EFFORTS DIRECTED TOWARDS AN ASYMMETRIC TOTAL SYNTHESIS OF THE ANTITUMOR ANTIBIOTIC FREDERICAMYCIN A AND A STUDY OF THE DIELS-ALDER REACTIONS OF A CARVONE-DERIVED DIENE

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Efforts Directed Towards an Asymmetric Total Synthesis of the Antitumor Antibiotic Fredericamycin A and a Study of the Diels-Alder Reactions of a Carvone-Derived Diene

by

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Abstract: Since its discovery in 1981, the antitumor antibiotic Fredericamycin A (**1**) has been the subject of extensive synthetic efforts focused mainly on construction of its 1,3-cyclopentanedione subunit. Six total syntheses of **1** in racemic form have been reported. An asymmetric synthesis of **1** was accomplished only very recently. We have devised a potentially enantioselective route to **1** 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. Reduction of 2',3'-dihydro-7'-methoxy-5'-methylspiro(cyclopentane-2,1'-(1*H*)indene)-1,3-dione (**132**) with Baker's yeast furnished (2*R*,3*R*)-2',3'-dihydro-3-hydroxy-7'-methoxy-5'-methylspiro(cyclopentane-2,1'-(1*H*)indene)-1-one (**142**). The absolute stereochemistry of **142** was determined through derivatization as camphorsulfonyl ester **143**, which was diastereomerically pure and crystalline. On the basis of the absolute stereochemistry of **142**, it was determined that ethyl 3,4,6-trimethoxy-2-[1,3]dithiolan-2-ylbenzoate (**144**) would be the required A ring synthon to lead to the natural enantiomer of **1**. The A ring synthon **144** was to be annulated to the CDEF synthon employing a tandem Michael-Claisen sequence. In a model reaction, deprotonated ethyl 2-[1,3]dithiolan-2-ylbenzoate (**114a**) reacted smoothly in a tandem Michael-Claisen process with (2*R**,3*S**)-2',3'-dihydro-7'-methoxy-5'-methyl-3-(trimethylsilyl)oxyspiro([4]cyclopentene-2,1'-(1*H*)indene)-1-one (**135**) to furnish (2*R**,3*S**,3a*S**)-4-[1,3]dithiolan-2-yl-2,2',3,3',3a,4-hexahydro-9-hydroxy-7'-methoxy-5'-methyl-3-(trimethylsilyl)oxyspiro((1*H*)-benz[*f*]indene-2,1'-(1*H*)indene)-1-one (**136**) in 85% yield.

Unfortunately, all attempts to convert *N*,*N*-diethyl-2-[1,3]dithiolan-2-yl-3,4,6-trimethoxybenzamide (**147**) to ester **144**, either directly or indirectly, were unsuccessful. However, the synthesis of ethyl 2-[1,3]dithiolan-2-yl-5,6-dimethoxybenzoate (**245**) was achieved. Deprotonation of **245**, followed by addition to a Michael acceptor, did not yield the expected tandem Michael-Claisen product, but unsymmetrically substituted phthalic thiothionoanhydride **250**. This unexpected elimination of ethene was circumvented by conversion of the dithiolane to a dithiane moiety. Deprotonated ethyl 2-[1,3]dithian-2-yl-5,6-dimethoxybenzoate (**258**) reacted smoothly with both 4-((*tert*-butyldimethylsilyl)oxy)spiro[4.5]dec-2-en-1-one (**119**) and (2*R**,3*R**)-3-acetoxy-2',3'-dihydrospiro([4]cyclopentene-2,1'-[1*H*]indene)-1-one (**249**) to furnish the expected tandem Michael-Claisen adducts in excellent overall yield.

Singlet oxygen often exhibits unusual facial selectivity in the Diels-Alder reaction, presumably due to the formation of a perepoxide intermediate. Our investigations into this unusual facial selectivity are presented, including attempts to extend this unusual facial selectivity to other dienophiles, such as *N*-phenylmaleimide, 4-phenyl-1,2,4-triazoline-3,5-dione (**276**), and tetracyanoethene.

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List of Abbreviations and Symbols

Ac	acetyl
acac	acetylacetone
AIBN	2,2'-azobisisobutyronitrile
APT	attached proton test
Bn	benzyl
Bu	butyl
CAN	ceric ammonium nitrate
cat	catalytic
CD	circular dichroism
Cmp	(-)-camphanyl
*m*CPBA	3-chloroperoxybenzoic acid
DBU	1.8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DDQ	2.3-dichloro-5.6-dicyano-1.4-benzoquinone
DEAD	diethyl azodicarboxylate
DHP	3.4-dihydro-2*H*-pyran
DIBAL-H	diisobutylaluminum hydride
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-dimethylaminopyridine
DME	1.2-dimethoxyethane
DMF	*N*.*N*-dimethylformamide

DMG	directed-metallation group
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DoM	directed *ortho*-metallation
E	electrophile
ee	enantiomeric excess
Et	ethyl
EWG	electron-withdrawing group
FG	functional group
FGI	functional group interconversion
FID	free induction decay
FT	Fourier transform
GC-MS	gas chromatograph coupled to a mass spectrometer
h	hour(s)
hv	ultraviolet irradiation
H$^-$arpoon	lithium 2,2,6,6-tetramethylpiperidine
hexamine	hexamethylenetetramine
HMDS	hexamethyldisilazide or bis(trimethylsilyl)amide
HMQC	heteronuclear multiple quantum correlation
HMPA	hexamethylphosphoramide
HRMS	high-resolution mass spectrum

IC_{50}	concentration that gives 50% inhibition of an enzyme or antagonism of a receptor
imid	imidazole
IR	infrared
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
Me	methyl
min	minute(s)
MINDO/3	Modified Intermediate Neglect of Differential Overlap
MOM	methoxymethyl
MS	mass spectrum
Ms	methanesulfonyl
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
NPM	*N*-phenylmaleimide
NOE	nuclear Overhauser enhancement
NOESY	2D-nuclear Overhauser effect spectroscopy
NR	no reaction
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
PPTS	pyridinium *para*-toluenesulfonate

PTC	phase-transfer catalysis
Pr	propyl
py or pyr	pyridine
RNA	ribonucleic acid
rt	room temperature
SAR	structure-activity relationship
sh	shoulder
SM	starting material
TBAB	tetra-*n*-butylammonium bromide
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
TES	triethylsilyl
Tf	trifluoromethanesulfonyl (triflyl)
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyranyl
TIPS	triisopropylsilyl

TLC	thin layer chromatography
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
p-Tol	*para*-tolyl
TosMIC	tosylmethyl isocyanide
TPS	triphenylsilyl
p-TsOH	*para*-toluenesulfonic acid
UV	ultraviolet
xs	excess

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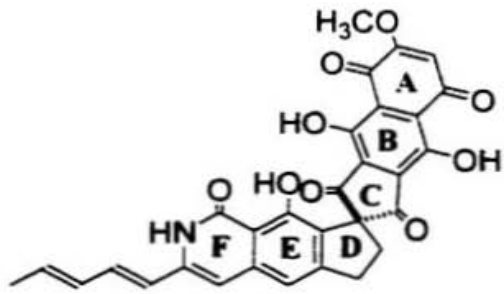
Chapter 1. Efforts Directed towards an Asymmetric Total Synthesis of the Antitumor Antibiotic Fredericamycin A.

Introduction

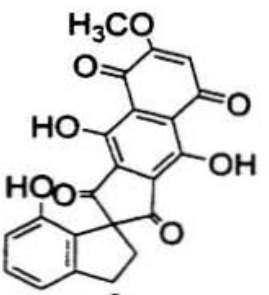
The antitumor antibiotic Fredericamycin A (**1**) was first isolated by Pandey *et al.*[1,2] from the FCRC-48 strain of the soil bacterium *Streptomyces griseus* at the National Cancer Institute in Frederick, Maryland, in 1981. Single-crystal X-ray diffraction pattern analysis was successful in establishing its structure after extensive spectroscopic studies failed to resolve tautomeric forms in the ABC subunit.[3] Primary to its novel molecular architecture is the spiro[4.4]nonane subunit previously unknown to compounds in the antibiotic or antitumor classes.



(+)-**1** : Fredericamycin A

Fredericamycin A exhibits potent *in vitro* activity against Gram-positive bacteria and fungi, and has been shown to be cytotoxic *in vitro* and active *in vivo* against several transplantable tumors in mice such as P388 leukemia, CD8F mammary and B16 melanoma. Unlike many antitumor agents, **1** does not show mutagenicity in the Ames test.[4] The origin of the antibiotic and antitumor properties of **1** appears to be through inhibition of RNA and protein biosynthesis.[4] Although studies on the single-electron oxidation of **1** and the role of **1** in the generation of oxygen free radicals initially

supported an indiscriminate mode of action,[5] subsequent investigations[6] have disputed these findings. It has since been determined that **1** inhibits DNA processing enzymes, 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).[7] The discovery that **1** may not interact directly or detectably with DNA[8] suggests direct enzyme inhibition or selective stabilization of a tertiary complex of DNA, topoisomerase and **1**. The observation that the analogue **2**, which lacks the functionalized F ring, was approximately 100 times less potent than **1** has shed further doubt on the hypothesis that indiscriminate redox properties of **1** are solely responsible for its biological activity.[9]



2

This promising biological profile and the unique structure of **1** have made it quite attractive as a lead compound for a new type of chemotherapeutic drug for human cancers.

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.[10a-w] These studies have culminated in six total syntheses[11-16] of **1** in racemic form and very recently the first asymmetric synthesis[17] of Fredericamycin A. When our

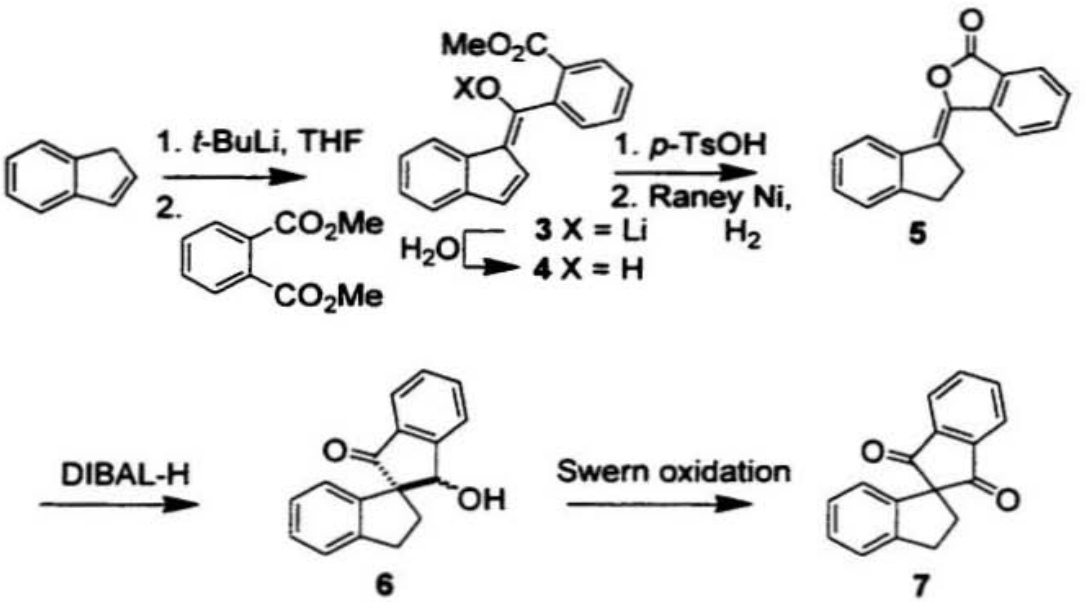
work was commenced in this area in 1996, an enantioselective synthesis of **1** had yet to be reported, and configuration of the sole stereogenic center in **1** was still unknown. In the interest of resolving these issues, we devised a potentially highly enantioselective route to **1** which relied on a tandem Michael-Claisen process for construction of the ABC subunit of **1**. Assembly of the spiro[4.4]nonane system was to employ the geminal acylation methodology developed in our laboratory[18] and the lone stereogenic center of **1** would then be introduced utilizing a reductase from *Saccharomyces cerevisiae*.[19] Before detailing the retrosynthetic analysis that led to the formulation of these synthetic plans and the results of our efforts, a review of the chemical literature dealing with the synthesis of **1** is in order.

Literature Review – Strategies for the Synthesis of Fredericamycin A

The vast majority of model studies on **1** have focused on the construction of the spiro CD linkage. Numerous partial structures differing in the levels of oxygenation have been prepared using a wide range of strategies. Several of these preliminary studies have led to total syntheses of **1**.

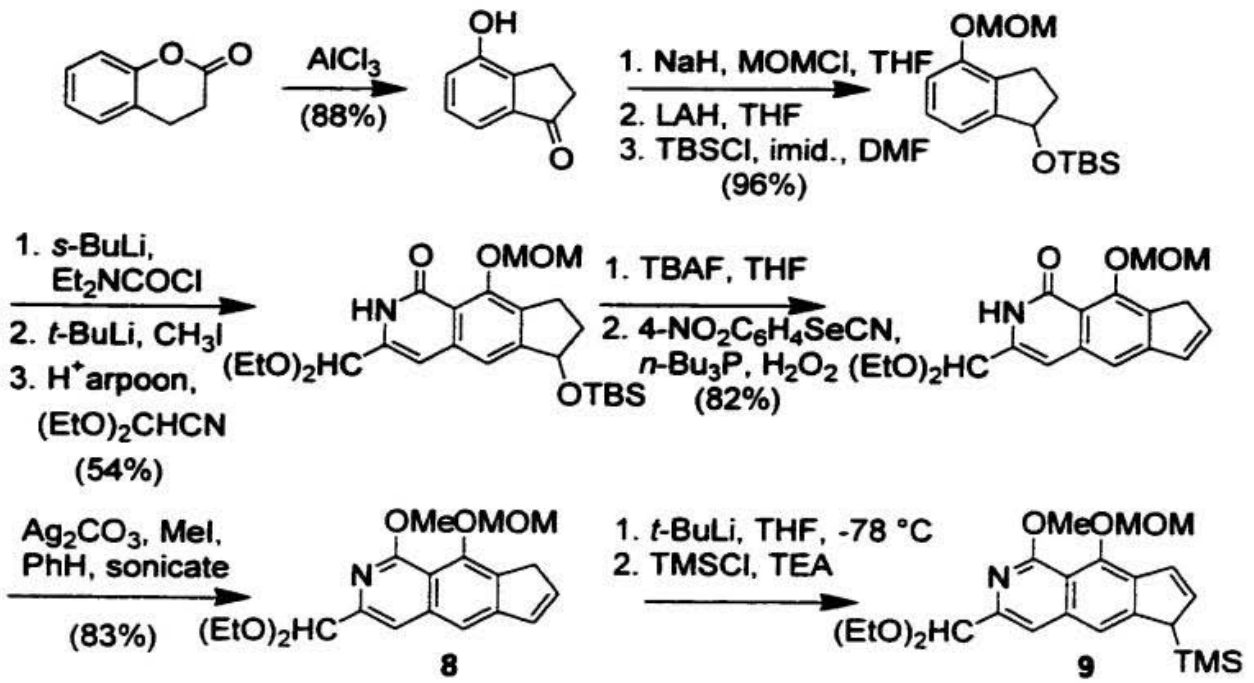
Bis-functionalization of Intact DE Synthons. T. Ross Kelly[10a] was the first to explore the fashionable strategy of forming the spiro CD linkage *via* bis-acylation of an indenyl anion (Scheme 1a). The initial attack of lithiated indene on dimethyl phthalate proceeded smoothly to furnish **3**. The desired Dieckmann condensation to yield the C ring, however, did not occur. Work-up of **3** provided **4** as a mixture of tautomeric forms that could not be cyclized directly under a variety of acidic or basic conditions. However, treatment of **4** with *para*-toluenesulfonic acid (*p*-TsOH) followed by selective hydrogenation of the endocyclic alkene furnished lactone **5**. Treatment of this lactone **5** with diisobutylaluminum hydride (DIBAL-H) generated a keto-enolate that underwent the desired cyclization reaction to provide **6** as a diastereomeric mixture of ketols. Swern oxidation (oxalyl chloride, dimethyl sulfoxide (DMSO), triethylamine (TEA), -78 °C) afforded the desired dione **7**. No yields were reported for any of these transformations.

Scheme 1a

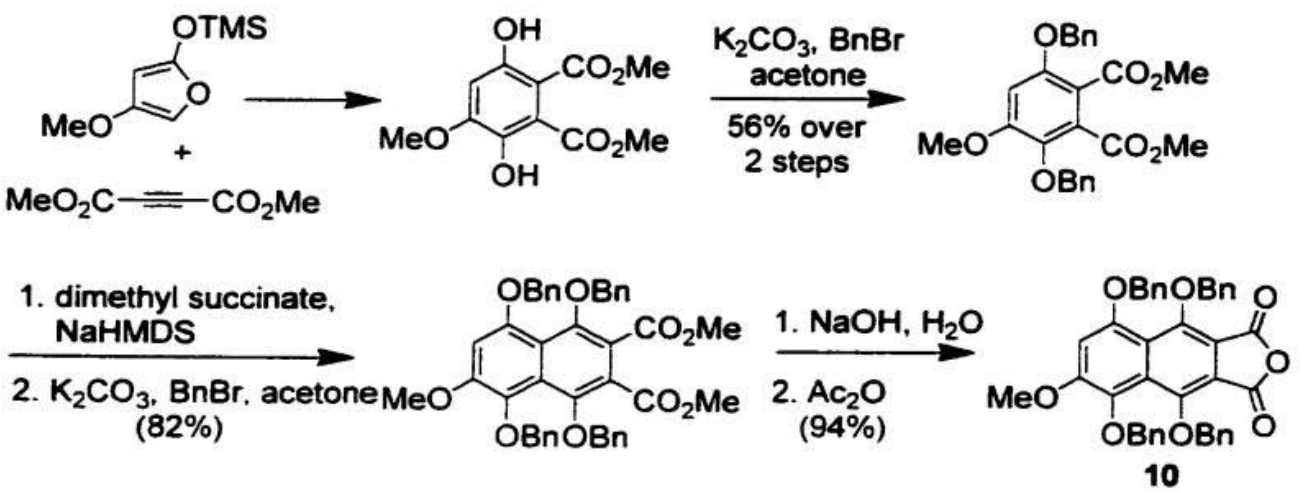


Kelly[10a, 11] successfully applied this strategy to the first total synthesis of **1** (Schemes 1b-1d) in 17 steps from dihydrocoumarin and methyl tetronate in 3.3% overall yield. The tendency of lithiated indene **8** to react from the undesired terminus of the allylic anion system necessitated a slight modification of the initial plan. This obstacle was overcome by converting **8** to **9** by trapping with chlorotrimethylsilane (TMSCl) before repeated lithiation (**11**) and reaction with anhydride **10**.

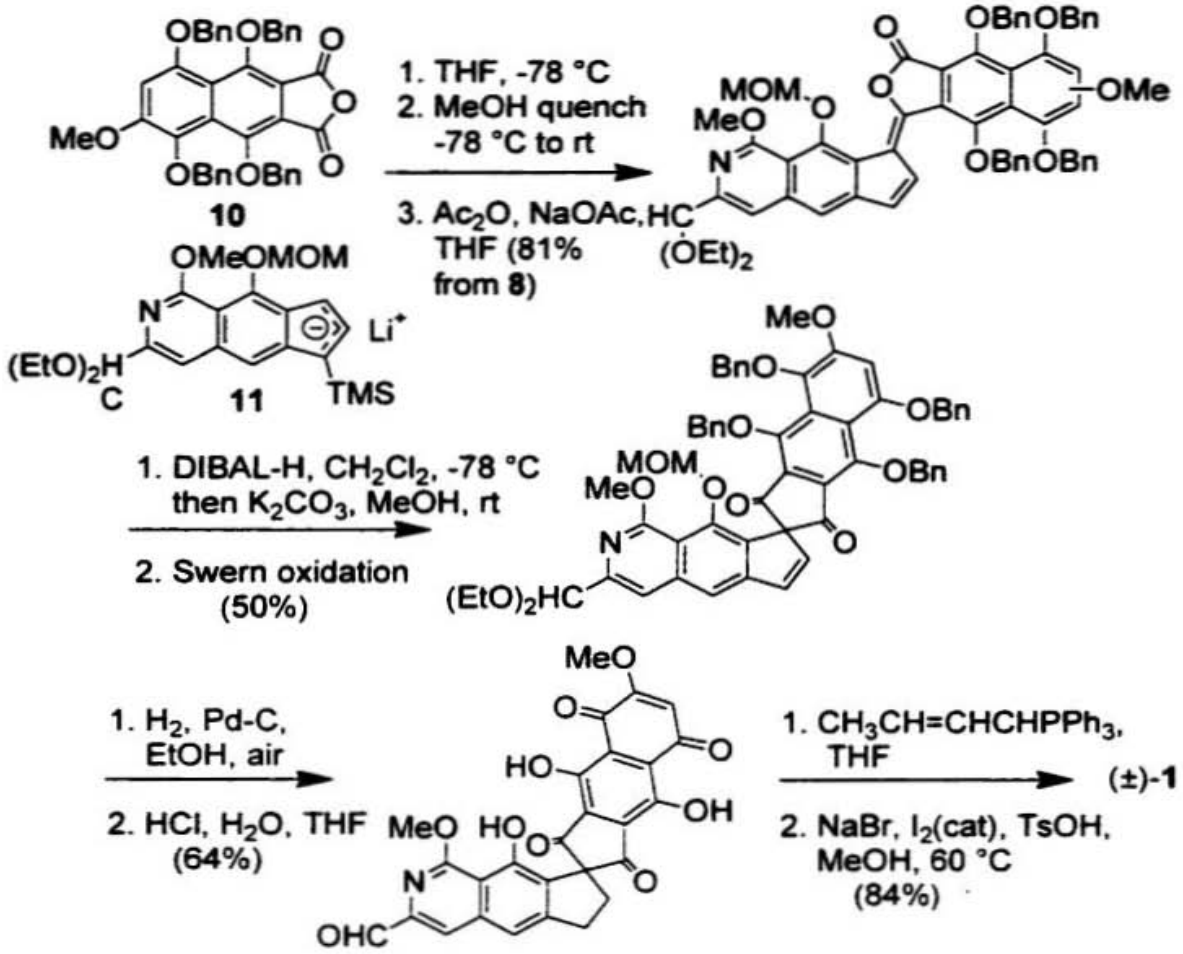
Scheme 1b



Scheme 1c

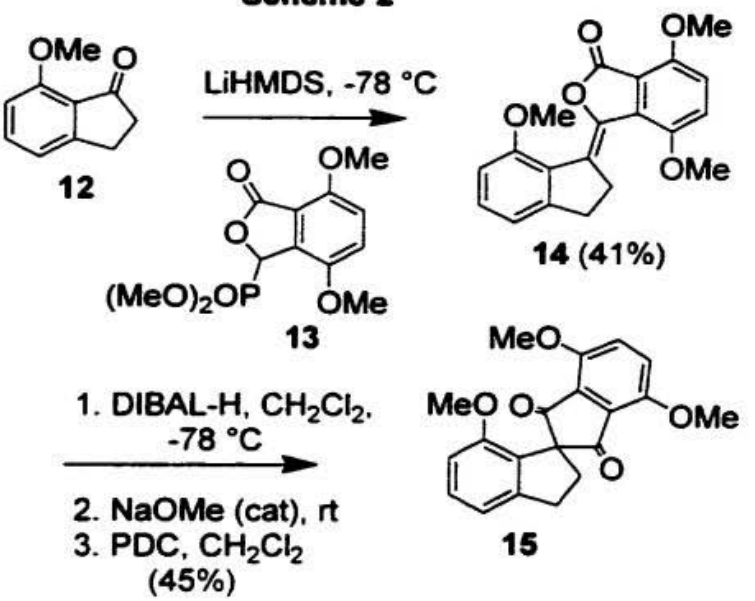


Scheme 1d



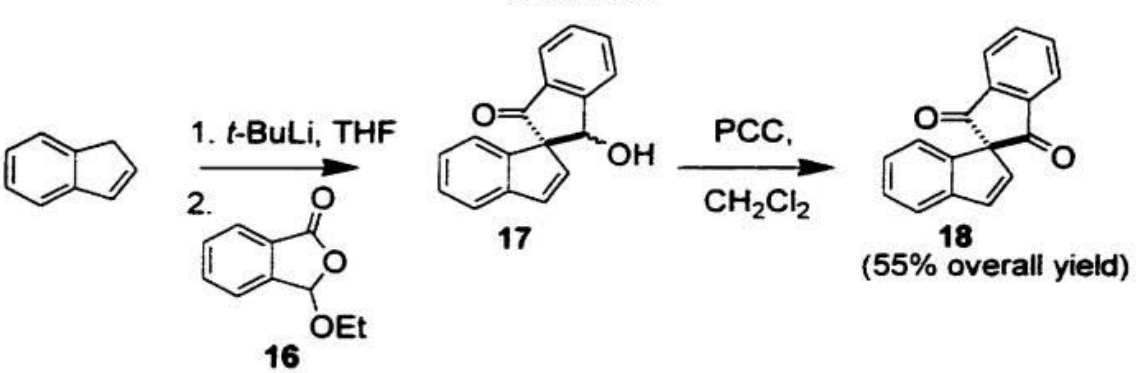
Watanabe[10b] (Scheme 2) prepared 3-(1'-indanylidene)phthalide **14** using a Horner-Wadsworth-Emmons reaction between indanone **12** and phosphonate **13**. Reduction of **14** using DIBAL-H, followed by addition of a catalytic amount of sodium methoxide resulted in an intramolecular aldol spirocyclization to form the C ring. Treatment of the resulting mixture of stereoisomeric spiroketoalcohols with pyridinium dichromate (PDC) afforded the fully oxygenated BCDE core **15**.

Scheme 2



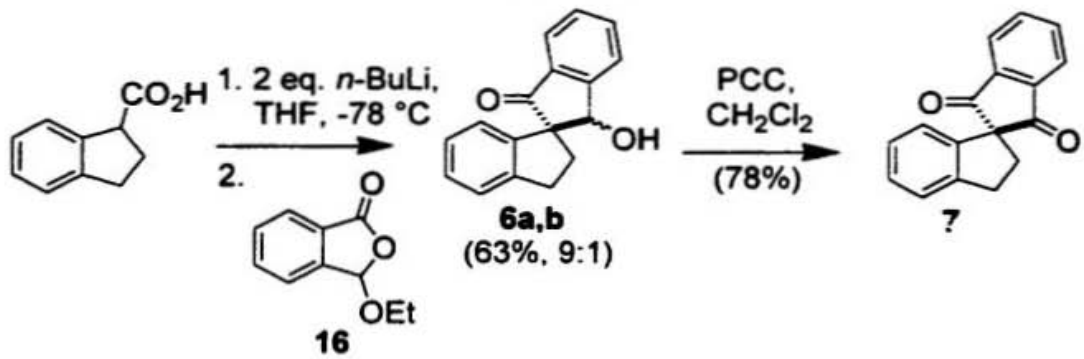
Kessar[10c] obtained **18** in a single operation by using phthalide **16** (Scheme 3). Indenyl anion attack onto the lactone carbonyl of **16** with concomitant expulsion of ethoxide generated a keto-aldehyde. The lithium ethoxide liberated in the initial process subsequently effected an intramolecular aldol spirocyclization reaction to furnish **17** as a mixture of stereoisomers. Oxidation afforded **18** in 55% overall yield.

Scheme 3



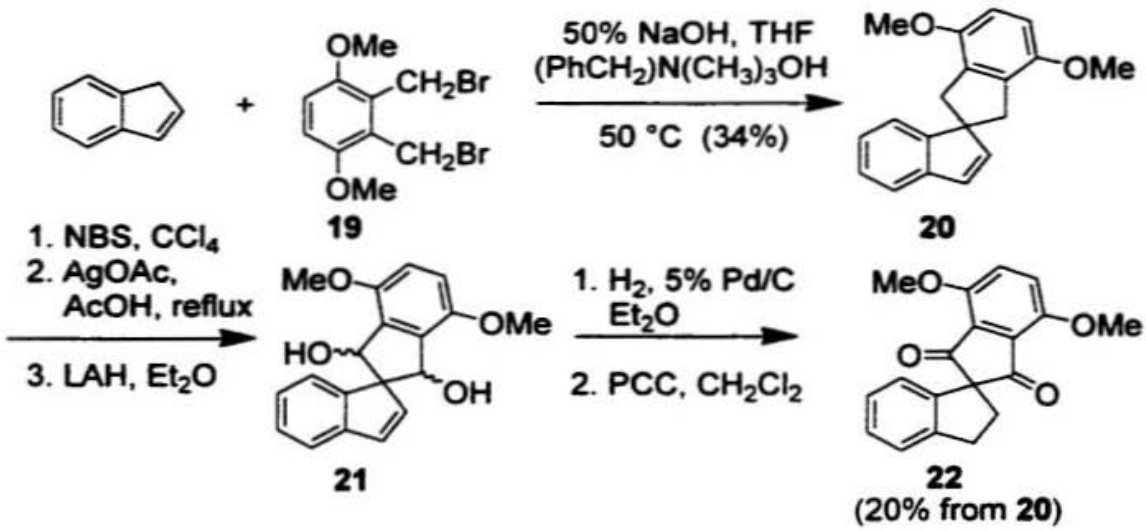
Similarly, Braun[10d] assembled the spiro CD linkage utilizing a tandem Claisen-decarboxylation-aldol reaction between indanecarboxylic acid and **16** (Scheme 4). Once again, pyridinium chlorochromate (PCC) oxidation of the keto-alcohol diastereomeric mixture (**6a,b**) gave **7** in 49% overall yield.

Scheme 4



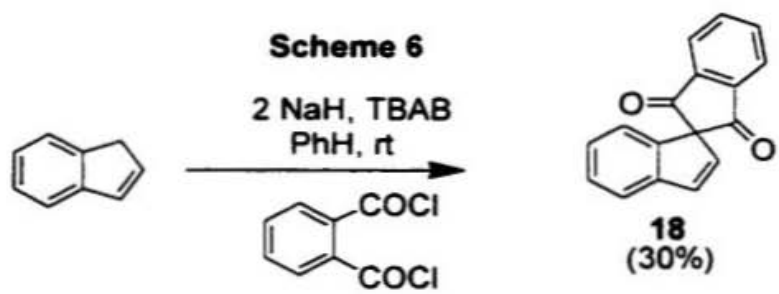
Julia[10e] reported the bis-alkylation of indene with dibromide **19** under phase-transfer catalysis (PTC) conditions (Scheme 5). The required oxygen functionality was introduced onto the C ring of **20** by a three step sequence: (i) benzylic bromination with *N*-bromosuccinimide (NBS), (ii) halide displacement from the 1,3-dibromide with silver acetate, and (iii) reduction of the resulting diacetate to diol **21** with lithium aluminum hydride. Hydrogenation of the double bond followed by PCC oxidation afforded dione **22** in 20% yield over five steps.

Scheme 5



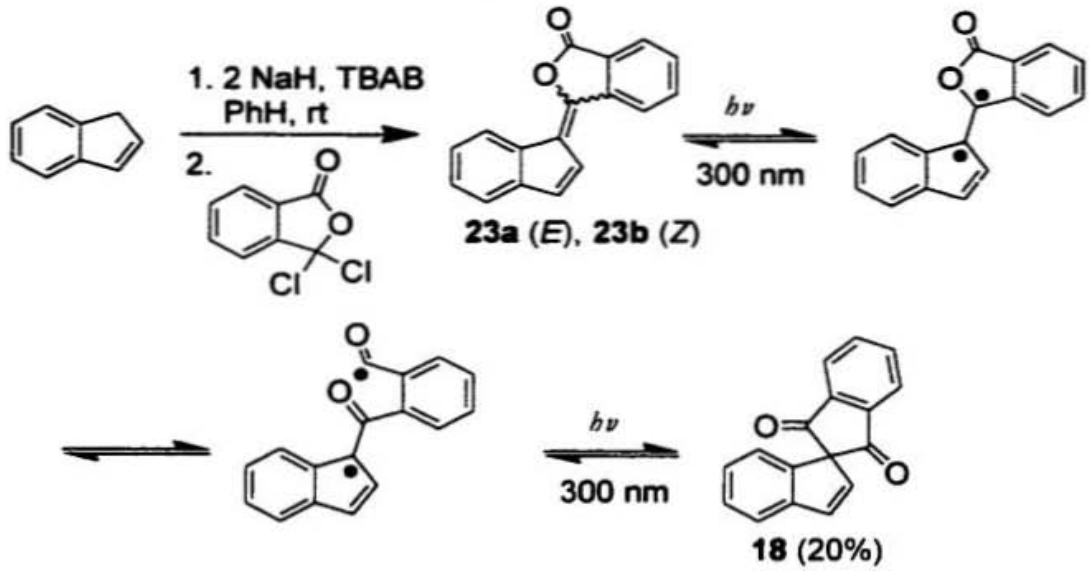
Ayyanger[10f] demonstrated that direct bis-acylation of a metallated indene to give **18** can occur in modest yield using the more reactive phthaloyl chloride in the presence of tetra-*n*-butylammonium bromide (TBAB) (Scheme 6).

Scheme 6



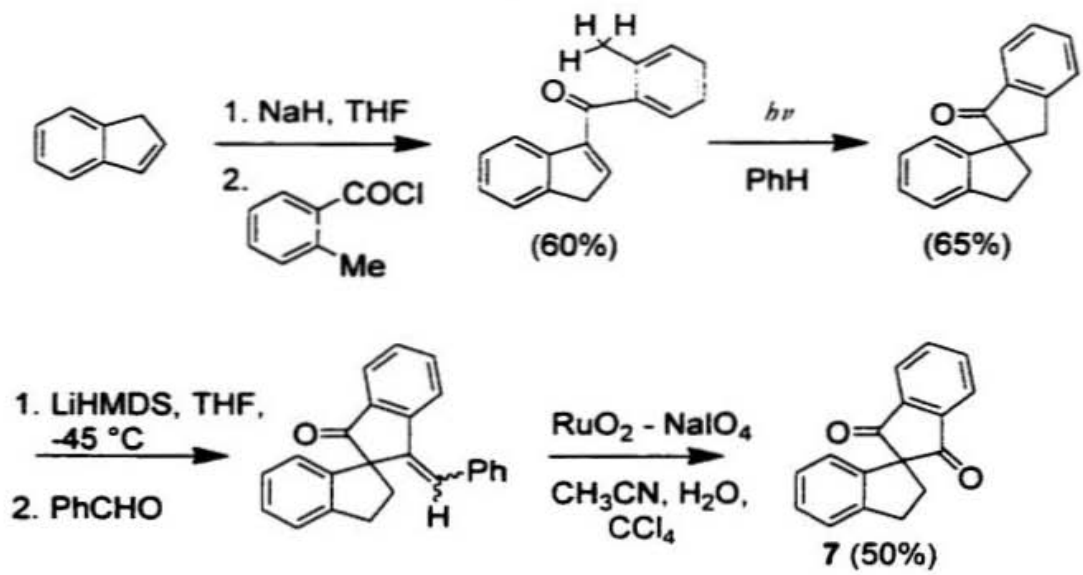
Ayyanger also prepared 3-(1'-indanylidene)phthalides **23a,b** that had previously been shown to rearrange to **18** upon treatment with DIBAL-H. Moreover, it was demonstrated that it was possible to accomplish the formation of **18** from **23a,b** photochemically (Scheme 7).[10f] Longer irradiation times resulted in the same photostationary mixture (**23a : 23b : 18**, 20%, 50%, and 20% isolated yields).

Scheme 7



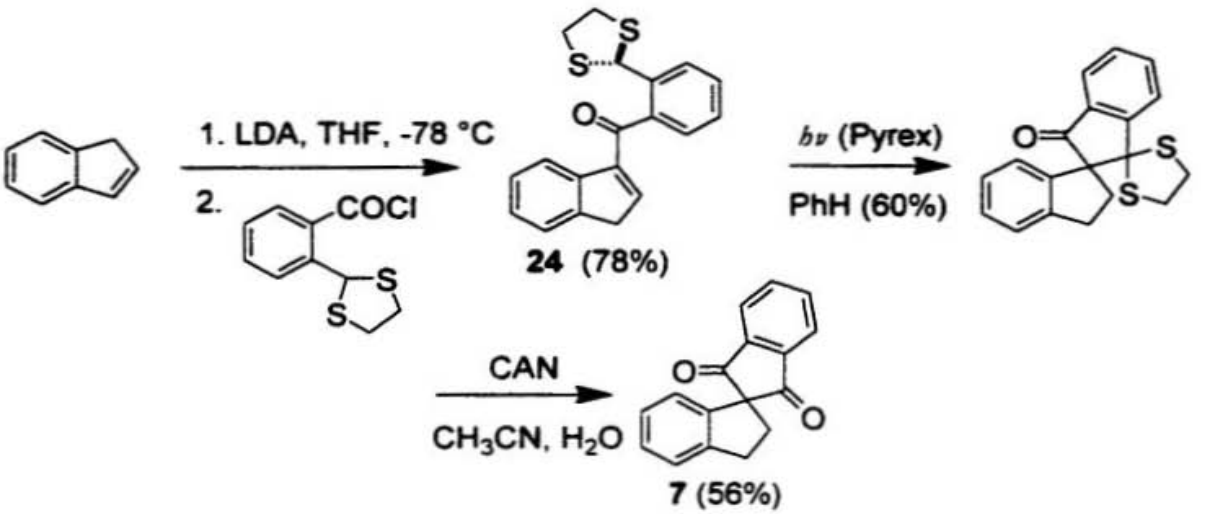
Mehta[10g] (Scheme 8) constructed BCDE subunit 7 using a novel photochemical 1,6-H abstraction/5-*exo*-*trig* radical spirocyclization strategy.

Scheme 8



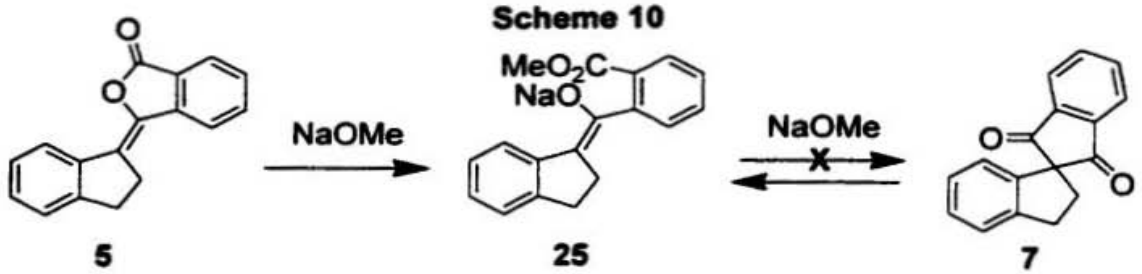
Pandey[10h] (Scheme 9) later reported a more efficient approach employing thioacetal **24**.

Scheme 9



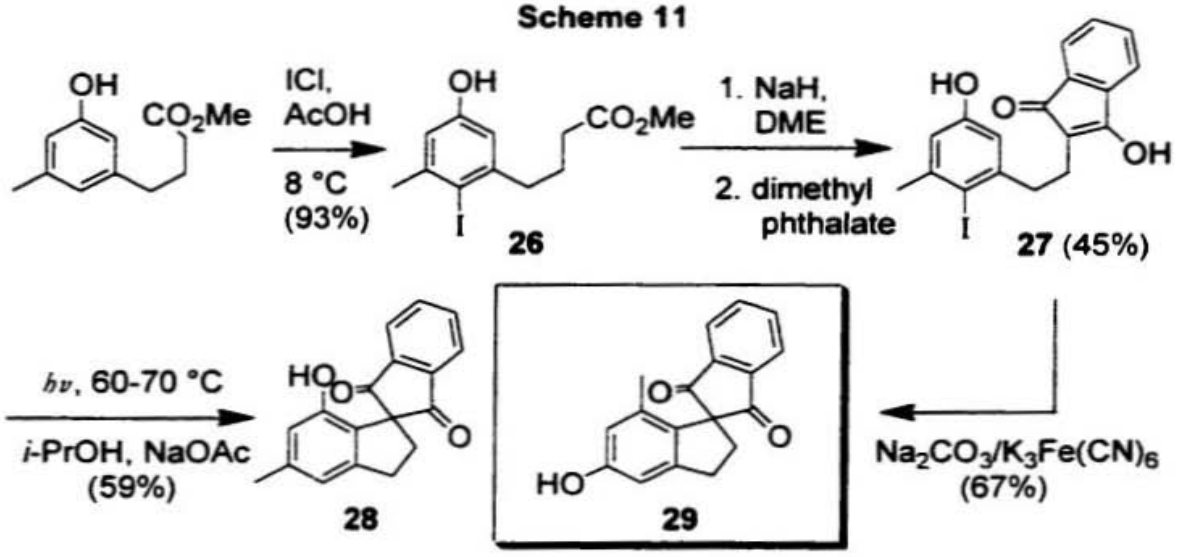
D Ring Annelation Strategies. The failure of Kelly's Dieckmann condensation tactic for the direct formation of the C ring dione from an acylated indene was likely a consequence of the stability of the intermediate enolate. the low reactivity of the conjugated ester moiety in **25** (Scheme 10). and that the Dieckmann cyclization is likely to fail when a stable enolate of the product cannot be formed. 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



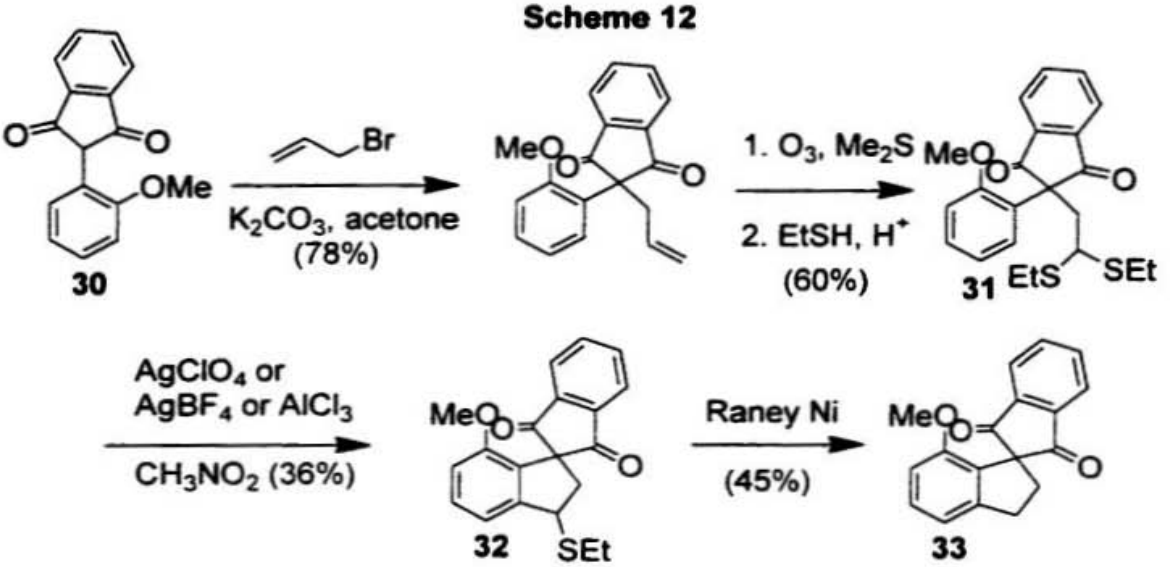
Kende[10i] reported the synthesis of BCDE fragment **28** employing a 5-*exo-trig* phenoxy-enoxy coupling.[10i] Assembly of the C ring was accomplished with a tandem Claisen-decarboxylation-Dieckmann sequence between **26** and dimethyl phthalate. Photolysis of the *p*-iodophenol generated a delocalized 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 **28** in 59% yield. It is noteworthy that oxidative cleavage of the C-I bond with $Na_2CO_3/K_3Fe(CN)_6$ gave only 8% of **28**. The major product **29** (67%) arose from the corresponding coupling *para* to the phenolic oxygen in **27**.

Scheme 11



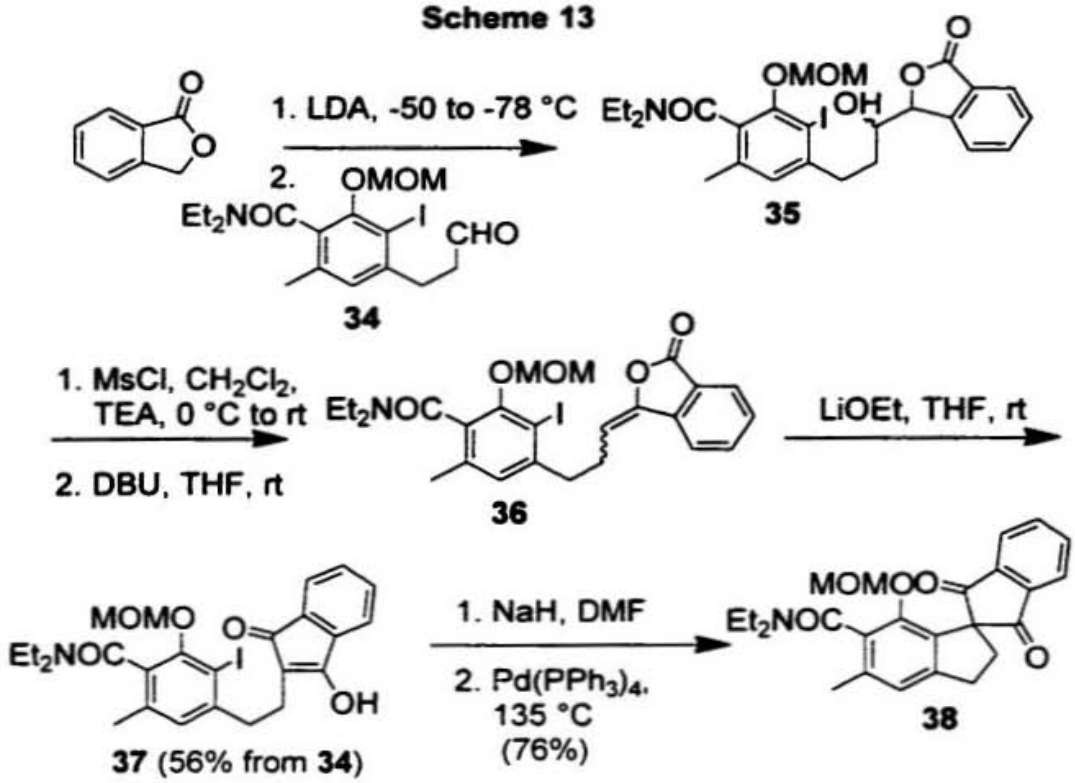
Starting from the known indane-1,3-dione **30**, available from phthalic anhydride and 2-methoxyphenylacetic acid, Braun[10j] prepared dithioacetal **31** (Scheme 12). Compound **31** participated in an intramolecular Friedel-Crafts type reaction upon treatment with $AgClO_4$, $AgBF_4$ or $AlCl_3$ in acetonitrile to furnish thioether **32** in modest yield. Raney nickel desulfurization provided the BCDE dione **33**.

Scheme 12



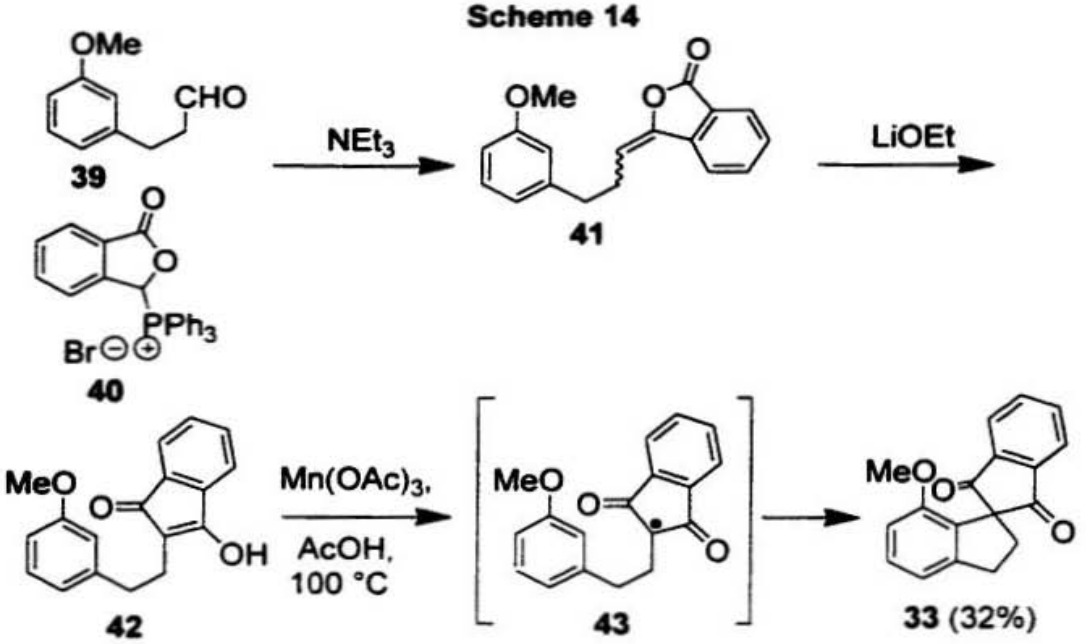
Ciufolini[10k] prepared BCDE fragment **38** using a palladium-catalyzed intramolecular arylation of **37** (Scheme 13). Addition of lithium phthalide to aromatic aldehyde **34** provided alcohol **35**. Base-induced elimination of the corresponding mesylate gave 3-alkylidenephthalide **36**, and smooth conversion to **37** was effected using LiOEt in THF. Oxidative addition of the sodium enolate of **37** to Pd^0, followed by heating to 135 °C, resulted in intramolecular reductive coupling with regeneration of Pd^0 to give **38** in 76% yield.

Scheme 13



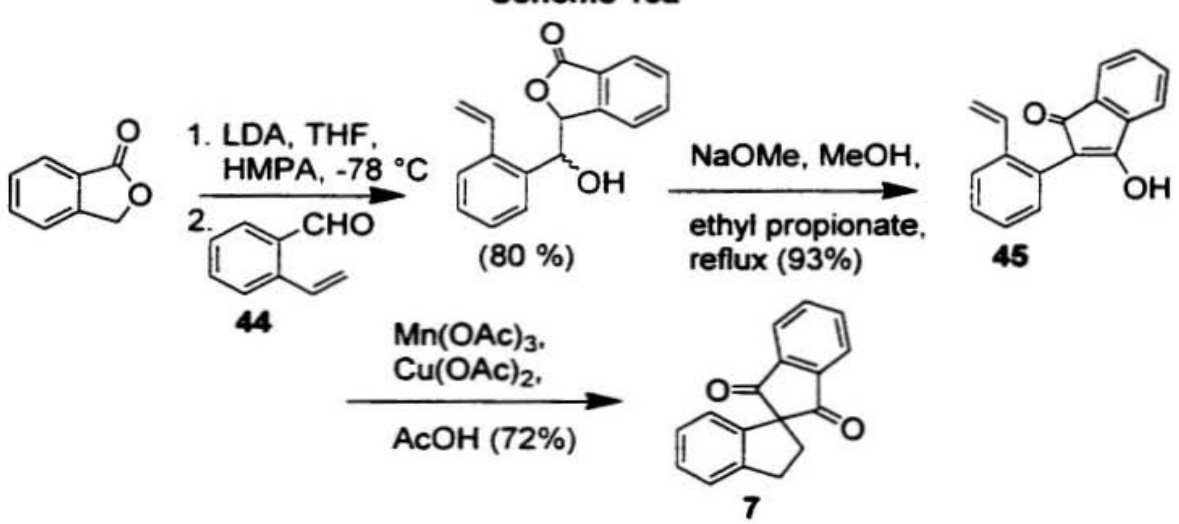
A similar strategy was employed by Narasimhan[101] in the synthesis of the BCDE model **33** (Scheme 14). The 3-alkylidenephthalide substrate **41** for the Dieckmann condensation was prepared in this case by Wittig olefination of aldehyde **39** with phosphonium salt **40**. Treatment of the Dieckmann condensation product **42** with $Mn(OAc)_3$ in hot acetic acid induced the intramolecular arylation reaction to give **33** via **43**.

Scheme 14



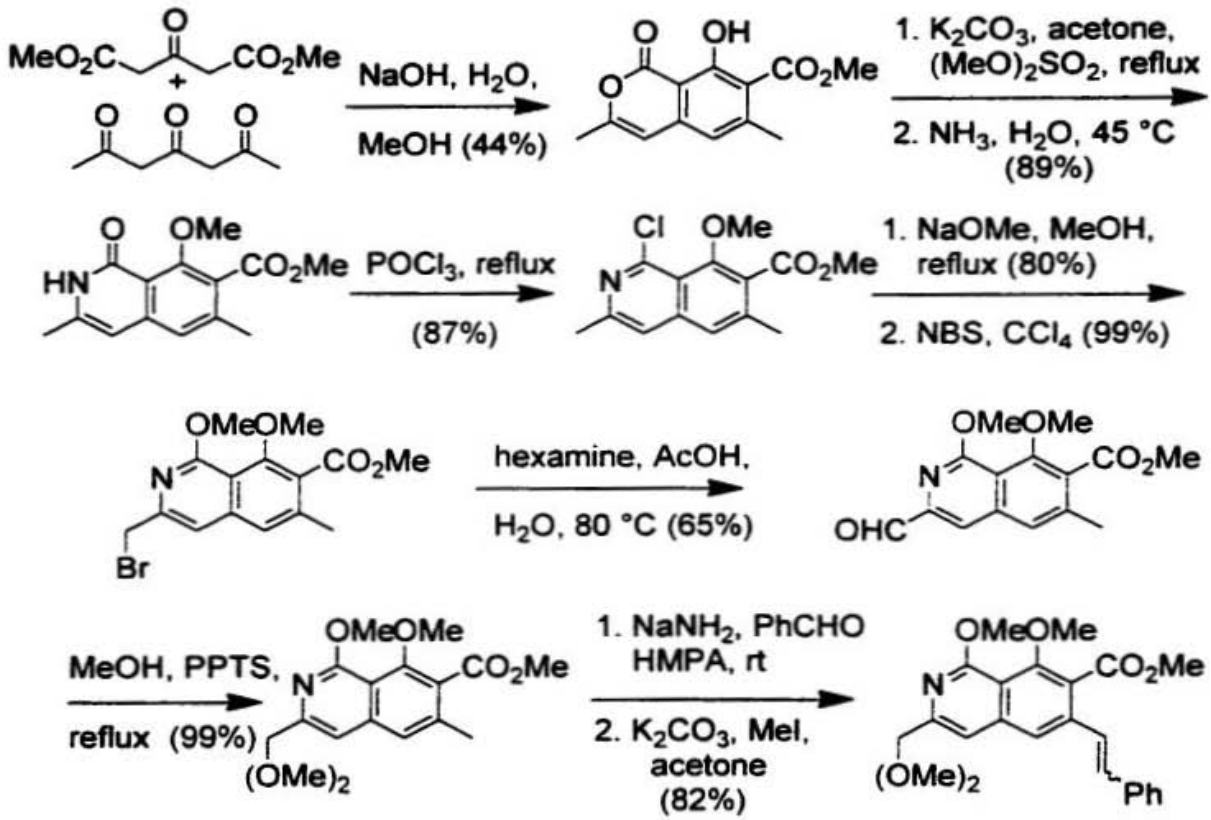
Rama Rao[10m] utilized Shapiro's Dieckmann conditions[20] for the synthesis of **45** from aldehyde **44** and phthalide (Scheme 15a). Formation of the BCDE model **7** was achieved in 72% yield from **45** *via* a usually disfavored 5-*endo-trig* radical cyclization.

Scheme 15a

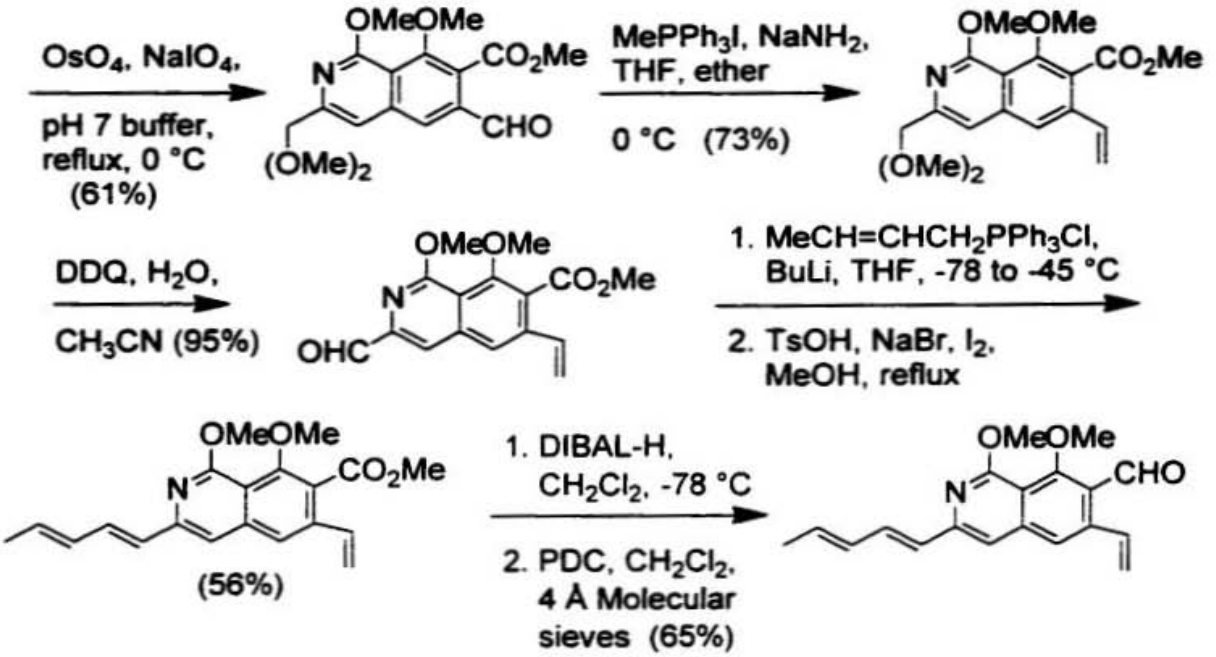


Rama Rao[14a,b] later achieved the total synthesis of **1** (33 steps) using this strategy (Scheme 15b-d). The seemingly indirect synthesis of **48** outlined in Scheme 15c reflects the inability of the orthoester derived from **46** to react with dimethyl acetylenedicarboxylate (DMAD) in a Diels-Alder [4 + 2] cycloaddition despite the observation that **47** easily reacted under the same conditions.

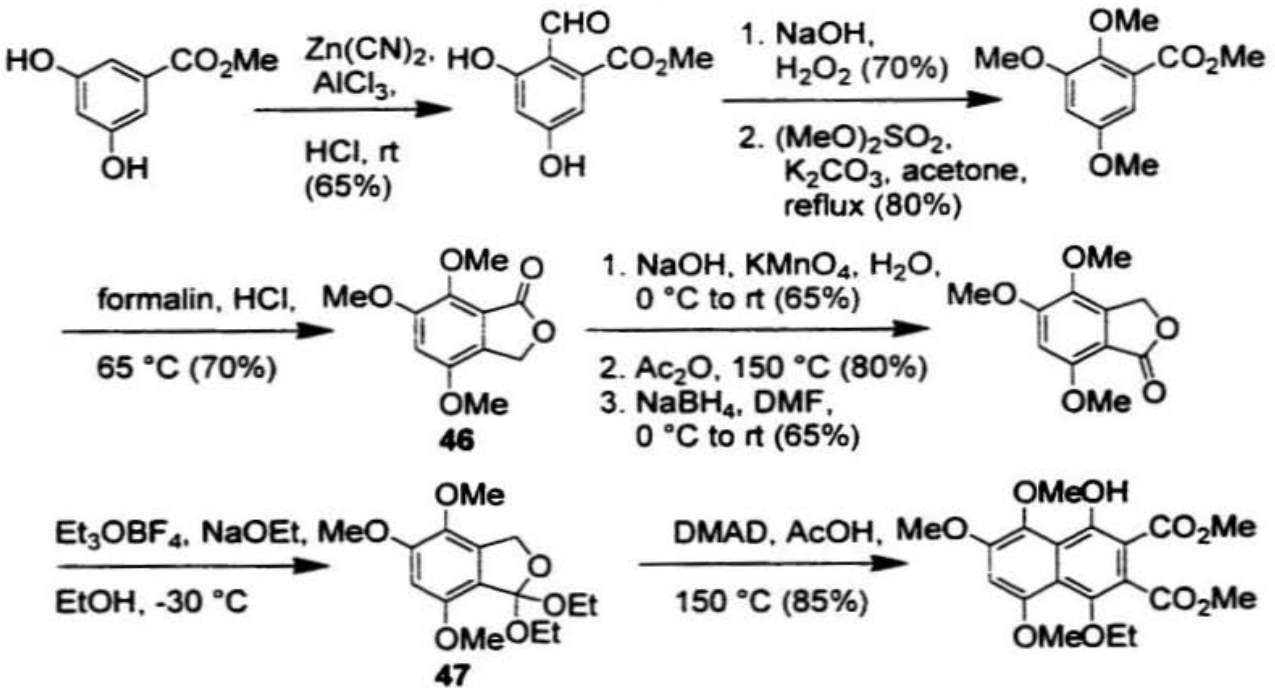
Scheme 15b



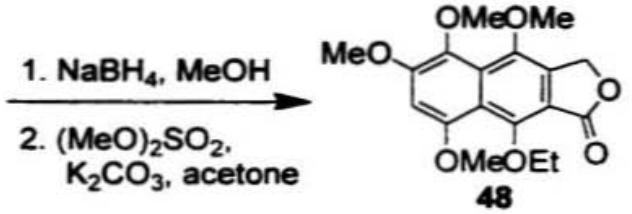
Scheme 15b (continued)



Scheme 15c

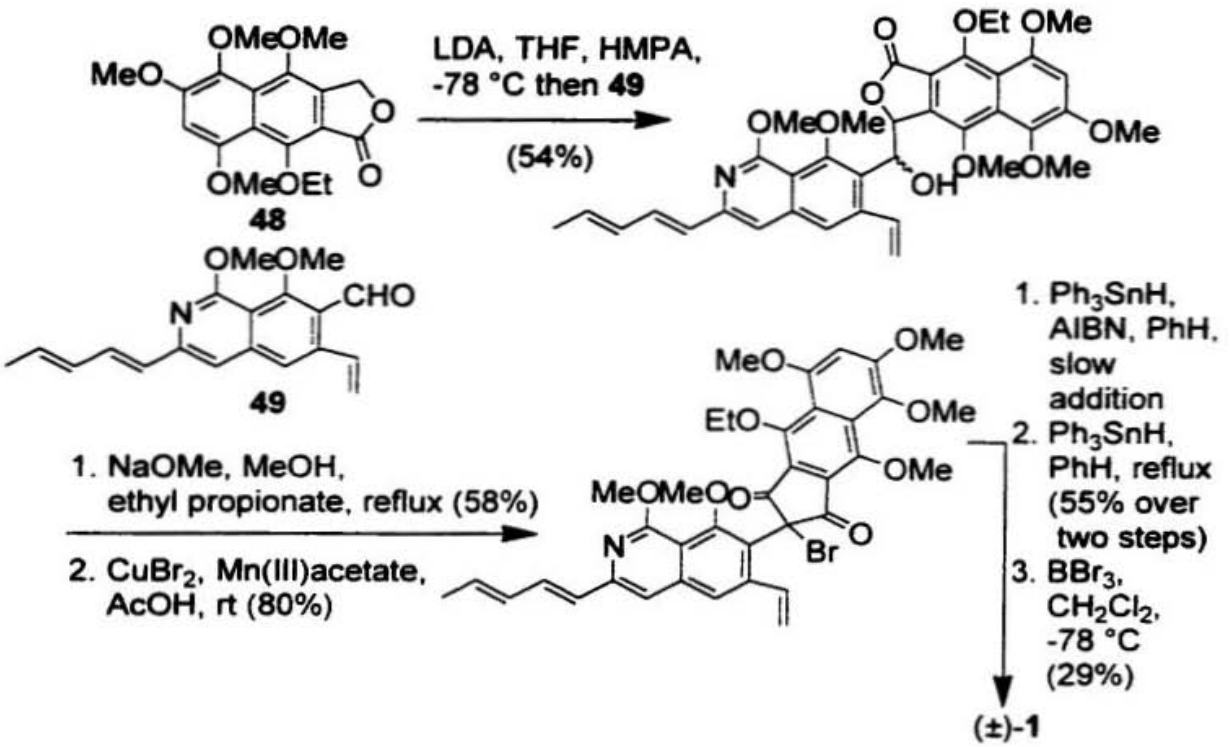


Scheme 15c (continued)



48

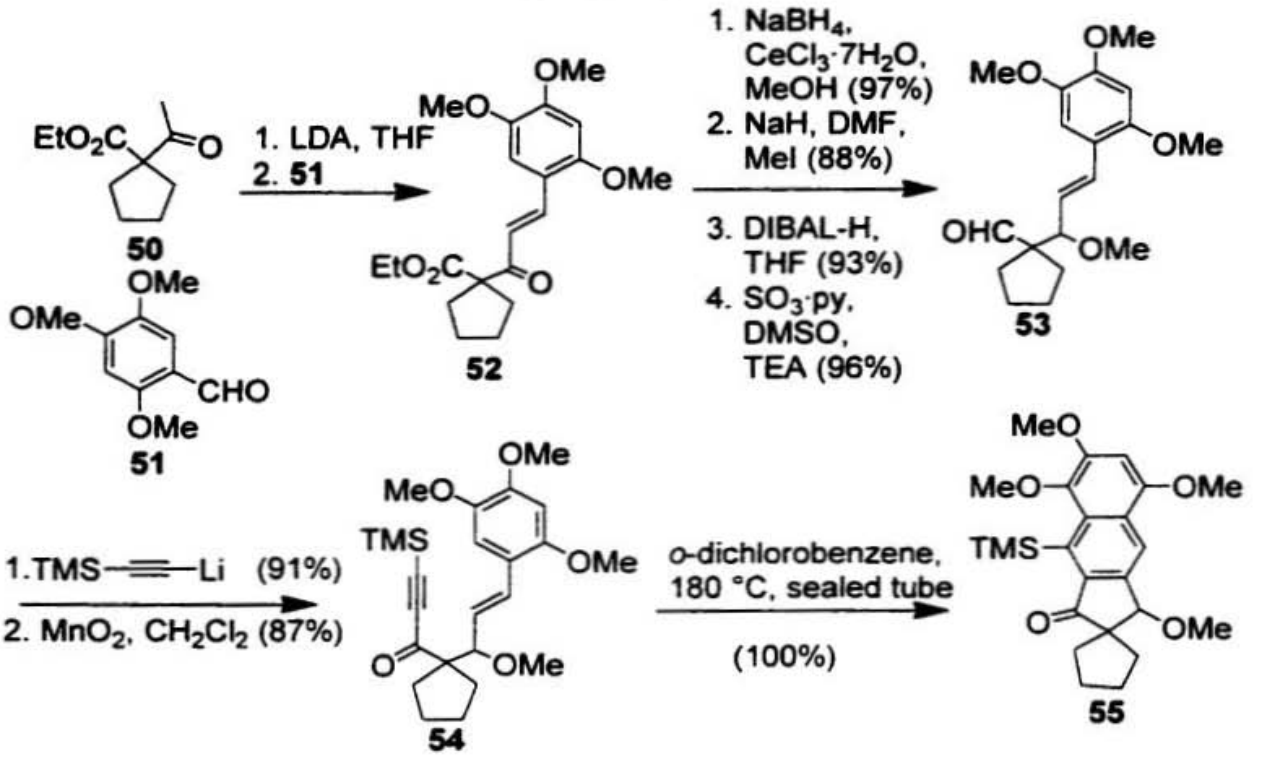
Scheme 15d



Other Novel Approaches. Terashima[10n] prepared the ABCD subunit **55** using an intramolecular dieneyne Diels-Alder strategy (Scheme 16).[10n] Aldol addition of the lithium enolate of **50** to 2,4,5-trimethoxybenzaldehyde (**51**) furnished enone **52**. Straightforward functional group interconversion (FGI) provided aldehyde **53**. Final assembly of the dieneyne **54** was achieved by addition of lithium trimethylsilylacetylide

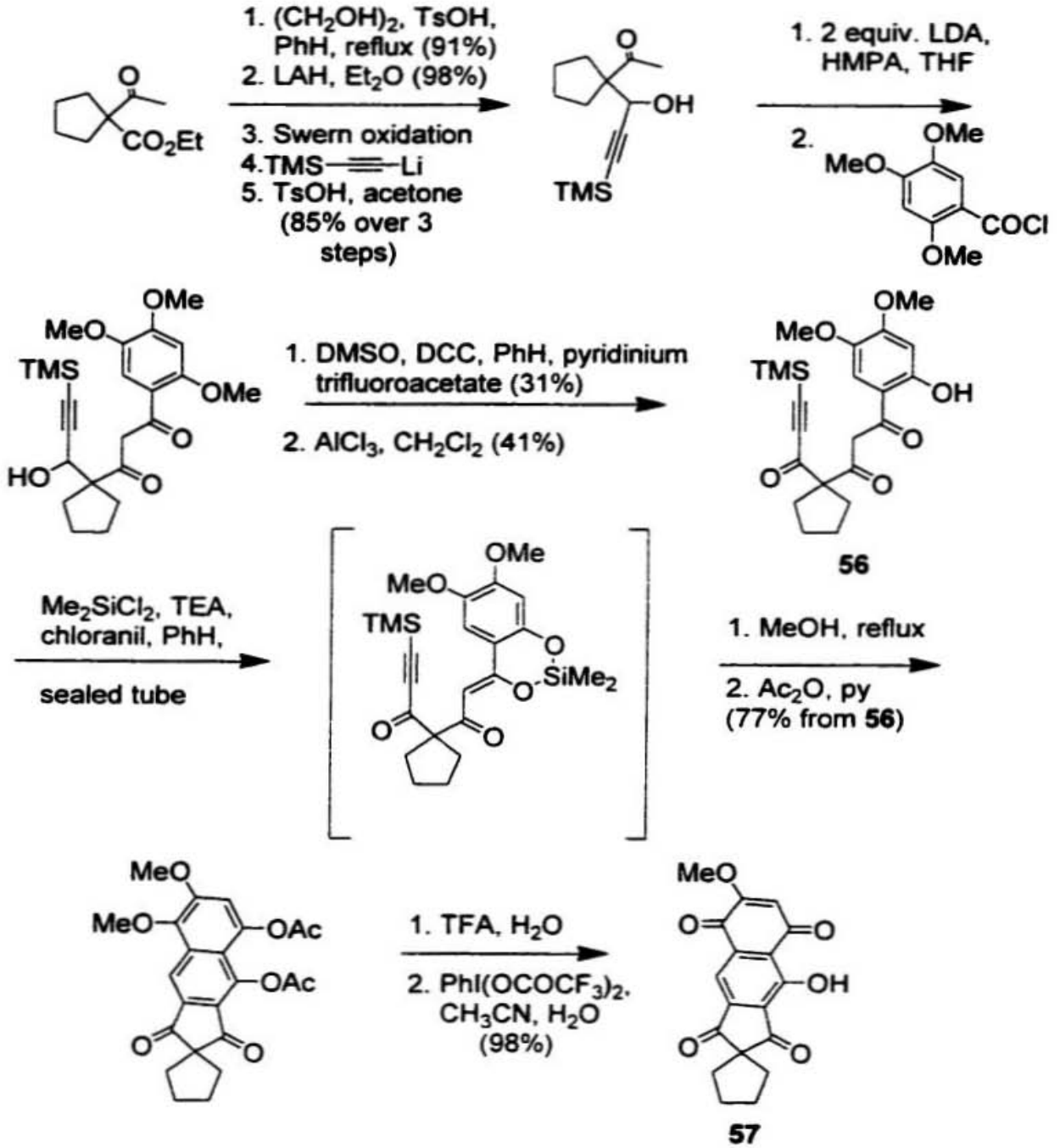
to **53** followed by oxidation of the resulting propargylic alcohol with MnO_2. Heating **54** in a sealed tube initiated a highly efficient intramolecular [4 + 2] cycloaddition leading to **55** in quantitative yield.

Scheme 16

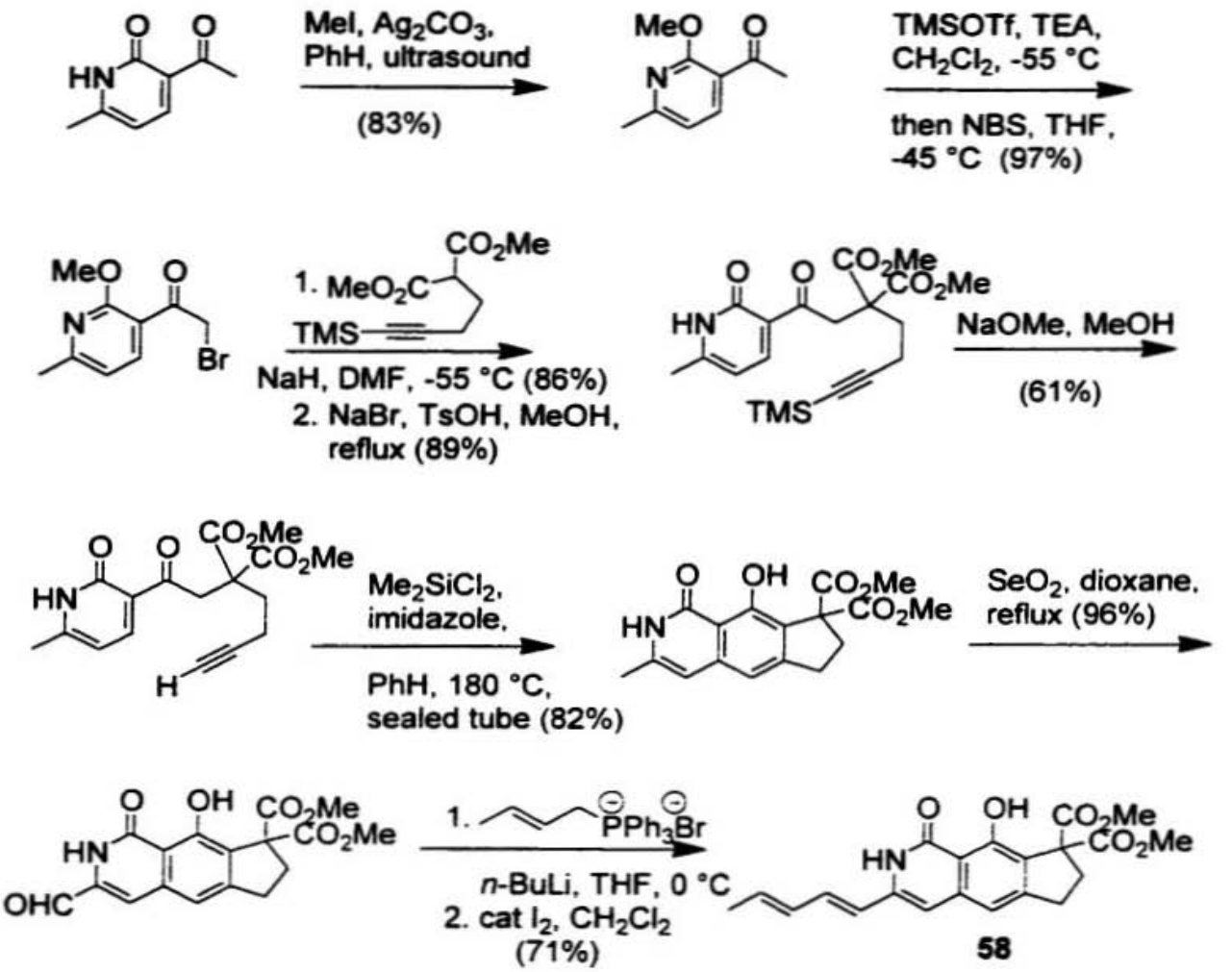


Unfortunately, Kita[10o] later reported that the B ring trimethylsilyl (TMS) group of **55** could not be converted into the required phenol under a variety of conditions. A modification of this strategy (Scheme 17) overcomes this difficulty, however the B ring of **57** is still lacking an oxygen that is found in **1**, and there are several disappointing yields in the route, including an oxidation of the propargylic alcohol (31%) and regioselective demethylation (41%) to yield **56**. Kita applied a similar approach for the assembly of fully functionalized DEF fragment **58** (Scheme 18).[10p]

Scheme 17

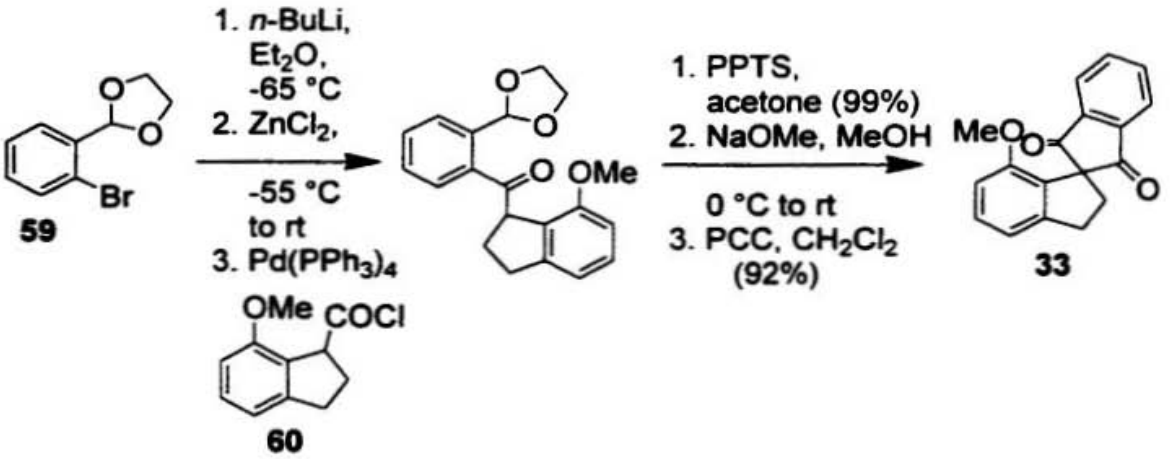

1. $(CH_2OH)_2$, TsOH, PhH, reflux (91%)
2. LAH, Et_2O (98%)
3. Swern oxidation
4. TMS—≡—Li
5. TsOH, acetone (85% over 3 steps)
1. 2 equiv. LDA, HMPA, THF
2.
1. DMSO, DCC, PhH, pyridinium trifluoroacetate (31%)
2. $AlCl_3$, CH_2Cl_2 (41%)
56
Me_2SiCl_2, TEA, chloranil, PhH,
sealed tube
1. MeOH, reflux
2. Ac_2O, py
(77% from 56)
1. TFA, H_2O
2. $PhI(OCOCF_3)_2$, CH_3CN, H_2O
(98%)
57

Scheme 18



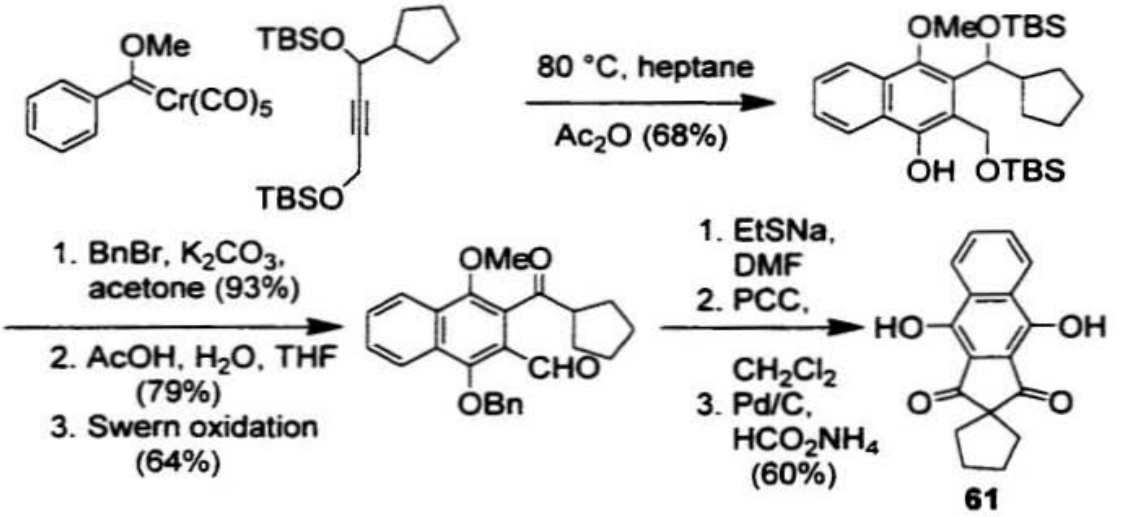
Andrew Evans[10q] assembled the BCDE fragment **33** using an aldol strategy similar to those previously discussed (Scheme 19). Union of B and DE ring synthons **59** and **60** was accomplished using a modified Negishi palladium-catalyzed cross-coupling.

Scheme 19

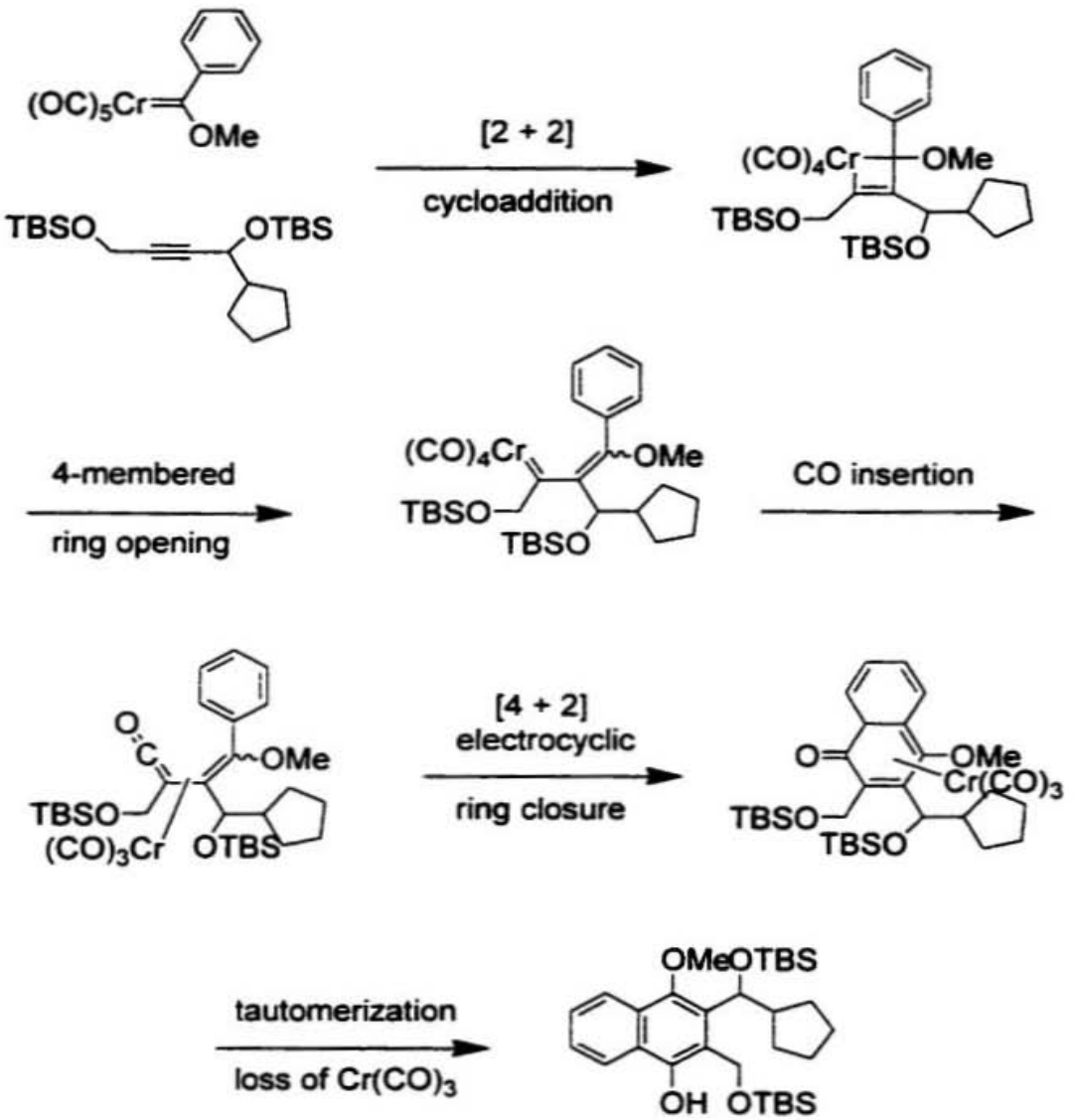


Boger's[10r] synthesis of model ABCD fragment **61** (Scheme 20a) employed an intermolecular alkyne-chromium carbene complex benzannelation (Scheme 20b). Final assembly of the CD spiro link was also accomplished in this instance *via* an intramolecular aldol reaction. Boger's total synthesis of **1** (29 steps) is outlined in Schemes 20c-e.[16]

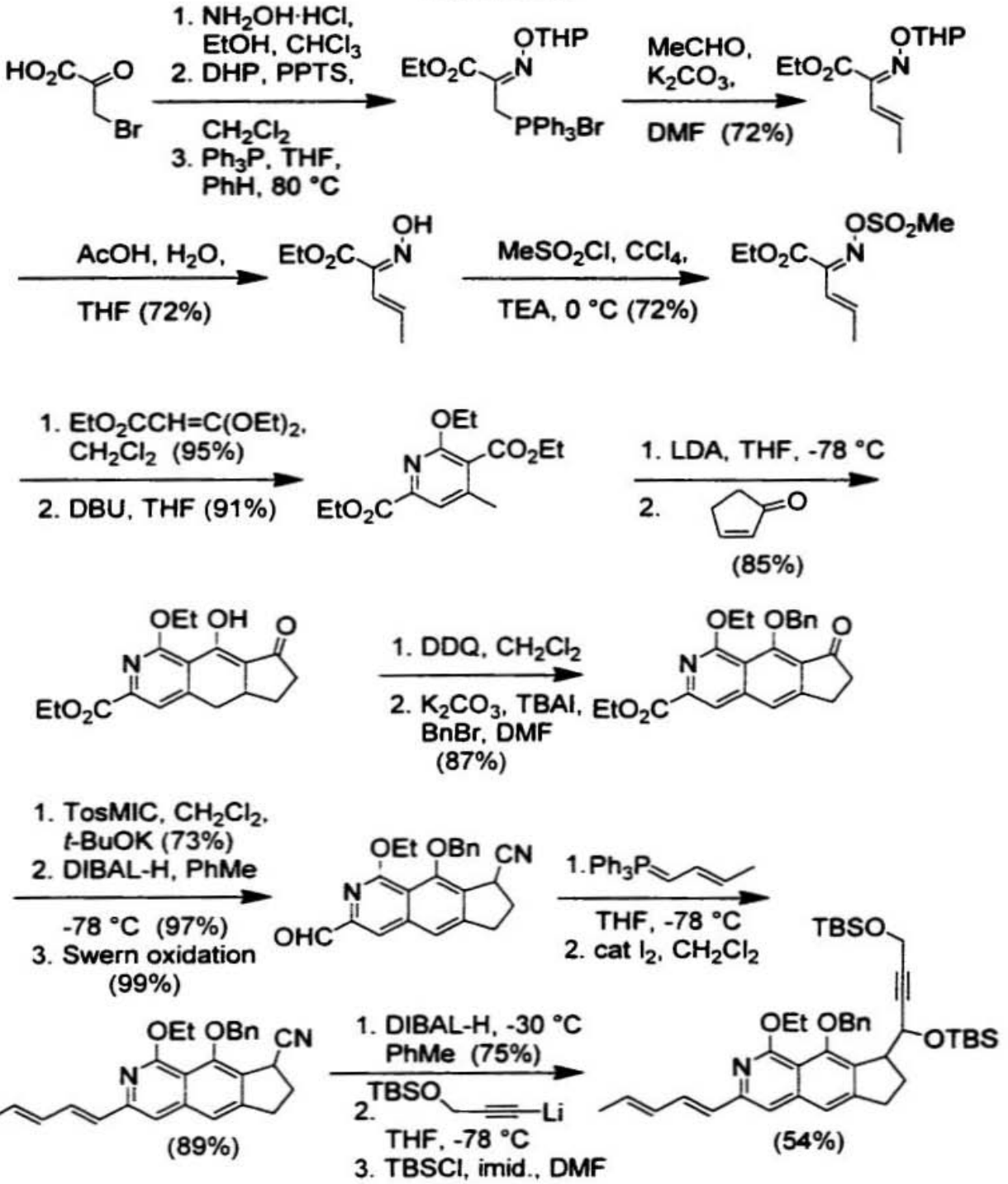
Scheme 20a



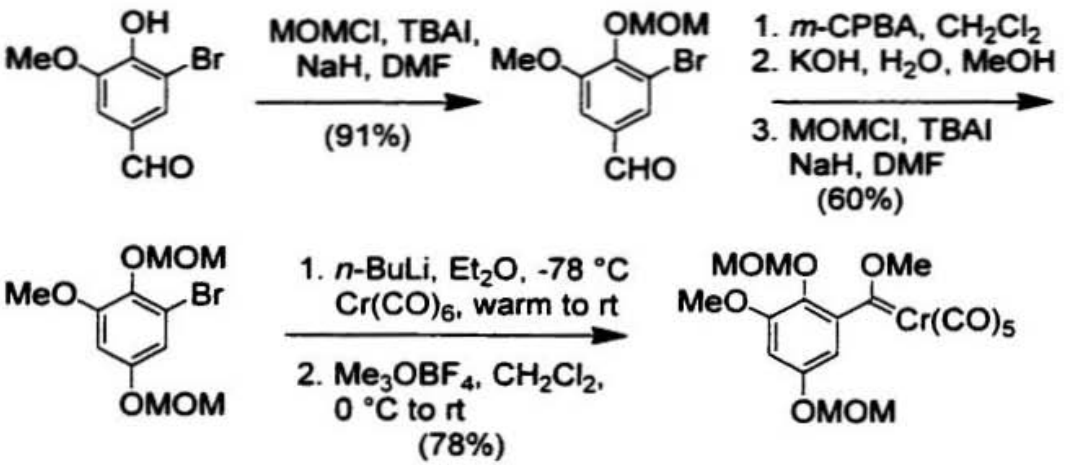
Scheme 20b. Alkyne-Chromium Carbene Complex Benzannellation



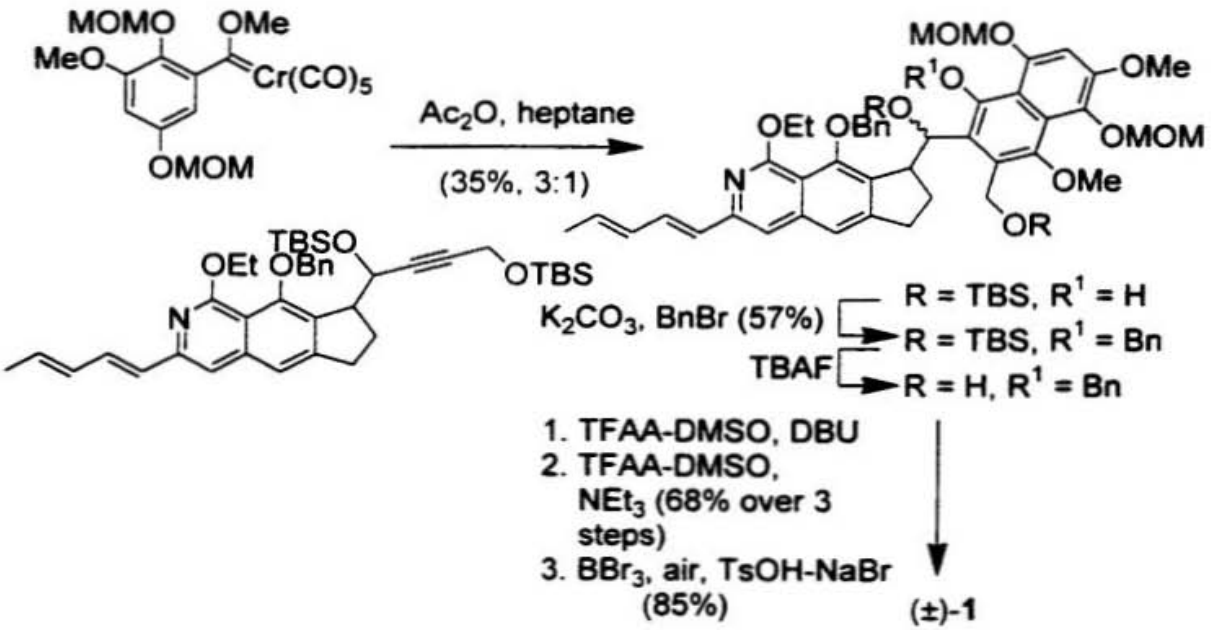
Scheme 20c


1. $NH_2OH{\cdot}HCl$, EtOH, $CHCl_3$
2. DHP, PPTS, CH_2Cl_2
3. Ph_3P, THF, PhH, 80 °C
MeCHO, K_2CO_3, DMF (72%)
AcOH, H_2O, THF (72%)
$MeSO_2Cl$, CCl_4, TEA, 0 °C (72%)
1. $EtO_2CCH{=}C(OEt)_2$, CH_2Cl_2 (95%)
2. DBU, THF (91%)
1. LDA, THF, -78 °C
2.
(85%)
1. DDQ, CH_2Cl_2
2. K_2CO_3, TBAI, BnBr, DMF (87%)
1. TosMIC, CH_2Cl_2, *t*-BuOK (73%)
2. DIBAL-H, PhMe -78 °C (97%)
3. Swern oxidation (99%)
1. $Ph_3P{=}$
THF, -78 °C
2. cat I_2, CH_2Cl_2
1. DIBAL-H, -30 °C PhMe (75%)
2.
THF, -78 °C
3. TBSCl, imid., DMF
(89%)
(54%)

Scheme 20d



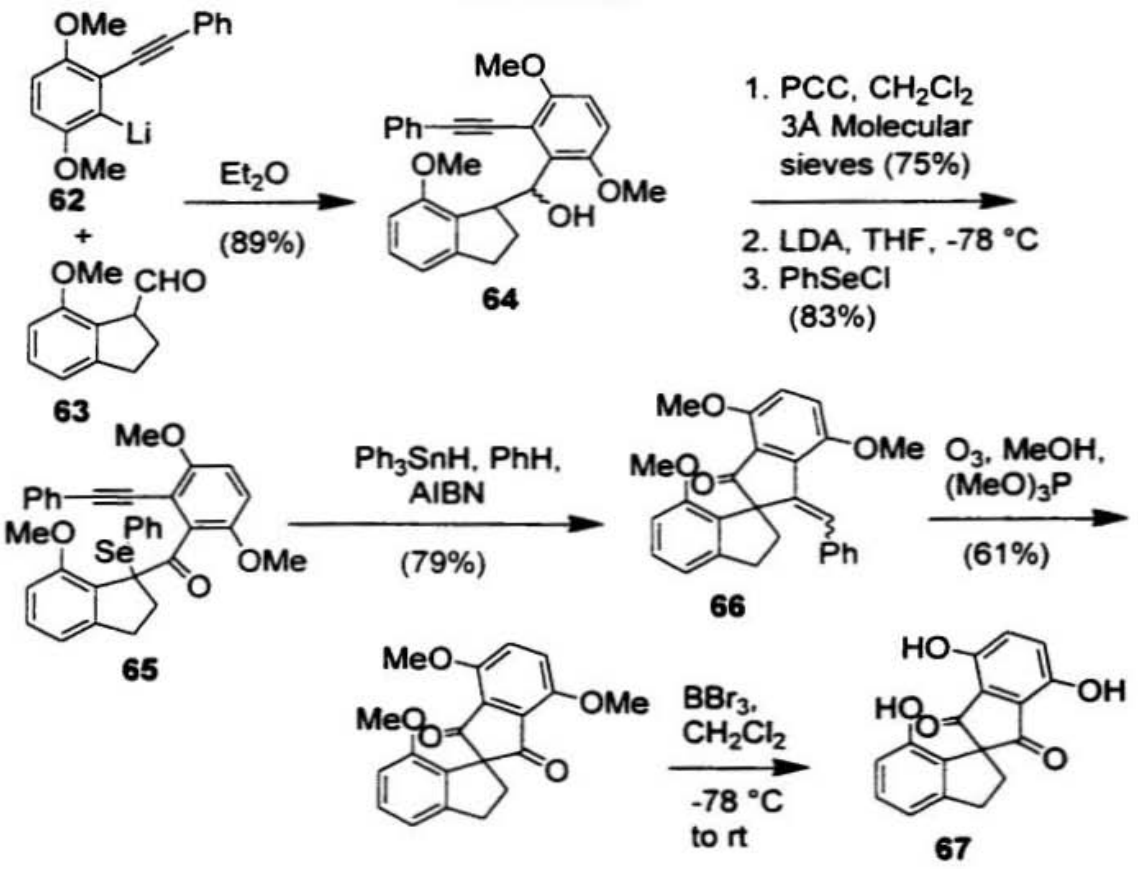
Scheme 20e



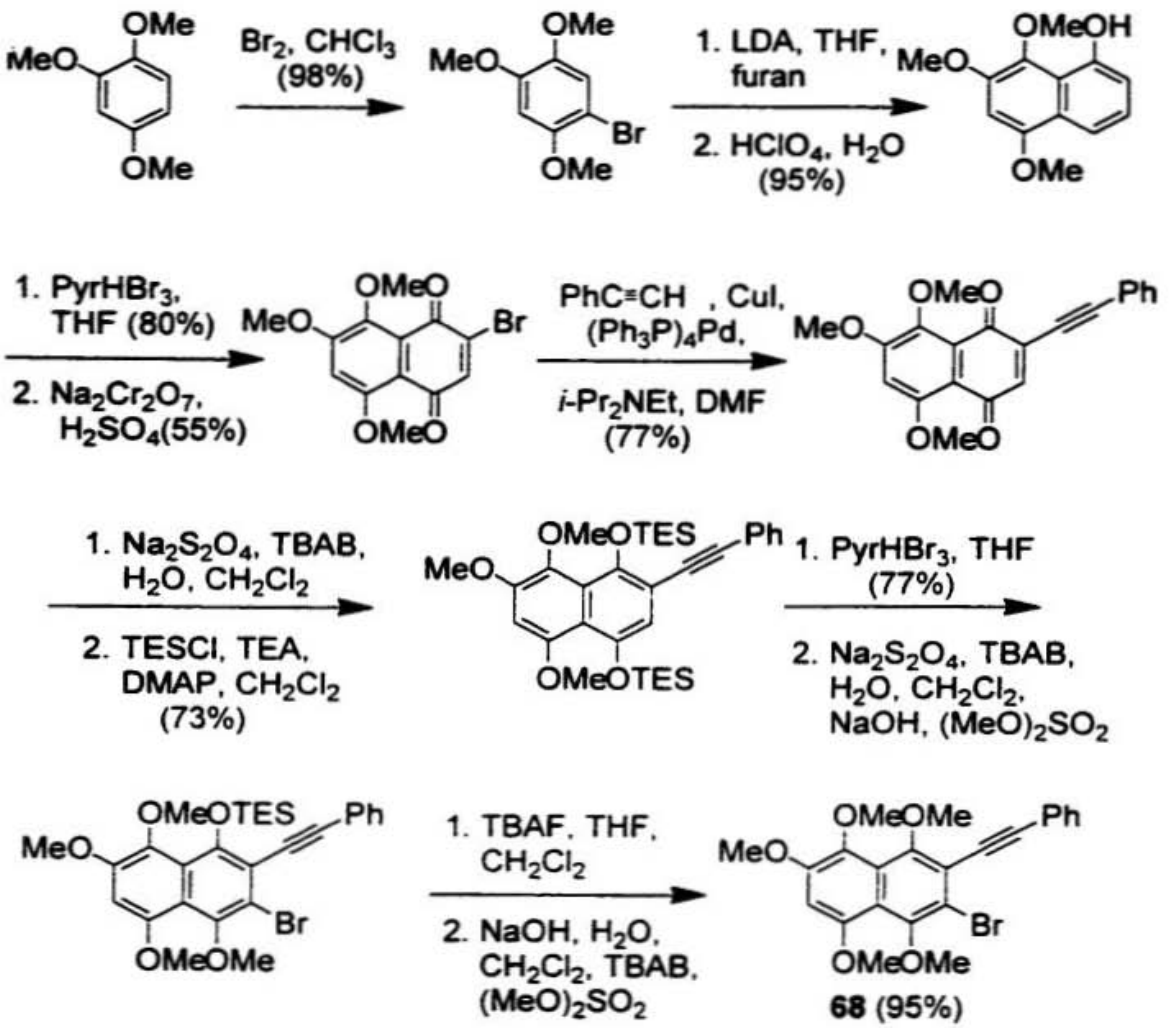
Clive[10s] constructed the spiro linkage present in **66** using a novel radical spirocyclization strategy (Scheme 21a). Nucleophilic addition of aryl lithium **62** to

aldehyde **63** furnished alcohol **64** in 89% yield. Conversion of **64** to organoselenide **65** was achieved by oxidation with PCC followed by treatment of the resulting ketone with LDA and phenylselenyl chloride. Subjection of **65** to triphenyltin hydride/2,2'-azobisisobutyronitrile (AIBN) generated a highly stabilized radical that underwent a favored 5-*exo-dig* cyclization to afford spirocyclized product **66** in satisfactory yield. The double bond in **66** was then cleaved using ozonolysis followed by demethylation with boron tribromide to furnish BCDE core **67**. Clive's total synthesis of **1** (34 steps) is illustrated in Schemes 21b-d.[12]

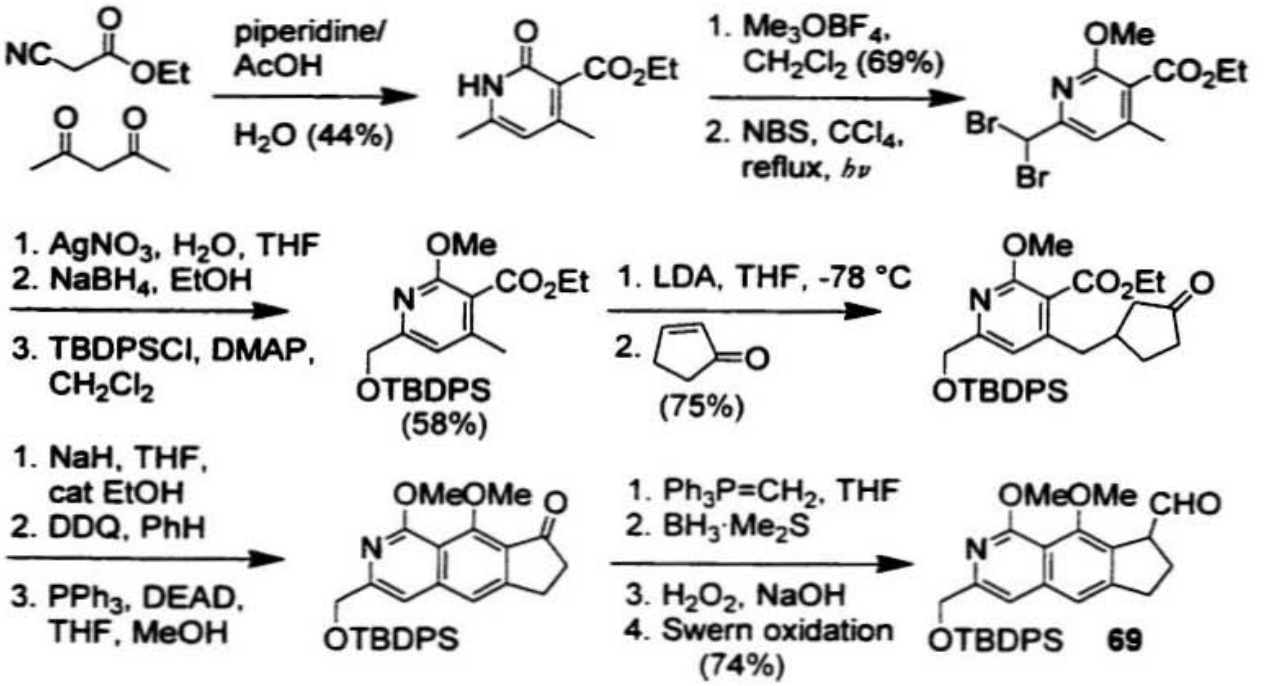
Scheme 21a



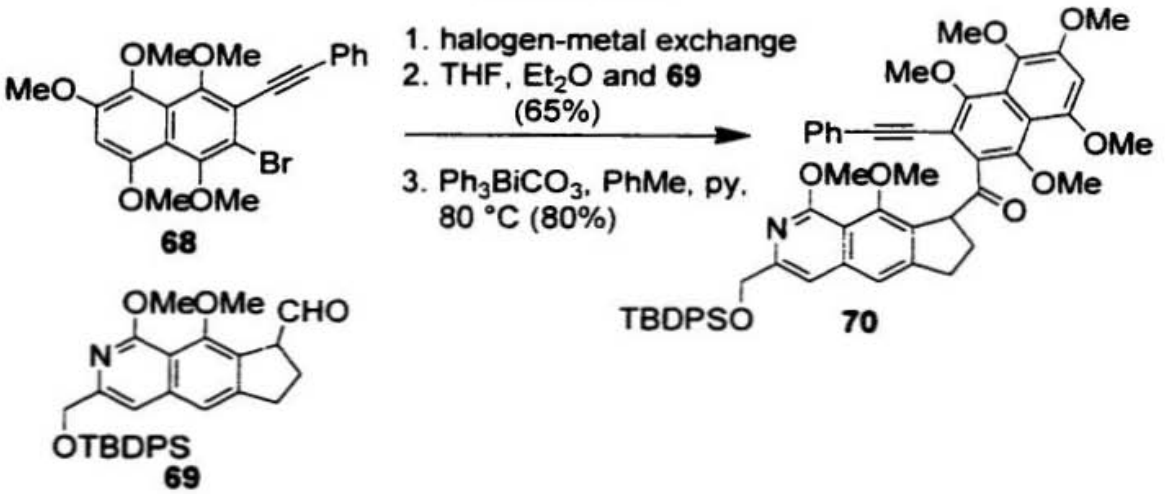
Scheme 21b


OMe
MeO
OMe
Br2, CHCl3
(98%)
Br
1. LDA, THF,
furan
2. HClO4, H2O
(95%)
OMeOH
1. PyrHBr3,
THF (80%)
2. Na2Cr2O7,
H2SO4(55%)
OMeO
PhC≡CH , CuI,
(Ph3P)4Pd,
i-Pr2NEt, DMF
(77%)
Ph
1. Na2S2O4, TBAB,
H2O, CH2Cl2
2. TESCl, TEA,
DMAP, CH2Cl2
(73%)
OMeOTES
1. PyrHBr3, THF
(77%)
2. Na2S2O4, TBAB,
H2O, CH2Cl2,
NaOH, (MeO)2SO2
OMeOMe
1. TBAF, THF,
CH2Cl2
2. NaOH, H2O,
CH2Cl2, TBAB,
(MeO)2SO2
68 (95%)

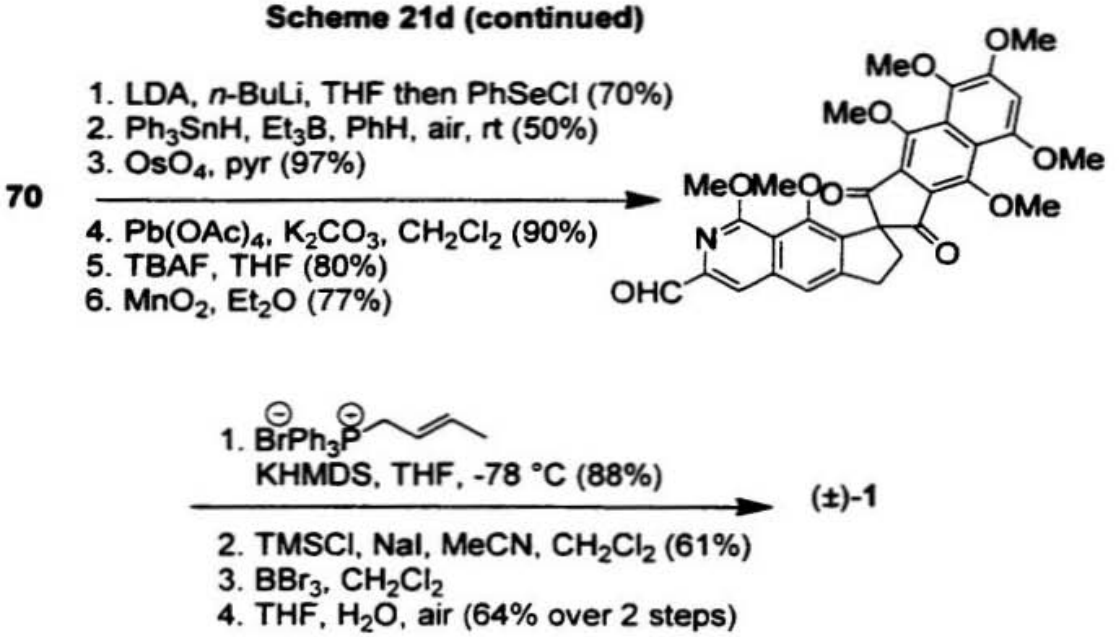
Scheme 21c



Scheme 21d

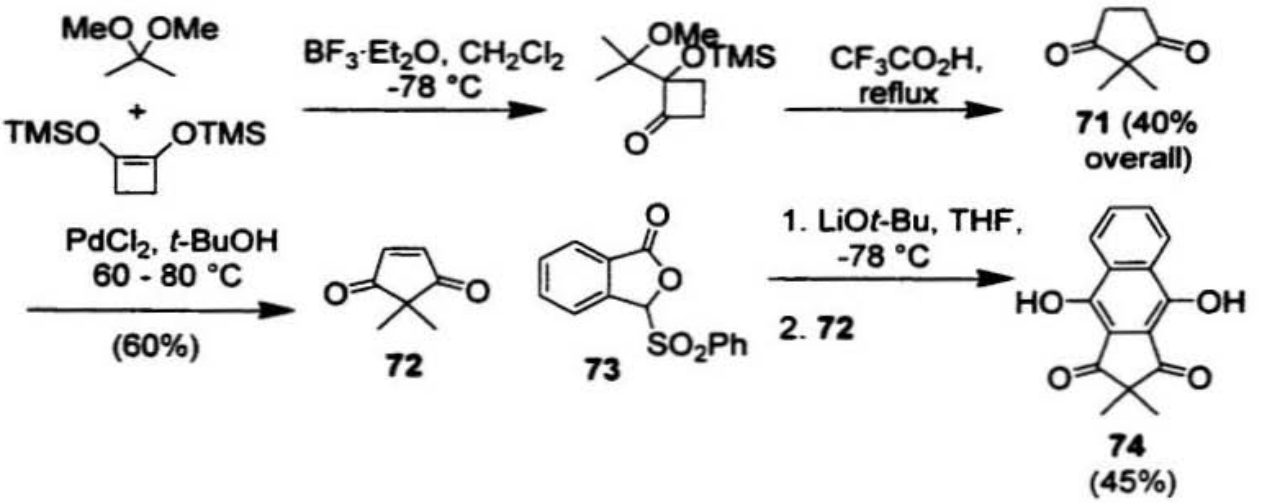


Scheme 21d (continued)



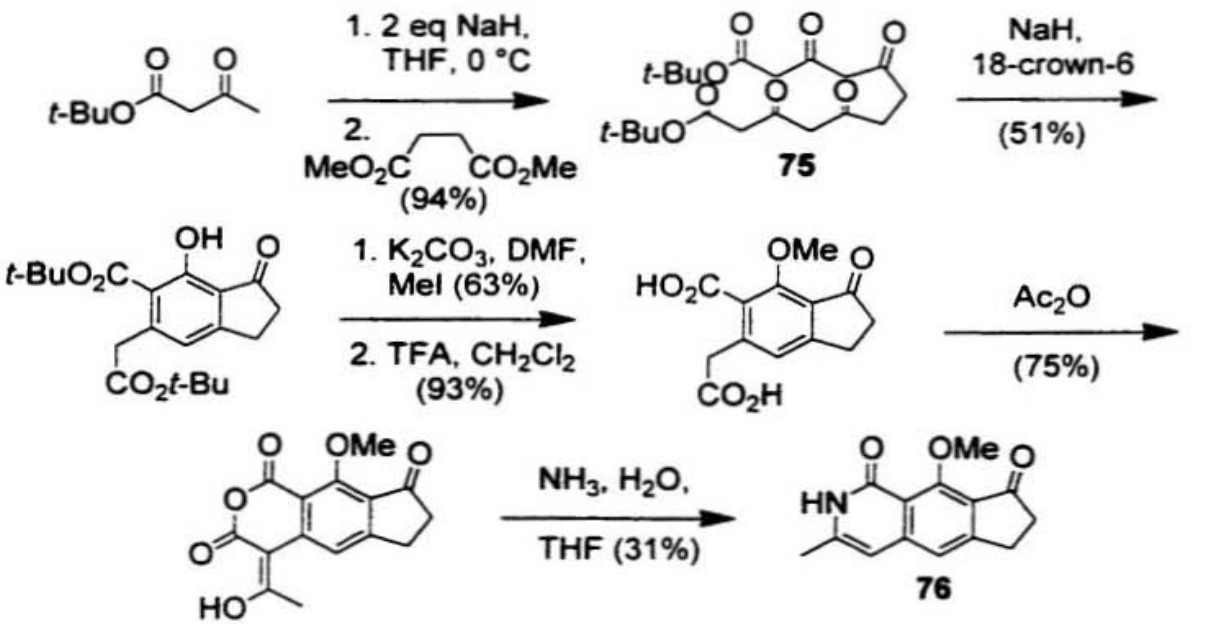
Parker[11t] utilized Kuwajima's geminal acylation methodology[21] to construct the C ring cyclopentane-1,3-dione model **71** (Scheme 22a). Oxidation of **71** provided enedione **72** that served as a Michael acceptor in a reaction with lithiated phthalide sulfone **73**. The B ring cyclization was accomplished by a concurrent intramolecular Dieckmann-type reaction of the resultant enolate onto the carbonyl of the lactone with subsequent aromatization to form **74**, albeit in low yield.

Scheme 22a



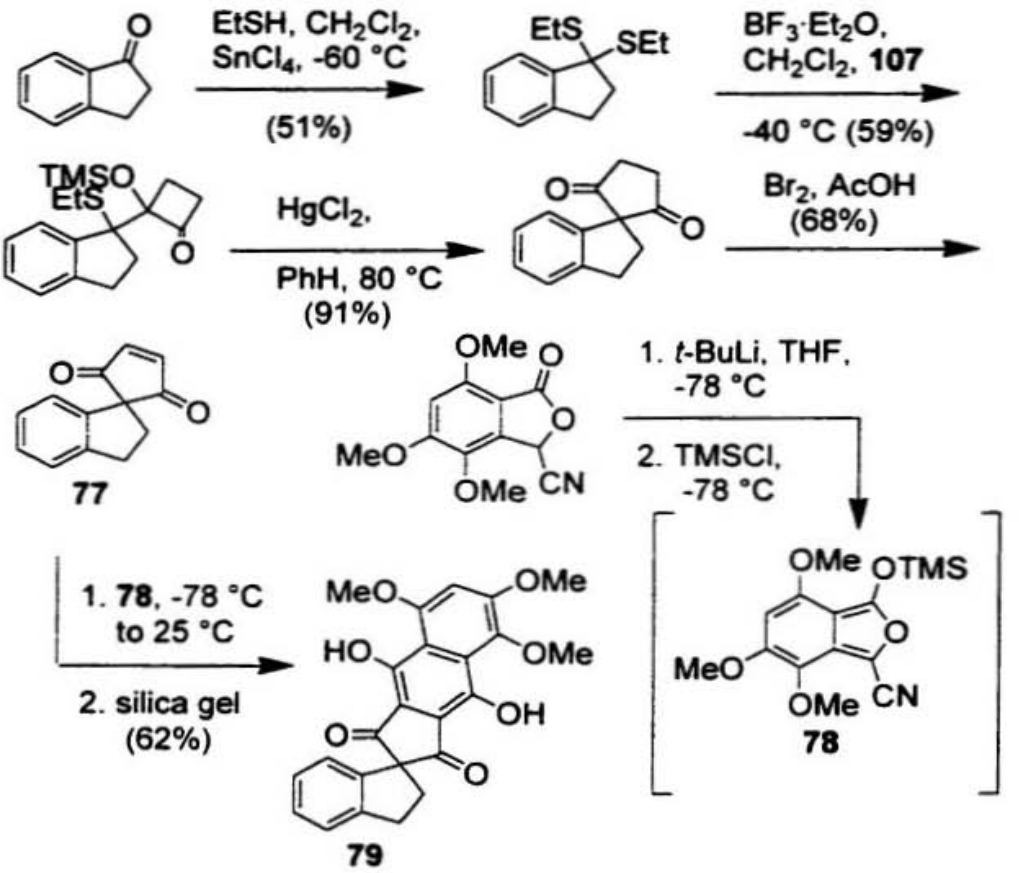
DEF fragment **76** was assembled using a biomimetic cyclization strategy employing polyketide **75** (Scheme 22b).[10u]

Scheme 22b



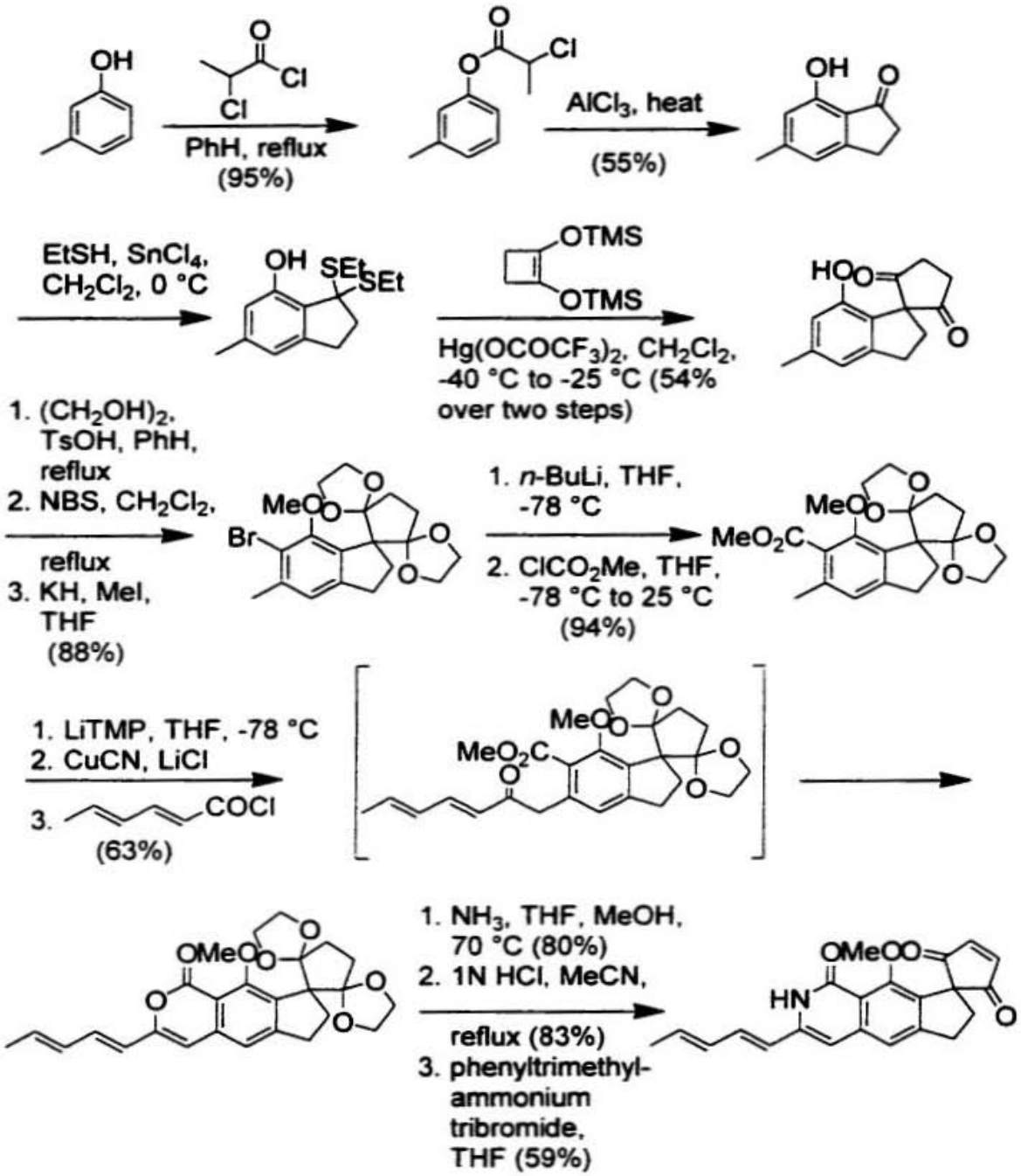
Bach[10v] (Scheme 23a) subsequently published the construction of model compound **79** possessing all requisite oxygen functionality in the ABC subunit using a strategy comparable to Parker's. Assembly of the ABCDE moiety was achieved through a Diels-Alder reaction between enedione **77** and isobenzofuran **78**.[10v]

Scheme 23a

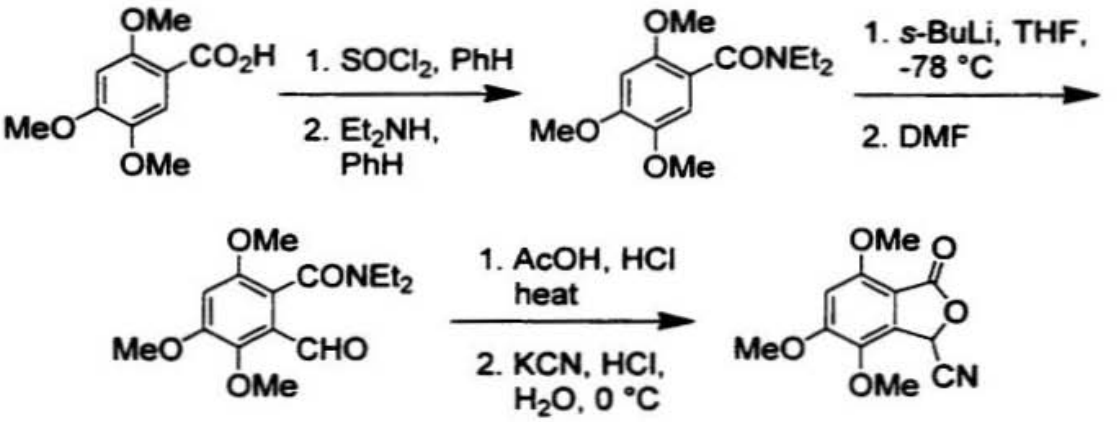


Bach and Julia independently synthesized **1** using similar strategies. Bach's synthesis (19 steps) is illustrated in Schemes 23b-d[15] while Julia's synthesis (18 steps) is outlined in Schemes 24a-c.[13]

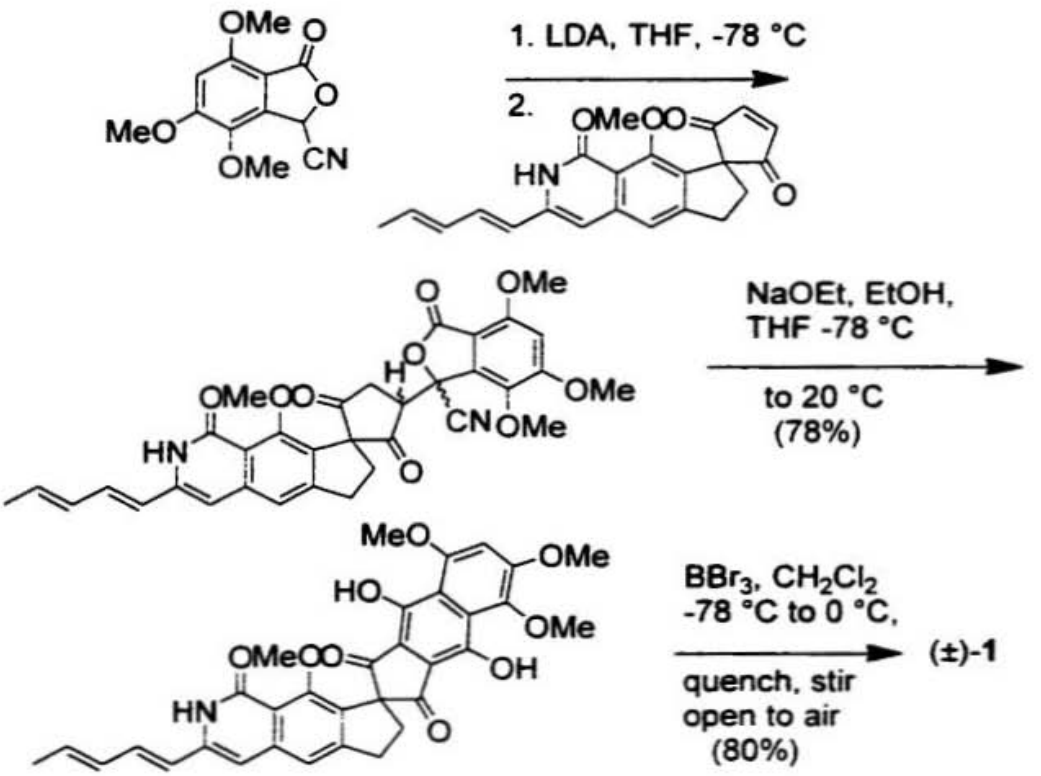
Scheme 23b


PhH, reflux
(95%)
AlCl3, heat
(55%)
EtSH, SnCl4,
CH2Cl2, 0 °C
Hg(OCOCF3)2, CH2Cl2,
-40 °C to -25 °C (54%
over two steps)
1. (CH2OH)2,
TsOH, PhH,
reflux
2. NBS, CH2Cl2,
reflux
3. KH, MeI,
THF
(88%)
1. n-BuLi, THF,
-78 °C
2. ClCO2Me, THF,
-78 °C to 25 °C
(94%)
1. LiTMP, THF, -78 °C
2. CuCN, LiCl
3.
(63%)
1. NH3, THF, MeOH,
70 °C (80%)
2. 1N HCl, MeCN,
reflux (83%)
3. phenyltrimethyl-
ammonium
tribromide,
THF (59%)

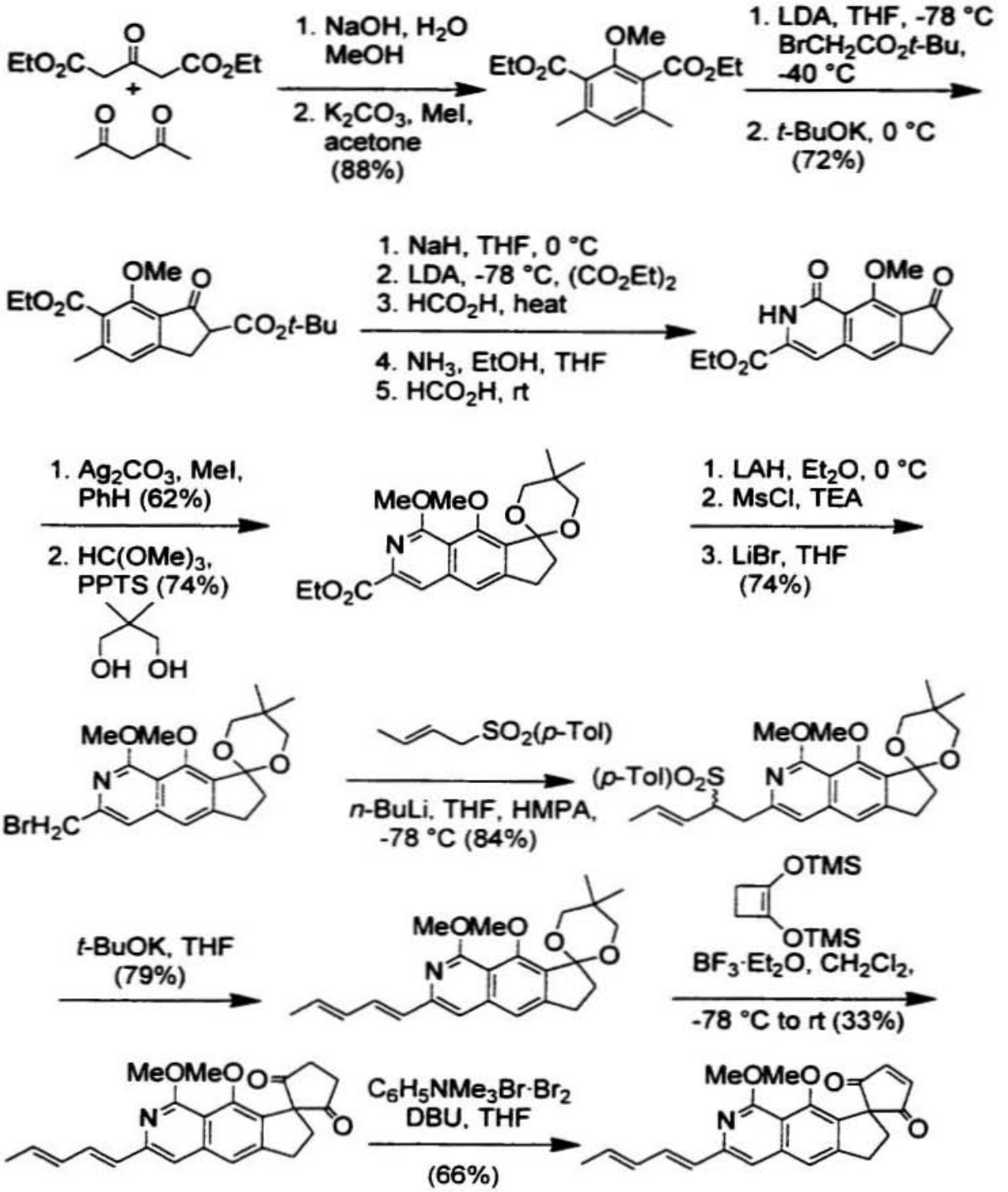
Scheme 23c



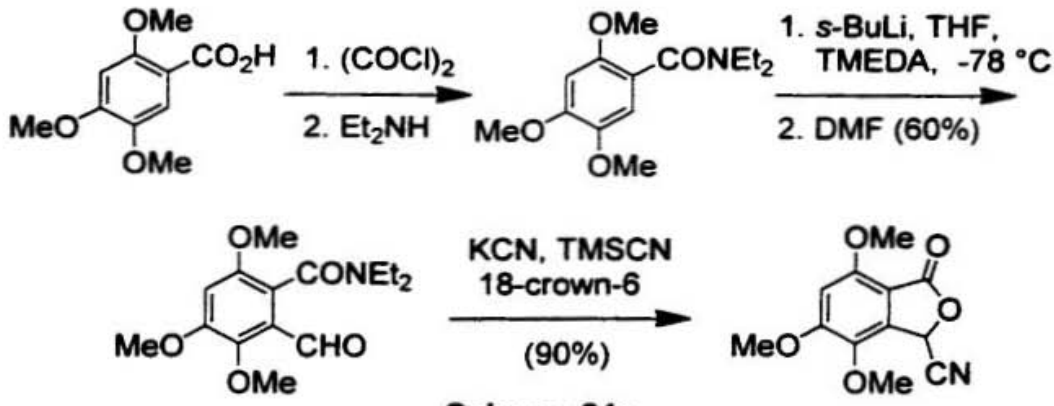
Scheme 23d



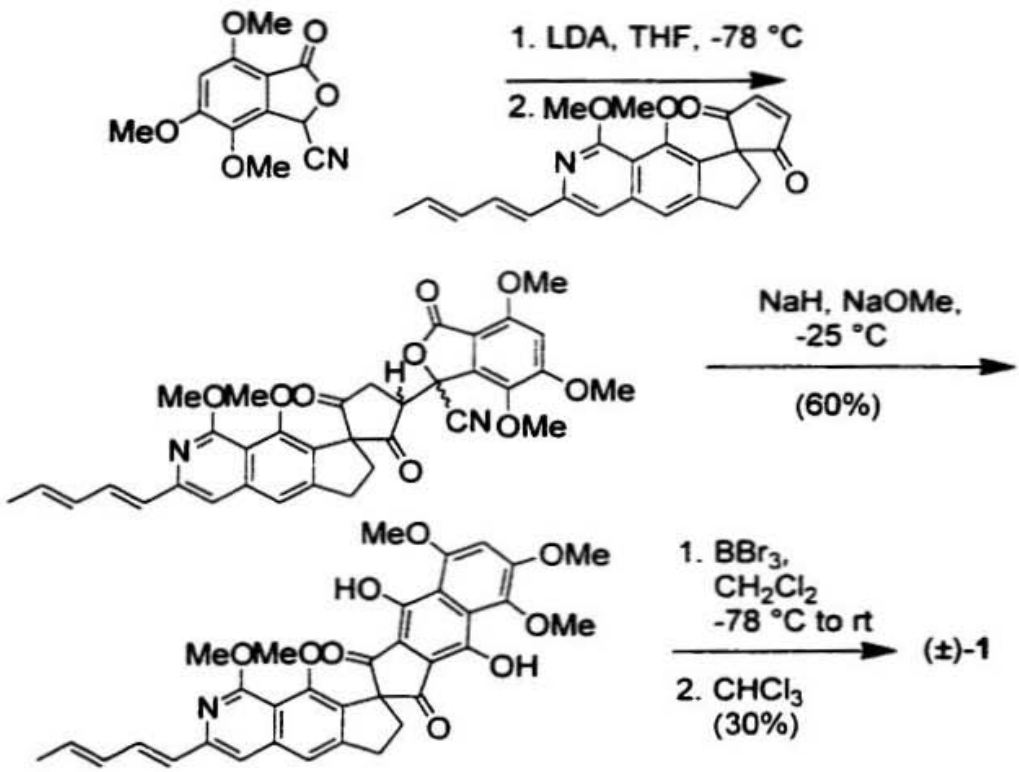
Scheme 24a


1. NaOH, H2O
MeOH
2. K2CO3, MeI,
acetone
(88%)
1. LDA, THF, -78 °C
BrCH2CO2t-Bu,
-40 °C
2. t-BuOK, 0 °C
(72%)
1. NaH, THF, 0 °C
2. LDA, -78 °C, (CO2Et)2
3. HCO2H, heat
4. NH3, EtOH, THF
5. HCO2H, rt
1. Ag2CO3, MeI,
PhH (62%)
2. HC(OMe)3,
PPTS (74%)
1. LAH, Et2O, 0 °C
2. MsCl, TEA
3. LiBr, THF
(74%)
n-BuLi, THF, HMPA,
-78 °C (84%)
t-BuOK, THF
(79%)
BF3·Et2O, CH2Cl2,
-78 °C to rt (33%)
C6H5NMe3Br·Br2
DBU, THF
(66%)

Scheme 24b



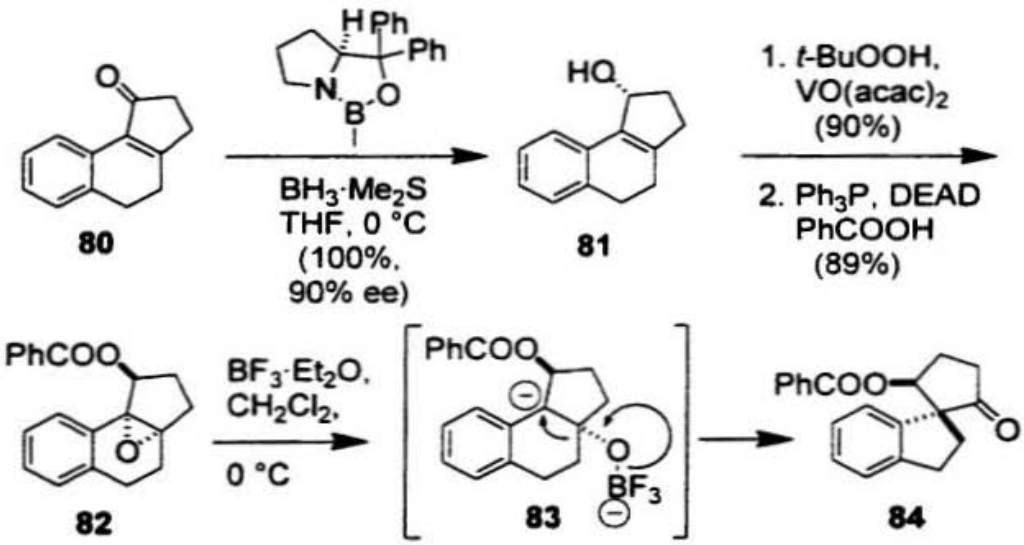
Scheme 24c



Kita[10w] accomplished the synthesis of the CDE subunit of **1** in enantiomerically pure form *via* $BF_3{\cdot}Et_2O$ catalyzed rearrangement of *trans*-α,β-epoxyacylate **82** (Scheme

25a). Enantioselective reduction of enone **80** with Corey's oxazaborolidine furnished allylic alcohol **81**. The hydroxyl group then directed epoxidation (*t*-BuOOH/$VO(acac)_2$) and was subsequently inverted employing the Mitsunobu reaction to give *trans*-α,β-epoxyacylate **82**. Stirring **82** in dichloromethane with one equivalent of $BF_3 \cdot Et_2O$ resulted in an advantageous stereospecific rearrangement, seemingly *via* **83**, to yield **84** in 90% ee. Use of (1*S*)-(-)-camphanic acid in the Mitsunobu protocol followed by recrystallization of the α,β-epoxyacylate prior to the rearrangment raised the ee up to 100%.

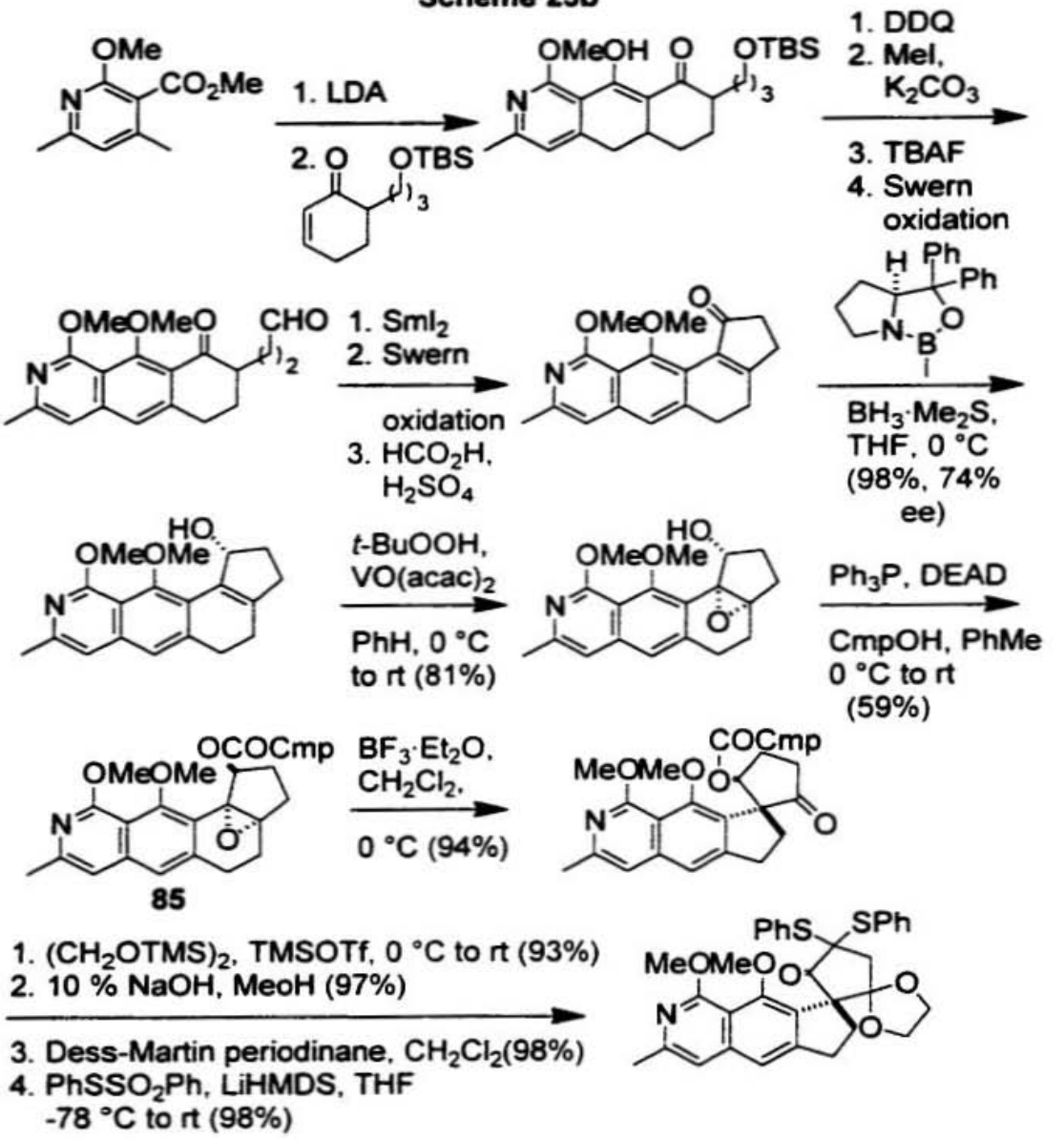
Scheme 25a



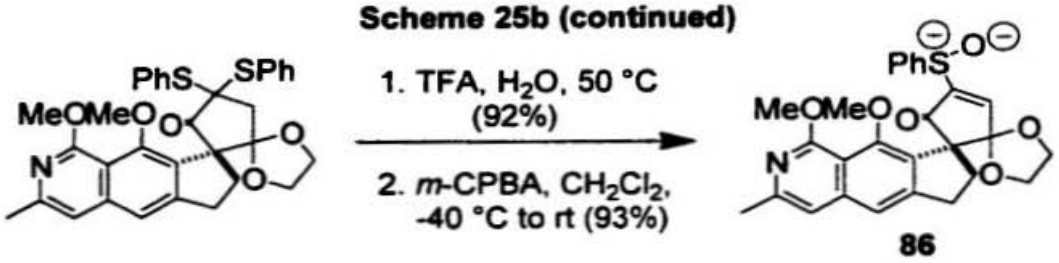
In 1999, Kita reported the first enantioselective synthesis of **1** (34 steps) through a [4 + 2] cycloaddition between ester **88** and enone **86** (Schemes 25b-e).[17] Both natural and *ent*-**1** were synthesized in parallel synthetic runs using regioisomers **87a** and **87b**. On the basis of the absolute stereochemistry of **86** (from X-ray structure of **85**) and the predicted regiochemical course of the [4 + 2] cycloaddition, the configuration of the

stereogenic center in **1** was ascertained to be *S* by comparison of the circular dichroism (CD) spectrum with that of natural Fredericamycin A.

Scheme 25b

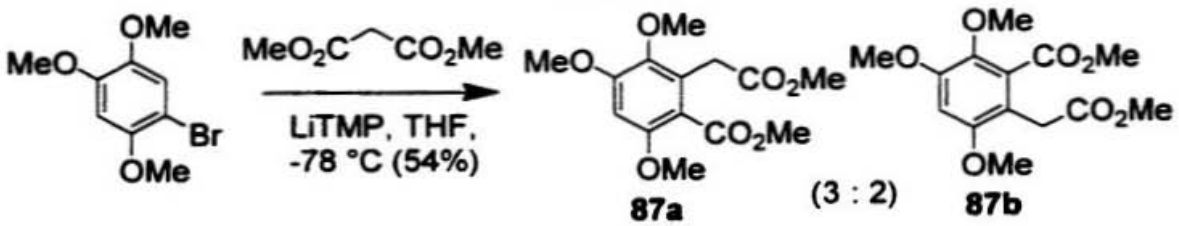


Scheme 25b (continued)



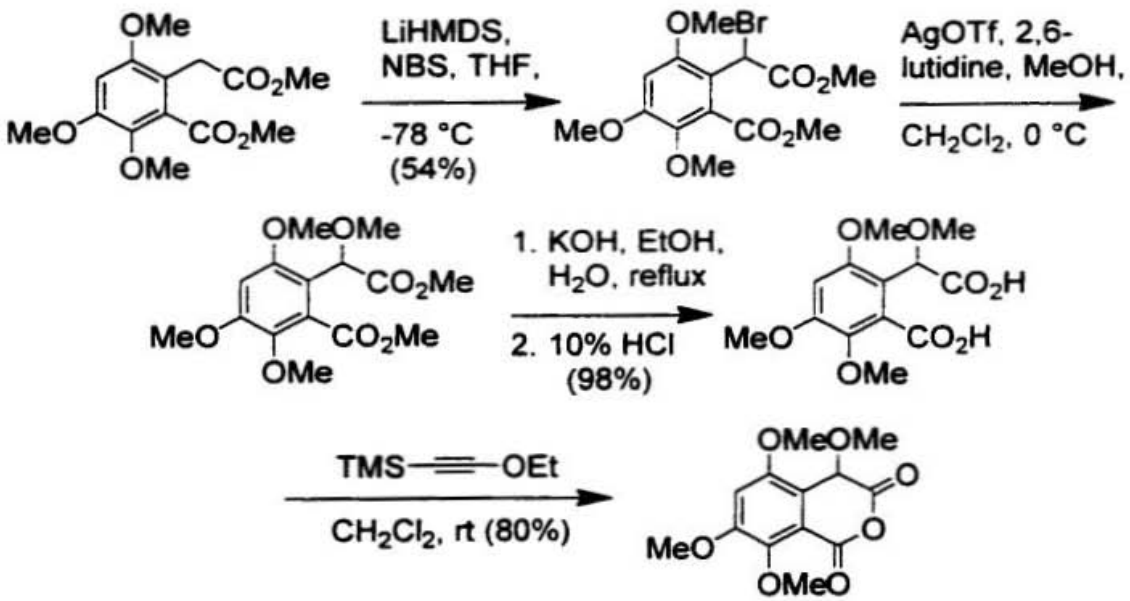
86

Scheme 25c

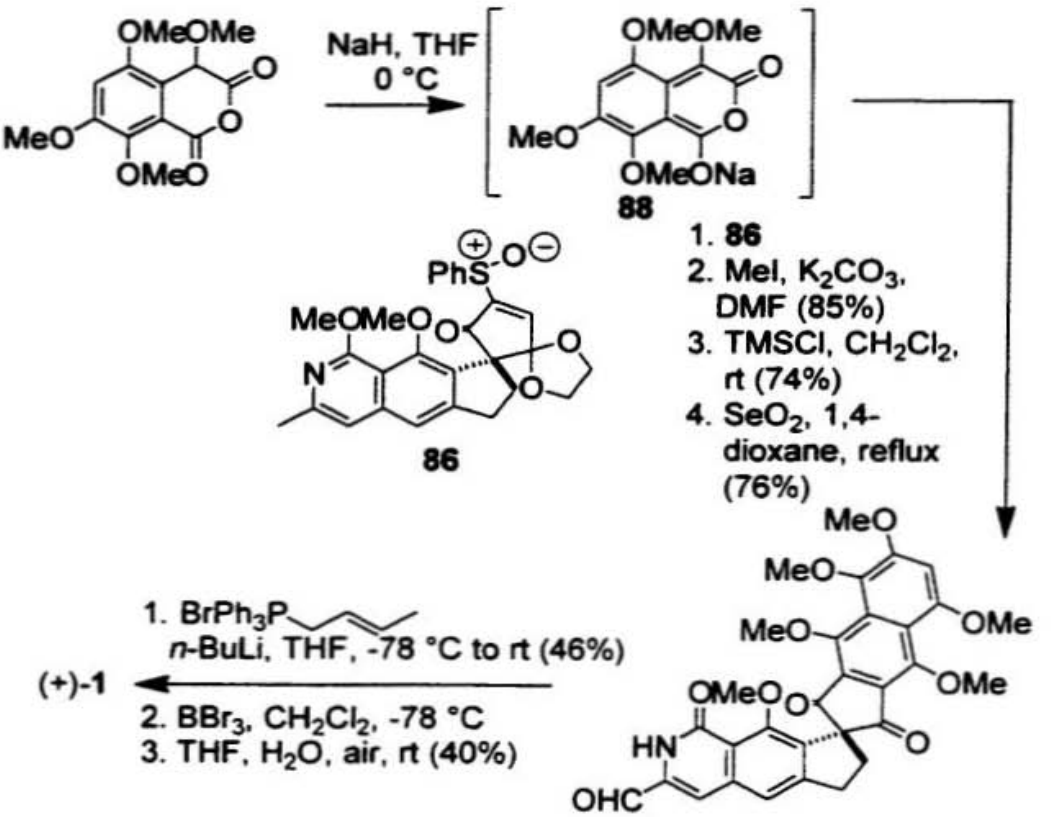


87a (3 : 2) **87b**

Scheme 25d



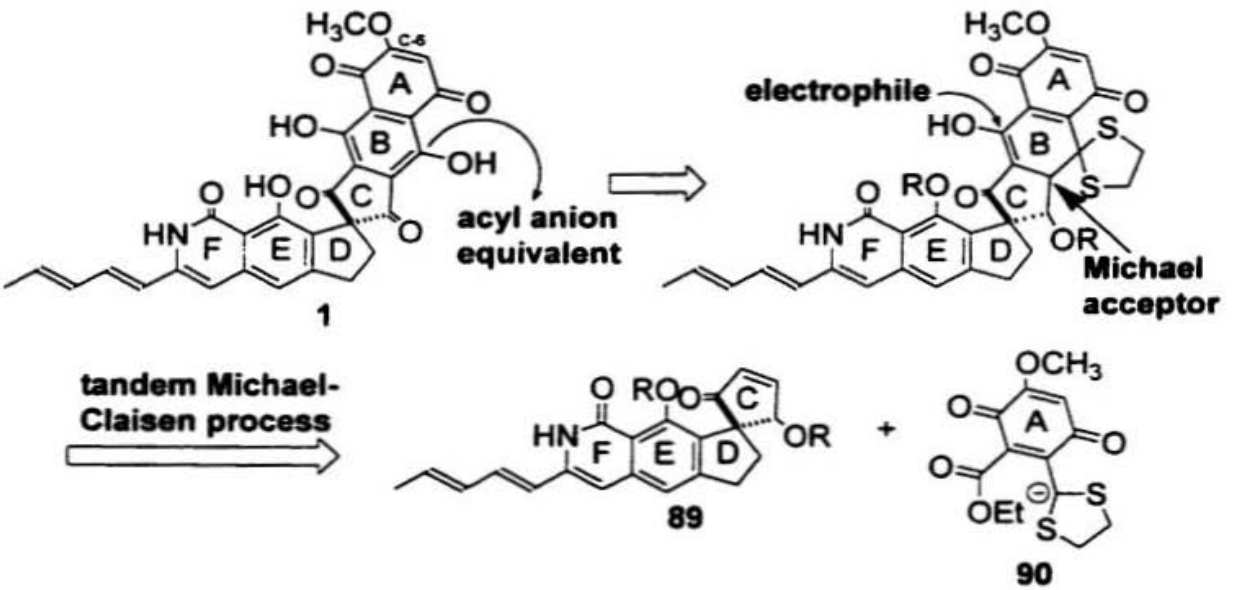
Scheme 25e


OMeOMe
MeO
OMeO
NaH, THF
0 °C
OMeOMe
MeO
OMeONa
88
1. 86
2. MeI, K2CO3, DMF (85%)
3. TMSCl, CH2Cl2, rt (74%)
4. SeO2, 1,4-dioxane, reflux (76%)
PhS
MeOMeO
N
86
MeO
MeO
MeO
OMe
OMe
OMeO
HN
OHC
1. BrPh3P
n-BuLi, THF, -78 °C to rt (46%)
(+)-1
2. BBr3, CH2Cl2, -78 °C
3. THF, H2O, air, rt (40%)

Retrosynthetic Analysis

Fredericamycin A (**1**) poses a significant challenge to the synthetic organic chemist because of its highly oxygenated ring system and the quaternary spiro center that is stereogenic due to the distal methoxyl at C-6. We rationalized that a convergent synthesis would be the most expedient approach to the synthesis of **1**, making a major retrosynthetic scission in **1** (Scheme 26a) resulting in CDEF synthon **89** and A ring synthon **90** that would be annulated using a tandem Michael-Claisen process.[22]

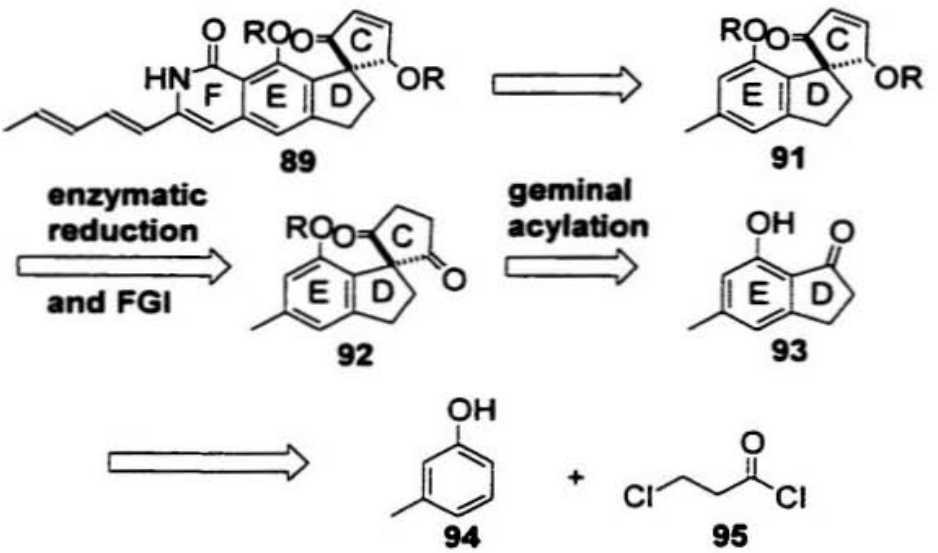
Scheme 26a



The CDEF subunit **89** could be simplified (Scheme 26b) to CDE subunit **91** possessing a methyl group *meta* to the E ring hydroxyl group that would serve as a "handle" to assist in the introduction of the F ring. Foremost in our strategy was the enzymatic monoreduction of **92** to furnish enantiomerically pure **91**.[19] It mattered little which enantiomer was obtained, as long as the reduction was highly enantioselective since the A

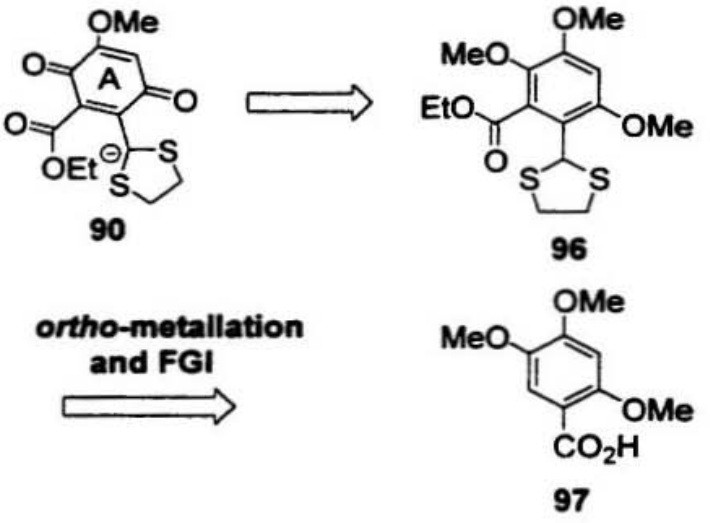
ring synthon could be modified to give either natural or the *ent*-form of **1**. Spirodiketone **92** would be synthesized employing geminal acylation methodology from our laboratories[18] on compound **93**, which might be assembled from the readily available starting materials *m*-cresol **94** and 3-chloropropionyl chloride **95** using a known procedure.[23]

Scheme 26b



As for the A ring synthon **90**, it seemed reasonable that it would be derived from aromatic precursor **96** that would be constructed *via* a relatively short synthetic pathway from the commercially available 2,4,5-trimethoxybenzoic acid **97** (Scheme 26c).

Scheme 26c



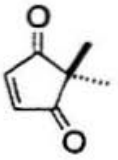
However, before carrying out the synthesis with the aforementioned substrates, some model studies to assess the effectiveness of (i) the enzymatic reduction and (ii) the tandem Michael-Claisen process on this system were in order.

Model Studies

Early Diels-Alder Reaction Investigations

While we eventually settled on the tandem Michael-Claisen process for the construction of the ABC subunit of **1**, early studies into the assembly of the Fredericamycin A skeleton centered around the Diels-Alder reaction.[24] The prevalence of six-membered rings in **1** dictated further investigation into the possibility of employing the Diels-Alder reaction for the synthesis of **1**.

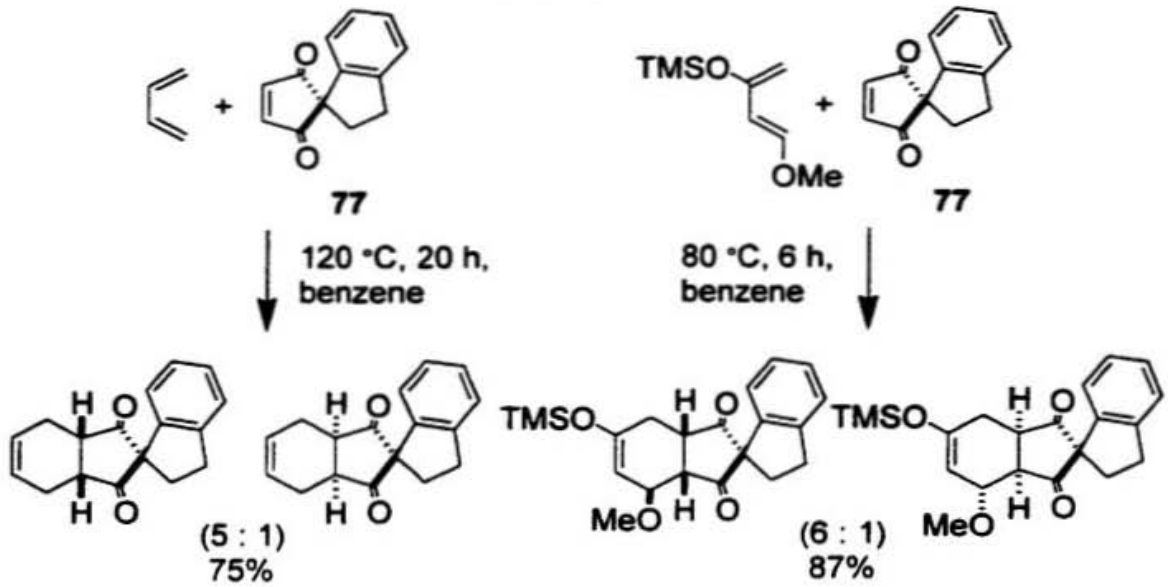
Seemingly contradictory evidence exists in the literature pertaining to the Diels-Alder reaction of spirocyclic enediones. Whilst Agosta and Smith[25] reported that **98** is a relatively sluggish dienophile as a result of steric interactions encountered in the *endo* transition mode, Bach and co-workers[10v] found that when spirocyclic enedione **77** was heated in the presence of either 1,3-butadiene or Danishefsky's diene, adducts were formed in excellent yield (Scheme 27).



98

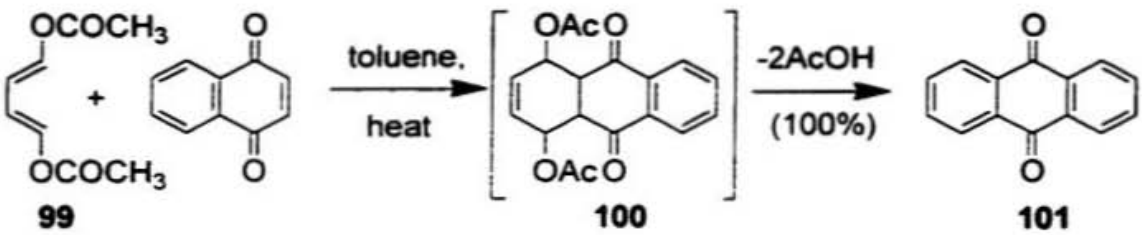
These adducts formed despite the fact that enediones are known to be poor dienophiles in the thermal Diels-Alder reaction,[26] although Lewis acids do improve their reactivity.[27] The facial selectivity in the reactions of **77** suggests that the phenyl ring is a more sterically demanding substituent than the methylene.

Scheme 27

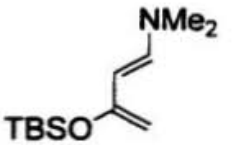


For our model studies, we choose (*E,E*)-1,4-diacetoxy-1,3-butadiene (**99**) as the diene as it possessed the requisite oxygen functionality found in **1**. Although **99** reacted with 1,4-naphthoquinone to yield **100**, this adduct could not be isolated as it readily eliminated two equivalents of acetic acid to yield anthraquinone **101** quantitatively (Scheme 28).

Scheme 28



Diene **99** was also heated under reflux in toluene in the presence of spirocyclic enedione **77**, yet no adduct was observed. This reaction was also attempted under Lewis acid catalysis conditions ($AlCl_3$, $SnCl_4$, $TiCl_4$), and no adduct was observed in these instances, either. It should be noted that the reaction of **77** with both Danishefsky's diene and the more reactive dimethylamino analogue of Danishefsky's diene **102**,[28] in our hands, did not furnish any of the desired adduct.

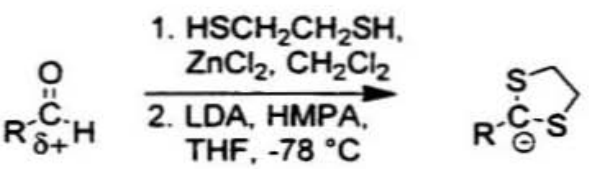


102

Preliminary Studies Employing a Tandem Michael-Aldol Strategy

Our annulation strategy was based on the utilization of an acyl anion equivalent, which may be referred to as "Umpolung" – a German term for a reversal of polarity. Essentially, an aldehyde, in which the carbon possesses a partial positive charge, undergoes a chemical transformation such that the hydrogen on that carbon is then relatively acidic, and can be removed using a strong base to make that carbon anionic in character (Scheme 29).[29]

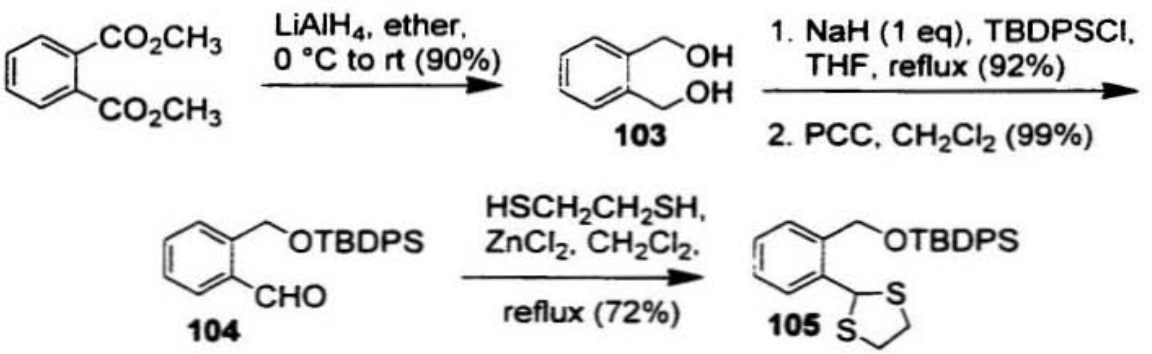
Scheme 29



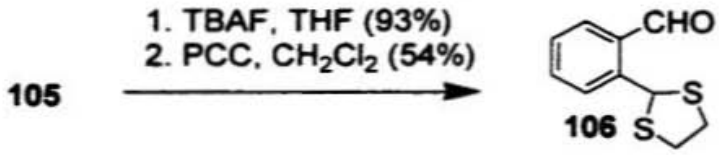
Rather than synthesize the complex A ring synthon **96**, we believed that it would be prudent to focus first our efforts on a synthesis of a less substituted molecule such as **106** that still possessed the essential functionality in a dithiolane and an electrophilic group in an *ortho* relationship.

The relatively cheap starting material dimethyl phthalate was reduced to 1,2-benzenedimethanol **103** using lithium aluminum hydride in 90% yield. Monoprotection of **103** was achieved in 92% yield using NaH and *tert*-butyldiphenylsilyl chloride (TBDPSCl) in THF. Oxidation of the remaining benzylic alcohol functionality furnished the benzaldehyde **104** in 99% yield, and its formyl group was subsequently protected using 1,2-ethanedithiol and $ZnCl_2$ to give dithiolane **105** in 72% yield. Deprotection of **105** using TBAF (93%) and oxidation of the benzylic alcohol functionality gave **106** in an unoptimized 54% yield (Scheme 30).

Scheme 30

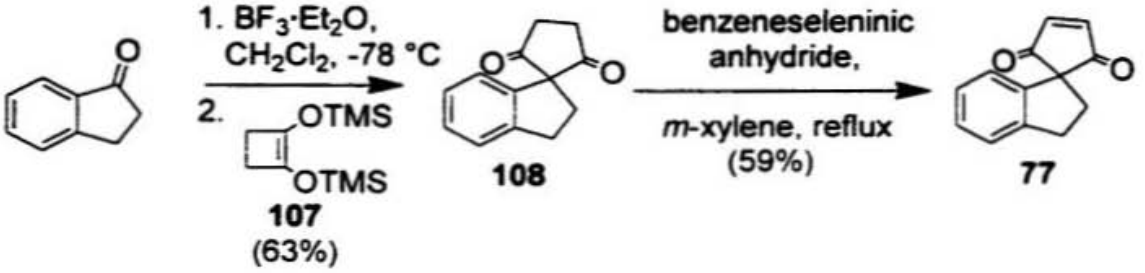


Scheme 30 (continued)



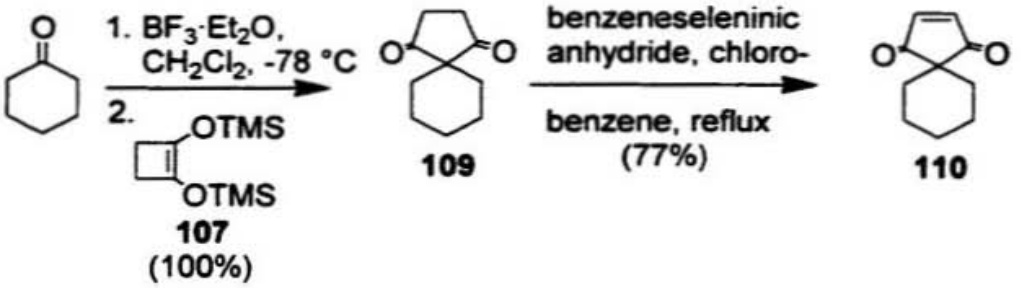
With this acyl anion equivalent **106** in hand, some simple Michael acceptors were needed in order to test the efficacy of the tandem Michael-aldol process. These Michael acceptors were synthesized *via* relatively short synthetic pathways (Schemes 31 and 32).

Scheme 31



The commercially available 1-indanone was converted to spiro diketone **108** in 63% yield employing the one-pot procedure developed in our laboratories.[18] 1,2-Bis[trimethylsilyl(oxy)]cyclobutene (**107**), though commercially available, was prepared from diethyl succinate using the procedure of Bloomfield and Nelke.[30] Oxidation of **108** was effected using benzeneseleninic anhydride in *m*-xylene under reflux to afford Michael acceptor **77** in modest yield. Compound **110** was synthesized in acceptable yield using an analogous pathway (Scheme 32).

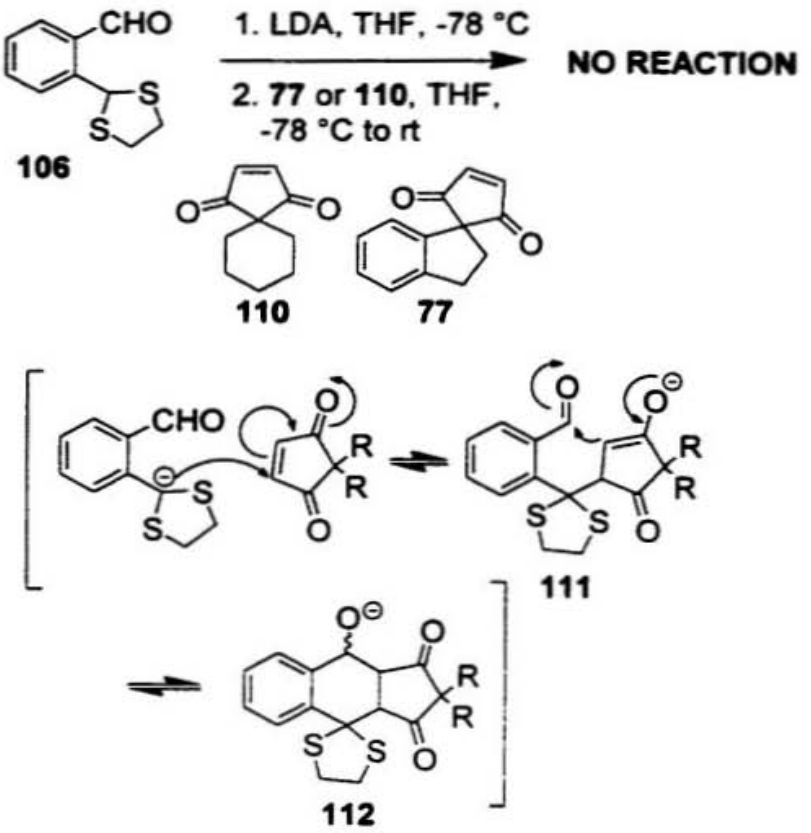
Scheme 32



With these Michael acceptors in hand, the tandem Michael-aldol process was attempted. Much to our dismay, when **106** was deprotonated with lithium diisopropylamide (LDA) at –78 °C and either enedione **77** or **110** was added and the reaction mixture warmed to room temperature, no adducts were observed and only starting materials were returned. A variety of conditions were employed in an attempt to effect the desired annulation, such as modifying the base (sodium hydride or *n*-BuLi), the solvent (THF, HMPA, DMF, and combinations thereof) as well as addition of copper(I) iodide to form the organocuprate. Unfortunately, none of these modifications resulted in anything other than the return of starting materials.

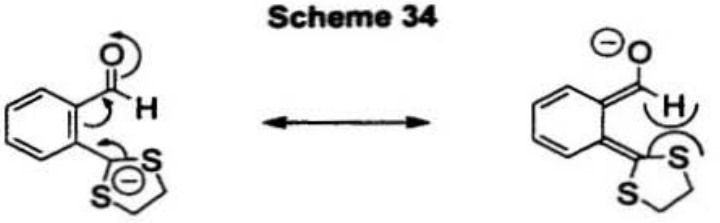
We postulated that no reaction was observed due to either resonance stabilization of the anion, or that the initial Michael addition and subsequent cyclization were reversible processes (Scheme 33).

Scheme 33



While we believe it plausible **112** would undergo a retro-aldol reaction to revert to **111**, it seemed unlikely that the initial Michael addition of lithiated **106** onto **77**, or **110** to furnish **111**, would be reversible processes. We are currently inclined to support the hypothesis that resonance stabilization of deprotonated **106** is the justification for the observation of returned starting materials (Scheme 34). Resonance form **113** may more closely represent deprotonated **106** than does resonance form **106a**.

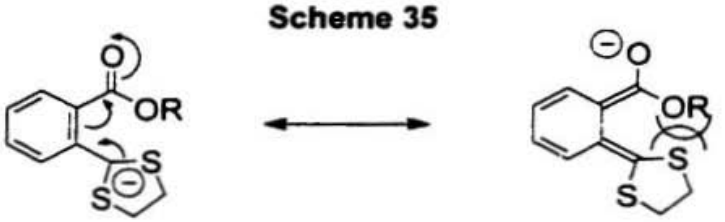
Scheme 34



106a **113**

If either hypothesis were correct, then appropriate modification of the electrophile (i.e., the aldehyde) might result in the desired annulation. Changing the aldehyde to an ester would have a two-fold effect. Resonance form **114** may be a more accurate representation of the deprotonated compound than is **115** due to unfavorable steric interactions in **115** (Scheme 35). Secondly, the reversibility of the reaction might be negated by the presence of a leaving group. Thus, the process would no longer be a tandem Michael-aldol, but a tandem Michael-Claisen.

Scheme 35



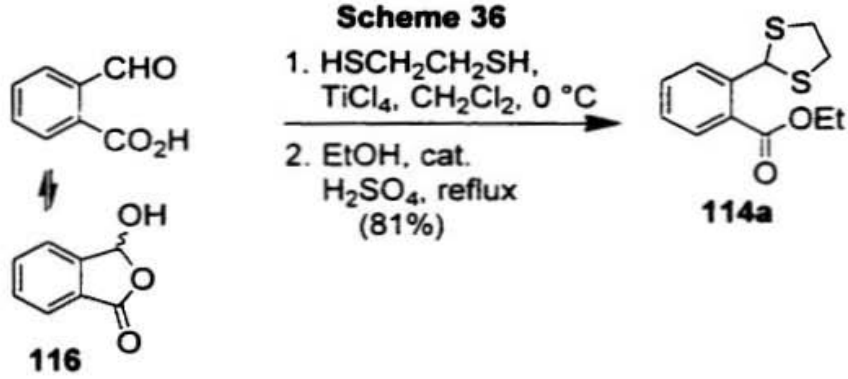
114 **115**

Tandem Michael-Claisen Process

Despite the disappointing results that were obtained from our model studies, we were still optimistic that the tandem Michael-Claisen process would be a viable strategy for the construction of the carbon skeleton found in **1**.

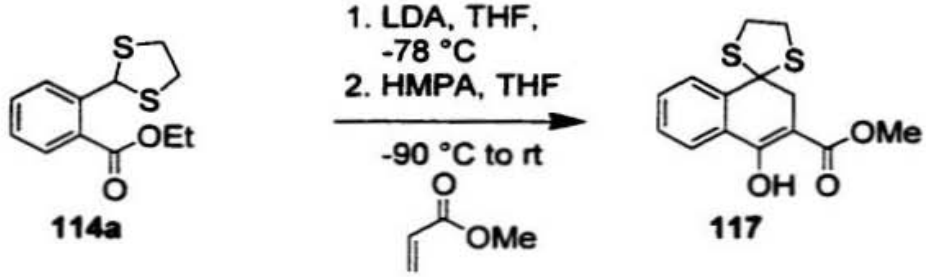
The synthesis of **114a** was carried out employing the protocol developed by Ozaki and co-workers.[22] Commercially available 2-carboxybenzaldehyde (**116**), which exists in both the ring-open and ring-closed equilibrium forms, was converted to the dithiolane. The crude product was Fischer esterified in ethanol under reflux in the presence of a catalytic amount of H_2SO_4 to furnish **114a** (Scheme 36) in excellent overall yield.

Scheme 36



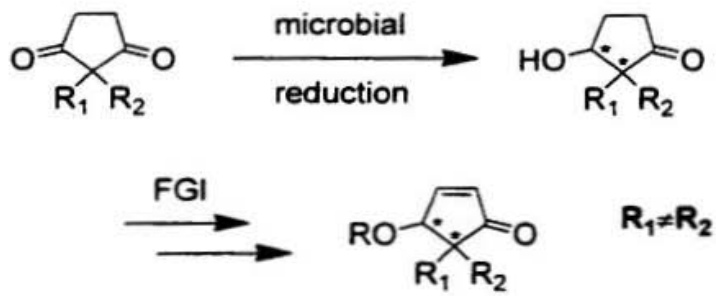
We also successfully repeated the procedure of Ozaki and co-workers by annulating **114a** in a tandem Michael-Claisen process with methyl acrylate to provide **117** (Scheme 37), albeit in a lower yield (56%) than the yield of the original authors (74%).

Scheme 37



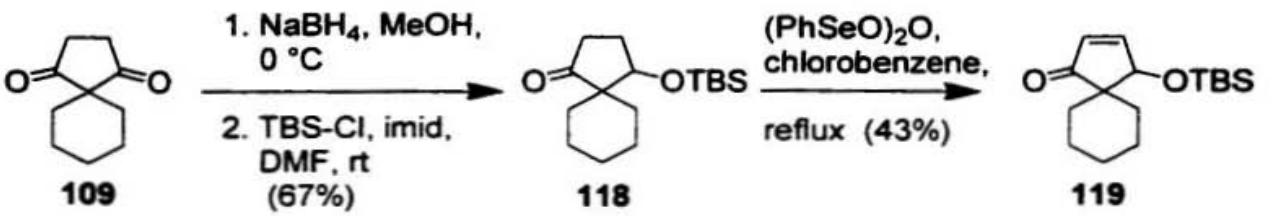
Though the tandem Michael-Claisen process worked reasonably well on methyl acrylate, our situation called for the Michael acceptor to be a spirocyclic enone, with a hydroxyl group in the γ-position. The Michael acceptor would be enantiomerically enriched, having its origins from a Baker's yeast reduction of a spirodiketone (Scheme 38).

Scheme 38



As the Baker's yeast reduction could only be carried out on a relatively small scale (*ca.* 250 mg) in our laboratories, it was judicious to test the reactivity with achiral Michael acceptors first. Several spirocyclic enones were synthesized. These synthetic pathways are outlined in Schemes 39 and 40.

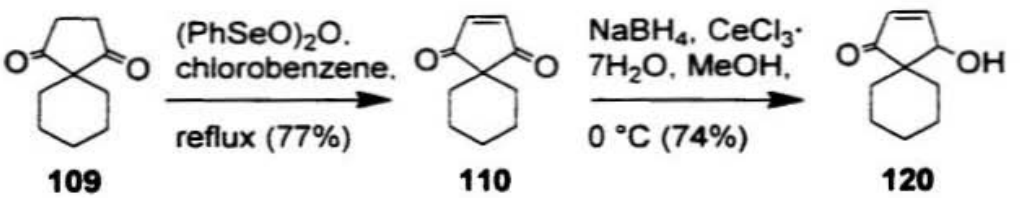
Scheme 39



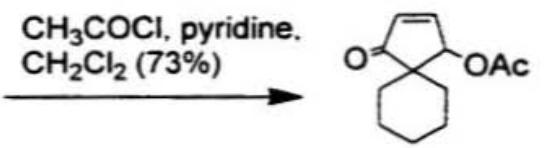
109 **118** **119**

Cautious addition of $NaBH_4$ to spirodiketone **109** followed by protection of the hydroxyl function furnished the *tert*-butyldimethylsilyl ether **118** in 67% yield over two steps. Formation of the α,β-unsaturated ketone was achieved through the use of benzeneseleninic anhydride in chlorobenzene (42-43% yield) under reflux to furnish spirocyclic enone **119**.

Scheme 40



109 **110** **120**



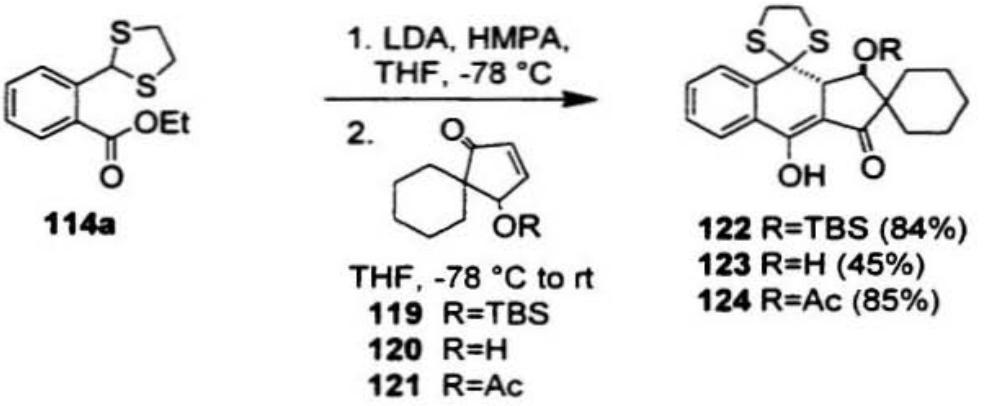
121

Spirodiketone **109** was oxidized in acceptable yield to enedione **110**, which was subsequently 1,2-reduced using the Luche conditions[31] to furnish allylic alcohol **120** in 74% yield. Acetylation of **120** using standard conditions[32] gave **121**. It is noteworthy

that all attempts to protect **120** as the TBS. TIPS or methyl ether all returned mainly starting material hence a slightly different synthetic route was used to obtain **119**.

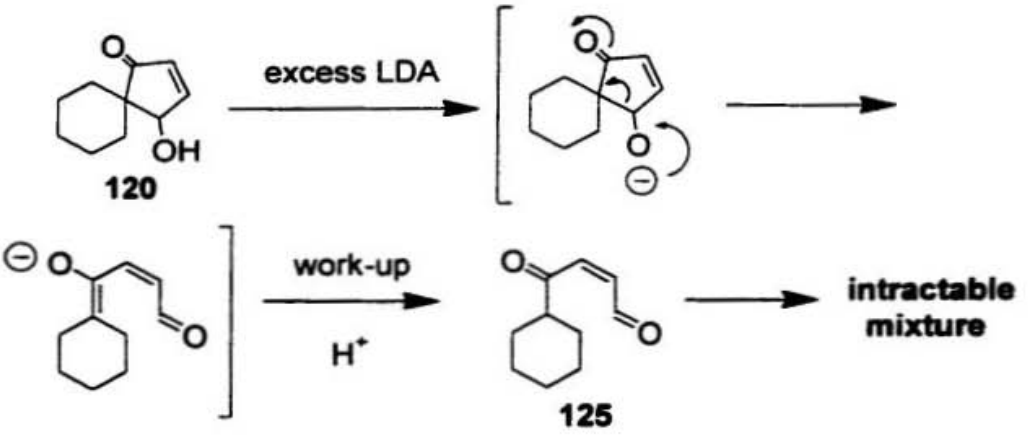
With three potential Michael acceptors **119**, **120** and **121** in hand, the tandem Michael-Claisen process was investigated for the construction of the ABC skeleton of **1** (Scheme 41).

Scheme 41



Much to our satisfaction, the tandem Michael-Claisen process proceeded in excellent yield to furnish the tetracyclic compounds **122** and **124**. When R = H, then the yield was much lower at 45%. This lower yield can be rationalized by deprotonation of the carbinol by the excess LDA, and the resulting species then undergoes a *retro*-aldol reaction to furnish **125**, which presumably forms an intractable mixture under work-up conditions (Scheme 42). Yields for the acetate – or TBS – protected species were very similar at 85% and 84%, respectively.

Scheme 42



The mechanistic rationale for the success of the tandem Michael-Claisen process is presented in Scheme 43. Initial attack of lithiated **114a**, *anti* to the –OR group, at the β-carbon of spirocyclic enone **119**, **120** or **121** resulted in the formation of enolate **126**. Due to close spatial proximity of this enolate to the ester moiety, subsequent cyclization readily occurred resulting in the formation of the tetracyclic compound **127**, which tautomerized readily to yield products **122**, **123** or **124**.

Not surprisingly, the relative stereochemistry about the newly formed ring junction was such that the C-3a hydrogen and the –OR group were in a *syn* relationship, meaning that the acyl anion equivalent attacked the β-carbon from the face opposite the –OR group. Only one diastereomer was observed in all three cases. When the C-3 hydrogen of **122** was irradiated in a nuclear Overhauser effect experiment, the C-3a hydrogen showed only a 2% nuclear Overhauser enhancement (NOE), unreasonably small if those two hydrogens were to be in a *syn* relationship (Figure 1).

Scheme 43

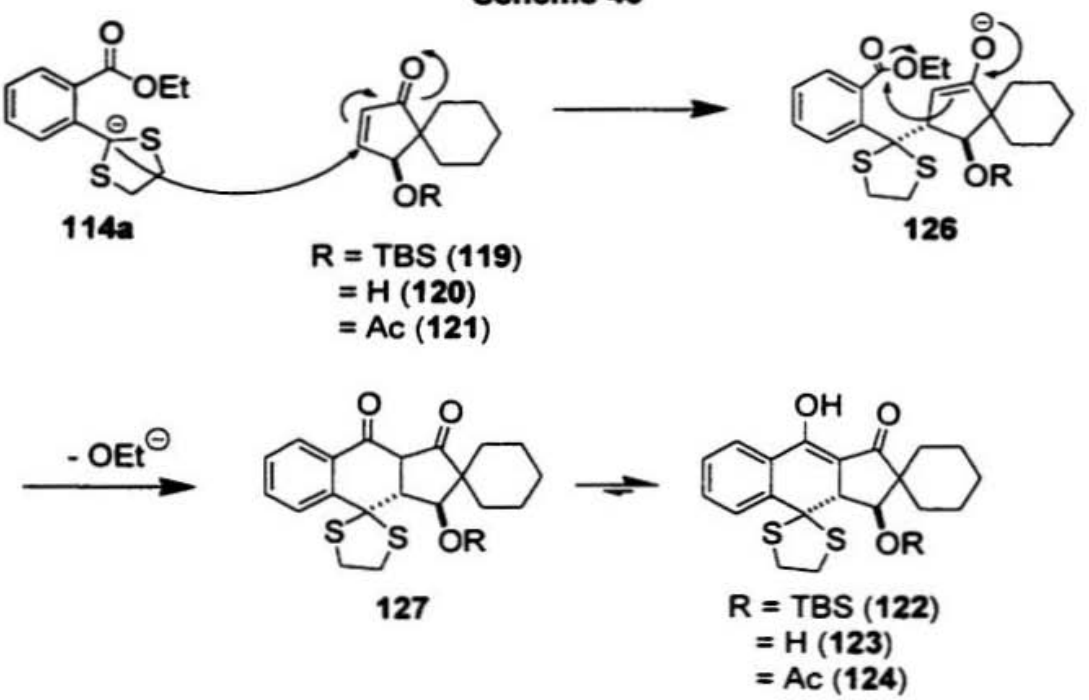
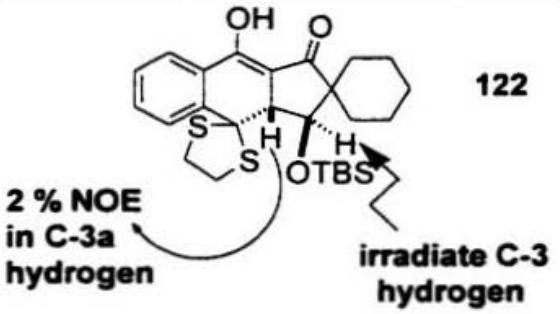


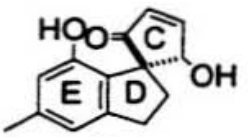
Figure 1: Nuclear Overhauser enhancements (NOE) used for assignment of the relative stereochemistry of 122



With these encouraging results, we attempted to extend the methodology to more complex synthons, such as a more highly functionalized spirocyclic enone as the Michael acceptor, the introduction of asymmetry through employment of a reductase from *Saccharomyces cerevisiae*, and a pentasubstituted A ring synthon.

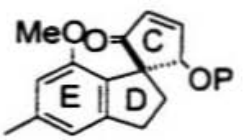
Synthesis of a More Highly Functionalized Michael Acceptor

As noted in the retrosynthetic analysis, our intent was to synthesize a CDE fragment such as **91** for the tandem Michael-Claisen process.



91

Given the basic medium of the reaction, we thought it wise to protect both the phenolic -OH and the allylic alcohol to avoid the deleterious effects of the *retro*-aldol reaction. Thus, synthon CDE was slightly modified into target compound **128**.

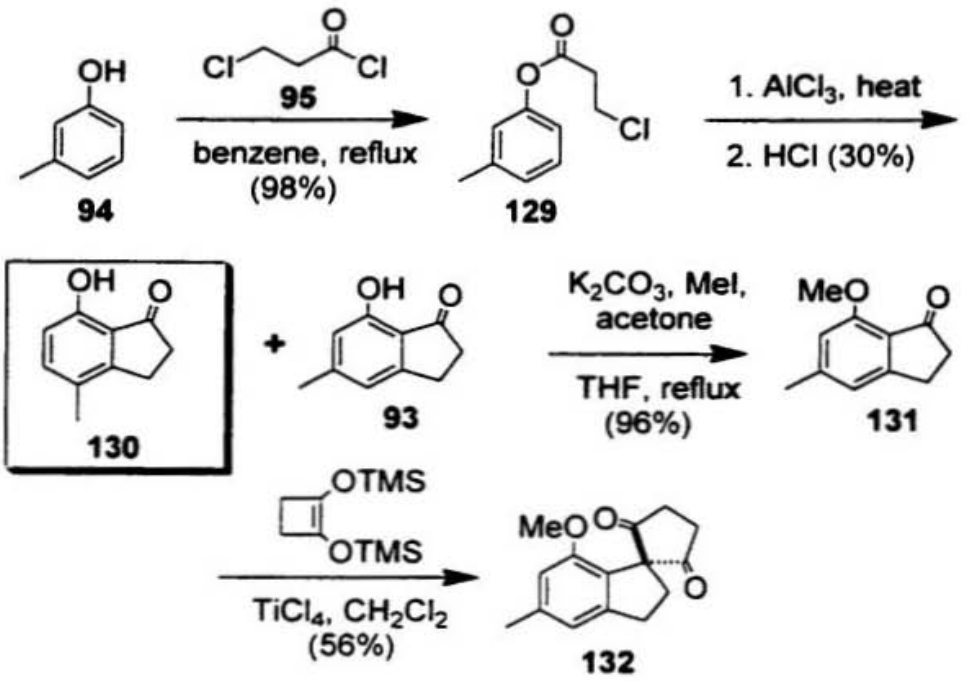


128

The synthesis of spirocyclic enone **128** is outlined in Schemes 44-46. Inexpensive *meta*-cresol (**94**) was heated in benzene under reflux with either 3-chloropropionyl chloride (**95**) or 2-chloropropionyl chloride. The resulting ester **129** was obtained in nearly quantitative yield. This reaction was carried out on a relatively large scale (*ca.* 75 g). To effect a Fries rearrangment, **129** and neat anhydrous aluminum trichloride were maintained at 90 °C for 1 hour, at 160 °C for 3 hours, and finally at 180 °C for 1 hour, after which the reaction mixture was cooled and **cautiously** treated with ice and concentrated hydrochloric acid using the conditions of Buryan *et al.*[23] Steam distillation furnished hydroxyindanone **93** in 30% yield on one occasion but only 17% on another.

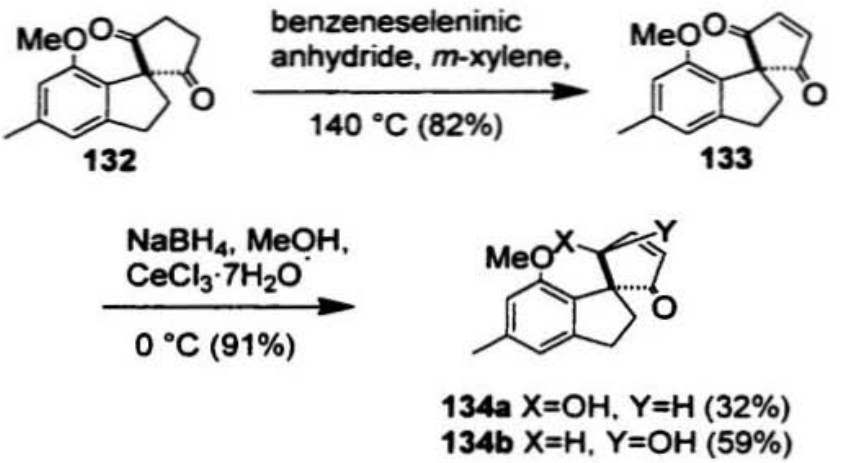
Bach and co-workers[15] did not report their yield of **93**, nor did they report the formation of regioisomer **130** as an annoying by-product.

Scheme 44



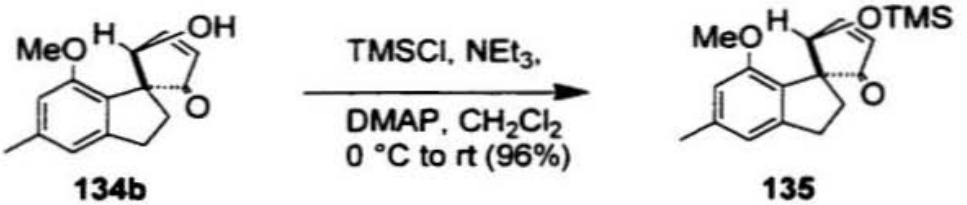
With **93** in hand, the phenol was protected as a methyl ether using a slight modification of the standard conditions.[33] We attempted to convert indanone **131** to **132** using our standard conditions for the geminal acylation.[18] Unfortunately, only starting material was returned. Apparently, boron trifluoride diethyl etherate was not a strong enough Lewis acid for this geminal acylation to transpire in this instance, so the stronger titanium tetrachloride was necessitated. The yield of **132**, however, was only 56%, based on recovered starting material. This reaction was carried out many times, and the yields ranged from 40-56%. This, however, is comparable with the yields of others using similar substrates.[10v,13,15]

Scheme 45



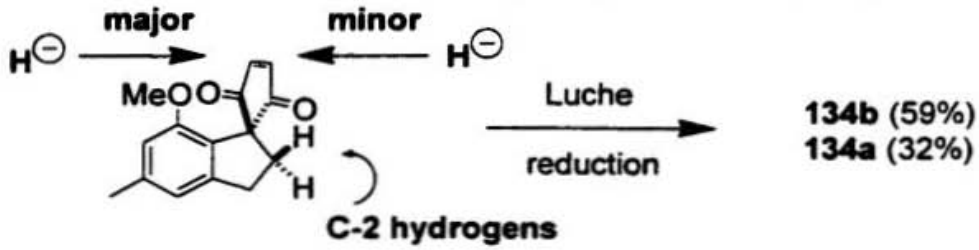
Spirodiketone **132** was converted to spirocyclic enedione **133** in excellent yield using benzeneseleninic anhydride in *meta*-xylene under reflux. The yield of **133** was slightly lower when the oxidation was carried out in chlorobenzene, which boils at the slightly lower temperature of 132 °C. Luche reduction[31] furnished two diastereomers in a 1.8 : 1 ratio and 91% overall yield. Once again, attempts to protect the allylic alcohol of either diastereomer as the TBS ether proved futile and merely returned starting material under a variety of conditions. In the end, we settled on protection of the major diastereomer **134b** as the TMS ether (Scheme 46).

Scheme 46



We rationalized that the Luche reduction of **133** to afford diastereomers **134a** and **134b** proceeded with the observed diastereoselectivity due to the C-2 hydrogens impeding, to a certain extent, attack of the hydride on that face of the enedione ring (Figure 2). It is also plausible that cerium, being a hard Lewis acid, has a tendency to

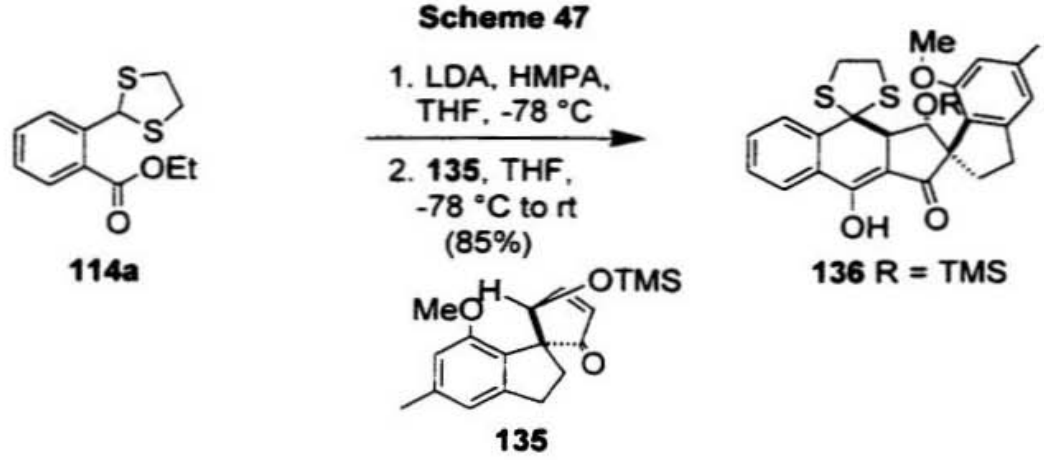
Figure 2: Observed diastereoselectivity in the Luche reduction of spirocyclic enedione 132



complex with the methoxyl, allowing hydride attack from what may be the more sterically hindered face.

It was not unexpected that when **114a** was deprotonated and enone **135** was added that the pentacyclic product **136** was obtained (Scheme 47). The reaction proceeded in excellent yield, furnishing only one diastereomer.

Scheme 47

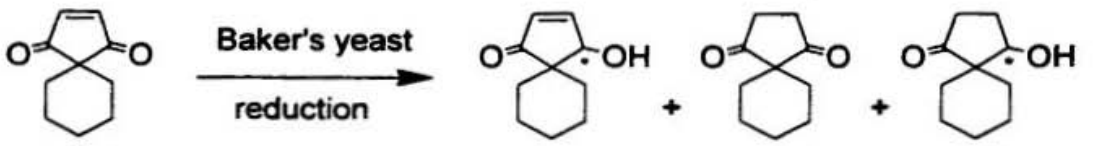


Enzymatic Reduction Methodology

Core to our strategy for the asymmetric total synthesis of **1** was the employment of a reductase from *Saccharomyces cerevisiae*, commonly referred to as a Baker's yeast reduction.[19] The use of Baker's yeast as an asymmetric reductant is quite widespread in organic synthesis, as evidenced by the number of reviews written on the subject.[34] This is not only a topic of academic interest, as the large scale production of chiral alcohols with Baker's yeast is a well-known industrial process.[35] The use of enzymes in organic synthesis has seen a huge ascent in the last decade as greater stereochemical control, including improved regio- and enantioselectivity, have become crucial factors in synthetic planning in both the academic and pharmaceutical realms.[36]

We began our studies with some relatively simple substrates in order to investigate which functionality would be tolerated. From these early studies, we learned that the reaction sequence would need to be as follows: reduction of the diketone, protection of the hydroxyl functionality, and finally introduction of the double bond to furnish an enone with a protected hydroxyl group in the γ-position (Scheme 38). This sequence was necessitated by the tendency of the enzymes of *Saccharomyces cerevisiae* to reduce the carbon-carbon double bond of enedione **110** (Scheme 48). Various conditions were employed in an attempt to circumvent this problem, but the competing 1,4-reduction could not be avoided and always led to the major product (Table 1). Moreover, from a practical standpoint, separation of **120a** and **137** was troublesome.

Scheme 48



110 120a 109 137

Table 1: Reactions of 110 with Baker's Yeast Under Varied Conditions

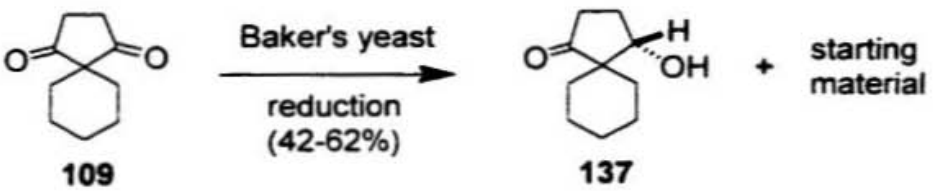
conditions	1,2-reduction (120a)	1,4-reduction (109)	1,2- and 1,4-reduction (137)
standard conditions[a]	17% by GC-MS 7% isolated	13% by GC-MS 17% isolated	70% by GC-MS 35% isolated
longer reaction time and more reagent[b]	5% isolated	0% isolated	48% isolated
shorter reaction time and less reagent[c]	16% isolated	18% isolated	27% isolated
shorter reaction time and slightly reduced temp[d]	5% isolated	7% isolated	43% isolated

[a]8.0 g of yeast, 18.0 g sucrose, 3 mL of 95% ethanol, and 100 mL of distilled H_2O/1.1 mmol of substrate at 32 °C for 48 h.
[b]standard conditions for 48 h, followed by an additional 8.0 g of yeast, 18.0 g of sucrose, and 3 mL of 95% ethanol for further 48 h.
[c]8.0 g of yeast, 18.0 g of sucrose, 3 mL of 95% ethanol, and 100 mL of distilled H_2O/1.7 mmol of substrate at 32 °C for 24 h. Recovered 1% starting material.
[d]8.0 g of yeast, 18.0 g of sucrose, 3 mL of 95% ethanol, and 100 mL of distilled H_2O/0.9 mmol of substrate at 30 °C for 24 h. Recovered 2% starting material.

On the basis of these results. we decided that it would be better to proceed with the enzymatic reduction on the spirodiketone species.

Therefore, reduction of **109** with Fleischmann's™ brand Baker's yeast resulted in yields of **137** ranging from 42-44%, though on one occasion the yield was as high as 62% (Scheme 49). While the absolute stereochemistry of the product, as the quaternary center in this particular case is not stereogenic, was not determined it can be postulated on the basis of prior studies that the configuration at C-3 should be *S*.[19] It should also be noted that a reduction of **109** using Danstar London™ Brewer's yeast was somewhat sluggish. The yield (determined by GC-MS analysis) of **137** was only 53% with 42% starting material (**109**), and trace amounts of an unknown product.

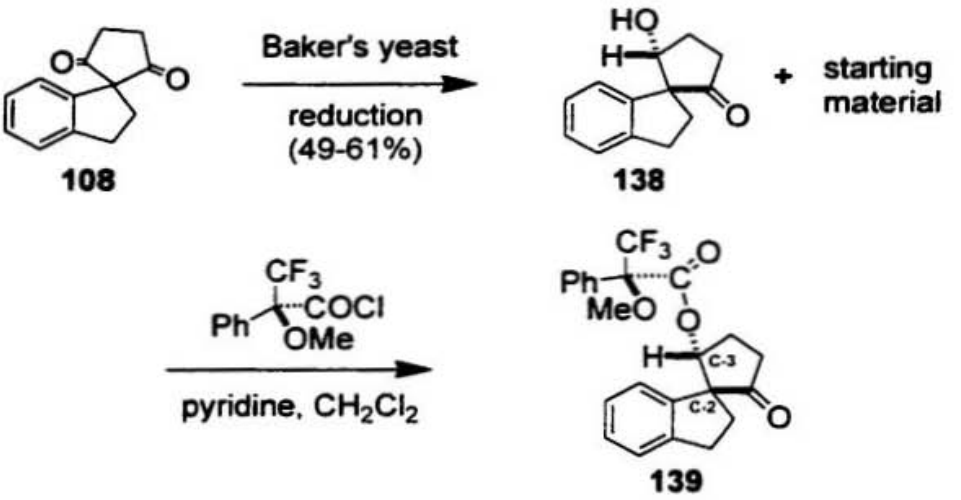
Scheme 49



109 **137**

The microbial reduction on **108** was carried out using the same conditions as for **109**. In this case. we were particularly interested in the configuration of the stereogenic centers at C-2 and C-3. The yields of isolated **138** ranged from 49-61%. Alcohol **138** was subsequently converted to the Mosher ester.[37] X-Ray crystallographic analysis was carried out on the crystalline product to determine the relative stereochemistry of ester **139**, and hence the absolute stereochemistry of **138** was determined by comparison with the known absolute stereochemistry of the acid chloride (Scheme 50).

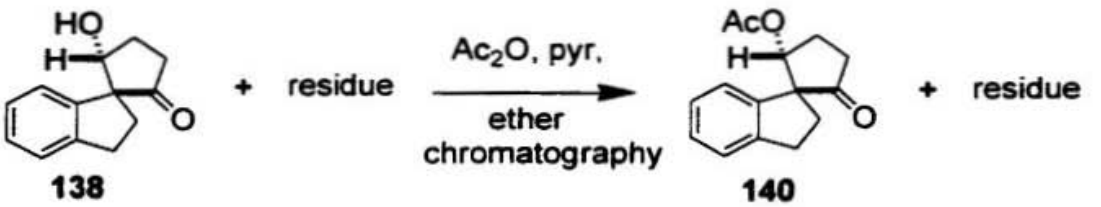
Scheme 50



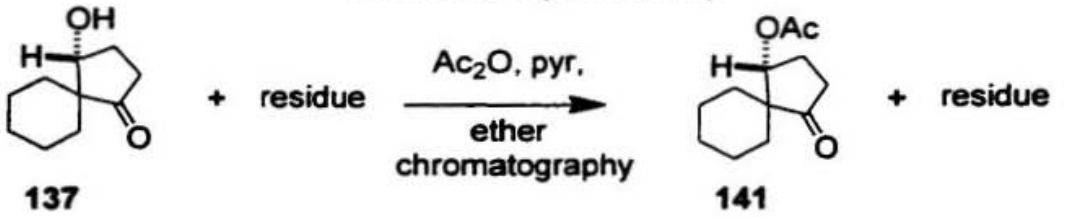
The absolute stereochemistry at C-3 was *R* and at C-2 the configuration was *S*.

We also found that, to ease purification, it was advantageous to make the acetate derivatives of **137** and **138** as they were crystalline compounds that had a distinct R_f value and were readily separable from a residue that remained from the yeast cells (Scheme 51).

Scheme 51

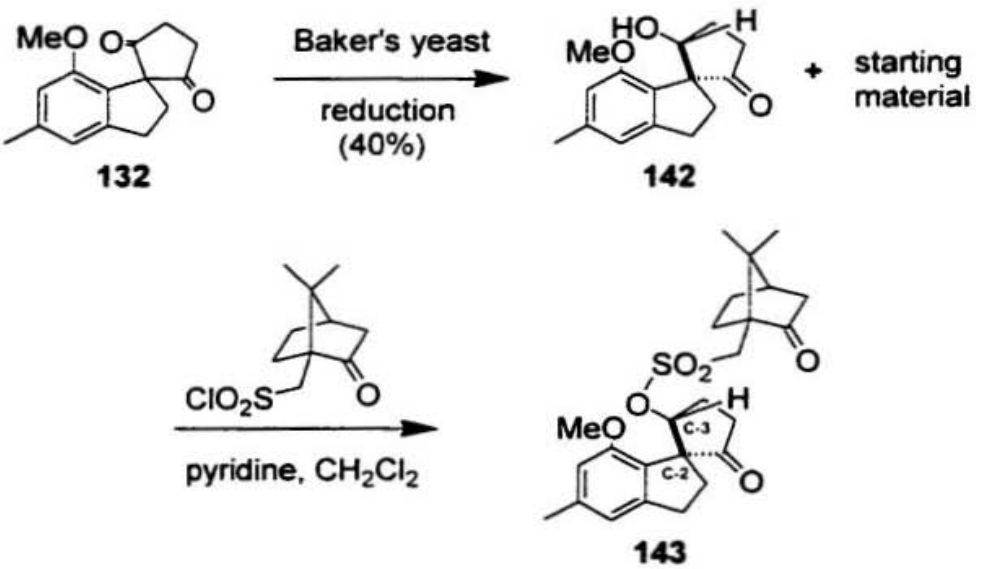


Scheme 51 (continued)



The stereochemical outcome of the enzyme-mediated reduction of the more functionalized compound **132** was important, so it was subjected to the standard Baker's yeast reduction conditions. Much to our delight, the reduction was highly diastereoselective, although the stereochemistry was opposite what we expected (Scheme 52).

Scheme 52

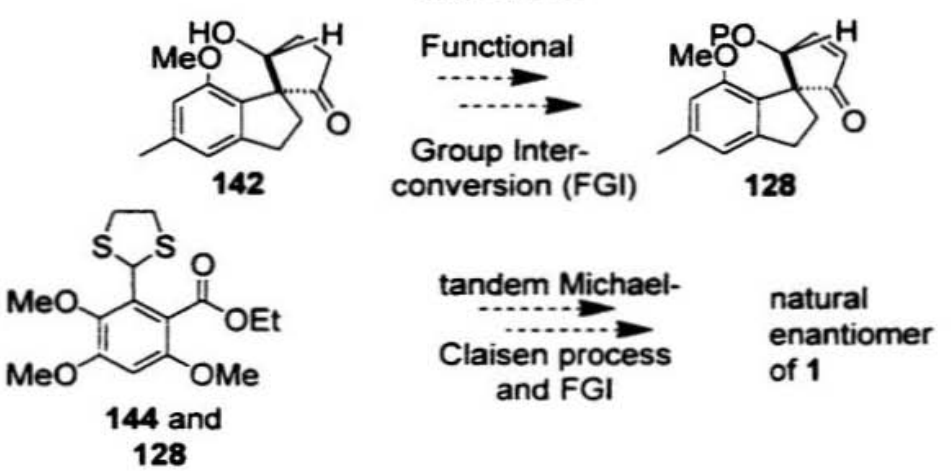


Compound **142** was treated with (1*S*)-(+)-10-camphorsulfonyl chloride to yield the corresponding sulfonyl ester **143**. This sulfonyl ester showed only one set of signals

in the ^{13}C NMR spectrum, which confirmed that the reduction was also highly enantioselective. The relative stereochemistry of **143** was determined by X-ray crystallographic analysis. As the absolute stereochemistry of the camphorsulfonyl chloride was known, the absolute stereochemistry of **142** was determined. The configuration at C-3 was found to be *R*, and the configuration at the quaternary C-2 was also *R*. It was somewhat surprising, but not at all a problem, that the reduction of **132** took place in a different sense to the reduction of **108**.

With the knowledge that the quaternary C-2 stereogenic center was *R*, a synthetic plan could be developed for an A ring synthon that would eventually lead to **1** (Scheme 53). This plan was attractive in that it could lead to natural or *ent*-**1**, and that a large number of analogues could be prepared by introducing small changes in the A ring synthon. With the mode of action of **1** still uncertain, it would be useful to prepare analogues to obtain a structure-activity relationship (SAR) in **1**.

Scheme 53



Synthesis of Various A Ring Synthons

N,N-Dialkyl Benzamides as Directors for *ortho*-Metallation

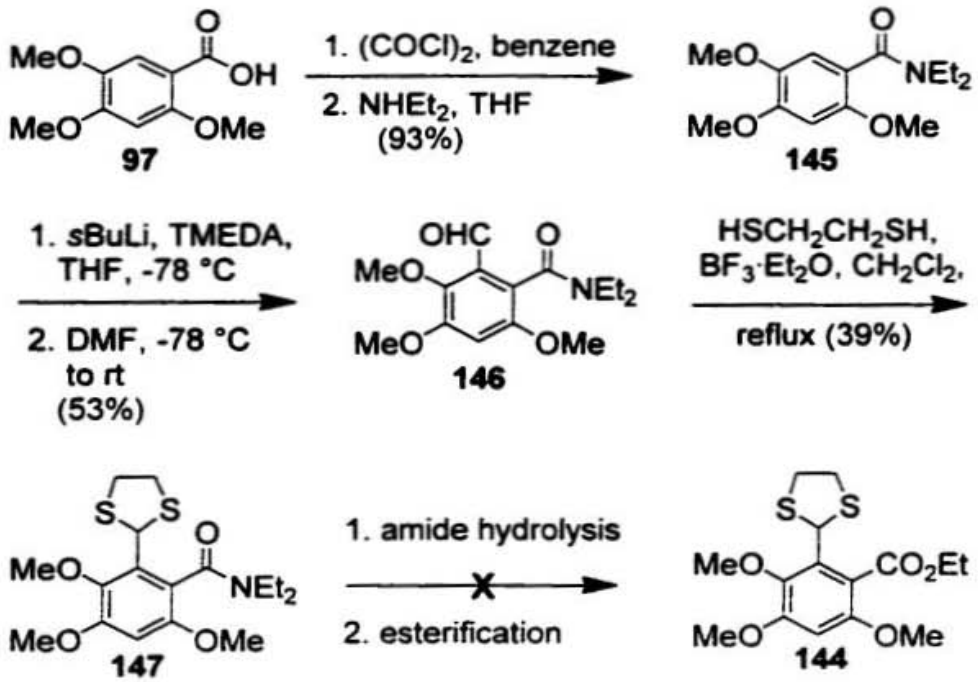
As stated in the retrosynthetic analysis, the construction of the A ring synthon would be facilitated by employment of directed *ortho*-metallation (DoM) chemistry. While the diverse number of reactions employing classical electrophilic substitution should not be denied in synthetic planning, they often suffer from harsh conditions and a lack of selectivity. Hence, a number of alternative methods for the assembly of polysubstituted aromatics has emerged, amongst them the DoM.[38]

We believed that the synthesis of **144** could be achieved by the relatively simple synthetic pathway outlined in Scheme 54. Conversion of commercially available 2,4,5-trimethoxybenzoic acid (**97**) to the corresponding *N,N*-diethylbenzamide furnished **145** in 93% overall yield. Lithiation of **145** under appropriate conditions followed by quenching with *N,N*-dimethylformamide (DMF) gave pentasubstituted aromatic **146** in modest 53% yield, and **146** was then protected as the dithiolane derivative **147** in an unoptimized yield of 39%. One might presume that derivatization of this conjugated aldehyde might require more vigorous conditions. Nonetheless, all conversions proceeded with relative ease, until hydrolysis of the amide function of **147** was attempted. The hydrolysis of the *N,N*-diethylbenzamide proved to be a formidable challenge – one that could not be overcome despite using a plethora of reagents and differing strategies (Scheme 55).

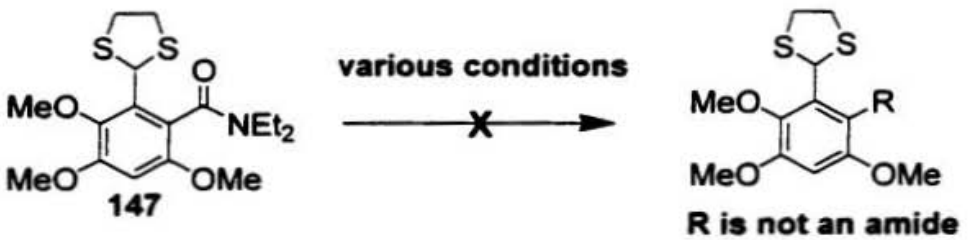
The recalcitrant nature of *N,N*-dialkylbenzamides to acid or base hydrolysis is well recognized.[38] Anchimeric assistance by *ortho*-introduced electrophiles, capable of

forming five- or six-membered-ring tetrahedral intermediates, can greatly enhance amide hydrolytic rates,[39] a feature that has been turned into synthetic benefit.[13,15]

Scheme 54



Scheme 55



R is not an amide

KOH, methanol, reflux
HCl, ethanol, reflux
LiOOH, water, reflux
$LiAlH(O^tBu)_3$, THF, reflux

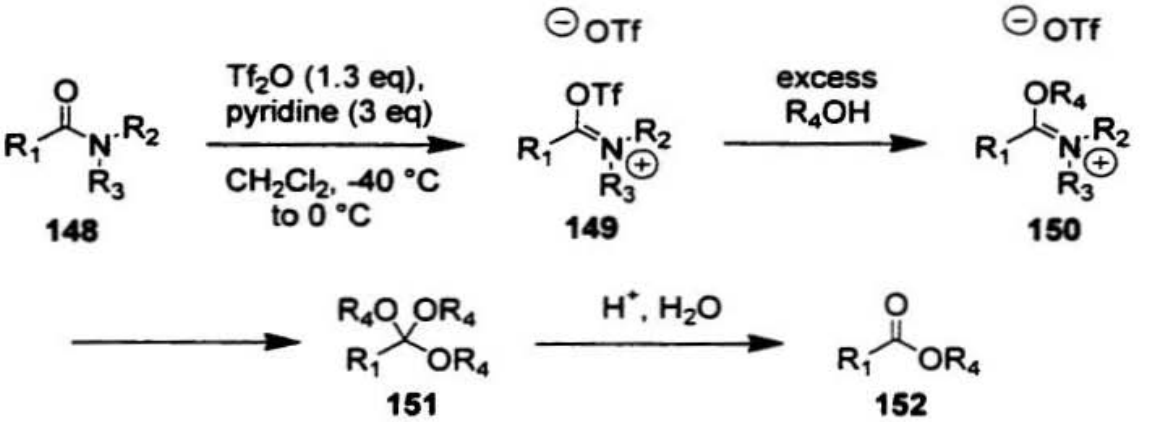
$LiBHEt_3$, THF, reflux
DIBAL-H, toluene, reflux
also attempted annulation with amide *in lieu* of 144

A large number of methods exist in the literature for amide hydrolysis.[40a-q,41] While many of these methods work well on simple substrates, they often fail and/or result in deleterious side effects when attempted on more complex substrates, though one very notable exception to this is the hydrolysis of a primary amide in the classic synthesis of vitamin B_{12} by Eschenmoser and Woodward.[40k,l] Base hydrolysis of **147** resulted in an intractable mixture of products, whereas attempted acid hydrolysis of **147** returned starting material. The use of lithium hydroperoxide, employing the conditions of Evans,[40o] also returned starting material. Using hydride-based reagents such as lithium tri-*tert*-butoxyaluminohydride, Super-Hydride® (lithium triethylborohydride) or diisobutylaluminum hydride in the hopes of converting **147** to either the corresponding aldehyde or alcohol, which could be more easily manipulated, also returned starting materials. This is presumably due to a combination of steric and electronic effects. It should also be noted that several attempts were made to effect an annulation using **147** *in lieu* of **144**, meaning that instead of an ethoxyl leaving group in the Claisen reaction, that a dialkylamino would be the leaving group. Unfortunately, this did not yield the desired product, but returned a mixture of products that could not be identified.

After Charette and Chua[41] published their results concerning the conversion of secondary and tertiary amides to esters, we were optimistic that their method (Scheme 56) could be extended to a more complex substrate such as **147**. Under Charette's conditions, a tertiary amide **148** is activated towards nucleophilic attack by forming an electrophilic triflate intermediate **149**. In the presence of an alcohol, this species is readily converted to an alkyl iminium ester **150**, which can then be converted to the

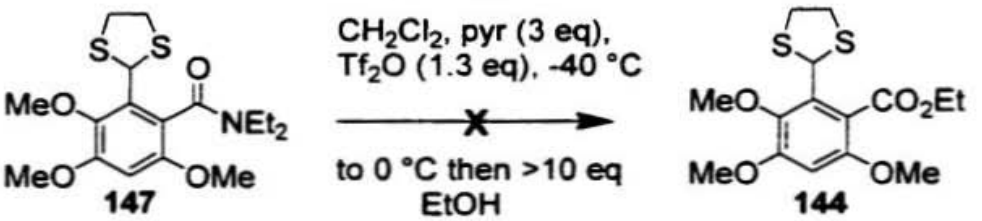
orthoester **151** by subsequent exposure to excess alcohol under very mildly acidic conditions (pyridine/pyridinium hydrotriflate). After aqueous work-up, the corresponding carboxylic ester **152** is obtained.

Scheme 56



When we attempted this one-pot procedure to convert **147** to **144**, we were unsuccessful (Scheme 57).

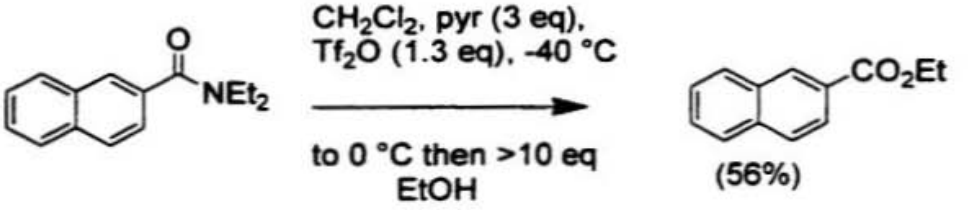
Scheme 57

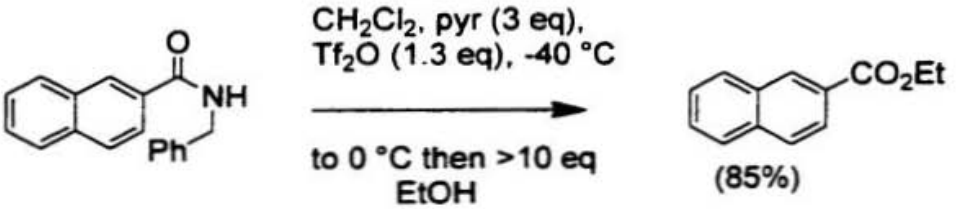


Though Charette's procedure worked reasonably well on simple substrates (56–95% conversions), only two of the fifteen substrates examined were benzamides and neither of these had even one substituent *ortho* to the amide, let alone two substituents (Scheme 58). Therefore, it is not unreasonable to postulate that initial formation of the electrophilic

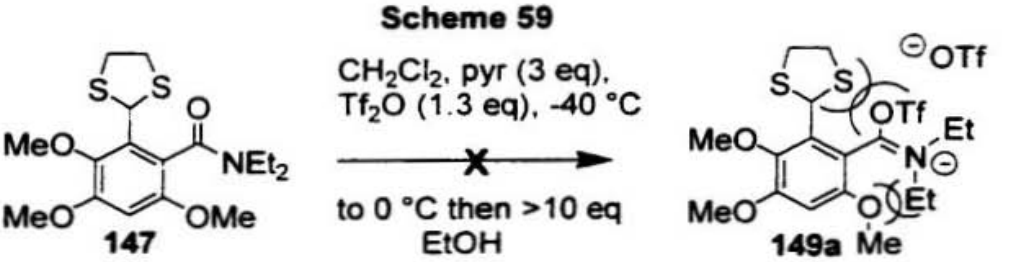
triflate intermediate **149a** never transpired due to unfavorable steric interactions, and thus the observation of returned starting material (Scheme 59).

Scheme 58

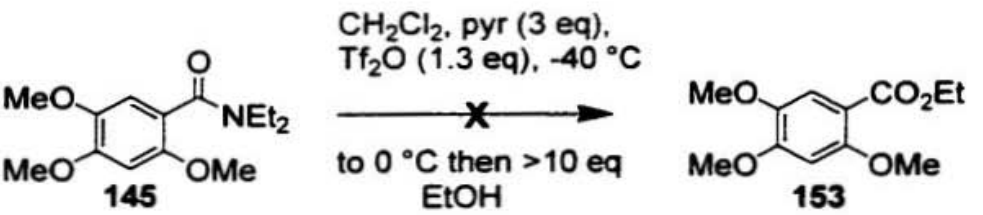




Scheme 59



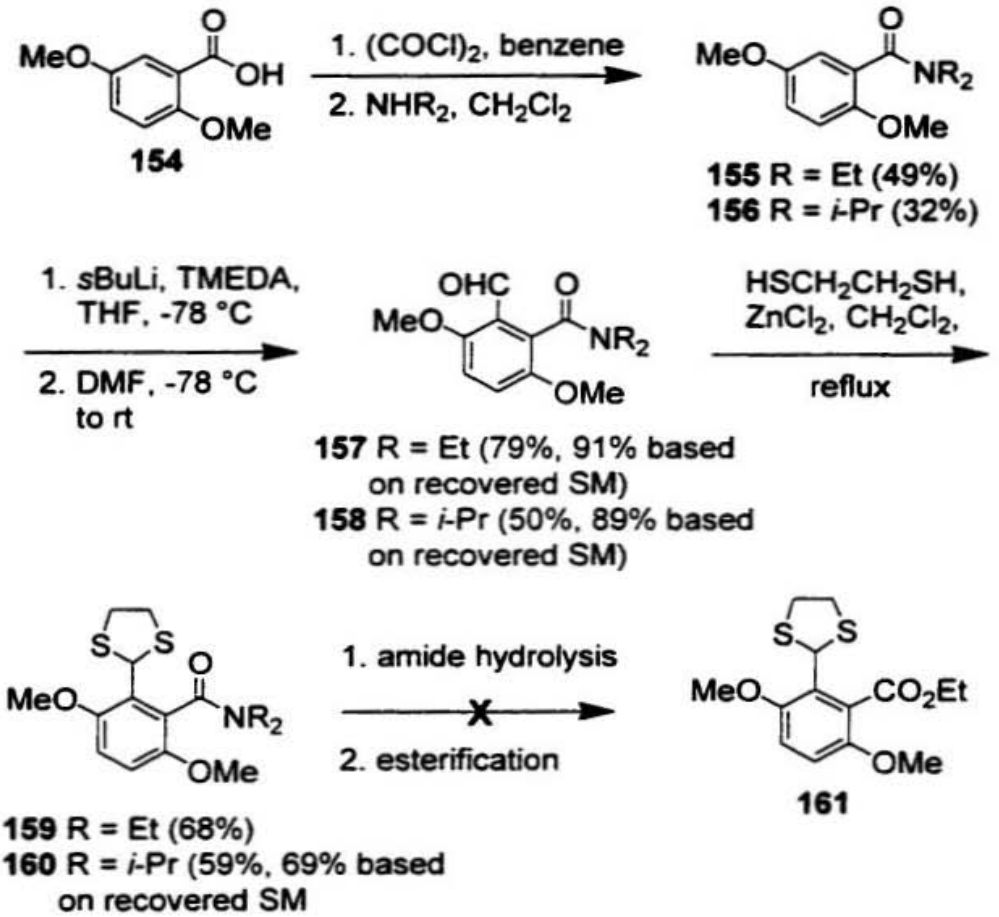
Scheme 60



Charette's procedure was also attempted on the slightly less functionalized **145**. Unfortunately, it did not yield **153**, but returned starting material (Scheme 60).

Several other polysubstituted aromatic compounds, lacking a methoxyl group *para* to the carboxylate group, were synthesized using similar methodology (Scheme 61). Again, all hydrolysis attempts on compounds **159** and **160** were without success.

Scheme 61



154

155 R = Et (49%)
156 R = *i*-Pr (32%)

157 R = Et (79%, 91% based on recovered SM)
158 R = *i*-Pr (50%, 89% based on recovered SM)

159 R = Et (68%)
160 R = *i*-Pr (59%, 69% based on recovered SM

161

Yields of tertiary benzamides **155** and **156** were unoptimized. It is noteworthy that the yield of **157** was 79%, significantly higher than the yield of **146** (53%), with the only structural difference being **155** lacks a methoxyl group *meta* to the lithiation site. The yield of **158** was slightly lower at 50%, but this was not entirely unexpected as a

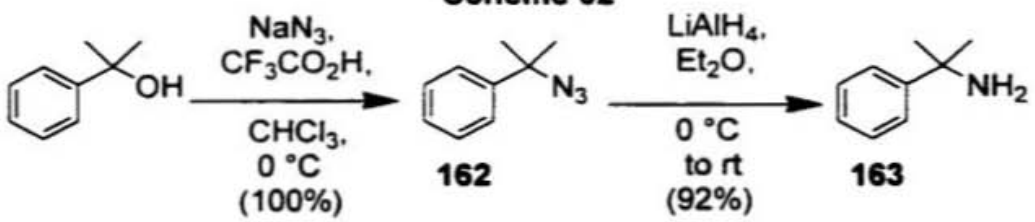
diisopropylbenzamide is known to be a slightly weaker directed-metallation group (DMG) than the diethyl equivalent.[38] Conversion of **157** to dithiolane **159** proceeded in acceptable 68% yield, and the conversion of **158** to dithiolane **160** took place in 59% yield. A wide array of reagents could not, however, transform either **159** or **160** to ester **161**.

N-Cumyl Benzamide as a Director for *ortho*-Metallation

Thus, one step removed from our key intermediate, the recalcitrant nature of the amide proved to be problematic. The objective was then to modify the amide such that it would be more amenable to hydrolysis, yet still effective as a DMG.

According to a recent publication by Snieckus and co-workers,[42] the *N*-cumyl benzamide was an effective DMG that also possessed mild hydrolytic lability, thus allowing facile manipulation. The synthesis of *N*-cumyl benzamide **164** is outlined in Schemes 62 and 63.

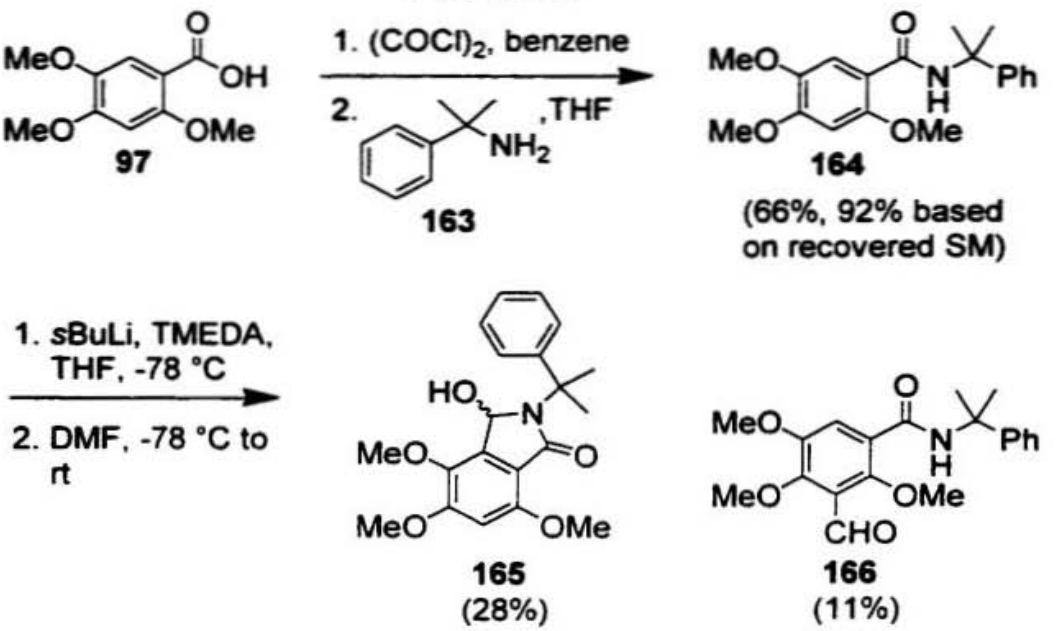
Scheme 62



Using a modification of the procedure of Balderman and Kalir,[43] commercially available cumyl alcohol was converted to azide **162** quantitatively using sodium azide in trifluoroacetic acid (TFA) and chloroform at 0 °C. Compound **162** was reduced to amine **163** in 92% yield with $LiAlH_4$ in diethyl ether at 0 °C to room temperature (Scheme 62)

instead of Raney nickel, as employed by Balderman and Kalir. With amine **163** in hand, the standard transformation of **97** to the corresponding acid chloride, followed by

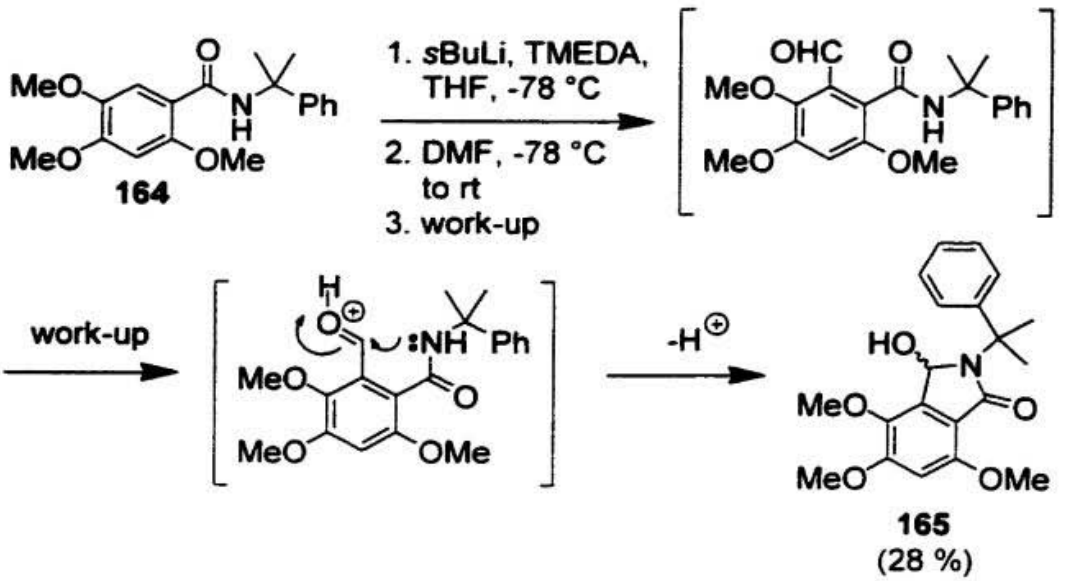
Scheme 63



addition of amine **163**, furnished *N*-cumyl benzamide **164** in 66% overall yield, 92% yield based on recovered starting material. Subjection of **164** to standard *ortho*-metallation conditions followed by quenching with *N,N*-dimethylformamide furnished two compounds, phthalimidine **165** in 28% yield and **166** in 11% yield, while the remainder of the material isolated from the product mixture was starting material (Scheme 63). Compound **166** was somewhat unexpected, as *ortho*-metallation in all previous reactions had occurred *ortho* to the amide, not *ortho* to the methoxyl groups, though *ortho*-metallation of anisoles is not an unknown process.[44] The formation of phthalimidine **165** can be rationalized as follows: the formyl group is readily protonated

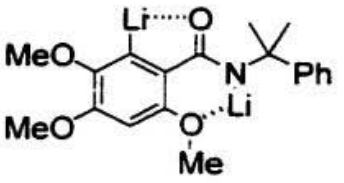
during work-up, and the adjacent secondary amide then cyclizes to yield phthalimidine **165** (Scheme 64).

Scheme 64



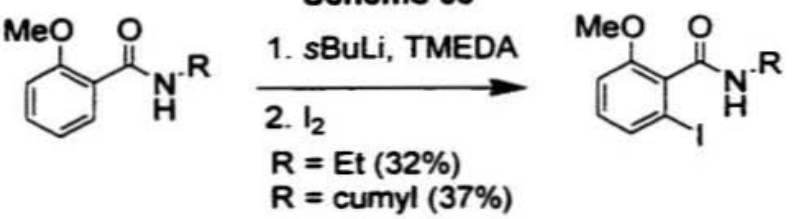
The low yields are not atypical for anisic acid derivatives, presumably due to the unfavorable strain imposed upon the 6.6.5-chelated tricycle (Figure 3). Snieckus and

Figure 3: Chelation in dilithiated 164



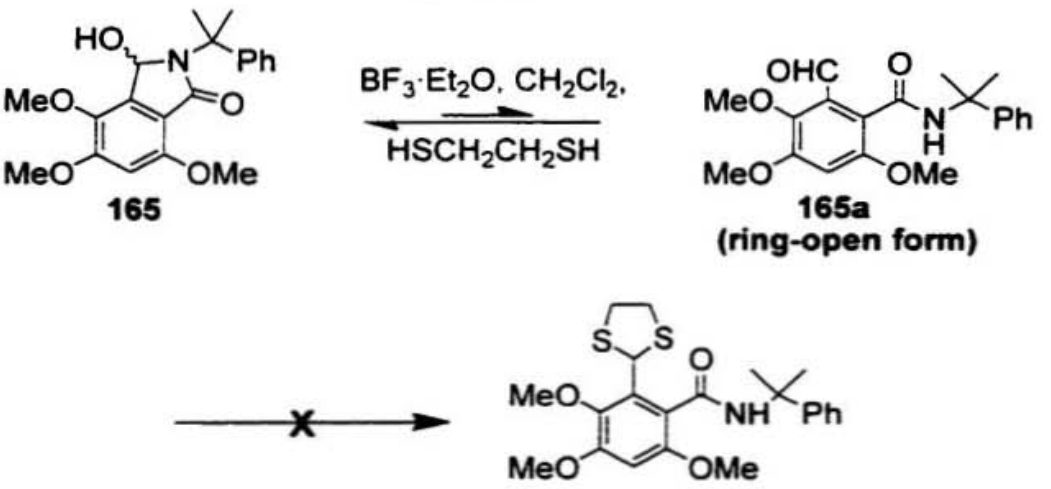
co-workers[45] also obtained poor yields in the reaction of several anisic acid derivatives (Scheme 65).

Scheme 65



We were hopeful that subjection of phthalimidine **165** to Lewis acid catalysis would result in ring opening, and that this ring-opened form could be "trapped" as the dithiolane. Unfortunately, treatment of **165** with $BF_3{\cdot}Et_2O$ and 1,2-ethanedithiol in dichloromethane did not furnish the desired product (Scheme 66).

Scheme 66



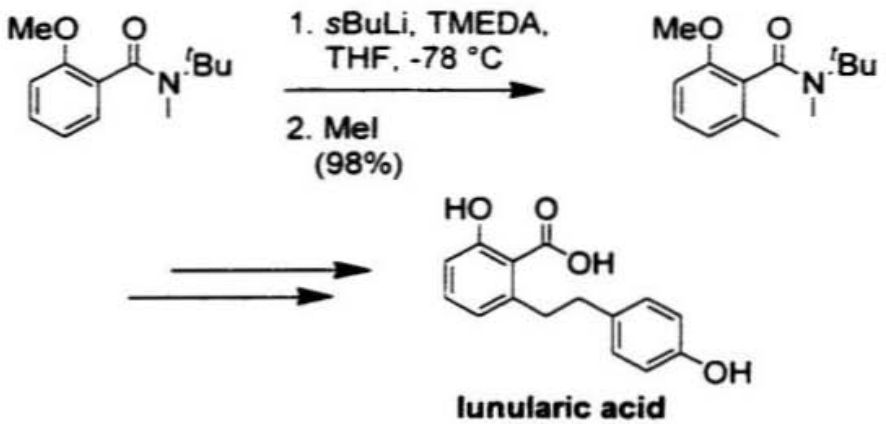
Also investigated was the possibility of protecting the problematic –NH as the *tert*-butyldimethylsilyl ether to avoid formation of phthalimidine **165**, as done in the total synthesis of thienamycin,[46a] racemic gabaculine,[46b] and asymmetric synthesis of the carbapenem antibiotic PS-5.[46c] Unfortunately, all attempts to isolate the protected adduct were unsuccessful and merely returned starting material. We postulate that this is either

due to unfavorable steric interactions or *O*-silylation which, upon aqueous work-up, desilylated and reverted back to starting material.

Other Amides as Directors for *ortho*-Metallation

Our investigations into an amide that would serve as an effective DMG, but would also be less resistant to hydrolysis, took us back to the tertiary benzamides, given the cyclization to phthalimidine **165** that plagued us with the secondary *N*-cumyl benzamide. Amongst these amides were the *N-tert*-butyl-*N*-methylbenzamide developed by Reitz and Massey,[47] used in the total synthesis of lunularic acid (Scheme 67). Their DoM reaction proceed in excellent yield (98%), and hydrolysis of the tertiary benzamide was carried out *via* a high yielding three-step process: (i) conversion of the *N-tert*-butyl-*N*-methylbenzamide to the secondary *N*-methylbenzamide by heating at reflux in TFA, (ii) conversion to the corresponding *N*-nitrosobenzamide, followed by (iii)

Scheme 67

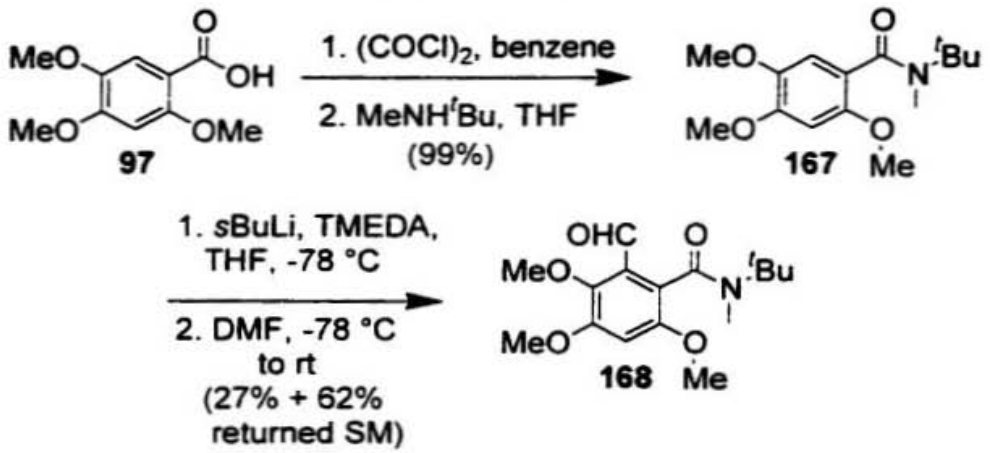


lunularic acid

treatment with ethanolic KOH at reflux to furnish the corresponding carboxylic acid in 81% yield over 3 steps.

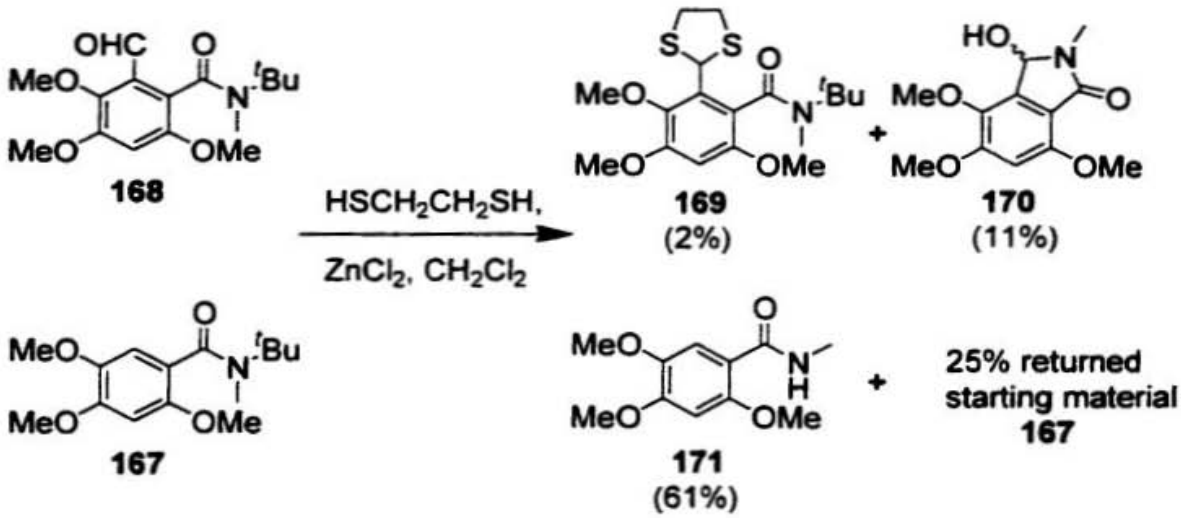
Encouraged by the results of Reitz and Massey, we set out to synthesize an *N*-*tert*-butyl-*N*-methylbenzamide with the requisite methoxyl functionality (Scheme 68). Whilst the formation of tertiary benzamide **167** from commercially available **97** took place in excellent yield, unfortunately the DoM reaction on compound **167** was poor, and separation of **168** from the starting material **167** proved to be troublesome.

Scheme 68

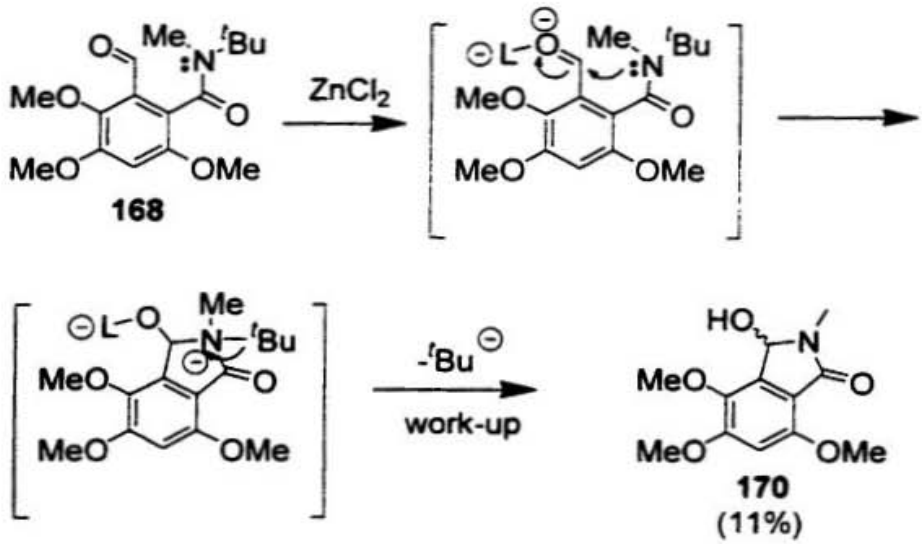


Nonetheless, we proceeded with the mixture and attempted to protect aromatic aldehyde **168** as the dithiolane derivative (Scheme 69) and to separate afterward. This returned a mixture of products, which were separable. Only 2% of desired **169** was obtained, obviously not a synthetically useful yield, while 11% of **170** was isolated, presumably from Lewis acid catalyzed removal of the ^{t}Bu group, followed by cyclization (Scheme 70). Most of the starting material **167** that was carried through also underwent a transformation to secondary benzamide **171**.

Scheme 69



Scheme 70

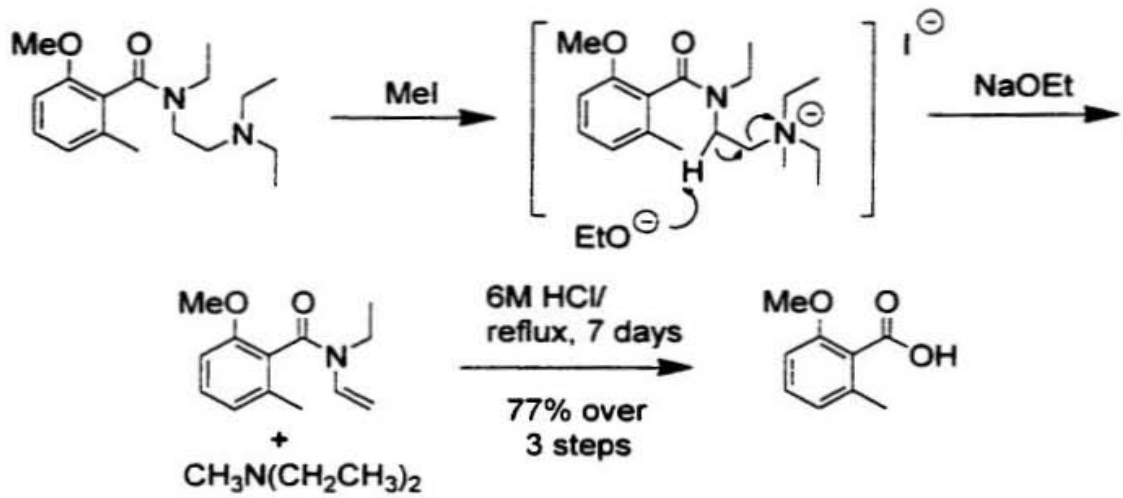


While it would seem reasonable that all of **171** and **167** would derive from **167**, given later observations in our Diels-Alder studies, we cannot be certain of this as some aldehydic substrates readily decarbonylated under mildly acidic conditions. Thus, it is

not improbable that some of **168** may have decarbonylated to furnish more **167**, which could then be converted to secondary benzamide **171** under those same mildly acidic conditions.

Another DMG that we hoped would provide a synthetically useful yield in the DoM reaction, and be sufficiently facile to manipulate afterwards was the "internal TMEDA" DMG developed by Comins and Brown.[48] The three-step sequence for the conversion of this tertiary benzamide to the corresponding carboxylic acid is shown in Scheme 71.

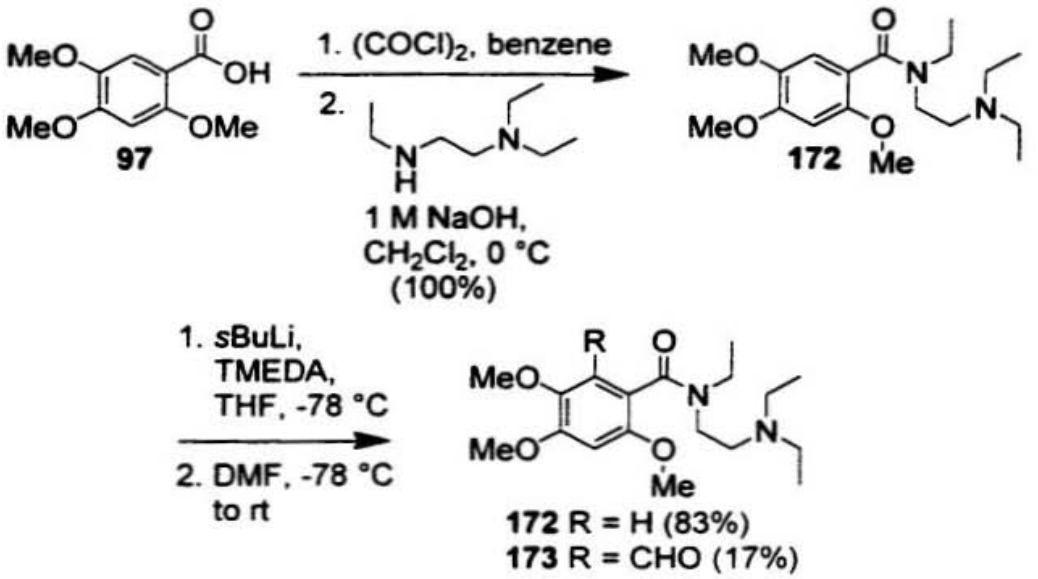
Scheme 71



Once again, while synthesis of the tertiary benzamide **172** proceeded in quantitative yield by a modification of the Schötten-Baumann procedure, subsequent attempts to *ortho*-formylate **172** resulted in unacceptably low yields (17%) of **173** (Scheme 72). Compounding the problem of this dismal yield was the difficulty of separating starting

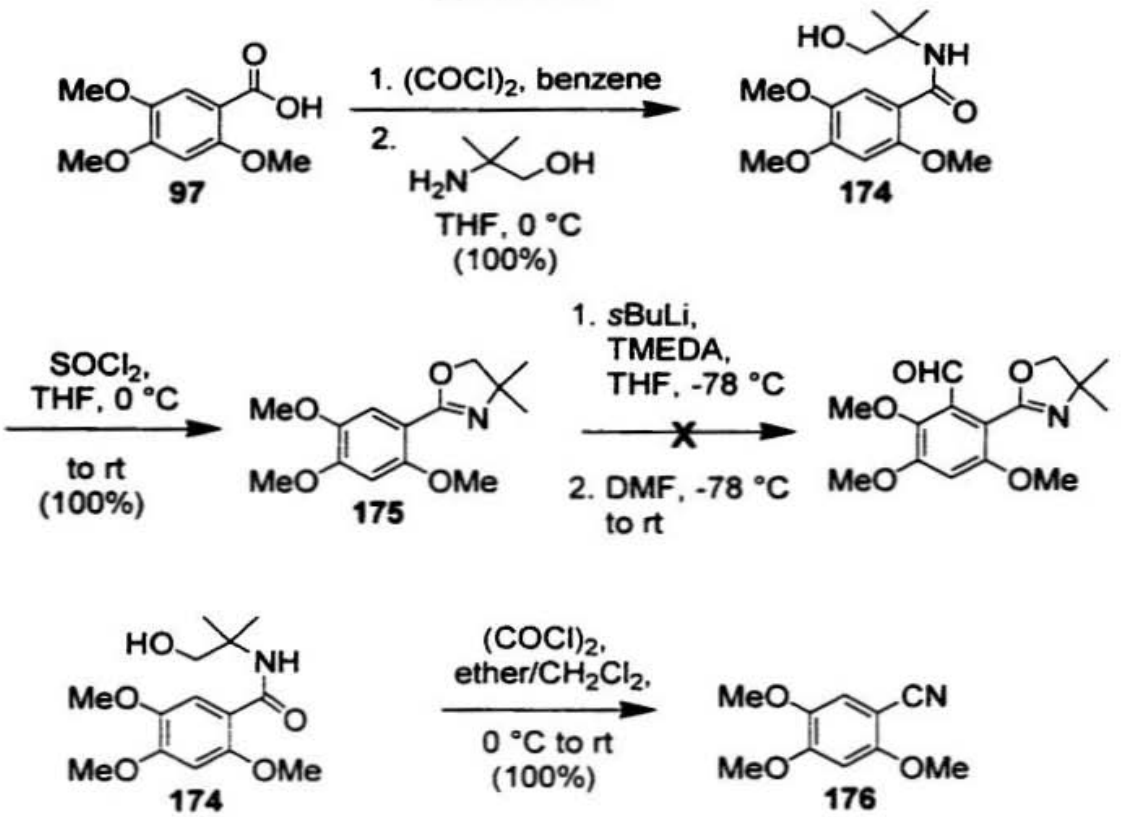
material **172** from **173**. As this transformation could not occur in synthetically useful yields, compound **173** was not carried any further in the sequence.

Scheme 72



The final amide constructed in our DoM studies was oxazoline **175**. Oxazolines are known to be effective DMG's, and are relatively susceptible to hydrolysis.[49a-g] Once more, while construction of oxazoline **175** occurred in quantitative yield *via* **174**, all attempts to introduce a formyl group *ortho* to the oxazoline group were futile and merely returned starting material. It is notable that when **174** was treated with oxalyl chloride in ether/dichloromethane for an extended period of time, then nitrile **176** was the only product isolated, in quantitative yield (Scheme 73).

Scheme 73

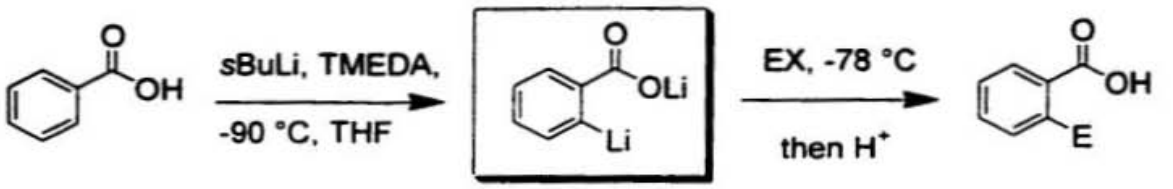


Other Functional Groups as Directors for *ortho*-Metallation

While amides are recognized as the most powerful and widely used DMG at the benzoic acid oxidation state,[50] given the obstinate nature of the amides investigated, an exploration into non-amide DMG's was in order.

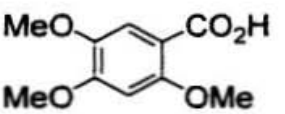
Mortier and co-workers[51] reported the direct lithiation of unprotected benzoic acids to yield *ortho*-substituted products in modest yield (Scheme 74). While this methodology worked on relatively simple, unfunctionalized benzoic acids, it could not be extended to more complex substrates such as **97**. Subjection of compound **97** to Mortier's conditions (*sec*-BuLi, TMEDA, THF) with DMF added as the electrophile,

Scheme 74



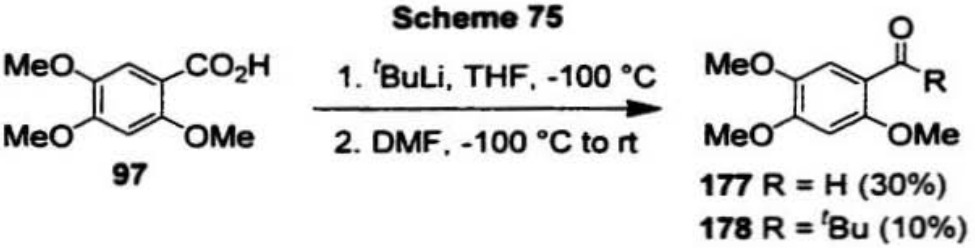
E = Me (65%)
E = SMe (52%)
E = Cl (48%)
E = Br (55%)

only returned starting material. When D_2O was added as the electrophile, no deuterium incorporation was observed onto **97**, hence no lithiation was believed to have occurred. A slight modification of Mortier's conditions resulted in the change of *sec*-BuLi to the stronger *tert*-BuLi. Interestingly, following these conditions, two compounds were isolated after work-up, aldehyde **177** in 30% yield, and ketone **178** in 10% yield (Scheme 75). Mortier[51a] also reported the formation of small amounts of ketones (i.e., less than 10%) under optimum conditions but did not report the formation of any aldehyde. A rationale for the unexpected formation of aldehyde **177** is presented in Scheme 76.



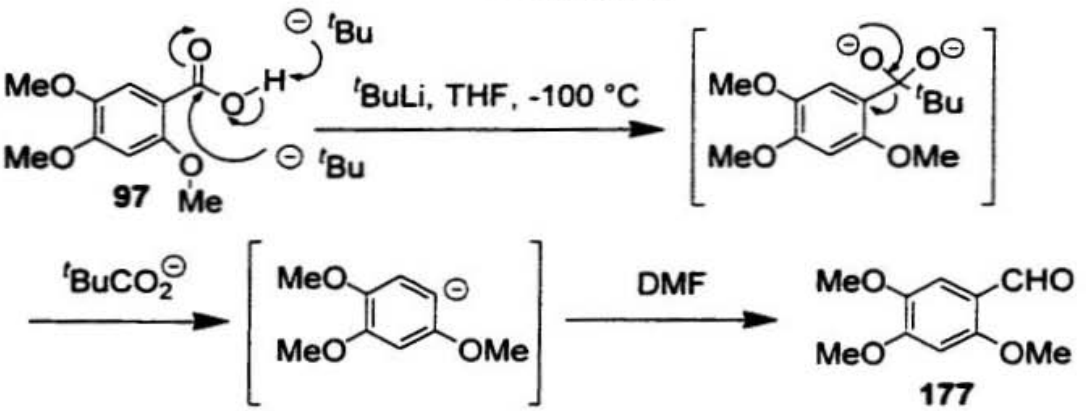
97

Scheme 75



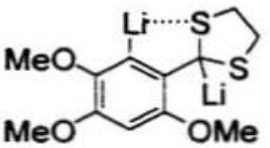
177 R = H (30%)
178 R = ^{t}Bu (10%)

Scheme 76



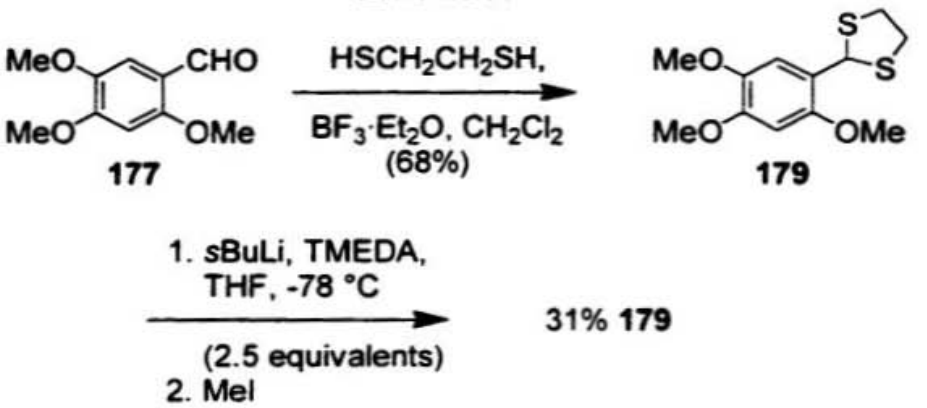
To the best of our knowledge, no precedent exists in the literature for the use of dithianes and/or dithiolanes as DMG's. Despite this, we hoped that the dianion generated by deprotonation of **179** would be stabilized by the lone pairs on the sulfur atoms (Figure 4), and that the dilithiated species would react with an appropriate electrophile to furnish a pentasubstituted aromatic compound that could be appropriately functionalized.

Figure 4: Possible chelation in dilithiated 179



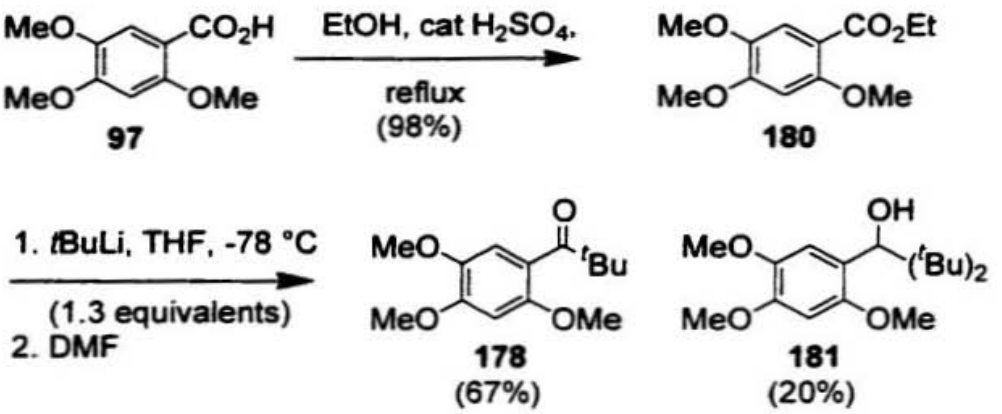
Despite the conversion of **177** to **179** in 68% yield, attempts to *ortho*-functionalize **179** were unsuccessful (Scheme 77) and only 31% of **179** was returned. the remainder of the material being an intractable mixture. Surprisingly. no methylation at C-1' was observed.

Scheme 77



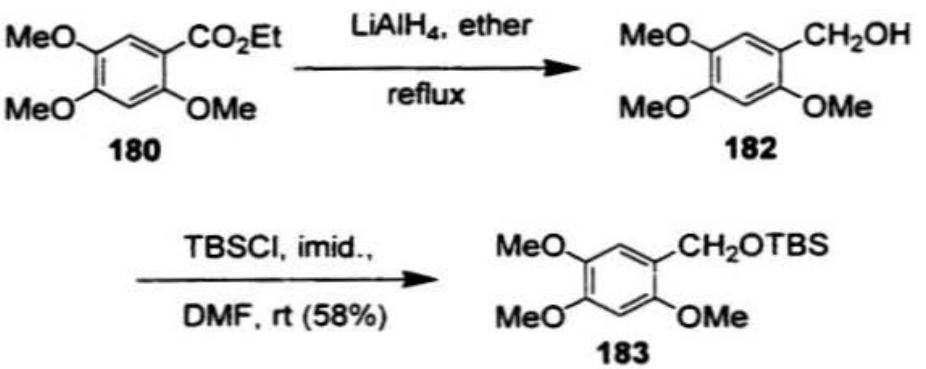
Sparse utilization of esters as the DMG exists in the literature. though a recent report[52] suggests that $CO_2CH_2{}^tBu$ may provide synthetically useful DoM chemistry. When ester **180** was subjected to *ortho*-lithiation conditions. it was not at all surprising that no measurable *ortho*-lithiation had transpired. but simple displacement of the ethoxide by *tert*-butyllithium had occurred to furnish **178**. as well as subsequent attack of *tert*-butyllithium on **178** to yield tertiary alcohol **181** (Scheme 78). Given the large amount of work in the literature directed towards amide hydrolysis after the DoM. one would suppose that if esters were reasonable DMG's. then their employment as DMG's would be much more widespread since esters are much more easily manipulated than are amides.

Scheme 78



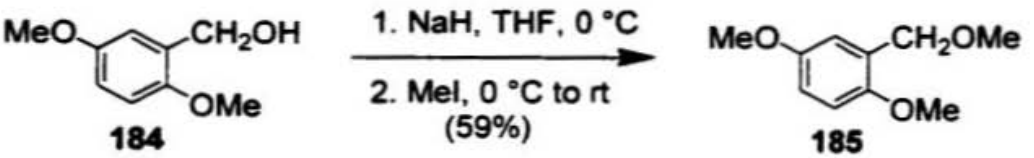
Also explored as potential DMG's were substrates **182** and **183** (Scheme 79). It is known that benzylic alcohols[53] and protected benzylic alcohols[54] can participate in DoM chemistry, though their strength as DMG's is certainly less than that of amides.[38] Yet, their easy manipulation after the DoM makes them attractive as potential DMG's. Unfortunately, both **182** and **183**, when subjected to the appropriate reaction conditions, did not furnish any *ortho*-functionalized product. A simpler analogue, compound **185**.

Scheme 79



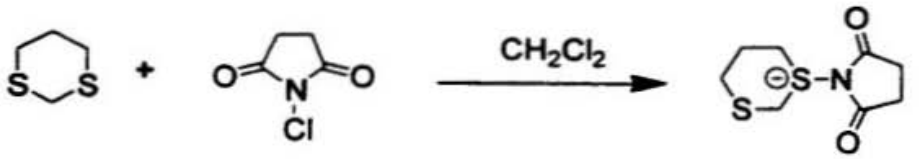
obtained by methylation of commercially available **184**, also showed no evidence of any *ortho*-functionalized product (Scheme 80) when subjected to similar conditions. We postulate, as did Rodrigo and co-workers[55] that the presence of a substituent *ortho* to the DMG seriously compromises the efficacy of the DoM reaction, presumably due to unfavorable steric interactions.

Scheme 80

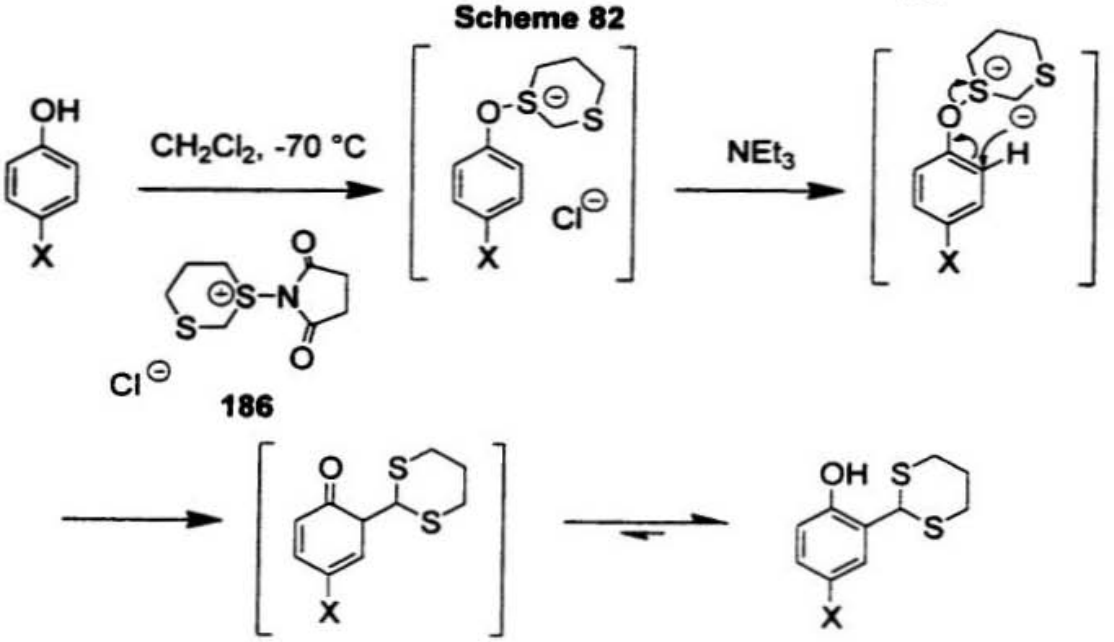


Also investigated was the possibility of having the formyl substituent added in protected form, i.e., as the dithiolane or dithiane. A dithiolane or a dithiane as an electrophilic species is not an unknown phenomenon,[56] and precedent exists in the literature for the *ortho*-formylation of phenols and aromatic amines.[57a-e] Ladislav and co-workers[57a] reported the reaction of 2-chloro-1,3-dithiane with various substituted phenols that led to 2-(1,3-dithianyl)phenols, albeit in poor yields (17–43%). Gassman[57b-e] also reported the reaction of **186**, obtained from the reaction of *N*-chlorosuccinimide with 1,3-dithiane (Scheme 81), with phenols[57b,e] and aromatic amines[57c,d] to yield *ortho*-substituted products in low yields (30–46%) (Scheme 82). Attempts to extend this methodology to compound **188**, obtained from commercially available 4-hydroxy-3-methoxybenzoic acid (**187**) *via* simple Fischer esterification (Scheme 83), were unsuccessful.

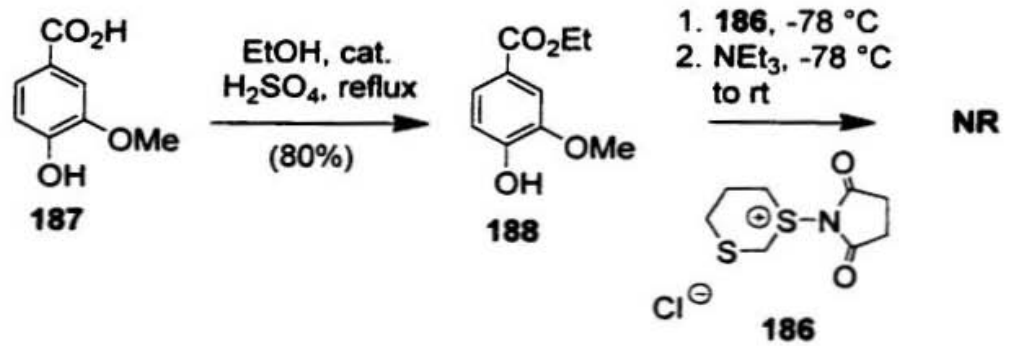
Scheme 81



Scheme 82



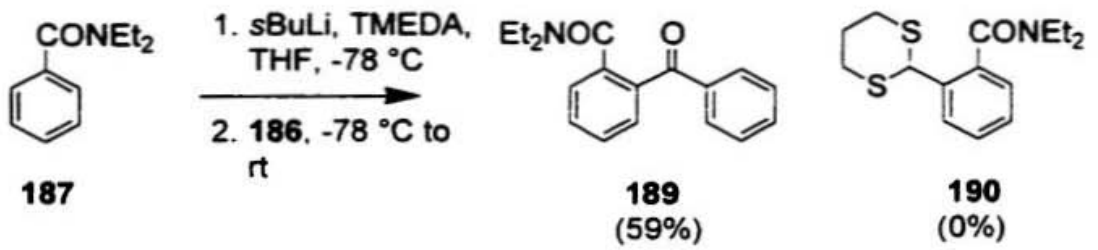
Scheme 83



Presumably, the electron donating group *ortho* to the hydroxyl sufficiently activated the ring to inhibit carbanion attack after triethylamine effected deprotonation. As this methodology could not be extended to model compound **188**, efforts were not undertaken to attempt this methodology on a more highly functionalized substrate.

After a thorough review of the literature, it is believed that dithiolanes and dithianes have not been employed as electrophiles in the DoM reaction. Notwithstanding this, model studies were undertaken to *ortho*-functionalize *N,N*-diethylbenzamide in this fashion. Deprotonation of *N,N*-diethylbenzamide using standard conditions, followed by addition of **186** merely resulted in self-condensation, yielding 59% of **189** (Scheme 84) and none of the desired product **190**.

Scheme 84



187 **189** (59%) **190** (0%)

Diels-Alder and Small-Molecule Extrusion Methodology

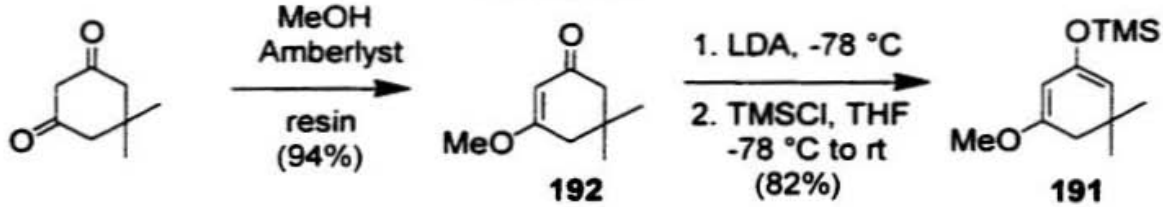
Another method for the synthesis of substituted aromatic molecules is the Diels-Alder reaction followed by small-molecule extrusion (Scheme 85).[58a-c]

Scheme 85

Therefore, by appropriate functionalization of the diene and the dienophile, followed by small-molecule extrusion after the [4 + 2] cycloaddition, a large number of A ring synthons might be synthesized.

Initial studies centered on the synthesis of a diene such as **191**, with oxygen functionality at the 1 and 3 positions on the diene. Acid-catalyzed formation of methyl enol ether **192** from commercially available dimedone, followed by subjection of **192** to Conia's[59] *O*-trimethylsilylation procedure furnished diene **191** in good overall yield

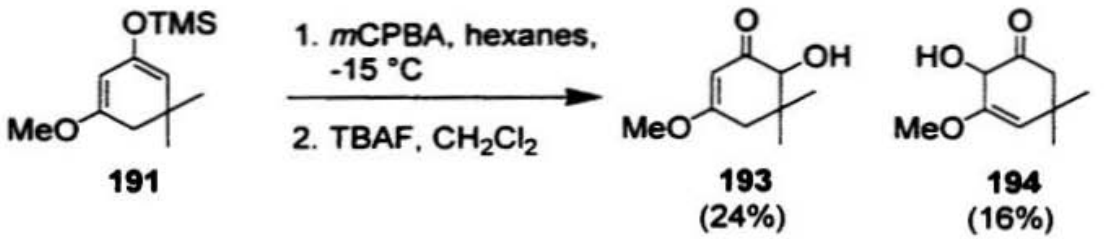
Scheme 86



(Scheme 86). With **191**, and derivatives thereof, the small molecule that would be eliminated after the [4 + 2] cycloaddition would be isobutene. The eventual goal was to synthesize a derivative of **191** with oxygen functionality at the 1, 2, and 4 positions of the

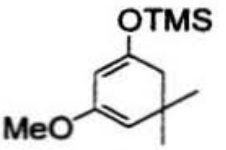
diene. This was effected by a Rubottom oxidation[60] of **191** to yield α-hydroxy ketone **193** (Scheme 87). In this exploratory reaction the yield of **193** was poor.

Scheme 87



191 **193** (24%) **194** (16%)

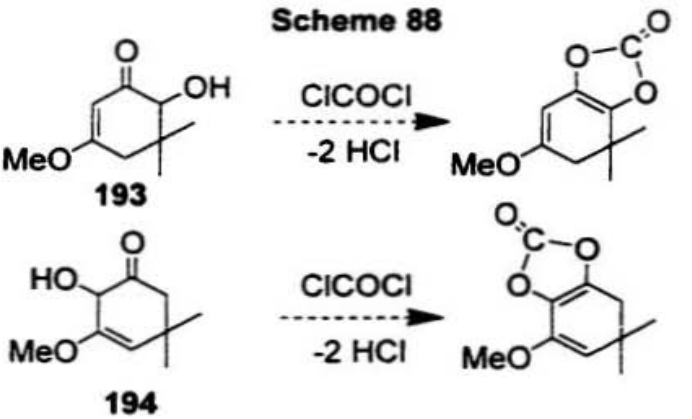
Regioisomer **194** was also isolated in 16% yield, presumably from epoxidation of the isomeric **195**, along with 40% of **192** from desilylation of **191**.



195

Thus, in order to obtain a diene with oxygen functionality in the 1,2, and 4 positions, either **193** or **194** could be "trapped" with phosgene (Scheme 88).

Scheme 88

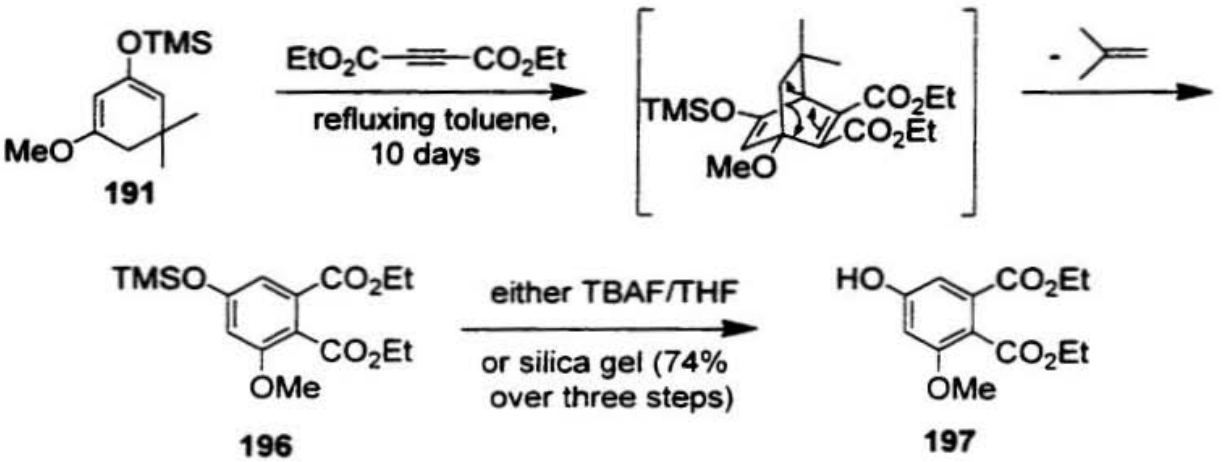


193

194

Our first studies were on the reaction of diene **191** with diethyl acetylenedicarboxylate. As expected, this furnished tetrasubstituted aromatic **196**, which, to facilitate handling, was desilylated by treatment with either TBAF or by silica gel chromatography, to furnish phenol **197** in 74% overall yield for cycloaddition, elimination of isobutene, and desilylation (Scheme 89).

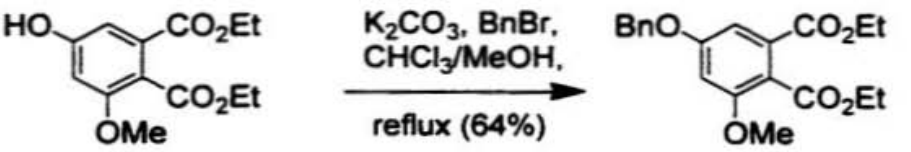
Scheme 89



Thus, in order to functionalize **197** appropriately for annulation in the tandem Michael-Claisen process, one of the ester moieties needed to be converted to a dithiolane. In order to carry this out, we were hopeful that one of the esters would be more reactive than the other, allowing for some degree of selectivity. Before attempting this, it seemed prudent to protect the phenol as a benzyl ether[61] (Scheme 90). Unfortunately, under varied reaction conditions, metal hydride reduction of **198** showed little selectivity and did not stop at the aldehyde, but reduced the aldehyde to the benzylic alcohol, which subsequently cyclized to furnish a lactone. Given this disappointing result, it appeared

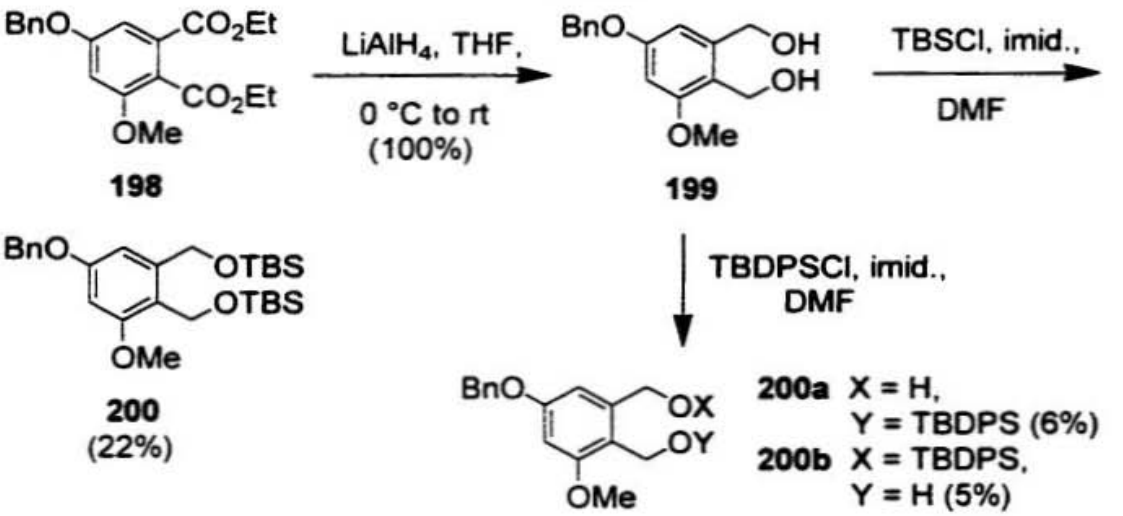
that reduction to diol **199** was the most viable option, followed by monoprotection of the less hindered alcohol.

Scheme 90



Whilst reduction of **198** to diol **199** was quantitative, the attempted monoprotection of **199** was surprisingly difficult (Scheme 91). Treatment of **199** with 1.3 equivalents of TBSCl furnished only one product, **200**, in 22% yield. No monoprotected species could be detected. In an attempt to inhibit this double protection, we went to the larger TBDPSCl, but the results were again disappointing, yielding only 5% and 6% of the isomeric monoprotected species.

Scheme 91



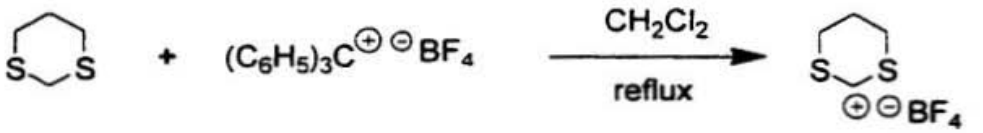
Given the difficulties that were encountered in attempts to functionalize after the cycloaddition and aromatization, a slight change in strategy was envisioned whereby an unsymmetrical dienophile would be employed in the Diels-Alder cycloaddition.

The target was dienophile **201**. The first-generation strategy was based on the

201

reaction of the anion derived from ethyl propiolate with the electrophilic 1,3-dithianyl tetrafluoroborate (**202**). Compound **202** is readily obtained by heating 1,3-dithiane and triphenylcarbenium tetrafluoroborate in dichloromethane under reflux (Scheme 92).[62]

Scheme 92



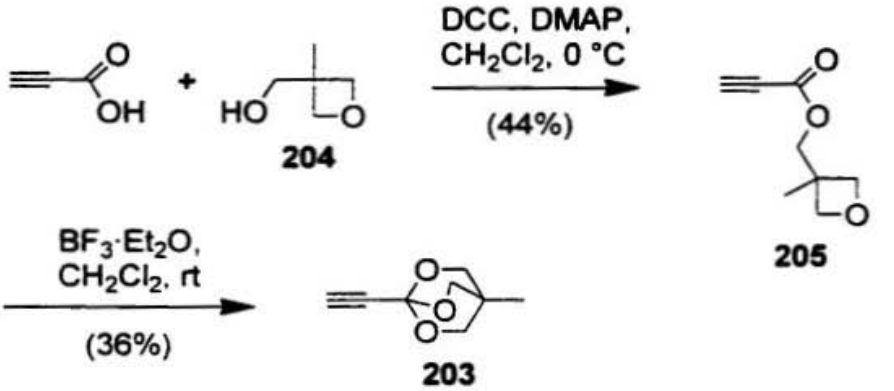
202

Much to our dismay, deprotonation of ethyl propiolate followed by addition of **202** under a wide range of reaction conditions did not yield any detectable amount of **201**. We rationalize that poor solubility of both the anion and **202** were the primary reasons for this observation.

The second-generation strategy was based on the preparation and use of a propiolate anion equivalent, compound **203**. We were optimistic that this anion would exhibit improved solubility over the anion of ethyl propiolate, and that the introduction of an electrophile into the β-position could be achieved, as done by Rousseau and co-

workers.[63] We followed Rousseau's procedure for the synthesis of **203** by starting with commercially available propiolic acid and esterifying with 3-methyl-3-(hydroxymethyl)oxetane (**204**) to furnish **205**. $BF_3{\cdot}Et_2O$-catalyzed rearrangement of **205** furnished the bridged ortho ester **203** (Scheme 93). While Rousseau did not report the necessity to purify **203** on silica gel pre-treated with triethylamine, we found, as did Corey and Raju,[64] that purification of bridged ortho esters should be on silica gel pre-treated with triethylamine. When crude **203** was subjected to untreated silica gel, rapid degradation of the crude product occurred.

Scheme 93

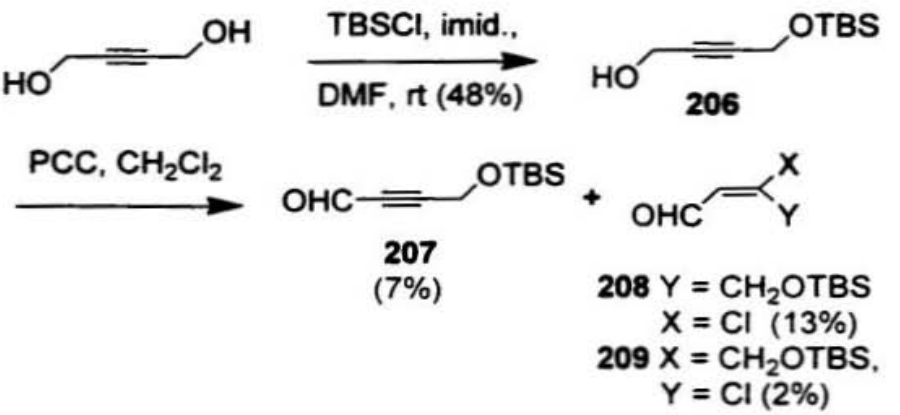


Again, as with the anion derived from ethyl propiolate, we observed no addition to the dithianyl moiety when **203** was deprotonated and **202** was added. Once more, it seemed to be due to poor solubility, presumably of the electrophilic **202**.

Presented with these less than encouraging results, it seemed that a more expedient route to **201** was *via* a six-step synthetic pathway that would provide this dienophile in sufficient quantity to see if the Diels-Alder cycloaddition was indeed a viable process. Thus, readily available 2-butyne-1,4-diol was monoprotected as the TBS

ether to furnish propargylic alcohol **206** in 48% yield, along with 15% of the doubly protected species. Initial attempts to oxidize **206** with PCC or PDC were largely unsuccessful, yielding at best 7% of ynal **207**. In fact, 13% of **208** and 2% of **209** were the only other isolable products, presumably having arisen from 1,4-conjugate addition of chloride (Scheme 94).

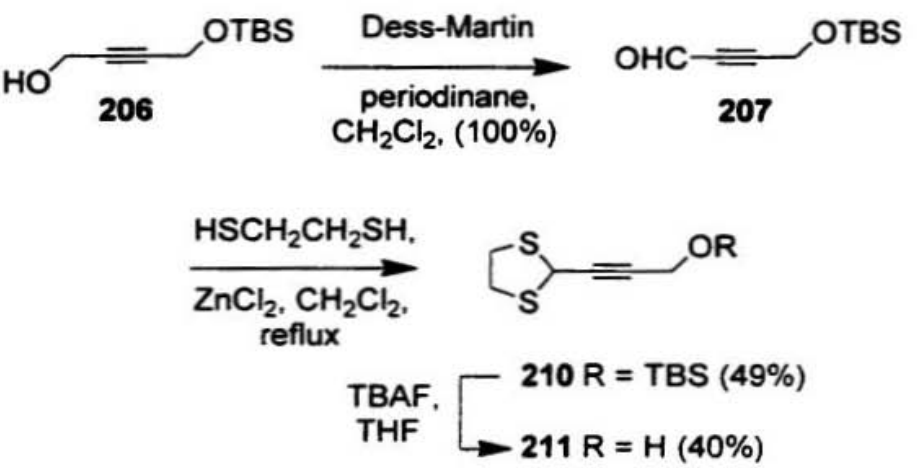
Scheme 94



Dess-Martin periodinane[65] proved to be the reagent of choice for oxidation of **206**, providing ynal **207** in quantitative yield. Other groups[66a-d] have reported the oxidation of **206** to **207** using different reagents, such as MnO_2,[66a,b] barium manganate,[66c] and the Swern protocol,[66d] but never in excellent yields. Also reported was the volatility and instability of **207**,[66b,d] though we found **207** to be non-volatile (no appreciable loss of mass after 12 hours on vacuum pump), but somewhat unstable over extended periods of time.

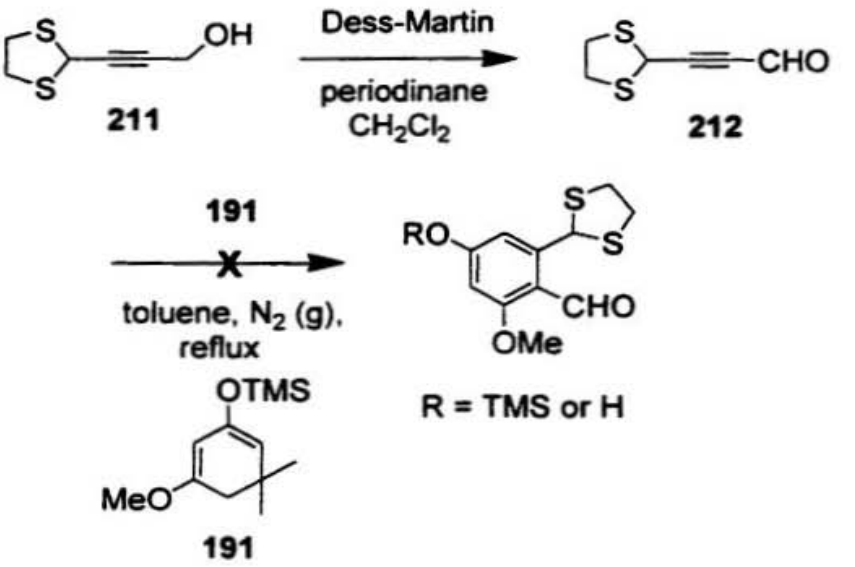
Subjection of ynal **207** to 1,2-ethanedithiol and zinc(II) chloride in dichloromethane under reflux furnished both dithiolane **210** in 49% yield and desilylated dithiolane **211** in 40% yield (Scheme 95). Compound **210** could also be converted to **211** by treatment with anhydrous TBAF in THF.

Scheme 95



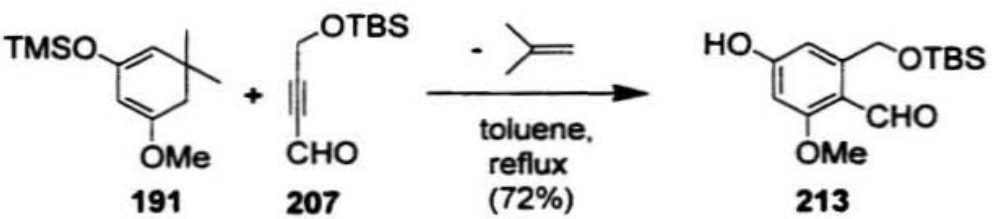
Conversion of propargylic alcohol **211** to ynal **212** proved to be troublesome. Dess-Martin periodinane oxidation of **211** appeared to work well from TLC analysis of the crude product mixture. However, attempts to work-up the reaction resulted in rapid destruction of the ynal. Modifications to the work-up were effected, such as keeping the pH neutral or slightly acidic, but still no **212** could be isolated after work-up. In the end, we decided to avoid the work-up of **212**. This crude dienophile was introduced to the diene **191** directly. Unfortunately, the cycloaddition was unsuccessful under a variety of conditions (Scheme 96).

Scheme 96



As the crude **212** proved to be unreactive as a dienophile in the Diels-Alder reaction, it was decided to instead employ ynal **207** as the dienophile. Though ynals such as **207** have served as substrates for a number of synthetic applications,[67a-f] there is no report of such an ynal serving as a Diels-Alder dienophile. Nonetheless, reaction of 1 equivalent of dienophile **207** with 1.5 equivalents of diene **191** in toluene under reflux for 7 days furnished 72% of tetrasubstituted aromatic **213** (Scheme 97). The structure of **213** was confirmed by X-ray crystallography.

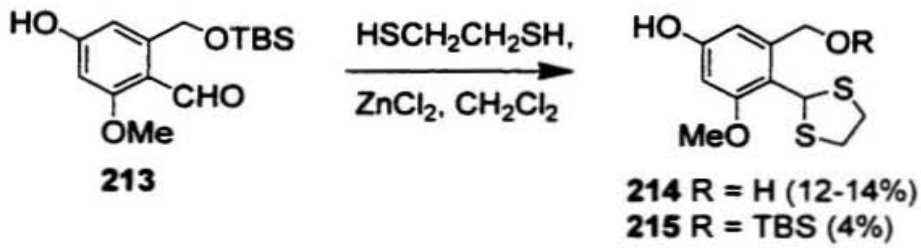
Scheme 97



Also recovered was 16% of unreacted **207**. but no other compounds were isolated. At this juncture, the strategy was to protect the aldehyde as a dithiolane and subsequently deprotect the benzylic alcohol and transform the alcohol functionality to an ester.

Attempts to transform **213** to dithiolane derivative **214** resulted in consistently low yields (Scheme 98). Small amounts of **215** were also isolated from the mixture.

Scheme 98

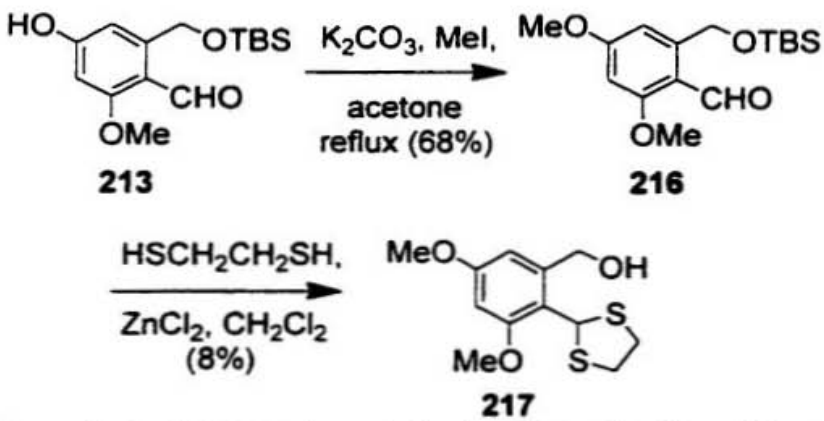


213

214 R = H (12-14%)
215 R = TBS (4%)

As **214** was a crystalline solid, its structure was confirmed by X-ray crystallography. We initially postulated that the poor mass recovery may have been due to incomplete

Scheme 99



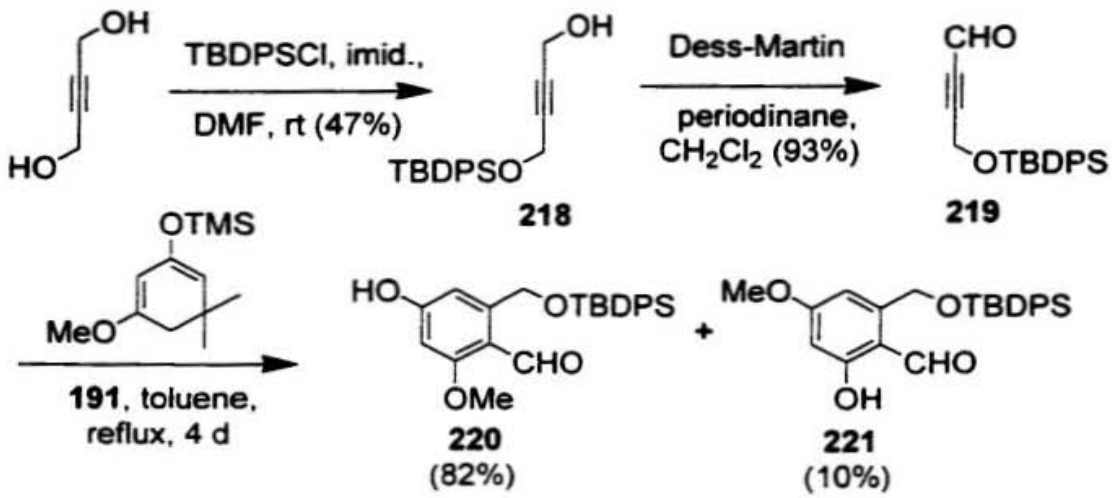
213 **216** **217**

extraction of the products during work-up, but exhaustive extraction of the aqueous layers with ethyl acetate yielded no additional material. Suspicious of the free hydroxyl group, it was protected as the methyl ether in 68% yield to furnish **216**, which was then

subjected to the same conditions as for the protection of **213**. Once more, the yield of **217** was surprisingly low (Scheme 99).

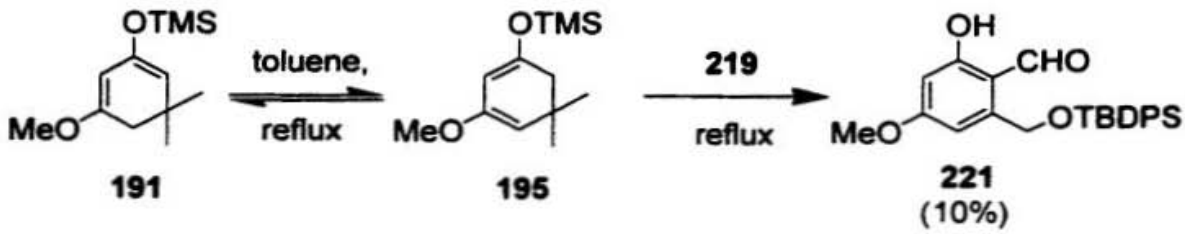
The more robust TBDPS ether, developed by Hanessian,[68] was assessed because it was apparent from the previous studies that the labile nature of the TBS group may have been a contributing factor to the poor yields. Dienophile **219** was synthesized in the

Scheme 100



same manner as dienophile **207**, *via* propargylic alcohol **218**. Ynal **219** and diene **191** were heated in toluene under reflux for 4 days, furnishing two regioisomeric adducts, **220** in 82% yield and **221** in 10% yield. This overall yield of 92% was exceptional considering that three separate processes were occurring: (i) [4π + 2π] cycloaddition, (ii) extrusion of isobutene, and (iii) spontaneous desilylation. Unlike the reaction of ynal **207** with diene **191**, which provided only one regioisomer (Scheme 97), the reaction of ynal **219** with diene **191** provided two regioisomers, presumably from thermal isomerization of **191** to **195** (Scheme 101), an allowed [1,5] H-shift.

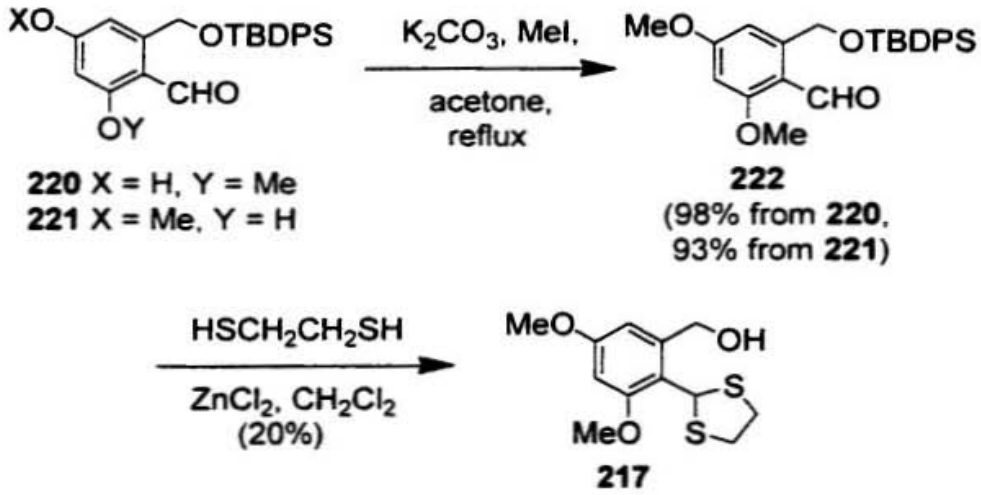
Scheme 101



191 **195** **221** (10%)

Methylation of either **220** or **221** furnished the same tetrasubstituted aromatic **222** (Scheme 102). Once again, conversion of **222** to the corresponding dithiolane derivative **217** yielded only 20% of the desired product.

Scheme 102



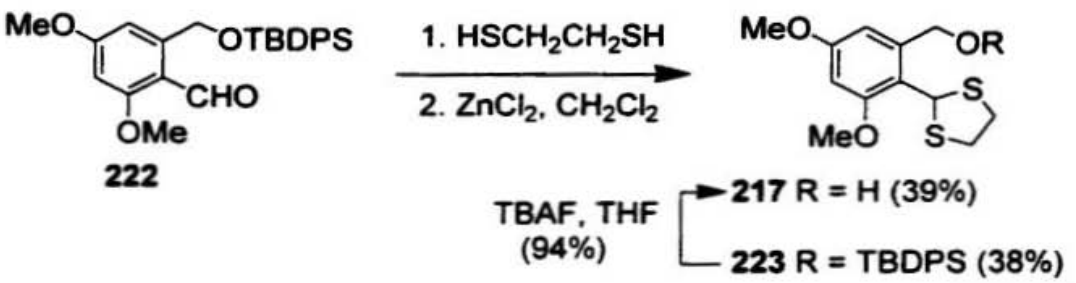
220 X = H, Y = Me
221 X = Me, Y = H

222 (98% from **220**, 93% from **221**)

217

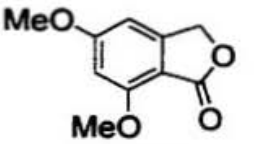
However, a simple change to the reaction protocol resulted in much improved yields of the desired substrates. By addition of 1,2-ethanedithiol to **222** *prior* to the addition of the Lewis acid catalyst, the combined yield of **217** and **223** jumped to 77% (Scheme 103). Thus, the reactions leading to either dithiolane derivative **217** or **223** must have been very much faster than the usual one-day stirring times would imply.

Scheme 103



Compound **223** can also be converted to **217** in 94% yield by treatment with TBAF in THF. Presumably, the $ZnCl_2$ attacks the substrate at a moderate rate, but in the presence of 1,2-ethanedithiol, the formation of the dithiolane is even faster. Thus addition of the catalyst last allows the desired reaction to proceed to a much greater extent.

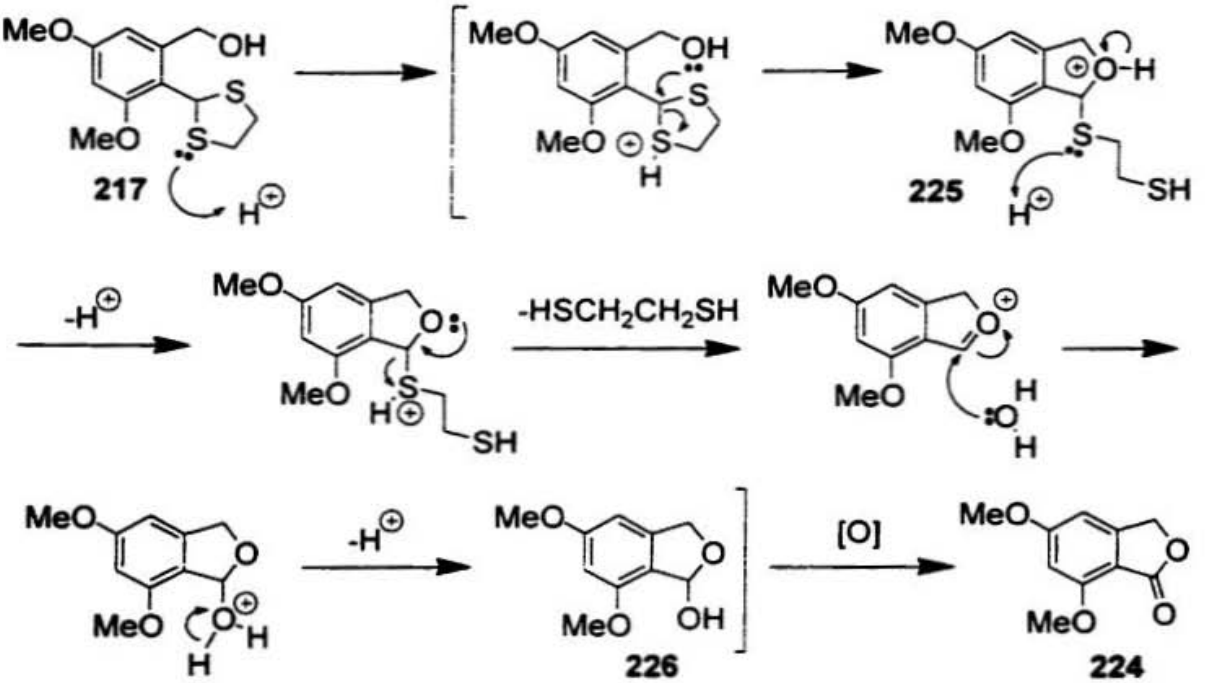
With compound **217** in hand, the next task was to oxidize the benzylic alcohol to the acid. Chromium-based reagents,[69a-d] ruthenium tetraoxide,[69e] sodium chlorite and catalytic 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) radical,[69f] MnO_4^- with a phase transfer catalyst,[69g] hydrogen peroxide and a catalyst,[69h] and PDC in DMF[69i-k] are amongst reagents available for the conversion of primary alcohols to carboxylic acids. $NaClO_2$,[70a,b] Ag_2O,[70c-m] and Corey's protocol[70n] are amongst reagents available for the conversion of aldehydes to carboxylic acids. These seemingly simple conversions often prove to be troublesome and may work only on simple monofunctionalized substrates. We chose Jones reagent as the oxidant and followed the procedure carried out by Oehlschlager and co-workers[69a] in which an acetone solution of **217** is added to the Jones reagent. By TLC, there was an apparently clean conversion of **217** to a new product. This compound was crystallized, and determined by X-ray analysis to be lactone **224**.



224

One mechanism for the formation of **224** is postulated in Scheme 104. Under the acidic conditions of the Jones oxidation, protonation on the dithiolane takes place facilitating ring formation in **225**. Displacement of 1,2-ethanedithiol followed by addition of water from the sulfuric acid solution leads to lactol **226**, which is then readily oxidized to lactone **224** in the presence of the Jones reagent.

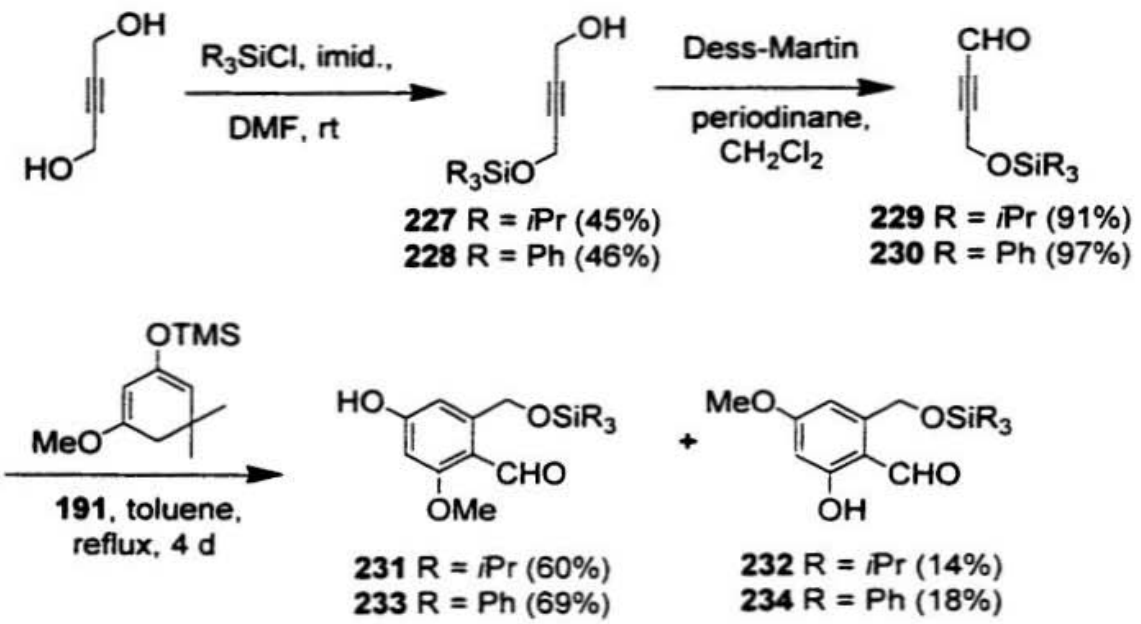
Scheme 104



As a side issue, we were interested in the formation of the minor regioisomer **221** in the Diels-Alder reaction of dienophile **219** and diene **191** as it possessed a pattern of

methylation complementary to that of the major regioisomer **220**. We postulated that the appearance of **221** in the reaction with **219** was the result of a slower rate of Diels-Alder addition with **219** than **207** such that isomerization of **191** to **195** was a competitive process with **219**. Investigating this phenomenon, we synthesized the somewhat bulkier dienophiles **229** and **230** *via* monoprotected trialkylsilyloxy ethers **227** and **228** (Scheme 105) for reaction with diene **191**. When the triisopropylsilyloxy ether **229** was employed

Scheme 105



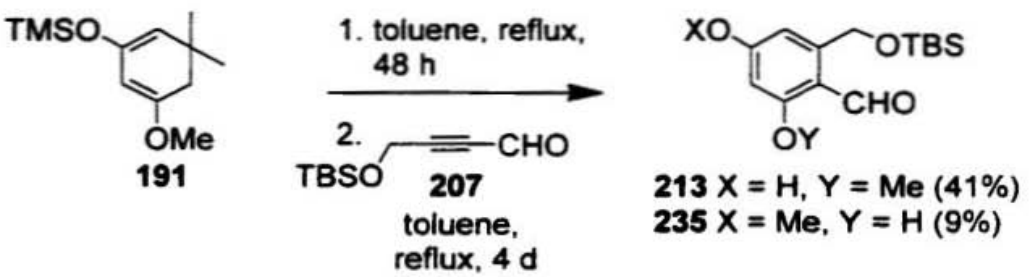
as the dienophile, 60% of the major regioisomer **231** was formed, compared to 14% of the minor regioisomer **232** along with 14% of returned dienophile **229**. When the triphenylsilyloxy ether **230** was employed as the dienophile, 69% of the major regioisomer **233** was formed, compared to 18% of the minor regioisomer **234** along with 7% of returned dienophile **230**. These results are summarized in Table 2.

Table 2: Summary of Investigations into Diels-Alder Reaction of Various Acetylenic Dienophiles with Diene 191.

	regioisomer from 191	regioisomer from 195	ratio	total yield	returned dienophile
207 TBS ether	72%	none detected		72% (86% based on recovered SM)	16%
219 TBDPS ether	82%	10%	8.2 : 1	92%	none detected
229 TIPS ether	60%	14%	4.3 : 1	74% (86% based on recovered SM)	14%
230 TPS ether	69%	18%	3.8 : 1	87% (94% based on recovered SM)	7%

Heating a toluene solution of **191** at reflux for 48 hours led to a 3.2:1 mixture of **191** and **195**, and addition of dienophile **207** to this solution now gave a mixture of **213** and the previously undetected isomer **235** (Scheme 106).

Scheme 106

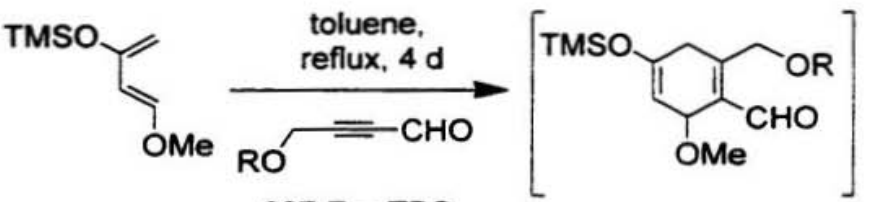


However, our simple hypothesis that the bulkier dienophiles **219**, **229**,and **230** might have slower rates in the Diels-Alder cycloaddition, thus allowing for thermal isomerization of **191** to **195**, was clearly not correct because a competitive reaction

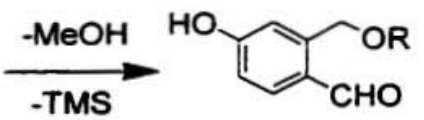
between equimolar amounts of **207** and **219** with diene **191** gave a 1:1 mixture of the corresponding TBS and TBDPS compounds.

In order to extend the use of these trialkylsilyloxy ethers as dienophiles, we reacted them with 1-methoxy-3-(trimethylsilyl)oxy-1,3-butadiene (Danishefsky's diene)[71] to give α-(trialkylsilyloxymethyl)benzaldehydes **236a-d**, after thermal elimination of methanol and hydrolysis of the trimethylsilyl ether groups during subsequent chromatography (Scheme 107). A competitive reaction between equimolar amounts of **207** and **219** with Danishefsky's diene also gave a 1:1 mixture of the corresponding TBS and TBDPS compounds.

Scheme 107



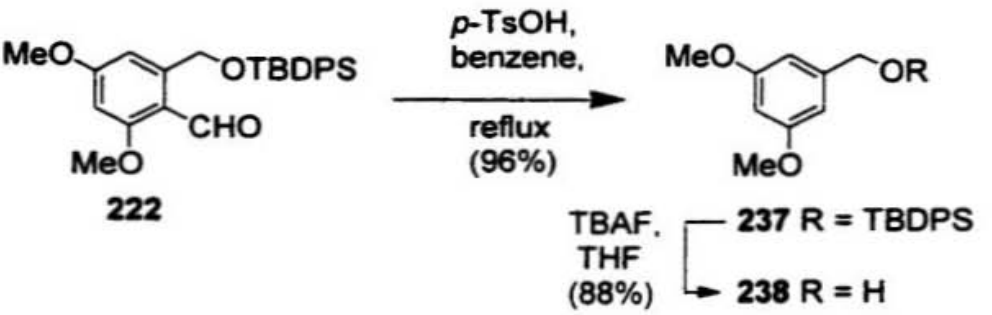
207 R = TBS
219 R = TBDPS
229 R = TIPS
230 R = TPS



236a R = TBS (79%, 96% based on recovered SM)
236b R = TBDPS (61%,100% based on recovered SM)
236c R = TIPS (75%, 85% based on recovered SM)
236d R = TPS (86%, 97% based on recovered SM)

When a benzene solution of **222** and *p*-TsOH was simply heated to reflux, **237** was obtained in 96% yield (Scheme 108). Desilylation of **237** furnished **238**, which was identical in all respects with the commercially available 3,5-dimethoxybenzyl alcohol.

Scheme 108



In the conversion of **222** to **217** and **223** (Scheme 103), the critical sensitivity of the order of addition was probably due largely to an unexpected facile acid-mediated decarbonylation reaction. Re-examination of the attempted conversion of **216** to **217** showed that, indeed, the symmetrical **238** was being formed in 17% yield. Obviously, this decarbonylation was an important factor for the poor yields observed in these attempted conversions. The relatively electron-rich 2,4-dimethoxybenzaldehyde could not be decarbonylated under these same conditions (*p*-TsOH, benzene, reflux), therefore the protected hydroxymethylene group was responsible for the ease of decarbonylation. Acid-mediated decarbonylation of aromatic aldehydes, including 2,4,6-trimethoxybenzaldehyde,[72] has been known for quite some time. However, the mechanism of a "reverse Gatterman-Koch reaction" has been postulated to involve loss of HCO^+, and strong acids, such as concentrated H_2SO_4, $HClO_4$, HCl, HBr or HNO_3 are the typical reagents.[73] Milder methods employ rhodium or palladium reagents.[74]

Recently, Ito and co-workers[75] reported the decarbonylation of two bis-(3-azulenecarbaldehyde)methane compounds with a mixture of acetic acid and pyrrole, but these azulene derivatives are very easily protonated in this medium. Decarboxylation of benzoic acid derivatives is accelerated by steric hindrance and the presence of electron donating groups,[76] but no report in the literature of similar behavior for decarbonylation could be found.

Dimethyl Acetal as a Director for *ortho*-Metallation

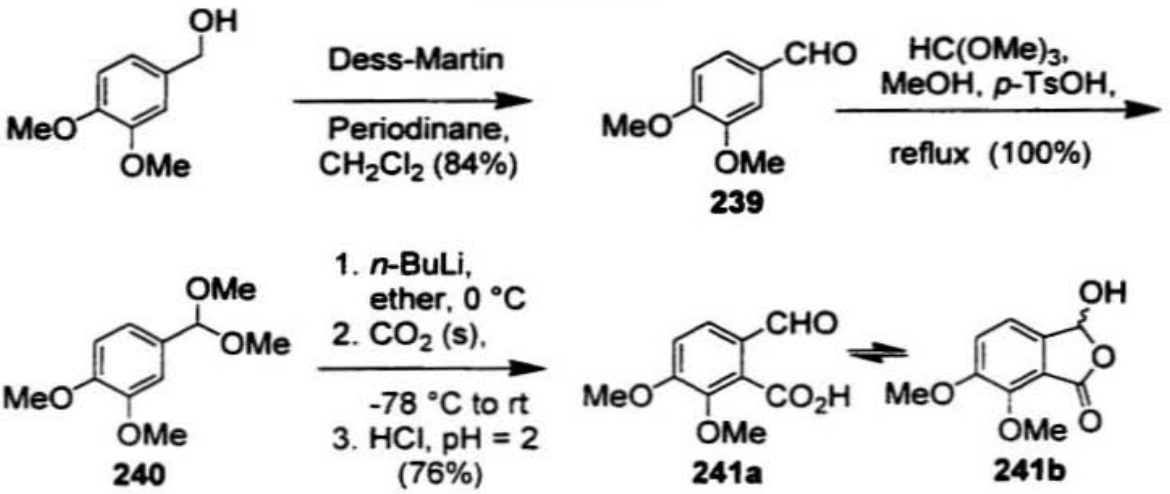
Given the unexpected decarbonylation problem, acid catalyzed cyclization difficulties, and possible oxidation of the sulfur atoms to the sulfoxide or sulfone by the oxidation of benzylic alcohol derivatives to the corresponding carboxylic acids, a method for the introduction of a substituent at the appropriate oxidation level was essential.

We settled upon the dimethyl acetal of 3,4-dimethoxybenzaldehyde as a suitable starting material for the synthesis of an appropriate A ring synthon.[55] If successful this would furnish an A ring synthon lacking one methoxyl group. It was our plan, however, to introduce this oxygen after the annulation, as precedent for this transformation existed in the literature.[77]

Though 3,4-dimethoxybenzaldehyde is commercially available, we started with 3,4-dimethoxybenzyl alcohol as this compound was on hand (Scheme 109). Aldehyde **239** could be prepared on a relatively large scale (*ca.* 20 g) from 3,4-dimethoxybenzyl alcohol using Dess-Martin periodinane.[65] Compound **239** was converted to dimethyl acetal **240** by the procedure of Wenkert and Goodwin[78] in quantitative yield. Regiospecific lithiation of **240** using *n*-BuLi in diethyl ether at 0 °C took place at C-2,

and reaction of this lithiated species with CO_2(s), followed by hydrolysis of the acetal furnished the phthalaldehydic acid analogue **241a** in 76% overall yield, which ^{1}H NMR spectroscopy revealed was in equilibrium with ring-closed form **241b**.

Scheme 109

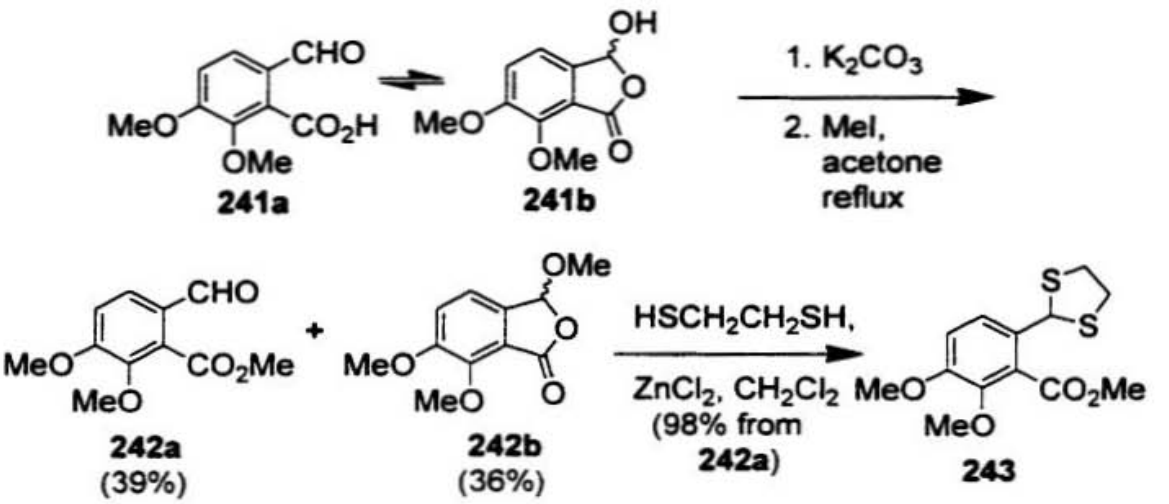


This methodology has several limitations. First, an oxygen cannot be *ortho* to the dimethyl acetal in **240** as it is postulated that complexation of the lithium with the acetal oxygen atom for *ortho*-deprotonation is sterically inhibited, altered or disfavored in some way by the *ortho* substituent. Secondly, the reaction calls for the placement of an alkoxy group in a *meta* arrangement to the acetal group. This is rationalized in terms of the lower acidity of the aromatic hydrogens in such a compound.[65] Though an oxygen is necessary in this position for natural **1**, this requirement limits the number of analogues that can be synthesized.

Compound **241a,b** was converted to an inseparable mixture of methyl ester **242a** and cyclized **242b** by treatment with K_2CO_3 followed by iodomethane, and heated in

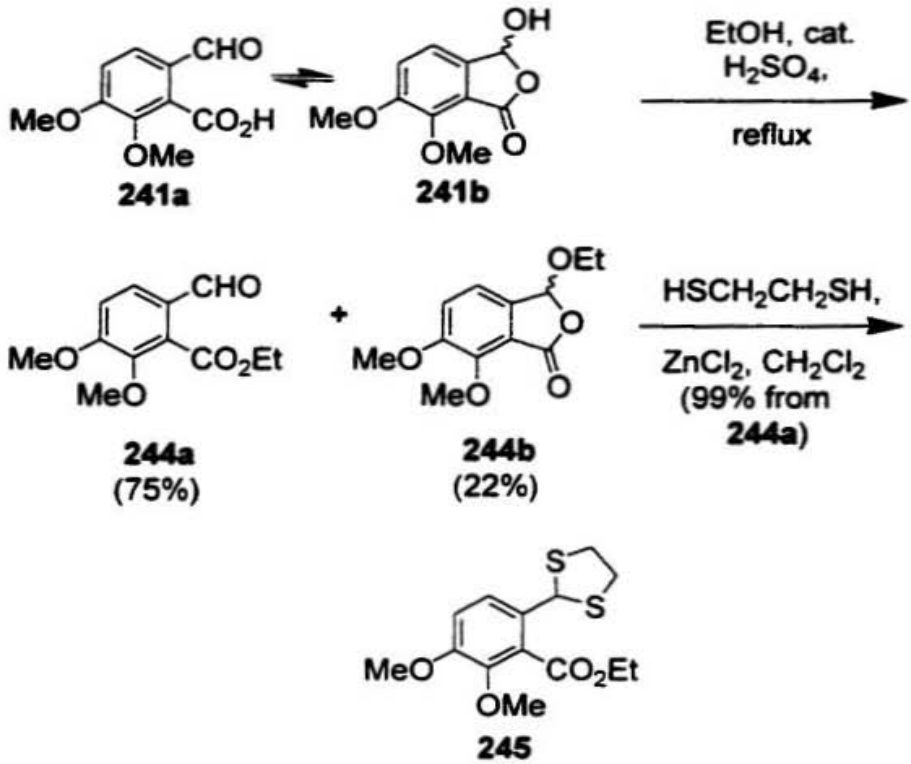
acetone under reflux (Scheme 110). Methyl ester **242a** was reacted with 1,2-ethanedithiol and zinc(II) chloride in dichloromethane to furnish the desired A ring synthon **243** in 98% yield from **242a**, along with unreacted **242b**. These were then separated by chromatography.

Scheme 110



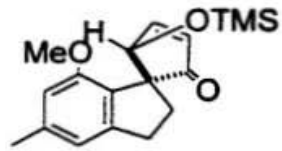
Disappointed with the yield of **242a** from **241a,b**, we subjected **241a,b** to Fischer esterification conditions (Scheme 111). Under acid catalysis conditions, the ratio of the ring-opened form to the ring-closed form was increased from 1.1:1 to 3.4:1. Once again, **244a** and **244b** were inseparable, but the mixture was carried forward and subjected to reaction with 1,2-ethanedithiol and zinc(II) chloride in dichloromethane to furnish **245** and unreacted **244b**. At this point, these were separated by chromatography.

Scheme 111



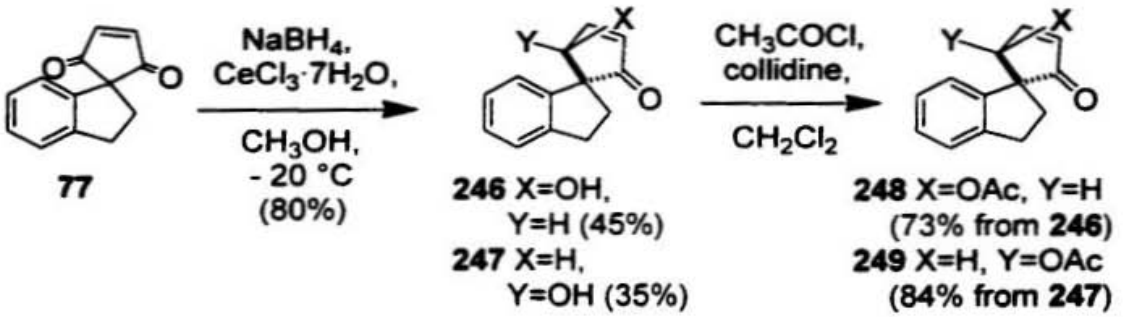
Tandem Michael-Claisen Process with Substituted A Ring Synthon

With the functionalized A ring synthon **245** in hand, we were confident that the previously employed tandem Michael-Claisen process could be effected to annulate **245** to CDE synthon **135**, or the less functionalized CDE synthons **248** or **249**. Diastereomers **248** and **249** were synthesized by a relatively simple route (Scheme 112).



135

Scheme 112



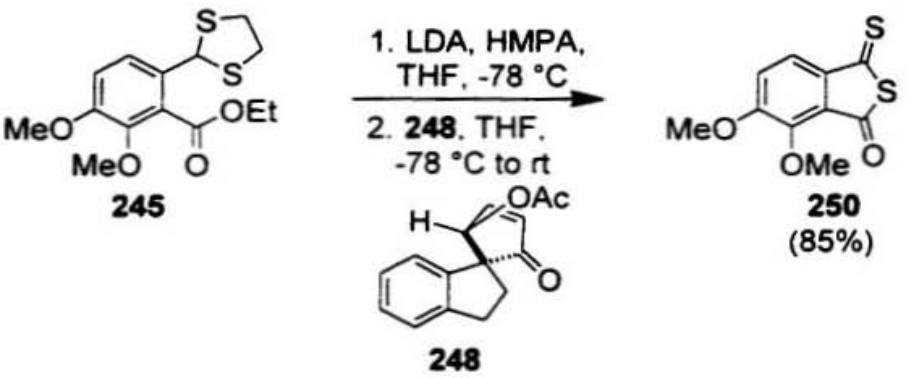
77

246 X=OH, Y=H (45%)
247 X=H, Y=OH (35%)

248 X=OAc, Y=H (73% from **246**)
249 X=H, Y=OAc (84% from **247**)

In each attempted annulation, i.e., addition of lithiated **245** to **135**, **248**, or **249**, the expected product was not returned. In each case, the only product that could be isolated from the reaction mixture was phthalic thiothionoanhydride **250** (Scheme 113).

Scheme 113



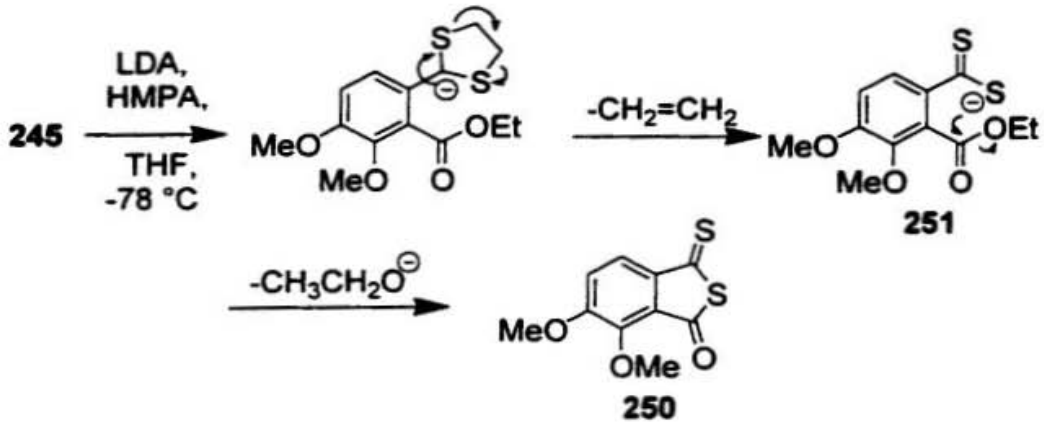
245

248

250
(85%)

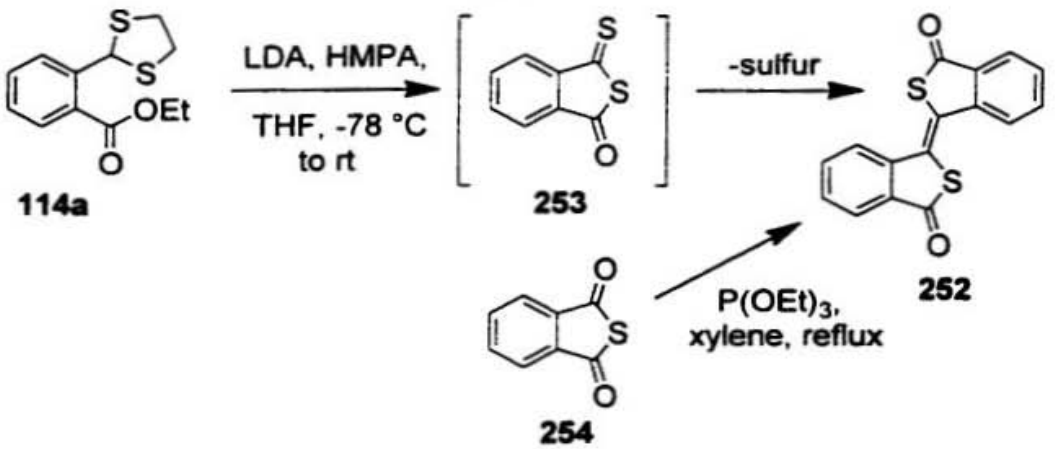
After a comprehensive review of the literature, it was ascertained that we had accomplished, albeit by chance, the first synthesis of an unsymmetrically substituted phthalic thiothionoanhydride.[79] The rationale for the formation of **250** is presented in Scheme 114. Fragmentation of dithiolane **245**, with loss of ethene, would give **251**, and cyclization would then lead to phthalic thiothionoanhydride **250**.

Scheme 114



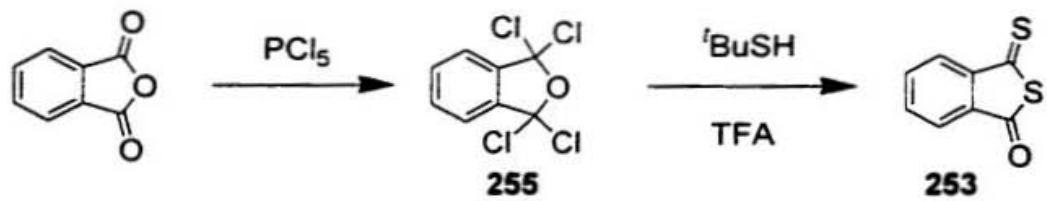
Not surprisingly, when **114a** was deprotonated and allowed to warm to room temperature in the absence of a Michael acceptor, 3,3'-bithiophthalide **252** was obtained in 83% yield, presumably *via* **253**. Compound **252** has been known for over 100 years as the product of reductive dimerization of phthalic thioanhydride **254**.[80] Cava and co-workers[81] have found that **253** is not stable as it readily loses sulfur to give **252** (Scheme 115).

Scheme 115

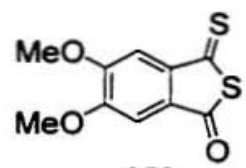


There are very few examples of analogues of anhydrides in which more than one oxygen is replaced by sulfur. These structurally-interesting compounds were not reported until the early 1980's.[82] The simple phthalate **253** was synthesized only once. To prepare **253**, Cava[81] began with phthalic anhydride. Treatment with PCl_5 afforded 1,1,3,3-tetrachloro-1,3-dihydroisobenzofuran **255**. Its reaction with 1,1-dimethylethanethiol in trifluoroacetic acid gave, after rearrangement, **253** (Scheme 116). The same procedure was used to obtain the dimethoxy compound **256** from the symmetrical 4,5-dimethoxyphthalic anhydride, but this procedure cannot be expected to provide only one phthalic thiothionoanhydride from an unsymmetrically substituted phthalate.

Scheme 116



255 **253**

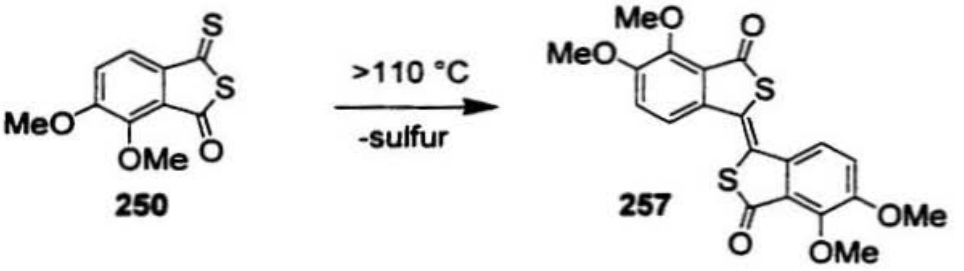


256

Cava noted that **256** was less prone to reductive dimerization than is **253**.[81] Similarly, **250** proved to be stable over an extended period of time at room temperature. Nevertheless, when molten **250** was heated above 110 °C, the dimeric compound **257** rapidly resolidified (Scheme 117). The ^1H NMR spectrum of **257** closely resembled the

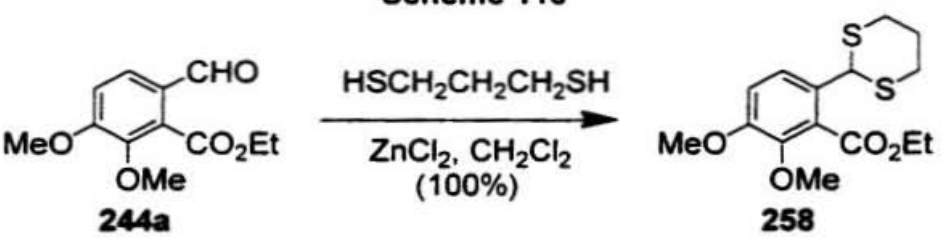
spectrum of **250**, but the melting point of **257** was above 310 °C, and molecular ions are the base peaks in their mass spectra.

Scheme 117



While this first synthesis of an unsymmetrically substituted phthalic thiothionoanhydride was interesting, our primary concern remained the synthesis of **1**. Thus, a modification to **245** was necessary to circumvent the formation of **250**. We postulated that a simple change of the dithiolane moiety to a dithiane would stop this undesired fragmentation, and allow for the tandem Michael-Claisen process to proceed. Conversion of **244a** to dithiane **258** was effected in excellent yield (Scheme 118).

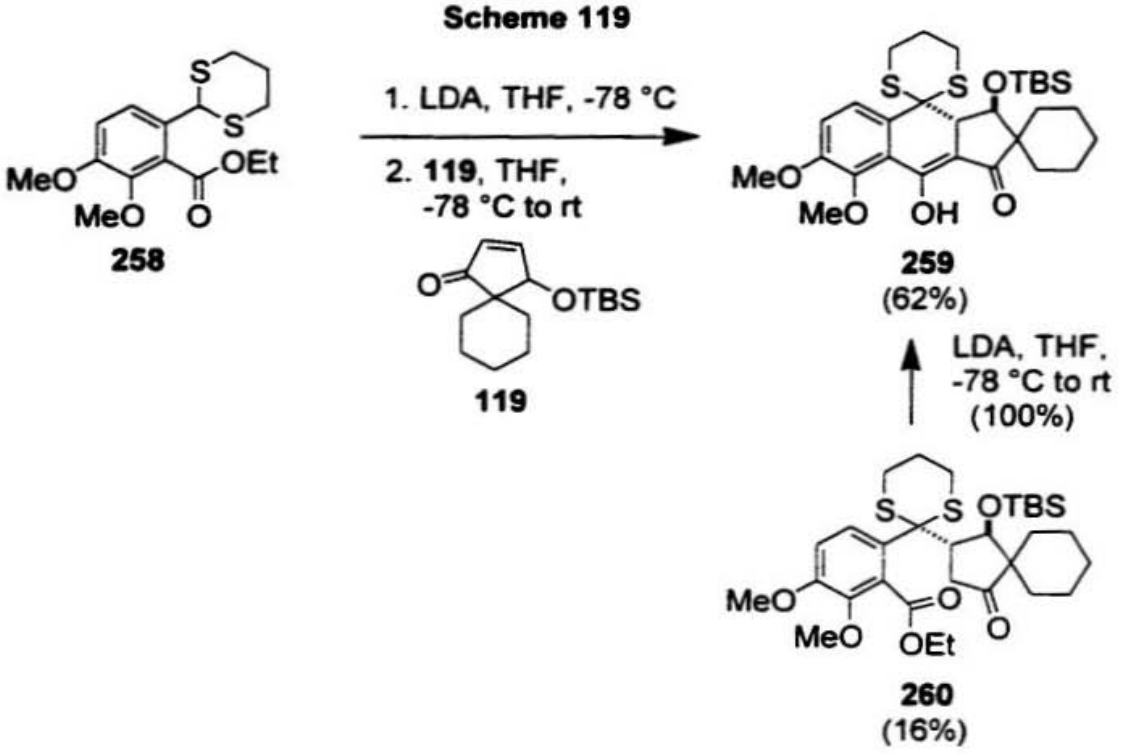
Scheme 118



With the tetrasubstituted A ring synthon **258** in hand, its deprotonation was effected with LDA at -78 °C, and Michael acceptor **119** was added. The solution was allowed to warm to room temperature. As expected, the tandem Michael-Claisen process proceeded efficiently yielding the advanced intermediate **259** in 62% yield and 16% of uncyclized

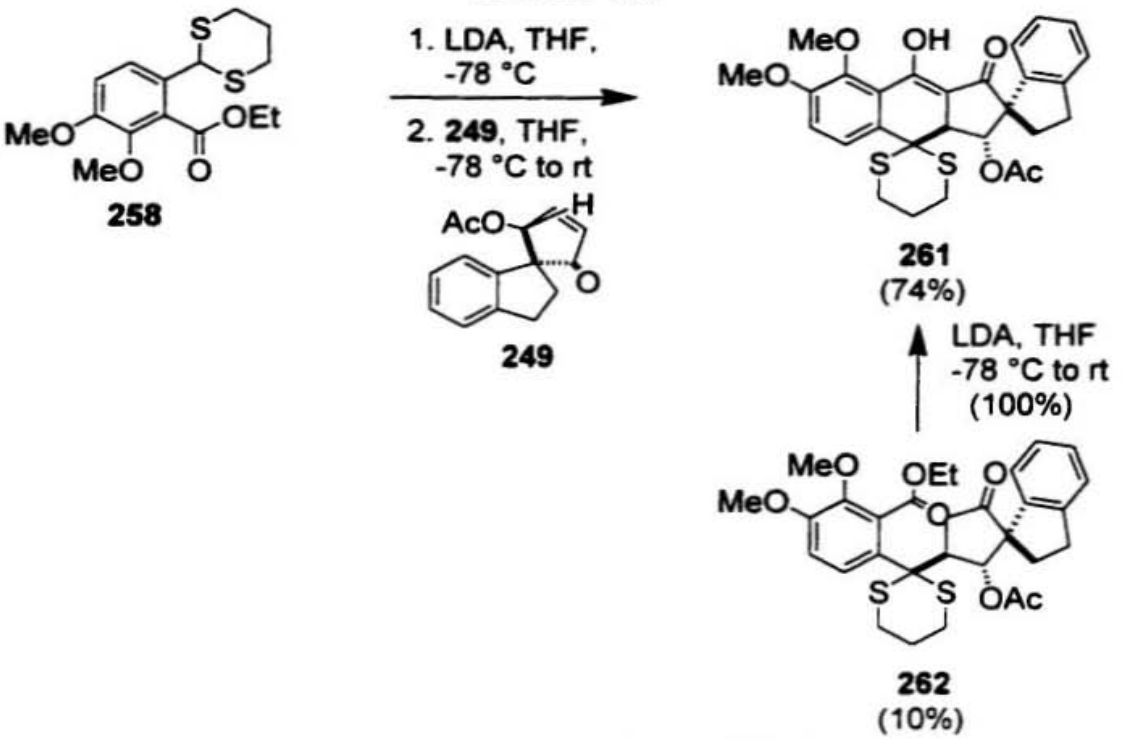
260 (Scheme 119). Subjection of **260** to LDA allowed for complete conversion of **260** to tetracycle **259**. As with the previous class of tandem Michael-Claisen processes, initial attack of the acyl anion equivalent occurred *anti* to the *tert*-butyldimethylsilyloxy group.

Scheme 119



Encouraged by this result with Michael acceptor **119**, we decided to effect the tandem Michael-Claisen process on CDE synthon **249**. Once more, deprotonation of **258** by LDA at -78 °C followed by addition of the spirocyclic enone **249** yielded pentacyclic compound **261** in 74% yield along with 10% of the uncyclized product **262** (Scheme 120). Treatment of **262** with LDA at -78 °C resulted in complete conversion to **261**. Highly functionalized compound **261** was crystallized, and X-ray crystallographic analysis confirmed its structure.

Scheme 120

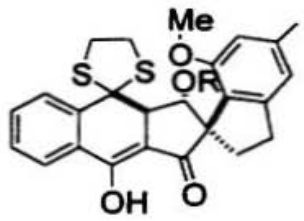


Considerations for Future Work

When this project was commenced in 1996, several goals were set. Among them was the need to develop a novel strategy for the construction of the skeleton of Fredericamycin A. It was also imperative that this strategy be compatible with enzymatic reduction methodology, allowing for the introduction of asymmetry.

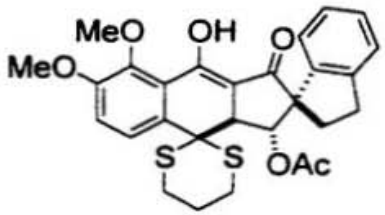
Employment of the tandem Michael-Claisen process is well-suited for use with the enzymatic reduction methodology. Therefore, in addition to the already existent methodology from our laboratories for the construction of the quaternary spirocenter, we have developed a tandem Michael-Claisen process that is compatible with the Baker's yeast reduction to build rapidly the skeleton found in Fredericamycin A.

While much has been accomplished, much remains to complete the total synthesis. While the A through E rings - with a high degree of functionality - are found in our models, the F ring is still lacking. Though our work concentrated primarily on the ABCDE pentacycle, we believe that the F ring could be introduced by taking advantage of the methyl group *meta* to the methoxyl on the E ring of **136**, using a process similar to Bach[15] for introduction of the F ring heterocycle. Or, we could explore further the utilization of the Beckmann rearrangement, as investigated by Crane.[18c]



136 R = TMS

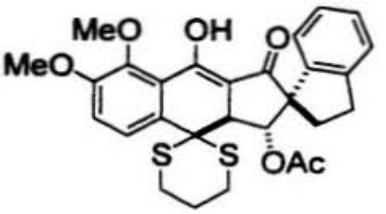
In terms of necessary functional group interconversions, pentacycle **261** is a few steps removed from the requisite functionality found in Fredericamycin A. Deprotection of the dithiane and acetate ester functions, followed by oxidation of the secondary alcohol at C-3 would result in the desired oxidation level in the BC rings. Treatment of the resulting compound with CAN or Fremy's salt is expected to introduce an oxygen at C-5 and oxidize the A ring to a quinone, as found in Fredericamycin A.



261

Though Fredericamycin A is a potent antitumor antibiotic, its cytotoxicity makes it use as a therapeutic agent prohibitive. Surprisingly, very little work has been carried out regarding the synthesis and testing for activity of molecules analogous to Fredericamycin A. One advantage of our synthetic route to the skeleton of Fredericamycin A is that it allows for the synthesis of a wide variety of analogues. We

have, in essence, differentiated the C-1 and C-3 oxygen-containing positions on the C ring, as well as having differentiated the C-4 and C-9 oxygen-containing positions on the B ring. This is important if analogue synthesis is to be carried out. For instance, the dithiane on the B ring could either be deprotected to yield the carbonyl, or reduced to the methylene by employing Raney nickel. The same rationale could be used on the C ring to furnish more analogues for SAR testing.



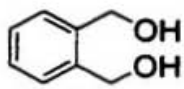
261

To conclude, we have developed an annulation strategy that is compatible with the introduction of asymmetry using Baker's yeast. Our long term goal is to complete the synthesis of Fredericamycin A, and then to synthesize a wide range of analogues for SAR testing.

Experimental Section

General Section. THF was distilled from sodium, using benzophenone as an indicator. Dichloromethane was distilled from CaH_2. The HMPA used in the tandem Michael-Claisen process. and the NEt_3 used in the diene formation were distilled from CaH_2 and stored over KOH. Reagents were purchased from Aldrich Chemical Company. All reactions were performed under N_2, unless specified otherwise. 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), w (weak), and br (broad). ^{1}H NMR spectra were obtained on either a General Electric GE/GN at 300 MHz or a Bruker Avance 500 MHz in $CDCl_3$ unless specified otherwise, and shifts are relative to internal tetramethylsilane. The following abbreviations are used in descriptions of ^{1}H NMR spectra: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and broad (br). Apparent coupling constants are reported. For spectral data obtained from inseparable mixtures, only clearly distinguished signals are reported. When mixtures were inseparable, product ratios were determined by integration of ^{1}H 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 either 75 or 125 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

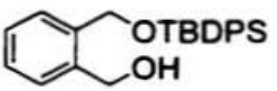
were obtained from spectra of mixtures. ^{19}F NMR spectra were recorded at 282 MHz; chemical shifts relative to $CFCl_3$. NMR FID data were processed using WinNUTS (Acorn NMR software) or BrukerNUTS (Bruker NMR software). Low resolution mass spectral data were obtained on a V.G. Micromass 7070HS instrument. High resolution mass spectral data were obtained at the University of Manitoba, Dalhousie University, and the University of Ottawa. Melting points were determined using a Fisher-Johns hot stage apparatus and are uncorrected. Data for the X-ray structures were obtained with a Rigaku AFC6S diffractometer, except for **278** which was obtained at the University of Alberta using a Bruker P4/rotating anode instrument equipped with a Bruker CCD detector. X-ray structure determinations were performed by Mr. David Miller. 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.



103

1,2-Benzenedimethanol (103). To a suspension of $LiAlH_4$ (4.60 g, 0.121 mol) in THF (100 mL) cooled to 0 °C was added dimethyl phthalate (10.5 g, 54.3 mmol) as a solution in THF (50 mL) dropwise over 20 min. The solution was warmed to rt and stirred for 15 h. Excess $LiAlH_4$ was quenched cautiously with sodium sulfate decahydrate, 95% ethanol, 50% ethanol and then H_2O. The resulting emulsion was washed with saturated sodium potassium tartrate (200 mL) and stirred for 2 h. The solution was extracted with CH_2Cl_2 (5 × 100 mL). The combined organic layers were dried over $MgSO_4$ to afford 6.73 g (90%) of **103** as a white

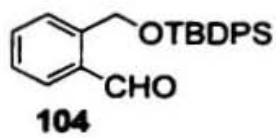
solid, mp 63-65 °C; IR (Nujol) ν_{max} 3300 (br), 1600 (s) cm^{-1}; ^1H NMR (300 MHz) δ 7.33-7.32 (4H, m, Ar**H**), 4.68 (4H, s, C**H**$_2$OH), 3.39 (2H, s, CH$_2$O**H**); ^{13}C NMR (75 MHz) δ 139.3 (2C, 0, C-1 and C-2), 129.7 (2C, 1, C-4 and C-5), 128.5 (2C, 1, C-3 and C-6), 64.1 (2C, 2, **C**H$_2$OH); MS *m/z* (%) 120 (92, M^+ - H_2O), 119 (80), 92 (23), 91 (100), 89 (11), 79 (28), 77 (37), 65 (26), 63 (11), 51 (20); HRMS calcd for C_8H_8O (M^+ - 18): 120.0575, found: 120.0566.



103a

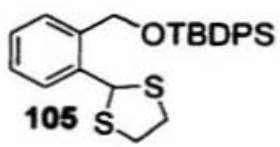
2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)benzenemethanol (103a). To a solution of **103** (1.23 g, 8.91 mmol) and sodium hydride (0.35 g, 8.75 mmol) in THF (50 mL) cooled to 0 °C was added TBDPSCl (2.89 g, 10.5 mmol) as a solution in THF (20 mL) dropwise. The solution was heated under reflux for 24 h. H_2O (2 × 50 mL) was added and the solution was extracted with CH_2Cl_2 (50 mL). The combined organic layers were washed with brine (50 mL) and dried over Na_2SO_4. Chromatography (20% ethyl acetate/hexanes) afforded 3.09 g (92%) of **103a** as a white solid. mp 72-74 °C; IR (CH_2Cl_2) ν_{max} 3400 (br), 1610 (s) cm^{-1}; ^1H NMR (300 MHz) δ 7.70 (4H, d, J = 6.6 Hz, Ar**H**), 7.45-7.16 (10H, m, Ar**H**), 4.79 (2H, s, C**H**$_2$OSi), 4.69 (2H, d, J = 4.2 Hz, C**H**$_2$OH), 3.03 (1H, br s, CH$_2$O**H**), 1.05 (9H, s, SiC**Me**$_3$); ^{13}C NMR (75 MHz) δ 139.5 (0, C-1), 138.1 (0, C-2), 135.6 (4C, 1), 132.7 (2C, 0), 129.9 (2C, 1), 129.0 (1), 128.7 (1), 128.2 (1), 127.9 (1), 127.8 (4C, 1), 65.0 (2, **C**H$_2$OSi), 63.7 (2, **C**H$_2$OH), 26.8 (3C, 3, SiC**Me**$_3$), 19.0 (0, Si**C**Me$_3$); MS *m/z* (%) 319 (4, M^+ - ^{t}Bu), 227 (12), 199 (39), 181 (37), 179 (19), 166 (13), 165 (11), 151

(54), 139 (60), 104 (20), 92 (10), 91 (100), 78 (14), 77 (39), 57 (29), 45 (13), 41 (22); HRMS calcd for $C_{20}H_{19}O_2Si$ (M^+ - ^{t}Bu): 319.1154, found: 319.1157.



104

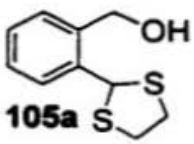
2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)benzaldehyde (104). A solution of **103a** (3.09 g, 8.21 mmol) in CH_2Cl_2 (50 mL) was added dropwise to a suspension of PCC (3.50 g, 16.2 mmol) in CH_2Cl_2 (100 mL). The black solution was stirred for 24 h. This mixture was passed through a Florisil column using CH_2Cl_2 as eluent to afford 3.06 g (99%) of **104** as a yellow oil; IR (CH_2Cl_2) ν_{max} 1695 (s), 1600 (s) cm^{-1}; ^1H NMR (300 MHz) δ 10.09 (1H, s, C**H**O), 7.87 (1H, d, J = 7.8 Hz, H-6), 7.74 (1H, t, J = 7.8 Hz, H-4), 7.70 (4H, d, J = 7.2 Hz), 7.57 (1H, t, J = 7.7 Hz, H-5), 7.40-7.32 (7H, m, Ar**H** and H-3), 5.22 (2H, s, C**H**$_2$OSi), 1.13 (9H, s, SiC**Me**$_3$); ^{13}C NMR (75 MHz) δ 192.7 (1, **C**HO), 143.5 (0, C-2), 135.4 (4C, 1), 133.9 (2C, 0), 133.2 (1, C-6), 132.7 (1, C-4), 129.7 (2C, 1), 129.0 (1), 127.7 (4C, 1), 127.1 (1), 116.5 (0, C-1), 63.6 (2, **C**H$_2$OSi), 26.8 (3C, 3, SiC**Me**$_3$), 19.3 (0, Si**C**Me$_3$); MS *m/z* (%) 317 (29, M^+ - ^{t}Bu), 227 (12), 212 (20), 211 (100), 200 (12), 199 (66), 181 (11), 167 (14), 119 (10), 105 (13), 91 (26), 77 (20), 65 (12), 45 (16), 41 (14); HRMS calcd for $C_{24}H_{26}O_2Si$: 374.1702, found: 374.1701.



105

2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)benzaldehyde (1,3-dithiolane derivative) (105). To anhydrous $ZnCl_2$ (1.23 g, 9.03 mmol) and 1,2-ethanedithiol (1.37 mL, 16.3 mmol) in CH_2Cl_2 (120 mL) was added **104** (3.06 g, 8.17 mmol) as a solution in CH_2Cl_2 (90 mL). The

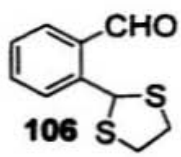
solution was heated under reflux for 72 h. The solution was washed with 1 M NaOH (3 × 75 mL). The combined aqueous layers were extracted with CH_2Cl_2 (2 × 75 mL). The combined organic layers were washed with brine (100 mL) and dried over Na_2SO_4. Chromatography (20% ethyl acetate/hexanes) afforded 2.65 g (72%) of **105** as a yellow oil; ^{1}H NMR (300 MHz) δ 7.82 (1H, d, J = 7.5 Hz, H-6), 7.70 (4H, d, J = 5.4 Hz), 7.44-7.21 (9H, m, Ar**H**), 5.93 (1H, s, H-1'), 4.87 (2H, s, C**H**$_2$OSi), 3.50-3.40 (2H, m, -SC**H**$_2$), 3.35-3.25 (2H, m, -SC**H**$_2$), 1.08 (9H, s, SiC**Me**$_3$).



105a

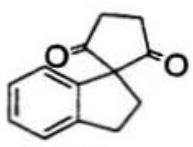
2-(Hydroxymethyl)benzaldehyde (1,3-dithiolane derivative) (105a). To a solution of **105** (401 mg, 0.891 mmol) in THF (20 mL) was added TBAF (1.8 mmol) as a solution in THF (1.8 mL). The solution was then stirred at rt for 24 h, diluted with CH_2Cl_2 (200 mL), washed with H_2O (2 × 75 mL) and brine (75 mL). The combined aqueous layers were extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried over $MgSO_4$. Chromatography (40% ethyl acetate/hexanes) afforded 175 mg (93%) of **105a** as a white solid, mp 59–62 °C; IR (Nujol) ν_{max} 3320 (br) cm^{-1}; ^{1}H NMR (300 MHz) δ 7.79 (1H, d, J = 7.2 Hz, H-6), 7.29-7.18 (3H, m, H-3, H-4 and H-5), 5.95 (1H, s, H-2'), 4.69 (2H, s, H-1'), 3.48-3.23 (4H, m, -SC**H**$_2$C**H**$_2$S-), 2.88 (1H, br s, -CH$_2$O**H**, disappears with D_2O shake); ^{13}C NMR (75 MHz) δ 138.2 (0, C-1 or C-2), 138.0 (0, C-1 or C-2), 128.9 (1), 128.6 (1), 128.3 (1), 128.0 (1), 62.9 (2, **C**H$_2$OH), 52.1 (1, C-2'), 39.9 (2C, 2, -S**C**H$_2$**C**H$_2$S-); MS *m/z* (%) 194 (3, M$^+$ - H_2O), 167 (11), 166 (100), 151 (23), 134 (21), 121 (11), 119 (22), 118 (37), 91 (34), 90

(20), 89 (14), 77 (11), 45 (24); HRMS calcd for $C_{10}H_{10}S_2$ (M^+ - 18): 194.0224, found: 194.0207.



106

2-[1,3]Dithiolan-2-ylbenzaldehyde (106). To a solution of **105a** (880 mg, 4.2 mmol) in CH_2Cl_2 (75 mL) was added PCC (1.38 g, 6.40 mmol) in one portion. The murky brown solution was stirred for 24 h. This crude mixture was passed through a Florisil column using CH_2Cl_2 as eluent and afforded 473 mg (54%) of **106** as a white solid, mp 65–67 °C; IR (Nujol) ν_{max} 1703 (s) cm^{-1}; ^1H NMR (300 MHz) δ 10.30 (1H, s, C**H**O), 8.00 (1H, d, J = 7.8 Hz, H-6), 7.79 (1H, d, J = 7.5 Hz, H-3), 7.58 (1H, t, J = 7.5 Hz, H-4), 7.46 (1H, t, J = 7.5 Hz, H-5), 6.66 (1H, s, H-2'), 3.51-3.36 (4H, m, -SC**H**$_2$C**H**$_2$S-); ^{13}C NMR (75 MHz) δ 192.8 (1, **C**HO), 142.9 (0, C-1 or C-2), 133.8 (1, C-3 or C-4), 133.7 (1, C-3 or C-4), 133.0 (0, C-1 or C-2), 129.1 (1, C-6), 128.3 (1, C-5), 51.2 (1, C-2'), 39.8 (2C, 2, -S**C**H$_2$**C**H$_2$S-); MS *m/z* (%) 210 (15, M^+), 183 (10), 182 (98), 150 (19), 149 (100), 122 (13), 121 (72), 118 (28), 90 (13), 89 (13), 78 (10), 77 (28), 63 (11), 61 (10), 51 (14), 45 (22); HRMS calcd for $C_{10}H_{10}OS_2$: 210.0173, found: 210.0189.

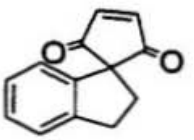


108

2',3'-Dihydrospiro(cyclopentane-2,1'-[1*H*]indene)-1,3-dione (108). BF_3-Et_2O (7.00 mL, 56.0 mmol) was added to a solution of 1-indanone (4.43 g, 33.5 mmol) in CH_2Cl_2 (140 mL). The mixture was stirred at rt for 30 min and then **107**, prepared by the method of Bloomfield and Nelke.[30] (14.0 g, 60.8 mmol) was added. The solution was stirred at rt for 24 h. H_2O (7.0

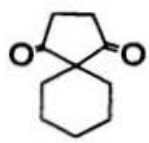
mL., 0.39 mol) was introduced followed 20 min later by BF_3·Et_2O (70 mL, 0.56 mol). The resulting black solution was stirred for 1.5 h. The solution was washed with H_2O (3 × 200 mL). The combined aqueous layers were extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with brine (200 mL) and dried over $MgSO_4$. Chromatography (40% ethyl acetate/hexanes) afforded 4.24 g (63%) of **108** as an orange solid. Spectra were as reported in ref. 18d.

2',3'-Dihydrospiro([4]cyclopentene-2,1'-[1*H*]indene)-1,3-dione (77).



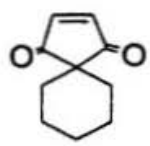
77

To a solution of **108** (611 mg, 3.06 mmol) in *m*-xylene (75 mL) was added benzeneseleninic anhydride (1.32 g, 3.67 mmol) in one portion. The solution was heated under reflux for 24 h. Solvent was removed *in vacuo* and chromatography (30% ethyl acetate/hexanes) afforded 355 mg (59%) of **77** as an orange solid: IR (Nujol) ν_{max} 1710 (s), 1547 (s) cm^{-1}; ^1H NMR (300 MHz) δ 7.50 (2H, s, H-4 and H-5), 7.33-7.10 (3H, m), 6.79 (1H, d, J = 7.2 Hz, H-7'), 3.23 (2H, t, J = 7.1 Hz, H-3'), 2.44-2.33 (2H, m, H-2'); ^{13}C NMR (75 MHz) δ 206.9 (2C, 0, C-1 and C-3), 150.2 (2C, 1, C-4 and C-5), 128.5 (1), 126.9 (1), 125.2 (1), 122.3 (1), 120.5 (0), 120.4 (0), 52.0 (0, C-1'), 31.8 (2), 30.9 (2); MS *m/z* (%) 198 (100, M^+), 170 (27), 169 (22), 142 (15), 141 (36), 116 (55), 115 (85), 89 (11), 63 (15), 58 (21), 55 (21); HRMS calcd for $C_{13}H_{10}O_2$: 198.0681, found: 198.0702.



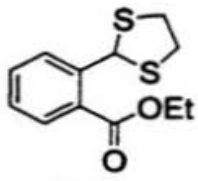
109

Spiro[4.5]decane-1,4-dione (109). $BF_3{\cdot}Et_2O$ (6.49 mL, 51.9 mmol) and **107** (16.1 g, 69.9 mmol) were added in succession to a solution of cyclohexanone (4.29 g, 43.7 mmol) in CH_2Cl_2 (250 mL) cooled to –78 °C. The mixture was stirred at –78 °C for 2.5 h then warmed to rt for 2 h. H_2O (6.5 mL, 0.36 mol) was introduced followed 10 min later by $BF_3{\cdot}Et_2O$ (82 mL, 0.66 mol) with the solution cooled to –78 °C. The resulting black solution was stirred for 24 h. The solution was washed with H_2O (2 × 400 mL). The combined aqueous layers were extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine (2 × 200 mL) and dried over $MgSO_4$. This crude mixture was passed through a Florisil column using CH_2Cl_2 as eluent to furnish 7.27 g (100%) of **109** as a white solid. Spectra were as reported in ref. 18.



110

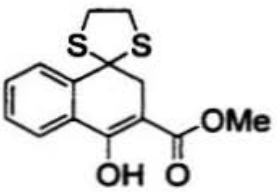
Spiro[4.5]dec-2-ene-1,4-dione (110). To a solution of **109** (2.75 g, 16.5 mmol) in chlorobenzene (150 mL) was added benzeneseleninic anhydride (7.15 g, 19.9 mmol) in one portion. The solution was heated under reflux for 144 h. Solvent was removed *in vacuo* and chromatography (20% ethyl acetate/hexanes) afforded 2.10 g (77%) of **110** as an orange solid. mp 71–74 °C; IR (Nujol) ν_{max} 1705 (s) cm^{-1}: ^1H NMR (300 MHz) δ 7.12 (2H, s, H-2 and H-3), 1.74 (5H, m), 1.55 (5H, m); ^{13}C NMR (75 MHz) δ 207.4 (2C, 0, C-1 and C-4), 146.7 (2C, 1, C-2 and C-3), 49.0 (0, C-5), 28.9 (2C, 2), 24.8 (2C, 2), 20.8 (2C, 2); MS *m/z* (%) 164 (49, M^+), 136 (17), 110 (21), 108 (11), 107 (13), 97 (28), 82 (100), 81 (10), 79 (15), 67 (18), 55 (15), 54 (45), 53 (17), 41 (23); HRMS calcd for $C_{10}H_{12}O_2$: 164.0837, found 164.0857.



114a

Ethyl 2-[1,3]dithiolan-2-ylbenzoate (114a). To a solution of 2-carboxybenzaldehyde (10.0 g, 66.9 mmol) in CH_2Cl_2 (100 mL) was added 1,2-ethanedithiol (8.45 mL, 0.101 mol), and the solution was cooled to 0 °C. To this solution was added $TiCl_4$ (12.7 g, 82.3 mmol), and the solution was stirred at rt for 24 h. The solution was washed with H_2O (200 and 100 mL) and brine (2 × 100 mL). The organic layer was dried over Na_2SO_4 to afford a white solid that was dissolved in absolute ethanol (200 mL) containing concentrated H_2SO_4 (1 mL) and heated under reflux for 24 h. Solvent was removed *in vacuo*. The solution was washed with H_2O (100 mL) and the aqueous layer extracted with ethyl acetate (2 × 200 and 100 mL). The combined organic layers were washed with saturated $NaHCO_3$ (aq) (100 mL), brine (100 mL) and dried over Na_2SO_4. Chromatography (10% ethyl acetate/hexanes) afforded 13.7 g (81% over two steps) of **114a** as a colorless oil: IR (Nujol) ν_{max} 3350 (br), 1719 (s), 1605 (s) cm^{-1}; ^1H NMR (300 MHz) δ 8.01 (1H, dd, J = 1.2, 8.1 Hz, H-6), 7.85 (1H, dd, J = 1.2, 8.1 Hz, H-3), 7.50 (1H, dt, J = 1.2, 7.7 Hz, H-4), 7.30 (1H, dt, J = 1.1, 7.5 Hz, H-5), 6.59 (1H, s, H-2'), 4.39 (2H, q, J = 7.1 Hz, -OCH_2CH_3), 3.47-3.31 (4H, m, -SCH_2CH_2S-), 1.41 (3H, t, J = 7.1 Hz, -OCH_2CH_3); ^{13}C NMR (75 MHz) δ 167.2 (0, C-1'), 142.9 (0, C-2), 132.1 (1, C-4), 130.3 (1, C-3), 129.3 (0, C-1), 129.0 (1, C-6), 127.3 (1, C-5), 61.3 (2, -OCH_2CH_3), 52.0 (1, C-2'), 39.7 (2C, 2, -SCH_2CH_2S-), 14.2 (3, -OCH_2CH_3); MS *m/z* (%) 254 (4, M^+), 225 (47), 209 (25), 208 (64), 182 (10), 181 (11), 180 (100), 165 (79), 152 (14), 149 (28), 134 (14), 133 (29), 121

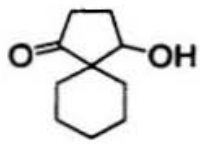
(20), 120 (22), 109 (15), 105 (19), 104 (14), 77 (36), 69 (11), 65 (10), 61 (30), 51 (15), 45 (26); HRMS calcd for $C_{12}H_{14}O_2S_2$: 254.0435, found 254.0450.



117

3,4-Dihydro-1-hydroxy-4-oxonaphthalene-2-carboxylic acid methyl ester (1,3-dithiolane derivative) (117). To a solution of LDA, prepared from *n*-BuLi (8.7 mmol) and diisopropylamine (1.21 mL, 8.7 mmol) in THF (30 mL) at –78 °C, was added **114a** (1.01 g, 3.97 mmol) and HMPA (0.68 mL, 3.9 mmol) as a solution in THF (15 mL) dropwise over 15 min. The solution was cooled to –90 °C and methyl acrylate (0.85 mL, 9.4 mmol) was added as a solution in THF (5 mL) dropwise over 5 min. The solution was warmed to rt. The reaction was quenched with 7% HCl (100 mL), and the solution was extracted with ethyl acetate (2 × 125 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (100 mL), water (100 mL) and brine (100 mL) and dried over Na_2SO_4. Chromatography (10% ethyl acetate/hexanes) afforded 72 mg (7%) of the starting material (**114a**) and 609 mg (52%) of **117** as a brown foam; IR (CCl_4) ν_{max} 3175 (br), 1655 (s), 1621 (s) cm^{-1}; ^1H NMR (300 MHz) δ 7.93 (1H, dd, J = 1.1, 7.7 Hz, H-8), 7.85 (1H, dd, J = 1.5, 7.8 Hz, H-5), 7.44 (1H, dt, J = 1.5, 7.7 Hz, H-6), 7.35 (1H, dt, J = 1.4, 7.5 Hz, H-7), 3.85 (3H, s, O**CH$_3$**), 3.43 (4H, s, -S**CH$_2$CH$_2$**S-), 3.28 (2H, s, H-3); ^{13}C NMR (75 MHz) δ 172.2 (0, C-1'), 164.7 (0, C-1), 142.5 (0, C-4a), 131.3 (1, C-6), 128.4 (0, C-8a), 127.8 (1, C-7), 126.2 (1, C-8), 124.9 (1, C-5), 97.2 (0, C-2), 67.8 (0, C-4), 51.8 (3, O**CH$_3$**), 39.8 (2C, 2, -S**CH$_2$CH$_2$**S-), 39.0 (2, C-3); MS *m/z* (%) 294 (57, M^+), 263 (11), 262 (42), 234 (31), 206 (13), 203 (17), 202 (100), 201 (15), 180 (12),

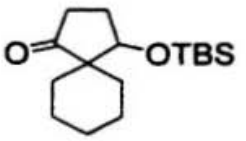
178 (13), 175 (19), 174 (12), 173 (12), 171 (11), 170 (41), 147 (23), 146 (28), 145 (26), 120 (13), 115 (17), 114 (22), 102 (16), 87 (17), 77 (12), 69 (11), 61 (27), 59 (13), 45 (21); HRMS calcd for $C_{14}H_{14}O_3S_2$: 294.0384, found: 294.0370.



118a

4-Hydroxyspiro[4.5]decan-1-one (118a). To a solution of **109** (640 mg, 3.86 mmol) in methanol (50 mL) cooled to 0 °C was added $NaBH_4$ (70 mg, 1.8 mmol) in one portion. The solution was stirred for 7 min and 0.5 M NH_4Cl (100 mL) was added. The solution was extracted with ethyl acetate (150, 100 and 75 mL). The combined organic layers were dried over $MgSO_4$ and solvent was removed *in vacuo* to afford **118a** as a yellow oil, the bulk of which was taken to the next step without purification: IR (Nujol) ν_{max} 3400 (br), 1737 (s) cm^{-1}; ^1H NMR (300 MHz) δ 4.34 (1H, br s, H-4), 2.53-1.93 (4H, m), 1.77–1.31 (10H, m); ^{13}C NMR (75 MHz) δ 222.5 (0, C-1), 74.7 (1, C-4), 54.1 (0, C-5), 34.0 (2), 30.7 (2), 27.6 (2), 25.5 (2), 25.4 (2), 21.9 (2), 21.7 (2); MS *m/z* (%) 168 (14, M^+), 150 (23), 124 (10), 112 (16), 111 (10), 109 (19), 108 (59), 96 (12), 95 (27), 94 (17), 93 (28), 83 (22), 82 (16), 81 (100), 80 (20), 79 (44), 77 (12), 69 (11), 68 (19), 67 (72), 57 (23), 55 (51), 54 (18), 53 (24), 43 (36), 42 (11), 41 (67), 40 (11); HRMS calcd for $C_{10}H_{16}O_2$: 168.1150, found: 168.1137.

4-((*tert*-Butyldimethylsilyl)oxy)spiro[4.5]decan-1-one (118). To a solution of **118a** in DMF (100 mL) was added imidazole (660 mg, 9.7 mmol) and TBSCl (1.46 g, 9.69 mmol) in one portion. The solution was stirred at rt for 24 h. To this solution was added



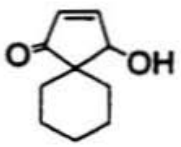
118

brine (100 mL) and this was extracted with hexanes (200, 150 and 2 × 100 mL). The combined organic layers were washed with brine (100 mL) and dried over $MgSO_4$. Chromatography (30% ethyl acetate/hexanes) afforded 733 mg (67% from **109**) of **118** as a yellow oil; IR (CCl_4) ν_{max} 1738 (s) cm^{-1}; ^1H NMR (300 MHz) δ 4.21 (1H, t, J = 3.2 Hz, H-4), 2.47-1.84 (4H, m), 1.67-1.28 (10H, m), 0.87 (9H, s, SiC**Me**$_3$), 0.10 (3H, s, Si**Me**), 0.08 (3H, s, Si**Me**); ^{13}C NMR (75 MHz) δ 221.6 (0, C-1), 76.1 (1, C-4), 54.5 (0, C-5), 34.1 (2), 30.8 (2), 28.3 (2), 26.0 (2), 25.8 (2), 25.6 (3C, 3, SiC**Me**$_3$), 22.3 (2), 21.9 (2), 18.0 (0, Si**C**Me$_3$), -4.3 (3, Si**Me**), -5.0 (3, Si**Me**); MS *m/z* (%) 282 (3, M^+), 226 (14), 225 (73), 181 (26), 133 (50), 130 (11), 129 (100), 107 (10), 105 (11), 101 (22), 95 (13), 91 (22), 79 (16), 75 (92), 73 (44), 67 (18), 59 (20), 55 (10), 41 (22).

119

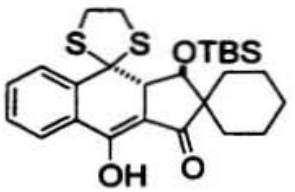
4-((*tert*-Butyldimethylsilyl)oxy)spiro[4.5]dec-2-en-1-one (119). To a solution of **118** (733 mg, 2.60 mmol) in chlorobenzene (50 mL) was added benzeneseleninic anhydride (1.12 g, 3.11 mmol) in one portion. The solution was heated under reflux for 24 h. Solvent was removed *in vacuo*, and chromatography (10% ethyl acetate/hexanes) afforded 312 mg (43%) of **119** as a colorless oil; IR ν_{max} 1714 (s) cm^{-1}; ^1H NMR (300 MHz) δ 7.32 (1H, dd, J = 2.6, 5.9 Hz, H-3), 6.08 (1H, dd, J = 1.4, 5.9 Hz, H-2), 4.58 (1H, dd, J = 1.1, 2.3 Hz, H-4), 1.88-1.25 (10H, m, H-6 to H-10), 0.91 (9H, s, SiC**Me**$_3$), 0.17 (3H, s, Si**Me**), 0.16 (3H, s, Si**Me**); ^{13}C NMR (75 MHz) δ 212.0 (0, C-1), 160.4 (1, C-3), 131.9 (1, C-2), 78.7 (1, C-4), 51.4 (0, C-5), 33.3 (2), 27.6 (2), 25.6 (3C, 3, SiC**Me**$_3$), 25.2 (2), 22.7 (2), 21.9 (2), 17.9 (0, Si**C**Me$_3$),

-4.1 (3, SiMe), -4.8 (3, SiMe); MS *m/z* (%) 280 (4, M^+), 224 (15), 223 (87), 155 (46), 81 (11), 79 (12), 75 (100), 73 (33), 67 (12), 59 (12), 41 (15); HRMS calcd for $C_{16}H_{28}O_2Si$: 280.1859, found: 280.1872.



120

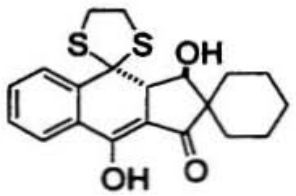
4-Hydroxyspiro[4.5]dec-2-en-1-one (120). To a solution of **110** (7.90 g, 48.1 mmol) in methanol (150 mL) cooled to 0 °C was added $CeCl_3 \cdot 7H_2O$ (8.97 g, 24.1 mmol) and $NaBH_4$ (1.19 g, 31.4 mmol) in one portion. The solution was stirred for 5 min and 0.5 M NH_4Cl (150 mL) was added. The solution was extracted with ethyl acetate (4 × 150 mL). The combined organic layers were washed with brine (2 × 100 mL) and dried over $MgSO_4$. Chromatography (50% ethyl acetate/hexanes) afforded 5.92 g (74%) of **120** as an orange oil; IR ν_{max} 3400 (br), 1703 (s) cm^{-1}; ^1H NMR (300 MHz) δ 7.48 (1H, dd, J = 2.4, 5.7 Hz, H-3), 6.14 (1H, dd, J = 1.4, 5.9 Hz, H-2), 4.67 (1H, dd, J = 1.5, 7.5 Hz, H-4), 1.97 (1H, d, J = 7.5 Hz, -OH), 1.84–1.24 (10H, m); ^{13}C NMR (75 MHz) δ 212.0 (0, C-1), 160.1 (1, C-3), 132.8 (1, C-2), 78.7 (1, C-4), 51.0 (0, C-5), 33.5 (2), 27.5 (2), 25.1 (2), 22.9 (2), 22.4 (2); MS *m/z* (%) 166 (26, M^+), 149 (11), 148 (49), 137 (22), 135 (13), 133 (11), 124 (12), 123 (36), 121 (15), 120 (29), 119 (10), 112 (10), 111 (54), 110 (34), 109 (23), 108 (14), 107 (16), 105 (10), 98 (27), 97 (44), 96 (16), 95 (29), 94 (15), 93 (20), 92 (14), 91 (27), 84 (100), 83 (20), 82 (24), 81 (65), 80 (14), 79 (57), 78 (11), 77 (26), 70 (14), 69 (11), 68 (15), 67 (55), 66 (12), 65 (16), 57 (17), 56 (40), 55 (76), 54 (18), 53 (38), 52 (10), 51 (16), 43 (24), 41 (80), 40 (13); HRMS calcd for $C_{10}H_{14}O_2$: 166.0994, found: 166.0998.



122

(3*R,3a*R**)-4-[1,3]-Dithiolan-2-yl-2,3,3a,4-tetrahydro-9-hydroxy-3-((*tert*-butyldimethylsilyl)oxy)spiro((1*H*)-benz[*f*]indene-2,1'-cyclohexane)-1-one (122).** To a solution of LDA, prepared from *n*-BuLi (4.0 mmol) and diisopropylamine (0.56 mL, 4.0 mmol) in THF (15 mL) at –78 °C, was added **114a** (468 mg, 1.84 mmol) and HMPA (0.31 mL, 1.8 mmol) as a solution in THF (10 mL) dropwise over 10 min. The solution was cooled to –90 °C and **119** (661 mg, 2.36 mmol) was added as a solution in THF (8 mL) dropwise over 10 min. The solution was warmed to rt. 1 M NH_4Cl (100 mL) was added and the solution was extracted with ethyl acetate (2 × 150 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (100 mL), water (75 mL) and brine (100 mL) and dried over Na_2SO_4. Chromatography (20% ethyl acetate/hexanes) afforded 755 mg (84%) of **122** as a brown solid, mp 58-61 °C; IR (Nujol) ν_{max} 3350 (br), 1720 (s) cm^{-1}; ^1H NMR (300 MHz) δ 7.84 (1H, d, J = 7.5 Hz, H-5 or H-8), 7.79 (1H, d, J = 7.5 Hz, H-5 or H-8), 7.45 (1H, t, J = 7.4 Hz, H-6 or H-7), 7.34 (1H, t, J = 7.4 Hz, H-6 or H-7), 4.50 (1H, d, J = 6.3 Hz, H-3), 3.58-3.40 (2H, m, -SC**H**$_2$), 3.46 (1H, d, J = 6.3 Hz, H-3a), 3.28-3.20 (1H, m, -SC**H**$_2$), 3.01-2.93 (1H, m, -SC**H**$_2$), 1.86-1.51 (10H, m, H-2' to H-6'), 0.96 (9H, s, SiC**Me**$_3$), 0.23 (3H, s, Si**Me**), 0.22 (3H, s, Si**Me**); NOE data δ 4.50 (3.46, 2%); ^{13}C NMR (75 MHz) δ 204.3 (0, C-1), 167.2 (0, C-9), 146.6 (0, C-8a), 131.7 (1, C-6 or C-7), 128.6 (0, C-4a), 127.6 (1, C-6 or C-7), 125.7 (1, C-5 or C-8), 125.7 (1, C-5 or C-8), 109.4 (0, C-9a), 80.3 (1, C-3), 74.2 (0, C-4), 53.0 (0, C-2), 50.1 (1, C-3a), 40.7 (2, -SCH$_2$**C**H$_2$S-), 36.9 (2, -S**C**H$_2$CH$_2$S-), 31.6, 28.2, 26.6 (3C, 3, SiC**Me**$_3$), 25.6, 18.6 (0, Si**C**Me$_3$), -1.2 (3, Si**Me**), -3.6 (3, Si**Me**); MS *m/z* (%) 488 (8,

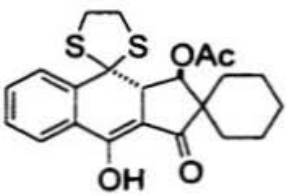
M^+), 413 (28), 395 (27), 371 (18), 297 (19), 263 (11), 262 (42), 261 (11), 234 (16), 203 (12), 202 (19), 181 (20), 135 (11), 81 (13), 75 (89), 73 (100), 61 (28), 59 (17), 57 (34), 55 (10), 45 (24), 41 (27); HRMS calcd for $C_{26}H_{36}O_3S_2Si$: 488.1875, found: 488.1861.



123

(3*R,3a*R**)-4-[1,3]-Dithiolan-2-yl-2,3,3a,4-tetrahydro-3,9-dihydroxyspiro((1*H*)-benz[*f*]indene-2,1'-cyclohexane)-1-one (123).** To a solution of LDA, prepared from *n*-BuLi (4.6 mmol) and diisopropylamine (0.64 mL, 4.6 mmol) in THF (15 mL) at –78 °C was added **114a** (540 mg, 2.12 mmol) and HMPA (0.36 mL, 2.1 mmol) as a solution in THF (10 mL) dropwise over 10 min. The solution was cooled to –90 °C, and **120** (350 mg, 2.11 mmol) was added as a solution in THF (5 mL) dropwise over 5 min. The solution was warmed to rt. The reaction was quenched with 7% HCl (100 mL), and the solution was extracted with ethyl acetate (2 × 125 mL). The combined organic layers were washed with saturated $NaHCO_3$ (75 mL), water (75 mL) and brine (75 mL) and dried over Na_2SO_4. Chromatography (30% ethyl acetate/hexanes) afforded 208 mg (39%) of **114a** (starting material) and 221 mg (28%) of **123** as a brown foam; IR (CCl_4) ν_{max} 3400 (br), 1679 (s), 1617 (s) cm^{-1}; ^1H NMR (300 MHz) δ 7.88 (1H, d, J = 7.5 Hz, H-5 or H-8), 7.79 (1H, d, J = 7.2 Hz, H-5 or H-8), 7.49 (1H, t, J = 7.2 Hz, H-6 or H-7), 7.36 (1H, t, J = 7.4 Hz, H-6 or H-7), 4.53 (1H, d, J = 7.8 Hz, H-3), 3.58 (2H, t, J = 5.7 Hz, -SC**H**$_2$), 3.45 (1H, d, J = 7.8 Hz, H-3a), 3.37-3.20 (2H, m, -SC**H**$_2$), 2.13-2.09 (1H, br s, -O**H**), 1.87-1.33 (10H, m, H-2' to H-6'); ^{13}C NMR (75 MHz) δ 206.0 (0, C-1), 163.2 (0, C-9), 144.7 (0, C-4a), 132.0 (1, C-6 or C-7), 128.2 (0, C-8a), 127.9 (1, C-

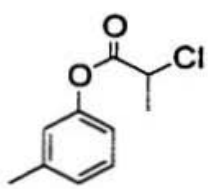
6 or C-7), 125.9 (1, C-5 or C-8), 125.4 (1, C-5 or C-8), 107.8 (0, C-9a), 79.4 (1, C-3), 73.2 (0, C-4), 52.5 (0, C-2), 49.3 (1, C-3a), 41.0 (2, -SCH_2CH_2S-), 39.7 (2, -SCH_2CH_2S-), 31.7 (2), 27.3 (2), 25.6 (2), 22.0 (2), 21.6 (2); MS *m/z* (%) 374 (36, M^+), 314 (11), 296 (16), 263 (15), 262 (13), 234 (10), 203 (15), 202 (21), 181 (32), 149 (16), 115 (11), 109 (12), 105 (16), 97 (10), 91 (12), 86 (60), 85 (10), 84 (100), 83 (26), 81 (26), 79 (13), 77 (14), 71 (44), 70 (12), 69 (27), 67 (20), 62 (28), 61 (19), 57 (48), 56 (19), 55 (47), 53 (11), 49 (14), 47 (23), 45 (69), 44 (22), 43 (67), 41 (57); HRMS calcd for $C_{20}H_{22}O_3S_2$: 374.1010, found: 374.1029.



124

(3*R,3a*R**)-3-Acetoxy-4-[1,3]-dithiolan-2-yl-2,3,3a,4-tetrahydro-9-hydroxyspiro((1*H*)-benz[*f*]indene-2,1'-cyclohexane)-1-one (124).** To a solution of LDA, prepared from *n*-BuLi (1.1 mmol) and diisopropylamine (0.15 mL, 1.1 mmol) in THF (5 mL) at –78 °C, was added **114a** (126 mg, 0.497 mmol) and HMPA (0.08 mL, 0.46 mmol) as a solution in THF (5 mL) dropwise over 2 min. The solution was cooled to –90 °C, and **121** (135 mg, 0.647 mmol) was added as a solution in THF (5 mL) dropwise over 5 min. The solution was warmed to rt. 1 M NH_4Cl (50 mL) was added and the solution was extracted with ethyl acetate (150, 75 and 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (100 mL), water (50 mL) and brine (75 mL) and dried over $MgSO_4$. Chromatography (50% ethyl acetate/hexanes) afforded 176 mg (85%) of **124** as a brown foam; IR (CCl_4) ν_{max} 1742 (s), 1674 (s), 1615 (s) cm^{-1}; ^1H NMR (300 MHz) δ 7.93 (1H, d, J = 8.1 Hz, H-5 or H-8),

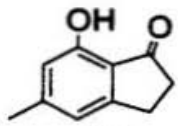
7.79 (1H, d, J = 8.1 Hz, H-5 or H-8), 7.50 (1H, t, J = 8.0 Hz, H-6 or H-7), 7.35 (1H, t, J = 7.4 Hz, H-6 or H-7), 5.92 (1H, d, J = 7.5 Hz, H-3), 3.61 (1H, d, J = 7.8 Hz, H-3a), 3.46-3.38 (2H, m, -SC**H**$_2$), 3.20-3.11 (2H, m, -SC**H**$_2$), 2.14 (3H, s, COC**H**$_3$), 1.71-1.42 (10H, m, H-2' to H-6'); ^{13}C NMR (75 MHz) δ 203.5 (0, C-1), 170.7 (0, O**C**OCH$_3$), 166.0 (0, C-9), 146.1 (0, C-8a), 132.6 (1, C-6 or C-7), 127.8 (1, C-6 or C-7), 126.3 (0, C-4a), 125.9 (1, C-5 or C-8), 125.7 (1, C-5 or C-8), 107.9 (0, C-9a), 78.5 (1, C-3), 73.0 (0, C-2), 52.2 (0, C-4), 48.0 (1, C-3a), 41.2 (2, -SCH$_2$**C**H$_2$S-), 39.4 (2, -S**C**H$_2$CH$_2$S-), 31.8, 28.9, 25.3, 21.8 (3, OCO**C**H$_3$); MS *m/z* (%) 416 (6, M$^+$), 358 (10), 357 (18), 356 (77), 297 (13), 296 (20), 295 (19), 264 (10), 81 (10), 67 (11), 61 (17), 60 (39), 59 (12), 55 (12), 45 (55), 44 (12), 43 (100), 42 (10), 41 (23); HRMS calcd for $C_{22}H_{24}O_4S_2$: 416.1116, found: 416.1099.



129a

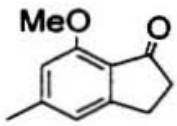
3-Methylphenyl (±)-2-chloropropanoate (129a). To a solution of *m*-cresol (50 mL, 0.48 mol) in benzene (56 mL) was added (±)-2-chloropropanoyl chloride (71 mL, 0.73 mol), and the resulting solution was heated under reflux for 24 h. Solvent was removed by distillation and the crude oil was distilled under vacuum to afford 83 g (87%) of **129a** as a colorless oil, bp 118-120 °C/1.5 mm Hg; IR ν_{max} 1766 (s), 1613 (s) cm^{-1}; ^{1}H NMR (300 MHz) δ 7.25 (1H, t, J = 7.7 Hz, H-5), 7.05 (1H, d, J = 7.5 Hz, H-4), 6.92 (1H, s, H-2), 6.91 (1H, d, J = 8.4 Hz, H-6), 4.58 (1H, q, J = 6.8 Hz, C**H**ClCH$_3$), 2.34 (3H, s, ArC**H**$_3$), 1.79 (3H, d, J = 6.9 Hz, CHClC**H**$_3$). ^{13}C NMR (75 MHz) δ 168.6 (0, **C**=O), 150.3 (0, C-1), 139.7 (0), 129.1 (1), 127.0 (1), 121.5 (1), 117.9 (1), 52.3 (1, **C**HClCH$_3$),

21.2 (3, $ArCH_3$ or $CHClCH_3$), 21.1 (3, $ArCH_3$ or $CHClCH_3$); MS *m/z* (%) 200 (2), 198 (8, M^+), 108 (100), 107 (12), 63 (10).



93

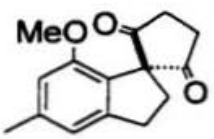
7-Hydroxy-5-methylindan-1-one (93). To **129a** (108 g, 0.545 mol) was added $AlCl_3$ (213 g, 1.60 mol), and the mixture was heated for 1 h at 90 °C, heated to 160 °C over 2 h, heated for 1 h at 160 °C, and then heated to 180 °C over 1 h. The crude mixture was cooled to 0 °C and concentrated HCl (255 mL) and H_2O (170 mL) was added dropwise over 3 h. Steam distillation of the mixture afforded 26.4 g (30%) of **93** as an orange solid, mp 114-117 °C; IR (Nujol) ν_{max} 3300 (br), 1710 (s) cm^{-1}; ^1H NMR (300 MHz) δ 8.95 (1H, s, O**H**), 6.74 (1H, s, H-4), 6.55 (1H, s, H-6), 3.03 (2H, t, J = 5.8 Hz, H-3), 2.67 (2H, t, J = 5.8 Hz, H-2), 2.36 (3H, s, Ar**CH$_3$**); ^{13}C NMR (75 MHz) δ 209.2 (0, C-1), 157.1 (0, C-7a), 155.4 (0, C-7), 149.4 (0, C-3a), 120.6 (0, C-5), 118.2 (1, C-4), 113.9 (1, C-6), 36.0 (2, C-2), 25.6 (2, C-3), 22.3 (3, C-5 methyl); MS *m/z* (%) 162 (100, M^+), 161 (30), 134 (14), 133 (10); HRMS calcd for $C_{10}H_{10}O_2$: 162.0681, found: 162.0693.



131

7-Methoxy-5-methylindan-1-one (131). A solution of **93** (552 mg, 3.41 mmol), K_2CO_3 (0.95 g, 6.9 mmol) and CH_3I (0.25 mL, 4.0 mmol) in acetone (50 mL) and THF (30 mL) was heated under reflux for 24 h. The solution was diluted with CH_2Cl_2 (100 mL) and washed with brine (2 × 50 mL). The combined aqueous layers were extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried over $MgSO_4$ and solvent was removed *in vacuo* to

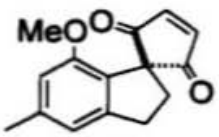
afford 575 mg (96%) of **131** as a yellow solid, mp 116-118 °C; IR (CCl_4) ν_{max} 1712 (s), 1610 (s) cm^{-1}. ^1H NMR (300 MHz) δ 6.82 (1H, s, H-4), 6.58 (1H, s, H-6), 3.93 (3H, s, OCH_3), 3.02 (2H, t, J = 5.9 Hz, H-3), 2.65 (2H, t, J = 5.9 Hz, H-2), 2.41 (3H, s, $ArCH_3$); ^{13}C NMR (75 MHz) δ 204.4 (0, C-1), 158.3 (0, C-7a), 147.9 (0, C-3a), 123.1 (0, C-5), 119.0 (1, C-4), 109.8 (1, C-6), 55.6 (3, OCH_3), 36.9 (2, C-2), 25.4 (2, C-3), 22.4 (3, C-5 methyl); MS *m/z* (%) 176 (100, M^+), 175 (25), 161 (12), 148 (10), 147 (88), 133 (11), 119 (12), 118 (10), 117 (22), 115 (18), 91 (12), 77 (14), 51 (12); HRMS calcd for $C_{11}H_{12}O_2$: 176.0837, found: 176.0849.



132

2',3'-Dihydro-7'-methoxy-5'-methylspiro(cyclopentane-2,1'-(1*H*)indene)-1,3-dione (132). To a solution of **131** (1.00 g, 5.68 mmol) in CH_2Cl_2 (100 mL) was added **107** (2.08 g, 9.03 mmol) and 1.0 M $TiCl_4$ in CH_2Cl_2 (6.80 mL, 6.80 mmol) and stirred at rt for 24 h. To this solution was added H_2O (6.7 mL) and $BF_3{\cdot}Et_2O$ (10.7 mL), and this mixture was stirred at rt for 2 h. The solution was washed with H_2O (2 × 100 mL). The combined aqueous layers were extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with brine (150 mL) and dried over $MgSO_4$. Chromatography (40% ethyl acetate/hexanes) afforded 701 mg (70%) of **131** (starting material) and 231 mg (17%) of **132** as a yellow solid. mp 99-100 °C: IR (CCl_4) ν_{max} 1727 (s), 1593 (s) cm^{-1}; ^1H NMR (300 MHz) δ 6.71 (1H, s, H-4'), 6.43 (1H, s, H-6'), 3.70 (3H, s, OCH_3), 3.15-2.76 (4H, m, H-2' and H-3'), 2.31 (4H, t, J = 7.5 Hz, H-4 and H-5), 2.30 (3H, s, $ArCH_3$); ^{13}C NMR (75 MHz) δ 216.0 (2C, 0, C-1 and C-3), 153.8 (0, C-7'), 147.5 (0), 140.6 (0), 128 (0), 118.2

(1, C-4'), 109.4 (1, C-6'), 65.7 (0, C-1'), 55.2 (3, OCH_3), 36.4 (2, C-2'), 35.5 (2, C-3'), 32.3 (2C, 2, C-4 and C-5), 21.7 (3, C-5' methyl); MS *m/z* (%) 244 (100, M^+), 188 (48), 174 (16), 159 (23), 145 (26), 131 (15), 129 (15), 128 (12), 115 (24), 94 (14); HRMS calcd for $C_{15}H_{16}O_3$: 244.1099, found: 244.1072.

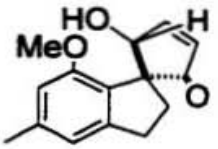


133

2',3'-Dihydro-7'-methoxy-5'-methylspiro([4]cyclopentene-2,1'-(1*H*)-indene)1,3-dione (133). To a solution of **132** (48 mg, 0.20 mmol) in *m*-xylene (50 mL) was added benzeneseleninic anhydride (90 mg, 0.25 mmol) in one portion. The solution was heated under reflux for 16 d. The solvent was removed *in vacuo*, and chromatography (20% ethyl acetate/hexanes) afforded 39 mg (83%) of **133** as an yellow solid, mp 104-106 °C; IR (CCl_4) ν_{max} 1707 (s), 1593 (s) cm^{-1}: ^1H NMR (300 MHz) δ 7.30 (2H, s, H-4 and H-5), 6.72 (1H, s, H-4'), 6.41 (1H, s, H-6'), 3.59 (3H, s, OCH_3), 3.12 (2H, t, J = 7.4 Hz, H-3'), 2.31 (2H, t, J = 7.4 Hz, H-2'), 2.31 (3H, s, $ArCH_3$): ^{13}C NMR (75 MHz) δ 206.3 (2C, 0, C-1 and C-3), 154.7 (0, C-7'), 154.6 (2C, 1, C-4 and C-5), 147.9 (0), 140.7 (0), 120.2 (0, C-5'), 117.9 (1, C-4'), 109.4 (1, C-6'), 60.8 (0, C-1'), 55.2 (3, OCH_3), 34.1 (2, C-2'), 32.0 (2, C-3'), 21.7 (3, C-5' methyl); MS *m/z* (%) 242 (100, M^+), 214 (10), 199 (11), 171 (42), 160 (10), 159 (19), 145 (16), 129 (17), 128 (17), 115 (25), 45 (10); HRMS calcd for $C_{15}H_{14}O_3$: 242.0943, found: 242.0922.

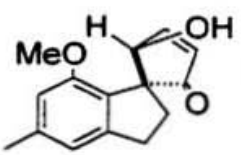
Reduction of enedione 133. To a solution of **133** (119 mg, 0.492 mmol) in methanol (15 mL) cooled to 0 °C was added $CeCl_3 \cdot 7H_2O$ (95 mg, 0.26 mmol) and $NaBH_4$ (14 mg, 0.38

mmol) in one portion. The solution was stirred for 6 min and 0.5 M NH_4Cl (15 mL) was added. The solution was extracted with ethyl acetate (100, 75 and 50 mL). The combined organic layers were washed with brine (100 mL) and dried over $MgSO_4$. Chromatography (50% ethyl acetate/hexanes) afforded 38 mg (32%) of **134a** as a yellow foam and 71 mg (59%) of **134b** as a white foam.



134a

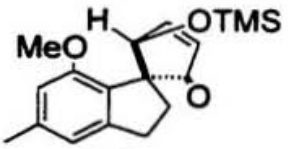
(2*R,3*R**)-2',3'-Dihydro-3-hydroxy-7'-methoxy-5'-methylspiro([4]cyclopentene-2,1'-(1*H*)indene)-1-one (134a).** Yellow foam; ^{1}H NMR (300 MHz) δ 7.62 (1H, dd, *J* = 2.4, 6.0 H-4), 6.77 (1H, s, H-4'), 6.53 (1H, s, H-6'), 6.33 (1H, d, *J* = 6.0 Hz, H-5), 4.73 (1H, dd, *J* = 2.6, 11.2 Hz, H-3), 3.71 (3H, s, OC**H**$_3$), 3.04 (2H, t, *J* = 7.2 Hz, H-3'), 2.73 (1H, d, *J* = 11.7 Hz, -O**H**), 2.45-2.05 (2H, m, H-2'), 2.33 (3H, s, ArC**H**$_3$).



134b

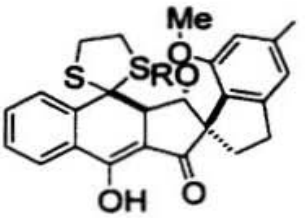
(2*R,3*S**)-2',3'-Dihydro-3-hydroxy-7'-methoxy-5'-methylspiro([4]cyclopentene-2,1'-(1*H*)indene)-1-one (134b).** White foam; IR (CCl_4) ν_{max} 3350 (br), 1714 (s) cm^{-1}; ^{1}H NMR (300 MHz) δ 7.41 (1H, dd, *J* = 2.0, 5.9 Hz, H-4), 6.67 (1H, s, H-4'), 6.46 (1H, s, H-6'), 6.25 (1H, d, *J* = 6.0 Hz, H-5), 5.07 (1H, apparent br s, H-3), 3.64 (3H, s, OC**H**$_3$), 2.94 (2H, t, *J* = 8.1 Hz, H-3'), 2.54-2.43 (2H, m, H-2'), 2.32 (3H, s, ArC**H**$_3$); NOE data δ 5.07 (3.64, 3%; 2.54-2.43, 1%); ^{13}C NMR (75 MHz) δ 209.6 (0, C-1), 161.5 (1, C-4), 155.1 (0, C-7'), 147.7 (0), 139.8 (0), 133.4 (1, C-5), 128.0 (0, C-7a'), 117.7 (1, C-4'), 109.5 (1, C-6'), 78.2 (1, C-3), 64.1 (0, C-1'), 55.1 (3, OCH_3), 32.3 (2, C-2'), 31.9 (2, C-3'), 21.7 (3, C-5' methyl); MS *m/z* (%) 244 (100, M$^+$), 227 (10), 199 (38), 198 (11), 190 (17), 187 (23), 185 (15), 184 (11), 183 (17), 173 (10), 169 (11), 161 (27), 160 (30), 159

(91), 155 (12), 147 (23), 145 (32), 141 (11), 135 (34), 131 (14), 129 (52), 128 (41), 127 (19), 128 (41), 127 (19), 117 (13), 116 (17), 115 (62), 91 (29), 77 (23), 65 (11), 63 (13), 55 (39), 51 (14); HRMS calcd for $C_{15}H_{16}O_3$: 244.1099, found: 244.1095.



135

(2*R,3*S**)-2',3'-Dihydro-7'-methoxy-5'-methyl-3-(trimethylsilyl)oxyspiro([4]cyclopentene-2,1'-(1*H*)indene)-1-one (135).** To a solution of **134b** (52 mg, 0.21 mmol) in CH_2Cl_2 (5 mL) cooled to 0 °C was added NEt_3 (40 μL, 0.3 mmol), DMAP (10 mg, 0.08 mmol) and TMSCl (40 μL, 0.3 mmol) in one portion. The solution was warmed to rt and stirred for 24 h. The solvent was removed *in vacuo*, and chromatography (30% ethyl acetate/hexanes) afforded 65 mg (97%) of **135** as a white solid. mp 78-79 °C; IR (Nujol) ν_{max} 1720 (s) cm^{-1}; ^1H NMR (300 MHz) δ 7.36 (1H, dd, *J* = 2.1, 5.7 Hz, H-4), 6.66 (1H, s, H-4'), 6.47 (1H, s, H-6'), 6.29 (1H, dd, *J* = 1.8, 6.0 Hz, H-5), 5.09 (1H, dd, *J* = 1.8, 1.8 Hz, H-3), 3.68 (3H, s, OC**H**$_3$), 2.91 (2H, t, *J* = 7.4 Hz, H-3'), 2.58-2.50 (1H, m, H-2'), 2.31 (3H, s, ArC**H**$_3$), 2.08-1.98 (1H, m, H-2'), -0.03 (9H, s, Si**Me**$_3$); ^{13}C NMR (75 MHz) δ 209.2 (0, C-1), 162.2 (1, C-4), 155.1 (0, C-7'), 147.9 (0), 139.5 (0), 132.8 (1, C-5), 127.8 (0, C-7a'), 117.8 (1, C-4'), 109.6 (1, C-6'), 78.0 (1, C-3), 64.7 (0, C-1'), 55.2 (3, O**C**H$_3$), 32.3 (2, C-2'), 31.8 (2, C-3'), 21.8 (3, C-5' methyl), -0.4 (3C, 3, Si**Me**$_3$); MS *m/z* (%) 316 (36, M$^+$), 288 (27), 199 (24), 198 (17), 185 (20), 183 (12), 159 (16), 129 (13), 75 (13), 73 (100), 45 (22); HRMS calcd for $C_{18}H_{24}O_3Si$: 316.1495, found: 316.1502.



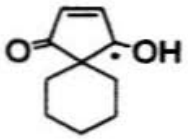
136 R = TMS

(2*R,3*S**,3a*S**)-4-[1,3]Dithiolan-2-yl-2,2',3,3',3a,4-hexahydro-9-hydroxy-7'-methoxy-5'-methyl-3-(trimethylsilyl)oxyspiro((1*H*)-benz[*f*]indene-2,1'-(*1H*)indene)-1-one (136).** To a solution of LDA, prepared from *n*-BuLi (0.35 mmol) and diisopropylamine (0.05 mL, 0.4 mmol) in THF (5 mL) at –78 °C was added **114a** (42 mg, 0.16 mmol) and HMPA (0.03 mL, 0.2 mmol) as a solution in THF (5 mL) dropwise over 2 min. The solution was cooled to –90 °C, and **135** (40 mg, 0.13 mmol) was added as a solution in THF (5 mL) dropwise over 5 min. The solution was warmed to rt. 1 M NH_4Cl (50 mL) was added and the solution was extracted with ethyl acetate (200, 75 and 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (100 mL), water (50 mL) and brine (75 mL) and dried over $MgSO_4$. Chromatography (20% ethyl acetate/hexanes) afforded 16 mg of **114a** and 45 mg (66%, 85% based on recovered starting material) of **136** as a brown foam, which after recrystallization from ethyl acetate was a yellow solid, mp 118–120 °C: IR (CCl_4) ν_{max} 3400 (br), 1721 (s), 1672 (s), 1614 (s), 1591 (s) cm^{-1}: ^1H NMR (300 MHz) δ 7.90 (1H, d, J = 8.1 Hz, H-5 or H-8), 7.85 (1H, d, J = 7.8 Hz, H-5 or H-8), 7.50 (1H, t, J = 8.0 Hz, H-6 or H-7), 7.37 (1H, t, J = 7.5 Hz, H-6 or H-7), 6.66 (1H, s, H-4'), 6.46 (1H, s, H-6'), 4.81 (1H, d, J = 4.8 Hz, H-3), 3.78 (1H, d, J = 4.5 Hz, H-3a), 3.63 (3H, s, OCH_3), 3.60-3.46 (2H, m, $-SCH_2-$), 3.32-3.25 (1H, m, $-SCH_2-$), 3.14-3.06 (1H, m, $-SCH_2-$), 3.09-2.91 (2H, m, H-3'), 2.74-2.64 (2H, m, H-2'), 2.30 (3H, s, $ArCH_3$), -0.18 (9H, s, $SiMe_3$): ^{13}C NMR (75 MHz) δ 202.3 (0, C-1), 164.9 (0, C-9), 157.0 (0, C-7'),

146.9 (0, C-8a), 139.3 (0, C-4a), 131.9 (1, C-6 or C-7), 128.8 (0, C-3a', C-5' or C-7a), 128.6 (0, C-3a', C-5' or C-7a), 127.6 (1, C-6 or C-7), 126.0 (1, C-5 or C-8), 125.9 (1, C-5 or C-8), 117.7 (1, C-4'), 111.6 (0, C-9a), 110.2 (1, C-6'), 81.2 (1, C-3), 74.8 (0, C-4), 67.4 (0, C-2), 55.7 (3, OCH_3), 53.5 (1, C-3a), 40.9 (2, C-3'), 38.1 (2, -SCH_2CH_2S-), 37.8 (2, -SCH_2CH_2S-), 32.0 (2, C-2'), 21.6 (3, C-5' methyl), 0.4 (3C, 3, $SiMe_3$); MS *m/z* (%) 524 (10, M^+), 435 (11), 434 (35), 432 (16), 431 (13), 362 (16), 342 (19), 299 (15), 263 (12), 262 (25), 234 (12), 202 (14), 188 (15), 187 (10), 161 (26), 159 (15), 149 (11), 145 (10), 129 (13), 115 (13), 105 (19), 77 (23), 75 (49), 73 (100), 71 (11), 69 (17), 60 (12), 57 (24), 55 (19), 51 (10), 45 (19), 43 (19), 41 (24).

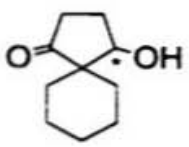
General Procedure for Baker's Yeast Reductions (also see page 63). Yeast reductions were conducted at 32 °C using a shaking water bath. Baker's yeast was Fleishmann's "Traditional" brand. Fermentation was initiated by shaking (10 min) a suspension of the yeast in an aqueous sucrose solution before the substrate was introduced as a solution in a small amount of 95% ethanol (or isopropanol) and 0.2% Triton X-100. Work-up was as follows: diethyl ether was added and the mixture was stirred for 15 h at rt. The mixture was decanted and filtered through Celite, and ethyl acetate was passed through the filter cake. The aqueous layer of the filtrate was re-extracted with ethyl acetate, and the combined organic solutions were washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was subjected to chromatography to separate the reduction product from unreacted diketone.

The range of yields for **120a** and **137** is reported in Table 1, page 63.



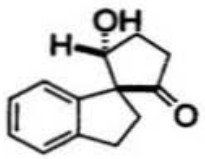
120a

(*S*)-4-Hydroxyspiro[4.5]dec-2-en-1-one (120a). Yellow oil; $[\alpha]_D$ = +96 (c = 0.0050, methanol); ^{1}H NMR (300 MHz) δ 7.48 (1H, dd, *J* = 2.6, 5.9 Hz, H-3), 6.15 (1H, dd, *J* = 1.0, 5.9 Hz, H-2), 4.68-4.66 (1H, apparent br s, H-4), 1.80-1.34 (10H, m, H-6 to H-10); ^{13}C NMR (75 MHz) δ 219.6 (0, C-1), 160.1 (1, C-3), 132.8 (1, C-2), 78.7 (1, C-4), 60.3 (0, C-5), 33.5 (2), 27.5 (2), 25.1 (2), 22.9 (2), 22.4 (2); MS *m/z* (%) 166 (56, M^+), 149 (19), 148 (82), 147 (15), 137 (39), 135 (19), 133 (30), 124 (16), 123 (54), 121 (20), 120 (65), 119 (19), 111 (71), 110 (47), 109 (32), 107 (24), 105 (16), 98 (32), 97 (63), 96 (23), 95 (39), 94 (19), 93 (17), 92 (13), 91 (37), 84 (89), 83 (25), 82 (34), 81 (56), 80 (13), 79 (53), 78 (13), 77 (35), 69 (19), 68 (15), 67 (42), 66 (13), 65 (20), 57 (16), 56 (37), 55 (100), 54 (21), 53 (43), 52 (13), 51 (21), 43 (19), 42 (10), 41 (57).



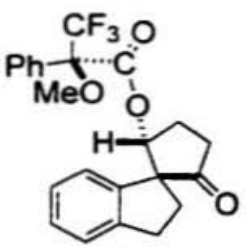
137

(*S*)-4-Hydroxyspiro[4.5]decan-1-one (137). Yellow oil: $[\alpha]_D$ = +87 (c = 0.0050, methanol): ^{1}H NMR (300 MHz) δ 4.34 (1H, t, *J* = 2.3 Hz, H-4), 2.53-1.93 (4H, m), 1.80-1.34 (10H, m); ^{13}C NMR (75 MHz) δ 221.2 (0, C-1), 75.4 (1, C-4), 54.2 (0, C-5), 34.1 (2), 31.0 (2), 27.9 (2), 25.7 (2), 25.6 (2), 22.2 (2), 22.1 (2); MS *m/z* (%) 168 (29, M^+), 150 (48), 132 (14), 125 (14), 124 (14), 112 (30), 111 (16), 109 (29), 108 (79), 107 (15), 99 (13), 96 (16), 95 (37), 94 (20), 93 (41), 91 (14), 83 (29), 82 (17), 81 (100), 80 (22), 79 (63), 78 (10), 77 (19), 69 (13), 68 (16), 67 (60), 57 (24), 56 (12), 55 (53), 54 (17), 53 (25), 43 (36), 42 (17), 41 (53).



138

(2*S*,3*R*)- 2',3'-Dihydro 3-hydroxyspiro(cyclopentane-2,1'-[1*H*]indene)-1-one (138). To a suspension of baker's yeast (8.13 g) and sucrose (18.14 g) in water (100 mL) was added **108** (291 mg, 1.46 mmol) in 3.0 mL of isopropanol and 0.2% Triton X-100 (12 mL). The suspension was shaken for 96 h and then baker's yeast (5.00 g) and sucrose (10.30 g) in water (40 mL) were added. The suspension was shaken for 48 h. Work-up followed by chromatography (0.5% CH_3OH/CH_2Cl_2) provided 21 mg (7%) of **108** and 167 mg (57%, 61% based on recovered starting material) of a clear yellow oil (**138** was determined to be the major enantiomer); IR ν_{max} 3420 (br), 1736 (s) cm^{-1}; ^1H NMR (300 MHz) δ 7.28-7.22 (3H, m, Ar**H**), 7.12 (1H, d, J = 6.6 Hz, H-7'), 4.27 (1H, apparent s, H-3), 3.05-2.99 (2H, m, H-3'), 2.72-2.62 (2H, m, H-2'), 2.47-1.96 (4H, m, H-4 and H-5); ^{13}C NMR (75 MHz) δ 220.3 (0, C-1), 145.9 (0, C-3a' or C-7a'), 140.5 (0, C-3a' or C-7a'), 128.3 (1), 126.8 (1), 125.9 (1), 124.8 (1), 75.7 (1, C-3), 68.3 (0, C-1'), 35.3 (2), 34.8 (2), 31.1 (2), 28.0 (2); MS *m/z* (%) 202 (44, M^+), 146 (46), 145 (14), 144 (13), 143 (72), 142 (15), 141 (10), 131 (12), 130 (19), 129 (24), 128 (35), 127 (10), 117 (64), 116 (44), 115 (100), 91 (39), 89 (23), 77 (13), 65 (12), 63 (21), 57 (11), 51 (14), 43 (11), 42 (11); HRMS calcd for $C_{13}H_{14}O_2$: 202.0994, found: 202.0992.

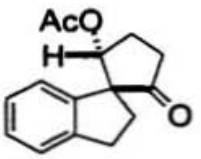


139a

Mosher's ester derivative 139 (derived from 138).[37] Colorless crystals: ^1H NMR (300 MHz) for **139a** δ 7.39-6.77 (9H, m, Ar**H**), 5.54 (1H, t, J = 3.3 Hz, H-3), 3.34 (3H, d, J = 0.6 Hz, -OC**H**$_3$), 3.06-2.90 (2H, m), 2.68-2.08 (6H, m); ^1H NMR (300 MHz) for **139b**,

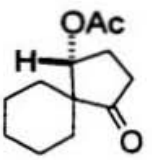
absolute stereochemistry not determined δ 7.39-6.77 (9H, m, Ar**H**), 5.50 (1H, t, J = 2.7 Hz, H-3), 3.25 (3H, d, J = 0.9 Hz, -O**C**$\mathbf{H_3}$), 3.06-2.90 (2H, m), 2.68-2.08 (6H, m); ^{19}F NMR (282 MHz) δ -71.6 (3F, s, **C**$\mathbf{F_3}$), -72.0 (3F, s, **C**$\mathbf{F_3}$); relative integration of ^{19}F signals is 4.07:1. Therefore the d.e. is 61%, and thus the e.e. from the enzymatic yeast reduction is also 61%; ^{13}C NMR (75 MHz) for **139a** δ 216.9 (0, C-1), 165.7 (0, O_2**C**PhCF_3OCH_3), 145.0 (0, C-3a' or C-7a'), 139.3 (0, C-3a' or C-7a'), 131.7 (0), 129.4 (1), 128.3 (2C, 1), 127.9 (1), 127.1 (2C, 1), 126.4 (1), 126.1 (1), 124.1 (1), 121.1 (0, **C**F_3), 117.3 (0, **C**CF_3), 80.8 (0, C-3), 65.7 (0, C-2), 55.2 (3, O**C**H_3), 35.8 (2), 34.6 (2), 30.7 (2), 26.6 (2); ^{13}C NMR (75 MHz) for **139b** δ 217.6 (0, C-1), 165.7 (0, O_2**C**PhCF_3OCH_3), 145.0 (0, C-3a' or C-7a'), 139.3 (0, C-3a' or C-7a'), 131.7 (0), 129.6 (1), 128.4 (2C, 1), 128.0 (1), 126.8 (2C, 1), 126.6 (1), 126.2 (1), 124.2 (1), 121.1 (0, **C**F_3), 117.3 (0, **C**CF_3), 80.7 (0, C-3), 65.6 (0, C-2), 55.2 (3, O**C**H_3), 35.9 (2), 34.4 (2), 30.8 (2), 26.5 (2); MS *m/z* (%) 418 (1, M^-), 202 (12), 201 (78), 190 (12), 189 (100), 184 (24), 156 (34), 143 (22), 141 (16), 128 (13), 115 (14), 105 (12); HRMS calcd for $C_{23}H_{21}F_3O_4$: 418.1392, found 418.139. The structure of major diastereomer **139a** was confirmed by X-ray crystallography.

Acetate ester formation. To solutions of crude monoreduced diketone **138** and **137** in diethyl ether were added pyridine (1.3 equivalents) and acetic anhydride (2 equivalents). The solutions were heated under reflux for 24 h, and solvent was removed *in vacuo*. Chromatography afforded the corresponding acetates as crystalline solids.



140

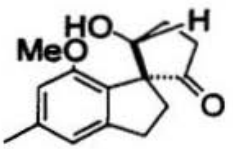
(2*S*,3*R*)-(+)-3-Acetoxy-2',3'-dihydrospiro(cyclopentane-2,1'-(1*H*)indene)-1-one (140), major enantiomer. Colorless crystals, mp 127–128 °C; IR (CCl_4) ν_{max} 1743 (s), 1642 (s) cm^{-1}; $[\alpha]_D$ = +124 (c = 0.0012, methanol); ^1H NMR (300 MHz) δ 7.22 (1H, d, J = 6.6 Hz, H-7'), 7.23-7.13 (2H, m, H-5' and H-6'), 7.06 (1H, d, J = 6.9 Hz, H-4'), 5.40 (1H, dd, J = 1.8, 4.5 Hz, H-3), 3.13-2.93 (2H, m, H-3'), 2.69-2.52 (2H, m, H-2'), 2.43-2.09 (4H, m, H-4 and H-5), 1.91 (3H, s, CH_3CO); ^{13}C NMR (75 MHz) δ 218.9 (0, C-1), 169.7 (0, CH_3CO), 145.5 (0, C-3a' or C-7a'), 140.5 (0, C-3a' or C-7a'), 128.0 (1), 126.2 (1), 126.0 (1), 124.3 (1), 77.6 (1, C-3), 66.2 (0, C-2), 35.7 (2), 34.7 (3, CH_3CO), 30.9 (2, C-2'), 26.5 (2), 21.0 (2); MS *m/z* (%) 244 (5, M^+), 202 (43), 201 (49), 184 (18), 157 (12), 156 (85), 155 (12), 147 (11), 146 (100), 143 (41), 142 (16), 141 (22), 130 (21), 129 (15), 128 (22), 117 (32), 116 (21), 115 (44), 91 (11), 43 (73); HRMS calcd for $C_{15}H_{16}O_3$: 244.1099, found 244.1098.



141

(4*S*)-(+)-4-Acetoxyspiro[4.5]decan-1-one (141). Colorless crystals, mp 70–71 °C; IR (CCl_4) ν_{max} 1736 (s) cm^{-1}; $[\alpha]_D$ = +118 (c = 0.0032, methanol); ^1H NMR (300 MHz) δ 5.44 (1H, dd, J = 1.5, 4.8 Hz, H-4), 2.41-2.17 (2H, m), 2.06 (3H, s, CH_3CO), 1.98-1.26 (12H, m); ^{13}C NMR (75 MHz) δ 219.9 (0, C-1), 170.3 (0, CH_3CO), 77.3 (1, C-4), 53.1 (0, C-5), 34.1 3, CH_3CO), 30.9 (2), 26.2 (2), 25.7 (2), 25.4 (2), 21.9 (2), 21.8 (2), 21.1 (2); MS *m/z* (%) 211 (24, M^+ + H), 167 (10), 152 (11), 151 (100), 150 (65), 124 (11), 122 (37), 112 (13), 109 (26), 108

(46), 107 (25), 96 (10), 94 (11), 93 (16), 81 (27), 80 (10), 79 (18), 67 (20), 43 (81), 41 (16); HRMS calcd for $C_{12}H_{18}O_3$: 210.1256, found 210.1254.

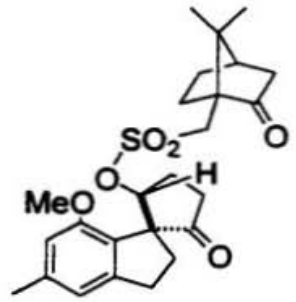


142

(2*R*,3*R*)- 2',3'-Dihydro-3-hydroxy-7'-methoxy-5'-methylspiro(cyclopentane-2,1'-(1*H*)indene)-1-one (142). To a suspension of baker's yeast (8.2 g) and sucrose (18.0 g) in water (100 mL) was added **132** (263 mg, 1.08 mmol) in 3.0 mL of 95% ethanol and 0.2% Triton X-100 (12 mL). The suspension was shaken for 48 h. Work-up followed by chromatography (50% ethyl acetate/hexanes) provided 106 mg (40%) of **132** and 64 mg of **142** (24%, 40% based on recovered starting material) as a clear yellow oil: IR (CCl_4) ν_{max} 3350 (br), 1744 (s), 1589 (s) cm^{-1}; ^1H NMR (300 MHz) δ 6.74 (1H, s, H-4'), 6.56 (1H, s, H-6'), 4.31 (1H, td, J = 2.4, 6.6 Hz, H-3), 3.76 (3H, s, OC**H**$_3$), 3.09 (1H, d, J = 6.6 Hz, O**H**), 3.07-2.67 (2H, m, H-3'), 2.41-1.97 (6H, m, H-2', H-2 and H-3), 2.38 (3H, s, ArC**H**$_3$); ^{13}C NMR (75 MHz) δ 220.2 (0, C-1), 155.1 (0, C-7'), 148.2 (0), 140.2 (0), 130.4 (0, C-7a'), 118.6 (1, C-4'), 110.3 (1, C-6'), 77.9 (1, C-3), 66.5 (0, C-1'), 55.6 (3, O**C**H$_3$), 37.5 (2, C-3'), 34.9 (2, C-2'), 31.4 (2, C-4), 29.9 (2, C-5), 21.6 (3, C-5' methyl); MS *m/z* (%) 246 (47, M$^+$), 190 (51), 188 (15), 187 (100), 175 (10), 161 (26), 160 (11), 159 (16), 147 (42), 145 (23), 131 (12), 129 (23), 128 (23), 127 (10), 115 (33), 107 (17), 91 (18), 77 (17), 57 (13), 55 (14), 43 (17), 41 (10); HRMS calcd for $C_{15}H_{18}O_3$: 246.1256, found: 246.1253.

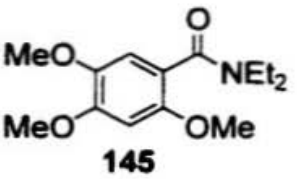
Camphorsulfonyl ester derivative 143 (derived from 142). White crystalline solid, mp 124-126 °C; IR (Nujol) ν_{max} 1752 (s), 1589 (s) cm^{-1}; ^1H NMR (300 MHz) δ 6.64 (1H, d,

J = 5.7 Hz, H-4'), 6.51 (1H, s, H-6'), 5.28-5.24 (1H, apparent br s, H-3), 3.76 (2H, s, SO_2CH_2), 3.75 (3H, s, OCH_3), 3.17-1.28 (15H, m), 2.27 (3H, s, $ArCH_3$), 0.70 (3H, s, CH_3), 0.63 (3H, s, CH_3); ^{13}C NMR (75 MHz) δ 217.7 (0), 213.8 (0), 156.0 (0, C-7'), 147.2 (0), 140.3 (0), 130.5 (0), 117.8 (1), 110.2 (1), 85.5 (1, C-3), 63.5 (0, C-1'), 57.5 (2, SO_2CH_2), 55.6 (3, OCH_3), 53.4, 47.4, 46.6, 42.3, 37.6, 35.8, 31.4, 28.6, 26.8, 24.3, 21.7, 19.5, 19.3; MS *m/z* (%) 460 (48, M^+), 246 (15), 245 (62), 229 (22), 228 (100), 227 (13), 218 (10), 217 (69), 201 (15), 200 (78), 199 (10), 190 (33), 189 (58), 188 (14), 187 (56), 186 (36), 185 (23), 175 (17), 174 (79), 173 (14), 172 (13), 161 (42), 159 (20), 151 (13), 145 (14), 129 (17), 128 (13), 123 (19), 115 (13), 109 (23), 91 (13), 85 (15), 81 (28), 79 (10), 67 (21), 57 (12), 55 (18), 43 (14), 41 (24); HRMS calcd for $C_{25}H_{32}O_6S$: 460.1919, found: 460.1915. The structure of **143** was determined by X-ray crystallography.



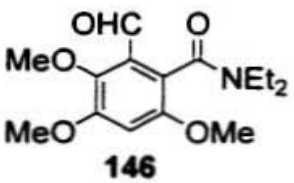
143

***N,N*-Diethyl-2,4,5-trimethoxybenzamide (145).** To a solution of **97** (3.00 g, 14.1 mmol) in benzene (180 mL) was added oxalyl chloride (2.5 mL, 29 mmol) dropwise. This cloudy white solution was stirred at rt for 4 h. The resulting clear yellow solution was then concentrated under reduced pressure to yield a white solid. To a solution of this in THF (100 mL) was added diethylamine (2.93 mL, 28.3 mmol) dropwise. The resulting cloudy white solution was stirred at rt overnight. H_2O (100 mL) was added and the solution was extracted with ethyl acetate (2 × 75 mL). The combined



145

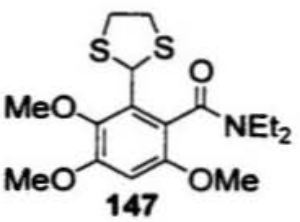
organic layers were washed with brine (100 mL) and dried over $MgSO_4$. Chromatography (5% CH_3OH/CH_2Cl_2) afforded 3.50 g (93% over two steps) of **145** as a yellow solid, mp 78–79 °C; IR (CCl_4) ν_{max} 1633 (s) cm^{-1}; ^1H NMR (300 MHz) δ 6.76 (1H, s, H-6), 6.52 (1H, s, H-3), 3.90 (3H, s, OCH_3), 3.84 (3H. s, OCH_3). 3.80 (3H. s, OCH_3), 3.56 (2H, apparent br s, CH_2CH_3). 3.19 (2H, q, J = 6.9 Hz. CH_2CH_3). 1.24 (3H, t, J = 6.9 Hz, CH_2CH_3), 1.05 (3H, t. J = 7.2 Hz. CH_2CH_3); ^{13}C NMR (75 MHz) δ 168.3 (0, C-1'), 149.9 (0), 149.4 (0), 143.1 (0), 118.0 (0, C-1), 111.0 (1, C-6), 97.4 (1, C-3), 56.5 (3, OCH_3), 56.3 (3, OCH_3), 55.9 (3, OCH_3), 42.8 (2, CH_2CH_3), 38.9 (2, CH_2CH_3), 13.9 (3, CH_2CH_3). 12.8 (3. CH_2CH_3); MS *m/z* (%) 267 (17, M^+), 195 (100); HRMS calcd for $C_{14}H_{21}NO_4$: 267.1469, found: 267.1456.



146

***N,N*-Diethyl-2-formyl-3,4,6-trimethoxybenzamide (146).** To a solution of TMEDA (4.16 mL. 27.6 mmol) and *s*-BuLi (28 mmol) in THF (150 mL) cooled to –78 °C was added dropwise **145** (3.50 g. 13.1 mmol) as a solution in THF (50 mL). The solution was stirred for 2.5 h at –78 °C and DMF (2.2 mL. 28 mmol) was added. The mixture was then warmed to rt. H_2O (75 mL) was added and the solution was extracted with ethyl acetate (3 × 150 mL). The combined organic layers were dried over $MgSO_4$. Chromatography (3% CH_3OH/CH_2Cl_2) afforded 2.06 g (53%) of **146** as a white solid, mp 74-78 °C; IR (CCl_4) ν_{max} 1693 (s). 1630 (s) cm^{-1}: ^1H NMR (300 MHz) δ 10.37 (1H. s, CHO), 6.75 (1H. s. H-5). 3.94 (3H. s. OCH_3). 3.91 (3H. s. OCH_3). 3.82 (3H. s. OCH_3). 3.79-3.42 (2H. m, CH_2CH_3). 3.07 (2H. q. J = 7.3 Hz. CH_2CH_3). 1.31 (3H. t. J = 7.4 Hz.

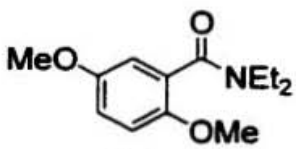
CH_2CH_3), 1.00 (3H, t, J = 7.2 Hz, CH_2CH_3); ^{13}C NMR (75 MHz) δ 189.5 (1, CHO), 166.4 (0, C-1'), 153.5 (0), 151.9 (0), 146.3 (0), 126.7 (0, C-2), 117.8 (0, C-1), 102.6 (1, C-5), 62.4 (3, OCH_3), 56.3 (3, OCH_3), 56.1 (3, OCH_3), 42.4 (2, CH_2CH_3), 38.4 (2, CH_2CH_3), 13.3 (3, CH_2CH_3), 12.0 (3, CH_2CH_3); MS *m/z* (%) 295 (6, M^+), 267 (13), 266 (65), 223 (100), 195 (40), 179 (11), 72 (18), 42 (10); HRMS calcd for $C_{15}H_{21}NO_5$: 295.1418, found: 295.1403.



147

***N,N*-Diethyl-2-formyl-3,4,6-trimethoxybenzamide, 1,3-dithiolane derivative (147).** To a solution of **146** (546 mg, 1.85 mmol) in CH_2Cl_2 (40 mL) was added BF_3·Et_2O (0.17 mL, 1.4 mmol) and 1,2-ethanedithiol (0.50 mL, 6.0 mmol). The cloudy yellow solution was stirred at rt for 2 d. The solution was washed with 1 M NaOH (2 × 75 mL). The combined aqueous layers were extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with brine (100 mL) and dried over $MgSO_4$. Chromatography (5% CH_3OH /CH_2Cl_2) afforded 266 mg (39%) of **147** as a white foam; IR (CH_2Cl_2) ν_{max} 1623 (s) cm^{-1}; ^1H NMR (300 MHz) δ 6.47 (1H, s, H-5), 5.65 (1H, s, H-2'), 3.92 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.87-3.49 (2H, m, CH_2CH_3), 3.62-3.54 (2H, m, -SCH_2), 3.36-3.29 (2H, m, -SCH_2), 3.14 (2H, q, J = 7.0 Hz, CH_2CH_3), 1.24 (3H, t, J = 7.1 Hz, CH_2CH_3), 1.06 (3H, t, J = 7.2 Hz, CH_2CH_3); ^{13}C NMR (75 MHz) δ 166.8 (0, C-1'), 153.7 (0), 150.7 (0), 142.3 (0), 131.8 (0, C-2), 118.6 (0, C-1), 97.2 (1, C-5), 60.5 (3, OCH_3), 55.9 (3, OCH_3), 55 (3, OCH_3), 48.6 (1, C-2'), 42.7 (2, CH_2CH_3), 40.9 (2C, 2, -SCH_2CH_2S-), 38.3 (2, CH_2CH_3), 13.6 (3,

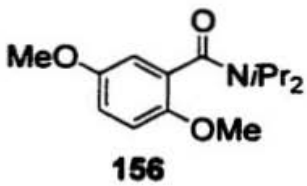
CH_2CH_3), 12.4 (3, CH_2CH_3); MS *m/z* (%) 371 (47, M^+), 311 (17), 310 (100), 282 (10), 270 (28), 250 (12), 239 (46), 237 (25), 195 (19), 149 (15), 72 (22), 45 (10), 29 (22); HRMS calcd for $C_{17}H_{25}NO_4S_2$: 371.1224, found: 371.1194.



155

***N,N*-Diethyl-2,5-dimethoxybenzamide (155).** To a solution of 2,5-dimethoxybenzoic acid (697 mg, 3.83 mmol) in benzene (50 mL) was added oxalyl chloride (0.67 mL, 7.7 mmol) dropwise. This cloudy white solution was stirred at rt for 75 min. The resulting clear light yellow solution was then concentrated under reduced pressure to yield a gelatinous yellow solid. To a solution of this in CH_2Cl_2 (50 mL), cooled to 0 °C, was added diethylamine (1.58 mL, 15.3 mmol) dropwise. The clear, light yellow solution was stirred at rt for 24 h. The solution was washed with H_2O (75 mL). The aqueous layer was extracted with ethyl acetate (2 × 75 mL). The combined organic layers were dried over $MgSO_4$. Chromatography (70% ethyl acetate/hexanes) afforded 449 mg (49% over two steps) of **155** as a white solid, mp 84-85 °C; IR (CCl_4) ν_{max} 1637 (s) cm^{-1}; ^1H NMR (300 MHz) δ 6.85 (1H, d, J = 2.4 Hz, H-3 or H-4), 6.84 (1H, s, H-6), 6.77 (1H, d, J = 2.4 Hz, H-3 or H-4), 3.78 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.60-3.53 (2H, m, CH_2CH_3), 3.16 (2H, q, J = 7.0 Hz, CH_2CH_3), 1.24 (3H, t, J = 7.2 Hz, CH_2CH_3), 1.05 (3H, t, J = 7.2 Hz, CH_2CH_3); ^{13}C NMR (75 MHz) δ 168.2 (0, C-1'), 153.6 (0, C-2 or C-5), 149.2 (0, C-2 or C-5), 127.6 (0, C-1), 114.8 (1), 112.9 (1), 112.3 (1), 56.1 (3, OCH_3), 55.7 (3, OCH_3), 42.7 (2, CH_2CH_3), 38.7 (2, CH_2CH_3), 13.9 (3, CH_2CH_3), 12.8 (3,

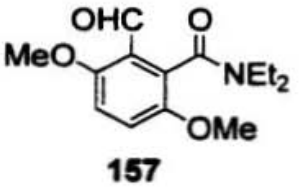
CH_2CH_3); MS *m/z* (%) 237 (21, M^+), 236 (15), 166 (10), 165 (100), 107 (10); HRMS calcd for $C_{13}H_{18}NO_3$ (M^+ - 1): 236.1287, found: 236.1284.



156

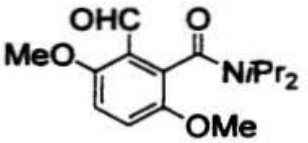
***N,N*-Diisopropyl-2,5-dimethoxybenzamide (156).** To a solution of 2,5-dimethoxybenzoic acid (1.49 g, 8.18 mmol) in benzene (50 mL) was added oxalyl chloride (1.43 mL, 16.4 mmol) dropwise. This cloudy white solution was stirred at rt for 1 h. The resulting clear, light yellow solution was then concentrated under reduced pressure to provide a gelatinous yellow solid. To a solution of this in CH_2Cl_2 (50 mL), cooled to 0 °C, was added diisopropylamine (2.87 mL, 20.5 mmol) dropwise. The clear, light yellow solution was stirred at rt for 1 h. The solution was washed with H_2O (100 mL). The aqueous layer was extracted with ethyl acetate (2 × 75 mL). The combined organic layers were washed with brine (100 mL) and dried over $MgSO_4$. Chromatography (30% ethyl acetate/hexanes) afforded 701 mg (32% over two steps) of **156** as a white solid, mp 86-88 °C; IR (CCl_4) ν_{max} 1636 (s) cm^{-1}; ^1H NMR (300 MHz) δ 6.82 (1H, d, J = 1.2 Hz, H-4), 6.81 (1H, s, H-6), 6.72 (1H, dd, J = 1.2, 3.2 Hz, H-3), 3.77 (3H, s, OC**H**$_3$), 3.77 (3H, s, OC**H**$_3$), 3.69 (1H, septet, J = 6.7 Hz, CH_3C**H**CH_3), 3.49 (1H, septet, J = 6.3 Hz, CH_3C**H**CH_3), 1.56 (3H, d, J = 1.8 Hz, C**H**$_3$$CHCH_3$), 1.54 (3H, d, J = 2.1 Hz, CH_3CHC**H**$_3$), 1.15 (3H, d, J = 6.9 Hz, C**H**$_3$$CHCH_3$), 1.05 (3H, d, J = 6.6 Hz, CH_3CHC**H**$_3$); ^{13}C NMR (75 MHz) δ 168.1 (0, C-1'), 153.7 (0, C-2), 149.2 (0, C-5), 129.2 (0, C-1), 114.3 (1, C-6), 112.3 (1, C-4), 112.2 (1, C-3), 56.1 (3, O**C**H_3), 55.8 (3, O**C**H_3), 50.9 (1, CH_3**C**HCH_3), 45.6 (1, CH_3**C**HCH_3), 20.8 (3, **C**H_3CHCH_3), 20.4 (3, CH_3CHCH_3),

20.4 (3, CH_3CHCH_3), 20.2 (3, CH_3CHCH_3); MS *m/z* (%) 265 (13, M^+), 222 (24), 166 (10), 165 (100); HRMS calcd for $C_{15}H_{23}NO_3$: 265.1678, found: 265.1687.



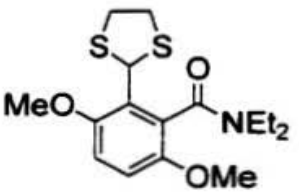
157

***N,N*-Diethyl-2-formyl-3,6-dimethoxybenzamide (157).** To a solution of TMEDA (0.52 mL, 3.4 mmol) and *s*-BuLi (3.4 mmol) in THF (20 mL) cooled to –78 °C was added dropwise **155** (409 mg, 1.72 mmol) as a solution in THF (10 mL). The solution was stirred for 2 h at –78 °C and DMF (0.27 mL, 3.5 mmol) was added. The mixture was warmed to rt. H_2O (75 mL) was added and the solution was extracted with ethyl acetate (2 × 75 mL). The combined organic layers were dried over $MgSO_4$. Chromatography (7% CH_3OH/CH_2Cl_2) afforded 58 mg (13%) of **155** and 362 mg (79%, 91% based on recovered starting material) of **157** as a yellow solid, mp 97-101 °C: IR (Nujol) ν_{max} 1710 (s), 1629 (s) cm^{-1}: ^1H NMR (300 MHz) δ 10.40 (1H, s, C**H**O), 7.09 (1H, d, J = 9.0 Hz, H-4 or H-5), 6.92 (1H, d, J = 9.6 Hz, H-4 or H-5), 3.85 (3H, s, OC**H**$_3$), 3.75 (3H, s, OC**H**$_3$), 3.75-3.39 (2H, m, C**H**$_2$CH$_3$), 3.04 (2H, q, J = 7.3 Hz, C**H**$_2$CH$_3$), 1.28 (3H, t, J = 7.2 Hz, $CH_2C\mathbf{H}_3$), 0.97 (3H, t, J = 7.1 Hz, $CH_2C\mathbf{H}_3$); ^{13}C NMR (75 MHz) δ 189.3 (1, **C**HO), 166.5 (0, C-1'), 156.2 (0, C-3 or C-6), 149.3 (0, C-3 or C-6), 127.6 (0, C-2), 121.8 (0, C-1), 118.3 (1, C-4 or C-5), 112.3 (1, C-4 or C-5), 56.4 (3, O**C**H$_3$), 56.2 (3, O**C**H$_3$), 42.3 (2, **C**H$_2$CH$_3$), 38.4 (2, **C**H$_2$CH$_3$), 13.2 (3, CH$_2$**C**H$_3$), 12.0 (3, CH$_2$**C**H$_3$); MS *m/z* (%) 237 (12), 236 (84, M^+ - CH_2CH_3), 194 (17), 193 (100), 165 (31), 163 (16), 149 (13), 120 (11), 107 (10), 92 (10), 79 (11), 72 (29), 51 (10), 42 (18); HRMS calcd for $C_{14}H_{19}NO_4$: 265.1314, found: 265.1335.



158

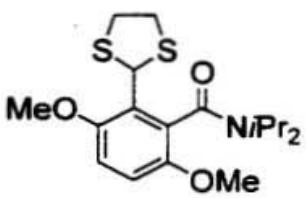
2-Formyl-*N,N*-diisopropyl-3,6-dimethoxybenzamide (158). To a solution of TMEDA (0.48 mL, 3.2 mmol) and *s*-BuLi (3.1 mmol) in THF (20 mL) cooled to –78 °C was added dropwise **156** (701 mg, 2.64 mmol) as a solution in THF (10 mL). The solution was stirred for 2 h at –78 °C and DMF (0.31 mL, 4.0 mmol) was added. The mixture was stirred at –78 °C for one hour and warmed to rt. H_2O (50 mL) was added and the solution was extracted with ethyl acetate (2 × 75 mL). The combined organic layers were dried over $MgSO_4$. Chromatography (7% CH_3OH/CH_2Cl_2) afforded 311 mg (44%) of **156** and 388 mg (50%, 89% based on recovered starting material) of **158** as a yellow-white solid; ^{1}H NMR (300 MHz) δ 10.35 (1H, s. C**H**O), 7.08 (1H, d, J = 9.0 Hz, H-5), 6.90 (1H, d, J = 8.7 Hz, H-4), 3.88 (3H, s, OC**H**$_3$), 3.78 (3H, s, OC**H**$_3$), 3.52 (1H, septet, J = 5.9 Hz, CH_3C**H**CH_3), 3.05-3.03 (1H, m, CH_3C**H**CH_3), 1.65 (3H, d, J = 7.2 Hz, C**H**$_3$CHCH_3), 1.56 (3H, d, J = 6.6 Hz, CH_3CHC**H**$_3$), 1.11 (3H, d, J = 5.7 Hz, C**H**$_3$CHCH_3), 1.08 (3H, d, J = 6.6 Hz, CH_3CHC**H**$_3$).



159

***N,N*-Diethyl-2-formyl-3,6-dimethoxybenzamide, 1,3-dithiolane derivative (159).** To a solution of **157** (317 mg, 1.20 mmol) in CH_2Cl_2 (75 mL) was added anhydrous $ZnCl_2$ (0.29 g, 2.1 mmol) and 1,2-ethanedithiol (0.22 mL, 2.6 mmol). The bright yellow solution was stirred at rt for 5 min, then heated at reflux for 72 h. The solution was washed with H_2O (2 × 100 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 75 mL). The organic layers were combined and washed with brine (100

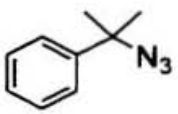
mL) and dried over $MgSO_4$. Chromatography (3% CH_3OH /CH_2Cl_2) afforded 279 mg (68%) of **159** as a white solid, mp 141–143 °C; IR (Nujol) ν_{max} 1626 (s) cm^{-1}; ^1H NMR (300 MHz) δ 6.88 (1H, d, J = 8.7 Hz, H-4 or H-5), 6.79 (1H, d, J = 9.0 Hz, H-4 or H-5), 5.72 (1H, s, H-2′), 3.86 (3H, s, OC**H**$_3$), 3.74 (3H, s, OC**H**$_3$), 3.70-3.60 (2H, m, C**H**$_2$CH$_3$), 3.65-3.48 (2H, m, -SC**H**$_2$), 3.31 (2H, t, J = 4.2 Hz, -SC**H**$_2$), 3.12 (2H, q, J = 6.4 Hz, C**H**$_2$CH$_3$), 1.25 (3H, t, J = 6.0 Hz, CH$_2$C**H**$_3$), 1.06 (3H, t, J = 6.2 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (75 MHz) δ 166.8 (0, C-1′), 152.6 (0, C-3 or C-6), 148.9 (0, C-3 or C-6), 127.4 (0, C-1 or C-2), 126.7 (0, C-1 or C-2), 113.5 (1), 111.0 (1), 56.6 (3, OCH$_3$), 56.0 (3, OCH$_3$), 48.8 (1, C-2′), 42.6 (2, CH$_2$CH$_3$), 41.1 (2, -SCH$_2$CH$_2$S-), 41.0 (2, -SCH$_2$CH$_2$S-), 38.3 (2, CH$_2$CH$_3$), 13.6 (3, CH$_2$CH$_3$), 12.5 (3, CH$_2$CH$_3$); MS *m/z* (%) 341 (32, M^+), 282 (11), 281 (17), 280 (100), 252 (18), 241 (12), 240 (41), 220 (19), 210 (11), 209 (62), 207 (27), 193 (10), 165 (40), 135 (10), 134 (14), 72 (49), 62 (13), 58 (18), 49 (14), 45 (32), 44 (14), 42 (10); HRMS calcd for $C_{16}H_{23}NO_3S_2$: 341.1119, found: 341.1112.



160

2-Formyl-*N*,*N*-diisopropyl-3,6-dimethoxybenzamide, 1,3-dithiolane derivative (160). To a solution of **158** (387 mg, 1.32 mmol) in CH_2Cl_2 (50 mL) was added anhydrous $ZnCl_2$ (0.22 g, 1.6 mmol) and 1,2-ethanedithiol (0.22 mL, 2.6 mmol). The bright yellow solution was stirred at rt for 5 min, then heated at reflux for 48 h. The solution was washed with H_2O (2 × 100 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 75 mL). The combined organic layers were washed with brine (100 mL) and dried over $MgSO_4$. Chromatography (3% CH_3OH /CH_2Cl_2) afforded 59 mg (15%) of

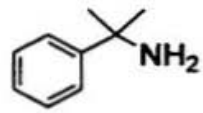
158 and 290 mg (59%, 69% based on recovered starting material) of **160** as a white foam; ^{1}H NMR (300 MHz) δ 6.85 (1H, d, J = 9.0 Hz, H-4), 6.76 (1H, d, J = 9.0 Hz, H-5), 5.76 (1H, s, H-2'), 3.86 (3H, s, OC**H**$_3$), 3.73 (3H, s, OC**H**$_3$), 3.72-3.62 (1H, m, $CH_3C\mathbf{H}CH_3$), 3.54-3.45 (1H, m, $CH_3C\mathbf{H}CH_3$), 3.66-3.56 (2H, m, -SC**H**$_2$), 3.37-3.28 (2H, m, -SC**H**$_2$), 1.58 (3H, d, J = 6.9 Hz, C**H**$_3$CHCH$_3$), 1.57 (3H, d, J = 6.6 Hz, $CH_3CHC\mathbf{H}_3$), 1.16 (3H, d, J = 6.3 Hz, C**H**$_3$CHCH$_3$), 1.11 (3H, d, J = 6.6 Hz, $CH_3CHC\mathbf{H}_3$); ^{13}C NMR (75 MHz) δ 166.5 (0, C-1'), 152.8 (0, C-6), 148.8 (0, C-3), 128.9 (0, C-2), 112.9 (1, C-4), 112.3 (0, C-1), 111.0 (1, C-5), 56.5 (3, O**C**H$_3$), 55.9 (3, O**C**H$_3$), 50.9 (1, $CH_3\mathbf{C}HCH_3$), 48.6 (1, C-2'), 45.8 (1, $CH_3\mathbf{C}HCH_3$), 41.3 (2, -S**C**H$_2$CH$_2$S-), 41.2 (2, -SCH$_2$**C**H$_2$S-), 20.9 (3, **C**H$_3$CHCH$_3$), 20.7 (3, CH$_3$CH**C**H$_3$), 20.5 (3, **C**H$_3$CHCH$_3$), 20.3 (3, CH$_3$CH**C**H$_3$).



162

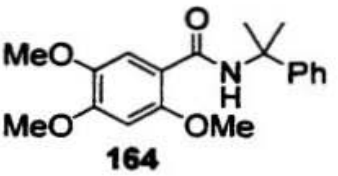
2-Azido-2-phenylpropane (162). To a solution of 2-phenyl-2-propanol (2.01 g, 14.8 mmol) in $CHCl_3$ (35 mL) cooled to −10 °C was added sodium azide (1.92 g, 29.5 mmol) and the mixture was stirred for 5 min. To this solution was added trifluoroacetic acid (6.0 mL, 7.8 mmol) as a solution in $CHCl_3$ (30 mL) over 10 minutes. The solution was then warmed to rt and stirred for 6 h. The solution was washed with concentrated NH_4OH (30 mL) and H_2O (100 mL). The organic layer was dried over $MgSO_4$ and solvent was removed *in vacuo* to afford 2.38 g (100%) of **162** as a colorless oil: IR ν_{max} 2104 (s), 1605 (s) cm^{-1}; ^{1}H NMR (300 MHz) δ 7.44 (2H, d, J = 7.5 Hz, H-2' and H-6'), 7.37 (2H, t, J = 7.5 Hz, H-3' and H-5'), 7.28 (1H, t, J = 7.8 Hz, H-4'), 1.64 (6H, s, H-1 and H-3); ^{13}C NMR (75 MHz) δ 144.6 (0, C-1'), 128.5 (2C, 1, C-3' and C-5'), 127.4 (1, C-4'), 125.1 (2C, 1, C-2' and C-

6'), 77.2 (0, C-2), 28.4 (2C, 3, C-1 and C-3); MS *m/z* (%) 119 (100, $M^+ - N_3$), 118 (44), 103 (10), 91 (67), 77 (41), 51 (12), 41 (25).



163

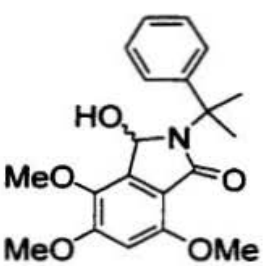
2-Phenyl-2-propanamine (163). To a solution of $LiAlH_4$ (0.56 g, 15 mmol) in diethyl ether (50 mL) cooled to 0 °C was added a solution of **162** (2.38 g, 14.8 mmol) in diethyl ether (20 mL) dropwise over 1 h. The solution was allowed to warm to rt and it was stirred overnight. To this solution was added $LiAlH_4$ (1.12 g, 30 mmol) and it was heated under reflux for 10 h. Excess $LiAlH_4$ was quenched cautiously with H_2O. The resulting emulsion was extracted with CH_2Cl_2 (100, 75 and 3 × 50 mL). The aqueous layer was basified with 1 M NaOH (100 mL) and extracted with CH_2Cl_2 (3 × 75 mL). The combined organic layers were washed with 1 M NaOH (100 mL) and dried over $MgSO_4$ to afford 1.83 g (92%) of **163** as a pale yellow oil: IR ν_{max} 3363 (br), 3284 (br), 1602 (s) cm^{-1}; ^1H NMR (300 MHz) δ 7.51 (2H, d, J = 7.3 Hz, H-2' and H-6'), 7.34 (2H, t, J = 7.3 Hz, H-3' and H-5'), 7.23 (1H, t, J = 7.2 Hz, H-4'), 1.56-1.50 (2H, br s, N**H**$_2$), 1.50 (6H, s, H-1 and H-3); ^{13}C NMR (75 MHz) δ 150.2 (0, C-1'), 128.0 (2C, 1, C-3' and C-5'), 126.0 (1, C-4'), 124.5 (2C, 1, C-2' and C-6'), 52.2 (0, C-2), 32.6 (2C, 3, C-1 and C-3); MS *m/z* (%) 120 (100, $M^+ - CH_3$), 119 (42), 118 (10), 91 (26), 77 (14), 42 (25), 41 (14); HRMS calcd for $C_9H_{12}N$ (M^- - 1): 134.0970, found: 134.0975.



164

***N*-Cumyl-2,4,5-trimethoxybenzamide (164).** To a solution of **97** (1.44 g, 6.79 mmol) in benzene (90 mL) was added oxalyl chloride (1.30 mL, 14.9 mmol) dropwise. This cloudy white solution was stirred at rt for 3 h. The resulting clear yellow solution was then concentrated under reduced pressure to provide a white solid. To a solution of this in THF (60 mL) was added **163** (1.83 g, 13.6 mmol) dropwise. The resulting cloudy white solution was stirred at rt for 24 h. H_2O (100 mL) was added and the solution was extracted with ethyl acetate (150, 100 and 75 mL). The combined organic layers were dried over $MgSO_4$. Chromatography (70% ethyl acetate/hexanes) afforded 398 mg (28%) of **97** and 1.48 g (66% over two steps, 92% based on recovered starting material) of **164** as a white solid, mp 131–132 °C; IR (CCl_4) ν_{max} 3386 (s), 1659 (s), 1606 (s) cm^{-1}; ^1H NMR (300 MHz) δ 8.40 (1H, br s, N**H**), 7.71 (1H, s, H-6), 7.46 (2H, d, J = 7.5 Hz, *ortho*), 7.34 (2H, t, J = 7.8 Hz, *meta*), 7.22 (1H, t, J = 7.4 Hz, *para*), 6.53 (1H, s, H-3), 3.97 (3H, s, OC**H**$_3$), 3.94 (3H, s, OC**H**$_3$), 3.85 (3H, s, OC**H**$_3$), 1.80 (6H, s, geminal dimethyl); ^{13}C NMR (75 MHz) δ 163.7 (0, C-1'), 152.3 (0, C-2), 151.9 (0, C-4'), 147.5 (0, C-4), 143.3 (0, C-5), 128.3 (2C, 1, *ortho*), 126.4 (1, *para*), 124.7 (2C, 1, *meta*), 114.0 (0, C-1), 113.8 (1, C-6), 96.6 (1, C-3), 56.8 (3, O**C**H$_3$), 56.1 (3, O**C**H$_3$), 56.1 (0, NH**C**(CH$_3$)$_2$Ph), 55.7 (3, O**C**H$_3$), 29.4 (2C, 3, geminal dimethyl); MS *m/z* (%) 329 (22, M^+), 211 (18), 196 (14), 195 (100), 91 (15), 77 (10), 43 (21), 41 (11); HRMS calcd for $C_{19}H_{23}NO_4$: 329.1627, found: 329.1632.

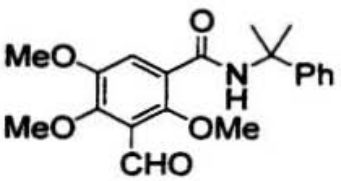
Formylation of benzamide 164. To a solution of **164** (599 mg, 1.82 mmol) and TMEDA (0.88 mL, 5.8 mmol) in THF (25 mL) at –78 °C was added *s*-BuLi (5.9 mmol) dropwise over 15 min. The resulting yellow solution was stirred for 2 h at –78 °C and DMF (0.31 mL, 4.0 mmol) was added. The mixture was stirred for 1 h at –78 °C, and saturated NH_4Cl (50 mL) was added and the solution warmed to rt. The solution was extracted with ethyl acetate (100 and 2 × 75 mL). The combined organic layers were dried over $MgSO_4$. Chromatography (50% ethyl acetate/hexanes) afforded 432 mg (72%) of **164**, 180 mg (28%) of **165** as a yellow foam, and 68 mg (11%) of **166** as a colorless oil.



165

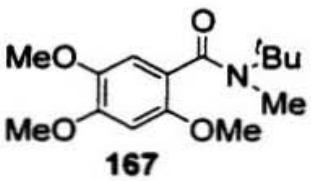
***N*-Cumyl-3-hydroxy-4,5,7-trimethoxy-(*1H*)-isoindole-1(*2H*)-one (165).** Yellow foam: IR (CCl_4) ν_{max} 3275 (br), 1697 (s), 1607 (s) cm^{-1}: ^1H NMR (300 MHz) δ 7.44 (2H, d, J = 8.1 Hz, H-3′ and H-7′), 7.30 (2H, t, J = 7.5 Hz, H-4′ and H-6′), 7.19 (1H, t, J = 7.1 Hz, H-5′), 6.46 (1H, s, H-6), 6.19 (1H, d, J = 8.4 Hz, H-3), 3.93 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 2.47 (1H, d, J = 8.4 Hz, -OH), 1.94 (3H, s, CH_3), 1.90 (3H, s, CH_3); ^{13}C NMR (75 MHz) δ 166.0 (0, C-1), 156.9 (0, C-7), 153.7 (0, C-5), 147.2 (0, C-2′), 147.2 (0, C-4), 137.6 (0, C-3a), 128.2 (2C, 1, C-4′ and C-6′), 126.4 (1, C-5′), 125.1 (2C, 1, C-3′ and C-7′), 124.8 (0, C-7a), 98.0 (1, C-6), 79.7 (1, C-3), 61.4 (3, OCH_3), 58.8 (3, OCH_3), 56.2 (3, OCH_3), 56.2 (0, C-1′), 28.8 (3, C-1′ methyl), 28.0 (3, C-1′ methyl); MS *m/z* (%) 357 (40, M^+), 342 (17), 252 (10), 239 (48), 238 (26), 224 (22), 223 (100), 222 (48), 208 (32), 207 (11), 181 (19), 134 (10), 119 (35).

103 (12), 91 (46), 79 (13), 78 (10), 77 (16), 43 (11), 41 (30); HRMS calcd for $C_{20}H_{23}NO_5$: 357.1576, found: 357.1594.



166

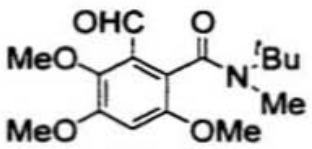
***N*-Cumyl-3-formyl-2,4,5-trimethoxybenzamide (166).** Colorless oil; IR ν_{max} 1693 (s), 1658 (s), 1605 (s) cm^{-1}; ^1H NMR (300 MHz) δ 10.45 (1H, s, C**H**O), 8.44 (1H, br s, N**H**), 7.89 (1H, s, H-6), 7.45 (2H, d, J = 7.5 Hz, *ortho*), 7.34 (2H, t, J = 7.7 Hz, *meta*), 7.24 (1H, t, J = 7.5 Hz, *para*), 4.01 (3H, s, OC**H**$_3$), 3.90 (3H, s, OC**H**$_3$), 3.88 (3H, s, OC**H**$_3$), 1.81 (6H, s, geminal dimethyl); ^{13}C NMR (75 MHz) δ 189.4 (1, **C**HO), 162.5 (0, C-1'), 155.2 (0, C-2), 151.6 (0, C-4), 149.4 (0, C-5), 146.6 (0, C-4'), 128.4 (2C, 1, *ortho*), 126.6 (1, *para*), 124.6 (2C, 1, *meta*), 124.5 (1, C-6), 123.1 (0, C-1 or C-3), 122.8 (0, C-1 or C-3), 63.7 (3, O**C**H$_3$), 62.2 (3, O**C**H$_3$), 56.1 (3, O**C**H$_3$), 55.7 (0, NH**C**(CH$_3$)$_2$Ph), 29.3 (2C, 3, C-3' geminal dimethyl); MS *m/z* (%) 88 (10), 86 (63), 84 (100), 49 (21), 47 (28); HRMS calcd for $C_{20}H_{23}NO_5$: 357.1576, found: 357.1565.



167

***N-tert*-Butyl-2,4,5-trimethoxy-*N*-methylbenzamide (167).** To a solution of **97** (3.00 g, 14.1 mmol) in benzene (180 mL) was added oxalyl chloride (2.50 mL, 28.7 mmol) dropwise. This cloudy white solution was stirred at rt for 4 h. The resulting clear yellow solution was then concentrated under reduced pressure to yield a gelatinous yellow solid. To a solution of this in THF (150 mL) was added *tert*-butylmethylamine (3.40 mL, 28.3 mmol) dropwise. The resulting clear, light yellow solution was stirred at rt for 96 h. H_2O (100 mL) was added and the solution was extracted with ethyl acetate

(200, 150 and 100 mL). The combined organic layers were washed with brine (100 mL) and dried over $MgSO_4$ to afford 3.94 g (99%) of **167** as a yellow solid, mp 89-91 °C; IR (CH_2Cl_2) ν_{max} 1631(s), 1605 (s) cm^{-1}; ^1H NMR (300 MHz) δ 6.81 (1H, s, H-6), 6.48 (1H, s, H-3), 3.89 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 2.81 (3H, s, NCH_3), 1.52 (9H, s, $NCMe_3$); ^{13}C NMR (75 MHz) δ 169.6 (0, C-1'), 149.8 (0, C-2), 149.4 (0, C-4), 143.1 (0, C-5), 120.4 (0, C-1), 111.1 (1, C-6), 97.5 (1, C-3), 56.7 (3, OCH_3), 56.2 (3, OCH_3), 55.9 (3, OCH_3), 33.6 (3, NCH_3), 27.9 (3C, 3, $NCMe_3$), 27.4 (0, $NCMe_3$); MS *m/z* (%) 281 (12, M^+), 196 (11), 195 (100), 57 (26), 43 (13), 41 (11); HRMS calcd for $C_{15}H_{23}NO_4$: 281.1627, found: 281.1616.

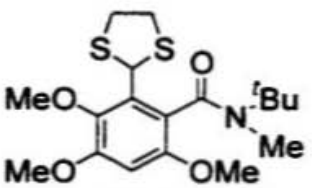


168

***N-tert*-Butyl-2-formyl-3,4,6-trimethoxy-*N*-methylbenzamide (168).** To a solution of TMEDA (2.40 mL, 15.9 mmol) and *s*-BuLi (17 mmol) in THF (100 mL) cooled to –78 °C was added dropwise **167** (3.94 g, 14.0 mmol) as a solution in THF (35 mL). The solution was stirred for 1 h at –78 °C and DMF (3.3 mL, 43 mmol) was added. The mixture was then warmed to rt and stirred overnight. H_2O (100 mL) was added and the solution was extracted with ethyl acetate (3 × 75 mL). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure to afford 3.60 g of an orange oil that was a mixture of **167** (62%) and **168** (27%) that was inseparable (able to obtain only an analytical sample) by flash chromatography (5% CH_3OH/CH_2Cl_2). Yellow oil; IR ν_{max} 1697 (s), 1639 (s), 1593 (s) cm^{-1}; ^1H NMR (300 MHz) δ 10.37 (1H, s, CHO), 6.73 (1H, s, H-5), 3.93 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 2.81 (3H, s,

NCH_3), 1.56 (9H. s. $NCMe_3$); ^{13}C NMR (75 MHz) δ 190.0 (1, CHO), 153.1 (0, C-3), 151.4 (0, C-6), 146.3 (0. C-4), 126.5 (0, C-1), 103.1 (1, C-5), 97.9 (0, C-2), 62.5 (3, OCH_3), 56.9 (3, OCH_3). 56.2 (3, OCH_3), 33.1 (3, NCH_3), 28.5 (0, $NCMe_3$), 28.0 (3C, 3, $NCMe_3$); MS *m/z* (%) 252 (25, M^+ - ^{t}Bu), 223 (64), 195 (13), 62 (39), 61 (10), 45 (100), 44 (33); HRMS calcd for $C_{12}H_{14}NO_5$ (M^+ - ^{t}Bu): 252.0872, found: 252.0859.

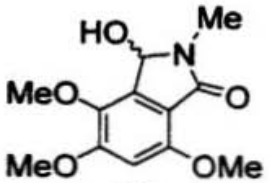
Attempted thioacetalization of 168. To a solution of a mixture of **168** (1.17 g, 3.81 mmol) and **167** (2.43 g. 8.71 mmol) in CH_2Cl_2 (150 mL) was added anhydrous $ZnCl_2$ (1.32 g, 9.69 mmol) and 1.2-ethanedithiol (0.81 mL, 9.7 mmol). The solution was then stirred at rt for 24 h. The solution was washed with H_2O (100 mL) and 1 M NaOH (100 mL). The combined aqueous layers were extracted with CH_2Cl_2 (100 mL) and ethyl acetate (100 mL). The combined organic layers were dried over $MgSO_4$. Chromatography (70% ethyl acetate/hexanes) afforded 604 mg (25%) of **167**. 24 mg (2% from **168**) of **169** as a white solid. 107 mg (11% from **168**) of **170** as a white solid. and 1.20 g (61% from **167**) of **171** as a white solid.



169

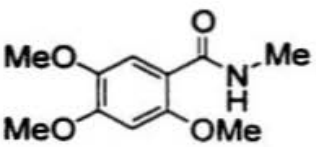
***N-tert*-Butyl-2-formyl-3,4,6-trimethoxy-*N*-methylbenzamide, 1,3-dithiolane derivative (169).** White solid, mp 155-157 °C; IR ν_{max} 1640 (s). 1605 (s) cm^{-1}; ^1H NMR (300 MHz) δ 6.45 (1H. s. H-5), 5.81 (1H. s, H-2'), 3.90 (3H, s. OCH_3), 3.86 (3H, s, OCH_3), 3.77 (3H. s. OCH_3). 3.65-3.52 (2H. m. $-SCH_2$), 3.37-3.27 (2H. m. $-SCH_2$). 2.74 (3H. s. NCH_3). 1.53 (9H. s. $NCMe_3$); ^{13}C NMR (75 MHz) δ 168.1 (0. C-1'), 153.4 (0, C-6). 150.7 (0, C-4). 142.3 (0. C-3). 131.4 (0, C-2). 121.7 (0, C-1), 97.8 (1, C-5), 60.7 (1, C-

2'), 56.8 (3, OCH_3), 56.6 (3, OCH_3), 56.0 (3, OCH_3), 48.3 (3, NCH_3), 40.9 (2, -SCH_2CH_2S-), 40.8 (2, -SCH_2CH_2S-), 33.7 (0, $NCMe_3$), 28.0 (3C, 3, $NCMe_3$); MS *m/z* (%) 385 (22, M^+), 328 (16), 324 (10), 299 (15), 298 (10), 271 (13), 270 (65), 269 (16), 268 (100), 239 (39), 237 (35), 236 (16), 222 (10), 72 (10), 57 (13), 41 (12); HRMS calcd for $C_{18}H_{27}NO_4S_2$: 385.1382, found: 385.1367.



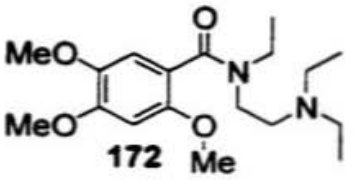
170

3-Hydroxy-4,5,7-trimethoxy-*N*-methyl-(*1H*)-isoindole-1(*2H*)-one (170). White solid; ^{1}H NMR (300 MHz) δ 7.91 (1H, br s, -O**H**), 7.75 (1H, s, H-3), 6.51 (1H, s, H-6), 3.94 (3H, s, O**CH$_3$**), 3.93 (3H, s, O**CH$_3$**), 3.90 (3H, s, O**CH$_3$**), 2.88 (3H, s, N**CH$_3$**).



171

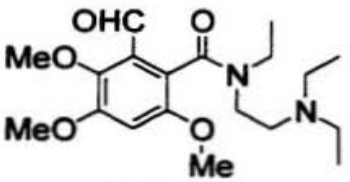
2,4,5-Trimethoxy-*N*-methylbenzamide (171). White solid, mp 135-136 °C; IR (Nujol) ν_{max} 3387 (s), 1630 (s), 1609 (s) cm^{-1}; ^{1}H NMR (300 MHz) δ 7.85 (1H, br s, N**H**), 7.78 (1H, s, H-6), 6.52 (1H, s, H-3), 3.95 (3H, s, O**CH$_3$**), 3.93 (3H, s, O**CH$_3$**), 3.91 (3H, s, O**CH$_3$**), 3.00 (3H, d, J = 4.8 Hz, N**CH$_3$**); ^{13}C NMR (75 MHz) δ 165.7 (0, C-1'), 152.3 (0, C-2), 152.0 (0, C-4), 143.1 (0, C-5), 113.9 (1, C-6), 113.0 (0, C-1), 96.3 (0, C-3), 56.5 (3, O**CH$_3$**), 56.1 (3, O**CH$_3$**), 56.0 (3, O**CH$_3$**), 26.4 (3, NH**CH$_3$**); MS *m/z* (%) 225 (78, M^+), 208 (13), 196 (17), 195 (100), 194 (12), 180 (10), 166 (17), 165 (12), 151 (10), 137 (12), 58 (20), 53 (10), 45 (15), 43 (41); HRMS calcd for $C_{11}H_{15}NO_4$: 225.1001, found: 225.1006.



172

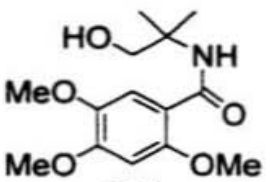
***N*-[2-(Diethylamino)ethyl]-*N*-ethyl-2,4,5-trimethoxybenzamide (172).** To a solution of **97** (3.00 g, 14.1 mmol) in benzene (150 mL) was added oxalyl chloride (2.50 mL, 28.7 mmol) dropwise. This cloudy white solution was stirred at rt overnight. The resulting clear yellow solution was then concentrated under reduced pressure to yield a white solid. To a stirred mixture at 0 °C of *N,N,N'*-triethylethylenediamine (2.54 mL, 14.1 mmol), 1 M NaOH (14 mL, 14 mmol) and CH_2Cl_2 (20 mL) was added dropwise over 45 min a solution of 2,4,5-trimethoxybenzoyl chloride in CH_2Cl_2 (50 mL). The mixture was stirred at rt overnight. This mixture was extracted with 7% HCl (3 × 20 mL). The combined aqueous layers were basified with 25% NaOH until pH = 12. The aqueous phase was extracted with CH_2Cl_2 (5 × 40 mL). The combined organic layers were dried over K_2CO_3 to afford 4.81 g (100%) of **172** as a yellow oil: IR ν_{max} 1630 (s) cm^{-1}; ^1H NMR (300 MHz) δ 6.76, 6.75 (1H, s, H-6), 6.51 (1H, s, H-3), 3.91, 3.90 (3H, s, OC**H**$_3$), 3.83 (3H, s, OC**H**$_3$), 3.80 (3H, s, OC**H**$_3$), 3.68-3.40 (2H, br s, O=CNC**H**$_2$CH$_2$N), 3.23 (2H, q, J = 7.1 Hz, O=CNC**H**$_2$CH$_3$), 2.74 (2H, t, J = 7.2 Hz, O=CNCH$_2$C**H**$_2$N), 2.62 (2H, q, J = 7.3 Hz, NC**H**$_2$CH$_3$), 2.34 (2H, q, J = 7.2 Hz, NC**H**$_2$CH$_3$), 1.25, 1.05 (3H, t, J = 7.2 Hz, O=CNCH$_2$C**H**$_3$), 1.09 (3H, t, J = 7.2 Hz, NCH$_2$C**H**$_3$), 0.87 (3H, t, J = 7.2 Hz, NCH$_2$C**H**$_3$); ^{13}C NMR (75 MHz) δ 168.7, 168.6 (0, C-1'), 149.9, 149.8 (0, C-2), 149.4, 149.3 (0, C-4), 143.1, 143.0 (0, C-5), 128.1, 117.8 (0, C-1), 111.1, 111.0 (1, C-6), 97.4, 97.2 (1, C-3), 56.4, 56.3 (3, OCH$_3$), 56.3 (3, OCH$_3$), 56.0, 55.9 (3, OCH$_3$), 51.3, 50.3 (2, NCH$_2$CH$_3$), 47.4, 47.2 (2, NCH$_2$CH$_2$), 46.5 (2, NCH$_2$CH$_3$), 44.1, 42.8 (2, NCH$_2$CH$_2$), 40.2 (2, NCH$_2$CH$_3$), 13.9, 12.8 (3, NCH$_2$CH$_3$).

12.0 (3, $NCH_2\mathbf{C}H_3$), 11.6 (3, NCH_2CH_3); MS *m/z* (%) 195 (20, M^+-143), 99 (44), 87 (22), 86 (100), 58 (16).



173

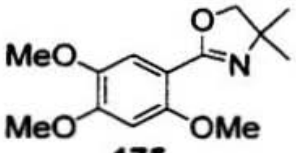
***N*-[2-(Diethylamino)ethyl]-*N*-ethyl-2-formyl-3,4,6-trimethoxybenzamide (173).** To a solution of TMEDA (2.30 mL, 15.2 mmol) and *s*-BuLi (15 mmol) in THF (80 mL) cooled to –78 °C was added dropwise **172** (4.73 g, 14.0 mmol) as a solution in THF (30 mL). The solution was stirred for 1 h at –78 °C and DMF (2.17 mL, 28.0 mmol) was added. The mixture was stirred at –78 °C for 2 h, warmed to rt and stirred overnight. This mixture was extracted with 5% HCl (25 and 2 × 20 mL). The combined aqueous layers were basified with 25% NaOH until pH = 12. The aqueous phase was extracted with ethyl acetate (5 × 40 mL). The combined organic layers were dried over K_2CO_3 to afford 4.80 g of a yellow-orange oil that was a mixture of **172** (83%) and **173** (17%) that was inseparable by flash chromatography: for **173** (from the mixture) ^{1}H NMR (300 MHz) δ 10.38, 10.37 (1H, s, C**H**O), 6.75, 6.74 (1H, s, H-5).



174

***N*-[(2-Hydroxy-(1,1-dimethyl))ethyl]-2,4,5-trimethoxybenzamide (174).** To a solution of **97** (3.05 g, 14.4 mmol) in benzene (150 mL) was added oxalyl chloride (2.50 mL, 28.7 mmol) dropwise. This cloudy yellow solution was stirred at rt for 5 h. The resulting clear yellow solution was then concentrated under reduced

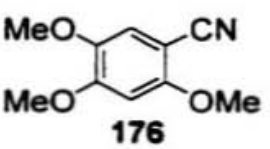
pressure to yield a white solid. To a solution of this in THF (100 mL) cooled to 0 °C was added 2-amino-2-methyl-1-propanol (2.80 mL, 29.3 mmol) dropwise. The resulting cloudy white solution was stirred at rt for 24 h. H_2O (50 mL) was added and the solution was extracted with ethyl acetate (2 × 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to yield 4.02 g (99% over two steps) of **174** as an orange-yellow oil; IR ν_{max} 3374 (br), 1637 (s), 1608 (s) cm^{-1}; ^1H NMR (500 MHz) δ 8.16 (1H, br s, -N**H**), 7.70 (1H, s, H-6), 6.52 (1H, s, H-3), 5.30 (1H, br s, -O**H**), 3.96 (3H, s, OC**H**$_3$), 3.94 (3H, s, OC**H**$_3$), 3.90 (3H, s, OC**H**$_3$), 3.68 (2H, s, -C**H**$_2$OH), 1.40 (6H, s, geminal dimethyl); ^{13}C NMR (125 MHz) δ 165.6 (0, **C**ONH), 152.5 (0, C-2), 152.4 (0, C-4), 143.5 (0, C-5), 113.7 (1, C-6), 113.1 (0, C-1), 96.8 (1, C-3), 71.2 (2, -**C**H$_2$OH), 56.8 (3, -O**C**H$_3$), 56.2 (3, -O**C**H$_3$), 56.1 (3, -O**C**H$_3$), 56.0 (0, NH**C**(CH$_3$)$_2$), 25.0 (2C, 3, geminal dimethyl); MS *m/z* (%) 195 (100, M^+ - 88); HRMS calcd for $C_{14}H_{21}NO_5$: 283.1420, found: 283.1398.



175

2,4,5-Trimethoxybenzoic acid, oxazoline derivative (175). To a solution of **174** (1.87 g, 6.61 mmol) in THF (100 mL) cooled to 0 °C was added thionyl chloride (0.72 mL, 9.9 mmol) dropwise. This cloudy white solution was stirred at rt for 24 h. 1 M NaOH (2 × 100 mL) was added and the solution was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and solvent removed under reduced pressure to yield 1.77 g (100%) of **175** as a beige solid, mp 84-85 °C; IR ν_{max} 1620 (s), 1595 (s) cm^{-1}; ^1H NMR (500 MHz) δ 7.31 (1H, s, H-6), 6.54 (1H, s, H-3), 4.08 (2H, s,

CH_2O), 3.92 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 1.39 (6H, s, geminal dimethyl); ^{13}C NMR (125 MHz) δ 161.0 (0, CO=N), 153.8 (0, C-2), 151.9 (0, C-4), 142.7 (0, C-5), 113.8 (1, C-6), 108.9 (0, C-1), 98.1 (1, C-3), 78.8 (2, CH_2O), 67.1 (0, $NC(CH_3)_2$), 57.3 (3, -OCH_3), 56.4 (3, -OCH_3), 55.9 (3, -OCH_3), 28.4 (2C, 3, geminal dimethyl); MS *m/z* (%) 266 (14), 265 (80, M^+), 251 (13), 250 (84), 236 (14), 222 (44), 220 (28), 209 (11), 208 (14), 195 (16), 194 (27), 193 (63), 192 (44), 182 (11), 181 (100), 180 (17), 179 (46), 178 (29), 166 (13), 165 (46), 164 (20), 151 (18), 150 (15), 125 (10), 117 (14), 77 (11), 72 (10), 69 (13), 56 (10), 55 (11), 45 (21), 41 (18). HRMS calcd for $C_{14}H_{19}NO_4$: 265.1314, found: 265.1315.

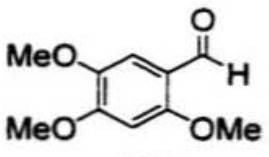


176

2,4,5-Trimethoxybenzonitrile (176). To a solution of **174** (4.02 g, 14.2 mmol) in ether (140 mL) and CH_2Cl_2 (40 mL) cooled to 0 °C was added oxalyl chloride (2.50 mL, 28.7 mmol) dropwise. This cloudy yellow solution was stirred at rt for 64 h. The contents were diluted with ether (200 mL) and washed with H_2O (100 mL) and 1 M NaOH (2 × 100 mL). The combined aqueous layers were extracted with ether (2 × 50 mL). The combined organic layers were dried over $MgSO_4$. Chromatography (70% ethyl acetate/hexanes) afforded 2.74 g (100%) of **176** as a white solid, mp 98-102 °C: IR (Nujol) ν_{max} 2220 (s), 1776 (s), 1753 (s), 1611 (s), 1590 (s) cm^{-1}; ^1H NMR (CD_3COCD_3, 500 MHz) δ 7.13 (1H, s, H-6), 6.85 (1H, s, H-3), 3.94 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 3.82 (3H, s, OCH_3); ^{13}C NMR (CD_3COCD_3, 125 MHz) δ 158.6 (0, C-2), 155.8 (0, C-4), 144.4 (0, C-5), 117.4 (0, C-1), 116.3 (1, C-6), 98.3 (1, C-3), 91.9 (0, CN), 57.1 (3, -OCH_3), 57.0 (3, -OCH_3), 56.6 (3, -

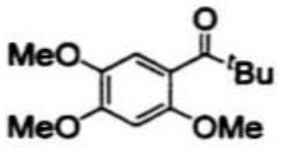
OCH_3); MS *m/z* (%) 193 (100, M^+), 179 (11), 178 (92), 150 (31), 135 (11), 77 (16), 76 (11), 69 (20), 55 (12); HRMS calcd for $C_{10}H_{11}NO_3$: 193.0739, found: 193.0746.

Attempted formylation of acid 97. To a solution of **97** (280 mg, 1.3 mmol) in THF (40 mL) cooled to –100 °C was added *t*-BuLi (4.3 mmol) dropwise. The bright yellow solution was stirred at –100 °C for 5 h and DMF (0.20 mL, 2.6 mmol) was added. The resulting colorless solution was allowed to warm to rt overnight. The excess *t*-BuLi was quenched with isopropanol (10 mL) and H_2O (10 mL). The solution was extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with brine (100 mL) and dried over $MgSO_4$. Chromatography (50% ethyl acetate/hexanes) afforded 77 mg (30%) of **177** as a yellow solid and 34 mg (10%) of **178** as a white solid.



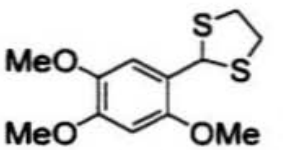
177

2,4,5-Trimethoxybenzaldehyde (177). Yellow solid, mp 61-63 °C; IR (CCl_4) ν_{max} 1676 (s), 1607 (s) cm^{-1}; ^1H NMR (300 MHz) δ 10.33 (1H, s, C**H**O), 7.33 (1H, s, H-6), 6.50 (1H, s, H-3), 3.98 (3H, s, OC**H**$_3$), 3.93 (3H, s, OC**H**$_3$), 3.89 (3H, s, OC**H**$_3$); ^{13}C NMR (75 MHz) δ 188.1 (1, **C**HO), 158.7 (0, C-2), 155.8 (0, C-4), 143.6 (0, C-5), 117.4 (0, C-1), 109.0 (1, C-6), 95.9 (1, C-3), 56.3 (3, O**C**H$_3$), 56.2 (3, O**C**H$_3$), 56.2 (3, O**C**H$_3$); MS *m/z* (%) 196 (100, M^+), 195 (13), 182 (57), 153 (17), 150 (21), 125 (24), 110 (14), 109 (10), 95 (11), 69 (16), 59 (10), 53 (16), 51 (15), 50 (10); HRMS calcd for $C_{10}H_{12}O_4$: 196.0736, found: 196.0755.



178

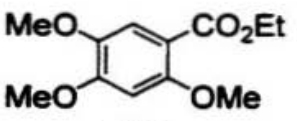
***tert*-Butyl-2,4,5-trimethoxyphenylketone (178).** White solid, mp 57-60 °C; IR (CCl_4) ν_{max} 1702 (s), 1607 (s) cm^{-1}; ^1H NMR (300 MHz) δ 6.61 (1H, s, H-6), 6.51 (1H, s, H-3), 3.91 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 1.22 (9H, s, CMe_3); ^{13}C NMR (75 MHz) δ 213.2 (0, C-1'), 150.2 (0), 149.9 (0), 142.6 (0), 122.3 (0, C-1), 110.8 (1, C-6), 97.2 (1, C-3), 56.5 (3, OCH_3), 56.2 (3, OCH_3), 56.0 (3, OCH_3), 44.9 (0, CMe_3), 26.9 (3C, 3, CMe_3); MS *m/z* (%) 252 (4, M^+), 196 (11), 195 (100); HRMS calcd for $C_{14}H_{20}O_4$: 252.1362, found: 252.1359.



179

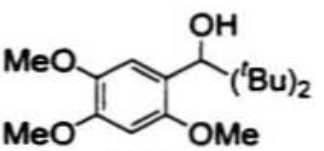
2,4,5-Trimethoxybenzaldehyde, 1,3-dithiolane derivative (179). To a solution of **177** (292 mg, 1.49 mmol) in CH_2Cl_2 (20 mL) was added 1,2-ethanedithiol (0.40 mL, 4.8 mmol) and $BF_3.Et_2O$ (0.13 mL, 1.0 mmol). The cloudy green solution was stirred at rt for 24 h. The solution was washed with 1 M NaOH (2 × 75 mL). The combined aqueous layers were extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with brine (75 mL) and dried over $MgSO_4$. Chromatography (30% ethyl acetate/hexanes) afforded 276 mg (68%) of **179** as a yellow oil: IR (CCl_4) ν_{max} 1610 (s) cm^{-1}; ^1H NMR (300 MHz) δ 7.32 (1H, s, H-6), 6.48 (1H, s, H-3), 6.09 (1H, s, H-1'), 3.86 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.50-3.44 (2H, m, -SCH_2), 3.36-3.30 (2H, m, -SCH_2); ^{13}C NMR (75 MHz) δ 151.0 (0), 149.3 (0), 143.1 (0), 119.4 (0, C-1), 112.0 (1, C-3), 97.2 (1, C-6), 56.7 (3, OCH_3), 56.5 (3, OCH_3), 56.1 (3, OCH_3), 49.1 (1, C-1'), 39.6 (2C, 2, -SCH_2CH_2S-); MS *m/z* (%) 272 (100, M^+), 244 (27), 214 (11), 213 (89), 212 (15),

211 (53), 179 (22), 168 (10), 151 (15), 69 (11), 45 (12); HRMS calcd for $C_{12}H_{16}O_3S_2$: 272.0541, found: 272.0523.



180

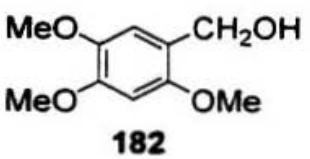
Ethyl 2,4,5-trimethoxybenzoate (180). To a solution of **97** (1.10 g, 5.18 mmol) in absolute ethanol (50 mL) was added concentrated H_2SO_4 (1 mL). This was heated under reflux for 72 h. Solvent was removed *in vacuo* and chromatography (5% CH_3OH/CH_2Cl_2) afforded 1.17 g (98%) of **180** as a white solid, mp 61-63 °C; IR (CCl_4) ν_{max} 1720 (s), 1600 (s) cm^{-1}; ^1H NMR (300 MHz) δ 7.41 (1H, s, H-6), 6.54 (1H, s, H-3), 4.35 (2H, q, J = 7.1 Hz, OCH_2CH_3), 3.94 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 1.38 (3H, t, J = 7.2 Hz, OCH_2CH_3); ^{13}C NMR (75 MHz) δ 165.5 (0, C-1'), 155.6 (0, C-2), 153.3 (0, C-4), 142.4 (0, C-5), 114.2 (1, C-6), 111.0 (0, C-1), 97.8 (1, C-3), 60.5 (2, OCH_2CH_3), 57.1 (3, OCH_3), 56.3 (3, OCH_3), 55.9 (3, OCH_3), 14.3 (3, OCH_2CH_3); MS *m/z* (%) 240 (100, M^+), 225 (46), 197 (22), 195 (80), 193 (16), 169 (12), 165 (11), 151 (10), 137 (21), 109 (11); HRMS calcd for $C_{12}H_{16}O_5$: 240.0998, found: 240.0946.



181

2,2,4,4-Tetramethyl-3-(2',4',5'-trimethoxyphenyl)pentan-3-ol (181). To a solution of **180** (1.17 g, 5.09 mmol) in THF (50 mL) cooled to –78 °C was added *t*-BuLi (6.6 mmol) dropwise. The bright yellow solution was stirred at –78 °C for 30 min and DMF (0.80 mL, 10 mmol) was added. The resulting pale yellow solution was allowed to warm to rt overnight. Excess *t*-BuLi was quenched with isopropanol (10 mL) and H_2O (10 mL).

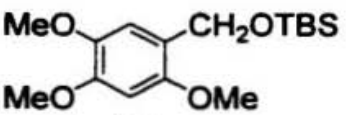
The solution was extracted with ethyl acetate (3 × 150 mL). The combined organic layers were washed with brine (100 mL) and dried over $MgSO_4$. Chromatography (40% ethyl acetate/hexanes) afforded 864 mg (67%) of **178** as a white solid and 204 mg (20%) of **181** as a yellow solid, mp 67-73 °C; IR (CCl_4) ν_{max} 3450 (br), 1607 (s) cm^{-1}; ^1H NMR (300 MHz) δ 7.08 (1H, s, H-6'), 6.56 (1H, s, -O**H**), 6.50 (1H, s, H-3'), 3.88 (3H, s, O**CH$_3$**), 3.86 (3H, s, O**CH$_3$**), 3.84 (3H, s, O**CH$_3$**), 1.13 (18H, s, 2C**Me$_3$**); ^{13}C NMR (75 MHz) δ 152.4 (0), 147.5 (0), 141.8 (0), 125.2 (0, C-1'), 114.8 (1, C-6'), 100.3 (1, C-3'), 86.7 (0, C-3), 59.0 (3, O**C**H$_3$), 56.3 (3, O**C**H$_3$), 55.7 (3, O**C**H$_3$), 43.3 (2C, 0, **C**Me$_3$), 29.7 (6C, 3, C**Me$_3$**); MS *m/z* (%) 253 (47, M^+ - ^{t}Bu), 222 (15), 221 (100), 169 (35), 168 (85), 154 (12), 85 (11), 57 (48), 43 (15), 41 (35); HRMS calcd for $C_{14}H_{21}O_4$ (M^+ - ^{t}Bu): 253.1440, found: 253.1408.



182

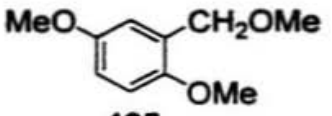
2,4,5-Trimethoxybenzyl alcohol (182). To a solution of **180** (1.50 g, 6.52 mmol) in diethyl ether (75 mL) was added $LiAlH_4$ (500 mg, 13 mmol) in one portion. The solution was stirred at rt for 24 h. The solution was washed with H_2O (100 mL). The aqueous layer was extracted with CH_2Cl_2 (4 × 40 mL). The combined organic layers were washed with brine (100 mL) and dried over $MgSO_4$. Chromatography (70% ethyl acetate/hexanes) afforded 990 mg (79%) of **182** as a white solid, mp 66-68 °C; IR (Nujol) ν_{max} 3350 (br), 1600 (s) cm^{-1}; ^1H NMR (300 MHz) δ 6.86 (1H, s, H-6), 6.54 (1H, s, H-3), 4.63 (2H, d, J = 6.6 Hz, C**H$_2$**OH), 3.90 (3H, s, O**CH$_3$**), 3.85 (3H, s, O**CH$_3$**), 3.85 (3H, s, O**CH$_3$**), 2.13 (1H, t, J = 6.6 Hz, CH$_2$O**H**); ^{13}C NMR (75 MHz) δ 151.6 (0), 149.1 (0),

142.7 (0), 120.4 (0, C-1), 113.1 (1, C-6), 97.2 (1, C-3), 61.4 (2, C-1'), 56.5 (3, O**C**H_3), 56.2 (3, O**C**H_3), 56.0 (3, O**C**H_3); MS *m/z* (%) 198 (100, M^+), 183 (44), 181 (20), 155 (11), 127 (10), 124 (10), 123 (16), 95 (26), 69 (16), 53 (11), 51 (12); HRMS calcd for $C_{10}H_{14}O_4$: 198.0892, found: 198.0906.



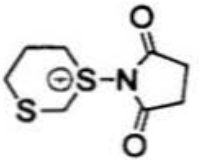
183

2,4,5-Trimethoxy-(((*tert*-butyldimethylsilyl)oxy)methyl)benzene (183). To a solution of **182** (123 mg, 0.623 mmol) in DMF (25 mL) was added imidazole (80 mg, 1.2 mmol) and TBSCl (190 mg, 1.3 mmol) in one portion. The solution was stirred at rt for 72 h. H_2O (50 mL) was added and the solution was extracted with hexanes (4 × 75 mL). The combined organic layers were dried over $MgSO_4$. Chromatography (30% ethyl acetate/hexanes) afforded 112 mg (58%) of **183** as a clear yellow oil: ^{1}H NMR (300 MHz) δ 7.07 (1H, s, H-6), 6.50 (1H, s, H-3), 4.71 (2H, s, C**H**$_2$O), 3.88 (3H, s, OC**H**$_3$), 3.85 (3H, s, OC**H**$_3$), 3.79 (3H, s, OC**H**$_3$), 0.95 (9H, s, SiC**Me**$_3$), 0.11 (6H, s, Si**Me**$_2$); ^{13}C NMR (75 MHz) δ 150.0 (0), 148.1 (0), 142.9 (0), 121.4 (0, C-1), 111.2 (1, C-6), 97.0 (1, C-3), 59.7 (2, C-1'), 56.3 (3, O**C**H_3), 56.2 (3, O**C**H_3), 56.1 (3, O**C**H_3), 25.9 (3C, 3, SiC**Me**$_3$), 18.3 (0, Si**C**Me$_3$), -5.3 (2C, 3, Si**Me**$_2$); MS *m/z* (%) 312 (3, M^-), 255 (23), 240 (24), 182 (11), 181 (100), 151 (13); HRMS calcd for $C_{16}H_{28}O_4Si$: 312.1757, found: 312.1733.



185

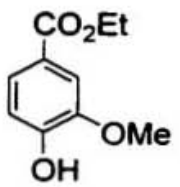
2,5-Dimethoxymethoxymethylbenzene (185). To a suspension of NaH (0.12 g, 5.0 mmol) in THF (30 mL) cooled to 0 °C was added a solution of **184** (706 mg, 4.19 mmol) in THF (15 mL). The solution was stirred at 0 °C for 1 h and CH_3I (0.33 mL, 5.3 mmol) was added and the solution was allowed to warm to rt. H_2O (50 mL) was added and the solution was extracted with ethyl acetate (3 × 75 mL). The combined organic layers were dried over $MgSO_4$. Chromatography (40% ethyl acetate/hexanes) afforded 452 mg (59%) of **185** as a yellow oil; IR ν_{max} 2834 (s), 1600 (s) cm^{-1}; ^1H NMR (300 MHz) δ 6.96 (1H, d, J = 1.8 Hz, H-3), 6.80 (1H, s, H-6), 6.79 (1H, d, J = 1.8 Hz, H-4), 4.48 (2H, s, CH_2O), 3.79 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.43 (3H, s, CH_2OCH_3); ^{13}C NMR (75 MHz) δ 153.5 (0, C-2 or C-5), 151.1 (0, C-2 or C-5), 127.6 (0, C-1), 114.5 (1, C-3), 113.1 (1, C-4), 111.2 (1, C-6), 69.4 (2, CH_2OCH_3), 58.3 (3, CH_2OCH_3), 55.9 (3, OCH_3), 55.7 (3, OCH_3); MS *m/z* (%) 182 (100, M^+), 167 (19), 152 (15), 151 (83), 139 (14), 137 (13), 135 (13), 121 (45), 108 (13), 91 (18), 78 (12), 77 (17), 65 (18), 51 (13), 45 (21); HRMS calcd for $C_{10}H_{14}O_3$: 182.0943, found: 182.0915.



186

2-(*N*-Succinimidyl)-1,3-dithiane (186). To a solution of *N*-chlorosuccinimide (0.76 g, 5.7 mmol) in CH_2Cl_2 (20 mL) was added a solution of 1,3-dithiane (594 mg, 4.94 mmol) in CH_2Cl_2 (15 mL). The slightly cloudy yellow solution was stirred for 120 h, and solvent was removed *in vacuo*. Chromatography (20% ethyl acetate/hexanes) afforded 201 mg (19%) of **186** as a yellow solid, mp 98-100 °C; IR (CCl_4) ν_{max} 1719 (s) cm^{-1}; ^1H NMR (300

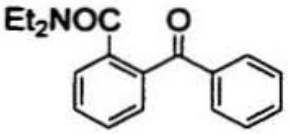
MHz) δ 6.06 (1H, s. H-2), 3.42 (2H. dt, J = 11.6. 3.5 Hz), 2.80 (2H. dt. J = 9.6. 3.5 Hz), 2.75 (4H, s, H-2′ and H-3′), 2.24-1.98 (2H. m); ^{13}C NMR (75 MHz) δ 175.0 (2C. 0, C-1′ and C-4′), 47.7 (1, C-1). 28.8 (2C. 2, C-2′ and C-3′), 28.1 (2C. 2, C-4 and C-6), 23.8 (2, C-5); MS *m/z* (%) 217 (92, M^+), 184 (19), 183 (29), 152 (20), 144 (11), 143 (85), 142 (11), 120 (11), 119 (30), 118 (100), 116 (11), 115 (65), 106 (12), 101 (17), 100 (28), 88 (10), 87 (21), 86 (13), 85 (41), 84 (11), 82 (14), 75 (11), 74 (67), 73 (17), 59 (12), 56 (38), 55 (91), 47 (13), 46 (41), 45 (61), 42 (13), 41 (39).



188

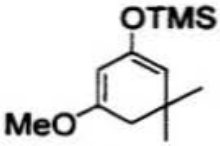
Ethyl 4-hydroxy-3-methoxybenzoate (188). To a solution of 4-hydroxy-3-methoxybenzoic acid (2.63 g, 15.6 mmol) in absolute ethanol (150 mL) was added concentrated H_2SO_4 (1 mL). This was heated under reflux for 24 h. Solvent was removed *in vacuo* and replaced with ethyl acetate (150 mL). The solution was washed with H_2O (2 × 100 mL). The combined aqueous layers were extracted with ethyl acetate (2 × 50 mL). The combined organic layers were dried over Na_2SO_4. Chromatography (40% ethyl acetate/hexanes) afforded 504 mg (19%) of 4-hydroxy-3-methoxybenzoic acid and 2.46 g (80%) of **188** as a colorless oil; IR ν_{max} 3350 (br), 1704 (s), 1598 (s) cm^{-1}; ^{1}H NMR (CD_3COCD_3, 500 MHz) δ 8.36 (1H, s. -O**H**), 7.57 (1H, d. J = 8.0 Hz. H-6), 7.55 (1H. s. H-2). 6.91 (1H, d. J = 8.5 Hz. H-5), 4.30 (2H, q. J = 7.0 Hz. -OC**H**$_2$CH$_3$). 3.90 (3H. s. OC**H**$_3$). 1.34 (3H. t, J = 7.0 Hz, -OCH$_2$C**H**$_3$); ^{13}C NMR (CD_3COCD_3, 500 MHz) δ 166.6 (0, **C**O$_2$CH$_2$CH$_3$), 152.1 (0, C-4), 148.1 (0, C-3), 124.6 (1. C-6), 123.0 (0. C-1), 115.6 (1, C-5). 113.2 (1. C-2), 61.1 (2, CO$_2$**C**H$_2$CH$_3$). 56.4 (3. -O**C**H$_3$). 14.7 (3. CO$_2$CH$_2$**C**H$_3$); MS *m/z* (%) 196 (57, M^+), 168 (19), 153 (11), 152

(16), 151 (100), 123 (19), 52 (15), 51(10); HRMS calcd for $C_{10}H_{12}O_4$: 196.0736, found: 196.0749.



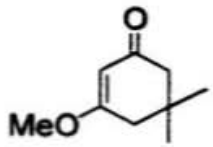
189

2-Benzoyl-*N*,*N*-diethylbenzamide (189). To a solution of TMEDA (0.17 mL, 1.1 mmol) and *s*-BuLi (1.1 mmol) in THF (10 mL) cooled to –78 °C was added dropwise *N*,*N*-diethylbenzamide (102 mg, 0.576 mmol) as a solution in THF (10 mL). The solution was stirred for 30 min at –78 °C, and a solution of **186** (115 mg, 0.529 mmol) in THF (15 mL) was added. The mixture was warmed to rt and stirred for 8 h. H_2O (100 mL) was added and the solution was extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine (100 mL) and dried over $MgSO_4$. Chromatography (50% ethyl acetate/hexanes) afforded 47 mg (59%) of **189** as a yellow oil; IR (CCl_4) ν_{max} 1667 (s). 1637 (s) cm^{-1}; ^1H NMR (300 MHz) δ 7.82-7.39 (9H, m, Ar**H**), 3.43 (2H, q, J = 7.0 Hz, CH_2CH_3), 3.27 (2H, q, J = 7.1 Hz, CH_2CH_3), 1.12 (3H, t, J = 7.4 Hz, CH_2CH_3), 1.07 (3H, t, J = 7.4 Hz, CH_2CH_3); ^{13}C NMR (75 MHz) δ 196.5 (0, **C**=O), 169.8 (0, **C**=ONEt$_2$), 138.2 (0), 137.1 (0), 136.8 (0), 132.9 (1), 130.7 (1), 130.1 (1), 129.7 (1), 128.2 (1), 128.0 (1), 126.6 (1), 43.1 (2, CH_2CH_3), 38.7 (2, CH_2CH_3), 13.6 (3, CH_2CH_3), 12.0 (3, CH_2CH_3); MS *m/z* (%) 210 (42), 209 (96, M^+ - NEt_2), 153 (12), 152 (24), 105 (15), 77 (25), 72 (100); HRMS calcd for $C_{14}H_9O_2$ (M^+ - NEt_2): 209.0603, found: 209.0611.



191

1-Methoxy-5,5-dimethyl-3-(trimethylsilyl)oxycyclohexa-1,3-diene (191). A solution of **192** (see page 179) (4.00 g, 26.0 mmol) in THF (40 mL) was added dropwise to a solution of LDA, prepared from *n*-BuLi (31.2 mmol) and diisopropylamine (4.80 mL, 34.2 mmol) in THF (50 mL), over 25 minutes at –78 °C. The solution was stirred at –78 °C for 1.5 h. TMSCl (6.50 mL, 51.2 mmol) was added dropwise, and the solution was warmed to rt. Most of the solvent was evaporated under reduced pressure, and pentane (100 mL) was added. The solution was filtered, and the filtrate was concentrated under reduced pressure. The oily residue was distilled under vacuum to afford 4.79 g (82%) of **191** (for which there were no signals in the ^{1}H NMR spectrum corresponding to **195**) as a colorless oil: bp 50-53 °C/0.4 mmHg; IR ν_{max} 1657 (s), 1608 (s) cm^{-1}; ^{1}H NMR (300 MHz) δ 4.72 (1H, narrow m, H-2), 4.38 (1H, d, J = 1.5 Hz, H-4), 3.58 (3H, s, -OC**H**$_3$), 2.09 (2H, d, J = 0.9 Hz, H-6), 1.02 (6H, s, C-5 geminal dimethyl), 0.20 (9H, s, Si**Me**$_3$); ^{1}H NMR (300 MHz, C_6D_6) δ 4.91 (1H, s, H-2), 4.55 (1H, q, J = 1.5 Hz, H-4), 3.16 (3H, d, J = 1.8 Hz, -OC**H**$_3$), 2.24 (2H, q, J = 0.9 Hz, H-6), 1.06 (3H, s, C**H**$_3$), 1.05 (3H, s, C**H**$_3$), 0.26 (3H, s, SiC**H**$_3$), 0.26 (3H, s, SiC**H**$_3$), 0.25 (3H, s, SiC**H**$_3$); NOE data δ 1.02 (4.38, 4%; 2.09, 3%); ^{13}C NMR (C_6D_6, 75 MHz) δ 160.6 (0, C-3), 148.8 (0, C-1), 107.2 (1, C-2), 94.6 (1, C-4), 54.7 (3, O**C**H$_3$), 43.0 (2, C-6), 33.0 (0, C-5), 29.4 (3, 2C, C-5 dimethyl), 0.7 (3, 3C, Si**Me**$_3$); MS m/z (%) 227 (25, M$^+$ + 1), 226 (24), 212 (17), 211 (100), 195 (20), 154 (28), 144 (16), 98 (75), 89 (11), 75 (22), 73 (49), 69 (20), 68 (42), 45 (13), 41 (11), 40 (13).



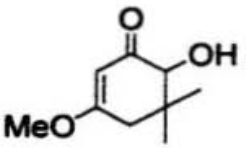
192

3-Methoxy-5,5-dimethylcyclohex-2-en-1-one (192). To a solution of 5,5-dimethyl-1,3-cyclohexanedione (10.0 g, 71.4 mmol) in methanol (300 mL) was added Amberlyst-15 resin (10.0 g). The solution was then stirred at rt for 24 h. The resin was filtered off, and the solvent was evaporated under reduced pressure. The residue was redissolved in benzene (150 mL), and the solution was dried over anhydrous $MgSO_4$. The benzene was evaporated under reduced pressure to yield 10.4 g (94%) of **192** as a yellow oil; IR ν_{max} 1656 (s), 1612 (s) cm^{-1}; ^1H NMR (300 MHz) δ 5.28 (1H. s, H-2), 3.61 (3H, s, OCH_3), 2.19 (2H, s, H-4 or H-6), 2.12 (2H, s, H-4 or H-6), 0.99 (6H, s, C-5 dimethyl); ^{13}C NMR (75 MHz) δ 199.1 (0, C-1). 176.7 (0. C-3), 100.8 (1. C-2). 55.4 (3, OCH_3). 50.4 (2, C-4 or C-6), 42.3 (2, C-4 or C-6), 32.2 (0, C-5). 28.0 (3, 2C, CH_3); MS *m/z* (%) 154 (32, M^+), 98 (100), 69 (38), 68 (75), 41 (13).

Rubottom Oxidation of diene 191. To a solution of **191** (1.25 g, 5.52 mmol) in hexanes (40 mL) cooled to –15 °C was added *m*-CPBA (1.05 g, 6.08 mmol) as a solution in hexanes (20 mL). The solution was stirred at –15 °C for 20 min and warmed to rt for 2 h. The solution was filtered, and solvent was removed *in vacuo* and replaced with pentane (50 mL). The solution was filtered again and the solvent removed *in vacuo*. To a solution of this in CH_2Cl_2 (90 mL) was added TBAF (10.0 mmol) as a solution in THF (10 mL). The solution was stirred at rt for 1.5 h. The solution was washed with saturated $NaHCO_3$ (2 × 100 mL). 7% HCl (50 mL) and saturated $NaHCO_3$ (2 × 100 mL). The organic layer was dried over $MgSO_4$. Chromatography (30% ethyl acetate/hexanes)

afforded 340 mg (40%) of **192**, 221 mg (24%) of **193** as a white solid, and 149 mg (16%) of **194** as a yellow-white solid.

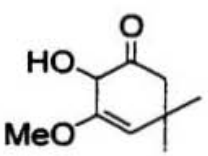
6-Hydroxy-3-methoxy-5,5-dimethylcyclohex-2-en-1-one (193).



193

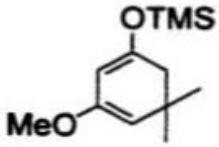
White solid, mp 64-65 °C; IR (CCl_4) ν_{max} 3400 (br), 1661 (s), 1610 (s) cm^{-1}; ^1H NMR (300 MHz) δ 5.43 (1H, s, H-2), 3.89 (1H, d, J = 1.5 Hz, H-6), 3.82 (1H, d, J = 1.5 Hz, -O**H**), 3.73 (3H, s, O**CH$_3$**), 2.54 (1H, d, J = 17.4 Hz, H-4), 2.25 (1H, d, J = 17.4 Hz, H-4), 1.22 (3H, s, **CH$_3$**), 0.88 (3H, s, **CH$_3$**); ^{13}C NMR (75 MHz) δ 198.7 (0, C-1), 177.0 (0, C-3), 98.4 (1, C-2), 79.1 (1, C-6), 56.1 (3, O**CH$_3$**), 42.9 (2, C-4), 38.2 (0, C-5), 27.6 (3, C-5 methyl), 18.2 (3, C-5 methyl); MS *m/z* (%) 170 (15, M^+), 141 (29), 99 (65), 98 (100), 72 (27), 69 (61), 68 (94), 57 (28), 55 (11), 53 (10), 43 (28), 41 (39), 40 (41); HRMS calcd for $C_9H_{14}O_3$: 170.0943, found: 170.0949.

2-Hydroxy-3-methoxy-5,5-dimethylcyclohex-3-en-1-one (194).



194

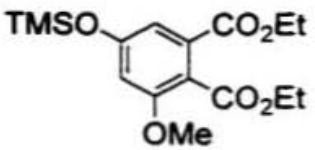
Yellow-white solid; ^1H NMR (300 MHz) δ 5.32 (1H, s, H-4), 4.15 (1H, s, H-2), 3.77 (3H, s, O**CH$_3$**), 2.42 (1H, d, J = 17.4 Hz, H-6), 2.22 (1H, d, J = 17.4 Hz, H-6), 1.12 (3H, s, **CH$_3$**), 1.04 (3H, s, **CH$_3$**); ^{13}C NMR (75 MHz) δ 198.3 (0, C-1), 174.9 (0, C-3), 101.0 (1, C-4), 74.8 (1, C-2), 56.3 (3, O**CH$_3$**), 48.9 (2, C-6), 37.4 (0, C-5), 26.8 (3, C-5 methyl), 21.2 (3, C-5 methyl); MS *m/z* (%) 170 (9, M^+), 142 (20), 128 (17), 114 (71), 86 (77), 75 (15), 69 (13), 57 (30), 56 (100), 55 (12), 43 (20), 41 (25).



195

3-Methoxy-5,5-dimethyl-1-(trimethylsilyl)oxycyclohexa-1,3-diene (195). Heating a solution of **191** in toluene for 48 h gave material with signals for **191** and **195** in a ratio of 3.2:1, respectively. For **195** (from the mixture): ^{1}H NMR (300 MHz) δ 4.99 (1H, m, H-2), 4.15 (1H, d, J = 1.5 Hz, H-4), 3.52 (3H, s, -OC**H**$_3$), 2.08 (2H, d, J = 1.5 Hz, H-6), 1.05 (6H, s, C-5 geminal dimethyl), 0.23 (9H, s, Si**Me**$_3$).

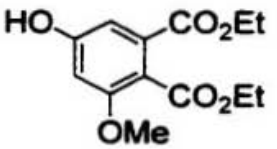
Diels-Alder reaction of diene 191. To a solution of diethyl acetylenedicarboxylate (5.27 g, 31.0 mmol) in toluene (150 mL) was added **191** (4.66 g, 20.6 mmol), and the solution was heated under reflux for 240 h. Solvent was removed *in vacuo* to afford crude **196**. To a solution of **196** in THF (100 mL) was added TBAF (40 mmol) as a solution in THF (40 mL). The solution was then stirred at rt for 24 h. H_2O (2 × 100 mL) was added and the solution was extracted with CH_2Cl_2 (2 × 75 mL). The combined organic layers were washed with brine (100 mL) and dried over $MgSO_4$. Chromatography (3% CH_3OH/CH_2Cl_2) afforded 4.08 g (74%) of **197** as an oil that crystallized upon standing.



196

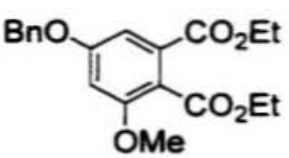
Diethyl 3-methoxy-5-(trimethylsilyl)oxyphthalate (196). Orange oil; IR ν_{max} 1725 (s), 1602 (s) cm^{-1}; ^{1}H NMR (300 MHz) δ 7.03 (1H, d, J = 2.4 Hz, H-6), 6.59 (1H, d, J = 2.4 Hz, H-4), 4.39 (2H, q, J = 7.1 Hz, OC**H**$_2$CH$_3$), 4.32 (2H, q, J = 7.0 Hz, OC**H**$_2$CH$_3$), 3.81 (3H, s, OC**H**$_3$), 1.37 (3H, t, J = 7.2 Hz, OCH$_2$C**H**$_3$), 1.34 (3H, t, J = 7.2 Hz, OCH$_2$C**H**$_3$), 0.29 (9H, s, Si**Me**$_3$); ^{13}C NMR (75 MHz) δ 167.4 (0, **C**O$_2$CH$_2$CH$_3$), 165.1 (0, **C**O$_2$CH$_2$CH$_3$), 157.7 (0, C-3 or C-5), 156.7 (0, C-3 or C-5), 130.0 (0, C-1),

118.9 (0, C-2), 112.8 (1, C-6), 107.7 (1, C-4), 62.9 (2, OCH_2CH_3), 61.3 (2, OCH_2CH_3), 56.1 (3, OCH_3), 13.9 (3, OCH_2CH_3), 13.8 (3, OCH_2CH_3), 0.0 (3C, 3, $SiMe_3$); MS *m/z* (%) 340 (48, M^+), 297 (14), 296 (11), 295 (52), 268 (36), 267 (100), 251 (36), 222 (10), 75 (21), 73 (69), 45 (11).



197

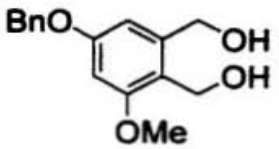
Diethyl 5-hydroxy-3-methoxyphthalate (197). colorless crystals, mp 101–102 °C; IR (Nujol) ν_{max} 3300 (br), 1720 (s), 1610 (s) cm^{-1}; ^1H NMR (300 MHz) δ 7.00 (1H, d, J = 2.4 Hz, H-6), 6.60 (1H, d, J = 2.4 Hz, H-4), 5.54 (1H, s, -O**H**), 4.38 (2H, q, J = 7.2 Hz, OCH_2CH_3), 4.32 (2H, q, J = 6.1 Hz, OCH_2CH_3), 3.80 (3H, s, OCH_3), 1.36 (3H, t, J = 7.4 Hz, OCH_2CH_3), 1.34 (3H, t, J = 6.5 Hz, OCH_2CH_3); ^{13}C NMR (75 MHz) δ 168.9 (0), 165.8 (0), 158.5 (0, C-3 or C-5), 157.9 (0, C-3 or C-5), 130.3 (0, C-1), 116.3 (0, C-2), 108.6 (1, C-6), 103.1 (1, C-4), 61.9 (2, OCH_2CH_3), 61.7 (2, OCH_2CH_3), 55.9 (3, OCH_3), 13.9 (3, OCH_2CH_3), 13.8 (3, OCH_2CH_3); MS *m/z* (%) 268 (18, M^+), 223 (35), 200 (22), 196 (13), 195 (100), 154 (19), 144 (10), 116 (14), 115 (13), 98 (66), 69 (25), 68 (51), 40 (18); HRMS calcd for $C_{13}H_{16}O_6$: 268.0947, found: 268.0938.



198

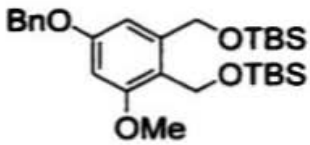
Diethyl 5-benzyloxy-3-methoxyphthalate (198). To a solution of **197** (4.05 g, 15.1 mmol) in $CHCl_3$/methanol (2:1, 150 mL) was added K_2CO_3 (8.35 g, 60.4 mmol) at 0 °C. The mixture was heated under reflux for 15 min, and benzyl bromide (2.3 mL, 19 mmol) was added. The mixture was heated under reflux for 48 h. The solution was filtered, and the solvent was removed *in vacuo*. Chromatography (3% CH_3OH/CH_2Cl_2)

afforded 246 mg (6%) of **197** and 3.44 g (64%, 68% based on recovered starting material) of **198** as a yellow solid; ^{1}H NMR (300 MHz) δ 7.43-7.35 (5H, m, Ar**H**), 7.16 (1H, apparent broad s, H-6), 6.72 (1H, d, J = 2.4 Hz, H-4), 5.11 (2H, s, PhC**H**$_2$), 4.43-4.30 (4H, m, -OC**H**$_2$CH$_3$), 3.81 (3H, s, OC**H**$_3$), 1.37 (6H, t, J = 7.1 Hz, -OCH$_2$C**H**$_3$).



199

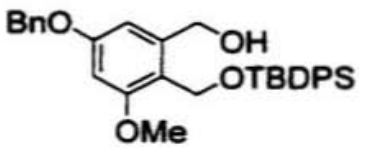
5-Benzyloxy-3-methoxy-1,2-benzenedimethanol (199). To a solution of $LiAlH_4$ (0.93 g, 25 mmol) in THF (150 mL) cooled to 0 °C was added a solution of **198** (3.44 g, 9.62 mmol) in THF (100 mL). The solution was allowed to warm to rt and stirred overnight. Excess $LiAlH_4$ was quenched cautiously with sodium sulfate decahydrate, 95% ethanol, 50% ethanol and then H_2O. The resulting emulsion was added to saturated sodium potassium tartrate (200 mL) and stirred overnight. The solution was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine (150 mL) and dried over $MgSO_4$ to afford 2.71 g (100%) of **199** as a white solid, mp 69–70 °C: IR ν_{max} 3350 (br), 1607 (s) cm^{-1}; ^{1}H NMR (300 MHz) δ 7.44-7.32 (5H, m, Ar**H**), 6.59 (1H, d, J = 2.4 Hz, H-6), 6.50 (1H, d, J = 2.4 Hz, H-4), 5.05 (2H, s, PhC**H**$_2$O), 4.71 (2H, s), 4.62 (2H, s), 3.78 (3H, s, OC**H**$_3$); ^{13}C NMR (75 MHz) δ 159.5 (0, C-3 or C-5), 158.9 (0, C-3 or C-5), 142.2 (0, C-1), 136.7 (0, C-2), 128.6 (2C, 1, *ortho*), 128.1 (1, *para*), 127.5 (2C, 1, *meta*), 120.3 (0), 106.5 (1, C-6), 98.9 (1, C-4), 70.0 (2), 64.1 (2), 55.7 (3, OCH$_3$), 55.7 (2); MS *m/z* (%) 274 (6, M$^+$), 91 (100); HRMS calcd for $C_{16}H_{18}O_4$: 274.1205, found: 274.1218.



200

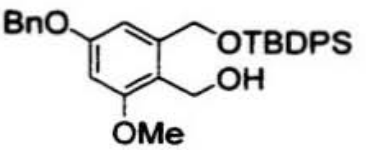
5-Benzyloxy-3-methoxy-(bis-1,2-((*tert*-butyldimethylsilyl)oxy)methyl)benzene (200). To a solution of **199** (489 mg, 1.78 mmol) in DMF (40 mL) was added imidazole (221 mg, 3.24 mmol) and TBSCl (321 mg, 2.13 mmol) in one portion. The solution was stirred at rt for 48 h. H_2O (100 mL) was added and the solution was extracted with petroleum ether (3 × 100 mL). The combined organic layers were washed with brine (100 mL) and dried over $MgSO_4$. Chromatography (20% ethyl acetate/hexanes) afforded 201 mg (22%) of **200** as a clear yellow oil; ^{1}H NMR (300 MHz) δ 7.46-7.32 (5H, m, Ar**H**), 6.86 (1H, d, J = 2.7 Hz, H-6), 6.42 (1H, d, J = 2.7 Hz, H-4), 5.07 (2H, s, PhC**H$_2$**), 4.88 (2H, s, C**H$_2$**OTBS), 4.70 (2H, s, C**H$_2$**OTBS), 3.77 (3H, s, OC**H$_3$**), 0.95 (9H, s, SiC**Me$_3$**), 0.88 (9H, s, SiC**Me$_3$**), 0.09 (6H, s, Si**Me$_2$**), 0.03 (6H, s, Si**Me$_2$**).

Attempted protection of diol 199. To a solution of **199** (154 mg, 0.560 mmol) in DMF (30 mL) was added imidazole (72 mg, 1.1 mmol) and TBDPSCl (0.13 mL, 0.50 mmol) in one portion. The solution was stirred at rt for 24 h. H_2O (50 mL) was added and the solution was extracted with petroleum ether (100 and 2 × 75 mL). The combined organic layers were washed with brine (100 mL) and dried over $MgSO_4$. Chromatography (30% ethyl acetate/hexanes) afforded 16 mg (6%) of **200a** as a clear yellow oil and 13 mg (5%) of **200b** as a clear yellow oil.



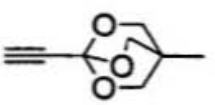
200a

5-Benzyloxy-3-methoxy-2-((*tert*-butyldiphenylsilyl)oxy)methylbenzyl alcohol (200a). Clear yellow oil; ^{1}H NMR (300 MHz) δ 7.70 (4H, d, J = 8.0 Hz, *ortho*), 7.46-7.34 (11H, m, Ar**H**), 6.68 (1H, d, J = 2.4 Hz, H-6), 6.41 (1H, d, J = 2.1 Hz, H-4), 5.09 (2H, s, PhC**H**$_2$), 4.85 (2H, s, C**H**$_2$OTBS), 4.72 (2H, d, J = 6.6 Hz, C**H**$_2$OH), 3.76 (1H, t, J = 6.5 Hz, -O**H**), 3.48 (3H, s, -OC**H**$_3$), 1.02 (9H, s, SiC**Me**$_3$).



200b

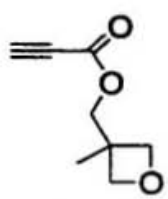
4-Benzyloxy-6-methoxy-2-((*tert*-butyldiphenylsilyl)oxy)methylbenzyl alcohol (200b). Clear yellow oil: ^{1}H NMR (300 MHz) δ 7.68 (4H, d, J = 8.0 Hz, *ortho*), 7.47-7.32 (11H, m, Ar**H**), 6.51 (2H, br s, H-3 and H-5), 4.98 (2H, s, PhC**H**$_2$), 4.77 (2H, s, C**H**$_2$OTBS), 4.67 (2H, d, J = 6.0 Hz, C**H**$_2$OH), 3.83 (3H, s, -OC**H**$_3$), 2.64 (1H, t, J = 6.0 Hz, -O**H**) 1.05 (9H, s, SiC**Me**$_3$).



203

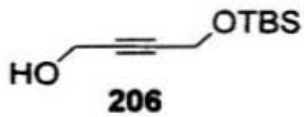
1-Ethynyl-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (203). Compound **205** (see page 186) (847 mg, 5.50 mmol) was dissolved in CH_2Cl_2 (50 mL) and stirred with $BF_3{\cdot}Et_2O$ (170 μL) at rt for 24 h. After treatment with NEt_3 (800 μL), the solvent was removed under vacuum, and the product was purified by chromatography on silica gel (pretreated with NEt_3) with CH_2Cl_2 as eluent to give 301 mg (36%) of pure **203** as a white crystalline solid, mp 150 °C (dec.); IR (CCl_4) ν_{max} 3262 (s), 2140 (s) cm^{-1}; ^{1}H NMR (300 MHz) δ 4.00 (6H, s, 3OC**H**$_2$), 2.56 (1H, s, **H**C≡C), 0.84 (3H, s, C**H**$_3$); ^{13}C NMR (75 MHz) δ 101.3 (0, C-1), 76.8 (0, HC≡**C**),

73.0 (2, 3C, CH_2), 70.6 (1, HC≡C), 30.2 (0, C-4), 14.3 (3, CH_3); MS *m/z* (%) 124 (15, $M^+ - CH_2O$), 96 (13), 95 (20), 81 (11), 79 (16), 67 (12), 55 (11), 54 (18), 53 (100), 43 (10), 41 (15). HRMS calcd for $C_8H_{10}O_3$ ($M^+ - CH_2O$): 124.0524, found: 124.0499.



205

Propiolic Acid 3-Methyl-3-(hydroxymethyl)oxetane ester (205). Compound **204** (11.7 g, 115 mmol) was stirred in CH_2Cl_2 (25 mL) with DCC (31.5 g, 154 mmol) and DMAP (0.69 g, 5.6 mmol) at 0 °C. Propiolic acid (8.00 g, 114 mmol) was added over 1 h, and the mixture was stirred 2 h. After filtration, the mixture was washed with 1% NH_4Cl solution (200 mL) and 5% $NaHCO_3$ solution (200 mL), and dried ($MgSO_4$). The solvent was removed under vacuum. The crude oil was distilled under vacuum to give 7.72 g (44%) of **205** as a colorless oil. bp 69-71 °C/0.8 mmHg; IR ν_{max} 3258 (s), 2118 (s), 1720 (s) cm^{-1}; ^1H NMR (300 MHz) δ 4.53 (2H, d, J = 6.6 Hz, CH_2 oxetane), 4.42 (2H, d, J = 6.6 Hz, CH_2 oxetane), 4.32 (2H, s, OCH_2), 2.93 (1H, s, CH), 1.37 (3H, s, CH_3); ^{13}C NMR (75 MHz) δ 152.5 (0, CO_2), 79.0 (2, 2C, CH_2 oxetane), 75.5 (1, CH), 74.1 (0, HC≡C), 70.1 (2, OCH_2), 38.7 (0, CH_2CCH_3), 20.7 (3, CH_3); MS *m/z* (%) 95 (23), 81 (17), 79 (23), 71 (15), 67 (18), 55 (18), 54 (25), 53 (100), 43 (18), 41 (29).

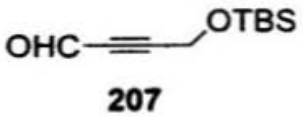


206

4-(*tert*-Butyldimethylsilyl)oxy-2-butyn-1-ol (206); representative procedure for monoprotection. To a solution of 2-butyne-1,4-diol (4.50 g, 52.2 mmol) and imidazole (7.36 g, 108 mmol) in DMF (200 mL) was added TBSCl (8.60 g, 57.1 mmol) in one portion. The

solution was stirred at rt for 24 h. H_2O (150 mL) was added. This was extracted with hexanes (2 × 200 and 2 × 100 mL). The combined hexane solutions were dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. Chromatography provided 5.01 g (48%) of **206** as a yellow oil; IR (CCl_4) ν_{max} 3300 (br) cm^{-1}; ^1H NMR (300 MHz) δ 4.37 (2H, t, J = 1.8 Hz, H-4), 4.32 (2H, dt, J = 1.7, 5.7 Hz, H-1), 1.54 (1H, t, J = 5.7 Hz, -O**H**), 0.92 (9H, s, SiC**Me**$_3$), 0.13 (6H, s, Si**Me**$_2$); ^{13}C NMR (75 MHz) δ 83.7 (0, C-2 or C-3), 83.2 (0, C-2 or C-3), 51.6 (2, C-1 or C-4), 50.6 (2, C-1 or C-4), 25.6 (3, 3C, SiC**Me**$_3$), 18.2 (0, Si**C**Me$_3$), -5.3 (3, 2C, Si**Me**$_2$); MS *m/z* (%) 143 (3, M^+ - ^{t}Bu), 125 (17), 75 (100); HRMS calcd for $C_{10}H_{20}O_2Si$: 200.1233, found: 200.1232.

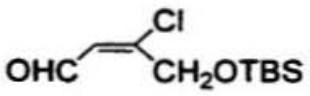
Attempted Oxidation of propargylic alcohol 206. To a solution of **206** (2.04 g, 10.2 mmol) in CH_2Cl_2 (180 mL) was added PCC (2.63 g, 12.2 mmol) in one portion. The black solution was stirred for 24 h. This mixture was passed through a Florisil column using CH_2Cl_2 as eluent and further purified by chromatography (20% ethyl acetate/hexanes) to afford 492 mg of a yellow oil that was still a mixture of three products by ^1H NMR: **207** (7%), **208** (13%) and **209** (2%).



207

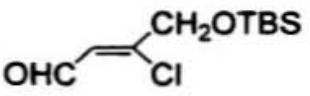
4-(*tert*-Butyldimethylsilyl)oxy-2-butynal (207). Clear yellow oil: IR ν_{max} 2258 (s), 2187 (s), 1676 (s) cm^{-1}; ^1H NMR (300 MHz) δ 9.24 (1H, s, H-1), 4.51 (2H, s, H-4), 0.92 (9H, s, SiC**Me**$_3$), 0.14 (6H, s, Si**Me**$_2$); ^{13}C NMR (75 MHz) δ 176.5 (1, C-1), 94.9 (0, C-3), 84.2 (0, C-2), 51.5 (2, C-4), 25.7 (3, 3C, SiC**Me**$_3$), 18.2 (0, Si**C**Me$_3$), -5.3 (3, 2C, Si**Me**$_2$); MS

m/z (%) 141 (32, M^+ - ^{t}Bu), 113 (100), 111 (55), 83 (15), 75 (22), 57 (25); HRMS calcd for $C_{10}H_{18}SiO_2$: 198.1076, found: 198.1069.



208

(*E*)-4-(*tert*-Butyldimethylsilyl)oxy-3-chlorobut-2-enal (208). ^{1}H NMR (300 MHz) δ 10.11 (1H, d, J = 7.2 Hz, H-1), 6.50 (1H, dt, J = 1.9, 7.2 Hz, H-2), 4.34 (2H, d, J = 1.9 Hz, H-4), 0.93 (9H, s, SiC**Me$_3$**), 0.12 (6H, s, Si**Me$_2$**); MS *m/z* (%) 234 (9, M^+), 177 (6), 149 (17), 113 (10), 95 (14), 93 (36), 83 (13), 75 (39), 73 (100), 57 (12).

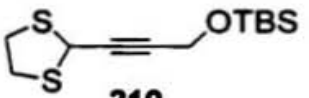


209

(*Z*)-4-(*tert*-Butyldimethylsilyl)oxy-3-chlorobut-2-enal (209). ^{1}H NMR (300 MHz) δ 10.19 (1H, d, J = 7.2 Hz, H-1), 6.30 (1H, dt, J = 1.5, 7.2 Hz, H-2), 4.68 (2H, d, J = 1.2 Hz, H-4), 0.92 (9H, s, SiC**Me$_3$**), 0.13 (6H, s, Si**Me$_2$**); MS *m/z* (%) 234 (9, M^+), 177 (6), 149 (17), 113 (10), 95 (14), 93 (36), 83 (13), 75 (39), 73 (100), 57 (12).

Improved Oxidation to 4-(*tert*-Butyldimethylsilyl)oxy-2-butynal (207); representative procedure. A solution of **206** (4.96 g, 24.8 mmol) in CH_2Cl_2 (200 mL) was added to a solution of Dess–Martin periodinane (13.5 g, 31.8 mmol) in CH_2Cl_2 (125 mL). The cloudy solution was stirred at rt for 3 h. The solution was diluted with diethyl ether (400 mL) and washed with 1 M aqueous NaOH (150, 75 and 50 mL) and H_2O (150 mL). The organic layer was dried over anhydrous $MgSO_4$. Flash chromatography gave 4.91 g (100%) of **207** as a yellow oil.

4-(*tert*-Butyldimethylsilyl)oxy-2-butynal, 1,3-dithiolane derivative (210) and 4-Hydroxybut-2-ynal, 1,3-dithiolane derivative (211). To a solution of **207** (824 mg, 4.16 mmol) in CH_2Cl_2 (75 mL) was added anhydrous $ZnCl_2$ (580 mg, 4.3 mmol) and 1,2-ethanedithiol (1.05 mL, 12.5 mmol). The solution was then stirred at rt for 24 h. The solution was washed with 1 M NaOH (3 × 75 mL). The combined aqueous layers were extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried over $MgSO_4$. Chromatography (20% ethyl acetate/hexanes) afforded 553 mg (49%) of **210** as a yellow oil and 266 mg (40%) of **211** as a yellow oil. For **210:**



210

clear yellow oil; IR ν_{max} 2227 (s) cm^{-1}; ^1H NMR (300 MHz) δ 5.16 (1H, t, J = 1.8 Hz, H-1), 4.35 (2H, d, J = 2.1 Hz, H-4), 3.48-3.28 (4H, m, -SC**H**$_2$C**H**$_2$S-), 0.90 (9H, s, SiC**Me**$_3$), 0.12 (6H, s, Si**Me**$_2$); ^{13}C NMR (75 MHz) δ 83.6 (0, C-2 or C-3), 82.9 (0, C-2 or C-3), 51.9 (2, C-4), 39.7 (1, C-1), 39.3 (2, 2C, -S**C**H$_2$**C**H$_2$S-), 25.8 (3, 3C, SiC**Me**$_3$), 18.2 (0, Si**C**Me$_3$), -5.1 (3, 2C, Si**Me**$_2$); MS *m/z* (%) 233 (13, M^+ - 41), 189 (33), 145 (21), 127 (11), 75 (100), 73 (24), 45 (18); HRMS calcd for $C_{12}H_{22}OS_2Si$: 274.0881, found: 274.0882. For

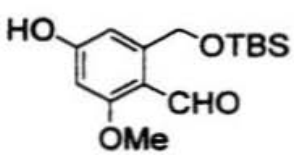
211

211: clear yellow oil; IR ν_{max} 3350 (br), 2216 (s) cm^{-1}; ^1H NMR (300 MHz) δ 5.17 (1H, t, J = 2.1 Hz, H-1), 4.32 (2H, dd, J = 2.0, 6.2 Hz, H-4), 3.50-3.29 (4H, m, -SC**H**$_2$C**H**$_2$S-), 1.62 (1H, t, J = 6.3 Hz, -O**H**); ^{13}C NMR (75 MHz) δ 84.3 (0, C-2 or C-3), 82.3 (0, C-2 or C-3), 50.7 (2, C-4), 39.4 (1, C-1), 39.2 (2, 2C, -S**C**H$_2$**C**H$_2$S-); MS *m/z* (%) 160 (8, M^+), 132 (88), 131 (24), 129 (32), 127 (71), 105 (25), 104 (91), 103 (66), 102 (25), 101 (11), 100 (15), 99 (30), 87 (48), 82 (10), 72 (13), 71 (86), 70 (15), 69 (51), 68 (62), 64 (18), 61 (27), 60 (19), 59 (44), 58 (28), 55

(18), 51 (13), 47 (10), 46 (16), 45 (100), 43 (24), 41 (14), 40 (39); HRMS calcd for $C_6H_8OS_2$: 160.0017, found: 160.0026.

212

Butynedial, mono 1,3-dithiolane derivative (212). To a solution of Dess-Martin periodinane (1.85 g, 4.36 mmol) in CH_2Cl_2 (30 mL) was added **211** (637 mg, 3.98 mmol) as a solution in CH_2Cl_2 (30 mL). The solution was stirred at rt for 10 min and ^{1}H NMR on the unpurified product revealed the formation of **212**; ^{1}H NMR (300 MHz) δ 9.23 (1H, s, C**H**O), 5.17 (1H, s, H-4), 3.51-3.34 (4H, m, -SC**H**$_2$C**H**$_2$S-).

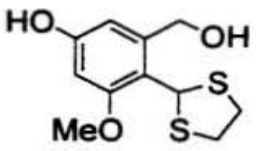


213

6-((*tert*-Butyldimethylsilyl)oxy)methyl-4-hydroxy-2-methoxybenzaldehyde (213): representative procedure for Diels–Alder with diene 191. A solution of **207** (619 mg, 3.13 mmol) and **191** (1.06 g, 4.69 mmol) in toluene (40 mL) was heated under reflux for 168 h. The solvent was evaporated under reduced pressure. Chromatography provided 98 mg (16%) of **207** and 665 mg (72%, 86% based on recovered starting material) of **213** as a white solid, mp 210 °C (dec.); IR (Nujol) ν_{max} 3380 (br), 1712 (s), 1552 (s) cm^{-1}; ^{1}H NMR (300 MHz) δ 10.43 (1H, s, C**H**O), 6.90 (1H, d, J = 2.1 Hz, H-5), 6.36 (1H, d, J = 2.1 Hz, H-3), 5.07 (2H, s, C**H**$_2$O), 3.88 (3H, s, OC**H**$_3$), 0.97 (9H, s, SiC**Me**$_3$), 0.13 (6H, s, Si**Me**$_2$); ^{1}H NMR (CD_3COCD_3, 300 MHz) δ 10.39 (1H, s, C**H**O), 9.47 (1H, br s, ArO**H**), 7.01 (1H, d, J = 1.2 Hz, H-5), 6.49 (1H, d, J = 1.5 Hz, H-3), 5.04 (2H, s, C**H**$_2$O), 3.92 (3H, s, OC**H**$_3$), 2.81 (1H, br s, CH$_2$O**H**), 0.98

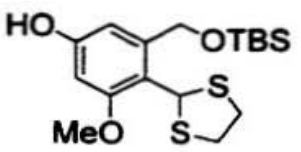
(9H, s, SiC**Me**$_3$), 0.13 (6H, s, Si**Me**$_2$); MS *m/z* (%) 296 (3, M$^+$), 240 (17), 239 (100), 165 (48), 75 (33), 73 (13). The structure of **213** was determined by X-ray crystallography.

Attempted thioacetylation of aldehyde 213. To a solution of **213** (153 mg, 0.517 mmol) in CH_2Cl_2 (25 mL) was added first anhydrous $ZnCl_2$ (70 mg, 0.52 mmol) and then 1,2-ethanedithiol (0.13 mL, 1.6 mmol). The solution was then stirred at rt for 24 h. The solution was washed with H_2O (2 × 50 mL). The combined aqueous layers were re-extracted with CH_2Cl_2 (2 × 75 mL). The combined organic layers were washed with brine (75 mL) and dried over anhydrous $MgSO_4$. Chromatography afforded 18 mg (14%) of **214** as a sparingly soluble yellow solid and 7 mg (4%) of **215** as a yellow residue.



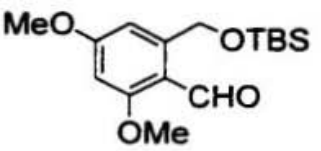
214

4-Hydroxy-6-hydroxymethyl-2-methoxybenzaldehyde, 1,3-dithiolane derivative (214). Yellow solid, mp 133-134 °C; IR (Nujol) ν_{max} 3350 (br), 1602 (s) cm^{-1}; ^{1}H NMR (300 MHz) δ 6.66 (1H, d, *J* = 2.7 Hz, H-5), 6.62 (1H, s, H-1'), 6.45 (1H, br s, ArO**H**), 6.39 (1H, d, *J* = 2.4 Hz, H-3), 5.01 (2H, d, *J* = 7.5 Hz, C**H**$_2$O), 3.82 (3H, s, OC**H**$_3$), 3.61-3.53 (2H, m, -SC**H**$_2$), 3.56 (1H, t, *J* = 7.5 Hz, CH$_2$O**H**), 3.44-3.34 (2H, m, -SC**H**$_2$); MS *m/z* (%) 258 (13, M$^+$), 212 (58), 199 (15), 198 (11), 197 (100), 179 (20), 166 (10), 165 (80), 164 (28), 137 (17), 122 (12), 107 (29), 105 (10), 77 (11), 69 (22), 65 (13), 61 (12), 51 (10), 45 (21), 43 (12); HRMS calcd for $C_{11}H_{14}O_3S_2$: 258.0384, found: 258.0362. The structure of **214** was determined by X-ray crystallography.



215

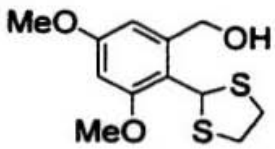
6-((*tert*-Butyldimethylsilyl)oxy)methyl-4-hydroxy-2-methoxybenzaldehyde, 1,3-dithiolane derivative (215). Yellow residue: ^{1}H NMR (300 MHz) δ 6.73 (1H, d, J = 3.0 Hz, H-5), 6.53 (1H, s, H-1'), 6.33 (1H, d, J = 2.7 Hz, H-3), 5.18 (2H, s, C**H**$_2$O), 3.81 (3H, s, OC**H**$_3$), 3.61-3.44 (2H, m, -SC**H**$_2$), 3.40-3.26 (2H, m, -SC**H**$_2$), 0.96 (9H, s, SiC**Me**$_3$), 0.12 (6H, s, Si**Me**$_2$); MS *m/z* (%) 372 (2, M$^+$), 311 (34), 279 (10), 214 (10), 213 (12), 212 (100), 181 (14), 179 (27), 165 (60), 105 (46), 75 (43), 73 (85), 62 (14), 61 (15), 59 (12), 57 (11), 45 (41), 44 (12), 43 (21), 41 (14); HRMS calcd for $C_{17}H_{28}O_3S_2Si$: 372.1249, found: 372.1243.



216

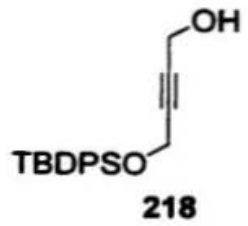
6-((*tert*-Butyldimethylsilyl)oxy)methyl-2,4-dimethoxybenzaldehyde (216); representative procedure for methylation. A solution of **213** (133 mg, 0.450 mmol), K_2CO_3 (0.12 g, 0.87 mmol) and CH_3I (0.10 mL, 1.6 mmol) in acetone (50 mL) was heated under reflux for 24 h. Brine (40 mL) was added, and the solution was extracted with ethyl acetate (3 × 75 mL). The combined organic layers were dried over $MgSO_4$. Chromatography provided 95 mg (68%) of **216** as a yellow solid, mp 63-64 °C; IR (Nujol) ν_{max} 1676 (s), 1600 (s) cm^{-1}; ^{1}H NMR (300 MHz) δ 10.45 (1H, s, C**H**O), 7.07 (1H, d, J = 2.1 Hz, H-5), 6.36 (1H, d, J = 2.1 Hz, H-3), 5.10 (2H, s, C**H**$_2$OSi), 3.89 (3H, s, OC**H**$_3$), 3.89 (3H, s, OC**H**$_3$), 0.98 (9H, s, SiC**Me**$_3$), 0.13 (6H, s, Si**Me**$_2$); ^{13}C NMR (CD_3COCD_3, 75 MHz) δ 189.7 (1, **C**HO), 166.5 (0, C-2 or C-4), 166.4 (0, C-2 or C-4), 149.3 (0, C-6), 115.7 (0, C-1), 104.3 (1, C-5), 96.7 (1, C-3), 64.3 (2,

CH_2OSi), 56.6 (3, OCH_3). 56.0 (3, OCH_3), 26.3 (3C, 3, $SiCMe_3$). 18.0 (0, $SiCMe_3$), -5.2 (2C, 3, $SiMe_2$); MS *m/z* (%) 310 (4, M^+), 254 (18), 253 (100), 179 (81), 75 (13), 73 (12); HRMS calcd for $C_{16}H_{26}O_4Si$: 310.1600, found: 310.1585.



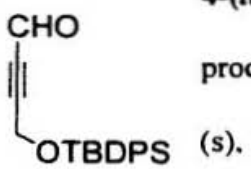
217

6-Hydroxymethyl-2,4-dimethoxybenzaldehyde, 1,3-dithiolane derivative (217). To a solution of **216** (85 mg, 0.273 mmol) in CH_2Cl_2 (25 mL) was added 1,2-ethanedithiol (0.07 mL, 0.84 mmol) and anhydrous $ZnCl_2$ (90 mg, 0.66 mmol). The solution was then stirred at rt for 24 h. The solution was washed with brine (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 40 mL), ethyl acetate (2 × 40 mL) and diethyl ether (2 × 40 mL). The combined organic layers were dried over $MgSO_4$. Chromatography (30% ethyl acetate/hexanes) afforded 6 mg (8%) of **217** as a white solid, mp 92-93 °C; IR (Nujol) ν_{max} 3400 (br), 1605 (s) cm^{-1}; ^1H NMR (CD_3COCD_3, 300 MHz) δ 6.86 (1H, d, J = 2.4 Hz, H-5), 6.54 (1H, s, H-1'), 6.47 (1H, d, J = 2.4 Hz, H-3), 5.07 (2H, d, J = 5.4 Hz, CH_2O), 4.05 (1H, t, J = 5.4 Hz, -OH), 3.85 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.59-3.51 (2H, m, $-SCH_2$), 3.38-3.28 (2H, m, $-SCH_2$); ^{13}C NMR (CD_3COCD_3, 75 MHz) δ 161.4 (0, C-2 or C-4), 146.2 (0, C-2 or C-4), 114.5 (0, C-6), 106.1 (1, C-5), 104.9 (0, C-1), 97.9 (1, C-3), 61.7 (2, CH_2OH), 56.5 (3, OCH_3), 55.6 (3, OCH_3), 47.3 (1, C-1'), 40.9 (2C, 2, $-SCH_2CH_2S-$); MS *m/z* (%) 272 (11, M^+), 226 (56), 213 (17), 212 (12), 211 (100), 193 (21), 180 (11), 179 (86), 178 (26), 151 (14), 149 (13), 136 (14), 121 (29), 77 (12), 69 (10), 45 (15).



218

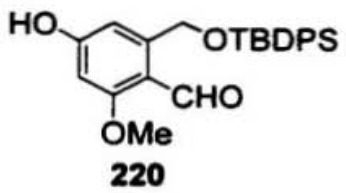
4-(*tert*-Butyldiphenylsilyl)oxy-2-butyn-1-ol (218). Preparation was by the procedure for **206**. Yield of **218:** 47%; clear yellow oil; IR ν_{max} 3400 (br) cm^{-1}; ^1H NMR (300 MHz) δ 7.73-7.70 (4H, m, Ar**H**), 7.46-7.37 (6H, m. Ar**H**), 4.36 (2H, t, J = 2.0 Hz, H-4), 4.18 (2H, dt, J = 1.9, 6.6 Hz, H-1), 1.73 (1H, t, J = 6.6 Hz, -O**H**), 1.06 (9H, s, SiC**Me**$_3$); ^{13}C NMR (75 MHz) δ 135.6 (1, 4C), 133.0 (0, 2C), 129.8 (1, 2C), 127.7 (1, 4C), 84.1 (0, C-2 or C-3), 83.4 (0, C-2 or C-3), 52.6 (2, C-1 or C-4), 51.0 (2, C-1 or C-4), 26.7 (3, 3C, SiC**Me**$_3$), 19.1 (0, Si**C**Me$_3$); MS *m/z* (%) 267 (21, M^+ - ^{t}Bu), 249 (24), 200 (18), 199 (100), 189 (15), 139 (61), 129 (10), 115 (10), 77 (18), 45 (17); HRMS calcd for $C_{16}H_{15}SiO_2$ (M^+ - ^{t}Bu): 267.0841, found: 267.0829.



219

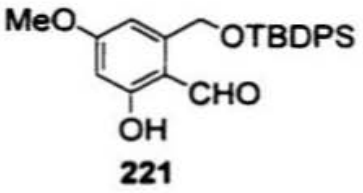
4-(*tert*-Butyldiphenylsilyl)oxy-2-butynal (219). Preparation was by the procedure for **207**. Yield of **219:** 93%; yellow oil; IR ν_{max} 2262 (s), 2189 (s), 1674 (s) cm^{-1}; ^1H NMR (300 MHz) δ 9.16 (1H, s, C**H**O), 7.71-7.68 (4H, m, Ar**H**), 7.46-7.39 (6H, m, Ar**H**), 4.49 (2H, s, H-4), 1.06 (9H, s, SiC**Me**$_3$); ^{13}C NMR (75 MHz) δ 176.4 (1, C-1), 135.5 (1, 4C), 132.2 (0, 2C), 130.0 (1, 2C), 127.9 (1, 4C), 94.6 (0, C-3), 84.4 (0, C-2), 52.3 (2, C-4), 26.6 (3, 3C, SiC**Me**$_3$), 19.1 (0, Si**C**Me$_3$); MS *m/z* (%) 265 (100, M^+ - ^{t}Bu), 247 (34), 239 (12), 237 (12), 236 (25), 235 (95), 207 (23), 199 (18), 197 (10), 187 (39), 181 (16), 115 (11), 105 (22), 91 (16), 77 (22), 45 (21). HRMS calcd for $C_{16}H_{13}SiO_2$ (M^+ - ^{t}Bu): 265.0685, found: 265.0697.

6-((*tert*-Butyldiphenylsilyl)oxy)methyl-4-hydroxy-2-methoxybenzaldehyde (220) and 6-((*tert*-butyldiphenylsilyl)oxy)methyl-2-hydroxy-4-methoxybenzaldehyde (221). Preparation was by the procedure for **213**. Yield of **220**: 82% and **221**: 10%. For **220**:



220

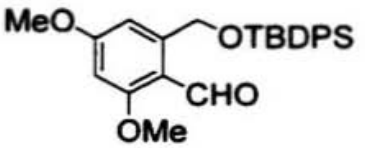
white solid, mp 181-182 °C; IR (Nujol) ν_{max} 3400 (br), 1713 (s), 1588 (s) cm^{-1}; ^1H NMR (CD_3COCD_3, 300 MHz) δ 10.30 (1H, s, C**H**O), 7.75-7.72 (4H, m, Ar**H**), 7.50-7.40 (6H, m, Ar**H**), 7.31 (1H, d, J = 1.8 Hz, H-5), 6.53 (1H, d, J = 1.8 Hz, H-3), 5.16 (2H, s, C$\mathbf{H_2}$O), 3.92 (3H, s, OC$\mathbf{H_3}$), 3.78 (1H, s, -O**H**), 1.12 (9H, s, SiC$\mathbf{Me_3}$); NOE data δ 5.16 (10.30, 2%; 7.31, 2%); ^{13}C NMR (CD_3COCD_3, 75 MHz) δ 189.3 (1, **C**HO), 166.7 (0, C-2 or C-4), 165.0 (0, C-2 or C-4), 148.9 (0, C-6), 136.2 (4C, 1), 134.2 (2C, 0), 130.8 (2C, 1), 128.8 (4C, 1), 114.9 (0, C-1), 106.0 (1, C-5), 97.9 (1, C-3), 65.3 (2, CH_2OSi), 56.5 (3, OCH_3), 27.3 (3C, 3, SiC$\mathbf{Me_3}$), 20.0 (0, SiCMe$_3$); MS *m/z* (%) 363 (57, M^+ - ^{t}Bu), 258 (20), 257 (100), 199 (39), 197 (12), 181 (12), 165 (23), 135 (11), 105 (13), 78 (10), 77 (27), 57 (31), 45 (14), 43 (10), 41 (31); HRMS calcd for $C_{21}H_{19}SiO_4$ (M^+ - ^{t}Bu): 363.1053, found: 363.1083. For **221**: yellow- orange solid, mp 82-84 °C; IR



221

(Nujol) ν_{max} 3380 (br), 1712 (s), 1620 (s) cm^{-1}; ^1H NMR (CD_3COCD_3, 300 MHz) δ 10.22 (1H, s, C**H**O), 7.81-7.71 (4H, m, Ar**H**), 7.51-7.37 (6H, m, Ar**H**), 6.55 (1H, d, J = 1.8 Hz, H-5), 6.39 (1H, d, J = 3.0 Hz, H-3), 5.13 (2H, s, C$\mathbf{H_2}$O), 3.85 (3H, s, OC$\mathbf{H_3}$), 3.25 (1H, s, -O**H**), 1.07 (9H, s, SiC$\mathbf{Me_3}$); NOE data δ 5.13 (10.30, 9%; 6.55, 6%); ^{13}C NMR (CD_3COCD_3, 75 MHz) δ 194.6 (1, **C**HO), 167.4 (0, C-2 or C-4), 167.3 (0, C-2 or C-4), 147.0 (0, C-6), 136.3 (4C, 1), 135.6 (2C, 0), 130.9 (2C, 1),

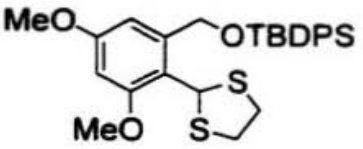
128.8 (4C, 1), 112.8 (0, C-1), 108.5 (1, C-5), 100.5 (1, C-3), 63.9 (2, $\mathbf{C}H_2OSi$), 56.2 (3, $O\mathbf{C}H_3$), 27.2 (3C, 3, $SiC\mathbf{Me}_3$), 19.8 (0, $Si\mathbf{C}Me_3$); MS *m/z* (%) 363 (64, M^+ - ^{t}Bu), 258 (20), 257 (100), 199 (35), 197 (15), 181 (10), 165 (16), 135 (22), 105 (11), 77 (24), 73 (15), 57 (14), 45 (11), 41 (17); HRMS calcd for $C_{21}H_{19}SiO_4$ (M^- - ^{t}Bu): 363.1053, found: 363.1046.



222

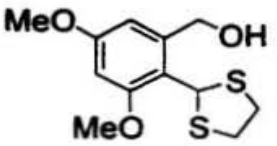
6-((*tert*-Butyldiphenylsilyl)oxy)methyl-2,4-dimethoxybenzaldehyde (222). Preparation was by the procedure for **216**. Yield of **222:** 98% from **220**, 93% from **221**: white solid, mp 77-78 °C; IR (Nujol) ν_{max} 1712 (s), 1675 (s), 1599 (s) cm^{-1}; ^1H NMR (CD_3COCD_3, 300 MHz) δ 10.33 (1H, s, C**H**O), 7.76-7.73 (4H, m, Ar**H**), 7.50-7.40 (6H, m, Ar**H**), 7.31 (1H, d, J = 2.0 Hz, H-5), 6.64 (1H, d, J = 2.0 Hz, H-3), 5.18 (2H, s, $C\mathbf{H}_2O$), 3.97 (3H, s, $OC\mathbf{H}_3$), 3.95 (3H, s, $OC\mathbf{H}_3$), 1.14 (9H, s, $SiC\mathbf{Me}_3$); NOE data δ 7.31 (5.18, 1%; 3.97, 3.95, 1%; 1.14, 1%), 6.64 (3.97, 3.95, 4%), 5.18 (7.50-7.40, 1%; 1.14, 1%); ^{13}C NMR (CD_3COCD_3, 75 MHz) δ 189.7 (1, **C**HO), 166.7 (0, C-2 or C-4), 166.3 (0, C-2 or C-4), 148.6 (0, C-6), 136.2 (4C, 1), 134.2 (2C, 0), 130.9 (2C, 1), 128.8 (4C, 1), 115.7 (0, C-1), 104.4 (1, C-5), 96.9 (1, C-3), 65.3 (2, $\mathbf{C}H_2OSi$), 56.7 (3, $O\mathbf{C}H_3$), 56.1 (3, $O\mathbf{C}H_3$), 27.3 (3C, 3, $SiC\mathbf{Me}_3$), 20.0 (0, $Si\mathbf{C}Me_3$); MS *m/z* (%) 377 (56, M^+ - ^{t}Bu), 272 (20), 271 (100), 199 (20), 179 (44), 149 (11), 136 (11), 135 (15), 105 (11), 77 (18), 57 (16), 41 (18); HRMS calcd for $C_{22}H_{21}SiO_4$ (M^- - ^{t}Bu): 377.1209, found: 377.1229.

Improved thioacetylation of 222; 6-((*tert*-butyldiphenylsilyl))oxymethyl-2,4-dimethoxybenzaldehyde, 1,3-dithiolane derivative (223). To a solution of **222** (314 mg, 0.724 mmol) in CH_2Cl_2 (60 mL) was first added 1,2-ethanedithiol (0.13 mL, 1.6 mmol) and then anhydrous $ZnCl_2$ (100 mg, 0.73 mmol). The solution was then stirred at rt for 24 h. The solution was washed with H_2O (50 mL). The aqueous layer was re-extracted with CH_2Cl_2 (4 × 50 mL). The combined organic layers were added to acetone (50 mL) and dried over anhydrous $MgSO_4$.



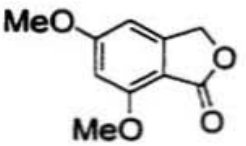
223

Chromatography afforded 76 mg (39%) of **217** and 140 mg (38%) of **223** as a colorless oil; IR (Nujol) ν_{max} 1603 (s) cm^{-1}; ^1H NMR (CD_3COCD_3, 300 MHz) δ 7.80-7.75 (4H, m, Ar**H**), 7.48-7.36 (6H, m, Ar**H**), 7.11 (1H, d, J = 3.0 Hz, H-5), 6.52 (1H, s, H-1'), 6.51 (1H, d, J = 3.0 Hz, H-3), 5.33 (2H, s, C**H**$_2$O), 3.85 (3H, s, OC**H**$_3$), 3.83 (3H, s, OC**H**$_3$), 3.13 (4H, s, -SC**H**$_2$C**H**$_2$S-), 1.13 (9H, s, SiC**Me**$_3$); ^1H NMR (C_6D_6, 300 MHz) δ 7.90-7.87 (2H, m, Ar**H**), 7.73-7.70 (4H, m, Ar**H**), 7.22-7.19 (4H, m, Ar**H**), 7.19 (1H, d, J = 2.4 Hz, H-5), 6.96 (1H, s, H-1'), 6.30 (1H, d, J = 2.4 Hz, H-3), 5.70 (2H, s, C**H**$_2$O), 3.50 (3H, s, OC**H**$_3$), 3.15 (3H, s, OC**H**$_3$), 2.63 (4H, s, -SC**H**$_2$C**H**$_2$S-), 1.09 (9H, s, SiC**Me**$_3$); ^{13}C NMR (CD_3COCD_3, 75 MHz) δ 161.4 (0, C-2 or C-4), 159.6 (0, C-2 or C-4), 144.9 (0, C-6), 136.3 (4C, 1), 134.4 (2C, 0), 130.1 (2C, 1), 128.4 (4C, 1), 113.9 (0, C-1), 105.1 (1, C-5), 97.7 (1, C-3), 63.4 (2, C**H**$_2$OSi), 56.5 (3, O**C**H$_3$), 55.5 (3, O**C**H$_3$), 46.7 (1, C-1'), 40.8 (2C, 2, -S**C**H$_2$**C**H$_2$S-), 27.4 (3C, 3, SiC**Me**$_3$), 19.7 (0, Si**C**Me$_3$); MS *m/z* (%) 510 (2, M^+), 453 (3), 271 (8), 228 (10), 227 (12), 226 (100), 199 (28), 179 (59), 135 (13), 104 (21), 57 (12).



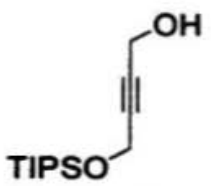
217

6-Hydroxymethyl-2,4-dimethoxybenzaldehyde, 1,3-dithiolane derivative (217). To a solution of **223** (235 mg, 0.460 mmol) in THF (50 mL) was added TBAF (3.7 mmol) as a solution in THF (3.7 mL). The solution was stirred at rt for 24 h. H_2O (100 mL) was added and the solution was extracted with ethyl acetate (4 × 50 mL). The combined organic layers were dried over $MgSO_4$. Chromatography (20%-50% ethyl acetate/hexanes) afforded 118 mg (94%) of **217** as a white solid, all spectral data were consistent with previously characterized material.



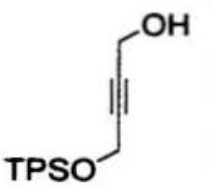
224

5,7-Dimethoxyphthalide (224). To a solution of CrO_3 (20 mg, 0.2 mmol) in 1.5 M H_2SO_4 (0.34 mL) cooled to 0 °C was added **217** as a solution in acetone (0.65 mL). The solution was stirred for 3 min, then ice (1 mL) and diethyl ether (3 mL) were added. The solution was extracted with diethyl ether (5 × 30 mL), and the aqueous layer was basified with 1 M NaOH until pH = 12 and extracted with diethyl ether (3 × 30 mL). The combined organic layers were dried over Na_2SO_4. Chromatography afforded 9.7 mg (93%) of **224** as dark brown crystals; ^{1}H NMR (300 MHz) δ 6.76 (1H, s, H-5), 6.60 (1H, s, H-3), 5.20 (2H, s, C**H**$_2$O), 3.92 (3H, s, OC**H**$_3$), 3.91 (3H, s, OC**H**$_3$); MS *m/z* (%) 194 (18, M^+), 176 (14), 165 (16), 150 (11), 149 (92), 148 (26), 135 (10), 111 (10), 99 (17), 97 (18), 95 (12), 85 (19), 83 (22), 81 (12), 71 (30), 70 (18), 69 (32), 67 (10), 57 (100), 56 (20), 55 (42), 43 (65), 41 (43). The structure of **224** was determined by X-ray crystallography.



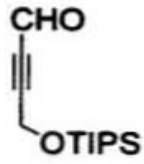
227

4-(Triisopropylsilyl)oxy-2-butyn-1-ol (227). Preparation was by the procedure for **206**. Yield of **227:** 45%; colorless oil; IR ν_{max} 3370 (br) cm^{-1}; ^1H NMR (500 MHz) δ 4.42 (2H, t, *J* = 1.5 Hz, H-4), 4.30 (2H, dt, *J* = 1.5, 6.3 Hz, H-1), 1.64 (1H, t, *J* = 6.3 Hz, -O**H**), 1.12 (3H, septet, *J* = 6.0 Hz, CH_3CHCH_3), 1.08 (18H, d, *J* = 6.0 Hz, CH_3CHCH_3); ^{13}C NMR (125 MHz) δ 84.6 (0, C-2 or C-3), 82.7 (0, C-2 or C-3), 51.9 (2, C-4), 51.2 (2, C-1), 17.9 (3, 6C, CH_3CHCH_3), 12.0 (1, 3C, CH_3CHCH_3); MS *m/z* (%) 199 (11, $M^+ - C_3H_7$), 131 (58), 115 (18), 103 (86), 89 (14), 77 (21), 75 (100), 61 (64), 59 (10), 45 (33), 41 (18); HRMS calcd for $C_{10}H_{19}O_2Si$ (M^+ - ^{t}Pr): 199.1154, found: 199.1178.



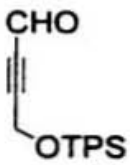
228

4-(Triphenylsilyl)oxy-2-butyn-1-ol (228). Preparation was by the procedure for **206**. Yield of **228:** 46%; clear yellow oil; IR ν_{max} 3380 (br) cm^{-1}; ^1H NMR (500 MHz) δ 7.66 (6H, d, *J* = 6.5 Hz, H-2′ and H-6′), 7.45 (3H, t, *J* = 7.5 Hz, H-4′), 7.39 (6H, t, *J* = 7.5 Hz, H-3′ and H-5′), 4.49 (2H, s, H-4), 4.12 (2H, d, *J* = 6.3 Hz, H-1), 1.25 (1H, t, *J* = 6. Hz, -O**H**); ^{13}C NMR (125 MHz) δ 135.5 (1, 6C, C-2′ and C-6′), 133.6 (0, 3C, C-1′), 130.2 (1, 3C, C-4′), 127.9 (1, 6C, C-3′ and C-5′), 84.1 (0, C-2 or C-3), 84.0 (0, C-2 or C-3), 52.5 (2, C-4), 51.1 (2, C-1); MS *m/z* (%) 343 (2, M^+ -1), 253 (26), 200 (18), 199 (100), 181 (11), 139 (16), 128 (13), 105 (10), 91 (11), 77 (20), 45 (15).



229

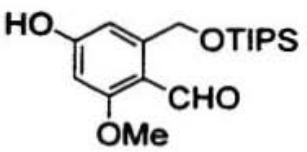
4-(Triisopropylsilyl)oxy-2-butynal (229). Preparation was by the procedure for **207**. Yield of **229:** 91%; clear yellow oil; IR ν_{max} 2257 (s), 2190 (s), 1681 (s) cm^{-1}; ^1H NMR (500 MHz) δ 9.24 (1H, s, H-1), 4.58 (2H, s, H-4), 1.13 (3H, septet, J = 6.0 Hz, CH_3CHCH_3), 1.08 (18H, d, J = 6.0 Hz, CH_3CHCH_3); ^{13}C NMR (125 MHz) δ 176.4 (1, C-1), 95.0 (0, C-3), 84.1 (0, C-2), 51.9 (2, C-4), 17.8 (3, 6C, CH_3CHCH_3), 11.9 (1, 3C, CH_3CHCH_3); MS *m/z* (%) 197 (42, M^+ - C_3H_7), 156 (13), 155 (100), 139 (15), 131 (13), 127 (65), 125 (10), 113 (16), 112 (10), 111 (69), 103 (13), 99 (20), 97 (21), 85 (11), 83 (14), 77 (11), 75 (50), 69 (11), 61 (46), 59 (21), 47 (10), 45 (69), 43 (37), 41 (45).



230

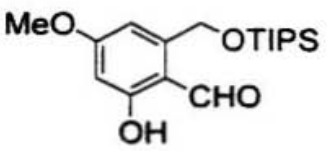
4-(Triphenylsilyl)oxy-2-butynal (230). Preparation was by the procedure for **207**. Yield of **230:** 97%; clear yellow oil; IR ν_{max} 2263 (s), 2190 (s), 1681 (s) cm^{-1}; ^1H NMR (500 MHz) δ 9.08 (1H, s, H-1), 7.65 (6H, d, J = 8.0 Hz, H-2' and H-6'), 7.47 (3H, t, J = 7.3 Hz, H-4'), 7.41 (6H, t, J = 7.0 Hz, H-3' and H-5'), 4.62 (2H, s, H-4); ^{13}C NMR (125 MHz) δ 176.2 (1, C-1), 135.4 (1, 6C, C-2' and C-6'), 132.8 (0, 3C, C-1'), 130.5 (1, 3C, C-4'), 128.1 (1, 6C, C-3' and C-5'), 94.2 (0, C-3), 84.8 (0, C-2), 52.2 (2, C-4); MS *m/z* (%) 342 (63, M^+), 341 (26), 314 (17), 313 (53), 312 (99), 284 (12), 283 (37), 265 (10), 264 (14), 263 (12), 259 (21), 247 (12), 237 (26), 236 (76), 235 (100), 234 (10), 207 (43), 199 (41), 197 (21), 191 (14), 187 (18), 183 (12), 182 (12), 181 (48), 180 (16), 155 (13), 152 (16), 129 (12), 115 (24), 105 (49), 91 (16), 78 (16), 77 (46), 53 (14), 51 (24), 45 (31).

4-Hydroxy-6-((triisopropylsilyl)oxy)methyl-2-methoxybenzaldehyde (231) and 2-hydroxy-6-((triisopropylsilyl)oxy)methyl-4-methoxybenzaldehyde (232). Preparation was by the procedure for **213**. Yield of **229:** 14%, **231:** 60% (70% based on recovered starting material) and **232:** 14% (16% based on recovered starting material). For **231**:



231

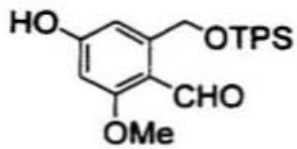
beige solid, mp 130 °C (dec.); IR (Nujol) ν_{max} 3330 (br), 1643 (s), 1610 (s), 1567 (s) cm^{-1}; ^1H NMR (500 MHz) δ 10.43 (1H, s, C**H**O), 6.99 (1H, d, J = 2.0 Hz, H-5), 6.36 (1H, d, J = 2.0 Hz, H-3), 5.82 (1H, s, -O**H**), 5.14 (2H, s, C$\mathbf{H_2}$O), 3.88 (3H, s, OC$\mathbf{H_3}$), 1.21 (3H, septet, J = 7.3 Hz, CH_3C**H**CH_3), 1.10 (18H, d, J = 7.0 Hz, C$\mathbf{H_3}$CHC$\mathbf{H_3}$); ^{13}C NMR (125 MHz) δ 190.0 (1, **C**HO), 165.6 (0, C-2 or C-4), 162.1 (0, C-2 or C-4), 150.0 (0, C-6), 114.9 (0, C-1), 105.1 (1, C-5), 96.6 (1, C-3), 63.8 (2, **C**H_2OSi), 55.9 (3, O**C**H_3), 18.1 (3, 6C, **C**H_3C**H**CH_3), 12.0 (1, 3C, CH_3**C**HCH_3); MS *m/z* (%) 295 (100, M^+ - *i*Pr), 223 (16), 195 (13), 165 (25), 75 (14), 61 (11), 43 (17); HRMS calcd for $C_{15}H_{23}O_4Si$ (M^+ - ^{i}Pr): 295.1366, found: 295.1372. For **232**: oily brown solid; IR (Nujol) ν_{max} 3370 (br), 1679 (s), 1612 (s), 1566 (s) cm^{-1}; ^1H NMR (500 MHz) δ 12.45 (1H, s, -O**H**), 10.15 (1H, s, C**H**O), 6.54 (1H, d, J = 2.3 Hz, H-5), 6.32 (1H, d, J = 2.3 Hz, H-3), 5.01 (2H, s, C$\mathbf{H_2}$O), 3.84 (3H, s, OC$\mathbf{H_3}$), 1.17 (3H, septet, J = 6.9 Hz, CH_3C**H**CH_3), 1.07 (18H, d, J = 6.9 Hz, C$\mathbf{H_3}$CHC$\mathbf{H_3}$); ^{13}C NMR (125 MHz) δ 193.2 (1, **C**HO), 166.5 (0, C-2 or C-4), 166.5 (0, C-2 or C-4), 146.4 (0, C-6), 112.0 (0, C-1), 107.7 (1, C-5), 99.5 (1, C-3), 62.8 (2, **C**H_2OSi), 55.6 (3, O**C**H_3), 18.0 (3, 6C, **C**H_3C**H**CH_3), 11.9 (1, 3C, CH_3**C**HCH_3); MS *m/z* (%) 295 (12, M^+ - C_3H_7), 227 (16), 155 (34), 144 (30), 131 (13),



232

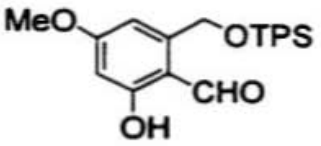
129 (10), 127 (27), 111 (13), 75 (39), 73 (21), 61 (23), 59 (15), 58 (17), 45 (32), 43 (100), 41 (22); HRMS calcd for $C_{15}H_{23}O_4Si$ (M^+ - 'Pr): 295.1366, found: 295.1346.

4-Hydroxy-2-methoxy-6-((triphenylsilyl)oxy)methylbenzaldehyde (233) and 2-hydroxy-4-methoxy-6-((triphenylsilyl)oxy)methylbenzaldehyde (234). Preparation was by the procedure for **213**. Yield of **230:** 7%, **233:** 69% (74% based on recovered starting material) and **234:** 18% (19% based on recovered starting material). For **233**:



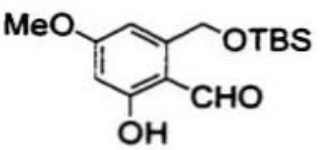
233

yellow solid (sparingly soluble in $CDCl_3$), mp 190 °C (dec.); IR (Nujol) ν_{max} 3400 (br), 1656 (s), 1604 (s), 1572 (s) cm^{-1}; ^1H NMR ($CDCl_3$ to which a drop of CD_3COCD_3 was added to improve solubility, 500 MHz) δ 10.34 (1H, s, C**H**O), 8.58 (1H, s, -O**H**), 7.64 (6H, d, J = 6.5 Hz, H-2' and H-6'), 7.42 (3H, t, J = 7.3 Hz, H-4'), 7.37 (6H, t, J = 7.3 Hz, H-3' and H-5'), 7.21 (1H, d, J = 1.6 Hz, H-5), 6.39 (1H, d, J = 1.6 Hz, H-3), 5.29 (2H, s, C**H**$_2$O), 3.85 (3H, s, OC**H**$_3$); ^{13}C NMR ($CDCl_3$ to which a drop of CD_3COCD_3 was added to improve solubility, 125 MHz) δ 189.6 (1, **C**HO), 165.5 (0, C-2 or C-4), 163.5 (0, C-2 or C-4), 148.3 (0, C-6), 135.3 (1, 6C, C-2' and C-6'), 133.9 (0, 3C, C-1'), 129.9 (1, 3C, C-4'), 127.8 (1, 6C, C-3' and C-5'), 114.3 (0, C-1), 105.4 (1, C-5), 96.8 (1, C-3), 64.3 (2, **C**H$_2$OSi), 55.7 (3, O**C**H$_3$); MS *m/z* (%) 440 (23, M^+), 364 (14), 363 (42), 259 (26), 257 (32), 199 (21), 181 (14), 165 (19), 164 (100), 77 (11); HRMS calcd for $C_{27}H_{24}O_4Si$: 440.1444, found: 440.1404.



234

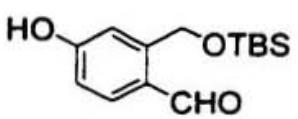
For **234**: yellow solid, mp 190 °C (dec.); IR (Nujol) ν_{max} 3400 (br), 1649 (s), 1628 (s) cm^{-1}; ^1H NMR (500 MHz) δ 12.41 (1H, s, -O**H**), 10.10 (1H, s, C**H**O), 7.61 (6H, d, J = 7.5 Hz, H-2′ and H-6′), 7.45 (3H, t, J = 7.5 Hz, H-4′), 7.39 (6H, t, J = 7.3 Hz, H-3′ and H-5′), 6.39 (1H, d, J = 2.3 Hz, H-5), 6.32 (1H, d, J = 2.3 Hz, H-3), 5.04 (2H, s, C$\mathbf{H_2}$O), 3.79 (3H, s, OC$\mathbf{H_3}$); ^{13}C NMR (125 MHz) δ 193.1 (1, **C**HO), 166.5 (0, C-2 or C-4), 166.5 (0, C-2 or C-4), 145.2 (0, C-6), 135.3 (1, 6C, C-2′ and C-6′), 133.3 (0, 3C, C-1′), 130.4 (1, 3C, C-4′), 128.0 (1, 6C, C-3′ and C-5′), 112.1 (0, C-1), 108.5 (1, C-5), 100.0 (1, C-3), 63.1 (2, **C**H_2OSi), 55.6 (3, O**C**H_3); MS *m/z* (%) 440 (24, M^+), 364 (12), 363 (44), 276 (22), 259 (23), 257 (28), 200 (11), 199 (61), 197 (10), 181 (21), 165 (17), 164 (100), 122 (16), 105 (10), 78 (15), 77 (32), 51 (10), 45 (20); HRMS calcd for $C_{27}H_{24}O_4Si$: 440.1444, found: 440.1442.



235

6-((*tert*-Butyldimethylsilyl)oxy)methyl-2-hydroxy-4-methoxybenzaldehyde (235). To a mixture of **191** and **195** (3.31:1) (1.26 g, 5.60 mmol) in toluene (25 mL) was added **207** (886 mg, 4.48 mmol) as a solution in toluene (50 mL), and the solution was heated under reflux for 96 h. Solvent was removed *in vacuo*. Chromatography (30% ethyl acetate/hexanes) afforded 428 mg (49%) of unreacted **207**, 547 mg (41%) of **213** as a white solid, and 117 mg (9%) of **235** as an orange oil; IR (Nujol) ν_{max} 3400 (br), 1676 (s), 1582 (s) cm^{-1}; ^1H NMR (500 MHz) δ 12.45 (1H, s, -O**H**), 10.14 (1H, s, C**H**O), 6.49 (1H, d, J = 2.3 Hz, H-5), 6.33 (1H, d, J = 2.3 Hz, H-3),

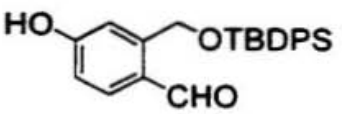
4.91 (2H, s, CH_2O), 3.84 (3H, s, OCH_3), 0.91 (9H, s, $SiCMe_3$), 0.09 (6H, s, $SiMe_2$); ^{13}C NMR (125 MHz) δ 193.3 (1, CHO), 166.6 (0, C-2 or C-4), 166.5 (0, C-2 or C-4), 146.2 (0, C-6), 112.1 (0, C-1), 108.1 (1, C-5), 99.6 (1, C-3), 62.7 (2, CH_2OSi), 55.6 (3, OCH_3), 25.8 (3C, 3, $SiCMe_3$), 18.2 (0, $SiCMe_3$), -5.3 (2C, 3, $SiMe_2$); MS *m/z* (%) 239 (100, M^+ - ^{t}Bu), 165 (47), 164 (10), 141 (24), 113 (19), 111 (37), 97 (10), 83 (11), 75 (81), 73 (25), 59 (10), 57 (10), 41 (12); HRMS calcd for $C_{11}H_{15}O_4Si$ (M^+ - ^{t}Bu): 239.0740, found: 239.0726.



236a

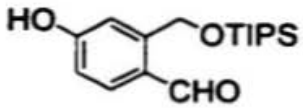
2-((*tert*-Butyldimethylsilyl)oxy)methyl-4-hydroxybenzaldehyde (236a); representative procedure for the Diels–Alder reaction with Danishefsky's diene. A solution of **207** (0.23 g, 1.2 mmol) and 1-methoxy-3-(trimethylsilyl)oxy-1,3-butadiene (0.30 mL, 1.5 mmol) in toluene (100 mL) was heated under reflux for 168 h. The solvent was evaporated under reduced pressure. Chromatography provided **236a** (224 mg, 73%) as a beige solid, 27 mg (7%) of the corresponding unhydrolyzed TMS ether, and 41 mg (18%) of unreacted **207** was recovered. For **236a**: beige solid, mp 104-106 °C; IR (Nujol) ν_{max} 3300 (br), 1658 (s), 1614 (s) cm^{-1}; ^1H NMR (500 MHz) δ 9.94 (1H, s, CHO), 7.71 (1H, d, J = 8.3 Hz, H-6), 7.30 (1H, br s, H-3), 7.14-7.04 (1H, br s, -OH), 6.87 (1H, dd, J = 8.3, 2.0 Hz, H-5), 5.14 (2H, s, CH_2O), 0.96 (9H, s, $SiCMe_3$), 0.13 (6H, s, $SiMe_2$); ^{13}C NMR (125 MHz) δ 192.0 (1, CHO), 161.6 (0, C-4), 147.9 (0, C-2), 137.3 (1, C-6), 125.7 (0, C-1), 113.6 (1, C-3 or C-5), 113.5 (1, C-3 or C-5), 62.8 (2, CH_2OSi), 26.0 (3, 3C, $SiCMe_3$), 18.4 (0, $SiCMe_3$), -5.4 (3, 2C, $SiMe_2$); MS *m/z* (%) 209

(100, M^+ - ^{t}Bu), 135 (42), 77 (11), 75 (64), 73 (13); HRMS calcd for $C_{10}H_{13}O_3Si$ (M^+ - ^{t}Bu): 209.0634, found: 209.0635.



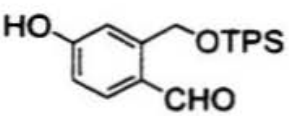
236b

2-((*tert*-Butyldiphenylsilyl)oxy)methyl-4-hydroxybenzaldehyde (236b). Preparation was by the procedure for **236a**. The yield of **236b** was 59%, corresponding unhydrolyzed TMS ether 2%, and recovered **219** 42%. For **236b**: brown solid, mp 117-118 °C; IR (Nujol) ν_{max} 3350 (br), 1673 (s), 1582 (s) cm^{-1}; ^{1}H NMR (500 MHz) δ 9.89 (1H, s, C**H**O), 7.70 (1H, d, J = 7.7 Hz, H-6), 7.68 (4H, d, J = 7.5 Hz, H-2' and H-6'), 7.40 (2H, t, J = 7.5 Hz, H-4'), 7.39 (1H, br s, H-3), 7.36 (4H, t, J = 7.0 Hz, H-3' and H-5'), 6.85 (1H, dd, J = 7.7, 2.3 Hz, H-5), 6.57-6.47 (1H, br s, -O**H**), 5.19 (2H, s, C**H**$_2$O), 1.11 (9H, s, SiC**Me**$_3$); ^{13}C NMR (125 MHz) δ 191.4 (1, **C**HO), 161.3 (0, C-4), 147.2 (0, C-2), 136.6 (1, C-6), 135.5 (1, 4C, C-2' and C-6'), 133.2 (0, 2C, C-1'), 129.8 (1, 2C, C-4'), 127.8 (1, 4C, C-3' and C-5'), 126.0 (0, C-1), 113.7 (1, C-3 or C-5), 113.6 (1, C-3 or C-5), 63.5 (2, **C**H$_2$OSi), 26.9 (3, 3C, SiC**Me**$_3$), 19.4 (0, Si**C**Me$_3$); MS *m/z* (%) 333 (43, M^+ - ^{t}Bu), 228 (20), 227 (100), 200 (11), 199 (60), 135 (12), 105 (10), 77 (19), 57 (13), 43 (12); HRMS calcd for $C_{20}H_{17}O_3Si$ (M^+ - ^{t}Bu): 333.0947, found: 333.0923.



236c

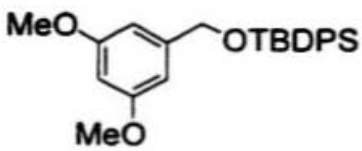
4-Hydroxy-2-((triisopropylsilyl)oxy)methylbenzaldehyde (236c). The yield of **236c** was 75% and recovered **229** 12%. For **236c** (elutes from column with some unreacted **229**): brown oil; IR (Nujol) ν_{max} 3400 (br), 1681 (s), 1602 (s), 1572 (s) cm^{-1}; ^1H NMR (500 MHz) δ 9.98 (1H, s, C**H**O), 7.69 (1H, d, J = 8.3 Hz, H-6), 7.36 (1H, br s, H-3), 6.84 (1H, dd, J = 8.3, 2.5 Hz, H-5), 5.21 (2H, s, C$\mathbf{H_2}$O), 1.21 (3H, septet, J = 7.2 Hz, CH_3CHCH_3), 1.11 (18H, d, J = 7.2 Hz, CH_3CHCH_3); NOE data δ 5.21 (9.98, 4%; 7.36, 7%); ^{13}C NMR (125 MHz) δ 191.6 (1, **C**HO), 160.9 (0, C-4), 148.1 (0, C-2), 137.2 (1, C-6), 126.1 (0, C-1), 113.3 (1, C-3 or C-5), 113.3 (1, C-3 or C-5), 63.0 (2, $\mathbf{C}H_2OSi$), 17.8 (3, 6C, CH_3CHCH_3), 11.9 (1, 3C, CH_3CHCH_3); MS *m/z* (%) 265 (100, $M^+ - C_3H_7$), 193 (39), 165 (15), 155 (23), 135 (27), 131 (24), 127 (19), 115 (17), 111 (13), 103 (45), 91 (15), 89 (11), 87 (17), 85 (10), 77 (17), 75 (83), 73 (29), 61 (52), 59 (46), 45 (22), 43 (16), 41 (14); HRMS calcd for $C_{14}H_{21}O_3Si$ (M^+ - ^{i}Pr): 265.1260, found: 265.1232.



236d

4-Hydroxy-2-((triphenylsilyl)oxy)methylbenzaldehyde (236d). The yield of **236d** was 75%, corresponding unhydrolyzed TMS ether 11%, and recovered **230** 11%. For **236d**: yellow solid, mp 134–136 °C; IR (Nujol) 3400 (br), 1713, 1656, 1597 cm^{-1}; ^1H NMR (500 MHz) δ 9.90 (1H, s, C**H**O), 7.69 (1H, d, J = 8.0 Hz, H-6), 7.65 (6H, d, J = 7.5 Hz, H-2′ and H-6′), 7.45 (3H, t, J = 7.0 Hz, H-4′), 7.39 (6H, t, J = 7.3 Hz, H-3′ and H-5′), 7.37 (1H, br s, H-3), 6.84 (1H, dd, J = 8.0, 3.0 Hz, H-5), 5.61 (1H, br s, -O**H**), 5.33 (2H, s, C$\mathbf{H_2}$O); NOE data δ 5.33 (9.90, 2%; 7.65, 6%; 7.37, 2%); ^{13}C NMR (125 MHz) δ

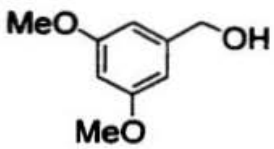
191.3 (1, **C**HO), 160.7 (0, C-4), 146.8 (0, C-2), 136.8 (1, C-6), 135.4 (1, 6C, C-2′ and C-6′), 133.7 (0, 3C, C-1′), 130.2 (1, 3C, C-4′), 128.0 (1, 6C, C-3′ and C-5′), 126.3 (0, C-1), 113.7 (1, C-3 or C-5), 113.5 (1, C-3 or C-5), 63.4 (2, **C**H_2OSi); MS *m/z* (%) 410 (5, M^+), 334 (28), 333 (100), 260 (16), 259 (65), 228 (17), 227 (85), 226 (24), 200 (12), 199 (66), 197 (12), 181 (30), 135 (15), 134 (87), 106 (15), 105 (27), 78 (14), 77 (44), 51 (13), 45 (14); HRMS calcd for $C_{26}H_{22}O_3Si$: 410.1338, found: 410.1340.



237

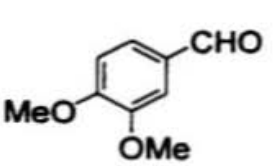
1-((*tert*-Butyldiphenylsilyl)oxy)methyl-3,5-dimethoxybenzene (237). To a solution of **222** (61 mg, 0.14 mmol) in benzene (50 mL) was added *p*TsOH (10 mg, 0.06 mmol). The solution was heated under reflux for 24 h. The solution was washed with brine (50 mL), and the aqueous layer was re-extracted with ethyl acetate (2 × 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure to afford 55 mg (96%) of **237** as a yellow oil: IR (Nujol) ν_{max} 1599 (s) cm^{-1}: ^{1}H NMR (500 MHz) δ 7.70-7.69 (4H, m, Ar**H**), 7.43-7.36 (6H, m, Ar**H**), 6.53 (2H, d, J = 2.0 Hz, H-2 and H-6), 6.35 (1H, t, J = 2.0 Hz, H-4), 4.72 (2H, s, C**H**$_2$O), 3.77 (6H, s, OC**H**$_3$), 1.10 (9H, s, SiC**Me**$_3$); ^{13}C NMR (125 MHz) δ 160.7 (2C, 0, C-3 and C-5), 143.6 (0, C-1), 135.6 (4C, 1, C-2′ and C-6′), 133.5 (2C, 0, C-1′), 129.7 (2C, 1, C-4′), 127.7 (4C, 1, C-3′ and C-5′), 103.7 (2C, 1, C-2 and C-6), 99.0 (1, C-4), 65.4 (2, **C**H_2OSi), 55.3 (2C, 3, O**C**H_3), 26.8 (3C, 3, SiC**Me**$_3$), 19.3 (0, Si**C**Me$_3$); MS *m/z* (%) 349 (100, M^+ - ^{t}Bu), 272 (13), 271 (61), 199 (25), 183

(12), 175 (11), 151 (63), 91 (17), 78 (15), 77 (22), 57 (10), 41 (11); HRMS calcd for $C_{21}H_{21}O_3Si$ (M^+ - ^{t}Bu): 349.1260, found: 349.1244.



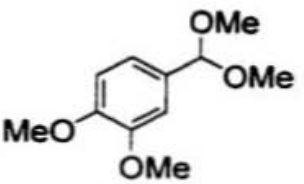
238

3,5-Dimethoxybenzyl alcohol (238). To a solution of **237** (324 mg, 0.677 mmol) in THF (40 mL) was added TBAF (2.5 mmol) as a solution in THF (2.5 mL). The solution was stirred at rt for 24 h. The solution was diluted with diethyl ether (100 mL) and washed with H_2O (50 mL). The aqueous layer was extracted with diethyl ether (3 × 40 mL). The combined organic layers were washed with brine (50 mL) and dried over $MgSO_4$. Chromatography (30% ethyl acetate/hexanes) afforded 71 mg (88%) of **238** as a white solid. mp 47-49 °C; IR (Nujol) ν_{max} 3300 (br), 1601 (s) cm^{-1}; ^1H NMR (500 MHz) δ 6.52 (2H, d, J = 2.0 Hz, H-2 and H-6), 6.39 (1H, t, J = 2.0 Hz, H-4), 4.63 (2H, s, C**H**$_2$O), 3.79 (6H, s, OC**H**$_3$); ^{13}C NMR (125 MHz) δ 161.0 (2C, 0, C-3 and C-5), 143.4 (0, C-1), 104.6 (2C, 1, C-2 and C-6), 99.7 (1, C-4), 65.4 (2, **C**H$_2$OSi), 55.3 (2C, 3, O**C**H$_3$); MS *m/z* (%) 168 (100, M^+), 167 (10), 151 (10), 139 (44), 137 (10), 125 (12), 109 (18), 77 (15), 65 (15), 41 (10); HRMS calcd for $C_9H_{12}O_3$: 168.0786, found: 168.0765.



239

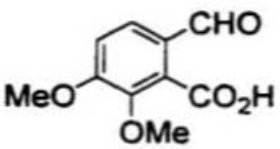
3,4-Dimethoxybenzaldehyde (239). To a solution of Dess-Martin periodinane (5.35 g, 12.6 mmol) in CH_2Cl_2 (75 mL) was added 3,4-dimethoxybenzyl alcohol (1.630 g, 9.70 mmol) as a solution in CH_2Cl_2 (75 mL). The cloudy solution was stirred at rt for 1 h. The solution was diluted with diethyl ether (200 mL) and washed with 1 M NaOH (2 × 100 mL) and H_2O (100 mL). The organic layer was dried over $MgSO_4$. Chromatography (50% ethyl acetate/hexanes) afforded 1.35 g (84%) of **239** as a yellow solid, mp 42-44 °C; IR (Nujol) ν_{max} 1702 (s), 1588 (s) cm^{-1}; ^1H NMR (300 MHz) δ 9.86 (1H, s, C**H**O), 7.47 (1H, dd, J = 8.4, 2.2 Hz, H-6), 7.42 (1H, d, J = 2.2 Hz, H-2), 6.99 (1H, d, J = 8.4 Hz, H-5), 3.98 (3H, s, OC**H**$_3$), 3.95 (3H, s, OC**H**$_3$); ^{13}C NMR (75 MHz) δ 190.9 (1, **C**HO), 154.4 (0, C-4), 149.6 (0, C-3), 130.1 (0, C-1), 126.8 (1, C-6), 110.3 (1, C-2 or C-5), 108.8 (1, C-2 or C-5), 56.1 (3, O**C**H$_3$), 56.0 (3, O**C**H$_3$); MS *m/z* (%) 166 (100, M$^+$), 165 (34), 151 (12), 95 (44), 79 (23), 77 (23), 67 (10), 65 (14), 63 (14), 52 (17), 51 (34), 50 (14), 41 (17); HRMS calcd for $C_9H_{10}O_3$: 166.0630, found: 166.0621.



240

3,4-Dimethoxybenzaldehyde, dimethyl acetal (240). A solution of **239** (1.35 g, 8.14 mmol) and a catalytic amount of *p*TsOH (50 mg) in methanol (20 mL) and trimethylorthoformate (20 mL) was heated under reflux for 24 h. The resulting solution was diluted with diethyl ether (200 mL) and washed with 5% NaOH:brine (1:1, 75 mL) and brine (75 mL). The combined aqueous layers were extracted with diethyl ether (2 × 50 mL). The organic layers were combined and dried over Na_2SO_4 to afford

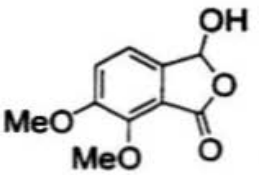
1.73 g (100%) of **240** as an orange oil; IR (Nujol) ν_{max} 1600 (s) cm^{-1}; ^1H NMR (300 MHz) δ 7.01-6.98 (2H. m, H-2 and H-6), 6.86 (1H. d, J = 9.0 Hz, H-5), 5.33 (1H, s, **CH**$(OCH_3)_2$), 3.90 (3H. s, O**CH**$_3$), 3.89 (3H. s, O**CH**$_3$), 3.33 (6H. s. CH(O**CH**$_3)_2$); ^{13}C NMR (75 MHz) δ 148.9 (0, C-3 or C-4), 148.8 (0, C-3 or C-4), 130.7 (0, C-1), 119.1 (1, C-6), 110.4 (1, C-2 or C-5), 109.3 (1, C-2 or C-5), 103.1 (1, **CH**$(OCH_3)_2$), 55.7 (3, O**CH**$_3$), 55.7 (3, O**CH**$_3$), 52.7 (2C, 3, CH(O**CH**$_3)_2$); MS *m/z* (%) 212 (11, M^+), 182 (11), 181 (100), 166 (21), 84 (11), 75 (17).



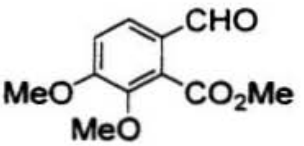
241a

2-Formyl-5,6-dimethoxybenzoic acid (241a) and 5,6-dimethoxyphthalaldehydic acid (241b). To a solution of **240** (3.58 g, 16.9 mmol) in diethyl ether (100 mL) cooled to 0 °C was added *n*-BuLi (19.4 mmol) dropwise over 25 min. The solution was stirred for 45 min then cooled to –78 °C. and several pieces of solid CO_2 were added. The reaction mixture was allowed to warm to rt. H_2O (50 mL) was added and the layers were separated. The aqueous layer was acidified with 5% HCl until pH 2 and extracted with diethyl ether (3 × 100 mL). The combined organic layers were dried over Na_2SO_4 to afford 2.70 g (76%) of **241a/b** as a white solid that was a mixture in solution by ^1H NMR. For **241a**: white solid. mp 144-145 °C; IR (Nujol) ν_{max} 3400 (br). 1720 (s), 1600 (s) cm^{-1}; ^1H NMR (CD_3COCD_3, 300 MHz) δ 11.30 (1H, br s. CO_2**H**). 9.90 (1H. s. C**H**O). 7.75 (1H. d. J = 8.4 Hz. H-3), 7.32 (1H. d. J = 8.4 Hz. H-4). 4.03 (3H. s. O**CH**$_3$). 3.85 (3H, s. O**CH**$_3$); ^{13}C NMR (CD_3COCD_3, 75 MHz) δ 189.7 (1. **C**HO). 166.6 (0. **C**O_2H). 141.2 (0. C-5 or C-6). 129.9 (0. C-5 or C-6). 120.3 (1. C-3 or C-4). 119.4 (1. C-3 or C-4). 62.1 (3.

OCH_3), 57.2 (3, OCH_3): MS *m/z* (%) 210 (84, M^+). 209 (15), 193 (32), 192 (10), 182 (74), 181 (16), 180 (52), 179 (12), 177 (27), 167 (16), 166 (23), 165 (49), 164 (19), 163 (38), 162 (24), 153 (25), 152 (21), 151 (30), 150 (19), 149 (60), 148 (14), 137 (43), 136 (27), 135 (48), 134 (14), 133 (17), 132 (18), 123 (15), 122 (33), 121 (28), 120 (18), 119 (23), 118 (13), 109 (43), 108 (21), 107 (100), 106 (35), 105 (33), 104 (30), 96 (10), 95 (21), 94 (11), 93 (15), 92 (18), 91 (13), 80 (15), 79 (55), 78 (39), 77 (54), 76 (38), 75 (20), 67 (11), 65 (49), 64 (13), 63 (37), 62 (27), 61 (11), 55 (16), 53 (39), 52 (28), 51 (82), 50 (49), 45 (14), 44 (14), 43 (21), 41 (18); HRMS calcd for $C_{10}H_{10}O_5$: 210.0528. found: 210.0510. For **241b**: ^{1}H NMR (CD_3COCD_3, 300 MHz) δ 7.44 (1H, d, J = 8.4 Hz, H-3), 7.31 (1H, d, J = 8.4 Hz, H-4), 6.82 (1H, d, J = 6.5 Hz, C**H**OH), 6.54 (1H, d, J = 6.5 Hz, CHO**H**), 3.98 (3H, s, OC**H**$_3$), 3.93 (3H, s, OC**H**$_3$).



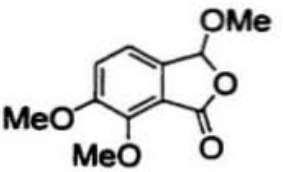
241b



242a

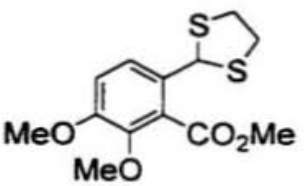
Methyl 2-formyl-5,6-dimethoxybenzoate (242a) and 5,6-dimethoxyphthalaldehydic acid, methyl ether (242b). A mixture of **241a/b** (201 mg, 0.955 mmol), K_2CO_3 (0.40 g, 2.9 mmol) and CH_3I (0.22 mL, 3.5 mmol) in acetone (50 mL) was heated under reflux for 3.5 h. H_2O (100 mL) was added and the solution was extracted with ethyl acetate (100 and 2 × 50 mL). The combined organic layers were dried over $MgSO_4$ to afford 161 mg of **242a** (39%) and **242b** (36%) as a yellow oil that was an inseparable mixture by flash chromatography. For **242a/b**: yellow oil (solidified upon standing); IR (Nujol) ν_{max} 1730 (s), 1712 (s), 1600 (s) cm^{-1}. For **242a**: ^{1}H NMR

(CD_3COCD_3, 300 MHz) δ 9.84 (1H, s, **CHO**), 7.76 (1H, d, J = 8.4 Hz, H-3), 7.34 (1H, d, J = 8.4 Hz, H-4), 4.03 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.55 (3H, s, CO_2CH_3). For



242b

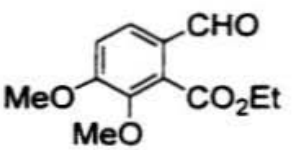
242b: ^1H NMR (CD_3COCD_3, 300 MHz) δ 7.45 (1H, d, J = 8.4 Hz, H-3), 7.29 (1H, d, J = 8.4 Hz, H-4), 6.29 (1H, s, $CHOCH_3$), 3.98 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 3.82 (3H, s, OCH_3). For **242a/b**: ^{13}C NMR (CD_3COCD_3, 75 MHz) δ 189.9 (1, **CHO**), 167.2 (0, CO_2CH_3 or CO_2CH), 166.4 (0, CO_2CH_3 or CO_2CH), 158.8 (0, C-5 or C-6), 155.2 (0, C-5 or C-6), 147.1 (0, C-5 or C-6), 138.7 (0, C-5 or C-6), 131.0 (1, C-3), 129.8 (0, C-1 or C-2), 128.2 (0, C-1 or C-2), 127.6 (0, C-1 or C-2), 124.2 (0, C-1 or C-2), 120.4 (1, C-3 or C-4), 119.6 (1, C-3 or C-4), 113.8 (1, C-4), 102.9 (1, $CHOCH_3$), 62.2 (3, OCH_3), 61.8 (3, OCH_3), 57.1 (3, OCH_3), 56.8 (3, OCH_3), 56.6 (3, OCH_3), 52.7 (3, OCH_3); MS *m/z* (%) 224 (42, M^+), 209 (79), 196 (29), 194 (22), 193 (98), 191 (10), 179 (28), 177 (10), 166 (13), 165 (100), 163 (38), 162 (12), 151 (11), 150 (20), 149 (24), 136 (12), 135 (18), 122 (29), 121 (15), 120 (13), 119 (12), 107 (21), 106 (12), 105 (17), 104 (13), 92 (10), 79 (23), 78 (18), 77 (34), 76 (19), 75 (10), 65 (14), 63 (15), 62 (11), 53 (13), 51 (29), 50 (17), 45 (23), 43 (10); HRMS calcd for $C_{11}H_{12}O_5$: 224.0685, found: 224.0682.



243

Methyl 2-[1,3]dithiolan-2-yl-5,6-dimethoxybenzoate (243). To a solution of **242a/b** (74 mg, 0.33 mmol) in CH_2Cl_2 (50 mL) was added anhydrous $ZnCl_2$ (90 mg, 0.66 mmol) and 1,2-ethanedithiol (0.12 mL, 1.4 mmol). The solution was stirred at rt for 2 h and washed with H_2O (2 × 50 mL). The combined aqueous layers were extracted

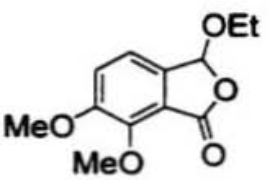
with CH_2Cl_2 (75 mL). The organic layers were combined and washed with brine (50 mL) and dried over $MgSO_4$. Chromatography (30% ethyl acetate/hexanes) afforded 97 mg (98%) of **243** as a colorless oil; IR (Nujol) ν_{max} 1727 (s), 1600 (s), 1577 (s) cm^{-1}; ^1H NMR (CD_3COCD_3, 300 MHz) δ 7.59 (1H, d, J = 8.7 Hz, H-3), 7.14 (1H, d, J = 8.7 Hz, H-4), 5.58 (1H, s, H-1'), 3.89 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.79 (3H, s, CO_2CH_3), 3.56-3.46 (2H, m, $-SCH_2-$), 3.39-3.30 (2H, m, $-SCH_2-$); ^{13}C NMR (CD_3COCD_3, 75 MHz) δ 168.0 (0, CO_2CH_3), 153.0 (0, C-6), 146.1 (0, C-5), 131.0 (0, C-1 or C-2), 129.9 (0, C-1 or C-2), 125.7 (1, C-3), 115.0 (1, C-4), 61.5 (3, OCH_3), 56.4 (3, OCH_3), 52.9 (3, OCH_3), 52.6 (1, C-1'), 40.8 (2C, 2, $-SCH_2CH_2S-$); MS *m/z* (%) 300 (18, M^+), 269 (13), 268 (10), 242 (11), 241 (17), 240 (100), 239 (52), 225 (17), 209 (20), 208 (12), 207 (29), 193 (40), 179 (10), 165 (13), 150 (10), 134 (13), 121 (10), 120 (10), 65 (15), 46 (39), 45 (24); HRMS calcd for $C_{13}H_{16}O_4S_2$: 300.0490, found: 300.0436.



244a

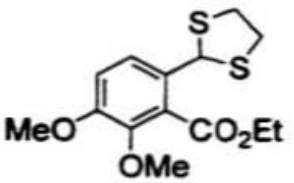
Ethyl 2-formyl-5,6-dimethoxybenzoate (244a) and 5,6-dimethoxyphthalaldehydic acid, ethyl ether (244b). To a solution of **241a/b** (566 mg, 2.70 mmol) in absolute ethanol (125 mL) was added catalytic concentrated H_2SO_4 (5 drops). The mixture was heated under reflux for 24 h. Solvent was removed *in vacuo* and replaced with ethyl acetate (150 mL). The solution was washed with H_2O (2 × 75 mL). The combined aqueous layers were extracted with ethyl acetate (2 × 75 mL). The organic layers were combined and dried over $MgSO_4$ to afford 622 mg of **244a** (75%) and **244b** (22%) as an orange oil. These were inseparable by flash chromatography. For **244a/b**:

clear orange oil (solidified upon standing); IR (Nujol) ν_{max} 1775 (s), 1737 (s), 1600 (s), 1573 (s) cm^{-1}. For **244a**: ^1H NMR (CD_3COCD_3, 300 MHz) δ 9.85 (1H, s, C**H**O), 7.75 (1H, d, J = 8.4 Hz, H-3), 7.33 (1H, d, J = 8.4 Hz, H-4), 4.38 (2H, q, J = 7.2 Hz, -O**C**$H_2$$CH_3$), 4.03 (3H, s, O**C**$H_3$), 3.83 (3H, s, O**C**$H_3$), 1.35 (3H, t, J = 7.2 Hz, -OCH_2**C**H_3); ^{13}C NMR (CD_3COCD_3, 75 MHz) δ 189.8 (1, **C**HO), 166.6 (0, **C**$O_2CH_2CH_3$), 158.8 (0, C-5 or C-6), 147.1 (0, C-5 or C-6), 130.8 (1, C-3), 130.4 (0, C-1 or C-2), 127.6 (0, C-1 or C-2), 113.7 (1, C-4), 61.9 (3, O**C**H_3), 61.8 (3, O**C**H_3), 56.8 (2, O**C**$H_2$$CH_3$), 14.5 (3, OCH_2**C**H_3). For **244b**: ^1H NMR (CD_3COCD_3, 300 MHz) δ 7.44 (1H, d, J = 8.1 Hz, H-3), 7.29 (1H, d, J = 8.1 Hz, H-4), 6.36 (1H, s, C**H**OCH_2CH_3), 4.38 (2H, q, J = 7.2 Hz, -O**C**$H_2$$CH_3$), 3.98 (3H, s, O**C**$H_3$), 3.93 (3H, s, O**C**$H_3$), 1.25 (3H, t, J = 7.2 Hz, -OCH_2**C**H_3); ^{13}C NMR (CD_3COCD_3, 75 MHz) δ 155.1 (0, C-5 or C-6), 139.1 (0, C-5 or C-6), 120.3 (1, C-3 or C-4), 119.6 (1, C-3 or C-4), 102.1 (1, **C**HOCH_2CH_3), 65.9 (3, O**C**H_3), 62.1 (3, O**C**H_3), 57.1 (2, O**C**$H_2$$CH_3$), 15.5 (3, OCH_2**C**H_3). For **244a/b**: MS *m/z* (%) 238 (15, M^+), 210 (25), 209 (100), 193 (66), 179 (16), 166 (15), 165 (47), 163 (23), 150 (10), 149 (12), 135 (12), 122 (15), 107 (18), 105 (12), 104 (11), 79 (16), 78 (11), 77 (22), 76 (12), 65 (10), 51 (22), 50 (10); HRMS calcd for $C_{12}H_{14}O_5$: 238.0841, found: 238.0826.



244b

Ethyl 2-[1,3]dithiolan-2-yl-5,6-dimethoxybenzoate (245). To a solution of **244a/b** (446 mg, 1.87 mmol) in CH_2Cl_2 (150 mL) was added anhydrous $ZnCl_2$ (330 mg, 2.4 mmol) and 1,2-ethanedithiol (0.45 mL, 5.4 mmol). The solution was stirred at rt for 1.5 h and

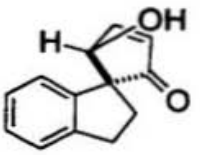


245

washed with H_2O (2 × 75 mL). The combined aqueous layers were extracted with CH_2Cl_2 (2 × 50 mL). The organic layers were combined, washed with brine (50 mL) and dried over $MgSO_4$. Chromatography (30% ethyl acetate/hexanes) afforded 580 mg (99%) of **245** as a white crystalline solid, mp 84-85 °C; IR (Nujol) ν_{max} 1720 (s), 1601 (s), 1579 (s) cm^{-1}; ^1H NMR (CD_3COCD_3, 300 MHz) δ 7.59 (1H, d, J = 8.7 Hz, H-3), 7.13 (1H, d, J = 8.7 Hz, H-4), 5.61 (1H, s, H-1'), 4.38 (2H, q, J = 7.2 Hz, -OC**H**$_2$CH$_3$), 3.89 (3H, s, OC**H**$_3$), 3.80 (3H, s, OC**H**$_3$), 3.55-3.47 (2H, m, -SC**H**$_2$), 3.39-3.29 (2H, m, -SC**H**$_2$), 1.37 (3H, t, J = 7.2 Hz, -OCH$_2$C**H**$_3$); ^{13}C NMR (CD_3COCD_3, 75 MHz) δ 167.5 (0, **C**O$_2$CH$_2$CH$_3$), 153.1 (0, C-6), 146.1 (0, C-5), 130.9 (0, C-1 or C-2), 130.2 (0, C-1 or C-2), 125.3 (1, C-3), 114.9 (1, C-4), 62.0 (3, O**C**H$_3$), 61.5 (2, O**C**H$_2$CH$_3$), 56.4 (3, O**C**H$_3$), 52.7 (1, C-1'), 40.8 (2C, 2, -S**C**H$_2$**C**H$_2$S-), 14.6 (3, -OCH$_2$**C**H$_3$); MS *m/z* (%) 314 (19, M^+), 285 (48), 269 (21), 268 (11), 242 (15), 241 (14), 240 (100), 225 (63), 209 (15), 207 (27), 193 (52), 179 (14), 165 (12), 150 (11), 122 (10), 61 (14), 45 (18), 43 (22); HRMS calcd for $C_{14}H_{18}O_4S_2$: 314.0647, found: 314.0648.

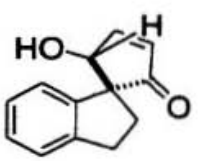
(2*R,3*S**)-2',3'-Dihydro-3-hydroxyspiro([4]cyclopentene-2,1'-[1*H*]indene)-1-one (246) and (2*R**,3*R**)-2',3'-dihydro-3-hydroxyspiro([4]cyclopentene-2,1'-[1*H*]indene)-1-one (247).** To a solution of **77** (355 mg, 1.79 mmol) in methanol (40 mL) cooled to –20 °C was added $CeCl_3$·$7H_2O$ (0.35 g, 0.94 mmol) and $NaBH_4$ (40 mg, 1.1 mmol) in one portion. The solution was stirred for 7 min, and the reaction was quenched with 0.5 M aqueous NH_4Cl (50 mL). The solution was extracted with ethyl acetate (2 × 75 and 50

mL). The combined organic layers were dried over Na_2SO_4. Chromatography (40% ethyl acetate/hexanes) afforded 160 mg (45%) of **246** as a colorless oil and 126 mg (35%) of **247** as a white solid. For **246**: colorless oil; ^{1}H NMR (300 MHz) δ 7.69 (1H, dd, J = 5.7, 2.1 Hz, H-4), 7.33-7.13 (3H, m, Ar**H**), 6.93 (1H, d, J = 7.5 Hz, H-7'), 6.47 (1H, dd, J = 6.0, 1.5 Hz, H-5), 4.82 (1H, br s, H-3), 3.19-3.02 (2H, m, H-3'), 2.65 (1H, m, H-2'), 2.16 (1H, m, H-2');



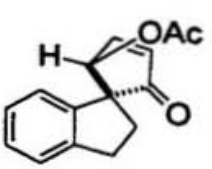
246

NOE data δ 4.82 (7.69, 3%; 6.93, 4%; 2.16, 3%); ^{13}C NMR (75 MHz) δ 207.1 (0, C-1), 162.5 (1, C-4), 146.1 (0, C-3a' or C-7a'), 140.2 (0, C-3a' or C-7a'), 135.2 (1), 128.4 (1), 126.6 (1), 125.5 (1, C-5), 124.0 (1), 79.0 (1, C-3), 66.4 (0, C-2), 34.2 (2, C-2' or C-3'), 31.5 (2, C-2' or C-3'); MS *m/z* (%) 200 (40, M$^+$), 155 (49), 154 (20), 153 (29), 152 (10), 141 (11), 129 (19), 128 (32), 127 (10), 117 (20), 116 (45), 115 (100), 91 (27), 89 (17), 76 (10), 65 (10), 63 (19), 55 (18), 51 (12); HRMS calcd for $C_{13}H_{12}O_2$: 200.0837, found: 200.0843. For **247**: white solid: mp 74-75 °C; IR ν_{max} 3300 (br), 1711 (s), 1600 (s) cm^{-1}; ^{1}H NMR (300 MHz) δ 7.56 (1H, dd, J = 5.9, 2.0 Hz, H-4), 7.27-7.08 (3H, m, Ar**H**), 6.88 (1H, d, J = 7.5 Hz, H-7'), 6.32 (1H, d, J = 6.0 Hz, H-5), 4.68 (1H, d, J = 3.3 Hz, H-3), 3.13-2.93 (2H, m, H-3'), 2.52 (1H, m, H-2'), 2.27 (1H, d, J = 4.5 Hz, -O**H**), 2.06 (1H, m, H-2'); NOE data δ 4.68 (7.56, 4%; 2.06, 4%); ^{13}C NMR (75 MHz) δ 207.6 (0, C-1), 162.8 (1, C-4), 145.7 (0, C-3a' or C-7a'), 140.3 (0, C-3a' or C-7a'), 134.7 (1), 128.1 (1), 126.2 (1), 125.1 (1, C-5), 124.2 (1), 78.6 (1, C-3), 66.2 (0, C-2), 34.1 (2, C-2' or C-3'), 31.3 (2, C-2' or C-3'); MS *m/z* (%) 200 (58, M$^+$), 183 (10), 155 (61), 154 (21), 153 (22), 141 (12), 129 (17), 128



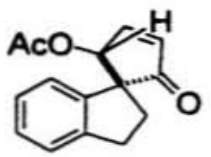
247

(28), 127 (10), 117 (26), 116 (50), 115 (100), 91 (14), 89 (11), 77 (11), 63 (14), 58 (10), 55 (19), 51 (12); HRMS calcd for $C_{13}H_{12}O_2$: 200.0837, found: 200.0840.



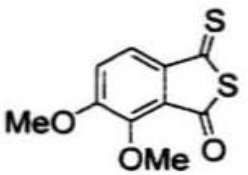
248

(2*R,3*S**)-3-Acetoxy-2',3'-dihydrospiro([4]cyclopentene-2,1'-[1*H*]indene)-1-one (248).** To a solution of **246** (145 mg, 0.726 mmol) in CH_2Cl_2 (25 mL) was added collidine (0.15 mL, 1.1 mmol) and acetyl chloride (0.20 mL, 2.8 mmol). The solution was stirred for 24 h and washed with H_2O (75 mL). The aqueous layer was extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine (75 mL) and dried over $MgSO_4$. Chromatography (30% ethyl acetate/hexanes) afforded 129 mg (73%) of **248** as a yellow oil; IR ν_{max} 1747 (s), 1726 (s), 1597 (s) cm^{-1}; ^1H NMR (300 MHz) δ 7.70 (1H, dd, J = 6.0, 2.4 Hz, H-4), 7.29-7.13 (3H, m, Ar**H**), 6.91 (1H, d, J = 7.2 Hz, H-7'), 6.49 (1H, dd, J = 5.7, 0.9 Hz, H-5), 5.85 (1H, dd, J = 2.4, 0.9 Hz, H-3), 3.23-2.91 (2H, m, H-3'), 2.40-2.30 (2H, m, H-2'), 2.12 (3H, s, OCOC**H**$_3$); ^{13}C NMR (125 MHz) δ 207.6 (0, C-1), 170.2 (0, O**C**OCH$_3$), 158.2 (1, C-4), 144.7 (0, C-3a' or C-7a'), 143.3 (0, C-3a' or C-7a'), 136.1 (1), 128.0 (1), 126.9 (1), 125.0 (1, C-5), 122.1 (1), 79.6 (1, C-3), 62.5 (0, C-2), 31.3 (2, C-2' or C-3'), 31.2 (2, C-2' or C-3'), 20.8 (3, OCO**C**H$_3$); MS *m/z* (%) 242 (7, M$^+$), 201 (19), 200 (62), 184 (11), 183 (53), 182 (45), 181 (10), 172 (14), 156 (28), 155 (89), 154 (43), 153 (33), 152 (16), 146 (27), 143 (16), 141 (15), 129 (18), 128 (32), 127 (13), 117 (22), 116 (32), 115 (71), 91 (18), 77 (13), 76 (12), 63 (10), 62 (10), 55 (21), 51 (10), 45 (24), 44 (10), 43 (100); HRMS calcd for $C_{15}H_{14}O_3$: 242.0943, found: 242.0928.



249

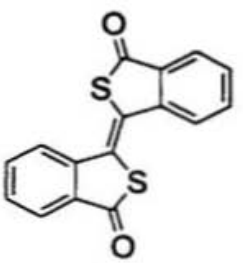
(2*R,3*R**)-3-Acetoxy-2',3'-dihydrospiro([4]cyclopentene-2,1'-[1*H*]indene)-1-one (249).** To a solution of **247** (114 mg, 0.571 mmol) in CH_2Cl_2 (25 mL) was added collidine (0.23 mL, 1.7 mmol) and acetyl chloride (0.12 mL, 1.7 mmol). The solution was stirred for 24 h and washed with H_2O (50 mL). The aqueous layer was extracted with ethyl acetate (2 × 50 mL). The combined organic layers were washed with brine (50 mL) and dried over $MgSO_4$. Chromatography (30% ethyl acetate/hexanes) afforded 115 mg (84%) of **249** as a colorless oil; ^{1}H NMR (300 MHz) δ 7.64 (1H, dd, J = 5.9, 2.6 Hz, H-4), 7.26-7.07 (3H, m, Ar**H**), 6.89 (1H, d, J = 8.1 Hz, H-7'), 6.56 (1H, dd, J = 6.0, 1.2 Hz, H-5), 5.83 (1H, dd, J = 2.1, 1.5 Hz, H-3), 3.18-3.00 (2H, m, H-3'), 2.54 (1H, m, H-2'), 2.29 (1H, m, H-2'), 1.62 (3H, s, OCOC**H**$_3$); ^{13}C NMR (75 MHz) δ 208.0 (0, C-1), 169.4 (0, O**C**OCH$_3$), 158.4 (1, C-4), 145.8 (0, C-3a' or C-7a'), 140.3 (0, C-3a' or C-7a'), 136.7 (1), 127.7 (1), 125.6 (1), 125.0 (1, C-5), 124.5 (1), 79.4 (1, C-3), 64.3 (0, C-2), 35.4 (2, C-2' or C-3'), 31.1 (2, C-2' or C-3'), 20.0 (3, OCO**C**H$_3$); HRMS calcd for $C_{15}H_{14}O_3$: 242.0943, found: 242.0934.



250

4,5-Dimethoxyphthalic thiothionoanhydride (250). To a solution of LDA, prepared from *n*-BuLi (0.91 mmol) and diisopropylamine (0.12 mL, 0.86 mmol) in THF (10 mL) cooled to –78 °C was added **245** (128 mg, 0.408 mmol) and HMPA (0.06 mL, 0.34 mmol) as a solution in THF (10 mL) dropwise over 3 min. The solution was cooled to –90 °C and **248** (120 mg, 0.496 mmol) was added as a solution in THF (10 mL) dropwise over 5 min

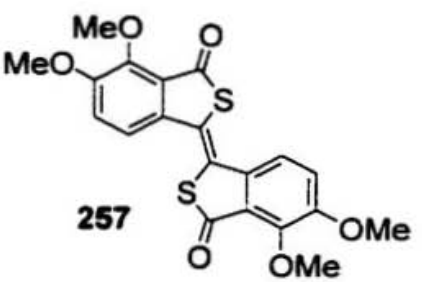
and the solution was warmed to rt. 1 M aqueous NH_4Cl (100 mL) was added and the solution was extracted with ethyl acetate (100, 75 and 50 mL). The combined organic layers were washed with brine (100 mL) and dried over $MgSO_4$. Chromatography (30% ethyl acetate/hexanes) afforded 83 mg (85%) of **250** as a brown foam (which formed brown needles on crystallization from CH_2Cl_2), mp 101-104 °C; IR (Nujol) ν_{max} 1713 (s), 1568 (s), 1265 (s) cm^{-1}; ^1H NMR (CD_3COCD_3, 300 MHz) δ 7.88 (1H, d, J = 8.1 Hz, H-7), 7.50 (1H, d, J = 8.1 Hz, H-6), 4.06 (3H, s, OC**H**$_3$), 3.96 (3H, s, OC**H**$_3$); ^1H NMR (300 MHz) δ 7.92 (1H, d, J = 8.7 Hz, H-7), 7.19 (1H, d, J = 8.7 Hz, H-6), 4.03 (3H, s, OC**H**$_3$), 4.00 (3H, s, OC**H**$_3$); ^{13}C NMR (CD_3COCD_3, 75 MHz) δ 220.1 (0, **C**=S), 190.4 (0, **C**=O), 161.2 (0, C-5), 146.9 (0, C-4), 138.5 (0, C-3a), 125.9 (0, C-7a), 120.9 (1, C-7), 118.8 (1, C-6), 62.1 (3, O**C**H_3), 57.6 (3, O**C**H_3); MS *m/z* (%) 242 (11), 241 (14), 240 (100, M^+), 207 (66), 181 (11), 179 (20), 153 (10), 150 (10), 149 (11), 121 (21), 120 (36), 106 (24), 104 (16), 94 (15), 93 (18), 78 (27), 77 (16), 76 (20), 69 (23), 65 (11), 63 (10), 62 (11), 50 (16); HRMS calcd for $C_{10}H_8O_3S_2$: 239.9915, found: 239.9902.



252

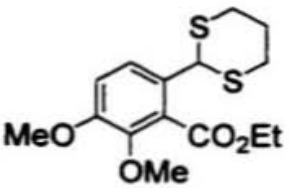
(*trans*)-3,3'-Bithiophthalide (252). To a solution of LDA, prepared from *n*-BuLi (1.6 mmol) and diisopropylamine (0.22 mL, 1.6 mmol) in THF (10 mL) cooled to –78 °C was added **114a** (173 mg, 0.681 mmol) and HMPA (0.10 mL, 0.57 mmol) as a solution in THF (10 mL) dropwise over 3 min. The solution was warmed to rt. The reaction was quenched with 1 M aqueous NH_4Cl (50 mL), and the solution was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried over $MgSO_4$.

Chromatography (30% ethyl acetate/hexanes) afforded 83 mg (82%) of **252** as a brown solid, mp > 310 °C; IR (Nujol) ν_{max} 1707 (s) cm^{-1}; ^1H NMR (300 MHz) δ 8.34 (2H, d, J = 8.1 Hz, H-7), 8.00 (2H, dd, J = 7.7, 0.8 Hz, H-4), 7.82 (2H, dt, J = 7.7, 1.4 Hz, H-5 or H-6), 7.60 (2H, m); MS *m/z* (%) 296 (100, M^+), 295 (14), 268 (14), 249 (12), 248 (14), 240 (31), 232 (25), 218 (10), 217 (56), 208 (13), 206 (38), 204 (14), 195 (16), 194 (11), 180 (14), 177 (14), 174 (10), 166 (10), 165 (55), 164 (71), 163 (14), 162 (10), 150 (19), 149 (91), 148 (17), 134 (12), 133 (15), 132 (34), 130 (28), 122 (12), 121 (45), 120 (76), 109 (11), 105 (11), 104 (19), 93 (13), 77 (34), 76 (25), 75 (11), 74 (10), 69 (24), 64 (40), 63 (12), 58 (14), 57 (11), 51 (14), 50 (16), 45 (20), 44 (13), 43 (32), 42 (13), 41 (22); HRMS calcd for $C_{16}H_8O_2S_2$: 295.9966, found: 295.9959.



257

(*trans*)-5,5',6,6'-Tetramethoxy-3,3'-bithiophthalide (257). A small sample of **250** was heated on the melting point apparatus until a sudden transformation from a brown oil to a dark black oil occurred at 110 °C. This resolidified to a yellow solid, mp > 310 °C; IR (Nujol) ν_{max} 1710 (s) cm^{-1}; ^1H NMR (CD_3COCD_3, 300 MHz) δ 7.92 (2H, d, J = 8.1 Hz, H-4), 7.20 (2H, d, J = 8.1 Hz, H-5), 4.02 (6H, s, OCH_3), 4.00 (6H, s, OCH_3); MS *m/z* (%) 418 (13, $M^+ + 2$), 416 (100, M^+), 401 (14), 242 (17), 200 (35), 183 (38), 170 (51), 143 (45), 130 (29), 41 (34), 28 (76).

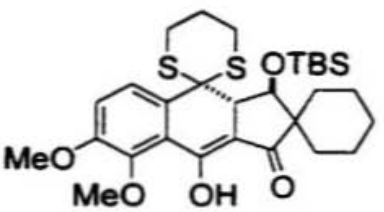


258

Ethyl 2-[1,3]dithian-2-yl-5,6-dimethoxybenzoate (258). To a solution of **244a** (856 mg, 3.60 mmol) in CH_2Cl_2 (180 mL) was added anhydrous $ZnCl_2$ (640 mg, 4.7 mmol) and 1,3-propanedithiol (0.94 mL, 9.4 mmol). The solution was stirred at rt for 1 h and washed with H_2O (100 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 75 mL). The organic layers were combined and washed with brine (100 mL) and dried over $MgSO_4$. Chromatography (30% ethyl acetate/hexanes) afforded 1.15 g (100%) of **258** as a white crystalline solid, mp 76-77 °C; IR (Nujol) ν_{max} 1726 (s), 1599 (s), 1579 (s) cm^{-1}; ^1H NMR (300 MHz) δ 7.41 (1H, d, J = 8.7 Hz, H-3), 6.95 (1H, d, J = 8.7 Hz, H-4), 5.22 (1H, s, H-1'), 4.45 (2H, q, J = 7.2 Hz, -OC**H**$_2$CH$_3$), 3.87 (3H, s, OC**H**$_3$), 3.86 (3H, s, OC**H**$_3$), 3.08-2.98 (2H, m, -SC**H**$_2$), 2.92-2.85 (2H, m, -SC**H**$_2$), 2.19-1.82 (2H, m, -SCH$_2$C**H**$_2$CH$_2$S-), 1.42 (3H, t, J = 7.1 Hz, -OCH$_2$C**H**$_3$); ^{13}C NMR (75 MHz) δ 166.5 (0, **C**O$_2$CH$_2$CH$_3$), 152.4 (0, C-6), 145.6 (0, C-5), 128.4 (0, C-1 or C-2), 128.1 (0, C-1 or C-2), 124.2 (1, C-3), 113.6 (1, C-4), 61.2 (3, O**C**H$_3$), 61.2 (2, O**C**H$_2$CH$_3$), 55.7 (3, O**C**H$_3$), 47.2 (1, C-1'), 32.2 (2C, 2, -**C**H$_2$CH$_2$**C**H$_2$S-), 24.8 (2, -SCH$_2$**C**H$_2$CH$_2$S-), 14.2 (3, -OCH$_2$**C**H$_3$); MS *m/z* (%) 328 (31, M$^+$), 299 (11), 283 (15), 282 (12), 235 (17), 225 (37), 223 (12), 222 (81), 209 (11), 194 (14), 193 (100), 165 (10), 45 (13), 41 (12); HRMS calcd for $C_{15}H_{20}O_4S_2$: 328.0803, found: 328.0804.

Annulation of dithiane 258 and enone 119. To a solution of LDA, prepared from *n*-BuLi (0.58 mmol) and diisopropylamine (0.08 mL, 0.6 mmol) in THF (10 mL) cooled to –78 °C was added **258** (139 mg, 0.423 mmol) as a solution in THF (8 mL) dropwise over

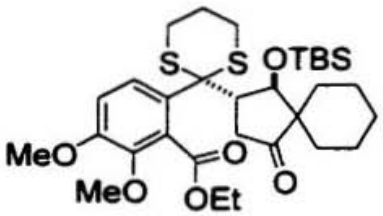
3 min. The solution was cooled to –90 °C, and **119** (152 mg, 0.542 mmol) was added as a solution in THF (8 mL) dropwise over 5 min. The solution was warmed to rt. 0.5 M aqueous NH_4Cl (100 mL) was added and the solution was extracted with ethyl acetate (100, 75 and 50 mL). The combined organic layers were washed with saturated $NaHCO_3$ (75 mL), water (75 mL) and brine (75 mL) and dried over $MgSO_4$. Chromatography (20% ethyl acetate/hexanes) afforded 23 mg (16%) of unreacted **258**, 148 mg (62%, 74% based on recovered starting material) of **259** as a brown foam, 42 mg (16%, 19% based on recovered starting material) of **260** as a brown foam.



259

(3*R,3a*R**)-3-(*tert*-Butyldimethylsilyl)oxy-4-[1,3]dithian-2-yl-2,3,3a,4-tetrahydro-9-hydroxy-7,8-dimethoxyspiro((1*H*)-benz[*f*]indene-2,1'-cyclohexane)-1-one (259).** Brown foam: ^{1}H NMR (300 MHz) δ 7.58 (1H, d, J = 8.4 Hz, H-5), 6.92 (1H, d, J = 8.4 Hz, H-6), 4.61 (1H, d, J = 6.0 Hz, H-3), 3.91 (3H, s, -OC**H**$_3$), 3.88 (3H, s, -OC**H**$_3$), 3.38 (1H, dt, J = 13.2, 3.1 Hz, -SC**H**$_2$), 3.14 (1H, d, J = 6.0 Hz, H-3a), 2.84 (1H, m, -SC**H**$_2$), 2.60 (1H, m, -SC**H**$_2$), 2.39 (1H, dt, J = 13.8, 2.1 Hz, -SC**H**$_2$), 2.27-2.12 (2H, m, -SCH$_2$C**H**$_2$CH$_2$S-), 1.93-1.24 (10H, m, H-2' to H-6'), 0.96 (9H, s, SiC**Me**$_3$), 0.32 (3H, s, Si**Me**), 0.24 (3H, s, Si**Me**): ^{13}C NMR (75 MHz) δ 203.3 (0, C-1), 169.7 (0, C-9), 152.9 (0, C-8), 149.3 (0, C-7), 139.2 (0, C-4a), 123.1 (0, C-8a), 122.6 (1, C-5), 112.9 (1, C-6), 105.6 (0, C-9a), 79.4 (1, C-3), 61.9 (3, -O**C**H$_3$), 55.9 (3, -O**C**H$_3$), 55.7 (0, C-2 or C-4), 53.0 (1, C-3a), 52.8 (0, C-2 or C-4), 31.2 (2), 29.4 (2, -S**C**H$_2$CH$_2$CH$_2$S-), 28.4 (2), 26.7 (3C, 3, SiC**Me**$_3$), 26.1 (2, -SCH$_2$CH$_2$**C**H$_2$S-), 25.5 (2, -SCH$_2$**C**H$_2$CH$_2$S-), 25.2 (2), 22.3 (2), 21.3 (2), 18.6 (0, Si**C**Me$_3$), -1.1 (3, Si**Me**), -3.4

(3, Si**Me**); MS *m/z* (%) 562 (61, M^+), 505 (6), 487 (10), 456 (12), 455 (11), 336 (23), 303 (12), 262 (10), 257 (10), 256 (16), 255 (100), 229 (16), 75 (44), 73 (54), 57 (13), 43 (11), 41 (22); HRMS calcd for $C_{29}H_{42}O_5S_2Si$: 562.2243, found: 562.2223.

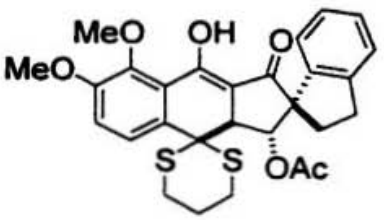


260

Ethyl (3*R,4*R**)-4-((*tert*-butyldimethylsilyl)oxy)-3-(2'-[1,3]dithian-2-yl-5',6'-dimethoxybenzoate) spiro[4.5]decan-1-one (260).** Brown foam; ^{1}H NMR (300 MHz) δ 7.70 (1H, d, J = 9.0 Hz, H-3'), 6.90 (1H, d, J = 9.0 Hz, H-4'), 4.40-4.32 (2H, br s, -OC**H**$_2$CH$_3$), 4.08 (1H, d, J = 6.0 Hz, H-4), 3.88 (3H, s, -OC**H**$_3$), 3.83 (3H, s, -OC**H**$_3$), 3.36 (1H, m, -SC**H**$_2$), 2.83 (1H, t, J = 13.3 Hz, -SC**H**$_2$), 2.72-2.49 (4H, m, -SC**H**$_2$ and H-2), 2.08-1.82 (3H, m, -SCH$_2$C**H**$_2$CH$_2$S- and H-3), 1.75-1.24 (10H, m, H-6 to H-10), 1.26 (3H, t, J = 7.5 Hz, -OCH$_2$C**H**$_3$), 1.00 (9H, s, SiC**Me**$_3$), 0.42 (3H, s, Si**Me**), 0.20 (3H, s, Si**Me**); MS *m/z* (%) 608 (2), 552 (16), 551 (43, M^+ - ^{t}Bu), 504 (10), 503 (31), 502 (85), 341 (11), 327 (17), 309 (10), 248 (33), 247 (13), 235 (11), 220 (14), 219 (100), 193 (10), 169 (12), 86 (26), 84 (40), 81 (10), 77 (10), 75 (82), 74 (10), 73 (66), 59 (22), 57 (29), 56 (10), 55 (18), 49 (10), 47 (17), 45 (10), 43 (39), 41 (37); HRMS calcd for $C_{27}H_{39}O_6S_2Si$ (M^+ - ^{t}Bu): 551.1957, found: 551.1950.

Annulation of dithiane 258 and enone 249. To a solution of LDA, prepared from *n*-BuLi (0.58 mmol) and diisopropylamine (0.08 mL, 0.6 mmol) in THF (10 mL) cooled to –78 °C was added **258** (125 mg, 0.382 mmol) as a solution in THF (8 mL) dropwise over 5 min. The solution was cooled to –90 °C and **249** (115 mg, 0.477 mmol) was added as a

solution in THF (8 mL) dropwise over 5 min and the solution was warmed to rt. The solution was washed with 0.5 M aqueous NH_4Cl (100 mL) and the aqueous layer was extracted with ethyl acetate (100 and 75 mL). The combined organic layers were washed with water (100 mL) and brine (100 mL) and dried over $MgSO_4$. Chromatography (40% ethyl acetate/hexanes-7% CH_3OH/CH_2Cl_2) afforded 148 mg (74%) of **261** as a brown foam and 21 mg (10%) of **262** as a brown foam. **(2*R**,3*R**,3a*R**)-3-Acetoxy-4-[1,3]dithian-2-yl-2,2',3,3',3a,4-hexahydro-9-hydroxy-7,8-dimethoxyspiro((1*H*)-benz[*f*]indene-2,1'-(1*H*)indene)-1-one (261).** Brown foam: ^{1}H NMR (300 MHz) δ 7.67 (1H, d, J = 8.7 Hz, H-5), 7.23-7.09 (3H, m, H-4', H-5' and H-6'), 7.01 (1H, d, J = 8.7 Hz, H-6), 7.00 (1H, d, J = 7.5 Hz, H-7'), 6.14 (1H, d, J = 6.0 Hz, H-3), 3.96 (3H, s, -OC**H**$_3$), 3.92 (3H, s, -OC**H**$_3$), 3.60 (1H, d, J = 6.0 Hz, H-3a), 3.27 (1H, dt, J = 13.0, 3.7 Hz, -SC**H**$_2$), 3.06 (2H, t, J = 7.7 Hz, H-3'), 2.91 (1H, dt, J = 14.1, 4.3 Hz, -SC**H**$_2$), 2.81-2.67 (2H, m, overlapping -SC**H**$_2$ and H-2'), 2.58-2.43 (2H, m, overlapping -SC**H**$_2$ and H-2'), 2.21-1.86 (2H, m, -SCH$_2$C**H**$_2$CH$_2$S-), 1.65 (3H, s, OCOC**H**$_3$); NOE data δ 6.14 (3.60, 3%; 2.58-2.50, 5%); ^{13}C NMR (75 MHz) δ 196.2 (0, C-1), 170.8 (0, C-9 or CH_3**C**O), 169.8 (0, C-9 or CH_3**C**O), 153.1 (0, C-8), 149.9 (0, C-7), 145.2 (0, C-3a' or C-7a'), 141.0 (0, C-3a' or C-7a'), 138.8 (0, C-4a), 127.7 (1, C-4', C-5', C-6' or C-7'), 125.8 (1, C-4', C-5', C-6' or C-7'), 125.0 (1, C-4', C-5', C-6' or C-7'), 124.7 (1, C-4', C-5', C-6' or C-7'), 123.0 (0, C-8a), 122.4 (1, C-5), 113.8 (1, C-6), 106.0 (0, C-9a), 78.6 (1, C-3), 61.9 (3, -O**C**H$_3$), 60.2



261

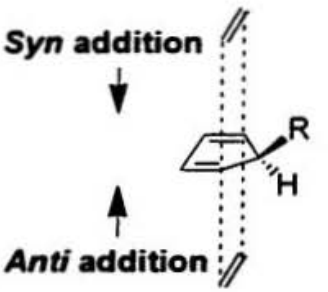
(0, C-2 or C-4), 56.3 (0, C-2 or C-4), 55.9 (3, -O**C**H_3), 51.9 (1, C-3a), 34.6 (2, C-2' or C-3'), 31.3 (2, C-2' or C-3'), 28.8 (2, -S**C**$H_2CH_2CH_2S$-), 25.5 (2, -S**C**$H_2CH_2CH_2S$-), 24.4 (2, -SCH_2**C**H_2CH_2S-), 20.5 (3, **C**H_3CO): MS *m/z* (%) 524 (12, M^+), 466 (14), 465 (31), 464 (100), 389 (17), 358 (12), 255 (45), 117 (11), 115 (18), 43 (67), 41 (10); HRMS calcd for $C_{28}H_{28}O_6S_2$: 524.1327, found: 524.1288. The structure of **261** was confirmed by X-ray crystallography.

Chapter 2. Study of the Diels-Alder Reactions of a Carvone-Derived Diene.

Introduction

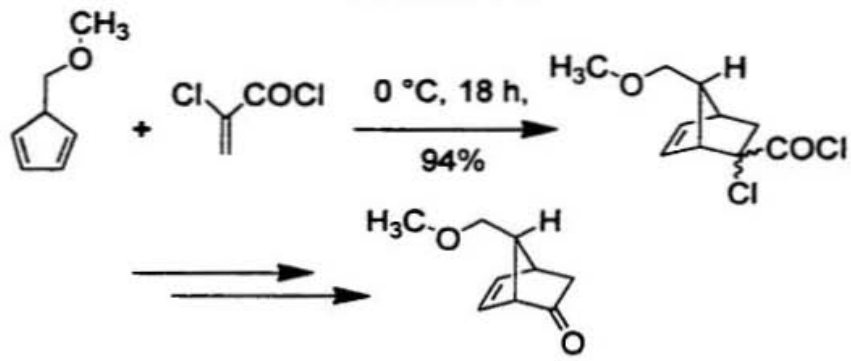
There is a stereochemical aspect of the Diels-Alder reaction that becomes important when the two faces of the π-bond system of the interacting diene and/or dienophile are not equivalent.[83] Cycloaddition to either face of an addend without a plane of symmetry results in diastereomeric products. The two modes of addition are called *syn* and *anti* with respect to the group, or structural moiety, that makes the two faces different. The *syn* and *anti* additions of a general dienophile to a monosubstituted cyclopentadiene are illustrated in Figure 5.

Figure 5: *Syn* and *anti* addition to a monosubstituted cyclopentadiene



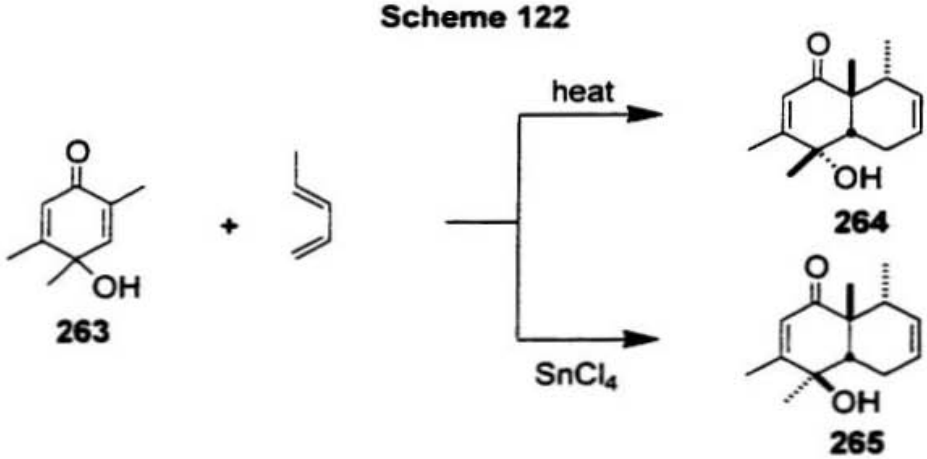
An example of a nonsymmetrical reaction described in the literature is the cycloaddition of α-chloroacryloyl chloride to 5-methoxymethylcyclopentadiene (Scheme 121). This is a key initial stage of the "Corey bicycloheptene route" to prostaglandins, and is totally *anti* diastereofacially selective.[84]

Scheme 121



When **263** is heated with (*E*)-piperyline, addition takes place *anti* to the 4-methyl group to furnish **264**. However, when **263** is reacted with (*E*)-piperyline under Lewis acid catalysis, opposite diastereofacial selectivity is observed to yield **265**, presumably from complexation of the hydroxyl group by $SnCl_4$, thereby transforming it into the larger of the two geminal substituents (Scheme 122).[85]

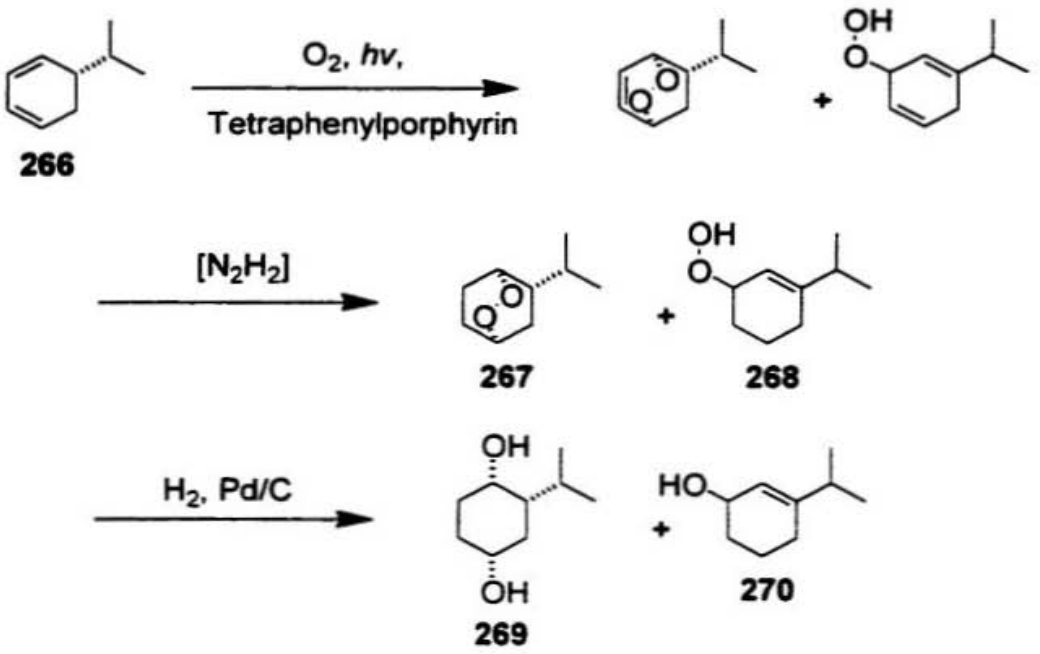
Scheme 122



Carpenter and Davis[86] reported unusual facial selectivity in the cycloaddition of singlet oxygen to a simple cyclic diene (Scheme 123). While it is known that polar substituents can influence the facial selectivity of singlet oxygen [4 + 2] cycloadditions,[87]

there appears to be no evidence that a simple alkyl substituent has a significant effect of this kind.

Scheme 123

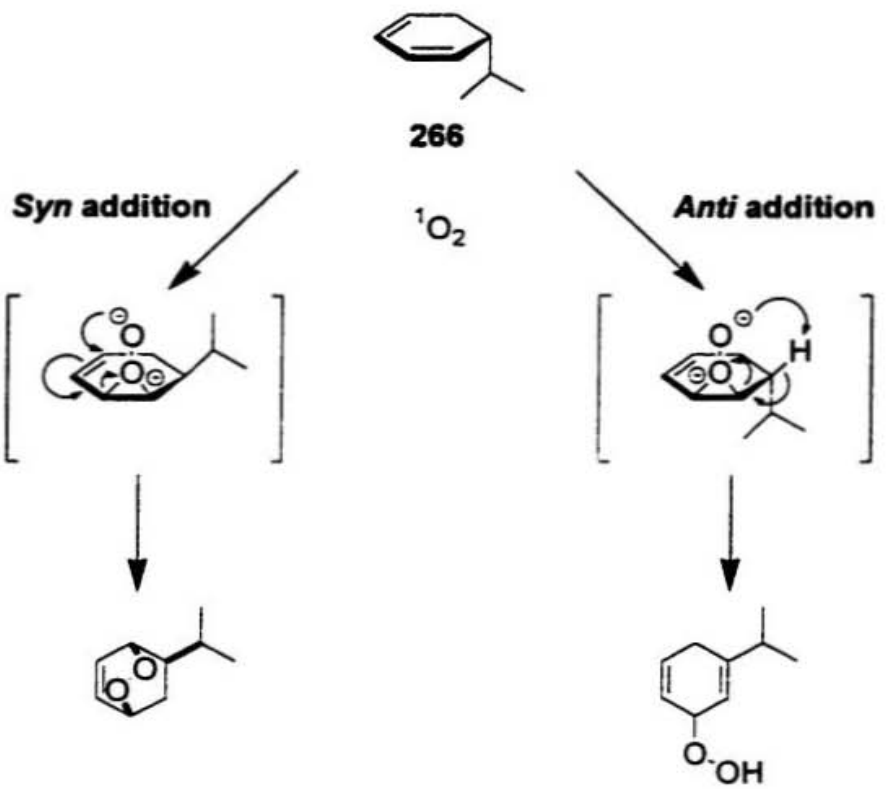


266 **267** **268** **269** **270**

Tetraphenylporphyrin-photosensitized addition of singlet oxygen to diene **266**, followed by reduction of the double bond with diimide, yielded a mixture of endoperoxide **267** and hydroperoxide **268**, in a combined isolated yield of approximately 60% and in a ratio of approximately 3:2, respectively. Direct reduction of this mixture with H_2 and a Pd catalyst furnished diol **269** and **270**. Unambiguous stereochemical assignment of **269** was made by comparison with previously synthesized material, thereby confirming the addition of singlet oxygen *syn* to the isopropyl group. Carpenter and Davis[86] postulated that approach of the oxygen from the *anti* face leads not to cycloaddition but rather to an 'ene' reaction – yielding the observed hydroperoxide after diimide reduction of the less

substituted double bond. Approach from the *syn* face could not yield this product, although an "ene" product derived from hydrogen abstraction from the secondary carbon could have been formed in principle. but this product was not detected (Scheme 124).

Scheme 124

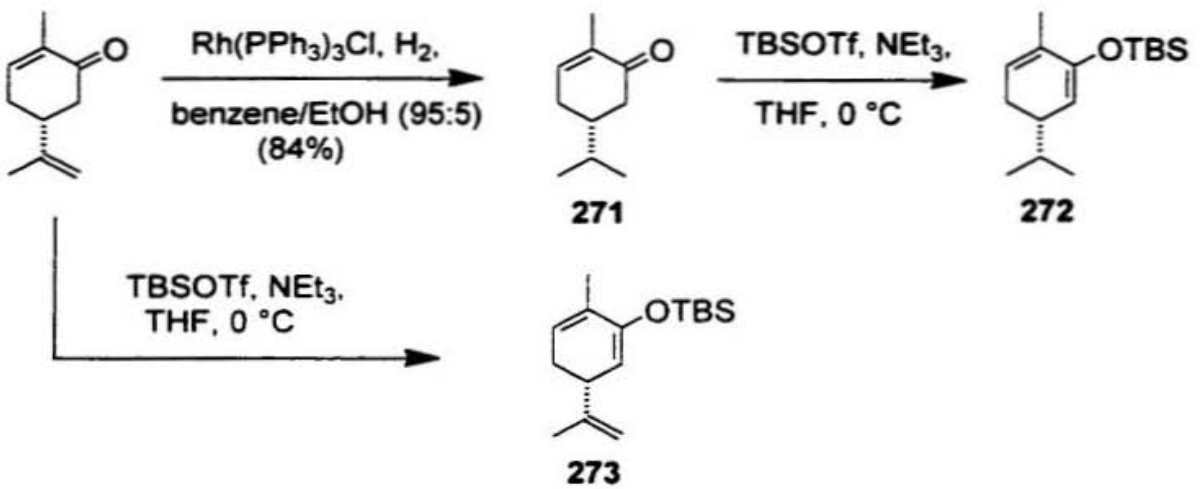


To see if this unusual facial selectivity was an anomaly, or could be extended to a wider range of dienophiles. the synthesis of a simple diene derived from carvone was effected, and it was reacted with various dienophiles.

Results and Discussion

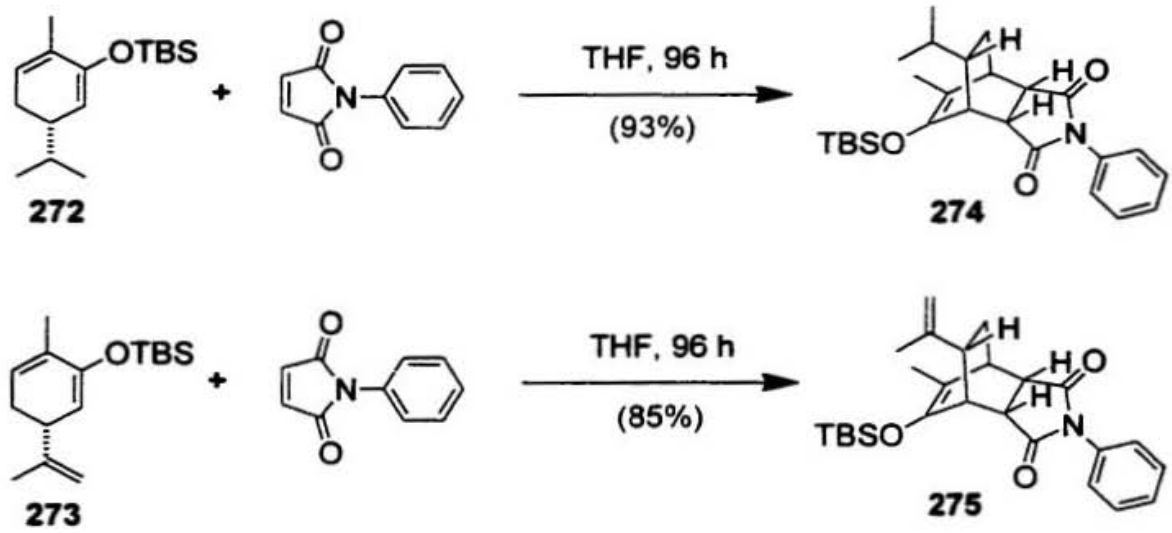
Readily available (-)-carvone was hydrogenated employing the procedure of Blay and co-workers.[88] Formation of the corresponding *tert*-butyldimethylsilyl enol ether **272** was effected by treatment of **271** with NEt_3 and TBSOTf at 0 °C. (-)-Carvone could also be converted to *tert*-butyldimethylsilyl enol ether **273** by subjection to these same conditions (Scheme 125). In neither case was the diene purified due to its instability. Crude dienes were reacted with the appropriate dienophile.

Scheme 125



Reactions of **272** and **273** with *N*-phenylmaleimide furnished adducts **274** and **275**, respectively (Scheme 126). Both reactions were diastereoselective, and addition of the dienophile occurred *anti* to the isopropyl or isopropylene group. As expected, the addition in both cases was *endo*.

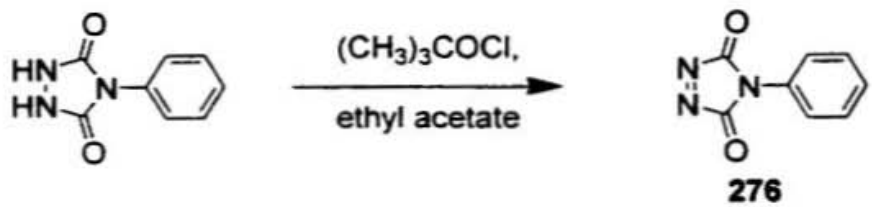
Scheme 126



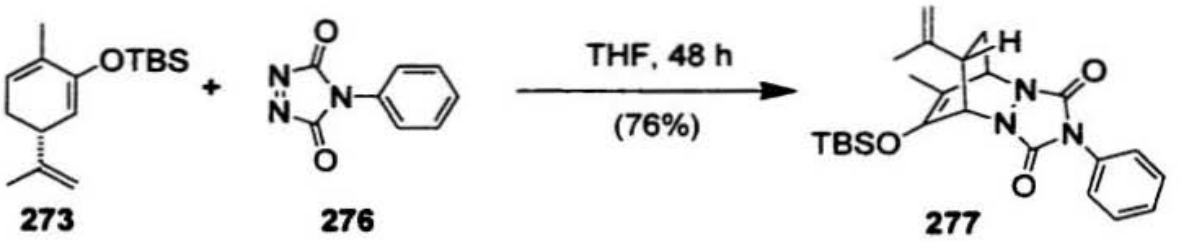
The addition for adducts **274** and **275** was determined to be *anti* to the isopropyl and isopropylene groups on the basis of NOE measurements. The yields of these adducts were excellent. In neither case was a minor diastereomer. occurring by addition *syn* to the alkyl substituent. detected.

Modification of the dienophile resulted in the employment of 4-phenyl-1.2.4-triazoline-3.5-dione (**276**) (Scheme 127). This was prepared from commercially available 4-phenylurazole by the method of Cookson and co-workers.[89]

Scheme 127



Scheme 128

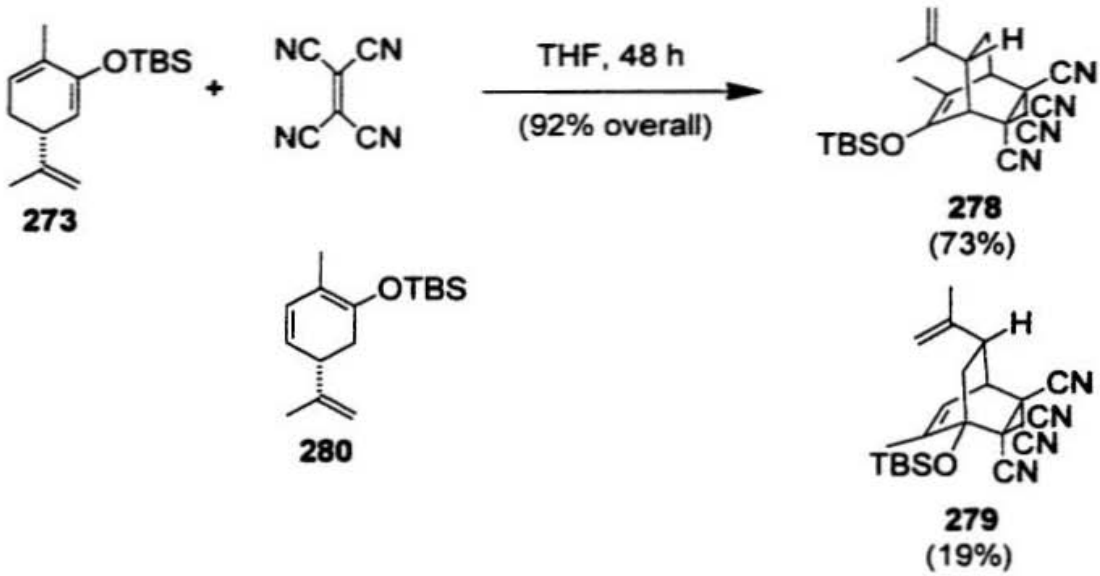


273 **276** **277**

Once more, only one diastereomer could be detected in the adduct mixture. As the facial selectivity could not be determined from NOE measurements. **277** was crystallized and the structure was determined by X-ray crystallographic analysis. This analysis confirmed the addition of the dienophile *anti* to the isopropylene group.

Reaction of **273** with tetracyanoethene furnished not one, but two adducts. These adducts were not diastereomeric as initially believed, but regioisomeric (Scheme 129). It seems likely that the minor adduct **279** arose from addition of tetracyanoethene to the regioisomeric diene **280**. Both adducts **278** and **279** arose from *anti* addition of tetracyanoethene to the regioisomeric dienes **273** and **280**, respectively. Formation of diene **280** is a competitive process in this reaction only, and thermal isomerization of **273** to **280** under the mild reaction conditions seems unlikely. More probable is the formation of **280** from a possible radical assisted double bond isomerization.

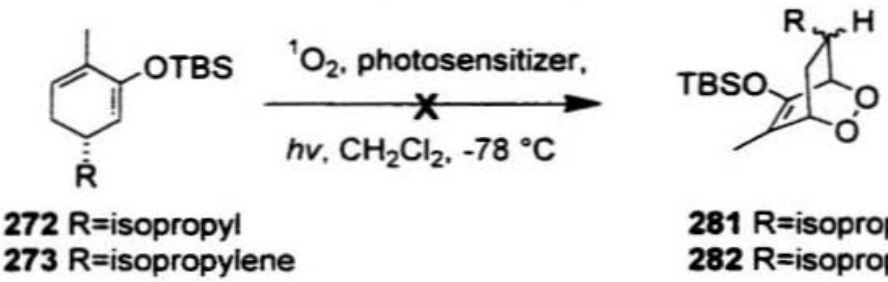
Scheme 129



The structures of adducts **278** and **279** were both confirmed by X-ray crystallographic analysis.

Finally, all attempts to detect either an endoperoxide such as **281** or **282** by the addition of singlet oxygen to dienes **272** or **273** were unsuccessful under various conditions (Scheme 130).

Scheme 130

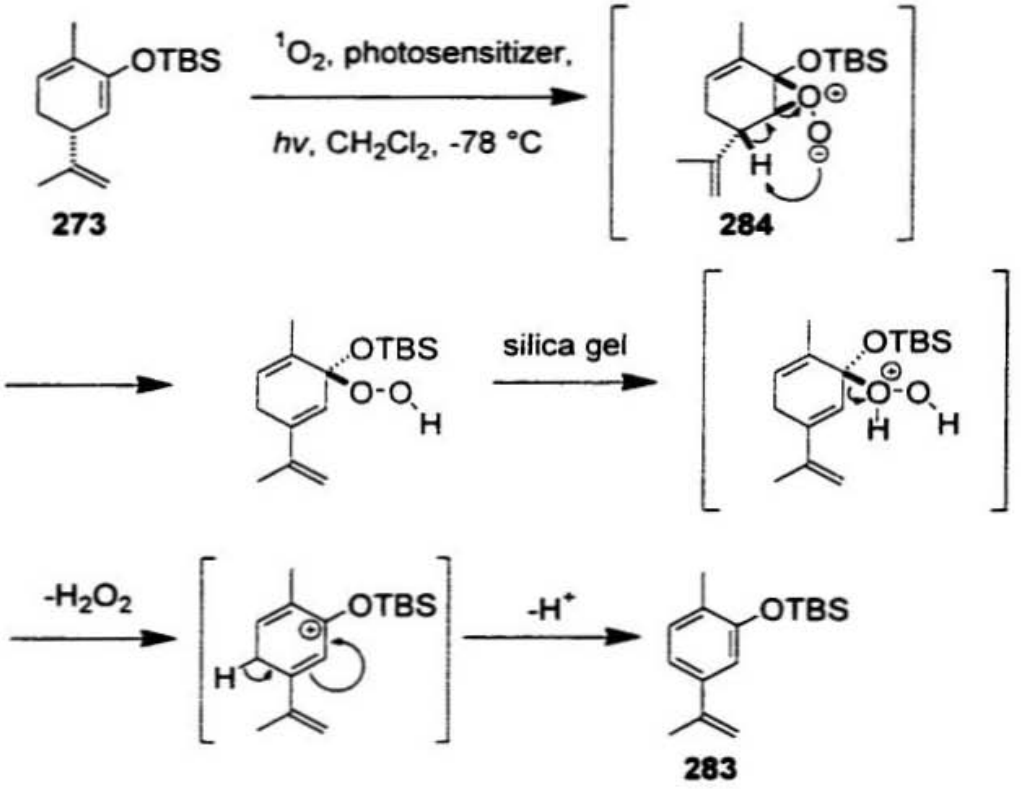


272 R=isopropyl
273 R=isopropylene

281 R=isopropyl
282 R=isopropylene

The reaction mixtures produced from **272** and **273** were complex. One may speculate that the instability of both the possible endoperoxide or the hydroperoxide – as noted by Carpenter[86] – made isolation and identification troublesome. However, in the subjection of diene **273** to singlet oxygen, one product was isolated and determined to be aromatic compound **283**. A mechanism for the formation of **283** is proposed, which goes through perepoxide **284**. consistent with the mechanism proposed by Carpenter (Scheme 131).

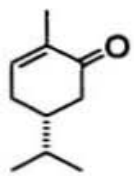
Scheme 131



Therefore, while no *syn* addition was observed for dienophiles such as *N*-phenylmaleimide, 4-phenyl-1,2,4-triazoline-3,5-dione or tetracyanoethene, we did observe the formation of compound **283**, which is postulated to arise from perepoxide **284**. This lends further credence to the argument that formation of a perepoxide intermediate is the first step in all of the common reaction modes of $^1O_2$ with dienes, i.e., "ene" reaction,[87] 2 + 2 cycloaddition,[89] and [4 + 2] cycloaddition. Perepoxide involvement in the [4 + 2] reaction was apparently first proposed by Dewar and Thiel[90] on the basis of MINDO/3 calculations. Paquette and co-workers[91] have experimentally shown that the facial selectivity for [4 + 2] reactions of $^1O_2$ with some tricyclic cyclopentadiene derivatives is different than that seen for all other [4 + 2] cycloadditions examined, indicating that the mechanism might be different from that of most Diels-Alder reactions. Tetracyanoethylene may have a different mechanism as well, such as a single electron transfer pathway.[92] The involvement of radical-ion pairs in [4 + 2] cycloadditions has been examined,[93a-c] and found to be plausible.

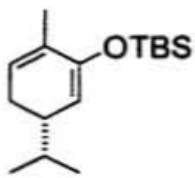
Experimental Section

General Section. See Chapter 1, pp. 121-122.



271

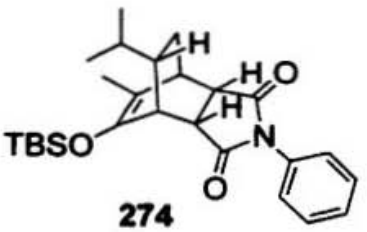
(*R*)-5-Isopropyl-2-methylcyclohex-2-enone (271). To $Rh(PPh_3)_3Cl$ (506 mg, 0.547 mmol) under an atmosphere of H_2(g) was added (-)-carvone (583 mg, 3.88 mmol) as a solution of benzene (40 mL) and absolute ethanol (3 mL). This dark red solution was stirred at rt for 24 h. The contents were washed with H_2O (100 mL), extracting the aqueous layer with CH_2Cl_2 (3 × 75 mL). The organic layers were combined and washed with brine (100 mL), and dried over $MgSO_4$. Silica gel chromatography (20% ethyl acetate/hexanes) afforded 493 mg (84%) of **271** as a colorless oil: IR ν_{max} 1672 (s) cm^{-1}; $[\alpha]_D$ = +8 (c = 0.0020, benzene): ^1H NMR (300 MHz) δ 6.75 (1H, dd, J = 3.5, 3.5 Hz, H-3), 2.54 (1H, m, H-4), 2.36 (1H, m, H-4), 2.12 (2H, m, H-6), 1.86 (1H, m, H-5), 1.77 (3H, s, C-2 methyl), 1.57 (1H, m, CH_3CHCH_3), 0.91 (6H, d, J = 7.0 Hz, CH_3CHCH_3); ^{13}C NMR (75 MHz) δ 200.6 (0, C-1), 145.2 (1, C-3), 135.1 (0, C-2), 41.9, 31.9, 29.7, 19.4, 15.5, 15.5; MS m/z (%) 152 (18, M^+), 111 (10), 109 (12), 82 (100), 81 (41), 79 (10), 69 (12), 55 (18), 54 (29), 53 (20), 43 (13), 41 (48); HRMS calcd for $C_{10}H_{16}O$: 152.1201, found: 152.1204.



272

(*S*)-2-(*tert*-Butyldimethylsilyl)oxy-6-isopropyl-3-methyl-1,3-cyclohexadiene (272). To a solution of **271** (413 mg, 2.71 mmol) in THF (20 mL) cooled to 0 °C was added *tert*-butyldimethylsilyl-trifluoromethylsulfonate (0.75 mL, 3.3 mmol) dropwise followed by

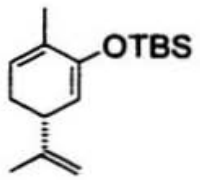
NEt_3 (0.57 mL, 4.1 mmol). This was stirred at 0 °C for 30 min. Due to the instability of **272**, no purification was carried out, and it was employed immediately.



274

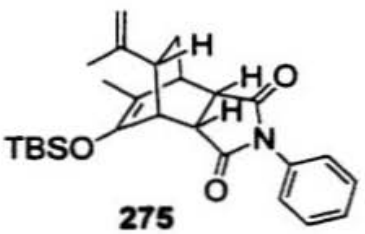
(3a*S*, 4*S*, 7*R*, 7a*R*, 8*S*)-6-(*tert*-Butyldimethylsilyl)oxy-3a,4,7,7a-tetrahydro-8-isopropyl-5-methyl-2-phenyl-4,7-ethano-1*H*-isoindole-1,3(2*H*)-dione (274). To the solution containing **272** was added *N*-phenylmaleimide (960 mg, 5.5 mmol) as a solution in THF (4 mL). The reaction mixture was stirred at rt for 96 h, after which time the solvent was removed by rotary evaporation. Silica gel chromatography (15% ethyl acetate/hexanes) afforded 1.11 g (93%) of **274** as a white solid, mp 132–135 °C; IR (CCl_4) ν_{max} 1712 (s) cm^{-1}; $[\alpha]_D$ = +10 (c = 0.0053, benzene); ^1H NMR (C_6D_6, 300 MHz) δ 7.50 (2H, d, J = 8.2 Hz, H-2′ and H-6′), 7.20 (2H, t, J = 7.8 Hz, H-3′ and H-5′), 7.04 (1H, t, J = 7.4 Hz, H-4′), 3.11 (1H, t, J = 2.5 Hz, H-7), 2.88 (1H, dd, J = 5.7, 2.8 Hz, H-4), 2.35 (1H, dd, J = 8.6, 3.0 Hz, H-7a), 2.30 (1H, dd, J = 8.7, 3.0 Hz, H-3a), 1.71 (3H, s, C-5 methyl), 1.29 (1H, m, H-9), 1.13 (1H, m, CH_3CHCH_3), 0.94 (1H, m, H-8), 0.92 (9H, s, Si**Me**$_3$), 0.82 (1H, m, H-9), 0.72 (6H, d, J = 6.5 Hz, **C**H_3CHCH_3), 0.26 (3H, s, Si**Me**), -0.06 (3H, s, Si**Me**); NOE data δ 3.11 (2.35, 5%; 0.94, 4%), 2.88 (1.71, 6%; 2.30, 5%), 2.35 (3.11, 4%), 2.30 (2.88, 3%), 1.71 (2.88, 5%), 1.29 (2.88, 3%; 2.30, 4%; 0.82, 20%), 1.13 (3.11, 3%; 0.72, 2%), 0.72 (1.13, 2%); ^{13}C NMR (C_6D_6, 75 MHz) δ 177.5 (0, C-1 or C-3), 177.2 (0, C-1 or C-3), 145.2 (0, C-6), 133.5 (0, C-1′), 129.1 (2C, 1, C-3′ and C-5′), 128.5 (1, C-4′), 127.0 (2C, 1, C-2′ and C-6′), 112.5 (0, C-5), 46.6 (1, C-7a), 44.6 (1, C-3a), 41.0 (1, C-7), 39.8 (1, C-4), 33.7 (1, CH_3CHCH_3), 32.3 (2, C-9), 26.1 (3C, 3, SiC**Me**$_3$), 21.5 (1, C-8), 20.8 (2C, 3,

CH_3CHCH_3), 18.4 (0, $SiCMe_3$), 14.4 (3, C-5 methyl), -3.3 (3, SiMe), -3.7 (3, SiMe); MS *m/z* (%) 382 (100, M^+ - ^{t}Bu), 209 (40), 165 (15), 91 (25), 79 (14), 77 (18), 75 (53), 73 (56), 59 (12), 43 (15), 41 (20); HRMS calcd for $C_{22}H_{28}NO_3Si$ (M^+ - ^{t}Bu): 382.1839, found: 382.1834. Anal. calcd for $C_{26}H_{37}NO_3Si$: C 71.03, H 8.48, N 3.19, found: C 71.26, H 8.74, N 3.14.



273

(*R*)-2-(*tert*-Butyldimethylsilyl)oxy-6-isopropenyl-3-methyl-1,3-cyclohexadiene (273). To a solution of (-)-carvone (312 mg, 2.07 mmol) in THF (15 mL) cooled to 0 °C was added *tert*-butyldimethylsilyltrifluoromethylsulfonate (0.57 mL, 2.5 mmol) dropwise followed by NEt_3 (0.43 mL, 3.1 mmol). This was stirred at 0 °C for 30 minutes. Due to the instability of **273**, no purification was carried out, and it was employed immediately.

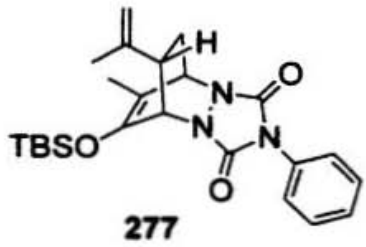


275

(3a*S*, 4*S*, 7*R*, 7a*R*, 8*R*)-6-(*tert*-Butyldimethylsilyl)oxy-3a,4,7,7a-tetrahydro-8-isopropenyl-5-methyl-2-phenyl-4,7-ethano-1*H*-isoindole-1,3(2*H*)-dione (275). To the solution containing **273** was added *N*-phenylmaleimide (0.71 g, 4.1 mmol) as a solution in THF (4.0 mL). The reaction mixture was stirred at rt for 96 h, after which time the solvent was removed by rotary evaporation. Silica gel chromatography (15% ethyl acetate/hexanes) afforded 776 mg (85%) of **275** as a white solid, mp 132–136 °C; IR (CCl_4) ν_{max} 1720 (s) cm^{-1}; $[\alpha]_D$ = +19 (c = 0.0039, benzene); ^{1}H NMR (300 MHz) δ 7.36-7.46 (3H, m, H-3′, H-4′ and H-

5'), 7.18 (2H, d, J = 7.5 Hz, H-2' and H-6'), 4.78 (1H, s, CH_3C=C**H**$_2$), 4.74 (1H, s, CH_3C=C**H**$_2$), 3.06 (1H, dd, J = 4.1, 3.3 Hz, H-7), 2.96 (1H, dd, J = 5.5, 3.1 Hz, H-4), 2.38 (1H, dd, J = 8.1, 3.3 Hz, H-7a), 2.30 (1H, dd, J = 8.1, 3.1 Hz, H-3a), 1.90 (1H, t, J = 7.1 Hz, H-8), 1.77 (3H, s, C-5 methyl), 1.68 (3H, s, C**H**$_3$C=CH_2), 1.43-1.51 (2H, m, H-9), 0.87 (9H, s, SiC**Me**$_3$), 0.11 (3H, s, Si**Me**), -0.04 (3H, s, Si**Me**); ^{1}H NMR (C_6D_6, 300 MHz) δ 7.43 (2H, d, J = 7.3 Hz, H-2' and H-6'), 7.16 (2H, t, J = 8.0 Hz, H-3' and H-5'), 7.00 (1H, t, J = 7.3 Hz, H-4'), 4.75 (2H, br s, CH_3C=C**H**$_2$), 3.01 (1H, dd, J = 3.3, 1.6 Hz, H-7), 2.88 (1H, dd, J = 5.5, 3.1 Hz, H-4), 2.38 (1H, dd, J = 8.1, 3.3 Hz, H-7a), 2.30 (1H, dd, J = 8.1, 3.1 Hz, H-3a), 1.90 (1H, t, J = 7.1 Hz, H-8), 1.67 (3H, s, C-5 methyl), 1.60 (3H, s, C**H**$_3$C=CH_2), 1.34 (1H, m, H-9 anti), 1.15 (1H, m, H-9 syn), 0.89 (9H, s, SiC**Me**$_3$), 0.18 (3H, s, Si**Me**), -0.05 (3H, s, Si**Me**); NOE data (C_6D_6) δ 3.01 (2.38, 6%; 1.90, 4%), 2.88 (2.30, 6%; 1.15, 3%), 2.38 (3.01, 7%; 1.90, 8%), 2.30 (2.88, 4%), 1.90 (3.01, 5%; 2.38, 9%; 1.34, 4%), 1.67 (2.88, 5%), 1.60 (4.75, 2%; 3.01, 3%; 1.90, 3%), 1.34 (2.88, 3%; 2.30, 4%; 1.90, 5%; 1.15, 14%), 1.15 (2.88, 4%; 1.34, 12%); ^{13}C NMR (75 MHz) δ 177.8 (0, C-1 or C-3), 177.1 (0, C-1 or C-3), 147.3 (0, C-6 or CH_3**C**=CH_2), 144.0 (0, C-6 or CH_3**C**=CH_2), 132.0 (0, C-1'), 129.0 (2C, 1, C-3' and C-5'), 128.4 (1, C-4'), 126.5 (2C, 1, C-2' and C-6'), 111.8 (0, C-5), 111.0 (2, CH_3C=**C**H$_2$), 46.5 (1, C-7a), 44.5, 44.3, 42.4, 39.0 (1, C-8), 31.2 (2, C-9), 25.5 (3C, 3, SiC**Me**$_3$), 22.3 (3, **C**H$_3$C=CH_2), 18.1 (0, Si**C**Me$_3$), 13.9 (3, C-5 methyl), -3.8 (3, Si**Me**), -4.1 (3, Si**Me**); MS *m/z* (%) 380 (100, M^+ - ^{t}Bu), 207 (19), 165 (19), 91 (25), 77 (10), 75 (25), 73 (36), 59 (10), 41 (12); HRMS calcd for $C_{22}H_{26}NO_3Si$ (M^+ - ^{t}Bu): 380.1682, found: 380.1666. Anal. calcd for $C_{26}H_{35}NO_3Si$: C 71.35, H 8.06, N 3.20, found: C 70.40, H 8.35, N 3.09.

(5*R*, 8*S*, 10*R*)-7-(*tert*-Butyldimethylsilyl)oxy-5,8-dihydro-10-isopropenyl-6-methyl-2-phenyl-5,8-ethano-1*H*-[1,2,4]-triazolo[1,2-*a*]pyridazine-1,3(2*H*)-dione (277). To a solution of (-)-carvone (293 mg, 1.95 mmol) in THF (35 mL) cooled to 0 °C was added *tert*-butyldimethylsilyltrifluoromethylsulfonate (0.53 mL, 2.3 mmol) dropwise followed by NEt_3 (0.41 mL, 2.9 mmol). This was stirred at 0 °C for 30 min. Due to the instability of **273**, no purification was carried out, and it was employed immediately. To the solution containing **273** was added 4-phenyl-1,2,4-triazoline-3,5-dione[89] (490 mg, 2.8 mmol) as a solution in THF (10 mL). The reaction mixture was stirred at rt for 48 h, after which time solvent was removed by rotary evaporation. Silica gel chromatography (10% ethyl acetate/hexanes) afforded 655 mg (76%) of **277** as a white crystalline solid, mp 128–130 °C: IR (CCl_4) ν_{max} 1720 (s) cm^{-1}: $[\alpha]_D$ = +38 (c = 0.0027, benzene): ^1H NMR (C_6D_6, 300 MHz) δ 7.71 (2H, d, J = 8.1 Hz, H-2′ and H-6′), 7.10 (2H, t, J = 8.0 Hz, H-3′ and H-5′), 6.94 (1H, t, J = 7.5 Hz, H-4′), 4.82 (1H, d, J = 3.0 Hz, H-8), 4.72 (1H, s, $CH_3C{=}C\mathbf{H}_2$), 4.68 (1H, s, $CH_3C{=}C\mathbf{H}_2$), 4.60 (1H, t, J = 3.0 Hz, H-5), 2.69 (1H, m, H-10), 1.95 (1H, m, H-11), 1.60 (3H, s, C-6 methyl), 1.47 (3H, s, $C\mathbf{H}_3C{=}CH_2$), 1.07 (1H, m, H-11), 0.90 (9H, s, $SiC\mathbf{Me}_3$), 0.28 (3H, s, $Si\mathbf{Me}$), 0.04 (3H, s, $Si\mathbf{Me}$); ^{13}C NMR (75 MHz) δ 155.7 (0, C-1 or C-3), 155.0 (0, C-1 or C-3), 144.2 (0, C-7 or $CH_3\mathbf{C}{=}CH_2$), 144.0 (0, C-7 or $CH_3\mathbf{C}{=}CH_2$), 131.5 (0, C-1′), 129.0 (2C, 1, C-3′ and C-5′), 128.0 (1, C-4′), 125.3 (2C, 1, C-2′ and C-6′), 113.5 (0, C-6), 112.0 (2, $CH_3C{=}\mathbf{C}H_2$), 58.0 (1, C-8), 56.1 (1, C-5), 42.6 (1, C-10), 29.8 (2, C-11), 25.4 (3C, 3, $SiC\mathbf{Me}_3$), 21.4 (3, $\mathbf{C}H_3C{=}CH_2$), 18.0 (0, $Si\mathbf{C}Me_3$),



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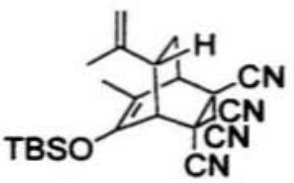
12.7 (3, C-6 methyl). -4.3 (3, SiMe). -4.6 (3. SiMe); MS *m/z* (%) 439 (14, M^+), 372 (16), 371 (16), 263 (28), 224 (23), 205 (28), 168 (10), 167 (17), 119 (13), 99 (10), 91 (22), 75 (29), 73 (100), 59 (19), 57 (12), 41 (21); HRMS calcd for $C_{24}H_{33}N_3O_3Si$: 439.2291, found: 439.2278. Anal. calcd for $C_{24}H_{33}N_3O_3Si$: C 65.57, H 7.57, N 9.56, found: C 65.59, H 7.55, N 9.37. The structure of **277** was determined by X-ray crystallography.

Diels-Alder reaction of diene 273 with tetracyanoethene. To a solution of (-)-carvone (1.09 g, 7.26 mmol) in THF (40 mL) cooled to 0 °C was added *tert*-butyldimethylsilyltrifluoromethylsulfonate (2.02 mL, 8.80 mmol) dropwise followed by NEt_3 (1.53 mL, 11.0 mmol). This was stirred at 0 °C for 30 min. Due to the instability of **273**. no purification was carried out. and it was employed immediately. To the solution containing **273** was added tetracyanoethene (1.37 g, 10.7 mmol) as a solution in THF (20 mL). The reaction mixture was stirred at rt for 48 h, after which time the solution was washed with H_2O (100 mL) and brine (100 mL) and dried over $MgSO_4$. Silica gel chromatography (10% ethyl acetate/hexanes) afforded 2.07 g (73%) of **278** as a white solid and 547 mg (19%) of **279** as a white solid.



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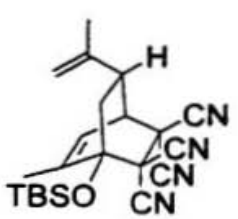
For **(1*R*,4*R*,7*R*)-6-(*tert*-Butyldimethylsilyl)oxy-2,2,3,3-tetracyano-7-isopropenyl-5-methylbicyclo[2.2.2]oct-5-ene (278).** White solid, mp 88–90 °C; IR (CCl_4) ν_{max} 2250 (s), 1677 (s) cm^{-1}; $[\alpha]_D$ = +8 (c = 0.0026, benzene); ^1H NMR (300 MHz) δ 4.96 (1H, s, $CH_3C=CH_2$), 4.80 (1H, s, $CH_3C=CH_2$), 3.36 (1H, t, *J* = 2.7 Hz, H-4), 3.18 (1H, d, *J* = 1.8 Hz, H-1), 2.87 (1H, t, *J* = 7.4 Hz, H-7), 2.37 (1H, m,

H-8), 1.89 (3H, s, C-5 methyl), 1.79 (3H, s. C**H**$_3$C=CH$_2$), 1.63 (1H, m, H-8), 0.96 (9H, s, SiC**Me**$_3$), 0.27 (3H, s, Si**Me**), 0.25 (3H, s, Si**Me**); ^{13}C NMR (75 MHz) δ 144.4 (0, C-6 or CH$_3$**C**=CH$_2$), 143.5 (0, C-6 or CH$_3$**C**=CH$_2$), 113.5 (0, C-5), 112.7 (2, CH$_3$C=**C**H$_2$), 111.7, 111.6, 111.4, 111.3, 49.2 (0, C-2 or C-3), 47.5 (0, C-2 or C-3), 44.5, 43.1, 38.2, 26.6 (2, C-8), 25.4 (3C, 3, SiC**Me**$_3$), 21.7 (3, C-5 methyl), 18.2 (0, Si**C**Me$_3$), 14.7 (3, **C**H$_3$C=CH$_2$), -3.5 (3, Si**Me**), -3.7 (3, Si**Me**); MS *m/z* (%) 335 (39, M$^+$ - ^{t}Bu), 208 (20), 207 (100), 165 (44), 133 (12), 91 (25), 75 (57), 73 (98), 68 (10), 59 (28), 57 (24), 45 (11), 43 (13), 41 (32); HRMS calcd for $C_{18}H_{19}N_4OSi$ (M$^+$ - ^{t}Bu): 335.1328, found: 335.1317. Anal. calcd for $C_{22}H_{28}N_4OSi$: C 67.31, H 7.19, N 14.27, found: C 67.22, H 7.11, N 14.22.



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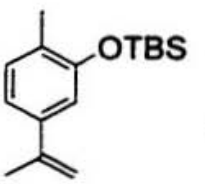
For (1*R*,4*R*,7*S*)-4-(*tert*-Butyldimethylsilyl)oxy-2,2,3,3-tetracyano-7-isopropenyl-5-methylbicyclo[2.2.2]oct-5-ene (279). White solid, mp 135–136 °C; IR (CCl_4) ν_{max} 2256 (s), 1649 (s) cm^{-1}; $[\alpha]_D$ = +6 (c = 0.0020, benzene): ^{1}H NMR (300 MHz) δ 6.09 (1H, d, *J* = 6.2 Hz, H-6), 4.94 (1H, s, CH$_3$C=C**H**$_2$), 4.68 (1H, s, CH$_3$C=C**H**$_2$), 3.37 (1H, d, *J* = 6.6 Hz, H-1), 2.99 (1H, dd, *J* = 9.2, 6.3 Hz, H-7), 2.59 (1H, dd, *J* = 13.4, 9.8 Hz, H-8), 2.03 (3H, s, C-5 methyl), 1.75 (3H, s, C**H**$_3$C=CH$_2$), 1.65 (1H, dd, *J* = 13.2, 6.0 Hz, H-8), 1.03 (9H, s, SiC**Me**$_3$), 0.39 (3H, s, Si**Me**), 0.27 (3H, s, Si**Me**); ^{13}C NMR (75 MHz) δ 146.2 (0, C-5 or CH$_3$**C**=CH$_2$), 143.3 (0, C-5 or CH$_3$**C**=CH$_2$), 122.3 (1, C-6), 113.3 (2, CH$_3$C=**C**H$_2$), 111.6, 111.5, 111.5, 110.9, 82.0 (0, C-4), 49.9 (0, C-2 or C-3), 44.7 (0, C-2 or C-3), 42.4 (1, C-1), 39.0 (1, C-7), 33.5 (2, C-8), 25.5 (3C, 3, SiC**Me**$_3$), 21.6 (3, **C**H$_3$C=CH$_2$), 18.5 (0, Si**C**Me$_3$), 17.8 (3, C-5 methyl), -1.5 (3, Si**Me**), -2.2 (3, Si**Me**); MS *m/z* (%) 335 (4, M$^+$ - ^{t}Bu), 264 (34), 249 (12), 223 (15), 207 (26), 205 (12), 165 (22), 133

(14), 128 (29), 91 (17), 76 (31), 75 (84), 73 (100), 69 (12), 59 (21), 57 (14), 41 (17); HRMS calcd for $C_{18}H_{19}N_4OSi$ (M^+ - ^{t}Bu): 335.1328, found: 335.1330. Anal. calcd for $C_{22}H_{28}N_4OSi$: C 67.31, H 7.19, N 14.27, found: C 67.17, H 7.38, N 13.90.



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1-(*tert*-Butyldimethylsilyl)oxy-5-isopropenyl-2-methylbenzene (283). To a solution of (-)-carvone (328 mg, 2.19 mmol) in THF (35 mL) cooled to 0 °C was added *tert*-butyldimethylsilyltrifluoromethylsulfonate (0.63 mL, 2.7 mmol) dropwise followed by NEt_3 (0.48 mL, 3.4 mmol). This was stirred at 0 °C for 30 min and solvent was removed under reduced pressure. Due to the instability of **273**, no purification was carried out, and it was employed immediately. To the solution containing **273** was added tetraphenylporphyrin (*ca.* 10 mg) as a solution in CH_2Cl_2 (50 mL). The reaction mixture was cooled to –78 °C and O_2 was bubbled through while irradiating with a 150 W sunlamp for 3 h. Silica gel chromatography (10% ethyl acetate/hexanes) afforded 245 mg of (-)-carvone and 47 mg (33% based on recovered starting material) of **283** as a yellow oil; IR ν_{max} 3086 (s) cm^{-1}; ^{1}H NMR (300 MHz) δ 7.08 (1H, d, J = 7.8 Hz, H-3), 6.98 (1H, dd, J = 7.8, 1.8 Hz, H-4), 6.88 (1H, d, J = 1.8 Hz, H-6), 5.29 (1H, s, CH_3C=C**H**$_2$), 5.01 (1H, s, CH_3C=C**H**$_2$), 2.19 (3H, s, Ar**CH**$_3$), 2.11 (3H, s, **CH**$_3$C=CH_2), 0.86 (9H, s, SiC**Me**$_3$), 0.22 (3H, s, Si**Me**), 0.01 (3H, s, Si**Me**); ^{13}C NMR (75 MHz) δ 153.0 (0, C-1), 143.0 (0), 140.0 (0), 130.6 (1, C-3), 128.2 (0), 118.2 (1, C-4), 115.8 (1, C-6), 111.5 (2, CH_3C=**C**H_2), 25.7 (3C, 3, SiC**Me**$_3$), 21.8 (3, **C**H_3C=CH_2), 18.3 (0, Si**C**Me_3), 16.6 (3, C-2 methyl), -2.9 (3, Si**Me**), -4.2 (3, Si**Me**); MS *m/z* (%) 262 (23, M^+), 206 (24),

205 (100), 131 (12), 91 (11), 75 (10), 73 (11); HRMS calcd for $C_{16}H_{26}OSi$: 262.1753, found: 262.1774.

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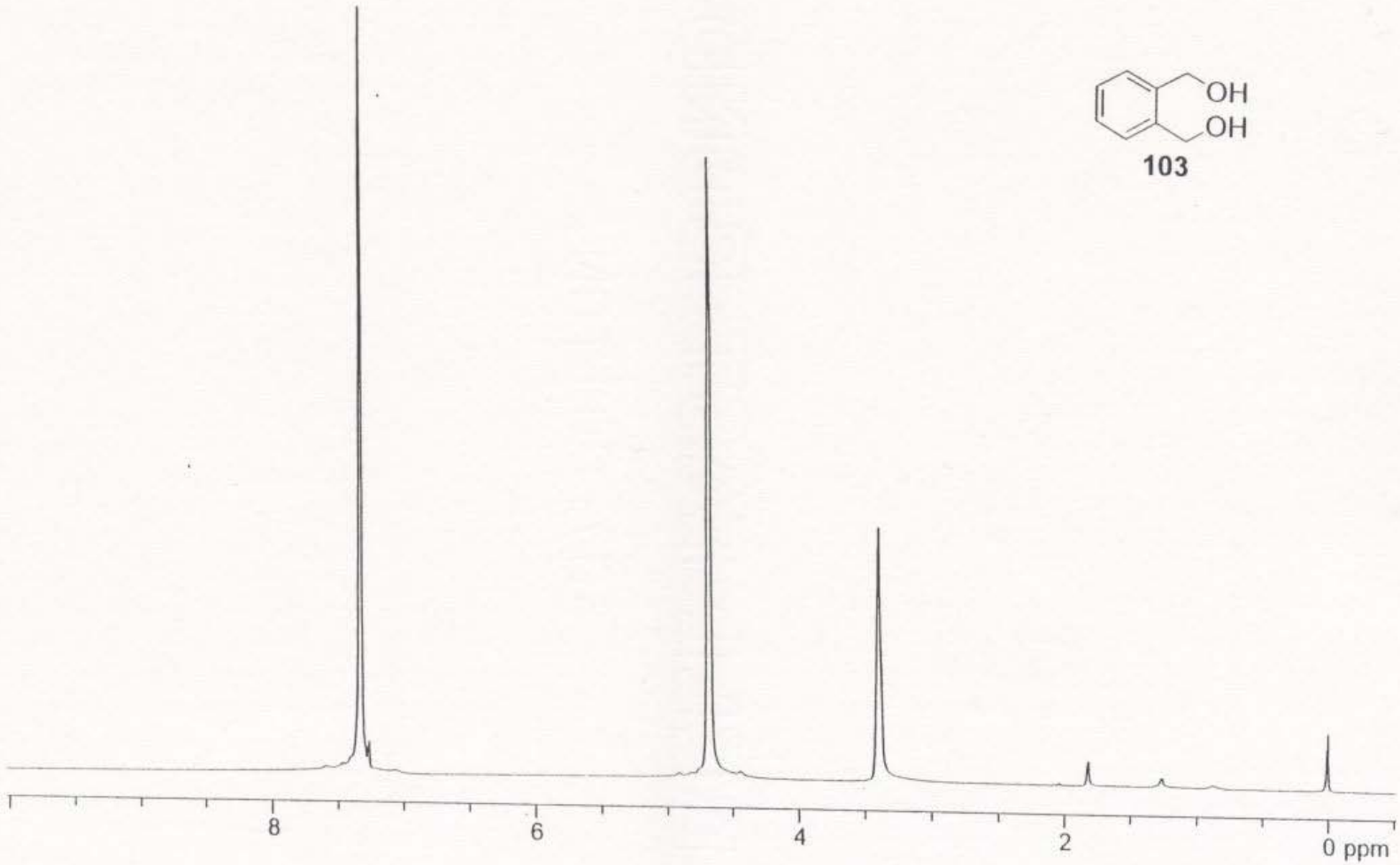
Appendix I

^{1}H and ^{19}F NMR Spectra and X-ray Structures for Chapter 1

^{1}H NMR spectra for compounds **103**, **103a**, **104**, **105**, **105a**, **106**, **108**, **77**, **109**, **110**, **114a**, **117**, **118a**, **118**, **119**, **120**, **122**, **123**, **124**, **129**, **93**, **131**, **132**, **133**, **134a**, **134b**, **135**, **136**, **120a**, **137**, **138**, **139a**, **140**, **141**, **142**, **143**, **145**, **146**, **147**, **155**, **156**, **157**, **158**, **159**, **160**, **162**, **163**, **164**, **165**, **166**, **167**, **168**, **169**, **170**, **171**, **172**, **173**, **174**, **175**, **176**, **177**, **178**, **179**, **180**, **181**, **182**, **183**, **185**, **186**, **188**, **189**, **191** (in both $CDCl_3$ and C_6D_6), **192**, **193**, **194**, **195**, **196**, **197**, **198**, **199**, **200**, **200a**, **200b**, **203**, **205**, **206**, **207**, **208/209** (inseparable mixture), **210**, **211**, **212**, **213** (in both $CDCl_3$ and CD_3COCD_3), **214**, **215**, **216**, **217**, **218**, **219**, **220**, **221**, **222**, **223** (in both CD_3COCD_3 and C_6D_6), **224**, **227**, **228**, **229**, **230**, **231**, **232**, **233**, **234**, **235**, **236a**, **236b**, **236c**, **236d**, **237**, **238**, **239**, **240**, **241a/241b** (ring-opened and ring-closed forms), **242a/242b** (ring-opened and ring-closed forms), **243**, **244a/244b** (ring-opened and ring-closed forms), **245**, **246**, **247**, **248**, **249**, **250**, **252**, **257**, **258**, **259**, **260** and **261**.

^{19}F NMR spectra for compound **139a**.

X-ray structures for compounds **139a**, **143**, **213**, **214**, **224** and **261**.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OH
103
8
6
4
2
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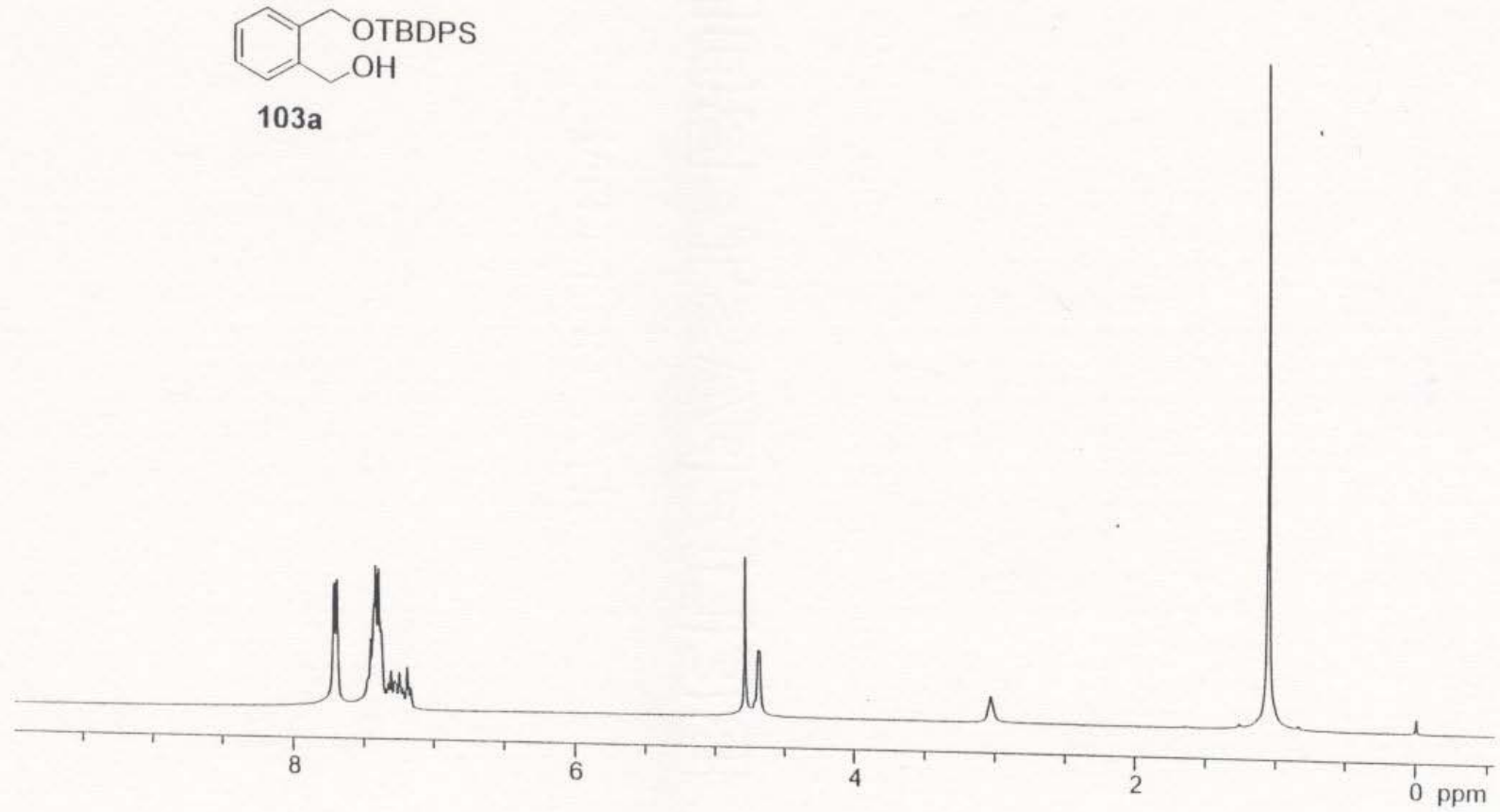
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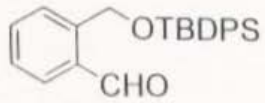
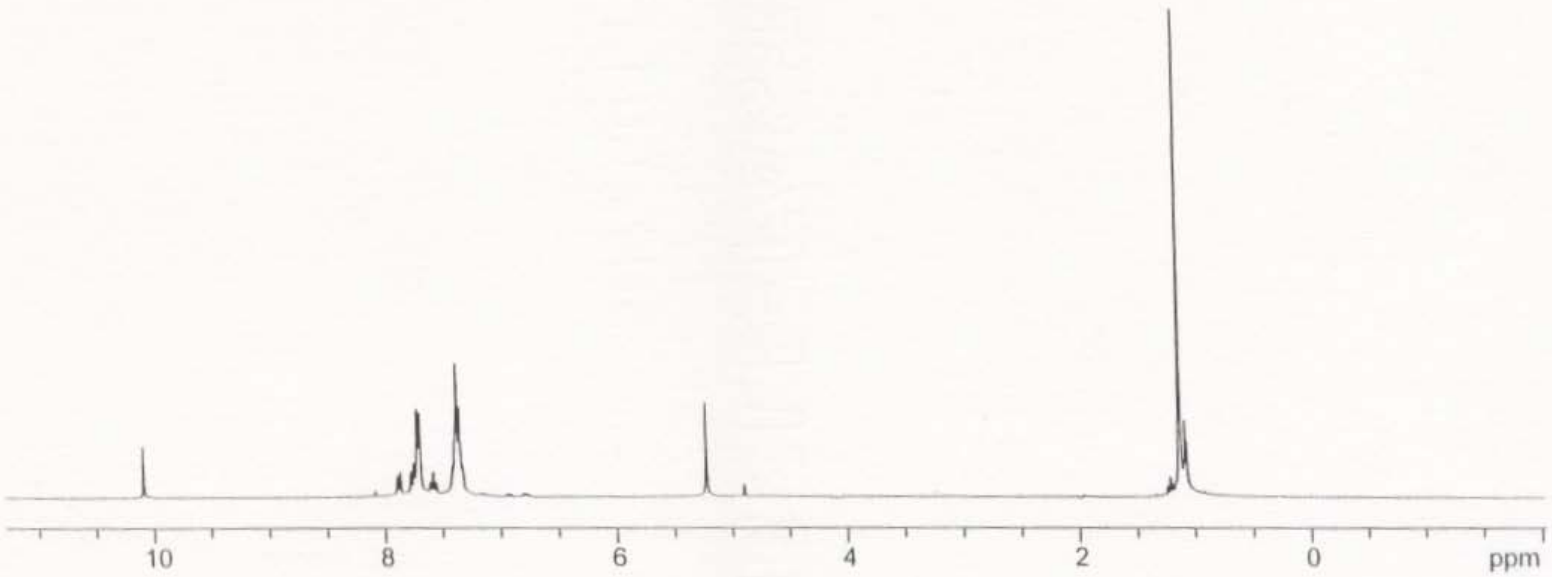
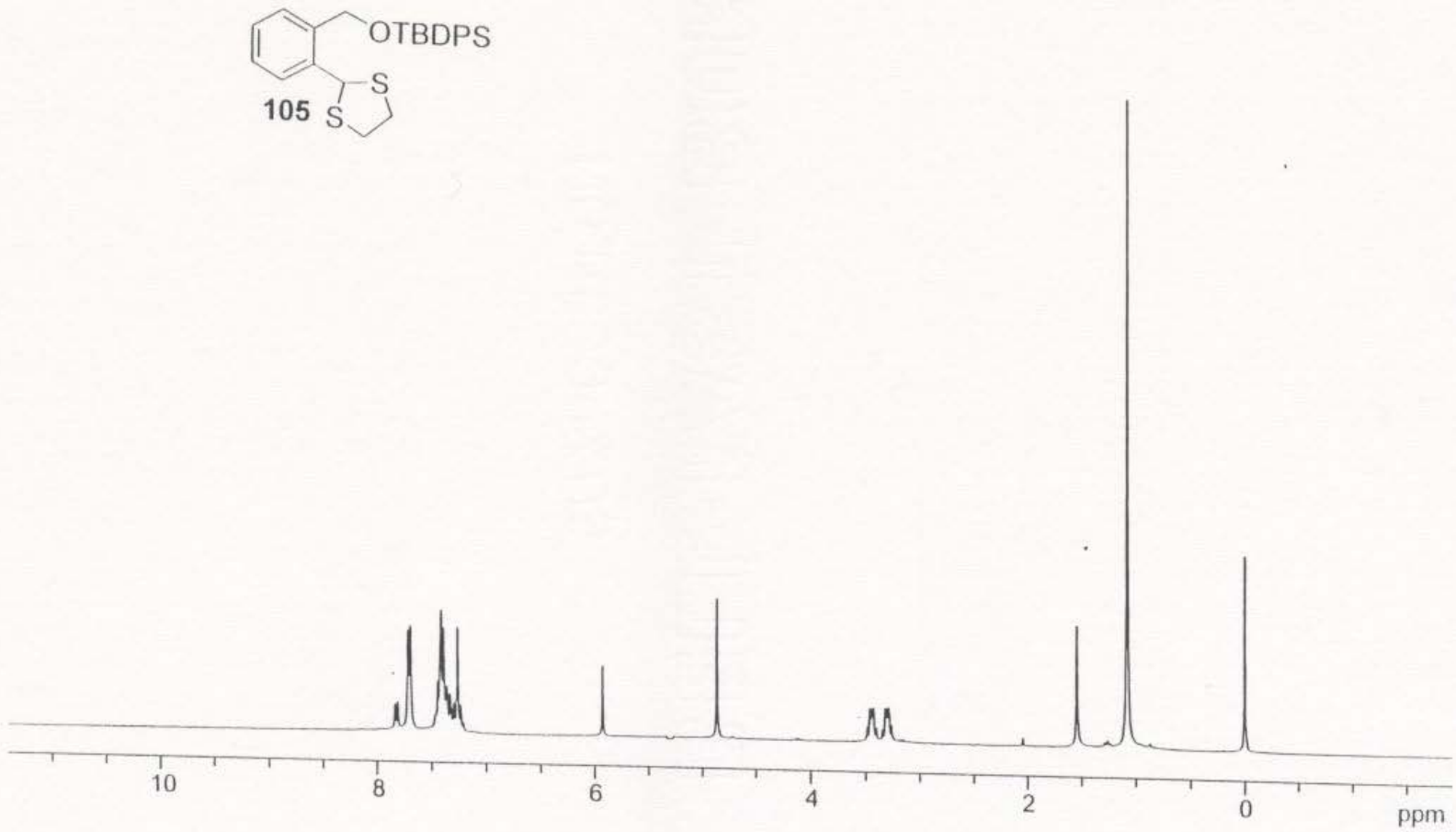


104

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S
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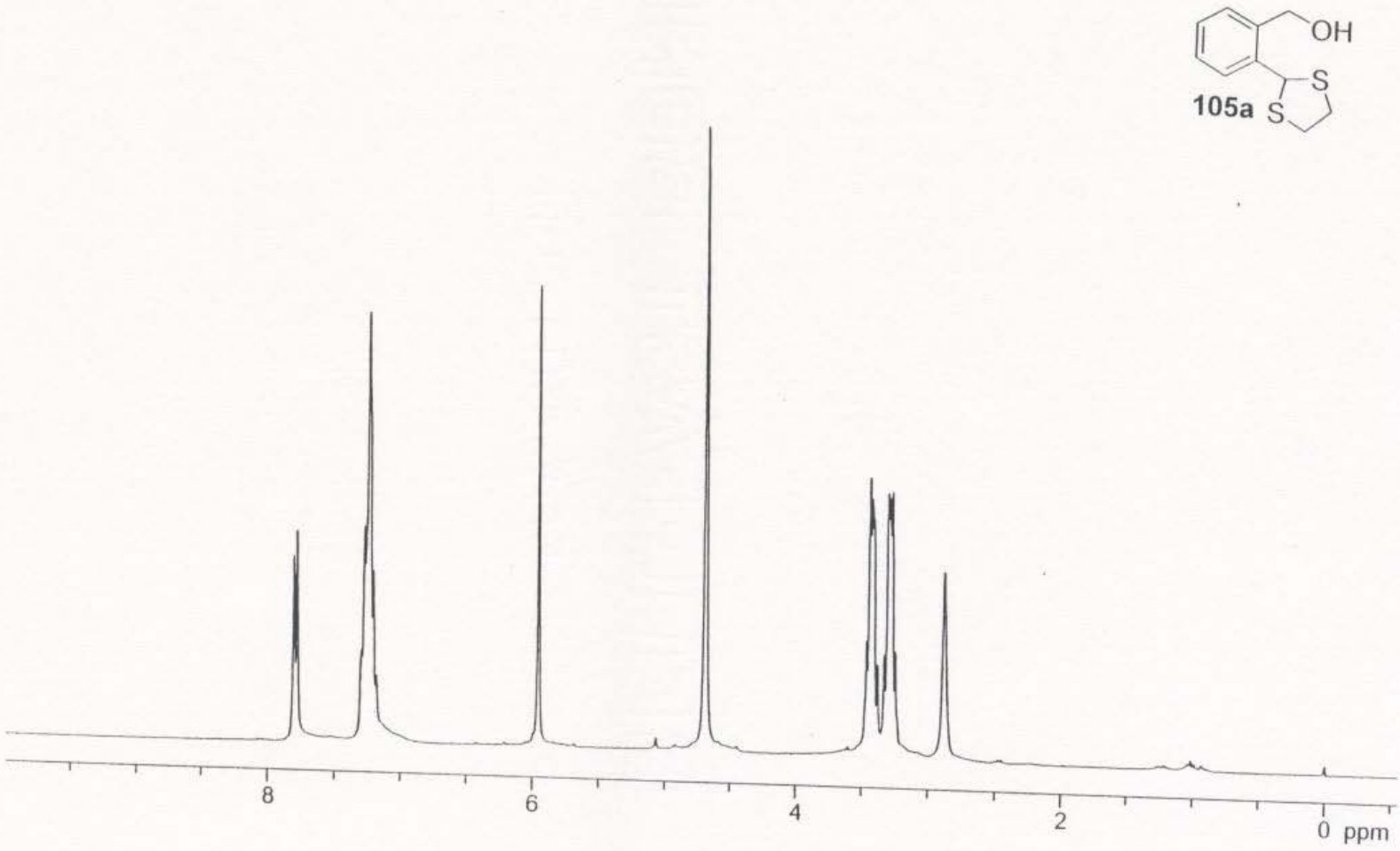
10
8
6
4
2
0
ppm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S
S
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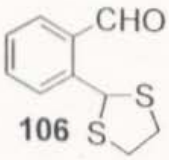
4
2
0 ppm



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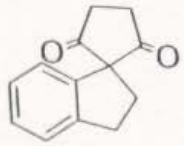

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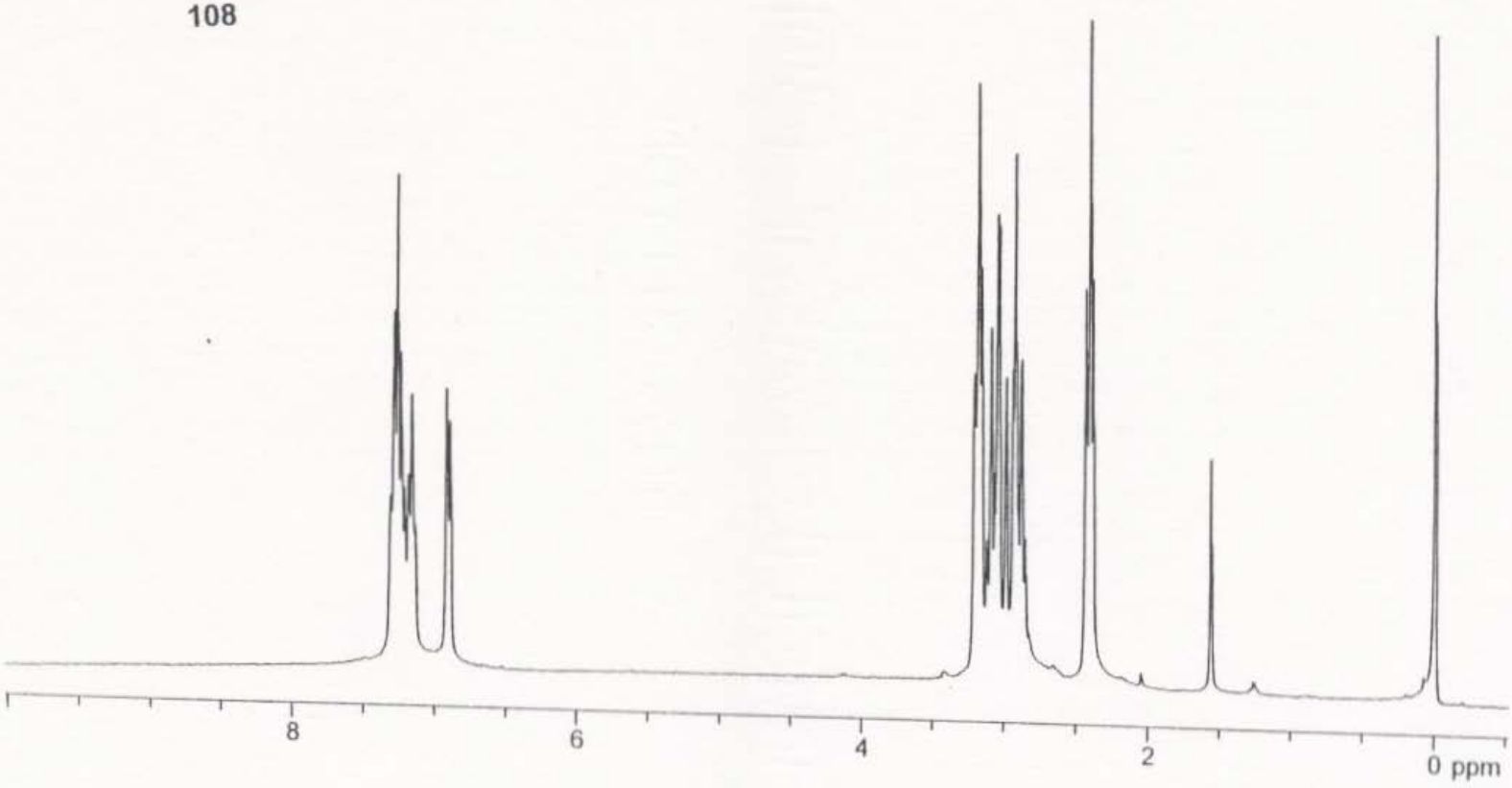

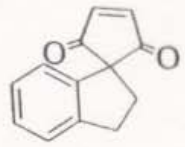

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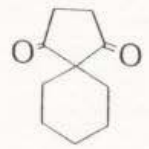

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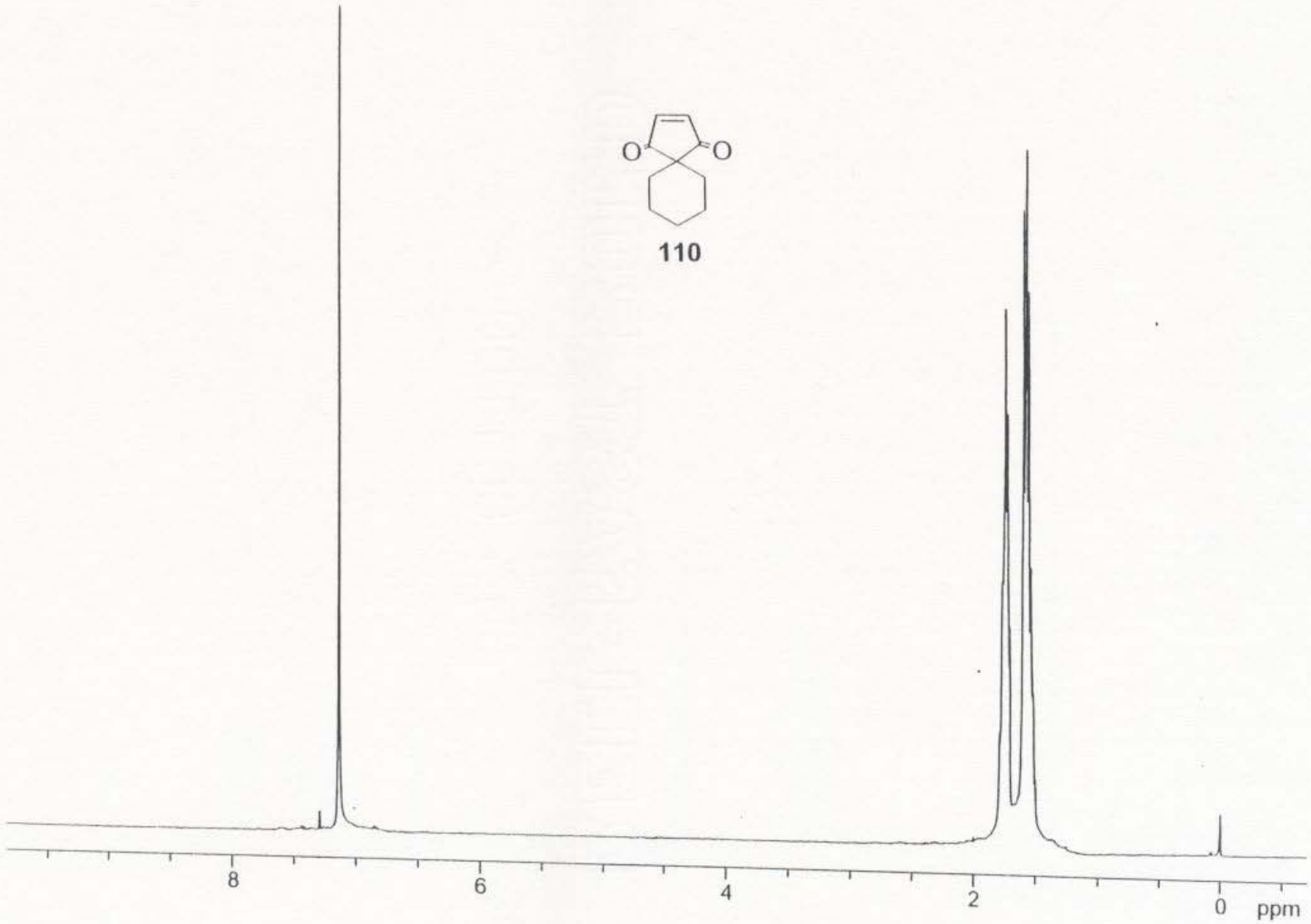

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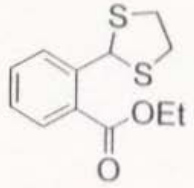

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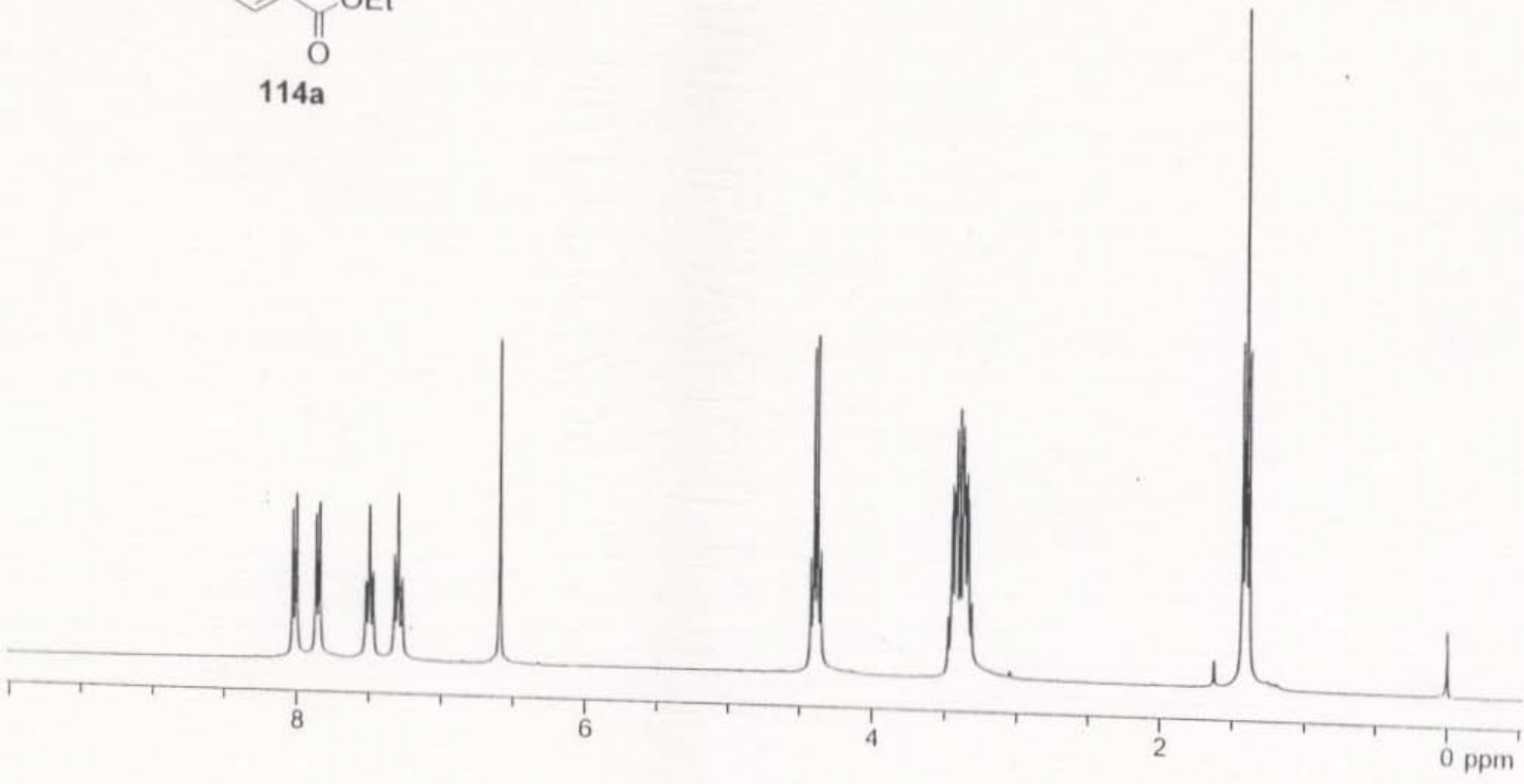

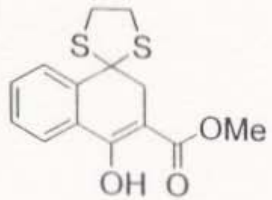

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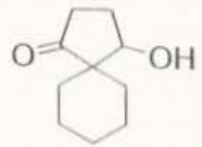

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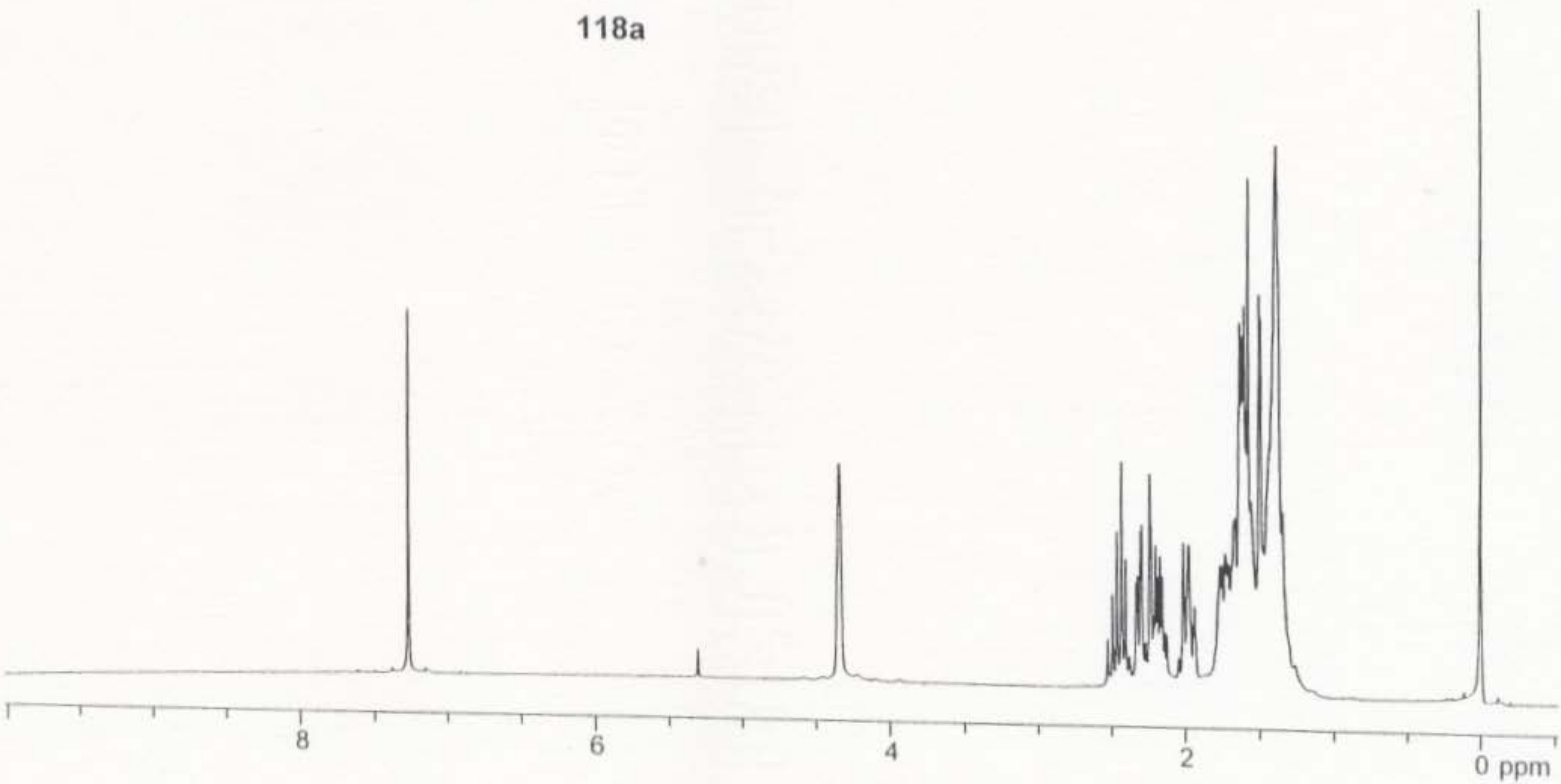

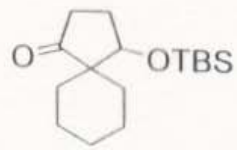

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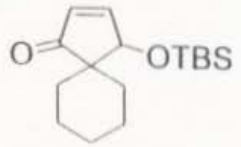

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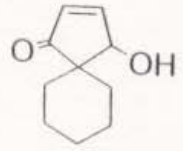

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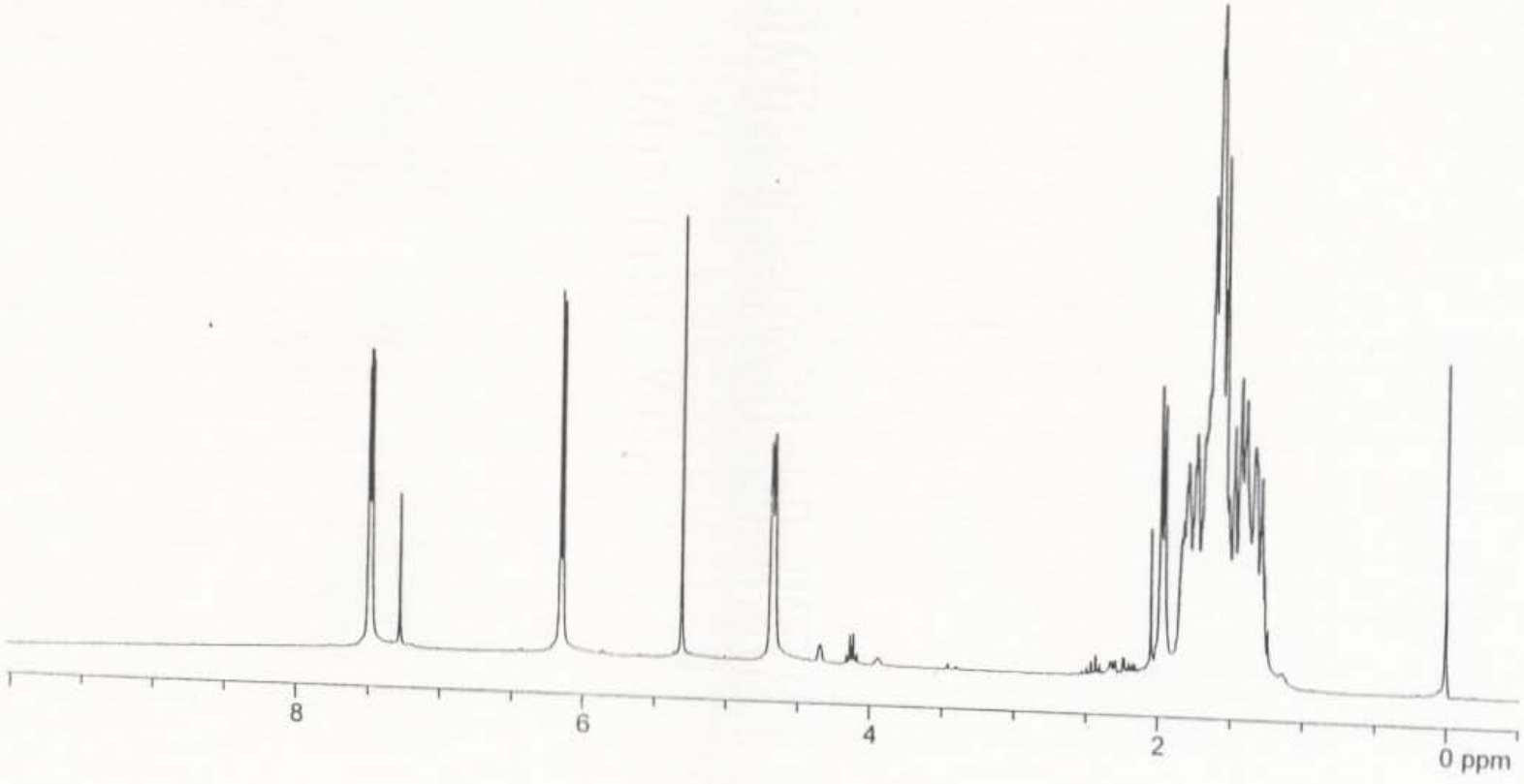

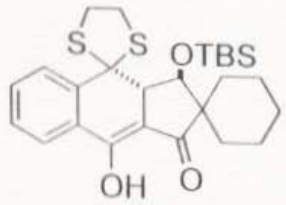

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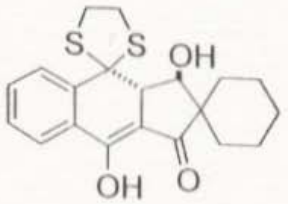

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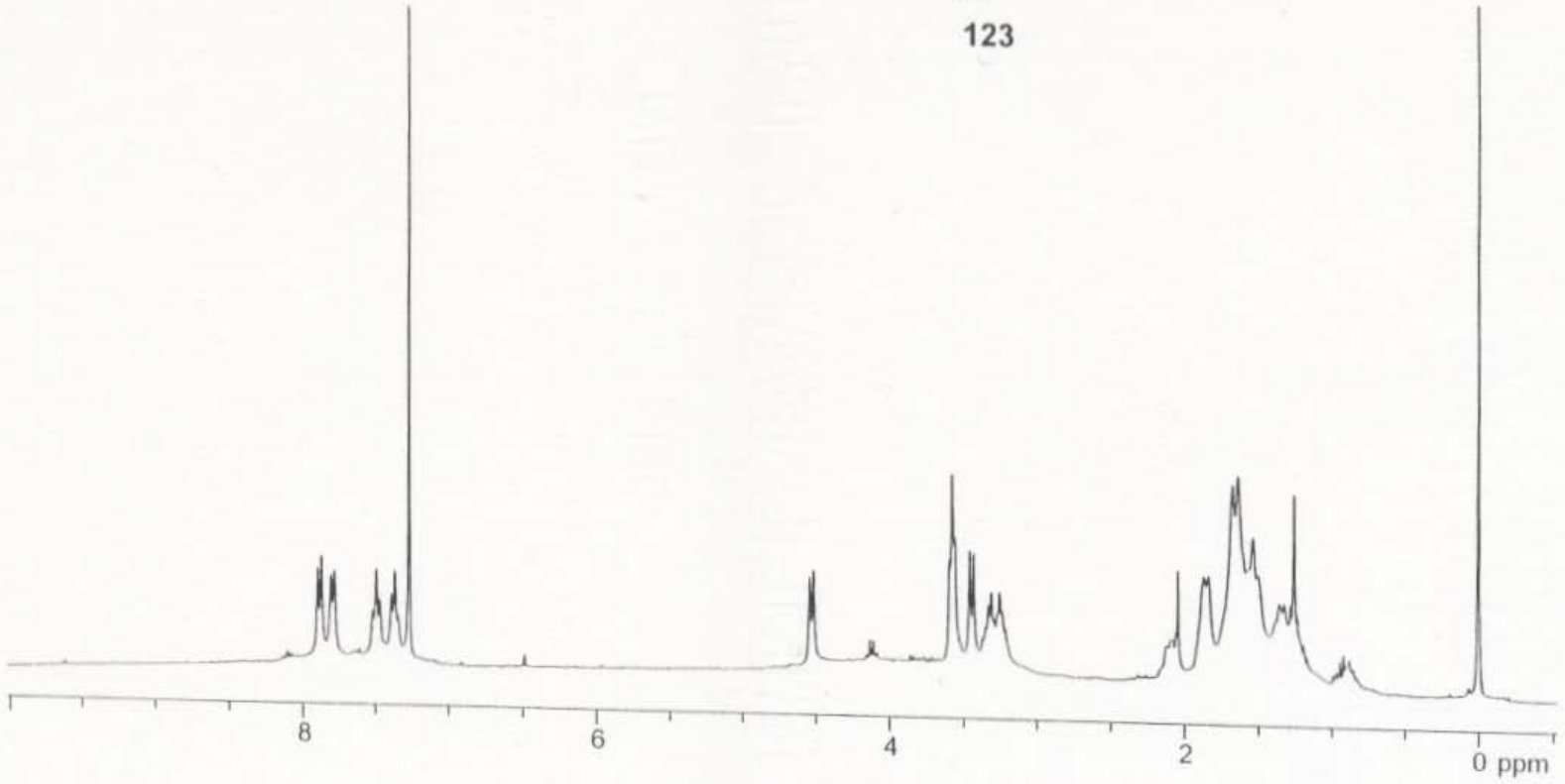

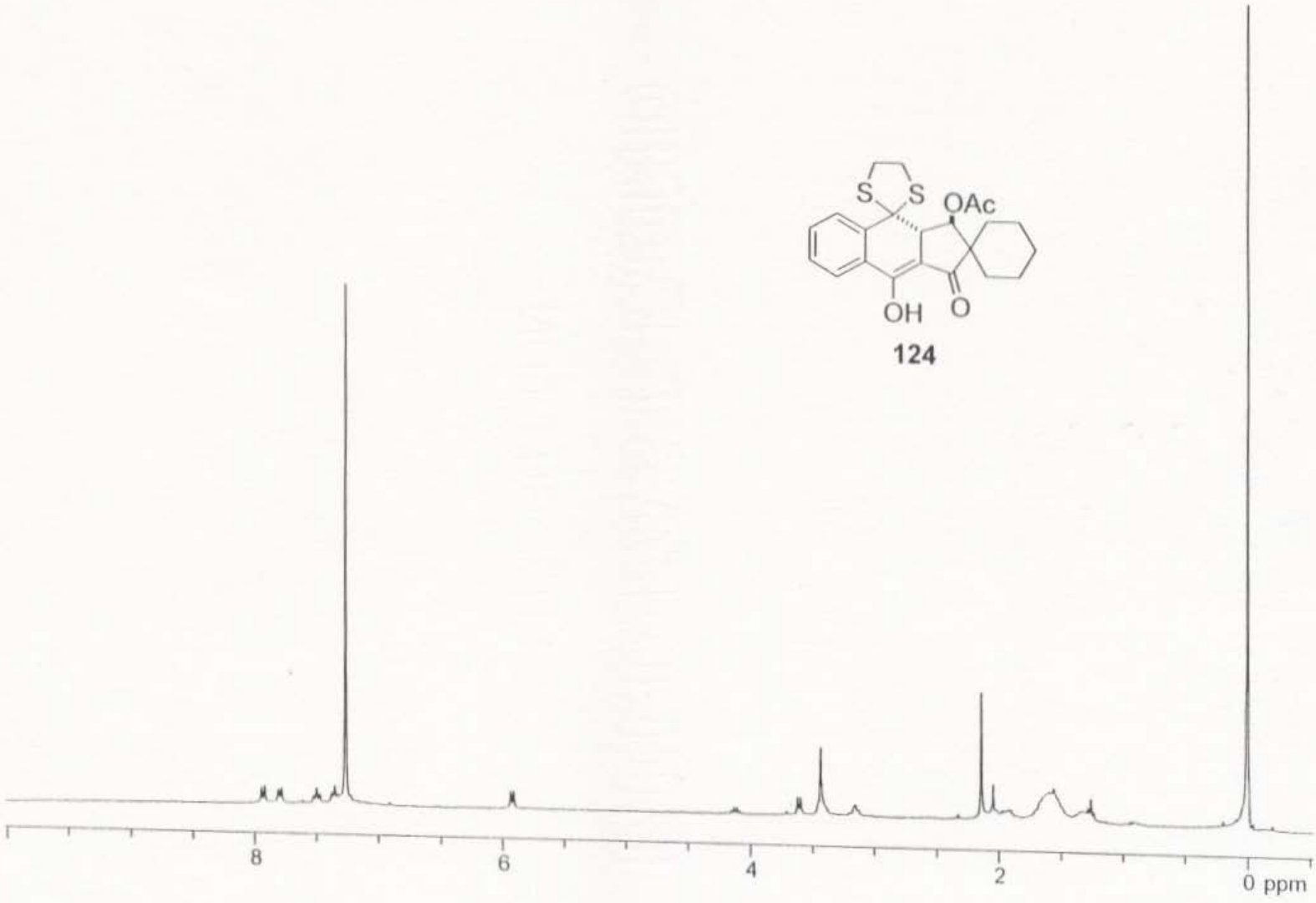

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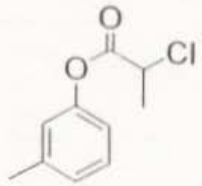

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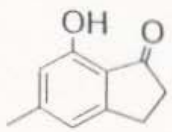

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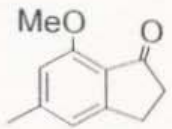

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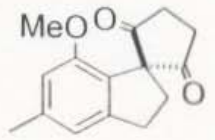

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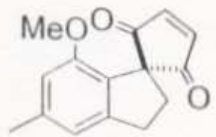

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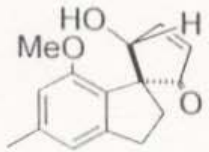

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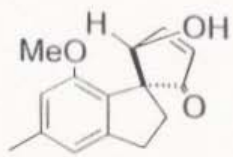

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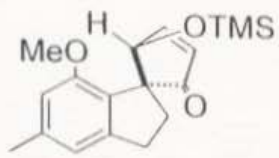

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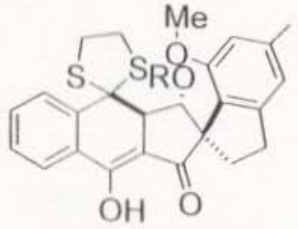
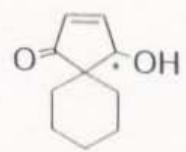
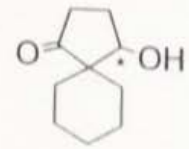


136 R = TMS



120a



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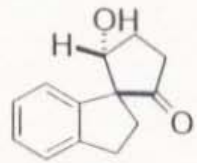

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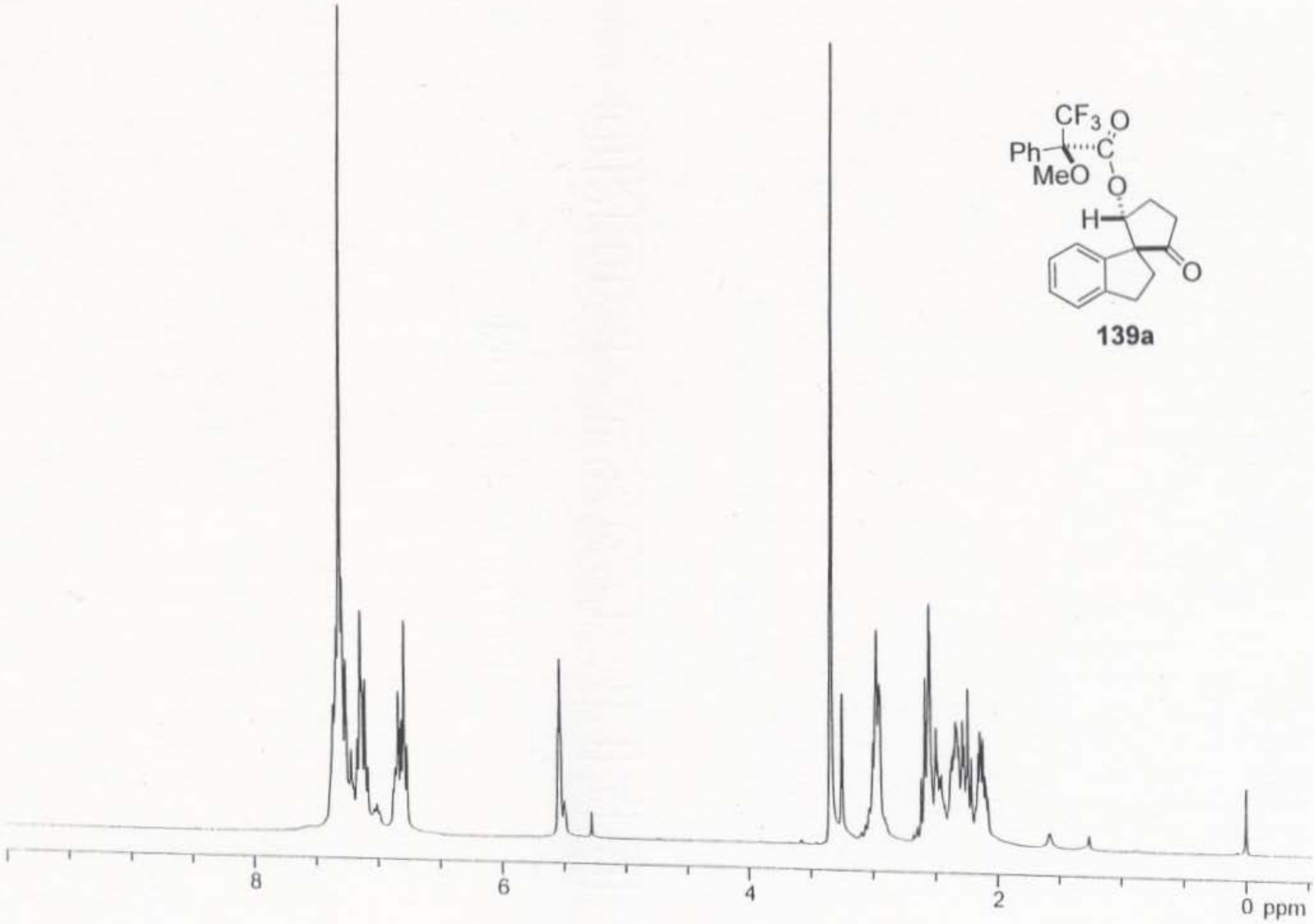
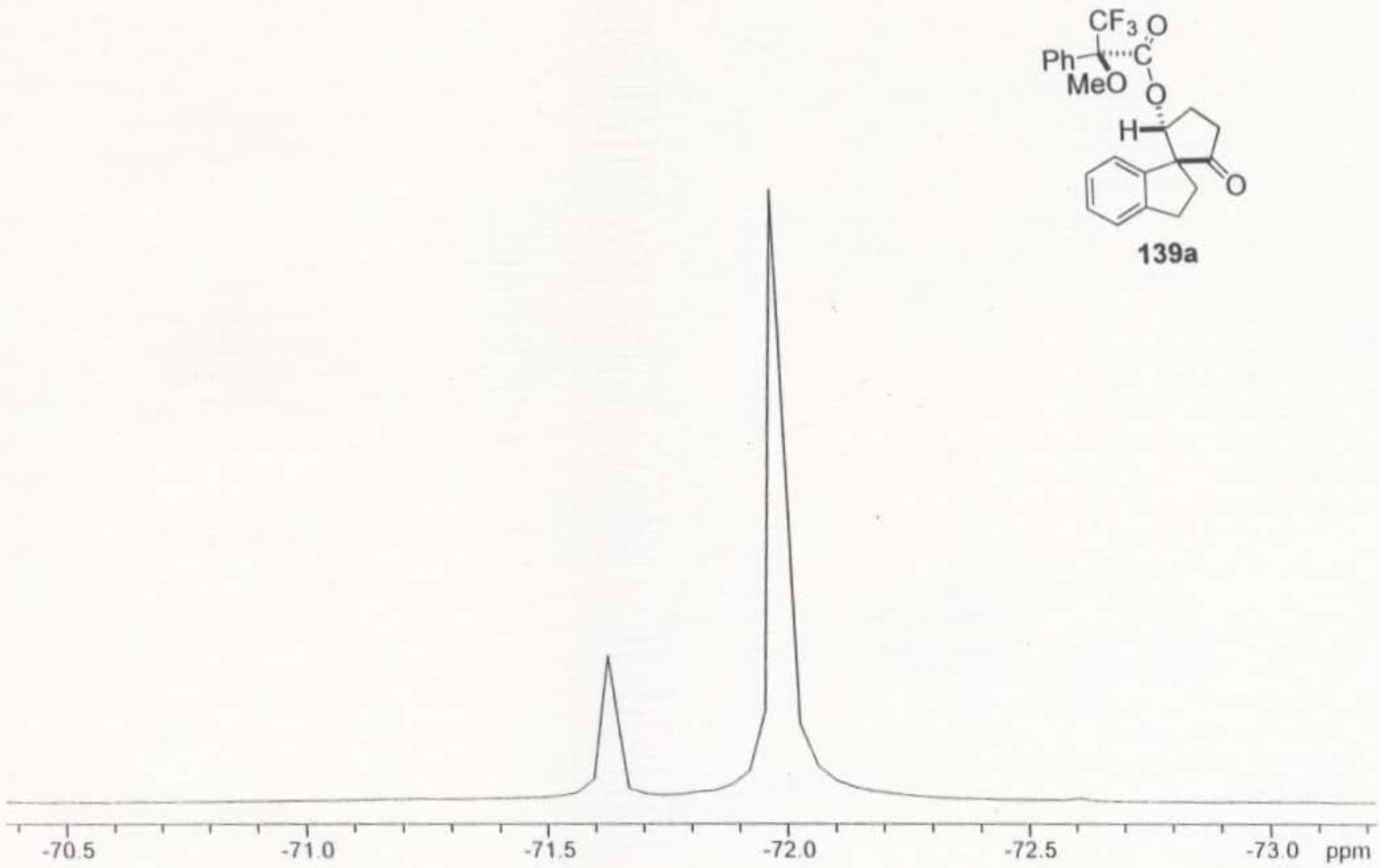
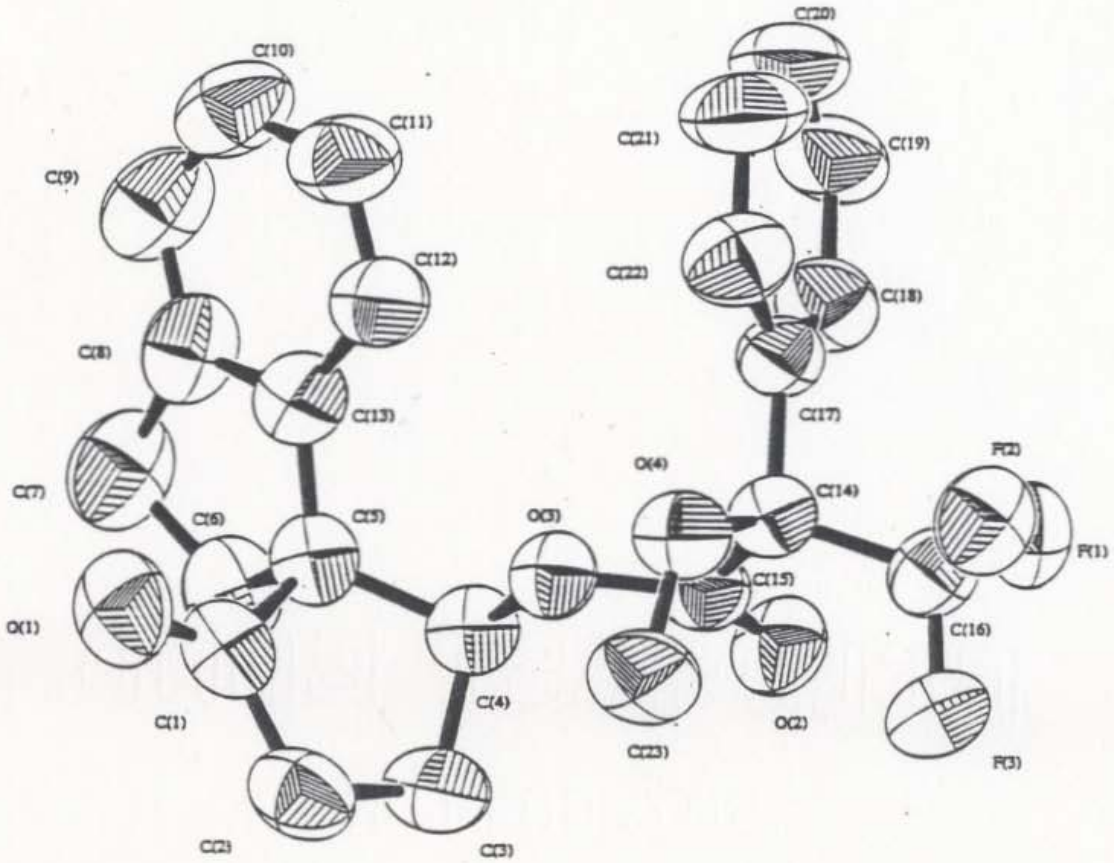
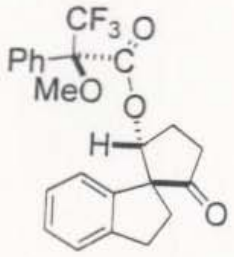


139a



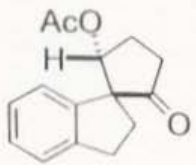
139a



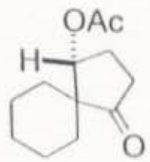


139a

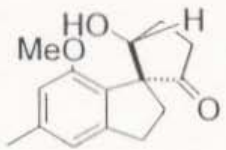
X-ray crystal structure (ORTEP) for **139a**



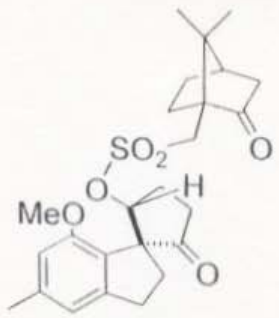
140



141



142



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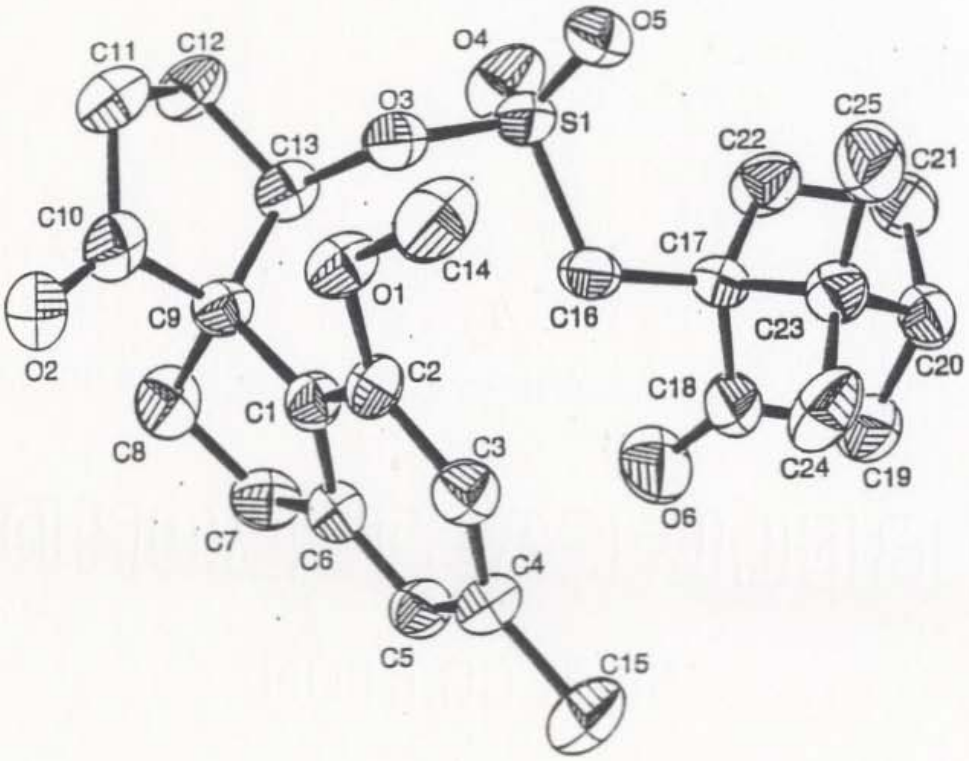
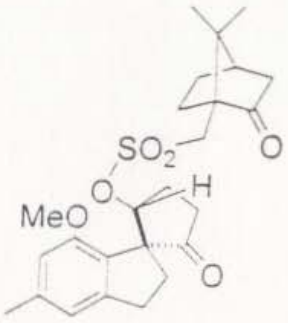
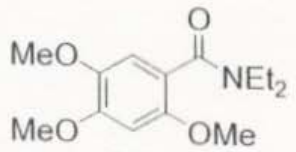


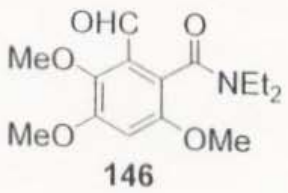


143

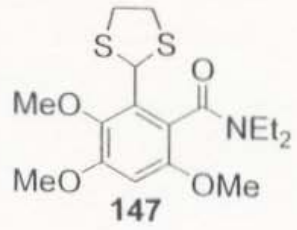
X-ray crystal structure (ORTEP) for **143**



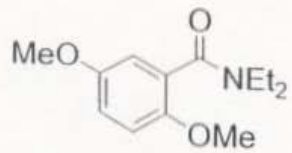
145



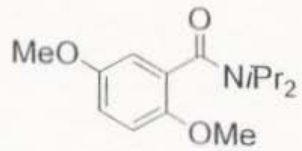
146



147



155



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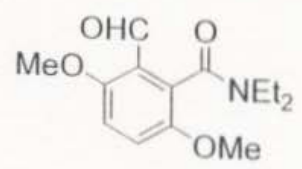
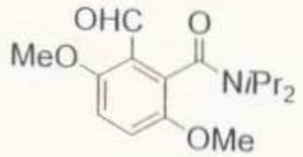


157



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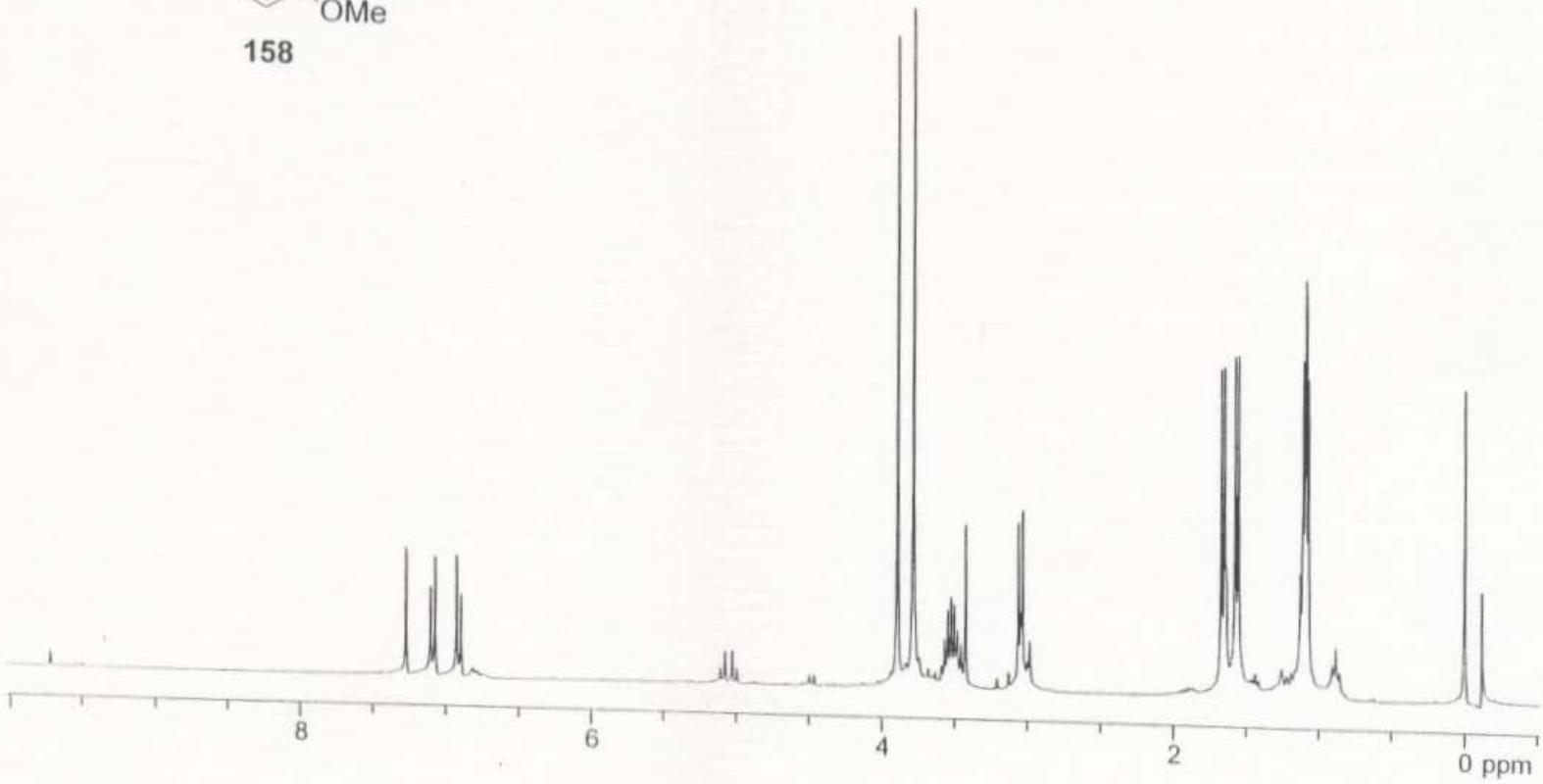

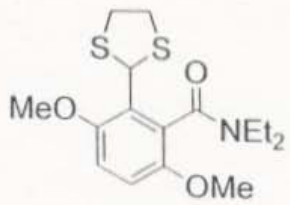

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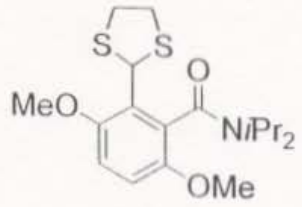

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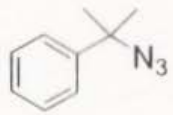

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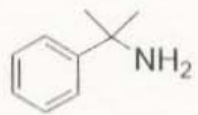

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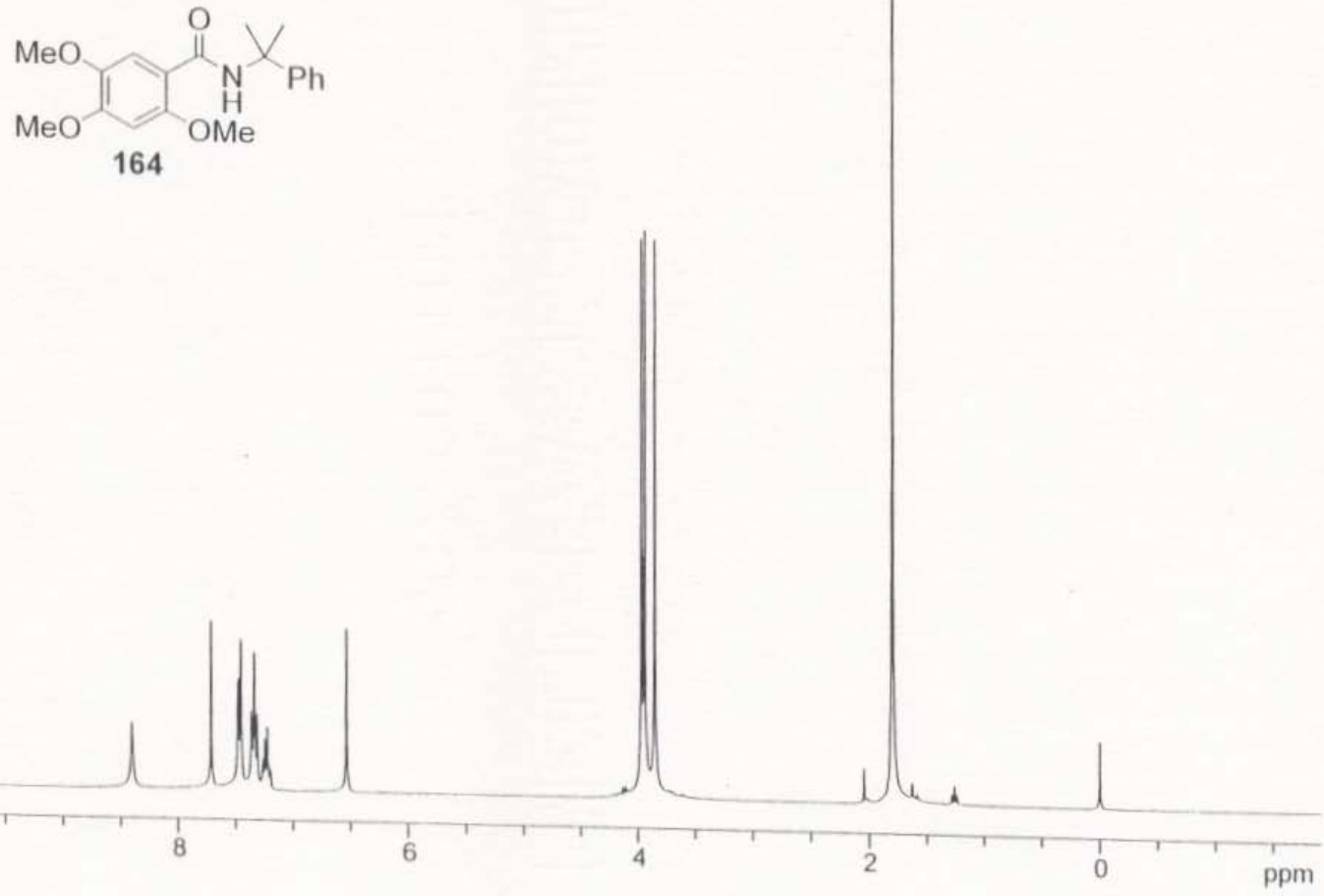
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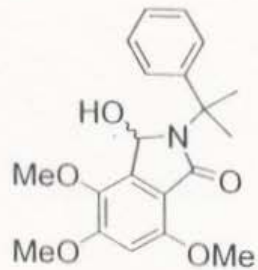

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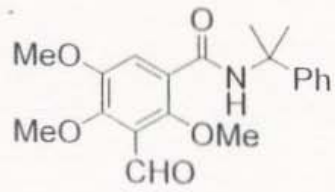

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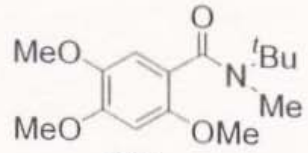

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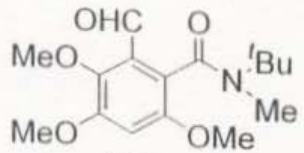

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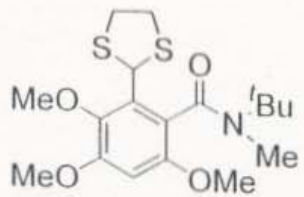

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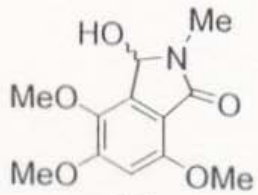

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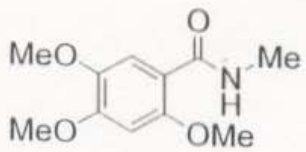

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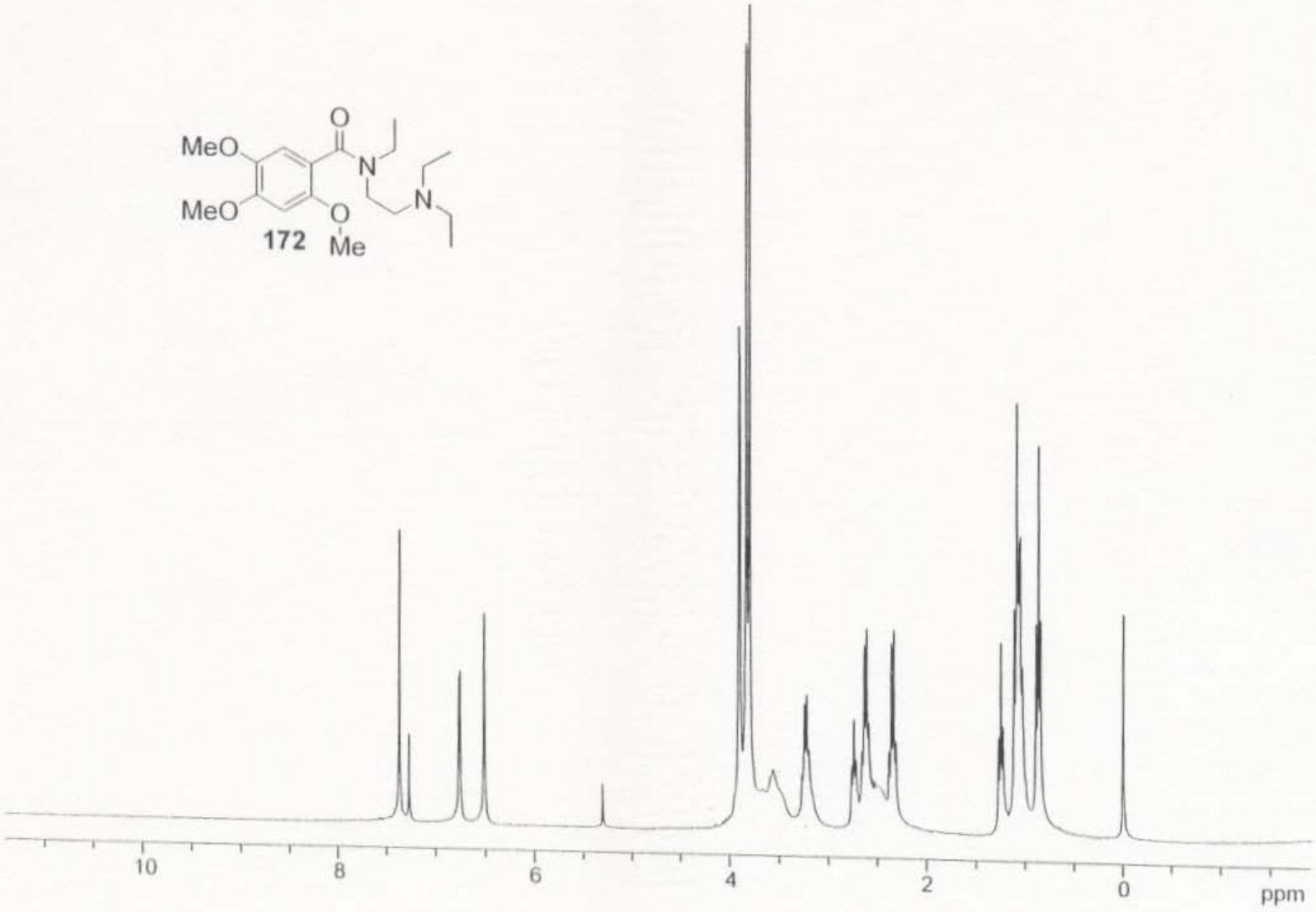
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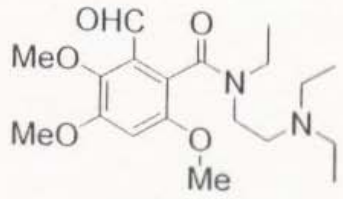

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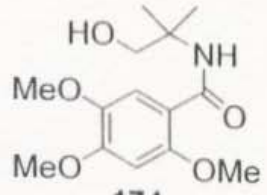

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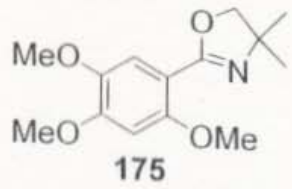

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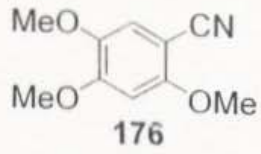

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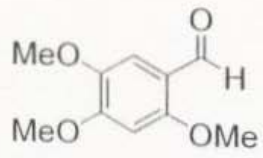

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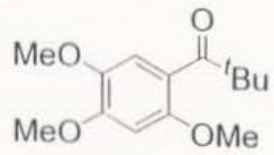

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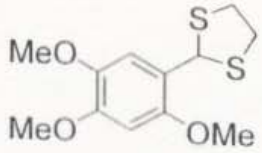

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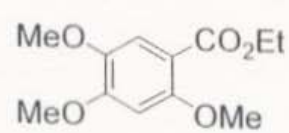

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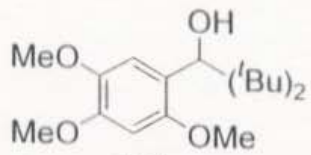

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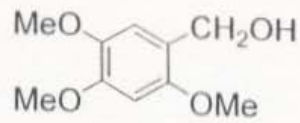

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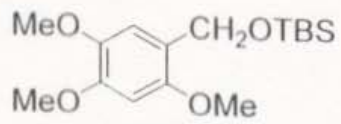

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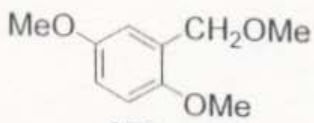

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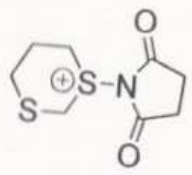

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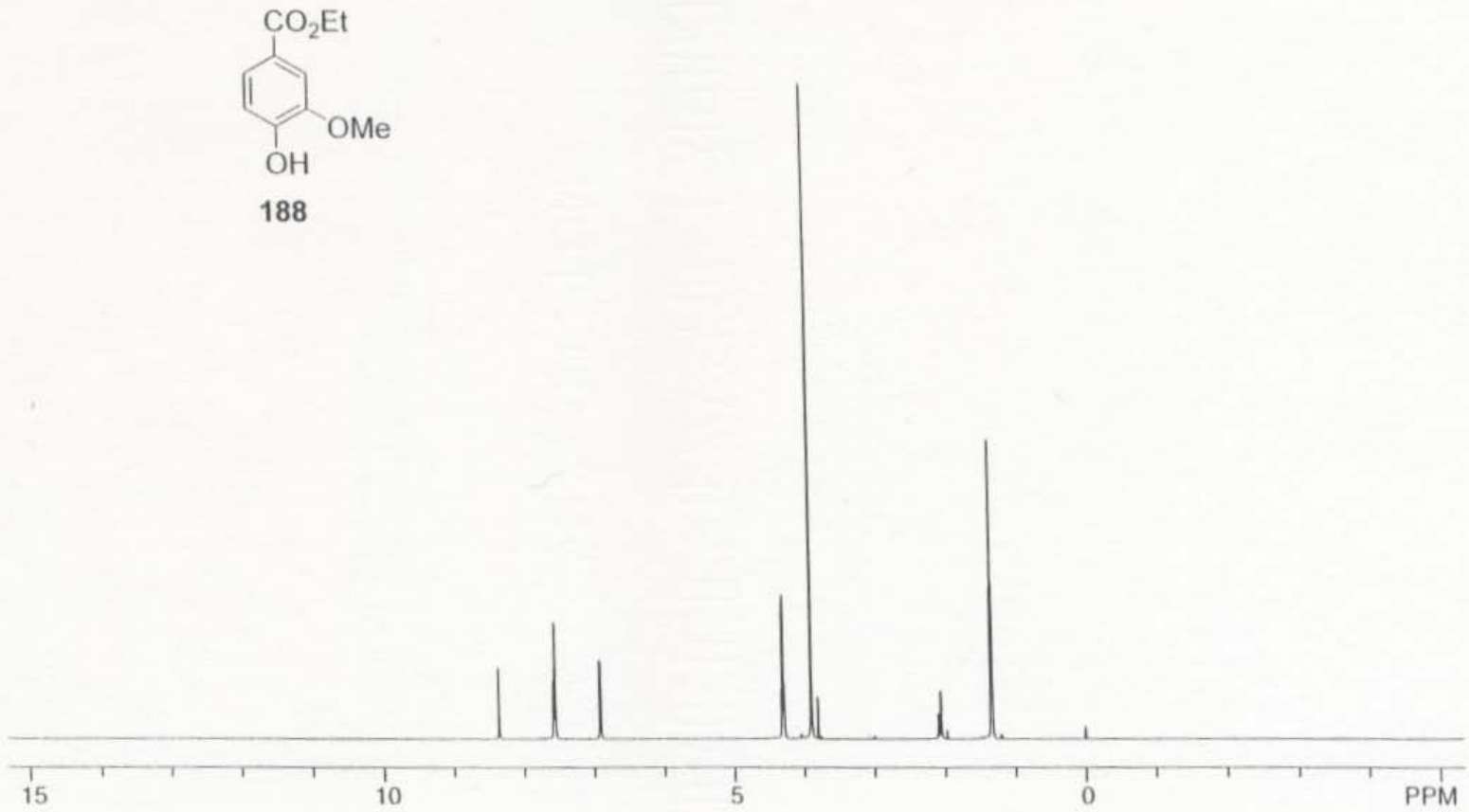

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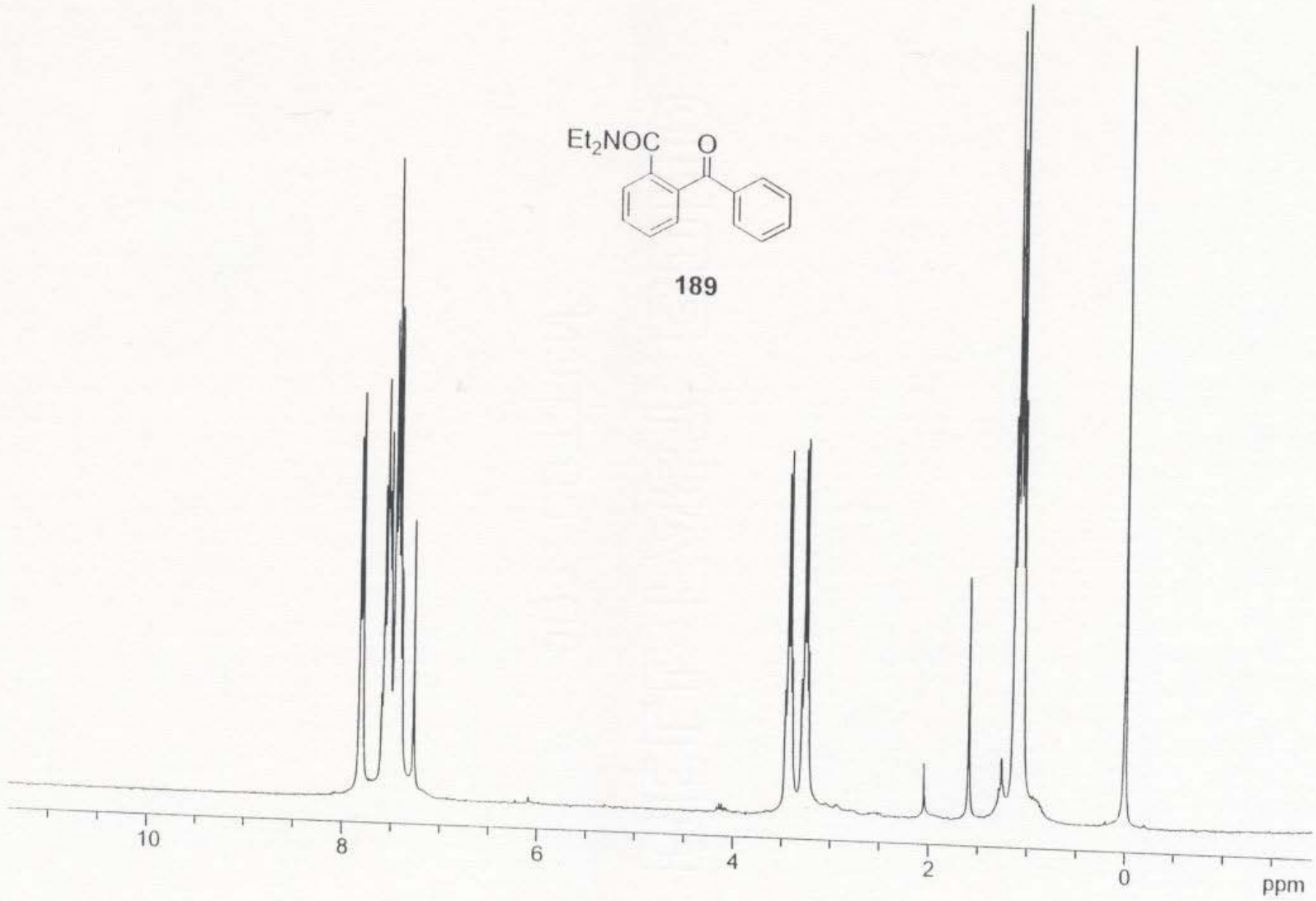
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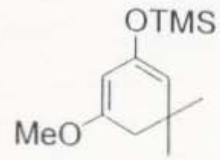

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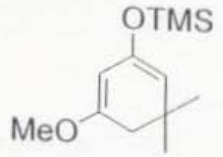

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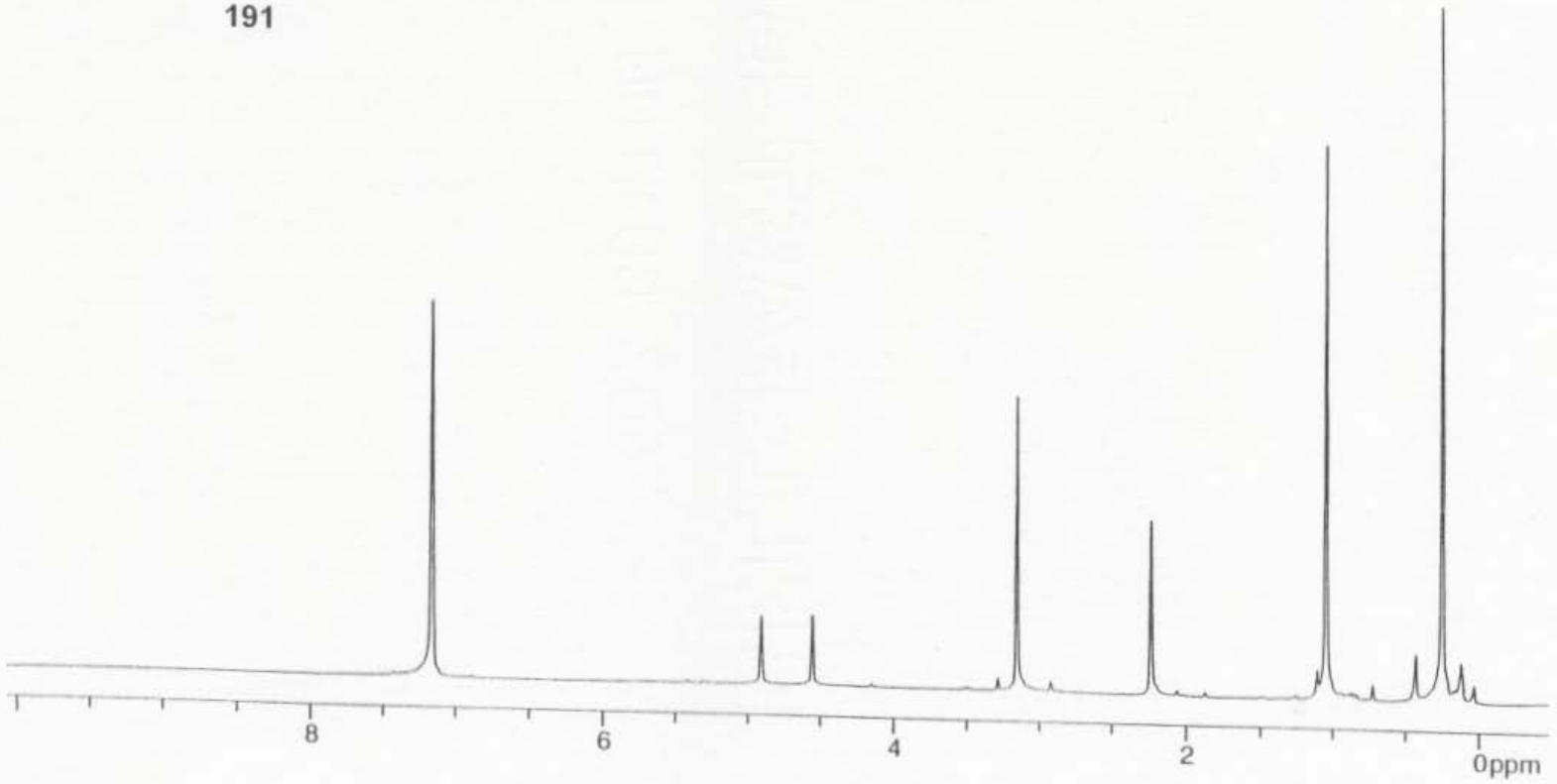

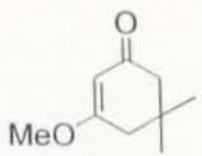

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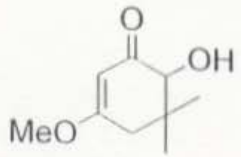

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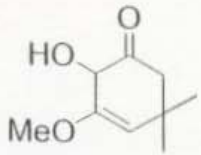

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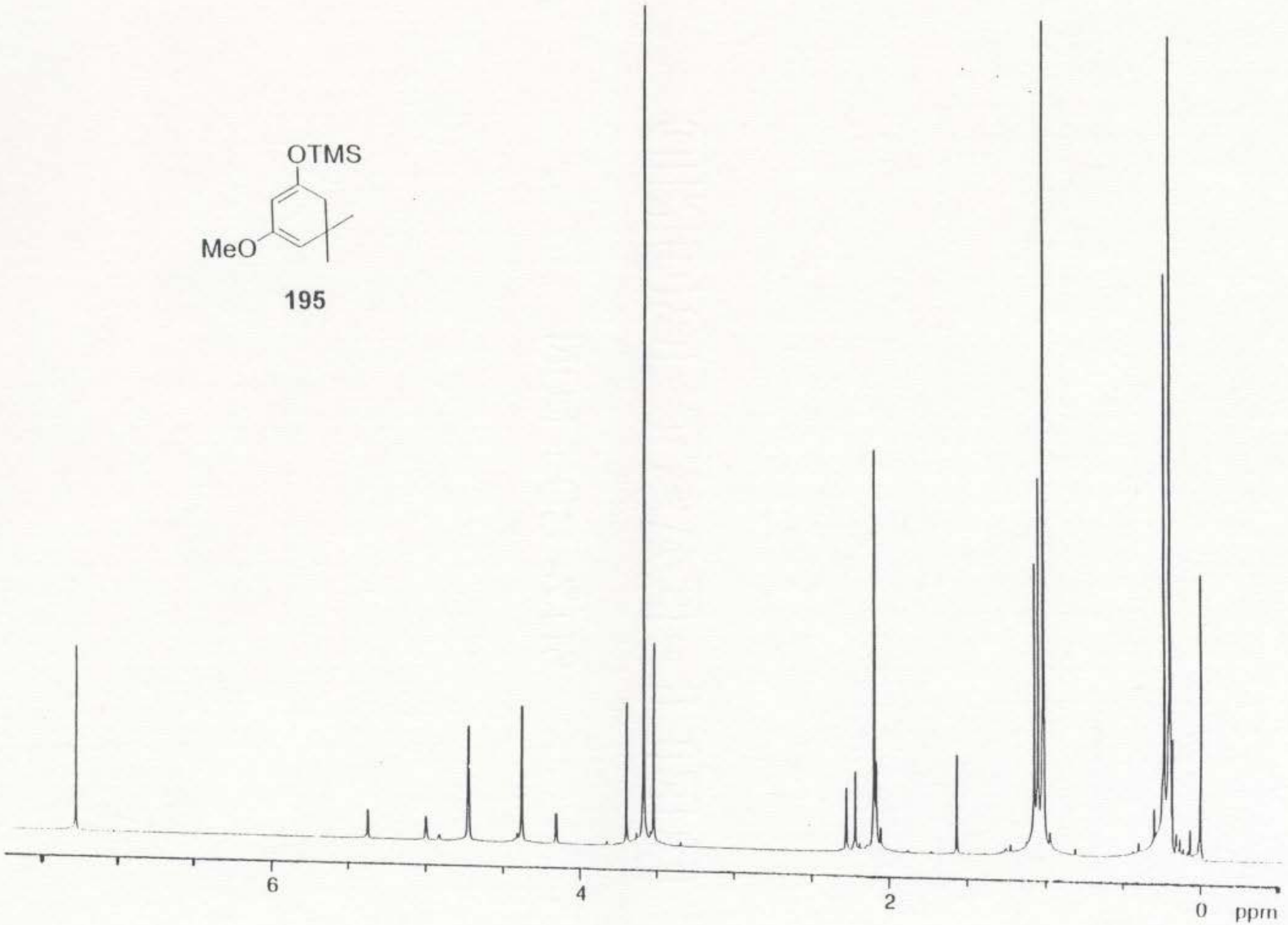

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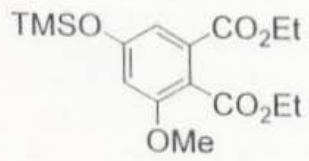

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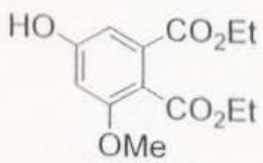

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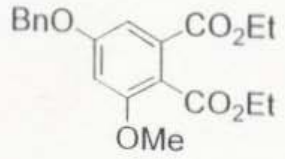

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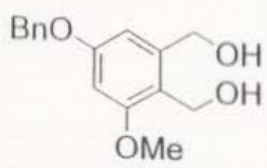

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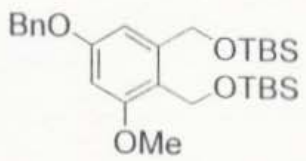

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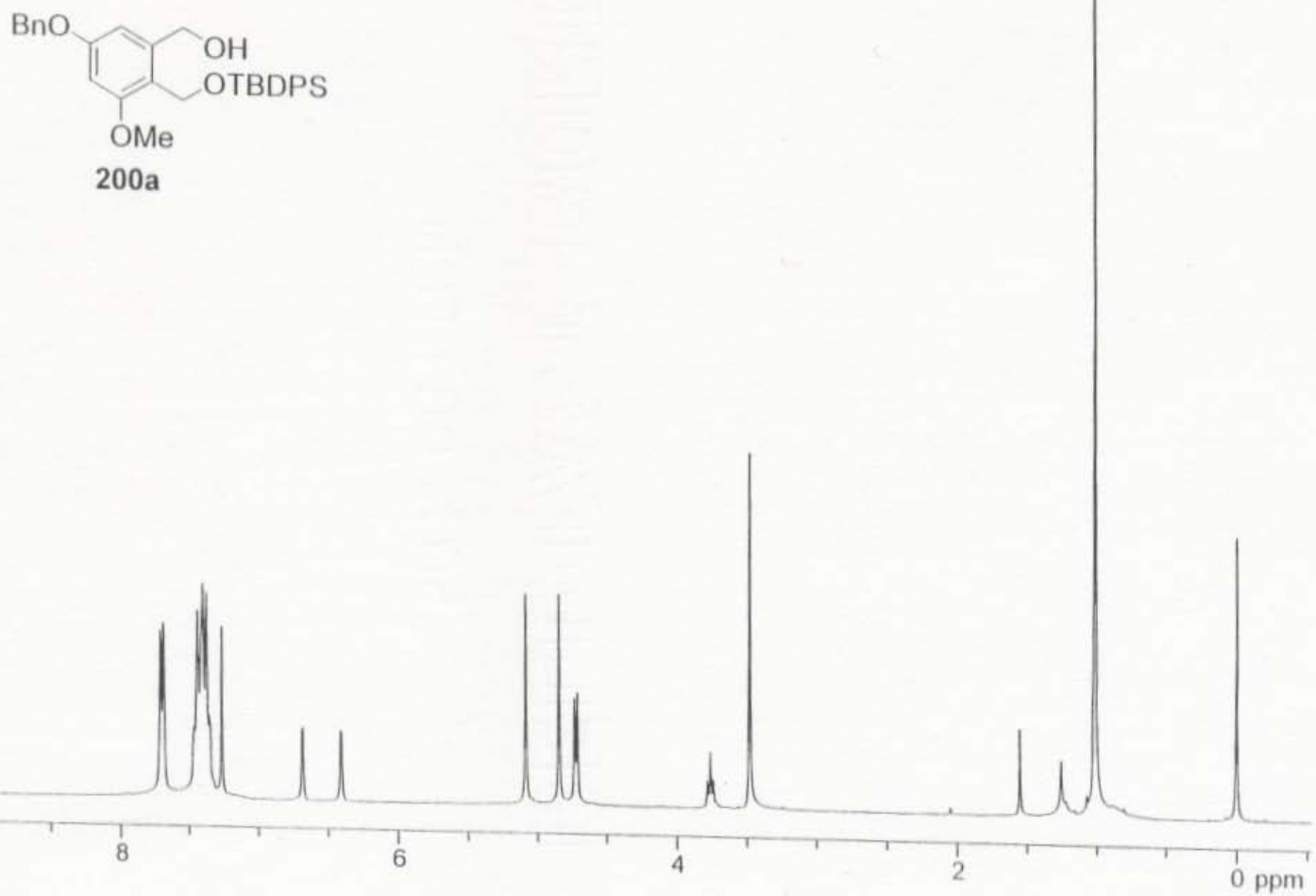

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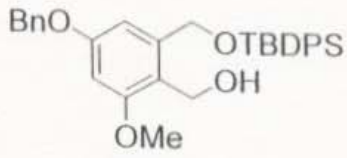

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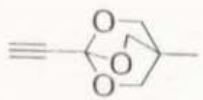

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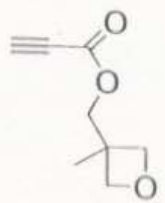

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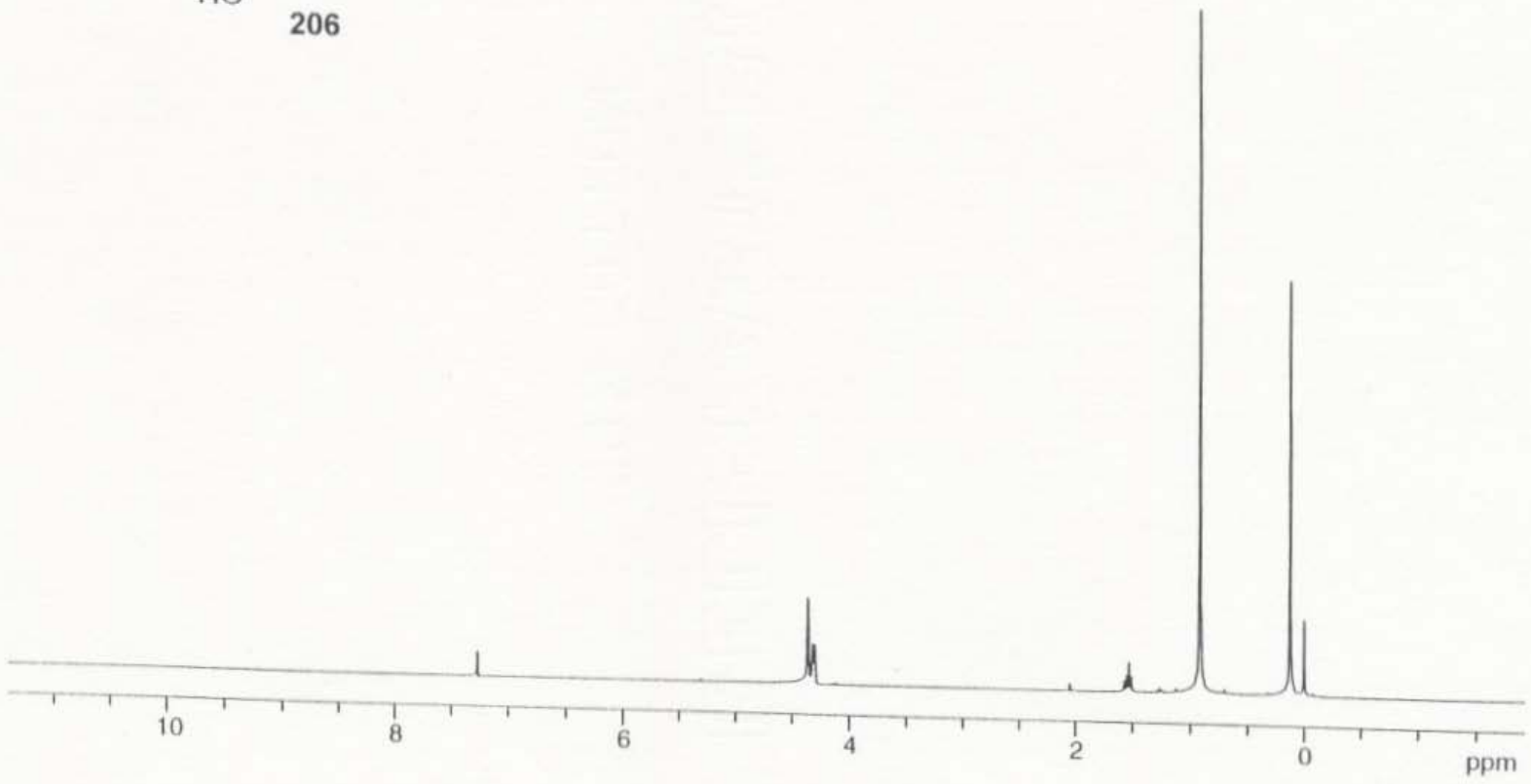

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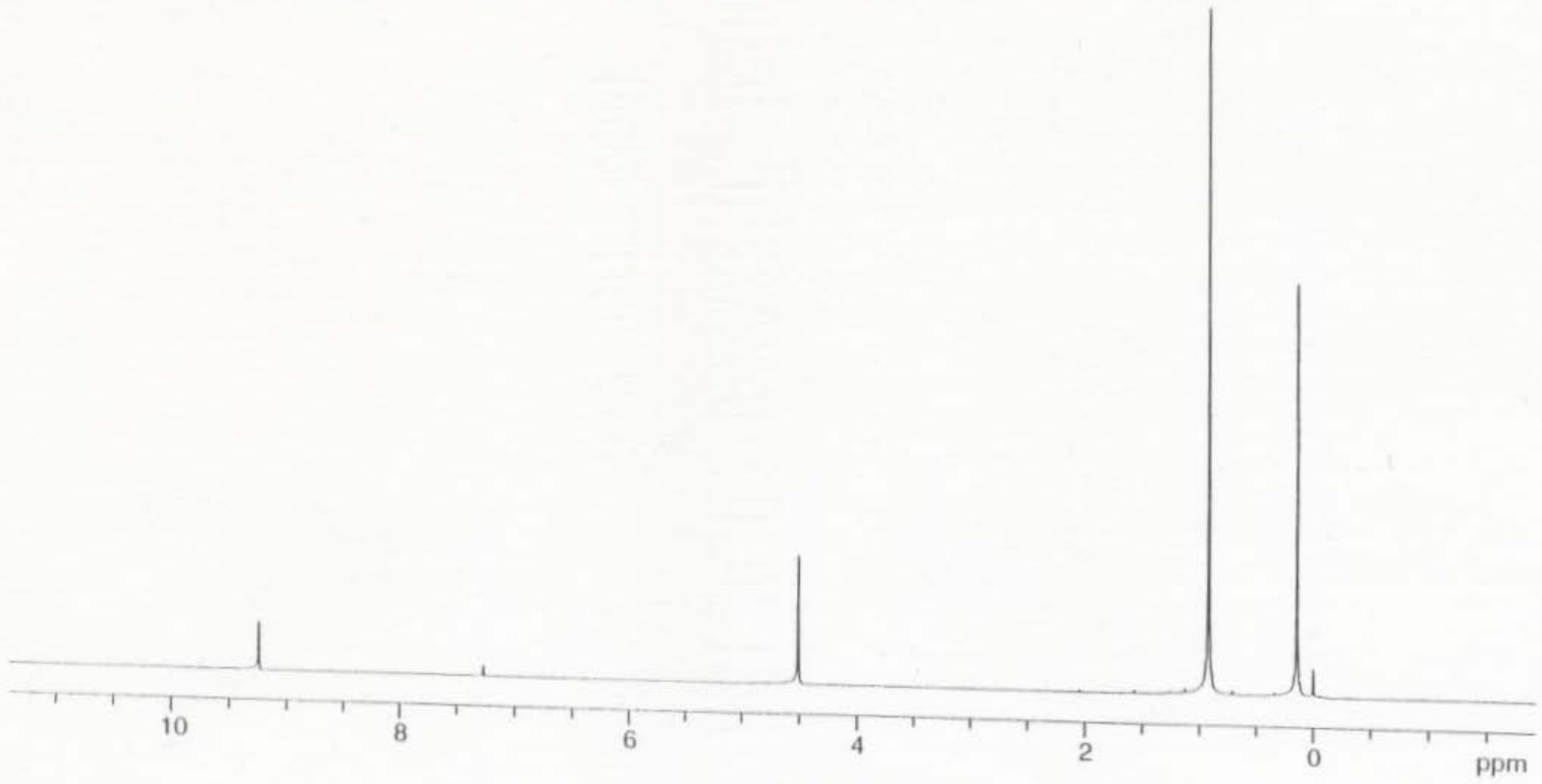

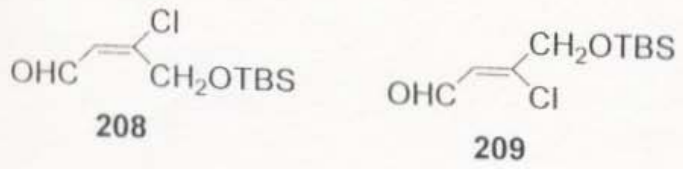

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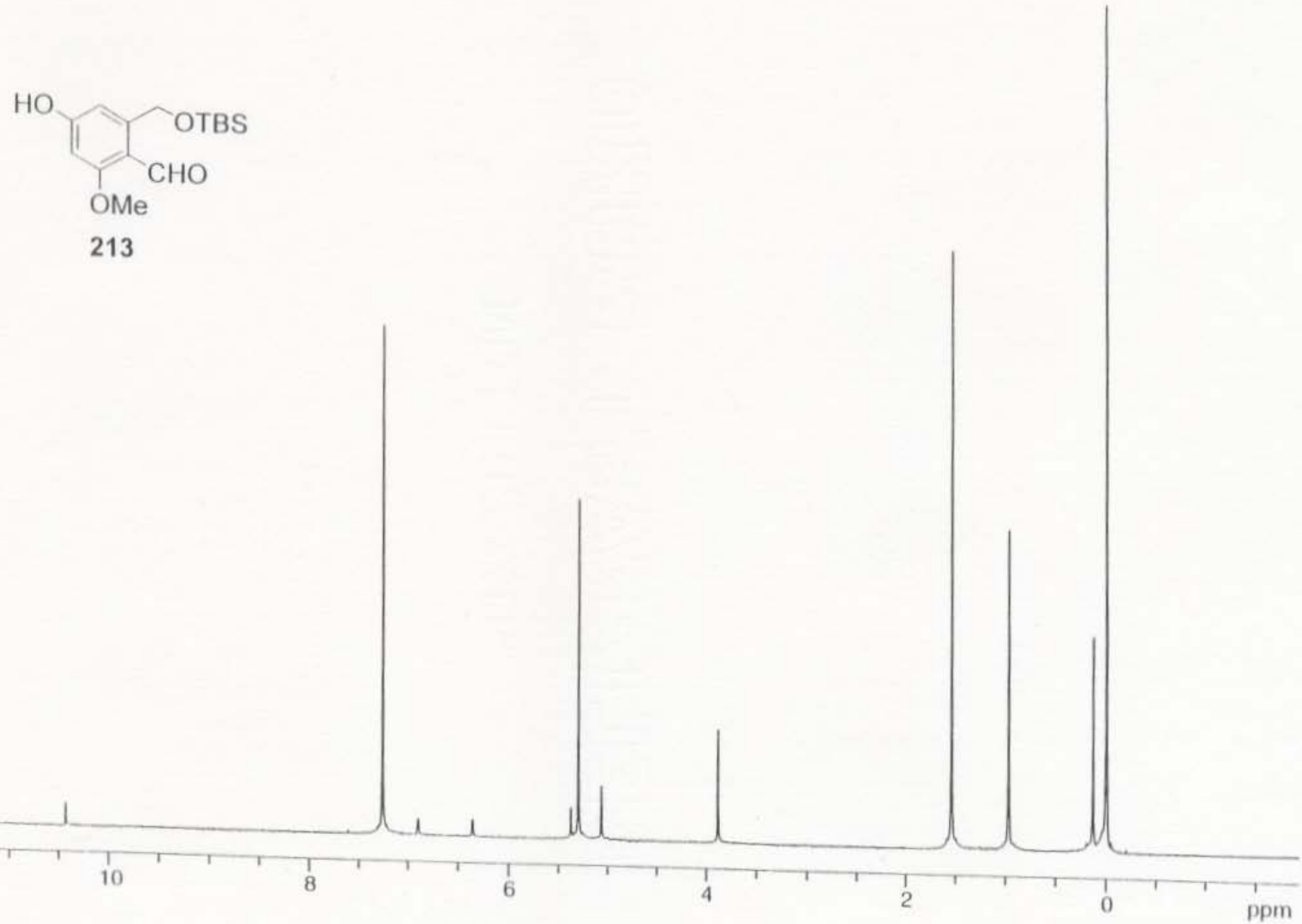
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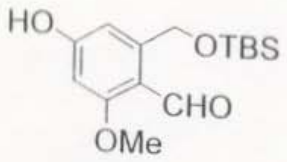
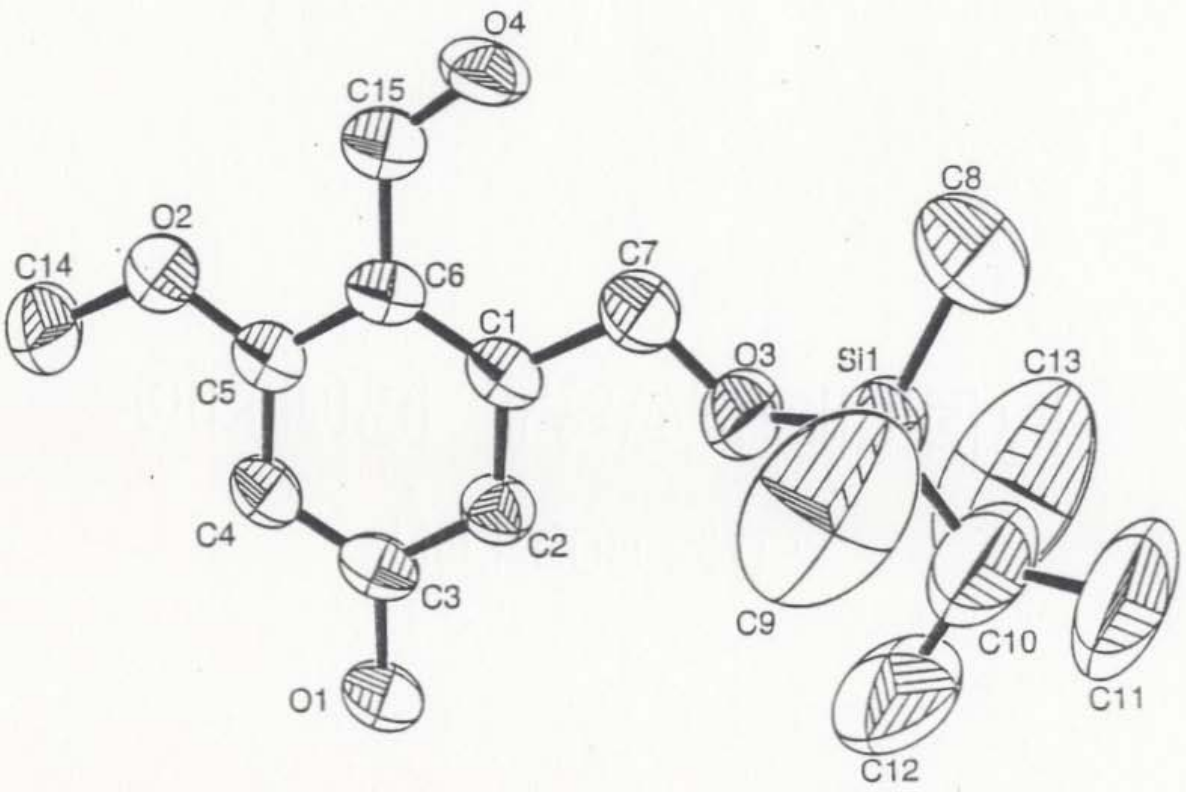
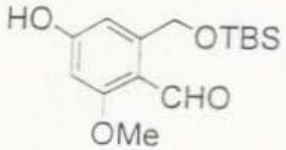


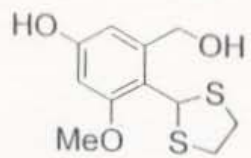
213



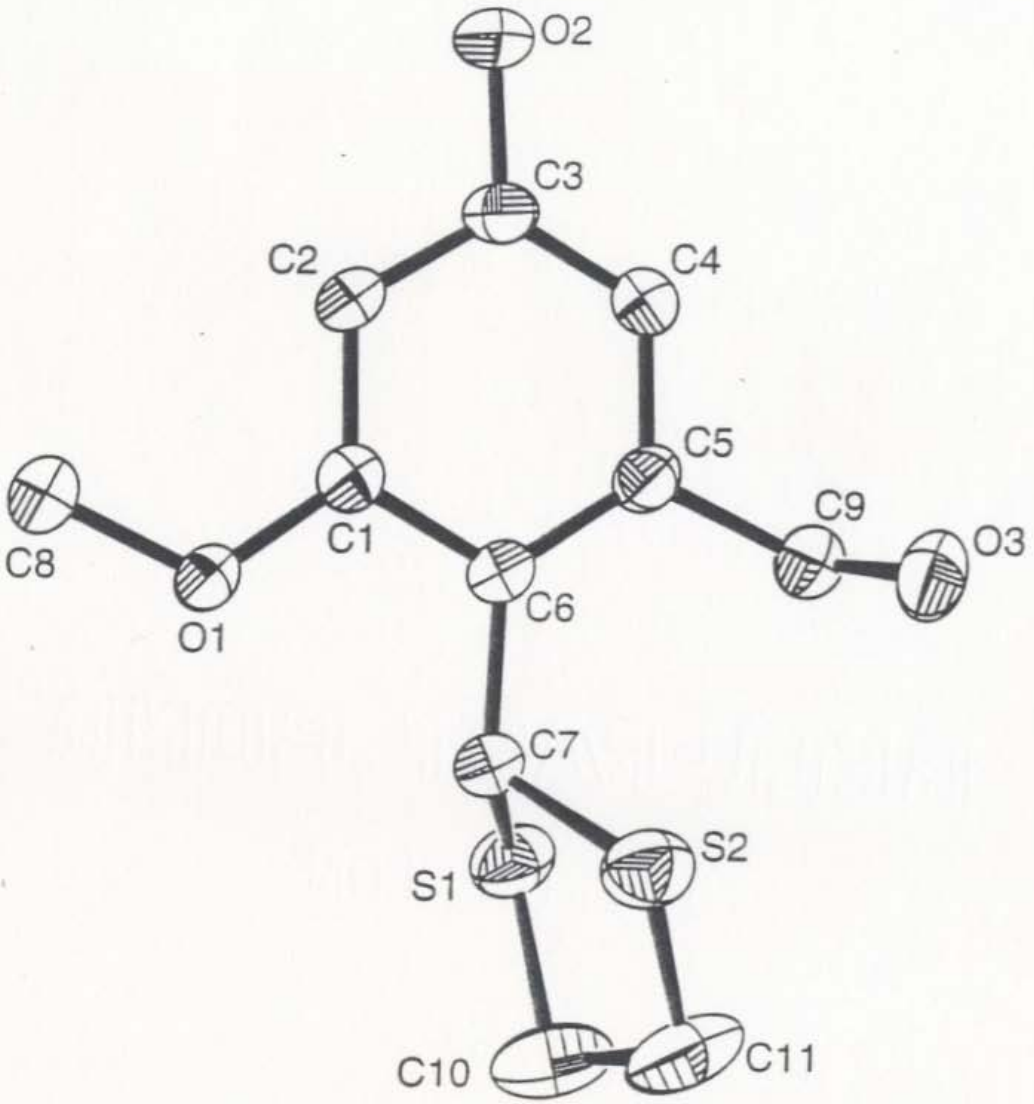


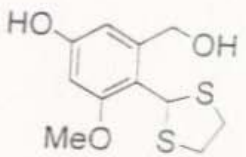
213

X-ray crystal structure (ORTEP) for **213**



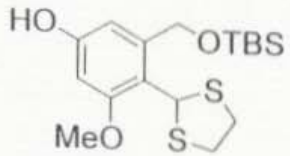
214



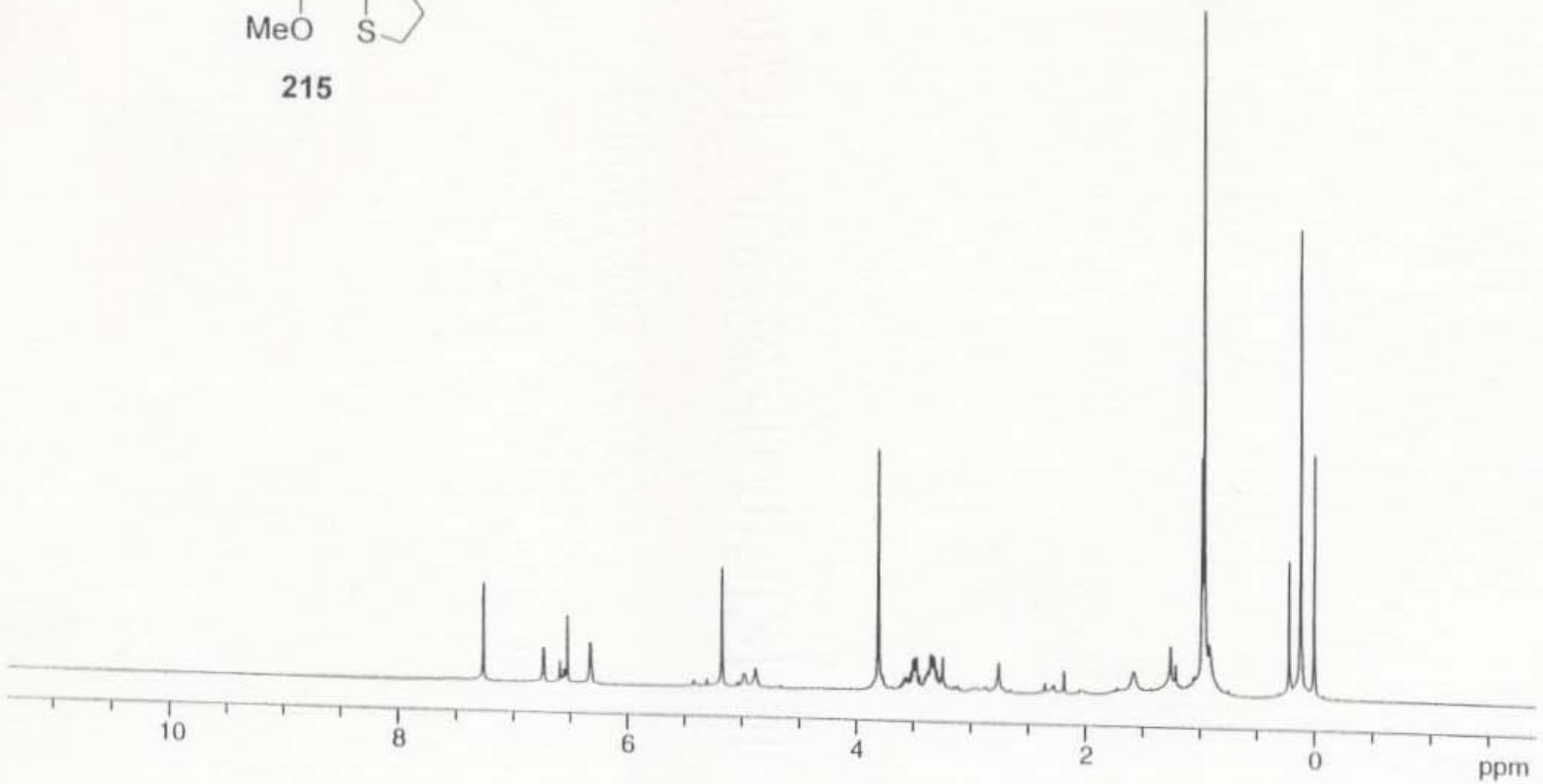


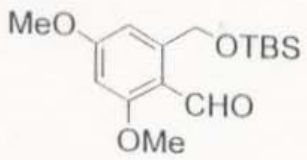
214

X-ray crystal structure (ORTEP) for **214**



215





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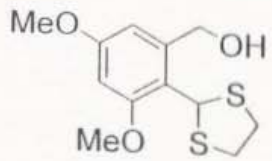

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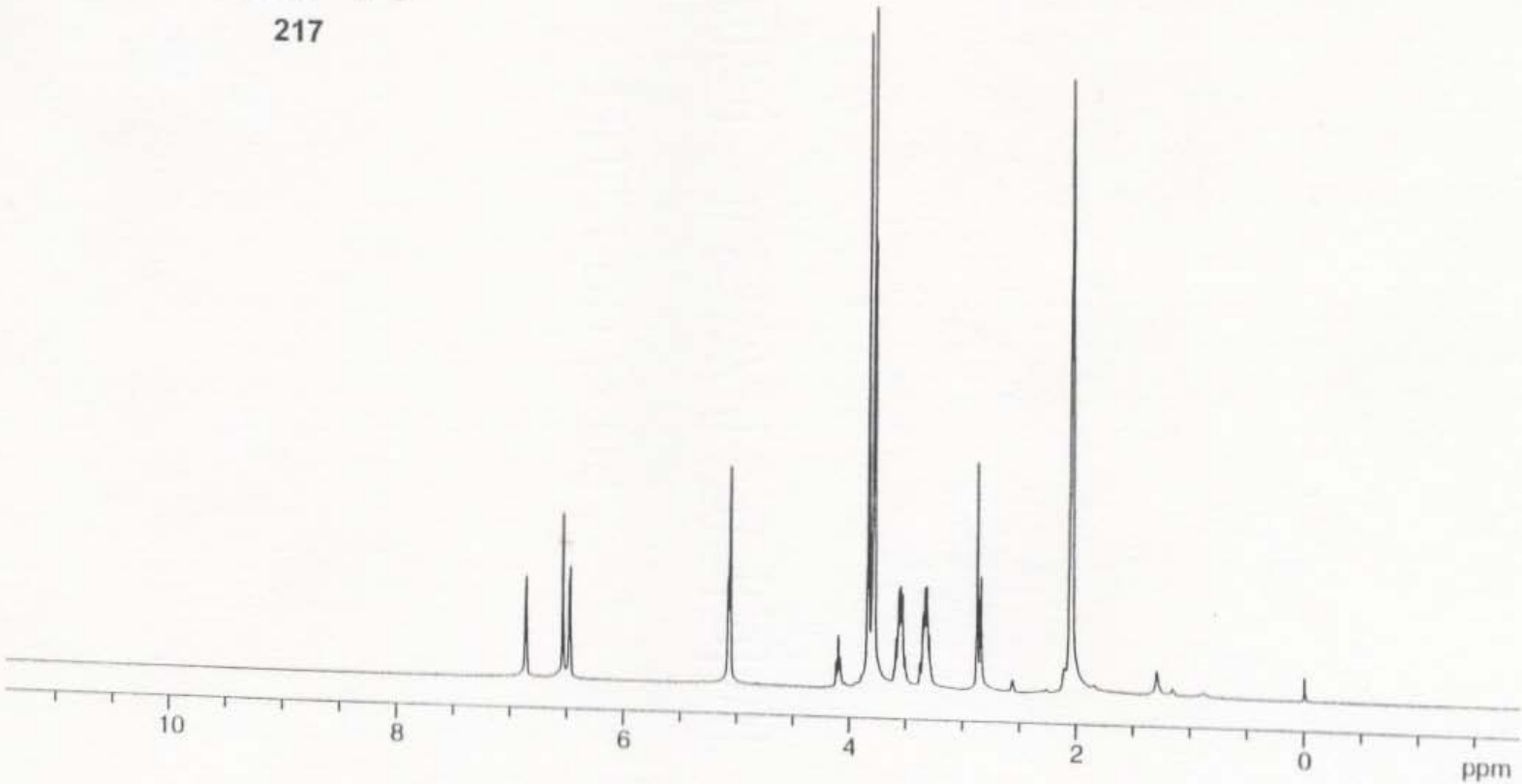

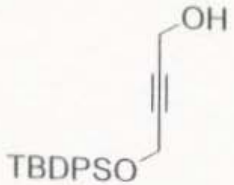

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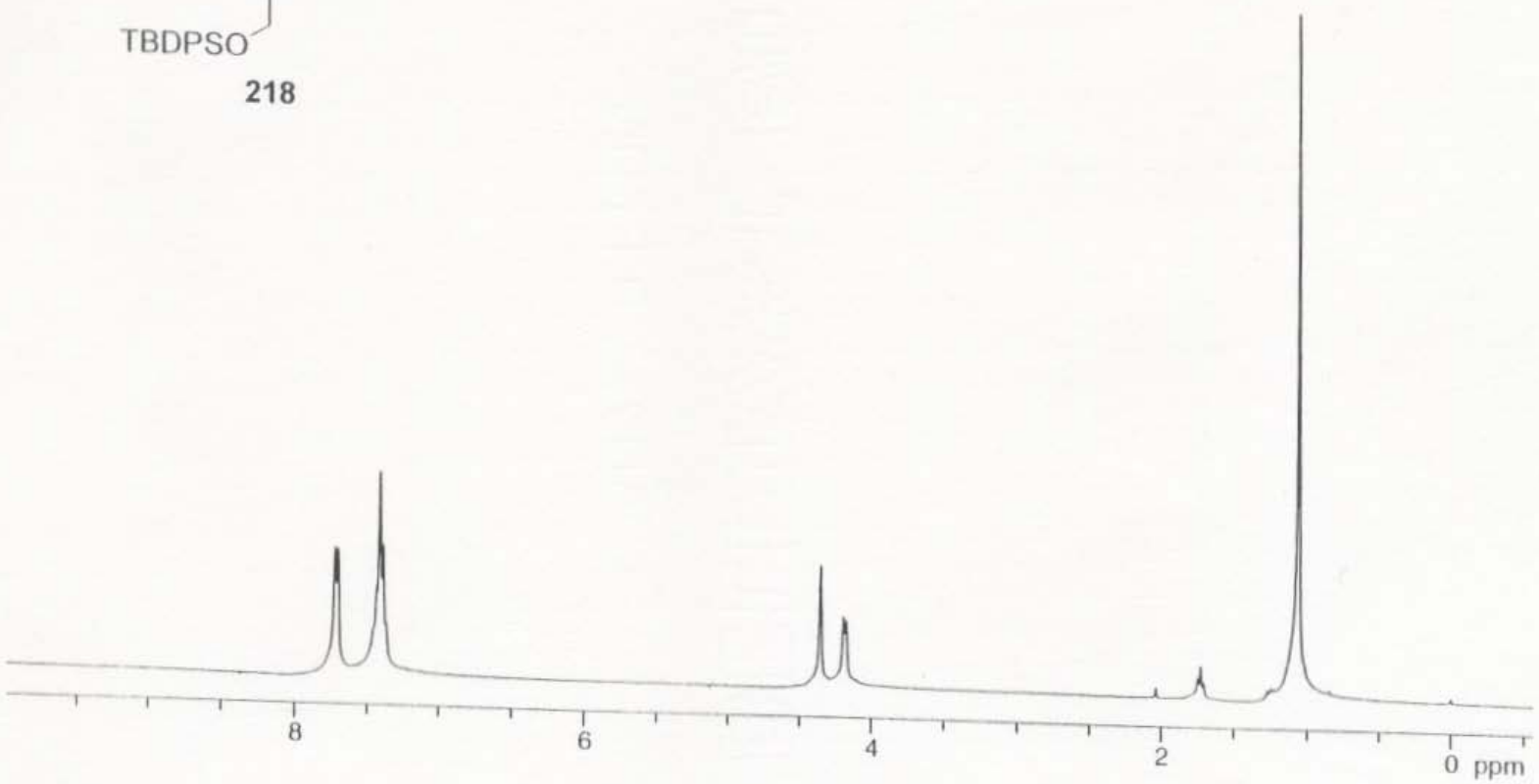

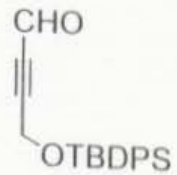

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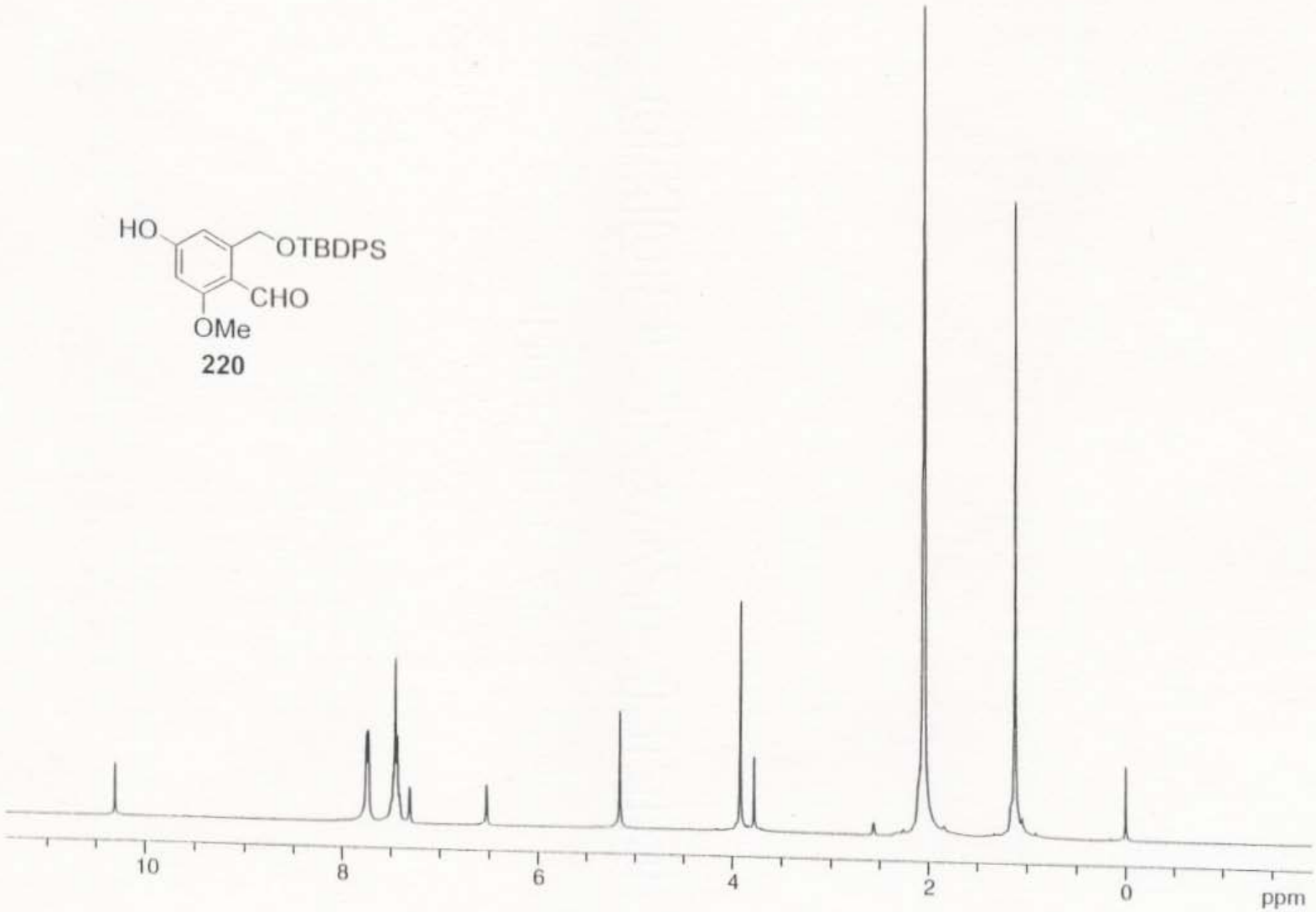
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CHO
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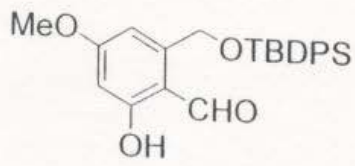
ppm



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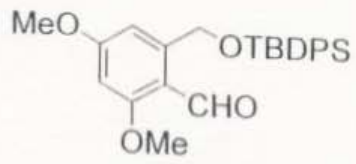

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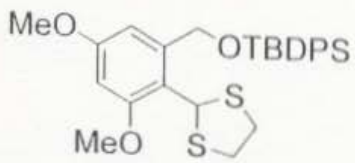

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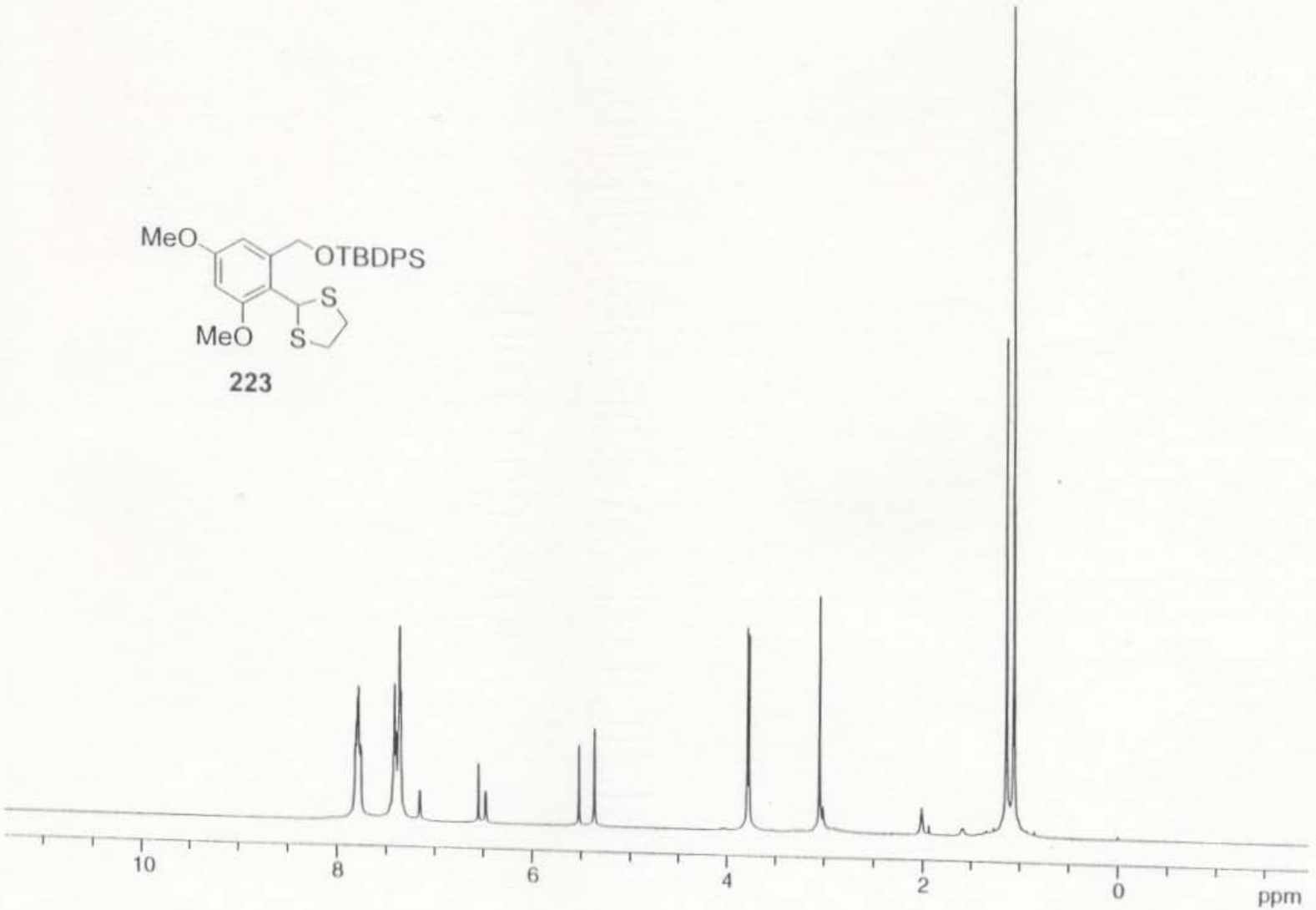
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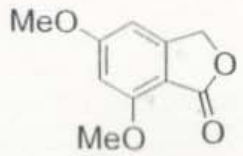
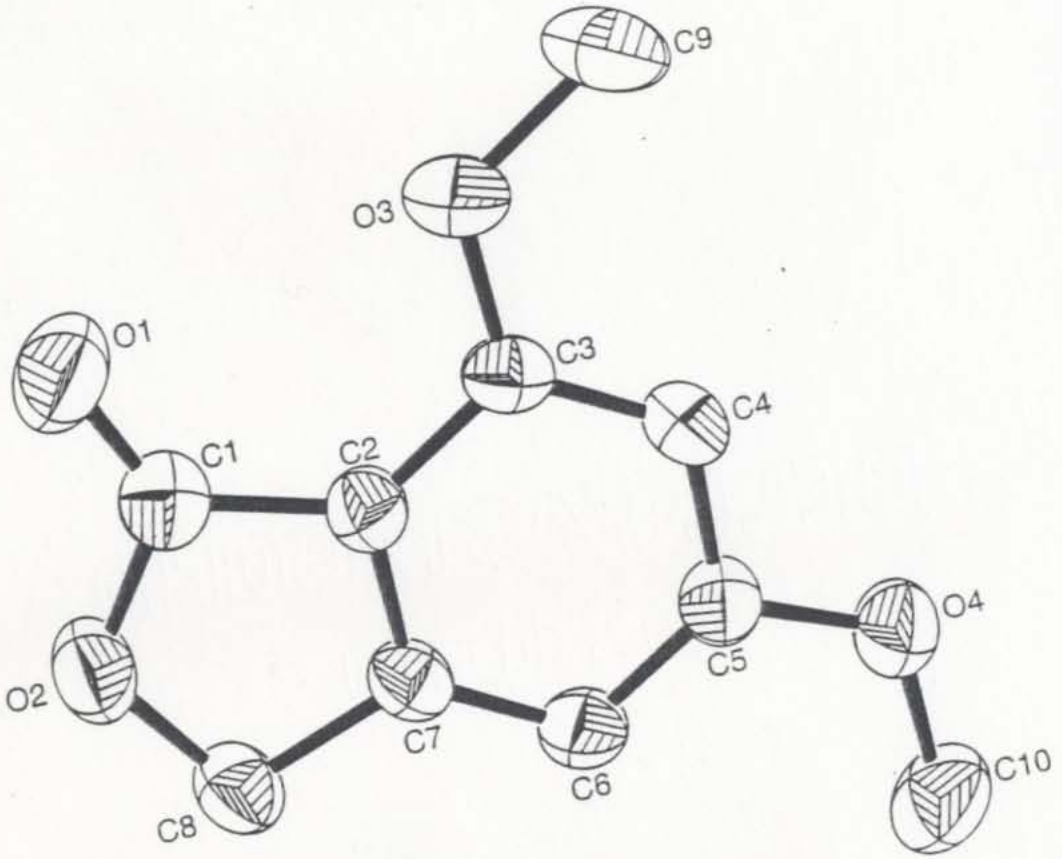
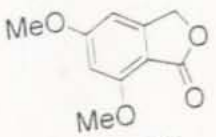
ppm



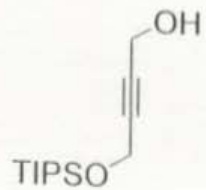
224



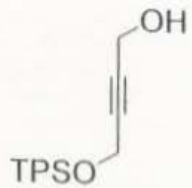


224

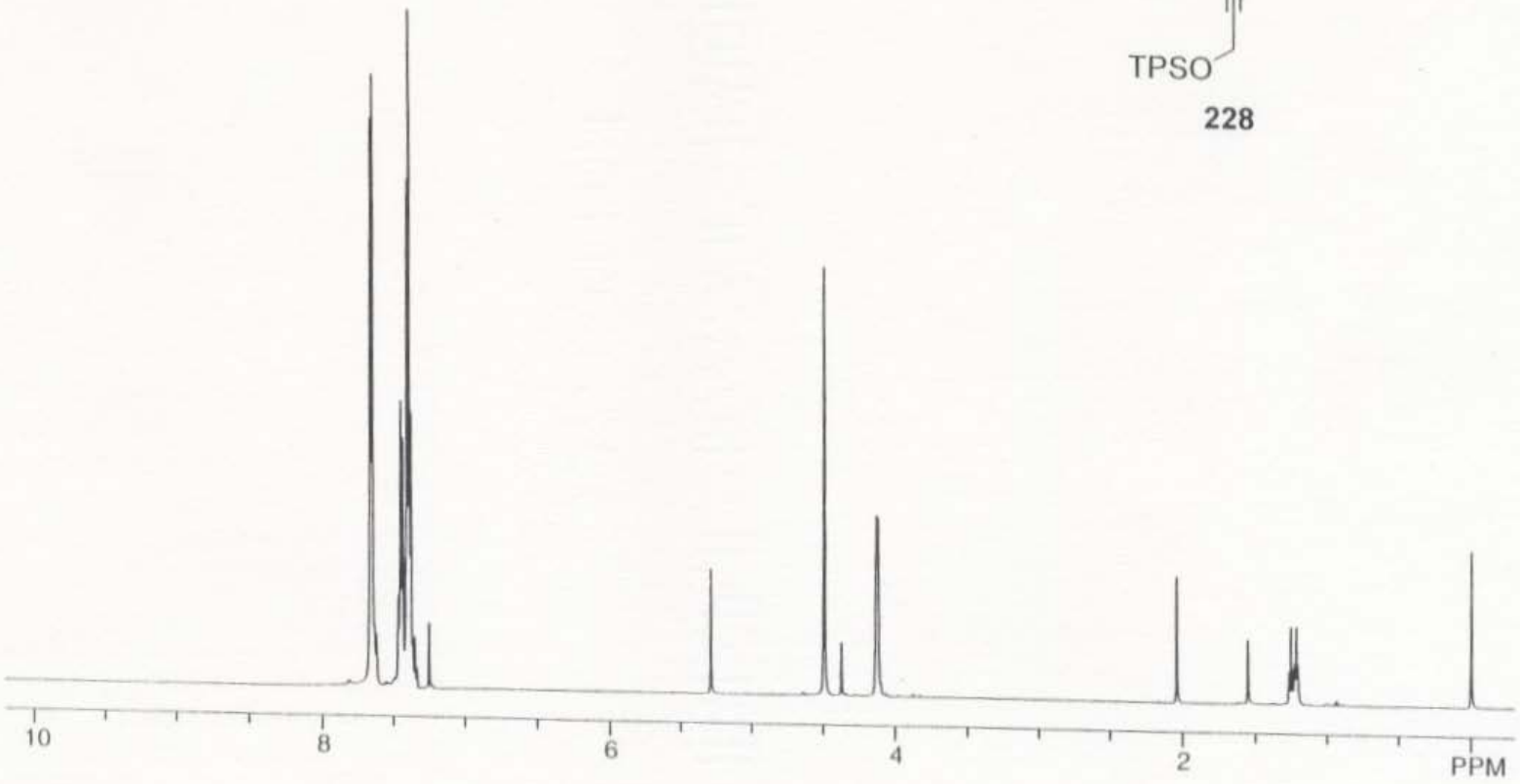
X-ray crystal structure (ORTEP) for **224**

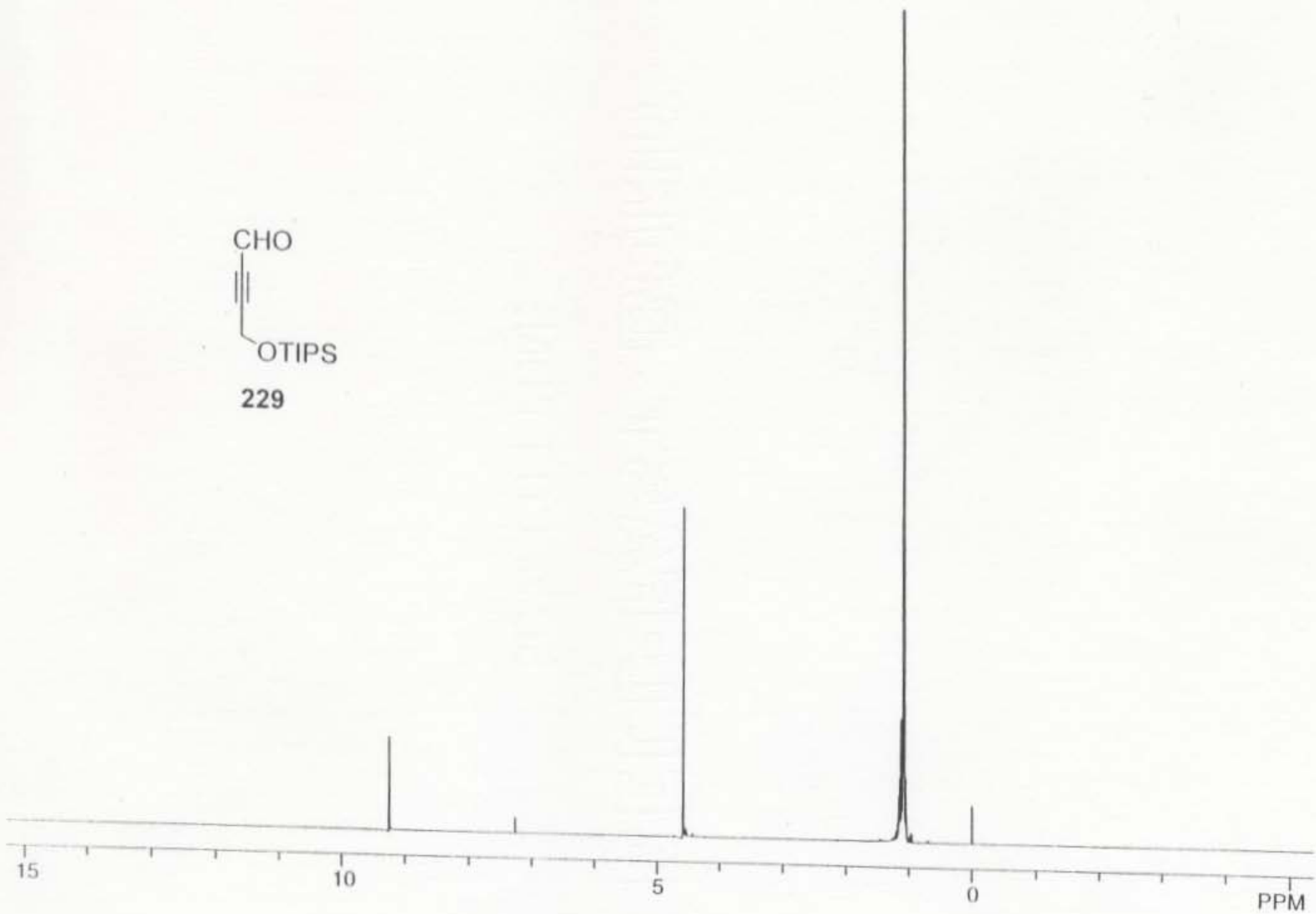


227



228





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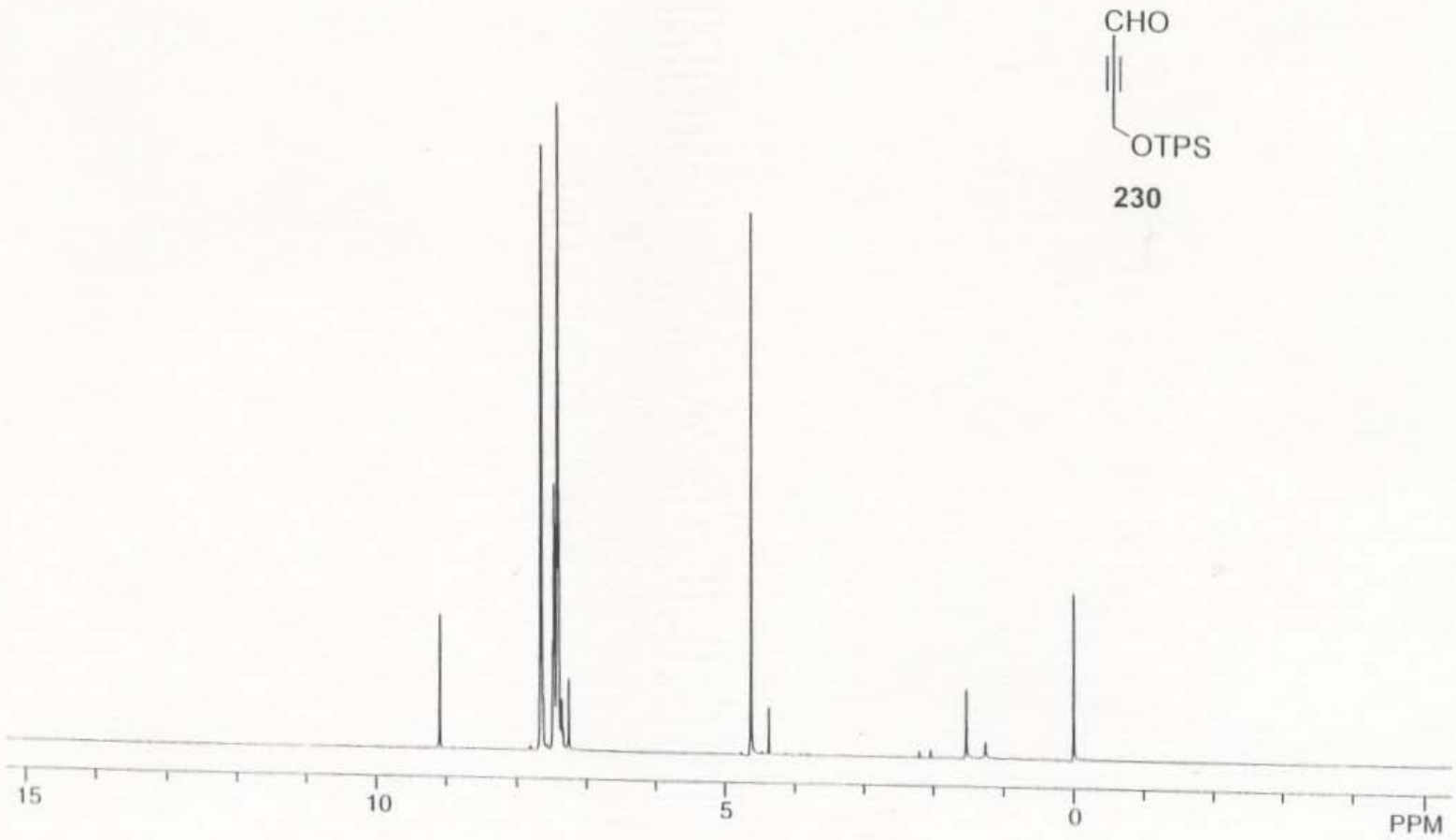

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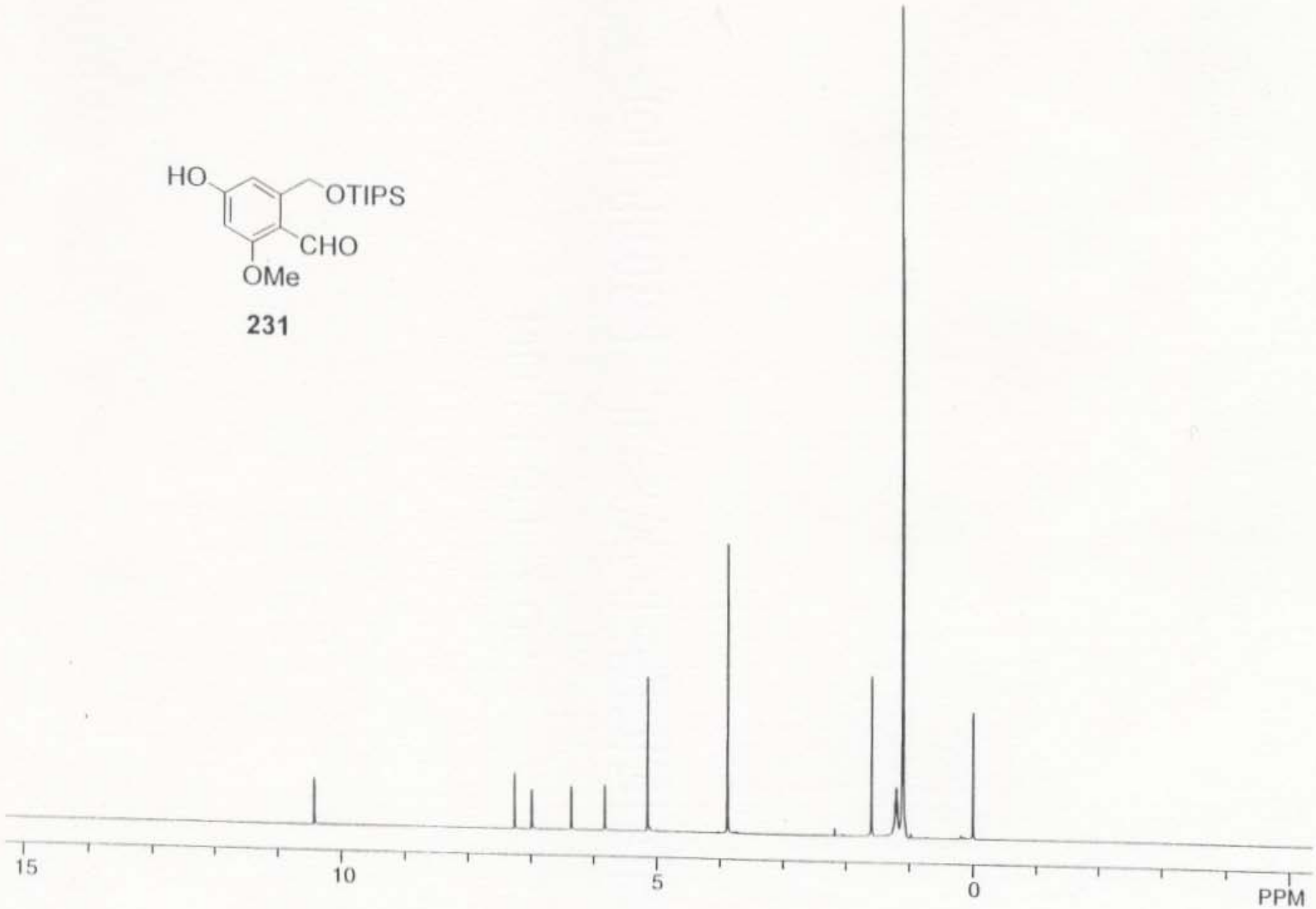

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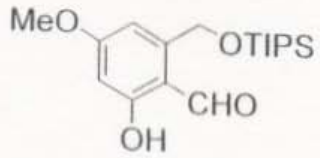

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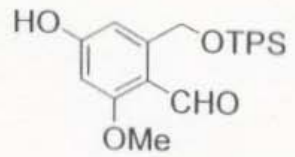

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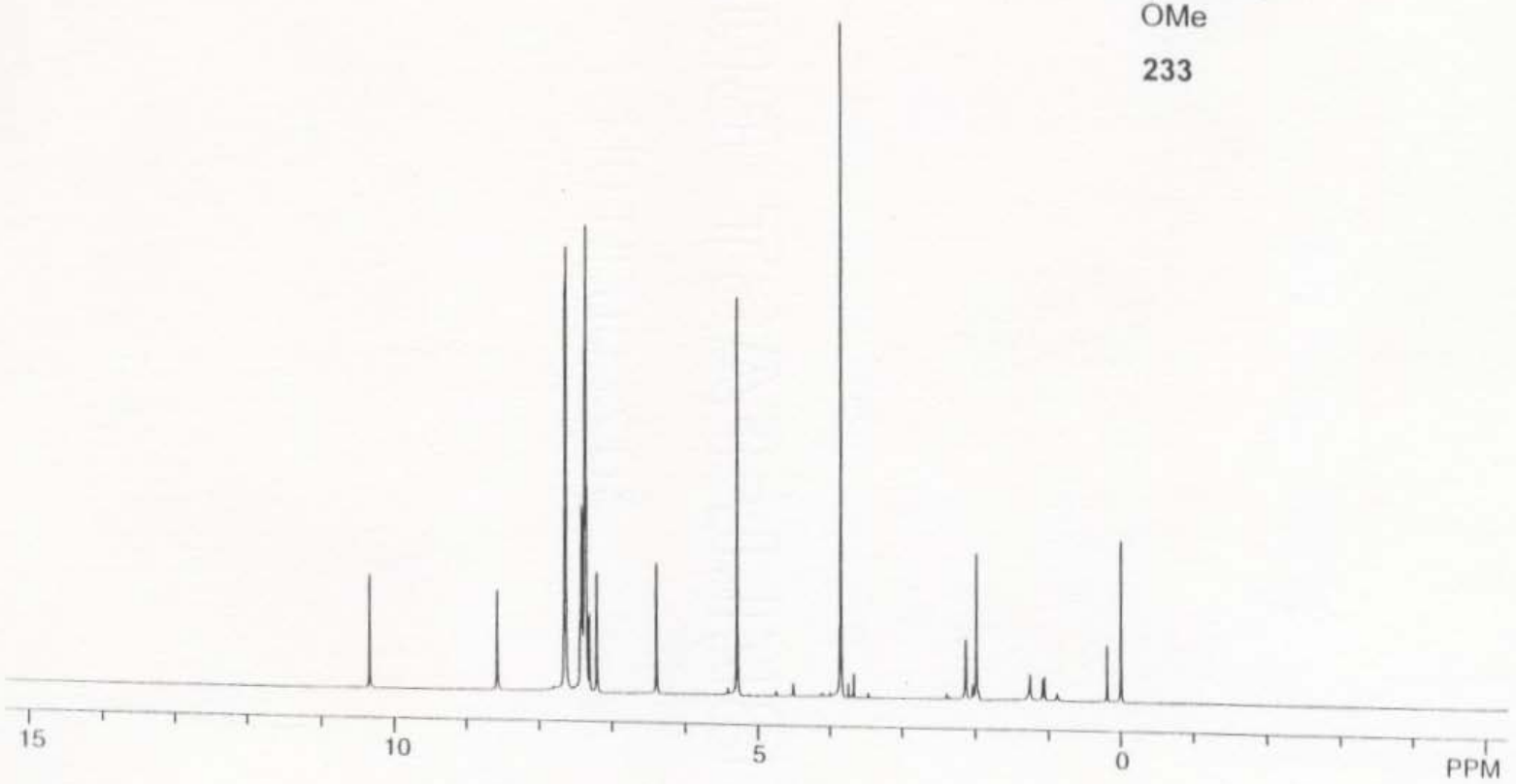
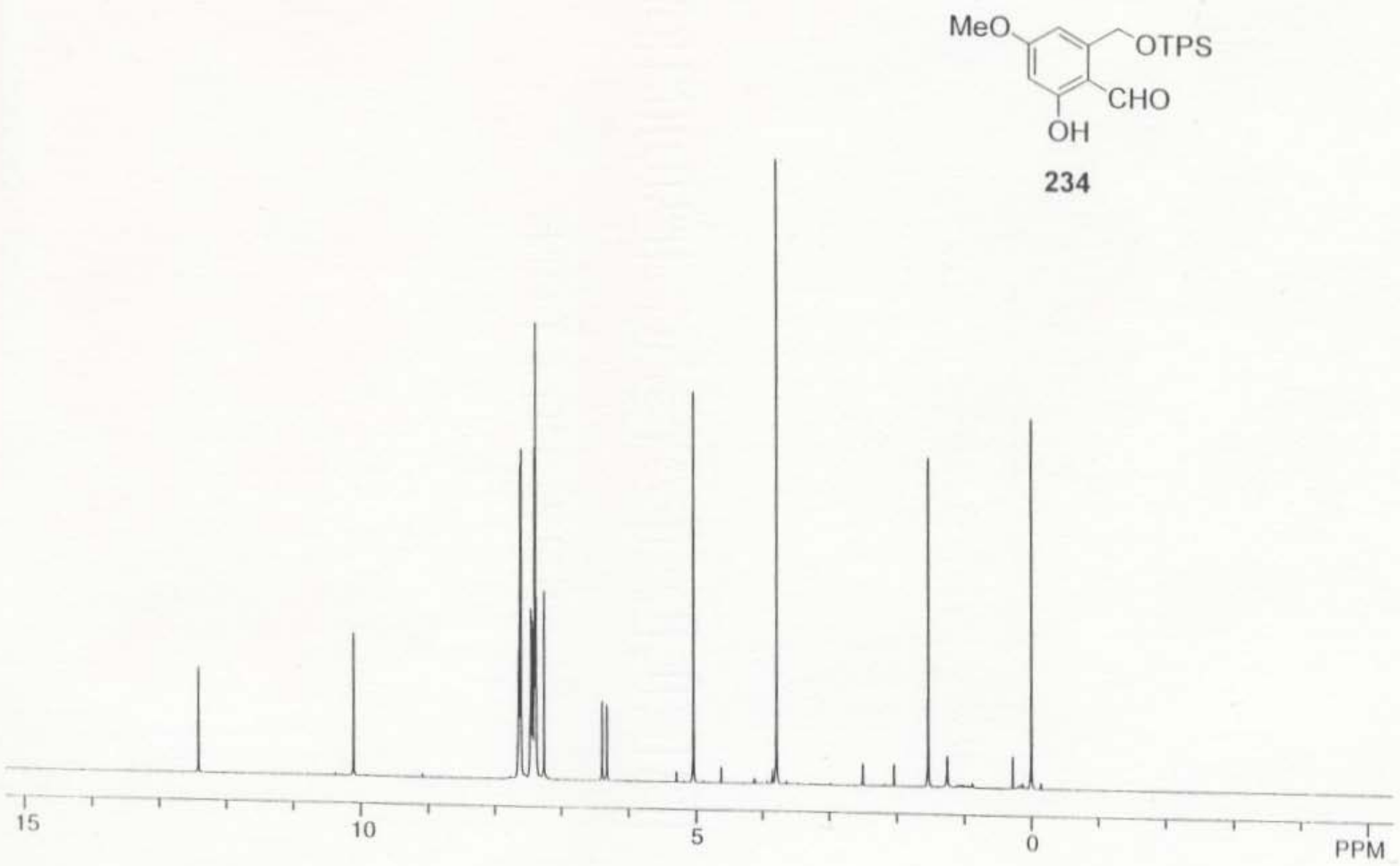
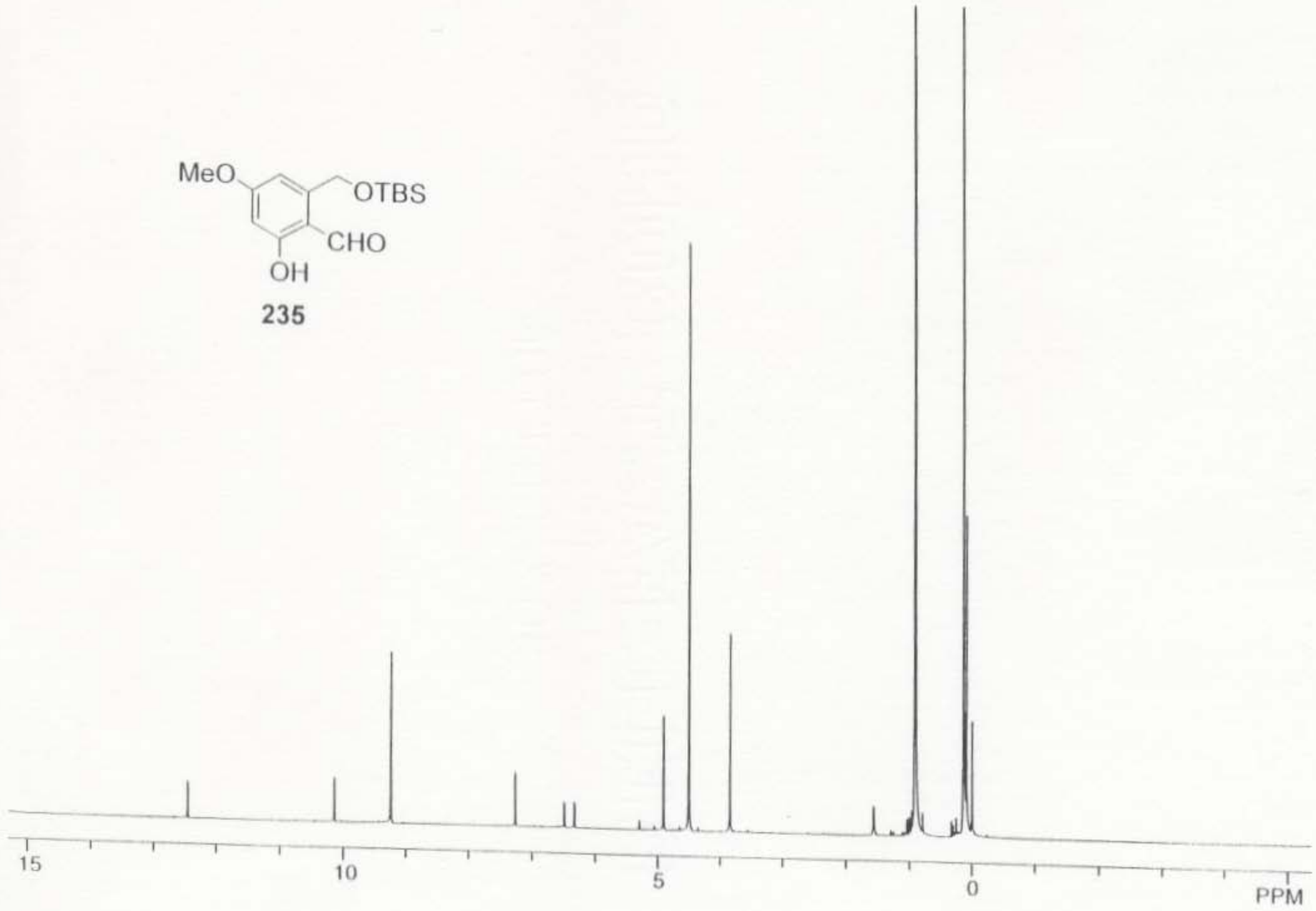




234



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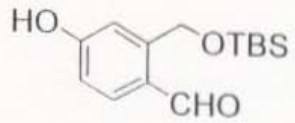
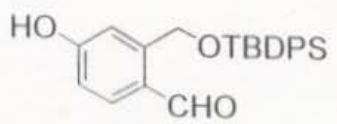
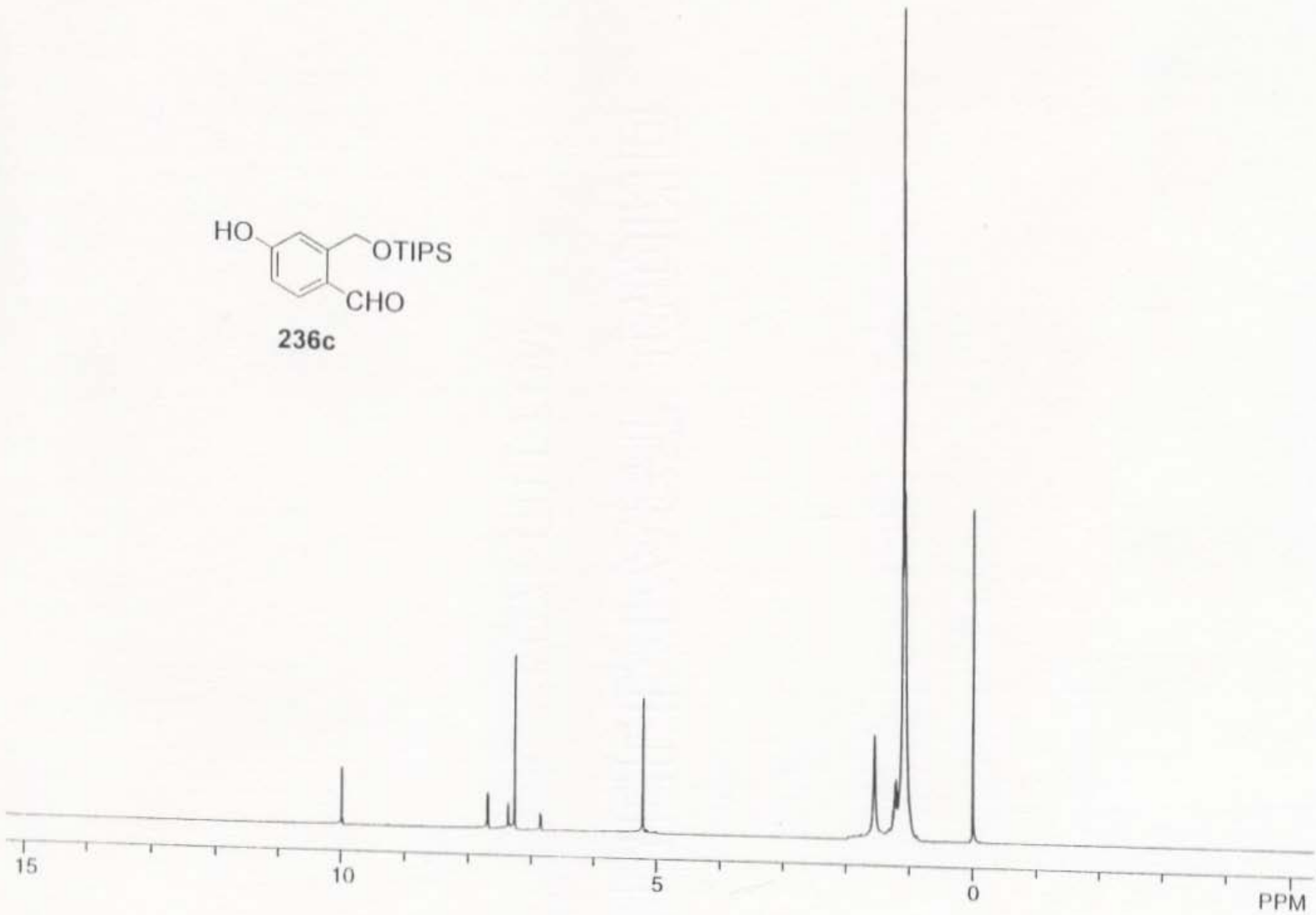


236a



236b



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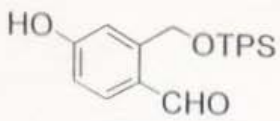

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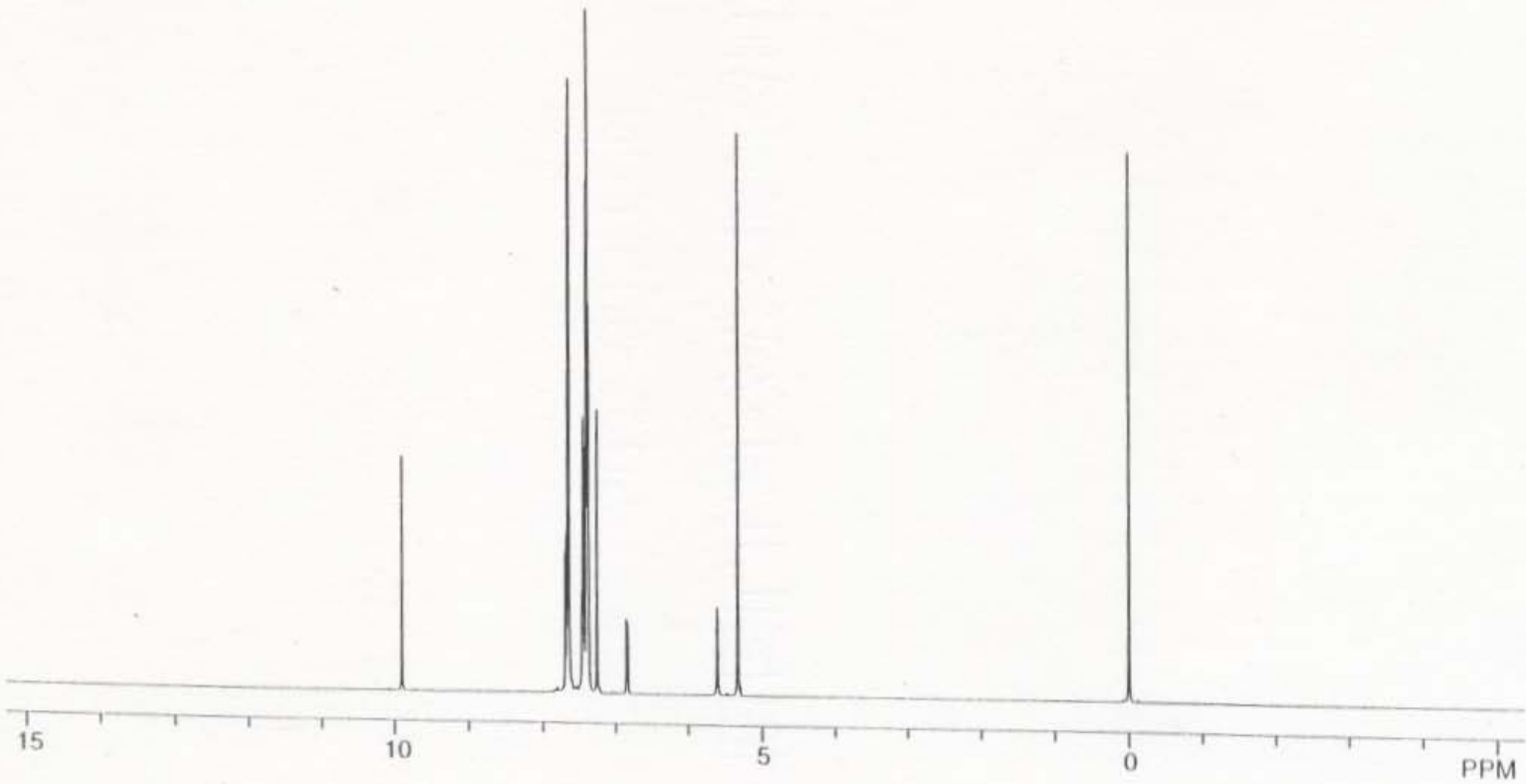

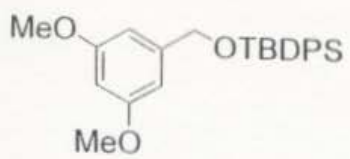

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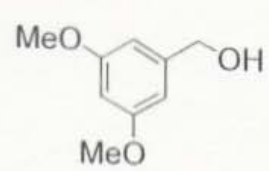
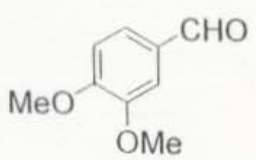


238



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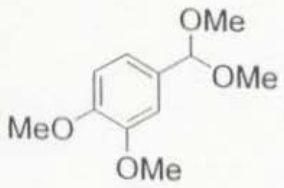

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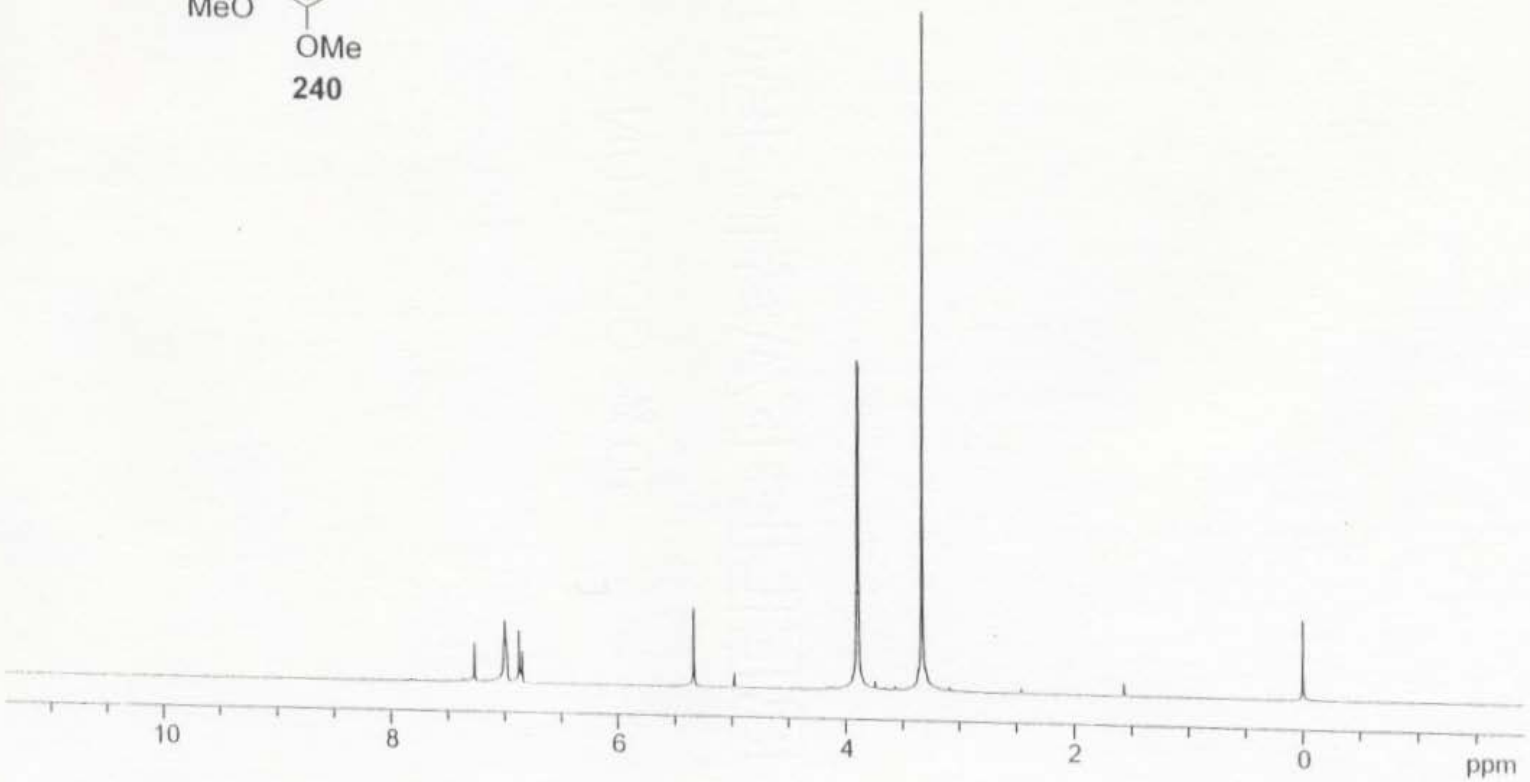

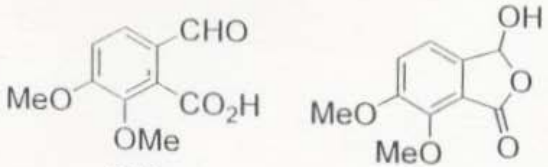

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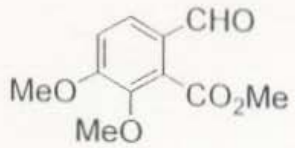
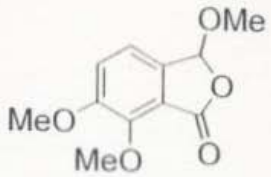
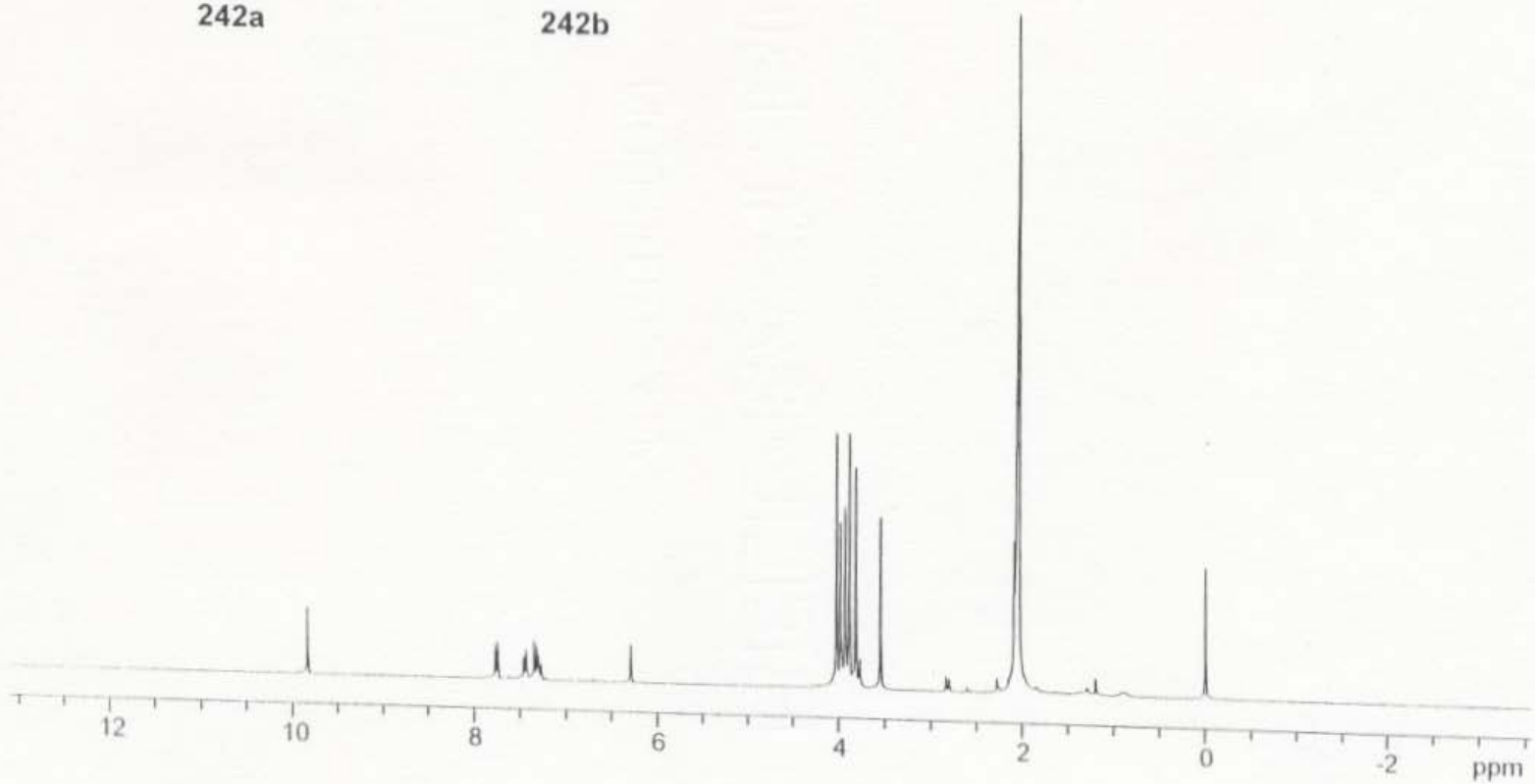
241b

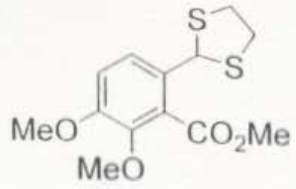


242a



242b





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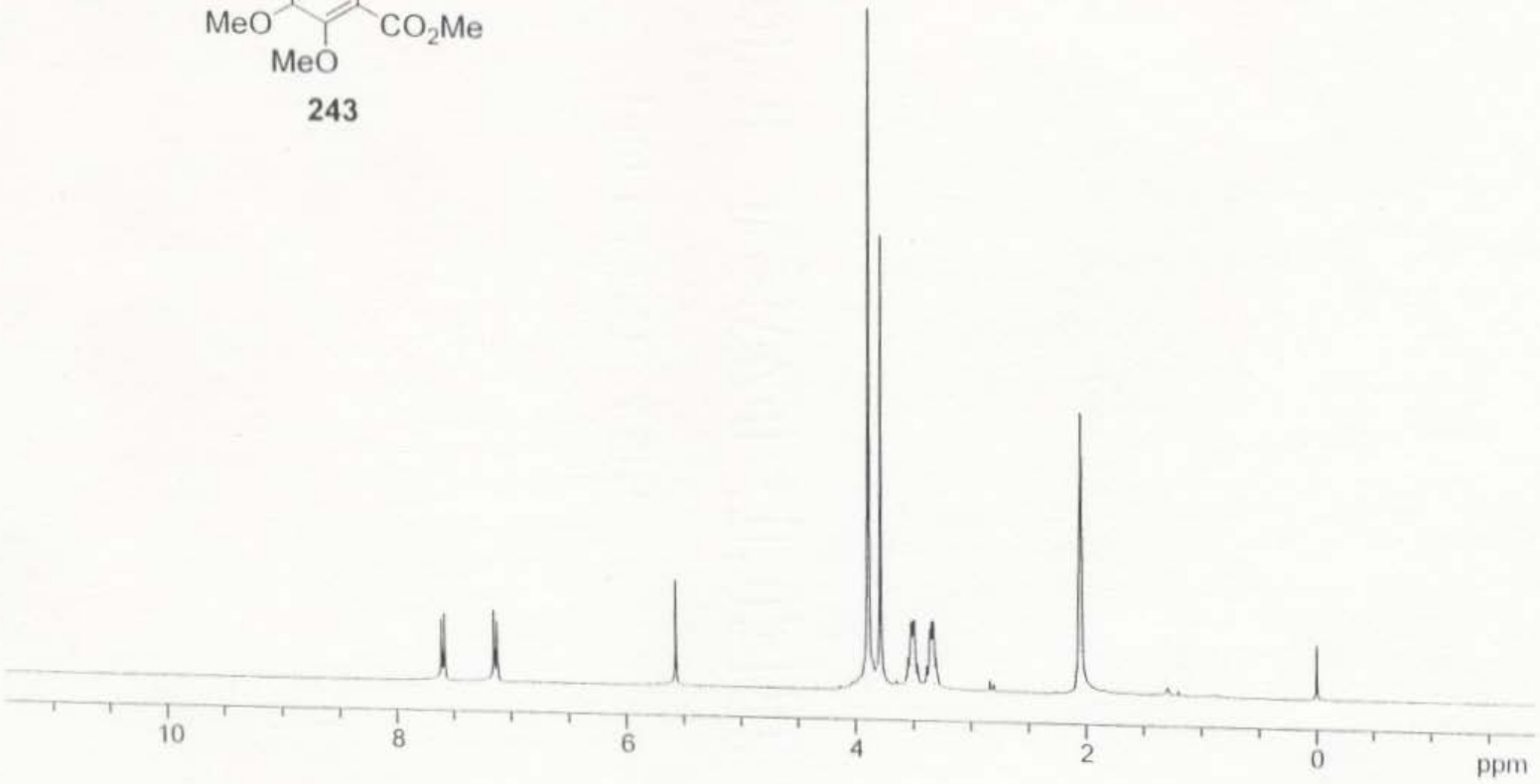
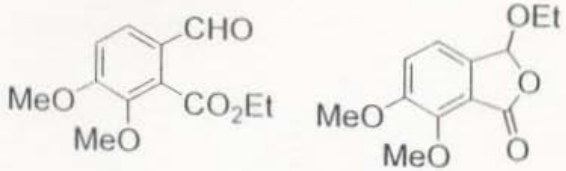
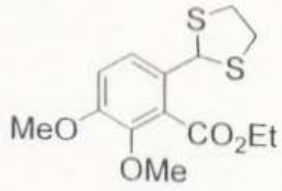




244a

244b



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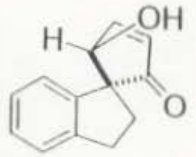

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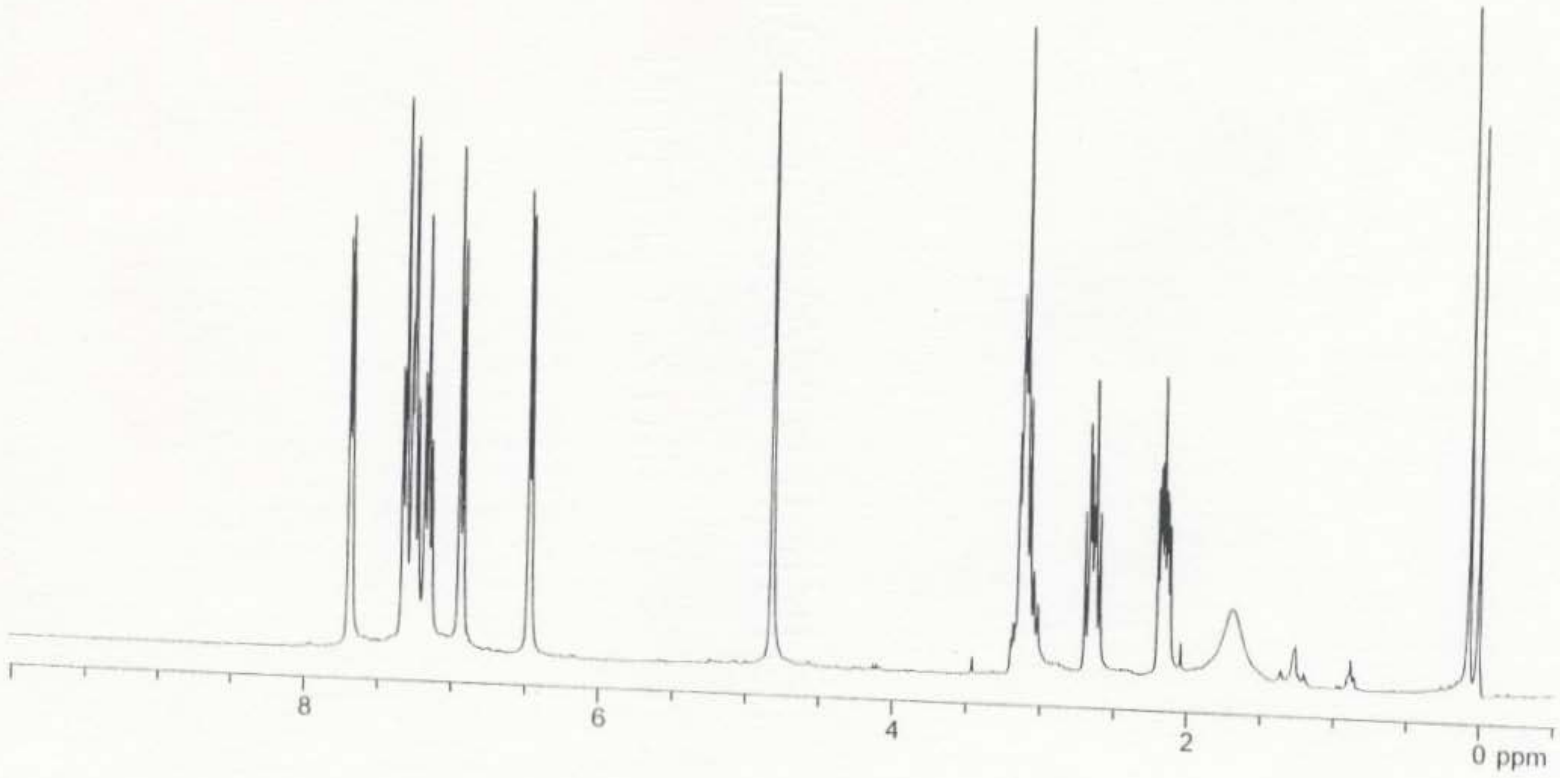

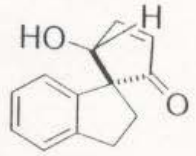

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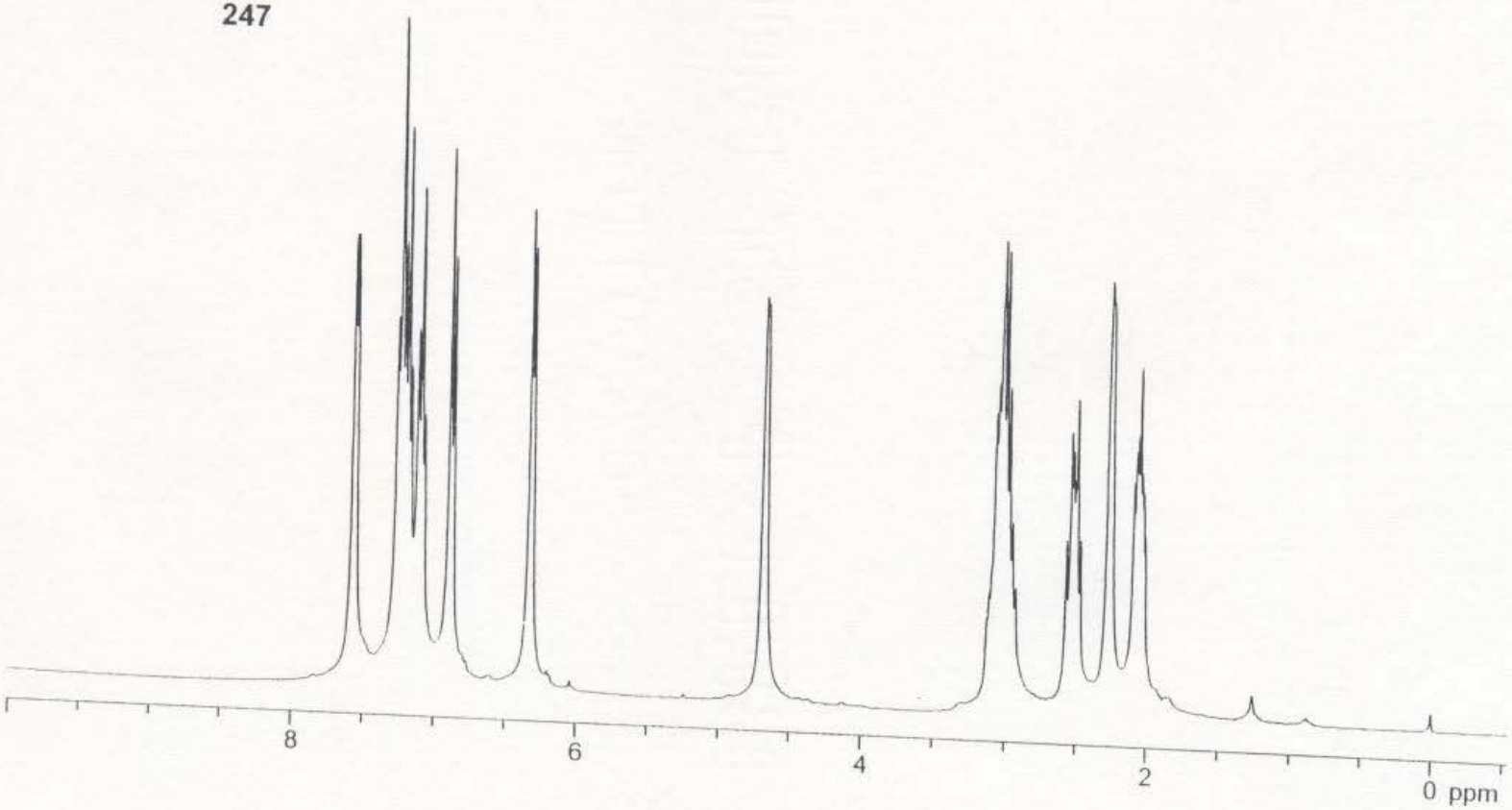

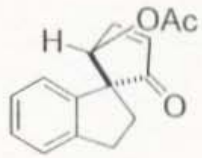

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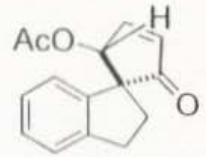

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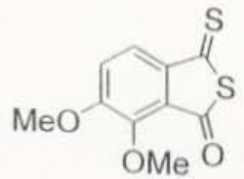

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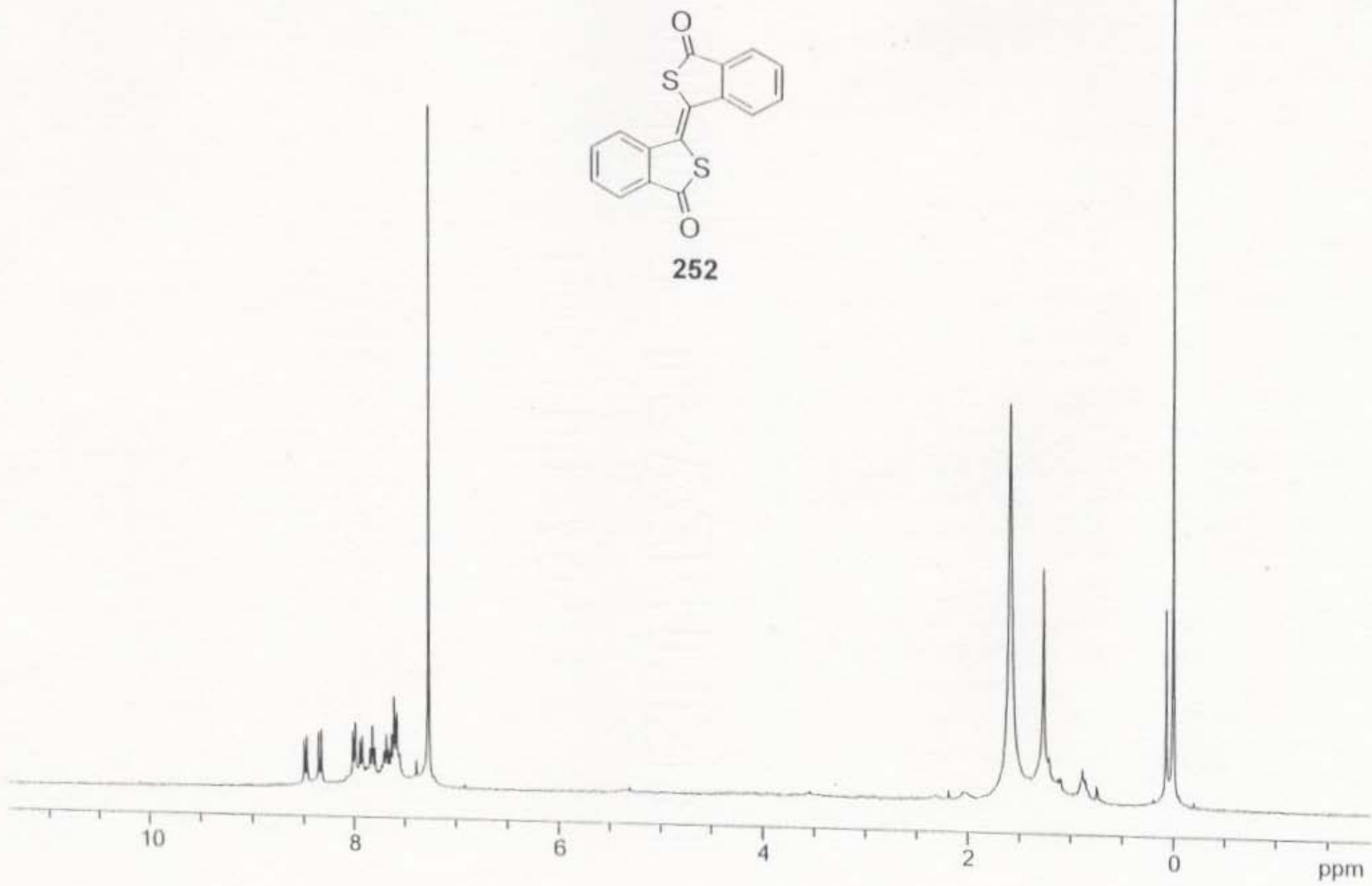

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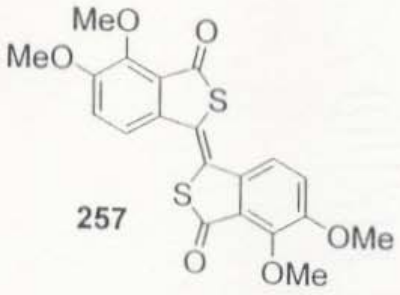

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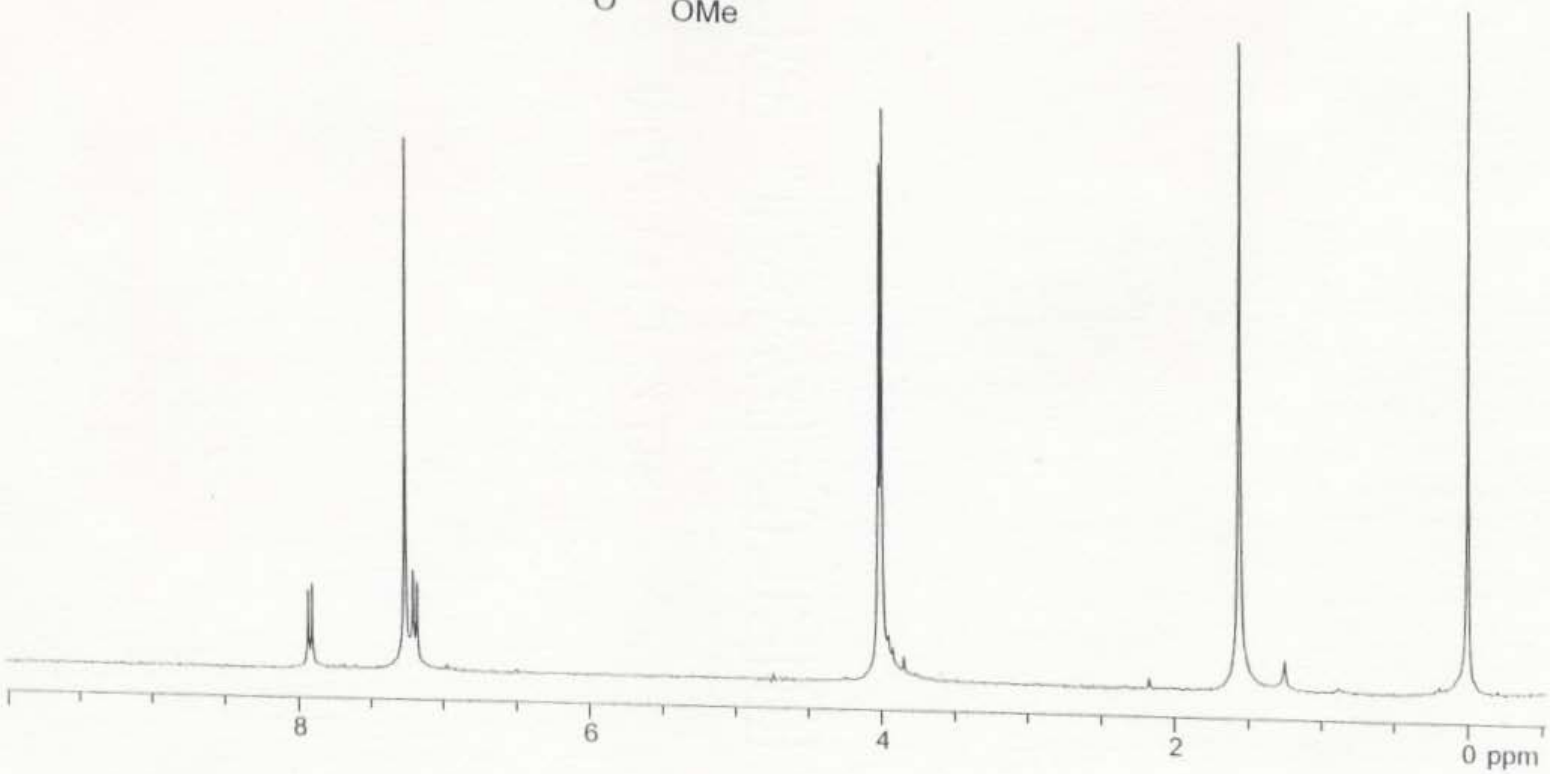

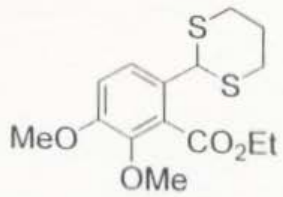

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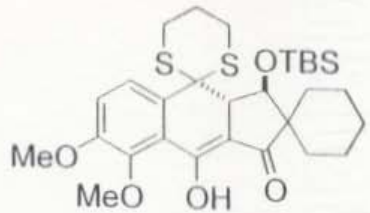

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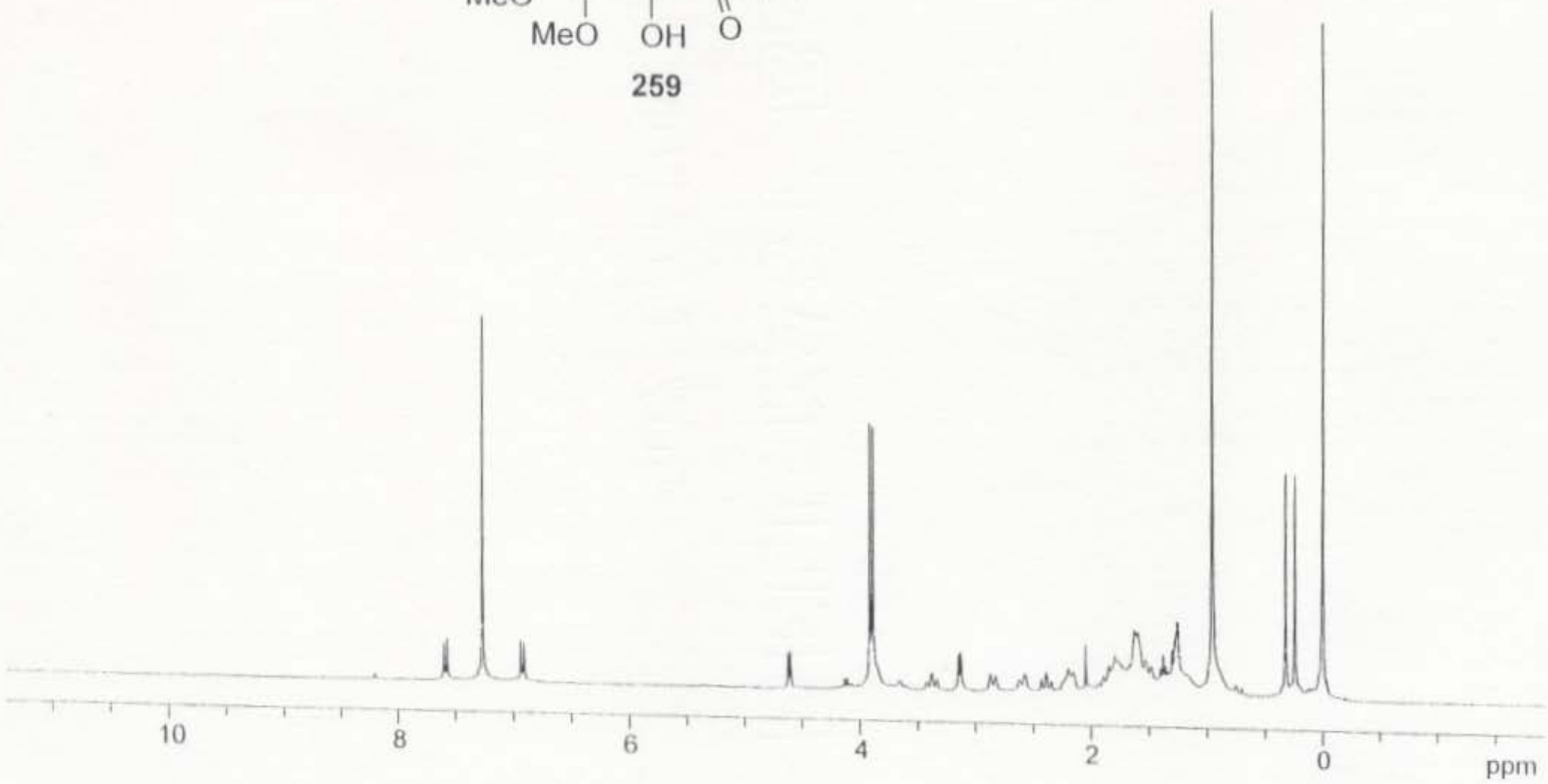

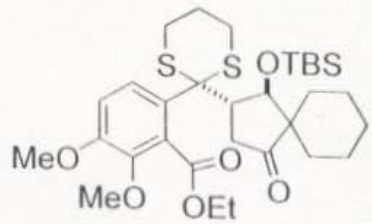

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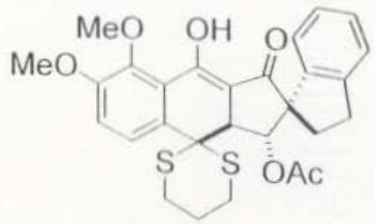

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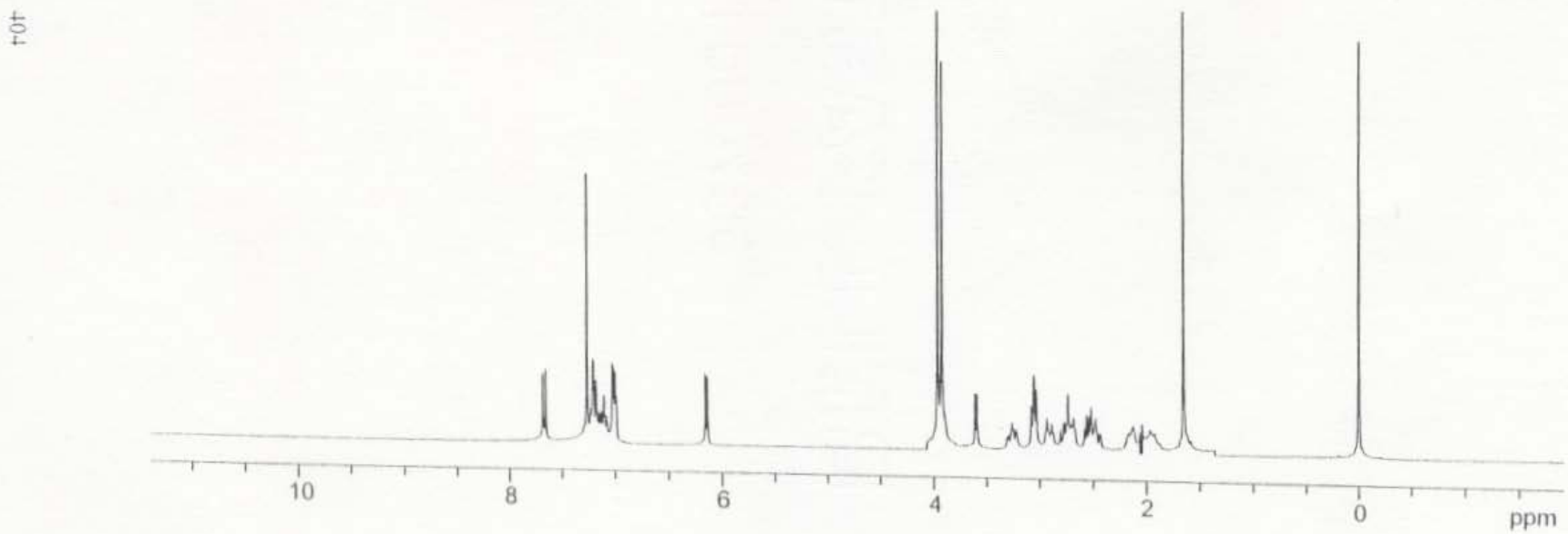
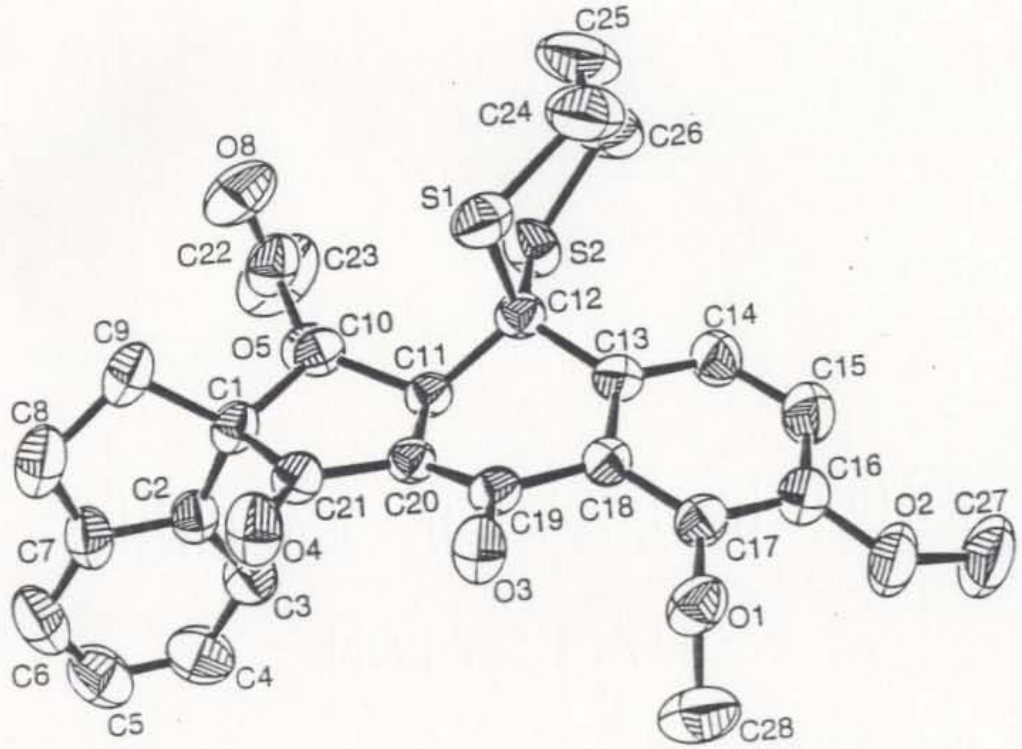
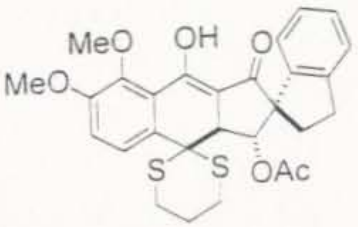






261

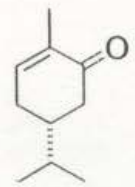
X-ray crystal structure (ORTEP) of **261**

Appendix II

^{1}H NMR Spectra and X-ray Structures for Chapter 2

^{1}H NMR spectra for compounds **271**, **274**, **275** ($CDCl_3$ and C_6D_6), **277**, **278**, **279** and **283**.

X-ray structures for compounds **277**, **278** and **279**.



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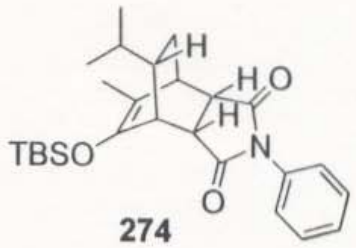
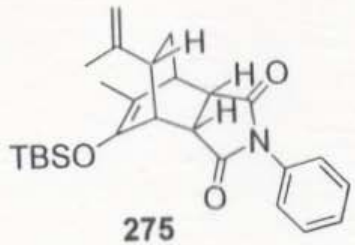


274



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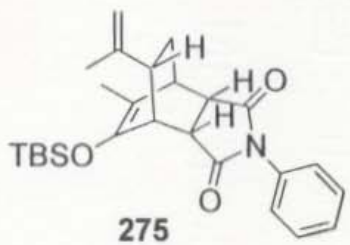

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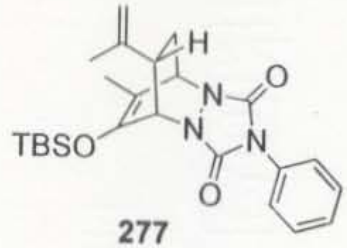

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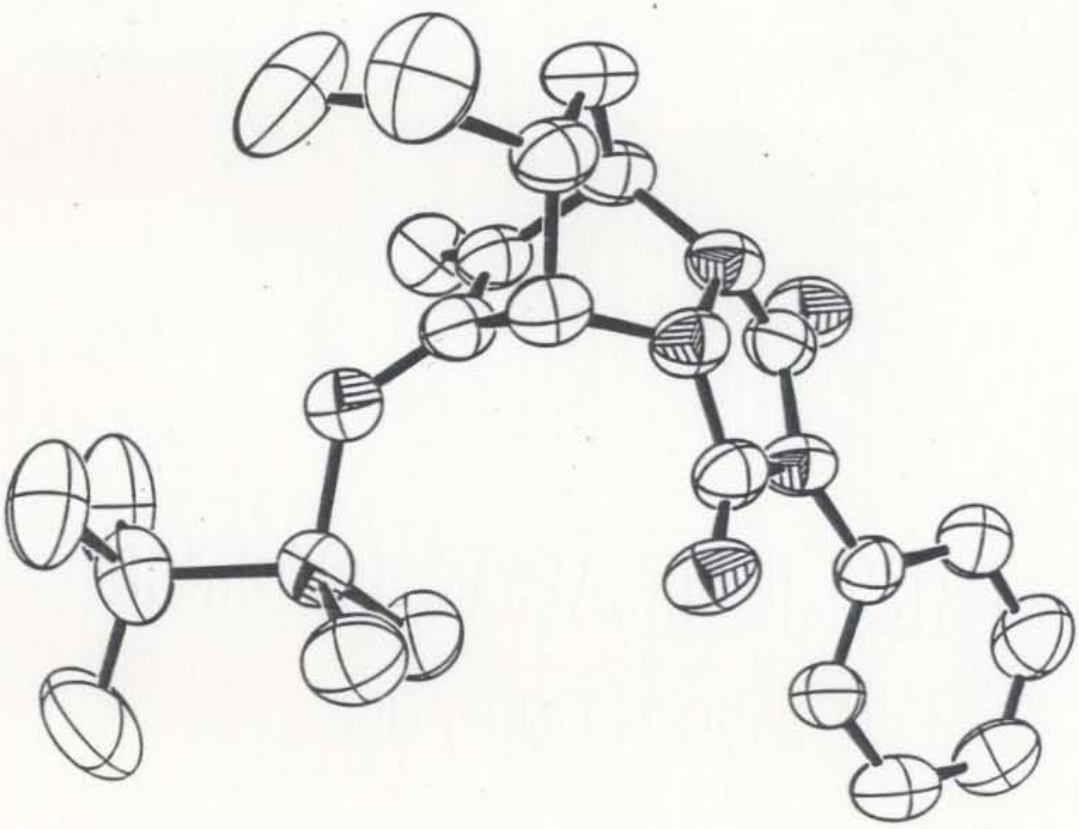
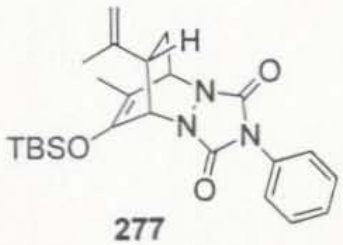
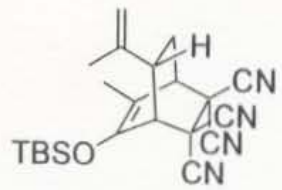


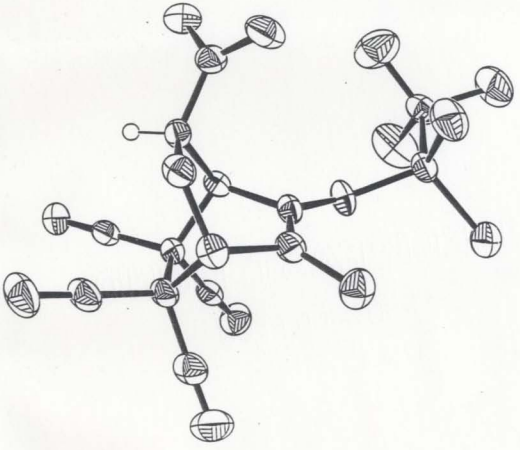


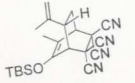
277

X-ray crystal structure (ORTEP) of **277**



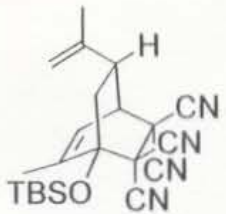
278





278

X-ray crystal structure (ORTEP) of **278**



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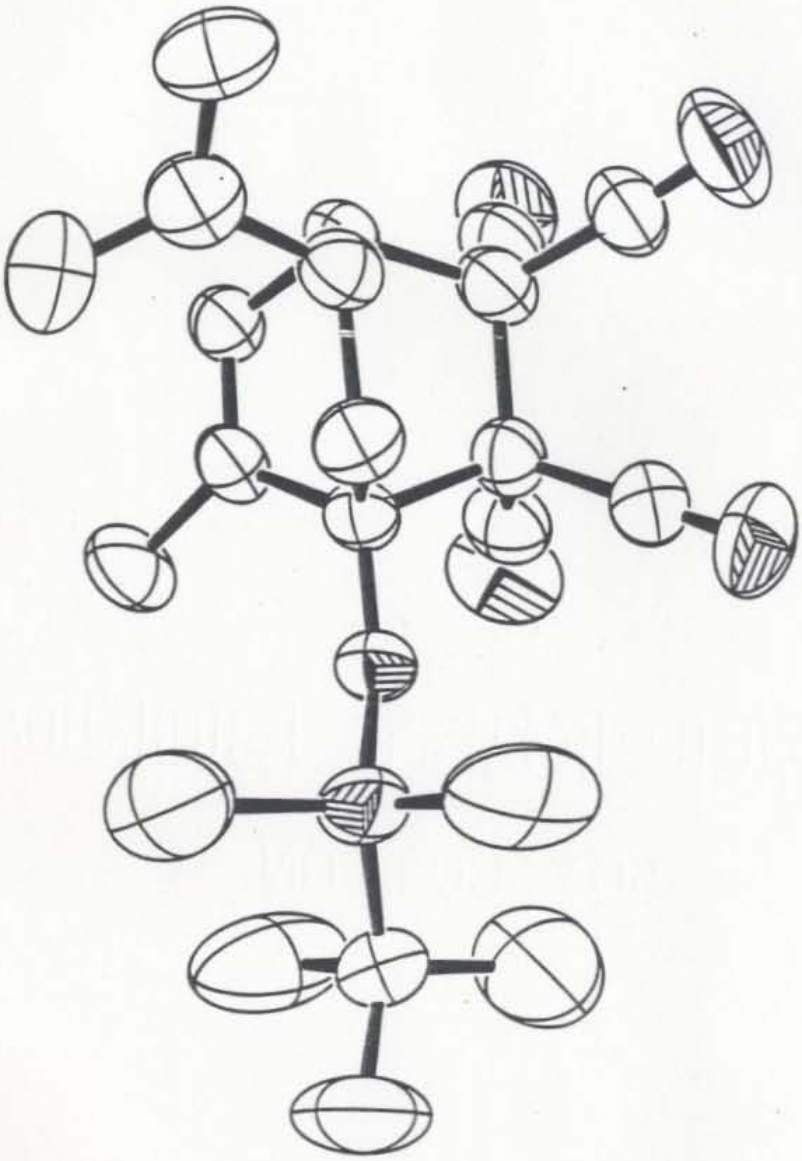
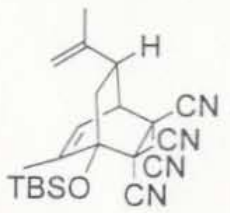
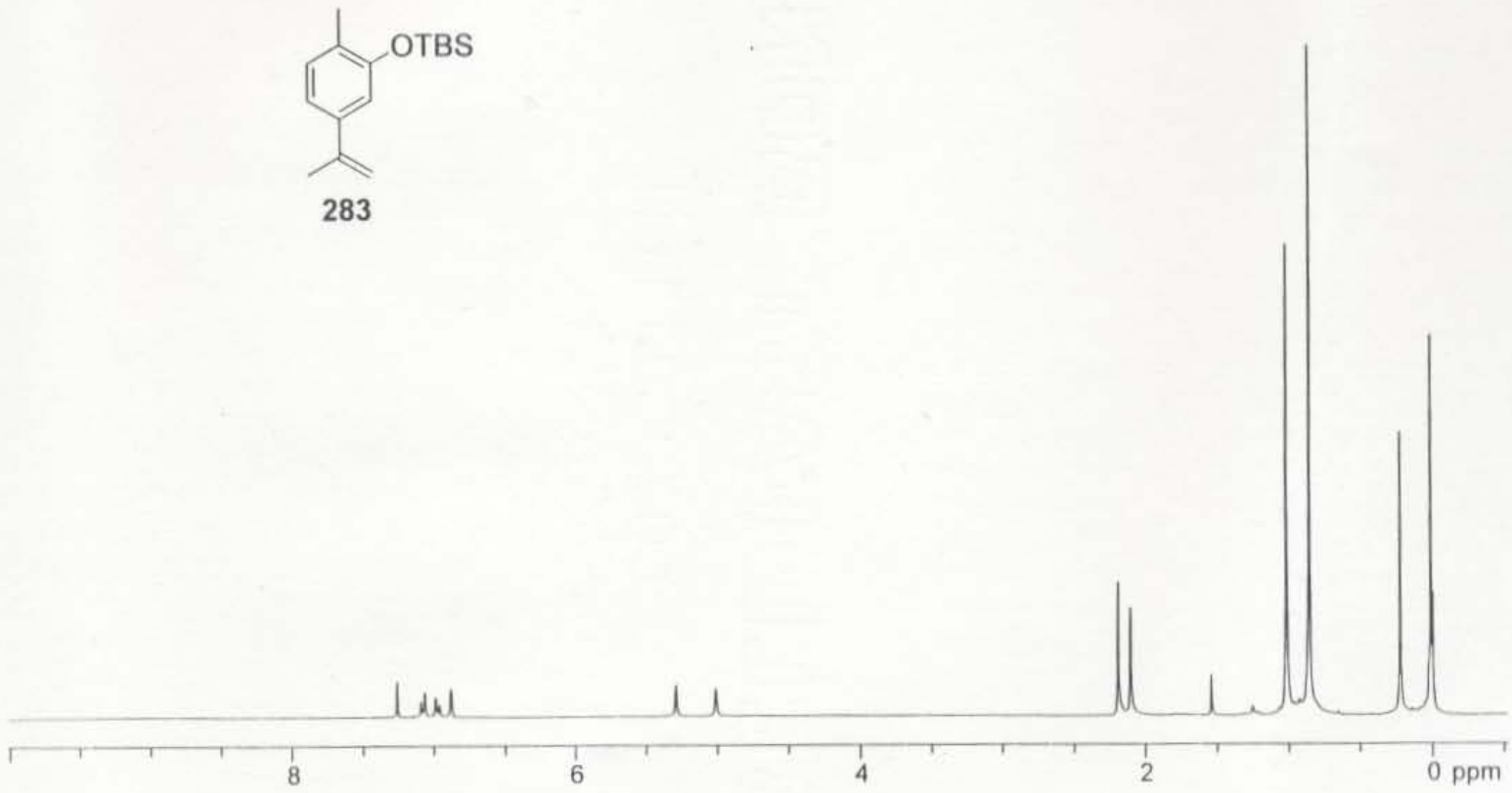




279

X-ray crystal structure (ORTEP) of **279**



283