A STUDY OF THE INTER- AND INTRAMOLECULAR DIELS-ALDER REACTIONS OF *ORTHO*-QUINONES AND THEIR MONOKETALS: APPLICATIONS TO THE SYNTHESIS OF THE VIRIDIN FAMILY OF STEROIDAL ANTIBIOTICS

by

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Abstract

Viridin (**1**), a powerful antifungal agent first isolated over 50 years ago, is a member of a family of furanosteroid antibiotics (**1-8**) which all share the unique tricyclic naphtho[1,8-*bc*]furan structural subunit for rings A-B-E containing an angular methyl group at the A-B ring junction. In this study directed at a first synthesis of viridin, a plan was devised for annulating two rings of this tricyclic subunit by a novel one-pot intramolecular Diels-Alder (IMDA) reaction of an *o*-quinonoid monoketal generated *in situ* by oxidation of the benz[*e*]indanone thiol ester **81** (a substituted *o*-methoxynaphthol) in the presence of excess (*E*)-2,4-pentadienol. The dienophilic reactivity of the *o*-quinonoid ring in such monoketals was promoted by both the placement of an electron-withdrawing substituent ($COSCH_3$) on the *o*-quinone ring, and by involving one of quinone double bonds in aromatic resonance. The thiol ester group was chosen as a synthetic precursor to the required angular methyl group in viridin as it was expected to provide a better handle for chemoselective reduction in the presence of other carbonyl groups. The pentacyclic advanced intermediate **80** was synthesized in 8 steps and 34% overall yield, which represents a first and efficient synthesis of the furanosteroid framework of viridin. The synthetic route began with a regiocontrolled intermolecular Diels-Alder reaction between methyl (*E*)-4,6-heptadienoate and the dienophilic *o*-quinone generated from commercially available 2,3-dihydroxybenzoic acid, and culminated with the installation of rings A and E by the novel one-pot IMDA reaction. A synthetic survey of regiocontrolled intermolecular Diels-Alder reactions of substituted *o*-quinones, along with some interesting rearrangements and further transformations of these adducts, was conducted in the course of this work. The selective desulfurization of the pentacyclic

thiol ester **80** and model thiol esters **79, 130** by a variety of reduction methods met with limited success. Furthermore, it was found that due to a general anomeric effect, the ketal group of the *exo* IMDA adducts, including *exo* pentacycle **80b**, could not be transformed to furanoid analogues by acid-catalyzed elimination of methanol in ring E. These complications propelled investigations toward a convergent synthesis of viridin which would utilize the tricyclic 5a-methylnaphtho[1,8-*bc*]furan system.

The novel one-pot IMDA reaction was investigated with several *o*-benzoquinone monoketals, generated from oxidation of substituted guaiacols **64-66** and **172-176** in the presence of excess (*E*)-2,4-pentadienol. In these reactions, the *o*-quinonoid species behaved as both a diene and a dienophile forming the bridged adducts **67** and **177** as the major IMDA product, along with the minor naphthofuran *endo*-adducts **68** and **178**, in good overall yield. The bridged IMDA adducts were subsequently converted to the naphthofuran compounds by way of Cope rearrangements, thereby allowing a rapid synthesis of the important tricyclic compound **68**, the structural subunit of both viridin (**1**) and xestoquinone (**12**), in two steps and 56% overall yield from commercial 2-methoxy-4-methylphenol **64**. Several analogues of **68** were also prepared for investigating the synthesis of viridin and analogues by various convergent routes, based on either a Diels-Alder strategy or tandem Michael additions. Although viridin was not synthesized in this endeavor, the dienophilic reactivity of *o*-benzoquinones and their monoketals was uncovered and efficiently manipulated for constructing advanced precursors of viridin and congeners.

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List of Abbreviations and Acronyms

1D	one-dimensional
2D	two-dimensional
AB_q	AB quartet
Ac	acetyl
Ac_2O	acetic anhydride
AIBN	2, 2'-azobis(isobutyronitrile)
Anal.	elemental analysis
aq	aqueous
Ar	aryl
ATPase	adenosine triphosphatase
BHT	butylated hydroxytoluene
BINAP	2, 2'-bis(diphenylphosphino)-1, 1'-binaphthyl
bp	boiling point
br	broad
Bu	butyl
calc'd	calculated
CAN	ceric ammonium nitrate
CI	chemical ionization
COSY	correlated spectroscopy
δ	chemical shift relative to tetramethylsilane internal standard
d	doublet
dd	doublet of doublets
ddd	doublet of doublet of doublet
DDQ	2, 3-dichloro-5, 6-dicyano-1, 4-benzoquinone
DEPT	distortionless enhancement by polarization transfer
DIBAL-H	diisobutylaluminum hydride
dm	doublet of a multiplet
DME	1, 2-dimethoxyethane
DMF	*N, N'*-dimethylformamide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
dt	doublet of a triplet
E^+	electrophile
EDG	electron donating group
E.G.	ethylene glycol
EI	electron impact
eq., equiv.	equivalents
Et	ethyl

ether	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
EWG	electron withdrawing group
FMO	frontier molecular orbital
FTIR	Fourier transform infrared
g	gram(s)
h	hour(s)
HMBC	heteronuclear multiple bond coherence
HMPA	hexamethylphosphoric triamide
HMQC	heteronuclear multiple quantum coherence
HPLC	high-performance/high-pressure liquid chromatography
HRMS	high resolution mass spectrum
i (as in *i*-Pr)	*isomeric* (as in isopropyl)
IC_{50}	inhibitor concentration at 50% enzyme inhibition
IMDA	intramolecular Diels-Alder
IR	infrared
J	coupling constant (units of Hz)
JMOD	*J*-modulated spectrum
LD_{50}	lethal dose in 50% of the animals tested
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
LiTMP	lithium 2, 2, 6, 6-tetramethylpiperidide
LRMS	low resolution mass spectrum
m	multiplet
M^+	molecular ion
m/e	mass-to-charge ratio
Me	methyl
MeOH	methanol
MHz	megahertz
min.	minutes
mM	millimoles per liter
mol	moles
MOM	methoxymethyl
mp	melting point
n (as in *n*-BuLi)	*normal* (not branched) butyl group
NMR	nuclear magnetic resonance
NOE (nOe)	nuclear Overhauser effect
NOEDS	NOE difference spectrum
NOESY	NOE spectroscopy
o	*ortho*

p (as in *p*-TsOH)	*para* (as in *para*-toluenesulfonic acid)
Pd/C	palladium-on-carbon
Ph	phenyl
PhH	benzene
PIDA	phenyliodosyl diacetate
PIFA	phenyliodosyl bis(trifluoroacetate)
PMO	perturbational molecular orbital
PPA	polyphosphoric acid
ppm	parts per million
pyr	pyridine
q	quartet
R_f	retention factor
s	singlet
S_N2	bimolecular nucleophilic substitution
sp.	*species*
t (as in *t*-BuLi)	*tert, tertiary* (as in *tert*-butyllithium)
t	triplet
TBDMS	*tert*-butyldimethylsilyl
TCE	1, 1, 2, 2-tetrachloroethane
Tf	triflate, trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMB	1, 2, 4-trimethylbenzene
TMS	trimethylsilyl
TOCSY	totally correlated spectroscopy
Ts, tosyl	*para*-toluenesulfonyl
TsOH	*para*-toluenesulfonic acid
vol	volume

CHAPTER 1

STRATEGIC INVESTIGATIONS TOWARD THE SYNTHESIS OF THE VIRIDIN FAMILY OF NATURAL PRODUCTS

1.1 Introduction

1.1.1 The Viridin Family of Natural Products

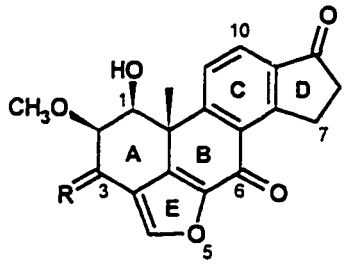
Over the past several decades, the steroids have been among the most well-studied classes of natural products, and some members which possess interesting structural features and biological activities have commanded even greater attention. Included in this category are the structurally unique viridin family of steroidal antibiotics[1] (**1-8**), all pentacyclic furanosteroids which contain a furan ring fused to rings A and B of the steroid ring system, and sometimes possess an aromatic ring C. Some members of this family have also exhibited biological activities ranging from selective antifungal activity to specific inhibition of cell signaling pathways.

Viridin (**1**), a secondary fungal metabolite of *Gliocladium virens*, was first isolated in 1945 by Brian and McGowan[2] from some strains of a mold erroneously identified at the time as *Trichoderma viride*, and which had exhibited powerful and selective antifungal activity. At minimum concentrations of the order of 0.003-0.006 μg/mL in aqueous media, viridin inhibited the germination of spores of *Botrytis allii*,

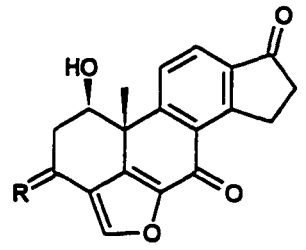
Colletotrichum lini, and *Fusarium caeruleum* fungi.[2b] Other fungal species such as *Penicillium expansum*, *Aspergillus niger*, and *Stachybotrus atra* were comparatively less sensitive to the fungistatic action of viridin, requiring minimum concentrations of 3.1-6.25 μg/mL to prevent germination of spores. While viridin has negligible antibacterial properties in tests against *Staphylococcus aureus*, *Escherichia coli*, and *Salmonella typhi*,[2b] limited antibiotic activity was exhibited against the plant pathogens *Rhizoctonia solani* and *Pythium ultimum*.[3]

During the 1960's, the structural elucidation of viridin was intensively investigated by Grove, Moffatt and co-workers using classical chemical degradation methods which had confirmed the presence of an aromatic ring, two easily reducible carbonyl groups, and one hydroxyl and one methoxyl functional group.[4] Mild oxidation of viridin with hydrogen peroxide furnished the tetracyclic acid **10** (Figure 1.2) and its subsequent transformation to the naphtho[2,3-*b*]furan **11** had established the location of the furan ring within the skeletal framework of viridin.[5] Unequivocal proof of the structure and relative configuration of viridin was confirmed soon after by X-ray crystallographic analysis,[6] which had clearly shown that the tricyclic naphtho[1,8-*bc*]furan subunit **9** (R=O) of viridin was indeed a highly strained structural moiety. Elucidation of the steroidal biosynthetic origin of viridin and its congeners by way of farnesyl pyrophosphate had also revealed that the absolute configuration for the C_{11b}-methyl substituent was β, as shown in (**1**).[7]

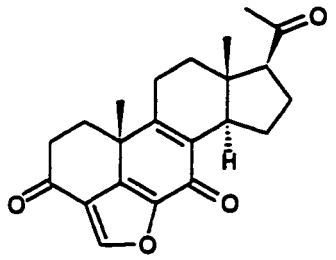
Figure 1.1: Molecular structures of the viridin family of furanosteroid antibiotics (**1-8**) and the tricyclic 5a-methyl-3,4,5a,8-tetrahydro-5*H*-naphtho[1,8-*bc*]furan-3,8-dione subunit **9**.



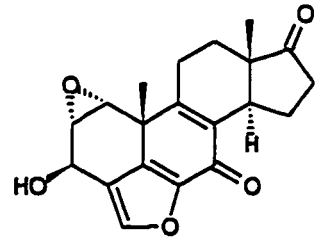
1 (R = O) **Viridin**
2 (R = α-H, β-OH) **Viridiol**



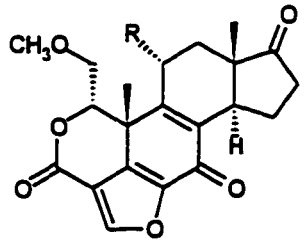
3 (R = O) **Demethoxyviridin**
4 (R = α-H, β-OH) **Demethoxyviridiol**



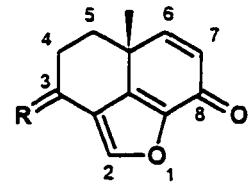
5 **Virone**



6 **Wortmannolone**

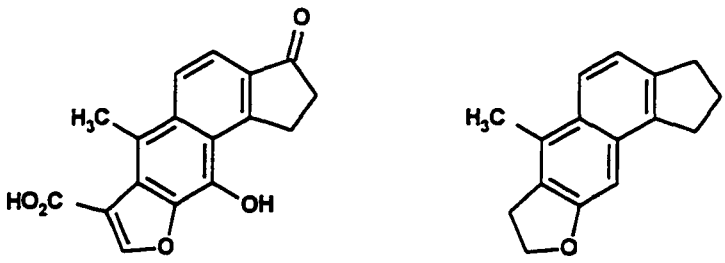


7 (R = OAc) **Wortmannin**
8 (R = H) **11-Desacetoxywortmannin**



9
(R = O or α-H, β-OH)

Figure 1.2: Mild oxidation of viridin (**1**) with hydrogen peroxide furnished the tetracyclic acid **10**, which was further transformed to naphtho[2,3-*b*]furan **11**.[5]



10 **11**

The remaining members of the viridin family of furanosteroids (**2-8**, Figure 1.1) also possess remarkable biological activities, although some have demonstrated levels of toxicity which have precluded their use as agricultural biocontrolling agents. The discovery and characterization of viridiol (**2**) from *Gliocladium virens* was reported in 1969, nearly 25 years following the discovery of viridin from the same mold.[8] Viridiol (**2**) was shown to be a phytotoxin which caused necrosis of cotton seedling radicles.[8b] Unlike viridin, (**2**) did not display any remarkable fungistatic action on representative fungi, but did exhibit herbicidal activity *in vitro* against pigweed seed, a significant weed pest in cotton fields. A preparation of dried and ground *G. virens* which was embedded in the pigweed-laden soil of a small cotton seed plantation had effectively prevented further growth of the weed with no damage to the new cotton seedlings. Unfortunately, the yield of viridiol from *G. virens* was highly dependent on the temperature and type of medium on which the fungus was grown. As a result, the large-scale agricultural use of viridiol as a biological herbicide was not economically feasible. Demethoxyviridin[9a] (**3**), an antifungal agent, and demethoxyviridiol[9b] (**4**), a phytotoxin (which caused necrosis of

corn plants) and mycotoxin (oral LD_{50}, day-old cockerels = 4.2 mg/kg), were isolated in 1975 as metabolites from *Nodulisporium hinnuleum*, a fungus which was formerly classified as *Apiospora camptospora*. Virone (**5**), a minor fungal metabolite from the fermentation of *Gliocladium virens* at 32°C, was identified in 1986 as a pregnane analogue of and possible biosynthetic precursor to viridin; however due to the low titer of this compound in the fermentation broth, its biological activity remains unknown.[10] Nonetheless, the structural elucidation of these congeners of viridin was comparatively expedient given the availability of X-ray crystallographic and nuclear magnetic resonance techniques and published data for viridin.

Other structural relatives of viridin are the wortmannin series of natural products which have also exhibited diverse bioactivity. Wortmannolone[10] (**6**) and wortmannin[11] (**7**) are metabolites from *Penicillium wortmannii*, and the latter has displayed highly specific antifungal activity at concentrations of 0.4-3.2 μg/mL against five fungal species, *Botrytis allii*, *B. cinerea*, *B. fabae*, *Cladosporium herbarum*, and *Rhizopus stolonifer*. In addition, both wortmannin and 11-desacetoxywortmannin[12] (**8**), the latter isolated from *Penicillium funiculosum*, have exhibited potent anti-inflammatory activity comparable to those of the known therapeutics indomethacin, dexamethasone, and phenylbutazone, despite having moderate toxicity in mammals[12a] (for 11-desacetoxywortmannin, LD_{50}, rat = 28 mg/kg compared to >3 mg/kg for dexamethasone). Yet another biological role which has recently been elucidated for both wortmannin (**7**) and demethoxyviridin (**3**) is the inhibition of fMet-Leu-Phe-stimulated superoxide production in the human neutrophil by non-competitively blocking phospholipase D (PLD) activation, an important enzyme involved in intracellular signal transduction.[13] It has been speculated that both demethoxyviridin and wortmannin may act at a common site along the signal

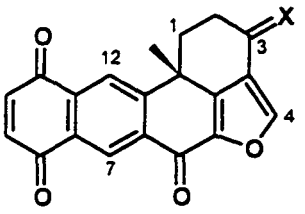
transduction pathway, perhaps by blocking the interaction between the fMet-Leu-Phe receptor and a GTP-binding protein that participates in PLD activation.

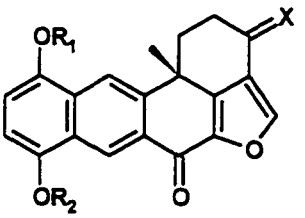
1.1.2 Natural Products Structurally Related to Viridin: Xestoquinone, Halenaquinone, and the Adociaquinones

Several marine sponge metabolites of polyketide biosynthetic origin also share the same tricyclic naphthofuran subunit **9** as do the members of the viridin family of natural products (Figure 1.3). The quinonoid natural products xestoquinone[14] (**12**) obtained from the marine sponge *Xestospongia sapra*, and halenaquinone[15] (**13**) from the sponge *Xestospongia exigua*, are functionalized benzo[6,7]phenanthro[10,1-*bc*]furans which only differ in either the presence or absence of a C-3 carbonyl group. Xestoquinone has demonstrated potent cardiotonic activity and positive inotropic action, as well as inhibition of Na,K-ATPase.[14b] Halenaquinone was first shown to exhibit antibacterial activity *in vitro* against *Staphylococcus aureus* and *Bacillus subtilis*.[15] More recently, halenaquinone has also exhibited irreversible inhibition of the oncogenic $pp60^{v\text{-}src}$ protein tyrosine kinase encoded by the Rous sarcoma virus (IC_{50} =1.5 μM) as well as inhibition of the epidermal growth factor (EGF) receptor protein tyrosine kinase (IC_{50}=19 μM).[16] Halenaquinone also halted the proliferation of several cultured cell lines which were transformed by these oncogenic protein tyrosine kinases.[16a] In fact, both halenaquinone and halenaquinol (**14**) are included among the most active inhibitors of protein tyrosine kinases, a group of enzymes which have been associated with proliferative disorders (i.e. cancer, psoriasis) and regulation of cell growth. The reduced

derivatives halenaquinol (**14**) and halenaquinol sulfate (**15**) are both secondary metabolites of *Xestospongia sapra*,[17] and their structures were determined by chemical conversion to their parent quinone (**13**). The series of adociaquinones A (**16**), B (**17**), and 3-ketoadociaquinone A (**18**), all isolated from the *Adocia sp.* sponge by Schmitz and Bloor,[18] each bear an additional 1,1-dioxo-1,4-thiazine ring fused to a pentacyclic framework that is structurally identical to either xestoquinone or halenaquinone, and proof of their chemical structures was confirmed by their synthesis from these parent compounds. Furthermore, xestoquinone, halenaquinone, and adociaquinones A and B all displayed potent inhibitory activity of the mammalian topoisomerases I (range for IC_{50} = 0.16-2.2 μg/mL)[19] and II (range of IC_{90} = 10-90 μM)[20], which are involved in DNA replication and transcription. In recent years, high levels of topoisomerase II have been detected in tumor cells,[21a] suggesting its possible role in the proliferation of cancer cells. Consequently, topoisomerase II is presently considered an important target for the development of antitumor therapeutic agents.[21b] It has been suggested that these natural products do not act as DNA intercalators, but rather interact with the enzyme by either preventing binding of DNA or by forming an irreversible, uncleavable drug-enzyme-DNA ternary complex.[20, 21b] When one considers the wide spectrum of bioactivity displayed by the xestoquinone family of natural products, coupled with their relative structural simplicity compared with members of the more complex viridin family, it became apparent that any synthetic effort would most appropriately be directed at either xestoquinone (**12**) or halenaquinone (**13**) as initial natural product targets. Moreover, efficient construction of a tricyclic naphthofuran moiety similar to **9** would serve as a convenient building block for the synthesis of any one of the aforementioned natural products.

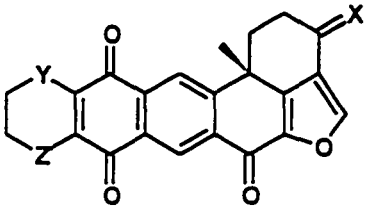
Figure 1.3: Molecular structures of quinonoid natural products related to xestoquinone.





12 (X = H, H) **Xestoquinone**
13 (X = O) **Halenaquinone**

14 (X = H, H; R_1=R_2=H) **Halenaquinol**
15 (X = H, H; R_1= SO_3Na, R_2=H) **Halenaquinol Sulfate**



16 (X = H, H; Y= NH; Z=SO_2) **Adociaquinone A**
17 (X = H, H; Y=SO_2; Z=NH) **Adociaquinone B**
18 (X = O; Y=NH; Z=SO_2) **3-Ketoadociaquinone A**

1.2 Synthetic Approaches Toward Xestoquinone, Halenaquinone, and the Adociaquinones

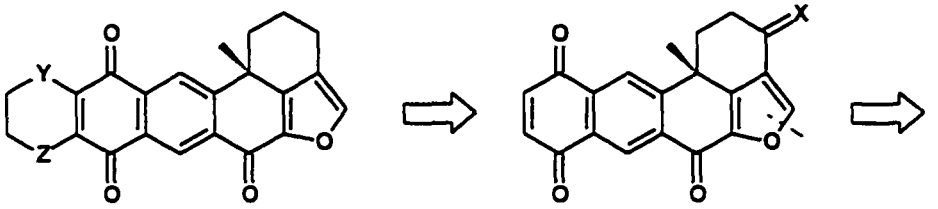
Viridin (**1**) and its analogues (**2-5**) have been known for several decades, yet despite their interesting bioactivities, there are no accounts of any synthetic investigations toward any member of this family of natural products. Furthermore, the synthesis of the furanosteroid ring system (systematically named as a 11b-methyl-cyclopenta[7,8]-phenanthro[10,1-*bc*]furan ring system), which possesses the highly strained 5a-methyl-

naphtho[1,8-*bc*]furan moiety **9**, had yet to be accomplished. By comparison, several syntheses of xestoquinone (**12**), halenaquinone (**13**), and their direct relatives (**14-17**) have been achieved in the past decade. It would therefore be worthwhile to review and critically examine the synthetic approaches which were employed in constructing the benzo[6,7]phenanthro[10,1-*bc*]furan ring system of this latter set of natural products, for an attempted first synthesis of viridin. Moreover, a general and efficient construction of **9**, a plausibly simple tricycle which has been synthesized only in recent years, would be the key to unlocking the pathways toward these compounds.

Harada and co-workers were the first to accomplish the syntheses of halenaquinone and halenaquinol in 1988,[22] xestoquinone and xestoquinol in 1990,[23] and more recently the adociaquinones A and B.[24] A composite retrosynthetic plan employed for the synthesis of all six natural products is presented in Scheme 1.1. The convergent synthetic strategy involved a Diels-Alder coupling of the diene generated from 3,6-dimethoxybenzocyclobutene **20** and the asymmetric dienophile **21**, the latter which was synthesized from optically pure (8a*R*)-(-)-Wieland-Miescher ketone **22** in 8 steps and 32% overall yield. The Diels-Alder adduct was subsequently air-oxidized to form the tetracyclic diosphenol **19** (where X=H for xestoquinone and X=OH for halenaquinone) which was suitably functionalized for oxidative ring-closure to form the furan ring. Oxidative cleavage of the hydroquinone dimethyl ether moiety afforded the quinonoid natural products (**12**) or (**13**), and treatment of xestoquinone (**12**) with excess hypotaurine (2-aminoethanesulfinic acid) in warm polar media (ethanol-CH_3CN-H_2O at 40°C) gave both adociaquinones A (**16**) and B (**17**) in 17% and 59% yields, respectively. While the convergent nature of this synthesis was appealing, the appropriate pieces had to be meticulously functionalized so that minimal adjustments were needed in order to apply

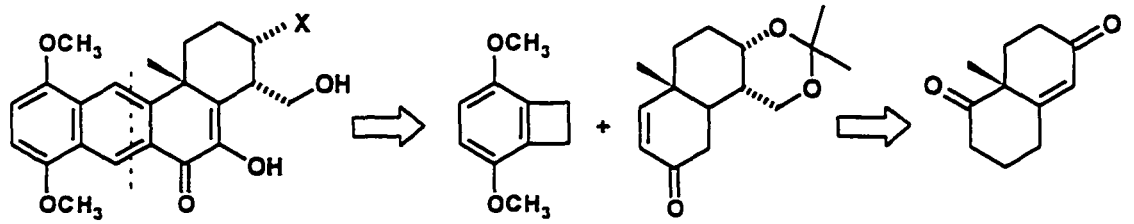
this synthetic plan to this group of natural product targets. The actual synthetic route was consequently tedious and generally inefficient in the range of 4-6% overall yields and 14-16 steps from **22**. The consideration of viridin (**1**) or any of its congeners (**2-5**) as a possible target by Harada's plan would likely be challenging and perhaps even unrewarding.

Scheme 1.1 [22-24]



16 (Y=NH; Z=SO_2) **Adociaquinone A**
17 (Y=SO_2; Z=NH) **Adociaquinone B**

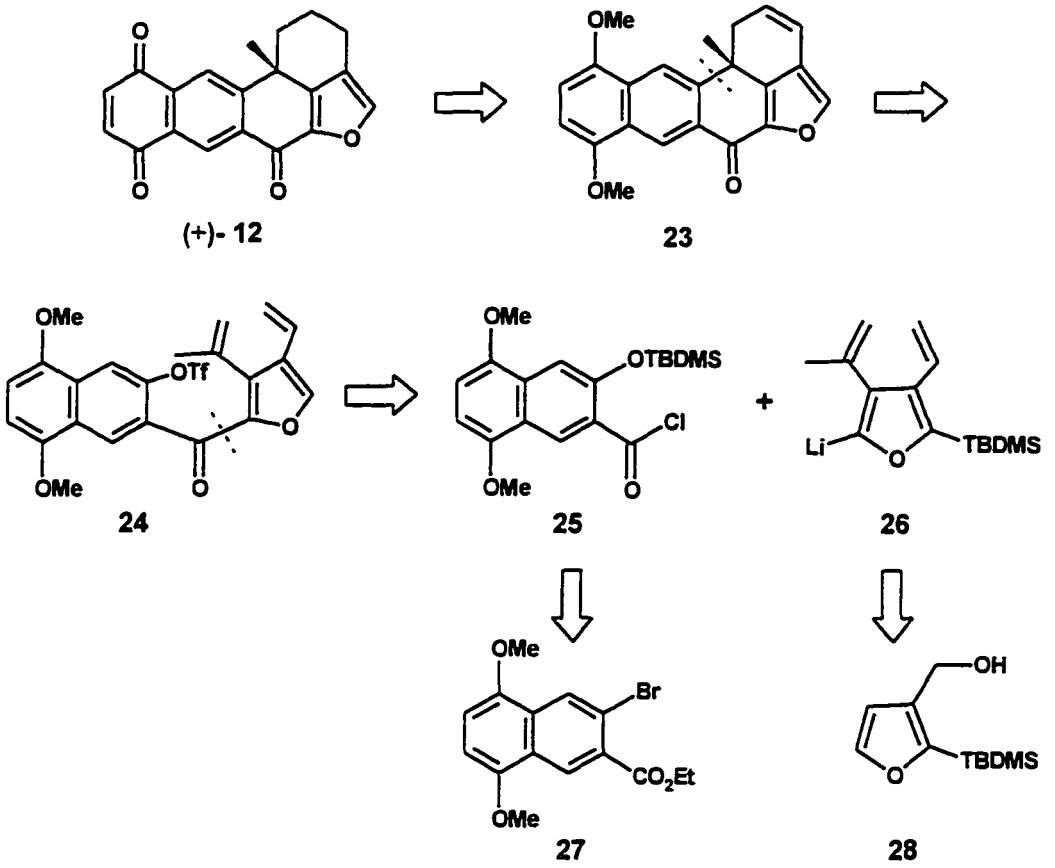
12 (X = H, H) **Xestoquinone**
13 (X = O) **Halenaquinone**



19 (X = H or OH) **20** **21** **22**

The asymmetric synthesis of (+)-xestoquinone (**12**), and also of (+)-halenaquinone (**13**) and (+)-halenaquinol (**14**), have been independently accomplished by two research groups. In the first total synthesis of (+)-xestoquinone (**12**) outlined retrosynthetically in Scheme 1.2, Keay and co-workers[25a] had demonstrated a palladium(0)-catalyzed polyene cyclization of the advanced aryl triflate intermediate **24**

Scheme 1.2 [25a]

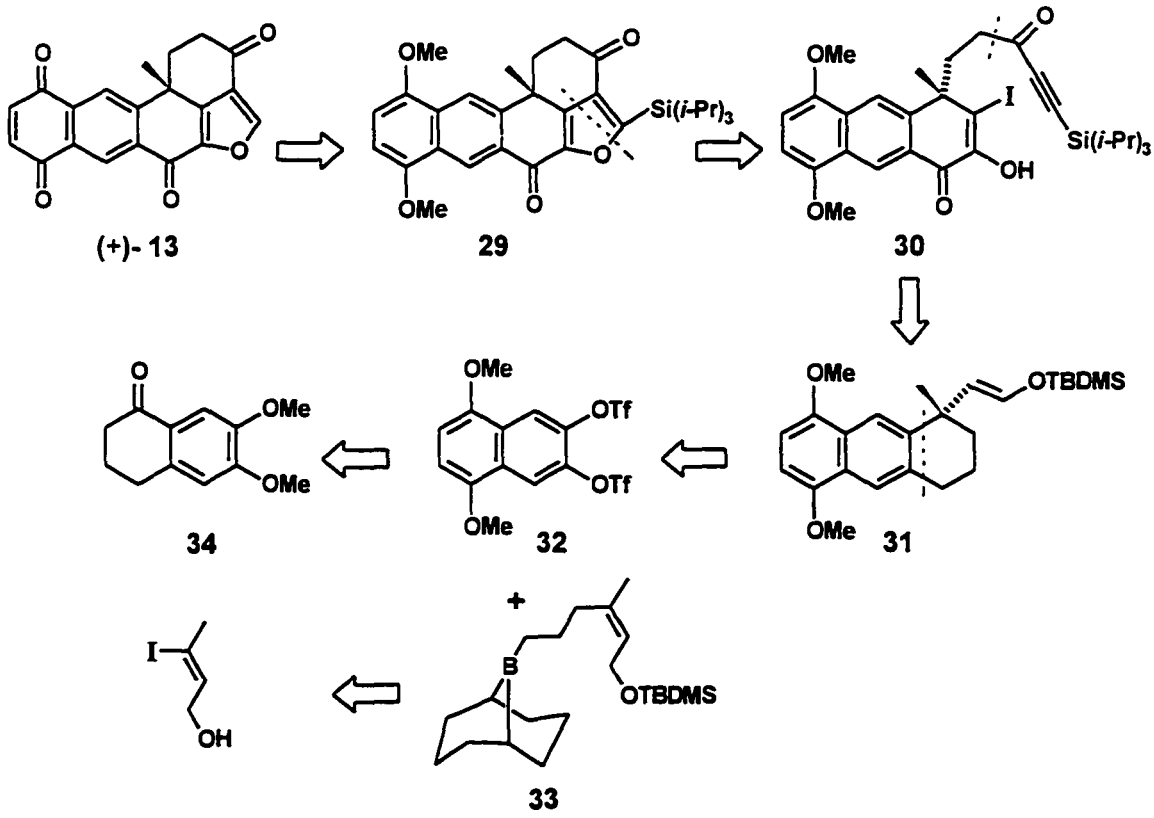


using (*S*)-(+)-BINAP as a chiral ligand,[25b] which produced the enantiomerically correct pentacyclic precursor **23** in 82% yield and 68% ee. Construction of the advanced triflate **24** required the coupling of the naphthoyl chloride **25**, formed in 5 steps and 53% yield from naphthyl bromide **27**, with the functionalized furan **26**, the latter prepared from the previously known 2-*t*-butyl-dimethylsilyl-3-hydroxylmethylfuran **28** in 5 steps and 77% yield by an *in situ* modified Suzuki cross-coupling reaction with 2-bromopropene.[26] While this comparatively short and efficient synthetic route (11 steps and 11.3% overall yield from furan **28**) also required the preparation of highly functionalized components to

form a specific target molecule, the strategy could potentially be modified for preparing other structurally related targets, including viridin (**1**).

An asymmetric synthesis of both (+)-halenaquinone (**13**) and (+)-halenaquinol (**14**) was recently reported by Shibasaki and co-workers.[27] The retrosynthetic analysis (Scheme 1.3) featured the first use of a tandem Suzuki cross-coupling and asymmetric Heck reaction between the functionalized borane **33** and the naphthyl ditriflate **32** (the latter prepared in 6 steps and 58% overall yield from the commercially available tetralone **34**) for construction of the advanced tricyclic intermediate **31**.

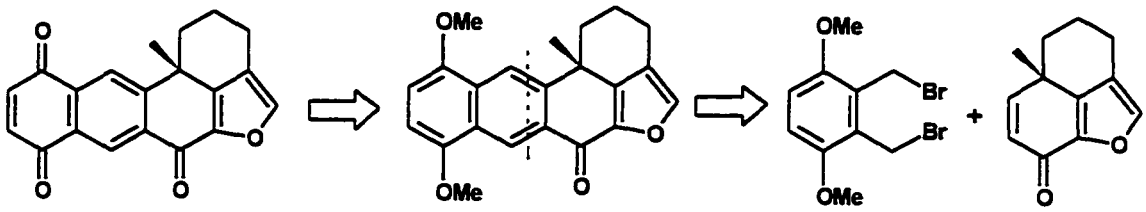
Scheme 1.3 [27]



After elaboration of the alkynyl side-chain in intermediate **30**, a one-step process to furnish the pentacyclic precursor **29** was achieved in good yield and enantioselectivity (72% yield, 87% ee) by way of an intramolecular palladium(0)-catalyzed cyclization. Although the key steps were well-crafted, the overall yield of this lengthy synthetic route (21 steps!) was unfortunately low (1-2% yield) due to the need for numerous protection and deprotection steps.

Among the natural products which possess the tricyclic subunit **9**, xestoquinone (**12**) is perhaps the most structurally simple synthetic target, since it contains a minimal number of functional groups and only one stereocenter. As such, the synthetic efforts of many research groups interested in the viridin family of natural products have been initially directed at the synthesis of xestoquinone. Devising a general, efficient and versatile synthetic strategy should therefore be paramount in such a synthetic plan, in order to realistically apply the strategy toward the synthesis of viridin (or any of its derivatives). Despite the impressive synthetic achievements just described, few research groups have succeeded in this endeavor. Included among the few are Kanematsu and co-workers, who have forged a simple and effective strategy in a formal synthesis of xestoquinone (**12**) (Scheme 1.4) as a prelude to synthesizing the more complex target, viridin.[28]

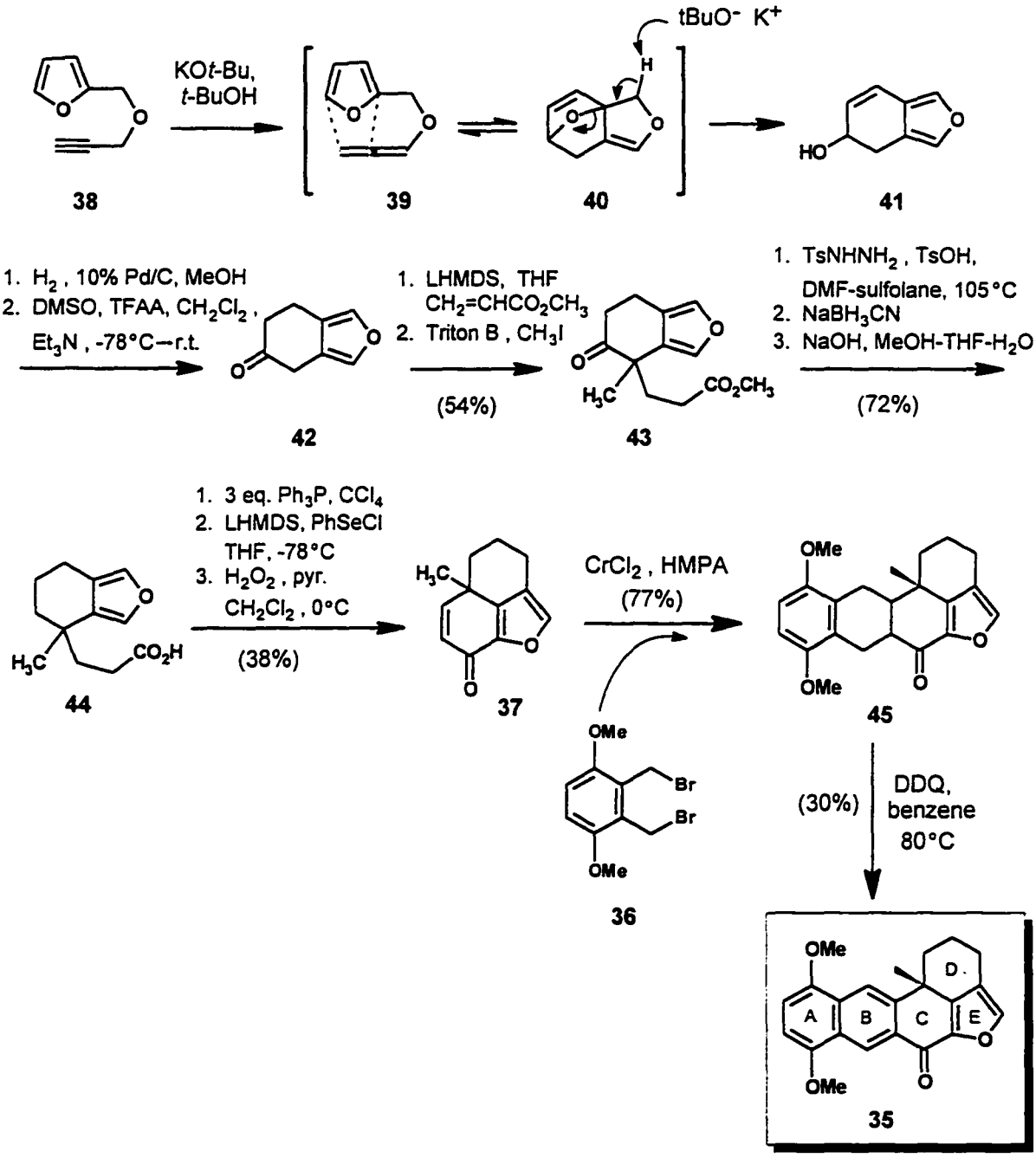
Scheme 1.4 [28a]



12 **35** **36** **37**

The retrosynthetic plan involved construction of the known advanced pentacycle[23] **35** by a Diels-Alder cycloaddition between the *o*-benzoquinodimethane generated *in situ* from dibromide **36**, and the naphtho[1,8-*bc*]furan dienophile **37**, the latter being an analogue of the structural subunit **9** (where R= H, H). Until that time, there were no reports of the preparation of a functionalized naphtho[1,8-*bc*]furan like **9** substituted at the angular C-5a position with a methyl group. The synthesis of this key component[28] was realized by the novel "furan ring transfer" methodology developed earlier by Kanematsu and co-workers.[29] Illustrated in Scheme 1.5, this new method involved the transformation of a 2-substituted furan **38** to the fused furan **41** by intramolecular Diels-Alder reaction of the intermediate allenyl furfuryl ether **39** generated from **38**, followed by a base-catalyzed ring-opening of the oxabicyclo adduct **40**. Following hydrogenation of a double bond in **41** and oxidation, the resulting ketone **42** was subjected to Michael addition with methyl acrylate, then subsequently alkylated with methyl iodide, furnishing furan **43** in 4 steps and 42% overall yield. Reductive deoxygenation *via* the tosylhydrazone of **43** followed by saponification of the pendant ester group gave the carboxylic acid **44**, which was annulated to the furan ring by an intramolecular Friedel-Crafts reaction using triphenylphosphine activation. The resultant tricyclic ketone was converted to the required enone **37** by α-phenylselenylation and subsequent oxidative elimination with hydrogen peroxide. The Diels-Alder reaction with the *o*-benzoquinodimethane generated *in situ* by treatment of dibromide **36** with chromium(II) chloride,[30] had produced the pentacyclic adduct **45** in good yield. Although the aromatization of the B-ring of **45** with

Scheme 1.5 [28a]

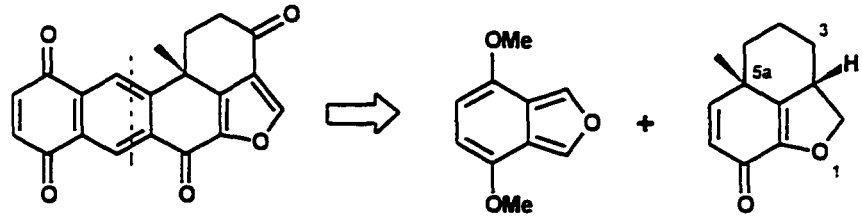


DDQ in refluxing benzene occurred in poor yield (30%), the synthesis of Harada's advanced pentacyclic precursor **35**, and hence a formal synthesis of xestoquinone (**12**),was accomplished in 12 steps and 1.5% overall yield from propargyl ether **38**.

Although Kanematsu's retrosynthetic plan in Scheme 1.4 was designed to be general and versatile, the actual synthesis of xestoquinone was rather inefficient due to the low yields obtained in certain reaction steps such as the Friedel-Crafts acylation of **44** and dehydrogenation of **45**. Nevertheless, this synthetic plan provoked one to contemplate synthesizing viridin by annulating a tricyclic enone like **9** or **37** with an array of possible reactive components.

Another recent attempt at a convergent synthesis of halenaquinone (**13**) utilizing a tricyclic dienophile such as **47** (Scheme 1.6) in a prospective Diels-Alder cycloaddition with the reactive 1,4-dimethoxyisobenzofuran **46** was investigated earlier in our laboratory.[31] Isobenzofurans, which can be generated *in situ* from their corresponding 2-hydroxyphthalans, have been known to operate as reactive dienes in Diels-Alder reactions with unactivated dienophiles.[32] The challenge therefore remained with the development of an efficient synthesis of the tricyclic dienophile similar to **9** which could improve upon the methods developed by Kanematsu and co-workers (shown in Scheme 1.5).

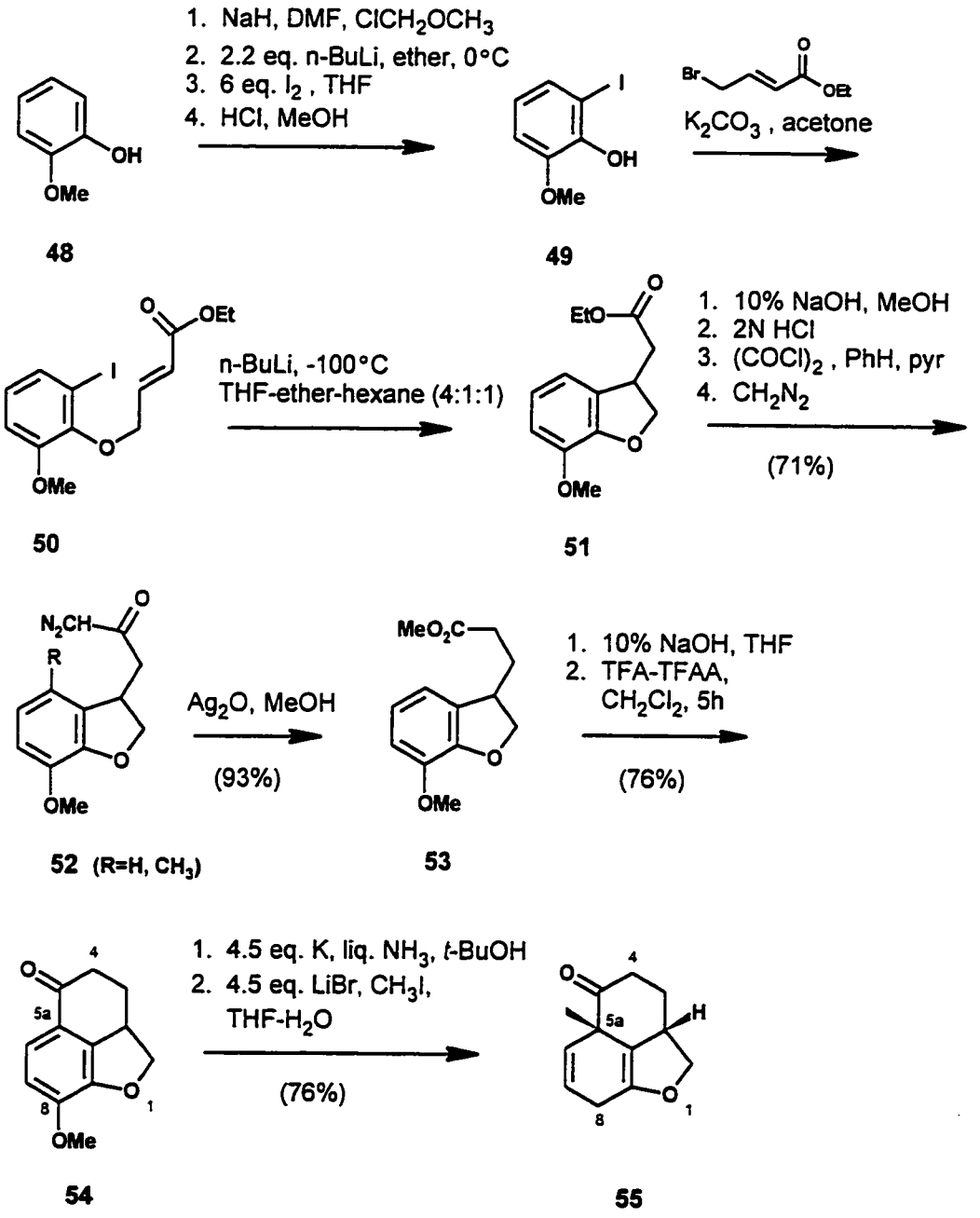
Scheme 1.6 [31]



13 **46** **47**

As illustrated in Scheme 1.7, a synthetic route to 3,4-dihydro-5a-methyl-2*H*-naphtho[1,8-*bc*]furan-5-one **55** was developed from guaiacol **48** in 12 steps and 12.6% overall yield, by way of 3-substituted 2,3-dihydrobenzo[*b*[furan intermediates. A key step involved a lithium-iodide exchange at -100°C and subsequent 5-*exo*-trig conjugate addition[33] which constructed the benzo[*b*]furan **51** in 5 steps and 33% overall yield from guaiacol **48**. The pendant ester group was then homologated by an Arndt-Eistert sequence. At this stage, all further attempts to cyclize the side-chain of either **52** (R = CH_3, prepared by similar methods) or **53** by cationic methods (TFA, BF_3) or by carbenoid intermediates (rhodium(II) acetate, Ag_2O) had failed. Consequently, the C-5a methyl substituent in **47** had to be installed after construction of the naphthofuran tricycle. Methyl ester **53** was then converted to the carboxylic acid and underwent intramolecular Friedel-Crafts acylation with (1:1) TFA-TFAA in good yield. The Birch reduction of **54**, which was accomplished using potassium metal in liquid ammonia and followed by the addition of lithium bromide and quenching with methyl iodide, had unexpectedly furnished the 5a-methyl-2*H*-naphtho[1,8-*bc*]furan derivative **55**. Although the unforeseen loss of the C-8 methoxyl group was not unusual in Birch reductions,[34] it did constitute a major setback in the synthetic plan since an oxygenated substituent at C-8 was not only the precursor to the benzylic ketone group in both halenaquinone (**13**) and xestoquinone (**12**), but was also needed to form the dienophilic enone **47** for Diels-Alder coupling to the isobenzofuran **46** (Scheme 1.6). Unfortunately, all further attempts at allylic oxidation of **55** failed because of the prevalence of unexpected rearrangements.[31]

Scheme 1.7 [31]


1. NaH, DMF, ClCH2OCH3
2. 2.2 eq. n-BuLi, ether, 0°C
3. 6 eq. I2 , THF
4. HCl, MeOH
OH
OMe
48
I
49
Br
OEt
K2CO3 , acetone
OEt
n-BuLi, -100°C
THF-ether-hexane (4:1:1)
50
EtO
1. 10% NaOH, MeOH
2. 2N HCl
3. (COCl)2 , PhH, pyr
4. CH2N2
(71%)
51
N2CH
R
Ag2O, MeOH
(93%)
52 (R=H, CH3)
MeO2C
53
1. 10% NaOH, THF
2. TFA-TFAA,
CH2Cl2, 5h
(76%)
4
5a
8
1
1. 4.5 eq. K, liq. NH3, t-BuOH
2. 4.5 eq. LiBr, CH3I,
THF-H2O
(76%)
54
H
55

The only natural product directly related to viridin (**1**) which has been synthesized to date is wortmannin (**7**) by a multistep sequence from the steroid hydrocortisone.[35] Although ring A in wortmannin has been oxidatively modified to a δ-lactone (Figure 1.1), the presence of the methoxymethyl group at C-1 is an indication that wortmannin could be synthesized from a naphthofuran subunit like **9** (or analogue thereof) followed by an oxidative ring-opening step to form the required lactone moiety. Accordingly, an efficient and general synthesis of a 5a-methylated naphtho[1,8-*bc*]furan analogue would therefore be the main entrance toward the viridin family as well as the xestoquinone family of compounds.

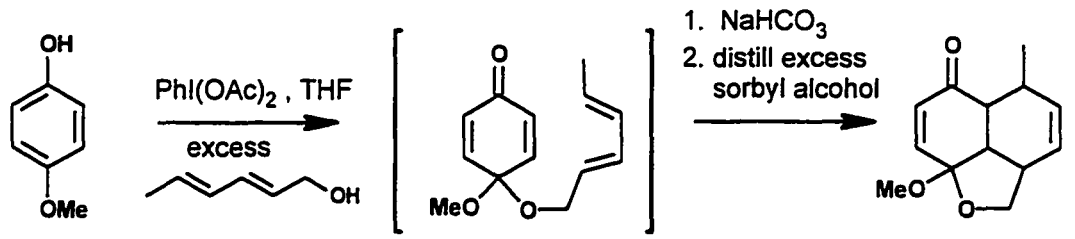
1.3 Origin of the Present Study

1.3.1 ortho-Benzoquinone Monoketals in Intramolecular Diels-Alder Reactions

The failures encountered earlier in our laboratory[31] for synthesizing the tricycle **47** had incited the conception of a new and fundamentally different strategy toward the synthesis of this compound. Morrow and co-workers[36] had exemplified the use of a mixed *para*-benzoquinone monoketal **56** to form a tricyclic naphtho[1,8-*bc*]furan derivative **57** (Scheme 1.8), which in turn had provoked the idea that the α-oxygenated 2,5-cyclohexadienone moiety of **58** (and also of viridin) could be derived from a dienophilic *ortho*-benzoquinone monoketal **59** by an intramolecular Diels-Alder (IMDA) reaction (Scheme 1.9). The characteristic reactivity of *ortho*-benzoquinones as dienes in Diels-Alder reactions, due to their inherent *s*-cis geometry, had been well-documented.[37]

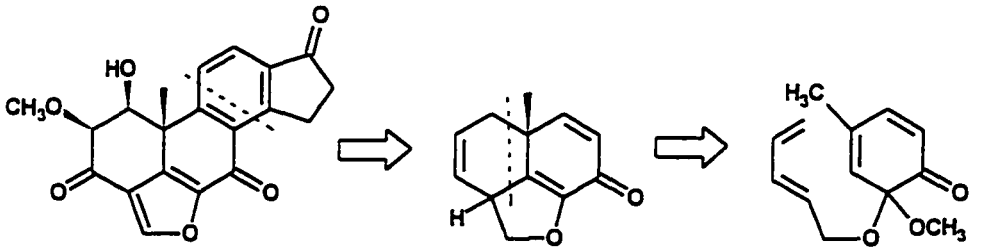
Coupled with their propensity to polymerize easily, there developed a challenge to investigate conditions whereby a functionalized *o*-benzoquinone monoketal could behave as a *dienophile* in a regiocontrolled cycloaddition.

Scheme 1.8 [36]



56 57

Scheme 1.9

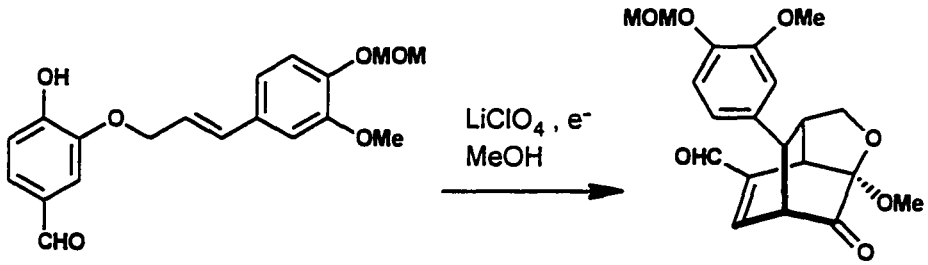


1
Viridin 58 59

At this preliminary point in our investigations, the use of *o*-benzoquinone monoketals as dienophiles in Diels-Alder reactions was largely unexplored (more recent examples will be discussed in chapter 3 which is devoted to this subject). By contrast, the employment of *o*-benzoquinone monoketals as *dienes* in Diels-Alder reactions had been known on a few occasions. Yamamura and co-workers[38] demonstrated how an *o*-benzoquinone monoketal, generated by electrochemical oxidation of phenol **60** in

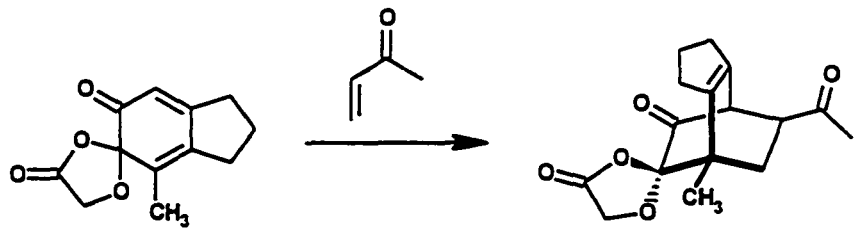
methanol, was spontaneously trapped in an intramolecular Diels-Alder reaction which formed adduct **61** along with its dimethyl acetal (Scheme 1.10). In their synthesis of the insecticide ryanodine, Deslongchamps and co-workers[39] reported a regioselective intermolecular Diels-Alder cycloaddition between a functionalized *o*-quinonoid monoketal **62** (developed from an indane precursor) and methyl vinyl ketone (Scheme 1.11). Much more is known about the IMDA reactions of the structurally related 2-substituted 2,4-cyclohexadienones (often generated by oxidation of the corresponding *o*-alkylated phenols with lead tetraacetate[40]), although most accounts have also employed these species as dienes in such reactions.[41]

Scheme 1.10 [38]



60 **61**

Scheme 1.11 [39]



62 **63**

1.3.2 Preliminary Model Studies of Dienophilic ortho-Benzoquinone and ortho-Naphthoquinone Monoketals

Preliminary investigations performed in our laboratory in 1993 were directed toward developing suitable oxidation conditions for generating *ortho*-benzoquinone monoketals *in situ* from their corresponding *o*-methoxyphenols in the presence of excess (*E*)-2,4-pentadienol. Among the wide variety of available oxidants, the hypervalent aryliodine(III) dicarboxylates[42] such as phenyliodosyl bistrifluoroacetate (PIFA) and phenyliodosyl diacetate (PIDA),[43] were reported to be mild yet effective oxidants of several substituted phenols.[42,44] The commercially available oxidant PIFA was specifically chosen since it is a slightly stronger oxidant than its analogue PIDA, and because it conveniently generates the volatile by-products iodobenzene and trifluoroacetic acid (TFA) which are easily removed during a work-up procedure. Consequently, a one-pot, three step synthesis of the 5a-methyl-naphtho[1,8-*bc*]furan analogue **68** (a precursor of tricycle **58**) was planned (Scheme 1.12) which consisted of: (i) PIFA-promoted oxidation of an *o*-methoxyphenol **64**, (ii) ketalization of the intermediate quinonoid cation with a 10-fold excess of (*E*)-2,4-pentadienol, and (iii) intramolecular Diels-Alder (IMDA) cycloaddition.[45]

Scheme 1.12 [45]

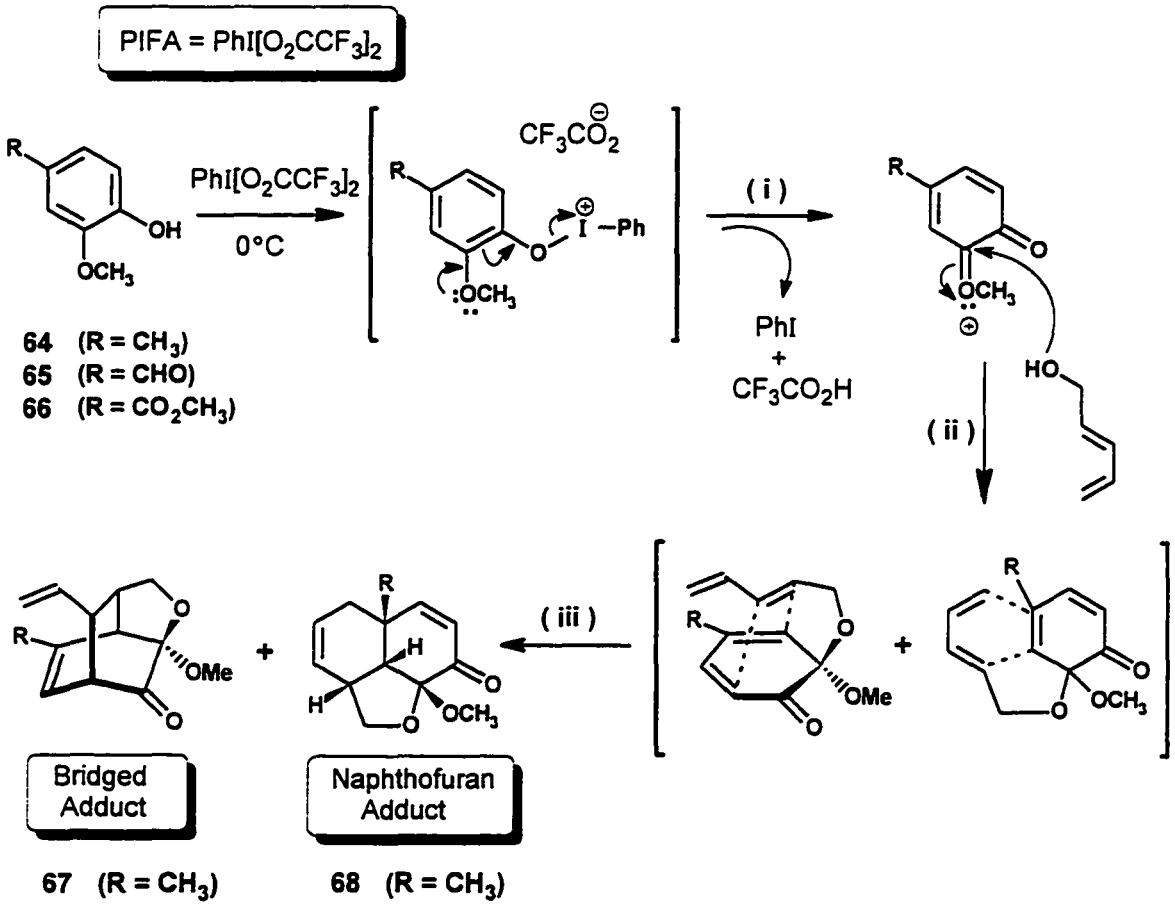
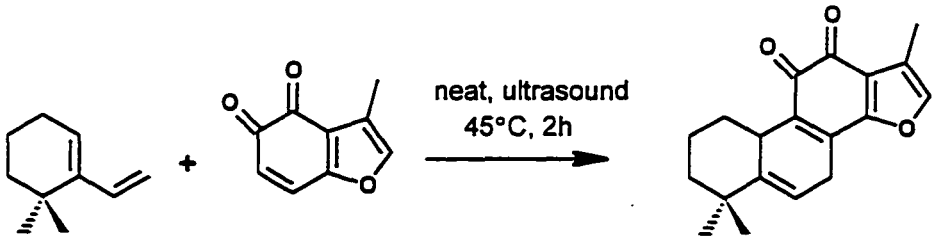


Table 1.1:[45] Preliminary results of the one-pot IMDA reaction with guaiacol derivatives **64-66**.

Guaiacol Derivative	Bridged Adduct (%-Yield)	Naphthofuran Adduct (%-Yield)
64 (R=CH_3)	**67** (<10%)	**68** (0%)
65 (R=CHO)	Decomposition	
66 (R=CO_2CH_3)	Decomposition	

Several derivatives of guaiacol (*o*-methoxyphenol) were tested for this three-step reaction sequence (Table 1.1). The case where R= CH_3 was investigated first as it could directly furnish **68**. Unfortunately, the only identifiable product which was isolated in poor yield was the bridged adduct **67**, resulting from the *o*-quinone ring behaving as the diene. In an attempt to enhance the dienophilic character of the C_3-C_4 double bond in the monoketal and force the formation of the naphthofuran tricycle, electron-withdrawing substituents (R=CHO, CO_2CH_3) were placed on the *o*-methoxyphenol precursor with the idea that either of these groups could be reduced to the required methyl substituent at a later stage. In both cases, however, inseparable mixtures of unidentifiable products were obtained, presumably due to decomposition of the intermediate quinones. Attention was then turned toward generating *o*-naphthoquinone monoketals which would only have one double bond available for annulation to a diene since the other *o*-quinone double bond was occupied in aromatic resonance. Although the use of aromatic derivatives of *o*-quinones as dienophiles in *intramolecular* processes had not yet been explored, there were several reports where *o*-naphthoquinones[46] and furano-*o*-benzoquinones[47] such as **70** have reacted as dienophiles in intermolecular cycloadditions, as in a classical synthesis

Scheme 1.13 [47b]

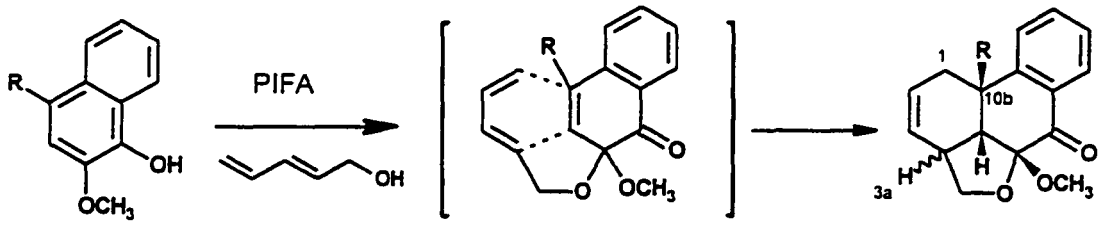


69 **70** **71**

of morphine,[46d] and for the synthesis of an abietane diterpenoid pigment (Scheme 1.13).[47]

Several substituted *o*-methoxynaphthols **72-75** were therefore prepared and subjected to the same oxidation conditions in the presence of excess (*E*)-2,4-pentadienol as with the phenolic substrates (Scheme 1.14, Table 1.2).[45] For the cases with substrates **72** (R= CH_3) and **73** (R= CHO) where the substituent R possessed a protonated carbon, the reaction had either failed (with **72**) or had produced the phenanthro[10,1-*bc*]furan *endo*-adduct **77a** (from **73**) in extremely poor yield (<5%).[45] In both cases, large quantities of resinous by-products had formed, presumably from reactive *p*-quinomethide species which may have polymerized.[48] When the *o*-methoxynaphthols **74** (R= CO_2CH_3) and **75** (R= $COSCH_3$) with electron-withdrawing ester substituents were tested, the three-step one-pot IMDA reaction proceeded smoothly to furnish the phenanthrofurans **78a-b** and **79a-b** (as mixtures of *endo* and *exo* isomers) in moderate overall yields. The structures and relative stereochemistry of both these pairs of diastereomeric adducts were confirmed by X-ray crystallography.[45] A thiol ester group was chosen for study since it could potentially be chemoselectively reduced to a methyl group in the presence of other carbonyl functional groups. Thus, it had appeared that the success of this one-pot oxidation-IMDA reaction sequence was dependent on: (i) the availability of only one dienophilic double bond for the *o*-quinonoid monoketal reactive species; and (ii) the presence of an electron-withdrawing group, free of hydrogens on the carbon atom, which not only enhanced the dienophilicity of this double bond, but also precluded the formation of resinous by-products during the oxidation step.

Scheme 1.14 [45]



72 (R = CH_3)
73 (R = CHO)
74 (R = CO_2CH_3)
75 (R = $COSCH_3$)

76

77 (R = CHO)
78 (R = CO_2CH_3)
79 (R = $COSCH_3$)

a: *endo* (β-H_{3a})
b: *exo* (α-H_{3a})

Table 1.2:[45] Preliminary results of the one-pot IMDA reaction with derivatives of *o*-methoxynaphthol **72-75**.

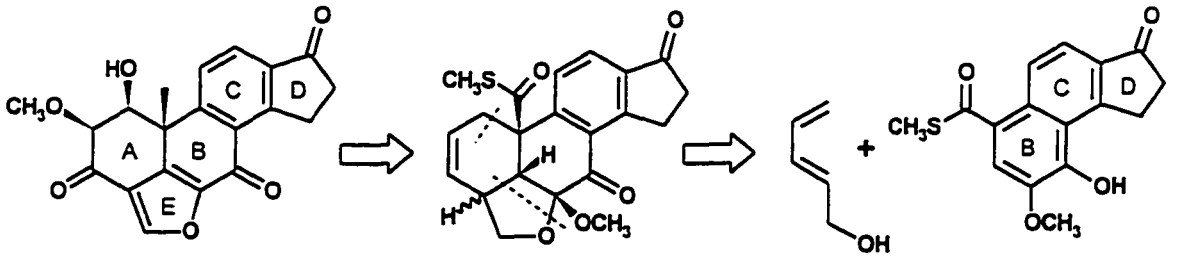
o-Methoxynaphthol Derivative	Diels-Alder Products (%-yield)	
	Endo-Adduct (a)	*Exo*-Adduct (b)
72 (R= CH_3)	Decomposition	
73 (R= CHO)	**77a** (<5%)	**77b** (0%)
74 (R= CO_2CH_3)	**78a** (34%)	**78b** (16%)
75 (R= $COSCH_3$)	**79a** (36%)	**79b** (12%)

1.4 Synthetic Plan Designed for Viridin

With these conclusions formulated, the initial plan for the synthesis of viridin (**1**) was designed (Scheme 1.15) where the advanced pentacyclic intermediate **80** contains a thiol ester group as the synthetic precursor to the methyl group of viridin. The annulation

of rings A and E would be effected by the one-pot IMDA reaction of the *o*-quinonoid monoketal species generated *in situ* from the benz[*e*]indanone thiol ester **81** and (*E*)-2,4-pentadienol. Accordingly, an efficient synthesis of this thiol ester **81** would constitute the first hurdle in our projected synthesis. Inspection of this compound revealed that it is a 1,2-dihydroxynaphthalene derivative which could conceivably be fashioned from a dienophilic *o*-benzoquinone core *via* intermolecular Diels-Alder reaction with a suitable diene. A systematic investigation of the Diels-Alder reactivity of substituted *o*-benzoquinones, generated *in situ* from their corresponding catechols, was therefore in order. The heartening results of this investigation will be presented in detail in chapter 2.

Scheme 1.15



1
Viridin

80

81

1.5 Summary

The viridin family of natural products (**1-8**) (Figure 1.1) are furanosteroid analogues which share a common tricyclic naphtho[1,8-*bc*]furan structural feature for rings A-B-E, possessing an angular methyl group at the junction of rings A and B. Each natural product presented has exhibited impressive biological activity, ranging from antifungal activity to anti-inflammatory activity. Members of the structurally related

xestoquinone family of natural products (**12-18**) (Figure 1.3), each of which also features the same tricyclic subunit, have all been synthesized by a variety of methods. An efficient yet general synthesis of a tricyclic moiety like **9** or **58** would be the key to unlocking the various pathways toward synthesizing any one of these aforementioned compounds (as in Schemes 1.6 and 1.9). Our preliminary efforts toward this end were directed at the novel use of *o*-benzoquinone mixed monoketals as dienophiles in intramolecular Diels-Alder reactions (Scheme 1.12). Some limitations of this methodology included the propensity of *o*-quinonoid species to behave as dienes and to polymerize uncontrollably. As a means of forcing the dienophilic reactivity of these *o*-quinone monoketals, the unsubstituted double bond was made unavailable by its participation in another aromatic ring. Investigations of the IMDA reactions of resultant *o*-naphthoquinone monoketals met with some success (Scheme 1.14), the result of which was reflected in a preliminary strategy for a proposed synthesis of viridin (Scheme 1.15). The retrosynthetic plan involved the preparation of the advanced pentacyclic thiol ester **80**, where rings A and E would be installed by the IMDA reaction of the corresponding *o*-quinonoid monoketal, generated *in situ* from oxidation of the benz[*e*]indanone thiol ester **81** in the presence of excess (*E*)-2,4-pentadienol. A projected synthesis of this thiol ester, essentially a 1,2-dihydroxynaphthalene derivative, from a suitable *o*-benzoquinone had been hypothesized, and a full investigation of the Diels-Alder reactivity of substituted *o*-benzoquinones as dienophiles was charted.

CHAPTER 2

PROGRESS TOWARD THE SYNTHESIS OF VIRIDIN:

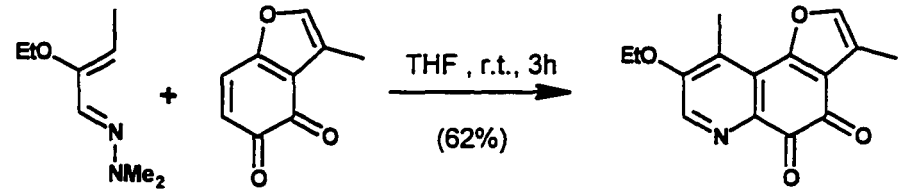
THE SYNTHETIC UTILITY OF SUBSTITUTED *ORTHO*-QUINONES AS DIENOPHILES IN INTERMOLECULAR DIELS-ALDER REACTIONS

2.1 General Overview of *ortho*-Quinones as Dienophiles in Diels-Alder Reactions.

The synthetic utility of substituted *ortho*-benzoquinones as both dienes and dienophiles in Diels-Alder [38, 47, 49] and hetero-Diels-Alder [37c, 50] cycloadditions has been exemplified in several creative natural product syntheses.[37] A major problem which has limited the widespread use of such compounds however, is their propensity toward polymerization.[51] In contrast to the comparatively more stable *o*-naphthoquinones, simple monosubstituted *o*-benzoquinones are better generated *in situ* by oxidation of the corresponding catechol in the reaction medium.[37, 51] The choice of oxidizing agent is an important one, as many of the commonly used reagents such as metallic oxides, periodates, ceric ammonium nitrate, and other quinones (*o*- or *p*-chloranil) are too harsh and form tar-like decomposition products. Nonetheless, some *o*-benzoquinones have been found to be stable and under certain reaction conditions such as high pressure or

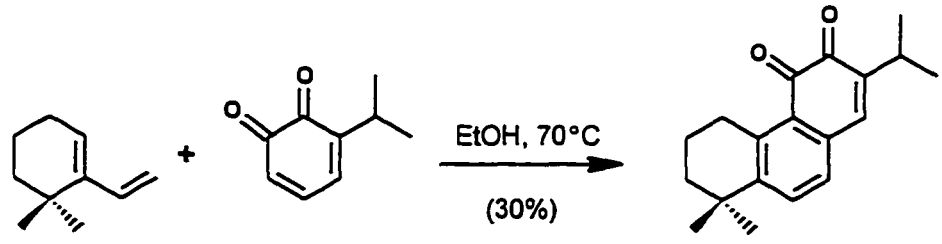
ultrasonication, underwent Diels-Alder reactions as dienophiles with unactivated dienes. One case in point is the use of dienophilic substituted furanoquinones like **70** (*cf.* Scheme 1.13) by Snyder and co-workers in efficient ultrasound-promoted Diels-Alder reactions with various cyclic dienes for the synthesis of abietanoid pigments, including the tanshinones and its derivatives.[47] In another case, the same furanoquinone **70** was used as the dienophile in a hetero-Diels-Alder cycloaddition with the aza-diene **82**, where the initial adduct eliminated dimethylamine and aromatized to the furoquinoline-4,5-dione **83** (Scheme 2.1).[49b] Most often, substituted *o*-benzoquinones which are somewhat stable are prepared as needed and used immediately, as in the reported cycloaddition between 3-isopropyl-*o*-benzoquinone **84** and the cyclic diene **69** which furnished the antioxidant rosmariquinone (**85**) (Scheme 2.2).[49c]

Scheme 2.1[49b]



82 **70** **83**

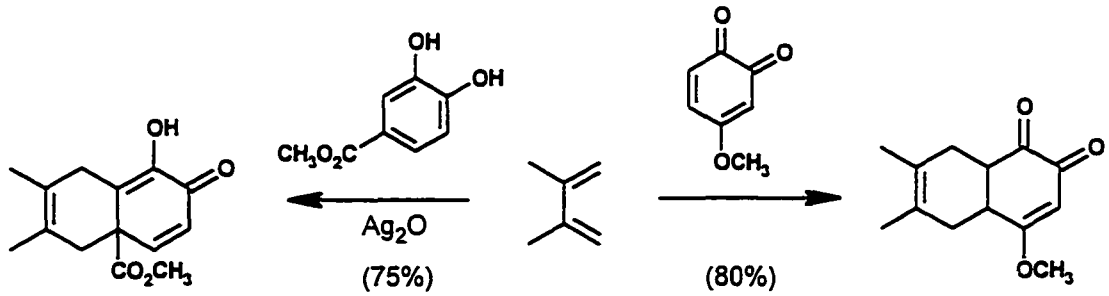
Scheme 2.2[49c]



69 **84** **85**

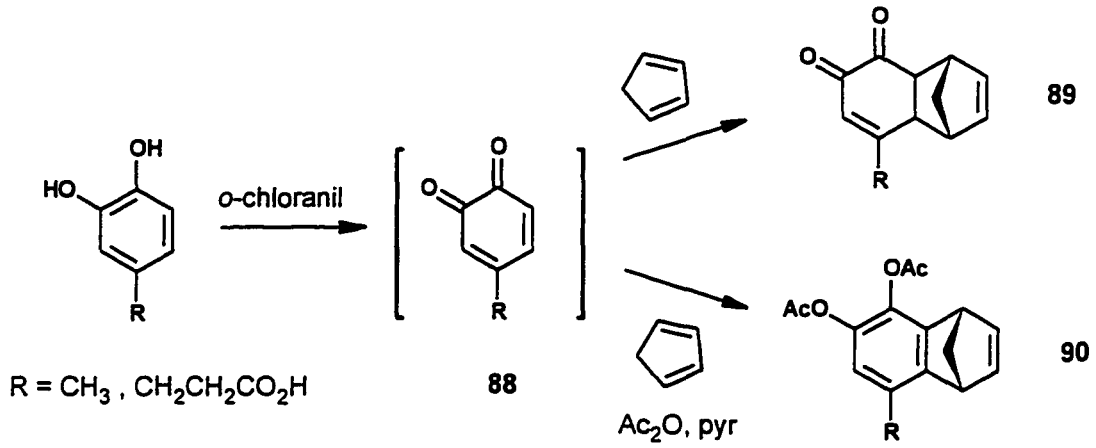
In their comprehensive studies of the reactivities and stabilities of numerous substituted *o*-benzoquinones, Ansell and co-workers had found that *o*-quinones could be forced to react as dienophiles in Diels-Alder reactions in the presence of an excess amount of a diene (10 to 20-fold molar equivalents), thereby suppressing the pathway leading to polymerization.[52a] Furthermore, the site of regioselective cycloaddition to this dienophilic *o*-quinone could be influenced by the placement of either an electron-withdrawing substituent (e.g. CO_2CH_3, CN) or an electron-donating substituent (e.g. CH_3, OCH_3) on the ring. Representative examples in Scheme 2.3 illustrate how an electron-withdrawing substituent had enhanced the dienophilicity of the quinone double bond on which it was situated, while an electron-donating substituent had reduced it, forcing the cycloaddition in this case to take place on the unsubstituted double bond.[52] Other examples of trapping unactivated 4-alkylated *o*-benzoquinones **88** as dienophiles in cycloadditions with cyclopentadiene have been documented (Scheme 2.4).[42c, 49f, 51, 53]

Scheme 2.3[52a]



86 **87**

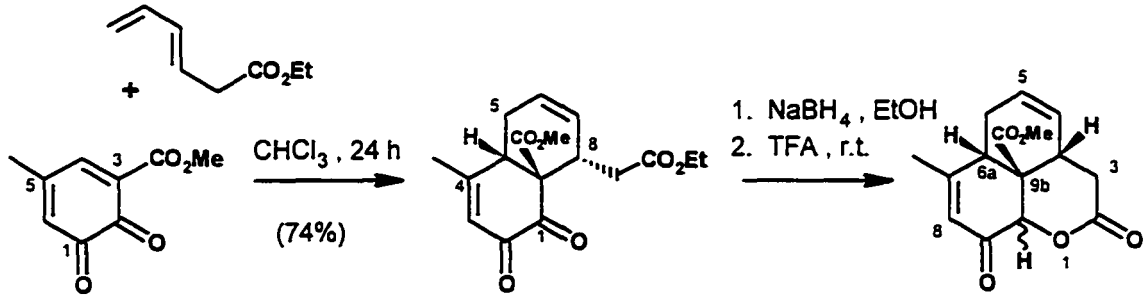
Scheme 2.4[53a]



In the years which followed the work pioneered by Ansell, other researchers had observed efficient regioselectivity in Diels-Alder reactions of substituted *o*-benzoquinones with *unsymmetrical* 1-substituted dienes. The position of an electron-withdrawing group (EWG) on the *o*-quinone ring could also influence the regiochemical orientation of the unsymmetrical diene, and cause the exclusive formation of the 'ortho' regioisomer (with respect to EWG) with *endo* stereochemical configuration.[54] An example was demonstrated by Weller and Stirchak in their efforts to synthesize the quassinoid Bruceantin, wherein the cycloaddition of the 3,5-disubstituted *o*-quinone **91** with ethyl (*E*)-3,5-hexadienoate (Scheme 2.5) had occurred exclusively at the C_3–C_4 double bond and only produced the *endo*-8-carbethoxymethyl adduct **92**, which was later reduced and lactonized to furnish the tricycle **93**, a C_{6a}-epimer of the quassinoid B-C-D ring system.[49e] In the opposite scenario, an electron-donating group (EDG) on the *o*-quinone ring could direct cycloaddition at the *other* more activated double-bond. An example of this latter case was nicely demonstrated by Danishefsky and co-workers who had developed a route to Δ^2-1-octalones involving a regiocontrolled Diels-Alder

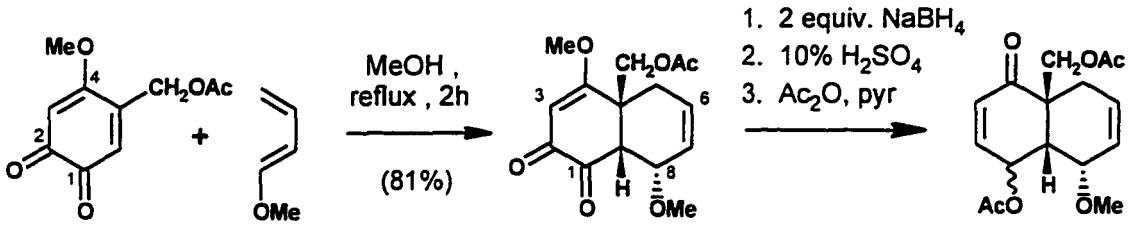
cycloaddition of 4-methoxy-5-acetoxymethyl-1,2-benzoquinone **94** with 1-methoxy-butadiene, which produced the *endo*-8-methoxy diastereomer **95** in good yield (Scheme 2.6).[49g] A few other research groups[49d, 55] have reported more examples of regiocontrolled cycloadditions of functionalized *o*-quinone dienophiles with unsymmetrical dienes. Pitea and co-workers attempted a theoretical rationalization for the regio- and stereoselective formation of 'ortho' *endo*-cycloadducts observed in reactions with *o*-quinones bearing an electron-withdrawing group at C_3 or C_4.[55] Using the reactions between 1-vinylcyclohexene with either 3- or 4-carbomethoxy-1,2-benzoquinone as models for study, the theoretical predictions made by the FMO approximations were in fact *opposite* to the experimentally observed regiochemistry (with respect to the diene) in the adducts, which were confirmed by X-ray crystallographic analysis. However, the results of a complete perturbational molecular orbital (PMO) theoretical analysis, which included terms reflecting the polar interactions of the *endo* transition state and the minimum energy for the non-bonding interactions of the adduct, were in good agreement with the experimental results.

Scheme 2.5[49e]



91 **92** **93**

Scheme 2.6[49g]



94 **95** **96**

It was evident that Diels-Alder adducts of *o*-benzoquinone dienophiles could serve as synthetically useful templates in natural product synthesis. In our proposed synthetic route toward viridin (**1**), a key concern was the efficient synthesis of the benz[*e*]indanone thiol ester **81** (*cf.* Scheme 1.15). Since no other methods at the time reported a short and efficient preparation of functionalized 1,2-dihydroxynaphthalenes (or 1,2-dihydroxy-*cis*-decalins) from simple starting materials, the potential use of *o*-benzoquinone dienophiles to prepare such compounds was investigated in our laboratory (see Scheme 2.7), and some of the results which were applied toward the synthesis of viridin are recounted in this work.

2.2 Results and Discussion

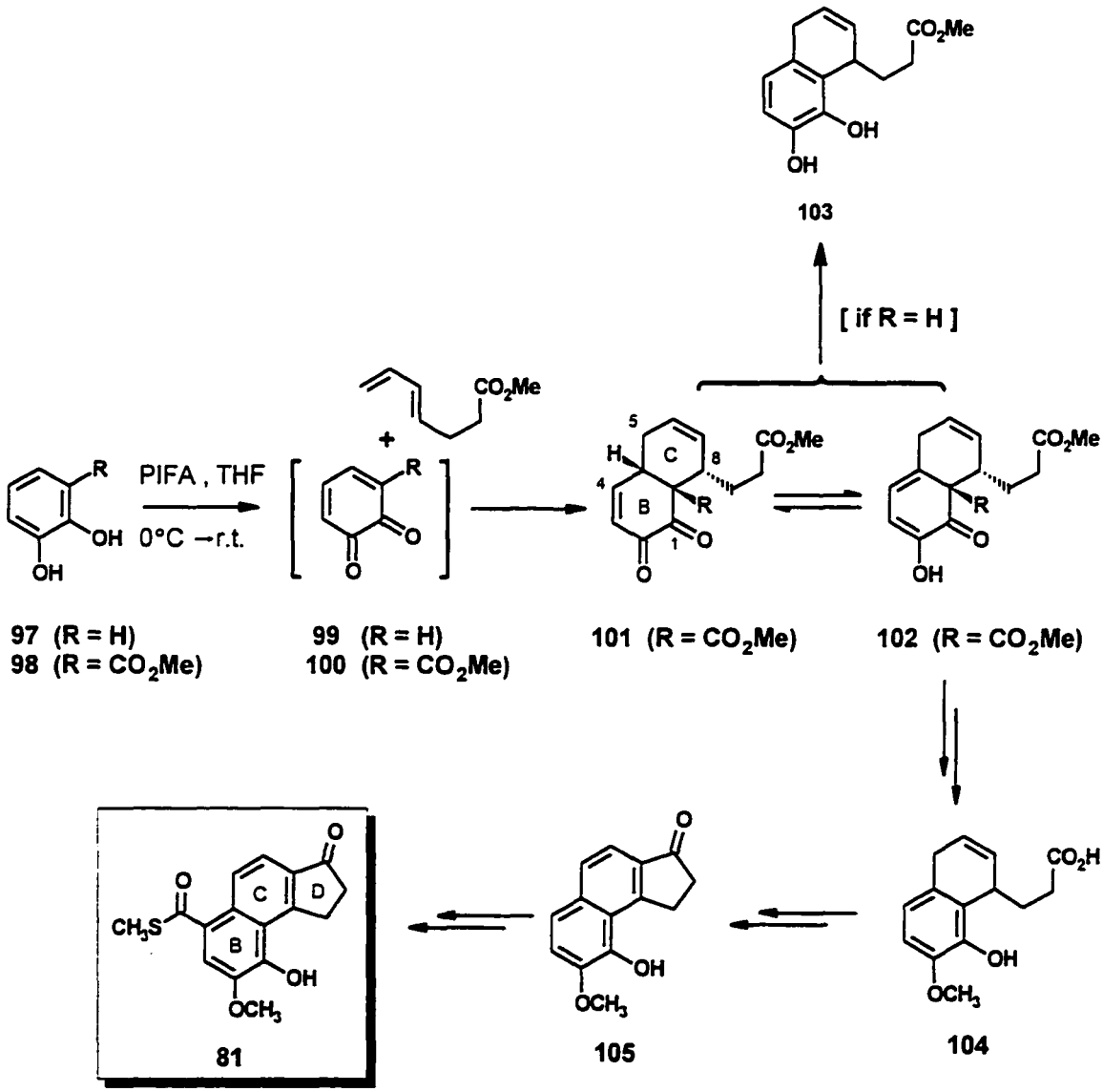
2.2.1. Initial Strategies for the Synthesis of Tricyclic Intermediate 81 by Intermolecular Diels-Alder Reactions of Substituted o-Benzoquinones

The first general strategy formulated for synthesizing the key benz[*e*]indanone tricycle **81** began with the intermolecular Diels-Alder reaction of a suitable *o*-benzoquinone, as outlined in Scheme 2.7. The diene chosen for this reaction was methyl

(*E*)-4,6-heptadienoate, efficiently prepared in 89% yield by the method of Hudlicky[56] which involved a Claisen-ortho ester rearrangement of the ketene acetal generated from 1,4-pentadien-3-ol and trimethyl orthoacetate. Given the reported success of Diels-Alder reactions between such *o*-benzoquinones and 1-substituted dienes, it was our belief that a high degree of regiochemical selectivity could be achieved by using this particular diene. The diene 2-vinyl-2-cyclopentene-1-one was not considered for several reasons which included: (i) its difficult and inefficient preparation,[57] (ii) potential instability toward polymerization, and (iii) its dual reactivity as a diene and dienophile. Due to the conflicting substituent effects, the outcome of a Diels-Alder reaction with 2-vinyl-2-cyclopenten-1-one would be difficult to predict since more than one regioisomer may result.

The unsubstituted *o*-benzoquinone **99** was initially tested as a dienophile in the Diels-Alder reaction, despite its notorious instability. Several attempts at either oxidizing guaiacol (*o*-methoxyphenol) with sodium meta-periodate[58] or catechol with PIFA[53] had furnished *o*-benzoquinone **99** in poor yield (range of 10-44%). Although the red solid product was difficult to handle since it often spontaneously and exothermically polymerized, a sufficient amount of sample was available to test the Diels-Alder reaction. Following the procedure of Snyder and co-workers,[47] the reaction was carried out under conditions of high pressure (11 kbar) in neat diene (20-fold excess). After a maximum of 2 days however, no products resembling the adduct **101** were identified. Reaction conditions using unconventional polar solvents (water or 3M $LiClO_4$ in ether) developed by Grieco to promote efficient Diels-Alder reactions with unactivated dienes were also considered.[59] Unfortunately, the attempted cycloaddition between **99** and sodium (*E*)-4,6-heptadienoate in water at ambient temperature failed, having only produced quinone

Scheme 2.7



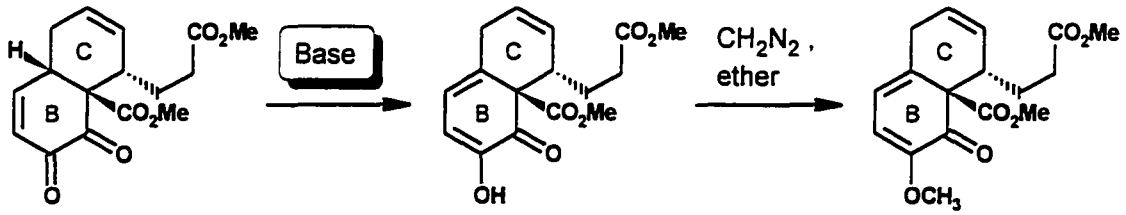
decomposition. A final effort to prepare the quinone **99** *in situ* by oxidation of catechol **97** with PIFA in the presence of a 20-fold excess of methyl (*E*)-4,6-heptadienoate also failed because of decomposition of the quinone. These initial failures therefore confirmed that unstable *o*-benzoquinone **99** was not suitable for use in a bimolecular

Diels-Alder reaction. Our attention had logically turned toward the placement of an electron-withdrawing group at C_3 of the quinone, following the lead originally developed by Ansell.[52a] An ester substituent was chosen for investigation because the anticipated 1,2-diketone product **101** would possess a vinylogous proton at C-4a that could be abstracted in order to furnish the diosphenol **102** (Scheme 2.7) In view of the projected synthesis of the benz[*e*]indanone target **81** which has a C-2 methoxyl group, diosphenol **102** would therefore be perfectly functionalized for specific methylation at the C-2 enol group.

Catechol **98** was prepared by esterification of commercially available 2,3-dihydroxybenzoic acid in acidic methanol, and oxidized with a slight excess of PIFA (1.2 equivalents) to the *o*-quinone **100** in the presence of a 10-fold excess of methyl (*E*)-4,6-heptadienoate at 0°C. The progress of the reaction could be monitored visually by the color changes of the reaction mixture. Upon addition of PIFA, the color became greenish-black, and within 2-6 h the color changed to greenish-red and ultimately to bright yellow. After several hours stirring at room temperature, the mixture was treated with mild base ($NaHCO_3$) in order to neutralize the TFA produced from the oxidation step. Two products were isolated, both yellow non-crystallizable oils, and were characterized as the 1,2-diketone **101**, the major product, and the diosphenol **102**, a minor product produced from the base treatment. The regiochemistry of both these compounds were deduced from 1D and 2D ^{1}H-NMR spectral analysis. The ^{1}H,^{1}H-TOCSY spectrum of diketone **101** had shown coupling correlations for H-4 with H-4a, as well as for H-4 with both H-5 protons. Furthermore, the multiplet signal for H-4a (3.35 ppm) contained three distinct coupling constants (measured by decoupling experiments) which were $J_{4a,5}$=11.7 Hz, $J_{4a,5'}$=6.3 Hz, and $J_{4a,4}$=6.0 Hz. The spectral evidence supporting the

regiochemistry shown in the diosphenol **102** was even more convincing, since the spectrum was less complex than that of **101** (Figure 2.1 a). The ^{1}H,^{1}H-TOCSY spectrum of diosphenol **102** clearly illustrated the coupling correlations between the following pairs of signals: H-5 with H-4, H-5 with H-6, and H-7 with H-8. Decoupling experiments on **102** (Figure 2.1 b-d) revealed that: (i) irradiation of the multiplet for H-5 (3.0 ppm) reduced the signal for H-6 (5.68 ppm) to a doublet ($J_{6,7}$=9.8 Hz), and also collapsed the signal for H-4 (6.25 ppm) to a doublet ($J_{4,3}$=6.9 Hz); (ii) irradiation of the multiplet for H-8 (3.45 ppm) had reduced the signal for H-7 (5.85 ppm) to a doublet of doublets ($J_{7,6}$=9.8 Hz, $J_{7,5}$=1.6 Hz).

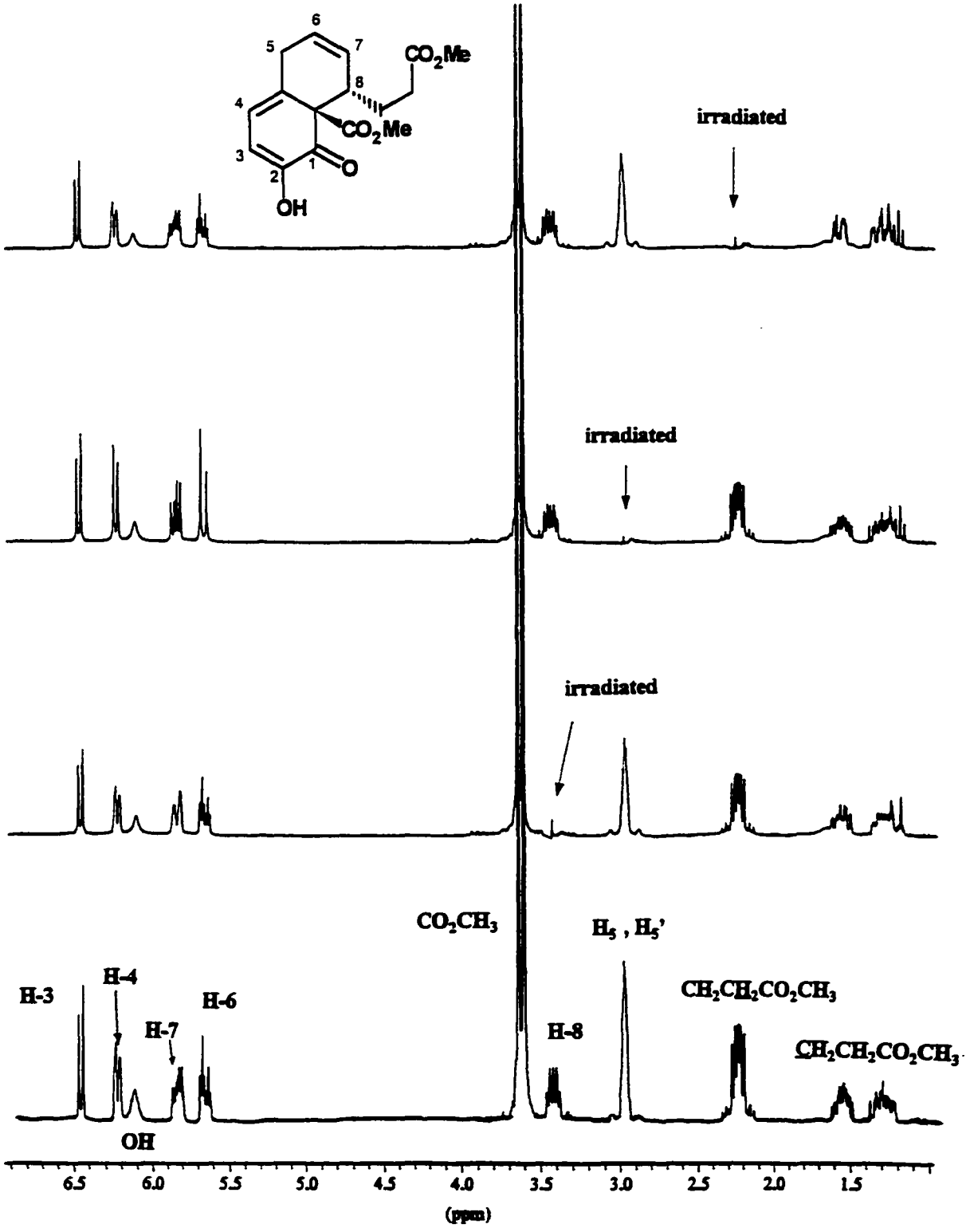
Scheme 2.8



101 **102** **106**

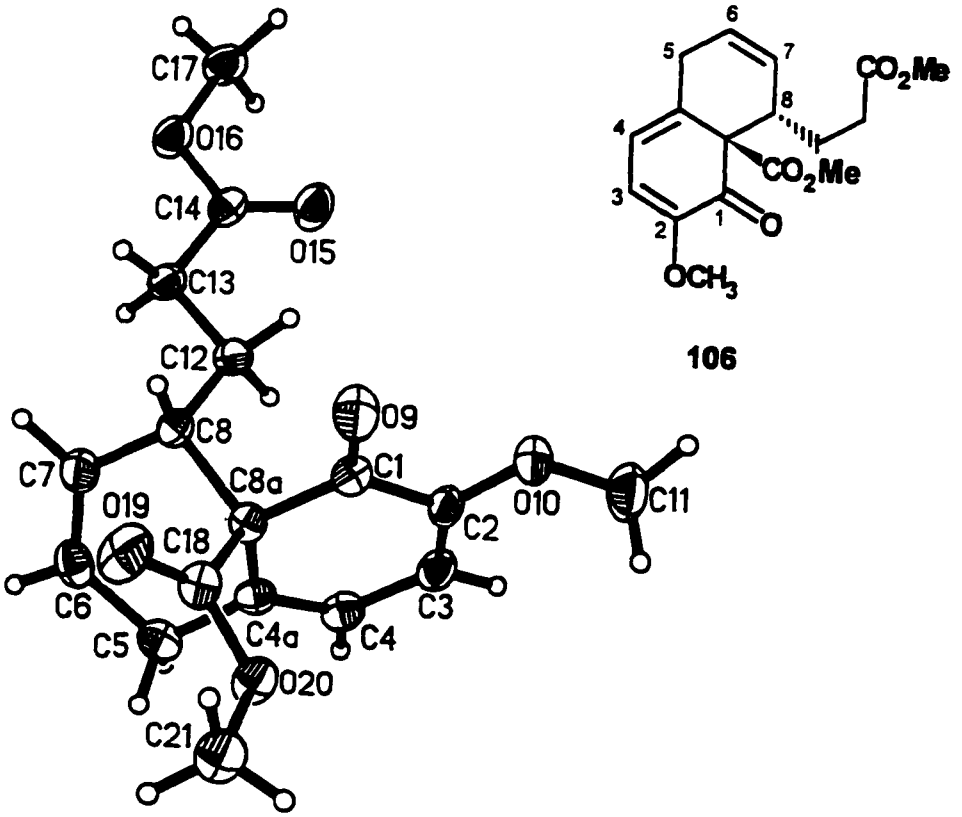
The fortuitous formation of diosphenol **102** was welcome in the initial route planned for synthesizing benzindanone **81**, since the compound was suitably functionalized for specific methylation at the C-2 hydroxyl group. Subsequent treatment of **102** with diazomethane had furnished the methyl enol ether **106** as colorless needles (Scheme 2.8). The X-ray crystallographic analysis of this compound confirmed the structure of the molecule determined by ^{1}H-NMR analysis and also the *endo*-configuration that is often observed in the Diels-Alder reaction (Figure 2.2). The yield of either **101** or **102** initially obtained from the Diels-Alder reaction were moderate

Figure 2.1: (a) ^{1}H-NMR spectrum, and (b-d) decoupled spectra (250 MHz) of diosphenol **102**.



however, and it was also observed that diosphenol **102** decomposed easily. Optimization of both the Diels-Alder reaction conditions and work-up procedure were therefore required in order to favor the predominant formation of either one of these compounds. It was soon found that by eliminating the treatment with $NaHCO_3$ and removing the excess diene by chromatography rather than distillation, the exclusive formation of the diketone **101** was achieved in excellent yield (96%).[60] Although the diosphenol was not formed efficiently in this one-pot Diels-Alder process, the high yield of **101** obtained in the first step of a projected synthesis of viridin was advantageous. The next challenge would be centered around the efficient keto-to-enol conversion of **101** to **102**.

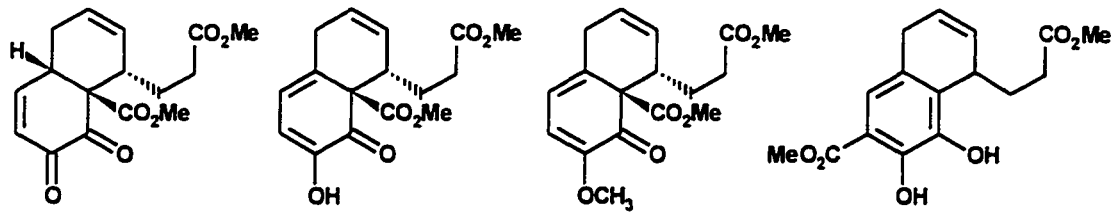
Figure 2.2: Molecular plot of the X-ray crystal structure of **106**.



Several conditions were investigated for efficient γ-enolization of diketone **101**. The use of large quantities of sodium bicarbonate and prolonged heating (24-48 h) were necessary for complete conversion of the diketone to the diosphenol **102**, regardless of the choice of solvent (THF, DME of DMF). Sodium hydride suspended in DME was a more effective system to use, requiring only a few hours of heating to cause complete conversion. In all cases however, the diosphenol **102** easily decomposed during the work-up and purification procedures. Various combinations of bases and polar solvents were tested, but due to its facile decomposition in basic media, the yield of **102** was usually moderate to poor, ranging from 44-75%. Acid-catalyzed conditions also failed to shift the keto-enol equilibrium in favor of the diosphenol. One attempt to trap the dienolate anion of **102** as a trimethylsilyl ether thereby circumventing decomposition was in fact successful. Treatment of the diketone **101** with potassium hydride and trimethylsilyl chloride in anhydrous DME for 2 h with mild heating, followed by quenching with dilute acid did furnish the diosphenol **102** in high yield (96% crude yield). Purification by silica gel chromatography unfortunately caused significant decomposition, reducing the yield significantly.

The observed sensitivity of compound **102** to various reagents prompted several attempts at directly converting either the diketone or the diosphenol to the more stable, crystalline methyl enol ether **106** (summarized in Table 2.1). Methylation of a pure sample of **102** with diazomethane furnished **106** in moderate yields which ranged from 48% to 77% (entry 1). An attempt to drive the formation of **106** by methylation of a 2:1 equilibrium mixture of diketone **101** and diosphenol **102** with diazomethane failed, since the reagent only reacted with the diosphenol in the mixture (entry 2). Treatment of the diketone with the acidic resin Dowex-50 in the presence of excess trimethyl orthoformate

Table 2.1: Conditions tested for the methylation of **101** or **102** to methyl enol ether **106**.



101 **102** **106** **107**

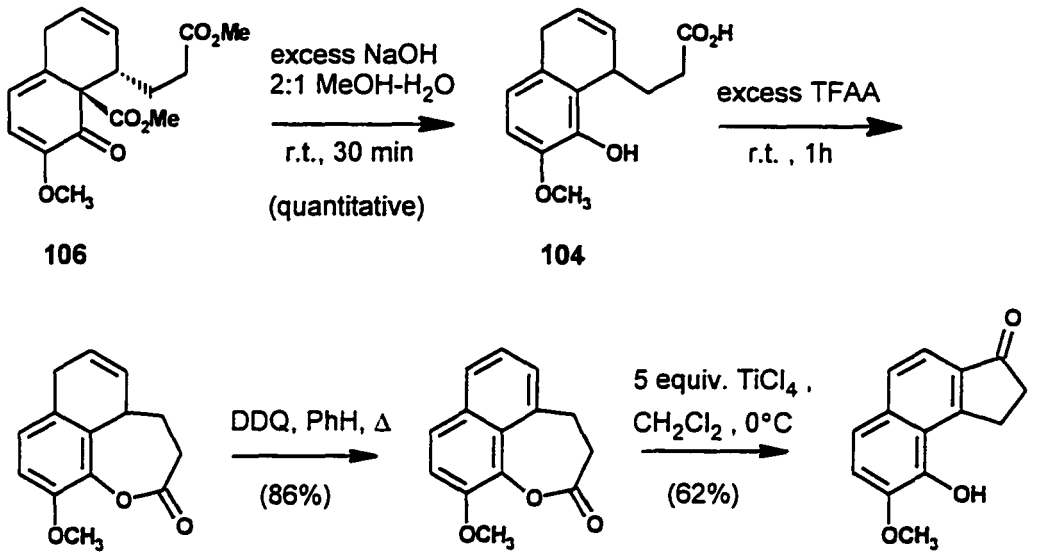
Entry	Starting Material	Reagent and Conditions	Product (%-Yield)
1	**102**	excess CH_2N_2 , ether, r.t.	**106** (48-77%)
2	**101** + **102** (2:1 ratio)	excess CH_2N_2 , ether, r.t.	**106** (<20%)
3	**101**	$CH(OMe)_3$,Dowex-50, MeOH, r.t→50°C	**106** (24%)
4	**101**	NaH ,Me_3OBF_4 ,DMF or DME, 0°C→ r.t	Complex mixture
5	**102**	excess Me_3OBF_4 ,dry CH_2Cl_2, 0°C→ r.t.	**107**
6	**101**	1. NaH, DME, Δ 2. 3N HCl 3. excess CH_2N_2	**106** (48% overall)

in methanol produced a small amount of **106** (24%) along with other unidentifiable methyl acetals as by-products (entry 3). The use of a neutral and reactive methylating agent such as trimethyloxonium tetrafluoroborate (Me_3OBF_4) was also investigated. Enolization of diketone **101** with sodium hydride in either DMF or DME, followed by

quenching with Me_3OBF_4, gave a mixture of unidentifiable products (entry 4). Treatment of the diosphenol **102** with the same reagent surprisingly produced a single product which was not the desired methyl enol ether **106**, but later characterized as the compound **107** having presumably arisen from an unexpected rearrangement (entry 5). (While this new compound **107** was not useful for the synthesis of viridin, its formation had triggered the investigation of rearrangements of these Diels-Alder adducts for synthesizing analogues of 1,2-dihydroxynaphthalenes, the results of which will be presented later in this chapter in section 2.3.) From these trials, it was concluded that the most effective conditions tested involved the enolization of the Diels-Alder diketone adduct **101** with sodium hydride in DME, quenching with dilute acid, and rapid methylation of the crude diosphenol product with diazomethane, which produced the methyl enol ether **106** in 48% overall yield (entry 6).

Despite the low overall yield of intermediate **106**, the synthetic effort toward the benz[*e*]indanone thiol ester **81** and viridin was continued according to the original plan. Saponification of **106** with excess methanolic sodium hydroxide gave the phenolic carboxylic acid **104** in quantitative yield, which was then treated with neat trifluoroacetic anhydride (TFAA) to give the lactone **108** in 87% overall yield from **106** (Scheme 2.9) Dehydrogenation of **108** using a stoichiometric amount of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone[61] (DDQ) in refluxing benzene afforded the naphthyl lactone **109** in 86% yield. Lastly, a $TiCl_4$-promoted Fries rearrangement[62] of **109** produced the benz[*e*]indanone **105**, albeit in moderate (40-62%) and inconsistent yield.

Scheme 2.9



106 **104**

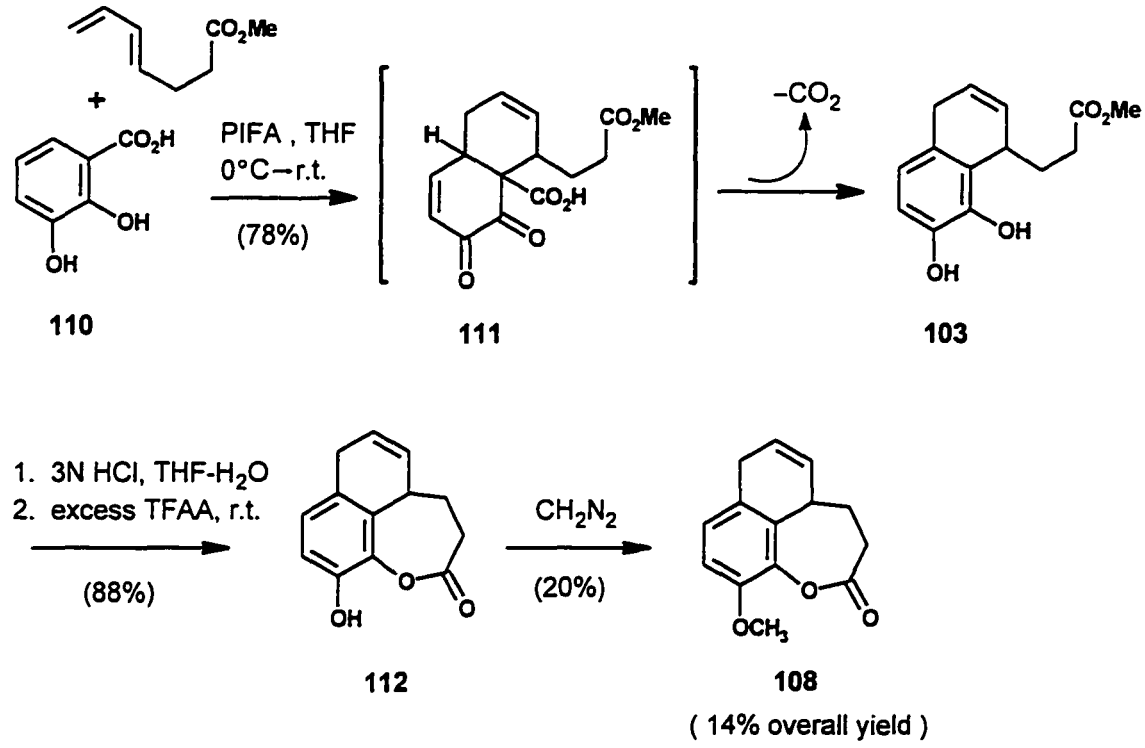
108 **109** **105**

(87% yield from **106**)

At this early stage, it was apparent that the synthetic route suffered from several limitations, which included: (i) the inefficient base-catalyzed keto-enol isomerization of the diketone adduct **101**, (ii) the moderate and irreproducible yield from methylation of diosphenol **102** with diazomethane, and now (iii) the moderate yield in the Fries rearrangement of naphthyl lactone **109**. Rather than proceed to install the thiol ester group in order to furnish **81**, our attention was temporarily concerned with revising the synthetic plan to obtain an improved overall yield of intermediate **105**.

One way to avoid dealing with an inefficient keto-enol isomerization step was to consider synthesizing an aromatic Diels-Alder adduct like **103** shown in Scheme 2.7. Although the preparation of this compound from *o*-benzoquinone **99** was not possible, a

Scheme 2.10



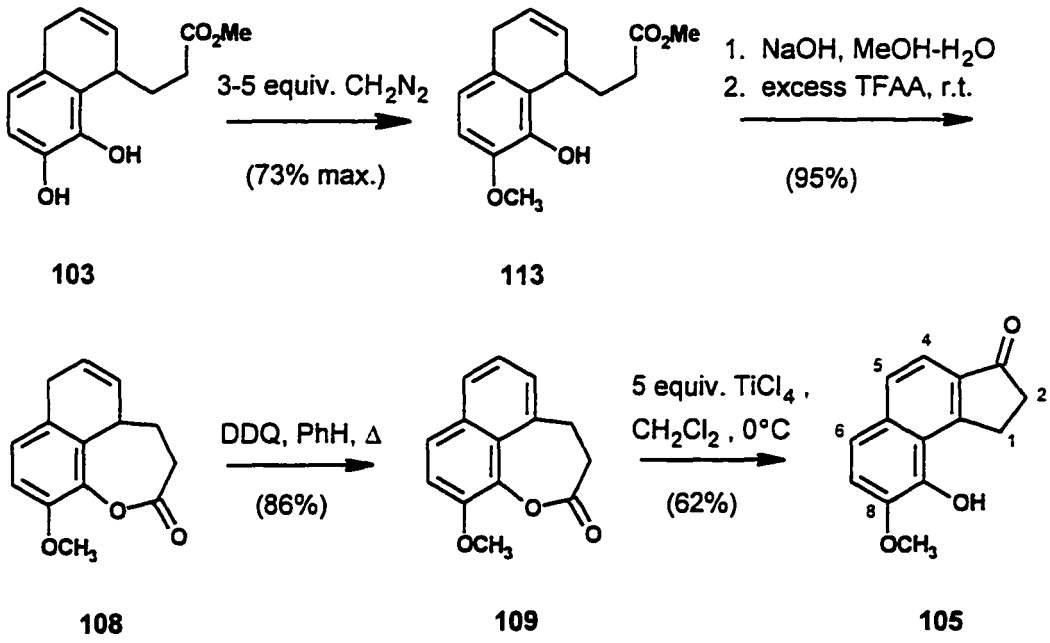
Diels-Alder reaction using 2,3-dihydroxybenzoic acid **110** and methyl (*E*)-4,6-heptadienoate was tried with the hope that the carboxylic acid group would survive the oxidation conditions with PIFA and exert regiocontrol on the cycloaddition like its ester analogue. The product isolated in good yield (78%) from this reaction was the 1,2-dihydroxy-5,8-dihydronaphthalene derivative **103,** presumably resulting from the spontaneous decarboxylation of the β-keto acid adduct **111** in the reaction medium (Scheme 2.10). This promising result not only solved the earlier problem of keto-enol tautomerism, but also uncovered a *de novo* synthesis of 1,2-dihydroxynaphthalenes by a one-pot process from a simple commercially available starting material. (A survey of

regiocontrolled Diels-Alder reactions of various substituted *o*-benzoquinones with several dienes was undertaken at this time and some chemical transformations of these adducts which lead to synthetically useful compounds will be discussed later in section 2.3 of this chapter.) The new synthetic route shown in Scheme 2.10 consequently began with this Diels-Alder reaction, and followed with the acidic hydrolysis of **103** and subsequent lactonization using TFAA to produce **112** in only 3 steps and 69% overall yield, a significant improvement from the original route. Unfortunately, the subsequent methylation step with diazomethane furnished the lactone **108** in very low yield, along with other products which may have formed by way of a ring-opened α-diazoketone. 'Three steps forward and one step back' seemed to be the name of the game in this endeavor.

Inspection of the ^{1}H-NMR spectrum of **103** revealed that the C_1-OH group was involved in hydrogen-bonding with the side-chain ester moiety (sharp singlet at 7.26 ppm). Coupled with the fact that the C_2-OH group was less sterically hindered, it was speculated that chemoselective methylation of the C_2-OH group could be achieved by treatment with a highly reactive methylating agent such as diazomethane. A third modification of the synthetic route was therefore charted according to Scheme 2.11. Compound **103** was reacted with a 3- to 5-fold excess of diazomethane, which produced **113** as the major product in moderate yields ranging between 50-73%, along with dimethylated and C_1-monomethylated minor products. Some technical drawbacks to this method involved the frequent preparation of large volumes of hazardous diazomethane, as well as the time-consuming separation of the desired phenol **113** from the product mixture by column chromatography. The side-chain ester group of **113** was then saponified and cyclized with TFAA to give the lactone **108** in nearly quantitative yield

(95%). The remaining two steps followed the route described earlier in Scheme 2.9, which lead to the construction of the benz[*e*]indanone **105** in 6 steps and 29% overall yield from 2,3-dihydroxybenzoic acid. To reach the important benz[*e*]indanone thiol ester **81**, a key intermediate in synthesizing viridin, the last step that remained was the installation of the thiol ester group at C_6 of **105**.

Scheme 2.11

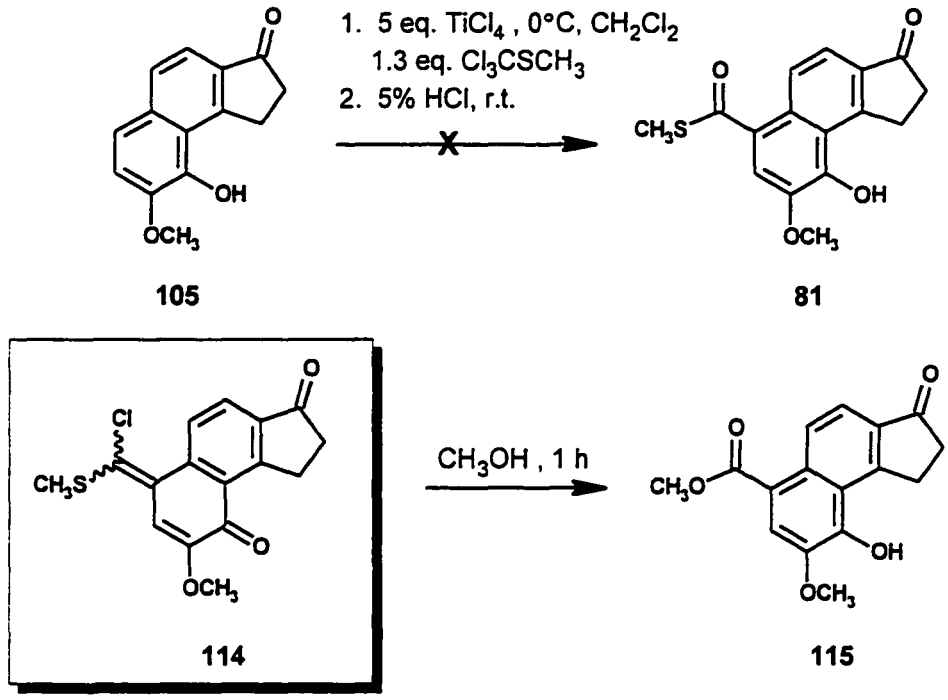


*2.2.2 Placement of the Thiol Ester Group on the Benz[e]indanone Intermediate **105***

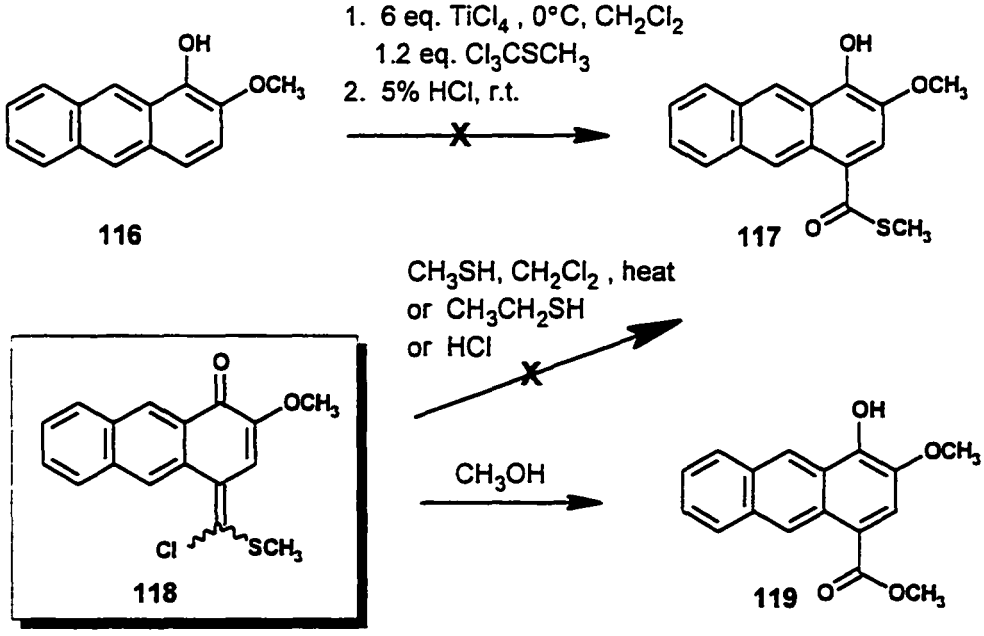
A convenient method for placing an acyl group on an aromatic ring is by Friedel-Crafts alkylation with the chlorinated analogue of this functional group, followed with

acidic hydrolysis which unmasks the carbonyl group.[63] Gross and Matthey[64] developed a general synthesis of arene thiol esters by the Friedel-Crafts reaction of activated aromatic compounds with trichloromethyl methyl sulfide, prepared by chlorination of dimethyl sulfide with phosphorus pentachloride.[65] Earlier work in our laboratory had validated the usefulness of this method on simple benzenoid and naphthalenoid substrates.[45] Compound **105** was therefore subjected to this Friedel-Crafts reaction in the presence of a stoichiometric amount of trichloromethyl methyl sulfide and a 5-fold excess of neat titanium tetrachloride at 0°C, followed by hydrolysis with dilute $HCl_{(aq)}$ (Scheme 2.12). To our surprise, the reaction product was not the desired thiol ester **81** but rather the 1,4-naphthoquinone methide derivative **114**, an intermediate in the formation of **81** which proved to be unusually stable. It was presumed that the extensive conjugation in **114** might have provided sufficient stabilization to resist acidic hydrolysis. The ^{1}H-NMR spectrum revealed a mixture of two geometric isomers, and low resolution mass spectrometric analysis confirmed the presence of one chlorine and one sulfur atom (*m/e*= 320, M^+, 100%; *m/e*=322, M+2, 43%; *m/e*=270, M-CH_3Cl, 17%). Several attempts to hydrolyze **114**, including heating with strong acid, failed to provide the desired thiol ester **81**. Repetition of the Friedel-Crafts reaction using either zinc(II) chloride or stannic chloride as the catalyst only produced more of the chlorinated quinone methide **114**. An observation was serendipitously made that after stirring **114** with methanol, the benz[*e*]indanone methyl ester **115** was produced (although in low overall yield from **105**). At this same time in our laboratory in other research directed at the synthesis of xestoquinone (**12**), a similar chlorinated quinone methide **118** was formed from a Friedel-Crafts reaction on 1-hydroxy-2-methoxyanthracene **116** (Scheme 2.13).[66] Many attempts

Scheme 2.12



Scheme 2.13[66]



were made at hydrolyzing **118** to its corresponding thiol ester **117**, including refluxing with a solution of methanethiol in methylene chloride, treatment with excess ethanethiol and also stirring in methanol; however, only exposure to methanol seemed to cause re-aromatization to the methyl ester **119**.[66] Repeated trials of the Friedel-Crafts reaction at various temperatures with other Lewis acids, including boron trifluoride-etherate and zinc(II) chloride, had only produced more of the undesired chlorinated compound **118**.[66]

Although the thiol ester **81** could not be synthesized by this route, a small quantity (<100 mg) of the analogous methyl ester **115** was available to validate the planned annulation of rings A and E of viridin by the one-pot three-step IMDA process which involved: (i) PIFA-promoted oxidation of **115**, (ii) ketalization in the presence of excess (*E*)-2,4-pentadienol, and (iii) intramolecular Diels-Alder reaction of the *o*-quinonoid monoketal (Scheme 2.14). Our expectations were met when two diastereomeric adducts **120a-b** (*endo* and *exo*, respectively) were isolated in about a 2:1 product ratio (estimated by TLC analysis), both pentacyclic methyl esters; however the yield of both products was low (< 10%), due to the small scale of this trial reaction. ^{1}H- and ^{13}C-NMR as well as mass spectrometric analyses supported the structures shown for these adducts (however an insufficient quantity of the *exo*-product **120b** was available for complete characterization). The high field (500 MHz) ^{1}H-NMR spectra (Figures 2.3 a,b) depicted a pair of signals for the diastereotopic set of protons H-1, H-1' and H-4, H-4' along with two signals assigned for the vinylic protons H-2 and H-3. The determination of the *endo* or *exo* relative configurations for these adducts was made by comparison of ^{1}H-NMR coupling constants with those measured for the *endo* and *exo* stereoisomers of the model phenanthro[10,1-*bc*]furans **78** and **79** (*cf.* Scheme 1.14), whose X-ray crystal structures had been obtained.[45] A diagnostic feature emerged from examination of the

^{1}H-NMR spectra which enabled the differentiation of *endo* and *exo* isomers from this IMDA reaction. For the *endo*-isomer in Figure 2.3a (where substituents at C_{3a}, C_{5a}, C_{11b}, and C_{11c} are all β-*cis*-related), the signal for H-11c is a doublet of doublets arising from vicinal coupling with H-3a (J= 8.6 Hz) and W-coupling with H-1β (J=2.2Hz). For the *exo*-isomer in Figure 2.3b (substituents at C_{5a}, C_{11b}, and C_{11c} are all β-*cis*-related; H-3a and H-11c are *trans*-related), the signal for H-11c is only a doublet from a large vicinal coupling with H-3a (J=12.3 Hz).

Scheme 2.14

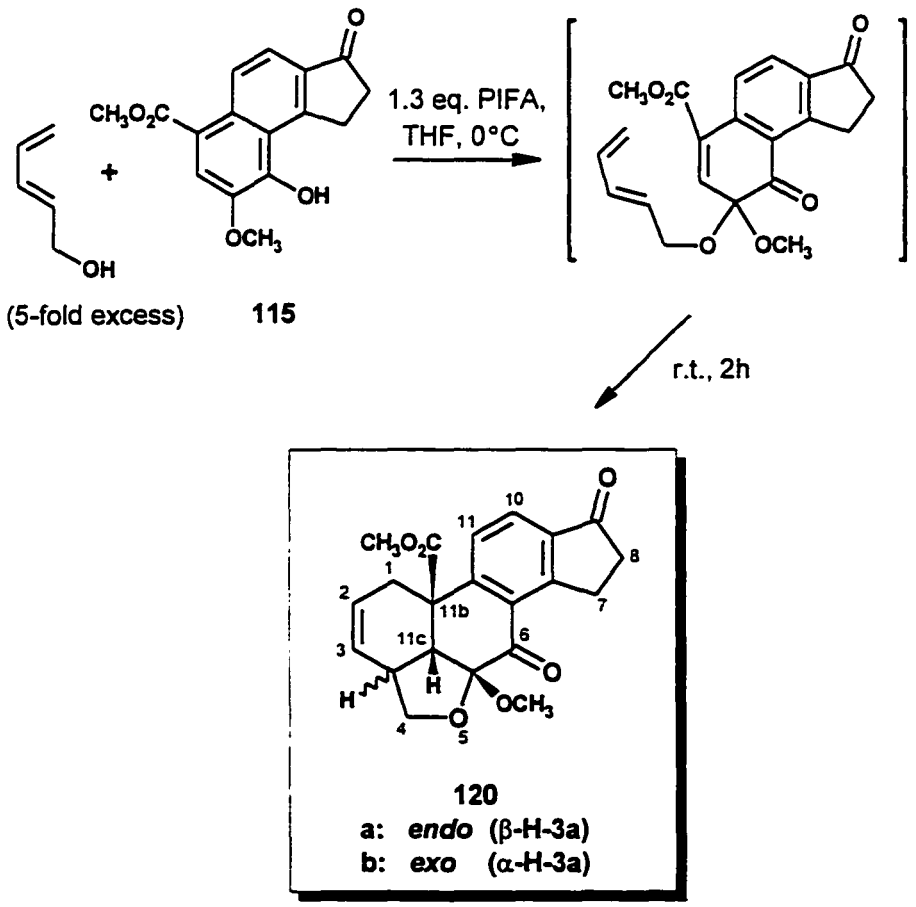


Figure 2.3 (a): High-field (500 MHz) ^{1}H-NMR spectrum of **120a** (*endo*).

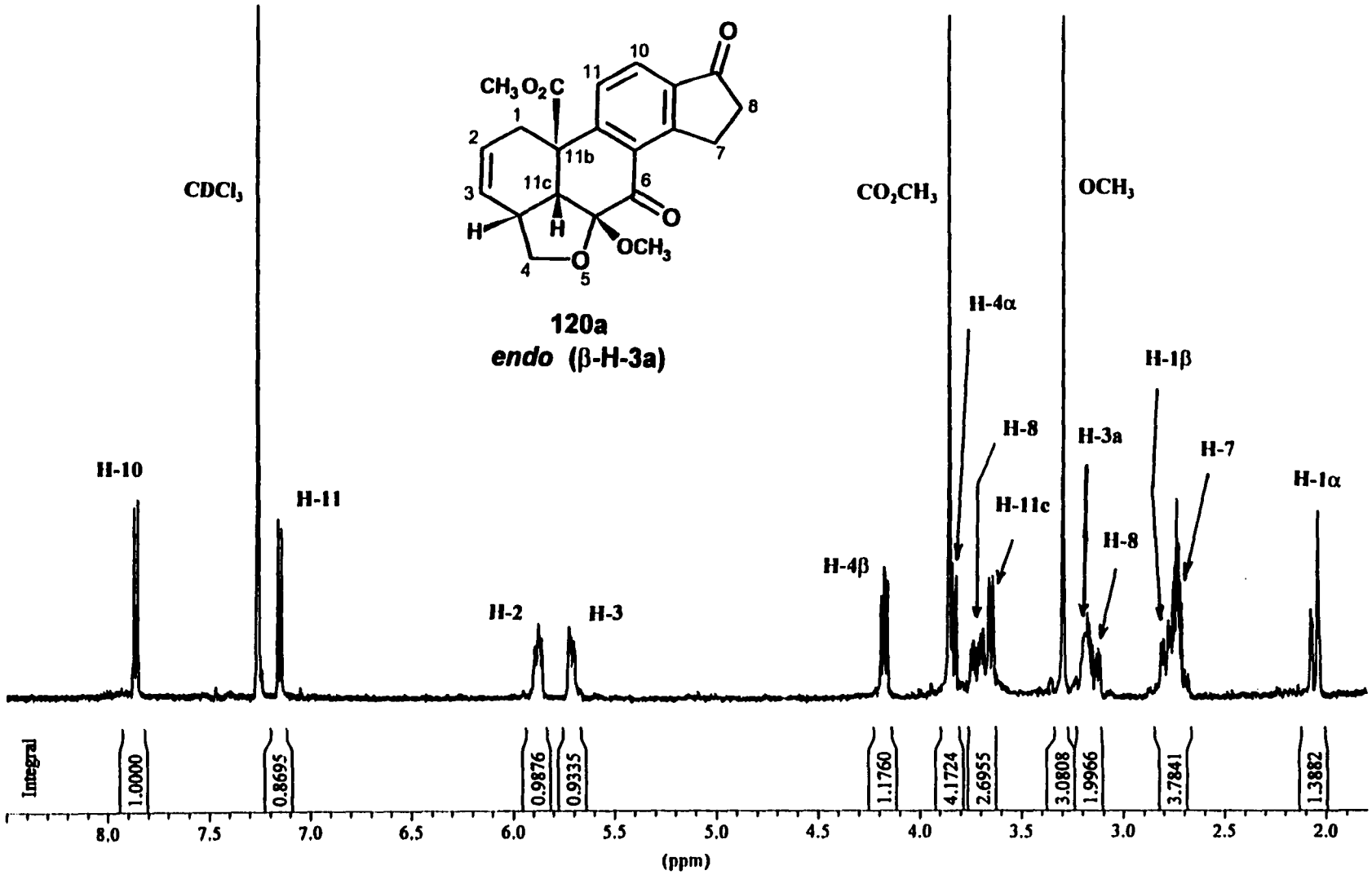
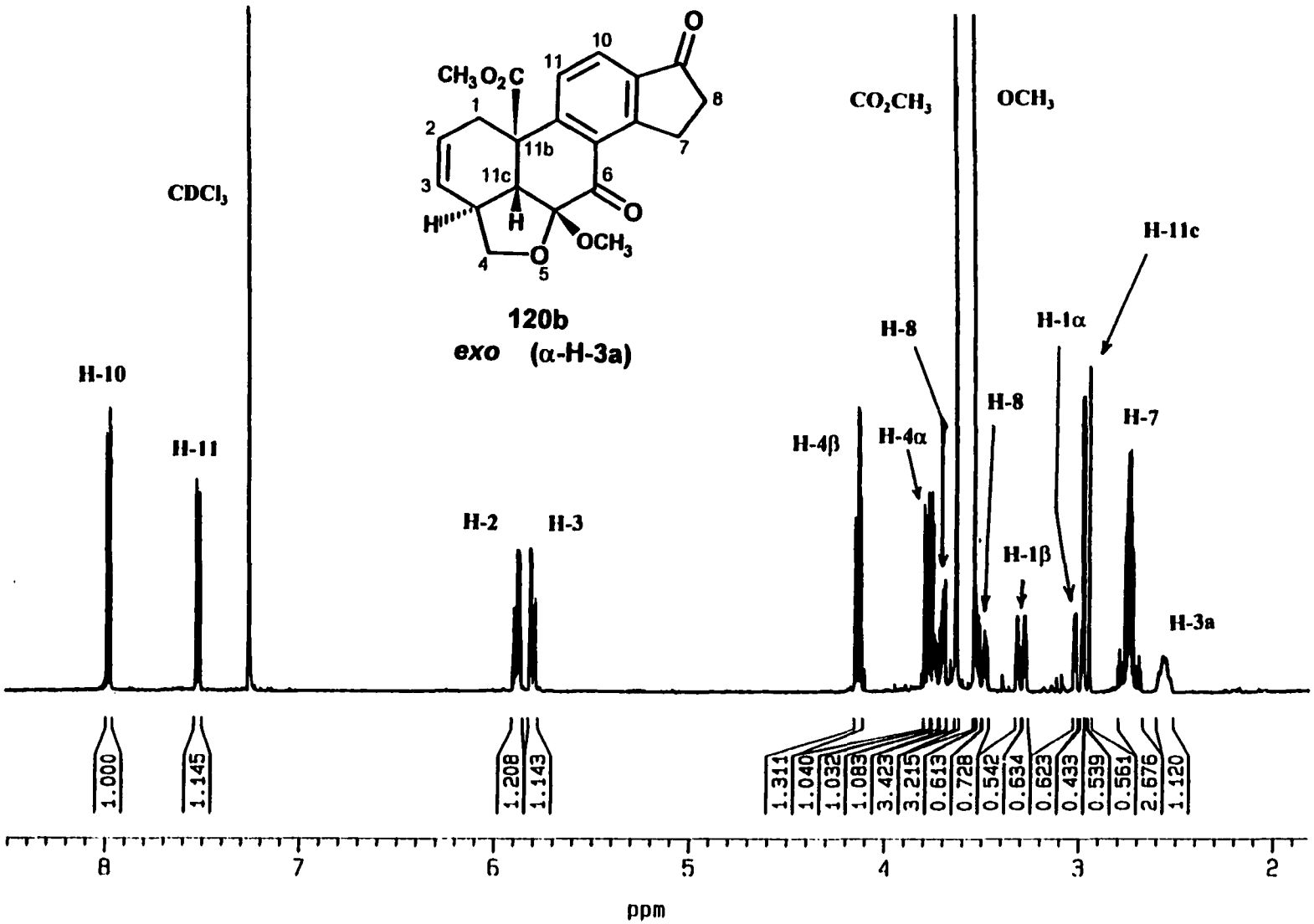


Figure 2.3 (b): High-field (500 MHz) ^{1}H-NMR spectrum of **120b** (*exo*).

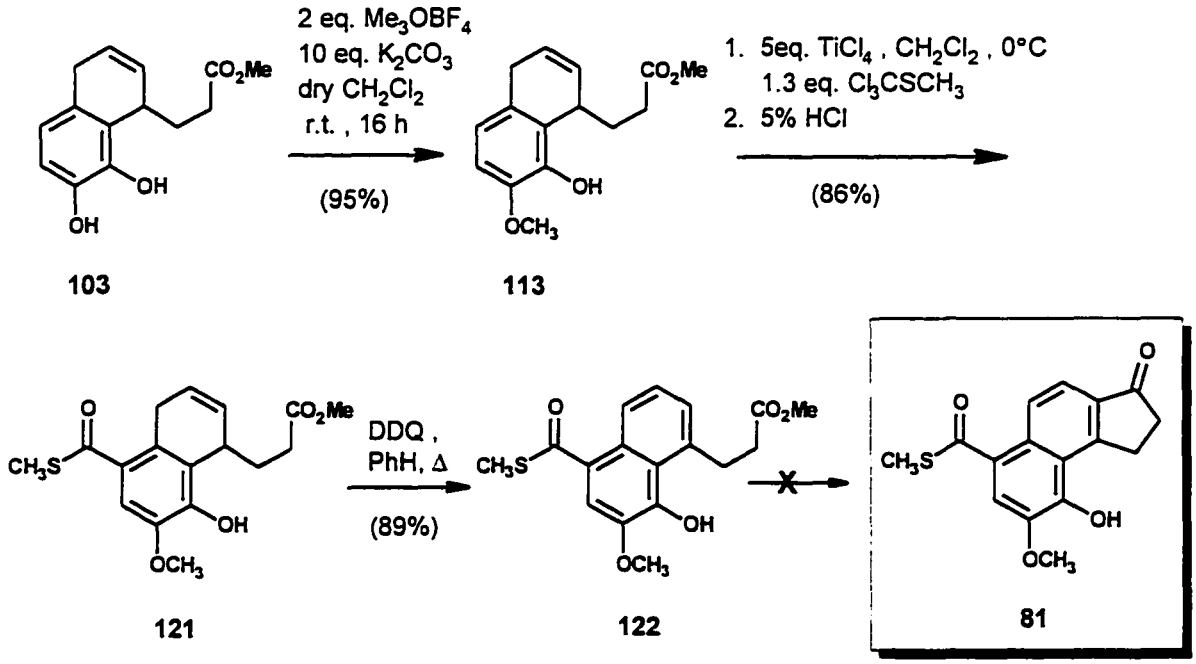


The success of having accomplished the first ever synthesis of the pentacyclic ring system of viridin was gratifying, and so the struggle to improve the synthetic route for the benz[*e*]indanone thiol ester **81** continued. It should be reiterated that the placement of the thiol ester group $COSCH_3$ (rather than CO_2CH_3) at C_{11b} in the pentacycles **120a-b** was expected to provide a better handle for chemoselective reduction of this group to the methyl group in viridin. This strategy was necessary since preliminary model experiments[45] had shown that the C_4-methyl group of the naphthol substrate **70** (*cf.* Scheme 1.14) could not withstand the oxidation step in the intramolecular Diels-Alder reaction.

In earlier work performed in our laboratory, the Friedel-Crafts method for introducing a thiol ester group was quite successful on benzenoid substrates. The synthetic route in Scheme 2.11 was consequently modified to allow the placement of the thiol ester group on the benzenoid intermediate **113**, prior to closure of the side-chain ester in forming the benz[*e*]indanone thiol ester **81**. In the course of revising this route, an improved method for the selective monomethylation at C_2 of catechol **103** was developed which avoided the preparation and use of diazomethane. Illustrated in Scheme 2.15, the Diels-Alder adduct **103** was selectively methylated to **113** in excellent yield (95%) by admixture with a 10-fold excess of potassium carbonate in methylene chloride, followed with two molar equivalents of Me_3OBF_4. The Friedel-Crafts reaction of **113** with trichloromethyl methyl sulfide and titanium tetrachloride neatly furnished the 5,8-dihydronaphthalene thiol ester **121** in a reproducibly good yield (86%). The dehydrogenation of **121** by direct addition of DDQ had initially proved to be troublesome, since the major reaction product was identified to be the *o*-naphthoquinone analogue. In order to avoid protection/deprotection steps for the exposed phenol group,

many attempts were made to systematically optimize the dehydrogenation conditions using various quinone oxidants (DDQ, *p*-chloranil) and hydrocarbon solvents (benzene, toluene, *p*-xylene). The best conditions required the slow dropwise addition of a solution of DDQ in benzene to a refluxing solution of **121** in benzene, which after several hours, afforded the naphthyl thiol ester **122** in a high yield (89%). The expression 'three steps forward and one step back' never rang more true than at this time, as the forthcoming closure of the side-chain proved to be among the more troublesome challenges to overcome in this synthetic route.

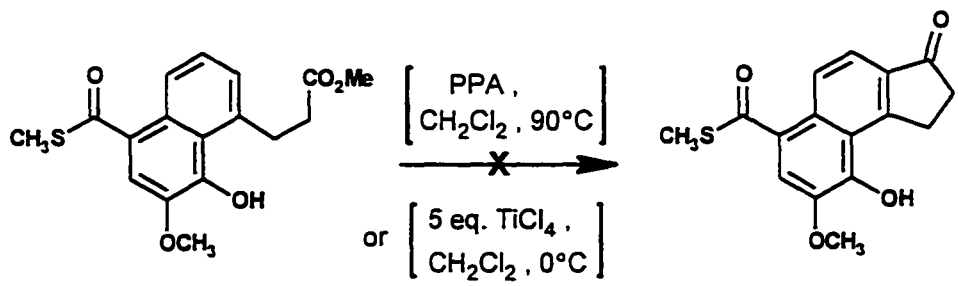
Scheme 2.15



A search of the literature had revealed that the preparation of substituted benz[*e*]indanones by either intramolecular Friedel-Crafts acylation or other short synthetic routes were uncommon and generally inefficient.[67] By contrast, numerous

citations were found for the preparation of 1-indanones *via* intramolecular Friedel-Crafts acylation of aryl carboxylic acid derivatives.[68] Although a wide assortment of Lewis and Brönsted acid catalysts have been employed in these reactions, the success of the intramolecular ring closure is highly dependent on the substitution of the aromatic ring.[69] The dual presence of *para*-disubstituted phenol and thiol ester groups in **122** exert a push-pull electronic resonance effect on the ring system, making it difficult to predict the outcome of the Friedel-Crafts acylation. Furthermore, the thiol ester group of intermediate **122** was presumed to be sensitive to hydrolytic conditions and would therefore interfere with forming the carboxylic acid (or acid halide). Consequently, a method which would effect the intramolecular acylation directly from the methyl ester **122**, rather than a carboxylic acid or acid chloride, was desired. As shown in Scheme 2.16, **122** was heated for several hours with polyphosphoric acid (PPA),[70] generated by mixing ortho-phosphoric acid with phosphorous pentoxide, which resulted in a charred product mixture. Treatment of **122** with excess titanium tetrachloride had only returned unreacted starting material.

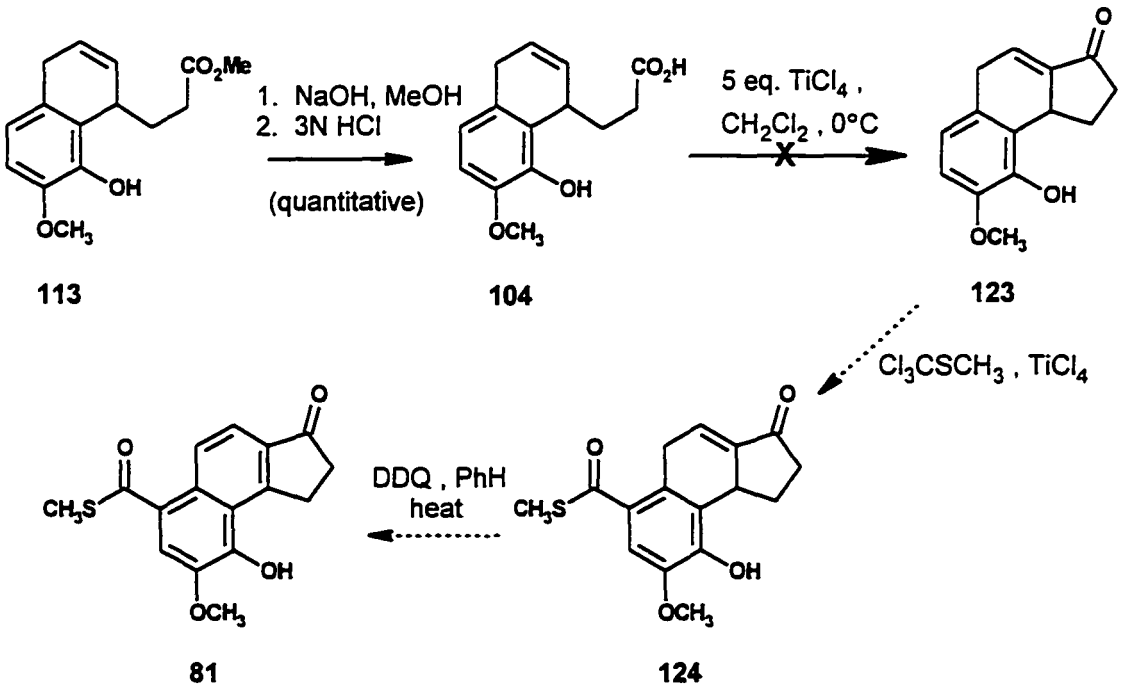
Scheme 2.16



122 **81**

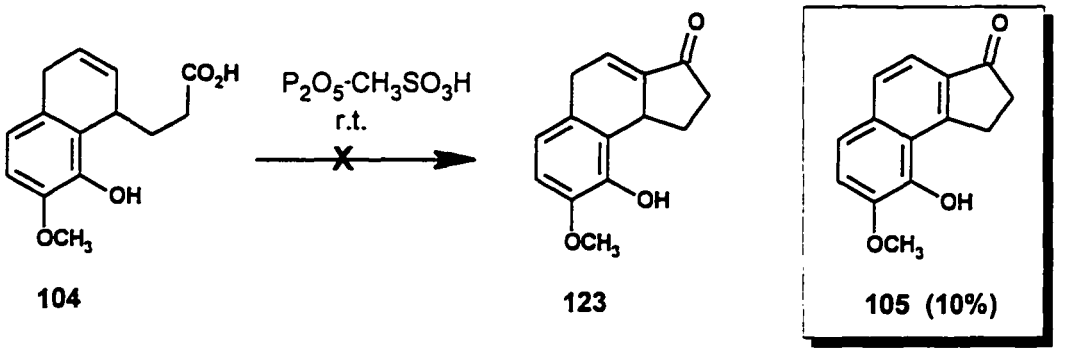
A new plan was devised based on the electrophilic addition of an acylium cation (generated from the side-chain ester group) to an alkene rather than an aromatic ring. The less well-known aliphatic Friedel-Crafts reaction[71] has been occasionally used to prepare cyclic α-enones by intramolecular acylation of vinyl carbons using activated carboxylic acids (i.e. acid chlorides, mixed anhydrides of organic and inorganic acids).[72] Many different activating reagents have been used, including Lewis acids $TiCl_4$,[71] $SnCl_4$,[72f] $AlCl_3$,[71, 72g] as well as the anhydrides PPA,[71a, 72c] P_2O_5-methanesulfonic acid system,[72e] and TFAA.[72a-d] The side-chain ester of **113** was first hydrolyzed with sodium hydroxide, and following acidic workup, the carboxylic acid **104** was generated in quantitative yield (Scheme 2.17). The new plan involved the intramolecular acylation of **104** to produce the

Scheme 2.17



tricyclic α-enone **123**, a benzenoid substrate for introducing the thiol ester group without complications. The last step of this plan involved dehydrogenation of thiol ester **124** with DDQ in order to furnish to the desired benz[*e*]indanone thiol ester **81**. The cyclization of **104** was tested with excess $TiCl_4$ at low temperature (0°C) for several hours, but no reaction was observed even after warming to room temperature.

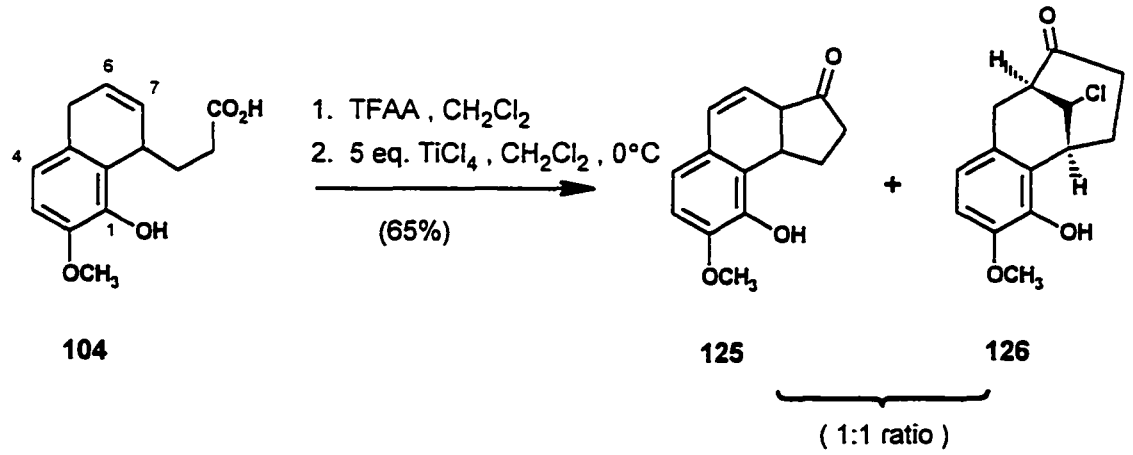
Scheme 2.18



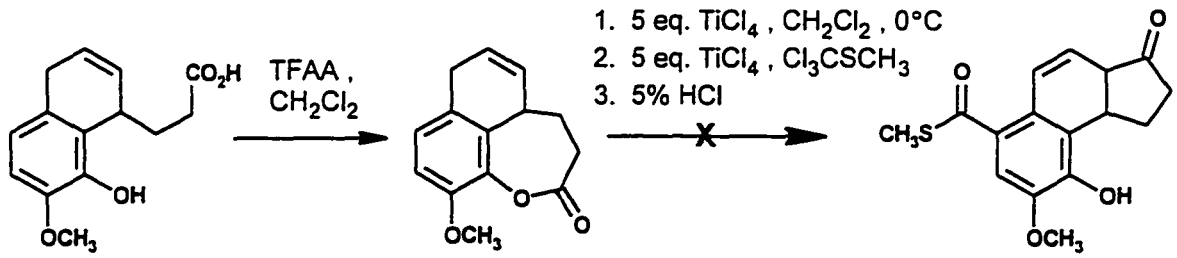
Following the method developed by Eaton and co-workers,[72e] the cyclization was next attempted using the mixed anhydride resulting from admixture of P_2O_5 and methanesulfonic acid (Scheme 2.18). Once again, the reaction did not produce **123**; rather the starting material **104** mostly decomposed at room temperature and offered only a small amount (≈10%) of aromatic benz[*e*]indanone **105**. Slightly milder reaction conditions were subsequently considered where carboxylic acid **104** was first lactonized with the C_1-phenol group in TFAA (Scheme 2.19). The intermediate lactone was isolated and an intramolecular acylation with excess $TiCl_4$ was attempted. Two products were isolated in moderate yield from this reaction in approximately equimolar quantities, which were characterized as structures **125** and **126**. The unexpected bicyclo product **126**

apparently resulted from electrophilic addition of the acyl cation to C_6 of the C_6–C_7 double bond in **104**; the presence of the chlorine atom was confirmed by mass spectrometric analysis (*m/e*= 266, M^+, 100%; *m/e*= 268, M+2, 35%). Although the actual yield of **125** (an isomer of **123**) was somewhat low, its formation was encouraging enough to consider a one-pot process on **104** that would also include a third Friedel-Crafts reaction with trichloromethyl methyl sulfide. Accordingly, carboxylic acid **104** was cyclized to the intermediate lactone **108** (Scheme 2.20) which was isolated, treated with excess $TiCl_4$ to cause the intramolecular acylation on the double bond, and then subjected to the Friedel-Crafts conditions. Unfortunately, a complex mixture of unidentifiable products was produced in this attempt, much of which was resinous in nature.

Scheme 2.19



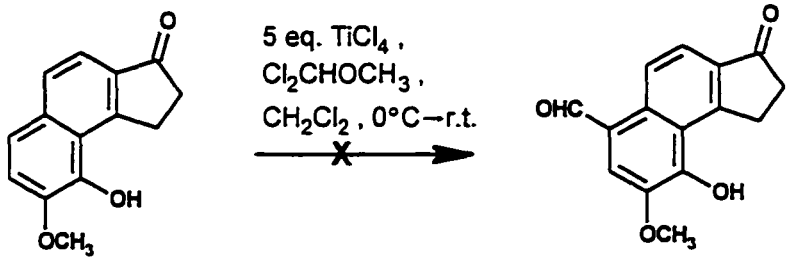
Scheme 2.20



104 **108** **127**

Since the presence of the thiol ester group was intended for reduction to the methyl group present in viridin *via* an intermediate aldehyde (or analogue thereof), a trial synthesis of the benz[*e*]indanone aldehyde **128** was therefore attempted. The tricyclic compound **105**, which was prepared earlier (*cf.* Scheme 2.11), was mixed with dichloromethyl methyl ether[63] and excess $TiCl_4$ at 0°C and slowly warmed to room temperature over several hours. The reaction had unfortunately produced a very small amount of the desired aldehyde **128** (<5% yield, insufficient for characterization) along with unreacted starting material (Scheme 2.21).

Scheme 2.21

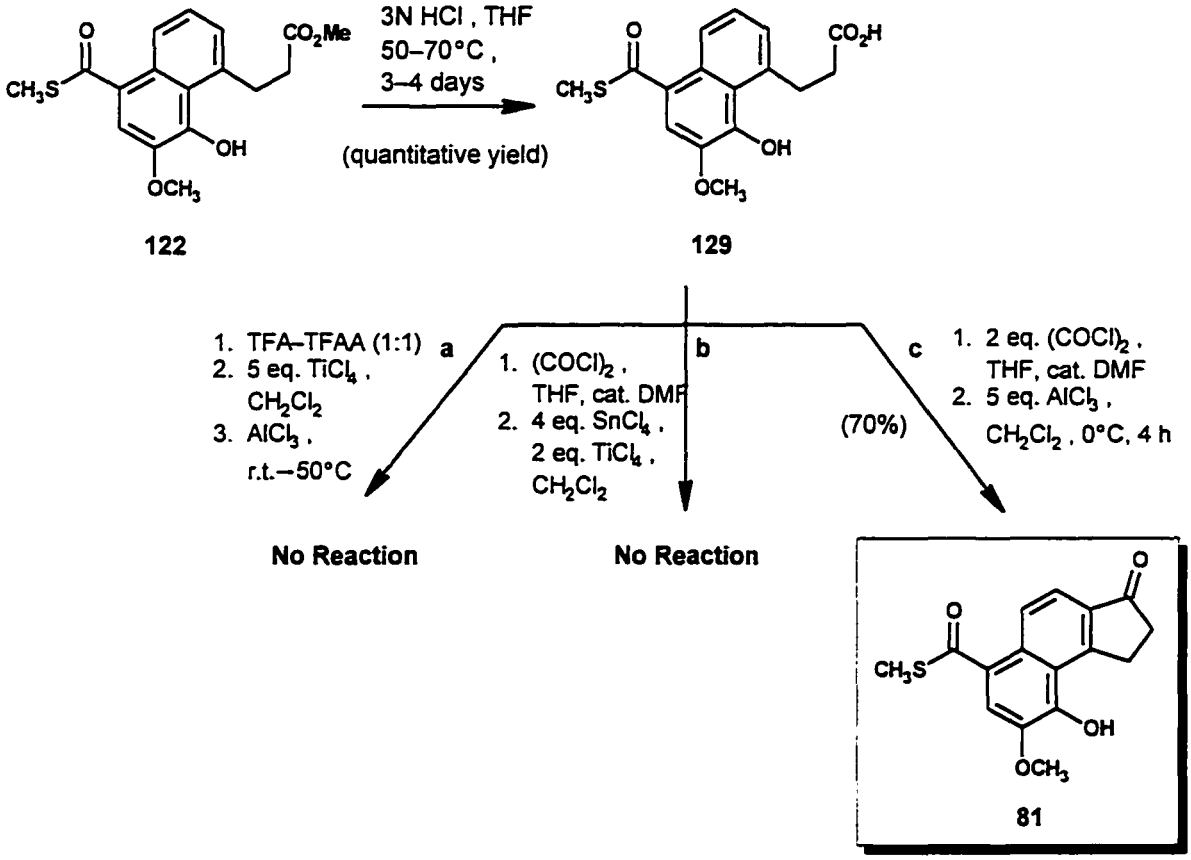


105 **128**

A method for selectively hydrolyzing the side-chain methyl ester of **122** without harming the thiol ester moiety was finally considered (Scheme 2.22). After careful experimentation, the reaction conditions developed for this procedure required acidic hydrolysis of **122** with 3N $HCl_{(aq)}$ in THF at 50-70°C over 3-4 days, which resulted in a quantitative yield of naphthylpropanoic acid **129**. The first attempt of the intramolecular acylation involved the intermediate formation of the naphthyl lactone using a 1:1-(vol/vol) mixture of TFA-TFAA, which was followed by treatment with excess $TiCl_4$ (reaction a). Since no reaction was observed by TLC, an excess amount of $AlCl_3$ was added to promote the acylation reaction; but after several hours at room temperature and even after mild heating for one hour, it was surprising that no reaction had occurred. It seemed that perhaps a more reactive intermediate was needed for the intramolecular acylation. Consequently, the acid chloride of **129** was prepared *in situ* by treatment with excess oxalyl chloride and a catalytic amount of DMF. After removal of all volatile solvents, the acid chloride was mixed with excess neat stannic chloride at 0°C (reaction b). Even after warming to room temperature, no reaction was observed by TLC. Excess $TiCl_4$ was also added to this reaction mixture in the hope of effecting the cyclization, but again no reaction products were observed by TLC. In both trials a and b, unreacted starting material was recovered. Success finally arrived when the Friedel-Crafts acylation of the acid chloride of **129** was performed using excess $AlCl_3$ at 0°C, giving the benz[*e*]indanone thiol ester **81** (reaction c). Some notable technical disadvantages in the synthesis of **81** included the very poor solubility of this compound in most organic solvents (except in DMSO and DMF), making its efficient isolation from the reaction mixture difficult and tedious. Furthermore, the requirement of using an excess amount of $AlCl_3$ also promoted the cleavage of the methoxyl group at room temperature, thus

necessitating a reaction temperature of 0°C. These technical limitations contributed significantly to the moderate yield of this reaction, which was typically of the order of 50% (the best recorded yield was 70%). After a significant span of several months of synthetic investigations, the ultimate arrival of this important intermediate **81** in the synthesis of viridin was both satisfying and invigorating, since the ensuing oxidation-IMDA reaction protocol was a proven success with the methyl ester analogue **115** (*cf.* Scheme 2.15).

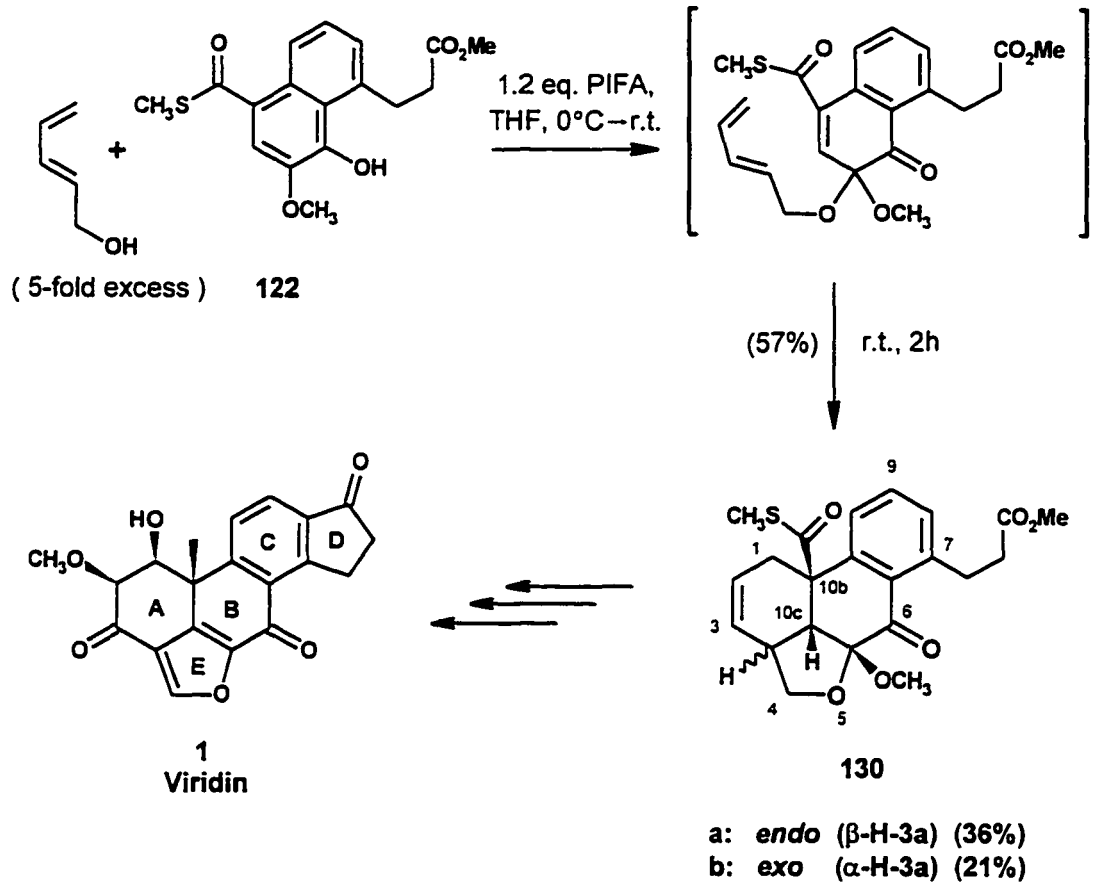
Scheme 2.22



2.2.3 *Intramolecular Diels-Alder Reactions of the o-Naphthoquinonoid Monoketals Generated from* **81** *and* **122** *with (E)-2,4-Pentadienol.*

The unexpected problems encountered over several months of investigating the synthesis of benz[*e*]indanone thiol ester **81** also led to the exploration of yet another strategy toward viridin (**1**). Due to the difficulties of cyclizing the pendant side-chain in **122**, a new synthetic plan was devised (Scheme 2.23) calling for the annulation of rings A and E of viridin by the tandem oxidation-IMDA reactions, to be followed afterward with the intramolecular cyclization of the side-chain (Scheme 2.23). When this plan was carried out, the one-pot three-step IMDA reaction sequence with naphthalene **122** proceeded smoothly and produced the tetracyclic phenanthro[10,1-*bc*]furans **130a-b** as a 2:1 mixture of *endo* and *exo* diastereomers in a combined yield of 57%. Experimentally, the progress of this three-step reaction was easily monitored visually, as the color of the reaction mixture changed from dark orange upon addition of PIFA to a final pale yellow. The determination of the relative configurations in **130a-b** were made by comparison of their ^{1}H-NMR spectra with those obtained for the isomers of model compounds **78** and **79** (*cf.* Scheme 1.14) whose relative configurations were confirmed by X-ray analysis.[45] Since the naphthalenoid precursor **122** was easily prepared in large quantities in only 4 steps and 57% overall yield from commercially available 2,3-dihydroxybenzoic acid (*cf.* Scheme 2.15), the Diels-Alder adducts **130a-b** were also used as models for studying the chemoselective reduction of the thiol ester group to the methyl group found in viridin (these efforts will be discussed shortly in section 2.2.4).

Scheme 2.23



Once a reasonable quantity (2-4 g) of benz[*e*]indanone thiol ester **81** was made available, the revised route outlined in Scheme 2.23 was no longer pursued. Several trials of the oxidation-IMDA reaction were carried out with **81** (Scheme 2.24). A persistent problem was the poor solubility of **81** in the reaction medium (THF), even at high dilution; heating did not greatly improve the solubility. Furthermore, the expected color change to dark orange, which was characteristic immediately after adding the oxidant PIFA in all IMDA reactions, was absent in this case. The poor yield of **80a-b** which resulted (e.g. 10-30%) raised the possibility that the rate of oxidation of benz[*e*]indanone

81 with PIFA at 0°C (typical conditions for the IMDA reaction) was unexpectedly slower than the rate with other naphthalenoid substrates. To probe this problem, the IMDA reaction on **81** was repeated at room temperature, and it was agreeably noted how the gold-colored turbid mixture had quickly transformed to a homogeneous dark orange solution within 2-3 min after addition of PIFA! In accordance with the observations made earlier for the IMDA reactions with the other naphthalenoid substrates, this rapid change in color was qualitatively attributed to the rate of oxidation of **81** with PIFA. Furthermore, by adding solid $NaHCO_3$ after 5 min. (following the color change to dark orange) in order to neutralize the TFA oxidation by-product, the yield of adducts **80a-b** had remarkably improved beyond the 75% mark, and the best recorded yield for this one-pot, three-step IMDA sequence on the benzindanone **81** was 86% (Scheme 2.24). The ^{1}H-NMR spectra of the diastereomers of **80a** and **80b** are shown in Figures 2.4a and 2.4b respectively, and they exhibit the same characteristic chemical shifts and coupling patterns observed with the analogous methyl ester adducts **120a-b** (*cf.* Figures 2.3 a, b). The synthesis of these pentacyclic thiol esters as a 2:1 mixture of *endo* and *exo* diastereomers (57% and 29% yields, respectively) was consequently achieved in 8 steps and 34% overall yield from commercially available 2,3-dihydroxybenzoic acid, and represents an efficient synthesis of the pentacyclic framework of the viridin family of natural products. Our attention naturally turned toward accomplishing what was considered the most critical of the remaining synthetic tasks: the selective reduction of the thiol ester group to the required methyl group of viridin.

Scheme 2.24

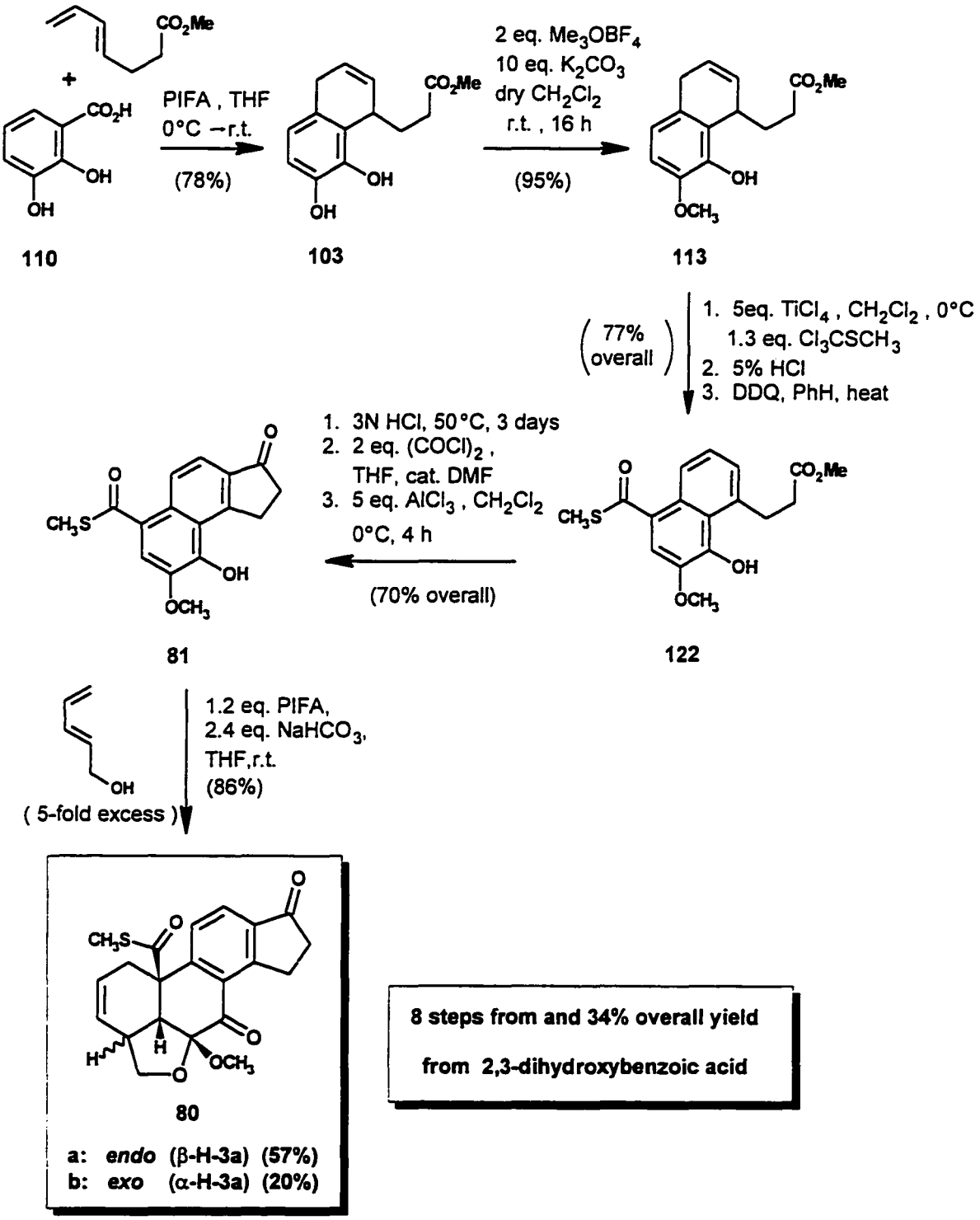

CO2Me
CO2H
OH
OH
PIFA , THF
0°C –r.t.
(78%)
110
103
2 eq. Me3OBF4
10 eq. K2CO3
dry CH2Cl2
r.t. , 16 h
(95%)
113
(77% overall)
1. 5eq. TiCl4 , CH2Cl2 , 0°C
1.3 eq. Cl3CSCH3
2. 5% HCl
3. DDQ, PhH, heat
1. 3N HCl, 50°C, 3 days
2. 2 eq. (COCl)2 ,
THF, cat. DMF
3. 5 eq. AlCl3 , CH2Cl2
0°C, 4 h
(70% overall)
CH3S
OCH3
81
122
1.2 eq. PIFA,
2.4 eq. NaHCO3,
THF,r.t.
(86%)
(5-fold excess)
80
a: endo (β-H-3a) (57%)
b: exo (α-H-3a) (20%)
8 steps from and 34% overall yield
from 2,3-dihydroxybenzoic acid

Figure 2.4 (a): High-field (500 MHz) ^{1}H-NMR spectrum of pentacycle **80a** (*endo*).

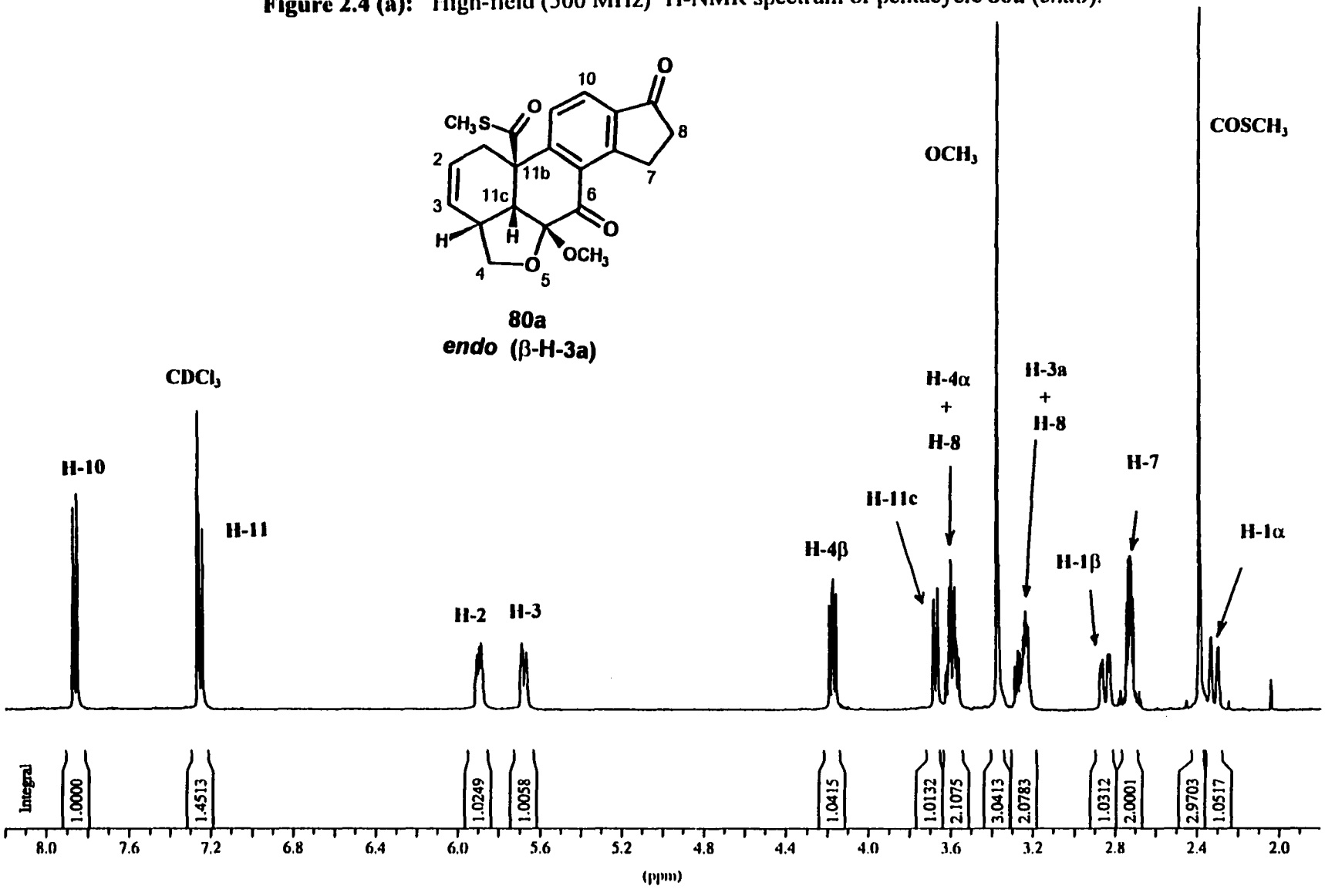
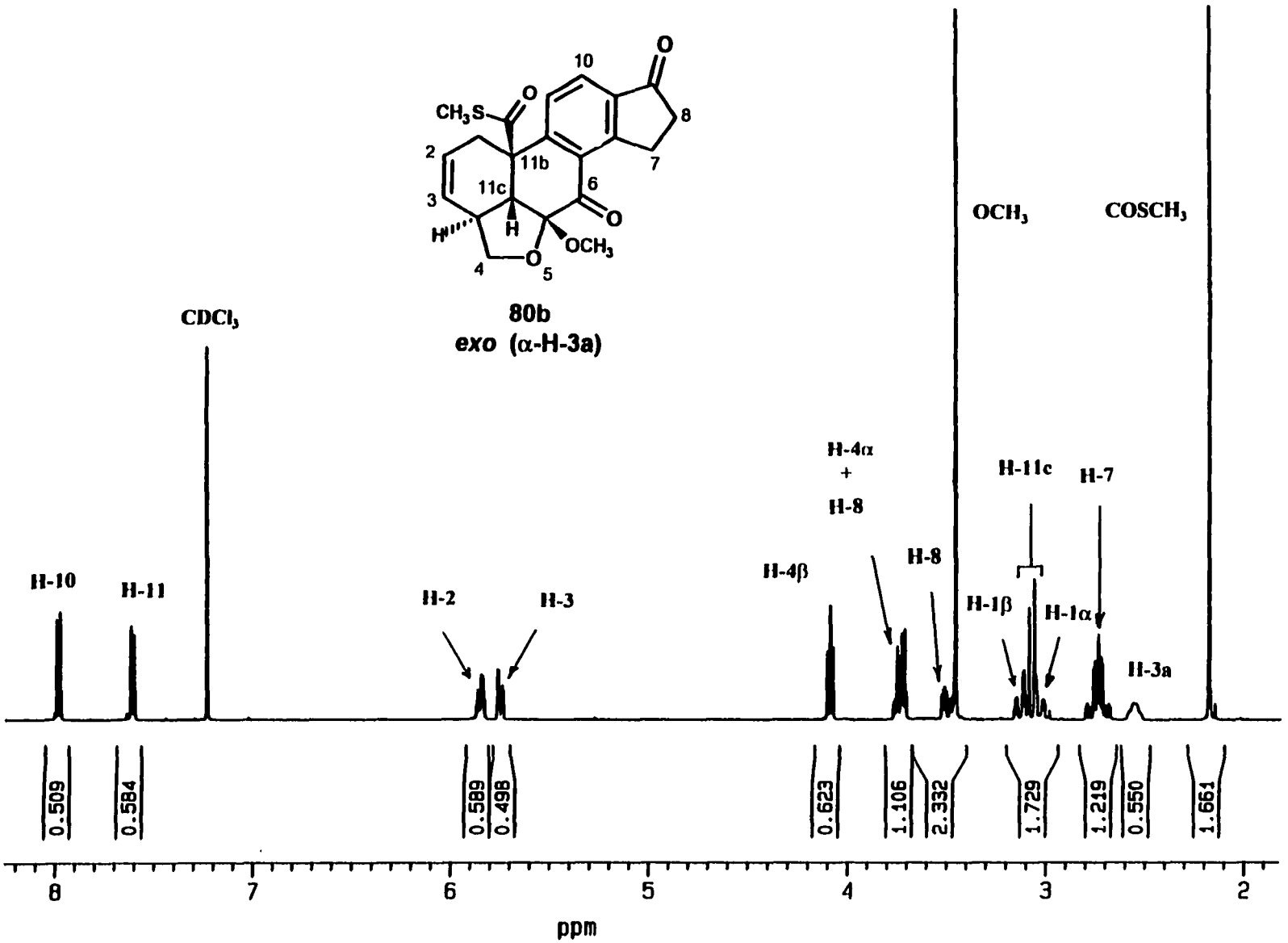


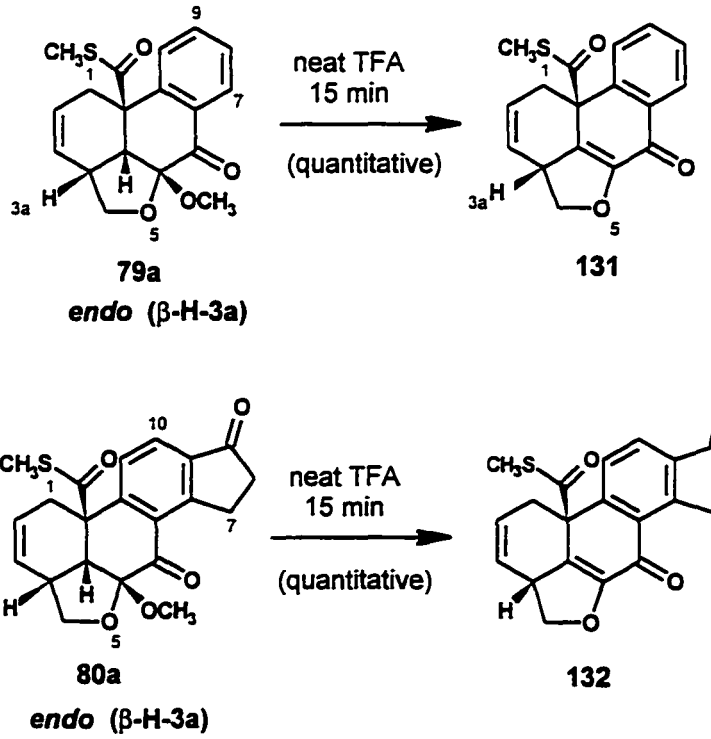
Figure 2.4 (b): High-field (500 MHz) ^{1}H-NMR spectrum of pentacycle **80b** (*exo*).



2.2.4 *Investigations of the Reductive Desulfurization of Pentacyclic Thiol Ester 80 and its Analogues*

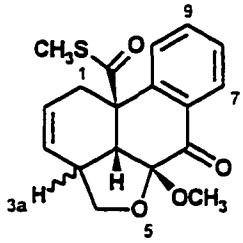
Several compounds which were available and easily synthesized were chosen as models for studying the selective reduction of the thiol ester group in pentacycles **80a-b** (Figure 2.5). The phenanthrofuranoid thiol esters **79a-b** described earlier were prepared from naphthalene thiol ester **75** (*cf.* Scheme 1.14),[45] and the analogous thiol esters **130a-b** were prepared from the IMDA reaction of **122** during the course of investigating the synthesis of viridin (Scheme 2.23). The demethoxylated analogues **131** and **132** were both prepared in quantitative yield from the *endo*-isomers **79a** and **80a** respectively, by elimination of methanol in neat TFA (Scheme 2.25).

Scheme 2.25



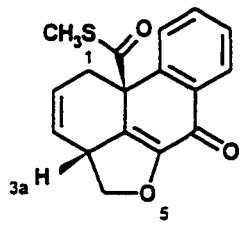
Typically, the reduction of thiol esters (or, esters in general) to alkanes occurs by formation of an intermediate aldehyde or alcohol.[73] Controlled reduction of the thiol ester group to an aldehyde intermediate was considered ideal for our purposes, since many reactions exist for selectively reducing an aldehyde in the presence of ketones to an alkane. Among the literature methods for reductive desulfurization of thiol esters,[74] most are not suitable for highly functionalized substrates, especially those which possess other carbonyl-containing functional groups. Consequently, the methods initially tested on these model compounds were those reported to be mild and selective.

Figure 2.5: Model thiol esters used for investigating conditions of reductive desulfurization.

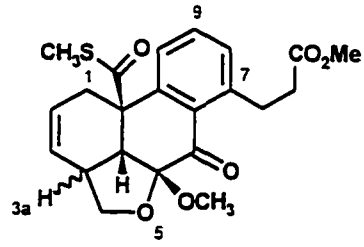


79

a: *endo* (β-H-3a)
b: *exo* (α-H-3a)

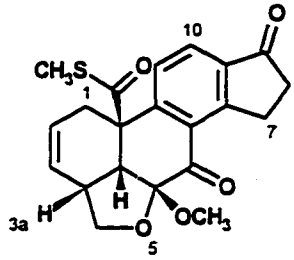


131



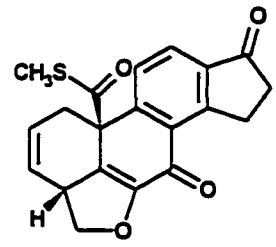
130

a: *endo* (β-H-3a)
b: *exo* (α-H-3a)



80a

***endo* (β-H-3a)**

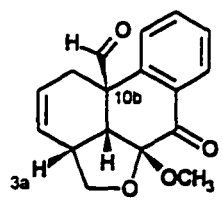


132

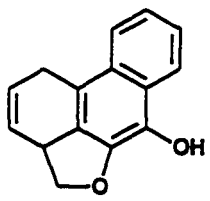
A facile method for reducing thiol esters to aldehydes involves hydrogenolysis using excess triethylsilane and catalytic palladium-on-carbon, which was developed by Fukuyama and co-workers.[75] They reported the selective reduction of several thiol ester substrates, which also possessed other ester and/or amide functional groups, to their corresponding aldehydes in efficient yields (84-97%). This seemingly convenient reaction was logically chosen for study on thiol esters **79a-b**, **130a-b**, **131**, and **80a** using the literature conditions (room temperature, dry acetone or dry CH_2Cl_2 as the solvent). The results of these trials are summarized in Table 2.2 (entries 1-3, 6-9, and 12-13) and the reduction products illustrated in Figure 2.6. The reaction performed somewhat inconsistently and dubiously, perhaps due to the heterogeneous nature of the conditions, since various reduction products were obtained in a broad range of yields. Repeated trials with **79a** and **79b** proved that this simple model thiol ester was not suitable for this reaction: the *endo*-isomer gave a poor yield of the aldehyde **133** (27%) together with a deformylated aromatic product **134**, while the *exo*-isomer did not react at all (Table 2.2, entries 1, 2). The formation of the deformylated aromatic product **134** was surprising but not unusual since it must have arisen from the aldehyde **133** by deformylation and aromatization. A test reaction with the demethoxylated thiol ester **131** (entry 3) had indeed rapidly furnished **134** as expected, thereby substantiating the labile character of the vinylogous aldehyde at C_{10b}. Furthermore, the success of this hydrogenolysis reaction was clearly substrate dependent. Repetition of the reaction using the same sources of triethylsilane, palladium-on-carbon and dry solvent with the three *endo*-substrates **79a**, **130a**, and **80a**, gave three very different results (entries 1, 6, and 12). In all cases, the reaction appeared to be slightly more exothermic in CH_2Cl_2 as solvent, sometimes producing over-reduced and/or aromatized by-products more readily. Although an

explanation for the wide spectrum of reactivity could not be found, it was nonetheless affected by the choice of solvent. A trial reaction with the pentacyclic thiol ester **80a** (entry 12) in either dry acetone or dry CH_2Cl_2 had after 4-5 days produced only a small amount of the desired aldehyde **138**, along with unreacted starting material. Very recently, trials with **80a** in 1:1 THF-CH_2Cl_2 had inconsistently produced what appeared to be the aldehyde **138** (by inspection of the ^{1}H-NMR spectrum). Unfortunately, a significant quantity of this aldehyde was not available at this time for complete characterization nor for examining its subsequent conversion to the corresponding C_{11b}-methyl analogue.

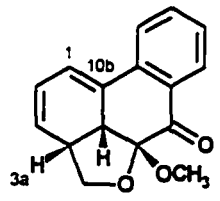
Figure 2.6: Assorted products obtained from reductions of various thiol esters.



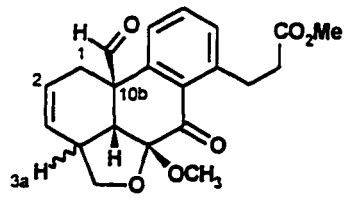
133
endo **(β-H-3a)**



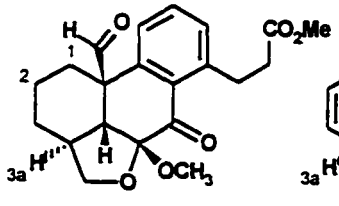
134



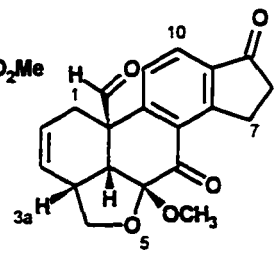
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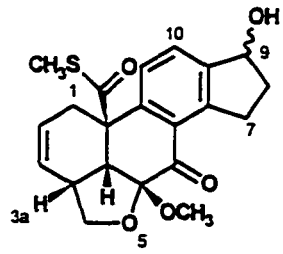
136
a: ***endo*** **(β-H-3a)**
b: ***exo*** **(α-H-3a)**



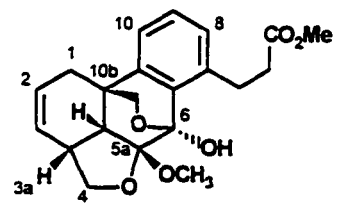
137
exo **(α-H-3a)**



138
endo **(β-H-3a)**



139



140

Table 2.2: Attempted reductive desulfurizations of model compounds.

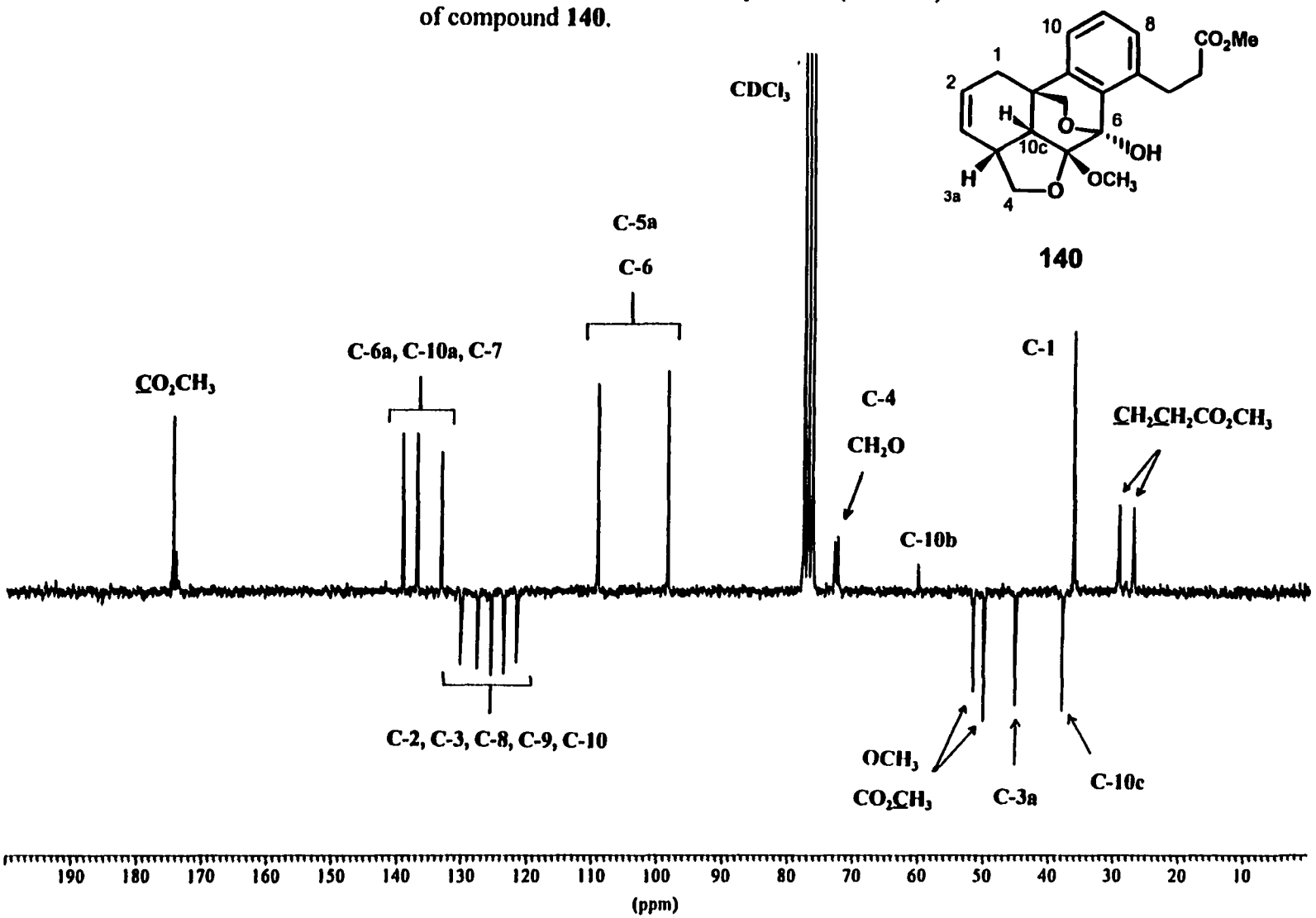
Entry	Substrate	Reaction Conditions	Solvent	Product(s) (%-Yield)
1	**79a** (*endo*)	Et_3SiH, cat. Pd/C, 3-4 days	acetone or CH_2Cl_2	**133** (27%) + **134** (major product)
2	**79a** (*exo*)	Et_3SiH, cat. Pd/C, 5 days	acetone or CH_2Cl_2	No Reaction
3	**131**	Et_3SiH, cat. Pd/C, 30 min	acetone	**134** (quantitative)
4	**79a** (*endo*)	Raney Ni, r.t, 4 days	EtOH	No Reaction
5	**79a** (*endo*)	Raney Ni, heat, 24h	EtOH	**135** (quantitative)
6	**130a** (*endo*)	Et_3SiH, cat. Pd/C, 3-4 days	CH_2Cl_2	**136a** *endo* (82%)
7	**130b** (*exo*)	Et_3SiH, cat. Pd/C, 3 days	CH_2Cl_2	**136b** *exo* (75%)
8	**130b** (*exo*)	10 eq. Et_3SiH, cat. Pd/C, 7 days	CH_2Cl_2	**137** (quantitative)
9	**130a-b** (*endo*+*exo*)	Et_3SiH, cat. Pd/C, 3 days	acetone	**136** *endo* + *exo* (83%)
10	**130a** (*endo*)	$NaBH_4$, r.t., 5h	EtOH	**140** (quantitative)
11	**136a** (*endo*)	$NaBH_4$, r.t., 15 min	EtOH	**140** (quantitative)
12	**80a** (*endo*)	Et_3SiH, cat. Pd/C, 4-5 days	acetone or CH_2Cl_2	**80a** (major) + **138** (minor) (≈3:1 ratio)
13	**80a** (*endo*)	Et_3SiH, cat. Pd/C, 1 day	1:1 THF-CH_2Cl_2	**138** (unavailable yield)
14	**80a** (*endo*)	Raney-Ni, r.t., 15 min	*i*-PrOH	Unidentified Products
15	**80a** (*endo*)	DIBAL-H, 0°C, 4h	THF	**139** (quantitative)
16	**132**	$NaBH_4$, r.t., 2h	EtOH	Complex Mixture

Some other well known methods for desulfurization also had to be investigated. For instance, several attempts were made to desulfurize thiol ester **79a** with Raney-Ni (W-2 grade). However, using standard conditions[74a] in ethanol, no reaction was observed

at room temperature over several days (entry 4). Upon heating at reflux for 24h, **79a** was quantitatively converted to **135** (entry 5), an unexpected product possibly arising from radical-induced deformylation and elimination steps. The combination of Raney-Ni in isopropanol (a hydrogen atom donor which is known to activate Raney-Ni)[76] was tried with the pentacyclic thiol ester **80a**, but at room temperature this reagent system rapidly and exothermically produced a mixture of products, none of which resembled an aldehyde or an alcohol (entry 14). Consequently, it was concluded that Raney-Ni was too harsh and nonselective for controlled desulfurization of **80**. Liu and co-workers had successfully demonstrated the use of sodium borohydride for the chemoselective reduction of glycidic and other functionalized thiol esters.[74b] Consequently, thiol ester **130a** was treated with a stoichiometric quantity of $NaBH_4$ in ethanol at room temperature, and after several hours, produced a single non-crystallizable desulfurized product which was not an aldehyde (entry 10). Reduction of the corresponding aldehyde **136a** with $NaBH_4$ also gave the same product in a much shorter reaction time (entry 11). Inspection of the ^{1}H-NMR spectra at various temperatures (218 K, 273 K, and 323 K) suggested the possibility that this product was participating in a rapid dynamic equilibrium. The reduction product was proposed to have the structure **140** (see Figure 2.6) which would have formed from transannular ketalization of the tetralone carbonyl group by the hydroxymethyl group at C_{10b}. Evidence in support of this structure was obtained from the low-temperature JMOD-^{13}C spectrum (50 MHz, 218 K) which exhibited two signals at 98.5 ppm and 109.2 ppm corresponding to the quaternary ketal carbons C_{5a} and C_6, and two signals at 72.5 ppm and 72.9 ppm for the methyleneoxy (CH_2O-) carbons, and was also lacking the signal for the tetralone carbonyl in the vicinity of 195 ppm (Figure 2.7 a). In addition, some interesting features of the low-temperature

(218 K) one-dimensional ^1H and two-dimensional ^1H, ^1H-TOCSY spectra at 500 MHz (Figures 2.7 b,c) were the sharp OH-singlet at 4.84 ppm, as well as an upfield doublet of doublets at 1.73 ppm (with coupling constants of 8.4 and 10.8 Hz) assigned as H-4α, which was correlated to both a multiplet at 3.85 ppm assigned as H-3a and a multiplet at 3.87 ppm corresponding to H-4β (determined from the TOCSY spectrum, Figure 2.7c). Examination of molecular models revealed that this structure was extremely bent (analogous to compound **147**, which will be discussed shortly) such that the H-4α proton was situated directly beneath the aromatic ring thereby shielding its signal to 1.73 ppm. The geminal coupling constant of 8.4 Hz measured for H-4α is consistent with those measured in the tetrahydrofuran rings of the starting materials **130a** and **136a**. Although this reduction product **140** was a masked alcohol, it was not used in any further transformations for synthesizing viridin when a reasonable quantity of the pentacyclic thiol esters **80** and **132** became available for reduction trials. In an attempt to prevent ketalization of the tetralone carbonyl group, the demethoxylated pentacyclic thiol ester **132** was selected for a trial reduction since it was considerably flatter than its methoxylated analogues **80a-b**. However treatment of **132** with $NaBH_4$ in ethanol at room temperature (entry 16) produced a complex mixture of products which not surprisingly included a mixture of diastereomeric C_9-benzylic alcohols. In a final attempt, the bulky reducing agent diisobutylaluminum hydride (DIBAL-H) was used on the pentacyclic thiol ester **80a**. Unfortunately, the benzylic alcohol **139** was formed in quantitative yield.

Figure 2.7 (a): Low-temperature (218 K) JMOD-^{13}C NMR spectrum (50 MHz) of compound **140**.



140

Figure 2.7 (b): Low-temperature (218 K) ^{1}H NMR spectrum (500 MHz) of compound **140**.

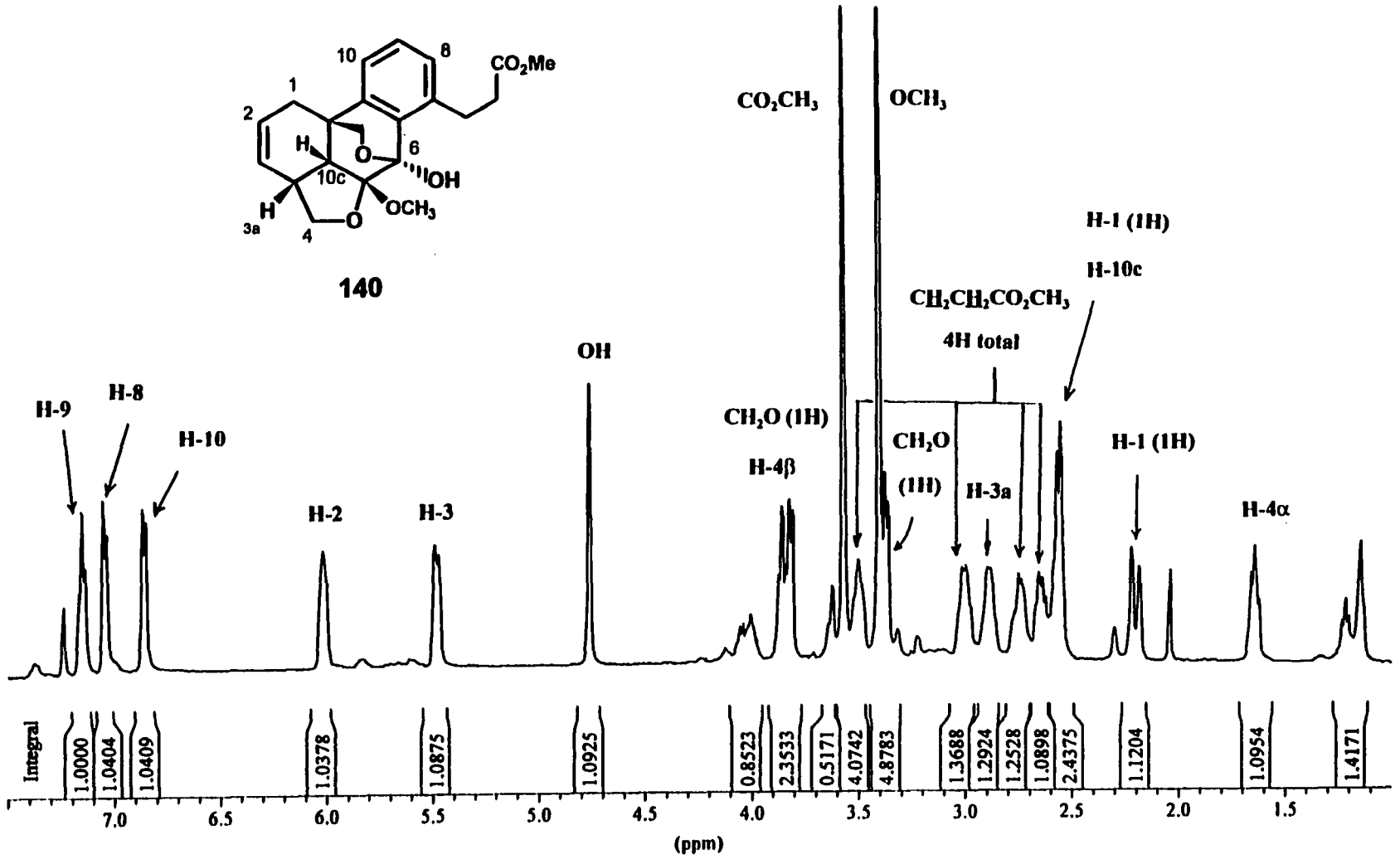
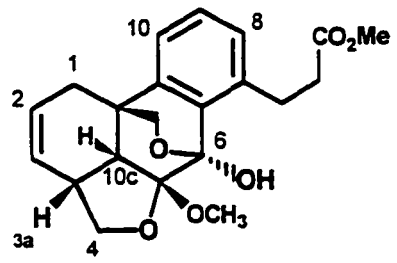
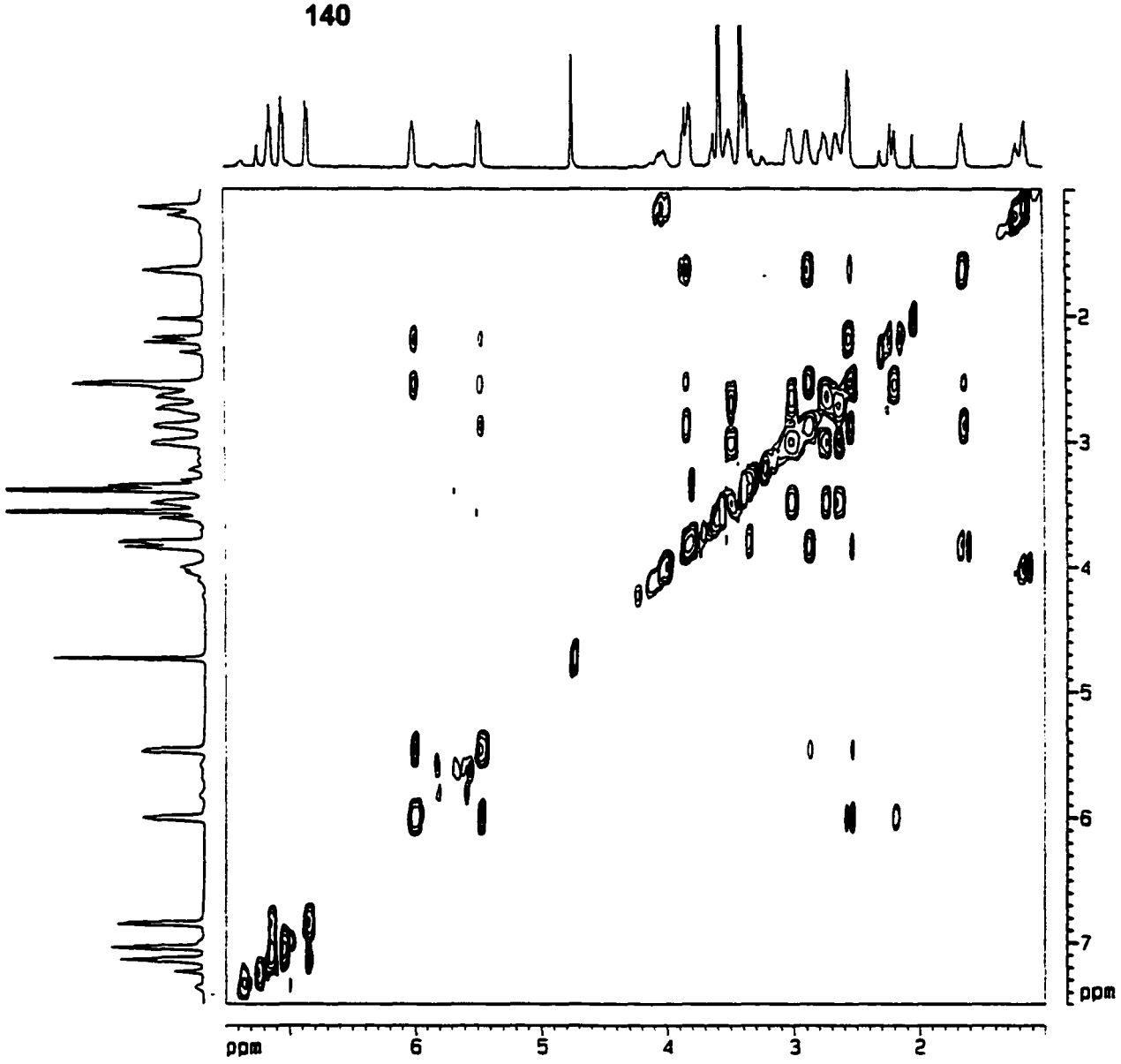


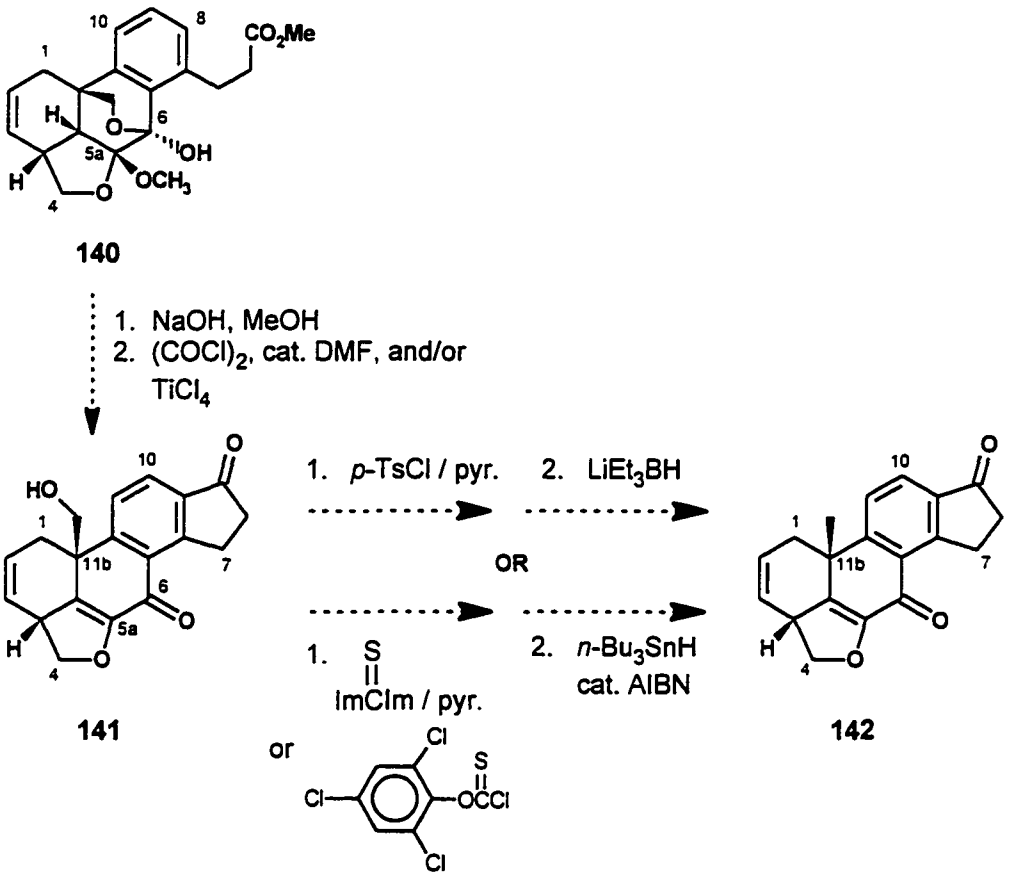
Figure 2.7 (c): ^{1}H, ^{1}H TOCSY spectrum (218 K, 500 MHz, $CDCl_3$, 20 ms mixing time) of compound **140**.



140



Scheme 2.26

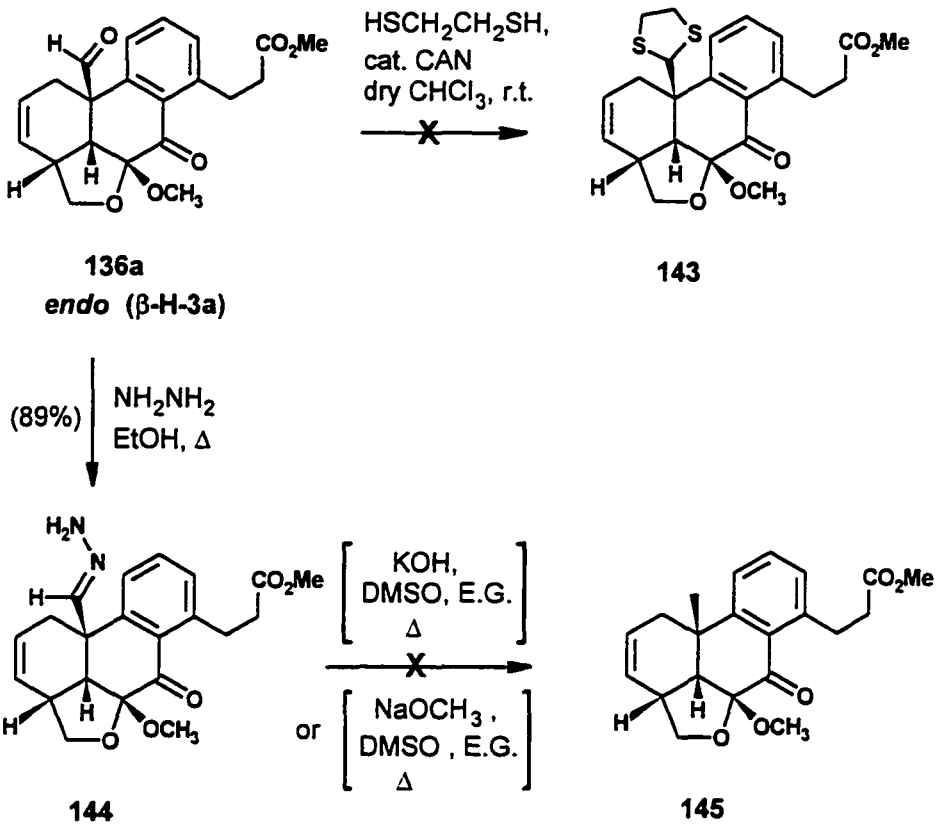


The results of trials with these well-known desulfurizing reagents were disappointing. It seemed that the advanced pentacyclic thiol esters **80** and **132** were too highly functionalized and unsuitable for reduction by hydride reducing agents. Although unpredictable at times, the reduction of thiol esters **130a-b** and **80a** using Fukuyama's method with triethylsilane and palladium-on-carbon were at times successful, and along with the noted chemoselectivity and simplicity of this method, it seemed that this reaction had potential once appropriate conditions were developed. Another possible route to viridin evolved from the unexpected reduction product **140**, and is represented in Scheme

2.26. In this hypothetical plan, the pendant side-chain could be hydrolyzed and then cyclized by Friedel-Crafts reaction (*via* the acid chloride or intermediate lactone) to furnish the pentacycle **141**. The cyclic hemi-ketal at C_6 could subsequently be opened with a suitable base, thereby unmasking the primary alcohol at C_{11b} for deoxygenation to a methyl group. Possible methods for deoxygenation may include conversion to the tosylate and S_N2-displacement by a hydride reducing agent (e.g. lithium triethylborohydride, $NaBH_4$),[77] or, conversion to a radicophilic moiety such as a 2,4,6-trichlorophenoxy-thionate[78] or a thioimidazole ester,[79] followed by treatment with tri-*n*-butylstannane to produce **142** possessing a C_{11b}-methyl group. These potential synthetic routes from **140** are currently being developed.

Despite the fact that a significant quantity of pentacyclic aldehyde **138** was not available, several ideas for converting the aldehydes **133** and **136a** to their C_{10b}-methyl analogues were investigated. One general method was the reduction of an aldehyde or its tosylhydrazone with metal (Na, Zn) cyanoborohydrides,[80] or with bulky organoboranes.[81] However, in trials which were performed within our laboratory in other related work, the model aldehyde **133** gave a reduction product which was structurally analogous to **140**.[66] There was also the concern that these highly functionalized vinylogous aldehydes were susceptible toward rearrangements in acidic media, when attempting to derivatize them. Consequently, a method for the selective thioacetalization of **136a** to the dithiane **143** using neutral conditions catalyzed by ceric ammonium nitrate (CAN) was attempted.[82] The plan called for the desulfurization of dithiane **143** using Raney-Ni or other methods[74] (Scheme 2.27). Unfortunately, no evidence of **143** was observed even after one week of reaction time.

Scheme 2.27

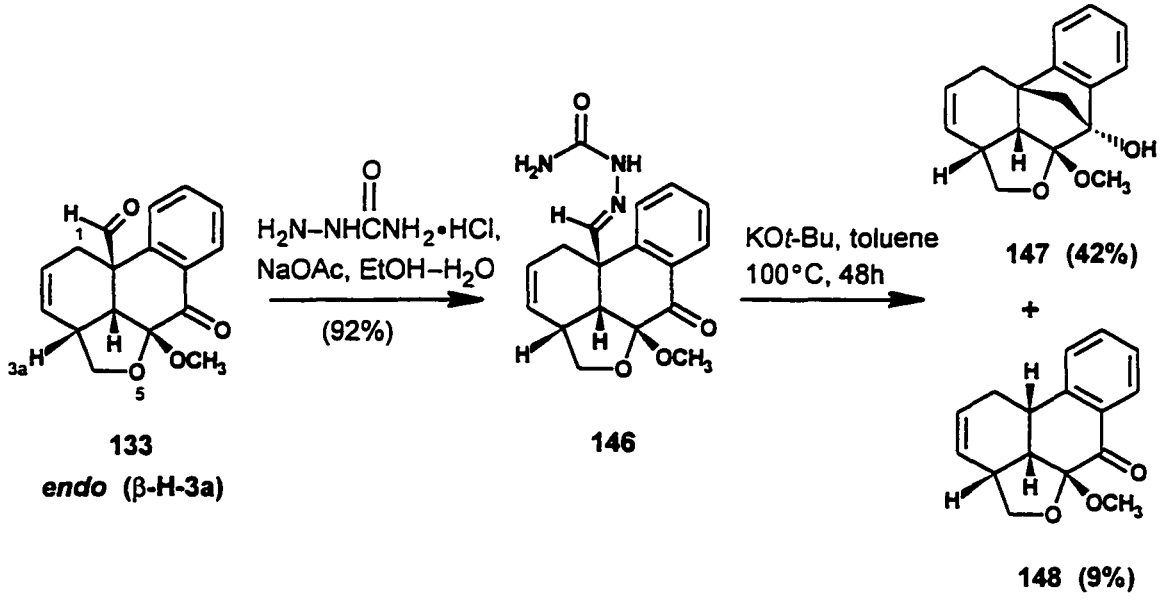


The next plan involved a modified Huang-Minlon Wolff-Kishner reduction[83] of aldehyde **136a** (Scheme 2.27) by the intermediate formation of the hydrazone **144** (89% yield) which was then heated to reflux in DMSO and ethylene glycol (E.G.) in the presence of excess potassium hydroxide.[84] Rather than the anticipated product **145**, a mixture of unidentifiable decomposition products resembling carboxylic acids resulted, probably from saponification of the side-chain ester group by KOH. To avoid such competing reactions, another reduction attempt was made with sodium methoxide as the base. The reduction was also unsuccessful, however, due to hydrolysis of the hydrazone

which returned the aldehyde precursor with a propanoic acid side-chain (not the methyl ester), as was interpreted by ^{1}H-NMR analysis.

Since it was apparent that a stable derivative of the aldehyde was required, our attention was diverted toward preparing a semicarbazone, which could be reduced to an alkane using the Henbest version of the Wolff-Kishner reduction.[85] The model aldehyde **133** was the test subject for this trial, and after treatment with semicarbazide hydrochloride and sodium acetate in a 1:1 mixture of ethanol-water (Scheme 2.28), the semicarbazone **146** was furnished in excellent yield (92%). Compound **146** was then mixed with freshly resublimed dry potassium *tert*-butoxide in anhydrous toluene, and heated at reflux for 48 h. Two distinct products were formed which were characterized as the methylene-bridged compound **147** (42%) and the deformylated product **148** (9%).

Scheme 2.28



133
***endo* (β-H-3a)**

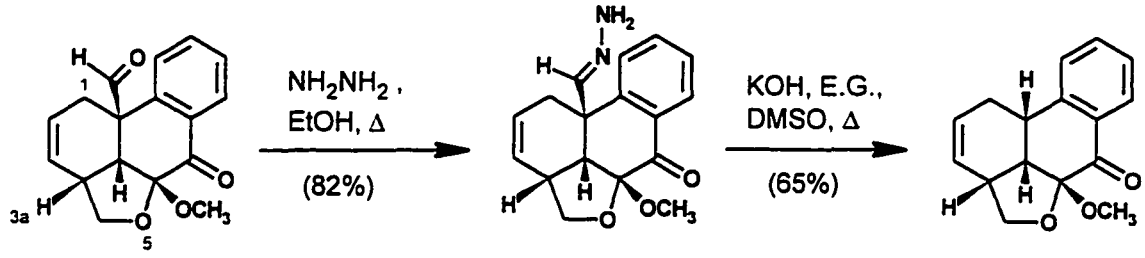
146

147 (42%)

+

148 (9%)

Scheme 2.29 [66]



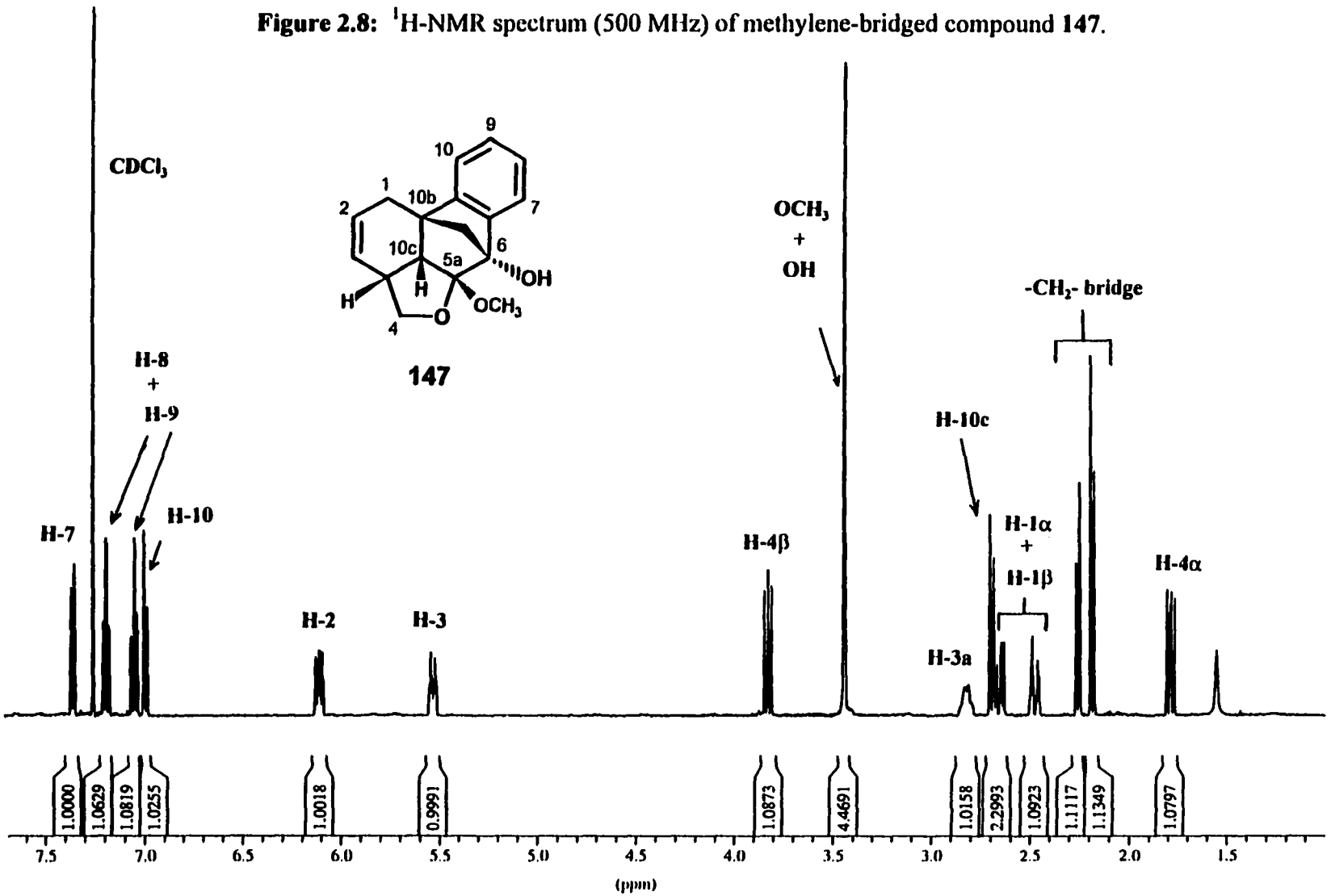
133
***endo* (β-H-3a)**

149

148

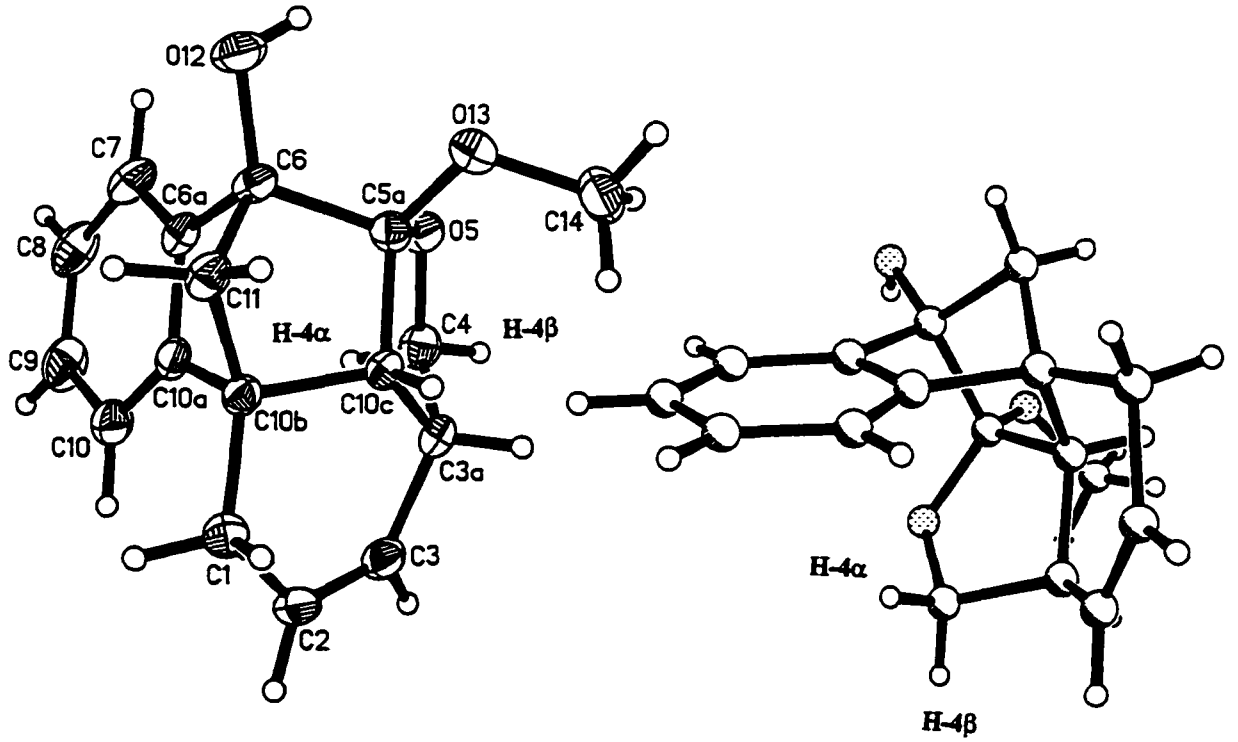
The formation of **148** was not unexpected since this same product had also been produced in other work performed earlier in our laboratory from the Wolff-Kishner reduction of hydrazone **149** (Scheme 2.29).[66] The bridged compound **147** was the major product and some clues for the elucidation of its structure were provided from its unusual ^{1}H-NMR spectrum (Figure 2.8), which was similar to that obtained for compound **140**. Decoupling experiments had revealed that the chemical shifts for the diastereotopic H-4 protons were uncharacteristically separated by 2 ppm. In addition, two doublets at 2.18 ppm and 2.25 ppm, each coupled by 8.1 Hz,[86] were attributed to the geminal diastereotopic protons of the bridging methylene group. Examination of the structure of **147** using molecular models showed that the H-4α proton was situated directly beneath the aromatic ring, which was confirmed by the X-ray crystal structure (Figure 2.9), and the degree of shielding experienced by this proton had justified the existence of the upfield multiplet at 1.8 ppm. Although compound **147** was not the product hoped for in carrying out the modified Wolff-Kishner reduction, it was considered a success since an alkyl group had formed from the transformation. It was speculated that perhaps the reaction conditions were too "dry" causing the intermediate methylene anion to quench itself by nucleophilic

Figure 2.8: ^{1}H-NMR spectrum (500 MHz) of methylene-bridged compound **147**.



addition to the tetralone carbonyl group. Also, the concave geometry of the semicarbazone **146** could have allowed the nucleophilic attack by this anion. In a future attempt of this reaction, a proton source such as *tert*-butanol would be added in order to favor formation of the desired angular methyl group. Unfortunately, a sufficient quantity of any model aldehyde was not within easy reach, due to the multistep sequence in preparing these thiol esters as well as the unpredictable temperament of the Pd-catalyzed desulfurization reaction with triethylsilane. Consequently, it is our hope that when a sufficient quantity of pentacyclic aldehyde **138** is available, the application of the Henbest-modified Wolff-Kishner reduction on its corresponding semicarbazone would at last furnish the structural framework of viridin, complete with the angular C_{11b}-methyl group. Efforts toward this end are still in progress.

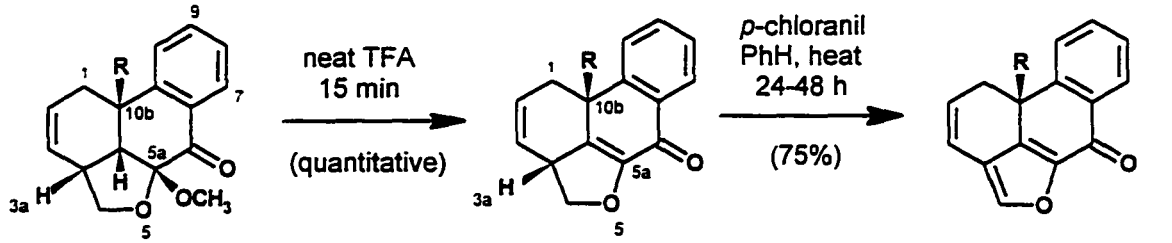
Figure 2.9: Molecular plot of the X-ray crystal structure of compound **147**.



2.2.5 *Studies of Other Ring Transformations*

During the course of investigating conditions for reductive desulfurization of the various thiol ester compounds described earlier, some chemical transformations in the furanoid ring E were studied. The first transformation considered in these compounds was the acid-catalyzed elimination of methanol in order to convert the ketal moiety at C_{5a} to an enol ether. The *endo*-isomers of the model thiol ester **79a** and of methyl ester **78a** were tested first since they were available. Both had reacted smoothly and quickly with neat TFA to provide the demethoxylated analogues **131** and **150** in quantitative yield (Scheme 2.30). Dehydrogenation of the dihydrofuran ring in **131** was accomplished next using *p*-chloranil, as it was a milder oxidant than DDQ and caused less side-reactions. After heating at reflux in benzene for 24-48 h, the furanoid product **151** was isolated in 75% yield.

Scheme 2.30



78a (R = CO_2CH_3)
79a (R = $COSCH_3$)

150 (R = CO_2CH_3)
131 (R = $COSCH_3$)

151 (R = $COSCH_3$)

The pentacyclic *endo*-thiol ester **80a** was tested next and reacted analogously to the model thiol ester **79a**, rapidly producing the demethoxylated analogue **132** in quantitative yield (*cf.* Scheme 2.25). An interesting turn of events occurred when this

relatively uneventful elimination reaction was attempted on the pentacyclic *exo*-isomer **80b**. After stirring in neat TFA for up to 48 h, it was surprising that no reaction was observed. Treatment of **80b** with excess zinc chloride in refluxing toluene did not improve matters, having only decomposed the compound. A final attempt of the elimination reaction using a 1:1 mixture of *endo* and *exo* isomers of the model thiol ester **79** in neat TFA for several hours gave a mixture of the demethoxylated product **131** and unreacted *exo*-thiol ester **79b** in nearly equal proportions. This peculiar resistance of *exo*-isomers toward elimination of methanol from the ketal moiety was also observed in two other cases with the *exo*-methyl ester **78b** and the related compound **152b**,[87] which was prepared in our laboratory for model studies toward a proposed synthesis of morphine (Figures 2.10 a, b).[88] X-ray crystal structures were obtained for both the *endo* and *exo* isomers of **78**, **79**, **152**, and for the pentacyclic *exo*-isomer **80b**, and the pertinent bond lengths and angles around the ketal carbon were compared (Table 2.3). An explanation for the *endo*-selective reactivity that was observed may be provided by the findings of Kirby and co-workers in their studies with C_2-substituted tetrahydropyrans.[89a] They had uncovered the relationship between the ground-state endocyclic and exocyclic C-O bond lengths (and O-C-O angles) of 2-aryloxytetrahydropyrans and the rate of acid-catalyzed hydrolysis to the hemiacetal (*via* an oxocarbonium ion intermediate). For these cyclic acetals, when the exocyclic leaving group (OAr) was axial (i.e. antiperiplanar relationship between the exocylic C_2-OAr bond and a lone-pair on the ring oxygen), the endocyclic C-O bond was shortened and the cleavable exocyclic C_2-OAr bond was lengthened, the amount of variation being dependent on the electronegativity of the exocyclic oxygen atom.[89b-c] These trends in the bond lengths were also evident for the aforementioned compounds made in our laboratory. The projections along C_{3a}-O_4 for both isomers of

152a-b shown in Figure 2.10 clearly illustrate that only the *endo*-isomer displays the antiperiplanar relationship between a lone pair of non-bonded electrons on the O_4-oxygen atom and the cleavable OCH_3 group positioned on C_{3a}. In the *exo*-isomer, the cleavable OCH_3 bisects the lone pair orbitals of the O_4-oxygen atom. The same structural patterns can be seen in projections along the C_{5a}-O_5 bond of the *endo* and *exo* isomers of **79a-b** and also the pentacyclic *exo*-isomer **80b** (see Figures 2.11 a-c). Confirmation is found in a comparison of the bond lengths and angles for these compounds. The *endo*-isomers **78a** and **79a** have shorter endocyclic C_{5a}-O_5 bonds and longer exocyclic C_{5a}-OCH_3 bonds than those found in the *exo*-isomers **78b** and **79b**, consistent with the findings for the anomeric effect made by Kirby and coworkers.[90] (The standard bond length for an sp^3-hybridized C-O single bond in typical organic compounds is 1.426 Å.[91]) The same trends exist for the *endo* and *exo* isomers **152a-b**. In the case of the pentacyclic thiol esters **80a-b**, the X-ray crystal structure was only available for the *exo*-isomer **80b** (Figure 2.11 c). The bond lengths in **80b** are nearly identical with those of the *exo*-methyl ester **78b** and *exo*-thiol ester **79b**. Hence, the exclusive preference for the *endo*-isomer in the acid-catalyzed elimination of methanol can be considered a generalized anomeric affect, and is promoted by the antiperiplanar relationship between the exocyclic (cleavable) OCH_3 group and a non-bonded lone pair of electrons on the furan ring oxygen. This conclusion constituted a major and unexpected drawback in the synthetic plan, since the pentacyclic *exo*-adduct **80b** obtained from the IMDA reaction could not be transformed to viridin. The realization of this serious synthetic obstacle (amongst others) in the road to viridin prompted the contemplation of a new and strategically different plan toward this target. Since a convergent strategy was originally preferred for synthesizing viridin and related natural products, the re-examination of the IMDA reaction of substituted *o*-benzoquinone

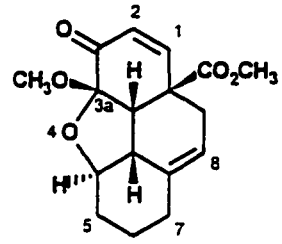
monoketals for preparing the C_{5a}-methylated naphthofuran tricycle **58** (*cf.* Scheme 1.9), or analogue thereof, was in order. The successes which were encountered in this endeavor will be discussed in detail in chapter 3.

Table 2.3: Bond lengths and bond angles for the structurally related *endo* and *exo* isomers of **78**, **79**, **152**, and **80b** (*exo*-isomer).

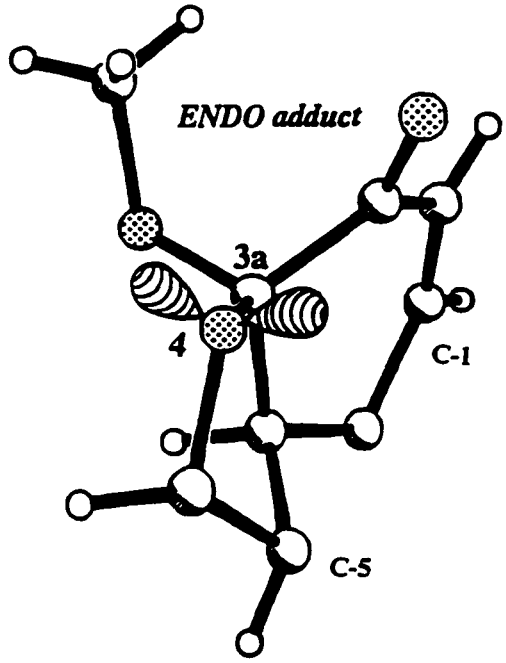
Compound	Bond Length (Å)		Bond Angle
	endocyclic	exocyclic	(deg)
78a (*endo*)	1.400 (C_{5a}–O_5)	1.425 (C_{5a}–OCH_3)	112.3 (O_5–C_{5a}–OCH_3)
78b (*exo*)	1.432 (C_{5a}–O_5)	1.400 (C_{5a}–OCH_3)	111.7 (O_5–C_{5a}–OCH_3)
79a (*endo*)	1.393 (C_{5a}–O_5)	1.434 (C_{5a}–OCH_3)	112.1 (O_5–C_{5a}–OCH_3)
79b (*exo*)	1.440 (C_{5a}–O_5)	1.394 (C_{5a}–OCH_3)	110.8 (O_5–C_{5a}–OCH_3)
80b (*exo*)	1.435 (C_{5a}–O_5)	1.400 (C_{5a}–OCH_3)	109.9 (O_5–C_{5a}–OCH_3)
152a (*endo*)	1.407 (C_{3a}–O_4)	1.416 (C_{3a}–OCH_3)	111.6 (O_4–C_{3a}–OCH_3)
152b (*exo*)	1.422 (C_{3a}–O_4)	1.401 (C_{3a}–OCH_3)	109.1 (O_4–C_{3a}–OCH_3)

Figure 2.10: Model compounds [87] **152a-b** and X-ray crystal structure projections along the C_{3a}-O_4 bond.[88]

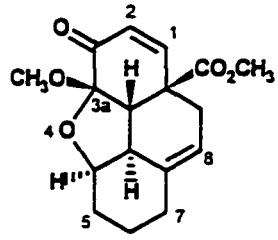
(a)



152 a
(endo)



(b)



152 b
(exo)

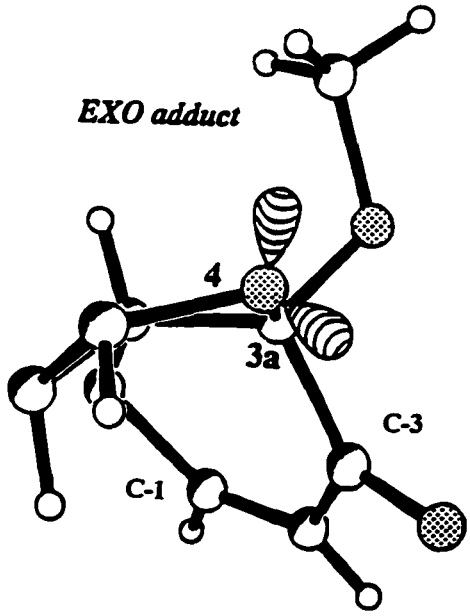
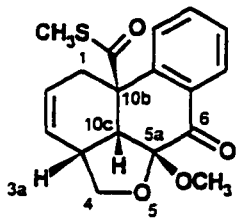


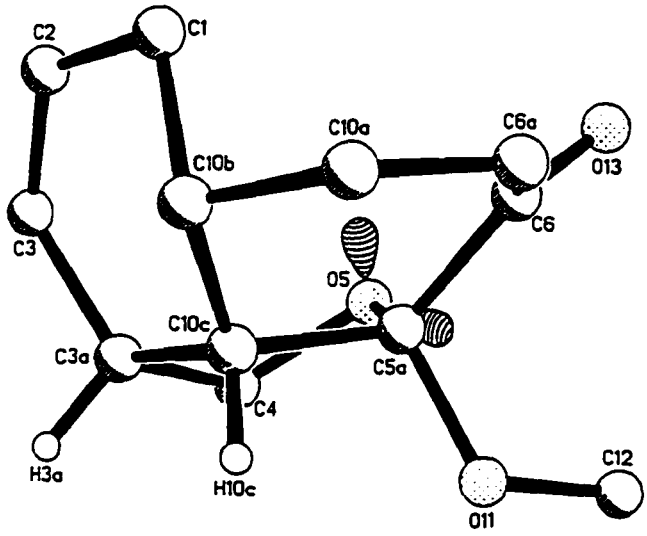
Figure 2.11: X-ray crystal structure projections along the C_{5a}–O_5 bond for model thiol esters (a) **79a** (*endo*), (b) **79b** (*exo*), and (c) pentacycle **80b** (*exo*).

(a)

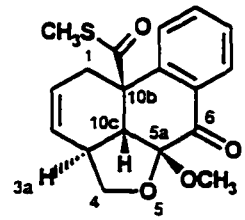


79a

endo **(β-H-3a)**



(b)



79b

exo **(α-H-3a)**

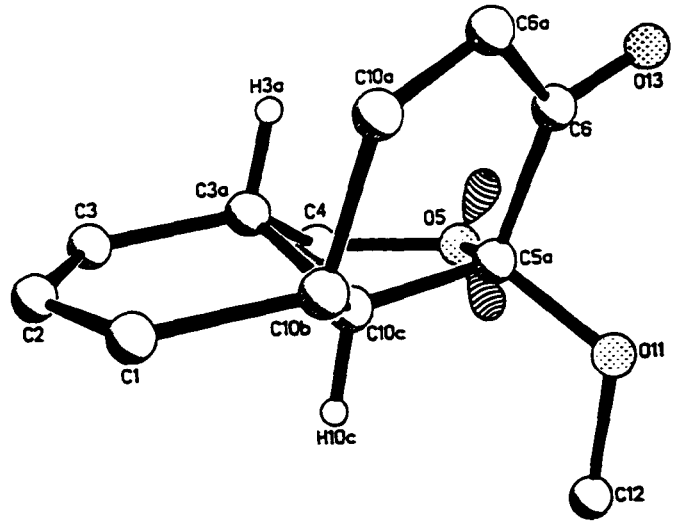
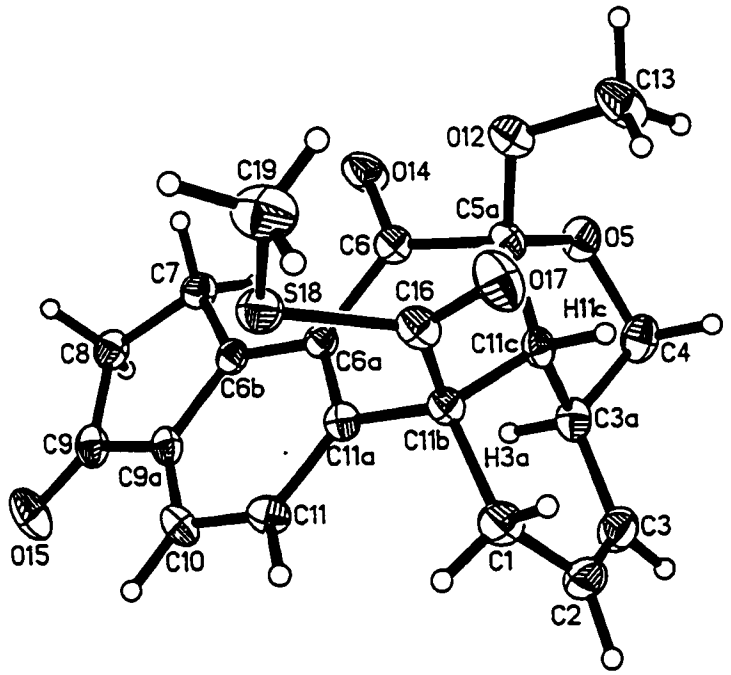
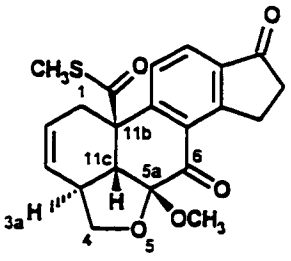


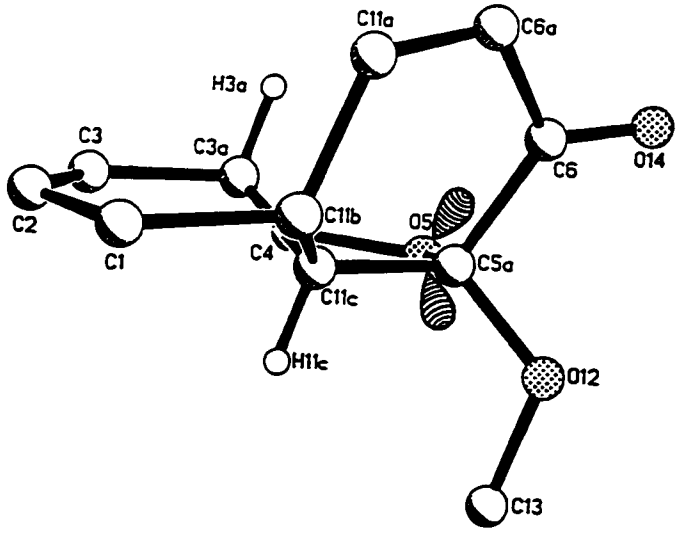
Figure 2.11 (c): X-ray crystal structure and projection along the C_{5a}–O_5 bond for pentacyclic thiol ester **80b** (*exo*).





80b

exo (α-H-3a)



2.3 The *de novo* Synthesis of 1,2-Dihydoxy-5,8-dihydronaphthalenes, Phenanthrenes, and Phenanthro[10,1-*bc*]furans: Rearrangements of the Diels-Alder Adducts of *ortho*-Benzoquinone Dienophiles and Further Transformations

The synthetic utility of *o*-benzoquinones substituted with an electron-withdrawing group (CO_2Me and CO_2H) at C_3 as dienophiles in cycloaddition reactions was highlighted earlier (*cf.* Schemes 2.7 and 2.10) in our efforts to synthesize the natural product viridin (**1**). The high yields and exclusive formation of the adducts **101** and **103** obtained in these Diels-Alder reactions were impressive (Scheme 2.31, Path I), and the notion that the positioning of the electron-withdrawing group on the *o*-quinone had influenced the regiochemical orientation of the diene was inferred. To further test this theory, methyl 3,4-dihydroxybenzoate **153** was subjected to the oxidation-Diels-Alder reaction sequence with the same diene, methyl (*E*)-4,6-heptadienoate (Scheme 2.31, Path II). The diosphenol adduct **156** was the only product formed in moderate yield (60%) due to quinone decomposition. The ^{1}H-NMR spectrum of this *endo*-product was similar to that of **102** (see Figure 2.12) and decoupling experiments showed that irradiation of the signal for the methine proton at H-5 caused an NOE enhancement of the signal corresponding to H-4. X-ray crystallographic analysis also confirmed the regiochemistry and the *endo*-stereochemistry of **156**.

Scheme 2.31 [60]

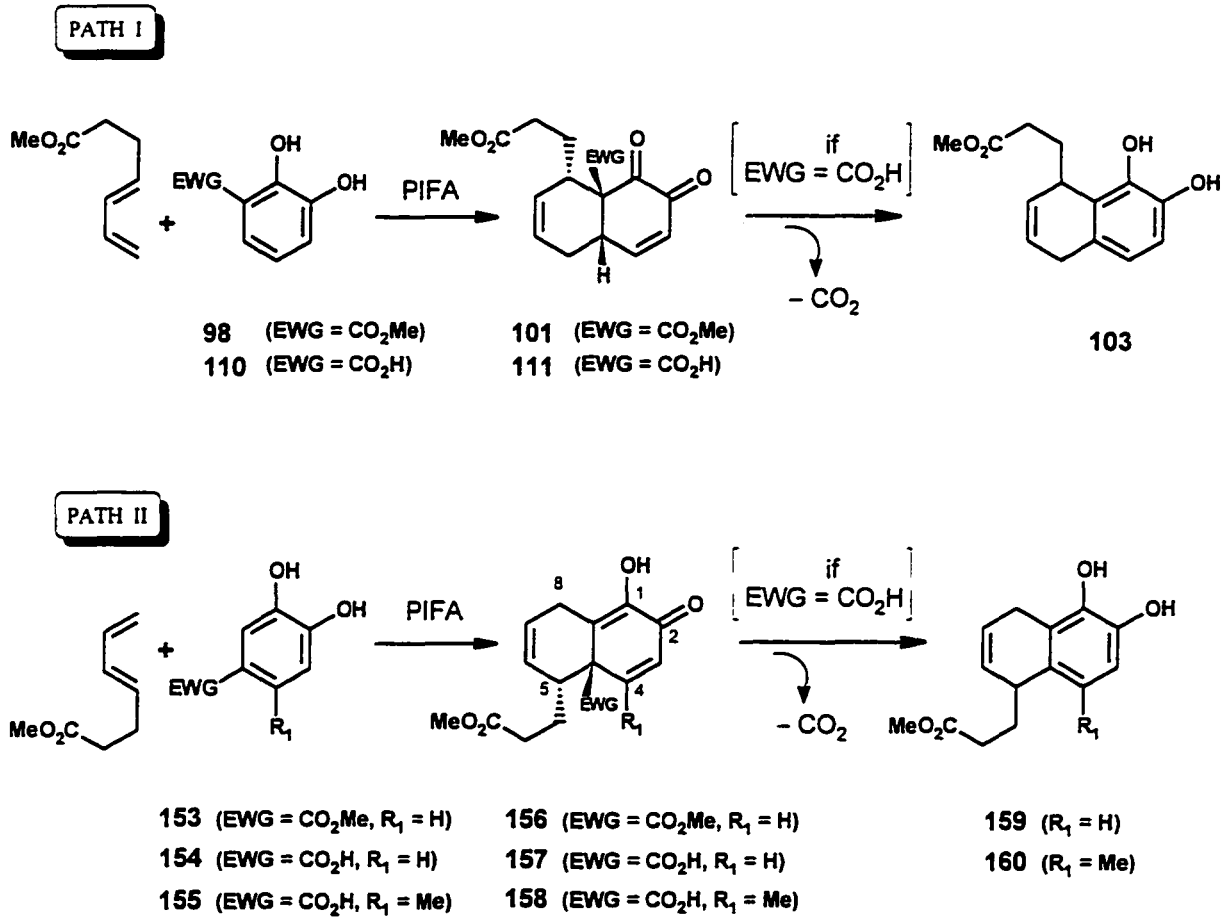
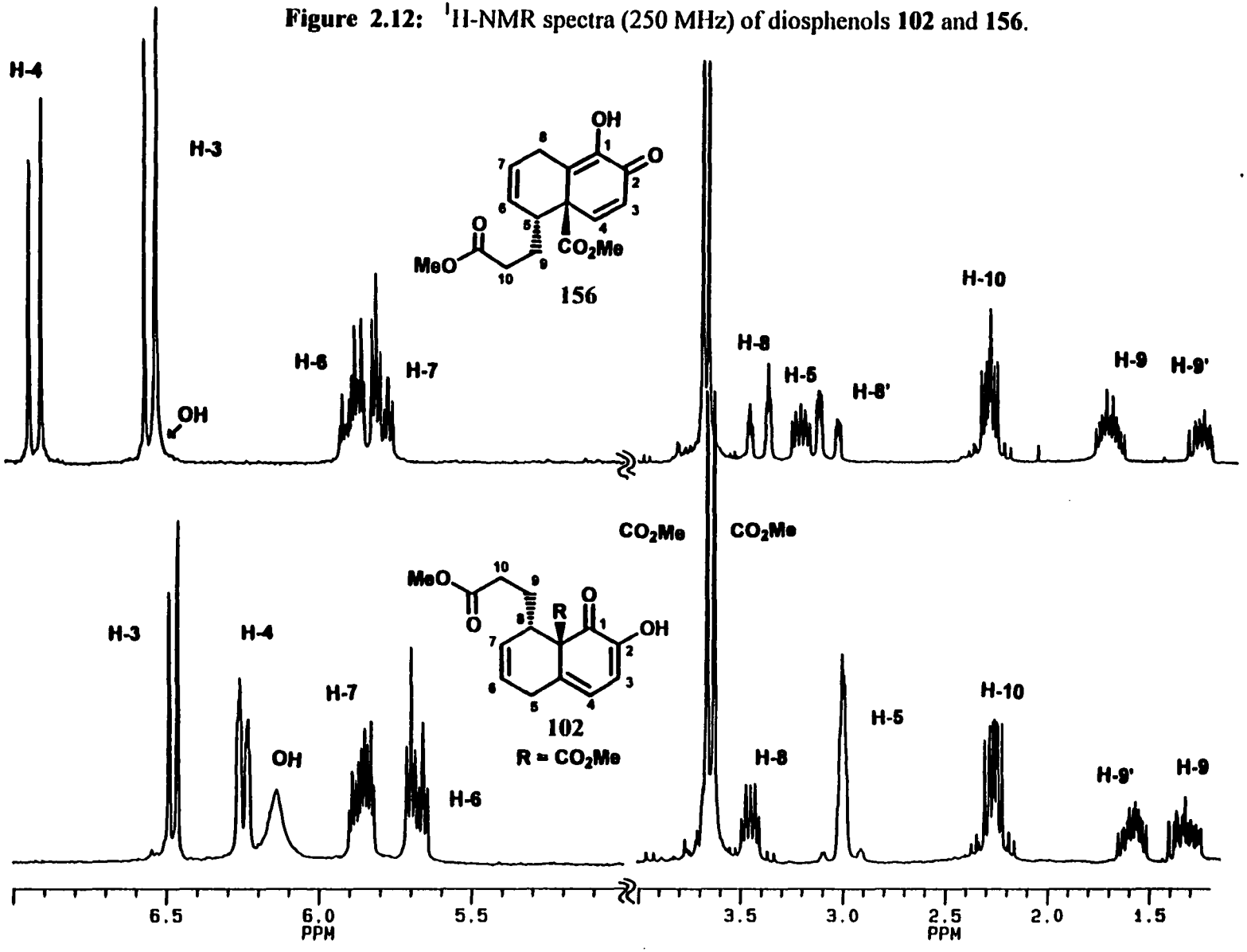


Table 2.4: Results of the intermolecular Diels-Alder reactions of substituted *o*-benzoquinones generated from catechols **98**, **110**, and **153-155** with methyl (*E*)-4,6-heptadienoate (Scheme 2.31).[60]

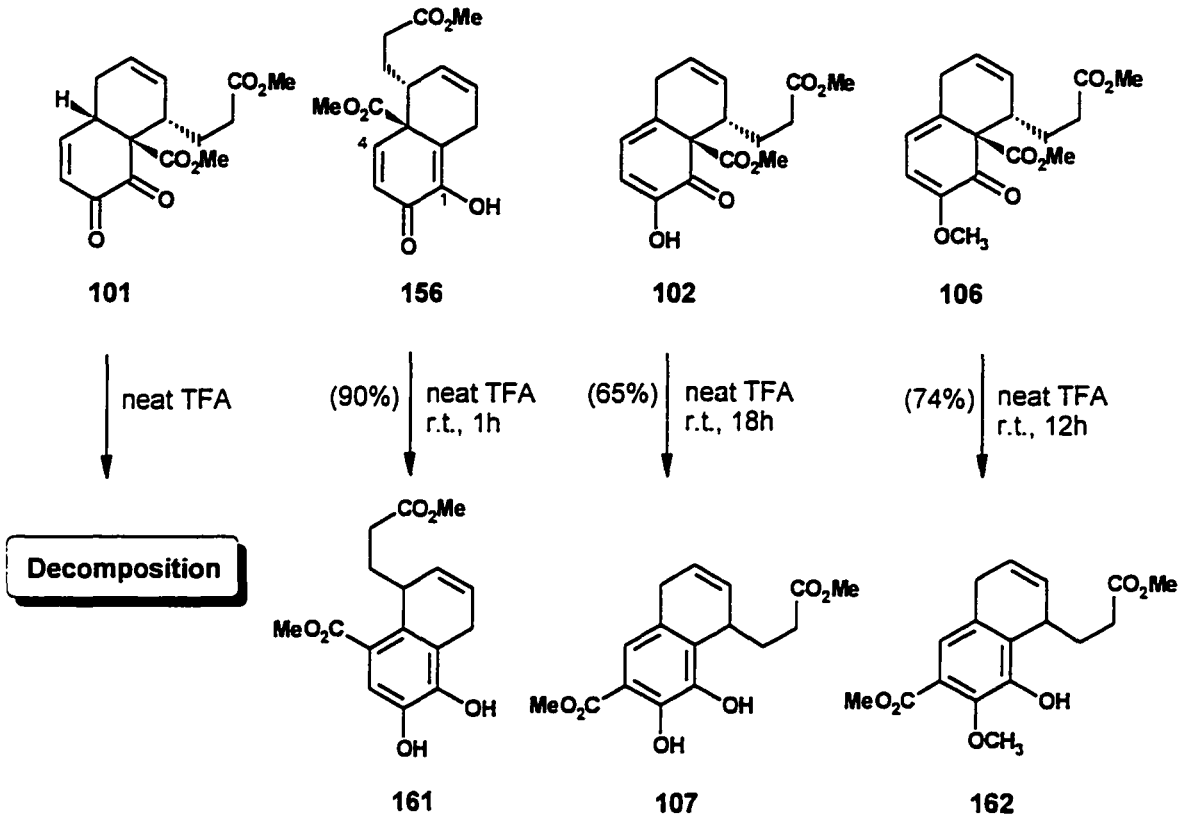
Entry	Reactant	Product	%-Yield
1	**98**	**101**	96%
2	**153**	**156**	60%
3	**110**	**103**	78%
4	**154**	**159**	22%
5	**155**	**160**	27%

Figure 2.12: ^{1}H-NMR spectra (250 MHz) of diosphenols **102** and **156**.



The impressive degree of regiocontrol witnessed in these reactions indicated a need for a systematic survey of intermolecular Diels-Alder reactions of other substituted *o*-benzoquinones and dienes. Some combinations of the cycloadditions between five unsymmetrical dienes and nine substituted *o*-benzoquinones, generated *in situ* from the corresponding catechols, were studied.[60] The reactions represented in Scheme 2.31 used methyl (*E*)-4,6-heptadienoate as the diene in the cycloadditions with the substituted *o*-quinones generated *in situ* by oxidation of the catechols **98**, **110**, and **153-155** with PIFA. In all cases, the position of the electron-withdrawing substituent (EWG) influenced the site of cycloaddition on the *o*-quinone ring, as illustrated in pathways I and II, and only *endo* 'ortho' adducts (with respect to EWG) were isolated. The ester substituent at either C_3 or C_4 of the *o*-quinone therefore directed the regiochemical orientation of the diene, as shown in the reactions with the *o*-quinones derived from catechols **98** and **153**. The products **102** (by enolization of **101** with base) and **156** are opposite regioisomers. The yields of these reactions were generally good (see Table 2.4) except for the catechols which reacted *via* pathway II, where some products were formed in poor to moderate yields (entries 4-5), possibly due to unstable *o*-quinonoid species. It was especially remarkable how the catechol carboxylic acids **110, 154** and **155** survived the oxidation conditions with PIFA without undergoing decarboxylation. Furthermore, the unisolable adducts **111, 157,** and **158** generated from these *o*-quinone carboxylic acids, which were either β- or γ-keto acids, presumably decarboxylated in the reaction medium to produce the 1,2-dihydroxy-5,8-dihydronaphthalene adducts **103, 159**, and **160**. Thus, a *de novo* synthesis of functionalized 1,2-dihydroxynaphthalenes by a one-pot process from simple starting materials was uncovered in this work.

Scheme 2.32



Effective regiocontrol was accomplished in these Diels-Alder reactions of *o*-quinone dienophiles with unsymmetrical dienes, with respect to both the site of cycloaddition on the *o*-quinonoid ring and the regiochemical orientation of the diene. However for some of the reactions performed in this study involving *o*-benzoquinones substituted with a formyl group (CHO) or a thiol ester group ($COSCH_3$), a mixture of products resulted due to rearrangements of the Diels-Alder adducts in the presence of TFA (the oxidation by-product).[92] The adducts formed *via* path II in Scheme 2.31 were functionalized 2,5-cyclohexadienones, which may be viewed as masked aromatic

compounds. Depending on the migratory aptitude of the electron-withdrawing group (EWG),[93] these adducts were predisposed to undergo facile dienone-phenol rearrangements in acidic media.[93c, 94] As a consequence of these observations, the non-aromatic Diels-Alder adducts **101** and **156**, as well as the analogues **102** and **106** which were prepared from **101** by enolization and O-methylation, were investigated for their abilities to undergo acid-catalyzed rearrangements. After treatment with neat TFA at room temperature, most of these aforementioned adducts underwent rearrangement to the phenol esters **107**, **161** and **162**, except for the α-diketone **101** which decomposed in strongly acidic media (Scheme 2.32 and Table 2.5).

Table 2.5: Rearrangements of **102**, **106** and **156** with the electrophilic reagents TFA, Me_3OBF_4, and Et_3OBF_4.

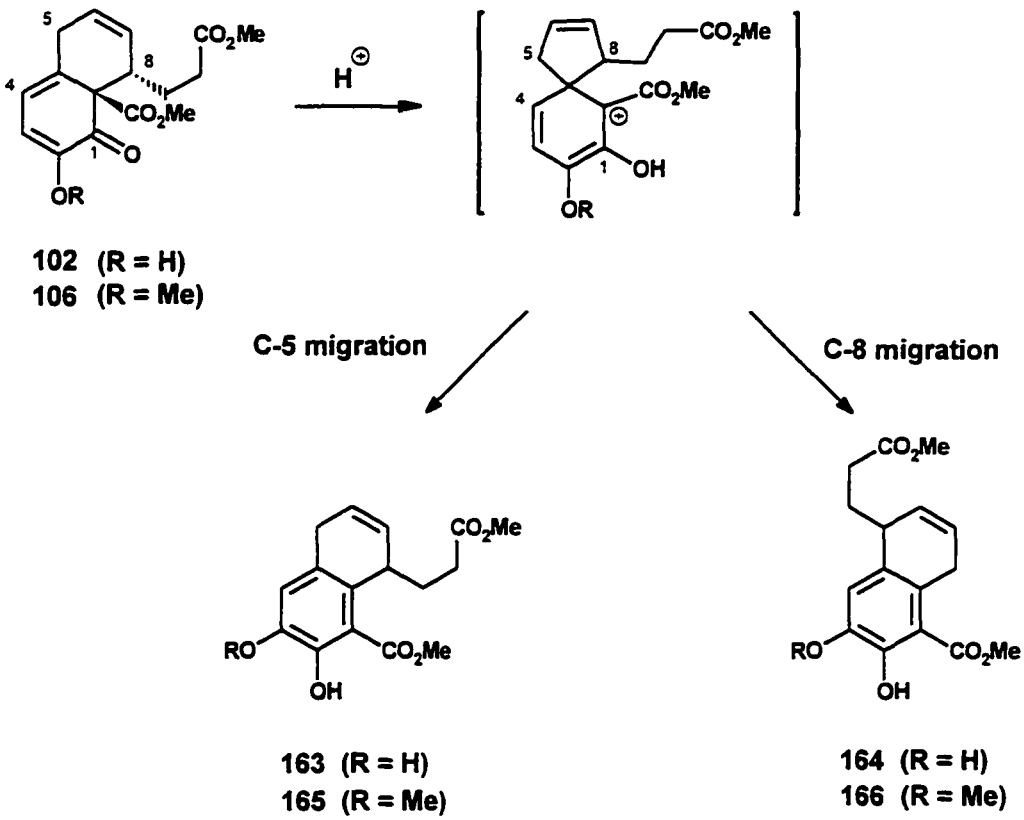
Entry	Substrate	Electrophile (E^+)	Reaction Time	Product (%-yield)
1	**102**	TFA (H^+)	18 h	**107** (65%)
2	**106**	TFA (H^+)	12 h	**162** (74%)
3	**102**	Me_3OBF_4 (Me^+)	24 h	**107** (60%)
4	**106**	Me_3OBF_4 (Me^+)	48 h	**162** (60%)
5	**102**	Et_3OBF_4 (Et^+)	10 h	**107** (59%)
6	**106**	Et_3OBF_4 (Et^+)	18 h	**162** (62%)
7	**156**	TFA (H^+)	0.5 h	**161** (90%)
8	**156**	Et_3OBF_4 (Et^+)	0.5 h	**161** (95%)

Although the reaction yields were only moderate, the migration of angular ester groups are uncommon, and in each case no other rearrangement products were isolated. The C_{4a}-ester group of the diosphenol adduct **156** (a 2,5-cyclohexadienone analogue)

underwent a rapid [1,2]-shift (dienone-phenol rearrangement)[95] to the C_4-position in the presence of TFA as well as Et_3OBF_4, and generated the aromatic product **161** in excellent yields (90% and 95% respectively; Table 2.5, entries 7-8). The familiar diosphenol **102** (a 2,4-cyclohexadienone analogue) also underwent rearrangement in TFA, albeit more sluggishly, and produced an aromatic ester **107** in moderate yield (65%) (Table 2.5, entry 1). The same product was also obtained in similar yield by treatment of **102** with Me_3OBF_4 at room temperature (entry 3), a surprising result observed in the early stages of our synthetic work toward viridin (*cf.* Table 2.1, entry 5, Section 2.2.1). The structure of the aromatic product **107** was not deduced immediately, since two other constitutional isomers **163** and **164** were proposed which could have formed *via* a spiro intermediate[94b, 96] (Scheme 2.33). If this rearrangement mechanism had operated, then the [1,2]-shift of either C_5 or C_8 would occur with roughly equal probability and result in a product mixture of **163** and **164**.[96a] The ^{1}H-NMR spectrum of the lone product obtained from rearrangement of **102** contained one aromatic proton (7.2 ppm), one hydrogen-bonded phenolic proton (10.6 ppm) and another phenolic proton (5.8 ppm), and the data could fit all three proposed structural isomers **107**, **163** and **164**. Since only one product was isolated from the reaction however, the latter two structures formed *via* the spiro intermediate were eliminated from consideration. Proof of the structure **107** as the product of rearrangement came from analysis of 2D-NMR correlated spectra (TOCSY, HMBC), the NOEDS spectrum and ultimately from the X-ray crystal structure.[92] Additional support was offered from the rearrangement of the O-methylated diosphenol **106** with TFA, which produced a single aromatic ester in 74% yield (Table 2.5, entry 2). The ^{1}H-NMR and ^{13}C-NMR spectral evidence for this product supported the structure

162 over structures **165** and **166,** due to the presence of a methoxyl group at C_2 and no hydrogen-bonded phenolic proton signals.

Scheme 2.33 [92]



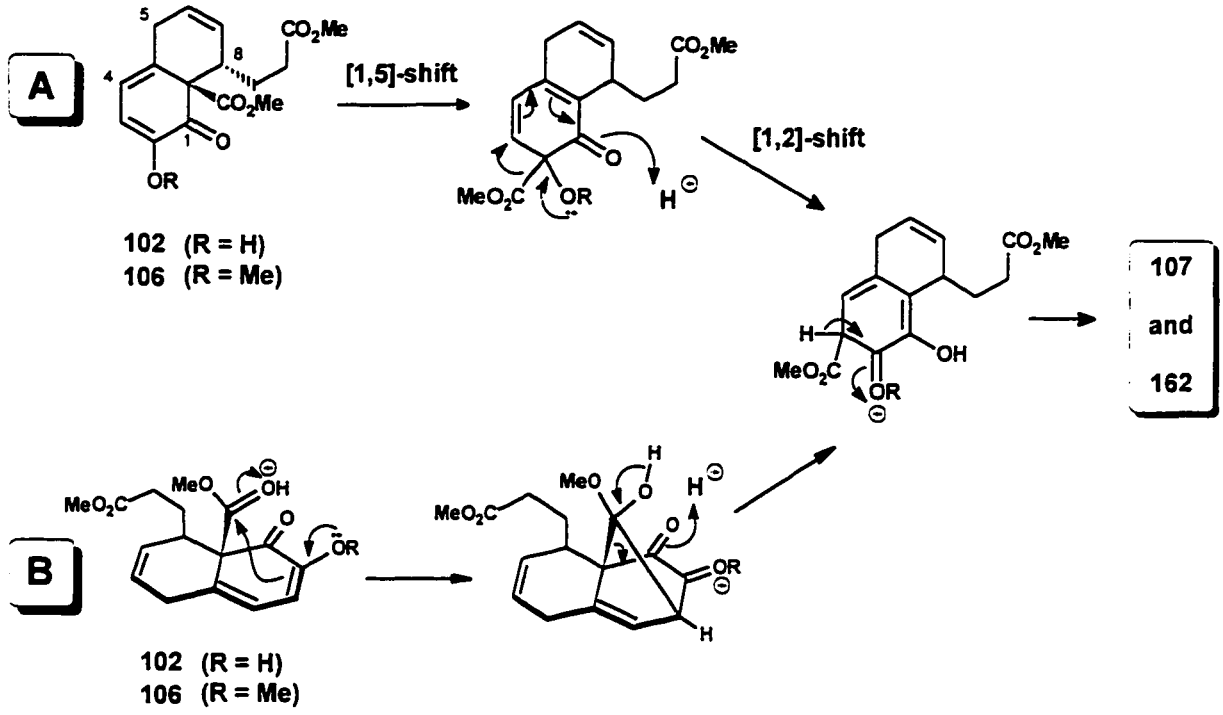
102 (R = H)
106 (R = Me)

163 (R = H)
165 (R = Me)

164 (R = H)
166 (R = Me)

In addition to the reactions promoted by TFA, rearrangements using the carbon electrophiles Me^+ (from Me_3OBF_4) and Et^+ (from Et_3OBF_4) were also carried out on compounds **102** and **106**; in each case, the same rearrangement products **107** and **162** were formed respectively, in moderate to good yields (Table 2.5, entries 3-6). Once the structures of these rearrangement products were elucidated, a mechanistic explanation for

Scheme 2.34 [92]

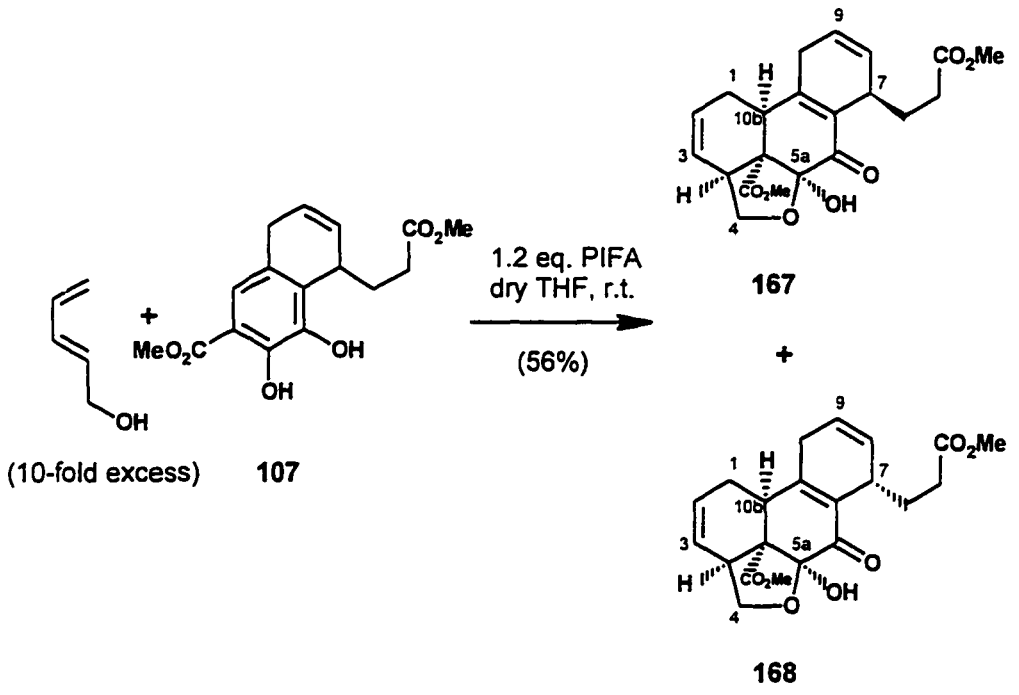


their formation was sought and two pathways **A** and **B** were proposed (in Scheme 2.34). In pathway **A**, the Diels-Alder adduct would undergo a [1,5]-shift of the angular ester group, followed by a [1,2]-shift which is promoted by an oxygen lone-pair of the C_2-substituent. (A mechanism similar to this one was proposed for the rearrangement of several *p*-benzoquinone Diels-Alder adducts bearing an angular acetyl group.[97] Using ^{2}H-labeled adducts as substrates, it was shown how the products obtained from rearrangement could not have resulted from a retro-Diels Alder/recombination sequence, but rather only from a [1,5]-shift.) In pathway **B**, the angular ester group is made susceptible for electrophilic attack by the action of the electrophile (H^+, Me^+ or Et^+), forming a bridged intermediate which would collapse to give the product. The experimental evidence disfavors pathway **B** since treatment of **102** or **106** with Et_3OBF_4

did not produce any ethyl ester at all, a compound which should have formed by this pathway. The mechanism proposed in pathway **A** however, is in agreement with the experimental results.

It is noteworthy that the two rearrangement products **107** and **161** (see Scheme 2.32) are substituted 1,2-dihydroxy-5,8-dihydronaphthalenes which differ in the position of the ester substituent at either C_3 or C_4 and also in the regiochemistry of the side-chain. Therefore, the use of *o*-benzoquinones as dienophiles in Diels-Alder reactions, and the subsequent acid-catalyzed rearrangement of their adducts, constituted a new and straightforward synthesis of differently functionalized 1,2-dihydroxynaphthalenes as templates for elaborating complex natural products. Few methods for efficiently preparing substituted 1,2-dihydroxynaphthalenes from simple starting materials have been reported in the literature.[98] If one were to oxidize these 1,2-dihydroxynaphthalenes templates to their corresponding *o*-quinonoid species, the ester group situated at either C_3 or C_4 in these compounds could serve as a directing group for a second intermolecular Diels-Alder cycloaddition. To demonstrate this idea, the compounds **107** and **161** were each oxidized with PIFA in the presence of a 10-fold excess of the simple unsymmetrical diene (*E*)-2,4-pentadienol (Scheme 2.35), using the standard conditions employed for all these cycloadditions.[92] From the reaction with **107**, two products **167** and **168** were isolated in approximately equal amounts and 56% combined yield. High-field ^{1}H-NMR analysis (500 MHz) revealed that these adducts were diastereomeric phenanthro[10,1-*bc*]furans (Figures 2.13 a, b), and the X-ray crystal structure obtained for adduct **167** (Figure 2.14) established the relative stereochemical configurations and that these adducts were epimeric at C_7.

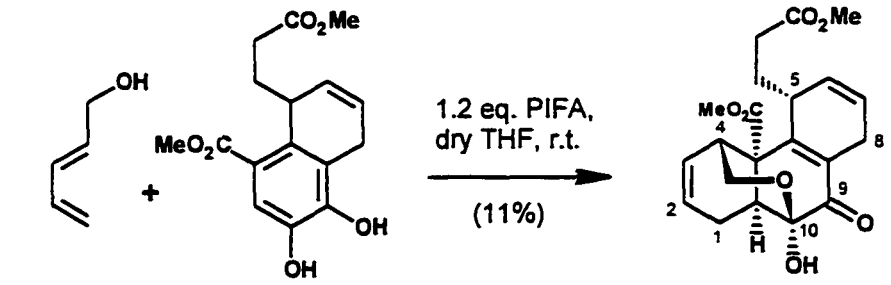
Scheme 2.35[92]



The second Diels-Alder reaction was attempted on **161** (with the directing ester substituent situated at C_4) and was not as successful, perhaps due to steric congestion at the reaction centers (Scheme 2.36). Only one adduct was isolated in 11% yield, which was characterized by ^{1}H- and ^{13}C-NMR analysis as the 4,10-methyleneoxy-bridged phenanthrene derivative **169**. The alternative structure **170** illustrated in Figure 2.15 had to be considered, and therefore a comparison of the ^{13}C-spectral data of the Diels-Alder product with the data obtained for two other known compounds **168** (a regioisomer of **169**) and **171** (an analogue of **170**) was attempted.[92] The actual ^{13}C-structural assignments more closely matched those of **168** than **171**, particularly at the ketal carbon α-positioned to the enone moiety. Moreover, the geminal coupling constant for the methyleneoxy bridging group in **169** was 11.9 Hz, which is more common with geminal

coupling constants in a tetrahydropyran ring than those found in the tetrahydrofuran rings of the known compounds **168** and **171** (J_{gem}=8.0-9.5 Hz).[86b] Since this adduct **169** could not be crystallized easily, the determination of the relative stereochemistry could not be performed by X-ray analysis. However, two-dimensional NOESY experiments indicated that H-4 and H-5β (refer to the numbering in Scheme 2.36) were in close proximity. If one assumes that the cycloaddition occurred preferentially from the less-hindered molecular face and with 2,4-pentadienol oriented *endo* to the *o*-quinonoid ring, then the relative configurations at C_4-H, C_{4a}-CO_2Me, C_5-$CH_2CH_2CO_2Me$ and C_{10a}-H are all *cis*-related. With this assumption, and the aid of molecular models, one can easily justify the observed NOE between H-4 and H-5β. *exo*-Cycloaddition could not have occurred, as cyclization of the pendant alcohol group to either of the two quinone carbonyl groups would not be geometrically possible. It was therefore demonstrated that the sequence of Diels-Alder→aromatization-rearrangement→Diels-Alder reactions can be exercised for building complex polycyclic ring systems from simple and commercially available benzenoid materials, and has potential use in natural product synthesis.

Scheme 2.36



(10-fold excess) **161** **169**

Figure 2.13: High-field (500 MHz) ^{1}H-NMR spectra of phenanthrofurans (a) **167** and (b) **168**.

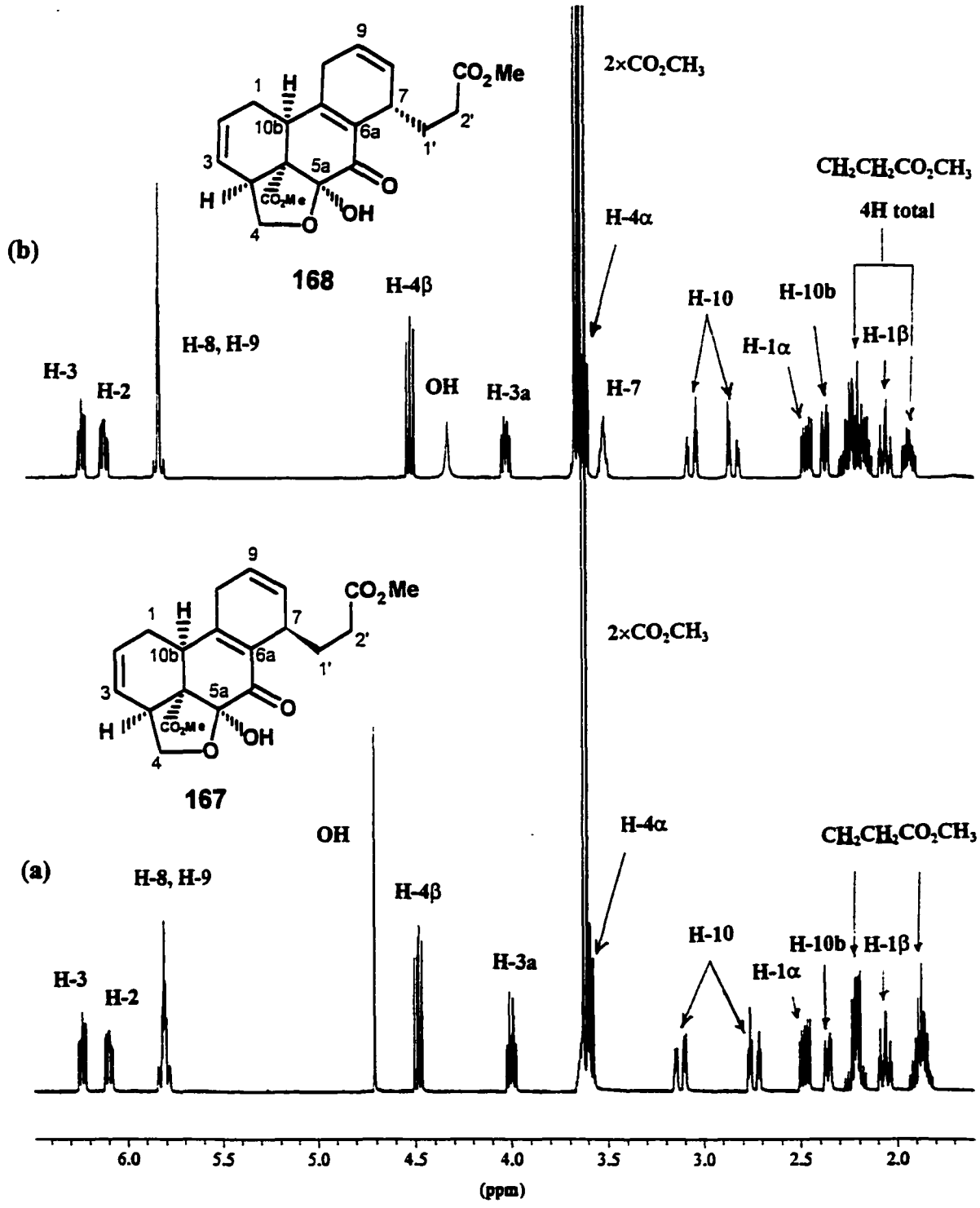
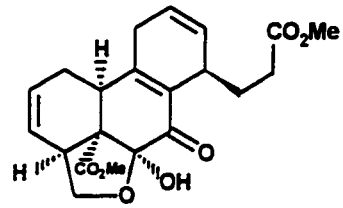


Figure 2.14: Molecular plot of the X-ray crystal structure of compound **167**.



167

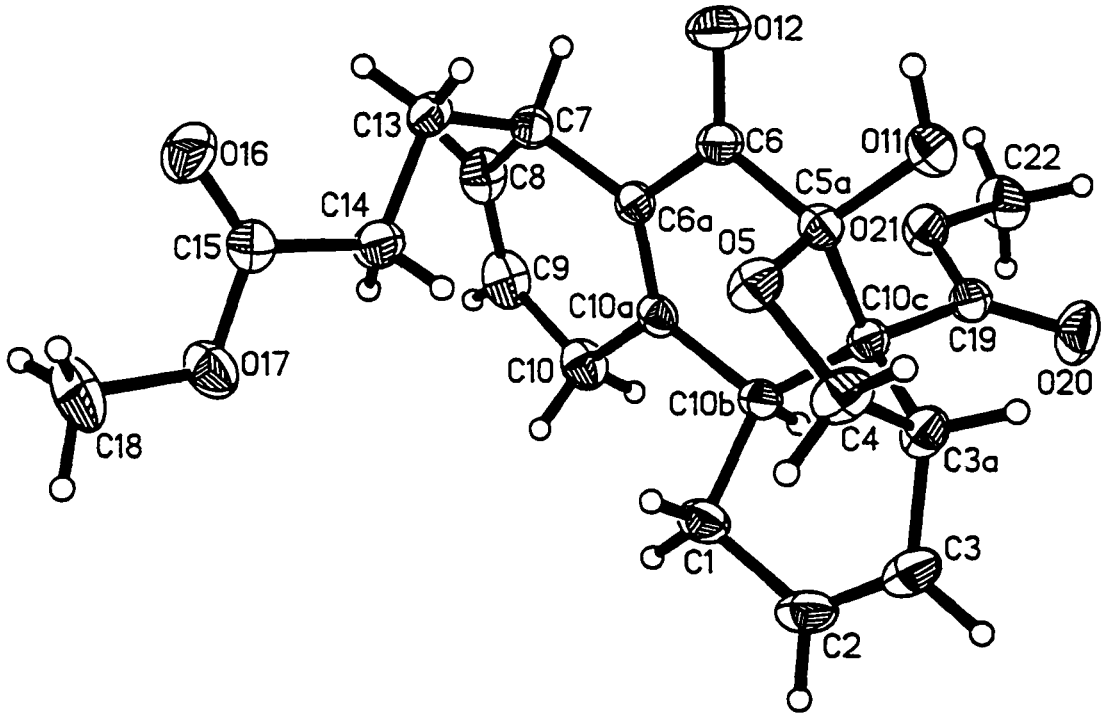
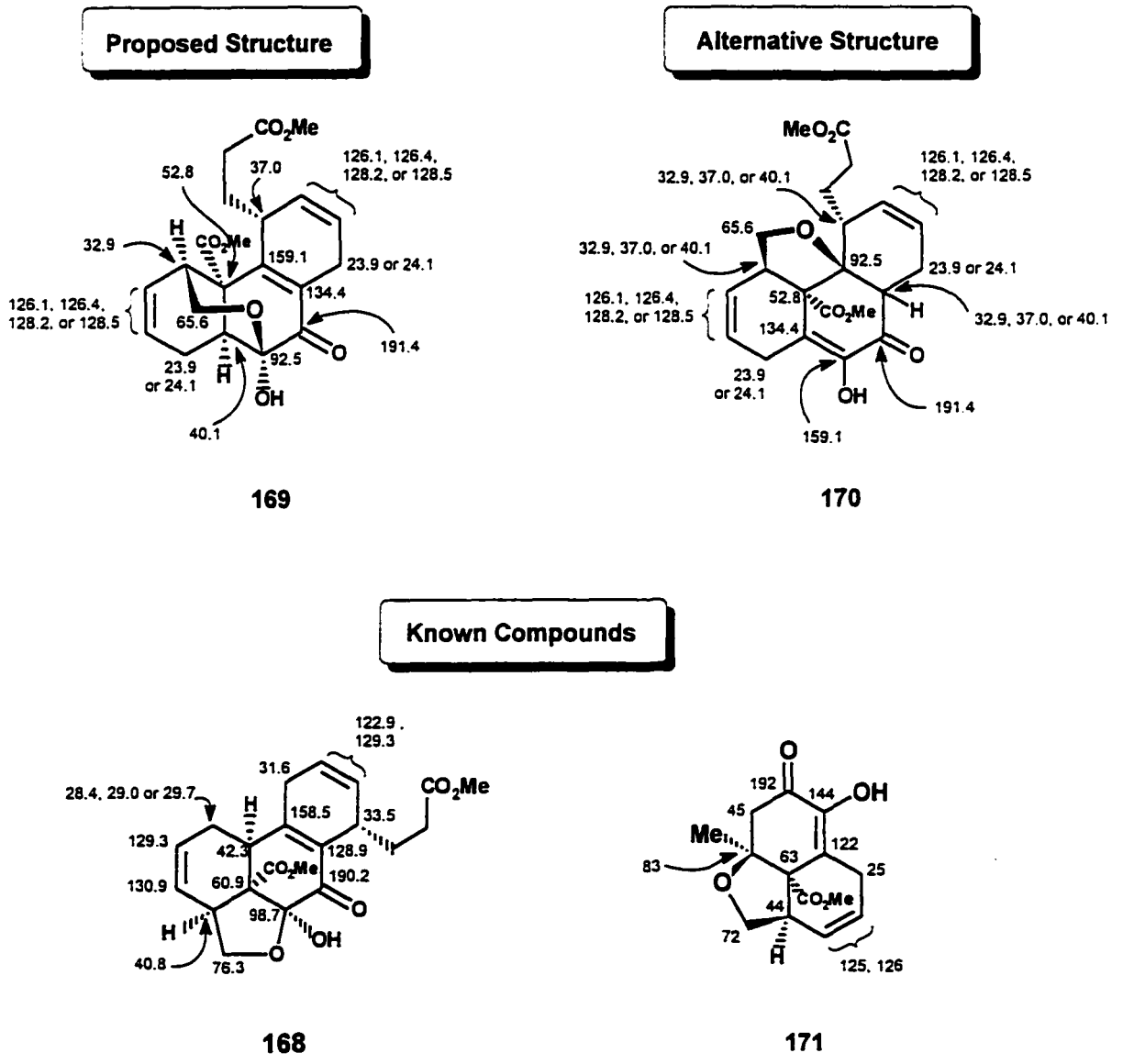


Figure 2.15: Comparison of ^{13}C-NMR spectral assignments for the known compounds **168** and **171** with the data obtained from the Diels-Alder adduct **169** and hypothetical structure **170**.[92]



2.4 Summary

The pentacyclic thiol ester **80**, an advanced precursor in the synthesis of viridin (**1**), was prepared in 8 steps and 34% overall yield from commercially available 2,3-dihydroxybenzoic acid. The thiol ester group was chosen so as to offer a means of chemoselective reduction to the methyl group in viridin, in the presence of other carbonyl functional groups. The initial step in the synthetic route involved the intermolecular Diels-Alder reaction between methyl (*E*)-4,6-heptadienoate and the *o*-benzoquinone species generated *in situ* from PIFA-promoted oxidation of 2,3-dihydroxybenzoic acid (Scheme 2.9). The substituted 1,2-dihydroxy-5,8-dihydronaphthalene **103**, which resulted from the spontaneous decarboxylation of the presumed Diels-Alder adduct **111**, was isolated in 78% yield. From a study of the intermolecular Diels-Alder reactions between the same diene and several *o*-benzoquinone esters **110** and **153-155**, it was concluded that the position of the electron-withdrawing ester substituent exerted a directing effect on two regiochemical aspects of the cycloaddition: (i) the site of cycloaddition on the *o*-quinone ring, and (ii) the orientation of the unsymmetrical diene (Scheme 2.31). Compound **103** was then selectively methylated at the less hindered C_2-phenol group with trimethyloxonium tetrafluoroborate, which furnished **113** in excellent yield (95%) (Scheme 2.15). With the construction of the key intermediate **81** in focus, the sequence of remaining chemical transformations was altered several times due to unexpected difficulties. Cyclization of the pendant ester side-chain in **113** gave the benzindanone analogue **105** in 4 steps which included sequentially, saponification of the ester moiety, lactonization with the C_1-phenol group, dehydrogenation, and $TiCl_4$-promoted Fries rearrangement (Scheme 2.11). All subsequent attempts to place the thiol

ester group at C_6 of benzindanone **105** by Friedel-Crafts methods failed, having instead furnished the chloronaphthoquinone methide **114** as a stable reaction product (Scheme 2.12). Only methanolysis would decompose the quinone methide **114** to a benzindanone methyl ester **115**, which was not the desired thiol ester **81**. Attachment of the thiol ester group proved to be highly successful on the benzenoid precursor **113** however, and the product **121** (formed in 86% yield) was aromatized to the naphthylpropanoic ester **122** by dehydrogenation with DDQ (89% yield) (Scheme 2.15). Closure of the side-chain in **122** to form the cyclopentenone D-ring in viridin proved to be an arduous task, as many Friedel-Crafts conditions were tested. Conditions were fortunately found for selectively hydrolyzing the side-chain methyl ester in forming carboxylic acid **129**, without harming the important thiol ester group. After conversion to the acid chloride and subsequent Friedel-Crafts acylation catalyzed by $AlCl_3$ (70% maximum yield), the benz[*e*]indanone thiol ester **81** was prepared (Scheme 2.22). The IMDA reaction was successfully validated with three *o*-quinonoid monoketals, generated *in situ* from the substrates **115**, **122** and **81** by oxidation with PIFA in the presence of excess (*E*)-2,4-pentadienol (Schemes 2.14, 2.23, and 2.24). The adducts **120a-b**, **130a-b** and **80a-b** respectively (as 2:1 mixtures of *endo* and *exo* diastereomers) were all formed in reasonably good yields ranging from 57% (for **130**) to a remarkable 86% (for **80**). All the adducts shared the same ^{1}H and ^{13}C-NMR spectral features with those of the model phenanthrofurans **78a-b** and **79a-b**, and their relative stereochemical configurations were determined by comparison with the ^{1}H-NMR spectra of the *endo* and *exo* adducts **78a-b** and **79a-b**, whose X-ray crystal structures had been obtained.[45]

Several attempts were made at selectively desulfurizing the thiol esters **79a-b**, **130a-b**, **80a**, **131** and **132**, in the hope that an aldehyde or alcohol product would result

(Table 2.2). The reagents which were tested included Raney-Ni (W-2 grade), sodium borohydride, DIBAL-H, and triethylsilane with palladium-on-carbon. Among the reagents tried, only Fukuyama's method using triethylsilane and palladium-on-carbon had successfully formed the aldehyde products **133**, **136a-b**, **137** and **138**, although the reaction had performed inconsistently and seemed to be substrate-dependent. Compound **140** was formed by $NaBH_4$ reduction of thiol ester **130a**, and was determined to be a masked C_{10b}-alcohol product. A plan for the potential conversion of **140** to the C_{10b}-methyl analogue **142** was proposed (Scheme 2.26), and efforts toward this end are currently underway. A sufficient amount of the pentacyclic aldehyde **138** was unfortunately not available, however some attempts were made to reduce the model aldehyde **133** to the corresponding methyl analogue. Conversion of aldehyde **133** to its semicarbazone **146** was followed with the Henbest version of the Wolff-Kishner reduction (Scheme 2.28). The two compounds obtained in this reaction were the deformylated product **148** (9%) and the methylene-bridged major product **147** (42%), the latter having resulted from nucleophilic addition of the reduced methylene anion with the tetralone carbonyl group. The reduction will be repeated once a significant quantity of the pentacyclic aldehyde **138** becomes available. In the course of examining other chemical transformations of the furan ring E, it was found that the acid-catalyzed elimination of methanol to produce an enol ether moiety was only possible with the *endo* Diels-Alder adducts **78a**, **79a**, **80a**, and **152a** (Scheme 2.30). The *exo*-isomers of these compounds could not be converted to their corresponding enol ethers, even under forcing conditions. After examining the X-ray structures of the *endo* and *exo* isomers for **78**, **79** and **152** (Fig. 2.10 and 2.11), it was clear that only the *endo*-isomers exhibited an antiperiplanar arrangement between the exocyclic cleavable C_{5a}–OCH_3 bond (C_{3a}-OCH_3

bond for **152**) and a lone pair orbital on the O_4-ring oxygen, a necessary requirement for the elimination of methanol. The resistance toward elimination exhibited by these *exo*-isomers could therefore be attributed to an anomeric effect, which constituted a serious limitation of the synthetic route developed thus far for viridin. Contemplation of a new convergent strategy for the synthesis of viridin was in order, and a reinvestigation of the intramolecular Diels-Alder reaction of simple *o*-benzenoid monoketals for constructing a 5a-methyl-naphthofuran derivative like **58** was planned (*cf.* Scheme 1.9).

Finally, rearrangements of the Diels-Alder adducts **102** and **106** were carried out with various electrophiles including H^+ (from TFA), Me^+ (from Me_3OBF_4), and Et^+ (from Et_3OBF_4) (Scheme 2.32, Table 2.5). Diels-Alder adduct **156** was converted to **161** by a dienone-phenol rearrangement, while the rearrangements of **102** to **107** and of **106** to **162** were proposed to have occurred by an initial [1,5]-shift followed with a [1,2]-shift (Scheme 2.34). The rearrangement products **107** and **162** were also 1,2-dihydroxynaphthalene derivatives differing in the position of an ester substituent (at either C_3 or C_4). Upon oxidation *in situ* with PIFA, the ester group in the resulting naphthoquinones regioselectively directed another Diels-Alder cycloaddition with the unsymmetrical diene (*E*)-2,4-pentadienol. The reaction with **107** produced two adducts **167** and **168** formed in *ca.* 1:1 ratio and 56% combined yield, which were determined to be epimeric at C_7. The reaction with **161** gave a single adduct **169** in poor yield (11%), probably as a result of steric congestion at the reaction centers. The structure was proposed to be the 4,10-methyleneoxy-bridged phenanthrene derivative **169** by comparison of its ^{13}C-NMR chemical shifts and geminal coupling constant in the bridging group with those of known compounds **168** and **171**. The synthetic utility of substituted *o*-quinones, and the effective regiocontrol exerted by an electron-withdrawing

substituent, was exercised in the reaction sequence Diels-Alder→rearrangement-aromatization→Diels-Alder. A new, efficient and versatile method was therefore developed for constructing functionalized 1,2-dihydroxynaphthalenes, which could act as synthetic precursors for more complex natural products.

CHAPTER 3

A REINVESTIGATION OF THE INTRAMOLECULAR DIELS-ALDER REACTION OF *ORTHO*-BENZOQUINONE MONOKETALS:

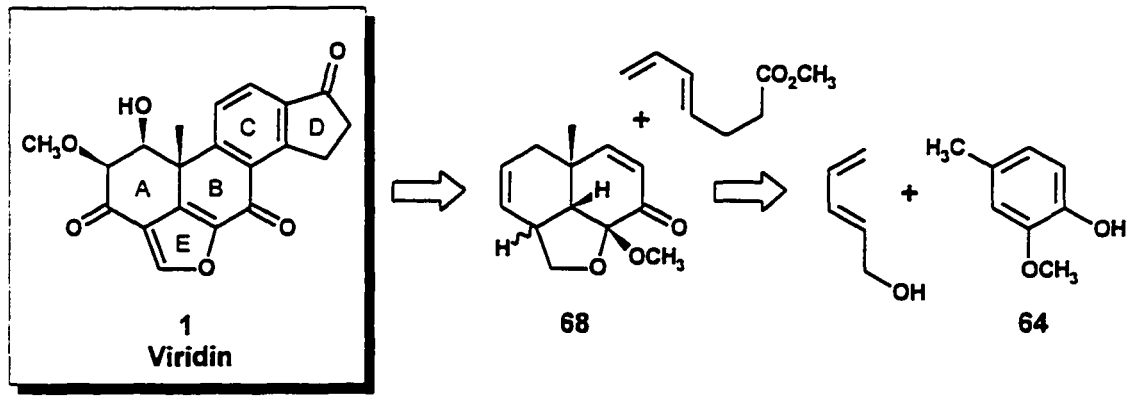
EFFORTS TOWARD THE CONVERGENT SYNTHESIS OF VIRIDIN AND CONGENERS

3.1 Revisiting the Intramolecular Diels-Alder Reaction of Mixed *o*-Benzoquinone Monoketals

Many unexpected detours were encountered on the road to viridin, but significant progress was achieved along this journey. The elaboration of the pentacyclic intermediate **80**, an advanced precursor of viridin, by the efficient one-pot oxidation-IMDA method was paramount among these achievements, as it represented the first and only synthesis of the pentacyclic framework of viridin. Unfortunately, with these successes came some unforeseen limitations, which included the inability to transform the pentacyclic *exo*-adduct **80b** to an advanced furanoid intermediate, as well as the troublesome chemoselective reduction of the angular thiol ester group to the methyl group of viridin. These synthetic obstacles ultimately provoked the adoption of a fundamentally new strategy which would incorporate the angular methyl group early on.

The new approach involved revisiting the original plan outlined in Scheme 3.1, which was based on a convergent coupling of a 5a-methyl-naphtho[1,8-*bc*]furan system (the tricyclic A-B-E subunit of viridin, which will be referred to as the 'naphthofuran' system) with a suitable diene (a precursor to ring D). Thus three years later, the synthesis of this naphthofuran structure **68** by the IMDA reaction of mixed *ortho*-benzoquinone monoketals generated from substituted guaiacols (*o*-methoxyphenols) and (*E*)-2,4-pentadienol was tackled once more (*cf.* Scheme 1.12).

Scheme 3.1



With the knowledge gained from our successes with regiocontrolled intermolecular cycloadditions of *o*-benzoquinone esters (*cf.* Scheme 2.31), it was not clear why the IMDA reaction performed earlier in our laboratory with the guaiacol ester **66** (among others) was reported to be unsuccessful (*cf.* Scheme 1.12).[45] It seemed dubious that the *o*-quinone species generated from oxidation of **66** with PIFA had not withstood ketalization with (*E*)-2,4-pentadienol and the subsequent IMDA reaction. Accordingly, the guaiacol ester **66** was the first substrate chosen for a re-trial of the one-pot oxidation-IMDA process. Using the standard reaction conditions employed earlier

with the naphthalenoid substrates **74**, **75**, **81**, and **122** (1.2 equiv. PIFA, 5-10 equiv. (*E*)-2,4-pentadienol), the IMDA reaction with **66** was in fact successful (Scheme 3.2 and Table 3.1), producing two adducts in a combined yield of 49%. The *o*-benzoquinone monoketal reacted as both a diene and dienophile to a similar extent, having formed the bridged adduct **177a** (22%) and the naphthofuran adduct **178a** (27%) respectively, in similar amounts. Due to the *s-cis* geometry of *o*-quinones, bicyclo[2.2.2]octenone analogues of the general structure **177** were known from other reports of IMDA reactions of *o*-quinone monoketals [99] and of *o*-quinol acetates,[41] and also in intermolecular cycloadditions of *o*-quinols.[100, 101] The successful formation of the naphthofuran adduct **178a** in this IMDA reaction, however, was the first of its kind and nicely demonstrated how the electron-withdrawing nature of the ester group rendered the *o*-quinone monoketal dienophilic in reactivity, although not exclusively in this manner.

The overall yield of the reaction with **66** was considerably improved to 80% (36% for naphthofuran **178a**, 44% for bridged adduct **177a**, Table 3.1 entry a)[102] by adding excess $NaHCO_3$ (two equivalents per mole of PIFA) shortly after the addition of PIFA, to neutralize the TFA produced during oxidation which may have partly consumed the naphthofuran product. The ^{1}H-NMR spectrum of the bridged adduct **177a** (Figure 3.1) was quite similar to that of the known compound **67**,[45] and the spectral assignments were confirmed by decoupling experiments. Irradiation of the signal for H-6 (3.38 ppm) had collapsed the signal for H-5 (7.16 ppm, dd, J = 6.9, 2.0 Hz) to a doublet (J = 2.0 Hz, long-range coupling with H-8). Also, irradiation of the signal for H-3 (2.41 ppm) reduced the downfield signal for one of the H-2 protons (4.22 ppm, dd, J = 8.2, 3.3 Hz) to a doublet (J = 8.2 Hz, geminal coupling), while having no effect on the upfield doublet corresponding to the other H-2 proton (3.88 ppm, d, J = 8.2 Hz).

Scheme 3.2 [88, 102]

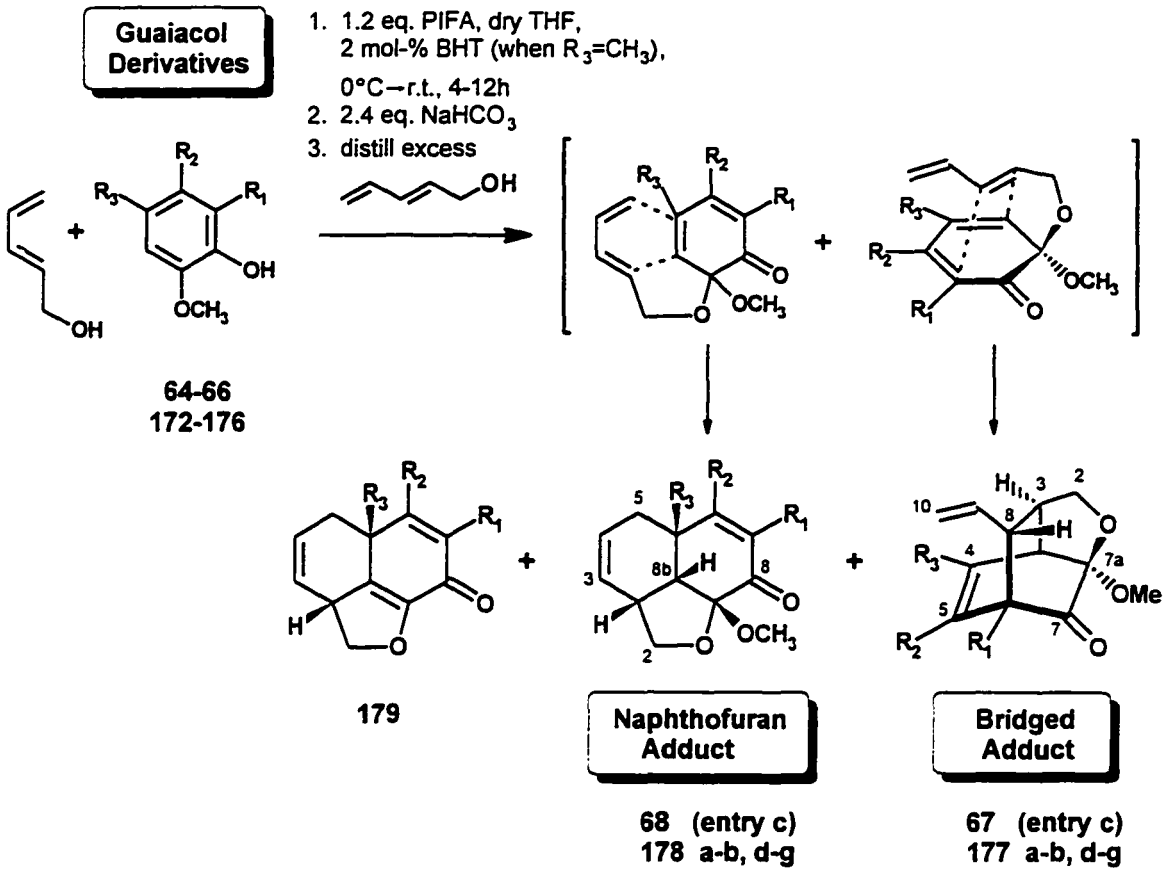
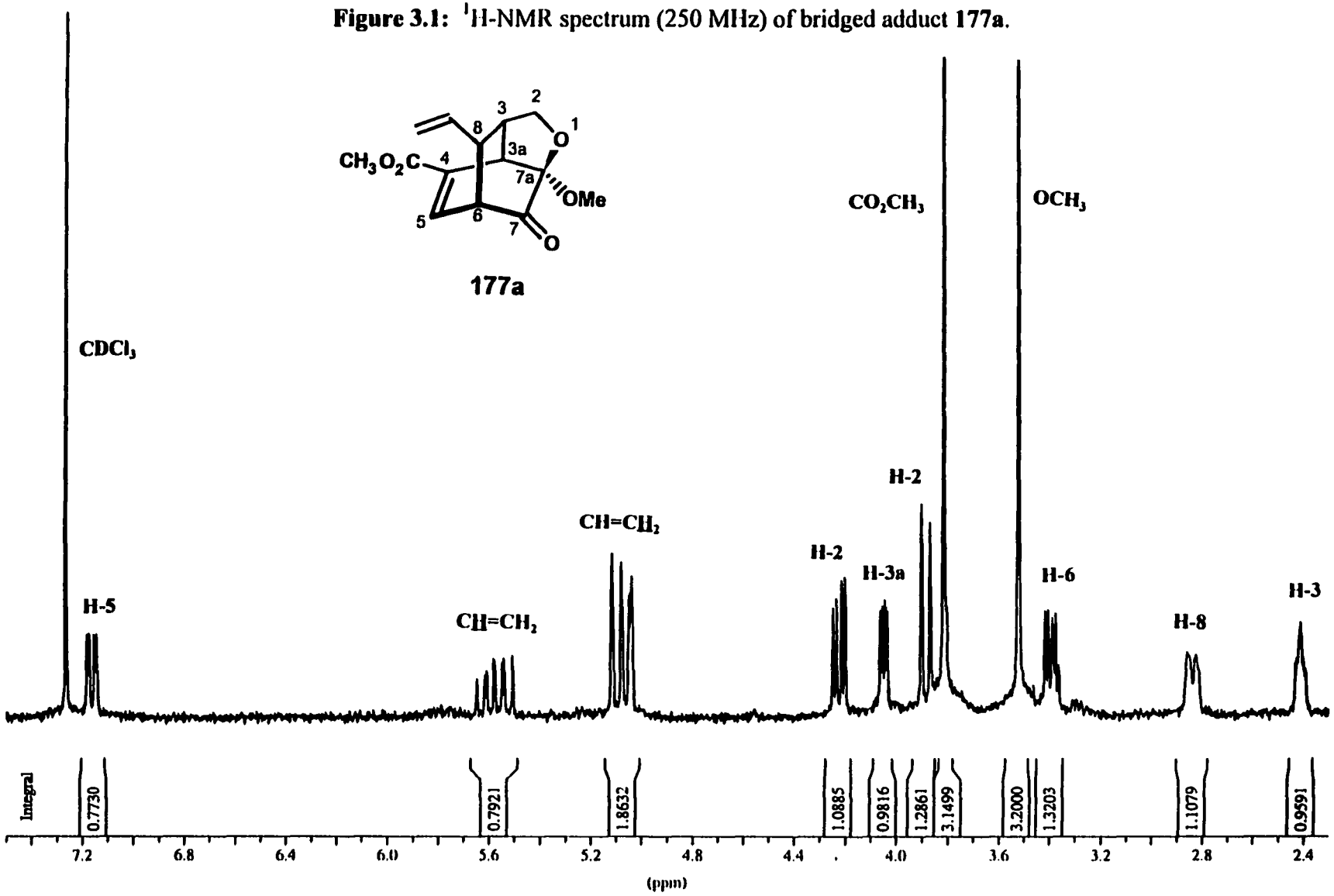


Table 3.1: Results of the IMDA reaction with guaiacols **64-66** and **172-176**.[88, 102]

Entry	Guaiacol Derivative	R_1	R_2	R_3	IMDA Products (% Yield) Bridged	Naphthofuran
a	**66**	H	H	CO_2CH_3	**177a** (44%)	**178a** (36%)
b	**172**	H	H	$COSCH_3$	**177b** (40%)	**178b** (37%)
c#	**64**	H	H	CH_3	**67** (61%)	**68** (8%)
d	**173**	I	H	CH_3	**177d** (72%)	**178d** (16%)
e	**174**	CO_2CH_3	H	CH_3	**177e** (65%)	**178e** (2%)
f	**175**	H	$COSCH_3$	CH_3	**177f** (65%)	**178f** (7%)
g	**176**	H	CH_3	$COSCH_3$	**177g** (52%)	**178g** (1%)
h	**65**	H	H	CHO	Complex Product Mixture	

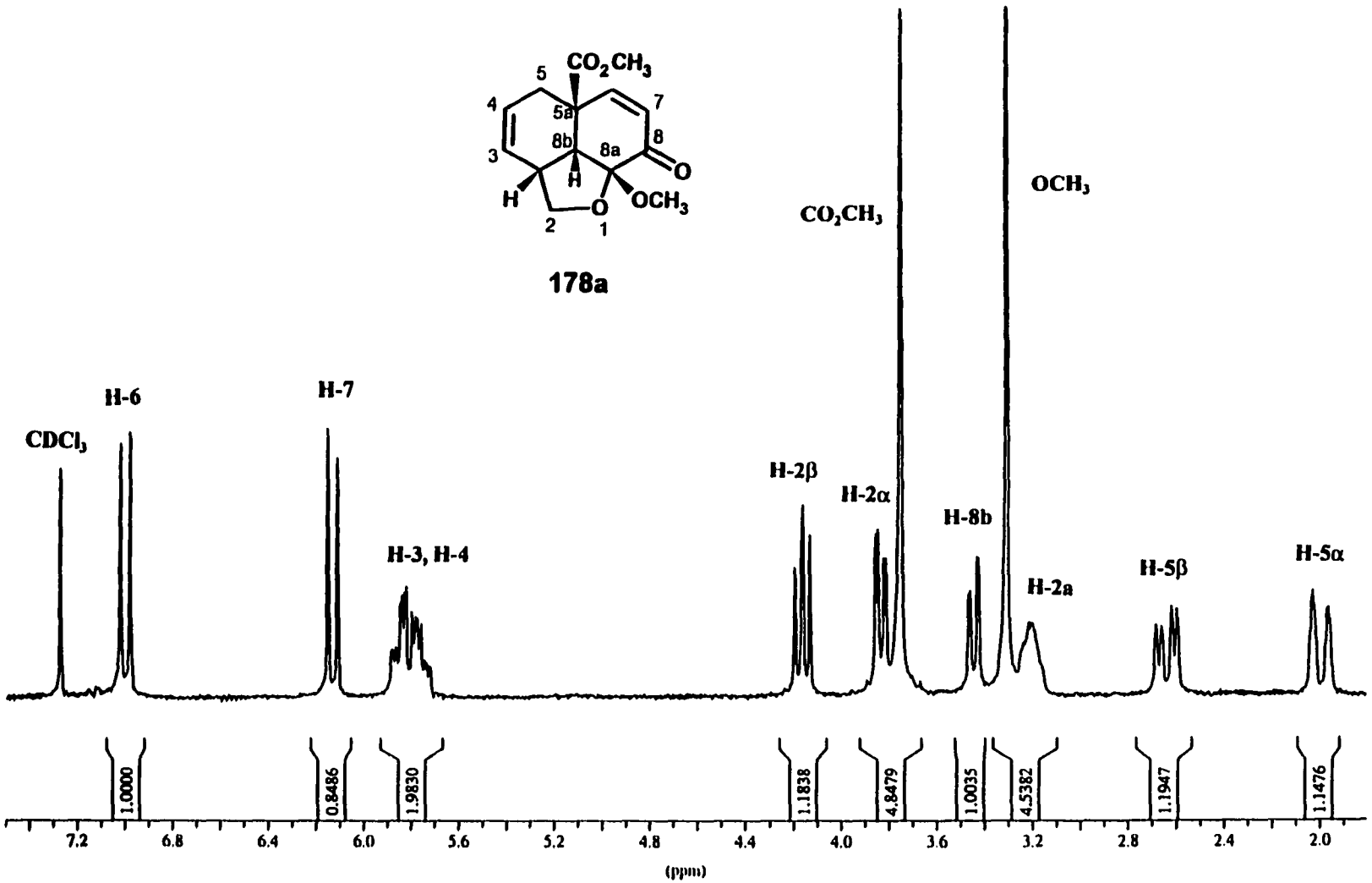
A small amount (3%) of the demethoxylated product **179c** was also isolated from this IMDA reaction.

Figure 3.1: ^{1}H-NMR spectrum (250 MHz) of bridged adduct **177a**.



177a

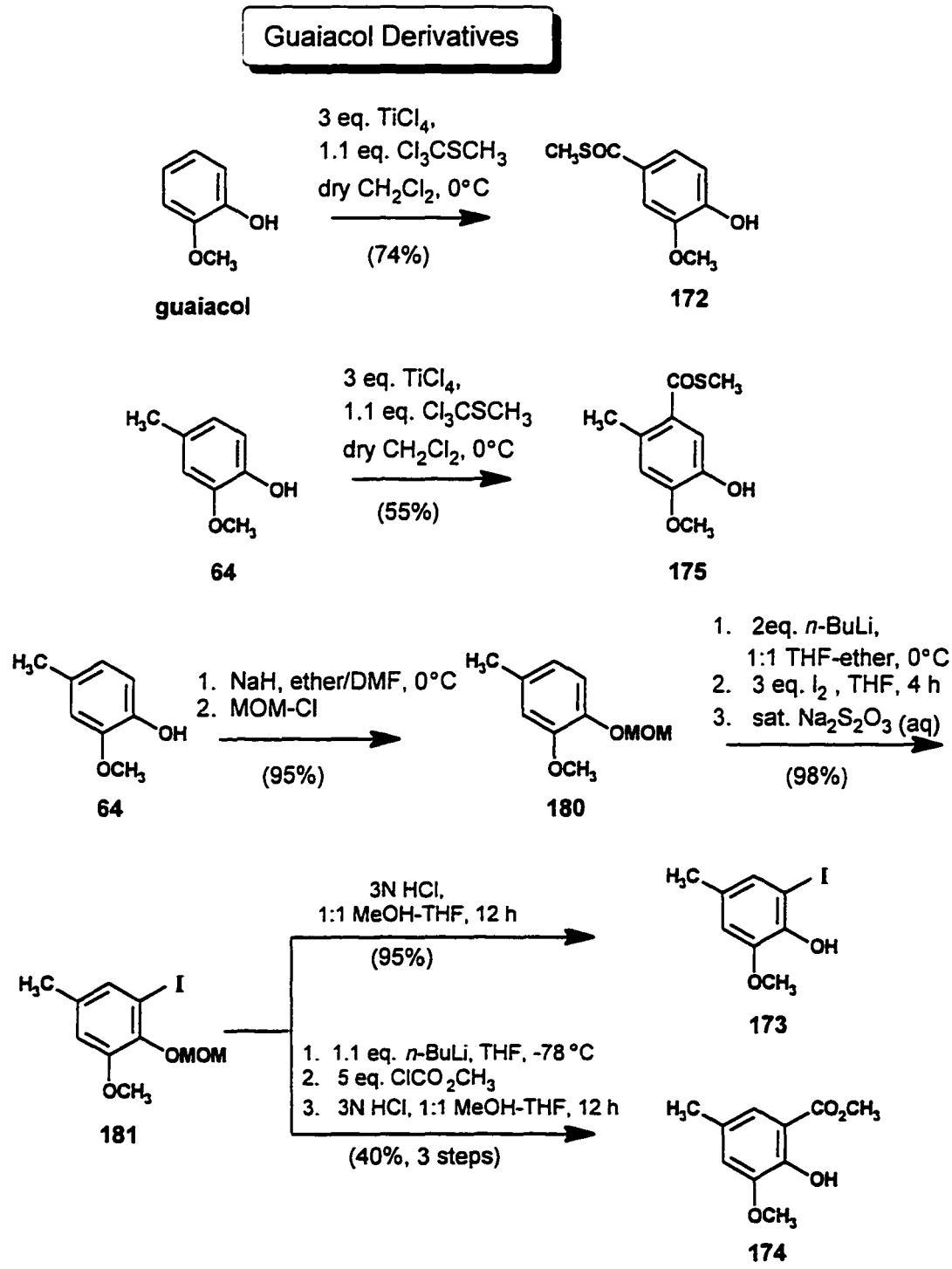
Figure 3.2: ^{1}H-NMR spectrum (250 MHz) of naphthofuran adduct **178a**.



Two features which were found in the ^{1}H-NMR spectrum of naphthofuran **178a** (Figure 3.2) were diagnostic of the structure and stereochemical configuration shown in Scheme 3.2. The presence of two downfield doublets (6.12 ppm and 6.99 ppm for the case of **178a**) were clearly representative of the enone protons H-7 and H-6, respectively. The *endo*-stereochemical configuration (2a-H, 5a-R_3, 8a-OCH_3, and 8b-H are all *cis*-related) of **178** was deduced from the doublet of doublets signal for H-8b (situated at 3.44 ppm for **178a**, J = 9.1, 1.5 Hz) which exhibited a small coupling constant of 1.5 Hz attributed to W-coupling with H-5β. This diagnostic small W-coupling constant was also found in the spectra of only *endo*-phenanthro[10,1-*bc*]furan adducts **78a, 79a**, **130a** and *endo*-pentacycles **80a** and **120a**. No other product resembling an *exo*-stereoadduct was isolated from this IMDA reaction.

With the premise that an electron-withdrawing group was necessary in order to form a naphthofuran adduct, the idea of synthesizing **68** (Scheme 3.1) by reductive desulfurization of a thiol ester analogue was contemplated. The guaiacol thiol ester **172** was subsequently prepared in good yield (74%) by a $TiCl_4$-catalyzed Friedel-Crafts reaction of guaiacol (*o*-methoxyphenol) with trichloromethyl methyl sulfide (Scheme 3.3). Using the modified IMDA conditions with added $NaHCO_3$, the reaction with **172** furnished the bridged adduct **177b** (40%) and the naphthofuran adduct **178b** (37%) in yield and product ratio similar to that observed with the guaiacol ester **66** (Table 3.1, entry b). The ^{1}H-NMR spectra of these products were nearly identical to those of **177a** and **178a**, and the *endo*-configuration was also apparent in **178b**. Since the reduction of naphthofuran thiol ester **178b** to methyl analogue **68** using Fukuyama's Pd-catalyzed hydrogenolysis method[75] would naturally involve the intermediate formation of an aldehyde, the IMDA reaction was also attempted with vanillin **65** (Table 3.1, entry h).

Scheme 3.3


Guaiacol Derivatives
3 eq. TiCl4,
1.1 eq. Cl3CSCH3
dry CH2Cl2, 0°C
(74%)
guaiacol
172
3 eq. TiCl4,
1.1 eq. Cl3CSCH3
dry CH2Cl2, 0°C
(55%)
64
175
1. NaH, ether/DMF, 0°C
2. MOM-Cl
(95%)
64
180
1. 2eq. n-BuLi,
1:1 THF-ether, 0°C
2. 3 eq. I2 , THF, 4 h
3. sat. Na2S2O3 (aq)
(98%)
3N HCl,
1:1 MeOH-THF, 12 h
(95%)
173
1. 1.1 eq. n-BuLi, THF, -78 °C
2. 5 eq. ClCO2CH3
3. 3N HCl, 1:1 MeOH-THF, 12 h
(40%, 3 steps)
181
174

Although the formyl group was sufficiently electron-withdrawing on the *o*-quinone system, the reaction was largely unsuccessful. Qualitative analysis of the crude product mixture by TLC revealed the presence of only two adducts, yet following the usual purification procedure (distillation, silica gel chromatography), complex mixtures of products were always isolated, some of which resembled the bridged and naphthofuran Diels-Alder adducts (by inspection of the ^{1}H-NMR spectrum). Since the product mixture became increasingly complex with repeated exposure to silica gel, it was speculated that the initial adducts may have transformed to the dienone structure **179h** (see Scheme 3.2) which would have easily undergone rearrangement and/or deformylation (similar to our earlier observations with intermolecular Diels-Alder adducts[92]).

It was noted much earlier (chapter 1) that the original trial of the IMDA reaction with 4-methyl-2-methoxyphenol **64** only produced the bridged adduct **67** in very low yield (<10%) and none of the desired naphthofuran adduct **68** (*cf.* Scheme 1.12).[45] The successes of the IMDA reaction with **66** and **172** (Table 3.1, entries a-b) necessitated the repetition of this reaction with **64** using the modified reaction conditions. The bridged adduct **67** did form as the expected major product (43%), along with a small quantity of the naphthofuran **68** (7%)! Despite the low yield, the celebrated arrival of **68** was considered a substantial leap forward in a prospective synthesis of viridin and related natural products. The challenges which remained were to optimize the total yield of the IMDA reaction and to alter the product ratio in favor of naphthofuran **68**. A sizable quantity of red polymeric material also formed in this reaction, presumably from decomposition of the quinone to a reactive *p*-quinone methide species. In the hope of controlling such processes, a suggestion was made to add a catalytic amount of a radical scavenger such as BHT (butylated hydroxytoluene) to the reaction with **64** (and for cases

where R_3= CH_3).[103] As well, the reaction temperature was elevated from 0°C to room temperature in an attempt to promote the Diels-Alder pathway over the polymerization pathway. These simple modifications of the reaction conditions had remarkable effects on the yield, which was soon optimized to 69% (61% for **67**, 8% for **68**; entry c, Table 3.1). The ^{1}H-NMR spectrum of the bridged adduct **67** (Figure 3.3) was identical to that obtained from the same compound synthesized three years earlier in our laboratory, and the spectrum for the new adduct **68** (Figure 3.4) was analogous to that of naphthofuran **178a** (where R_3=CO_2CH_3); as well, the signal for H-8b (a doublet of doublets) exhibited a small W-coupling of 0.8 Hz which was indicative of the *endo* configuration. Although a small amount of the demethoxylated dienone **179c** was also formed at times in this reaction (from exposure of **68** to trace amounts of TFA), the Diels-Alder product ratio always favored the bridged adduct **67**. It was evident from the ratios of bridged and naphthofuran products formed in the IMDA reactions with guaiacols **64**, **66**, and **172** (entries a-c, Table 3.1 and Scheme 3.2) that the electron-withdrawing power of the substituent R_3 and the dienophilic reactivity of the resulting *o*-quinone monoketal were directly related.

As extensions of the synthetic program aimed at viridin, several other examples of the oxidation-IMDA reaction sequence were performed with the guaiacol derivatives **173-176** (entries d-g, Table 3.1). The thiol esters **172** and **175** were prepared by Friedel-Crafts reaction of commercially available guaiacol and 2-methoxy-4-methylphenol **64** (respectively) with trichloromethyl methyl sulfide (Scheme 3.3),[64] and thiol ester **176** was prepared earlier in our laboratory by the same method.[104] The iodoguaiacol derivative **173** was synthesized from **64** by a known procedure which was developed some years earlier in our laboratory (Scheme 3.3).[105] The phenol group of **64** was first protected as

Figure 3.3: ^{1}H-NMR spectrum (250 MHz) of bridged adduct **67**.

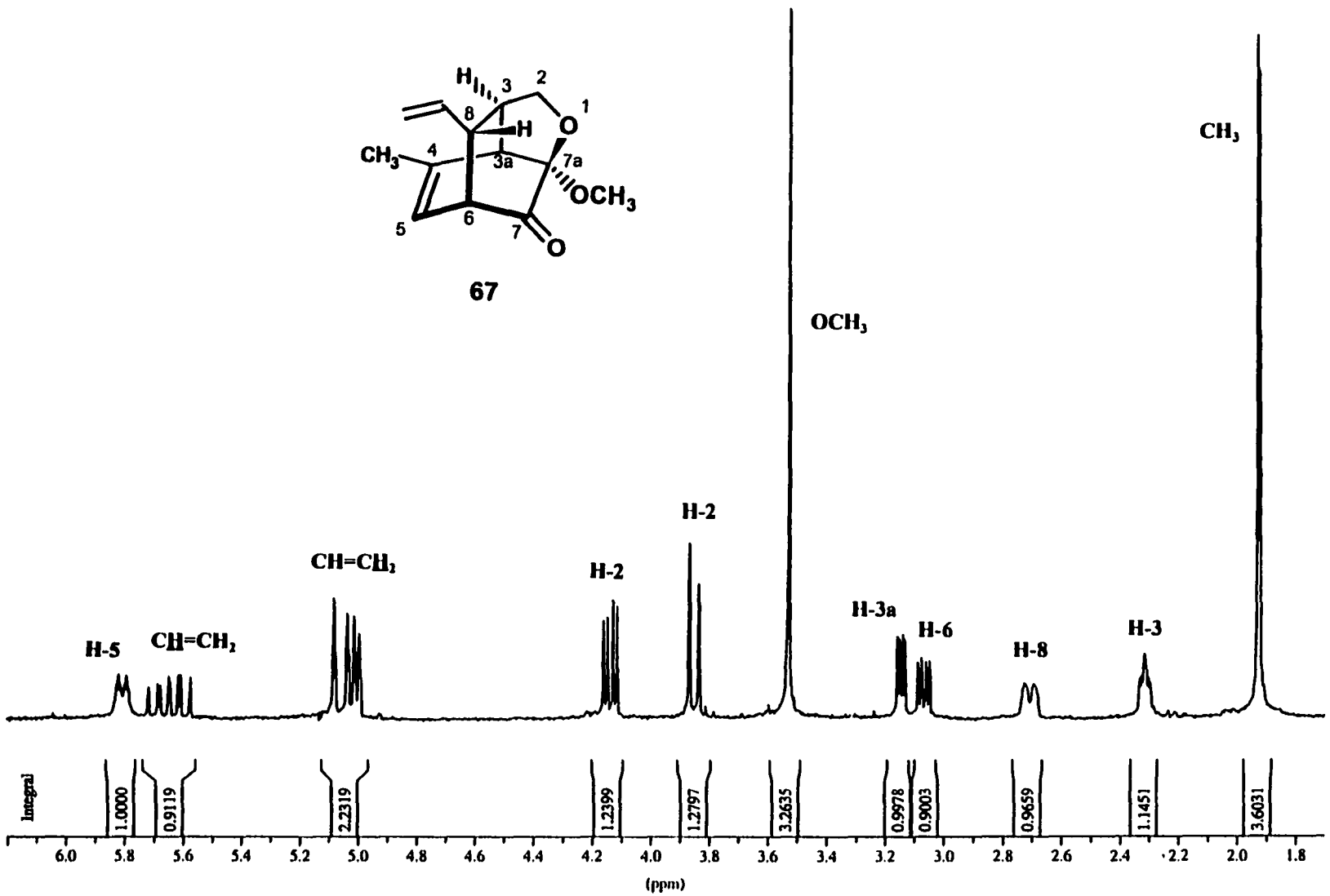
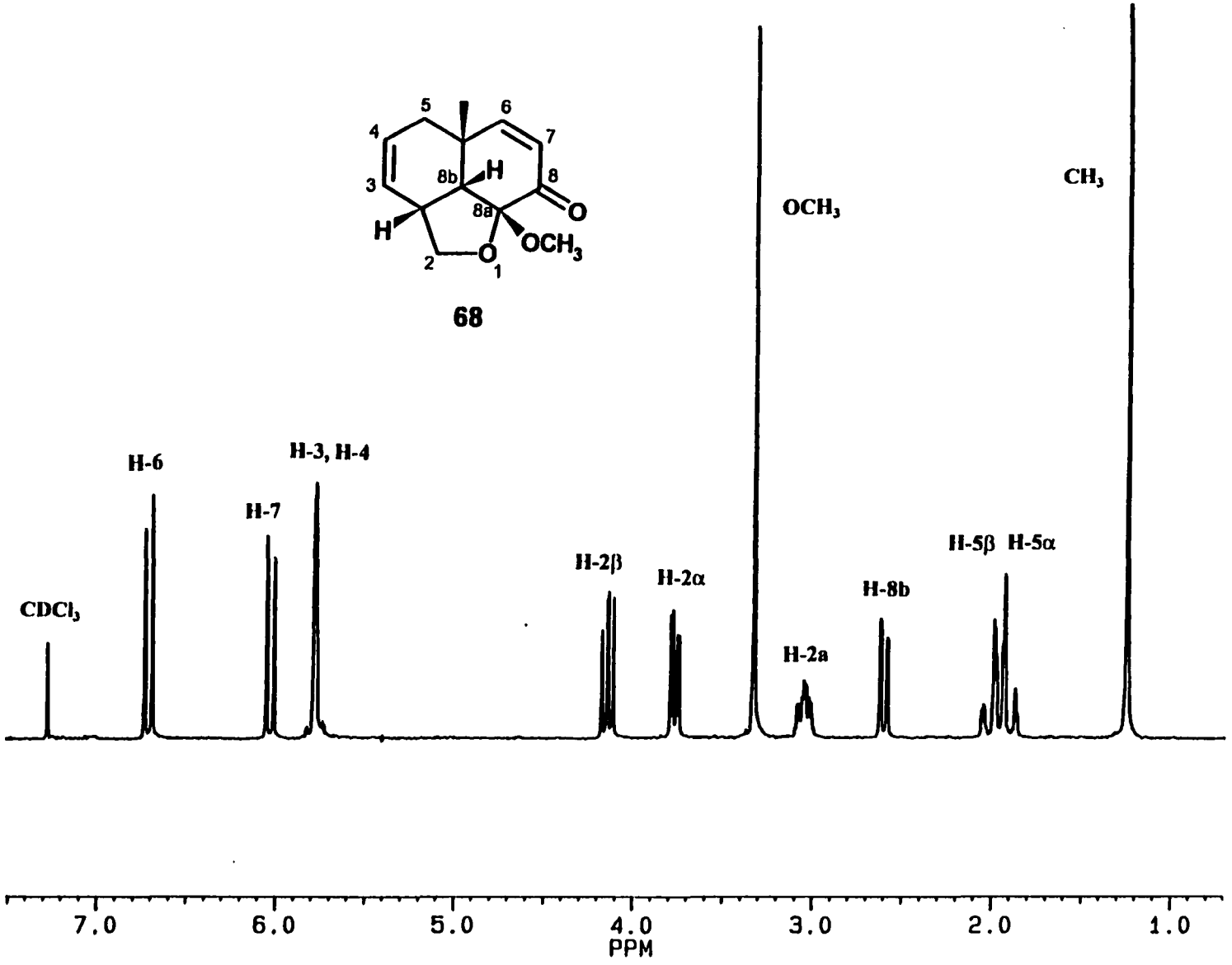


Figure 3.4: ^{1}H-NMR spectrum (250 MHz) of naphthofuran **68**.

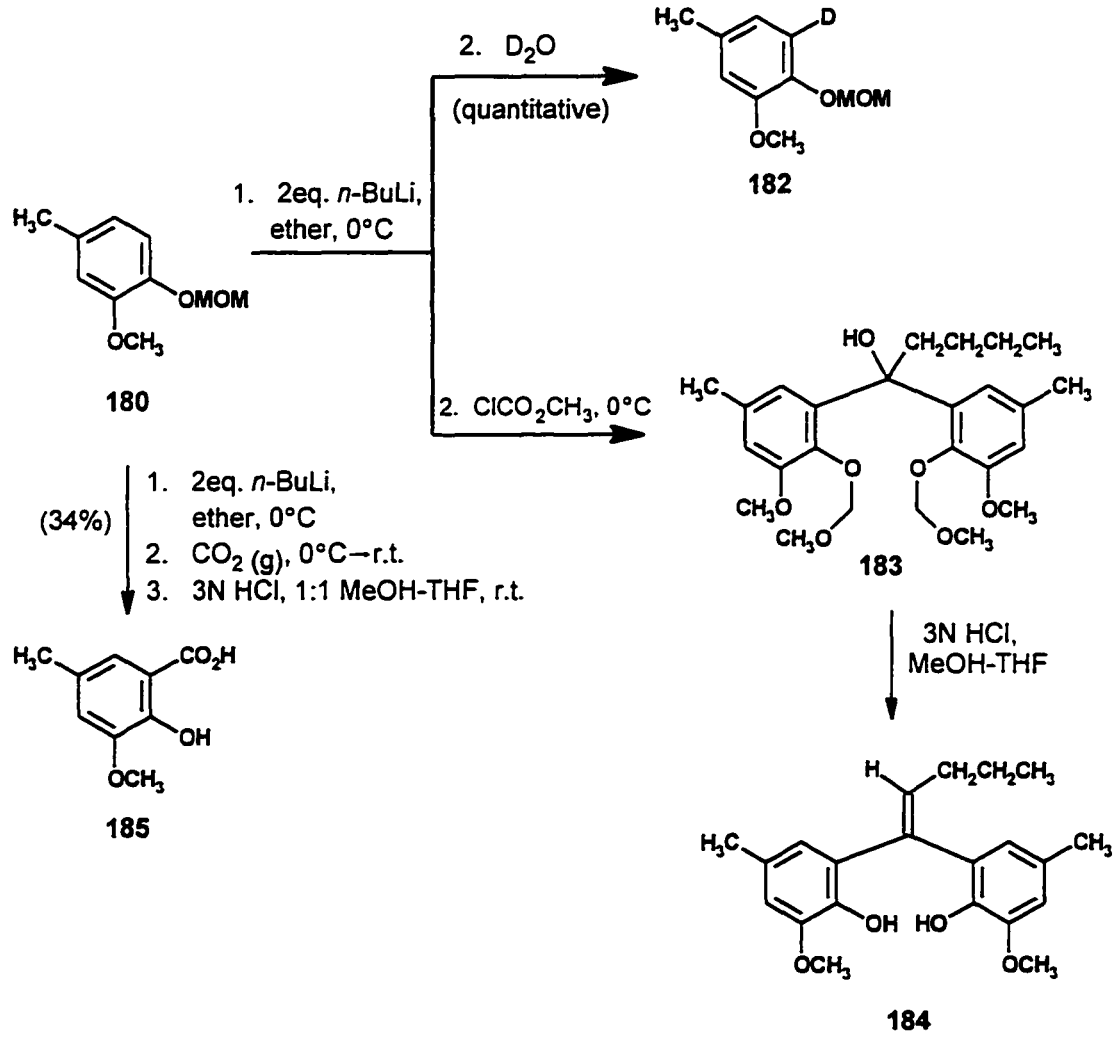


the methoxymethyl (MOM) ether **180** (95% yield), then subjected to directed *ortho*-lithiation with cold (0°C) *n*-BuLi, followed by quenching with excess iodine in anhydrous THF. After stirring for 4 h, the excess iodine was neutralized with a saturated solution of sodium thiosulfate, which gave the MOM-protected iodinated compound **181** in 98% yield. Cleavage of the protecting group by stirring with a solution of 3N HCl in 1:1 MeOH-THF produced **173** in nearly quantitative yield (95%).

The salicylate derivative **174** was more troublesome to prepare. As depicted in Scheme 3.4, compound **180** was first subjected to directed *o*-lithiation reaction with 2 molar equivalents of *n*-BuLi at 0°C.[106] These lithiation conditions were effective, since a trial experiment where the lithiated species was quenched with deuterium oxide did produce the *o*-deuterated compound **182** in quantitative yield. However, upon quenching the same lithiated species with methyl chloroformate (at 0°C), the dimerized compound **183** was formed as the main product, which after acidic hydrolysis (to cleave the MOM group) gave **184**. Repeated trials of this lithiation reaction with **180** where the conditions or the order of addition of the reagents were altered only resulted in more of the unwanted dimer **184**. An attempt to *o*-lithiate **180** followed by quenching with gaseous CO_2 (bubbled into the reaction mixture over 8 h) inefficiently produced the carboxylic acid **185** in a meager 34% yield. Finally, it was found that the salicylate **174** could be synthesized by rapid lithium-iodide exchange of **181** with a stoichiometric amount of *n*-BuLi at -78°C (5 min. process) followed by acylation with excess methyl chloroformate (see bottom of Scheme 3.3). Qualitative analysis of the crude reaction product by TLC showed only one major product and little or no by-products. However after removal of the protecting group by stirring in acid, the product mixture always became complex and after repeated trials, the best overall yield for the pure salicylate **174** from **181** using this

procedure was only 40% (over 3 steps). It should be noted that only one other method for preparing compound **174** was recorded in the literature by Suzuki and co-workers (in 64% yield), and it involved a Pd-catalyzed carbonylation of the bromo-analogue of phenol **173** (the conditions required $CO_{(g)}$, cat. $Pd(OAc)_2$, cat. 1,1'-bis(diphenylphosphino)-ferrocene, MeOH, DMF, *n*-Bu_3N, 100°C, 17 h).[107]

Scheme 3.4



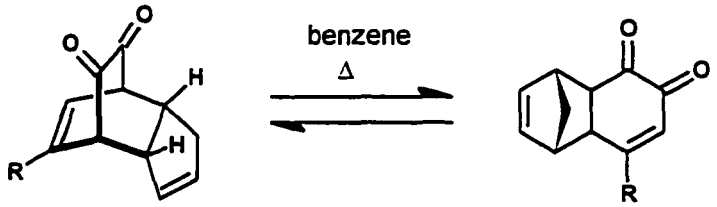
The IMDA reactions with these derivatives **173-176** gave moderate to excellent total yields of adducts **177d-g** and **178d-g** (see Table 3.1). With the exception of reactions in entries **a** and **b**, the bridged adduct was usually the major product, and the naphthofuran adduct always possessed the *endo* relative configuration, as was deduced from the signal for H-8b in their ^{1}H-NMR spectra. No *exo*-stereoadduct for the naphthofuran structure was ever observed in these IMDA reactions of *o*-benzoquinone monoketals, and this level of stereocontrol was rewarding in a synthesis of viridin, given the known resistance of the *exo*-products of this kind toward elimination of methanol from the ketal carbon.

3.2 Cope Rearrangements of the Bridged IMDA Adducts: A Gateway Toward the Synthesis of Xestoquinone, Morphine and Viridin

Inspection of the structure of the bridged products disclosed the presence of a 1,5-diene system, and therefore the conversion of the bridged structure **177** to the naphthofuran **178** by a Cope rearrangement was theoretically possible. Ansell and co-workers had studied the Cope rearrangement of the Diels-Alder adducts **186** and **187** produced from several substituted *o*-benzoquinones with cyclopentadiene (Scheme 3.5), and found that the bicyclo-adducts **186** were thermodynamically favored.[52c] Furthermore, when the rearrangements were carried out in the presence of excess maleic anhydride, no products from its reaction with cyclopentadiene were found, suggesting that the rearrangements were intramolecular and not occurring by a retro-Diels-Alder/recombination sequence. In a more recent example aimed at the synthesis of the

clerodane diterpenoids, an anionic oxy-Cope rearrangement served as the key step in the efficient conversion of several 2-vinylbicyclo[2.2.2]oct-5-en-2-ols **188** to the naphthofuran analogues **189** (Scheme 3.6).[99b-c] Hudlicky and co-workers had also reported the Cope rearrangement of a functionalized bicyclo[2.2.2]octene similar to **188** in their model studies directed at the synthesis of (-)-morphine.[101]

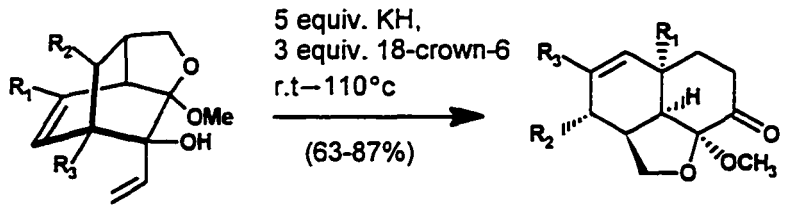
Scheme 3.5[52c]



186 **187**

R = H, Me, Ph, *t*-Bu, OMe, Cl

Scheme 3.6[99b-c]

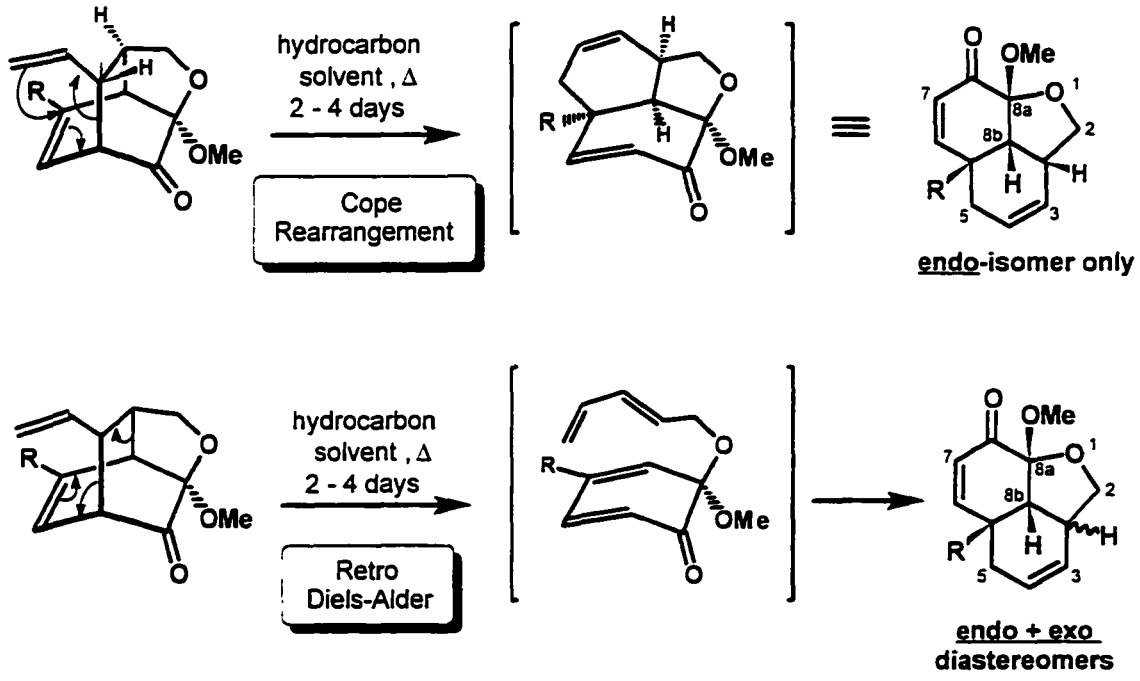


188 R_1 = H; Me; CO_2Me; R_2 = H; Me; R_3 = H; OMe **189**

Our bridged IMDA adduct **177a** was tested first for the Cope rearrangement, and after heating in redistilled toluene for 24 h, an approximate 1:1 mixture of compounds **177a** and **178a** was observed by TLC analysis. Repeating this reaction at higher temperature in boiling *p*-xylene favored the naphthofuran **178a** (21% yield) and its

demethoxylated derivative **179a** (44% yield) with 93% conversion (Scheme 3.8 and Table 3.2, entry 1). When the reaction was carried out in 1,2,4-trimethylbenzene (bp ≈168°C), the product ratio for **178a** (46% yield) and **179a** (20% yield) was essentially reversed (Table 3.2, entry 2). In both trials however, the overall yield was moderate and given the easy formation of **179a**, it seemed that heating accelerated decomposition of the naphthofuran **178a**.

Scheme 3.7



As illustrated in Scheme 3.7, the Cope rearrangement should stereospecifically produce the naphthofuran compound with *endo* relative stereochemical configurations (i.e. 2a-H, 5a-R group, 8a-OMe, and 8b-H are all *cis*-related), yet if the same conversion occurred by a retro Diels-Alder/recombination sequence, then one would expect a

mixture of *endo* and *exo* adducts. In the rearrangement with **177a**, only one isomer was isolated and its ^{1}H-NMR spectrum was identical to the *endo* IMDA product **178a** and displayed the same characteristic W-coupling between H-8b and H-5β. On the basis of spectral evidence, it was therefore concluded that the interconversion of the bridged to the naphthofuran compounds occurs by a Cope rearrangement, which is in accordance with the earlier findings of Ansell.[52c]

Naturally, the Cope rearrangement of the bridged compound **67** was contemplated next in order to furnish a sufficient quantity of the valuable 5a-methyl-naphthofuran analogue **68**. This reaction had been performed much earlier in our laboratory by heating **67** in boiling benzene, but that attempt failed.[104] Heating **67** in boiling toluene (bp ≈ 110°C) over 2 days showed no evidence of **68** by TLC analysis, while heating in boiling *p*-xylene (bp ≈ 137-138°C) caused some rearrangement to **68**. Sufficient thermal energy input was achieved by heating **67** in boiling 1,2,4-trimethylbenzene (bp ≈ 168°C) over 2 days, which furnished **68** in 81% yield and **179c** in 8% yield (95% conversion) (Table 3.2, entry 6).[102] As was observed in the reaction of **177a**, the Cope product **68** also possessed the *endo*-relative configuration by examination of its ^{1}H-NMR spectrum. Further evidence in support of this stereochemical configuration was obtained when methanol was eliminated from **68** by treatment with TFA to produce the demethoxy-analogue **179c**. The X-ray crystal structure of **179c** showed a *cis*-relationship between H-2a and the methyl group at C_{5a} (Figure 3.5). The forcing conditions required for this rearrangement, compared to the case with **177a**, was unexpected and so an indication which suggested that **67** and **68** were in equilibrium seemed appropriate. Using Gaussian 94 software to perform *ab initio* calculations[108] of the gas phase enthalpies for bridged compound **67** and naphthofuran **68**, it was found that

Scheme 3.8 [88]

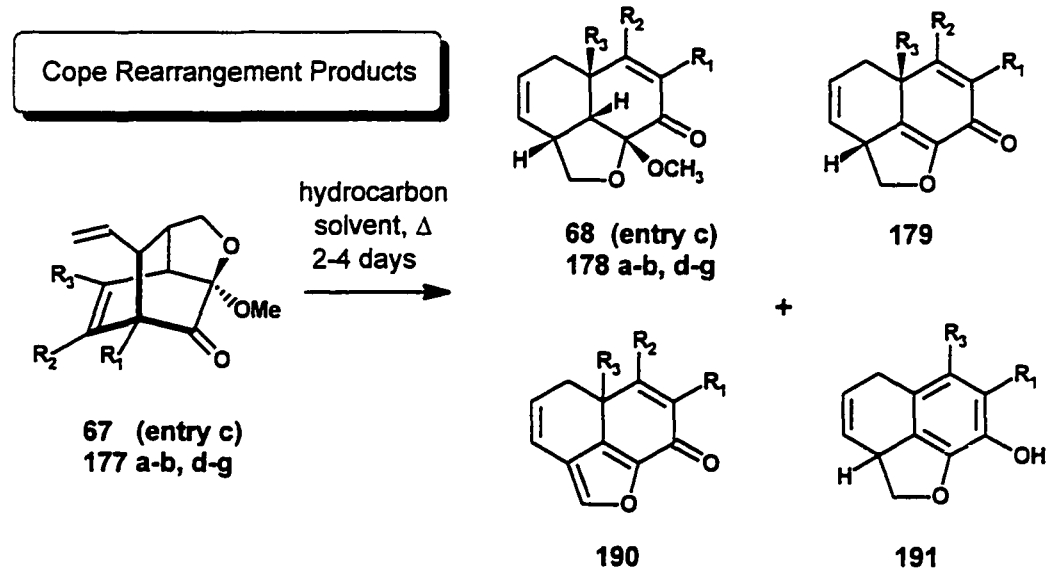


Table 3.2 : Thermal Cope rearrangements of bridged IMDA adducts in various solvents.[88]

Bridged Adduct	R_1	R_2	R_3	Entry	Solvent* (% conversion)	Cope Reaction Products (% Yields)
177a	H	H	CO_2CH_3	1	*p*-xylene (93%)	**178a** (21%)+**179a** (44%)
				2	TMB (100%)	**178a** (46%)+**179a** (20%)
177b	H	H	$COSCH_3$	3	decane (84%)	**178b** (81%)
				4	*p*-xylene (100%)	**178b** (6%)+**191b** (28%)
				5	TMB (100%)	**191b** (42%)
67	H	H	CH_3	6	TMB (95%)	**68** (81%)+**179c** (8%)
177d	I	H	CH_3	7‡	TMB (100%)	**178d** (38%)
				8‡	decane# (100%)	**190d** (50%)
				9‡	TCE# (61%)	**190d** (70%)
177e	CO_2CH_3	H	CH_3	10	TCE (100%)	**178e** (10%)+**190e** (32%)
177f	H	$COSCH_3$	CH_3	11	decane (72%)	**190f** (25%)
177g	H	CH_3	$COSCH_3$	12	decane	decomposition

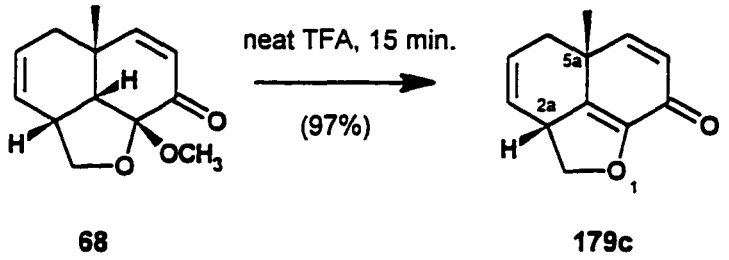
* TMB ≡ 1,2,4-trimethylbenzene; TCE ≡ 1,1,2,2-tetrachloroethane

‡ Iodine was also produced in this reaction.

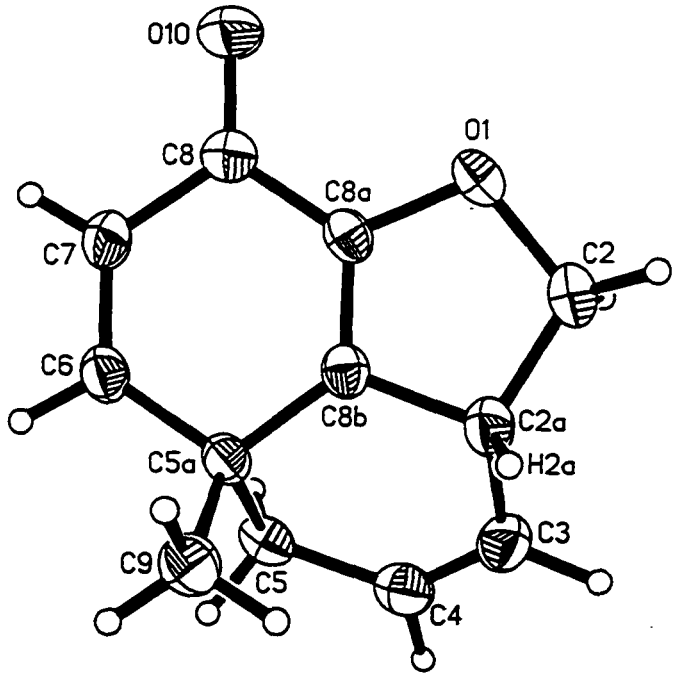
\# Some thermal rearrangements performed in decane and TCE resulted in significant decomposition.

the difference in enthalpy was very small and slightly in favor of forming **68** (ΔH = -0.19 kcal/mol), and may not be significant within the accuracy of the calculation. Therefore, in the gas phase the energies of **67** and **68** are similar enough to justify a 50:50 equilibrium of the two compounds at room temperature.[108] Presumably in the solution phase at high temperature, the entropies and interactions with the hydrocarbon solvent are significant enough to perturb the equilibrium in favor of **68**.

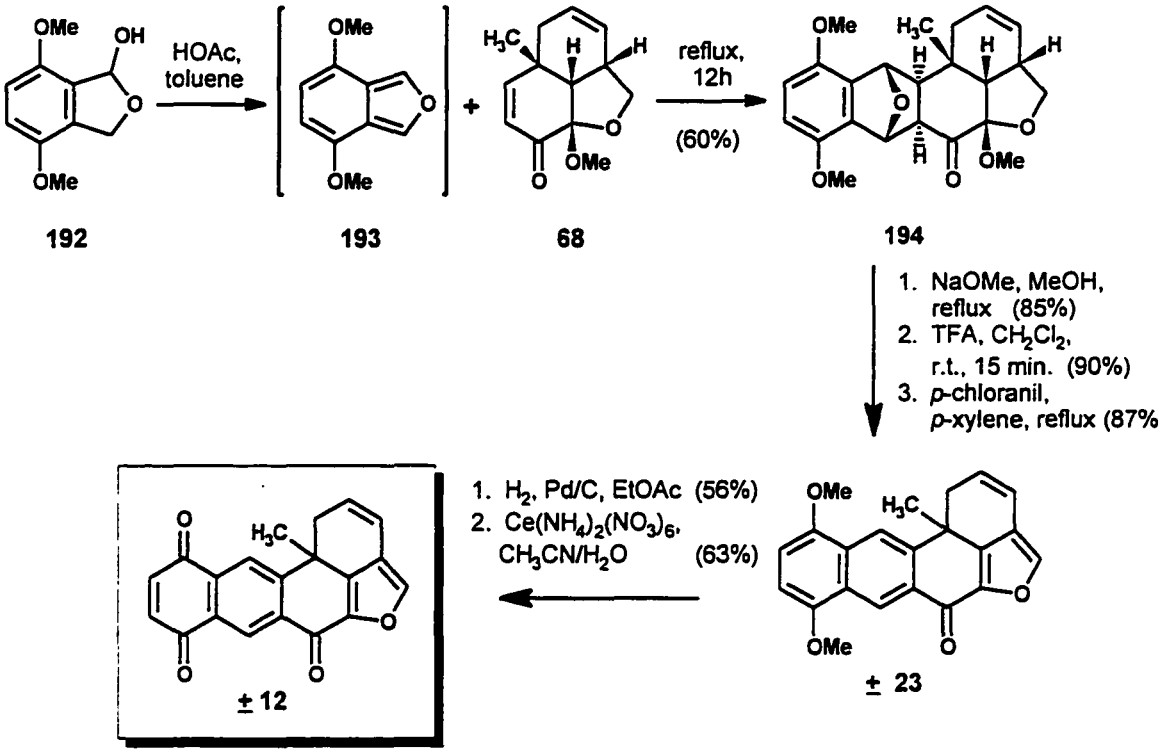
Figure 3.5: Elimination of methanol from **68** by treatment with TFA, and the molecular plot of the X-ray crystal structure of demethoxy-analogue **179c**.



68 **179c**



Scheme 3.9 [102, 109]



The successful outcome of this rearrangement was a breakthrough since the once elusive 5a-methyl-naphthofuran **68** (or its dienone analogue **179c**) was now easily prepared in 56% overall yield from commercially available 2-methoxy-4-methylphenol **64** by the two-step IMDA-Cope rearrangement sequence, undoubtedly the shortest and most efficient synthesis ever reported for this important compound.[102] With **68** in hand, plans to synthesize xestoquinone (**12**) and viridin (**1**) were charted. Xestoquinone (**12**) was the more simple target, and a rapid synthesis of this natural product was soon developed in a collaborative effort within our research group,[102, 109] which involved a face-selective *exo*-cycloaddition of the enone moiety of **68** with 4,7-dimethoxy-

isobenzofuran[110] **193** (Scheme 3.9). Racemic xestoquinone (±)-(**12**) was obtained in eight steps and 7.4% overall yield from 2-methoxy-4-methylphenol **64**.[102]

The Cope rearrangements of the remaining IMDA bridged adducts were also investigated for the purpose of generating a functionalized analogue of naphthofuran **68** which could be used for synthesizing viridin. An assortment of naphthofuran-like products which included the dienone **179**, the furanoid analogue **190** and the phenol **191**, were isolated in these studies and the results are summarized in Scheme 3.8 and Table 3.2.[88] It should be mentioned that concurrent research describing the IMDA and subsequent Cope reactions of the substituted guaiacols **64-66** was reported by Hsiu and Liao[111] shortly after our work in this area was first published. The rearrangement of bridged thiol ester **177b** in decane gave **178b** in good yield (81%) (Table 3.2, entry 3), but when the reaction was carried out in aromatic hydrocarbon solvents like *p*-xylene or 1,2,4-trimethylbenzene (entries 4-5), the phenol product **191b** was produced (in low yield), presumably from a dienone-phenol rearrangement of intermediate **179b** which had formed by elimination of methanol from the actual Cope product **178b**. The yield of **191b** increased when the reaction was conducted at a higher temperature in boiling 1,2,4-trimethylbenzene (42%). (In our studies of dienone-phenol rearrangements of intermolecular Diels-Alder adducts described earlier in section 2.3, the migratory aptitudes of the angular substituents of 2,5-cyclohexadienones were observed to follow the order: $CHO > COCH_3 > COSCH_3 > CO_2CH_3$.[92])

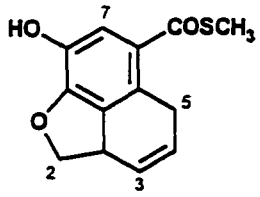
The rearrangement of bridged ester **177e** was also tried in order to furnish the naphthofuran **178e** for application in a convergent synthesis of viridin, where the ester group at R_1 could serve as a handle for coupling to a suitable D-ring component (the strategies underlying this effort will be discussed in more detail later). However after

several attempts performed in various solvents, the reaction was often unsuccessful since **177e** seemed to decompose easily with elevated temperatures. The best result in this case was obtained by heating in 1,1,2,2-tetrachloroethane (bp ≈146°C) which gave **178e** in 10% yield and **190e** in 32% yield (Table 3.2, entry 10), along with many unidentified decomposition products. The idea of preparing **178e** by lithium-iodide exchange of an α-iodoenone such as **178d**, followed by quenching with methyl chloroformate, was then contemplated. As a result, the Cope rearrangement of **177d** was carried out in 1,2,4-trimethylbenzene (Table 3.2, entry 7), which only produced a small quantity of **178d** (38%) and copious amounts of iodine. Upon switching to the non-aromatic solvents decane (bp ≈189°C) and 1,1,2,2-tetrachloroethane (Table 3.2, entries 8-9), reasonable quantities of the furanoid products **190d** were generated (50% and 70% yields, respectively). (The attempted conversion of these iodoenones **178d** and **190d** to the enone esters **178e** and **190e** for synthesizing viridin will be highlighted shortly.) Finally, the last two examples for this study of the Cope rearrangement were carried out with bridged adducts **177f-g** (Table 3.2, entries 11-12). Compound **177f** could only be converted to **190f** in 25% yield with 72% conversion by heating in refluxing decane (bp ≈189°C); unreacted starting material was also recovered. Heating the isomeric bridged thiol ester **177g** in boiling decane only led to complete decomposition, while heating in lower-boiling solvents caused no reaction at all. Although the reactions with some of the bridged adducts were experimentally unsatisfactory, the Cope rearrangement of the bridged structure **177** appeared to be general and furnished a significant quantity of the naphthofuran analogues **178**, **179**, or **190-191** in most cases.[88] Consequently, the synthetic utility of the tandem IMDA-Cope reaction sequence which was proven earlier

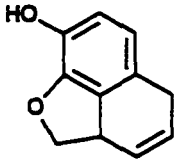
in the rapid and efficient synthesis of xestoquinone (**12**), would also be tested in the forthcoming synthetic investigations of other related natural products.

The phenolic compound **191b**, described earlier as having resulted from elimination and dienone-phenol rearrangement of the actual Cope product **178b**, was noted for its structural similarity to three of the rings in morphine **196** (Scheme 3.10) As part of a model study directed at the synthesis of morphine, the preparation of the tricyclic phenol **195**, a derivative of **191b**, was undertaken. The oxidation-IMDA reaction with 4-hydroxy-3-methoxybenzoic acid in the presence of excess (*E*)-2,4-pentadienol was first proposed for this task (Scheme 3.11), where it was thought that the intermediate γ-keto acid **197**, would spontaneously decarboxylate in the reaction medium and directly furnish **195** (Scheme 3.11) Unfortunately, two attempts of this reaction failed to give any recognizable cycloadducts.

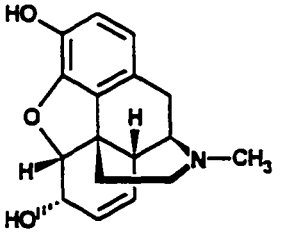
Scheme 3.10



191b

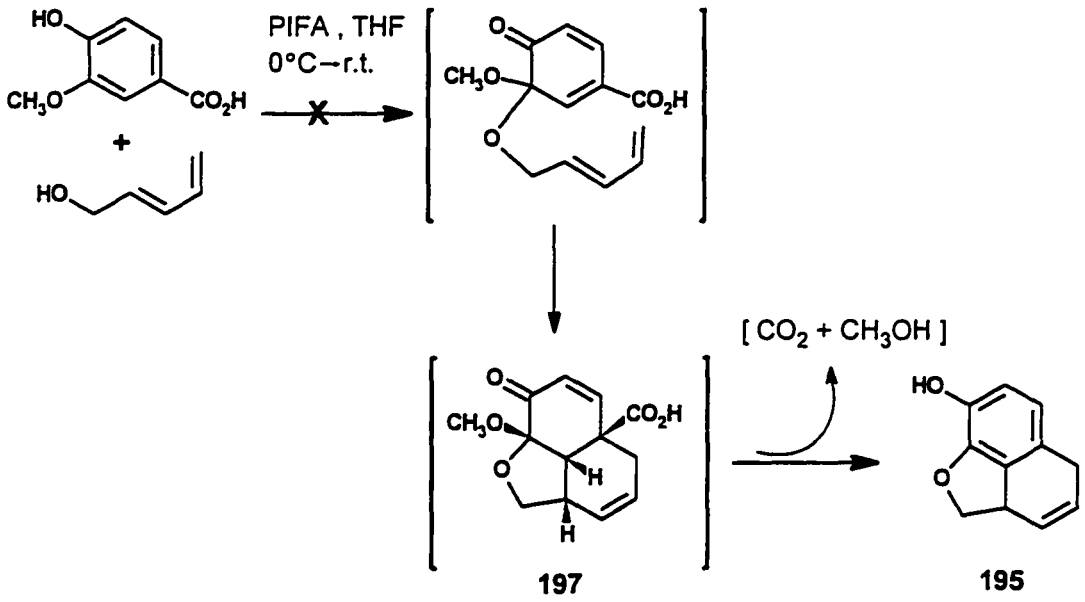


195



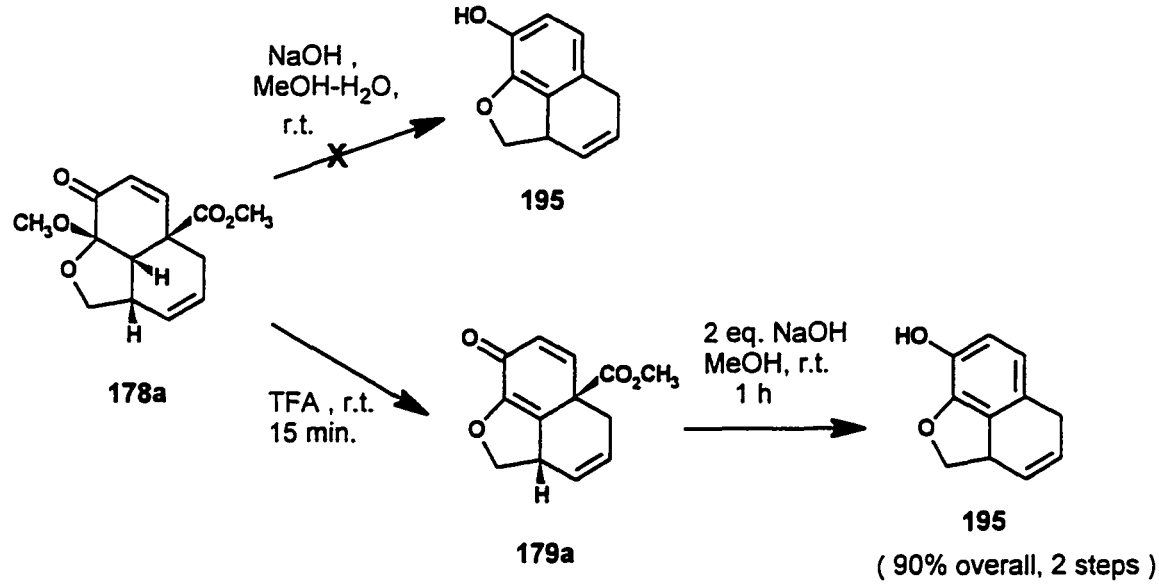
196
(-) Morphine

Scheme 3.11

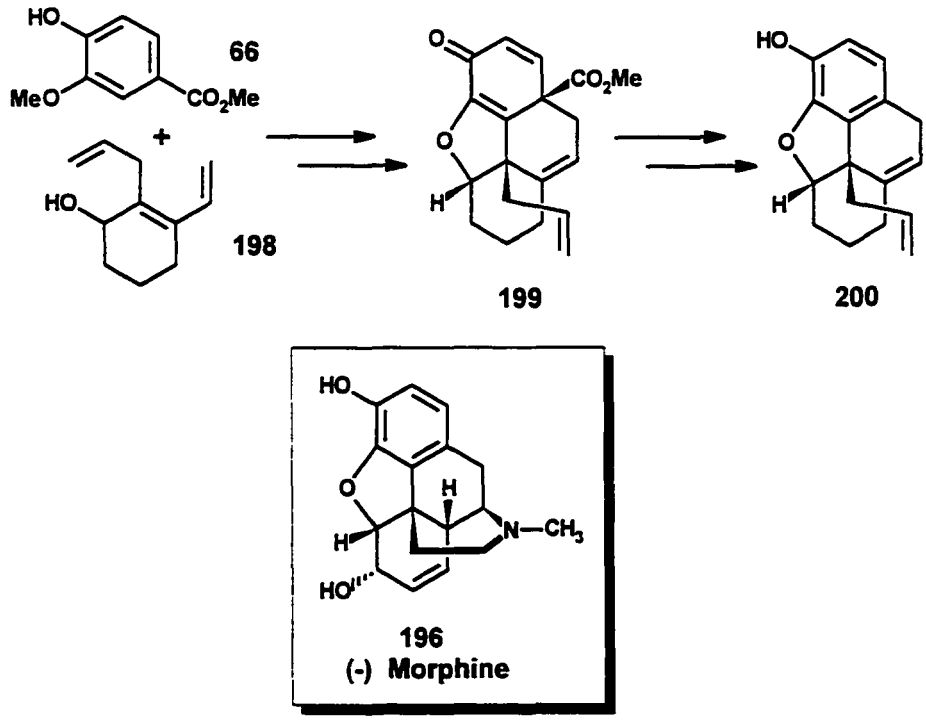


Attention was next turned toward utilizing the naphthofuran ester **178a**, synthesized earlier from the IMDA reaction with **66** (*cf.* Scheme 3.2), which was hydrolyzed with sodium hydroxide, but each attempt of this reaction only resulted in a complex mixture of products none of which resembled **195** (Scheme 3.12). Success arrived when methanol was eliminated from **178a** in neat TFA (room temperature, 15 min.) to provide dienone **179a** which following hydrolysis with base, produced **195** in excellent overall yield (90%, 2 steps). It was therefore concluded from this model study that the general phenolic derivative **195** could be prepared by the basic hydrolysis of the general dienone derivative **179** obtained by acid-catalyzed elimination of methanol from the naphthofuran **178**. The versatility of this synthetic method was exemplified in a creative synthesis of the phenanthrofuran **200** (Scheme 3.13) developed by a co-worker in our research group for a prospective enantioselective synthesis of (-)-morphine.[88, 109]

Scheme 3.12



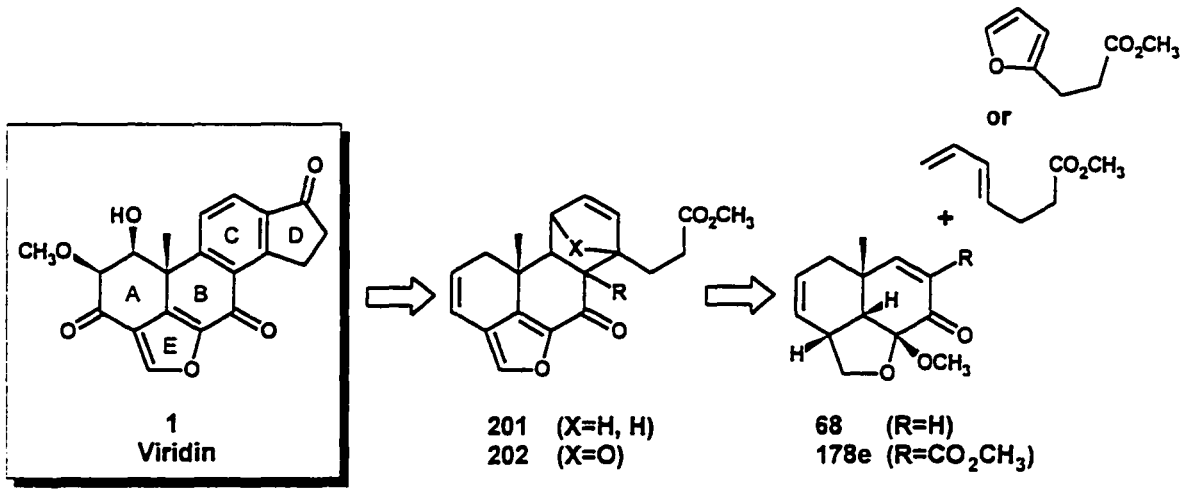
Scheme 3.13 [88, 109]



3.3 Strategies Directed at a Convergent Synthesis of Viridin

3.3.1 Diels-Alder Cycloaddition Methods

Scheme 3.14



A sizable quantity of the tricyclic compound **68** was now attainable by the tandem IMDA-Cope reaction sequence, and following the strategy employed earlier for the synthesis of xestoquinone (**12**), a convergent approach for synthesizing viridin was designed with an intermolecular Diels-Alder coupling in mind (Scheme 3.14). Two different naphthofurans **68** (R= H) and **178e** (R= CO_2CH_3) were proposed as the dienophile in a [4+2] cycloaddition with a suitable diene. Using either methyl (*E*)-4,6-heptadienoate or methyl 3-(2-furyl)propanoate as the diene, the reaction would either furnish the adduct **201** (X=H, H) or **202** (X=O), respectively. Although unactivated, both these dienes are easily prepared in one step from commercially available starting materials. (The diene 2-vinyl-2-cyclopenten-1-one, a logical choice for annulation with

68, was not considered for the various reasons mentioned earlier (see section 2.2.1) which include difficulty in preparation, instability toward polymerization, and possible dual reactivity as diene and dienophile in cycloaddition reactions.) Lewis acid catalysis of these reactions was a definite consideration, given the known sluggish reactivity of cycloalkenones in Diels-Alder reactions with simple unactivated dienes.[112,113] Compound **178e** was a suitable choice for a dienophile since it possessed an additional ester group on α-carbon of the enone. If the reaction with **68** were to be unsuccessful, then **178e** could be used in order to amplify the dienophilicity of the enone double bond and promote the Diels-Alder reaction. Furthermore, the ester group could later be removed by hydrolysis since the resultant cycloadduct **201** ($R=CO_2CH_3$) would be a β-ketoester. Liu and co-workers have successfully adapted 'doubly-activated' cycloalkenone-α-esters as dienophiles with unreactive dienes in numerous examples of Lewis acid-catalyzed Diels-Alder reactions.[114]

The naphthofurans **68**, **179c**, and **190c** were first studied for reaction with methyl (*E*)-4,6-heptadienoate, a diene which was already available in a large quantity. Scheme 3.15 and Table 3.3 summarizes the attempted Diels-Alder reactions under a variety of conditions. When dienophile **68** was heated at reflux in 1,2,4-trimethylbenzene (bp ≈ 168°C) for up to 24 h, no reaction occurred (Table 3.3, entry 1). With the addition of 25 mol-% $ZnCl_2$, no reaction with **68** was noted until the mixture was warmed to 50°C, where shortly after, the dienone **179c** was formed in an estimated 75% yield (entry 2). A solution of **68** in dry CH_2Cl_2 was subsequently mixed in the presence of 10 mol-% $AlCl_3$ at room temperature and after 4 days, a complex mixture resulted which included the products **179c** (29%), **190c** (8%) and the new interesting cycloadduct **203** (7%). The key ^{1}H-NMR spectral evidence which supported the structure proposed for **203** was the

Scheme 3.15

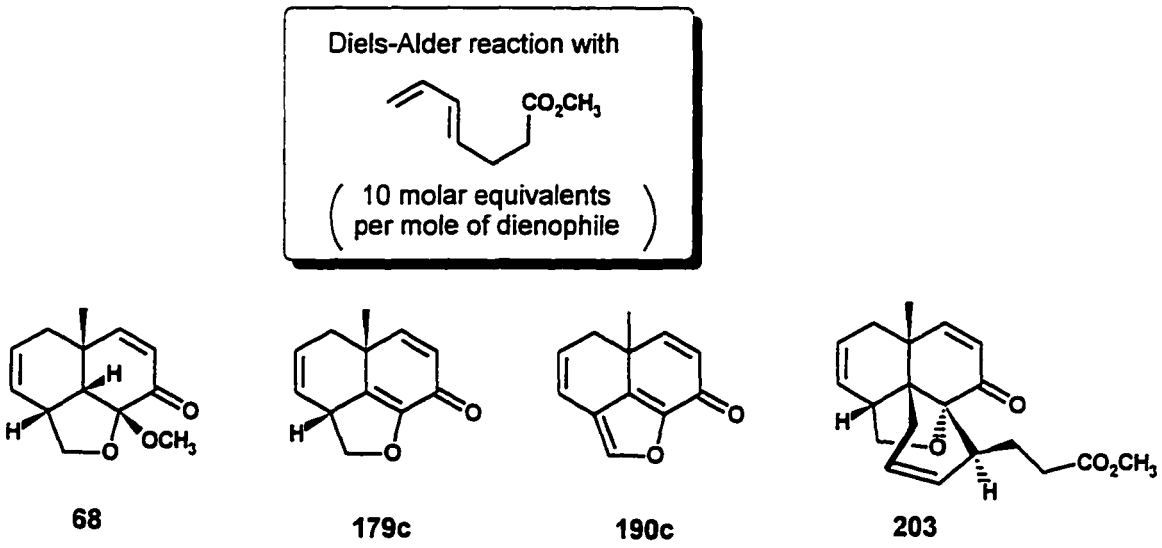


Table 3.3: Results of Diels-Alder reactions between methyl (*E*)-4,6-heptadienoate and the dienophiles **68**, **179c**, and **190c**.

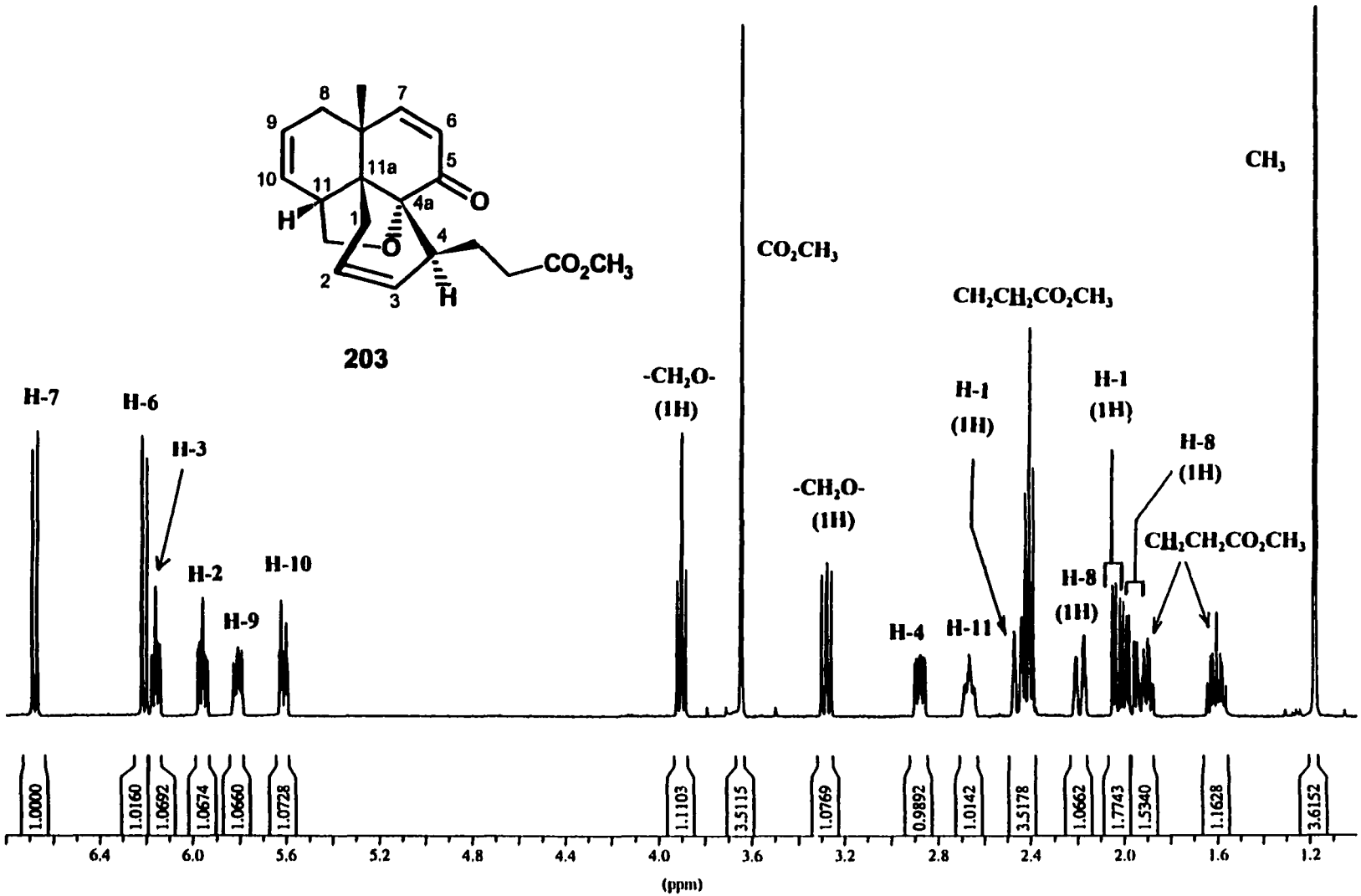
Entry	Dienophile	Reaction Conditions	Products (%-yield)
1	**68**	1,2,4-TMB*, heat, 24 h	No Reaction
2	**68**	25 mol-% $ZnCl_2$, 1,2,4-TMB, 50°C, 0.5 h	**179c** (≈75%)
3	**68**	10 mol-% $AlCl_3$, CH_2Cl_2, r.t., 4 days	**179c** (29%), **190c** (8%), **203** (7%)
4	**68**	10 mol-% $ZnCl_2$, CH_2Cl_2, r.t., 10 days	**179c**, **203**, unreacted **68**
5	**68**	ultrasonication, 40°C, 24 h	**179c** (≈20%), unreacted **68**
6	**68**	 Na_2CO_3, H_2O, 80°C, 36 h	No Reaction
7	**179c**	10 mol-% $AlCl_3$, CH_2Cl_2, r.t.	**203** and complex mixture
8	**179c**	ultrasonication, 24 h, 40°C	**190c** (≤10%), unreacted **179c**
9	**190c**	ultrasonication, 24 h, 40°C	No Reaction
10	**190c**	5M $LiClO_4$, ether, r.t., 10 h	Decomposition

* TMB ≡ 1,2,4-trimethylbenzene

presence of two downfield doublets (6.2 and 6.8 ppm) indicative of the enone protons, as well as four other signals (1H each) for the remaining alkene protons and a new singlet at 3.66 ppm for the methoxyl group (Figure 3.6). Confirmation of the novel ring system in **203** was ultimately obtained from its X-ray crystal structure, which depicted the new cyclohexene ring adopting a slight 'boat' conformation (Figure 3.7). The formation of **203** presumably arose from dienone **179c** which had formed in this reaction, where chelation of the Lewis acid to both the interior enone moiety and furan oxygen of **179c** must have promoted elimination and subsequent cycloaddition at this site. In another attempt of a Lewis acid-catalyzed reaction, a solution of **68** in CH_2Cl_2 was mixed with 10 mol-% $ZnCl_2$ at room temperature, but after 10 days, the product mixture mostly contained unreacted starting material along with small quantities of **179c** and **203** (Table 3.3, entry 4). The catalyzed reaction with dienone **179c** and 10 mol-% $AlCl_3$ at room temperature also furnished **203** among several other unidentified products (Table 3.3, entry 7). It was therefore concluded that Lewis acid-catalyzed cycloaddition with **68** would always produce cycloadduct **203** arising from the dienone analogue **179c**.

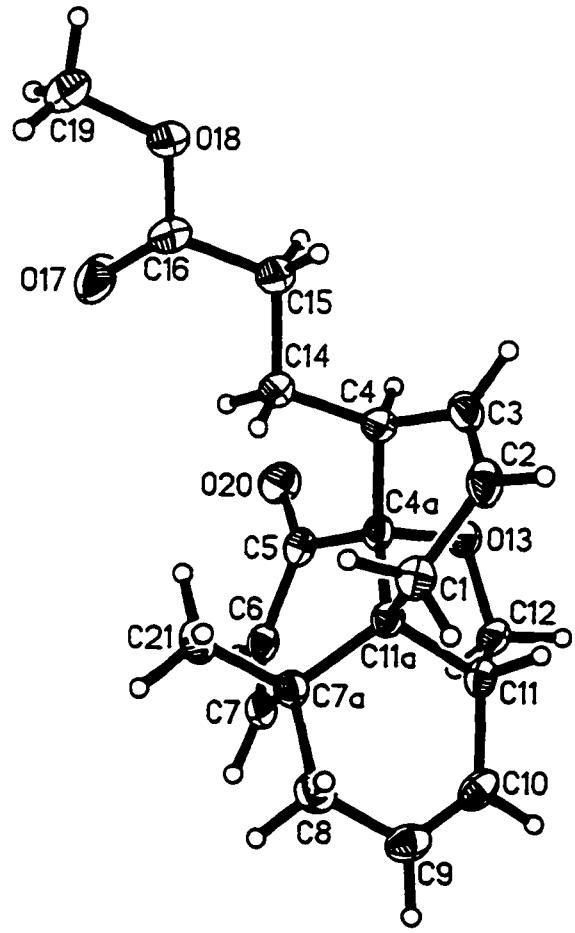
Ultrasonication was a method successfully used by Snyder and co-workers to promote Diels-Alder reactions with unreactive dienes.[47] A mixture of **68** in a 10-fold excess of neat methyl (*E*)-4,6-heptadienoate was subjected to ultrasonication at 40°C (temperature of the water bath), however after a period of 24 h, a small amount of **179c** (estimated at ≈20%) was observed by qualitative TLC analysis along with unreacted starting material (entry 5). Interestingly, ultrasonication of **179c** with excess diene over a period of 24 h produced a small amount of furan **190c** (estimated ≤10% by TLC analysis; entry 8). The same reaction was repeated with **190c**, which was synthesized for this purpose by dehydrogenation of **179c** with *p*-chloranil in boiling *p*-xylene (87% yield);

Figure 3.6: ^{1}H-NMR spectrum (500 MHz) of cycloadduct **203**.



however no reaction was observed after 24 h (entry 9). A trial reaction in aqueous media was attempted with **68**, an idea which had been developed by Grieco and co-workers for promoting Diels-Alder reactions with unactivated dienes and/or dienophiles.[59a] Methyl (*E*)4,6-heptadienoate was first hydrolyzed with sodium hydroxide in aqueous methanol, giving (*E*)-4,6-heptadienoic acid in 91% yield which was then mixed with Na_2CO_3 and **68** in water, and heated at 80°C for 36 h (entry 6). Unfortunately, no reaction was observed by TLC analysis of the reaction mixture.

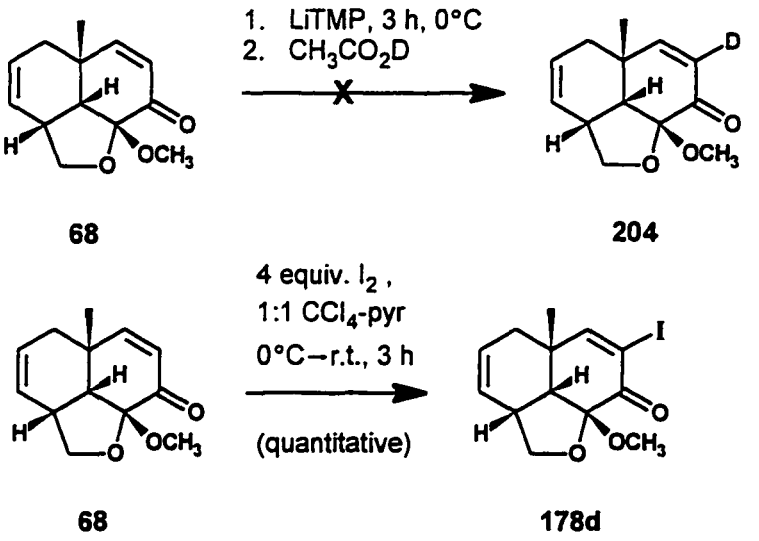
Figure 3.7: Molecular plot of the X-ray crystal structure of cycloadduct **203**.



Although **203** was not the desired Diels-Alder adduct, its formation indicated that cycloaddition could take precedence over processes which decomposed the naphthofuran dienophile; however a strategy would be needed which discouraged the Diels-Alder reaction with the interior enone moiety. To this end, the furanoid dienophile **190c** was considered for a cycloaddition with methyl (*E*)-4,6-heptadienoate conducted in the polar ionic medium of 5M $LiClO_4$ in anhydrous ether at room temperature (entry 10), conditions which were developed by Grieco and co-workers for promoting cycloadditions in unconventional solvents.[59b] Unfortunately, after several hours, a complex mixture of decomposition products resulted, possibly from Lewis acid-catalyzed ring-opening of the furan, since the ^{1}H-NMR analysis of two major products isolated from this mixture neither displayed the singlet for the furan proton (7.5 ppm) nor the singlet for the 5a-methyl group (1.3 ppm).

Due to these failures, the Diels-Alder reaction with the doubly activated dienophile **178e** was planned next, according to Scheme 3.14. One disadvantage in this plan was that the yield of **178e** from either the IMDA reaction or the Cope rearrangement of **177e** was inadequate, making it difficult to obtain a sufficient quantity of this compound for testing. An attempt to lithiate **68** at the α-enone carbon was made using the hindered base lithium 2,2,6,6-tetramethylpiperidide (LiTMP), but after quenching the mixture with deuterated acetic acid (CH_3CO_2D), only decomposition was observed (Scheme 3.16). As a consequence, the idea of generating large quantities of **178e** by lithium-iodide exchange of the α-iodoenone **178d** and subsequent acylation with methyl chloroformate was pursued. Fortunately, an improved synthesis of **178d** was soon accomplished by adapting a recent procedure for the efficient α-iodination of cycloalkenones.[115] A solution of I_2 (4-fold excess) in 1:1 pyridine-carbon tetrachloride

Scheme 3.16



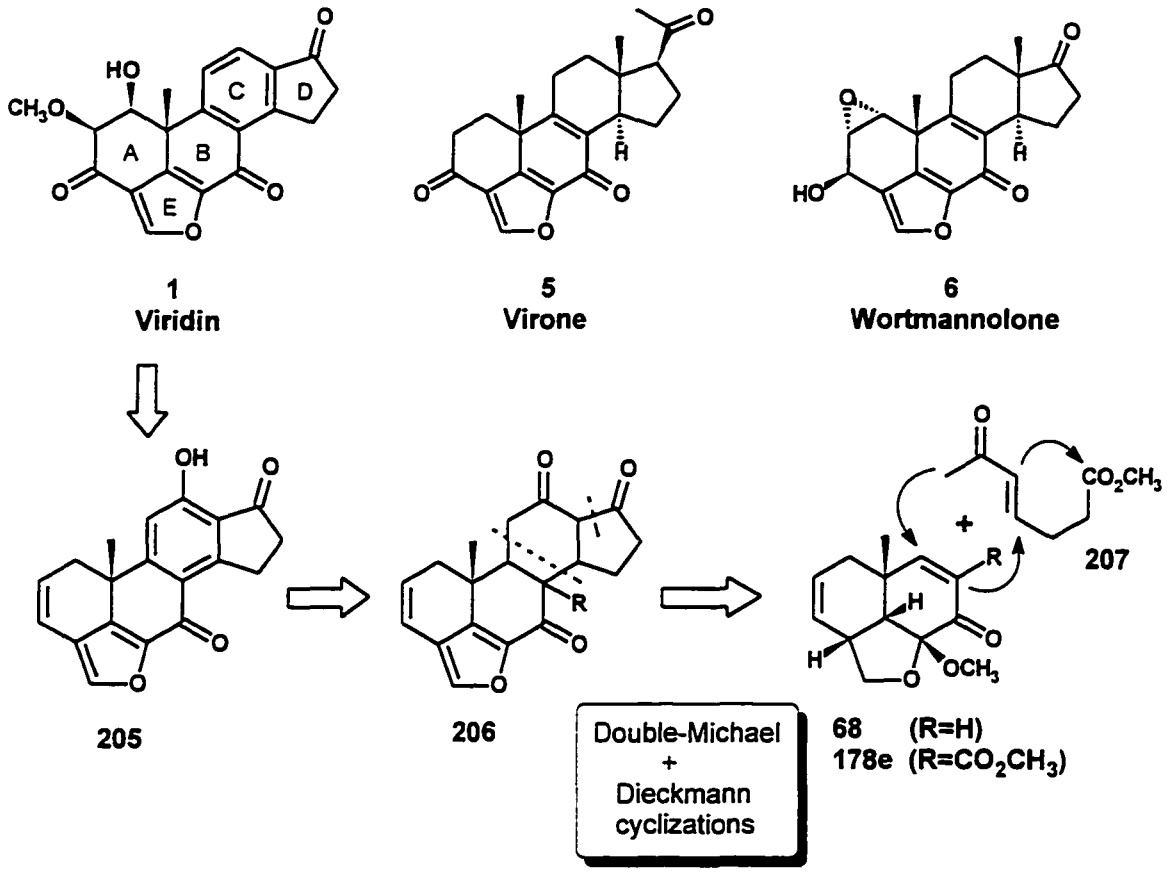
was added dropwise to a cooled solution (0°C) of **68** in the same solvent system, whereby the iodoenone **178d** was produced in quantitative yield (Scheme 3.16). However, the subsequent trials of lithiating **178d** and quenching with an electrophile generated mixed results. Treatment of **178d** with a slight excess of *n*-BuLi at -78°C for 10 min., followed with the addition of excess methyl chloroformate returned most of the starting material (95%) and a small quantity of the protonated naphthofuran **68** (5%) (product ratios were estimated from the ^{1}H-NMR spectrum of the mixture). In order to assess whether or not lithiation had actually occurred, the reaction was repeated with *n*-butyllithium for 1 h (at -78°C) prior to quenching with D_2O, but once again only unreacted starting material was recovered. Lithiation of **178d** was also attempted with 2.2 equiv. of *t*-BuLi at -95°C,[116] but after quenching with deuterated acetic acid, gave an approximate 1:1 mixture of the deuterated product **204** and unexchanged starting material. Since a sufficient quantity of **178e** was not easily made available, the proposed Diels-Alder cycloaddition could not be performed at this time, and instead will be considered in future investigations. With the

difficulties encountered in generating appropriate components and reaction conditions for a successful Diels-Alder coupling, our attention was diverted toward other annulation methods, including the Michael addition.

3.3.2 The Tandem Double Michael-Dieckmann Cyclization Strategy

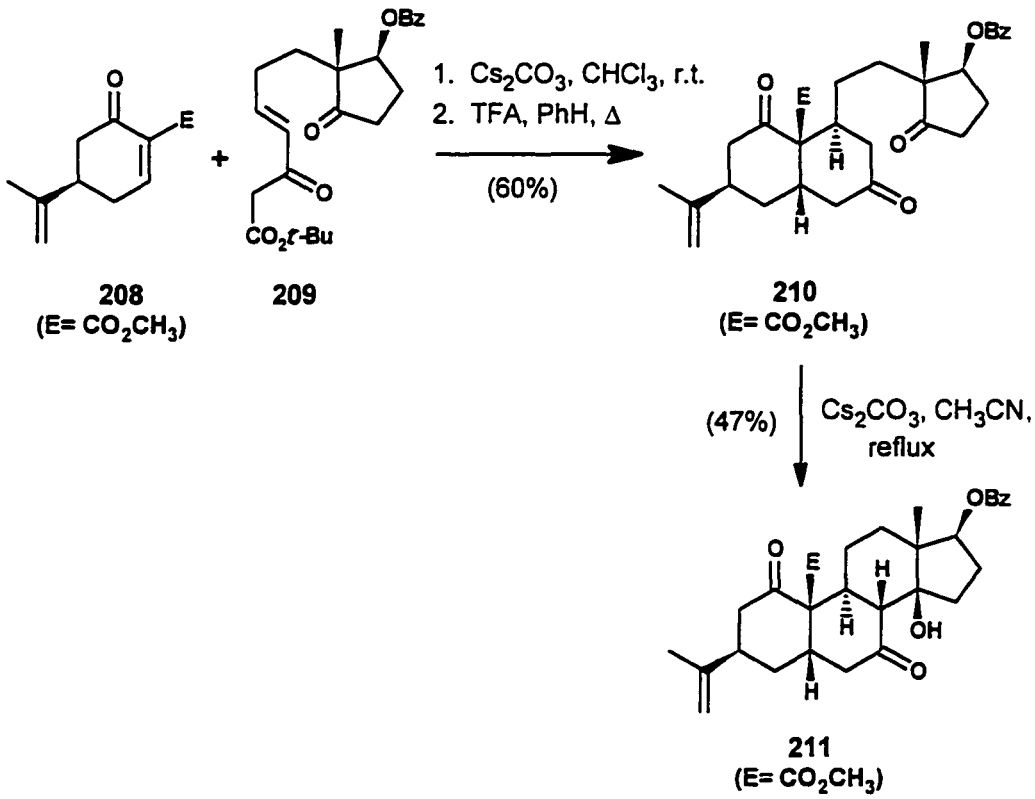
In a new strategy which strayed from cycloaddition methods, the enone system of naphthofuran **68** (or **178e**) was also viewed as a Michael acceptor for addition by the Michael donor generated from **207**, as shown in the retrosynthetic plan in Scheme 3.17. This new tandem strategy would therefore incorporate two sequential Michael additions in order to construct ring C of viridin, and a subsequent Dieckmann cyclization which would formulate ring D. The additional carbonyl group in ring C of **206** could be deoxygenated by an approach which would involve aromatizing rings C and E first, then deoxygenating the resulting phenol **205** perhaps by conversion to an aryl triflate followed by a Pd(0)-catalyzed reduction (e.g. $Pd(PPh_3)_4$) with tri-*n*-butylstannane.[117] An attractive feature of this versatile annulation strategy is its capability for constructing the skeletal systems of the related natural products virone (**5**) and wortmannolone (**6**). Both of these compounds possess an angular methyl group at the C-D ring junction, which could potentially be installed by an additional α-alkylation step with methyl iodide following the tandem reaction sequence.

Scheme 3.17



Numerous accounts exist in the literature describing tandem anionic additions for elaborating carbocyclic skeletons of natural products, often with a high degree of stereocontrol.[118-123] An illustrative and creative example of this strategy (Scheme 3.18) was developed by Deslongchamps and co-workers in synthesizing the 14-hydroxysteroid **211** by a cesium carbonate catalyzed double Michael addition of donor **209** with the activated acceptor **208**, followed with a stereocontrolled intramolecular Aldol condensation of **210**.[120a]

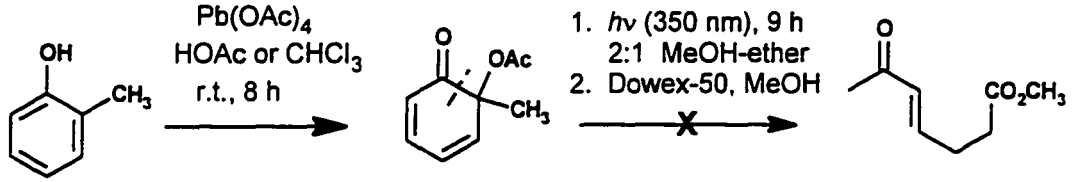
Scheme 3.18 [120a]



208 (E= CO_2CH_3) **209** **210** (E= CO_2CH_3) **211** (E= CO_2CH_3)

Although many refinements of the general synthetic plan depicted in Scheme 3.17 can be made, our efforts were initially focused on preparing the Michael donor **207** in an effective manner, and two different procedures were undertaken for this task.[124] The first procedure involved an initial Wessely oxidation of *o*-cresol [40a, 125] followed with photolytic cleavage using ultraviolet light (Scheme 3.19).[126] Although every attempt of the Wessely oxidation of *o*-cresol produced copious amounts of polymeric material, the literature did report that a maximum yield of 29% can be obtained for **212**. Repeated trials of this reaction were conducted in glacial acetic acid and chloroform as the solvent,

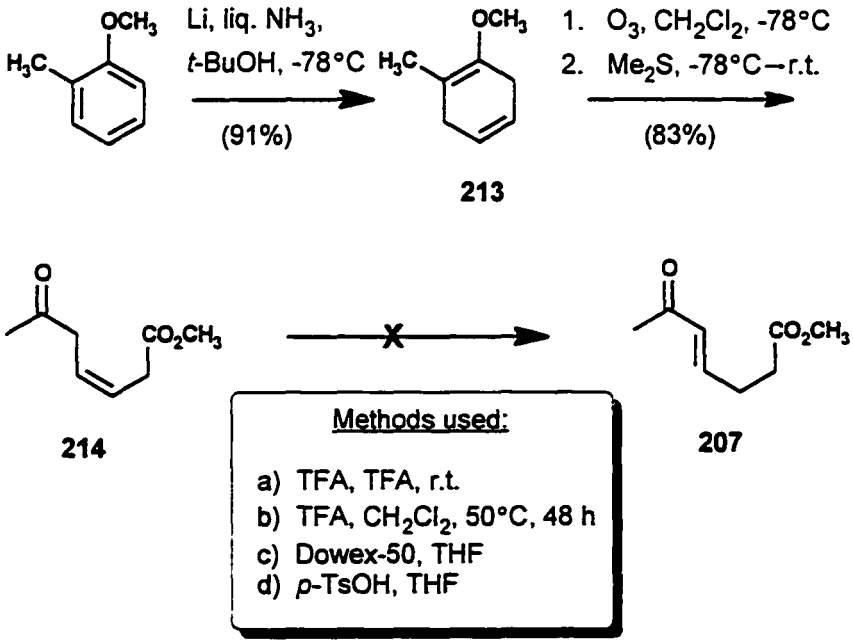
Scheme 3.19



212 **207**

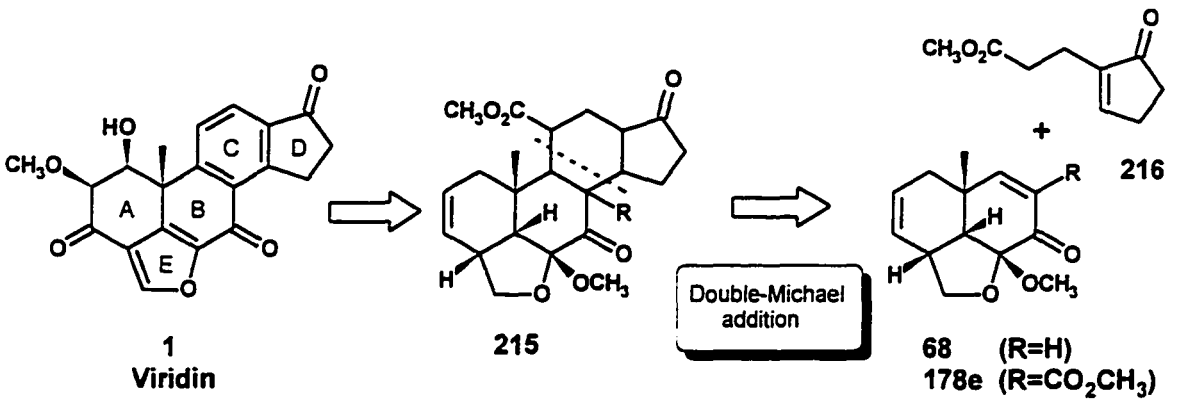
yet the best yield ever obtained for **212** (isolated among two other isomeric quinol acetates) was only 10%. With this small quantity of **212** in hand, the photolysis reaction was attempted using a 350 nm-source of ultraviolet light. After a period of 9 h, only a small portion of **212** was converted to a new product, which could not be positively identified as **207** (or its derivative). Since this synthetic approach was generally unsuccessful, the procedures shown in Scheme 3.20 were quickly adopted.

Scheme 3.20



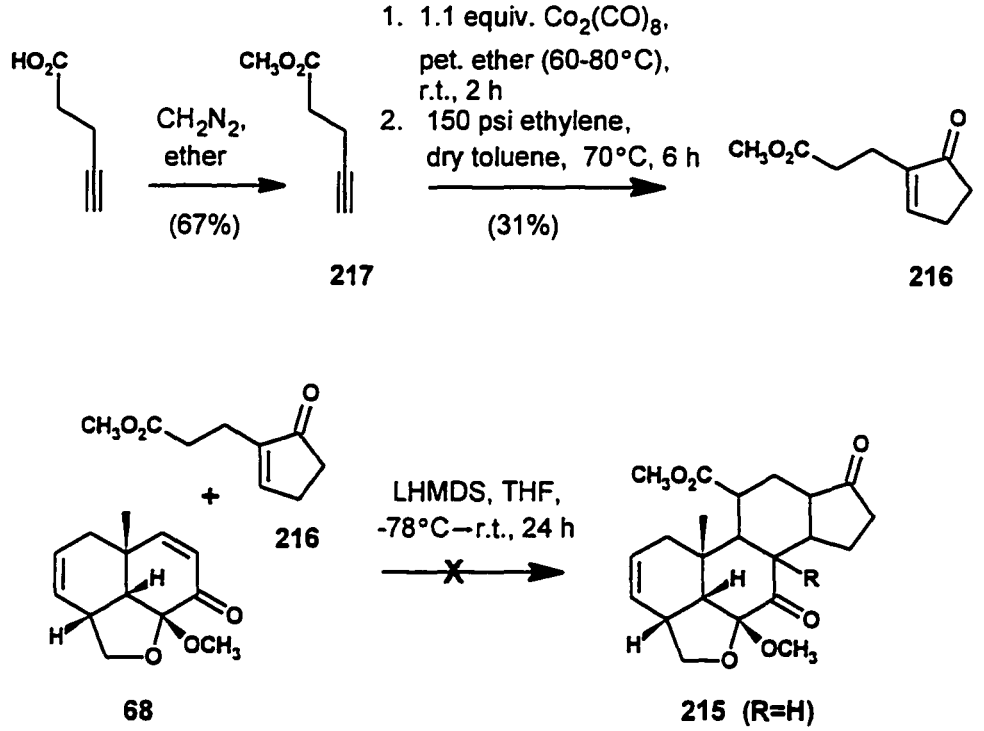
The Birch reduction of 2-methylanisole[127] was temperamental at first, but after several trials it was found that dropwise addition of a mixture of 2-methylanisole and *t*-butanol (as the proton source) in dry THF to the blue-black solution of lithium wire (4-fold excess) dissolved in liquid ammonia (condensed from the gaseous form) formed **213** in an excellent and reproducible yield (91%), and this represents the most efficient preparation of this compound ever recorded (Scheme 3.20). The selective ozonolysis of **213** which followed was not as straightforward, due to the presence of two potential sites for cleavage. Although Stork reported that this selective ozonolysis was performed in 1:1 MeOH-THF at -78°C,[124] these conditions always resulted in over-oxidation and gave a mixture of 3- and 4-carbon dimethyl acetals. Consequently, a calibrated amount of ozone was delivered to a solution of **213** in anhydrous CH_2Cl_2 at -78°C, and following reductive work-up with dimethyl sulfide,[128] produced an acyclic ester in 83% yield which resembled **214** by ^{1}H-NMR spectral analysis. This crude compound **214** was then subjected to the double-bond isomerization using a variety of mildly acidic conditions (Scheme 3.20). Unfortunately, reagents such as TFA, *p*-TsOH and Dowex-50 resin when used at room temperature, caused no conversion at all, and heating **214** with a catalytic amount of either TFA or Dowex-50 gave decomposition products whose ^{1}H-NMR spectra lacked signals for a methyl ester and sometimes the alkene protons as well. Clearly with the level of functionalization present in **214**, the susceptibility toward inter- or intramolecular cyclization is enormous, so that the formation of **207** by this method would demand special reaction and isolation conditions.

Scheme 3.21



As time was an important consideration at this stage, a new donor component **216** was proposed for annulating with the acceptor **68** (or **178e**), as shown in Scheme 3.21. In previous work directed at the synthesis of estrone methyl ether developed in our laboratory,[129] a rapid synthesis of the cyclopentenone ester **216** was developed using the Pauson-Khand reaction[130] (Scheme 3.22). 4-Pentynoic acid was converted to its methyl ester **217** with diazomethane (Scheme 3.22), which was then stirred with cobalt octacarbonyl in petroleum ether (60-80°C) to form a cobalt-containing complex of **217**. The filtrate from this reaction was concentrated, redissolved in anhydrous toluene and heated at 70°C in a Monel stainless steel reactor which was pressurized up to 150 psi with ethylene. After tedious purification procedures, the pure cyclopentenone ester **216** was usually obtained in the vicinity of 30% yield. Compound **216** was then treated with a stoichiometric amount of lithium hexamethyldisilazide (LHMDS) at -78°C, followed shortly afterward by the slow addition of naphthofuran **68** (in dry THF). Unfortunately, this attempt of the double Michael addition strategy failed to provide any evidence of **215**, and only returned unreacted starting materials along with a small quantity of a product which resembled a dimer of the cyclopentenone ester **216**. Due to lack of time,

Scheme 3.22



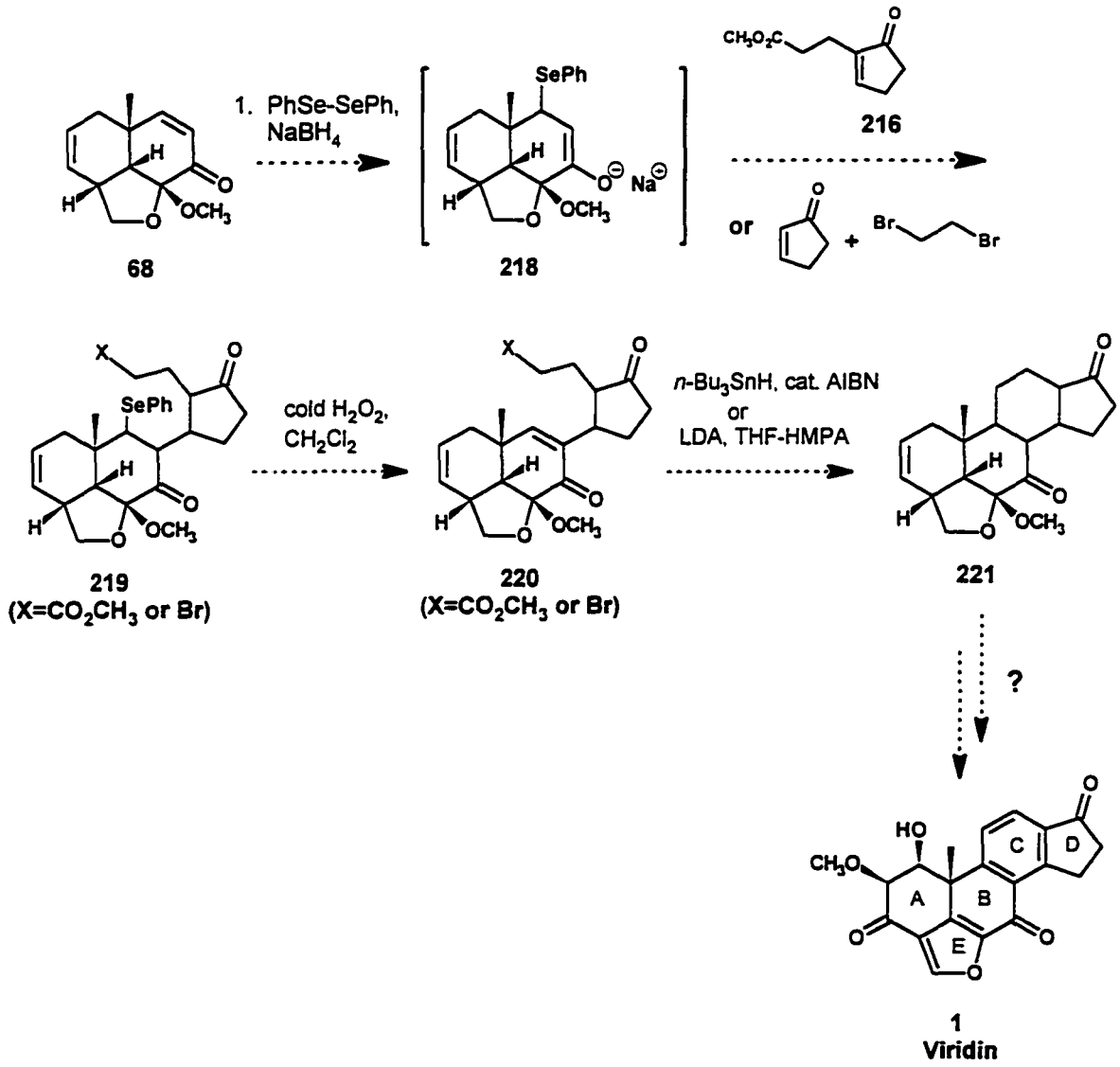
no further work could be performed on developing the double Michael strategy; however, when the condensation in Scheme 3.22 was recently repeated (by a co-worker) using 2.2 equiv. of lithium diisopropylamide (LDA) at -78°C, the reaction failed altogether, having only decomposed **68**.[131] Potential success might be met if the naphthofuran **178e** were to be used, as its double activation of the enone system may render it more susceptible for conjugate attack. However, an efficient method to prepare **178e** needs to be developed first. Nonetheless, the cyclopentenone ester **216** is an important and useful intermediate in manipulating the tandem anionic annulation strategy of Scheme 3.21 toward a prospective first synthesis of viridin (**1**) and also of its biologically active congeners, virone (**5**) and wortmannonlone (**6**).

3.4 Future Considerations for a Convergent Synthesis of Viridin

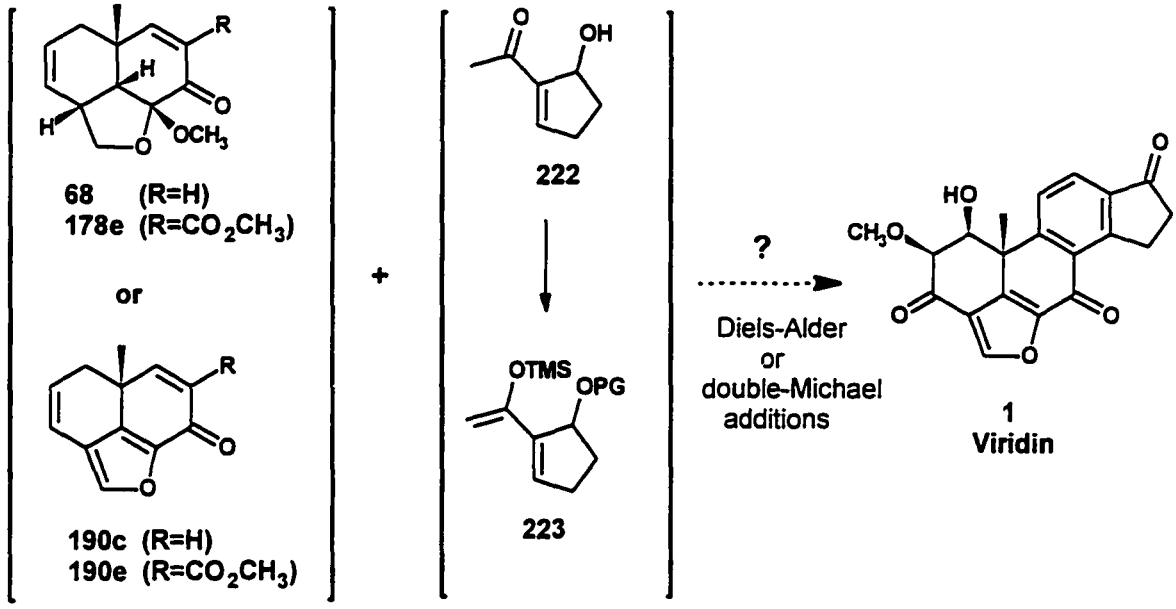
There are many constructive modifications which one can apply to the general convergent strategies outlined in Schemes 3.14 and 3.21. Due to the lack of opportunity, some of these could not be attempted in practice, however they remain sound synthetic proposals nonetheless. The α-iodonaphthofuran **178d**, which was efficiently and rapidly prepared in three steps from 2-methoxy-4-methylphenol **64** in about 55% overall yield, is a particularly useful synthetic intermediate since a variety of methods exist for coupling vinyl iodides to cyclopentenones such as **216**. Radical methods which use tri-*n*-butylstannane (sometimes with Lewis acid catalysis) have been employed,[132] and the conversion of **178d** to an organocuprate for conjugate addition to **216** may also be considered, as was effectively demonstrated in a copper(I)-catalyzed conjugate addition involving **216** and a vinylmagnesium iodide for synthesizing estrone methyl ether developed earlier in our laboratory.[129] Another twist on the double conjugate addition strategy could involve the use of sodium benzeneselenolate generated *in situ* by sodium borohydride reduction of diphenyldiselenide,[133] as shown in Scheme 3.23. An acceptor for the second conjugate attack may either be **216** or 2-cyclopentenone followed by alkylation with 1,2-dibromoethane. The anticipated bromide product **219** (X=Br) could also be obtained from the corresponding ester ($X=CO_2CH_3$, formed from **216**) by either a Hunsdiecker reaction or by treatment with lead tetraacetate and potassium bromide. The enone system could be restored as in **220** by oxidative elimination of the selenoxide **219**.[134] Closure of ring C to form **221** may be attempted by a radical coupling in **220** catalyzed with tri-*n*-butylstannane and the initiator AIBN.[135] Alternatively, the selenide intermediate **219** with a pendant ester group ($X=CO_2CH_3$) may be first converted to

enone **220** by oxidative elimination, after which an intramolecular Michael addition could be attempted to close ring C. In both these approaches the saturated analogue **221** will result, and it is hoped that the subsequent dehydrogenation of ring C and furan ring E for synthesizing viridin will proceed smoothly.

Scheme 3.23



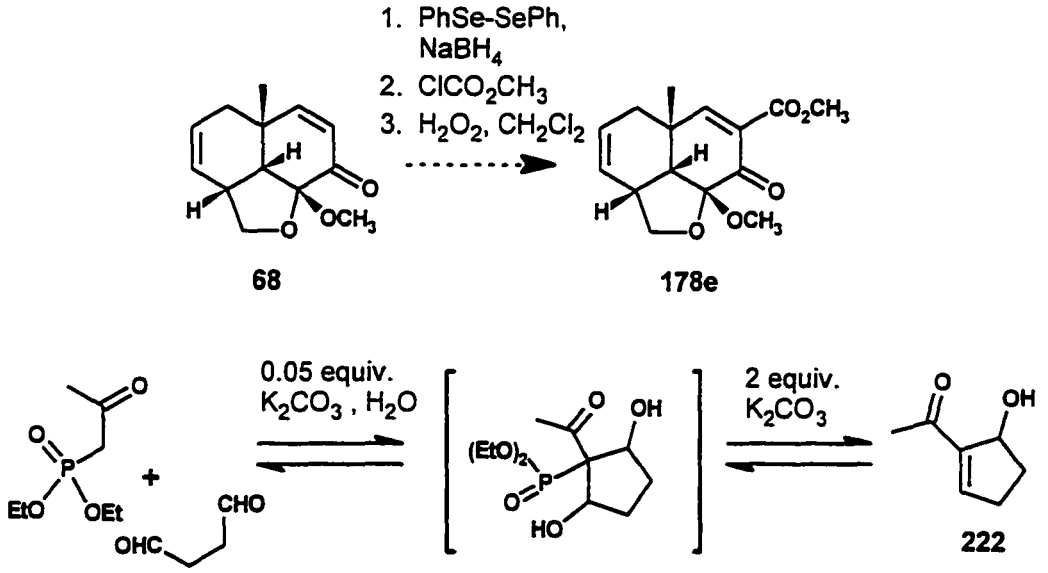
Scheme 3.24



Finally, the Diels-Alder approach should not be overlooked in a convergent synthesis of viridin (Scheme 3.24), since there are still several promising combinations one could envisage with the naphthofuran dienophiles **178e**, **190c** and **190e** and a suitable diene component such as **223**. A reasonable quantity of **178e** might be obtained by the conjugate attack of **68** with diphenyldiselenide, followed by acylation with methyl chloroformate and then oxidative elimination of the selenide group (Scheme 3.25). A one-step procedure for synthesizing **222** in 70.5% yield was developed by Graff *et al.*[136] which involved tandem Horner-Wittig and intramolecular aldol reactions between diethylphosphono(2-propanone) and succinaldehyde in basic media (the latter generated from acidic hydrolysis of 2,5-dimethoxytetrahydrofuran). The potential for a successful Diels-Alder cycloaddition between one of the prospective dienophiles shown in Scheme 3.24 (especially with the doubly activated candidates **178e** and **190e**) and **223** is high,

since the latter is an activated diene which may form an adduct with the correct regiochemistry for viridin. Alternatively, the silyl protecting group in **223** may be cleaved in order to generate a donor for Michael addition to any one of enones shown. The possibilities are indeed endless, and only a sampling are proposed here for consideration in future work geared at synthesizing viridin or any related natural products.

Scheme 3.25



3.5 Summary

The one-pot IMDA reaction of mixed *o*-benzoquinone monoketals, generated from oxidation of the substituted guaiacols **64-66** and **172-176** in the presence of excess (*E*)-2,4-pentadienol, was reinvestigated in order to synthesize naphthofurans with the general structure **178**. With the exception of the reaction with vanillin **65**, the IMDA

reactions were generally successful (Scheme 3.2, Table 3.1) where the *o*-quinone monoketal intermediates had reacted as both a diene and a dienophile, thereby producing (respectively) the bridged adduct **177** (or **67**, for R_1=R_2=H, R_3=CH_3) and the naphthofuran adduct **178** (or **68**, for R_1=R_2=H, R_3=CH_3). The dienophilicity of these monoketal intermediates was increased with the electron-withdrawing strength of group R_3, as was noted by the increasing proportion of naphthofuran adduct in the product mixtures. Only *endo*-naphthofuran adducts were obtained, and their relative stereochemical configuration was deduced from the ^{1}H-NMR signal of H-8b, which exhibited small W-coupling (≈1.0-1.5 Hz) with H-5β, a diagnostic feature found in the spectra of all *endo*-IMDA adducts. The Cope rearrangements of the bridged IMDA adducts were effected by heating in various hydrocarbon solvents (Scheme 3.7 and Table 3.2), and gave an assortment of products **178**, **179**, **190** and **191** which resulted from further transformations of the actual Cope product **178**. The shortest recorded synthesis of the important 5a-methyl-naphthofuran **68** was now accomplished in two steps and 56% overall yield by the Cope rearrangement of the bridged adduct **67**, generated by the oxidation-IMDA reaction with commercially available **64**. A gateway toward (-)-morphine was later developed from the realization that the Cope product **191b** was a tricyclic subunit of this notorious natural product (Scheme 3.10). A model study for a prospective synthesis of morphine involved preparing compound **195** in 2 steps and 90% yield by tandem hydrolysis and dienone-phenol rearrangement of the dienone **179a** (Scheme 3.12), which exemplified the versatility of the IMDA-Cope reaction sequence for constructing polycyclic subunits of natural products.

Two convergent strategies for synthesizing viridin from the naphthofuran **68** were developed in Schemes 3.14, 3.17 and 3.21. In the Diels-Alder approach, several

cycloadditions were attempted between the diene methyl (*E*)4,6-heptadienoate and dienophiles **68**, **179c**, and **190c**, but most were unsuccessful, having only formed small amounts of the undesired cycloadduct **203** in a few cases. Although the enone **178e** was as suitable dienophile under consideration, the preparation of this compound by lithium-iodide exchange of **178d** and subsequent acylation with methyl chloroformate was not successful. The second general approach centered on tandem double Michael-Dieckmann cyclizations with **207** as the Michael donor and **68** as the Michael acceptor. Although the synthesis of **207** was attempted by two different routes (Schemes 3.19 and 3.20), both were unsuccessful in the final steps. A new Michael donor **216** was prepared next by a known procedure, however in one attempt of the conjugate addition using LHMDS with **68** as acceptor, only a dimer of **68** was produced along with unreacted starting materials. Several refinements of these synthetic plans for viridin were proposed for future consideration and are highlighted in Schemes 3.23-3.25.

CHAPTER 4

EXPERIMENTAL PROCEDURES AND DATA

4.1 Technical Notes

All air-sensitive and moisture-sensitive reactions were performed under inert atmosphere (argon) in oven-dried glassware. Tetrahydrofuran (THF), diethyl ether (Et_2O), benzene, and toluene were distilled from sodium benzophenone ketyl, while methylene chloride, hexane, pyridine (pre-dried with KOH), *p*-xylene, petroleum ether 60-80°C, 1,1,2,2-tetrachloroethane, dimethylsulfoxide and *N*,*N*-dimethylformamide were distilled from calcium hydride. 1,1,2,2-Tetrachloroethane was stirred over $CaCO_3$, then distilled from calcium hydride. Acetone was refluxed and distilled from P_2O_5. Anhydrous methanol, anhydrous ethanol and anhydrous dimethoxyethane (DME) were purchased from Aldrich Chemical Company, Inc. in air-tight Sure Seal® bottles. Decane and 1,2,4-trimethylbenzene were purchased from Aldrich Chemical Company, Inc. and were not further purified. All reagents were purchased from Aldrich Chemical Company, Inc. including **110** and **154**, unless otherwise noted. Methyl 2,3-dihydroxybenzoate **98** was prepared by esterification of the corresponding benzoic acid **110** by standard methods (i.e. reflux with conc. H_2SO_4 and MeOH).

Thin-layer chromatography was performed using E. Merck 5554 pre-coated silica gel 60 F_{254} aluminum sheets, and all TLC plates were developed with an oxidizing stain solution consisting of ceric ammonium sulfate and hexammonium heptamolybdate in 1.8 M H_2SO_4 solution (see preparation in section 4.2). Silica gel chromatography was

performed on Merck 9385 silica gel 60 (230-400 mesh) under applied forced air pressure, and eluant systems were typically comprised of ethyl acetate and hexane, the specific ratio as indicated for each product isolated. Neutral alumina, Brockman Type I (~150 mesh) was purchased from Aldrich Chemicals, and was used for purifying compound **216**. Melting points were measured on a Gallenkamp melting point apparatus and are uncorrected for stem temperature. Fourier transform infrared spectra (FTIR) were obtained from a Bomem MB-100 spectrometer as either neat films between NaCl cells, or as KBr discs, and only the strongest and/or diagnostic bands are noted. All NMR spectroscopic analyses (^{1}H, ^{13}C, and ^{31}P nuclei) were performed on Bruker AMX-500, AM-300, AM-250, and AC-200 instruments. Samples were prepared in deuterated solvents including $CDCl_3$, acetone-d_6, or DMSO-d_6 and chemical shifts were determined relative to the reference solvent signal. Chemical shifts for ^{1}H NMR spectra obtained in $CDCl_3$ were determined relative to tetramethylsilane internal standard (δ 0.00). For many of the new compounds, the exact spectral assignments (^{1}H and ^{13}C) were determined using 1-D and 2-D spectroscopic techniques which include ^{13}C-JMOD, ^{13}C-DEPT, NOEDS, TOCSY, COSY, NOESY, HMQC, and HMBC, and by comparison of spectral data within a series of related structures. The ^{1}H-NMR data is entered in the following order: chemical shift (ppm), structural assignment, integration, multiplicity, coupling constants (Hz). Low and high resolution mass spectral analyses were performed at the Southwestern Ontario Regional Mass Spectrometry Center, McMaster University (Hamilton, Ontario). Low resolution mass spectrometric analyses (LRMS) were performed on a Finnigan 4500 quadrupole mass spectrometer calibrated with perfluorotributylamine (FC43) for both electron impact (EI) and chemical ionization (CI) methods. High resolution mass spectrometric analyses (HRMS) for determining

elemental composition were carried out on pure compounds at a mass resolution of 3000-5000 with a VG Analytical ZAB-R double focusing mass spectrometer. Low resolution GC-MS analyses were performed on a Hewlett-Packard 5890 Series II/5971A MSD instrument equipped with a fused silica column (30m×0.25mm×0.25μm, cross-linked 5% phenylmethyl silicone). Significant fragment peaks are reported as *m/e* (% abundance relative to base peak), and are assigned wherever relevant. Elemental analyses were performed by M-H-W Laboratories, Phoenix, Arizona (USA).

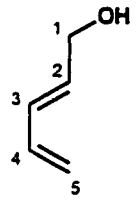
The following compounds were prepared either by known procedures or prepared earlier by members of our research group: trichloromethyl methyl sulfide[65] (Cl_3CSCH_3); phenanthro[10,1-*bc*]furan methyl esters[45] (**78a-b**); phenanthro[10,1-*bc*]furan thiol esters[66] (**79a-b**); *S*-methyl (4-hydroxy-3-methoxy-6-methyl)benzenethioate[104] (**176**); 3,4-dihydroxy-6-methylbenzoic acid[104] (**155**); 2-methoxy-4-methylphenol methoxymethyl ether[105] (**180**); 6-methyl-6-acetoxy-2,4-cyclohexadien-1-one[40a] (**215**); 2-[2'-[(methoxy)-carbonyl]ethyl]-2-cyclopenten-1-one (**216**).[129, 130a] A significantly improved procedure for the preparation of (*E*)-2,4-pentadienol[137] was developed in this work (see section 4.3). The IUPAC nomenclature rules[138] were followed as closely as possible in naming each of the new compounds listed below; however the numbering scheme for all of the polycyclic compounds were assigned according to the ring-system class outlined in the Chemical Abstract Service's Ring Index[139] rather than the IUPAC-recommended priorities.

4.2 Preparation of Ce(IV)-Mo(VI)-H_2SO_4 developing solution for TLC analysis

A 4-L solution was prepared by dissolving 40g $(NH_4)Ce(SO_4)_2$ (ceric ammonium sulfate) and 100g $(NH_4)_6Mo_7O_{24}\cdot H_2O$ (hexammoniumheptamolybdate) in 3.6-L deionized water and 400 mL conc. H_2SO_4. The mixture was stirred at room temperature for 30 min. until it appeared as a homogenous dark yellow solution.

4.3 Synthesis of (*E*)-2,4-pentadienol

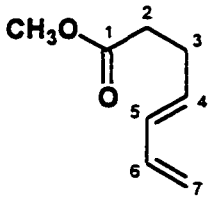
Freshly distilled 1,4-pentadien-3-ol (a.k.a. divinyl carbinol; 25g, 0.29 mol; bp≈ 36°C @ 20 torr) was mixed with 30 mL of distilled THF and cooled in ice. About 10 mL of a 1:1 mixture of conc. H_2SO_4 and H_2O (i.e. 10 mL of 9M H_2SO_4) was carefully added, and the pale yellow mixture was stirred for 24-48 h at room temperature. The mixture was then neutralized in ice by adding solid Na_2CO_3 (until mildly basic in pH), then extracted into 300 mL ether. After separation of the aqueous phase, the ether layer was washed twice with brine solution, dried (Na_2SO_4), and the ether solvent was evaporated. The crude residual oil was then distilled under reduced pressure to give (*E*)-2,4-pentadienol as a colorless oil (15.12g, 60.5% yield; bp ≈ 56-58°C @ 15-20 torr). The ^{1}H-NMR and IR spectral data were in complete agreement with the values reported in the literature.[137] The compound was inhibited from polymerization with a few crystals of hydroquinone, and was always stored under argon atmosphere at 4°C. Under these storage conditions, the shelf-life of this compound (at 4°C) was approximately 5-7 months.



bp 56-58°C at 15-20 torr; **^{1}H NMR (250 MHz, $CDCl_3$), δ (ppm):** 4.13 (H-1, 2H, m), 5.10 (H-5, 1H, d, J = 9.8 Hz), 5.20 (H-5, 1H, d, J = 16.7 Hz), 5.83 (H-2, m), 6.19-6.42 (H-3 and H-4, m).

4.4 Synthesis of methyl (*E*)-4,6-heptadienoate

Into a 500 mL round-bottomed flask fitted with a reflux condenser was added freshly distilled 1,4-pentadien-3-ol (32.78g, 0.389 mol; bp = 36°C @ 20 torr), trimethyl orthoacetate (248 mL, 1.95 mol, 5 equiv.) and HPLC-grade benzene (80 mL). A catalytic amount of propanoic acid (1.45 mL, 0.02 mol, 5 mol-%) was then added and the mixture was heated at 95°C for 10 h (i.e. usually overnight). The benzene and excess trimethyl orthoacetate were distilled off (atmospheric pressure) over several hours, and the residual oil left behind (crude product) was distilled under reduced pressure using a Vigreux fractionating column (bp = 75°C @ 20 torr). The pure product (48.6 g, 89% yield), a colorless oil with an unpleasant odor, was usually inhibited from polymerization by adding a few crystals of hydroquinone and storing under argon at 4°C (stable for about 1 yr).



bp 75-78°C at 15-20 torr; **IR (neat film):** 2970, 1740, 1438, 1200, 1005 cm^{-1}; **^{1}H NMR (250 MHz, $CDCl_3$), δ (ppm):** 2.43 ($C\underline{H}_2C\underline{H}_2CO_2CH_3$, 4H, narrow m), 3.68 ($CO_2CH_3$, 3H, s), 4.98 (H-7, 1H, dd, J = 8.3, 1.3 Hz), 5.12 (H-7, 1H, dd, J = 14.6, 1.3 Hz), 5.70 (H-4, m, $J_{4,5}$ = 14.6 Hz), 6.08 (H-5, dd, J = 14.6, 9.2 Hz), 6.27 (H-6, ddd, J = 8.3, 15.2, 9.1 Hz); **^{13}C NMR (50 MHz, $CDCl_3$), δ (ppm):** 27.5, 33.3 (C-2, C-3), 51.2 ($CO_2\underline{C}H_3$), 115.4 (C-7), 131.7, 132.3, 136.6 (C-4, C-5, C-6), 172.9 ($\underline{C}O_2CH_3$); **LRMS (EI) *m/e*:** 140 (63%, M^+), 109 (21%, M-OCH_3), 98 (22%, M-CH_2CO), 80 (100%, M-[CO+CH_3OH]), 67 (86%), 53 (39%), 41 (76%); **HRMS (EI):** Calc'd for $C_8H_{12}O_2$: 140.0837; Found: 140.0837.

4.5 Preparation of trichloromethyl methyl sulfide

The general method of Boberg *et al.*[65] was performed. All glassware was oven-dried at 110°C for 24 h prior to use. Into a 3-neck 1L-round bottomed flask was weighed (in the fumehood) phosphorus pentachloride (470 g, 2.25 mol). The flask was equipped with a mechanical stirrer (glass shaft, teflon stirrer), pressure-equalized dropping funnel, and reflux condenser. With gentle stirring, freshly distilled dimethyl sulfide (42 mL, 0.56 mol; bp =36°C @ 760 torr, distilled from $CaCl_2$) was added dropwise from the funnel over 20 min., and the solid mass was heated in an oil bath at 100°C (external temperature) under argon atmosphere. After a period of 8h, the viscous yellow liquid mixture was cooled to room temperature, then in ice for several hours in order to precipitate the excess PCl_5 and PCl_3 by-product. The mixture was filtered to remove the solid mass, washing with cold carbon tetrachloride (dried over $CaCl_2$). The filtrate, which contains the product along with dissolved PCl_3 and $POCl_3$, was fractionally

distilled twice under reduced pressure using a Vigreux fractionating column. Trichloromethyl methyl sulfide, which distilled at ≈40°C at 8-10 torr, was a corrosive colorless liquid (48.5g, 52% yield) with a noxious and unpleasant odor, and should be kept at 4°C in a glass-stoppered flask. The phoshorus-containing compounds PCl_3, PCl_5 and $POCl_3$, were detected by ^{31}P-NMR analysis, and had the following chemical shifts (referenced to a standard containing H_3PO_4 in THF): δ 222 ppm (PCl_3), δ 6.8 ppm ($POCl_3$), and δ -78.5 ppm (PCl_5).

4.6 General procedure for the oxidation-intramolecular Diels-Alder (IMDA) reactions of substrates **64-66**, **72-75**, **81**, **115**, **122**, and **172-176** with (*E*)-2,4-Pentadienol

To a solution of the *o*-methoxyphenols **64-66** and **172-176**, or *o*-methoxynaphthols **72-75** and **122**, or benz[*e*]indanones **81** and **115** in dry THF (≈ 0.1 M) was added 5-10 equivalents of (*E*)-2,4-pentadienol (freshly distilled, bp ≈58-60°C @ 15-20 torr), and the mixture was cooled (0°C) under argon atmosphere. (A catalytic amount of BHT (2 mol-%) was added as a radical scavenger for reactions with derivatives of 2-methoxy-4-methylphenol **64**.) Bis(trifluoroacetoxy)iodobenzene[43] (a.k.a. PIFA; 1.2 equivalents) was then added in small portions (approximately 0.2-0.5 g each) over 2-5 minutes, after which the mixture usually became homogenous orange-red. For some substrates which included all the *o*-methoxyphenols **64-66** and **172-176** and the benz[*e*]indanone thiol ester **81**, solid $NaHCO_3$ (2.4 equivalents) was added to neutralize the TFA by-product of oxidation, and usually enhanced reaction yields. The mixture gradually lightened in color to pale yellow after 4-6 h, indicating a complete reaction. The volatile solvents (THF, TFA) were removed and the residual oil was extracted into EtOAc and washed with brine solution

until the aqueous layer was near pH 6. The EtOAc layer was dried (Na_2SO_4), filtered, and concentrated, and then the excess (*E*)-2,4-pentadienol was distilled under reduced pressure. The crude orange residue left behind was purified by column chromatography (silica gel 60, typically 1:4 EtOAc-hexane eluant).

4.7 General procedure for Cope rearrangements

All hydrocarbon solvents used for the Cope rearrangements, except for decane and 1,2,4-trimethylbenzene, were distilled from calcium hydride granules and stored under argon. The bridged compounds **67**, **177a-b** and **177d-g** were mixed with 5-15 mL of hydrocarbon solvent and heated at reflux (using a water condenser) over 24-72 h under an atmosphere of argon. When the reaction was complete (although not for all cases tested) by TLC qualitative analysis, the mixture was cooled to room temperature and then the solvent was removed by distillation at reduced pressure. The residual brown oil was then purified by column chromatography (silica gel 60, 1:4→1:2 EtOAc-hexane eluant).

4.8 General procedure for TFA-promoted elimination of methanol

The naphthofurans **178a-b** and **68**, phenanthrofurans **78a-b** and **79a-b**, and pentacycles **80a-b** were treated with neat TFA (5-10 mL) at room temperature. Only the *endo*-adducts underwent elimination, where after 15-30 min., the deep yellow solution was concentrated *in vacuo*, and the dark residue purified by column chromatography (silica gel 60, 1:4→1:2 EtOAc-hexane eluant gradient). The pure demethoxylated products were usually readily crystallized from ether.

4.9 General procedure for rearrangements with TFA

The compounds **102**, **106**, and **156** were mixed with an excess amount of TFA (10-20 equivalents) and stirred at room temperature under an argon atmosphere for time periods ranging from 0.5-18 h, as monitored by TLC. The excess TFA was evaporated *in vacuo*, and the crude residue was extracted into ether, washed with brine solution, dried (Na_2SO_4), filtered and concentrated. The crude product was further purified either by recrystallization in ether, or by column chromatography (silica gel 60, 1:4 EtOAc-hexane eluant).

4.10 General procedure for rearrangements with trialkyloxonium tetrafluoroborates (R_3OBF_4)

The compounds **102**, **106**, and **156** were dissolved in dry CH_2Cl_2 and cooled to 0°C. Approximately 1.2 equivalents of R_3OBF_4 (R= Me or Et), either as a 1M solution in dry CH_2Cl_2 (for Et_3OBF_4) or as a neat crystalline solid (for Me_3OBF_4), was added under an argon atmosphere. The resulting brown mixture was stirred at 0°C for 30 min and then at room temperature for 10-48 h. The reaction was quenched with a sat. NH_4Cl solution, and the CH_2Cl_2 layer was separated, washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to a black oil. The crude product was purified by column chromatography (silica gel 60, 1:4 EtOAc-hexane eluant).

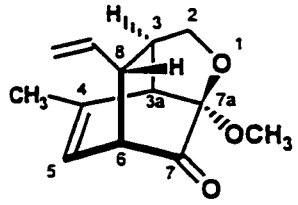
4.11 Preparation of diazomethane

Diazomethane was always prepared when needed as a dilute solution in diethyl ether, and should never be stored indefinitely at 4°C. Following the general notes and procedures described by Black,[140] Diazald® purchased from Aldrich Chemical Company, Inc. was used to generate diazomethane and the reaction was performed using the Aldrich Diazald Microkit® in a good fumehood behind an explosion-proof shield. Generally, 1.5 molar proportions of diazomethane are prepared per mole of reactant to be methylated. Typically, for every mole of diazomethane to be generated, about 1.5 molar equivalents of Diazald® as a 0.6 M solution diethyl ether, and 5 molar equivalents of KOH as a 5M solution in 1:1 EtOH-H_2O were required. Into a round-bottomed fire-polished distillation flask (at least 250 mL) was added KOH and the 1:1 EtOH-H_2O solution, and the mixture was warmed until the external temperature of the water bath (for heating) was 65°C. The distillation apparatus from the Diazald kit required a Claisen Y-tube attached to the round-bottomed flask, on top of which sat a conical dropping funnel (at least 125 mL) and adaptor connected to the condenser, which in turn was connected to a receiver adapter and a receiving round-bottomed flask. From the side-arm of the receiver adapter was attached a short piece (12 cm) of Tygon® tubing which was immersed into a flame-polished test-tube filled half-way with ether. Both the receiving flask and this test-tube were immersed in salted ice-baths and kept cold throughout the procedure. Once the water bath was warm at 65°C (but should not exceed 70°C), the ether solution of Diazald was dripped into the boiling flask at an approximate rate of 1 drop per second. About 1 min. had passed until the yellow ethereal solution of diazomethane began to condense in

the receiving flask. The distillation may require from 1-3 h of time, and when complete the glassware was rinsed with ether (which was also collected). The diazomethane solution was always kept cold and loosely capped. Excess diazomethane was neutralized with glacial acetic acid, whereby the evolution of $N_{2\,(g)}$ was quickly observed.

4.12 Synthesis of **67** and **68** by IMDA reaction with 2-methoxy-4-methylphenol **64** and (*E*)-2,4-Pentadienol

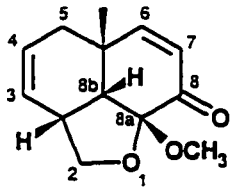
The general procedure for the IMDA reaction described in section 4.6 was followed, using 2-methoxy-4-methylphenol **64** (2.0 g, 0.0145 mmol), freshly distilled (*E*)-2,4-pentadienol (6.09 g, 0.0725 mol, 5 equiv.), BHT (0.064 g, 0.29 mmol, 0.02 equiv.), $NaHCO_3$ (2.92 g, 0.0348 mol, 2.4 equiv.) and PIFA (7.48 g, 0.0174 mmol, 1.2 equiv.) in dry THF (30 mL). After stirring for 4 h at room temperature, the mixture became pale yellow in color. Solvents were removed *in vacuo*, excess pentadienol was removed by distillation under reduced pressure (bp= 58-60°C@20 torr), and the residual viscous red oil was directly purified by column chromatography (silica gel 60, 1:4 EtOAc-hexane eluant), affording the products **68** (0.263 g, 8% yield) as a pale gold oil, and **67** (1.94 g, 61% yield) as white prisms from ether.



67

(3,8-*trans*)-7a-Methoxy-4-methyl-8-vinyl-2,3,3a,6,7,7a-hexahydro-3,6-methano-benzofuran-7-one (**67**)

mp 87-89°C; **IR(KBr):** 2961, 1739, 1442, 1332, 1240, 1012 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm):** 1.93 (CH_3, 3H, s), 2.32 (H-3, m), 2.71 (H-8, m), 3.07 (H-6, dd, J = 6.7, 2.9 Hz), 3.15 (H-3a, dd, J = 4.4, 2.1 Hz), 3.53 (OCH_3, 3H, s), 3.85 (H-2, 1H, d, J = 8.1 Hz), 4.14 (H-2, 1H, dd, J = 8.1, 3.3 Hz), 5.02 (CH=C$\underline{H}_2$, 1H, dd, J_{cis}= 10.4 Hz), 5.06 (CH=C$\underline{H}_2$, 1H, d, J_{trans}= 17.1 Hz), 5.65 (C$\underline{H}$=CH_2, ddd, J_{trans}= 17.1, J_{cis}= 10.2, $J_{9,8}$= 8.2 Hz), 5.80 (H-5, dm, J = 6.6, 1.6 Hz); **^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm):** 21.3 (CH_3), 42.9 (C-3), 46.8 (C-8), 47.9 (C-3a), 51.5 (OCH_3 and C-6), 73.8 (C-2), 100.4 (C-7a), 115.6 (-CH=$\underline{C}H_2$), 120.0 (C-5), 138.8 (-$\underline{C}$H=CH_2), 139.2 (C-4), 200.9 (C-7); **LRMS(CI, NH_3) *m/e*:** 238 (100%, M+NH_4), 221 (17%, M+H), 206 (9%, [M-CH_3OH]+NH_4), 189 (25%, M-OCH_3); **HRMS(EI):** Calc'd for $C_{12}H_{16}O_2$ (M^+-CO fragment): 192.1150; Found: 192.1145 (No M^+ was observed in the EI spectrum); **Anal.** Calc'd for $C_{13}H_{16}O_3$: C, 70.88%; H, 7.32%. Found: C, 70.78%; H, 7.11%.



68

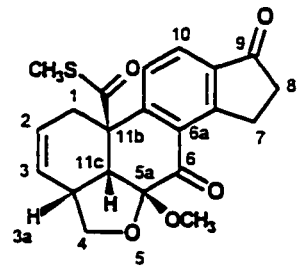
(*syn* 2a-H, 5a-CH_3, 8a-OCH_3, 8b-H)-8a-Methoxy-5a-methyl-2a,5,5a,8,8a,8b-hexahydro-2*H*-naphtho[1,8-*bc*]furan-8-one (**68**)

IR (neat film): 2923, 1689, 1454, 1045 cm^{-1}; **^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm):** 1.24 (CH_3, 3H, s), 1.89 (H-5α, 1H, dm, J = 15.0 Hz), 2.01 (H-5β, 1H, dm, J = 15.0, 1.0 (W-coupling with H-8b) Hz), 2.59 (H-8b, dd, J = 9.4, 0.9 (W-coupling with H-5β) Hz), 3.04 (H-2a, m), 3.31 (OCH_3, 3H, s), 3.76 (H-2α, 1H, dd, J = 8.5, 3.3 Hz), 4.14 (H-2β, 1H, dd, J = 8.4, 7.3 Hz), 5.78 (H-3 and H-4, 2H total, fused m), 6.02 (H-7, d, J = 10.0 Hz), 6.71 (H-6, d, J = 10.1 Hz); **^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm):** 28.3 (CH_3), 35.3 (C-5a), 37.2 (C-2a), 37.7 (C-5), 50.5 (OCH_3), 53.3 (C-8b), 72.6 (C-2), 102.9 (C-8a), 125.7,

129.4 (C-3 and C-4), 126.9 (C-7), 159.1 (C-6), 191.4 (C-8); **LRMS (EI) *m/e*:** 220 (22%, M^+), 189 (100%, M-OCH_3), 161 (18%, M-[CO+OCH_3]), 147 (30%), 133 (20%), 119 (17%), 91 (20%); **HRMS (EI):** Calc'd for $C_{13}H_{16}O_3$: 220.1099; Found: 220.1102.

4.13 Synthesis of Pentacycles **80a** (*endo*) and **80b** (*exo*) by IMDA reaction of **81** with (*E*)-2,4-Pentadienol

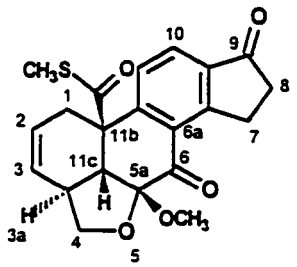
The benz[*e*]indanone thiol ester **81** (0.480 g, 1.59 mol) was mixed with freshly distilled (*E*)-2,4-pentadienol (1.3 g, 0.016 mol, 10 equiv.; bp ≈56°C @ 15 torr) and 20 mL distilled THF. At room temperature, PIFA (0.82 g, 1.9 mmol, 1.2 equiv.) was added, and when the mixture became homogenous orange in appearance (*ca.* 2 min), solid $NaHCO_3$ (0.27 g, 3.2 mmol, 2 equiv.) was added. The reaction was stirred for 4 h, after which the volatile solvents (THF, TFA) were evaporated *in vacuo*. Excess 2,4-pentadienol was then distilled off, and the remaining orange residue was extracted into EtOAc (200 mL), washed with brine solution, dried (Na_2SO_4), and concentrated to a crude dark orange oil which partly crystallized. The crystalline product which was filtered off was identified as the *exo*-isomer **80b** (0.177 g, 29% yield). The orange oil was purified by column chromatography (silica gel 60, 1:3 EtOAc-hexane eluant), which afforded the *endo*-isomer **80a** (0.346 g, 57% yield) as white microcrystals from ether.



80a

(*Endo*)-[*syn*-3a-H, 5a-OCH_3, 11b-$COSCH_3$, 11c-H]-11b-[(methylthio)carbonyl]-5a-methoxy-1,3a,4,5a,6,7,8,9,11b,11c-decahydrocyclopenta[7,8]phenanthro[10,1-*bc*]furan-6,9-dione (**80a**)

mp 142-144°C; **IR (KBr):** 2929, 1712, 1675, 1591, 1323, 1026 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm):** 2.32 (H-1α, 1H, ddd, *J* =17.3, 5.0, 2.2 Hz), 2.39 ($COSCH_3$, 3H, s), 2.73 (H-7, 2H, m), 2.85 (H-1β, 1H, m, *J* = 17.3, 5.3, 1.4 Hz), 3.25 (H-3a + H-8 (1H), 2H total, m), 3.38 (OCH_3, 3H, s), 3.60 (H-4α, 1H, dd, *J* = 8.5, 3.4 Hz; and H-8, 1H, m), 3.67 (H-11c, dd, *J* =8.8, 1.6 Hz), 4.17 (H-4β, 1H, dd, *J* =8.5, 6.7 Hz), 5.67 (H-3, m, *J* =9.9 Hz), 5.69 (H-2, m, *J* = 9.9 Hz), 7.25 (H-11, d, *J* =8.1 Hz), 7.86 (H-10, d, *J* =8.1 Hz); **^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm):** 12.5 ($COS\underline{C}H_3$), 25.7 (C-8), 34.2 (C-1), 36.5 (C-7), 38.4 (C-3a), 49.9 (C-11c), 50.5 (OCH_3), 55.7 (C-11b), 73.2 (C-4), 104.8 (C-5a), 125.9, 126.0 (C-2, C-11), 127.8, 130.0 (C-3, C-10), 131.1, 137.7 (C-6a, C-9a), 150.0 (C-6b), 156.0 (C-11a), 190.7 ($\underline{C}OSCH_3$), 202.1 (C-6), 205.7 (C-9); **LRMS (EI) *m/e*:** 384 (4%, M^+), 356 (7%, M-CO), 337 (100%, M-SCH_3), 309 (35%, M-$COSCH_3$), 277 (65%), 249 (79%), 235 (32%), 207 (58%), 179 (74%), 165 (40%), 138 (35%); **HRMS (EI):** Calc'd for $C_{21}H_{20}O_5S$: 384.1031; Found: 384.1037.



80b

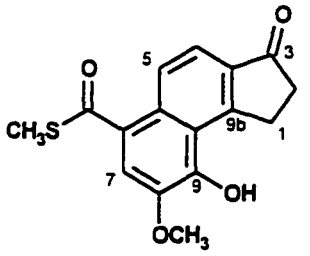
(*Exo*)-[*syn*-5a-OCH_3, 11b-$COSCH_3$, 11c-H; *anti*-3a-H, 11c-H]-11b-[(methylthio)-carbonyl]-5a-methoxy-1,3a,4,5a,6,7,8,9,11b,11c-decahydrocyclopenta[7,8]phenanthro-[10,1-*bc*]furan-6,9-dione (**80b**)

mp 201-203°C; **IR (KBr):** 2918, 1708, 1660, 1584, 1423, 1322. 1256, 1078 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm):** 2.18 ($COSCH_3$, 3H, s), 2.56 (H-3a, m), 2.74 (H-7, 2H, m), 3.03 (H-1α, 1H, m, *J* = 18.8 Hz), 3.07 (H-11c, d, *J* = 12.3 Hz), 3.14 (H-1β, 1H, ddd, *J* = 18.8, 5.9, 3.5 Hz), 3.46 (OCH_3, 3H, s), 3.50 (H-8, 1H, m), 3.73 (H-4α, 1H, dd, *J* = 7.3, 11.2 Hz; and H-8, 1H, m), 4.09 (H-4β, 1H, t, *J* = 7.0 Hz), 5.75 (H-3, ddd, *J* =9.8, 4.1, 2.0 Hz), 5.86 (H-2, ddd, *J* = 9.8, 6.8, 3.4 Hz), 7.61 (H-11, d, *J* =8.1 Hz), 7.99 ppm (H-10, d, *J* =8.0 Hz); **^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm):** 13.4 ($COS\underline{C}H_3$), 28.3 (C-8), 35.1 (C-1), 36.6 (C-7), 40.7 (C-3a), 49.3 (C-11c), 50.9 (OCH_3), 55.6 (C-11b), 70.2 (C-4), 100.8 (C-5a), 124.0, 127.7, 128.3, 128.6 (C-2, C-3, C-10, C-11), 130.2, 139.1 (C-6a, C-9a), 146.9 (C-6b), 158.9 (C-11a), 192.0 ($\underline{C}OSCH_3$), 202.8 (C-6), 206.1 (C-9); **LRMS (EI) *m/e*:** 384 (4%, M^+), 337 (100%, M-SCH_3), 277 (17%), 249 (28%), 207 (14%), 179 (18%), 165 (10%); **HRMS (EI):** Calc'd for $C_{21}H_{20}O_5S$: 384.1031; Found: 384.1018.

4.14 Synthesis of 9-hydroxy-8-methoxy-6-[(methylthio)carbonyl]-1,2-dihydrobenz[*e*]indene-3-one (**81**)

To a cooled solution (0°C) of the carboxylic acid **129** (2.2 g, 6.9 mmol) in dry THF (30 mL) was added by syringe (argon atmosphere) oxalyl chloride (1.2 mL, 13.8 mmol, 2 equiv.) followed with 4 drops of DMF (HPLC-grade). The exothermic release of $CO_{(g)}$ and $CO_{2(g)}$ was immediately observed, which subsided after 15 min. After stirring for 2h, all the volatile substances were evaporated *in vacuo* (using a drying tube filled with Drierite® dessicant), and the resulting orange oil was taken up in dry CH_2Cl_2 (50 mL) and cooled to 0°C. Aluminum chloride (4.58 g, 34.4 mmol) was then added to the flask in small portions, and the dark brown mixture was stirred at 0°C for 3-4h. The

reaction was quenched by the addition of 5% (vol/vol) $HCl_{(aq)}$ (40 mL) in an ice bath, then stirred for 1h at room temperature. The brown emulsion was filtered through micro-fiberglass filter paper and dried under vacuum to give a tan amorphous solid **81** (1.45 g, 70% yield).



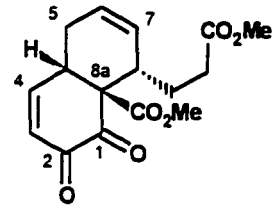
81

IR (KBr): 3297 (OH), 1684, 1582, 1186, 1115, 799 cm^{-1}; **^{1}H NMR (250 MHz, $CDCl_3$)** δ **(ppm):** 2.55 (SCH_3, 3H, s), 2.76 (H-1, 2H, m), 3.80 (H-2, 2H, m), 4.09 ($OC\underline{H}_3$, 3H,s), 6.67 (OH, s), 7.69 (H-4, d, J = 9.1 Hz), 7.93 (H-7, s), 8.45 (H-5, d, J= 9.0 Hz); **^{13}C NMR (50 MHz, DMSO-d^6)** δ **(ppm):** 12.4 (SCH_3), 29.2 (C-1), 35.6 (C-2), 57.7 ($O\underline{C}H_3$), 118.1, 119.1 (C-5, C-7), 122.2 (C-6), 124.4 (C-4), 126.0 (C-9a), 128.7, 134.2 (C-9b, C-3a), 142.5 (C-5a), 148.6 (C-8), 156.1 (C-9), 192.8 ($\underline{C}OSCH_3$), 205.9 (C-3); **LRMS (EI)** ***m/e*:** 302 (37%, M^+), 255 (100%, M-SCH_3), 227 (5%, M-$COSCH_3$), 212 (9%), 157 (20%), 128 (28%), 115 (12%); **HRMS (EI):** Calc'd for $C_{16}H_{14}O_4S$: 302.0613. Found: 302.0615; **Anal.** Calc'd for $C_{16}H_{14}O_4S$: C, 63.56%; H, 4.67%; S, 10.60%. Found: C, 63.56%; H, 4.41%; S, 10.66%.

4.15 Synthesis of (*syn* 4a-H, 8-H, 8a-CO_2CH_3)-8a-[(methoxy)carbonyl]-8-[2'-[(methoxy)carbonyl]-ethyl]-1,2,4a,5,8,8a-hexahydronaphthalene-1,2-dione (**101**)

To a cooled mixture (0°C) of freshly distilled methyl (4*E*)-4,6-heptadienoate (30.82 g, 0.22mol, bp≈ 75°C@20 mmHg) and methyl 2,3-dihydroxybenzoate (3.7 g,

0.022 mol) in 40 mL of dry THF was carefully added (i.e. small portions) phenyliodosyl bis[trifluoroacetate] (a.k.a. PIFA; 14.19 g, 0.033mol). The resulting green-black mixture was stirred for 30 minutes at 0°C, and then at room temperature for 4-6 h, until a final orange-yellow color indicated a complete reaction. The volatile solvents (THF and TFA by-product) were evaporated *in vacuo*, and the crude dark red oil (containing excess diene) was purified by silica gel chromatography, using a gradient of 1:7→2:3 EtOAc/hexane. The pure product **101** was a bright yellow viscous oil (6.44 g, 96% yield).

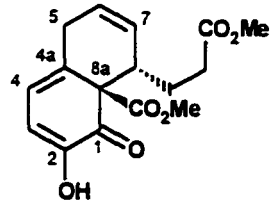


101

IR (neat film): 2951, 1731, 1693 (CO), 1246; **^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm):** 1.7-2.0 (H-5 (1H) and $C\underline{H}_2CH_2CO_2CH_3$ (1H), complex m), 2.2-2.7 ($C\underline{H}_2C\underline{H}_2CO_2CH_3$ (3H), H-5 (1H), and H-8, complex m), 3.35 (H-4a, ddd, *J*= 11.7, 6.3, 6.0 Hz), 3.66 ($CH_2CH_2CO_2C\underline{H}_3$, s, 3H), 3.76 (8a-$CO_2C\underline{H}_3$, s, 3H), 5.66 (H-6, m, *J*= 10.1, 2.4 Hz), 5.76 (H-7, dd, *J*= 10.1, 2.0 Hz), 6.32 (H-3, d, *J*= 9.9 Hz), 7.37 (H-4, dd, *J*= 9.9, 6.3 Hz); **^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm):** 25.0 ($\underline{C}H_2CH_2CO_2CH_3$), 31.8, 32.1 (C-5, $CH_2\underline{C}H_2CO_2CH_3$), 40.3, 42.5 (C-4a, C-8), 51.5, 53.1 (2x $CO_2\underline{C}H_3$), 66.0 (C-8a), 122.8 (C-7), 126.9 (C-6), 129.9 (C-3), 155.6 (C-4), 171.9, 173.0 (2x $\underline{C}O_2CH_3$), 183.6 (C-2), 190.8 (C-1); **LRMS (EI) *m/e*:** 306 (13%, M^+), 275 (68%), 215 (100%), 187 (88%), 173 (59%), 139 (67%), 107 (67%), 91 (60%); **HRMS (EI):** Calc'd for $C_{16}H_{18}O_6$: 306.11034; Found: 306.11099.

4.16 Synthesis of (*syn* 8-H,8a-CO_2CH_3)-8-[2'-[(methoxy)carbonyl]ethyl]-8a-[(methoxy)-carbonyl]-2-hydroxy-1,5,8,8a-tetrahydronaphthalene-1-one (**102**)

In an oven-dried round-bottom flask, KH (0.116 g of 35% mineral oil suspension; 1.01 mmol) was washed with 10 mL of dry hexane. Anhydrous dimethoxyethane (DME, 30 mL) was transferred to this flask, followed with trimethylsilylchloride (0.54 mL, 4.2 mmol), and the mixture stirred. A solution of diketone **101** (0.259 g, 0.844 mmol) dissolved in 20 mL anhydrous DME was transferred by cannula into this reaction flask, and the resulting yellow mixture was heated to reflux for 4-5 h, until the final mixture appeared orange-brown in color. The mixture was then cooled in ice, carefully diluted with sat. NH_4Cl (20 mL), and rendered mildly acidic with 1N HCl. The crude product was extracted into 100 mL EtOAc, and this layer was washed twice with brine solution (50 mL each), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to a crude orange oil (0.291 g). Purification of the crude oil by silica gel chromatography, using 1:4 EtOAc-Hexane eluant system, afforded **102** as a bright yellow semi-solid product (0.213 g, 82%).



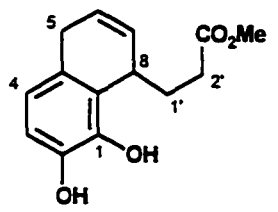
102

IR (neat film): 3418 (br, OH), 1736 (C=O, esters), 1645 (C=O, dienone), 1216 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm):** 1.33 ($\underline{CH_2}CH_2CO_2CH_3$, 1H, m, *J*= 13.2, 6.0 Hz), 1.58 ($\underline{CH_2}CH_2CO_2CH_3$, 1H, m, *J*=12.7, 6.5, 5.8 Hz), 2.27 ($CH_2\underline{CH_2}CO_2CH_3$, 2H, m, *J*= 14.6, 9.7 Hz), 3.00 (H-5, 2H, narrow m, *J*=20.9 Hz), 3.45 (H-8, 1H, m, *J*= 10.7, 5.3, 4.8 Hz), 3.63, 3.66 (2xCO_2CH_3, s, 2x3H), 5.68 (H-6, dt, *J*= 9.9, 3.4 Hz), 5.85 (H-7, m, *J*=

9.8, 5.3 Hz), 6.13 (OH, broad s), 6.25 (H-4, dd, *J*= 6.9, 2.0 Hz), 6.48 (H-3, d, *J* =6.9 Hz); **^{13}C NMR (50 MHz, $CDCl_3$), δ (ppm):** 26.2 (C-8), 31.4, 32.8 ($\underline{C}H_2\underline{C}H_2CO_2CH_3$), 45.6 (C-5), 51.7, 53.4 ($2xCO_2CH_3$), 65.9 (C-8a), 116.3, 119.0, 126.2, 128.4 (C-3, C-4, C-6, C-7), 138.4 (C-4a), 145.9 (C-2), 167.8 (8a-$\underline{C}O_2CH_3$), 173.4 ($CH_2CH_2\underline{C}O_2CH_3$), 193.7 (C-1); **LRMS (EI) *m/e*:** 306 (1.5%, M^+), 275 (4.0%, M-OCH_3), 247 (16%, M-CO_2CH_3), 215 (46%), 187 (26%), 173 (100%), 143 (23%), 115 (31%).

4.17 Synthesis of 8-[2'-[(methoxy)carbonyl]ethyl]-1,2-dihydroxy-5,8-dihydronaphthalene (**103**)

A solution of 2,3-dihydroxybenzoic acid (2.0 g, 0.013 mol) in dry THF (30 mL) was mixed with excess freshly distilled methyl (4*E*)-4,6-heptadienoate (20.06 g, 0.143 mol; bp= 75°C, 20 mmHg), and stirred under argon atmosphere for 10 min at 0°C prior to the careful addition of bis[trifluoroacetoxy]iodobenzene (a.k.a. PIFA) (6.71 g, 0.0156mol) in small portions. The resulting dark solution was stirred for 2h while warming to room temperature. The reaction mixture was then concentrated *in vacuo*, and the excess diene removed by chromatography (silica gel 60, 1:6 EtOAc-hexane eluant). *(Note: distillation is preferred for reactions with ≥20 mmol of reactant).* The crude product, a yellow oil, was precipitated as a white powder in 1:4 ether-hexane (2.51 g, 77.7 % yield), which was recrystallized as pale yellow prisms in 1:4 EtOAc-hexane.

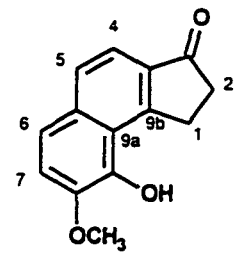


103

mp 90°-92°C; **IR (KBr):** 3388 (OH), 3020, 2952, 1710 (CO), 1626, 1496, 1443, 1264, 797, 732 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm):** 1.82 ($C\underline{H}_2CH_2CO_2CH_3$, m, *J*= 14.2, 8.8 Hz), 2.02 ($C\underline{H}_2CH_2CO_2CH_3$, m, *J*=14.1, 10.1, 8.5 Hz), 2.37 ($CH_2C\underline{H}_2CO_2CH_3$, 1H, dt, *J*= 17.4, 5.6 Hz), 2.51 ($CH_2C\underline{H}_2CO_2CH_3$, 1H, ddd, *J*=17.4, 10.1, 5.4 Hz), 3.30 (H-5, 2H, dm, *J*= 21.3 Hz), 3.54 (H-8, m, *J*= 8.8, 6.2 Hz), 3.73 (CO_2CH_3, s, 3H), 5.73 (OH at C-2, s), 5.97 (H-6 and H-7, 2H, m), 6.56 (H-4, d, *J*= 8.1 Hz), 6.75 (H-3, d, *J*= 8.1 Hz), 7.26 (OH H-bonded, sharp singlet); **^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm):** 29.4, 30.2, 31.2 (C-5, $\underline{C}H_2\underline{C}H_2CO_2CH_3$), 33.2 (C-8), 52.2 ($CH_2CH_2CO_2\underline{C}H_3$), 113.1 (C-3), 119.5 (C-4), 124.5, 126.9ppm (C-4a, C-8a), 126.1, 127.4 (C-6, C-7), 141.2, 142.2 (C-1, C-2), 177.4 ($CH_2CH_2\underline{C}O_2CH_3$); **LRMS (EI, GCMS) *m/e*:** No molecular ion, 216 (62%, M-CH_3OH), 161 (47%), 143 (100%), 131 (14%), 115 (67%); **Anal.** Calc'd. for $C_{16}H_{18}O_6$: C, 67.73%; H, 6.49 %. Found: C, 67.86%; H, 6.70%.

4.18 Synthesis of 9-hydroxy-8-methoxy-2,3-dihydro-1*H*-benz[*e*]indene-3-one (**105**)

A cooled solution (0°C) of **109** (1.47 g, 6.44 mmol) in 100 mL dry CH_2Cl_2 was treated with a large excess of neat titanium tetrachloride (20 mL, 0.182 mol, d= 1.726 g/mL) under argon atmosphere, and stirred for 1h. The reaction was then quenched at 0°C by the careful addition of 100 mL of 5% v/v $HCl_{(aq)}$. The CH_2Cl_2 layer was separated, and the aqueous layer extracted again with CH_2Cl_2 (20 mL). The combined CH_2Cl_2 extracts were further washed with water, dried (Na_2SO_4) and concentrated *in vacuo* to afford a crude brown oil. The pure product was obtained by washing this crude oil with a small amount of ether, which dissolved the impurities and left behind **105** as a tan amorphous solid (0.712 g, 48.5% yield).

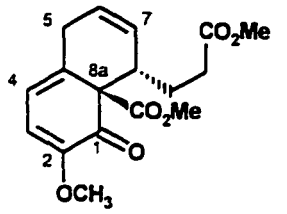


105

IR (KBr): 3220 (OH), 1673 (CO), 1343, 1280, 1090, 828 cm^{-1}; **^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm):** 2.74 (H-2, 2H, m), 3.77 (H-1, 2H, m), 4.03 (OCH_3, s, 3H), 6.29 (OH, sharp s), 7.35, 7.44 (H-6 and H-7, 2H, each d (AB_q) J = 8.8 Hz), 7.55, 7.64 (H-4 and H-5, 2H, each d (AB_q) , J= 8.5 Hz); **^{13}C NMR (50 MHz, DMSO-d^6) δ (ppm):** 28.7 (C-2), 35.7 (C-1), 56.8 ($O\underline{C}H_3$), 116.5, 116.9, 119.3 (C-5, C-6, C-7), 121.8 (C-9a), 128.0 (C-4), 132.3, 133.7 (C-3a, C-9), 143.7, 144.0 (C-9b, C-5a), 156.1 (C-8), 206.1 (C-3); **LRMS (EI) *m/e*:** 228 (100%, M^+), 213 (72%), 185 (23%), 157 (14%), 128 (15 %), 115 (5%); **Anal.** Calc'd for $C_{14}H_{12}O_3$: C, 73.67%; H, 5.29%. Found: C, 73.60%; H, 5.42%.

4.19 Synthesis of (*syn* 8-H, 8a-CO_2CH_3)-8-[2'-[(methoxy)carbonyl]ethyl]-8a-[(methoxy)carbonyl]-2-methoxy-1,5,8,8a-tetrahydronaphthalene-1-one (**106**)

To a chilled solution (0°C) of enol **102** (0.43 g, 1.4 mmol) in diethyl ether (20 mL) was added dropwise over 30 min. a freshly prepared ethereal solution of diazomethane (CH_2N_2) (*ca.* 4.2 mmol in 30 mL diethyl ether). The excess CH_2N_2 was neutralized with glacial acetic acid, and the ether phase was washed with water (4×50 mL) until mildly acidic (pH 5). The ether phase was dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give **106** as white needles (0.39 g, 87% yield).



106

mp 116-117°C; **IR (KBr):** 2961, 1744 (CO, esters), 1671 (CO, dienone), 1642 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm):** 1.33 ($C\underline{H}_2CH_2CO_2CH_3$, 1H, m, *J*= 13.2, 10.7, 5.7 Hz), 1.63 ($C\underline{H}_2CH_2CO_2CH_3$, 1H, m, *J*= 13.1, 6.0,4.3 Hz), 2.24 ($CH_2C\underline{H}_2CO_2CH_3$, m, 2H, *J*= 16.3, 6.1 Hz), 2.95 (H-5, dm, 2H, *J*=21.0 Hz), 3.39 (H-8, m, *J*= 10.8, 5.3, 4.8 Hz), 3.58, 3.62, 3.69 ($2xCO_2CH_3$, OCH_3, each signal 3H, s), 5.63 (H-6, t, *J*= 9.8, 6.7 Hz), 5.83 (H-7, m, *J*= 9.8, 5.3 Hz), 6.18 (H-3, d, *J*= 7.1 Hz), 6.21 (H-4, dd, *J*= 7.1, 1.2 Hz); **^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm):** 26.2 (C-8), 31.4, 32.5 ($\underline{C}H_2\underline{C}H_2CO_2CH_3$), 45.3 (C-5), 51.5, 53.1 ($2xCO_2\underline{C}H_3$), 55.4 ($O\underline{C}H_3$), 66.3 (C-8a), 113.7, 118.2, 125.8, 128.7 (C-3, C-4, C-6, C-7), 138.2 (C-4a), 149.7 (C-2), 167.9 (8a-$\underline{C}O_2CH_3$), 173.4 ($CH_2CH_2\underline{C}O_2CH_3$), 192.3 (C-1); **LRMS (EI) *m/e*:** 320 (<0.5%, M^+), 289 (2%, M-OCH_3), 261 (5%, M-CO_2CH_3), 229 (35%, M-[CO_2CH_3+CH_3OH]), 187 (100%), 155 (16%), 115 (16%); **HRMS (EI):** Calc'd for $C_{17}H_{20}O_6$: 320.12599; Found: 320.12670; **Anal.** Calc'd for $C_{17}H_{20}O_6$: C, 63.74; H, 6.29. Found: C, 64.00; H, 6.34.

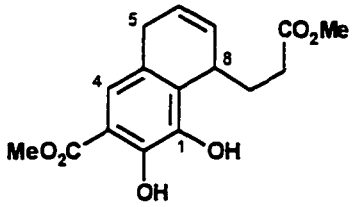
4.20 Synthesis of 8-[2'-[(methoxy)carbonyl]ethyl]-3-[(methoxy)carbonyl]-1,2-dihydroxy-5,8-dihydronaphthalene (**107**)

Following the procedure described in section 4.9 for rearrangements with TFA, compound **102** (0.20 g, 0.65 mmol) was mixed with neat TFA (5 mL) at room

temperature. The reaction was complete after 12-16 h. The crude product was recrystallized in ether and gave grey-white prisms (0.13 g, 65% yield).

Following the procedure described in section 4.10 for rearrangements with Me_3OBF_4, compound **102** (0.35 g, 1.14 mmol) was dissolved in dry CH_2Cl_2 (10 mL) and mixed with Me_3OBF_4 (0.23 g, 1.55 mmol) at 0°C. The reaction was stirred at 0°C for 30 min., then at room temperature for 24 h. The pure product **107** was obtained as grey-white prisms from ether (0.21 g, 60% yield).

Following the procedure described in section 4.10 for rearrangements with Et_3OBF_4, compound **102** (0.843 g, 2.75 mmol) was dissolved in dry CH_2Cl_2 (50 mL) and mixed with Et_3OBF_4 (3.3 mL of 1M solution in CH_2Cl_2, 3.31 mmol, 1.2 equiv.) at 0°C. The pure product **107** was obtained as a grey-white solid (0.497 g, 59% yield).



107

mp 74°-76°C; **IR (KBr):** 3410 (H-bonded OH, sharp), 2953 (C-H), 1720 (C=O), 1674, 1445, 781, 688 cm $^{-1}$; **^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm):** 2.00 ($C\underline{H}_2CH_2CO_2CH_3$, 1H, m, *J*= 5.3, 4.5 Hz), 2.16 ($CH_2C\underline{H}_2CO_2CH_3$, 2H, m, *J*= 5.3 Hz), 2.30 ($C\underline{H}_2CH_2CO_2CH_3$, 1H, m, *J*= 9.6 Hz), 3.28 (H-5, dm, 2H, *J*= 20.9 Hz), 3.60 ($CH_2CH_2CO_2C\underline{H}_3$, 3H, s), 3.83 (H-8, narrow m), 3.94 (Ar-$CO_2C\underline{H}_3$, 3H, s), 5.78 (OH at C-1, s), 5.89 (H-7, dm, *J*= 9.9, 3.3 Hz), 6.0 (H-6, ddd, *J*= 9.9, 4.8, 2.2 Hz), 7.16 (H-4, s), 10.6 (H-bonded OH at C-2, s); **^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm):** 29.2, 29.6, 30.4 (C-5, $\underline{C}H_2\underline{C}H_2CO_2CH_3$), 33.8 (C-8), 51.4 ($CH_2CH_2CO_2\underline{C}H_3$), 52.2 ($CO_2\underline{C}H_3$ at C-3), 110.3 (C-3), 118.9 (C-4), 125.8 (C-6), 128.0 (C-7), 126.6 (C-4a), 130.7 (C-8a), 141.7 (C-

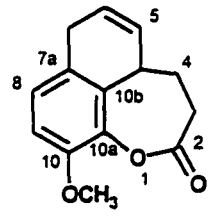
1), 146.1 (C-2), 170.6 ($\underline{C}O_2CH_3$ at C-3), 174.3 ($CH_2CH_2\underline{C}O_2CH_3$); **LRMS (EI)** ***m/e***: 306 (M^+, 13%), 274 (15%, M-CH_3OH), 219 (23%), 187 (100%), 159 (17%), 84 (25%); **Anal.** Calc'd for $C_{16}H_{18}O_6$: C, 62.74%; H, 5.92%. Found: C, 62.92%; H, 5.94%.

4.21 Synthesis of 10-methoxy-2-oxo-3,4,4a,7-tetrahydro-2*H*-naphth[1,8-*bc*]-oxepin (**108**)

Method A: A deoxygenated solution of **106** (0.993 g, 3.10 mmol) in 20 mL absolute methanol was mixed with a deoxygenated solution of NaOH (3.09 g, 0.0773 mol) in 50 mL of 1:1 methanol-water, at room temperature for 30 min. The mixture was then washed with ether to remove organic impurities, and the alkaline aqueous layer was separated, diluted with ethyl acetate (100 mL) and acidified to pH 2 with 3N HCl. The ethyl acetate extract was washed with water, dried (Na_2SO_4), filtered and concentrated to a brown oil, which was redissolved in CH_2Cl_2 (20 mL) and treated with excess trifluoroacetic anhydride (TFAA; 2.2 mL, 0.015 mol). After 1h at room temperature, all volatile solvents were evaporated *in vacuo*, and the residual oil was dissolved in ether, washed twice with water, dried (Na_2SO_4), and concentrated. The resulting orange oil was further purified by chromatography (silica gel 60, 2:3 EtOAc-hexane eluant) which gave colorless prisms from ether (0.603 g, 84.5% yield).

Method B: A deoxygenated solution of **113** (0.307 g, 1.17 mmol) in 30 mL of absolute methanol was treated with a deoxygenated solution (30 mL) of 1N NaOH. After 30 min., the reaction was complete, and the mixture was washed with ether to remove

impurities. The alkaline layer was separated, diluted with ethyl acetate (50 mL), and acidified with 3N HCl to pH 3. The ethyl acetate layer was washed twice with water, dried (Na_2SO_4), and concentrated to a pale yellow oil. The oil was redissolved in CH_2Cl_2 (5 mL) and treated with excess trifluoroacetic anhydride (TFAA; 3.3 mL, 0.02 mol) for 1h. All volatile solvents were evaporated *in vacuo*, and the residual oil extracted into ether, washed twice with water, dried (Na_2SO_4), and concentrated to colorless crystals (0.257 g, 95% yield).

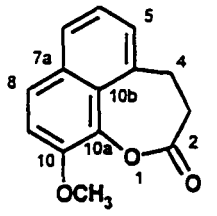


108

mp 93°-94°C; **IR (KBr):** 2924 (C-H), 1753 (C=O), 1500, 1283 (Ar-OCH_3), 1141, 796, 660 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm):** 1.69 (H-4, 1H, m, *J*= 12.0, 9.0 Hz), 2.45 (H-3, 2H, m), 2.55 (H-4, 1H, m, *J*= 8.6 Hz), 3.40 (H-7, 2H, m, *J*= 21.7 Hz), 3.70 (H-4a, m, *J*= 9.1, 8.3 Hz), 3.85 (OCH_3, 3H, s), 5.82-5.92 (H-5, H-6, 2H, m, *J*= 10.1 Hz), 6.87 (H-9, d, *J* = 8.5 Hz), 6.98 (H-8, d, *J*= 8.5 Hz); **^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm):** 28.4, 30.7, 33.6 (C-3, C-4, C-7), 32.7 (C-4a), 56.1 ($O\underline{C}H_3$), 111.5 (C-9), 124.2, 125.7, 126.4 (C-5, C-6, C-8), 126.1, 127.7 (C-7a, C-10a), 140.1 (C-10b), 147.5 (C-10), 171.3 (C-2); **LRMS (EI) *m/e*:** 230 (29%, M^+), 175 (33%), 143 (100%), 115 (67%), 103 (11%), 77 (12%); **Anal.** Calc'd. for $C_{14}H_{14}O_3$: C, 73.03%; H, 6.13%. Found: C, 72.93%; H, 5.98%.

4.22 Synthesis of 10-methoxy-2-oxo-3,4-dihydro-2*H*-naphth[1,8-*bc*]oxepin (**109**)

A solution of **108** (0.298 g, 1.29 mmol) in 30 mL of dry benzene was mixed with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (0.294 g, 1.29 mmol), and the dark orange mixture was heated at reflux for 30 min, when the mixture has a brown and turbid appearance. The mixture is cooled to room temperature, filtered to remove the hydroquinone by-product, and the filtrate was evaporated *in vacuo* to give a crude green-black oil, which was purified by flash chromatography (silica gel 60, 1:1 EtOAc-hexane eluant), and crystallized with ether to afford **109** as bright yellow microcrystals (0.253 g, 86% yield).

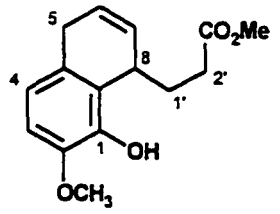


109

mp 118-120°C; **IR (KBr):** 2997, 1763 (C=O), 1600, 1274, 1129, 820 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm):** 3.01 and 3.41 ($C\underline{H}_2C\underline{H}_2CO_2$-, 4H, m), 4.01 ($OCH_3$, 3H, s), 7.25 (H-7 and H-8, 2H, m), 7.34 (H-9, d, J = 9.0 Hz), 7.68 (H-6, m), 7.70 (H-5, d, J =9.1 Hz); **^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm):** 31.1, 34.7 (C-3, C-4), 57.2 ($O\underline{C}H_3$), 103.2, 124.7, 130.2, 133.8 (C-4a, C-7a, C-10a, C-10b), 114.6 (C-9), 123.4, 127.0, 127.3, 127.5 (C-5, C-6, C-7, C-8), 148.4 (C-10), 171.9 (C-2); **LRMS (EI) *m/e*:** 228 (100%, M^+), 200 (33%, M-CO), 185 (78%), 171 (31%), 157 (33%), 143 (26%), 115 (20%); **HRMS (EI):** Calc'd for $C_{14}H_{12}O_3$: 228.0786. Found: 228.0786; **Anal.** Calc'd. for $C_{14}H_{12}O_3$: C, 73.67%; H, 5.29%; Found: C, 73.72%; H, 5.40%.

4.23 Synthesis of 8-[2'-[(methoxy)carbonyl]ethyl]-1-hydroxy-2-methoxy-5,8-dihydronaphthalene (**113**)

The best method for synthesizing **113** by methylation of **103** involved the use of trimethyloxonium tetrafluoroborate, rather than diazomethane, as the methylating reagent. A solution of **103** (0.60 g, 2.42 mmol) in anhydrous CH_2Cl_2 (40 mL) was stirred with oven-dried K_2CO_3 (3.34g, 0.0242 mol, 10 equiv.) for 30 min. at room temperature. The mixture was then cooled to 0°C and purged with argon prior to adding Me_3OBF_4 (0.715 g, 4.83 mmol, 2 equiv.). The reaction was stirred for 1 h at 0°C, then overnight (16-24 h) at room temperature. A saturated solution of NH_4Cl was carefully added to this mixture (in ice), followed by 5% HCl to neutralize the excess base. The product was extracted three times into 100-mL portions of CH_2Cl_2, then dried (Na_2SO_4), filtered, and concentrated to a dark brown oil. The product was purified by column chromatography (silica gel 60, 1:4 EtOAc-hexane eluant) which gave **113** (0.60 g, 95% yield) as a pale yellow oil.



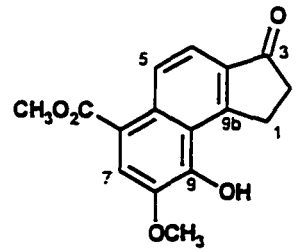
113

IR (neat): 3465, 2952, 1731, 1494, 1258, 793, 690 cm^{-1}; **^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm):** 1.93-2.37 ($C\underline{H}_2C\underline{H}_2CO_2CH_3$, 4H, m), 3.28 (H-5, 2H, m), 3.59 (CO_2CH_3, s, 3H), 3.82 (H-8, m), 3.89 (OCH_3, s, 3H), 5.77 (OH, sharp s), 5.86 (H-6, dm, J = 10.0 Hz), 6.0 (H-7, dm, J= 10.0 Hz), 6.61 (H-4, d, J= 8.3 Hz), 6.72 (H-3, d, J= 8.3 Hz); **^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm):** 29.4, 29.9, 30.4 ($\underline{C}H_2\underline{C}H_2CO_2CH_3$ and C-5), 33.5 (C-8), 51.3

($CO_2\underline{C}H_3$), 56.1 (OCH_3), 108.9 (C-3), 118.7 (C-4), 124.1 (C-8a), 125.9, 128.5 (C-6 and C-7), 128.7 (C-4a), 142.6 (C-1), 144.8 (C-2), 174.6 ($\underline{C}O_2CH_3$); **LRMS (EI)** ***m/e:*** 262 (42%, M^+), 230 (7%, M-CH_3OH), 202 (7%, M-[CO+CH_3OH]), 187 (16%), 175 (51%), 143 (100%), 131 (17%), 115 (68%); **HRMS (EI):** Calc'd for $C_{15}H_{18}O_4$: 262.1205; Found: 262.1205.

4.24 Synthesis of **114** and **115** by Friedel-Crafts reaction with **105**

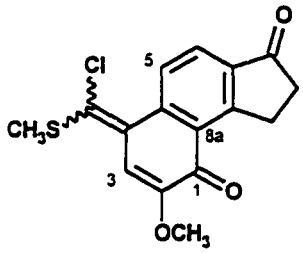
To a cooled solution (0°C) of **105** (0.50 g, 2.2 mmol) in dry CH_2Cl_2 was added (by syringe) trichloromethyl methyl sulfide (0.47 g, 2.9 mmol, 1.3 equiv.) and neat $TiCl_4$ (1.2 mL, 10.9 mmol, 5 equiv.), and the purple-black mixture was stirred under argon atmosphere for 2.5 h while warming to room temperature. The reaction was quenched with 5% $HCl_{(aq)}$ and stirred for several hours. The red CH_2Cl_2 phase was separated and combined with two CH_2Cl_2 extracts of the upper acidic layer. The pooled CH_2Cl_2 extracts were washed once with brine solution, then dried (Na_2SO_4), filtered, and concentrated to an amorphous crude orange solid which contained **114** and unreacted **105** (0.13 g, 0.57 mmol). The orange solid was stirred for 2 h with methanol, then concentrated to a pale-yellow amorphous solid **115** (0.090 g, 20% yield).



115

6-[(methoxy)carbonyl]-9-hydroxy-8-methoxy-1,2-dihydrobenz[*e*]indene-3-one (**115**)

IR (KBr): 3262 (OH), 1682, 1585, 1197 cm^{-1}; **^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm):** 2.79 (H-1 or H-2, 2H, m), 3.84 (H-2 or H-1, 2H, m), 4.03 and 4.12 ($OC\underline{H}_3$ and $CO_2C\underline{H}_3$, each s, 2x3H), 6.75 (OH, sharp s), 7.75 (H-4, d, J = 9.1 Hz), 8.14 (H-7, s), 8.96 (H-5, d, J= 9.1 Hz); **^{13}C NMR (50 MHz, DMSO-d^6) δ (ppm):** 29.3 (C-1), 35.6 (C-2), 52.1 ($CO_2\underline{C}H_3$), 56.9 ($O\underline{C}H_3$), 117.2 (C-6), 118.8, 120.1 (C-5, C-7), 121.6 (C-9a), 124.9 (C-4), 131.3, 133.8 (C-9b, C-3a), 142.6 (C-5a), 148.9 (C-8), 156.2 (C-9), 168.2 ($\underline{C}O_2CH_3$), 206.1 (C-3); **LRMS (EI) *m/e*:** 286 (100%, M^+), 255 (35%, M-OCH_3), 228 (4%), 155 (8%), 128 (11%); **HRMS (EI):** Calc'd for $C_{16}H_{14}O_5$: 286.0841; Found: 286.0839.



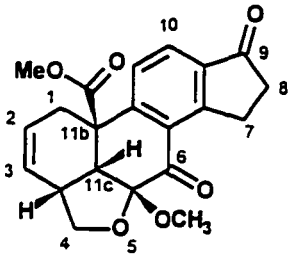
114

4-[(1'-chloro-1'-methylthio)methyl]-2-methoxycyclopenta[7,8]naphtho-1,4-quinone methide-7-one (**114**)

^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 2.73 (SCH_3, 3H, s), 2.79 (H-1, 2H, m), 3.62 (H-2, 2H, m), 3.89 (OCH_3, 3H, s), 7.28 (H-7, s), 7.93 (H-5, d, J = 7.8 Hz), 8.54 (H-4, d, J = 7.8 Hz); **LRMS (EI) *m/e*:** 322 (43%, M+2), 320 (100%, M^+), 305 (32%, M-CH_3), 277 (55%, M-[CO+CH_3]), 270 (17%, M-CH_3Cl), 255 (48%), 241 (11%), 171 (10%), 139 (10%). No further analyses were performed as there was insufficient sample available, and because this compound was not useful for synthesizing viridin.

4.25 Synthesis of pentacyclic methyl esters **120a-b** by IMDA reaction with **115**

Freshly distilled (2*E*)-2,4-pentadienol (0.121 g, 1.43 mmol; bp = 56°C, 20 mmHg) was added to a cooled solution (0°C) of **115** (0.082 g, 0.29 mmol) in 15 mL dry THF, followed by the addition of PIFA (0.16 g, 0.37 mmol). The reaction was stirred at room temperature for 4h, followed by the removal of THF *in vacuo*. The orange residual oil was concentrated and purified by chromatography (silica gel 60, 1:4→2:3 EtOAc-hexane eluant gradient) to afford **120a** as pale yellow semi-solid, and **120b** as white microcrystals from ethyl acetate.

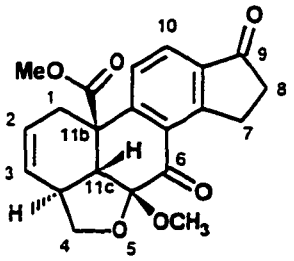


120a
(*endo*)

endo-(*syn*-3a-H, 5a-OCH_3, 11b-CO_2CH_3, 11c-H)-11b-[(methoxy)carbonyl]-5a-methoxy-1,3a,4,5a,6,9,11b,11c-octahydro[cyclopenta[7,8]phenanthro[10,1-*bc*]furan]-6,9-dione (**120a**)

IR (KBr): 2931, 1718 (CO), 1592, 1436, 1245, 1040 cm^{-1}; **^{1}H NMR (250 MHz, $CDCl_3$)** δ **(ppm):** 2.05 (H-1α, 1H, dm, *J* =17.0 Hz (gem), 2.74 (H-8, 2H, m), 2.82 (H-1β, m, partly obscured by H-8, 1H), 3.18 (H-3a, m, *J* =6.6 Hz), 3.29 (OCH_3, s, 3H), 3.65 (H-11c, dd, *J* =8.6 and 2.2 Hz (latter from W-coupling)), 3.75 (H-7, 2H, m), 3.82 (H-4α, d, partly obscured by CO_2CH_3 singlet), 3.86 (CO_2CH_3, s, 3H), 4.17 (H-4β, dd, *J* =8.5 (geminal), 6.5 Hz), 5.71 (H-3, m, *J* =9.8 Hz), 5.88 (H-2, m), 7.16 (H-11, d, *J* =8.0 Hz), 7.87 (H-10, d, *J* =8.0 Hz); **^{13}C NMR (50 MHz, $CDCl_3$)** δ **(ppm):** 25.7, 35.0, 36.3 (C-1, C-7, C-8), 37.9 (C-11c), 50.0 (C-3a), 50.1 ($CO_2\underline{C}H_3$), 50.4 (C-11b), 52.9 ($O\underline{C}H_3$), 73.1 (C-4), 104.1

(C-5a), 124.9, 126.4, 128.1, 128.2 (C-2, C-3, C-10, C-11), 130.1, 137.5 (C-6a, C-9a), 150.8 (C-6b), 156.1 (C-11a), 172.9 ($\underline{C}O_2CH_3$), 190.7 (C-9), 205.5 (C-6); **LRMS (EI)** ***m/e*:** 368 (20%, M^+), 336 (29%, M-CH_3OH), 308 (20%, M-[CO+CH_3OH]), 277 (19%), 249 (37%), 221 (21%), 207 (26%), 178 (43%), 165 (35%), 152 (27%), 115 (22%), 99 (48%), 59 (100%); **HRMS (EI):** Calc'd for $C_{21}H_{20}O_6$: 368.1259; Found: 368.1253.



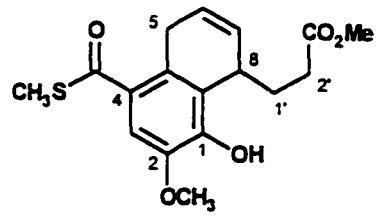
120b (*exo*)

exo-(*anti*-3a-H,11c-H; *syn*-5a-OCH_3, 11b-CO_2CH_3,11c-H)-11b-[(methoxy)carbonyl]-5a-methoxy-1,3a,4,5a,6,9,11b,11c-octahydro[cyclopenta[7,8]phenanthro[10,1-*bc*]furan]-6,9-dione (**120b**)

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 2.55 (H-3a, m), 2.74 (H-7 or H-8, 2H, m), 2.95 (H-11c, d, J=12.3 Hz), 3.01 (H-1α, 1H, dm, J=18.8, 3.9, 2.3 Hz), 3.28 (H-1β, 1H, dm, J =18.7, 5.8, 3.5, 2.2 Hz), 3.51 (H-8, 1H, m), 3.54 (OCH_3, 3H, s), 3.63 (CO_2CH_3, 3H, s), 3.72 (H-8, 1H, m), 3.77 (H-4α, 1H, dd, J=7.3, 11.2 Hz), 4.13 (H-4β, 1H, dd, J=7.1 Hz), 5.80 (H-3, m, J =9.8, 4.0 Hz), 5.88 (H-2, m, J =9.7, 6.6, 3.7 Hz), 7.52 (H-11, d, J =8.2 Hz), 7.98 (H-10, d, J =8.0 Hz); **LRMS (EI) *m/e*:** 368 (11%, M^+), 336 (38%, M^+-CH_3OH), 308 (28%), 277 (30%), 249 (69%), 221 (44%), 178 (100%), 165 (71%), 152 (46%), 115 (26%), 99 (45%). No further analyses were performed as there was insufficient sample available.

4.26 Synthesis of 8-[2'-[(methoxy)carbonyl]ethyl]-4-[(methylthio)carbonyl]-1-hydroxy-2-methoxy-5,8-dihydronaphthalene (**121**)

A solution of **113** (3.15 g, 0.012 mol) in 70 mL dry CH_2Cl_2 was mixed at 0°C with trichloromethyl methyl sulfide (2.38 g, 0.0144 mol, 1.2 equiv.) in a 500 mL round-bottomed flask which was purged with argon. While cold, neat $TiCl_4$ (6.6 mL, 0.060 mol, 5 equiv.) was transferred to the flask *via* syringe, after which the mixture turned opaque and purple-black in color. The reaction was allowed to stir under argon at 0°C for 1h, and then was quenched by careful dropwise addition of 200 mL of 5% HCl, after which the mixture becomes bright orange in color. After having stirred for 1h, the methylene chloride layer was separated, and the acidic aqueous layer washed twice more with 100 mL portions of CH_2Cl_2. The combined CH_2Cl_2 extracts were then washed free of residual acid with brine solution until the washings measured pH 6, then dried (Na_2SO_4), filtered and concentrated *in vacuo* to an orange-brown oil. The crude product was purified by chromatography (silica gel 60, 1:4 EtOAc-hexane eluant), to afford the pure product **121** as a bright yellow semi-solid (3.49 g, 86.5% yield), which was crystallized to yellow needles in diethyl ether.



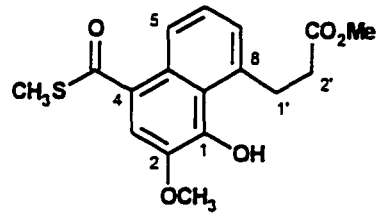
121

mp 68-70°C; **IR (KBr):** 3422 (OH), 2940 (CH), 1730 (CO_2CH_3), 1663 ($COSCH_3$), 1470, 1298 (Ar-OCH_3); **^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm):** 1.93-2.39 ($CH_2CH_2CO_2CH_3$, 4H, m), 2.42 (SCH_3, 3H, s), 3.44-3.57 (H-5, 2H, dm, J_{gem}=22.3 Hz, J_{vic}=2.9 Hz), 3.59

(CO_2CH_3, 3H, s), 3.83 (H-8, m), 3.92 (OCH_3, 3H, s), 5.86 (H-7, m, $J_{6,7}$=9.9; J_{vic}=2.1 Hz), 5.97 (H-6, ddd, $J_{6,7}$=9.9; J_{vic}=4.9, 2.3 Hz), 6.26 (OH, s), 7.32 (H-3, s); **^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm):** 12.3 (SCH_3), 27.9, 30.1, 30.3 ($\underline{C}H_2\underline{C}H_2CO_2CH_3$ and C-5), 33.3 (C-8), 51.3 ($CO_2\underline{C}H_3$), 56.1 ($O\underline{C}H_3$), 109.8 (C-3), 125.4 (C-4), 125.9, 127.1 (C-6, C-7), 127.8, 129.1 (C-4a, C-8a), 143.6 (C-1), 146.2 (C-2), 174.3 ($\underline{C}O_2CH_3$), 193.1 ($\underline{C}OSCH_3$); **LRMS (EI) *m/e*:** 336 (3%, M^+), 305 (6%, M-OCH_3), 289 (93%, M-SCH_3), 257 (35%), 201 (100%), 159 (15%); **Anal.** Calc'd for $C_{17}H_{20}O_5S$: C, 60.69%; H, 5.99%; S, 9.53%. Found: C, 60.72%; H, 5.96%; S, 9.27%.

4.27 Synthesis of 8-[2'-[(methoxy)carbonyl]ethyl]-4-[(methylthio)carbonyl]-1-hydroxy-2-methoxy-naphthalene (**122**)

A solution of **121** (3.49 g, 0.0104 mol) in 100 mL dry benzene was stirred under argon atmosphere and heated to a gentle reflux in a 500 mL two-necked round-bottomed flask, fitted with a reflux condenser and pressure-equalized dropping funnel. A solution of DDQ (2.36 g, 0.0104 mol) in 100 mL dry benzene was transferred by cannula into the dropping funnel, and added dropwise over 30 min. to the heated mixture. The whole mixture was refluxed for 4h, producing a turbid brown solution. After cooling to room temperature, the mixture was filtered to remove hydroquinone by-product, washed with benzene, and the filtrate concentrated to a black-green oil. This crude product was purified by chromatography (using 1:3 EtOAc-hexane as eluant), to afford a yellow semi-solid (3.09 g, 89% yield), which can discolor upon standing to a yellow-brown solid (should be stored under inert atmosphere in the dark until next use). The pure product **122** was a white powder from ether.



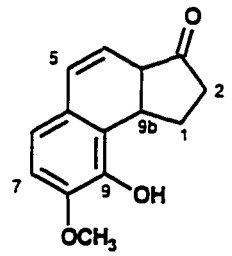
122

mp 174-176°C; **IR (KBr):** 3146 (OH), 1686, 1652, 1574, 1104, 878, 767 cm^{-1}; **^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm):** 2.53 (SCH_3, 3H, s), 2.74 ($CH_2\underline{CH_2}CO_2CH_3$, 2H, t, $J\approx$ 7.8 Hz), 3.63 ($\underline{CH_2}CH_2CO_2CH_3$, 2H, t, $J \approx$ 7.8 Hz), 3.67 (CO_2CH_3, 3H, s), 4.06 (OCH_3, 3H, s), 6.79 (OH, s), 7.29-7.37 (H-6, H-7, 2H, m), 7.84 (H-3, s), 8.37 (H-5, dd, $J_{5,6}$ =8.3, $J_{5,7}$= 1.6 Hz); **^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm):** 12.8 (SCH_3), 32.5, 36.9 ($\underline{C}H_2\underline{C}H_2CO_2CH_3$), 51.5 ($CO_2CH_3$), 57.3 ($OCH_3$), 114.6 (C-3), 122.5 (C-4), 124.1, 126.2, 129.0 (C-5, C-6, C-7), 127.88, 127.97 (C-8a, C-8), 136.7 (C-4a), 140.6 (C-1), 145.5 (C-2), 173.9 ($\underline{C}O_2CH_3$), 193.8 ($\underline{C}OSCH_3$); **LRMS (EI) *m/e*:** 334 (45%, M^+), 302 (9%, M-CH_3OH), 287 (53%, M-SCH_3), 255 (100%), 227 (49%), 201 (19%), 155 (12%), 128 (15%); **Anal.** Calc'd for $C_{17}H_{18}O_5S$: C, 61.06%; H, 5.42%; S, 9.59%. Found: C, 61.27%; H, 5.47%; S, 9.37%.

4.28 Synthesis of **125** and **126** by aliphatic Friedel-Crafts reaction with **104**

The starting carboxylic acid **104** (0.83 g, 3.34 mmol), prepared by saponification of **113** with excess NaOH in 1:1 MeOH-H_2O at room temperature, was dissolved in CH_2Cl_2 (3 mL) and treated with trifluoroacetic anhydride (5.0 mL, 0.035 mol, 10 equiv.) for 1 h at room temperature. All volatile solvents were subsequently evaporated *in vacuo*, and the residual brown oil redissolved in dry CH_2Cl_2 (20 mL) and cooled to 0°C under argon atmosphere. Neat $TiCl_4$ (1.85 mL, 0.017 mol, 5 equiv.) was syringed into this flask,

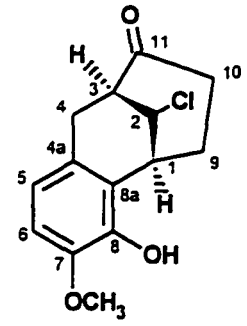
and the dark brown mixture was stirred for 1 h, while warming up to room temperature. The reaction was then quenched with 5% v/v $HCl_{(aq)}$ (75 mL), and the products were extracted into CH_2Cl_2 (100 mL). The CH_2Cl_2 extract was separated, washed with brine solution, dried (Na_2SO_4), filtered, and concentrated to an orange foam (0.805 g). The crude product was purified by chromatography (silica gel 60, 1:9→1:3 EtOAc-hexane gradient), affording a white foam-like semi-solid (0.502 g, 65% yield), which was approximately 1:1 mixture of products **125** and **126**. The compounds were separated by fractional crystallization in ether, where **126** was crystallized as colorless prisms. Compound **125** remained in the mother liquor, which was then purified (silica gel 60, 1:4 EtOAc-hexane eluant) to obtain dark crystals from ether.



125

9-hydroxy-8-methoxy-2,3,3a,9b-tetrahydro-1*H*-benz[*e*]indene-3-one (**125**)

mp 136-138°C; **IR (KBr):** 3315 (OH), 2937 (CH), 1702 (C=O), 1620, 1496, 1437, 1274 (Ar-OCH_3); **^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm):** 1.79 (H-9b, m, *J* =10.6, 9.5 Hz), 2.33 (H-2, 2H, m), 3.25 (H-3a, dm, *J* =9.5 Hz), 3.82 (H-1, 2H, m), 3.88 (OCH_3, 3H, s), 5.50 (H-4, dd, *J* = 9.8, 2.2 Hz), 5.71 (OH, sharp s), 6.43 (H-5, dd, *J* =9.5, 3.3 Hz), 6.63, 6.71 (H-6 and H-7, 2H, each d (AB_q), *J*= 8.2 Hz); **^{13}C NMR (63 MHz) δ (ppm):** 28.2 (C-1), 33.4 (C-9b), 36.8 (C-2), 47.1 (C-3a), 56.0 (OCH_3), 108.3 (C-7), 118.9, 119.5, 127.7 (C-4, C-5, C-6), 121.6 (C-5a), 125.1 (C-9a), 142.6 (C-9), 146.4 (C-8), 219.3 (C-3); **LRMS (EI) *m/e*:** 230 (100%, M^+), 187 (15%), 174 (87%), 159 (66%), 131 (30%), 115 (17%), 103 (15%), 77 (14%); **HRMS (EI):** Calc'd for $C_{14}H_{12}O_3$: 230.0943; Found: 230.0943.



126

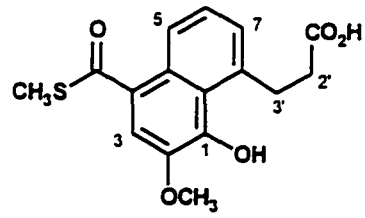
2-Chloro-8-hydroxy-7-methoxy-1,2,3,4-tetrahydro-1,3-propanonaphthalene-11-one (**126**)

IR (neat film): 3444, 2942, 1709, 1496, 1262, 1093 cm^{-1}; **^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm):** 1.96, 2.23 (H-9 and H-10, each 2H m), 2.68 (H-5, 1H, d, J_{gem}=18.0 Hz), 3.07 (H-8 or H-6, m), 3.46 (H-5, 1H, dd, J_{gem}=18.0, J_{vic}=6.9 Hz), 3.86 (H-6 or H-8, m), 3.89 (OCH_3, 3H, s), 4.48 (CHCl, t, J =3.4 Hz), 5.74 (OH, s), 6.65, 6.78 (H-3 and H-4, 2H, each d (AB_q) , J= 8.3 Hz); **^{13}C NMR (75 MHz) δ (ppm):** 27.7. 28.5, 34.9 (C-4, C-9, C-10), 35.3, 52.2, 56.0, 57.9 (C-1, C-2, C-3, and OCH_3), 109.6 (C-6), 118.9 (C-5), 121.0, 126.3 (C-4a, C-8a), 143.1, 144.7 (C-7, C-8), 210.7 (C-11); **LRMS (EI) *m/e*:** 268 (37%, M+2), 266 (100%, M^+), 231 (33%, M-Cl), 203 (21%, M-COCl), 187 (26%), 174 (20%), 162 (16%), 143 (4%), 115 (6%); **HRMS (EI):** Calc'd for $C_{14}H_{15}O_3Cl$: 266.0709; Found: 266.0713.

4.29 Synthesis of 3-(2-hydroxy-4-[(methylthio)carbonyl]-2-methoxynaphth-8-yl)-propanoic acid (**129**)

To a solution of the naphthyl thiol ester **122** (2.0 g, 5.9 mmol) in THF (50 mL) was added 20 mL of 3N $HCl_{(aq)}$ and the mixture was heated at 50-60°C (internal temperature) for 3 days, until all the starting material was consumed (monitored by TLC).

The mixture was then cooled, and THF was evaporated *in vacuo*. The residue was extracted into ether, and washed with brine solution until the aqueous phase was near pH 6. The ether layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford **129** as a pale yellow amorphous solid (2.178 g crude yield).

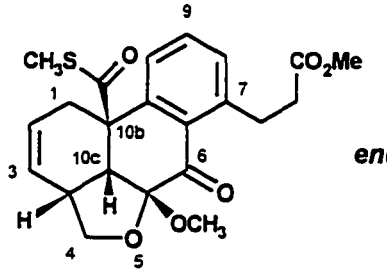


mp 148-150°C; **IR (KBr):** 3400-2800 (COOH, OH), 1682 (broad), 1575, 1340, 1292, 1106 cm^{-1}; **^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm):** 2.53 ($COSCH_3$, 3H, s), 2.80 ($CH_2CH_2CO_2H$, 2H, dd, J = 7.5, 8.1 Hz), 3.64 ($CH_2CH_2CO_2H$, 2H, dd, J = 7.6, 8.0 Hz), 4.06 (OCH_3, 3H, s), 6.82 (OH, sharp s), 7.31 (H-6 and H-7, 2H, m), 7.84 (H-3, s), 8.38 (H-5, dd, J = 8.0, 1.9 Hz); **^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm):** 12.8 ($COS\underline{C}H_3$), 32.3, 36.6 ($\underline{C}H_2\underline{C}H_2CO_2H$), 57.3 ($O\underline{C}H_3$), 114.6 (C-3), 122.7 (C-4), 124.2, 126.2, 129.0 (C-5, C-6, C-7), 127.8, 127.9 (C-8, C-8a), 136.4 (C-4a), 140.6 (C-1), 145.4 (C-2), 178.2 (CO_2H), 193.8 ($\underline{C}OSCH_3$); **LRMS (EI) *m/e*:** 320 (79%, M^+), 273 (100%, M-SCH_3), 255 (85%, M-[SCH_3+H_2O]), 227 (51%), 213 (8%), 155 (7%), 128 (13%); **HRMS (EI):** Calc'd for $C_{16}H_{16}O_5S$: 320.0718; Found: 320.0712.

4.30 Synthesis of phenanthrofuran thiol esters **130a-b** by IMDA reaction with **122**

Freshly distilled (2*E*)-2,4-pentadienol (8.440 g, 0.100 mol, 10 equiv.; bp=56°C@20 mmHg) was added to a cooled solution (0°C) of **122** (3.36 g, 0.0100 mol) in 100 mL dry THF, followed by the addition of PIFA (5.175 g, 0.0120 mol). The dark

orange mixture was stirred for 3-4 h while warming from 0°C to room temperature, after which time the final color appeared as bright yellow. Solid $NaHCO_3$ (1.68 g, 0.02 mol) was then added to the flask, and the mixture stirred an additional 15 min., prior to evaporation of all volatile solvents *in vacuo* (THF, TFA by-product). Excess 2,4-pentadienol was removed by distillation under reduced pressure, and the crude residual oil extracted into 300 mL EtOAc, washed with water (2×100 mL), dried (Na_2SO_4), filtered, and concentrated to an orange oil. The diastereomeric products were chromatographically separated (silica gel 60, 1:4→2:3 EtOAc-hexane eluant) to afford both pure *endo*-**130a** as colorless prisms (1.49 g, 36% yield), as well as pure *exo*-**130b** as white microcrystals (0.887 g, 21% yield).

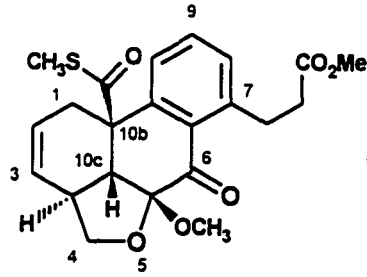


130a
***endo* (β-H-3a)**

(*endo*)-[*syn* 3a-H,5a-H,10b-H,10c-$COSCH_3$]-7-[2'-[(methoxy)carbonyl]ethyl]-5a-methoxy-10b-[(methylthio)carbonyl]-3a,4,5a,6,10b,10c-hexahydro-1*H*-phenanthro[10,1-*bc*]furan-6-one (**130a**)

mp 135-136°C; **IR (KBr):** 2950 (CH), 1733, 1705, 1668, 1586, 1429, 1288, 1173 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm):** 2.38 (H-1α, 1H, dm, J =17.6, 1.9 Hz), 2.53 ($C\underline{H}_2CH_2CO_2CH_3$, 1H, m), 2.76 (H-1β and $C\underline{H}_2CH_2CO_2CH_3$, 2H, m), 3.08 (H-3a, m, J = 6.86, 9.16 Hz), 3.20 ($CH_2C\underline{H}_2CO_2CH_3$, 2H, m), 3.36 (H-10c, d, J =4.6 Hz), 3.38 (OCH_3, 3H, s), 3.62 (H-4α, 1H, d, J =8.77 Hz), 3.63 (CO_2CH_3, 3H, s), 4.13 (H-4β, 1H, dd, J_{gem} = 8.4, J_{vic} = 6.8 Hz), 5.61 (H-3, m, J =9.9, 3.8 Hz), 5.87 (H-2, m), 7.07 (H-10, d, J =8.0 Hz), 7.27 (H-8, d, J =7.63 Hz), 7.38 (H-9, dd, J =7.63, 8.0 Hz); **^{13}C NMR (63 MHz,**

$CDCl_3$) δ (ppm): 12.3 ($COS\underline{C}H_3$), 28.4, 33.4, 35.6 (C-1, $\underline{C}H_2\underline{C}H_2CO_2CH_3$), 38.3 (C-10c), 48.9 (C-3a), 50.4, 51.5 ($O\underline{C}H_3$, $CO_2\underline{C}H_3$), 54.8 (C-10b), 73.1 (C-4), 105.7 (C-5a), 124.6, 125.6, 126.9, 130.3, 132.1 (C-2, C-3, C-8, C-9, C-10), 133.2 (C-6a), 142.1, 142.9 (C-7, C-10a), 173.3 ($\underline{C}O_2CH_3$), 192.8 ($\underline{C}OSCH_3$), 202.7 (C-6); **LRMS (EI) *m/e*:** 416 (3%, M^+), 385 (8%, M-OCH_3), 369 (100%, M-SCH_3), 337 (17%), 309 (16%), 277 (12%), 249 (32%), 221 (30%), 179 (25%), 165 (20%), 138 (18%); **Anal.** Calc'd for $C_{22}H_{24}O_6S$: C, 63.44%; H, 5.81%; S, 7.69%. Found: C, 63.24%; H, 5.82%; S, 7.84%.



130b
***exo* (α-H-3a)**

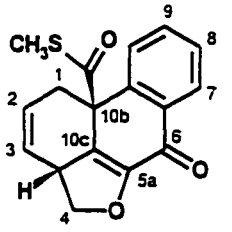
(*exo*)-[5a,10b,10c-*syn*;3a,10c-*anti*]-7-[2'-[(methoxy)carbonyl]ethyl]-5a-methoxy-10b-[(methylthio)carbonyl]-3a,4,5a,6,10b,10c-hexahydro-1*H*-phenanthro[10,1-*bc*]furan-6-one (**130b**)

mp 107-109°C; **IR (KBr):** 2944 (CH), 1735, 1694, 1664, 1587, 1442, 1300, 1133, 993 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm):** 2.33 (SCH_3, 3H, s), 2.55 (H-3a, m), 2.63 ($C\underline{H}_2CH_2CO_2CH_3$, 1H, m, J =9.5, 8.4, 6.5 Hz), 2.80 ($C\underline{H}_2CH_2CO_2CH_3$, 1H, m, J =8.8, 8.4, 6.1 Hz), 2.98-3.04 ppm (H-1, 2H, m, overlaps H-10c), 3.02 (H-10c, d, J =12.2 Hz), 3.23-3.35 ppm ($CH_2\underline{C}H_2CO_2CH_3$, 2H, m), 3.38 ppm ($OCH_3$, 3H, s), 3.66 ($CO_2CH_3$, 3H, s), 3.72 (H-4α, 1H, dd, J_{gem}= 7.2, J_{vic}= 11.5 Hz), 4.07 (H-4β, 1H, dd, J_{gem}= 7.2, J_{vic}= 6.8 Hz), 5.75 (H-3, dm, J =9.9 Hz), 5.82 (H-2, m, J =9.9 Hz), 7.39 (H-8 and H-10, 2H, dd, J= 7.6, 8.0 Hz), 7.51 (H-9, t, J= 7.63 Hz); **^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm):** 13.2 ($COS\underline{C}H_3$), 30.7, 34.8, 35.3 (C-1, $\underline{C}H_2\underline{C}H_2CO_2CH_3$), 41.3 (C-10c), 48.9 (C-3a), 50.6, 51.5 ($O\underline{C}H_3$, $CO_2\underline{C}H_3$), 55.0 (C-10b), 70.1 (C-4), 101.3 (C-5a), 123.8, 127.0, 127.6,

132.6, 132.8 (C-2, C-3, C-8, C-9, C-10), 131.7 (C-6a), 140.8, 145.3 (C-7, C-10a), 173.5 ($\underline{C}O_2CH_3$), 192.8 ($\underline{C}OSCH_3$), 203.5 (C-6); **LRMS (CI, NH_3) *m/e*:** 434 (74%, M+NH_4), 417 (7%, M+H), 385 (10%, M-OCH_3), 369 (100%, M-SCH_3), 354 (32%), 341 (7%), 293 (18%), 249 (5%), 221 (9%), 178 (3%); **Anal.** Calc'd for $C_{22}H_{24}O_6S$: C, 63.44%; H, 5.81%; S, 7.69%. Found: C, 63.26%; H, 5.59%; S, 7.77%.

4.31 Synthesis of (*syn* 3a-H, 10b-$COSCH_3$)-10b-[(methylthio)carbonyl]-3a, 4, 6, 10b-tetrahydro-1*H*-phenanthro[10,1-*bc*]furan-6-one (**131**)

Compound **79a** (0.136 g, 0.41 mmol) was treated with 2 mL neat TFA at room temperature, and after 20 min., the reaction was complete by TLC analysis. The excess TFA was evaporated, and the residue extracted into EtOAc (100 mL), washed with water (until pH was near neutral), dried (Na_2SO_4), filtered, and concentrated to afford **131** as light pink crystalline plates (0.127 g) in quantitative yield.



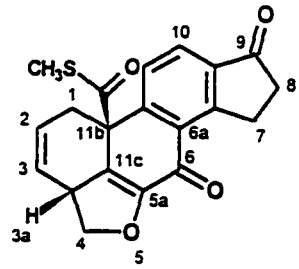
131

mp (decomposed ≥145°C); **IR (KBr):** 1667, 1191, 994, 750 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm):** 2.15 (H-1, 1H, obscured m), 2.22 ($COSCH_3$, 3H, s), 3.77 (H-1, 1H, dd, J = 17.3, 3.5 Hz), 4.16 (H-4 (1H) and H-3a, 2H total, m), 5.05 (H-4, 1H, narrow m), 5.78 (H-2 and H-3, 2H total, m), 7.48-7.66 (H-8, H-9, H-10, 3H total, m), 8.31 (H-7, d, J = 7.6 Hz); **^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm):** 12.2 ($COSCH_3$), 37.6 (C-1), 41.0 (C-3a), 55.6 (C-10b), 76.7 (C-4), 126.1, 126.3, 126.6, 127.4, 128.4 and 132.7 (C-2, C-3, C-7, C-

8, C-9, C-10), 132.0 (broadened signal, C-6a and C-10c), 142.5 (C-5a), 150.2 (C-10a), 197.9 ($COSCH_3$); **LRMS (EI)** ***m/e*****:** 298 (4%, M^+), 270 (4%, M-CO), 223 (55%, M-$COSCH_3$), 195 (39%), 165 (100%), 152 (30%), 75 (68%, $COSCH_3$), 47 (42%, SCH_3); **HRMS (EI):** Calc'd for $C_{17}H_{14}O_3S$: 298.0664; Found: 298.0666; **Anal.** Calc'd for $C_{17}H_{14}O_3S$: C, 68.44; H, 4.73; S, 10.74. Found: C, 67.20; H, 4.90; S, 10.43.

4.32 Synthesis of (*syn*-3a-H, 11b-$COSCH_3$)-11b-[(methylthio)carbonyl]-3a, 4, 6, 7, 8, 9, 11b-heptahydro[cyclopenta[7,8]phenanthro[10,1-*bc*]furan]-6,9-dione (**132**)

The *endo*-pentacyclic thiol ester **80a** (0.10 g, 0.26 mmol) was treated with neat TFA (5 mL) at room temperature, and after 15 min., the reaction was complete. The TFA was evaporated, and the residue extracted into EtOAc (100 mL), washed with water twice, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford **132** (0.090 g, 98% yield) as white microcrystals.



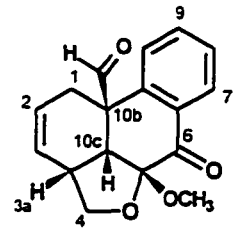
132

mp decomposes >160°C; **IR (KBr):** 1714, 1662, 1406, 1064 cm^{-1}; **^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm):** 2.17 (H-1α, 1H, obscured m), 2.24 ($COSCH_3$, 3H, s), 2.75 (H-7, 2H, m), 3.75 (H-8, 2H, m), 3.81 (H-1β, 1H, obscured m), 4.18 (H-4α (1H) and H-3a, 2H total, m), 5.05 (H-4β, 1H, distorted dd), 5.79 (H-2 and H-3, 2H total, narrow m), 7.55 (H-11, d, J = 8.1 Hz), 7.93 (H-10, d, J = 8.1 Hz); **^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm):** 12.3 ($COSCH_3$), 28.2 (C-1), 36.3, 37.9 (C-7 and C-8), 40.9 (C-3a), 56.3 (C-11b), 76.4 (C-4),

126.3, 126.4, 126.5 and 127.1 (C-2, C-3, C-10 and C-11), 129.5 (C-11c), 130.9 (C-6a), 137.9 (C-9a), 149.3 (C-5a), 150.5 (C-6b), 157.7 (C-11a), 176.3 (C-6), 197.1 ($COSCH_3$), 206.2 (C-9); **LRMS (EI)** ***m/e*****:** 352 (18%, M^+), 324 (9%, M-CO), 277 (100%, M-$COSCH_3$), 249 (12%), 207 (32%), 178 (24%), 152 (7%), 75 (10%, $COSCH_3$); **HRMS (EI):** Calc'd for $C_{20}H_{16}O_4S$: 352.0769; Found: 352.0771.

4.33 Synthesis of **133** and **134** by desulfurization of thiol ester **79a**

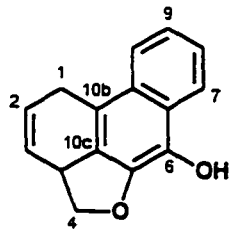
The *endo*-thiol ester **79a** (0.50 g, 1.5 mmol), which was prepared according to the procedure of Randhawa,[66] was dissolved in dry CH_2Cl_2 (7 mL) and mixed with a catalytic amount of 10% Pd/C (0.08 g, 75 μmol, 0.05 equiv.) and then lastly with triethylsilane (1.2 mL, 7.6 mmol, 5 equiv.). The reaction was initially exothermic, then allowed to stir at room temperature for 5 days while monitoring the reaction progress by TLC. The mixture was then filtered through a pad of Celite, washing with CH_2Cl_2, and the filtrate was concentrated *in vacuo* to give a white solid immersed in a viscous yellow oil. The white solid was removed by filtration and crystallized in ether to afford the aldehyde **133** as white needles (0.115 g, 27% yield). Characterization of this product was also reported by Randhawa.[66] The yellow oil from the crude product was purified by column chromatography (silica gel 60, 100% hexane→1:9 EtOAc-hexane eluant gradient), and gave the phenanthrophenol **134** (yield was undetermined). Since **134** was an undesired product, it was not characterized fully.



133

(*endo*)-[*syn*-3a-H, 5a-OCH_3, 10b-CHO, 10c-H]-10b-formyl-5a-methoxy-3a,4,5a,6,10b,10c-hexahydro-1*H*-phenanthro[10,1-*bc*]furan-6-one (**133**)

mp 138-139°C; **IR (KBr):** 2955, 1739, 1703, 1584, 1162 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm):** 2.04 (H-1α, 1H, m, J = 17.3 Hz), 2.62 (H-1β, 1H, m, J = 17.3, 5.6 Hz), 3.11 (H-3a, m), 3.28 (OCH_3, 3H, s), 3.41 (H-10c, dd, J = 8.5, 1.7 Hz), 3.87 (H-4α, 1H, dd, J = 8.5, 1.8 Hz), 4.20 (H-4β, 1H, dd, J = 8.5, 6.5 Hz), 5.70 (H-3, dm, J = 9.9 Hz), 5.84 (H-2, m), 7.08 (H-10, dd, J = 7.0, 0.9 Hz), 7.44 (H-8 or H-9, dt, J = 7.6, 1.2 Hz), 7.54 (H-9 or H-8, dt, J = 7.6, 1.5 Hz), 7.89 (H-7, dd, J = 7.6, 1.5 Hz), 9.82 (CHO, s); **^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm):** 33.1 (C-1), 37.2 (C-10c), 47.9 (C-3a), 50.0 (OCH_3), 51.1 (C-10b), 72.9 (C-4), 104.1 (C-5a), 113.4 (C-6a), 124.9, 125.2, 128.3, 128.7, 129.2, 133.7 (C-2, C-3, C-7, C-8, C-9, C-10), 143.0 (C-10a), 190.7 (C-6), 201.2 (CHO).



134

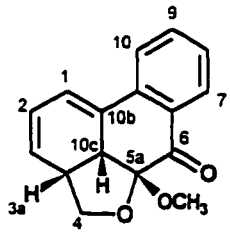
6-hydroxy-3a,4-dihydro-1*H*-phenanthro[10,1-*bc*]furan (**134**)

^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 3.45 (H-1, 1H, m), 3.77 (H-1, 1H, dm, J = 18.6 Hz), 4.08 (H-4 (1H) and H-3a, 2H total, m), 4.96 (H-4, 1H, narrow m), 5.86 (OH, s), 6.09 (H-3, dd, J = 10.1, 3.0 Hz), 6.22 (H-2, m), 7.41 (H-8 and H-9, 2H, overlapping t, J = 7.3 Hz), 7.78 (H-7 or H-10, 1H, d, J = 7.8 Hz), 8.16 (H-10 or H-7, 1H, d, J = 7.8 Hz). This

compound was not useful for synthesizing viridin and therefore was not characterized completely.

4.34 Synthesis of [*syn*-3a-H, 5a-OCH_3, 10c-H]-5a-methoxy-3a,5a,6,10c-tetrahydro-4*H*-phenanthro[10,1-*bc*]furan-6-one (**135**)

A solution of *endo*-thiol ester **79a** (0.20 g, 0.61 mmol) in 10 mL of warm ethanol was carefully added (under argon atmosphere) to a suspension of excess wet Raney Ni (W-2 grade) in 20 mL ethanol. The mixture was heated at reflux while monitoring the reaction progress by TLC. After 24h, a single product was observed on TLC and the reaction was cooled to room temperature, then filtered through a pad of Celite while washing with 95% ethanol. The filtrate was concentrated to a crude oil which was purified by column chromatography (silica gel 60, 1:3 EtOAc-hexane eluant) which quantitatively gave **135** as a colorless oil.



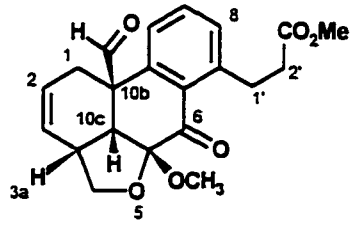
135

^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 3.35 (H-3a, m), 3.52 (H-10c, d, *J* = 10.3 Hz), 3.61 (OCH_3, 3H, s), 3.68 (H-4α, 1H, dd, *J* - 7.7, 8.9 Hz), 4.28 (H-4β, 1H, dd, *J* = 7.8, 8.6 Hz), 5.98 (H-3, dd, *J* = 9.5, 4.7 Hz), 6.10 (H-2, dd, *J* = 9.4, 5.6 Hz), 6.57 (H-1, dd, *J* = 5.2, 1.8 Hz), 7.32 (H-8 or H-9, ddd, *J* = 8.0, 7.0, 1.4 Hz), 7.47 (H-9 or H-8, ddd, *J* = 8.0, 7.0, 1.4 Hz), 7.58 (H-10, dd, *J* = 7.9, 1.0 Hz), 8.03 (H-7, dd, *J* = 7.6, 1.3 Hz); **^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm):** 36.7 (C-3a), 47.6 (C-10c), 52.3 (OCH_3), 75.2 (C-4), 103.6

(C-5a), 121.7, 124.1, 124.2, 126.6, 128.0, 128.5, 134.1 (C-1, C-2, C-3, C-7, C-8, C-9, C-10), 126.9 (C-6a), 129.6 (C-10a), 139.3 (C-10b), 191.3 (C-6); **LRMS (EI)** ***m/e*****:** 254 (60%, M^+), 225 (100%, M-[CHO]), 195 (26%, M-[CO+OCH_3]), 165 (14%); **HRMS (EI):** Calc'd for $C_{16}H_{14}O_3$: 254.0943; Found: 254.0932.

4.35 Synthesis of (*endo*)-[*syn*-3a-H, 5a-OCH_3, 10b-CHO, 10c-H]-7-[2'-[(methoxy)-carbonyl]ethyl]-10b-formyl-5a-methoxy-3a,4,5a,6,10b,10c-hexahydro-1*H*-phenanthro[10,1-*bc*]furan-6-one (**136a**)

In a 25-mL round-bottomed flask was dissolved **130a** (0.225 g, 0.540 mmol) in dry CH_2Cl_2 (8 mL), followed consecutively by the addition of a catalytic amount of 10% Pd-on-carbon (27 μmol, 30 mg, 0.05 equiv.), and then triethylsilane (260 μL, 1.62 mmol, 3 equiv.). The mixture was stirred under argon atmosphere for 3 days, then filtered through a 1" pad of Celite, washing with CH_2Cl_2. The filtrate was concentrated *in vacuo* to afford a semi-solid, which was filtered and washed with ether to give **136a** as a white powdered solid (0.163 g, 82% yield).



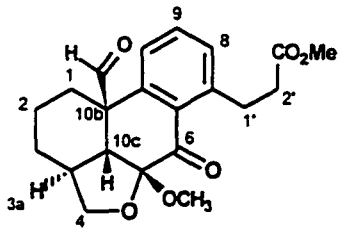
136a

mp 133-134°C; **IR (neat film):** 2950, 2910 cm^{-1}, 1726, 1588, 1445, 1165, 1030 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm):** 2.11 (H-1α, 1H, dm, J =17.7, 2.4 Hz), 2.57 (H-1β, 1H, dm, J =5.7, 1.4 Hz (latter from W-coupling with H-10c)), 2.61 ($CH_2CH_2CO_2CH_3$,

1H, m, J_{gem}=16.0, 8.9, 6.9 Hz), 2.84 ($C\underline{H}_2CH_2CO_2CH_3$, 1H, ddd, J=16.1, 9.0, 6.3 Hz), 3.06 (H-3a, m), 3.15 ($CH_2C\underline{H}_2CO_2CH_3$, 2H, m), 3.31 ($OCH_3$, 3H, s), 3.33 (H-10c, dd, J =8.7, 1.6 (W-coupling with H-1β), 3.68 (CO_2CH_3, 3H, s), 3.77 (H-4α, 1H, dd, J_{gem}=8.5, 2.0 Hz), 4.16 (H-4β, 1H, dd, J_{gem}=8.5, 6.4 Hz), 5.67 (H-3, dm, J =10.1, 2.8 Hz), 5.87 (H-2, m, J =10.1 Hz), 6.92 (H-10, dd, J =7.8, 0.9 Hz), 7.29 (H-8, dd, J =7.8, 0.7 Hz), 7.39 (H-9, t, J =7.7 Hz), 9.74 (CHO, s); **^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm):** 28.5, 31.8, 35.8 (C-1, $\underline{C}H_2\underline{C}H_2CO_2CH_3$), 37.3 (C-10c), 47.4 (C-3a), 50.9 (C-10b), 50.2, 51.6 ($O\underline{C}H_3$, $CO_2\underline{C}H_3$), 72.9 (C-4), 104.9 (C-5a), 123.4, 125.2, 128.7, 130.4, 132.5 (C-2, C-3, C-8, C-9, C-10), 132.4 (C-6a), 143.19, 143.25 (C-7, C-10a), 173.2 ($\underline{C}O_2CH_3$), 192.7 (C-6), 201.1 ($\underline{C}HO$); **LRMS (EI) *m/e*:** 370 (32%, M^+), 338 (60%, M-CH_3OH), 310 (62%, M-[CH_3OH+CO]), 279 (99%), 249 (66%), 237 (77%), 221 (80%), 179 (89%), 165 (100%); **Anal.** Calc'd for $C_{21}H_{22}O_6$: C, 68.09%; H, 5.99%. Found: C, 67.96%; H, 6.04%.

4.36 Synthesis of **137** by attempted desulfurization of **130b**

To a solution of the *exo*-thiol ester **130b** (13 mg, 30.5 μmol) in dry CH_2Cl_2 (2 mL) was added, in the following sequence, a catalytic amount of 10% Pd/C and triethylsilane (0.050 mL, 0.31 mmol, 10 equiv.). After 3 days, the *exo*-aldehyde **136b** was observed on TLC, but the reaction was stirred an additional 5 days before workup. The mixture was filtered through a pad of Celite, washing with CH_2Cl_2, then concentrated and purified by chromatography (silica gel 60, 1:3 EtOAc-hexane eluant) to a colorless oil, which was characterized as the over-reduced aldehyde **137**. Only ^{1}H-NMR analysis was performed, as this compound was not useful for synthesizing viridin.



137

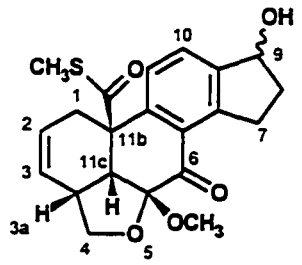
^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.24-1.35 and 1.83-1.89 (H-2 and H-3, 4H, m), 1.79 (H-1α, 1H, m), 1.93 (H-3a, m), 2.41 (H-10c, d, J =12.4 Hz), 2.51 (H-1β, dm, J =15.2 Hz), 2.64 ($C\underline{H}_2CH_2CO_2CH_3$, 1H, ddd, J_{gem}= 16.2, J= 8.5, 6.6 Hz), 2.77 ($C\underline{H}_2CH_2CO_2CH_3$, 1H, ddd, J_{gem}= 16.2, J = 8.6, 6.5 Hz), 3.32 ($CH_2C\underline{H}_2CO_2CH_3$, 2H, m, J = 16.2 Hz), 3.58 and 3.66 (OCH_3 and CO_2CH_3, 2x3H, s), 3.68 (H-4, 1H, dd, J_{gem}=7.6, 11.0 Hz), 4.00 (H-4, 1H, dd, J_{gem}=7.5, 6.6 Hz), 7.24 (H-10, d, J =7.6 Hz), 7.34 (H-8, d, J =7.6 Hz), 7.52 (H-9, t, J =7.7 Hz), 9.59 (CHO, s).

4.37 Synthesis of **138** by desulfurization of pentacyclic thiol ester **80a**

The *endo* thiol ester **80a** (0.030 g, 0.078 mmol) was dissolved in 1:1 CH_2Cl_2-THF (10 mL) and mixed with a catalytic amount of 10% Pd/C and lastly with excess triethyl silane (50 μL, 0.31 mmol, 4 equiv.), after which the reaction was temporarily exothermic. The mixture was stirred for 24 h, and then no more starting material was observed by TLC analysis. The mixture was filtered through Celite, washing with CH_2Cl_2, and concentrated to a yellow oil which contained the crude product **138** along with another isomeric aldehyde (which could not be positively identified yet appeared to resemble the C-3a epimer of **138** by ^{1}H-NMR analysis), as well as Et_3SiSCH_3 by product. The yield of **138** was not possible to determine due to the small scale of this reaction, and since only a crude ^{1}H-NMR spectrum was obtained, the characterization of **138** was incomplete.

4.38 Synthesis of **139** by reduction of **80a** with DIBAL-H

To a cooled solution (0°C) of the *endo* pentacyclic thiol ester **80a** (0.030 g, 0.080 mmol) in dry THF (5 mL) was added 1M DIBAL-H in hexane (80 μL, 0.08 mmol, 1 equiv.). The yellow solution was stirred for 6 h while warming to room temperature, after which unreacted starting material was still present (by TLC analysis). A second equivalent of DIBAL-H was added (70 μL, 0.07 mmol), and the mixture was stirred overnight at room temperature. The reaction was then quenched by adding water then 5% HCl (5 mL), and the product extracted into EtOAc, washing twice with brine solution. The EtOAc extract was dried (Na_2SO_4), filtered, and concentrated to a yellow oil. The ^{1}H-NMR spectrum of the crude product revealed a pair of isomeric peaks for some signals as well as the presence of the $COSCH_3$ peaks. The diastereomeric products were characterized from this spectrum as **139** (epimeric at C_9), and were formed in quantitative yield.



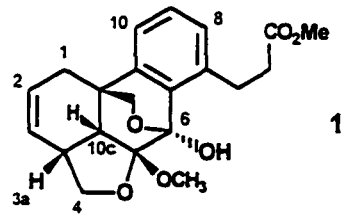
139

^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 2.2 (H-1, 1H, m), 2.3 ($COSCH_3$, 3H, s), 2.68 (H-7, 2H, m), 2.78 (H-1, 1H, obscured m), 3.15 (H-3a and H-8 (1H), 2H total, m), 3.32 (OCH_3, 3H, s), 3.57 (H-4 (1H) and H-11c, m), 4.1 (H-4, 1H, m), 5.18 (H-9, m), 5.58 (H-3, m), 5.82 (H-2, m), 7.0 (H-10, minor isomer, d), 7.18 (H-10, major isomer, d), 7.45 (H-11, minor isomer, d), 7.82 (H-11, major isomer, d).

4.39 Synthesis of **140** by reduction of **130a**

Method A: Following the procedure of Liu *et al.*,[74b] the *endo*-thiol ester **130a** (0.054 g, 0.13 mmol) was dissolved in 98% ethanol (2 mL), and then $NaBH_4$ (7.3 mg, 0.19 mmol) was added. After 5 h at room temperature, the reaction was complete (by TLC analysis; also the reaction became transparent yellow in appearance), and was quenched with sat. NH_4Cl solution . The mixture was extracted into EtOAc (30 mL), washed with brine, dried (Na_2SO_4), filtered, and concentrated to give the product **140** as a colorless oil in quantitative yield.

Method B: The *endo*-aldehyde **136a** (0.070 g, 0.19 mmol) was dissolved (with gentle warming) in absolute ethanol (3 mL), and $NaBH_4$ (0.012 g, 0.32 mmol) was added. The initially turbid mixture was stirred at room temperature and became a homogeneous solution after one minute. The reaction was complete after 30 min., and was quenched with sat. NH_4Cl solution. The mixture was extracted into EtOAc (50 mL), washed with brine, dried (Na_2SO_4), filtered and concentrated to a colorless oil which was identified to be **140** by ^{1}H-NMR at -50°C (223 K).



140

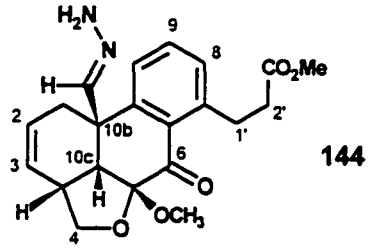
[*syn*-3a-H, 5a-OCH_3, 10b,6-methyleneoxy, 10c-H]-7-[2'-[(methoxy)carbonyl]ethyl]-6-hydroxy-5a-methoxy-10b,6-methyleneoxy-3a,4,5a,6,10b,10c-hexahydro-1*H*-phenanthro[10,1-*bc*]furan (**140**)

^{1}H NMR (500 MHz, 218 K, $CDCl_3$) δ (ppm): 1.66 (H-4α, 1H, dd, J_{gem}= 8.4, J_{vic}= 10.8 Hz), 2.20 (H-1β, 1H, d, J = 17.2 Hz), 2.57 (H-10c and H-1 (1H), narrow m, J = 7.2 Hz), 2.66, 2.75, 3.01, 3.50 ($C\underline{H}_2C\underline{H}_2CO_2CH_3$, 1H each signal, each narrow m), 2.89 (H-3a, narrow m), 3.37 (-CH_2O-, 1H, obscured d, J = 7.4 Hz), 3.40 (OCH_3, 3H, s), 3.57 ($CO_2C\underline{H}_3$, 3H, s), 3.81 (-CH_2O-, 1H, obscured d, J = 6.8 Hz), 3.87 (H-4β, obscured dd, J_{gem}= 8.4 Hz), 4.76 (OH, sharp s), 5.48 (H-3, narrow m), 6.02 (H-2, narrow m), 6.86 (H-10, d, J = 7.3 Hz), 7.05 (H-8, d, J = 7.4 Hz), 7.17 (H-9, t, J= 7.4 Hz); some of the ^{1}H-NMR signals for compound **140** at -50°C (218 K) are somewhat broadened, due to a dynamic equilibrium process; **^{13}C NMR (50 MHz, 218 K, $CDCl_3$) δ (ppm):** 27.1, 29.3 ($\underline{C}H_2\underline{C}H_2CO_2CH_3$), 36.3 (C-1), 38.0 (C-10c), 45.3 (C-3a), 50.1, 51.7 (OCH_3 and CO_3CH_3), 60.2 (C-10b), 72.5, 72.9 (C-4 and -CH_2O-), 98.5, 109.2 (C-5a and C-6), 121.6, 123.6, 125.6, 127.7, 130.2 (C-2, C-3, C-8, C-9, C-10), 133.3, 136.9, 139.1 (C-6a, C-10a, C-7), 174.4 (CO_2CH_3); **LRMS (EI) *m/e*:** 372 (20%, M^+), 341 (27%, M-OCH_3), 311 (100%, M-[OCH_3+CH_2O), 279 (53%), 221 (53%), 165 (53%). No further characterization was possible, as this compound decomposed during chromatographic purification on silica gel.

4.40 Synthesis of hydrazone **144**

To a cloudy mixture of the aldehyde **136a** (0.20 g, 0.54 mmol) in absolute ethanol (10 mL) was added hydrazine (0.14 mL, 4.3 mmol, 8 equiv.), and the mixture was heated to reflux through a mini-Soxhlet extractor, filled with molecular sieves (4Å), on top of which was fitted a reflux condenser. After 4 h, the homogeneous colorless solution was cooled to room temperature and the ethanol and excess hydrazine were evaporated *in*

vacuo. The residue was dried under vacuum at room temperature for 24 h to afford **144** as a white powder (0.185 g, 89% yield).



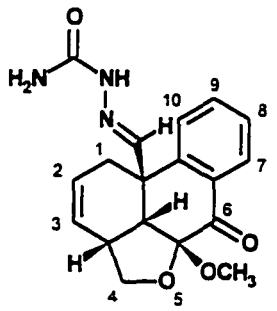
144

[syn-3a-H, 5a-OCH_3, 10b-CHN–NH_2, 10c-H]-7-[2'-[(methoxy)carbonyl]ethyl]-10b-formyl-5a-methoxy-3a,4,5a,6,10b,10c-hexahydro-1H-phenanthro[10,1-*bc*]furan-6-one-10b-hydrazone (**144**)

IR (KBr): 3314 (NH_2), 2886, 1643 (br), 1460, 1029 cm^{-1}; **^{1}H NMR (250 MHz, $CDCl_3$)** δ **(ppm):** 2.12 (H-1α, 1H, dm, J =15.7 Hz), 2.42 ppm (H-1β, 1H, dm, J =15.7), 2.63 ($C\underline{H}_2CH_2CO_2CH_3$, 1H, m), 2.85 ($C\underline{H}_2CH_2CO_2CH_3$, 1H, m), 3.08 ppm (H-3a, broad m), 3.17 ppm ($CH_2C\underline{H}_2CO_2CH_3$, 2H, m), 3.30 ppm ($OCH_3$, 3H, s), 3.43 ppm (H-10c, d, J =9.3 Hz), 3.68 ($CO_2C\underline{H}_3$, 3H, s), 3.67 (H-4α, 1H, dd, partly obscured by signal for CO_2CH_3), 4.13 (H-4β, 1H, dd, J_{gem}=7.7, J_{vic}=6.8 Hz), 5.35-5.55 (NH_2, broad), 5.67 (H-3, dm, J =10.5 Hz), 5.81 (H-2, m), 7.10 (H-10, d, J =7.5 Hz), 7.22 (H-8, d, J =7.5 Hz), 7.35 (H-9, t, J =7.5 Hz), 7.38 (CH=N, s); **LRMS (EI) *m/e*:** 385 (50%, M+H), 353 (100%, M^+-OCH_3), 325 (25%, M^+-CO_2CH_3), 311 (23%), 278 (20%), 221 (22%), 165 (34%); **Anal.** Calc'd for $C_{21}H_{24}N_2O_5$: C, 65.61%; H, 6.29%; N, 7.29%. Found: C, 61.43%; H, 6.22%; N, 7.71%.

4.41 Synthesis of semicarbazone **146**

Semicarbazide hydrochloride (0.043 g, 0.39 mmol, 1.1 equiv.) and sodium acetate (0.037 g, 0.46mmol, 1.3 equiv.) were dissolved in a solution of 1:1 EtOH-H_2O (5mL), to which was added the aldehyde **136a** (0.10 g, 0.35 mmol). The mixture was stirred well at room temperature for 1 h, then chilled for 15 min. The milky mixture was filtered, washing the filter cake with ice-cold water. The white solid product (good purity) was vacuum-dried over dessicant ($CaSO_4$), and gave a yield of 109 mg (91.6% yield) and was recrystallized in hot ethanol to afford colorless prisms.



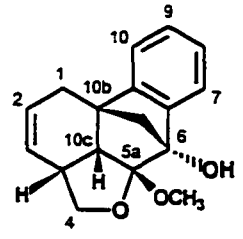
146

[syn-3a-H, 5a-OCH_3, 10b-CHN–$NHCONH_2$, 10c-H]-10b-formyl-5a-methoxy-3a, 4, 5a, 6, 10b, 10c-hexahydro-1H-phenanthro[10,1-*bc*]furan-6-one-10b-semicarbazone (**146**) mp 227-229°C; **IR (KBr):** 3603, 3380 (NH_2 doublet), 3177, 1710, 1692, 1609, 1408, 1033 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm):** 2.38 (H-1, 2H, m), 3.12 (H-3a, 1H, m), 3.33 ppm (H-4α, 1H, d, J =8.9 Hz), 3.38 (OCH_3, 3H, s, and H-10c, buried m), 4.16 (H-4β, 1H, dd, J_{gem}= 8.3, J_{vic}= 7.2 Hz), 4.70 (NH_2, 1H, broad s), 5.67 (H-3, m, J = 9.8 Hz), 5.85 (H-2, m, J = 9.9 Hz), 6.25 (NH_2, 1H, broad s), 7.06 (N<u>H</u>$CONH_2$, 1H, sharp s), 7.18 (H-10, d, J = 7.7 Hz), 7.40, 7.53 (H-8 and H-9, 2H, each t, J =7.5 Hz), 7.81 (H-7, d, J = 7.3 Hz), 8.55 (<u>H</u>C=N-$NHCONH_2$, s); **^{13}C NMR (75 MHz, DMSO-d^6) δ (ppm):** 33.6 (C-1), 37.8 (C-10c), 41.8 (C-10b), 48.0, 49.3 ($O\underline{C}H_3$, C-3a), 72.2 (C-4), 105.0 (C-5a),

124.6, 125.5, 127.3, 127.6, 127.9, and 133.4 (C-2, C-3, C-7, C-8, C-9, C-10), 133.9 (C-6a), 145.3 (HC=N-NHCONH$_2$), 145.7 (C-10a), 156.7 (HC=N-NHCONH$_2$), 190.9 (C-6); **LRMS (EI)** ***m/e*****:** 341 (4%, M$^+$), 310 (11%, M-OCH$_3$), 298 (8%, M-CONH$_2$), 282 (40%, M-NHCONH$_2$), 266 (22%), 222 (42%), 195 (31%), 165 (42%), 115 (20%), 86 (17%), 44 (100%); **HRMS (EI):** Calc'd for $C_{18}H_{19}N_3O_4$: 341.1376; Found: 341.1393.

4.42 Synthesis of **147** and **148** by Henbest-modified Wolff-Kishner reduction of **146**

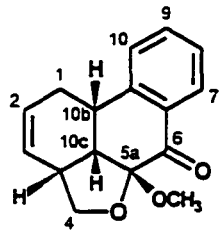
Following the procedure of Grundon *et al.*,[85a] potassium *tert*-butoxide was freshly resublimed (80-100°C @ 0.6 torr) and then transferred (in a glove-box) into an oven-dried 50 mL round-bottomed flask (0.079 g, 0.71 mmol, 1.5 equiv.), and dissolved in anhydrous toluene (10 mL). The vacuum-dried semicarbazone **146** (0.16 g, 0.47 mmol) was then added to this solution, and the mixture was heated at reflux for 48 h as the reaction was being monitored by TLC. After this time, the turbid dark brown mixture was cooled to 0°C, and quenched with sat. NH_4Cl (10 mL). The aqueous layer was separated, and the toluene layer was washed once with brine, dried (Na_2SO_4), filtered and concentrated. The residual brown oil was purified by column chromatography (silica gel 60, 1:6→1:4 EtOAc-hexane eluant gradient), which furnished two reaction products **147** (0.053 g, 42% yield) and **148** (0.011 g, 9% yield), both as colorless prisms.



147

[*syn*-3a-H, 5a-OCH_3, 6,10b-CH_2, 10c-H]-6-hydroxy-6,10b-methano-3a,5a,6,10b,10c-pentahydro-1*H*, 4*H*-phenanthro[10,1-*bc*]furan (**147**)

mp 120-122°C; **IR (KBr):** 3503 (OH), 2950, 1614, 1458 cm^{-1}; **^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm):** 1.79 (H-4α, 1H, dd, J_{gem}= 8.1, J_{vic}= 10.2 Hz), 2.18 (-C<u>H</u>$_2$-, 1H, d, J = 8.1 Hz), 2.25 (-C<u>H</u>$_2$-, 1H, d, J =8.1 Hz), 2.46 (H-1, 1H, dm, J =16.8 Hz), 2.67 (H-1, 1H, dd, J = 5.9, 1.0 Hz), 2.74 (H-10c, d, J = 12.8 Hz), 2.82 (H-3a, m), 3.44 (OCH_3, 3H, s), 3.46 (OH, s), 3.83 (H-4β, 1H, dd, J = 8.2, 9.14 Hz), 5.53 (H-3, dm, J = 9.9 Hz), 6.11 (H-2, m, J = 9.9, 5.9 Hz), 6.98 (H-10, d, J = 7.2 Hz), 7.04 (H-8 or H-9, t, J = 7.2 Hz), 7.19 (H-9 or H-8, t, J = 7.2 Hz), 7.36 (H-7, d, J = 7.3 Hz); **^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm):** 30.1, 30.9 (C-1, -<u>C</u>H$_2$-), 38.3 (C-10c), 43.9 (C-10b), 50.7 (OCH_3), 53.7 (C-3a), 62.7 (C-6), 74.2 (C-4), 88.6 (C-5a), 114.5 (C-6a or C-10a), 119.7, 123.1, 124.7, 125.3, 126.3, 129.3 (C-2, C-3, C-7, C-8, C-9, C-10), 144.9 (C-10a or C-6a); **LRMS (EI) *m/e*:** 270 (100%, M^+), 253 (23%, M-OH), 239 (14%, M-OCH_3), 210 (57%), 202 (56%), 165 (36%), 144 (55%), 131 (58%), 115 (55%); **HRMS (EI):** Calc'd for $C_{17}H_{18}O_3$: 270.1256; Found: 270.1248.



148

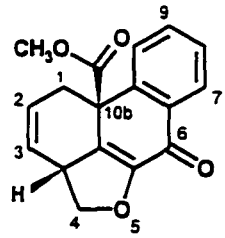
[*syn*-3a-H, 5a-OCH_3, 10b-H, 10c-H]-5a-methoxy-3a,4,5a,6,10b, 10c-hexahydro-1*H*-phenanthro[10,1-*bc*]furan-6-one (**148**)

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 2.23 (H-1α, 1H, m, J = 16.4, 4.8, 2.0 Hz), 2.41 (H-10c, dd, J = 12.6, 6.6 Hz), 2.75 (H-1β, 1H, ddd, J = 16.8, 10.2, 5.2 Hz), 2.88 (H-10b, m, J = 12.1, 4.5 Hz), 3.29 (H-3a, narrow m), 3.59 (OCH_3, 3H, s), 3.89 (H-4α, 1H, t, J_{gem}

= 8.3 Hz), 4.39 (H-4β, 1H, dd, J_{gem} = 8.4, J = 9.5 Hz), 5.85 (H-3, m, J = 9.8 Hz), 5.98 (H-2, m, J = 9.6 Hz), 7.30 (H-10, d, J = 7.7 Hz), 7.38 (H-8, t, J = 7.6 Hz), 7.57 (H-9, t, J = 7.6 Hz), 7.95 (H-7, d, J = 7.7 Hz); **^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm):** 26.7 (C-1), 31.3 (C-10b), 37.1 (C-3a), 50.6 (OCH_3), 51.5 (C-10c), 74.2 (C-4), 103.6 (C-5a), 123.9, 126.2, 126.5, 127.1, 128.1, 133.9 (C-2, C-3, C-7, C-8, C-9, C-10), 133.2 (C-6a), 144.7 (C-10a), 191.7 (C-6).

4.43 Synthesis of (*syn*-3a-H, 10b-CO_2CH_3)-10b-[(methoxy)carbonyl]-3a,4,6,10b-tetrahydro-1*H*-phenanthro[10,1-*bc*]furan-6-one (**150**)

Methyl ester **78a** (0.128 g, 0.407 mmol) was treated with 5 mL neat TFA, and stirred for 30 min. at room temperature. The excess TFA was then evaporated *in vacuo*, and the crude residue extracted into EtOAc, washed with brine solution until the pH was near 6, dried (Na_2SO_4), and concentrated to afford **150** (0.111 g, 96.5%) as pale pink crystals.



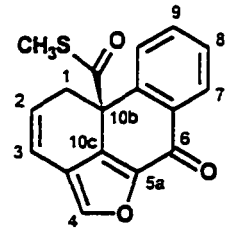
150

mp 171-173°C; **IR (KBr):** 2885, 1739, 1663, 1594, 1222, 1190, 746 cm^{-1}; **^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm):** 2.15 (H-1, 1H, dm, J = 17.0 Hz), 3.65 (H-1, 1H, buried m, J = 17.1 Hz), 3.66 (CO_2CH_3, 3H, s), 4.05 (H-3a, m), 4.14 (H-4α, 1H, dd, J = 7.6, 10.7 Hz), 4.98 (H-4β, 1H, dd, J = 7.7, 9.5 Hz), 5.79 (H-2 and H-3, 2H, m), 7.47-7.66 (H-8, H-9, H-10, 3H total, m, J = 7.8, 1.6 Hz), 8.30 (H-7, dd, J = 7.5, 1.8 Hz); **^{13}C NMR (50 MHz,**

$CDCl_3$) δ (ppm): 39.3 (C-1), 41.4 (C-3a), 48.6 (C-10b), 53.3 ($CO_2\underline{C}H_3$), 76.6 (C-4), 126.0, 126.5, 126.6, 127.2, 128.2, 132.5 (C-2, C-3, C-7, C-8, C-9, C-10), 132.2 (C-6a), 133.7 (C-10c), 142.3 (C-5a), 148.3 (C-10a), 171.6 (C-6), 175.7 ($\underline{C}O_2CH_3$); **LRMS (EI)** ***m/e*:** 282 (93%, M^+), 223 (100%, M-CO_2CH_3), 195 (43%), 165 (47%), 152 (16%), 115 (6%); **HRMS (EI):** Calc'd for $C_{17}H_{14}O_4$: 282.0892; Found: 282.0875; **Anal.** Calc'd for $C_{17}H_{14}O_4$: C, 72.33%; H, 4.99%. Found: C, 71.80%; H, 5.29%.

4.44 Synthesis of 10b-[(methylthio)carbonyl]-6,10b-dihydro-1*H*-phenanthro-[10,1-*bc*]furan-6-one (**151**)

Compound **131** (0.3 g, 1.0 mmol) was mixed with *p*-chloranil (0.272 g, 1.1 mmol, 1.1 equiv.) in 30 mL *p*-xylene, and the mixture was heated at reflux for 48 h. After cooling to room temperature, the mixture was filtered through a pad a Celite and the filtrate was concentrated *in vacuo* to a dark green oil. The crude product mixture was separated by column chromatography (silica gel 60, 1:4 EtOAc-hexane eluant) which gave unreacted starting material (0.185 g, 0.385 mmol) and **151** (0.085 g, 0.287 mmol) as pink crystalline plates from ether (75% yield, based on the portion of **131** which reacted).



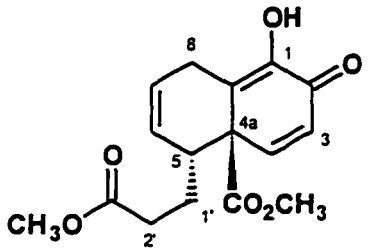
151

mp 162-164°C; **IR (KBr):** 1666, 1410, 1346, 921 cm^{-1}; **^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm):** 2.07 ($COSCH_3$, 3H, s), 2.47 (H-1, 1H, dt, J = 16.5, 2.7 Hz), 3.87 (H-1, 1H, dd, J = 16.5, 6.2 Hz), 6.07 (H-2, ddd, J = 9.7, 6.3, 2.2 Hz), 6.62 (H-3, dd, J = 9.6, 2.8 Hz),

7.49-7.69 (H-8, H-9, and H-10, 3H total, m), 7.66 (H-4, s), 8.38 (H-7, dd, J = 7.5, 1.8 Hz); **^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm):** 12.7 ($COSCH_3$), 31.9 (C-1), 53.1 (C-10b), 118.6 (C-2), 121.6 (C-3a), 126.8, 128.1, 128.5, 128.6, 132.6 (C-3, C-7, C-8, C-9, C-10), 134.3, 136.3 (C-6a and C-10c), 140.5 (C-5a), 141.5 (C-4), 146.6 (C-10a), 172.4 (C-6), 199.4 ($COSCH_3$); **LRMS (EI) *m/e*:** 296 (5%, M^+), 268 (15%, M-CO), 221 (100%, M-$COSCH_3$), 193 (42%), 165 (69%), 139 (5%), 105 (7%); **HRMS (EI):** Calc'd for $C_{17}H_{12}O_3S$: 296.0507; Found: 296.0497; **Anal.** Calc'd for $C_{17}H_{12}O_3S$: C, 68.90%; H, 4.08%; S, 10.82%. Found: C, 68.71%; H, 4.27%; S, 10.61%.

4.45 Synthesis of (*syn*-4a-CO_2CH_3, 5-H)-4a-[(methoxy)carbonyl]-5-[2'-[(methoxy)-carbonyl]ethyl]-1-hydroxy-2,4a,5,8-tetrahydronaphthalene-2-one (**156**)

Freshly distilled methyl (4*E*)-4,6-heptadienoate (8.34 g, 0.0595 mol, 10 equiv.; bp=75°C, 20 torr) was mixed with methyl 3,4-dihydroxybenzoate (1.00 g, 5.95 mmol) and dry THF (50 mL) at 0°C, followed lastly by the addition of PIFA in small portions (3.07 g, 7.14 mmol, 1.2 equiv.). The green-black mixture was allowed to stir over 3 h while gradually warming up to room temperature, after which time the mixture appeared orange-yellow in color. All volatile solvents (THF, TFA by-product) were evaporated *in vacuo*, and the crude residual oil purified by chromatography (silica gel 60, 1:4 EtOAc-hexane eluant) to give a white solid **156** (1.086 g, 60% yield), which could be recrystallized in ether-hexane to white microcrystals.



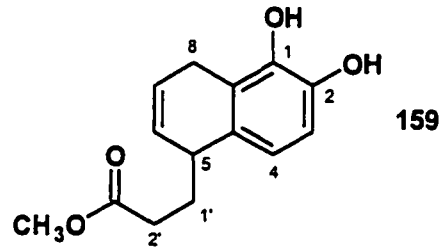
156

mp 117°-118°C; **IR (KBr):** 3365 (H-bonded OH stretch, sharp), 2951 (C-H), 1733, 1652, 1604, 1214 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm):** 1.21, 1.68 ($C\underline{H}_2CH_2CO_2CH_3$, 2H, m), 2.30 ($CH_2C\underline{H}_2CO_2CH_3$, 2H, m), 3.06 (H-8, 1H, dm, *J*= 22.6, 6.0 Hz), 3.18 (H-5, m, *J*= 10.4, 6.0, 4.4 Hz), 3.38 (H-8, 1H, dm, *J*= 22.6, 2.7 Hz), 3.64, 3.66 ($2xCO_2CH_3$, each signal 3H, s), 5.77 (H-7, ddd, *J*= 9.8, 6.8, 3.4 Hz), 5.87 (H-6, dm, *J*= 9.8, 6.0 Hz), 6.53 (H-3, d, *J*= 9.7 Hz), 6.68 (H-bonded OH, sharp s), 6.91 (H-4, d, *J*= 9.8 Hz); **^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm):** 25.9, 26.5 (C-8, $\underline{C}H_2CH_2CO_2CH_3$), 31.3 ($CH_2\underline{C}H_2CO_2CH_3$), 42.3 (C-5), 51.6, 53.3 ($2xCO_2\underline{C}H_3$), 56.5 (C-4a), 124.9 (C-8a), 126.1, 127.4, 128.9 (C-3, C-6, C-7), 145.0 (C-1), 149.0 (C-4), 170.5, 173.3 ($2x\underline{C}O_2CH_3$), 180.1 (C-2); **LRMS (EI) *m/e*:** No molecular ion (M^+) detected, 274 (37%, M^+-CH_3OH), 242 (14%), 215 (75%), 187 (100%), 173 (55%); **LRMS (CI, NH_3) *m/e*:** 324 (24%, $M+NH_4$), 292 (100%), 275 (16%); **Anal.** Calc'd. for $C_{16}H_{18}O_6$: C, 62.73%; H, 5.92%. Found: C, 62.82%; H, 5.93%.

4.46 Synthesis of 5-[2'-[(methoxy)carbonyl]ethyl]-1,2-dihydroxy-5,8-dihydronaphthalene (**159**)

Freshly distilled methyl (4*E*)-4,6-heptadienoate (9.09 g, 0.0649 mol, 10 equiv.; bp=75°C at 20 mmHg) was mixed with dry, distilled THF (20 mL) and 3,4-dihydroxybenzoic acid (1.00 g, 6.49 mmol), and cooled to 0°C under argon atmosphere,

prior to addition of PIFA (3.48 g, 8.11 mmol, 1.25 equiv.) in small portions. The reddish-brown mixture was stirred for 2 h at room temperature, and then solvent was evaporated. The residual dark brown oil was purified by chromatography (silica gel 60, 1:4 EtOAc-hexane eluant) to afford a pale-yellow oil (0.35 g, 22% yield), which had auto-oxidized to the corresponding naphthalene within several days at room temperature.

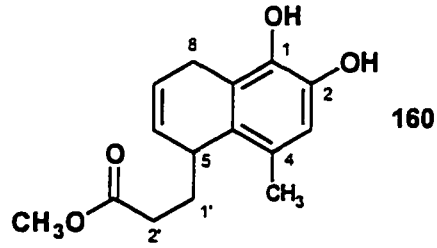


159

IR (neat film): 3394 (OH), 3028, 2952, 1718, 1628, 1260, 799, 698 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm):** 1.95-2.37 ($C\underline{H}_2C\underline{H}_2CO_2CH_3$, 4H, m, *J*= 14.3, 9.5, 7.3 Hz), 3.18 (H-8, 1H, dm, *J*= 21.9 Hz), 3.35 (H-8, 1H, dm, *J*= 21.9 Hz), 3.51 (H-5, m, *J*= 6.9 Hz), 3.60 (CO_2CH_3, 3H, s), 5.36, 5.45 (2xOH, s), 5.80 (H-6, dm, *J*= 10.2, 4.4 Hz), 6.02 (H-7, dm, *J*= 10.2 Hz), 6.63, 6.72 (H-3 and H-4, d, *J*= 8.0 Hz); **^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm):** 24.4 (C-8), 29.9 ($\underline{C}H_2CH_2CO_2CH_3$), 32.9 ($CH_2\underline{C}H_2CO_2CH_3$), 37.4 (C-5), 51.6 ($CO_2\underline{C}H_3$), 113.5 (C-3), 119.5 (C-4), 122.3 (C-8a), 124.7 (C-7), 128.3 (C-6), 130.5 (C-4a), 140.7, 141.1 (C-1, C-2), 174.9 ($\underline{C}O_2CH_3$); **LRMS (EI) *m/e*:** 248 (55%, M^+), 173 (40%), 161 (45%), 143 (100%), 115 (68%); **HRMS (EI):** Calc'd for $C_{14}H_{16}O_4$: 248.1048; Found: 248.1046.

4.47 Synthesis of 5-[2'-[(methoxy)carbonyl]ethyl]-4-methyl-1,2-dihydroxy-5,8-dihydronaphthalene (**160**)

Catechol **155** (0.15 g, 0.89 mmol) which was prepared earlier in our laboratory,[104] was mixed with methyl (*E*)-4,6-heptadienoate (1.25 g, 8.9 mmol, 10 equiv.) in redistilled THF (20 mL) and cooled to 0°C prior to adding PIFA (0.46 g, 1.07 mmol, 1.2 equiv.) in small portions. The brown mixture was stirred at room temperature for 2 h, then the volatile solvents were evaporated , leaving a dark oil which was purified by column chromatography (silica gel 60, 1:4 EtOAc-hexane eluant). The pure product **160** (0.063 g, 27% yield) was isolated as a yellow viscous oil.



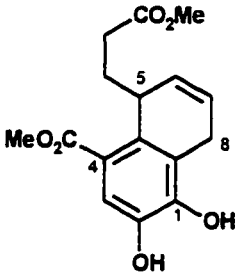
160

^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.93 (CH_3, 3H, s), 2.1-2.4 ($C\underline{H}_2C\underline{H}_2CO_2CH_3$, 4H total, complex m), 3.08-3.30 (H-8, 1H, m), 3.6 (H-5, 1H, obscured m), 3.63 (CO_2CH_3, 3H, s), 5.65-5.98 (H-6 and H-7, 2H total, complex m), 6.18 (OH, s), 6.56 (OH, s), 7.21 (H-3, s). This compound decomposed rather easily and therefore could not be adequately characterized.

4.48 Synthesis of 5-[2'-[(methoxy)carbonyl]ethyl]-4-[(methoxy)carbonyl]-1,2-dihydroxy-5,8-dihydronaphthalene (**161**)

Following the procedure described in section 4.9 for rearrangements with TFA, compound **156** (0.11 g, 0.36 mmol) was mixed with neat TFA (5 mL) at room temperature. The reaction was complete in 30 min, and gave the rearranged product **161** (0.099 g, 90% yield) as colorless crystals from ether.

Following the procedure described in section 4.10 for rearrangements with Et_3OBF_4, compound **156** (0.105 g, 0.326 mmol) was dissolved in dry CH_2Cl_2 (5 mL), cooled to 0°C, and mixed with Et_3OBF_4 (0.4 mL of 1M solution in CH_2Cl_2, 0.4 mmol, 1.2 equiv.). After 2h the reaction was complete. The crude product (0.102 g, >95% yield) was recrystallized in ether and gave **161** as colorless microcrystals.



161

mp 122-124°C; **IR (KBr):** 3459 (OH, sharp), 3281 (OH, broad), 1701 (CO, broad), 1602 cm^{-1}; **^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm):** 1.94 ($CH_2CH_2CO_2CH_3$, 2H, m, J = 9.7, 5.6 Hz), 2.13 ($CH_2CH_2CO_2CH_3$, 1H, m, J = 15.8, 9.9, 6.0 Hz), 2.34 ($CH_2CH_2CO_2CH_3$, 1H, m, J = 15.6, 10.0, 5.6 Hz), 3.12 (H-8, 1H, dm, J = 21.9 Hz), 3.44 (H-8, 1H, dm, J = 21.8, 4.8 Hz), 3.59, 3.82 (2×CO_2CH_3, each signal 3H, s), 4.51 (H-5, broad m), 5.91 (H-6, ddd, J = 9.9, 5.2, 2.6 Hz), 6.02 (H-7, ddd, J = 9.9, 4.8, 2.1 Hz), 7.41 (H-4, s); **^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm):** 24.7 ($\underline{C}H_2CH_2CO_2CH_3$), 30.6 ($CH_2\underline{C}H_2CO_2CH_3$), 33.1 (C-8), 35.1 (C-5),

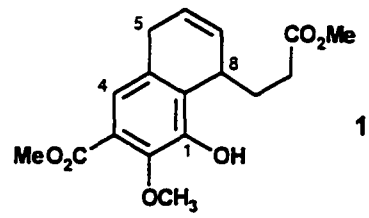
51.6 and 51.9 (2 x $CO_2\underline{C}H_3$), 116.7 (C-3), 119.2 (C-4), 123.9 (C-8a), 124.4 (C-7), 128.9 (C-6), 135.2 (C-4a), 139.9 (C-2), 146.2 (C-1), 168.9 ($\underline{C}O_2CH_3$ at C-4), 175.3 ($CH_2CH_2\underline{C}O_2CH_3$); **LRMS (CI, NH_3)** ***m/e*****:** 324 (17%, M+NH_4), 307 (5%, M+H), 292 (100%), 275 (17%, M-OCH_3); **HRMS (CI):** Calc'd for $C_{16}H_{18}O_6$: 306.1103; Found: 306.1102; **Anal.** Calc'd for $C_{16}H_{18}O_6$: C, 62.73%; H, 5.92%. Found: C, 62.75%; H, 5.78%.

4.49 Synthesis of 3-[(methoxy)carbonyl]-8-[2'-[(methoxy)carbonyl]ethyl]-1-hydroxy-2-methoxy-5,8-dihydronaphthalene (**162**)

Following the procedure described in section 4.9 for rearrangements with TFA, compound **106** (0.20 g, 0.63 mmol) was mixed with neat TFA (5 mL) at room temperature. The reaction was complete after 12-16 h. The product **162** was obtained as a pale golden oil (0.148 g, 74% yield).

Following the procedure described in section 4.10 for rearrangements with Me_3OBF_4, compound **106** (0.30 g, 0.94 mmol) was dissolved in dry CH_2Cl_2 (25 mL) and mixed with Me_3OBF_4 (0.17 g, 1.15 mmol) at 0°C. The reaction was stirred at 0°C for 30 min., then at room temperature for 48 h. The pure product **162** was obtained as a pale gold oil (0.181 g, 60% yield).

Following the procedure described in section 4.10 for rearrangements with Et_3OBF_4, compound **106** (0.30 g, 0.94 mmol) was dissolved in dry CH_2Cl_2 (20 mL) and mixed with Et_3OBF_4 (1.1 mL of 1M solution in CH_2Cl_2, 1.1 mmol, 1.2 equiv.) at 0°C. The reaction was stirred at 0°C for 30 min., then at room temperature for 18 h. The pure product **162** was obtained as a pale gold oil (0.187 g, 62% yield).



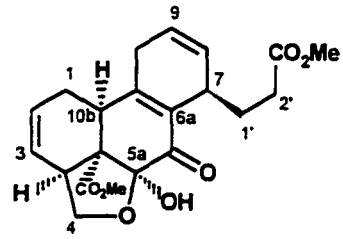
162

IR (neat film): 3419 (OH), 2946 (CH), 1723 (broad, C=O), 1437, 1306, 1250 (OCH_3) cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm):** 2.01 ($C\underline{H}_2CH_2CO_2CH_3$, m, 1H, *J*= 12.6 Hz), 2.15 ($CH_2C\underline{H}_2CO_2CH_3$, m, 2H, *J*= 12.5, 5.6 Hz), 2.31 ($C\underline{H}_2CH_2CO_2CH_3$, m, 1H, *J*= 12.4, 6.2 Hz), 3.34 (H-5, dm, 2H, *J*= 21.2, 2.2 Hz), 3.59 ($CH_2CH_2CO_2C\underline{H}_3$, 3H, s), 3.79 (H-8, broad s), 3.89, 3.91 ppm ($ArCO_2C\underline{H}_3$ and $OC\underline{H}_3$, each 3H, s), 5.89 (H-7, dm, *J*= 9.8, 3.6 Hz), 6.0 (H-6, ddd, *J*= 9.9, 4.5, 2.3 Hz), 6.18 (OH, s), 7.21 (H-4, s); **^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm):** 29.5, 29.8, 30.4 (C-5, $\underline{C}H_2\underline{C}H_2CO_2CH_3$), 34.0 (C-8), 51.4, 52.0 (2x $CO_2\underline{C}H_3$), 62.3 (OCH_3), 120.9 (C-3), 121.7 (C-4), 125.6 (C-6), 128.1 (C-7), 129.9, 131.7 (C-4a, C-8a), 144.8 (C-1), 146.9 (C-2), 165.9 ($\underline{C}O_2CH_3$ at C-3), 174.3 ($CH_2CH_2\underline{C}O_2CH_3$); **LRMS (EI) *m/e*:** 320 (5%, M^+), 288 (17%, M-CH_3OH), 257 (11%), 233 (18%), 201 (100%), 157 (15%), 115 (17%); **HRMS (EI):** Calc'd for $C_{17}H_{20}O_6$: 320.1259; Found: 320.1266.

4.50 Synthesis of **167** and **168** by Diels-Alder reaction with **107** with (*E*)-2,4-pentadienol

To a cooled solution (0°C) of **107** (0.2 g, 0.683 mmol) and freshly distilled (*E*)-2,4-pentadienol (0.4 g, 4.78 mmol, 7 equiv., bp= 62°C@20 torr) in dry THF (10 mL) was added PIFA (0.35 g, 0.82 mmol, 1.2 equiv.) in small portions. The reaction was stirred under argon for 8 h while warming to room temperature to give a final yellow-orange solution, which then concentrated *in vacuo* to an orange oil. Purification by column

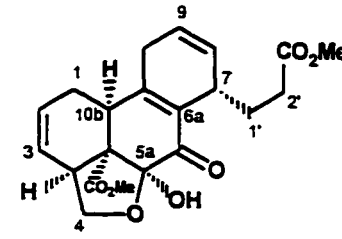
chromatography (silica gel 60, 1:3 EtOAc-hexane eluant) furnished a white solid (0.148 g, 56% yield) consisting of a 1:1 diastereomeric mixture of products **167** and **168**, which were further resolved by silica gel chromatography using 1:9 ether-CH_2Cl_2 as eluant.



167

(*syn*- 3a-H, 5a-OH, 7-H, 10b-H, 10c-CO_2CH_3)-5a-hydroxy-10c-[(methoxy)-carbonyl]-7-[2'-[(methoxy)carbonyl]ethyl]-3a,4,5a,6,7,10,10b,10c-octahydro-1*H*-phenanthro[10,1-*bc*]furan-6-one (**167**)

mp 122-124°C (colorless prisms from ether); **IR (KBr):** 3462 (OH, sharp), 1739, 1677, 1235 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm):** 1.87 ($C\underline{H}_2CH_2CO_2CH_3$, 2H, m, *J*= 15.4, 8.9 Hz), 2.06 (H-1, 1H, ddd, *J*= 18.2, 11.7, 3.1 Hz), 2.21 ($CH_2C\underline{H}_2CO_2CH_3$, 2H, m), 2.35 (H-10b, dd, *J*= 11.6, 4.2 Hz), 2.47 (H-1, 1H, ddd, *J*= 15.1, 7.5, 4.9 Hz), 2.74 (H-10, 1H, dt, *J*= 23.1, 4.1 Hz), 3.12 (H-10, 1H, dd, *J*= 23.1, 5.4 Hz), 3.59 (H-4, 1H, dd, *J*= 8.0, 7.1 Hz), 3.60, 3.62 (each CO_2CH_3, 3H, s), 3.62 (H-7, m), 4.00 (H-3a, m, *J*= 9.8, 7.0 Hz), 4.48 (H-4, 1H, dd, *J*= 9.8, 8.0 Hz), 4.71 (OH, s), 5.81 (H-8 and H-9, 2H, narrow m, *J*= 9.3, 6.1 Hz), 6.10 (H-2, 1H, ddd, *J*= 9.1, 7.5, 3.3 Hz), 6.24 (H-3, 1H, ddd, *J*= 9.1, 7.0, 3.0 Hz); **LRMS (EI) *m/e*:** 388 (2%, M^+), 371 (100%, M-OH), 338 (33%), 237 (13%), 195 (24%), 165 (30%); **HRMS (EI):** Calc'd for $C_{21}H_{24}O_7$: 388.1522; Found: 388.1530.



168

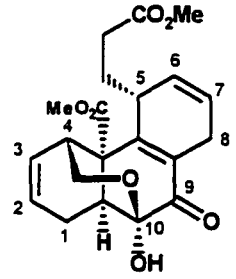
(*syn* 3a-H, 5a-OH, 10b-H, 10c-CO_2CH_3; *anti* 7-H, 10b-H)-5a-hydroxy-10c-[(methoxy)-carbonyl]-7-[2'-[(methoxy)carbonyl]ethyl]-3a,4,5a,6,7,10,10b,10c-octahydro-1*H*-phenanthro[10,1-*bc*]furan-6-one (**168**)

mp 125-127°C (white microcrystals from ether-hexane); **IR (KBr):** 3446 (OH, sharp), 1745, 1715 (CO for each CO_2CH_3), 1622 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm):** 1.93 ($C\underline{H}_2CH_2CO_2CH_3$, 1H, m), 2.04 (H-1, 1H, ddd, *J*= 15.1, 11.8, 3.1 Hz), 2.12-2.28 ($C\underline{H}_2C\underline{H}_2CO_2CH_3$, 3H, m), 2.35 (H-10b, dd, *J*= 11.8, 4.4 Hz), 2.45 (H-1, 1H, ddd, *J*=15.1, 7.6, 3.1 Hz), 2.83 (H-10, 1H, dd, *J*=23.1, 5.6 Hz), 3.05 (H-10, 1H, dt, *J*=23.1, 4.1 Hz), 3.51 (H-7, narrow m), 3.60 (H-4, 1H, dd, *J*= 8.0, 6.0 Hz), 3.63 and 3.66 (each CO_2CH_3, 3H, s), 4.01 (H-3a, ddd, *J*= 9.6, 6.7, 6.5 Hz), 4.32 (OH, s), 4.51 (H-4, 1H, dd, *J*= 9.6, 8.1 Hz), 5.81 (H-8 and H-9, 2H, narrow m), 6.09 (H-2, m, *J*= 9.3, 7.6, 3.1 Hz), 6.22 (H-3, m, *J*= 9.2, 7.0, 3.0 Hz); **^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm):** 28.4, 29.0, 29.7 (C-1, $\underline{C}H_2\underline{C}H_2CO_2CH_3$), 31.6 (C-10), 33.5 (C-7), 40.8 (C-3a), 42.3 (C-10b), 51.6, 52.7 (2x $CO_2\underline{C}H_3$), 60.9 (C-10c), 76.3 (C-4), 98.7 (C-5a), 122.9 (C-8 or C-9), 128.9 (C-6a), 129.28, 129.32 (C-2, and C-8 or C-9), 130.9 (C-3), 158.5 (C-10a), 171.9, 174.4 (2x $\underline{C}O_2CH_3$), 190.2 (C-6); **LRMS (EI) *m/e*:** 388 (2%, M^+), 371 (100%, M-OH), 357 (9%, M-OCH_3), 338 (16%), 301 (34%, M-$CH_2CH_2CO_2CH_3$), 195 (27%), 165 (36%); **HRMS (EI):** Calc'd for $C_{21}H_{24}O_7$: 388.1522; Found: 388.1534.

4.51 Synthesis of **169** Diels-Alder reaction with **161** and (*E*)-2,4-pentadienol

To a cooled solution (0°C) of **161** (0.35 g, 1.16 mmol) and freshly distilled (*E*)-2,4-pentadienol (0.8 g, 9.5 mmol, 8 equiv., bp= 62°C@20 torr) in dry THF (10 mL) was added PIFA (0.6 g, 1.39 mmol, 1.2 equiv.) in small portions. The solution was stirred

under argon for 24 h at room temperature, and then concentrated *in vacuo*. The resulting yellow oil was purified by column chromatography (silica gel 60, 1:4 EtOAc-hexane eluant) which gave **169** (51 mg, 11%) as a colorless oil.



169

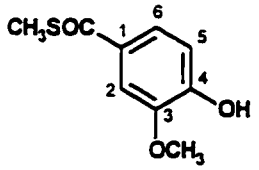
(*syn* 4-H, 4a-CO_2CH_3, 10-OH, 10a-H; *anti* 4-H, 5-H)-10-hydroxy-5-[2'-[(methoxy)-carbonyl]ethyl-4a-(methoxy)carbonyl-4,10-methyleneoxy-1,4,4a,5,8,9,10,10a-octahydrophenanthrene-9-one (**169**)

IR (neat film): 3442 (OH), 1733 (CO), 1679 (CO), 1437, 733 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$)** δ **(ppm):** 1.54 ($C\underline{H}_2CH_2CO_2CH_3$, 1H, m, *J*= 14.4, 7.2 Hz), 1.73 ($C\underline{H}_2CH_2CO_2CH_3$, 1H, m), 2.25 ($CH_2C\underline{H}_2CO_2CH_3$, 2H, broad t, *J*= 8.5 and 7.7 Hz), 2.38 (H-1, 1H, dd, *J*= 19.5, 7.2 Hz), 2.54 (H-4, narrow m), 2.69 (H-8, broad d, *J* = 21.5 Hz), 2.75 (H-1, 1H, broad d, *J*= 19.5 Hz), 2.85 (H-10a, d, *J*= 7.2 Hz), 3.26 (H-5, 1H, narrow m), 3.31 (H-8, ddd, *J* = 21.6, 5.4, 2.0 Hz), 3.63 ($C\underline{H}_2O$, 1H, d, *J*= 11.8 Hz), 3.65 ($CO_2C\underline{H}_3$, 3H, s), 3.73 ($C\underline{H}_2O$, 1H, dd, *J*= 11.9, 2.6 Hz), 3.79 ($CO_2C\underline{H}_3$, 3H, s), 4.92 (OH, s), 5.86 (H-2, H-3 and H-7, 3H, m, *J*= 10.5 Hz), 6.02 (H-6, m, *J*= 9.4, 5.5 Hz); **^{13}C NMR (63 MHz, $CDCl_3$)** δ **(ppm):** 23.9 and 24.1 (C-1, C-8), 29.8 and 30.5 ($\underline{C}H_2\underline{C}H_2CO_2CH_3$), 32.9 (C-4), 37.0 (C-5), 40.1 (C-10a), 51.6 and 52.5 (each $CO_2\underline{C}H_3$), 52.8 (C-4a), 65.6 ($\underline{C}H_2O$), 92.5 (C-10), 126.1, 126.4, 128.2 and 128.5 (C-2, C-3, C-6 and C-7), 134.4 (C-8a), 159.1 (C-4b), 172.1 and 173.2 (each $\underline{C}O_2CH_3$), 191.4 (C-9); **LRMS (EI) *m/e*:** 389 (82%, M+H), 388 (24%, M^+),

370 (26%, M-H_2O), 357 (25%, M-OCH_3), 301 (52%), 195 (60%), 165 (100%); **HRMS (EI):** Calc'd for $C_{21}H_{24}O_7$: 388.1522; Found: 388.1512.

4.52 *S*-Methyl (4-hydroxy-3-methoxy)benzenethioate (**172**)

To a cooled solution (0°C) of guaiacol (*o*-methoxyphenol) (2.0 g, 0.016 mol) and trichloromethyl methyl sulfide (2.93 g, 0.0177mol, 1.1 equiv.) in dry CH_2Cl_2 (50 mL) was added neat titanium tetrachloride (5.28 mL, 0.048 mol, 3 equiv.), and the resulting orange-black solution was stirred at 0°C under argon for 2 h. The reaction was quenched in an ice bath with 100 mL of 5% $HCl_{(aq)}$ then stirred for 30 min at room temperature. The CH_2Cl_2 layer was separated, and the aqueous acidic layer washed with two more aliquots (25 mL each) of CH_2Cl_2. The combined CH_2Cl_2 extracts were then washed twice with brine solution, dried (Na_2SO_4), filtered, and concentrated to a greenish-black oil (strong sulfur stench-use the fumehood!). The crude oil was purified by column chromatography (silica gel 60, 1:4 EtOAc-hexane eluant) and gave a pale-yellow oil as the major product which was crystallized in ether to afford **172** as white microcrystals (2.35g, 74% yield).



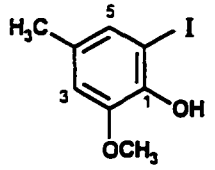
172

mp 54-56°C; **IR (KBr):** 3340 (OH), 1646, 1595, 1514, 1282, 1165 cm^{-1}; **^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm):** 2.46 ($COSCH_3$, 3H, s), 3.94 (OCH_3, 3H, s), 6.10 (OH, broad s), 6.94 (H-5, dd, J = 8.5 Hz), 7.47 (H-2, d, J = 1.9 Hz), 7.62 (H-6, dd, J = 8.4, 1.9 Hz); **^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm):** 11.7 ($COS\underline{C}H_3$), 56.1 (OCH_3), 109.0 (C-5), 114.1 (C-

2), 122.2 (C-6), 129.8 (C-1), 146.4 (C-4), 150.4 (C-3), 191.1 ($\underline{C}OSCH_3$); **LRMS (EI) *m/e*:** 198 (8%, M^+), 151 (100%, M-SCH_3), 123 (11%, M-$COSCH_3$), 108 (7%), 84 (10%); **Anal.** Calc'd for $C_9H_{10}O_3S$: C, 54.53%; H, 5.08%; S, 16.17%. Found: C, 54.85%; H, 5.15%; S, 15.91%.

4.53 Synthesis of 6-iodo-2-methoxy-4-methylphenol (**173**)

The unpurified **181** (0.766 g, 2.486 mmol) was dissolved in a 1:1 mixture of MeOH-THF (15 mL), and then 3N HCl (2 mL) was added after which the reaction was observed to be slightly exothermic. After stirring for 12 h (i.e. overnight) at room temperature, all volatile solvents were evaporated *in vacuo* and the residue was then extracted into EtOAc (100 mL) and washed with brine solution until the pH of the aqueous phase was neutral. The EtOAc extract was dried (Na_2SO_4), filtered, and concentrated to a crude dark oil, which formed tan crystals of **173** (0.626 g, 95% yield) upon standing in ether-hexane.



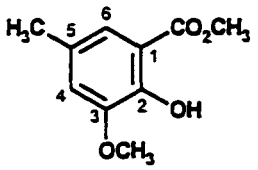
173

IR (neat film): 3457, 2939, 1587, 1492, 1261, 1037. 939, 835, 763 cm^{-1}; **^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm):** 2.25 (CH_3, 3H, s), 3.86 (OCH_3, 3H, s), 5.90 (OH, sharp s), 6.63 (H-3, d, J = 1.3 Hz), 7.11 (H-5, d, J = 1.1 Hz); **^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm):** 20.6 (CH_3), 56.1 (OCH_3), 81.0 (C-6), 111.8 (C-3), 130.9 (C-5), 131.3 (C-4), 143.8 (C-2), 145.7 (C-1); **LRMS (EI) *m/e*:** 264 (100%, M^+), 249 (40%, M-CH_3), 221 (17%), 137 (M-

I, 10%), 127 (I, 19%), 122 (28%), 94 (39%); **HRMS (EI):** Calc'd for $C_8H_9O_2I$: 263.9647; Found: 263.9661.

4.54 Synthesis of methyl 2-hydroxy-3-methoxy-5-methylbenzoate (**174**)

To a cooled solution (-78°C) of **181** (0.50 g, 1.62 mmol) in 2:1 THF-ether (20 mL) was added 1.6 M *n*-BuLi (1.1 mL, 1.78 mmol, 1.1 equiv.) under argon atmosphere, and the mixture was stirred for 5 min, then quenched by the rapid addition of methyl chloroformate (0.63 mL, 8.1 mmol, 5 equiv.) at -78°C. The mixture was warmed up to 0°C, then quenched with a solution of sat. NH_4Cl (5 mL) and extracted into EtOAc (50 mL), washed with brine solution, dried (Na_2SO_4), and concentrated to a yellow oil. The product was redissolved in 1:1 MeOH-THF (10 mL) and treated with 3N HCl (2 mL) and stirred overnight (12 h) at room temperature. The volatile solvents were evaporated, and the residue extracted into ether, washing with brine solution until neutral pH. The ether layer was dried (Na_2SO_4), filtered and concentrated *in vacuo* to a dark brown oil which was purified by column chromatography (silica gel 60, 1:4 EtOAc-hexane eluant) to afford **174** (0.126 g, 40% yield from **181**) as white needles from ether. The spectral data (^1H and ^{13}C NMR) for this compound were in complete agreement with the literature values reported by Hosoya *et al.*[107]

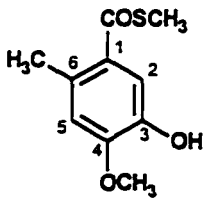


174

mp 80-81°C; **^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm):** 2.29 (CH_3, 3H, s), 3.89 and 3.94 (CO_2CH_3 and OCH_3, each 3H, s), 6.86 (H-4, d, J = 1.6 Hz), 7.23 (H-6, d, J = 1.2 Hz), 10.79 (H-bonded OH, s); **^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm):** 20.9 (CH_3), 52.2 and 56.1 ($CO_2\underline{C}H_3$ and OCH_3), 112.0 (C-1), 117.9 and 120.5 (C-4 and C-6), 127.8 (C-5), 148.2 and 149.9 (C-2 and C-3), 170.8 ($\underline{C}O_2CH_3$).

4.55 Synthesis of *S*-methyl (4-hydroxy-3-methoxy-6-methyl)benzenethioate (**175**)

To a cooled (0°C) solution of 2-methoxy-4-methylphenol **64** (1.0 g, 7.24 mmol) and trichloromethyl methylsulfide (1.44 g, 8.69 mmol, 1.2 equiv.) in dry CH_2Cl_2 (30 mL) was added neat titanium tetrachloride (2.4 mL, 0.022 mol, 3 equiv.), after which the red-black mixture was stirred under argon for 2 h while warming to room temperature. The reaction was quenched with 50 mL 5% $HCl_{(aq)}$ and stirred for 30 min., and then the CH_2Cl_2 layer was separated. The aqueous layer was extracted with two more aliquots of CH_2Cl_2 (20 mL each), and these extracts were combined, washed several times with brine solution until the pH of the washings were neutral, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude green-black oil was purified by column chromatography (silica gel 60, 1:4 EtOAc-hexane eluant), and gave **175** (0.852 g, 55% yield) as white microcrystals.



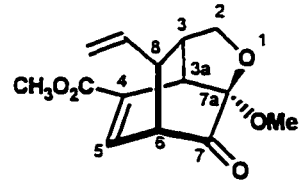
175

mp 69-70°C; **IR (KBr):** 3354, 1661, 1618, 1574, 1516, 1278, 1114, 872 cm^{-1}; **^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm):** 2.41 ($COSCH_3$, 3H,s), 2.48 (CH_3, 3H, s), 3.96 (OCH_3, 3H,

s), 5.48 (OH, sharp s), 6.69 (H-5, s), 7.47 (H-2, s); **^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm):** 12.2 ($COSCH_3$), 20.6 (CH_3), 55.9 (OCH_3), 113.5, 115.1 (C-2 and C-5), 129.6, 130.4 (C-1 and C-6), 142.9 (C-3), 149.0 (C-4), 193.1 ($COSCH_3$); **LRMS (EI)** ***m/e*****:** 212 (24%, M^+), 165 (100%, M-SCH_3), 137 (8%, M-$COSCH_3$); **HRMS (EI):** Calc'd for $C_{10}H_{12}O_3S$: 212.0507; Found: 212.0514.

4.56 Synthesis of **177a** and **178a** by IMDA reaction with methyl vanillate **66** and (*E*)-2,4-pentadienol

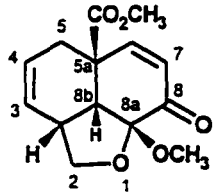
The general procedure for the IMDA reaction in section 4.6 was followed, using methyl vanillate **66** (2.0 g, 0.011 mol), freshly distilled (*E*)-2,4-pentadienol (4.6 g, 0.055 mol, 5 equiv.; bp ≈56°C @ 15-20 torr), PIFA (5.62 g, 0.0131 mol, 1.2 equiv.), and solid $NaHCO_3$ (2.2 g, 0.026 mol, 2.4 equiv.) in dry THF (40 mL). The mixture was stirred overnight, then the solvent was removed and the residual oil was extracted into ether, washed with brine solution, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The excess (*E*)-2,4-pentadienol was removed by distillation, and the crude orange residue was purified by column chromatography (silica gel 60, 1:4→1:3 EtOAc-hexane eluant gradient) which afforded **177a** (1.28 g, 44% yield) as a colorless oil, and **178a** (1.04 g, 36% yield) as a yellow oil.



177a

(3,8-*trans*)-4-[(methoxy)carbonyl]-7a-methoxy-8-vinyl-2,3,3a,6,7,7a-hexahydro-3,6-methanobenzofuran-7-one (**177a**)

IR (neat film): 2966, 1731 (broad), 1630, 1445, 1272, 960, 779, 758 cm^{-1}; **^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm):** 2.41 (H-3, narrow m), 2.83 (H-8, m), 3.39 (H-6, dd, J = 7.0, 3.0 Hz), 3.52 (OCH_3, 3H, s), 3.81 (CO_2CH_3, 3H, s), 3.88 (H-2, 1H, d, J =8.2 Hz), 4.04 (H-3a, dd, J = 4.4, 2.0 Hz), 4.22 (H-2, 1H, dd, J = 8.2, 3.3 Hz), 5.03-5.11 (CH=C$\underline{H}_2$, 2H, m, J = 17.2, 10.0 Hz), 5.50-5.64 (C$\underline{H}$=CH_2, 1H, m, J =17.0, 10.0, 8.0 Hz), 7.16 (H-5, dd, J = 6.9, 2.0 Hz); **^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm):** 41.4, 42.5, 46.6 (C-8, C-3, C-3a), 51.2, 52.3 (OCH_3 and CO_2CH_3), 52.5 (C-6), 73.4 (C-2), 99.2 (C-7a), 116.5 (CH=$\underline{C}H_2$), 132.7 (C-4), 135.1 (C-5), 137.6 (C-9), 164.3 ($\underline{C}O_2CH_3$), 199.4 (C-7); **LRMS (EI) *m/e*:** No molecular ion observed; 236 (86%, M-CO), 221 (37%), 189 (26%), 145 (28%), 117 (100%), 91 (45%); **LRMS (Electrospray, CH_3CN-H_2O+NH_4OAc) *m/e*:** 282 (68%, M+NH_4), 233 (100%, M-OCH_3). This compound appeared to have decomposed or rearranged during mass spectrometric and elemental analysis methods.



178a

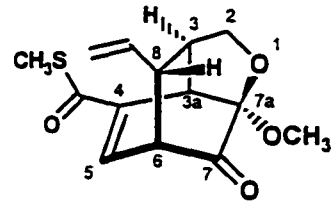
[*syn*-2aH, 5a-CO_2CH_3, 8a-OCH_3, 8b-H]-5a-[(methoxy)carbonyl]-8a-methoxy-2a,5,5a,8,8a,8b-hexahydro-2*H*-naphtho[1,8-*bc*]furan-8-one (**178a**)

IR (neat film): 2949, 1714 (broad), 1444, 1270, 1050, 822 cm^{-1}; **^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm):** 2.00 (H-5α, 1H, dm, J_{gem}= 16.0 Hz), 2.63 (H-5β, 1H, ddd, J_{gem}=15.9, J_{vic}= 5.6, J_W= 1.4 Hz), 3.22 (H-2a, m), 3.31 (OCH_3, 3H, s), 3.44 (H-8b, dd, J_{vic}= 9.1, J_W=1.5 Hz), 3.75 (CO_2CH_3, 3H, s), 3.84 (H-2α, 1H, dd, J_{gem}= 8.5, J_{vic}= 2.4 Hz), 4.16 (H-2β, 1H, dd, J_{gem}= 8.5, J_{vic}= 7.2 Hz), 5.72-5.74 (H-3 or H-4, 1H, m, J = 9.7 Hz), 5.75-5.79 (H-4 or H-3, 1H, m, J = 9.9 Hz), 6.12 (H-7, d, J = 10.2 Hz), 6.99 (H-6, d, J = 10.1 Hz); **^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm):** 35.3 (C-5), 37.7 (C-8b), 47.5 (C-5a), 49.1 (C-2a),

50.3, 52.9 (OCH_3, CO_2CH_3), 73.2 (C-2), 102.4 (C-8a), 124.5, 128.4, 130.9 (C-3, C-4, C-7), 150.9 (C-6), 173.7 (CO_2CH_3), 190.2 (C-8); **LRMS (EI)** ***m/e*****:** 264 (5%, M^+), 233 (100%, M-OCH_3), 207 (27%), 191 (25%), 173 (16%), 145 (17%), 117 (16%); **HRMS (EI):** Calc'd for $C_{14}H_{16}O_5$: 264.0997; Found: 264.0991.

4.57 Synthesis of **177b** and **178b** by IMDA reaction with **172** and (*E*)-2,4-Pentadienol

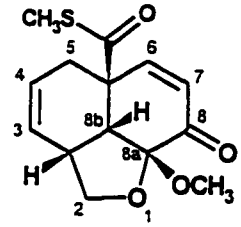
The general procedure for the IMDA reaction described in section 4.6 was followed, using **172** (1.0 g, 5.04 mmol) and (*E*)-2,4-pentadienol (2.9 g, 0.035 mol, 7 equiv.), and oxidized with PIFA (2.6 g, 6.05 mmol, 1.2 equiv.) in dry THF (20 mL). After stirring for 4 h at room temperature, solid $NaHCO_3$ was added (0.85g, 0.01 mol, 2 equiv.) and the mixture stirred 15 min. Solvents were removed *in vacuo*, and excess pentadienol was removed by distillation under reduced pressure (bp= 58-60°C @ 20 torr), and the crude residue was extracted into EtOAc (300 mL), washed twice with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to an orange oil. This oil was then purified by column chromatography (silica gel 60, 1:4 EtOAc-hexane eluant), where the products **177b** (0.562 g, 40% yield) and **178b** (0.531 g, 37% yield) were isolated as pale yellow oils.



177b

(3,8-*trans*)-7a-Methoxy-4-[(methylthio)carbonyl]-8-vinyl-2,3,3a,6,7,7a-hexahydro-3,6-methanobenzofuran-7-one (**177b**)

IR (neat film): 2979, 1753, 1654, 1186, 1027, 731 cm^{-1}; **^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm):** 2.40 ($COSCH_3$, 3H, s), 2.43 (H-3, buried m), 2.85 (H-8, m), 3.40 (H-6, dd, J = 6.9, 2.9 Hz), 3.52 (OCH_3, 3H, s), 3.88 (H-2, 1H, d, J = 8.3 Hz), 4.08 (H-3a, dd, J = 4.4, 2.2 Hz), 4.23 (H-2, 1H, dd, J = 8.3, 3.4 Hz), 5.05-5.12 ($CH=C\underline{H}_2$, 2H total, overlapped dd, J_{trans}= 17.2, J_{cis}= 10.1, $J_{10,8}$= 1.0 Hz), 5.58 ($C\underline{H}=CH_2$, 1H, ddd, J_{trans}= 17.2, J_{cis}= 10.1, $J_{9,8}$= 8.0 Hz), 7.16 (H-5, dd, J = 6.9, 2.2 Hz); **^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm):** 11.3 (SCH_3), 41.1, 42.3, 46.5 (C-3, C-3a, C-8), 51.1, 52.3 (OCH_3, C-6), 73.3 (C-2), 99.1 (C-7a), 116.5 (C-10), 134.8 (C-5), 137.4 (C-9), 139.9 (C-4), 188.9 (C-7), 198.8 ($\underline{C}OSCH_3$); **LRMS (CI, NH_3):** 298 (100%, M+NH_4), 281 (7%, M+H), 252 (65%, M-CO), 205 (31%, M-$COSCH_3$), 173 (10%), 145 (10%), 117 (13%); **HRMS (EI):** Calc'd for $C_{13}H_{16}O_3S$ (M-CO fragment): 252.0820; Found: 252.0818.



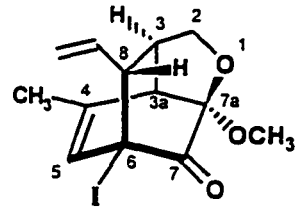
(*syn* 2a-H, 5a-$COSCH_3$, 8a-OCH_3, 8b-H)-5a-[(methylthio)carbonyl]-8a-methoxy-2a,5,5a,8,8a,8b-hexahydro-2*H*-naphtho[1,8-*bc*]furan-8-one (**178b**)

IR (neat film): 2934, 1685 (broad), 1437, 1112, 1038 cm^{-1}; **^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm):** 2.10 (H-5α, 1H, dm, J = 16.3, 2.4 Hz), 2.34 ($COSCH_3$, 3H, s), 2.70 (H-5β, 1H, dm, J = 16.3, 4.4, 1.5 Hz), 3.18 (H-2a, m), 3.33 (OCH_3, 3H, s), 3.48 (H-8b, dd, J = 9.2, 1.4 Hz), 3.80 (H-2α, 1H, dd, J = 8.6, 3.1 Hz), 4.17 (H-2β, 1H, dd, J = 8.5 Hz, 7.2 Hz), 5.80 (H-3 and H-4, 2H, m), 6.17 (H-7, d, J = 10.1 Hz), 6.89 (H-6, d, J = 10.1 Hz); **^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm):** 12.2 ($COS\underline{C}H_3$), 35.3 (C-5), 37.9 (C-8b), 49.6 (C-2a), 50.6 (OCH_3), 54.4 (C-5a), 72.9 (C-2), 102.6 (C-8a), 124.9, 129.3, 130.9 (C-3, C-4, C-7),

150.4 (C-6), 190.3 ($\underline{C}OSCH_3$), 201.9 (C-8); **LRMS (EI)** ***m/e*****:** 280 (4%, M^+), 251 (3%, [M-OCH_3]+2), 249 (45%, M-OCH_3), 233 (88%, M-SCH_3), 206 (100%, [M-$COSCH_3$]+H), 205 (48%, M-$COSCH_3$), 173 (96%, M-[$COSCH_3$+CH_3OH]), 159 (37%), 145 (60%), 117 (78%), 91 (40%); **HRMS (EI):** Calc'd for $C_{14}H_{16}O_4S$: 280.0769; Found: 280.0762.

4.58 Synthesis of **177d** and **178d** by IMDA reaction with **173** and (*E*)-2,4-pentadienol

The general procedure for the IMDA reaction described in section 4.6 was followed, using the iodophenol **173** (1.77 g, 6.69 mmol), freshly distilled (*E*)2,4-pentadienol (3.93 g, 0.0468 mol, 7 equiv.), BHT (0.03 g, 0.13 mmol, 2 mol-%) and PIFA (3.45 g, 8.03 mmol, 1.2 equiv.). (The $NaHCO_3$ was added at the end of this reaction to neutralize the TFA by-product.) After 16 h stirring at room temperature, the pale yellow mixture was treated with $NaHCO_3$ (1.25 g, 0.015mol, 2.2 equiv.), and the volatile solvents evaporated *in vacuo*. The residue was extracted into EtOAc (150 mL), washed with brine solution, dried (Na_2SO_4), and concentrated to a dark yellow oil which was distilled under reduced pressure to remove the excess pentadienol. The crude residue left behind was purified by column chromatography (silica gel 60, 1:4 EtOAc-hexane eluant), which produced the pure products **177d** (1.67 g, 72% yield) as a white crystals (from ether), and **178d** (0.373 g, 16% yield) as a pale yellow oil (which could be crystallized from ether).



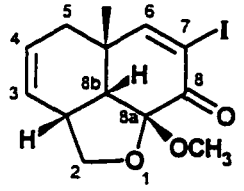
177d

(3,8-*trans*)-6-iodo-7a-methoxy-4-methyl-8-vinyl-2,3,3a,6,7,7a-hexahydro-3,6-methano-benzofuran-7-one (**177d**)

mp 119-120°C; **IR (KBr):** 2957, 1734, 1638, 1442, 1199 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm):** 1.93 (CH_3, d, *J* = 1.6 Hz), 2.54 (H-3, m, *J* = 4.6, 3.5, 1.5 Hz), 2.90 (H-8, d, *J* = 9.1 Hz), 3.15 (H-3a, dd, *J* = 4.5, 2.0 Hz), 3.58 (OCH_3, 3H, s), 3.88 (H-2, 1H, d, *J* = 8.4 Hz), 4.12 (H-2, 1H, dd, *J* = 8.4, 3.4 Hz), 5.11 (CH=C$\underline{H}_2$, 1H, dm, *J* = 17.0 Hz), 5.18 (CH=C$\underline{H}_2$, 1H, dm, *J* = 10.3 Hz), 5.74 (H-9, ddd, *J* = 16.9, 10.2, 9.1 Hz), 6.0 (H-5, narrow m); **^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm):** 20.7 (CH_3), 44.2 (C-3), 48.2 (C-8 or C-3a), 52.3 (OCH_3), 54.9 (C-6), 57.2 (C-3a or C-8), 73.9 (C-2), 97.6 (C-7a), 117.9 (CH=$\underline{C}H_2$), 127.8 (C-5), 138.3 ($\underline{C}$H=CH_2), 139.6 (C-4), 187.5 (C-7); **LRMS (CI, NH_4OH):** 364 (100%, M+NH_4), 347 (50%, M+H), 332 (22%, M-OCH_3+NH_4), 315 (15%, M-OCH_3), 238 (6%, M-I+NH_4), 219 (5%, M-I); **HRMS (EI):** Calc'd for $C_{12}H_{15}O_2I$ (No molecular ion was observed in the EI mass spectrum): 318.0117; Found: 318.0122; **Anal.** Calc'd for $C_{13}H_{15}IO_3$: C, 45.11%; H, 4.37%; I, 36.66%. Found: C, 45.14%; H, 4.26%; I, 36.43%.

4.59 Synthesis of (*syn* 2a-H, 5a-CH_3, 8a-OCH_3, 8b-H)-7-iodo-8a-methoxy-5a-methyl-2a,5,5a,8,8a,8b-hexahydro-2*H*-naphtho[1,8-*bc*]furan-8-one (**178d**)

This compound was formed as the minor Diels-Alder adduct for the IMDA reaction with **173** described above. It was also prepared in very high yield by the α-iodination of **68** using the method reported by Johnson *et al.*[115] A solution of pure naphthofuran **68** (0.094 g, 0.42 mmol) in 10 mL of 1:1 pyridine (distilled from CaH_2) and CCl_4 was cooled to 0°C. A solution of iodine (0.453 g, 1.79 mmol, 4.2 equiv.) in 5 mL 1:1 pyridine-CCl_4 was slowly added from a pressure-equalized dropping funnel under argon atmosphere. The dark mixture was stirred for 3 h at 0°C, and then diluted with ether (80 mL). The ether extract was washed sequentially with water (40 mL), then sat. $Na_2S_2O_3$ solution (40 mL), and finally water (20 mL), and then dried ($MgSO_4$), filtered, and concentrated *in vacuo* to a clear oil. Residual pyridine was removed by evaporation under reduced pressure (1.0 torr), leaving behind a semi-solid which was recrystallized with ether-hexane to give **178d** (0.148 g, quantitative yield) as light tan microcrystals.



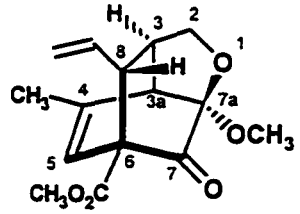
178d

mp 81-82°C; **IR (neat film):** 2930, 1700 (CO), 1454, 1053 cm^{-1}; **^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm):** 1.25 (CH_3, 3H, s), 1.89-2.08 (H-5, 2H, m), 2.64 (H-8b, dd, J = 9.2, 0.9 Hz), 3.02 (H-2a, m), 3.26 (OCH_3, 3H, s), 3.78 (H-2α, 1H, dd, J = 8.6, 3.1 Hz), 4.15 (H-2β, 1H, dd, J = 8.6, 7.3 Hz), 5.77 (H-3 and H-4, 2H, narrow m), 7.35 (H-6, s); **^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm):** 28.1 (CH_3), 37.3 (C-8b), 37.6 (C-5), 39.5 (C-5a), 51.1 (C-3a), 53.8 (OCH_3), 73.0 (C-2), 98.1 (C-7), 102.7 (C-8a), 125.6, 129.4 (C-3 and C-4), 166.5 (C-6), 186.3 (C-8); **LRMS (CI, NH_4OH):** 364 (17%, M+NH_4), 332 (71%, M-CH_3OH+NH_4), 315 (100%, M-OCH_3), 314 (52%, M-CH_3OH), 219 (9%, M-I), 187 (5%,

M-[I+CH_3OH]), 159 (3%), 119 (7%); **Anal.** Calc'd for $C_{13}H_{15}O_3I$: C, 45.11%; H, 4.37%; I, 36.66%. Found: C, 45.23%; H, 4.47%; I, 37.79%.

4.60 Synthesis of **177e** and **178e** by IMDA reaction with **174** and (*E*)-2,4-pentadienol

The general procedure for the IMDA reaction described in section 4.6 was followed, using **174** (0.167 g, 0.851 mmol), (*E*)-2,4-pentadienol (0.50 g, 5.96 mmol, 7 equiv.), BHT (5 mg, 17 μmol, 2 mol-%), and PIFA (0.439 g, 1.02 mmol, 1.2 equiv.) all mixed in dry THF (30 mL) at 0°C. The reaction was stirred overnight, after which time $NaHCO_3$ was added (0.157 g, 1.87 mmol, 2.2 equiv.). The volatile solvents were evaporated, and the residue was extracted into EtOAc (150 mL), washed with brine solution, dried (Na_2SO_4), and concentrated *in vacuo* to an oil which still contained excess pentadienol. The purification of the crude oil by column chromatography (silica gel 60, 1:3 EtOAc-hexane eluant) gave a mixture of IMDA products **177e** (0.155 g, 65% yield) as white microcrystals, and **178e** (0.005 g) as a gold oil. Insufficient sample of **178e** was available for characterization.



177e

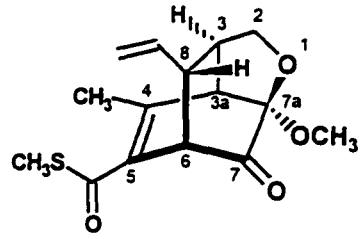
(3,8-*trans*)-6-[(methoxy)carbonyl]-7a-methoxy-4-methyl-8-vinyl-2,3,3a,6,7,7a-hexahydro-3,6-methano-benzofuran-7-one (**177e**)

mp 94-96°C; **IR (KBr):** 2960, 1757, 1724, 1435, 1272, 1221, 1050, 1020 cm^{-1}; **^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm):** 1.96 (CH_3, 3H, s), 2.37 (H-3, m), 3.11 (H-3a, obscured m),

3.14 (H-8, d, J = 9.2 Hz), 3.56 (OCH_3, 3H, s), 3.81 (CO_2CH_3, 3H, s), 3.93 (H-2, 1H, d, J = 8.2 Hz), 4.17 (H-2, 1H, dd, J = 8.3, 3.3 Hz), 5.02 (-CH=C$\underline{H}_2$, 1H, d, J = 10.3 Hz), 5.08 (-CH=C$\underline{H}_2$, 1H, d, J = 17.2 Hz), 5.52 (-C$\underline{H}$=CH_2, ddd, J = 17.2, 10.0, 9.1 Hz), 7.04 (H-5, broad s); **^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm):** 21.3 (CH_3), 43.7 (C-3), 48.6, 49.9 (C-3a, C-8), 52.1, 52.5 ($CO_2\underline{C}H_3$, OCH_3), 63.6 (C-6), 73.6 (C-2), 100.3 (C-7a), 117.4 (-CH=$\underline{C}H_2$), 119.7 (C-5), 136.4 (-$\underline{C}$H=CH_2), 138.8 (C-4), 168.8 ($\underline{C}O_2CH_3$), 196.2 (C-7); **LRMS (EI) *m/e*:** No M^+ observed; 250 (48%, M-CO), 219 (9%, M-CO_2CH_3), 183 (24%), 159 (40%), 131 (55%), 91 (41%), 59 (100%, CO_2CH_3); **LRMS (CI, NH_4OH) *m/e*:** 279 (3%, M+H), 250 (27%, M-CO), 247 (100%, M-OCH_3); **HRMS (EI):** Calc'd for $C_{14}H_{18}O_4$ (M-CO fragment): 250.1205; Found: 250.1210.

4.61 Synthesis of **177f** and **178f** by IMDA reaction with **175** and (*E*)-2,4-pentadienol

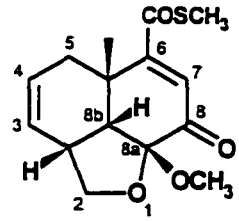
The general procedure for the IMDA reaction described in section 4.6 was followed, using **175** (0.480 g, 2.26 mmol), (*E*)-2,4-pentadienol (0.95 g, 0.011 mol, 2 equiv.), BHT (0.010 g, 45.2 μmol, 2 mol-%), and PIFA (1.17 g, 2.71 mmol, 1.2 equiv.), all mixed in 10 mL dry THF at 0°C, and gradually warmed to room temperature. After 3 h, the volatile solvents were removed, and the residue extracted into ether (100 mL), washed with water several times, then dried (Na_2SO_4), filtered, and concentrated *in vacuo* to an oil. The excess dienol was distilled off, and the residue was purified by column chromatography (silica gel 60, 1:3 EtOAc-hexane eluant), which gave the products **177f** (0.431 g, 65% yield) as white crystals, and **178f** (0.046 g, 7% yield) as a yellow oil.



177f

(3,8-*trans*)-7a-methoxy-5-[(methylthio)carbonyl]-4-methyl-8-vinyl-2,3,3a,6,7,7a-hexahydro-3,6-methano-benzofuran-7-one (**177f**)

mp 90-93°C; **IR (KBr):** 2940, 1746, 1650, 1606, 1429, 1117, 1020, 886 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm):** 2.32, 2.33 ($COSCH_3$ and CH_3, each 3H, s), 2.40 (H-3, narrow m), 2.79 (H-8, broad d, J = 7.8 Hz), 3.24 (H-3a, d, J = 3.24 Hz), 3.53 (OCH_3, 3H, s), 3.71 (H-6, d, J = 3.1 Hz), 3.85 (H-2, 1H, d, J = 8.3 Hz), 4.17 (H-2, 1H, dd, J = 8.3, 3.4 Hz), 5.04 (CH=C$\underline{H}_2$, 1H, d, J = 10.1 Hz), 5.07 (CH=C$\underline{H}_2$, 1H, d, J = 17.1 Hz), 5.58 (C$\underline{H}$=CH_2, ddd, J = 17.0, 10.3, 7.9 Hz); **^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm):** 11.9 (COS$\underline{C}H_3$), 20.9 (CH_3), 42.5 (C-3), 46.0 (C-8), 51.88 and 51.92 (OCH_3, C-3a), 52.3 (C-6), 73.6 (C-2), 99.5 (C-7a), 116.6 (CH=$\underline{C}H_2$), 129.3 (C-5), 137.3 ($\underline{C}$H=CH_2), 147.5 (C-4), 189.4 ($\underline{C}OSCH_3$), 199.4 (C-7); **LRMS (EI) *m/e*:** 295 (2%, M+H), 266 (100%, M-CO), 247 (36%, M-SCH_3), 219 (22%, M-$COSCH_3$), 199 (46%), 191 (29%), 162 (16%), 159 (19%), 131 (13%); **HRMS (EI):** Calc'd for $C_{14}H_{18}O_3S$ (M-CO fragment): 266.0977; Found: 266.0968.



178f

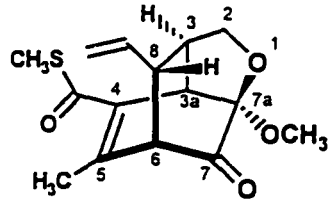
(*syn* 2a-H, 5a-CH_3, 8a-OCH_3, 8b-H)-8a-methoxy-5a-methyl-6-[(methylthio)carbonyl]-2a,5,5a,8,8a,8b-hexahydro-2*H*-naphtho[1,8-*bc*]furan-8-one (**178f**)

IR (neat film): 2935, 1690, 1670, 1453, 1068 cm^{-1}; **^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm):** 1.25 (CH_3, 3H, s), 2.00 (H-5, 1H, d, J = 15.2 Hz), 2.37 (H-5, 1H, partially obscured m), 2.39 (SCH_3, 3H, s), 2.66 (H-8b, dd, J = 9.2, 1.5 Hz), 3.10 (H-2a, m), 3.23 (OCH_3, 3H, s), 3.81 (H-2α, 1H, dd, J = 8.4, 2.5 Hz), 4.12 (H-2β, 1H, dd, J = 8.5, 7.0 Hz), 5.73 (H-3 and H-4, 2H, narrow m), 6.42 (H-7, s); **^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm):** 12.1 ($COS\underline{C}H_3$), 24.6 (CH_3), 36.6 (C-5a), 37.2 (C-2a), 37.7 (C-5), 50.0 (OCH_3), 54.2 (C-8b), 72.8 (C-2), 103.3 (C-8a), 125.1, 128.1, 128.3 (C-3, C-4, C-7), 164.5 (C-6), 190.4 (C-8), 193.5 ($\underline{C}OSCH_3$); **LRMS (EI) *m/e*:** 294 (12%, M^+), 279 (7%, M-CH_3), 247 (7%, M-SCH_3), 219 (15%, M-$COSCH_3$), 187 (20%), 159 (26%), 138 (41%), 131 (54%), 91 (70%); **HRMS (EI):** Calc'd for $C_{15}H_{18}O_4S$: 294.0926; Found: 294.0919.

4.62 Synthesis of **177g** and **178g** by IMDA reaction with **176** and (*E*)-pentadienol

The general procedure for the IMDA reaction described in section 4.6 was followed, using the substituted guaiacol[104] **176** (0.50 g, 2.36 mmol), (*E*)-2,4-pentadienol (1.38 g, 0.0165 mol, 7 equiv.), BHT (0.01 g, 47.2μmol, 2 mol-%) and PIFA (1.22 g, 2.83 mmol, 1.2 equiv.), mixed in 10 mL dry THF at 0°C. After warming to room temperature over several hours, the volatile solvents were evaporated from the pale-yellow mixture, and the residue was extracted into ether (100 mL), washed with water several times, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to an oil. The excess dienol was distilled off, and the crude product mixture purified and separated by column chromatography (silica gel 60, 1:9→1:4 EtOAc-hexane eluant). The bridged adduct **177g** (0.364 g) was isolated as a pale yellow oil in 52% yield, but a very small quantity of **178g** (0.01 g) was

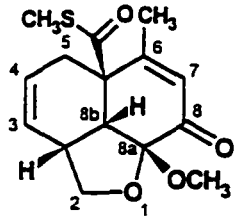
obtained in <1% yield; this latter product had similar ^{1}H-NMR spectral features as **178b**, but could not be characterized fully.



177g

(3,8-*trans*)-7a-methoxy-4-[(methylthio)carbonyl]-5-methyl-8-vinyl-2,3,3a,6,7,7a-hexahydro-3,6-methano-benzofuran-7-one (**177g**)

IR (neat film): 2938, 1746, 1667, 1433, 1077, 1024, 890 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm):** 2.25 (CH_3, 3H, s), 2.40 ($COSCH_3$, 3H, s), 2.46 (H-3, m), 2.80 (H-8, m), 3.12 (H-3a, narrow m), 3.57 (OCH_3, 3H, s), 3.86 (H-2, 1H, d, J = 8.5 Hz), 3.95 (H-6, d, J = 4.7 Hz), 4.20 (H-2, 1H, dd, J = 8.5, 3.5 Hz), 5.05-5.14 (CH=C$\underline{H}_2$, 2H, J = 17.6, 9.4 Hz), 5.54 (C$\underline{H}$=CH_2, ddd, J = 17.3, 9.7, 7.6 Hz); **^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm):** 11.9 ($COSCH_3$), 21.7 (CH_3), 42.4, 43.2, 45.9 (C-3, C-3a, C-8), 50.3 (OCH_3), 60.8 (C-6), 73.4 (C-2), 103.1 (C-7a), 116.8 (CH=$\underline{C}H_2$), 131.0 (C-4), 137.0 ($\underline{C}$H=CH_2), 146.1 (C-5), 189.6 ($\underline{C}OSCH_3$), 199.0 (C-7); **LRMS (CI, NH_3) *m/e*:** 312 (15%, M+NH_4), 295 (8%, M+H), 280 (17%, M-OCH_3+NH_4), 263 (56%, M-OCH_3), 247 (35%, M-SCH_3), 219 (100%, M-$COSCH_3$), 187 (43%), 159 (32%), 131 (68%), 115 (32%), 91 (68%), 75 (25%, $COSCH_3$); **HRMS (EI):** Calc'd for $C_{14}H_{18}O_3S$ (M-CO fragment): 266.0977; Found: 266.0963.



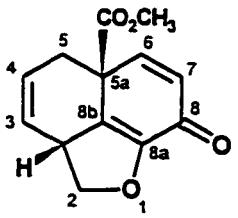
178g

(*syn* 2a-H, 5a-$COSCH_3$, 8a-OCH_3, 8b-H)-5a-[(methylthio)carbonyl]-8a-methoxy-6-methyl-2a,5,5a,8,8a,8b-hexahydro-2*H*-naphtho[1,8-*bc*]furan-8-one (**178g**)

^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.96 (CH_3, 3H, d, *J* = 1.2 Hz), 2.33 ($COSCH_3$, 3H, s), 2.27-2.30 (H-5, 2H, m), 3.17 (H-2a, broad m), 3.35 (OCH_3, 3H, s), 3.47 (H-8b, dd, *J* = 9.3, 1.5 Hz), 3.73 (H-2α, 1H, dd, *J* = 8.6, 3.5 Hz), 4.16 (H-2β, 1H, *J* = 8.5, 7.1 Hz), 5.70-5.90 (H-3 and H-4, 2H, m), 6.07 (H-7, q, *J* = 1.2 Hz).

4.63 Synthesis of (*syn* 2a-H, 5a-CO_2CH_3)-5a-[(methoxy)carbonyl]-2a,5,5a,8-tetrahydro-2*H*-naphtho[1,8-*bc*]furan-8-one (**179a**)

The general procedure for the Cope rearrangement described in section 4.7 was followed, by heating the bridged compound **177a** (0.53 g, 2.0 mmol) in *p*-xylene (10 mL) for 48 h. After removal of the solvent by distillation, the crude product mixture was separated by column chromatography (silica gel 60, 1:4 EtOAc-hexane eluant), which gave the naphthofuran **178a** (0.101 g, 21% yield) and the demethoxylated **179a** (0.191 g, 0.822 mmol, 44% yield), along with unconverted bridged reactant **177a** (0.040 g, 0.15 mmol; 93% reaction conversion). The pure product **179a** was a pale yellow oil, which eventually crystallized from ether to colorless prisms.



179a

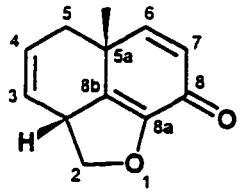
mp 67-69°C; **IR (KBr):** 2946, 1720, 1655, 1432, 1311, 1195, 1130, 1038, 927 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm):** 2.19 (H-5, 1H, dm, J = 17.5 Hz), 3.22 (H-5, 1H, dd, J = 17.5, 4.5 Hz), 3.75 (CO_2CH_3, 3H, s), 4.11 (H-2 (1H) and H-2a, 2H total, m), 4.91 (H-2, 1H, dd, J = 8.8, 6.9 Hz), 5.75 (H-3 and H-4, 2H total, m), 6.34 (H-7, d, J = 9.8 Hz), 7.01 (H-6, d, J = 9.8 Hz); **^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm):** 38.0 (C-5), 41.4 (C-2a), 49.3 (C-5a), 53.3 ($CO_2\underline{C}H_3$), 76.6 (C-2, obscured by $CDCl_3$ triplet), 124.7, 127.5 (C-3 and C-4), 130.5 (C-7), 133.3 (C-8b), 146.4 (C-6), 148.9 (C-8a), 170.1 ($\underline{C}O_2CH_3$), 177.0 (C-8); **LRMS (EI) *m/e*:** 232 (22%, M^+), 201 (5%, M-OCH_3), 173 (74%, M-CO_2CH_3), 145 (48%, M-[CO_2CH_3+CO]), 115 (72%), 91 (77%), 59 (100%, CO_2CH_3); **HRMS (EI):** Calc'd for $C_{13}H_{12}O_4$: 232.0736; Found: 232.0733.

4.64 Synthesis of [*syn* 2a-H, 5a-CH_3]-5a-methyl-2a,5, 5a,8-tetrahydro-2*H*-naphtho[1,8-*bc*]furan-8-one (**179c**)

This compound was obtained by one of two methods: Cope rearrangement of **67**, and (b) TFA-promoted elimination of methanol from **68**.

Cope rearrangement: The general procedure described in section 4.7 was followed, dissolving **67** (1.40 g, 6.35 mmol) in 1,2,4-trimethylbenzene (10 mL) and heating at reflux for 48 h. After cooling to room temperature and removing the solvent by distillation, the crude products were purified by column chromatography (silica gel 60, 1:4 EtOAc-hexane eluant), which afforded **68** (1.075 g, 81% yield) as a pale gold oil, **179c** (0.099 g, 8% yield) as colorless needles from ether, and also unreacted **67** (0.069 g, 0.313 mmol; reaction was 95% conversion).

TFA-promoted elimination: The general procedure in section 4.8 was followed, using **68** (1.0 g, 4.54 mmol) and 10 mL neat TFA. After 30 min., the reaction was complete and the TFA evaporated to give a dark orange oil which was extracted into ether (150 mL), washed several times with brine solution or water, then dried (Na_2SO_4), filtered and concentrated *in vacuo*. The pale orange residue readily crystallized on standing to give **179c** (0.83 g, 97% yield) as colorless needles.



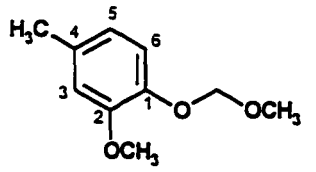
179c

mp 86-88°C; **IR (KBr):** 2878, 1680 (CO), 1646 (C=C), 1130 cm^{-1}; **^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm):** 1.28 (CH_3, 3H, s), 2.09 (H-5, 1H, dm, J = 18.1 Hz), 2.32 (H-5, 1H, dm, J = 17.7, 4.3 Hz), 3.91 (H-2a, m, J = 10.2, 2.2 Hz), 4.03 (H-2, 1H, dd, J = 8.3, 10.3 Hz), 4.84 (H-2, 1H, dd, J = 8.3, 9.9 Hz), 5.75 (H-3 and H-4, 2H total, fused m), 6.20 (H-7, d, J = 9.8 Hz), 6.90 (H-6, d, J = 9.7 Hz); **^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm):** 21.6 (CH_3), 37.8 (C-5a), 39.6 (C-5), 40.6 (C-2a), 76.2 (C-2), 125.5, 126.4 (C-3 and C-4), 128.5 (C-7), 139.7 (C-8b), 147.4 (C-8a), 154.9 (C-6), 177.7 (C-8); **LRMS (EI) *m/e*:** 188 (100%, M^+), 173 (12%, M-CH_3), 158 (49%, M-CH_2O), 147 (47%), 115 (64%), 91 (41%), 84 (71%); **HRMS (EI):** Calc'd for $C_{12}H_{12}O_2$: 188.0837; Found: 188.0848; **Anal.** Calc'd for $C_{12}H_{12}O_2$: C, 76.57%; H, 6.43%. Found: C, 76.36%; H, 6.23%.

4.65 Synthesis of 2-methoxy-4-methylphenol methoxymethyl ether (**180**)

In a 3-necked 250 mL round-bottomed flask fitted with a reflux condenser and pressure-equalized dropping funnel was added sodium hydride (1.59 g as the 60%

dispersion in mineral oil; 0.0398 mol, 1.1 equiv.) and 10 mL of anhydrous hexane, and the mixture was stirred shortly to extract the mineral oil component. The hexane washing was then removed using a cannula under positive argon pressure, and then dry ether (50 mL) and dry DMF (10 mL) were added to the flask, and the mixture was cooled (0°C). A solution of 2-methoxy-4-methylphenol **64** (5.0 g, 0.0362 mol) in dry ether (20 mL) was then added dropwise in to the flask and stirred in ice for 30 min. Neat chloromethyl methylether was added slowly (over 30 min.) to the flask, and the mixture became milky in appearance. The reaction was stirred for 2 h while warming up to room temperature, then was quenched by the careful addition of 30 mL of water, and diluted with ether (300 mL). The ether extract was washed first with brine solution, then dilute $NaHCO_3$ solution, and lastly with brine solution (to ensure a neutral pH of the washings), then dried (Na_2SO_4) and concentrated to a golden oil, which was distilled under reduced pressure (bp =132°C @ 20 torr) to afford **180** (6.27 g, 95% yield) as a colorless and clear oil.



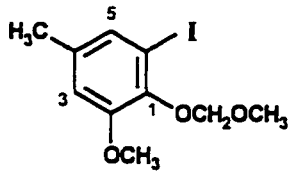
180

IR (neat film): 2923, 1591, 1470, 811, 762 cm^{-1}; **^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm):** 2.29 (CH_3, 3H, s), 3.50 ($OCH_2O\underline{C}H_3$, 3H, s), 3.85 (OCH_3, 3H, s), 5.18 ($O\underline{C}H_2OCH_3$, 2H, s), 6.68 (H-5, dd, J = 8.1, 0.9 Hz), 6.71 (H-3, s), 7.02 (H-6, d, J = 8.0 Hz); **^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm):** 20.9 (CH_3), 55.7, 55.9 ($O\underline{C}H_3$ and $OCH_2O\underline{C}H_3$), 95.7 ($O\underline{C}H_2OCH_3$), 112.8 (C-6), 116.7 (C-3), 120.9 (C-5), 132.3 (C-4), 144.1 (C-1), 149.6 (C-2); **LRMS (EI) *m/e*:** 182 (22%, M^+), 152 (26%, M-CH_2O), 137 (9%, M-CH_2OCH_3), 109

(6%), 91 (9%), 77 (7%), 45 (100%, CH_2OCH_3); **HRMS (EI):** Calc'd for $C_{10}H_{14}O_3$: 182.0943; Found: 182.0943.

4.66 Synthesis of 6-iodo-2-methoxy-4-methylphenol methoxymethyl ether (**181**)

To a cooled (0°C) solution of **180** (7.5 g, 0.0412 mol) in dry ether (250 mL) and dry THF (30 mL) under argon atmosphere was added dropwise 1.6 M *n*-BuLi (56.6 mL, 0.0906 mol, 2.2 equiv.), and the mixture was stirred for 1 h at 0°C. A solution of iodine (31.4 g, 0.124 mol, 3 equiv.) in dry THF (150 mL) was added dropwise (under argon atmosphere) while stirring the dark brown mixture well. After 4 h, the reaction was quenched at 0°C with the addition of excess (200 mL) sat. $Na_2S_2O_3$ (sodium thiosulfate) solution (which neutralized the excess I_2 and discharged the brown color). The mixture was extracted into ether (500 mL), and washed with brine solution and water several times. The ether layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo* to a brown viscous oil **181** (12.49 g, 98% yield) which was of high purity. This compound eventually crystallized to colorless prisms at 4°C (in the dark).



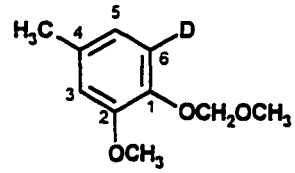
181

IR (neat film): 2924 (strong), 1591, 1562, 1467 (broad), 1153, 952 (broad) cm^{-1}; **^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm):** 2.27 (CH_3, 3H, s), 3.67 and 3.82 ($CH_2OC\underline{H}_3$ and OCH_3, each 3H, s), 5.14 ($C\underline{H}_2OCH_3$, 2H, s), 6.69 (H-3, d, J = 1.2 Hz), 7.19 (H-5, d, J = 1.0 Hz); **^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm):** 21.1 (CH_3), 55.8 (OCH_3), 58.3 ($CH_2O\underline{C}H_3$), 92.4 (C-6), 98.8 ($O\underline{C}H_2OCH_3$), 114.0 (C-3), 130.8 (C-5), 136.1 (C-4), 143.2

(C-2), 151.8 (C-1); **LRMS (EI) *m/e*:** 308 (53%, M^+), 277 (34%, M-OCH_3), 263 (22%, M-CH_2OCH_3), 181 (60%, M-I), 121 (13%), 91 (10%), 45 (100%, CH_2OCH_3).

4.67 Synthesis of 6-deuterio-2-methoxy-4-methylphenol methoxymethyl ether (**182**)

To a cooled solution (0°C) of **180** (0.1g, 0.55 mmol) in dry ether (5 mL) was added 1.6 M *n*-BuLi in hexane (0.75 mL, 1.21 mmol, 2.2 equiv.). The resulting cloudy solution was stirred for 1 h at 0°C under argon atmosphere, and was then quenched with excess D_2O (1 mL). The mixture was extracted into ether (20 mL), and washed with brine, dried (Na_2SO_4), filtered, and concentrated to a golden oil (0.11 g), which was of high purity.

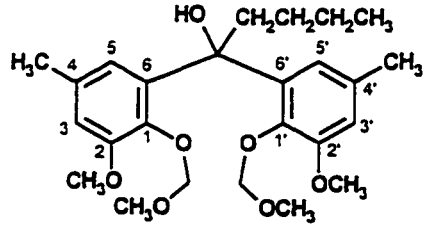


182

^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 2.30 (CH_3, 3H, s), 3.52 (OCH_2OCH_3, 3H, s), 3.85 (OCH_3, 3H, s), 5.18 (OCH_2OCH_3, 2H, s), 6.68 (H-5, broad singlet from small coupling with adjacent D), 6.72 (H-3, s). No further characterization was performed with this sample, as this experiment only served to prove whether or not *o*-lithiation of **180** could occur.

4.68 Synthesis of **183** and **184** by *o*-lithiation of **180** and acylation with methyl chloroformate

To a cooled solution (0°C) of **180** (1.0 g, 5.5 mmol) in dry ether (30 mL) was added dropwise (under argon atmosphere) 1.6 M *n*-BuLi (7.6 mL, 0.012 mol, 2.2 equiv.). The resulting pale yellow milky mixture was stirred for 1 h at 0°C, and then methyl chloroformate (distilled from $CaCO_3$) was added to this mixture, during which time the reaction became somewhat exothermic, and the color changed to homogeneous blue and then finally to bright yellow. After 30 min., the reaction was quenched with a solution of sat. NH_4Cl, and the mixture was extracted into ether (300 mL). The ether layer was washed with sat. NH_4Cl, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to a pale yellow oil which was further purified by column chromatography (silica gel 60, 1:4 EtOAc-hexane eluant) to give **183** as a beige semi-solid. This compound was usually immediately hydrolyzed by dissolution in methanol (20 mL) and mixing with TFA (2-5 mL) at room temperature for several hours. All volatile solvents were then evaporated, which furnished compound **184** in quantitative yield as beige crystals of high purity.

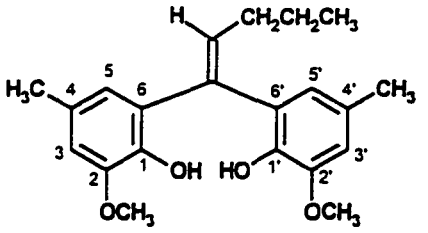


183

1,1-bis[(1-methoxymethylenoxy-2-methoxy-4-methyl)phen-6-yl]-1-pentanol (**183**)

^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 0.89 (-$(CH_2)_3CH_3$, 3H, t, J = 7.3 Hz), 1.14-1.48 (-$CH_2CH_2CH_2CH_3$, 4H, m), 2.34 (-$CH_2CH_2CH_2CH_3$, 2H, obscured t), 2.37 (Ar-CH_3, 3H, s), 3.46 (OCH_2OCH_3, 3H, s), 3.78 (Ar-OCH_3, 3H, s), 4.13 (OCH_2OCH_3, 1H), 4.38 (OCH_2OCH_3, 1H), 4.77 (OH, s), 6.64 (H-3, d, J = 1.2 Hz), 7.19 (H-5, d, J = 1.2 Hz); **LRMS (EI) *m/e*:** 448 (<1%, M^+), 341 (35%, M-[2×CH_2OCH_3]-OH), 325 (100%, [*m/e*

341-OH]), 311 (17%), 165 (24%), 151 (15%), 136 (3%). No further characterization was performed as this was not a useful compound.



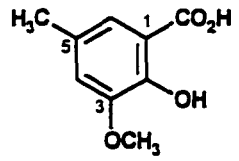
184

1,1-bis[(1-hydroxy-2-methoxy-4-methyl)phen-6-yl]-1-pentene (**184**)

mp 107-109°C; **IR (KBr):** 3363 (OH, strong), 2943 (strong), 1595, 1493, 1223, 1096, 839 (strong) cm^{-1}; **^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm):** 0.89 (-$CH_2CH_2C\underline{H}_3$, 3H, t, *J* - 7.4 Hz), 1.44 (-$CH_2C\underline{H}_2CH_3$, 2H, m, *J* = 7.4 Hz), 2.03 (-$C\underline{H}_2CH_2CH_3$, 2H, m, *J* = 7.3 Hz), 2.24 (2×Ar-CH_3, 6H, s), 3.79 and 3.83 (2×Ar-OCH_3, each 3H, s), 5.83 and 5.93 (2×OH, each 1H, s), 6.01 (C=C$\underline{H}$$CH_2CH_2CH_3$, 1H, t *J* = 7.3 Hz), 6.49 (H-3, 1H, d, *J* = 1.6 Hz), 6.58 (H-5, H-5' and H-3', 3H total, m, *J* = 1.7 Hz); **^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm):** A pair of signals was observed for each carbon in the two rotamers of this compound; 14.4, 14.5 (-$CH_2CH_2\underline{C}H_3$), 20.9, 21.1 (Ar-CH_3), 22.4 and 31.5 (-$\underline{C}H_2\underline{C}H_2CH_3$), 55.7, 55.9 (Ar-O$\underline{C}H_3$), 110.7, 110.8 (C=$\underline{C}$$HCH_2CH_2CH_3$), 122.1, 122.2 (C-3, C-3'), 136.0, 136.1 (C-5, C-5'), 126.5, 128.6, 128.9, 129.5, 132.3 (C-1, C-1', C-4, C-4', C-6, C-6'), 139.9, 140.3, 146.5 (C-2, C-2' and $\underline{C}$=$CHCH_2CH_2CH_3$); **LRMS (EI)** ***m/e*:** 342 (100%, M^+), 325 (12%, M-OH), 311 (7%, M-OCH_3), 299 (11%, M-$CH_2CH_2CH_3$), 287 (6%), 205 (4%), 191 (9%), 175 (11%), 151 (2%); **HRMS (EI):** Calc'd for $C_{21}H_{26}O_4$: 342.1831; Found: 342.1829.

4.69 Synthesis of 2-hydroxy-3-methoxy-5-methylbenzoic acid (**185**)

To a cooled solution (0°C) of **180** (0.50g, 2.74 mmol) in dry ether (30 mL) was added 1.6 M *n*-BuLi (3.8 mL, 6.04 mmol, 2.2 equiv.), and the white milky mixture was stirred for 1 h at 0°C. Anhydrous $CO_{2\ (g)}$ was bubbled in over the headspace of the reaction for 6 h (at 0°C), as the mixture became more homogeneous and pale grey-blue in appearance. The reaction was quenched with a solution of sat. NH_4Cl, and was extracted into EtOAc (100 mL), washed with brine solution and then with 50% Na_2CO_3 solution. The basic aqueous layer was then separated, reacidified and the product extracted into EtOAc, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to a pale yellow semi-solid (0.212g, 34% yield). The product was then stirred with 3N HCl (2 mL) dissolved in 1:1 MeOH-THF (10 mL), for 24 h at room temperature. The volatile solvents were removed, and the residue extracted into EtOAc, washed with brine solution, dried (Na_2SO_4), and concentrated to furnish **185** (0.21 g, 34% yield) as white needles.

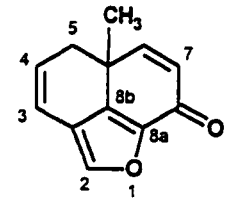


185

mp 181-183°C; **IR (KBr):** 2905, 1658, 1453, 1236, 1149 cm^{-1}; **^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm):** 2.29 (CH_3, 3H, s), 3.89 (OCH_3, 3H, s), 6.90 (H-4, d, J = 1.6 Hz), 7.29 (H-6, d, J = 1.2 Hz), 10.4 (COOH, broad s); **LRMS (EI) *m/e*:** 182 (100%, M^+), 164 (86%, M-H_2O), 136 (93%, M-[CO+H_2O]), 121 (34%), 106 (19%), 65 (31%); **HRMS (EI):** Calc'd for $C_9H_{10}O_4$: 182.0579; Found: 180.0576. **Anal.** Calc'd for $C_9H_{10}O_4$: C, 59.34%; H, 5.53%. Found: C, 59.53%; H, 5.55%.

4.70 Synthesis of 5a-methyl-5a,8-dihydro-5*H*-naphtho[1,8-*bc*]furan-8-one (**190c**)

The dienone **179c** (0.114 g, 0.603 mmol) was mixed *p*-chloranil (0.164 g, 0.666 mmol, 1.1 equiv.) in 10 mL distilled *p*-xylene, and the solution was heated at reflux for 48 h. After cooling down to room temperature, the turbid mixture was filtered through a pad of Celite, washing with benzene. The filtrate was concentrated *in vacuo* to a dark green oil, then purified by column chromatography (silica gel 60, 1:4 EtOAc-hexane eluant) to give **190c** (0.097 g, 87% yield) as shiny plates from ether.

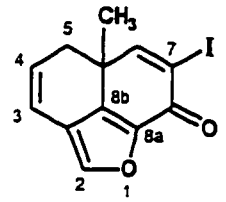


190c

IR (neat film): 1656, 1446, 1066, 826, 668 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm):** 1.36 (CH_3, 3H, s), 2.30 (H-5, 1H, dm, J = 16.9, 2.6 Hz), 2.46 (H-5, 1H, ddd, J = 16.5, 5.8, 0.9 Hz), 5.94 (H-4, ddd, J = 9.7, 5.8, 2.6 Hz), 6.24 (H-7, d, J = 9.7 Hz), 6.54 (H-3, ddd, J = 9.7, 3.0, 0.9 Hz), 6.96 (H-6, d, J = 9.7 Hz), 7.49 (H-2, s); **^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm):** 25.8 (CH_3), 33.4 (C-5), 36.3 (C-5a), 118.1 (C-4), 120.8 (C-2a), 127.9 (C-3), 130.1 (C-7), 140.7 (C-2), 144.2, 144.8 (C-8a and C-8b), 152.7 (C-6), 174.3 (C-8); **LRMS (EI) *m/e*:** 186 (100%, M^+), 171 (27%, M-CH_3), 158 (78%, M-CO), 143 (25%), 129 (32%), 115 (78%); **HRMS (EI):** Calc'd for $C_{12}H_{10}O_2$: 186.0681; Found: 186.0686.

4.71 Synthesis of 7-iodo-5a-methyl-5a,8-dihydro-5*H*-naphtho[1,8-*bc*]-furan-8-one (**190d**)

The general procedure for Cope rearrangements described in section 4.7 was followed by heating the bridged adduct **177d** (0.153 g, 0.442 mmol) in decane (10 mL) at full reflux for 24 h. (This bridged compound only completely dissolved in decane above 100 °C.) The dark mixture was then cooled and the decane was removed by distillation under reduced pressure (bp ≈ 58°C@ 20 torr). The residue was purified by column chromatography (silica gel 60, 1:4 EtOAc-hexane eluant), which gave **190d** (0.069 g, 50% yield) as white needles from ether.

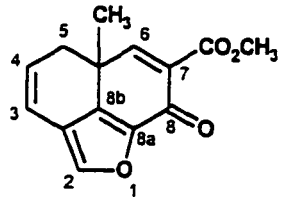


190d

mp 145-147°C; **IR (KBr):** 1662, 1548, 1456, 1056, 831, 740 cm^{-1}; **^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm):** 1.38 (CH_3, 3H, s), 2.35 (H-5, 1H, dm, J = 16.6 Hz), 2.45 (H-5, 1H, dd, J = 16.4, 5.7 Hz), 5.93 (H-4, ddd, J = 9.7, 5.7, 2.5 Hz), 6.56 (H-3, dd, J = 9.8, 2.4 Hz), 7.46 (H-2, s), 7.75 (H-6, s); **^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm):** 22.4 (CH_3), 32.9 (C-5), 39.8 (C-5a), 106.8 (C-7), 118.1 (C-4), 120.9 (C-2a), 127.8 (C-3), 140.2 (C-8a), 141.2 (C-2), 145.1 (C-8b), 160.7 (C-6), 168.2 (C-8); **LRMS (EI) *m/e*:** 312 (51%, M^+), 185 (100%, M-I), 157 (38%, M-[I+CO]), 128 (54%), 114 (20%); **HRMS (EI):** Calc'd for $C_{12}H_9O_2I$: 311.9647; Found: 311.9648; **Anal.** Calc'd for $C_{12}H_9O_2I$: C, 46.18%; H, 2.91%; I, 40.66%. Found: C, 45.59%; H, 3.23%; I, 39.94%.

4.72 Synthesis of 7-[(methoxy]carbonyl]-5a-methyl-5a,8-dihydro-5*H*-naphtho-[1,8-*bc*]furan-8-one (**190e**)

The general procedure for the Cope rearrangement described in section 4.7 was followed by heating **177e** (0.092 g, 0.33 mmol) in 1,1,2,2-tetrachloroethane at reflux for 48 h. After cooling to room temperature, the solvent was distilled under reduced pressure (bp =43°C@20 torr) and the dark brown residue was purified by column chromatography (silica gel 60, 1:3 EtOAc-hexane eluant), which gave **190e** (0.028 g, 0.106 mmol, 32% yield) along with **178e** (<10 mg).

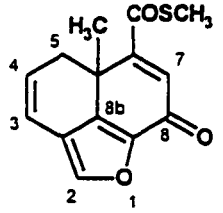


190e

IR (neat film): 2953, 1738, 1675, 1435, 1260 cm^{-1}; **^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm):** 1.41 (CH_3, 3H, s), 2.44 (H-5, 2H, overlapping m, J = 5.6 Hz), 3.89 (CO_2CH_3, 3H, s), 5.94 (H-4, ddd, J = 9.7, 5.6, 2.6 Hz), 6.58 (H-3, ddd, J = 9.7, 2.9, 1.2 Hz), 7.52 (H-2, s), 7.64 (H-6, s); **^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm):** 25.4 (CH_3), 32.9 (C-5), 35.5 (C-5a), 52.5 (OCH_3), 118.0 (C-4), 120.5 (C-2a), 127.5 (C-3), 133.4 (C-7), 141.3 (C-2), 143.5 and 143.7 (C-8a and C-8b), 157.4 (C-6), 165.7 (C-8), 169.7 (CO_2CH_3); **LRMS (EI) *m/e*:** 244 (50%, M^+), 213 (14%, M-OCH_3), 184 (100%, M-[CO_2+CH_3OH]), 157 (16%), 145 (22%), 128 (78%), 113 (15%), 59 (35%, CO_2CH_3); **HRMS (EI):** Calc'd for $C_{14}H_{12}O_4$: 244.0736; Found: 244.0736.

4.73 Synthesis of 5a-methyl-6-[(methylthio)carbonyl]-5a,8-dihydro-5*H*-naphtho-[1,8-*bc*]furan-8-one (**190f**)

The general procedure for the Cope rearrangement described in section 4.7 was followed by heating **177f** (0.152 g, 0.516 mmol) in 12 mL decane for 24 h. After cooling and removal of the solvent by distillation, the crude mixture was purified by column chromatography (silica gel 60, 1:4 EtOAc-hexane eluant; extensive decomposition had occurred), and returned unreacted **177f** (0.042 g, 0.143 mmol) along with the Cope product **190f** (0.024 g, 0.092 mol; 25% yield with 72% conversion) as a bright yellow oil.

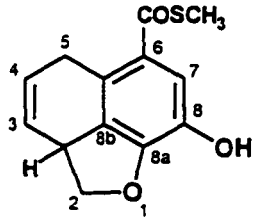


190f

IR (neat film): 2938, 1664, 1456, 1433, 1097, 1058, 80, 732 cm $^{-1}$; **^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm):** 1.56 (CH_3, 3H, s), 2.38 (H-5, 1H, dm, J = 17.4 Hz), 2.42 ($COSCH_3$, 3H, s), 2.94 (H-5, 1H, dd, J = 17.1 Hz), 5.96 (H-4, ddd, J = 9.7, 8.5, 6.2 Hz), 6.56 (H-3, dd, J = 9.8, 3.2 Hz), 7.07 (H-7, s), 7.54 (H-2, s); **^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm):** 12.2 (SCH_3), 26.3 (CH_3), 32.2 (C-5), 37.9 (C-5a), 117.1 (C-4), 120.8 (C-2a), 128.6 (C-3), 134.7 (C-7), 141.6 (C-2), 144.1, 146.0 (C-8a, C-8b), 157.7 (C-6), 172.7 (C-8), 192.8 ($\underline{C}OSCH_3$); **LRMS (EI) *m/e*:** 260 (7%, M^+), 213 (12%, M-SCH_3), 185 (33%, M-$COSCH_3$), 169 (10%), 156 (11%), 128 (37%), 114 (18%), 77 (25%), 63 (29%), 43 (100%); **HRMS (EI):** Calc'd for $C_{14}H_{12}O_3S$: 260.0507; Found: 260.0511.

4.74 Synthesis of 8-hydroxy-6-[(methylthio)carbonyl]-2a,5,5a-trihydro-2*H*-phenanthro[10,1-*bc*]furan (**191b**)

The general procedure for the Cope rearrangement described in section 4.7 was followed by heating **177b** (0.148 g, 0.528 mmol) in 1,2,4-trimethylbenzene (5 mL) at reflux for 48 h. After cooling the mixture to room temperature and removing solvent, the residue was purified by column chromatography (silica gel 60, 1:4 EtOAc-hexane eluant) and gave **191b** (0.055 g, 0.223 mol, 42% yield) as yellow crystals from ether.

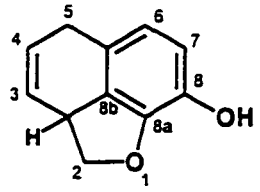


191b

IR (neat film): 3388 (OH), 2926, 1750, 1656, 1598, 1332, 1182, 1127, 948, 772, 740 cm^{-1}; **^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm):** 2.42 ($COSCH_3$, 3H, s), 3.27-3.45 (H-5, 1H, m, J = 21.5 Hz), 3.72-3.86 (H-5, 1H, m, J =21.5 Hz), 3.95 (H-2a, m), 4.20 (H-2, 1H, dd, J = 12.6, 7.7 Hz), 4.84 (OH, broad s), 5.02 (H-2, 1H, dd, J = 8.6, 7.7 Hz), 5.95 (H-3, dm, J = 9.7 Hz), 6.07 (H-4, m, J = 9.6 Hz), 7.50 (H-7, s); **LRMS (EI) *m/e*:** 249 (5%, M+H), 233 (47%), 206 (72%), 173 (58%), 145 (57%), 131 (29%), 117 (100%), 115 (89%), 91 (59%). This compound had auto-oxidized after some time to the 5*H*-naphtho[1,8-*bc*]furan analogue, and therefore could not be characterized completely.

4.75 Synthesis of 8-hydroxy-2a, 5-dihydro-2*H*-naphtho[1,8-*bc*]furan (**195**)

The naphthofuran **178a** (0.18 g, 0.68 mmol) was treated with neat TFA (5 mL), and after 20 min., the elimination reaction was complete. The excess TFA was evaporated, and the residue extracted into ether (100 mL), washed with water, dried (Na_2SO_4), filtered, and concentrated to a brown oil which was purified by column chromatography (silica gel 60, 1:3 EtOAc-hexane eluant). The pure product **179a** was then redissolved in methanol (10 mL) and then NaOH (0.06 g, 1.4 mmol, 2 equiv.) was added to the solution. After stirring at room temperature for 1 h, the mixture was neutralized (in ice) with 3N HCl. The volatile solvents were evaporated *in vacuo* and the residue re-extracted into EtOAc, washed with water twice, dried (Na_2SO_4), and concentrated afford **195** (0.110 g, 90% overall yield) as pale brown microcrystals with good purity.

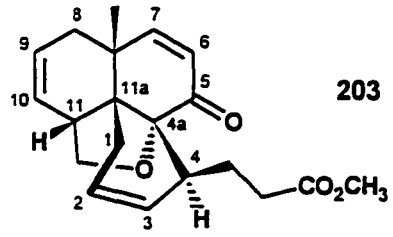


195

mp 90-92°C; **IR (neat film):** 3374, 1634, 1506, 1460, 1315, 1229, 1071 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm):** 3.21-3.26 (H-5, 2H, m), 3.96 (H-2a, broad m), 4.08 (H-2, 1H, d, J = 7.3 Hz), 4.82 (OH, broad), 4.96 (H-2, 1H, dd, J = 8.1, 7.4 Hz), 5.97 (H-3, dm, J = 9.9 Hz), 6.09 (H-4, m), 6.63 (H-6, d, J = 8.1 Hz), 6.72 (H-7, d, J = 8.1 Hz); **^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm):** 28.6 (C-5), 38.7 (C-2a), 78.9 (C-2), 116.0 (C-7), 120.0 (C-6), 124.9 (C-4), 125.1 (C-5a), 128.9 (C-8b), 129.5 (C-3), 138.3 (C-8), 144.2 (C-8a); **LRMS (EI) *m/e*:** 174 (100%, M^+), 145 (15%, M-CHO), 131 (16%), 115 (20%), 103 (5%), 91 (7%); **HRMS (EI):** Calc'd for $C_{11}H_{10}O_2$: 174.0681; Found: 174.0677.

4.76 Synthesis of **203** by Diels-Alder reaction with **68** and methyl (*E*)-4,6-heptadienoate

The naphthofuran **68** (0.21 g, 0.93 mmol) was mixed with freshly distilled methyl (*E*)-4,6-heptadienoate (1.3 g, 9.3 mmol, 10 equiv.) in dry CH_2Cl_2 (5 mL), and then aluminum chloride (0.014 g, 0.1 mmol, ≈10 mol-%) was added to this mixture which was stirred at room temperature for 4 days. The reaction was quenched by the addition of water, and the products extracted into CH_2Cl_2. The organic extract was washed with brine solution, dried (Na_2SO_4), concentrated *in vacuo* and purified by column chromatography (silica gel 60, 1:4 EtOAc-hexane eluant) to produce **179c** (0.051 g, 29% yield), **190c** (0.015 g, 8% yield), and **203** (0.022 g, 7% yield) which was later crystallized in ether to colorless plates.



203

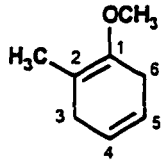
^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.18 (CH_3, 3H, s), 1.61 ($C\underline{H}_2CH_2CO_2CH_3$, 1H, m, J = 12.2, 7.8 Hz), 1.89 ($C\underline{H}_2CH_2CO_2CH_3$, 1H, m, J = 12.7, 7.9 Hz), 1.95 (H-8, 1H, dd, J = 17.3, 6.35 Hz), 2.01 (H-1, 1H, dd, J = 15.4, 7.0 Hz), 2.19 (H-8, 1H, ddd, J = 17.3, 5.3, 2.9 Hz), 2.41 ($CH_2C\underline{H}_2CO_2CH_3$, 2H, t, J = 8.0 Hz), 2.45 (H-1, 1H, dt, J = 15.4, 2.7 Hz), 2.67 (H-11, m, J = 8.4, 3.1 Hz), 2.88 (H-4, ddd, J = 9.6, 6.5, 3.0 Hz), 3.28 (CH_2O-, 1H, dd, J = 11.4, 8.7 Hz), 3.65 (CO_2CH_3, 3H, s), 3.91 (CH_2O-, 1H, t, J = 8.6 Hz), 5.61 (H-10, dt, J = 10.0, 3.0 Hz), 5.81 (H-9, m, J = 10.0 Hz), 5.96 (H-2, ddd, J = 9.6, 6.9, 2.8 Hz),

6.16 (H-3, ddd, J = 9.6, 6.6, 2.9 Hz), 6.20 (H-6, d, J = 10.0 Hz), 6.68 (H-7, d, J = 10.0 Hz); **^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm):** 25.1 ($\underline{C}H_2CH_2CO_2CH_3$), 29.9 (C-1), 30.3 ($CH_3$), 33.4 ($CH_2\underline{C}H_2CO_2CH_3$), 36.5 (C-8), 36.7 (C-11a), 39.6 (C-4), 51.4 (C-7a), 51.5 (CO_2CH_3), 52.1 (C-11), 70.4 (CH_2O), 90.6 (C-4a), 125.6, 126.3 (C-9 and C-10), 126.8 (C-2), 131.1 (C-6), 132.1 (C-3), 160.3 (C-7), 173.9 ($\underline{C}O_2CH_3$), 193.1 (C-5); **LRMS (EI) *m/e*:** 329 (10%, M+H), 244 (17%), 218 (22%), 189 (100%), 146 (34%), 131 (29%), 91 (42%); **HRMS (EI):** Calc'd for $C_{20}H_{25}O_4$ (M+H fragment):329.1753; Found: 329.1735; **Anal.** Calc'd for $C_{20}H_{24}O_4$: C, 73.15%; H, 7.37%. Found: C, 72.90%; H, 7.28%.

4.77 Synthesis of 1-methoxy-2-methyl-1,4-cyclohexadiene (**213**)

The procedure reported by Stork and White[127a] was followed, with a few modifications. A 500 mL two-necked round-bottomed flask was fitted with a pressure-equalized dropping funnel and a dry-ice condenser (-78°C, containing dry ice-acetone slush) with its outlet connected to a scrubber filled with KOH and finally to a gas bubbler. Liquid NH_3 (150 mL) was condensed from the gaseous form into this flask which was cooled in a dry ice-acetone bath (-78°C). Lithium wire (1.36 g, 0.196 mol, 4 equiv.) was cut into small 1 cm-long pieces, rinsed in dry hexane, and added carefully to the liq. NH_3. The blue-black solution was stirred for 20 min. at -78°C prior to adding dropwise a mixture of 2-methylanisole (6 g, 0.049 mol), *t*-BuOH (20 mL, 0.206 mol, 4.2 equiv.) and dry THF (30 mL). Once addition was complete, the mixture was stirred for 1 h while warming up to -50°C, after which time a solution of *t*-BuOH (25 mL) and dry THF (10 mL) was slowly added. When the temperature was near -30°C, 5 mL of water was carefully added which decolorized the solution, and the liquid ammonia was allowed

to evaporate over 4 h (keep fumehood sash low!). The mixture was then diluted with water (50 mL) and ether (200 mL), and the ether layer was separated and washed with large volumes of water until the pH was near 8, then dried (Na_2SO_4), filtered, and concentrated to a gold oil. The product was purified by distillation under reduced pressure (bp = 86°C @ 20 torr), which furnished **213** (5.53 g, 91% yield) as a colorless oil. The ^{1}H-NMR spectra was in agreement with the reported literature values.[127b]



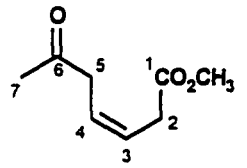
213

bp 86°C at 20 torr; **^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm):** 1.65 (CH_3, narrow m), 2.6-2.9 (H-3 and H-6, 4H total, m), 3.54 (OCH_3, 3H, s), 5.59-5.75 (H-4 and H-5, 2H total, overlapping m).

4.78 Synthesis of methyl (*Z*)-6-oxo-3-heptenoate (**214**) by selective ozonolysis of **213**

Into a 100 mL two-necked round-bottomed flask was added a solution of **213** (1.00g, 8.05 mmol) in dry CH_2Cl_2 (30 mL) which was cooled to -78°C (acetone-dry ice bath). One neck of the flask (B-14 ground glass joint) was fitted with a thermometer adapter which held a Pasteur pipette attached to the Teflon ozone-inlet tubing, while the other neck (B-24 ground glass joint) was connected to an exit bubbler (no rubber septa should be used, only glass gas adapters). The ozone generator was calibrated to deliver ≈2.5 mmol O_3 per minute using the following settings: (i) voltage output = 50%, (ii) oxygen source = compressed air, (iii) air inlet pressure = 10 psi, (iv) flowmeter bead ≈ 5 SCHF. Ozone was bubbled in for about 5-10 min. and was stopped at the first indication

of a blue color (due to excess ozone). The solution was purged with argon for 10 min. (at -78°C), then excess dimethyl sulfide (3 mL, 0.04 mol, 5 equiv.) was added and the mixture was allowed to warm up to room temperature over 3 h. All the volatile solvents were evaporated, and the residue was extracted into EtOAc (100 mL) and washed with water several times (50 mL portions) to remove DMSO by-product. The EtOAc layer was dried (Na_2SO_4), filtered, and concentrated to a viscous oil (crude yield 1.052g, 83% yield). This compound was of good purity and used immediately, as it was susceptible to decomposition upon distillation.



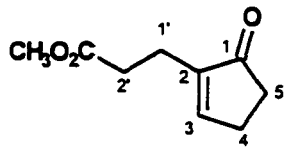
214

^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 2.20 (CH_3CO-, 3H, s), 2.70 and 2.88 (2×CH_2, 4H, dm), 3.78 (CO_2CH_3, 3H, s), 5.58-5.75 (CH=CH, 2H, broad m). No other data was available to confirm the structure assigned for this compound.

4.79 Synthesis of 2-[2'-[(methoxy)carbonyl]ethyl]-2-cyclopenten-1-one (**216**)

The procedure described by Horne[129] was followed to prepare methyl 4-pentynoate **217** in 67% yield by treatment of commercial 4-pentynoic acid with an ethereal solution of diazomethane (for preparation of diazomethane, see section 4.11). Into an oven-dried 250 mL two-necked round-bottomed flask was weighed cobalt octacarbonyl $Co_2(CO)_8$ (10.06 g, 0.0294 mol, 1.1 equiv.) which was dissolved in dry petroleum ether 60-80°C (30 mL) and placed in an ice-bath. Methyl 4-pentynoate **217**

(3.0 g, 0.0268 mol) was added neat from a pressure-equalized dropping funnel, and the evolution of $CO_{(g)}$ could be observed from the bubbler (keep fumehood sash low!) as the reaction was allowed to warm up to room temperature over 2 h. The red-black mixture was then filtered, the filtrate was concentrated *in vacuo* to a dark-red oil and then redissolved with 30 mL dry toluene, placed into the glass insert of a Monel-type pressure reactor, sealed tightly and pressurized up to 150 psi with ethylene. The reaction was stirred and heated to 70°C within the reactor (monitored with a thermocouple insert) for 6 h. After cooling to room temperature, the pressure was slowly released, and the black tar-like mixture was filtered through Celite washing with copious amounts of toluene. The solvent was distilled from this filtrate using a Vigreux fractionating column, and the black residue was redissolved in CH_2Cl_2 (5 mL) and applied to a column packed dry with neutral activated alumina (Brockman, type I, ~150 mesh). The colored cobalt-containing by-products were eluted first with petroleum ether 60-80°C (300 mL), then the product was eluted using a solvent gradient 1:4→1:2 EtOAc-hexane ($R_f \approx 0.3$ on silica developed in 1:2 EtOAc-hexane). The crude dark yellow oil was purified by Kugelrohr distillation (bp ≈ 83-87°C @ 0.25 torr) which furnished **216** (1.4 g, 31% yield) as a colorless oil. The ^{1}H-NMR spectrum was identical to that reported by Horne.[129]



216

^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 2.54 ($CH_2CH_2CO_2CH_3$, 4H total, broad s), 2.42 and 2.59 (H-4 and H-5, 4H total, obscured m), 3.68 (CO_2CH_3, 3H, s), 7.38 (H-3, broad s).

APPENDIX

X-ray Crystallographic Data for Compounds 79a, 79b, 80b, 106, 147, 167, 179c, and 203

Technical Notes 263

Crystal data for compound **79a** 264

Crystal data for compound **79b** 270

Crystal data for compound **80b** 276

Crystal data for compound **106** 282

Crystal data for compound **147** 288

Crystal data for compound **167** 294

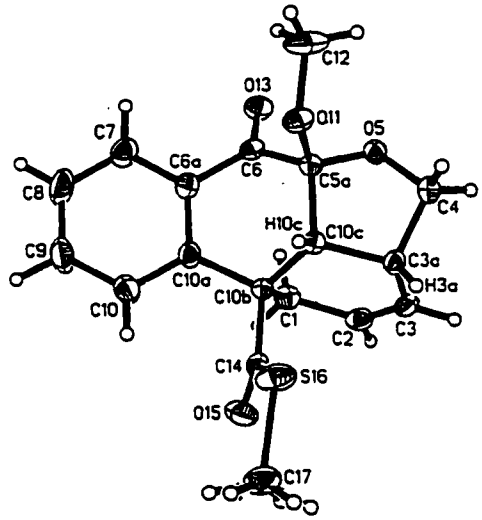
Crystal data for compound **179c** 300

Crystal data for compound **203** 306

Technical Notes

Crystal structures were performed by Dr. Nicholas Taylor of the Department of Chemistry, University of Waterloo, on a LT2 equipped Siemens P4 diffractometer using MoKα radiation (λ = 0.71073 Å). Data were collected by the ω-scan method with a scan width of 1.2° using variable scan speeds, the scan rate being determined by a fast prescan. Background measurements were made at the beginning and end of each scan for a total of half the scan time. Data were corrected for Lorentz and polarization effects and by face-indexed analytical absorption methods. The structures were solved by direct methods and refined by full-matrix least-squares methods using Siemens SHELXTL IRIS software. The function minimized in the least-squares process was $w(F_o-F_c)^2$. Hydrogen atoms were easily found by difference Fourier syntheses and included in the refinements with refined isotropic thermal parameters. In the final cycles of refinement, weighting schemes of the form $w^{-1} = \sigma^2(F)$ as well as extinction corrections were employed. Final difference maps revealed no anomalous electron density peaks or holes. Supplemental data includes a complete listing of atomic coordinates, bond lengths and angles and anisotropic thermal parameters.

Crystal Data for Compound 79a



Crystal Data

Empirical Formula	$C_{18}H_{18}O_4S$
Color; Habit	Colourless polyhedron
Crystal Size (mm)	0.42{110}x0.70{102}
Crystal System	Orthorhombic
Space Group	Pccn
Unit Cell Dimensions	a = 20.1677(14) Å
	b = 9.9506(8) Å
	c = 15.7650(11) Å
Volume	3163.7(6) $Å^3$
Z	8
Formula Weight	330.4
Density(calc.)	1.387 g/cm^3
Absorption Coefficient	2.23 cm^{-1}
F(000)	1392

Data Collection

Diffractometer Used	Siemens P4
Radiation	MoKα (λ = 0.71073 Å)
Temperature (K)	160
Monochromator	Highly oriented graphite crystal
2θ Range	4.0 to 60.0°
Scan Type	ω
Scan Speed	Variable; 3.00 to 30.00°/min. in ω
Scan Range (ω)	1.20°
Background Measurement	Stationary crystal and stationary counter at beginning and end of scan, each for 25.0% of total scan time
Standard Reflections	3 measured every 100 reflections
Index Ranges	$0 \leq h \leq 28$, $0 \leq k \leq 14$ $0 \leq \ell \leq 22$
Reflections Collected	4614
Independent Reflections	4614
Observed Reflections	3233 ($F > 6.0\sigma(F)$)
Absorption Correction	Face-indexed numerical
Min./Max. Transmission	0.8692 / 0.9244

Solution and Refinement

System Used	Siemens SHELXTL IRIS
Solution	Direct Methods
Refinement Method	Full-Matrix Least-Squares
Quantity Minimized	$\sum w(F_o - F_c)^2$
Extinction Correction	χ = 0.00046(4), where $F^* = F \left[1 + 0.002\chi F^2/\sin(2\theta) \right]^{-1/4}$
Hydrogen Atoms	Refined isotropic U, riding Methyl groups
Weighting Scheme	$w^{-1} = \sigma^2(F)$
Number of Parameters Refined	266
Final R Indices (obs. data)	R = 3.51 %, wR = 3.63 %
(R Indices (all data)	R = 4.92 %, wR = 3.68 %)
Goodness-of-Fit	2.66
Largest and Mean Δ/σ	0.002, 0.000
Data-to-Parameter Ratio	12.2:1
Largest Difference Peak	0.31 $e\text{Å}^{-3}$
Largest Difference Hole	-0.33 $e\text{Å}^{-3}$

Table 1. Atomic coordinates ($x10^4$) and equivalent isotropic displacement coefficients ($Å^2 x10^4$)

	x	y	z	U(eq)
C(1)	3585.4(8)	2913(2)	1709(1)	238(5)
C(2)	3997.7(8)	3452(2)	2423(1)	258(5)
C(3)	4466.4(9)	2744(2)	2796(1)	254(5)
C(3a)	4627.9(8)	1306(2)	2590(1)	211(5)
C(4)	4392.7(8)	364(2)	3297(1)	241(5)
O(5)	3708.9(5)	88(1)	3080.4(7)	231(3)
C(5a)	3709.0(7)	-155(2)	2210(1)	181(4)
C(6)	3012.7(8)	3(2)	1847(1)	198(4)
C(6a)	3000.7(8)	288(2)	926(1)	220(5)
C(7)	2511.0(9)	-279(2)	417(1)	305(5)
C(8)	2497(1)	-6(2)	-442(1)	403(6)
C(9)	2965(1)	855(3)	-782(1)	434(7)
C(10)	3449(1)	1432(2)	-276(1)	351(6)
C(10a)	3480.5(8)	1154(2)	585(1)	221(5)
C(10b)	3962.1(7)	1821(2)	1205(1)	191(4)
C(10c)	4246.5(7)	749(2)	1811.6(9)	172(4)
O(11)	3904.9(5)	-1504(1)	2012.5(8)	246(3)
C(12)	3536.5(9)	-2528(2)	2445(2)	425(7)
O(13)	2519.0(6)	-184(1)	2269.9(7)	267(3)
C(14)	4519.2(8)	2547(2)	708(1)	242(5)
O(15)	4447.5(7)	3669(1)	430.6(8)	376(4)
S(16)	5259.2(2)	1628.7(5)	549.2(3)	365(1)
C(17)	5743(1)	2821(2)	-48(1)	425(7)

* Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor

Table 2. Bond lengths (Å)

C(1)-C(2)	1.498(2)	C(1)-C(10b)	1.546(2)
C(2)-C(3)	1.318(2)	C(3)-C(3a)	1.502(2)
C(3a)-C(4)	1.532(2)	C(3a)-C(10c)	1.551(2)
C(4)-O(5)	1.447(2)	O(5)-C(5a)	1.393(2)
C(5a)-C(6)	1.525(2)	C(5a)-C(10c)	1.542(2)
C(5a)-O(11)	1.434(2)	C(6)-C(6a)	1.480(2)
C(6)-O(13)	1.212(2)	C(6a)-C(7)	1.392(2)
C(6a)-C(10a)	1.403(2)	C(7)-C(8)	1.381(3)
C(8)-C(9)	1.384(3)	C(9)-C(10)	1.385(3)
C(10)-C(10a)	1.387(2)	C(10a)-C(10b)	1.530(2)
C(10b)-C(10c)	1.543(2)	C(10b)-C(14)	1.549(2)
O(11)-C(12)	1.434(2)	C(14)-O(15)	1.208(2)
C(14)-S(16)	1.768(2)	S(16)-C(17)	1.801(2)

Table 3. Bond angles (°)

C(2)-C(1)-C(10b)	111.4(1)	C(1)-C(2)-C(3)	122.8(2)
C(2)-C(3)-C(3a)	124.6(2)	C(3)-C(3a)-C(4)	111.0(1)
C(3)-C(3a)-C(10c)	113.8(1)	C(4)-C(3a)-C(10c)	101.7(1)
C(3a)-C(4)-O(5)	103.9(1)	C(4)-O(5)-C(5a)	105.4(1)
O(5)-C(5a)-C(6)	110.6(1)	O(5)-C(5a)-C(10c)	107.5(1)
C(6)-C(5a)-C(10c)	115.7(1)	O(5)-C(5a)-O(11)	112.1(1)
C(6)-C(5a)-O(11)	105.6(1)	C(10c)-C(5a)-O(11)	105.3(1)
C(5a)-C(6)-C(6a)	113.8(1)	C(5a)-C(6)-O(13)	122.3(1)
C(6a)-C(6)-O(13)	123.7(1)	C(6)-C(6a)-C(7)	120.0(1)
C(6)-C(6a)-C(10a)	118.9(1)	C(7)-C(6a)-C(10a)	121.2(2)
C(6a)-C(7)-C(8)	120.0(2)	C(7)-C(8)-C(9)	119.2(2)
C(8)-C(9)-C(10)	121.0(2)	C(9)-C(10)-C(10a)	120.9(2)
C(6a)-C(10a)-C(10)	117.8(2)	C(6a)-C(10a)-C(10b)	117.3(1)
C(10)-C(10a)-C(10b)	124.6(2)	C(1)-C(10b)-C(10a)	108.8(1)
C(1)-C(10b)-C(10c)	110.5(1)	C(10a)-C(10b)-C(10c)	109.4(1)
C(1)-C(10b)-C(14)	106.8(1)	C(10a)-C(10b)-C(14)	109.8(1)
C(10c)-C(10b)-C(14)	111.5(1)	C(3a)-C(10c)-C(5a)	103.6(1)
C(3a)-C(10c)-C(10b)	115.3(1)	C(5a)-C(10c)-C(10b)	113.2(1)
C(5a)-O(11)-C(12)	114.8(1)	C(10b)-C(14)-O(15)	121.8(1)
C(10b)-C(14)-S(16)	116.3(1)	O(15)-C(14)-S(16)	121.8(1)
C(14)-S(16)-C(17)	101.0(1)		

Table 4. Anisotropic displacement coefficients ($Å^2 \times 10^4$)

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	221(8)	208(8)	285(9)	27(7)	0(7)	19(7)
C(2)	311(9)	180(8)	282(9)	-43(7)	57(7)	-36(7)
C(3)	286(9)	261(10)	214(8)	-107(7)	-3(7)	-33(7)
C(3a)	168(8)	266(9)	198(8)	-19(6)	-20(6)	-4(7)
C(4)	244(8)	267(9)	213(8)	-12(7)	-44(7)	8(7)
O(5)	224(6)	289(6)	180(6)	-35(5)	7(5)	21(5)
C(5a)	184(7)	172(7)	188(7)	5(6)	12(6)	-3(6)
C(6)	185(7)	160(7)	249(8)	-8(6)	11(6)	-12(7)
C(6a)	177(7)	251(9)	233(8)	10(7)	-3(6)	-18(7)
C(7)	204(8)	395(10)	316(9)	-42(8)	-27(8)	-29(9)
C(8)	294(9)	607(14)	308(10)	-95(10)	-94(9)	-79(10)
C(9)	373(11)	721(16)	206(9)	-113(11)	-65(8)	15(10)
C(10)	312(10)	513(13)	228(9)	-113(9)	-19(7)	46(9)
C(10a)	190(7)	274(8)	199(8)	-4(6)	-18(6)	0(7)
C(10b)	186(7)	203(8)	184(8)	-27(6)	3(6)	17(6)
C(10c)	152(7)	191(7)	174(7)	5(6)	10(6)	-10(6)
O(11)	222(6)	166(6)	350(7)	-2(5)	10(5)	-7(5)
C(12)	295(10)	205(9)	774(17)	-34(8)	48(10)	120(10)
O(13)	182(5)	287(6)	331(6)	-9(5)	51(5)	42(5)
C(14)	246(8)	299(9)	179(7)	-82(7)	-8(6)	-21(7)
O(15)	399(8)	356(8)	373(8)	-73(6)	6(6)	160(6)
S(16)	288(2)	336(3)	470(3)	-74(2)	177(2)	-48(2)
C(17)	401(12)	515(14)	361(11)	-205(11)	179(10)	-83(11)

The anisotropic displacement factor exponent takes the form:

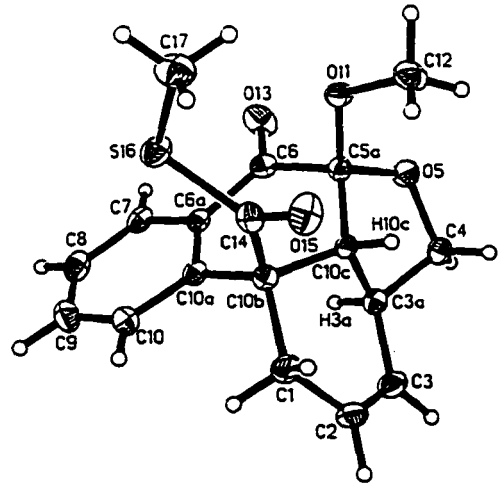
$-2\pi^2(h^2a^{*2}U_{11} + \ldots + 2klb^*c^*U_{23})$

Table 5. H-Atom coordinates ($x10^4$) and isotropic displacement coefficients ($Å^2 x10^3$)

	x	y	z	U
H(1x)	3428(9)	3587(17)	1320(11)	28(5)
H(1y)	3137(9)	2564(18)	1941(11)	31(5)
H(2)	3888(9)	4327(19)	2612(12)	41(6)
H(3)	4717(9)	3112(18)	3258(12)	35(5)
H(3a)	5095(8)	1208(17)	2519(11)	24(5)
H(4x)	4657(8)	-477(17)	3294(11)	24(5)
H(4y)	4384(7)	753(16)	3863(10)	17(4)
H(7)	2196(8)	-873(18)	671(11)	26(5)
H(8)	2182(9)	-431(19)	-770(12)	37(6)
H(9)	2934(11)	1030(22)	-1399(14)	66(7)
H(10)	3721(9)	2002(18)	-498(12)	30(5)
H(10c)	4514(7)	159(16)	1470(10)	16(4)
H(12x)	3663	-3389	2222	56(7)
H(12y)	3068	-2406	2367	90(9)
H(12z)	3632	-2505	3041	94(10)
H(17u)*	6077	3220	304	38(11)
H(17v)*	5451	3496	-272	81(19)
H(17w)*	5940	2364	-521	60(14)
H(17x)*	5642	2769	-642	69(16)
H(17y)*	6203	2641	55	83(18)
H(17z)*	5650	3702	171	47(13)

* Occupancy 0.5

Crystal Data for Compound 79b



Crystal Data

Empirical Formula	$C_{18}H_{18}O_4S$
Color; Habit	Colourless prism
Crystal Size (mm)	0.44{101}x0.30{011}x0.52{11$\bar{1}$}
Crystal System	Triclinic
Space Group	P$\bar{1}$
Unit Cell Dimensions	a = 8.585(1) Å
	b = 8.900(1) Å
	c = 10.279(1) Å
	α = 83.797(8)°
	β = 78.662(8)°
	γ = 83.276(8)°
Volume	761.9(1) Å^3
Z	2
Formula Weight	330.4
Density(calc.)	1.440 g/cm^3
Absorption Coefficient	2.31 cm^{-1}
F(000)	348

Data Collection

Diffractometer Used	Siemens P4
Radiation	MoKα (λ = 0.71073 Å)
Temperature (K)	160
Monochromator	Highly oriented graphite crystal
2θ Range	4.0 to 56.0°
Scan Type	ω
Scan Speed	Variable; 3.00 to 30.00°/min. in ω
Scan Range (ω)	1.20°
Background Measurement	Stationary crystal and stationary counter at beginning and end of scan, each for 25.0% of total scan time
Standard Reflections	3 measured every 100 reflections
Index Ranges	$0 \leq h \leq 11$, $-11 \leq k \leq 11$ $-13 \leq \ell \leq 13$
Reflections Collected	3915
Independent Reflections	3674 (R_{int} = 1.06%)
Observed Reflections	3241 ($F > 6.0\sigma(F)$)
Absorption Correction	Face-indexed numerical
Min./Max. Transmission	0.9055 / 0.9399

Solution and Refinement

System Used	Siemens SHELXTL IRIS
Solution	Direct Methods
Refinement Method	Full-Matrix Least-Squares
Quantity Minimized	$\sum w(F_o - F_c)^2$
Extinction Correction	χ = 0.0061(5), where $F^* = F \left[1 + 0.002\chi F^2/\sin(2\theta) \right]^{-1/4}$
Hydrogen Atoms	Refined, isotropic U
Weighting Scheme	$w^{-1} = \sigma^2(F)$
Number of Parameters Refined	281
Final R Indices (obs. data)	R = 3.08 %, wR = 3.73 %
(R Indices (all data)	R = 3.43 %, wR = 3.75 %)
Goodness-of-Fit	3.61
Largest and Mean Δ/σ	0.001, 0.000
Data-to-Parameter Ratio	11.5:1
Largest Difference Peak	0.34 $eÅ^{-3}$
Largest Difference Hole	-0.25 $eÅ^{-3}$

Table 1. Atomic coordinates ($x10^4$) and equivalent isotropic displacement coefficients ($Å^2 x10^4$)

	x	y	z	U(eq)
C(1)	5896(2)	1503(2)	3134(2)	220(4)
C(2)	7225(2)	2350(2)	2308(1)	243(4)
C(3)	7063(2)	3728(2)	1691(1)	231(4)
C(3a)	5429(2)	4534(1)	1739(1)	174(4)
C(4)	5108(2)	6246(2)	1825(1)	206(4)
O(5)	3394(1)	6481(1)	2294(1)	224(3)
C(5a)	2802(2)	5063(1)	2872(1)	166(4)
C(6)	1863(2)	4506(2)	1916(1)	182(4)
C(6a)	2247(1)	2914(1)	1539(1)	161(4)
C(7)	1484(2)	2487(2)	569(1)	201(4)
C(8)	1732(2)	1015(2)	206(1)	243(4)
C(9)	2714(2)	-58(2)	826(1)	263(4)
C(10)	3495(2)	355(2)	1773(1)	223(4)
C(10a)	3306(2)	1846(1)	2134(1)	159(4)
C(10b)	4165(2)	2297(1)	3180(1)	157(3)
C(10c)	4303(1)	4015(1)	3007(1)	148(3)
O(11)	1655(1)	5276(1)	4018.4(9)	196(3)
C(12)	2178(2)	5848(2)	5096(2)	273(5)
O(13)	833(1)	5362(1)	1492(1)	299(3)
C(14)	3228(2)	1976(1)	4620(1)	186(4)
O(15)	3773(1)	2217(1)	5568(1)	282(3)
S(16)	1343.1(4)	1320.2(4)	4780.9(3)	235(1)
C(17)	621(2)	1491(2)	6533(2)	294(5)

* Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor

Table 2. Bond lengths (Å)

C(1)-C(2)	1.507(2)	C(1)-C(10b)	1.563(2)
C(2)-C(3)	1.324(2)	C(3)-C(3a)	1.493(2)
C(3a)-C(4)	1.526(2)	C(3a)-C(10c)	1.524(2)
C(4)-O(5)	1.453(2)	O(5)-C(5a)	1.440(2)
C(5a)-C(6)	1.540(2)	C(5a)-C(10c)	1.520(2)
C(5a)-O(11)	1.394(1)	C(6)-C(6a)	1.492(2)
C(6)-O(13)	1.214(2)	C(6a)-C(7)	1.402(2)
C(6a)-C(10a)	1.412(2)	C(7)-C(8)	1.381(2)
C(8)-C(9)	1.386(2)	C(9)-C(10)	1.387(2)
C(10)-C(10a)	1.399(2)	C(10a)-C(10b)	1.528(2)
C(10b)-C(10c)	1.535(2)	C(10b)-C(14)	1.554(2)
O(11)-C(12)	1.435(2)	C(14)-O(15)	1.210(2)
C(14)-S(16)	1.755(1)	S(16)-C(17)	1.802(2)

Table 3. Bond angles (°)

C(2)-C(1)-C(10b)	116.2(1)	C(1)-C(2)-C(3)	126.0(1)
C(2)-C(3)-C(3a)	119.1(1)	C(3)-C(3a)-C(4)	121.7(1)
C(3)-C(3a)-C(10c)	110.9(1)	C(4)-C(3a)-C(10c)	98.8(1)
C(3a)-C(4)-O(5)	103.7(1)	C(4)-O(5)-C(5a)	109.7(1)
O(5)-C(5a)-C(6)	108.6(1)	O(5)-C(5a)-C(10c)	103.9(1)
C(6)-C(5a)-C(10c)	112.1(1)	O(5)-C(5a)-O(11)	110.8(1)
C(6)-C(5a)-O(11)	103.5(1)	C(10c)-C(5a)-O(11)	117.9(1)
C(5a)-C(6)-C(6a)	118.6(1)	C(5a)-C(6)-O(13)	119.7(1)
C(6a)-C(6)-O(13)	121.7(1)	C(6)-C(6a)-C(7)	117.2(1)
C(6)-C(6a)-C(10a)	122.7(1)	C(7)-C(6a)-C(10a)	120.1(1)
C(6a)-C(7)-C(8)	120.5(1)	C(7)-C(8)-C(9)	119.8(1)
C(8)-C(9)-C(10)	120.2(1)	C(9)-C(10)-C(10a)	121.4(1)
C(6a)-C(10a)-C(10)	117.9(1)	C(6a)-C(10a)-C(10b)	120.8(1)
C(10)-C(10a)-C(10b)	121.2(1)	C(1)-C(10b)-C(10a)	114.6(1)
C(1)-C(10b)-C(10c)	106.6(1)	C(10a)-C(10b)-C(10c)	110.4(1)
C(1)-C(10b)-C(14)	107.2(1)	C(10a)-C(10b)-C(14)	112.2(1)
C(10c)-C(10b)-C(14)	105.3(1)	C(3a)-C(10c)-C(5a)	100.8(1)
C(3a)-C(10c)-C(10b)	113.8(1)	C(5a)-C(10c)-C(10b)	117.6(1)
C(5a)-O(11)-C(12)	116.4(1)	C(10b)-C(14)-O(15)	120.6(1)
C(10b)-C(14)-S(16)	116.7(1)	O(15)-C(14)-S(16)	122.7(1)
C(14)-S(16)-C(17)	99.5(1)		

Table 4. Anisotropic displacement coefficients ($Å^2 \times 10^4$)

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	188(6)	191(6)	286(7)	16(5)	-91(6)	8(5)
C(2)	165(7)	271(7)	289(7)	30(5)	-51(6)	-53(6)
C(3)	168(6)	283(7)	233(7)	-35(6)	-3(5)	-31(6)
C(3a)	178(6)	191(6)	156(6)	-39(5)	-31(5)	-2(5)
C(4)	209(7)	191(6)	217(7)	-54(5)	-28(5)	6(5)
O(5)	212(5)	146(4)	300(5)	-21(4)	-33(4)	26(4)
C(5a)	175(6)	147(6)	177(6)	-15(5)	-43(5)	-1(5)
C(6)	166(6)	213(6)	164(6)	-7(5)	-38(5)	3(5)
C(6a)	145(6)	189(6)	146(6)	-37(5)	-16(5)	-3(5)
C(7)	164(6)	268(7)	179(6)	-52(5)	-44(5)	4(5)
C(8)	249(7)	320(8)	185(6)	-100(6)	-50(5)	-44(6)
C(9)	329(8)	219(7)	253(7)	-61(6)	-40(6)	-65(6)
C(10)	253(7)	191(6)	225(7)	-16(5)	-48(5)	-17(5)
C(10a)	149(6)	188(6)	136(6)	-37(5)	-11(5)	0(5)
C(10b)	156(6)	150(6)	165(6)	-12(5)	-46(5)	8(5)
C(10c)	144(6)	157(6)	149(6)	-19(5)	-45(5)	-8(5)
O(11)	166(5)	245(5)	180(5)	6(4)	-35(4)	-54(4)
C(12)	266(7)	340(8)	231(7)	22(6)	-74(6)	-117(6)
O(13)	324(6)	279(5)	325(6)	96(5)	-194(5)	-56(4)
C(14)	224(6)	149(6)	187(6)	-20(5)	-63(5)	20(5)
O(15)	344(6)	348(6)	186(5)	-108(5)	-102(4)	16(4)
S(16)	214(2)	290(2)	198(2)	-76(1)	-8(1)	-7(1)
C(17)	319(8)	313(8)	208(7)	-14(7)	27(6)	7(6)

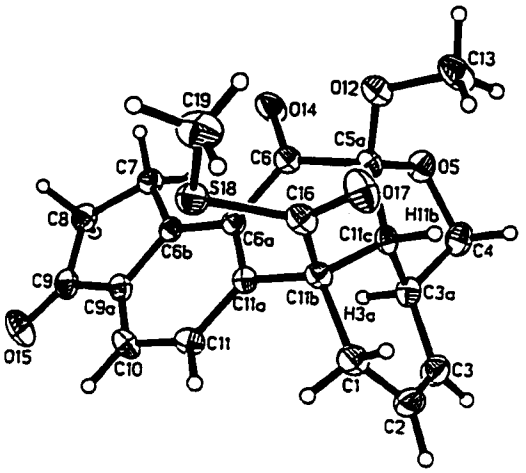
The anisotropic displacement factor exponent takes the form:

$-2\pi^2(h^2a^{*2}U_{11} + \ldots + 2klb^*c^*U_{23})$

Table 5. H-Atom coordinates ($x10^4$) and isotropic displacement coefficients ($Å^2 x10^3$)

	x	y	z	U
H(1x)	6008(20)	470(19)	2825(16)	33(5)
H(1y)	6108(20)	1323(18)	4041(17)	32(5)
H(2)	8295(22)	1839(20)	2270(17)	39(5)
H(3)	7995(22)	4205(19)	1198(17)	36(5)
H(3a)	4987(19)	4315(17)	986(15)	23(4)
H(4x)	5665(17)	6598(16)	2456(14)	16(4)
H(4y)	5350(18)	6860(17)	961(15)	24(4)
H(7)	846(20)	3198(18)	147(16)	29(4)
H(8)	1262(20)	728(18)	-475(17)	31(4)
H(9)	2854(21)	-1095(20)	615(17)	36(5)
H(10)	4156(20)	-393(18)	2209(16)	30(4)
H(10c)	4695(17)	4292(16)	3763(15)	19(4)
H(12x)	1211(22)	6231(20)	5705(18)	38(5)
H(12y)	2779(22)	6724(20)	4746(18)	41(5)
H(12z)	2896(23)	5064(21)	5543(19)	46(5)
H(17x)	465(27)	2539(27)	6738(21)	68(7)
H(17y)	-310(29)	1019(26)	6808(23)	70(7)
H(17z)	1337(28)	993(25)	7048(22)	67(7)

Crystal Data for Compound 80b



Crystal Data

Empirical Formula	$C_{21}H_{20}O_5S$
Color; Habit	Colourless prism
Crystal Size (mm)	0.42{10$\bar{1}$}x0.24{010}x0.26{011}
Crystal System	Monoclinic
Space Group	$P2_1/n$
Unit Cell Dimensions	$\underline{a}$ = 8.176(1) Å
	$\underline{b}$ = 15.265(2) Å
	$\underline{c}$ = 14.020(2) Å
	β = 92.918(7)°
Volume	1747.4(4) Å^3
Z	4
Formula Weight	384.4
Density(calc.)	1.461 g/cm^3
Absorption Coefficient	2.17 cm^{-1}
F(000)	808

Data Collection

Diffractometer Used	Siemens P4
Radiation	MoKα (λ = 0.71073 Å)
Temperature (K)	160
Monochromator	Highly oriented graphite crystal
2θ Range	4.0 to 52.0°
Scan Type	ω
Scan Speed	Variable; 3.00 to 30.00°/min. in ω
Scan Range (ω)	1.20°
Background Measurement	Stationary crystal and stationary counter at beginning and end of scan, each for 25.0% of total scan time
Standard Reflections	3 measured every 100 reflections
Index Ranges	$0 \leq h \leq 10$, $0 \leq k \leq 18$ $-17 \leq \ell \leq 17$
Reflections Collected	3685
Independent Reflections	3438 (R_{int} = 1.10%)
Observed Reflections	2595 ($F > 6.0\sigma(F)$)
Absorption Correction	Face-indexed numerical
Min./Max. Transmission	0.9431 / 0.9573

Solution and Refinement

System Used	Siemens SHELXTL IRIS
Solution	Direct Methods
Refinement Method	Full-Matrix Least-Squares
Quantity Minimized	$\Sigma w(F_o - F_c)^2$
Extinction Correction	χ = 0.00026(4), where $F^* = F [1 + 0.002\chi F^2/\sin(2\theta)]^{-1/4}$
Hydrogen Atoms	Refined isotropic U
Weighting Scheme	$w^{-1} = \sigma^2(F)$
Number of Parameters Refined	325
Final R Indices (obs. data)	R = 3.04 %, wR = 3.10 %
(R Indices (all data)	R = 4.19 %, wR = 3.17 %)
Goodness-of-Fit	2.11
Largest and Mean Δ/σ	0.003, 0.000
Data-to-Parameter Ratio	8.0:1
Largest Difference Peak	0.26 $e\text{Å}^{-3}$
Largest Difference Hole	-0.22 $e\text{Å}^{-3}$

Table 1. Atomic coordinates ($x10^4$) and equivalent isotropic displacement coefficients ($Å^2 x10^4$)

	x	y	z	U(eq)
C(1)	2489(3)	1936(1)	3455(1)	254(6)
C(2)	1026(3)	1555(1)	3913(1)	295(7)
C(3)	628(3)	717(1)	3914(1)	293(7)
C(3a)	1619(2)	72(1)	3393(1)	230(6)
C(4)	1943(3)	-852(1)	3747(2)	280(7)
O(5)	3339(2)	-1127.1(8)	3222.6(9)	261(4)
C(5a)	4175(2)	-375(1)	2874(1)	201(6)
C(6)	3941(2)	-369(1)	1780(1)	208(6)
C(6a)	3076(2)	386(1)	1312(1)	176(5)
C(6b)	2495(2)	311(1)	358(1)	178(5)
C(7)	2614(2)	-458(1)	-310(1)	219(6)
C(8)	1673(2)	-169(1)	-1232(1)	238(6)
C(9)	1071(2)	749(1)	-1061(1)	235(6)
C(9a)	1662(2)	1003(1)	-84(1)	196(5)
C(10)	1423(2)	1786(1)	386(1)	234(6)
C(11)	1985(2)	1864(1)	1325(1)	213(6)
C(11a)	2805(2)	1182(1)	1803(1)	178(5)
C(11b)	3450(2)	1283(1)	2839(1)	186(5)
C(11c)	3372(2)	395(1)	3337(1)	188(5)
O(12)	5868(2)	-477.6(8)	3032.0(9)	273(4)
C(13)	6424(3)	-573(2)	4010(2)	352(8)
O(14)	4447(2)	-978.1(9)	1330.0(9)	337(5)
O(15)	223(2)	1189.9(9)	-1608.5(9)	361(5)
C(16)	5241(2)	1611(1)	2908(1)	215(6)
O(17)	6066(2)	1560.5(9)	3644.9(9)	326(5)
S(18)	5950.2(6)	2086.8(3)	1868.4(3)	257(2)
C(19)	7957(3)	2418(2)	2310(2)	378(8)

* Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor

Table 2. Bond lengths (Å)

C(1)-C(2)	1.503(3)	C(1)-C(11b)	1.558(3)
C(2)-C(3)	1.319(3)	C(3)-C(3a)	1.490(3)
C(3a)-C(4)	1.515(3)	C(3a)-C(11c)	1.522(3)
C(4)-O(5)	1.451(3)	O(5)-C(5a)	1.435(2)
C(5a)-C(6)	1.536(2)	C(5a)-C(11c)	1.509(3)
C(5a)-O(12)	1.400(2)	C(6)-C(6a)	1.487(2)
C(6)-O(14)	1.208(2)	C(6a)-C(6b)	1.401(2)
C(6a)-C(11a)	1.419(2)	C(6b)-C(7)	1.508(3)
C(6b)-C(9a)	1.386(2)	C(7)-C(8)	1.534(3)
C(8)-C(9)	1.510(3)	C(9)-C(9a)	1.481(2)
C(9)-O(15)	1.212(2)	C(9a)-C(10)	1.384(3)
C(10)-C(11)	1.376(3)	C(11)-C(11a)	1.393(2)
C(11a)-C(11b)	1.528(2)	C(11b)-C(11c)	1.527(2)
C(11b)-C(16)	1.546(3)	O(12)-C(13)	1.429(3)
C(16)-O(17)	1.207(2)	C(16)-S(18)	1.753(2)
S(18)-C(19)	1.796(2)		

Table 3. Bond angles (°)

C(2)-C(1)-C(11b)	115.1(2)	C(1)-C(2)-C(3)	125.3(2)
C(2)-C(3)-C(3a)	120.0(2)	C(3)-C(3a)-C(4)	123.1(2)
C(3)-C(3a)-C(11c)	110.4(2)	C(4)-C(3a)-C(11c)	99.8(1)
C(3a)-C(4)-O(5)	103.4(2)	C(4)-O(5)-C(5a)	110.0(1)
O(5)-C(5a)-C(6)	107.9(1)	O(5)-C(5a)-C(11c)	104.6(1)
C(6)-C(5a)-C(11c)	113.0(1)	O(5)-C(5a)-O(12)	109.9(1)
C(6)-C(5a)-O(12)	103.3(1)	C(11c)-C(5a)-O(12)	117.9(1)
C(5a)-C(6)-C(6a)	118.5(1)	C(5a)-C(6)-O(14)	119.2(2)
C(6a)-C(6)-O(14)	122.3(2)	C(6)-C(6a)-C(6b)	119.2(2)
C(6)-C(6a)-C(11a)	122.1(1)	C(6b)-C(6a)-C(11a)	118.7(2)
C(6a)-C(6b)-C(7)	128.9(2)	C(6a)-C(6b)-C(9a)	119.9(2)
C(7)-C(6b)-C(9a)	111.2(1)	C(6b)-C(7)-C(8)	104.7(2)
C(7)-C(8)-C(9)	106.7(2)	C(8)-C(9)-C(9a)	107.2(1)
C(8)-C(9)-O(15)	126.6(2)	C(9a)-C(9)-O(15)	126.2(2)
C(6b)-C(9a)-C(9)	110.1(2)	C(6b)-C(9a)-C(10)	121.6(2)
C(9)-C(9a)-C(10)	128.3(2)	C(9a)-C(10)-C(11)	118.8(2)
C(10)-C(11)-C(11a)	121.6(2)	C(6a)-C(11a)-C(11)	119.3(2)
C(6a)-C(11a)-C(11b)	119.6(1)	C(11)-C(11a)-C(11b)	121.1(2)
C(1)-C(11b)-C(11a)	115.6(1)	C(1)-C(11b)-C(11c)	106.3(1)
C(11a)-C(11b)-C(11c)	108.9(1)	C(1)-C(11b)-C(16)	105.1(1)
C(11a)-C(11b)-C(16)	111.9(1)	C(11c)-C(11b)-C(16)	108.7(1)
C(3a)-C(11c)-C(5a)	101.6(1)	C(3a)-C(11c)-C(11b)	111.9(1)
C(5a)-C(11c)-C(11b)	117.7(2)	C(5a)-O(12)-C(13)	115.3(2)
C(11b)-C(16)-O(17)	121.2(2)	C(11b)-C(16)-S(18)	115.8(1)
O(17)-C(16)-S(18)	123.0(1)	C(16)-S(18)-C(19)	99.5(1)

Table 4. H-Atom coordinates ($x10^4$) and isotropic displacement coefficients ($Å^2 x10^3$)

	x	y	z	U
H(1x)	3220(24)	2136(13)	3971(14)	34(6)
H(1y)	2188(23)	2450(13)	3096(13)	26(5)
H(2)	345(25)	1989(13)	4228(14)	31(5)
H(3)	-326(25)	534(13)	4205(14)	35(6)
H(3a)	1123(20)	2(11)	2732(11)	13(4)
H(4x)	1034(26)	-1244(13)	3598(14)	35(6)
H(4y)	2283(23)	-892(13)	4411(14)	32(6)
H(7x)	2141(22)	-991(12)	-32(12)	20(5)
H(7y)	3737(22)	-600(11)	-411(12)	19(5)
H(8x)	752(24)	-535(12)	-1400(13)	27(5)
H(8y)	2380(25)	-163(13)	-1767(14)	36(6)
H(10)	849(22)	2266(11)	61(13)	22(5)
H(11)	1789(23)	2394(13)	1627(13)	28(5)
H(11c)	3816(20)	453(10)	3971(12)	13(4)
H(13x)	5711(22)	-938(12)	4353(12)	15(5)
H(13y)	6399(25)	-23(15)	4335(14)	37(6)
H(13z)	7515(29)	-832(15)	3993(15)	48(7)
H(19x)	8495(31)	1919(17)	2580(17)	64(8)
H(19y)	7863(32)	2882(17)	2723(18)	68(9)
H(19z)	8529(36)	2606(18)	1711(22)	87(10)

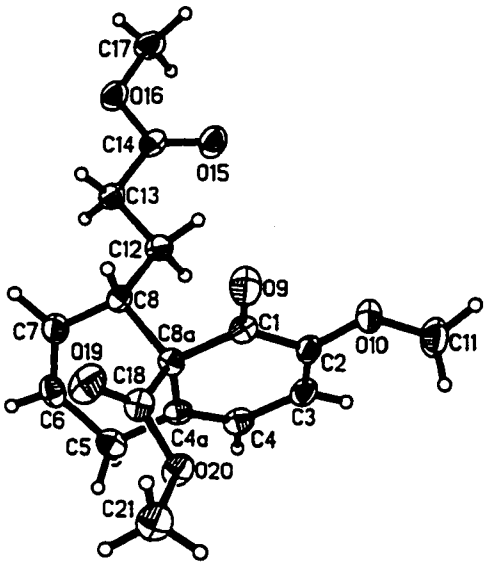
Table 5. Anisotropic displacement coefficients ($Å^2 x 10^4$)

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	340(12)	197(11)	223(11)	38(9)	-23(9)	-63(8)
C(2)	320(12)	337(12)	227(11)	89(10)	15(9)	-58(9)
C(3)	243(11)	389(13)	250(11)	10(10)	50(9)	12(9)
C(3a)	236(10)	260(10)	194(10)	-40(8)	5(8)	9(8)
C(4)	321(12)	276(11)	248(11)	-68(9)	60(9)	6(9)
O(5)	339(8)	166(7)	283(7)	-33(6)	67(6)	24(6)
C(5a)	219(10)	167(9)	215(10)	-10(8)	-15(8)	32(7)
C(6)	221(10)	191(10)	211(10)	-3(8)	2(8)	-12(8)
C(6a)	166(9)	181(9)	181(9)	-8(8)	13(7)	8(7)
C(6b)	166(9)	183(9)	189(9)	-29(7)	35(7)	13(7)
C(7)	240(11)	221(10)	196(10)	5(9)	13(8)	-34(8)
C(8)	237(11)	292(11)	185(10)	-30(9)	1(8)	-26(8)
C(9)	237(10)	255(10)	215(10)	-64(8)	13(8)	39(8)
C(9a)	199(9)	207(10)	182(9)	-36(8)	1(7)	31(8)
C(10)	259(10)	179(10)	259(10)	-1(8)	-41(8)	54(8)
C(11)	237(10)	137(9)	263(10)	-9(8)	1(8)	-23(8)
C(11a)	177(9)	166(9)	190(9)	-36(8)	5(7)	1(7)
C(11b)	213(9)	145(9)	198(9)	-3(8)	-9(7)	-18(7)
C(11c)	240(10)	181(10)	140(9)	-15(8)	-18(8)	-1(7)
O(12)	252(7)	286(8)	278(7)	33(6)	-30(6)	24(6)
C(13)	386(14)	322(13)	331(13)	46(11)	-159(11)	-26(10)
O(14)	479(9)	279(8)	248(8)	188(7)	-34(6)	-50(6)
O(15)	498(10)	304(8)	264(8)	1(7)	-138(7)	51(6)
C(16)	269(10)	125(9)	247(10)	-3(8)	-15(8)	-25(8)
O(17)	343(8)	321(8)	301(8)	-97(7)	-125(7)	43(6)
S(18)	241(3)	243(3)	290(3)	-8(2)	28(2)	12(2)
C(19)	265(12)	326(14)	541(16)	-47(11)	2(11)	21(12)

The anisotropic displacement factor exponent takes the form:

$-2\pi^2(h^2a^{*2}U_{11} + \ldots + 2klb^*c^*U_{23})$

Crystal Data for Compound 106



Crystal Data

Empirical Formula	$C_{17}H_{20}O_6$
Color; Habit	Yellow plate fragment
Crystal Size (mm)	0.40{100}x0.32{010}x0.86{001}
Crystal System	Orthorhombic
Space Group	$Pca2_1$
Unit Cell Dimensions	$\underline{a}$ = 7.974(2) Å
	$\underline{b}$ = 13.425(2) Å
	$\underline{c}$ = 14.818(2) Å
Volume	1586.3(4) $Å^3$
Z	4
Formula Weight	320.3
Density(calc.)	1.341 g/cm^3
Absorption Coefficient	1.02 cm^{-1}
F(000)	680

Data Collection

Diffractometer Used	Siemens R3m/V
Radiation	MoKα (λ = 0.71073 Å)
Temperature (K)	298
Monochromator	Highly oriented graphite crystal
2θ Range	4.0 to 60.0°
Scan Type	ω
Scan Speed	Variable; 2.93 to 29.30°/min. in ω
Scan Range (ω)	1.20°
Background Measurement	Stationary crystal and stationary counter at beginning and end of scan, each for 25.0% of total scan time
Standard Reflections	2 measured every 100 reflections
Index Ranges	$0 \leq h \leq 11$, $0 \leq k \leq 18$ $0 \leq \ell \leq 20$
Reflections Collected	2610
Independent Reflections	2418 (R_{int} = 1.23%)
Observed Reflections	1672 ($F > 6.0\sigma(F)$)
Absorption Correction	Face-indexed numerical
Min./Max. Transmission	0.9598 / 0.9695

Solution and Refinement

System Used	Siemens SHELXTL PLUS (VMS)
Solution	Direct Methods
Refinement Method	Full-Matrix Least-Squares
Quantity Minimized	$\sum w(F_o - F_c)^2$
Extinction Correction	χ = 0.00188(10), where $F^* = F \left[1 + 0.002\chi F^2/\sin(2\theta) \right]^{-1/4}$
Hydrogen Atoms	Refined isotropic U
Weighting Scheme	$w^{-1} = \sigma^2(F)$
Number of Parameters Refined	288
Final R Indices (obs. data)	R = 3.30 %, wR = 2.52 %
(R Indices (all data)	R = 4.61 %, wR = 2.58 %)
Goodness-of-Fit	2.16
Largest and Mean Δ/σ	0.013, 0.001
Data-to-Parameter Ratio	5.8:1
Largest Difference Peak	0.16 $e\text{Å}^{-3}$
Largest Difference Hole	-0.11 $e\text{Å}^{-3}$

Table 1. Atomic coordinates ($x10^4$) and equivalent isotropic displacement coefficients ($Å^2 x10^3$)

	x	y	z	U(eq)
C(1)	-4428(3)	8169(2)	9195(2)	40.8(8)
C(2)	-3857(3)	9199(2)	9037(2)	43.2(8)
C(3)	-2983(4)	9687(2)	9669(2)	50(1)
C(4)	-2579(3)	9245(2)	10526(2)	45.9(8)
C(4a)	-3065(3)	8336(2)	10768(2)	39.7(7)
C(5)	-2692(4)	7866(2)	11657(2)	50(1)
C(6)	-2221(3)	6784(2)	11559(2)	51(1)
C(7)	-2334(4)	6290(2)	10801(2)	50.1(9)
C(8)	-2905(3)	6731(2)	9924(2)	39.3(8)
C(8a)	-4000(3)	7683(2)	10105(2)	36.7(7)
O(9)	-5202(3)	7708(1)	8632(2)	65.6(7)
O(10)	-4324(2)	9541(1)	8211(2)	57.8(7)
C(11)	-3944(6)	10568(3)	8021(4)	77(2)
C(12)	-1448(3)	6981(2)	9293(2)	44.8(8)
C(13)	-178(3)	6139(2)	9197(2)	46.0(9)
C(14)	1002(3)	6331(2)	8423(2)	44.8(9)
O(15)	1025(2)	7066(1)	7965(2)	65.4(8)
O(16)	2018(2)	5554(1)	8275	55.4(7)
C(17)	3213(4)	5694(3)	7545(3)	60(1)
C(18)	-5720(3)	7372(2)	10491(2)	44.5(8)
O(19)	-6270(3)	6550(1)	10512(2)	69.5(8)
O(20)	-6514(2)	8185(1)	10794(2)	51.6(6)
C(21)	-8179(4)	8032(3)	11169(3)	61(1)

* Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor

Table 2. Bond lengths (Å)

C(1)-C(2)	1.475(3)	C(1)-C(8a)	1.536(4)
C(1)-O(9)	1.208(4)	C(2)-C(3)	1.338(4)
C(2)-O(10)	1.360(4)	C(3)-C(4)	1.439(5)
C(4)-C(4a)	1.330(3)	C(4a)-C(5)	1.490(4)
C(4a)-C(8a)	1.514(4)	C(5)-C(6)	1.507(4)
C(6)-C(7)	1.309(5)	C(7)-C(8)	1.498(5)
C(8)-C(8a)	1.570(3)	C(8)-C(12)	1.529(4)
C(8a)-C(18)	1.544(4)	O(10)-C(11)	1.440(4)
C(12)-C(13)	1.524(4)	C(13)-C(14)	1.505(4)
C(14)-O(15)	1.198(4)	C(14)-O(16)	1.340(3)
O(16)-C(17)	1.454(4)	C(18)-O(19)	1.188(3)
C(18)-O(20)	1.339(3)	O(20)-C(21)	1.454(4)

Table 3. Bond angles (°)

C(2)-C(1)-C(8a)	118.0(2)	C(2)-C(1)-O(9)	121.9(3)
C(8a)-C(1)-O(9)	120.1(2)	C(1)-C(2)-C(3)	120.6(3)
C(1)-C(2)-O(10)	112.0(2)	C(3)-C(2)-O(10)	127.4(2)
C(2)-C(3)-C(4)	122.2(2)	C(3)-C(4)-C(4a)	123.5(3)
C(4)-C(4a)-C(5)	124.6(3)	C(4)-C(4a)-C(8a)	120.0(3)
C(5)-C(4a)-C(8a)	115.3(2)	C(4a)-C(5)-C(6)	111.9(3)
C(5)-C(6)-C(7)	123.6(3)	C(6)-C(7)-C(8)	124.4(3)
C(7)-C(8)-C(8a)	110.1(2)	C(7)-C(8)-C(12)	112.7(2)
C(8a)-C(8)-C(12)	110.3(2)	C(1)-C(8a)-C(4a)	115.7(2)
C(1)-C(8a)-C(8)	108.7(2)	C(4a)-C(8a)-C(8)	108.0(2)
C(1)-C(8a)-C(18)	104.1(2)	C(4a)-C(8a)-C(18)	110.6(2)
C(8)-C(8a)-C(18)	109.7(2)	C(2)-O(10)-C(11)	116.2(3)
C(8)-C(12)-C(13)	113.5(2)	C(12)-C(13)-C(14)	111.1(2)
C(13)-C(14)-O(15)	125.6(2)	C(13)-C(14)-O(16)	111.7(2)
O(15)-C(14)-O(16)	122.7(3)	C(14)-O(16)-C(17)	114.7(2)
C(8a)-C(18)-O(19)	126.0(2)	C(8a)-C(18)-O(20)	108.9(2)
O(19)-C(18)-O(20)	125.0(2)	C(18)-O(20)-C(21)	116.4(2)

Table 4. H-Atom coordinates ($x10^4$) and isotropic displacement coefficients ($Å^2 x10^3$)

	x	y	z	U
H(3)	-2703(35)	10364(19)	9517(18)	55(8)
H(4)	-1947(31)	9585(17)	10944(18)	51(8)
H(5x)	-1778(40)	8192(25)	12000(21)	75(10)
H(5y)	-3704(42)	7914(23)	12076(21)	77(10)
H(6)	-1898(31)	6458(17)	12078(17)	42(7)
H(7)	-2010(28)	5564(16)	10740(15)	42(7)
H(8)	-3660(35)	6249(19)	9578(19)	62(8)
H(11x)	-4389(42)	10650(24)	7347(24)	79(10)
H(11y)	-4486(46)	10961(25)	8398(25)	94(14)
H(11z)	-2679(54)	10683(23)	8013(27)	106(13)
H(12x)	-1826(27)	7152(16)	8661(16)	36(6)
H(12y)	-874(36)	7609(21)	9494(19)	58(8)
H(13x)	-768(29)	5517(18)	9101(16)	44(7)
H(13y)	536(32)	6062(17)	9760(17)	41(7)
H(17x)	4060(37)	6276(23)	7748(20)	73(10)
H(17y)	2587(49)	5812(22)	6864(24)	95(11)
H(17z)	3762(47)	5135(27)	7531(30)	108(13)
H(21x)	-8660(50)	7544(34)	10714(32)	129(16)
H(21y)	-8134(46)	7712(27)	11767(26)	96(13)
H(21z)	-8613(42)	8664(24)	11120(23)	81(11)

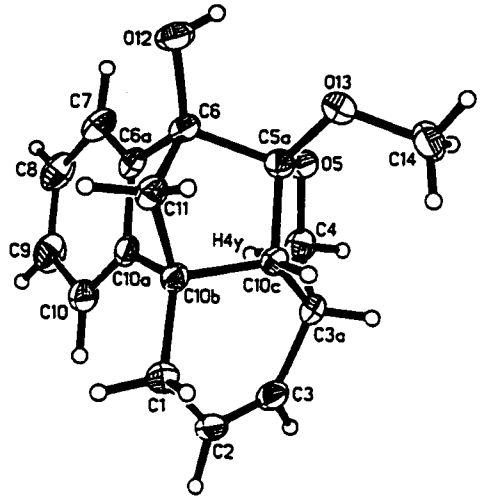
Table 5. Anisotropic displacement coefficients ($Å^2 x 10^3$)

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	36(1)	41(1)	45(1)	0(1)	-4(1)	-4(1)
C(2)	43(1)	38(1)	49(2)	7(1)	4(1)	5(1)
C(3)	53(2)	34(1)	61(2)	-4(1)	7(2)	-2(1)
C(4)	41(1)	42(1)	54(2)	-8(1)	-2(1)	-13(1)
C(4a)	33(1)	43(1)	43(1)	0(1)	1(1)	-7(1)
C(5)	44(2)	62(2)	43(2)	-4(1)	-4(1)	-4(1)
C(6)	42(2)	62(2)	50(2)	5(1)	1(1)	18(2)
C(7)	52(2)	46(1)	52(2)	5(1)	3(1)	7(1)
C(8)	41(1)	33(1)	44(1)	-2(1)	-1(1)	-2(1)
C(8a)	32(1)	37(1)	41(1)	-3(1)	-1(1)	0(1)
O(9)	80(1)	54(1)	62(1)	-12(1)	-27(1)	2(1)
O(10)	68(1)	49(1)	57(1)	7(1)	0(1)	13(1)
C(11)	92(3)	53(2)	87(3)	6(2)	8(3)	25(2)
C(12)	49(1)	44(1)	42(1)	5(1)	0(1)	-3(1)
C(13)	48(2)	40(1)	50(2)	5(1)	3(1)	-3(1)
C(14)	42(1)	39(1)	53(2)	1(1)	-4(1)	-4(1)
O(15)	62(1)	52(1)	83(2)	12(1)	20(1)	12(1)
O(16)	52(1)	46(1)	68(1)	12(1)	12(1)	1(1)
C(17)	56(2)	56(2)	67(2)	10(2)	14(2)	-7(2)
C(18)	37(1)	45(1)	51(2)	-5(1)	-6(1)	1(1)
O(19)	52(1)	49(1)	107(2)	-18(1)	13(1)	-5(1)
O(20)	34.8(9)	46(1)	74(1)	0.7(8)	8.5(9)	3(1)
C(21)	35(2)	64(2)	84(3)	0(1)	11(2)	6(2)

The anisotropic displacement factor exponent takes the form:

$-2\pi^2(h^2a^{*2}U_{11} + \ldots + 2klb^*c^*U_{23})$

Crystal Data for Compound 147



Crystal Data

Empirical Formula	$C_{17}H_{18}O_3$
Color; Habit	Colourless prism
Crystal Size (mm)	0.54{100}x0.40{021}
Crystal System	Monoclinic
Space Group	$P2_1/c$
Unit Cell Dimensions	$\underline{a}$ = 7.279(1) Å
	$\underline{b}$ = 16.774(2) Å
	$\underline{c}$ = 10.988(1) Å
	β = 97.133(5)°
Volume	1331.2(3) $Å^3$
Z	4
Formula Weight	270.3
Density(calc.)	1.349 g/cm^3
Absorption Coefficient	0.91 cm^{-1}
F(000)	576

Data Collection

Diffractometer Used	Siemens P4
Radiation	MoKα (λ = 0.71073 Å)
Temperature (K)	295
Monochromator	Highly oriented graphite crystal
2θ Range	4.0 to 52.0°
Scan Type	ω
Scan Speed	Variable; 3.00 to 30.00°/min. in ω
Scan Range (ω)	1.20°
Background Measurement	Stationary crystal and stationary counter at beginning and end of scan, each for 25.0% of total scan time
Standard Reflections	3 measured every 100 reflections
Index Ranges	$0 \leq h \leq 8$, $0 \leq k \leq 20$ $-13 \leq \ell \leq 13$
Reflections Collected	2823
Independent Reflections	2615 (R_{int} = 1.12%)
Observed Reflections	1944 ($F > 6.0\sigma(F)$)
Absorption Correction	Face-indexed numerical
Min./Max. Transmission	0.9620 / 0.9701

Solution and Refinement

System Used	Siemens SHELXTL IRIS
Solution	Direct Methods
Refinement Method	Full-Matrix Least-Squares
Quantity Minimized	$\Sigma w(F_o-F_c)^2$
Extinction Correction	χ = 0.0034(2), where $F^* = F\ [\ 1 + 0.002\chi F^2/\sin(2\theta)\ ]^{-1/4}$
Hydrogen Atoms	Riding model, refined isotropic U
Weighting Scheme	$w^{-1} = \sigma^2(F)$
Number of Parameters Refined	200
Final R Indices (obs. data)	R = 3.62 %, wR = 3.65 %
(R Indices (all data)	R = 4.70 %, wR = 3.70 %)
Goodness-of-Fit	2.88
Largest and Mean Δ/σ	0.001, 0.000
Data-to-Parameter Ratio	9.7:1
Largest Difference Peak	0.19 $e\text{Å}^{-3}$
Largest Difference Hole	-0.14 $e\text{Å}^{-3}$

Table 1. Atomic coordinates ($x10^4$) and equivalent isotropic displacement coefficients ($Å^2 x10^4$)

	x	y	z	U(eq)
C(1)	1907(2)	3976(1)	-234(2)	436(7)
C(2)	93(3)	3555(1)	-128(2)	459(7)
C(3)	-721(3)	3510(1)	888(2)	440(6)
C(3a)	-50(2)	3955(1)	2045(2)	373(6)
C(4)	637(3)	3488(1)	3225(2)	426(6)
O(5)	2035(2)	3974.0(7)	3901(1)	403(4)
C(5a)	2802(2)	4521.9(9)	3115(2)	333(5)
C(6)	4801(2)	4311(1)	2816(2)	347(6)
C(6a)	4832(2)	3419(1)	2660(2)	351(6)
C(7)	5710(2)	2821(1)	3374(2)	456(7)
C(8)	5485(3)	2045(1)	2953(2)	567(8)
C(9)	4386(3)	1872(1)	1863(2)	576(8)
C(10)	3463(3)	2476(1)	1168(2)	459(7)
C(10a)	3690(2)	3250(1)	1581(2)	347(5)
C(10b)	2951(2)	4047(1)	1042(1)	323(5)
C(10c)	1633(2)	4444.2(9)	1866(1)	312(5)
C(11)	4663(2)	4571(1)	1443(2)	372(6)
O(12)	6296(2)	4633.5(8)	3589(1)	510(5)
O(13)	2927(2)	5275.8(7)	3666(1)	457(5)
C(14)	1204(3)	5664(1)	3760(2)	568(8)

* Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor

Table 2. Bond lengths (Å)

C(1)-C(2)	1.515(3)	C(1)-C(10b)	1.514(2)
C(2)-C(3)	1.330(3)	C(3)-C(3a)	1.503(2)
C(3a)-C(4)	1.544(2)	C(3a)-C(10c)	1.507(2)
C(4)-O(5)	1.437(2)	O(5)-C(5a)	1.423(2)
C(5a)-C(6)	1.571(2)	C(5a)-C(10c)	1.528(2)
C(5a)-O(13)	1.400(2)	C(6)-C(6a)	1.506(2)
C(6)-C(11)	1.561(2)	C(6)-O(12)	1.403(2)
C(6a)-C(7)	1.380(2)	C(6a)-C(10a)	1.390(2)
C(7)-C(8)	1.383(3)	C(8)-C(9)	1.385(3)
C(9)-C(10)	1.390(3)	C(10)-C(10a)	1.379(3)
C(10a)-C(10b)	1.532(2)	C(10b)-C(10c)	1.550(2)
C(10b)-C(11)	1.544(2)	O(13)-C(14)	1.428(3)

Table 3. Bond angles (°)

C(2)-C(1)-C(10b)	107.9(1)	C(1)-C(2)-C(3)	125.1(2)
C(2)-C(3)-C(3a)	123.3(2)	C(3)-C(3a)-C(4)	119.7(2)
C(3)-C(3a)-C(10c)	110.2(1)	C(4)-C(3a)-C(10c)	101.7(1)
C(3a)-C(4)-O(5)	106.3(1)	C(4)-O(5)-C(5a)	111.0(1)
O(5)-C(5a)-C(6)	115.1(1)	O(5)-C(5a)-C(10c)	105.9(1)
C(6)-C(5a)-C(10c)	102.7(1)	O(5)-C(5a)-O(13)	109.3(1)
C(6)-C(5a)-O(13)	106.4(1)	C(10c)-C(5a)-O(13)	117.7(1)
C(5a)-C(6)-C(6a)	106.0(1)	C(5a)-C(6)-C(11)	100.9(1)
C(6a)-C(6)-C(11)	99.7(1)	C(5a)-C(6)-O(12)	117.1(1)
C(6a)-C(6)-O(12)	115.5(1)	C(11)-C(6)-O(12)	115.4(1)
C(6)-C(6a)-C(7)	132.1(2)	C(6)-C(6a)-C(10a)	106.4(1)
C(7)-C(6a)-C(10a)	121.5(2)	C(6a)-C(7)-C(8)	117.8(2)
C(7)-C(8)-C(9)	121.2(2)	C(8)-C(9)-C(10)	120.7(2)
C(9)-C(10)-C(10a)	118.4(2)	C(6a)-C(10a)-C(10)	120.4(2)
C(6a)-C(10a)-C(10b)	107.3(1)	C(10)-C(10a)-C(10b)	132.3(1)
C(1)-C(10b)-C(10a)	113.7(1)	C(1)-C(10b)-C(10c)	107.4(1)
C(10a)-C(10b)-C(10c)	111.2(1)	C(1)-C(10b)-C(11)	127.1(1)
C(10a)-C(10b)-C(11)	98.9(1)	C(10c)-C(10b)-C(11)	97.1(1)
C(3a)-C(10c)-C(5a)	107.5(1)	C(3a)-C(10c)-C(10b)	114.5(1)
C(5a)-C(10c)-C(10b)	104.2(1)	C(6)-C(11)-C(10b)	94.0(1)
C(5a)-O(13)-C(14)	115.6(1)		

Table 4. H-Atom coordinates ($x10^4$) and isotropic displacement coefficients ($Å^2 x10^3$)

	x	y	z	U
H(1x)	2627	3680	-753	58(6)
H(1y)	1671	4497	-582	44(5)
H(2)	-519	3301	-850	60(6)
H(3)	-1772	3164	891	42(5)
H(3a)	-1020	4308	2224	31(4)
H(4x)	-357	3392	3704	53(6)
H(4y)	1149	2985	3018	38(5)
H(7)	6434	2946	4141	44(5)
H(8)	6095	1619	3426	71(7)
H(9)	4276	1332	1574	68(7)
H(10)	2672	2357	425	48(5)
H(10c)	1270	4962	1551	32(4)
H(11x)	5725	4412	1065	37(5)
H(11y)	4429	5131	1324	36(5)
H(12)	5979	4803	4153	91(11)
H(14x)	1448	6189	4089	105(9)
H(14y)	501	5378	4302	138(12)
H(14z)	482	5715	2972	98(9)

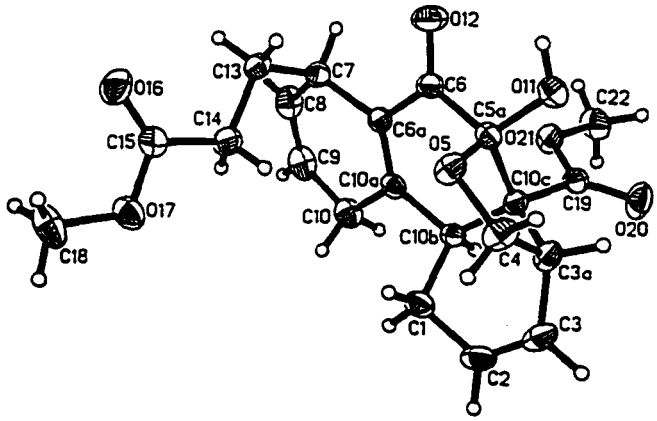
Table 5. Anisotropic displacement coefficients ($Å^2 x 10^4$)

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	426(11)	537(12)	335(10)	115(10)	2(9)	6(9)
C(2)	407(11)	517(12)	414(11)	78(10)	-106(9)	-91(9)
C(3)	297(10)	465(11)	534(12)	-15(9)	-39(9)	-68(9)
C(3a)	246(9)	444(11)	429(10)	40(8)	37(8)	-23(8)
C(4)	361(10)	480(12)	454(11)	-52(9)	114(9)	18(9)
O(5)	382(7)	509(8)	319(7)	-55(6)	49(5)	59(6)
C(5a)	346(10)	343(9)	308(9)	-10(8)	36(8)	16(8)
C(6)	260(9)	423(10)	346(10)	-26(8)	-7(7)	37(8)
C(6a)	237(8)	422(10)	400(10)	36(8)	59(7)	80(8)
C(7)	312(10)	535(12)	510(12)	30(9)	1(9)	174(10)
C(8)	406(12)	469(13)	822(16)	108(10)	55(11)	229(12)
C(9)	511(13)	381(12)	838(17)	111(10)	89(12)	2(11)
C(10)	415(11)	426(11)	527(12)	77(9)	29(10)	-65(9)
C(10a)	270(9)	408(10)	371(10)	66(8)	71(7)	22(8)
C(10b)	286(9)	388(10)	293(9)	51(8)	32(7)	30(7)
C(10c)	288(9)	314(9)	327(9)	57(7)	8(7)	17(7)
C(11)	316(9)	424(11)	380(10)	20(8)	62(8)	89(8)
O(12)	348(7)	740(10)	423(8)	-109(7)	-35(6)	-39(7)
O(13)	465(8)	446(8)	449(8)	-25(6)	17(6)	-114(6)
C(14)	680(15)	540(13)	490(13)	140(12)	92(12)	-119(11)

The anisotropic displacement factor exponent takes the form:

$-2\pi^2(h^2a^{*2}U_{11} + \ldots + 2klb^*c^*U_{23})$

Crystal Data for Compound 167



Crystal Data

Empirical Formula	$C_{21}H_{24}O_7$
Color; Habit	Colourless prism fragment
Crystal Size (mm)	0.56{100}x0.44{011}x0.42{01$\bar{1}$}
Crystal System	Triclinic
Space Group	P$\bar{1}$
Unit Cell Dimensions	a = 7.720(1) Å
	b = 10.036(1) Å
	c = 13.052(1) Å
	α = 100.826(9)°
	β = 98.998(9)°
	γ = 105.222(7)°
Volume	935.6(3) Å^3
Z	2
Formula Weight	388.4
Density(calc.)	1.379 g/cm^3
Absorption Coefficient	1.03 cm^{-1}
F(000)	412

Data Collection

Diffractometer Used	Siemens P4
Radiation	MoKα (λ = 0.71073 Å)
Temperature (K)	295
Monochromator	Highly oriented graphite crystal
2θ Range	4.0 to 52.0°
Scan Type	ω
Scan Speed	Variable; 3.00 to 30.00°/min. in ω
Scan Range (ω)	1.20°
Background Measurement	Stationary crystal and stationary counter at beginning and end of scan, each for 25.0% of total scan time
Standard Reflections	3 measured every 100 reflections
Index Ranges	$0 \leq h \leq 9$, $-11 \leq k \leq 11$ $-16 \leq \ell \leq 15$
Reflections Collected	3930
Independent Reflections	3644 (R_{int} = 1.21%)
Observed Reflections	2768 ($F > 6.0\sigma(F)$)
Absorption Correction	Face-indexed numerical
Min./Max. Transmission	0.9553 / 0.9662

Solution and Refinement

System Used	Siemens SHELXTL IRIS
Solution	Direct Methods
Refinement Method	Full-Matrix Least-Squares
Quantity Minimized	$\Sigma w(F_o - F_c)^2$
Extinction Correction	χ = 0.0117(8), where $F^* = F \left[1 + 0.002\chi F^2/\sin(2\theta) \right]^{-1/4}$
Hydrogen Atoms	Riding model, refined isotropic U
Weighting Scheme	$w^{-1} = \sigma^2(F) + 0.00008F^2$
Number of Parameters Refined	278
Final R Indices (obs. data)	R = 3.99 %, wR = 4.95 %
(R Indices (all data)	R = 4.96 %, wR = 5.04 %)
Goodness-of-Fit	2.79
Largest and Mean Δ/σ	0.002, 0.000
Data-to-Parameter Ratio	10.0:1
Largest Difference Peak	0.19 $e\text{Å}^{-3}$
Largest Difference Hole	-0.16 $e\text{Å}^{-3}$

Table 1. Atomic coordinates ($x10^4$) and equivalent isotropic displacement coefficients ($Å^2 x10^3$)

	x	y	z	U(eq)
C(1)	7309(3)	7917(2)	6168(2)	50.0(8)
C(2)	6646(3)	8437(2)	5230(2)	55.6(9)
C(3)	4905(3)	8301(2)	4933(2)	54.5(9)
C(3a)	3541(3)	7563(2)	5497(1)	45.5(7)
C(4)	3107(3)	5930(2)	5168(2)	52.7(8)
O(5)	3426(2)	5463(1)	6139.5(9)	45.6(5)
C(5a)	3231(2)	6512(2)	6964(1)	37.2(6)
C(6)	4028(2)	6195(2)	7997(1)	39.0(6)
C(6a)	6000(2)	6728(2)	8408(1)	34.6(6)
C(7)	6748(3)	6108(2)	9278(1)	40.9(7)
C(8)	8622(3)	6993(2)	9873(2)	55.1(8)
C(9)	9667(3)	8000(2)	9530(2)	58.1(8)
C(10)	9055(3)	8385(2)	8515(2)	51.4(8)
C(10a)	7043(2)	7733(2)	8022(1)	35.4(6)
C(10b)	6356(2)	8302(2)	7098(1)	36.1(6)
C(10c)	4233(2)	7922(2)	6732(1)	35.8(6)
O(11)	1383(2)	6429(1)	6903(1)	52.2(5)
O(12)	2978(2)	5485(2)	8434(1)	62.9(6)
C(13)	6725(3)	4568(2)	8823(1)	44.6(7)
C(14)	7866(3)	4502(2)	7982(2)	57.8(9)
C(15)	8257(3)	3132(2)	7650(1)	42.5(7)
O(16)	7705(2)	2072(1)	7936(1)	63.7(6)
O(17)	9400(2)	3273(1)	6982(1)	57.1(6)
C(18)	10145(4)	2121(3)	6684(2)	82(1)
C(19)	3607(3)	9137(2)	7270(1)	40.2(7)
O(20)	2752(2)	9773(2)	6822(1)	67.1(7)
O(21)	4166(2)	9433(1)	8326.8(9)	48.0(5)
C(22)	3878(3)	10694(2)	8928(2)	57.3(9)

* Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor

Table 2. Bond lengths (Å)

C(1)-C(2)	1.490(3)	C(1)-C(10b)	1.554(3)
C(2)-C(3)	1.302(4)	C(3)-C(3a)	1.496(3)
C(3a)-C(4)	1.544(3)	C(3a)-C(10c)	1.557(2)
C(4)-O(5)	1.441(2)	O(5)-C(5a)	1.413(2)
C(5a)-C(6)	1.517(3)	C(5a)-C(10c)	1.533(2)
C(5a)-O(11)	1.396(2)	C(6)-C(6a)	1.449(2)
C(6)-O(12)	1.218(2)	C(6a)-C(7)	1.504(3)
C(6a)-C(10a)	1.345(2)	C(7)-C(8)	1.483(2)
C(7)-C(13)	1.542(3)	C(8)-C(9)	1.314(3)
C(9)-C(10)	1.490(3)	C(10)-C(10a)	1.500(2)
C(10a)-C(10b)	1.510(3)	C(10b)-C(10c)	1.555(2)
C(10c)-C(19)	1.519(3)	C(13)-C(14)	1.514(3)
C(14)-C(15)	1.484(3)	C(15)-O(16)	1.190(2)
C(15)-O(17)	1.335(3)	O(17)-C(18)	1.438(4)
C(19)-O(20)	1.195(3)	C(19)-O(21)	1.330(2)
O(21)-C(22)	1.448(3)		

Table 3. Bond angles (°)

C(2)-C(1)-C(10b)	110.9(2)	C(1)-C(2)-C(3)	120.2(2)
C(2)-C(3)-C(3a)	120.5(2)	C(3)-C(3a)-C(4)	112.0(2)
C(3)-C(3a)-C(10c)	113.8(1)	C(4)-C(3a)-C(10c)	103.3(1)
C(3a)-C(4)-O(5)	106.7(1)	C(4)-O(5)-C(5a)	106.5(1)
O(5)-C(5a)-C(6)	105.3(1)	O(5)-C(5a)-C(10c)	104.0(1)
C(6)-C(5a)-C(10c)	117.0(1)	O(5)-C(5a)-O(11)	110.9(1)
C(6)-C(5a)-O(11)	110.5(2)	C(10c)-C(5a)-O(11)	108.8(2)
C(5a)-C(6)-C(6a)	118.6(2)	C(5a)-C(6)-O(12)	118.2(1)
C(6a)-C(6)-O(12)	123.1(2)	C(6)-C(6a)-C(7)	115.9(1)
C(6)-C(6a)-C(10a)	120.2(2)	C(7)-C(6a)-C(10a)	123.9(1)
C(6a)-C(7)-C(8)	112.1(2)	C(6a)-C(7)-C(13)	110.9(1)
C(8)-C(7)-C(13)	110.7(2)	C(7)-C(8)-C(9)	123.5(2)
C(8)-C(9)-C(10)	122.9(2)	C(9)-C(10)-C(10a)	114.4(2)
C(6a)-C(10a)-C(10)	120.3(2)	C(6a)-C(10a)-C(10b)	125.1(1)
C(10)-C(10a)-C(10b)	114.6(1)	C(1)-C(10b)-C(10a)	109.1(2)
C(1)-C(10b)-C(10c)	113.1(1)	C(10a)-C(10b)-C(10c)	116.2(1)
C(3a)-C(10c)-C(5a)	100.0(1)	C(3a)-C(10c)-C(10b)	113.7(2)
C(5a)-C(10c)-C(10b)	112.0(1)	C(3a)-C(10c)-C(19)	110.7(2)
C(5a)-C(10c)-C(19)	111.3(2)	C(10b)-C(10c)-C(19)	109.0(1)
C(7)-C(13)-C(14)	111.3(2)	C(13)-C(14)-C(15)	115.8(2)
C(14)-C(15)-O(16)	127.1(2)	C(14)-C(15)-O(17)	109.0(2)
O(16)-C(15)-O(17)	123.9(2)	C(15)-O(17)-C(18)	117.3(2)
C(10c)-C(19)-O(20)	125.6(2)	C(10c)-C(19)-O(21)	111.0(2)
O(20)-C(19)-O(21)	123.3(2)	C(19)-O(21)-C(22)	116.5(2)

Table 4. Anisotropic displacement coefficients ($Å^2 x 10^3$)

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	59(1)	45(1)	55(1)	21(1)	32(1)	13(1)
C(2)	83(2)	46(1)	48(1)	22(1)	38(1)	14(1)
C(3)	95(2)	40(1)	38(1)	28(1)	25(1)	14(1)
C(3a)	61(1)	44(1)	36(1)	24(1)	9(1)	10(1)
C(4)	71(1)	44(1)	39(1)	14(1)	9(1)	7(1)
O(5)	61(1)	33(1)	41(1)	14(1)	10(1)	6(1)
C(5a)	36(1)	37(1)	39(1)	12(1)	10(1)	8(1)
C(6)	42(1)	37(1)	40(1)	12(1)	15(1)	12(1)
C(6a)	40(1)	32(1)	34(1)	15(1)	11(1)	6(1)
C(7)	49(1)	47(1)	33(1)	21(1)	15(1)	12(1)
C(8)	59(1)	63(1)	40(1)	25(1)	0(1)	4(1)
C(9)	44(1)	56(1)	59(1)	12(1)	-4(1)	-5(1)
C(10)	40(1)	45(1)	63(1)	7(1)	10(1)	8(1)
C(10a)	38(1)	30(1)	40(1)	13(1)	13(1)	3(1)
C(10b)	44(1)	27(1)	42(1)	12(1)	19(1)	8(1)
C(10c)	45(1)	33(1)	35(1)	18(1)	14(1)	10(1)
O(11)	37(1)	60(1)	61(1)	14(1)	11(1)	20(1)
O(12)	47(1)	82(1)	61(1)	4(1)	15(1)	39(1)
C(13)	56(1)	46(1)	42(1)	22(1)	17(1)	20(1)
C(14)	87(2)	47(1)	59(1)	34(1)	38(1)	21(1)
C(15)	45(1)	42(1)	36(1)	14(1)	3(1)	4(1)
O(16)	84(1)	42(1)	72(1)	23(1)	25(1)	18(1)
O(17)	58(1)	51(1)	64(1)	20(1)	24(1)	4(1)
C(18)	81(2)	76(2)	97(2)	45(2)	31(2)	0(1)
C(19)	48(1)	38(1)	43(1)	20(1)	17(1)	12(1)
O(20)	96(1)	71(1)	58(1)	59(1)	18(1)	20(1)
O(21)	67(1)	45(1)	41(1)	31(1)	17(1)	6(1)
C(22)	71(1)	47(1)	57(1)	27(1)	24(1)	-2(1)

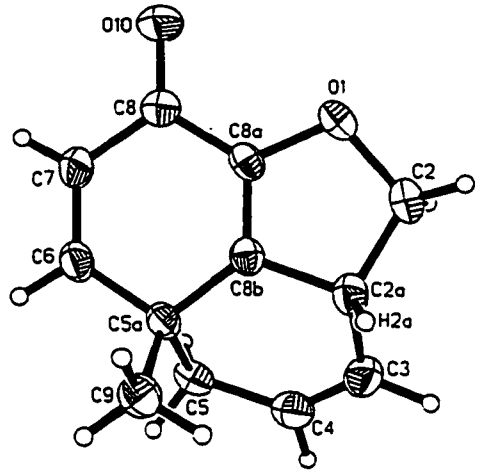
The anisotropic displacement factor exponent takes the form:

$-2\pi^2(h^2a^{*2}U_{11} + \ldots + 2klb^*c^*U_{23})$

Table 5. H-Atom coordinates ($x10^4$) and isotropic displacement coefficients ($Å^2 x10^3$)

	x	y	z	U
H(1x)	7031	6901	5964	64(6)
H(1y)	8619	8322	6403	60(6)
H(2)	7505	8885	4848	65(6)
H(3)	4493	8667	4342	63(6)
H(3a)	2427	7812	5338	50(5)
H(4x)	1851	5493	4790	70(7)
H(4y)	3896	5676	4715	57(6)
H(7)	5943	6080	9770	42(5)
H(8)	9104	6809	10538	76(7)
H(9)	10871	8525	9956	78(7)
H(10x)	9334	9400	8642	71(7)
H(10y)	9739	8086	8010	65(6)
H(10b)	6808	9320	7338	40(5)
H(11)	752	5745	7182	134(12)
H(13x)	7215	4191	9388	53(5)
H(13y)	5482	3983	8515	58(6)
H(14x)	7226	4692	7360	95(8)
H(14y)	9010	5250	8246	101(9)
H(18x)	10972	2075	7298	132(13)
H(18y)	9167	1240	6436	119(11)
H(18z)	10795	2257	6124	147(13)
H(22x)	3970	10662	9665	125(11)
H(22y)	4784	11526	8875	131(12)
H(22z)	2683	10749	8639	118(11)

Crystal Data for Compound 179c



Crystal Data

Empirical Formula	$C_{12}H_{12}O_2$
Color; Habit	Colourless needle prism fragment
Crystal Size (mm)	0.20{110}x0.90{001}
Crystal System	Monoclinic
Space Group	C2/c
Unit Cell Dimensions	a = 18.378(2) Å
	b = 7.690(1) Å
	c = 13.565(2) Å
	β = 96.355(8)°
Volume	1905.4(5) $Å^3$
Z	8
Formula Weight	188.2
Density(calc.)	1.312 g/cm^3
Absorption Coefficient	0.88 cm^{-1}
F(000)	800

Data Collection

Diffractometer Used	Siemens P4
Radiation	MoKα (λ = 0.71073 Å)
Temperature (K)	160
Monochromator	Highly oriented graphite crystal
2θ Range	4.0 to 60.0°
Scan Type	ω
Scan Speed	Variable; 3.00 to 30.00°/min. in ω
Scan Range (ω)	1.20°
Background Measurement	Stationary crystal and stationary counter at beginning and end of scan, each for 25.0% of total scan time
Standard Reflections	3 measured every 100 reflections
Index Ranges	$-25 \leq h \leq 25$, $0 \leq k \leq 10$ $0 \leq \ell \leq 18$
Reflections Collected	2880
Independent Reflections	2770 (R_{int} = 1.44%)
Observed Reflections	2012 ($F > 6.0\sigma(F)$)
Absorption Correction	Face-indexed numerical
Min./Max. Transmission	0.9667 / 0.9872

Solution and Refinement

System Used	Siemens SHELXTL IRIS
Solution	Direct Methods
Refinement Method	Full-Matrix Least-Squares
Quantity Minimized	$\sum w(F_o - F_c)^2$
Hydrogen Atoms	Refined isotropic U
Weighting Scheme	$w^{-1} = \sigma^2(F)$
Number of Parameters Refined	176
Final R Indices (obs. data)	R = 4.75 %, wR = 5.00 %
(R Indices (all data)	R = 6.24 %, wR = 5.08 %)
Goodness-of-Fit	3.16
Largest and Mean Δ/σ	0.002, 0.000
Data-to-Parameter Ratio	11.4:1
Largest Difference Peak	0.39 $eÅ^{-3}$
Largest Difference Hole	-0.20 $eÅ^{-3}$

Table 1. Atomic coordinates ($x10^4$) and equivalent isotropic displacement coefficients ($Å^2 x10^4$)

	x	y	z	U(eq)
O(1)	1373.8(6)	3270(2)	3932.6(8)	332(4)
C(2)	1654(1)	1510(3)	3799(1)	379(6)
C(2a)	1378(1)	932(2)	2733(1)	305(5)
C(3)	1933(1)	115(2)	2139(1)	357(5)
C(4)	2101.8(9)	790(3)	1294(1)	352(5)
C(5)	1783.3(9)	2432(2)	817(1)	292(5)
C(5a)	1047.3(8)	2971(2)	1203(1)	262(5)
C(6)	892.4(9)	4856(2)	993(1)	308(5)
C(7)	865(1)	6057(2)	1696(1)	336(5)
C(8)	1007.4(9)	5694(2)	2767(1)	303(5)
C(8a)	1163.8(8)	3865(2)	2981(1)	260(5)
C(8b)	1145.2(8)	2651(2)	2285(1)	248(4)
C(9)	424(1)	1837(3)	680(1)	337(6)
O(10)	1004.4(7)	6830(2)	3404.7(9)	427(4)

* Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor

Table 2. Bond lengths (Å)

O(1)-C(2)	1.466(2)	O(1)-C(8a)	1.384(2)
C(2)-C(2a)	1.544(2)	C(2a)-C(3)	1.505(3)
C(2a)-C(8b)	1.498(2)	C(3)-C(4)	1.327(3)
C(4)-C(5)	1.508(3)	C(5)-C(5a)	1.560(2)
C(5a)-C(6)	1.498(2)	C(5a)-C(8b)	1.479(2)
C(5a)-C(9)	1.548(2)	C(6)-C(7)	1.332(2)
C(7)-C(8)	1.475(2)	C(8)-C(8a)	1.458(2)
C(8)-O(10)	1.230(2)	C(8a)-C(8b)	1.325(2)

Table 3. Bond angles (°)

C(2)-O(1)-C(8a)	104.8(1)	O(1)-C(2)-C(2a)	107.3(1)
C(2)-C(2a)-C(3)	116.7(1)	C(2)-C(2a)-C(8b)	100.1(1)
C(3)-C(2a)-C(8b)	109.4(1)	C(2a)-C(3)-C(4)	122.4(2)
C(3)-C(4)-C(5)	125.6(2)	C(4)-C(5)-C(5a)	112.8(1)
C(5)-C(5a)-C(6)	110.3(1)	C(5)-C(5a)-C(8b)	105.9(1)
C(6)-C(5a)-C(8b)	110.5(1)	C(5)-C(5a)-C(9)	108.7(1)
C(6)-C(5a)-C(9)	110.0(1)	C(8b)-C(5a)-C(9)	111.4(1)
C(5a)-C(6)-C(7)	123.8(1)	C(6)-C(7)-C(8)	123.9(2)
C(7)-C(8)-C(8a)	112.8(1)	C(7)-C(8)-O(10)	123.0(2)
C(8a)-C(8)-O(10)	124.2(1)	O(1)-C(8a)-C(8)	122.2(1)
O(1)-C(8a)-C(8b)	114.5(1)	C(8)-C(8a)-C(8b)	123.3(1)
C(2a)-C(8b)-C(5a)	123.2(1)	C(2a)-C(8b)-C(8a)	110.5(1)
C(5a)-C(8b)-C(8a)	125.5(1)		

Table 4. Anisotropic displacement coefficients ($Å^2 x 10^4$)

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O(1)	410(7)	384(7)	205(5)	17(6)	41(5)	26(5)
C(2)	486(12)	362(11)	283(9)	35(9)	21(8)	89(8)
C(2a)	348(9)	290(9)	278(8)	1(8)	34(7)	57(7)
C(3)	370(10)	309(9)	375(9)	62(8)	-35(7)	-9(8)
C(4)	282(9)	428(11)	337(9)	54(8)	-5(7)	-84(8)
C(5)	269(8)	381(10)	229(8)	-33(7)	40(6)	-43(7)
C(5a)	278(8)	294(9)	210(7)	10(7)	16(6)	3(6)
C(6)	367(9)	302(9)	246(8)	0(8)	-8(7)	54(7)
C(7)	437(10)	242(9)	320(9)	24(8)	-2(7)	58(7)
C(8)	306(9)	307(9)	299(8)	-7(7)	38(7)	-30(7)
C(8a)	263(8)	309(9)	213(7)	-15(7)	46(6)	30(7)
C(8b)	238(8)	271(8)	240(7)	-3(6)	44(6)	34(6)
C(9)	288(9)	362(10)	348(9)	-24(8)	-22(7)	-25(8)
O(10)	578(8)	339(7)	361(7)	5(6)	37(6)	-102(6)

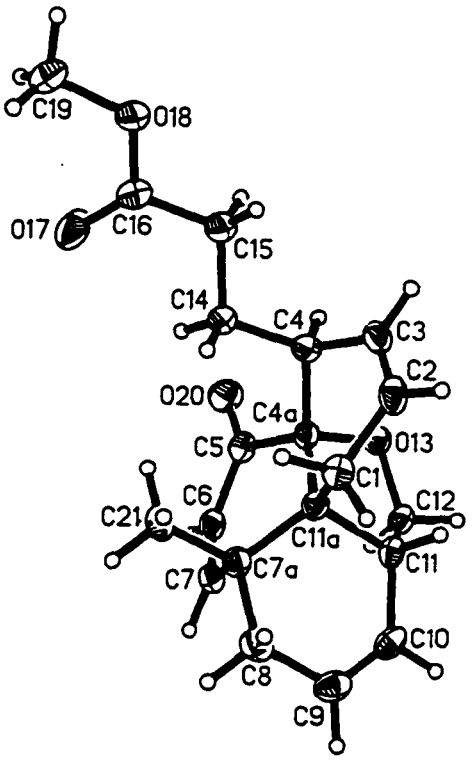
The anisotropic displacement factor exponent takes the form:

$-2\pi^2(h^2a^{*2}U_{11} + \ldots + 2klb^*c^*U_{23})$

Table 5. H-Atom coordinates ($x10^4$) and isotropic displacement coefficients ($Å^2 x 10^3$)

	x	y	z	U
H(2x)	1478(10)	800(25)	4335(13)	43(5)
H(2y)	2206(12)	1598(26)	3919(15)	59(6)
H(2a)	943(8)	114(21)	2709(11)	25(4)
H(3)	2159(11)	-1012(26)	2413(14)	52(6)
H(4)	2494(11)	179(25)	935(15)	53(6)
H(5x)	1719(9)	2316(21)	91(13)	29(4)
H(5y)	2140(11)	3368(24)	909(13)	42(5)
H(6)	827(9)	5223(22)	293(13)	37(5)
H(7)	761(11)	7183(26)	1526(15)	49(6)
H(9x)	380(11)	2084(25)	-20(15)	47(6)
H(9y)	-55(11)	2100(25)	955(14)	50(6)
H(9z)	517(11)	618(28)	855(14)	49(6)

Crystal Data for Compound 203



Crystal Data

Empirical Formula	$C_{20}H_{24}O_4$
Color; Habit	Colourless needle plate fragment
Crystal Size (mm)	0.18{100}x0.76{010}x0.40{001}
Crystal System	Monoclinic
Space Group	C2/c
Unit Cell Dimensions	$\underline{a}$ = 18.758(3) Å
	$\underline{b}$ = 10.367(1) Å
	$\underline{c}$ = 17.439(2) Å
	β = 104.808(7)°
Volume	3278.6(9) $Å^3$
Z	8
Formula Weight	328.4
Density(calc.)	1.331 g/cm^3
Absorption Coefficient	0.91 cm^{-1}
F(000)	1408

Data Collection

Diffractometer Used	Siemens P4
Radiation	MoKα (λ = 0.71073 Å)
Temperature (K)	160
Monochromator	Highly oriented graphite crystal
2θ Range	4.0 to 54.0°
Scan Type	ω
Scan Speed	Variable; 3.00 to 30.00°/min. in ω
Scan Range (ω)	1.20°
Background Measurement	Stationary crystal and stationary counter at beginning and end of scan, each for 25.0% of total scan time
Standard Reflections	3 measured every 100 reflections
Index Ranges	$0 \leq h \leq 23$, $0 \leq k \leq 13$ $-22 \leq \ell \leq 21$
Reflections Collected	3696
Independent Reflections	3586 (R_{int} = 2.36%)
Observed Reflections	2644 ($F > 6.0\sigma(F)$)
Absorption Correction	Face-indexed numerical
Min./Max. Transmission	0.9630 / 0.9848

Solution and Refinement

System Used	Siemens SHELXTL IRIS
Solution	Direct Methods
Refinement Method	Full-Matrix Least-Squares
Quantity Minimized	$\sum w(F_o - F_c)^2$
Extinction Correction	χ = 0.00028(2), where $F^* = F \left[1 + 0.002\chi F^2 / \sin(2\theta) \right]^{-1/4}$
Hydrogen Atoms	Refined isotropic U
Weighting Scheme	$w^{-1} = \sigma^2(F)$
Number of Parameters Refined	314
Final R Indices (obs. data)	R = 3.37 %, wR = 3.34 %
(R Indices (all data)	R = 4.51 %, wR = 3.40 %)
Goodness-of-Fit	2.40
Largest and Mean Δ/σ	0.002, 0.000
Data-to-Parameter Ratio	8.4:1
Largest Difference Peak	0.27 $eÅ^{-3}$
Largest Difference Hole	-0.16 $eÅ^{-3}$

Table 1. Atomic coordinates ($x10^5$) and equivalent isotropic displacement coefficients ($Å^2 x10^4$)

	x	y	z	U(eq)
C(1)	18074(9)	50520(16)	21205(9)	255(5)
C(2)	9939(9)	51831(15)	20357(10)	299(6)
C(3)	5139(9)	47280(15)	14039(10)	290(6)
C(4)	7783(8)	40794(14)	7537(9)	242(5)
C(4a)	14135(8)	48790(13)	5899(8)	210(5)
C(5)	16955(8)	43122(14)	-989(9)	241(5)
C(6)	24615(9)	45705(14)	-1006(9)	245(5)
C(7)	29664(8)	48149(14)	5674(9)	244(5)
C(7a)	28069(8)	47443(14)	13741(9)	229(5)
C(8)	34047(9)	54779(16)	19833(10)	291(5)
C(9)	33804(9)	68928(16)	18223(9)	296(6)
C(10)	27619(9)	74766(15)	14612(9)	268(5)
C(11)	20285(8)	68224(13)	12211(9)	225(5)
C(11a)	20302(8)	53250(13)	13364(8)	204(5)
C(12)	16009(8)	70560(14)	3723(9)	233(5)
O(13)	10607(6)	60565(9)	2204(6)	244(3)
C(14)	9766(9)	26588(14)	9444(10)	252(5)
C(15)	3112(9)	18609(15)	10053(11)	299(6)
C(16)	4689(8)	4393(15)	10313(9)	265(5)
O(17)	9603(8)	-604(11)	8264(9)	577(6)
O(18)	-168(6)	-2283(10)	13136(7)	356(4)
C(19)	849(12)	-16109(17)	13629(14)	402(7)
O(20)	12670(6)	37725(11)	-6489(7)	352(4)
C(21)	28784(9)	33047(16)	15983(10)	287(6)

* Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor

Table 2. Bond lengths (Å)

C(1)-C(2)	1.501(2)	C(1)-C(11a)	1.555(2)
C(2)-C(3)	1.319(2)	C(3)-C(4)	1.507(3)
C(4)-C(4a)	1.537(2)	C(4)-C(14)	1.534(2)
C(4a)-C(5)	1.547(2)	C(4a)-C(11a)	1.574(2)
C(4a)-O(13)	1.458(2)	C(5)-C(6)	1.462(2)
C(5)-O(20)	1.219(2)	C(6)-C(7)	1.324(2)
C(7)-C(7a)	1.513(2)	C(7a)-C(8)	1.535(2)
C(7a)-C(11a)	1.562(2)	C(7a)-C(21)	1.540(2)
C(8)-C(9)	1.492(2)	C(9)-C(10)	1.317(2)
C(10)-C(11)	1.494(2)	C(11)-C(11a)	1.565(2)
C(11)-C(12)	1.512(2)	C(12)-O(13)	1.426(2)
C(14)-C(15)	1.524(2)	C(15)-C(16)	1.502(2)
C(16)-O(17)	1.189(2)	C(16)-O(18)	1.334(2)
O(18)-C(19)	1.446(2)		

Table 3. Bond angles (°)

C(2)-C(1)-C(11a)	113.1(1)	C(1)-C(2)-C(3)	120.6(2)
C(2)-C(3)-C(4)	120.1(2)	C(3)-C(4)-C(4a)	108.6(1)
C(3)-C(4)-C(14)	111.9(1)	C(4a)-C(4)-C(14)	113.7(1)
C(4)-C(4a)-C(5)	112.0(1)	C(4)-C(4a)-C(11a)	116.4(1)
C(5)-C(4a)-C(11a)	115.4(1)	C(4)-C(4a)-O(13)	104.4(1)
C(5)-C(4a)-O(13)	100.5(1)	C(11a)-C(4a)-O(13)	105.9(1)
C(4a)-C(5)-C(6)	117.6(1)	C(4a)-C(5)-O(20)	119.9(1)
C(6)-C(5)-O(20)	122.2(2)	C(5)-C(6)-C(7)	121.0(2)
C(6)-C(7)-C(7a)	122.8(1)	C(7)-C(7a)-C(8)	109.7(1)
C(7)-C(7a)-C(11a)	110.3(1)	C(8)-C(7a)-C(11a)	110.3(1)
C(7)-C(7a)-C(21)	104.9(1)	C(8)-C(7a)-C(21)	107.7(1)
C(11a)-C(7a)-C(21)	113.8(1)	C(7a)-C(8)-C(9)	112.0(1)
C(8)-C(9)-C(10)	121.5(1)	C(9)-C(10)-C(11)	124.1(1)
C(10)-C(11)-C(11a)	116.3(1)	C(10)-C(11)-C(12)	114.9(1)
C(11a)-C(11)-C(12)	105.5(1)	C(1)-C(11a)-C(4a)	111.6(1)
C(1)-C(11a)-C(7a)	110.5(1)	C(4a)-C(11a)-C(7a)	113.7(1)
C(1)-C(11a)-C(11)	107.5(1)	C(4a)-C(11a)-C(11)	102.0(1)
C(7a)-C(11a)-C(11)	111.0(1)	C(11)-C(12)-O(13)	103.9(1)
C(4a)-O(13)-C(12)	107.8(1)	C(4)-C(14)-C(15)	112.3(1)
C(14)-C(15)-C(16)	112.1(1)	C(15)-C(16)-O(17)	125.5(2)
C(15)-C(16)-O(18)	111.9(1)	O(17)-C(16)-O(18)	122.7(1)
C(16)-O(18)-C(19)	116.4(1)		

Table 4. Anisotropic displacement coefficients ($Å^2 x 10^4$)

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	315(9)	250(8)	216(8)	15(7)	96(7)	24(7)
C(2)	390(9)	241(8)	337(9)	56(7)	221(8)	34(7)
C(3)	277(9)	240(8)	403(10)	36(7)	176(8)	49(7)
C(4)	208(8)	218(8)	300(8)	1(6)	65(7)	15(6)
C(4a)	224(7)	168(7)	243(8)	27(6)	66(6)	15(6)
C(5)	292(8)	197(7)	233(8)	18(6)	65(7)	9(6)
C(6)	307(8)	215(8)	247(8)	14(7)	131(7)	-22(6)
C(7)	227(8)	222(8)	303(8)	17(6)	104(7)	-15(6)
C(7a)	226(8)	226(8)	232(8)	17(6)	51(6)	-1(6)
C(8)	254(9)	344(9)	260(9)	14(7)	37(7)	-30(7)
C(9)	321(9)	329(9)	237(8)	-86(8)	68(7)	-74(7)
C(10)	390(9)	223(8)	202(8)	-60(7)	95(7)	-38(6)
C(11)	297(8)	185(7)	217(8)	20(6)	107(6)	-4(6)
C(11a)	241(8)	186(7)	200(7)	12(6)	85(6)	3(6)
C(12)	271(8)	173(8)	259(8)	-3(6)	72(7)	14(6)
O(13)	243(6)	190(5)	284(6)	19(4)	38(4)	42(4)
C(14)	236(8)	209(8)	318(9)	-4(7)	83(7)	17(7)
C(15)	255(9)	255(8)	389(10)	-6(7)	89(8)	36(7)
C(16)	270(8)	264(8)	258(8)	-59(7)	65(7)	-15(7)
O(17)	701(10)	256(6)	1010(12)	-53(6)	648(9)	-83(7)
O(18)	281(6)	252(6)	569(8)	-24(5)	169(6)	70(5)
C(19)	428(11)	249(9)	564(13)	-76(8)	190(10)	12(9)
O(20)	350(6)	395(7)	297(6)	-40(5)	59(5)	-119(5)
C(21)	277(9)	260(9)	322(10)	74(7)	71(8)	37(7)

The anisotropic displacement factor exponent takes the form:

$-2\pi^2(h^2a^{*2}U_{11} + \ldots + 2klb^*c^*U_{23})$

Table 5. H-Atom coordinates ($x10^4$) and isotropic displacement coefficients ($Å^2 x10^3$)

	x	y	z	U
H(1x)	1967(8)	4148(15)	2325(9)	27(4)
H(1y)	2088(8)	5634(15)	2532(9)	25(4)
H(2)	838(9)	5600(16)	2475(10)	36(5)
H(3)	-18(9)	4802(15)	1334(9)	32(5)
H(4)	384(9)	4130(14)	259(9)	25(4)
H(6)	2576(9)	4511(16)	-609(10)	33(4)
H(7)	3482(9)	4937(15)	575(10)	33(4)
H(8x)	3356(9)	5293(15)	2506(10)	34(5)
H(8y)	3889(9)	5131(15)	1971(10)	34(5)
H(9)	3830(9)	7368(16)	1988(10)	37(5)
H(10)	2767(8)	8409(16)	1364(9)	29(4)
H(11)	1729(8)	7190(14)	1553(9)	25(4)
H(12x)	1329(8)	7904(14)	306(8)	20(4)
H(12y)	1901(8)	7000(14)	-10(9)	24(4)
H(14x)	1363(9)	2579(15)	1439(9)	28(4)
H(14y)	1175(8)	2281(15)	529(9)	25(4)
H(15x)	-103(10)	1987(16)	550(11)	44(5)
H(15y)	133(9)	2086(16)	1464(10)	34(5)
H(19x)	545(13)	-1835(21)	1748(14)	76(8)
H(19y)	94(13)	-1957(22)	875(15)	80(8)
H(19z)	-332(13)	-1962(22)	1513(13)	79(8)
H(21x)	2482(9)	2775(15)	1266(9)	29(4)
H(21y)	2877(9)	3144(16)	2153(11)	39(5)
H(21z)	3359(9)	2992(16)	1558(10)	35(5)

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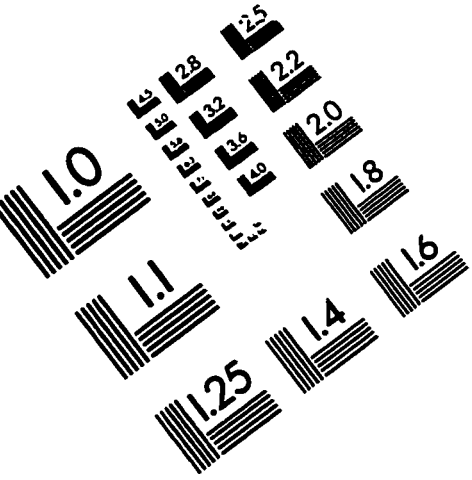
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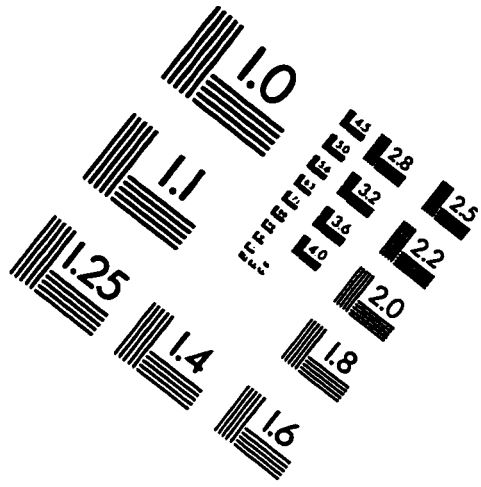
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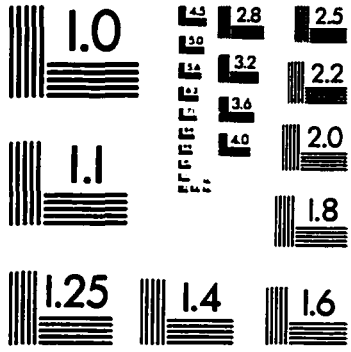
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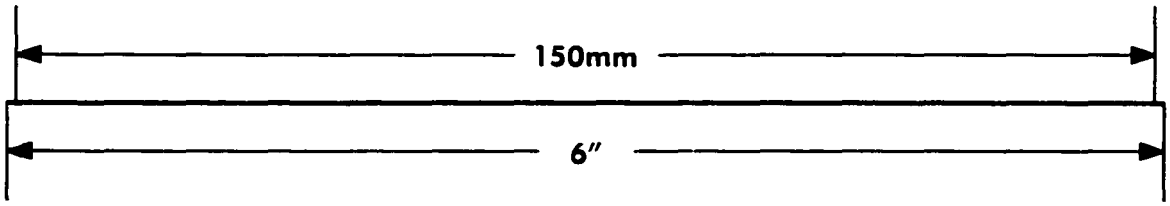
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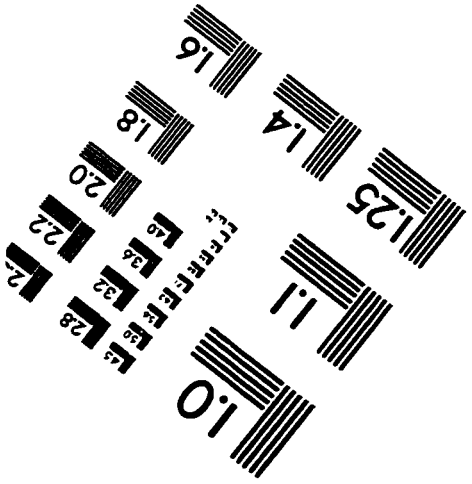
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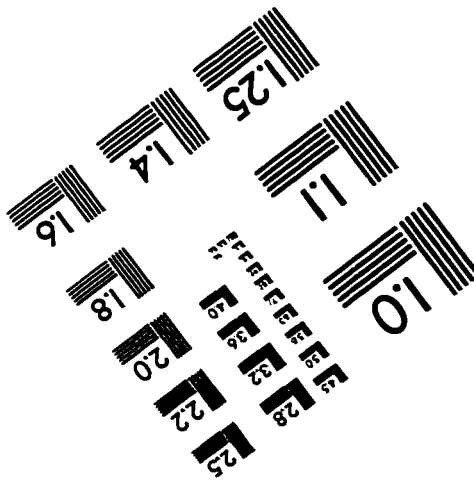












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