GEMINAL ACYLATION OF KETONES AND ACETALS: USE OF METHYL-SUBSTITUTED ANALOGUES OF 1,2-BIS [TRIMETHYLSILYL(OXY)] CYCLOBUTENE AND APPLICATION OF THIS METHODOLOGY IN MODEL STUDIES AIMED TOWARD AN ENANTIOSELECTIVE SYNTHESIS OF THE ANTITUMOR ANTIBIOTIC FREDERICAMYCIN A

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Geminal Acylation of Ketones and Acetals: Use of Methyl-Substituted Analogues of 1,2-Bis[trimethylsilyl(oxy)]cyclobutene and Application of this Methodology in Model Studies Aimed Toward an Enantioselective Synthesis of the Antitumor Antibiotic Fredericamycin A

by

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Abstract: The $BF_3 \cdot Et_2O$-catalyzed geminal acylation of ketones and acetals with 3-methyl-1,2-bis(trimethylsilyloxy)cyclobutene (**3**) provided methylcyclopentanediones in yields that ranged from 40 to 94%. The best substrates were unhindered cyclohexanones. With acetals, stereochemical preferences in the initial Mukaiyama-like aldol step giving cyclobutanones translated into the stereochemistry of the ultimate cyclopentanedione products. With ketones, equilibration of the initial cyclobutanone compounds resulted in cyclopentanedione products with a different stereochemical preference. The *gem*-dimethyl cyclobutene reagent **4** reacted with ketones to give *gem*-dimethylcyclopentanediones in modest yield. The process was much more stereochemically efficient than the reaction with **3**. Rearrangement from the initial cyclobutanone compound was partially diverted towards air-sensitive 3-furanone compounds and ring-opened 1,2-diones. Use of BCl_3 as the Lewis acid in reactions of ketones with **4** inhibited cyclobutanone equilibration by formation of five-membered borate-containing compounds. Conversion to the corresponding diol cyclobutanones with hydrofluoric acid and thence to dimethylcyclopentanediones with trifluoroacetic acid provided dimethylcyclopentanediones in synthetically acceptable yields.

Treatment of aromatic ketones with 1,2-bis(trimethylsilyloxy)cyclobutene **1** or its methylated analogues **3** and **4** in the presence of $BF_3 \cdot Et_2O$ smoothly led to products of geminal acylation, i.e., 2,2-disubstituted 1,3-cyclopentanedione derivatives. Yields ranged from 42 to 76 %. Minor products (up to 27%) were lactones that are proposed to have arisen by an alternate rearrangement pathway from a common cyclobutanone intermediate.

Since its discovery in 1981, the antitumor antibiotic fredericamycin A (**91**) has been the subject of extensive synthetic efforts focused mainly on construction of its spiro-1,3-cyclopentanedione subunit. Six total syntheses of **91** in racemic form have been reported. An asymmetric synthesis of fredericamycin A was accomplished only very recently. We have devised a potentially enantioselective route to fredericamycin A relying on precedents set in our laboratory for the construction of spiro-1,3-cyclopentanediones and their reduction in an enantioselective manner by Baker's yeast. The naphthoquinone portion of **91** was to be constructed by a silicon-tethered photochemical [2+2] cycloaddition or alternatively an intermolecular Diels-Alder reaction. The isoquinoline fragment was to be introduced using a Beckmann rearrangement strategy. A review of the literature dealing with **91** and the results of our own preliminary studies directed toward an enantioselective synthesis of this interesting molecule are presented.

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Acknowledgements

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List of Abbreviations and Symbols

Ac	acetyl
acac	acetylacetonate
AIBN	2,2'-azobis(isobutyronitrile)
AM1	Austin Model 1
APT	attached proton test
Bn	benzyl
Bu	butyl
CAN	ceric ammonium nitrate
ca.	approximately
cat	catalytic
CD	circular dichroism
m-CPBA	3-chloroperoxybenzoic acid
Cmp	(-)-camphanyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DHP	dihydropyran
DIBAL-H	diisobutylaluminum hydride
DM	Dess-Martin

DMAD	dimethyl acetylenedicarboxylate
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DNP	dinitrophenyl
DNPH	dinitrophenylhydrazone
dr	diastereoselectivity ratio
ee	enantiomeric excess
Et	ethyl
FG	functional group
FID	free induction decay
FMO	frontier molecular orbital
GC-MS	gas chromatograph coupled to a mass spectrometer
h	hour(s)
hν	ultraviolet irradiation
H^+arpoon	lithium 2,2,6,6-tetramethylpiperidide
hexamine	hexamethylenetetramine
HMDS	hexamethyldisilazide or bis(trimethylsilyl)amide
HMPA	hexamethylphosphoramide
HRMS	high-resolution mass spectrum

IC_{50}	concentration of inhibiting agent resulting in a 50 % reduction in enzyme activity
Imid	imidazole
IR	infrared
LAH	$LiAlH_4$, lithium aluminum hydride
LDA	lithium diisopropylamide
Me	methyl
MEM	2-methoxyethoxymethyl
min	minute(s)
MOM	methoxymethyl
MS	mass spectrum
Ms	mesyl
NBS	*N*-bromosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
NPM	*N*-phenylmaleimide
NOE	nuclear Overhauser enhancement
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PPTS	pyridinium *para*-toluenesulfonate
PTC	phase-transfer catalysis
py or pyr	pyridine
RNA	ribonucleic acid

rt	room temperature
sh	shoulder
TBAB	tetra-*n*-butylammonium bromide
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
TES	triethylsilyl
Tf	trifluoromethanesulfonate (triflate)
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidide
TMS	trimethylsilyl
p-Tol	*para*-tolyl
TosMIC	tosylmethyl isocyanide
p-TsOH	*para*-toluenesulfonic acid
UV	ultraviolet
xs	excess

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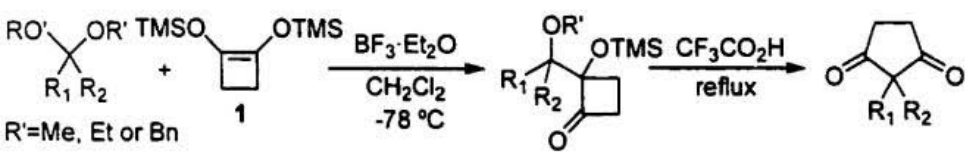
Chapter 1. Geminal Acylation of Ketones and Acetals with Methyl-Substituted Analogues of 1,2-Bis(trimethylsilyloxy)cyclobutene.

Introduction

Geminal acylation of an acetal with 1,2-bis(trimethylsilyloxy)cyclobutene (**1**) is a powerful method for the construction of a variety of 1,3-cyclopentanediones (Scheme 1 with R_1 and R_2 = various alkyl substituents). This methodology, first introduced by Kuwajima and co-workers,[1] is comprised of a two-step process. The first event is a Lewis acid-catalyzed Mukaiyama-like aldol reaction yielding an isolable α-(trimethylsilyloxy)cyclobutanone. Treatment of this cyclobutanone with trifluoroacetic acid induces a 1,2-migration of the acyl function. This bond reorganization results in a 1.3-cyclopentanedione. The reaction sequence was named geminal acylation to reflect the net displacement of a C=O double bond by two acyl groups.

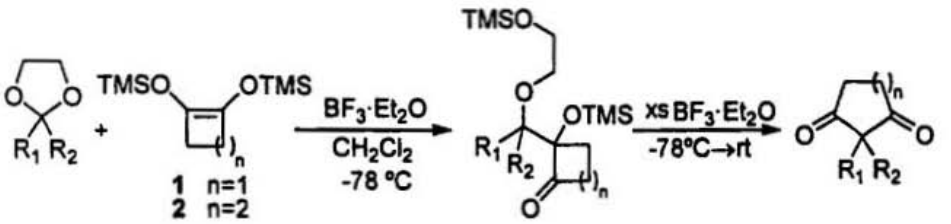
Scheme 1



Wu and Burnell later observed that conversion of acetals to 1,3-cyclopentanediones could be effected in a single operation.[2,3] Treatment of the more synthetically useful 1,3-dioxolanes with several equivalents of **1** and a large excess of $BF_3{\cdot}Et_2O$ at low temperature gave a cyclobutanone intermediate that was not isolated. In the presence of this large excess of Lewis acid, the 1,2-acyl migration occurred *in situ* (Scheme 2). Yields of cyclopentanedione were significantly improved using this

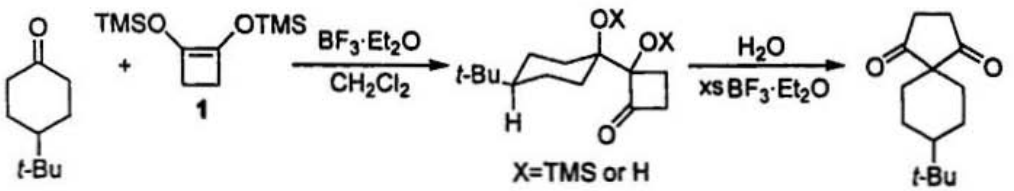
modification. It was also shown that 1,3-cyclohexanediones could be formed in high yield by substituting 1,2-bis(trimethylsilyloxy)cyclopentene (**2**) for **1** (n=2, Scheme 2).[4]

Scheme 2



Ketones do not undergo Mukaiyama-aldol reactions with enol-silyl ethers at the lower temperatures employed for the more reactive aldehydes and acetals. However, Mukaiyama noted that the desired reaction does occur at room temperature (rt).[5] Kuwajima stated that the aldol reaction between ketones and **1** did not proceed under a variety of acidic or basic conditions.[1] Jenkins and Burnell[6] found that the Mukaiyama-type reaction of **1** with ketones does occur if the reaction is conducted at rt. Cyclobutanone intermediates were isolated as bis-silyl ethers or as the corresponding diols depending on the reaction conditions. Optimal conditions for the initial Mukaiyama-like step typically employed 1.5 equivalents of **1** and an equivalent of $BF_3{\cdot}Et_2O$. Rearrangement of the intermediate cyclobutanone in the same vessel required the addition of a small quantity of water prior to the introduction of a large excess of $BF_3{\cdot}Et_2O$. The reaction of 4-*tert*-butylcyclohexanone with **1** produced the bis-silylated cyclobutanone originating from equatorial delivery of **1** onto the carbonyl (Scheme 3). Kuwajima made a similar observation with the corresponding dimethyl acetal.[1]

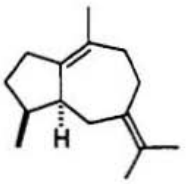
Scheme 3



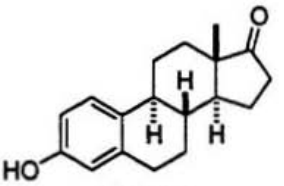
The yields of 1,3-cyclopentanediones from ketone substrates rivaled or exceeded those obtained from the corresponding acetals. Thus, the formation of an acetal is no longer a prerequisite for geminal acylation onto a ketone center. The clear advantage of this method in synthesis is a reduction in the number of steps.

The synthetic utility of the geminal acylation reaction is further illustrated when one considers that a quarternary center is formed in concert with a cyclopentane ring. The geminal acylation reaction also represents a powerful spiroannelation method when an alicyclic ketone or acetal is used. The ability to fashion such hindered geometries about carbon is one of the more challenging tasks confronting a synthetic organic chemist. It therefore is not surprising that synthetic approaches to a diverse array of natural products (Fig. 1) such as trichothecanes,[7] β-bulnesene,[8] estrone,[9] isokhusimone,[2] pentalenene,[10] and fredericamycin A,[11] have relied on geminal acylation as a key transformation.[12]

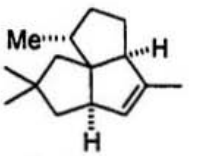
Fig. 1. Natural products that have been synthesized by routes that relied on geminal acylation as a key transformation.



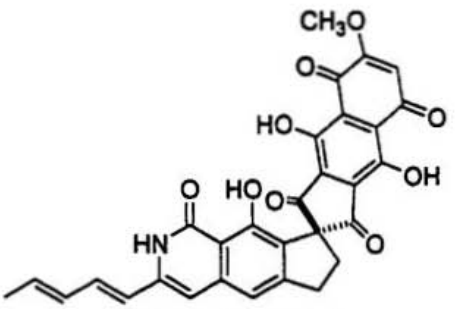
β-Bulnesene



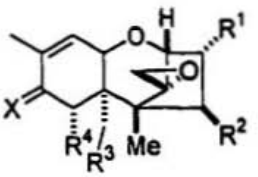
Estrone



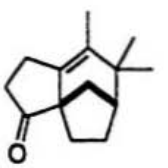
Pentalenene



Fredericamycin A



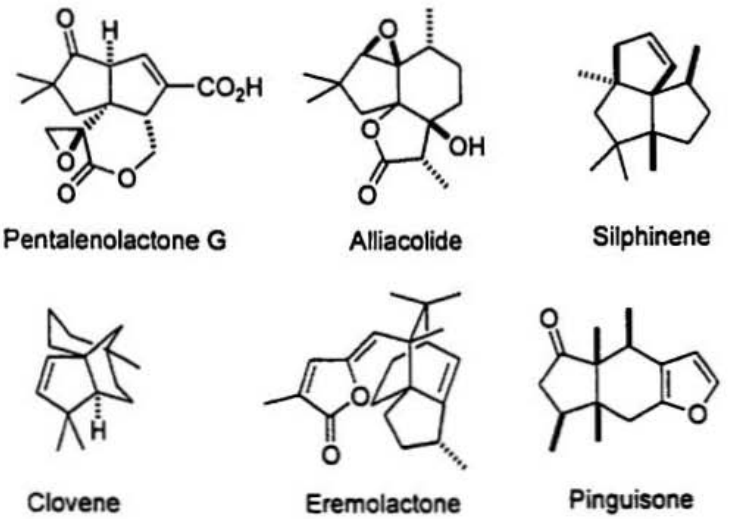
Trichothecanes



Isokhusimone

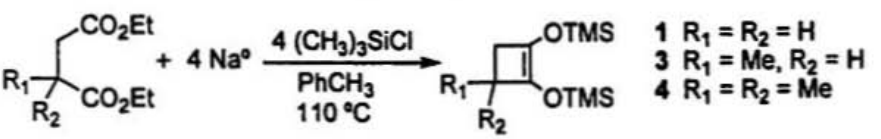
A variety of interesting natural products possess cyclopentane subunits decorated with methyl or *gem*-dimethyl substituents. Some representative examples are illustrated below in Figure 2.

Fig. 2. Natural Products that could potentially be synthesized using the geminal acylation reaction employing methyl-substituted analogues of **1** as a key step.



Synthetic routes to these molecules employing the geminal acylation methodology could potentially be designed using methyl-substituted versions (**3, 4**) of **1**. These can be prepared from the corresponding methyl- and dimethylsuccinic acid esters via an acyloin condensation (Scheme 4).[13,14] Key questions regarding the reactivity of **3** and **4** in the initial aldol-type reaction and the course of rearrangement of the cyclobutanone, as well as issues of regio- and stereochemistry, must first be addressed before such future synthetic journeys can commence.

Scheme 4

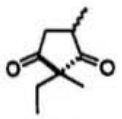
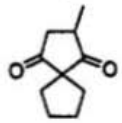
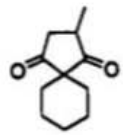
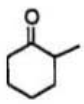
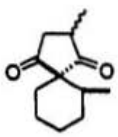
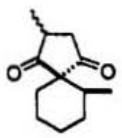
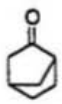
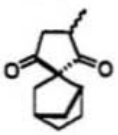
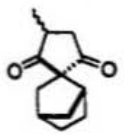
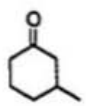
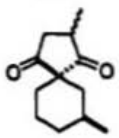
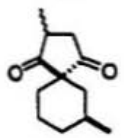
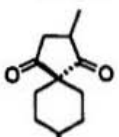
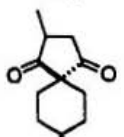


Results and Discussion

Reactions of Ketones and Acetals with Methylcyclobutene 3. A variety of ketones and their corresponding acetals, derived from 1,2-ethanediol, were treated with **3** and $BF_3 \cdot Et_2O$ following the procedure developed for the reaction of **1** with ketones.[6] In this procedure, the initial aldol reaction was mediated by $BF_3 \cdot Et_2O$ in dichloromethane under anhydrous conditions, and then the second, rearrangement step was initiated by addition of water and a large excess of $BF_3 \cdot Et_2O$. As can be seen in Table 1, the yields of cyclopentanediones ranged from modest to excellent. Trends were similar to those seen previously in the reactions of **1** with both ketones[6] and acetals.[2,3] The ketones gave similar, or better, yields than did the acetals. Unencumbered cyclohexanones and their acetals gave the best yields (entries 3, 6, 7). Cyclopentanone and its acetal (entry 2) gave more modest yields of the spiro-diketone **6**. α-Substitution had a deleterious effect on the efficiency of geminal acylation, especially with the acetal (entries 4 and 5).

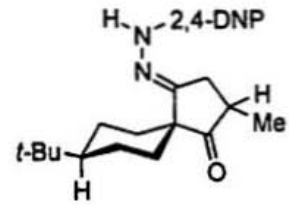
Reactions with **3** introduced a stereochemical complexity that had not been present in reactions with **1**. The reaction with butanone and its acetal (entry 1) provided **5a** and **5b** with no diastereoselectivity whatsoever. However, with 4-*tert*-butylcyclohexanone and its acetal (entry 7) some modest selectivity was apparent. An X-ray crystal structure of a 2,4-dinitrophenylhydrazone derivative **11c** revealed that the major isomer obtained from the ketone was **11a**. Selectivity was also evident in reactions between **3** and other substituted cyclohexanones and their acetals (entries 4–6). (Although it was not feasible to determine rigorously the stereochemistry of each component in these product mixtures, the relative stereochemistry at the spiro centers was inferred from

Table 1. Reactions of **3** with Ketones and Their Corresponding Acetals Derived from 1,2-Ethanediol

entry	substrate	product(s)	from ketone		from acetal	
			yield (%)	diastereomeric ratio (%)	yield (%)	diastereomeric ratio (%)
1		 **5a,b**	82	**a:b** 1:1	79	**a:b** 1:1
2		 **6**	49	-	40	-
3		 **7**	93	-	81	-
4		 **8a,b**  **8c,d**	75	**a:b:c:d** 3.8:3.0:1.4:1	57	**a:b:c:d** 2.9:1.7:3.1:1
5		 **9a,b**  **9c,d**	87	**a:b:c:d** 5.0:4.6:1.5:1	56	**a:b:c:d** 7.1:1.8:15:1
6		 **10a,b**  **10c,d**	91	**a:b:c:d** 4.2:4.1:1.1:1	91	**a:b:c:d** 1:1.2:1.4:1.4
7	 *t*-Bu	 *t*-Bu **11a**  *t*-Bu **11b**	92	**a:b** 3.1:1	94	**a:b** 1:2.2 (1:7.5)[a]

[a] Ratio obtained from the dibenzyl acetal

results presented below.) It is important to note that the selectivity was clearly different, even complementary, with ketones and their corresponding acetals.

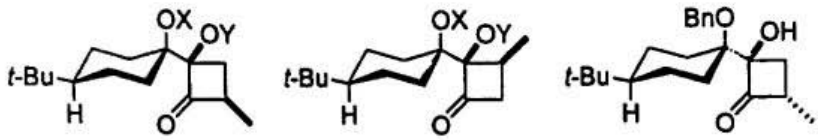


11c

In an effort to illuminate the reason for the stereochemical difference between the ketone and the acetal versions of the geminal acylation, the products were isolated after only the first step in the reactions of 4-*tert*-butylcyclohexanone and its acetal with **3**. The ketone provided two cyclobutanone compounds **12a** and **12b** in a 3.3 : 1 ratio, which was very similar to the 3.1 : 1 ratio for the cyclopentanedione products in entry 7. (Minor amounts of **11a** and **11b**, in a 2.6 : 1 ratio, were also detected in the crude product even when no water or extra $BF_3{\cdot}Et_2O$ were added.) Comparison of the ^{13}C NMR chemical shifts of signals arising from the cyclohexyl moiety with those of the known, equatorial product with **1**[6] indicated that both of the cyclobutanone compounds had arisen by equatorial attack on the ketone.[a] Considerable similarities between the NMR spectra of **12a** and **12b** (p. 187-189) and the spectra of **15a** and **15b** (p. 190-193) allowed assignment of the structures of **12a** and **12b**. The isolation of intermediates from acetals

[a] With the norbornyl system, *exo* addition of **3** was very likely favored with both the ketone and its acetal, but, as can be seen in entry 5, this system showed the largest, yet obviously different, stereoselectivities with ketone and acetal.

was carried out in conjunction with an evaluation of the stereoselectivity of the geminal acylation with different acetals.



12a X = H Y = H
13a X = Me Y = TMS
14a X = Bn Y = TMS
15a X = Bn Y = H

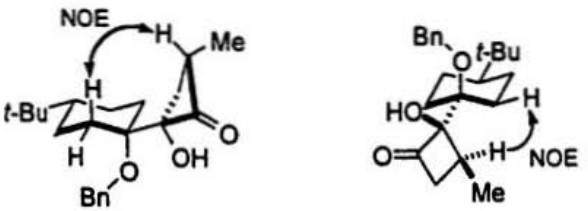
12b X = H Y = H
13b X = Me Y = TMS
14b X = Bn Y = TMS
15b X = Bn Y = H

16

Reaction of the acetal derived from 2,2-dimethyl-1,3-propanediol gave cyclopentanediones **11a** and **11b** in a 1 : 2.4 ratio, which was not significantly different from the 1 : 2.2 ratio for the acetal derived from 1,2-ethanediol. Cyclobutanone derivatives from the dimethyl and dibenzyl acetals were obtained by following Kuwajima's procedure.[1] The dimethyl acetal provided cyclobutanone compounds **13a** and **13b** in a 1 : 4.1 ratio. When this mixture was stirred in trifluoroacetic acid (TFA), **11a** and **11b** were produced in a ratio of 1 : 3.6. The use of a dibenzyl acetal further improved selectivity. Cyclobutanones **14a** and **14b** were obtained in 1 : 7.4 ratio. In TFA, this mixture rearranged to **11a** and **11b** in a 1 : 7.5 ratio. Cyclobutanones **14a** and **14b** were desilylated with tetrabutylammonium fluoride (TBAF) to keto-alcohols **15a** and **15b**, and these proved to be separable by chromatography. During chromatography, a fraction of **15a** also showed a set of ^{1}H NMR signals attributed tentatively to a very small amount of **16**. Nuclear Overhauser enhancement (NOE) measurements with both **15a** and **15b** established that the hydrogen of the methine of the cyclobutanone moiety was *syn* to the cyclohexane ring (Fig. 3). Hydrogenolysis of the benzyl groups of either **15a** or **15b** over Pd on charcoal in ethanol/acetic acid provided a mixture of **12a** and **12b** in a 5.2 : 1 ratio,

which provided evidence of acid-mediated equilibration between **12a** and **12b**. This was exactly the ratio predicted by the Austin Model 1 (AM1)[15] calculated relative energies of **12a** and **12b**.

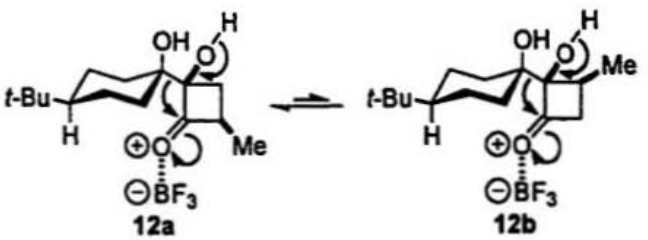
Fig. 3. Nuclear Overhauser enhancements (NOE) used for assignment of the relative stereochemistry of cyclobutanones **15a** and **15b**.



15a **15b**

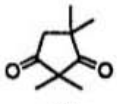
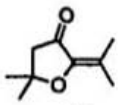
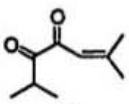
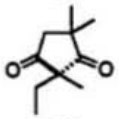
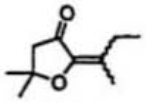
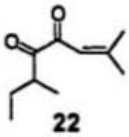
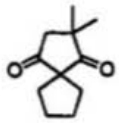
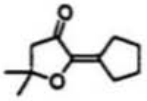
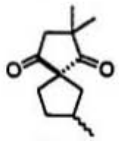
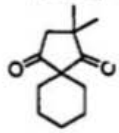
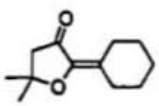
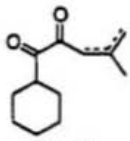
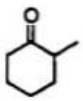
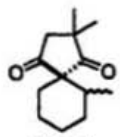
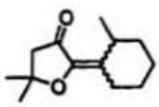
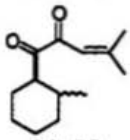
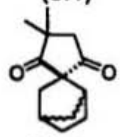
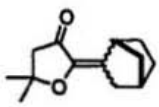
These results lead to the following generalizations regarding reactions with **3**. The cyclobutanones obtained from acetals undergo rearrangement to cyclopentanediones by inversion at the cyclohexyl C–1, with little stereochemical scrambling. This was also true for the processes with **1** for both acetals[1b] and ketones.[6] Thus, the stereochemistry of the cyclopentanediones derived from acetals was largely determined by stereochemical preferences in the first, aldol reaction. The stereochemistry of the cyclopentanediones derived from ketones was generally opposite to that from acetals, and appeared to reflect equilibration to the thermodynamically preferred cyclobutanone (Scheme 5).

Scheme 5



Reactions of Ketones with gem-Dimethyl Cyclobutene 4. The results of reactions of **4** with several ketones are presented in Table 2. Cyclobutene **3** had shown a considerable reluctance to add to its face *syn* to the methyl, but with cyclobutene **4** steric hindrance between a methyl on the cyclobutene and the ketone substrate seemed unavoidable. Hence, it was not surprising that in many examples with **4** the yields of the cyclopentanediones were modest, and a very significant proportion of intractable material was generally obtained. Addition of water and extra $BF_3 \cdot Et_2O$ was not necessary to effect rearrangement to cyclopentanediones from any of the enone substrates. The reaction with 2-cyclohexen-1-one (entry 10) only gave a 32% yield of **40**, but this was still considerably better than had been seen in the reaction of cyclohexenone with **1**.[6] Both isophorone and 4,4-dimethylcyclohex-2-en-1-one (entries 11 and 12) gave good yields of cyclopentanediones, although with the former there was some isomerization (ca. 15 %) of the double bond during reaction. A comparison of the ^{13}C NMR spectrum of the predominant cyclopentanedione product from isophorone with the spectra of products from **1**[3,6] led to the assignment of structure **41**.

Table 2. Reactions of **4** with Ketones

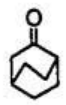
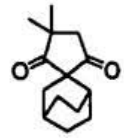
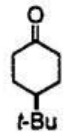
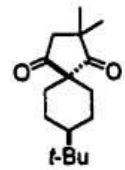
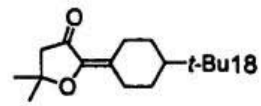
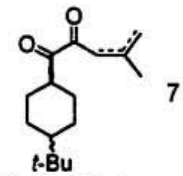
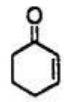
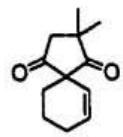
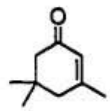
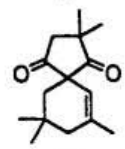
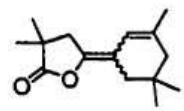
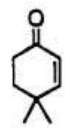
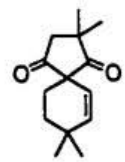
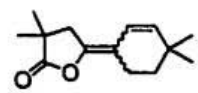
entry	substrate	products and yields (%)		
		cyclopentanedione	furanone	1,2–dione
1		 22 **17**	 26 **18**	 <2 **19**
2		 22 **20**	 24 **21a,b** (1:1)	 <5 **22**
3		 36 **23**	 <5 **24**	
4		 30 **25a,b** (2.8:1)		
5		 40 **26**	 16 **27**	 16 **28a,b** (1.2:1)
6[a]		 12 **29a,b** (8:1)	 24 **30a,b** (1.4:1)	 16 **31, 32** (2.4:1)
7[b]		 47 **33a,b** (>100:1)	 33 **34a,b** (1.5:1)	

[a] Two molar equivalents of **4** were used in this reaction.

[b] Chromatographic separation of **33a** and **34a,b** was incomplete.

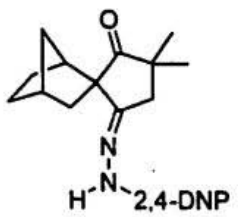
Yields reflect the isolated yields and the proportion of **33a** and **34a,b** (GC-MS) in a mixed fraction.

Table 2. Reactions of **4** with Ketones (continued)

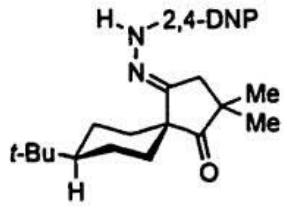
entry	substrate	products and yields (%)		
		cyclopentanedione	furanone	1,2–dione
8		 70 **35**		
9[c]	 *t*-Bu	 40 *t*-Bu **36a**	 *t*-Bu 18 **37**	 *t*-Bu 7 **38a,b; 39a,b** (1.2:1)
10		 32 **40**		
11		 56 **41**	 24 **42a,b** (*E*/*Z* 1.9:1)	
12		 71 **43**	 7 **44a,b** (*E*/*Z* 1:1)	

[c] Reaction of the 1,3-dioxalane derived from 4-*tert*-butylcyclohexanone with **4**, under the one-pot conditions developed for acetals with **1**,[3] gave a 1.2:1 mixture of **36a** and its epimer **36c** in a total yield of 36%. As this process showed essentially no stereoselectivity, reactions of acetals with **4** were not pursued further.

In spite of the poor yields, cyclopentanediones were produced from **4** with much higher stereoselectivity than had been seen from **3**. In two instances (entries 7 and 9) one diastereomer of the cyclopentanedione was produced predominantly, and the structures of their 2,4-dinitrophenylhydrazone derivatives (**33c** and **36b**) were determined by X-ray crystallography.

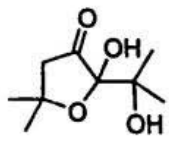


33c

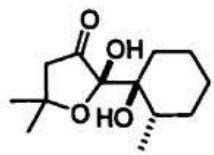


36b

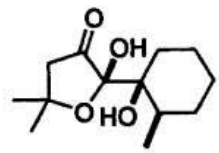
The yields with **4** suffered from synthetically troublesome, yet mechanistically interesting, side-reactions that repeatably produced substituted furanones, 1,2-diones, and lactones. The proportion of furanone in the product mixtures did not seem to correlate in a straightforward way with the structure of the ketone substrate. A comparison of entries 7 and 8 illustrates this. Furanones were formed with little to no geometrical preference (entries 2, 6, and 7), and they oxidized readily in air to dihydroxy compounds. Characterization of oxidation products **45** and **46a/b**, derived from **18** and **30a/b**, was helpful in establishing the general structure of the furanones.



45



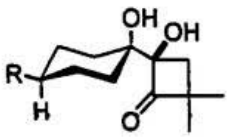
46a



46b

1,2-Diones were isolated in lesser amounts. Careful analysis by ^{1}H NMR of the reactions with cyclohexanone (entry 5), and 4-*tert*-butylcyclohexanone (entry 9) showed that the β,γ–unsaturated compounds (**28a**, **38a**, and **39a**) were initially formed, and these rapidly isomerized in the reaction medium to α,β–unsaturated diones (**28b**, **38b**, and **39b**). A secondary rearrangement process led to minor amounts of lactones **42a,b** and **44a,b** from enone substrates (entries 11 and 12).

The dimethylcyclobutanone compounds **47** and **48** were prepared from the corresponding ketones by working up the reaction mixture without addition of extra $BF_3{\cdot}Et_2O$ and water. The structure of **48** was determined unequivocally by X-ray

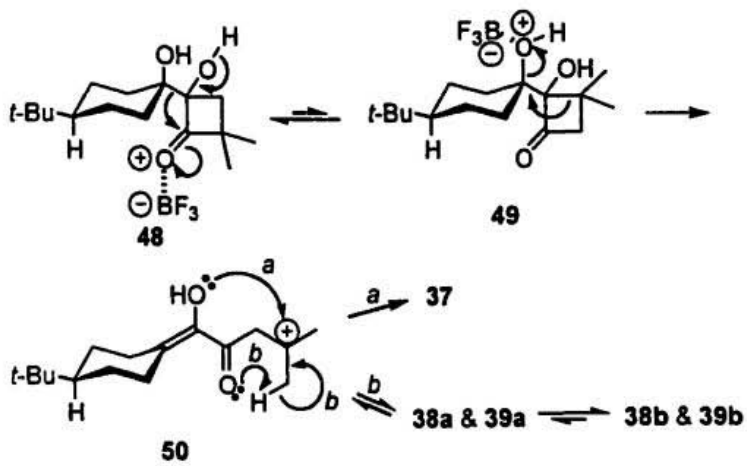


47 R = H
48 R = *t*-Bu

crystallography. This showed the reaction had resulted from equatorial addition with respect to the cyclohexanone ring, and that the new C–C bond was to C-1 of cyclobutene **4**. Prolonged treatment of cyclopentanediones with $BF_3{\cdot}Et_2O$ did not provide any furanone, but when **47** was added to neat $BF_3{\cdot}Et_2O$ the result was a 3 : 1 mixture of **26** and **27**. On the other hand, treatment of **47** with dilute $BF_3{\cdot}Et_2O$ in dichloromethane provided only cyclopentanedione **26**. Similarly, cyclobutanone **48** in neat $BF_3{\cdot}Et_2O$ provided **36a** and **37** in an 8 : 1 ratio. With dilute $BF_3{\cdot}Et_2O$ in dichloromethane the ratio improved to 13 : 1, and $BF_3{\cdot}Et_2O$ in dichloromethane in the presence of a small amount of

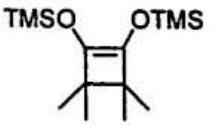
water provided **36a** exclusively. The formation of furanone and the 1,2-diones can be rationalized as illustrated (Scheme 6) with the reaction of 4-*tert*-butylcyclohexanone.

Scheme 6

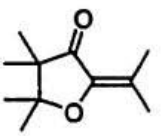


The equilibrium between **12a** and **12b** suggests that **48** might equilibrate with cyclobutanone **49**. We were unable to observe **49**, but an AM1 calculation[15] indicated that **49** should be 6.1 kcal/mol higher in energy than **48**. Whereas both **12a** and **12b** rearranged to 1,3-diketones, an alternate pathway to the tertiary carbocation **50** presents itself with **49**. (Furanones were never observed in reactions with **1** or **3**, so the intermediacy of a carbocationic intermediate was suspected.) Cyclization of **50** gives the furanone **37**, or deprotonation of **50** with the internal assistance of an oxygen would give the terminal double bond in **38a** and **39a**. Evidence for the latter stage of this hypothesis is that treatment of a solution of the mixture of **31** and **32** in $CDCl_3$ with $BF_3{\cdot}Et_2O$ provided some **30a,b**, but treatment of furanones with acid (with or without water) under an inert atmosphere did not give any 1,2-diketone. Additional support for the proposed

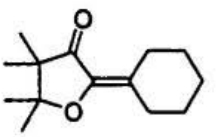
series of events came from the reactions of two ketones with the tetramethylcyclobutene **51**.[14] No cyclopentanedione was produced using the conditions employed with **4**. Instead, furanone **52** (31% yield) was the only isolated product from the reaction with acetone, and **53** (35 % yield) was the only isolated product from cyclohexanone.



51



52



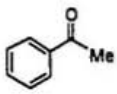
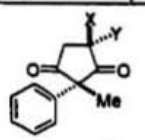
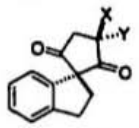
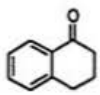
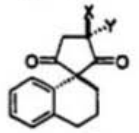
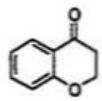
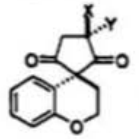
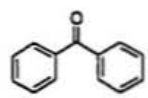
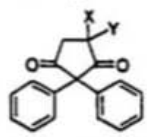
53

Reaction of 1, 3 and 4 with Aromatic Ketones and Acetals. Unlike the reactions of their saturated counterparts, α,β-unsaturated ketones provided cyclopentanediones directly, without the addition of water and excess $BF_3 \cdot Et_2O$. This might be attributed to allylic stabilization of a positive charge in the transition state of the rearrangement. We reasoned that a similar benzylic stabilization could arise with aromatic ketones, which might lead to an improvement in the procedure for the reaction of these substrates with **1** and an opportunity to carry out geminal acylation of aromatic ketones with both **3** and **4**.

Five aromatic substrates were subjected to very similar reaction conditions. For **1** and **3**, the ketone and 1.5 equivalents of freshly distilled $BF_3 \cdot Et_2O$ were dissolved in dry CH_2Cl_2, and 2–3 equivalents of the bis(trimethylsilyloxy)cyclobutene were added while maintaining anhydrous conditions. For **4**, the only difference was that up to 3 equivalents of $BF_3 \cdot Et_2O$ were employed. The reaction mixture was stirred at room temperature for

approximately 24 hours (h). Straightforward aqueous work-up followed by flash chromatography provided the geminally acylated product, a 1,3-diketone. The results are summarized in Table 3.

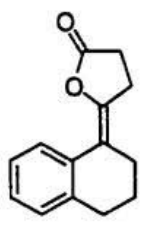
Table 3. Reactions of five aromatic ketones with cyclobutenes **1**, **3**, and **4**.

substrate	1,3-diketone product	with **1**	with **3**	with **4**
		**54** X = Y = H, 70%	**62a** X = Me, Y = H **62b** X = H, Y = Me a/b 1:2.6, 77% (from acetal: a/b 1:1.2, 63%)	**67** X = Y = Me, 76%[a]
		**55** X = Y = H, 75%	**63a** X = Me, Y = H **63b** X = H, Y = Me a/b 1.8:1, 62% (from acetal: a/b 1:1.5, 55%)	**68** X = Y = Me, 69%
		**56** X = Y = H, 42% (+ **57**, 2%)	**64a** X = Me, Y = H **64b** X = H, Y = Me a/b 1.5:1, 52% (from acetal: a/b 1:2.3, 48%)	**69** X = Y = Me, 65% (+ **70a**, **70b** 2.6:1, 15%)
		**58** X = Y = H, 45% (+ **59a**, **59b** 1.5:1, 11%)	**65a** X = Me, Y = H **65b** X = H, Y = Me a/b 1.2:1, 49%	**71** X = Y = Me, 54% (+ **72a**, **72b** 2.6:1, 27%)[b]
		**60** X = Y = H, 75% (+ **61**, 12%)[c]	**66** X = Me, Y = H, 71%	**73** X = Y = Me, 68% (+ **74** 16%)

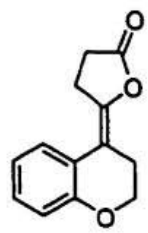
[a] An 85% yield of a 9:1 mixture of **67** and two isomeric compounds.
[b] Sum of isolated yields plus proportion of a fraction containing a mixture of **71** and **72a,b**.
[c] An 87% yield of a 6.3:1 mixture of **60** and **61**.

The yields of **54**, **55**, **56**, and **58** (from **1** with acetophenone, 1-indanone, 1-tetralone, and 4-chromanone) were similar to the yields by the earlier procedure that involved adding H_2O to the reaction mixture,[6] which in turn were generally better than the reactions with acetals derived from aromatic ketones.[3,12e] The acetal of benzophenone

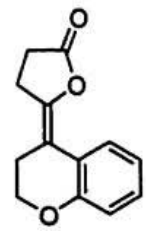
was reported by Ayyangar[12e] to react with **1** to give only a trace of **60**, whereas the conversion of benzophenone to **60** was 75% under these anhydrous conditions. The reactions with 1-tetralone, 4-chromanone, and benzophenone also gave minor amounts of lactones **57**, **59a,b**, and **61**, respectively.



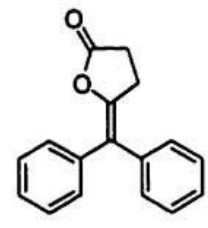
57



59a



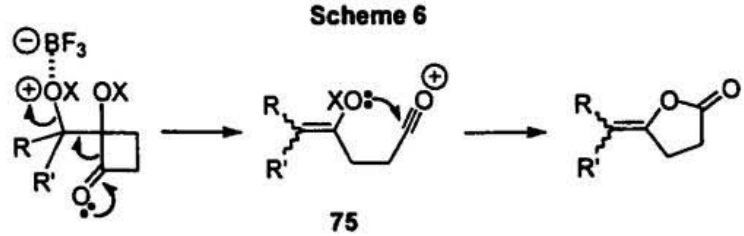
59b



61

Similar lactones had been observed in the reactions of enones with **4**, and Pandey reported the photochemical conversion of **55** and **56** to the corresponding lactones.[16] In our case, we postulate the formation of these lactones by the process shown in Scheme 7. Acid-promoted elimination of the benzylic oxygen function could lead not only to 1,2-acyl shift (and thence to the 1,3-cyclopentanedione) but also to rupture of the four-membered ring to produce the acylium ion in **75**. Attack of the conjugated enol moiety onto the acylium ion would give the lactone.

Scheme 6

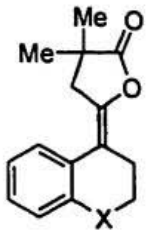


75

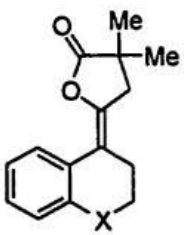
Yields in the reactions of (racemic) **3** with the five substrates mirrored those with **1**: 1-tetralone and 4-chromanone gave lower yields, near 50%. Unlike the products derived from **1** and **4**, those from **3** were complicated by diastereoisomerism, except in the case of **66**. Very modest stereochemical preferences were noted, with acetophenone showing the largest stereoselectivity, albeit only 2.6 : 1. When acetals were prepared from acetophenone, 1-indanone, and 1-tetralone, and these were reacted with **3**, geminal acylation products were obtained in slightly lower yields and again with modest diastereoselectivities. Production of the isomer that had been more abundant from the ketone reactions was reduced in the reactions with acetals. In the cases of 1-indanone and 1-tetralone, the diastereoselectivities were opposite to the reactions of their corresponding acetals. AM1 calculations[15] gave no difference in the energies of **62a** and **62b**, so any stereoselectivity was likely to be the consequence of a kinetically controlled process. We suggest that the stereoselectivity was a result of facial selectivity in the initial aldol process since a regiochemical preference in the initial aldol step would have no remaining manifestation in a racemic product. It was curious that lactone products were not isolated from the reactions with **3**, although small amounts of carbonyl-containing secondary products were detected by IR and NMR spectroscopy.

Geminal acylation using **4** with the five substrates gave 1,3-diketones in moderate yield. With acetophenone, **67** was the dominant component of the product, which also contained small amounts of isomeric compounds that were inseparable by flash chromatography. The reactions of **4** with 1-tetralone and 4-chromanone provided minor, but significant, amounts of the lactone pairs **70a,b** and **72a,b** (2.6 : 1 ratio in each case),

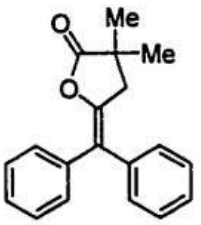
and NOE measurements indicated that the *E*-isomer was the more abundant isomer.[b] A lactone **74** was also a by-product of the reaction with benzophenone.



70a X = CH_2
72a X = O

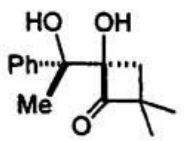


70b X = CH_2
72b X = O

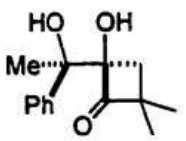


74

Solutions of diketone **71** in CH_2Cl_2 were stirred for 24 hours at room temperature with 4 equivalents of $BF_3{\cdot}Et_2O$ under anhydrous conditions, and with 15 equivalents of $BF_3{\cdot}Et_2O$ and 6 equivalents of water. In neither case were lactones **72a,b** observed. Furthermore, when the reaction of **4** with acetophenone was conducted at –20 °C it was possible to intercept two diastereomeric cyclobutanone intermediates **76** and **77**, in a 5.7 : 1 ratio.[c] (The relative stereochemistry of the minor product was determined by X-ray crystallography.) Thus, the regioselectivity of the initial aldol step was very high, and facial selectivity was responsible for the production of **76** over **77**. The process shown in Scheme 7 would also account for the formation **70a,b**, **72a,b**, and **74**.



76

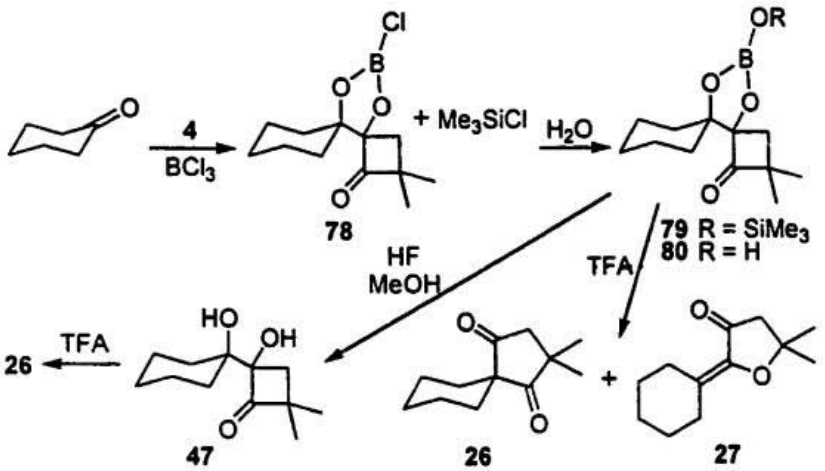


77

[b] The ^{1}H NMR spectra of the (minor) *Z*-lactones **70b** and **72b** showed one aromatic resonance just downfield of δ 8. This feature was used to assign the *Z*-lactone structures to **57** and **59b**.
[c] Similar attempts to obtain cyclobutanone intermediates from 1-indanone and 1-tetralone at –20 °C gave only the 1,3-diketone and lactone products.

Geminal Acylation of Ketones Mediated by Boron Trichloride. To explore the possibility that the Lewis acid might both mediate the initial aldol reaction and inhibit subsequent equilibration of the initially formed cyclobutanone, reactions of **4** with BCl_3 were conducted at –78 °C in an NMR tube and on a preparative scale. Scheme 8 presents the salient features of the novel process, which proceeds with the incorporation of boron by the formation of five-membered borate-containing compounds.

Scheme 8

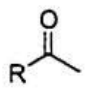
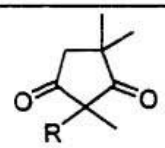
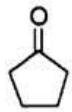
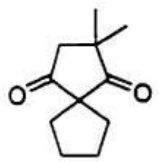
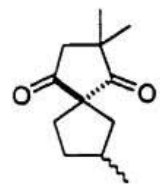
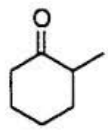
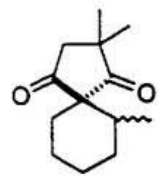


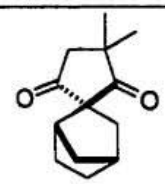
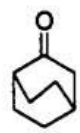
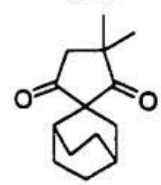
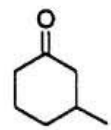
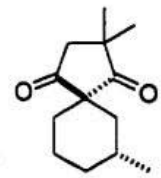
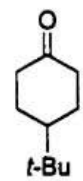
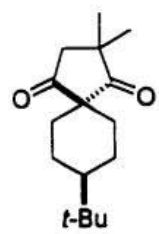
Addition of cyclohexanone to a solution of BCl_3 (^{11}B NMR δ 46.3) in CD_2Cl_2 resulted in a signal for the complexed BCl_3 at δ 8.3 in the ^{11}B NMR spectrum.[17a] Introduction of **4** (^{29}Si NMR[17b] δ 18.4 and 18.0) initiated the disappearance, over several hours, of the BCl_3-cyclohexanone complex and the emergence of a ^{11}B NMR signal at δ 27.6, which was ascribed to a very labile compound **78**, and a ^{29}Si NMR signal at δ 29.9, which was identified as Me_3SiCl by admixture with genuine Me_3SiCl (in a separate

experiment). Addition of water to the reaction medium caused the immediate disappearance of the ^{11}B NMR signal at δ 27.6 and the emergence of a signal at δ 20.3. At the same time, the Me_3SiCl signal was replaced by a ^{29}Si NMR signal at δ 16.5. Aqueous work-up gave a mixture of **79**, the hydrolyzed product **80**, and the diol-cyclobutanone **47** (2.4 : 1.2 : 1, respectively). (Introduction of a large amount of Me_3SiCl before work-up afforded only **79** and **47**, in a 6.5 : 1 ratio.) Spectral data supporting the structure of **79** included peaks in its infrared spectrum (IR) at 1785 (C=O) and 1456 (B–O) cm^{-1}, a 9-proton singlet at δ 0.19 in its ^1H NMR spectrum, ^{13}C NMR signals at δ 215.5 (C=O), 99.3 and 88.1 (quaternary C–O's), and 0.97 ($SiMe_3$), and the ^{11}B and ^{29}Si NMR signals noted above. The ^{11}B NMR signal for **80** was at δ 21.9, and the IR spectrum included an absorption at 3214 cm^{-1} (BO–H). Thus, the labile nature of the B–Cl bond, relative to the B–F bonds of BF_3, allowed the initial aldol to take place by an association of the boron with both the carbonyl oxygen and an oxygen on **4**. Rearrangement of **47** in TFA gave only diketone **26**, but stirring a 6.5 : 1 mixture of the borates **79** and **80** in TFA at rt overnight gave both **26** and 3-furanone **27** (1.2 : 1). Nevertheless, HF in methanol smoothly converted **79** and **80** to a mixture of **47** and **26** (7.4 : 1), and the rearrangement to **26** was completed in 87% yield from cyclohexanone by the addition of TFA without the production of any 3-furanone **27**.

A one-pot procedure was developed based on the above findings. Geminal acylations were carried out on a variety of ketones. The results are summarized in Table 4.

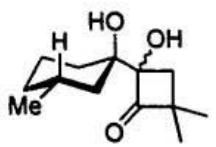
Table 4. BCl_3 Mediated Reactions of **4** with Various Ketones.

substrate	product	yield (%)
		
	17 R = CH_3	83
	20 R = CH_2CH_3	75
	86 R = $CH_2C_6H_5$	51
	67 R = C_6H_5	47
		81
	23	
		46
	25a,b (2:1)	
		29
	29a,b (1:2)	

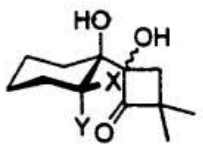
substrate	product	yield (%)
		82
	33a	
		97
	35	
		85
	81	
		98
	36a	

There was a great improvement in the overall yields of the diketones over the previous procedure with $BF_3 \cdot Et_2O$. The relative stereochemistry of diketones **36a** and **33a** was the same as from the $BF_3 \cdot Et_2O$ procedure, and the stereoselectivity in their production was at least as good as with $BF_3 \cdot Et_2O$. The relative stereochemistry of **81**, the

only product from 3-methylcyclohexanone, was established by an X-ray structure of the 2,4-dinitrophenylhydrazone (2,4-DNPH) derivative **82**. Diketone **81** was derived from two cyclobutanone-diol compounds **83a,b**. Comparison of their ^{13}C NMR shifts with those of **48** and other similar compounds indicated that they differed only in the face of **4** that had been attacked. However, 2-methylcyclohexanone was an exceptional substrate with regard to both yield and stereoselectivity. It appeared that the initial aldol step with this substrate took place in a reasonable yield, but six diol intermediates were produced in a ratio of 8.4 : 1.9 : 1.9 : 1.1 : 1 : 1. Two of these, the major diol **84** and one of the minor diols **85**, were isolated by chromatography. The structures of these were evident from the NMR data, although the relative configurations at C-2 of the cyclobutanone moiety could not be determined.



83a,b



84 X = H, Y = Me
85 X = Me, Y = H

Whereas **85** rearranged cleanly to **29b** in TFA, the major diol **84** gave only small amounts of diketone **29a** and 3-furanones **30a,b** along with intractable material. Except with acetophenone, starting materials were largely returned when conjugated ketones (isophorone, 1-indanone, and α-tetralone) were subjected to the one-pot procedure with **3** and BCl_3. Acetophenone gave dione **67** in 52 % yield.

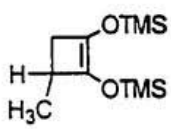
In summary, the mechanism of action of BCl_3 differs in an important way from that of $BF_3{\cdot}Et_2O$ because BCl_3 not only induces the initial aldol reaction, it is incorporated

into a cyclic borate that inhibits subsequent equilibration of the aldol product. The use of BCl_3 now makes the formation of 4,4-dimethyl-1,3-cyclopentanediones by geminal acylation a very attractive synthetic methodology.

Experimental Section

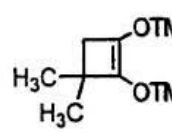
General Section. Compounds **3**, **4**, and **51** were obtained using the method for the preparation of **1** of Bloomfield and Nelke.[13] The CH_2Cl_2 used in the geminal acylation reactions was distilled from CaH_2. All reactions were performed under N_2. "Work-up" usually consisted of addition of the reaction mixture to H_2O, extraction of the aqueous layer with CH_2Cl_2, washing with brine, drying of the combined organic solutions over anhydrous $MgSO_4$ or Na_2SO_4, and evaporation of the solvent under vacuum. Flash chromatography ("chromatography") used 230-400 mesh silica gel. IR spectra were recorded on a Mattson FT-IR instrument as thin films unless otherwise noted. Relative intensities of absorption bands are indicated using the following abbreviations: s (strong), m (medium) and w (weak). ^1H NMR spectra were obtained on a General Electric GE-300 NB at 300 MHz in $CDCl_3$ unless specified otherwise, and shifts are relative to internal tetramethylsilane. The following abbreviations are used in descriptions of ^1H NMR spectra: s (singlet), d (doublet), t (triplet) and q (quartet), m (multiplet) and br (broad). For spectral data obtained from mixtures, only clearly distinguished signals are reported. Most product ratios were determined by integration of ^1H NMR spectra. NOE measurements were made from difference spectra and are reported as: saturated signal (observed signal, enhancement). ^{13}C NMR spectra were recorded at 75 MHz; chemical shifts are relative to solvent; the number of attached protons as determined by APT and heteronuclear correlation spectra follows each chemical shift in parentheses. Overlap may have prevented the reporting of all resonances when the spectral data of minor components were obtained from spectra of mixtures. ^{11}B NMR spectra were recorded at

96.3 MHz; chemical shifts relative to an external $BF_3 \cdot Et_2O$ standard. ^{29}Si NMR spectra were recorded at 59.6 MHz; shifts were relative to an external chlorotrimethylsilane reference. NMR FID data were processed using WinNuts (Acorn NMR software). Low and high resolution mass spectral data were obtained on a V.G. Micromass 7070HS instrument. Melting points were determined using a Fisher-Johns hot stage apparatus and were uncorrected. Data for the X-ray structures were obtained with a Rigaku AFC65 diffractometer. X-ray structure data collection and structure determinations were performed by Dr. John Bridson and Mr. David Miller. Ultraviolet (UV) spectra were recorded on a Varian Cary 5E instrument. GC-MS spectra were recorded using a Hewlett Packard model 5890 gas chromatograph coupled to a model 5970 mass selective detector. A 12.5 m fused silica capillary column with cross linked dimethylsilicone as the liquid phase was used for the GC-MS analyses.



3

3-Methyl-1,2-bis(trimethylsilyloxy)cyclobutene (3). Colorless liquid, bp_{5mm} 69–72 °C; IR 1720 cm^{-1}; ^1H NMR δ 2.45 (1H, m, H3), 2.36 (1H, dd, J = 4.3, 10.0 Hz, H4), 1.65 (1H, dd, J = 1.2, 10.0 Hz, H4), 1.10 (3H, d, J = 6.6 Hz, C3-methyl), 0.21 (9H, s), 0.20 (9H, s); ^{13}C NMR δ 125.4 (0, C2), 119.6 (0, C1), 34.9 (2, C4), 33.3 (1, C3), 17.8 (3, C3-methyl), 0.35 (6C, 3); MS 244 (34, M^+), 229 (19), 148 (12), 147 (83), 75 (12), 73 (100), 45 (20).

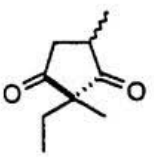


4

3,3-Dimethyl-1,2-bis(trimethylsilyloxy)cyclobutene (4). Colorless liquid, bp_{3mm} 60–61 °C; IR 1727 cm^{-1}; ^1H NMR δ 1.97 (2H, s, H4), 1.12 (6H, s, C3-methyl), 0.21 (9H, s), 0.18 (9H, s); ^{13}C NMR δ 128.6 (0, C2), 118.3 (0, C1), 42.7 (2, C4), 38.6 (0, C3), 24.2 (2C, 3, C3-methyls), 0.35 (6C, 3); MS

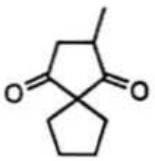
258 (33, M^+), 242 (24), 152 (13), 148 (11), 147 (67), 75 (32), 74 (10), 73 (100), 69 (10), 60 (12), 58 (18), 57 (18), 56 (14), 55 (22); HRMS calcd for $C_{12}H_{26}O_2Si_2$ 258.1470, found 258.1472.

General procedure for the reactions of 3 with ketones or acetals. Based on the procedure of Jenkins and Burnell,[6] to a solution of ketone or acetal (2.0 mmol) in CH_2Cl_2 (10.0 mL) were successively added $BF_3{\cdot}Et_2O$ (0.30 mL, 2.4 mmol) and **3** (0.73 g, 3.0 mmol). The mixture was stirred at rt for 24 h before H_2O (0.30 mL) was introduced, followed 10 minutes (min) later by $BF_3{\cdot}Et_2O$ (3.7 mL, 30 mmol). The resulting black solution was stirred for 24 h. Work-up and decolorization of a CH_2Cl_2 solution by activated charcoal and filtration through Florisil, gave the cyclopentanedione product(s). For yields and product ratios see Table 1.



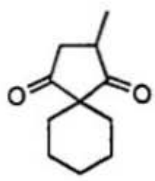
5a,b

2-Ethyl-2,4-dimethylcyclopentane-1,3-dione (5a,b). From spectra of the mixture: IR 1765 (m), 1723 (s) cm^{-1}; ^1H NMR δ 3.10–2.96 (1H from each, two overlapping dd, H5), 2.96–2.77 (1H from each, m, H4), 2.37 (1H, dd, J = 8.7, 18.3 Hz, H5), 2.29 (1H, dd, J = 9.3, 18.0 Hz, H5), 1.80–1.55 (2H from each, m, ethyl CH_2), 1.29 (3H from each, d, J = 6.9 Hz, C4-methyl), 1.12 (3H, s, C2-methyl), 1.09 (3H, s, C2-methyl), 0.81 (3H, t, J = 7.5 Hz, ethyl CH_3), 0.76 (3H, t, J = 7.5 Hz, ethyl CH_3); ^{13}C NMR δ 219.0/218.6 (0, C3), 216.3/216.1 (0, C1), 57.2/57.0 (0, C2), 44.5/43.7 (2, C5), 41.7/40.9 (1, C4), 29.4/28.2 (2, ethyl CH_2), 20.2 (3), 17.9 (3), 15.7 (3), 15.1 (3), 9.4/8.9 (3, ethyl CH_3); MS 154 (48, M^+), 139 (41), 84 (37), 69 (100), 55 (11), 42 (19), 41 (37); HRMS calcd for $C_9H_{14}O_2$ 154.0993, found 154.0985.



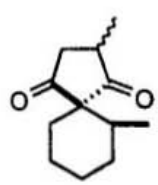
6

2-Methylspiro[4.4]nonane-1,4-dione (6). Tan-colored oil; IR 1761 (m), 1719 (s) cm^{-1}; ^1H NMR δ 3.02 (1H, dd, J = 10.3, 17.7 Hz, H3), 2.88 (1H, m, H2), 2.35 (1H, dd, J = 8.2, 17.7 Hz, H3), 1.90–1.70 (8H, m, H6-H9), 1.29 (3H, d, J = 7.0 Hz, C2-methyl); ^{13}C NMR δ 220.4 (0, C1), 217.6 (0, C4), 61.9 (0, C5), 42.3 (2, C3), 39.7 (1, C2), 35.4 (2), 32.4 (2), 25.1 (2), 25.3 (2), 13.7 (3, C2-methyl); MS 166 (98, M^+), 151 (12), 138 (12), 125 (19), 97 (56), 96 (100), 95 (20), 70 (12), 69 (29), 68 (54), 67 (29), 55 (16), 42 (34), 41 (41), 40 (23); HRMS calcd for $C_{10}H_{14}O_2$ 166.0993, found 166.0995.



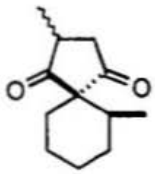
7

2-Methylspiro[4.5]decane-1,4-dione (7). Yellow oil; IR 1760 (m), 1718 (s) cm^{-1}; ^1H NMR δ 3.00 (1H, dd, J = 10.4, 17.6 Hz, H3), 2.90 (1H, m, H2), 2.34 (1H, dd, J = 8.2, 17.6 Hz, H3), 1.90–1.42 (10H, m, H6-H10), 1.27 (3H, d, J = 6.9 Hz, C2-methyl); ^{13}C NMR δ 218.0 (0, C1), 215.3 (0, C4), 55.5 (0, C5), 43.1 (2, C3), 40.3 (1, C2), 30.5 (2), 28.6 (2), 24.9 (2), 20.5 (2), 20.3 (2), 15.6 (3, C2-methyl); MS 180 (100, M^+), 151 (12), 138 (14), 126 (38), 125 (25), 113 (11), 111 (32), 110 (42), 109 (17), 99 (16), 82 (21), 81 (25), 79 (13), 70 (10), 69 (17), 67 (79), 55 (18), 54 (26), 53 (18), 43 (13), 42 (38), 41 (63), 40 (14); HRMS calcd for $C_{11}H_{16}O_2$ 180.1149, found 180.1168.



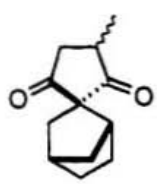
8a,b

2,6-Dimethylspiro[4.5]decane-1,4-dione (8a-d). Spectra of the mixture: IR 1758 (m), 1716 (s) cm^{-1}; MS 194 (97, M^+), 180 (11), 179 (89), 152 (13), 140 (20), 139 (34), 138 (12), 126 (93), 125 (26), 124 (13), 123 (15), 111 (10), 110 (10), 109 (100), 96 (12), 95 (22), 81 (59), 79 (16), 77 (11), 69 (18), 68 (17), 67 (57), 55 (35), 54 (13), 53 (29), 43 (18), 42 (52), 41 (78), 40 (14); HRMS calcd for $C_{12}H_{18}O_2$ 194.1306, found 194.1285. For **8a** from the mixture: ^1H NMR δ 3.03

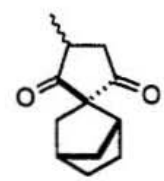


8c,d

(1H, dd, J = 10.6, 18.2 Hz, H3), 2.12 (1H, dd, J = 9.0, 18.2 Hz, H3), 1.25 (3H, d, J = 6.9 Hz, C2-methyl), 0.705 (3H, d, J = 6.6 Hz, C6-methyl); ^{13}C NMR δ 219.6 (0, C1), 215.6 (0, C4), 60.4 (0, C5), 45.1 (2, C3), 40.0 (1, C2), 34.9 (1, C6), 32.8 (2), 28.9 (2), 25.3 (2), 20.1 (2), 18.5 (3, C6-methyl), 14.8 (3, C2-methyl). For **8b** from the mixture: ^{1}H NMR δ 2.70 (1H, overlapped dd, H3), 2.41 (1H, overlapped dd, H3), 1.31 (3H, d, J = 7.0 Hz, C2-methyl), 0.74 (3H, d, J = 6.9 Hz, C6-methyl); ^{13}C NMR δ 219.8 (0, C1), 217.2 (0, C4), 60.0 (0, C5), 44.1 (2, C3), 43.1 (1, C2), 36.3 (1, C6), 32.2 (2), 29.1 (2), 25.3 (2), 20.2 (2), 18.1 (3, C6-methyl), 16.5 (3, C2-methyl). For **8c** from the mixture: ^{1}H NMR δ 3.08 (1H, dd, J = 10.5, 18.8 Hz, H3), 2.18 (1H, dd, J = 6.9 Hz, H3), 0.715 (3H, d, J = 6.4 Hz, C6-methyl); ^{13}C NMR δ 218.3 (0, C1), 216.5 (0, C4), 60.7 (0, C5), 44.6 (2, C3), 39.9 (1, C2), 35.2 (1, C6), 32.9 (2), 28.9 (2), 25.4 (2), 20.2 (2), 18.3 (3, C6-methyl), 14.8 (3, C2-methyl). For **8d** from the mixture: ^{1}H NMR δ 2.42 (1H, overlapped dd, H3), 1.32 (3H, d, J = 7.0 Hz, H3), 0.75 (3H, d, J = 6.3 Hz, C6-methyl); ^{13}C NMR δ 218.6 (0, C1), 216.2 (0, C4), 59.6 (0, C5), 43.6 (2, C3), 35.7 (1, C6), 32.0 (2), 19.9 (2), 16.3 (3, C2-methyl).



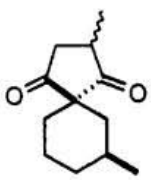
9a,b



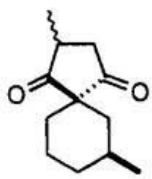
9c,d

4'-Methylspiro(bicyclo[2.2.1]heptane-2,2'-cyclopentane)-1',3'-dione (9a-d). Spectra of the mixture: IR 1758 (m), 1716 (s) cm^{-1}; MS 192 (39, M^{+}), 163 (56), 127 (12), 126 (100), 122 (14), 94 (11), 93 (55), 79 (21), 77 (11), 67 (18), 66 (18), 65 (20), 53 (15), 42 (11), 41 (30); HRMS calcd for $C_{12}H_{18}O_2$ 192.1149, found 192.1147. For **9a** from the mixture: ^{1}H NMR δ 1.20 (3H, d, J = 6.9 Hz, C4-methyl); ^{13}C NMR δ 215.5 (0, C3'), 213.1 (0, C1'), 66.4 (0, C2), 49.2 (1), 44.0 (2), 39.5 (1), 37.3 (2), 36.9 (1), 33.0 (2), 28.0 (2), 24.1 (2), 15.4 (3, C4'-methyl); For **9b** from the mixture: ^{1}H NMR δ 2.82 (1H, dd,

J = 9.0, 16.5 Hz, H5), 2.55 (1H, br m), 2.46 (1H, dd, J = 9.8, 16.5 Hz), 2.46 (1H, m), 2.36 (1H, m), 1.44 (3H, d, J = 7.2 Hz); ^{13}C NMR δ 216.1 (0, C3'), 213.2 (0, C1'), 65.4 (0, C2), 48.6 (1), 43.9 (2), 42.1 (1), 37.1 (2), 36.7 (1), 33.9 (2), 27.7 (2), 24.5 (2), 17.6 (3, C4'-methyl). For **9c** from the mixture: ^{1}H NMR δ 3.23 (1H, dd, J = 11.4, 19.0 Hz, H5), 2.94 (1H, br m), 2.48 (1H, m), 2.36 (1H, m), 2.15 (1H, dd, J = 8.7, 19.0 Hz, H5), 1.22 (3H, d, J = 6.9 Hz, C4'-methyl); ^{13}C NMR δ 215.2 (0, C3'), 212.4 (0, C1'), 66.5 (0, C2), 49.1 (1), 43.2 (2), 40.5 (1), 37.0 (2), 36.8 (1), 32.8 (2), 27.8 (2), 24.5 (2), 14.3 (3, C4'-methyl). For **9d** from the mixture: ^{13}C NMR δ 216.5 (0, C3'), 213.4 (0, C1'), 42.8 (2), 41.8 (1), 37.6 (2), 34.1 (2), 27.7 (2), 17.6 (3, C4'-methyl).



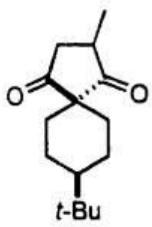
10a,b



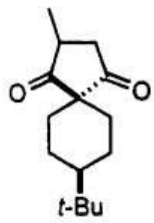
10c,d

2,7-Dimethylspiro[4.5]decane-1,4-dione (10a-d). Spectra of the mixture: IR 1761 (m), 1718 (s) cm^{-1}; MS 194 (86, M^{+}), 151 (10), 139 (18), 138 (65), 127 (12), 126 (100), 125 (28), 124 (14), 123 (12), 109 (12), 99 (14), 96 (13), 95 (39), 93 (10), 82 (23), 81 (56), 79 (14), 70 (17), 69 (31), 68 (14), 67 (30), 55 (30), 54 (12), 53 (15), 43 (17), 42 (24), 41 (52), 40 (12); HRMS calcd for $C_{12}H_{18}O_2$ 194.1306, found 194.1306. ^{1}H NMR for each isomer contains δ 3.03 (1H, m, H3), 2.88 (1H, m, H2), 2.33 (1H, m, H3), 2.00 (1H, m, H7), 1.27 (3H, d, J = 6.9 Hz, C2-methyl), (0.857 (3H, d, J = 6.3 Hz) 0.86 (3H, d, J = 6.6 Hz), 0.85 (3H, d, J = 6.6 Hz), C7-methyl). For **10a/b**: ^{13}C NMR δ 217.9/217.9 (0, C1), 215.64/215.59 (0, C4), 56.5 (0, C5), 43.3 (2, C3), 40.9 (1, C2), 38.1/36.8 (2), 33.76 (2), 33.4 (2), 28.9 (2), 26.53/26.46 (1, C7), 22.5/22.4 (3, C7-methyl), 20.96/20.90 (2), 15.9 (3, C2-methyl). For **10c/d**: ^{13}C NMR δ 218.2/218.1 (0, C1), 215.0 (0, C4), 56.6/56.5 (0, C5), 43.4/43.3 (2, C3), 40.3/40.2 (1, C2), 38.6/36.5 (2), 33.80 (2),

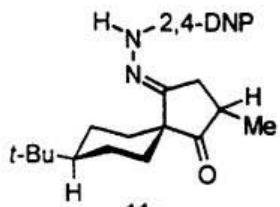
30.9 (2), 28.5 (2), 26.7/26.3 (1, C7), 22.6/22.3 (3, C7-methyl), 21.02/20.8 (2), 15.7/15.6 (3, C2-methyl).



11a



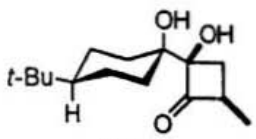
11b



11c

***t*-8-*tert*-Butyl-2-methyl-*r*-1-spiro[4.5]decane-1,4-dione (11a) and *c*-8-*tert*-butyl-2-methyl-*r*-1-spiro[4.5]decane-1,4-dione (11b).** Spectra of the mixture: IR 1756 (m), 1713 (s) cm^{-1}; MS 236 (44, M^+), 221 (17), 181 (12), 180 (88), 179 (39), 139 (12), 138 (15), 126 (24), 125 (26), 109 (23), 81 (19), 79 (14), 67 (12), 57 (100), 55 (15), 53 (13), 43 (17), 42 (10), 41 (54); HRMS calcd for $C_{15}H_{24}O_2$ 236.1775, found 236.1773. For **11a** from the mixture: ^1H NMR δ 2.96 (1H, dd, J = 10.4, 17.4 Hz, H3), 2.33 (1H, dd, J = 7.7, 17.4 Hz, H3), 1.26 (3H, d, J = 7.0 Hz, C2-methyl); ^{13}C NMR δ 218.2 (0, C1), 215.4 (0, C4), 55.3 (0, C5), 46.8 (1, C8), 43.2 (2, C3), 40.8 (1, C2), 32.3 (0, *t*-butyl), 31.2 (2), 29.7 (2), 27.3 (3C, 3, *t*-butyl), 21.7 (2), 21.6 (2), 15.7 (3, C2-methyl). For **11b** from the mixture: ^1H NMR δ 3.02 (1H, dd J = 10.4, 18.0 Hz, H3). 2.33 (1H, dd, J = 8.9, 18.0 Hz, H3), 1.27 (3H, d, J = 6.9 Hz, C2-methyl); ^{13}C NMR δ 218.1 (0, C1), 215.3 (0, C4), 55.4 (0, C5), 46.8 (1, C8), 43.3 (2, C3), 40.1 (1, C2), 32.3 (0, *t*-butyl), 31.7 (2), 29.3 (2), 27.3 (3C, 3, *t*-butyl), 21.7 (2), 21.5 (2), 15.4 (3, C2-methyl). For the 4-(2,4-dinitrophenylhydrazone) derivative **11c** (derived from **11a**, purified by recrystallization): orange solid, mp 194.5–197.5 °C; IR (Nujol) 3301, 1747, 1712, 1615, 1589 cm^{-1}; ^1H NMR δ 11.11 (1H, br s), 9.12 (1H, d, J = 2.6 Hz), 8.31 (1H, dd, J = 2.5, 9.6 Hz), 7.92 (1H, d, J = 9.6 Hz), 3.27 (1H, dd, J = 10.4, 17.6 Hz), 2.83 (1H, br m), 2.43 (1H, dd, J = 8.7, 17.6 Hz), 1.85–1.60 (8H, m), 1.31 (3H, d, J = 2.9 Hz), 1.14 (1H, br m), 0.95

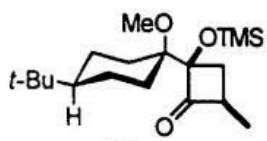
(9H, s); ^{13}C NMR δ 218.3 (0), 164.5 (0), 145.0 (0), 138.0 (0), 130.0 (1), 129.3 (0), 123.4 (1), 116.3 (1), 52.7 (0), 46.9 (1), 40.4 (1), 33.4 (2), 32.6 (2), 31.4 (2), 31.3 (2), 27.4 (3C, 3), 21.5 (2), 15.7 (3); MS 416 (2, M^+), 81 (15), 79 (16), 78 (10), 77 (12), 68 (16), 67 (12), 57 (100), 55 (21), 53 (12), 43 (15), 41 (70); HRMS calcd for $C_{21}H_{28}O_5N_4$ 416.2058, found 416.2047. The structure of **11c** was determined by X-ray crystallography.



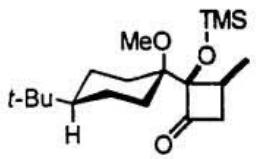
12a

(2*R/S*,4*R/S*)-2-(*c*-4-*tert*-Butyl-*r*-1-hydroxycyclohexyl)-2-hydroxy-4-methylcyclobutanone 12a and (2*R/S*,3*S/R*)-2-(*c*-4-*tert*-butyl-*r*-1-hydroxycyclohexyl)-2-hydroxy-3-methyl-cyclobutanone 12b. Compound **3** (0.34 g, 1.4 mmol) was added to a solution of 4-*tert*-butylcyclohexanone (219 mg, 1.42 mmol) and $BF_3{\cdot}Et_2O$ (0.17 mL) in CH_2Cl_2 (7.0 mL). The mixture was stirred at rt for 4.5 h. Work-up gave an oily, tan solid (304 mg). ^{1}H NMR analysis revealed this to be a mixture of **12a** and **12b** in a 3.3 : 1 ratio, and **11a** and **11b** in a 2.6 : 1 ratio, with the ratio of cyclobutanone compounds to cyclopentanediones being 6 : 1. Cyclobutanones **12a** and **12b** could not be separated by flash chromatography. Spectra of the mixture: IR 3453, 3357, 1767 cm^{-1}; MS no M^+, 236 (2), 166 (18), 155 (23), 137 (11), 123 (11), 109 (13), 98 (21), 95 (20), 83 (11), 82 (10), 81 (28), 71 (10), 69 (14), 67 (15), 57 (100), 55 (22), 53 (10), 43 (26), 42 (11), 41 (49); HRMS calcd for $C_{15}H_{24}O_2$ (M^+ - H_2O) 236.1775, found 236.1775. For **12a** from the mixture: ^{1}H NMR δ 3.30 (1H, br s, OH), 3.05 (1H, br m, H4), 2.58 (1H, apparent t, J = 11.8 Hz, H3), 1.86 (1H, m), 1.81–1.45 (4H, m), 1.45–1.27 (3H, m), 1.24 (3H, d, J = 7.3 Hz, C4-methyl), 0.96 (1H, m, H4'), 0.87 (9H, s, *t*-butyl); ^{13}C NMR δ 215.7 (0, C1), 94.5 (0, C2), 72.7 (0, C1'), 49.6 (1, C4), 47.7 (1, C4'), 32.6 (2, C2), 32.4 (0, *t*-butyl), 32.3 (2), 30.9 (2), 27.5 (3C, 3, *t*-butyl), 21.9

(2), 21.8 (2), 14.4 (3, C4-methyl). For **12b** from the mixture: ^{1}H NMR δ 2.48 (1H, dd, J = 6.0, 17.8 Hz, H4), 1.18 (3H, d, J = 6.9 Hz, C3-methyl); ^{13}C NMR δ 213.6 (0, C1), 95.2 (0, C2), 73.3 (0, C1'), 50.6 (1, C4), 47.6 (1, C4'), 32.5 (0, *t*-butyl), 32.4 (2), 32.1 (2), 30.6 (2), 27.5 (3C, 3, *t*-butyl), 21.8 (2), 21.7 (2), 14.4 (3, C3-methyl).



13a

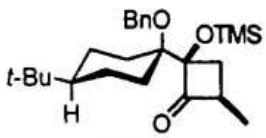


13b

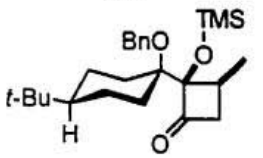
(2*R/S*,4*R/S*)-2-(*c*-4-*tert*-Butyl-*r*-1-methoxycyclohexyl)-4-methyl-2-(trimethylsilyloxy)cyclobutanone 13a and (2*R/S*,3*S/R*)-2-(*c*-4-*tert*-butyl-*r*-1-methoxycyclohexyl)-3-methyl-2-(trimethylsilyloxy)cyclobutanone 13b. Based on the procedure of Kuwajima,[1] compound **3** (0.53 g, 2.1 mmol) was added dropwise over 2–3 min to a solution at –78 °C of 4-*tert*-butylcyclohexanone dimethyl acetal (0.39 g, 2.0 mmol) and $BF_3{\cdot}Et_2O$ (0.24 mL) in CH_2Cl_2 (3.0 mL). After stirring at this temperature for 6 h, the reaction mixture was poured into aqueous $NaHCO_3$ solution (10 mL) and extracted with Et_2O (2 x 40 mL). The combined organic layers were washed with H_2O (40 mL) and brine (40 mL) and dried over anhydrous $MgSO_4$. Evaporation of the solvent under vacuum left a viscous, colorless oil (0.66 g, 99%) as a 1 : 4.1 mixture of **13a** and **13b**. Spectra of the mixture: IR 1775 (s) cm^{-1}; MS 340 (2, M$^+$), 170 (12), 169 (100), 81 (23), 75 (13), 73 (64), 67 (11), 59 (14), 57 (43), 41 (18); HRMS calcd for $C_{19}H_{36}O_3Si$ 340.2432, found 340.2413. For **13a** from the mixture: ^{1}H NMR δ 3.29 (3H, s, OCH_3), 0.14 (9H, s, OTMS); ^{13}C NMR δ 214.2 (0, C1), 97.1 (0, C2), 22.5 (2), 22.3 (2), 14.5 (3, C4-methyl), 1.7 (3C, 3, OTMS). For **13b** from the mixture: ^{1}H NMR δ 3.28 (3H, s, OCH_3), 2.94 (dd, J = 10.7, 18.0 Hz, H4), 2.83–2.68 (m, H3), 2.33 (dd, J = 6.3, 18.0 Hz, H4), 2.19–2.05 (2H, m), 1.84–1.70 (1H, m), 1.67–1.44 (2H, m), 1.40–1.00 (3H, m), 1.12 (3H, d, J = 7.1 Hz, C3-methyl), 1.00–0.87

(1H, m, H4'), 0.84 (9H, s, *t*-butyl), 0.16 (9H, s, OTMS); ^{13}C NMR δ 212.2 (0, C1), 99.3 (0, C2), 75.9 (0, C1'), 51.7 (3, OCH_3), 50.1 (2, C4), 47.3 (1, C4'), 32.2 (2), 27.5 (3C, 3, *t*-butyl and 1C, 2), 27.1 (1, C3), 22.2 (2), 22.1 (2), 15.2 (3, C3-methyl), 1.8 (3C, 3, OTMS).

This mixture of **13a** and **13b** (114 mg, 0.335 mmol) was stirred in TFA (1.0 mL) at rt for 20 h. Work-up afforded 82.6 mg of a pale brown oil consisting largely of **11a** and **11b** in a 1 : 3.6 ratio.



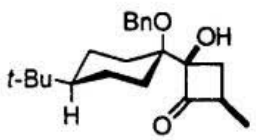
14a



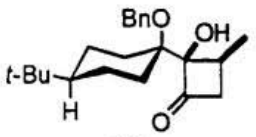
14b

(2*R/S*,4*R/S*)-2-(*r*-1-Benzyloxy-*c*-4-*tert*-butylcyclohexyl)-4-methyl-2-(trimethylsilyloxy)cyclobutanone 14a and (2*R/S*,3*S/R*)-2-(*r*-1-benzyloxy-*c*-4-*tert*-butylcyclohexyl)-3-methyl-2-(trimethylsilyloxy)cyclobutanone 14b. Based on the procedure of Kuwajima,[1] compound **3** (0.54 g, 2.2 mmol) was added over 2–3 min to a CH_2Cl_2 (3.0 mL) solution of 4-*tert*-butylcyclohexanone dibenzyl acetal (0.70 g, 2.0 mmol) and $BF_3{\cdot}Et_2O$ (0.25 mL) at –78 °C. Stirring at this temperature for 9.5 h. followed by work-up and chromatography gave 0.79 g (96%) of a white solid, consisting of a 1 : 7.4 mixture of **14a** and **14b**. Spectra of the mixture: IR 1775 cm^{-1}; MS 416 (0.3, M$^+$), 245 (12), 143 (13), 92 (14), 91(100), 75 (13), 73 (46), 57 (19). For **14a** from the mixture: ^{1}H NMR δ 4.68 (1H, d, J = 10.0 Hz, benzyl), 4.61 (1H, d, J = 10.0 Hz, benzyl), 0.16 (9H, s, OTMS); ^{13}C NMR δ 213.8 (0, C1), 97.5 (0, C2), 75.9 (0, C1'), 65.3 (2, benzyl), 48.4 (1, C4'), 33.7 (2), 28.0 (2), 22.4 (2), 14.6 (3, C4-methyl), 1.7 (3C, 3, OTMS). For **14b** from the mixture: ^{1}H NMR δ 7.50–7.18 (5H, m, aryl), 4.58 (1H, d, J = 11.7 Hz, benzyl), 4.49 (1H, d, J = 11.7 Hz, benzyl), 2.92 (1H, m, H4), 2.86 (1H, br m, H3), 2.40–2.26 (2H, overlapping m), 1.89 (1H, m, H4), 1.68–1.50 (2H, m), 1.42 (1H, m), 1.33–1.24 (2H, m), 1.20 (1H, apparent dd, J = 4.7, 12.2

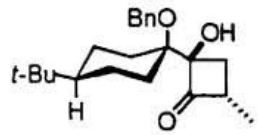
Hz), 1.13 (3H, d, J = 7.0 Hz, C3-methyl), 0.98 (1H, br m, H4'), 0.85 (9H, s, *t*-butyl), 0.19 (9H, s, OTMS); ^{13}C NMR δ 212.0 (0, C1), 140.0 (0), 128.2 (1), 127.1 (1), 127.0 (1), 99.5 (0, C2), 76.1 (0, C1'), 65.4 (2, benzyl), 50.2 (2, C4), 47.1 (1, C4'), 33.0 (2), 32.4 (0, *t*-butyl), 27.8 (2), 27.5 (3C, 3, *t*-butyl), 27.1 (1, C3), 22.2 (2), 22.1 (2), 15.3 (3, C3-methyl), 1.8 (3C, 3, OTMS).



15a



15b



16

(2*R/S*,4*R/S*)-2-(*r*-1-Benzyloxy-*c*-4-*tert*-butylcyclohexyl)-2-hydroxy-4-methylcyclobutanone 15a and (2*R/S*,3*S/R*)-2-(*r*-1-benzyloxy-*c*-4-*tert*-butylcyclohexyl)-2-hydroxy-3-methylcyclobutanone 15b. Treatment of the above mixture of **14a,b** (0.20 g, 0.48 mmol) with TBAF (0.60 mL, 1.0 M in THF) in Et_2O (4.0 mL), followed by chromatography afforded **15a** and **15b** (total 0.142 g, 84%). ^{1}H NMR signals for a very minor third isomer, tentatively ascribed structure **16**, were noted in some fractions that were mainly **15a**. IR (mixture) 3506 (m), 1775 (s), 1607 (w), 1497 (m) cm^{-1}. MS (mixture) no M$^+$, 155 (13), 92 (13), 91 (100), 86 (28), 84 (46), 81 (16), 79 (15), 67 (10), 57 (67), 55 (14), 47 (13), 43 (21), 41 (36). For **15a**: ^{1}H NMR δ 7.60–7.21 (5H, m, aryl), 4.71 (1H, d, J = 11.1 Hz, benzyl), 4.40 (1H, d, J = 11.0 Hz, benzyl), 3.45 (1H, s, OH), 3.00 (1H, m, H4), 2.59 (1H, apparent t, J = 12.2 Hz, H3), 2.04 (1H, ddd, J = 3.0, 6.0, 13.2 Hz), 1.96 (1H, ddd, J = 3.1, 6.1, 13.2 Hz), 1.72 (1H, dd, J = 9.2, 12.2 Hz, H3 *syn* to methyl), 1.71–1.58 (2H, m), 1.55–1.27 (4H, m), 1.24 (3H, d, J = 7.2 Hz, C4-methyl), 1.01 (1H, m, H4'), 0.87 (9H, s, *t*-butyl); NOE data 3.00 (2.59, 2%; 2.04-1.96, 1.6%; 1.24, 6%), 2.59 (3.00, 3%; 1.72, 22%; 1.48-1.39, 9%), 2.04-1.96 (4.71, 1.2%; 3.00, 1%; 4.40, 3%; 1.48-1.39, 31%), 1.72 (2.59, 9%; 1.24, 2%); ^{13}C NMR δ 214.8

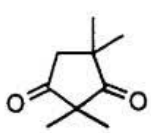
(0, C1), 138.7 (0, aryl), 128.4 (2C, 1), 127.5 (2C, 1), 95.6 (0, C2), 76.9 (0, C1'), 64.4 (2, benzyl), 49.0 (1, C4), 47.4 (1, C4'), 32.8 (2, C3), 32.4 (0, *t*-butyl), 31.2 (2), 28.3 (2), 27.5 (3C, 3, *t*-butyl), 22.0 (2C, 2, C3', C5'), 14.4 (3, C4-methyl). For **15b**: ^{1}H NMR δ 7.54–7.20 (5H, m, aryl), 4.73 (1H, d, J = 11.2 Hz, benzyl), 4.42 (1H, d, J = 11.2 Hz, benzyl), 3.35 (1H, s, OH), 2.99 (1H, dd, J = 10.4, 17.7 Hz, H4), 2.62 (1H, br m, H3), 2.48 (1H, dd, J = 6.4, 17.7 Hz, H4 *syn* to methyl), 2.08 (1H, ddd, J = 3.2, 6.2, 13.7 Hz), 1.93 (1H, ddd, J = 3.1, 6.0, 12.9 Hz), 1.64 (2H, m), 1.55–1.26 (4H, m), 1.20 (3H, d, J = 7.0 Hz, C3-methyl), 1.02 (1H, m), 0.87 (9H, s, *t*-butyl); NOE data 4.73 (2.08, 3%), 2.99 (2.62, 4.5%; 2.48, 13%), 2.62 (2.99, 4%; 1.49-1.36, 6.5%; 1.20, 4%), 2.48 (2.99, 8%; 1.20, 1.6%), 2.08 (4.42, 3%; 1.49-1.36, 13%), 1.93 (1.36, 16%), 1.20 (2.62, 4%; 2.48, 4%); ^{13}C NMR δ 212.2 (0, C1), 138.8 (0, aryl), 128.4 (2C, 1), 127.5 (2C, 1), 95.9 (0, C2), 77.5 (0, C1'), 64.6 (2, C4), 50.1 (2, benzyl), 47.4 (1, C3), 32.4 (0, *t*-butyl), 30.8 (2), 28.3 (1, C4'), 27.8 (2), 27.4 (3C, 3, *t*-butyl), 22.0 (2C, 2), 14.1 (3, C3-methyl). For tentative **16** (from mixture of **15a** and **16**): ^{1}H NMR δ 4.75 (1H, overlapped d, benzyl), 4.49 (1H, d, J = 11.3 Hz, benzyl), 2.29 (1H, dd, J = 11.4, 12.9 Hz, H3), 1.84 (1H, dd, J = 9.9, 12.9 Hz, H3), 1.17 (3H, d, J = 6.5 Hz, C4-methyl).

A mixture of **15a,b** (105 mg, 0.251 mmol) was stirred in TFA (1.0 mL) at rt for 4 h. Work-up afforded 76 mg of an oily, yellow solid consisting largely of **11a** and **11b**, in a ratio of 1 : 7.5.

Hydrogenolysis of 15a and 15b. A mixture of **15a** and **15b** (4.3 : 1; 64 mg, 0.19 mmol) in EtOH (3.5 mL) and AcOH (0.5 mL) with 10% Pd on charcoal (15 mg) under H_2 (1 atm) for 18 h gave 42 mg (96%) of **12a** and **12b** (5.1 : 1).

Homogeneous **15b** (58 mg, 0.17 mol) in EtOH (3.5 mL) and AcOH (0.5 mL) with 10% Pd on charcoal (13 mg) under H_2 (1 atm) for 48 h gave 42 mg (100%) of **12a** and **12b** (5.2 : 1).

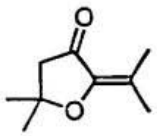
General procedure for the reactions of 4 with ketones. $BF_3 \cdot Et_2O$ (0.30 mL, 2.4 mmol) and **4** (0.84 g 3.2 mmol) were added in succession to a solution of the ketone (2.0 mmol) in CH_2Cl_2 (10.0 mL). The mixture was stirred at rt for 24 h. H_2O (0.30 mL) was introduced followed 10 min later by $BF_3 \cdot Et_2O$ (3.7 mL, 30 mmol). The resulting black solution was stirred for 1-3 h, except for the reaction with 2-methylcyclohexanone, which required 24 h. Work-up gave the crude product, consisting of cyclopentanedione(s), furanone(s), and 1,2-dione(s). Flash chromatography (hexane with an increasing proportion of EtOAc) could usually effectively separate the three types of product, but cyclopentanedione diastereomers, geometric isomers of furanones, and isomeric 1,2-diones were generally not separable in this way. Furanones were susceptible to oxidation in air. Yields and product ratios for the individual reactions are given in Table 2.



17

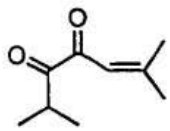
2,2,4,4-Tetramethyl-1,3-cyclopentanedione (17). Faint yellow oil (faint yellow solid below 4 °C); IR 1763 (m), 1725 (s) cm^{-1}; ^1H NMR δ 2.66 (2H, s, H5), 1.25 (6H, s, C2-methyls), 1.17 (6H, s, C4-methyls); ^{13}C NMR δ 220.8 (0, C3), 216.4 (0, C1), 51.6 (0, C2), 50.1 (2, C5), 46.6 (0, C4), 25.5 (2C, 3, C4-methyls), 21.4 (2C, 3, C2-methyls); MS 154 (15, M^+), 70 (100), 42 (31), 41 (16); HRMS calcd for $C_9H_{14}O_2$ 154.0993, found 154.0993.

4,5-Dihydro-2-isopropylidene-5,5-dimethyl-3(2*H*)-furanone (18).



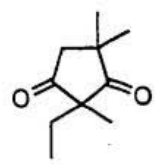
18

Yellow oil; IR 1724 (s), 1644 (m) cm^{-1}; ^1H NMR δ 2.48 (2H, s, H4), 2.07 (3H, s), 1.79 (3H, s), 1.39 (6H, s, C5-methyls); ^{13}C NMR δ 199.7 (0, C3), 143.3 (0, C2'), 120.1 (0, C2), 77.9 (0, C5), 50.5 (2, C4), 28.1 (2C, 3, C5-methyls), 19.5 (3), 16.8 (3); MS 154 (42, M^+), 139 (24), 130 (14), 83 (78), 71 (24), 70 (100), 59 (28), 56 (30), 55 (30), 43 (38), 42 (47), 41 (38).



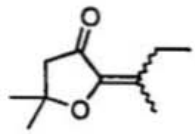
19

2,6-Dimethylhept-5-ene-3,4-dione (19). Yellow oil; ^1H NMR δ 6.71 (1H, m, H5), 3.47 (1H, septet, J = 6.9 Hz, H2), 2.26 (3H, d, J = 1.2 Hz), 2.02 (3H, d, J = 1.2 Hz), 1.10 (6H, d, J = 6.9 Hz, H1, C2-methyl); MS (from GC-MS) 154 (5, M^+), 128 (10), 83 (12), 70 (33), 59 (23), 57 (10), 56 (43), 55 (11), 44 (31), 43 (100), 41 (31).



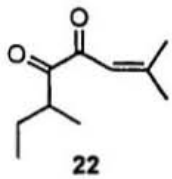
20

2-Ethyl-2,4,4-trimethylcyclopentane-1,3-dione (20). Yellow oil; IR 1764 (m), 1722 (s) cm^{-1}; ^1H NMR δ 2.67 (1H, d, J = 18.2 Hz, H5), 2.57 (1H, d, J = 18.2 Hz, H5), 1.67 (2H, q, J = 7.5 Hz, ethyl CH_2), 1.25 (3H, s, C4-methyl), 1.24 (3H, s, C4-methyl), 1.15 (3H, s, C2-methyl), 0.80 (3H, t, J = 7.5 Hz, ethyl CH_3); ^{13}C NMR δ 221.2 (0, C3), 216.5 (0, C1), 56.7 (0, C2), 51.1 (2, C5), 46.2 (0, C4), 29.0 (2, ethyl CH_2), 26.5 (3, C4-methyl), 24.5 (3, C4-methyl), 20.3 (3, C2-methyl), 9.3 (3, ethyl CH_3); MS 168 (11, M^+), 91 (16), 90 (26), 85 (15), 84 (68), 83 (61), 81 (12), 73 (72), 70 (12), 69 (55), 67 (13), 59 (14), 57 (26), 56 (100), 55 (85), 53 (19), 43 (67), 41 (86); HRMS calcd for $C_{10}H_{16}O_2$ 168.1149, found 168.1158.



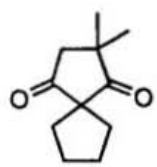
21a,b

(*E*)- and (*Z*)-4,5-Dihydro-2-isobutylidene-5,5-dimethyl-3(2*H*)-furanone (21a,b). From spectra of the mixture: IR 1725, 1639 cm^{-1}; ^1H NMR δ 2.58 (2H, q, J = 7.5 Hz, ethyl CH_2), 2.16 (2H, q, J = 7.5 Hz, ethyl CH_2), 2.482 (2H, s, H4), 2.475 (2H, s, H4), 2.06 (3H, s, C2'-methyl), 1.78 (3H, s, C2'-methyl), 1.39 (6H, s, C5-methyls), 1.38 (6H, s, C5-methyls), 1.02 (3H, t, J = 7.5 Hz, ethyl CH_3), 1.00 (3H, t, J = 7.5 Hz, ethyl CH_3); ^{13}C NMR δ 200.5 (0, C3), 199.6 (0, C3), 143.3 (0, C2'), 142.9 (0, C2'), 126.6 (0, C2), 126.0 (0, C2), 78.1 (0, C5), 78.0 (0, C5), 50.7 (2, C4), 50.6 (2, C4), 28.21 (3, C5-methyls), 28.16 (3, C5-methyls), 26.4 (2), 23.4 (2), 16.9 (3), 14.5 (3), 12.9 (3), 11.4 (3); MS 168 (62, M^+), 153 (18), 85 (13), 84 (98), 83 (22), 69 (100), 57 (17), 56 (33), 55 (31), 43 (33), 41 (76).



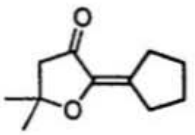
22

2,6-Dimethyloct-2-ene-4,5-dione (22). Yellow oil; IR 1710, 1677, 1618 cm^{-1}; ^1H NMR δ 6.72 (1H, m, H3), 3.36 (1H, q, J = 6.7 Hz, H6), 2.06 (3H, s), 2.02 (3H, s), 1.69 (1H, m, H7), 1.38 (1H, m, H7), 1.07 (3H, d, J = 7.0 Hz, C6-methyl), 0.88 (3H, t, J = 7.4 Hz, H8); ^{13}C NMR δ 205.2 (0), 188.2 (0), 163.4 (0, C3), 117.5 (1, C2), 40.0 (1, C6), 28.5 (3), 25.3 (2), 21.6 (3), 15.0 (3), 11.5 (3); MS 168 (2, M^+), 83 (100), 57 (16), 55 (32), 41 (10).



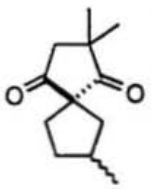
23

2,2-Dimethylspiro[4.4]nonane-1,4-dione (23). Pale yellow oil; IR 1761 (m), 1721 (s) cm^{-1}; ^1H NMR δ 2.62 (2H, m, H3), 1.93–1.75 (8H, m, H6-H9), 1.24 (6H, s, C2-methyls); ^{13}C NMR δ 221.6 (0, C1), 216.4 (0, C4), 61.6 (0, C5), 50.9 (2, C3), 46.4 (0, C2), 36.5 (2C, 2), 27.2 (2C, 2), 25.2 (2C, 3, C2-methyls); MS 180 (26, M^+), 96 (100), 68 (25), 41 (14); HRMS calcd for $C_{11}H_{16}O_2$ 180.1149, found 180.1139.



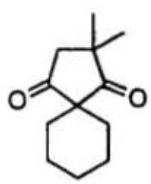
24

2-Cyclopentylidene-4,5-dihydro-5,5-dimethyl-3(2*H*)-furanone (24). ^{1}H NMR (impure sample) δ 2.78 (2H, m), 2.48 (2H, s, H4), 1.42 (6H, s, C5-methyls); MS (from GC-MS) 180 (33, M^+), 96 (100), 68 (35), 41 (32).



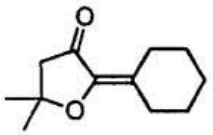
25a,b

2,2,7-Trimethylspiro[4.4]nonane-1,4-dione (25a,b). From spectra of the mixture: IR 1760 (m), 1721 (s) cm^{-1}; for major isomer: ^{1}H NMR δ 2.64 (1H, d, J = 17.8 Hz, H3), 2.56 (1H, d, J = 17.8 Hz, H3), 2.25 (1H, br m, H7), 2.05–1.68 (4H, m), 1.55–1.30 (2H, m), 1.22 (6H, s, C2-methyls), 1.04 (3H, d, J = 6.6 Hz, C7-methyl); ^{13}C NMR δ 221.5 (0, C1), 216.0 (0, C4), 61.9 (0, C5), 50.9 (2, C3), 46.2 (0, C2), 44.3 (2), 36.2 (2), 35.9 (1, C7), 35.3 (2), 25.3 (3, C2-methyl), 25.1 (3, C2-methyl), 18.6 (3, C7-methyl); for minor isomer: ^{1}H NMR δ 1.23 (6H, s, C2-methyls); ^{13}C NMR δ 221.3 (0, C1), 216.2 (0, C4), 62.0 (0, C5), 50.7 (2, C3), 46.3 (0, C2), 43.8 (2), 35.8 (1, C7), 35.6 (2), 35.2 (2), 25.2 (3, C2-methyl), 25.0 (3, C2-methyl), 19.5 (3, C7-methyl). MS 194 (22, M^+), 111 (14), 110 (100), 95 (26), 82 (11), 81 (12), 68 (26), 67 (44), 56 (11), 55 (12), 53 (10), 41 (32), 40 (20); HRMS calcd for $C_{12}H_{18}O_2$ 194.1306, found 194.1322.



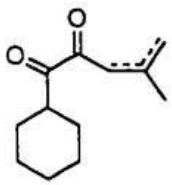
26

2,2-Dimethylspiro[4.5]decane-1,4-dione (26). White solid, mp 41.5–43 °C; IR 1760 (m), 1719 (s) cm^{-1}; ^{1}H NMR δ 2.61 (2H, m, H3), 1.75–1.40 (10H, m, H6-H10), 1.22 (6H, s, C2-methyls); ^{13}C NMR δ 220.3 (0, C1), 216.3 (0, C4), 54.9 (0, C5), 50.3 (2, C3), 46.2 (0, C2), 30.5 (2, C8), 25.7 (2C, 3, C2-methyls), 25.0 (2C, 2), 20.6 (2C, 2); MS 194 (38, M^+), 111 (12), 110 (100), 82 (24), 81 (10), 67 (55), 55 (10), 54 (15), 53 (10), 41 (29); HRMS calcd for $C_{12}H_{18}O_2$ 194.1306, found 194.1320.



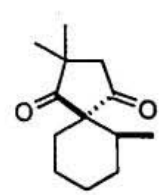
27

2-Cyclohexylidene-4,5-dihydro-5,5-dimethyl-3(2*H*)-furanone (27). Yellow oil; IR 1724, 1637 cm^{-1}; ^1H NMR δ 2.74 (2H, m), 2.48 (2H, s, H4), 2.25 (2H, apparent triplet, J = 5.4 Hz), 1.65–1.40 (6H, m, H3'-H5'), 1.38 (6H, s, C2-methyls); ^{13}C NMR δ 200.8 (0, C3), 140.8 (0, C1'), 128.7 (0, C1), 77.8 (0, C5), 50.9 (2, C4), 28.6 (2), 28.1 (2C, 3, C5-methyls), 27.9 (2), 27.3 (2), 26.3 (2), 25.9 (2); MS 194 (38, M^+), 111 (12), 110 (100), 82 (24), 81 (10), 67 (55), 55 (10), 54 (15), 53 (10), 41 (29).



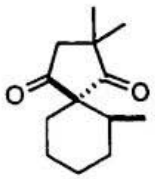
28a,b

1-Cyclohexyl-4-methylpent-4-ene-1,2-dione (28a) and 1-cyclohexyl-4-methylpent-3-ene-1,2-dione (28b). An attempt to separate a 1.2 : 1 mixture by preparative TLC led predominantly to isomerization of **28a** to **28b**. For **28a** (from the mixture): ^1H NMR δ 4.97 (1H, m, H5), 4.79 (1H, m, H5), 3.13 (1H, m, H1'), 3.44 (2H, s, H3), 1.77 (3H, s, C4-methyl); MS (from GC-MS) 194 (4, M^+), 83 (100), 55 (31). For **28b**: yellow oil; IR 1710, 1678, 1613 cm^{-1}; ^1H NMR δ 6.69 (1H, m, H3), 3.24 (1H, m, H1'), 2.26 (3H, s), 2.01 (3H, s), 1.79 (3H, m), 1.70 (1H, m), 1.30 (4H, m); ^{13}C NMR δ 204.5 (0), 188.3 (0), 163.3 (0, C4), 117.6 (1, C3), 43.1 (1, C1'), 28.5 (3), 27.8 (2C, 2), 25.8 (2), 25.4 (2C, 2), 21.6 (3); MS (from GC-MS) 194 (2, M^+), 111 (39), 83 (100), 55 (70).



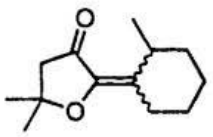
29a

2,2,6-Trimethylspiro[4.5]decane-1,4-dione (29a,b). For **29a**: IR 1759 (m), 1717 (s) cm^{-1}; ^1H NMR δ 2.69 (1H, d, J = 18.3 Hz, H3), 2.39 (1H, d, J = 18.3 Hz, H3), 1.26 (3H, s, C2-methyl), 1.20 (3H, s, C2-methyl), 0.74 (3H, d, J = 6.5 Hz, C6-methyl); ^{13}C NMR δ 222.0 (0, C1), 216.2 (0, C4), 60.4 (0, C5), 51.9 (2, C3), 45.6 (0, C2), 35.7 (1, C6), 33.8 (2), 29.0 (2), 26.8 (3, C2-methyl), 25.4 (2), 24.6 (3, C2-methyl), 20.4 (2), 18.7 (3, C6-methyl). From spectra of the



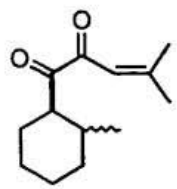
29b

mixture: **29b**: ^{1}H NMR δ 2.74 (1H, d, J = 18.6 Hz, H3), 2.46 (1H, d, J = 18.6 Hz, H3), 1.29 (3H, s, C2-methyl), 1.16 (3H, s, C2-methyl), 0.73 (3H, d, J = 6.2 Hz, C6-methyl); MS 208 (57, M^+), 193 (38), 153 (13), 140 (34), 124 (38), 110 (10), 109 (100), 95 (10), 96 (13), 81 (27), 67 (33), 56 (12), 55 (21), 53 (12), 41 (29); HRMS calcd for $C_{13}H_{20}O_2$ 208.1462, found 208.1458.



30a,b

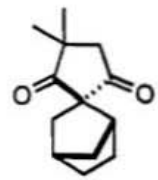
4,5-Dihydro-5,5-dimethyl-2-(2-methylcyclohexylidene)-3(2*H*)-furanone (30a,b). From spectra of the mixture: UV (cyclohexane) 291 nm (ε = 9,600); IR 1721, 1630 cm^{-1}; ^{1}H NMR δ 4.02 (1H, m, H2'), 3.64 (1H, br d, J = 14.6 Hz, H6'), 2.98 (1H, m, H2'), 2.60 (1H, m, H6'), 2.48 (2H, s, H4), 2.47 (2H, s, H4), 1.94 (1H, m, H6'), 1.40 (3H, s), 1.384 (3H, s), 1.376 (3H, s), 1.36 (3H, s), 1.11 (6H, d, J = 7.2 Hz, C2'-methyl); ^{13}C NMR δ 201.1 (0, C3), 200.4 (0, C3), 140.8 (0, C1'), 140.6 (0, C1'), 133.0 (0, C2), 132.6 (0, C2), 77.9 (0, C5), 77.8 (0, C5), 51.0 (2, C4), 33.1 (2), 32.7 (2), 29.7 (1, C2'), 26.7 (1, C2'), 28.1 (4C, 3, C5-methyls), 27.5 (2), 27.1 (2), 23.7 (2, C6'), 21.3 (2, C6'), 20.6 (2), 20.4 (2), 19.0 (3, C2'-methyl), 17.7 (3, C2'-methyl); MS 208 (100, M^+), 193 (19), 152 (26), 125 (18), 124 (73), 123 (14), 113 (36), 112 (21), 109 (95), 96 (30), 95 (52), 84 (35), 83 (29), 81 (69), 79 (21), 77 (11), 69 (17), 68 (30), 67 (74), 56 (62), 55 (51), 54 (15), 53 (32), 43 (31), 42 (12), 41 (77), 40 (11); HRMS calcd for $C_{13}H_{20}O_2$ 208.1462, found 208.1470.



31, 32

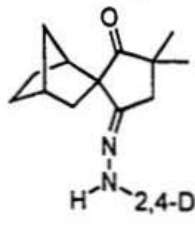
***(trans)*- (31) and (*cis*)-4-Methyl-1-(2-methylcyclohexyl)pent-3-ene-1,2-dione (32).** From spectra of a 2.4 : 1 mixture: IR 1706, 1676, 1614 cm^{-1}; for **31**: ^{1}H NMR δ 6.74 (1H, m, H3), 3.06 (1H, m, H1'), 2.26 (3H, s, C4-methyl), 2.02 (3H, s, C4-methyl), 0.79 (3H, d, J = 6.2 Hz, C2'-methyl); ^{13}C NMR δ 204.9 (0), 187.9 (0), 163.5 (0), 117.1 (1, C3), 49.4 (1, C1'), 20.6 (3,

C2'-methyl). For **32**: ^{1}H NMR δ 6.67 (1H, m, H3), 3.46 (1H, m, H1'), 2.26 (3H, s), 2.02 (3H, s), 0.81 (3H, d, J = 6.4 Hz, C2'-methyl); ^{13}C NMR δ 204.8 (0), 188.5 (0), 163.2 (0), 117.4 (1, C3), 45.7 (1, C1'), 14.9 (3, C2'-methyl); MS 208 (3, M^+), 97 (30), 83 (100), 55 (33).



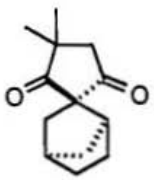
33a

(1*R/S*,2*S/R*,4*S/R*)-4',4'-Dimethylspiro(bicyclo[2.2.1]heptane-2,2'-cyclopentane)-1',3'-dione (33a). Yellow oil; IR 1758 (m), 1717 (s) cm^{-1}; ^{1}H NMR δ 2.72 (1H, d, J = 16.9 Hz, H5), 2.43 (1H, d, J = 16.9 Hz, H5), 2.49 (1H, m), 2.36 (1H, m), 2.05 (1H, m), 1.69 (1H, ddd, J = 2.9, 4.0, 12.2 Hz), 1.53 (1H, br m), 1.43 (3H, s, C4-methyl), 1.42–1.28 (4H, m), 1.23 (1H, m), 1.04 (3H, s, C4-methyl); ^{13}C NMR δ 218.5 (0, C3), 213.6 (0, C1), 64.8 (0, C2), 51.2 (2, C5), 49.1 (1), 46.1 (0, C4), 37.4 (2), 36.7 (1), 34.5 (2), 27.7 (2), 26.5 (3, C4-methyl), 25.6 (3, C4-methyl), 24.6 (2); MS 206 (54, M^+), 177 (31), 140 (76), 122 (85), 94 (13), 93 (100), 83 (12), 79 (20), 77 (10), 67 (19), 66 (17), 65 (17), 56 (10), 55 (12), 53 (13), 41 (29); HRMS calcd for $C_{13}H_{18}O_2$ 206.1306, found 206.1313. For the 1'-(2,4-dinitrophenylhydrazone) derivative **33c** (purified by recrystallization): red-orange solid, mp 199.5–201 °C; IR (Nujol) 3307, 1747, 1739 cm^{-1}; ^{1}H NMR δ 11.2 (1H, br s), 9.15 (1H, d, J = 2.6 Hz), 8.36 (1H, dd, J = 2.5, 9.6 Hz), 7.99 (1H, d, J = 9.6 Hz), 2.81 (1H, d, J = 16.6 Hz), 2.49 (1H, d, J = 16.6 Hz), 2.41 (2H, apparent t, J = 4.2 Hz), 2.15 (1H, m), 1.96 (1H, ddd, J = 2.7, 3.9, 12.0 Hz), 1.73 (1H, dd, J = 2.8, 12.1 Hz), 1.69–1.55 (2H, m), 1.49 (1H, br m), 1.40–1.28 (2H, m); ^{13}C NMR δ 218.9 (0), 162.1 (0), 145.1 (0), 138.0 (0), 130.2 (1), 129.2 (0), 123.4 (1), 116.1 (1), 61.1 (0), 48.6 (1), 45.7 (0), 39.4 (2), 37.6 (2), 37.3 (2), 36.8 (1), 28.1 (2), 26.6 (3), 26.2 (3), 24.4 (2); MS 386 (43, M^+), 351 (20), 340



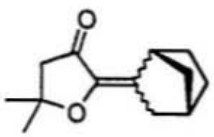
33c

(12), 320 (38), 319 (11), 285 (15), 204 (16), 189 (28), 138 (28), 120 (10), 105 (13), 95 (13), 94 (12), 93 (34), 92 (22), 91 (46), 83 (10), 82 (19), 81 (18), 80 (16), 79 (40), 78 (18), 77 (46), 75 (13), 67 (79), 66 (20), 65 (41), 63 (16), 56 (10), 55 (55), 54 (11), 53 (29), 52 (12), 51 (13), 43 (26), 42 (11), 41 (100); HRMS calcd for $C_{19}H_{22}N_4O_5$ 386.1589, found 386.1569. The structure of **33c** was determined by X-ray crystallography.



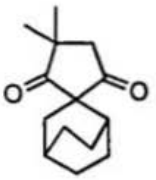
33b

(1*R/S*,2*R/S*,4*S/R*)-4',4'-Dimethylspiro(bicyclo[2.2.1]heptane-2,2'-cyclopentane)-1',3'-dione (33b). One chromatographic fraction contained a minor amount of the isomer **33b** along with **33a**. Signals for **33b** in the mixture: ^{1}H NMR δ 2.88 (1H, d, J = 18.1 Hz, H5), 1.33 (3H, s, C4-methyl), 1.13 (3H, s, C4-methyl).



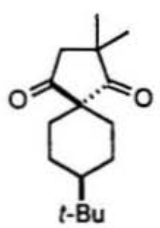
34a,b

2-(2-Bicyclo[2.2.1]heptylidene)-4,5-dihydro-5,5-dimethyl-3(2*H*)-furanone (34a,b). From spectra of the mixture: IR 1726, 1658 cm^{-1}; for the major isomer: ^{1}H NMR δ 3.87 (1H, m), 2.47 (2H, s, H4), 1.41 (6H, s, C5-methyls); ^{13}C NMR δ 199.4 (0, C3), 140.2 (0, C1'), 133.3 (0, C2), 78.9 (0, C5). For the minor isomer: ^{1}H NMR δ 3.05 (1H, m), 2.45 (2H, s, H4), 1.38 (6H, s, C5-methyls); ^{13}C NMR δ 200.3 (0, C3), 139.5 (0, C1), 132.5 (0, C2), 79.0 (0, C5); MS 206 (80, M$^+$), 191 (15), 178 (24), 123 (16), 122 (82), 94 (23), 93 (100), 80 (22), 79 (27), 77 (11), 66 (16), 65 (22), 53 (13), 41 (16).

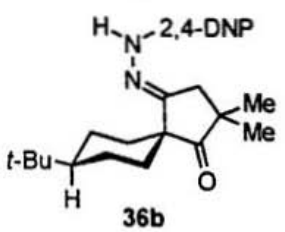


35

4',4'-Dimethylspiro(bicyclo[2.2.2]octane-2,2'-cyclopentane)-1',3'-dione (35). Tan-colored solid, mp 30–32 °C; IR 1755 (m), 1714 (s) cm^{-1}; ^1H NMR δ 2.88 (1H, d, J = 17.3 Hz, H5), 2.40 (1H, d, J = 17.3 Hz, H5), 1.82 (1H, m), 1.78–1.71 (3H, m), 1.71–1.63 (2H, m), 1.63–1.52 (2H, m), 1.52–1.41 (2H, m), 1.38 (3H, s, C4-methyl), 1.37–1.29 (2H, m), 1.06 (3H, s, C4-methyl); ^{13}C NMR δ 218.4 (0, C3), 214.3 (0, C1), 61.5 (0, C2), 49.9 (2, C5), 45.7 (0, C4), 32.4 (1), 28.1 (2), 26.7 (3, C4-methyl), 25.8 (3, C4-methyl), 24.4 (2), 24.0 (2), 23.1 (1), 21.6 (2), 20.9 (2); MS 220 (59, M^+), 141 (13), 140 (89), 137 (11), 136 (100), 125 (20), 108 (15), 107 (27), 93 (25), 89 (14), 81(20), 80 (37), 79 (70), 78 (11), 77 (28), 67 (17), 66 (16), 65 (11), 56 (13), 55 (20), 53 (23), 43 (10), 41 (62); HRMS calcd for $C_{14}H_{20}O_2$ 220.1462, found 220.1459.



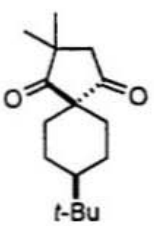
36a



36b

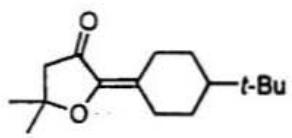
***t*-8-*tert*-Butyl-2,2-dimethyl-*r*-1-spiro[4.5]decane-1,4-dione (36a).** White solid, mp 84–86 °C; IR 1752 (m), 1713 (s) cm^{-1}; ^1H NMR δ 2.60 (2H, m, H3), 1.80–1.37 (8H, m, H6, H7, H9, H10), 1.21 (6H, s, C2-methyls), 1.06 (1H, br m, H8), 0.87 (9H, s, *t*-butyl); ^{13}C NMR δ 220.5 (0, C1), 216.1 (0, C4), 55.0 (0, C5), 50.4 (2, C3), 46.8 (1, C8), 46.3 (0, C2), 32.4 (0, *t*-butyl), 31.4 (2C, 2), 27.3 (3C, 3, *t*-butyl), 25.3 (2C, 3, C2-methyls), 21.9 (2C, 2); MS 250 (68, M^+), 235 (20), 194 (73), 193 (38), 166 (16), 152 (10), 151 (10), 140 (20), 139 (19), 123 (11), 110 (42), 109 (42), 107 (12), 95 (19), 83 (14), 82 (12), 81 (33), 79 (14), 67 (16), 57 (100), 56 (13), 55 (25), 53 (16), 43 (18), 41 (55); HRMS calcd for $C_{16}H_{26}O_2$ 250.1931, found 250.1952. For the 4-(2,4-dinitrophenylhydrazone) derivative **36b** (purified by recrystallization): orange

solid, mp 234–235 °C; IR (Nujol) 3312 (m), 1746 (m), 1712 (sh), 1618 (s), 1595 (s), 1518 (m) cm^{-1}; ^1H NMR δ 11.12 (1H, br s), 9.13 (1H, d, J = 2.5 Hz), 8.32 (1H, dd, J = 2.5, 9.6 Hz), 7.93 (1H, d, J = 9.6 Hz), 2.78 (2H, m), 1.75–1.65 (8H, m), 1.25 (6H, s), 1.17 (1H, br m), 0.95 (9H, s); ^{13}C NMR δ 220.8 (0), 164.6 (0), 145.0 (0), 137.9 (0), 130.0 (1), 129.2 (0), 123.4 (1), 116.3 (1), 52.6 (0), 46.8 (1), 46.0 (0), 38.7 (2), 33.1 (2C, 3), 32.6 (0), 27.4 (3C, 3), 25.8 (2C, 3), 21.7 (2C, 2); MS 430 (64, M^+), 373 (30), 320 (18), 319 (39), 318 (21), 248 (19), 233 (13), 138 (12), 82 (20), 81 (18), 69 (10), 67 (14), 57 (100), 55 (36), 43 (16), 41 (48); HRMS calcd for $C_{22}H_{30}O_5N_4$ 430.2214, found 430.2239. The structure of **36b** was determined by X-ray crystallography.



36c

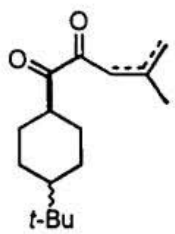
***c*-8-*tert*-Butyl-2,2-dimethyl-*r*-1-spiro[4.5]decane-1,4-dione (36c).** Only unequivocal signals, from mixture: ^1H NMR δ 2.59 (2H, s, H3), 1.25 (6H, s, C2-methyls), 0.88 (9H, s, *t*-butyl); ^{13}C NMR δ 220.6 (0, C1), 216.4 (0, C4), 54.1 (0, C5), 50.1 (2, C3), 46.8 (1, C8), 46.3 (0, C2), 32.4 (0, *t*-butyl), 31.3 (2C, 2), 27.4 (3C, 3, *t*-butyl), 25.9 (2C, 3, C2-methyls), 21.3 (2C, 2).



37

2-(4-*tert*-Butylcyclohexylidene)-4,5-dihydro-5,5-dimethyl-3(2*H*)-furanone (37). Yellow oil; IR 1724 (s), 1640 (s) cm^{-1}; ^1H NMR δ 3.82 (1H, m), 2.80 (1H, m), 2.51 (1H, d, J = 17.6 Hz, H4), 2.45 (1H, d, J = 17.6 Hz, H4), 1.89 (2H, m), 1.73 (2H, m), 1.40 (3H, s, C5-methyl), 1.38 (3H, s, C5-methyl), 1.14 (1H, m, H4'), 0.83 (9H, s, *t*-butyl); ^{13}C NMR δ 200.8 (0, C3), 140.5 (0, C1'), 128.4 (0, C2), 77.9 (0, C5), 50.9 (2, C4), 47.8 (1, C8), 32.5 (0, *t*-butyl), 28.7 (2), 28.5 (2), 28.2 (3, C5-methyl), 28.1 (3, C5-methyl), 28.0 (2), 27.5 (3C, 3, *t*-butyl), 25.9 (2); MS 250 (100, M^+), 166 (35), 151 (14),

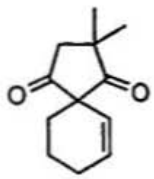
123 (19), 110 (15), 109 (22), 107 (19), 95 (24), 83 (16), 82 (15), 81 (33), 79 (10), 69 (11), 67 (13), 57 (72), 56 (11), 55 (19), 53 (14), 41 (41).



38a,b ; 39a,b

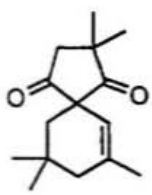
(*cis*)-1-(4-*tert*-Butylcyclohexyl)-4-methylpent-4-ene-1,2-dione (38a), (*cis*)-1-(4-*tert*-butylcyclohexyl)-4-methylpent-3-ene-1,2-dione (38b), (trans)-1-(4-*tert*-butylcyclohexyl)-4-methylpent-4-ene-1,2-dione (39a), and (*trans*)-1-(4-*tert*-butylcyclohexyl)-4-methylpent-3-ene-1,2-dione (39b). Initially obtained in a 7.7 : 2.5 : 1.1 : 1 ratio, respectively. Preparative TLC gave only **38b** and **39b** in a 2.6 : 1 ratio. From spectra of the mixtures: IR (mixture of **38b, 39b**) 1706, 1677, 1614 cm^{-1}; for **38a**: ^1H NMR δ 5.01 (1H, m), 4.84 (1H, m), 3.44 (2H, s, H3), 1.79 (3H, s, C4-methyl), 0.83 (9H, s, *t*-butyl). For **38b**: ^1H NMR δ 6.61 (1H, m, H3), 3.44 (1H, m, H1'), 2.25 (3H, s), 2.00 (3H, s), 0.86 (9H, s, *t*-butyl); ^{13}C NMR δ 205.9 (0), 189.4 (0), 163.1 (0), 117.9 (1), 48.0 (1, H1'), 39.1 (3), 32.5 (0, *t*-butyl), 28.5 (2), 28.4 (2), 27.4 (3C, 3, *t*-butyl), 26.6 (2C, 2), 23.6 (3). For **39a**: ^1H NMR δ 4.97 (1H, m), 4.80 (1H, m), 3.04 (1H, m, H1'). For **39b**: ^1H NMR δ 6.70 (1H, m, H3), 3.15 (1H, tt, J = 3.2, 11.8 Hz, H1'), 2.25 (3H, s), 2.00 (3H, s); ^{13}C NMR δ 204.6 (0), 188.2 (0), 163.3 (0), 117.6 (1), 47.4 (1), 43.3 (3), 32.4 (0, *t*-butyl), 28.6 (2), 27.5 (2C, 2), 26.5 (2C, 2), 21.6 (3); MS (mixture of **38b, 39b**) 250 (2, M^+), 83 (100), 57 (25), 55 (11).

Procedure for the reactions of 4 with enones. $BF_3{\cdot}Et_2O$ (0.74 mL, 6.0 mmol) and **4** (1.55 g, 6.0 mmol) were added in succession to a solution of the ketone (2.0 mmol) in CH_2Cl_2 (10 mL) at –78 °C. The mixture was stirred at rt for 24 h before work-up. Chromatography provided the products. Yields and product ratios for the individual reactions are given in Table 2.



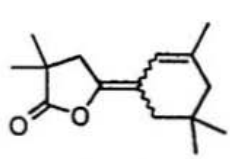
40

2,2-Dimethylspiro[4.5]dec-6-ene-1,4-dione (40). Oily tan solid, mp 30–32 °C; IR 1764 (m), 1722 (s), 1649 (w) cm^{-1}; ^1H NMR δ 6.16 (1H, td, J = 3.8, 9.9 Hz, H7), 5.22 (1H, td, J = 2.2, 9.9 Hz, H6), 2.75 (1H, d, J = 17.7 Hz, H3), 2.63 (1H, d, J = 17.7 Hz, H3), 2.20–2.04 (2H, m, H8), 1.95–1.68 (4H, m, H9, H10), 1.31 (3H, s, C2-methyl), 1.22 (3H, s, C2-methyl); ^{13}C NMR δ 218.5 (0, C1), 214.1 (0, C4), 133.3 (1, C7), 120.6 (1, C6), 58.5 (0, C5), 50.2 (2, C3), 46.9 (0, C2), 29.2 (2), 25.7 (3, C2-methyl), 25.1 (3, C2-methyl), 23.8 (2, C8), 17.2 (2); MS 192 (15, M^+), 108 (100), 80 (42), 79 (33), 77 (11), 41 (13). HRMS calcd for $C_{12}H_{16}O_2$ 192.1149, found 192.1148.



41

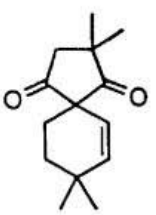
2,2,7,9,9-Pentamethylspiro[4.5]dec-6-ene-1,4-dione (41). Yellow oil, contaminated with isomeric compound(s) (approximately 15%); IR 1766 (m), 1724 (s), 1665 (w) cm^{-1}; ^1H NMR δ 5.00 (1H, d, J = 1.4 Hz, H6), 2.70 (1H, d, J = 17.0 Hz, H3), 2.64 (1H, d, J = 17.0 Hz, H3), 1.77 (1H, overlapped d), 1.71 (3H, d, J = 1.2 Hz, C7-methyl), 1.65 (1H, d, J = 13.8 Hz, H10), 1.52 (1H, d, J = 13.8 Hz, H10), 1.22 (3H, s), 1.21 (3H, s), 1.00 (3H, s), 0.95 (3H, s); ^{13}C NMR δ 218.4 (0, C1), 213.6 (0, C4), 139.3 (0, C7), 113.9 (1, C6), 61.5 (0, C5), 50.2 (2, C3), 47.0 (0, C2), 43.1 (2), 39.9 (2), 30.2 (3), 30.0 (0, C9), 28.2 (3), 25.5 (3), 25.3 (3), 24.5 (3); MS 34 (24, M^+), 150 (100), 135 (17), 107 (77), 91 (27), 79 (16), 77 (13), 55 (12), 41 (32); HRMS calcd for $C_{15}H_{22}O_2$ 234.1619, found 234.1613.



42a,b

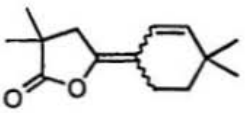
(*E*)- (42a) and (*Z*)-3,4-Dihydro-3,3-dimethyl-5-(3,5,5-trimethylcyclohex-2-enylidene)-2-furanone (42b). From spectra of the mixture: UV (cyclohexane) 267 nm (ε = 8,700); IR 1797 (s), 1686 (m), 1636 (m), 1086 (s) cm^{-1}; for **42a**: ^1H NMR δ 5.74 (1H, dd, J = 1.4, 3.0 Hz,

H2'), 2.76 (2H, s, H4), 2.15 (2H, apparent t, J = 1.8 Hz), 1.85 (2H, br s), 1.77 (3H, br s, C3'-methyl), 1.29 (6H, s, C3-methyls), 0.91 (6H, s, C5'-methyls); NOE data 5.74 (2.76, 7%; 1.77, 4%), 2.76 (5.74, 13%, 1.29, 6%); ^{13}C NMR δ 180.4 (0, C2), 145.0 (0), 135.8 (0), 116.9 (1, C2'), 113.0 (0), 44.8 (2, C4), 40.0 (0, C3), 38.6 (2), 36.5 (2), 29.8 (0, C5'), 28.32 (2C, 3, C5'-methyl), 25.0 (2C, 3, C3-methyls), 24.3 (3, C3'-methyl). For **42b**: ^{1}H NMR δ 6.26 (1H, dd, J = 1.4, 2.8 Hz, H2'), 2.69 (2H, br s, H4), 1.85 (4H, br s, H4', H6'), 1.77 (3H, br s, C3'-methyl), 1.28 (6H, s, C3-methyls), 0.92 (6H, s, C5'-methyls); NOE data 6.26 (1.77, 2%), 2.69 (1.85, 6%, 1.28, 8%); ^{13}C NMR δ 180.3 (0, C2), 140.6 (0), 135.1 (0), 116.6 (1, C2'), 112.0 (0), 44.8 (2, C4), 39.9 (0, C3), 39.0 (2), 37.8 (2), 30.3 (0, C5'), 28.38 (2C, 3, C5'-methyl), 25.0 (2C, 3, C3-methyls), 24.0 (3, C3'-methyl); MS 234 (23, M^+), 150 (100), 135 (13), 107 (63), 91 (21), 79 (15), 77 (11), 41 (24).



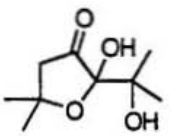
43

2,2,8,8-Tetramethylspiro[4.5]dec-6-ene-1,4-dione (43). White solid, mp 41–42 °C; IR (Nujol) 1756 (m), 1723 (s) cm^{-1}; ^{1}H NMR δ 5.87 (1H, d, J = 9.9 Hz, H7), 5.09 (1H, d, J = 9.8 Hz, H6), 2.74 (1H, d, J = 17.6 Hz, H3), 2.66 (1H, d, J = 17.6 Hz, H3), 1.84–1.50 (4H, m, H9, H10), 1.30 (3H, s), 1.22 (3H, s), 1.06 (3H, s), 1.04 (3H, s); ^{13}C NMR δ 218.3 (0, C1), 213.9 (0, C4), 143.3 (1, C7), 118.3 (1, C6), 58.8 (0, C5), 50.3 (2, C3), 46.9 (0, C2), 31.9 (2), 31.1 (0, C8), 29.2 (3), 29.1 (3), 26.9 (2), 25.7 (3), 25.2 (3); MS 220 (19, M^+), 205 (12), 136 (44), 121 (100), 93 (15), 91 (15), 77 (18), 41 (20). HRMS calcd for $C_{14}H_{20}O_2$ 220.1462, found 220.1464.



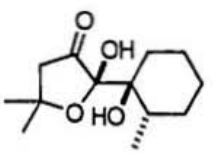
44a,b

(*E*)- and (*Z*)-3,4-Dihydro-3,3-dimethyl-5-(4,4-dimethylcyclohex-2-enylidene)-2-furanone (44a,b). ^{1}H NMR (selected signals from mixture) δ 6.37 (1H, d, J = 10.0 Hz), 5.86 (1H, d, J = 9.9 Hz), 5.56 (1H, d, J = 9.9 Hz), 5.52 (1H, d, J = 9.9 Hz), 2.75 (2H, apparent t, J = 1.6 Hz), 2.70 (2H, br s), 1.31 (6H, s), 1.02 (6H, s).

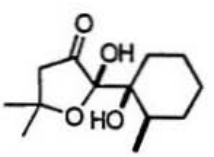


45

4,5-Dihydro-2-hydroxy-2-(1-hydroxy-1-methylethyl)-5,5-dimethyl-3(2*H*)-furanone (45). Exposure of **18** to air left **45** as a yellow oil: IR 3468 (s), 1760 (s), 1660 (w) cm^{-1}; ^{1}H NMR δ 3.64 (1H, OH), 2.64 (1H, d, J = 18.0 Hz, H4), 2.55 (1H, OH), 2.43 (1H, d, J = 18.0 Hz, H4), 1.49 (3H, s), 1.46 (3H, s), 1.27 (3H, s), 1.26 (3H, s); ^{13}C NMR δ 213.6 (0, C3), 100.2 (0, C2), 78.1 (0), 73.9 (0), 49.1 (2, C4), 29.7 (3), 29.4 (3), 23.9 (3), 22.9 (3); MS no M$^+$, 171 (2), 155 (4), 130 (34), 105 (24), 87 (19), 85 (34), 84 (25), 83 (26), 69 (27), 59 (87), 57 (10), 56 (100), 55 (13), 43 (61), 41 (46).



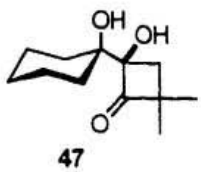
46a



46b

(1'*R/S*,2*R/S*,2'*R/S*)- (46a) and (1'*R/S*,2*R/S*,2'*S/R*)-4,5-Dihydro-2-hydroxy-2-(1-hydroxy-2-methylcyclohexyl)-5,5-dimethyl-3(2*H*)-furanone (46b). Exposure of **30a/b** to air left a waxy yellow solid. Chromatography provided a colorless oil consisting of **46a** and **46b** in a 1.5 : 1 ratio. Crystallization occurred during refrigeration to provide a small, homogenous sample of **46a**: colorless solid; mp 107.5-109.5 °C; IR 3434, 1762 cm^{-1}; ^{1}H NMR δ 3.69 (1H, s, OH), 2.63 (1H, d, J = 18.7 Hz, H4), 2.53 (1H, s, OH), 2.42 (1H, d, J = 18.7 Hz, H4), 2.08–1.84 (3H, m), 1.70–1.50 (3H, m), 1.49 (3H, s, C5-methyl), 1.43 (3H, s, C5-methyl), 1.42–1.20 (3H, m), 1.00 (3H, d, J = 7.3 Hz, C2'-methyl); ^{13}C NMR δ 213.6 (0, C3), 100.5 (0, C2),

77.7 (0), 77.2 (0), 48.3 (2, C4), 34.2 (1, C2'), 30.3 (3, C5-methyl), 29.8 (3, C5-methyl), 29.4 (2), 26.5 (2), 21.0 (2), 19.8 (2), 16.2 (3, C2'-methyl); MS no M^+, 225 (4), 223 (10), 213 (13), 211 (32), 141 (11), 139 (13), 124 (10), 123 (12), 113 (68), 112 (13), 111 (22), 95 (56), 84 (17), 83 (100), 81 (10), 69 (16), 68 (15), 67 (16), 59 (20), 57 (11), 56 (48), 55 (77), 45 (16), 44 (11), 43 (54), 42 (13), 41(57); HRMS calcd for $C_{13}H_{21}O_3$ (M^+ - OH) 225.1490, found 225.1470. The structure of **46a** was determined by X-ray crystallography. For **46b**: ^{1}H NMR δ 3.74 (1H, s, OH), 2.58 (1H, d, J = 18.4 Hz, H4), 2.49 (1H, d, J = 18.4 Hz, H4), 2.22 (1H, s, OH), 1.48 (3H, s, C5-methyl), 1.47 (3H, s, C5-methyl), 1.05 (3H, d, J = 7.4 Hz, C2'-methyl), 1.77 (2H, apparent triplet); ^{13}C NMR δ 214.0 (0, C3), 100.4 (0, C2), 78.6 (0), 76.8 (0), 48.5 (2, C4), 35.4 (1, C2'), 30.0 (3, C5-methyl), 29.6 (3, C5-methyl), 24.8 (2), 21.1 (2), 20.8 (2), 19.7 (2), 16.6 (3, C2'-methyl).

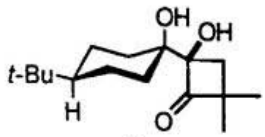


47

2-Hydroxy-2-(1-hydroxycyclohexyl)-4,4-dimethylcyclobutanone (47). White solid; mp 145–148 °C; IR (Nujol) 3452, 1766 cm^{-1}; ^{1}H NMR δ 3.38 (1H, br s, OH), 2.18 (1H, d, J = 12.8 Hz, H3), 1.91 (1H, d, J = 12.8 Hz, H3), 1.83 (1H, m), 1.73 (1H, br m), 1.67–1.40 (6H, m), 1.36 (3H, s, C4-methyl), 1.27–1.16 (2H, m), 1.15 (3H, s, C4-methyl); ^{13}C NMR δ 220.0 (0, C1), 92.6 (0, C2), 73.3 (0, C1'), 55.2 (0, C4), 38.6 (2, C3), 32.1 (2), 29.6 (2), 25.6 (2), 24.7 (3, C4-methyl), 20.9 (3, C4-methyl), 20.8 (2), 20.7 (2); MS no M^+, 194 (10), 111 (10), 110 (100), 99 (30), 82 (22), 81 (33), 70 (30), 69 (14), 67 (47), 55 (19), 43 (37), 42 (13), 41 (32); HRMS calcd for $C_{12}H_{18}O_2$ (M^+ - H_2O) 194.1307, found 194.1311.

Compound **47** (10.1 mg, 47.5 mmol) was stirred with $BF_3{\cdot}Et_2O$ (1.1 mL) for 2 h. Work-up gave a yellow oil (11.8 mg), which ^{1}H NMR revealed to be a 3.0 : 1 mixture of **26** and **27**. A solution of **47** (18.3 mg, 86.2 mmol) in CH_2Cl_2 (1.7 mL) and $BF_3{\cdot}Et_2O$

(0.18 mL) was stirred for 15 h at rt. Work-up gave an oily, brown solid (24.4 mg), which contained only **26** but no trace of **27**.



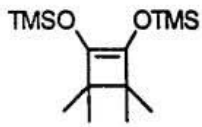
48

2-(*c*-4-*tert*-Butyl-*r*-1-hydroxycyclohexyl)-2-hydroxy-4,4-dimethylcyclobutanone (48). White solid; mp 158–159.5 °C; IR 3495, 3404, 1761 cm^{-1}; ^1H NMR δ 3.30 (1H, br s, OH), 2.15 (1H, dd, J = 0.9, 12.9 Hz, H3), 1.91 (1H, d, J = 12.9 Hz, H3), 1.90 (1H, m), 1.72–1.40 (6H, m), 1.37 (3H, s, C4-methyl), 1.31 (1H, br m), 1.16 (3H, s, C4-methyl), 0.96 (1H, apparent tt, J = 2.9, 11.8 Hz, H4'), 0.87 (9H, s, *t*-butyl); ^{13}C NMR δ 220.0 (0, C1), 92.6 (0, C2), 72.9 (0, C1'), 55.2 (0, C4), 47.7 (1, C4'), 38.7 (2, C3), 32.6 (2), 32.4 (0, *t*-butyl), 30.2 (2), 27.5 (3C, 3, *t*-butyl), 24.7 (3, C4-methyl), 21.8 (2), 21.6 (2), 20.9 (3, C4-methyl); MS 268 (5, M^+), 250 (21), 240 (22), 235 (12), 222 (13), 207 (18), 194 (10), 193 (12), 167 (16), 166 (100), 165 (23), 155 (76), 151 (18), 138 (11), 137 (20), 130 (12), 123 (25), 114 (16), 113 (14), 110 (17), 109 (39), 107 (12), 98 (40), 97 (20), 96 (16), 95 (57), 86 (12), 85 (25), 84 (13), 83 (36), 82 (24), 81 (64), 80 (10), 79 (14), 71 (12), 70 (35), 69 (24), 67 (24), 57 (100), 56 (18), 55 (36), 43 (41), 42 (11), 41 (54); HRMS calcd for $C_{16}H_{26}O_2$ (M^+ - H_2O) 250.1931, found 250.1933. The structure of **48** was determined by X-ray crystallography.

Compound **48** (60.8 mg, 0.227 mmol) was stirred with $BF_3{\cdot}Et_2O$ (1.0 mL) for 20 h. Work-up gave 56.0 mg of a mixture of **36a** and **37** in a 8 : 1 ratio by GC-MS.

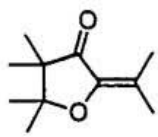
A solution of **48** (122 mg, 0.489 mmol) in CH_2Cl_2 (10 mL) and $BF_3{\cdot}Et_2O$ (0.90 mL) was stirred for 21 h at rt. Work-up gave an oily, tan solid (107 mg), consisting of a 13 : 1 mixture of **36a** and **37** by GC-MS.

A solution of **48** (84 mg, 0.31 mmol) in CH_2Cl_2 (1.6 mL) with $BF_3{\cdot}Et_2O$ (0.58 mL) and H_2O (50 mL) was stirred for 23 h at rt. Work-up gave **36a** as pale yellow solid (77 mg, 98%).



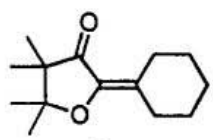
51

3,3,4,4-Tetramethyl-1,2-bis(trimethylsilyloxy)cyclobutene (51). Colorless liquid, $bp_{2.5mm}$ 83–87.8 °C; IR 1719 cm^{-1}; ^1H NMR δ 1.01 (12H, s, C3, C4-methyls), 0.20 (6H, s, OTMS); ^{13}C NMR δ 128.2 (2C, 0, C1, C2), 43.9 (2C, 0, C3, C4), 21.8 (4C, 3, C3, C4-methyls), 0.6 (6C, 3, OTMS); MS 286 (29, M^+), 271 (10), 243 (14), 181 (14), 147 (42), 75 (16), 73 (100), 45 (18); HRMS calcd for $C_{14}H_{30}O_2Si_2$ 286.1783, found 286.1783.



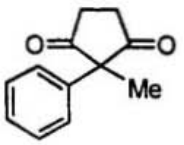
52

4,5-Dihydro-2-isopropylidene-4,4,5,5-tetramethyl-3(2*H*)-furanone (52). Yellow oil (31% yield from acetone); UV (cyclohexane) 285 nm (ε = 10,000); IR 1726 (s), 1605 (s) cm^{-1}; ^1H NMR δ 2.08 (3H, s), 1.79 (3H, s), 1.22 (6H, s), 1.00 (6H, s); ^{13}C NMR δ 205.2 (0, C2), 141.8 (0, C2'), 121.1 (0, C3), 83.1 (0, C5), 51.0 (0, C4), 23.5 (2C, 3), 19.5 (3C, 3), 17.1 (3); MS 182 (40, M^+), 168 (15), 168 (15), 167 (10), 153 (10), 85 (17), 84 (100), 71 (23), 70 (56), 69 (67), 55 (17), 43 (38), 42 (21), 41 (50); HRMS calcd for $C_{11}H_{18}O_2$ 182.1306, found 182.1298.



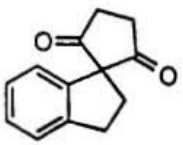
53

2-Cyclohexylidene-4,5-dihydro-4,4,5,5-tetramethyl-3(2*H*)-furanone (53). Tan-colored oil (35% yield from cyclohexanone); ^1H NMR δ 2.74 (2H, m), 2.25 (2H, distorted t), 1.75–1.40 (6H, m, H3'-H5'), 1.22 (3H, s), 1.00 (3H, s); ^{13}C NMR δ 206.0 (0, C2), 139.0 (0, C2'), 129.4 (0, C3), 82.9 (0, C5), 51.2 (0, C4), 28.6 (2), 28.1 (2), 27.2 (2), 26.4 (2), 26.2 (2), 23.4 (3), 19.6 (3).



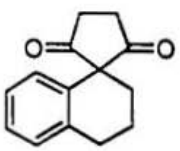
54

2-Methyl-2-phenylcyclopentane-1,3-dione (54). A solution of acetophenone (241 mg, 2.01 mmol), $BF_3 \cdot Et_2O$ (0.30 mL, 2.4 mmol), and **1** (0.73 g, 3.2 mmol) in CH_2Cl_2 (10 mL) was stirred at rt for 25.5 h. Work-up gave a viscous, tan-colored oil (406 mg). Chromatography (0.5/99.5 MeOH/CH_2Cl_2) afforded **54** as a pale yellow oil (267 mg, 70%). Spectra were as reported in ref. 3.

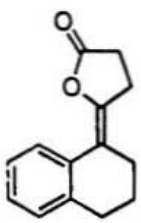


55

2',3'-Dihydrospiro(cyclopentane-1,1'-[1*H*]indene)-2,5-dione (55). A solution of 1-indanone (1.33 g, 10.0 mmol), $BF_3 \cdot Et_2O$ (1.85 mL, 15.1 mmol), and **1** (3.70 g, 16.1 mmol) in CH_2Cl_2 (36 mL) was stirred at rt for 24 h. Work-up gave a brown resin. Chromatography (40/60 EtOAc/petroleum ether) provided a yellow solid (1.48 g, 75%). Spectra were as reported in ref. 6.

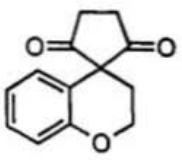


56

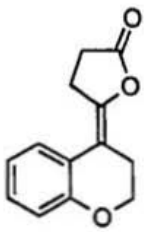


57

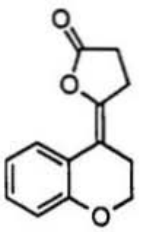
1,',2',3',4'-Tetrahydrospiro(cyclopentane-1,1'-naphthalene)-2,5-dione (56) and 3,4-dihydro-5-(1-naphthylidene)-2-furanone (57). A solution of 1-tetralone (226 mg, 1.54 mmol), $BF_3 \cdot Et_2O$ (0.30 mL, 2.4 mmol), and **1** (0.71 g, 3.1 mmol) in CH_2Cl_2 (10.0 mL) was stirred at rt for 19 h. Work-up supplied a tan-colored resin (407 mg). Chromatography (30/70 EtOAc/petroleum ether) provided **56** as a white solid (139 mg, 42%) as well as recovered 1-tetralone (47 mg, 21%) and **57** as a beige solid (2 mg, 2%); IR (CCl_4) 1803 (s) cm^{-1}; ^1H NMR δ 8.04 (1H, d, J = 7.7 Hz), 7.24–7.06 (3H, m), 3.01 (2H, apparent t, J = 8.6 Hz), 2.85–2.66 (4H, m), 2.37 (2H, apparent t, J = 6.2 Hz), 1.86 (2H, m). Spectra for **56** were as reported in ref. 6.



58

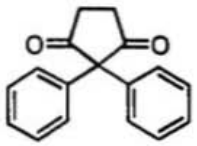


59a

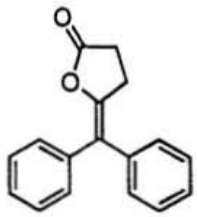


59b

1',2',3',4'-Tetrahydro-4'-oxaspiro(cyclopentane-1,1'-naphthalene)-2,5-dione (58) and (*E*)- and (*Z*)-3,4-dihydro-5-(1-(1',2',3',4'-tetrahydro-4-oxanaphthylidene))-2-furanone (59a,b). A solution of 4-chromanone (254 mg, 1.71 mmol), $BF_3 \cdot Et_2O$ (0.32 mL, 2.6 mmol), and **1** (0.79 g, 3.4 mmol) in CH_2Cl_2 (10 mL) was stirred at rt for 23 h. Work-up gave a tan-colored resin (432 mg). Chromatography (0.5/99.5 MeOH/CH_2Cl_2) provided **58** (168 mg, 45%) as a pale yellow solid, mp 110–111.5 °C and **59a,b** as a gummy, yellow solid (40 mg, 11%) (1.5 : 1 mixture of geometric isomers). For **58**: IR (CCl_4) 1721 (s), 1603 (w), 1581 (w) cm^{-1}; ^1H NMR δ 7.19 (1H, dt, J = 1.3, 7.7 Hz), 6.91 (1H, d, J = 7.4 Hz), 6.85 (1H, t, J = 7.4 Hz), 6.58 (1H, dd, J = 1.6, 7.7 Hz), 4.33 (2H, t, J = 5.2 Hz), 3.02 (4H, symmetric m), 2.08 (2H, t, J = 5.1 Hz); ^{13}C NMR δ 213.6 (2C, 0, C2, C5), 155.2 (0), 129.2 (1), 128.0 (1), 120.9 (1), 117.7 (1), 117.6 (0), 60.7 (2), 60.0 (0, C1), 35.2 (2C, 2, C3, C4), 28.9 (2); MS 216 (100, M^+), 160 (32), 146 (21), 132 (27), 131 (81), 103 (11), 77 (16), 51 (19); HRMS calcd for $C_{13}H_{12}O_3$ 216.0786, found 216.0775. For **59a,b**: from spectra of the mixture: IR (CCl_4) 1800 (s), 1670 (m), 1124 (s) cm^{-1}; **59a**: ^1H NMR (discernable signals) δ 7.19 (1H, br d, J = 7.8 Hz), 2.53 (2H, br t). **59b**: ^1H NMR (discernable signals) δ 8.10 (1H, dd, J = 1.6, 8.0 Hz), 3.25 (2H, br t). ^{13}C NMR (signals for both isomers) δ 174.9/174.0 (0, C2), 154.6/153.7 (0), 143.5/142.5 (0), 108.3/104.7 (0), 65.9/65.5 (2); MS 216 (100, M^+), 160 (34), 148 (16), 146 (22), 133 (10), 132 (27), 131 (79), 120 (23), 103 (11), 92 (12), 86 (35), 84 (55), 80 (10), 77 (17), 63 (11), 55 (11), 51 (20), 47 (13); HRMS calcd for $C_{13}H_{12}O_3$ 216.0786, found 216.0774.

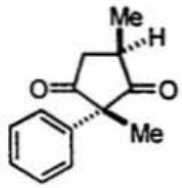


60

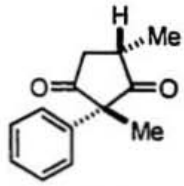


61

2,2-Diphenylcyclopentane-1,3-dione (60) and 3,4-dihydro-5-(diphenylmethylene)-2-furanone (61). A solution of benzophenone (277 mg, 1.52 mmol), $BF_3{\cdot}Et_2O$ (0.30 mL, 2.4 mmol), and **1** (0.70 g, 3.0 mmol) in CH_2Cl_2 (10 mL) was stirred at rt for 22 h. Work-up afforded an oily brown solid. Chromatography (0.5/99.5 MeOH/CH_2Cl_2) gave a beige solid (330 mg) composed of **60** and **61** in a 6.3 : 1 ratio. Further chromatography (20/80 EtOAc/petroleum ether) provided analytical samples of each component. For **60**: pale yellow solid; mp 158–160 °C; ^{1}H NMR δ 7.40–7.28 (6H, m), 7.12–7.04 (4H, m), 2.96 (4H, s, H4, H5); ^{13}C NMR δ 211.3 (2C, 0, C1, C3), 136.5 (2C, 0), 128.9 (1), 128.1 (1), 72.2 (0), 36.0 (2C, 2, C4, C5); IR (Nujol) 1721 (s) cm^{-1}; MS 250 (100, M^+), 222 (11), 194 (12), 167 (17), 166 (44), 165 (53), 83 (11), 82 (12); HRMS calcd for $C_{17}H_{14}O_2$ 250.0993, found 250.1001. For **61**: Yellow solid, mp 103.5–106.5 °C; IR 1804 (s), 1657 (m), 1597 (w), 1495 (m), 1113 (s) cm^{-1}; ^{1}H NMR δ 7.44–7.16 (10H, m, aryl), 2.92 (2H, m), 2.70 (2H, m); ^{13}C NMR δ 174.7 (0, C2), 146.2 (0), 138.7 (0), 137.5 (0), 129.9 (2C, 1), 129.2 (2C, 1), 128.6 (2C, 1), 127.9 (2C, 1), 127.3 (1), 126.8 (1), 118.5 (0), 27.5 (2), 25.9 (2); MS 250 (100, M^+), 222 (14), 194 (12), 167 (18), 166 (40), 165 (53), 83 (11), 82 (11); HRMS calcd for $C_{17}H_{14}O_2$ 250.0993, found 250.0995.



62a

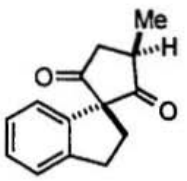


62b

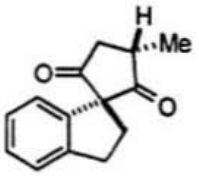
(2*R,4*R**)- (62a) and (2*R**,4*S**)-2,4-Dimethyl-2-phenyl-1,3-cyclopentanedione (62b).** *(a)* A solution of acetophenone (236 mg, 1.97 mmol), $BF_3{\cdot}Et_2O$ (0.29 mL, 2.3 mmol), and **3** (0.77 g, 3.2 mmol) in CH_2Cl_2 (10 mL) was stirred at rt for 26 h. Work-up provided a tan oil (490 mg). Chromatography (0.5/99.5 MeOH/ CH_2Cl_2) gave a yellow oil (304 mg, 77%) as a 1 : 2.6 mixture of **62a** and **62b**.

(b) To a solution of acetophenone ethylene acetal (326 mg, 1.98 mmol) in CH_2Cl_2 (10 mL) at –78 °C was added $BF_3{\cdot}Et_2O$ (0.37 mL, 3.0 mmol) and **3** (1.46 g, 6.00 mmol). After stirring at rt for 26 h, work-up gave a yellow resin (902 mg). Chromatography (0.5/99.5 MeOH/CH_2Cl_2) gave a yellow oil (265 mg, 63%) as a 1 : 1.2 mixture of **62a** and **62b**. Further chromatography (20/80 EtOAc/hexanes) provided a small sample of each isomer for NMR analysis. For the **62a,b** mixture: IR 1765 (m), 1724 (s), 1600 (w), 1494 (m) cm^{-1}; MS 202 (8, M^+), 132 (45), 105 (14), 104 (100), 103 (42), 78 (61), 77 (42), 63 (15), 52 (12), 51 (34), 50 (11), 42 (21), 41 (34); HRMS calcd for $C_{13}H_{14}O_2$ 202.0993, found 202.0990. For **62a**: colorless oil; ^1H NMR δ 7.39–7.25 (3H, m), 7.25–7.17 (2H, m), 3.13 (1H, dd, J = 11.7, 18.2 Hz, H5), 3.01 (1H, m, H4), 2.34 (1H, dd, J = 8.0, 18.2 Hz, H5), 1.43 (3H, s, C2-methyl), 1.28 (3H, d, J = 6.9 Hz, C4-methyl); ^{13}C NMR δ 215.0 (0, C4), 212.6 (0, C1), 137.4 (0), 129.3 (2C, 1), 127.8 (1), 126.2 (2C, 1), 62.1 (0, C2), 43.9 (2, C5), 40.8 (1, C4), 20.1 (3, C2-methyl), 14.7 (3, C4-methyl). For **62b**: Pale yellow oil; ^1H NMR δ 7.40–7.25 (3H, m), 7.25–7.19 (2H, m), 2.98 (1H, dd, J = 9.6, 16.7 Hz, H5 *syn* to phenyl), 2.86 (1H, m, H4), 2.53 (1H, dd, J = 8.6, 16.7 Hz, H5), 1.43 (3H, s, C2-methyl), 1.29 (3H, d, J = 7.1 Hz, C4-methyl); NOE data 2.53 (2.98, 6%; 2.86, 4%), 1.43 (7.22, 8%; 2.86, 2%); ^{13}C NMR δ 216.2 (0, C4), 212.7 (0, C1), 137.0 (0),

129.0 (2C, 1), 127.7 (1), 126.4 (2C, 1), 61.0 (0, C2), 43.7 (2, C5), 42.0 (1, C4), 20.8 (3, C2-methyl), 16.9 (3, C4-methyl).



63a

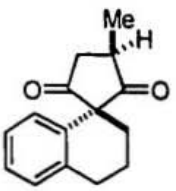


63b

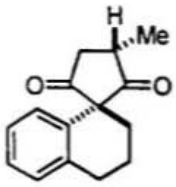
(2*R,4*R**)- (63a) and (2*R**,4*S**)-2',3'-Dihydro-4-methylspiro(cyclopentane-2,1'-[1*H*]indene)-1,3-dione (63b).** *(a)* A solution of 1-indanone (259 mg, 1.96 mmol), $BF_3 \cdot Et_2O$ (0.36 mL, 3.0 mmol), and **3** (1.45 g, 5.93 mmol) in CH_2Cl_2 (10.0 mL) was stirred at rt for 25 h. Work-up gave a yellow resin (853 mg). Chromatography (1/99 MeOH/ CH_2Cl_2) gave a viscous, yellow oil (261 mg, 62%) as a 1.8 : 1 mixture of **63a** and **63b**.

(b) To a solution of 1-indanone ethylene acetal (338 mg, 1.92 mmol) in CH_2Cl_2 (10 mL) at –78 °C was added $BF_3 \cdot Et_2O$ (0.35 mL, 2.8 mmol) and **3** (1.43 g, 5.85 mmol). After stirring at rt for 24 h, work-up gave a yellow resin (790 mg). Chromatography (1/99 MeOH/ CH_2Cl_2) gave a viscous, yellow oil (228 mg, 55%) as a 1 : 1.5 mixture of **63a** and **63b**. Further chromatography (20/80 EtOAc/petroleum ether) provided a small sample of each isomer for NMR analysis. For the **63a,b** mixture: IR 1765 (m), 1721 (s) cm^{-1}; MS 214 (77, M^+), 145 (12), 144 (100), 117 (13), 116 (85), 115 (75), 41 (12); HRMS calcd for $C_{14}H_{14}O_2$ 214.0993, found 214.0997. For **63a**: viscous, yellow oil; ^1H NMR δ 7.30 (1H, d, J = 8.0 Hz), 7.23 (1H, apparent t, J = 7.4 Hz), 7.15 (1H, apparent t, J = 7.2 Hz), 6.93 (1H, d, J = 7.7 Hz), 3.32 (1H, m, H5), 3.29–3.09 (3H, m, H4, H3'), 2.59–2.32 (2H, m, H2'), 2.49 (1H, m, H5), 1.37 (3H, d, J = 7.3 Hz, C4-methyl); ^{13}C NMR δ 214.9 (0, C3), 212.8 (0, C1), 144.6 (0), 141.0 (0), 128.1 (1), 126.7 (1), 125.2 (1), 122.2 (1), 69.5 (0, C2), 44.1 (2, C5), 41.6 (1, C4), 32.6 (2), 31.6 (2), 15.1 (3, C4-methyl).

For **63b**: viscous, pale yellow oil; ^{1}H NMR δ 7.30 (1H, d, J = 7.5 Hz), 7.24 (1H, apparent t, J = 7.2 Hz), 7.16 (1H, apparent t, J = 7.4 Hz), 6.83 (1H, d, J = 7.1 Hz), 3.26–3.09 (3H, m, H3', H5), 3.02 (1H, m, H4), 2.62 (1H, dd, J = 9.6, 18.0 Hz, H5 *syn* to phenyl), 2.49–2.26 (2H, m, H2'), 1.41 (3H, d, J = 6.8 Hz, C4-methyl); NOE data 6.83 (2.62, 1%), 2.62 (6.83, 2%; 3.19 dd, 6%; 3.02, 2%; 1.41, 1%), 1.41 (6.83, 2%; 3.02, 5%; 2.62, 4%); ^{13}C NMR δ 216.3 (0, C3), 212.7 (0, C1), 145.3 (0), 140.8 (0), 128.1 (1), 126.8 (1), 124.9 (1), 123.2 (1), 69.1 (0, C2), 44.5 (2, C5), 41.9 (1, C4), 35.6 (2), 31.5 (2), 15.1 (3, C4-methyl).



64a

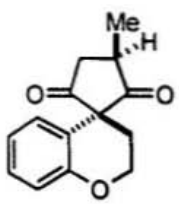


64b

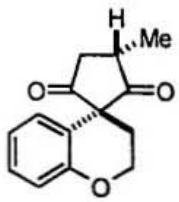
(2*R,4*R**)- (64a) and (2*R**,4*S**)-1',2',3',4'-Tetrahydro-4-methylspiro(cyclopentane-2,1'-naphthalene)-1,3-dione (64b).** *(a)* A solution of 1-tetralone (288 mg, 1.97 mmol), $BF_3{\cdot}Et_2O$ (0.36 mL, 2.9 mmol), and **3** (1.45 g, 5.92 mmol) in CH_2Cl_2 (5.0 mL) was stirred at rt for 22 h. Work-up gave a yellow resin (883 mg). Chromatography (0.5/99.5 MeOH/ CH_2Cl_2) gave a pale yellow oil (179 mg, 52%) as a 1.5 : 1 mixture of **64a** and **64b**. A second fraction (64 mg) consisting of both **64a** and **64b** (1.6 : 1) and 1-tetralone (87 % diketones, 13% 1-tetralone by GC-MS) was also obtained.

(b) To a solution of 1-tetralone ethylene acetal (356 mg, 1.87 mmol) in CH_2Cl_2 (10 mL) at –78 °C was added $BF_3{\cdot}Et_2O$ (0.35 mL, 2.8 mmol) and **2** (1.38 g, 5.64 mmol). After stirring at rt for 26 h, work-up gave a yellow resin (879 mg). Chromatography (0.5/99.5 MeOH/ CH_2Cl_2) gave a yellow oil (205 mg, 48%) as a 1 : 2.3 mixture of **64a** and **64b**. Further chromatography (20/80 EtOAc/petroleum ether) provided a small sample of each isomer for NMR analysis. For the **64a,b** mixture: IR 1763 (m), 1720 (s) cm^{-1}; MS 228 (81, M^+), 185 (18), 159 (12), 158 (88), 157 (13), 131 (21), 130 (100), 129 (90), 128 (61),

127 (26), 115 (62), 102 (12), 77 (16), 75 (10), 65 (10), 63 (10), 51 (15), 42 (12), 41 (24); HRMS calcd for $C_{15}H_{16}O_2$ 228.1149, found 228.1137. For **64a**: yellow resin; ^{1}H NMR δ 7.23–7.12 (2H, m), 7.08 (1H, m), 6.56 (1H, d, J = 7.6 Hz), 3.11 (1H, m, H5), 3.08–2.92 (2H, m, H4), 2.85 (2H, m, H4'), 2.69 (1H, br dd, J = 8.5, 16.1 Hz, H5), 2.14–1.79 (4H, m, H2', H3'), 1.45 (3H, d, J = 7.1 Hz, C4-methyl); ^{13}C NMR δ 217.0 (0, C3), 214.8 (0, C1), 138.4 (0), 132.2 (0), 129.9 (1), 127.9 (1), 127.5 (1), 126.3 (1), 61.5 (0, C1), 43.7 (1, C4), 43.2 (2, C5), 31.5 (2), 28.7 (2, C4'), 18.0 (2), 16.5 (3, C4-methyl). For **64b**: colorless resin; ^{1}H NMR δ 7.22-7.12 (2H, m), 7.09 (1H, m), 6.48 (1H, d, J = 7.8 Hz), 3.32 (1H, dd, J = 10.4, 18.3 Hz, H4), 3.20 (1H, m, H4), 2.84 (2H, m, H4'), 2.48 (1H, dd, J = 8.6, 18.3 Hz, H5 *syn* to methyl), 2.11–1.81 (4H, m, H2', H3'), 1.37 (3H, d, J = 6.6 Hz, C4-methyl); NOE data 2.48 (6.48, 1%; 3.32, 5%; 3.20, 3%), 1.37 (6.48, 2%; 3.20, 6%; 2.48, 4%); ^{13}C NMR δ 217.2 (0, C3), 213.9 (0, C1), 138.5 (0), 132.0 (0), 129.6 (1), 128.7 (1), 127.5 (1), 126.2 (1), 63.0 (0, C1), 44.6 (2, C5), 40.0 (1, C4), 32.1 (2), 28.7 (2, C4'), 18.0 (2), 15.4 (3, C4-methyl).



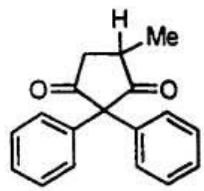
65a



65b

(2*R,4*R**)- (65a) and (2*R**,4*S**)-1',2',3',4'-Tetrahydro-4-methyl-4'-oxaspiro(cyclopentane-2,1'-naphthalene)-1,3-dione (65b).** A solution of 4-chromanone (214 mg, 1.44 mmol), $BF_3{\cdot}Et_2O$ (0.27 mL, 2.2 mmol) and **3** (1.06 g, 4.34 mmol) in CH_2Cl_2 (10 mL) was stirred at rt for 23 h. Work-up gave a bright yellow resin (622 mg). Chromatography (0.5/99.5 MeOH/ CH_2Cl_2) gave a pale yellow resin (164 mg, 49%) as a 1.2 : 1 mixture of **65a** and **65b**. Further chromatography (30/70 EtCAc/hexane) provided samples of each isomer for NMR analysis. For the **65a,b** mixture: IR 1766 (w), 1722 (s), 1606 (w), 1583 (w), 1227 (m) cm^{-1}; MS 230

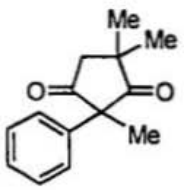
(42, M^+), 160 (46), 132 (33), 131 (100), 103 (15), 78 (10), 77 (19), 51 (12); HRMS calcd for $C_{14}H_{14}O_3$ 230.0942, found 230.0956. For **65a**: white resin; ^{1}H NMR δ 7.17 (1H, ddd, J = 1.5, 7.2, 8.4 Hz), 6.90 (1H, dd, J = 0.9, 8.3 Hz), 6.83 (1H, ddd, J = 1.3, 7.2, 7.8 Hz), 6.60 (1H, dd, J = 1.6, 7.8 Hz), 4.43 (1H, ddd, J = 4.2, 6.8, 11.3 Hz, H3'), 4.32 (1H, ddd, J = 4.0, 7.0, 11.3 Hz, H3'), 3.25–3.05 (2H, m, H5, H4), 2.64 (1H, m, H5), 2.06 (2H, m, H2'), 1.43 (3H, d, J = 7.0 Hz, C4-methyl); ^{13}C NMR δ 215.6 (0, C3), 213.5 (0, C1), 155.1 (0), 129.2 (1), 127.6 (1), 120.9 (1), 118.0 (1), 117.9 (0), 61.1 (2, C3'), 56.2 (0, C2), 43.4 (1, C4), 43.3 (2, C5), 28.9 (2), 16.0 (3, C4-methyl). For **65b**: white resin; ^{1}H NMR δ 7.19 (1H, m), 6.90 (1H, m), 6.85 (1H, m), 6.50 (1H, dd, J = 1.6, 7.8 Hz), 4.30 (2H, symmetric m, H3'), 3.31 (1H, dd, J = 10.5, 18.4 Hz, H5), 3.16 (1H, m, H4), 2.09 (2H, symmetric m, H2'), 2.56 (1H, dd, J = 9.1, 18.4 Hz, H5 *syn* to methyl), 1.41 (3H, d, J = 7.1 Hz, C4-methyl); NOE data 2.56 (6.50, 1%; 3.31, 7%, 3.16, 2%, 1.41, 1%), 1.41 (6.50, 2%; 3.16, 5%, 2.56, 3%); ^{13}C NMR δ 216.3 (0, C3), 212.7 (0, C1), 155.5 (0), 129.3 (1), 128.6 (1), 121.0 (1), 118.0 (0), 117.7 (1), 60.8 (2, C3'), 57.8 (0, C2), 44.7 (2, C5), 40.4 (1, C4), 29.9 (2), 15.3 (3, C4-methyl).



66

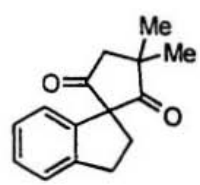
4-Methyl-2,2-diphenylcyclopentane-1,3-dione (66). A solution of benzophenone (268 mg, 1.47 mmol), $BF_3{\cdot}Et_2O$ (0.27 mL, 2.2 mmol), and **3** (1.08 g, 4.4 mmol) in CH_2Cl_2 (10 mL) was stirred at rt for 26 h. Work-up provided a yellow resin (670 mg). Chromatography (0.5/99.5 MeOH/ CH_2Cl_2) afforded **66** as a yellow solid (275 mg, 71%), mp 86.5–88.5 °C; IR (CCl_4) 1727 (s), 1600 (w), 1495 (m) cm^{-1}; ^{1}H NMR δ 7.40–7.27 (6H, m), 7.20–7.12 (2H, m), 7.30–6.95 (2H, m), 3.20 (1H, dd, J = 10.6, 17.9 Hz, H5), 3.07 (1H, m, H4), 2.54 (1H, dd, J = 8.7, 17.9 Hz, H5), 1.35 (3H, d, J = 7.0 Hz, C4-methyl); ^{13}C NMR δ

213.6 (0, C3), 210.7 (0, C1), 137.3 (0), 136.4 (0), 129.8 (1), 128.9 (1), 128.5 (1), 128.4 (1), 128.0 (1), 127.9 (1), 127.6 (1), 44.3 (2, C5), 41.8 (1, C4), 15.6 (3, C4-methyl); MS 264 (100, M^+), 221 (12), 194 (46), 167 (19), 166 (90), 165 (90); HRMS calcd for $C_{18}H_{16}O_2$ 264.1149, found 264.1161.



67

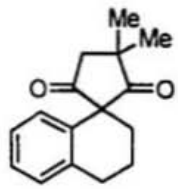
2,4,4-Trimethyl-2-phenylcyclopentane-1,3-dione (67). A solution of acetophenone (233 mg, 1.94 mmol), $BF_3{\cdot}Et_2O$ (0.72 mL, 5.8 mmol), and **4** (1.50 g, 5.80 mmol) in CH_2Cl_2 (10 mL) was stirred at rt for 21 h. Work-up gave a dark brown oil (846 mg). Chromatography (0.5/99.5 MeOH/ CH_2Cl_2) provided a tan-colored oil (356 mg) that was 90% **67** and 10% two isomeric compounds by GC-MS. Preparative layer chromatography (25/75 EtOAc/hexanes) afforded an analytical sample of **67** as a pale yellow oil; IR 1764 (m), 1724 (s), 1600 (w), 1494 (m) cm^{-1}; ^1H NMR δ 7.40–7.20 (5H, m, aryl), 2.77 (1H, d, J = 17.4 Hz, H5), 2.58 (1H, d, J = 17.4 Hz, H5), 1.47 (3H, s), 1.24 (3H, s), 1.23 (3H, s); ^{13}C NMR δ 218.3 (0, C3), 213.2 (0, C1), 137.4 (0, C1'), 129.1 (2C, 1), 127.7 (1), 126.2 (2C, 1), 60.9 (0, C2), 50.8 (2, C5), 46.9 (0, C4), 26.2 (3), 25.8 (3), 22.0 (3); MS 216 (70, M^+), 133 (14), 132 (100), 104 (70), 103 (12), 78 (10); HRMS calcd for $C_{14}H_{16}O_2$ 216.1149, found 216.1153.



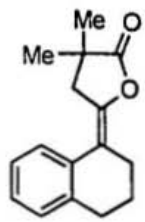
68

2',3'-Dihydro-4,4-dimethylspiro(cyclopentane-2,1'-[1*H*]indene)-1,3-dione (68). A solution of 1-indanone (260 mg, 1.96 mmol), $BF_3{\cdot}Et_2O$ (0.36 mL, 2.9 mmol), and **4** (1.55 g, 6.00 mmol) in CH_2Cl_2 (10 mL) was stirred at rt for 26 h. Work-up provided a viscous orange–brown oil (876 mg). Chromatography (1/99 MeOH/ CH_2Cl_2) gave **68** as a yellow solid (311 mg, 69%), mp 65–66.5 °C; IR 1764 (m), 1722 (s) cm^{-1}; ^1H NMR δ 7.28 (1H, apparent t, J =

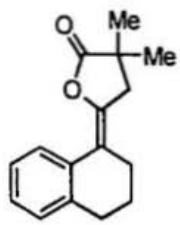
7.0 Hz), 7.23 (1H, apparent dt, J = 1.2, 7.4 Hz), 7.15 (1H, apparent t, J = 7.1 Hz), 6.85 (1H, d, J = 7.5 Hz), 3.18 (2H, m, H3'), 2.87 (1H, d, J = 17.7 Hz, H5), 2.76 (1H, d, J = 17.6 Hz, H5), 2.50–2.30 (2H, m, H2'), 1.39 (3H, s, C4-methyl), 1.30 (3H, s, C4-methyl); ^{13}C NMR δ 218.9 (0, C3), 213.0 (0, C1), 145.3 (0), 141.2 (0), 128.2 (1), 126.9 (1), 125.1 (1), 123.0 (1), 68.4 (0, C2), 51.5 (2, C5), 46.9 (0, C4), 36.2 (2, C2'), 31.8 (2, C3'), 25.8 (3, C4-methyl), 24.0 (3, C4-methyl); MS 228 (39, M^+), 145 (11), 144 (100), 116 (53), 115 (35); HRMS calcd for $C_{15}H_{16}O_2$ 228.1149, found 228.1149.



69



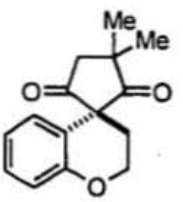
70a



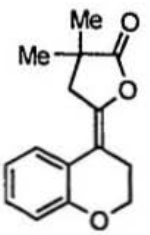
70b

1',2',3',4'-Tetrahydro-4,4-dimethylspiro(cyclopentane-2,1'-naphthalene)-1,3-dione (69) and 3,4-dihydro-3,3-dimethyl-5-(1-(1,2,3,4-tetrahydronaphthyl)idene)-2-furanone (70a,b). A solution of 1-tetralone (292 mg, 2.00 mmol), $BF_3{\cdot}Et_2O$ (0.37 mL, 3.0 mmol), and **4** (1.55 g, 6.0 mmol) in CH_2Cl_2 (10 mL) was stirred at rt for 24 h. Work-up gave a dark brown oil (929 mg). Chromatography (0.5/99.5 MeOH/ CH_2Cl_2) provided **69** pale yellow solid (312 mg, 65%), mp 97–98.5 °C and a yellow resin (75 mg, 15%) consisting of geometrical isomers **70a,b** in a 2.6 : 1 ratio. A small amount of the major isomer **70a** as a beige solid, mp 69–71.5 °C, was obtained in homogeneous form by preparative layer chromatography. For **69**: IR 1764 (m), 1719 (s), 1495 (w) cm^{-1}; ^{1}H NMR δ 7.24–7.04 (3H, m), 6.55 (1H, d, J = 7.8 Hz), 2.98 (1H, d, J = 18.3 Hz, H5), 2.85 (2H, apparent t, J = 6.0 Hz, H4'), 2.70 (1H, d, J = 18.3 Hz, H5), 2.10–1.88 (4H, m, H2', H3'), 1.44 (3H, s, C4-methyl), 1.34 (3H, s, C4-methyl); ^{13}C NMR δ 219.7 (0, C3), 214.6 (0, C1), 138.5 (0), 132.0 (0), 129.8 (1), 128.5 (1), 127.6 (1), 126.3 (1), 62.7 (0, C2), 50.7 (2, C5), 46.5 (0, C4), 32.7 (2),

28.7 (2, C4'), 26.6 (3, C4-methyl), 26.0 (3, C4-methyl), 18.0 (2); MS 242 (46, M^+), 159 (14), 158 (100), 130 (44), 129 (23), 128 (15), 115 (15); HRMS calcd for $C_{16}H_{18}O_2$ 242.1306, found 242.1300. For **70a**: UV (cyclohexane) 271 nm (ε = 7,730); IR 1795 (s), 1667 (m), 1600 (w) cm^{-1}; ^1H NMR δ 7.16 (4H, br s, aryl), 3.02 (2H, narrow m, H4), 2.74 (2H, m, H4'), 2.65 (2H, m), 1.80 (2H, apparent pentet, J = 6.4 Hz), 1.30 (6H, s, C3-methyls); NOE data 7.16 (3.02, 9%; 2.74, 4%), 3.02 (7.16, 24%; 1.30, 7%), 1.30 (3.02, 10%); ^{13}C NMR δ 179.8 (0, C2), 142.2 (0, C1'), 139.4 (0), 133.5 (0), 128.5 (1), 126.32 (1), 126.28 (1), 125.5 (1), 114.7 (0, C5), 41.9 (2, C4), 40.1 (0, C3), 30.4 (2, C4'), 25.2 (2), 24.8 (2C, 3, C3-methyls), 22.7 (2); MS 242 (29, M^+), 159 (13), 158 (100), 130 (58), 129 (39), 128 (23), 127 (10), 115 (30), 57 (11), 55 (14), 43 (12), 41 (24); HRMS calcd for $C_{16}H_{18}O_2$ 242.1306, found 242.1307. For **70b** (discernable signals from spectrum of mixture): ^1H NMR δ 8.07 (1H, br d, J = 7.5 Hz), 2.85 (2H, m, H4), 2.79 (2H, t, J = 6.2 Hz), 2.36 (2H, br t, J = 6.4 Hz), 1.86 (2H, apparent pentet, J = 6.3 Hz), 1.36 (6H, s, C3-methyls).

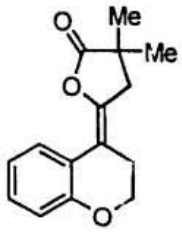


71



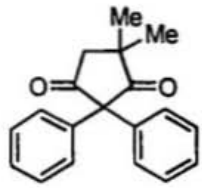
72a

1',2',3',4'-Tetrahydro-4,4-dimethyl-4-oxaspiro(cyclopentane-2,1'-naphthalene)-1,3-dione (71) and 3,4-dihydro-3,3-dimethyl-5-(1-(1,2,3,4-tetrahydro-4-oxanaphthyl)idene)-2-furanone (72a,b). A solution of 4-chromanone (306 mg, 2.07 mmol), $BF_3{\cdot}Et_2O$ (0.76 mL, 6.2 mmol), and **4** (1.60 g, 6.20 mmol) in CH_2Cl_2 (10 mL) was prepared at –78 °C. The mixture was then stirred at rt for 24 h. Work-up gave a black tar (968 mg). Chromatography (0.5/99.5 MeOH/ CH_2Cl_2) provided **71** as a tan- colored resin (196 mg, 39%), **72a,b** (2.6 : 1) as a tan resin (116 mg, 23%), and third fraction (94 mg) consisting of **71** and **72a,b** in a 4 : 1 ratio. A small

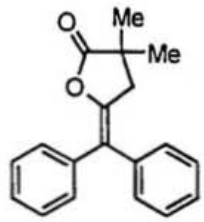


72b

amount of the major lactone **72a** as a white solid, mp 164-165 °C, was obtained in homogeneous form by repeated chromatography (0.5/99.5 MeOH/ CH_2Cl_2). For **71**: IR 1766 (m), 1722 (s), 1607 (m), 1583 (m), 1491 (m) cm^{-1}; ^1H NMR δ 7.18 (1H, ddd, J = 1.7, 7.2, 8.3 Hz), 6.90 (1H, dd, J = 1.2, 8.4 Hz), 6.84 (1H, apparent dt, J = 1.3, 7.5 Hz), 6.55 (1H, dd, J = 1.6, 7.8 Hz), 4.34 (2H, m, H3'), 2.95 (1H, d, J = 18.1 Hz, H5), 2.80 (1H, d, J = 18.2 Hz, H5), 2.11 (2H, m, H2'), 1.41 (3H, s, C4-methyl), 1.38 (3H, s, C4-methyl); ^{13}C NMR δ 220.6 (0, C3), 215.0 (0, C1), 156.1 (0, C5'), 135.9 (0, C10'), 129.6 (1), 128.6 (1), 121.1 (1), 117.9 (1), 59.9 (2, C3'), 56.2 (0, C2), 49.7 (2, C5), 45.5 (0, C4), 29.0 (2, C2'), 24.9 (3, C4-methyl), 23.9 (3, C4-methyl); MS 244 (37, M^+), 161 (11), 160 (100), 132 (56), 131 (100), 103 (14), 78 (10), 77 (19), 41 (12); HRMS calcd for $C_{15}H_{16}O_3$ 244.1099, found 244.1102. For **72a**: UV (cyclohexane) 302 nm (ε = 8,600), 272 nm (ε = 8,100); IR (CCl_4) 1791 (s), 1682 (m), 1604 (w), 1572 (w) cm^{-1}; ^1H NMR δ 7.14 (2H, m), 6.89 (2H, m), 4.23 (2H, t, J = 5.7 Hz, H3'), 3.08 (2H, br s, H4), 2.80 (2H, br t, J = 5.7 Hz, H2'), 1.35 (6H, s, C3-methyls); NOE data 3.08 (7.14, 23%; 1.35, 7%), 1.35 (3.08, 10%); ^{13}C NMR δ 179.3 (0, C2), 154.6 (0), 141.1 (0), 128.19 (1), 126.2 (1), 120.2 (1), 120.1 (0), 117.3 (1), 109.0 (0), 66.2 (2, C3'), 41.7 (2, C4), 40.0 (0, C3), 25.1 (2C, 3, C3-methyls), 24.5 (2, C2'); MS 244 (33, M^+), 161 (11), 160 (93), 132 (47), 131 (100), 103 (15), 83 (33), 77 (21), 55 (11), 41 (13); HRMS calcd for $C_{15}H_{16}O_3$ 244.1099, found 244.1112. For **72b** (discernable signals from spectra of mixture): ^1H NMR δ 8.09 (1H, dd, J = 1.6, 8.1 Hz), 2.85 (2H, br s, H4), 2.52 (2H, apparent t, J = 5.6 Hz), 1.37 (6H, s, C3-methyls); ^{13}C NMR δ 153.7 (0), 140.3 (0), 129.2 (1), 128.24 (1), 120.9 (1), 116.9 (1), 65.6 (2, C3'), 40.3 (2, C4), 26.2 (2, C2'), 25.2 (2C, 3, C3-methyls).

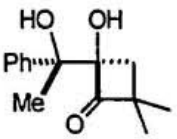


73

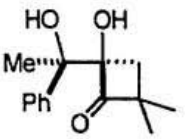


74

4,4-Dimethyl-2,2-diphenylcyclopentane-1,3-dione (73) and 3,4-dihydro-3,3-dimethyl-5-(diphenylmethylene)-2-furanone (74). A solution of benzophenone (240 mg, 1.32 mmol), $BF_3 \cdot Et_2O$ (0.49 mL, 4.0 mmol), and **4** (1.03 g, 4.0 mmol) in CH_2Cl_2 (6.6 mL) was prepared at –78 °C. The mixture was then stirred at rt for 23 h. Work-up provided a brown tar (652 mg). Chromatography (15/85 EtOAc/petroleum ether, then 0.5/99.5 MeOH/CH_2Cl_2) yielded **73** as a white solid (250 mg, 68%), mp 67-68 °C, and **74** as a pale yellow solid (58 mg, 16%), mp 111-113 °C. For **73**: IR (Nujol) 1764 (sh), 1723 (s), 1597 (w), 1580 (sh), 1493 (m) cm^{-1}; ^1H NMR δ 7.40–7.23 (6H, m), 7.15–7.03 (4H, m), 2.78 (2H, s, H5), 1.39 (6H, s, C4-methyls); ^{13}C NMR δ 216.4 (0, C3), 211.2 (0, C1), 137.4 (2C, 0), 128.7 (1), 127.8 (1), 51.3 (2, C5), 47.3 (0, C2), 26.1 (2C, 3, C4-methyls); MS 278 (41, M^+), 195 (12), 194 (75), 167 (14), 166 (100), 165 (28), 164 (62), 41 (14); HRMS calcd for $C_{19}H_{18}O_2$ 278.1306, found 278.1310. For **74**: UV (cyclohexane) 273 nm (ε = 10,000); IR (Nujol) 1803 (s), 1672 (m), 1599 (w), 1497 (w), 1076 (s) cm^{-1}; ^1H NMR δ 7.40–7.17 (10H, m, aryl), 2.77 (2H, s, H4), 1.33 (6H, s, C3-methyls); ^{13}C NMR δ 179.9 (0, C2), 144.1 (0, C1'), 138.8 (0), 137.5 (0), 130.0 (1), 129.4 (1), 128.5 (1), 128.0 (1), 127.2 (1), 126.9 (1), 119.3 (0), 41.6 (2, C4), 39.8 (0, C3), 24.7 (2C, 3, C3-methyls); MS 278 (16, M^+), 194 (38), 182 (27), 166 (44), 165 (4), 140 (35), 105 (100), 77 (67), 57 (12), 55 (14), 51 (30), 43 (10), 41 (16); HRMS calcd for $C_{19}H_{18}O_2$ 278.1306, found 278.1312.



76



77

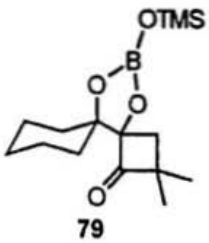
(1'*R,2*S**)- (76) and (1'*R**,2*R**)-4,4-Dimethyl-2-hydroxy-2-(1-hydroxy-1-phenylethyl)cyclobutanone (77).** A solution of acetophenone (0.41 g, 3.4 mmol) in CH_2Cl_2 (10 mL) was cooled to –78 °C before $BF_3{\cdot}Et_2O$ (0.42 mL, 3.4 mmol) and **4** (0.97 g, 3.7 mmol) were added. The temperature was raised to –20 °C, and the mixture was stirred for 29 h. The mixture was poured into H_2O, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, and concentrated under vacuum to give a yellow viscous oil (0.76 g) composed of acetophenone, **76**, **67**, and **77** in a ratio of 11 : 5.7 : 3.4 : 1 by ^1H NMR. Flash chromatography using an increasing proportion of EtOAc in hexanes provided **76** (167 mg, 21%) and **77** (29 mg, 4%). Major diastereomer **76**: white solid, mp 79.5–80.5 °C; IR 3456 (s), 1770 (s), 1602 (w), 1497 (m) cm^{-1}; ^1H NMR (CD_3OD) δ 7.45 (2H, d, J = 7.1 Hz), 7.29 (2H, apparent t, J = 7.4 Hz), 7.21 (1H, apparent t, J = 7.0 Hz), 2.35 (1H, d, J = 12.5 Hz, H3), 1.72 (1H, d, J = 12.5 Hz, H3), 1.64 (3H, s), 1.18 (3H, s), 0.51 (3H, s); ^{13}C NMR (CD_3OD) δ 219.7 (0, C1), 145.8 (0, C1'), 128.8 (2C, 1), 128.4 (2C, 1), 128.0 (1), 94.6 (0, C2), 76.1 (0, C2'), 55.2 (0, C4), 40.5 (2, C3), 25.5 (3), 25.0 (3), 20.8 (3); MS no M^+, 216 (8), 133 (10), 132 (100), 122 (16), 121 (19), 118 (10), 105 (20), 104 (45), 77 (23), 70 (25), 43 (86), 42 (11), 41 (12); HRMS calcd for $C_{14}H_{16}O_2$ (M^+ - H_2O) 216.1149, found 216.1155. Minor diastereomer **77**: white solid, mp 150–151.5 °C; IR (Nujol) 3392 (m), 1769 (m) cm^{-1}; ^1H NMR (CD_3OD) δ 7.57 (2H, d, J = 7.2 Hz), 7.29 (2H, apparent t, J = 7.4 Hz), 7.20 (1H, apparent t, J = 7.2 Hz), 2.33 (1H, d, J = 12.5 Hz, H3), 1.67 (3H, s), 1.47 (1H, d, J = 12.5 Hz, H3), 1.21 (3H, s), 1.02 (3H, s); ^{13}C NMR (CD_3OD) δ 221.0 (0,

C1), 146.4 (0), 128.6 (2C, 1), 128.0 (2C, 1), 127.9 (1), 94.0 (0, C2), 76.0 (0, C2'), 55.1 (0, C4), 40.6 (2, C3), 25.4 (3), 24.5 (3), 21.2 (3); MS no M^+, 216 (12), 133 (10), 132 (100), 121 (31), 118 (11), 105 (25), 104 (49), 78 (10), 77 (32), 70 (28), 51 (11), 43 (98), 42 (12), 41 (19); HRMS calcd for $C_{14}H_{16}O_2$ (M^+ - H_2O) 216.1149, found 216.1144. The relative stereochemistry of **77** was determined by X-ray crystallography.

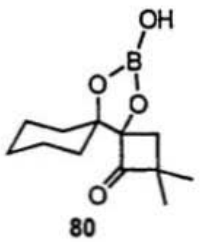
General procedure for the BCl_3-catalyzed reaction of ketones and 4. BCl_3 (3.2 mL) and then **3** (0.84 g, 3.2 mmol) were added to a solution of the ketone (2.0 mmol) in CH_2Cl_2 (5.0 mL) at –78 °C. This was stirred at –78 °C for 24 to 37 h, or at –22 °C for 6 to 8 h, or warmed to rt overnight. The mixture was recooled to –78 °C before a solution of 50% HF (1.6 mL) in MeOH (3.4 mL) was added, and the mixture was stirred for 10 min. The mixture was warmed to rt and stirred for 1 h. The mixture was concentrated under reduced pressure. The residue was stirred in TFA (6.0 mL) for 24 h. CH_2Cl_2 was added, and the solution was washed with H_2O, to which solid $NaHCO_3$ was added to give pH 7, and then the solution was dried over anhydrous granular Na_2SO_4. Concentration under vacuum gave brown material to which hexanes (50 mL) were added. The resulting solution was passed through Florisil (3 cm x 1.5 cm), flushing with additional hexanes (100 mL). Solvent evaporation from the combined filtrates gave the diketone product. Further purification, when necessary, was accomplished by flash chromatography. See Table 5 for specific reaction conditions for each substrate.

Table 5. Reaction products and conditions

Substrate	Product	Side-Product	Specific reaction conditions (based on the General Procedure)
Acetone	**17**	–	–78 °C for 23 h
Acetone	**87**		–78 °C for 23 h, aqueous work-up after HF step
2-Butanone	**20***	–	–78 °C for 37 h
Phenylacetone	**86**	**88a,b**	Reactants mixed at –78 °C, but the reaction was allowed to warm slowly to rt overnight
Acetophenone	**67**	**89**	Reactants mixed at –78 °C, but then reaction warmed to rt for 6 h. Ratio of **67** to **89** 3.8 : 1
Cyclopentanone	**33**	–	–78 °C for 36 h
3-Methylcyclopentanone	**25a,b**	–	Reactants mixed at –78 °C, but then reaction maintained –22 °C for 6 h
Cyclohexanone	**26**	–	–78 °C for 34 h
2-Methylcyclohexanone	**29a,b**	**30a,b**	Reactants mixed at –78 °C, but reaction warmed to rt and stirred overnight. Ratio of **29a,b** to **30a,b** 1 : 1
Bicyclo[2.2.1]heptanone	**33a**	–	Reactants mixed at –78 °C, but reaction allowed to warm slowly to rt overnight
Bicyclo[2.2.2]octanone	**35**	**90**	–78 °C for 15 min, –22 °C for 7 h. Ratio of **35** to **90** 1 : 1
Bicyclo[2.2.2]octanone	**35**	–	–78 °C for 15 min, –22 °C for 7 h, but then aqueous work-up before TFA
3-Methylcyclohexanone	**82**	–	–78 °C for 36 h
4-*t*-Butylcyclohexanone	**36a**	–	–78 °C for 29 h



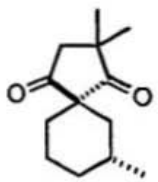
79



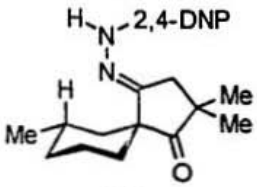
80

12-Bora-2,2-dimethyl-11,13-dioxa-12-(trimethylsilyloxy)-dispiro[3.0.5.3]triscadecan-1-one (79) and 12-bora-12-hydroxy-2,2-dimethyl-11,13-dioxadispiro-[3.0.5.3]triscadecan-1-one (80). Compound **3** (0.86 g, 3.3 mmol) was added over 5 min to a solution of cyclohexanone (0.20 g, 2.1 mmol) and BCl_3 (3.3 mL) in CH_2Cl_2 (5.0 mL) at –78 °C. The resulting solution was stirred at –78 °C for 11 h. Aqueous work-up, drying of the solution over anhydrous Na_2SO_4, and evaporation of the solvent gave a mixture of white solid (**47**, 127 mg) and a yellow oil (**79** and **80** in a 2 : 1 ratio, 459 mg). The sample consisting of just **79** and **80** was obtained by washing the oil off the solid with hexanes. For **79**: ^{1}H NMR δ 2.29 (1H, d, J = 13.2 Hz, H3), 2.07 (1H, d, J = 13.2 Hz, H3), 1.29 (3H, s, C2-methyl), 1.16 (3H, s, C2-methyl), 0.19 (9H, s, OTMS); ^{11}B NMR (CD_2Cl_2): δ 20.3; ^{13}C NMR (CD_2Cl_2) (partial data): δ 215.5 (0, C1), 99.3 (0), 88.1 (0), 82.3 (0), 39.6, 34.8, 34.5, 26.0, 24.1, 22.6, 22.3, 22.1, 0.97 (3C, 3); ^{29}Si NMR (CD_2Cl_2): δ 16.5. For **80**: ^{1}H NMR δ 2.32 (1H, d, J = 13.5 Hz, H3), 2.12 (1H, d, J = 13.5 Hz, H3), 1.30 (3H, s, C2-methyl), 1.18 (3H, s, C2-methyl); ^{11}B NMR (CD_2Cl_2): δ 21.9.

The mixture of **79** and **80** (0.584 g) was stirred in TFA (3.0 mL) at rt for 20 h. Work-up provided a brown oil (0.408 g). ^{1}H NMR analysis showed the presence of **26** and **27** (1.5 : 1).



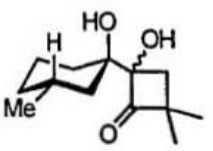
81



82

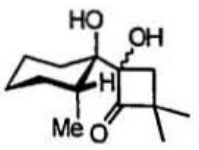
(5*R,7*S**)-2,2,7-Trimethylspiro[4.5]decane-1,4-dione (81).** Very pale yellow crystals from EtOAc-hexane; mp 59.5–61 °C; IR (Nujol) 1762 (m), 1722 (s) cm^{-1}; ^1H NMR δ 2.61 (2H, s, H3), 1.93 (1H, br m, H7), 1.81 (1H, m), 1.72 (1H, m), 1.68–1.55 (2H, m), 1.53 (1H, m), 1.48 (1H, apparent dq, J = 3.9, 12.9 Hz), 1.222 (3H, s, C2-methyl), 1.215 (3H, s, C2-methyl), 1.15 (1H, d, J = 13.2 Hz), 0.92 (1H, apparent dt, J = 4.8, 14.1 Hz), 0.86 (3H, d, J = 6.9 Hz, C7-methyl); ^{13}C NMR δ 220.1 (0, C1), 216.3 (0, C4), 56.0 (0, C5), 50.4 (2, C3), 46.4 (0, C2), 38.3 (2), 33.7 (2), 30.5 (2), 26.7 (1, C7), 25.5 (3, C2-methyl), 25.3 (3, C2-methyl), 22.4 (3, C7-methyl), 21.1 (2); MS 208 (M^+, 64), 152 (25), 140 (44), 139 (11), 125 (15), 124 (100), 96 (21), 95 (16), 82 (12), 81 (76), 69 (13), 68 (13), 67 (19), 56 (12), 55 (28), 54 (11), 53 (20), 41 (56), 40 (14); HRMS calcd for $C_{13}H_{20}O_2$ 208.1462, found 208.1454. For the 4-(2,4-dinitrophenylhydrazone) derivative **82**: orange crystals from MeCN-CH_2Cl_2–hexane, mp 231–233 °C; IR (Nujol) 3308 (m), 1742 (m), 1711 (w), 1614 (m), 1590 (m), 1517 (m), 1500 (m) cm^{-1}; ^1H NMR δ 11.11 (1H, br s), 9.14 (1H, d, J = 2.6 Hz), 8.39 (1H, dd, J = 2.5, 9.5 Hz), 7.88 (1H, d, J = 9.5 Hz), 2.77 (2H, s), 2.18–1.88 (2H, m), 1.82 (1H, m), 1.75–1.50 (4H, m), 1.33 (1H, apparent triplet, J = 12.8 Hz), 1.25 (3H, s), 1.24 (3H, s), 1.01 (1H, apparent dq, J = 3.4, 12.9 Hz), 0.92 (3H, d, J = 6.6 Hz); ^{13}C NMR δ 220.3 (0), 164.7 (0), 145.0 (0), 138.0 (0), 130.3 (1), 129.3 (0), 123.4 (1), 116.4 (1), 53.8 (0), 46.0 (0), 40.3 (2), 38.8 (2), 33.8 (2), 32.1 (2), 26.7 (1), 25.8 (2C, 3), 22.6 (3), 21.3 (2); MS 388 (M^+, 15), 320 (11), 319 (31), 273 (10), 206 (15), 167 (12), 165 (20), 164 (20), 138 (11), 122 (10), 107 (12), 105 (13), 95 (39), 94 (14), 93 (25), 83 (11), 82 (37), 81 (32), 80 (20), 79 (29), 78 (11), 77 (27), 69 (19), 68 (11), 67 (53), 66 (10), 65 (13), 63 (12), 56

(15), 55 (100), 54 (15), 53 (36), 52 (11), 43 (23), 42 (15), 41 (96); HRMS calcd for $C_{19}H_{24}N_4O_5$ 388.1770, found 388.1745. The structure was determined by X-ray crystallography.



83a,b

(1'*R,3'*R**)-2-Hydroxy-4,4-dimethyl-2-(1-hydroxy-3-methylcyclohexyl)-cyclobutanone (83a,b).** A 1 : 1 mixture of epimers (at C-2) was obtained by aqueous work-up after the HF/MeOH treatment. For this mixture: IR (Nujol) 3471 (s), 3342 (s), 1765 (s) cm^{-1}; ^1H NMR δ 3.44 (1H, br s, OH), 2.18 (1H, d, J = 12.8 Hz, H3), 2.17 (1H, d, J = 12.9 Hz, H3), 1.91 (2H, d, J = 12.8 Hz, H3), 1.87-1.84 (2H, m), 1.36 (6H, s, C4-methyl), 1.155 (3H, s, C4-methyl), 1.153 (3H, s, C4-methyl), 0.90 (6H, d, J = 6.4 Hz, C3'-methyl); ^{13}C NMR δ 220.0 (0, C1), 92.6 (0, C2), 92.5 (0, C2), 74.0 (0, C1'), 55.2 (0, C4), 38.6 (2, C3), 38.0 (2), 34.4 (2), 31.7 (2), 29.2 (2), 27.3 (1, C3'), 27.0 (1, C3'), 20.9 (2), 20.6 (2), 24.7 (3, C4-methyl), 22.5 (3, C3'-methyl), 20.9 (3, C4-methyl); MS no M^+, 208 (M^+ - H_2O, 8), 124 (100), 113 (35), 96 (28), 95 (50), 82 (10), 81 (72), 70 (38), 56 (10), 55 (15), 43 (26), 42 (12), 41 (14); HRMS calcd for $C_{13}H_{20}O_2$ (M^+ - H_2O) 208.1462, found 208.1454.

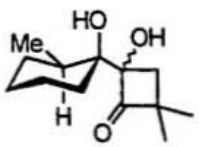


84

(1'*R,2x,2'*R**)-2-Hydroxy-4,4-dimethyl-2-(1-hydroxy-2-methylcyclohexyl)-cyclobutanone (84).** Yellow solid; mp 113.5–116 °C; IR 3461 (s), 1773 (m) cm^{-1}; ^1H NMR δ 3.60 (1H, br s, OH), 2.15 (1H, dd, J = 0.6, 12.8 Hz, H3), 2.00 (1H, d, J = 12.8 Hz, H3), 1.66 (1H, br m), 1.36–1.17 (8H, m), 1.37 (3H, s, C4-methyl), 1.16 (3H, s, C4-methyl), 1.00 (3H, d, J = 6.8 Hz, C2'-methyl); ^{13}C NMR δ 218.9 (0, C1), 94.4 (0, C2), 74.1 (0, C1'),

55.3 (0, C4), 39.0 (2, C3), 36.3 (1, C2'), 34.0 (2), 30.9 (2), 25.7 (2), 24.8 (3, C4-methyl), 21.5 (3, C4-methyl), 21.0 (2), 17.5 (3, C2'-methyl); MS 226 (M^+, 0.54), 208 ($M^+ - H_2O$, 9), 198 (16), 193 (16), 127 (11), 125 (15), 124 (100), 123 (17), 114 (11), 113 (74), 109 (83), 96 (78), 94 (58), 85 (20), 83 (16), 81 (50), 71 (14), 70 (50), 69 (44), 68 (18), 67 (44), 57 (32), 56 (20), 55 (41), 53 (13), 45 (21), 43 (91), 42 (18), 41 (67); HRMS calcd for $C_{13}H_{20}O_2$ ($M^+ - H_2O$) 208.1462, found 208.1440.

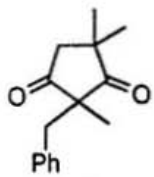
Stirring **84** (9 mg) in TFA (1 mL) at rt for 7 h provided only 2 mg of a brown oil, which consisted of a 1 : 1 mixture of **29a** and **30a,b** (1 : 1).



85

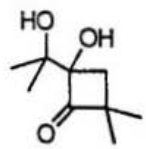
(1'*R,2x,2'*S**)-2-Hydroxy-4,4-dimethyl-2-(1-hydroxy-2-methylcyclohexyl)-cyclobutanone (85).** White solid; mp 139–141.5 °C; ^{1}H NMR δ 2.45 (1H, s, OH), 2.44 (1H, d, J = 12.3 Hz, H3), 1.84 (1H, d, J = 12.3 Hz, H3), 1.91 (1H, br m), 1.73–1.63 (2H, m), 1.63–1.47 (2H, m), 1.47–1.36 (4H, m), 1.35 (3H, s, C4-methyl), 1.20 (3H, s, C4-methyl), 1.03 (3H, d, J = 7.5 Hz, C2'-methyl); ^{13}C NMR δ 218.5 (0, C1), 94.3 (0, C2), 74.7 (0, C1'), 55.4 (0, C4), 38.4 (2, C3), 34.7 (1, C2'), 29.2 (2), 27.1 (2), 25.1 (3, C4-methyl), 21.3 (3, C4-methyl), 20.9 (2), 19.6 (2), 15.8 (3, C2'-methyl); MS 226 (M^+, 0.2), 208 (14), 193 (31), 139 (12), 127 (15), 125 (15), 124 (71), 123 (38), 121 (12), 113 (55), 109 (100), 96 (49), 95 (65), 85 (10), 83 (13), 81 (52), 71 (16), 70 (70), 69 (36), 68 (23), 67 (43), 57 (20), 56 (16), 55 (35), 45 (19), 43 (68), 42 (20), 41 (40); HRMS calcd for $C_{13}H_{22}O_3$ 226.1568, found 226.1568.

Diol **85** (11 mg) was dissolved in trifluoroacetic acid–d_1 at rt. ^{1}H NMR after only 5 min revealed rearrangement to **29b** was complete. Aqueous work-up provided **29b** as a yellow oil (10 mg).



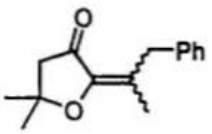
86

2-Benzyl-2,4,4-trimethyl-1,3-cyclopentanedione (86). Yellow oil; IR 1764 (m), 1724 (s), 1604 (w), 1496 (m) cm^{-1}; ^{1}H NMR δ 7.27–7.14 (3H, m), 7.08–6.98 (2H, m), 2.99 (1H, d, J = 12.8 Hz, benzyl), 2.92 (1H, d, J = 12.8 Hz, benzyl), 2.43 (1H, d, J = 18.4 Hz, H5), 1.74 (1H, d, J = 18.3 Hz, H5), 1.27 (3H, s), 1.12 (3H, s), 0.62 (3H, s); ^{13}C NMR δ 221.3 (0, C3), 216.9 (0, C5), 136.3 (0), 130.0 (2C, 1), 128.4 (2C, 1), 127.1 (1), 58.6 (0, C2), 51.8 (2, C5), 46.1 (0, C4), 42.5 (2, benzyl), 26.7 (3), 23.0 (3), 22.4 (3); MS 230 (M^+, 36), 146 (45), 145 (17), 118 (70), 117 (25), 115 (11), 105 (21), 91 (100), 83 (12), 65 (18), 56 (13), 55 (11), 41 (39); HRMS calcd for $C_{15}H_{18}O_2$ 230.1306, found 230.1314.



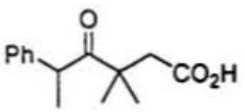
87

2-Hydroxy-2-(1-hydroxy-1-methylethyl)-4,4-dimethylcyclobutanone (87). White solid; mp 80–80.5 °C; IR (Nujol) 3448 (s), 3417 (s), 1773 (m) cm^{-1}; ^{1}H NMR δ 3.44 (2H, br s, OH), 2.13 (1H, d, J = 12.6 Hz, H3), 2.00 (1H, br, OH), 1.94 (1H, d, J = 12.6 Hz, H3), 1.37 (3H, s), 1.28 (3H, s), 1.23 (3H, s), 1.17 (3H, s); ^{13}C NMR δ 219.8 (0, C1), 92.2 (0, C2), 72.4 (0, C2'), 55.4 (0, C4), 39.0 (2, C3), 25.3 (3), 24.7 (3), 22.9 (3), 20.9 (3); MS 154 no M^+, (M^+- H_2O, 5), 71 (10), 70 (100), 59 (26), 43 (12), 42 (24); HRMS calcd for $C_9H_{14}O_2$ (M^+- H_2O) 154.0993, found 154.0986.



88a,b

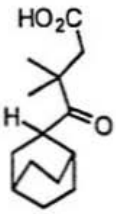
5,5-Dimethyl-2-(phenylisopropylidene)-3(*2H*)-furanone (88a,b). A 1 : 1 (*E*)/(*Z*) mixture of 3-furanones was obtained in 15% yield as a side-product in the reaction that provided **18**. UV (cyclohexane) 290 nm, (ε=10,700); IR 1724 (s), 1639 (s), 1602 (m), 1494 (m) cm^{-1}; ^1H NMR δ 7.31–7.14 (5H, m, aryl), 3.95, 3.48 (each 2H, s, benzyl), 2.56, 2.53 (each 2H, s, H4), 1.99, 1.70 (each 3H, s, C2'-methyl), 1.43, 1.42 (each 6H, s, C5-methyls); ^{13}C NMR δ 200.5 (0, C2), 200.0 (0, C2), 144.0 (0, C2'), 143.4 (0, C2'), 139.8 (0), 139.2 (0), 128.8 (1), 128.7 (1), 128.24 (1), 128.18 (1), 126.02 (1), 125.91 (1), 122.6 (0, C3), 122.2 (0, C3), 78.5 (0, C5), 78.3 (0, C5), 50.7 (2, C4), 39.2 (2, benzyl), 35.7 (2, benzyl), 28.30 (3, C5-methyl), 28.25 (3, C5-methyl), 17.1 (3, C2'-methyl), 14.6 (3, C2'-methyl); MS 230 (M^+, 74), 174 (14), 146 (42), 145 (41), 131 (18), 119 (12), 118 (100), 117 (53), 116 (10), 115 (23), 105 (31), 103 (11), 91 (51), 83 (11), 78 (16), 77 (12), 69 (10), 65 (14), 58 (10), 55 (11), 51 (11), 43 (11), 41 (39).



89

3,3-Dimethyl-4-oxo-5-phenylhexanoic acid (89). White solid; mp 132–133 °C; IR (Nujol) 3500–2400 (m), 1713 (m) cm^{-1}; ^1H NMR δ 11.5 (1H, very br, OH), 7.41–7.30 (2H, m), 7.26 (1H, apparent tt, J = 1.5, 7.2 Hz, H4'), 7.22–7.15 (2H, m), 3.70 (1H, q, J = 7.0 Hz, H5), 2.72 (1H, d, J = 17.9 Hz, H2), 2.58 (1H, d, J = 17.9 Hz, H2), 1.38 (3H, d, J = 7.0 Hz, C5-methyl), 1.17 (3H, s, C3-methyl), 1.11 (3H, s, C3-methyl); ^{13}C NMR δ 208.4 (0, C4), 182.1 (0, C1), 140.3 (0, C1'), 128.9 (2C, 1), 127.9 (2C, 1), 127.2 (1, C4'), 53.1 (1, C5), 50.4 (2, C2), 39.8 (0, C3), 25.9 (3, C3-methyl), 24.5 (3, C3-methyl), 17.3 (3, C5-methyl); MS no M^+, 217 (M^+-OH, 2), 216 (M^+- H_2O, 8), 132 (15), 129 (16), 106 (92), 105 (63), 104 (15), 103 (11), 101 (50),

91 (21), 79 (12), 77 (19), 59 (100), 55 (10), 43 (44); HRMS calcd for $C_{14}H_{17}O_2$ (M^+- OH) 217.1228, found 217.1226; calcd for $C_{14}H_{16}O_2$ (M^+- H_2O) 216.1149, found 216.1155.



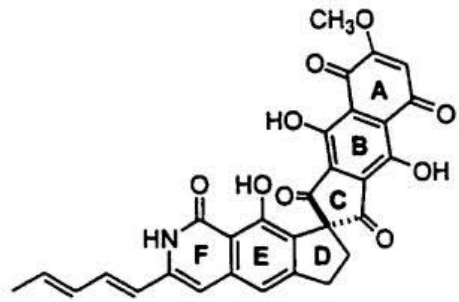
90

4-(2-Bicyclo[2.2.2]octyl)-3,3-dimethyl-4-oxobutanoic acid (90). The General Procedure with bicyclo[2.2.2]octanone gave a 1 : 1 mixture of a tan-colored oil (**35**) and a white solid (**90**) that isolated by repeated washings with hexanes to remove the oily fraction, followed by recrystallization from hexanes-CH_2Cl_2: mp 156.5–157 °C; IR (Nujol) 3600–2200 (m), 1704 (s) cm^{-1}; ^1H NMR δ 2.82 (1H, d, J = 17.8 Hz, H2), 2.68 (1H, d, J = 17.8 Hz, H2), 2.60 (1H, m), 2.04 (1H, apparent dt, J = 2.2, 6.4 Hz), 2.00 (1H, apparent dt, J = 2.2, 6.3 Hz), 1.90 (1H, m), 1.69–1.57 (2H, m), 1.57–1.44 (3H, m), 1.42 (1H, m), 1.40–1.34 (2H, m), 1.32 (1H, m), 1.26 (3H, s, C3-methyl), 1.24 (3H, s, C3-methyl); ^{13}C NMR δ 210.4 (0, C4), 183.6 (0, C1), 50.7 (2, C2), 49.5 (1), 39.9 (0, C3), 27.2 (1), 26.7 (2), 26.4 (2), 25.6 (3, C3-methyl), 25.3 (3, C3-methyl), 25.2 (2), 25.0 (2), 23.8 (1), 21.4 (2); MS 238 (M^+, 1), 220 (28), 157 (36), 139 (27), 137 (15), 136 (71), 136 (71), 133 (11), 129 (12), 111 (13), 110 (12), 109 (100), 108 (10), 107 (19), 101 (29) , 94 (10), 93 (15), 92 (40), 91 (12), 88 (46), 83 (21), 81 (18), 80 (20), 79 (41), 77 (14), 67 (93), 59 (52), 55 (33), 53 (14), 43 (37), 41 (46); HRMS calcd for $C_{14}H_{22}O_3$ 238.1568, found 238.1573; calcd for $C_{14}H_{20}O_2$ (M^+-H_2O) 220.1462, found 220.1464.

Chapter 2. Model Studies Aimed Toward an Enantioselective Synthesis of the Antitumor Antibiotic Fredericamycin A.

Introduction

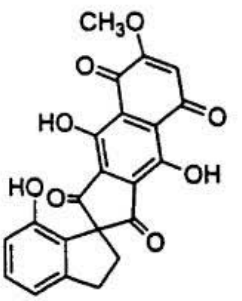
The antitumor antibiotic fredericamycin A was first isolated by Pandey *et al.* from a strain of the soil bacterium *Streptomyces griseus* at the National Cancer Institute in Frederick, Maryland, in 1981.[18,19] Single-crystal X-ray diffraction pattern[20] analysis was successful in establishing its structure after extensive spectroscopic studies failed to resolve tautomeric forms in the ABC subunit.[21] Central to its novel molecular architecture is the carbocyclic spiro[4.4]nonane subunit previously unknown to compounds in the antibiotic or antitumor classes.



(+)-**91** : Fredericamycin A

Fredericamycin A exhibits potent *in vitro* cytotoxicity as well as efficacious antitumor activity in a variety of tumor models such as P388 leukemia, CD8F mammary and B16 melanoma and fredericamycin A does not show mutagenicity in the Ames test.[22] The origin of the antibiotic and antitumor properties of **91** appears to be through inhibition of RNA and protein biosynthesis.[22] Although studies on the single-electron oxidation of fredericamycin A and its role in the generation of oxygen free radicals

initially supported an indiscriminate mode of action,[23] more recent investigations[24] have disputed these findings. It has since been determined that fredericamycin A inhibits DNA topoisomerases I and II at biologically relevant concentrations (total inhibition at 4.4 and 7.4 μm, respectively) and DNA polymerase α at higher concentrations (IC_{50} 93 μm).[24] The finding that **91** may not act directly or detectably with DNA[22] suggests direct enzyme inhibition or selective stabilization of a tertiary complex of DNA, topoisomerase and **91**.[26b] The observation that an analogue of **91** lacking the functionalized F ring (**92**) was approximately 100 times less potent has shed further doubt on the hypothesis that the indescriminate redox properties of **91** are solely responsible for its biological activity.[27,28] This promising biological profile and the unique structure of **91** have made it quite attractive as a lead compound for a new type of chemotherapeutic drug for human cancers.



92

The synthetically challenging spiro[4.4]nonane subunit has been the subject of extensive synthetic efforts as evidenced by the large number of model studies aimed at its construction.[28] To date, these studies have culminated in six total syntheses[11b,c,26,28a,30,31] of **91** in racemic form and very recently an asymmetric synthesis[32] of fredericamycin A. At the time when we began work in this area, an enantioselective synthesis of **91** had yet

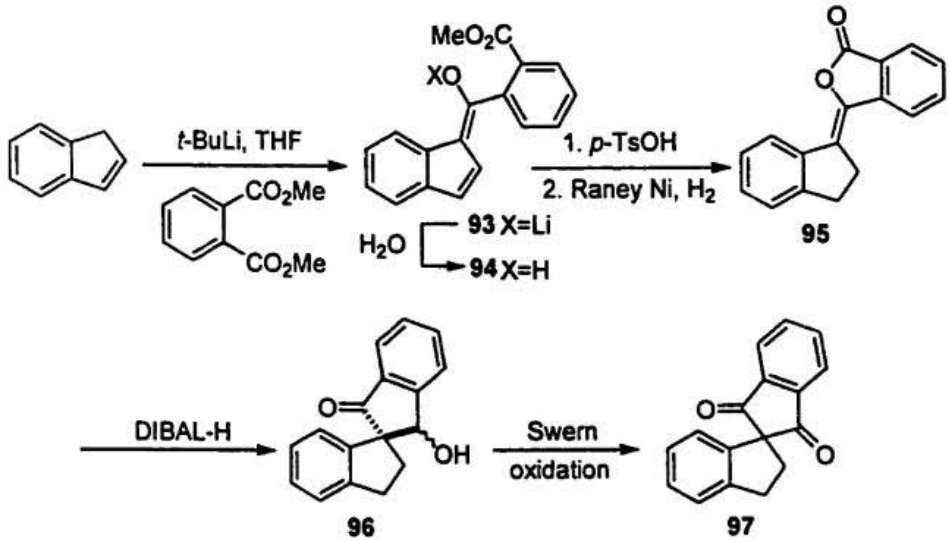
to be reported, and the configuration of the single stereogenic center in **91** was unknown. In the interest of resolving these issues we devised two potentially highly enantioselective routes to **91**. One relied on a novel silicon-tethered [2 + 2] photocycloaddition and the other a regiochemically controlled Diels-Alder reaction for assembly of the AB portion of **91**. Construction of the spiro[4.4]nonane system was to employ the geminal acylation methodology developed in our laboratory.[2,3,6] Before detailing the retrosynthetic analysis that led to the formulation of these synthetic plans and the results of synthetic studies using model systems, a review of the chemical literature dealing with the synthesis of **91** is presented below.

Literature Review - Strategies for the Synthesis of Fredericamycin A

The large majority of exploratory synthetic work on **91** has focused on the construction of the spiro CD linkage. Numerous partial structures differing in the levels of oxygenation in the B, D and E rings have been prepared using a variety of strategies. Several of these preliminary studies have culminated in total syntheses of fredericamycin A.

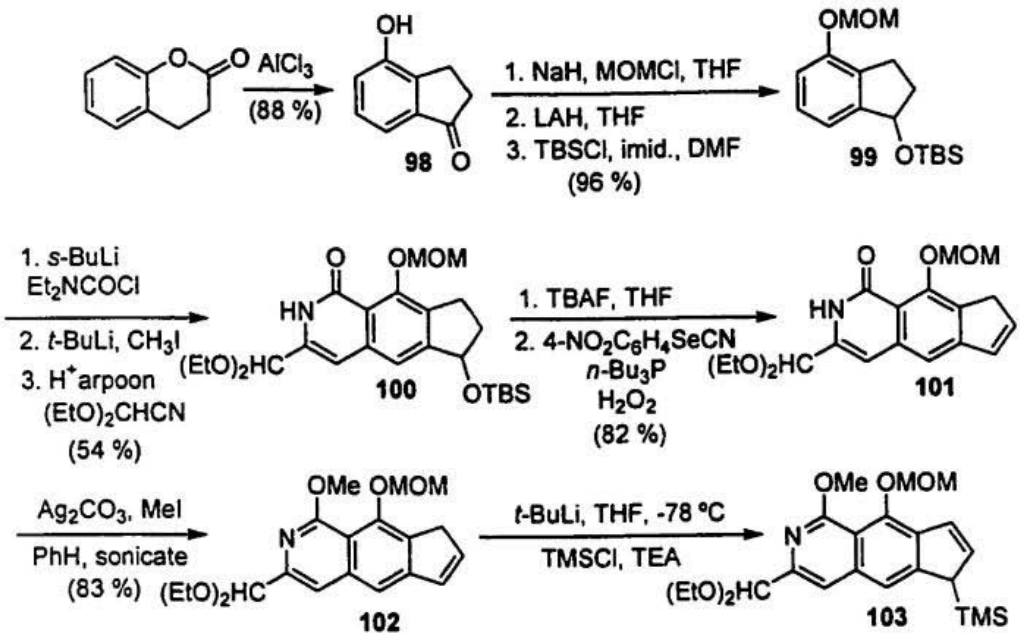
Bis-Functionalization of Intact DE Synthons. Ross Kelly was the first to explore the popular strategy of forming the spiro CD linkage by bis-acylation of an indenyl anion (Scheme 1a).[28a] The initial attack of lithiated indene on dimethyl phthalate proceeded smoothly to give **93**. However, the anticipated Dieckmann condensation did not occur to form the C ring. Work-up provided **94** as a mixture of tautomeric forms that could not be cyclized directly under a variety of acidic or basic conditions. Treatment of **94** with *para*-toluenesulfonic acid (*p*-TsOH) followed by selective hydrogenation of the endocyclic alkene gave lactone **95**. Treatment of **95** with diisobutylaluminum hydride (DIBAL-H) generated a keto-enolate that underwent the desired cyclization reaction to provide **96** as a stereoisomeric mixture of ketols. Swern oxidation (oxalyl chloride, dimethyl sulfoxide (DMSO), -78 °C, triethylamine (TEA)) afforded the desired dione **97**. No yields were reported for any of these transformations.

Scheme 1a

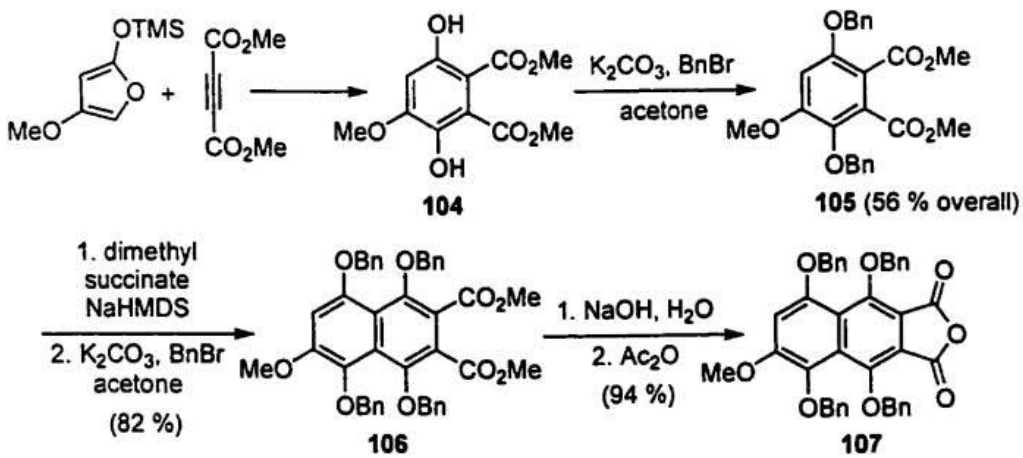


Kelly successfully applied this strategy to the first total synthesis of **91** (Schemes 1b-1d) in 17 steps from dihydrocoumarin and methyl tetronate in 3.3 % overall yield.[28a,29] The propensity of lithiated indene **102** to react from the undesired terminus of the allylic anion system necessitated modification of his initial plan. Success was achieved by conversion of **102** to regioisomeric **103** by trapping with chlorotrimethylsilane before repeated lithiation (**108**) and reaction with phthalate **107**.

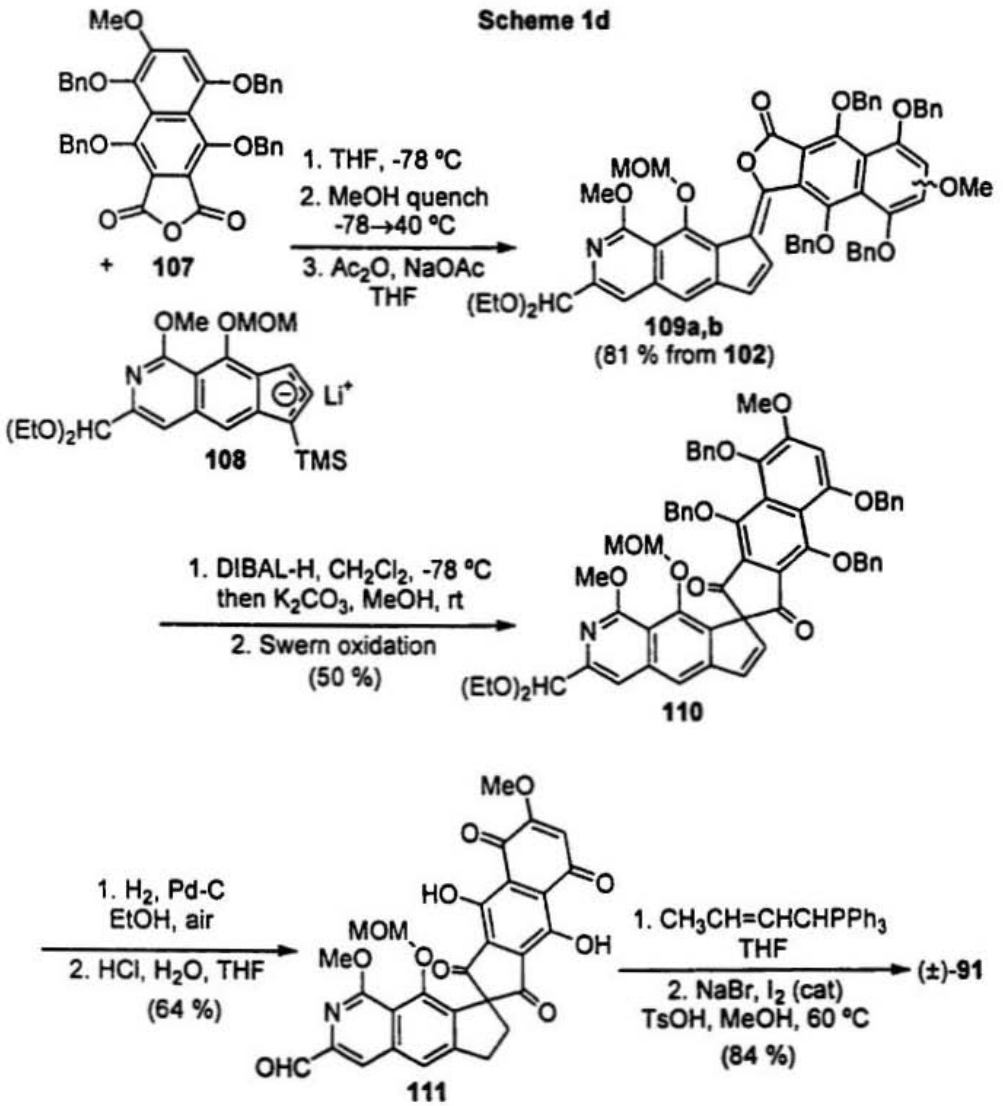
Scheme 1b



Scheme 1c

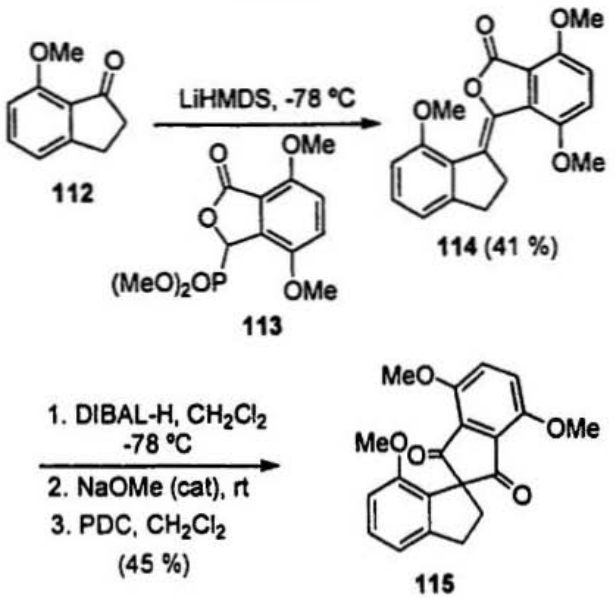


Scheme 1d



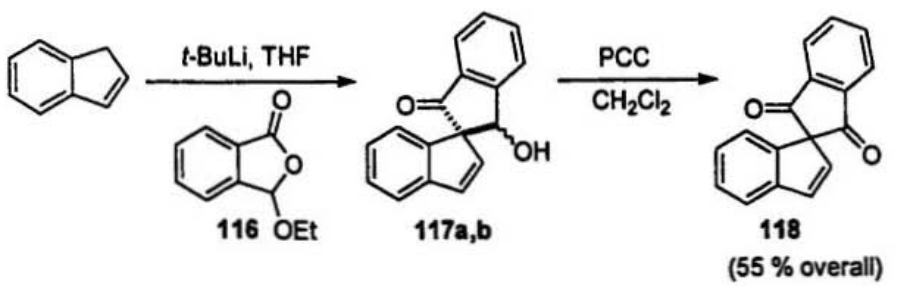
Watanabe (Scheme 2) prepared 3-(1'-indanylidene)phthalide **114** using a Horner-Wadsworth-Emmons reaction between indanone **112** and phosphonate **113**.[28b] Reduction of **114** using DIBAL-H followed by addition of a catalytic amount of sodium methoxide invoked the intramolecular aldol spirocyclization to form the C ring. Oxidation of the resulting mixture of stereoisomeric spiroketoalcohols with pyridinium dichromate (PDC) afforded the fully oxygenated BCDE core fragment **115**.

Scheme 2



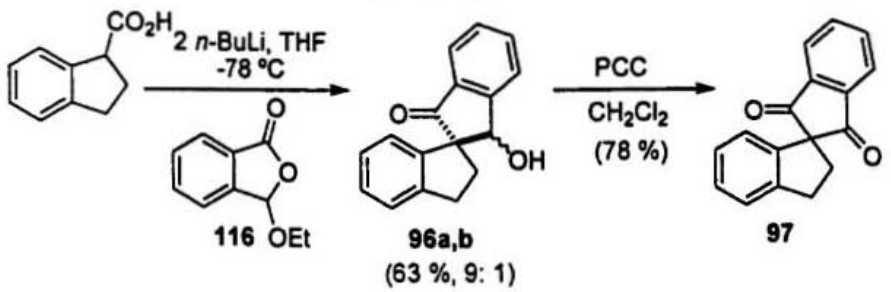
Kessar formed spiro model **118** in a single operation by using phthalide **116** (Scheme 3).[28c] Attack of the indenyl anion onto the lactone carbonyl with concomitant expulsion of ethoxide generated a keto-aldehyde. The lithium ethoxide liberated in the initial process subsequently effected an intramolecular aldol reaction to give **117a,b**. Oxidation with pyridinium chlorochromate (PCC) afforded core fragment **118** in 55 % overall yield.

Scheme 3



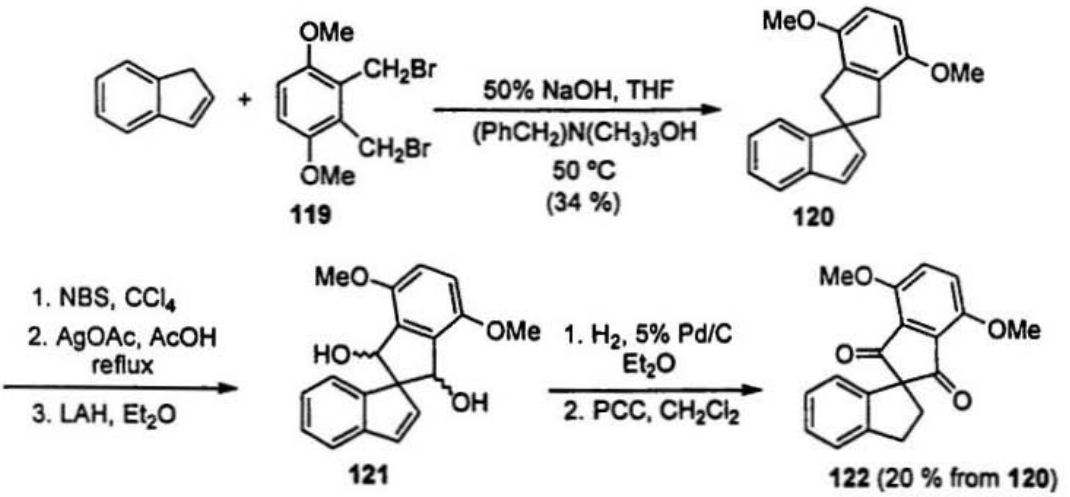
Braun constructed the spiro CD linkage via a tandem Claisen-decarboxylation-aldol reaction between indanecarboxylic acid and **116** (Scheme 4).[28d] PCC oxidation of the resulting 9:1 mixture of keto-alcohol diastereomers (**96a,b**) gave **97** in 49% overall yield for this short sequence.

Scheme 4



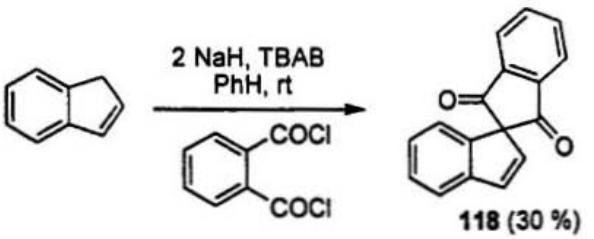
Julia reported the bis-alkylation of indene with dibromide **119** under conditions of phase-transfer catalysis (Scheme 5).[28e] Introduction of the required oxygen functionality into the C ring of **120** was accomplished by benzylic bromination with *N*-bromo-succinimide (NBS), halide displacement from the 1,3-dibromide with silver acetate and reduction of the resulting diacetate to the diol (**121**) with lithium aluminum hydride (LAH). Hydrogenation of the double bond followed by PCC oxidation afforded dione **122** in 20 % overall yield.

Scheme 5



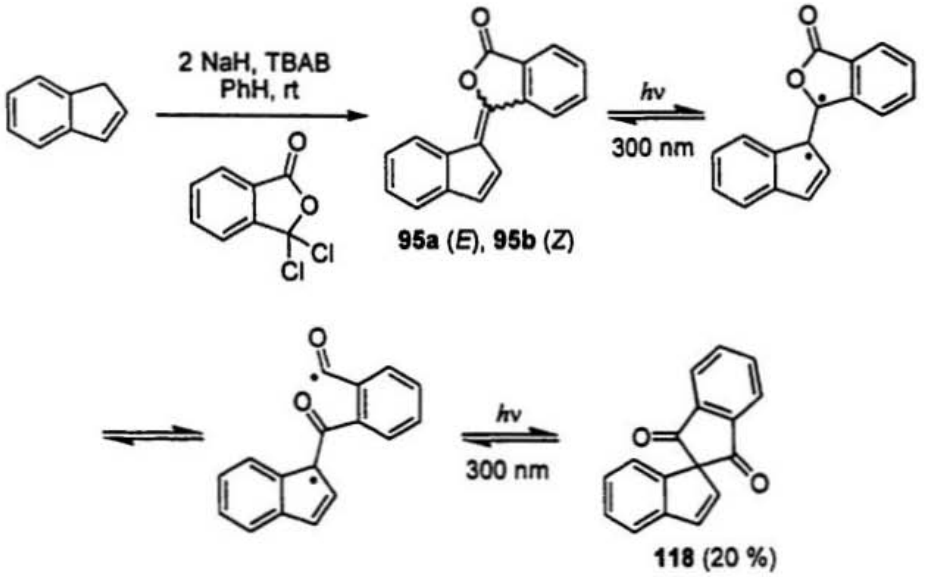
Ayyangar demonstrated that direct bis-acylation of a metallated indene to give **118** can occur in modest yield using the more reactive phthaloyl chloride in the presence of tetra-*n*-butylammonium bromide (TBAB) (Scheme 6).[28f]

Scheme 6



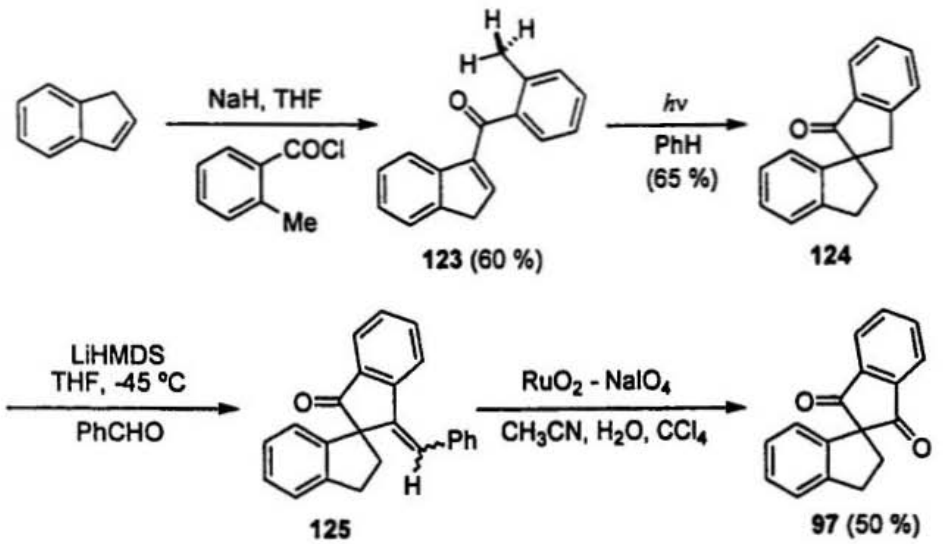
Ayyangar also prepared 3-(1'-indanylidene)phthalides **95a,b** that had previously been shown to undergo rearrangement to **118** on treatment with DIBAL-H. He subsequently demonstrated that it was possible to accomplish the formation of **118** from **95a,b** photochemically (Scheme 7).[28f] Longer irradiation times resulted in the same photostationary mixture (**95a** : **95b** : **118**, 20 %, 50 %, 20 % isolated yields).

Scheme 7



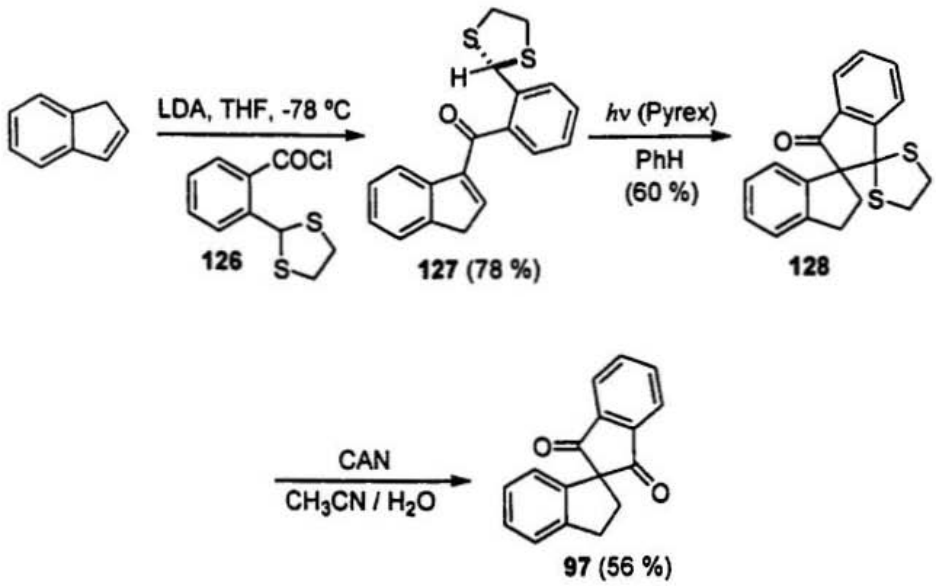
Mehta (Scheme 8) constructed BCDE subunit **97** using a novel photochemical 1,6-H abstraction/5-exo-trig radical spirocyclization strategy.[28g]

Scheme 8



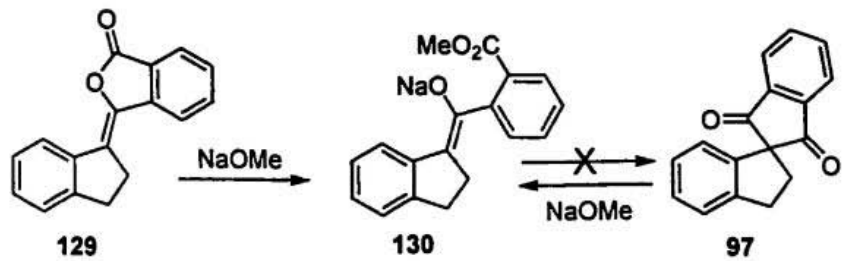
Pandey (Scheme 9) later reported a more efficient approach employing thioacetal **127**.[28h]

Scheme 9



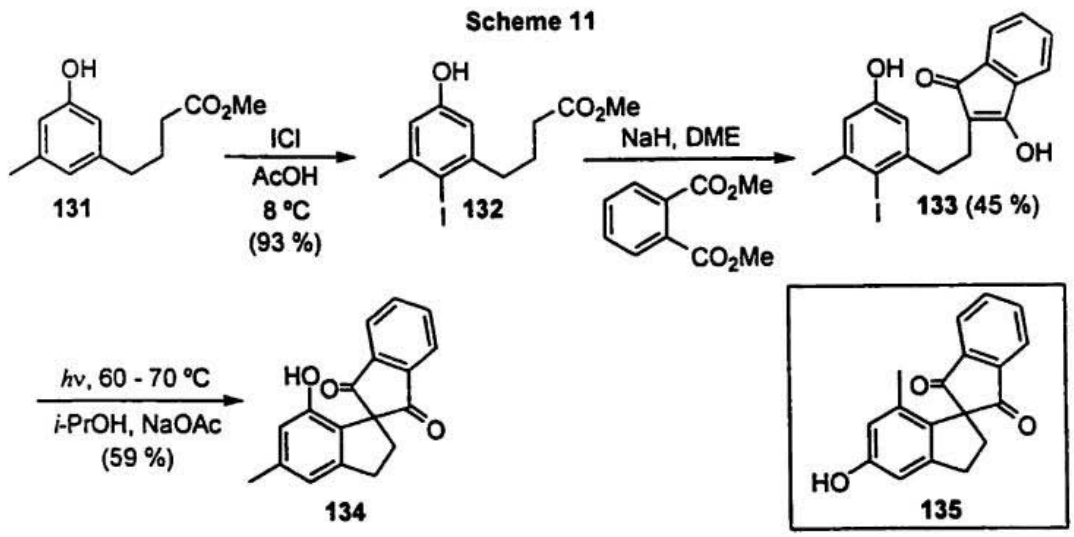
D-ring Annelation Strategies. The failure of Kelly's Dieckmann condensation tactic for the direct formation of the C ring dione from an acylated indene was likely a consequence of the stability of the intermediate enolate coupled with the low reactivity of the conjugated ester moiety in **130** (Scheme 10). The discovery that this reaction proceeds readily in similar systems lacking an intact D ring has led to the development of several D ring annelation strategies for final assembly of the spiro[4.4]nonane subunit.

Scheme 10



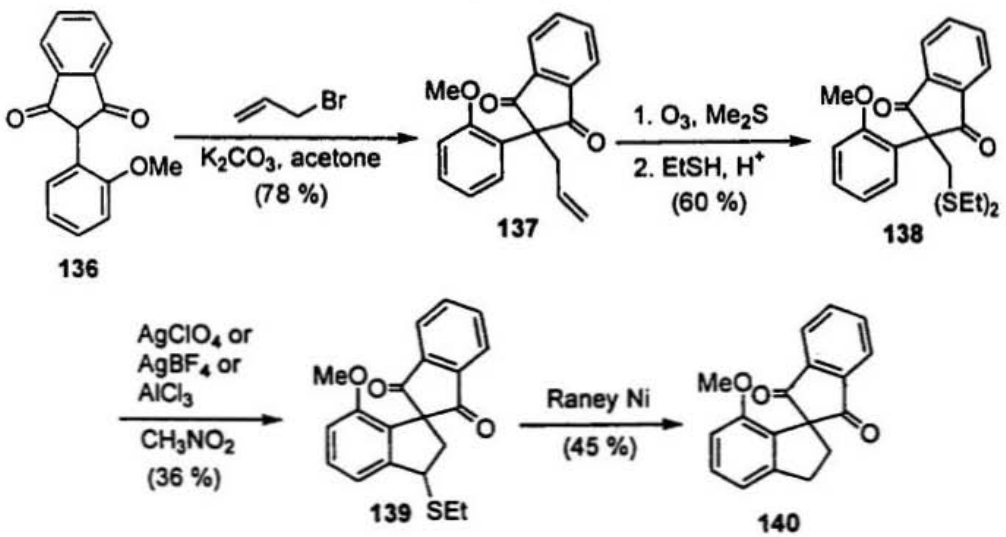
Kende reported the synthesis of BCDE fragment **134** employing a 5-exo-trig phenoxy-enoxy coupling.[28i] C ring assembly was accomplished with a tandem Claisen-decarboxylation-Dieckmann reaction between **132** and dimethyl phthalate. Photolysis of the *p*-iodophenol generated a delocalized radical that participated in a 5-exo-trig cyclization *ortho* to the phenolic oxygen onto the enol-tautomer of the 1,3-dione to provide **134** in 59 % yield. Interestingly, oxidative cleavage of the C-I bond with Na_2CO_3/K_3FeCN_6 gave only 8 % of **134**. The major product **135** (67 %) arose from the corresponding coupling *para* to the phenolic oxygen in **133**.

Scheme 11



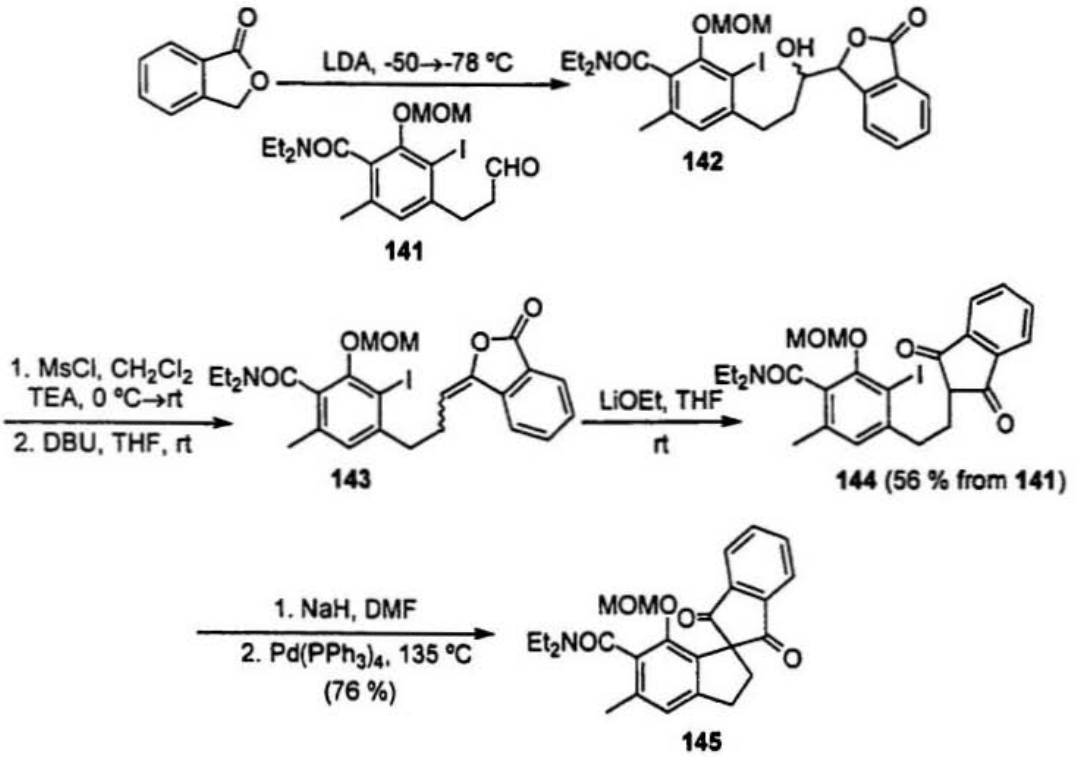
Starting from the known indane-1,3-dione **136**, available from phthalic anhydride and 2-methoxyphenylacetic acid, Braun prepared thioacetal **138** (Scheme 12).[28j] **138** participated in an intramolecular Friedel-Crafts type reaction upon treatment with either of the indicated Lewis acids to give thioether **139**. Raney nickel desulphurization provided BCDE dione **140**.

Scheme 12



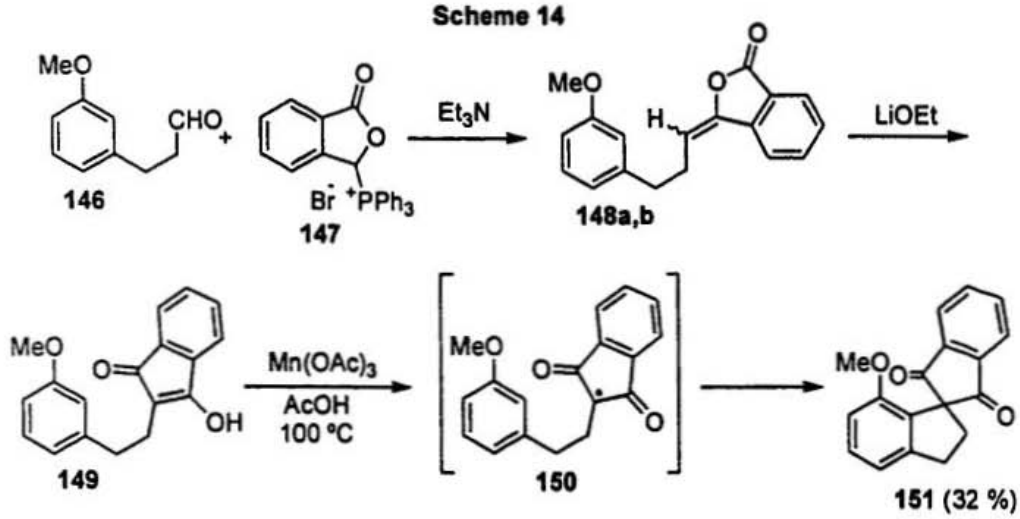
Ciufolini prepared BCDE fragment **145** using a palladium promoted intramolecular arylation of β-diketone **144** (Scheme 13).[28k] Addition of lithium phthalide to aldehyde **141** provided alcohol **142**. Base-induced elimination of the corresponding mesylate gave 3-alkylidenephthalide **143**. Smooth conversion to β-diketone **144** was effected with LiOEt in THF. Oxidative addition of the sodium enolate of **144** to Pd^0 followed by heating to 135 °C resulted in intramolecular reductive coupling with regeneration of Pd^0 to give **145** in 76 % yield.

Scheme 13



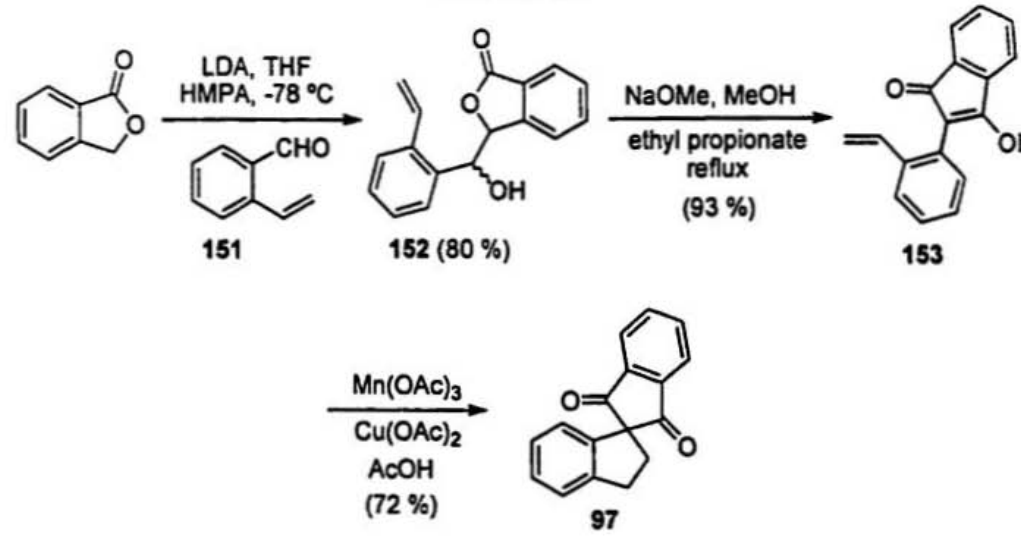
A similar strategy was used by Narasimhan in the synthesis of BCDE model **151** (Scheme 14).[281] The 3-alkylidenephthalide substrate (**148a,b**) for the Dieckmann condensation was prepared in this case by Wittig olefination of aldehyde **146** with phosphonium salt **147**. Treatment of **149** with $Mn(OAc)_3$ in hot acetic acid induced the intramolecular arylation reaction to give **151** via **150**.

Scheme 14



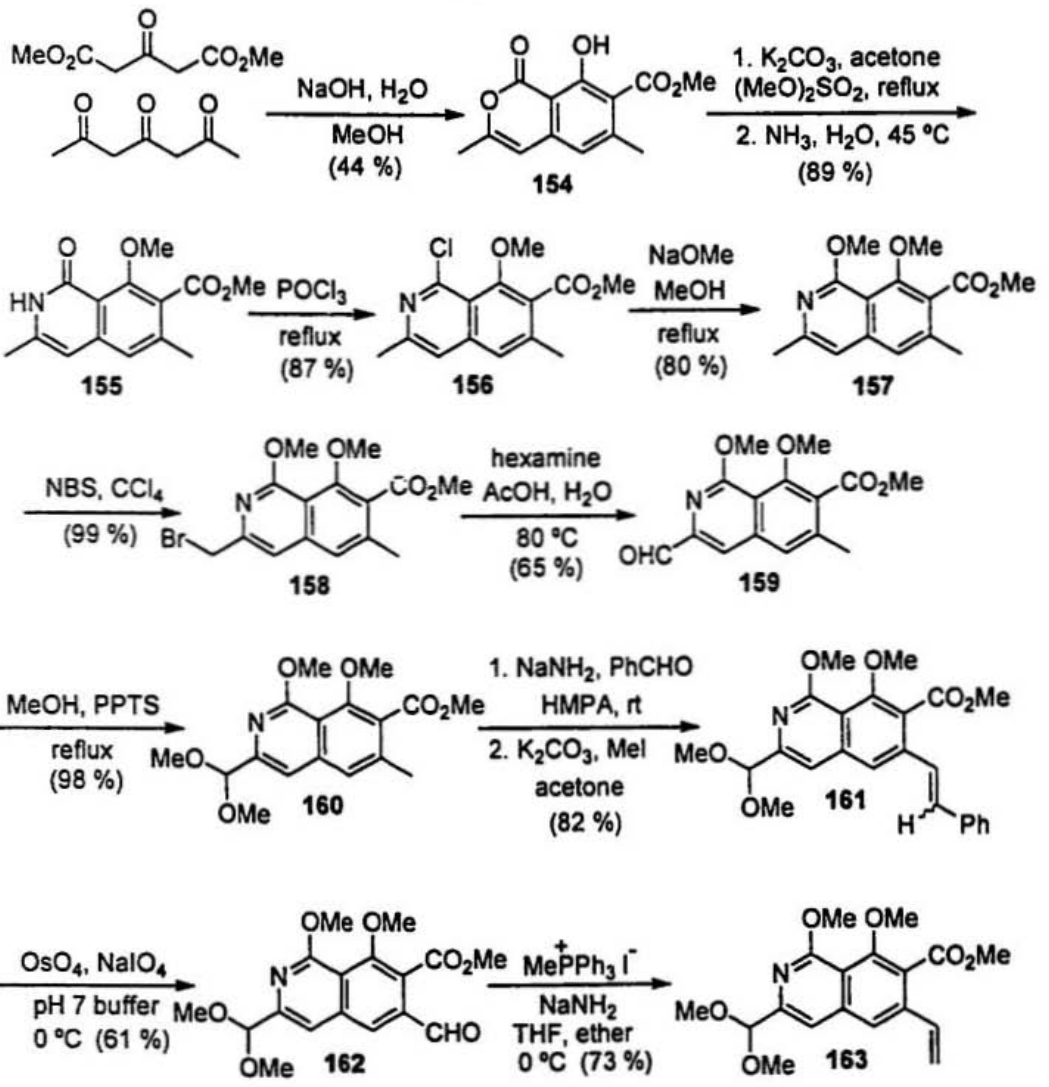
Rama Rao utilized Shapiro's Dieckmann conditions[33] for the synthesis of **153** from aldehyde **151** and phthalide (Scheme 15a).[28m] Formation of the BCDE model **97** was achieved in 72 % yield from **153** via a usually disfavored 5-endo-trig radical cyclization.

Scheme 15a

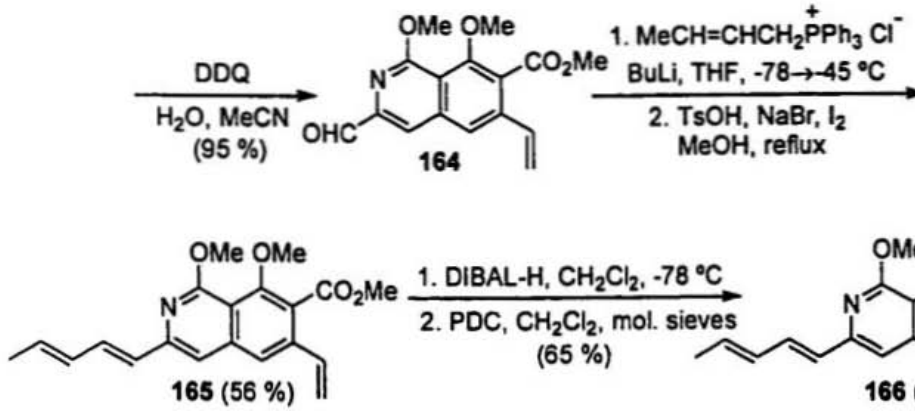


Rama Rao later achieved the total synthesis of **91** (33 steps) using this strategy (Scheme 15b-d). The seemingly circuitous synthesis of **174** outlined in Scheme 15c reflects the inability of the orthoester derived from **170** to react with dimethyl acetylenedicarboxylate (DMAD) in a Diels-Alder addition despite the observation that **172** reacted readily under the same conditions.

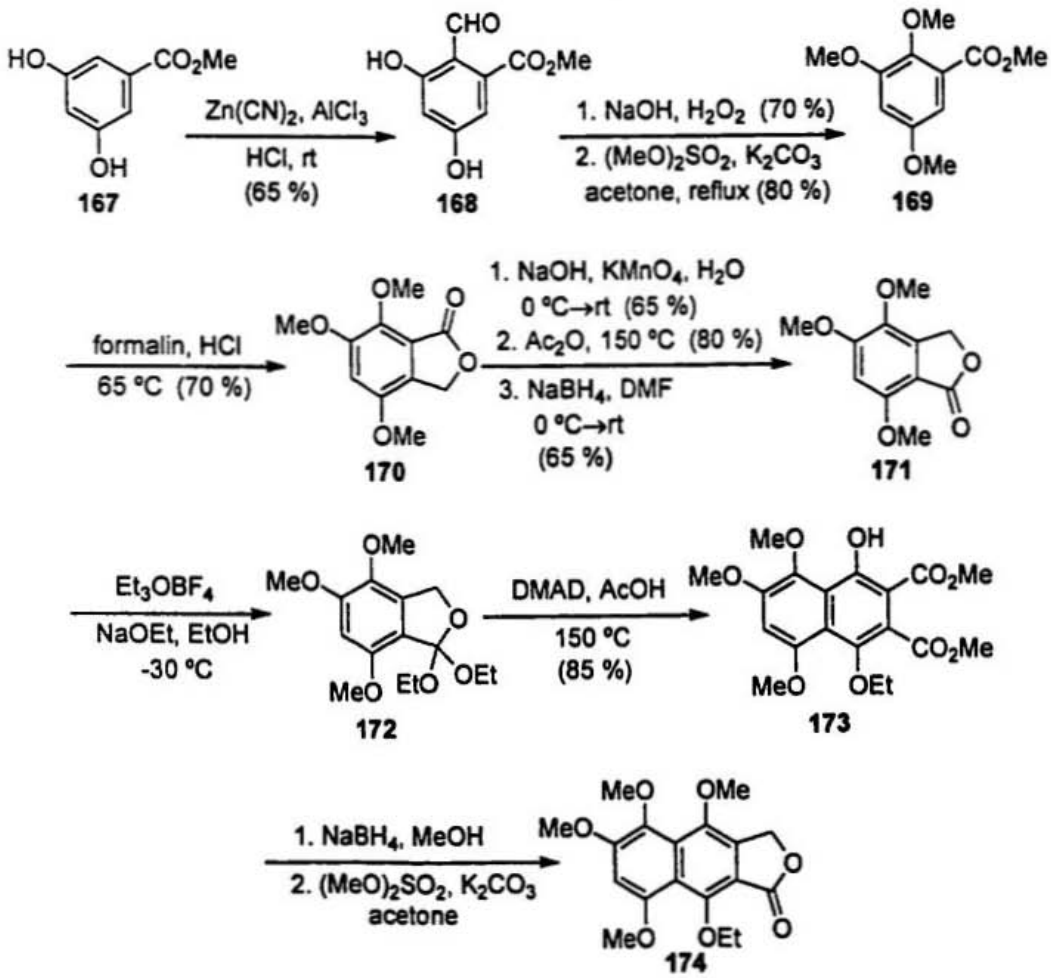
Scheme 15b



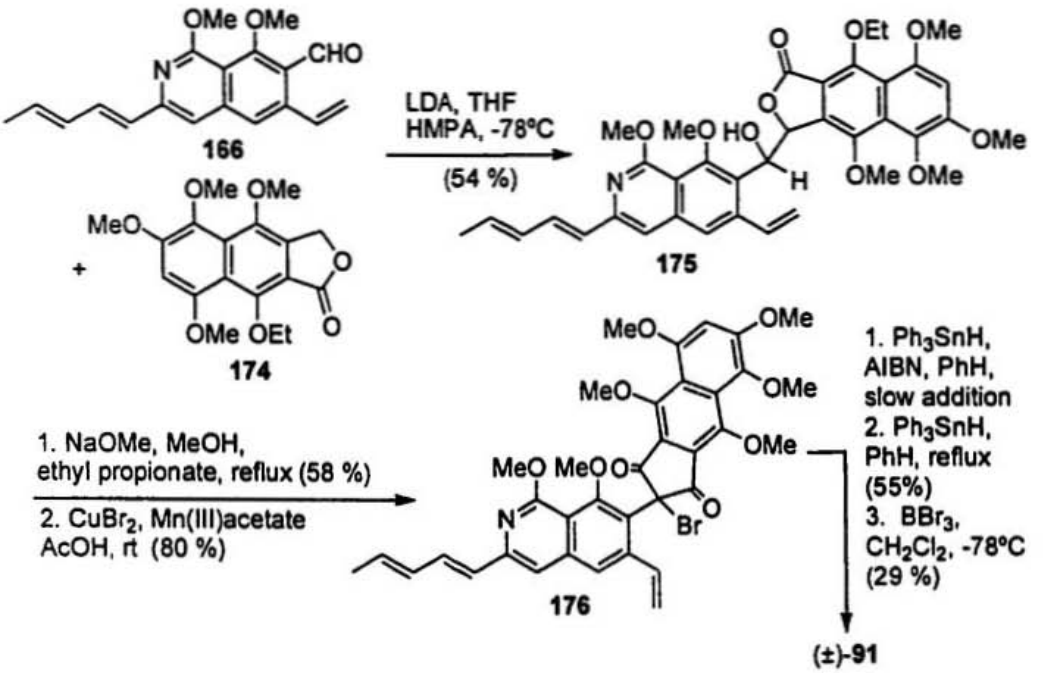
Scheme 15b (continued)



Scheme 15c

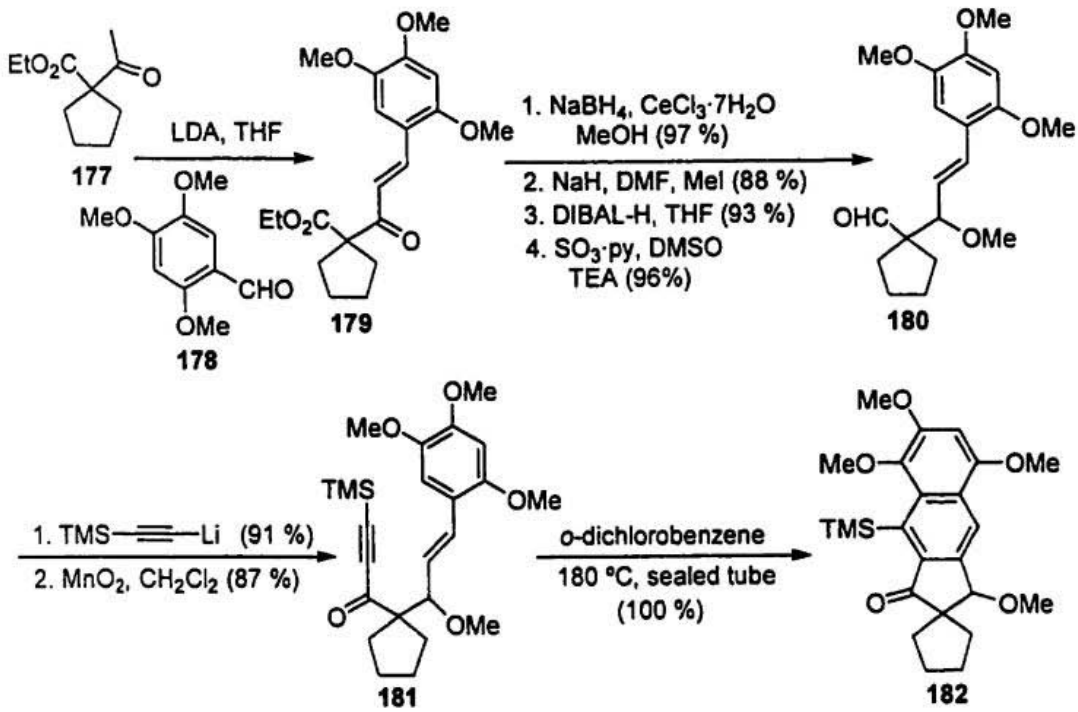


Scheme 15d



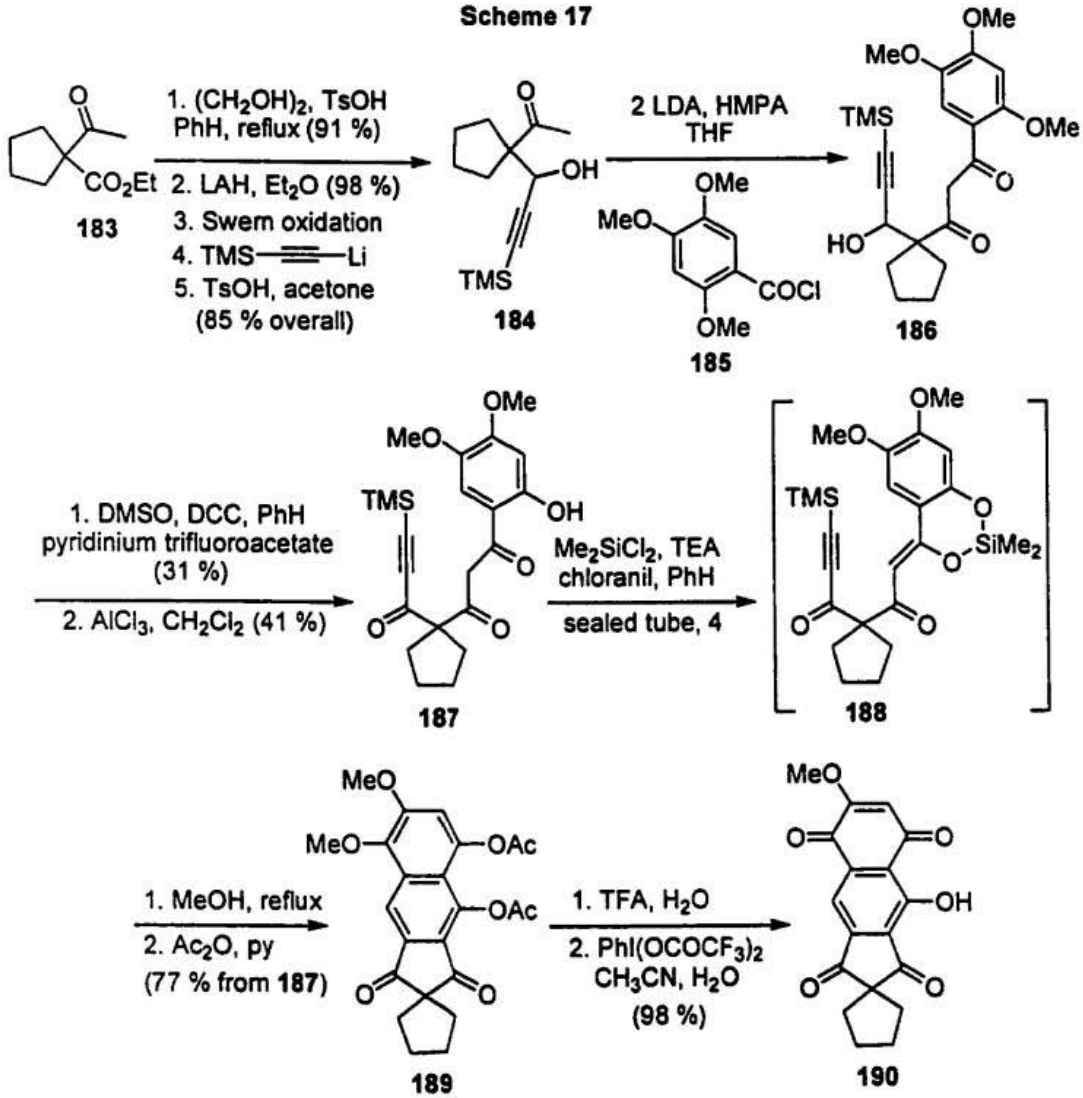
Other Novel Approaches. Terashima prepared ABCD fragment **182** using an intramolecular dieneyne Diels-Alder strategy (Scheme 16).[28n] Aldol addition of the lithium enolate of **177** to **178** gave enone **179**. A series of straightforward functional group (FG) transformations provided aldehyde **180**. Final assembly of dieneyne **181** was achieved by addition of lithiated trimethylsilylacetylene to **180** followed by oxidation of the resulting propargylic alcohol with MnO_2. Heating **181** in a sealed tube initiated a highly efficient [4 + 2] cycloaddition leading to **182** in quantitative yield.

Scheme 16

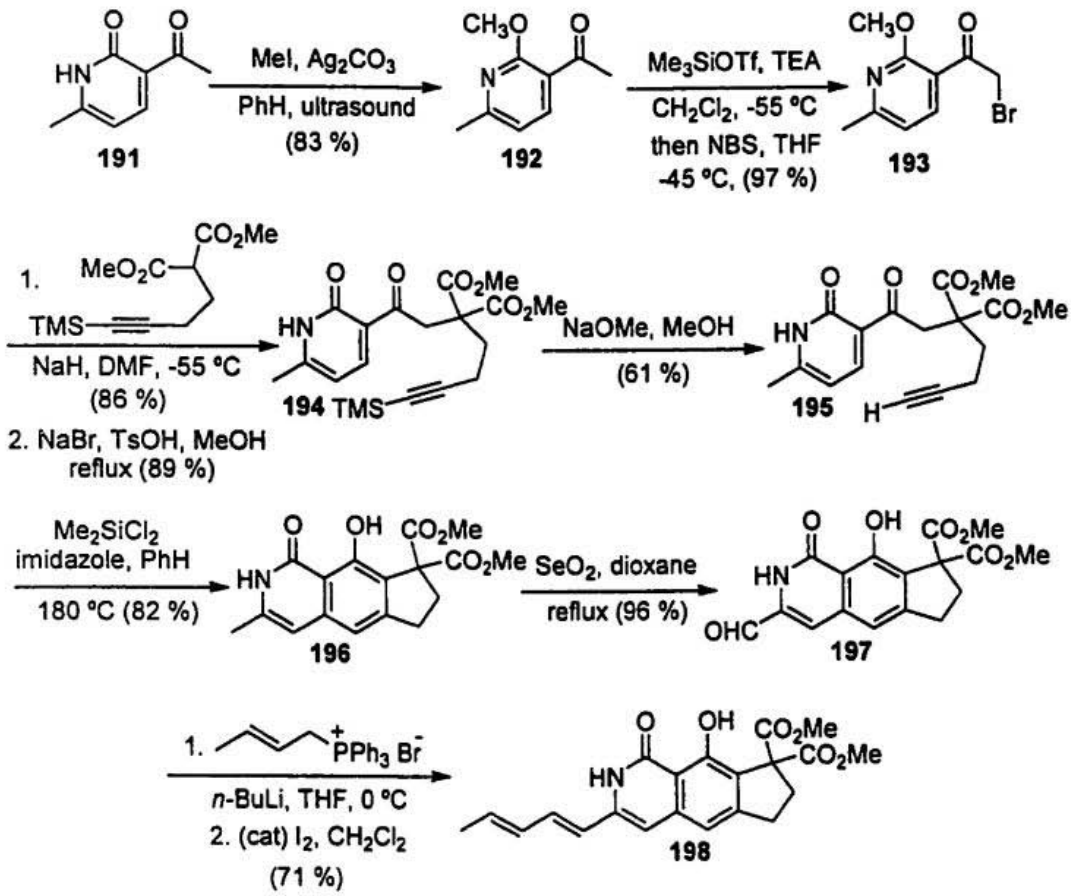


Kita later reported that the B-ring trimethylsilyl (TMS) group of **182** could not be converted into the required phenol under a variety of conditions.[28o] Kita's modification (Scheme 17) overcomes this difficulty, however, the B ring of **190** is still lacking a second oxygen found in **91**. Kita applied a similar approach for the assembly of fully functionalized DEF fragment **198** (Scheme 18).[28p]

Scheme 17

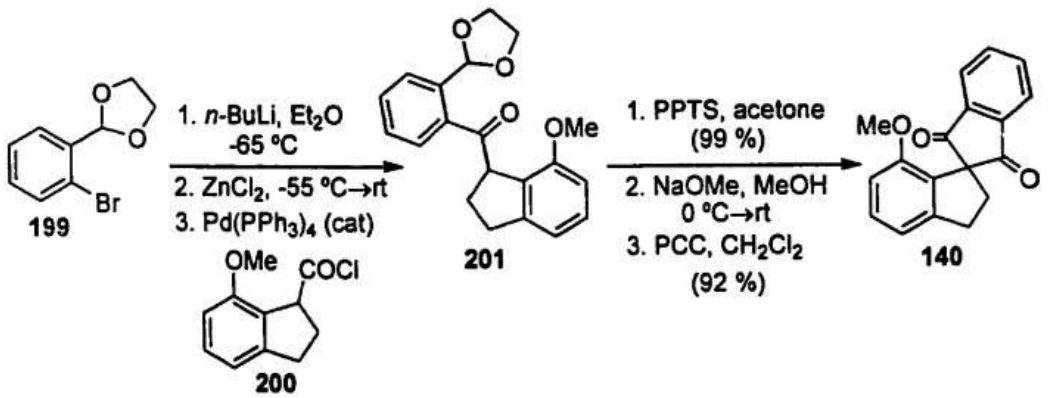

1. $(CH_2OH)_2$, TsOH
PhH, reflux (91 %)
2. LAH, Et_2O (98 %)
3. Swern oxidation
4. TMS—≡—Li
5. TsOH, acetone
(85 % overall)
183
184
2 LDA, HMPA
THF
185
186
1. DMSO, DCC, PhH
pyridinium trifluoroacetate
(31 %)
2. $AlCl_3$, CH_2Cl_2 (41 %)
187
Me_2SiCl_2, TEA
chloranil, PhH
sealed tube, 4
188
1. MeOH, reflux
2. Ac_2O, py
(77 % from 187)
189
1. TFA, H_2O
2. $PhI(OCOCF_3)_2$
CH_3CN, H_2O
(98 %)
190

Scheme 18



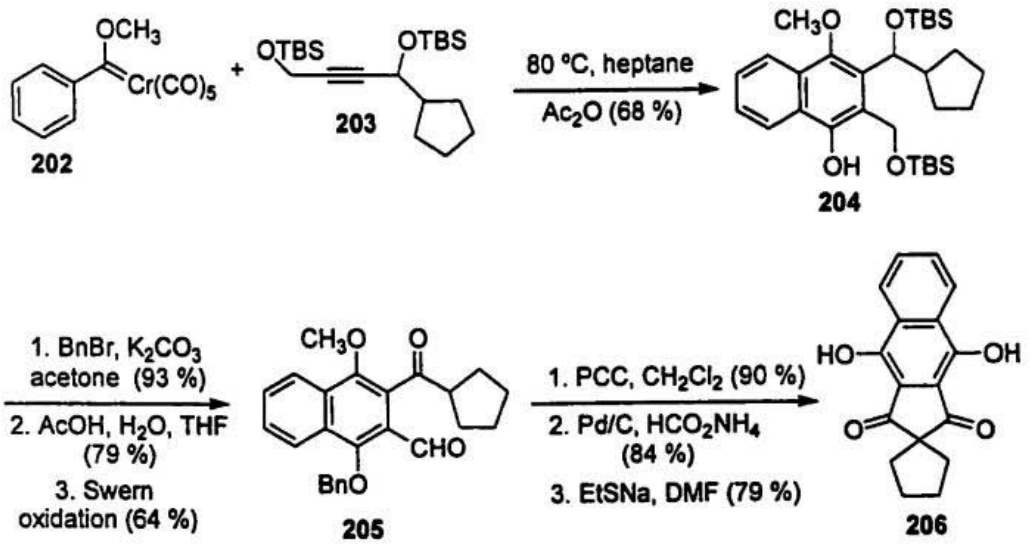
Andrew Evans assembled BCDE fragment **140** using an aldol strategy similar to those previously discussed (Scheme 19).[28q] Union of B and DE ring synthons **199** and **200** was accomplished using a modified Negishi palladium-catalyzed cross-coupling.

Scheme 19

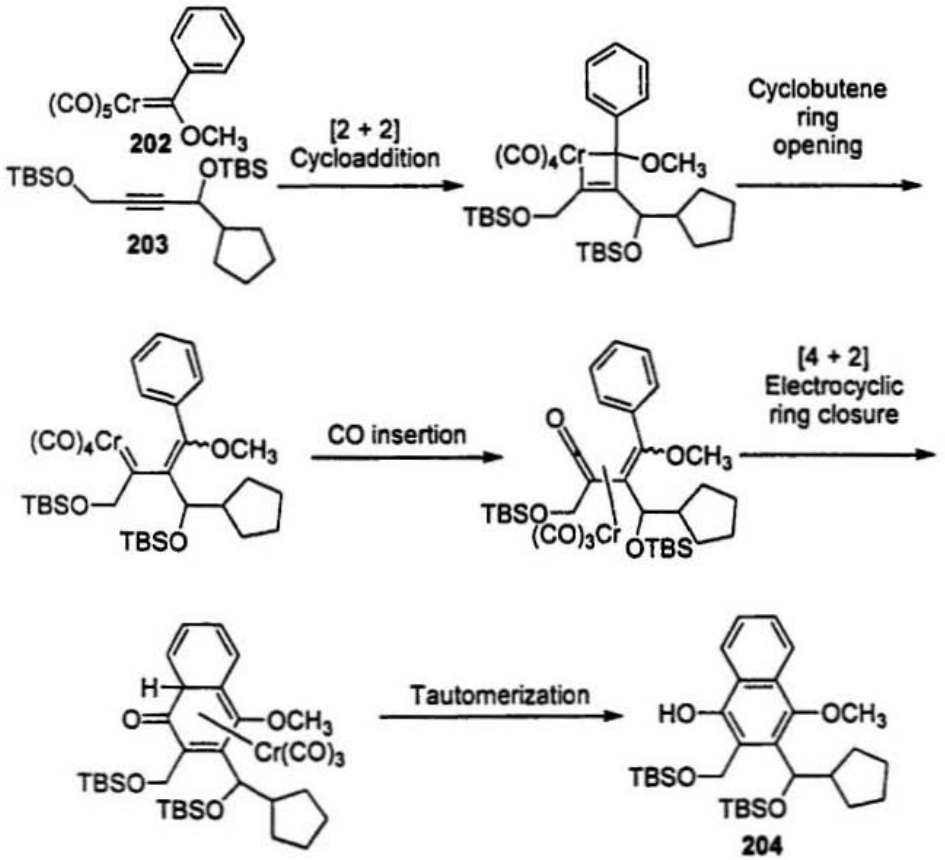


Dale Boger's synthesis of model ABCD fragment **206** (Scheme 20a) employed an intermolecular alkyne-chromium carbene complex benzannelation (Scheme 20b).[28r] Final assembly of the CD spiro link was also accomplished in this instance with an intramolecular aldol reaction. Boger's total synthesis of **91** (29 steps) is outlined in Schemes 20c-e.[26]

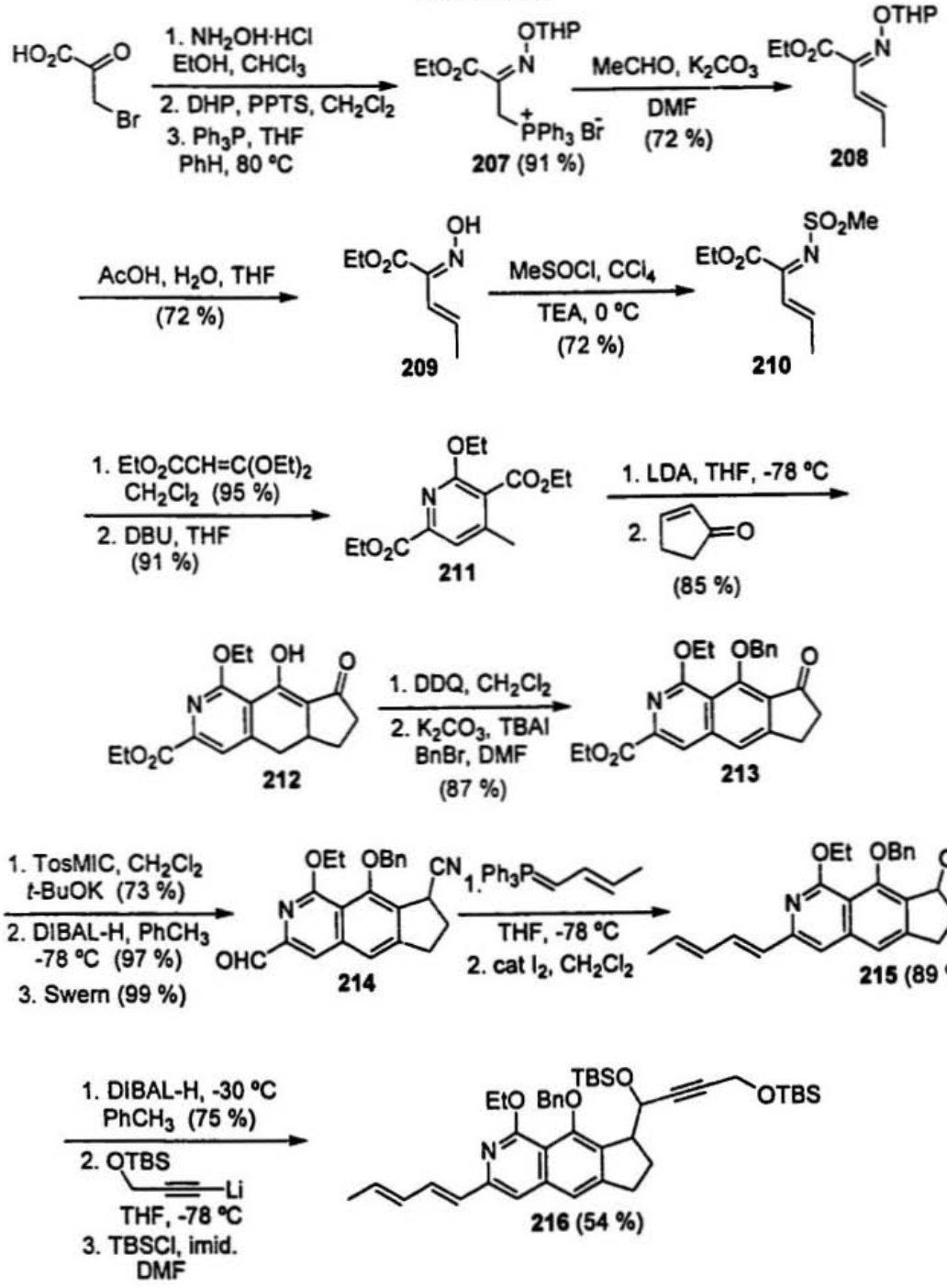
Scheme 20a



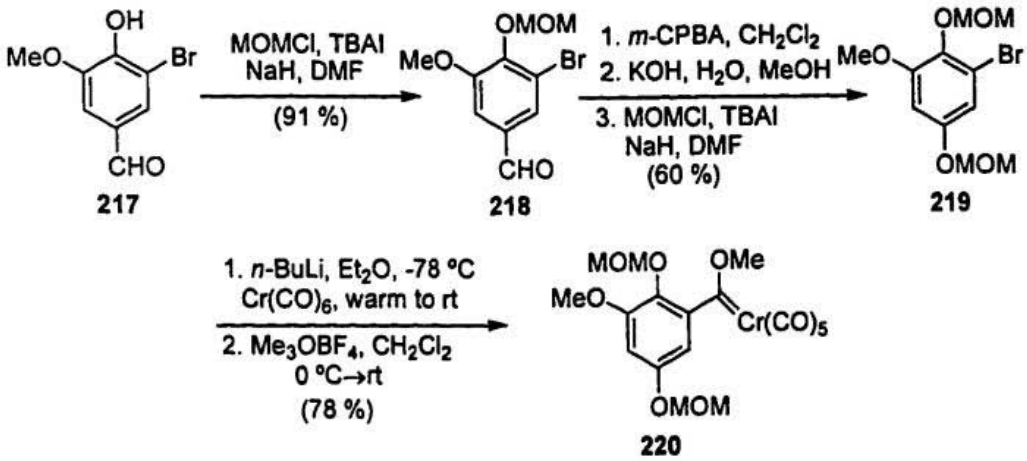
Scheme 20b. Alkyne-Chromium Carbene Complex Benzannellation



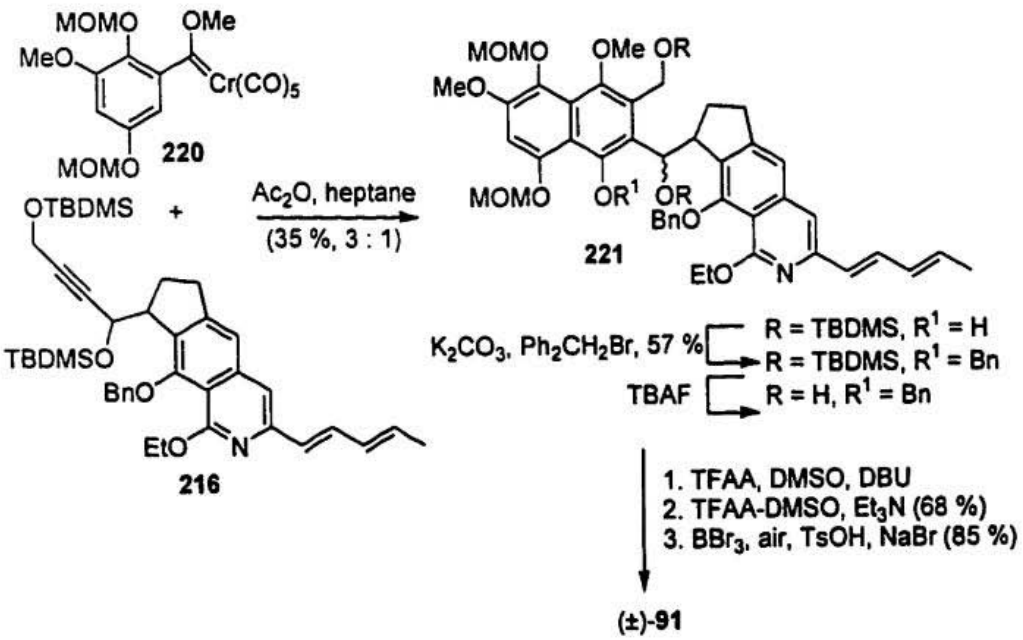
Scheme 20c


1. NH2OH·HCl
EtOH, CHCl3
2. DHP, PPTS, CH2Cl2
3. Ph3P, THF
PhH, 80 °C
207 (91 %)
MeCHO, K2CO3
DMF
(72 %)
208
AcOH, H2O, THF
(72 %)
209
MeSOCl, CCl4
TEA, 0 °C
(72 %)
210
1. EtO2CCH=C(OEt)2
CH2Cl2 (95 %)
2. DBU, THF
(91 %)
211
1. LDA, THF, -78 °C
2.
(85 %)
212
1. DDQ, CH2Cl2
2. K2CO3, TBAI
BnBr, DMF
(87 %)
213
1. TosMIC, CH2Cl2
t-BuOK (73 %)
2. DIBAL-H, PhCH3
-78 °C (97 %)
3. Swern (99 %)
214
1. Ph3P
THF, -78 °C
2. cat I2, CH2Cl2
215 (89 %)
1. DIBAL-H, -30 °C
PhCH3 (75 %)
2. OTBS
THF, -78 °C
3. TBSCl, imid.
DMF
216 (54 %)

Scheme 20d

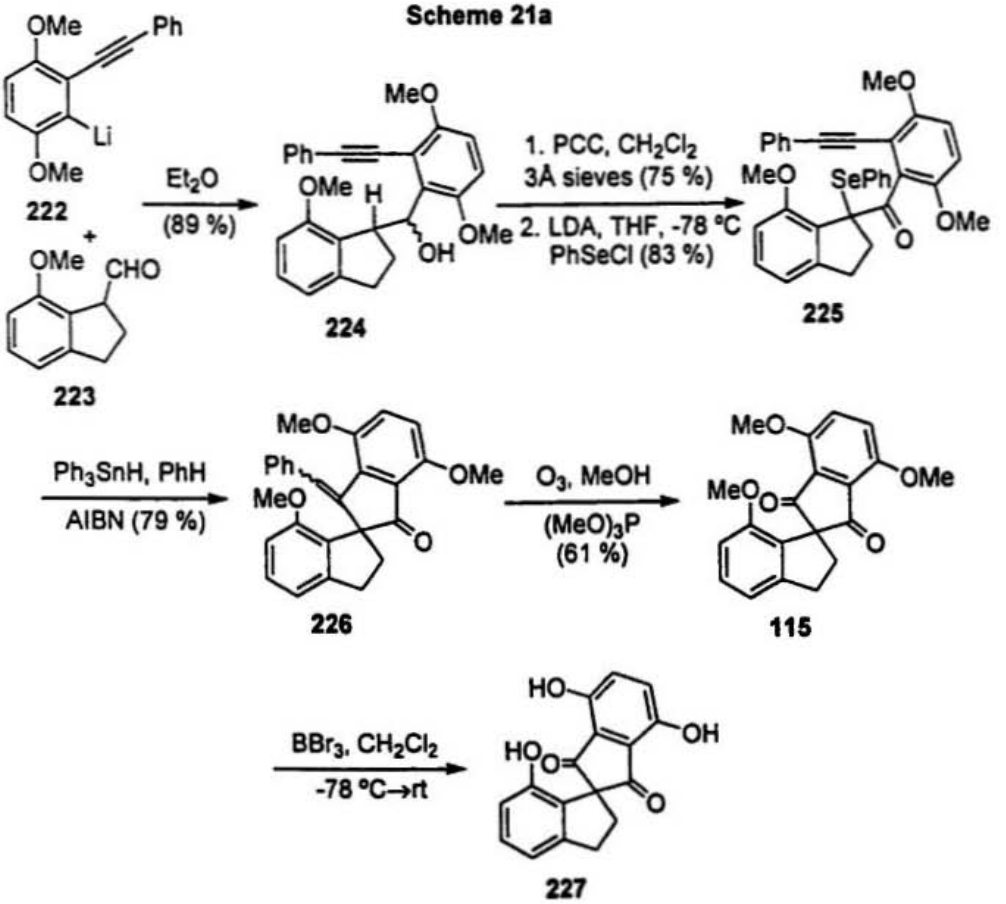


Scheme 20e

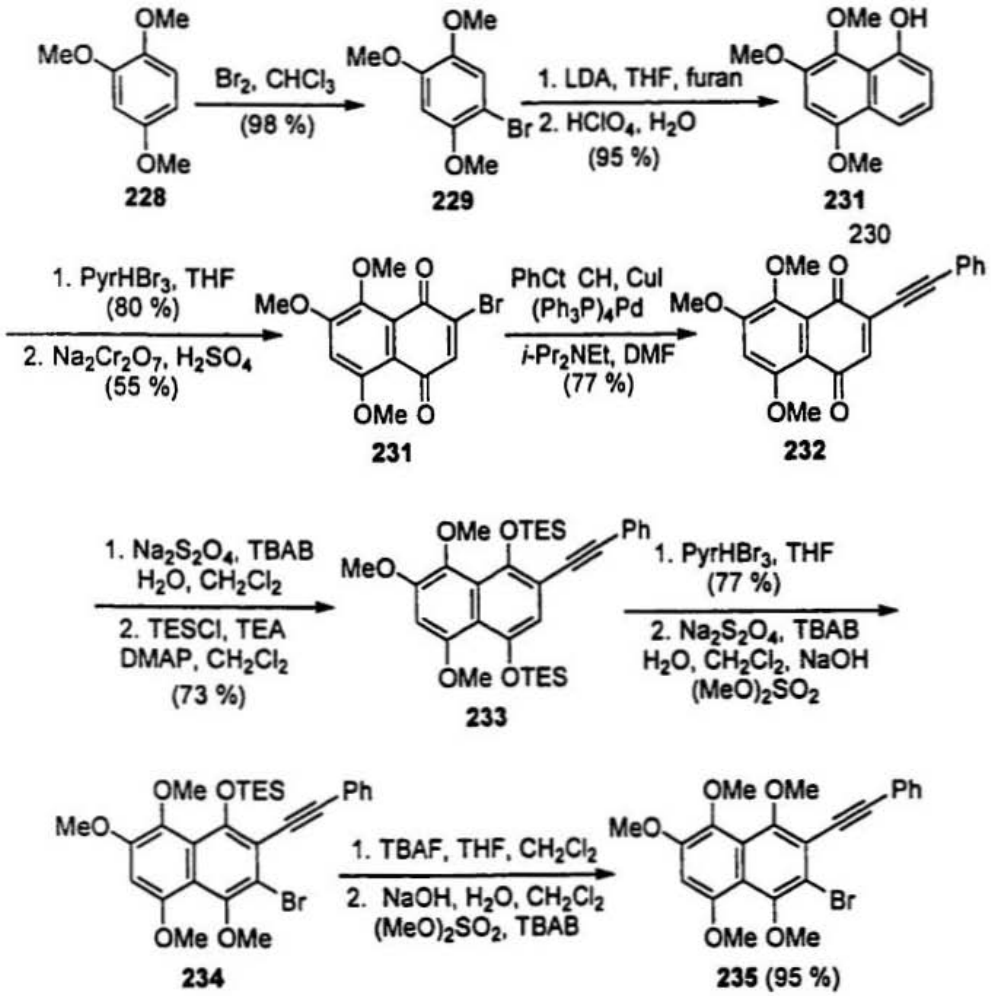


Derrick Clive constructed the spiro linkage present in **91** using a novel radical spirocyclization strategy (Scheme 21a).[28s] Nucleophilic addition of aryl lithium **222** to aldehyde **223** afforded alcohol **224**. Conversion of **224** to organoselenide **225** was accomplished by oxidation with PCC and treatment of the resultant ketone with LDA and phenylselenyl chloride. Treatment of **225** with triphenyltin hydride/2,2'-azobisisobutyronitrile (AIBN) generated a highly stabilized radical that underwent a favored 5-*exo*-dig cyclization to afford spirocyclized product **226**. Ozonolytic cleavage of the double bond in **226** followed by demethylation with boron tribromide afforded BCDE fragment **227**. Clive's total synthesis of **91** (34 steps) is illustrated in Schemes 21b-d.[30]

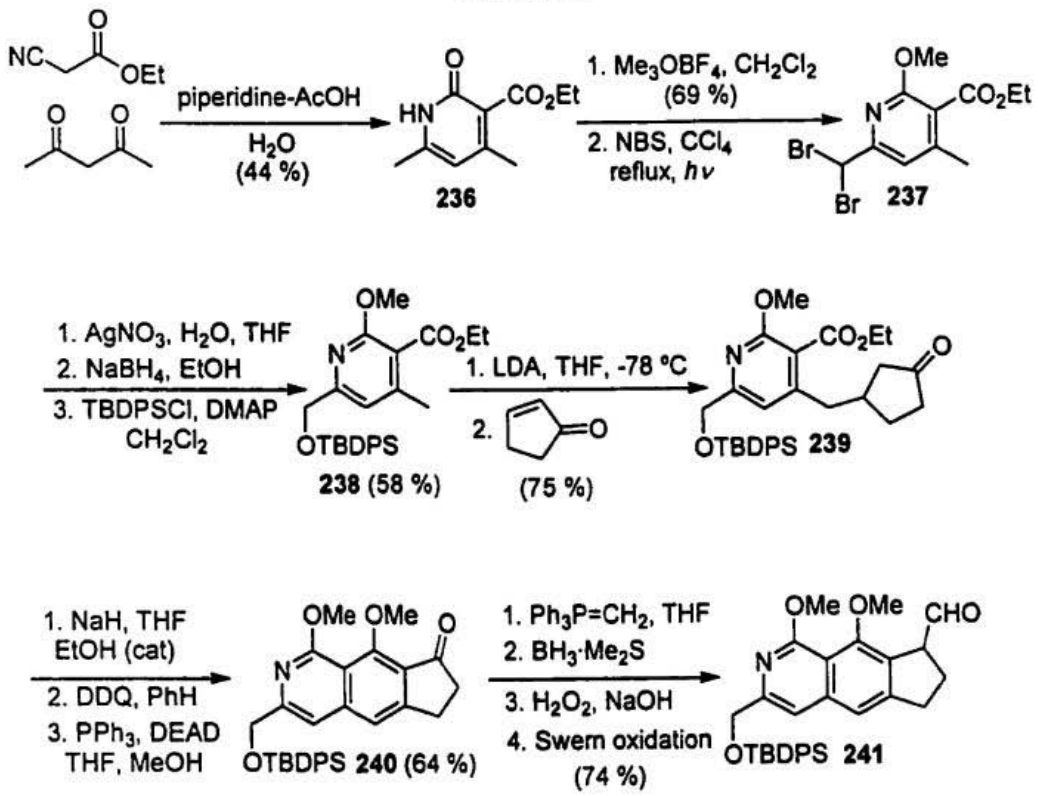
Scheme 21a



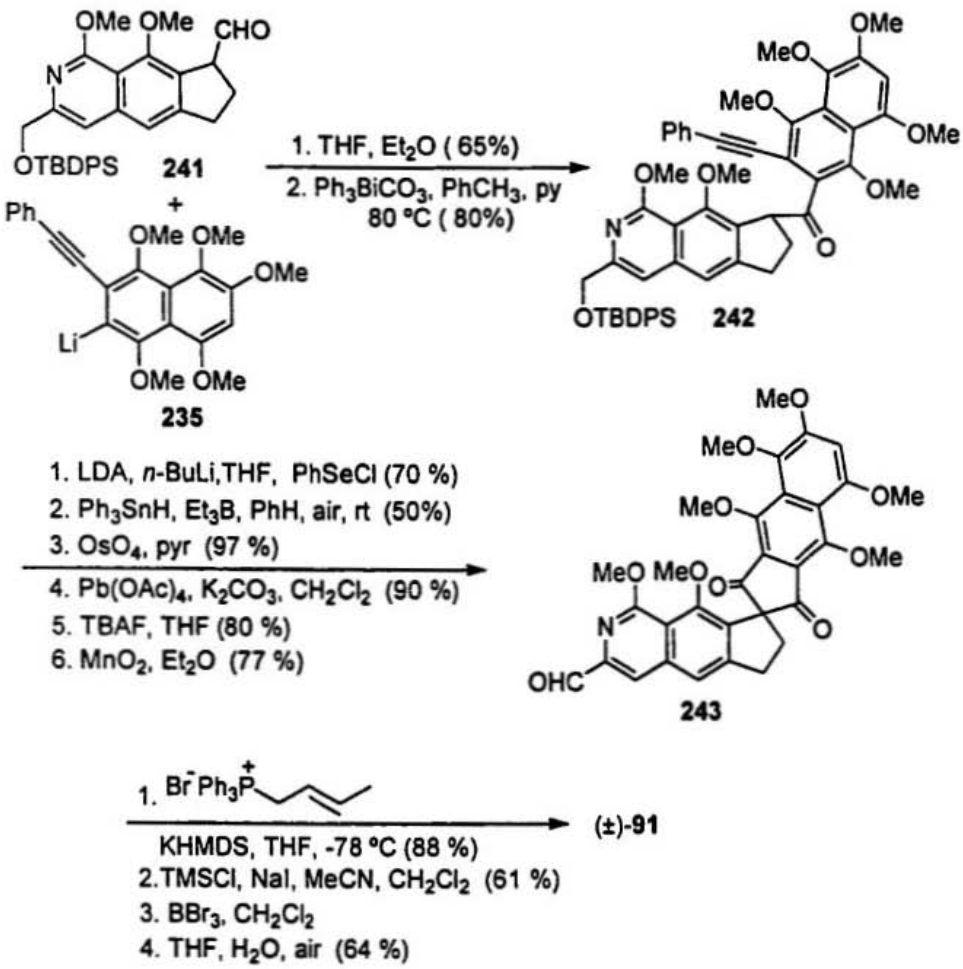
Scheme 21b


OMe
MeO
OMe
228
Br2, CHCl3
(98 %)
Br
229
1. LDA, THF, furan
2. HClO4, H2O
(95 %)
OMe OH
231
230
1. PyrHBr3, THF
(80 %)
2. Na2Cr2O7, H2SO4
(55 %)
O
231
PhCt CH, CuI
(Ph3P)4Pd
i-Pr2NEt, DMF
(77 %)
Ph
232
1. Na2S2O4, TBAB
H2O, CH2Cl2
2. TESCl, TEA
DMAP, CH2Cl2
(73 %)
OTES
233
1. PyrHBr3, THF
(77 %)
2. Na2S2O4, TBAB
H2O, CH2Cl2, NaOH
(MeO)2SO2
234
1. TBAF, THF, CH2Cl2
2. NaOH, H2O, CH2Cl2
(MeO)2SO2, TBAB
235 (95 %)

Scheme 21c

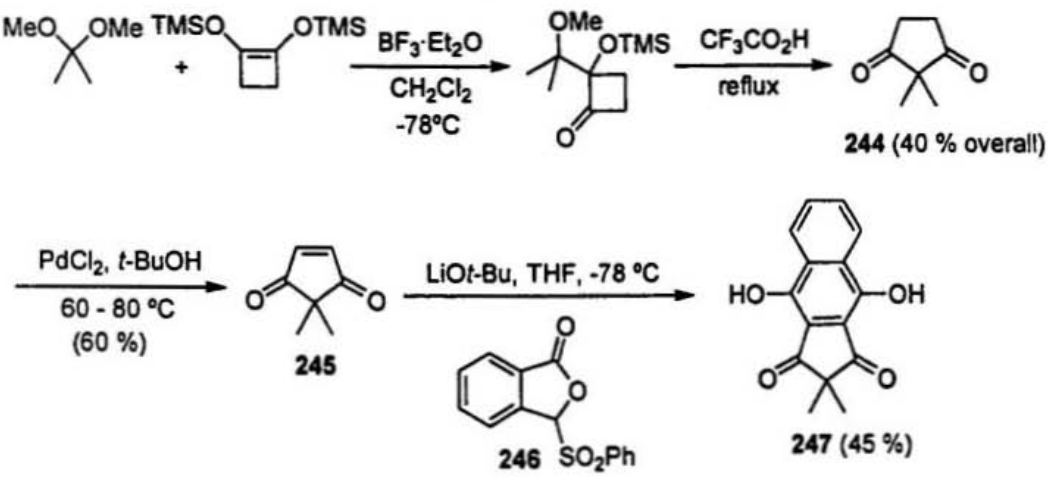

piperidine-AcOH
H_2O
(44 %)
236
1. Me_3OBF_4, CH_2Cl_2
(69 %)
2. NBS, CCl_4
reflux, $h\nu$
237
1. $AgNO_3$, H_2O, THF
2. $NaBH_4$, EtOH
3. TBDPSCl, DMAP
CH_2Cl_2
238 (58 %)
1. LDA, THF, -78 °C
2.
(75 %)
239
1. NaH, THF
EtOH (cat)
2. DDQ, PhH
3. PPh_3, DEAD
THF, MeOH
240 (64 %)
1. $Ph_3P{=}CH_2$, THF
2. $BH_3{\cdot}Me_2S$
3. H_2O_2, NaOH
4. Swern oxidation
(74 %)
241

Scheme 21d



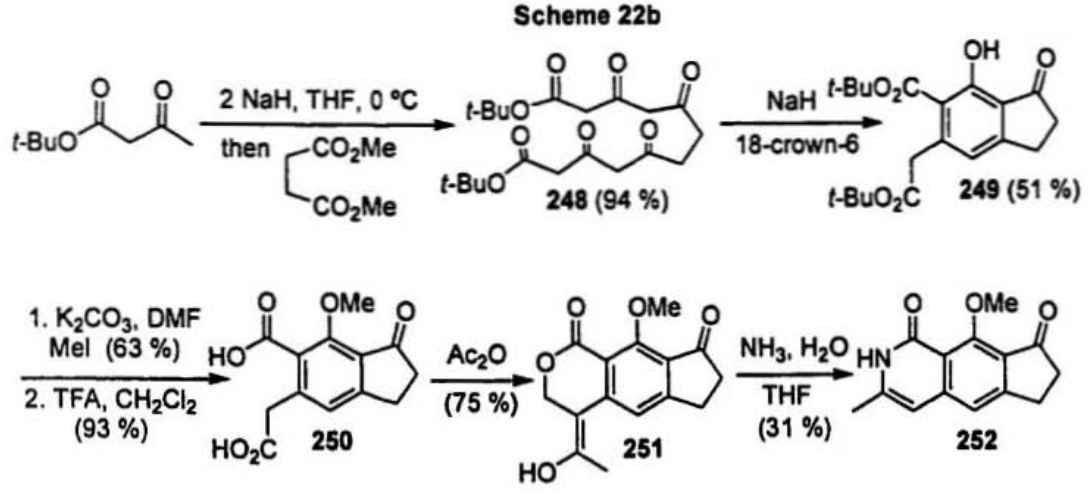
Parker utilized Kuwajima's geminal acylation methodology to construct C ring cyclopentane-1,3-dione model **244** (Scheme 22a).[11a] Dehydrogenation of **244** provided enedione **245** that served as a Michael acceptor in a reaction with lithiated phthalide sulfone **246**. Closure of the B ring was accomplished by a concomitant intramolecular Dieckmann-type reaction of the resultant enolate onto the carbonyl of the lactone with subsequent aromatization to form **247**.

Scheme 22a



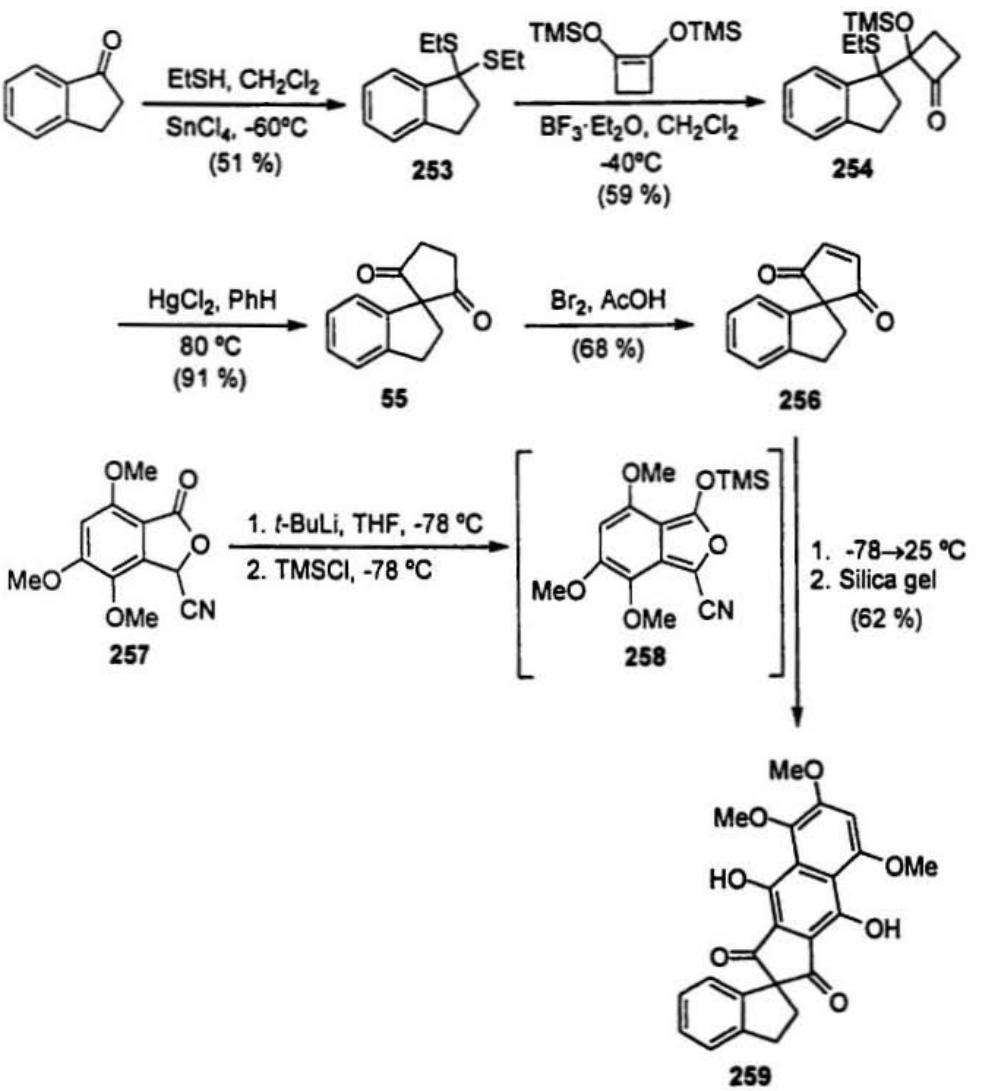
DEF fragment **252** was assembled using a biomimetic cyclization strategy employing polyketide **248** (Scheme 22b).[28t]

Scheme 22b



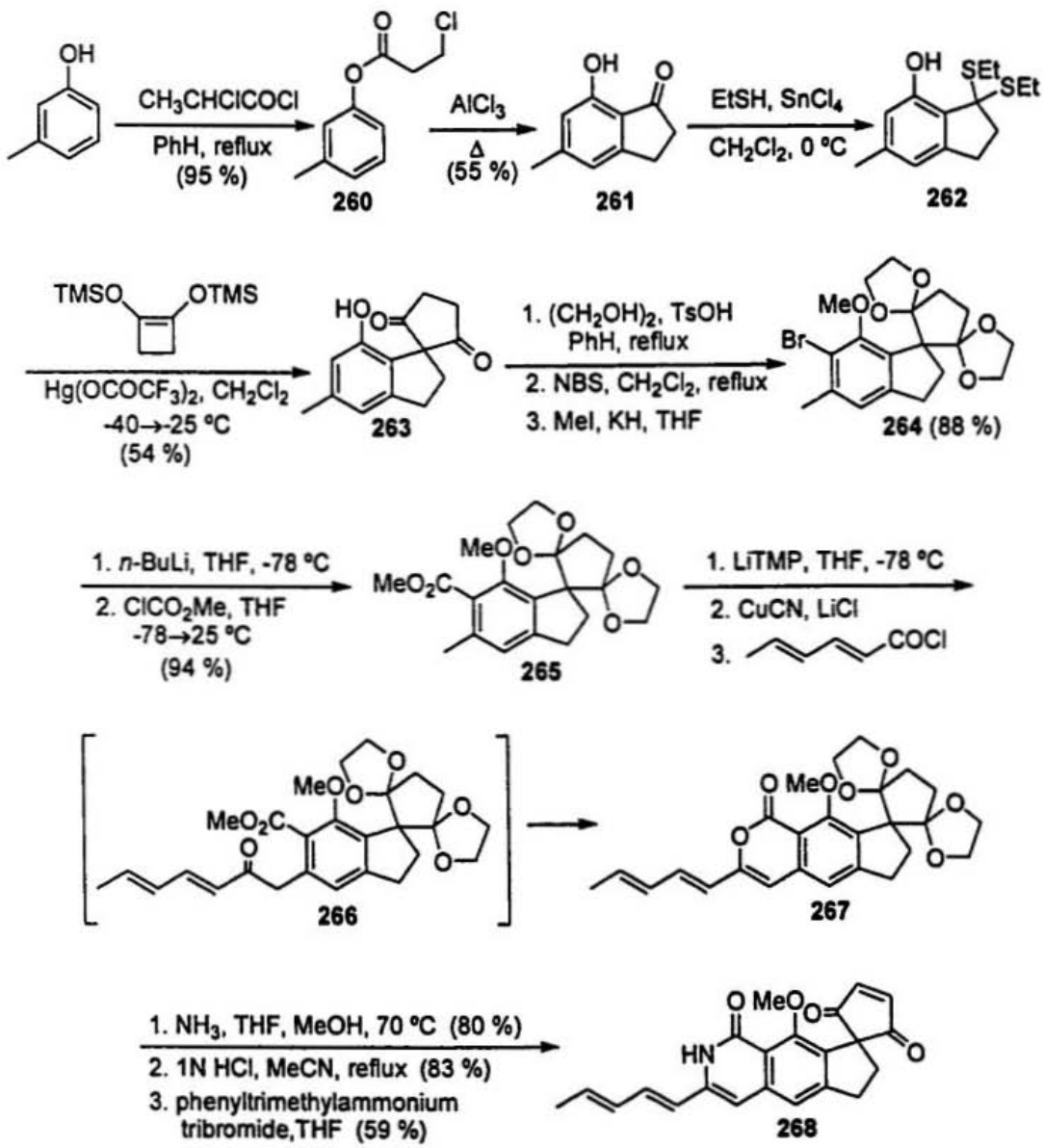
Bach (Scheme 23a) later reported the synthesis of a model compound (**259**) possessing all the required oxygens in the A, B and C rings using a strategy similar to Parker's. Assembly of the AB portion was achieved by a Diels-Alder reaction between enedione **256** and isobenzofuran **258**.[28u]

Scheme 23a

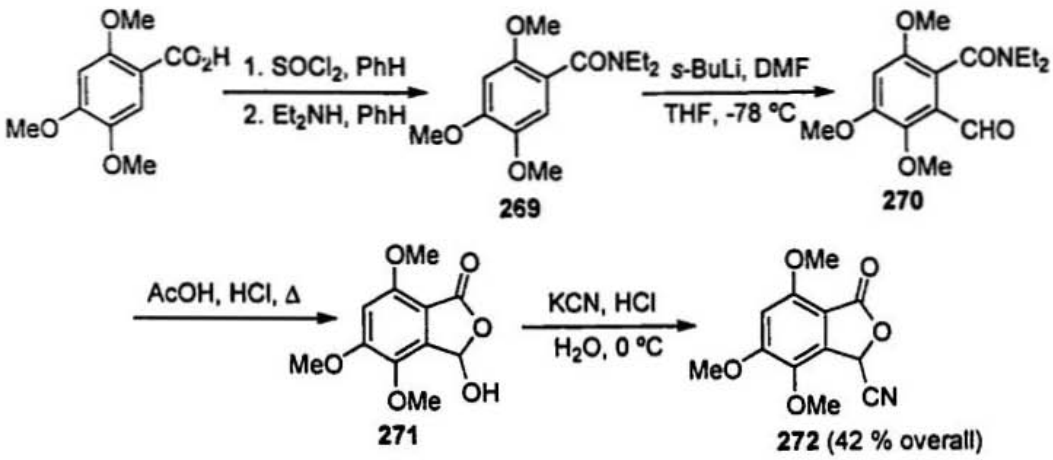


Bach and Julia independently synthesized **91** using this strategy. Bach's synthetic route (19 steps) is illustrated in Schemes 23b-d.[11c] Julia's synthesis (18 steps) is illustrated in Schemes 24a-c.[11b]

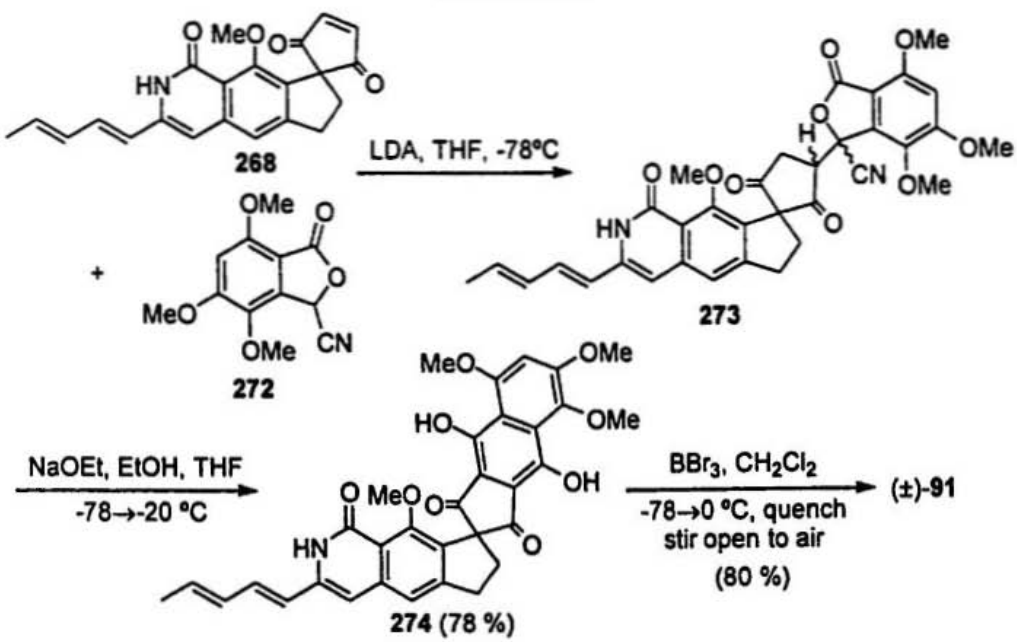
Scheme 23b



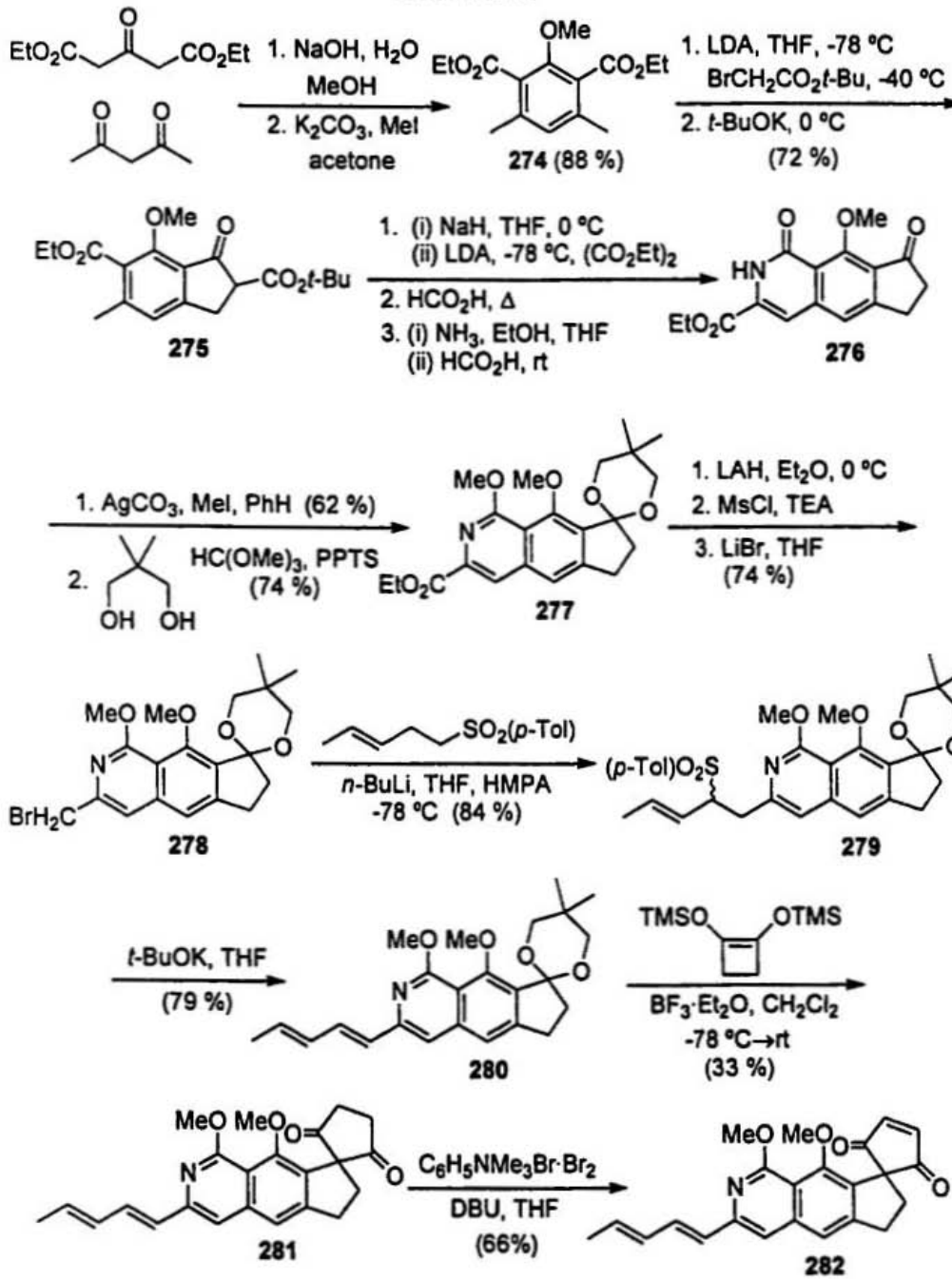
Scheme 23c



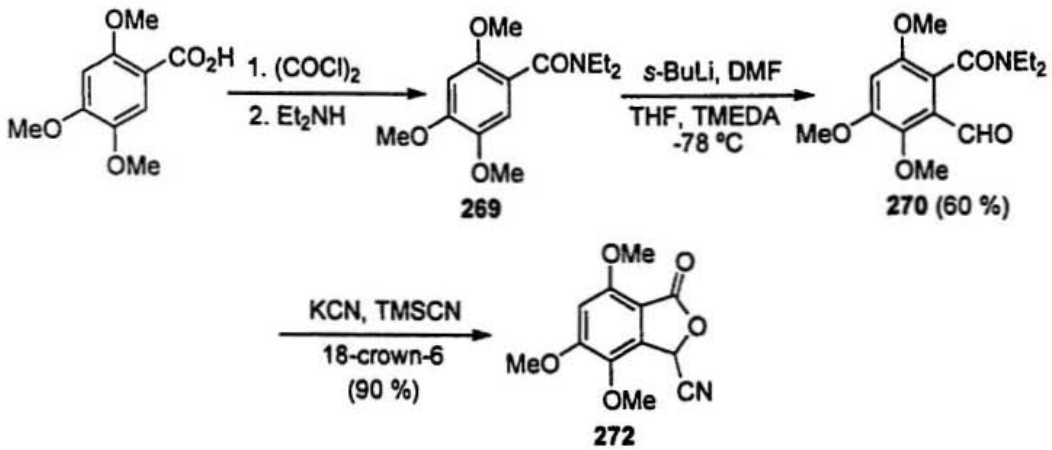
Scheme 23d



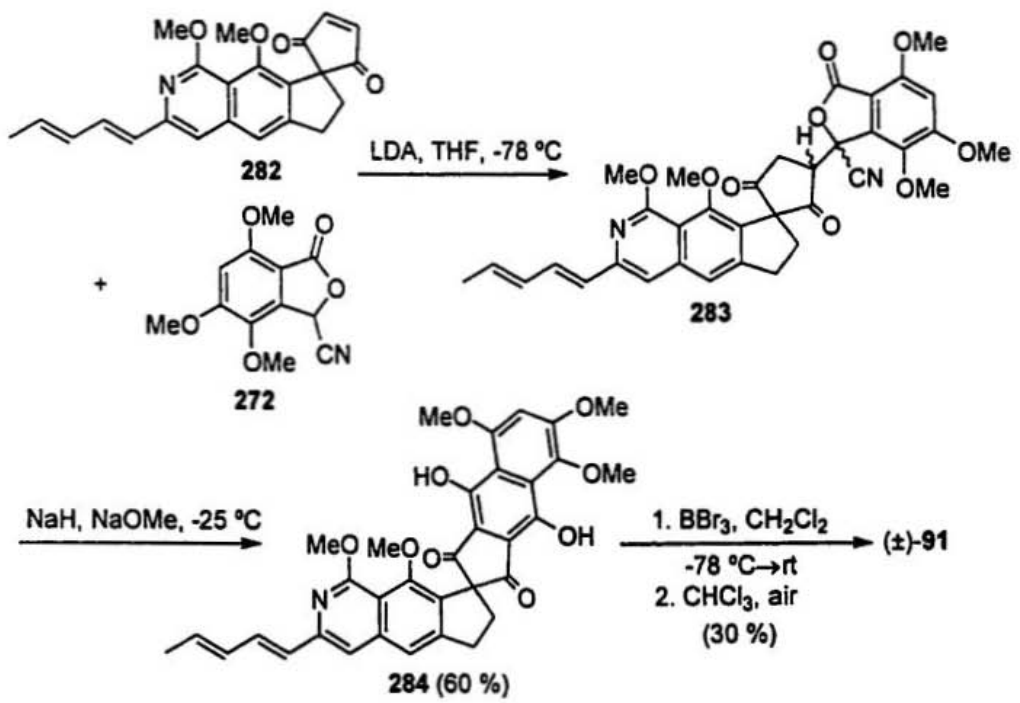
Scheme 24a


1. NaOH, H2O
MeOH
2. K2CO3, MeI
acetone
274 (88 %)
1. LDA, THF, -78 °C
BrCH2CO2t-Bu, -40 °C
2. t-BuOK, 0 °C
(72 %)
275
1. (i) NaH, THF, 0 °C
(ii) LDA, -78 °C, (CO2Et)2
2. HCO2H, Δ
3. (i) NH3, EtOH, THF
(ii) HCO2H, rt
276
1. AgCO3, MeI, PhH (62 %)
2.
HC(OMe)3, PPTS
(74 %)
277
1. LAH, Et2O, 0 °C
2. MsCl, TEA
3. LiBr, THF
(74 %)
278
n-BuLi, THF, HMPA
-78 °C (84 %)
279
t-BuOK, THF
(79 %)
280
BF3·Et2O, CH2Cl2
-78 °C→rt
(33 %)
281
C6H5NMe3Br·Br2
DBU, THF
(66%)
282

Scheme 24b

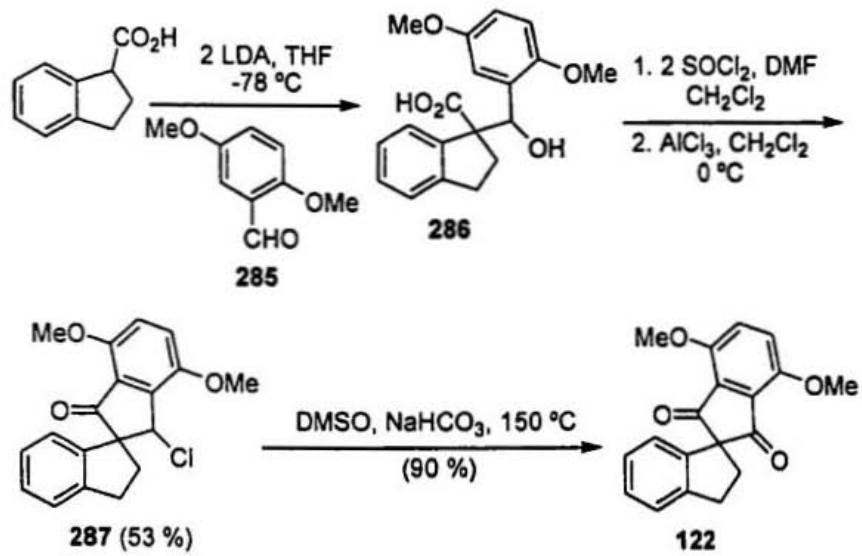


Scheme 24c

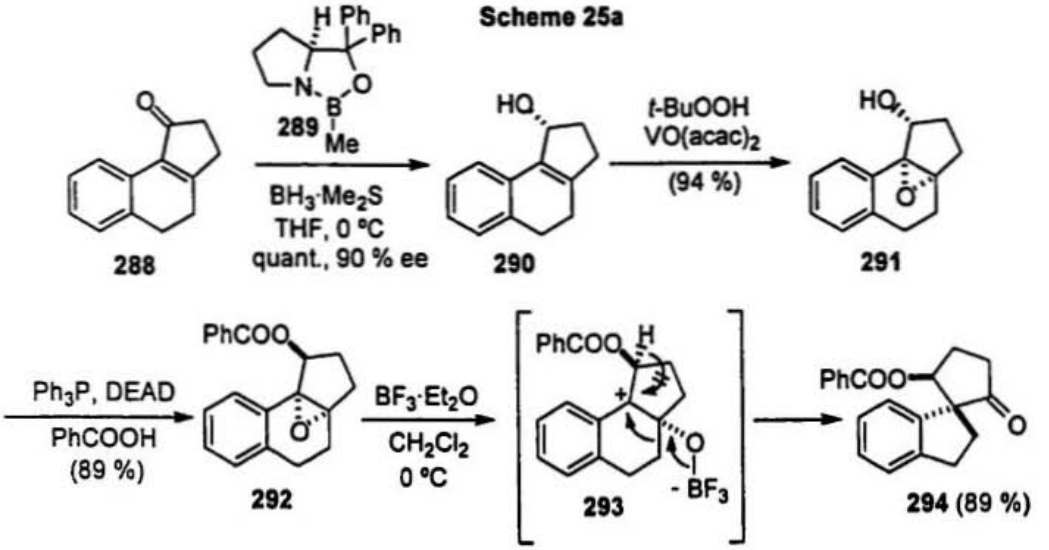


Julia also explored the possibility of forming the C ring using an intramolecular Friedel-Crafts acylation (Scheme 24d).[11b] Though successful in producing **122**, this approach was not amenable to a synthesis of **91**.

Scheme 24d

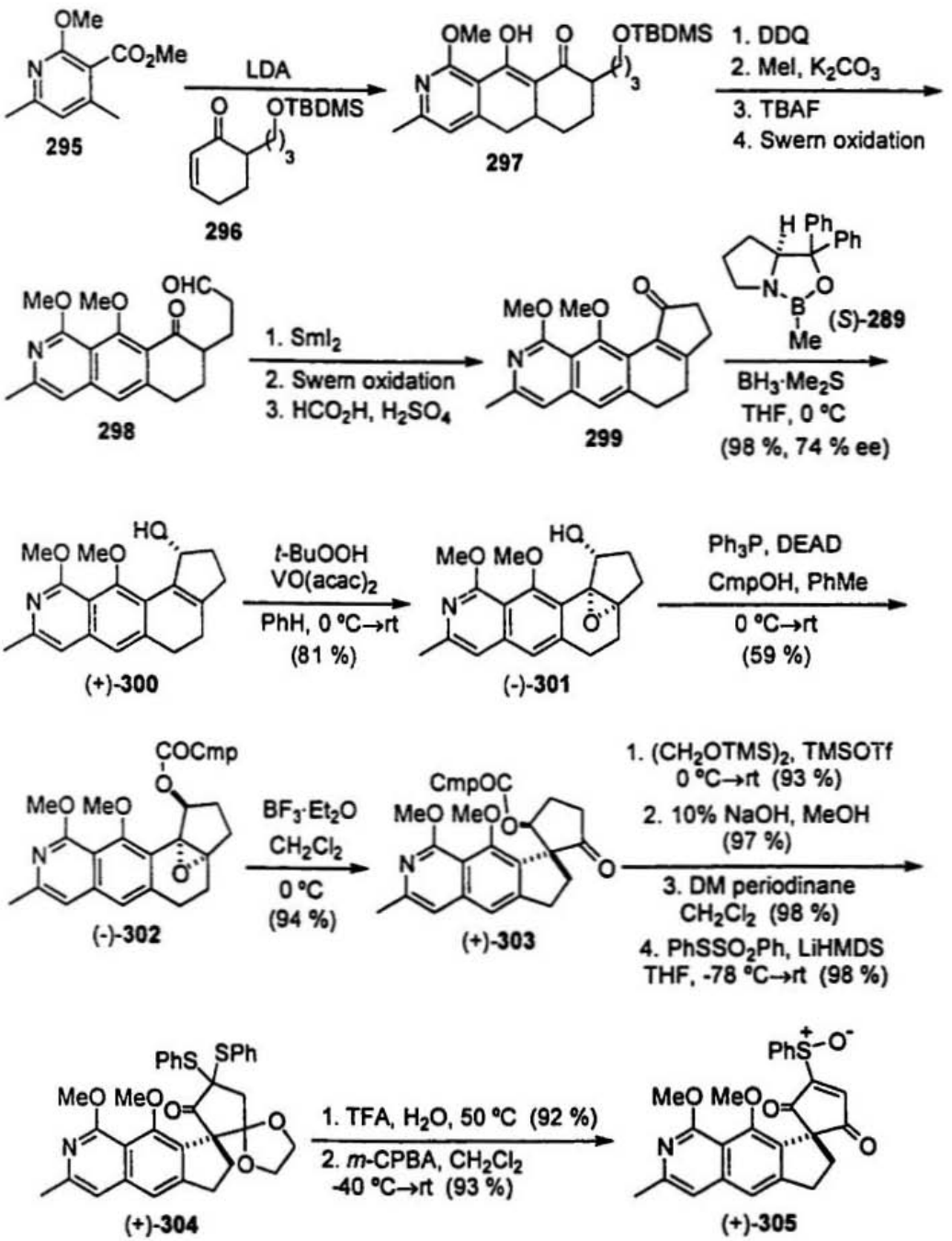


Kita accomplished the formation of the CDE portion of **91** in optically active form by $BF_3 \cdot Et_2O$ catalyzed rearrangement of *trans*-α,β-epoxyacylate **292** (Scheme 25a).[28v] Enantioselective reduction of enone **288** with Corey's L-proline-derived reducing reagent (**289**) gave allylic alcohol **290**. A heteroatom-directed epoxidation with *t*-BuOOH/$VO(acac)_2$ followed by Mitsunobu inversion of the hydroxyl-bearing stereocenter gave *trans*-α,β-epoxyacylate **292**. Stirring **292** in dichloromethane with an equivalent of $BF_3 \cdot Et_2O$ resulted in a stereospecific rearrangement, presumably via **293**, to give **294** in 90 % ee. Use of (1*S*)-(-)-camphanic acid in the Mitsunobu procedure followed by recrystallization of the α,β-epoxyacylate prior to rearrangement raised the enantiomeric excess from 90 to 100 %.

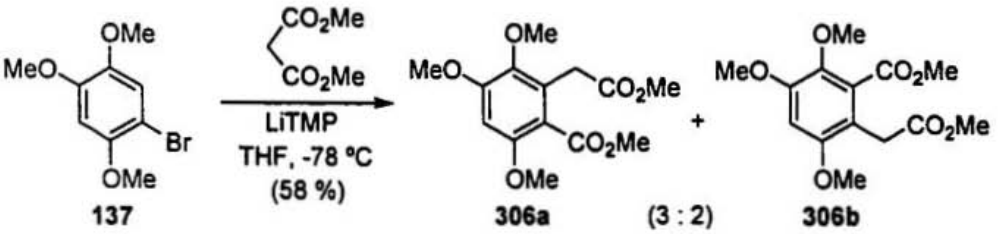


Kita recently reported the first enantioselective synthesis of **91** (34 steps) through an anionic [4 + 2] cycloaddition between homophthalate ester **306a** and enedione **305** (Schemes 25 b-d).[32] Both natural and *ent*-**91** were synthesized in separate runs using **306a** and **306b** (Scheme 25e). Based on the known stereochemistry of **305** (from an X-ray structure of **302**) and the predicted regiochemical course of the [4 + 2] cycloaddition, the configuration of the stereogenic center in **91** was ascertained to be *S* by comparison of the circular dichroism (CD) spectrum with that of natural fredericamycin A.

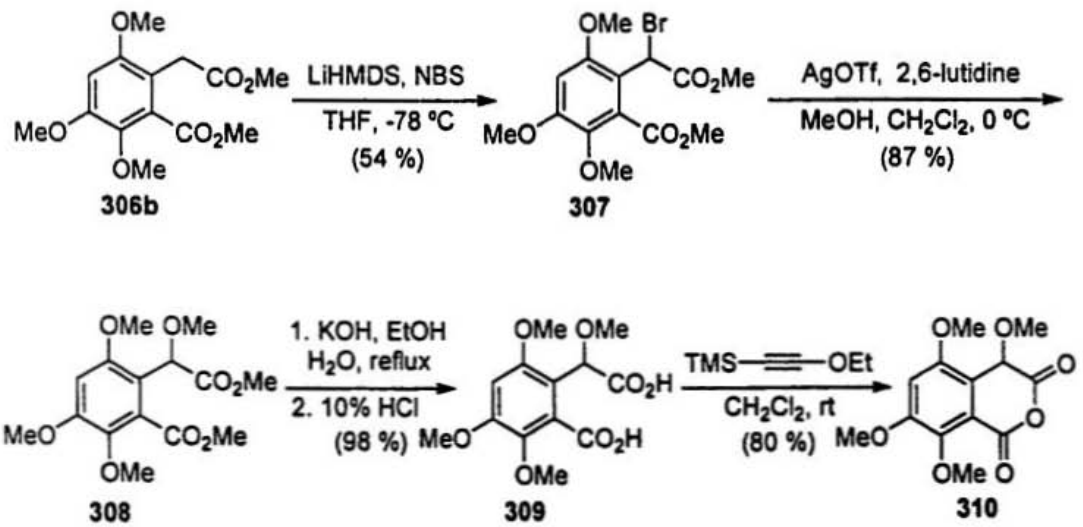
Scheme 25b


OMe
CO2Me
N
295
LDA
O
OTBDMS
()3
296
OMe OH O OTBDMS
()3
297
1. DDQ
2. MeI, K2CO3
3. TBAF
4. Swern oxidation
MeO MeO OHC
O
298
1. SmI2
2. Swern oxidation
3. HCO2H, H2SO4
MeO MeO O
299
H Ph
Ph
N
O
B
Me
(S)-289
BH3·Me2S
THF, 0 °C
(98 %, 74 % ee)
MeO MeO HO
(+)-300
t-BuOOH
VO(acac)2
PhH, 0 °C→rt
(81 %)
MeO MeO HO
O
(-)-301
Ph3P, DEAD
CmpOH, PhMe
0 °C→rt
(59 %)
COCmp
O
MeO MeO
O
(-)-302
BF3·Et2O
CH2Cl2
0 °C
(94 %)
CmpOC
MeO MeO
O
O
(+)-303
1. (CH2OTMS)2, TMSOTf
0 °C→rt (93 %)
2. 10% NaOH, MeOH
(97 %)
3. DM periodinane
CH2Cl2 (98 %)
4. PhSSO2Ph, LiHMDS
THF, -78 °C→rt (98 %)
PhS SPh
MeO MeO
O
O
O
(+)-304
1. TFA, H2O, 50 °C (92 %)
2. m-CPBA, CH2Cl2
-40 °C→rt (93 %)
PhS+ O-
MeO MeO
O
O
(+)-305

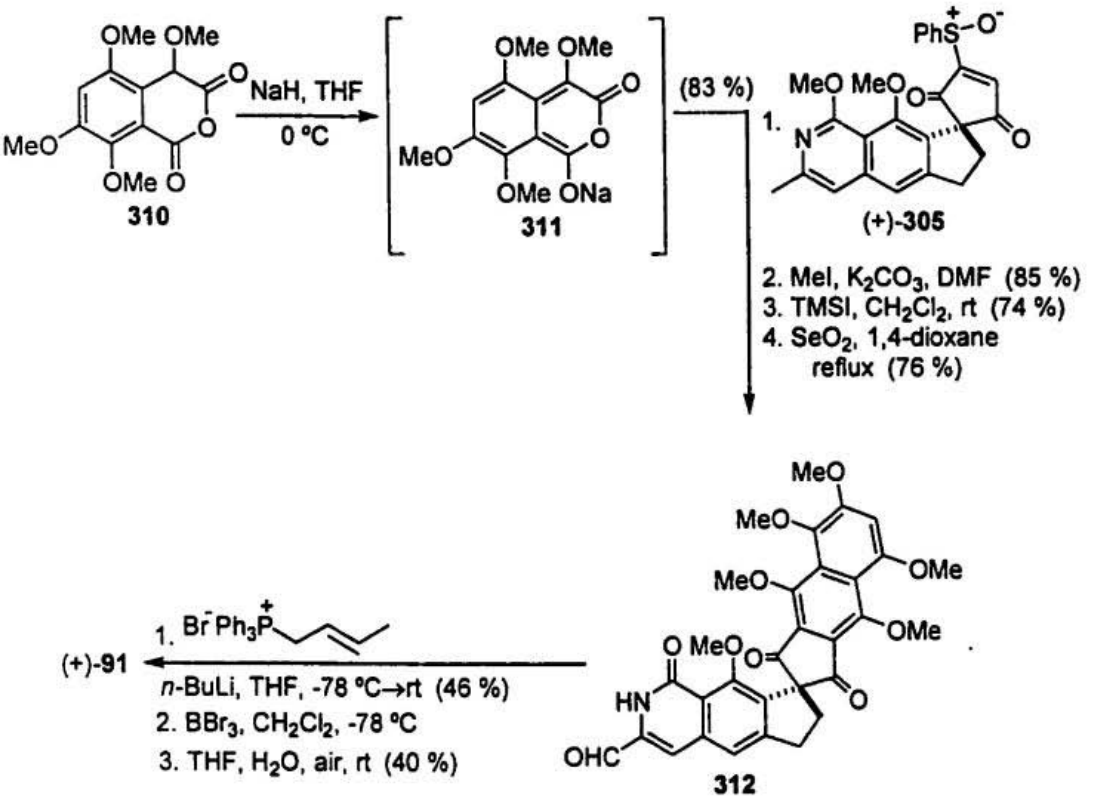
Scheme 25c



Scheme 25d



Scheme 25e


OMe OMe
NaH, THF
0 °C
MeO
OMe O
310
OMe OMe
MeO
OMe ONa
311
(83 %)
1.
MeO MeO
PhS
(+)-305
2. MeI, K2CO3, DMF (85 %)
3. TMSI, CH2Cl2, rt (74 %)
4. SeO2, 1,4-dioxane
reflux (76 %)
MeO
MeO
MeO
OMe
OMe
O MeO
HN
OHC
312
1. Br Ph3P
(+)-91
n-BuLi, THF, -78 °C→rt (46 %)
2. BBr3, CH2Cl2, -78 °C
3. THF, H2O, air, rt (40 %)

Retrosynthetic Analysis and Preliminary Studies

In fredericamycin A the absolute configuration of the single stereocenter, located at the spiro ring junction between the C and D rings, is determined by the position of the remote A-ring methoxy substituent. We reasoned that use of the geminal acylation protocol for C ring dione assembly would be perfectly suited for an asymmetric synthesis of **91** in light of the precedent set in our laboratory for the enantioselective reduction of spiro-1,3-cyclopentanediones by Baker's yeast.[10b]

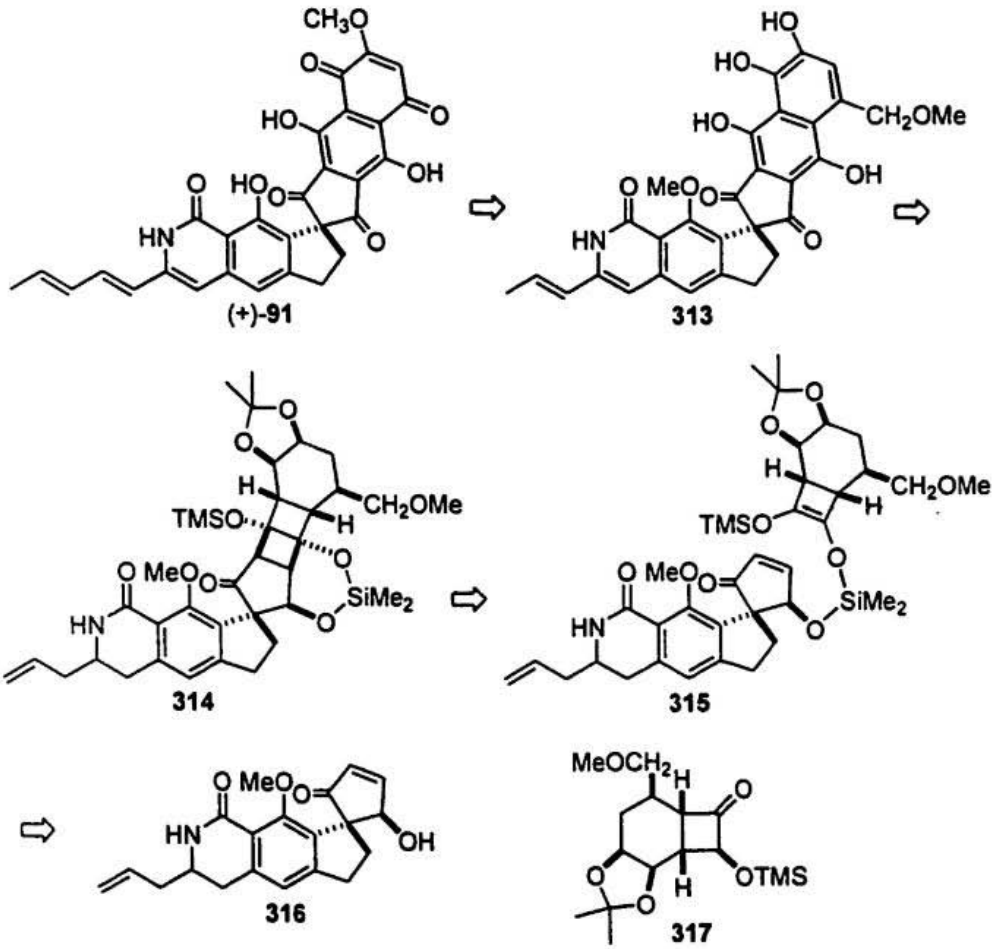
Regiocontrolled Photoaddition Involving a Disposable Silicon Tether

Our retrosynthetic disassembly of fredericamycin A is illustrated in Schemes 26a,b and c. We chose a silicon-tethered [2 + 2] photoaddition[34] between enone **316** and the silyl-enol ether of racemic cyclobutanone **317** followed by oxidative scission of the latent diol-flanked central bond of the resulting bicyclo[2.2.0]hexane in **314** for introduction of the AB portion of **91**. Subsequent oxidation, conversion of the remote A ring hydroxyl to a methyl ether and introduction of the F ring diene appendage would provide one of either natural **91** or its enantiomer. From Kita's recently published asymmetric synthesis of **91** (Schemes 25b-25e),[32] it appears that our initial guess of the absolute configuration of **91** was correct.

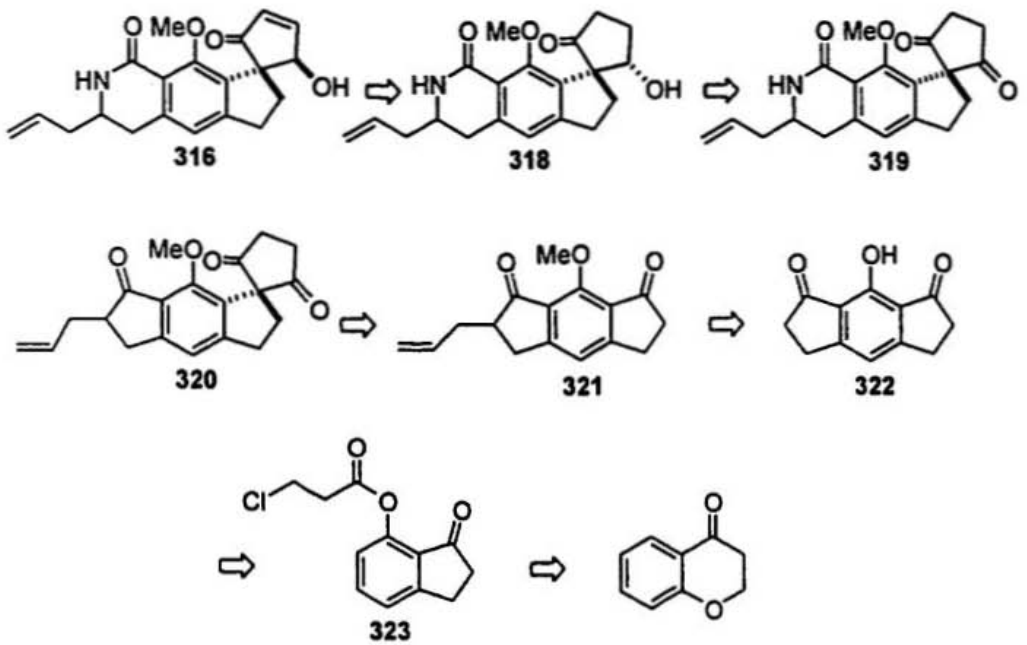
Reduction of dione **319** (Scheme 26b) with Baker's yeast is anticipated to yield the *S* configuration at both the hydroxyl bearing stereocenter and the spiro center in **318**.[10b] For the tethered [2 + 2] cycloaddition, analysis using molecular models suggested the *endo* mode of addition would be preferred. Inversion of the stereochemistry at the hydroxyl-bearing stereocenter in **318** using Mitsonobu's conditions[35] was planned prior to

the tethering operation since delivery of the silyl-enol ether to the face of the enone *anti* to the aromatic portion of **314** would likely occur more readily.

Scheme 26a

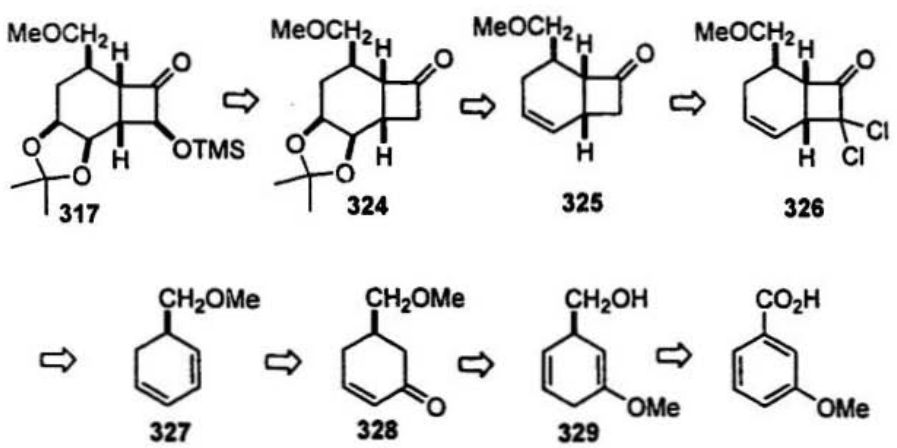


Scheme 26b



Retrosynthetic disassembly of cyclobutanone **317** is shown in Scheme 26c. Our plan for the assembly of **317** relied on the ease with which fused bicyclic cyclobutanones are formed from the addition of dichloroketene to intraannular 1,3-dienes.[36]

Scheme 26c

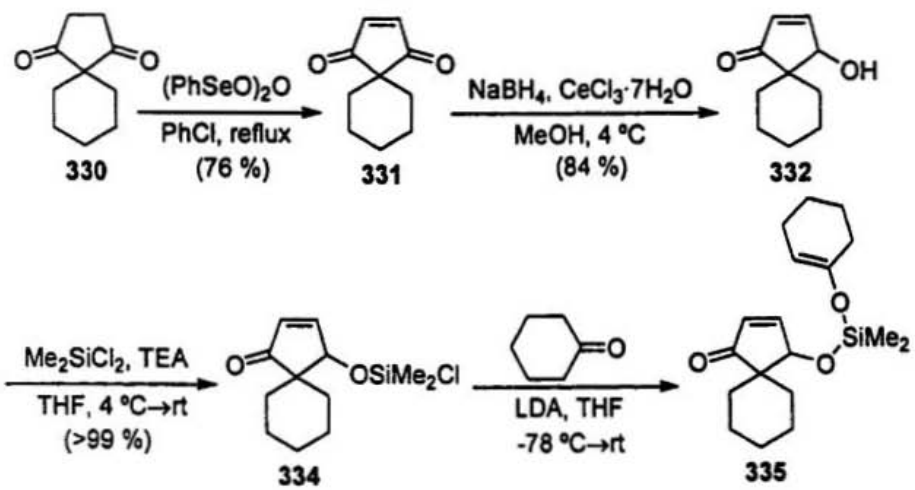


Two of the required A ring oxygens in **91** were to originate from the 1,2-diol formed by dihydroxylation of the double bond in **325**. The third oxygen was to be introduced at the end of the synthesis by conversion of the A-ring methyl ether in **313** (Scheme 26a) to an aldehyde, followed by a Baeyer-Villiger oxidation.[37] Enone **328**, from which diene **327** was to be fashioned using a Shapiro reaction,[38] should have been readily available from *m*-anisic acid by Birch reduction, conversion of the carboxylic acid function to the hydroxymethyl handle for introduction of the remaining A ring oxygen, and acidic hydrolysis of the enol ether.[39] While the addition of dichloroketene to **327** would occur without any regiochemical preference likely resulting in a low yield of **326**, it was anticipated that this material would be available in large quantities using this route.

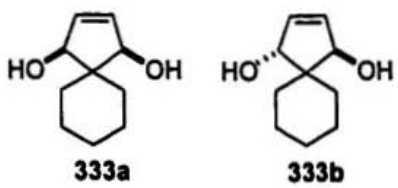
A CDEF fragment similar to dione **319** (Scheme 26b) had previously been assembled by geminal acylation of an indanone acetal with **1** (see **253** (Scheme 23a) and **280** (Scheme 24a)).[11b,11c] We aimed to synthesize the C ring in a similar fashion, however, our plan for the construction of the F ring differed from previous syntheses of **91**. We envisioned that the isoquinolinone portion could be formed using a Beckmann rearrangement. Thus, it should have been possible to assemble dione **319** from symmetrical ketone **322**, which might arise through a Fries rearrangment employing acylated phenol **323**. The required 7-hydroxyindanone was readily available from 4-chromanone by aluminum trichloride-catalyzed rearrangement.[40]

To begin assessment of the viability of the tethered photoaddition, we selected model compound **335** as our initial target. Compound **335** was assembled as illustrated in Scheme 27a.

Scheme 27a



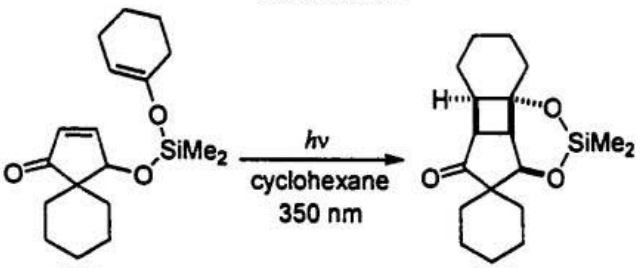
Diketone **330**, available from cyclohexanone and **1**,[6] was oxidized to enedione **331** with benzeneseleninic anhydride.[41] Luche reduction[42] gave **332** along with a 14 % yield of a mixture of *cis*- and *trans*-1,4-diols (**333a,b**).



333a **333b**

Treatment of **332** with a large excess of dichlorodimethylsilane provided silyl ether **334** that was added to the lithium enolate[43] of cyclohexanone to give **335**. Irradiation of a cyclohexane solution of the crude material from the unoptimized trapping experiment gratifyingly produced *endo*-photoadduct **336** (Scheme 27b).

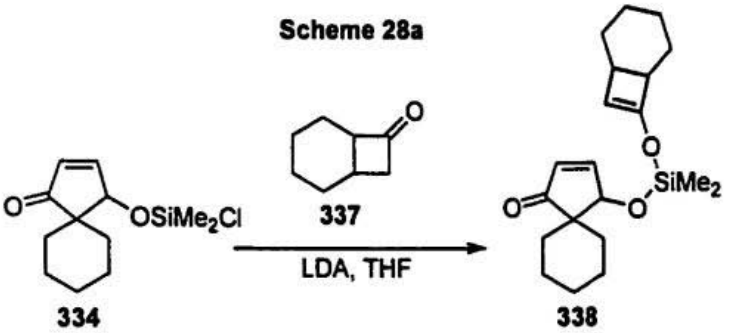
Scheme 27b



335 **336** (19 % from **332**)

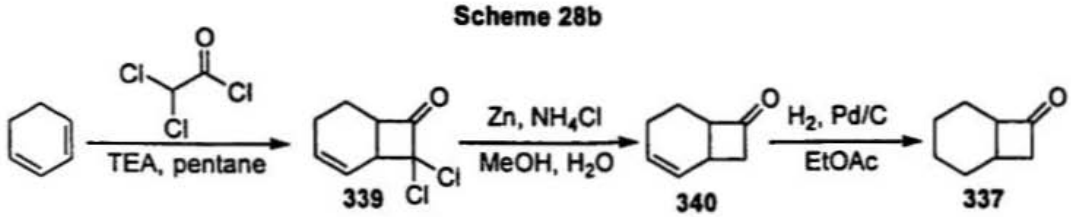
Encouraged by this result, we next sought to determine if we could construct a similar system from **334** and bicyclo[4.2.0]octan-2-one (**337**) (Scheme 28a). Compound **337** was prepared by hydrogenation of **340**, the dehalogenated product of the addition of dichloroketene to cyclohexadiene (Scheme 28b).[36]

Scheme 28a



334 **338**

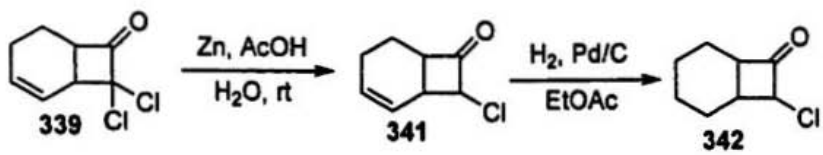
Scheme 28b



Treatment of **337** with LDA at -78 °C followed by the addition of **334** produced a complex mixture of products, none of which were identified as **338**. An examination of the literature on this subject revealed that the standard amide deprotonation protocol for the generation of enolates[43] typically fails with cyclobutanones.[44] Cyclobutanone enolates can however be formed by a metal-halogen exchange reaction using an α-chlorocyclobutanone.[44]

Monochlorocyclobutanone **341** was prepared from **339** by monodechlorination followed by catalytic hydrogenation of the double bond (Scheme 28c). Attempts to trap the lithium enolate of **337**, generated by treatment of **342** with Me_2CuLi at -78 °C in ether, with **334** failed to produce detectable amounts of **338**.

Scheme 28c

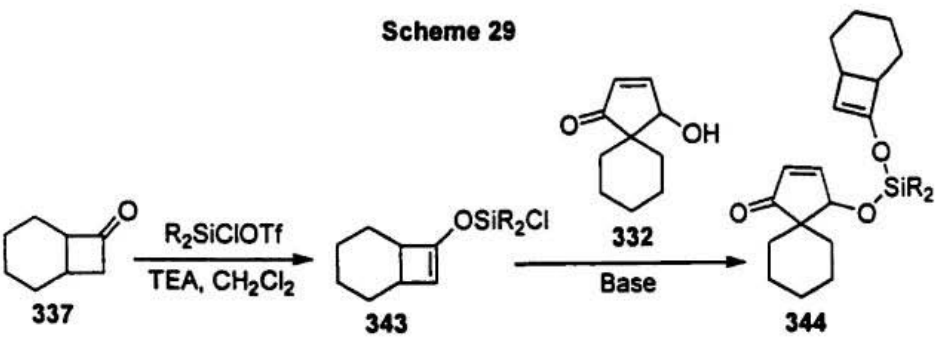


Another commonly used method for generating silyl-enol ethers from ketones employs silyl triflates in the presence of an amine base.[45a,b] We reasoned that it might be possible to construct **338** by treatment of **332** with the chlorodialkylsilyl enol ether of **337** made in this manner (Scheme 29). The lack of a literature precedent for the preparation

of chlorodimethylsilyl trifluoromethanesulfonate limited our choices to the bulkier silylating reagents chloro-di-*tert*-butysilyl trifluoromethanesulfonate and chlorodiphenylsilyl trifluoromethanesulfonate. These reagents can be prepared from the commercially available chlorosilanes by treatment with trifluoromethanesulfonic acid.[46] The reaction of chlorodimethylsilane with trifluoromethanesulfonic acid gave dimethylsilyl trifluoromethanesulfonate instead of the desired chlorodimethylsilyl trifluoromethanesulfonate.

Attempts to prepare **344** (R=*t*-Bu, Scheme 29) using a variety of conditions for the tethering step (TEA or DBU at rt or reflux, LDA at -41 °C) did not provide any evidence supporting the formation of **344**. Faced with this disappointing result, we decided to redesign our synthetic strategy for the introduction of the AB portion of **91**.

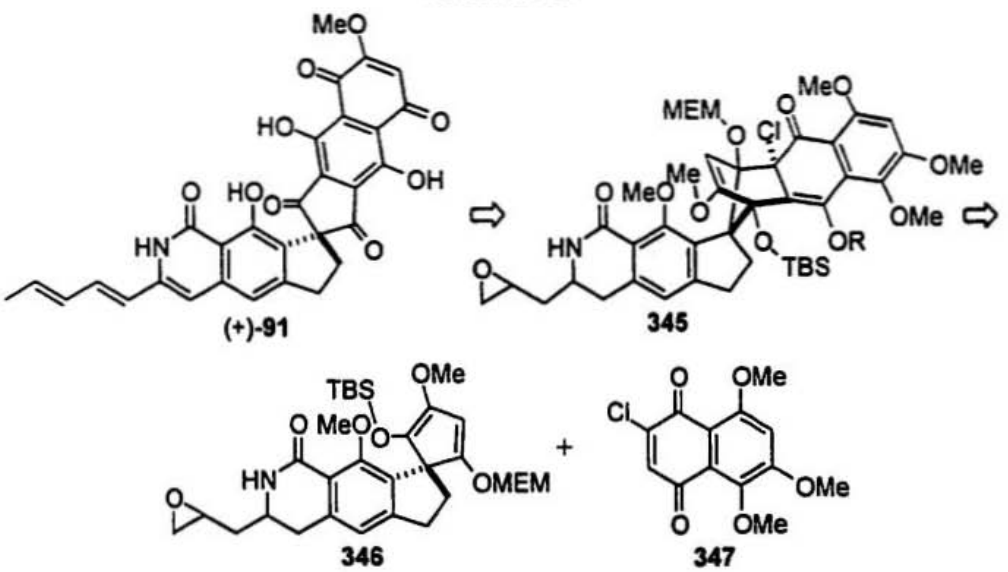
Scheme 29



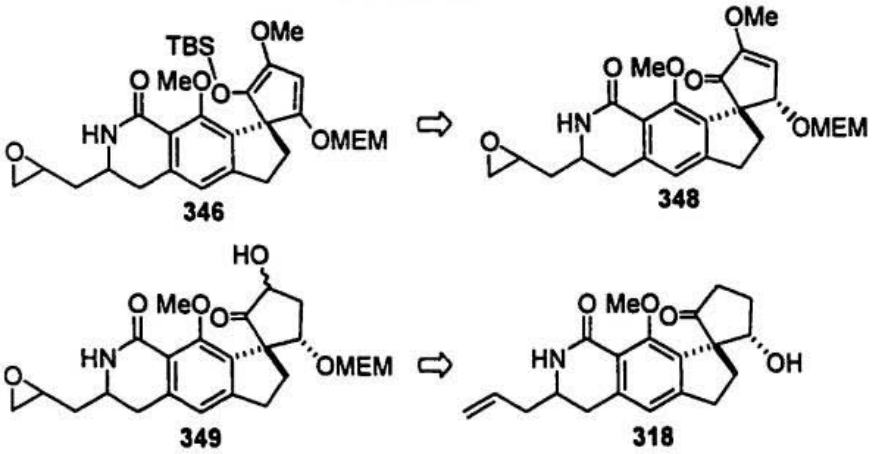
Regiocontrolled Diels-Alder Strategy - Retrosynthetic Analysis

Our second idea for an enantioselective synthesis of **91** relied on a Diels-Alder reaction for introduction of the AB naphthoquinone. The high level of regiocontrol available in this reaction was well-suited to our strategy based on ketol **318**. In contrast to the Diels-Alder strategies used in previous syntheses of **91** by Julia,[11b] Bach,[11c] and Kita,[32] we envisioned forming the diene component from **318** (Scheme 30b). Diels-Alder addition of chloronaphthoquinone **347** to **346** (Scheme 30a), excision of the extraneous two-carbon bridge on treatment of **345** with fluoride ion (Scheme 30c), introduction of the diene by a Stille coupling using the aldehyde present in **350** and application of Clive's demethylation/oxidation protocol[30] (Scheme 21d) was anticipated to give (+)-**91**.

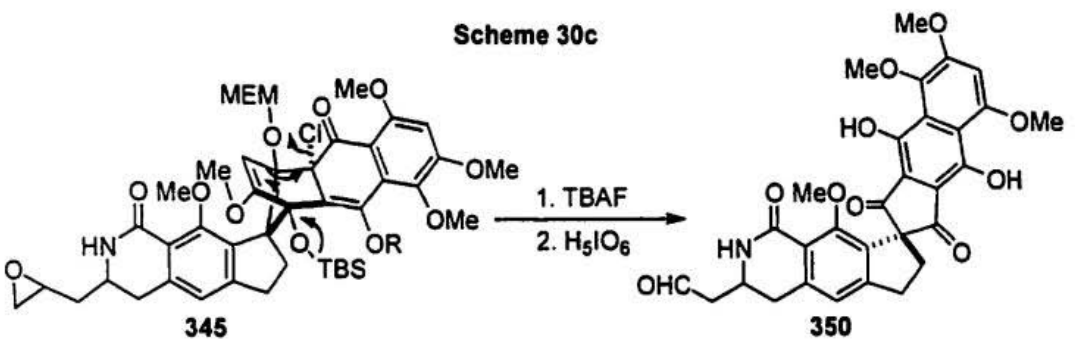
Scheme 30a



Scheme 30b

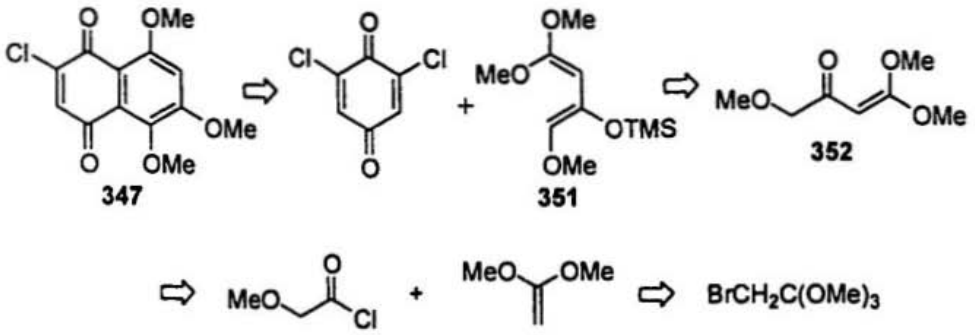


Scheme 30c



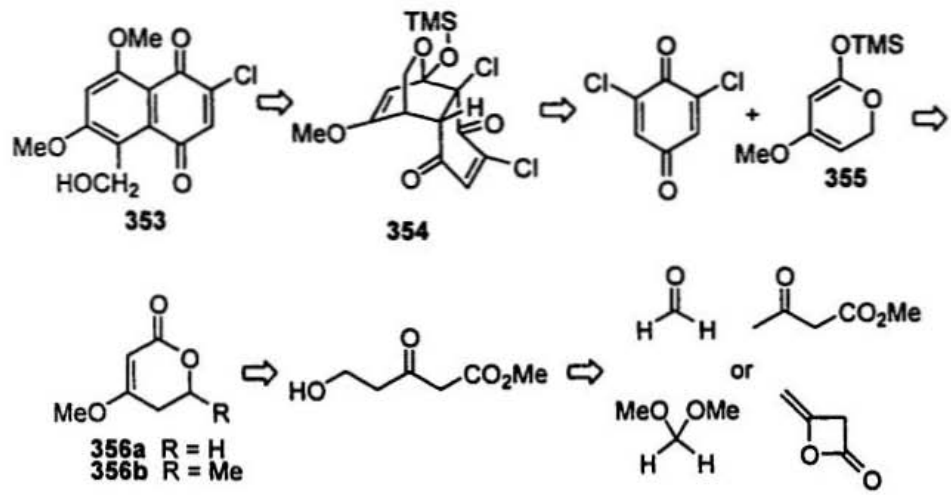
We planned to prepare chloronaphthoquinone **347** via aromatization of the product from the Diels-Alder addition of 2,5-dichloro-1,4-benzoquinone to Brassard's diene **351**[47a] (Scheme 30d). Compound **351** is available from **352**, the product of a thermal ring opening of the cyclobutene-derived from the [2 + 2] cycloaddition of methoxyketene to ketene dimethyl acetal.[47a,48]

Scheme 30d



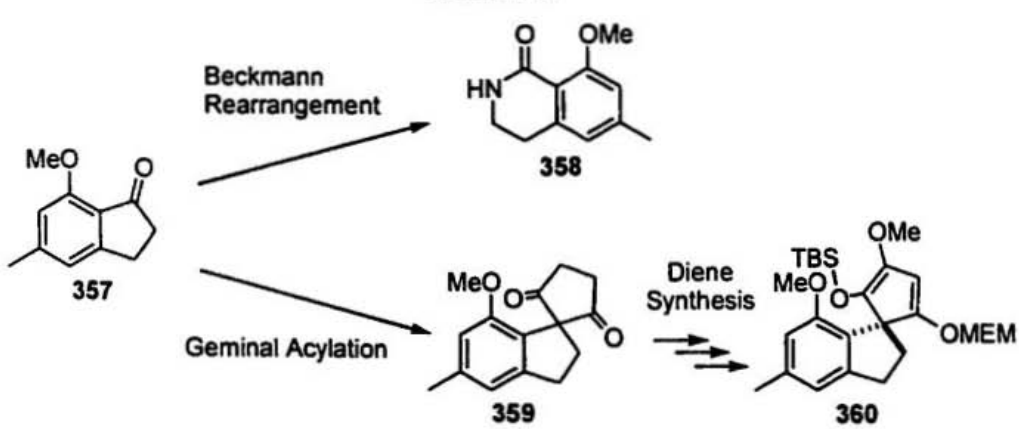
In the event that our synthesis of **347** was unsuccessful, we could also proceed with the crucial Diels-Alder step using naphthoquinone **353**, the aromatized product of a Diels-Alder addition of 2,6-dichloro-1,4-benzoquinone to diene **355** (Scheme 30e). We planned to construct **354** by treatment of **356a** with LDA followed by trapping of the resultant anion as a silyl ether. 5,6-Dihydro-2-pyrone **356b** has previously been prepared from the dianion of methylacetoacetate and acetaldehyde, as well as by $TiCl_4$-promoted addition of diketene to the dimethyl acetal of acetaldehyde.[49a,b] However, in the interest of selectively introducing the remaining A ring oxygen of **91** by Baeyer-Villiger type oxidation[37] while avoiding extra protection steps needed to preserve the C ring ketone functionalities, it would be sensible to explore the possibility of preparing **356a**. Since the stereochemistry at the asymmetric center in **91** was unknown when we started work in this area, we aimed to devise a synthetic plan that would concurrently provide both enantiomers of fredericamycin A. Note that access to enantiomeric **91** should be possible by substituting 2,5-dichloro-1,4-benzoquinone for 2,6-dichloro-1,4-benzoquinone into either of Schemes 30d or e.

Scheme 30e



The symmetry of ketone **322** (Scheme 26c) made it possible to use compound **357** as the model for both the studies on formation of the F ring by a Beckmann rearrangement strategy and for the construction of diene **360** (Scheme 31). Compound **357** was prepared by methylation (K_2CO_3, MeI, acetone, reflux (97 % yield)) of phenol **261** from Bach's synthesis of **91**[11c] (Scheme 23b).

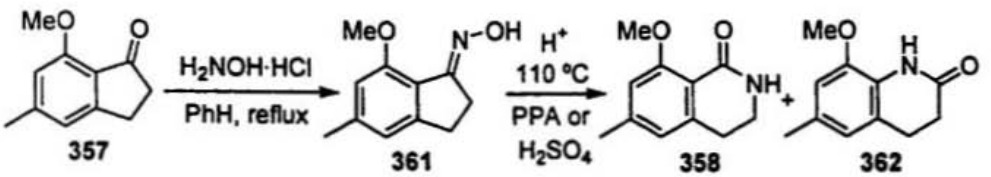
Scheme 31



F Ring Construction: Beckmann Rearrangement

In a Beckmann rearrangement (Scheme 32), **357** might potentially form the desired isoquinoline **358** by migration of the alkyl group or quinoline **362** by migration of the aryl group.[50a]

Scheme 32



Depending on the substrate and reaction conditions, either a trigonal (Scheme 33a) or tetrahedral (Scheme 33b) mechanism or a mixture of both processes may be in operation.[50b] The bond reorganization may also be concerted or involve discrete nitrenium and nitronium ions, respectively.[51a,b,d]

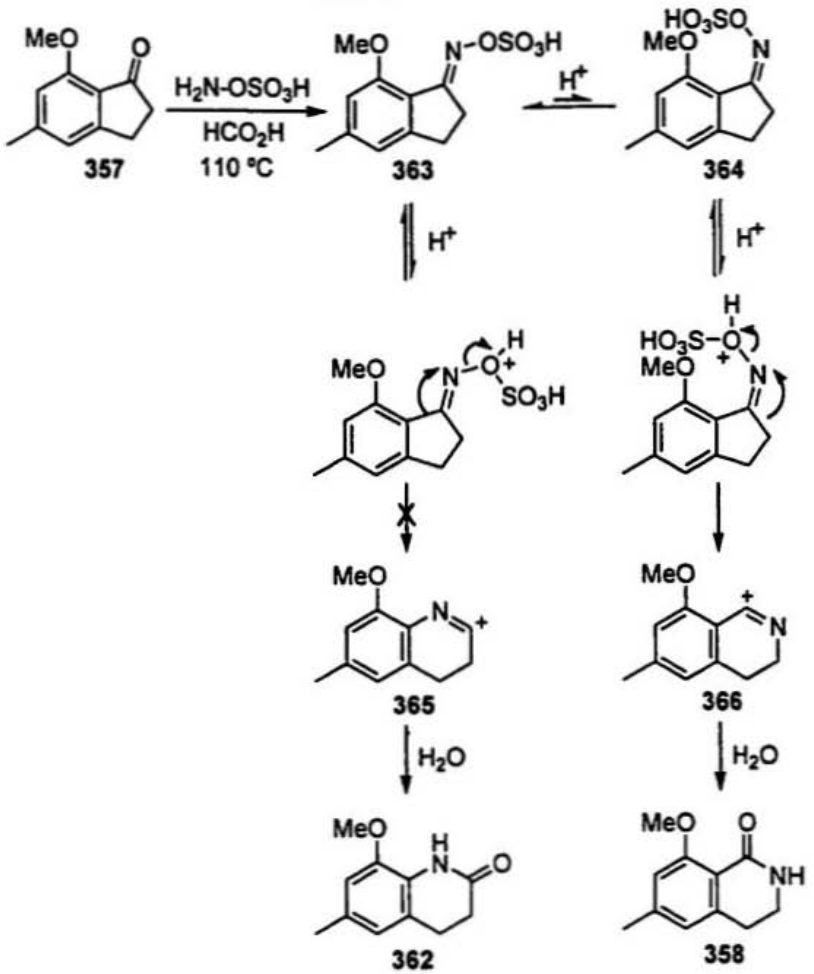
For a Beckmann rearrangement proceeding via a concerted trigonal process, under conditions where rearrangement is faster than oxime isomerization, migration of the bond situated *anti* and coplanar to the N-O bond of the thermodynamically favored oxime would lead to the major product. If oxime isomerization is faster or the process proceeds via a nitrenium ion, the relative migratory aptitudes of the two oxime substituents will determine the product ratio. Migratory aptitudes will play the major role in determining the course of the rearrangement in the tetrahedral mechanism, as oxime geometry is no longer a controlling factor. Migratory aptitudes are known from the work of Beckmann and Schmidt to depend on a variety of factors such as the identity and orientation of the

leaving group, the solvent and catalyst, electronic variables, torsional strain and other conformational factors associated with the substrate.[52]

Yields tend to be moderate under classical Beckmann conditions for rearrangement of free indanone oximes (Scheme 32).[50a] The process can be facilitated by conversion of the oxime OH to a mesylate or tosylate, although this requiries an additional synthetic step.[51a] Olah's procedure (hydroxylamine-*O*-sulfonic acid, formic acid (97 %), 110 °C) accomplishes formation of the activated oxime and the Beckmann rearrangement in a single operation.[53] When **357** was treated with hydroxylamine-*O*-sulfonic acid in refluxing formic acid (88 %), the desired isoquinoline **358** was produced in quantitative yield.

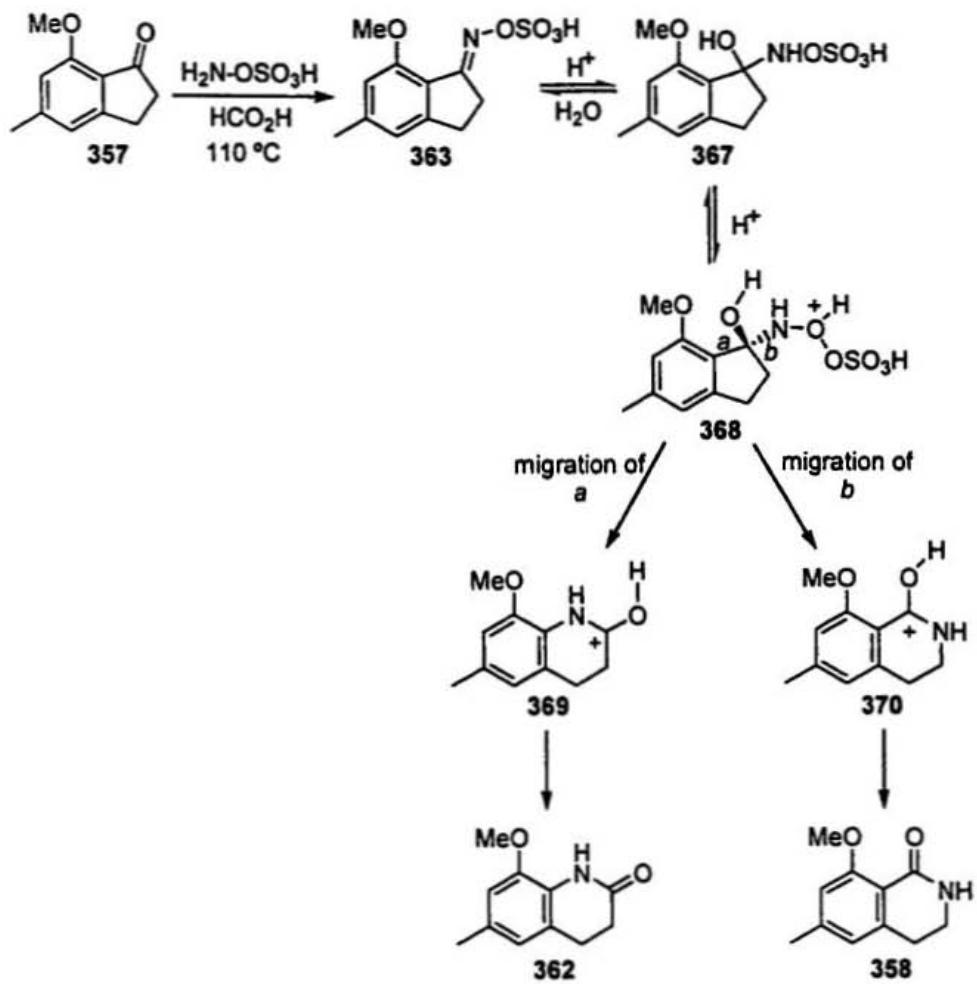
It is generally accepted that Beckmann rearrangements proceed via the concerted trigonal process, as shown in Scheme 33a.[51a] If this is true for the conversion of **357** to **358**, the structure of the product should correlate with the geometry of the oxime from which it originated. Upon initial examination, this seemed unlikely since the transformation would have had to occur through the less stable geometrical isomer **364**. Migration of the aryl group would cause greater torsional strain than migration of the alkyl group in the transition state of the Beckmann rearrangement of 1-indanones.[50a,51c,d] Thus, the experimental result may reflect this if oxime isomerization was faster than rearrangement in this instance.

Scheme 33a



The corresponding tetrahedral process (Scheme 33b) introduces an additional consideration that may better explain the observed selectivity and yield. Acid-assisted nucleophilic attack of water onto oxime **363** would give tetrahedral intermediate **367**, which could rearrange following protonation of the oxime oxygen to give **362** or **358** via migration of bond *a* or *b* respectively.

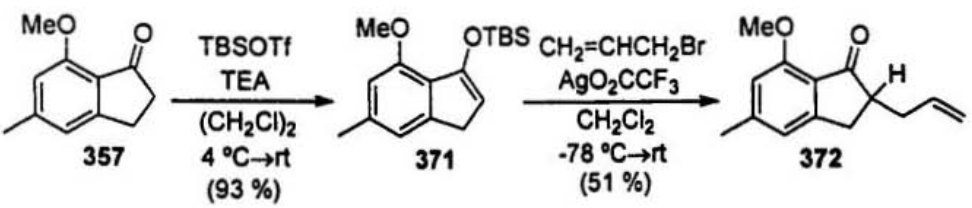
Scheme 33b



The developing positive charge at the ex-carbonyl carbon can be delocalized into the aromatic ring in **370** but not in **369**. Thus, migration of bond *b* would be favored as a result of stabilization of the transition state leading to **358**. Note that similar benzylic stabilization of the positive charge in **366** (Scheme 33a) is precluded due to the orthogonal relationship of the sp^2 orbital at the ex-carbonyl carbon and the aromatic π-electron cloud.

Application of this methodology in a synthesis of **91** would necessitate that pre-existing functionality be present to facilitate introduction of the F-ring diene appendage near the end of the synthesis. We envisioned an allyl group serving as a suitable surrogate for this purpose. Introduction of the F ring diene sidechain could then be accomplished by a Stille coupling[54] following conversion of the terminal olefin into the requisite enol triflate. To test the effect of this added functionality on the course of the Beckmann rearrangement, we prepared α-allylindanone **372** by treatment of enol silyl ether **371** with allyl bromide in the presence of silver trifluoroacetate (Scheme 34).[55]

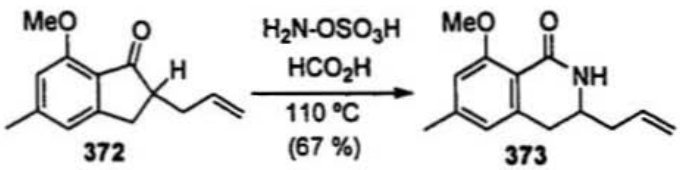
Scheme 34



357 **371** **372**

When **372** was subjected to Olah's one-pot Beckmann conditions, in an unoptimized experiment, the desired dihydroisoquinoline **373** was produced in 67 % yield (Scheme 35) along with recovered **372** (*ca.* 10 %). With the viability of this strategy for construction of the F ring established, we next focused on fashioning the C ring diene crucial to our synthetic plan for Diels-Alder assembly of the naphthoquinone portion of **91**.

Scheme 35



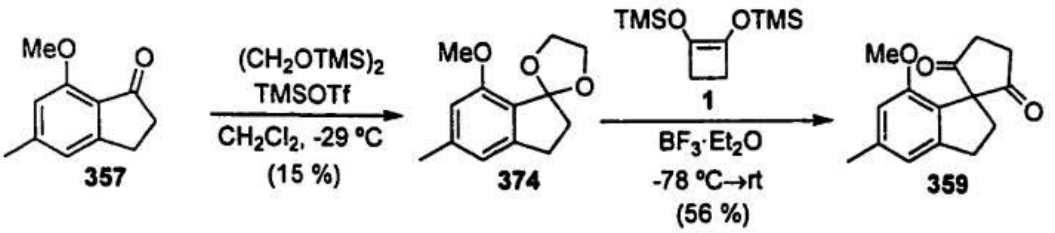
372 373

Diels-Alder Strategy - Efforts Directed at Synthesis of the C Ring Diene

In order to differentiate between the two ketone functionalities in **321** (Scheme 26b), the geminal acylation reaction to form the C ring of **91** might be carried out before the Beckmann rearrangement. The presence of a geminally-substituted center next to both carbonyl functions in **320** should direct oxime formation to the less hindered carbonyl of the remaining indanone nucleus. Likewise, the presence of the allyl group should have a similar directing effect on the geminal acylation reaction.

To begin our investigations into construction of the C ring diene, we had originally planned to prepare **359** by direct geminal acylation of **357**. However, the $BF_3{\cdot}Et_2O$-catalyzed reaction of **357** with **1** returned the starting indanone unchanged. In contrast, the corresponding ethylene acetal **374** reacted smoothly with **1** to produce the desired spiro-1,3-diketone **359** (Scheme 36). The anticipated difficulty associated with direct geminal acylation of the less hindered indanone in **321** would require prior selective formation of an acetal at that site, a difficult task owing to the reversibility of this reaction and likely only a small energy difference between both possible acetals. Thus, if conditions could not be found for direct geminal acylation of the methoxyindanone, additional protection steps would be necessary to avoid formation of the oxime at the less hindered site.

Scheme 36

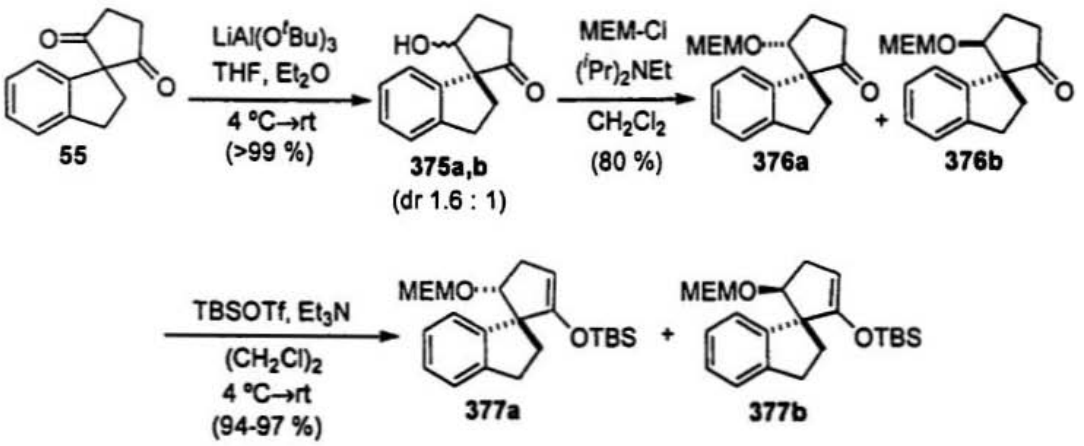


Acetal **374** was prepared in 15 % yield using the conditions of Noyori.[56] The major component of the reaction mixture was **357**, recovered in 74 % yield. Similar experiments conducted at -41 °C with 1-indanone and 1-tetralone provided the corresponding ethylene acetals in 78 % and 90 % yield.

The added synthetic operation and the need for optimization of the conditions for forming an ethylene acetal from **357** prompted us to assess the viability of our Diels-Alder plan for the construction of the ABC portion of **91** starting from **55** (Scheme 37).

Cyclopentanedione **55** was prepared from 1-indanone in 75 % yield. Monoreduction of **55** with lithium tri-*tert*-butoxyaluminohydride gave a 1.6 : 1 mixture of diastereomeric ketols **375a,b** (Scheme 37). Analytical samples of each diastereomer as 2-methoxyethoxymethyl (MEM) ethers[57] **376a,b** were obtained by column chromatography. NOE measurements on **376b** revealed that hydride delivery *anti* to the aromatic portion of **55** resulted in production of the major ketol diastereomer **375a**. Treatment of the mixture of **376a,b** with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) in the presence of triethylamine (TEA) resulted in smooth conversion to the corresponding silyl-enol ethers **377a,b**.

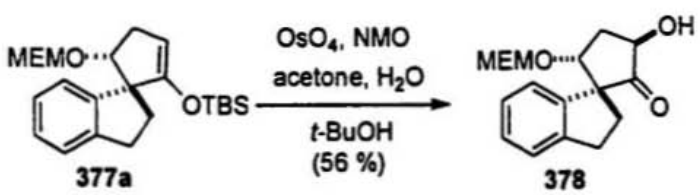
Scheme 37



We planned to introduce a hydroxyl group α to the carbonyl functionality in **376a,b** either by epoxidation or dihydroxylation of the mixture of enol ethers **377a,b**. Rubottom oxidation (*m*-chloroperoxybenzoic acid (*m*-CPBA), $NaHCO_3$)[58a] produced a complex mixture of products whereas attempted epoxidation with methyltrioxorhenium/hydrogen peroxide[58b] resulted only in the hydrolysis of the enol

silyl ether to regenerate **376a,b**. Attempted dihydroxylation with catalytic amounts of OsO_4 using either *N*-methylmorpholine-*N*-oxide (NMO) (Upjohn conditions)[58c] or *tert*-butylhydroperoxide (Sharpless conditions)[58d] as the stoichiometric oxidant also failed to produce any of the desired α-hydroxy ketone. Attempts to dihydroxylate **377a,b** using a stoichiometric proportion of OsO_4 in the presence of a catalytic amount of pyridine in aqueous acetone resulted only in hydrolytic regeneration of **376a,b**. Interestingly, when a stoichiometric amount of OsO_4 was added in one portion to the reaction of **377a** under the Upjohn conditions, **378** was produced as a single diastereomer in 56 % yield (Scheme 38a).

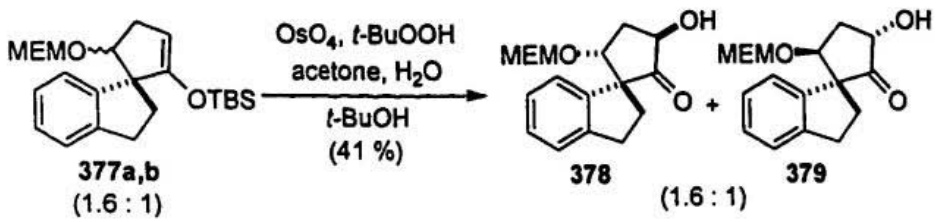
Scheme 38a



377a **378**

Addition of 0.25 equivalents of OsO_4 to the reaction of **377a,b** (1.6 : 1) under Sharpless conditions was sufficient to force the reaction to completion (Scheme 38b) producing **378** and a second diastereomer **379** (1.6 : 1, respectively) in 41 % yield. The stereochemistries of **378** and **379** were both established by NOE measurements in the ^1H NMR.

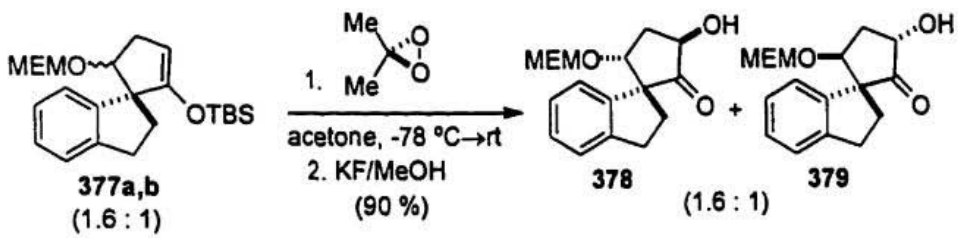
Scheme 38b



377a,b (1.6 : 1) **378** **379** (1.6 : 1)

Faced with modest yields of **378** and **379** and the prospect of using large amounts of expensive and toxic osmium tetroxide, we next turned our attention to the versatile oxidant dimethyl dioxirane.[58c] Treatment of the mixture **377a,b** with a freshly prepared 0.1 M solution of dimethyl dioxirane in acetone followed by opening of the resulting three-membered acetal with methanolic potassium fluoride resulted in clean conversion to **378** and **379** (Scheme 38c).

Scheme 38c

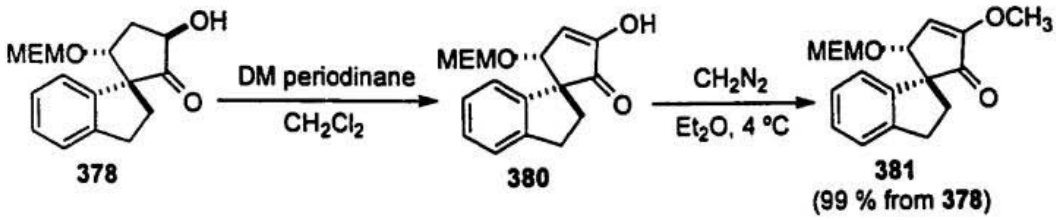


377a,b (1.6 : 1) **378** **379** (1.6 : 1)

The fact that only two of the four possible diastereomers were produced in the epoxidation and dihydroxylation reactions meant that **377a** and **377b** must have each given only one product. The observed stereochemistries of **378** and **379** correlated with preferential delivery of the oxidant *anti* to the MEM ether substituent.

Oxidation of the secondary alcohol in **378** with Dess-Martin periodinane[59] gave enol **380**. Treatment of **380** with diazomethane afforded methyl ether **381** in 99% overall yield (Scheme 39). We were now in a position to evaluate our synthetic plan for the construction of the ABCDE portion of **91**.

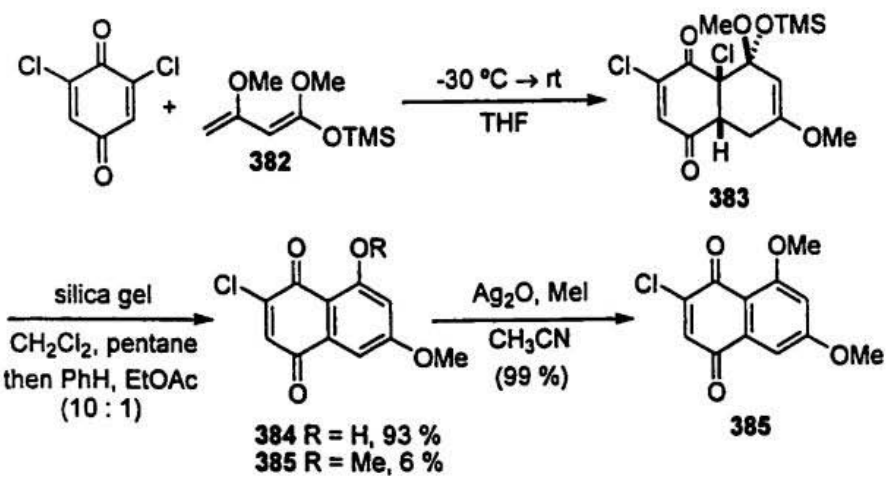
Scheme 39



378 **380** **381** (99 % from **378**)

We planned to form diene **386** by deprotonation at the γ-position of enone **381** followed by trapping of the resulting dienolate as a silyl ether.[60] We selected **385** as a suitable model for chloronaphthoquinone **347**. Quinone **385** was prepared according to the method of Brassard (Scheme 40).[47b]

Scheme 40



382

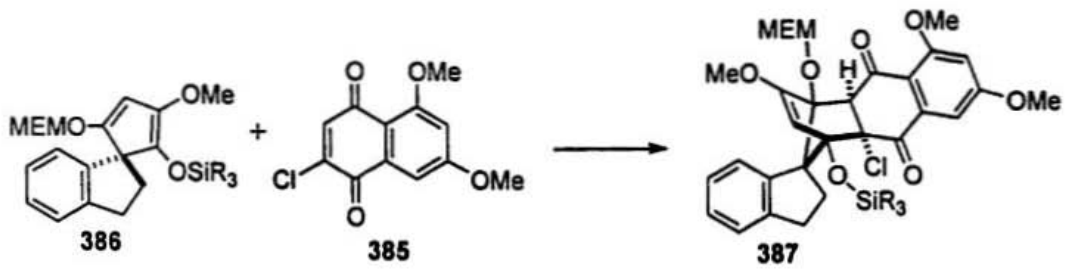
383

384 R = H, 93 %
385 R = Me, 6 %

385

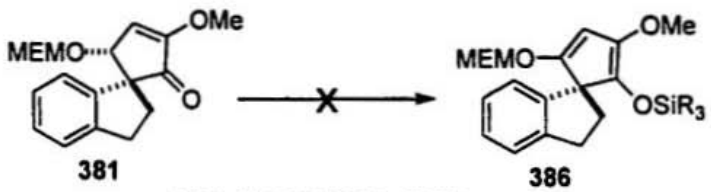
It was anticipated that the addition of chloronaphthoquinone **385** to **386** could be carried out in a highly regioselective manner (Scheme 41) based on well-known frontier molecular orbital (FMO) considerations in the Diels-Alder reaction.

Scheme 41



Our attempts to prepare **387** by treatment of **381** with LDA and chlorotrimethylsilane at -78 °C followed by the addition of **385** produced a complex mixture of products. A similar experiment employing *N*-phenylmaleimide (NPM) as the dienophile failed to provide any of the corresponding Diels-Alder adduct. If diene **386** did form, the absence of a reaction with NPM would be unusual. The brown color that developed following the addition of **381** to LDA suggests **381** decomposed under these conditions. Attempts to form **386** under a variety of other conditions (Scheme 42) returned unreacted **381**.

Scheme 42



381 **386**

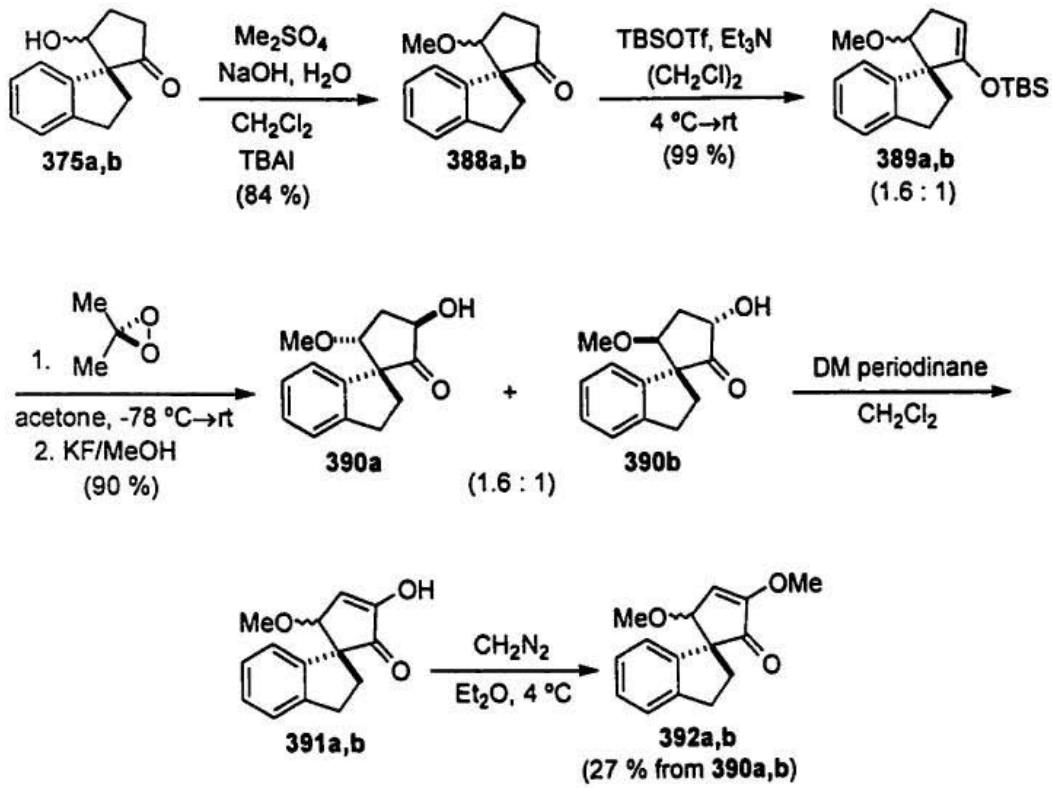
-LDA, THF, TMSCl, -78 °C
-TEA, TBSOTf, 1,2-DCE, 4 °C→rt
-NaH, THF, TBSCl, rt
-KH, THF, TBSCl, rt
-KH, 18-crown-6, THF, TBSCl, rt
-LiHMDS, THF, -95 °C, TBSCl
-LiHMDS, THF, -78 °C, TBSOTf
-LiHMDS, THF, -29 °C, TBSCl

Examination of the crude product mixture from the reaction of **381** with LDA revealed that the MEM protecting group was no longer present. The absence of any reaction with lithium bis(trimethylsilylamide) (LiHMDS) may suggest that removal of the γ-hydrogen in **381** may be suppressed by surrounding steric encumbrance. In the absence of the desired reaction, other destructive processes possibly involving loss of the MEM ether, may have been initiated with LDA. If this were true, use of a less labile methyl-ether protecting group at this center seemed like a reasonable solution to the problem.

From the outset we were keenly aware of the retro aldol reaction possible with the β-hydroxy ketone functionality in **375a,b** under the strongly basic conditions usually required for methyl ether formation. Fortunately, under conditions of phase-transfer catalysis (PTC), it was possible to convert **375a,b** to the corresponding methyl ethers **388a,b** in 84 % yield (Scheme 43).[61] α-Hydroxylation of **388a,b** proceeded smoothly to give only two diastereomeric hydroxyketones **390a,b**. The diastereoselectivity of this reaction paralleled that seen with **377a,b**. The low yield for the oxidation and etherification sequence leading to **392a,b** was a consequence of purification problems

experienced in the oxidation step. The iodo- and iodosobenzoic acids produced from the Dess-Martin reagent were not completely separable from the enol products **391a,b** by repeated filtration or chromatography.

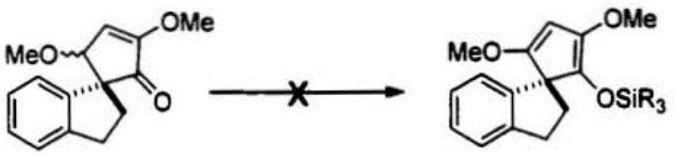
Scheme 43



Unfortunately, a change in the protecting group did not alter the reactivity of the enone in the manner desired (Scheme 44). Attempts to form diene **393** using LDA resulted in decomposition as before. Reactions employing alkali metal salts of bis(trimethylsilylamine) at low temperatures returned unreacted **392a,b**. The absence of deuterium incorporation in a deuterium oxide quench experiment conducted at -78 °C was indicative of a lack of significant deprotonation at this temperature. When the reaction

was carried out at 4 °C, the material decomposed in the same manner as with LDA. Use of the trimethylsilyl triflate/triethylamine (TEA) combination also resulted in decomposition of **392a,b**.

Scheme 44



392a,b **393**

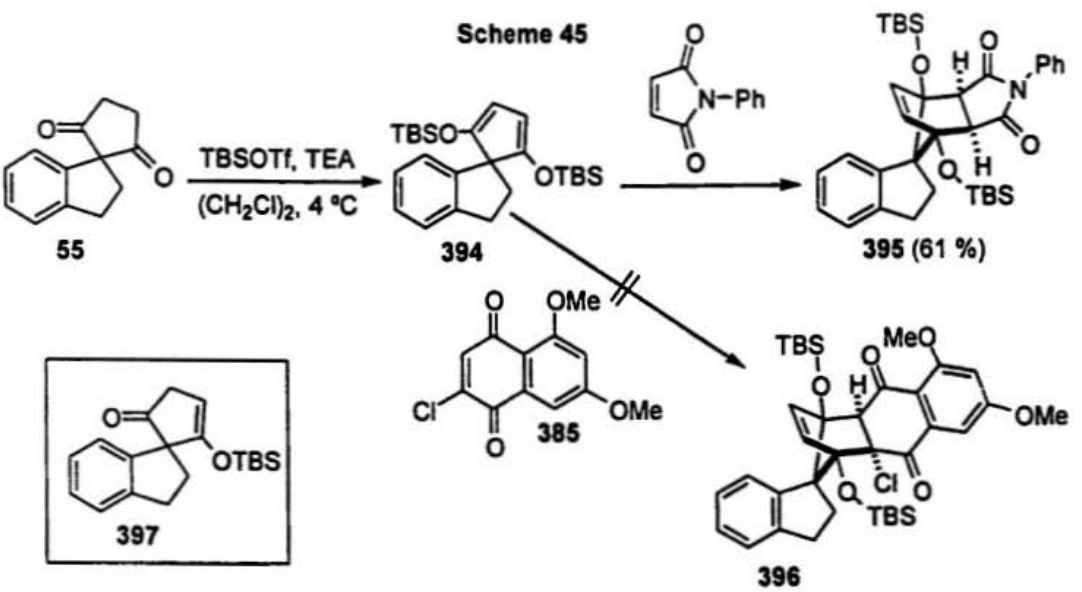
-LDA, THF, -78 °C, TBSCl
-LDA, HMPA, TMEDA, -78 °C, TBSCl
-LDA, HMPA, TMEDA, -78 °C, TMSCl
-LiHMDS, THF, -78 °C, TMSCl
-LiHMDS, THF, HMPA, -78 °C, TMEDA, TMSCl
-KHMDS, THF, -78 °C, TMSCl
-KHMDS, THF, 4 °C, TMSCl
-TEA, TMSOTf, 4°C
-TEA, TMSOTf, rt

Considerations for Future Work

In order to proceed with our plan for an enantioselective synthesis of fredericamycin A, the crucial Diels-Alder union of the model quinone and diene systems must first be established. Quantitative deprotonation methods for diene preparation from **381** or **392a,b** may have proved ineffective due to an instability of the dienolate intermediate (if this species even formed under these reaction conditions). Use of a 2-methoxy-1,4-dione system and employing equilibrating conditions for silyl-enol ether formation[60] may provide access to the desired diene since conversion of the initially formed β,γ-enone into a fully conjugated system should be favored energetically.

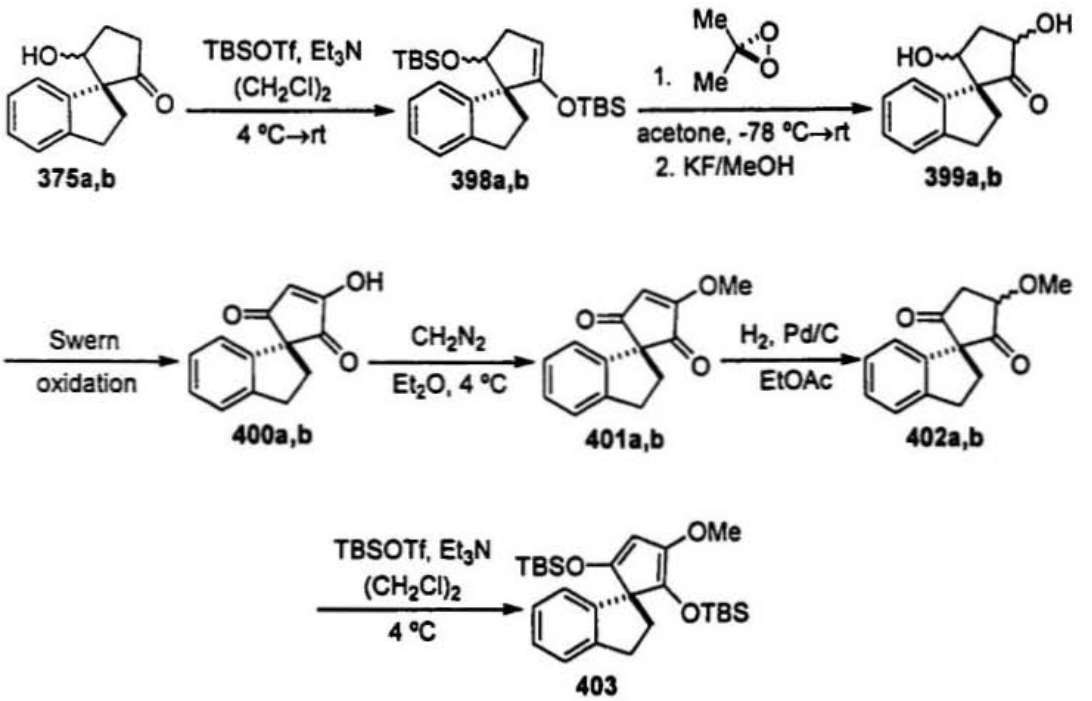
The viability of such a strategy was soon established when the corresponding diene (**394**) lacking the regiocontrolling oxygen was readily prepared from **55**. Compound **394** reacted instantaneously with *N*-phenylmaleimide providing adduct **395** in 61 % yield after recrystallization (Scheme 45). Unfortunately, no reaction was observed with **385** returning only monosilylated enone **397** after workup.

Scheme 45



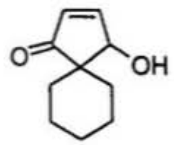
The presence of an additional electron donating methoxy substituent in **386** should result in an increase in reactivity relative to **394**. Whether or not the magnitude of this enhancement will be adequate to achieve a Diels-Alder addition of **385** to **386** remains to be seen. In the event a diene such as **386** cannot be prepared from an enone such as **381**, an alternate synthetic route has been provided for future consideration in Scheme 46. Note that only minor revisions to our original plan would be required.

Scheme 46

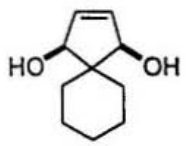


Experimental Section

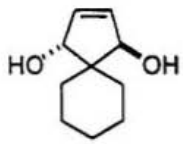
General Section. See Chapter 1, p. 24.



332



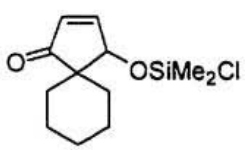
333a



333b

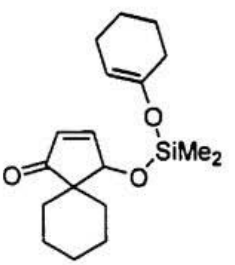
4-Hydroxyspiro[4.5]dec-2-en-1-one (332), and (1*R*/S, 4*S*/R)- and (1*R*/S, 4*R*/S)-1,4-dihydroxyspiro[4.5]dec-2-ene (333a,b). $NaBH_4$ (107 mg, 2.82 mmol) was added in one portion to a mixture of **331** (712 mg, 4.34 mmol) and $CeCl_3 \cdot 7H_2O$ (806 mg, 2.16 mmol) in methanol (12 mL) cooled to 4 °C. The reaction mixture was stirred for 5 min 20 s, quenched by the addition of aqueous NH_4Cl solution, poured into water (60 mL) and extracted with EtOAc (3 x 50 mL). The extracts were combined, washed with saturated NaCl aqueous solution (75 mL), dried ($MgSO_4$) and concentrated to give a viscous, faint yellow oil consisting of **332** and **333a,b** (9 : 1 by GC-MS). Chromatography (50/50 EtOAc-petroleum ether) provided **332** as a viscous, faint yellow oil (604 mg, 84 %) and a colorless resin (64 mg) consisting of **333a,b** (1.3 : 1). For **332**: IR 3418 (m), 1697 (s), 1596 (w) cm^{-1}; ^1H NMR δ 7.48 (1H, dd, J = 2.6, 5.8 Hz, H3), 6.15 (1H, dd, J = 1.0, 5.8 Hz, H2), 4.67 (1H, ddd, J = 1.0, 2.6, 8.1 Hz, H4), 1.81 (1H, d, J = 8.1 Hz, OH), 1.91-1.24 (10H, m, H6-H10); ^{13}C NMR δ 212.5 (0, C1), 160.7 (1, C3), 132.5 (1, C2), 78.6 (1, C4), 51.1 (0, C5), 33.5 (2), 27.6 (2), 25.1 (2), 22.9 (2), 22.3 (2); MS (GC-MS) 166 (20, M^+), 148 (36), 137 (20), 135 (10), 133 (14), 123 (29), 121 (10), 120 (36), 119 (17), 111 (38), 110 (29), 109 (19), 107 (18), 98 (19), 97 (37), 96 (16), 95 (23), 94 (13), 93 (13), 92 (10), 91 (26), 84 (73), 83 (19), 82 (22), 81 (39), 80 (12), 79 (46), 78 (10), 77 (24), 70 (10), 69 (16), 68 (14), 67 (35), 66 (10), 65 (17), 57 (14), 56 (33), 55 (100), 54 (19), 53 (36), 52 (10), 51 (18), 43 (19), 41

(63). Discernable signals from spectra of the mixture of **333a,b**: major isomer: ^{1}H NMR δ 5.92 (2H, s, H2, H3), 4.51 (2H, s, H1, H4); ^{13}C NMR δ 136.3 (2C, C2, C3), 81.2 (2C, C1, C4), 47.0 (0, C5); minor isomer: ^{1}H NMR δ 6.07 (2H, s, H2, H3), 4.10 (2H, s, H1, H4); ^{13}C NMR δ 135.5 (2C, C2, C3), 81.1 (2C, C1, C4), 47.4 (0, C5). MS (GC-MS) 168 (18, M^{+}), 150 (32), 148 (11), 124 (12), 112 (19), 111 (20), 110 (10), 109 (21), 108 (55), 107 (16), 97 (15), 96 (15), 95 (32), 94 (21), 93 (31), 91 (16), 85 (10), 84 (24), 83 (29), 82 (19), 81 (100), 80 (26), 79 (60), 78 (12), 77 (18), 70 (10), 69 (16), 68 (20), 67 (71), 66 (10), 65 (13), 57 (27), 56 (18), 55 (72), 54 (22), 53 (31), 51 (14), 44 (11), 43 (42), 42 (14), 41 (67).



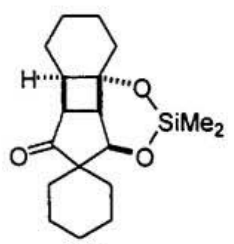
334

4-(Chlorodimethylsilyloxy)spiro[4.5]dec-2-en-1-one (334). A solution composed of **332** (809 mg, 4.87 mmol) and Et_3N (0.69 mL, 4.9 mmol) in dry THF (3.4 mL) was added dropwise to dichlorodimethylsilane (3.0 mL, 25 mmol) in THF (2.0 mL) cooled to 4 °C. The mixture was stirred at rt for 18 h, and the solvent was evaporated to give a mixture of solid and oil. The oil portion was rinsed free from the solid with dry hexanes. The combined washings were filtered and concentrated to provide **334** as a faint yellow oil (1.26 g, >99 %); ^{1}H NMR δ 7.43 (1H, dd, J = 2.4, 5.8 Hz, H3), 6.14 (1H, d, J = 5.8 Hz, H2), 4.67 (1H, d, J = 2.4 Hz, H4), 1.80 (1H, m), 1.72-1.22 (9H, m), 0.57 (3H, s, $SiCH_3$), 0.55 (3H, s, $SiCH_3$); ^{13}C NMR δ 211.4 (0, C1), 159.3 (0, C3), 132.7 (0, C2), 79.3 (1, C4), 51.0 (0, C5), 33.3 (2), 27.7 (2), 25.1 (2), 22.7 (2), 22.0 (2), 3.1 (3, $SiCH_3$), 2.2 (3, $SiCH_3$).



335

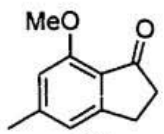
4-((1-Cyclohexenyloxy)dimethylsilyloxy)spiro[4.5]dec-2-en-1-one (335). A solution of cyclohexanone (148 mg, 1.50 mmol) in THF (0.92 mL) was added dropwise to freshly prepared LDA (1.5 mmol) in hexanes (0.60 mL) and THF (2.0 mL) cooled to -78 °C. The resulting mixture was stirred at -78 °C for 30 min prior to the dropwise introduction of **334** (395 mg, 1.53 mmol) in THF (0.75 mL) with warming to rt over 3.5 h. The mixture was concentrated, the residue treated with dry hexanes, and filtered. Evaporation of the solvent from the filtrate yielded crude **335** as a yellow oil (392 mg). This material was used in the next step without additional purification. IR 1713 (s), 1671 (m) cm^{-1}; ^1H NMR δ 7.43 (1H, dd, J = 2.4, 5.7 Hz, H3), 6.10 (1H, dd, J = 0.8, 5.7 Hz, H2), 4.94 (1H, m, H2'), 4.76 (1H, dd, J = 0.8, 2.4 Hz, H4), 2.08-1.94 (4H, m), 1.75-1.22 (14H, m), 0.28 (3H, s, $SiCH_3$), 0.25 (3H, s, $SiCH_3$).



336

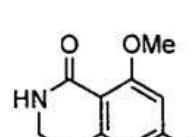
(1*R/S*, 5*S/R*, 10*R/S*, 11*S/R*, 14*R/S*)-3,3-Dimethyl-2,4-dioxa-3-silaspiro(cyclohexane-1',13-tetracyclo[9.2.1.$0^{5,10}0^{5,14}$]tetradecane)-12-one (336). A solution of **335** (392 mg) in cyclohexane (5.0 mL) was irradiated at 350 nm in a Rayonet photochemical reactor for 20 h. Evaporation of the solvent and chromatography (5/95 EtOAc-petroleum ether) of the residue provided **336** as a white solid (73 mg, 19 % from **334**); mp 80-81 °C; IR (CCl_4) 1731 cm^{-1}; ^1H NMR δ 4.52 (1H, d, J = 6.2 Hz, H1), 2.78 (1H, overlapped m, H10), 2.71 (1H, t, J = 6.7 Hz, H14), 2.47 (1H, t, J = 7.3 Hz, H11), 2.00 (1H, m), 1.88-1.13 (17H, m), 0.20 (3H, s, $SiCH_3$), 0.17 (3H, s, $SiCH_3$); NOE data 4.52 (2.78, 1.6 %; 2.71, 6 %), 2.71 (4.52, 6 %; 2.47, 4 %), 2.47 (2.78, 2 %; 2.71, 2 %); ^{13}C NMR δ 221.5 (0, C12), 72.6 (1, C1), 70.5 (0, C5), 59.2 (0, C13), 48.4 (1), 46.2

(1), 40.4 (1, C11), 38.9 (2), 30.7 (2), 25.6 (2), 25.5 (2), 24.2 (2), 22.1 (2), 21.9 (2), 21.0 (2), 20.3 (2), 0.3 (3, $SiCH_3$), -1.7 (3, $SiCH_3$); MS 320 (38, M^+), 224 (13), 222 (12), 210 (12), 209 (87), 195 (16), 194 (20), 181 (18), 171 (33), 169 (17), 168 (62), 156 (17), 155 (100); HRMS calcd for $C_{18}H_{28}O_3Si$ 320.1806, found 320.1786.



357

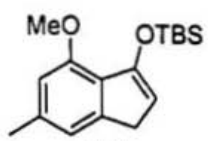
7-Methoxy-5-methyl-1-indanone (357). 7-Hydroxy-5-methyl-1-indanone (2.73 g, 16.8 mmol), K_2CO_3 (2.87 g, 20.8 mmol) and iodomethane (2.0 mL, 32 mmol) were stirred together in refluxing acetone (40 mL) for 18 h. After cooling to rt, the mixture was filtered and the solvent was evaporated leaving a solid residue that was dissolved in CH_2Cl_2 (50 mL) and washed with H_2O (60 mL). The aqueous layer was adjusted to pH 7 with 6 M HCl, extracted with CH_2Cl_2 (3 x 50 mL), the organic layers were combined, dried (Na_2SO_4) and concentrated to give **2** as a yellow solid (2.92 g, 98 %). Mp 127-129 °C; IR 1698 cm^{-1}; ^1H NMR δ 6.82 (1H, s) 6.58 (1H, s) 3.93 (3H, s, OCH_3) 3.02 (2H, m) 2.65 (2H, m), 2.42 (3H, s, C7-methyl); ^{13}C NMR δ 204.3 (0, C1), 158.2 (0), 157.8 (0), 147.9 (0), 123.0 (0), 119.0 (1), 109.8 (1), 55.6 (3, C7-methoxy), 36.9 (2), 25.4 (2), 22.3 (3, C5-methyl); MS 177 (12), 176 (M^-, 100), 175 (27), 161 (14), 148 (12), 147 (99), 133 (14), 129 (12), 119 (16), 118 (14), 117 (30), 115 (25), 105 (18), 103 (15), 91 (17), 90 (13), 77 (2), 63 (11), 62 (14), 51 (16), 45 (27); HRMS calcd for $C_{11}H_{12}O_2$, 176.0837, found 176.0852.



358

3,4-Dihydro-8-methoxy-6-methyl-(2*H*)isoquinolinone (358). A mixture of **357** (362 mg, 2.05 mmol), hydroxylamine-*O*-sulfonic acid (353 mg, 3.12 mmol) and 88 % formic acid (5.0 mL) was heated to reflux for 14 h, cooled in ice, adjusted to pH 8-9 with 6M NaOH, diluted with an equal volume of water and extracted with chloroform (4 x 50 mL). The extracts were

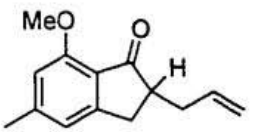
combined, dried ($MgSO_4$), and the solvent was evaporated to give **358** as a tan solid (395 mg, >99 %). Recrystallization of a portion from benzene afforded an analytical sample as a beige solid; mp 219 °C (decomposition); IR (Nujol) 3209 (s), 1721 (w), 1660 (m), 1567 (m) cm^{-1}; ^1H NMR δ 10.07 (1H, br s, NH), 6.73 (1H, s), 6.56 (1H, s), 3.92 (3H, s, C8-methoxy), 2.99 (4H, s, H3, H4), 2.37 (3H, s, C6-methyl); ^{13}C NMR δ 162.2 (0, C1), 156.1 (0), 150.7 (0), 141.7 (0), 121.7 (0), 118.2 (1), 109.6 (1), 55.2 (3, C8-methoxy), 28.5 (2), 26.0 (2), 22.0 (3, C6-methyl); MS 191 (27, M^+), 175 (13), 174 (100), 145 (12), 144 (25), 131 (10), 117 (16), 116 (10), 115 (16), 105 (10), 91 (12), 78 (12), 77 (12), 51 (10); HRMS calcd for $C_{12}H_{13}NO_2$ 191.0946, found 191.0946.



371

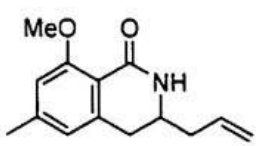
1-(*tert*-Butyldimethylsilyloxy)-7-methoxy-5-methyl-(3*H*)indene (371). *tert*-Butyldimethylsilyl trifluoromethanesulfonate (0.60 mL, 2.6 mmol) was added dropwise to a stirred solution of **357** (451 mg, 2.56 mmol) and Et_3N (0.39 mL, 2.8 mmol) in dry 1,2-dichloroethane (4.0 mL) cooled to 4 °C. The mixture was held at 4 °C for 10 min, then at rt for 1 h. The mixture was concentrated under vacuum and extracted with dry pentane (5 x 5 mL). The extracts were combined and the solvent was evaporated leaving **371** as a yellow oil (692 mg, 93 %); IR 1609 cm^{-1}; ^1H NMR δ 6.82 (1H, s), 6.59 (1H, s), 5.24 (1H, t, J = 2.4 Hz, H2), 3.82 (3H, s, C7-methoxy), 3.18 (2H, d, J = 2.4 Hz, H3), 2.37 (3H, s, C5-methyl), 1.01 (9H, s, *t*-butyl), 0.20 (6H, s, $SiCH_3$); ^{13}C NMR δ 153.8 (0), 153.4 (0), 145.8 (0), 136.3 (0), 126.6 (0), 117.8 (1), 110.1 (1), 104.9 (1, C2), 55.2 (3, C7-methoxy), 33.6 (2, C3), 25.7 (3C, 3, *t*-butyl), 21.7 (3, C5-methyl), 18.2 (0, *t*-butyl), -4.9 (2C, 3, $SiCH_3$); MS 290 (8, M^+), 234 (11), 233 (43), 220 (14), 219 (62), 218 (100), 217 (13), 203 (37), 165 (12), 159 (12), 147

(22), 135 (37), 115 (12), 89 (18), 77 (13), 75 (30), 73 (59), 59 (20), 57 (13), 45 (10), 41 (15).



372

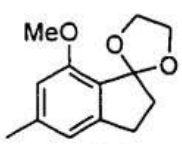
2-Allyl-7-methoxy-5-methylindanone (372). A solution composed of **371** (686 mg, 2.36 mmol), allyl bromide (0.24 mL, 2.8 mmol) and CH_2Cl_2 (1.8 mL) was added dropwise to a stirred slurry of silver trifluoroacetate (577 mg, 2.61 mmol) in CH_2Cl_2 (2.4 mL) at -78 °C. The resulting mixture was stirred at -78 °C for 45 min, warmed to rt over 30 min, filtered (Celite) and concentrated. Chromatography (40/60 EtOAc-petroleum ether) provided **372** as a yellow oil (260 mg, 51 %); IR 1704 (s), 1640 (m), 1609 (s) cm^{-1}; ^1H NMR δ 6.80 (1H, s), 6.59 (1H, s), 5.80 (1H, symmetric m, H2'), 5.14-5.00 (2H, m, H3'), 3.93 (3H, s, C7-methoxy), 3.15 (1H, dd, J = 8.4, 18.0 Hz, H3), 2.79-2.62 (3H, m, H2, H3, H1'), 2.41 (3H, s, C5-methyl), 2.20 (1H, m, H3'); ^{13}C NMR δ 205.0 (0, C1), 157.7 (0), 156.5 (0), 147.9 (0), 135.5 (1, C2'), 122.3 (0), 118.8 (2, C3'), 116.5 (1), 109.7 (1), 55.4 (3, C7-methoxy), 46.6 (1, C2), 35.8 (2, C1'), 31.4 (2, C3), 22.2 (3, C5-methyl); MS 216 (42, M^+), 176 (27), 175 (100), 174 (18), 162 (10), 129 (11), 115 (19), 91 (16), 77 (10); HRMS calcd for $C_{14}H_{16}O_2$ 216.1149, found 216.1160.



373

3-Allyl-3,4-dihydro-7-methoxy-5-methyl-(2*H*)isoquinolinone (373). A mixture of **372** (241 mg, 1.12 mmol), hydroxylamine-*O*-sulfonic acid (195 mg, 1.72 mmol) and 88 % formic acid (3.0 mL) was heated to reflux for 1 h, cooled in ice, adjusted to pH 7-8 with 6M NaOH, diluted with an equal volume of water and extracted with chloroform (3 x 30 mL). The extracts were combined, dried ($MgSO_4$) and concentrated. Chromatography (28/72 acetone-petroleum ether) gave a yellow resin (199 mg) that solidified on trituration with

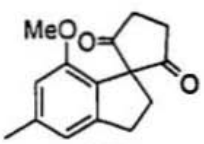
hexanes. Recrystallization from hexanes afforded an analytical sample of **373** as a faint-yellow solid (148 mg). Evaporation of the mother liquor left a viscous, yellow oil (47 mg) consisting of a 1 : 1 mixture of **372** and **373** (total 67 %). For **373**: mp 132-133.5 °C; IR (Nujol) 3247 (s), 1636 (w), 1606 (m), 1591 (m) cm^{-1}; ^1H NMR δ 10.03 (1H, br s, NH), 6.72 (1H, s), 6.58 (1H, s), 5.84 (1H, m, H2'), 5.15-4.97 (2H, m, H3'), 3.92 (3H, s, C7-methoxy), 3.60 (1H, m, H3), 3.09 (1H, dd, J = 8.2, 17.0 Hz, H4), 2.91 (1H, m, H2'), 2.75 (1H, dd, J = 1.6, 17.0 Hz, H4), 2.37 (3H, s, C5-methyl), 2.23 (1H, m, H3'); ^{13}C NMR δ 163.5 (0, C1), 156.0 (0), 149.2 (0), 141.8 (0), 136.5 (1, C2'), 121.3 (0), 118.3 (1), 116.3 (2, C3'), 109.6 (1), 55.1 (3, C7-methoxy), 38.6 (1, C3), 36.0 (2, C1'), 34.4 (2, C4), 22.0 (3, C5-methyl); MS 231 (3, M^+), 215 (42), 214 (50), 210 (11), 200 (21), 198 (11), 182 (13), 175 (15), 174 (100), 173 (14), 172 (11), 159 (12), 144 (12), 131 (15), 130 (16), 115 (17), 105 (14), 91 (11), 77 (17), 51 (12), 43 (16), 41 (22); HRMS calcd for $C_{14}H_{17}NO_2$ 231.1258, found 231.1266.



374

2',3'-Dihydro-7'-methoxy-5'-methyl-1,3-dioxaspiro(cyclopentane-2,1'-(1*H*)indene) (374). Trimethylsilyl trifluoromethanesulfonate (50 μL, 280 μmol) was added to a dichloromethane (4.2 mL) solution of **357** and 1,2-bis(trimethylsilyloxy)ethane (1.02 g, 4.94 mmol) cooled to -29 °C. The mixture was stirred at this temperature for 48 h, quenched by the addition of dry pyridine (0.12 mL), poured into a saturated $NaHCO_3$ aqueous solution (15 mL) and extracted with ether (3 x 15 mL). The combined extracts were dried over a 1 : 1 mixture of Na_2SO_4 and Na_2CO_3. Evaporation of the solvent gave an oily, beige solid (862 mg) that consisted of a 4.8 : 1 mixture of **357** and **374**. Chromatography (40/60 EtOAc-hexanes) gave recovered ketone **357** as a faint yellow solid (490 mg) and **374** as a yellow oil (127 mg; 15 %); IR

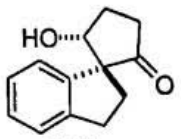
1600, 1459 cm^{-1}; ^1H NMR δ 6.63 (1H, s), 6.53 (1H, s), 4.27-4.16 (2H, m), 4.07-3.96 (2H, m), 3.83 (3H, s, OCH_3), 2.84 (2H, apparent t, J = 6.9 Hz), 2.32 (3H, s, C5'-methyl), 2.28 (2H, apparent t, J = 6.9 Hz); ^{13}C NMR δ 155.7 (0, C7'), 146.3 (0), 141.2 (0), 130.4 (0), 117.9 (1), 117.8 (0, C2), 109.8 (1), 65.7 (2C, 2, C4, C5), 55.1 (3, OCH_3), 38.4 (2), 28.0 (2), 21.7 (3, C5'-methyl); MS 220 (61, M^+), 190 (22), 189 (16), 177 (26), 176 (28), 175 (45), 162 (16), 161 (100), 160 (13), 149 (20), 147 (33), 145 (21), 131 (14), 129 (10), 117 (19), 115 (30), 105 (11), 103 (13), 91 (24), 78 (12), 77 (23), 65 (12), 63 (12), 51 (16), 43 (12).



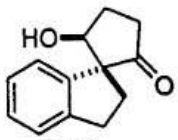
359

2',3'-Dihydro-7'-methoxy-5'-methylspiro(cyclopentane-2,1'-(1*H*)indene)-1,3-dione (359). $BF_3{\cdot}Et_2O$ (0.14 mL, 1,1 mmol) and **1** (259 mg, 1.1 mmol) as a solution in CH_2Cl_2 (0.84 mL) were added in succession to a -78 °C solution of **374** (123 mg, 557 μmol) in CH_2Cl_2 (2.2 mL). The mixture was stirred at -78 °C for 5 min then at rt for 2h, poured into H_2O (30 mL) and extracted with CH_2Cl_2 (2 x 30 mL). The combined extracts were dried (Na_2SO_4) and concentrated. Chromatography (0.5/99.5 MeOH/CH_2Cl_2) afforded **359** as a white solid (76 mg, 56 %); mp 110–112.5 °C; IR (CCl_4) 1722 (s), 1592 (m) cm^{-1}; ^1H NMR δ 6.70 (1H, s), 6.43 (1H, s), 3.69 (3H, s, OCH_3), 3.11 (2H, t, J = 7.4), 3.07-2.72 (4H, symmetric m, H3, H4), 2.32 (2H, overlapped t), 2.30 (3H, s, C5'-methyl); ^{13}C NMR δ 215.9 (2C, 0, C2, C5), 153.7 (0, C7'), 147.4 (0), 140.5 (0), 127.4 (0), 118.1 (1), 109.3 (1), 65.6 (0, C1), 55.1 (3, OCH_3), 36.3 (2C, 2, C3, C4), 35.4 (2), 32.2 (2), 21.7 (3, C5'-methyl); MS 245 (15), 244 (39, M^+), 188 (67), 174 (20), 160 (10), 159 (29), 145 (44), 131 (24), 130 (13),

129 (23), 128 (22), 117 (17), 116 (12), 115 (46), 91 (16), 55 (12); HRMS calcd for $C_{15}H_{16}O_3$ 244.1098, found 244.1086.

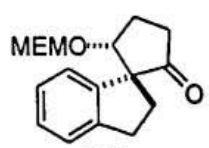


375a

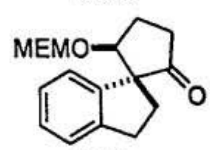


375b

(2*R/S*,3*R/S*)- (375a) and (2*R/S*,3*S/R*)-2',3'-Dihydro-3-hydroxy-spiro(cyclopentane-2,1'-(1*H*)indene)-1-one (375b). A solution of **55** (1.98 g, 9.89 mmol) in anhydrous ether (95 mL) was cooled to 4 °C and treated with a 1.0 M solution of $LiAlH(Ot\text{-}Bu)_3$ in THF (10.2 mL). The resulting slurry was stirred at 4 °C for 10 min, then at rt for 30 min, poured into water (100 mL), acidified to pH ~2-3 with 6 M HCl and extracted with ethyl acetate (4 x 60 mL). The extracts were combined, washed with a saturated $NaHCO_3$ aqueous solution (150 mL), dried ($MgSO_4$) and concentrated to give a mixture of **375a,b** (1.7 : 1) as a tan-colored oil (1.99 g, 99 %). Compounds **375a** and **375b** could not be separated by flash chromatography. From spectra of the mixture: for **375a**: ^{1}H NMR δ 7.10 (1H, m), 4.23 (1H, br s, H3), 1.62 (br s, OH); ^{13}C NMR δ 220.4 (0, C1), 145.5 (0), 140.5 (0), 127.7 (1), 126.2 (1), 125.8 (1), 124.2 (1), 75.4 (1, C3), 67.8 (0, C2), 34.9 (2), 34.4 (2), 30.7 (2), 27.8 (2); for **375b**: ^{1}H NMR δ 6.98 (1H, m), 4.43 (1H, apparent t, J = 6.4 Hz, H3); ^{13}C NMR δ 218.5 (0, C1), 145.4 (0), 142.7 (0), 127.3 (1), 126.2 (1), 124.4 (1), 122.7 (1), 76.3 (1, C3), 67.3 (0, C2), 35.1 (2), 28.7 (2).



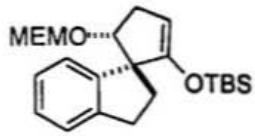
376a



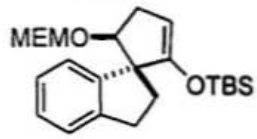
376b

(2*R/S*,3*R/S*)- (376a) and (2*R/S*,3*S/R*)-2',3'-Dihydro-3-((methoxy-ethoxy)methoxy)spiro(cyclopentane-2,1'-(1*H*)indene)-1-one (376b). **375a,b** (1.93 g, 9.54 mmol), diisopropylethylamine (3.4 mL, 19 mmol) and 2-methoxyethoxymethyl chloride (2.2 mL, 20 mmol) were stirred together in dry CH_2Cl_2 (16 mL) for 60 h, poured into water (50 mL)

and extracted with CH_2Cl_2 (2 x 40 mL). The combined extracts were dried (Na_2SO_4) and concentrated. Chromatography (60/40 EtOAc-hexanes) gave a tan-colored oil (2.23 g, 80 %) consisting of a mixture of **376a,b**. Additional chromatography afforded samples of each diastereomer, however complete separation was not achieved. For **376a**: yellow oil; IR 1740 cm^{-1}; ^1H NMR δ 7.23-7.13 (4H, m, H4'-H7'), 4.65 (1H, d, J = 7.2 Hz, H1''), 4.37 (1H, d, J = 7.2 Hz, H1''), 4.27 (1H, apparent t, J = 3.4 Hz, H3), 3.46 (1H, ddd, J = 3.2, 6.3, 10.4 Hz), 3.31 (3H, s, OCH_3), 3.37-3.28 (2H, overlapped m), 3.17 (1H, ddd, J = 3.1, 5.6, 10.5 Hz), 3.05-2.96 (2H, m, H3'), 2.62 (1H, m), 2.45 (1H, m), 2.31-2.02 (4H, m); ^{13}C NMR δ 219.4 (0, C1), 145.0 (0), 141.0 (0), 127.4 (1), 126.7 (1), 125.9 (1), 123.8 (1), 93.6 (2, C1''), 80.1 (1, C3), 71.3 (2), 66.7 (2), 66.4 (0, C2), 58.6 (3, OCH_3), 35.4 (2), 34.4 (2), 30.7 (2, C3'), 26.0 (2). For **376b**: yellow oil; IR 1742 cm^{-1}; ^1H NMR δ 7.26-7.13 (3H, m, H4'-H6'), 7.01 (1H, m, H7'), 4.74 (1H, d, J = 6.9 Hz, H1''), 4.57 (1H, J = 6.9 Hz, H1''), 4.43 (1H, dd, J = 5.4, 7.8 Hz, H3), 3.57 (1H, m), 3.43-3.35 (3H, m), 3.34 (3H, s, OCH_3), 3.09-2.92 (2H, m, H3'), 2.68-2.31 (4H, m, H2', H4, H5), 2.14-1.95 (2H, m, H2', H4); NOE data 7.01 (4.43, 2.2 %), 4.43 (7.01, 3.6 %; 3.57, 1.5 %), 3.57 (4.43, 1.4 %); ^{13}C NMR δ 217.4 (0, C1), 145.3 (0), 143.0 (0), 127.5 (1), 126.4 (1), 124.5 (1), 122.8 (1, C7'), 93.8 (2, C1''), 80.8 (1, C3), 71.3 (2), 66.6 (2), 66.3 (0, C2), 58.7 (3, OCH_3), 35.4 (2, C3), 30.9 (2, C3'), 29.4 (2, C4), 25.9 (2, C2'); MS 290 (3, M^+), 129 (13), 89 (54), 59 (100); HRMS calcd for $C_{17}H_{22}O_4$ 290.1517, found 290.1535.



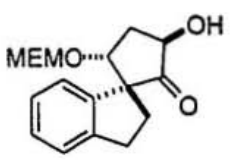
377a



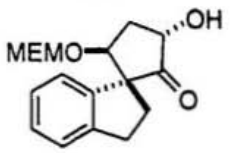
377b

(4*R/S*,5*R/S*)- (377a) and (4*R/S*,5*S/R*)-1-(*tert*-Butyldimethylsilyloxy)-2',3'-dihydro-4-((methoxyethoxy)methoxy)-spiro(cyclopentane-5,1'-(1*H*)indene)-1-ene (377b). *tert*-Butyldimethylsilyl trifluoromethanesulfonate (1.40 mL, 6.1 mmol) was added dropwise to a stirred solution of **376a,b** (1.68 g, 5.79 mmol) and Et_3N (0.90 mL, 6.5 mmol) in dry 1,2-dichloroethane (9.0 mL) cooled to 4 °C. The mixture was held at 4 °C for 10 min, then at rt for 2 h, concentrated under vacuum and extracted with dry pentane (5 x 5 mL). The extracts were combined and the solvent was evaporated to give a mixture of **377a,b** as a yellow oil (2.26g, 96 %). Chromatography provided homogenous samples of each diastereomer. For **377a**: colorless oil; IR 1642 cm^{-1}; ^1H NMR δ 7.20-7.06 (4H, m, H4'-H7'), 4.58 (1H, t, J = 2.3 Hz, H2), 4.54 (1H, d, J = 7.0 Hz, H1''), 4.41 (1H, d, J = 7.0 Hz, H1''), 4.27 (1H, dd, J = 5.6, 7.2 Hz, H4), 3.46 (1H, m), 3.39 (2H, apparent t, J = 4.8 Hz), 3.34 (3H, s, OCH_3), 3.24 (1H, m), 2.93 (2H, t, J = 7.4 Hz, H3'), 2.66 (1H, ddd, J = 2.7, 7.2, 14.9 Hz), 2.46-2.31 (2H, m, H3, H2'), 2.02 (1H, m), 0.72 (9H, s, *t*-butyl), 0.10 (3H, s, $SiCH_3$), -0.08 (3H, s, $SiCH_3$); ^{13}C NMR δ 157.4 (0, C1), 144.7 (0), 143.2 (0), 126.7 (1), 125.8 (1), 125.5 (1), 124.0 (1), 96.8 (1, C2), 94.5 (2, C1''), 82.6 (1, C4), 71.6 (2), 66.6 (2), 63.5 (0, C5), 58.9 (3, OCH_3), 34.6 (2), 34.1 (2), 31.1 (2, C3'), 25.4 (3C, 3, *t*-butyl), 17.8 (0, *t*-butyl), -4.8 (3, $SiCH_3$), -5.4 (3, $SiCH_3$); MS 405 (2, M^+), 315 (11), 299 (13), 298 (28), 287 (12), 155 (14), 133 (13), 89 (24), 75 (26), 73 (100), 59 (64), 45 (11). For **377b**: colorless oil; IR 1640 cm^{-1}; ^1H NMR δ 7.18-7.03 (4H, m, H4'-H7'), 4.67 (1H, d, J = 6.8 Hz, H1''), 4.53 (1H, t, J = 2.3 Hz, H2), 4.50 (1H, d, J = 6.8 Hz, H1''), 4.32 (1H, t, J = 6.6 Hz, H4), 3.54 (1H, m), 3.41-3.24 (3H, m), 3.30 (3H, s, OCH_3), 2.92 (2H, t, J = 7.4 Hz, H3'), 2.63 (1H,

overlapped ddd, J = 2.7, 7.2, 14.5 Hz), 2.56 (1H, overlapped m), 2.03 (1H, td, J = 8.1, 13.2 Hz), 0.67 (9H, s, *t*-butyl), 0.11 (3H, s, $SiCH_3$), -0.02 (3H, s, $SiCH_3$); ^{13}C NMR δ 157.1 (0, C1), 146.3 (0), 144.9 (0), 126.7 (1), 126.0 (1), 124.0 (1), 123.2 (1), 96.5 (1, C2), 94.2 (2, C1''), 82.9 (1, C4), 71.5 (2), 66.5 (2), 63.0 (0, C5), 58.8 (3, OCH_3), 33.3 (2), 31.3 (2, C3'), 28.8 (2), 25.2 (3C, 3, *t*-butyl), 17.7 (0, *t*-butyl), -4.8 (3, $SiCH_3$), -5.4 (3, $SiCH_3$).



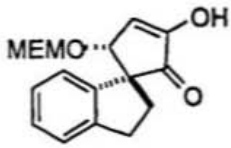
378



379

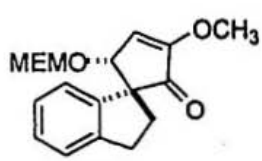
(2*R/S*,4*R/S*,5*R/S*)- (378) and (2*R/S*,4*S/R*,5*R/S*)-2',3'-Dihydro-2-hydroxy-4-((methoxyethoxy)methoxy)spiro(cyclopentane-5,1'-(1*H*)indene)-1-one (379). A solution of **377a,b** (1.66 g, 4.12 mmol) in acetone (6.0 mL) was treated with freshly prepared dimethyldioxirane (63 mL, ~0.1 M in acetone) at -15 °C. The mixture was warmed to rt, concentrated under reduced pressure and the residue treated with saturated KF in methanol (75 mL) with stirring for 25 min. The mixture was concentrated to ~30 mL volume, poured into water (75 mL) and extracted with ethyl acetate (4 x 60 mL). The combined extracts were washed with a saturated NaCl aqueous solution (60 mL), dried ($MgSO_4$), and the solvent was evaporated to give a viscous, orange oil (1.22 g). Chromatography (30/70 EtOAc-petroleum ether) provided **378** (489 mg) and **379** (285 mg) as viscous, faint yellow oils; a mixed fraction (44 mg) was also isolated (total: 65 % of theoretical). TLC analysis revealed that significant deterioration of the sample had occurred during the second (heated) evaporation. In a separate experiment, using 230 μmol of a 2.2 : 1 mixture of **377a,b** and conditions described below for **388a,b**, no such deterioration was seen. ^1H NMR analysis of the isolated yellow oil (72 mg) indicated this material consisted of **378, 379** and fluoro-*tert*-butyldimethylsilane (2.2 : 1 : 1). For **378**: IR 3427, 1744 cm^{-1}; ^1H NMR δ 7.26-7.19 (2H,

m), 7.19-7.10 (1H, m), 7.05 (1H, d, J = 7.7 Hz, H7'), 4.62 (1H, symmetric m, H2), 4.53 (1H, d, J = 7.2 Hz, H1"), 4.27 (1H, d, J = 4.0 Hz, H4), 4.16 (1H, d, J = 7.2 Hz, H1"), 3.43 (1H, m), 3.38-3.25 (2H, overlapped m), 3.31 (3H, s, OCH_3), 3.11-3.00 (3H, m), 2.82 (1H, d, J = 2.1 Hz, OH), 2.71 (1H, dd, J = 8.3, 13.5 Hz, H3 *syn* H2), 2.31 (1H, td, J = 9.1, 12.3 Hz, H2'), 2.08-1.95 (2H, m, H2', H3 *syn* H4); NOE data 4.62 (7.05, 1.6 %; 2.71, 4 %), 4.27 (4.53, 1.6 %; 2.08-1.95, 8 %), 2.71 (4.62, 13 %; 4.53, 2 %; 4.27, 1.1 %; 2.08-1.95, 14 %); ^{13}C NMR δ 220.3 (0, C1), 144.7 (0), 141.4 (0), 127.7 (1), 126.6 (1), 126.2 (1, C7'), 124.0 (1), 94.0 (2, C1"), 75.8 (1, C4), 73.7 (1, C2), 71.4 (2), 66.5 (2), 64.8 (0, C5), 58.9 (3, OCH_3), 37.3 (2, C2'), 35.0 (2, C3), 30.8 (2, C3'); MS 306 (0.7, M^+), 129 (14), 117 (11), 89 (44), 59 (100), 45 (15); HRMS calcd for $C_{17}H_{22}O_5$ 306.1466, found 306.1468. For **379**: IR 3427, 1747 cm^{-1}; ^1H NMR δ 7.28-7.11 (3H, m, H4'-H6'), 7.00 (1H, d, J = 7.1 Hz, H7'), 4.81 (1H, d, J = 7.1 Hz, H1"), 4.65 (1H, d, J = 7.1 Hz, H1"), 4.50 (1H, t, J = 8.8 Hz, H2), 4.36 (1H, t, J = 4.6 Hz, H4), 3.67 (1H, m), 3.56 (1H, m), 3.49-3.43 (2H, m), 3.34 (3H, s, OCH_3), 3.06-2.91 (2H, m, H3'), 2.70 (1H, br s, OH), 2.68-2.48 (2H, m, H2', H3 *syn* H2), 2.34-2.12 (2H, m, H2', H3 *syn* H4); NOE data 7.00 (4.36, 1.6 %; 2.34-2.12, 2 %), 4.50 (OH, 6 %; 2.68-2.48, 5 %), 4.36 (7.00, 3 %; 4.81, 1.1 %; 4.65, 1.6 %, 2.32-2.12, 3 %); ^{13}C NMR δ 218.5 (0, C1), 144.4 (0), 143.8 (0), 127.3 (1), 126.4 (1), 124.3 (1), 123.2 (1, C7'), 93.9 (2, C1"), 77.9 (1, C4), 72.1 (1, C2), 71.2 (2), 66.7 (2), 64.9 (0, C5), 58.5 (3, OCH_3), 34.5 (2, C3), 30.8 (2, C3'), 30.7 (2, C2'); MS 306 (0.4, M^+), 141 (11), 129 (15), 128 (11), 117 (11), 115 (19), 89 (48), 59 (100), 45 (21); HRMS calcd for $C_{17}H_{22}O_5$ 306.1466, found 306.1454.



380

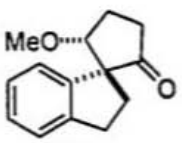
(4*R/S*,5*R/S*)-2',3'-Dihydro-2-hydroxy-4-((methoxyethoxy)-methoxy)spiro(cyclopentane-5,1'-(1*H*)indene)-2-en-1-one (380). A solution of **378** (462 mg, 1.51 mmol) in CH_2Cl_2 (20 mL) was treated with Dess-Martin periodinane (760 mg, 1.80 mmol) with stirring at rt for 30 min. The solvent was evaporated and the residue was treated with ether and filtered (Celite). Solvent removal from the filtrate gave a yellow-orange resin (464 mg) that was used without further purification in the next step. Chromatography (38/62 acetone-petroleum ether) of a portion (116 mg) from another experiment using the same conditions afforded **380** as a yellow resin (91 mg, 86 %); IR 3600-2400 (m), 1715 (s), 1661 (m), 1635 (m) cm^{-1}; ^1H NMR δ 7.23 (1H, d, J = 7.4 Hz), 7.18 (1H, dt, J = 1.2, 7.4 Hz), 7.10 (1H, t, J = 7.4 Hz), 7.00 (1H, d, J = 7.4 Hz), 6.57 (1H, d, J = 3.0 Hz, H3), 4.67 (1H, d, J = 3.0 Hz, H4), 4.46 (1H, d, J = 7.1 Hz, H1"), 4.33 (1H, d, J = 7.1 Hz, H1"), 3.50 (1H, m), 3.39 (2H, t, J = 4.4 Hz), 3.34 (3H, s, OCH_3), 3.22-2.96 (3H, m), 2.47 (1H, ddd, J = 7.0, 8.8, 13.0 Hz, H2'), 2.15 (1H, m, H2'); ^{13}C NMR δ 203.5 (0, C1), 154.5 (0, C2), 144.9 (0), 141.0 (0), 127.6 (1), 127.3 (1, C3), 125.9 (1), 125.7 (1), 124.4 (1), 95.0 (2, C1"), 79.6 (1, C4), 71.4 (2), 66.9 (2), 63.7 (0, C5), 58.8 (3, OCH_3), 35.7 (2, C2'), 31.2 (2, C3'); MS 304 (0.4, M^+), 170 (17), 142 (11), 141 (24), 115 (24), 89 (53), 59 (100), 45 (35); HRMS calcd for $C_{17}H_{20}O_5$ 304.1310, found 304.1298.



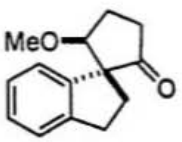
381

(4*R/S*,5*R/S*)-2',3'-Dihydro-2-methoxy-4-((2-methoxyethoxy)-methoxy)spiro(cyclopentane-5,1'-(1*H*)indene)-2-en-1-one (381). A solution of **380** (459 mg, 1.51 mmol) in ether (5.0 mL) was treated with diazomethane (3.3 mL, ~0.18 M in ether) at 4 °C. The mixture was warmed to rt with occasional swirling over 45 min. Nitrogen was bubbled through the solution

until the yellow color of diazomethane had dissipated. Solvent evaporation yielded **381** as a viscous, yellow oil (477 mg, 99 % over two steps); IR 1722, 1632 cm^{-1}; ^1H NMR δ 7.23 (1H, d, *J* = 7.4 Hz), 7.18 (1H, dt, *J* = 1.4, 7.4 Hz), 7.12 (1H, t, *J* = 7.4 Hz), 7.03 (1H, d, *J* = 7.4 Hz), 6.47 (1H, d, *J* = 3.0 Hz, H3), 4.69 (1H, d, *J* = 3.0 Hz, H4), 4.47 (1H, d, *J* = 7.2 Hz, H1"), 4.35 (1H, d, *J* = 7.2 Hz, H1"), 3.56 (1H, m), 3.41 (2H, t, *J* = 4.4 Hz), 3.36 (3H, s, OCH_3), 3.22-2.97 (3H, m), 2.53 (1H, ddd, *J* = 7.3, 8.9, 13 Hz, H2'), 2.18 (1H, ddd, *J* = 4.7, 8.3, 13 Hz, H2'); ^{13}C NMR δ 201.5 (0, C1), 158.1 (0, C2), 145.0 (0), 141.1 (0), 127.5 (1), 125.9 (1), 125.8 (1), 124.4 (1), 124.2 (1, C3), 95.1 (2, C1"), 79.4 (1, C4), 71.5 (2), 67.0 (2), 64.4 (0, C5), 58.9 (3, OCH_3), 57.2 (3, C2 methoxy), 36.0 (2, C2'), 31.2 (2, C3'); MS 318 (4, M^+), 213 (14), 141 (10), 89 (44), 59 (100), 45 (16); HRMS calcd for $C_{18}H_{22}O_5$ 318.1466, found 318.1452.

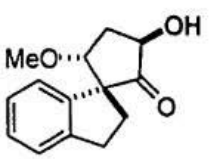


388a

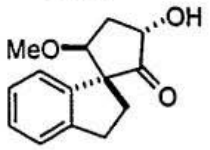


388b

(2*R/S*,3*R/S*)- (388a) and (2*R/S*,3*S/R*)-2',3'-Dihydro-3-methoxy-spiro(cyclopentane-2,1'-(1*H*)indene)-1-one (388b). Dimethyl sulfate (4.5 mL, 48 mmol), **375a,b** (1.52 g, 7.52 mmol), CH_2Cl_2 (20 mL), tetra-*n*-butylammonium iodide (110 mg, 300 μmol) and 50 % NaOH solution (3 mL H_2O, 3 g NaOH) were rapidly stirred together at rt for 21 h. The reaction vessel contents were poured into water and extracted with CH_2Cl_2 (4 x 40 mL). The combined extracts were dried ($MgSO_4$) and concentrated. Chromatography (25/75 acetone-hexanes) afforded an orange oil (1.36 g, 84 %) consisting of a mixture of **388a,b**. Discernable signals from a ^1H NMR spectrum of the mixture: **388a**: δ 3.82 (1H, t, *J* = 3.4 Hz), 3.20 (3H, s, C3-methoxy); **388b**: δ 4.02 (1H, dd, *J* = 4.6, 7.8 Hz, H3), 3.24 (3H, s, C3-methoxy).

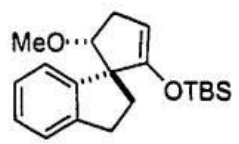


390a

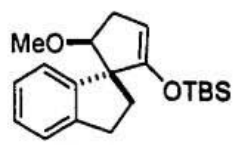


390b

(4*R/S*,5*R/S*)- (389a) and (4*R/S*,5*S/R*)-1-(*tert*-Butyldimethylsilyl-oxy)-2',3'-dihydro-4-methoxyspiro(cyclopentane-5,1'-(1*H*)-indene)-1-ene (389b). *tert*-Butyldimethylsilyl trifluoromethane-sulfonate (1.7 mL, 7.6 mmol) was added dropwise to a stirred solution of **388a,b** (1.54 g, 7.10 mmol) and Et_3N (1.2 mL, 9.4 mmol) in dry 1,2-dichloroethane (11 mL) cooled to 4 °C. The mixture was held at 4 °C for 15 min, then at rt for 3 h before it was concentrated under vacuum and extracted with dry pentane (5 x 5 mL). The extracts were combined and the solvent was evaporated to give a yellow oil (2.32 g, 99 %), a mixture of **389a,b**. Discernable signals from a ^1H NMR spectrum of the mixture: **389a**: δ 4.55 (1H, t, J = 2.4 Hz, H2), 3.92 (1H, dd, J = 6.6, 7.4 Hz, H4), 3.11 (1H, s, C4-methoxy), 0.71 (9H, s, *t*-butyl), 0.09 (3H, s, $SiCH_3$), -0.14 (3H, s, $SiCH_3$); **389b**: δ 4.50 (1H, t, J = 2.4 Hz, H2), 3.95 (1H, dd, J = 6.2, 7.0 Hz, H4), 3.18 (3H, s, C4-methoxy), 0.65 (9H, s, *t*-butyl), 0.10 (3H, s, $SiCH_3$), -0.05 (3H, s, $SiCH_3$).



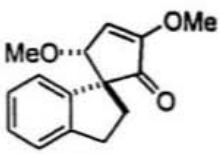
389a



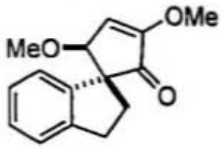
389b

(2*R/S*,4*R/S*,5*R/S*)- (390a) and (2*R/S*,4*S/R*,5*R/S*)-2',3'-Dihydro-2-hydroxy-4-methoxyspiro(cyclopentane-5,1'-(1*H*)indene)-1-one (390b). A solution of **389a,b** (2.30 g, 6.97 mmol) in acetone (10 mL) was treated with freshly prepared dimethyldioxirane (115 mL, ~0.1 M in acetone) at -20 °C. The mixture was warmed to rt over 30 min with occasional swirling, stirred with saturated KF in methanol (75 mL) for 25 min, dried ($MgSO_4$), concentrated, diluted with dichloromethane and dried ($MgSO_4$) again. Evaporation of the solvent gave a viscous, yellow oil (1.74 g) consisting of **390a,b** and fluoro-*tert*-butyldimethylsilane (1.9 : 1 : 1). Chromatography (30/70 EtOAc-petroleum ether) of a portion (180 mg) provided **390a** (66 mg) and **390b**

(33 mg) as colorless resins (total: 59 % of theoretical). For **390a**: IR 3436, 1744 cm^{-1}; ^1H NMR δ 7.27-7.09 (4H, m, H4'-H7'), 4.55 (1H, dd, J = 8.6, 11.5 Hz, H2), 3.77 (1H, d, J = 4.1 Hz, H4), 3.30 (1H, br s, OH), 3.04 (3H, s, C4-methoxy), 3.02 (2H, overlapped ddd, J = 1.3, 8.6, 13.4 Hz, H3'), 2.74 (1H, ddd, J = 1.3, 8.6, 13.4 Hz, H3 *syn* to H2), 2.29 (1H, dt, J = 8.6, 12.5 Hz, H2'), 2.00 (1H, m, H2'), 1.92 (1H, m, H3 *syn* to H4); NOE data 4.55 (7.15, 1.3 %; 2.74, 2 %), 3.77 (3.04, 4 %; 2.00, 3 %; 1.92, 3 %); ^{13}C NMR δ 220.0 (0, C1), 144.9 (0), 141.4 (0), 127.7 (1), 126.7 (1), 126.3 (1), 124.0 (1), 81.6 (1, C4), 73.3 (1, C2), 65.0 (0, C5), 57.6 (3, C4-methoxy), 37.2 (2, C2'), 33.8 (2, C3), 30.4 (2, C3'); MS 232 (5, M^+), 200 (14), 181 (13), 170 (19), 160 (23), 146 (13), 143 (12), 142 (13), 141 (29), 129 (11), 117 (24), 116 (18), 115 (45), 91 (11), 86 (62), 84 (100), 63 (11), 49 (15), 47 (24); HRMS calcd for $C_{14}H_{16}O_3$ 232.1098, found 232.1096. For **390b**: IR 3426, 1746 cm^{-1}; ^1H NMR δ 7.26 (1H, d, J = 7.4 Hz), 7.21 (1H, dt, J = 1.4, 7.4 Hz), 7.14 (1H, t, J = 7.4 Hz), 7.00 (1H, d, J = 7.4 Hz, H7'), 4.46 (1H, t, J = 8.6 Hz, H2), 3.92 (1H, t, J = 4.4 Hz, H4), 3.32 (3H, s, C4-methoxy), 3.08-2.92 (2H, m, H3'), 2.87 (1H, br s, OH), 2.66-2.50 (2H, m, H2', H3 *syn* to H2), 2.27-2.07 (2H, m, H2', H3 *syn* to H4); NOE data 7.00 (3.92, 1 %; 2.27-2.07, 2 %), 4.46 (2.66-2.50, 2 %), 3.92 (7.00, 1.4 %; 3.32, 3 %; 2.27-2.07, 2 %); ^{13}C NMR δ 218.9 (0, C1), 144.8 (0), 144.4 (0), 127.8 (1), 126.7 (1), 124.8 (1), 123.3 (1), 82.3 (1, C4), 72.6 (1, C2), 65.3 (0, C5), 57.5 (3, C4-methoxy), 33.4 (2, C3), 31.2 (2, C3'), 30.6 (2, C2'); MS 232 (20, M^+), 214 (17), 200 (13), 186 (20), 183 (31), 181 (12), 174 (14), 161 (10), 160 (88), 156 (11), 155 (17), 154 (14), 153 (10), 146 (38), 145 (20), 143 (23), 141 (16), 130 (14), 129 (25), 128 (43), 127 (14), 117 (100), 116 (48), 115 (92), 97 (27), 89 (11), 65 (11), 63 (16), 51 (13), 45 (13), 43 (15); HRMS calcd for $C_{14}H_{16}O_3$ 232.1098, found 232.1097.



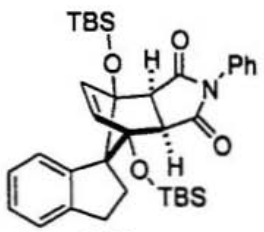
392a



392b

(4*R/S*,5*R/S*)- (392a) and (4*R/S*,5*S/R*)-2',3'-Dihydro-2,4-dimethoxyspiro(cyclopentane-5,1'-(1*H*)indene)-2-en-1-one (392b). A solution of **390a,b** (1.43 g, 6.16 mmol) in CH_2Cl_2 (90 mL) was treated with Dess-Martin periodinane (3.50 g, 8.25 mmol) while stirring at rt for 45 min. Solvent removal from the filtrate gave an orange resin containing **391a,b** and a mixture of iodo- and iodosobenzoic acids. Attempts to isolate **391a,b** from this mixture by chromatography were unsuccessful. A solution of this crude material in ether (15 mL) was treated with diazomethane (50 mL, ~0.26 M in ether) at 4 °C. The mixture was warmed to rt with occasional swirling over 45 min. Solvent evaporation yielded a viscous, brown oil (1.53 g). Chromatography (30/70 acetone-hexanes) gave a viscous, brown oil (608 mg) that was chromatographed further (50/50 EtOAc-hexanes) to yield **392a** (133 mg), **392b** (54 mg) and a mixed fraction **392a,b** (228 mg) as yellow resins (total 415 mg, 27 % over two steps). For **392a**: IR 1721 (s), 1632 (m), 1607 (m) cm^{-1}; ^1H NMR δ 7.26-7.17 (2H, m), 7.13 (1H, t, J = 7.2 Hz), 7.05 (1H, d, J = 7.2 Hz), 6.42 (1H, d, J = 2.9 Hz, H3), 4.27 (1H, d, J = 2.9 Hz, H4), 3.81 (3H, s, C2-methoxy), 3.25-2.99 (2H, m, H3'), 2.94 (3H, s, C4-methoxy), 2.56 (1H, ddd, J = 7.3, 9.1, 13.0 Hz, H2'), 2.13 (1H, ddd, J = 4.7, 8.4, 13.0 Hz, H2'); ^{13}C NMR δ 201.6 (0, C1), 158.2 (0, C2), 144.9 (0), 140.6 (0), 127.6 (1), 126.0 (1), 125.5 (1), 124.3 (1), 123.6 (1, C3), 83.6 (1, C4), 64.3 (0, C5), 57.6 (3, C4-methoxy), 57.2 (3, C2-methoxy), 36.0 (2, C2'), 31.2 (2, C3'); MS 244 (50, M^+), 214 (15), 213 (100), 153 (10), 141 (26), 117 (10), 116 (15), 115 (53), 104 (10), 85 (77), 63 (12); HRMS calcd for $C_{15}H_{16}O_3$ 244.1098, found 244.1100. For **392b**: IR 1721, 1631 cm^{-1}; ^1H NMR δ 7.27 (1H, d, J = 7.4 Hz), 7.21 (1H, dt, J = 1.3, 7.4 Hz), 7.14 (1H, t, J = 7.4 Hz), 6.91 (1H, d, J

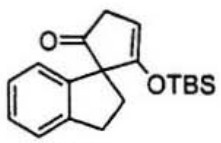
= 7.4 Hz), 6.49 (1H, d, J = 2.8 Hz, H3), 4.35 (1H, d, J = 2.8 Hz, H4), 3.83 (3H, s, C2-methoxy), 3.36 (3H, s, C4-methoxy), 3.18 (1H, m, H3'), 3.03 (1H, m, H3'), 2.51 (1H, ddd, J = 6.1, 8.6, 13.4 Hz, H2'), 2.26 (1H, ddd, J = 6.0, 8.8, 13.4 Hz, H2'); ^{13}C NMR δ 201.7 (0, C1), 158.0 (0, C2), 144.8 (0), 144.3 (0), 127.7 (1), 126.6 (1), 124.9 (1), 123.0 (1, C3), 122.2 (1), 83.6 (1, C4), 63.6 (0, C5), 57.8 (3, C4-methoxy), 57.2 (3, C2-methoxy), 31.4 (2, C3'), 30.8 (2, C2'); MS 244 (38, M^+), 214 (16), 213 (100), 181 (10), 153 (16), 141 (25), 128 (10), 117 (14), 116 (14), 115 (51), 85 (82), 63 (11); HRMS calcd for $C_{15}H_{16}O_3$ 244.1098, found 244.1090.



395

(3aα,4β,7β,7aα,8*r*)-4,7-Bis(*tert*-butyldimethylsilyloxy)-3a,4,7,7a-tetrahydro-2-phenyl-4,7-methanospiro(isoindole-8,1'-(1*H*)indene)-1,3(2*H*)dione (395). *tert*-Butyldimethylsilyl trifluoromethanesulfonate (0.23 mL, 1.0 mmol) was added dropwise to a stirred solution of **50** (100 mg, 500 μmol) and Et_3N (0.14 mL, 1.0 mmol) in dry 1,2-dichloroethane (2.2 mL) cooled to 4 °C. The mixture was held at 4 °C for 5 min and then warmed to rt for 2h before *N*-phenylmaleimide (81 mg, 470 μmol) was introduced. The mixture was stirred for 30 min, poured into water (60 mL) and extracted with CH_2Cl_2 (2 x 30 mL). The extracts were dried ($MgSO_4$) and the solvent was evaporated to give a beige solid (302 mg). Recrystallization from hexanes yielded **395** as colorless, rectangular prisms (170 mg, 61 %); mp 184-185 °C; IR (Nujol) 1778 (w), 1717 (s), 1599 (w), 1500 (m) cm^{-1}; ^{1}H NMR δ 7.53-7.32 (4H, m), 7.22-7.11 (4H, m), 7.00 (1H, m), 6.38 (2H, s, H5, H6), 3.45 (2H, s, H3a, H7a), 2.93 (2H, t, J = 7.4 Hz, H3'), 2.19 (2H, t, J = 7.4 Hz, H2'), 0.72 (9H, s, *t*-butyl), 0.11 (3H, s, $SiCH_3$), -0.32 (3H, s, $SiCH_3$); NOE data 6.38 (7.53-7.32, 7 %; 7.22-7.11, 4 %, 0.11, 4 %; -0.32, 3 %), 3.45 (2.19, 21 %), 2.93

(7.22-7.11, 8 %; 2.19, 5 %), 2.19 (3.45, 29 %; 2.93, 7 %); ^{13}C NMR δ 174.9 (2C, C1, C3), 147.2 (0), 139.9 (0), 134.4 (2C, 1, C5, C6), 131.9 (0), 129.1 (2C, 1), 128.5 (1), 128.2 (1), 127.8 (1), 126.6 (2C, 1), 124.9 (1), 124.7 (1), 89.4 (2C, 0, C4, C7), 86.1 (0, C8), 53.0 (2C, 1, C3a, C7a), 30.3 (2, C3'), 28.0 (2, C2'), 35.4 (6C, 3, *t*-butyl), 18.0 (2C, 0, *t*-butyl), -3.0 (2C, 3, $SiCH_3$), -3.5 (2C, 3, $SiCH_3$); MS no M^+, 430 (20), 429 (25), 173 (17), 75 (10), 73 (100), 45 (17).



397

4-(*tert*-Butyldimethylsilyloxy)-2',3'-dihydrospiro(cyclopentane-5,1'-(1*H*)indene)-3-en-1-one (397). *tert*-Butyldimethylsilyl trifluoromethanesulfonate (0.48 mL, 2.1 mmol) was added dropwise to a stirred solution of **50** (210 mg, 1.05 mmol) and Et_3N (0.30 mL, 2.2 mmol) in dry 1,2-dichloroethane (1.5 mL) cooled to 4 °C. The mixture was stirred at rt for 3 h before the introduction of **385** (188 mg, 789 μmol) as a solution in benzene (1.8 mL) and 1,2-dichloroethane (2.5 mL). The mixture was stirred at rt for 1h, heated to reflux for 3.5 h, cooled to rt, poured into water (75 mL) and extracted with CH_2Cl_2 (2 x 50 mL). The combined extracts were dried ($MgSO_4$) and concentrated to give a black tar (611 mg). Chromatography (10/90 EtOAc-hexanes) provided **397** as a tan-colored oil (163 mg); IR 1752, 1637 cm^{-1}; ^{1}H NMR δ 7.24 (1H, d, J = 7.2 Hz), 7.18 (1H, dt, J = 1.5, 7.2 Hz), 7.12 (1H, t, J = 7.2 Hz), 6.92 (1H, d, J = 7.2 Hz), 5.00 (1H, t, J = 2.2 Hz, H3), 3.14 (1H, overlapped dd, J = 2.2, 22.2 Hz, H2), 2.96 (1H, overlapped dd, J = 2.2, 22.2 Hz, H2), 3.24-2.97 (2H, overlapped m), 2.34-2.26 (2H, m), 0.74 (9H, s, *t*-butyl), 0.18 (3H, s, $SiCH_3$), -0.01 (3H, s, $SiCH_3$); ^{13}C NMR δ 216.0 (0, C1), 156.5 (0, C4), 145.0 (0), 142.5 (0), 127.6 (1), 126.3 (1), 124.7 (1), 122.8 (1), 96.7 (1, C3), 66.1 (0, C5), 40.7 (2, C2), 32.3 (2), 31.6 (2), 25.2 (3C, 3, *t*-butyl), 17.8 (0, *t*-butyl), -4.6 (3, $SiCH_3$), -5.3 (3, $SiCH_3$); MS

314 (2, M^+), 286 (35), 258 (16), 257 (75), 230 (10), 229 (44), 210 (11), 155 (15), 115 (12), 75 (100), 73 (53), 59 (18), 55 (14), 45 (22).

References

(1) (a) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1977**, *99*, 961–963. (b) Shimada, J.; Hashimoto, K.; Kim, B. H.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 1759–1773. (c) Nakamura, E.; Kuwajima, I. *Organic Syntheses*; Wiley: New York, 1987; Vol. 65, pp 17–25.

(2) (a) Wu, Y.-J.; Burnell, D. J. *Tetrahedron Lett.* **1988**, *29*, 4369–4372. (b) Burnell, D. J.; Wu, Y.-J. *Can. J. Chem.* **1990**, *68*, 804–811.

(3) Wu, Y.-J.; Strickland, D. W.; Jenkins, T. J.; Liu, P.-Y.; Burnell, D. J. *Can. J. Chem.* **1993**, *71*, 1311–1318.

(4) Wu, Y.-J.; Burnell, D. J. *Tetrahedron Lett.* **1989**, *30*, 1021–1024.

(5) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503–7509.

(6) Jenkins, T. J.; Burnell, D. J. *J. Org. Chem.* **1994**, *59*, 1485–1491.

(7) Anderson, W. K.; Lee, G. E. *J. Org. Chem.* **1980**, *45*, 501–506.

(8) Oppolzer, W.; Wylie, R. D. *Helv. Chim. Acta* **1980**, *63*, 1198–1203.

(9) Burnell, D. J.; Wu, Y.-J. *Can. J. Chem.* **1989**, *67*, 816–819.

(10) (a) Wu, Y.-J.; Zhu, Y.-Y.; Burnell, D. J. *J. Org. Chem.* **1994**, *59*, 104–110. (b) Zhu, Y.-Y.; Burnell, D. J. *Tetrahedron: Asymm.* **1996**, *7*, 3295–3304.

(11) (a) Parker, K. A.; Koziski, K. A.; Breault, G. *Tetrahedron Lett.* **1985**, *26*, 2181–2184. (b) Saint-Jalmes, L.; Lila, C.; Xu, J. Z.; Moreau, L.; Pfeiffer, B.; Eck, G.; Pelsez, L.; Rolando, C.; Julia, M. *Bull. Soc. Chim. France* **1993**, *130*, 447–449. (c) Wendt, J. A.; Gauvreau, P. J.; Bach, R. D. *J. Am. Chem. Soc.* **1994**, *116*, 9921–9926.

(12) Other development and synthetic uses of Lewis acid-catalyzed geminal acylation with **1**: (a) Anderson, W. K.; Lee, G. E. *Synth. Commun.* **1980**, *10*, 351–354. (b) Nakamura, E.; Shimada, J; Kuwajima, I. *J. Chem. Soc., Chem. Commun.* **1983**, 498–499. (c) Bunnelle, W. H.; Shangraw, W. R. *Tetrahedron* **1987**, *43*, 2005–2011. (d) Martinez, R. A.; Rao, P. N.; Kim, H. K. *Synth. Commun.* **1989**, *19*, 373–377. (e) Pandey, B.; Khire, U. R.; Ayyangar, N. R. *Synth. Commun.* **1989**, *19*, 2741–2747. (f) Liu, P.-Y.; Burnell, D. J. *J. Chem. Soc., Chem. Commun.* **1994**, 1183–1184. (g) Balog, A.; Curran, D. P. *J. Org. Chem.* **1995**, *60*, 337–344. (h) Balog, A.; Geib, S. J.; Curran, D. P. *J. Org. Chem.* **1995**, *60*, 345–352. (i) Liu, P.-Y.; Wu, Y.-J.; Burnell, D. J. *Can. J. Chem.* **1997**, *75*, 656–664.

(13) Bloomfield, J. J.; Nelke, J. M. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, pp 167–172.

(14) Rühlmann, K. *Synthesis* **1971**, 236–253.

(15) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902–3909 using SPARTAN, Version 4.1 (Wavefunction, Inc., Irvine, CA).

(16) Pandey, B.; Reddy, R. S.; Kumar, P. *J. Chem. Soc., Chem. Commun.* **1993**, 870–871.

(17) (a) Nöth, H.; Wrackmeyer, B. in *Nuclear Magnetic Resonance Spectroscopy of Boron Compounds*; *NMR, Basic Principles and Progress*; Diehl, P.; Fluck, E.; Kosfeld, R., Eds.; Springer-Verlag, Berlin, 1978; Vol. 14. (b) Marsmann, H. in *Oxygen-17 and Silicon-29*; *NMR, Basic Principles and Progress*; Diehl, P.; Fluck, E.; Kosfeld, R., Eds.; Springer-Verlag, Berlin, 1981; Vol. 17.

(18) Pandey, R. C.; Toussaint, M. W.; Stroshane, R. M.; Geoghegan, R. F., Jr.; White, R. J. *J. Antibiot.* **1981**, *34*, 1389–1401.

(19) Biosynthesis: Byrne, K. M.; Hilton, B. D.; White, R. J.; Misra, R.; Pandey, R. C. *Biochemistry* **1985**, *24*, 478–486.

(20) Misra, R.; Pandey, R. C.; Silverton, J. V. *J. Am. Chem. Soc.* **1982**, *104*, 4478–4479.

(21) Misra, R.; Pandey, R. C.; Hilton, B. D.; Roller, P. P.; Silverton, J. V. *J. Antibiot.* **1987**, *40*, 786–802.

(22) Warnick-Pickle, D. J.; Byrne, K. M.; Pandey, R. C.; White, R. J. *J. Antibiot.* **1981**, *34*, 1402–1407.

(23) Hilton, B. D.; Misra, R.; Zweier, J. L. *Biochemistry* **1986**, *25*, 5533–5539.

(24) Dalal, N. S.; Shi, X. *Biochemistry* **1989**, *28*, 748–750.

(25) Latham, M. D.; King, C. K.; Gorycki, P.; Macdonald, T. L.; Ross, W. E. *Cancer Chemother. Pharamcol.* **1989**, *24*, 167–171.

(26) (a) Boger, D. L. *J. Heterocycl. Chem.* **1996**, *33*, 1519–1531. (b) Boger, D. L.; Hueter, O.; Mbiya, K.; Zhang, M. *J. Am. Chem. Soc.* **1995**, *117*, 11839–11849.

(27) (a) Water-soluble potassium salt: Misra, R. *J. Antibiot.* **1988**, *41*, 976–981. (b) Derivatives: Yokoi, K.; Hasegawa, H.; Narita, M.; Asaoka, T.; Kukita, K.; Ishizeka, S.; Nakajima, T. Jpn Patent 152468, 1985; *Chem. Abstr.* **1986**, *104*, 33948j. (c) C ring expanded to six atoms: Clive D. L. J.; Kong, X. L.; Paul C. C. *Tetrahedron* **1996**, *52*, 6085–6116.

(28) (a) Kelly, T. R.; Bell, S. H.; Ohashi, N.; Armstrong-Chong, R. J. *J. Am. Chem. Soc.* **1988**, *110*, 6471–6480. (b) Watanabe, M.; Morimoto, H.; Furukawa, S.

Heterocycles **1993**, *36*, 2681–2686. (c) Kessar, S. V.; Vohra, R.; Kaur, N. P.; Singh, K. N.; Singh, P. *J. Chem. Soc., Chem. Commun.* **1994**, 1327–1328. (d) Baskaran S.; Nagy, E.; Braun, M. *Liebigs Ann./Recueil* **1997**, 311–312. (e) Eck, G.; Julia, M.; Pfeiffer, B.; Rolando, C. *Tetrahedron Lett.* **1985**, *26*, 4725–4726. (f) Naik, S. N.; Pandey, B.; Ayyangar, N. R. *Synth. Commun.* **1988**, *18*, 633–638. (g) Mehta, G.; Subrahmanyam, D. *Tetrahedron Lett.* **1987**, *28*, 479–480. (h) Pandey, B.; Khire, U. R.; Ayyangar, N. R. *J. Chem. Soc., Chem. Commun.* **1990**, 1791–1792. (i) Kende, A. S.; Ebetino, F. H.; Ohta, T. *Tetrahedron Lett.* **1985**, *26*, 3063–3066. (j) Braun, M.; Veith, R. *Tetrahedron Lett.* **1986**, *27*, 179–182. (k) Ciufolini, M. A.; Browne, M. E. *Tetrahedron Lett.* **1987**, *28*, 171–174. (l) Aidhen, I. S.; Narasimhan, N. S. *Tetrahedron Lett.* **1989**, *30*, 5323–5324. (m) Rao, A. V. R.; Singh, A. K.; Reddy, K. M.; Ravikumar, K. *J. Chem. Soc., Perkin Trans. 1* **1993**, 3171–3177. (n) Toyota, M.; Terashima, S. *Tetrahedron Lett.* **1989**, *30*, 829–832. (o) Kita, Y.; Okunaka, R.; Honda, T.; Kondo, M.; Tamura, O.; Tamura, Y. *Chem. Pharm. Bull.* **1991**, *39*, 2106–2114. (p) Kita, Y.; Ueno, H.; Kitagaki, S.; Kobayashi, K.; Iio, K.; Akai, S. *J. Chem. Soc., Chem. Commun.* **1994**, 701–702. (q) Evans, P. A.; Brandt, T. A. *Tetrahedron Lett.* **1996**, *37*, 1367–1370. (r) Boger, D. L.; Jacobson, I. C. *J. Org. Chem.* **1990**, *55*, 1919–1928. (s) Clive, D. L. J.; Angoh, A. G.; Bennett, S. M. *J. Org. Chem.* **1987**, *52*, 1339–1342. (t) Parker, K. A.; Breault, G. A. *Tetrahedron Lett.* **1986**, *27*, 3835–3838. (u) Evans, J. C.; Klix, R. C.; Bach, R. D. *J. Org. Chem.* **1988**, *53*, 5519–5527. (v) Kita, Y.; Kitagaki, S.; Imai, R.; Okamoto, S.; Mihara, S.; Yoshida, Y.; Akai, S.; Fujioka, H. *Tetrahedron Lett.* **1996**, *37*, 1817–1820.

(29) Kelly, R. T.; Ohashi, N.; Armstrong-Chong, R. J.; Bell, S. H. *J. Am. Chem. Soc.* **1986**, *108*, 7100–7101.

(30) (a) Clive, D. L. J.; Tao, Y.; Khodabocus, A.; Wu, Y.-J.; Angoh, A. G.; Bennett, S. M.; Boddy, C. N.; Bordeleau, L.; Kellner, D.; Kleiner, G.; Middleton, D. S.; Nichols, C. J.; Richardson, S. R.; Vernon, P. G. *J. Chem. Soc., Chem. Commun.* **1992**, 1489–1490. (b) Clive, D. L. J.; Tao, Y.; Khodabocus, A.; Wu, Y.-J.; Angoh, A. G.; Bennett, S. M.; Boddy, C. N.; Bordeleau, L.; Kellner, D.; Kleiner, G.; Middleton, D. S.; Nichols, C. J.; Richardson, S. R.; Vernon, P. G. *J. Am. Chem. Soc.* **1994**, *116*, 11275–11286.

(31) (a) Rao, A. V. R.; Singh, A. K.; Rao, B. V.; Reddy, K. M. *Tetrahedron Lett.* **1993**, *34*, 2665–2668. (b) Rao, A. V. R.; Singh, A. K.; Rao, B. V.; Reddy, K. M. *Heterocycles* **1994**, *37*, 1893–1912.

(32) Kita, Y.; Higuchi, K.; Yoshida, Y.; Iio, K.; Kitagaki, S.; Akai, S.; Fujioka, H. *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 683–686.

(33) Shapiro, S. L.; Geiger, K.; Freedman, L. *J. Org. Chem.*, **1960**, *25*, 1860–1865.

(34) (a) Bols, M.; Skrydstrup, T. *Chem. Rev.* **1995**, *95*, 1253–1277. (b) Gauthier, D. R., Jr.; Zandi, K. S.; Shea, K. J. *Tetrahedron,* **1998**, *54*, 2289–2338.

(35) Mitsunobu, O.; Kimura, J.; Iiizumi, K.; Yanagida, N. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 510–513.

(36) Dichloroketene + cyclopentadiene: Stevens, H. C.; Reich, D. A.; Brandt, D. R.; Fountain, K. R.; Gaughan, E. J. *J. Am. Chem. Soc.* **1965**, *87*, 5257-5259.

(37) House, H. O. *Modern Synthetic Reactions*, 2nd Ed. W. A. Benjamin: Menlo Park, CA, 1972; pp 324-329.

(38) (a) Shapiro, R. H. in *Organic Reactions*; Dauben, W.G., Ed.; Wiley: New York, 1976; Vol. 23, pp 405–507. (b) Chamberlin, A. R.; Bloom, S. H. in *Organic Reactions*; Paquette, L. A., Ed.; Wiley: New York, 1993; Vol. 39, pp 1–84.

(39) (a) Watt, G. W. *Chem. Rev.* **1950**, *50*, 317–379. (b) Chapman, O. L.; Fitton, P. *J. Am. Chem. Soc.* **1963**, *85*, 41-47.

(40) Loewenthal, H. J. E.; Schatzmiller, S. J. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2149–2157.

(41) Jenkins, T. J.; Ph.D. Thesis, Memorial University of Newfoundland, St. John's, NF, 1994. p. 91.

(42) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454–5459.

(43) House, H. O.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1971**, *36*, 2361–2371.

(44) Clark, G. R.; Lin, J.; Nikaido, M. *Tetrahedron Lett.* **1984**, *25*, 2645–2648.

(45) (a) Emde, H.; Domsch, D.; Feger, H.; Frick, U.; Götz, A.; Hergott, H. H.; Hofmann, K.; Kober, W.; Krägeloh, K.; Oesterle, T.; Steppan, W.; West, W.; Simchen, G. *Synthesis* **1982**, 1–26. (b) Bellus, D.; Ernst, B. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 797–827.

(46) Gillard, J. W.; Fortin, R.; Grimm, E. L. *Tetrahedron Lett.* **1991**, *32*, 1145–1148.

(47) (a) Grandmaison, J.-L.; Brassard, P. *J. Org. Chem.* **1978**, *43*, 1435–1438. (b) Savard, J.; Brassard, P. *Tetrahedron* **1984**, *40*, 3455–3464.

(48) (a) Waters, P. M.; McElvain, S. M. *J. Am. Chem. Soc.* **1940**, *62*, 1482–1484. (b) McElvain, S. M.; Anthes, H. I.; Shapiro, S. H. *J. Am. Chem. Soc.* **1942**, *64*, 2525–2531.

(49) (a) Huckin, S. N.; Weiler, L. *Can. J. Chem.* **1974**, *52*, 2157–2164. (b) Izawa, T.; Mukaiyama, T. *Chem. Lett.* **1975**, 161–164.

(50) (a) Lansbury, P. T.; Mancuso, N. R. *Tetrahedron Lett.* **1965**, 2445–2450. (b) Krow, G. R.; Szczepanski, S. *J. Org. Chem.* **1982**, *47*, 1153–1156.

(51) (a) Craig, D. *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 7, pp 689–702. (b) Donaruma, L. G.; Heldt, W. Z. in *Organic Reactions*; Cope, A.C., Ed.; Wiley: New York, 1960; Vol. 11, pp 1–156. (c) Huisgen, R.; Witte, J.; Walz, W.; Waltraud, J. *Liebigs Ann. Chem.* **1957**, *604*, 191-202. (d) Smith, P. A. S. in *Molecular Rearrangements*; De Mayo, P., Ed.; Wiley: New York, 1963; Vol. 1, pp 457-592.

(52) (a) Krow, G. *Tetrahedron* **1981**, *37*, 1283–1307. (b) Krow, G. *Tetrahedron* **1981**, *37*, 2697–2724.

(53) Olah, G. A.; Fung, A. P. *Synthesis* **1979**, 537–538.

(54) (a) Scott, W. J.; Crisp, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4630–4632. (b) Scott, W. J.; Crisp, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 7500–7506. (c) Ritter, K. *Synthesis* **1993**, 735–762.

(55) (a) Jefford, C. W.; Sledski, A. W.; Lelandais, P.; Boukouvalas, J. *Tetrahedron Lett.* **1992**, *33*, 1855–1858. (b) Angers, P.; Canonne, P. *Tetrahedron Lett.* **1994**, *35*, 367–370.

(56) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357–1358.

(57) Corey, E. J.; Gras, J.-L.; Ulrich, P. *Tetrahedron Lett.* **1976**, *17*, 809–812.

(58) (a) Rubottom, G. M.; Vazquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* **1974**, *15*, 4319–4322. (b) Stankovic, S.; Espenson, J. H. *J. Org. Chem.* **1998**, *63*, 4129–

4130. (c) McCormick, J. P.; Tomasik, W.; Johnson, M. W. *Tetrahedron Lett.* **1981**, *22*, 607–610. (d) Akashi, K.; Palermo, R. E.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 2063–2066. (e) Adam, W.; Hadjiarapoglou, L.; Wang, X. *Tetrahedron Lett.* **1989**, *30*, 6497–6500.

(59) (a) Dess, D. B.; Martin, J. C.; *J. Org. Chem.* **1983**, *48*, 4155–4156. (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

(60) Brownbridge, P. *Synthesis* **1983**, 85–104.

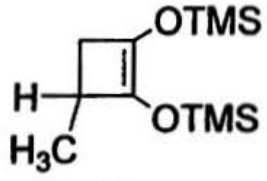
(61) Merz, A. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 846–847.

Appendix I

^{1}H and ^{13}C NMR Spectra and X-ray Structures for Chapter 1

^{1}H and ^{13}C NMR spectra for compounds **3**, **4**, **6**, **7**, **11c**, **12a**, **12b** (^{1}H only) **15a**, **15b**, **17**, **18**, **20**, **23**, **26**, **27**, **28b**, **29a**, **33a**, **33c**, **35**, **36a**, **36b**, **37**, **40**, **43**, **45**, **46a**, **47**, **48**, **51**, **52**, **53**, **57** (^{1}H only) **58**, **60**, **61**, **62a**, **62b**, **63a**, **63b**, **64a**, **64b**, **65a**, **65b**, **66**, **67**, **68**, **69**, **70a**, **71**, **72a**, **73**, **74**, **76**, **77**, **79**, **81**, **82**, **84**, **85**, **86**, **87**, **89** and **90**. Spectra obtained for chromatographically inseparable mixtures of diastereomers have not been included.

X-ray structures for compounds **11c**, **33c**, **36b**, **46a**, **48** and **77**.



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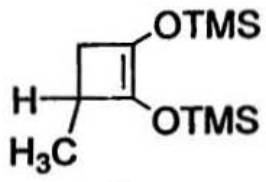

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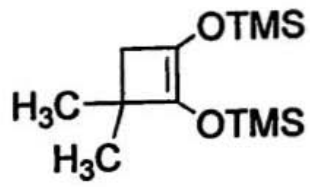

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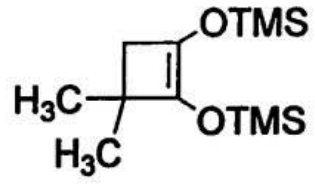

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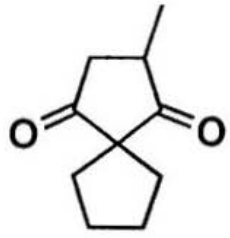

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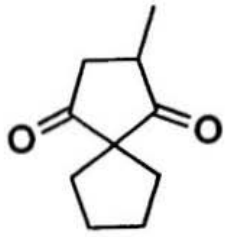

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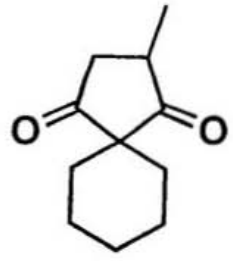

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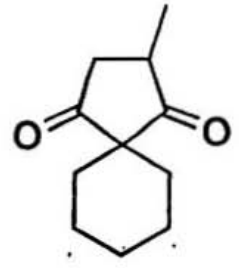

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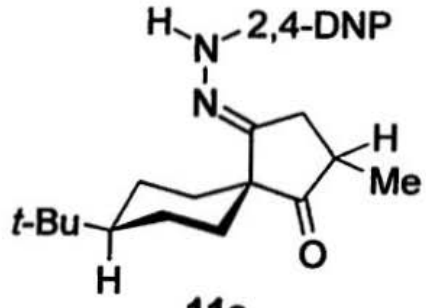

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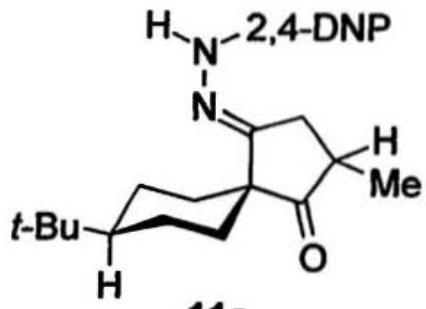

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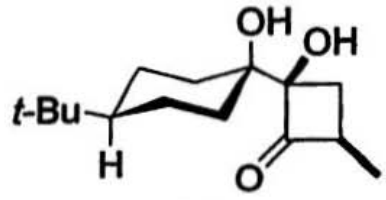

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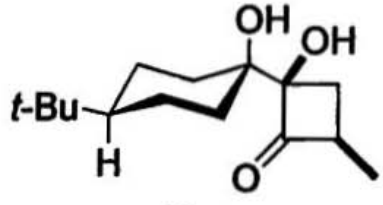

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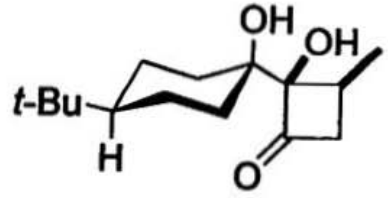

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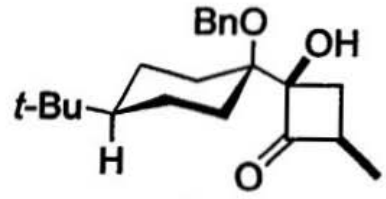

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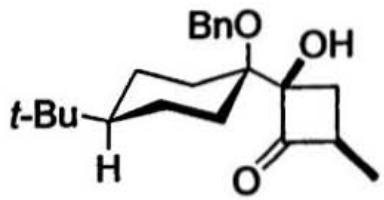

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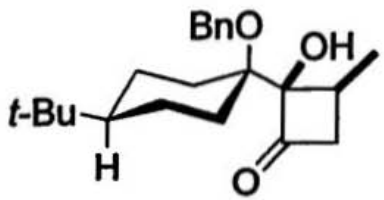

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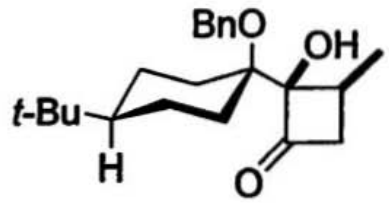

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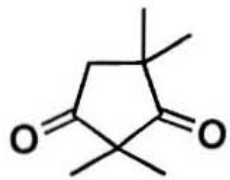

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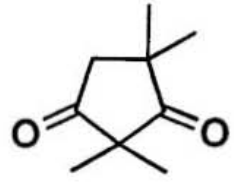

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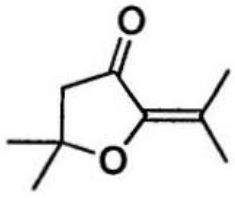

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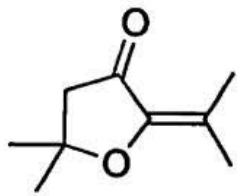

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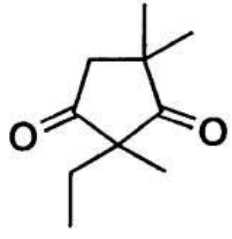

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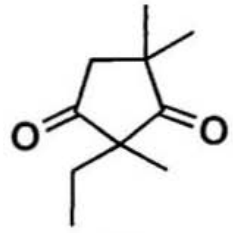

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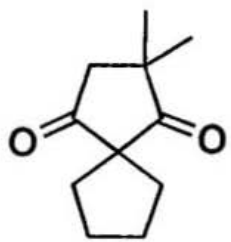

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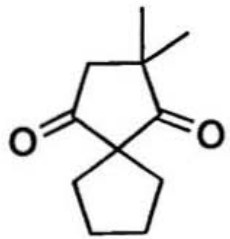

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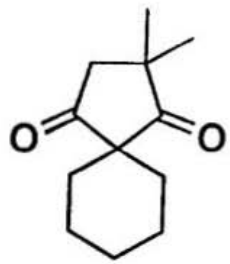

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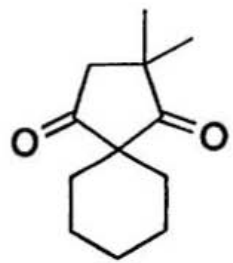

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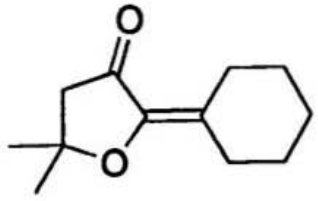

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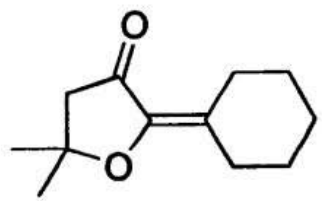

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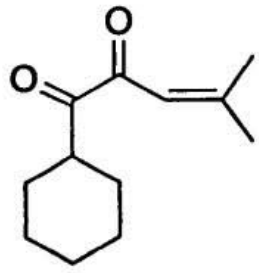

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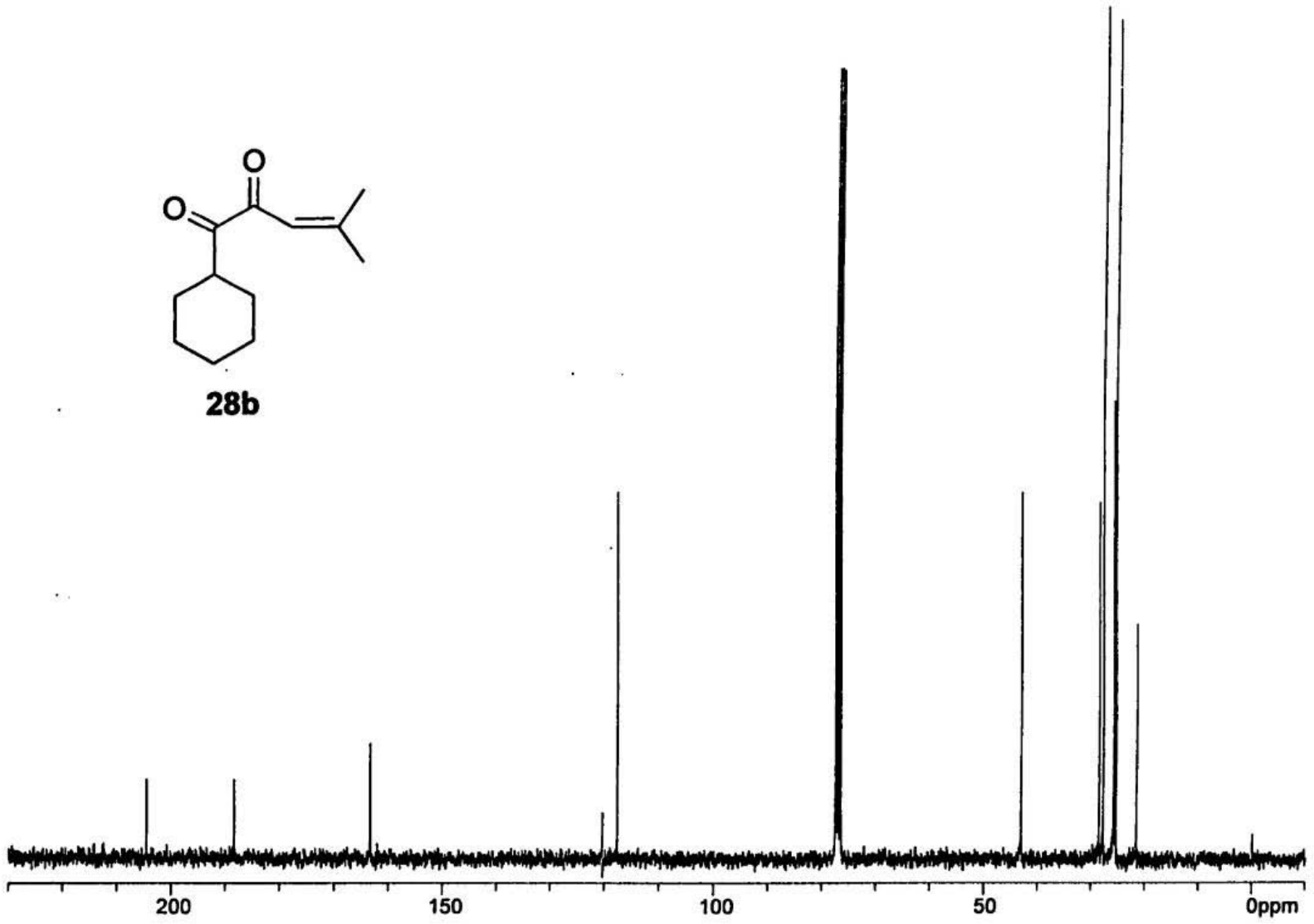
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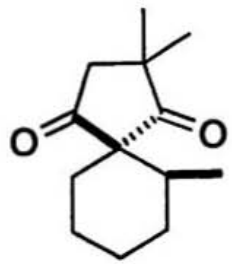

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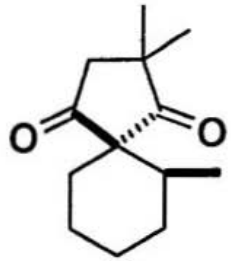

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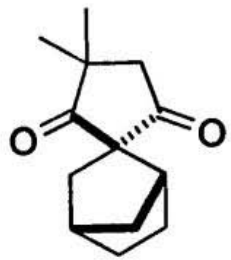

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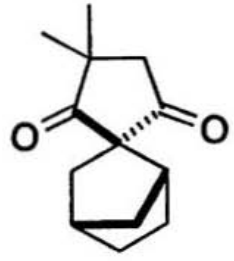

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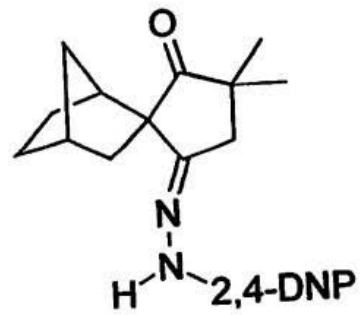

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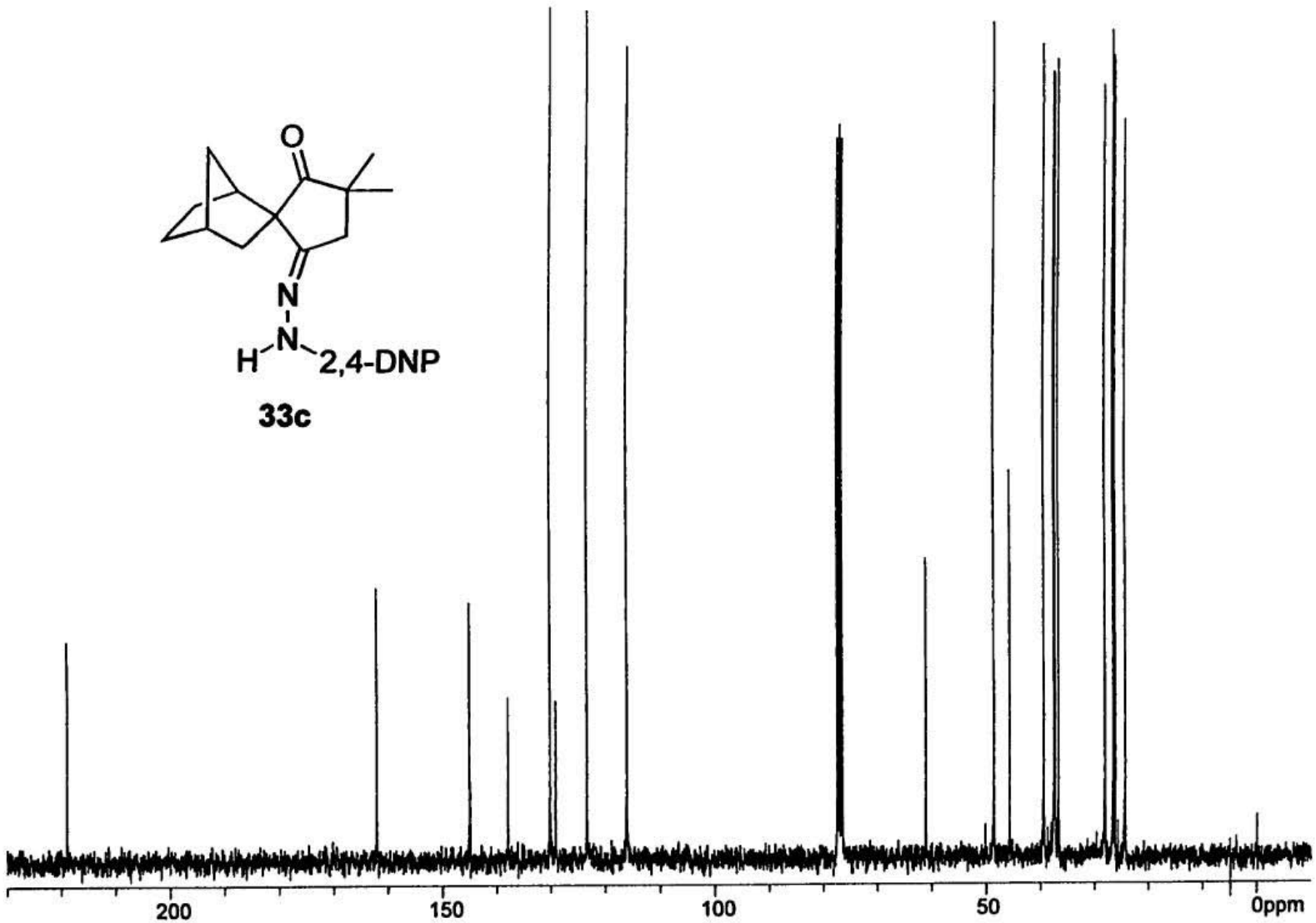

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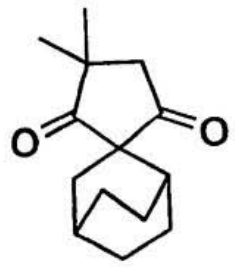

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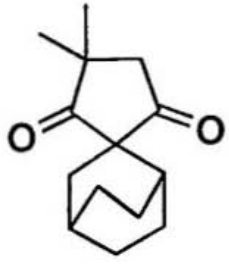

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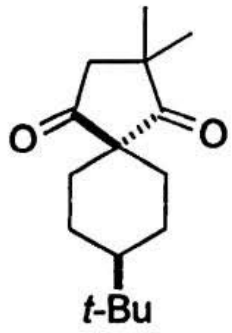

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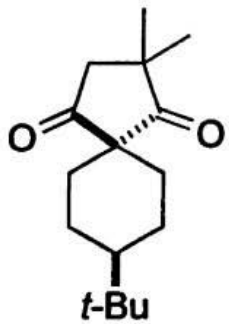

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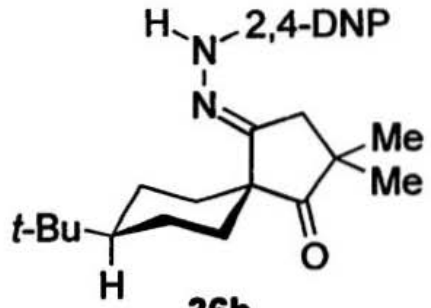

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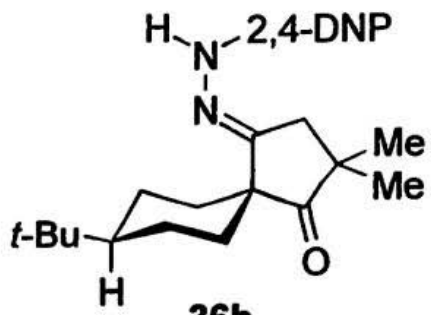

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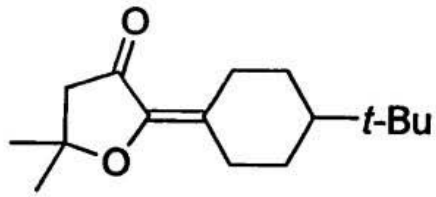

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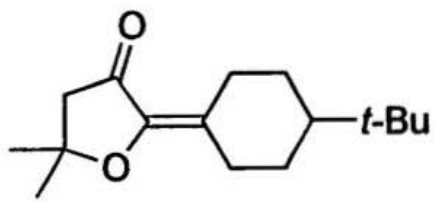

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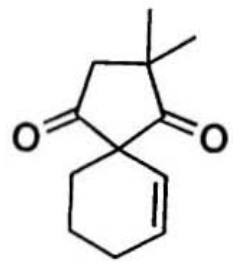

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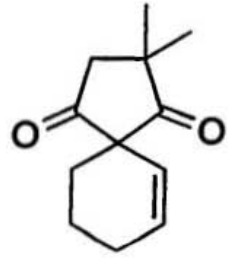

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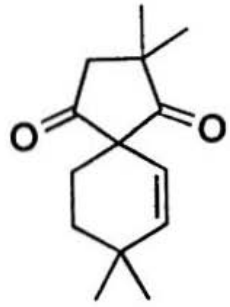

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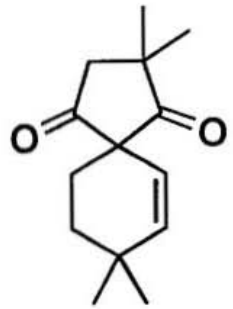

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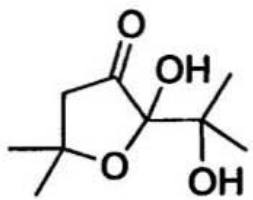

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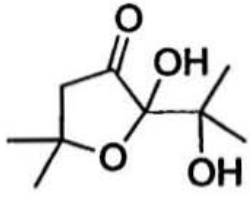

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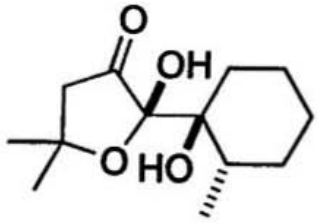

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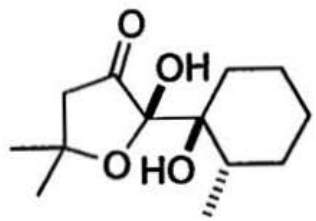

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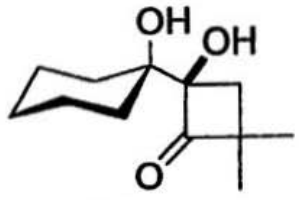

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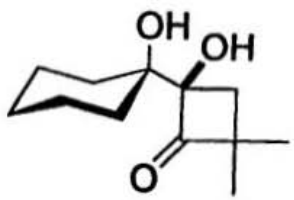

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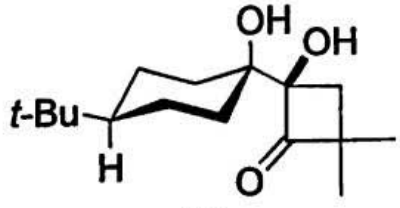

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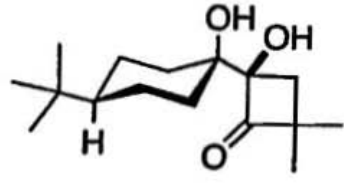
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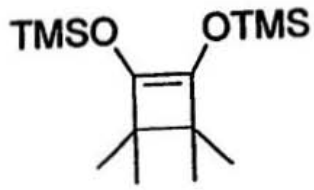

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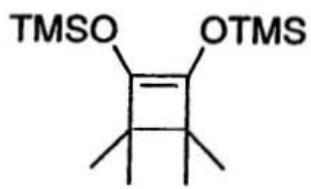

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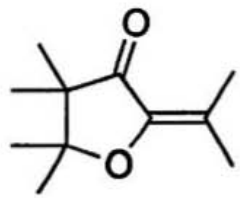

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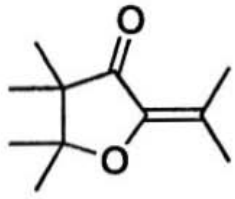

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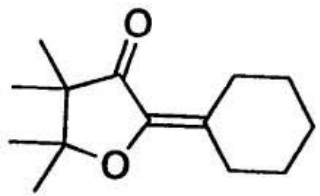

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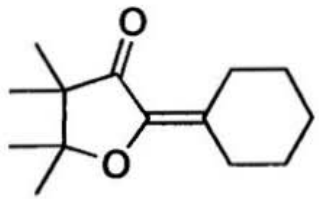

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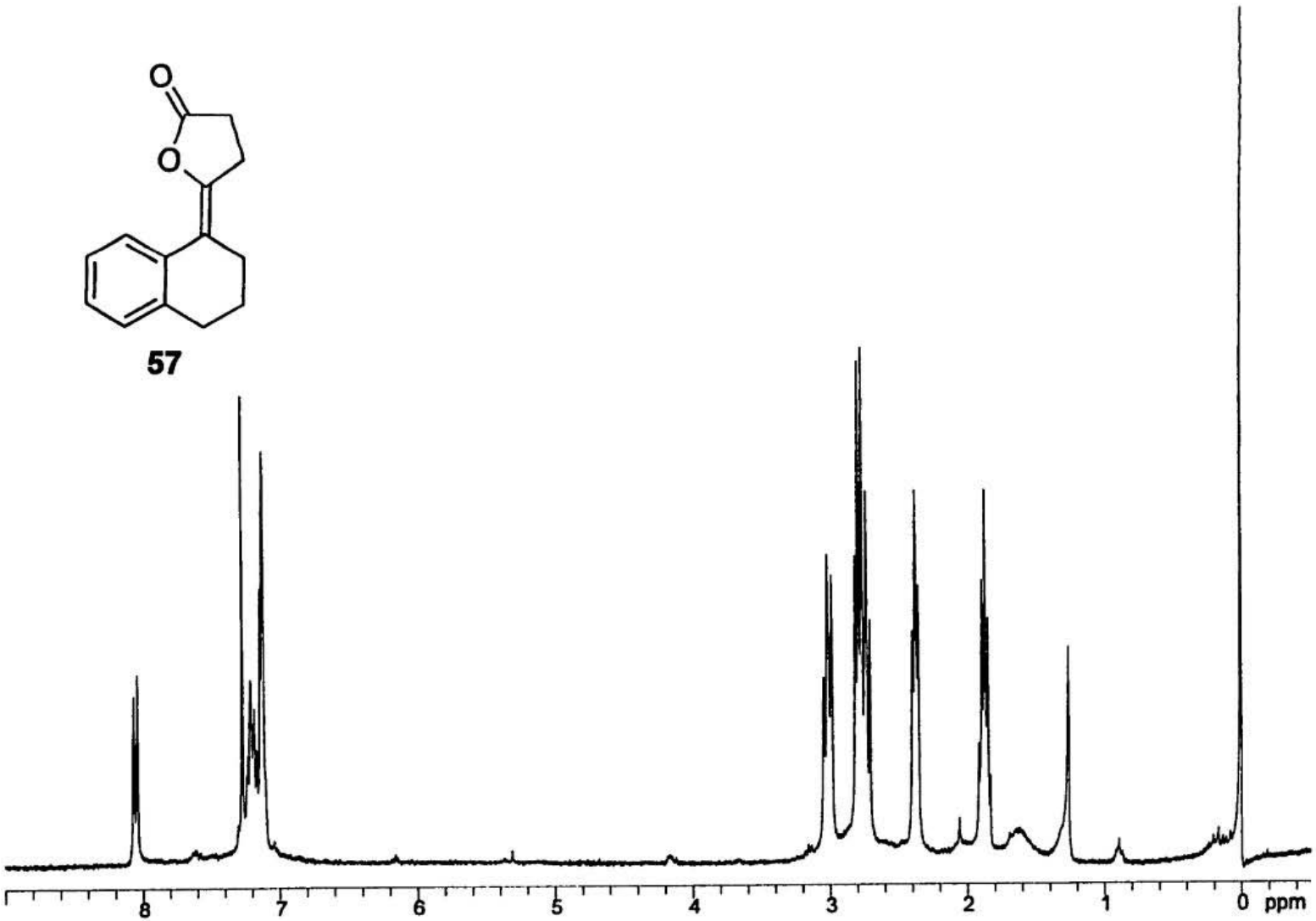

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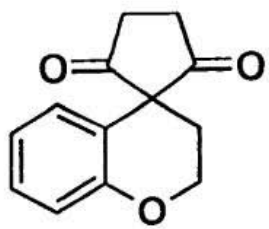

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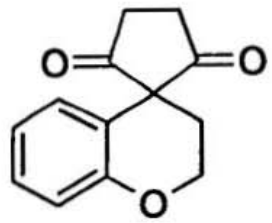

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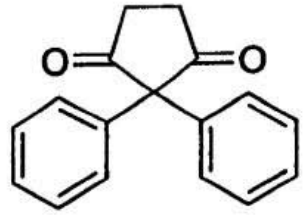

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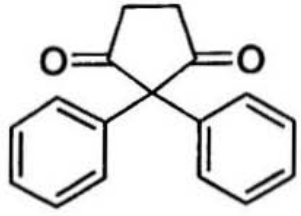

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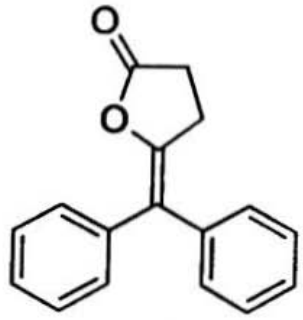

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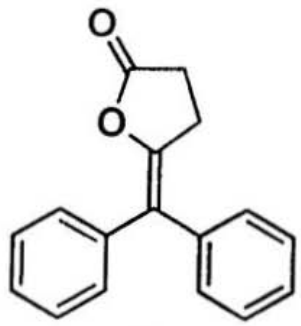

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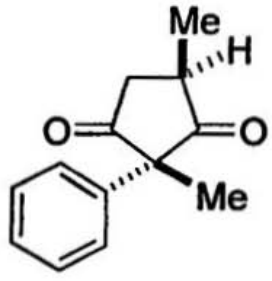

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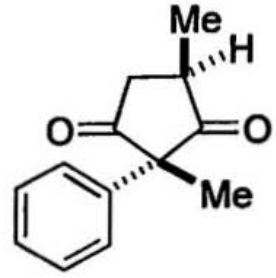

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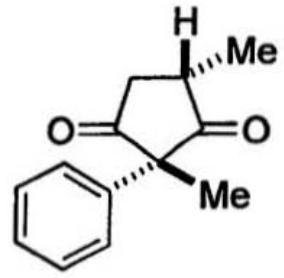

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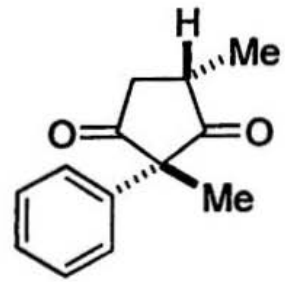

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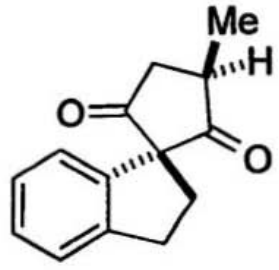

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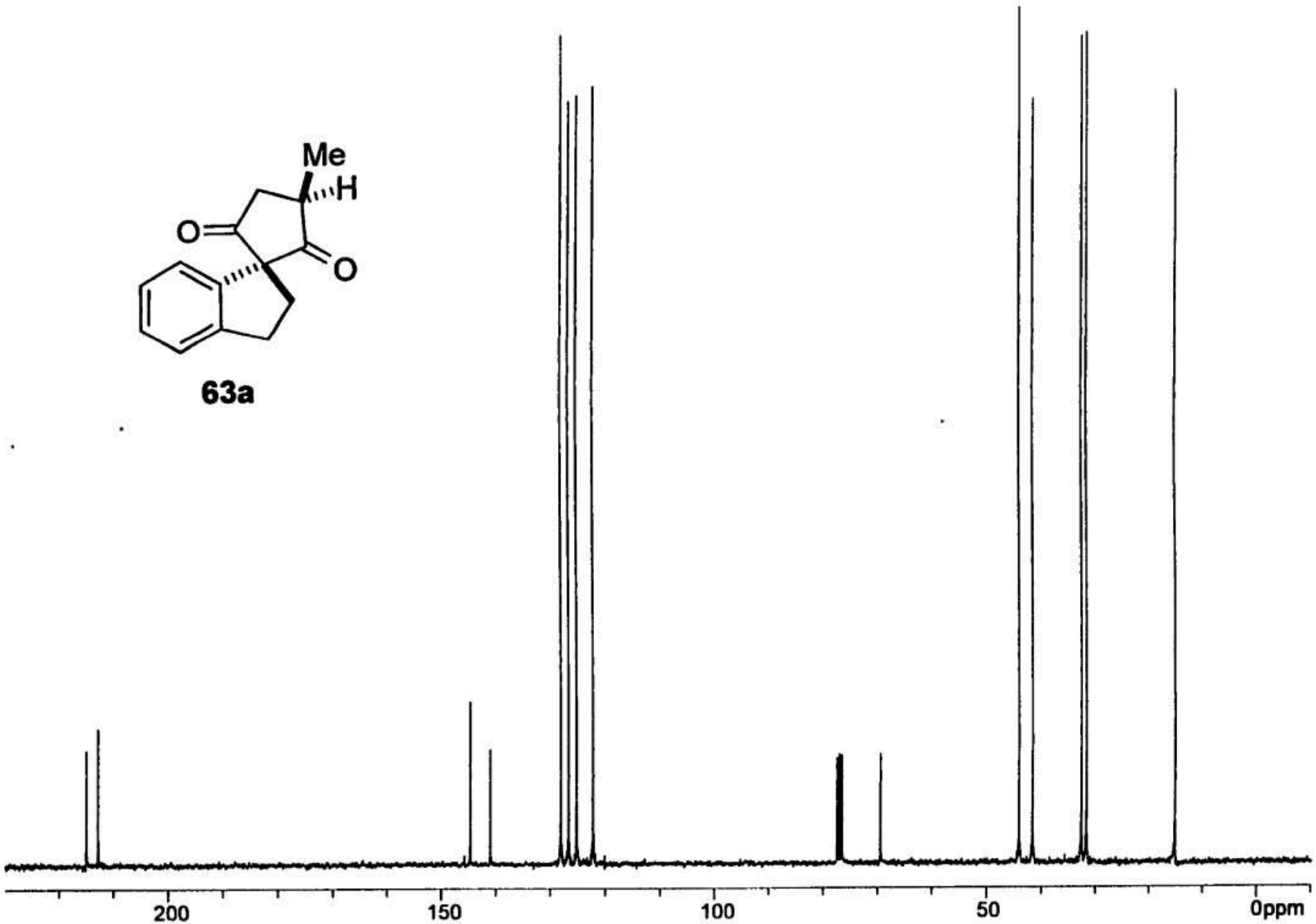
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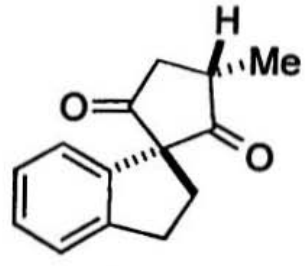

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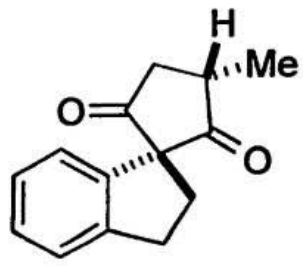

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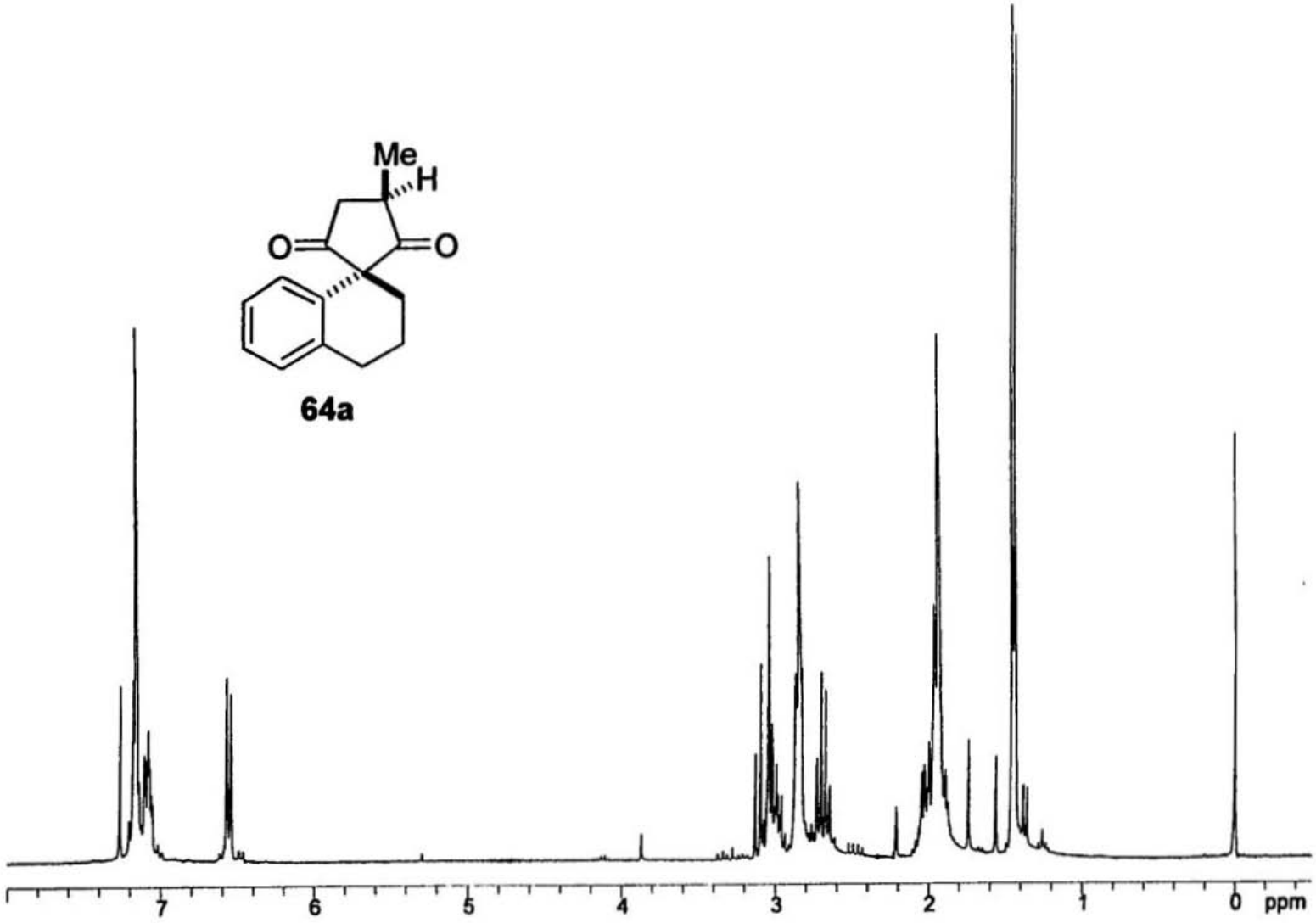

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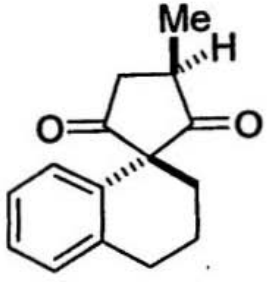

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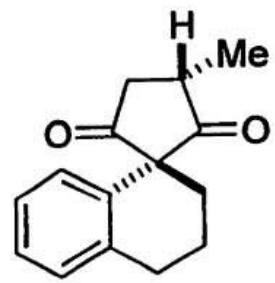

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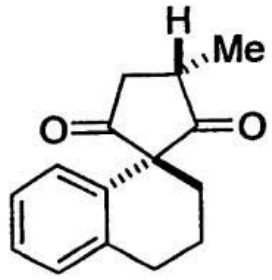

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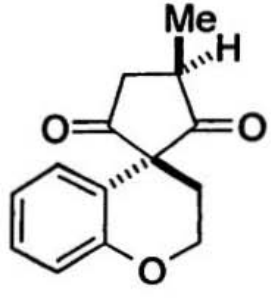

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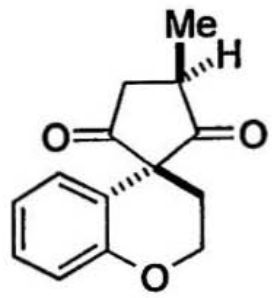

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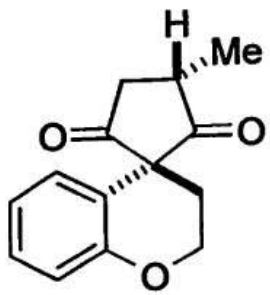

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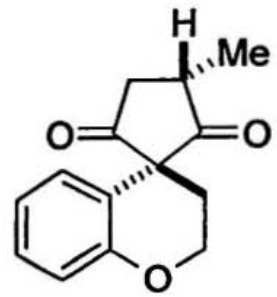

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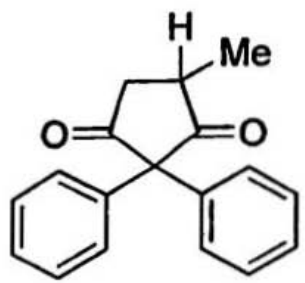

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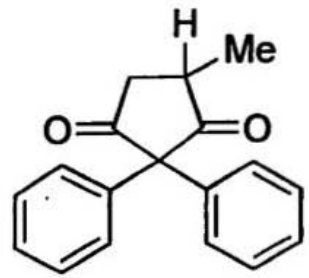

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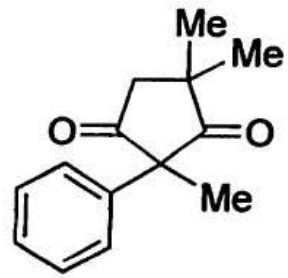

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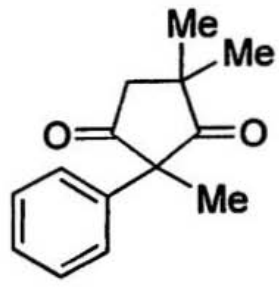

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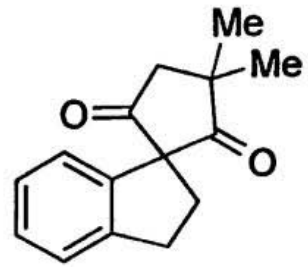

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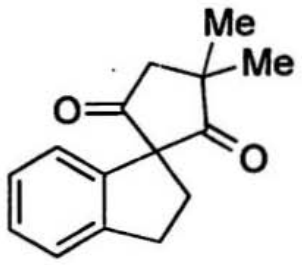

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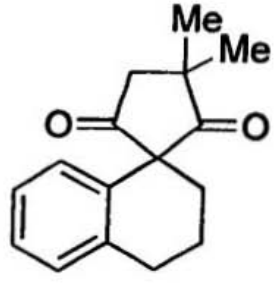

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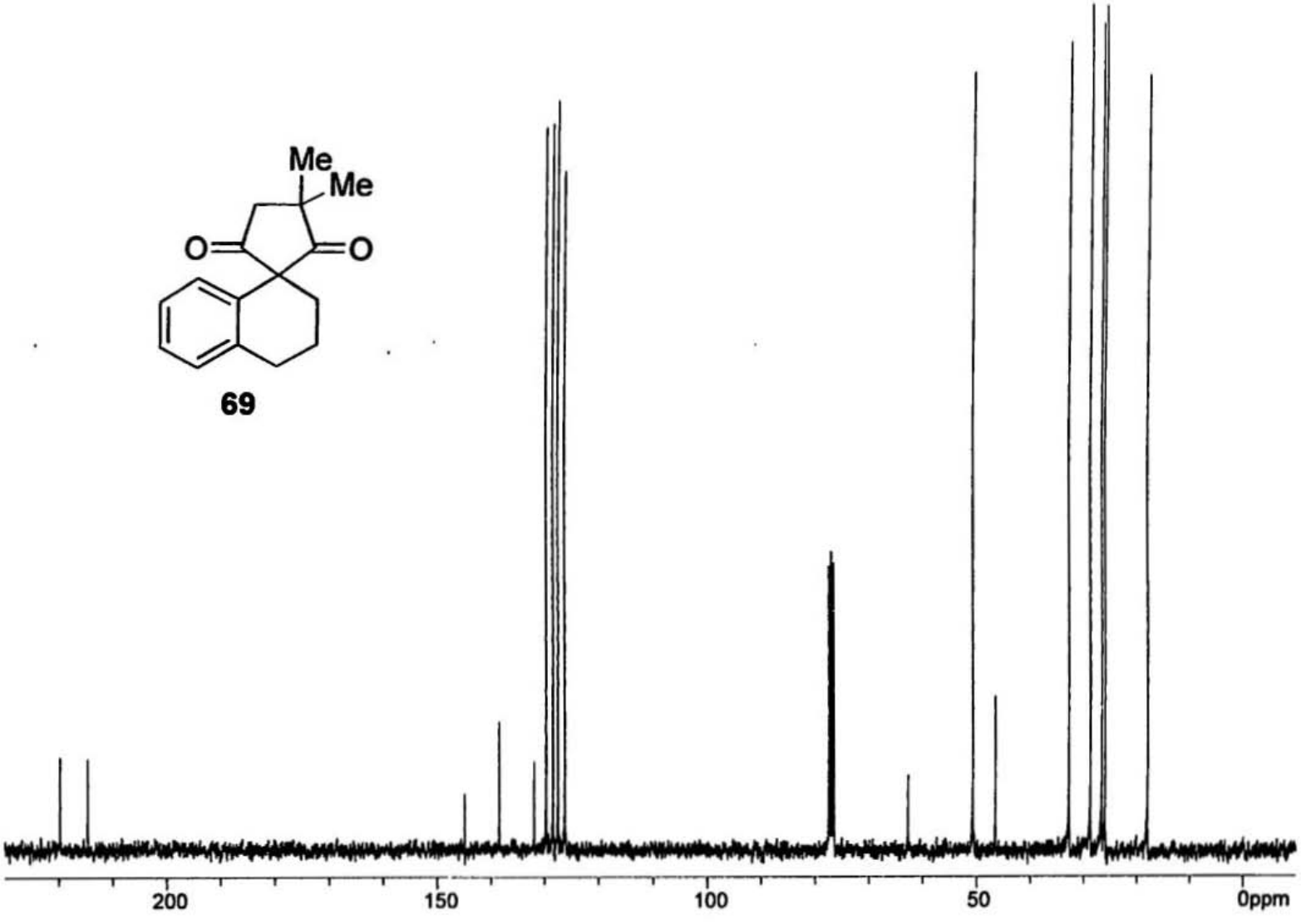

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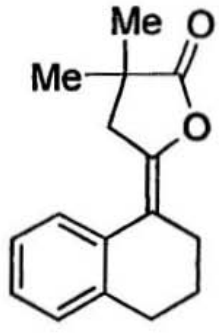

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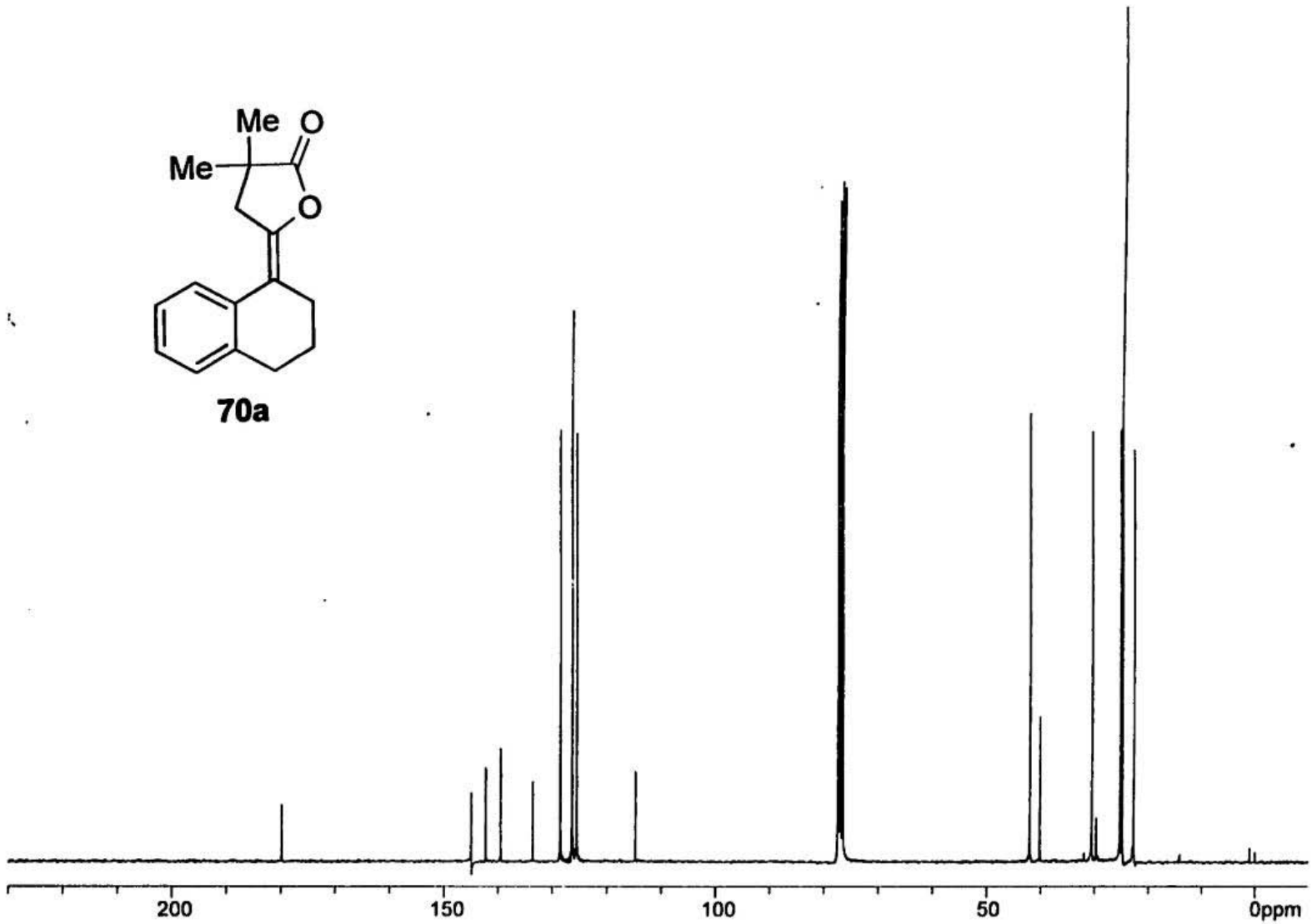
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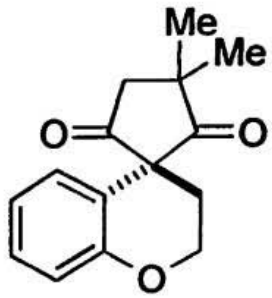

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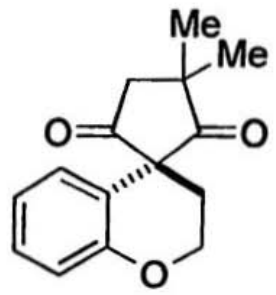

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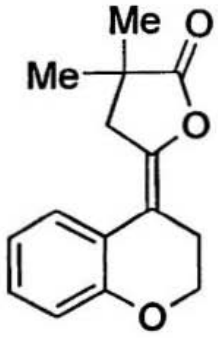

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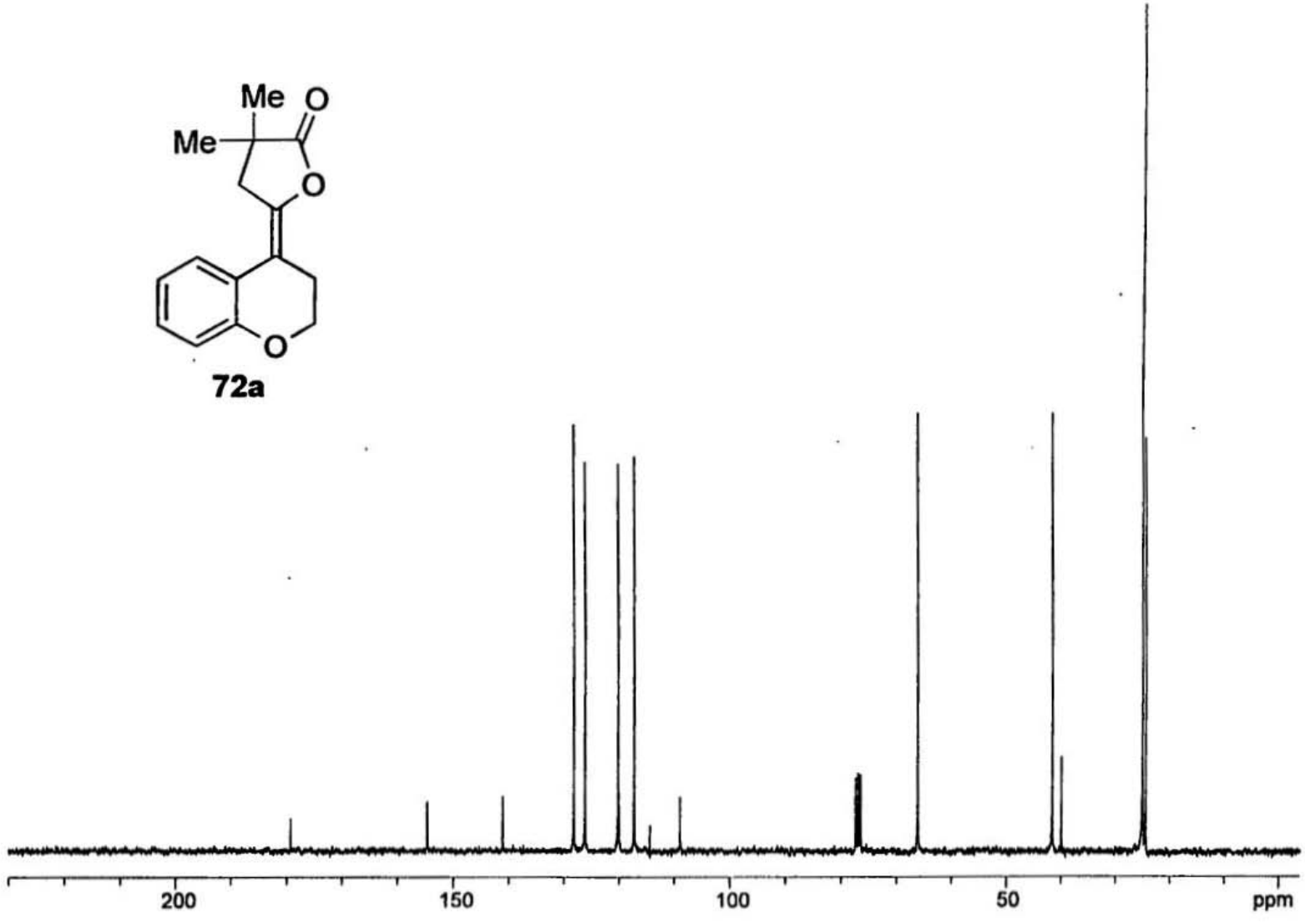

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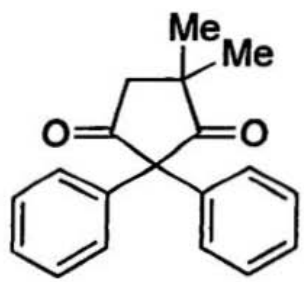

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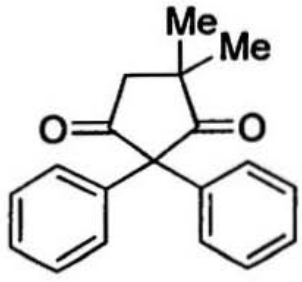

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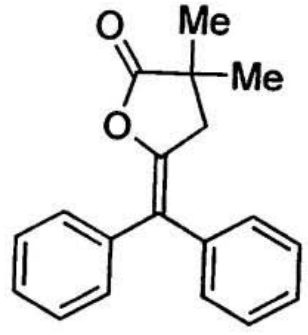

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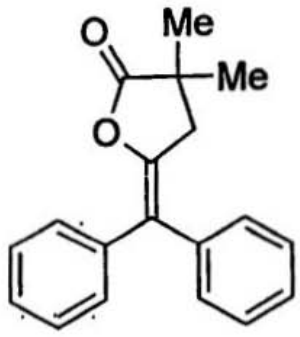

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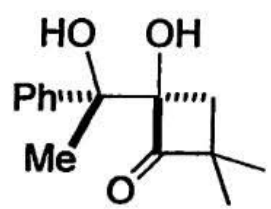

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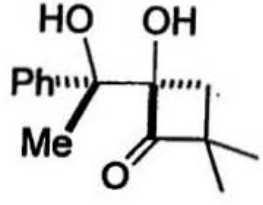

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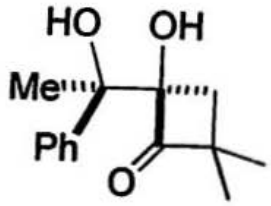

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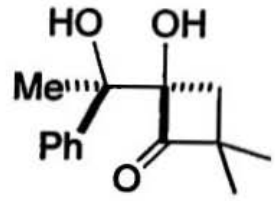

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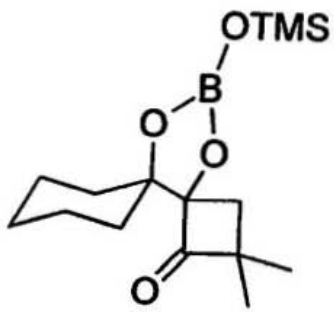

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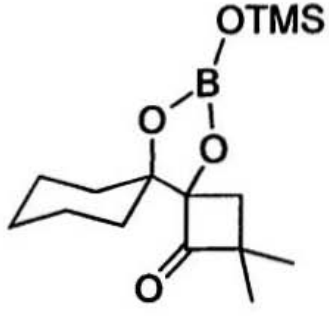

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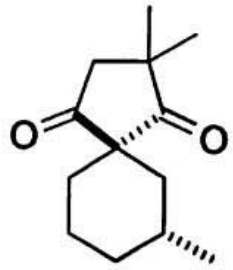

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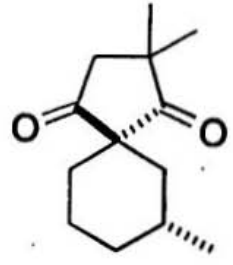

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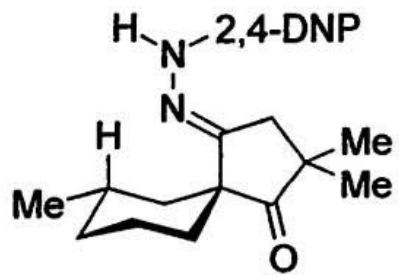

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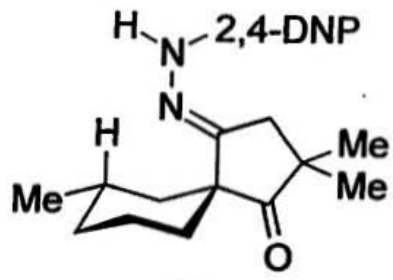

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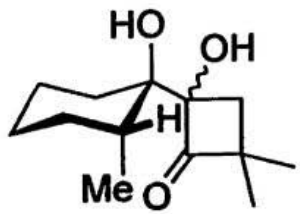

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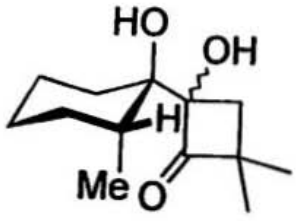

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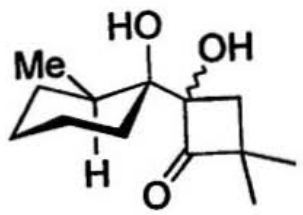

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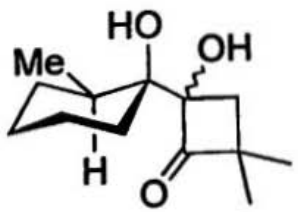

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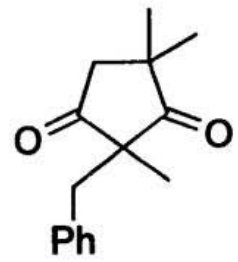

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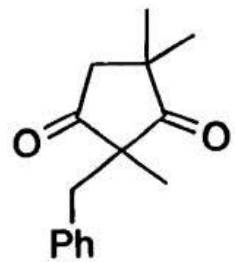

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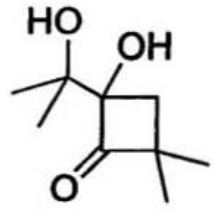

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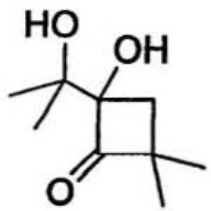

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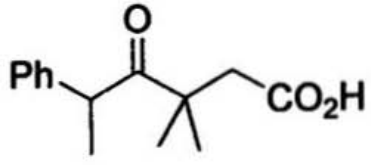

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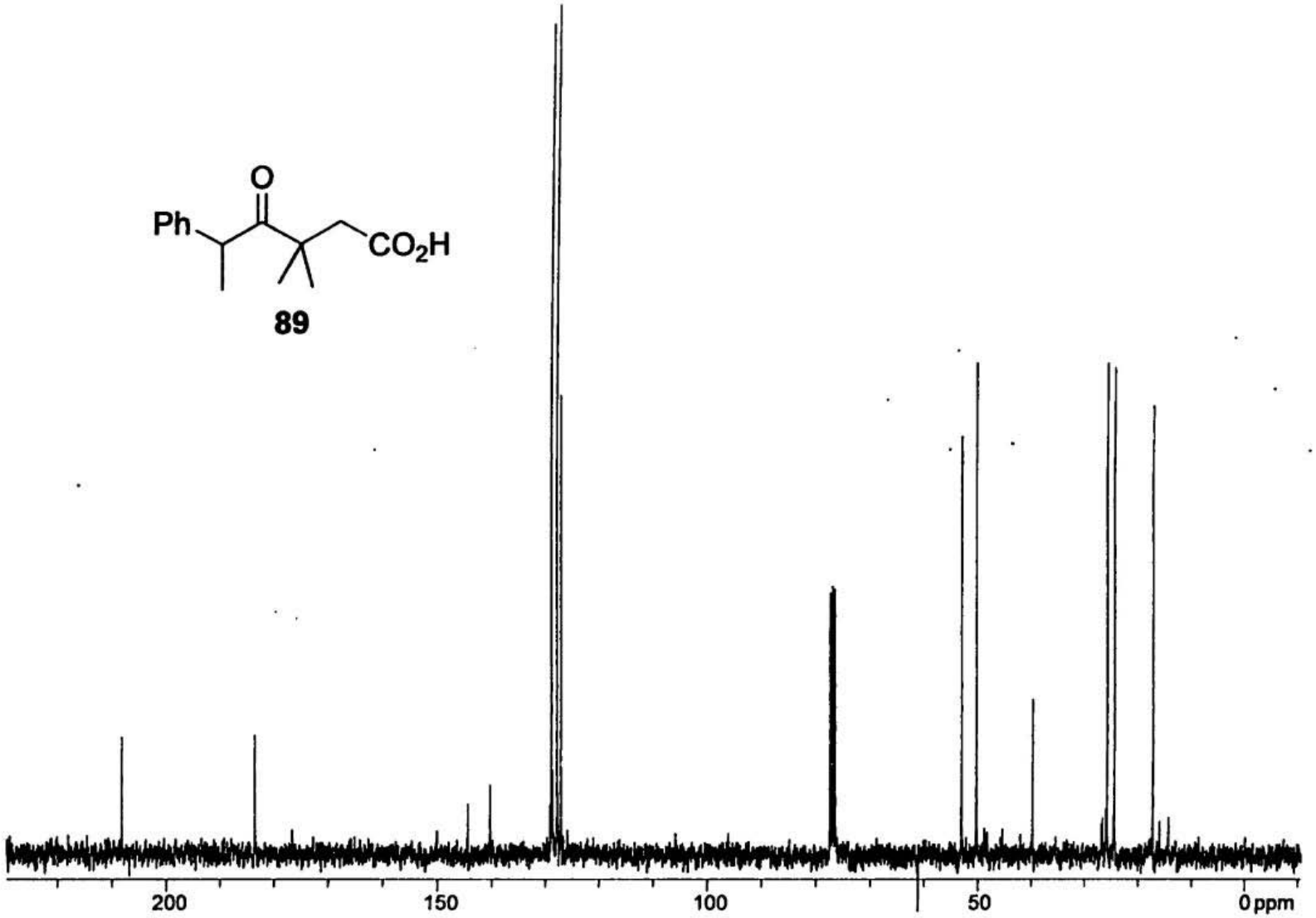

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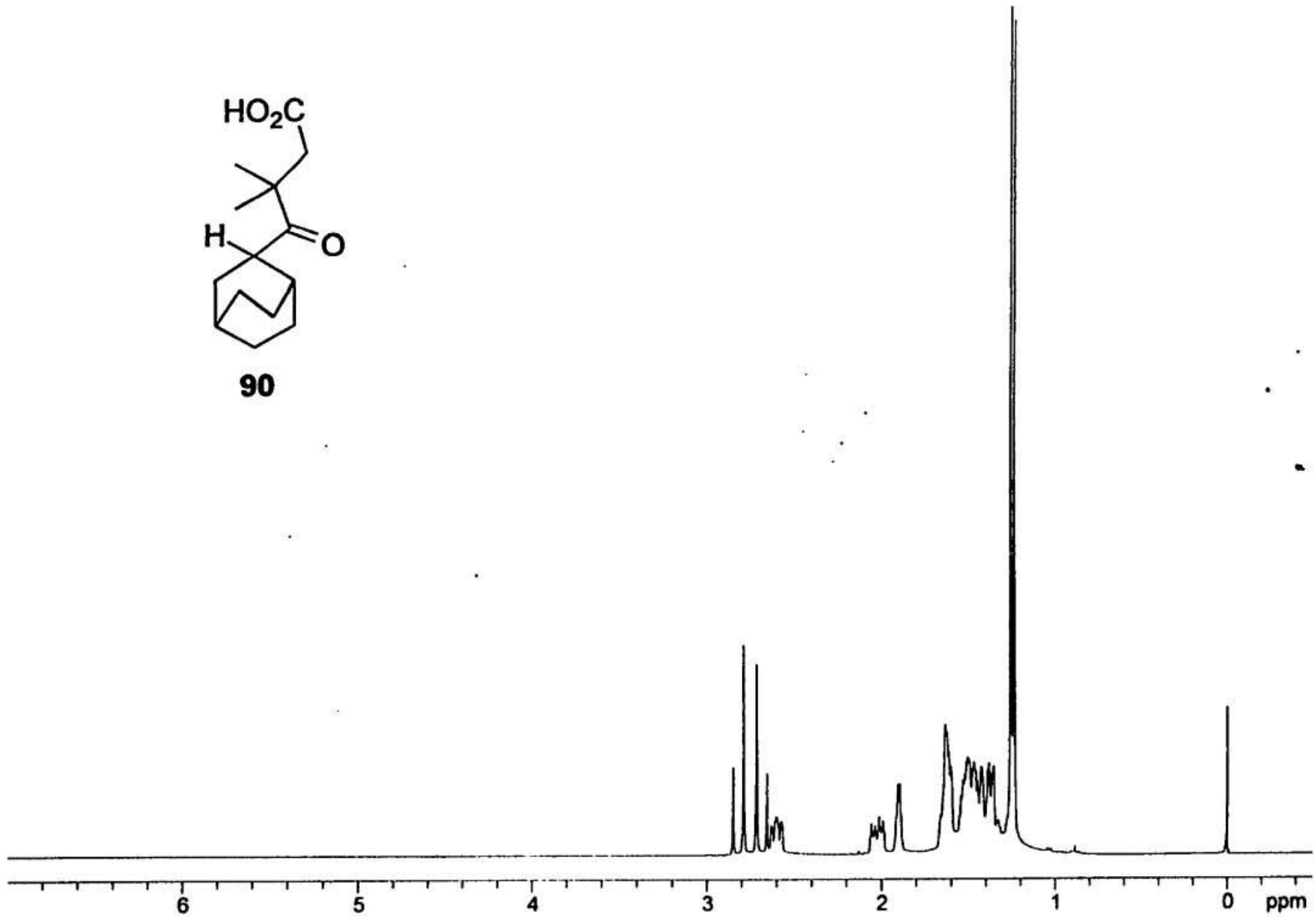
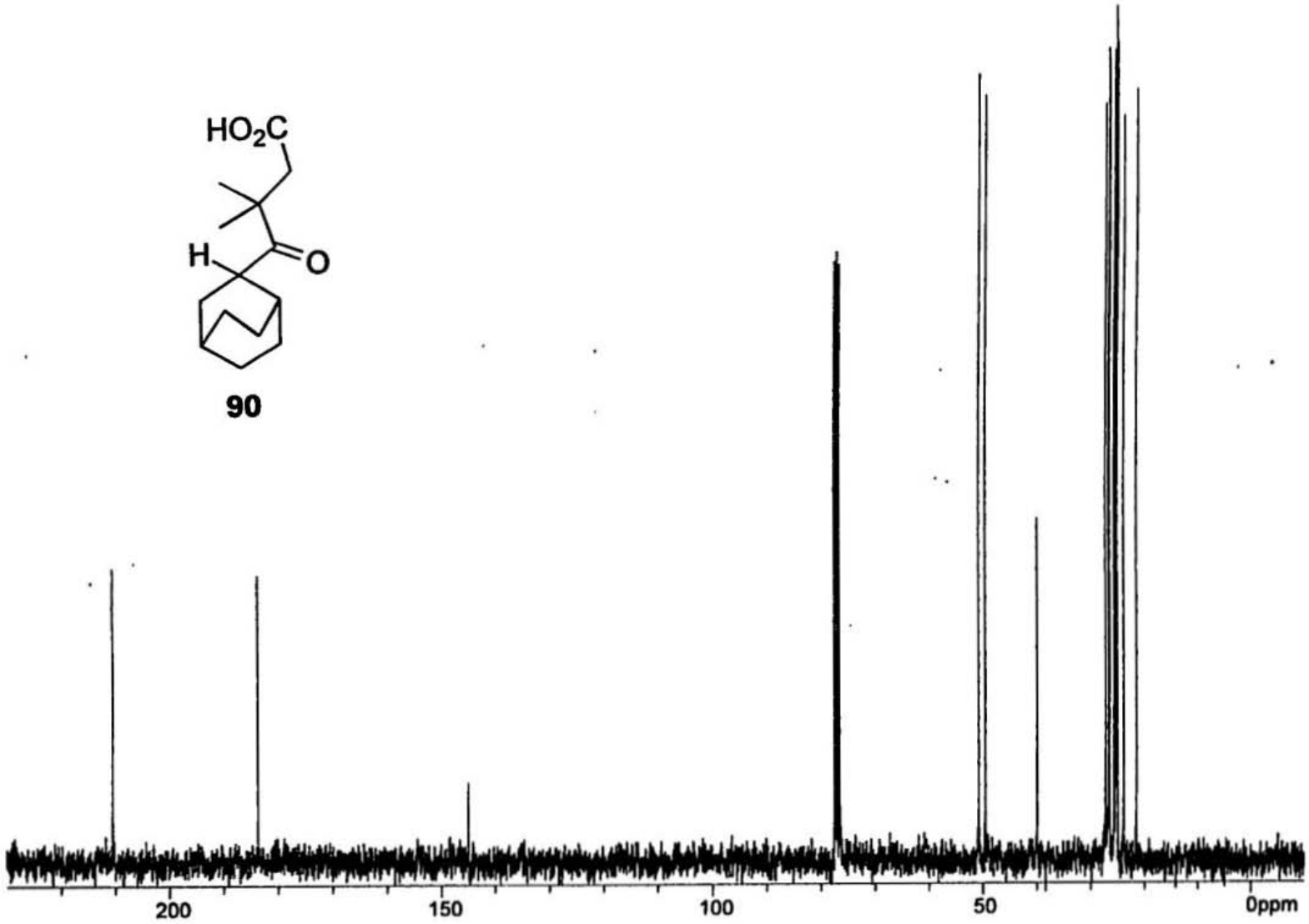


90



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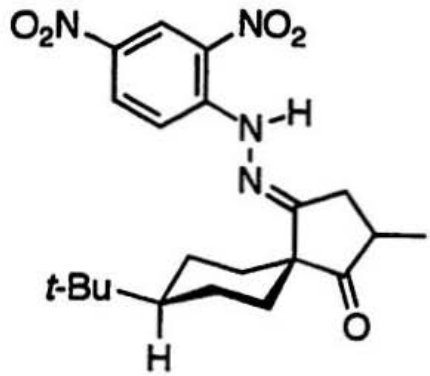
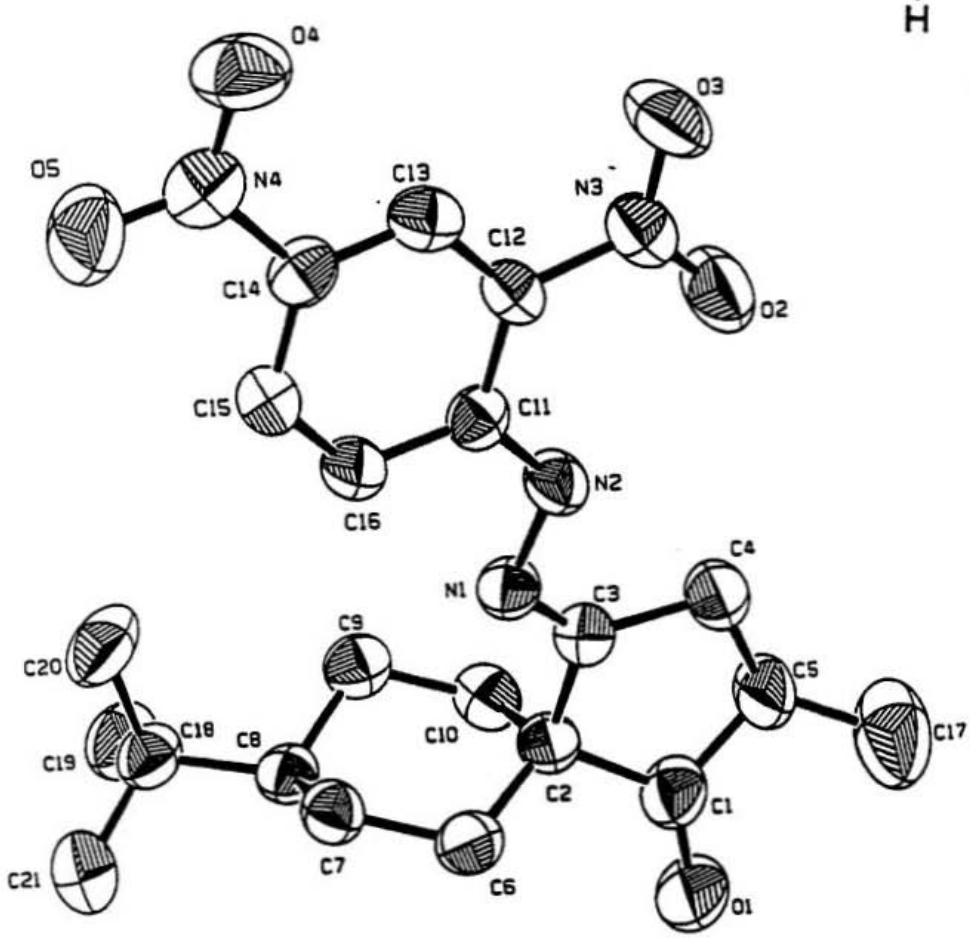
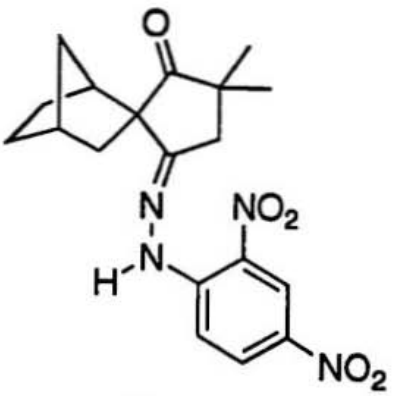


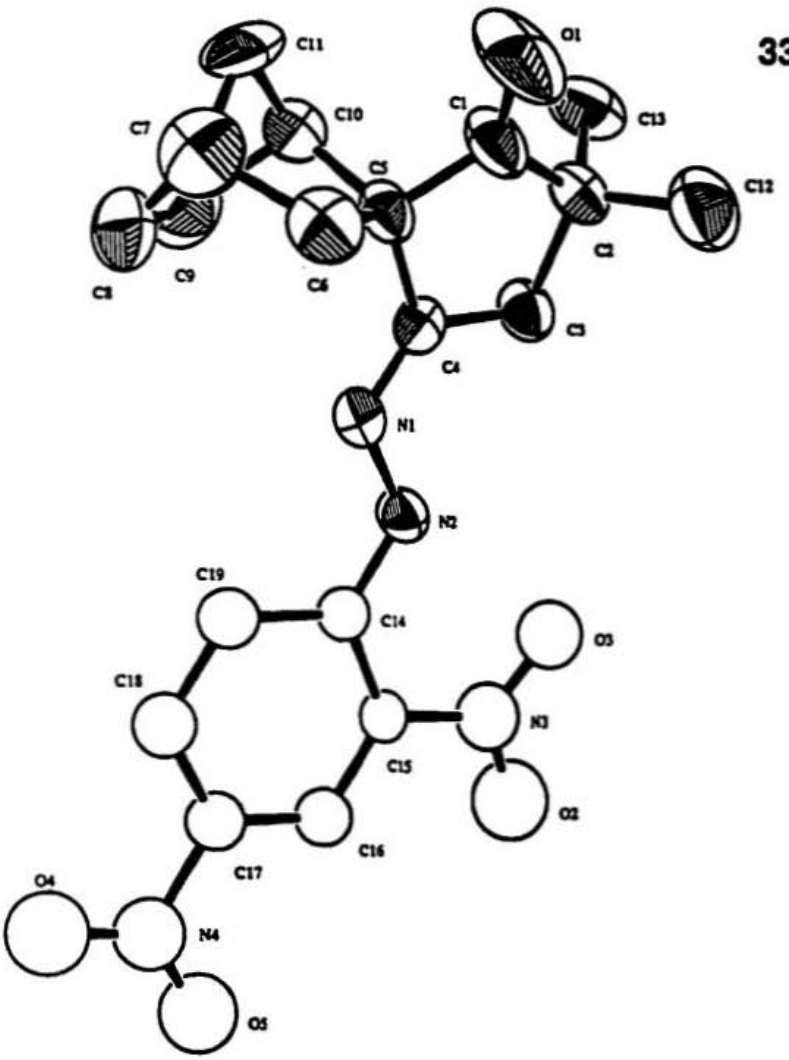
11c



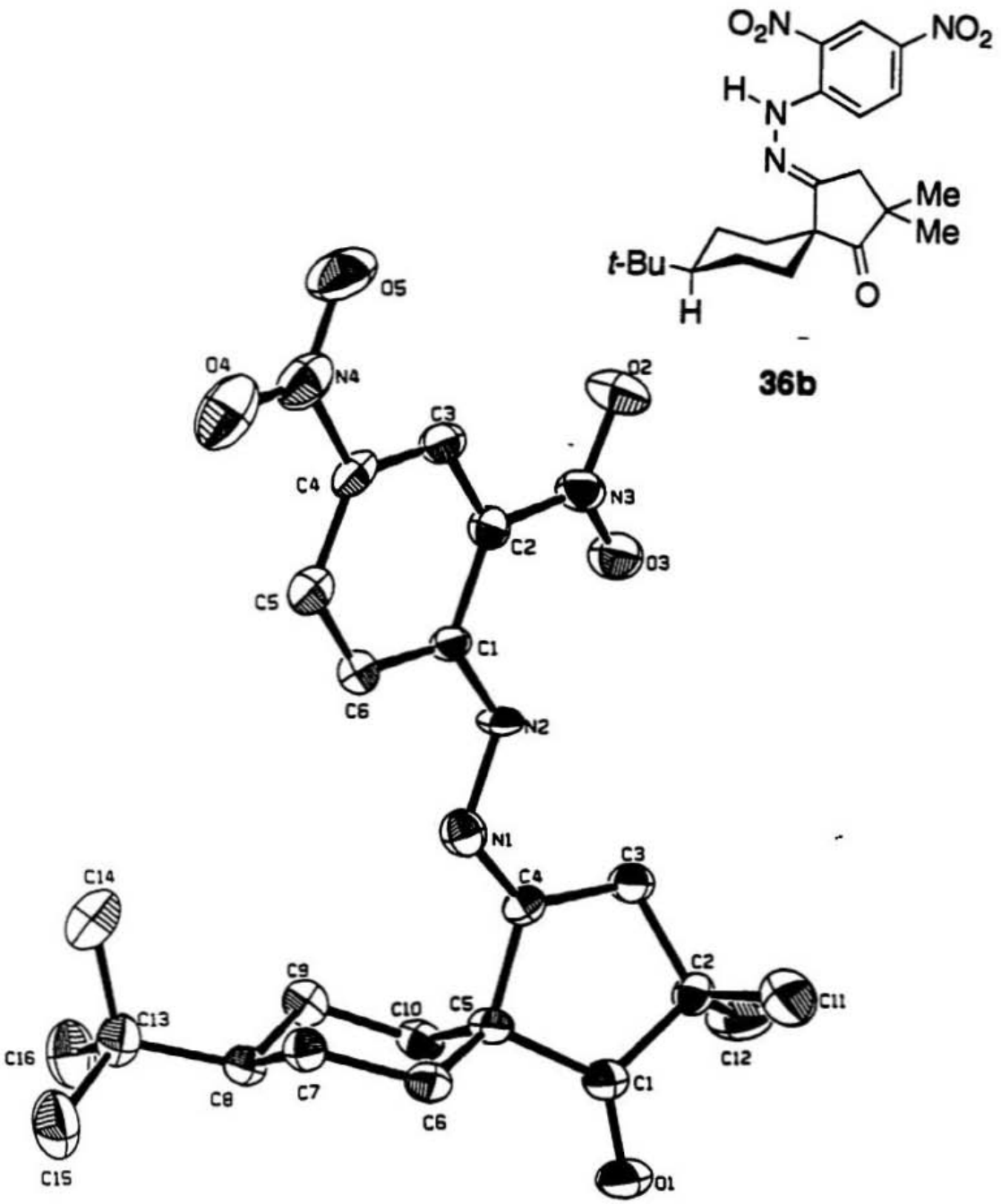
X-ray crystal structure (ORTEP) for **11c**



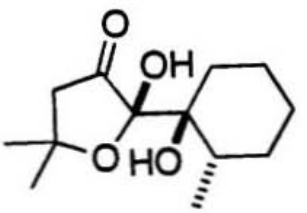
33c



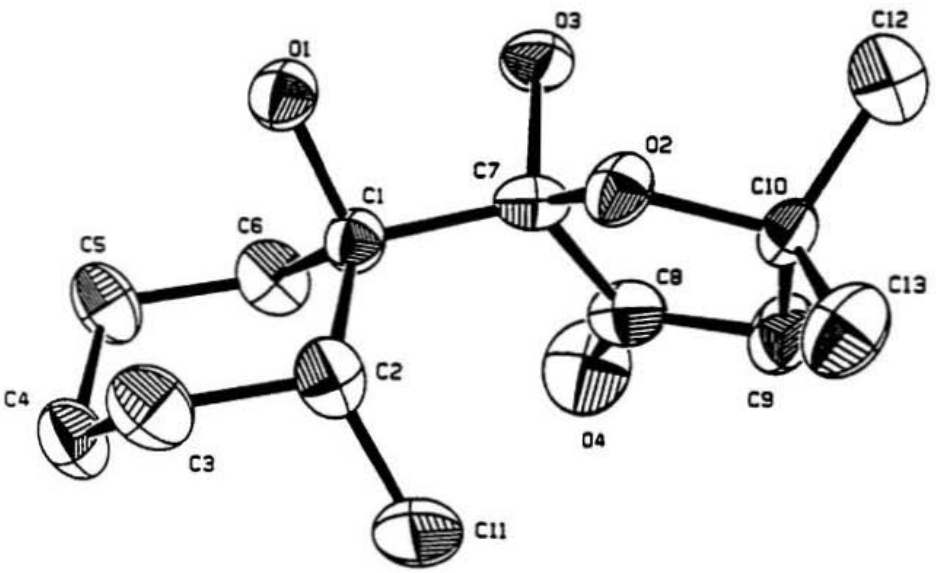
X-ray crstal structure (ORTEP) for **33c**



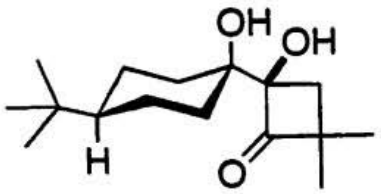
X-ray crystal structure (ORTEP) for **36b**



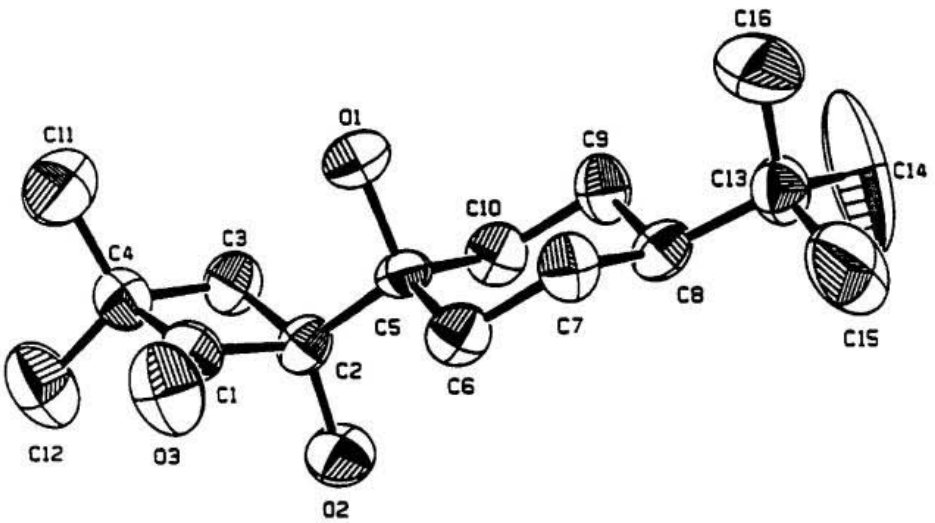
46a



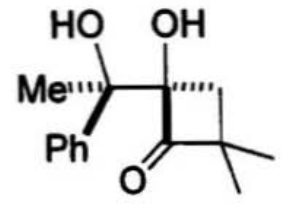
X-ray crystal structure (ORTEP) for **46a**



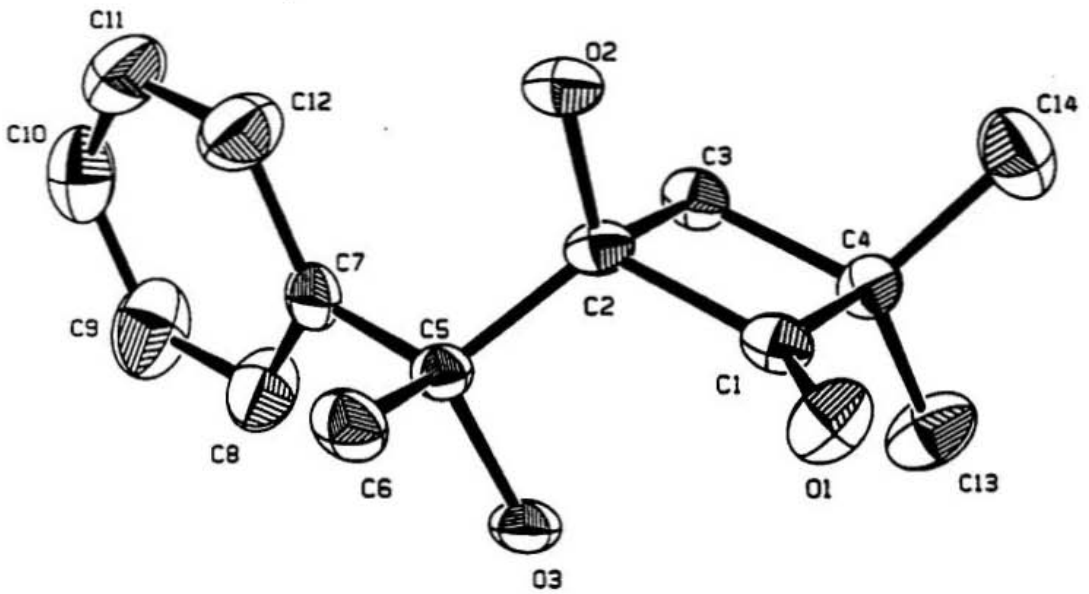
48



X-ray crystal structure (ORTEP) for **48**



77

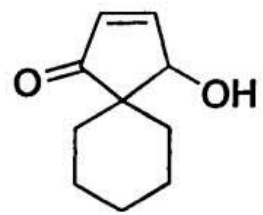


X-ray crystal structure (ORTEP) for **77**

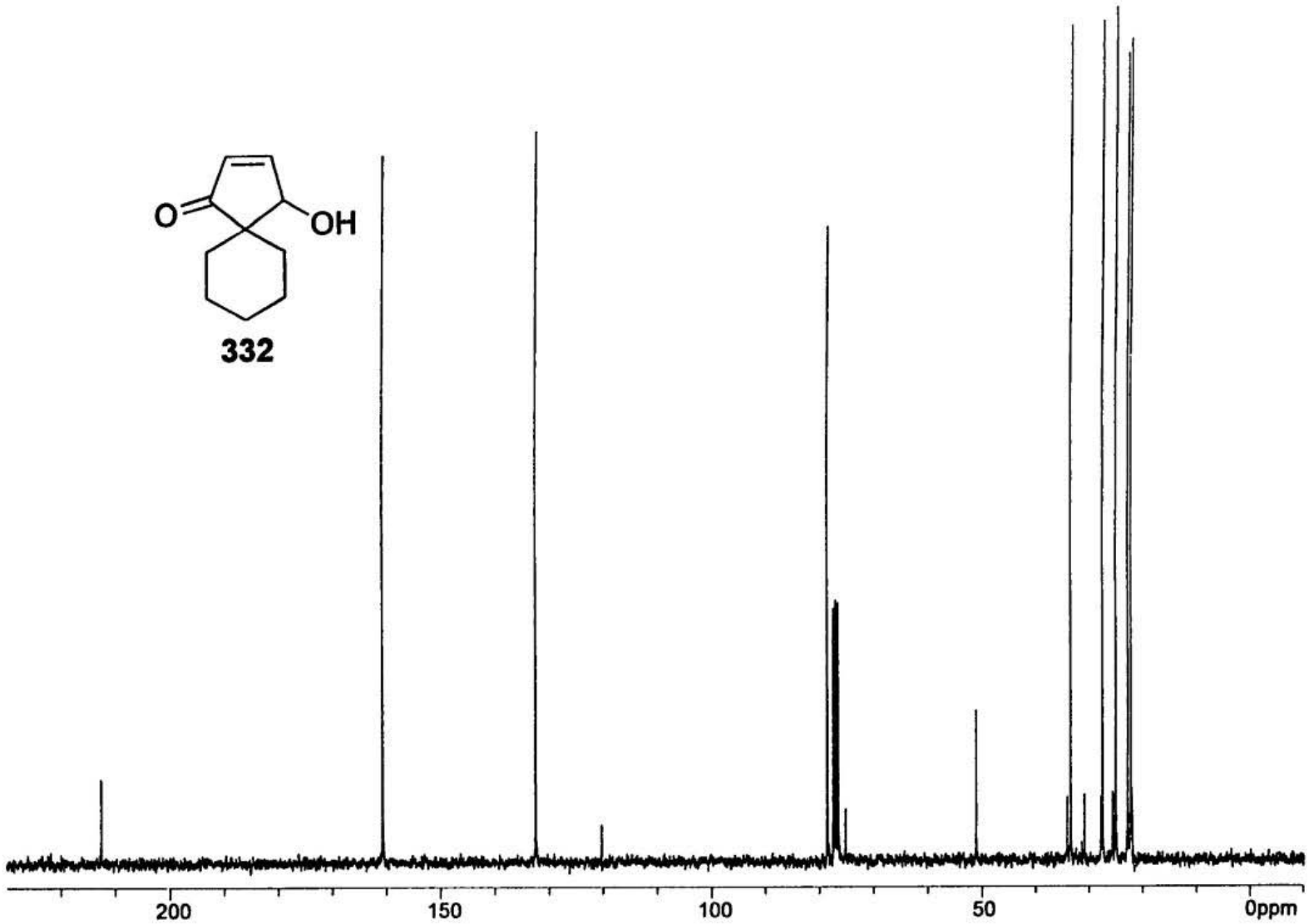
Appendix II

^{1}H and ^{13}C NMR Spectra for Chapter 2

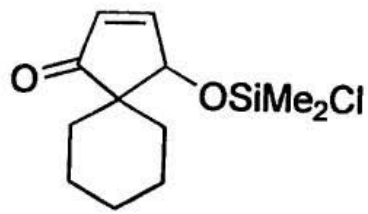
^{1}H and ^{13}C NMR spectra for compounds **332, 334, 336, 357, 358, 371, 372, 373, 374, 359, 376a, 376b, 377a, 377b, 378, 379, 380, 381, 390a, 390b, 392a, 392b, 395** and **397**.



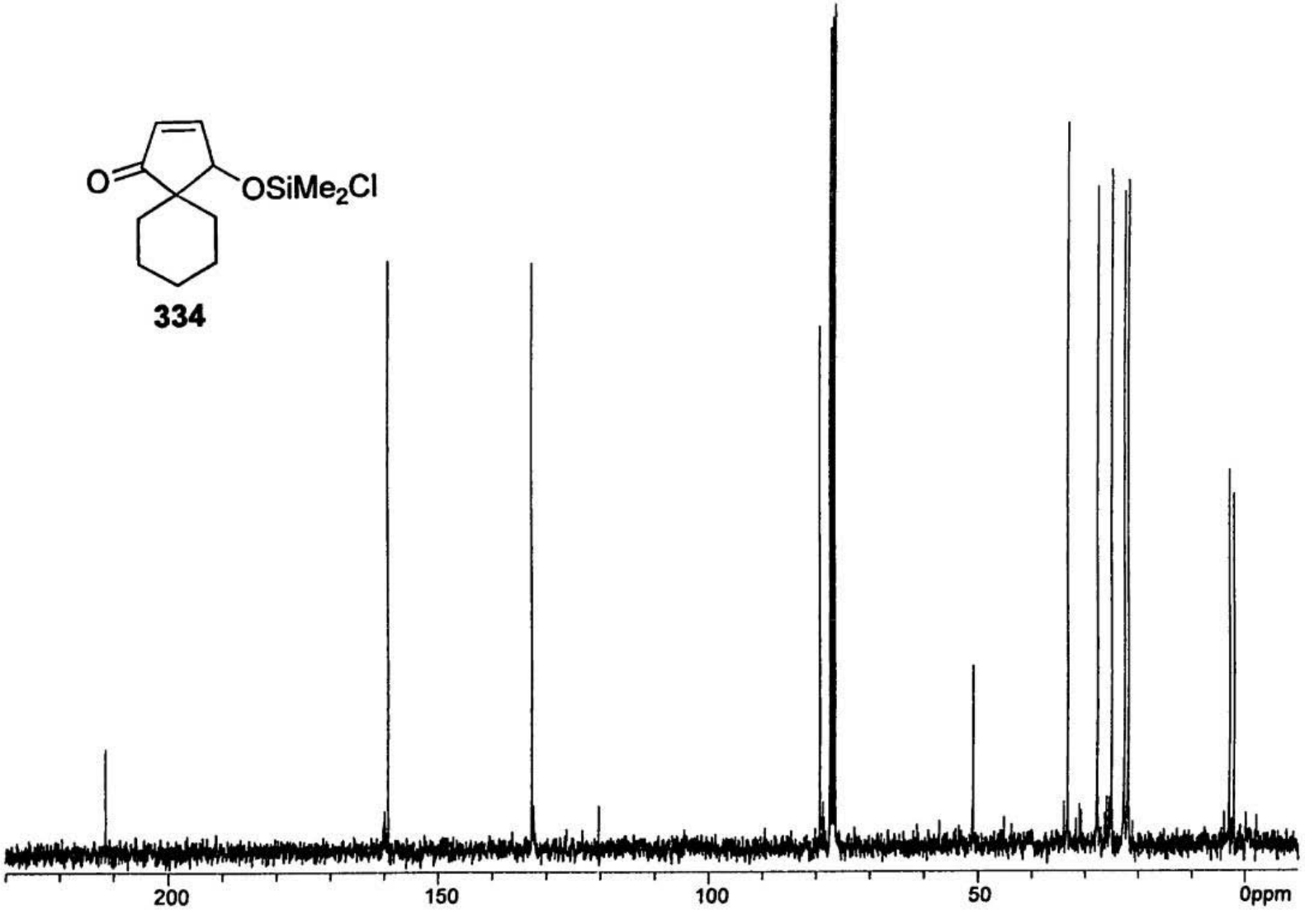
332



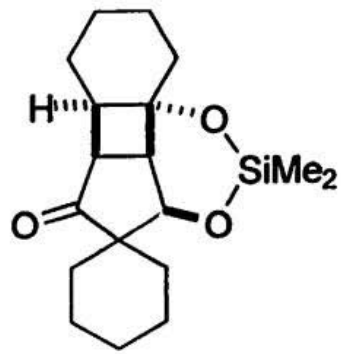
332



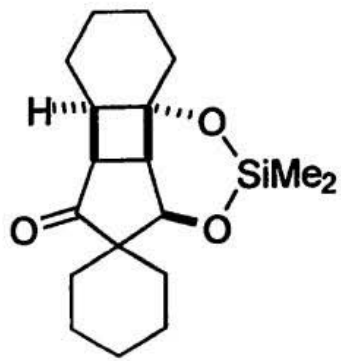
334



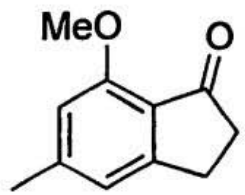
334



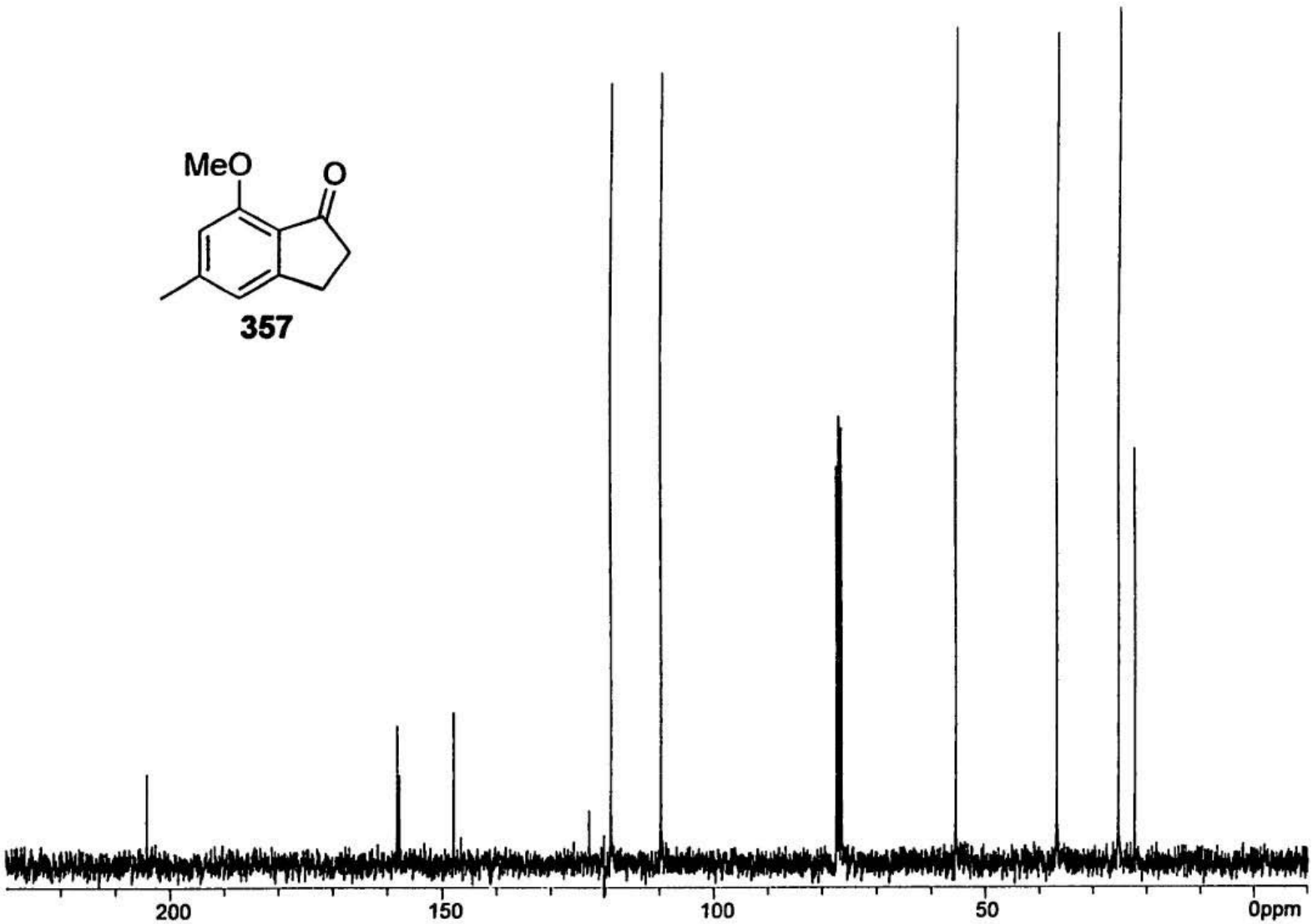
336



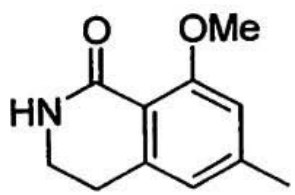
336



357



357



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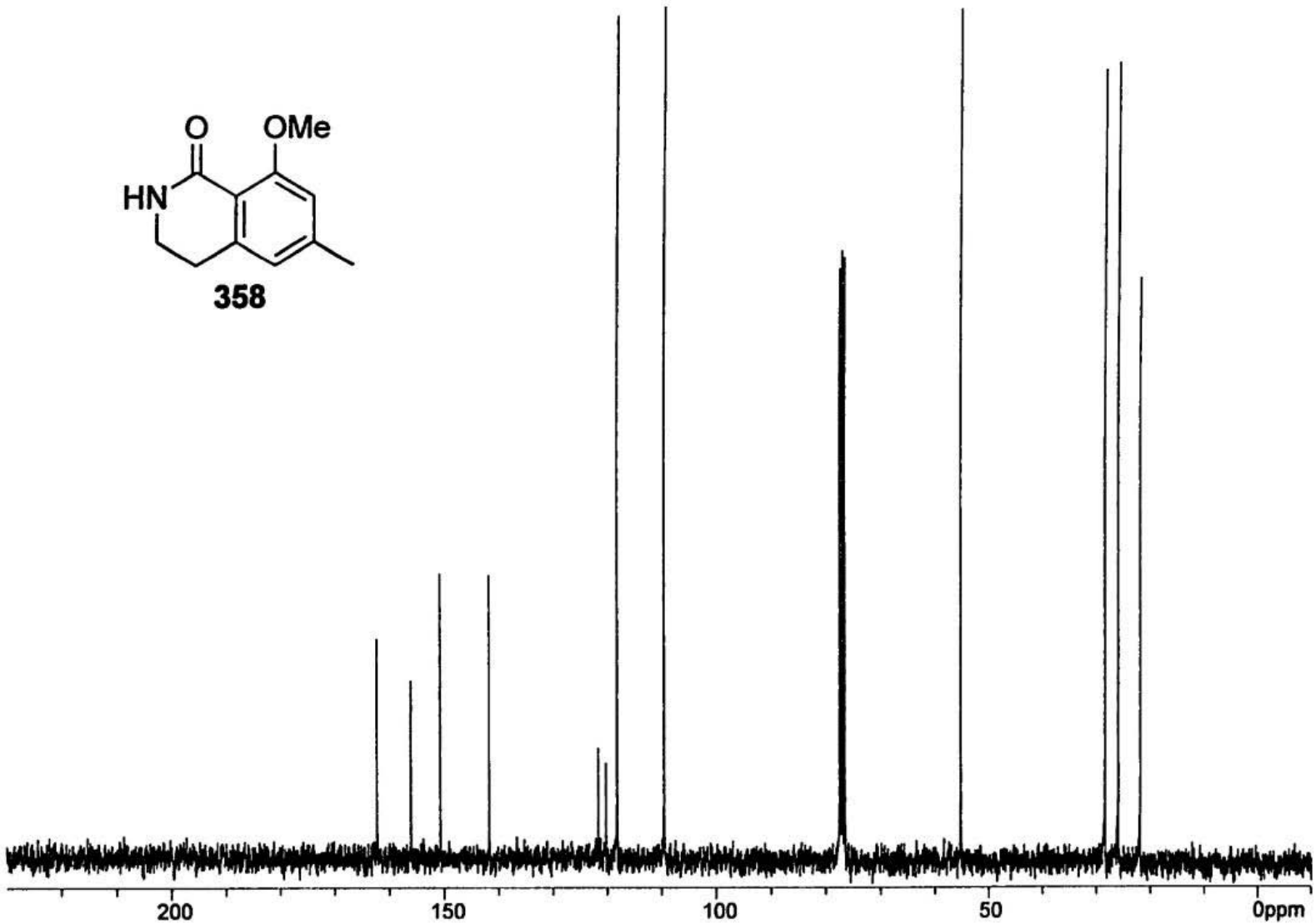
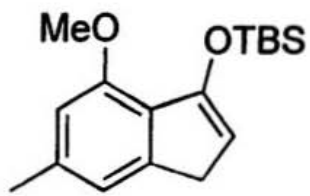
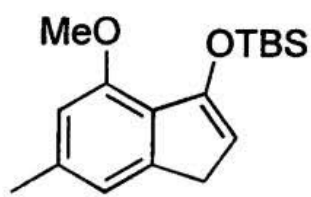


358



371



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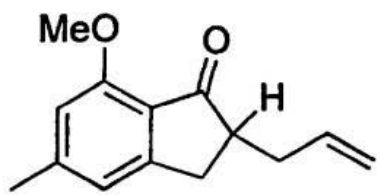

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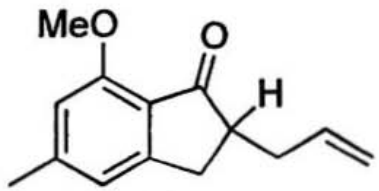

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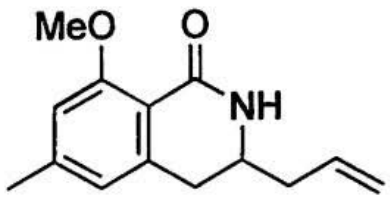

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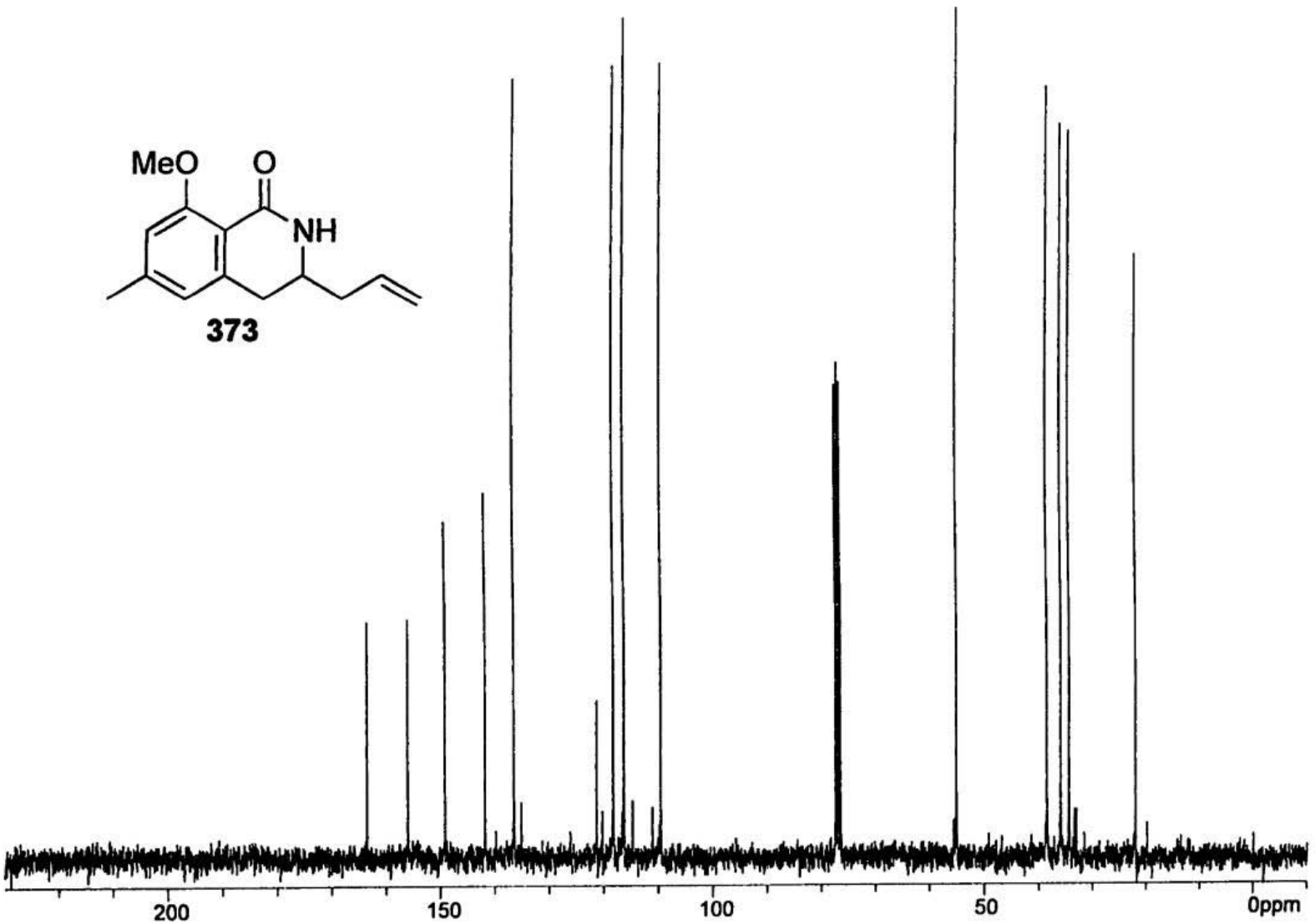
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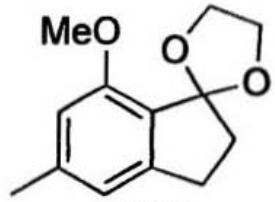
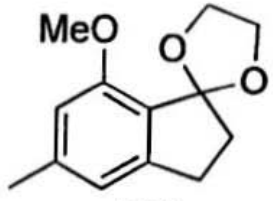
O
NH
373
200
150
100
50
0ppm



374



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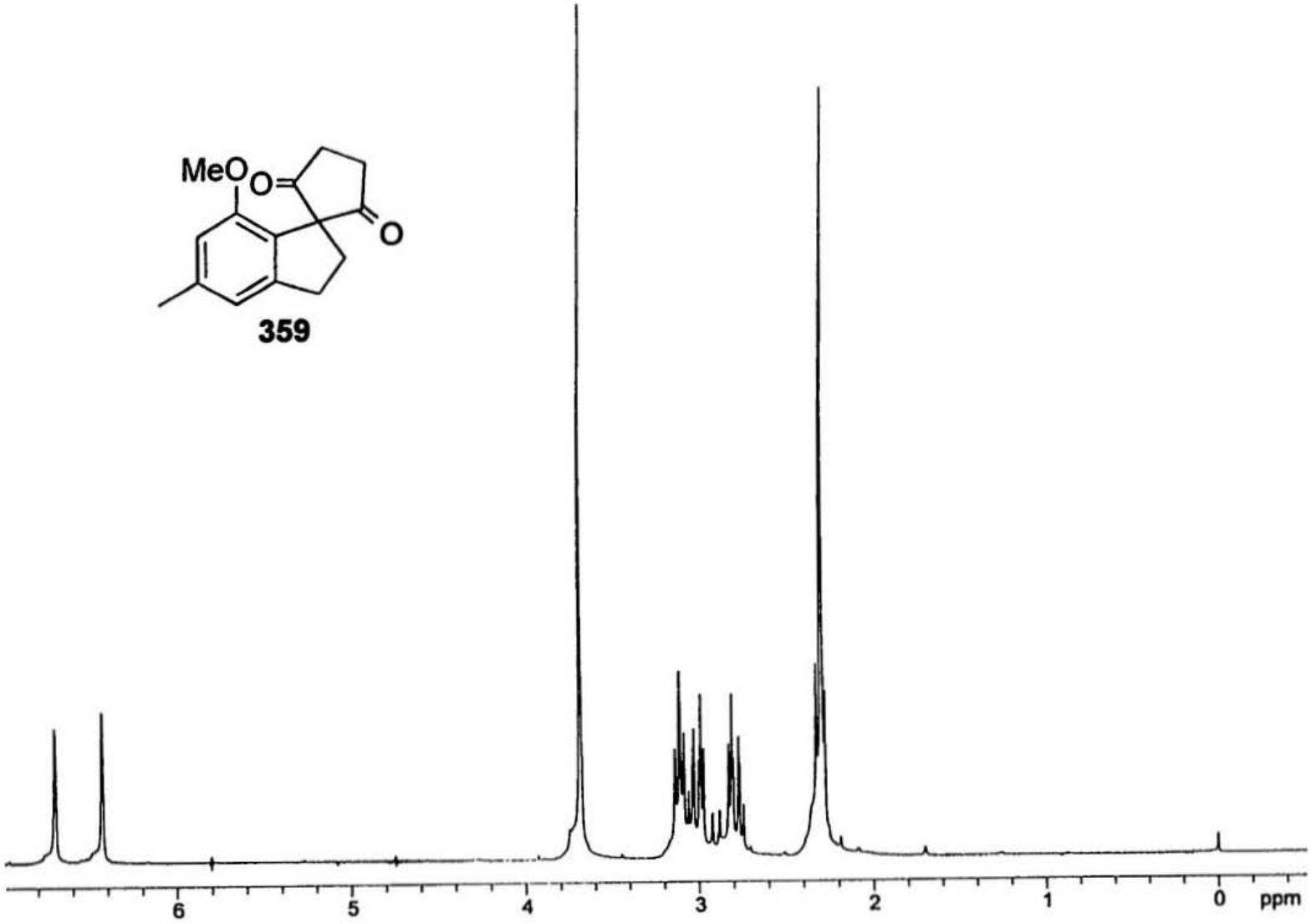
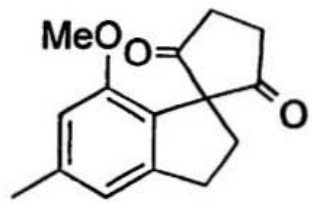
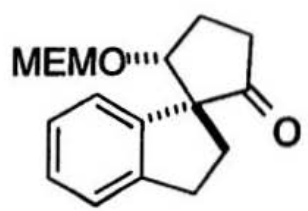


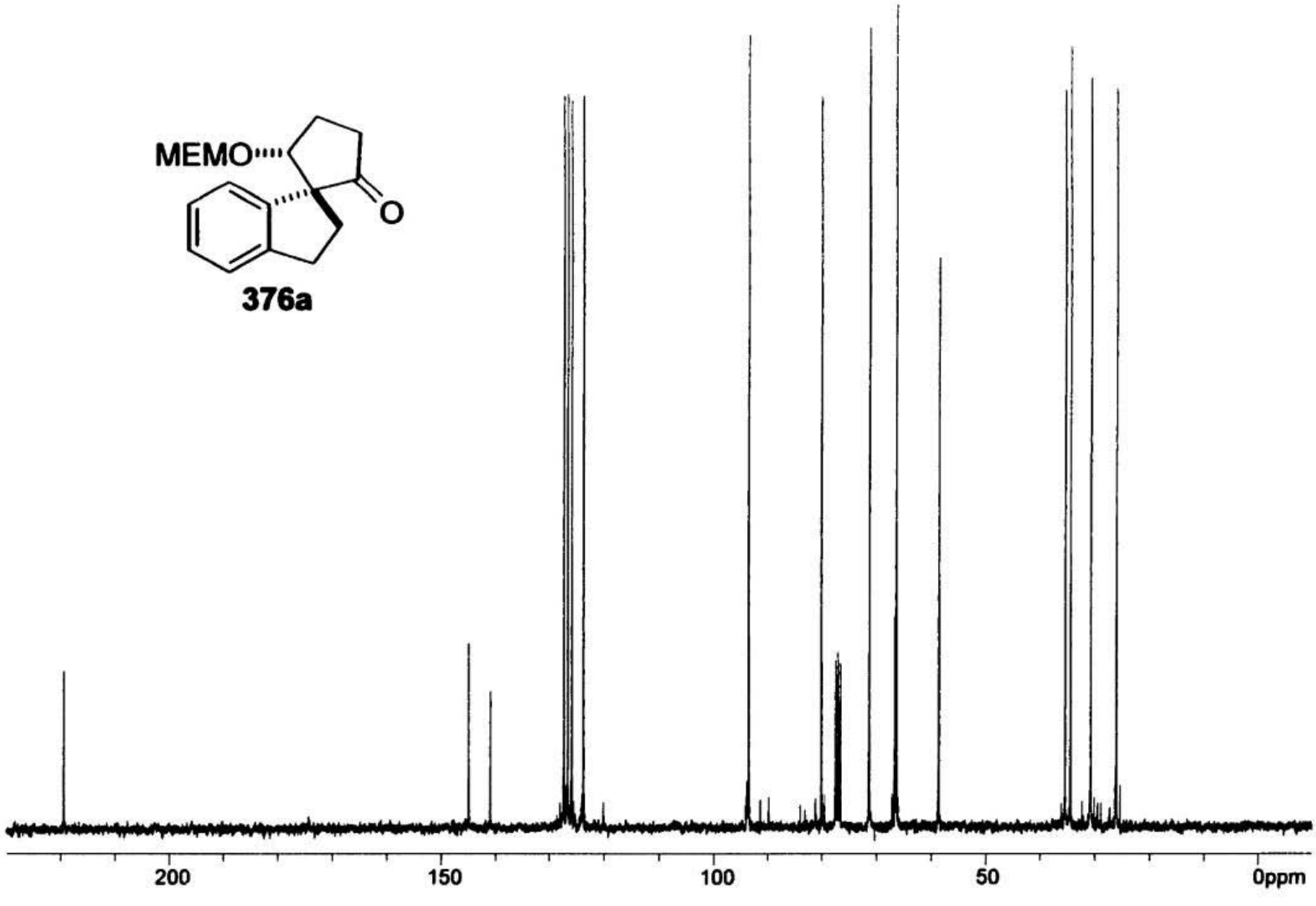
359

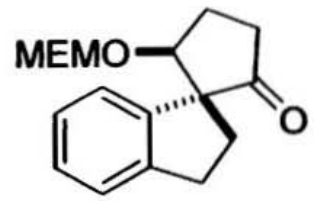


359



376a


MEMO
O
376a
200
150
100
50
0ppm



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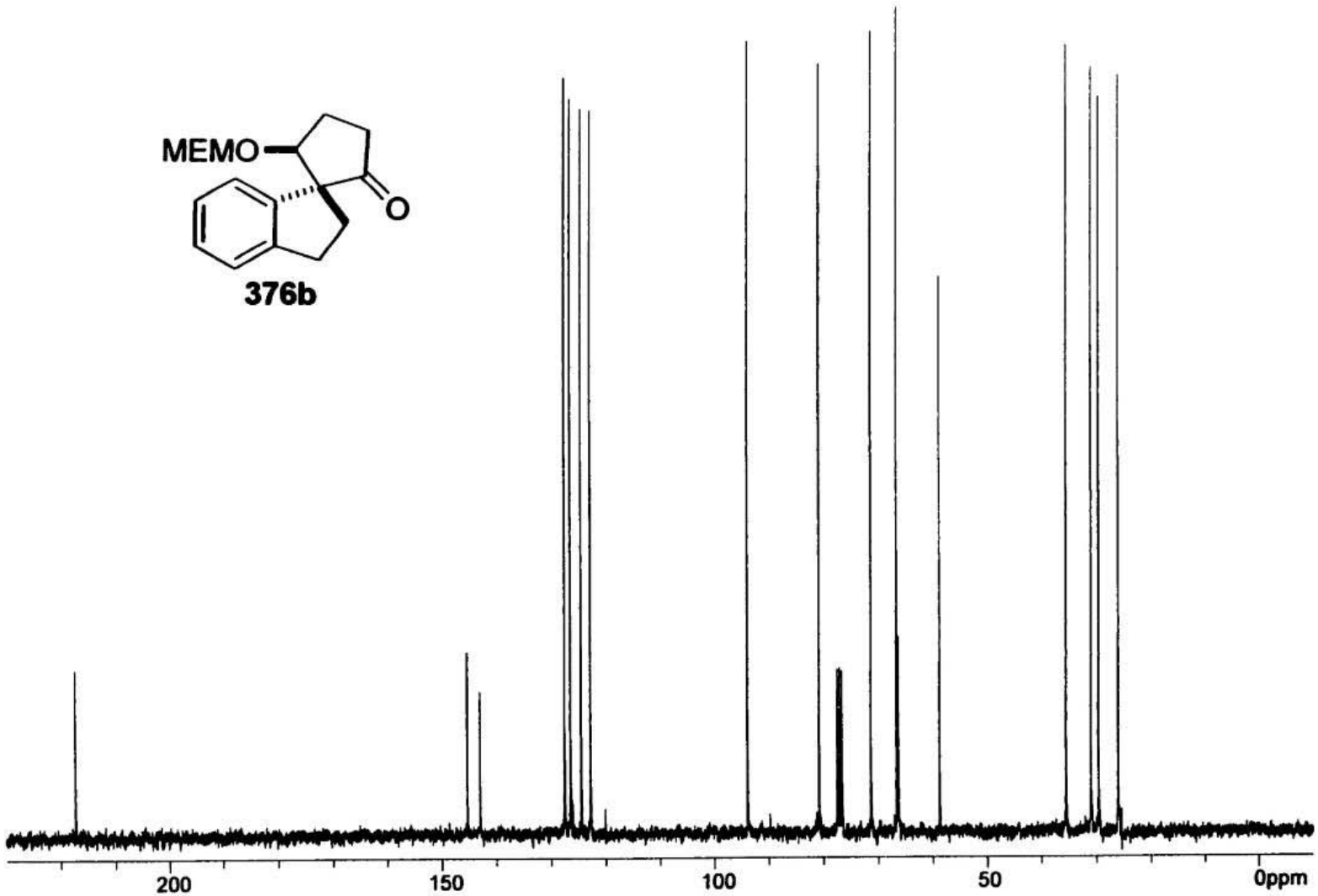
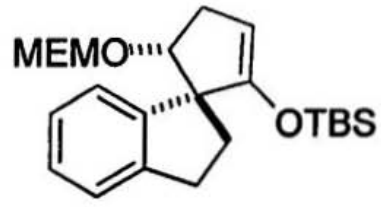

MEMO
O
376b
200
150
100
50
0ppm



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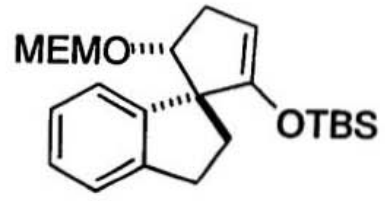

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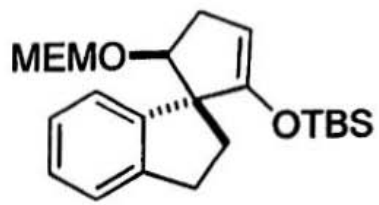
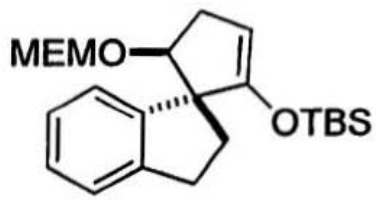


377b



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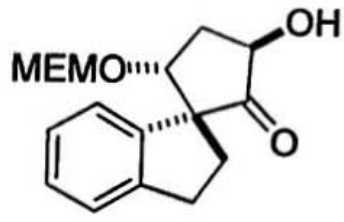

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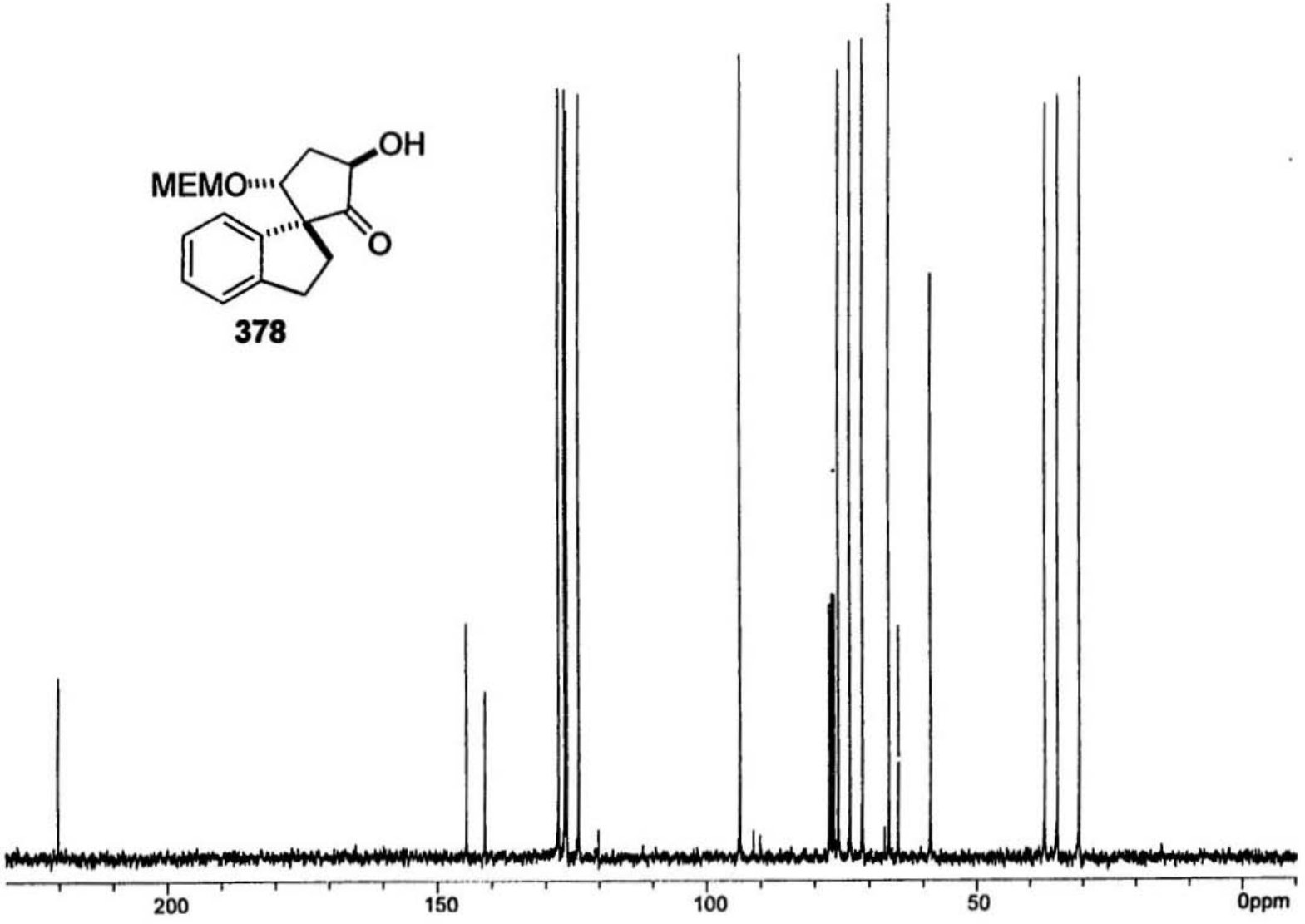

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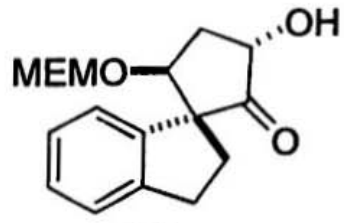
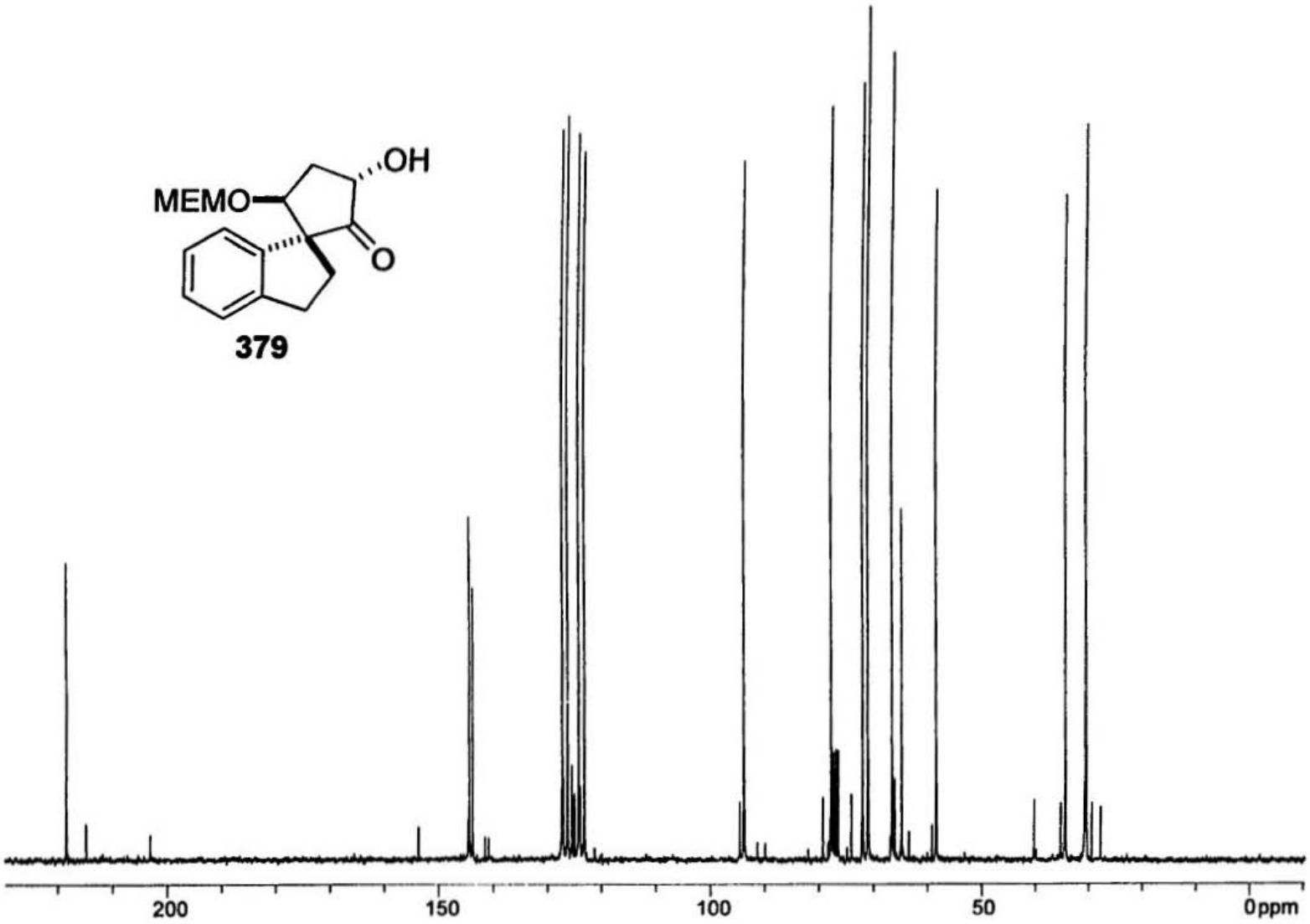
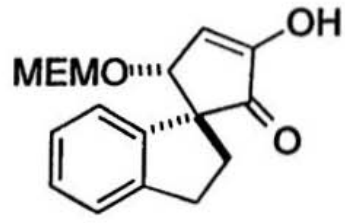


379



379



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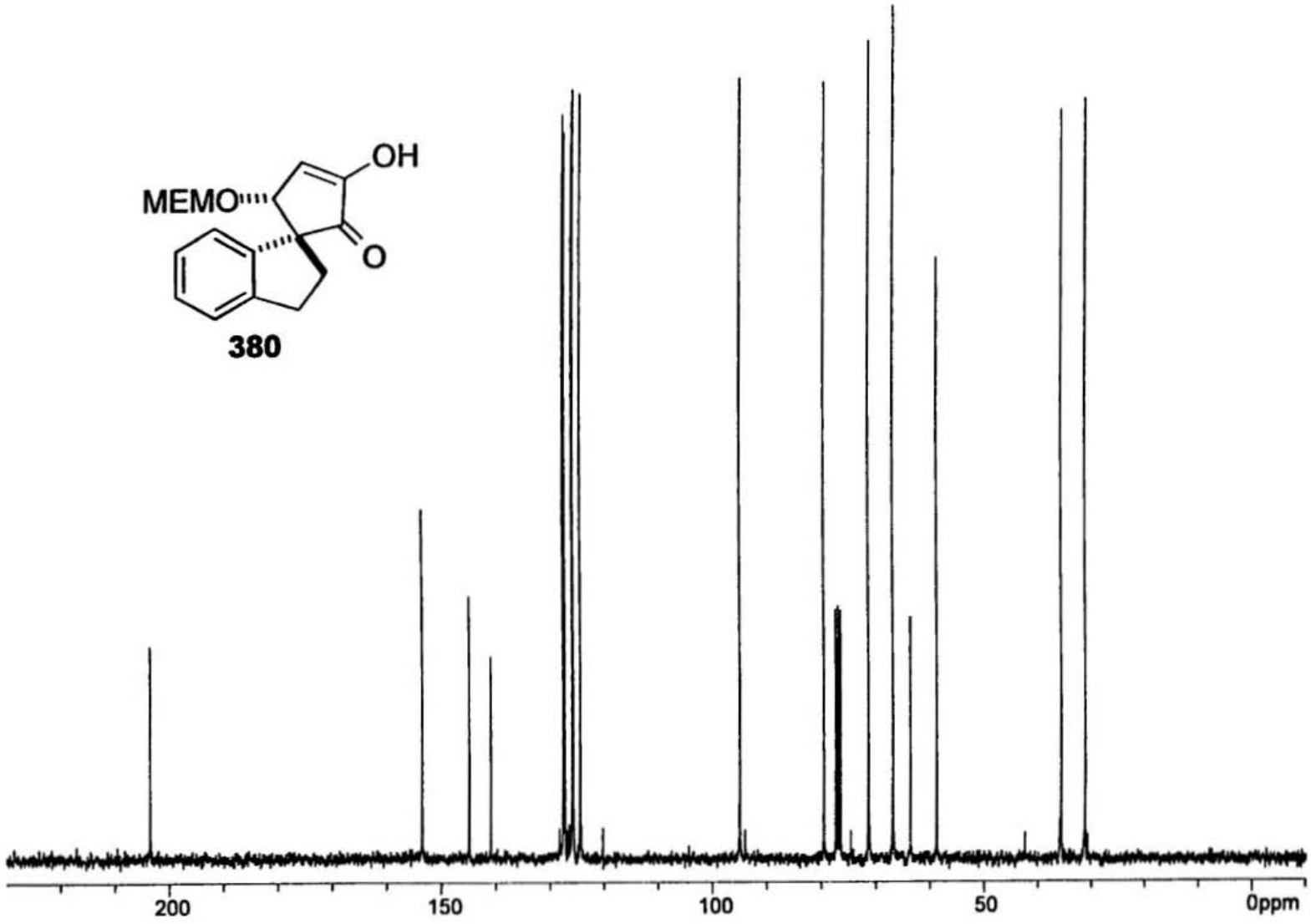
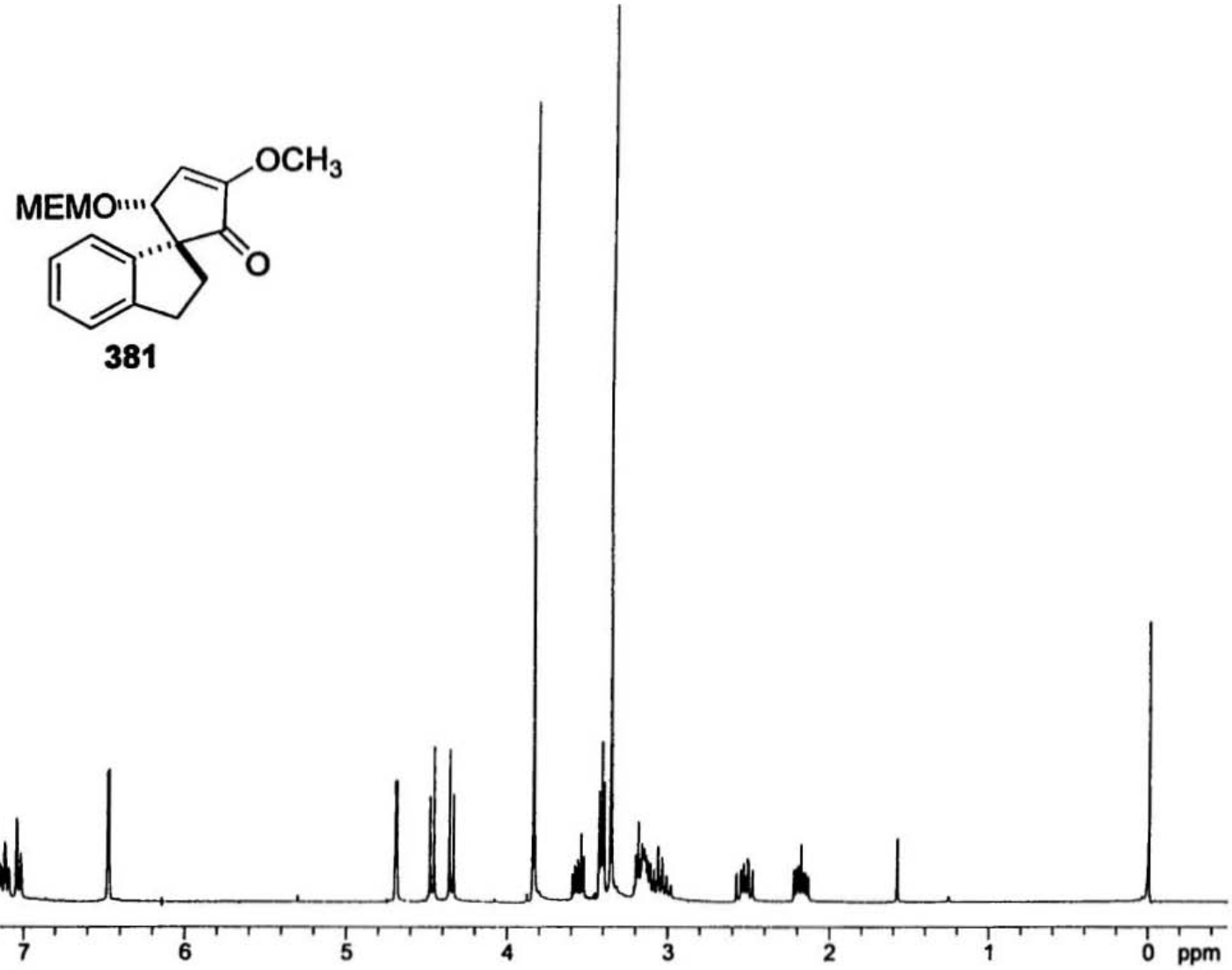
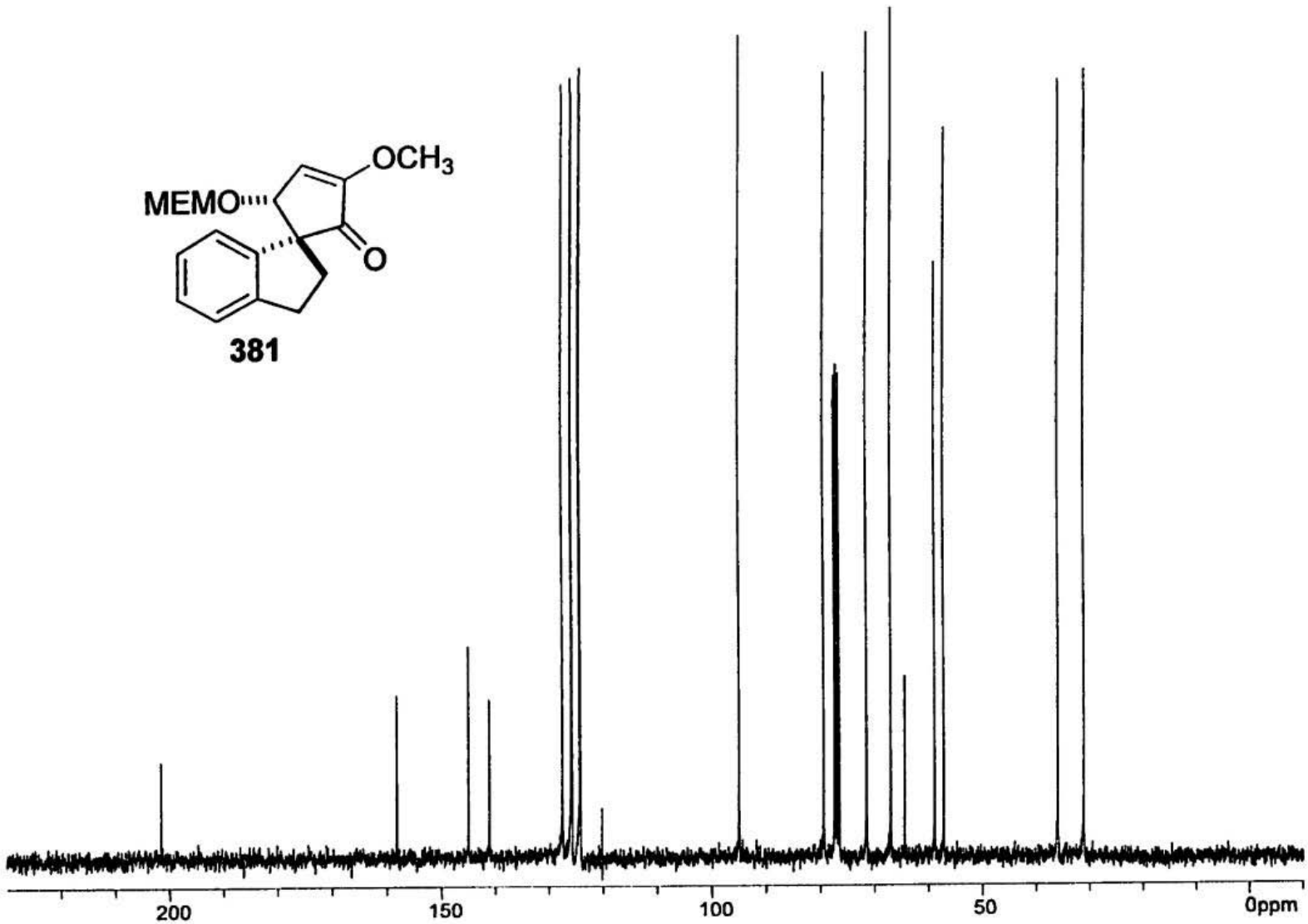
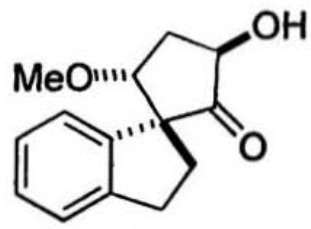

OH
MEMO
O
380
200
150
100
50
0ppm



381


MEMO
OCH3
O
381
200
150
100
50
0ppm



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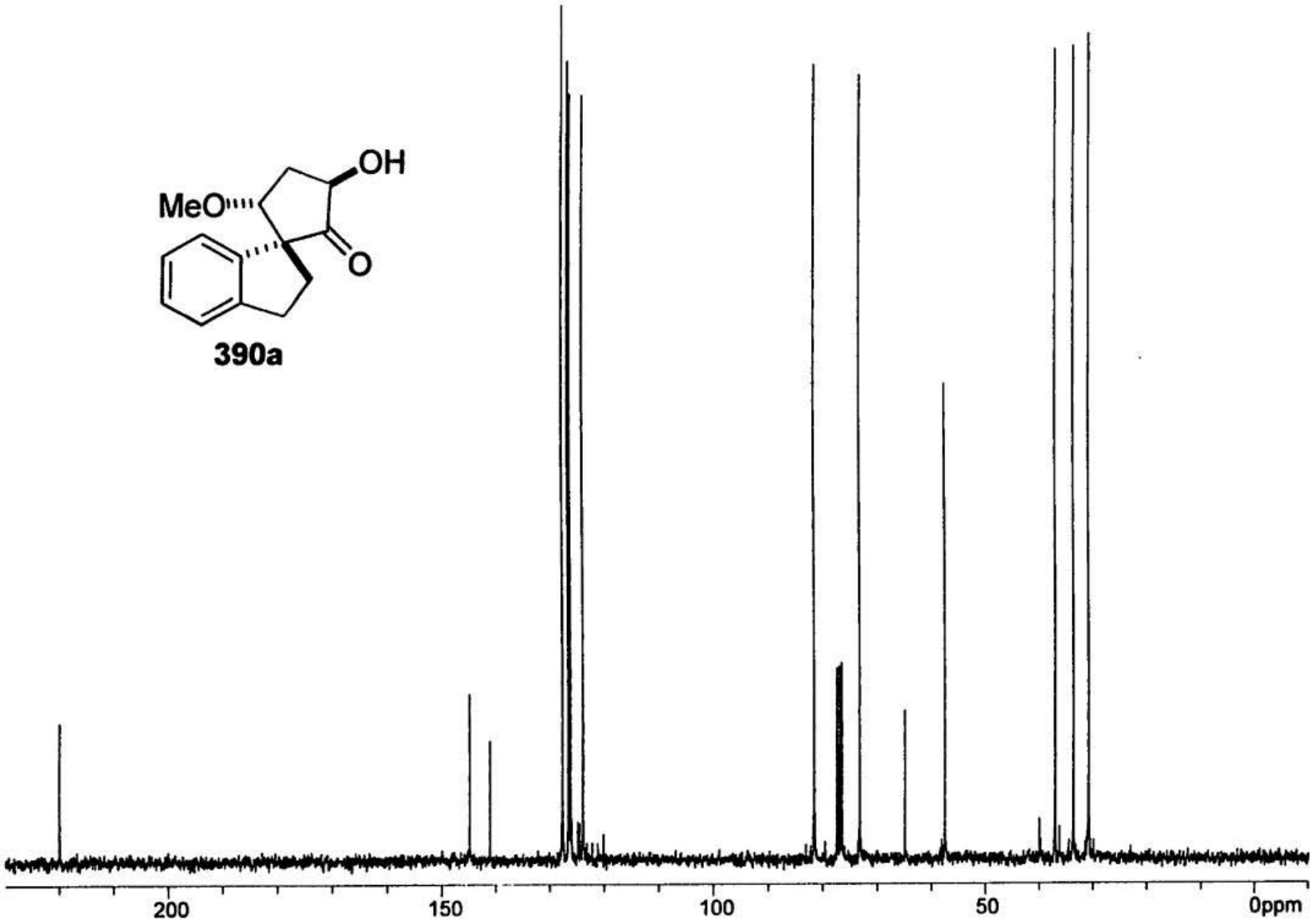
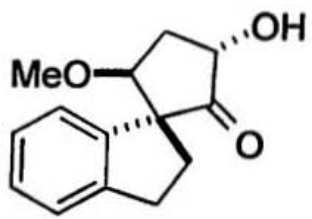

OH
MeO
O
390a
200
150
100
50
0ppm



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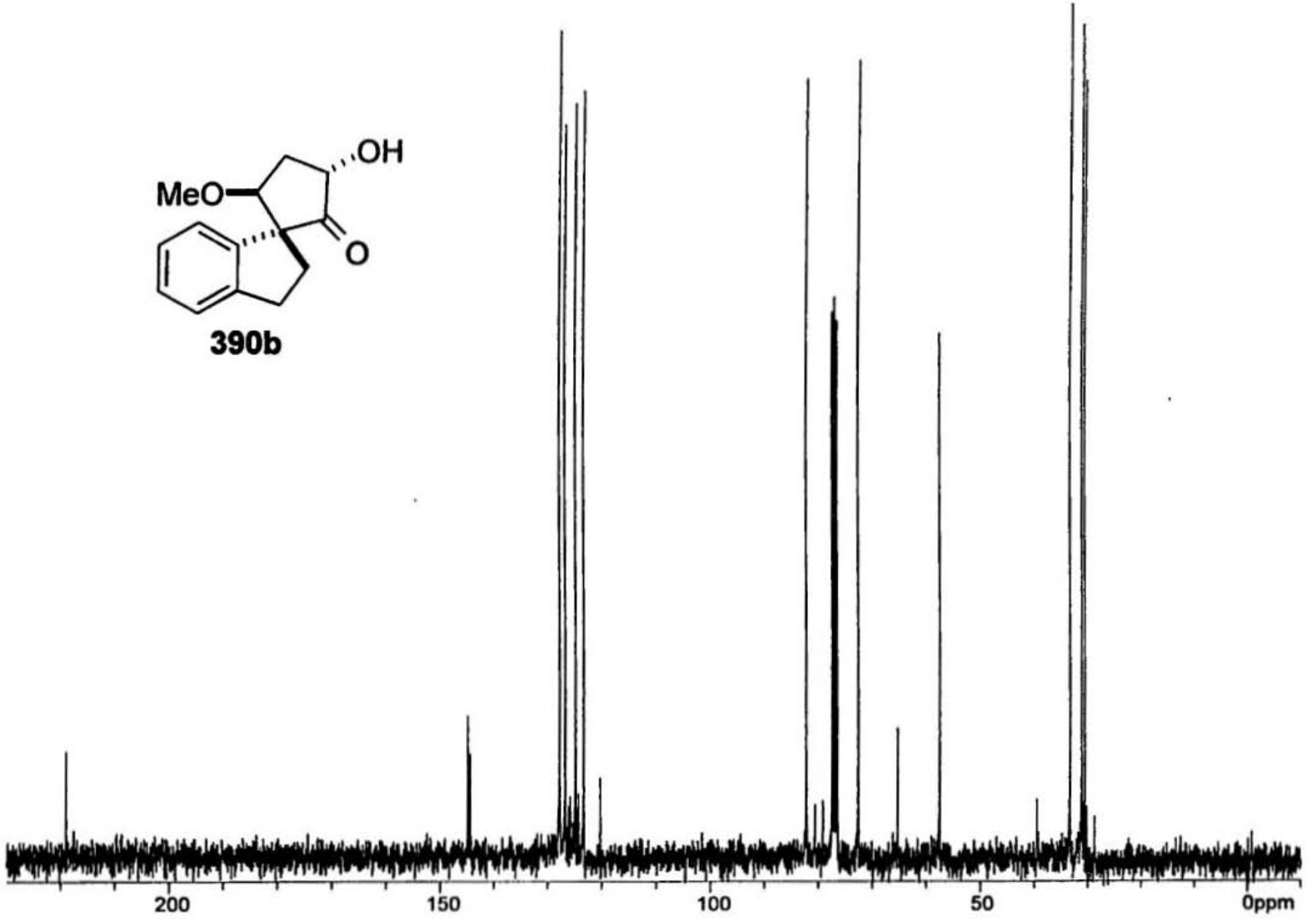

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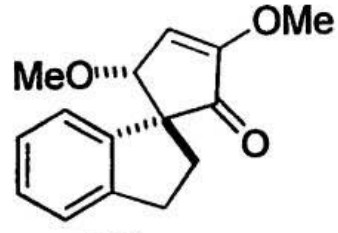

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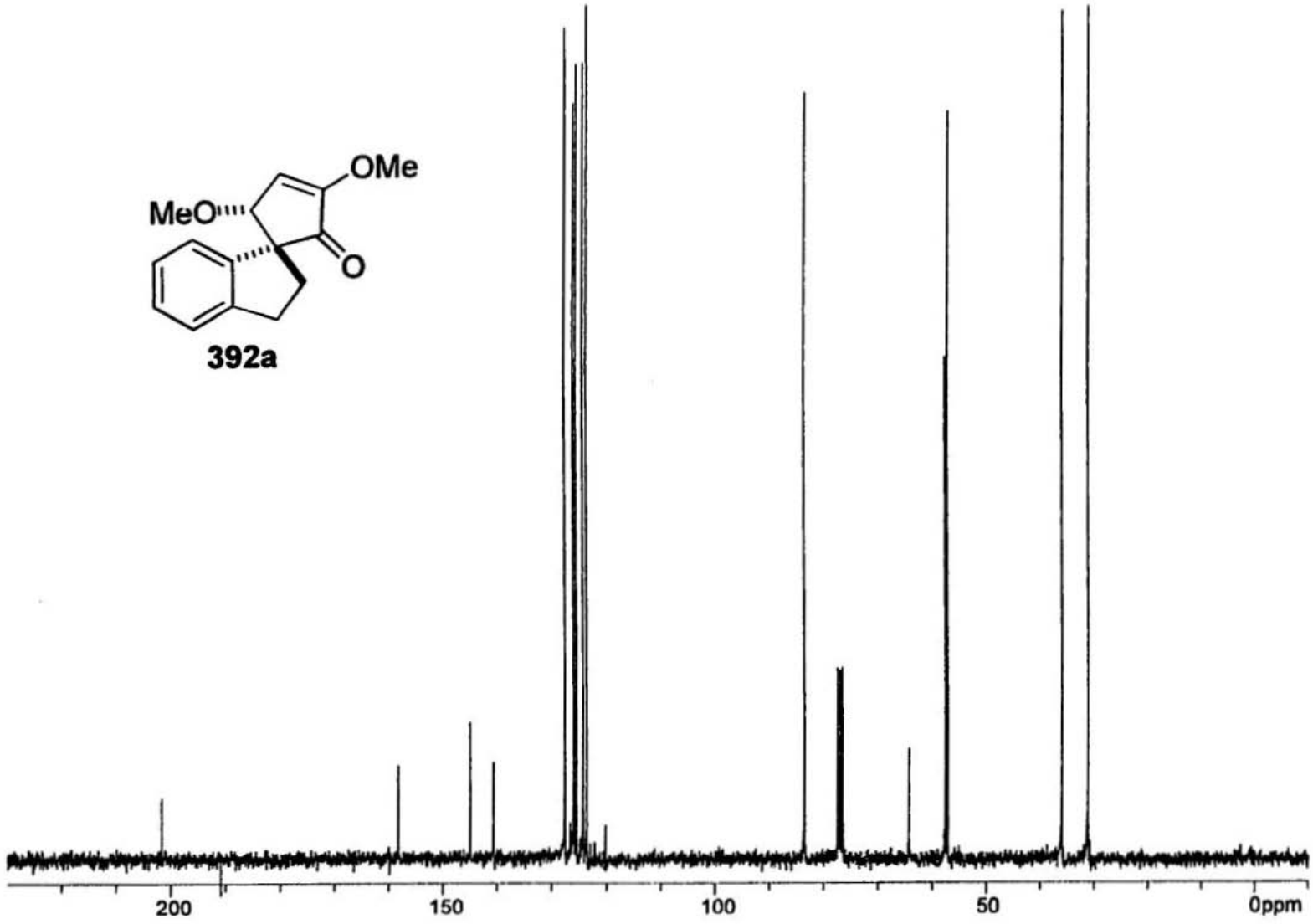

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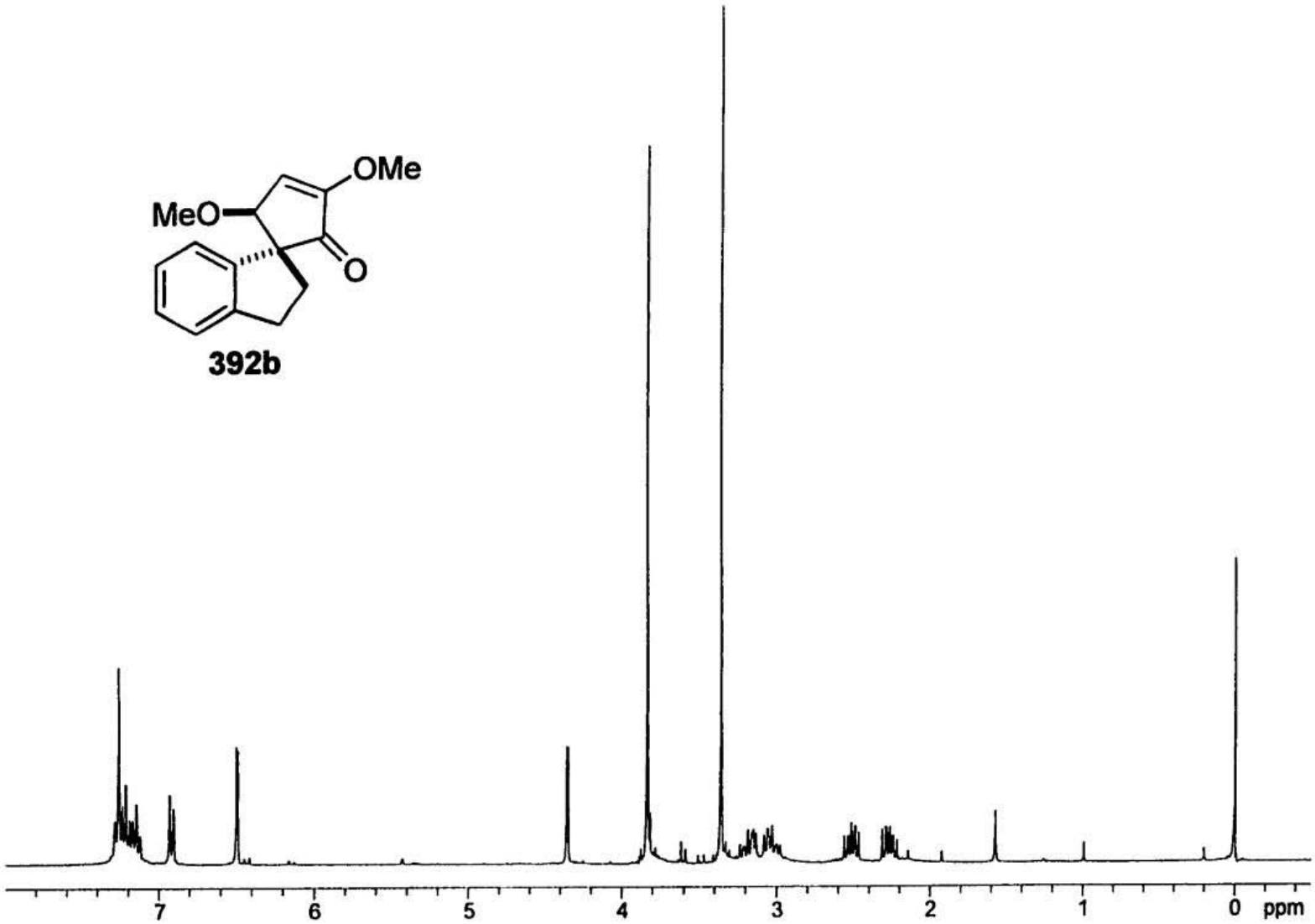

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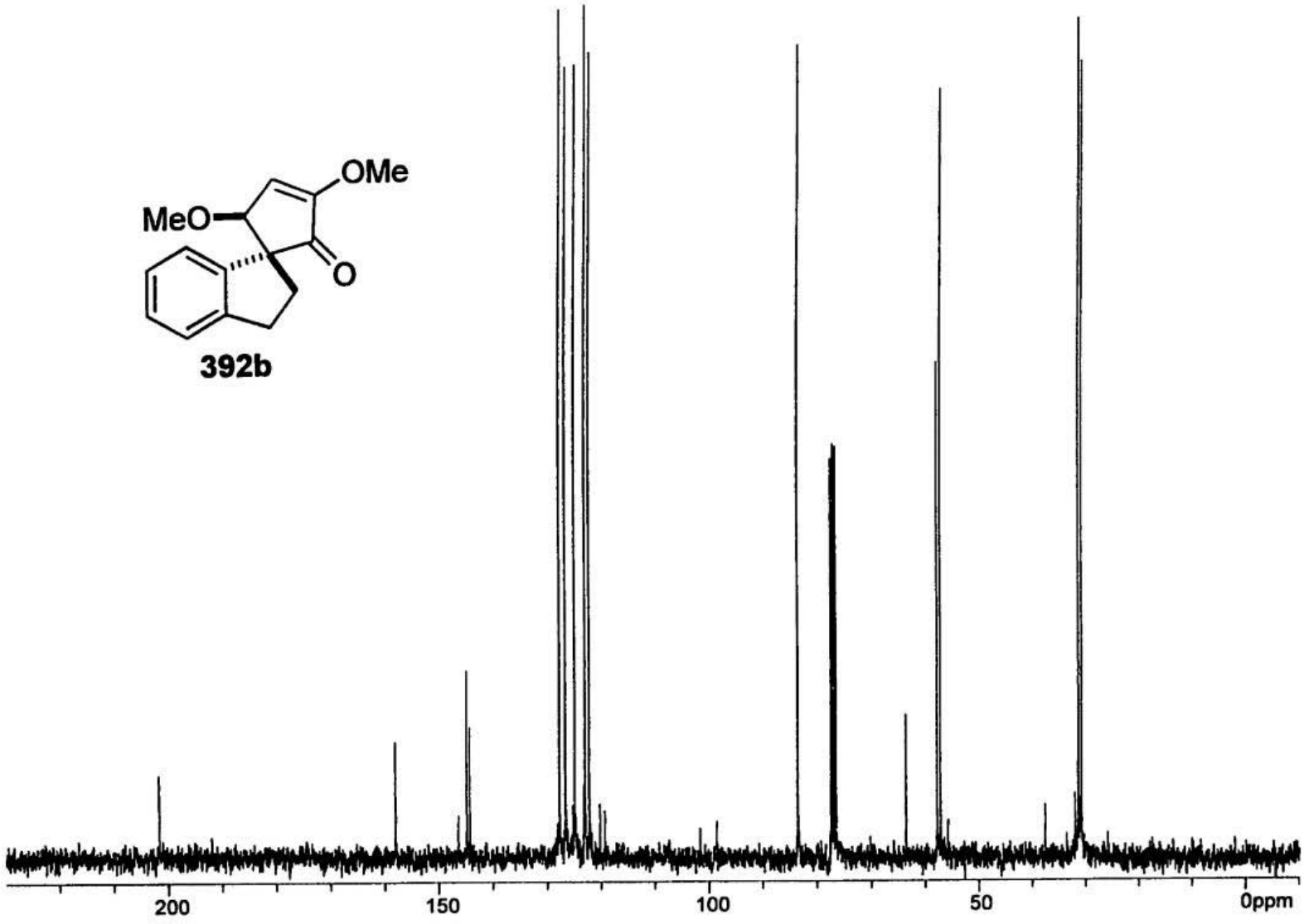

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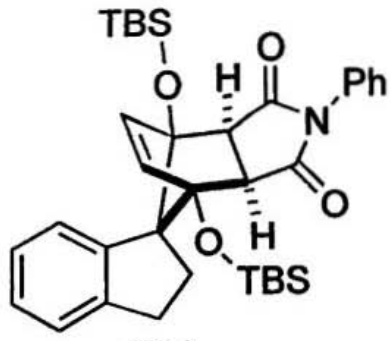

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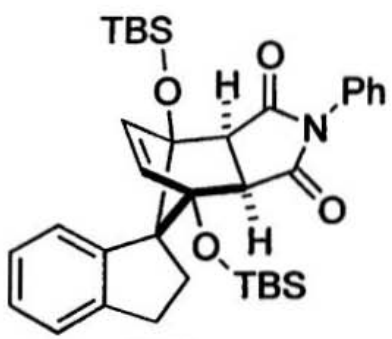

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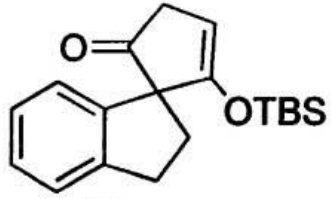

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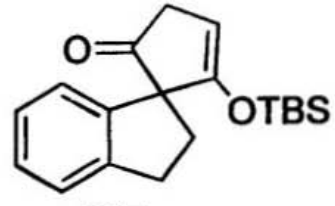

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