at reflux proceeded smoothly to give the ethylene ketal **82** in 85% yield after vacuum distillation. This ketal **82** was treated with three equivalents of cyclobutene **77** and fifteen equivalents of $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at -78°C for six hours, and the resulting mixture was stirred overnight while attaining room temperature. After column chromatography on silica gel **83** was obtained as colorless crystals in an 82% yield. The IR spectrum of **83** showed absorption maxima at 1760 (shoulder) and 1717 cm^{-1} for the ring carbonyls. In the ^1H NMR spectrum, the four methylene protons in the 1,3-cyclopentanedione moiety were found as multiplets at δ 2.51-3.07 ppm. The newly formed carbonyls appeared at δ 213.1 in the ^{13}C NMR spectrum.

Initial efforts to convert **83** into **69** were *via* free-radical bromination and subsequent dehydrobromination. Spiro-diketone **83** was heated with 1.1 equivalents of *N*-bromosuccinimide (NBS) in CCl_4 for three hours, after which time GC-MS analysis indicated a 1 : 1 mixture of **69** and **84** or **85**. The mass spectra of **84** or **85** showed prominent molecular ions at *m/z* 254 and 256. Since the Diels-Alder reaction of this mixture with cyclopentadiene could give a mixture of adducts, an alternative procedure to prepare **69** was adopted. It is known that 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) can function as a dehydrogenating reagent in the presence of *p*TSA.[50] Indeed, treatment of **83** with 1.1 equivalents of DDQ and a catalytic amount of *p*TSA in benzene under reflux did produce **69**, but the reaction was extremely slow. The optimum conditions involved a large excess of DDQ and a very long reaction time, resulting in an 80% yield of **69** after column chromatography. A two-proton ^1H NMR signal at δ 7.21 and new resonances at δ 147.5 and 148.6 in the ^{13}C NMR spectrum confirmed the structure **69**. It was later found that the conversion of **83** into **69** could be achieved in less than one hour by heating a chlorobenzene solution of **83** and phenyl selenenic anhydride at 110°C. However, the yield was lower (*ca.* 68%).[51]

Scheme 7

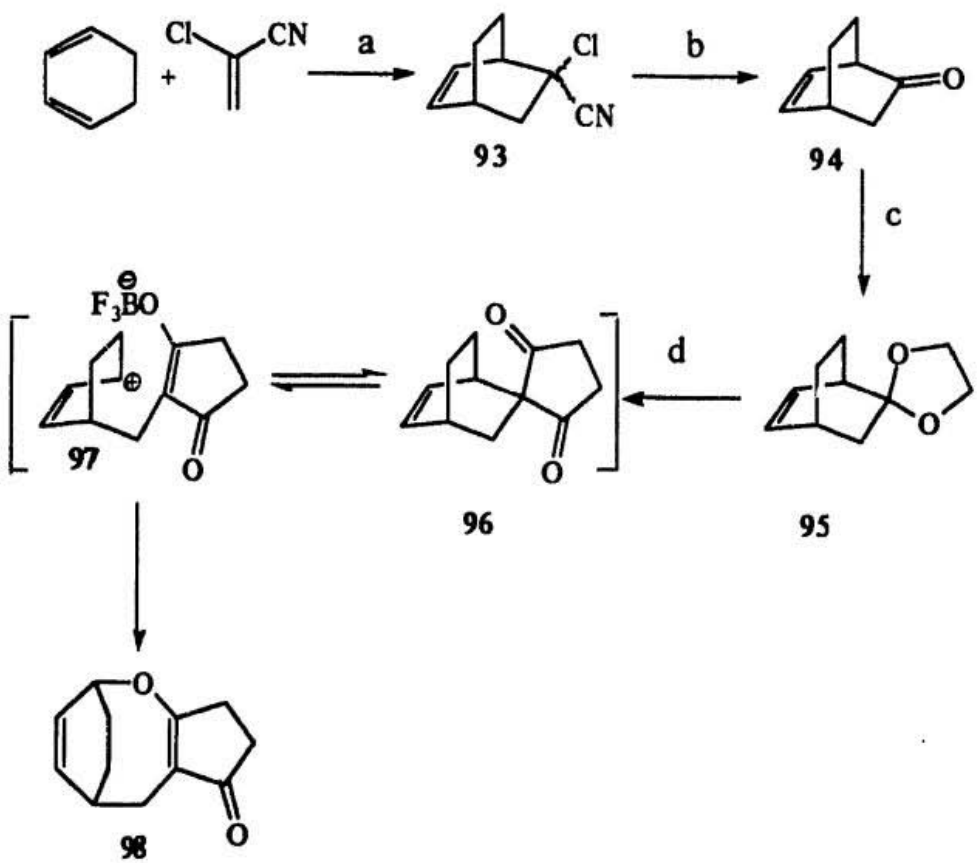


Reagents: (a) heat, benzene; (b) KOH, DMSO; (c) ethylene glycol *p*TSA, benzene; (d) $BF_3{\cdot}Et_2O$, 77

The sequence of reactions outlined in Scheme 7 was used to try to prepare the spiro-diketone **89**. Heating a benzene solution of freshly distilled cyclopentadiene and 2-chloroacrylonitrile produced a mixture of two epimers **86**, which was directly hydrolyzed to ketone **87** by treatment with potassium hydroxide in wet DMSO.[52] of this ketone proceeded smoothly. However, when this ketal was treated with a large excess of $BF_3{\cdot}Et_2O$ and 3 equivalents of **77**, as was used for ketal **82**, two products were obtained after chromatography. Prominent IR absorptions for the major product were at 3404 cm^{-1} (broad) and 1621 cm^{-1}. This product therefore contained a hydroxyl group and a

conjugated carbonyl group. The signal at δ 203.6 in its ^{13}C NMR spectrum indicated the carbonyl group. Signals at δ 137.4, 134.8, and 84.2, each of which was shown to bear one proton using APT, provided support for the presence of a carbon-carbon double bond and a sp^3 carbon attached to oxygen. This compound was assigned structure **91**. The ^{13}C NMR spectrum of the minor component was very similar to that of **91**, but it had no broad hydroxyl absorption in its IR spectrum. Structure **92** was proposed for this compound. These two undesired products probably resulted from the rearrangement of the desired spiro-diketone **89** through an allylic carbocation intermediate **90**.

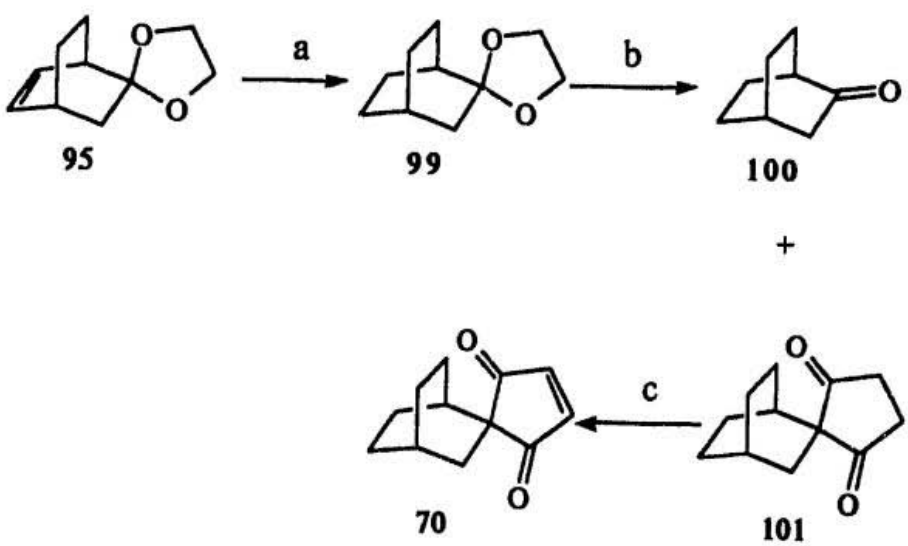
Scheme 8



Reagents: (a) heat, benzene; (b) KOH, DMSO; (c) ethylene glycol, *p*TSA, benzene; (d) $BF_3{\cdot}Et_2O$, 77

The reactions depicted in Scheme 8 were employed to prepare the symmetrical dienophile **70**. The Diels-Alder reaction of 1,3-cyclohexadiene with 2-chloroacrylonitrile gave a mixture of the two epimers **93**, which gave **94**, upon treatment with sodium hydroxide in wet DMSO.[52] Since compound **94** was quite volatile, it was directly ketalized with ethylene glycol and *p*TSA in benzene under reflux. Ketal **95** was obtained in 90% overall yield from 1,3-cyclohexadiene. The ^{1}H NMR spectrum of **95** showed the olefinic protons at δ 6.33 and 6.24, and the four methylene protons of the dioxolane moiety gave rise to a signal at δ 3.91. When ketal **95** was treated with a large excess of $BF_3{\cdot}Et_2O$ and 3 equivalents of **77**, we isolated a rearranged product **98** as the only product instead of the spiro-diketone **96**. In this case, only the cyclized product was obtained possibly due to the longer reaction time employed. Catalytic hydrogenation of **95** produced the saturated ketal **99** in quantitative yield. Treatment of the ketal **99** with

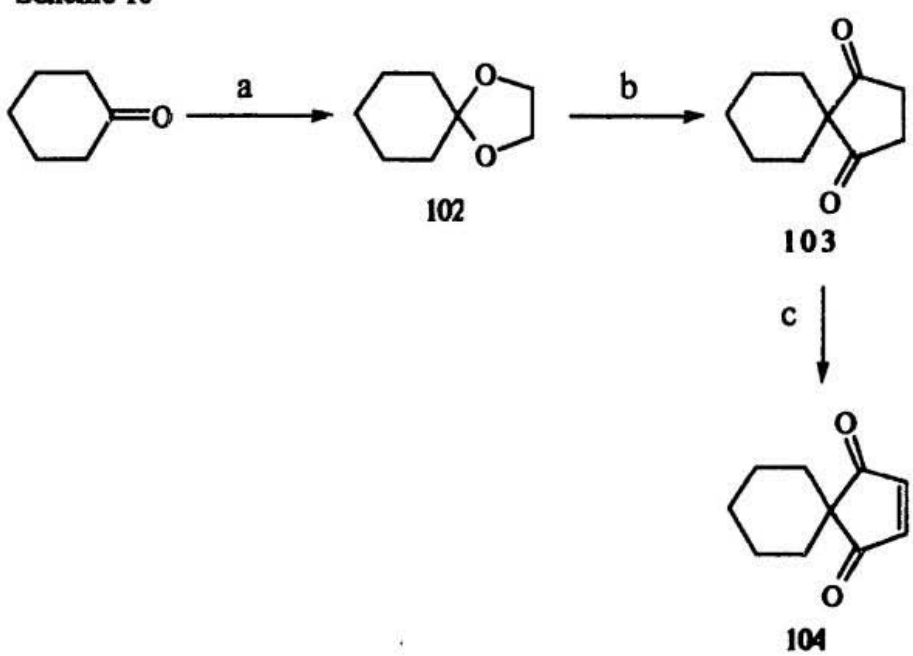
Scheme 9



Reagents: (a) H_2, Pd-C, EtOAc; (b) $BF_3{\cdot}Et_2O$, 77; (c) *p*TSA, DDQ, benzene, reflux or $(PhSeO)_2O$, chlorobenzene, 110°C.

$BF_3 \cdot Et_2O$ and cyclobutene **77**, afforded **101** in 74% isolated yield, accompanied by a small amount of the hydrolyzed starting material **100**. The IR maxima for **101** at 1738 (shoulder) and 1718 cm^{-1} indicated the 1,3-cyclopentanedione moiety. The ^{13}C NMR spectrum of **101** showed eight signals: four methylenes (δ 21.2, 24.1, 26.5, and 34.0), two methines (δ 23.0 and 32.1), one quaternary carbon (δ 62.4) and one carbonyl signal (δ 213.2), of which four were significantly larger in size as expected for a symmetrical molecule. The dehydrogenation of **101** was achieved cleanly, but very slowly, with a large excess of DDQ and a catalytic amount of *p*TSA in benzene under reflux. In this way, **70** was obtained in yields as high as 90% after column chromatography. An IR absorption maximum at 1692 cm^{-1} was ascribed to the conjugated enone system. The olefinic proton resonance at δ 7.15 (2H, s) and the carbon resonance at δ 147.2 confirmed the structure of **70**. As anticipated, eight signals, of which four were significantly larger, were observed in the ^{13}C NMR spectrum.

Scheme 10

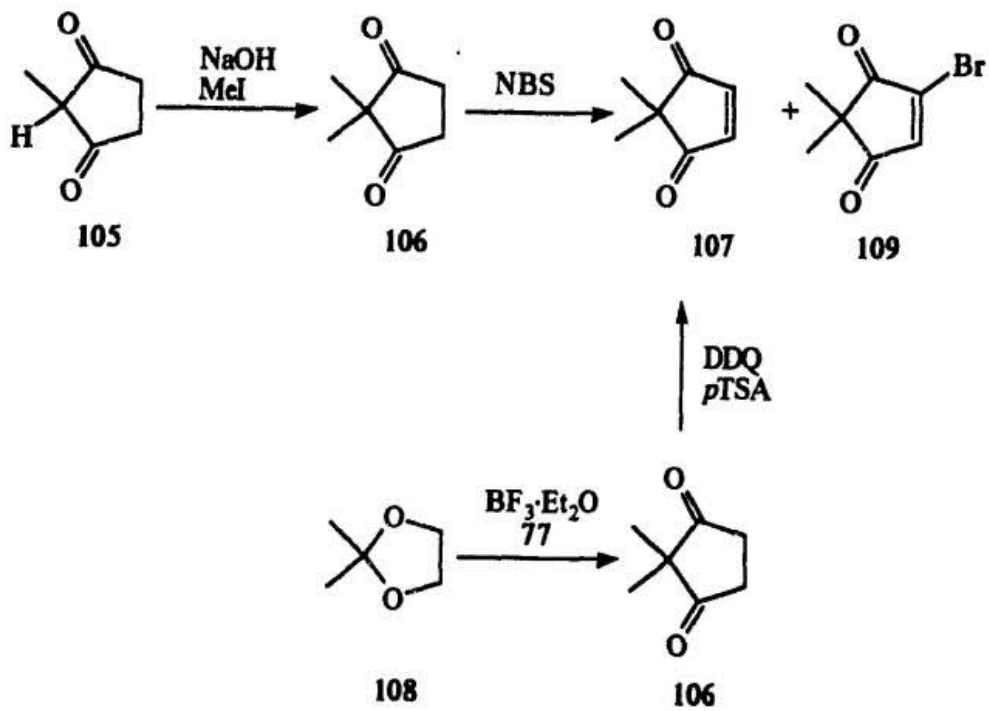


102 **103** **104**

Reagents: (a) ethylene glycol, *p*TSA, C_6H_6, reflux; (b) $BF_3 \cdot Et_2O$, 77; (d)PTSA, DDQ, C_6H_6, reflux.

Cyclohexanone was converted into **104** by the same sequence as was followed for norcamphor (**81**) to **69** (Scheme 10). Cyclohexanone ethylene ketal (**102**) underwent smooth spiro-annulation with **77** and $BF_3 \cdot Et_2O$ to give **103** in an 89% yield after column chromatography. The structure of **103** was proven by its IR absorption maximum at 1716 cm^{-1} and a four-proton singlet at δ 2.68 in its ^1H NMR spectrum. Compound **103** was converted into **104** in 73% yield by acid-catalysed reaction with DDQ in benzene. As expected, the ^{13}C NMR spectrum of **104** showed only six signals: three methylenes (δ 20.7, 24.7 and 28.9), one methine (δ 146.6), one quaternary carbon (δ 48.8) and one carbonyl (δ 207.6).

Scheme 11



105 **106** **107** **109**

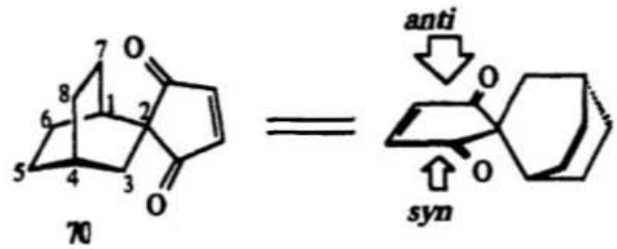
108 **106**

2,2-Dimethylcyclopent-4-ene-1,3-dione (**107**) could be prepared from 2,2-dimethylcyclopentane-1,3-dione (**106**) which was available by either α-methylation of **105** or by geminal acylation of ketal **108** (Scheme 11). The isolated yield of the geminal acylation

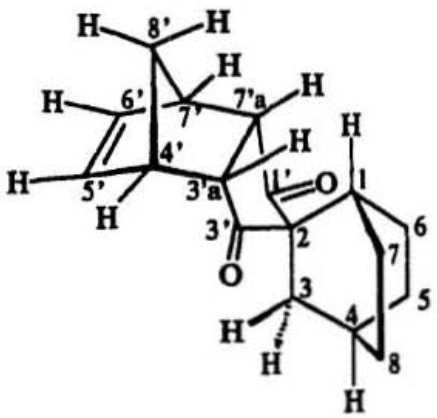
reaction (55%) was relatively low simply due to the high volatility of **106**. The dehydrogenation of **106** could be achieved by using either DDQ with *p*TSA, or by the NBS-dehydrobromination method. Treatment of **106** with a large excess of DDQ and a catalytic amount of *p*TSA in benzene under reflux produced **107**. However, removal of the residual DDQ needed column chromatography on silica gel, which resulted in a significant loss of product. Diketone **106** was reacted with NBS in CCl_4 according to the method of Agosta and Smith.[53] After filtration to remove the succinimide, the resulting filtrate was carefully distilled to give **107**, the distillate was accompanied by a small amount of the bromide **109**, whose mass spectrum showed the prominent parent ions at *m/z* 202 and 204. Spectroscopic data of **107** were in full agreement with those in the literature.[53]

III. Results

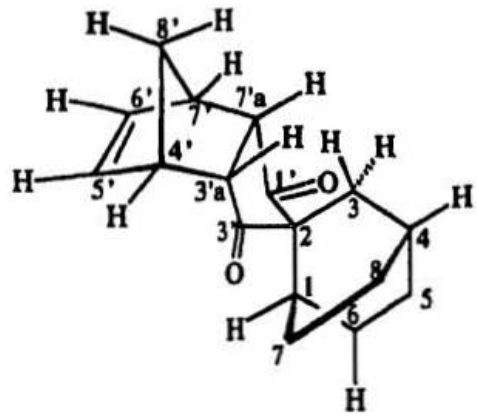
Since compound **70** has a symmetry plane bisecting the alkane, its cycloaddition was examined first. A benzene solution of **70** and an excess of cyclopentadiene was heated overnight. Four adducts (**110**, **111**, **112**, and **113**) are possible. GC-MS analysis of the crude product indicated a poorly resolved mixture of three products. The separation of these adducts required considerable experimentation. Fractional crystalization using a variety of solvent systems was unsuccessful. The three adducts were eventually separated by column chromatography on silica gel using pure benzene as the eluent. The unequivocal assignment of the stereochemistry of the three isomers was achieved by ^{1}H NOE experiments with the assistance of ^{13}C NMR, the attached proton test (APT), a ^{1}H-^{1}H correlation spectrum (COSY), and ^{1}H-^{13}C correlation spectra (HETCOR). The ^{1}H NMR spectrum (in C_6D_6) of the first eluted adduct showed the olefinic protons (C-5'H & C-6'H) at δ 5.86, which on saturation resulted in a 2% NOE at δ 3.08. Thus the two-proton multiplet at δ 3.08 was assigned to C-4'H & C-7'H. When the multiplet at δ 3.08 (C-4'H & C-7'H) was saturated, NOE's at δ 5.86 (C-5'H & C-6'H, 4%), δ 2.86 (a methine as revealed by the ^{1}C-^{1}H correlation spectrum, 1.4%), δ 1.28 (a methylene proton, 1.5%) and 0.98 (another methylene proton, 2%) were observed. Clearly, the C-8' methylene protons could be assigned the signals at δ 1.28 and 0.98, and the C-3'a and C-7'a protons resonated at δ 2.86. Saturation of this signal at δ 2.86 (C-3'aH & C-7'aH) produced NOE's at δ 0.98 (C-8'H_{anti}, 4%), δ 3.08 (C-4'H & C-7'H, 3%) and δ 1.44 (a methine as indicated by the ^{13}C-^{1}H correlation spectrum, 3%). The 4% NOE between the *anti* proton at C-8' and the C-7'a & C-3'a protons suggested that this adduct must have come from an *endo* addition. There was a 3% NOE between the C-3'a and C-7'a protons and one methine that could only be either the C-1 proton or the C-4 proton. However, if this methine were C-4 (i.e. *syn-endo* adduct **112**), no NOE effect between this methine proton and the protons α to the carbonyls would be anticipated due to the



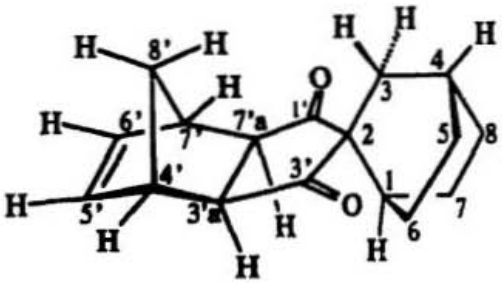
70



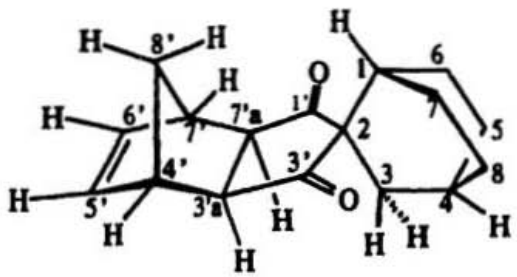
110 (*anti--endo*)



111 (*syn--endo*)



112 (*anti--exo*)



113 (*syn--exo*)

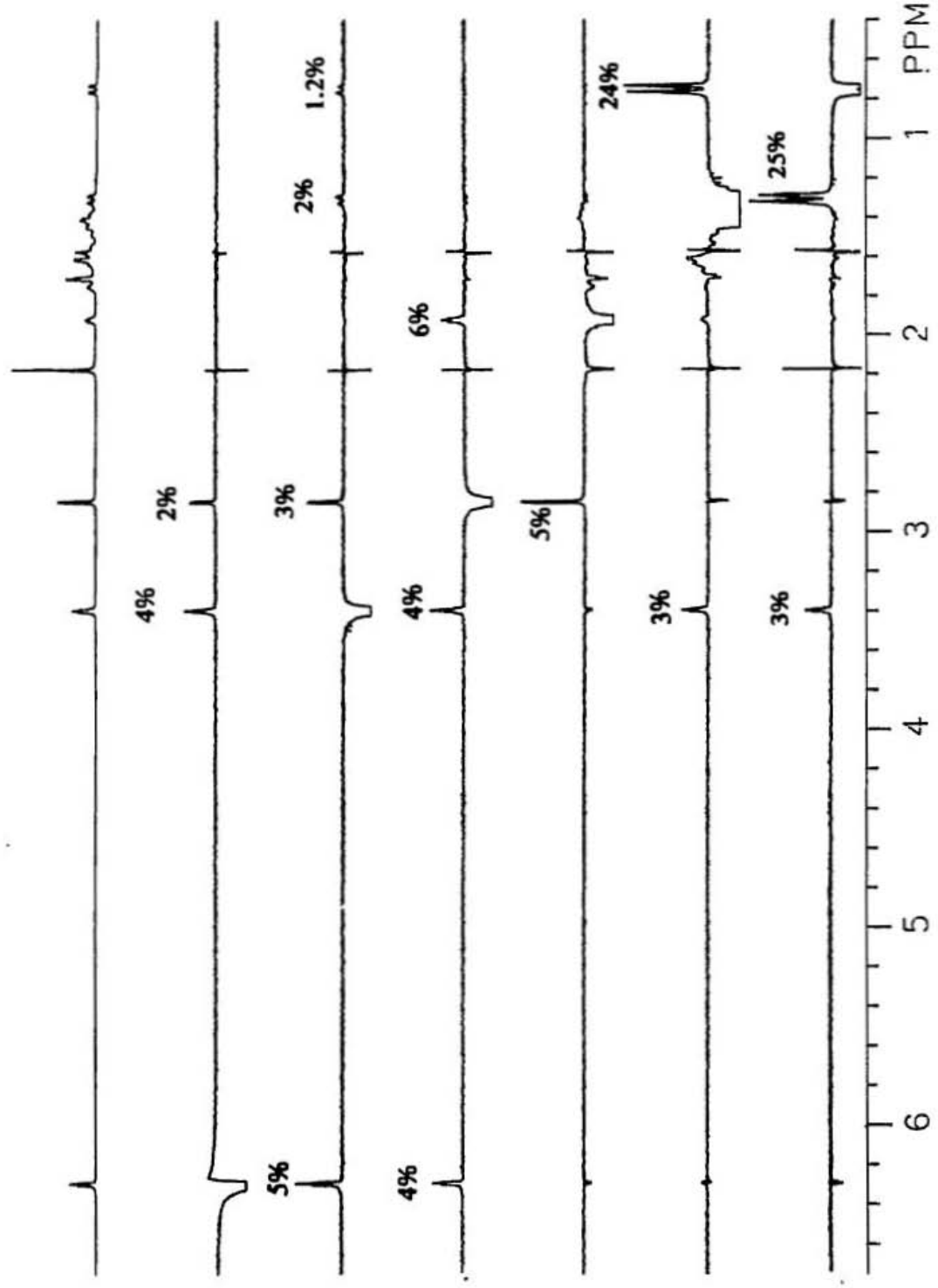


Figure 9. ^{1}H NMR NOE spectra of 112

distance involved. Thus, this methine could be assigned to the C-1 proton, which meant close proximity between the C-1 proton and the protons α to the carbonyls in the *anti-endo* adduct **110**. This assignment was fully supported by the following findings. When the methylene protons at δ 1.74 were saturated, NOE's at δ 5.86 (C-5'H & C-6'H, 1%) and δ 1.55 (a methine, as shown by the ^{13}C-^{1}H correlation spectrum, 4%) were found. Obviously, a methylene which is spatially close to both olefinic protons and a methine, must have been the C-3 methylene in **110**. Consequently, the C-4 methine could be assigned to the δ 1.55 signal, which confirmed our previous assignment of the C-1 methine at δ 1.44. The propinquity of the C-3 methylene with the olefinic protons is consistent with *anti-endo* adduct **110**. As expected, the ^{13}C NMR spectrum showed eleven signals, of which six were larger.

The structures of the other adducts were assigned in the same fashion as for **110**. Saturation of the olefinic signal (δ 6.30) in the ^{1}H NMR spectrum of the second eluted adduct resulted in a significant NOE of the signal due to the protons α to the carbonyls, and *vice versa* (see Figure 9). Thus, the structure of the adduct could only have resulted by *exo* addition, *i.e.*, either **112** or **113**. When the protons α to the carbonyls were saturated, we noticed a 6% NOE of the signal at δ 1.95 due to a methine, which, as shown by the ^{13}C-^{1}H correlation spectrum, could only be either the C-1 or the C-4 methine. Saturation of this signal at δ 1.95 gave rise to a 4% NOE of the protons α to the carbonyls. Since the C-4 proton in the *syn-exo* adduct (**113**) is too far away to have a significant NOE effect on the protons α to the carbonyls, then the signal at δ 1.95 must have been due to the C-1 proton, and adduct must have been **112** derived from the *anti-exo* addition. Adduct **112** was a symmetrical molecule as seen from its ^{13}C NMR spectrum.

The last eluted, very minor adduct could only have been either **111** (*syn-endo*) or **113** (*syn-exo*). As the *endo* reaction is generally favored over *exo* due to secondary orbital interactions, we believed that this adduct was **111**. This was indeed fully confirmed by the following spectroscopic evidence. Saturation of the olefinic signal at δ 6.09 resulted in

NOE's at δ 3.46 (C-4'H & C-7'H, 3%) and δ 1.82 (C-7 methine, 4%). The C'-8 protons were assigned at δ 1.52 and δ 1.64 by the NOE experiment on saturation of the signal due to C-4' and C-7' protons. The NOE results demonstrated the proximity of the protons α to the carbonyls and the *anti* proton on the methano bridge (*i.e.* C-8'H_{anti}) as well as the C-1 methylene. Thus, there was no doubt that the third isomer was the *syn-endo* adduct **111**. The ^{13}C NMR spectrum showed eleven signals, of which six were larger, a fact consistent with the symmetry of the molecule.

With the unambiguous assignment of all the adducts, the ratio of the three isomers was examined. Since the three adducts were not well resolved in the gas chromatogram, and the separation needed repeated chromatography on silica gel with benzene as eluent, the integrations of the distinct signals for each isomer in the ^{1}H NMR of the crude reaction product were determined and compared. The olefinic protons of adducts **110**, **111** and **112** appeared as broad singlets as δ 5.95, 6.09 and 6.29, respectively, and their ratio was 47 : 5 : 48. Neither gas chromatography nor ^{1}H NMR analysis of the crude product gave any sign of a *syn-exo* adduct **113**. The ratio of the adducts was shown to have arisen under kinetic control by the fact that no pure adduct would equilibrate in benzene under reflux.

The Diels-Alder reaction of dienophile **69** with an excess of cyclopentadiene in boiling benzene was studied next. GC-MS analysis of the crude product indicated a mixture of all four possible diastereomers, with mass spectra that were almost identical. Repeated chromatography on silica gel with pure benzene as eluent provided all four pure adducts, and the stereochemistry of each was established in the same fashion as for the adducts derived from the symmetrical dienophile **70**. In this case, the ^{1}H and ^{13}C NMR spectra of the adducts were relatively complicated due to a lack of symmetry in the adducts. For the first eluted adduct, saturation of the double doublet at δ 3.03 (C-3'aH) resulted in a significant NOE of the signal at δ 1.00 (C-8'H_{anti}) and of the signal at δ 2.13 (C-1 methine), and *vice versa*. Thus, the structure of the adduct could only have been **114**, the

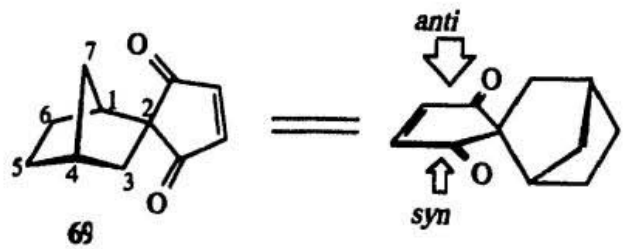
product of *endo* addition, *anti* to the C-1 methine.

The second eluted product had NOE data that established proximity between the protons α to the carbonyls and the olefinic protons, suggesting the product of an *exo* addition. Saturation of the signal at δ 2.92 (C-3'aH) and δ 2.74 (C-1 methine) gave small NOE's at δ 2.54 (0.5%) and δ 2.92 (2%), which suggested that the protons α to the carbonyls were in the neighbourhood of the C-1 methine. Therefore, the *anti-exo* structure **116** was assigned to this product.

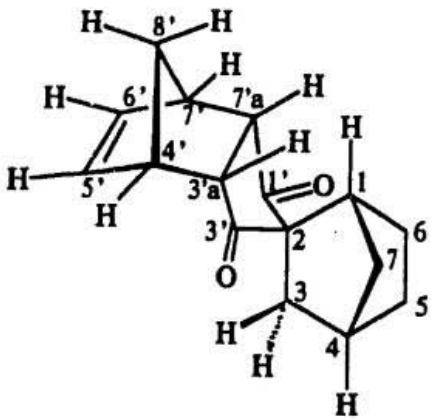
For the third eluted adduct, we observed significant NOE's between the signals due to the olefinic protons and the proton on the C-1 methine, as well as NOE's between the protons α to the carbonyls and the *anti* proton on the methano bridge (C-8'H_{anti}). This could be consistent only with structure **115**, the result of an *endo* addition, *syn* to the C-1 methine of **69**.

The last eluted, minor adduct could only have been **117** derived from *syn-exo* addition since the other products had been unambiguously assigned **114**, **115** and **116**. To confirm our previous assignment, an NOE experiment on this minor adduct was conducted. Indeed, the stereochemistry of the final adduct, **117**, was evident from NOE's between the C-1 proton and the α protons, as well as NOE's between the olefinic protons and the protons α to the carbonyls.

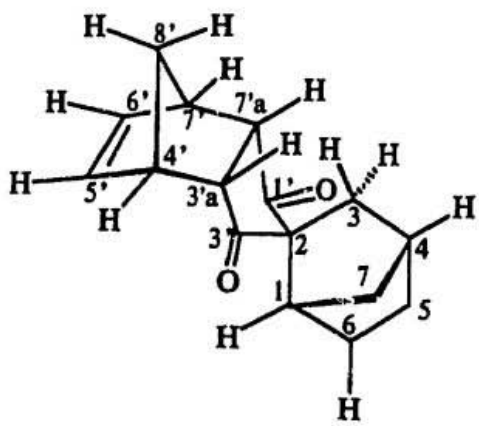
As in the cycloaddition of **70** with cyclopentadiene, the ratio of all the adducts was calculated from the careful integration of the ^{1}H NMR spectrum of the crude product. The olefinic proton resonances of adducts could be assigned at δ 5.92-5.79 (2H, for **114**), δ 6.09-6.19 (2H, for **115**), and 6.30 (4H, for **116** plus **117**), with their ratio being 70 : 30 : 28. The ratio of adducts **116** to **117** was established as follows. The multiplets at δ 2.54 and 2.44 were ascribed to the proton of adduct **117** and the proton of adduct **116** in the ^{1}H NMR spectrum of the crude addition product, and the ratio of **116** to **117** was 47 : 8.5. Thus, a simple calculation indicated that adducts **114**, **115**, **116** and **117** were formed in a ratio of 50 : 22 : 24 : 4, respectively.



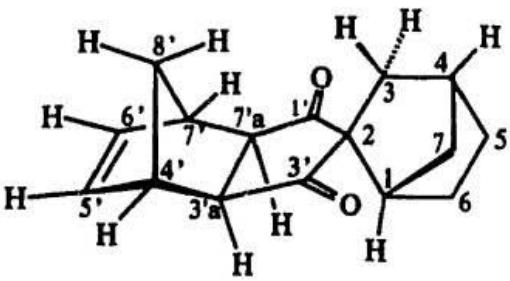
69



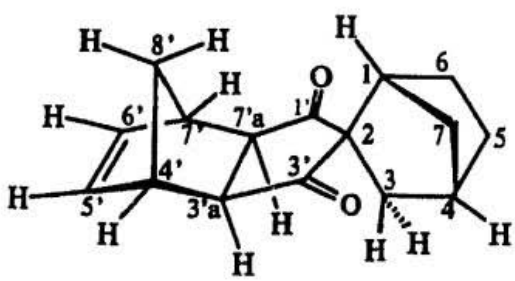
114 (*anti--endo*)



115 (*syn--endo*)



116 (*anti--exo*)

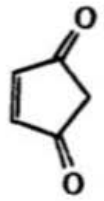


117 (*syn--exo*)

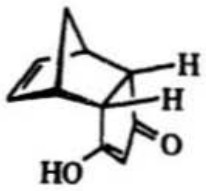
The cycloadditions of **69** and **70** with cyclopentadiene provided relatively large proportions of the *exo* addition products: with **70** the *endo* to *exo* ratio was 52 : 48, and with **69** the *endo* to *exo* ratio was 72 : 28. However, as reported by Agosta and Smith[53] in 1971, the cycloaddition of 2,2-dimethylcyclopent-4-ene-1,3-dione (**107**) afforded the *endo* adduct **120** in a yield of only 46%, but no *exo* addition product, **121**, was mentioned. On the other hand, Paquette *et al.*[54] claimed that **107** reacted with cyclopentadiene to provide a mixture of *endo* (**120**) and *exo* (**121**) adducts, with **120** slightly predominanting. The inconsistency of Agosta's work with our results as well as the difference between Agosta's and Paquette's reports stimulated the re-evaluation of the *endo-exo* selectivity with the simple dienophiles **118**, **104** and **107**.

Addition of **118** to cyclopentadiene in boiling benzene gave a single adduct in nearly quantitative yield.[55] The ^{13}C NMR resonances at δ 199.6 (C-3 & C-7) and 108.7 (C-2) indicated that the product was completely enolized. Saturation of the the doublet at δ 1.47 (C-8H_{anti}) in the ^{1}H NMR spectrum of the adduct resulted in a 5% NOE of the signal at δ 3.21, which is due to the protons α to the carbonyls. This could be only in agreement with structure **119**, the result of *endo* addition.

In contrast, the cycloaddition of **107** with cyclopentadiene provided two adducts, which were separated by column chromatography. Each isomer showed seven carbon resonances, of which five were larger, as expected considering the symmetry of the adducts. Of the two adducts, only the minor one showed a significant NOE between the protons α to the carbonyls and the olefinic protons so it was assigned struture **121**, the result of *exo* addition. Therefore the major adduct (**120**) was formed *via* an *endo* transition state. The ratio of these two adducts was derived from the integration of the olefinic signals of each isomer in the ^{1}H NMR spectrum of the crude product. The ratio of **120** to **121** was 76 : 24, a result different from both Paquette's (around 50 : 50) and Agosta's (100% *endo*). It is worthy of note that the cycloaddition with **104** proceeded much more slowly than that with **118**, a fact consistent with the result reported by Agosta and Smith.



118



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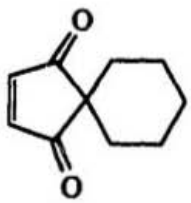

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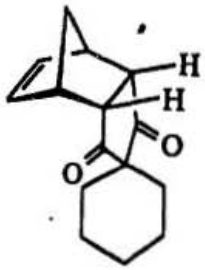

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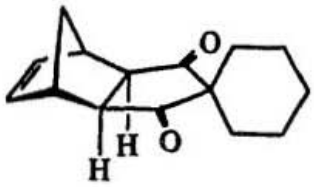

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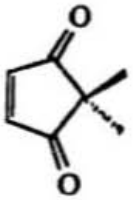

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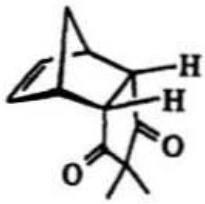

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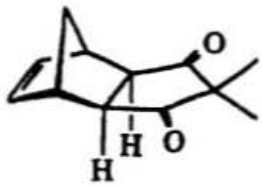


121

The last dienophile examined was **104**. Like **107**, dienophile **104**, upon cycloaddition with cyclopentadiene in boiling benzene, yielded a mixture of two adducts, whose stereochemistry was established from the NOE data. For the minor product, the NOE's demonstrated the propinquity of the protons α to the carbonyls (C-3'aH & C-7'aH) and the olefinic protons. The minor product was therefore the *exo* adduct **123** and the major one was *endo* adduct **122**. The multiplets at δ 6.04 and 6.30 in the ^{1}H NMR spectrum of

the crude addition product were due to the olefinic protons of adducts **122** and **123**, respectively. Integration of those signals revealed that the ratio of **122** to **123** was 73 : 27.

IV. Discussion

The *endo-exo* and π-facial stereoselectivity in the cycloadditions of 2,2-disubstituted cyclopent-4-ene-1,3-dione derivatives with cyclopentadiene is summarized in Table 10. Dienophile **118** reacted with cyclopentadiene much faster than did **107**, a fact ascribable to steric hindrance between the C-2 substituent of **74** and the hydrogens on cyclopentadiene in the *endo* transition state (see Figure 10). Retarding the rate of *endo*-addition would allow the reaction *via* an *exo* transition state to become competitive. Furthermore the data listed in Table 10 would support the view that the more sterically encumbered the dienophile in the *endo* region is, the more *exo* adduct is formed.

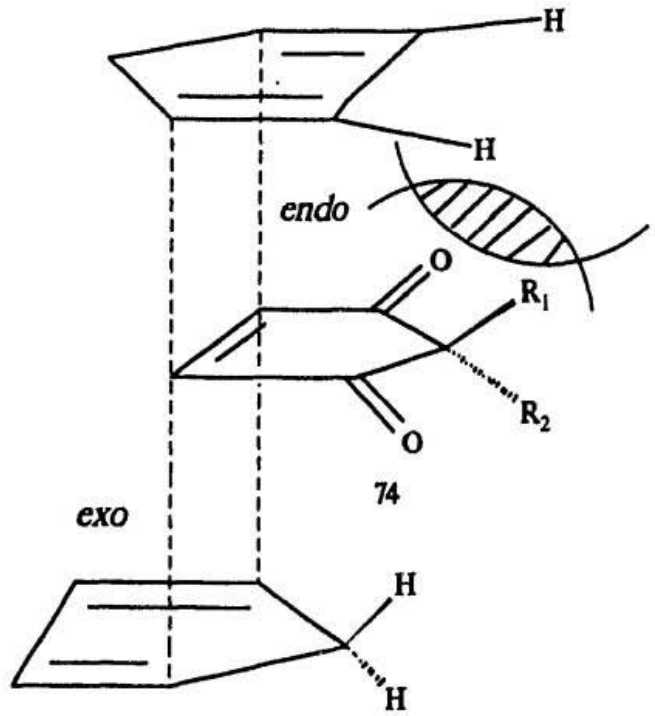
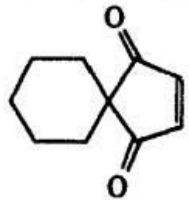
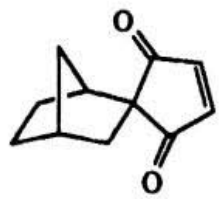
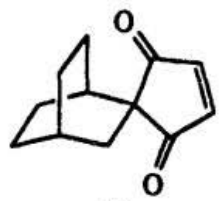


Figure 10. Steric interaction at the transition state of 5,5-disubstituted cyclopent-4-ene-1,3-dione with cyclopentadiene

Table 10. Cycloaddition with cyclopentanediene

Entry	Dienophile	*endo*	*exo*	% of *endo*
		anti : *syn*	% of *anti*	
1	 **118**	—	—	100
2	 **104**	—	—	73
3	 **107**	—	—	76
4	 **69**	70 : 30	85	72
5	 **70**	90 : 10	100	52

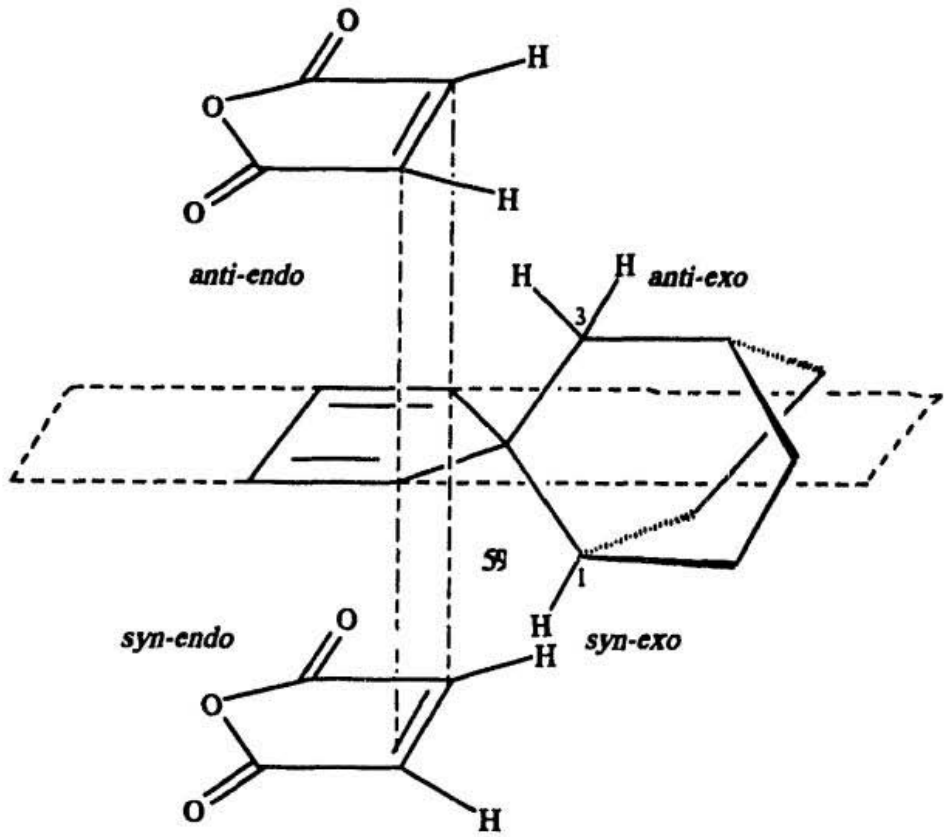


Figure 11. The transition state of 5,5-disubstituted cyclopentadiene with maleic anhydride

It is interesting to compare the *endo*/*exo* ratio of diene **58** in the cycloaddition with Z-ethylenic dienophiles (100% *endo*) with that of the complementary dienophile **69** in the cycloaddition with cyclopentadiene (72 : 28), as well as that of diene **59** (100% *endo*) with that of dienophile **70** (52 : 48). This difference can be easily understood by examining the *endo* and *exo* transition states of the cycloadditions involving diene **59** (or **58**) and dienophile **70** (or **69**). For example, there is a significant steric interaction between the hydrogens on C-3 and C-1 of the diene **59** and the olefinic protons of the dienophile in the *exo* region as seen from Figure 11, therefore, the *endo* adducts were formed exclusively. The situation was *reversed* in the cycloaddition of the dienophile **70** with cyclopentadiene. As shown in Figure 12, steric interaction between the hydrogens on C-3

and C-1 of the dienophile **70** and the hydrogens on cyclopentadiene in the *endo* transition state could be significant, which allow the rate of *exo* addition to be similar. The same argument can be applied to rationalize the big difference in the *endo/exo* selectivity between diene **58** and **69**.

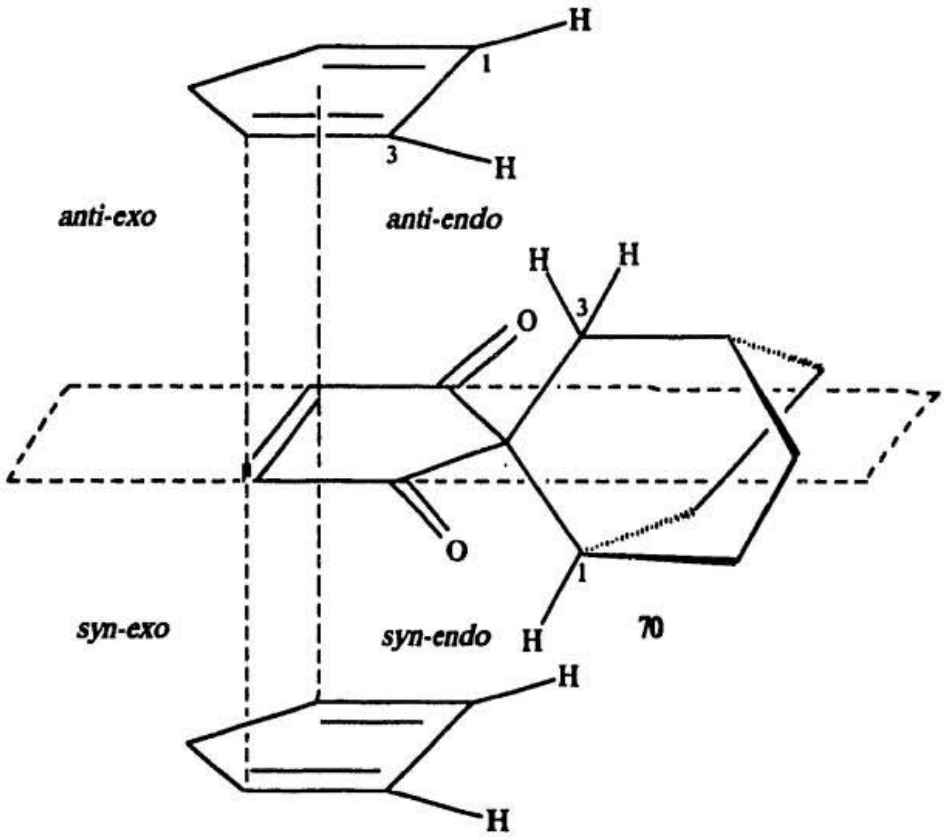
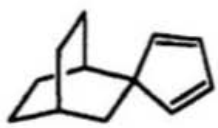


Figure 12. The transition state of 5,5-disubstituted cyclopent-4-ene-1,3-dione with cyclopentadiene

The steric interactions in the *endo* and *exo* transition states are very different. The π-facial stereoselectivity of both **69** and **70** in the *exo*-addition mode was shown to be very high (see Table 10). Indeed, the cycloaddition of **70** with cyclopentadiene afforded only one *exo* adduct **112**, which was the result of addition *anti* to the C-1 methine, whereas in the case of dienophile **69** the ratio of *exo-anti* to *exo-syn* to the C-1 methine (*i.e.*, **116** to **117**) was 85 : 15. The *endo* additions appeared to be less selective: with **70**

the ratio of *anti-endo* (*i.e.*, **110**) to *syn-endo* (*i.e.*, **111**) was 90 : 10, and with **69** the ratio of *anti-endo* (*i.e.*, **114**) to *syn-endo* (*i.e.*, **115**) was 70 : 30. The lower π-facial selectivity in the *endo*-addition mode was perhaps due to the greater distance between the hydrogens on cyclopentadiene and the hydrogens on C-1 and C-3 of the dienophiles in the transition state.

Table 11. Cycloaddition of cyclopentadiene derivatives with Z-ethylenic dienophiles

Entry	Diene	*anti* : *syn*	% of *endo*	Ref.
1	 **58**	*ca*. 70 : 30	100	39a
2	 **59**	*ca*. 88 : 12	100	39b

Finally, it is important to compare the ratios of *anti-endo* to *syn-endo* of dienophile **69** (or **70**) with that of diene **58** (or **59**) (see Table 10 and Table 11). It is remarkable that these ratios with dienophiles **69** and **70** were very similar to the adduct ratios obtained when the complementary dienes **58** and **59** reacted with *Z*-ethylenic dienophiles. Diene **59** underwent cycloadditions with *Z*-ethylenic dienophiles in boiling dichloromethane to afford the adduct ratios of *anti-endo* to *syn-endo* in a narrow range around 88 : 12. Diene

58 was shown to be less stereoselective than diene **59**, just as dienophile **69** was less stereoselective than **70**. The cycloadditions of diene **58** with *Z*-ethylenic dienophiles in boiling dichloromethane gave adduct ratios of *anti-endo* to *syn-endo* about 70 : 30.

For a given [4 + 2] cycloaddition with normal electron demand (see Figure 1b), an electron-donating group will raise the diene HOMO, thereby resulting in the stronger interaction between the HOMO (diene) and the LUMO (dienophile). Since an electron-donating group will raise the energy of the dienophile LUMO, the interaction between the HOMO (diene) and the LUMO (dienophile) will be weaker. Thus for a given electron-donating or electron-withdrawing group, the electronic effects on a diene will be opposite to (or very different from) those on a dienophile. This conclusion may be extended to the π-facial stereoselectivity of the Diels-Alder reactions as well. If the π-facial selectivity of the cycloadditions involving diene **58** (or **59**) is controlled completely by electronic factors, then this π-facial stereoselectivity of these dienes should be reversed (or changed significantly) from that of the complementary dienophile **69** (or **70**). However, the steric interactions in the reactions of the plane-nonsymmetrical diene and the reactions of its corresponding plane-nonsymmetrical dienophile should be very similar. Therefore, the π-facial selectivity of diene **58** (or **59**) should be roughly the same in the case of the complementary dienophile **69** (or **70**). The fact that the adduct ratios were very close in the cycloadditions of **58** and **69**, and also **59** and **70**, suggests very strongly that the steric interactions were responsible for the π-facial stereoselectivity observed in these spiro addends. However, this did not necessarily mean the absence of the electronic factors. Indeed, the ^{13}C NMR data for **58** and **59** indicated a significant amount of orbital mixing between their framework σ orbitals and their π-systems.* Unlike the *iso*dicyclopentadiene systems reported by Paquette and coworkers, the electronic factors are not important in

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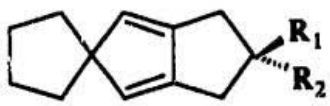
* At present, we are still uncertain about the orbital mixing of the bicyclic σ orbital framework with dienophile π_s orbital in the dienophile systems **69** and **70** by examining their ^{13}C NMR chemical shifts.

controlling π-facial stereoselectivity in the Diels-Alder reactions involving our spiro-addends.

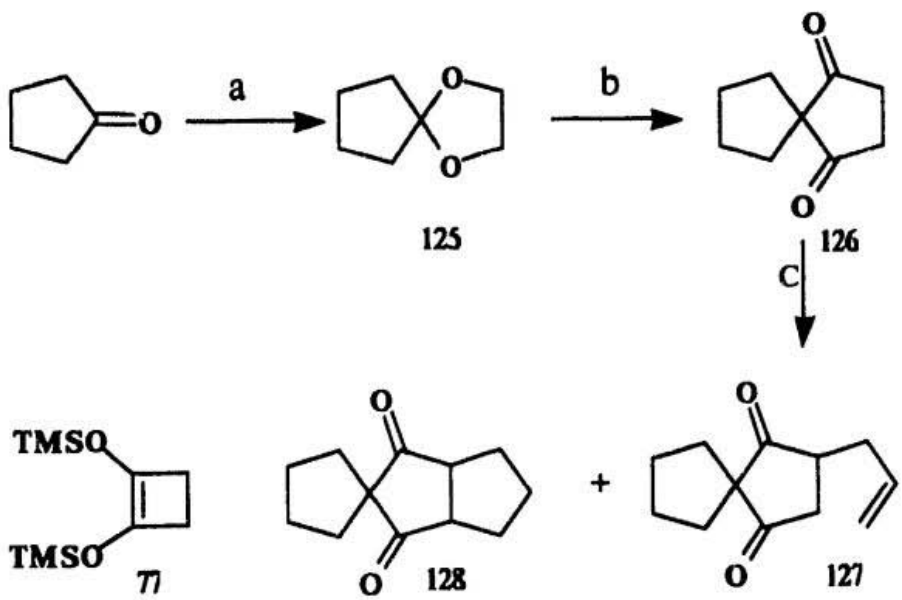
V. Studies of the π-facial stereoselectivity of diene 124b

As discussed earlier, Paquette and coworkers explained the π-facial stereoselectivity of the Diels-Alder reactions of spiro dienes **55-57** by electronic factors.[38] If this is true, then the plane nonsymmetrcal diene **124b** should have similar π-facial stereoselectivity as spiro dienes **55-57** even though the methyl group is further away from the reacting carbons of the diene moiety.

Scheme 12

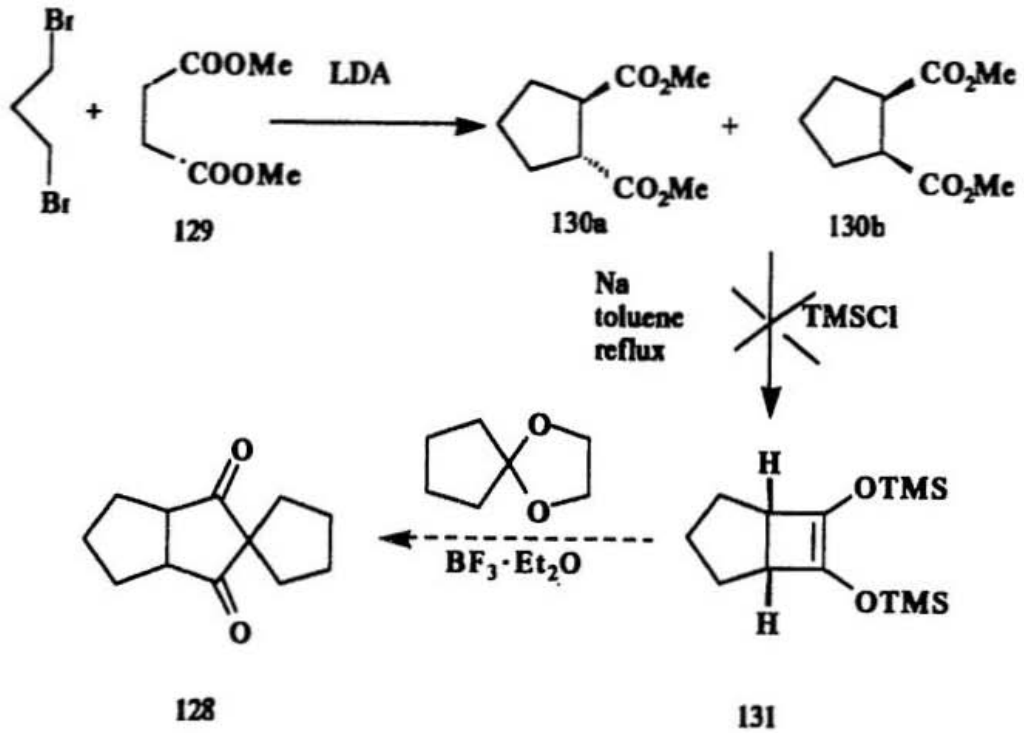


124 (a) $R_1 = R_2 = H$
(b) R_1 = Me , $R_2 = H$



Reagents : (a) ethylene glycol, pTSA; (b) 77, $BF_3{\cdot}Et_2O$;
(c) LDA, $I(CH_2)_3I$, HMPA.

Scheme 13



129 **130a** **130b**

128 **131**

A synthesis of diene **124b** was envisioned from its corresponding diketone. A model reaction was undertaken using the plane-symmetrical diketone **128**. Ketal **125** which was obtained from cyclopentanone was treated with **77** following the standard procedure developed in this group and outlined in Scheme 12. After purification we isolated **126** in 68% yield. The structure of **126** was assigned by its spectroscopic data. The IR spectrum showed a strong absorption maximum at 1720 cm^{-1} for the carbonyls. That only five signals in its ^{13}C NMR spectrum was observed confirmed that the structure was symmetrical. Deprotonation of this diketone with two equivalents of lithium diisopropylamide (LDA) followed by addition of HMPA and 1,3-diiodopropane generated a mixture. Analysis of this mixture by GC-MS indicated that it contained only 20% of **128**, 8% of **127**, and 48% of recovered starting material. Attempts to improve the yield were unsucessful. A different route via the compound **131** was then examined, as outlined in

Scheme 13.

In principle, spiro-diketone **128** could be synthesized directly from cyclopentanone ketal by a geminal acylation reaction with **131** in the presence of $BF_3 \cdot Et_2O$. Thus, treatment of dimethyl succinate with two equivalents of LDA at −78°C followed by addition of HMPA and 1,3-dibromopropane produced a 10 : 1 crude mixture of *trans* and *cis* isomers, which was purified by vacuum distillation. The structures were elucidated by comparing their spectra with literature data.[56] However, when this mixture of diesters was treated with freshly cut sodium and chlorotrimethylsilane in refluxing toluene, only a trace amount of the *cis* isomer could be converted into the coupled product **131**, with unreacted *trans* isomer being recovered.[57] Unfortunately, equilibration of **130a** to its *cis* isomer **130b** did not occur under these reaction conditions. Thus, dienes **124a** and **124b** could not be obtained.

VI Experimental

General Procedures

All reactions requiring nonaqueous conditions were performed in oven-dried glassware under a positive pressure of dry nitrogen. Solvents and reagents were purified by distillation. Tetrahydrofuran (THF) was distilled from sodium metal/benzophenone. Chlorotrimethylsilane(TMSCl), dichloromethane, diisopropylamine, toluene, benzene, and diethyl ether ("ether") were distilled from calcium hydride. Pyridine was dried over anhydrous potassium hydroxide and distilled. Cyclopentadiene was freshly distilled by fraction distillation of dicyclopentadiene. The phrase "work-up" means extraction of the crude product with diethyl ether or dichloromethane, washing the organic layer with water and with saturated sodium chloride, drying over anhydrous magnesium sulfate, filtration, and concentration by solvent removal with a rotary evaporator, and the term "*in vacuo*" refers to the removal of the solvent with a rotary evaporator followed by evacuation to constant sample weight. All reactions were monitored by gas chromatography-mass spectrometry (GC-MS) or thin-layer chromatography (TLC) on commercial plates (Merck 60F-254). The plates were visualized by UV fluorescence, or staining with iodine, or spraying with an aqueous solution of phosphomolybdic acid, ceric sulphate and sulfuric acid followed by heating the plate (*ca.* 125°C). Flash chromatography was performed according to the method of Still and coworkers[58] on Merck Type 60 silica gel, 230-240 mesh. Melting points (mp) were determined on a Fisher-Johns apparatus and are uncorrected. Infrared (IR) spectra were recorded on either a Perkin Elmer 283 spectrophotometer (and were corrected by using polystyrene film as calibration standard) or a Mattson FT-IR instrument, and the abbrevation br means a broad absorption, s means strong absorption, m means medium absorption, w means weak absorption, and sh is a shoulder. Nuclear magnetic resonance (NMR) spectra were obtained in $CDCl_3$ solution, unless otherwise noted, on a General Electric GE 300-NB (300 MHz) instrument; chemical shifts were measured relative to internal standards: tetramethylsilane (TMS) for ^1H

and $CDCl_3$ (δ 77.0 ppm) for ^{13}C NMR. Multiplicities are described by the following abbrevations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (double doublet), tt (triple triplet), mm (multiple multiplets), and br (broad). Following the ^{13}C NMR chemical shifts are bracketed the number of attached protons. The NMR assignments were assisted by attached proton test (APT), and ^{1}H-^{1}H correlation (COSY) and ^{13}C-^{1}H correlation (HET-CORR) 2-D spectra. For the AB spin systems obtained in the 300 MHz spectra, the chemical shifts δ_A and δ_B were calculated according to equations (1) and (2),[59] respectively.

$$\delta_A = \frac{\nu - \frac{1}{2}\Delta\nu}{300} \tag{1}$$

$$\delta_B = \frac{\nu + \frac{1}{2}\Delta\nu}{300} \tag{2}$$

ν and $\Delta\nu$ were derived from equations (3) and (4), respectively,

$$\nu = \frac{\nu_1 + \nu_4}{2} = \frac{\nu_2 + \nu_3}{2} \tag{3}$$

$$\Delta\nu = [(\nu_1 - \nu_4)(\nu_2 - \nu_3)]^{1/2} \tag{4}$$

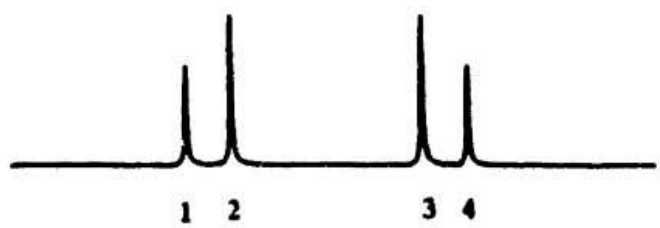


Figure 13. ^{1}H NMR spectrum of an AB system

where, as shown in Figure 13, ν_1, ν_2, ν_3, and ν_4 represent the observed frequencies (Hz) of the four peaks in the AB quartet. ^{1}H NMR nuclear Overhauser enhancement (NOE) data were obtained from sets of interleaved experiments (16K) of 8 transients cycled 12 to 16 times through the list of irradiated frequencies. The decoupler was gated on in continuous wave (CW) mode for 6 seconds with sufficient attenuation to give a 70-90% reduction in intensity of the irradiated peak. Frequency changes were preceded by a 60 second delay. Four scans were used to equilibrate spins before data acquisition, but a relaxation delay was not applied between scans at the same frequency. NOE difference spectra were obtained from zero-filled 32K data tables to which a 1 to 2 Hz exponential line-broadening function had been applied. Except where noted, both the low and the high resolution mass spectra (MS) data were obtained on a V.G. Micromass 7070HS instrument. A Hewlett-Packard system (model 5890 gas chromatograph coupled to a model 5970 mass selective detector) equipped with a Hewlett-Packard 12.5 m fused silica capillary column with cross-linked dimethylsilicone as the liquid phase was used for GC-MS analysis.

Spiro(bicyclo[2.2.1]heptane-2,2'-5-cyclopentane-1,3-dione) (83)

The norcamphor ethylene ketal **82** (440 mg, 2.86 mmol) in CH_2Cl_2 (60 mL) was stirred at -78°C as freshly distilled $BF_3{\cdot}Et_2O$ (5.3 mL, 43 mmol) was added, followed over a period of 5 min by a solution of **77** (1.9 mL, 7.2 mmol) in CH_2Cl_2 (6 mL).[49] The mixture was allowed to attain room temperature while stirring overnight. The solution was added slowly to an ice-cooled saturated $NaHCO_3$ solution, and the aqueous layer was extracted with CH_2Cl_2 (×3). The combined organic extracts were washed with saturated $NaHCO_3$ (×2), saturated NaCl (×2), and dried over $MgSO_4$. Flash chromatography of the residue (5% ethyl acetate in hexane) provided **83** as colorless crystals (413 mg, 82%): mp 108-109°C (lit.[48] mp 109.5-110.5°C); IR (film) ν_{max}: 1760 (sh) and 1717 cm^{-1}; ^{1}H NMR δ: 1.18-1.57 (mm, 6H), 1.76-1.89 (mm, 2H), 2.37 (br t, bridgehead H, 1H), 2.48 (br d, bridgehead H, 1H), and 2.51-3.07 (mm, 4H); ^{13}C NMR δ: 24.5 (2), 28.0

(2), 32.9 (2), 34.4 (2), 35.3 (2), 37.0 (1), 37.2 (2), 48.9 (1), 66.6 (0), and 213.1 (2C, 0); MS (from GC-MS) *m/z* (%): 178 (19, M^+), 149 (46), 112 (100), 93 (15), 67 (19), 66 (12), and 65 (13). *Exact mass* calcd. for $C_{11}H_{14}O_2$: 178.0993; found: 178.1002.

Spiro(bicyclo[2.2.1]heptane-2,2'-cyclopent-4-ene-1,3-dione) (69)

Method A: A solution of **83** (125 mg, 0.70 mmol) and *N*-bromosuccinimide (111 mg, 0.77 mmol) in CCl_4 (30 mL) was heated at reflux for three hours. The white precipitate was removed by filtration before concentration *in vacuo*. Flash chromatography of the residue (5% ethyl acetate in hexane) gave an inseparable mixture of two compounds (**69**, and **84** and/or **85**) in *ca.* 1 : 1 ratio. For **84** and/or **85**: MS (from GC-MS) *m/z* (%): 256 and 254 (33, M^+), 190 (96), 188 (100), 175 (47), 147 (19), 91 (25), 80 (65), 79 (55), 77 (21), 67 (53), and 66 (18).

Method B: A solution of **83** (288 mg, 1.62 mmol), dichlorodicyanobenzoquinone (DDQ) (1.83 g, 8.10 mmol) and *p*TSA (60 mg) in benzene (40 mL) was heated at reflux for two weeks.[50] Some black material was removed by filtration through a plug of SiO_2 with ether as the eluent. Concentration of the solution under vacuum provided an orange-brown liquid, which was purified by flash column chromatography (5% ethyl acetate in hexane) to give **69** (228 mg, 80%) as pale yellow crystals: mp 70.5-71.5°C; IR (film) ν_{max}: 1702 cm^{-1}; ^1H NMR δ: 1.82-1.25 (m, 7H), 2.10 (br d, J = 9.8 Hz, 1H), 2.29 (br s, bridgehead H, 1H), 2.41 (br s, bridgehead H, 1H), and 7.21 (s, 2H); ^{13}C NMR δ: 24.9 (2), 27.9 (2), 35.0 (2), 37.1 (1), 38.4 (2), 48.0 (1), 57.1 (0), 145.3 (1), 148.5 (1), 205.5 (0), and 206.0 (0); MS (from GC-MS) *m/z* (%): 176 (34, M^+), 110 (100), 97 (11), 89 (16), 82 (21), 80 (32), 79 (22), 77 (15), 67 (22), 65 (16), 54 (20), and 53 (15). *Exact mass* calcd. for $C_{11}H_{12}O_2$: 176.0837; found: 176.0830.

Bicyclo[2.2.1]hept-5-en-2-one (87)

A solution of freshly distilled cyclopentadiene (1.20 g, 18.2 mmol) and 2-chloroacrylonitrile (4.4 mL, 54 mmol) in 80 mL of benzene was refluxed overnight.[52]

The solvent was evaporated and the residue was dissolved in dimethyl sulfoxide (DMSO) (40 mL) and treated with aqueous potassium hydroxide (prepared from 2.40 g of solid potassium hydroxide and 35 mL of water). The solution was stirred overnight. Then the reaction mixture was extracted with ether (×4), and the organic layer was washed with water and saturated NaCl. The solvent was removed by simple distillation, and the residue (1.90 g) was used for next step without further purification: MS (from GC-MS) *m/z* (%): 108 (10, M^+), 79 (14), 77 (9), 66 (100), 65 (15), 51 (11), 50 (9), and 42 (6).

Spiro(bicyclo[2.2.1]hept-5-ene-2,2'-1,3-dioxolane) (88)

A benzene solution of crude **87** (1.90 g, 17.6 mmol), ethylene glycol (excess, 5 mL), and a catalytic amount of *p*TSA was heated under reflux overnight. The resulting reaction mixture was worked-up, and flash chromatography (1% ethyl acetate in hexane) gave **88** (2.27 g, 82% overall yield from cyclopentadiene) as a yellow oil: IR (film) ν_{max}: 2975 (s) and 1333 (m) cm^{-1}; ^1H NMR δ 1.50 (dd, J = 3.5, 12.2 Hz, 1H), 1.63-1.68 (m, 1H), 1.74 (d, J = 8.6 Hz, 1H), 1.85 (dd, J = 3.7, 12.2 Hz, 1H), 2.64 (narrow d, J = 1.4 Hz, 1H), 2.82 (br s, bridgehead H, 1H), 3.84-3.98 (m, 4H), 6.08 (dd, J = 3.2, 5.6 Hz, 1H), and 6.31 (dd, J = 2.9, 5.6 Hz, 1H); ^{13}C NMR δ 39.8 (2), 40.4 (1), 48.6 (2), 48.9 (1), 63.7 (2), 64.2 (2), 117.8 (0), 132.7 (1), and 139.0 (1); MS (from GC-MS) *m/z* (%): 152 (1, M^+), 86 (100), 79 (17), 77 (13), 66 (17), 65 (10), 51 (11), 43 (29), and 42 (71).

8-Oxatricyclo[7.2.1.$0^{3,6}$]dodeca-3(7),10-dien-4-one (91) and **2-((4-hydroxyl)-2-cyclopentenylmethyl)cyclopentane-1,3-dione (92)**

The ketal **88** (202 mg, 1.33 mmol) in CH_2Cl_2 (40 mL) was stirred at -78°C as freshly distilled $BF_3{\cdot}Et_2O$ (2.5 mL, 20 mmol) was added followed over a period of 5 min by a solution of **77** (0.9 mL, 3.3 mmol) in 6 mL of CH_2Cl_2. The mixture was allowed to attain room temperature while stirring overnight. The solution was worked-up. After purification by flash chromatography (5% ethyl acetate in hexane) 108 mg of **91** (42%) and 29 mg of **92** (12%) were isolated as colorless oils. For **91**: IR (film) ν_{max}: 3404 (br),

1683 (m), and 1621 (s) cm^{-1}; ^1H NMR δ: 2.18-2.67 (m, 9H), 5.10 (d, J = 5.5 Hz, 1H), 5.90-6.00 (m, 1H), and 6.12-6.16 (m, 4H); ^{13}C NMR δ: 17.5 (2), 26.5 (2), 32.6 (2), 34.2 (1), 36.9 (2), 84.2 (1), 110.0 (0), 134.8 (1), 137.4 (1), 184.5 (0), and 203.6 (0); MS *m/z* (%): 176 (6, M^+), 66 (100), 65 (20), 55 (17), 54 (24), and 40 (14). For **92**: IR (film) ν_{max}: 1690 (m) and 1611 (s) cm^{-1}; ^1H NMR δ: 1.93 (d, J = 14.0 Hz, 1H), 2.21-2.60 (m, 7H), 3.06 (m, 1H), 5.33 (dd, J = 2.6, 6.1 Hz, 1H), 5.81 (dd, J = 2.6, 5.5 Hz, 1H), 6.29 (dd, J = 2.7, 5.5 Hz, 1H); ^{13}C NMR δ: 28.0 (2), 32.2 (2), 33.4 (2), 38.1 (1), 40.1 (2), 85.2 (1), 115.4 (0), 126.8 (1), 144.4 (1), 179.6 (0), and 207.7 (0); MS (from GC-MS) *m/z* (%): 194 (14, M^+), 91 (36), 89 (12), 66 (100), 65 (27), and 41 (9).

Bicyclo[2.2.2]oct-5-en-2-one (94)

A solution of 1,3-cyclohexadiene (1.2 mL, 13 mmol) and 2-chloroacrylonitrile (1.1 mL, 14 mmol) in 80 mL benzene was refluxed overnight. The solvent was evaporated, and the residue was directly dissolved in DMSO (40 mL) and treated with aqueous potassium hydroxide (prepared from 2.12 g of solid potassium hydroxide and 30 mL water), and stirred overnight at room temperature. The reaction mixture was extracted with ether (×4). The combined organic layers were washed with 1N HCl (×2), water, and saturated NaCl. The solvent was removed by simple distillation and the residue was used for the next step without further purification. IR (film) ν_{max}: 1726 (s) cm^{-1}; ^1H NMR δ: 1.51-1.74 (mm, 3H), 1.83-1.90 (mm, 2H), 2.03 (m, 1H), 2.99 (m, bridgehead H, 1H), 3.14 (m, bridgehead H, 1H), 6.20 (m, 1H), and 6.49 (m, 1H); ^{13}C NMR δ: 22.1 (2), 23.8 (2), 32.0 (1), 40.0 (2), 48.1 (2), 127.9 (1), 136.6 (1), and 212.1 (0); MS (from GC-MS) *m/z* (%): 122 (12, M^+), 80 (100), 79 (80), and 77 (17).

Spiro(bicyclo[2.2.2]oct-5-ene-2,2'-1,3-dioxolane) (95)

A solution of crude product **94**, ethylene glycol (2.1 mL, 38 mmol) and a catalytic amount of *p*TSA was heated under reflux overnight. The resulting reaction mixture was worked-up, and flash chromatography (3% ethyl acetate in hexane) gave **94** (1.88 g 90%

overall yield from 1,3-cyclohexadiene) as a colorless liquid: IR (film) ν_{max}: 3048 (m), 2943 (s), and 1369 (m) cm^{-1}; ^1H NMR δ: 1.13-1.34 (mm, 2H), 1.55-1.76 (mm, 3H), 1.87-1.95 (m, 1H), 2,58 (br s, bridgehead H, 1H), 2.66 (br s, bridgehead H, 1H), 3.91 (s 4H), 6.24 (m 1H), and 6.33 (m, 1H); ^{13}C NMR δ: 22.2 (2), 23.7 (2), 30.8 (1), 38.0 (1), 40.9 (2), 63.6 (2), 63.8 (2), 112.6 (0), 131.3 (1), and 134.5 (1); MS (from GC-MS) *m/z* (%): 166 (3, M^+), 91 (11), 87 (80), 86 (100), 80 (28), 79 (39), 78 (15), 77 (26), 51 (15), 43 (47), 42 (56), and 41 (44).

8-Oxatricyclo[7.2.2.0^{3,7}]triscadeca-3(7),10-dien-4-one (98)

The ketal **95** (182 mg, 1.10 mmol) was treated with $BF_3{\cdot}Et_2O$ (2.0 mL, 16 mmol) and **77** (0.7 mL, 2.8 mmol) in the same manner as for ketal **88**. After purification by flash chromatography (6% ethyl acetate in hexane) 117 mg of **98** (56%) was isolated as the only product: mp 72-74°C; IR (film) ν_{max}: 1682 (m) and 1619 (s) cm^{-1}; ^1H NMR δ: 1.55-1.62 (m, 2H), 2.08-2.77 (m, 9H), 4.65 (br s, 1H), 5.87-5.93 (m, 1H), and 6.05-6.16 (m, 1H); ^{13}C NMR δ: 21.0 (2), 22.9 (2), 24.7 (2), 26.3 (2), 29.2 (1), 33.1 (2), 74.6 (1), 112.7 (0), 124.5 (1), 133.4 (1), 182.4 (0), and 204.1 (0); MS (from GC-MS) *m/z* (%): 190 (6, M^+), 112 (52), 111 (24), 80 (100), 79 (72), 76 (31), 55 (20), 54 (15), 53 (18), 51 (20), and 41 (17). *Exact mass* calcd. for $C_{12}H_{14}O_2$: 190.0993; found: 190.0988.

Spiro(bicyclo[2.2.2]octane-2,2'-1,3-dioxolane) (99)

To a solution of **95** (0.94 g, 5.7 mmol) in EtOAc (30 mL) was added 10% palladium on charcoal (50 mg). After shaking for one hour under an atmosphere of H_2 (50 psi) the mixture was filtered to remove the catalyst, and the filtrate was concentrated. Flash chromatography of the residue (3% ethyl acetate in hexane) provided **99** (0.86 g, 90%) as a colorless liquid: ^1H NMR δ: 1.46 (m, 3H), 1.62 (br s, bridgehead H, 1H), 1.78 (m, 4H), and 3.84-3.94 (m, 4H); ^{13}C NMR δ: 21.3 (2C, 2), 24.2 (2C, 2), 26.0 (1), 31.9 (1), 40.8 (2), 63.5 (2C, 2), and 110.7 (0); MS (from GC-MS) *m/z* (%): 168 (30, M^+), 125 (100), 99 (33), 81 (15), 79 (15), 67 (16), 65 (60), 55 (35), 53 (17), 43 (18), 42 (32), and 41 (44).

Spiro(bicyclo[2.2.2]octane-2,2'-cyclopentane-1,3-dione) (101)

Ketal **99** (428 mg, 2.55 mmol) in CH_2Cl_2 (*ca.* 50 mL) was cooled to −78°C before freshly distilled $BF_3{\cdot}Et_2O$ (4.8 mL, 38 mmol) was added, followed by dropwise addition of a solution of **77** (2.0 mL, 7.6 mmol) in CH_2Cl_2 (5 mL). The solution was allowed to attain room temperature while stirring overnight. The reaction was quenched by slow addition of saturated $NaHCO_3$ solution. The aqueous layer was re-extracted with CH_2Cl_2 (×3), and the combined organic extracts were washed with H_2O and saturated NaCl solution, then dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (4% ethyl acetate in hexane) of the brown residue gave **101** as colorless crystals (362 mg, 74%) and hydrolyzed starting material **100** (72 mg, 17%). For **101**: mp 99-100°C; IR (film) ν_{max}: 1738 (sh) and 1718 (s) cm^{-1}; ^1H NMR δ: 1.35-1.49 (m, 4H), 1.61-1.68 (m, 6H), 1.76 (br s, bridgehead H, 1H), 1.83 (br s, bridgehead H, 1H), 2.56 (m, 2H), and 3.00 (m, 2H); ^{13}C NMR δ: 21.2 (2C, 2), 23.0 (1), 24.1 (2C, 2), 26.5 (2), 32.1 (1), 34.0 (2C, 2), 62.4 (0), and 213.1 (2C, 0); MS (from GC-MS) *m/z* (%): 192 (25, M^+), 112 (100), 81 (23), 80 (15), 79 (40), 77 (21), 55 (20), 53 (20), and 41 (27). *Exact mass* calcd. for $C_{12}H_{16}O_2$: 192.1150; found: 192.1141. For **100**: IR (film) ν_{max}: 1727 (s) cm^{-1}; ^1H NMR δ: 1.50-1.85 (m, 5H), 2.16 (apparent sextet, J = 3.0 Hz, 1H), and 2.24 (m, 2H); ^{13}C NMR 23.2 (2C, 2), 24.4 (2C, 2), 27.7 (1), 42.1 (1), 44.5 (2), and 217.8 (0). MS (from GC-MS) *m/z* (%): 124 (17, M^+), 81 (33), 80 (100), 79 (22), 67 (42), 55 (36), 54 (46), and 41 (39). *Exact mass* calcd. for $C_8H_{12}O$: 124.0888; found: 124.0885.

Spiro(bicyclo[2.2.2]octane-2,2'-cyclopent-4-ene-1,3-dione) (70)

A solution of **92** (362 mg, 1.87 mmol), DDQ (1.27 g, 5.6 mmol), and *p*TSA (50 mg) in benzene (40 mL) was heated under reflux for two weeks. The excess DDQ was removed by filtration through a plug of SiO_2 with ether as the eluent. Concentration of the filtrate under reduced pressure gave an orange-brown liquid, which was purified by flash chromatography (4% ethyl acetate in hexane) to provide 332 mg (90%) of **70** as pale yellow crystals: mp 110-111°C; IR (film) ν_{max}: 1692 (s) cm^{-1}; ^1H NMR δ:

1.33-1.43 (m, 2H), 1.49-1.57 (m, 3H), 1.66-1.69 (m, 2H), 1.71-1.75 (m, 2H), 1.77-1.90 (m, 3H), and 7.15 (s, 2H); ^{13}C NMR δ: 22.4 (2C, 2), 23.5 (1), 24.4 (2C, 2), 28.4 (2), 31.8 (1), 53.6 (0), 147.2 (2C, 1), and 205.9 (2C, 0); MS (from GC-MS) *m/z* (%): 190 (49, M^+), 124 (41), 110 (100), 94 (38), 93 (25), 91 (42), 82 (59), 81 (50), 80 (24), 79 (81), 78 (21), 77 (61), 67 (38), 66 (21), 65 (28), 55 (48), 54 (61), 53 (55), 52 (23), 52 (33), and 41 (52). *Exact mass* calcd. for $C_{12}H_{14}O_2$: 190.0993; found: 190.0995.

Spiro[4.5]decane-1,4-dione (103)

A CH_2Cl_2 solution of the cyclohexanone ketal (264 mg, 1.86 mmol) was treated as the same manner as for ketal **99** with $BF_3{\cdot}Et_2O$ (3.4 mL, 28 mmol) and **77** (1.2 mL, 4.6 mmol). After work-up, the yellow residue was passed through a small pad of Florisil which was washed with five volumes of ether. Evaporation of the combined solvents *in vacuo* gave **103** (275 mg, 89% crystallized from ethyl acetate) as colorless crystals: mp 60-61°C (lit[48] mp 61-62°C); IR (film) ν_{max}: 1755 (w) and 1720 (s) cm^{-1}; ^{1}H NMR δ: 1.4-1.7 (m, 10H), and 2.677 (s, 4H); ^{13}C NMR δ: 20.4 (2C, 2), 24.9 (2), 29.2 (2C, 2), 34.3 (2C, 2), 55.9 (0), and 215.8 (2C, 0); MS *m/z* (%): 166 (100, M^+), 137 (25), 124 (32), 112 (61), 111 (46), 85 (46), 81 (37), 67 (74), and 56 (44); *Exact mass* calcd. for $C_{10}H_{14}O_2$: 166.0993; found: 166.0985.

Spiro[4.5]dec-3-ene-1,4-dione (104)

A solution of **103** (174 mg, 1.05 mmol), DDQ (1.21 g, 5.3 mmol), and a catalytic amount of *p*TSA in benzene (*ca.* 50 mL) was heated under reflux for one week. The resulting solution was passed through a plug of SiO_2 to remove the much of the black color. After concentration *in vacuo*, the orange-brown residue was flash chromatographed (5% ethyl acetate in hexane) to afford 126 mg (73%) of **104**: mp 86-87.5°C; IR (film) ν_{max}: 1696 cm^{-1}; ^{1}H NMR δ: 1.50-1.60 (m, 6H), 1.71-1.78 (m, 4H), and 7.16 (s, 2H); ^{13}C NMR δ: 20.7 (2C, 2), 24.7 (2), 28.9 (2C, 2), 48.9 (0), 146.6 (2C, 1), and 207.3 (2C, 0); MS (from GC-MS) *m/z* (%): 164 (34, M^+), 136 (15), 110 (24), 107 (18), 97 (35), 82

(100), 81 (16), 79 (21), 68 (15), 67 (21), 55 (22), 54 (64), 53 (29), and 41 (26). *Exact mass* calcd. for $C_{10}H_{12}O_2$: 164.0837; found: 164.0841.

2,2-Dimethyl-1,3-cyclopentanedione (106)

The ketal **108** (210 mg, 2.06 mmol) in CH_2Cl_2 (30 mL) was treated as above with $BF_3{\cdot}Et_2O$ (3.8 mL, 31 mmol) and **77** (1.6 ml, 3.8 mmol). The crude product consisted of 93% of **106** as revealed by GC-MS analysis. Chromatography (6% ethyl acetate in hexane) of the crude product gave **106** (125 mg, 68%) as a colorless oil: IR (film) ν_{max}: 1725 cm^{-1}; ^1H NMR δ: 1.15 (s, 6H), and 2.81 (s, 4H); ^{13}C NMR δ: 20.2 (2C, 3), 34.5 (2C, 2), 52.6 (0), and 216.3 (2C, 0); MS (from GC-MS) *m/z* (%): 124 (54, M^+), 111 (19), 83 (18), 70 (100), 56 (23), 55 (21), and 42 (83). *Exact mass* calcd. for $C_7H_{10}O_2$: 126.0680; found: 126.0678.

2,2-Dimethylcyclopent-4-ene-1,3-dione (107)

Method A: A solution of **106** (125 mg, 0.99 mmol), DDQ (674 mg, 2.97 mmol), and a catalytic amount of *p*TSA (40 mg) in benzene (30 mL) was heated under reflux for three days. After filtration, GC-MS of the eluent indicated that it contained 85% of desired product. Unfortunately, it was very difficult to remove the solvent because the product was very volatile.

Method B: A solution of **106** (125 mg, o.99 mmol) and *N*-bromosuccinimide (192 mg, 1.09 mmol) in CCl_4 (30 mL) was heated under reflux for three hours.[53] The white precipitate was removed by filtration, and the solution, which contained 95% of the product (**107**), was concentrated by careful distillation and the residue was used for the Diels-Alder reaction without further purification. IR (film) ν_{max}: 1710 cm^{-1}; ^1H NMR δ: 1.17 (s, 6H) and 7.23 (s, 2H); ^{13}C NMR δ: 19.5 (2C, 3), 46.3 (0), 147.0 (2C, 1), and 207.6 (2C, 0); MS (from GC-MS) *m/z* (%): 126 (1, M^+), 124 (46), 95 (27), 82 (100), 81 (39), 68 (15), 67 (48), 55 (22), 54 (87), 53 (52), 42 (47), and 41 (69).

Diels-Alder reaction of spiro(bicyclo[2.2.2]octane-2,2'-3-cyclopent-4-ene-1,3-dione

A solution of the dienophile **70** (361 mg, 1.90 mmol) and a large excess of cyclopentadiene (1.5 mL) in benzene (40 mL) was heated under reflux overnight. After removal of the solvent *in vacuo*, the ^{1}H NMR spectrum of the residue showed signals for dicyclopentadiene and for three adducts (**110**, **111**, and **112**) in a ratio of 47 : 5 : 48, respectively. This crude reaction mixture was separated by flash chromatography (pure benzene) to afford **110** (208 mg, 43%), **111** (20 mg, 4%), and **112** (214 mg, 44%) each as colorless crystals.

For **110**: mp 186-188°C; IR (film) ν_{max}: 1748 (m) and 1711 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.72-1.29 (m, 13H), 1.90 (m, 1H), 3.37 (m, 2H), 3.56 (m, 2H), 5.95 (m 2H); ^{1}H NMR (C_6D_6) δ: 0.98 (br d, J = 8.4 Hz, 1H), 1.28 (dt, J = 1.7, 8.4 Hz, 1H), 1.44 (m, 1H), 1.55 (m, 1H), 1.71-1.56 (m, 4H), 1.74 (m, 2H), 2.86 (apparent dd, J = 1.6, 2.7 Hz, 2H), 3.08 (m, 2H), 5.86 (apparent t, J = 1.8 Hz, 2H); NOE data (C_6D_6): irradiate 5.86: NOE 3.08 (2%); irradiate 3.08: NOE's at 5.86 (4%), 2.86 (1.4%), 1.28 (1.5%), 0.98 (2%); irradiate 2.86: NOE's at 3.08 (3%), 1.44 (3%), 0.98 (4%); irradiate at 1.74: NOE's at 5.86 (1.3%), 1.55 (4%); irradiate 0.98: NOE's at 3.08 (2%), 2.86 (4%), 1.28 (24%); ^{13}C NMR ($CDCl_3$) δ: 21.2 (2C, 2), 22.8 (1), 24.1 (2C, 2), 25.6 (2), 30.3 (1), 41.5 (2C, 1), 51.2 (2C, 1), 51.6 (2), 69.0 (0), 134.8 (2C, 1), and 214.0 (2C, 0); ^{13}C NMR (C_6D_6) δ: 21.6 (2C, 2), 23.6 (1), 24.7 (2C, 2), 26.1 (2), 30.5 (1), 45.4 (2C, 1), 51.5 (2C, 1), 51.7 (2), 69.3 (0), 135.2 (2C, 1), and 213.0 (2C, 0); MS (from GC-MS) *m/z* (%): 256 (16, M^+), 191 (35), 190 (64), 148 (32), 130 (16), 110 (45), 94 (19), 93 (16), 92 (21), 91 (60), 82 (30), 81 (34), 80 (17), 79 (53), 77 (37), 67 (28), 66 (100), 65 (44), 55 (28), 53 (28), 51 (15), and 41 (38). *Exact mass* calcd. for $C_{17}H_{20}O_2$: 256.1462; found: 256.1469.

For **111**: mp 107-109°C; IR (film) ν_{max}: 1702 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.17 (br m, 2H), 1.47 (narrow m, 2H), 1.52 (br d, J = 8.5 Hz, 1H), 1.64 (br d, J = 8.5 Hz, 1H), 1.41-1.64 (m, 4H), 1.73 (apparent quintet, J = 3.1 Hz, 1H), 1.82 (apparent quintet, J = 3.1 Hz, 1H), 2.20 (br m, 2H), 3.34 (m, 2H), 3.46 (m, 2H), 6.09 (narrow m, 2H); NOE data

($CDCl_3$): irradiate 6.09: NOE's at 3.46 (3%), 1.82 (4%); irradiate 3.46: NOE's at 6.09 (5%), 1.64 (3%), 1.52 (2%); irradiate at 3.34: NOE's at 1.52 (3%), 1.47 (0.5%); irradiate 2.20: NOE's at 6.09 (0.5%), 1.82 (6%), 1.17 (20%); irradiate 1.82: NOE's at 6.09 (5%); irradiate 1.17: NOE's at 2.20 (21%), 1.82 (9%); ^{13}C NMR ($CDCl_3$) δ: 21.2 (2C, 2), 24.4 (2C, 2), 24.6 (1), 25.3 (1), 35.3 (2), 47.1 (1), 52.4 (1), 53.0 (2), 60.2 (0), 136.0 (2C, 1), and 217.9 (2C, 0); MS essentially the same as for **110**. *Exact mass* calcd. for $C_{17}H_{20}O_2$: 256.1462; found: 256.1466.

For **112**: mp 162.5-164°C; IR (film) ν_{max}: 1745 (m) and 1706 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.74 (d, J = 9.5 Hz, 1H), 1.30 (dt, J = 1.7, 9.5 Hz, 1H), 1.32-1.65 (m, 8H), 1.75 (m, 1H), 1.95 (m, 1H), 2.86 (d, J = 1.5 Hz, 2H), 3.38 (br s, 1H), and 6.30 (t, J = 1.6 Hz, 2H); ^1H NMR (C_6D_6) δ: 0.66 (d, J = 9.4 Hz, 1H), 1.04 (dt, J = 1.7, 9.4 Hz, 1H), 1.10 (dd, J = 3.1, 11.5 Hz, 2H), 1.27 (br t, J = 11.5 Hz, 2H), 1.43 (quintet, J = 3.0 Hz, 1H), 1.53-1.75 (m, 5H), 1.89 (m, 2H), 2.28 (d, J = 1.7 Hz, 2H), 3.25 (m, 2H), and 5.88 (t, J = 1.7 Hz, 2H); NOE data ($CDCl_3$): irradiate 6.30: NOE's at 3.38 (4%), 2.86 (2%); irradiate 3.38: NOE's at 6.30 (5%), 2.86 (3%), 1.30 (2%), 0.74 (1.3%); irradiate 2.86: NOE's at 6.30 (4%), 3.38 (4%), 1.95 (6%); irradiate 1.95: NOE's at 2.86 (4%); irradiate 1.30: NOE's at 3.38 (3%), 0.74 (24%); irradiate 0.74: NOE's at 3.38 (3%), 1.30 (25%); ^{13}C NMR ($CDCl_3$) δ: 21.4 (2C, 2), 23.0 (1), 24.1 (2C, 2), 26.2 (2), 31.8 (1), 45.2 (2), 46.5 (2C, 1), 52.3 (2C, 1), 71.1 (0), 138.4 (2C, 1), and 213.9 (2C, 0); MS essentially the same as for **110**. *Exact mass* calcd. for $C_{17}H_{20}O_2$: 256.1462; found: 256.1461.

Diels-Alder reaction of spiro(bicyclo[2.2.1]heptane-2,1'-3-cyclopentene-2,5-dione (69)

A solution of the dienophile **69** (187 mg, 1.06 mmol) and a large excess of cyclopentadiene (1.5 mL) in benzene (40 mL) was heated under reflux overnight. After removal of the solvent *in vacuo*, the ^1H NMR spectrum of the residue showed signals for dicyclopentadiene and for four adducts (**114**, **115**, **116**, and **117**) in a ratio of 50 : 22 : 24 : 4, respectively. Flash chromatography (pure benzene) of the crude reaction mixture

provided **114** (114 mg, 44%), **115** (42 mg, 16%), **116** (50 mg, 19%), and **117** (5 mg, 2%) as colorless crystals.

For **114**: mp 128-129°C; IR (film) ν_{max}: 1747 (m) and 1708 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.14 (dddd, J = 1.4, 1.4, 2.8, 9.9 Hz, 1H), 1.21 (dd, J = 2.7, 12.1 Hz, 1H), 1.21-1.64 (m, 7H), 1.74 (d of apparent quintets, J = 1.8, 9.9 Hz, 1H), 2.27 (narrow m, 1H), 2.49 (narrow m, 1H), 3.38 (m, 2H), 3.42 (dd, J = 4.7, 9.4 Hz, 1H), 3.60 (dd, J = 4.9, 9.4 Hz, 1H), 5.92 (dd, J = 2.8, 5.3 Hz, 1H), 5.97 (dd, J = 2.5, 5.3 Hz, 1H); ^1H NMR (C_6D_6) δ: 0.91 (dddd, J = 1.5, 1.5, 2.7, 9.8 Hz, 1H), 1.00 (dd, J = 1.8, 8.5 Hz, 1H), 1.06 (br m, 1H), 1.28 (dt, J = 1.8, 8.5 Hz, 1H), 1.39 (dd, J = 2.9, 11.9 Hz, 1H), 1.30-1.44 (m, 2H), 1.46 (br m, 1H), 1.82 (ddd, J = 3.0, 4.3, 11.9 Hz, 1H), 1.84 (d of apparent quintets, J = 2.0, 9.8 Hz, 1H), 2.09 (narrow m, 1H), 2.13 (narrow m, 1H), 2.74 (dd, J = 4.5, 9.6 Hz, 1H), 3.03 (dd, J = 4.4, 9.6 Hz, 1H), 3.09 (m, 2H), 5.81 (dd, J = 2.8, 5.6 Hz, 1H), and 5.87 (dd, J = 2.9, 5.6 Hz, 1H); NOE data (C_6D_6): irradiate 5.87 & 5.81: NOE's at 3.09 (2%); irradiate 3.03: NOE's at 2.74 (5%), 2.13 (3%), 1.00 (3%); irradiate 2.74: NOE's at 3.09 (1.1%), 3.03 (3%), 1.00 (2%); irradiate 2.13 & 2.09: NOE's at 3.03 (4%), 2.74 (0.8%), 1.39 (1.4%), 1.06 (2%), 0.91 (4%); irradiate 1.00 & 0.91: NOE's at 3.09 (2%), 3.03 (2%), 2.74 (3%), 2.13 & 2.09 (4%), 1.84 (17%), 1.28 (7%); ^{13}C NMR ($CDCl_3$) δ: 24.3 (2), 27.9 (2), 31.8 (2), 36.7 (2), 36.7 (1), 45.3 (1), 45.4 (1), 47.2 (1), 51.5 (1), 51.8 (2), 52.2 (1), 73.0 (0), 134.7 (1), 135.3 (1), 214.0 (0), and 214.3 (0); ^{13}C NMR (C_6D_6) δ: 24.7 (2), 28.4 (2), 32.0 (2), 36.9 (2), 37.3 (1), 45.5 (1), 45.7 (1), 47.2 (1), 51.6 (1), 51.8 (2), 52.3 (1), 73.0 (0), 134.9 (1), 135.5 (1), 212.8 (0) and 213.1 (0); MS (from GC-MS) *m/z* (%): 242 (52, M^+), 177 (80), 176 (94), 147 (28), 110 (47), 91 (41), 80 (40), 67 (27), 66 (100), 65 (35), 41 (15). *Exact mass* calcd. for $C_{16}H_{18}O_2$: 242.1307; found: 242.1306.

For **115**: mp 97.5-99°C; IR (film) ν_{max}: 1702 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.27 (dd, J = 2.8, 11.6 Hz, 1H), 1.05-1.72 (m, 8H including 1H at δ 1.27), 1.85 (m, 1H), 2.12 (dm, J = 9.8 Hz, 1H), 2.29 (narrow m, 1H), 2.50 (narrow m, 1H), 3.24 (dd, J = 4.3, 9.0 Hz, 1H), 3.28 (dd, J = 4.1, 9.0 Hz, 1H), 3.48 (m, 2H), 6.09 (dd, J = 2.8, 5.5 Hz, 1H), and 6.19

(dd, J = 2.8, 5.5 Hz, 1H); ^{1}H NMR (C_6D_6) δ: 0.88 (br d, J = 8.4 Hz, 1H), 1.03 (m, 1H), 1.08 (d of multiplets, J = 9.4 Hz, 1H), 1.22 (dt, J = 1.6, 8.4 Hz, 1H), 1.23 (dd, J = 3.0, 11.6 Hz, 1H), 1.38-1.62 (m, 3H), 2.11 (dt, J = 3.0, 11.6 Hz, 1H), 2.13 (m, 1H), 2.38 (d of apparent quintets, J = 1.8, 9.6 Hz, 1H), 2.42 (narrow m, 1H), 2.69 (symmetrical m, 2H), 3.08 (m, 1H), 3.11 (m, 1H), 5.78 (dd, J = 2.9, 5.6 Hz, 1H), and 5.86 (dd, J = 2.9, 5.6 Hz, 1H); NOE data (C_6D_6): irradiate 5.86 & 5.78: NOE's at 3.11 & 3.08 (2%), 2.42 (2%); irradiate 3.11 & 3.08: NOE's at 5.86 (4%), 5.78 (4%), 2.69 (3%), 1.22 (3%), 0.88 (1.5%); irradiate 2.69: NOE's at 3.11 & 3.08 (4%), 0.88 (4%); irradiate 2.24 & 2.38: NOE's at 5.86 (7%), 5.78 (3%), 1.08 (22%); irradiate 0.84: NOE's at 3.11 & 3.08 (3%), 2.69 (6%), 1.22 (19%); ^{13}C NMR ($CDCl_3$) δ: 23.8 (2), 27.7 (2), 36.7 (1), 38.8 (2), 43.1 (2), 45.7 (1), 47.2 (1), 47.5 (1), 52.4 (1), 53.0 (1), 53.2 (2), 64.0 (0), 134.9 (1), 136.4 (1), 218.5 (0), and 218.5 (0); ^{13}C NMR (C_6D_6) δ: 23.8 (2), 28.3 (2), 37.3 (2), 39.1 (2), 43.3 (2), 45.9 (1), 47.3 (1), 47.6 (1), 52.4 (1), 53.0 (1), 53.1 (2), 63.7 (0), 135.0 (1), 136.5 (1), 217.1 (0), and 217.2 (0); MS essentially the same as for **114**. *Exact mass* calcd. for $C_{16}H_{18}O_2$: 242.1306; found: 242.1313.

For **116**: mp 142-143°C; IR (film) ν_{max}: 1745 (m) and 1706 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 0.78 (br d, J = 9.4 Hz, 1H), 1.20 (dddd, J = 1.4, 1.5, 2.9, 10.0 Hz, 1H), 1.31 (d of quintets, J = 1.7, 9.4 Hz, 1H), 1.33-1.59 (m, 5H), 1.76-1.84 (m, 2H), 2.35 (m, 1H), 2.54 (m, 1H), 2.74 (dt, J = 1.4, 8.8 Hz, 1H), 2.92 (dt, J = 1.4, 8.8 Hz, 1H), 3.36 (m, 1H), 3.41 (m, 1H), and 6.32 (narrow m, 2H); ^{1}H NMR (C_6D_6) δ: 0.66 (br d, J = 9.3 Hz, 1H), 0.91 (dddd, J = 1.4, 1.5, 2.9, 9.9 Hz, 1H), 1.03 (d of apparent quintets, J = 1.7, 9.3 Hz, 1H), 0.98-1.13 (m, 1H), 1.24-1.49 (m, 1H), 1.53 (dd, J = 2.7, 12.0 Hz, 1H), 1.86 (d of apparent quintets, J = 1.9, 9.9 Hz, 1H), 1.95 (ddd, J = 3.1, 4.2, 12.0 Hz, 1H), 2.11-2.14 (m, 2H), 2.16 (dt, J = 1.3, 8.9 Hz, 1H), 2.44 (dt, J = 1.3, 8.9 Hz, 1H), 3.23 (m, 1H), 3.24 (m, 1H), and 5.89 (narrow m, 2H); NOE data ($CDCl_3$): irradiate 6.32: NOE's at 3.41 & 3.36 (5%), 2.92 (3%), 2.74 (3%); irradiate approx. 3.39 (3.41 & 3.36): NOE's at 6.32 (8%), 2.92 (0.7%), 2.74(1.5%), 1.31 (1.1%), 0.78 (2%); irradiate 2.92: NOE's at 6.32

(3%), 3.36 (0.6%), 2.54 (0.5%); irradiate 2.74: NOE's at 2.92 (2%), 1.20 (0.9%); irradiate 2.35: NOE's at 1.20 (<0.5%); irradiate 0.78: NOE's at 3.41 & 3.36 (4%), 1.31 (21%); ^{13}C NMR ($CDCl_3$) δ: 24.5 (2), 28.0 (2), 32.2 (2), 36.9 (2), 36.9 (1), 45.2 (2), 46.8 (2C, 1), 48.5 (1), 52.7 (1), 53.3 (1), 75.0 (0), 138.5 (1), 138.6 (1), 213.7 (0), and 214.1 (0); ^{13}C NMR (C_6D_6) δ: 24.8 (2), 28.4 (2), 32.4 (2), 37.1 (2), 37.5 (1), 45.3 (2), 47.0 (2C, 1), 48.4 (1), 52.7 (1), 53.4 (1), 75.0 (0), 138.5 (2C, 1), 212.5 (0), and 212.9 (0); MS essentially the same as for **114**. *Exact mass* calcd. for $C_{16}H_{18}O_2$: 242.1307; found: 242.1313.

For **117**: IR (film) ν_{max}: 1738 (m) and 1703 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.24 (ddt, J = 4.0, 5.8, 12.3 Hz, 1H), 1.30 (br d, J = 9.4 Hz, 1H), 1.32 (dm, J = 9.8 Hz, 1H), 1.41 (dd, J = 2.7, 11.7 Hz, 1H), 1.43 (dt, J = 1.5, 9.4 Hz, 1H), 1.76 (ddd, J = 3.3, 3.5, 11.7 Hz, 1H), 2.15 (dddd, J = 3.0, 3.2, 9.0, 12.3 Hz, 1H), 2.25 (d of apparent quintets, J = 1.9, 9.8 Hz, 1H), 2.37 (m, 1H), 2.54 (m, 1H), 2.63 (narrow m, 2H), 3.37 (m, 1H), 3.39 (m, 1H), and 6.31 (m, 2H); ^{1}H NMR (C_6D_6) δ: 0.99-1.16 (m, 4H), 1.27 (dd, J = 2.9, 11.6 Hz, 1H), 1.36-1.60 (m, 3H), 2.06-2.17 (m, 3H), 2.36-2.48 (m, 3H), 3.12 (m, 1H), 3.16 (m, 1H), and 5.82 (m, 2H); NOE data ($CDCl_3$): irradiate 6.31: NOE's at 3.39 & 3.37 (6%), 2.63 (3%); irradiate 3.39 & 3.37: NOE's at 6.31 (7%), 2.63 (4%), 1.43 (~0.5%), 1.30 (1.3%); irradiate 2.63: NOE's at 6.31 (3%), 3.39 & 3.37 (3%); irradiate 2.54: NOE's at 1.30 (5%), 1.24 (2%); irradiate 2.15: NOE's at 2.54 (2%), 1.24 (12%); irradiate 1.76: NOE's at 2.63 (0.4%), 2.37 (5%), 1.41 (13%); MS essentially the same as for **114**. *Exact mass* calcd. for $C_{16}H_{18}O_2$: 242.1307; found: 242.1315.

Diels-Alder reaction of cyclopent-4-ene-1,3-dione (118)

A solution of **118** (Aldrich Chemical Co., 204 mg, 2.13 mmol) and cyclopentadiene (0.5 mL) in benzene (30 mL) was heated under reflux for 8 hours.[55] After removal of the solvent under vacuum, the residue was crystallized from MeOH to yield **119** (307 mg, 89%) as rapidly interchanging enols: mp 185-186°C (lit.[55] mp: 169.5-170.5°C); ^{1}H NMR (C_5D_5N) δ: 1.47 (d, J = 8.2 Hz, 1H), 1.67 (d, J = 8.2 Hz, 1H), 3.16 (m, 2H), 3.21 (m, 2H), 5.37 (s, 1H), and 6.12 (br s, 2H); NOE data (C_5D_5N): irradiate 6.12: NOE's at

3.16 (4%), 1.47 (14%); irradiate 1.47: NOE's at 3.21 (5%), 3.16 (3%), 1.67 (16%); ^{13}C NMR (C_5D_5N) δ: 44.4 (1), 49.8 (2C, 1), 52.8 (2), 108.7 (2), 133.6 (2C, 1), and 199.0 (2C, 0); MS (from GC-MS) *m/z*: 162 (5, M^+), 91 (15), 66 (100), 65 (14), and 42 (10). *Exact mass* calcd. for $C_{10}H_{10}O_2$:162.0681; found: 162.0680.

Diels-Alder reaction of 2,2-dimethylcyclopenta-4-ene-1,3-dione: (3aβ,7aβ)- (120) and (3aα,7aα)-3a,4,7,7a-tetrahydro-2,2-dimethyl-4,7-methanoindene-1,3-dione (121)

A solution of **107** (135 mg, 1.09 mmol) and 1.5 mL of cyclopentadiene in benzene (40 mL) was heated under reflux overnight.[53] The ^1H NMR spectrum of the crude reaction mixture indicated two adducts in a ratio of 76 : 24. Flash chromatography (pure benzene) afforded **120** (145 mg, 70%) and **121** (43 mg, 21%) as colorless crystals.

For **120**: mp: 64-65°C; IR (film) ν_{max}: 1715 cm^{-1}; ^1H NMR δ: 0.91 (s, 3H), 1.05 (s, 3H), 1.55 (br d, J = 8.6 Hz, 1H), 1.64 (dt, J = 1.6, 8.6 Hz, 1H), 3.45 (m, 2H), 3.53 (dd, J = 1.7, 2.9 Hz, 2H), and 6.04 (narrow t, J = 1.7 Hz, 2H); ^{13}C NMR δ: 14.8 (3), 22.1 (3), 45.7 (2C, 1), 51.0 (2C, 1), 51.7 (2), 57.9 (0), 134.9 (2C, 1), and 216.6 (2C, 0); MS (from GC-MS) *m/z* (%): 190 (1, M^+), 125 (72), 124 (25), 96 (10), 91 (25), 82 (54), 67 (13), 66 (100), 65 (25), 42 (19), and 41 (33). *Exact mass* calcd. for $C_{12}H_{14}O_2$: 190.0993; found: 190.0992.

For **121**: mp: 92.5-94°C; IR (film) ν_{max}: 1714 cm^{-1}; ^1H NMR δ: 0.87 (br d, J = 9.5 Hz, 1H), 1.14 (s, 3H), 1.21 (s, 3H), 1.38 (d of apparent quintets, J = 1.7, 9.5 Hz, 1H), 2.87 (narrow d, J = 1.6 Hz, 2H), 3.41 (narrow t, J = 1.6 Hz, 2H), and 6.32 (narrow t, J = 1.7 Hz, 2H); NOE data: irradiate 6.32: NOE's at 3.41 (4%), 2.87 (2%); irradiate 3.41: NOE's at 6.32 (5%), 2.87 (2%), 1.38 (2%), 0.87 (2%); irradiate 2.87: NOE's at 6.32 (3%), 3.41 (3%); ^{13}C NMR δ: 16.4 (3), 23.7 (3), 45.4 (2), 47.6 (2C,1), 52.7 (2C, 1), 60.8 (0), 138.4 (2C, 1), and 216.7 (2C, 0); MS essentially the same as for **120**. *Exact mass* calcd. for $C_{12}H_{14}O_2$: 190.0993; found: 190.0994.

Diels-Alder reaction of spiro[5,4]dec-3-ene-1,4-dione: (3aβ,7aβ)- (122) and (3aα,7aα)-3a,4,7,7a-tetrahydrospiro(cyclopentane-1,4'-4-methano-indene-1,3-dione) (123)

A solution of **104** (249 mg, 1.52 mmol) and cyclopentadiene (0.5 mL) in benzene (30 mL) was heated under reflux overnight. The ^{1}H NMR spectrum of the residue after concentration indicated that along with some dicyclopentadiene there were two adducts present, in a ratio of 73 : 27. Purification of the crude reaction mixture by flash chromatography (pure benzene) provided **122** (268 mg, 78%) and **123** (75 mg, 21%) as colorless crystals.

For **122**: mp 87-88°C; IR (film) ν_{max}: 1707 cm^{-1}; ^{1}H NMR δ: 1.36-1.76 (m, 12H) including 1.62 (br d, J = 8.7 Hz, 1H), 3.41-3.47 (m, 4H), and 6.04 (br s, 2H); ^{13}C NMR δ: 19.9 (2), 20.2 (2), 24.4 (2), 24.9 (2), 31.0 (2), 40.6 (2C, 1), 0.8 (2C, 1), 51.8 (2), 61.6 (0), 135.2 (2C, 1), and 216.5 (2C, 0); MS (from GC-MS) *m/z* (%): 230 (1, M^+), 165 (72), 164 (47), 97 (71), 91 (39), 82 (77), 67 (32), 66 (100), 65 (34), 55 (23), 54 (32), 53 (22), and 41 (33). *Exact mass* calcd. for $C_{15}H_{18}O_2$: 230.1306; found: 230.1297.

For **123**: mp 93-94°C; IR (film) ν_{max}: 1707 cm^{-1}; ^{1}H NMR δ: 0.89 (br d, J = 9.4 Hz, 1H), 1.36 (d of apparent quintets, J = 1.7, 9.4 Hz, 1H), 1.44-1.87 (m, 10H), 2.79 (apparent narrow d, J = 1.5 Hz, 2H), 3.38 (apparent narrow t, J = 1.6 Hz, 2H), and 6.30 (t, J = 1.7 Hz, 2H); NOE data: irradiate 6.30: NOE's at 3.39 (5%), 2.79 (2%); irradiate 3.39: NOE's at 6.30 (6%), 2.79 (3%), 1.36 (3%), 0.89 (2%); irradiate 2.79: NOE's at 6.30 (4%), 3.39 (5%); irradiate 1.36: NOE's at 3.39 (4%), 0.89 (28%); irradiate 0.89: NOE's at 3.39 (3%), 1.361 (28%); ^{13}C NMR δ: 20.4 (2), 20.8 (2), 24.9 (2), 26.0 (2), 32.4 (2), 45.6 (2), 47.6 (2C, 1), 52.4 (2C, 1), 64.3 (0), 138.5 (2C, 0), and 216.2 (2C, 0); MS essentially the same as for **122**. *Exact mass* calcd. for $C_{15}H_{18}O_2$: 230.1306; found: 230.1315.

Spiro[4.4]nonane-1,4-dione (126)

The cyclopentanone ethylene ketal **125** (208 mg, 1.63 mmol) was treated with

$BF_3 \cdot Et_2O$ (3.0 mL, 24 mmol) and **77** (1.1 ml, 4.1 mmol) as was done with **83**. After purification by flash chromatography (5% ethyl acetate in hexane) **126** (168 mg, 68%) was obtained as colorless crystals: mp:58-59.5°C; IR (film) ν_{max}: 1720 cm^{-1}; ^1H NMR δ: 1.61 (br s, 8H), 2.48 (br s, 4H); ^{13}C NMR δ: 26.6 (2C, 2), 34.6 (2C, 2), 34.7 (2C, 2), 63.0 (0), and 215.8 (2C, 0); MS *m/z* (%): 152 (100, M^+), 124 (35), 111 (48), 97 (52), 96 (44), 95 (33), 69 (28), 68 (52), 67 (61), 56 (61), 55 (29), and 41 (37). *Exact mass* cald. for $C_9H_{12}O_2$ required: 152.0837; found: 152.0818.

Spiro(bicyclo[3.3.0]octane-1,3-dione-2,1'-cyclopentane) (128)

A 50 mL round-bottomed flask was oven-dried and evacuated on a vacuum line then flushed with nitrogen three times. Anhydrous THF (20 mL) was cooled to 0°C, and diisopropylamine (0.4 mL, 2.9 mmol) was added followed by *n*-butyllithium (1.6M solution in hexane) (1.7 mL, 2.7 mmol). After 30 min, the solution was cooled to -78°C with Dry Ice-acetone bath and **126** (197 mg, 1.30 mmol) in 3 mL of THF was introduced. HMPA (2 mL) and 1,3-diiodopropane (0.2 mL, 1.4 mmol) were added to the reaction after 40 min. The reaction mixture was stirred for two hours before it was quenched with water. The aqueous layer was extracted with ether (×4). The combined organic extracts were washed with water and saturated NaCl then dried over $MgSO_4$. Analysis of the crude reaction mixture by GC-MS indicated that it contained 20% of the desired product **128**, 8% of **128** (which has the same molecular ion peak as **128** and we tentatively assigned structure **128**), and 48% of starting material **126**. This mixture was purified by repeated flash chromatography (4% ethyl acetate in hexane) to provide 45 mg (18%), of 95% pure diketone **128** as a yellow oil and **126** (72 mg, 36%). for **128**: IR (film) ν_{max}: 1716 cm^{-1}; ^1H NMR δ: 1.07-1.20 (m, 2H), 1.41-1.86 (m, 10H), 1.91-2.01 (2H), and 3.16-3.36 (m, 2H); ^{13}C NMR δ: 31.4 (2C, 2), 31.5 (4C, 2), 39.2 (2C, 2), 51.6 (2C, 1), 64.9 (0), and 219.7 (2C, 0); MS (from GC-MS) *m/z* (%): 192 (14, M^+), 97 (49), 96 (37), 68 (100), 67 (73), 65 (18), 55 (24), 53 (25), 43 (27), 42 (24), and 41 (80). *Exact mass* calcd. for $C_{12}H_{16}O_2$: 192.1149; found: 192.1139. For **127**: MS (from GC-MS) *m/z* (%): 192 (47,

M^+), 97 (87), 96 (56), 95 (24), 68 (100), 67 (60), and 41 (52).

Dimethyl *trans*-cyclopentane-1,2-dicarboxylate (130)

A 250 mL oven-dried round-bottomed flask was evacuated on a vacuum line and flushed with nitrogen three times. Anhydrous THF (80 mL) was cooled to 0°C, then diisopropylamine (3.67 mL, 6.22 mmol) followed by *n*-butyllithium (1.6 M in hexane) (15.6 mL, 25.0 mmol) were introduced. After 30 min, the solution was cooled to −78°C with a Dry Ice-acetone bath, and the diester **129** (1.74 g, 11.9 mmol) in 10 mL of THF was introduced. After stirring for 40 min, 6 mL of HMPA and dibromopropane (1.33 mL, 13.1 mmol) was added to the reaction mixture. The reaction was allowed to stand for another two hours before it was quenched by water. After work-up and concentration by rotary evaporation, the combined residues for three trials were combined and purified by distillation at reduced pressure to afford 4.53 g (68%) of **130**: ^{1}H NMR δ: 1.42-1.56 (m, 4H), 1.74-1.78 (m, 2H), 2.80-2.84 (m, 2H), and 3.39 (s, 6H); ^{13}C NMR δ: 25.5 (2), 30.5 (2C, 2), 47.1 (2C, 3), 51.9 (2C, 1), and 175.3 (2C, 0); MS (from GC-MS) *m/z* (%): 155 (22, M^+ − OMe), 154 (18), 126 (58), 95 (39), 68 (21), 67 (100), 66 (22), 59 (31), and 41 (31).

***cis*-Bis(trimethylsilyloxy)bicyclo[3.2.0]hepta-1-ene (131)**

A 250 mL three-necked round bottomed flask was equipped with a mechanical stirrer, a reflux condenser and a dropping funnel and maintained under a nitrogen atmosphere. The flask was charged with 80 mL of toluene and 2.24 g (97.4 mmol) of freshly cut sodium. The solvent was brought to gentle reflux and then the stirrer was operated at full speed until the sodium was fully dispersed. The stirrer speed was reduced and a mixture of 4.53g (24.4 mmol)of ester **130** and chlorotrimethylsilane (12.4 mL, 94.7 mmol) in 40 mL of toluene were added over one hour. The solvent was maintained under reflux during and after the addition. After five hours of additional stirring, the contents of the flask were cooled and filtered under nitrogen. The pale yellow filtrate was concentrated

by simple distillation. GC-MS of this crude reaction mixture indicated that only very small amount of acyloin product was present (5%) and the major component was starting material.

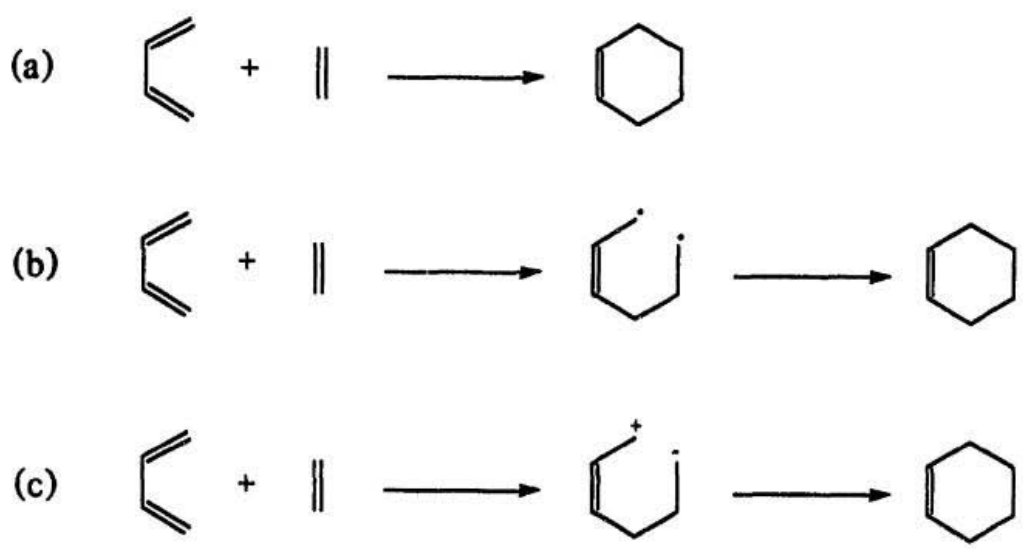
Chapter 2

MECHANISTIC STUDIES OF THE DIELS-ALDER REACTION

I. Introduction

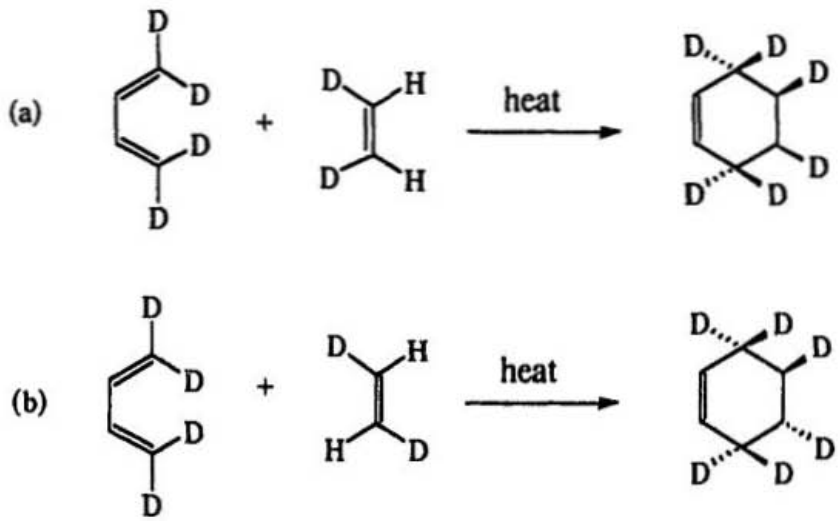
The Diels-Alder reaction is very widely used in organic synthesis since its discovery more than a half of century ago.[1] However, the mechanism of the Diels-Alder reaction still remains controversial. In fact, three types of mechanism have been considered for the Diels-Alder reaction (Scheme 14).[60-65] Mechanism (*a*) involves no intermediate but a cyclic transition state. The reaction is concerted with both bonds being partially formed at the transition state. However, the transition state can be either symmetrical (synchronous) with both new C-C bonds formed to an equal extent, or unsymmetrical (asynchronous)

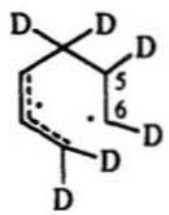
Scheme 14



with one of the new C-C bonds being almost completely formed while the other is still very weak, depending on the nature of the addends. Mechanism (*b*) occurs in two kinetically distinct steps via a diradical intermediate. Since a diradical would collapse to the product with little or no activation energy, the first step must be rate-determining. Mechanism (*c*) is similar to mechanism (*b*), but the intermediate formed is a diion instead of a diradical.

Scheme 15





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A large number of both experimental[66,67] and theoretical[68] studies have been carried out to distinguish these mechanisms. The bulk of the evidence suggests that most Diels-Alder reactions proceed via the concerted mechanism (*a*). Some of the experiments that support mechanism (*a*) are summarized as follows:

(1) retention of the stereochemistry in both the diene and the dienophile

If a completely free diradical or diion were formed, then the reaction could not be stereospecific. However, nearly all Diels-Alder reactions proceed in a stereospecific fashion. Recently, Houk *et al.*[69] reported that the reactions of 1,1,4,4-tetradeuterio-1,3-butadiene with *cis*- or *trans*-deuterioethylene took place without any scrambling of stereochemistry (Scheme 15). The energy barrier of rotation of a single bond (between C-5 and C-6) in the potential diradical intermediate **132** is only 0-0.4 kcal/mol, which is the experimental and theoretical range of rotational barriers in primary radicals. Thus, if diradical **132** were formed in the reaction, we would expect extensive scrambling of stereochemistry. The complete retention of stereochemistry is consistent with a concerted mechanism for the reaction of butadiene with ethylene, but this does not prove that the process is synchronous.

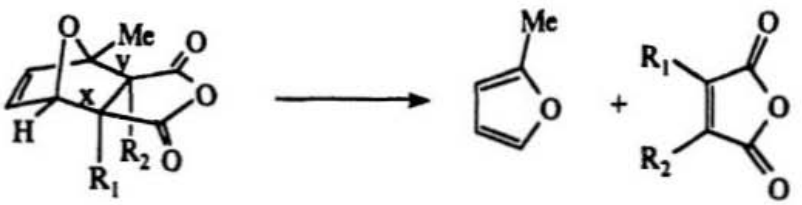
(2) secondary deuterium kinetic isotope effects

Seltzer *et al.*[70] reported that the deuterium isotope effect k_I/k_{II} in the decomposition reaction of **133** (Scheme 16) was equal to 1.00, within experimental error. This result strongly indicated that the bond breaking of X and Y proceeds via a symmetrical transition state. Otherwise, there would have been a smaller secondary isotope effect if the bond X broke before bond Y. According to the principle of microscopic reversibility, the mechanism of the reverse reaction should involve simultaneous formation of bonds X and Y. A similar experiment was conducted by Sickle *et al.* [71, 72] on the forward reaction and their results were consistent with this.

Recently, Gajewski *et al.*[73] studied the secondary deuterium kinetic isotope effects on the Diels-Alder reactions of isoprene-d_0, -d_2, and -d_4 with four dienophiles (see Scheme 16). The inverse kinetic isotope effect observed at the β site of acrylonitrile was half of the maximum value expected, and the inverse isotope effect at the α position was even smaller. This indicated an early unsymmetrical transition state. Similar results were obtained for α-cyanoacrylonitrile. The kinetic isotope effect for the reaction of

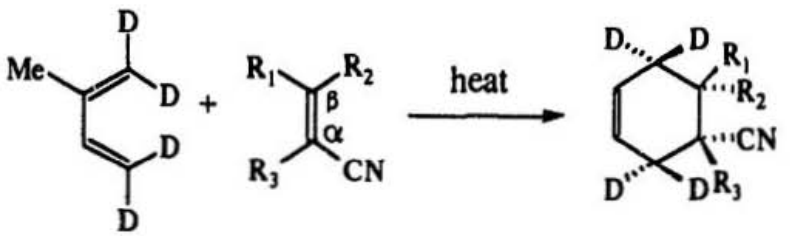
fumaronitrile with isoprene-d_4 was twice that with isoprene-d_2, implying the same effects at both α and β sites. The inverse kinetic isotope effects for methyl *trans*-cyanoacrylate at both bond-making sites were one-third of the maximum expected value. All these results are in accord with a concerted mechanism, but with an unsymmetrical transition state.

Scheme 16



133

I $R_1 = H$, $R_2 = D$
II $R_1 = D$, $R_2 = H$



$R_1 = R_2 = R_3 = H$ (Acrylonitrile)
$R_1 = CN$; $R_2 = R_3 = H$ (Fumaronitrile)
$R_3 = CN$; $R_1 = R_2 = H$ (α-Cyanoacrylonitrile)
$R_1 = COOEt$; $R_2 = R_3 = H$ (ethyl *trans*-cyanoacrylate)

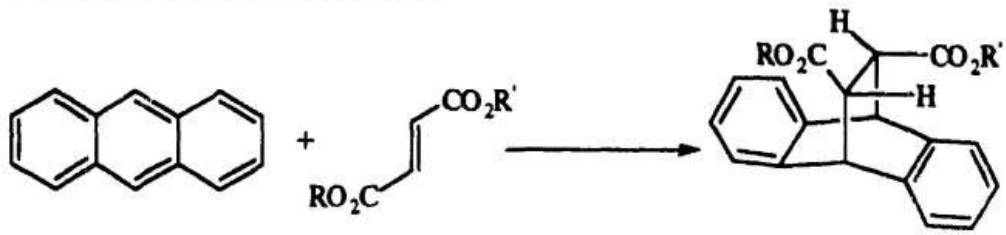
(3) quantitative measures of cooperativity in disubstituted dineophiles as examined by both optical induction and activation energies

The principle that synchronous reactions exhibit cooperativity in asymmetric induction derives directly from transition state theory and can be described as follows. When the reacting centers contain two or more chiral groups, the overall asymmetric induction

is the arithmetic product of that achieved by each group acting independently if the reaction is synchronous. Tolbert *et al.*[74] investigated the uncatalysed cycloadditions of anthracene with several dienophiles, and the observed and expected diastereomeric ratios are shown in Table 12. The diastereomeric ratio for methyl *l*-bornyl fumarate cycloaddition is 1.25 : 1. According to the principle of cooperativity, the ratio for di-*l*-bornyl fumarate cycloaddition should be 1.56 : 1, which is indeed within experimental error of the observed ratio, 1.53 : 1. Similarly, the predicted ratio for dimenthyl fumerate cycloaddition, 1.39 : 1, is within experimental error of the observed ratio, 1.36 : 1 (see Table 12). The fact that the uncatalysed Diels-Alder reaction exhibited cooperativity in asymmetric induction confirms a synchronous mechanism. However, Dewar *et al.*[63] believed that this argument regarding the synchronicity of the Diels-Alder reaction was inconclusive. It should be noted that cooperativity vanished when the reactions shown in Table 12 were carried out in the presence of Lewis acids, e.g. $AlCl_3$. The disappearance of the cooperativity in the presence of Lewis acids implies a change in transition state from synchronous to asynchronous due to the fact that Lewis acids help to enhance asymmetric induction by increasing the steric interaction at one end of the dienophile. Theoretical studies also showed that Lewis acid catalysed Diels-Alder reactions proceed by a concerted, but asynchronous, mechanism.[74]

Hancock and coworkers[75] studied the mechanism of the Diels-Alder reaction by using a somewhat different approach, i.e., by measuring the degree of the asynchronicity based on rate coefficients. Considering cycloadditions of cyclopentadiene with ethylene, monosubstituted ethenes (R-CH=CH_2), and 1,2-disubstituted ethenes (R-CH=CH-R), the corresponding rate coefficients could be described as k_a, k_b, and k_c, respectively. The coefficients k_b' and k_b'' can be calculated by equations (5) and (6), respectively. Dewar *et al.* predicted that k_b' should be equal to k_b in the case of a synchronous process and k_b'' should be equal to k_b in the case of a purely two-step process. The measure of the

Table 12: Anthracene Cycloaddition[74]



R	R'	diastereomeric ratio
Me	Me	1.00
Me	*l*-bornyl	1.25
l-bornyl	*l*-bornyl	1.53 (1.56[a])
Me	*l*-menthyl	1.18
l-menthyl	*l*-menthyl	1.36 (1.39[a])

[a] Numbers in brackets represent the predicted ratios.

Table 13. Second order rate coefficients and DASYN values for Diels-Alder reactions of cyclopentadiene with monosubstituted ethenes (R-CH=CH_2) and *trans*-1,2-disubstituted ethenes (R-CH=CH-R)[75]

R	k_c /10^{-4}u[a]	k_b /10^{-4}u	k_b' /10^{-4}u	k_b'' /10^{-4}u	DASYN /10^{-3}
p-$ClC_6H_4SO_2$	15894.2	0.550	0.2060	7947.1	0.04
$C_6H_5SO_2$	3761.1	0.322	0.1002	1880.6	0.12
p-$MeC_6H_5SO_2$	2236.4	0.225	0.0773	1118.2	0.13
p-$MeOC_6H_4SO_2$	1520.3	0.181	0.0637	760.2	0.15

[a] u = dm^3 mol^{-1} S^{-1}

degree of asynchronicity (DASYN) could be determined following equation (7). The values for k_b, k_b', k_b'', and k_c and DASYN for several dienophiles are shown in Table 13. Obviously, the rate coefficients (k_b values) agree quite well with predicted values (k_b') as calculated by equation (5), and hence the mechanism may be considered synchronous. Furthermore, it would be difficult to invoke asymmetry arguments with these dienophiles.

$$k_b' = [k_c \times k_a]^{1/2} \tag{5}$$

$$k_b'' = \frac{1}{2}(k_c + k_a) \tag{6}$$

$$DASYN = \frac{k_b - k_b'}{k_b'' - k_b'} \tag{7}$$

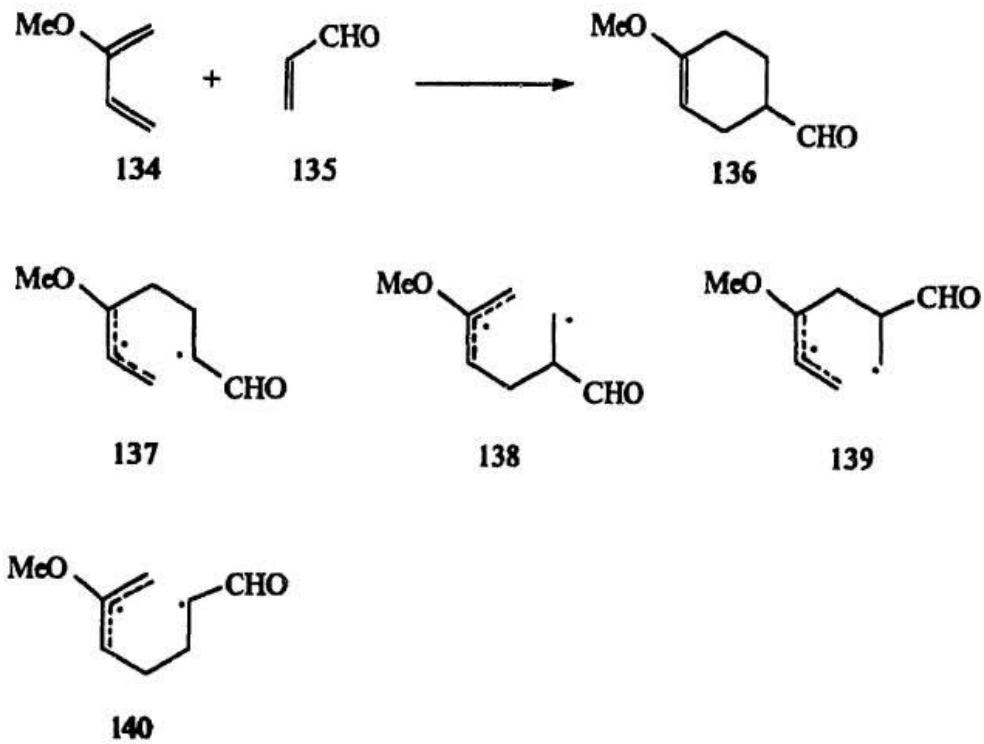
(4) insensitivity of the reaction rate to solvent effects

It is well known that the nature of the solvent has very little effect on the rate of the Diels-Alder reaction. Thus, mechanism (*c*) (Scheme 14) involving a diionic intermediate, is unlikely because polar solvents would increase the rate of a reaction in which charged species are developed in the transition state.

Dewar *et al.*[64] proposed that the Diels-Alder reaction is a concerted but asynchronous process. According to the definition, the mechanism is actually somewhere between mechanism (*a*) and mechanism (*b*). Their argument was that cycloadditions in general proceed via very unsymmetrical transition states, close to diradicals in structure and with the same energies as those of the corresponding diradicals. The chemical evidence for this proposition came from the substituent effects and regioselectivity of the Diels-Alder reaction. Based on this theory, the regioselectivity and reaction rates can be predicted in a quanlitative sense by simply assuming that the transition state corresponds in each case to diradicals. For example, the reaction of 2-methoxybutadiene with acrolein can give four possible diradicals **137-140**, of which **137** is the most stabilized (see Scheme 17). The reaction should therefore afford the *para*- isomer **136**, as is indeed

observed. The so-called *ortho* rule can be described in the same way. The diradical mechanism has been supported by extensive computational studies performed by Dewar and his coworkers.

Scheme 17



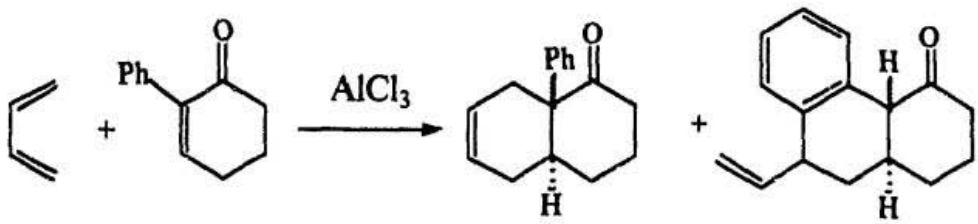
134 **135** **136** **137** **138** **139** **140**

Mechanisms (*b*) and (*c*) (Scheme 14) were found in only a few cases. For instance, as shown in Scheme 18, the reaction of **141** with butadiene provided a mixture of **142** and **143** via intermediate **144**.[76]

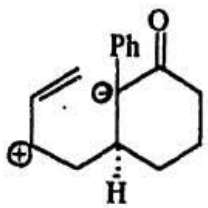
From the above discussion, it can be seen that there is little doubt that most Diels-Alder reactions are concerted, and the question in dispute is whether the process is synchronous or asynchronous. Theoretical studies have shown that the Diels-Alder reaction can be synchronous if both the reactants have twofold symmetry, and the reaction takes place via an unsymmetrical transition state (i.e., is asynchronous) if the addends are

unsymmetrical. However, the Woodward-Hoffmann theory of pericyclic reactions made most organic chemists believe that the Diels-Alder reaction is not merely concerted but also synchronous.

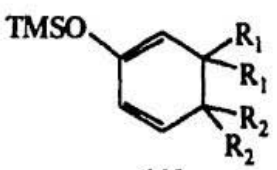
Scheme 18



141 142 143



144



145

a: $R_1 = R_2 = H$
b: $R_1 = Me$, $R_2 = H$
c: $R_1 = H$, $R_2 = Me$

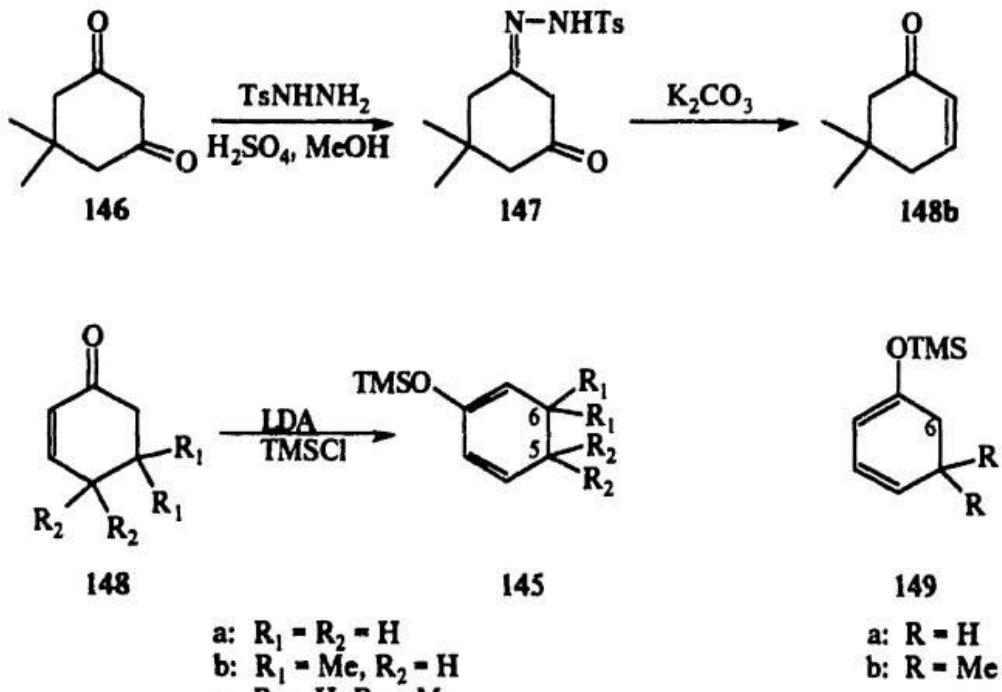
To date, there is only a little experimental evidence that can indicate the degree of asynchronicity in the transition state of the Diels-Alder reaction. We decided to investigate the nature of the transition state by comparing the relative reaction rates of dienes

145a, **145b**, and **145c** in reactions with both symmetrical and unsymmetrical dienophiles. The relative reaction rates of **145b** *versus* **145c** should give a clue to the synchronicity of the transition states, and the following section details our studies in this area.

II. Results

The preparation of dienes **145a-c** is outlined in Scheme 19. Enone **148b** was synthesized from dimedone **146** following a literature procedure.[77] Deprotonation of enones **148** with lithium diisopropylamide (LDA) followed by trapping with chlorotrimethylsilane (TMSCl) gave **145** cleanly.[78,79] However, purification of these enol ethers by chromatography on silica gel or Florisil always resulted in a significant amount of the hydrolyzed material **148**. Since our experiments required an accurate measurement of the relative amounts of the starting dienes, the dienes purified in this way were unacceptable. After a period of experimentation, pure dienes were obtained by the following procedure. When the reaction was over, the resulting solution was concentrated *in vacuo* to remove most of the THF. The residue was diluted with anhydrous pentane, and the precipitated LiCl was removed by filtration. The filtrate was concentrated, and the remaining liquid was distilled under reduced pressure to afford the dienes **145** in good yield. The structure and the purity of each diene was confirmed by NMR spectroscopy (both ^{1}H and ^{13}C). For enones **148a** and **148b**, both thermodynamic and kinetic products were possible (**145a**, **145b** and/or **149a** , **149b**). However, under these conditions of kinetic control only the desired diene was generated as revealed by a single set of resonances in the ^{13}C spectra and by the ^{1}H NMR spectra for either **145a** or **145b**. For example, in the preparation of diene **145b**, if diene **149b** was also formed, a high-field singlet for its C-6 methylene would have been apparent in the ^{1}H NMR spectrum of the product. In fact, the only methylene signal appeared as a double doublet, and one of the olefinic signals was a singlet, which confirmed that the diene indeed had the structure **145b**. The dienes prepared in this way could be stored under nitrogen in a refrigerator (at *ca.* 0°C) for more than a month. Mixtures of dienes **145a** and **145b**, **145a** and **145c**, and **145b** and **145c** were obtained by mixing the pure dienes. The ratios of the dienes were then determined by accurate integration of ^{1}H NMR spectra. The dienophile

Scheme 19



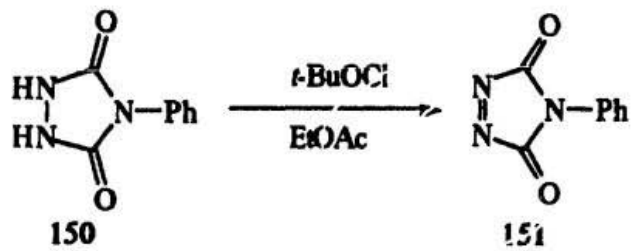
146 147 148b

148 145 149

a: $R_1 = R_2 = H$
b: $R_1 = Me, R_2 = H$
c: $R_1 = H, R_2 = Me$

a: R = H
b: R = Me

Scheme 20



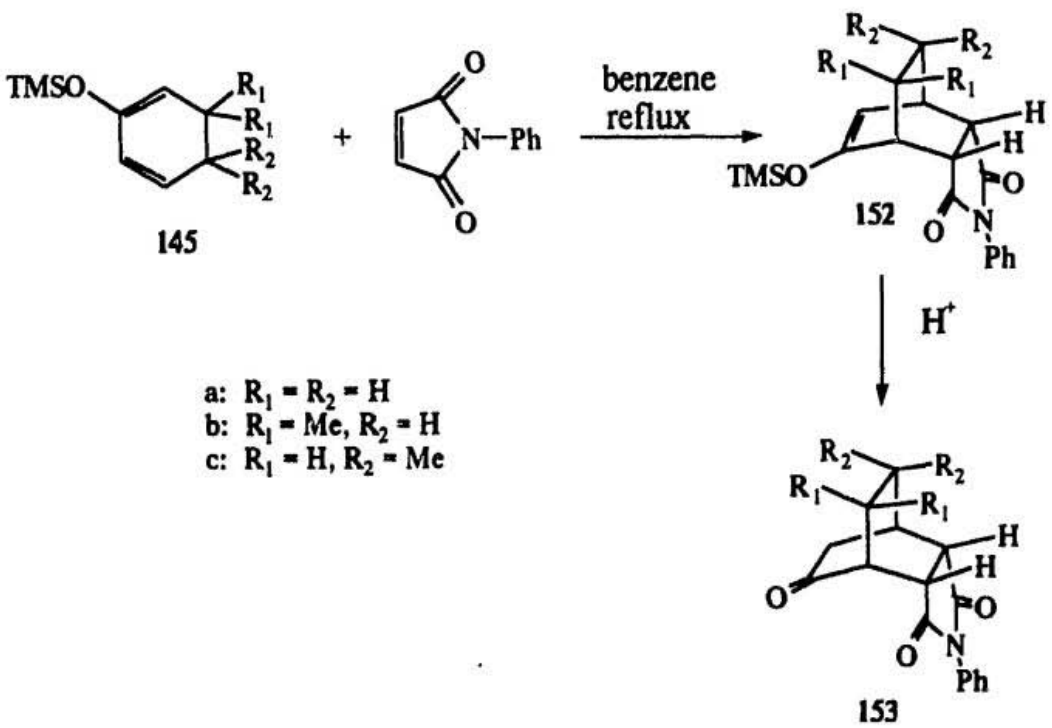
150 151

4-phenyl-1,2,4-triazoline-3,5-dione (**151**) was prepared from 4-phenylurazole (**150**) according to a literature procedure (Scheme 20).[80,81]

With pure dienes in hand, the Diels-Alder reactions with some symmetrical dienophiles were investigated first . Before we carried out competitive experiments, reactions of the individual dienes **145a-c** with these symmetrical dienophiles were conducted.

Cycloadditions of each of diene with *N*-phenylmaleimide proceeded smoothly in refluxing benzene. In each case, only the product of *endo* addition was obtained. The adducts **152a-c** were characterized fully. For example, a signal at δ 4.98 in the ^{1}H NMR spectrum of adduct **152a** and two olefinic resonances (δ 154.6 and 100.5) in its ^{13}C NMR spectrum indicated the presence of the double bond of the enol ether. Its mass spectrum showed a fragment at *m/z* 168, corresponding to the mass of **145a**, which must arise via the homolytic *retro*-Diels-Alder reaction of the adduct **152a** (Scheme 22). The adducts could be isolated by simply washing the oily reaction mixture with anhydrous pentane, or hydrolyzed to the more stable corresponding ketones by treatment with dilute hydrochloric acid. The structures of the hydrolysis products were confirmed by both ^{1}H and ^{13}C NMR spectra with the assistance of two-dimensional spectra. Then, a mixture of **145b** and **145c** in a 1 : 1 molar ratio was heated with 0.5 molar equivalents of *N*-phenylmaleimide in benzene for thirty hours. After removal of the solvent, the ^{1}H NMR

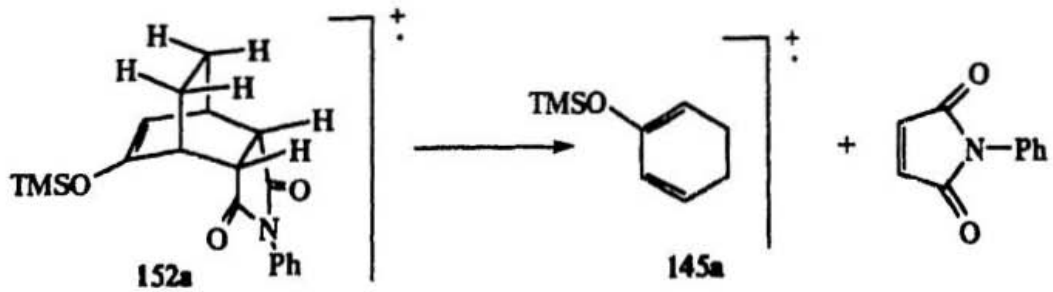
Scheme 21



a: $R_1 = R_2 = H$
b: $R_1 = Me$, $R_2 = H$
c: $R_1 = H$, $R_2 = Me$

spectrum of the crude reaction mixture showed signals for both **152b** and **152c** in a 1.0 : 1 ratio. The competitive reactions of **145a** *versus* **145b**, **145a** *versus* **145c**, and **145b** *versus* **145c** were carried out in the same way. The ratio of reaction rates was calculated based on Equation (8)[82] (see Experimental). All the ratios of reaction rates are listed in Table 14.

Scheme 22



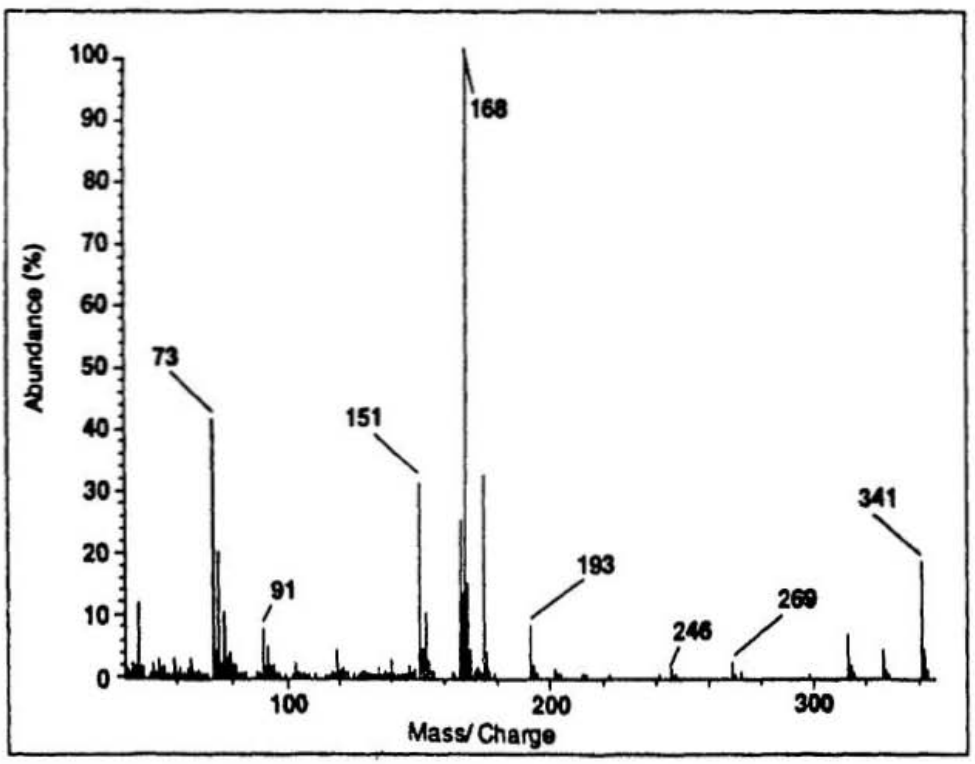
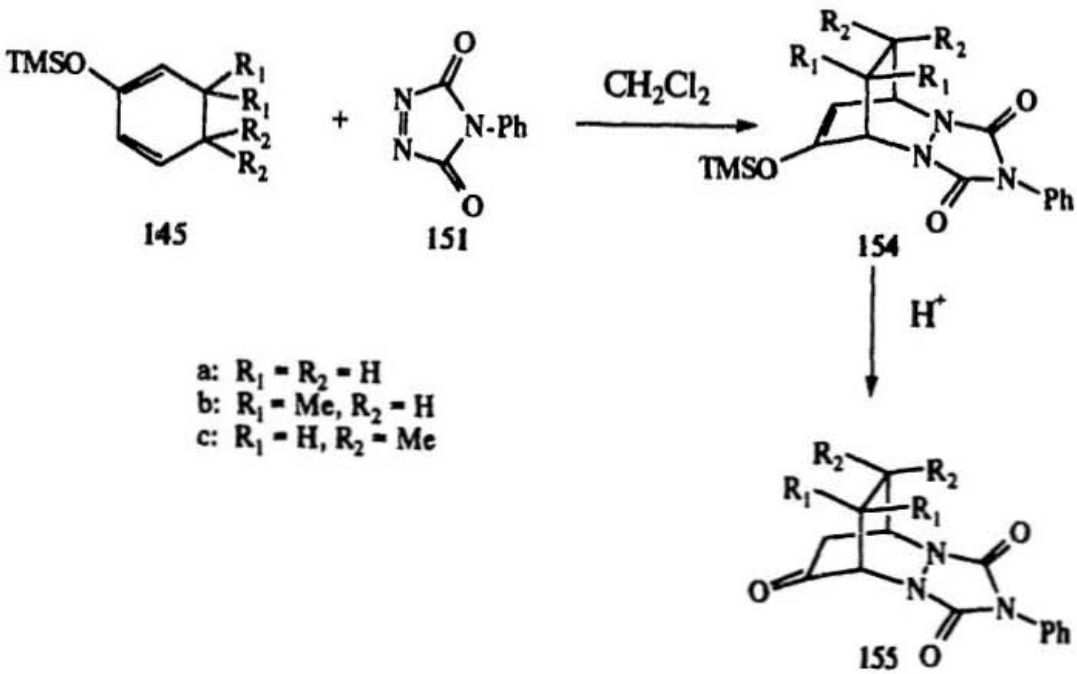


Figure 14. MS spectrum (from GC-MS) of adduct **152a**

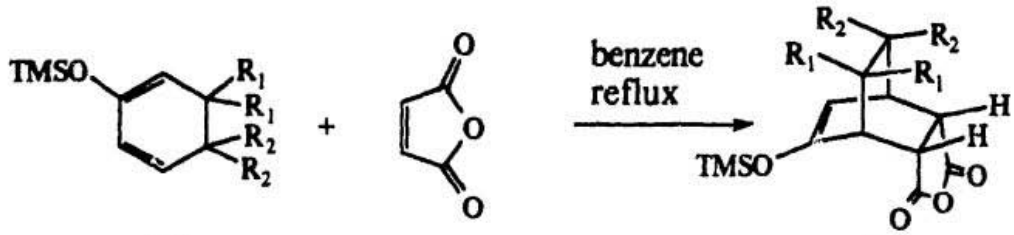
Similar experiments were performed with *N*-phenyl-1,2,4-triazoline-3,5-dione (**151**)[80] with subsequent hydrolysis of the adducts (Scheme 23). Since this dienophile is very reactive, the individual reactions could be carried out in dichloromethane at room temperature. However, competitive reactions were conducted in the same solvent as before, benzene, to reduce possible differences due to solvent effects.

Scheme 23



With the dienophiles maleic anhydride, *para*-benzoquinone, and diethyl acetylenedicarboxylate (Schemes 24-26), longer reaction times were required. In the cases of maleic anhydride and *para*-benzoquinone, the adducts were not hydrolyzed because hydrolysis of the adducts was always accompanied by unwanted reactions. Fortunately, the adducts themselves could be separated without hydrolysis by column chromatography with Florisil as the absorbant.

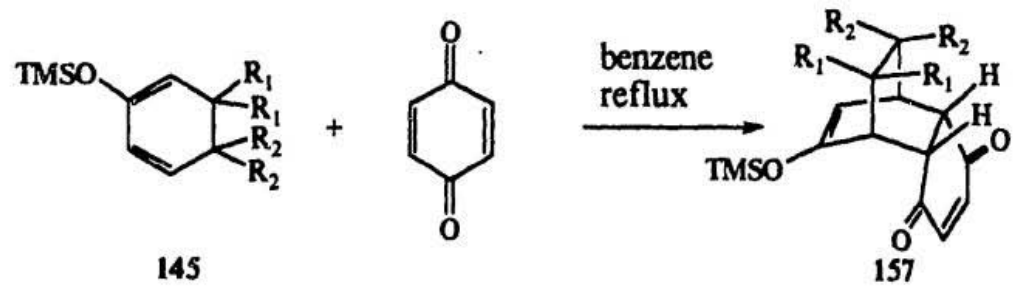
Scheme 24



145 156

a: $R_1 = R_2 = H$
b: $R_1 = Me, R_2 = H$
c: $R_1 = H, R_2 = Me$

Scheme 25

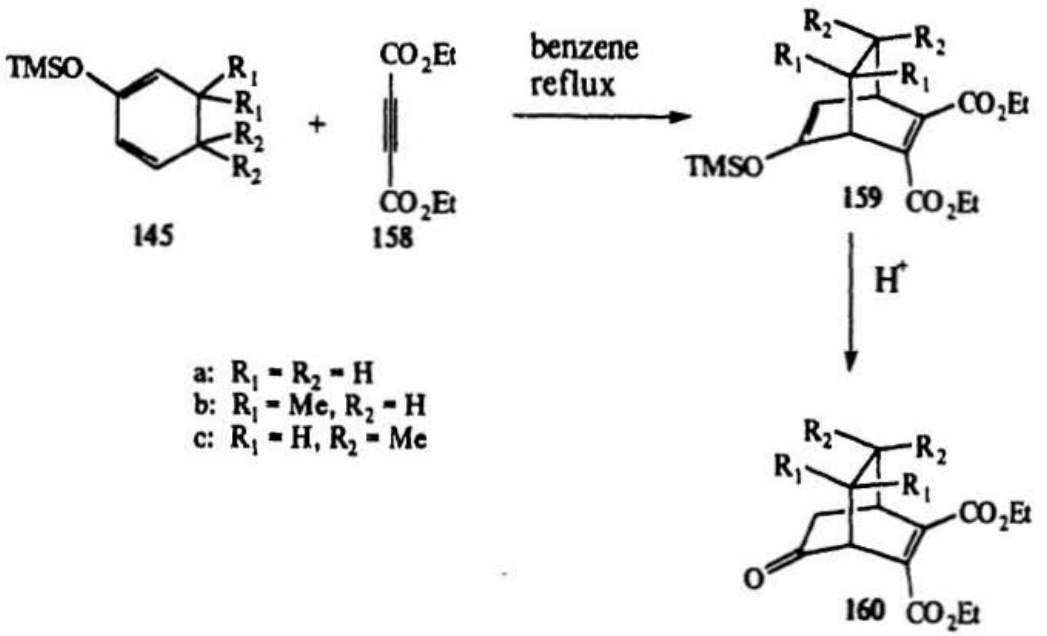


145 157

a: $R_1 = R_2 = H$
b: $R_1 = Me, R_2 = H$
c: $R_1 = H, R_2 = Me$

The cycloaddition with diethyl acetylenedicarboxylate in benzene under reflux was quite sluggish. In an attempt to accelerate the reaction, it was repeated using a toluene solution at reflux. However, when diene **145a** was subjected to these conditions, a highly UV-active compound was isolated by column chromatography that had a mass spectrum with a prominent parent ion at *m/z* 238. The IR spectrum showed an absorption maximum for a carbonyl group at 1715 cm^{-1}. In its ^1H NMR spectrum, there were aromatic signals at δ6.94 and 7.74 for protons, next to electron-donating and electron-withdrawing group,

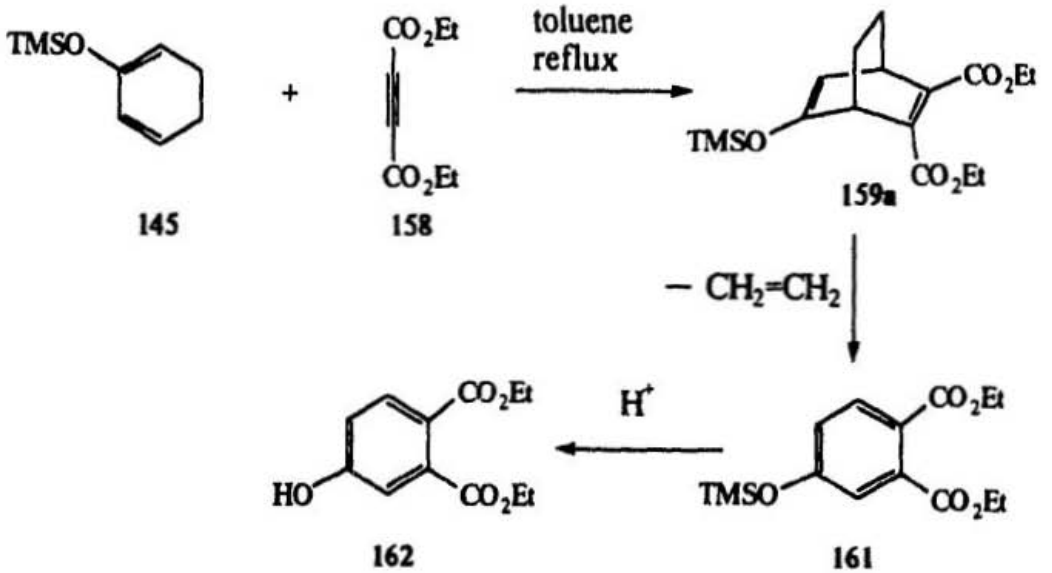
Scheme 26



145 158 159 160

a: $R_1 = R_2 = H$
b: $R_1 = Me, R_2 = H$
c: $R_1 = H, R_2 = Me$

Scheme 27

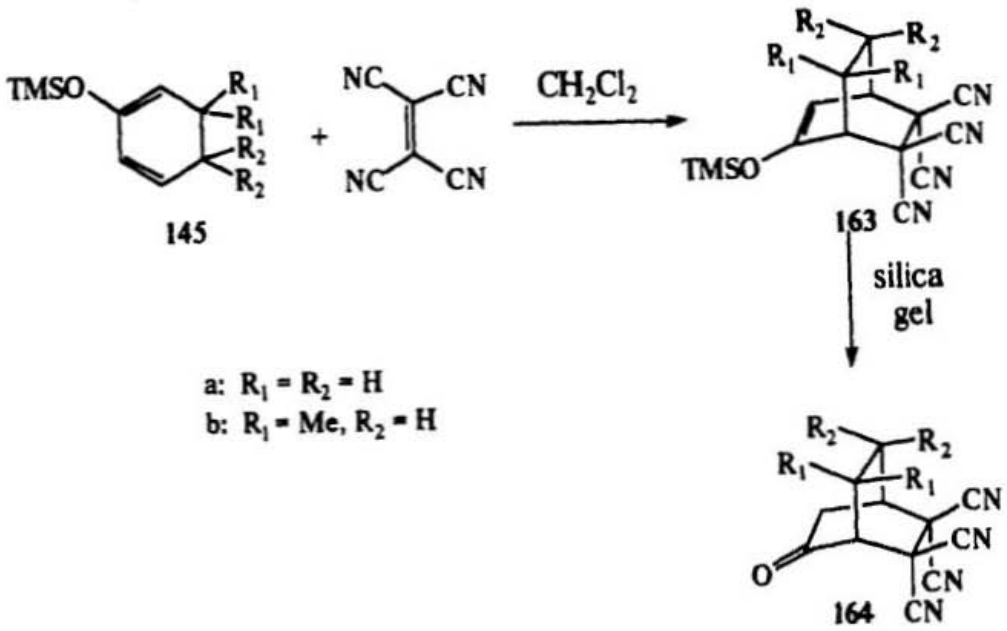


145 158 159a 161 162

respectively. This compound was assigned structure **162** (see Scheme 27). Adducts **159b** and **159c** underwent similar reactions in refluxing toluene. The formation of **162** must involve the *retro*-Diels-Alder reaction of adduct **159**. Since this *retro*-Diels-Alder reaction might result in unreliable estimates of the ratios in the competitive reactions, the reactions in benzene at reflux were continued, but with longer reaction times. The relative rates are presented in Table 14.

The cycloadditions of **145a** with tetracyanoethylene[83,84] (Scheme 28) in dichloromethane at room temperature proceeded very cleanly to give the adduct, which was purified by washing the crude oily reaction mixture with pentane three times. When the crude adduct was passed through a silica gel column, hydrolysis of the silyl enol ether occurred. The hydrolyzed product was also formed to be relatively unstable. For diene **145b**, the Diels-Alder reaction with tetracyanoethylene did take place, but with a significant amount of side-product formation. The major product resulted from the Diels-Alder cycloaddition, and the hydrolyzed product was obtained by chromatography on silica gel. In the case of diene **145c**, the Diels-Alder reaction competed with [2 + 2] cycloaddition (Scheme 29). Two products were obtained after chromatography on silica gel. The disappearance of the olefinic proton signals in the ^{1}H NMR spectra of both adducts indicated that hydrolysis had taken place during the separation process. For the major product, the IR spectrum showed an absorption at 1678 cm^{-1} for a conjugated carbonyl and at 2571 cm^{-1}, characteristic of a nitrile group. A singlet at δ 6.02 in its ^{1}H NMR spectrum was consistent with a hydrogen on a carbon bearing two electron-withdrawing nitriles. Two olefinic protons at δ 5.98 and 6.91 confirmed the presence of the conjugated double bond. The compound was assigned structure **167**. The spectroscopic data of the minor product was consistent with structure **165c**. It is worth noting that all of these adducts were unstable in both acidic and basic conditions. The adducts could be kept for only a few hours before decomposition occurred, even under nitrogen. Therefore, the competitive reactions were carried out in $CDCl_3$ directly in NMR tubes.

Scheme 28



145

a: $R_1 = R_2 = H$
b: $R_1 = Me$, $R_2 = H$

Scheme 29

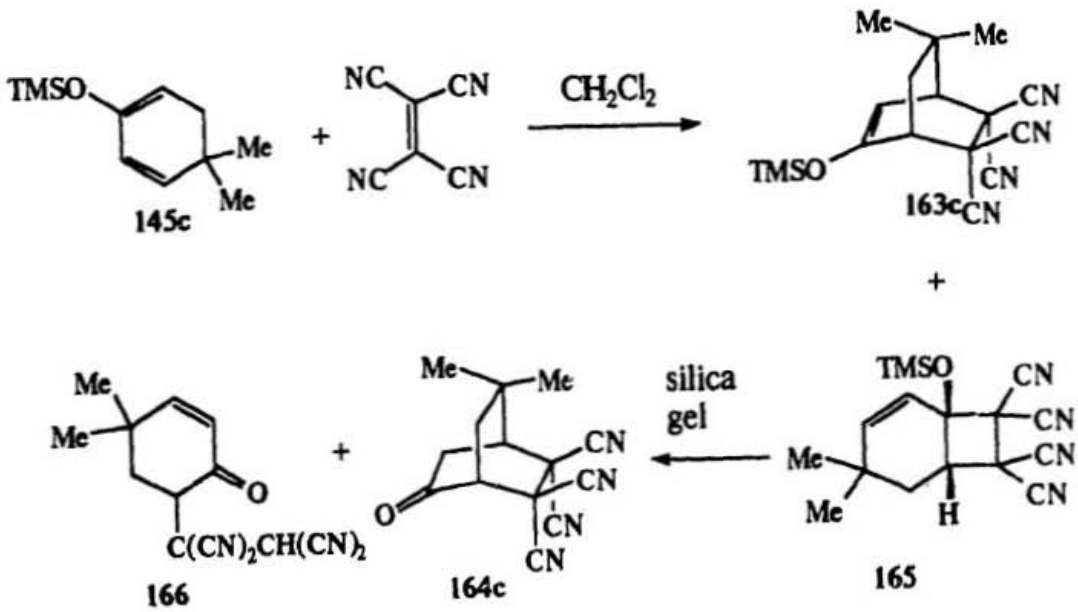
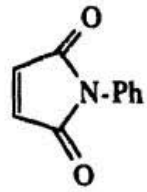
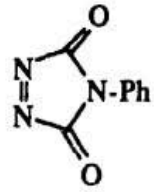
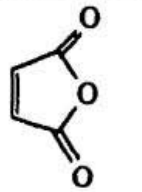
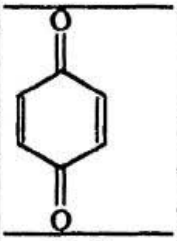
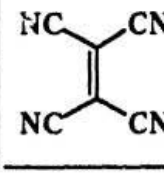
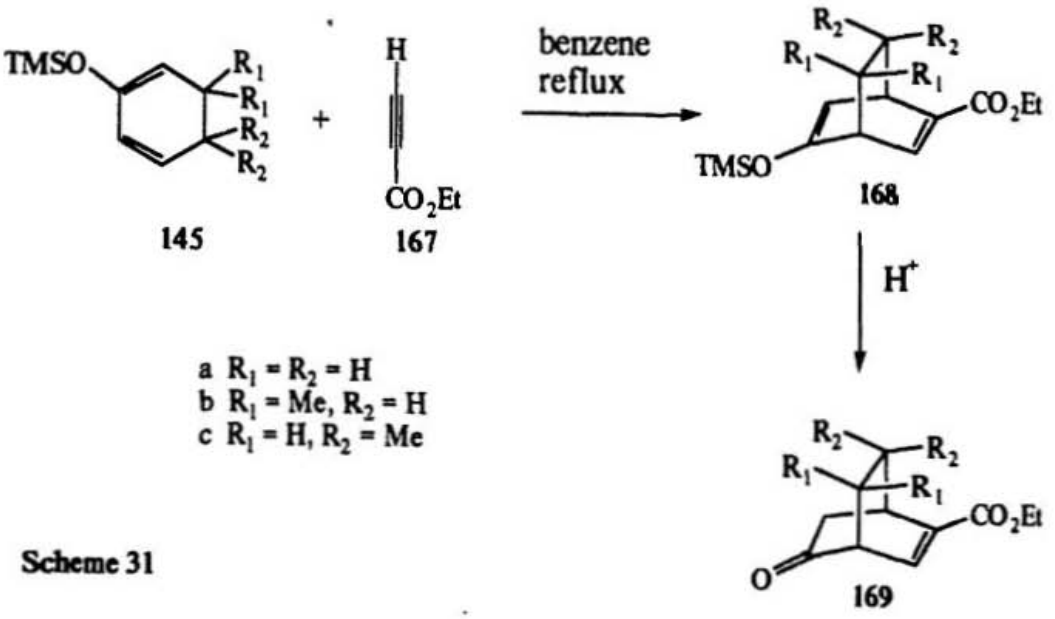


Table 14. Relative reaction rates for Diels-Alder reactions of dienes **145a-c** with different dienophiles

entry	dienophile	relative rate ratios		
		145b : 145c	**145a : 145b**	**145a : 145c**
1		1.2 : 1	9.4 : 1	18 : 1
2		1.5 : 1	1.1 : 1	1.6 : 1
3		1.2 : 1	8.4 : 1	17 : 1
4		1 : 1	25 : 1	18 : 1
5		7.3 : 1	2.2 : 1	16 : 1
6		1 : 5.4	64 : 1	10 : 1

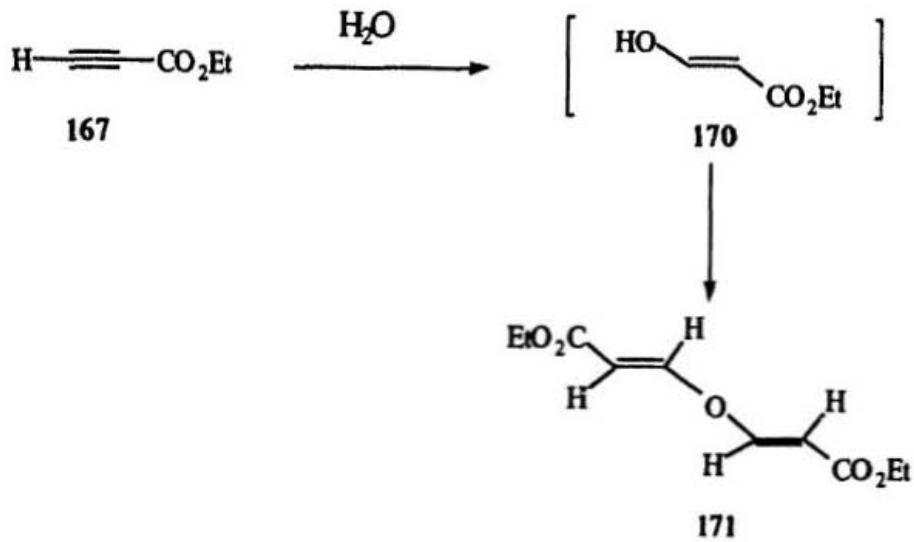
Scheme 30



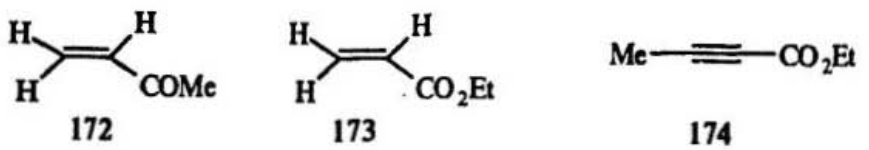
145 167 168 169

a $R_1 = R_2 = H$
b $R_1 = Me, R_2 = H$
c $R_1 = H, R_2 = Me$

Scheme 31



167 170 171



172 173 174

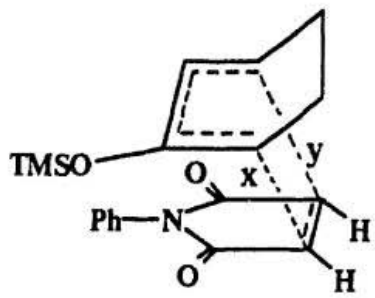
Then we attempted to investigate the Diels-Alder reactions of these three dienes with some unsymmetrical dienophiles. With 3-buten-2-one (**173**), ethyl acrylate (**174**), and methyl 2-butenoate (**175**) the reaction was too slow to be useful. Ethyl propiolate reacted with dienes **145a** and **145b** relatively slowly. The adducts (**168a** and **168b**) were isolated as hydrolysis products (**169a** and **169b**) after chromatography (Scheme 30). However, the reaction of ethyl propiolate with diene **145c** was prohibitively slow. No adduct was detected after refluxing for three days. The structure of the adduct for diene **145b** was determined by both its ^{1}H and ^{13}C NMR spectra. A doublet at δ 2.96 for the bridgehead hydrogen (C-1 hydrogen) indicated that the *para*-isomer was obtained as was expected (otherwise, a singlet would have been apparent for the *meta*-isomer). Competitive reactions with this dienophile were not successful. From their individual reactions it could be concluded qualitatively that dienes **145a** and **145b** reacted with ethyl propiolate much faster than did diene **145c**. With ethyl propiolate, there was always a side product which was assigned structure **171**. Compound **171** was formed probably via intermediate **170** as outlined in Scheme 31.

In summary, the cycloadditions of diene **145a** proceeded much faster than those of dienes **145b** and **145c** in most cases examined. With the symmetrical dienophiles, except with tetracyanoethylene, **145b** reacted slightly faster than **145c**, while the difference in rate ratio was very large in the case of diethyl acetylenedicarboxylate. In contrast, the reactivity of dienes **145b** and **145c** was reversed in cycloadditions with tetracyanoethylene. These results are rationalized in the following section.

III. Discussion

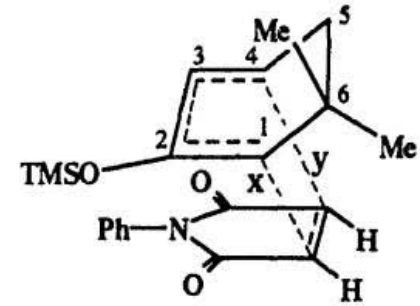
The cycloadditions of dienes **145a-c** with the symmetrical dienophiles except tetracyanoethylene, will be discussed first. Let us suppose that the Diels-Alder reactions were asynchronous with one of the new C-C bonds being almost completely formed while the other is still weak. Due to the presence of the electron-donating trimethylsilyloxy group at C-2 of the dienes we would expect that the shorter bond would be the one (*x*) between C-1 of the diene and the dienophile.[3] Since in each of the transition states (see **175-177** in Figure 15) bond *y* is longer than bond *x*, then unfavorable steric interactions in the transition state **176** should have been larger than that in **177** because of the proximity of the dienophile to a methyl group in the former. Consequently, diene **145c** should react faster than **145b**. However, if the reaction takes place by a synchronous process (with the new C-C bonds formed to similar extents at the transition states as shown in Figure 15 (**178-180**), the steric repulsion in transition states **179** and **180** should be very similar, and the two dienes **145b** and **145c** should react at similar rates. If the reaction rate of diene **145a** is similar to that of either **145b** or **145c**, the reaction must proceed by an asynchronous process or the reaction is insensitive to steric effects. In contrast, the hindrance in the transition state **175** should be much smaller than dienes **145b** and **145c** for synchronous processes. As a result diene **145a** would react much faster than either **145b** or **145c**.

Our experimental results are outlined in Table 14. It can be seen that diene **145a** does indeed react faster than either **145b** or **145c** in all cases except with dienophile **151**. The relative rates of reaction of **145b** and **145c** were similar except in entry (5). Thus, the data with the symmetrical dienophiles are consistent with a high degree of synchronicity at the transition state. The small differences in rate betwen **145b** and **145c** were opposite to what we predicted based on the premise that the reaction might proceed via an asynchronous process (see **176** and **177**). The slightly faster reaction rate for diene **145b**



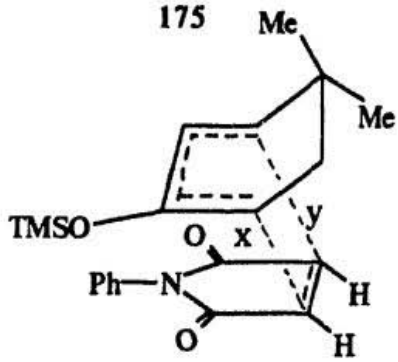
x < y

175



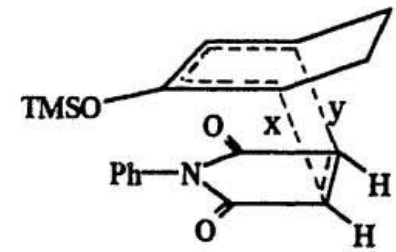
x < y

176



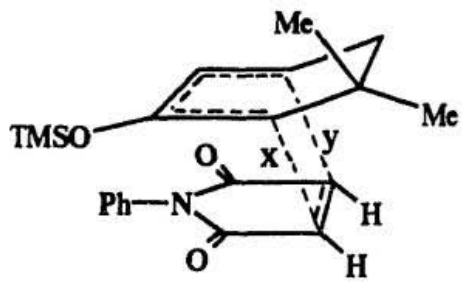
x < y

177



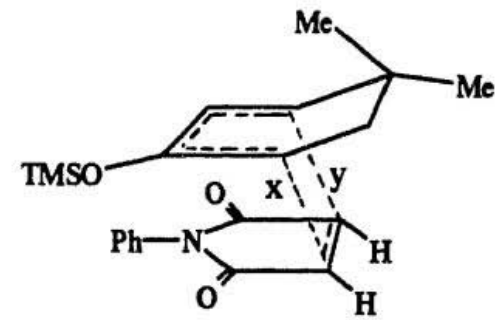
x = y

178



x = y

179



x = y

180

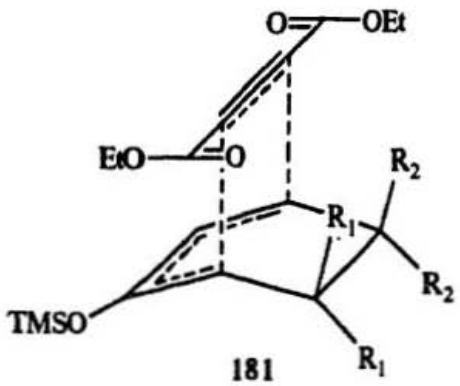
Figure 15. The transition states of the Diels-Alder reactions of dienes **145a-c** with *N*-phenylmaleimide (**175-177** for a synchronous process, and **178-180** for an asynchronous process)

probably resulted from the small inductive effect that might raise the coefficient of the HOMO at C-1 of **145b** due to the presence of two methyl groups.

It is interesting to note that dienes **145a-c** reacted with *N*-phenyl-1,2,4-triazoline-1,3-dione (**151**) with very similar reaction rates. This can be understood in terms of the Reactivity-Selectivity Principle,[85] which states that the selectivity of a species varies inversely with its reactivity. *N*-Phenyl-1,2,4-triazoline-1,3-dione is a very reactive dienophile, so essentially no selectivity was observed with this dienophile.

The relative reaction rates with the acetylenic dienophiles were quite different from those of the ethylenic dienophiles. Dienes **145a** and **145b** reacted with diethyl acetylenedicarboxylate with comparable reaction rates, whilst diene **145c** reacted much more slowly than did diene **145b**. For the unsymmetrical dienophile ethyl propiolate, there is a large difference in rate between dienes **145b** and **145c** as became evident in the reactions of the pure dienes. As mentioned before, if the reaction were to proceed via an asynchronous process, diene **145c** would react faster than diene **145b** with either a symmetrical or an unsymmetrical dienophile. Our results can be explained in the following way. We believe that the reaction proceeds by a synchronous process for the symmetrical diethyl acetylenedicarboxylate, but that the two ester groups would have different conformations at the transition state. The ester group that is further from the trimethylsilyloxy group would probably have a fixed conformation to be in a plane parallel to the diene moiety in order to activate the triple bond. The ester group closer to the trimethylsilyloxy group may have a more mobile conformation and therefore it might rotate to minimize the steric interactions at the transition state. As a result, in the case of diene **145c**, there would be a strong steric interaction between the ester group and a methyl group of the diene at the transition state (see **181** in Figure 16). For dienes **145a** and **145b** the steric interaction at the transition state would be similar and small. So diene **145b** reacted with diethyl acetylenedicaboxylate at similar rate to that of diene **145a**, which was much faster

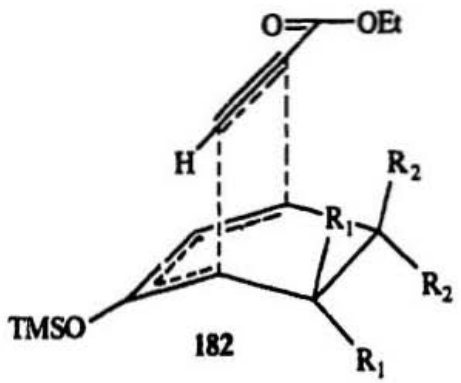
than the reaction of diene **145c**. Likewise, the ester group in ethyl propiolate might have a fairly fixed conformation to be in a plane parallel to the diene moiety in order to activate the triple bond at the transition state, therefore the steric interaction in the case of diene **145c** would retard the reaction (see **182** in Figure 17). Furthermore, ethyl propiolate is less reactive than the symmetrical diethyl acetylenedicarboxylate, so no adduct was detected for diene **145c**. Further series of experiments are in progress to confirm this proposition.



181

145a: $R_1 = R_2 = H$
145b: $R_1 = CH_3, R_2 = H$
145c: $R_1 = H, R_2 = CH_3$

Figure 16. The transition states of the Diels-Alder reactions of dienes **145a-c** with diethyl acetylenedicarboxylate.



182

145a: $R_1 = R_2 = H$
145b: $R_1 = CH_3, R_2 = H$
145c: $R_1 = H, R_2 = CH_3$

Figure 17. The transition states of the Diels-Alder reactions of dienes **145a-c** with ethyl propiolate.

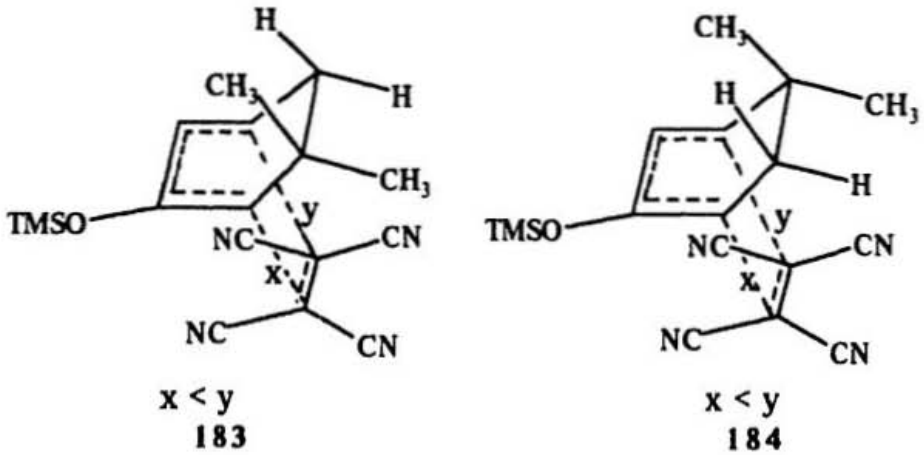
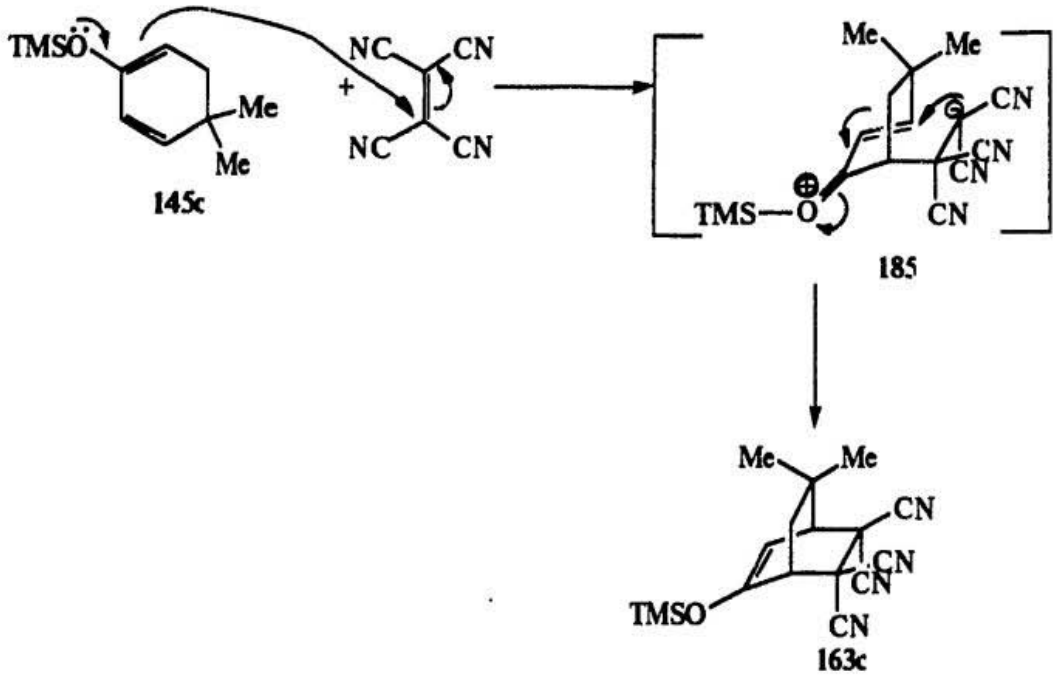


Figure 18. The transition states of the Diels-Alder reactions of dienes 145b and 145c with tetracyanoethylene

As seen in Table 14, diene **145c** reacted much faster than **145b** in the cycloadditions with tetracyanoethylene,[83,84] which suggested very unsymmetrical (asynchronous) transition states and therefore possibly a different mechanism. This is illustrated in the transition states **183** and **184** (Figure 18), in which bond *y* must be much longer than bond *x*. The steric interaction between the methyl group and the dienophile in **183** should be very severe compared to that in **184**. Hence, the addition of **145b** was very slow relative to that of **145c**. At this stage, we cannot preclude the possibility of mechanisms (*b*) and (*c*) involving a diradical or a diionic intermediate with tetracyanoethylene.[84] However, if the reaction were indeed concerted, it must have proceeded via a very unsymmetrical transition state, probably close to a diradical in nature as proposed by Dewar *et al.*[63] An ionic mechanism could be considered to be a double Michael process, as illustrated in Scheme 32.

Scheme 32



In summary, the reaction of dienes **145a-c** with the symmetrical ethylenic dienophiles *N*-phenylmaleimide, *para*-benzoquinone and maleic anhydride proceeded via a synchronous, concerted transition state. When the dienophile was tetracyanoethylene, a different mechanism operated: either a concerted process with a very unsymmetrical transition state or a two-step mechanism, with a diradical or a diion intermediate.

IV Experimental

General

All of the reactions, except hydrolysis of the adducts, were carried out under a nitrogen atmosphere. *N*-Phenylmaleimide was crystallized from cyclohexane; benzoquinone was sublimed several times under vacuum (at *ca.* 40°C), maleic anhydride was sublimed at *ca.* 50°C under vacuum. Once prepared, the dienes were stored under nitrogen at 0°C. The relative rates of reaction were calculated from the result of the competitive experiments using the following equation:[82]

$$\frac{k_a}{k_b} = \frac{log[A] - log([A] - [AX])}{log[B] - log([B] - [BX])} \qquad (8)$$

where [A] and [B] were the initial concentrations of the dienes; [AX] and [BX] were the final concentrations of their adducts.

5,5-Dimethyl-2-cyclohexen-1-one (148b)

A 500 mL of round-bottomed flask was charged with dimedone **146** (5.60 g, 40.0 mmol), tosyl hydrazide (7.66 g, 41.3 mmol), 100 mL of anhydrous methanol, and a few drops of concentrated H_2SO_4.[77] After standing for 20 min, a white precipitate formed, and the reaction mixture was stirred overnight at room temperature. The methanol was removed *in vacuo*. Potassium carbonate (44.2 g, 320 mmol) and 300 mL of water were added to the residue, and the resulting solution was heated to steam distill the product. The largely aqueous distillate was saturated with NaCl and extracted with ether (5 × 40 mL), and the combined organic extracts were washed with saturated NaCl solution and dried ($MgSO_4$). The solvent was removed *in vacuo* to give a yellow oil that was purified by flash chromatography (3% ethyl acetate in hexane). The enone **148b** (2.28 g, 46%) was isolated as a pale yellow liquid: IR (film) ν_{max}: 1660 (s) cm^{-1}; ^1H NMR δ: 0.98 (s, 6H), 2.28 (br s, 4H), 6.03 (d, J = 10.0 Hz, 1H), and 6.88 (m, 1H); ^{13}C NMR δ: 28.3 (2C, 3), 33.8 (0), 39.8 (2), 51.7 (2), 128.9 (1), 148.5 (1), and 199.8 (0); MS (from GC-MS) *m/z*

(%): 124 (20, M^+), 109 (4), 96 (5), 68 (100), and 41 (10). *Exact mass* calcd. for $C_8H_{12}O$: 124.0888; found: 124.0870.

6,6-Dimethyl-2-(trimethylsilyloxy)-1,3-cyclohexadiene (145b)[78, 79]

An oven-dried 100 mL round-bottomed flask was evacuated on a vacuum line and flushed with nitrogen three times. Anhydrous THF (60 mL) was added at 0°C followed by diisopropylamine (1.5 mL, 11 mmol) and by *n*-butyllithium (1.4 M solution in hexane) (6.3 mL, 10 mmol). After 30 min, the solution was cooled to -78°C and the enone **148b** (1.14 g, 9.19 mmol) in 6 mL of THF was introduced. The reaction mixture was stirred for one hour and chlorotrimethylsilane (TMSCl) (2.3 mL, 18 mmol) was added at -78°C. The reaction was warmed to room temperature gradually then allowed to stand for another two hours. After concentration *in vacuo* the residue was diluted with 100 mL of anhydrous pentane. The precipitated LiCl was removed by filtration. Evaporation of the solvent gave a crude product, which was purified by distillation under reduced pressure to afford diene **145b** (1.80 g, 86%) as a colorless oil: bp 55-57°C/5 mmHg; IR (film) ν_{max}: 1649 (m) cm^{-1}; ^1H NMR δ: 0.17 (s, 9H), 0.99 (s, 6H), 2.04 (dd, J = 1.8, 3.6 Hz, 2H), 4.64 (s, 1H), 5.65 (dd, J = 1.8, 9.6 Hz, 1H), and 5.70-5.77 (m, 1H); ^{13}C NMR δ: 0.1 (3C, 3), 28.7 (2C, 3), 31.7 (0), 38.0 (2), 114.7 (1), 125.7 (1), 127.5 (1), and 146.5 (0); MS (from GC-MS) *m/z* (%): 196 (15, M^+), 182 (17), 181 (100), 165 (81), 91 (23), 82 (29), 75 (31), 73 (65), and 45 (33).

5,5-Dimethyl-2-(trimethylsilyloxy)-1,3-cyclohexadiene (145c)

An oven-dried 100 mL round-bottomed flask was evacuated on a vacuum line and flushed with nitrogen three times. Anhydrous THF (60 mL) was added at 0°C followed by diisopropylamine (1.8 mL, 13 mmol) and by *n*-butyllithium (1.4 M solution in hexane) (7.4 mL, 12 mmol). After 30 min the enone **148c** (1.34 g, 10.8 mmol) in 8 mL of THF was introduced. The reaction mixture was stirred for one hour and chlorotrimethylsilane (TMSCl) (2.7 mL, 22 mmol) was added at 0°C. The reaction mixture was warmed to

room temperature gradually then it was allowed to stand for another two hours. After concentration *in vacuo* the residue was diluted with 100 mL of anhydrous pentane. The precipitated LiCl was removed by filtration. Evaporation of the solvent gave a crude product, which was purified by distillation under reduced pressure to afford diene **145c** (1.86 g, 88%) as a colorless oil: bp 55-57°C/5 mmHg; IR (film) ν_{max}: 1652 (m) cm^{-1}; ^1H NMR δ: 0.18 (s, 9H), 1.00 (s, 6H), 2.12 (d, J = 4.5 Hz, 2H), 4.79 (tt, J = 1.6, 4.8 Hz, 1H), and 5.54 (d, J = 1.2 Hz, 2H); ^{13}C NMR δ: 0.2 (3C, 3), 27.6 (2C, 3), 31.2 (0), 37.0 (2), 101.5 (1), 123.8 (1), 140.1 (1), and 147.1 (0); MS (from GC-MS) *m/z* (%): 196 (28, M^+), 182 (16), 181 (100), 165 (46), 75 (24), 73 (62), and 45 (17).

2-(Trimethylsilyloxy)-1,3-cyclohexadiene (145a)

The preparation of this diene was essentially the same as for **145b**. An oven-dried 100 mL round-bottomed flask was evacuated on a vacuum line and flushed with nitrogen three times. Anhydrous THF (60 mL) was added at 0°C followed by diisopropylamine (2.4 mL, 17 mmol) and by *n*-butyllithium (1.4 M solution in hexane) (9.8 mL, 16 mmol). After 30 min the solution was cooled to -78°C and the enone **148a** (1.40 g, 14.3 mmol) in 8 mL of THF was introduced. The reaction mixture was stirred for one hour and chlorotrimethylsilane (TMSCl) (3.7 mL, 29 mmol) was added at -78°C. The reaction was warmed to room temperature gradually then allowed to stand for another two hours. After concentration *in vacuo*, the residue was diluted with anhydrous pentane. The precipitated LiCl was removed by filtration. Evaporation of the solvent gave a crude product, which was purified by distillation under reduced pressure to afford diene **145a** (2.02 g, 84%) as a colorless oil: bp 43-45°C/ 5 mmHg (lit.[78] 56-58°C/ 6 mmHg); IR (film) ν_{max}: 1649 cm^{-1}; ^1H NMR δ: 0.19 (s, 9H), 2.03-2.21 (m, 4H), 4.85-4.89 (m, 1H), and 5.68 (dq, J = 1.8, 9.9 Hz, 1H), and 5.85 (dt, J = 3.6, 9.9 Hz, 1H); ^{13}C NMR δ: 0.1 (3C, 3), 21.7 (2), 22.5 (2), 102.3 (1), 126.4 (1), 128.8 (1), and 148.0 (0); MS (from GC-MS) *m/z* (%): 169 (5, $M^+ + 1$), 168 (33, M^+), 153 (15), 151 (23), 73 (100), 45 (24), and 43 (24).

4-Phenyl-1,2,4-triazoline-3,5-dione (151)[80]

A 100 mL round-bottomed flask in a cold water bath was flushed with nitrogen and charged with ethyl acetate (12 mL) and 4.40 g (25.1 mmol) of 4-phenylurazole and *tert*-butyl hypochlorite[81] (2.8 mL, 25 mmol) was added to the flask over a period of approximately 20 min. After the addition was complete, the resulting suspension was stirred for 40 min at room temperature. The solvent was removed on a rotary evaporator, while keeping the temperature below 40°C. The last traces of solvent were removed with a high-vacuum pump. The product was sublimed under vacuum, yielding 2.14 g (86%) of the triazoline **151** as carmine-red crystals which decomposed (165-175°C) before melting: IR (film) ν_{max}: 1767 (s) and 1750 (s) cm^{-1}; ^1H NMR δ: 7.42-7.59 (m).

(3aα,4β,7β,7aα)-8,8-Dimethyl-2-phenyl-3a,4,7,7a-tetrahydro-5-(trimethylsilyloxy)-4,7-ethanoisoindole-1,3-dione (152b)

To a benzene solution of diene **145b** (194 mg, 0.99 mmol), was added *N*-phenylmaleimide (172 mg, 0.99 mmol). The mixture was heated at reflux for two days. After concentration *in vacuo*, the oily residue was washed with a small amount of anhydrous pentane three times to provide the adduct **152b** (385 mg, 93%) as a colorless oil: ^1H NMR δ: 0.16 (s, 9H), 0.99 (s, 3H), 1.11 (s, 3H), 1.32 (d, J = 2.7 Hz, 2H), 2.56 (br t, J = 2.5 Hz, 1H), 2.87 (dd, J = 2.9, 8.0 Hz, 1H), 3.13 (apparent sextet, J = 3.1 Hz, 1H), 3.32 (dd, J = 3.4, 8.1 Hz, 1H), 4.82 (dd, J = 1.9, 6.9 Hz, 1H), 7.20-7.23 (m, 2H), and 7.32-7.45 (m, 3H); ^{13}C NMR δ: 0.1 (3C, 3), 28.6 (2), 30.8 (3), 33.9 (0), 34.2 (3), 41.1 (1), 41.8 (2), 44.1 (1), 49.3 (1), 96.8 (1), 126.3 (2C, 1), 128.3 (1), 128.9 (2C, 1), 132.0 (0), 155.9 (0), 178.0 (0), and 178.2 (0); MS (from GC-MS) *m/z* (%): 369 (6, M^+), 314 (18), 313 (71), 193 (30), 181 (28), 166 (100), 152 (52), and 73 (42).

(3aα,4β,7β,7aα)-8,8-Dimethyl-3a,4,6,7,7a-pentahydro-2-phenyl-4,7-ethanoisoindole-1,3,5-trione (153b)

A solution of **152b** (192 mg, 0.52 mmol) and a few drops of 0.5 N HCl in MeOH (20 mL) was stirred for 30 min. The solvent was removed *in vacuo* and the residue was diluted with ethyl acetate and water. The aqueous layer was extracted with ethyl acetate (×4), the combined organic extracts were washed with water, then saturated NaCl and dried over $MgSO_4$. Flash chromatography (8% ethyl acetate in hexane) of the residue gave **153b** (143 mg, 92%) as colorless crystals: mp 245-246°C; IR (film) ν_{max}: 1710 cm^{-1}; ^1H NMR δ: 1.05 (s, 3H), 1.20 (s, 3H), 1.62 (apparent dt, J = 2.4, 13.9 Hz, 1H), 1.70 (dd, J = 3.3, 13.9 Hz, 1H), 2.18 (apparent dt, J = 2.6, 19.5 Hz, 1H), 2.25 (br d, J = 19.5 Hz, 1H), 2.60 (d, J = 3.7 Hz, 1H), 2.84 (apparent sextet, J = 3.1 Hz, 1H), 3.11 (ddd, J = 1.3, 3.6, 9.5 Hz, 1H), 3.51 (dd, J = 3.7, 9.5 Hz, 1H), 7.19 (distorted d, J = 7.0 Hz, 2H), and 7.38-7.50 (m, 3H); ^{13}C NMR δ: 28.8 (3), 31.2 (1), 31.3 (0), 31.5 (3), 39.4 (2), 39.6 (1), 40.3 (2), 42.0 (1), 55.6 (1), 126.3 (1), 128.9 (2C, 1), 129.2 (2C, 1), 131.3 (0), 176.5 (0), 176.9 (0), and 210.2 (0); MS (from GC-MS) *m/z* (%): 298 (19, $M^+ + 1$), 297 (37, M^+), 282 (37), 269 (25), 108 (33), 107 (39), 93 (79), 91 (77), 79 (31), 77 (55), 66 (27), and 65 (28). *Exact mass* calcd. for $C_{18}H_{19}NO_3$: 297.1364; found: 297.1351.

(3aα,4β,7β,7aα)-9,9-Dimethyl-2-phenyl-3a,4,7,7a-tetrahydro-5-(trimethylsilyloxy)-4,7-ethanoisoindole-1,3-dione (152c)

To a benzene solution of diene **145c** (219 mg, 1.08 mmol), was added *N*-phenylmaleimide (186 mg, 1.08 mmol). The reaction was heated at reflux for two days. After concentration *in vacuo*, the oily residue was washed with a small amount of anhydrous pentane three times to provide the adduct **152c** (358 mg, 90%) as a colorless oil: ^1H NMR δ: 0.17 (s, 9H), 0.98 (s, 3H), 1.12 (s, 3H), 1.39 (dd, J = 3.2, 12.9 Hz, 1H), 1.46 (dd, J = 3.2, 12.9 Hz, 1H), 2.72 (dd, J = 3.4, 7.0 Hz, 1H), 2.92-2.97 (m, 2H), 3.32 (dd, J = 3.4, 8.2 Hz, 1H), 5.01 (dd, J = 1.9, 6.9 Hz, 1H), 7.20-7.23 (m, 2H), and 7.35-7.46 (m, 3H); ^{13}C NMR δ: 0.1 (3C, 3), 29.3 (3), 30.9 (3), 34.5 (0), 40.0 (2), 40.5 (1), 42.2 (1), 43.1 (1), 44.0 (1), 126.4 (2C, 1), 128.3 (1), 128.9 (2C, 1), 134.1 (0), 153.2 (0), 177.4 (0), and 178.8 (0); MS (from GC-MS) *m/z* (%): 369 (1, M^+), 313 (34), 193 (25), 167 (16), 166 (100),

151 (91), 91 (22), 77 (17), 75 (27), 73 (77), and 45 (27).

(3aα,4β,7β,7aα)-3a,4,6,7,7a-Pentahydro-9,9-dimethyl-2-phenyl-4,7-ethanoisoindole-1,3,5-trione (153c)

A solution of **152c** (215 mg, 0.58 mmol) and a few drops of 0.5 N HCl in MeOH (20 mL) was stirred for 30 min. The solvent was removed by rotary evaporation, and the residue was diluted with ethyl acetate and water. The aqueous layer was extracted with ethyl acetate (×4). The combined organic extracts were washed with water, then saturated NaCl and dried over $MgSO_4$. Purification of the the crude product by flash chromatography (8% ethyl acetate in hexane) gave **153c** (160 mg, 94%) as colorless crystals: mp 201-202°C; IR (film) ν_{max}: 1711 (s) cm^{-1}; ^1H NMR δ: 1.10 (s, 3H), 1.18 (s, 3H), 1.70 (dd, J = 3.0, 14.0 Hz, 1H), 1.73 (dd, J = 3.0, 14.0 Hz, 1H), 2.08 (dd, J = 2.6, 20.2 Hz, 1H), 2.35 (apparent q, J =3.1 Hz, 1H), 2.60 (apparent dt, J = 2.3, 20.2 Hz, 1H), 2.86 (apparent q, J = 3.0 Hz, 1H), 3.21 (dd, J = 3.3, 9.6 Hz, 1H), 3.50 (ddd, J = 2.1, 3.5, 9.6 Hz, 1H), 7.17 (distorted d, J = 7.3 Hz, 2H), and 7.34-7.48 (m, 3H); ^{13}C NMR δ: 29.1 (3), 29.7 (3), 30.6 (0), 37.5 (2), 38.1 (2), 40.2 (1), 40.5 (1), 41.3 (1), 45.9 (1), 126.2 (2C, 1), 128.7 (1), 129.0 (2C, 1), 131.3 (0), 175.9 (0), 177.6 (0), and 210.6 (0); MS (from GC-MS) (%): 297 (100, M^+), 282 (18), 241 (19), 108 (24), 107 (21), 93 (45), 91 (49), 79 (21), 77 (39), 66 (20), and 65 (17). *Exact mass* calcd. for $C_{18}H_{19}NO_3$: 297.1364; found: 297.1366.

(3aα,4β,7β,7aβ)-3a,4,7,7a-Tetrahydro-2-phenyl-5-(trimethylsilyloxy)-4,7-ethano-isoindole-1,3-dione (152a)

To a benzene solution of diene **145a** (182 mg, 1.09 mmol), was added *N*-phenyl-maleimide (189 mg, 1.09 mmol). The reaction mixture was heated at reflux overnight. After concentration *in vacuo*, the residue was washed with a small amount of anhydrous pentane three times to afford the product **152a** (349 mg, 94%) as a colorless oil: ^1H NMR δ: 0.16 (s, 9H), 1.40-1.53 (m, 2H), 1.55-1.65 (m, 2H), 2.92 (dd, J = 3.0, 8.2 Hz, 1H), 2.99

(dd, J = 3.1, 8.2 Hz, 1H), 3.03 (m, 1H), 3.20-3.21 (m, 1H), 4.98 (dd, J = 2.1, 6.9 Hz, 1H), 7.21-7.27 (m, 2H), and 7.33-7.46 (m, 3H); ^{13}C NMR δ: 0.1 (3C, 3), 24.0 (2), 25.3 (2), 32.6 (1), 37.8 (1), 44.4 (1), 45.0 (1), 100.5 (1), 126.3 (2C, 1), 128.3 (1), 128.9 (2C, 1), 129.2 (0), 154.6 (0), 177.3 (0), and 178.1 (0); MS (from GC-MS) *m/z* (%): 341 (32, M^+), 175 (39), 168 (100), 166 (29), 151 (36), 75 (23), 73 (54), and 45 (16).

(3aα,4β,7β,7aα)-3a,4,6,7,7a-Pentahydro-2-phenyl-4,7-ethanoisoindole-1,3,5-trione (153a)

A solution of **152a** (167 mg, 0.49 mmol) and a few drops of 0.5 N HCl in MeOH (20 mL) was stirred for 30 min. The solution was diluted with ethyl acetate and water, and the aqueous layer was extracted with ethyl acetate (×4). The combined organic extracts were washed with water, then saturated NaCl and dried over $MgSO_4$. Purification of the residue by flash chromatography (8% ethyl acetate in hexane) gave **153a** (126 mg, 95%) as colorless crystals: mp: 225-226°C; IR (Nujol) ν_{max}: 1730 (sh) and 1700 (s) cm^{-1}; ^{1}H NMR δ: 1.82-1.99 (m, 2H), 1.97-2.03 (m, 2H), 2.27 (m, 1H), 2.33 (ddd, J = 1.4, 2.8, 19.9 Hz, 1H), 2.84 (sextet, J = 3.0 Hz, 1H), 2.95 (dd, J = 3.0, 6.2 Hz, 1H), 3.18 (ddd, J = 1.3, 3.6, 9.6 Hz, 1H), 3.28 (dd, J = 3.5, 9.6 Hz, 1H), 7.16-7.27 (m, 2H), and 7.40-7.49 (m, 3H); ^{13}C NMR δ: 21.6 (2), 23.4 (2), 30.0 (1), 40.9 (2), 42.6 (1), 42.7 (1), 43.9 (1), 126.3 (2C, 1), 128.8 (2C, 1), 131.2 (0), 175.9 (0), 176.9 (0), and 210.6 (0); MS (from GC-MS) *m/z* (%): 269 (100, M^+), 213 (17), 79 (26), and 77 (18). *Exact mass* calcd. for $C_{15}H_{15}NO_3$: 269.1051; found: 269.1051.

Competitive reactions with *N*-phenylmaleimide

A benzene solution (5 mL) of dienes **145b** and **145c** (total 28.2 mg, 0.14 mmol) in a 1 : 2.0 ratio (by ^{1}H NMR integration) and *N*-phenylmaleimide (12.2 mg, 0.07 mmol) was heated at reflux for two days. After evaporation of the solvent, ^{1}H NMR analysis of the residue showed signals for unreacted dienes **145b/c** and for adducts **152b** and **152c** in a ratio of 1 : 1.8 (**152b** : **152c**). The ratio of reaction rates of dienes **145b** *versus* **145c**

calculated by Equation (8) was 1.2 : 1.

A benzene solution of dienes **145a** and **145b** (total 28 mg, 0.15 mmol) in 1 : 2 ratio (by ^{1}H NMR integration) and *N*-phenylmaleimide (9.0 mg, 0.05 mmol) was heated at reflux for 30 hours. After evaporation of the solvent, ^{1}H NMR analysis of the residue showed signals for **152a** and **152b** in a ratio of 2.7 : 1, respectively. The ratio of reaction rates of diene **145a** *versus* **145b** calculated by the Equation (8) was 9.4 : 1.

A benzene solution (5 mL) of dienes **145a** and **145c** (total 47.0 mg, 0.25 mmol) in a 1 : 3.7 ratio (by ^{1}H NMR integration) and *N*-phenylmaleimide (7.4 mg, 0.04 mmol) was heated at reflux for 30 hours. After evaporation of the solvent, ^{1}H NMR analysis of the residue showed signals for **152a** and **152c** in a ratio of 3.3 : 1, respectively. The ratio of reaction rates of diene **145a** *versus* **145c** calculated by Equation (8) was 18 : 1.

(4aβ,7β)-2,4,7-Triaza-4,7-dihydro-8,8-dimethyl-2-phenyl-5-(trimethylsilyloxy)-4,7-ethanoindane-1,3-dione (154b)

To a solution of diene **145b** (94 mg, 0.48 mmol) in 10 mL of CH_2Cl_2 was added dropwise dienophile **151** (85 mg, 0.48 mmol) in 2 mL of CH_2Cl_2 under nitrogen. The red color of the dienophile disappeared instantly. The reaction mixture was concentrated *in vacuo* and the oily residue was washed with pentane three times to provide adduct **154b** (159 mg, 89%) as an oily liquid: ^{1}H NMR δ: 0.22 (s, 9), 1.07 (s, 3H), 1.31 (s, 3H), 1.42 (dd, J = 3.0, 12.9 Hz, 1H), 1.86 (dd, J = 3.0, 12.9 Hz, 1H), 4.22 (d, J = 2.4 Hz, 1H), 4.84-4.88 (m, 1H), 5.16 (dd, J = 2.4, 6.3 Hz, 1H), and 7.35-7.47 (m, 5H); MS (from GC-MS) *m/z* (%): 371 (0.2, M^+), 195 (52), 181 (17), 179 (27), 119 (15), 91 (17), 75 (17), 73 (100), and 45 (28).

(4β,7β)-2,3a,7a-Triaza-8,8-dimethyl-2-phenyl-4,6,7-trihydro-4,7-ethanoindane-1,3,5-trione (155b)

A solution of **154b** (124 mg, 0.33 mmol) and a few drops of 0.5 N HCl in methanol

(15 mL) was stirred for 30 min. The solvent was removed by rotary evaporation, and the residue was diluted with ethyl acetate and water. The aqueous layer was extracted with ethyl acetate (×4). The combined organic extracts were washed with water, then saturated NaCl and dried ($MgSO_4$). Flash chromatography (8% ethyl acetate in hexane) gave **155b** (90 mg, 91%) as colorless crystals: mp 238-240°C; IR ν_{max} (Nujol): 1774 (sh) and 1708 (s) cm^{-1}; ^1H NMR δ (C_5D_5N): 0.96 (s, 3H), 1.15 (s, 3H), 1.61 (dd, J = 2.1, 14.0 Hz, 1H), 1.87 (dt, J = 3.2, 14.0 Hz, 1H), 2.67 (dd, J = 2.2, 19.2 Hz, 1H), 3.14 (dt, J = 3.0, 19.2 Hz, 1H), 4.53 (s, 1H), 4.87-4.91 (m, 1H), 7.30 (m, 1H), 7.35-7.41 (m, 2H), and 7.70-7.74 (m, 2H); ^{13}C NMR δ (C_5D_5N): 27.7 (3), 27.8 (3), 33.5 (0), 39.8 (2), 41.8 (2), 50.6 (1), 67.3 (1), 126.2 (2C, 1), 128.3 (1), 129.2 (2C, 1), 132.6 (0), 153.0 (2C, 0), and 201.6 (0); MS (from GC-MS) *m/z* (%): 299 (32, M^+), 271 (32), 215 (16), 214 (85), 119 (100), 95 (25), 94 (23), 55 (18), and 41 (17). *Exact mass* calcd. for $C_{16}H_{17}N_3O_3$: 299.1269; found: 299.1269.

(4β,7β)-2,3a,7a-Triaza-4,7-dihydro-9,9-dimethyl-2-phenyl-5-(trimethylsilyloxy)-4,7-ethanoindane-1,3-dione (154c)

To a solution of diene **145c** (110 mg, 0.56 mmol) in 10 mL of CH_2Cl_2 was added dropwise dienophile **151** (98 mg, 0.56 mmol) in 2 mL of CH_2Cl_2 under nitrogen. The red color of the dienophile disappeared instantly. The crude reaction mixture was concentrated *in vacuo*, and the oily residue was washed with pentane three times to provide the adduct **154c** (186 mg, 90%) as a colorless oil: ^1H NMR δ: 0.22 (s, 9H), 1.04 (s, 3H), 1.32 (s, 3H), 1.56 (dd, J = 2.7, 13.2 Hz, 1H), 1.89 (dd, J = 3.3, 13.2 Hz, 1H), 4.42 (d, J = 6.6 Hz, 1H), 4.63 (dd, J = 2.7, 5.7 Hz, 1H), 5.28 (dd, J = 3.6, 6.6 Hz, 1H), and 7.35-7.50 (m, 5H); MS (from GC-MS) *m/z* (%): 371 (3, M^+), 316 (10), 315 (43), 181 (15), 169 (10), 168 (66), 119 (27), 96 (15), 91 (16), 75 (16), 73 (100), 55 (12), 45 (28), and 41 (22).

(4β,7β)-2,3a,7a-Triaza-4,7-dihydro-9,9-dimethyl-2-phenyl-4,7-ethanoindane-

1,3,5-trione (155c)

A solution of **154c** (104 mg, 0.28 mmol) and a few drops of 0.5 N HCl in 15 mL of methanol was stirred for 30 min. The solvent was removed by rotary evaporation and the residue was worked-up as for **155b**. Chromatography (8% ethyl acetate in hexane) of the crude product gave **155c** (77 mg, 92%) as colorless crystals: mp 181-183 °C; IR ν_{max} (Nujol): 1740 (sh) and 1708 (s) cm^{-1}; ^1H NMR (CD_3COCD_3) δ: 1.21 (s, 3H), 1.34 (s, 3H), 2.10 (dd, J = 2.7, 14.7 Hz, 1H), 2.21 (dd, J = 3.9, 14.7 Hz, 1H), 2.78 (dd, J = 3.0, 19.5 Hz, 1H), 2.96 (dd, J = 2.4, 19.5 Hz, 1H), 4.36 (t, J = 2.7 Hz, 1H), 4.45 (dd, J = 2.7, 3.9 Hz, 1H), and 7.37-7.58 (m, 5H); ^{13}C NMR (CD_3COCD_3) δ: 27.6 (3), 29.3 (3), 34.0 (0), 39.4 (2), 40.1 (2), 59.3 (1), 60.6 (1), 126.7 (2C, 1), 128.6 (1), 129.5 (2C, 1), 133.1 (0), 152.6 (0), 153.9 (0), and 202.1 (0); MS (from GC-MS) *m/z* (%): 299 (22, M^+), 271 (22), 214 (42), 119 (100), 95 (32), 94 (34), 91 (23), 69 (24), 55 (33), and 41 (41). *Exact mass* calcd. for $C_{16}H_{17}N_3O_3$: 299.1269; found: 299.1269.

(4β,7β)-2,3a,7a-Triazo-4,7-dihydro-2-phenyl-5-(trimethylsilyloxy)-4,7-ethano-indane-1,3-dione (154a)

To a solution of diene **145a** (82 mg, 0.49 mmol) in 10 mL of CH_2Cl_2 was added dropwise dienophile **151** (85 mg, 0.49 mmol) in 2 mL of CH_2Cl_2 dropwise. The red color of the dienophile disappeared instantly. The crude reaction mixture was concentrated *in vacuo*. The oily residue was washed with pentane three times to yield the adduct **154a** (164 mg, 97%) as a colorless oil: IR (film) ν_{max}: 1772 (sh), 1715 (s), and 1631 (w) cm^{-1}; ^1H NMR δ: 0.22 (s, 9H), 1.59-1.84 (m, 2H), 2.12-2.23 (m, 2H), 4.73 (t, J = 2.4, 1H), 4.96 (dt, J = 2.7, 6.3 Hz, 1H), 5.28 (dd, J = 2.4, 2.4 Hz, 1H), 7.33-7.42 (m, 1H), 7.43 (s, 2H), and 7.45 (s, 2H); ^{13}C NMR δ: −0.1 (3C, 3), 22.4 (2), 24.2 (2), 51.9 (1), 55.4 (1), 100.5 (1), 125.4 (2C, 1), 128.1 (1), 129.0 (2C, 1), 131.5 (0), and 153.8 (2C, 0); MS *m/z* (%): 343 (8, M^+), 275 (31), 249 (13), 168 (11), 166 (14), 151 (25), 119 (49), 91 (16), 75 (30), and 73 (100). *Exact mass* calcd. for $C_{17}H_{21}N_3O_3Si$: 343.1351; found: 343.1351.

Competitive reactions with dienophile 151

To a benzene (5 mL) solution of dienes **145b** and **145c** (total 18.7 mg, 0.10 mmol) in a 1 : 2.0 ratio (by ^{1}H NMR integration) was added dienophile **151** (7.4 mg, 0.04 mmol) in 0.5 mL of benzene. The reaction mixture was stirred for 30 min at room temperature. After evaporation of the the solvent, analysis of the ^{1}H NMR spectrum of the residue showed signals for unreacted dienes **145b/c** and for adducts **154b** and **154c** in a ratio of 1 : 1.5 (**154b** : **154c**). The ratio of reaction rates of diene **145b** *versus* **145c** calculated by the Equation (8) was 1.5 : 1.

To a benzene (5 mL) solution of dienes **145a** and **145b** (total 29.8 mg, 0.17 mmol) in a 1 : 2 ratio (by ^{1}H NMR integration) was added dienophile **151** (7.2 mg, 0.04 mmol) in 0.5 mL of benzene. The reaction mixture was stirred for 30 min at room temperature. After evaporation of the solvent, analysis of the ^{1}H NMR spectrum of the residue showed signals for **154a** and **154b** in a ratio of 1 : 1.9, respectively. The ratio of reaction rates of diene **145a** *versus* **145b** calculated by Equation (8) was 1.1 : 1.

To a benzene (5 mL) solution of dienes **145a** and **145c** (total 68 mg, 0.37 mmol) in a 1 : 1.0 ratio (by ^{1}H NMR integration) in 2 mL of benzene was added dienophile **151** (36 mg, 0.21 mmol). The reaction mixture was stirred for 30 min at room temperature. After evaporation of the solvent, analysis of the ^{1}H NMR spectrum of the residue showed signals for **154a** and **154c** in a ratio of 1 : 1.6, respectively. The ratio of the reaction rates of diene **145a** *versus* **145c** by Equation (8) was 1.6 : 1.

(3aα,4β,7β,7aα)-3a,4,7,7a-Tetrahydro-8,8-dimethyl-2-oxa-5-(trimethylsilyloxy)-4,7-ethanoindane-1,3-dione (156b)

A solution of diene **145b** (134 mg, 0.69 mmol) and maleic anhydride (68 mg, 0.69 mmol) in 30 mL of benzene was heated at reflux for two days. The solvent was removed *in vacuo*. Chromatography of the crude product through Florisil (0.5% ethyl acetate in hexane) provided the adduct **156b** (179 mg, 89%) as a colorless oil: IR (film) ν_{max}: 1863

(sh), 1780 (s), and 1633 (m) cm^{-1}; ^1H NMR δ: 0.20 (s, 9H), 0.98 (s, 3H), 1.06 (s, 3H), 1.26 (d, J = 2.7 Hz, 1H), 1.27 (d, J = 3.6 Hz, 1H), 2.50 (dd, J = 2.1, 3.6 Hz, 1H), 3.00 (dd, J = 3.3, 8.7 Hz, 1H), 3.06-3.11 (m, 1H), 3.42 (dd, J = 3.6, 8.7 Hz, 1H), and 4.83 (dd, J = 2.1, 6.9 Hz, 1H); ^{13}C NMR δ: -0.2 (3C, 3), 28.4 (3), 33.4 (0), 34.0 (3), 40.9 (1), 42.0 (1), 44.6 (1), 49.2 (1), 97.5 (1), 156.3 (0), 172.9 (0), and 173.1 (0). MS (from GC-MS) *m/z* (%): 296 (1, M^+), 279 (15), 196 (18), 182 (16), 181 (100), 166 (25), 151 (42), 75 (16), and 73 (34).

(3aα,4β,7β,7aα)-3a,4,7,7a-Tetrahydro-8,8-dimethyl-2-oxa-5-(trimethylsilyloxy)-4,7-ethanoindane-1,3-dione (156c)

A solution of diene **145c** (165 mg, 0.84 mmol) and maleic anhydride (83 mg, 0.84 mmol) in 30 mL of benzene was heated at reflux for two days. After evaporation of the solvent, chromatography of the residue through Florisil (0.5% ethyl acetate in hexane) afforded the adduct **156c** (216 mg, 87%) as a colorless oil: IR (film) ν_{max}: 1861 (sh), 1780 (s), and 1636 (m) cm^{-1}; ^1H NMR δ: 0.20 (s, 9H), 0.97 (s, 3H), 1.08 (s, 3H), 1.33 (dd, J = 2.4, 12.9 Hz, 1H), 1.46 (dd, J = 3.3, 12.9 Hz, 1H), 2.68 (dd, J = 3.3, 6.9 Hz, 1H), 2.91 (quintet, J = 3.0 Hz, 1H), 3.08 (dd, J = 3.3, 8.7 Hz, 1H), 3.47 (dd, J = 3.3, 8.7 Hz, 1H), and 6.03 (dd, J = 2.4, 7.2 Hz, 1H); ^{13}C NMR δ: -0.1 (3C, 3), 29.2 (2), 30.6 (3), 34.0 (0), 39.6 (3), 39.8 (1), 42.9 (1), 43.7 (1), 43.9 (1), 101.6 (1), 153.5 (0), 172.2 (0), and 173.6 (0); MS (from GC-MS) *m/z* (%): 238 (34), 166 (97), 151 (100), 91 (21), 77 (17), 75 (32), and 73 (71).

(3aα,4β,7β,7aβ)-3a,4,7,7a-Tetrahydro-2-oxa-5-(trimethylsilyloxy)-4,7-ethano-indane-1,3-dione (156a)

A solution of diene **145a** (129 mg, 0.77 mmol) and maleic anhydride (75 mg, 0.77 mmol) in 30 mL of benzene was heated at reflux for two days. The solvent was removed *in vacuo*. Chromatography of the residue through Florisil (0.5% ethyl acetate in hexane) provided the adduct **156a** (187 mg, 92%) as a colorless liquid: IR (film) ν_{max}: 1840 (m),

1780 (s), and 1634 (m) cm^{-1}; ^1H NMR δ: 0.19 (s, 9H), 1.41-1.64 (m, 4H), 2.99 (m, 1H), 3.08 (dd, J = 3.0, 8.7 Hz, 1H), 3.14 (dd, J = 3.3, 8.7 Hz, 1H), 3.17-3.21 (m, 1H), and 5.00 (dd, J = 2.4, 7.2 Hz, 1H); ^{13}C NMR δ: -0.2 (3C, 3), 23.2 (2), 24.5 (2), 32.5 (1), 37.6 (1), 44.9 (1), 45.5 (1), 101.1 (1), 154.9 (0), 172.2 (0), and 173.0 (0); MS (from GC-MS): 266 (7, M^+), 168 (100), 166 (20), 153 (21), 151 (37), 77 (19), 75 (40), 73 (77), and 45 (39).

Competitive reactions with maleic anhydride

A mixture of dienes **145b** and **145c** (total 25.2 mg, 0.14 mmol) in a 1 : 2.0 ratio (by ^1H NMR integration) and maleic anhydride (8.8 mg, 0.09 mmol) in 5 mL of benzene was refluxed for 30 hours. After evaporation of the solvent, analysis of the ^1H NMR spectrum of the crude reaction mixture showed signals for unreacted dienes **145a/b** and for adducts **156b** and **156c** in a ratio of 1 : 1.8 (**156b** : **156c**). The ratio of reaction rates of diene **145b** *versus* **145c** calculated by Equation (8) was 1.2 : 1.

A mixture of dienes **145a** and **145b** (total 79.4 mg, 0.43 mmol) in a 1 : 2 ratio (by ^1H NMR integration) and maleic anhydride (17.9 mg, 0.18 mmol) in 5 mL of benzene was heated at reflux for 30 hours. After evaporation of the solvent, analysis of the ^1H NMR spectrum of the crude reaction mixture showed signals for **156a** and **156b** in a ratio of 1.9 : 1, respectively. The ratio of reaction rates of diene **145a** *versus* **145b** calculated by Equation (8) was 8.4 : 1.

A mixture of dienes **145a** and **145c** (total 64 mg, 0.34 mmol) in a 1 : 3.7 ratio (by ^1H NMR integration) and maleic anhydride (6.8 mg, 0.069 mmol) in 5 mL of benzene was heated for 30 hours. After evaporation of the solvent, analysis of the ^1H NMR spectrum of the crude reaction mixture showed signals for **156a** and **156c** in a ratio of 2.6 : 1, respectively. The ratio of reaction rates of diene **145a** *versus* **145c** calculated by Equation (8) was 17 : 1.

(4aα,5β,8β,8aα)-4a,5,8,8a-Tetrahydro-9,9-dimethyl-6-(trimethylsilyloxy)-4,7-ethano-

1,4-naphthoquinone (157b)

A solution of diene **145b** (128 mg, 0.78 mmol) and *para*-benzoquinone (84 mg, 0.78 mmol) in 30 mL of benzene was heated at reflux overnight, after which time analysis of the reaction mixture by GC-MS indicated that no side reactions had taken place, but a significant amount of starting material was left. (When a reaction was allowed to proceed longer, aromatic side products formed.) After evaporation of the solvent the crude product, which was contaminated by both starting materials, was obtained. Purification by either recrystallization or chromatography were unsuccessful. However, the starting materials could be removed under high vacuum, and the product was isolated in this way. Adduct **157b** was obtained (90% pure by GC-MS) (94.2 mg, 48%) as a slightly yellow oil: ^{1}H NMR δ: 0.13 (s, 9H), 0.88 (s, 3H), 1.07 (s, 3H), 1.22 (dd, J = 3.0, 12.6 Hz, 1H), 1.40 (dd, J = 2.7, 12.9 Hz, 1H), 2.53 (t, J = 2.4 Hz, 1H), 2.86 (dd, J = 2.4, 9.0 Hz, 1H), 3.03-3.23 (m, 1H), 3.27 (dd, J = 2.1, 6.9 Hz, 1H), 4.67 (dd, J = 2.1, 6.9 Hz, 1H) and 6.80 (s, 2H); MS (from GC-MS) *m/z* (%): 304 (2, M^+), 181 (100), 166 (18), 165 (17), 151 (26), 82 (21), 75 (22), 73 (61), and 45 (24).

(4aα,5β,8β,8aα)-4a,5,8,8a-tetrahydro-10,10-dimethyl-6-(trimethylsilyloxy)-4,7-ethano-1,4-naphthoquinone (157c)

A solution of diene **145c** (178 mg, 0.91 mmol) and *para*-benzoquinone (98 mg, 0.91 mmol) in 30 mL of benzene was heated at reflux for overnight, after which time analysis of the reaction mixture by GC-MS indicated that no side reactions had taken place, but there was some amount of starting material left. After evaporation of the solvent the crude product, which was contaminated by both starting materials, was obtained. Purification by either recrystallization or chromatography were unsuccessful. However, the starting materials could be removed under high vacuum pump and the product isolated this way **157c** was obtained (96% pure by GC-MS) (184.2 mg, 67%): ^{1}H NMR δ: 0.20 (s, 9H), 0.98 (s, 3H), 1.17 (s, 3H), 1.48 (dd, J = 3.0, 12.9 Hz, 1H), 1.55 (dd, J = 2.7, 12.9 Hz,

1H), 2.79 (dd, J = 3.0, 6.9 Hz, 1H), 2.86 (quintet, J = 2.4 Hz, 1H), 3.03 (dd, J = 2.1, 9.0 Hz, 1H), 3.32 (dd, J = 3.0, 9.0 Hz, 1H), 5.04 (dd, J = 2.1, 6.9 Hz, 1H), and 6.78 (s, 2H); MS (from GC-MS) *m/z* (%): 304 (1, M^+), 248 (16), 181 (16), 167 (16), 166 (100), 151 (55), 91 (13), 82 (86), 75 (20), 73 (51), 54 (18), and 45 (22). *Exact mass* calcd. for $C_{15}H_{20}O_3Si$: 304.1493; found: 304.1496.

(4aα,5β,8β,8aα)-5,8-Ethano-4a,5,8,8a-tetrahydro-6-(trimethylsilyloxy)-1,4-naphthoquinonone (157a)

A solution of diene **145a** (208 mg, 1.24 mmol) and *para*-benzoquinone (134 mg, 1.24 mmol) in 40 mL of benzene was refluxed overnight. After evaporation of the solvent, the crude product was crystalized from pentane to provide **157a** (295 mg, 86%) as pale yellow crystals: mp 96-97°C; IR (film) ν_{max}: 1668 (s) and 1633 (m) cm^{-1}; ^1H NMR δ: 0.13 (s, 9H), 1.36-1.47 (m, 1H), 1.54-1.74 (m, 3H), 2.90-3.00 (m, 3H), 3.15-3.20 (m, 1H), 4.95 (dd, J = 2.0, 7.0 Hz, 1H), and 6.68 (s, 2H); ^{13}C NMR δ: 0.1 (3C, 3), 25.3 (2), 26.0 (2), 36.2 (1), 41.1 (1), 49.5 (1), 50.0 (1), 102.2 (1), 141.8 (1), 142.1 (1), 155.5 (0), 197.9 (0), and 199.0 (0); MS (from GC-MS) *m/z* (%): 276 (2, M^+), 169 (15), 168 (97), 151 (28), 82 (18), 77 (16), 75 (43), 73 (100), and 45 (36). *Exact mass* calcd. for $C_{15}H_{20}O_3Si$: 276.1181; found: 276.1180.

Competitive reactions with *para*-benzoquinone

A solution of dienes **145b** and **145c** (total 142 mg, 0.72 mmol) a 1 : 1 in ratio (by ^1H NMR integration) and *para*-benzoquinone (39 mg, 0.36 mmol) in 10 mL of benzene was refluxed overnight. After evaporation of the solvent, analysis of the ^1H NMR spectrum of the residue showed signals for **157b** and **157c** in a ratio of 1.0 : 1, respectively. The ratio of reaction rates of diene **145b** *versus* **145c** calculated by Equation (8) was 1.0 : 1.

A solution of dienes **145a** and **145b** (total 42 mg, 0.22 mmol) in a 1 : 1.96 ratio (by ^1H NMR integration) and *para*-benzoquinone (8.9 mg, 0.08 mmol) in 10 mL of benzene

was heated at reflux overnight. After evaporation of the solvent, analysis of the ^{1}H NMR spectrum of the residue showed signals for **157a** and **157b** in a ratio of 9.0 : 1, respectively. The ratio of reaction rates of diene **145a** *versus* **145b** calculated by Equation (8) was 25 : 1.

A solution of dienes **145a** and **145c** (total 62 mg, 0.33 mmol) in a 1 :3.7 ratio (by ^{1}H NMR integration) and *para*-benzoquinone (7.8 mg, 0.07 mmol) in 10 mL of benzene was heated at reflux overnight. After evaporation of the solvent, analysis of the ^{1}H NMR spectrum of the residue showed signals for **157a** and **157c** in a ratio of 3.7 : 1, respectively. The ratio of reaction rates of diene **145a** *versus* **145c** calculated by Equation (8) was 18 : 1.

Diethyl 7,7-dimethylbicyclo[2.2.2]oct-5-en-2-one-5,6-dicaboxylate (160b)

A solution of diene **145b** (135 mg, 0.69 mmol) and diethyl acetylenedicarboxylate (585 mg, 3.45 mmol) in 30 mL of benzene was heated at reflux for three days. The reaction mixture was concentrated *in vacuo*, and the residue was directly treated with 0.5 mL of 0.5 N HCl in 10 mL of methanol. The mixture was allowed to stand for 30 min before water was added. The aqueous layer was extracted with ethyl acetate four times, and the combined organic extracts were washed with water, then saturated NaCl and dried ($MgSO_4$). Flash chromatography of the residue by (4% ethyl acetate in hexane) afforded **160b** (176 mg, 88%) as a colorless oil: IR (film) ν_{max}: 1715 (s) and 1625 (m) cm^{-1}; ^{1}H NMR δ 0.93 (s, 3H), 1.02 (s, 3H), 1.20 (t, J = 7.0 Hz, 3H), 1.23 (t, J = 7.0 Hz, 3H), 1.47 (dt, J = 1.3, 18.6 Hz, 1H), 2.07 (dt, J = 2.8, 18.6 Hz, 1H), 3.10 (s, 1H), 3.26 (quintet, J = 2.8 Hz, 1H), 4.14 (q, J = 7.2 Hz, 2H), and 4.17 (q, J = 7.2 Hz, 2H); ^{13}C NMR δ 13.8 (2C, 3), 29.4 (3), 30.3 (3), 34.8 (1), 35.0 (0), 37.2 (2), 39.6 (2), 61.2 (2C, 2), 62.2 (2), 134.8 (0), 141.7 (0), 164.6 (0), 165.4 (0), and 208.6 (0); MS (from GC-MS) *m/z* (%): 294 (49, M^+), 249 (31), 220 (56), 207 (46), 206 (42), 205 (33), 191 (25), 180 (13), 179 (100), 178 (82), 177 (25), 165 (30), 164 (21), 163 (40), 137 (20), 133 (35), 119 (37), 107 (38), 105 (30), 93 (20), 91 (43), 79 (20), 77 (26), and 41 (20). *Exact mass* calcd. for

294.1466; found: 294.1467.

Diethyl 8,8-dimethylbicyclo[2.2.2]oct-5-en-2-one-5,6-dicarboxylate (160c)

To a solution of diene **145c** (145 mg, 0.74 mmol) and diethyl acetylenedicarboxylate (830 mg, 3.70 mmol) in 30 mL of benzene was heated at reflux for three days. The reaction mixture was concentrated *in vacuo*, and the residue was treated with 0.5 mL of 0.5 N HCl in 10 mL of methanol. The reaction was allowed to stand for 30 min before water was added. The aqueous layer was extracted with ethyl acetate four times, and the combined organic extracts were washed with water, and saturated NaCl then dried ($MgSO_4$). Chromatography (5% ethyl acetate in hexane) of the crude reaction mixture provided **160c** (187 mg, 86%) as a slightly yellow oil: IR (film) ν_{max}: 1715 (s) and 1625 (m) cm^{-1}; ^1H NMR δ: 1.07 (s, 3H), 1.16 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H), 1.33 (q, J = 7.1 Hz, 3H), 2.08 (dd, J = 3.6, 13.5 Hz, 1H), 2.47 (dd, J = 2.5, 19.0 Hz, 1H), 2.90 (dd, J = 2.6, 2.7 Hz, 1H), 3.52 (dd, J = 2.4, 3.3 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), and 4.28 (q, J = 7.1 Hz, 2H); ^{13}C NMR δ: 13.6 (2C, 3), 27.8 (3), 31.0 (3), 33.8 (0), 34.9 (2), 38.2 (2), 46.6 (1), 50.5 (1), 60.9 (2), 61.0 (2), 132.3 (0), 144.9 (0), 164.0 (0), 165.7 (0), and 208.5 (0); MS (from GC-MS) *m/z* (%): 294 (20, M^+), 251 (36), 249 (22), 207 (32), 206 (29), 205 (100), 192 (28), 191 (28), 179 (39), 178 (39), 177 (24), 163 (28), 133 (27), 119 (24), 107 (29), 105 (23), 91 (34), 77 (22), and 41 (23). *Exact mass* calcd. for $C_{16}H_{22}O_5$: 294.1466; found: 294.1458.

Diethyl bicyclo[2.2.2]oct-5-en-2-one-5,6-dicarboxylate (160a)

A solution of diene **145a** (128 mg, 0.76 mmol) and diethyl acetylenedicarboxylate (390 mg, 2.28 mmol) in 30 mL of benzene was heated at reflux for two days. The reaction mixture was concentrated *in vacuo*, and the residue was directly treated with 0.5 mL of 0.5N HCl in 10 mL of methanol. The reaction was allowed to stand for 30 min before water was added. The aqueous layer was extracted with ethyl acetate four times, the combined organic extracts were washed with water, and saturated NaCl then dried ($MgSO_4$).

Chromatography (4% ethyl acetate in hexane) afforded product **160a** (185 mg, 91%) as a slightly yellow oil: IR (film) ν_{max}: 1729 (s) and 1637 (w) cm^{-1}; ^1H NMR δ: 1.29-1.35 (m, 6H), 1.71-1.88 (m, 3H), 1.96-2.06 (m, 1H), 2.16 (m, 2H), 3.43 (quintet, J = 2.7 Hz, 1H), 3.63 (dd, J = 2.4, 2.7 Hz, 1H), and 4.21-4.31 (m, 4H); ^{13}C NMR δ: 13.8 (2C, 3), 22.5 (2), 23.8 (2), 34.7 (1), 38.7 (2), 49.3 (1), 61.2 (2C, 2), 134.1 (0), 143.0 (0), 164.2 (0), 165.4 (0), and 208.7 (0); MS (from GC-MS) *m/z* (%): 266 (13, M^+), 221 (17), 192 (17), 179 (25), 178 (22), 151 (100), 150 (44), 149 (27), 123 (22), 105 (17), 79 (25), and 77 (19). *Exact mass* calcd. for $C_{14}H_{18}O_5$: 266.1153; found: 266.1157.

Diethyl 4-hydroxyphthalate (162)

A solution of diene **145a** (163 mg, 0.97 mmol) and diethyl acetylenedicarboxylate (332 mg, 1.94 mmol) in 30 mL of toluene was heated at reflux overnight. The reaction mixture was concentrated *in vacuo*, and the residue was treated directly with 0.5 mL of 0.5 N HCl in 10 mL of methanol for 30 min. Water was added, and the aqueous layer was extracted with ethyl acetate four times. The combined organic extracts were washed with water, and saturated NaCl then dried ($MgSO_4$) to yield product **162** (212 mg, 92%) as a yellow oil: IR (film) ν_{max}: 3371 (broad), 1715 (s), and 1604 (m) cm^{-1}; ^1H NMR δ: 1.31-1.37 (m, 6H), 4.28-4.40 (m, 4H), 6.94 (dd, J = 2.5, 8.6 Hz, 1H), 7.03 (d, J = 2.5 Hz, 1H), and 7.74 (d, J = 8.6 Hz, 1H); ^{13}C NMR δ: 13.8 (3), 13.9 (3), 61.4 (2), 62.0 (2), 115.1 (1), 117.0 (0), 121.0 (0), 131.7 (1), 135.7 (0), 159.7 (1), 167.0 (0), and 169.3 (0); MS (from GC-MS) *m/z* (%): 238 (13, M^+), 193 (21), 166 (12), 165 (100), 137 (6), 121 (6), 120 (5), 81 (5), and 63 (5). *Exact mass* calcd. for $C_{12}H_{14}O_5$: 238.0840; found: 238.0846.

Competitive reactions with diethyl acetylenedicarboxylate

A mixture of dienes **145b** and **145c** (total 109 mg, 0.56 mmol) in a 1 : 2.0 ratio (by ^1H NMR integration) and diethyl acetylenedicarboxylate (47 mg, 0.28 mmol) in 10 mL of benzene was heated at reflux for two days. After evaporation of the solvent, analysis of

the ^{1}H NMR spectrum of the residue showed signals for **159b** and **159c** in a ratio of 2.8 : 1, respectively. The ratio of reaction rates of diene **145b** *versus* **145c** calculated by Equation (8) was 7.8 : 1.

A mixture of dienes **145a** and **145b** (total 38 mg, 0.20 mmol) in a 1 : 2.0 ratio (by ^{1}H NMR integration) and diethyl acetylenedicarboxylate (11 mg, 0.06 mmol) in 10 mL of benzene was heated at reflux for two days. After evaporation of the solvent, analysis of the ^{1}H NMR spectrum of the residue showed signals for **159a** and **159b** in a ratio of 1 : 1. The ratio of reaction rates of diene **145a** *versus* **145b** calculated by Equation (8) was 2.2 : 1.

A mixture of dienes **145a** and **145c** (total 73 mg, 0.38 mmol) in 1.0 : 3.7 ratio (by ^{1}H NMR integration) and diethyl acetylenedicarboxylate (14 mg, 0.08 mmol) in 10 mL of benzene was heated at reflux for two days. After evaporation of the solvent, analysis of the ^{1}H NMR spectrum of the residue showed signals for **159a** and **159c** in a ratio of 3.59 : 1, respectively. The ratio of reaction rates of diene **145a** *versus* **145c** calculated by Equation (8) was 16 : 1.

5,5,6,6-Tetracyano-7,7-dimethyl-2-(trimethylsilyloxy)bicyclo[2.2.2]oct-2-ene (163b) and 5,5,6,6-tetracyano-7,7-dimethylbicyclo[2.2.2]octan-2-one (164b)

To a dichloromethane (15 mL) solution of diene **145b** (107 mg, 0.55 mmol) was added tetracyanoethylene (71 mg, 0.55 mmol). The reaction was stirred for 30 min. After concentration *in vacuo*, the crude reaction mixture was analysed by ^{1}H NMR then purified by chromatography (8% ethyl acetate in hexane) to give the hydrolysis product **164b** (78 mg, 56%). for **163b**: ^{1}H NMR δ: 1.10 (s, 3H), 1.27 (s, 3H), 2.13 (dd, J = 1.8, 5.1 Hz, 1H), 2.19 (dd, J = 1.8, 5.1 Hz, 1H), 2.81 (d, J = 1.8 Hz, 1H), 3.47 (ddd, J = 2.4, 2.4, 6.9 Hz, 1H), and 5.04 (dd, J = 1.8, 7.2 Hz, 1H); MS (from GC-MS) *m/z* (%): 309 (1, $M^+ - CH_3$), 182 (17), 181 (100), 165 (16), 128 (54), 82 (62), 73 (22), and 45 (7); for **164b**: IR (Nujol) ν_{max}: 2363 (w), 2253 (w), and 1747 (s) cm^{-1}; ^{1}H NMR (CD_2Cl_2) δ: 1.10 (s,

3H), 1.54 (s, 3H), 1.82 (dd, J = 3.0, 15.3 Hz, 1H), 2.27 (dd, J = 3.0, 15.6 Hz, 1H), 2.64 (dd, J = 3.6, 20.4 Hz, 1H), 2.87 (dt, J = 3.0, 20.4 Hz, 1H), and 3.18 (quintet, J 3.0 Hz, 1H); ^{13}C NMR (CD_2Cl_2) δ: 29.3 (3), 31.0 (0), 33.3 (2), 35.8 (2), 38.0 (3), 38.7 (0), 41.3 (0), 59.5 (1), 110.9 (0), 111.1 (0), 111.3 (0), 111.8 (0), and 199.8 (0); MS (from GC-MS) *m/z* (%): 225 (14, M^+ - CN), 211 (15), 210 (100), 209 (6), 155 (6), 140 (6), 128 (6), and 127 (6). *Exact mass* calcd. for $C_{14}H_{12}N_4O$: 252.1010; found: 252.1007.

5,5,6,6-Tetracyano-8,8-dimethyl-2-(trimethylsilyloxy)bicyclo[2.2.2]oct-2-ene (163c), 5,5,6,6-tetracyano-8,8-dimethylbicyclo[2.2.2]octan-2-one (164c), and 4,4-dimethyl-6-(1,1,2,2-tetracyanoethyl)-2-cyclohexene-1-one (166)

To a dichloromethane (15 mL) solution of diene **145c** (88 mg, 0.45 mmol) was added tetracyanoethylene (58 mg, 0.45 mmol). The reaction mixture was stirred for 10 min. After concentration *in vacuo*, the residue was analysed by ^{1}H NMR then chromatography provided **166** (42 mg, 32%) as colorless crystals and a mixture of **164c** and **166** in *ca.* 1 : 8 ratio (45 mg, 37%).* For **163c**: ^{1}H NMR δ (CD_2Cl_2): 1.31 (s, 3H), 1.33 (s, 3H), 1.66 (dd, J = 3.6, 14.7 Hz, 1H), 2.03 (dd, J = 2.4, 14.7 Hz, 1H), 3.16 (d, J = 7.2 Hz, 1H)), 3.20-3.23 (m, 1H), and 5.36 (dd, J = 1.8, 7.2 Hz, 1H); MS (from GC-MS) *m/z* (%): 309 (3, M^+), 196 (25), 182 (15), 181 (100), 165 (10), 82 (12), 75 (47), 73 (94), 56 (24), 45 (30), 43 (10), and 41 (11); for **164c**: ^{1}H NMR (CD_2Cl_2) δ: 1.15 (s, 3H), 1.54 (s, 3H), 1.96 (dd, J = 3.6, 16.0 Hz, 1H), 2.18 (dd, J = 2.7, 16.0 Hz, 1H), 2.79 (dd, J = 2.4, 3.6 Hz, 1H), 2.79 (dd, J = 2.4, 21.0 Hz, 1H), 2.95 (dd, J = 3.6, 21.0 Hz, 1H), and 3.07 (dd, J = 2.7, 3.6 Hz, 1H); for **166**: mp 134-137°C (dec.); IR (Nujol) ν_{max}: 2571 (w) and 1678 (s) cm^{-1}; ^{1}H NMR δ (CD_2Cl_2): 1.31 (s, 3H), 1.33 (s, 3H), 2.21 (dd, J = 3.1, Hz, 1H), 2.34 (ddd, J = 1.9, 1.9, 12.9 Hz, 1H), 3.33 (dd, J = 4.6, 14.0 Hz, 1H), 5.98 (d, J = 10.1 Hz, 1H), 6.02 (s, 1H), and 6.91 (dd, J = 1.9, 10.1 Hz, 1H); ^{13}C NMR (CD_2Cl_2) δ: 25.0

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* If the reaction was carried out at 0°C, **166** was formed as a single product.

(3), 30.0 (3), 31.1 (2), 35.0 (0), 40.0 (1), 42.1 (0), 45.9 (1), 108.0 (0), 108.6 (0), 109.7 (0), 110.4 (0), 125.5 (1), 162.7 (1), and 194.0 (0); MS *m/z* (%): 252 (1, M^+), 226 (10), 225 (52), 211 (15), 210 (100), 198 (17), 183 (53), 155 (19), 128 (17), 96 (79), 82 (23), 67 (22), 53 (25), 51 (18), 42 (20), and 41 (35). *Exact mass* calcd. for $C_{14}H_{12}N_4O$: 252.1010; found: 252.0996.

5,5,6,6-Tetracyano-2-(trimethylsilyloxy)bicyclo[2.2.2]oct-2-ene (163a)

To a dichloromethane (15 mL) solution of diene **145a** (102 mg, 0.61 mmol) was added tetracyanoethylene (78 mg, 0.61 mmol). The reaction mixture was stirred for 20 min. After concentration *in vacuo*, the crude product was washed with pentane three times to provide **163a** (168 mg, 93%) as colorless crystals: mp 122-124°C (dec.); IR (Nujol) ν_{max}: ^{1}H NMR δ: 1.57-1.86 (m, 2H), 2.13-2.24 (m, 2H), 3.23-3.25 (m, 1H), 3.49-3.54 (m, 1H), and 5.24 (dd, J = 1.6, 7.2 Hz, 1H); ^{13}C NMR δ: 19.0 (2), 20.2 (2), 41.0 (1), 43.2 (0), 44.2 (0), 45.1 (1), 99.8 (1), 111.0 (0), 111.2 (0), 111.6 (0), 112.1 (0), and 154.4 (0); MS (from GC-MS) *m/z* (%): 296 (1, M^+), 170 (5), 169 (16), 168 (100), 153 (33), 75 (23), 73 (61), and 45 (19).

Competitive reactions with tetracyanoethylene

To a $CDCl_3$ (0.5 mL) solution of dienes **145b** and **145c** (total 21 mg, 0.11 mmol) in a 1 : 2.0 ratio (by ^{1}H NMR integration) in an NMR tube was added tetracyanoethylene (6 mg, 0.05 mmol). Analysis of the ^{1}H NMR spectrum of this reaction mixture showed signals for **163b** and **163c** in a ratio of 1 : 7.3, respectively. The ratio of reaction rates of diene **145b** *versus* **145c** calculated by Equation (8) was 1 : 5.4.

To a $CDCl_3$ (0.5 mL) solution of dienes **145a** and **145b** (total 36 mg, 0.19 mmol) in a 1 : 2 ratio (by ^{1}H NMR integration) in an NMR tube was added tetracyanoethylene (7 mg, 0.05 mmol). Analysis of the ^{1}H NMR spectrum of this reaction mixture showed signals for **163a** and **163b** in a ratio of 15 : 1, respectively. The ratio of reaction rates of diene **145a** *versus* **145b** calculated by Equation (8) was 64 : 1.

To a $CDCl_3$ (0.5 mL) solution of dienes **145a** and **145c** (total 30 mg, 0.16 mmol) in a 1 : 1 ratio (by ^1H NMR integration) in an NMR tube was added tetracyanoethylene (10 mg, 0.08 mmol). Analysis of the ^1H NMR spectrum of this reaction mixture showed signals for **163a** and **163c** in a ratio of 5.6 : 1, respectively. The ratio of reaction rates of diene **145a** *versus* **145c** calculated by Equation (8) was 10 : 1.

Ethyl 7,7-dimethylbicyclo[2.2.2]oct-5-en-2-one-5-carboxylate (169b) and diethyl 3,3'-oxydiacrylate (171)

A mixture of diene **145b** (138 mg, 0.71 mmol) and ethyl propiolate (3 mL excess) in 30 mL of benzene was heated at reflux for seven days. After evaporation of the solvent, the residue was treated with 0.5 mL of 0.5 N HCl in 10 mL of methanol for 30 min. The reaction mixture was diluted with ethyl acetate. After work-up the same as for **169**, chromatography (5% ethyl acetate in hexane) of the crude product provided **169b** (51 mg, 32%), **171** (88 mg), and the hydrolyzed starting material **148b** (43 mg, 31%). For **169b**: IR (film) ν_{max}: 1714 (s) cm^{-1}; ^1H NMR δ: 0.96 (s, 3H), 1.09 (s, 3H), 1.32 (t, J = 7.3 Hz, 3H), 1.43-1.55 (m, 1H), 1.62 (dd, J = 2.8, 13.0 Hz, 1H), 2.03 (dd, J = 1.5, 2.8 Hz, 1H), 2.96 (d, J = 6.8 Hz, 1H), 3.53 (sextet, J = 2.7 Hz, 1H), 4.23 (dq, J = 1.7, 7.2 Hz, 2H), and 7.17 (dd, J = 2.2, 6.8 Hz, 1H); ^{13}C NMR δ: 14.2 (3), 30.0 (3), 30.9 (3), 32.4 (2), 35.9 (0), 38.0 (1), 40.2 (2), 60.8 (1), 62.8 (2), 138.5 (1), 139.0 (0), 164.2 (0), and 210.9 (0); MS (from GC-MS) *m/z* (%): 222 (61, M^+), 180 (73), 177 (15), 165 (100), 151 (28), 138 (18), 137 (45), 121 (27), 119 (18), 110 (20), 107 (95), 106 (23), 105 (25), 93 (100), 91 (51), 79 (19), 77 (23), 65 (21), and 41 (17). *Exact mass* calcd. for $C_{13}H_{18}O_3$: 222.1255; found: 222.1243; for **171**: mp 112-113°C; IR (film) ν_{max}: 1720 (s) and 1613 (m) cm^{-1}; ^1H NMR δ: 1.29 (t, J = 7.1 Hz, 6H), 4.20 (q, J = 7.2 Hz, 4H), 5.65 (d, J = 12.1 Hz, 2H), and 7.58 (d, J = 12.2 Hz, 2H); ^{13}C NMR δ: 14.2 (2C, 3), 60.5 (2C, 2), 104.2 (2C, 1), 157.2 (2C, 1), and 166.0 (2C, 0); MS (from GC-MS) *m/z* (%): 214 (2, M^+), 169 (57), 129 (30), 112 (21), 101 (26), 99 (44), 97 (94), 88 (16), 84 (28), 71 (100), 70 (32), 69 (49), 54 (21), 53 (25), 45 (21), 44 (21), 43 (30), 42 (35), and 41 (17). *Exact mass* calcd. for $C_{10}H_{14}O_5$:

214.0840; found: 214.0835.

Ethyl bicyclo[2.2.2]oct-5-en-2-one-5-carboxylate (169a)

A mixture of diene **145a** (129 mg, 0.77 mmol) and ethyl propiolate (3 mL, excess) in 30 mL of benzene was heated at reflux for 5 days. After evaporation of the solvent, the residue was directly treated with 0.5 mL of 0.5 N HCl in 10 mL of methanol for 30 min. After work-up, chromatography (4% ethyl acetate in hexane) of the crude product afforded **169a** (71 mg, 48%) and **171** (84 mg). For **169a**: IR (film) ν_{max}: 1725 (s) and 1620 (m) cm^{-1}; ^{1}H NMR δ: 1.32 (t, J = 7.0 Hz, 3H), 1.50-2.02 (m, 4H), 2.07-2.09 (m, 2H), 3.33-3.36 (m, 1H), 3.62 (d, J = 2.2 Hz, 1H), 4.24 (q, J = 7.0 Hz, 2H), and 7.21 (d, J = 6.8 Hz, 1H); ^{13}C NMR δ: 14.1 (3), 22.4 (2), 24.0 (2), 31.8 (1), 39.5 (2), 49.5 (1), 60.2 (2), 138.0 (0), 139.8 (0), 164.0 (0), and 210.8 (0); MS (from GC-MS) m/z (%): 194 (27, M^{+}), 152 (59), 151 (56), 123 (79), 107 (36), 91 (30), 88 (43), 79 (100), 76 (28), 77 (55), and 51 (21).

Chapter 3

SYNTHETIC STUDIES ON PREZIZAENE SESQUITERPENES

I Introduction

(-)-Prezizanol (**186**) and (-)-prezizaene (**187**) were first isolated from the essential oil of *Eremophila georgei* by Ghisalberti and his coworkers.[87] Their structures were elucidated by both chemical degradation[87] and X-ray crystallographic analysis in 1976.[88] Two years later, Bhattacharyya *et al.*[89,90] reported the isolation of (+)-prezizaene (**187**), first described by Anderson *et al.*[91] in 1971, and (+)-allokhusiol (**188**) from Indian vetiver oil.[92] These sesquiterpenes, along with (-)-khusimone (**189**),[93] (-)-zizaene* (**190**),[94,95] (+)-zizanoic acid (**191**)[96-98] and (-)-epi-zizanoic acid (**192**)[99] that were isolated from the essential oil of vetiver varieties, contain the tricyclo[6.2.1.$0^{1,5}$]undecane ring system. All these tricyclic sesquiterpenes were found only in vetiver oil, sandalwood and agarwood oil and they all have strong woody fragrances. The interesting structure-odor relationship among these tricyclic sesquiterpenes and their structural complexity has made the design of synthetic routes to the tricyclo[6.2.1.$0^{1,5}$]undecane ring system a challenging problem in organic synthesis.

A possible biosynthesis of the prezizaene type (**186-188**) and the zizaene family (**189-192**) of sesquiterpenes is outlined in Scheme 33. Yoshikoshi[100] suggested that zizaene might biogenetically be derived from μ-curcumene (**194**) via carbocations **195**, **196** and **197**. Zizaene (**190**) may be converted into khusimone (**189**) in several oxidative

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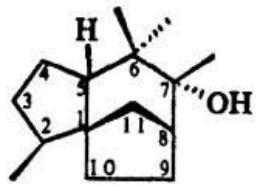
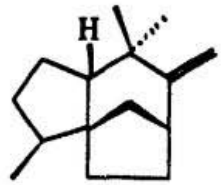
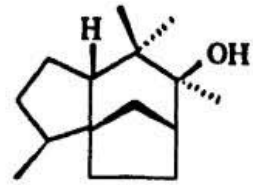
* Alternative names appearing in literature include tricyclovetivene,[94a] khusinene,[94c] and khusene.[97c]



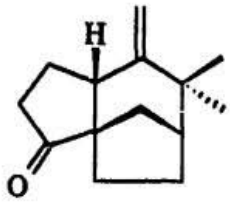
Prezizanol (186)



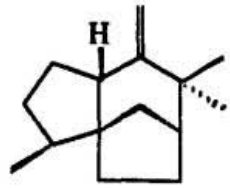
Prezizaene (187)



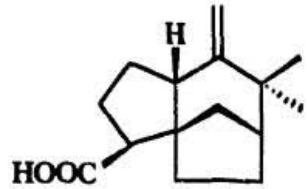
Allokhusiol (188)



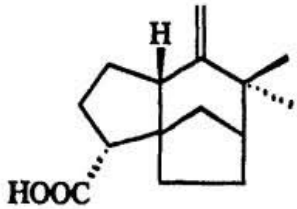
Khusimone (189)



Zizaene (190)



Zizanoic Acid (191)



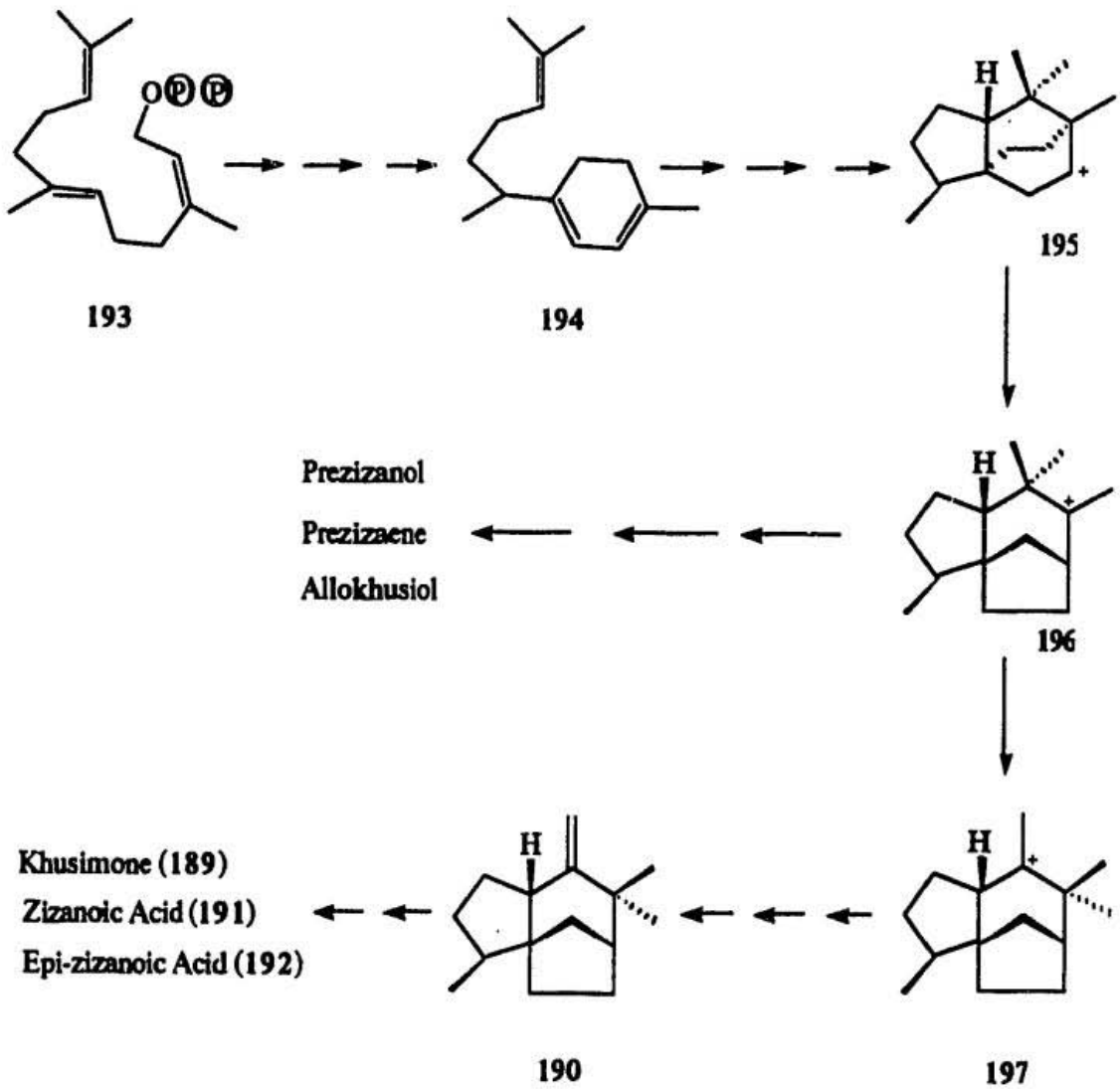
Epi-zizanoic Acid (192)

steps and the prezizaene sesquiterpenes (*i.e.*, **186**, **187**, **188**) may be formed from carbocation **196**.

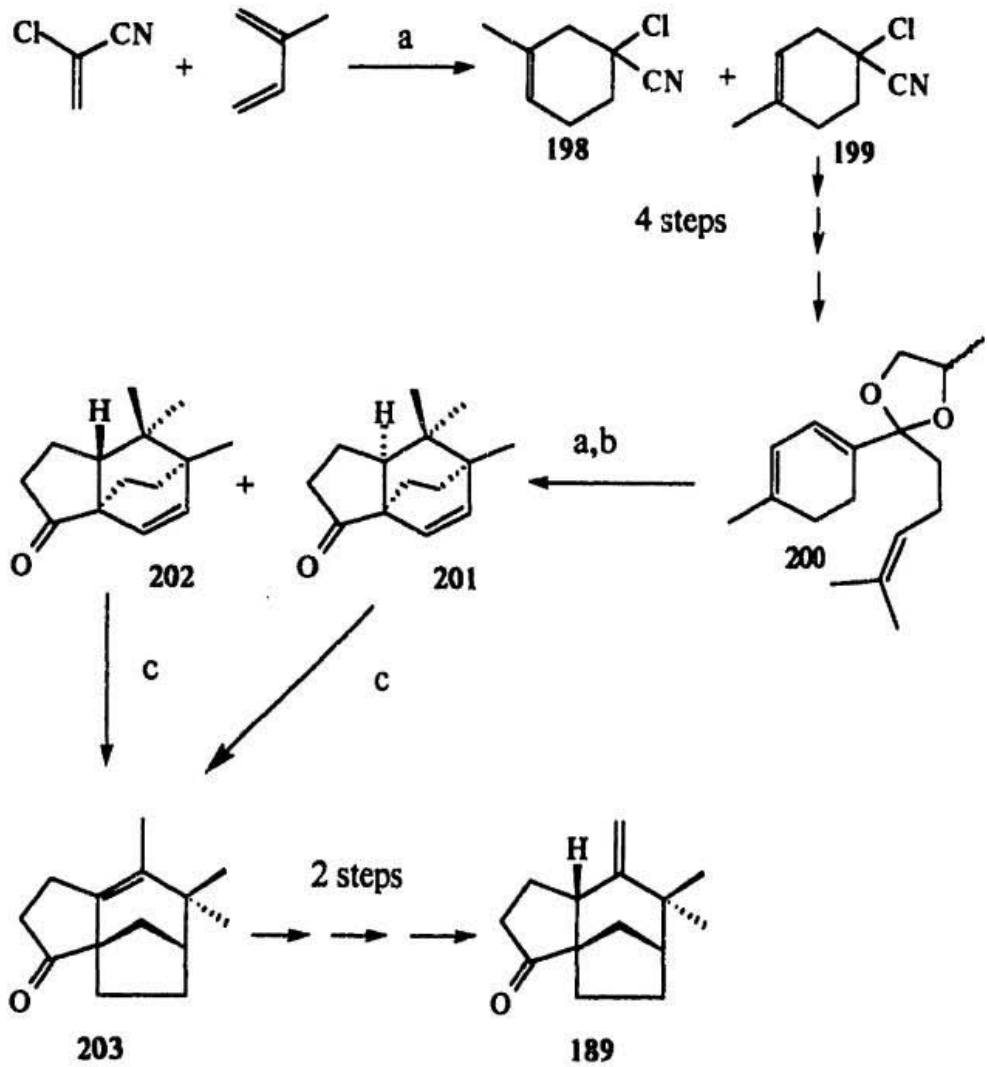
Apart from the degradation of natural zizanoic acid to (-)-khusimone (**189**),[101] the first total synthesis of (±)-khusimone was accomplished by Büchi and his coworkers as outlined in Scheme 34.[102] A key step in Büchi's synthesis was based on the biosynthesis of zizaene sesquiterpenes. The Diels-Alder reaction of α-chloroacrylonitrile and isoprene gave a mixture of two isomers **198** and **199**, of which the latter was converted into ketal

200 in four steps. Ketal **200** was heated to effect cycloaddition and followed by hydrolysis of the crude product furnished a 3 : 1 mixture of two epimeric ketones, **201** and **202**, respectively, in 55% yield. Ketone **202**, upon treatment with *p*TSA, produced an 80% yield of isokhusimone (**203**). Isokhusimone (**203**) can also be prepared from ketone **201**, but in only 15% yield. The contrathermodynamic isomerization of isokhusimone (**203**) to khusimone (**189**) was achieved in two steps. Büchi's synthesis is quite short (ten steps), but involves two isomer separations, and gives khusimone (**189**) in only 1.7% overall yield.

Scheme 33



Scheme 34

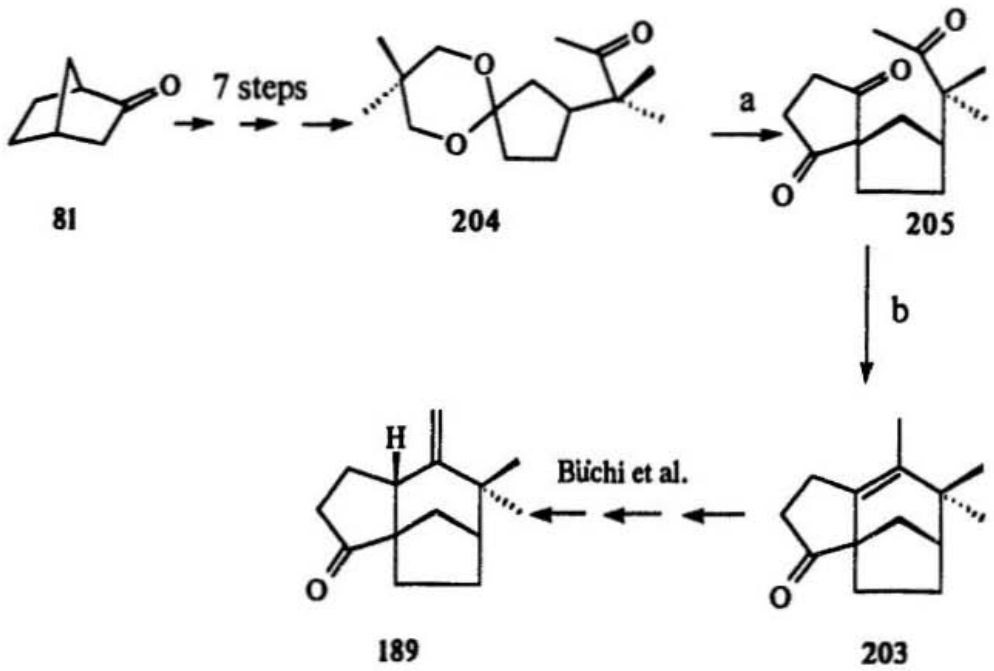


(a) heat; (b) H_3O^+; (c)*p*TSA, C_6H_6.

Recently, Burnell and Wu[103] developed the short synthesis of (±)-isokhusimone (**203**) that is documented in Scheme 35. The monoketal **204**, available from norcamphor (**81**) in seven steps, underwent a geminal acylation reaction with 1,2-bis(trimethylsilyloxy)cyclobutene (**77**) to afford triketone **205** in 85% yield. Triketone **205** was converted into isokhusimone (**203**) in 78% yield by means of a titanium-

induced carbonyl coupling reaction. The synthesis of isokhusimone (**203**) required nine steps from norcamphor, and it provided **203** in 35% overall yield.

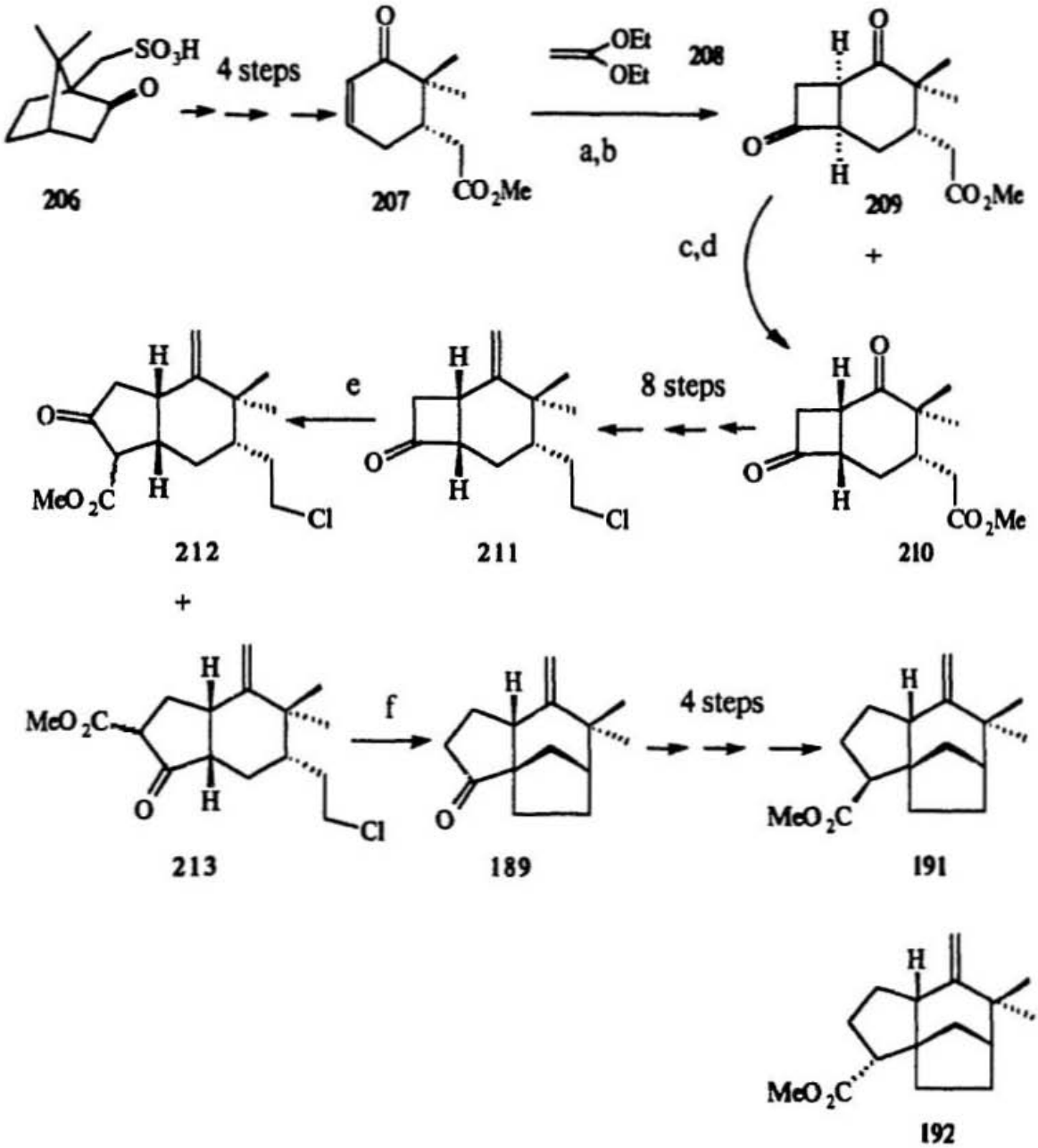
Scheme 35



(a) BF_3-Et_2O, 77; (b) $TiCl_3$, Zn/Cu

Liu reported the total synthesis of (-)-khusimone, (+)-zizanoic acid, and (-)-epi-zizanoic acid as shown in Scheme 36.[104] The enone **207**, available from (-)-camphor-10-sulfonic acid in four steps, was subjected to photoaddition with 1,1-diethoxyethene, followed by hydrolysis to give a 5 : 8 mixture of diketone esters **209** and **210**, of which only the latter was synthetically useful. Thus, **209** was converted into its isomer **210** in two steps. The desired isomer **210** was transformed into keto chloride **211** in eight steps. One-carbon expansion of the cyclobutanone ring was effected by treatment with ethyl diazoacetate and boron trifluoride. After separation, the desired keto ester **213** underwent concomitant decarboxylation and ring closure to provide (-)-khusimone (**189**). (+)-Zizanoic acid (**191**) and (-)-epi-zizanoic acid (**192**) were prepared from

Scheme 36

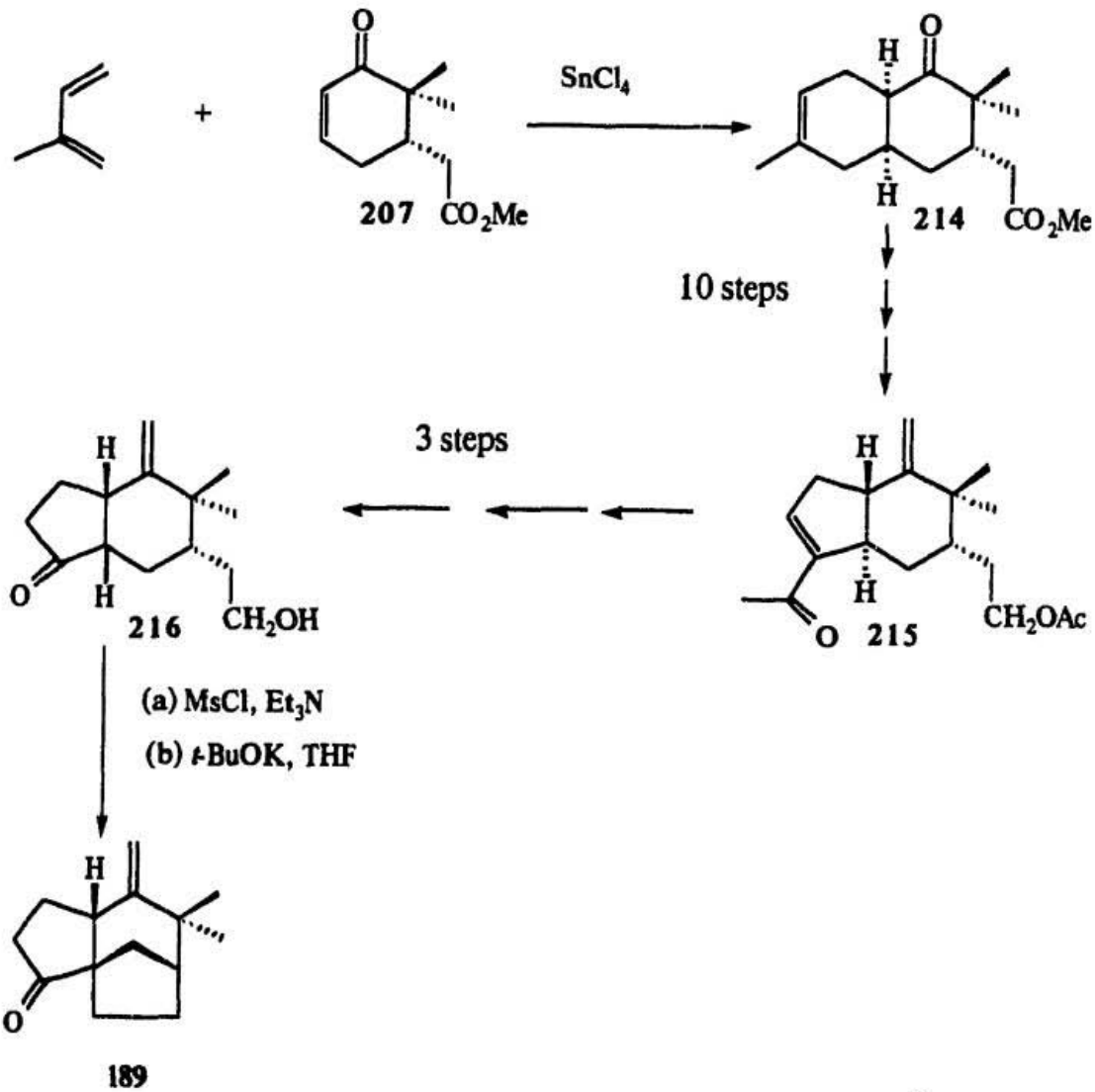


(a) hν, **208**; (b) H_3O^+; (c) pyridinium perbromide, HOAc; (d) Zn, HOAc;

(e) $N_2CHCOOEt$, $BF_3 \cdot Et_2O$; (f) NaOH, MeOH.

(-)-khusimone (**189**) in a straightforward fashion. This synthesis of (-)-khusimone required sixteen steps, involving two isomer separations, and provided optically active khusimone (**189**) in 2.7% overall yield.

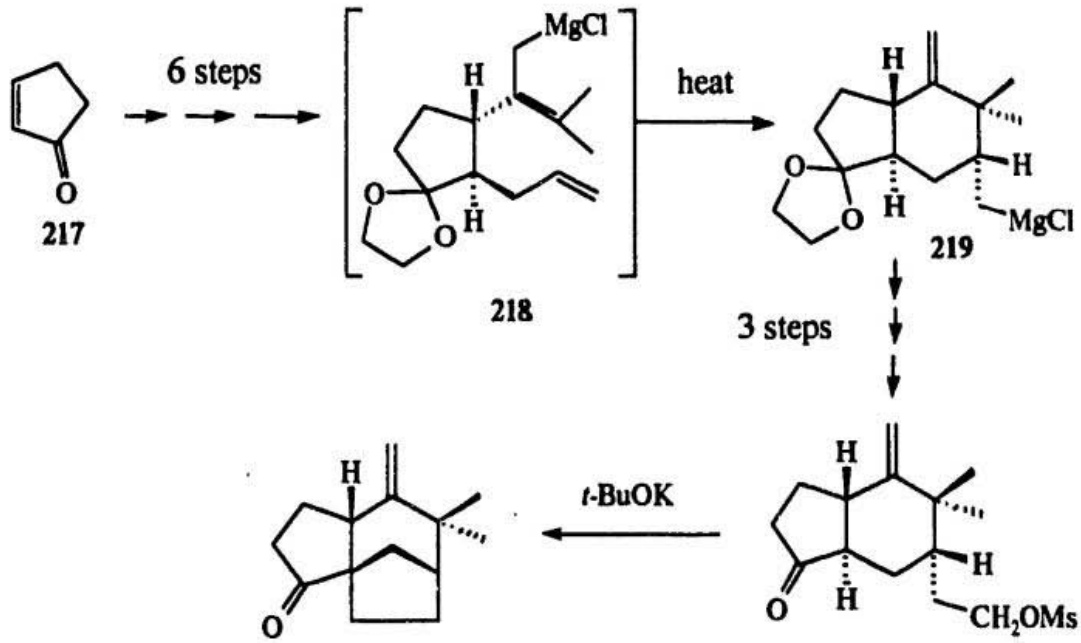
Scheme 37



Mori's synthesis of (-)-khusimone (**189**) started with the Lewis acid-catalysed Diels-Alder reaction of enone **207** with isoprene (Scheme 37).[105] The desired adduct **214** was isolated in only 35% yield. Ring contraction and many other modifications led to keto-alcohol **216** via acetate **215** in thirteen steps. Mesylation of **216** followed by cyclization

with potassium *tert*-butoxide provided (-)-khusimone. The overall yield of (-)-khusimone from keto ester **207** through fifteen steps was 6.9%.

Scheme 38



A **B**

Figure19. The transition states of the ene reaction of 218

Oppolzer and his coworkers carried out elegant syntheses of both racemic and chiral khusimone (**189**) via an intramolecular type 2 "magnesium-ene" reaction as summarized in Scheme 38.[106] The Grignard reagent **218** prepared from cyclopentenone in six steps

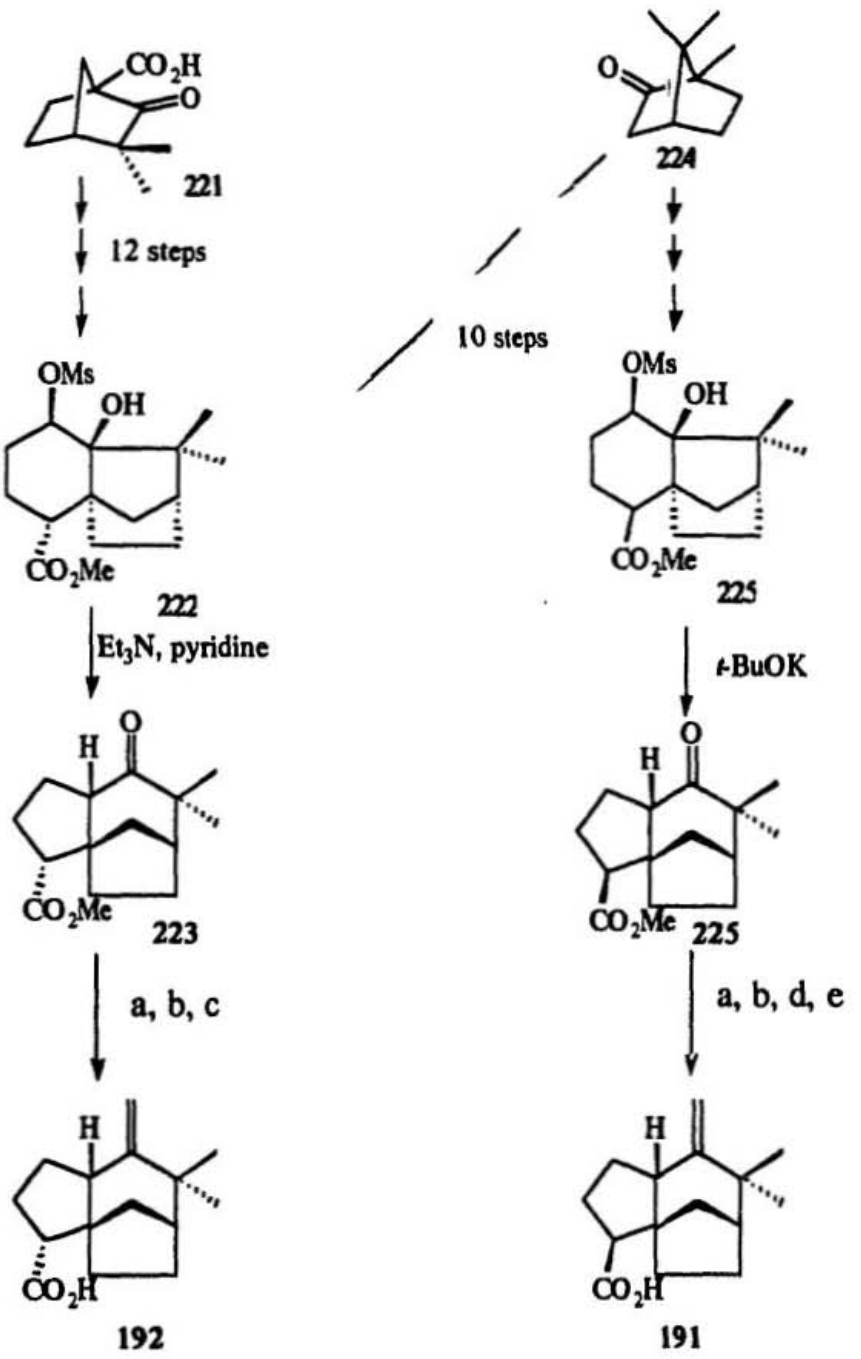
was heated to furnish the cyclized organomagnesium chloride **219**, which was converted into mesylate **220** in a straightforward fashion. Treatment of **220** with base gave khusimone (**189**). The remarkable stereoselectivity in the key step can be rationalized by examining the alternative transition states A and B (see Figure 19). Indeed, **B** shows a boat conformation for the developing cyclohexane ring, thereby resulting in a severe flagpole repulsion of the C-7 methyl and the C-1 hydrogen, whereas this type of steric interaction is absent in transition state A. Thus, A should be favored over B, leading to the *cis* relationship between C-5 hydrogen and C-8 hydrogen. In Oppolzer's synthesis, khusimone (**189**) was obtained from cyclopentenone by a sequence of eleven synthetic operations in 11% overall yield.

The first total synthesis of epi-zizanoic acid (**192**) was accomplished by Yoshikoshi and his coworkers (Scheme 39).[107] The key intermediate **222**, prepared via a twelve-step sequence from acid **221**, was treated with strong base to produce the keto-ester **223**. Epi-zizanoic acid (**192**) was derived from **223** in four steps.

MacSweeney's[108] synthesis of zizanoic acid (**191**) and epi-zizanoic acid (**192**), also shown in Scheme 39, was very similar to Yoshikoshi's synthesis. The key reaction involved was the rearrangement of a tricyclic[6.2.1.0^{1,6}]undecane system to form the desired tricyclo[6.2.1.0^{1,5}]undecane skeleton. Thus, treatment of **225** with triethylamine in pyridine gave **226**. Likewise, compound **222** was obtained from **221**.

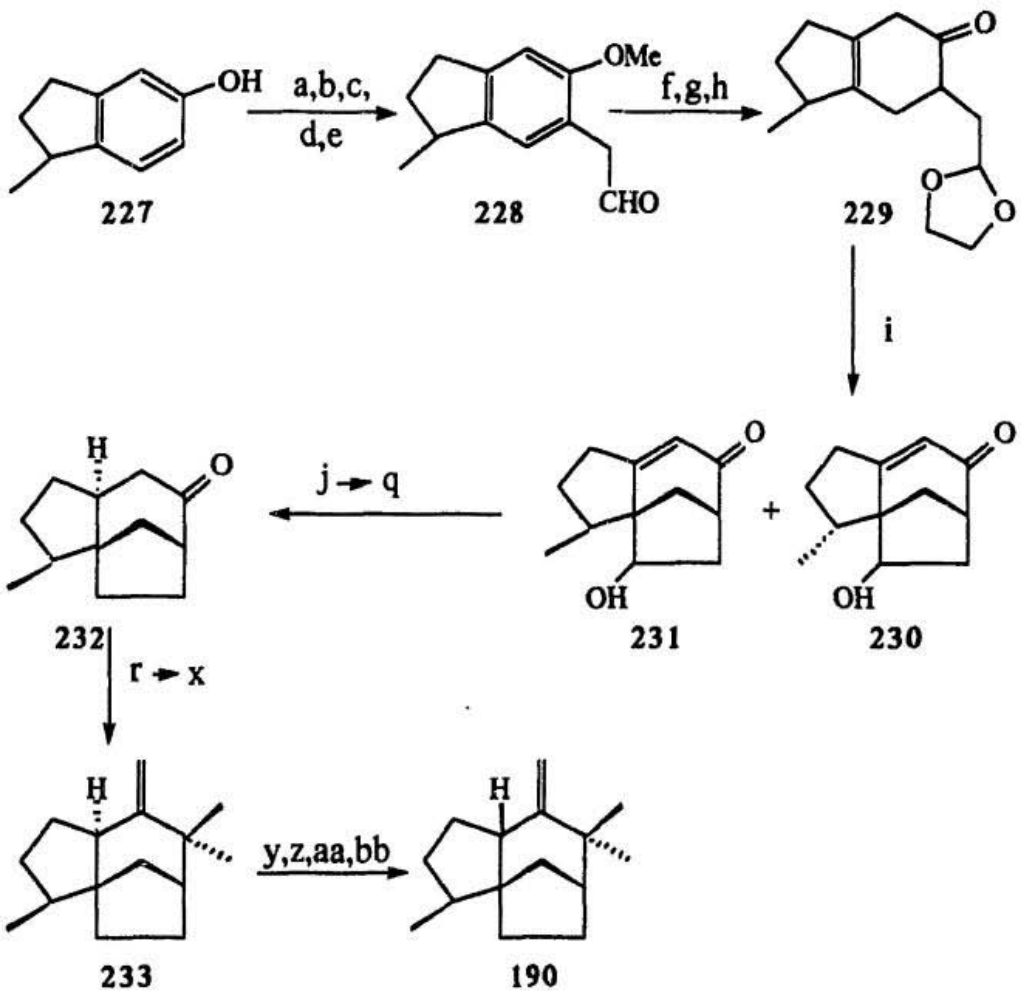
Weisner and his coworkers achieved the first total synthesis of zizaene (**190**) as shown in Scheme 40.[109] The synthesis commenced with dihydroindanol **227**, which was alkylated via Claisen rearrangement of the allyl ether. The resulting phenol was methylated and then converted into aldehyde **228**. Protection of the aldehyde and Birch reduction followed by gentle hydrolysis produced the unconjugated enone **229**. This enone underwent acid-initiated cyclization to furnish a mixture of tricyclic epimers **230** and **231** in a ratio of 2 : 3. After separation, the desired epimer **231** was converted into ketone **232** in eight steps.

Scheme 39



(a) $LiAlH_4$; (b) Jones' oxidation; (c) $Ph_3P{=}CH_2$ (d) MeMgBr; (e) $POCl_3$, pyridine

Scheme 40



(a) K_2CO_3, CH_2=CH-CH_2Cl; (b) heat; (c) Me_2SO_4, NaOH; (d) NaClO, OsO_4; (e) $NaIO_4$; (f) *p*TSA, ethylene glycol; (g) Li, NH_3; (h) $(COOH)_2$; (i) HOAc; (j) Ac_2O, pyridine; (k) H_2, Pd/C; (l) ethylene glycol, *p*TSA; (m) KOH, MeOH; (n) CS_2, MeI; (o) heat; (p) Raney Ni, H_2; (q) 80% HOAc; (r) $BrCH_2COOEt$, pyridine; (s) KOH, MeOH; (t) CH_2=PPh_3; (u) CH_2I_2, Zn-Cu; (v) H_2, Adams catalyst; (w) Br_2, HgO; (x) Li_2CO_3, DMF; (y) OsO_4; HIO_4; (z) NaOMe, MeOH; (aa) MeLi; (bb) Ac_2O, pyridine; heat.

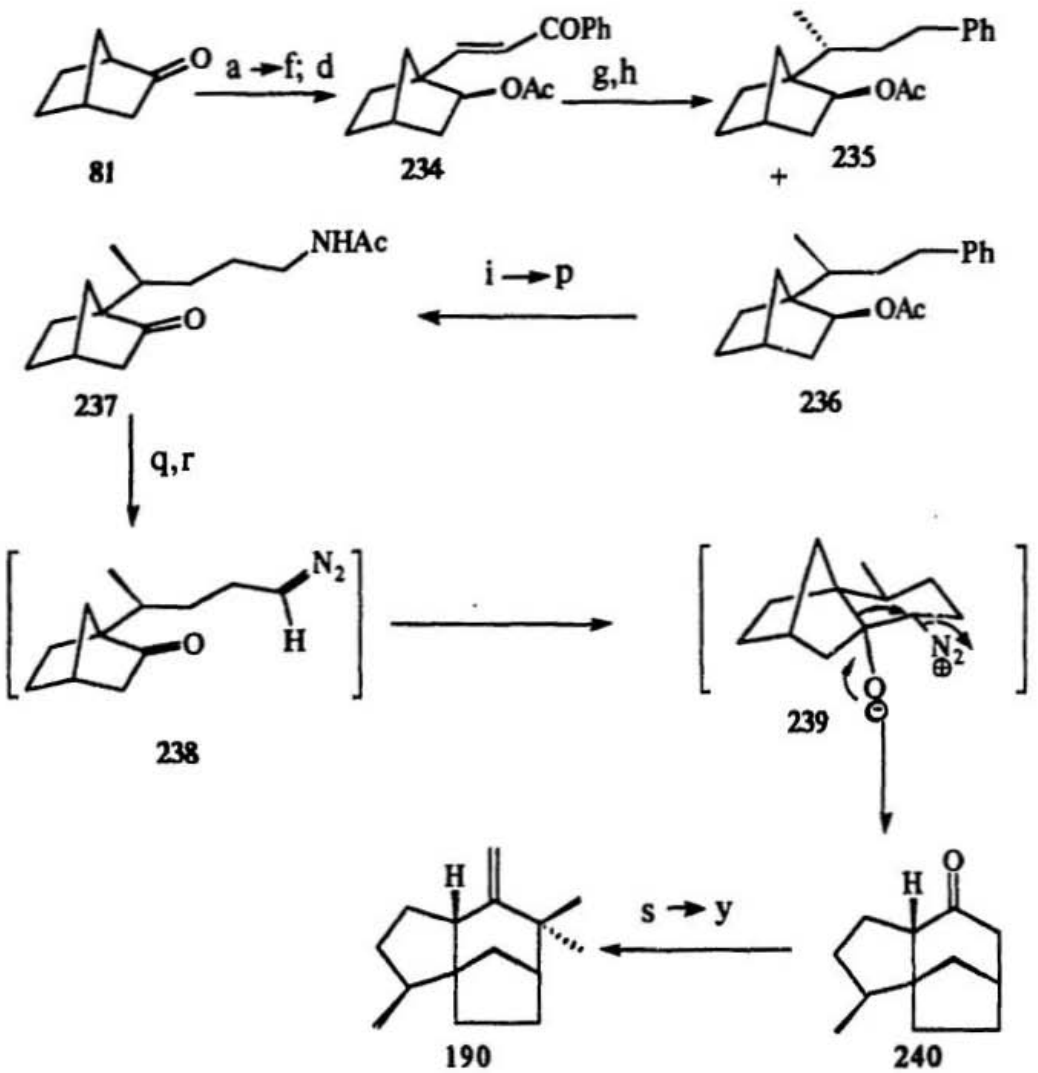
Hydrogenation of the double bond occurred *trans* to the methyl group leading to the incorrect relative stereochemistry on the C-5 compared to zizaene (**190**). The double bond of **233** was cleaved to give a ketone, which was epimerized with base. After separation, the desired C-5 epimer was treated with methyllithium followed by elimination to

generate zizaene (**190**). The Weisner synthesis required 28 steps, and it involved two isomer separations.

Coates' synthesis of zizaene (**190**) is depicted in Scheme 41.[110] This synthesis began with norcamphor (**81**), which was transformed into enone **234** in seven steps. Compound **234** was subjected to Michael addition and Wolff-Kishner deoxygenation to generate a 1 : 2 mixture of two diastereomers **235** and **236**, respectively. By a routine series of steps, the major epimer **236** was converted into keto amide **237**. Nitrosation of **237** with dinitrogen tetroxide followed by the reaction with base generated the diazoketone **238**, which underwent spontaneous cyclization and rearrangement to afford a single tricyclic ketone **240**. The high stereoselectivity of the cyclization can be rationalized as follows. An intramolecular *exo* approach to the carbonyl would give diazonium alkoxide intermediate **239** in which $-N_2^+$ is located at an equatorial position as a result of minimization of charge separation, and, consequently, the carbon-carbon bond would migrate concertedly antiparallel to the nitrogen leaving group to give the observed tricyclic ketone **240**. The introduction of the *gem*-dimethyl group into ketone **239** and installation of an exocyclic methylene unit was achieved in seven steps. The Coates synthesis required twenty-six steps. It involved two isomer separations, and produced zizaene in 0.2% overall yield.

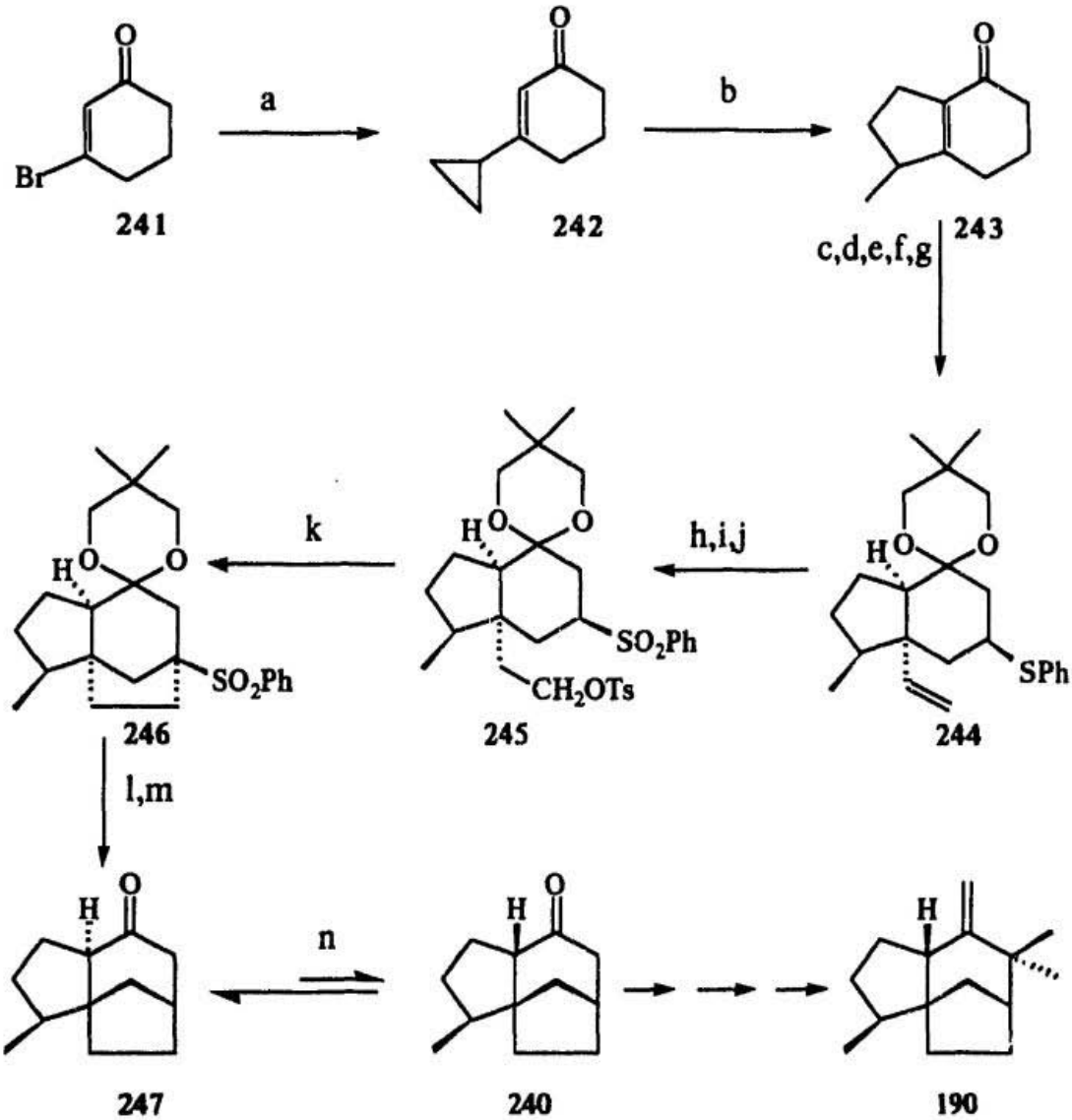
Piers and Banville carried out the formal synthesis of zizaene that is outlined in Scheme 42.[111] Thermal vinylcyclopropane rearrangement followed by base-catalysed conjugation of the double bond provided enone **243**. Lithium divinylcopper attacked the enone from the sterically less hindered face of the double bond (i.e., opposite the methyl group), the double bond was introduced by the selenoxide method, thiophenol was added, and the resulting ketone was ketalized to give **244**. Hydroboration and tosylation followed by oxidation of the resulting sulfide produced sulfone **245**, which cyclized to **246** on treatment with base. The benzenesulfonyl group was removed, and the ketal was

Scheme 41



(a) $Ph(CH_2)_3MgBr$; (b) 50% H_2SO_4, HOAc; (c) NBS; (d) $CaCO_3$, DMA; (e) NBA, $HClO_4$; (f) H_2CrO_4; (g) $(CH_3)_2CuLi$; (h) KOH, NH_2NH_2; (i) O_3, HOAc; (j) H_2CrO_4; (k) $(COCl)_2$, C_6H_6; (l) NH_3; (m) $LiAlH_4$; (n) Ac_2O, pyridine; (o) KOH, MeOH; (p) $CrO_3(C_5H_5N)_2$; (q) N_2O_4, NaOAc; (r) NaOMe, MeOH; (s) NaH, EtOCHO; (t) n-BuSH, *p*TSA; (u) Li, NH_3, MeI; (v) NaOMe, MeOH; (w) $PhSCH_2Li$; (x) n-BuLi, PhCOCl; (y) Li, NH_3.

Scheme 42



(a) lithium phenylthio(cyclopropyl)cuprate; (b) heat; basic alumina; (c) $(CH_2{=}CH)_2CuLi\ Me_2S$; (d) LDA; PhSSPh; (e) $NaIO_4$; (f) PhSH, n-Bu_4NF; (g) *p*TSA, $HOCH_2C(CH_3)_2CHOH$; (h) $BH_3\ Me_2S$; H_2O_2, NaOH; (i) TsCl, Py; (j) *m*CPBA; (k) *t*-BuOK; 9l) Na-Hg; (m) $(COOH)_2$; (n) NaOMe, MeOH.

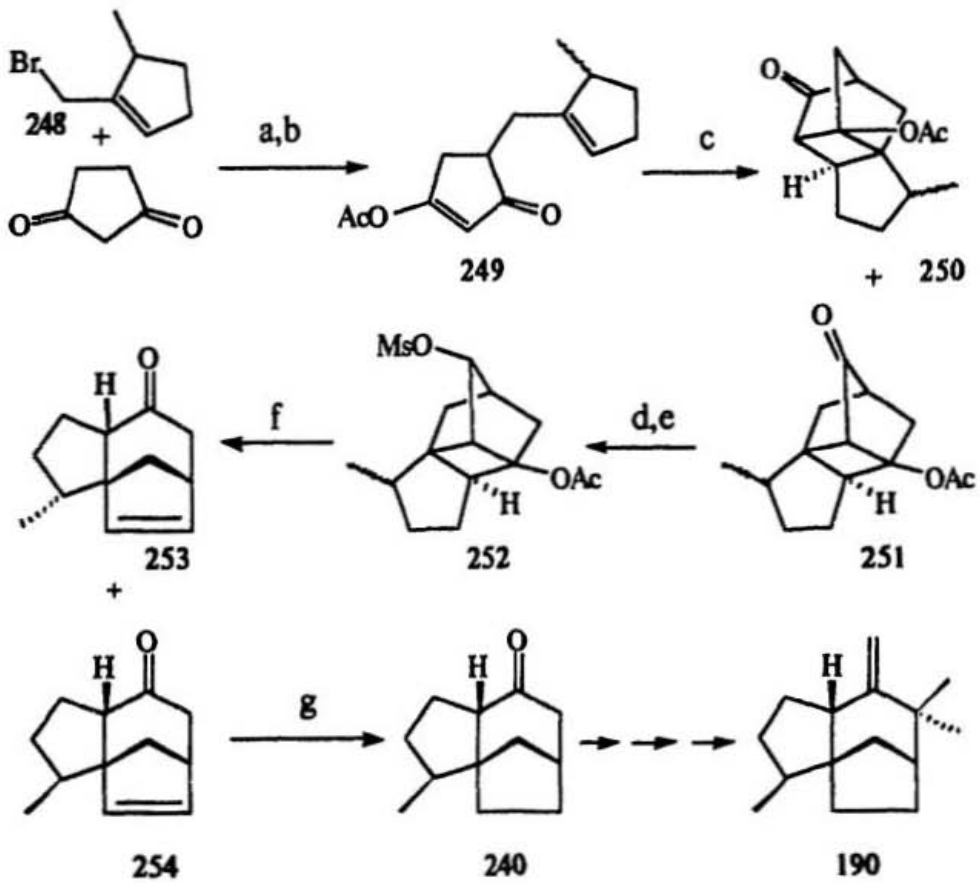
deprotected to generate tricyclic ketone **247**, which possessed the incorrect stereochemistry at C-5. Base-induced epimerization produced a 2 : 1 mixture of **247** and **240**, of which the minor product had been converted into zizaene by Coates and his coworkers. The Piers synthesis of the tricyclic ketone **240** required fourteen steps from bromide **241**; it involved one isomer separation.

Pattenden and Barker[112] applied [2 + 2] photocyclization to the synthesis of the Coates-Sowerby tricyclic ketone **240** as shown in Scheme 43. This synthesis began with the alkylation of the dianion derived from cyclopentane-1,3-dione with the bromide **248**. The resulting enol was converted into a mixture of isomeric enol acetates in which acetate **249** was predominant. This mixture of enol acetates was irradiated to give a 3 : 7 mixture of the photoadducts **250** and **151**. After separation, the major photoadduct **251** was reduced with sodium borohydride, and the resulting alcohol was mesylated to afford **252**. Compound **252** underwent simultaneous saponification and Grob fragmentation to form a 2 : 1 mixture of methyl epimers **253** and **254**. Hydrogenation of the minor epimer **254** produced the ketone **240**.

The first total synthesis of (+)-prezizaene was accomplished by Coates and his coworkers as summarized in Scheme 44.[113] The keto-ester **255**, available from (+)-pulegone in three steps, underwent base-catalyzed Michael addition to 3-buten-2-one, and the resulting product was cyclized to give the bicyclic enone **256** and its epimer in a 6 : 1 ratio, respectively. The major isomer **256** was assigned a *cis* stereochemistry based on the assumption that the Michael addition would occur preferentially on the side of the cyclopentanone ring opposite the methyl group. Hydrogenation of the isomer mixture proceeded stereospecifically to afford predominantly the corresponding saturated keto-ester with the *cis* ring junction, which was transformed into **257** by a straightforward sequence of steps. After benzoylation and deprotection, the keto amide underwent nitrosation by treatment with dinitrogen tetroxide to provide *N*-nitrosoamide **258**. Compound **258** was then treated with base to give a 1 : 1.2 mixture of the isomeric ketones **260** and

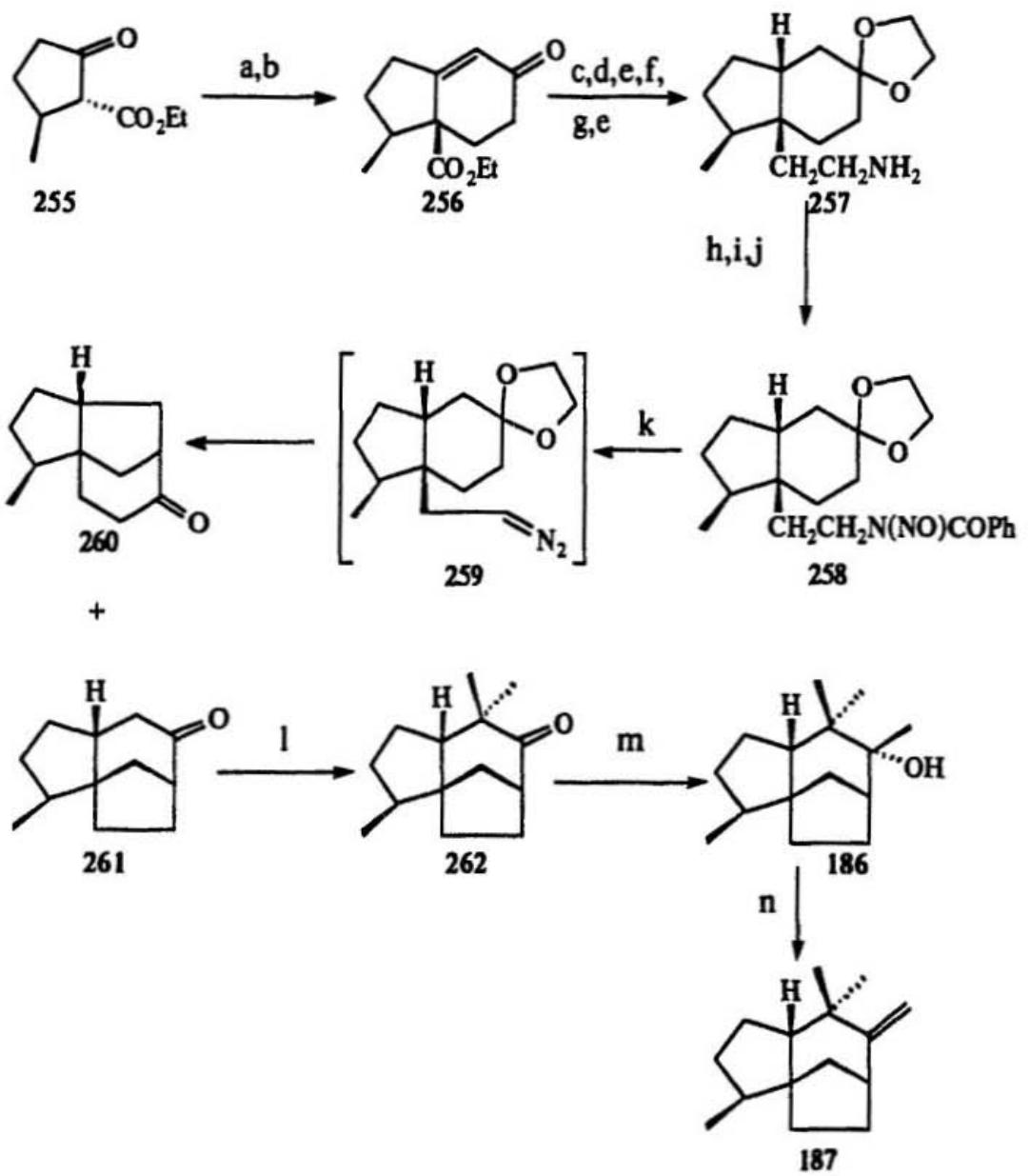
261, resulting from the spontaneous cyclization and rearrangement of the diazo ketone intermediate **259**. Introduction of the *gem*-dimethyls to the major epimer **261** followed by addition of methyllithium produced prezizanol (**186**), and dehydration of prezizanol afforded prezizaene (**187**).

Scheme 43



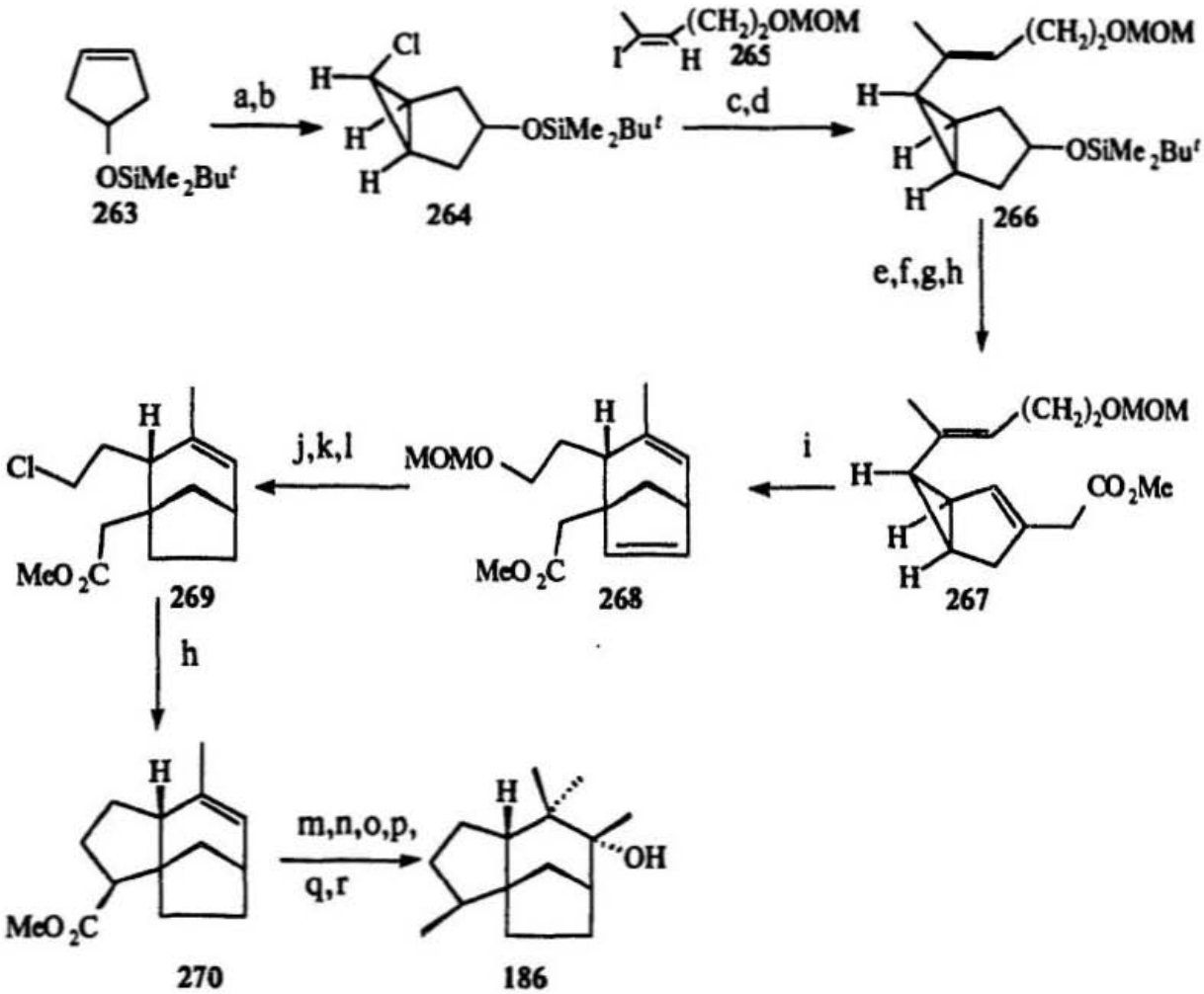
(a) *n*-BuLi ; (b) Ac_2O, pyridine; (c) hν; (d) $NaBH_4$; (e) MsCl, Et_3N
(f) NaOH; (g) H_2, Pd-C.

Scheme 44



(a) CH_2=CH-$COCH_3$; (b) pyrrolidine, HOAc, H_2O; (c) H_2, Pd-C; (d) ethylene glycol, *p*TSA; (e) $LiAlH_4$; (f) MsCl, Et_3N; (g) NaCN, $Et_3N^+HCl^-$; (h) PhCOCl; (i) H_3O^+; (j) N_2O_4; (k) *t*-BuOK; (l) KH, MeI; (m) MeLi; (n) MsCl, Et_3N.

Scheme 45

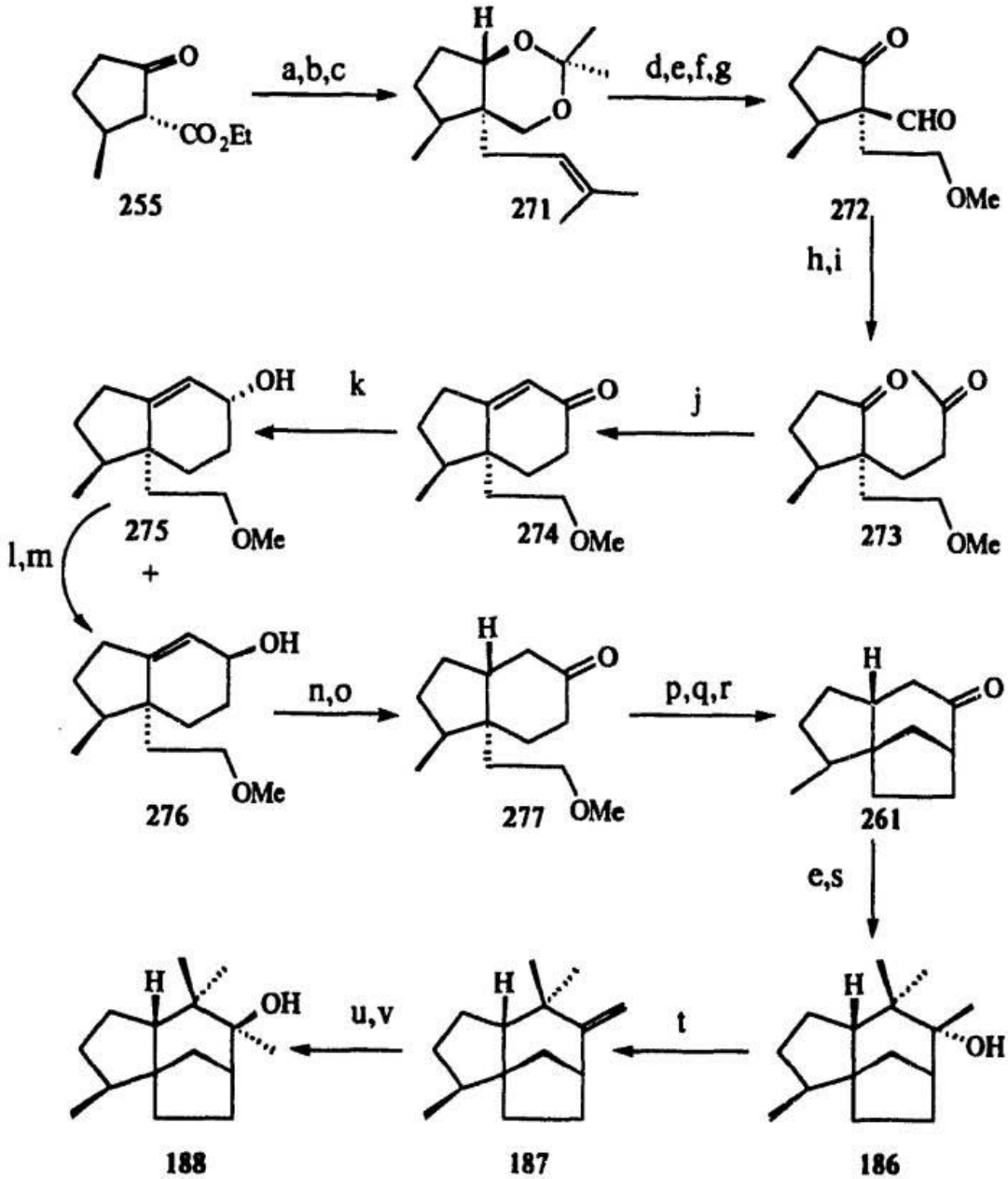


(a) NaOH, $CHCl_3$; (b) *t*-BuLi, H_2O; (c) (4,4'-di-*tert*-butylbiphenyl)$^-Li^+$, $ZnCl_2$; (d) **265**, $Pd(PPh_3)_4$; (e) n-BuNF; (f) PCC; (g) $[(MeO)_2POCH_2CO_2Me]Li$; (h) *i*-Pr_2NLi; (i) heat; (j) H_2, $(PPh_3)_3RhBr$; (k)PTSA, MeOH; (l) CCl_4, PPh_3, Et_3N; (m) $LiAlH_4$; (n) TsCl, DMAP; (o) BH_3·Me_2S; H_2O_2, $NaOH_,$; (p) $LiEt_3BH$; (q) KH, MeI; (r) MeLi; (s) MsCl, *i*-Pr_2NEt.

Piers and his coworkers completed the total synthesis of (±)-prezizanol and (±)-prezizaene as outlined in Scheme 45.[114] The chlorocyclopropane **264**, readily prepared from the silyl ether **263** in two steps, was treated with lithium 4,4'-di-*tert*-butylbiphenylide, the resulting cyclopropyl-lithium reagent was converted into the corresponding organozinc chloride, and the latter species underwent a palladium-catalyzed coupling reaction with the vinyl iodide **265** to give **266**. Conversion of **266** into **267** was achieved via a four-step sequence. Compound **267** was distilled at 110°C to furnish the bicyclic diene **268** resulting from Cope rearrangement. Selective hydrogenation of **268**, deprotection of the hydroxyl, followed by the reaction with Ph_3P-CCl_4-Et_3N, produced the desired chloride **269**, which, upon treatment with base, underwent intramolecular alkylation to furnish the tricyclic ester **270**. This ester was further transformed into (±)-prezizanol (**186**) and (±)-prezizaene (**187**) in seven and eight steps, respectively. These syntheses of prezizanol and prezizaene required twenty and twenty-one steps, respectively, from silyl ether **263**.

Recently, Mori and his coworkers[115] reported the total synthesis of (-)-prezizanol, (-)-prezizaene, and (-)-allokhusiol shown in Scheme 46. Their approach began with the keto-ester **255**, available as in Coates' synthesis. Alkylation of **255** with prenyl bromide, reduction of the resulting keto-ester with $LiAlH_4$, and ketalization of the diol with 2,3-dimethoxypropane afforded the ketal **271**, which was converted into the dione **273** via aldehyde **272**. Compound **273** underwent base-induced intramolecular aldol condensation to furnish the enone **274**. Since both catalytic hydrogenation and Birch reduction of the enone **274** gave a bicyclic ketone with a *cis* ring junction, a stereoselective hydroxyl-directed hydrogenation strategy was employed. Reduction of the enone **274** with $NaBH_4$ gave a 82 : 18 mixture of two epimers **275** and **276**, of which the minor one (*i.e.*, **276**) was the desired product. Fortunately, conversion of **275** into **276** was readily achieved by following the Mitsunobu procedure.[116] Hydrogenation of **276** by using the rhodium catalyst, [Rh(NBD)(DIPHOS-4)ClO_4][117] provided the *trans*-fused alcohol,

Scheme 46



(a) NaH, $(CH_3)_2C{=}CH\text{-}CH_2Br$; (b) $LiAlH_4$; (c) $(CH_3)_2C(OMe)_2$, *p*TSA; (d) O_3, $NaBH_4$; (e) MeI, KH; (f) HOAc; (g) $(COCl)_2$, DMSO, Et_3N; (h) $Ph_3P{=}CHCOCH_3$; (i) H_2, Pd-C; (j) KOH; (k) $NaBH_4$; (l) PPh_3, DEAD, $PhCO_2H$; (m) K_2CO_3; (n) H_2, $[Rh(NBD)(DIPhOS\text{-}4)]ClO_4$; (o) Jones' oxidation; (p) BBr_3, NaI; (q) TsCl, pyridine; (r) *t*-BuOK; (s) MeLi; (t) MsCl, Et_3N; (u) $Hg(OAc)_2$; (v) $NaBH_4$, NaOH.

which was oxidized to give the *trans*-fused hydrindanone **277**. Ether cleavage, tosylation, and base-induced ring closure afforded the tricyclic ketone **261**, which was transformed into (-)-prezizanol, (-)-prezizaene, and (-)-allkhusiol in a straightforward fashion.

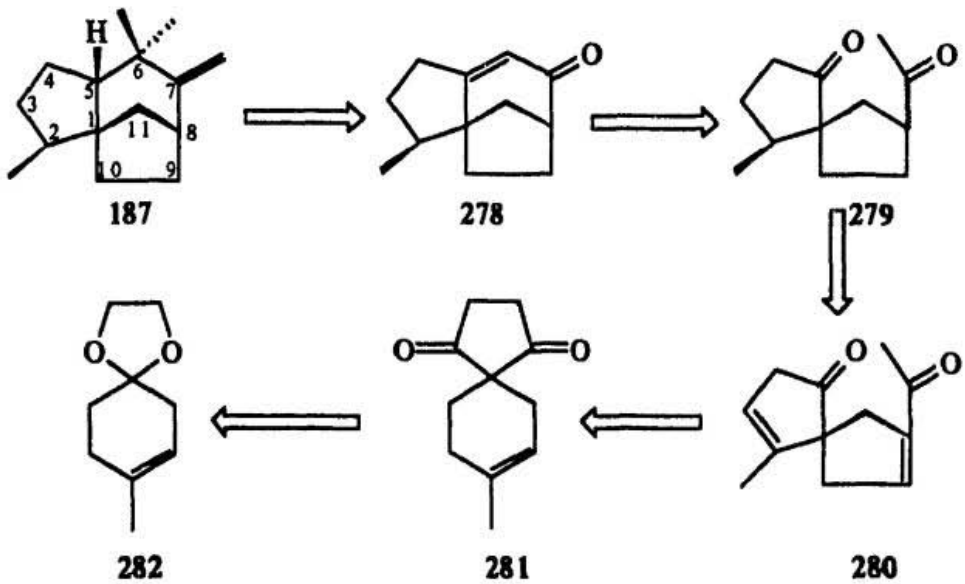
The prezizaene type (**186-188**) and the zizaene family of sesquiterpenes have been chosen as popular targets for synthetic organic chemists during the past twenty years. Clearly, a short and efficient approach to the tricyclo[6.2.1.$0^{1,5}$]undecane ring system with appropriate functionalities still remains a challenging problem.

From the above review, it can be seen that most of the previous syntheses of zizaene or prezizaene sesquiterpenes were designed on the basis of either A ring or C ring disconnection. The following section details our synthetic studies in this area.

II. Results and Discussion

Our retrosynthetic analysis is illustrated in Scheme 47. The tricyclic enone **278**, which could serve as a precursor in the synthesis of a number of sesquiterpenes like prezizaene (**187**), might be prepared from diketone **279**. The conversion of spiro-diketone **281** to compound **279** should be readily achievable via enone **280**. The geminal acylation reaction of ketal **282** with cyclobutene **77** would provide spiro-diketone **281**.

Scheme 47



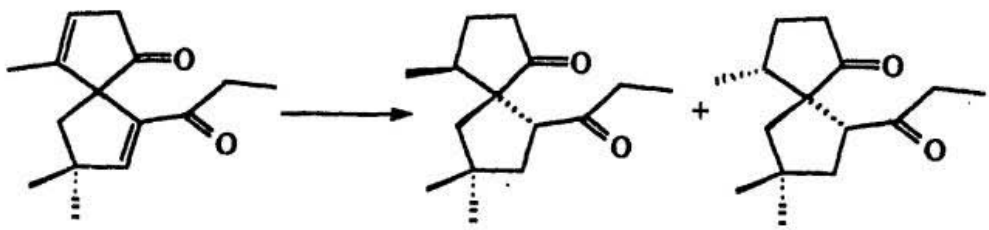
187 **278** **279**

280 **281** **282**

Before we undertook this synthetic approach, we realized that stereochemical control at C-2 and C-5 might be problematic. Clearly, the stereochemical outcome at C-5 will result from the reduction of the enone double bond in **278**. If one assumes that catalytic hydrogenation of the enone double bond in **278** occurs from the less sterically hindered face, then the correct stereochemistry at C-5 would be anticipated. If the catalytic hydrogenation results in the undesired stereochemistry at C-5, hydroxyl-directed hydrogenation could be used to provide the product with the correct stereochemistry at C-5. The stereochemical problem at C-2 (i.e., **280** → **279**) might be overcome by changing the reaction

conditions. In a synthetic study towards the total synthesis of (±)-pentalenene and (±)-epi-pentalenene, Wu and Burnell had earlier discovered that a 1 : 6 mixture of **284** and **285** was produced when compound **283** underwent catalytic hydrogenation. In contrast, when enone **283** was subjected to Birch reduction followed by catalytic hydrogenation, the mixture of **284** and **285** was formed in a 4 : 1 ratio. We hoped that Birch reduction of **280** followed by catalytic hydrogenation would afford compound **279** as the major product.

Scheme 48



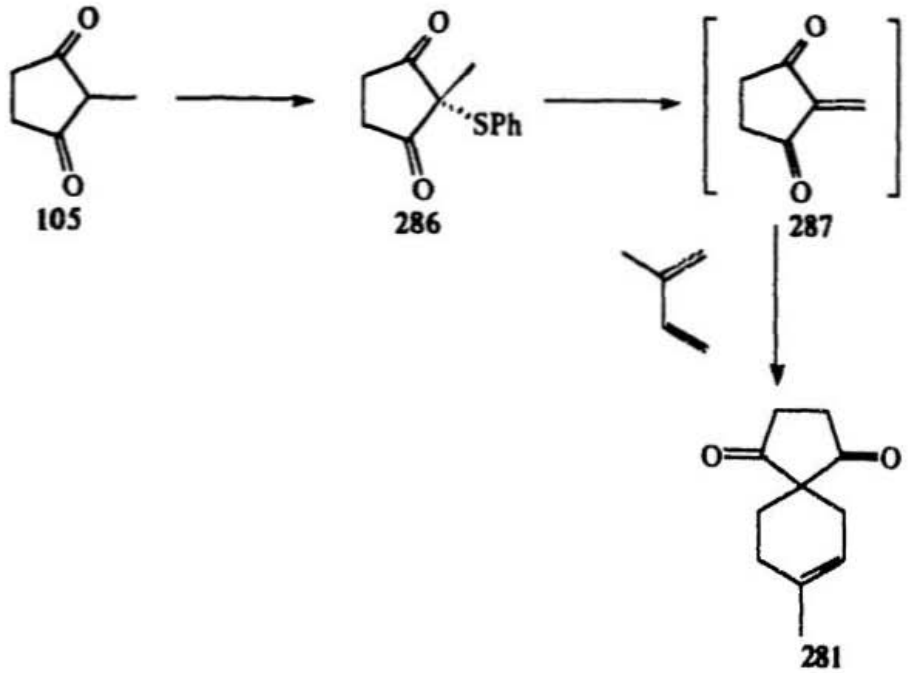
283 **284** **285**

Conditions	Ratio (**284** : **285**)
H_2, Pd/C	1.0 : 6.0
Li/NH_3; H_2, Pd/C	4.0 : 1.0

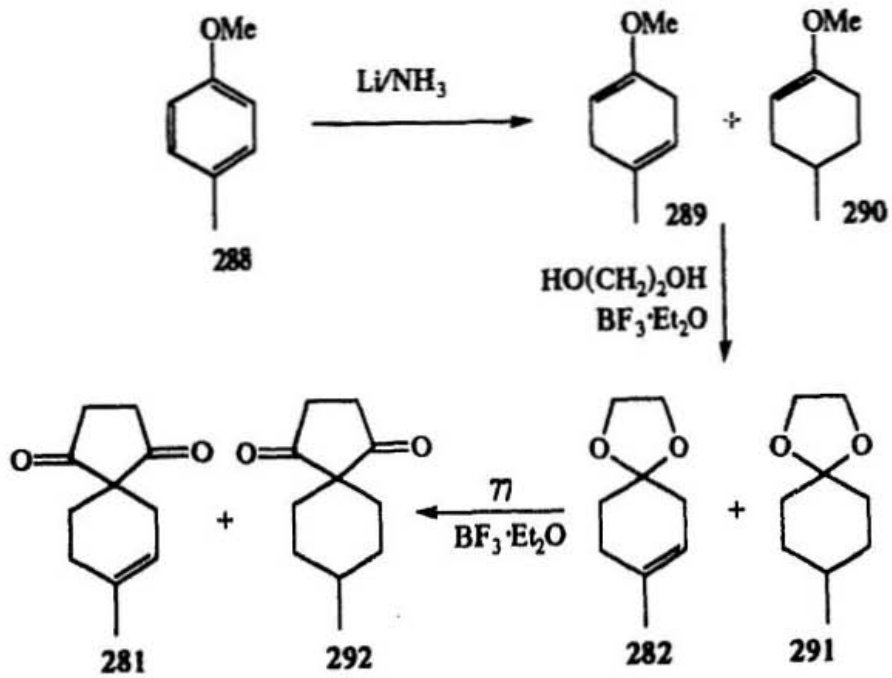
A synthesis of spiro-diketone **281** was reported in 1986 by Bunnelle and co-workers[119] as outlined in Scheme 49. 2-Methylcyclopentane-1,3-dione (**105**) underwent phenylsulfenation to give compound **286**, which was oxidized with a peracid. The generated dienophile **287** was trapped *in situ* with isoprene to provide the adduct **281**. Unfortunately, the overall yield from **105** was very low, so this sequence was not suitable for our synthesis.

Our preparation of spiro-diketone **281** required a convenient supply of ketal **282**. We deemed 4-methylanisole (**288**) to be a reasonable starting material for the synthesis of ketal **282**. Birch reduction of **288** following the procedure of Isobe *et al.*[120] proceeded smoothly to give the desired product **289**, which was accompanied by a small amount of

Scheme 49



Scheme 49

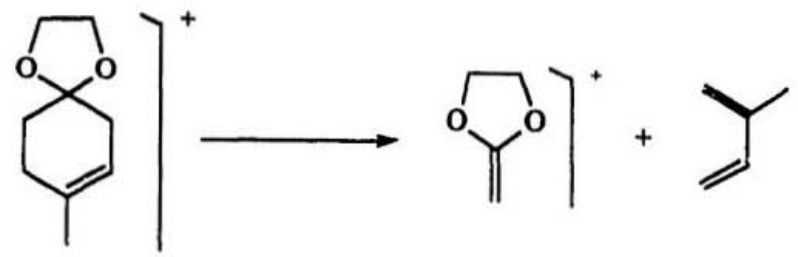


the over-reduced product **290**. The ratio of **289** to **290** was 10 : 1 as revealed by GC-MS analysis. Initially it was thought that the excess lithium employed was responsible for the over-reduction. In fact, even when 0.9-1 equivalents of lithium were used, the over-reduced product was observed along with a considerable amount of the starting material. No difference was found when lithium metal was replaced with sodium metal. The structure of the desired product **289** was confirmed by the following transformation. Treatment of the crude reaction mixture of **289** and **290** from the above Birch reduction with $BF_3{\cdot}Et_2O$ and ethylene glycol in benzene[120] afforded cleanly a mixture of ketals **282** and **291** in a ratio of 10 : 1, respectively. The position of the double bond in ketal **282** was established by its mass spectrum (Figure 20), in which the base peak at *m/z* 86 corresponded to the fragment **293** (Scheme 51). This fragment resulted from the *retro*-Diels-Alder cleavage of ketal **282**. The ^1H NMR spectrum of **282** showed a narrow doublet at δ 1.69 for the methyl group and one olefinic multiplet at δ 5.93. This fact was consistent with structure **282** only. Since neither fractional distillation nor flash column chromatography on silica gel gave satisfactory separation of ketals **282** and **291**, it was decided to leave the separation until a later stage.

To this end, the mixture of ketals **282** and **291** was exposed to a large excess of $BF_3{\cdot}Et_2O$ and three equivalents of cyclobutene **77** following the general procedure for geminal acylation developed in this laboratory.[49] Since the ratio of **282** to **291** was 10 : 1 by GC-MS analysis before the reaction, we were surprised that what was obtained was a 4 : 1 (GC-MS ratio) mixture of spiro-diketones **281** and **292**. After careful flash column chromatography on silica gel, pure diketone **281** and a mixture of **292** and **281** were obtained in only 40% combined yield. The structure of **281** was confirmed by the following spectroscopic data. The IR spectrum showed a broad absorption maximum at 1716 cm^{-1} for the 1,3-cyclopentanedione moiety. In the ^1H NMR spectrum, a multiplet at δ 2.61-3.00 ppm with an integration of four protons was due to the four methylene protons adjacent to the carbonyls, and a one-proton multiplet at δ 5.40 and a singlet at δ 1.70 were

attributed to the olefinic proton and the methyl group, respectively. For the side product **292**, its mass spectrum showed a molecular ion at *m/z* 180. In its ^{1}H NMR spectrum a methyl doublet appeared at δ 0.94, but no olefinic signal was observed. Apparently, the geminal acylation reaction with ketal **291** was faster than that with ketal **282**. The reason for the difference is not understood. Our attempts to increase the ratio of the desired diketone **281** by changing the reaction conditions were unsuccessful. Since the yield for the preparation of compound **281** was low, we turned to an alternative route (see Scheme 52).

Scheme 51



282 **293**

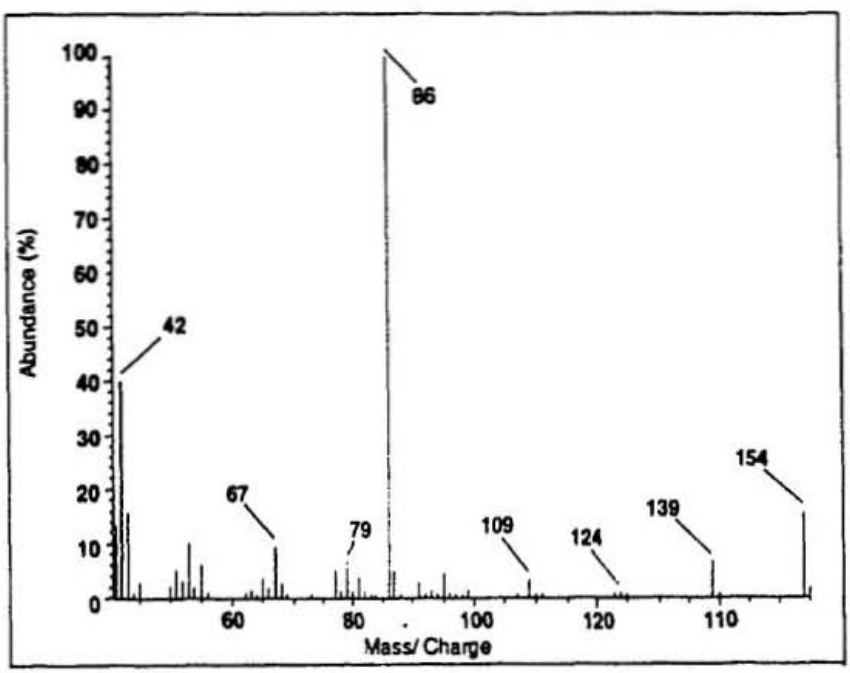
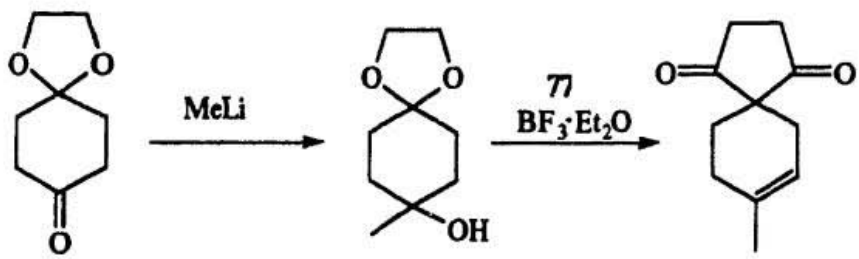


Figure 20. Mass spectrum (from GC-MS) of **282**

Addition of methyllithium to 1,4-cyclohexanedione *mono*-ethylene ketal (**294**), a commercially available starting material, produced the tertiary alcohol **295** in 89% yield along with 8% recovered starting material, which was recycled. Absorption maxima at 3400 cm^{-1} (broad) and 3260 cm^{-1} (sharp) in the IR spectrum of **295** corresponded to the hydrogen-bonded hydroxyl and the free hydroxyl, respectively. The two quarternary carbon resonances appeared at δ 108.6 and 68.6, of which the latter was due to the carbon bearing the hydroxyl group. Next, this ketal-alcohol was treated with $BF_3 \cdot Et_2O$ and cyclobutene **77** in dichloromethane following our general procedure for geminal acylation. After flash column chromatography on silica gel we obtained 78% yield of the diketone **281**. Clearly, $BF_3 \cdot Et_2O$ initiated both the geminal acylation of the ketal and the dehydration of the tertiary alcohol. Thus, the reaction of ketal-alcohol **295** with cyclobutene **77** provided an efficient approach to the spiro-diketone **281**.

Scheme 52

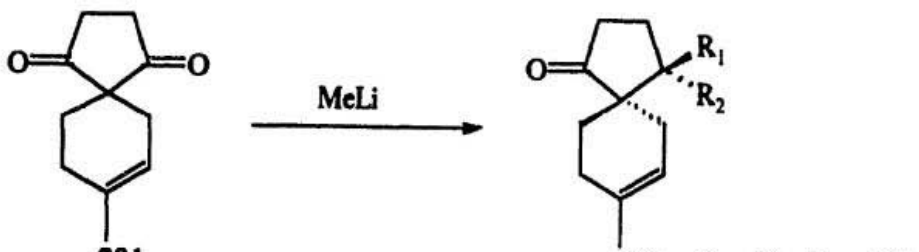


294 **295** **281**

The spiro-diketone **281** was treated with three equivalents of methyllithium in diethyl ether at -78°C. ^1H NMR spectrum of the crude product indicated a 4 : 1 mixture of isomeric alcohols, whose mass spectra were almost identical. Careful flash column chromatography of the crude product on silica gel furnished the major epimer, and the minor epimer along with a small amount of starting material. Both alcohols showed IR absorption maxima for a carbonyl: 1728 cm^{-1} for the major and 1723 cm^{-1} for the minor, and an hydroxyl: 3480 cm^{-1} for the major and 3499 cm^{-1} for the minor. The quarternary

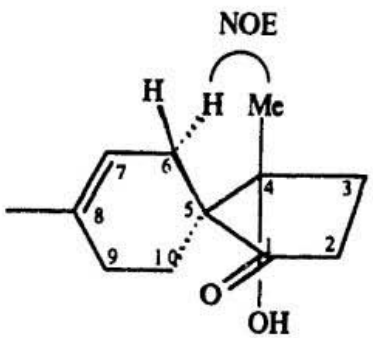
carbons connected to the hydroxyl groups in the major and the minor alcohols were located at δ 79.6 and 80.5, respectively, in their ^{13}C NMR spectra. The relative stereochemistry of these two adducts was assigned in the following way. Examination of molecular models of both isomers suggested that there could be a significant NOE between a C-6 hydrogen and the C-4 methyl with isomer **296a**, and between the C-10 hydrogens and the C-4 methyl of adduct **296b**. In the ^{1}H NMR spectrum of the major adduct, the olefinic proton's resonance appeared as a multiplet at δ 5.33. Then, the C-6 hydrogen signal were easily located at δ 2.93 by means of a COSY-90 spectrum This assignment was confirmed by the fact that saturation of the olefinic signal resulted in a 2% NOE at δ 2.93 (and a 1% NOE of the methyl signal at δ 1.67). When the C-4 methyl singlet at δ 1.27 was saturated, a 3% NOE of the C-6 hydrogens at δ 2.93 was observed (see Figure 21). This NOE established the *syn* relationship between the double bond and the C-4 methyl group. therefore, the major adduct was **296a**, and the minor adduct must have been compound **296b**. The facial selectivity observed in this case is noteworthy,

Scheme 53



281

296a: R_1 = Me; R_2 = OH
296b: R_1 = OH; R_2 = Me



296a

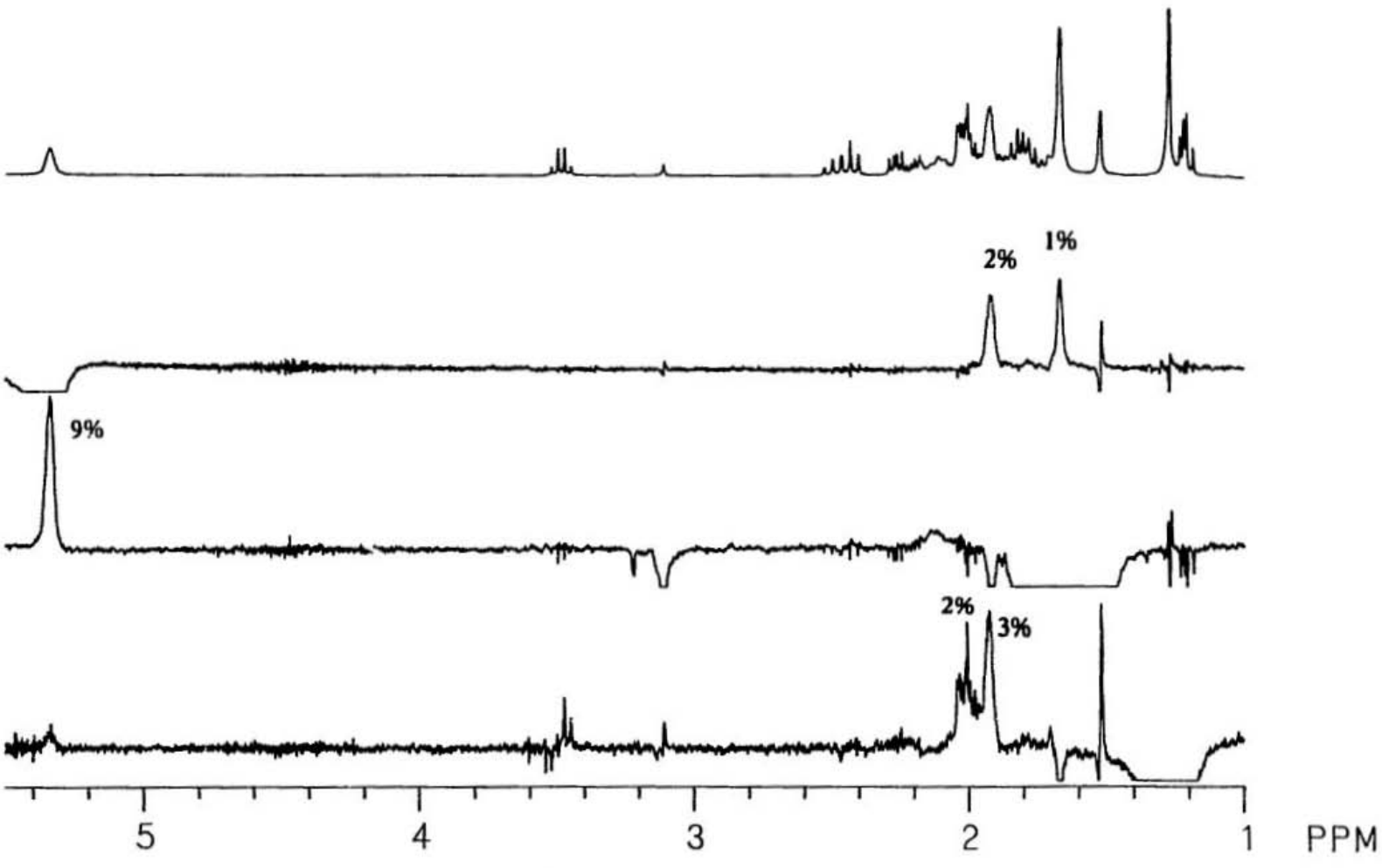
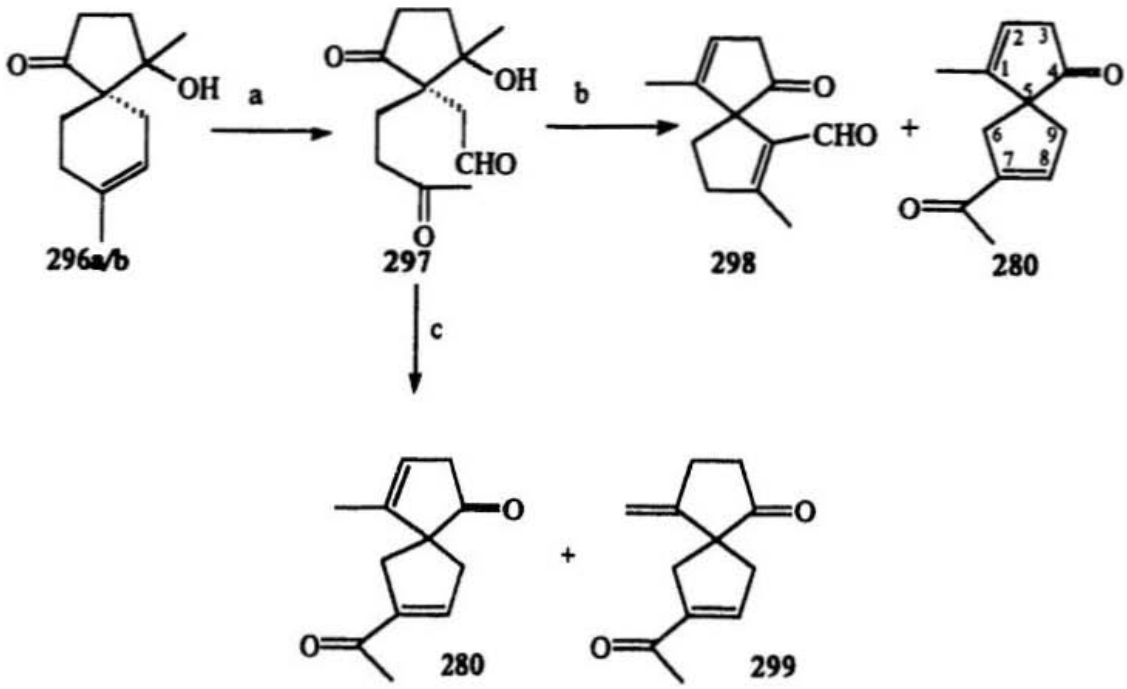


Figure 21. 1H NMR NOE spectra of 296a

and we have launched a systematic study of the facial selectivity involved in this type of spiro compound. The detailed results will be presented in Chapter Four of this thesis.

Although the isomeric alcohols **296a/b** could be separated by flash column chromatography, for our synthesis it was unnecessary to separate them. Thus, the mixture of the keto-alcohols **296a/b** was subjected to ozonolysis followed by reduction with dimethyl sulfide. The crude keto-aldehyde **297** was treated with *p*TSA in boiling benzene to afford a mixture of two products as shown by GC-MS analysis. The mass spectra of both products showed the same molecular ion at *m/z* 190, which suggested that these products were derived from **296a/b** by elimination of two molar equivalents of water. Using flash column chromatography on silica gel one product could be isolated, but the other could only be obtained in a mixture of both compounds. The ^{1}H NMR spectrum of the pure product showed a one-proton singlet at δ 9.81, indicative of an aldehyde. Integration of the olefinic region revealed only one proton and the two methyl groups appeared as a singlet at δ 2.24 and a double doublet at δ 1.63 in the ^{1}H NMR spectrum. This pure compound was therefore assigned structure **298**. Its IR absorption maxima were observed at 1740 cm^{-1} for the nonconjugated ring carbonyl and 1655 cm^{-1} for the conjugated carbonyl group. The assignment of the structure of the minor product was achieved in a similar fashion. A methyl singlet at δ 2.24 in its ^{1}H NMR spectrum and a base peak at *m/z* 43 in its mass spectrum implied a methyl ketone. Furthermore, a conjugated olefinic proton was found as a multiplet at δ 6.65. Thus structure **280** was assigned to the minor isomer. In order to confirm this assignment, a COSY-90 experiment was performed. As we expected, there was a strong cross peak between the conjugated olefinic proton (C-8 **H**) and the adjacent methylene protons (**CH$_2$** at C-9) (see structure **296a**). We were surprised to find that aldehyde **298** was the predominant product when **297** was treated with *p*TSA in boiling benzene. Since only the minor isomer **280** from the above reaction was useful for our synthesis, we examined other conditions.

Scheme 54

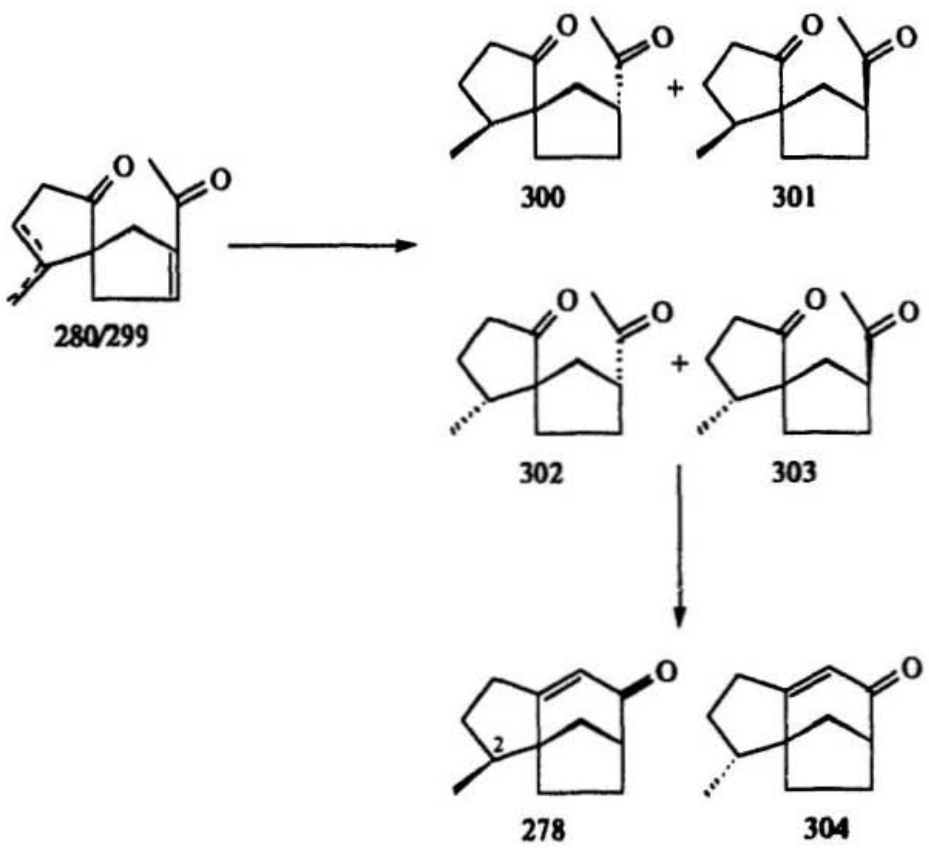


(a) O_3/Me_2S; (b) *p*TSA, C_6H_6; (c) Et_3N, MsCl

In general, an aldol condensation can be induced by employing either an acid or a base. As acidic conditions in our case resulted in the predominant formation of the undesired isomer (i.e., **298**), basic conditions were evaluated. However, compound **297** would very likely undergo *retro*-aldol reaction under strongly basic conditions due to the presence of the hydroxyl and carbonyl groups.[121] With this in mind, a mixture of mesyl chloride and triethylamine was used. It was hoped that this would initiate the elimination of the tertiary alcohol to allow cyclization to proceed. Indeed, no aldehyde **298** was formed when **297** was treated with the above reagents, but instead we obtained a 1 : 1 mixture of two inseparable products, one of which was **280** as revealed by comparing the spectra (^1H and ^{13}C NMR) of the mixture with those of the material we had obtained before. The structure of the other product was elucidated from its ^1H and ^{13}C NMR spectra

available by subtracting the signals due to **280** from those of the mixture. The ^{13}C NMR spectrum in combination with the APT spectrum showed four olefinic resonances: one methylene (δ 106.2), one methine (δ 144.1) and two quarternary carbons (δ 153.4 and 143.1), indicating **299** . The ^{1}H NMR spectrum revealed the nonconjugated olefinic protons as a double triplet and a quartet at δ 4.96 and 5.67. Structure **299** was assigned to this product. Since compound **299** could also be used for our synthesis these experimental conditions were satisfactory.

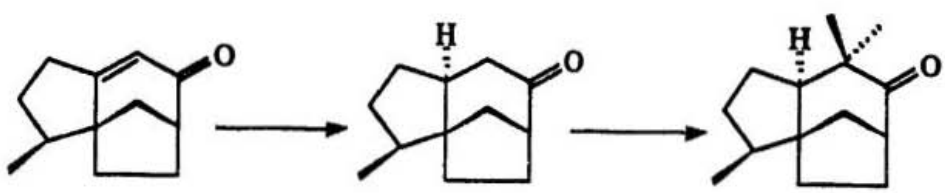
Scheme 55



Based on the results obtained during a synthetic study toward the total synthesis of pentalenene in our group,[118] direct cyclization of either **280** or **299** would be difficult due to ring strain. Catalytic hydrogenation of the mixture of **280** and **299** over 10% Pd-C

gave quantitatively mixtures each of which contained a pair of isomers, **300/301** and **302/303**, as identified by both GC-MS analysis and ^{13}C NMR spectra. The IR spectra of both mixtures showed absorption maxima at 1732 cm^{-1} for the ring carbonyls and 1708 cm^{-1} for the side chain carbonyls. All four isomers underwent aldol condensation with potassium *tert*-butoxide in benzene at room temperature to provide the cyclized products in a 78% yield after flash chromatography. Although only one spot appeared on the TLC plate, both GC-MS and ^{1}H NMR analysis indicated a 1 : 1.2 mixture of two isomers. These isomers had almost identical mass spectra. Not surprisingly, the two isomers proved to be very difficult to separate by flash column chromatography on silica gel Eventually, they could be separated by flash column chromatography on 20% silver nitrate-impregnated silica gel. For the major isomer, the IR spectrum showed an absorption maximum at 1676 cm^{-1} for the conjugated ring carbonyl. A three-proton doublet at δ 0.94 and a one-proton multiplet at δ 5.74 in its ^{1}H NMR spectrum were attributed to the methyl group and the olefinic hydrogen, respectively. Accordingly, the two olefinic and carbonyl resonances in its ^{13}C NMR spectrum were located at δ 180.7, 119.6 and 204.3. The IR spectrum of the minor isomer was very similar to that of the major one. However, its ^{1}H NMR spectrum showed the methyl doublet at δ 1.04, and the olefinic proton appeared as a singlet at δ 5.74. The remaining problem was the assignment of the relative stereochemistry at C-2. Unfortunately, NOE experiments on these two cyclization products were inconclusive. Thus, an alternative solution was sought.

Scheme 56



278 **232** **305**

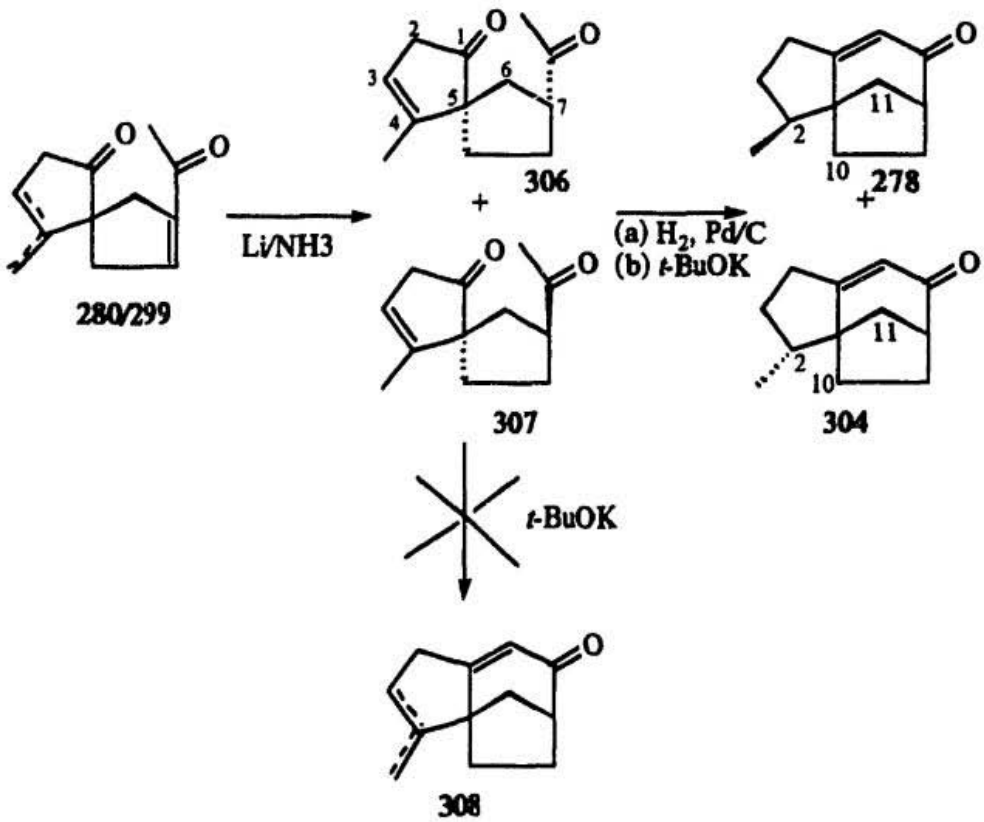
The relative stereochemistry of the cyclization products can be determined by conversion to known compounds. With this idea in mind, the major isomer was catalytically hydrogenated. After flash column chromatography on silica gel, the saturated ketone was obtained in quantitative yield. The ^{1}H NMR spectrum of the hydrogenation product indicated the complete disappearance of the olefinic proton signal, and the IR spectrum showed an absorption maximum at 1714 cm^{-1} for a carbonyl on a saturated ring. In the ^{1}H NMR spectrum, a methyl doublet was observed at δ 0.92. The ^{1}H NMR and IR spectra were consistent with those of compound **232** reported by Wiesner and coworkers.[109] It was thus clear that the minor product of the cyclization reaction was **278**. This assignment was corroborated by converting the hydrogenation product **232** into another known compound **305**, which had been previously prepared by Mori and coworkers.[115] The introduction of the geminal dimethyl groups into **232** was achieved by treatment with potassium hydride and an excess of iodomethane in THF.[122] Column chromatography of the crude product on silica gel provided **305** in 82% yield. The geminal methyl groups appeared as singlets at δ 1.17 and 1.05 in its ^{1}H NMR spectrum. The spectral data were indistinguishable from those of **305** reported by Mori *et al.*[115] Since the major isomer was unambiguously assigned as **304**, then the minor one must have been **278** (*vide infra*).

As the cyclization products **304** and **278** were formed in a ratio of 1.2 : 1, then it would be reasonable to pressume that the ratio of **300/301** to **302/303** was 1.2 : 1 as well. Alternatively, it could be pressumed that the facial selectivity of catalytic hydrogenation of the unconjugated double bond was 1.2 : 1. It was disappointing, but not surprising that this poor facial selectivity was observed, as the steric environment on both faces of the nonconjugated double bond seemed roughly the same. Since the ratio of the cyclization products (1.2 : 1) was not high enough for our synthesis, a Birch reduction sequence (Scheme 57) was evaluated.

Compound **280/299**, upon treatment with lithium in liquid ammonia, gave a mixture of several products. This mixture was oxidized with PCC. When the resulting mixture of

diketones (containing four isomers **306/307**) was treated with either a base or an acid, no cyclization to **308** was observed. The mixture of diketones was catalytically hydrogenated, and the resulting crude product was treated directly with potassium *tert*-butoxide in benzene. After column chromatography on silica gel, cyclization products **278** and **304** were obtained in a combined yield of 74%. The ratio of **278** to **304** was only sightly improved to 1.2 : 1.0, as revealed by both GC-MS and ^{1}H NMR analysis.

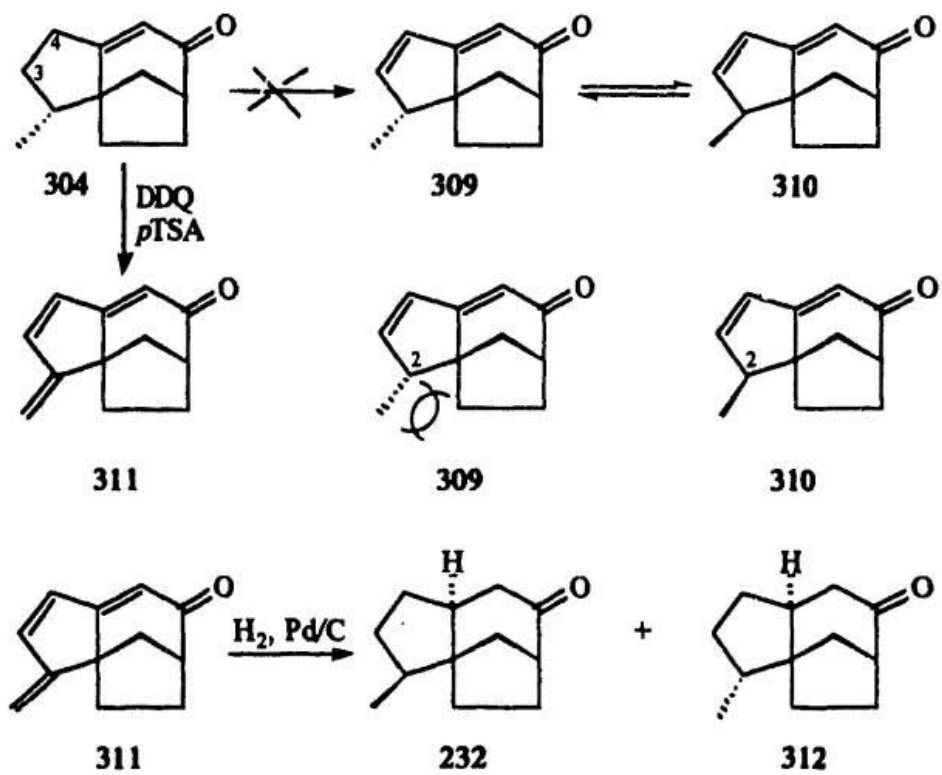
Scheme 57



Our next proposal to convert the undesired isomer **304** into the desired one originated from the different thermodynamic stabilities of the two isomers. Examination of the molecular models of **304** and **278** suggested that the steric interaction between the C-2 methyl and the C-10 methylene in **304** must be larger than that between the C-2 methyl and the C-11 methylene in **278**, which in turn suggested that **278** should be the

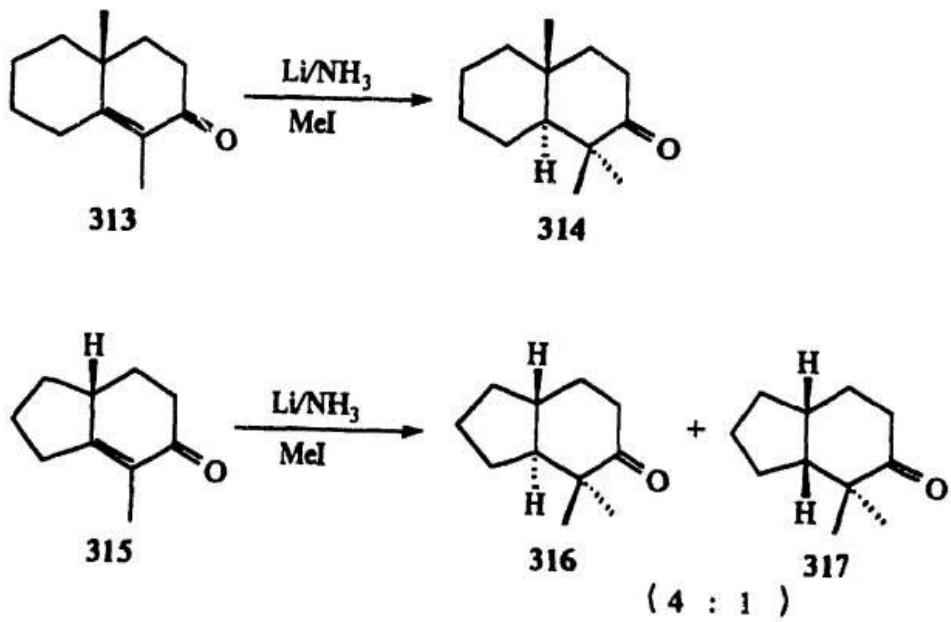
thermodynamically favored product. Epimerization at C-2 of **309** would require the introduction of a double bond between C-3 and C-4. Barton and coworkers[51] reported that benzeneselenic anhydride can be used to introduce a double bond next to a carbonyl. However, when a chlorobenzene solution of **304** was heated overnight with benzeneselenic anhydride, no formation of **309** was detected. It was decided to evaluate the use of DDQ in benzene since it had been successfully employed to prepare the 2,2-disubstituted cyclopent-2-ene-1,3-dione derivatives from their corresponding cyclopentane-1,3-diones for our π-facial selectivity studies (see Chapter 1). The reaction of **304** with DDQ in boiling benzene was fast, being complete in one hour. The resulting product appeared to be **311** (Scheme 58) as tentatively assigned according to its mass spectrum and ^{1}H NMR spectrum. Consequently, we were unable to make **309** for the proposed epimerization (**309** $\rightleftharpoons$ **310**). It should be mentioned that catalytic hydrogenation of **311** produced *ca.* a 1 : 1.2 ratio of **232** and its methyl epimer **312**.

Scheme 58

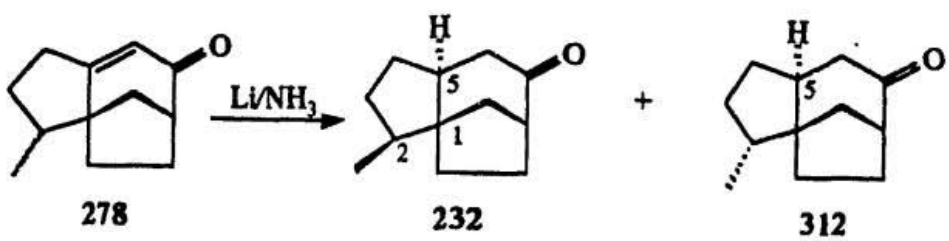


As hydrogenation of **278** gave the incorrect stereochemistry at C-5 relative to natural zizaene and prezizaene, a solution was sought which might alleviate this problem. Stork and coworkers[123] reported that reductive alkylation of octalone **313** (Scheme 59) gave **314** exclusively, while a 4 : 1 mixture of **316** and **317** was formed when tetrahydrindanone **315** was subjected to the same conditions. With this in mind, enone **278** was submitted to Birch reduction with lithium in liquid ammonia. Surprisingly, the same products as with catalytic hydrogenation were obtained (Scheme 60). The stereochemistry of **312** at C-5 was tentatively assigned.

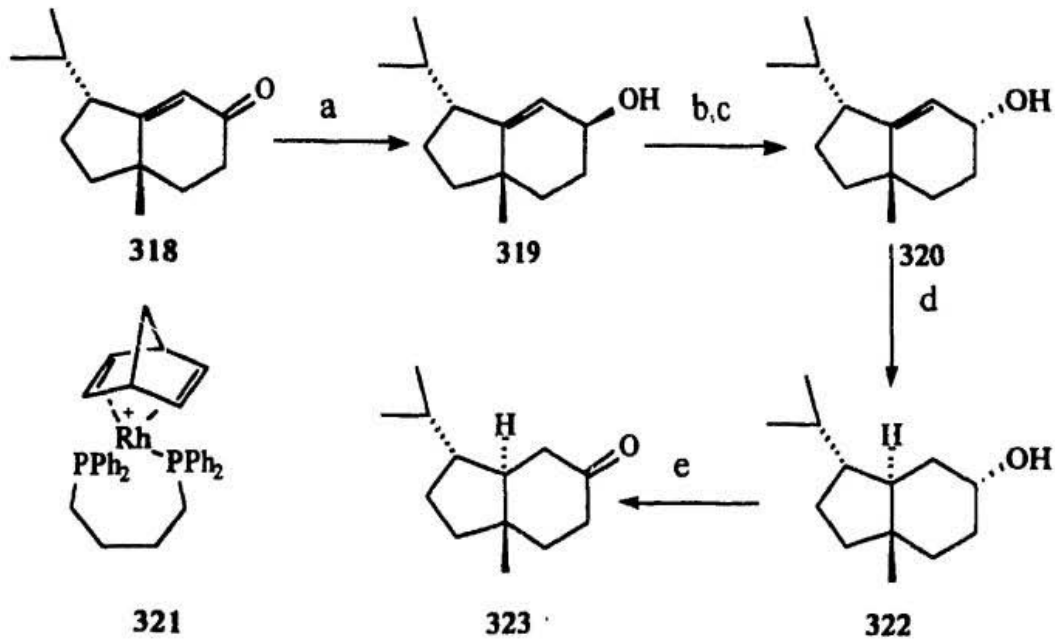
Scheme 59



Scheme 60



Scheme 61



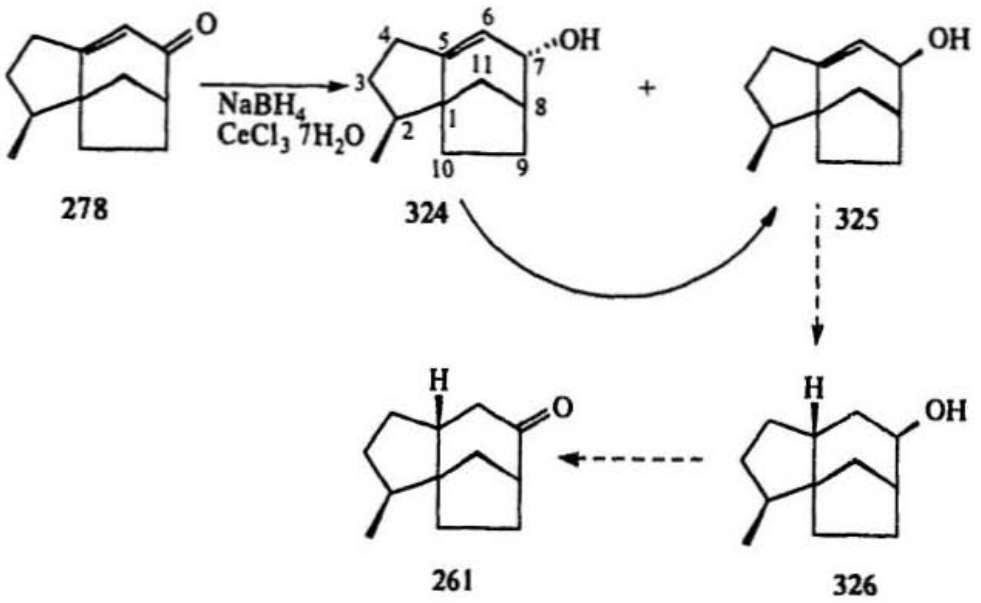
(a) $LiAlH_4$; (b) DEAD, PPh_3, PhCOOH; (c) K_2CO_3, MeOH; (d) H_2, **321**; (e) PCC; (f) $NaBH_4$.

Given the undesired stereochemistry at C-5 in **232**, an alternative route to the natural *trans* isomer **261** was considered. Evans and Morrissey[117] reported that some soluble rhodium (I) catalysts can effect hydroxyl-directed hydrogenations of unsaturated alcohols. For instance, the *trans* isomer **323** (Scheme 61) was required in the total synthesis of retigeranic acid.[124] The enone **318** was reduced to give alcohol **319**. Inversion of the alcohol center in **319** was effected *via* the Mitsunobu procedure. Hydrogenation of **320** with Evans' Rh (I) catalyst **321** in THF followed by Jones oxidation provided **323** *via* **322**. A similar strategy was applied by Mori *et al.*[115] to the syntheses of prezizaene and its family members. Thus, Mitsunobu reaction in combination with hydroxyl-directed hydrogenation appeared to be the solution to the stereochemical problem at C-5 in **232**.

Enone **278** (Scheme 62) was reduced with $NaBH_4$ in methanol with cerium (III)

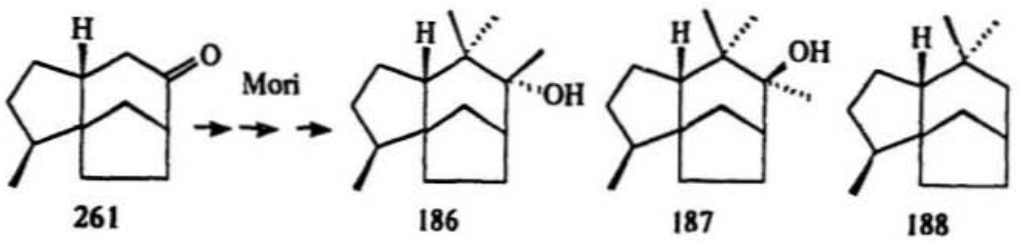
chloride at room temperature. Although GC-MS and TLC analysis showed only one compound, the ^{1}H NMR spectrum indicated a mixture of two isomers in a ratio of 9 : 1. In the ^{1}H NMR spectrum of the crude product, the vinyl hydrogen and the carbinol hydrogen in the major and minor isomers were located at δ 5.12 (quintet) and 4.57 (m), δ 5.18 (d) and 3.82 (m), respectively. In order to establish the relative stereochemistry of the hydroxyl in these two isomers, NOE experiments was performed. For the major isomer, saturation of the methyl doublet at δ 0.86 resulted in a 1.2% NOE of a multiplet in the region of δ 1.48 ppm. As shown by a ^{1}H-^{13}C correlation spectrum, this multiplet was due to hydrogens of a methylene group. Examination of molecular models of both possible isomers (i.e., **324** and **325**) suggested that this methylene could be one of C-3, C-4, or C-11. In addition, a 1% NOE was observed of the same multiplet at δ 1.48 when the signal due to the hydrogen at C-7 (δ 4.57) was saturated. Since both the C-3 and the C-10 methylenes are too far away from the carbinol hydrogen to experience this NOE, the multiplet at δ 1.48 must arise from the C-11 methylene hydrogens. Consequently, the carbinol hydrogen must be *cis* to the C-11 methylene hydrogens so that an NOE is possible. Therefore, the major isomer was assigned structure **324**, and, of course, the minor one could be only **325**. As the separation of both isomers was difficult by flash column chromatography on silica gel, it was hoped that the reduction of **278** would provide either **324** or **325**, but not both. Thus, **278** was again with reduced $NaBH_4/CeCl_3$ in methanol, but at -78°C. This time only **324** was formed as revealed by ^{1}H NMR. Alcohol **324** could be isolated in yields as high as 94%. Alcohol **324** was then treated with Mitsonobu reagents followed by hydrolysis with sodium methoxide in methanol according to the literature procedure.[125] After flash column chromatography on silica gel a 53% yield was obtained of the mixture of **325** and **324** in a 95 : 5 ratio as clearly indicated by ^{1}H NMR. It was hoped that hydrogenation of **325** with Evans' Rh (I) catalyst **321** will give the desired product **326**, which in turn might be oxidized by PCC to **261**. Since Mori *et al.* have directly converted **261** into prezizanol(**186**), prezizaene(**187**) and allokhusiol(**188**)

in a straightforward fashion (Scheme 63), our approach will constitute a formal syntheses of these natural products.

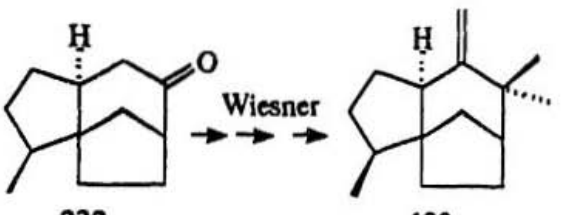


278 324 325 261 326

Scheme 63



261 186 187 188



232 190

As mentioned earlier, compound **232** possessed the incorrect stereochemistry at C-5 with respect to natural zizaene. Nevertheless, Wiesner and coworkers did manage to transform this compound into zizaene(**190**) in a few steps. Thus **232** should serve as a precursor to zizaene as well. The shortcoming associated with our synthesis lies in the relatively low stereochemical control at C-2 methyl group, but our approach was quite short and the yield in each step is high. The strategy developed in this synthetic study provides a novel entry to both zizaene and prezizaene sesquiterpenoids, and it further demonstrates the synthetic use of the geminal acylation reaction for the total synthesis of natural products.

III Experimental*

1-Methoxy-4-methyl-1,4-cyclohexadiene (289)

4-Methylanisole (**288**) (3.20 g, 26.2 mmol) was dissolved in THF (10 mL) and added to liquid ammonia (40 mL) at -40°C. To this mixture was added freshly cut lithium metal (0.18 g, 26.2 mmol) in portions and the resulting blue solution was stirred for 30 min at -40°C before solid NH_4Cl was added (until the blue color disappeared). After warming to room temperature the solvents were removed *in vacuo*. The pale yellow residue was extracted with ether (×4), and the combined organic extracts were washed with water and saturated NaCl, then dried ($MgSO_4$), and concentrated to give 3.07 g of crude product as a yellow oil. GC-MS analysis of this crude product indicated that it was a mixture of the desired product **289** and over-reduced product **290** in a *ca.* 10 : 1 ratio. This crude product was used for next step without purification. For **289**: MS (from GC-MS) *m/z* (%): 124 (47, M^+), 110 (44), 109 (95), 81 (37), 79 (40), 68 (73), 67 (100), 53 (65), 51 (31), 42 (23), and 41 (62); for **290**: MS (from GC-MS) *m/z* (%): 126 (8, M^+), 84 (47), 83 (26), 56 (39), 55 (100), 45 (38), 44 (27), 43 (71), 42 (40), and 41 (76).

8-Methyl-1,4-dioxaspiro[4.5]dec-7-ene (282)

To a solution of the crude material obtained above (3.07 g) and ethylene glycol (10 mL, excess) in THF (40 mL) was added $BF_3{\cdot}Et_2O$ (1.0 mL) with cooling in an ice bath under nitrogen. After stirring for 20 min the residue was poured into cold $NaHCO_3$ solution (40 mL) and extracted with four portions of ether. The combined extracts were washed with water and saturated NaCl, dried over $MgSO_4$ then concentrated to give a colorless oil, which was purified by flash chromatography (1% ethyl acetate in hexane) to afford a product containing 90% of the desired ketal **282** along with 10% of **291** as a

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* For General Procedures, see Chapter 1: Experimental Section

colorless oil (3.39 g, 84% overall yield from **288**): IR (film) ν_{max}: 2928 (s) and 1447 (m) cm^{-1}; for **282**: ^1H NMR δ: 1.69 (br s, 3H), 1.76 (t, J = 6.6 Hz, 2H), 2.16 (apparent t, J = 6.3 Hz, 2H), 2.22 (br s, 2H), 3.96 (s, 4H), and 5.30 (m, 1H); ^{13}C NMR δ: 22.9 (3), 29.0 (2), 30.8 (2), 35.3 (2), 64.1 (2C, 2), 107.7 (0), 118.3 (1), and 133.4 (0); MS (from GC-MS) *m/z* (%): 154 (16, M^+), 86 (100), 53 (10), 43 (16), 42 (40), and 41 (14). For **291**: ^1H NMR δ: 0.91 (d, J = 6.3 Hz, 3H), 1.20-1.65 (m, 9H), and 3.92 (s, 4H); ^{13}C NMR δ: 21.4 (3), 31.1 (1), 32.0 (2C, 2), 34.3 (2C, 2), 63.8 (2C, 2), and a quaternary carbon was not found due to its low intensity; MS (from GC-MS) *m/z* (%): 156 (1, M^+), 99 (100), 86 (21), 55 (35), 42 (18), and 41 (18).

8-Methylspiro[4.5]dec-7-ene-1,4-dione (281)

The ethylene ketal mixture **282** and **291** (215 mg, 1.42 mmol) was treated with $BF_3{\cdot}Et_2O$ (2.6 mL, 21 mmol) and the cyclobutene **77** (1.1 mL, 4.2 mmol) following our standard procedure.[49] Flash chromatography (4% ethyl acetate in hexane) provided 85 mg (34%) of the desired diketone **281** as colorless crystals and 30 mg of a mixture of **281** and **292**. For **281**: mp 76-77°C; IR (film) ν_{max}: 1716 (s) and 1410 (m) cm^{-1}; ^1H NMR δ: 1.70 (br s, 3H), 1.75 (t, J = 6.3 Hz, 2H), 2.02 (apparent t, J = 5.7 Hz, 2H), 2.13 (sextet, J = 2.1 Hz, 2H), 2.61-3.00 (m, 4H), and 5.40 (m, 1H); ^{13}C NMR δ: 23.3 (3), 25.7 (2), 26.7 (2), 27.6 (2), 34.2 (2C, 2), 55.1 (0), 116.7 (1), 132.8 (0), and 214.7 (2C, 0); MS (from GC-MS) *m/z* (%): 178 (62, M^+), 149 (25), 136 (22), 135 (100), 121 (34), 107 (31), 94 (21), 93 (35), 91 (45), 57 (21), 55 (43), 53 (41), 51 (29), 43 (24), and 41 (39). *Exact mass* calcd. for $C_{11}H_{14}O_2$: 178.0993; found: 178.0991. For **292**: MS (from GC-MS) *m/z* (%): 180 (38, M^+), 124 (29), 112 (50), 111 (28), 85 (32), 81 (77), 79 (28), 68 (29), 67 (54), 56 (51), 55 (100), 53 (58), 45 (24), 42 (38), and 41 (99).

8-Methyl-1,4-dioxaspiro[4.5]decan-8-ol (295)

To a solution of 1,4-cyclohexanedione *mono*-ethylene ketal **294** (2.40 g, 15.6 mmol) in anhydrous ether (80 mL) was added 1.4 M methyllithium solution in ether (13.4 mL,

18.7 mmol) at -78°C. The reaction mixture was stirred for another at two hours at -78°C before water was added. The aqueous layer was extracted with ether (×3). The combined organic extracts were washed with water and saturated NaCl, then dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography (8% ethyl acetate in hexane) to provide **295** (2.43 g, 91%) as colorless crystals and recovered starting material **294** (0.19 g, 7%): For **295**: mp 68-69°C; IR (film) ν_{max}: 3300 (br) and 3263 (sharp) cm^{-1}; ^1H NMR δ: 1.25 (s, 3H), 1.54-1.72 (m, 6H), 1.80 (s, OH), 1.84-1.94 (m, 2H), and 3.94 (m, 4H); ^{13}C NMR δ: 29.6 (3), 30.6 (2C, 2), 36.5 (2C, 2), 64.0 (2C, 2), 68.6 (0), and 108.6 (0); MS (from GC-MS) *m/z* (%): 172 (0.5, M^+), 100 (85), 99 (100), 86 (56), 71 (13), 55 (24), and 42 (15).

Spiro-diketone 281 from ketal alcohol 295

The ketal alcohol **295** (1.53 g, 9.94 mmol) was treated with $BF_3{\cdot}Et_2O$ (18.3 mL, 149 mmol) and the cyclobutene **77** (7.9 mL, 30 mmol) according to the standard procedure. Purification of the crude reaction mixture by flash chromatography (5% ethyl acetate in hexane) afforded **281** (1.23 g, 78%) as colorless crystals. All spectra of this compound were indistinguishable from those of spiro-diketone prepared from ketal **282**.

(4*R,5*S**)- (296a) and (4*R**,5*R**)-4-Hydroxy-4,8-dimethylspiro[4.5]dec-7-en-1-one (296b)**

To a solution of diketone **281** (603 mg, 3.39 mmol) in anhydrous ether (40 mL) was added 1.4 M methyllithium solution in ether (4.8 mL, 6.78 mmol) at -78°C. The reaction mixture was stirred for another two hours at -78°C before water was added. The aqueous layer was extracted with ether (×4). The combined organic extracts were washed with water and saturated NaCl, then dried over $MgSO_4$ and concentrated *in vacuo*. Chromatography (6% ethyl acetate in hexane) of the residue gave 454 mg of **296a** (69%), 131 mg of **296b** (20%) and 42 mg of recovered diketone **281** (6%), each as colorless crystals. For **296a**: mp 67-68°C; IR (film) ν_{max}: 3480 (br) and 1728 (s) cm^{-1}; ^1H NMR δ: 1.27 (s,

3H), 1.67 (br s, 3H), 1.68-2.04 (m, 7H including a multiplet at 1.92 for two hydrogens and OH), 2.00-2.24 (m, 3H), 2.38-2.54 (m, 1H), and 5.31 (narrow d, J = 1.5 Hz, 1H); NOE data ($CDCl_3$): irradiate 5.31: NOE at 1.67 (1%), 1.92 (2%); irradiate 1.67: NOE at 5.31 (9%); irradiate 1.27: NOE at 1.92 (3%); ^{13}C NMR δ: 23.0 (2), 23.3 (3), 24.5 (3), 27.00 (2), 28.5 (2), 34.0 (2), 34.3 (2), 53.7 (0), 79.6 (0), 117.7 (1), 134.0 (0), and 220.6 (0); MS (from GC-MS) *m/z* (%): 194 (10, M^+), 136 (57), 121 (26), 119 (18), 118 (37), 93 (25), 91 (24), 79 (23), 77 (25), 55 (23), 43 (100), and 41 (25). *Exact mass* calcd. for $C_{12}H_{18}O_2$: 194.1306; found: 194.1310. For **296b**: mp 98-99°C; IR (film) ν_{max}: 3499 (br) and 1723 (s) cm^{-1}; ^1H NMR δ: 1.28 (s, 3H), 1.48-1.65 (m, 2H), 1.68 (br s, 3H), 1.86-2.18 (m, 7H including OH), 2.34-2.40 (m, 2H), and 5.46 (m, 1H); ^{13}C NMR δ: 22.6 (3), 23.3 (3), 25.2 (2), 26.8 (2), 33.3 (2), 33.6 (2), 54.3 (0), 85.5 (1), 118.8 (1), 133.2 (0), and 219.9 (0); MS: essentially the same as for **296a**. *Exact mass* calcd. for $C_{12}H_{18}O_2$: 194.1306; found: 194.1307.

3-Hydroxy-3-methyl-2-(3-oxobutyl)-2-(2-oxoethyl)cyclopentan-1-one

Ozone was passed through a solution of alcohols **296a/b** (254 mg, 1.3 mmol) in dichloromethane (40 mL) at -78°C until the blue color persisted. The excess ozone was removed by bubbling oxygen through the solution until the blue color disappeared. The reaction system was purged with nitrogen to remove the remaining oxygen. Then dimethyl sulfide (3 mL) was introduced, and the reaction mixture was stirred overnight during which time the reaction was allowed to attain room temperature. Evaporation of the solvent *in vacuo* gave crude **297** (91% pure by GC-MS analysis) as a yellow oil: MS (from GC-MS) *m/z* (%): 226 (1, M^+), 165 (12), 147 (10), 141 (11), 110 (10), 109 (18), 99 (39), 71 (11), 55 (14), 43 (100), and 41 (10).

6-Formyl-4,7-dimethylspiro[4.4]nona-3,6-dien-1-one (298)

The solution of crude **297** obtained above and a catalytic amount of *p*TSA (50 mg) in benzene (40 mL) was heated to reflux with a Barrett water-separator for two hours.

Saturated $NaHCO_3$ was added when the reaction had cooled to near room temperature. The aqueous layer was extracted with ether (×3). The combined organic extracts were washed with saturated $NaHCO_3$, water and saturated NaCl then dried over $MgSO_4$. After concentration *in vacuo* the brown residue was purified by flash chromatography (4% ethyl acetate in hexane) to afford 77 mg of **298** (31%) as slightly yellow oil and 113 mg of a mixture of **298** and **280** (45%) in a 1 : 1.2 ratio. For **298**: IR (film) ν_{max}: 1739 (s), 1654 (s), and 1620 (m) cm^{-1}; ^1H NMR δ: 1.63 (dd, J = 1.7, 2.4 Hz, 3H), 1.80-2.17 (m, 2H), 2.23 (s, 3H), 2.69 (m, 2H), 2.86 (dt, J = 3.3, 22.9 Hz, 1H), 3.24 (dt, J = 2.4, 22.9 Hz, 1H), 5.74 (q, J = 1.8 Hz, 1H), and 9.08 (s, 1H); ^{13}C NMR δ: 15.3 (3), 16.0 (3), 33.0 (2), 40.7 (2), 43.5 (2), 69.2 (2), 122.3 (1), 139.9 (0), 143.4 (0), 167.6 (0), 187.3 (1), and 221.4 (0); MS (from GC-MS) *m/z* (%): 190 (55, M^+), 147 (73), 133 (21), 119 (100), 105 (40), 91 (73), 79 (31), 77 (54), 65 (28), 53 (33), 51 (42), 50 (14), and 41 (46). *Exact mass* calcd. for $C_{12}H_{14}O_2$: 190.0993; found: 190.0984.

7-Acetyl-4-methylspiro[4.4]nona-3,7-dien-1-one (280) and 7-acetyl-4-methylene-spiro[4.5]non-7-en-1-one (299)

To a solution of crude **297** obtained from alcohols **296a/b** (206 mg, 1.06 mmol) in CH_2Cl_2 (20 mL) was added triethylamine (3 mL) followed by methanesulfonyl chloride (0.5 mL, excess) dropwise at 0°C. The reaction mixture was stirred for one hour at room temperature. Then the reaction mixture was poured into 50 mL of water. The aqueous layer was extracted with CH_2Cl_2 (×3). The combined organic extracts were washed with 1 N HCl, water and saturated NaCl then dried over $MgSO_4$. After concentration *in vacuo*, the residue was purified by flash chromatography (5% ethyl acetate in hexane) to provide an inseparable mixture of **280** and **299** (138 mg, 68% total yield from alcohols **296a/b**) as a colorless oil. IR (film) ν_{max}: 1742 (s), 1664 (s), and 1630 (m) cm^{-1}; For **280**: ^1H NMR δ (from the mixture): 1.71 (q, J = 2.4 Hz, 3H), 2.34 (s, 3H), 2.40-3.42 (m, 6H), 5.67 (t, J = 1.8 Hz, 1H), and 6.65 (m, 1H); ^{13}C NMR δ: 13.5 (3), 26.3 (3), 27.3 (2), 38.9 (2), 41.4 (2), 57.5 (0), 119.5 (0), 140.7 (0), 143.1 (0), 153.4 (0), 195.4 (0), and 218.7

(0); MS (from GC-MS) *m/z* (%): 190 (0.2, M^+), 162 (15), 119 .23), 91 (24), 43 (100), and 41 (15). For **299**: ^{1}H NMR δ (from the mixture): 2.34 (s, 3H), 2.40-3.42 (m, 8H), 4.90 (t, J = 1.8 Hz, 1H) 5.01 (t, J = 1.8 Hz, 1H), and 6.66 (m, 1H); ^{13}C NMR δ: 27.7 (3), 39.0 (2), 41.0 (2), 42.2 (2), 43.2 (2), 58.6 (0), 106.2 (1), 140.9 (0), 142.1 (0), 144.1 (0), 195.4 (0), and 220.5 (0); MS: essentially the same as **280**. *Exact mass* calcd. for $C_{12}H_{14}O_2$: 190.0993; found: 190.0993.

(4*R,5*S**,7*S**)- (300), (4*R**,5*S**,7*R**)- (301), (4*R**,5*R**,7*R**)- (302), and (4*R**,5*R**,7*S**)-7-Acetyl-4-methylspiro[4.4]nonan-1-one (303)**

To a solution of the mixture of **280** and **299** (213 mg, 1.12 mmol) in methanol (30 mL) was added 10% palladium on charcoal (50 mg). After shaking for one hour under H_2 (50 psi) the black suspension was filtered to remove the catalyst, and the filtrate was concentrated. Flash chromatography of the residue (5% ethyl acetate in hexane) provided 60 mg (27%) of the minor products (which were a pair of epimers at C-2, either **300/302** or **301/303**, in a 1 : 1.2 ratio) and 144 mg (66%) of the major products (which were also a pair of epimers at C-2, **301/303** or **300/302**, in a 1 : 1.2 ratio) in that order of elution as colorless oils. For the minor products: IR (film) ν_{max}: 1733 (s) and 1709 (s) cm^{-1}; ^{1}H NMR δ: 1.01 (d, J = 6.3 Hz, 6H), 1.28-2.40 (m, 28H including two singlets at 2.18 and 2.17 for two methyl groups), 3.08-3.22 (m, 2H); ^{13}C NMR (**300/301** or **301/303**) δ: 15.2/14.4 (3), 27.4/27.7 (2), 27.9/28.2 (2), 29.2/29.2 (1), 30.3/28.6 (2), 34.8/32.9 (2), 35.4/35.4 (2), 40.3/40.1 (3), 51.5/51.3 (0), 59.8/59.5 (0), 210.2/210.1 (0), and 223.0/222.4 (0); MS (from GC-MS) *m/z* (%): 194 (6, M^+), 133 (16), 111 (57), 95 (21), 67 (22), 55 (25), 43 (100), and 41 (30). *Exact mass* calcd. for $C_{12}H_{18}O_2$: 194.1306; found: 194.1306. For the major products (**301/303** or **300/302**): IR (film) ν_{max}: 1732 (s) and 1709 (s) cm^{-1}; ^{1}H NMR δ: 1.01 (d, J = 2.7 Hz, 3H), 1.03 (d, J = 2.4 Hz, 3H), 1.40-2.41 (m, 28H including two singlets at 2.17 and 2.19 for two methyl groups), 2.78-2.90 (m, 2H); ^{13}C NMR (**300/302** or **301/303**) δ: 14.9/14.8 (3), 27.3/27.4 (2), 28.0/28.2 (1), 28.3/28.5 (2), 28.8/31.0 (2), 35.0/34.6 (2), 35.5/35.2 (2), 40.6/40.5 (3), 53.1/52.8 (1),

59.2/59.2 (0), 209.4/209.3 (0), and 222.1/221.5 (0). MS essentially the same as for the minor isomers. *Exact mass* calcd. for $C_{12}H_{18}O_2$: 194.1306; found: 194.1299.

($1R^*,2R^*,8R^*$)- (278) and ($1R^*,2S^*,8R^*$)-2-Methyltricyclo[6.2.1.0^{1,5}]undecan-5-en-7-one (304)

To a solution of epimers **300/302** and **301/303** (190 mg, 0.98 mmol) in dry benzene (30 mL) was added potassium *tert*-butoxide (220 mg, 1.96 mmol) at room temperature, and the reaction was closely monitored by TLC. When TLC showed the complete conversion (roughly 20 min), water was added. The aqueous layer was extracted with ether (×3). The combined organic extracts were washed with water and saturated NaCl, then dried over $MgSO_4$. Concentration *in vacuo* gave a slightly yellow oil, which was purified by flash chromatography (5% ethyl acetate in hexane) to provide a mixture of epimers **278** and **304** (119 mg, 70%) in a 1 : 1.2 ratio. For the separation of these isomers and their spectral data see below.

($1R^*,2R^*,5R^*,8R^*$)-2-Methyltricyclo[6.2.1.0^{1,5}]undecan-7-one (232)

The tricyclic enone **278** (88 mg, 0.50 mmol), dry benzene (30 mL) and 10% palladium on carbon (50 mg) was shaken under 50 psi of hydrogen for one hour. The resulting suspension was filtered through a silica gel plug and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (6% ethyl acetate in hexane) to give of **232** (80 mg, 91%) as a colorless oil: IR (film) ν_{max}: 1714 (s) cm^{-1}; ^{1}H NMR δ: 0.92 (d, J = 6.6 Hz, 3H), 1.26-1.60 (m, 5H), 1.67-2.42 (m, 7H), 2.13 (dd, J = 4.5, 17.4 Hz, 1H), 2.52 (dd, J = 8.4, 17.7 Hz, 1H), and 2.66 (dd, J = 5.1, 7.8 Hz, 1H); ^{13}C NMR δ: 14.0 (3), 26.6 (2), 30.3 (2), 32.0 (2), 32.1 (2), 32.8 (2), 38.5 (1), 39.7 (2), 44.9 (1), 49.3 (1), 52.5 (0), and 215.7 (0); MS (from GC-MS) *m/z* (%): 178 (23, M^+), 135 (24), 134 (36), 108 (21), 107 (46), 95 (30), 94 (43), 93 (75), 91 (43), 81 (36), 80 (33), 79 (77), 77 (46), 68 (40), 67 (81), 65 (26), 55 (65), 53 (36), and 41 (100). *Exact mass* calcd. for $C_{12}H_{18}O$: 178.1357; found: 178.1353.

($1R^*,2R^*,5R^*,8R^*$)-2,6,6-Trimethyltricyclo[6.2.1.0^{1,5}]undecan-7-one (305)

A flask was charged with KH (35% w/w dispersion in mineral oil) (155 mg, 1.36 mmol), which was washed with hexane three times. The flask was then immersed in a water bath maintained at 25°C. THF (30 mL) was introduced followed by dropwise addition of the tricyclic ketone (81 mg, 0.45 mmol) in 4 mL of THF. After 5 min of stirring, iodomethane (0.5 mL, excess) was added dropwise. The reaction mixture was stirred for another 30 min then treated cautiously with 5 mL of water. The aqueous layer was extracted with ether (×3), and the combined organic layers were washed with saturated NaCl and dried over anhydrous K_2CO_3. After concentration *in vacuo*, the residue was purified by flash chromatography (4% ethyl acetate in hexane) to provide (77 mg, 82%) of **305** as a colorless oil: IR (film) ν_{max}: 1704 cm^{-1}; ^{1}H NMR δ: 0.90 (d, J = 6.9 Hz, 3H), 1.05 (s, 3H), 1.17 (s, 3H), 1.99-1.21 (m, 12H), and 2.73 (dd, J = 4.5 Hz, 1H); ^{13}C NMR δ: 14.5 (3), 24.5 (3), 25.9 (2), 27.2 (2), 30.6 (2), 31.1 (2), 31.7 (0), 32.9 (3), 37.1 (2), 38.6 (1), 50.1 (1), 53.5 (0), 57.3 (1), and 220.0 (0); MS (from GC-MS) *m/z* (%): 206 (12, M$^+$), 135 (23), 95 (21), 94 (46), 93 (34), 91 (25), 82 (26), 81 (22), 79 (41), 77 (26), 69 (36), 67 (51), 55 (46), 53 (23), 43 (22), and 41 (100). *Exact mass* calcd. for $C_{14}H_{22}O$: 206.1670; found: 206.1686.

($5R^*,7S^*$)- (306) and ($5R^*,7R^*$)-7-Acetyl-4-methylspiro[4.4]non-3-en-1-one (307)

To lithium (40 mg, excess) in liquid ammonia (30 mL) at -78°C was added a solution of **280/299** (142 mg, 0.75 mmol) in THF (5 mL). The reaction temperature was raised to -35°C, and the mixture was stirred for *ca*. 30 min, whereupon solid NH_4Cl was added cautiously (the blue color disappeared immediately), and the ammonia was allowed to evaporate overnight. The residue was extracted with ether (×3). The combined organic extracts were washed with water and saturated NaCl, then dried over $MgSO_4$, and concentrated *in vacuo*. The resulting crude product was treated with pyridinium chlorochromate (650 mg, 3.0 mmol) in CH_2Cl_2 (30 mL) overnight. Filtration through a Florisil pad removed a black precipitate, and five volumes of ether were passed through

the pad. The combined solutions were concentrated *in vacuo* to give an oily product (**306/307**) (126 mg, 87%), which was used for next step without separation: MS of the mixture (from GC-MS) *m/z* (%): 192 (22, M^+), 164 (35), 149 (30), 121 (51), 119 (23), 105 (26), 93 (41), 91 (36), 79 (44), 77 (31), 55 (25), 43 (100), and 41 (24).

6-Acetyl-4-methylspiro[4.4]nonan-1-one (300-303) from the Birch reduction route

To a solution of the crude material obtained above (126 mg) in anhydrous methanol (30 mL) was added 10% palladium on charcoal (50 mg) slowly. After shaking for one hour under hydrogen (50 psi) the solution was filtered to remove the catalyst, and the filtrate was concentrated *in vacuo*. Flash chromatography (6% ethyl acetate in hexane) of the residue provided two components (the major: 80 mg, 63%; the minor: 31 mg, 24%) which contained the same epimers as the products obtained by direct hydrogenation. The spectroscopic data were identical with those obtained by direct hydrogenation.

2-Methyltricyclo[6.2.1.$0^{1,5}$]undec-5-en-7-one (278 and 304) from the Birch reduction route

To a solution of epimers **300/302** and **301/303** (98 mg, 0.51 mmol) in dry benzene (30 mL) was added potassium *tert*-butoxide (114 mg, 1.01 mmol) at room temperature, and the reaction was monitored by TLC. When TLC showed complete conversion (roughly 20 min), water was added. The aqueous layer was extracted with ether (×3). The combined organic extracts were washed with water and saturated NaCl, then dried over $MgSO_4$. Concentration *in vacuo* gave a slightly yellow oil which was purified by flash chromatography (5% ethyl acetate in hexane) to provide a mixture of two epimers **278** and **304** (64 mg, 72%), but in a 1.2 : 1 ratio. The spectroscopic data were indentical with those obtained by the direct hydrogenation route.

Preparation of 20% silver nitrate-impregnated silica gel

All operations were performed in the dark since silver nitrate is sensitive to light. To

a 250 mL round-bottomed flask containing silica gel (30 g) was added an aqueous solution of silver nitrate (prepared from 7.5 g of silver nitrate and 10 mL of deionized water), and a minimum amount of deionized water was added until all the silica gel was soaked. The flask was shaken and the resulting slurry was evaporated *in vacuo* until most of the water was removed. The flask was then placed in an oven maintained at 135°C for overnight. After cooling the 20% silver nitrate-impregnated silica gel was ready to use.

Separation of the epimers of 2-methyltricyclo[6.2.1.0^{1,5}]undecan-7-one (278 and 304)

A 1.2 : 1 mixture of **278** and **304** (148 mg) was chromatographed on 20% silver nitrate-impregnated silica gel with 2% ethyl acetate in hexane as the eluent to provide **278** (48 mg, 32%) and **304** (29 mg, 20%) with the remainder as a mixture of **278** and **304** in *ca.* 1 : 1 ratio. For **278**: IR (film) ν_{max}: 1677 (s) cm^{-1}; ^{1}H NMR δ: 0.94 (d, J = 6.9 Hz, 3H), 1.47-1.62 (m, 3H), 1.71-1.82 (m, 3H), 1.99-2.20 (m, 3H), 2.56-2.62 (m, 2H), 2.88-2.92 (m, 1H), and 5.74 (q, J = 1.8 Hz, 1H); ^{13}C NMR δ: 16.7 (3), 25.5 (2), 30.4 (2), 32.6 (2), 36.0 (2), 39.5 (1), 40.3 (2), 50.2 (1), 57.0 (0), 119.6 (0), 180.7 (0), and 204.3 (0); MS (from GC-MS) *m/z* (%): 176 (42, M$^+$), 135 (100), 133 (22), 105 (17), 91 (35), 79 (22), 77 (16), and 41 (15). *Exact mass* calcd. for $C_{12}H_{16}O$: 176.1200; found: 176.1204. For **304**: IR (film) ν_{max}: 1678 cm^{-1}; ^{1}H NMR δ: 1.04 (d, J = 6.6 Hz, 3H), 1.37-1.63 (m, 3H), 1.71-1.84 (m, 3H), 1.98-2.17 (m, 3H), 2.42-2.66 (m, 2H), 2.83-2.86 (m, 1H), and 5.72 (q, J = 1.8 Hz, 1H); ^{13}C NMR δ: 16.6 (3), 25.3 (2), 26.0 (2), 32.3 (2), 32.4 (2), 38.8 (1), 42.0 (2), 49.5 (1), 56.2 (0), 119.4 (0), 180.9 (0), and 204.1 (0); MS essentially the same as for **278**. *Exact mass* calcd. for $C_{12}H_{16}O$: 176.1200; found: 176.1206.

Dehydrogenation of epimers 278 and 304 with DDQ

A solution of epimers **278** and **304** (54 mg, 0.30 mmol) and DDQ (231 mg, 1.14 mmol) and catalytic amount of *p*TSA (30 mg) in dry benzene (30 mL) was heated at reflux for two hours. The black preciptate was filtered off and the filtrate was

concentrated *in vacuo*. Purification of the residue by chromatography (5% ethyl acetate in hexane) gave an oily product **311** (36 mg, 68%): IR (film) ν_{max}: 1661 (s) and 1611 (m) cm^{-1}; ^1H NMR δ: 1.64-1.87 (m, 3H), 1.90 (dd, J = 5.4, 10.5 Hz, 1H), 2.02 (dd, J = 4.5, 11.4 Hz, 1H), 2.21-2.32 (m, 1H), 3.07 (br t, J = 6.3 Hz, 1H), 5.08 (s, 1H), 5.73 (s, 1H), 5.57 (d, J = 6.3 Hz, 1H), and 6.92 (d, J = 5.3 Hz, 1H); MS (from GC-MS) *m/z* (%): 172 (26, M^+), 144 (14), 131 (100), 129 (12), 128 (12), 115 (15), 77 (23), and 51 (12).

(1*R,2*R**,7*S**,8*R**)-2-Methyltricyclo[6.2.1.0^{1,5}]undec-5-en-7-ol (324)**

A solution of tricyclic enone **278** (29 mg, 0.17 mmol) and cerium chloride heptahydrate (2124 mg, 0.33 mmol) in dry methanol (15 mL) was added $NaBH_4$ (13 mg, 0.33 mmol) at -78°C. The resulting reaction mixture was stirred for 30 min at that temperature. After which period water and ether was added. The aqueous layer was extracted with four portions of ethyl acetate. The combined organic extracts were washed with water and saturated NaCl then dried over $MgSO_4$. After concentration the residue was purified by flash chromatography (5% ethyl acetate in hexane) to afford alcohol **324** as a colorless oil (27 mg, 93%): IR (film) ν_{max}: 3291 (br) and 1454 (m) cm^{-1}; ^1H NMR δ 0.86 (d, J = 7.0 Hz, 3H), 1.21-1.36 (m, 2H), 1.42-1.80 (m, 3H), 1.82-2.01 (m, 3H), 2.20-2.38 (m, 2H), 2.40-2.45 (m, 1H), 4.57 (m, 1H), and 5.13 (quintet, J = 2.1 Hz, 1H); ^{13}C NMR δ: 16.9 (3), 21.4 (2), 28.6 (2), 32.6 (1), 38.0 (2), 38.3 (2), 40.1 (1), 41.9 (2), 53.1 (0), 74.2 (1), 116.9 (1), and 140.9 (0); MS (from GC-MS) *m/z* (%): 178 (1, M^+), 160 (38, $M^+ - H_2O$), 145 (11), 132 (34), 131 (100), 118 (11), 117 (10), 115 (22), 91 (26), 77 (10). *Exact mass* calcd. for $C_{12}H_{18}O$: 178.1357; found: 178.1347.

Sodium borohydride reduction of the mixture of 278 and 305

To a solution of tricyclic enones **278** and **305** (61 mg, 0.34 mmol) and cerium chloride heptahydrate (256 mg, 0.68 mmol) in dry methanol (20 mL) was added $NaBH_4$ (13 mg, 0.34 mmol) at -78°C. After work-up, the oily product was purified by flash chromatogrphy (5% ethyl acetate in hexane) to provide an inseparable mixture of two methyl

epimers (55 mg, 89%). For **324** methyl epimer: ^{1}H NMR δ: (from the mixture): 0.92 (d, J = 6.6 Hz, 3H). 1.26-1.97 (m, including oH), 2.12-2.45 (m, 3H), 4.57 (m, 1H), and 5.09 (q, J = 2.1 Hz, 1H); ^{13}C NMR δ: 13.8 (3), 21.1 (2), 27.8 (2), 28.7 (2), 32.4 (1), 38.9 (1), 39.1 (2), 41.1 (2), 52.7 (0), 74.4 (1), 117.0 (1), and 155.2 (0). IR and MS is essentially the same as **324**.

(1R^*,2R^*,7R^*,8R^*)-2-Methyltricyclo[6.2.1.0^{1,5}]undec-5-en-7-ol (325) and its methyl epimer

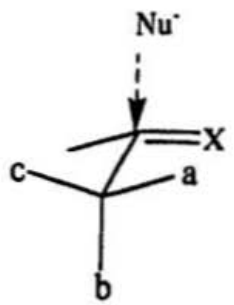
To a solution of **324** and its methyl epimer (42 mg, 0.24 mmol) in dry benzene (30 mL) was added triphenylphosphine (62 mg, 0.24 mmol), benzoic acid (29 mg, 0.24 mmol) and diethyl azodicarboxylate (DEAD) (41 mg, 0.24 mmol), and the mixture was stirred for 1 hour at room temperature. At this point, the reaction was still incomplete (TLC control). Further portions of triphenylphosphine (62 mg, 0.24 mmol), benzoic acid (29 mg, 0.24 mmol) and diethyl azodicarboxlate (41 mg, 0.24 mmol) were added. After an additional hour, the solvent was evaporated and the residue was employed for the next step without further purification: MS (from GC-MS) m/z (%): 282 (16, M^+), 177 (22), 161 (26), 160 (68), 145 (41), 133 (28), 132 (31), 131 (32), 117 (53), 105 (100), 91 (64), and 77 (41). To a solution of the benzoate in methanol, was added K_2CO_3 (2.0 g) and the mixture was stirred for one hour. The methanol was evaporated and the residue was extracted with ether (×4). The organic extracts were washed with water and saturated NaCl, then dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel to give an inseparable mixture of **311** and its methyl epimer (26.8 mg, 64%). IR (film) ν_{max}: 3291 (br) and 1454 (m) cm^{-1}; For **325**: ^{1}H NMR (from the mixture) δ: 0.90 (d, J = 7.2 Hz, 3H), 1.16-1.62 (m, 7H including OH), 1.82-1.88 (m, 3H), 2.28-2.39 (m, 3H), 3.82 (br s, 1H), and 5.32 (m, 1H); MS essentially the same as **324**. For **325**'s methyl epimer: ^{1}H NMR (from the mixture) δ: 0.97 (d, J = 6.6 Hz, 3H), the rest of the signals were buried in the signals of its isomer.

Chapter 4

STEREOSELECTIVITY IN NUCLEOPHILIC ADDITIONS TO SPIRO-DIKETONES

I. Introduction

The addition of a nucleophile to a carbonyl group is one of the most important C-C bond-forming processes. To date much effort has been made to rationalize and predict the diastereoselectivity of these reactions. Suggestions involving arguments of thermodynamic stability, steric interactions, frontier orbitals, and transition-state stabilization and destabilization by electronic factors have been made to account for these observations.[126-130]



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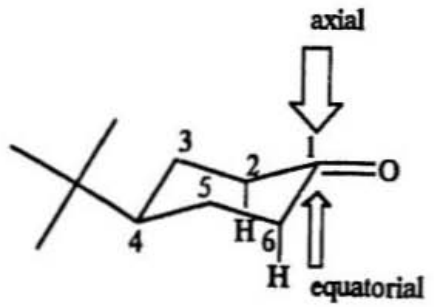

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In 1968 Felkin *et al.*[130b] proposed that allylic bonds prefer to be in a staggered conformation with respect to the partial bond to the nucleophile as shown in **327**. This proposition has been widely accepted as the textbook explanation of the stereochemistry of nucleophilic addition to cyclohexanone. It is well known that axial attack of a nucleophile, such as a metal hydride, to cyclohexanone derivatives predominates over equatorial addition (see **328**). As indicated in Figure 22, cyclohexanone has a distorted chair conformation at the transition state. According to the Felkin theory, the equatorial

transition state is destabilized relative to the axial one because of torsional strain. In the case of equatorial attack, the incipient bond would eclipse the axial carbon hydrogen bonds at C-2 and C-6 and hence destabilize the corresponding transition state.

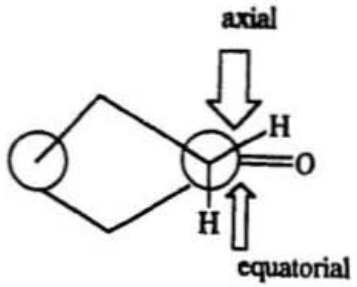


Figure 22. Felkin-Anh torsional strain model

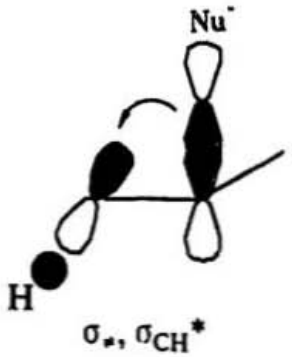


Figure 23. High-lying σ_{*} orbital of the incipient bond delocalized in a hyperconjugative interaction into vacant σ_{CH}^{*} orbitals (**Felkin-Anh model**)

The Felkin model was supported by Anh and Eisenstein's[131] *ab initio* calculations. They explained the stereochemistry of nucleophilic addition to a carbonyl group in terms of the stabilizing interaction of the incipient bond with the vicinal σ bonds. They postulated that a high-lying σ orbital of the incipient bond (σ_{*}) would be delocalized into vacant σ^{*} orbitals (σ_{CH}) associated with the α-carbons by means of hyperconjugation (Figure 23). In order to optimize hyperconjugation between σ_{*} and σ_{CH}^{*} and to avoid

torsional strain effects, the nucleophile would attack the carbonyl group in an antiperiplanar manner. Anh and Eistenstein concluded that in any reaction with asymmetric induction, a search for antiperiplanarity between the incipient bond and an adjacent σ bond should lead to the most favorable transition states assuming all other things being equal. This is often referred to as the antiperiplanar effect. Since with cyclohexanone the transition state structure involves a distorted chair conformation, the axial attack may attain better antiperiplanarity to the C2-H_{ax} and C6-H_{ax} bonds than equatorial attack to the C2-C3 and C5-C6 bonds. Consequently, in many cases, nucleophiles add preferentially from the more sterically hindered, axial face. Clearly, if the ring is flattened as shown in Figure 24, equatorial attack cannot approach antiperiplarity, while axial attack can, and consequently axial selectivity will increase. Likewise, ring puckering should reduce the axial selectivity. This is often called the "flattening rule": the more flattened the ring, the more axial attack there is. This rule has been verified by a number of experiments. For

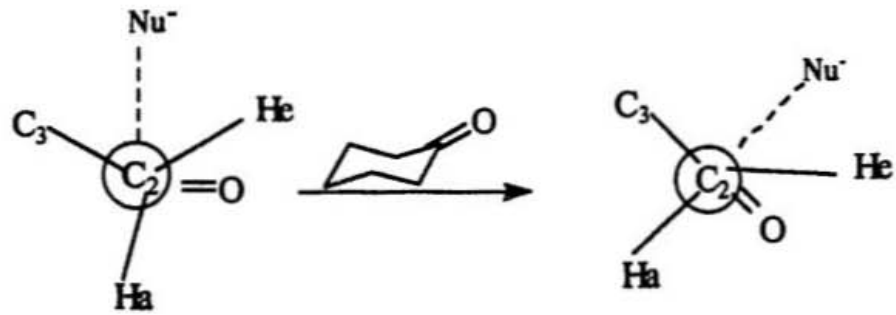
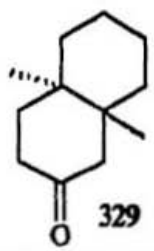
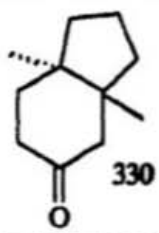
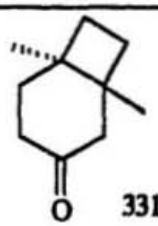


Figure 24. Axial attack increases as cyclohexane ring becomes flattened

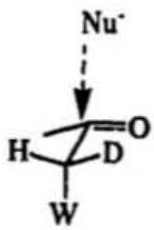
instance, as indicated in Table 15,[132] the percentage of axial attack increases from **329** to **331**, as the cyclohexanone ring becomes flatter. The variation of stereoselectivities of nucleophilic additions to C-3 and C-5 heteroatom derivatives of cyclohexanone have also been rationalized in terms of the "flattening rule". The axial selectivity of hydride reductions of 1,3-dioxolan-5-ones[133] was found to be higher than that of the corresponding cyclohexanones. This fact was attributed to the shorter C-O bonds in the ring, which

make the six-membered ring much flatter than cyclohexanone itself. In contrast, nucleophilic addition to 1,3-dithiolan-5-one proceeded with highly equatorial selectivity. As revealed by X-ray analysis, the longer C-S bonds in 1,3-dithiolan-5-one [134] make the ring more puckered.

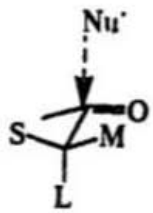
Table 15. Percentage of axial attack with increasing flattening of cyclohexanone ring

Entry	$LiAlH_4$	$NaBH_4$	CH_3MgI
 329	85%	88%	32%
 330	90%	90%	43%
 331	94%	94%	55%

Anh and Eistenstein's proposition was supported by extensive computational studies performed by Houk and coworkers.[135] Based on *ab initio* calculations, electron-donating groups (D) appeared to disfavor an antiperiplanar conformation, and an electron-withdrawing (W) group favored an antiperiplanar conformation with respect to the incoming nucleophile (see **332**). From the steric point of view, the carbonyl group should be arranged as shown in **333** (S = small; M = medium; L = large group). Houk's calculations also indicated that the addition of a hydride ion to a carbonyl group was increasingly stabilized by an antiperiplanar σ bond as the σ^*-orbital energies became lower. It should be noted that a nucleophile prefers to approach a carbonyl group antiperiplanar to the polar ligand of the lowest σ^*-orbital energy, not the ligand of greatest steric hindrance, *i. e.* the "stereoelectronic effect" dominates over the steric effect. Houk's proposition , which was consistent with the Felkin model, is often referred to as the Felkin-Anh model.



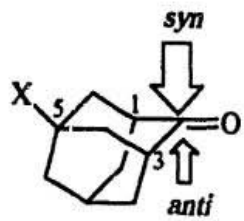
332



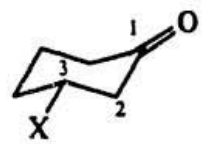
333

The Felkin-Anh model based mainly on the torsional strain and hyperconjugation between the high lying σ orbital of the incipient bond ($\sigma_{\neq}$) and vacant σ^* orbitals (σ_{CH}) in the transition state of the addition of a nucleophile to a carbonyl, has been widely accepted. It has played a significant role in understanding the stereoselectivities of a variety of addition reactions. It has proved to be successful in predicting the stereoselectivity of nucleophilic addition to chiral acyclic ketones. Nevertheless, there has been some criticism regarding the assumption and predictions of this model. For example, le Noble and

coworkers[136-140] reported the substituent effects on the stereoselectivities of addition reactions to 5-substituted adamantanone derivatives **334**. In this case, electron-withdrawing 5-substituents led to a small preference for *syn* addition, while electron-donating 5-substituents caused a slight preference for anti addition. Johnson *et al.*[21b] investigated the stereoselectivities of nucleophilic additions to cyclohexanone derivatives **335**. They observed that axial (*syn*) addition is increased if the substituent X is electron-withdrawing and decreased if X is electron-donating substituent. These experimental results are not easy to rationalize in terms of the Felkin-Anh model. In the case of 5-substituted adamantanones **334**, the Felkin-Anh model would predict a preference for an attack *anti* to an electron-withdrawing substituent. This prediction is certainly opposite to the experimental results reported by le Noble and coworkers.



334



335

Cieplak[21] explained the stereoselectivities of nucleophilic additions to cyclohexanones based on the concept of transition state stabilization by electron donation from an antiperiplanar σ orbital into a $\sigma_{\neq}^{*}$ orbital, a low lying vacant orbital of the forming bond (Figure 25). Electron-donating abilities of some common bonds are arranged in the following order: C-S > C-H > C-C > C-O.[22] There are two antiperiplanar C-H bonds in the transition state of axial attack on cyclohexanone, but there are two antiperiplanar C-C bonds in the transition state of equatorial attack. The C-H bond is a better σ-donor than the C-C bond, so the stabilization energy SE (σ, $\sigma_{\neq}^{*}$) of the axial approach should be greater than that of the equatorial addition. Consequently, axial addition predominates

despite the unfavorable steric interactions. The Cieplak model has proved to be quite successful in rationalizing a number of substituent effects on stereoselectivities of nucleophilic additions. As mentioned previously, the Felkin-Anh model cannot explain the stereoselectivities of the nucleophilic additions to 5-substituted adamantanone derivatives **334** and cyclohexanone derivatives **335**. In the case of **334**, if X is electron-withdrawing, C3-C4 and C1-C6 would become poorer electron-donors thus more axial addition should be expected. Likewise, more equatorial addition should be observed if X is an electron-donating substituent. The same argument can be applied to explain the variation of stereoselectivity of reduction in **335**. The stereoselectivities observed in the reductions of ketones **336**,[141] **337**,[142] and **338**[143] are fully consistent with predictions based on the Cieplak's hyperconjugative model.

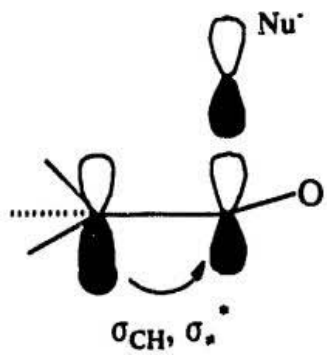


Figure 25. Stabilizing interaction of the incipient bond σ_{*}^{*} orbital with neighboring occupied orbitals σ_{CH} (Cieplak Model)

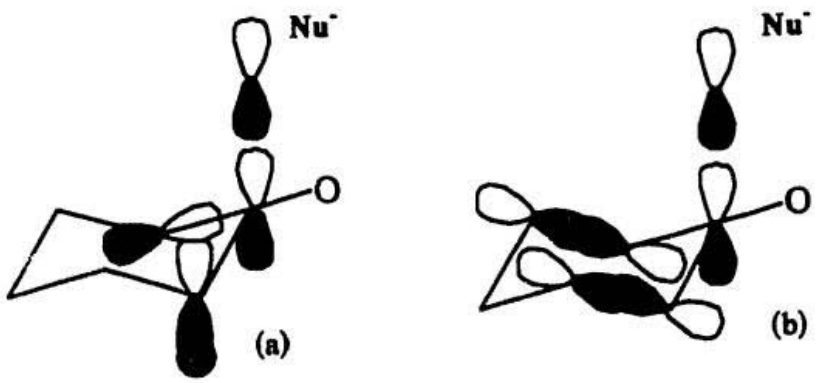
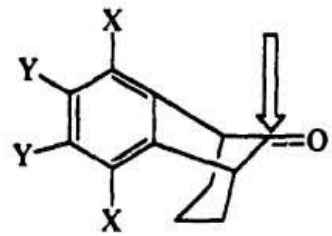


Figure 26. Stabilizing interactions of the incipient bond with neighboring occupied orbitals (a) by axial and (b) by equatorial

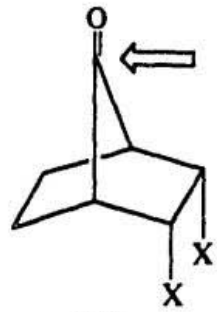


X = Y = F 100%
X = Y = Cl 92%
X = Y = H 62%
X = OCH_3 Y = H 45%

336

X = NO_2 79%
X = Cl 63%
X = Br 63%
X = OCH_3 43%
X = O^- 30%
X = NH_2 36%

337

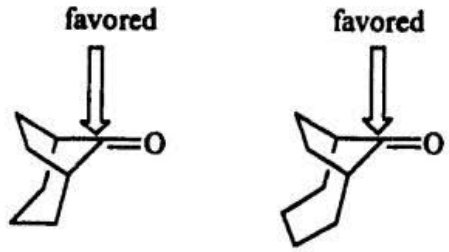


X = $COOCH_3$ 77-90%
X = Et 17-29%

338

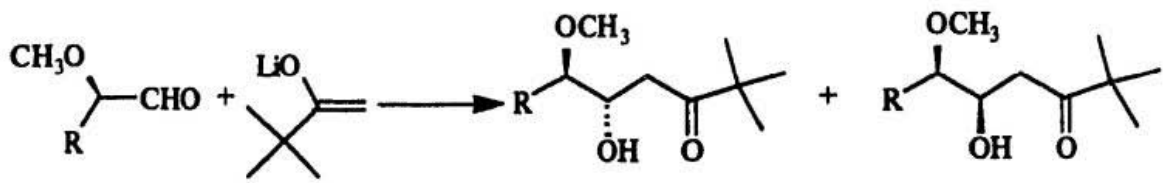
The Cieplak model has been successfully employed to rationalize a large variety of substituent effects on stereoselectivities of nucleophilic additions. However, in the case of nucleophilic additions to bicyclic ketones such as **339** and **340**,[144,145] the Cieplak theory can become awkward since there are two C-C bonds on each side of the carbonyl group. The stereoselectivities observed in these cases can be predicted according to the Felkin-Anh model, which is based on the flatness of the two rings. The nucleophile would approach **339** or **340** predominantly from the side of the smaller ring. As a result, the torsional strain about the C_{co}-C_{α} bond is smaller in the transition state. Although the stereoselectivity of nucleophilic additions to cyclohexanone derivatives can be correctly predicted in terms of the Cieplak model, it does not predict correctly the stereoselectivity of nucleophilic additions to chiral acyclic carbonyl compounds. For instance, in the case

of **341**, in which an electron-withdrawing group is attached to a chiral acyclic ketone or aldehyde, the Felkin-Anh model suggests that the antiperiplanar relationship between the nucleophile and the electron-withdrawing group would be the factor governing stereoselectivity. However, Heathcock and his coworkers[146] showed that the amount of formation of **344** increases as the size of the alkyl group increases. The Felkin-Anh model explains this result, but Cieplak model would suggest the opposite trend of stereoselectivity.



339 **340**

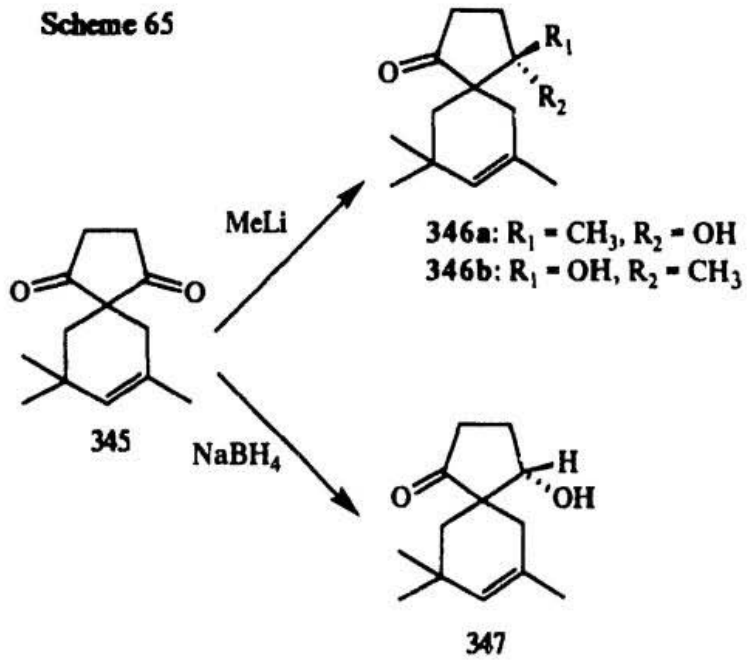
Scheme 64



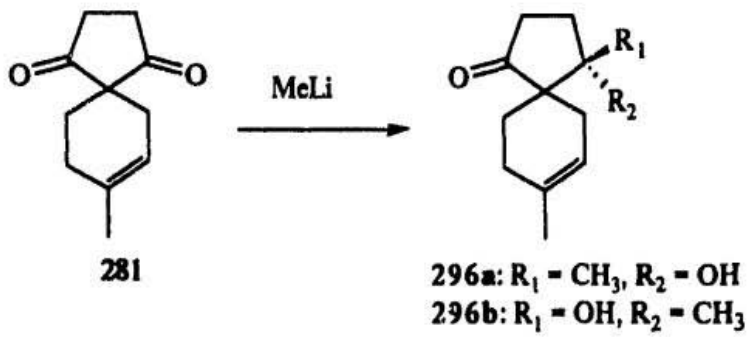
341 **342** **343** **344**

In a synthetic study toward the total synthesis of pentalenene, Wu [121] reported that sodium borohydride reduction of spirodiketone **345** (Scheme 65) proceeded to give **347** exclusively and addition of methyllithium to the spirodiketone generated **346a** and **346b** in a 63 : 1 ratio. During our synthesis of the prezizaene skeleton we obtained a related result: addition of methyllithium to **281** provided **296a** and **296b** in 4 : 1 ratio. Yoshikoshi *et al.*[147] reported that reaction of **348** with dimethylsulphonium methylide yielded a single oxirane derivative **349**. In all cases, the nucleophiles approached the carbonyl groups from the same face as the cyclohexene double bond.

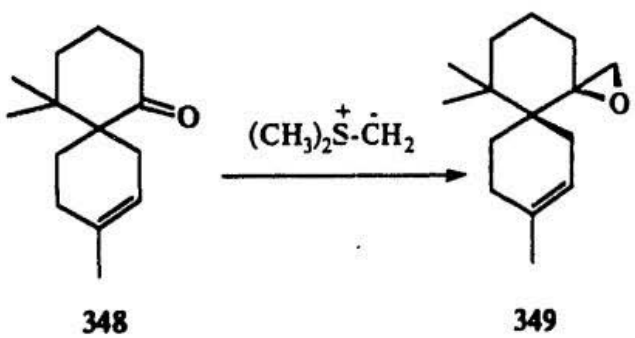
Scheme 65



Scheme 66



Scheme 67

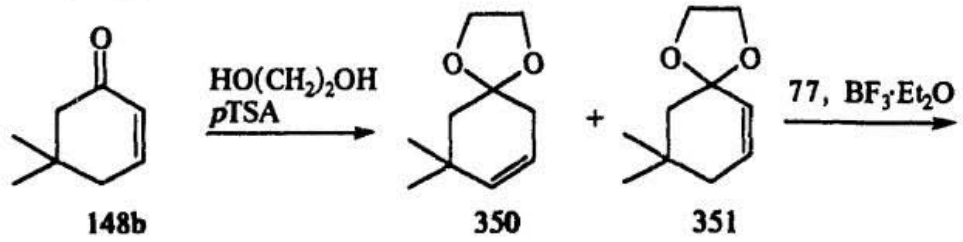


It has been suggested by Yoshikoshi *et al.* that this stereoselectivity arises from a steric effect. Since the double bond is relatively far away from the carbonyl group, we believed that steric interactions alone could not account for this stereoselectivity. Thus, we conducted a systematic study of the origin of the facial stereoselectivities in the nucleophilic additions to a series of spirodiketones, which could be potentially useful in the design of syntheses of natural products.

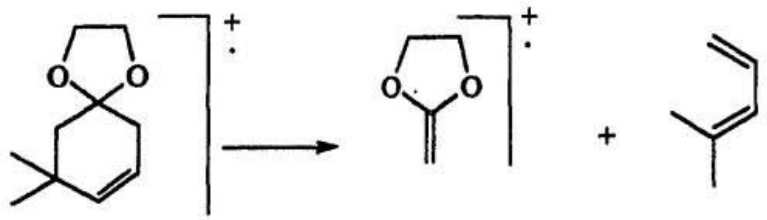
II. Preparation of the Spiro-diketones

The spiro-diketones required for our studies were prepared by geminal acylation reactions of the corresponding ketals with cyclobutene **77** following the general procedure developed in this laboratory. Treatment of enone **148b** (Scheme 68) with a large excess of ethylene glycol and a catalytic amount of *p*TSA in benzene under reflux overnight produced a 14 : 1 mixture of ketals **350** and **351**. These two ketals could be differentiated by their distinctive mass spectra. The mass spectrum of ketal **350** is shown in Figure 27. The fragment at *m/z* 86 corresponds to **352**, which arises via the homolytic *retro*-Diels-Alder reaction of **350** (Scheme 69). Likewise, the peak at *m/z* 112 in the mass spectrum of **351**, depicted in Figure 28, can be rationalized as a fragment with the formula $C_6H_8O_2$ (**353**). Exposure of this ketal mixture to **77** and a large excess of $BF_3{\cdot}Et_2O$ following our general procedure gave a single new substance, as revealed by GC-MS analysis of the crude product. Purification of the crude product by flash chromatography gave colorless crystals of **354** in a 74% yield and a small amount of hydrolyzed starting material. The crystals showed an IR absorption maximum for the ring carbonyls at 1724 cm^{-1}. In the ^1H NMR spectrum, two two-proton multiplets at δ 2.66 and 3.00 were attributed to the protons next to the carbonyl groups. The carbonyls were found at δ 214.0 in the ^{13}C NMR spectrum. The position of the double bond was determined by comparison of the chemical shifts in the ^1H NMR spectra of **354** with those of spiro-diketone **345**. For **345**, the double bond position was unequivocally determined by means of NOE experiments.[121] If the spiro-diketone was **355** instead, a relatively high-field olefinic proton would be expected due to the proximity of the carbonyl groups, which would shield the protons on C-6. In fact, the olefinic protons were found at δ 5.52 and 5.72. Direct catalytic hydrogenation of **354** afforded **356** in 93% isolated yield.

Scheme 68



Scheme 69



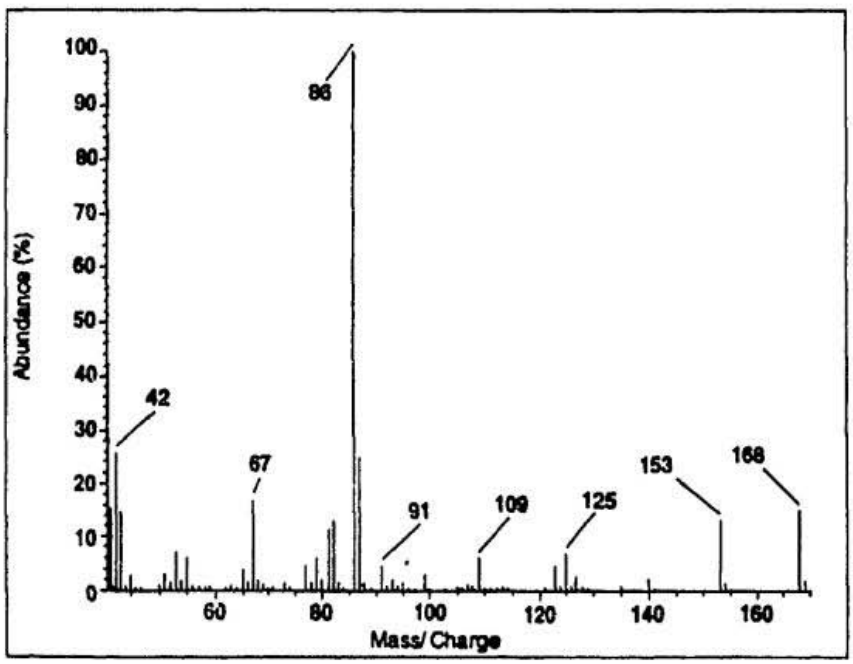
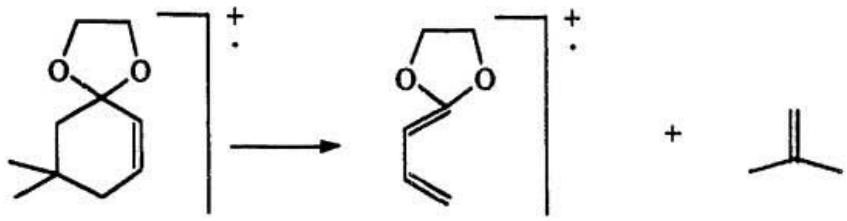


Figure 27. Mass spectrum (from GC-MS) of **350**

Scheme 70`



351 **353**

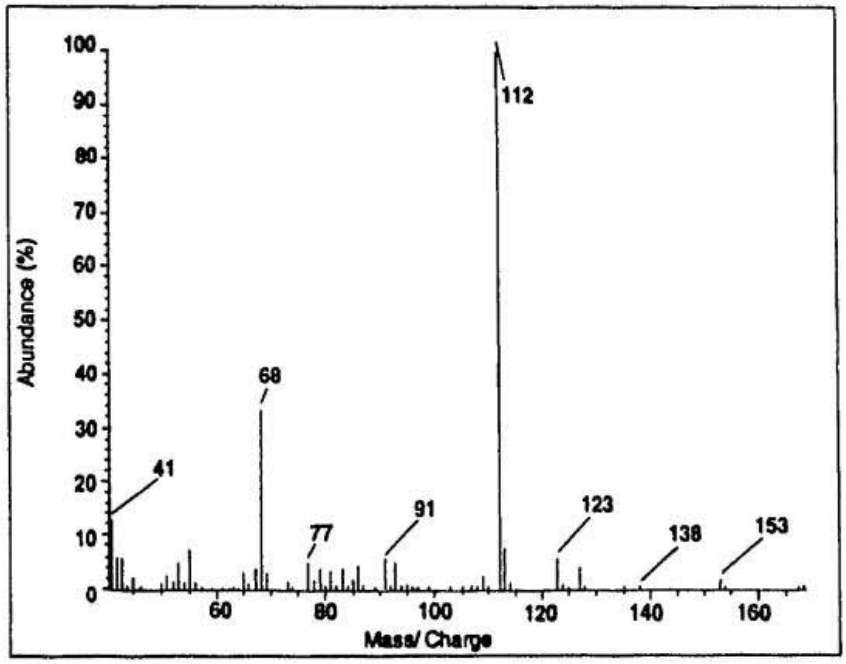
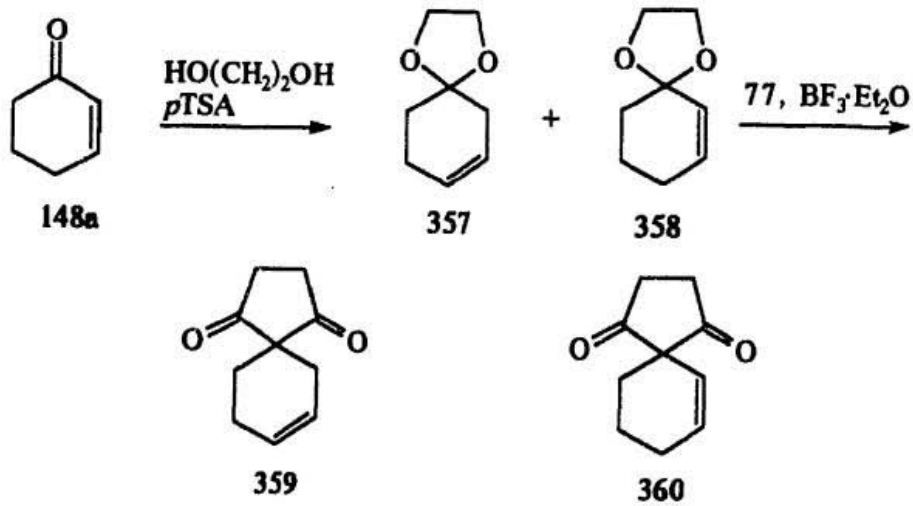


Figure 28. Mass spectrum (from GC-MS) of 351

Ketals **357** and **358** were obtained from 2-cyclohexen-1-one (**148a**) by treatment with a large excess of ethylene glycol and catalytic amount of *p*TSA in refluxing benzene (Scheme 71). Careful fractional distillation gave the pure ketal **357** and a mixture of ketals **357** and **358** in a 4 : 5 ratio. The subsequent geminal acylation reaction with pure **357** was carried out following our standard procedure to give one product only as indicated by GC-MS analysis of the crude product. IR absorption maximum of the product appeared at 1718 cm^{-1} for the ring carbonyls. The two two-proton multiplets at δ 2.72

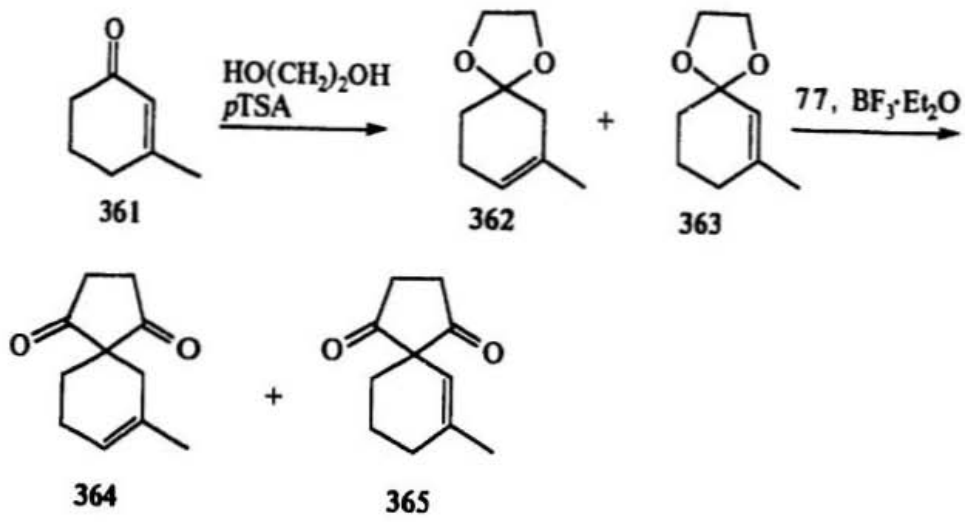
and 2.92 in its ^{1}H NMR spectrum clearly indicated the presence of the cyclopentanedione moiety. The position of the double bond in **359** was unambiguously established on the basis of its ^{1}H NMR spectrum. The multiplet at δ 2.15 attributed to the protons α to the double bond and an apparent triplet at δ 1.74 represented the protons β to the double bond. The ratio of the α protons to β protons was 2 : 1 as calculated from the integration, which allowed structure **359** only.

Scheme 71



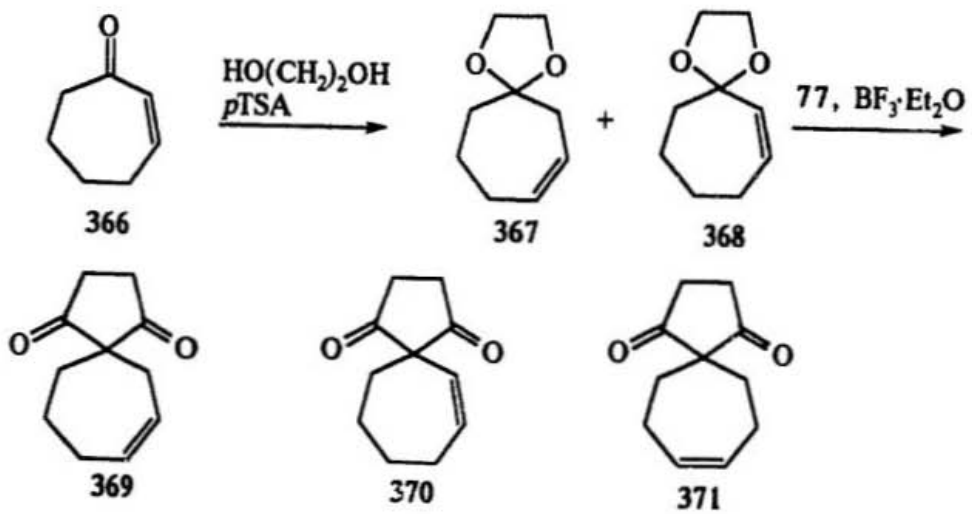
Similarly, ketalization of enone **361** generated a mixture of ketals **362** and **363** in a 14 : 1 ratio (Scheme 72) after flash chromatography. This ketal mixture when treated with cyclobutene **77** in the presence of a large excess of $BF_3 \cdot Et_2O$ gave an 11 : 1 mixture of spiro-diketones **364** and **365** as shown by both GC-MS analysis and ^{1}H NMR spectroscopy. Careful chromatography afforded pure **364** and a mixture of **364** and **365**. These two double bond isomers could be easily distinguished by examining their ^{1}H NMR spectra. The olefinic proton for the major isomer was located at δ 5.54 while the olefinic proton for the minor compound **365** was found at δ 4.97.

Scheme 72



361 362 363 364 365

Scheme 73



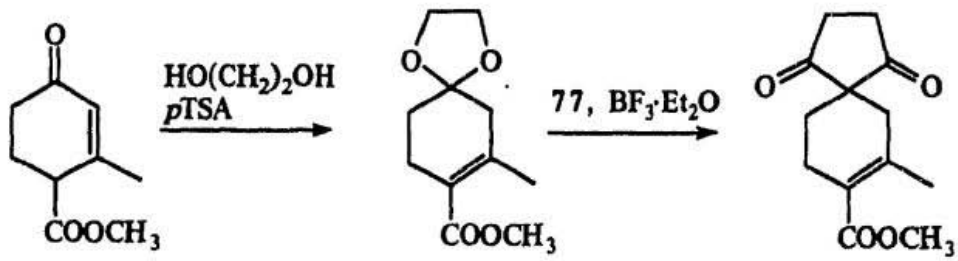
366 367 368 369 370 371

The seven-membered ring ketal **367** (Scheme 73) was obtained from enone **366** as the only product in the same manner as for ketals **350** and **351**. Treatment of this ketal (**367**) with $BF_3{\cdot}Et_2O$ and **77** following the standard procedure gave the spiro-diketone **369** in 35% yield only. No formation of **370** was observed. The position of the double bond was determined as follows: the multiplets at δ 2.24-2.32 with integration of four hydrogens corresponded to the protons α to the double bond and the higher-field multiplet at δ 1.69-1.86 with an integration of four protons was attributable to the protons β to

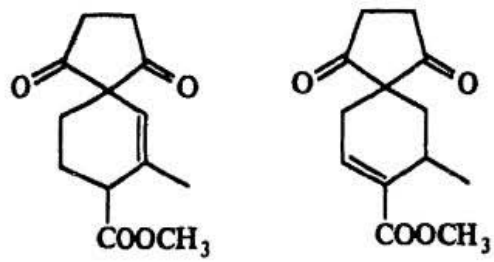
the double bond. This could be **369** or **371**. If the spiro-diketone formed were **370**, then we would expect that the ratio of the protons α to the double bond to the protons β to the double bond would be 1 : 3. The more symmetrical structure **371** was precluded because the ^{13}C NMR spectrum of the product showed nine resonances.

The ketal **373** (Scheme 74) was obtained from keto-ester **372** as the only product. This ketal was treated with a large excess of $BF_3{\cdot}Et_2O$ and three equivalents of cyclobutene **77** to give a mixture of the double bond isomers **374** and **376** in a ratio of 9 : 1. This mixture was carefully chromatographed to give pure **374** and a mixture of diketones **374** and **376**. The formation of **375** in this case was not detected.

Scheme 74



372 **373** **374**



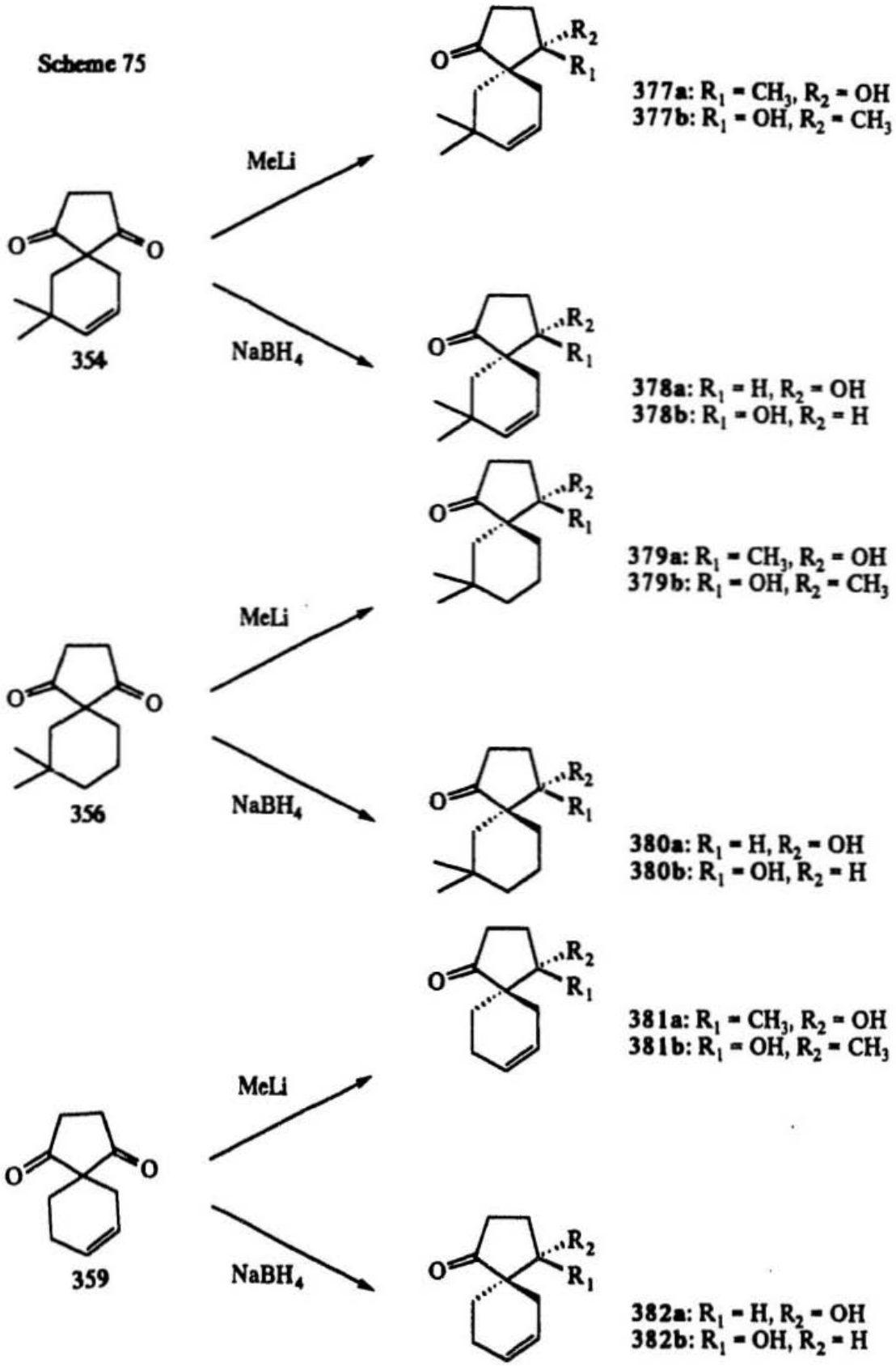
375 **376**

III. Results and Discussion

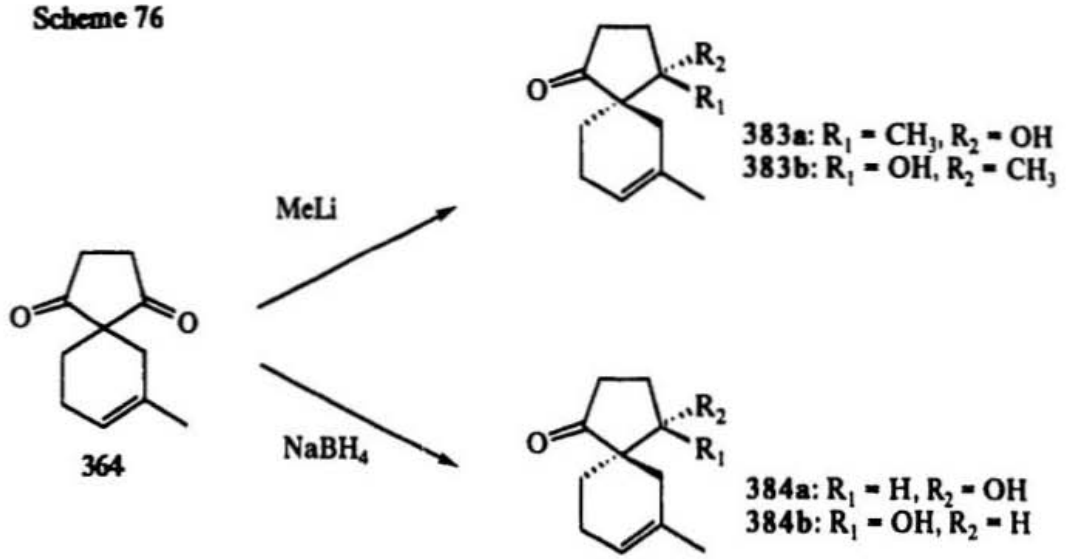
The spiro-diketones were treated with methyllithium and with sodium borohydride. Typical results were as follows. Addition of methyllithium to spiro-diketone **354** (Scheme 75) produced a mixture of two epimers in a ratio of 6.4 : 1 (**377a** : **377b**) as revealed by integration of the ^{1}H NMR spectrum of the crude reaction mixture. This mixture could be separated by flash chromatography. Broad peaks at 3463 cm^{-1} in the IR spectrum of the major, and at 3454 cm^{-1} for the minor, indicated the presence of hydroxyl groups. The absorptions at 1726 cm^{-1} for the major, and 1731 cm^{-1} for the minor, were attributed to the five-membered ring carbonyls. Tnree singlets at δ 1.15, 1.03, and 0.93 in the ^{1}H NMR spectrum of the major product must arise from the three methyl groups. Likewise, three singlets, at δ 1.29, 0.99, and 0.89, were observed in the ^{1}H NMR spectrum of the minor compound. The stereochemistry of the major product was determined by NOE measurements. Reduction of **354** with sodium borohydride (0.25 equivalents) was carried out in methanol at room temperature. Integration of the ^{1}H NMR spectrum of the crude mixture demonstrated that a 14 : 1 mixture of two epimers (**378a** : **378b**) had formed. The broad absorptions at 3473 cm^{-1} in the IR spectrum of the major, and 3447 cm^{-1} for the minor, were due to the presence of the hydroxyl groups. The carbonyl group stretchings were found at 1728 cm^{-1} and 1730 cm^{-1} for the major and the minor isomer, respectively. The multiplets at δ 4.29 for the major and δ 4.34 for the minor isomer were attributed to the protons on the carbon bearing the hydroxyl groups. The stereochemistry of the major isomer was elucidated from the NOE data, as described in the Experimental section.

For the other spiro-diketones the reactions were performed in the same manner as for spiro-diketone **354** (see Scheme 75,76, 78). The results were summarized in Table 16. The stereochemistry of **384a** was determined by X-ray crystallography (see Figure 29).

Scheme 75


MeLi
NaBH4
354
356
359
R2
R1
377a: R1 = CH3, R2 = OH
377b: R1 = OH, R2 = CH3
378a: R1 = H, R2 = OH
378b: R1 = OH, R2 = H
379a: R1 = CH3, R2 = OH
379b: R1 = OH, R2 = CH3
380a: R1 = H, R2 = OH
380b: R1 = OH, R2 = H
381a: R1 = CH3, R2 = OH
381b: R1 = OH, R2 = CH3
382a: R1 = H, R2 = OH
382b: R1 = OH, R2 = H

Scheme 76



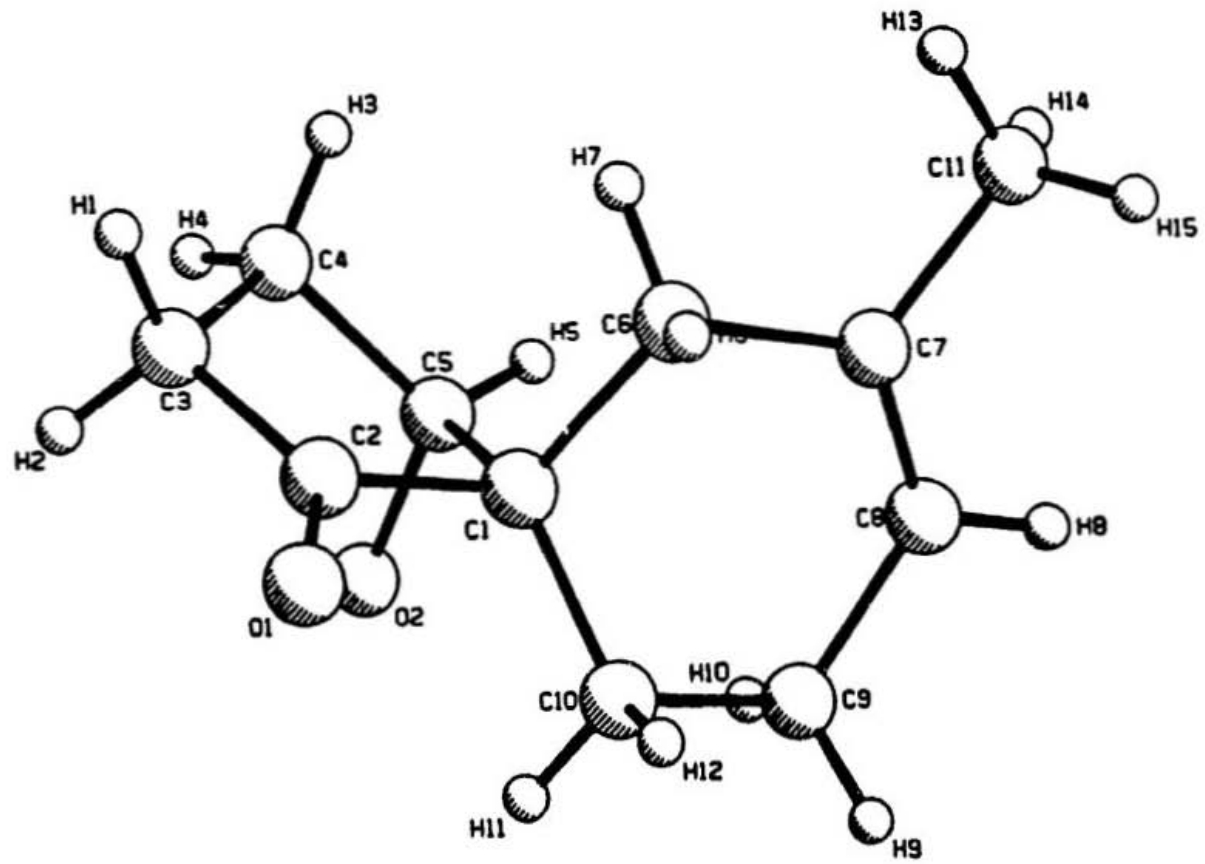
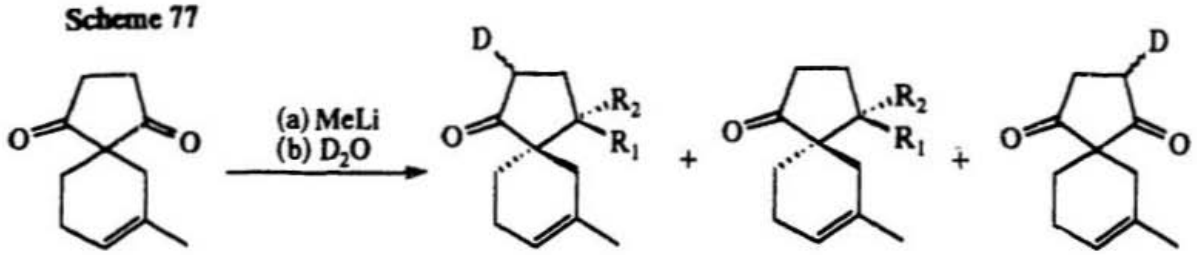


Figure 29. Perspective views of **384a** (Hydrogen atoms have been added to show the relative stereochemistry).

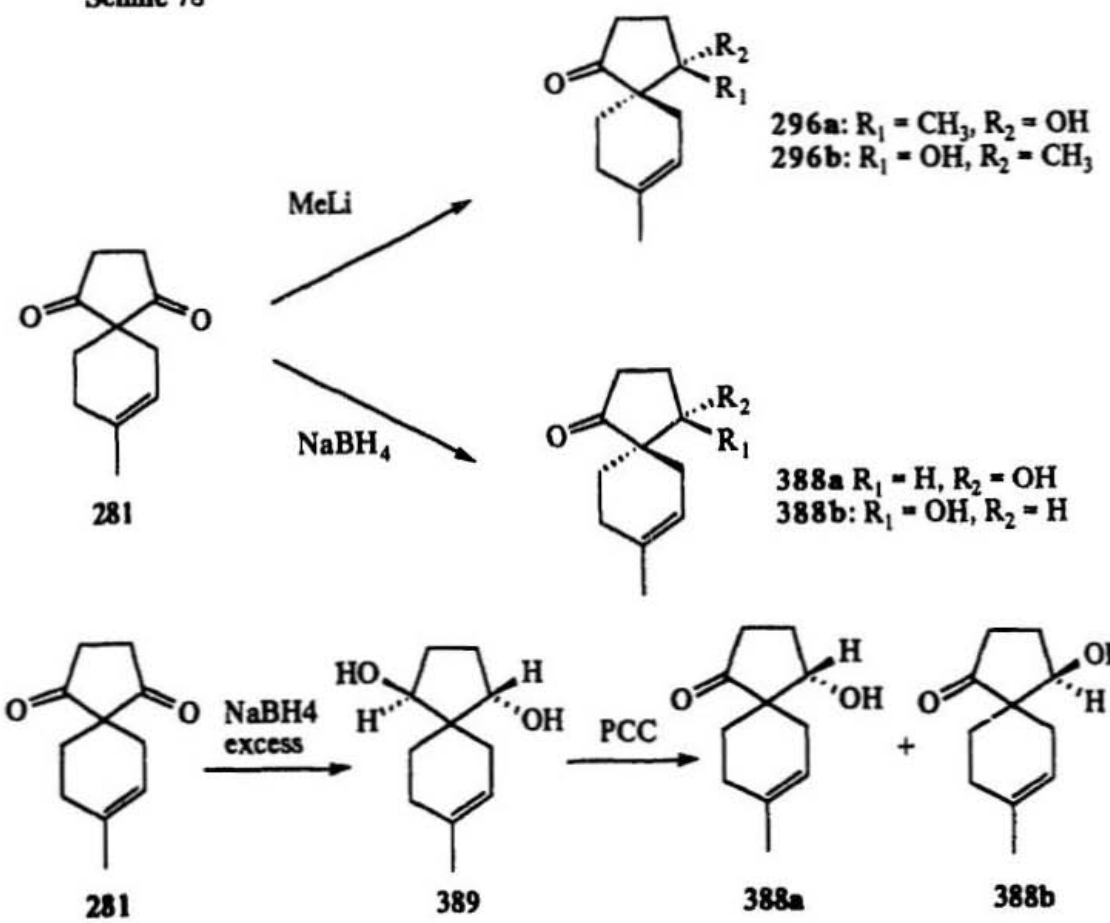
Scheme 77



364

385a: $R_1 = CH_3$, $R_2 = OD$ **386a**: $R_1 = CH_3$, $R_2 = OD$ **387**
385b: $R_1 = OD$, $R_2 = CH_3$ **386b**: $R_1 = OD$, $R_2 = CH_3$

Schme 78



296a: $R_1 = CH_3$, $R_2 = OH$
296b: $R_1 = OH$, $R_2 = CH_3$

281

388a $R_1 = H$, $R_2 = OH$
388b: $R_1 = OH$, $R_2 = H$

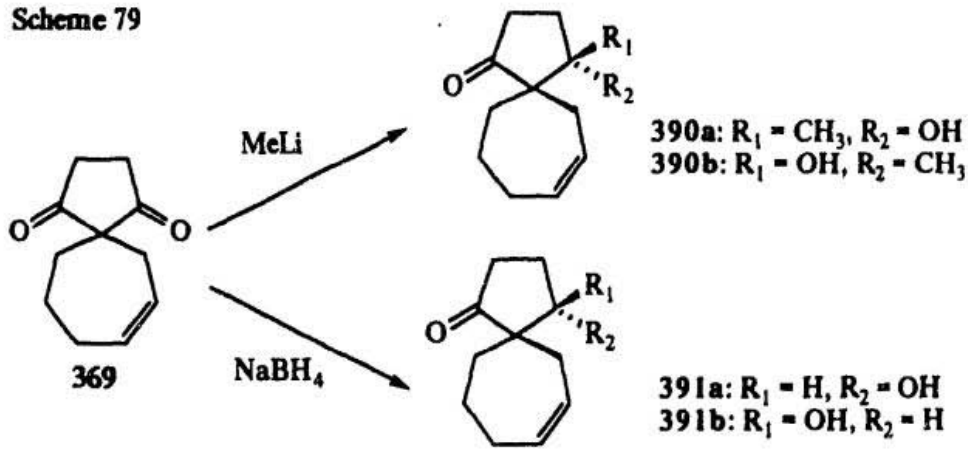
281 **389** **388a** **388b**

In all the cases examined, addition of an excess of methyllithium generated *mono* alcohols only. It was suspected that this result may have been due to the rapid formation of an enolate of one of the carbonyls. This was tested by conducting the reaction of methyllithium with spiro-diketone **364** followed by quenching the reaction mixture with

deuterated water (D_2O) (Scheme 77). Analysis of the crude reaction product by GC-MS indicated that the product was a mixture of **385** and **386**. Also some deuterated starting material (**387**) was recovered. This was indeed in agreement with the formation of an enolate. It therefore appeared that methyllithium acted initially as a base, then a second equivalent underwent the nucleophilic attack on the remaining ketone.

The spiro-diketone **281** was also reduced with an excess of sodium borohydride and the *trans* diol **389** was obtained after purification. The structure of **389** was evident from its ^{13}C NMR spectrum. If the *cis* diol were produced, the ^{13}C NMR spectrum would show only nine signals because of its symmetry. In fact, eleven resonances were observed in the ^{13}C NMR spectrum of this compound. The relative stereochemistry was confirmed by converting this diol into a mixture *mono*-alcohols **388a/b** by oxidation with one equivalent of PCC.

Scheme 79



Scheme 80

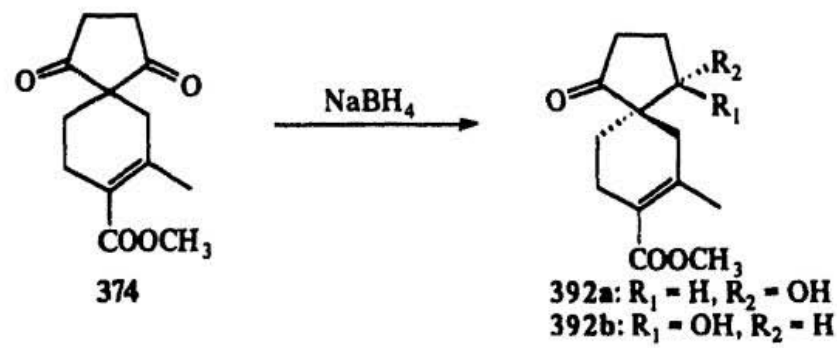
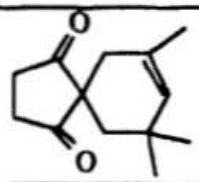
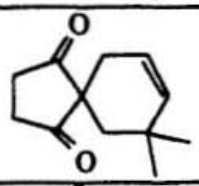
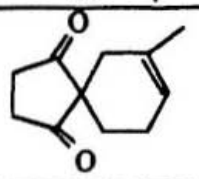
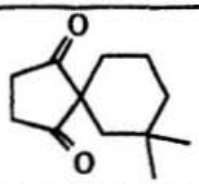
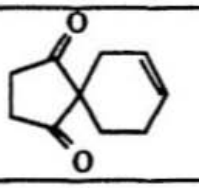
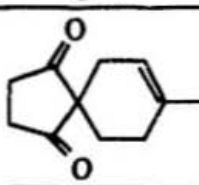
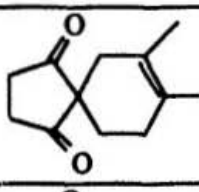
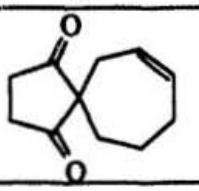
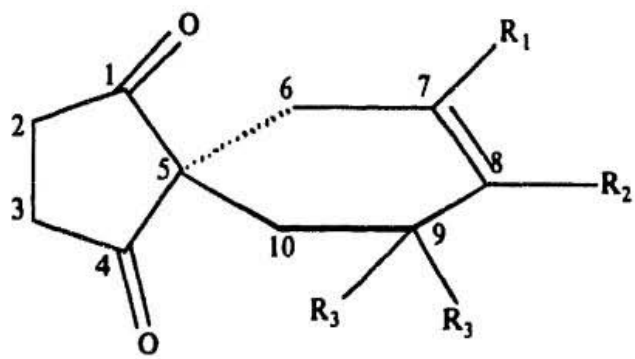


Table 16. Product ratios of nucleophilic additions to various spiro-diketones

Entry	Substrate	*syn* : *anti*	
		$NaBH_4$	MeLi
1[121]	 345	100% *syn*	63 : 1
2	 354	14 : 1	6.4 : 1
3	 364	7 : 1	6 : 1
4	 356	6.7 : 1	3.0 : 1
5	 359	6.0 : 1	5.0 : 1
6	 281	2.5 : 1	4.0 : 1
7	 CO_2Et 374	12 : 1	/
8	 369	2 : 1	1.5 : 1

It can be seen from Table 16 that *syn* addition was favored in all the cases examined. If one assumes that the observed stereoselectivity arose from steric effects, then the more distant centers C-7 and C-9 (see **393**) must have been responsible for the predominant *syn* addition because C-6 and C-10 are both methylenes. Consequently, more *syn* addition would be expected when R_1 is replaced by a smaller group or R_3 is replaced by a bulkier group. Additionally, the size of the R_2 group should not make any difference to the stereoselectivity. This argument is contradicted by the results presented in Table 16. When R_1 in **354** (R_1 = H, Entry 2) was replaced by a methyl group, the resulting substrate **345** showed a much higher stereoselectivity for *syn* addition ($NaBH_4$: 100% *syn versus* 14 : 1; MeLi: 63 :1 *versus* 6.4 : 1). Likewise, compound **364** was found to be more stereoselective than **359** (see Entry 3 and Entry 5). Furthermore, R_2 did contribute significantly to the *syn/anti* ratio as a comparison of Entry 5 and Entry 6 reveals. It can be concluded that steric interactions cannot be the main reason for the preferred *syn* addition in these systems.

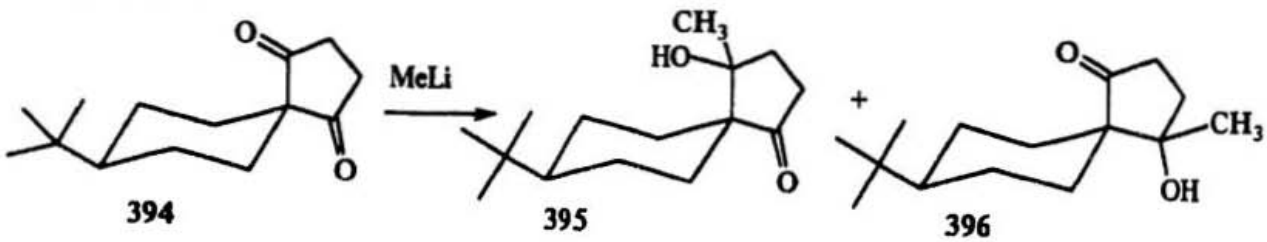


393

Although C-6 and C-10 must exert a very similar steric influence on reactions at either carbonyl, the geminal disubstituents at C-9 might contribute sterically. The *anti* face of a carbonyl might be blocked by the pseudo-axial substituent at C-9, but at any instant in time only one of these two substituents at C-9 can be pseudo-axial with respect

to the cyclohexene moiety. If the carbonyl in the pseudo-axial position is more reactive than the one in the pseudo-equatorial position, steric interactions might be of importance in determining the stereochemistry of nucleophilic additions to these spiro-diketones. This would not be trivial to determine with a cyclohexene ring. The strong preference for a *t*-butyl group to occupy the equatorial position on a cyclohexane ring has made it a useful group for the study of conformational effects. Addition of methyllithium to spiro-diketone **394**[*] generated a mixture of two epimers **395** and **396** in a 2.5 : 1 ratio, which was determined by integration of an inverse-gated ^{13}C NMR spectrum in which the contribution of the heteronuclear NOE was removed. Attempts to separate this mixture by flash chromatography or recrystallization were unsuccessful. This mixture showed IR absorption at 3392 cm^{-1} for hydroxyl groups and 1723 cm^{-1} for a five-membered ring carbonyl. The ^{1}H NMR spectra of these two isomers were almost identical. However, two sets of resonances were found in the ^{13}C NMR spectrum of this mixture. For instance, the carbonyl resonances were observed at δ 220.6 for the major and δ 222.3 for the minor isomer. The ^{13}C NMR data suggested that the major isomer was **396**,[**] *i.e.*, the equatorial carbonyl is more reactive, therefore it seems unlikely that the stereoselectivity is controlled by the steric interactions.

Scheme 81



394 **395** **396**

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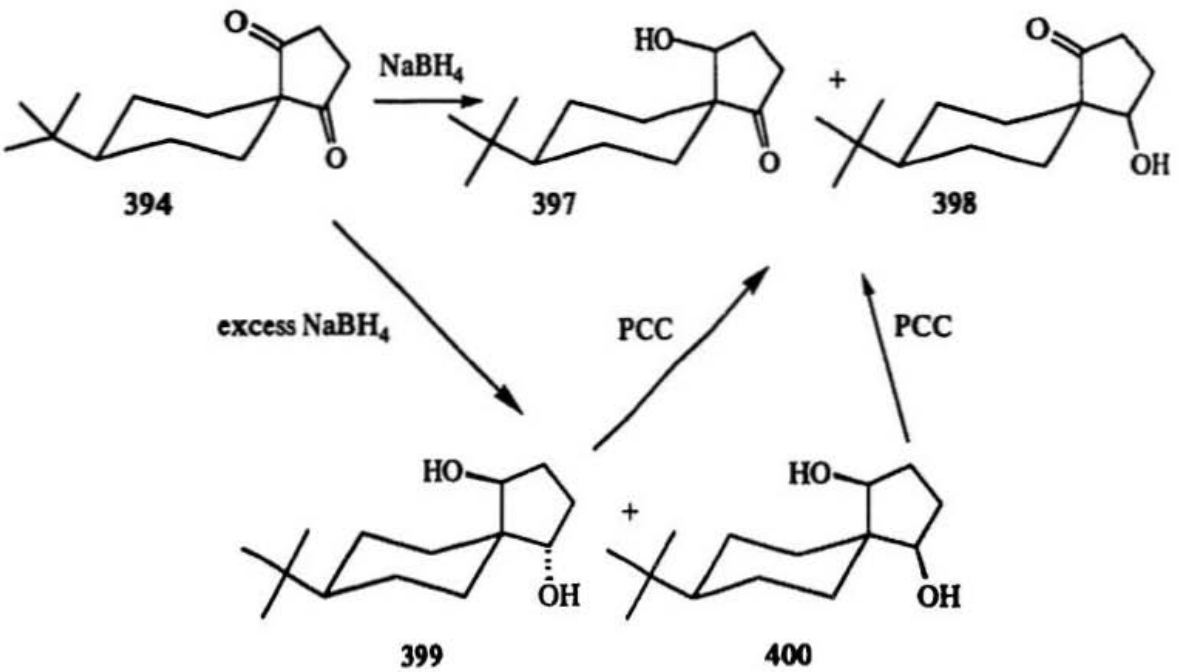
[*] The spiro-diketone **394** was kindly provided by T. J. Jenkins of our laboratory.

[**] The structure of **396** was confirmed by X-ray crystallography.

Reduction of **394** with 0.25 equivalents of sodium borohydride at room temperature afforded a mixture of two isomers **397** and **398** in a ratio of 18 : 1 as revealed by integration of the ^{1}H NMR of the crude reaction mixture. This mixture showed absorption at 3325 cm^{-1} for the hydroxyl group and at 1706 cm^{-1} for the carbonyl group in the IR spectrum. Likewise, the carbonyl groups were observed at δ 223.0 for the major and δ 222.1 for the minor isomer in the ^{13}C NMR spectrum. The carbons connected to the hydroxyl groups were found at δ 79.2 for the major and δ 73.6 for the minor isomers. These spectral data suggested that this mixture was two *mono*-alcohols **397** and **398**. In the case of **398**, the chemical shift for C-4 was shielded (higher-field) compared to its isomer **397** (79.2 *versus* 73.6). We believed that this difference resulted from a γ-gauche effect so in this case it was the axial carbonyl that was more reactive.

Scheme 82



When the spiro-diketone **394** was subjected to reduction with an excess of sodium borohydride, we obtained a mixture of two compounds, which could be easily separated by flash chromatography. The major product had an R_f value on TLC that was almost the

same as for the *mono* alcohols **397** and **398**. Its IR spectrum showed absorptions at 3490 and 3360 cm^{-1} for the hydroxyl function, but there was no absorption for a carbonyl group. Triplets at δ 4.15 and 3.64 in its ^{1}H NMR spectrum were consistent with hydrogens on the carbons connected to the hydroxyl groups. We concluded that this compound must be the diol. Indeed, X-ray diffraction analysis confirmed its structure as the *cis* diol **400** (see Figure 30). The minor product showed IR absorption at 3352 cm^{-1} for the hydroxyl group. The doublet at δ 4.17 and a triplet at δ 3.94 were probably due to the protons on carbons bearing the hydroxyl groups. Based on this result this minor product was believed to be the *trans*-diol. In fact, when this material was carefully oxidized by one equivalent of pyridium chlorochromate (PCC) a *ca.* 1 : 1 mixture of two *mono* epimers was obtained that had spectroscopic data identical with those of **397** and **398**.

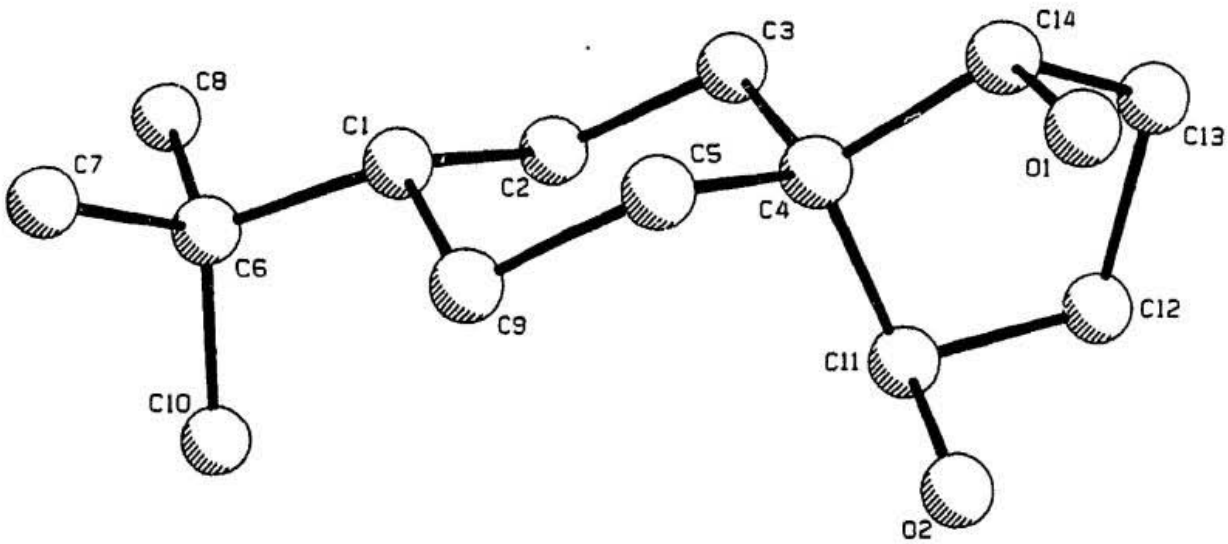
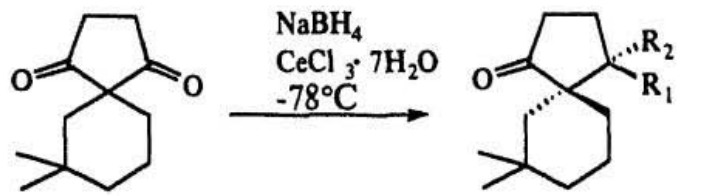


Figure 30. X-Ray crystal structure of 400

It has been reported that the reduction of the ketone with sodium borohydride in the presence of cerium(III) chloride proceeds preferentially from the more sterically hindered

face.[148] If the facial selectivity in the nucleophilic addition to spirodiketones resulted from a steric effect, we would expect that the stereoselectivity would decrease or reverse in the presence of cerium(III) chloride. When diketone **356** was treated with sodium borohydride and cerium(III) chloride at -78°C, a mixture of two epimers in a higher ratio (**380a** : **380b** = 16 : 1) was obtained. We believed that the higher stereoselectivity under this condition was due simply to the lower temperature.

Scheme 83



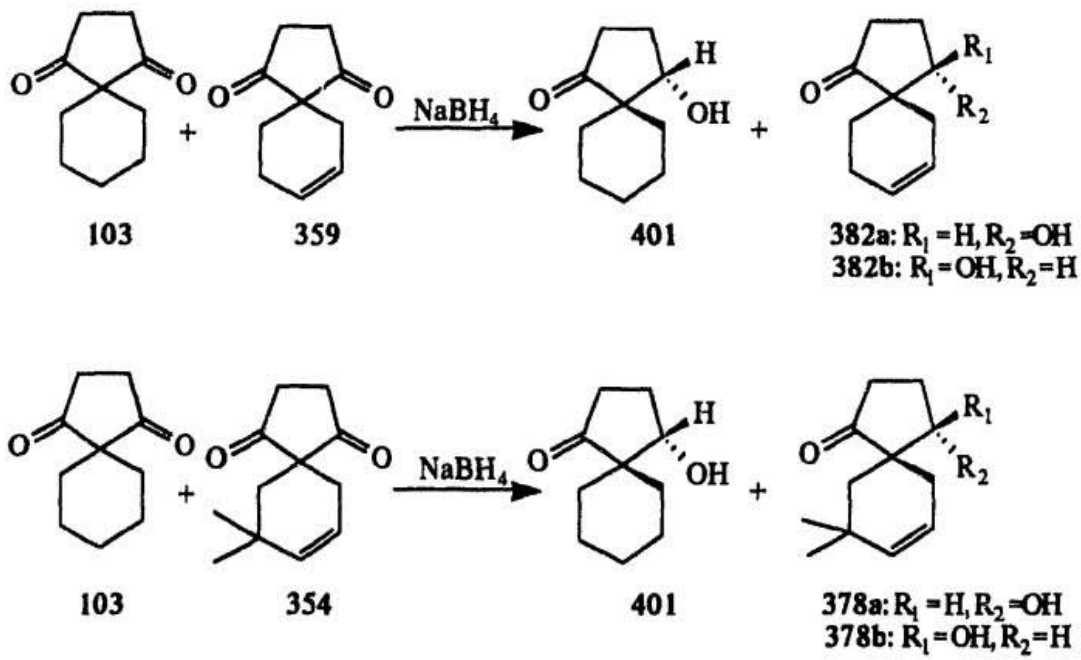
356

380a: R_1 = H, R_2 = OH
380b: R_1 = OH, R_2 = H

Experiments were also conducted to compare the rates of reaction of spiro-diketones **359** and **354** with simple diketone **103** (Scheme 84). Steric hindrance would retard the nucleophilic addition to either **359** or **354** based on an assumption that the stereoselectivity was attributed to the steric effects. Therefore, both diketones **354** and **359** might react more slowly than **103**. Treatment of a 1 : 1 mixture of **359** and **103** with limited sodium borohydride produced alcohols **382a/b** and **401** in a ratio of 1.5 : 1 as determined from the ^{1}H NMR spectrum of the crude product. This implied that the spirodiketone **359** reacted 1.5 times faster than did **103** with sodium borohydride. Examining the structures of these two diketones, the only difference between them is the presence of the double bond in **359**. Then, it must be this double bond which makes the diketone **359** more reactive than **103**. Similarly, reduction was carried out with a 1 : 1 mixture of **354** and **103** with sodium borohydride at room temperature. Analysis of the ^{1}H NMR spectrum of the crude product showed signals for **378a/b** and **401** in a ratio of 5 : 1. Again, it was both

the double bond and the methyl groups which activated the *syn* face of the diketone **354**. Consequently, compound **354** was reduced more than five times faster than **103**. These results further confirmed that the steric effects were not responsible for the facial selectivity.

Scheme 84



The main difference between the two faces of these spirodiketones was a C_7-C_8 double bond compared to a C_8-C_9 single bond. A simple mechanism could be that the nucleophiles associated directly with the double bond before, or during the addition (see Figure 31). According to this hypothesis, a substituent that increases the electron density of the double bond, regardless of its position on the double bond, should increase the proportion of *syn* addition, and a substituent that decreases the electron density of the double bond should decrease the proportion of *syn* addition. When the C-7 hydrogen in **354** was replaced by a methyl group (**345**, Entry 1), *syn* addition was indeed increased (for MeLi:

63 : 1 *versus* 6.4 : 1; for $NaBH_4$: 100% *syn versus* 14 : 1). However, replacement of C-8 hydrogen in **364** with an electron withdrawing substituent COOEt (**374**, Entry 7) showed higher facial selectivity than **364** (for $NaBH_4$: 9 : 1 *versus* 12.0 : 1). These results were contrary to the above prediction. Therefore, the facial selectivity of nucleophilic additions in this series of spirodiketones were not due to a direct association of the nucleophilic agent with the double bond.

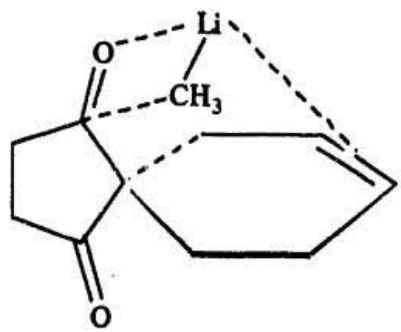
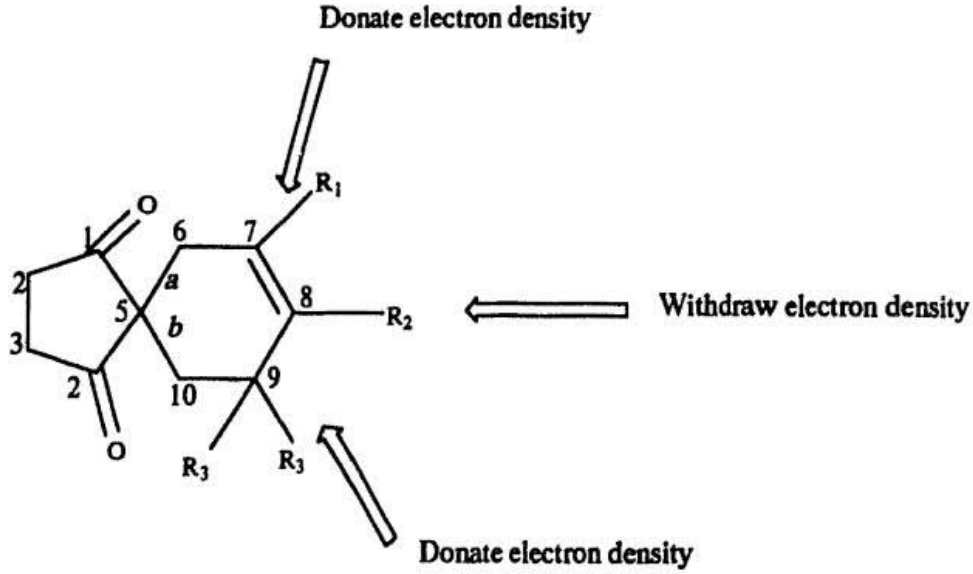


Figure 31. Direct association of methyllithium with the double bond of the spiro-diketone in the transition state

If the Felkin-Anh model is considered, the transition state is stabilized by electron transfer from the nucleophile into the low-lying *anti*-orbital of the vicinal bond. The nucleophile prefers to add to the carbonyl group *anti* to the less electron rich bond. The C_5-C_{10} σ bond in **393** is more electron-rich than the C_5-C_6 σ bond because C-6 is connected to an sp^2 carbon while C-10 is linked to the allylic sp^3 carbon. Consequently, the σ-orbital energy of C_5-C_6 is higher than that of C_5-C_{10}. In another words, the Felkin-Anh model suggests that the nucleophilic addition should be preferred on the *anti* face. Clearly, this prediction is contrary to what we have observed.



The predominantly *syn* additions of nucleophiles to our spiro-diketones are consistent with predictions based on the Cieplak hyperconjugative model. According to this model, delocalization of σ electrons in the electron-rich antiperiplanar bond into the incipient σ^* orbital lowers the transition state energy. Therefore, the facial selectivity can be correlated with the ability of the adjacent bonds to donate electron density (Figure 32). Although both C-6 and C-10 are methylenes, one might consider bond *a* to be less willing to relinquish electron density than bond *b*, because *a* would in turn receive less inductive assistance through a C-C bond to an sp^2 carbon than would *b*, which is attached to an allylic sp^3 carbon. A substituent that increases the ability of *b* to donate electron density, or a substituent that decreases the ability of *a* to donate electron density, should both enhance the facial selectivity. As seen in Table 16, compound **345** is much more stereoselective than **354** (see Entry 1 and Entry 2). This fact can be rationalized as follows:

addition of a methyl group to C-7 of **354** increases the electron-donating ability of bond *b* making the difference between *a* and *b* larger. Therefore, relatively less *anti* addition should be anticipated. Likewise, the geminal methyl groups at C-9 must donate electron density to *b* therefore enhancing the facial selectivity. In contrast, a carboxyethyl group on C-8 in **374** must make *a* a poorer electron-donor relative to *b*, thereby resulting in higher facial selectivity than **364** (see Entry 7 and Entry 3).

In sharp contrast with **359**, compound **369** showed only a slight preference for *syn* addition (see Entry 5 and Entry 8). In the case of **369**, the conformation of the seven-membered ring is more flexible than the corresponding six-membered ring in **359**, therefore, the stabilization effect due to electron donation from an antiperiplanar σ orbital into a low-lying vacant orbital of the forming bond $\sigma^*_{\neq}$ may not be as important as in the case of **359**.

It can be concluded that the *syn/anti* ratios shown in Table 15 can be explained reasonably well in terms of the Cieplak model. The loosely termed electronic effect is mainly responsible for the observed *syn* addition. However, we do not preclude a steric contribution. In fact, in some cases, such as compounds **345** and **356**, a combination of electronic and steric effects is probably the reason for the predominant *syn* addition.

IV Experimental*

9,9-Dimethyl-1,4-dioxaspiro[4.5]dec-7-ene (350) and 9,9-dimethyl-1,4-dioxaspiro[4.5]dec-6-ene (351)

A solution of enone **148b** (1.42 g, 11.4 mmol) which was obtained from dimedone **146** (see Chapter 2: Experimental), ethylene glycol (5 mL, excess) and *p*TSA (200 mg) in benzene (60 mL) was heated under reflux overnight with a Barrett water separator. Solid $NaHCO_3$ was added after the reaction mixture had cooled. The solution was diluted with water. The aqueous layer was extracted with ether (×3), and the combined organic extracts were washed with water and saturated NaCl. The solution was dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give a yellow oil. Careful flash chromatography (1% ethyl acetate in hexane) gave a mixture of **350** and **351** in a ratio of 14 : 1 as a colorless oil (0.82 g, 42%): IR (film) ν_{max}: 2954 (s) and 1360 (m) cm^{-1}. For **350**: ^1H NMR δ: 1.07 (s, 6H), 1.66 (s, 2H), 2.21 (m, 2H), 3.94 (s, 4H), 5.46 (m, 1H), and 5.49 (dd, J = 3.0, 9.9 Hz, 1H); ^{13}C NMR δ: 29.9 (2C, 3), 34.5 (0), 34.8 (2), 43.9 (2), 63.8 (2C, 2), 108.3 (0), 120.2 (1), and 136.9 (1); MS (from GC-MS) *m/z* (%): 168 (8, M^+), 153 (8), 86 (100), 82 (12), 81 (9), 43 (16), 42 (28), and 41 (18). For **351**: ^1H NMR δ: 1.01 (s, 6H), 1.71 (s, 2H), 1.84 (m, 2H), 3.94 (s, 4H), 5.82-5.90 (m, 1H), and 5.55 (m, 1H); ^{13}C NMR δ: 29.7 (2C, 3), 38.3 (0), 38.8 (2), 46.1 (2), 63.9 (2C, 2), 105.5 (0), 126.1 (1), and 130.4 (1); MS (from GC-MS) *m/z* (%): 168 (1, M^+), 112 (100), 86 (12), 68 (32), and 41 (15).

9,9-Dimethylspiro[4.5]dec-7-ene-1,4-dione (354)

A solution of the ketal mixture **350** and **351** (214 mg, 1.28 mmol) in CH_2Cl_2 (40 mL) was cooled to -78°C. Freshly distilled $BF_3{\cdot}Et_2O$ (2.4 mL, 19 mmol) was added followed, dropwise, by a solution of **77** (1.0 mL, 3.8 mmol) in 5 mL of dry CH_2Cl_2. The

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* For General Procedures, see Chapter 1: Experimental Section

resulting yellow solution was stirred overnight, over which time the solution was allowed to attain room temperature. This mixture was added slowly to an ice-cooled saturated $NaHCO_3$ solution, and the aqueous layer was extracted with CH_2Cl_2 (×3). The combined organic extracts were washed with water and saturated NaCl, then dried over $MgSO_4$. After concentration *in vacuo* the residue was purified by flash chromatography (5% ethyl acetate in hexane) to provide **354** as colorless crystals (181 mg, 74%): mp 59.5-61°C; IR (film) ν_{max}: 1764 (sh), 1724 (s), and 1428 (m) cm^{-1}; ^1H NMR δ: 0.99 (s, 6H), 1.73 (s, 2H), 2.15 (m, 2H), 2.62-2.68 (m, 2H), 2.98-3.12 (m, 2H), 5.52 (dt, J = 2.1, 10.1 Hz, 1H), 5.72 (dt, J = 3.8, 10.1 Hz, 1H); ^{13}C NMR δ: 24.4 (2), 29.6 (2C, 3), 32.1 (0), 34.5 (2), 43.0 (2C, 2), 57.8 (0), 121.0 (1), 135.1 (1), and 214.0 (2C, 0); MS (from GC-MS) *m/z* (%): 192 (28, M^+), 149 (57), 135 (32), 117 (43), 107 (32), 93 (75), 91 (97), 79 (41), 77 (86), 67 (55), 65 (55), 57 (34), 55 (68), 53 (57), 51 (42), 43 (50), and 41 (100). *Exact mass* calcd. for $C_{12}H_{16}O_2$: 192.1149; found: 192.1145.

7,7-Dimethylspiro[4.5]decane-1,4-dione (356)

To a solution of spiro-diketone **354** (207 mg, 1.08 mmol) in methanol (30 mL) was added 10% palladium on activated carbon (50 mg) slowly. The solution was shaken for two hours under hydrogen (50 psi). The resulting black suspension was filtered to remove the catalyst, and the filtrate was concentrated *in vacuo*. Flash chromatography of the residue (6% ethyl acetate in hexane) provided **356** (194 mg, 93%) as a colorless oil: IR (film) ν_{max}: 1757 (sh) and 1722 (s) cm^{-1}; ^1H NMR δ: 0.94 (s, 6H), 1.32-1.36 (m, 2H), 1.46 (s, 2H), 1.53-1.57 (m, 4H), 2.61-2.67 (m, 2H), and 2.90-2.97 (m, 2H); ^{13}C NMR δ: 17.4 (2), 26.0 (2), 29.3 (2C, 3), 30.7 (0), 34.1 (2C, 2), 37.6 (2), 43.0 (2), 57.5 (0), and 214.8 (2C, 0); MS (from GC-MS) *m/z* (%): 194 (17, M^+), 125 (100), 97 (20), 95 (29), 81 (22), 79 (24), 69 (52), 67 (33), 56 (20), 55 (57), 53 (33), 43 (26), and 41 (87). *Exact mass* calcd. for $C_{12}H_{18}O_2$: 194.1306; found: 194.1300.

1,4-Dioxaspiro[4.5]dec-7-ene (357) and 1,4-dioxaspiro[4.5]dec-6-ene (358)

A solution of 2-cyclohexen-1-one **148a** (2.50 g, 25 mmol), ethylene glycol (7.0 mL, excess), and *p*TSA (400 mg) in benzene (60 mL) was heated under reflux overnight with a Barrett water separator. Saturated $NaHCO_3$ solution was added when the reaction mixture had cooled. The aqueous layer was extracted with ether (×3), and the combined organic layers were washed with water and saturated NaCl. The organic solution was then dried over anhydrous $MgSO_4$ and evaporated *in vacuo*. Fractional distillation of the residue provided two fractions: homogeneous **357** (1.81 g, 26%) and a **4** : 5 mixture of **357** and **358** (1.02 g, 14%). For **357**: ^{1}H NMR δ: 1.76 (t, J = 6.5 Hz, 2H), 2.62 (m, 4H), 3.98 (s, 4H), 5.56-5.66 (m, 1H), and 5.68-5.78 (m, 1H); ^{13}C NMR δ: 24.4 (2), 30.9 (2), 35.6 (2), 64.2 (2C, 2), 107.7 (0), 124.1 (1), and 126.3 (1); MS (from GC-MS) *m/z* (%): 140 (40, M^+), 125 (15), 86 (100), 67 (11), 43 (13), 42 (36), and 41 (13). For **358** (from the mixture): ^{1}H NMR δ: 1.70-1.83 (m, 4H), 1.96-2.07 (m, 2H), 3.92-4.01 (m, 4H), 5.56-5.75 (m, 1H), and 5.93-6.05 (m, 1H); ^{13}C NMR δ: 20.6 (2), 24.7 (2), 33.3 (2), 64.2 (2C, 2), 105.5 (0), 127.3 (1), and 132.7 (1); MS (from GC-MS): *m/z* (%): 140 (2, M^+), 112 (100), 79 (14), 68 (40), and 55 (11).

Spiro[4.5]dec-7-ene-1,4-dione (359)

A solution of the ketal **357** (119 mg, 0.85 mmol) in CH_2Cl_2 (50 mL) was treated with $BF_3{\cdot}Et_2O$ (1.6 mL, 12.8 mmol) and **77** (0.6 mL, 2.1 mmol), in the same way as for ketals **350** and **351**, to give **359** (91 mg, 75%): mp 53-54°C; IR (film) ν_{max}: 1749 (sh), 1716 (s), and 1438 (m) cm^{-1}; ^{1}H NMR δ: 1.73 (t, J = 6.1 Hz, 2H), 2.82 (m, 8H), and 5.76 (m, 2H); ^{13}C NMR δ: 20.8 (2), 25.8 (2), 27.0 (2), 34.1 (2C, 2), 55.3 (0), 122.9 (1), 125.4 (1), and 214.4 (2C, 0); MS (from GC-MS) *m/z* (%): 164 (100, M^+), 136 (44), 135 (36), 122 (28), 121 (24), 108 (22), 107 (43), 81 (17), 80 (53), 79 (93), 78 (15), 77 (37), 56 (17), 55 (25), 53 (15), 51 (17), and 43 (17). *Exact mass* calcd. for $C_{10}H_{12}O_2$: 164.0837; found: 164.0843.

A 4 : 5 mixture of **357** and **358** (114 mg, 0.82 mmol) was treated with $BF_3{\cdot}Et_2O$ (1.5 mL, 12 mmol) and **77** (0.5 mL, 2.0 mmol) as above to give **359** (95 mg, 71%) as the

only product.

7-Methyl-1,4-dioxaspiro[4.5]dec-7-ene (362) and 7-methyl-1,4-dioxaspiro[4.5]dec-6-ene (363)

The enone **361** (1.34 g, 12.2 mmol) was treated with ethylene glycol (8.0 mL) and *p*TSA (300 mg) in the same way as for enone **148b** to give a mixture of **362** and **363** (0.88 g, 47%) in a ratio of 14 : 1 ratio after chromatography (1% ethyl acetate in hexane) as a colorless oil: IR (film) ν_{max}: 2930 (s) and 1366 (m) cm^{-1}. For **362**: ^{1}H NMR δ: 1.69 (br s, 5H), 2.19 (br s, 4H), 3.99 (br s, 4H), and 5.43 (m, 1H); ^{13}C NMR δ: 23.1 (3), 23.9 (2), 30.3 (2), 40.1 (2), 64.1 (2C, 2), 108.1 (0), 120.0 (1), and 131.4 (0); MS (from GC-MS) *m/z*: 154 (22, M^+), 139 (10), 86 (100), 43 (14), 42 (34), and 41 (12). For **363**: MS (from GC-MS) *m/z* (%): 154 (12, M^+), 126 (100), 111 (11), 99 (20), 82 (29), 79 (23), 67 (73), 55 (12), and 41 (12).

7-Methylspiro[4.5]dec-7-ene-1,4-dione (364) and 7-methylspiro[4.5]dec-6-ene-1,4-dione (365)

A 14 : 1 mixture of **362** and **363** (219 mg, 1.42 mmol) was treated with $BF_3{\cdot}Et_2O$ (2.6 mL, 21 mmol) and **77** (1.1 mL, 4.3 mmol), in the same way as for ketals **350** and **351**, to give **364** (104 mg, 41%) and a mixture of **364** and **365** (89 mg, 35%) in a 11.2 : 1 ratio after flash chromatography (5% ethyl acetate in hexane). For **364**: IR (film) ν_{max}: 1759 (sh), 1721 (s), and 1435 (m) cm^{-1}; ^{1}H NMR δ: 1.73 (dd, J = 5.1, 6.2 Hz, 2H), 1.77 (br s, 3H), 2.07 (br s, 2H), 2.16 (m, 2H), 2.69-3.04 (m, 4H), and 5.54 (m, 1H); ^{13}C NMR δ: 21.1 (2), 23.2 (3), 27.5 (2), 30.1 (2), 34.1 (2C, 2), 56.3 (0), 119.5 (1), 130.2 (0), and 214.4 (2C, 0); MS (from GC-MS) *m/z* (%): 178 (52, M^+), 149 (21), 135 (48), 121 (35), 94 (27), 93 (40), 91 (53), 79 (100), 78 (20), 77 (77), 67 (26), 65 (35), 57 (20), 55 (50), 53 (47), 43 (45), 42 (27), and 41 (48). *Exact mass* calcd. for $C_{11}H_{14}O_2$: 178.0993; found: 178.0987. For **365** (from the mixture): ^{1}H NMR δ: 4.97 (br s, 1H), the rest of the signals were buried in the signals of the major isomer; ^{13}C NMR δ: 17.7 (2), 23.9 (3), 27.9 (2),

28.8 (2), 24.5 (2C, 2), 59.8 (0), 113.9 (1), 141.3 (0), and 214.2 (2C, 0); MS (from GC-MS) *m/z* (%): 178 (4, M^+), 79 (10), 58 (19), 57 (16), 56 (14), 43 (100), 42 (17), and 41 (24).

1,4-Dioxaspiro[4.6]undec-7-ene (367)

The enone **366** (1.29 g, 11.7 mmol) was treated with ethylene glycol (5 mL) and *p*TSA (200 mg), in the same way as for enone **148b**, to give only ketal **367** (1.08 g, 57%) as a colorless oil: IR (film) ν_{max}: 2920 (s) and 1446 (m) cm^{-1}; ^1H NMR δ: 1.58-1.66 (m, 2H), 1.92-1.96 (m, 2H), 2.14-2.19 (m, 2H), 3.93 (narrow sextet, J = 1.2 Hz, 2H), 5.56-5.64 (m, 1H), and 5.88-5.96 (m, 1H); ^{13}C NMR δ: 22.5 (2), 28.0 (2), 37.1 (2), 40.5 (2), 64.1 (2C, 2), 108.5 (0), 124.5 (1), and 133.2 (1); MS (from GC-MS) *m/z* (%): 154 (10, M^+), 125 (100), 99 (56), 86 (17), 82 (18), 81 (35), 79 (22), 68 (17), 67 (24), 55 (39), 54 (18), 53 (23), and 41 (32).

Spiro[4.6]undec-7-ene-1,4-dione (369)

The ketal **367** (342 mg, 2.22 mmol) was treated with $BF_3{\cdot}Et_2O$ (4.1 mL, 33 mmol) and **77** (1.8 mL, 6.7 mmol), in the same way as for ketals **350** and **351**. Chromatography (5% ethyl acetate in hexane) of the crude reaction mixture gave **369** only (138 mg, 35%) as a colorless oil: IR (film) ν_{max}: 1718 (s) and 1443 (m) cm^{-1}; ^1H NMR δ: 1.73 (m, 2H), 1.84 (m, 2H), 2.28 (m, 4H), 2.77 (m, 4H), 5.54 (m, 1H), and 5.89 (m, 1H); ^{13}C NMR δ: 20.2 (2), 28.9 (2), 30.2 (2), 32.4 (2), 34.3 (2C, 2), 58.5 (0), 123.8 (1), 133.9 (1), and 214.6 (2C, 0); MS (from GC-MS) *m/z* (%): 178 (86, M^+), 112 (41), 111 (98), 95 (35), 93 (37), 91 (55), 83 (37), 79 (100), 77 (49), 68 (54), 67 (60), 65 (33), 57 (30), 56 (31), 55 (86), 44 (51), and 41 (61). *Exact mass* calcd. for $C_{11}H_{14}O_2$: 178.0993; found: 178.0996.

8-Carbethoxy-7-methyl-1,4-dioxaspiro[4.5]dec-7-ene (373)

The enone ester **372** (585 mg, 3.38 mmol) was treated with ethylene glycol (5 mL, excess) and *p*TSA (80 mg) the same as for enone **148b**. Chromatography of the crude

product (6% ethyl acetate in hexane) provided **373** only as a colorless oil (533 mg, 84%): IR (film) ν_{max}: 1712 cm^{-1}; ^1H NMR δ: 1.28 (t, J = 7.2 Hz, 3H), 1.74 (t, J = 6.6 Hz, 2H), 2.01 (s, 3H), 2.37 (s, 2H), 3.98 (s, 4H), and 4.17 (q, J = 7.2 Hz, 2H); ^{13}C NMR δ: 14.0 (3), 21.4 (3), 25.3 (2), 30.4 (2), 43.1 (2), 59.7 (2), 64.2 (2C, 2), 107.0 (0), 123.3 (0), 142.9 (0), and 167.9 (0); MS (from GC-MS) *m/z* (%): 182 (7, M^+), 154 (21), 126 (32), 109 (70), 98 (100), 81 (37), 79 (30), 53 (39), and 41 (46).

8-Carbethyoxy-7-methylspiro[4.5]dec-7-ene-1,4-dione (374) and 8-carbethoxy-9-methylspiro[4.5]dec-7-ene-1,4-dione (376)

The ketal **373** (225 mg, 1.24 mmol) was treated with $BF_3{\cdot}Et_2O$ (2.3 mL, 18 mmol) and **77** (0.7 mL, 2.5 mmol), the same as for ketals **350** and **351**. Chromatography of the crude product (7% ethyl acetate in hexane) afforded a mixture of **374** and **376** as a colorless oil (223 mg, 72%) in a *ca.* 11 : 1 ratio: IR (film) ν_{max}: 1721 (s), 1645(m), and 1480 cm^{-1}. For **374**: ^1H NMR δ: 1.29 (t, J = 7.2 Hz, 3H), 1.74 (t, J = 6.3 Hz, 2H), 2.11 (s, 3H), 2.24 (s, 2H), 2.38 (br s, 2H), 2.64-3.03 (m, 4H), and 4.18 (q, J = 6.9 Hz, 2H); ^{13}C NMR δ: 14.2 (3), 21.5 (3), 22.2 (2), 28.2 (2), 33.6 (2), 34.2 (2), 56.4 (0), 59.8 (2C, 2), 122.7 (0), 143.4 (0), 167.5 (0), and 213.8 (2C, 0); MS (from GC-MS) *m/z* (%): 250 (6, M^+), 205 (26), 204 (100), 177 (26), 176 (75), 175 (24), 91 (45), 77 (32), and 55 (27). *Exact mass* calcd. for $C_{14}H_{18}O_4$: 250.124; found: 250.1206. For **376**: ^1H NMR δ: 5.11 (s, 1H), the remaining signals were buried in the signals due to the major isomer; ^{13}C NMR δ: 14.1 (3), 22.9 (3), 25.0 (2), 34.7 (2), 44.4 (1), 56.4 (0), 60.8 (2C, 2), 117.5 (1), 137.5 (0), 172.9 (0), and 213.2 (2C, 0); MS (from GC-MS) *m/z* (%): 250 (27, M^+), 177 (100), 131 (41), 121 (41), 93 (28), 91 (59), 77 (53), and 55 (27).

(4R*,5R*)- (377a) and (4R*,5S*)-4-Hydroxy-4,9,9-trimethylspiro[4.5]dec-7-en-1-one (377b)

To a solution of diketone **354** (147 mg, 0.77 mmol) in anhydrous ether (40 mL) was added a 1.4 M methyllithium solution in ether (1.6 mL, 2.3 mmol) at -78°C. The reaction

mixture was stirred for another two hours at -78°C before it was cautiously quenched with water. The aqueous layer was extracted with ether (×3). The combined organic extracts were washed with water and saturated NaCl, then dried over $MgSO_4$ and concentrated *in vacuo*. The ^1H NMR spectrum of the residue indicated that it was a 6.4 : 1 mixture of two epimers (**377a** : **377b**). Purification of the residue by flash chromatography (4% ethyl acetate in hexane) provided **377a** (166 mg, 85%) and **377b** (12 mg, 6%) as colorless oils. For **377a**: IR (film) ν_{max}: 3463 (br), 1726, and 1460 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.93 (s, 3H), 1.03 (s, 3H), 1.15 (s, 3H), 1.78 (br s, OH), 1.89-1.99 (m, 4H), 2.14-2.31 (m, 3H), 2.54-2.63 (m, 1H), 5.48 (dt, J = 2.1, 10.2 Hz, 1H), and 5.66 (ddd, J = 3.0, 4.8, 10.2 Hz, 1H); ^1H NMR (C_6D_6) δ: 0.80 (s, 3H), 0.97 (s, 3H), 1.00 (s, 3H), 1.35-1.50 (m, 2H), 1.61-1.93 (m, 6H including OH), 2.16-2.28 (m, 1H), 5.48 (dm, J = 10.2 Hz, 1H), and 5.63 (ddd, J = 2.7, 5.1, 10.2 Hz, 1H); NOE data (C_6D_6): irradiate 5.61: NOE 5.46-5.51 (8), 1.82-1.90 (2%); irradiate 5.46-5.51: NOE 5.60-5.61 (8%), 1.00 (2%), 0.97 (2.5%); irradiate 1.00 and 0.97: NOE 1.64-1.70 (5), 5.46-5.51 (11%); irradiate 0.80: NOE 1.38-1.48 (6%), and 1.82-1.90 (1%); ^{13}C NMR ($CDCl_3/C_6D_6$) δ: 24.4/24.3 (3), 25.5/26.0 (2), 28.3/28.7 (3), 32.0/32.0 (0), 32.6/32.7 (3), 33.4/33.6 (2), 34.2/34.1 (2), 38.3/38.3 (2), 55.1/55.2 (0), 78.0/77.7 (1), 121.6/122.4 (1), 136.4/136.5 (0), and 219.8/218.0 (0); MS (from GC-MS) *m/z* (%): 208 (3, M^+), 132 (19), 107 (14), 99 (20), 91 (20), 55 (20), 43 (100), and 41 (33). *Exact mass* calcd. for $C_{13}H_{20}O_2$: 208.1462; found: 208.1466. For **377b**: IR (film) ν_{max}: 3454 (br), 1731 (s), and 1460 cm^{-1}; ^1H NMR δ: 0.89 (s, 3H), 0.99 (s, 3H), 1.29 (s, 3H), 1.43-1.63 (m, 3H including a broad singlet at 1.56 for OH), 1.84-2.46 (m, 6H), 5.48 (d of quintets, J = 1.5, 10.2 Hz, 1H), and 5.74 (ddd, J = 2.7, 5.1, 10.2 Hz, 1H); MS essentially the same as for **356**. *Exact mass* calcd. for $C_{13}H_{20}O_2$: 208.1462; found: 208.1468.

(4R*,5S*)- (378a) and (4R*,5R*)-4-Hydroxy-9,9-dimethylspiro[4.5]dec-7-en-1-one (378b)

To a solution of diketone **354** (124 mg, 0.65 mmol) in methanol (30 mL) was added sodium borohydride (6.2 mg, 0.16 mmol) in portions at room temperature. The reaction mixture was stirred for 30 min. Water was added to the reaction mixture and much of the methanol was evaporated *in vacuo*. The residue was diluted with ether and water (1 : 1) and extracted with ether (×3). The combined organic extracts were washed with water and saturated NaCl, then dried over $MgSO_4$ and concentrated *in vacuo*. ^{1}H NMR of the residue indicated that a 14 : 1 mixture of epimers (**378a** : **378b**) was produced. Purification of the residue by flash chromatography (6% ethyl acetate in hexane) provided **378a** (110 mg, 87%) as colorless crystals and **378b** (8 mg, 7%) as a colorless oil. For **378a**: mp 58-59°C; IR (film) ν_{max}: 3473 (br), 1728 (s), and 1459 (m) cm^{-1}; ^{1}H NMR δ: 1.04 (s, 3H), 1.07 (s, 3H), 1.70 (m, 2H), 1.84 (m, 2H), 2.00-2.24 (m, 3H), 2.29-2.32 (m, 1H), 2.44-2.49 (m, 1H), 4.28 (m, 1H), and 5.46-5.55 (m, 2H); ^{13}C NMR δ: 28.0 (2), 30.0 (3), 30.9 (0), 31.7 (3), 33.2 (2), 35.2 (2C, 2), 53.6 (0), 74.4 (1), 120.0 (1), 137.7 (1), and 222.0 (0); MS (from GC-MS) *m/z* (%): 194 (1, M^+), 107 (29), 91 (40), 77 (41), 67 (38), 65 (26), 55 (45), 53 (32), 43 (64), 42 (20), and 41 (100). *Exact mass* calcd. for $C_{12}H_{18}O_2$: 194.1306; found: 194.1308. For **378b**: IR (film) ν_{max}: 3447 (br), 1730 (s), and 1460 cm^{-1}; ^{1}H NMR δ: 1.01 (s, 3H), 1.09 (s, 3H), 1.45 (d, J = 4.1 Hz, 1H), 1.70 (d, J = 4.1 Hz, 1H), 1.57 (dd, J = 4.1, 16.2 Hz, 2H), 1.80-1.92 (m, 2H), 2.07-2.10 (m, 2H), 2.20-2.42 (m, 4H), 4.34 (m, 1H), 5.53-5.57 (m, 1H), and 5.68-5.71 (m, 1H); MS essentially the same as **378a**. *Exact mass* calcd. for $C_{12}H_{18}O_2$: 194.1306; found: 194.1298. These two alcohols were converted into the same ketone **354** upon oxidation with PCC.

Reaction of diketone 356 with methyllithium

The diketone **356** (90 mg, 0.46 mmol) was treated with methyllithium (0.7 mL, 0.9 mmol), the same as for **354**, to provide an oily product, which contained a mixture of epimers in a ratio of 3 : 1 (**379a : 379b**) as revealed by ^{1}H NMR integration. Chromatography (6% ethyl acetate in hexane) of this mixture failed to separate the two epimers (85 mg, 86%) as a colorless oil recovered and 7 mg of starting material **356** (8%) was

recovered also.

(4R*,5S*)-4-Hydroxy-4,7,7-trimethylspiro[4.5]decan-1-one (379a)

To a solution of keto alcohol **377a** (142 mg, 0.68 mmol) in methanol (30 mL) was added 10% palladium on activated carbon (50 mg) slowly. The solution was shaken for two hours under hydrogen (50 psi). The resulting black suspension was filtered to remove the catalyst and the filtrate was purified by chromatography (6% ethyl acetate in hexane) to afford **379a** (135 mg, 94%): IR (film) ν_{max}: 3450 (br) and 1726 (s) cm^{-1}; ^1H NMR δ: 0.91 (s, 3H), 0.94 (s, 3H), 0.99-1.17 (m, 2H), 1.12 (s, 3H), 1.49 (s, 2H), 1.51-1.55 (m, 1H), 1.62-1.66 (m, 1H), 1.75 (br s, OH), 1.84-1.96 (m, 3H), 2.05-2.21 (m, 1H), and 2.44-2.55 (m, 1H); ^{13}C NMR δ: 18.7 (2), 24.0 (3), 25.9 (3), 26.1 (2), 30.8 (0), 32.9 (2), 34.0 (2), 35.0 (3), 38.5 (2), 38.5 (2), 55.2 (0), 78.6 (1), and 220.4 (0); MS (from GC-MS) *m/z* (%): 210 (14, M^+), 152 (47), 141 (10), 137 (15), 109 (38), 99 (17), 95 (19), 81 (15), 69 (22), 67 (12), 55 (24), 43 (100), and 41 (38). *Exact mass* calcd. for $C_{13}H_{22}O_2$: 210.1619; found: 210.1610.

(4R*,5R*)-4-Hydroxy-4,7,7-trimethylspiro[4.5]decan-1-one (379b)

The minor keto alcohol **377b** (5.3 mg, 0.02 mmol) was hydrogenated with 10% palladium on carbon (*ca.* 20 mg), the same as with the major isomer **377a**. Chromatography (5% ethyl acetate in hexane) of the crude product afforded **379b** (3.2 mg, 59%) as a colorless oil: IR (film) ν_{max}: 3443 (br) and 1728 (s) cm^{-1}; ^1H NMR δ: 0.84 (s, 3H), 0.88 (s, 3H), 0.90 (s, 3H), and 1.02-2.04 (mm, 13H including OH); MS essentially the same as for **379a**. *Exact mass* calcd. for $C_{13}H_{22}O_2$: 210.1619; found: 210.1621.

(4R*,5S*)- (380a) and (4R*,5R*)-4-Hydroxy-7,7-dimethylspiro[4.5]decan-1-one (380b)

The diketone **356** (129 mg, 0.67 mmol) was reduced with sodium borohydride (6.5 mg, 0.17 mmol), the same as for diketone **354**. Analysis of the ^1H NMR spectrum of the

crude product showed signals for **380a** and **380b** in a ratio of 6.7 : 1. Chromatography of the crude product failed to separate the mixture of epimers (107 mg, 82%): IR (film) ν_{max}: 3460 (br) and 1726 (s) cm^{-1}. For **380a**: ^1H NMR δ: 0.97 (s, 3H), 1.00 (s, 3H), 1.02-1.50 (m, 8H), 1.85 (br s, OH), 1.95-2.45 (m, 4H), and 4.46 (br s, 1H); ^{13}C NMR δ: 19.2 (2), 26.7 (3), 27.9 (3), 29.5 (0), 31.0 (2), 33.0 (2), 33.3 (2), 36.8 (2), 38.7 (2), 55.0 (0), 74.7 (1), and 222.2 (0); MS (from GC-MS) *m/z* (%): 196 (13, M^+), 181 (26), 121 (21), 109 (69), 95 (27), 93 (20), 81 (37), 79 (26), 70 (23), 69 (100), 57 (22), 55 (59), 53 (24), 43 (52), and 41 (100).

(4R*,5S*)- (381a) and (4R*,5R*)-4-Hydroxy-4-methylspiro[4.5]dec-7-en-1-one (381b)

The diketone **364** (139 mg, 0.84 mmol) was treated with methyllithium (1.2 mL, 1.69 mmol), the same as for **354**, to provide a 5.0 : 1 mixture of two epimers, which were separated by flash chromatography (4% ethyl acetate in hexane) to give **381a** (116 mg, 76%) and **381b** (15 mg, 10%) as colorless oils. For **381a**: IR (film) ν_{max}: 3486 (br), 1727 (s), and 1440 cm^{-1}; ^1H NMR δ: 1.28 (s, 3H), 1.75-1.87 (m, 2H), 1.93-2.28 (m, 8H including OH), 2.41-2.53 (m, 1H), 5.62-5.69 (m, 1H), and 5.72-5.79 (m, 1H); ^{13}C NMR δ: 22.0 (2), 22.4 (2), 24.3 (3), 27.8 (2), 33.9 (2), 34.1 (2), 53.9 (0), 79.4 (0), 123.8 (1), 126.9 (1), and 220.6 (0); MS (from GC-MS) *m/z* (%): 180 (6, M^+), 122 (24), 107 (13), 105 (12), 104 (21), 99 (12), 91 (12), 81 (19), 80 (11), 79 (32), 78 (10), 77 (17), 55 (17), 53 (14), 51 (10), 43 (100), and 41 (23). *Exact mass* calcd. for $C_{11}H_{16}O_2$: 180.1149; found: 180.1139. For **381b**: IR (film) ν_{max}: 3477 (br) and 1729 (s) cm^{-1}; ^1H NMR δ: 1.30 (s, 3H), 1.46-1.57 (m, 2H), 1.92-2.18 (8H including OH), 2.34-2.40 (m, 1H), and 5.71-5.83 (m, 2H). MS essentially the same as **381a**.

(4R*,5S*)- (382a) and (4R*,5R*)-4-Hydroxyspiro[4.5]dec-7-en-1-one (282b)

The spiro-diketone **364** (133 mg, 0.81 mmol) was reduced with sodium borohydride (7.7 mg, 0.32 mmol), the same as for **354**, to provide a 6.0 : 1 (determined by integration

of an inverse-gated ^{13}C NMR spectrum in which NOE contributions were removed) mixture of two epimers (127 mg, 94%), which were inseparable by flash chromatography: IR (film) ν_{max}: 3447 (br), 1727, and 1437 (s) cm^{-1}. For **382a**: ^{1}H NMR δ: 1.52-2.60 (m, 11H including two OH), 4.23-4.31 (m, 1H), 5.57-5.69 (m, 1H), and 5.70-5.82 (m, 1H); ^{13}C NMR δ: 22.2 (2), 22.3 (2), 28.4 (2), 30.7 (2), 34.3 (2), 52.6 (0), 75.3 (1), 123.4 (1), 127.6 (1), and 221.4 (0); MS (from GC-MS) *m/z* (%): 166 (M^+), 133 (15), 122 (25), 107 (32), 106 (41), 105 (27), 104 (34), 91 (58), 81 (25), 79 (100), 78 (29), 77 (41), 55 (31), 53 (25), and 41 (34). For **382b**: ^{1}H NMR was almost identical with **382a**; ^{13}C NMR δ: 25.2 (2), 27.4 (2), 27.9 (2), 30.9 (2), 34.1 (2), 52.6 (0), 77.2 (1), 125.5 (1), 126.2 (1), and 220.5 (0); MS essentially the same as for **382a**. *Exact mass* calcd. for $C_{10}H_{14}O_2$: 166.0993; found: 166.0994.

(4R*,5S*)- (383a) and (4R*,5R*)-4-Hydroxy-4,7-dimethylspiro[4.5]dec-7-en-1-one (383b)

The spiro-diketone **364** (148 mg, 0.83 mmol) was treated with methyllithium (1.2 mL, 1.7 mmol), the same as for **354**, to provide a 6 : 1 mixture of epimers (**383a** : **383b**). Chromatography (6% ethyl acetate in hexane) failed to separate the two epimers (138 mg, 86%): IR (film) δ_{max}: 3467 (br), 1729, and 1447 (s) cm^{-1}. For **383a**: ^{1}H NMR δ: 1.26 (s, 3H), 1.64-2.53 (m, 14H including OH and a singlet at δ 1.67 for the methyl group), and 5.46 (m, 1H); ^{13}C NMR δ: 22.2 (2), 22.4 (2), 23.6 (3), 24.4 (3), 32.7 (2), 34.0 (2), 34.2 (2), 54.7 (0), 79.5 (0), 121.0 (1), 130.8 (0), and 220.8 (0); MS (from GC-MS) *m/z* (%): 194 (43, M^+), 136 (31), 133 (30), 121 (27), 119 (32), 99 (52), 95 (44), 79 (27), 77 (26), 55 (25), 43 (100), and 41 (26). *Exact mass* calcd. for $C_{12}H_{18}O_2$: 194.1306, found: 194.1288. For **383b**: ^{1}H NMR δ: 1.30 (s, 3H), the rest of the signals were buried in the signals of the major isomer; MS essentially the same as **382a**.

(4R*,5S*)- (384a) and (4R*,5R*)-4-Hydroxy-7-methylspiro[4.5]dec-7-en-1-one (384b)

The spiro-diketone **364** (144 mg, 0.81 mmol) was reduced with sodium borohydride (7.7 mg, 0.20 mmol), the same as for **354**, to provide a 7 : 1 mixture of two epimers (**384a** : **384b**) of which the major isomer was isolated by crystallization (4 : 1 hexane/ether). For **384a**: mp 74-75°C; IR (film) ν_{max}: 3454 (br), 1729, and 1448 (s) cm^{-1}; ^1H NMR δ: 1.65 (br s, 3H), 1.67-1.83 (m, 9H including OH), 2.32 (dd, J = 3.3, 8.9 Hz, 1H), 2.45-2.59 (m, 1H), 4.20 (br s, 1H), and 5.49 (br s, 1H); ^{13}C NMR δ: 21.9 (2), 22.2 (2), 23.6 (3), 28.2 (2), 34.3 (2), 35.2 (2), 53.2 (0), 75.1 (1), 121.3 (1), 130.3 (1), and 221.9 (0); MS (from GC-MS) *m/z* (%): 180 (51, M^+), 147 (35), 121 (100), 120 (30), 119 (37), 118 (28), 105 (61), 95 (37), 93 (88), 91 (71), 79 (58), 77 (51), 67 (34), 55 (46), 53 (31), 43 (41), and 41 (53). *Exact mass* calcd. for $C_{11}H_{16}O_2$: 180.1149; found: 180.1152. For **384b** (from the mixture): ^1H NMR δ: 1.67 (br s, 3H), 2.01-2.84 (m, 10H), 2.82 (br s, OH), 4.27 (br s, 1H), and 5.42 (br s, 1H); ^{13}C NMR δ: 23.2 (2), 25.2 (3), 26.7 (2), 27.6 (2), 31.1 (2), 33.9 (2), 52.5 (0), 78.7 (1), 119.5 (1), 132.8 (0), and 220.8 (0). MS essentially the same as for **384a**.

Reaction of diketone 364 with methyllithium followed by quenching with D_2O

To a solution of diketone **364** (38 mg, 0.21 mmol) in anhydrous ether (20 mL) was added a 1.4 M methyllithium solution in ether (0.5 mL, 0.4 mmol) at -78°C. The reaction mixture was stirred for another two hours at -78°C before deuteroiated water (3 mL) was added. The solution was extracted with ether three times and the combined organic extracts were dried over $MgSO_4$. After concentration *in vacuo* the crude product was analysed by GC-MS directly. MS (from GC-MS) for **385a/b** or **386a/b**: 196 (21, M^+), 195 (33, M^+ - 1), 137 (29), 135 (24), 134 (40), 119 (43), 100 (34), 95 (48), 93 (41), and 43 (100). MS (from GC-MS) for **387**: 179 (7, M^+), 136 (23), 134 (100), 92 (44), 91 (45), and 41 (29).

($4R^*,5S^*$)- (388a) and ($4R^*,5R^*$)-4-Hydroxy-8-methylspiro[4.5]dec-7-en-1-one (388b)

The diketone **281** (79 mg, 0.45 mmol) was reduced with sodium borohydride (4.4 mg, 0.11 mmol), the same as for diketone **354**, to give a 2.5 : 1 mixture of two epimers (**388a** : **388b**) as indicated by the ^{1}H NMR spectrum of the crude product. Chromatography of the crude product (6% ethyl acetate in hexane) failed to separate the two epimers (80 mg, 89%) as a colorless oil: IR (film) ν_{max}: 3449 (br), 1727 (s), and 1448 (m) cm^{-1}. For **388a**: ^{1}H NMR δ: 1.55-2.60 (m, 13H including the singlet at δ 1.67 for the methyl group), 2.82 (br s, OH), 4.20 (br s, 1H), and 5.30 (br s, 1H); ^{13}C NMR δ: 22.5 (2), 23.2 (3), 26.8 (2), 28.2 (2), 30.8 (2), 34.2 (2), 52.5 (0), 74.7 (1), 117.0 (1), 134.5 (0), and 222.7 (0); MS (from GC-MS) *m/z* (%): 180 (22, M^+), 136 (77), 121 (41), 120 (53), 107 (34), 105 (72), 93 (75), 92 (31), 91 (67), 79 (79), 77 (77), 68 (31), 67 (52), 65 (35), 57 (30), 55 (74), 53 (59), 51 (34), 43 (72), and 41 (100). For **388b**: ^{1}H NMR δ: 5.44 (br s, 1H), the rest of the signals were buried in the signals of the major isomer; ^{13}C NMR δ: 23.2 (3), 25.2 (2), 26.7 (2), 27.6 (2), 31.1 (2), 33.9 (2), 52.5 (0), 78.7 (1), 119.1 (1), 132.8 (0), and 221.8 (0); MS essentially the same as for **356a**. *Exact mass* for the mixture calcd. for $C_{11}H_{16}O_2$: 180.1149; found: 180.1152.

(1S*,4R*)-8-Methylspiro[4.5]dec-7-ene-1,4-diol (389)

The diketone **281** (99 mg, 0.55 mmol) was reduced with sodium borohydride (41 mg, 1.11 mmol) in methanol (30 mL) at room temperature, in the same way as for **354**. Chromatography of the residue provided diol **389** (90 mg, 89%) as a colorless oil: IR (film) ν_{max}: 3362 (br) and 1439 (m) cm^{-1}; ^{1}H NMR δ: 1.50 (m, 3H), 1.66 (br s, 3H), 1.70-1.74 (m, 2H), 2.02-2.18 (m, 7H including two OH's), 3.92 (dd, J = 4.8, 6.3 Hz, 1H), 4.02 (t, J = 3.6 Hz, 1H), and 5.38 (narrow t, J = 1.5 Hz, 1H); ^{13}C NMR δ: 23.3 (3), 25.2 (2), 27.6 (2C, 2), 29.6 (2), 29.7 (2), 46.5 (0), 76.3 (1), 76.7 (1), 119.8 (1), and 134.3 (0); MS (from GC-MS) *m/z* (%): 182 (2, M^+), 164 (42), 131 (40), 120 (61), 118 (26), 107 (28), 105 (100), 95 (26), 93 (42), 92 (32), 91 (57), 83 (25),79 (62), 77 (49), 67 (38), 55 (39), 53 (25), 43 (30), and 41 (53). *Exact mass* calcd. $C_{11}H_{16}O$ ($M^+ - H_2O$): 164.1200; found: 164.1197.

Oxidation of diol 389

To a solution of diol **389** (84 mg, 0.46 mmol) in dichloromethane (30 mL) was added pyridinium chlorochromate (PCC) (199 mg, 0.92 mmol). The resulting brown solution was stirred at room temperature overnight. Filtration through a Florisil pad removed a black precipitate. Five volumes of ether were passed through the pad, and concentration of the combined organic solutions *in vacuo* provided a mixture of two epimers (69 mg, 84%) in *ca.* 1 : 1 ratio. The spectra of these two epimers were identical with those of **388a** and **388b**.

(4R*,5S*)- (390a) and (4R*,5R*)-4-Hydroxy-4-methylspiro[4.6]undec-7-en-1-one (390b)

Diketone **369** (46 mg, 0.3 mmol) was treated with methyllithium (0.4 mL, 0.56 mmol) at -78°C, in the same way as for **354**. The ^{1}H NMR of the crude product indicated that it was a 1.5 : 1 mixture of epimers (**390a** : **390b**). Chromatography failed to separate these isomers (41 mg, 83 %): IR (film) ν_{max}: 3460 (br), 1728 (s), and 1446 (m) cm^{-1}; ^{1}H NMR δ: 1.31 (s, 3H), 1.38 (s, 3H), 1.24-2.41 (m, 24H), 5.41-5.56 (m, 2H), 5.64-5.79 (m, 2H); MS (from GC-MS) *m/z* (%): 194 (7, M^+), 134 (36), 119 (28), 93 (24), 91 (27), 79 (26), 43 (100), and 41 (29). *Exact mass* calcd. for $C_{12}H_{18}O_2$: 194.1306; found: 194.1304.

(4R*,5S*)- (391a) and (4R*,5R*)-4-Hydroxyspiro[4.6]undec-7-en-1-one (391b)

The diketone **369** (68 mg, 0.43 mmol) was treated with sodium borohydride (4 mg, 0.11 mmol) at room temperature, in the same way as for **345**. The ^{1}H NMR of the crude product indicated that it was a 2 : 1 mixture of two epimers (**391a**: **391b**). Chromatography failed to separate them (67 mg, 87 %): IR (film) ν_{max}: 3459 (br), 1728 (s), and 1447 (m) cm^{-1}. For **391a**: ^{1}H NMR δ: 1.21-2.53 (m, 13H including OH), 4.39 (br s, 1H), and 5.76-6.00 (m, 2H); ^{13}C NMR δ: 21.6 (2), 27.3 (2), 28.4 (2), 31.3 (2), 33.5 (2), 35.8 (2), 56.0 (0), 75.0 (1), 127.7 (1), 133.9 (1), and 221.5 (0); MS (from GC-MS) *m/z* (%): 162

(12, M^+), 113 (28), 95 (53), 93 (32), 91 (38), 79 (57), 77 (34), 68 (27), 67 (47), 57 (27), 55 (53), 53 (36), 43 (49), 42 (21), and 41 (100). For **391b**: ^{1}H NMR δ: 1.21-2.53 (mm, 13H including OH), 4.39 (br s, 1H), and 5.63-5.66 (m, 2H); ^{13}C NMR δ: 22.1 (2), 27.4 (2), 28.8 (2), 29.0 (2), 32.2 (2), 33.8 (2), 55.6 (2), 75.0 (1), 126.2 (1), 135.4 (1), and 220.4 (0). MS essentially the same as for **391a**.

(4R*,5S*)- (392a) and (4R*,5R*)-Carbethoxy-4-hydroxy-7-methylspiro[4.5]dec-7-en-1-one (392b)

The diketone **374** (176 mg, 0.8 mmol) was treated with sodium borohydride (8 mg, 0.2 mmol) in methanol at room temperature, the same as for **354**. Integration of an inverse gated ^{13}C NMR spectrum in which NOE effects were removed showed the signals for **392a** and **392b** in a ratio of 12 : 1. Chromatography failed to separate the two epimers: IR (film) ν_{max}: 3520 (br), 1732 (s), 1710 (s), and 1680 (m) cm^{-1}; For **392a**: ^{1}H NMR δ: 1.30 (t, J = 7.2 Hz, 3H), 1.67-2.58 (m, 14H including OH and a broad singlet at δ 2.01 for the methyl group), 4.17 (s, 1H), and 4.19 (q, J = 7.2 Hz, 2H); ^{13}C NMR δ ($CDCl_3/C_5D_5N$): 13.8/14.6 (3), 21.3/22.1 (3), 21.7/23.1 (2), 22.9/24.0 (2), 27.8/28.9 (2), 33.9/35.0 (2), 38.2/39.0 (2), 52.2/53.2 (0), 59.7/60.2 (2), 74.3/74.6 (1), 124.1/125.0 (0), 142.0/143.9 (0), 167.8/168.2 (0), and 220.3/220.9 (0). MS *m/z* (%): 252 (3, M^+), 207 (22), 206 (100), 150 (18), 119 (21), 91 (21), 77 (16), and 41 (19). For **392b**: ^{1}H NMR δ (C_5D_5N): 4.39 (m, 1H), the rest of the signals were buried in the signals of the major isomer; ^{13}C NMR δ (C_5D_5N): 14.6 (3), 22.1 (3), 22.3 (2), 27.6 (2), 28.8 (2), 34.1 (2), 34.6 (2), 57.5 (2), 53.8 (0), 74.5 (1), 125.3 (0), 146.6 (0), 168.1 (0), and 220.4 (0); MS essentially the same as for **392a**. *Exact mass* calcd. for $C_{14}H_{18}O_3$ (M^+ - C_2H_6O): 206.0942; found: 206.0935.

(4R*)-*trans*- (395) and (4R*)-*cis*-8-*tert*-Butyl-4-hydroxy-4-methylspiro[4.5]decan-1-one (396)

The diketone **394** (128 mg, 0.58 mmol) was treated with methyllithium (0.8 mL, 1.2 mmol), the same as for **354**. The ^{1}H NMR spectrum of the crude product suggested that it was a single isomer. However, ^{13}C NMR showed two sets of signals in a ratio of 2.5 : 1 (**395** : **396**) as determined by integration of an inverse-gated ^{13}C NMR spectrum in which the contributions of NOE were removed. Chromatography failed to separate the two isomers (117 mg, 86%): IR (film) ν_{max}: 3392 (br) and 1723 (s) cm^{-1}. For **395**: ^{1}H NMR δ: 0.85 (s, 9H), 1.24 (s, 3H), 1.26-3.49 (m, 7H including a broad singlet at 1.46 for OH); ^{13}C NMR δ: 22.3 (3), 22.5 (2), 22.7 (2), 25.7 (2), 27.5 (3C, 3), 29.4 (2), 32.2 (0), 33.2 (2), 33.8 (2), 47.6 (1), 54.6 (0), 80.3 (0), and 220.6 (0); MS (from GC-MS) *m/z* (%): 238 (20, M^+), 180 (33), 124 (26), 123 (24), 109 (38), 99 (30), 81 (24), 79 (20), 57 (77), 55 (31), 43 (100), and 41 (56). For **396**: ^{1}H NMR was very similar to that of the major isomer **395**; ^{13}C NMR δ: 22.7 (2), 23.0 (2C, 2), 27.0 (3), 27.3 (3C, 3), 29.7 (2), 32.3 (0), 34.0 (2), 34.8 (2), 46.8 (1), 55.1 (0), 80.7 (0), and 222.3 (0); MS essentially the same as for **395**. *Exact mass* calcd. for $C_{15}H_{26}O_2$: 238.1931; found: 238.1923.

(4R*)-*trans*- (397) and (4R*)-*cis*-8-*tert*-Butyl-4-hydroxyspiro[4.5]decan-1-one (398)

The diketone **394** (116 mg, 0.52 mmol) was treated with sodium borohydride (5 mg, 0.13 mmol) in methanol (20 mL) at room temperature, in the same way as for **354**. Chromatography of the crude product (6% ethyl acetate in hexane) gave a fraction (108 mg, 92%) of *mono*-alcohols as a mixture of two isomers in a ratio of 18 : 1 (**397** : **398**) and 4 mg (4%) of *trans*-diol **399**. For **397** and **398**: IR (film) ν_{max}: 3425 (sharp), 3325 (br), and 1706 (s) cm^{-1}. For **397**: ^{1}H NMR δ: 0.86 (s, 9H), 1.31-1.44 (m, 3H), 1.55-1.70 (m, 4H), 1.81-1.94 (m, 2H), 2.18-2.47 (m, 5H including OH), and 3.87 (m, 1H); ^{13}C NMR δ: 22.0 (2), 22.4 (2), 26.2 (2), 27.1 (2), 27.5 (3C, 3), 31.4 (2), 32.3 (0), 34.6 (2), 47.6 (1), 51.9 (0), 79.2 (1), and 220.3 (0); MS (from GC-MS) *m/z* (%): 224 (4, M^+), 168 (17), 167 (29), 150 (32), 149 (29), 112 (17), 109 (15), 108 (36), 107 (36), 95 (26), 93 (21), 81 (30), 79 (31), 67 (26), 57 (100), 55 (37), 43 (29), and 41 (63). For **398**: ^{1}H NMR δ: 4.47 (br s, 1H), the rest of the signals were buried in the signals of the major isomer

397; ^{13}C NMR δ: 23.4 (2), 26.3 (2), 27.5 (2), 27.4 (3C, 3), 28.2 (2), 29.7 (0), 31.6 (2), 34.0 (2), 47.3 (1), 54.8 (0), 73.6 (1), and 222.1 (0); MS essentially the same as for **397**.

(1R*,4S*)-8-*tert*-Butylspiro[4.5]decane-1,4-diol (400)

The diketone **394** (124 mg, 0.56 mmol) was treated with $NaBH_4$ (42 mg, 1.1 mmol) in methanol (20 mL) at room temperature, the same as for **354**, to provide **400** (97 mg, 77%) as colorless crystals and 21 mg (17%) of **399** after flash chromatography (6% ethyl acetate in hexane). For **400**: mp 122.5-124°C; IR (film) ν_{max}: 3425 (sharp) and 3361 (br) cm^{-1}; ^{1}H NMR δ: 0.86 (s, 9H), 1.01-1.28 (m, 7H including two OH), 1.56-1.64 (m, 1H), 1.73-2.20 (m, 5H), 2.25-2.30 (m, 1H), 2.38 (d, J = 5.7 Hz, 1H), 2.49 (d, J = 7.8 Hz, 1H), 3.65 (t, J = 5.1 Hz, 1H), and 4.15 (dd, J = 6.0, 6.6 Hz, 1H); ^{13}C NMR δ: 23.3 (2), 23.8 (2), 27.0 (2), 27.5 (3C, 3), 31.1 (2), 32.0 (2), 32.4 (0), 32.9 (2), 48.0 (1), 50.2 (0), 75.2 (1), and 83.5 (1); MS *m/z* (%): 208 (0.1, $M^+ - H_2O$), 190 (2, $M^+ - 2H_2O$), 134 (11), 133 (25), 93 (10), 91 (14), 81 (12), 67 (15), 57 (56), 55 (16), 43 (16), and 41 (36). *Exact mass* calcd. for $C_{14}H_{22}$ ($M^+ - 2H_2O$): 190.1720; found: 190.1727. For **399**: mp 87.5-89°C; IR (film) ν_{max}: 3352 (br) cm^{-1}; ^{1}H NMR δ: 0.86 (s, 9H), 0.99-1.60 (m, 10H including two OH's), 1.64-1.85 (m, 3H), 2.04-2.24 (m, 2H), 3.94 (t, J = 8.1 Hz, 1H), and 4.17 (t, J = 6.0 Hz, 1H); ^{13}C NMR δ: 22.9 (2), 24.4 (2), 26.2 (2), 27.5 (3C, 3), 29.4 (2), 29.6 (2), 29.9 (2), 32.4 (0), 48.0 (1), 48.2 (0), 74.5 (1), and 78.4 (1); MS (from GC-MS) *m/z* (%): 208 (12, $M^+ - H_2O$), 151 (25), 134 (19), 133 (39), 107 (19), 91 (25), 81 (25), 67 (28), 57 (100), 55 (23), and 41 (49).

Competitive reduction of diketones 359 and 103 with sodium borohydride .

A 1 : 1 (determined by ^{1}H NMR integration) mixture of **359** and **103** (72 mg, 0.44 mmol) was reduced with sodium borohydride (2.1 mg, 0.06 mmol) the same as for diketone **354**. ^{1}H NMR of the crude product showed signals for **382a/b** and **402** in a ratio of 1.5 : 1. The reaction rate ratio calculated based on Equation (8) (see Experimental of Chapter 2) was 1.5 : 1.

Competitive reduction of diketones 354 and 103 with sodium borohydride

A 1 : 1 (determined by ^{1}H NMR integration) mixture of **354** and **103** (81 mg, 0.44 mmol) was treated with sodium borohydride (2.1 mg, 0.06 mmol) the same as for **354**. ^{1}H NMR of the crude product showed signals for **378a/b** and **402** in a ratio of 5 : 1. The reaction rate ratio calculated based on Equation (8) was 5.1 : 1.

Reduction of 366 in the presence of cerium(III) chloride

To a solution of **366** (88 mg, 0.45 mmol) and cerium(III) chloride (169 mg, 0.45 mmol) in methanol (30 mL) was added sodium borohydride (4.1 mg, 0.11 mmol) at -78°C. The reaction mixture was stirred for two hours at -78°C before water was added. Much of the methanol was evaporated, and the residue was diluted with ethyl acetate and water. The aqueous layer was extracted with ethyl acetate (×3). The combined organic extracts were washed with water and saturated NaCl, then dried over $MgSO_4$. After concentration *in vacuo*, ^{1}H NMR of the crude reaction mixture indicated that it was a 15 : 1 mixture of two epimers (**380a/b** (79 mg, 89%).

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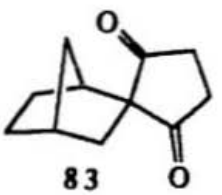
Appendix

The selected ^{1}H NMR spectra of the synthetic samples were arranged according to the order in which they appear in the text. For the instruments employed, see **General Procedures** in Chapter one.



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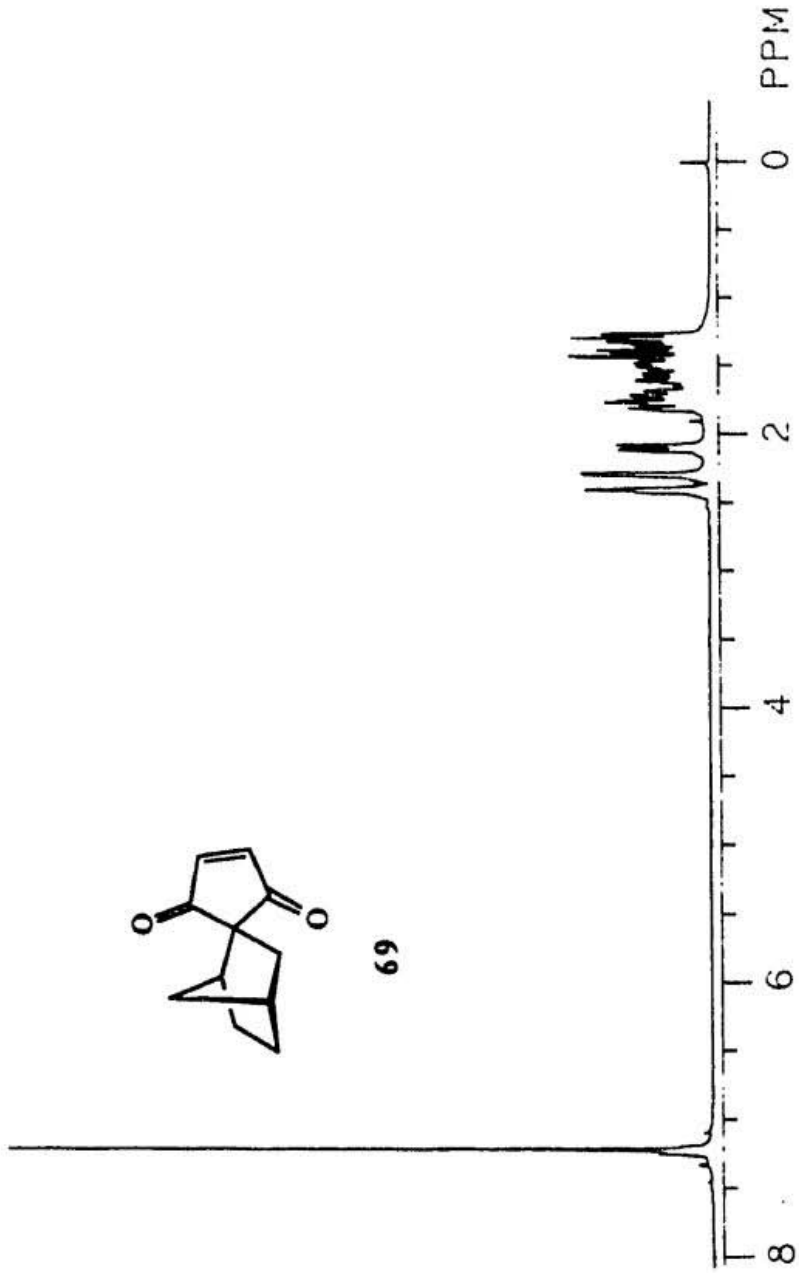

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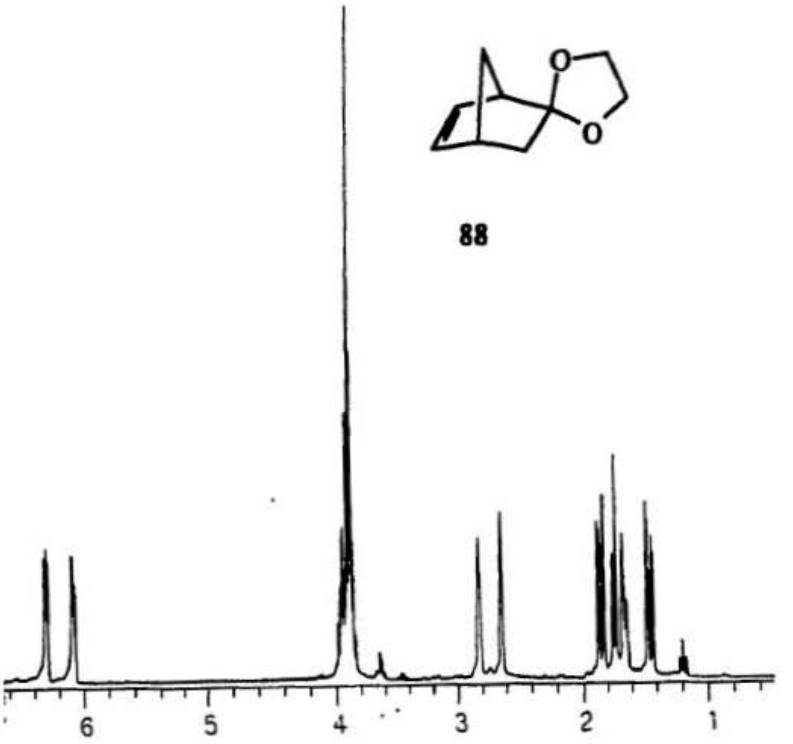

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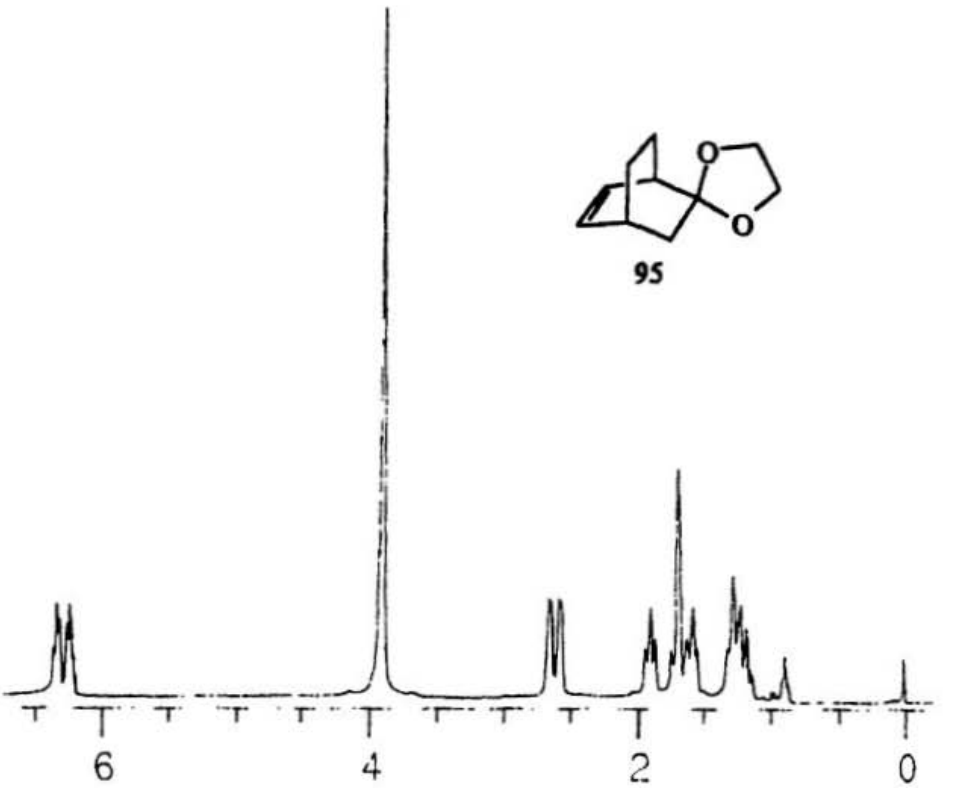

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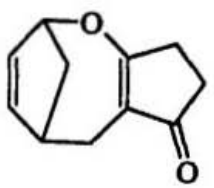

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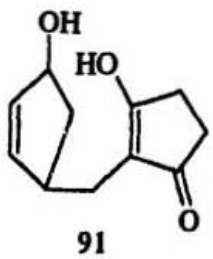

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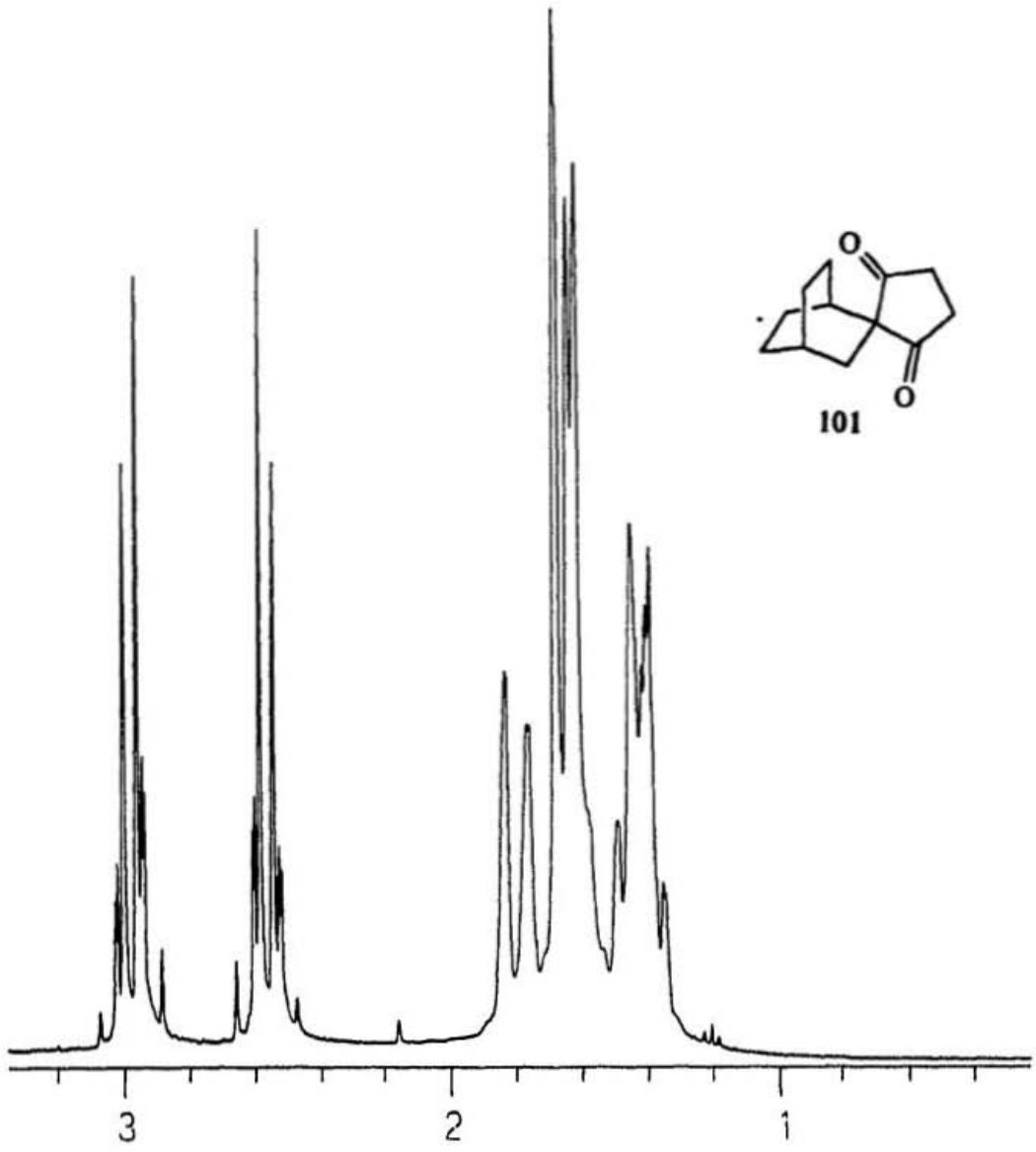

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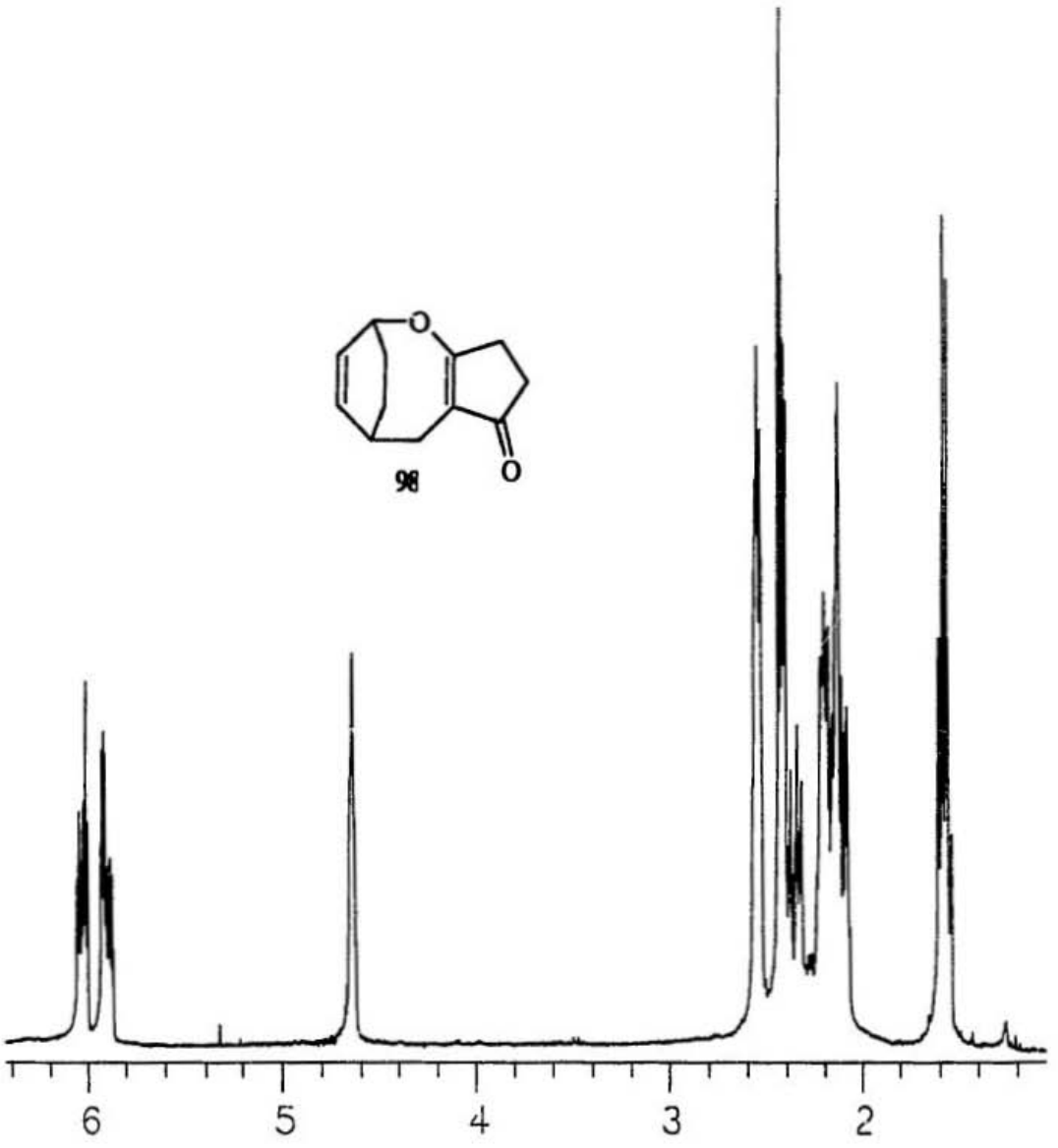
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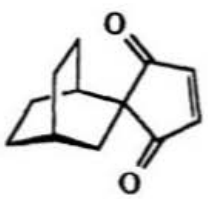

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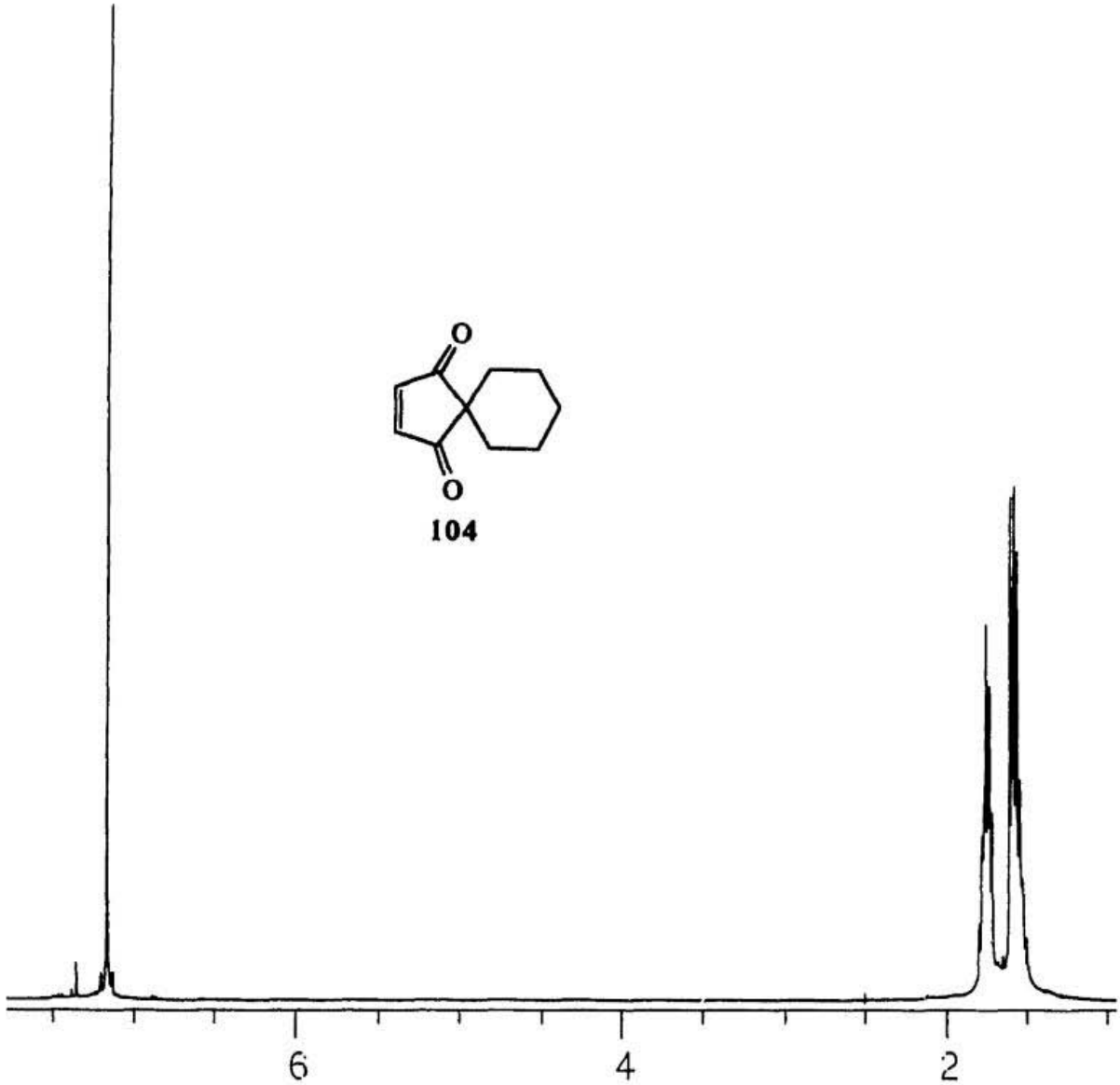

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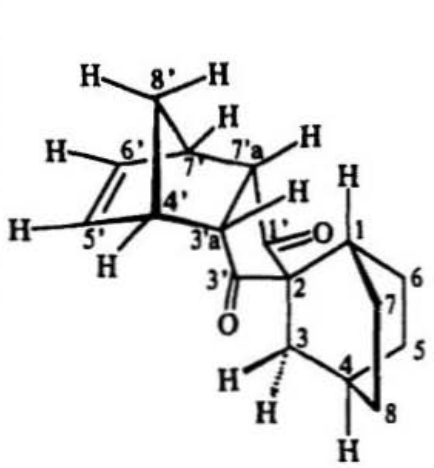

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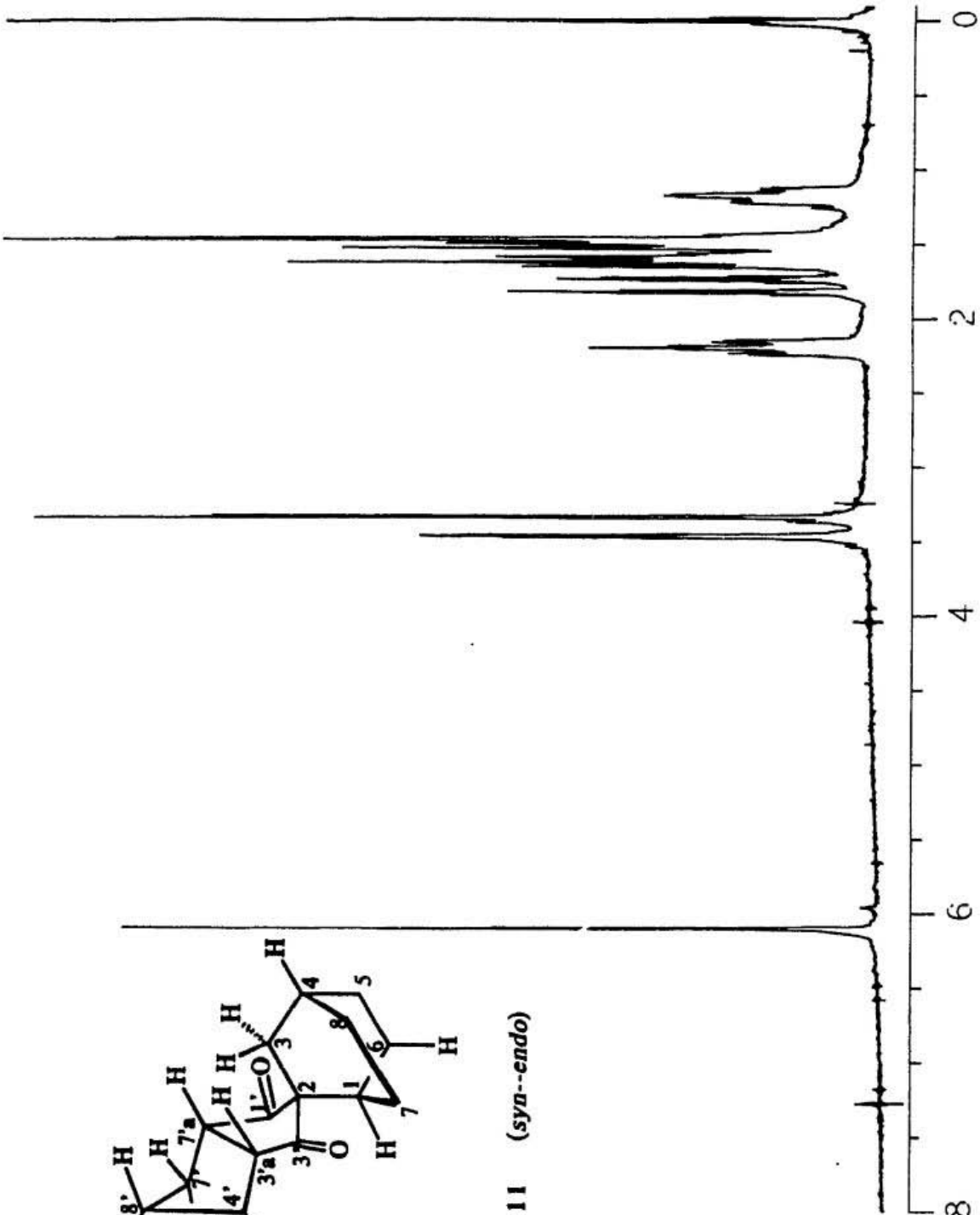

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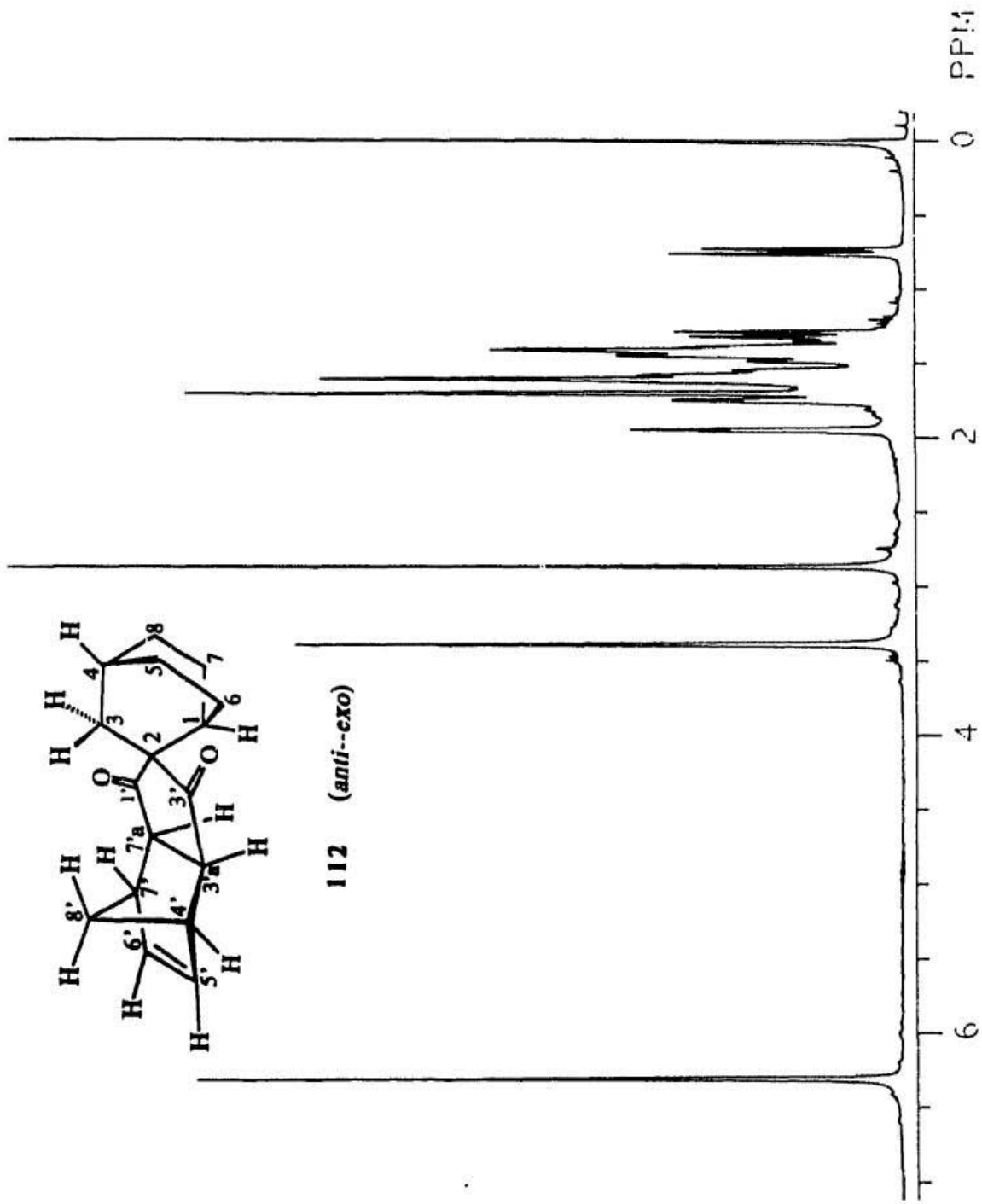

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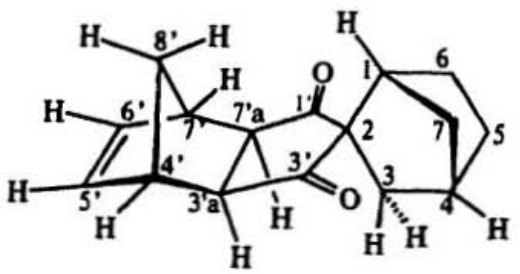
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H
H
H

117 (*syn--exo*)

3.01
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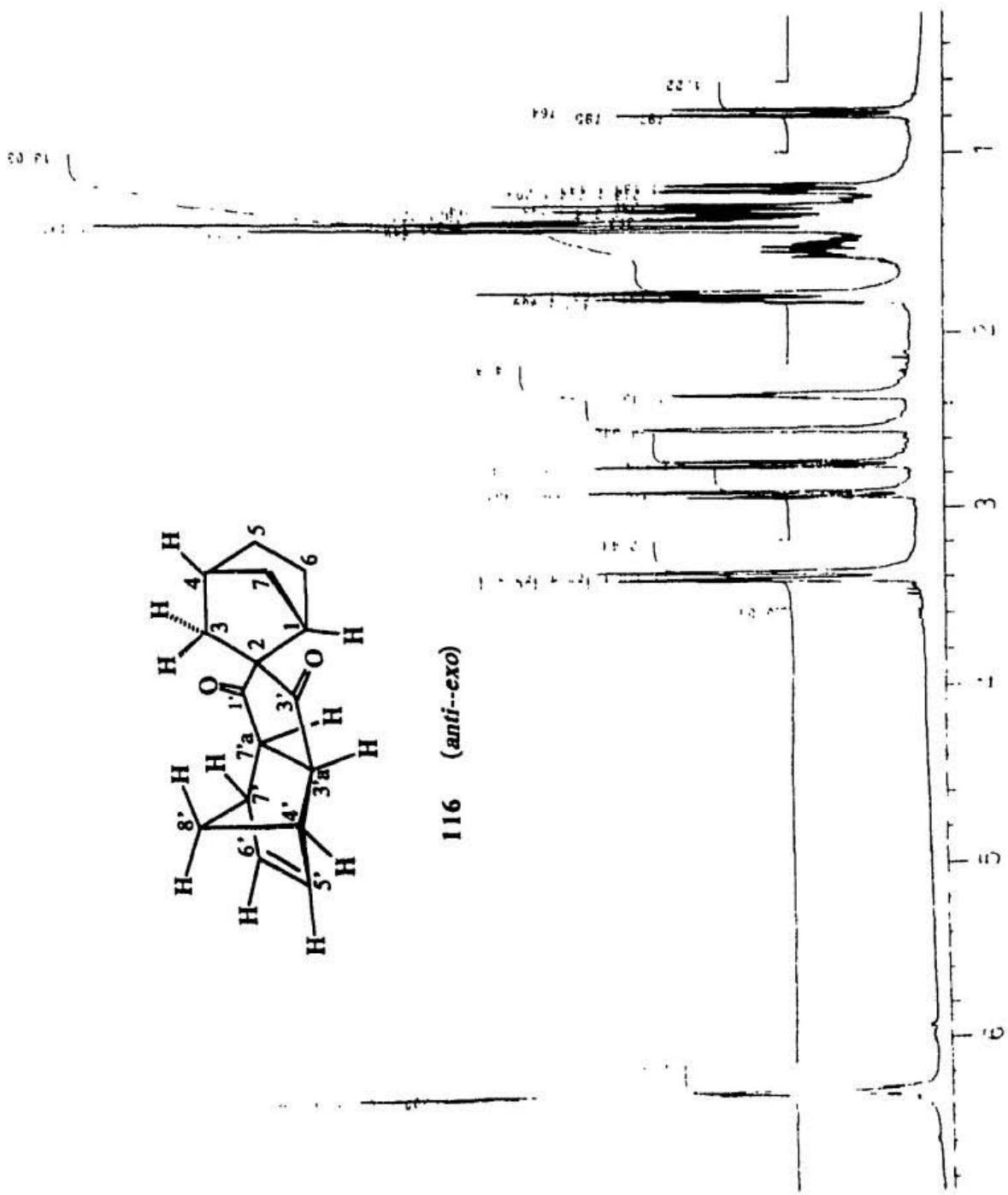

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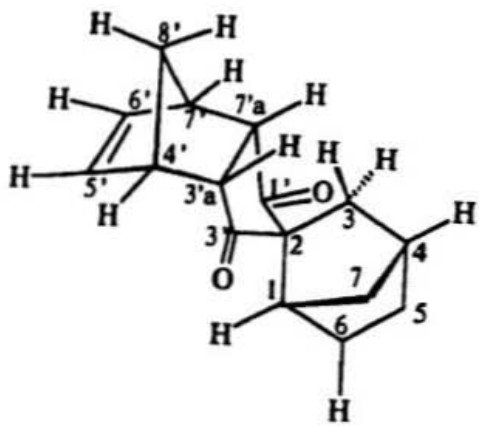

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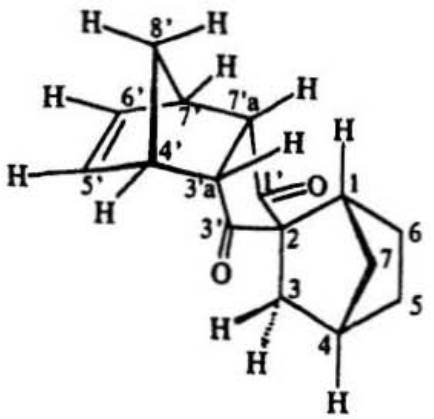

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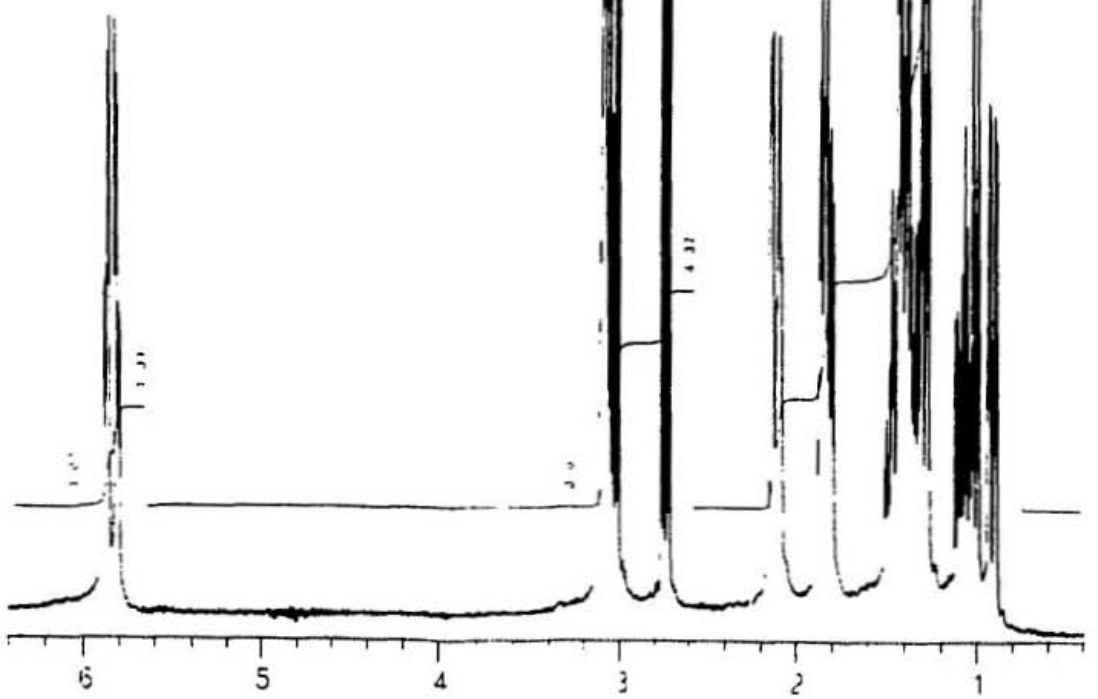

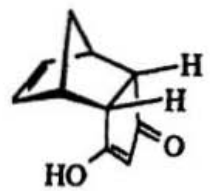

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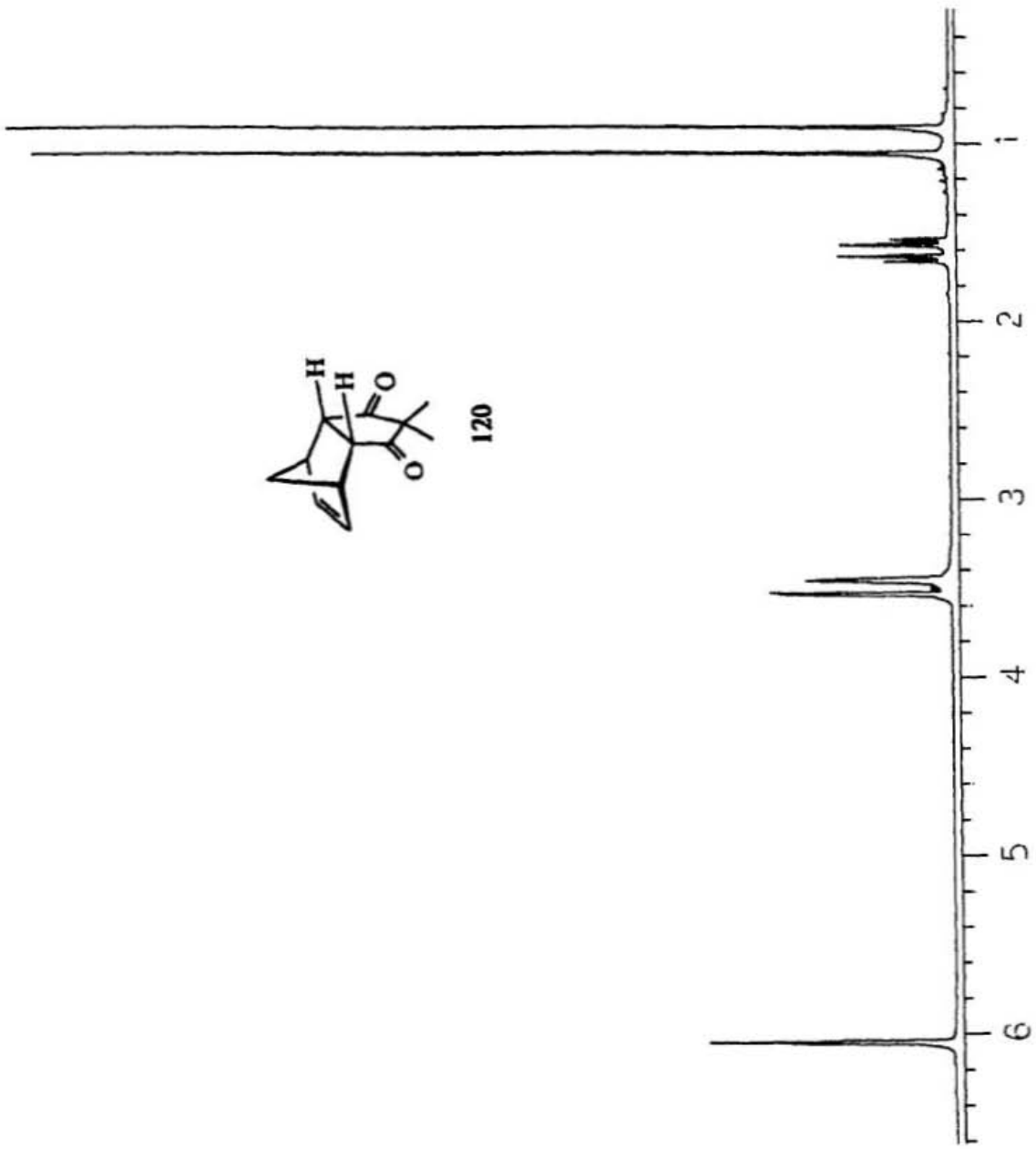
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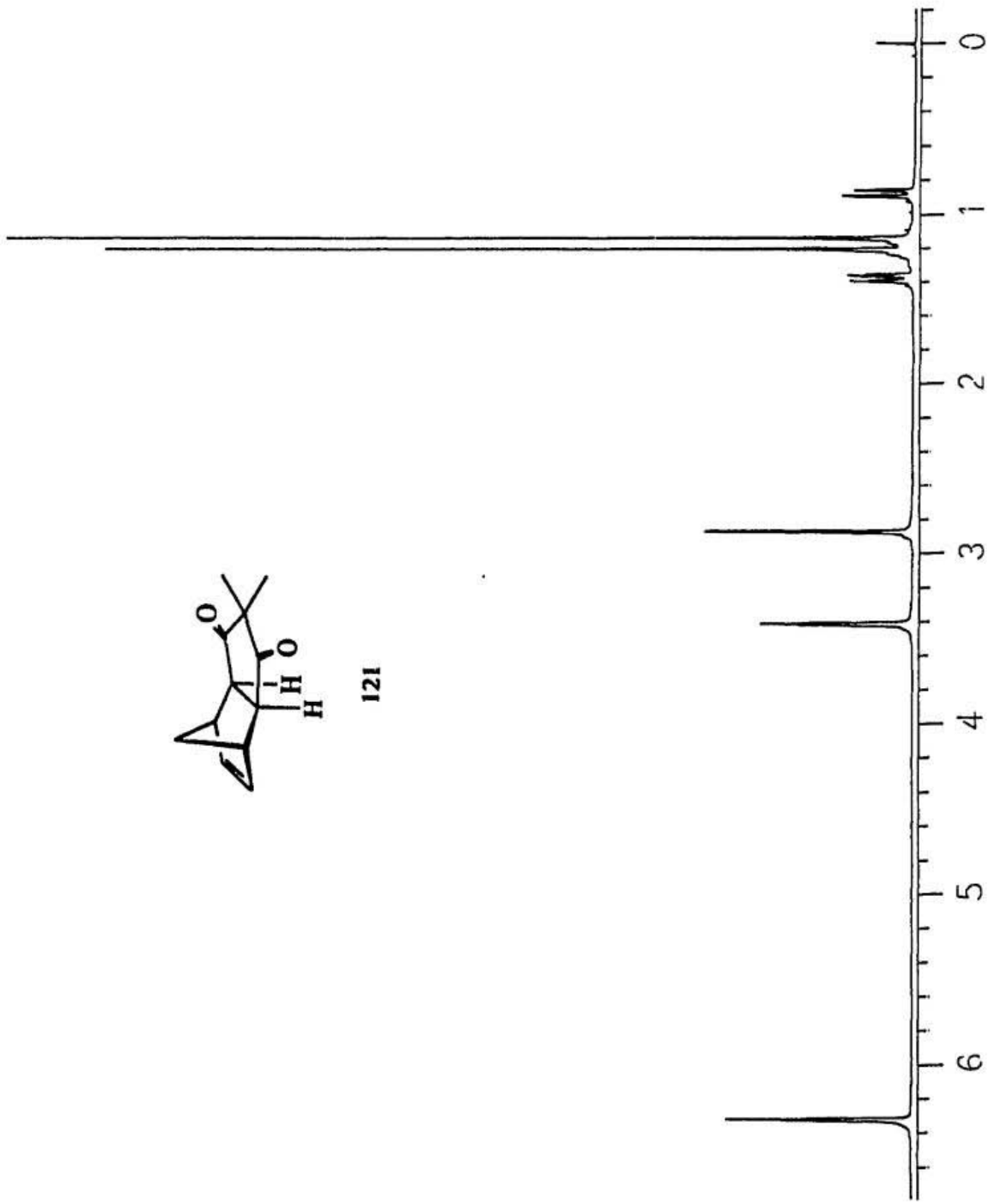

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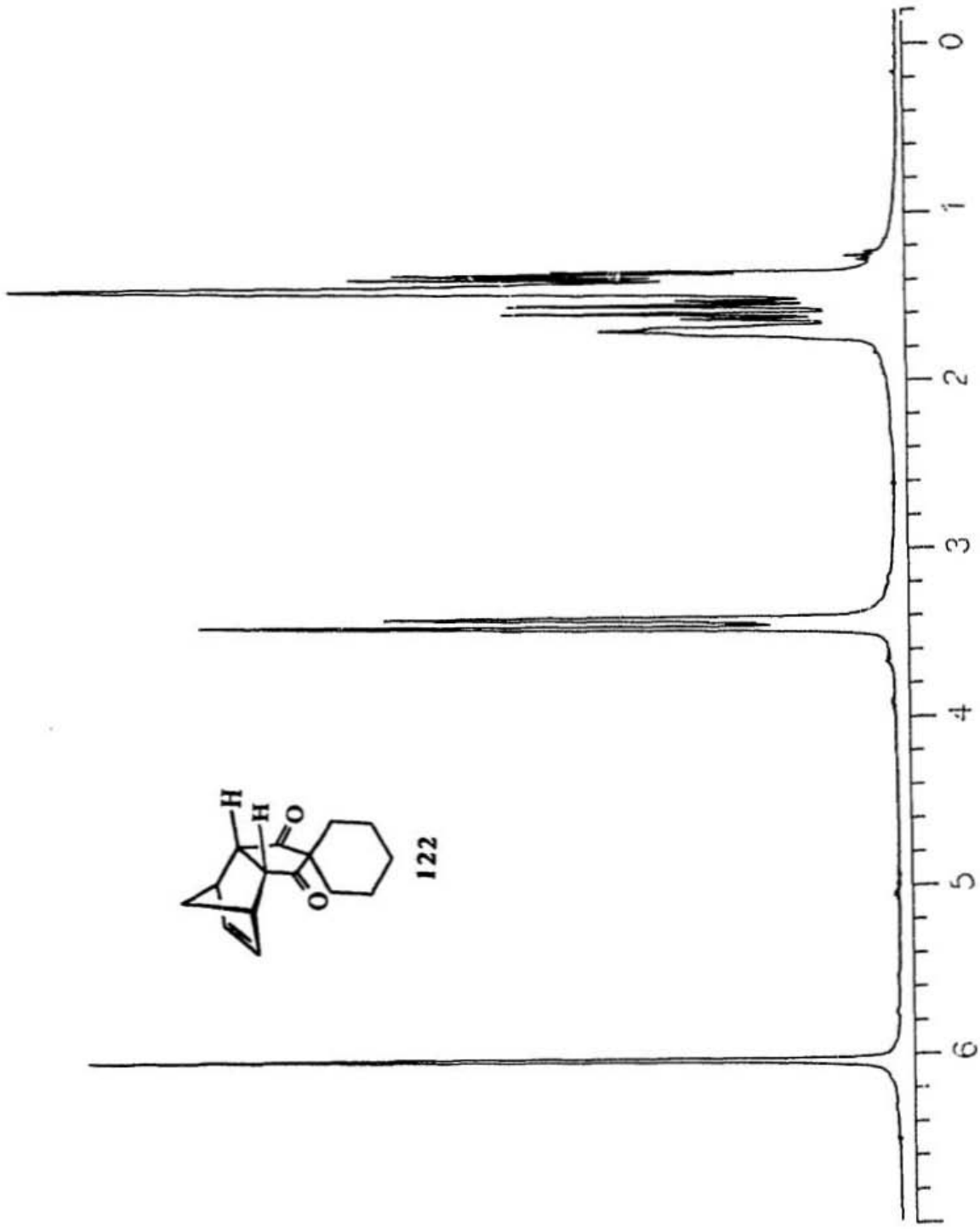

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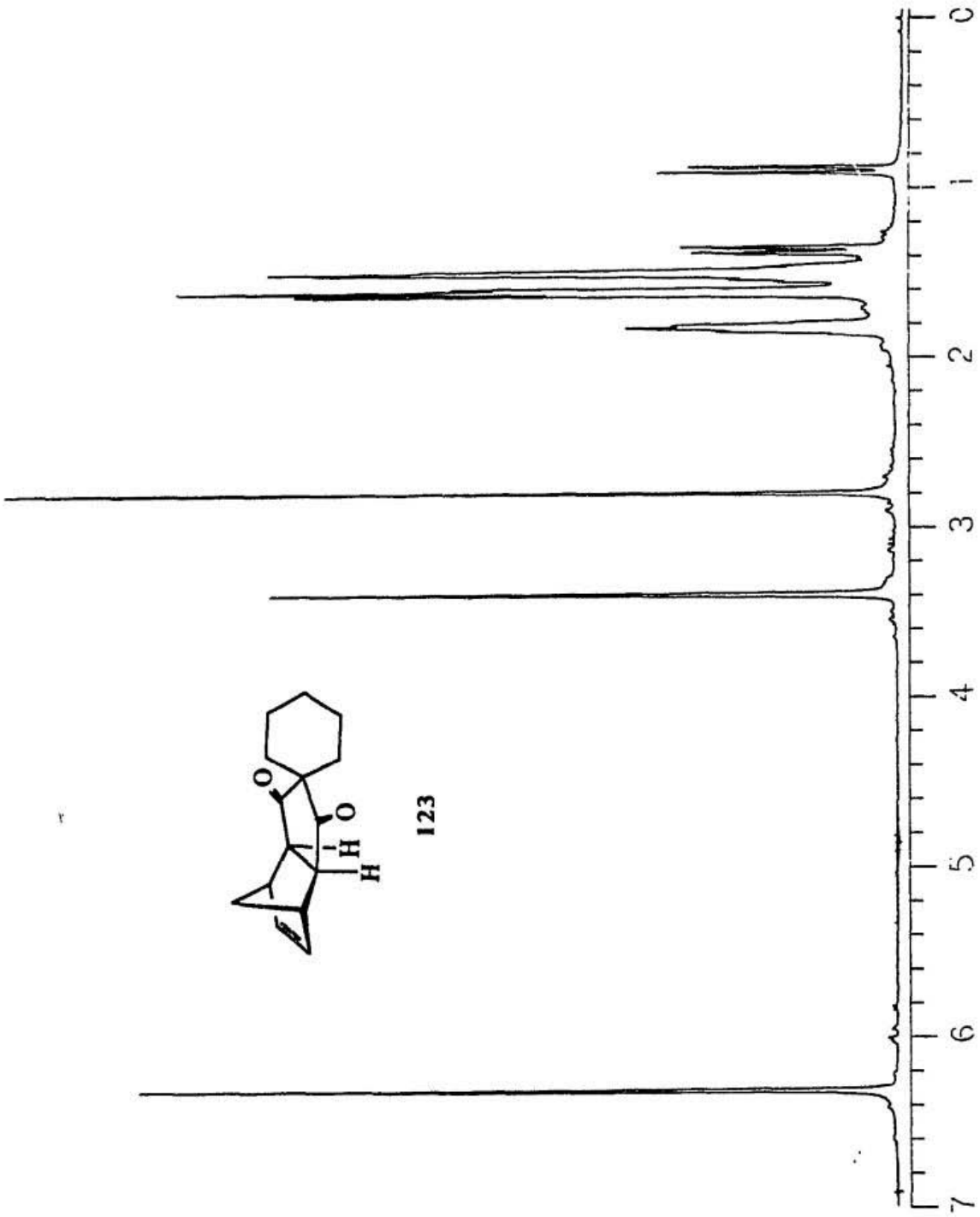

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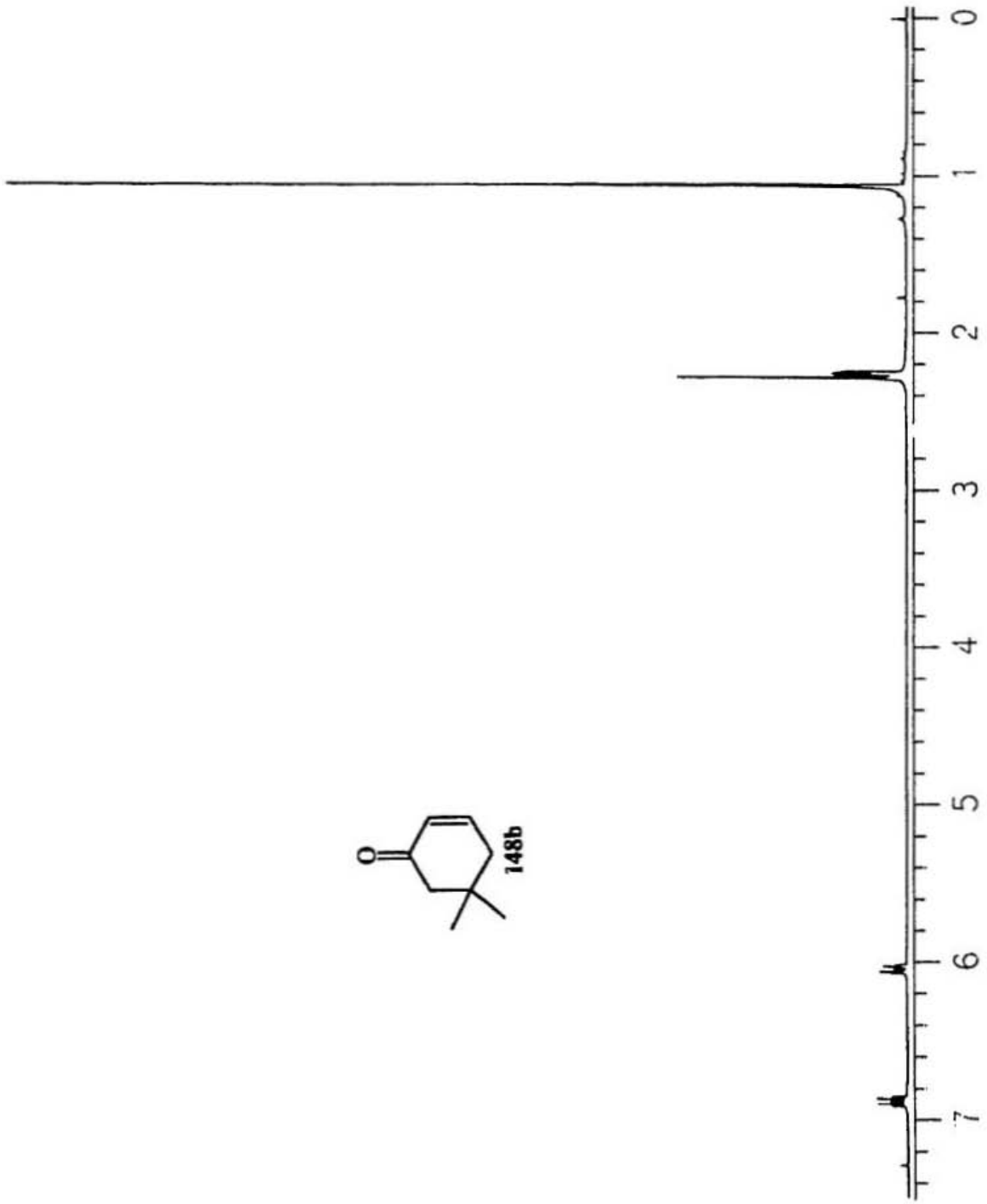
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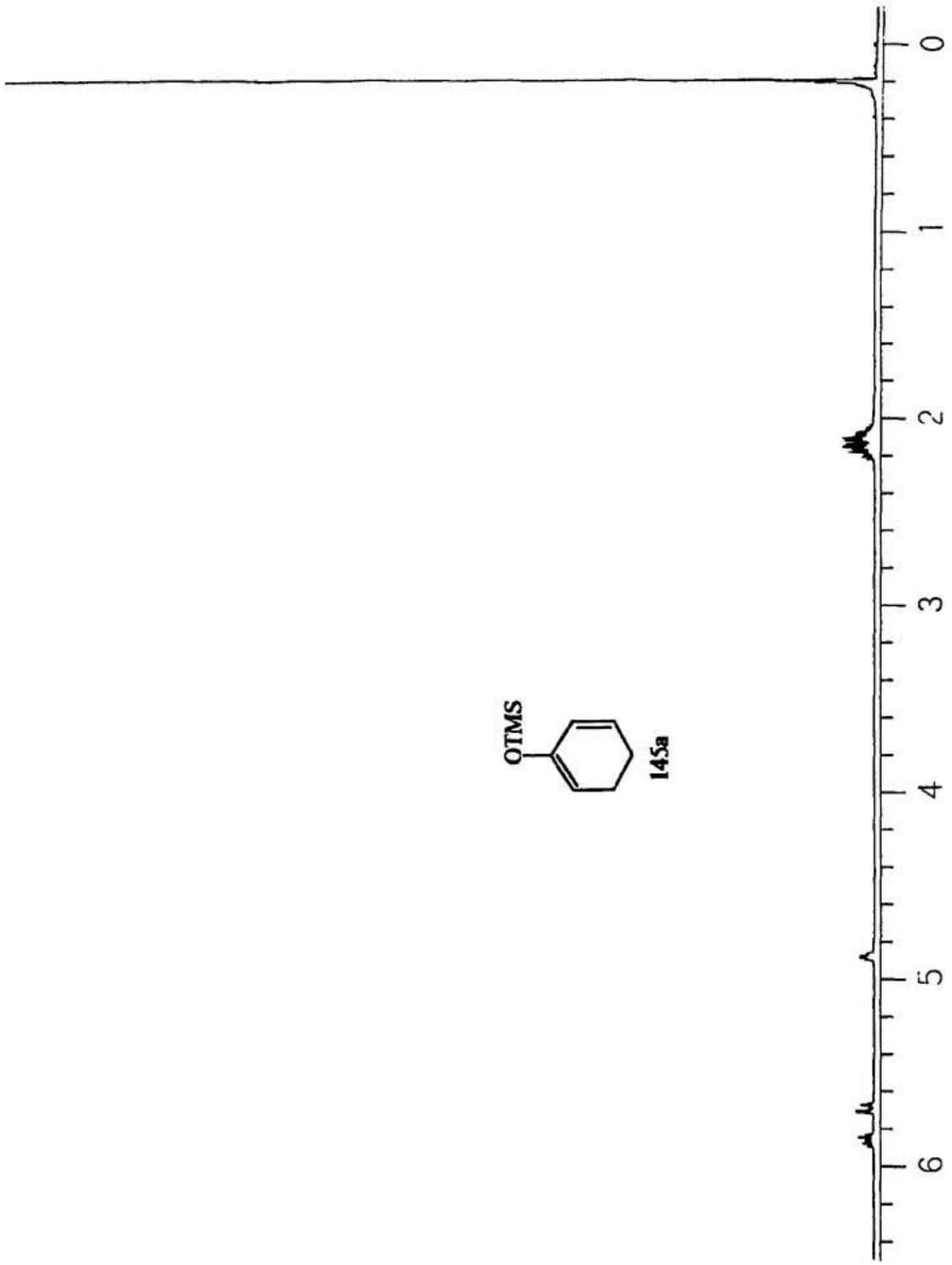
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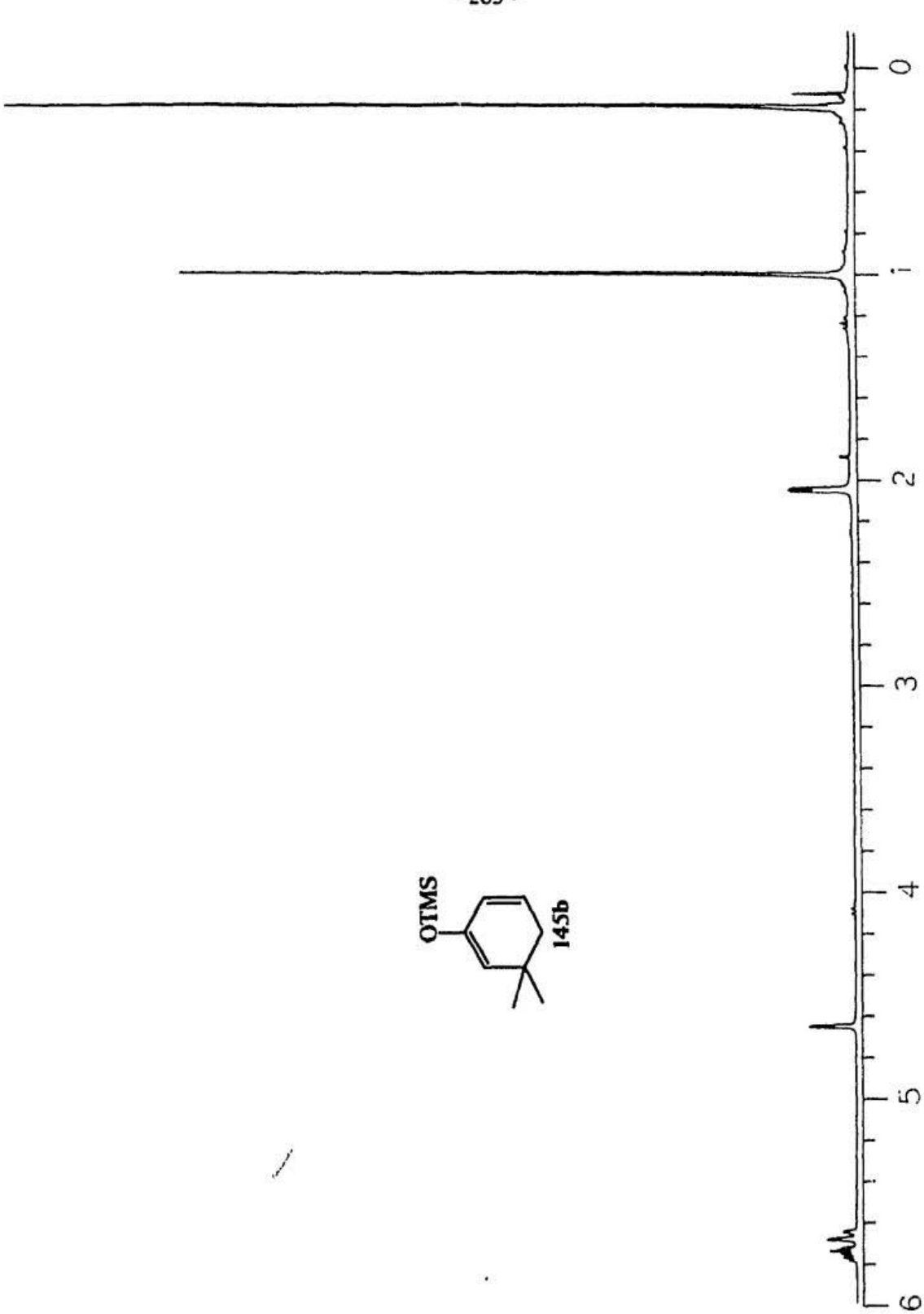
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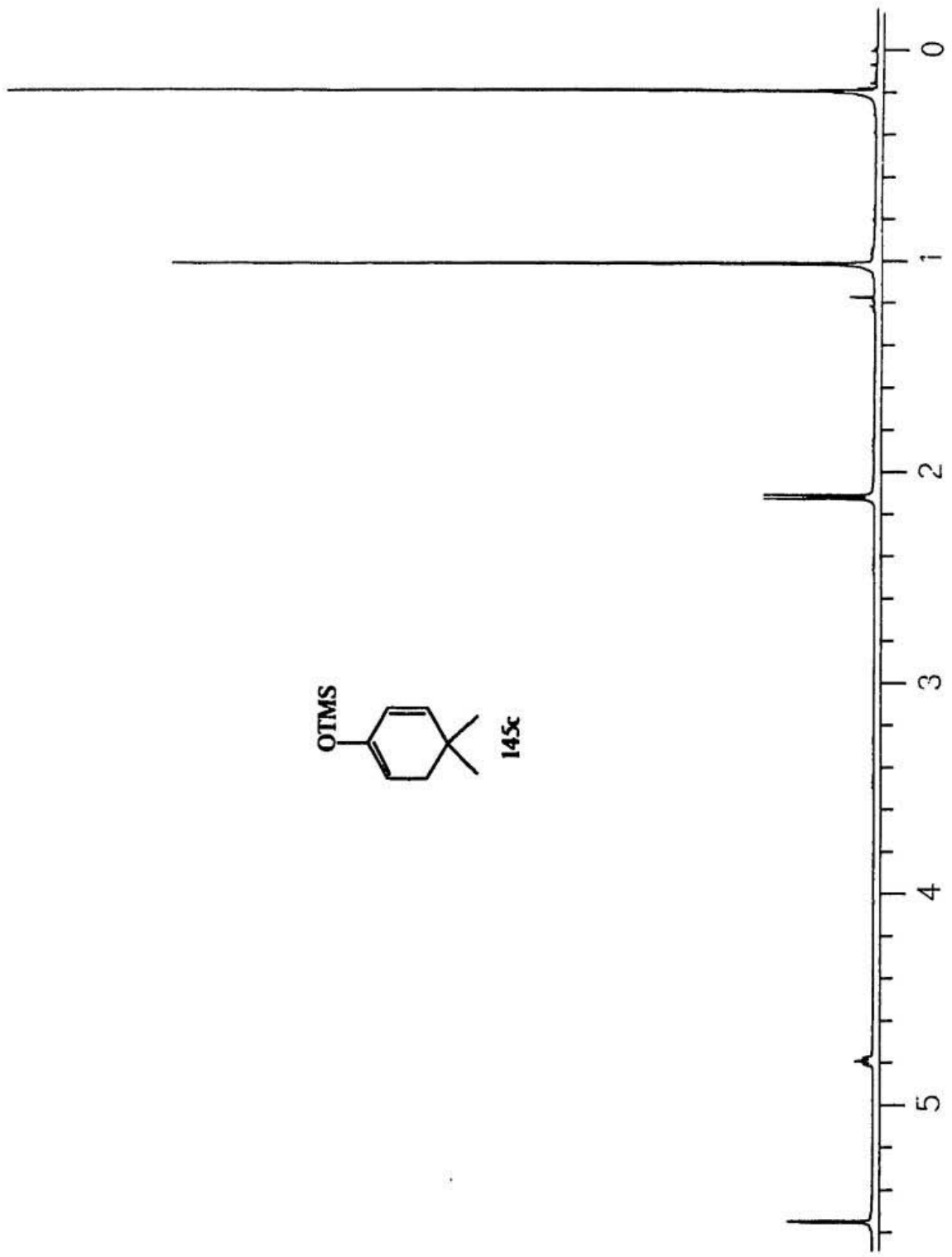
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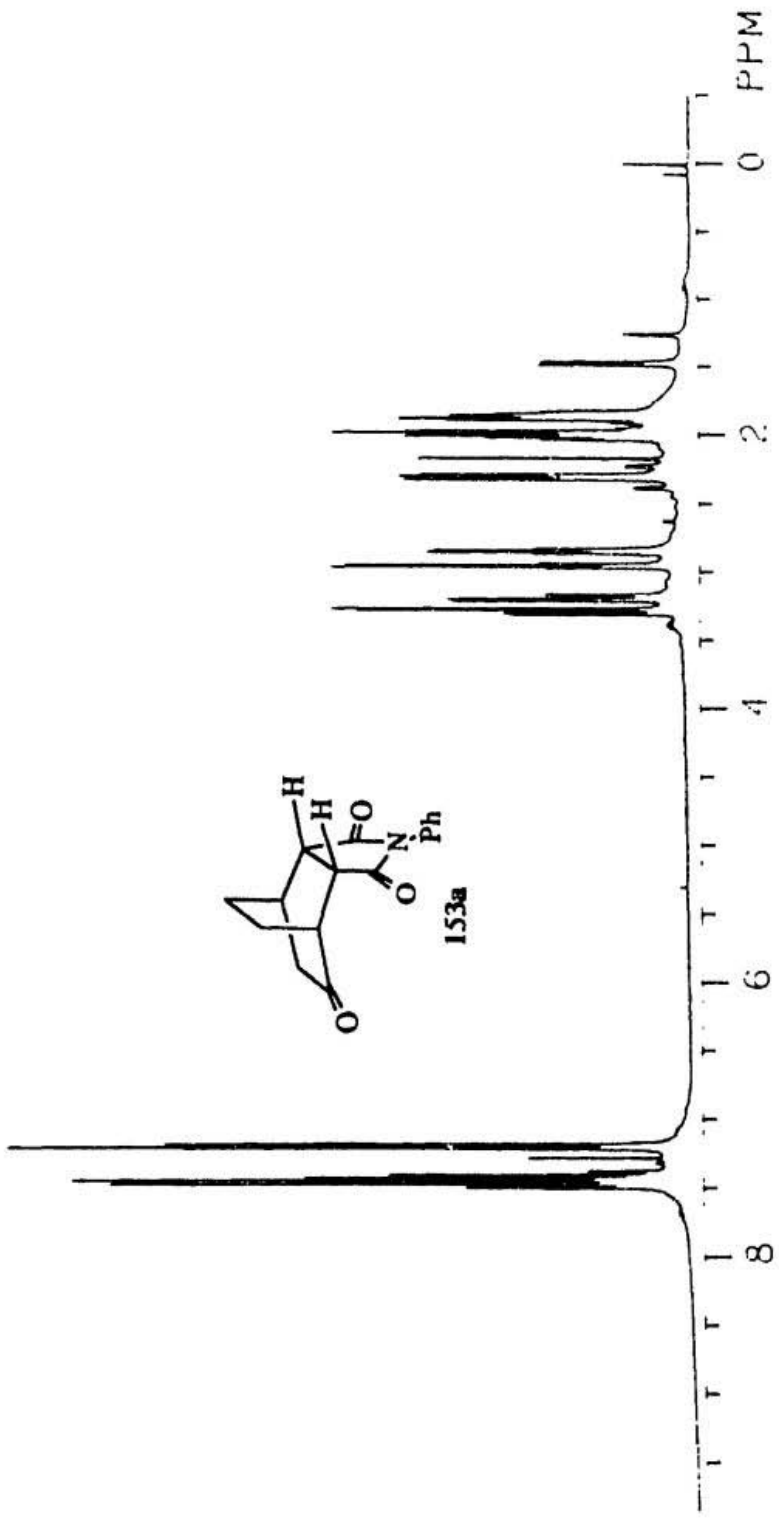
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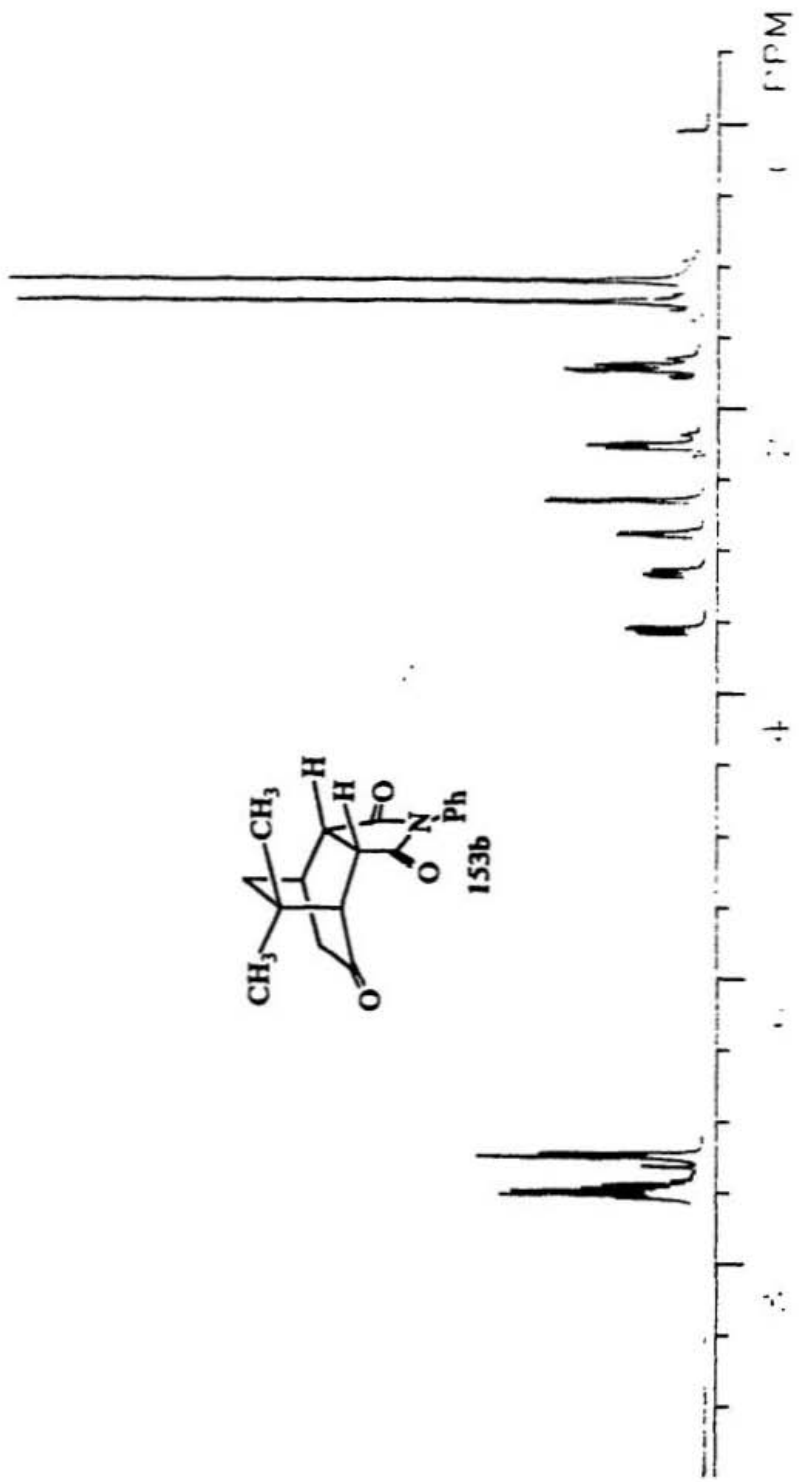

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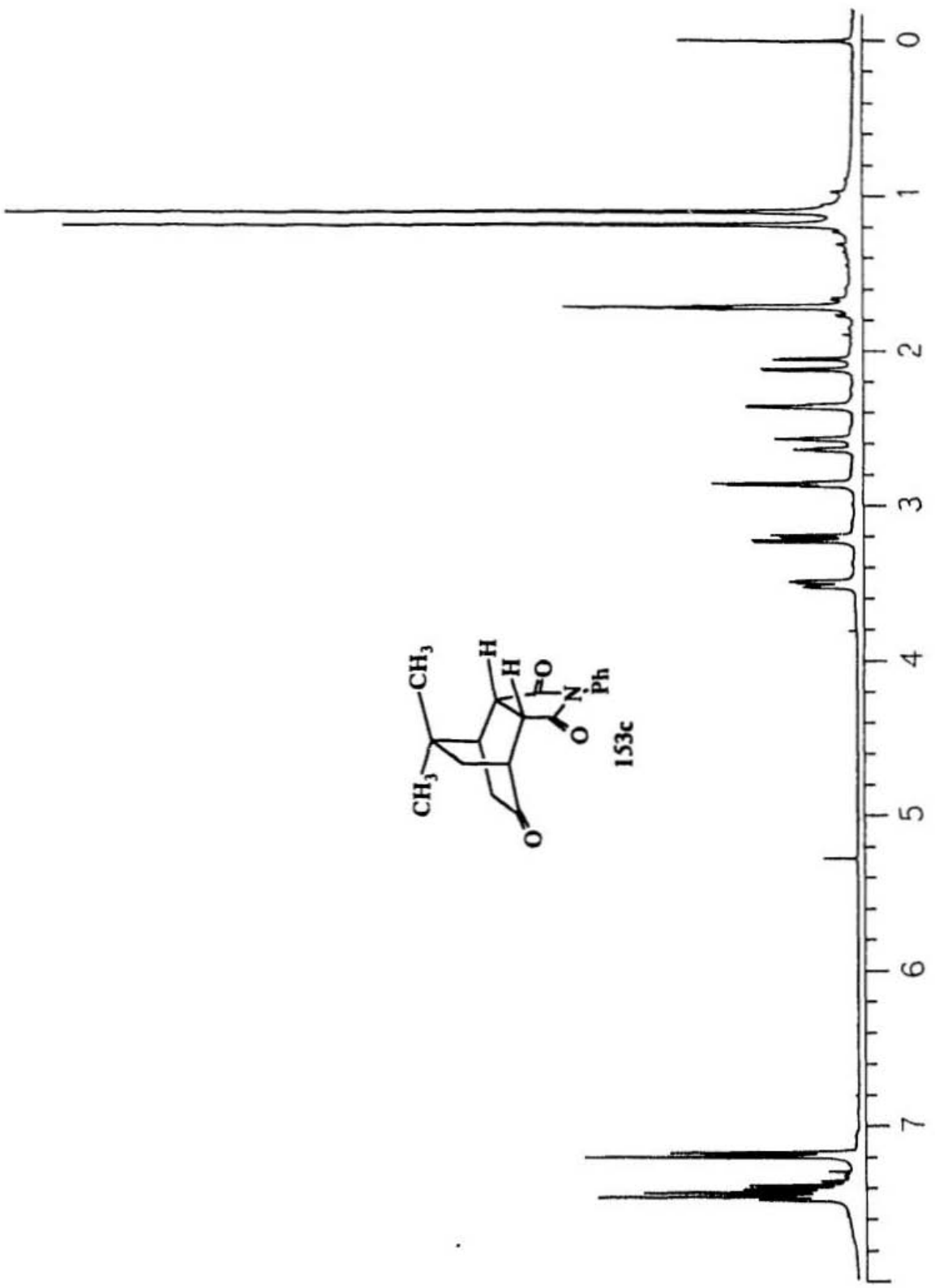
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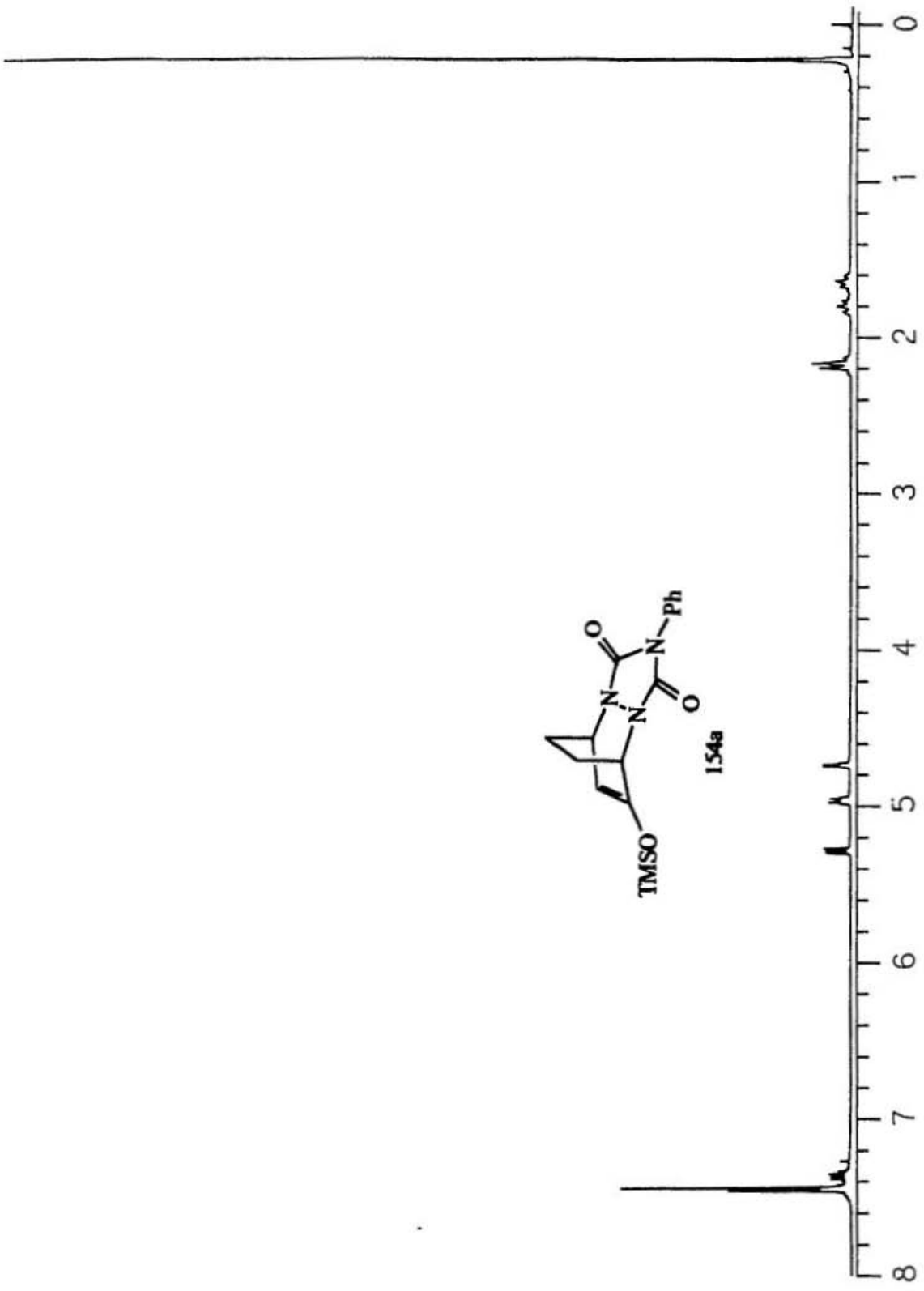
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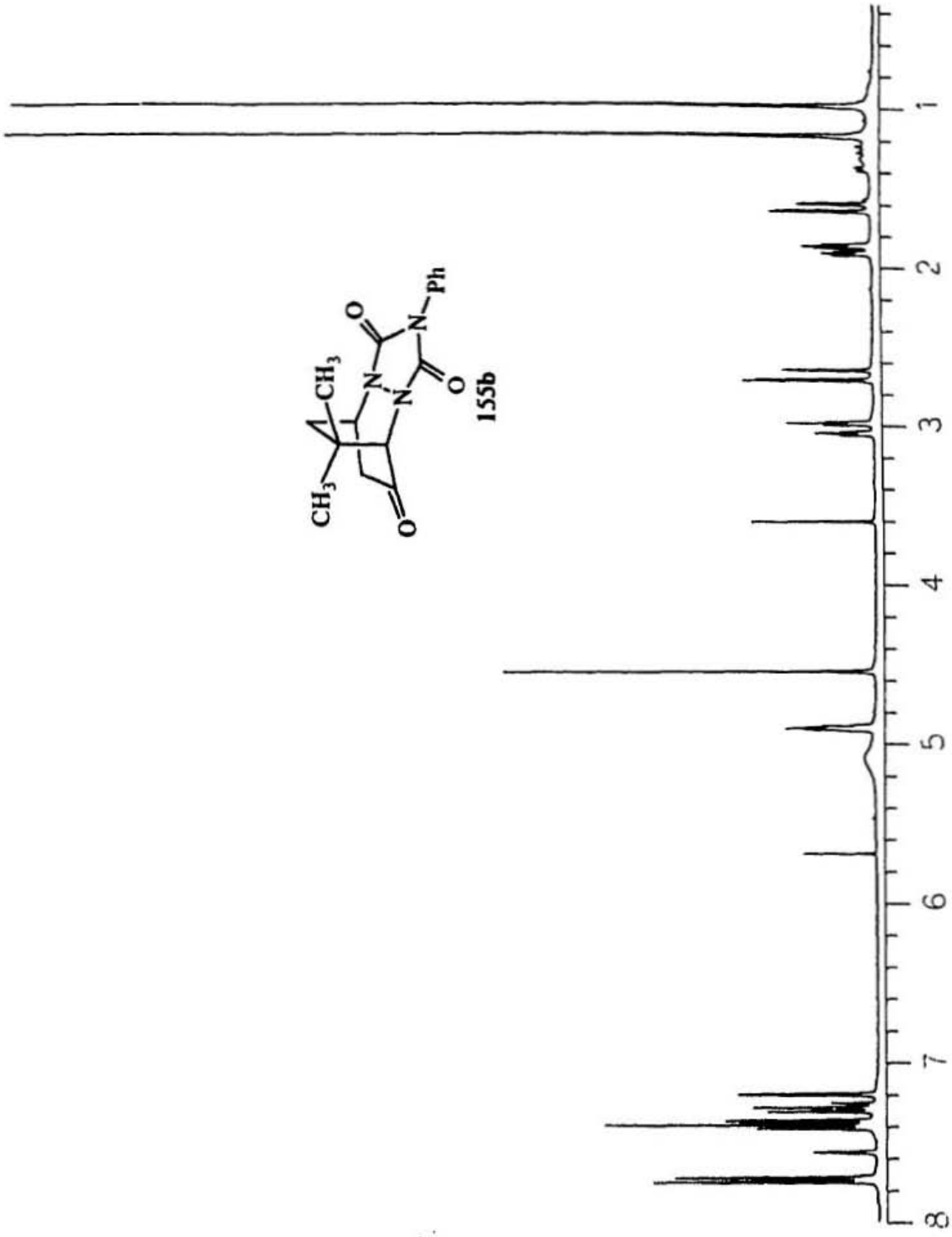
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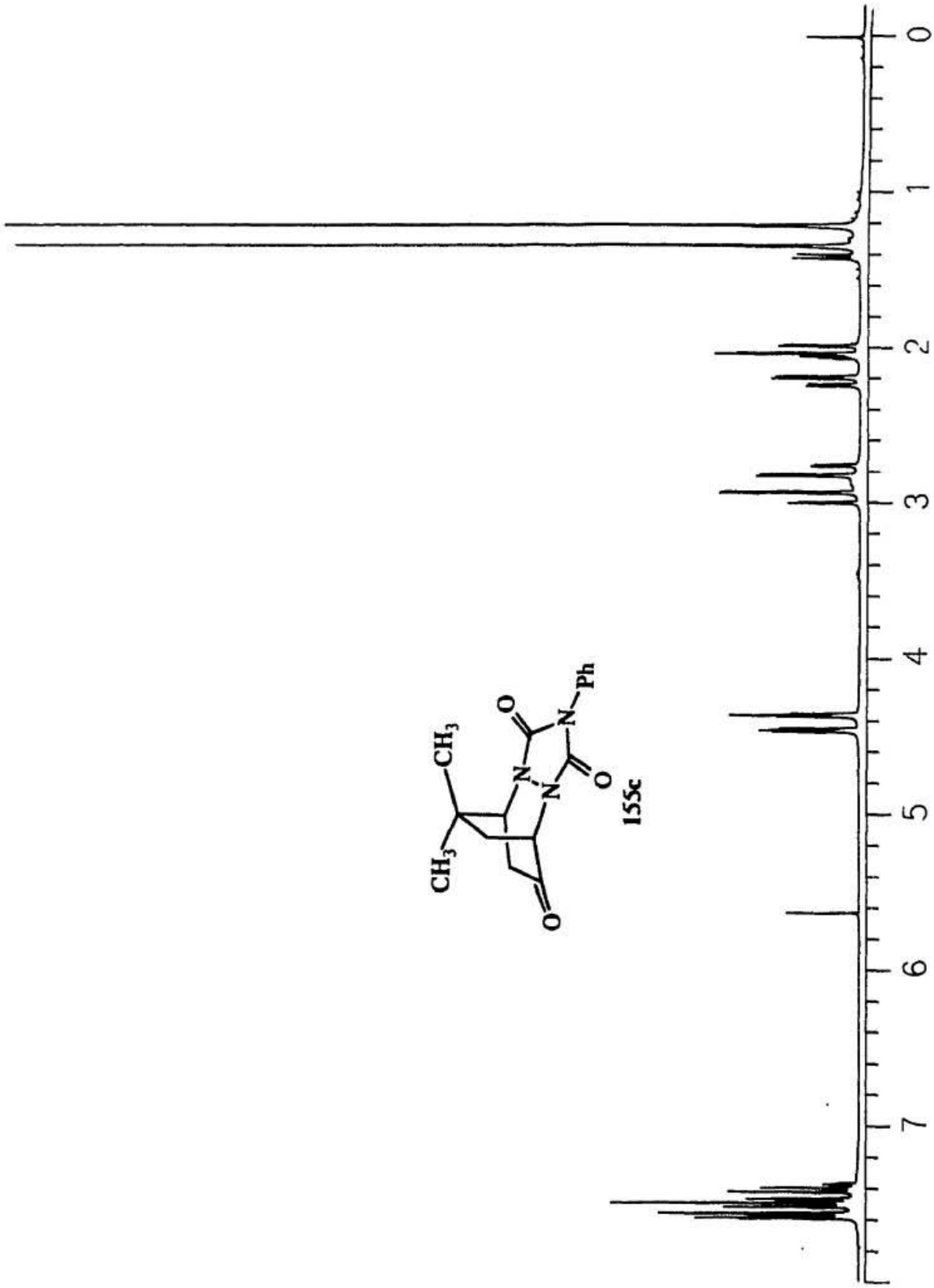
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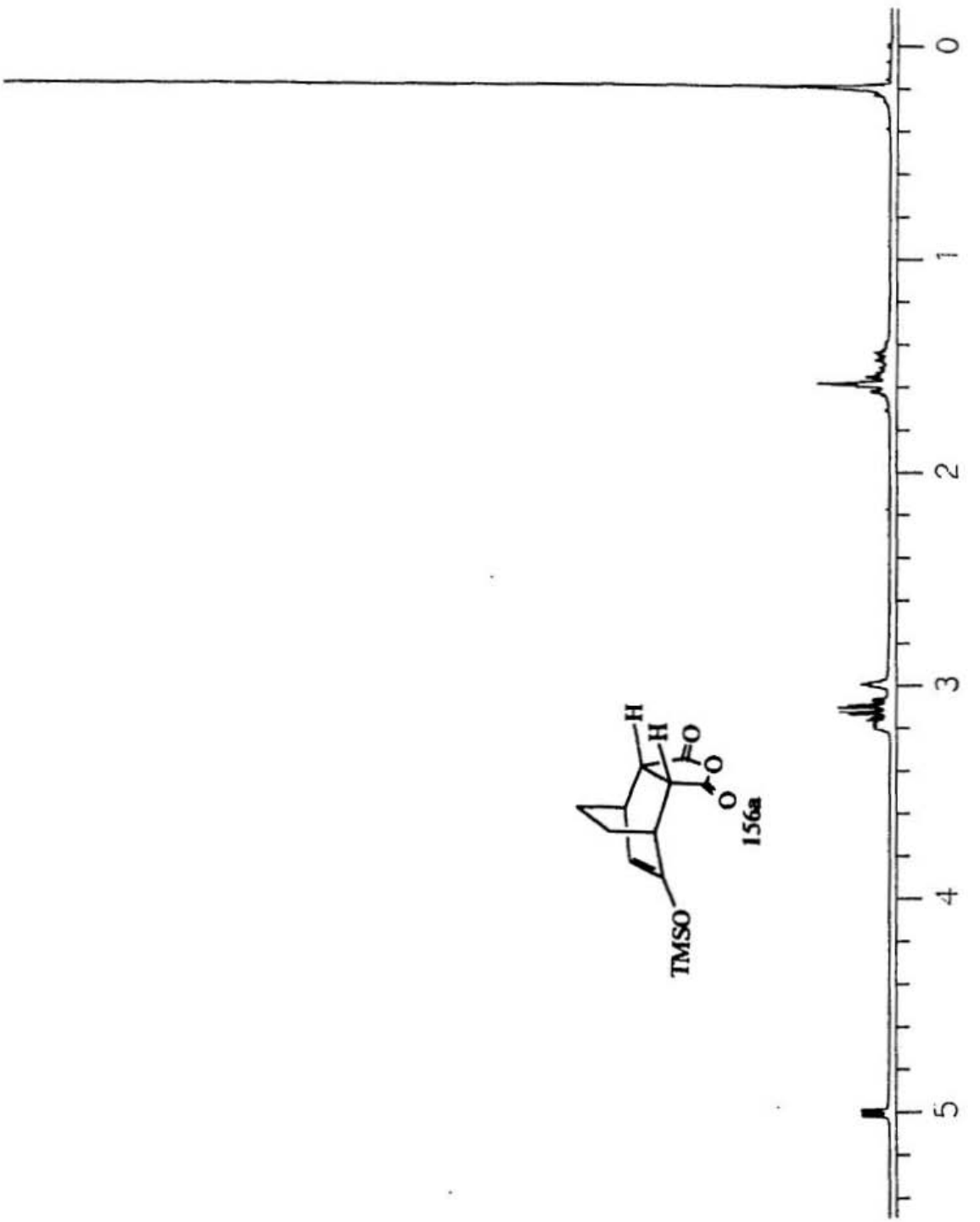
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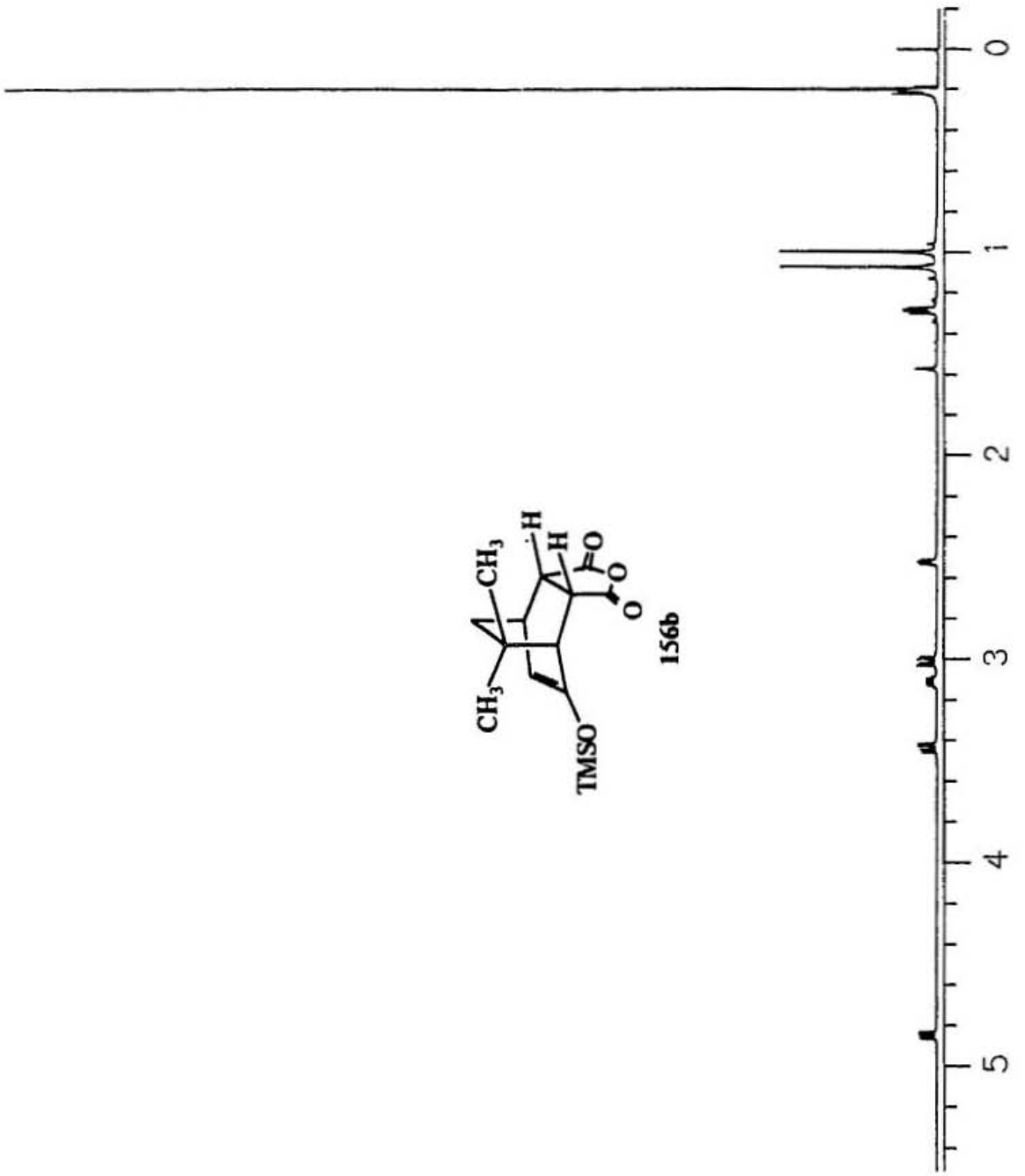
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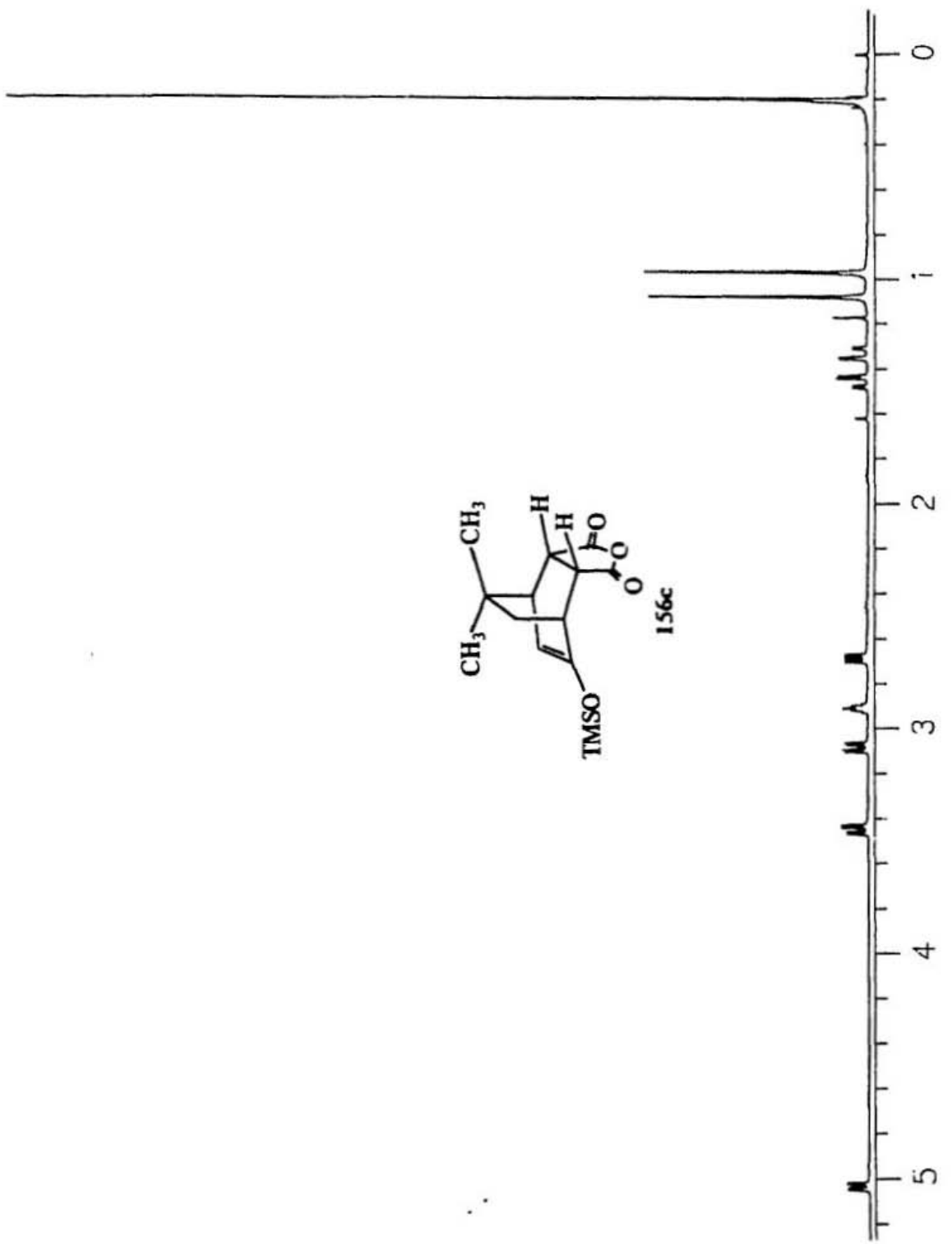
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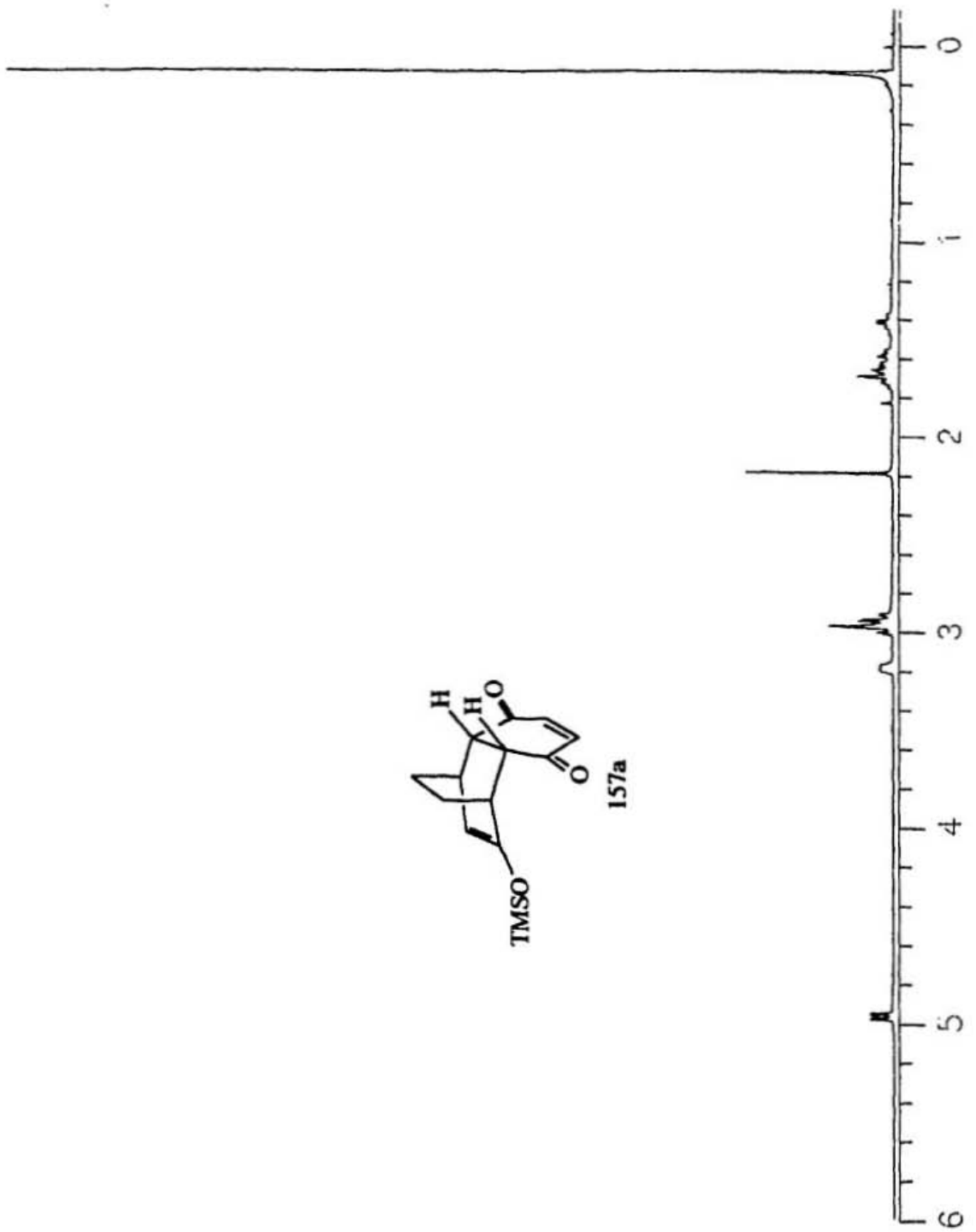
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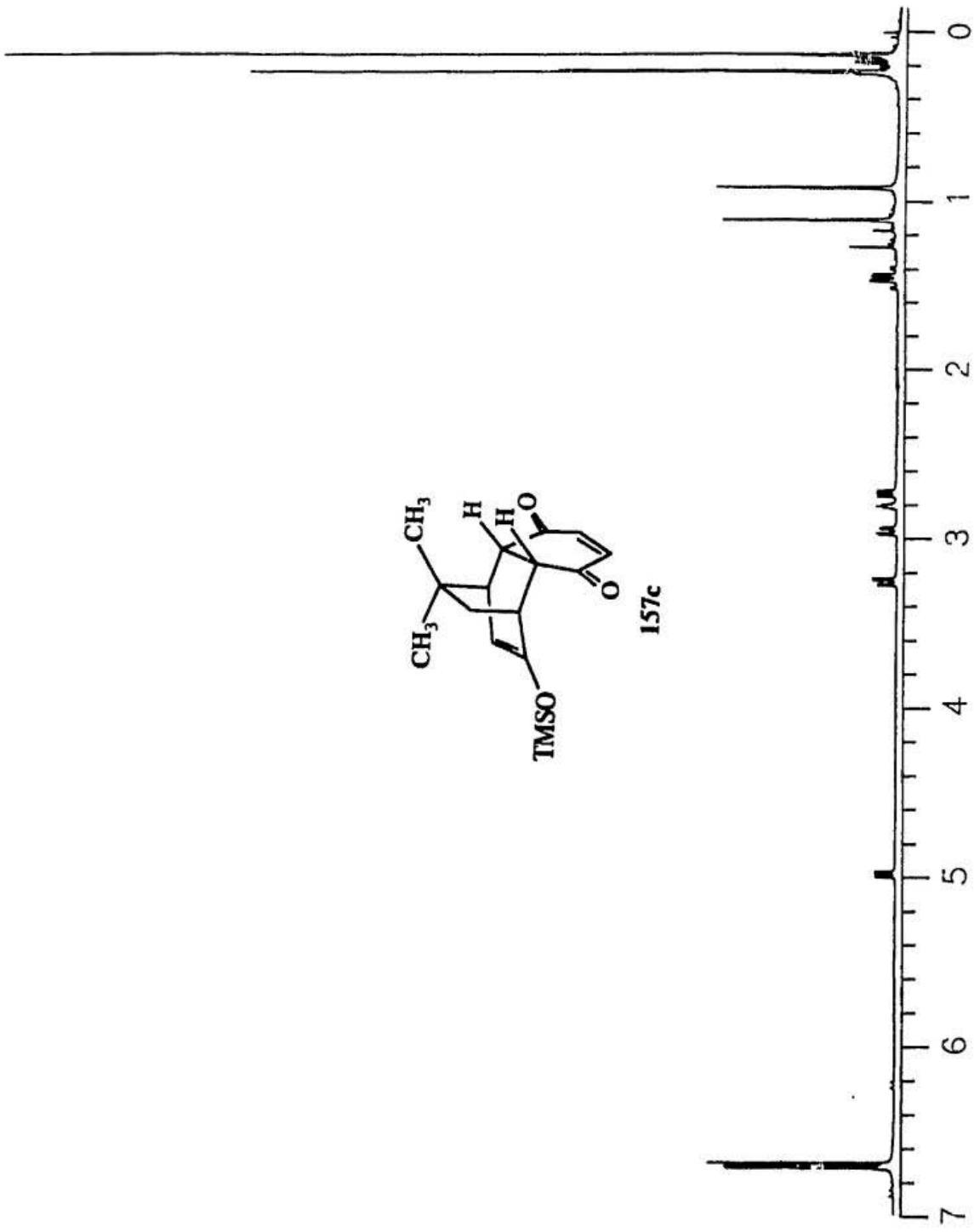
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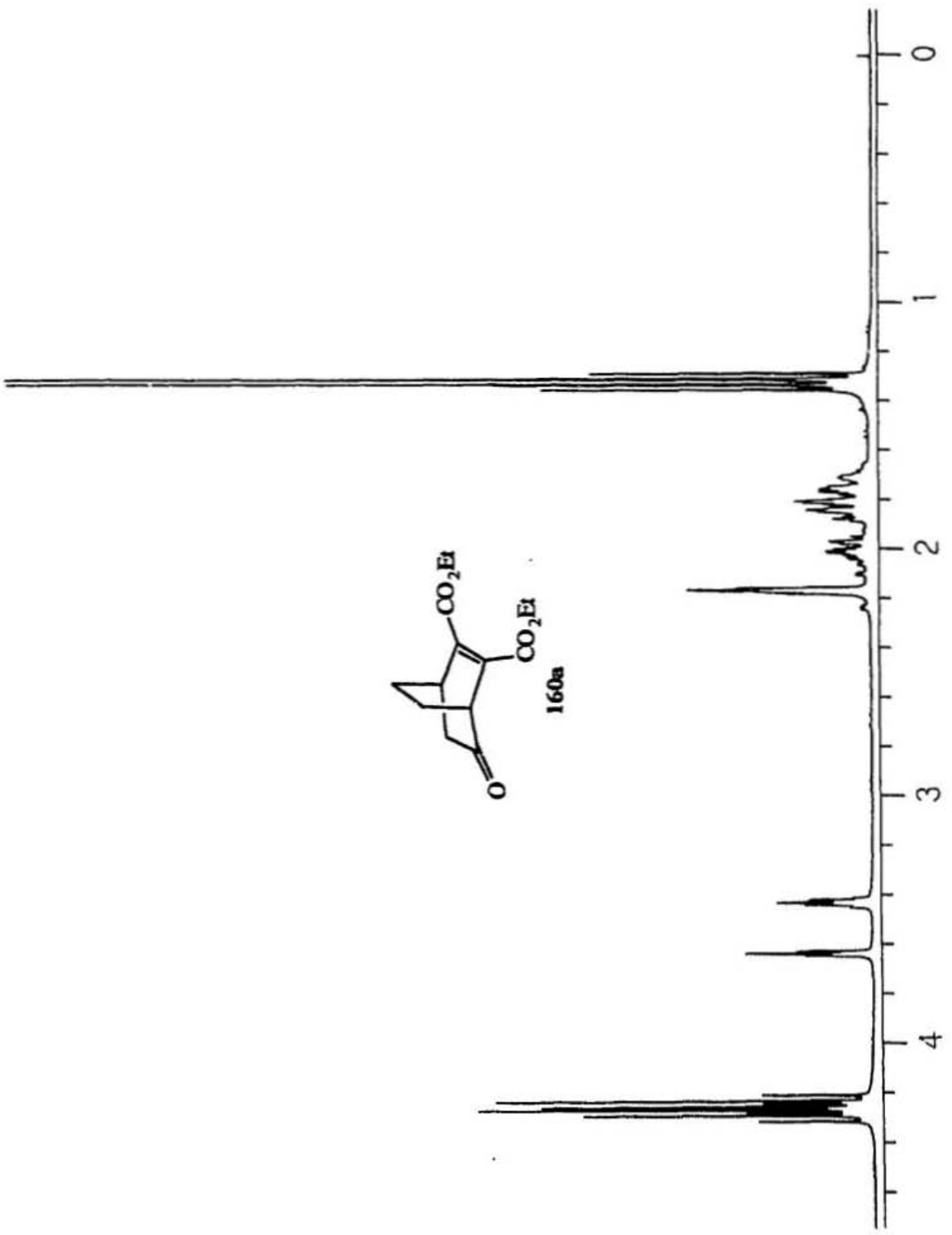
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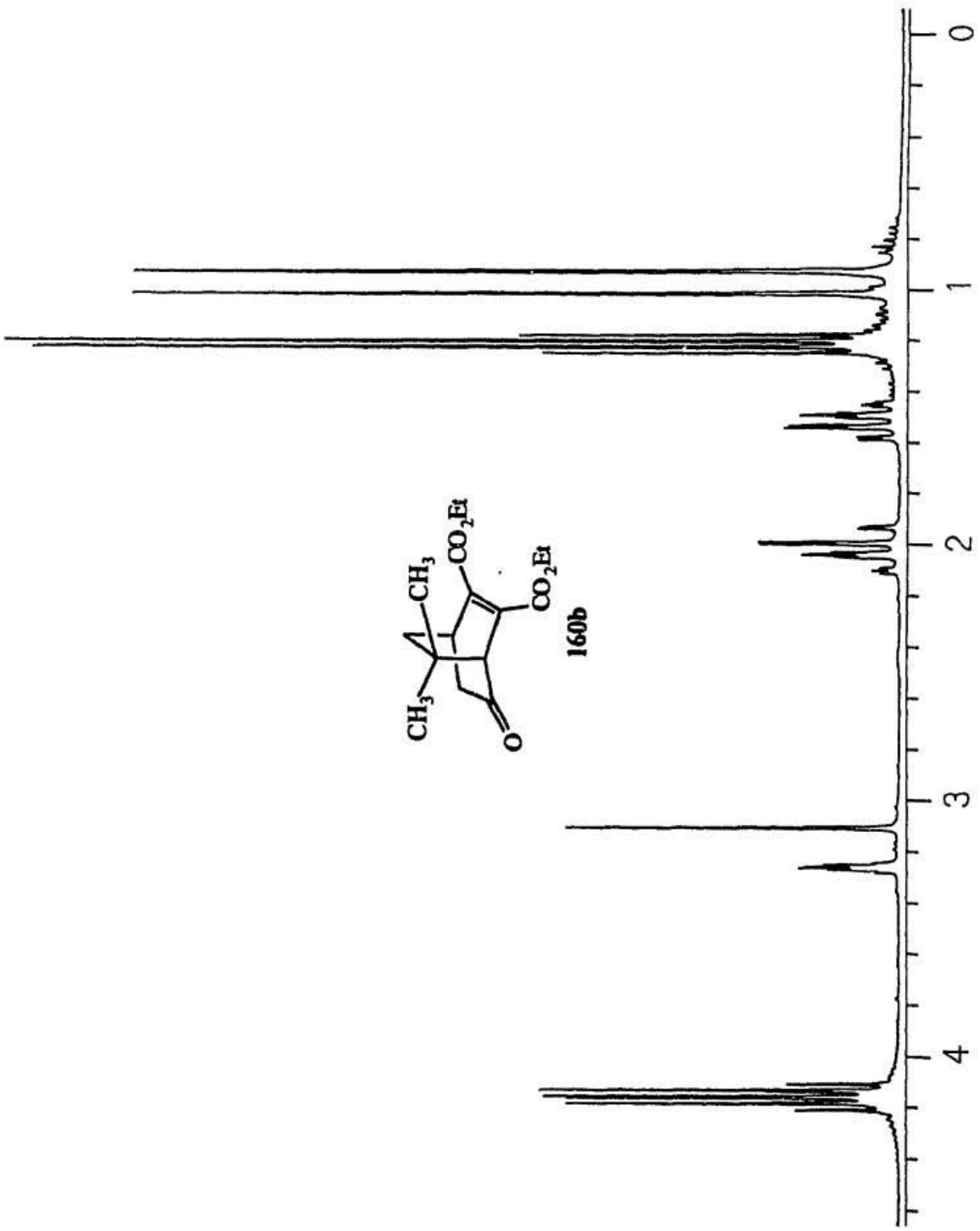
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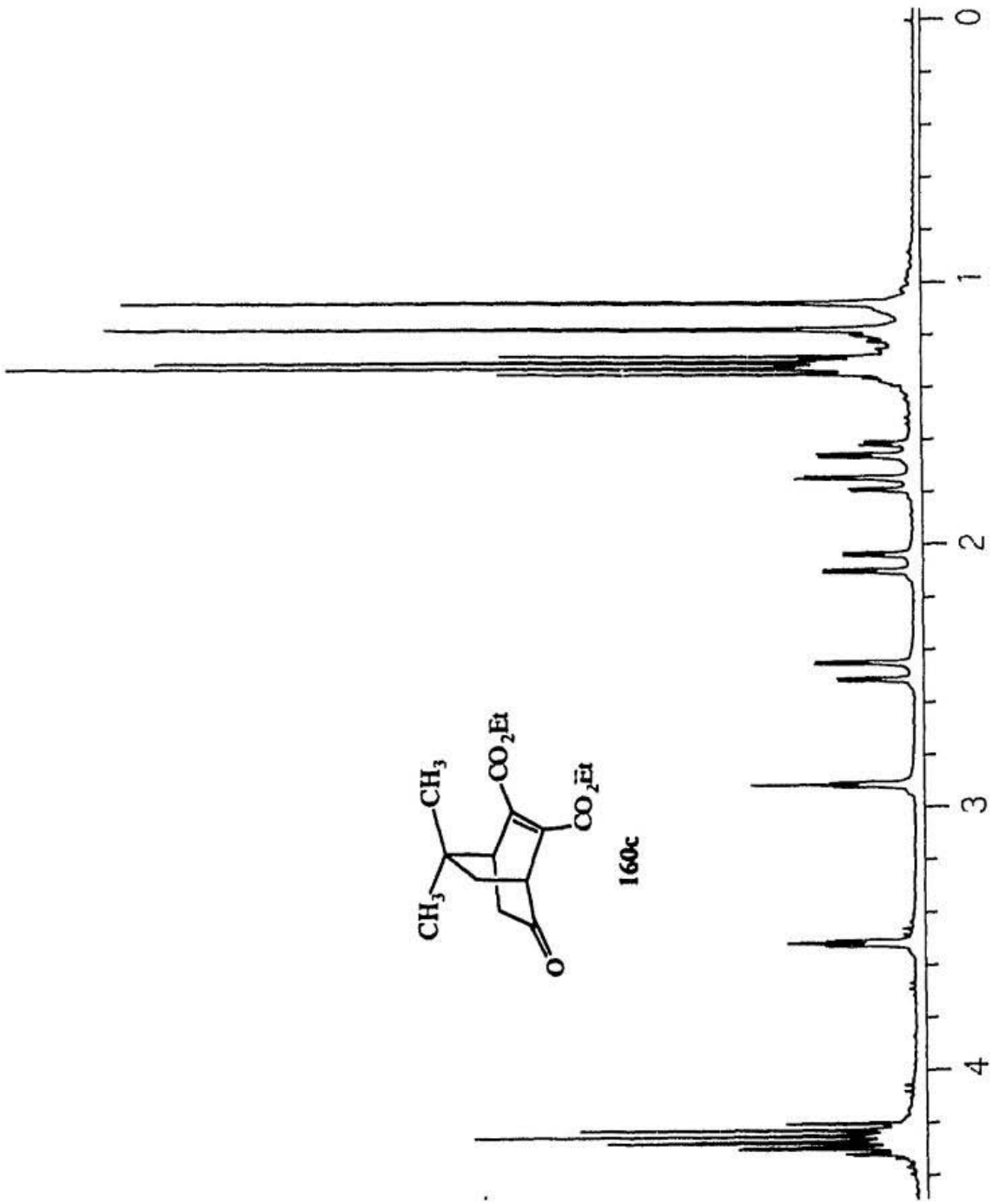
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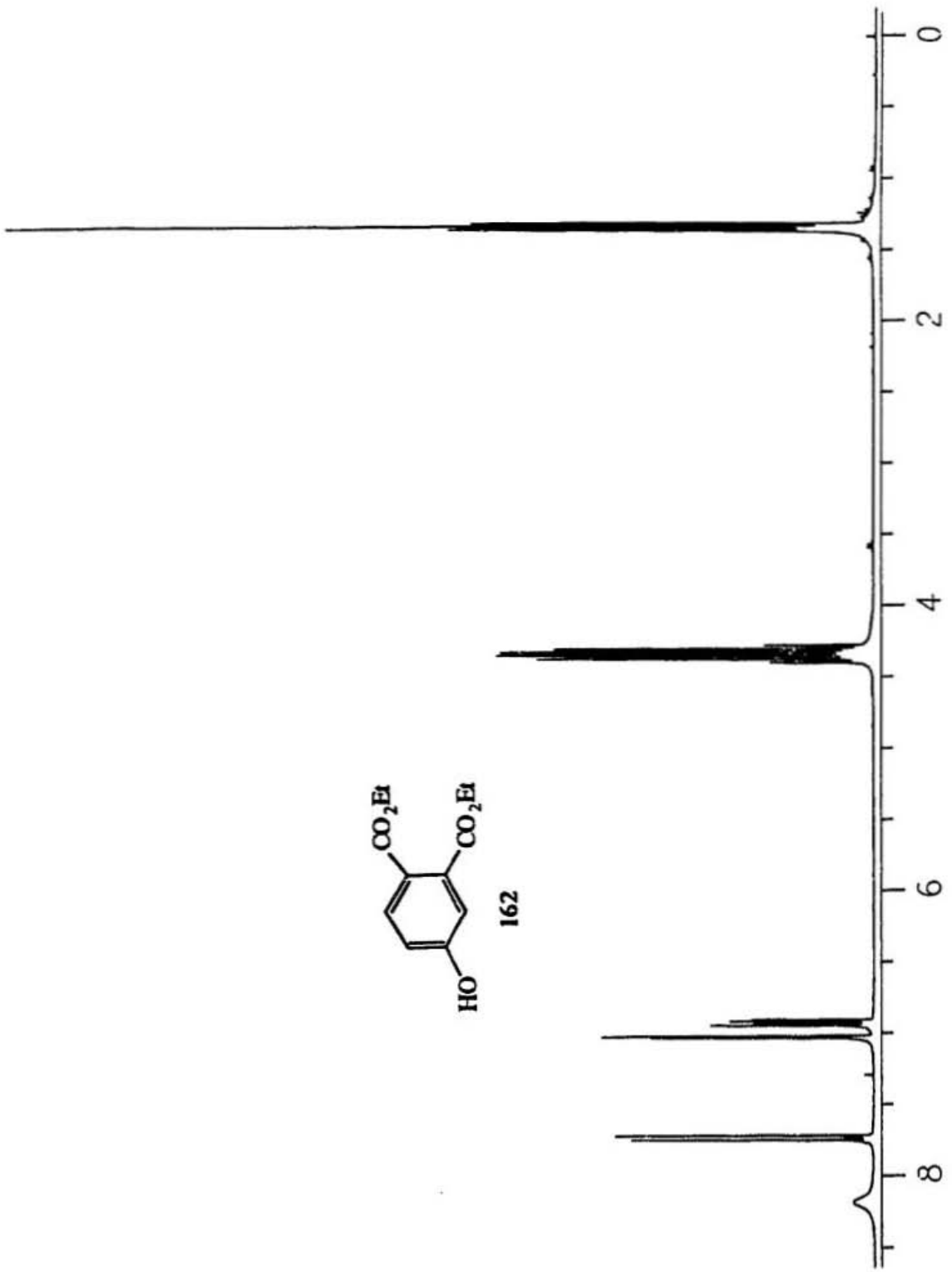
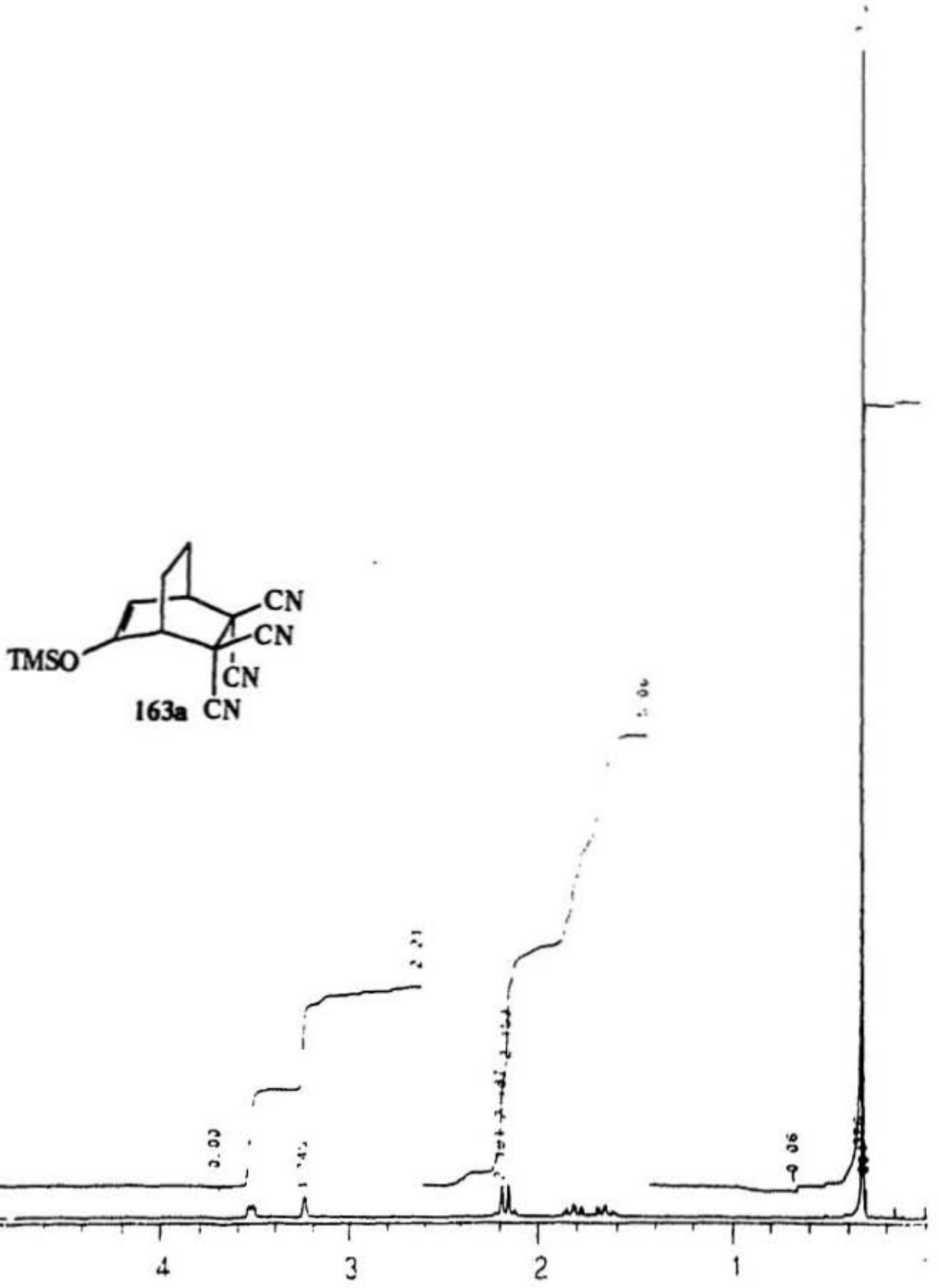
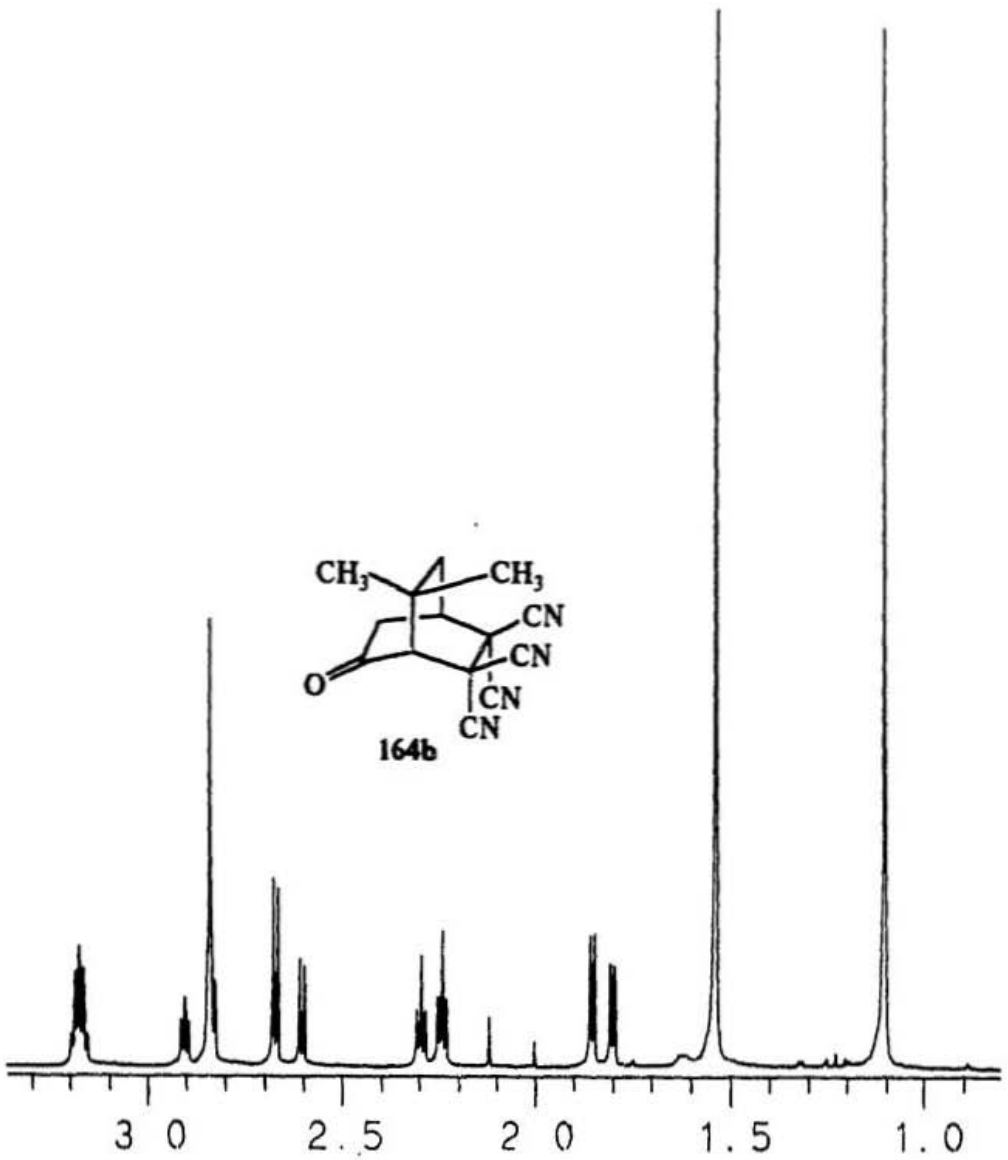
3
4

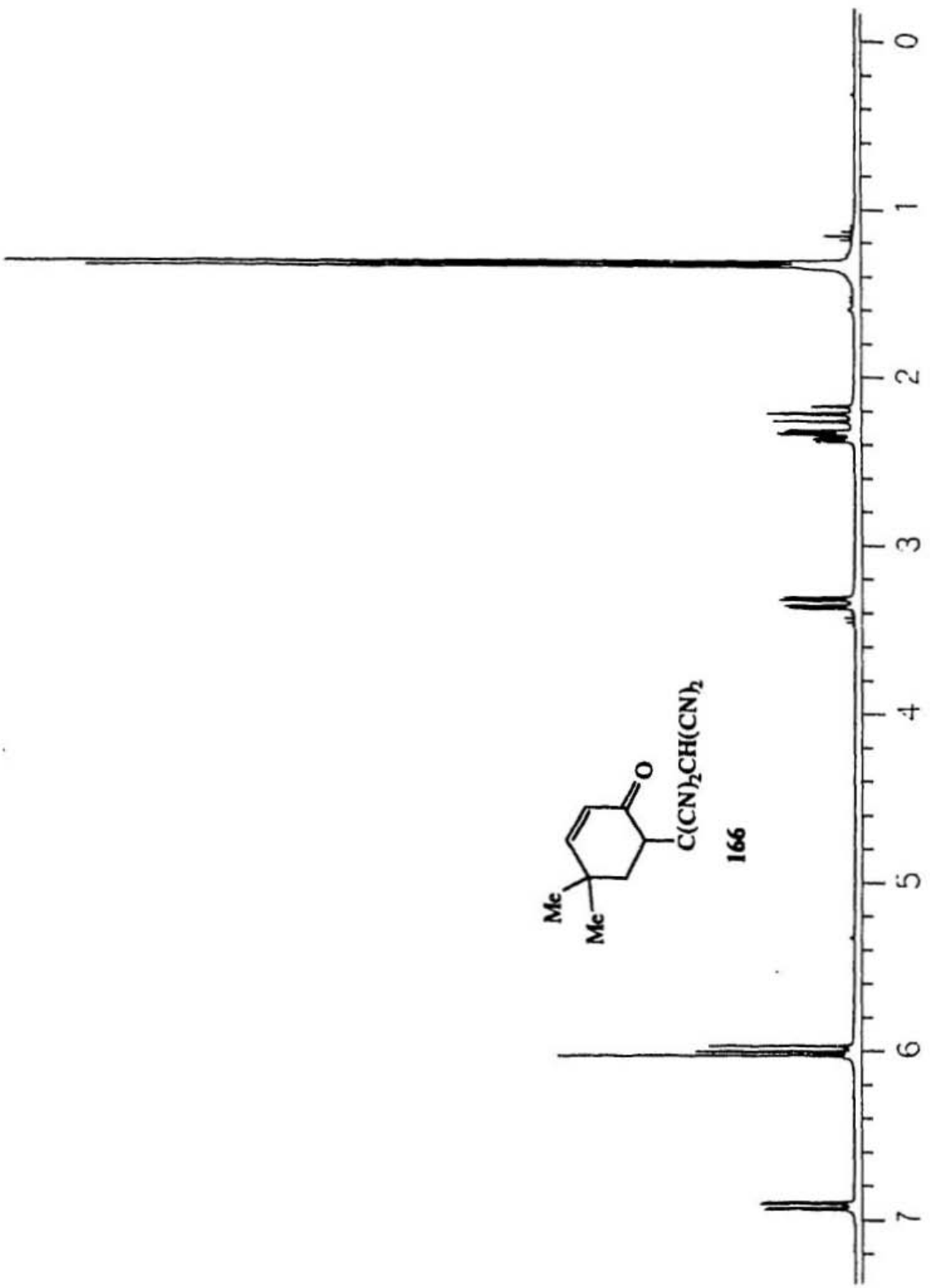


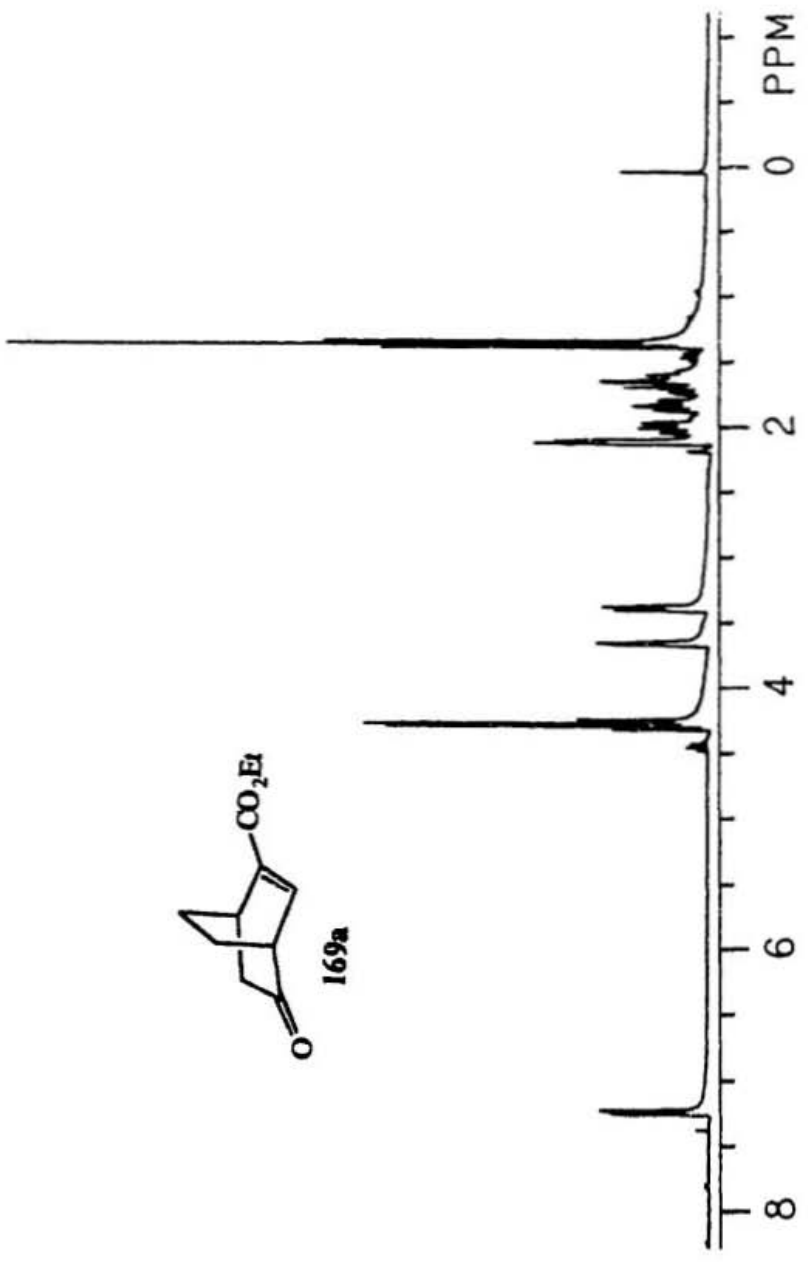
162

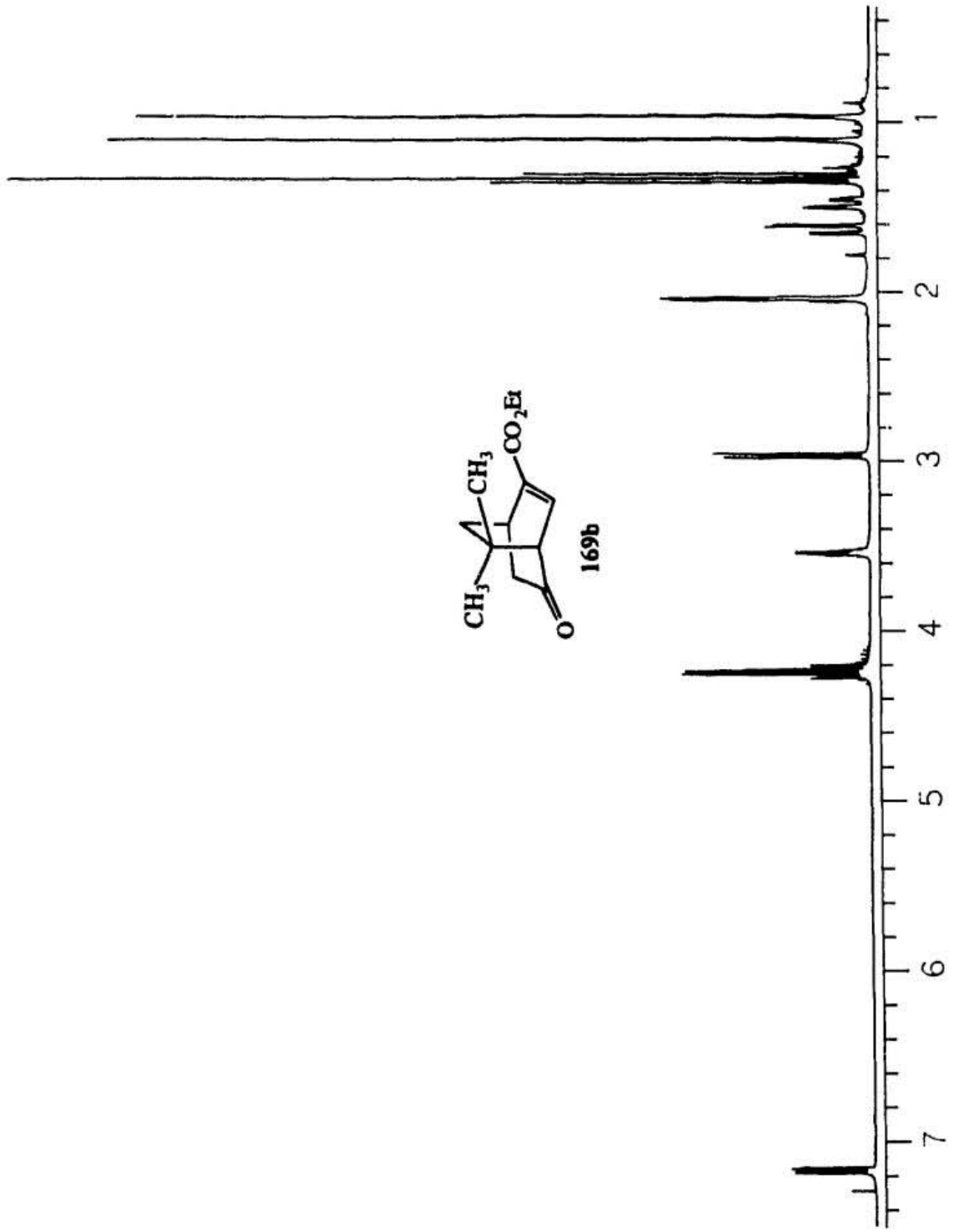

CN
CN
TMSO
CN
163a CN
5
4
3
2
1

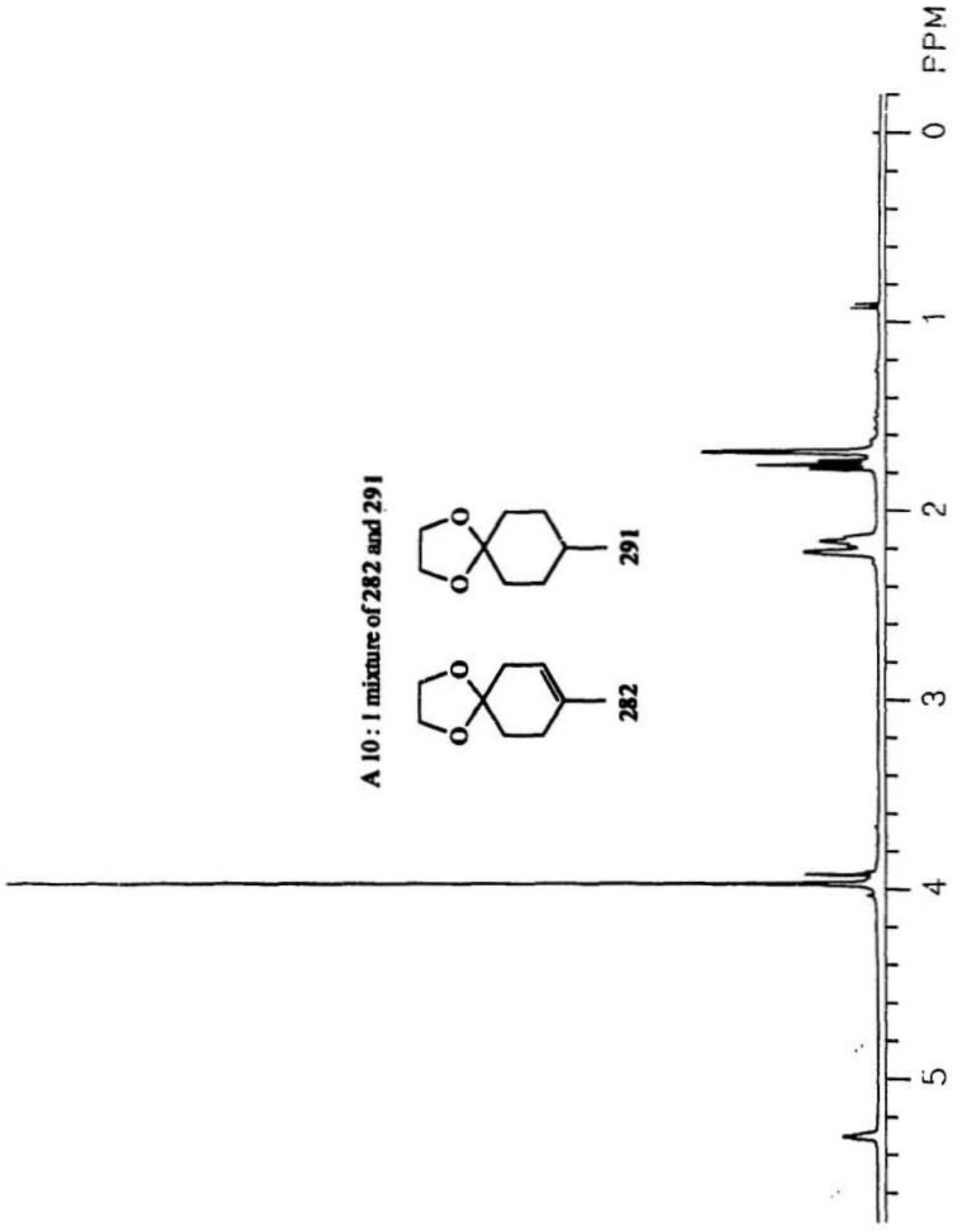


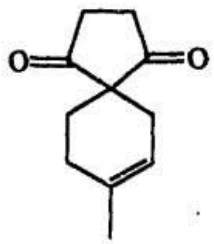
164b


Me
Me
O
C(CN)2CH(CN)2
166
0
1
2
3
4
5
6
7

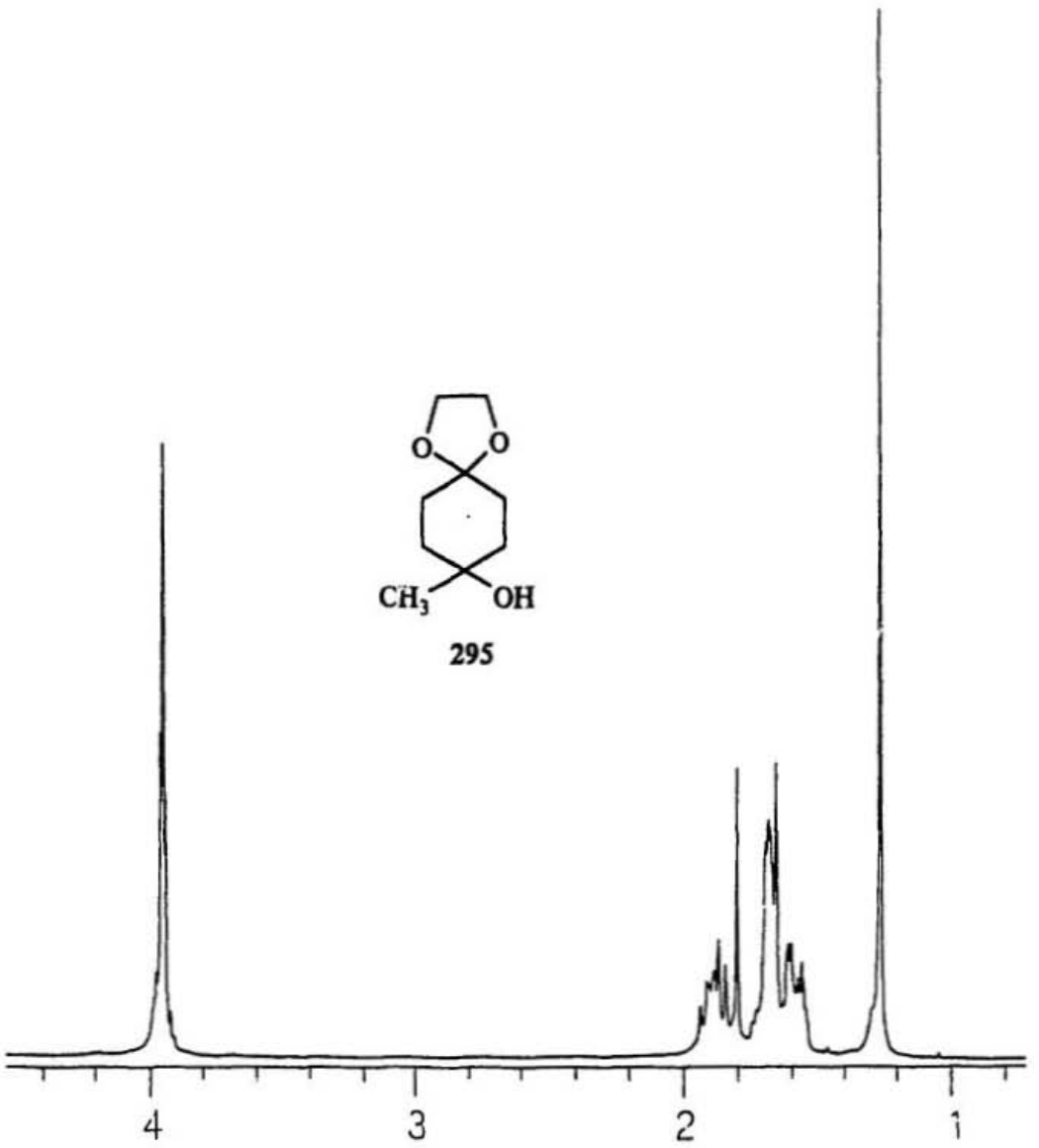

CO2Et
O
169a
8
6
4
2
0
PPM


CH3
CO2Et
CH3
O
169b
1
2
3
4
5
6
7

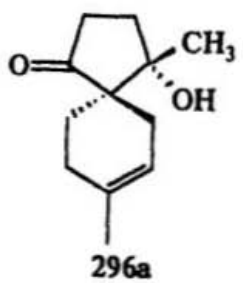

A 10 : 1 mixture of 282 and 291
291
282
5
4
3
2
1
0
PPM



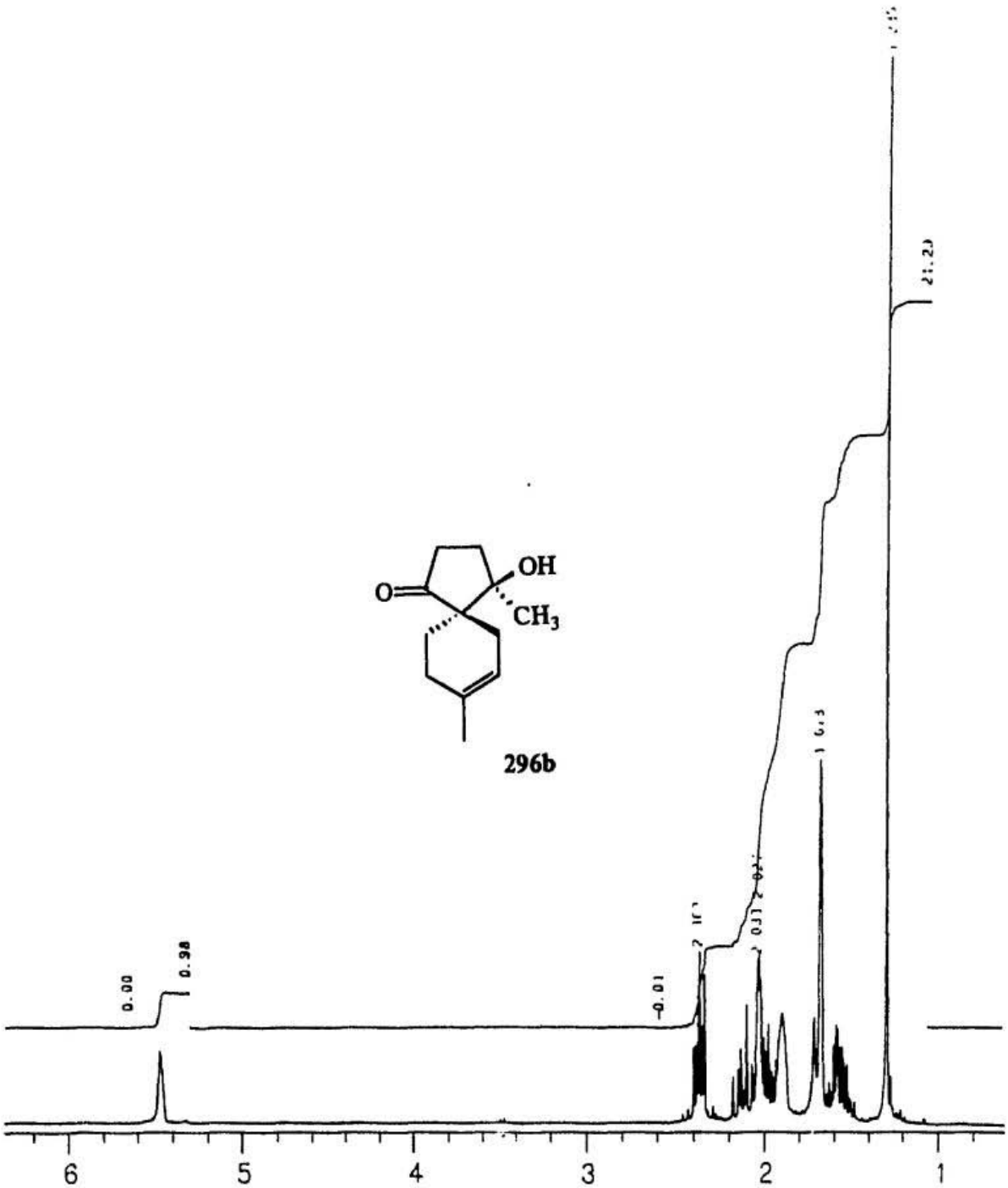
281



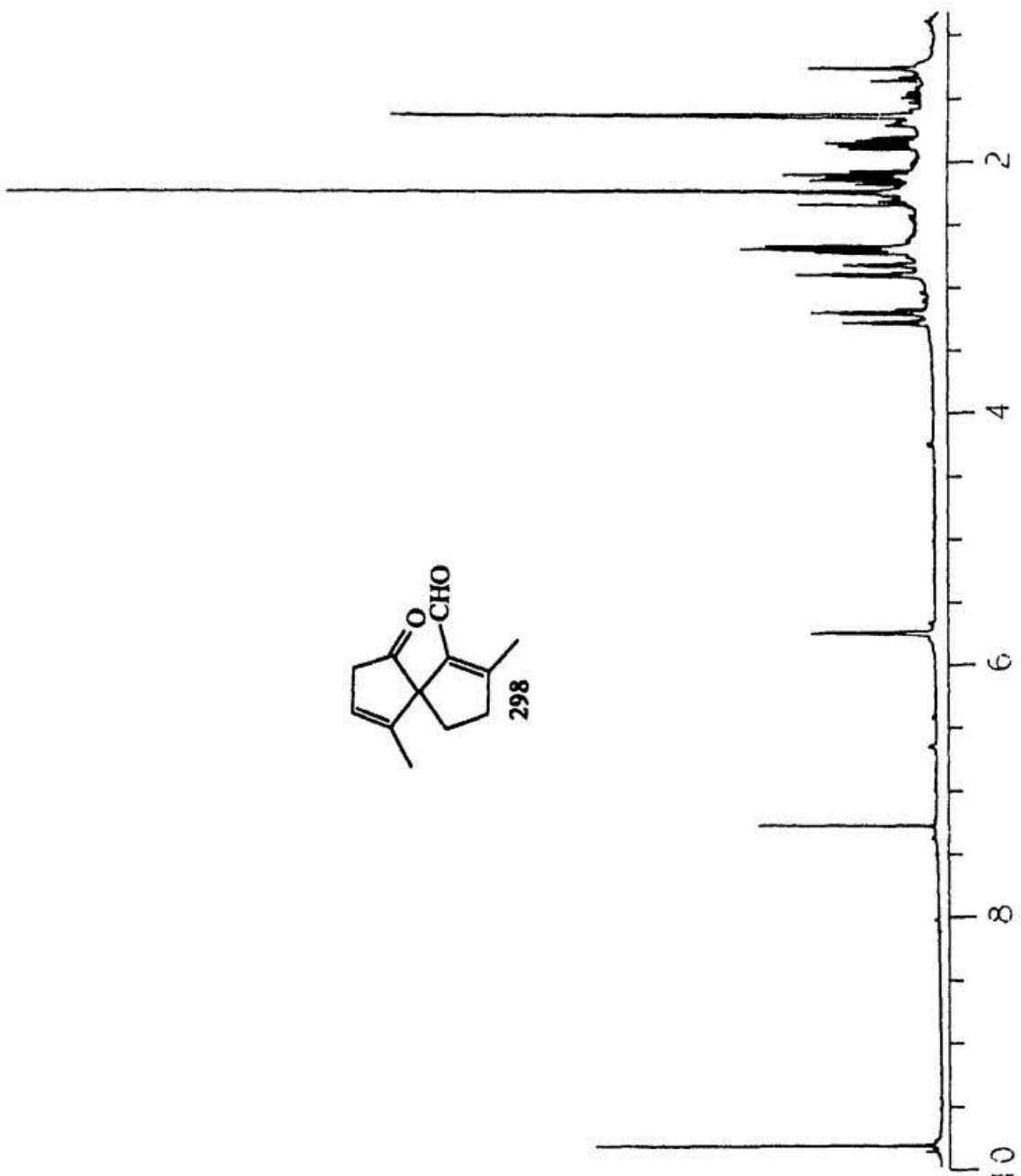
295



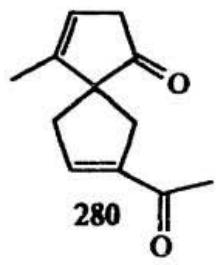
296a



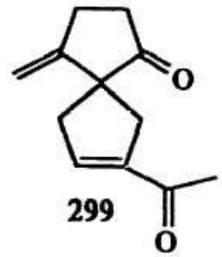
296b


O
CHO
298
10
8
6
4
2

A 1 : 1 mixture of 280 and 299

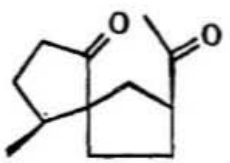


280

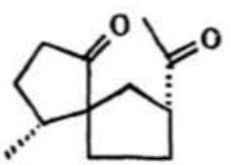


299

A 1.2 : 1 mixture of 302 and 301

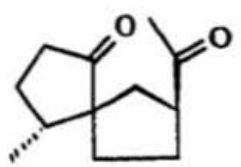


301

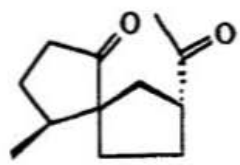


302

A 1.2 : 1 mixture of **303** and **300**

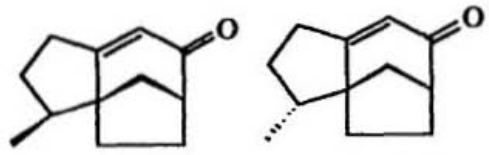


303

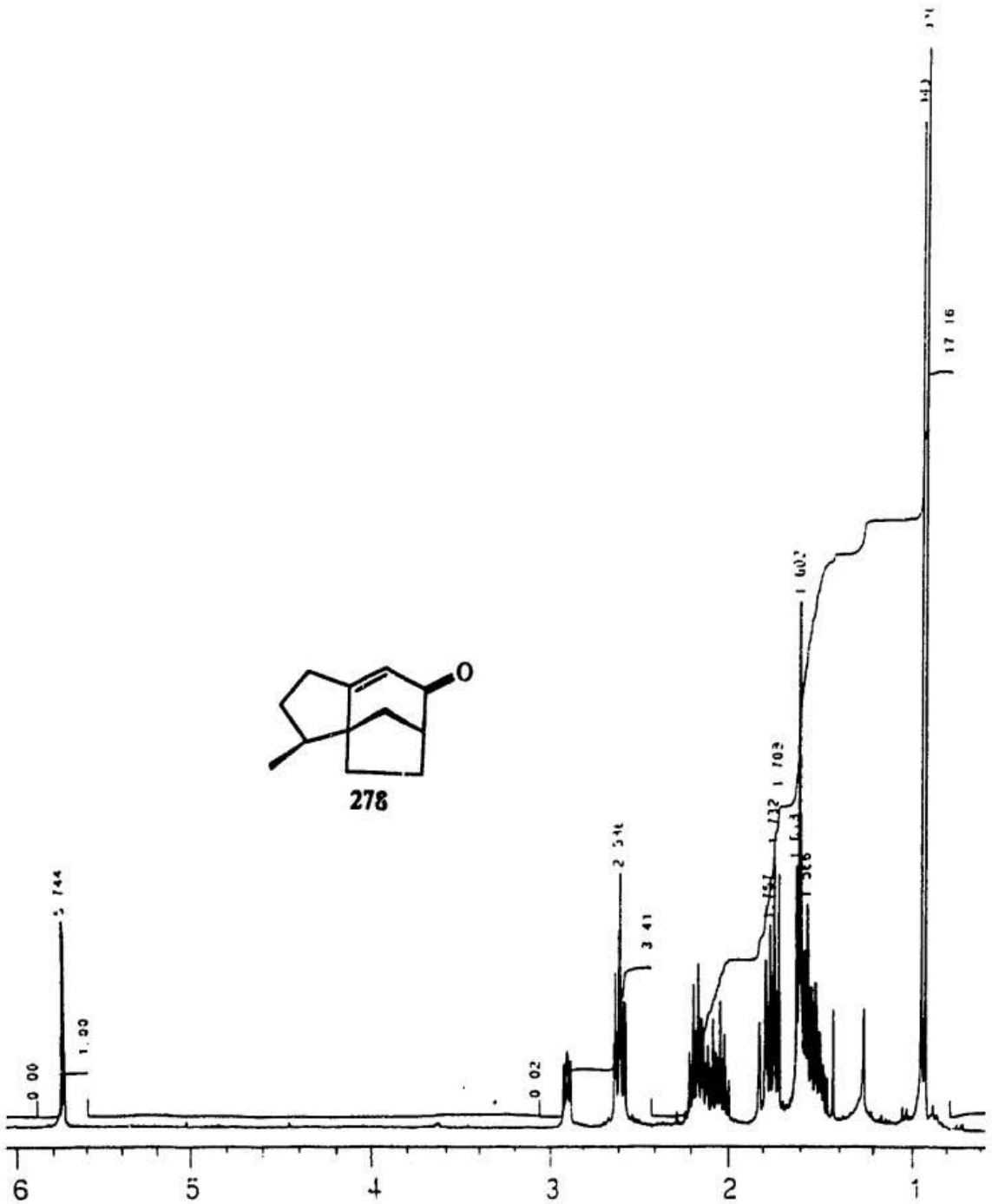


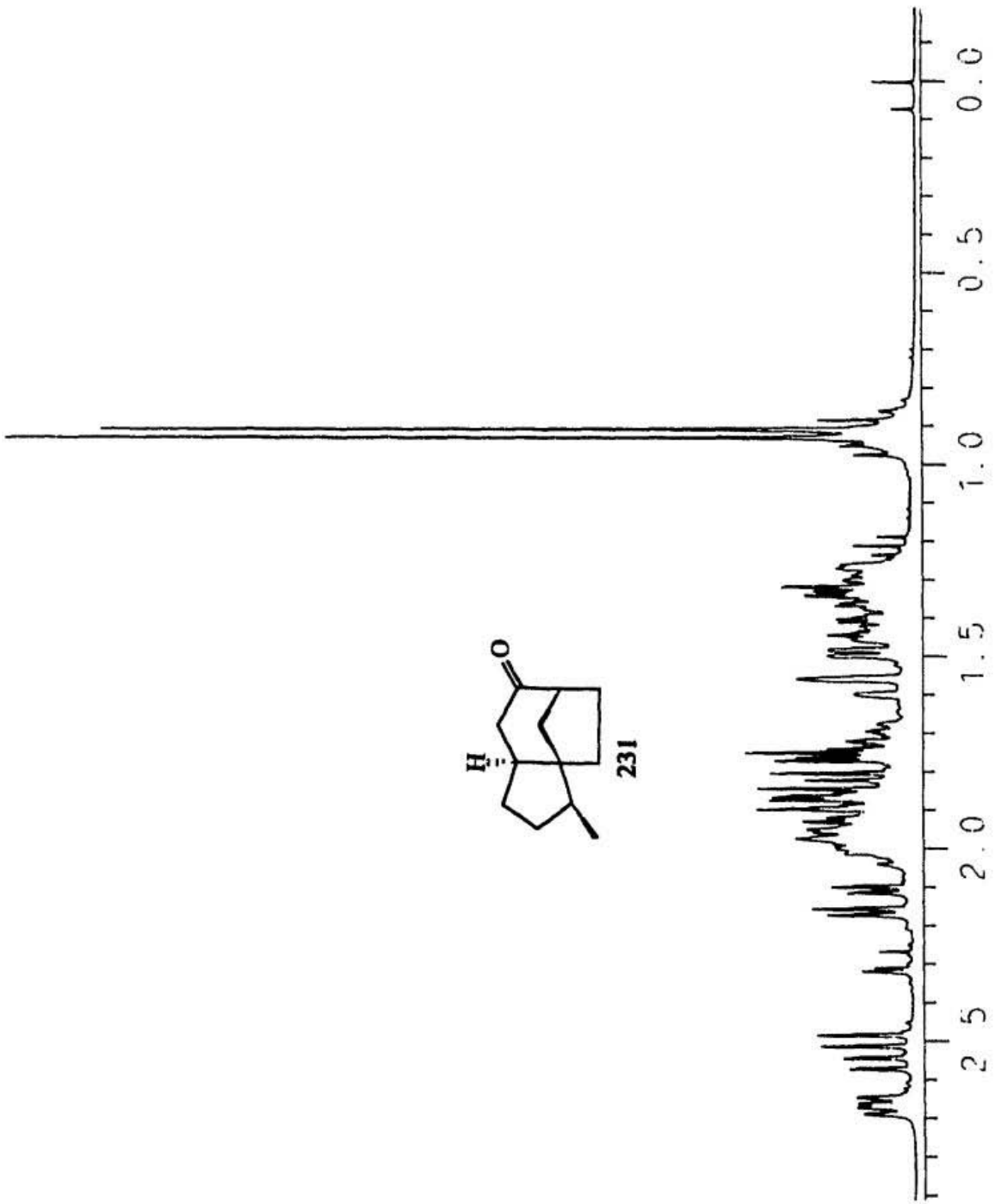
300

A 1 : 1.2 mixture of 278 and 304 from direct hydrogenation of 280/299



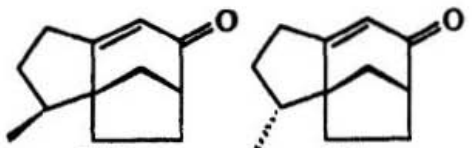
278 **304**


O
278
6
5
4
3
2
1



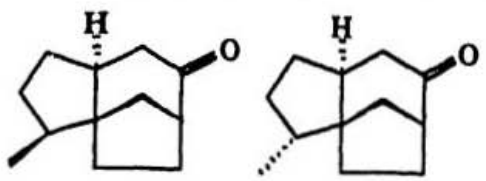
231

A 1.2 :1 mixture of **278** and **304** from Birch reduction and hydrogenation of **280** and **299**



278 **304**

A 1.2 : 1 mixture of **232** and **312**
from Birch reduction of **278** and **304**

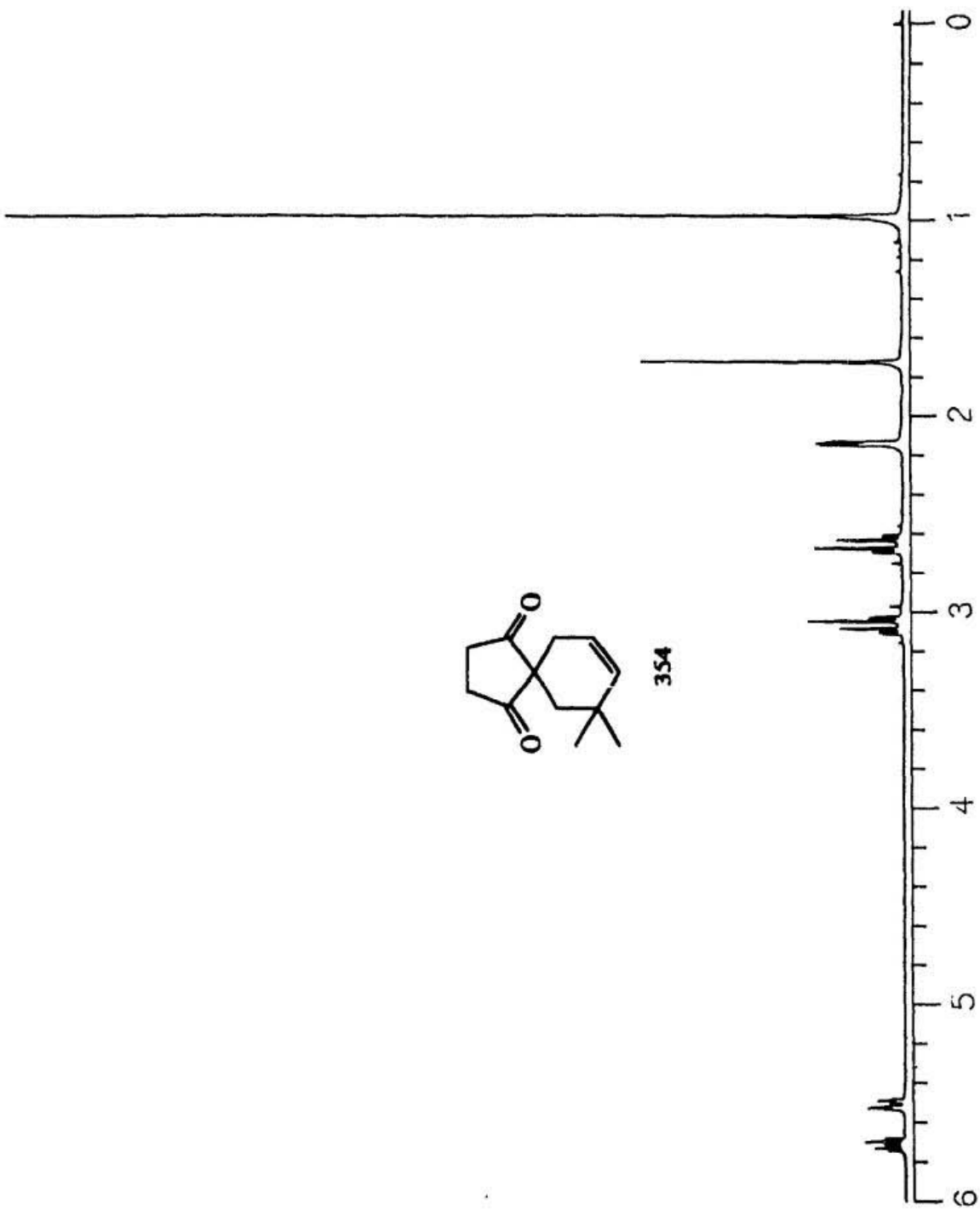


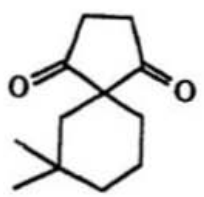
232 **312**

A 1 : 9.5 mixture of 324 and 325

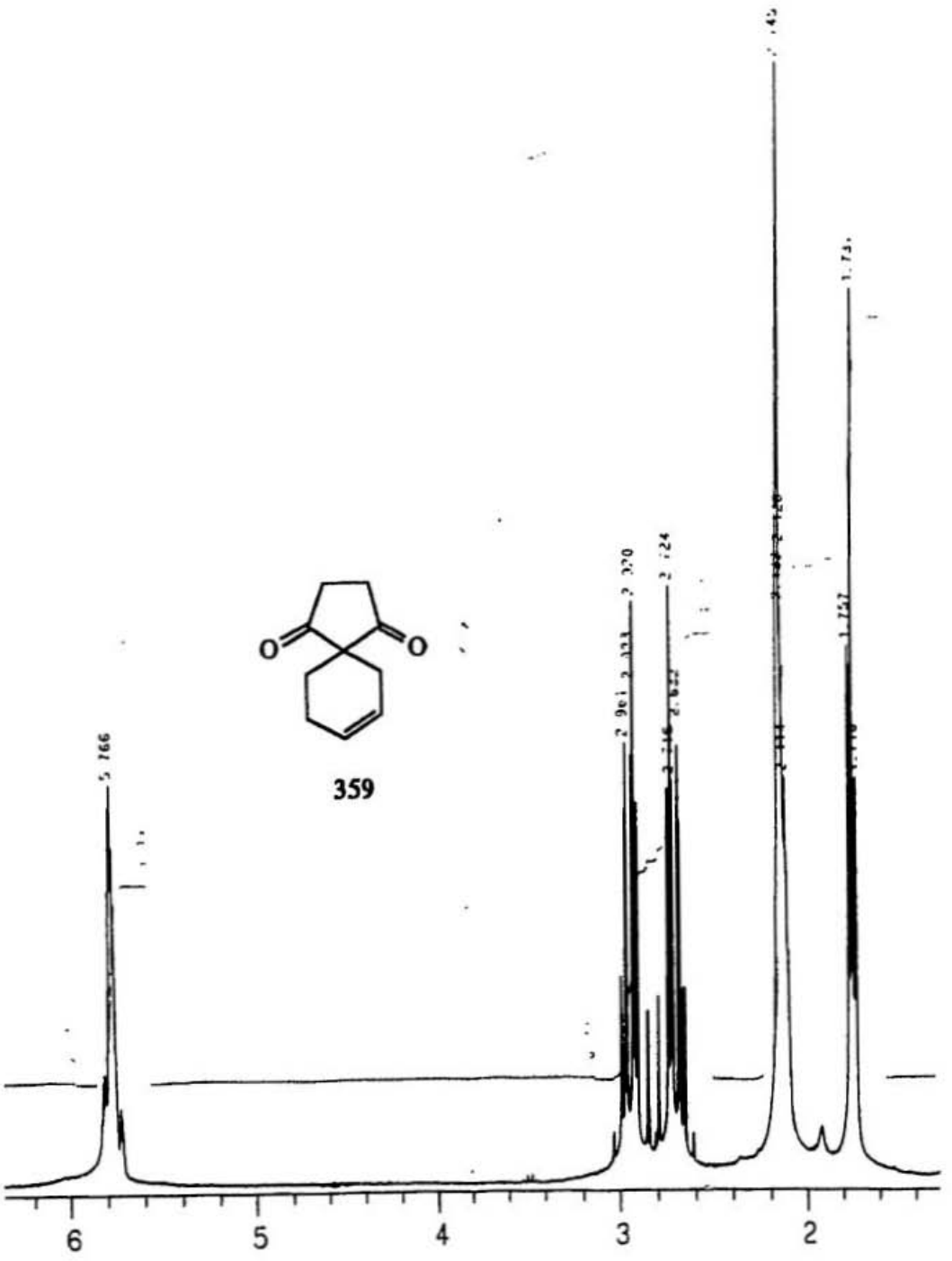
324

325

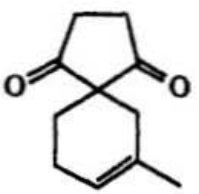

O
O
354
0
1
2
3
4
5
6



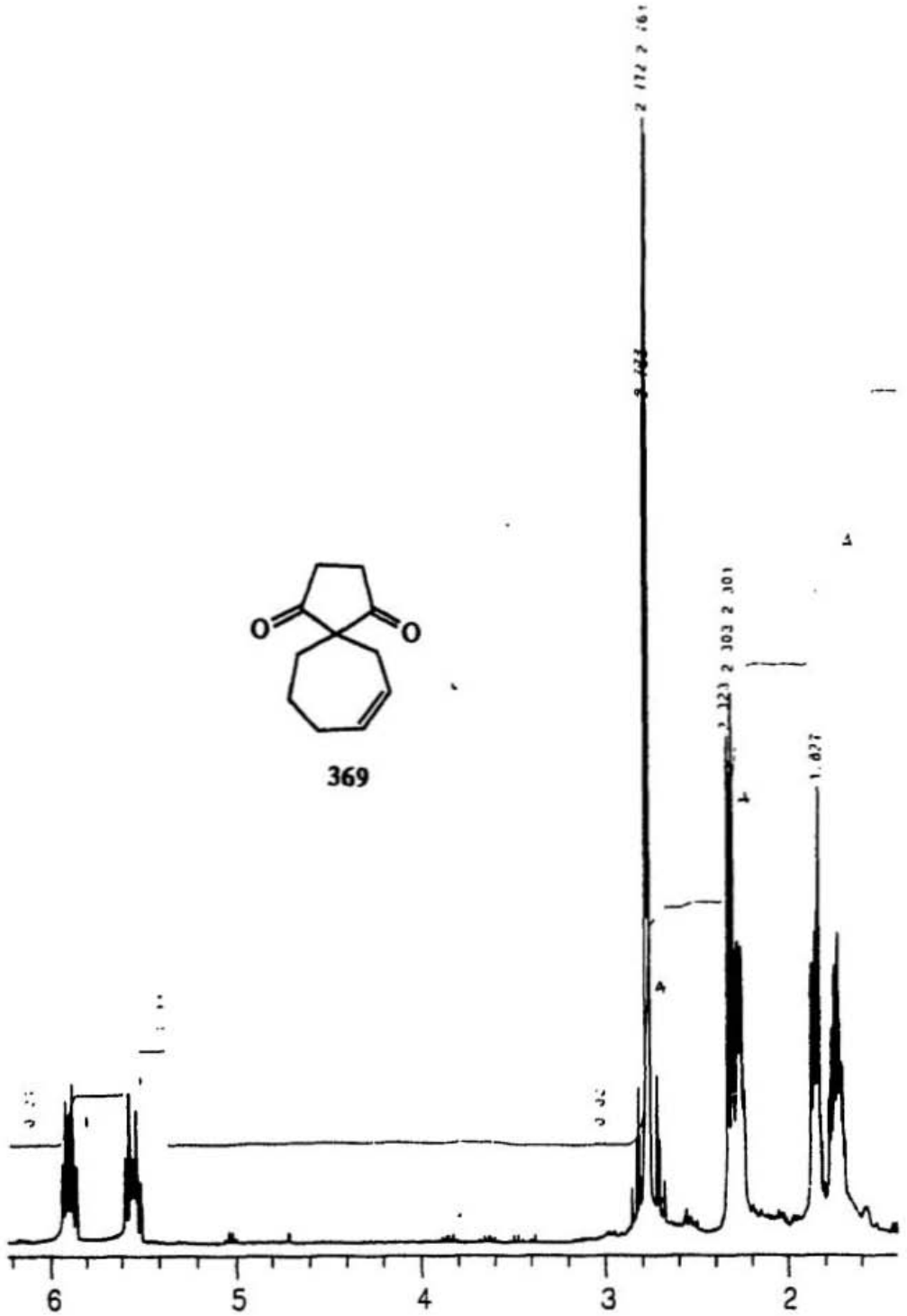
356



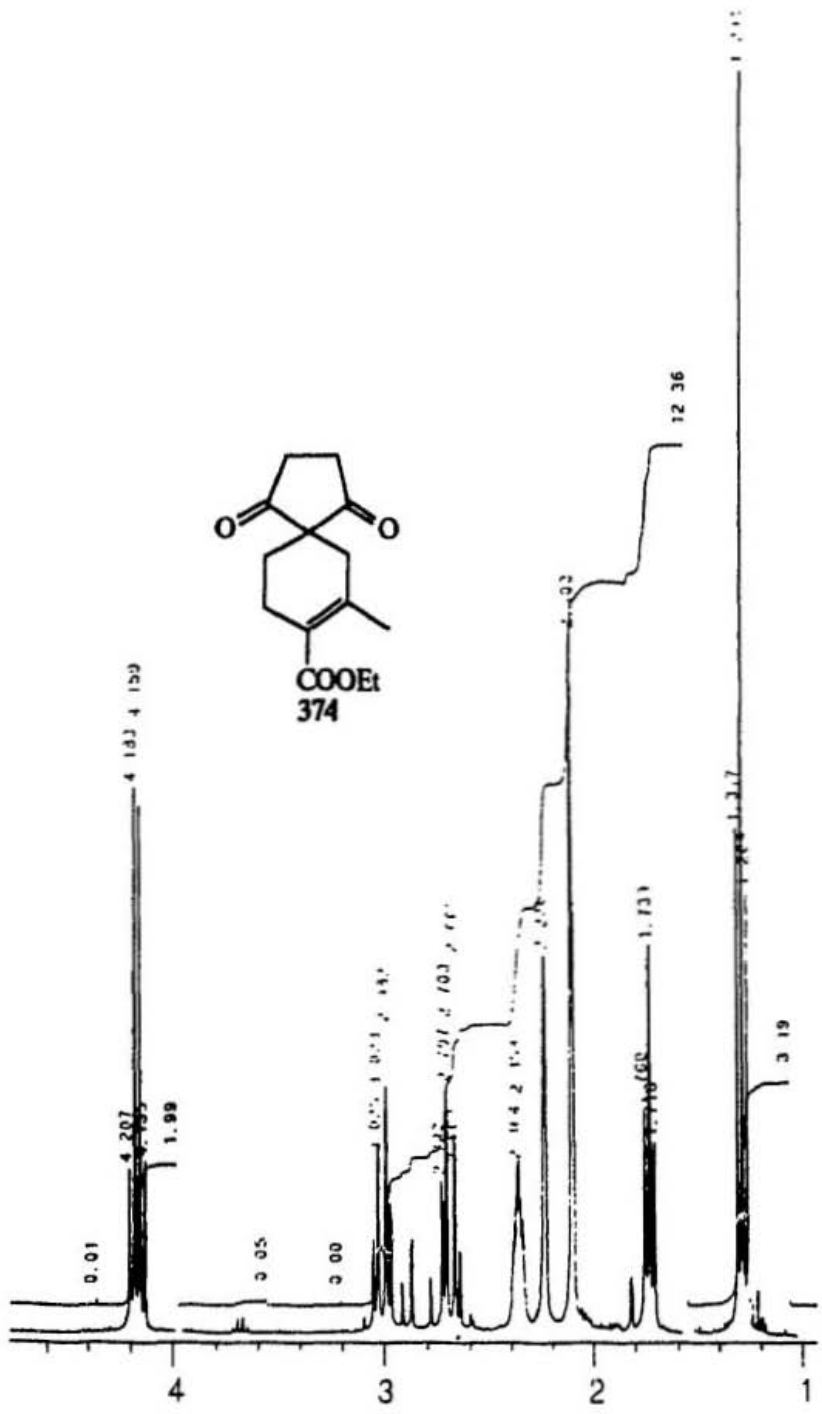
359

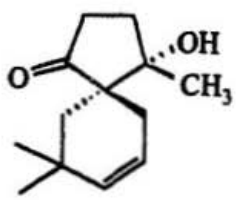


364

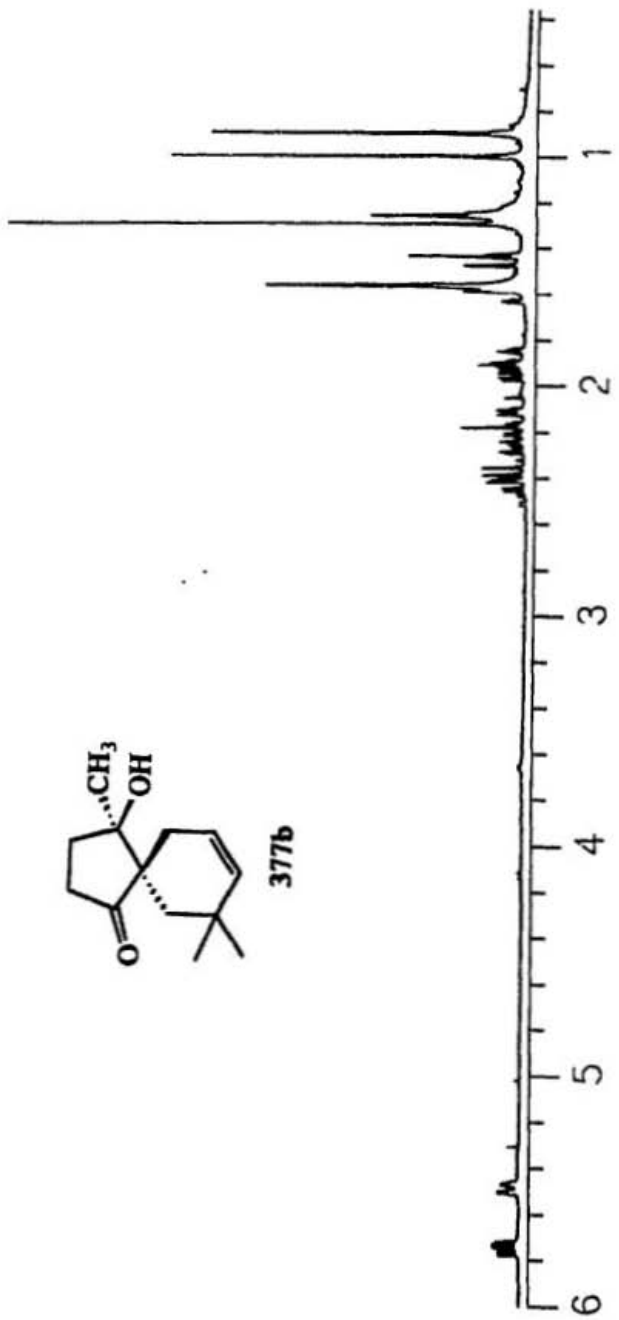


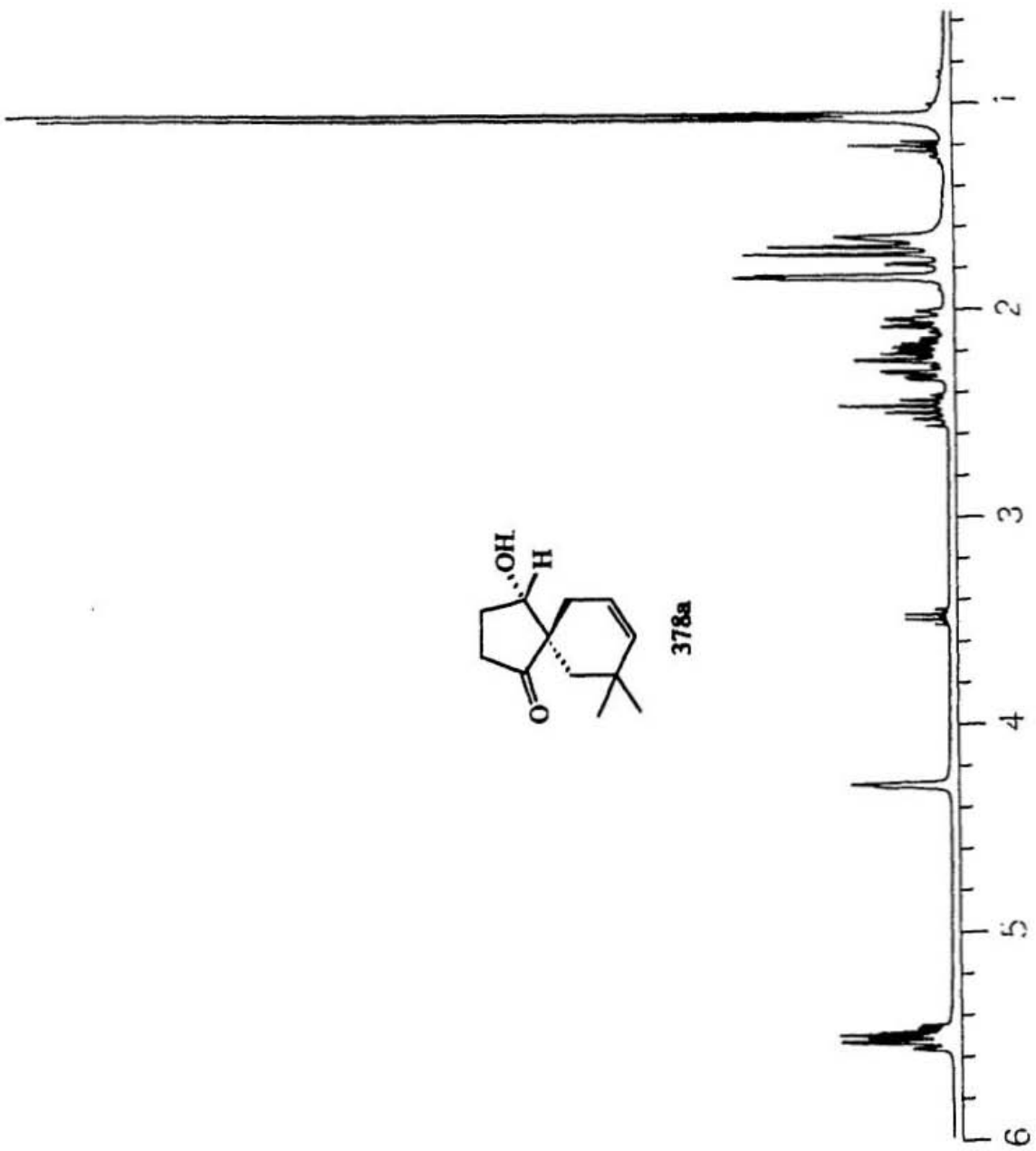
369

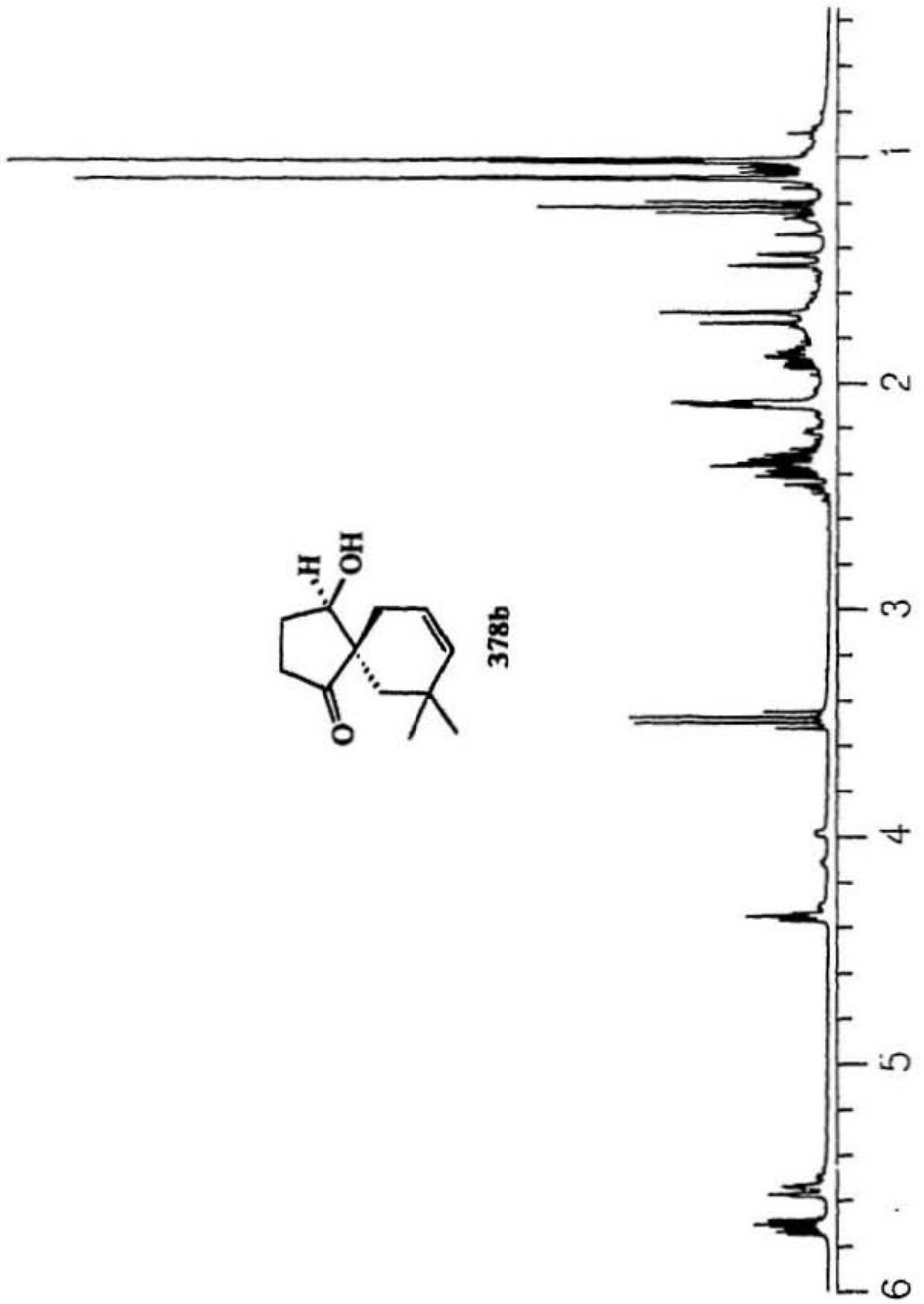

O
O
COOEt
374
12.36
1.99
3.19
4
3
2
1

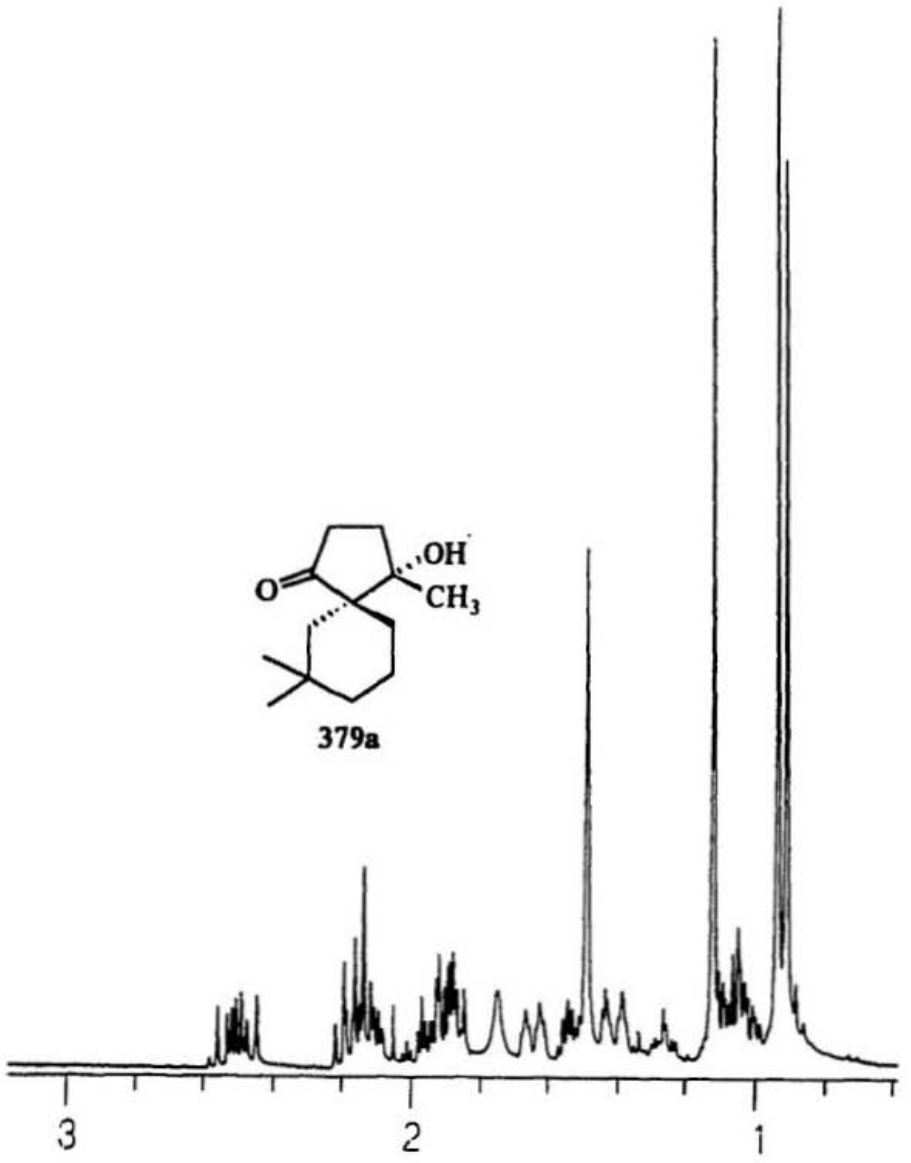


377a

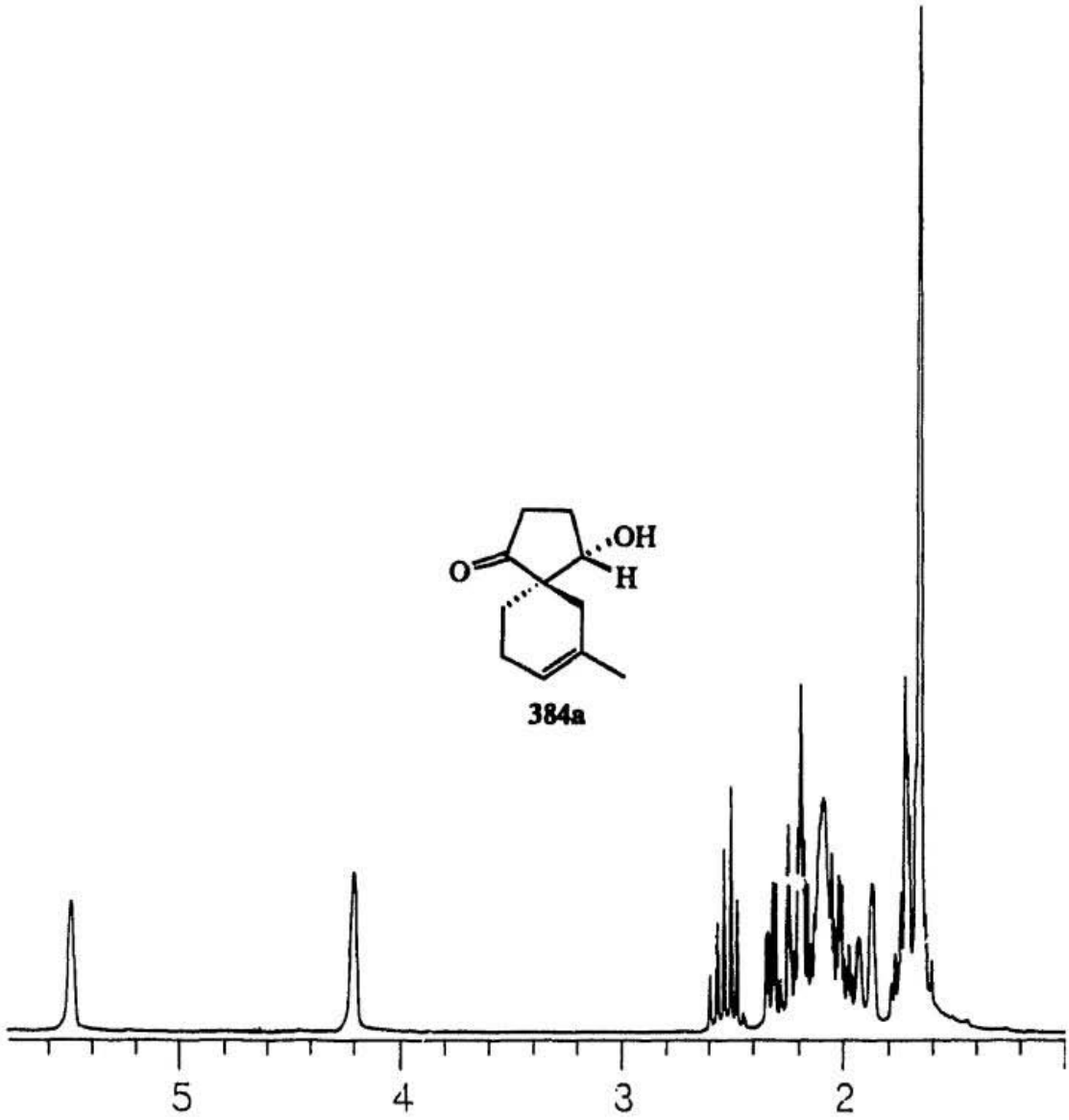

CH3
OH
O
377b
1
2
3
4
5
6


OH
H
O
378a
1
2
3
4
5
6

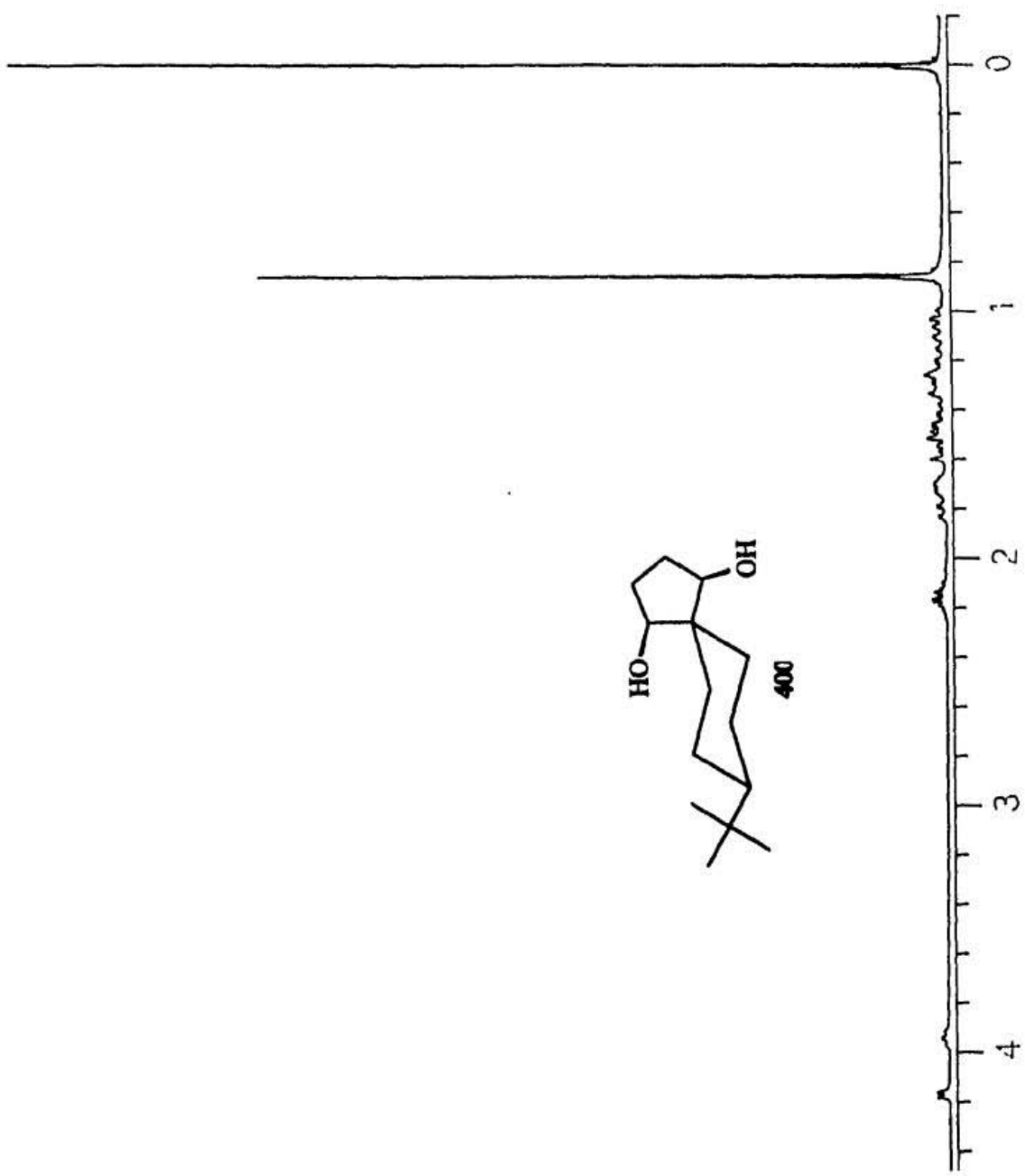

H
OH
O
378b
1
2
3
4
5
6



379a



384a


HO
OH
400
0
1
2
3
4