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SYNTHETIC STUDIES TOWARDS THE VIRIDIN FAMILY OF STEROIDAL ANTIBIOTICS

by

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A thesis

presented to the University of Waterloo

in fulfillment of the

thesis requirement for the degree of

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in

Chemistry

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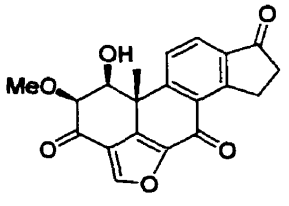
I sincerely thank all the people with whom I worked, proctored, took courses, chatted, drank beer and had chicken wings. They kept me sane and made my life less miserable, and I hope I did the same for them. Last but not least, I would like to thank my wife Rosana for being such an extraordinary person. She rose above and beyond the call of duty by putting up with my frustration, odd hours, bad moods and general stubbornness. Without her this work would never have been completed, and I am truly grateful for all her love and support.

To my beloved wife Rosana,

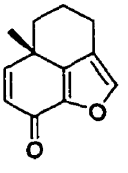
my light and my life.

Abstract

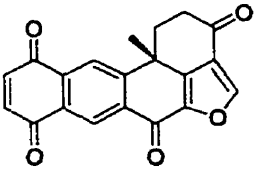
The viridin (**2**) family of fungal metabolites has been known for over 55 years, but it has been the subject of very few synthetic studies, mostly because of the difficulties associated with the synthesis of the ABE fragment **37**. The intramolecular Diels-Alder (IMDA) methodology developed in our laboratory provides a fast route to naphthofuranone **76**, thus making the assembly of the ABE fragment a relatively simple matter. The Diels-Alder reactions of **76** and derived compounds have been examined as a possible route to **2**, but very little success was obtained. Alternatively, the IMDA reactions of benzindanones have also been investigated, ultimately leading to the synthesis of the pentacyclic skeleton of viridin. Epoxidation and singlet oxygen and permanganate oxidations of model compounds were examined in attempts to install the carbonyl on ring A, but that could not be accomplished by any of these methods. Instead, use of diene **201b** in the IMDA reaction followed by hydrolysis of the thioether moiety not only delivered the carbonyl in the desired position, but also led to the shortest synthesis of halenaquinone (**38**) reported to date.



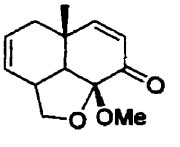
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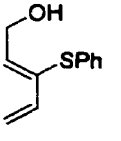
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38



76



201b

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List of Abbreviations and Acronyms

1D	one-dimensional
2D	two-dimensional
Ac	acetyl
Anal.	elemental analysis
Ar	aryl
B^-	base
BHT	butylated hydroxytoluene
Bn	benzyl
br	broad
Bu	butyl
Bz	benzoyl
Calc.	calculated
CAN	ceric ammonium nitrate
COSY	correlated spectroscopy
Cy	cyclohexyl
δ	chemical shift
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
dd	doublet of doublets
ddd	doublet of doublet of doublet
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
ddt	doublet of doublet of triplet
DEAD	diethyl azodicarboxylate
DIBAL	diisobutylaluminum hydride
dm	doublet of multiplets
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
dppf	1,1'-diphenylphosphinoferrocene
dppp	1,3-bis(diphenylphosphino)propane
dq	doublet of quartets
dt	doublet of triplets
E, E^+	electrophile
ee	enantiomeric excess
EI	electron impact
Et	ethyl
EWG	electron withdrawing group
FTIR	Fourier transform infrared
GC/MS	gas chromatography/mass spectrometry
[H]	reduction, hydrogenation
hν	irradiation
HMPA	hexamethylphosphoric triamide

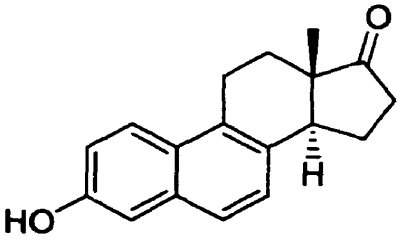
HMQC	heteronuclear multiple quantum coherence
HPLC	high-performance/high-pressure liquid chromatography
HRMS	high resolution mass spectrum
i	*iso, isomeric*
IMDA	intramolecular Diels-Alder
INOC	intramolecular nitrile oxide cycloaddition
IR	infrared
J	coupling constant (units of Hz)
JMOD	*J*-modulated spectrum
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LRMS	low resolution mass spectrum
m	*meta*
m	multiplet
m/z	mass-to-charge ratio
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MOM	methoxymethyl
mp	melting point
Ms	methanesulfonyl
NMR	nuclear magnetic resonance
Nu, Nu^-	nucleophile
[O]	oxidation
p	*para*
PCC	pyridinium chlorochromate
PG	protecting group
Ph	phenyl
PIFA	phenyliodosyl bis(trifluoroacetate)
Piv	pivaloyl
PPA	polyphosphoric acid
ppm	parts per million
Pr	propyl
q	quartet
qn	quintet
Red-Al	sodium bis(2-methoxyethoxy)aluminum hydride
s	singlet
t	*tert, tertiary*
t	triplet
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butylhydroperoxide
Tf	triflate, trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran

TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMS	trimethylsilyl
TPP	tetraphenylporphine
Ts	*para*-toluenesulfonyl

CHAPTER 1 – INTRODUCTION

1.1. Steroids

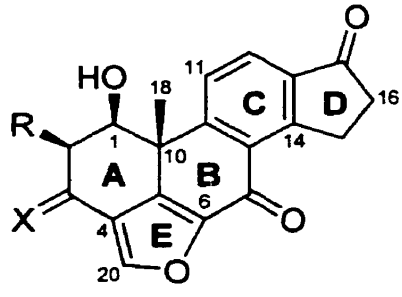
The importance of steroids in nature cannot be overstated. Found in virtually all animals, as well as in plants, they are essential constituents of cell membranes, also possessing important regulatory functions in the secondary metabolism of many multicellular organisms.[1] Not surprisingly, steroids have exerted great fascination for synthetic chemists, with the first total synthesis of the simplest steroid - equilenin (**1**)- dating as far back as 1939[2], just 7 years after the general structure of steroids had been established.[3] Since then, representative examples of most classes of biologically active steroids have been prepared in the laboratory, and routes have been developed to tackle the many synthetic problems posed by those compounds[4]. Despite all the progress made, however, some targets remain elusive, and the challenges posed by steroidal systems to the creativity of synthetic chemists are far from over. In particular, the structures of the viridin family of pentacyclic antibiotics[5] highlight many of the problems in the synthesis of steroidal compounds that are still not resolved, and the following chapters detail our progress in the total synthesis of such compounds.



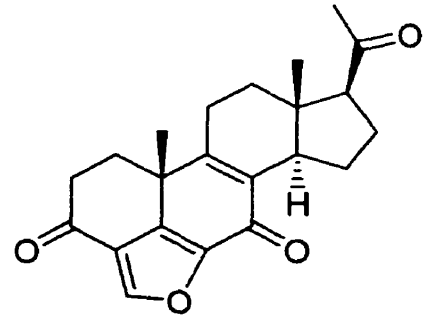
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1.2. The Viridin Family of Fungal Metabolites[5]

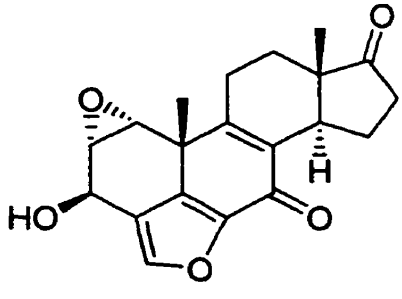
Viridin (**2**) was first isolated in 1945 as a secondary metabolite from the fungus *Gliocladium virens*,[6] and was also found later in fungi of the *Trichoderma* genus. Extensive chemical degradation studies,[7] aided by ^{1}H NMR spectroscopy[7e] and later by X-ray crystallography,[8] led to the determination of the structure of **2**, which contains a furan ring fused between C-4 and C-6 of a steroidal framework, an unusual feature that defined a whole new class of compounds.[5] Other unusual features present in **2** are the highly oxygenated ring A and the aromatic ring C. In biological essays **2** showed remarkable species specific fungistatic action, but no significant antibacterial activity.[9]



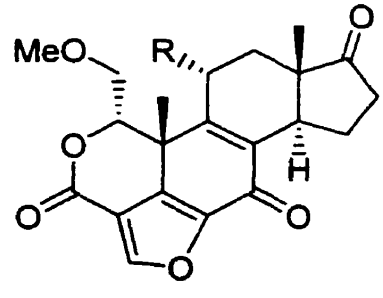
2: Viridin (X = O; R = OMe)
3: Demethoxyviridin (X = O; R = H)
4: Viridiol (X = α-H, β-OH; R = OMe)
5: Demethoxyviridiol (X = α-H, β-OH; R = H)



6: Virone



7: Wortmanolone

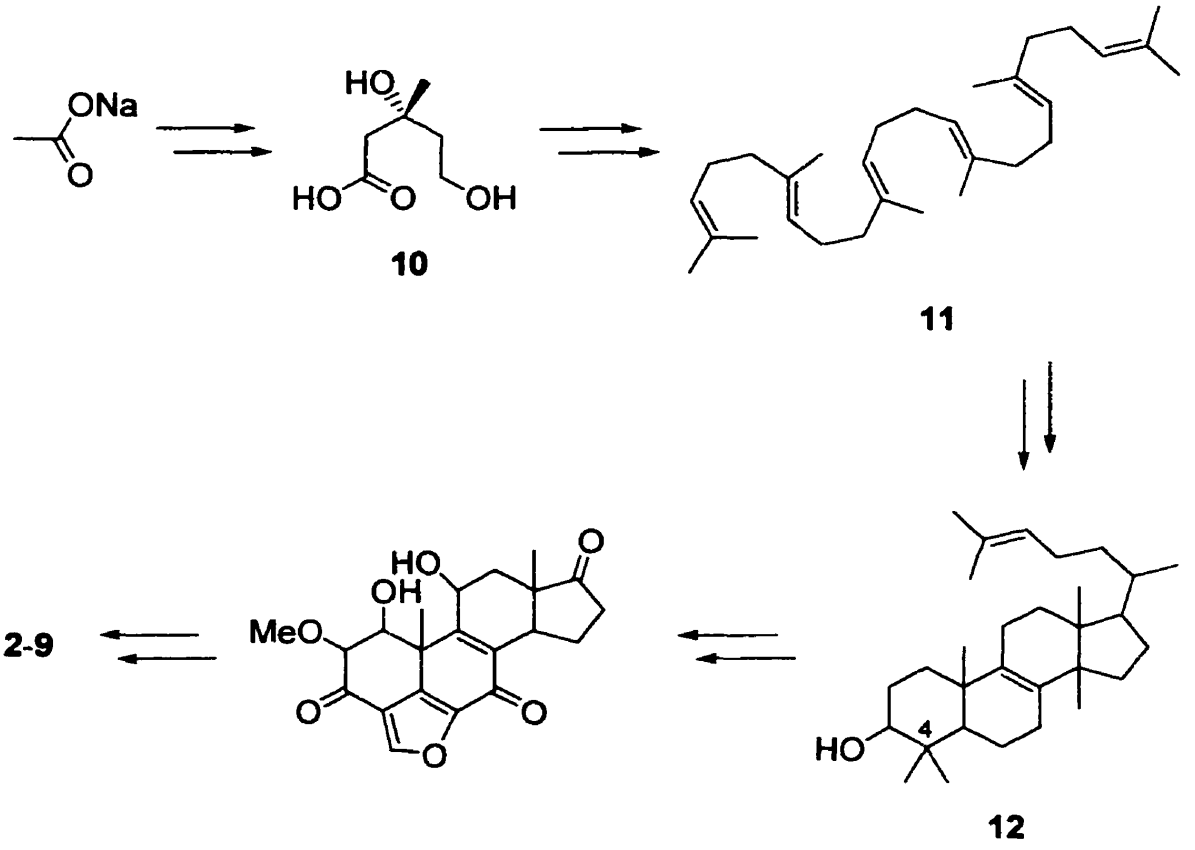


8: Wortmannin (R = OAc)
9: 11-Desacetoxywortmannin (R = H)

A number of species of fungi have yielded several other related metabolites: *Gliocladium sp.* also yielded viridiol (**4**)[10] and virone (**6**);[11] demethoxyviridin (**3**)[12] and demethoxyviridiol (**5**)[13] were isolated from *Nodolisporium hinnuleum* and wortmannolone (**7**),[11] wortmannin (**8**)[14] and 11-desacetoxywortmannin (**9**)[15] were found in *Penicillium sp.*, with **8** also being isolated from *Myrothecium roridium.*[16] While some of these compounds exhibited little antifungal or phytotoxic activity,[12,13,17] **5**, **8** and **9** are noteworthy exceptions. Both **8** and **9** are potent anti-inflammatory agents,[18] **5** and **8** have been shown to inhibit some phospholipases,[19] and **8** has also attracted some attention as a potent inhibitor of phosphatidylinositol 3-kinase in guinea pigs' neutrophils[20] and also the kinase[21] of smooth muscle.

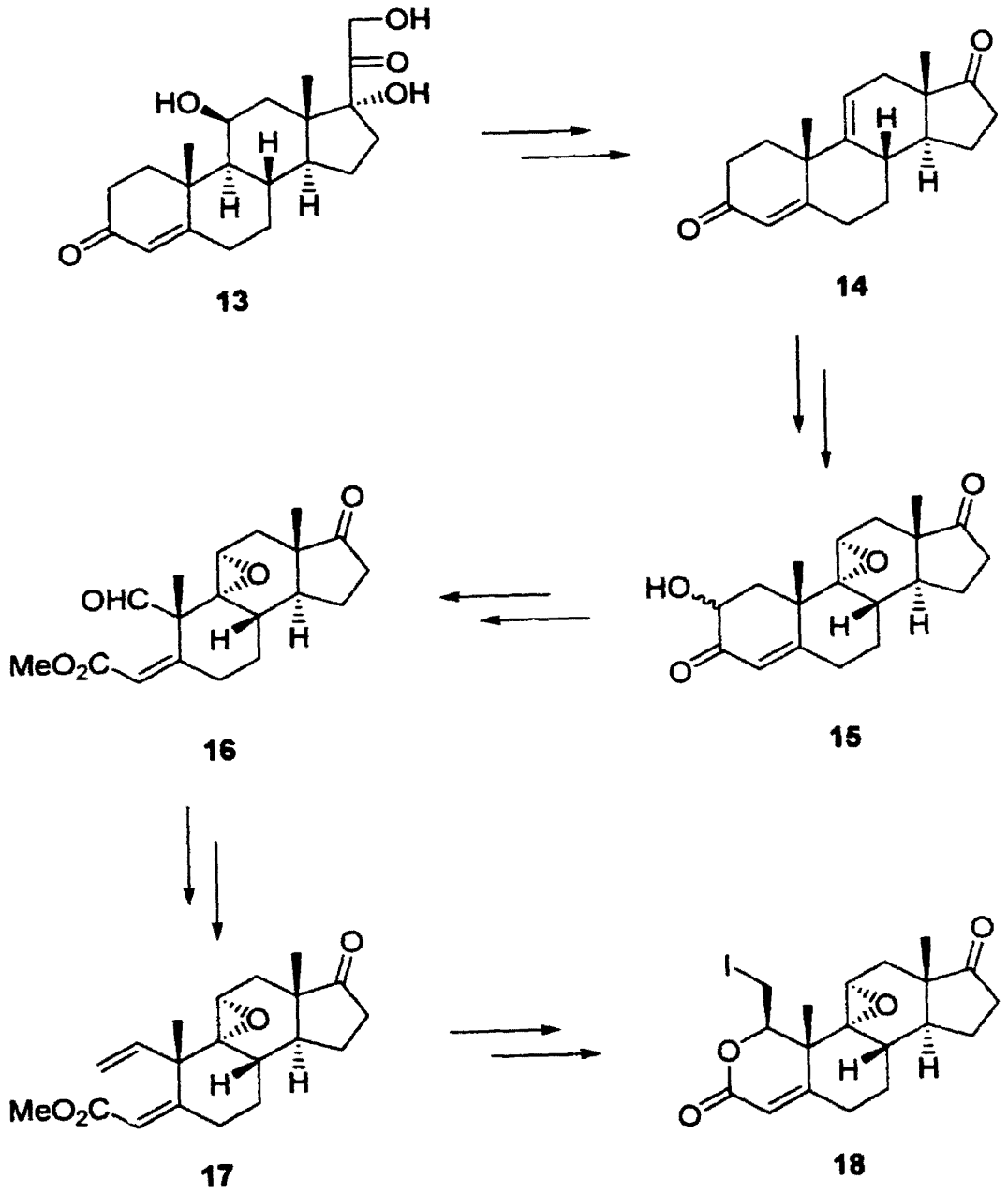
Investigations of the patterns of incorporation of isotopically labeled acetate and mevalonic acid (**10**) by fungal cultures showed that compounds **2-9** are synthesized in much the same way as mammalian steroids, with squalene (**11**) and lanosterol (**12**) as intermediates (Scheme 1.1).[22] Further investigations suggest that the cleavage of the steroidal side chain and the order of removal of the C-4 methyl groups from **12** are also consistent with the biosynthetic pathways of steroids in mammals. Despite these similarities, the fungal metabolites are regarded as triterpenes in origin, since C-20 of ring E can be traced back to one of the C-4 methyl groups of **12**,[22c,e] and only compounds with both C-4 methyl groups removed are classified as steroids.

Scheme 1.1

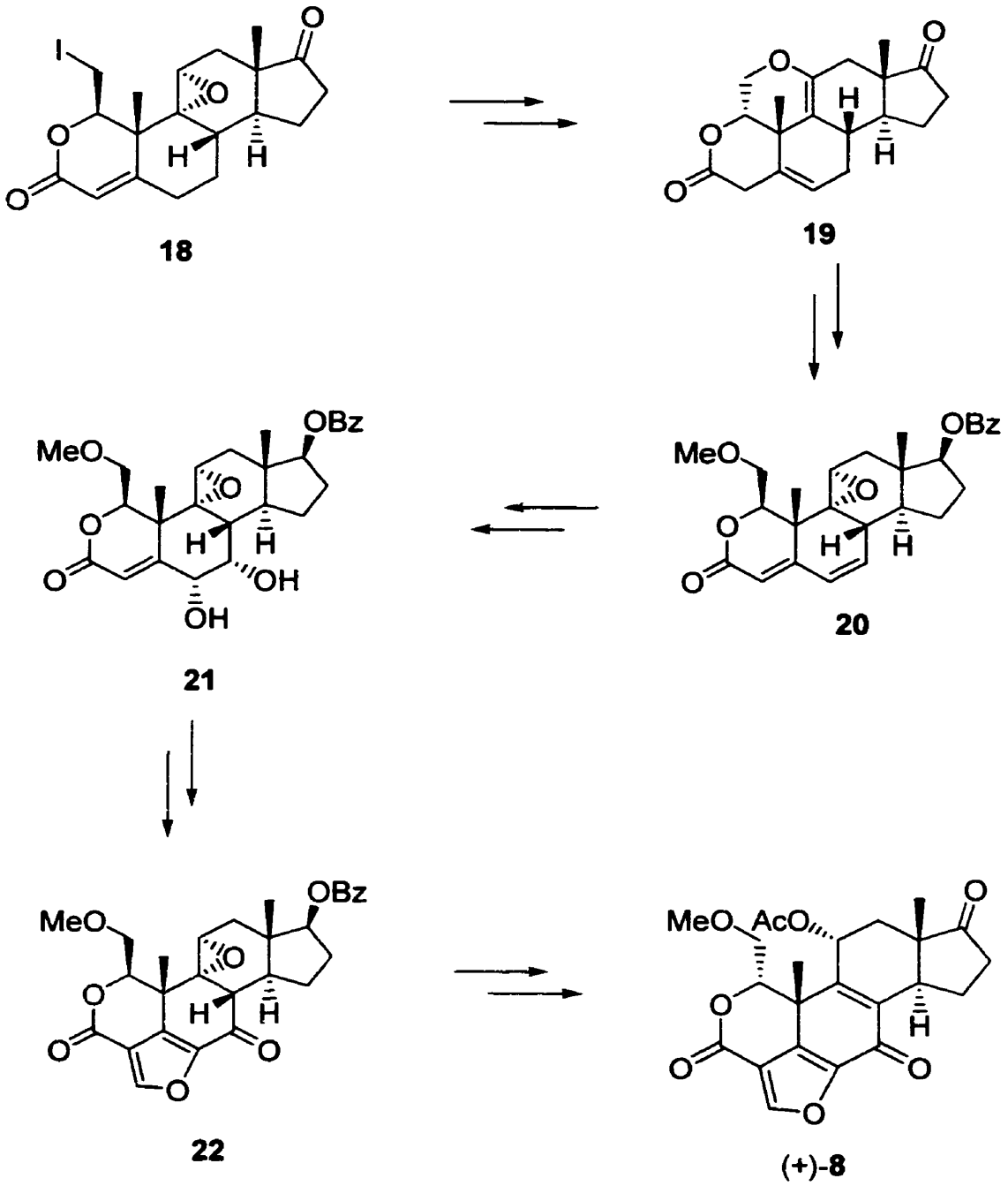


Although the viridin family of fungal metabolites has been known for over fifty years, only the synthesis of **8** has been reported so far (Scheme 1.2), albeit through a long and low yielding route.[23] Starting from hydrocortisone (**13**), dehydration and oxidative cleavage of the steroidal side chain gave **14**, which was then oxidized to **15**. Treatment with $NaIO_4$ gave tricyclic compound **16**, and **17** was formed by converting the aldehyde moiety into an alkene. Iodolactonization affords **18**, which is transformed into **19** in 4 steps (Scheme 1.3). A sequence of cleverly engineered oxidation and reduction steps generates **20**, which is first oxidized to **21** and then converted to **22**. A series of protecting group manipulations and oxidation of the alcohol functionality on ring D finally gives **8** in approximately 0.04% yield over 34 steps.

Scheme 1.2

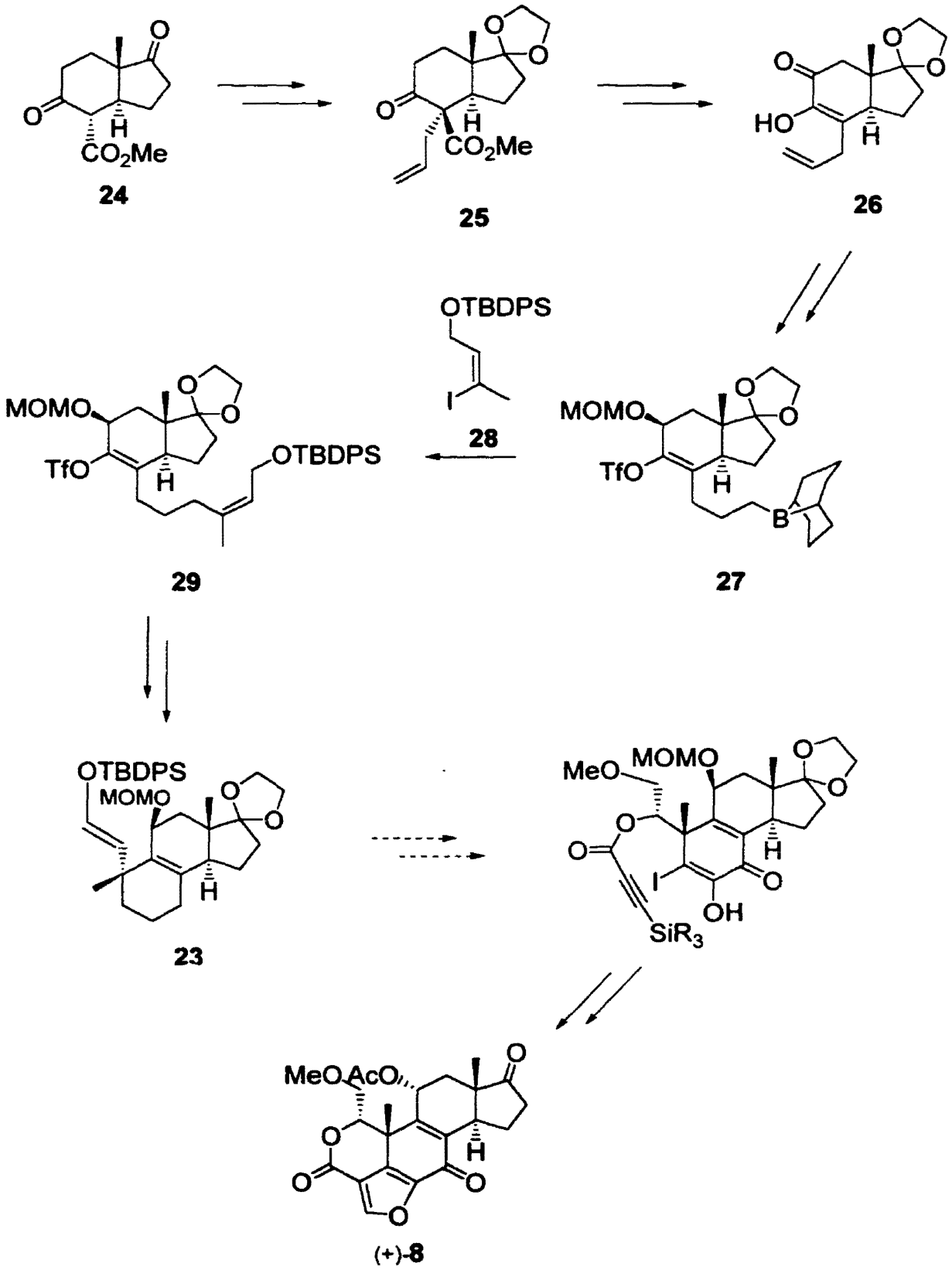


Scheme 1.3



The obvious shortcomings of Shibasaki's synthesis led him to investigate an alternative approach to the preparation of **8**.[24] Building on his successful asymmetric synthesis of halenaquinone (*vide infra*),[25] he devised a new synthetic route (Scheme 1.4),

Scheme 1.4



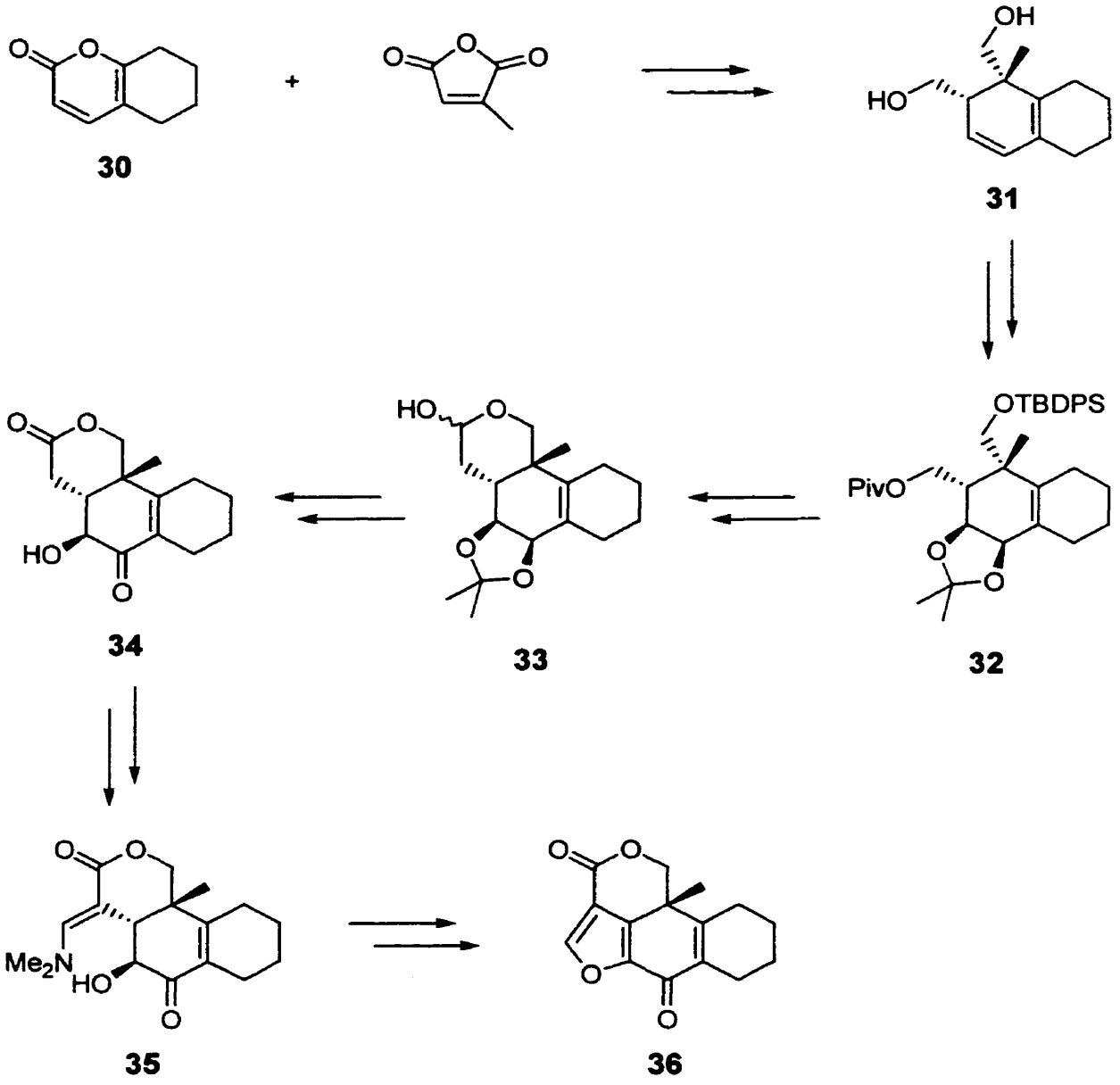
which so far has reached intermediate **23**. Known diketoester **24**[26] is alkylated, then selectively protected to give **25**, which is decarboxylated and subsequently oxidized to diketone **26**. Compound **27** is generated in 4 more steps, after which a Suzuki cross-coupling with iodide **28** produces triflate **29**. Conversion to **23** is achieved via an intramolecular Heck reaction, and the remaining steps still to be completed – and presumably leading to wortmannin (**8**) - are only presented in the retrosynthetic analysis, without any detail.

The synthesis of a simplified analogue of **8** and **9** has also been reported (Scheme 1.5).[27] Thus, lactone **30**[28] is reacted with citraconic anhydride, and the resulting Diels-Alder adduct is reduced to give diol **31**. Selective hydroxylation together with protecting group manipulations give acetonide **32**, which is converted into hemiacetal **33** in 5 steps. Further oxidation yields lactone **34**, which gave enamine **35** upon reaction with tris(dimethylamino)methane. Oxidation of **35** to a diketone followed by treatment with acid gives tetracycle **36**, which corresponds to the ABCE fragment of **8** and **9**. Based on this strategy, the authors have also presented a retrosynthetic plan to **8**, but the actual synthesis is yet to be reported. This brief account represents the total synthetic effort hitherto recorded towards viridin (**2**), wortmannin (**8**) and related natural products, thus hinting at how much research is still necessary in this field.

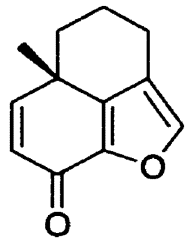
1.3. Natural Products Structurally Related to Viridin

Although viridin and related compounds are an unique class of compounds, they share the tricyclic naphthofuran moiety **37** (rings A, B and E) with a group of polycyclic quinones isolated from tropical marine sponges. The first such natural product to be

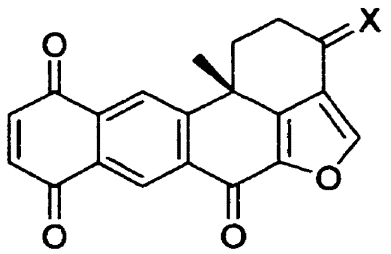
Scheme 1.5



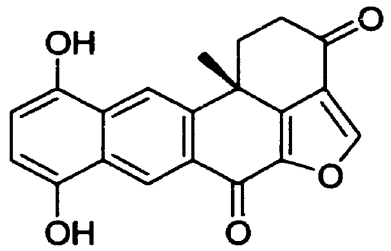
reported was halenaquinone (**38**),[29] obtained from *Xestospongia exigua*, with *X. sapra* later yielding xestoquinone (**39**)[30] and halenaquinol (**40**).[31] Adociaquinones A (**41**) and B (**42**) were isolated from sponges of the species *X. carbonaria*,[32] and in recent years several other quinones based on the parent pentacyclic ring system 1*H*-benzo[6,7]phenanthro[10,1-*bc*]furan have also been characterized.[33]



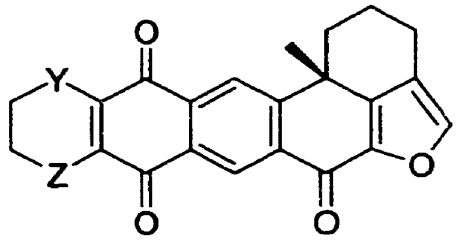
37



38: X = O
39: X = H, H



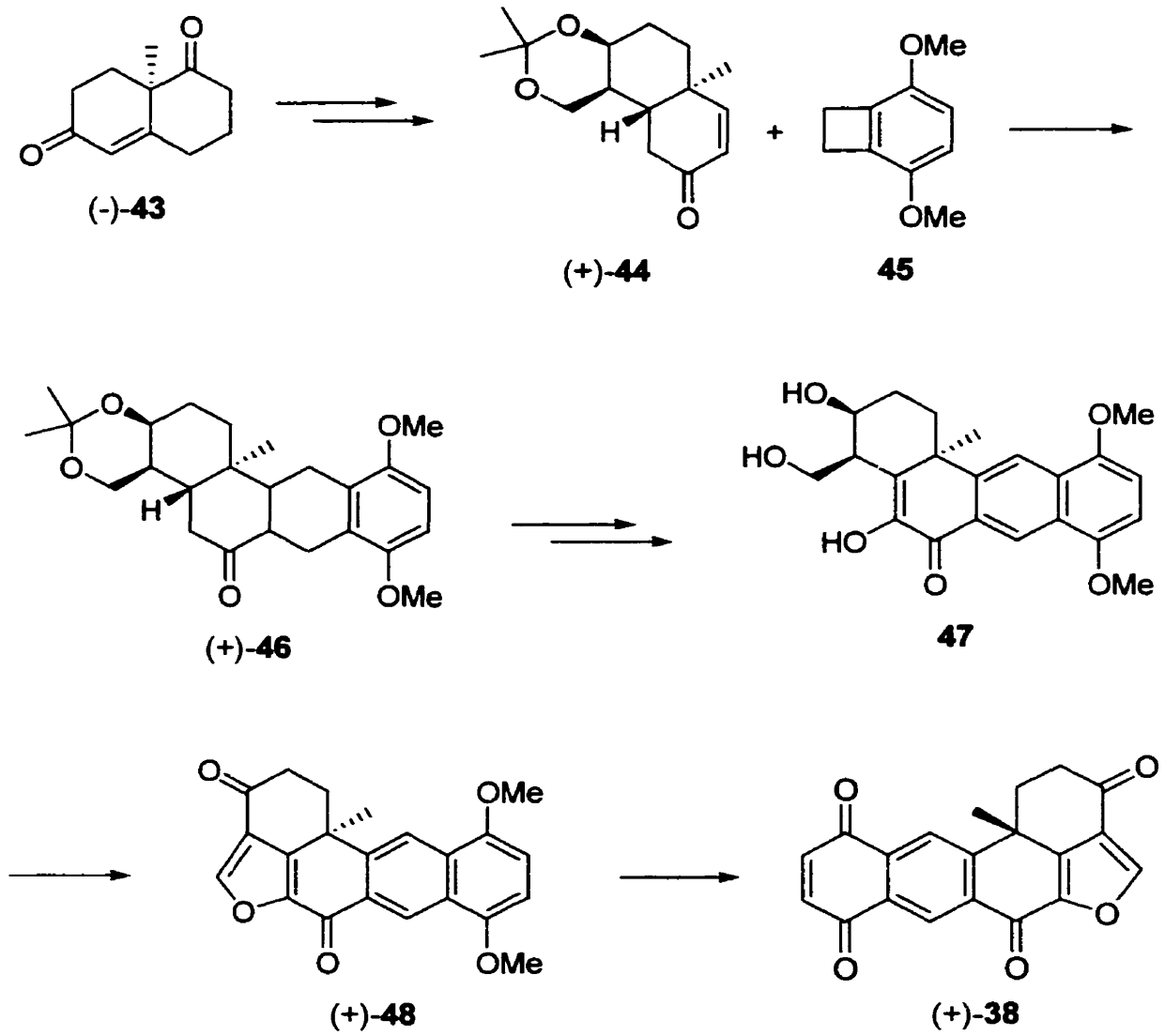
40



41: Y = NH; Z = SO_2
42: Y = SO_2; Z = NH

Halenaquinone (**38**) was first investigated for its antibacterial activity,[29] but much more interest in it has arisen from its inhibitory effect on some tyrosine kinases, a property also shared by **40**.[33a,34] Tyrosine kinases have been associated with regulation of cell growth, and the discovery of effective inhibitors may have implications on the development of treatments for proliferative diseases, such as cancer and psoriasis. Compounds **39**, **41** and **42**, on the other hand, have been shown to inhibit topoisomerase II,[33b,35] an enzyme involved in the replication of DNA that plays a role in the proliferation of cancer cells.[36] In addition, **39** is also a powerful cardiotonic agent due to its positive inotropic effect on cardiac muscle.[30,37]

Scheme 1.6

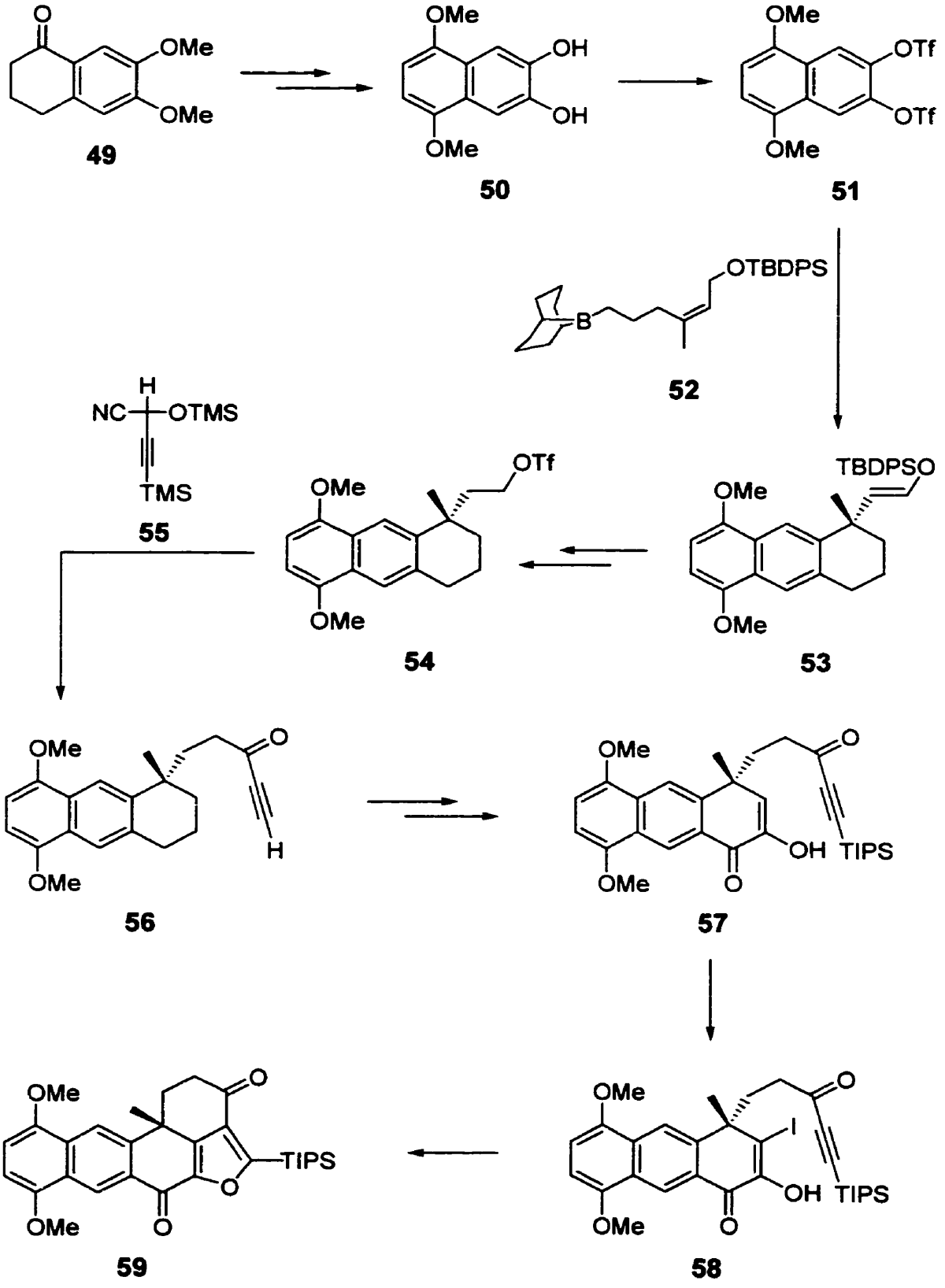


Compared to the fungal metabolites, the marine quinones are much more accessible synthetic targets, and, given their much more interesting biological properties, it is not surprising that several total syntheses of such compounds have been reported. Despite the structural differences, an analysis of such syntheses is indeed relevant to the present work, particularly those steps concerned with the preparation of the tricyclic ABE moiety **37** or its equivalent.

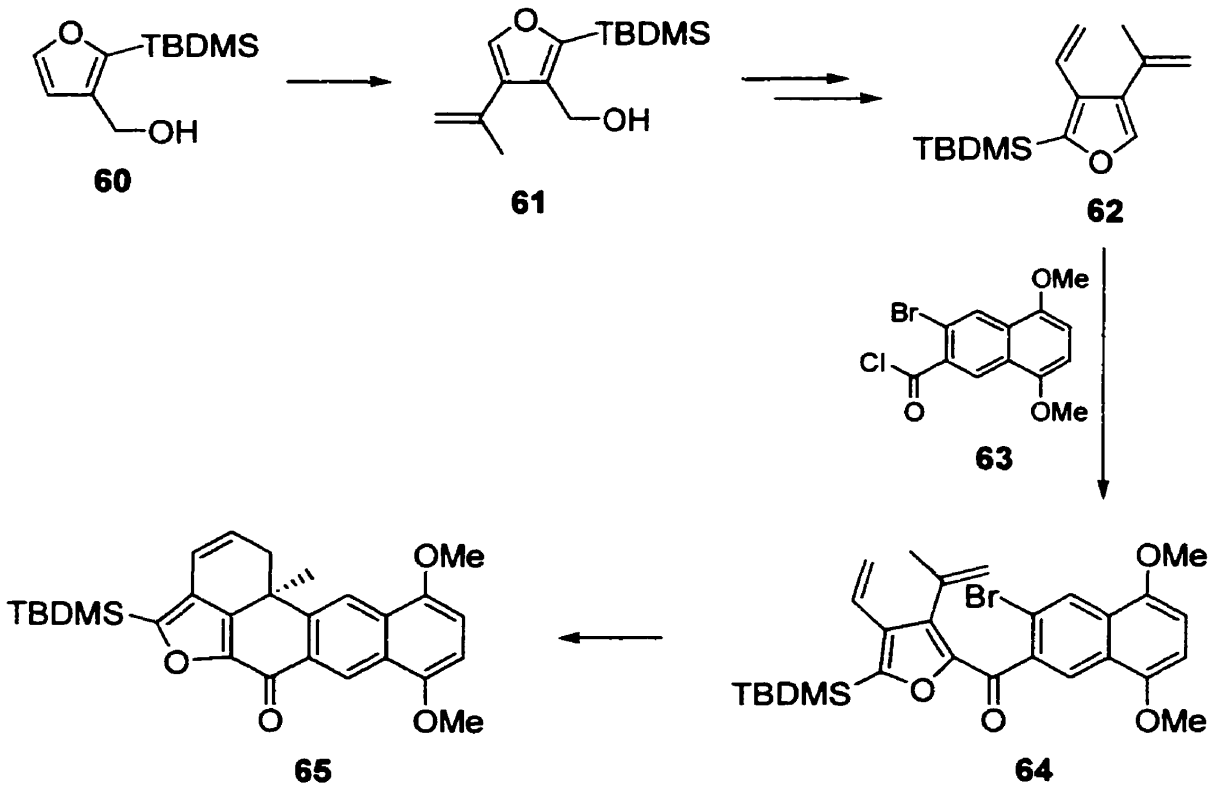
The first successful synthetic effort towards the marine quinones was Harada's synthesis of (+)-**38**[38] (Scheme 1.6). Starting from optically pure Wieland-Miescher ketone (-)-**43**,[39] enone (+)-**44** was assembled in 8 steps and then subjected to a Diels-Alder reaction with the *ortho*-quinodimethane generated *in situ* from **45** to afford tetracycle (+)-**46**. After the aromatization of ring C, air oxidation and removal of the acetonide protecting group gave diosphenol **47**, which, upon Pfitzner-Moffatt oxidation of the alcohol moieties, spontaneously dehydrates to form (+)-**48**. Finally, deprotection of the hydroquinone dimethyl ether moiety by oxidative cleavage gave (+)-**38** in approximately 2% yield over 14 steps. Reduction of the quinone ring in (+)-**38** gave (+)-**40**,[40] and slight modifications to Harada's procedure led to the synthesis of (+)-**39**, from which both **41** and **42** were also prepared.[41]

The asymmetric synthesis of **38** and **40** has also been achieved by Shibasaki (Scheme 1.7).[25] Commercially available tetralone **49** was oxidized to dihydroxynaphthalene **50**, which was then transformed into ditriflate **51**. A cascade Suzuki cross-coupling / asymmetric Heck reaction between **51** and alkylborane **52** gave tricycle **53**, subsequently converted to triflate **54**. Acetylene **55** was then used as an acyl anion equivalent to produce ketone **56**, which was converted into compound **57** via a lengthy sequence of oxidations and protecting group manipulations. Iodination of **57** gives the highly functionalized **58**, which undergoes a palladium catalyzed cyclization to produce pentacycle **59** and, after desilylation, **48** was obtained. The remainder of the synthesis was carried out according to the procedure described by Harada,[38] giving (+)-**38** in less than 2% yield over 21 steps.

Scheme 1.7


O
OMe
OMe
49
OMe
OH
OH
OMe
50
OMe
OTf
OTf
OMe
51
OTBDPS
B
52
H
NC
OTMS
TMS
55
OTf
OMe
OMe
54
TBDPSO
OMe
OMe
53
OMe
O
H
OMe
56
OMe
O
OH
TIPS
OMe
O
57
OMe
O
I
OH
TIPS
OMe
O
58
OMe
O
TIPS
O
OMe
O
59

Scheme 1.8

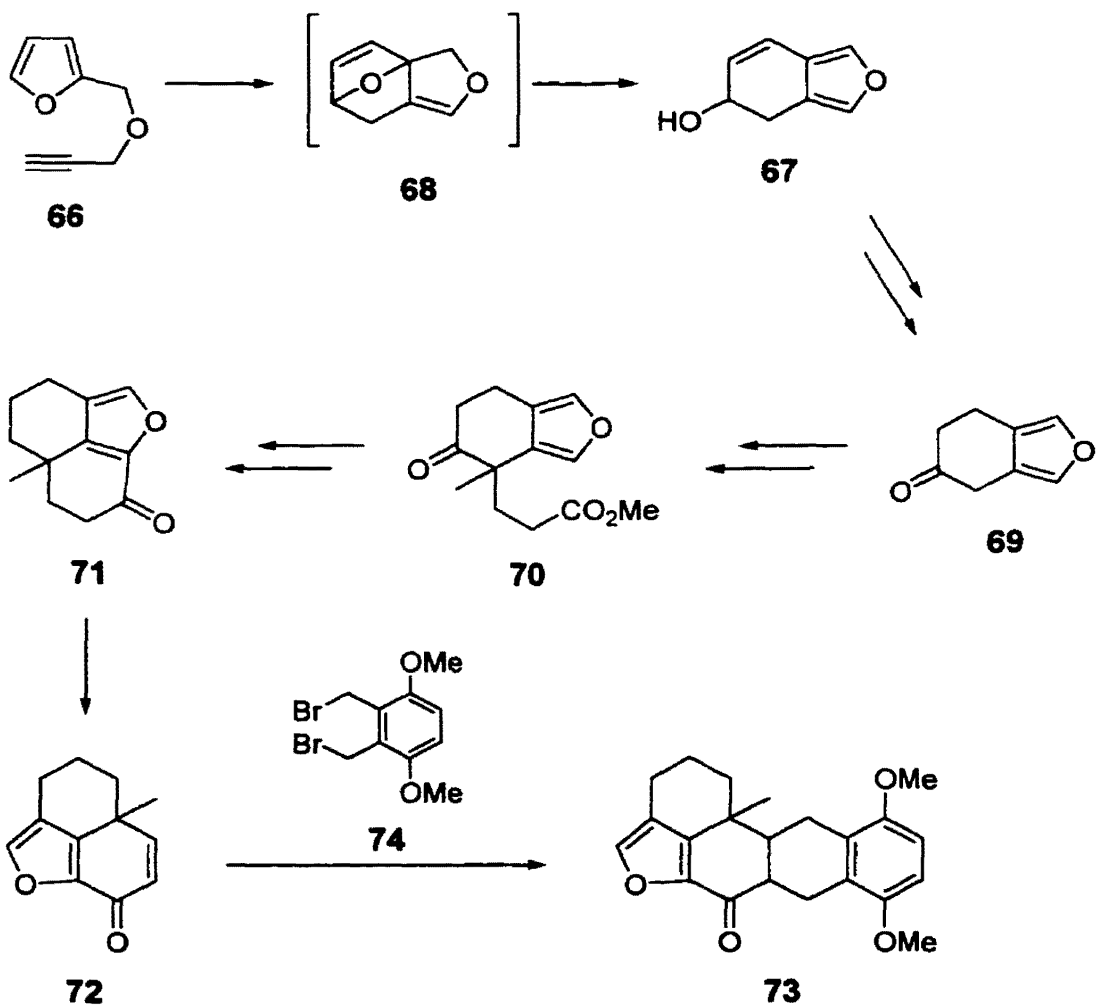


Xestoquinone (**39**) has also been the subject of an asymmetric synthesis by Keay (Scheme 1.8),[42] who started from the readily available furyl alcohol **60**. Lithiation of **60** followed by an *in situ* Suzuki cross-coupling[43] led to furan **61**, which was converted to **62** by an oxidation-Wittig reaction sequence. The α-anion of **62** was then condensed with acid chloride **63** to give ketone **64**, which was then subjected to a palladium catalyzed asymmetric polyene cyclization[44] that produced pentacycle **65** in 68% ee. Reduction of the double bond on ring A, desilylation of the furan moiety and oxidation of ring D to a *para*-quinone gave **39** in 11% yield over 11 steps.

An interesting route to **39** has been examined by Kanematsu (Scheme 1.9).[45] Using the previously developed furan ring transfer methodology,[46] furan **66** was

converted in one pot into bicyclic alcohol **67** via intermediate **68**. Reduction of the double bond and subsequent oxidation gave ketone **69**, which was doubly alkylated to give compound **70**. Reductive deoxygenation followed by an intramolecular Friedel-Crafts acylation produced ketone **71**, later converted to enone **72** through the application of selenium chemistry. Pentacycle **73** was assembled in a Diels-Alder reaction between **72** and an *ortho*-quinodimethane generated *in situ* from dibromide **74**,[47] and after two more steps gave **39** in 1.5% yield over 11 steps.

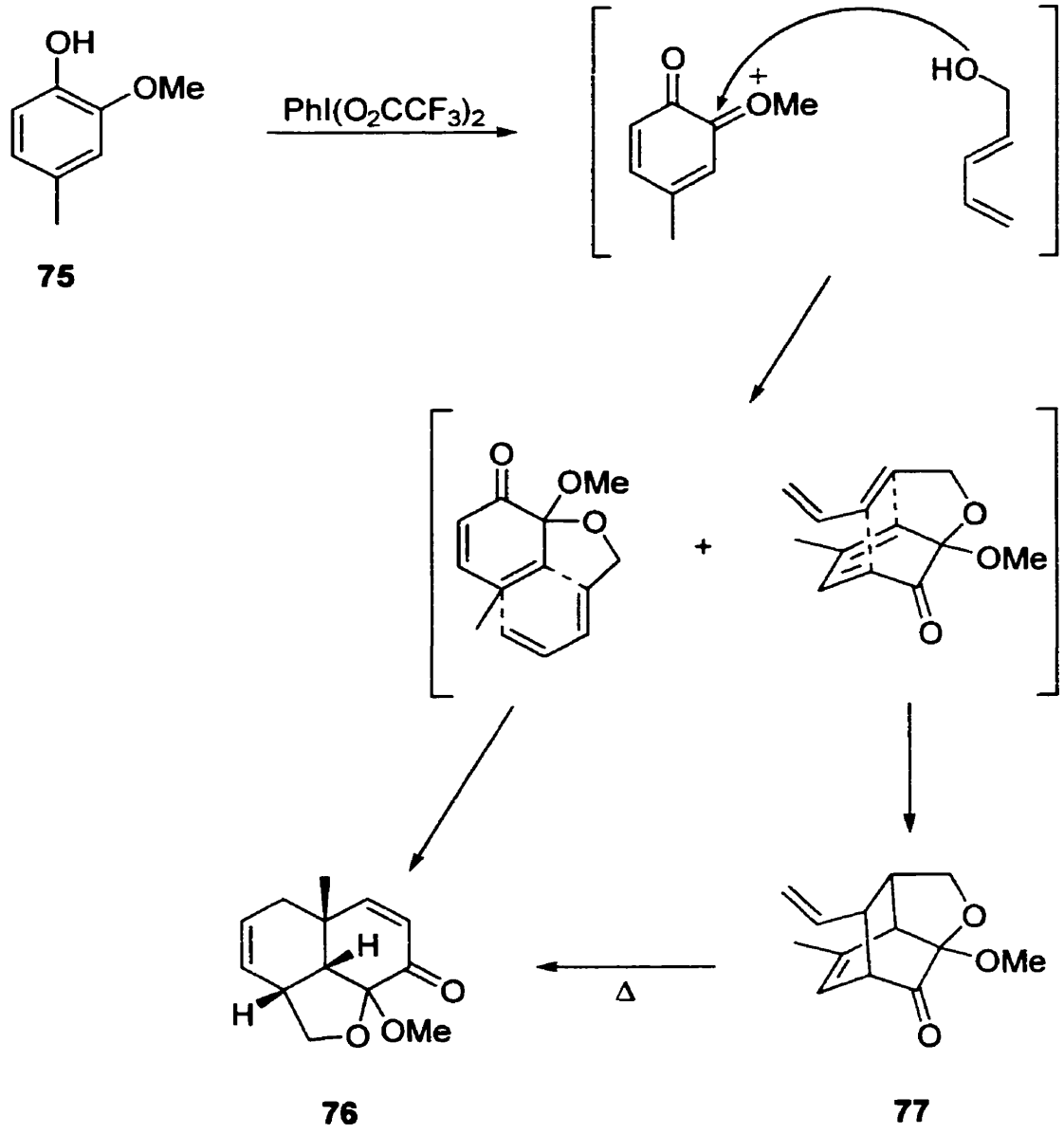
Scheme 1.9



While the syntheses discussed so far are elegant ways to achieve their respective targets, their adaptation to a general route to viridin and related metabolites is difficult, since the furanoid ring E is in all cases assembled as a fully unsaturated moiety, which severely limits further oxidative transformations on the molecule and, as a result, requires the preparation of highly functionalized starting materials.

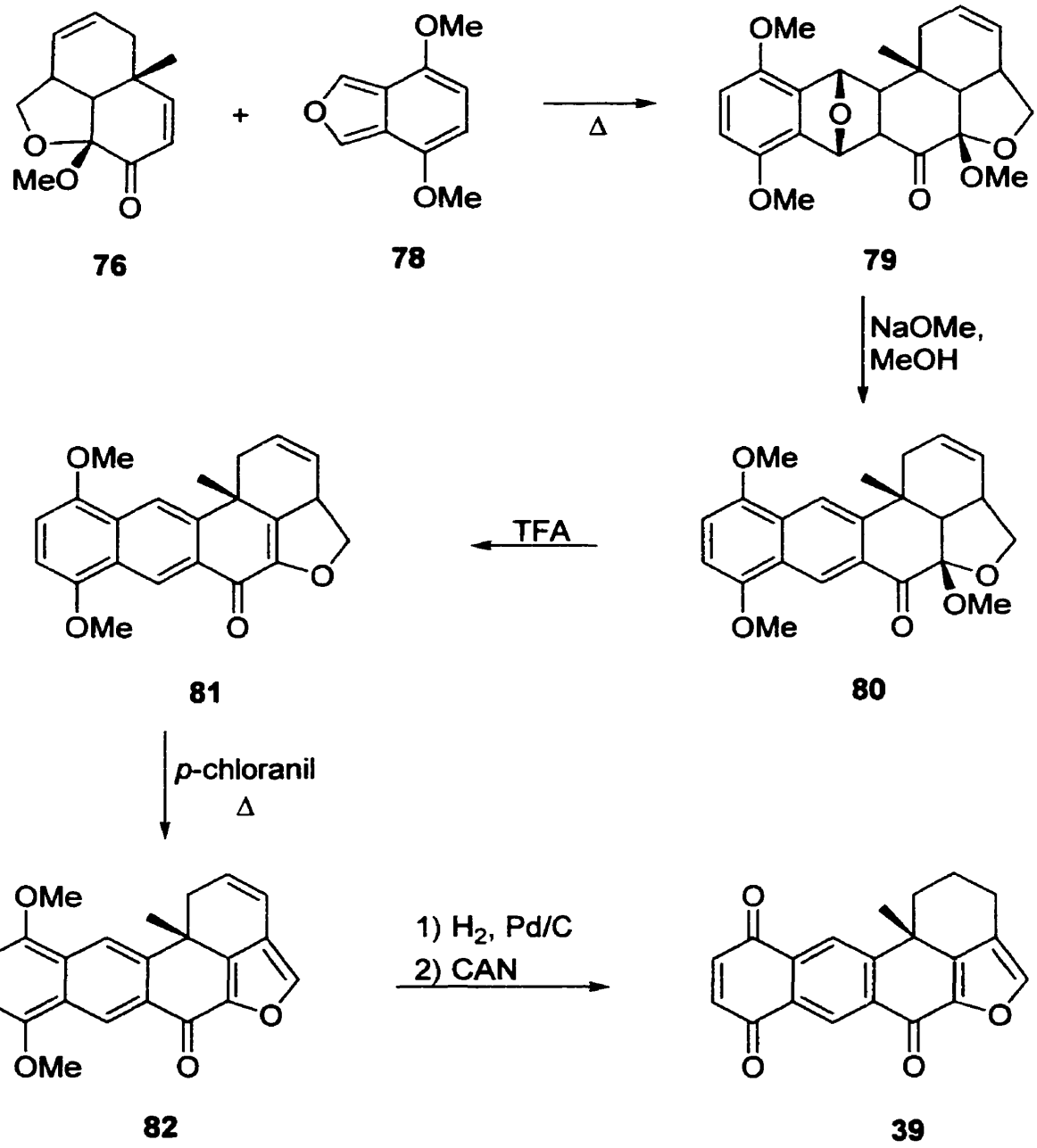
Such limitations, however, have been mitigated by Rodrigo's synthesis of **39**.[48] Commercial phenol **75** is oxidized by hypervalent iodine in the presence of 2,4-pentadien-1-ol to give the *ortho*-quinone monoketal (Scheme 1.10). Depending on whether the quinone moiety acts as a dienophile or diene, an intramolecular Diels-Alder (IMDA) reaction gives naphthofuranone **76** or bridged adduct **77**,[49] both as single diastereomers. Compound **76** corresponds to the kinetically favored *endo* adduct, and the stereochemistry of **77** is a direct result of the tethering of the dienophile to the quinone ring. While the yields of tricycle **76** were generally low, a Cope rearrangement in refluxing 1,2,4-trimethylbenzene converts **77** into **76**, once again forming only the *endo* isomer to give a combined yield of 57% over two steps. Isobenzofuran **78**[50] is then reacted with naphthofuranone **76** to give compound **79** (Scheme 1.11), which is aromatized to pentacycle **80** by reaction with sodium methoxide in refluxing methanol. Treatment with TFA forms enone **81**, and the furan moiety is aromatized to **82** by reacting with *para*-chloranil in refluxing xylene. Hydrogenation of the double bond on ring A and oxidation of ring D using CAN then gives **39** in 18% yield over eight steps, the shortest and highest yielding synthesis for any of these marine quinones to date.

Scheme 1.10



75 **76** **77**

Scheme 1.11



76 **78** **79** **80** **81** **82** **39**

1.4. Synthetic Strategies towards the Viridin Family of Fungal Metabolites

The development of the IMDA methodology[49] corresponds to a significant step towards the synthesis of the viridin family of fungal metabolites. Besides providing a fast and high yielding way of assembling the ABE fragment without the aromatized furan ring, it also provides the double bond in ring A as a convenient handle for prospective subsequent oxidative functionalization of the molecule. Thus, the synthesis of viridin and related compounds can now be approached from two fronts (Figure 1.1): reacting naphthofuranone **76** with a suitable diene (route **a**) or preforming the BCD fragment and then reacting it with 2,4-pentadien-1-ol (route **b**). Both routes, as well as our attempts to functionalize ring A will be discussed in the next chapters.

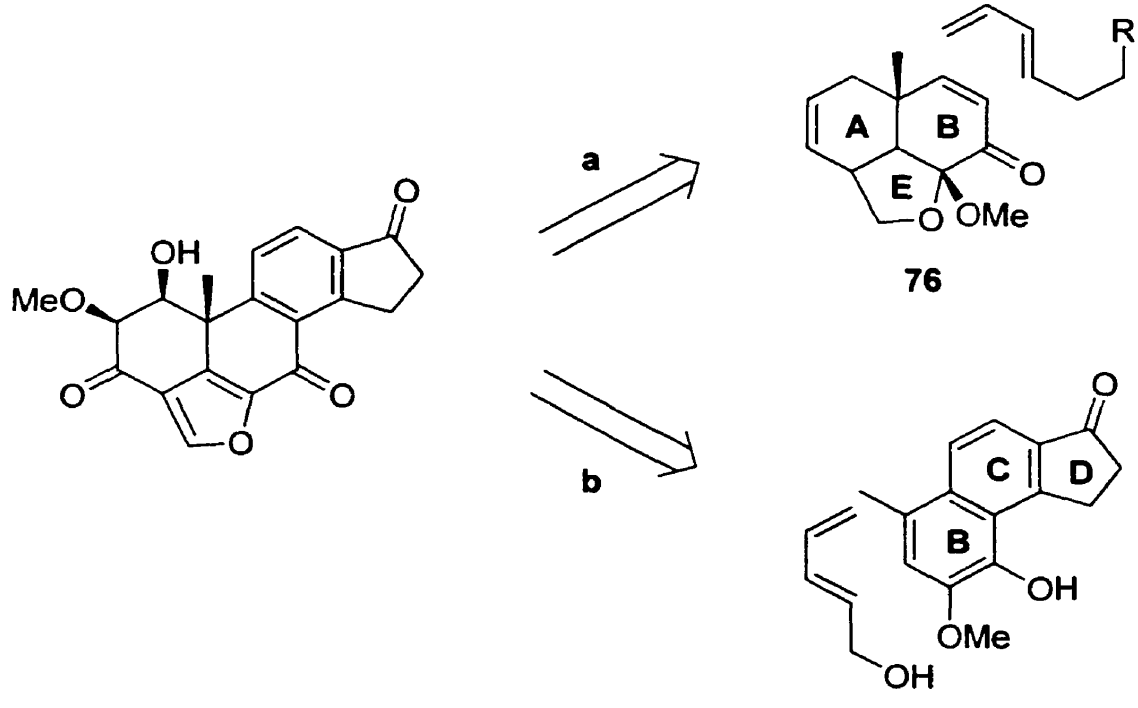


Figure 1.1: Possible approaches towards viridin and related compounds

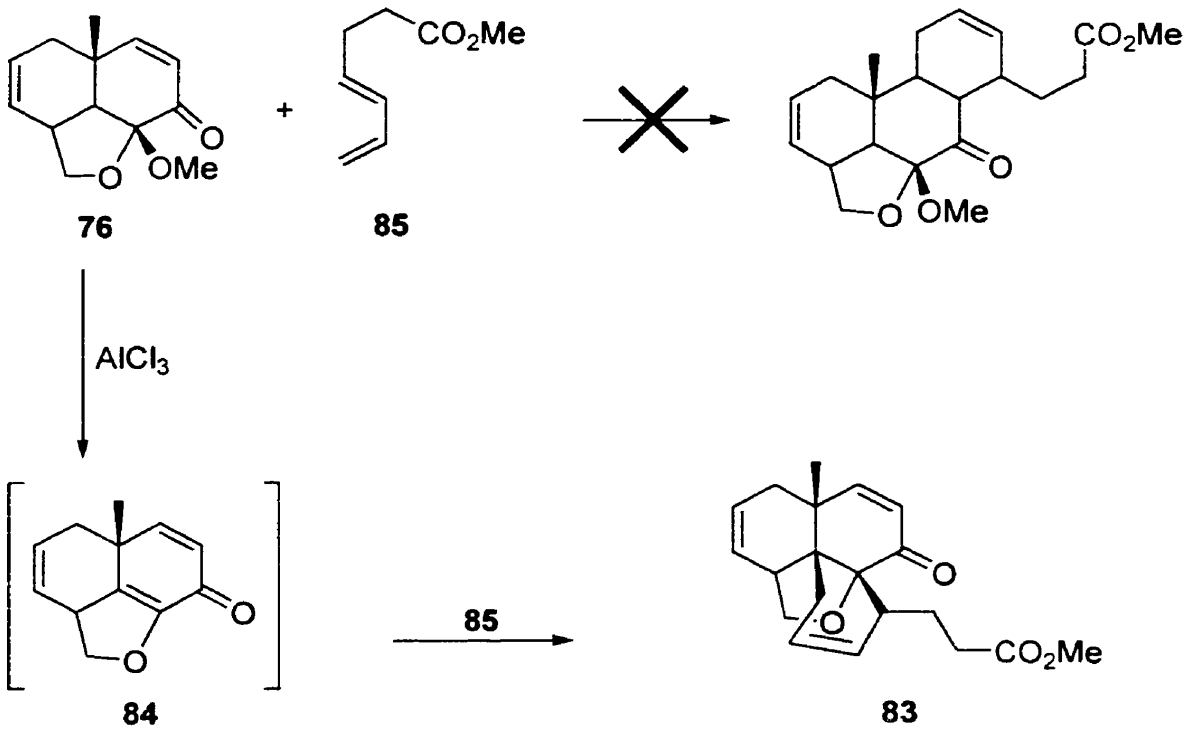
CHAPTER 2 – THE ABE NAPHTHOFURANONE APPROACH

2.1. Preliminary Studies

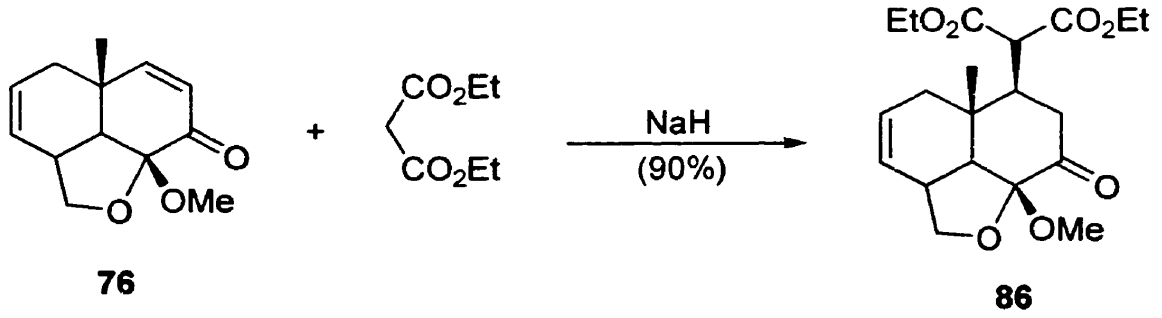
Given the success achieved in the synthesis of xestoquinone (**39**),[48] it seemed natural for us to start our investigations by examining the Diels-Alder reactions of naphthofuranone **76**. However, like most cyclohexenones, **76** was a poor dienophile and we had little success with its reactions with dienes other than isobenzofurans. Attempts to drive the reaction by adding a Lewis acid catalyst led to severe decomposition of **76**, and only small quantities of adduct **83** were isolated.[51] Presumably, the Lewis acid promotes elimination of methanol from **76** to form dienone **84**, which then undergoes a Diels-Alder reaction with diene **85** (Scheme 2.1). The cycloaddition, however, did not proceed with the desired chemoselectivity, which led us to consider Michael addition reactions as an alternative route to the pentacyclic framework of viridin. Preliminary tests using diethyl malonate were quite successful in producing adduct **86** (Scheme 2.2) as a single diastereomer, presumably arising from attack at the β face, since the α face is highly concave and therefore not very accessible for the nucleophile. The successful synthesis of **86** led us use Stork's procedure to prepare enone **87** (Scheme 2.3),[52] with the intent of using it in an ambitious cascade double Michael addition-Dieckman condensation approach (Scheme 2.4).[53] Unfortunately, only polymerization of **87** was observed, and we believe that naphthofuranone **76** is such a poor Michael acceptor that even though the formation of doubly stabilized anion **88** provides a thermodynamic incentive for the reaction, the self-condensation of the enolate of **87** occurs at a much faster rate. Attempts to make **87** a more reactive Michael donor by converting it into ketoester **89** also resulted

in polymerization of the starting material, evidencing that further activation of the Michael donor was not viable. Instead, preparation of a more reactive ABE naphthofuranone fragment appeared to be necessary if this approach was to be successfully used in the synthesis of any of the fungal metabolites.

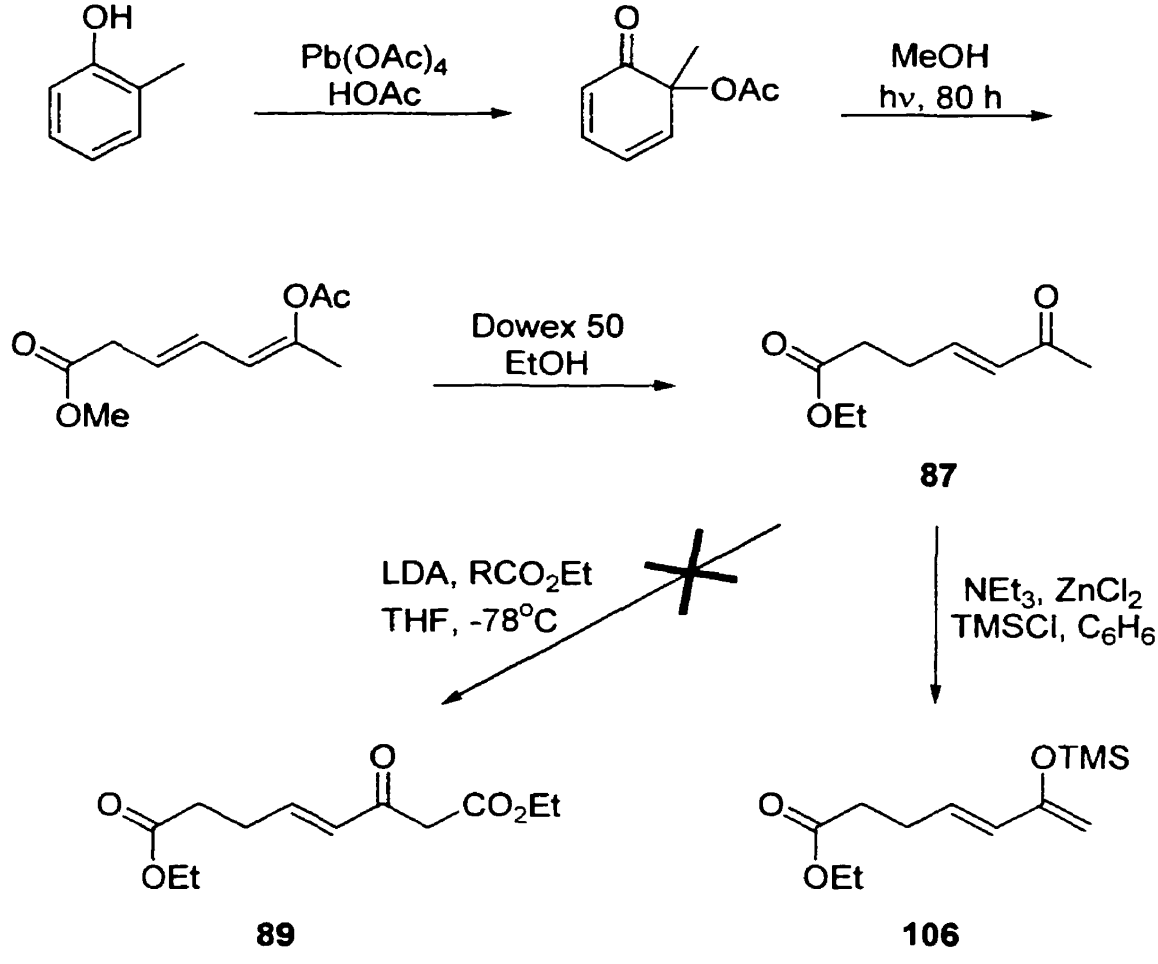
Scheme 2.1



Scheme 2.2



Scheme 2.3[52b]



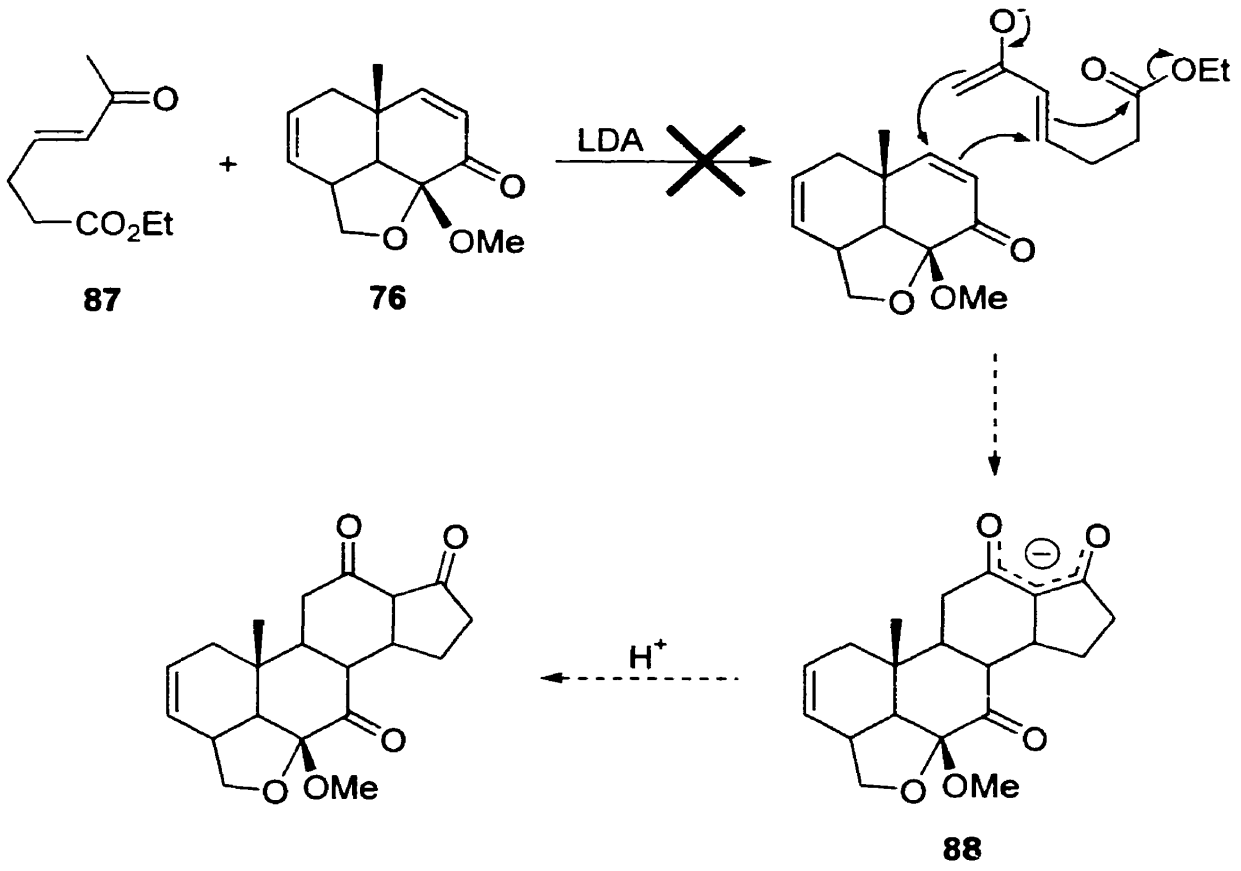
R = CN, Cl

2.2. Quest for a more Reactive Naphthofuranone

Despite their relative lack of reactivity in Diels-Alder reactions, cyclohexenones are important building blocks in organic synthesis. The addition of a second electron withdrawing substituent – generally a carboalkoxy[54] or cyano[55] group – α to the ketone moiety is a commonly used artifice that turns cyclohexenones into considerably more reactive dienophiles. Liu, for instance, has used carbomethoxy cyclohexenones in the total synthesis of several natural products (Scheme 2.5),[54] and we thus believed that

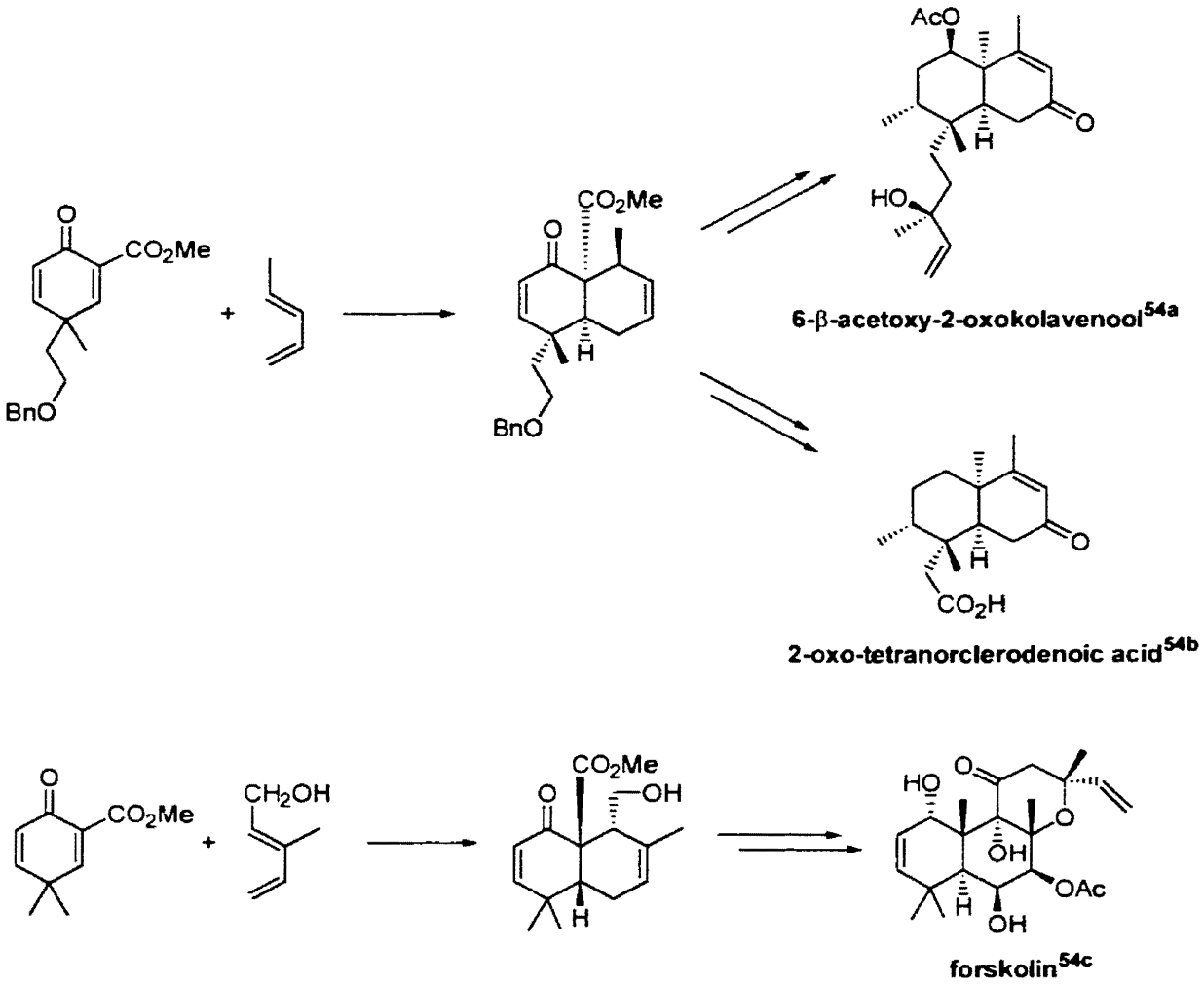
naphthofuranone **90** (Scheme 2.7) would be a reactive enough intermediate to allow us to achieve the synthesis of viridin (**2**) and related compounds.

Scheme 2.4



Cyclic α-carboalkoxy enones are usually prepared from β-keto esters (Scheme 2.6), either by condensation with the dialkyl acetal of an aldehyde[56] or by the use of selenium chemistry.[57] Given the complexity of the ABE naphthofuranone intermediates, however, none of those methods could be easily applied, and alternative routes to **90** had to be sought.

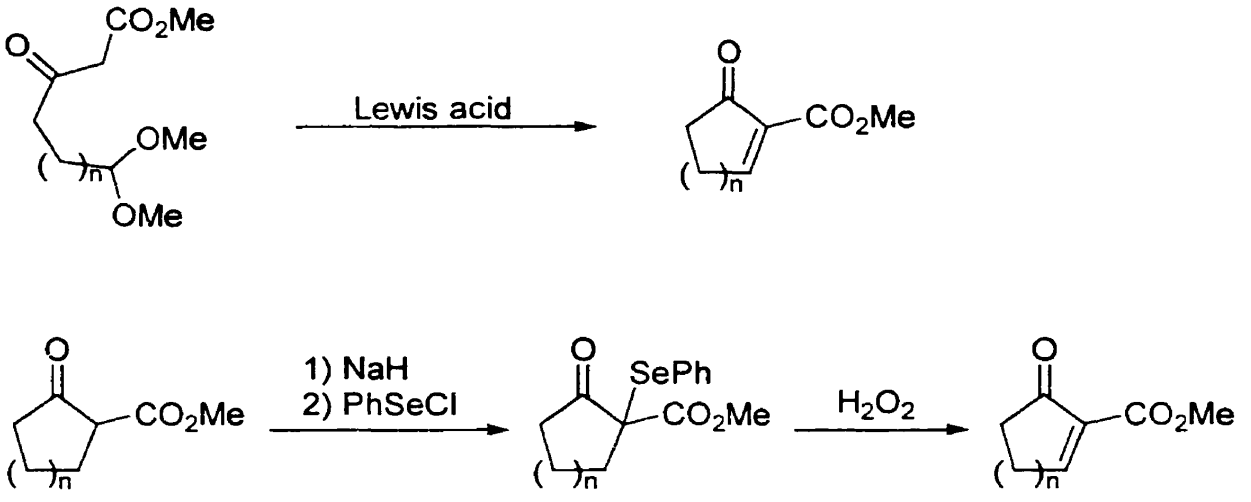
Scheme 2.5



The obvious route to **90** (Scheme 2.7) consisted of an IMDA reaction[49,58] between 2,4-pentadien-1-ol (**91**) and benzoate **92**, which, as is always the case with IMDA reactions involving benzenoid monoketals, gave only minor quantities of the tricyclic species **90**, with most of the product being represented by bridged adduct **93**.[59] It had been previously noted in our laboratory that the Cope rearrangement of adducts bearing bridgehead substituents generally results in poor yields,[58] but upon reflux in

1,2,4-trimethylbenzene, **93** gave highly irreproducible product distributions, with none of the expected tricycle **90** being formed. Instead, **94** and **95** were the only products isolated from the reaction mixture, which suggested the occurrence of some sort of intermolecular redox process, and we therefore attempted to improve such results by decreasing the concentration of the substrate in the reaction mixture. Unfortunately, both dilution and the use of different solvents (nitrobenzene, 1,1,2,2-tetrachloroethane and 1,2-diethoxyethane) for the Cope rearrangement failed to generate **90** to any synthetically useful extent.

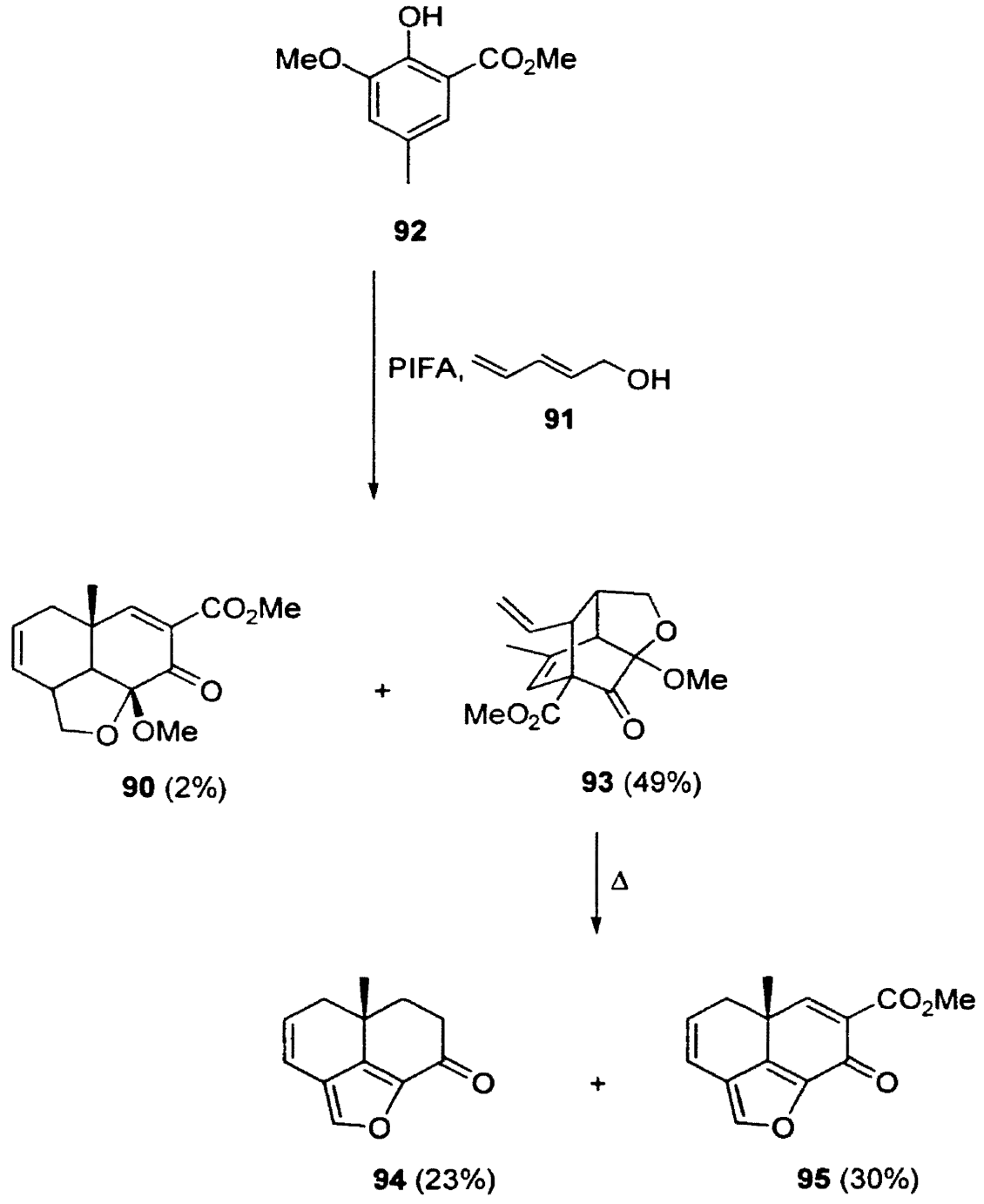
Scheme 2.6



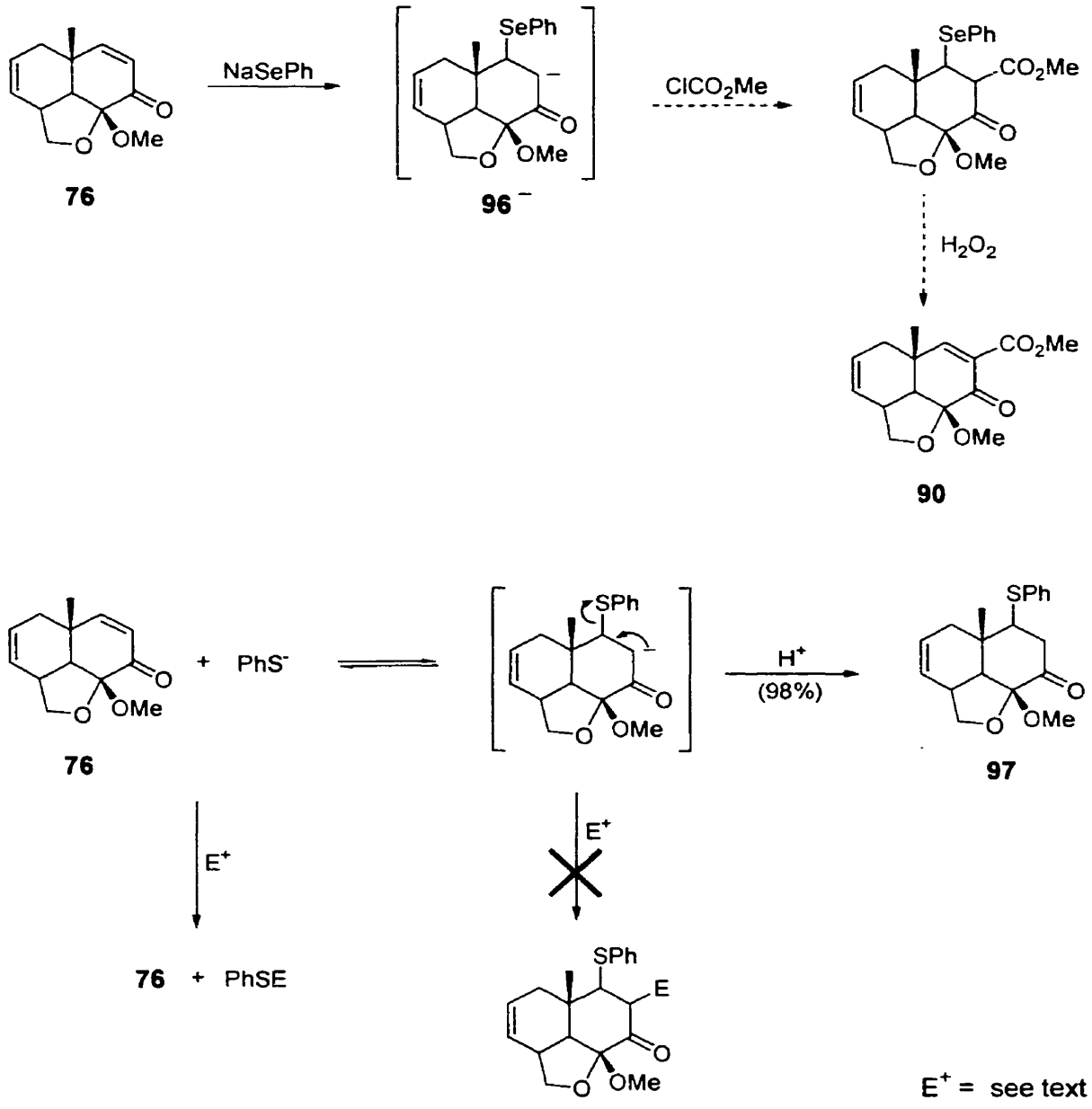
Our search for a better route to **90** led us to investigate the reactions of benzeneselenolate and benzenethiolate anions. It is well documented in the literature that such anions[60] can be used in tandem Michael addition-aldol reactions, which suggested to us that the reaction sequence outlined in Scheme 2.8 could be a viable route to **90**. While benzeneselenolate anions can be easily generated by reducing $(PhSe)_2$ with $NaBH_4$[61] or Na metal,[62] only dismal yields of the Michael addition product **96** were obtained due to

the extremely fast reoxidation of $PhSe^-$ to $(PhSe)_2$, regardless of how much care was taken to exclude oxygen from the reaction vessel. Benzenethiolate was found to be much more resistant to oxidation than its selenium analogue, and 1,4-addition to **76** proceeded

Scheme 2.7



Scheme 2.8

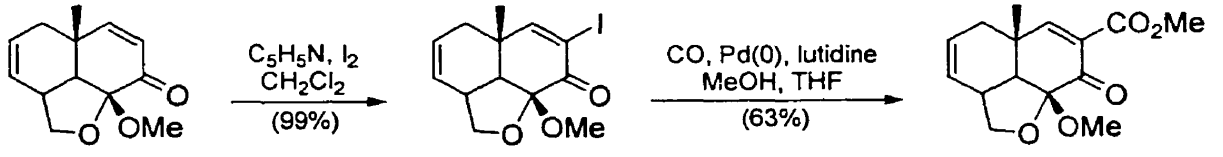


smoothly to give sulfide **97** in nearly quantitative yields. As previously observed with **86**, both **96** and **97** were also isolated as single diastereomers, providing further evidence of the inaccessibility of the α face of **76**. Despite the high yields obtained in the synthesis of **97**, attempts to quench its enolate with methyl chloroformate were completely unsuccessful, with only naphthofuranone **76** and $PhSCO_2Me$ being isolated. Similar

results were obtained with $NCCO_2Et$, CS_2/MeI and Me_2CO_3, and attempts to trap the anion of **97** with TMSCl also failed. Such results indicate that benzenethiolate anions react with electrophiles much faster than the enolate of **97** does, which - given the reversible nature of the Michael reaction[63] - causes the regeneration of the starting naphthofuranone **76**.

The synthesis of **90** was finally achieved via the two step sequence depicted in Scheme 2.9. Thus, we started by reacting **76**, pyridine and iodine in dichloromethane solution[64] to give iodo enone **98**, which is subsequently reacted with methanol and carbon monoxide in the presence of 2,6-lutidine and a palladium catalyst[65] to produce the desired ketoester **90** in fairly reasonable yield. Despite the promising results, the synthesis of **90** was plagued by highly irreproducible results, much later found to be caused by poisoning of the palladium catalyst by sulfur[66] from the thiosulfate used for removing excess iodine after the first step. This discovery led us to reexamine the experimental procedure for the preparation of iodide **98**, and use of ascorbic acid[67] instead of $Na_2S_2O_3$ eliminated any problems in the subsequent step, so that **90** was obtainable in 63% yield.

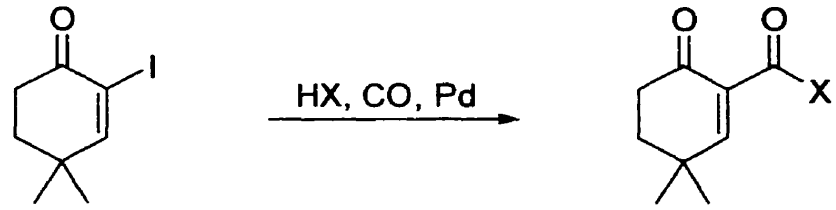
Scheme 2.9



76 **98** **90**

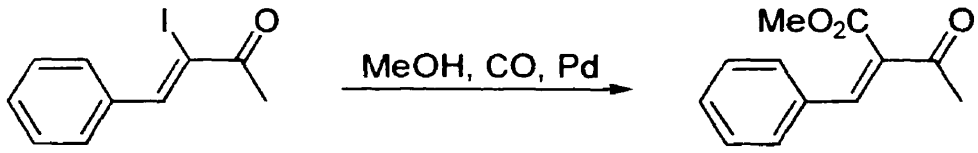
Since the preparation of iodide **98** from phenol **75** is rather long and involves some costly starting materials, we attempted to use 2-iodocyclohexenone as a model

Scheme 2.10

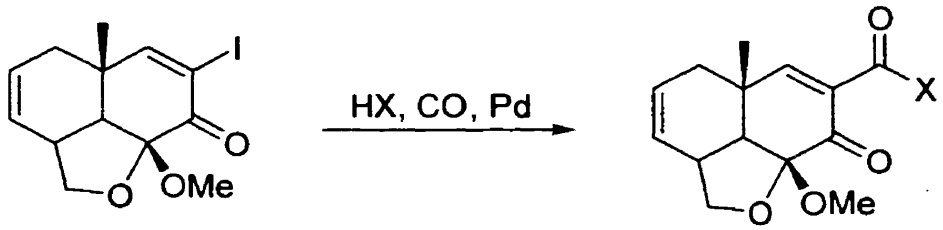


99

100 a: X = OMe
b: X = *n*-BuO
c: X = NEt_2
d: X = morpholin-4-yl

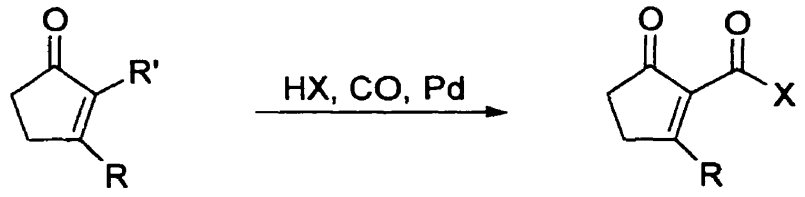


101 **102**



98

103 a: X = NEt_2
b: X = *n*-BuNH
c: X = morpholin-4-yl

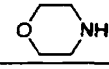
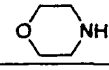


104 a: R = H, R' = I
b: R = H, R' = Br
c: R = Me, R' = I
d: R = Me, R' = Br

105 a: R = H, X = OEt
b: R = H, X = OMe
c: R = Me, X = OMe

compound in the optimization of the reaction conditions, but, curiously, in all instances only cyclohexenone and phenol were detected in any appreciable yield. Although the palladium catalyzed oxidation of α-iodocyclohexenones to phenolic products by CO had been previously reported,[68] the successful methoxycarbonylation of **98** encouraged us to launch a more comprehensive investigation of the reactions of α-haloenones, looking at a broader range of substrates and nucleophiles (Scheme 2.10, Table 2.1).[69] Our observations show that the carbonylation reaction is fairly general, with esters being

Table 2.1 – Carbonylation of α-haloeneones in the presence of nucleophiles

Substrate	nucleophile	product	isolated yield (%)
99[64b]	MeOH	**100a**	68
99	*n*-BuOH	**100b**	62
99	$HNEt_2$	**100c**	64
99		**100d**	77
101[64a]	MeOH	**102**	51
98	$HNEt_2$	**103a**	62
98	$PhNH_2$	**76**	41
98	*n*-$BuNH_2$	**103b**	43
98		**103c**	55
98	MeOH	**90**	63
104a[64a]	EtOH	**105a**	58
104a	MeOH	**105b**	55
104b	EtOH	**105a**	28
104b	MeOH	**105b**	29
104c[64a]	MeOH	**105c**	42
104d	MeOH	**105c**	13

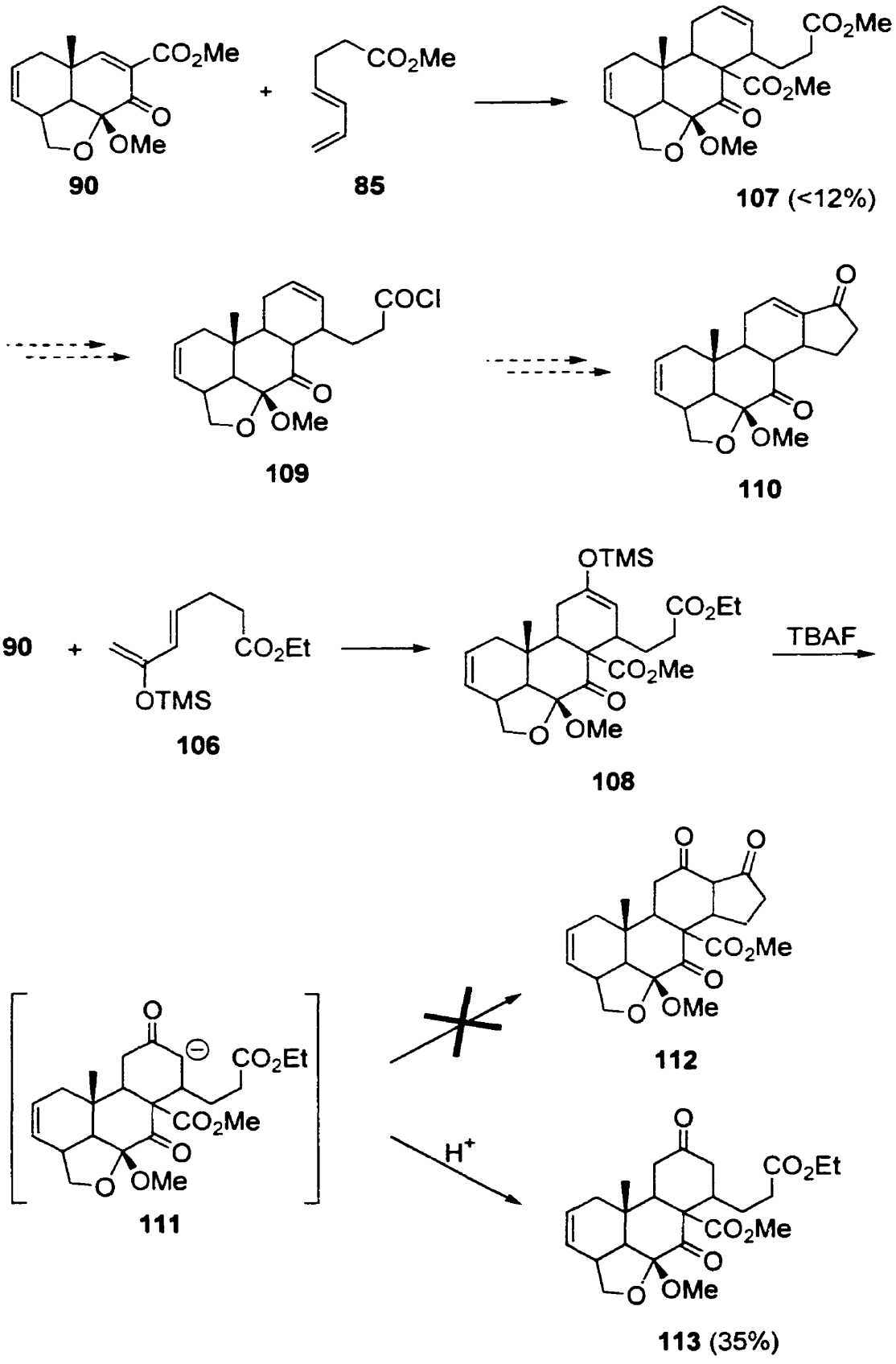
produced from a variety of cyclic enones, and only cyclohexenones with no quaternary carbons failing to yield the expected cross-coupling products. Also, the synthesis of ester **102** from iodide **101** illustrates that this methodology might also be used with acyclic

ketones. It is important, however, to point out that the attempted preparation of acyclic α-haloenones using the pyridine/iodine method usually results in the polymerization of the starting material,[64a] and even in favorable cases the yields are quite low. Use of sulfides (PhSH, *i*-PrSH, $C_5H_{11}SH$) as nucleophiles did not give the corresponding thioesters, which may also be due to the poisoning of the palladium catalyst either by the thiols themselves or by sulfur impurities[66] contained in the reagents used. Most amines, on the other hand, gave amides in good yields, particularly when secondary amines were used, and only aniline failed to yield the desired anilide. As with other palladium catalyzed cross-coupling reactions, bromides proved to be less reactive than iodides, and although the reactions of chlorides were not investigated, we expect them to be essentially unreactive, in line with results typically observed in related reactions.[70]

While the reaction conditions for individual substrates have not been optimized, it is clear that the iodination-carbonylation sequence is a fast and convenient way to prepare α-carboalkoxy and also α-carbamoyl enones, especially cyclic ones. Furthermore, this methodology is - to the best of our knowledge - the only route that allows α,β-unsaturated ketones to be used as starting materials.

Once ketoester **90** was prepared, its reactivity towards dienes **85** and **106** - prepared in situ from ketoester **87** - was investigated (Scheme 2.11). Ideally, both adducts **107** and **108** could be employed to easily generate the pentacyclic framework of **2** and related natural products. Our synthetic strategy called for the conversion of **107** into the corresponding acid chloride **109**, which would then be cyclized to compound **110** via an intramolecular Friedel-Crafts type reaction,[71] Heck coupling[70b,72] or radical process,[73] all of which have been reported in the literature as routes to cyclic ketones. Treatment of

Scheme 2.11


CO2Me
OMe
90
85
107 (<12%)
COCl
109
110
OTMS
CO2Et
106
TBAF
108
111
H+
112
113 (35%)

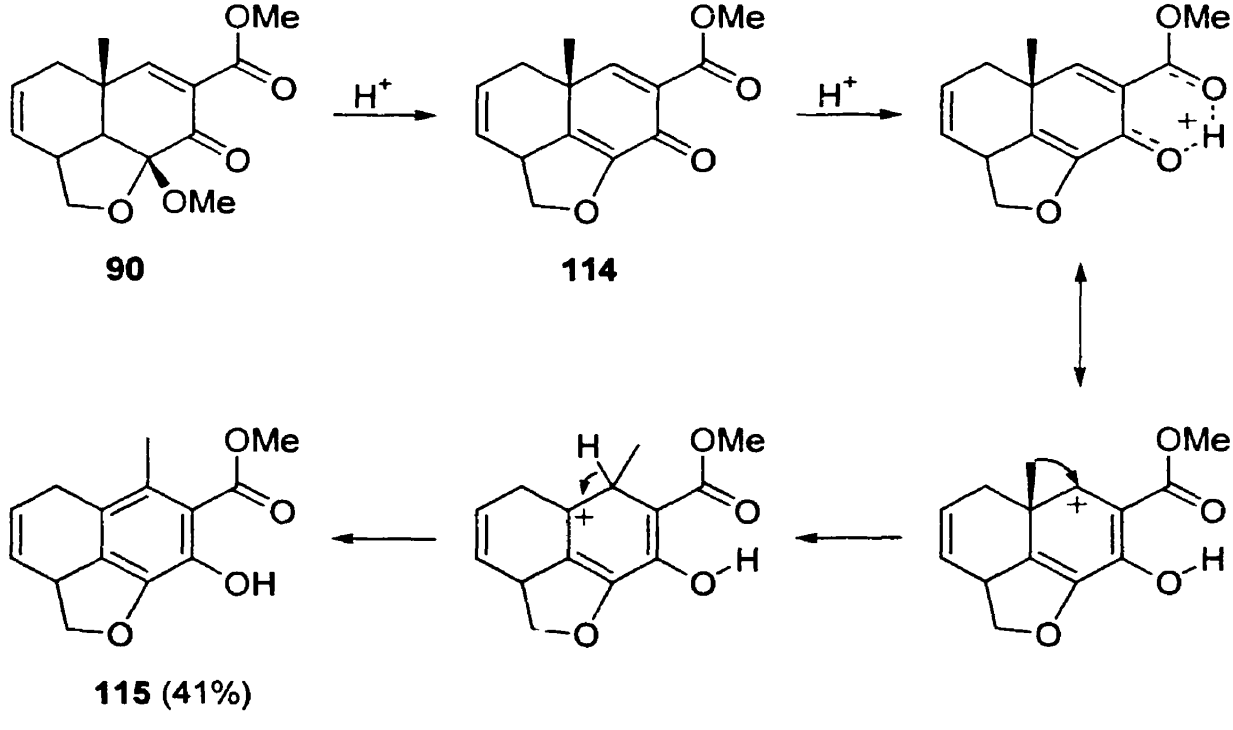
compound **108** with fluoride,[74] on the other hand, generates enolate **111**, which is expected to undergo a Dieckman condensation to yield **112**, with the formation of intermediate similar to **88** as driving force.

Using the same conditions successfully employed by others in similar systems,[54] the reactions of **90** with dienes **85** and **106** were carried out, and although the desired adducts were indeed formed, yields were quite discouraging, with adduct **107** being produced in such low yields that its presence could only be inferred from NMR spectra, and no actual sample could be isolated. The much more reactive Danishefsky-type diene[75] **106** also gave the corresponding adduct **108** in disappointing yield (ca. 35%), and upon treatment with TBAF[74] **108** did not undergo the expected Dieckman condensation, producing only **113**, which unfortunately was thermally unstable and could only be characterized by ^{1}H NMR spectroscopy. Such poor results, coupled with the numerous difficulties encountered in the preparation of diene precursor **87**,[52] seriously compromised further efforts towards the fungal metabolites by this route.

The low dienophilicity of **90** was particularly frustrating when compared to some excellent results reported in the literature for similar systems.[54] In all such systems, however, the stereochemistry of the cycloadduct is reported as *endo* (Scheme 2.5), and since naphthofuranone **76** is known to give exclusively the *exo* adduct when reacting with isobenzofurans,[48,49] it seemed reasonable to us to assume that **90** would exhibit the same behavior. With so much riding on secondary orbital interactions and given that **90** possesses a quaternary carbon α to the enone moiety, we hoped that elimination of methanol to form dienone **114** could produce a more reactive dienophile, since a flatter and less sterically crowded structure would presumably be more accessible to an *endo*

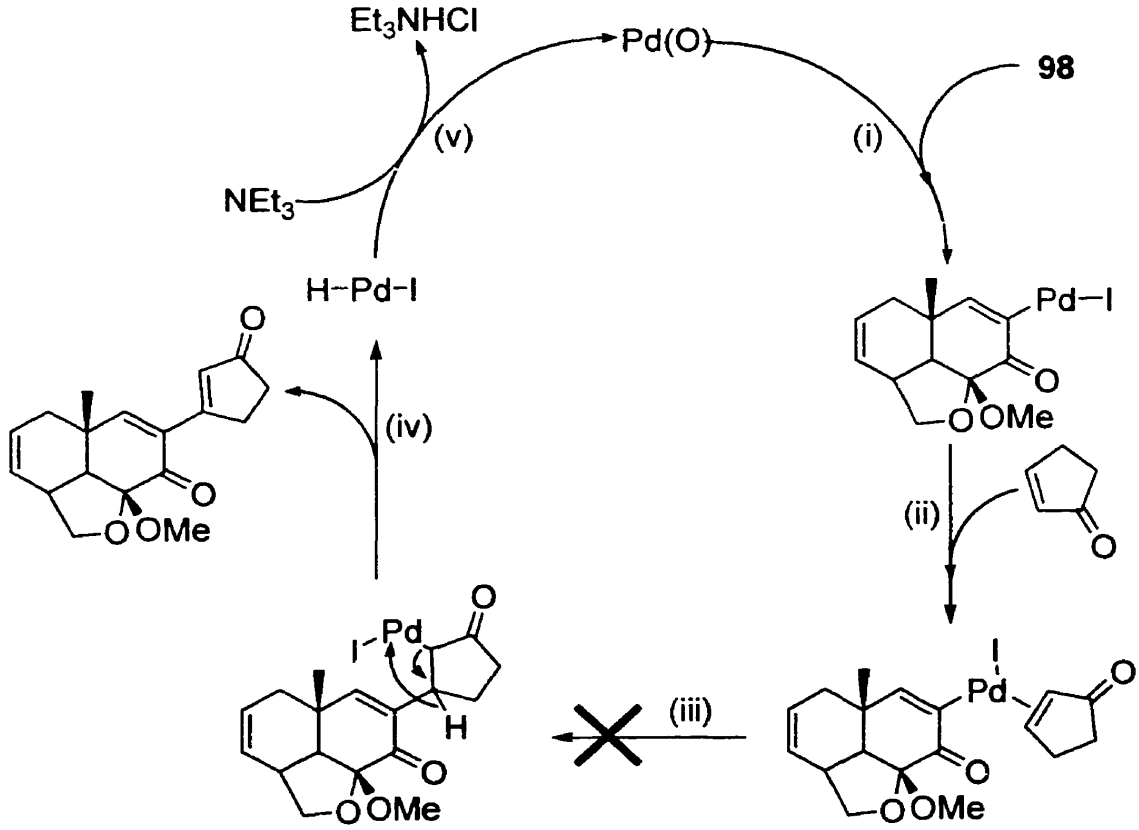
approach of the diene. Elimination of methanol from naphthofuranones had been traditionally done in our laboratory by treatment with neat TFA at room temperature for 15 minutes,[51] but, under these conditions, **90** produced only phenol **115** via a methyl migration, a simple 1,2-alkyl shift in the carbocation formed by protonation of the carbonyl, which can also be seen as the equivalent of an acid catalyzed intramolecular Michael addition of a methyl anion to the doubly activated vinyl moiety (Scheme 2.12). Still, carrying out the reaction under much milder conditions eventually led to **114** in quantitative yield. Unfortunately, in line with results previously observed in the synthesis of xestoquinone,[76] dienone **114** proved to be an even worse dienophile than **90**, and no product was isolated when **114** was reacted with dienes **85** or **106**.

Scheme 2.12



A final attempt at assembling the carbon skeleton of the fungal metabolites from an ABE naphthofuranone involved a Heck coupling[77] of compound **98** and 2-cyclopenten-1-one (Scheme 2.13), which unfortunately led only to the recovery of the starting iodide. Since the successful synthesis of **90** from **98** demonstrates very clearly that (i) oxidative addition of the α-iodo enone to the metal center does indeed take place, we believe that cyclopentenone is too bulky and rigid to either (ii) coordinate to the metal center or – most likely - (iii) undergo migratory insertion into the metal-carbon bond. In fact, most examples of Heck couplings involve terminal alkenes, and although there are reports involving more sterically crowded systems, those are often examples of intramolecular reactions.[77]

Scheme 2.13



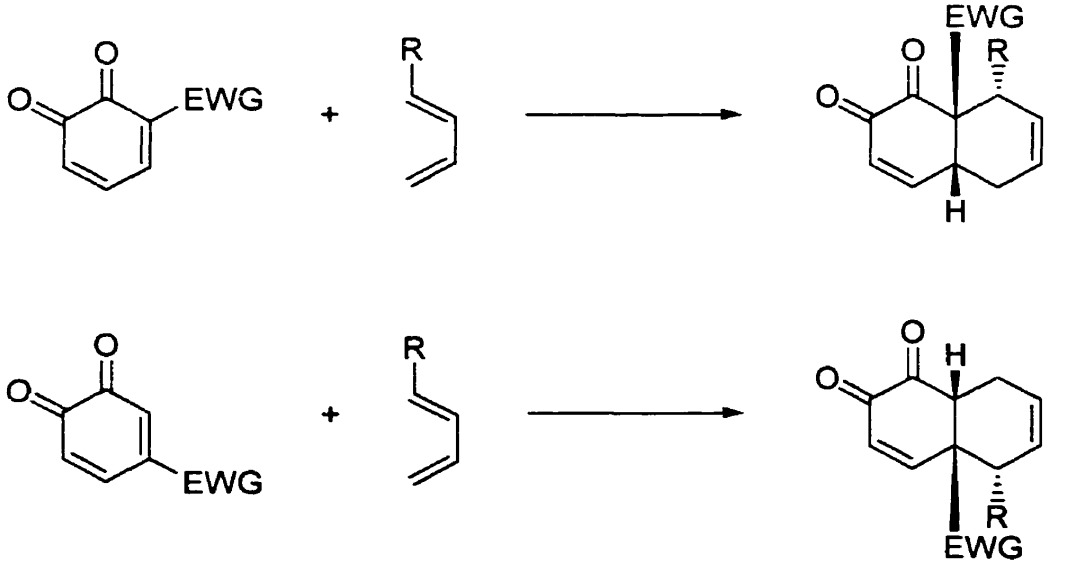
Since our attempts at assembling the pentacyclic framework of **2** by attaching rings C and D to the ABE fragment gave quite disappointing results, we concentrated our efforts on an alternative synthetic route, which has the ABE benzindanone as its starting point.

CHAPTER 3 – THE BENZINDANONE APPROACH

3.1. Preliminary Studies

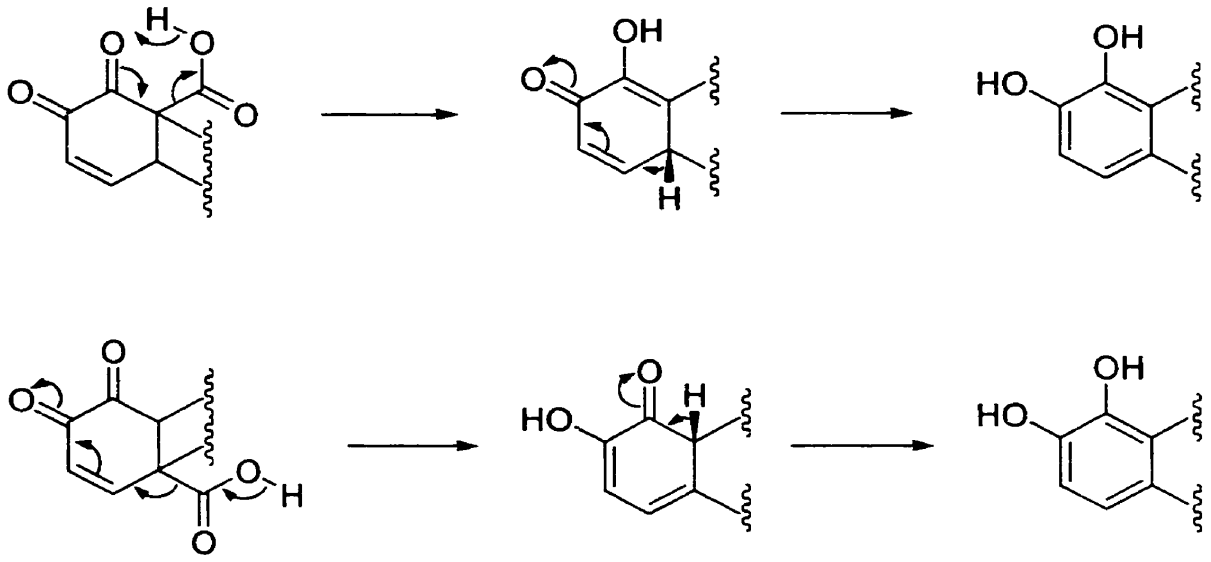
It is a well known fact that *ortho*-quinones[78] and their respective monoketals,[79] due to the inherent s-*cis* geometry of their diene moieties, react mainly as dienes in Diels-Alder reactions. In addition, *ortho*-benzoquinones are also prone to dimerization by such a cycloaddition and to substantial decomposition, which limits their applications in organic synthesis.[80] The presence of an electron withdrawing group on the quinone, however, dramatically alters its reactivity, making it less prone to dimerization and also enabling *ortho*-benzoquinones to be used as dienophiles.[81,82] Also, the position of the electron withdrawing group on the quinone ring completely controls the outcome of the reaction, determining not only which of the double bonds on the quinone ring is attacked, but also the regiochemistry of the attack by the diene, with only the "*ortho*" adduct being formed (Scheme 3.1). In the particular case of carboxy *ortho*-quinones, however,

Scheme 3.1



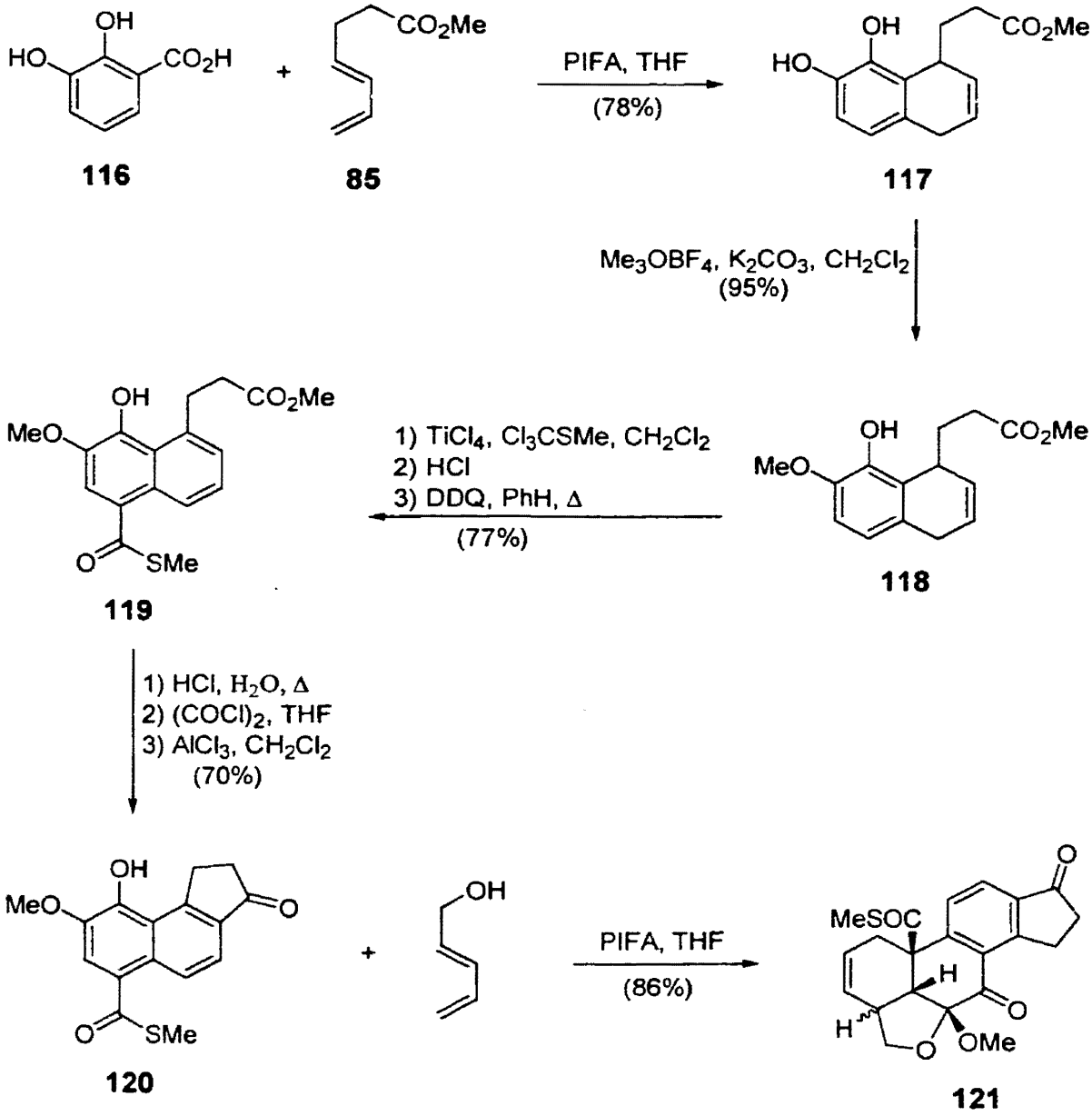
spontaneous decarboxylation takes place to yield a catechol (Scheme 3.2), and such quinones can therefore be employed as convenient benzyne equivalents, with the advantage of a total control over the regioselectivity of the cycloaddition.[82]

Scheme 3.2



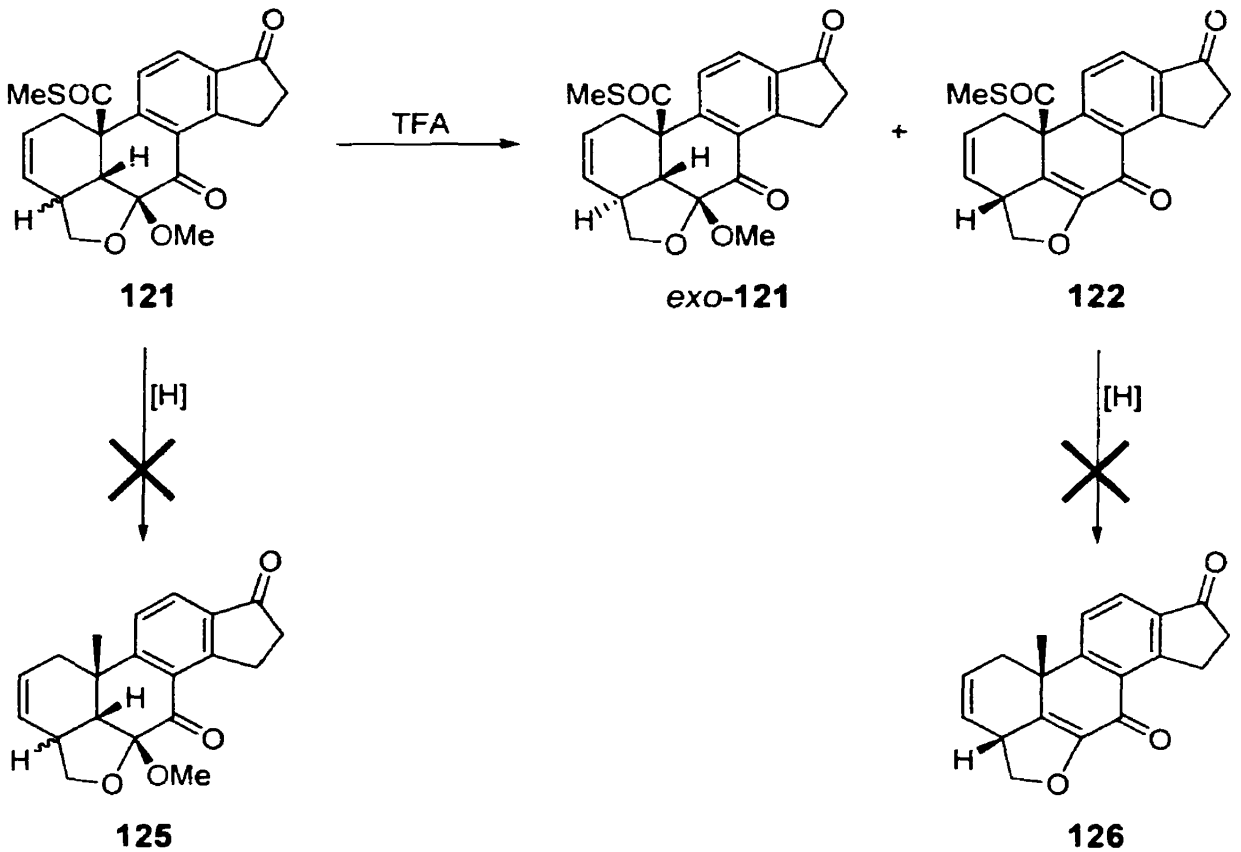
The usefulness of α-carboxy *ortho*-quinones - easily generated *in situ* from dihydroxybenzoic acids[82] - together with the poor yields obtained in the Diels-Alder reactions of naphthofuranones **76**, **90** and **114** with dienes led us to focus our efforts on the benzindanone route, which had been also previously investigated in our laboratory (Scheme 3.3), with a certain degree of success.[49,51] The previously developed approach started by oxidizing benzoic acid **116** in the presence of diene **85** to produce adduct **117**. Selective methylation with Me_3OBF_4[83] affords **118**, which is converted into **119** via a Friedel-Crafts acylation followed by aromatization with DDQ.[84] Hydrolysis of the ester moiety, treatment with oxalyl chloride and an intramolecular Friedel-Crafts acylation gave benzindanone **120**, which corresponds to the BCD fragment of viridin. Oxidation of

Scheme 3.3



120 in the presence of 2,4-pentadien-1-ol (**91**) produced pentacycle **121**, but, unlike benzenoid systems, which give exclusively the *endo* adducts, **121** was isolated as a 3:1 mixture of the *endo* and *exo* isomers. Such differences can be explained by the fact that the IMDA reaction of benzoquinone systems is almost certainly irreversible, thus giving only the kinetically favored *endo* adduct, whereas naphthoquinones react reversibly to

Scheme 3.4



give a product distribution that reflects the relative thermodynamic stability of both possible stereoisomers.[49] Treatment of both isomers of **121** with TFA converted *endo*-**121** into **122** quantitatively, but *exo*-**121** remained unscathed (Scheme 3.4). Studies by others on related tetracycle **123**[51] (Figure 3.1) and similar substrates[58] showed that the *exo* adducts possess geometric constraints that prevent the alignment of the atomic orbitals necessary for the formation of oxonium ion **124**, and thus loss of methanol cannot take place. While the lack of reactivity exhibited by *exo*-**121** was considered a minor setback in the route to viridin (**2**), Carlini subsequently had indeed to abandon that approach, when all attempts to selectively reduce the thioester moiety of **121** and **122** failed to produce the desired pentacycles **125** and **126** with the angular methyl group. Studies

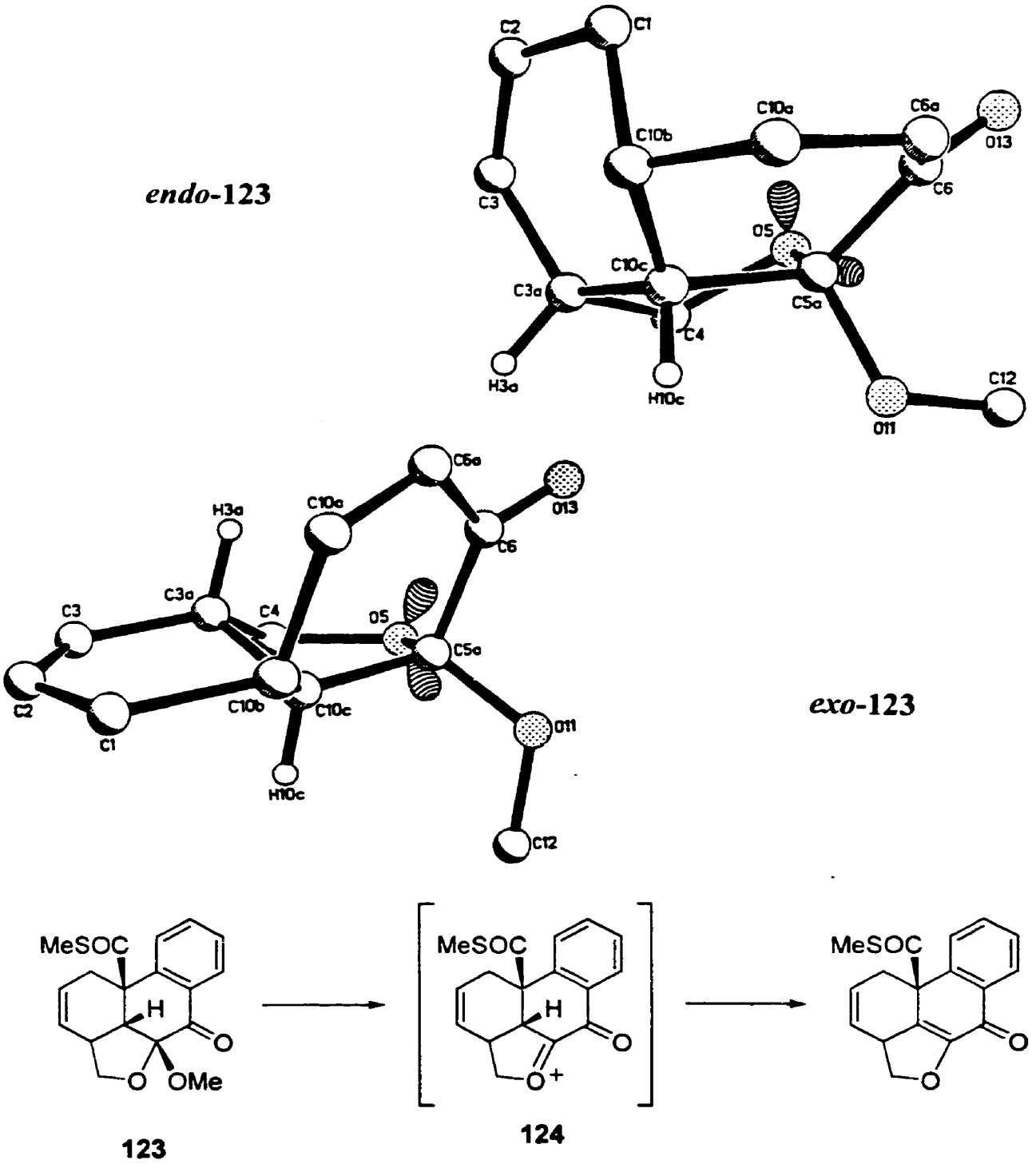
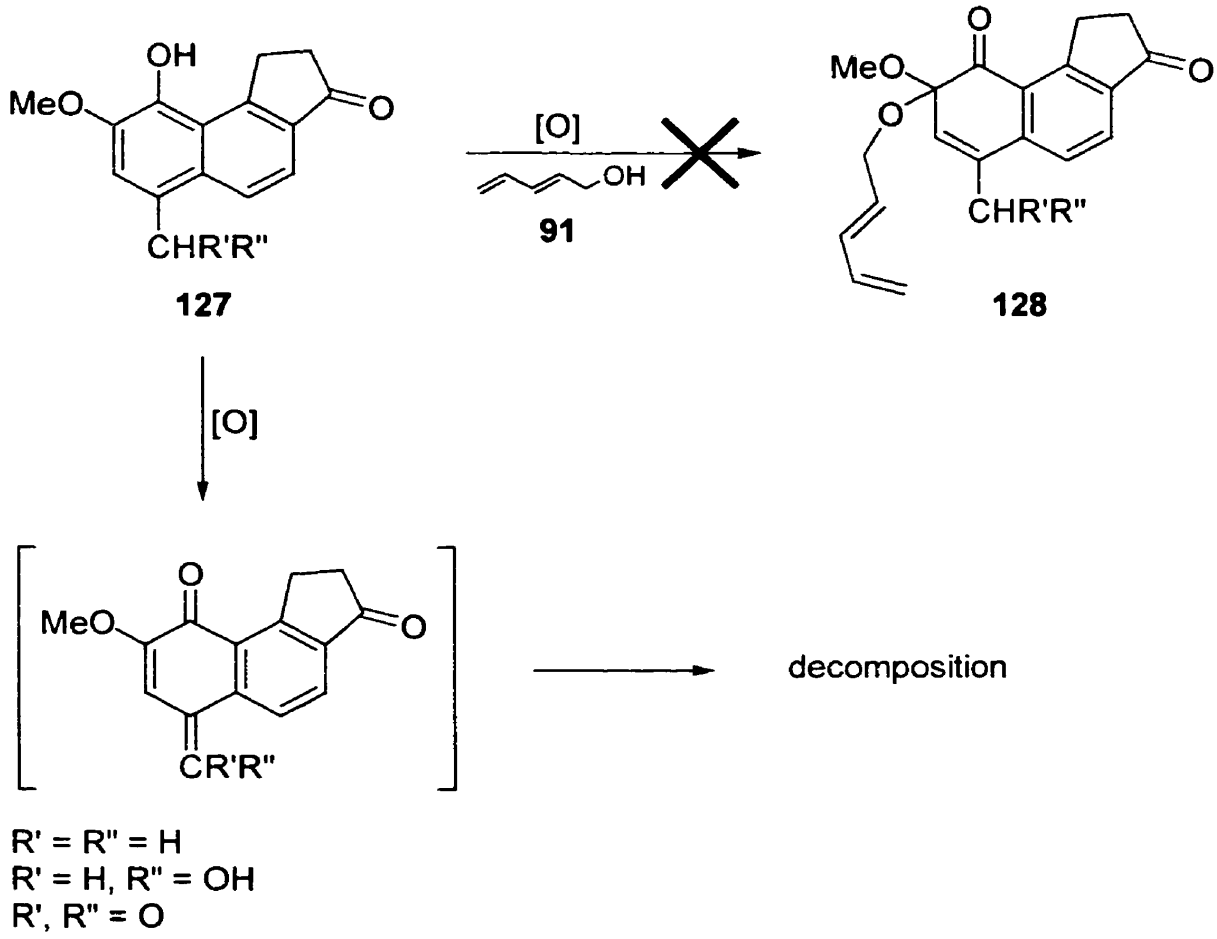


Figure 3.1: X-ray crystal structures of isomeric tetracycles **123**. Notice the position of the lone electron pairs of O5 relative to the C5a-O11 bond.

conducted on **121** and structurally similar model substrates did indeed accomplish the conversion of the thioester into an aldehyde, but further reduction lead mostly to deformylation, generally accompanied by aromatization of ring B.[51]

Scheme 3.5

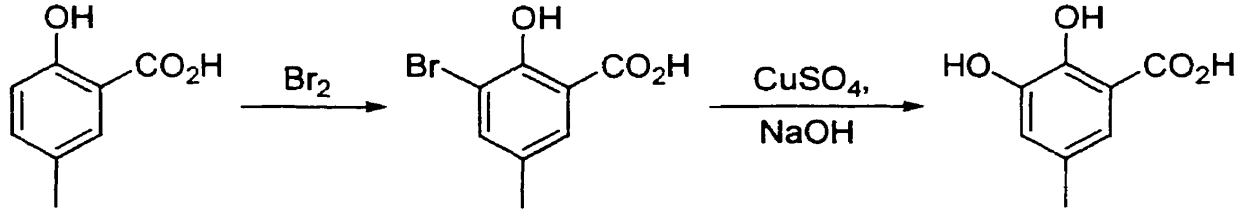


3.2. The Friedel-Crafts Route

In an attempt to circumvent the problems previously encountered in the reduction of **121** and **122**, we decided to start out with the methyl group already in place. Naphthalenoid systems such as benzindanone **127** (R = R' = H), however, have been

found not to give the desired intermediate **128** when oxidized in the presence of **91** (Scheme 3.5). Instead, only decomposition was observed,[49,85] presumably via the formation of *para*-quinomethide species,[86] which made it clear that our new route to **2** would require a partially hydrogenated (benzenoid) version of compound **127** as an intermediate. We therefore set out to synthesize a suitably substituted candidate for testing this hypothesis.

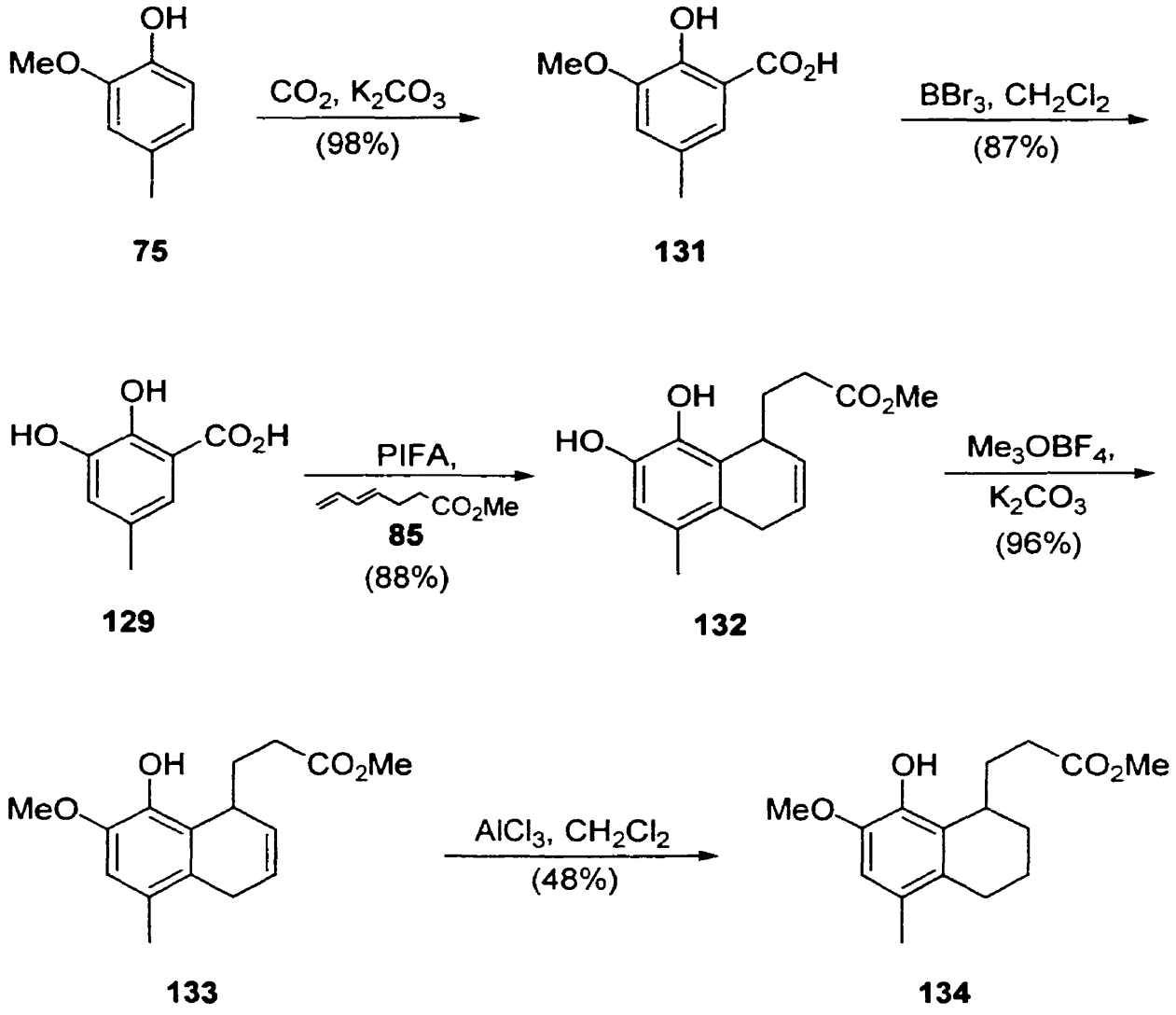
Scheme 3.6



130 **129**

The initial step in our proposed route consisted of a Diels-Alder reaction between diene **85** and known benzoic acid **129**, which reportedly could be prepared from salicylic acid **130** (Scheme 3.6).[87] While the bromination of **130** proceeded uneventfully, the following step requires that large volumes of solutions be handled under oxygen free conditions, which made the reaction operationally quite difficult to carry out. In addition, the isolation of **129** required several days of continuously extracting the aqueous phase with EtOAc, to produce only minimal quantities of product, about 1% yield from the bromide precursor. Deterred by such results, we set out to find a new synthetic route to benzoic acid **129**. The reaction between the anions of a phenol and CO_2, known as Kolbe-Schmitt carboxylation,[88] generates hydroxycarboxylic acids, but attempts to prepare **129**

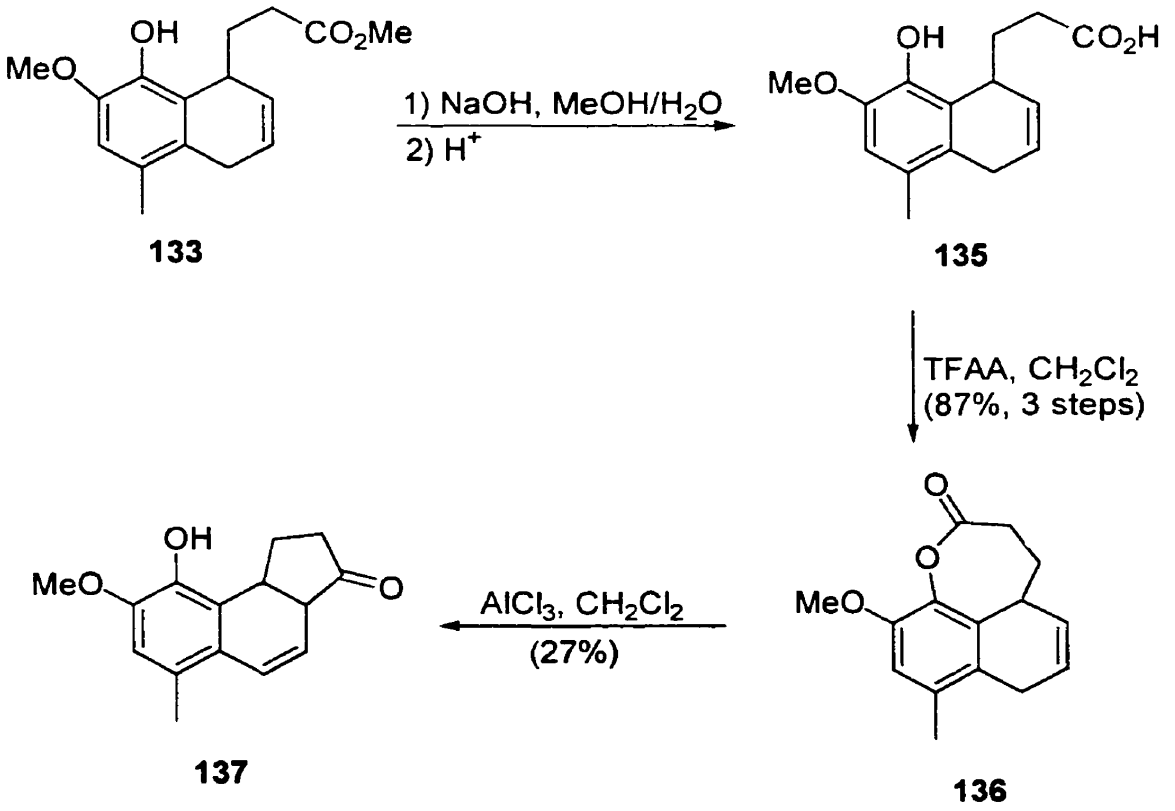
Scheme 3.7



from 4-methylcatechol led only to a very water soluble product, presumably arising from the double carboxylation of the starting material. Alternatively, the same Kolbe-Schmitt carboxylation was used to convert phenol **75** into benzoic acid **131**, and subsequent treatment of **131** with BBr_3[89] demethylated the ether to produce catechol **129** (Scheme 3.7) in 85% overall yield. Following our usual IMDA protocol,[49] compound **129** was then oxidized in the presence of **85** to yield, as expected, the "*ortho*" adduct **132**. Selective methylation was carried out according to Carlini's method[5951] to give ester **133**, which

was then treated with $AlCl_3$ in CH_2Cl_2 in the hope that the acylation of the double bond would take place.[71] Since alkyl esters usually do not undergo Friedel-Crafts type reactions, it was not surprising that the cyclopentanone ring D did not close. We were, however, quite puzzled when the ^1H NMR of the product showed no vinyl signals and an unexpectedly high number of aliphatic protons, suggesting that tetrahydronaphthalene **134** was the product isolated from the reaction mixture. Both ^{13}C NMR and mass spectrometry confirmed the structure of **134**, but we have not been able to propose any mechanism that accounts for the origin or identity of the reducing agent. Nevertheless, given the lack of synthetic utility of compound **134**, such results were not investigated any further.

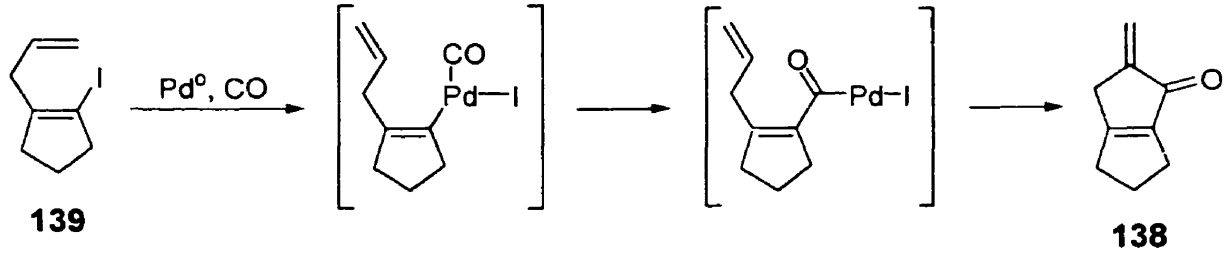
Scheme 3.8



133 **135** **136** **137**

As an alternative, ester **133** was hydrolyzed with NaOH to yield carboxylic acid **135** (Scheme 3.8), which, without any further purification, was treated with TFAA to form a mixed anhydride that spontaneously cyclizes to afford lactone **136** in excellent yields. Tricycle **137** was generated by an intramolecular Friedel-Crafts reaction,[71] but the yields, around 25%, were mediocre at best. Several attempts to increase the yield by changing the reaction conditions or employing different acid catalysts (BF_3, $TiCl_4$, PPA, H_2SO_4) also met with little success, which led us to investigate alternative routes to closing the cyclopentanone ring D.

Scheme 3.9

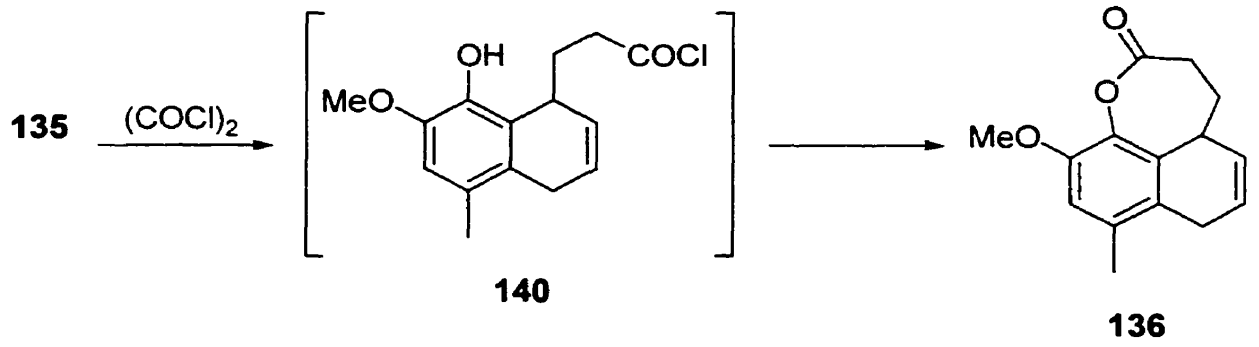


139 **138**

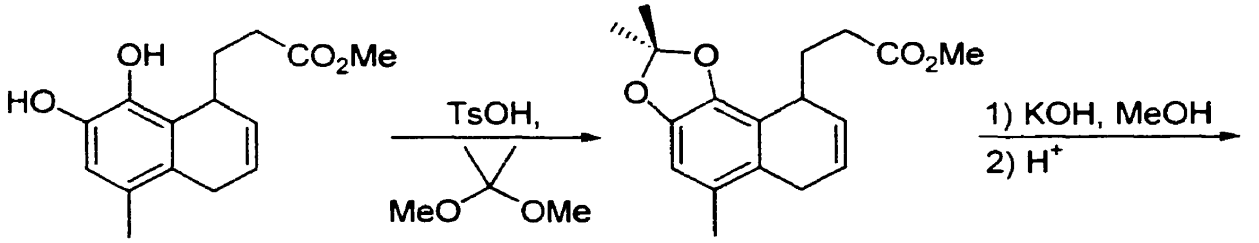
3.3. The Heck Reaction Approach

Cross coupling reactions of alkyl chloroformates[90] and acyl chlorides[70b] with organometallic species have been reported in the literature, and compound **138** has been prepared from iodide **139** via a palladium catalyzed tandem carbonylation-intramolecular Heck reaction (Scheme 3.9).[72] Such results suggested to us that it would be possible to effect the closure of ring D via an intramolecular Heck reaction (Scheme 3.10). Since generation of acyl chloride **140** in the presence of a free phenolic hydroxyl group leads only to lactone **136**, compound **132** was reacted with 2,2-dimethoxypropane in the presence of TsOH[91] to give acetonide **141**, which was hydrolyzed to the corresponding

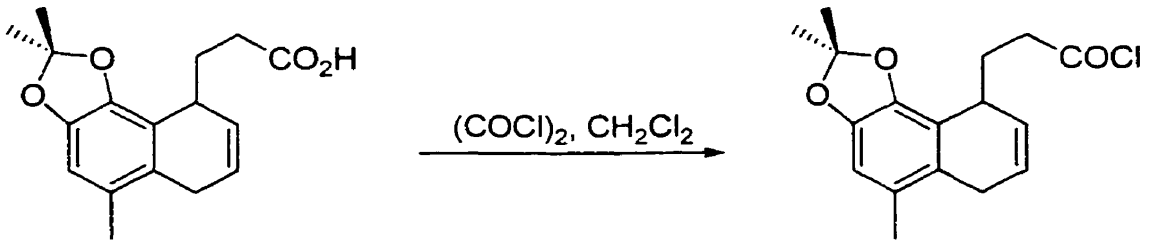
Scheme 3.10



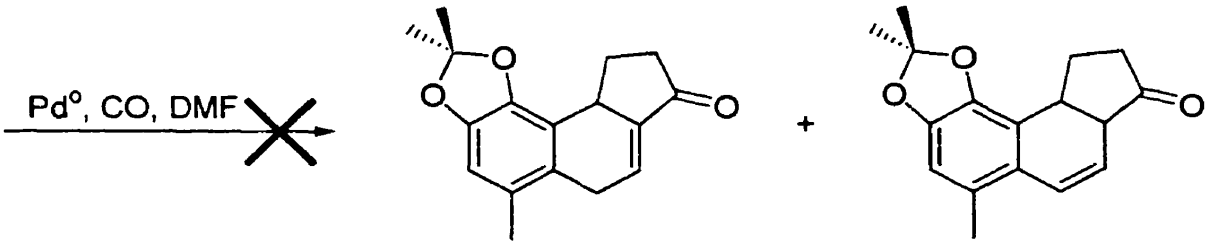
140 136



132 141 (93%)

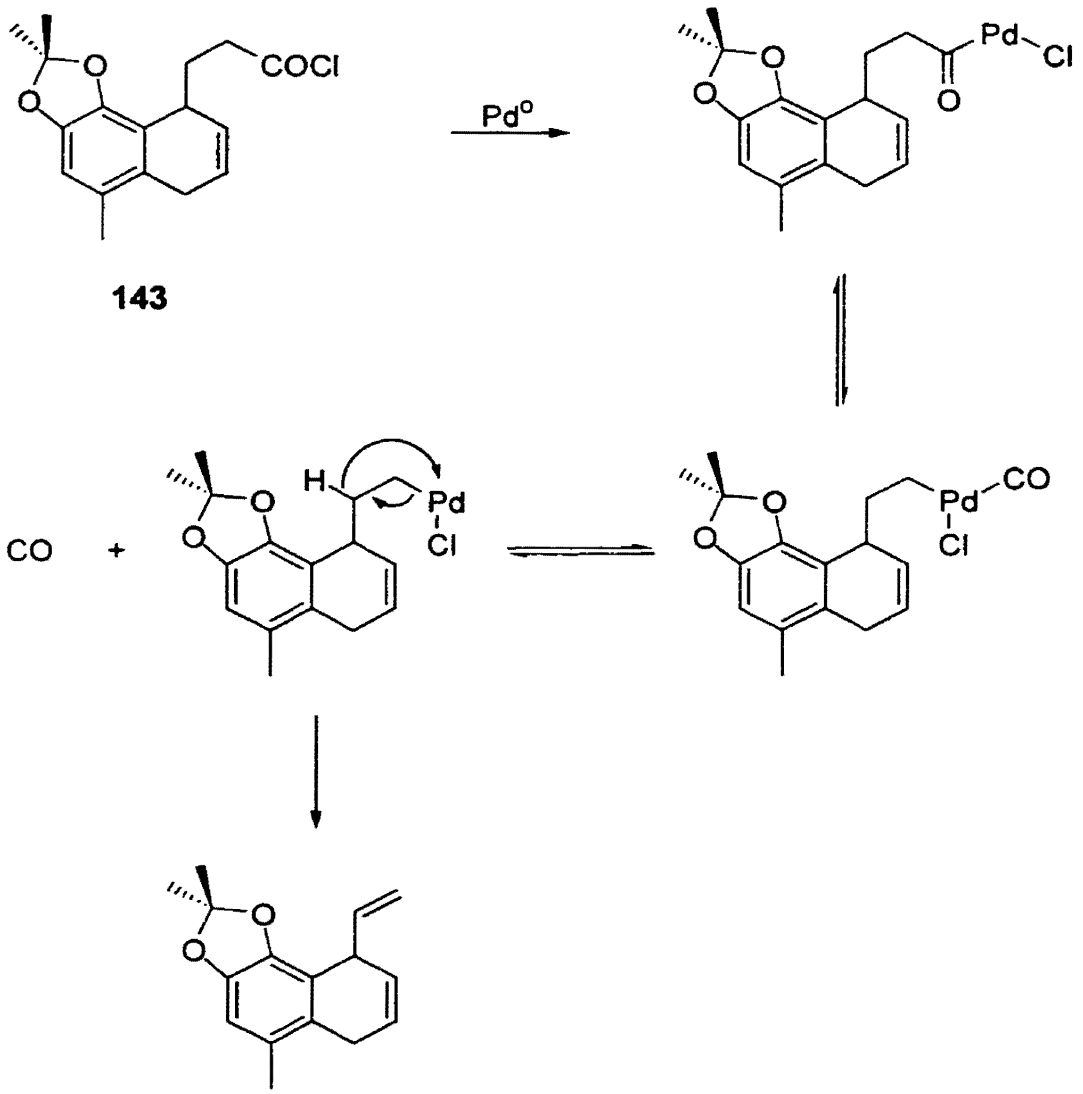


142 (92%) 143



144 145

Scheme 3.11



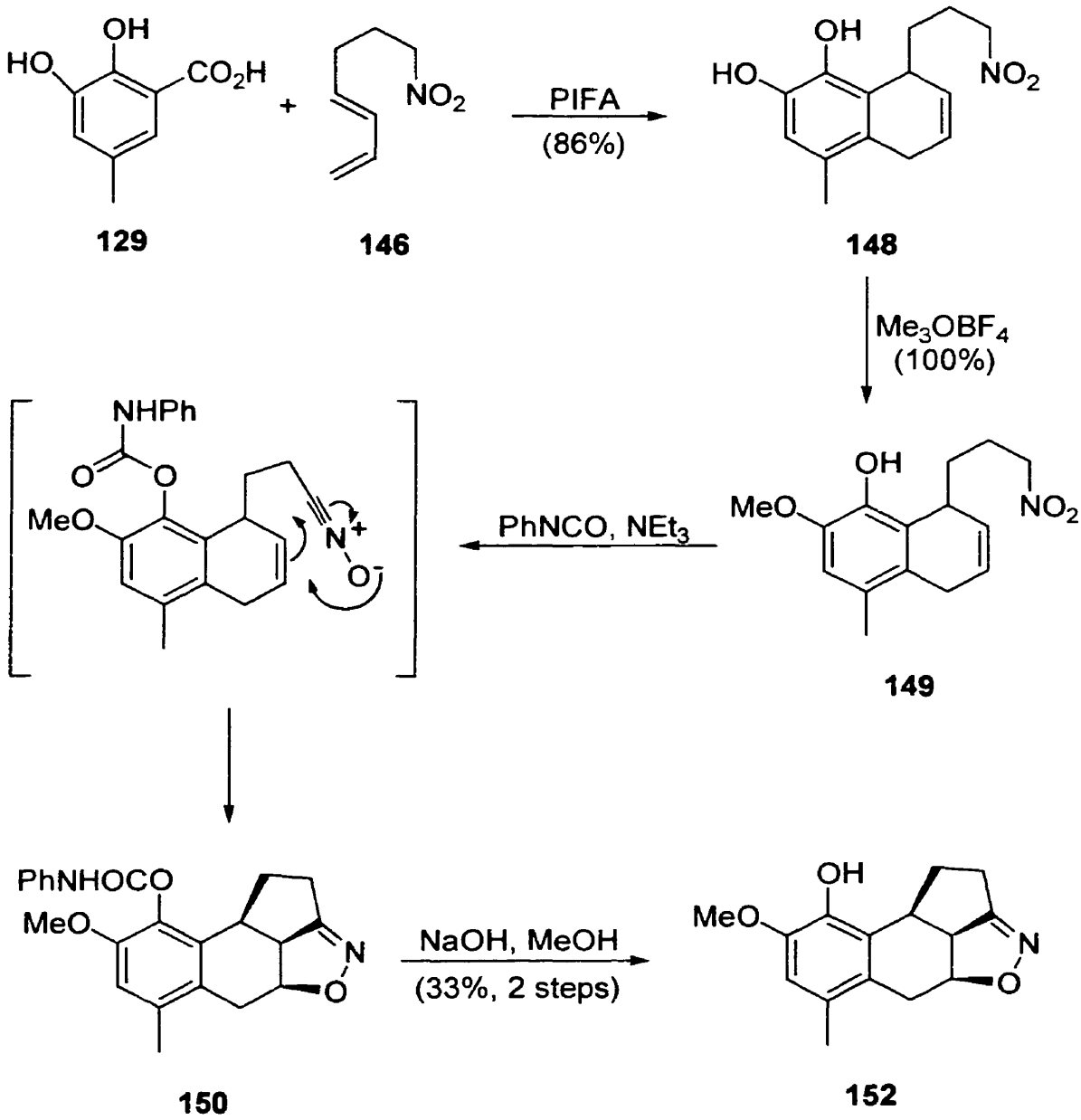
carboxylate and subsequently converted to acid **142**. Reaction between **142** and oxalyl chloride led to the *in situ* generation of acid chloride **143**, which was then treated with $Pd(PPh_3)_4$ under a CO atmosphere. While the presence of CO prevents decarbonylation[92] and subsequent β-hydride elimination[93] from taking place (Scheme 3.11), no benzindanone **144** or **145** was produced, with only starting acid **142** being isolated after work-up. These results led us to doubt that acid chloride **143** had actually been formed,

but when the reaction mixture was treated with MeOH before aqueous work-up, ester **141** was produced in almost quantitative yield, suggesting that optimizing the reaction conditions might afford the desired tricycle. The optimization of palladium catalyzed reactions is still largely based on trial and error, and we have examined the effect of phosphines with different sterical and electronic properties (dppp, dppf, PCy_3), using both MeCN and DMF as solvents. Unfortunately, all our attempts were equally fruitless, forcing us to abandon the Heck reaction route to a suitable BCD substrate.

3.4. The Nitrile Oxide Cycloaddition

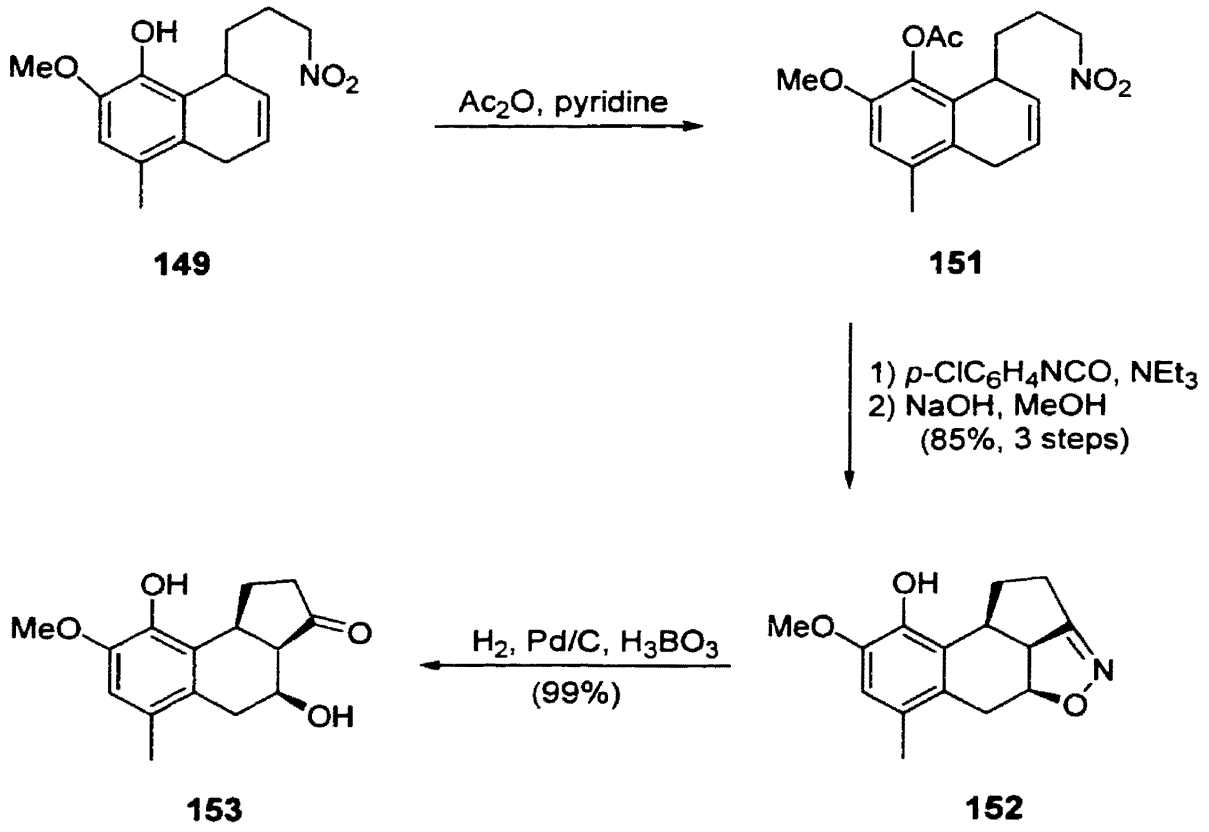
The minimal success achieved in using ester **85** to assemble the BCD benzindanone prompted us to re-evaluate our strategy, and a new synthetic plan was formulated. Although our new route (Scheme 3.12) was still based on the original Diels-Alder reaction of an *ortho*-quinone, we expected to assemble the cyclopentanone ring D via an intramolecular nitrile oxide cycloaddition (INOC) reaction. A particular case of 1,3-dipolar cycloadditions, reactions between nitrile oxides and alkenes have been widely employed not only in the synthesis of heterocyclic compounds,[94] but also as an alternative route to aldol condensation products,[95] since isoxazolines can be reduced to β-hydroxyketones with predictable stereochemistry under relatively mild conditions (Scheme 3.13). For us to be able to employ an INOC reaction, however, ester **85** had to be replaced by nitrodiene **146**,[96] and while **146** is easily prepared by reacting $AgNO_2$ with known iodide **147**, the synthesis of the latter is quite long and expensive (Scheme 3.14).[97] Our efforts, however, were rewarded when the new synthetic approach finally delivered the BCD fragment in excellent yields.

Scheme 3.12



Thus, benzoic acid **129** was oxidized to an *ortho*-quinone in the presence of nitrodiene **146** to give adduct **148**, which was selectively methylated using the same conditions previously discussed. Treatment of **149** with PhNCO and NEt_3 then promoted dehydration of the nitroalkyl side chain,[98] yielding isooxazoline **150** via an INOC

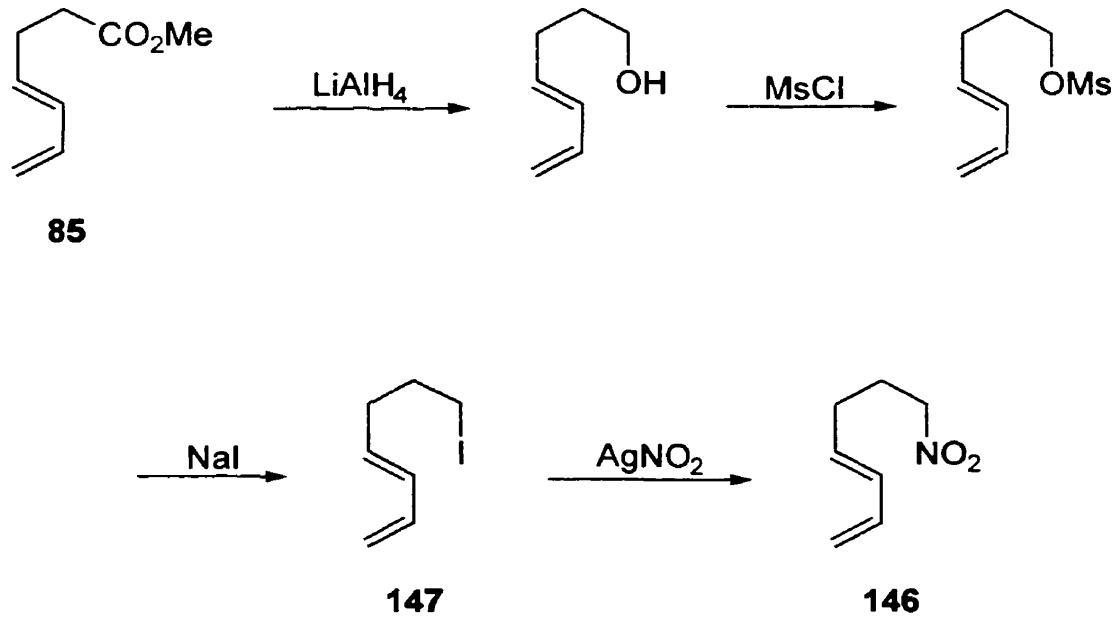
Scheme 3.13



reaction. However, in addition to the low yields (ca. 45%), hydrolysis of the carbamate moiety of **150** required quite harsh conditions, leading to an even greater loss of material. Such problems were overcome (Scheme 3.13) by acetylating the hydroxyl moiety prior to the INOC reaction, and also by the use of a more reactive isocyanate, which resulted, after removal of the acetate, in an almost twofold increase in the yields of **152**. Hydrogenation of compound **152** in the presence of water and H_3BO_3[95b] then afforded a one pot reduction of the oxazoline ring and hydrolysis of the resulting imine to give hydroxyketone **153** in practically quantitative yields. The relative stereochemistry of **150** and **152** is a direct consequence of both the mechanism of the nitrile oxide cycloaddition

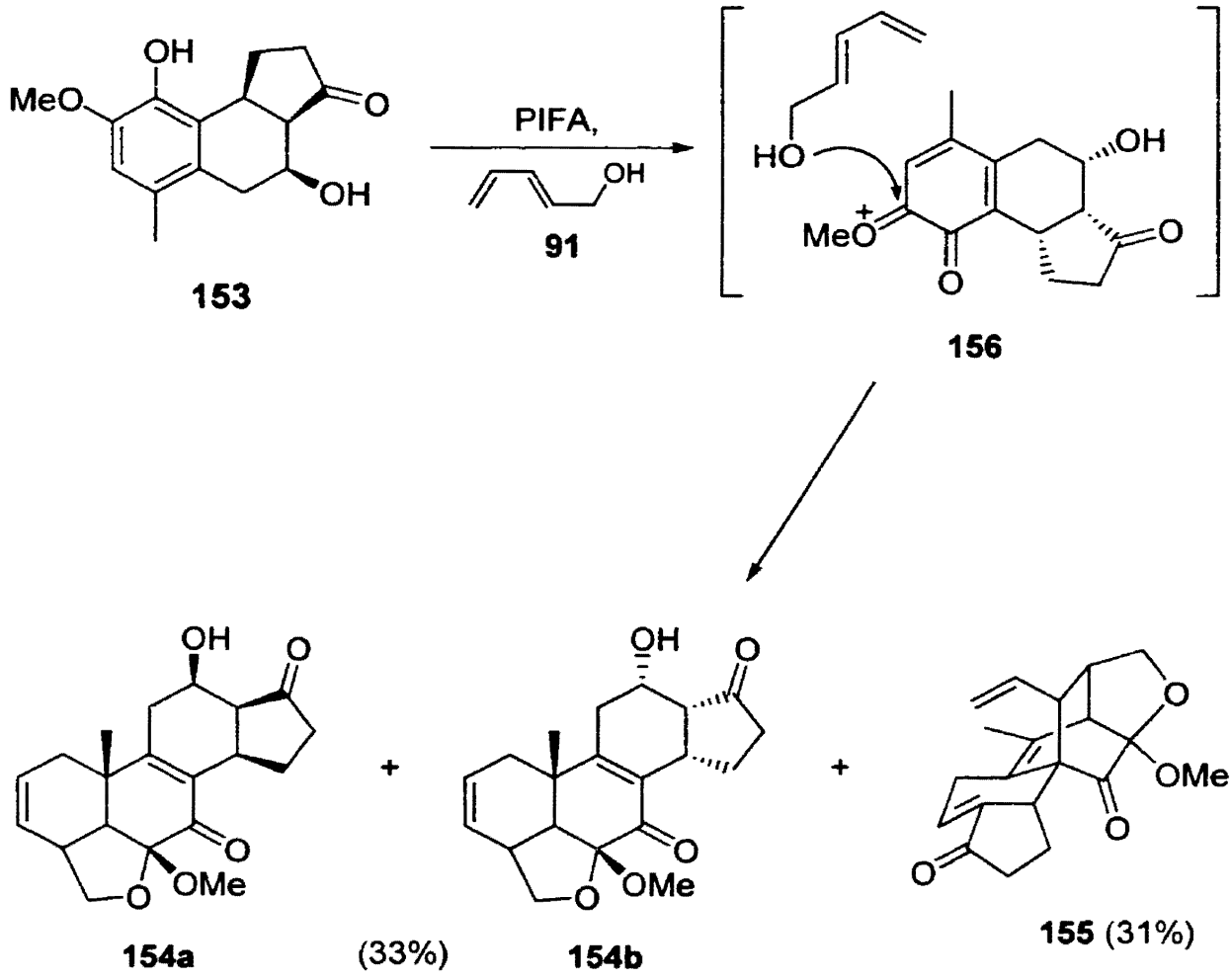
(suprafacial with respect to both alkene and dipole) and the tethering of the dipole, and since the hydrogenation of **152** does not affect the relative stereochemistry of the molecule, the structure of ketone **153** is also established.

Scheme 3.14



Once the BCD fragment was assembled, it was subjected to the usual IMDA reaction conditions,[49] which resulted in the severe decomposition of the reagents, making purification of the products impossible. Despite that, separation by flash chromatography was attempted, and our reward came as the ^{1}H NMR spectrum of one of the fractions hinted at the presence of pentacycle **154**. Thus, the IMDA reaction was attempted once again, but this time the oxidizing agent was added over a period of 4 hours to a hot (50°C) solution of **91** and **153** in THF. Such procedure keeps the concentration of the reactive intermediate **156** at a minimum, thus reducing the risk of dimerization and also ensuring the presence of a large excess of dienol **91** to form the *ortho*-quinone

Scheme 3.15



monoketal. The success of our approach was evidenced when purification of the reaction products (Scheme 3.15) led to the isolation of bridged adduct **155** (Figure 3.2) and also of a mixture of diastereomers **154a** and **154b**, which could not be separated by flash chromatography. Compounds **154a** and **154b** arise from **91** attacking intermediate **156** from above or below the plane of the quinonoid ring respectively, and their approximate 4:3 ratio suggest that the stereochemistry of both the CD ring junction and the C-4 hydroxyl group have only a minor influence on the stereoselectivity of the formation of the *ortho*-quinone monoketal. However, since the synthesis of the pentacyclic framework

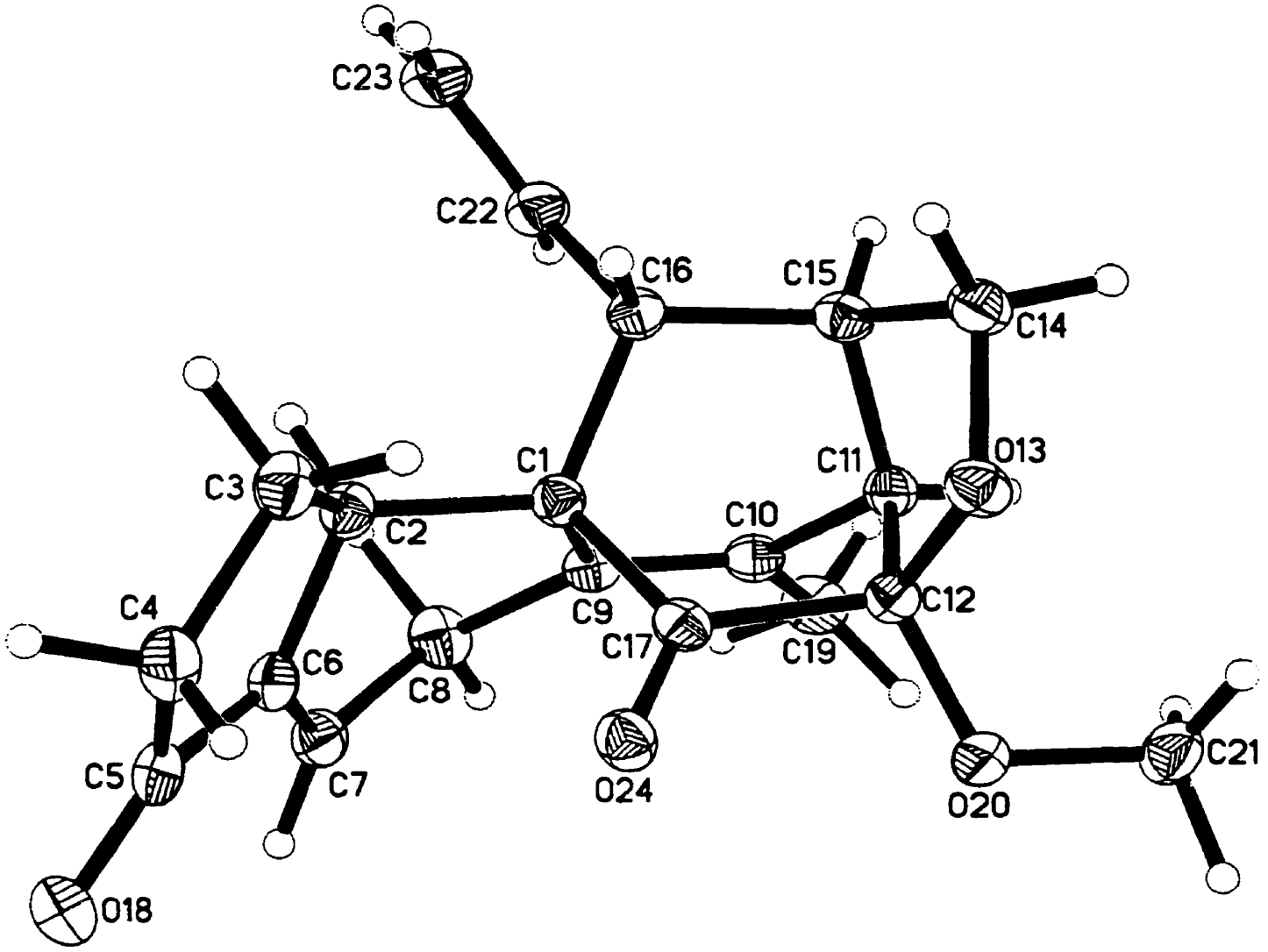
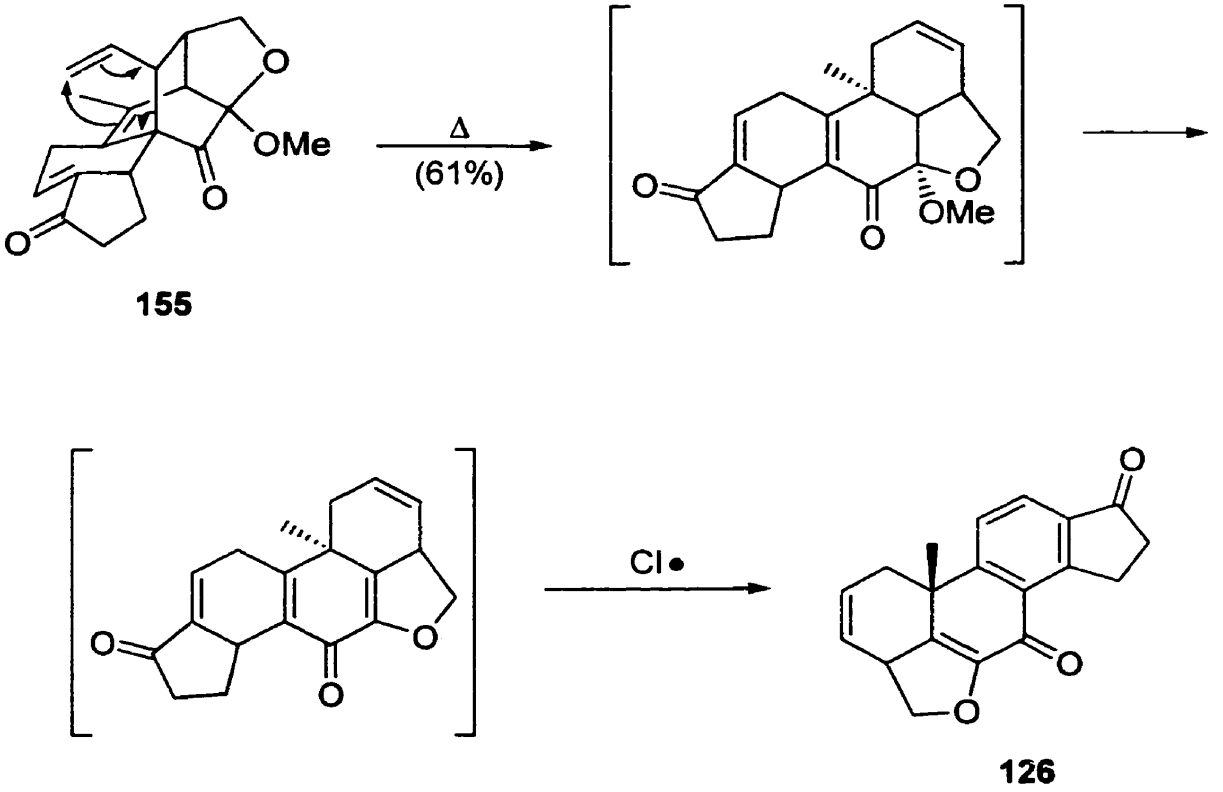


Figure 3.2: X-ray crystal structure of bridged adduct **155**

of **2** requires that ring C be aromatized, the formation of **154** as a mixture of diastereomers did not cause much concern, and no further attempts at separation were made before the next step in the synthesis. Bridged adduct **155**, on the other hand, is isolated as a single diastereomer, presumably because steric hindrance prevents the formation of the other isomer. It is also noteworthy that **155** arises from spontaneous dehydration, which takes place despite the fact that reaction conditions are kept neutral by the presence of $NaHCO_3$ in the reaction mixture.

Scheme 3.16



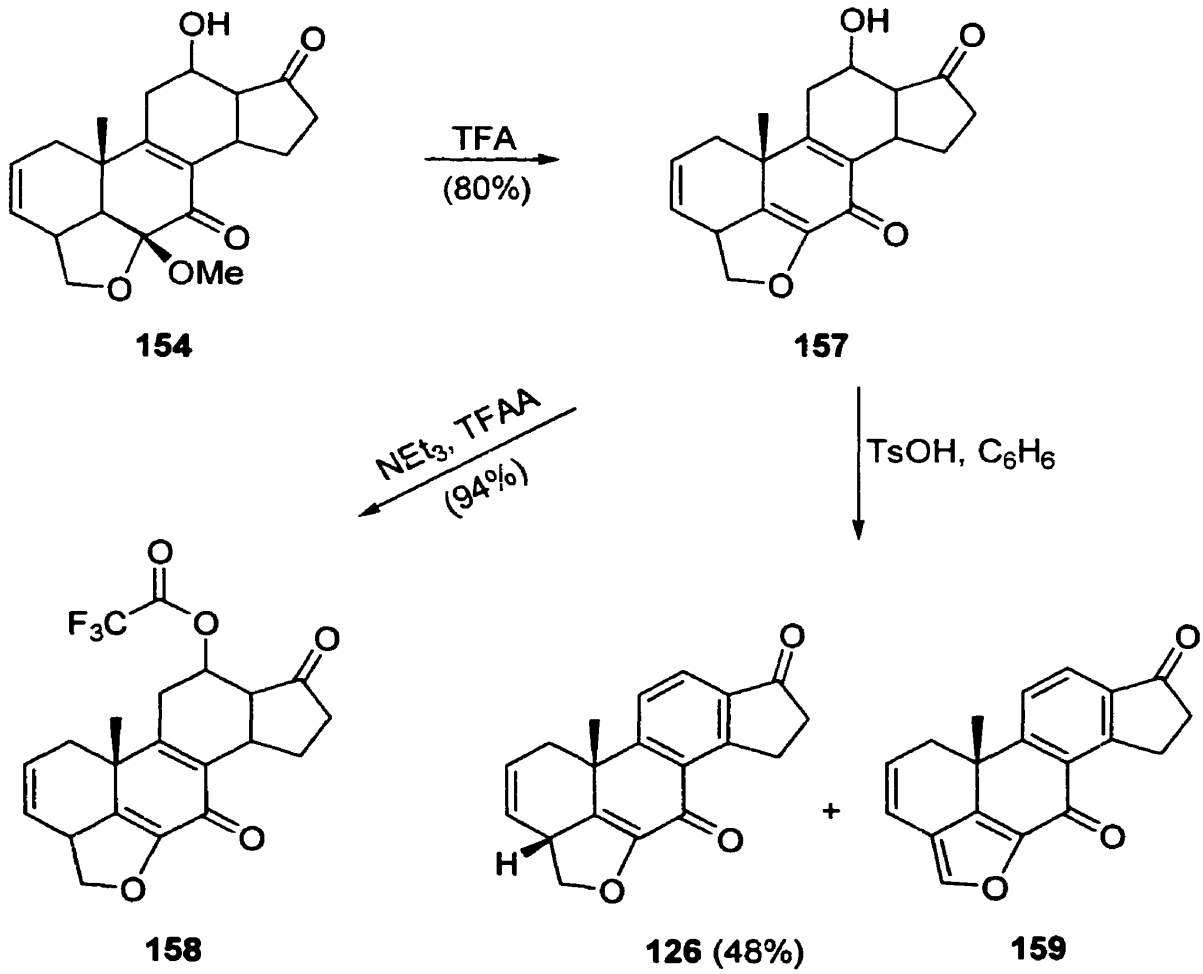
155

126

Upon reflux in 1,1,2,2-tetrachloroethane, bridged compound **155** undergoes a Cope rearrangement with subsequent loss of methanol and aromatization of ring C -

possibly due to radical chlorination followed by dehydrochlorination - to yield pentacycle **126** (Scheme 3.16), which corresponds exactly to the carbon framework of **2**. Conversion of diastereomers **154** to pentacycle **126**, however, was not as straightforward. Treatment of **154** with TFA (Scheme 3.17) caused the elimination of methanol to form dienone **157** as a mixture of diastereomers, but the hydroxyl group remained unaffected. Also, attempts to dehydrate **157** by reacting it with methanesulfonyl chloride in pyridine[99] resulted only in the decomposition of the starting material, which led us to investigate the

Scheme 3.17

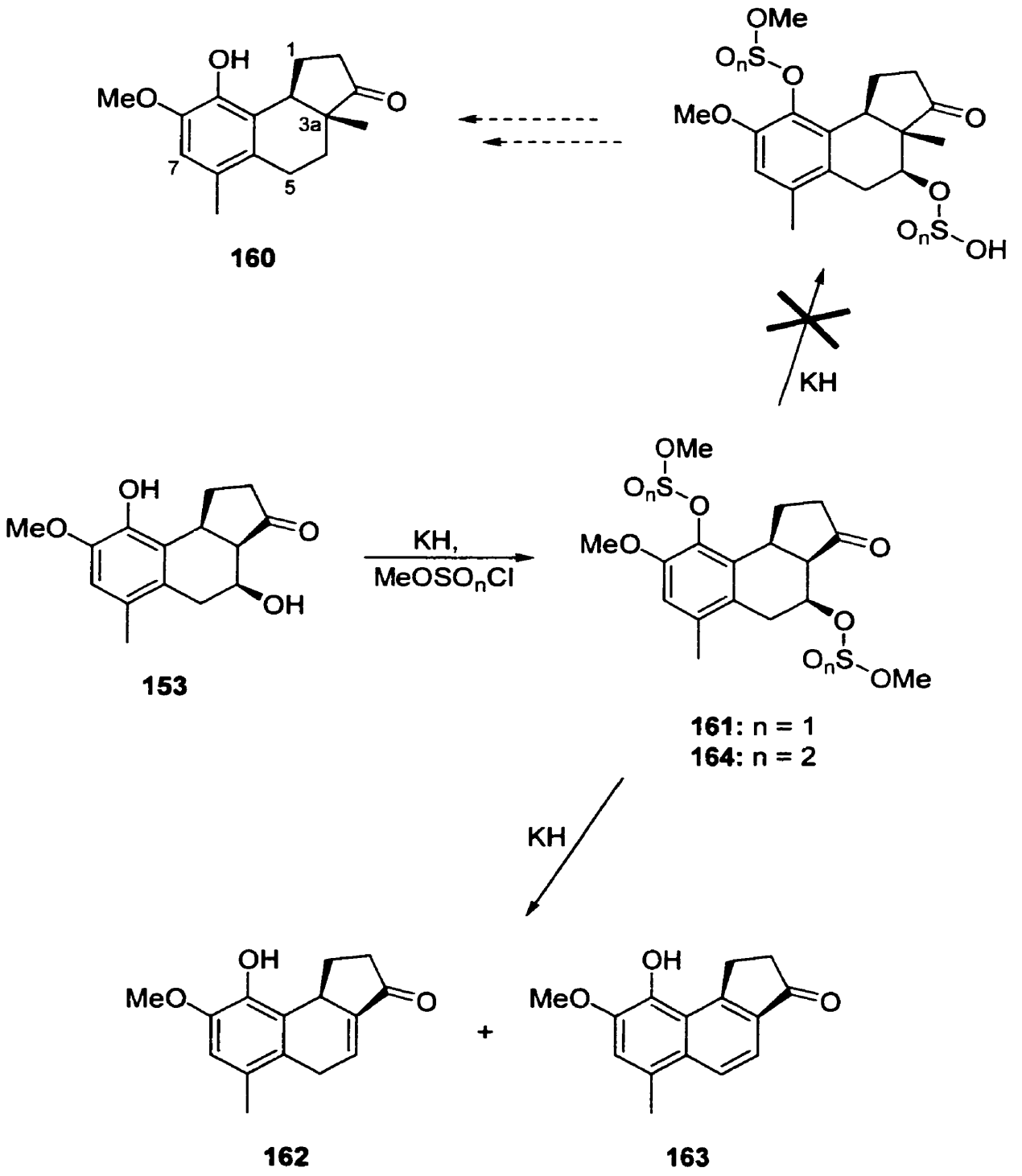


use of TFAA and NEt_3 as an alternative, since it has been reported to give good results in systems where MsCl and pyridine failed.[100] Once again, our efforts were thwarted by some unusual chemical behavior, and only the acylated product **158** was isolated, suggesting to us that the geometry of the molecule does not allow for an E2 elimination to take place. We therefore set out to reexamine the acid catalyzed dehydration of dienone **157**, and treatment of it with TsOH in hot benzene[101] with exposure to air finally accomplished not only the desired dehydration, but also the aromatization of ring C, presumably due to air oxidation. To a certain extent, aromatization of ring E was also observed, and pentacycle **159** was isolated as a side product, which can, alternatively, also be generated in 60% yield by refluxing compound **126** with *p*-chloranil[102] in xylenes. In subsequent experiments, we demonstrated that **126** could also be prepared directly from **154**, by reacting the diastereomeric mixture with TsOH in benzene. In addition, a careful control of the reaction temperature considerably minimizes the formation of furan **159**, but we have not been able to totally prevent it. It should be pointed out that although **2** exhibits an aromatic ring E, the sensitivity of furan rings to acid and oxidizing reagents made a dihydrofuran ring more desirable at this point, leaving the aromatization of ring E for the very end of the synthesis.

3.5. Attempted Modifications of the Route

The success of our synthetic route to the pentacyclic skeleton of **2**, with an overall yield of 19% over just 9 steps,[103] inspired us to investigate its possible application to access the other fungal metabolites of the viridin family. A crucial step for that is the synthesis of BCD benzindanone **160**, which exhibits typical steroidal stereochemistry,

Scheme 3.18

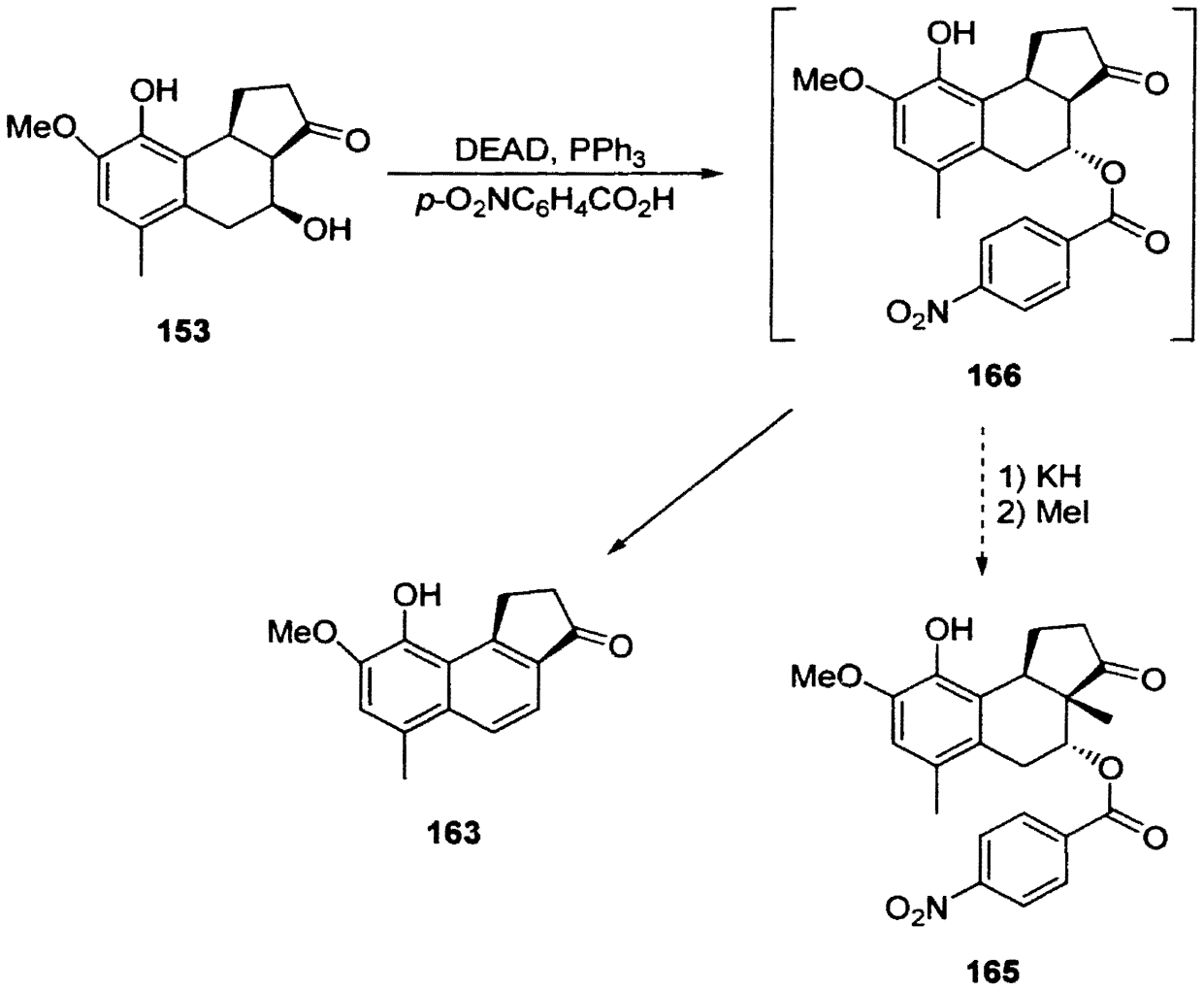

OH
1
MeO
O
3a
7
5
160
OMe
O_nS
O
MeO
O
O
O_nS
OH
KH
OH
MeO
O
OH
153
KH,
$MeOSO_nCl$
OMe
O_nS
O
MeO
O
O
O_nS
OMe
161: n = 1
164: n = 2
KH
OH
MeO
O
+
OH
MeO
O
162
163

with rings C and D fused in a *trans* manner, and an angular methyl group attached to C-3a (C-13 according to standard steroid numbering). Based on the fact that methyl sulfate[104] and also methyl sulfite[105] have both been used as methylating agents, our initial route to **160** started with the preparation of **161** by treating benzindanone **153** with KH and subsequently with MeOSOCl.[106] Due to the presumed instability of sulfite **161**, it was not isolated, and a third equivalent of KH was added instead. While we were quite aware of the possibility of elimination taking place, the geometry of the enolate did not seem to favor that[107] and we thus hoped that, once the thermodynamic anion was formed, an intramolecular alkylation[108] would occur to install the methyl group on the ring junction with the right relative stereochemistry (Scheme 3.18). Unfortunately our fears were quite justified, and work up of the reaction mixture only led to the isolation of elimination product **162** and fully aromatized benzindanone **163**, which probably arises from air oxidation of **162**. Similar results were observed when $MeOSO_2Cl$[109] was used to form sulfate **164**.

Another approach to the same benzindanone **160** relied on a Mitsunobu reaction[110] to invert the relative stereochemistry of the hydroxyl group, while at the same time replacing it by a bulkier substituent that would effectively block one of the faces of the molecule (Scheme 3.19). Generation of the thermodynamic enolate followed by methylation would then yield benzindanone **165** with the desired *trans* CD ring junction. Our efforts, however, once again met with little success, as compound **163** was the only product detected, indicating that elimination takes place under the Mitsunobu reaction conditions, and we believe that such elimination takes place after nitrobenzoate **166** is formed, as indicated by the favorable geometry of its enolate.[107] However, **166** has not

been isolated and, as seen for compounds **161** and **164**, the possibility that elimination takes place right after the reaction between benzindanone **153** and DEAD-PPh_3 complex cannot be discounted.

Scheme 3.19



It is important to point out the striking differences in reactivity between pentacycles **154** and **157** and benzindanone **153**. While compounds **154** and **157** proved to be quite resistant to an array of dehydration methods, the presence of an aromatic B

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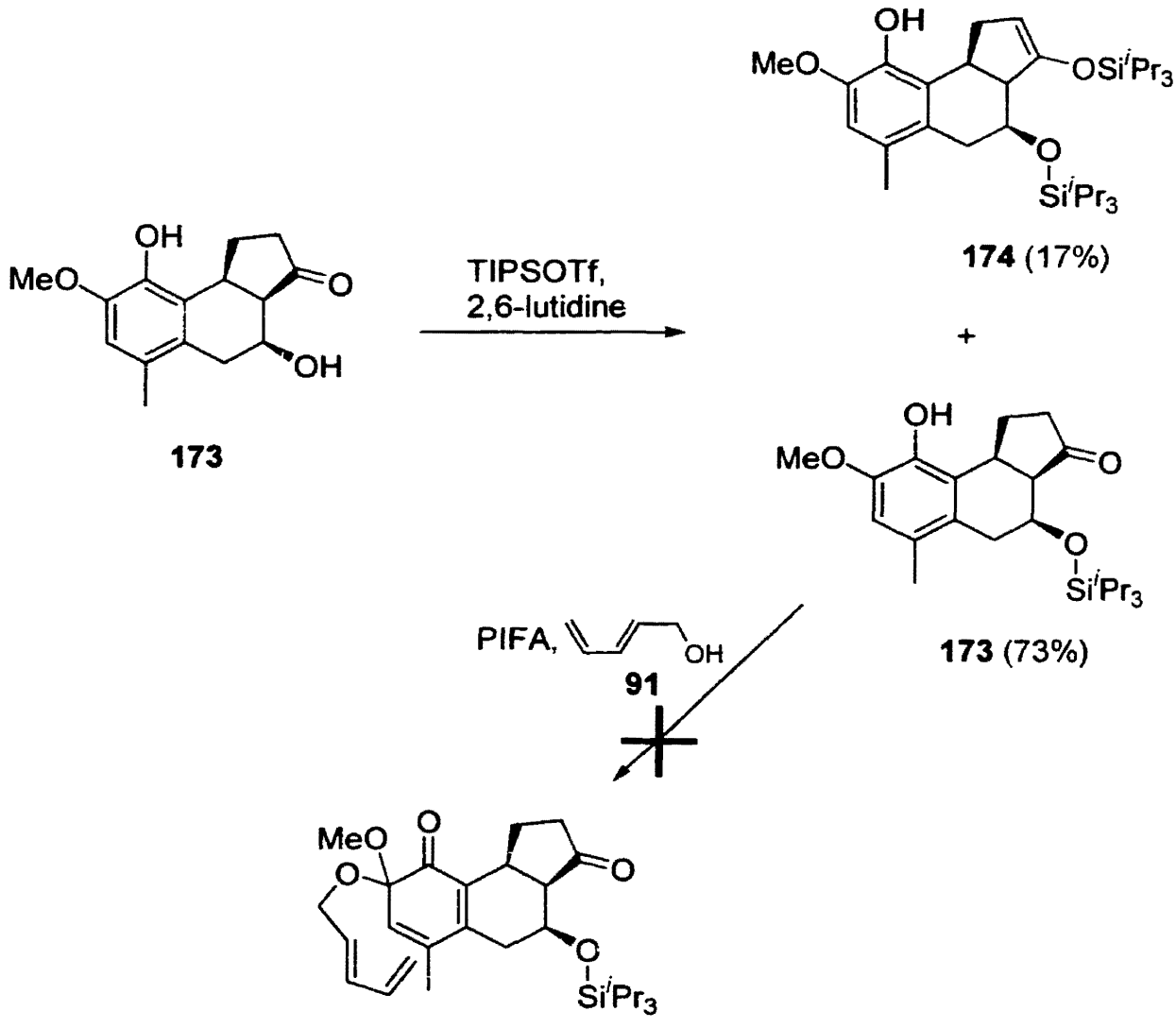
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ring junction after the pentacyclic carbon skeleton **154** has been assembled. Still, an adaptation of classical steroidal chemistry[111] was also considered as a possible route to **160**. Thus, catechol **167** is protected as acetonide **168** (Scheme 3.20), which is then condensed with aldehyde **169**[112] to give styrene **170**. After hydrogenation, a Friedel-Crafts reaction would close ring C, forming a new styrene **171**. The hydrogenation of similar compounds is known to give the desired *trans* ring junction,[111] and we hoped to prepare intermediate **172** in such a way. While the metal-halogen exchange in **168** occurred quite readily, the lithiated species did not react at the carbonyl group of the aldehyde, with deprotonation of **169** taking place instead.[113] Transmetallation to form a Grignard reagent was also ineffective. The use of organometallic reagents derived from oxophilic cations such as cerium[114] or titanium[115] makes it possible to do nucleophilic additions onto carbonyls of enolization-prone substrates, and we therefore considered yet another transmetallation. Our efforts, however, were halted by some discouraging results obtained in a parallel investigation. As previously discussed, the stereochemical features of benzindanone **153** have little bearing on the outcome of the IMDA product **154**. Unlike **2**, however, relative stereochemistry is of paramount importance in any route leading to several of the other members of the viridin family of fungal metabolites.[5] To address such issues, we initially attempted the separation of diastereomers **154a** and **154b** by preparative HPLC and, although the separation was not complete, pure samples of both diastereomers could be obtained. We then examined the attachment of a protecting group to the C-4 hydroxyl group of **153** as a way of increasing the steric hindrance on one side of the molecule and thereby also increasing the diastereoselectivity of the IMDA reaction. Our previous experience with the methylation of catechols **117**, **132** and **148**

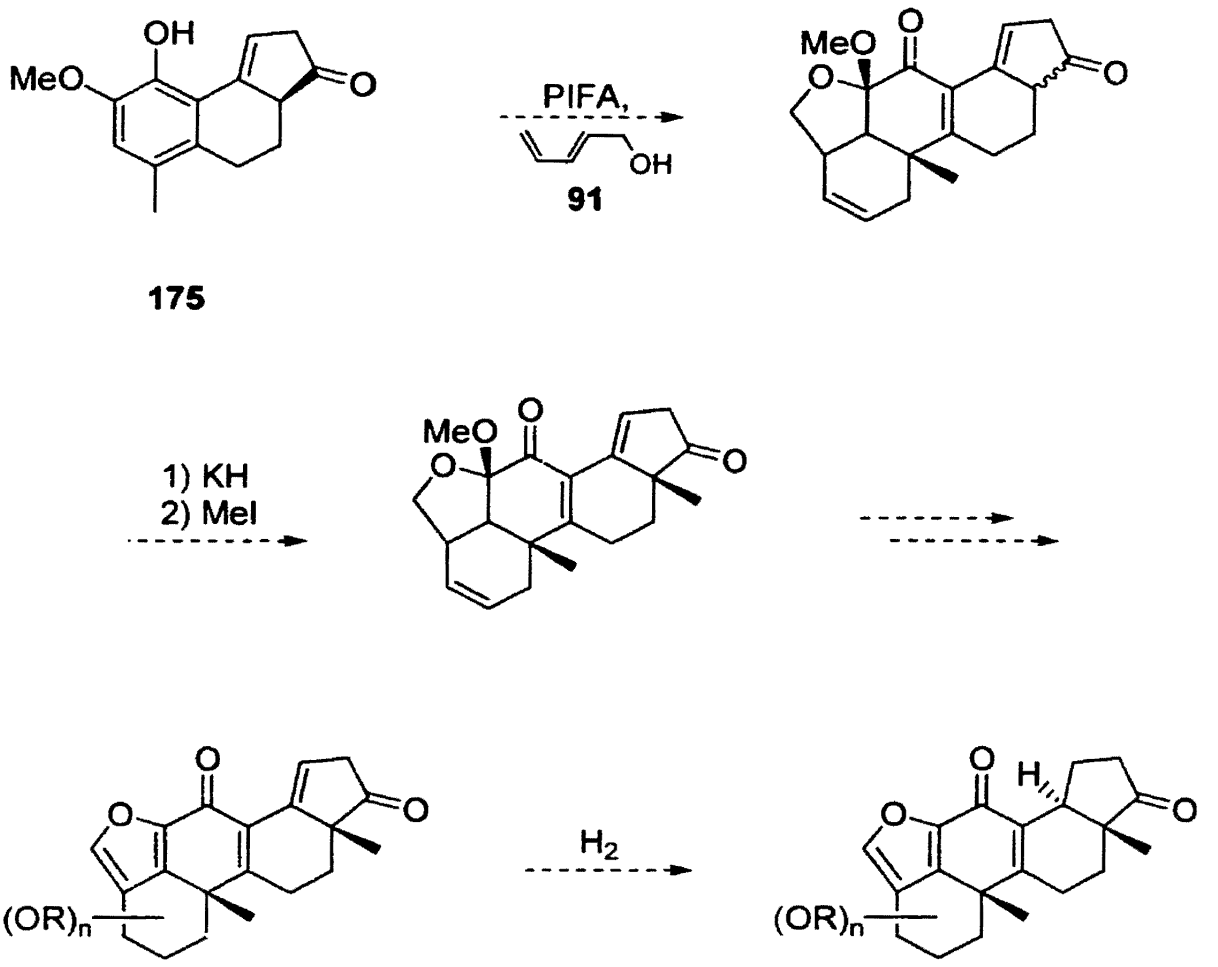
Scheme 3.21



indicated that the phenolic hydroxyl group was too hindered to react, and as expected, reaction between **153** and TIPSOTf[116] generated silyl ether **173** (Scheme 3.21) in excellent yields, along with minor quantities of bis(silyl ether) **174**. Ideally, the presence of such a bulky group blocking one of the faces would force dienol **91** to attack the *ortho*-quinonoid intermediate from the opposite side, thus yielding much higher diastereomeric excesses of the pentacycle. In reality, however, this lead only to the almost quantitative recovery of starting material **173**, and we believe that the presence of

the TIPS protecting group causes so much steric crowding that it effectively prevents the attack of the phenol on the oxidizing agent.

Scheme 3.22



Based on all those results, we believe that benzindanone **175** would be a more suitable intermediate in the synthesis of several compounds related to **6**, since its adduct from the reaction with **91** lends itself quite well to methylation from the β face (Scheme 3.22) due to the convex shape of the molecule. Also, further along the synthetic route, after the formation of the aromatic furan ring E, the molecule acquires a much flatter

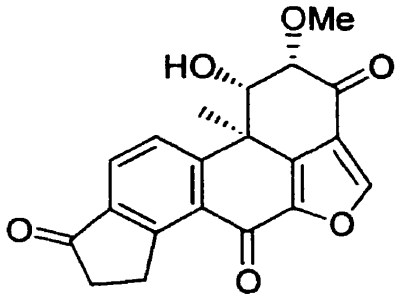
geometry, and hydrogenation of the vinyl moiety on ring D would presumably result in the desired *trans* ring junction, as was the case in the synthesis of other steroids.[111] The development of an efficient synthetic route to **175**, however, will certainly be a fairly difficult task, since migration of the double bond into conjugation with both the carbonyl group and aromatic ring might be extremely facile.

Despite the difficulties encountered in the adaptation of our synthetic route to other members of the viridin family of fungal metabolites (**6-9**), the successful preparation of pentacycle **126** is a significant step towards a future synthesis of compounds **2-5**. We therefore set out to investigate the use of the double bond in ring A as a handle for the oxidative functionalization of the molecule.

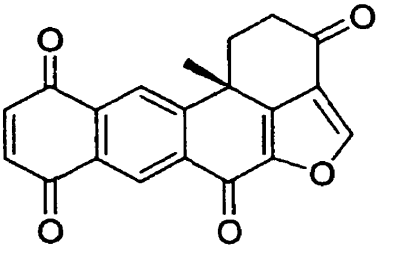
CHAPTER 4 – STUDIES TOWARDS THE FUNCTIONALISATION OF RING A

4.1. Initial Investigations

Once the pentacyclic carbon skeleton of viridin (**2**) had been assembled, it was necessary to investigate the functionalization of ring A in order to complete the synthesis. After consideration of the structural similarities between **2** and halenaquinone (**38**) and also of the simpler substitution pattern present on ring A of the latter, it seemed to us that a synthesis of **38** would be a suitable prelude to any investigation of a route to the fungal metabolites.



2

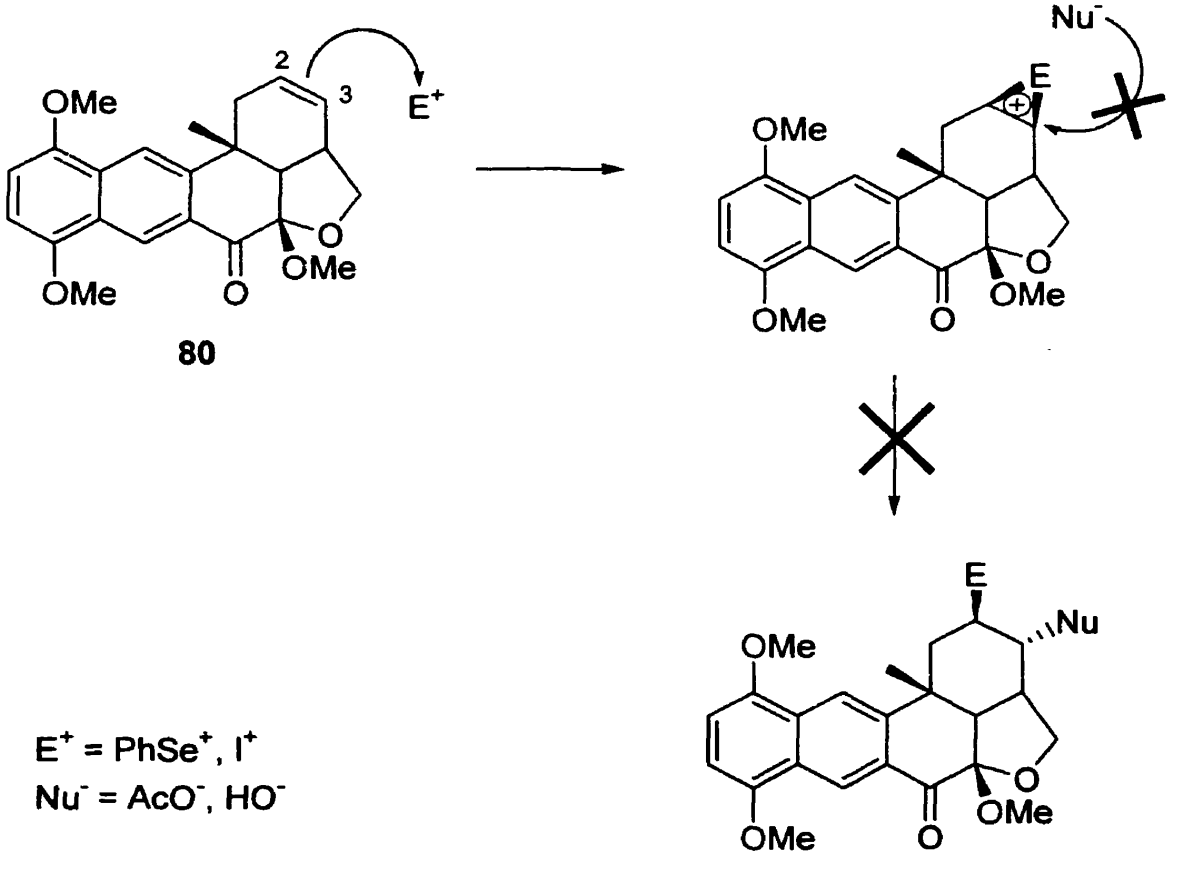


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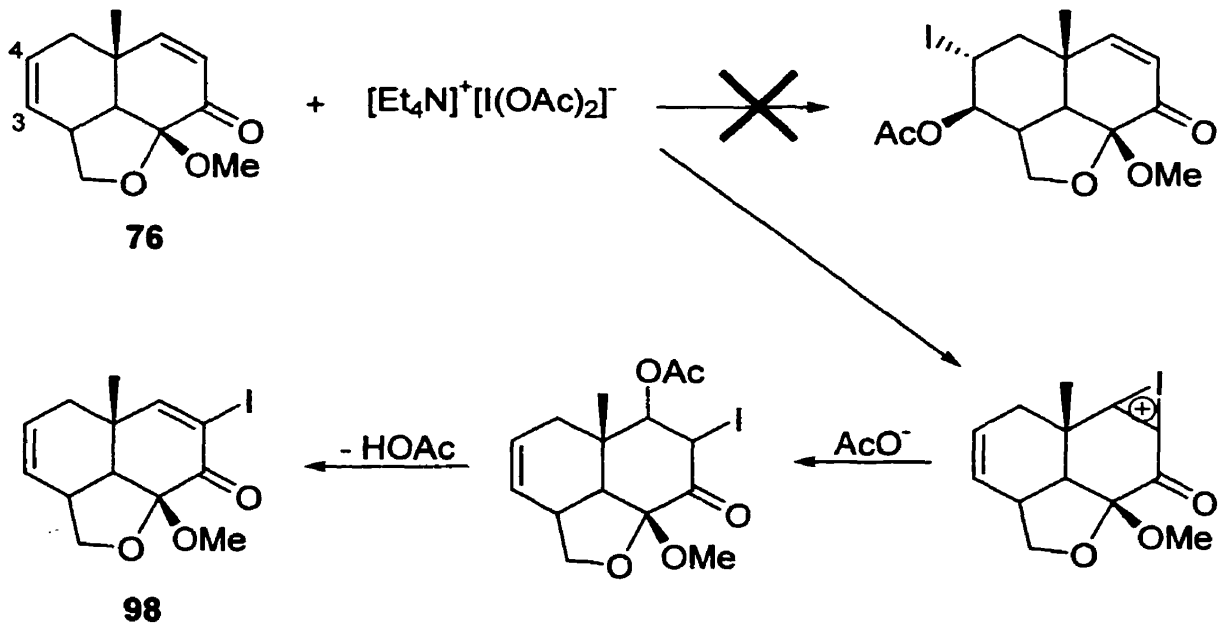
Using both naphthofuranone **76** and pentacycle **80** as substrates, our initial goal was to first create some differentiation between carbons 2 and 3 of **80** - or carbons 3 and 4 of **76** - and then selectively convert C-3 into a carbonyl. Thus, **80**[48] was treated with PhSeBr in the presence of acetic acid,[117] but unfortunately no reaction took place (Scheme 4.1), and, likewise, only starting material was recovered from the reaction between **80** and HOI. Our choice of reagents was based on the belief that the expected diaxial ring opening[118] would deliver the oxygenated substituent to the desired position at

C-3, but our results suggest that in both cases nucleophilic attack onto the cyclic cation at the α face is precluded by steric hindrance arising from the highly bent shape of the molecule (for an analogous structure, see Figure 4.1). Although the formation of the intermediate cyclic cation has not been established by any analytical technique, several successful attempts at functionalizing the vinyl moiety in ring A (*vide infra*) clearly demonstrated that attack of the double bond from the β face does indeed take place. We therefore believe that the recovery of the starting material arises either from a reversible electrophilic attack onto the double bond or from the quenching of the cyclic cation by an undetermined nucleophile, but we have not investigated the matter any further.

Scheme 4.1



Scheme 4.2



Based on our previous results, we were not surprised to verify that treatment of **76** with $Et_4NI(OAc)_2$[119] failed to give the desired acetoxy iodide (Scheme 4.2), but addition of a second equivalent of the reagent led to the formation of α-iodoenone **98** in nearly quantitative yield, which was quite unexpected, as enones are generally unreactive towards electrophiles. The fact that $Et_4NI(OAc)_2$ is reactive enough to attack the enone moiety, combined with the need for a second equivalent of the iodinating reagent for the observed reaction to take place provides further evidence that the double bond on ring A is indeed attacked, and that steric hindrance prevents the nucleophile from reacting with the cationic intermediate.

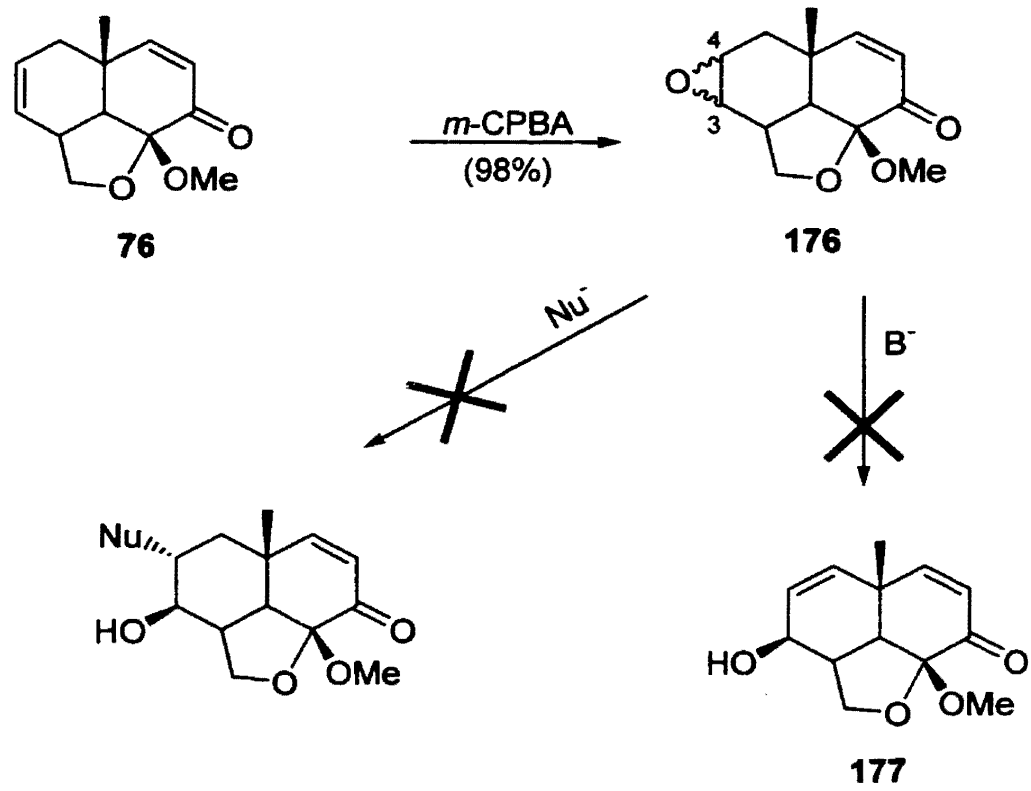
4.2. The Epoxidation Route

Reaction of **76** with *m*-CPBA in CH_2Cl_2 gave a 6:1 mixture of isomeric epoxides **176** (Scheme 4.3), with the β epoxide being presumably the major component, since the

β face is readily accessible for the epoxidizing reagent. Our strategy was to use a ring opening reaction to create some differentiation between C-3 and C-4, hopefully cleaving the epoxide at the C-4-oxygen bond. Due to the relative stereochemistry of the epoxide ring, we believed that α-**176** would undergo ring opening reactions much more easily than the β isomer, and we therefore tried to optimize the reaction conditions to increase the α:β ratio. Unfortunately, variations in solvent, temperature, concentration and amount of reagent all failed to yield α-**176** in reasonable yields. In addition, separation of the isomeric epoxides by chromatography was not a straightforward matter, and we thus carried on our investigations using **176** as a mixture of both isomers. As expected, reaction between **176** and NaOMe or NaSPh led only to recovery of most of the starting material, but, interestingly, such recovered starting material consisted exclusively of β-**176**, indicating that the α isomer is indeed more reactive. Still, we were not able to isolate any ring opening products. Base promoted ring opening of **176** was also attempted without success. Lithium[120] and magnesium[121] dialkylamides derived from 2,2,6,6-tetramethylpiperidine, diisopropylamine and pyrrolidine, as well as KO^{t}Bu all failed to react with **176** to give allylic alcohol **177**. Attempts to prepare a silyl ether of **177** via reaction of **176** with TMSOTf in the presence of DBU[122] were also fruitless, and thus we saw it fit to start investigating the use of stronger Lewis acids as catalysts for the epoxide ring opening. We feared, however, that treatment of epoxide **176** with acid would jeopardize the subsequent Diels-Alder reaction with isobenzofuran **78** by causing elimination of methanol to form a dienone. Our experience with related compounds shows that dienones are much worse dienophiles than the corresponding enones, and we therefore decided to assemble pentacyclic epoxide **178** (Scheme 4.4) prior to any

attempts at further functionalizing ring A. In addition, we believed that the use of **178** would make side reactions less likely, since the reactive enone moiety was no longer present.

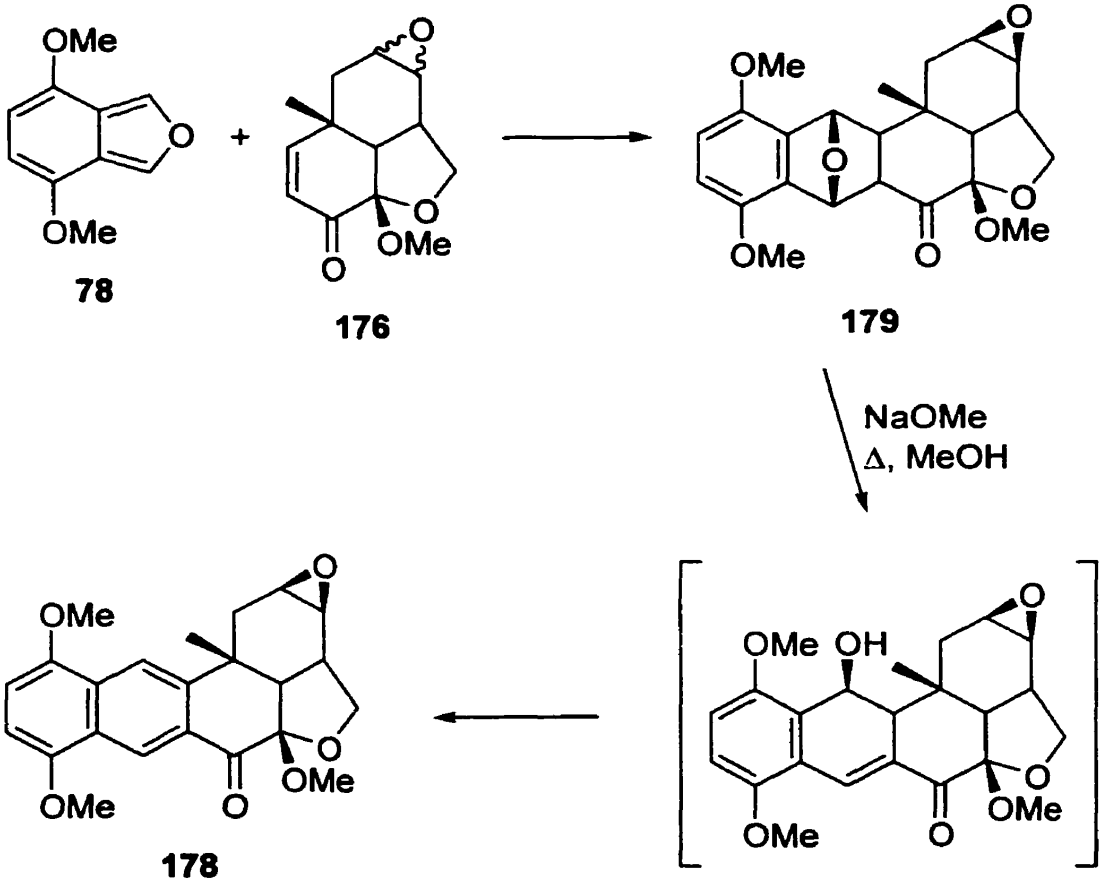
Scheme 4.3



The initial synthetic route to epoxide **178** involved the reaction between pentacycle **80** and *m*-CPBA, but the yields obtained were quite low. A much more successful approach (Scheme 4.4) capitalized on the unreactivity of **176** towards nucleophilic attack. Thus, **176** is reacted with isobenzofuran **78** to give bridged adduct

179, which is then converted to **178** by refluxing with NaOMe in MeOH. It is important to point out that, although the starting epoxide **176** was a mixture of both α and β isomers, only one isomer of **179** - and consequently also of **178** - has been isolated from the reaction mixture. Analysis of **178** by x-ray diffraction (Figure 4.1) demonstrated that the isolated product was indeed the β isomer, indicating that once again α-**176** has reacted via an undetermined alternative pathway.

Scheme 4.4



Reactions between epoxides and DMSO in the presence of a catalytic amount of TFA[123] are known to yield α-hydroxyketones, but **178** did not react at all under those

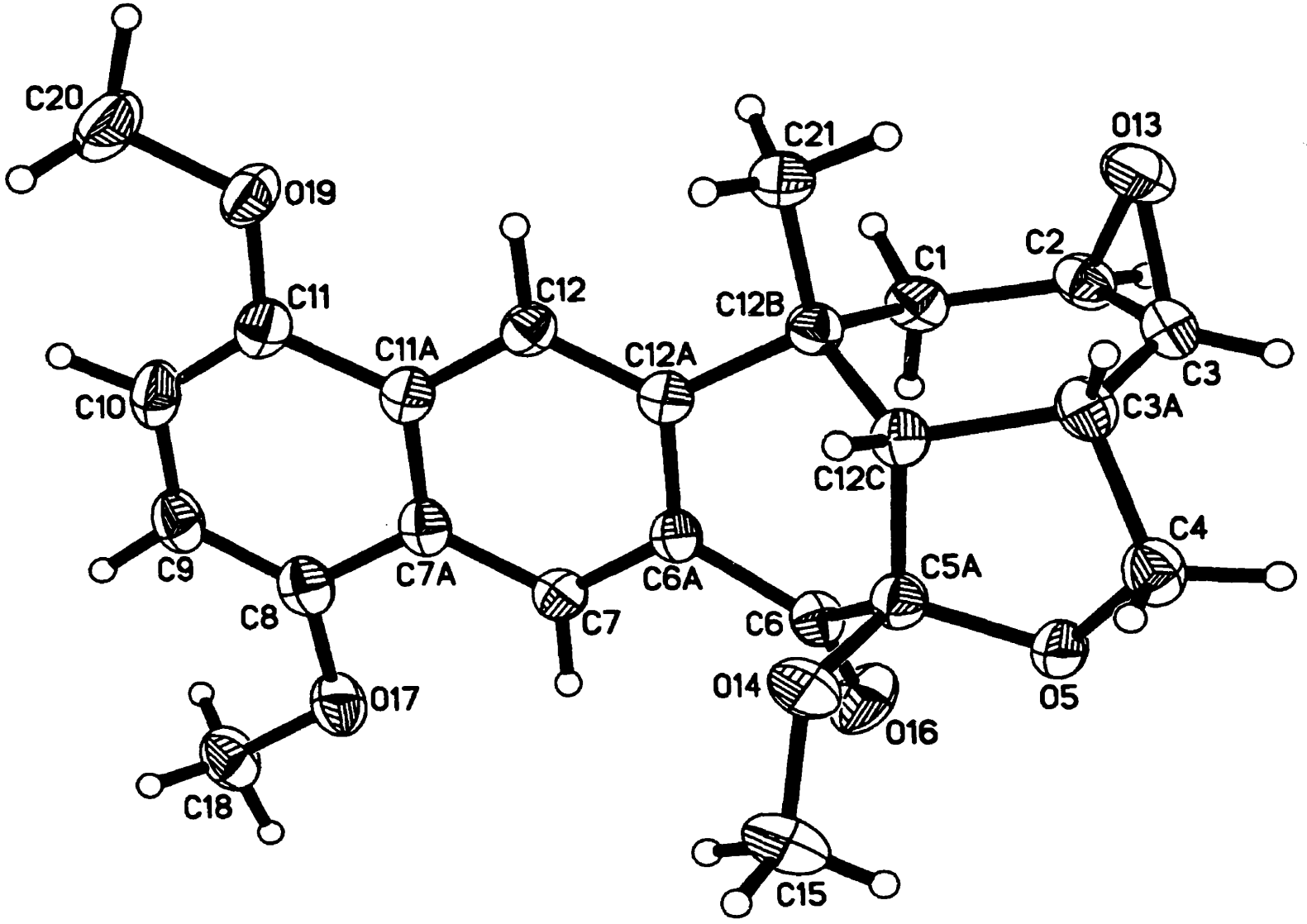


Figure 4.1: X-ray crystal structure of epoxide **178**

conditions, demonstrating once again the inertness of these epoxides towards nucleophilic attack from the α face. Equally disappointing were the results of the treatment of **178** with $LiClO_4$,[124] which failed to rearrange the epoxide moiety of **178** into a ketone, leading only to the recovery of the starting material instead. As we considered the use of harsher Lewis acids, an analysis of the crystal structure of **178** (Figure 4.1) suggested that a bulky Lewis acid would favor the epoxide ring opening to occur with the desired regiochemistry, since cleaving the epoxide at the C-2-oxygen bond not only places the Lewis acid in a quasi-equatorial position, but also avoids the 1,3 diaxial interaction with the C-12b methyl group that would arise if the C-3-oxygen bond was cleaved instead. Unfortunately, both bis[4-bromo-2,6-di-*tert*-butylphenoxy]methyl aluminum and [4-bromo-2,6-di-*tert*-butylphenoxy]dimethylaluminum[125] did not promote the opening of the epoxide, but an interesting reaction took place when **178** was treated with a solution of Lewis acid **180**. According to reports in the literature,[126] such conditions lead to the formation of β-amino alcohols (Scheme 4.5), but in our case only starting material and epoxide **181** (Figure 4.2) were isolated from the reaction mixture, with only about 10% of **178** being converted to **181**, regardless of how much Lewis acid was used. Compound **180** is generated by mixing Me_3Al and pyrrolidine in a 1:1 molar ratio, but very surprisingly the use of fresh Me_3Al led to a completely unreactive species, leading us to believe that partially hydrolyzed Me_3Al was the species responsible for the inversion of the epoxide ring. Later investigations showed that the presence of pyrrolidine is necessary for the reaction to proceed, and based on these results, we tentatively propose (Scheme 4.6) that compound **182** is the species responsible for establishing an equilibrium between epoxides **178** and **181**. Since addition of water to

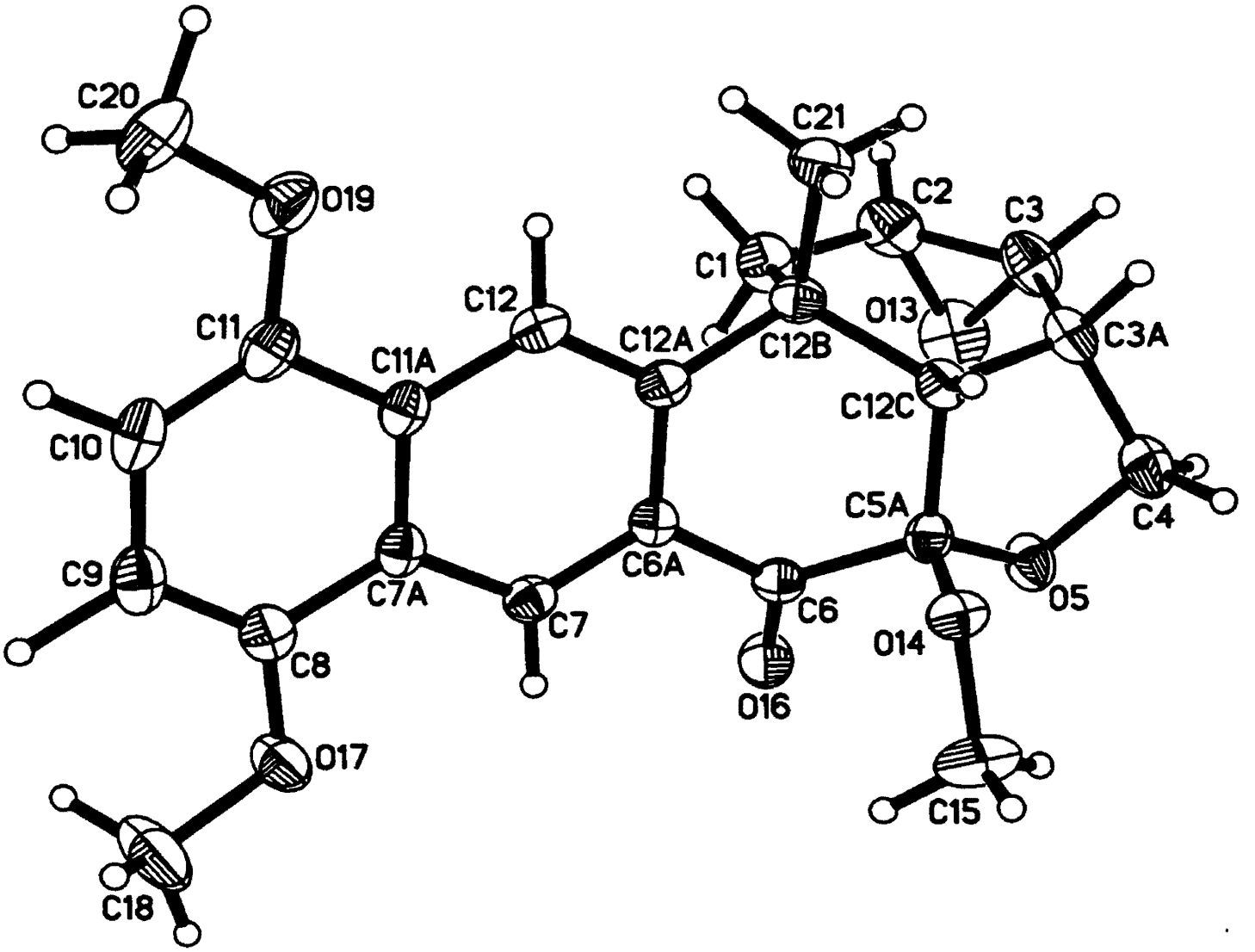
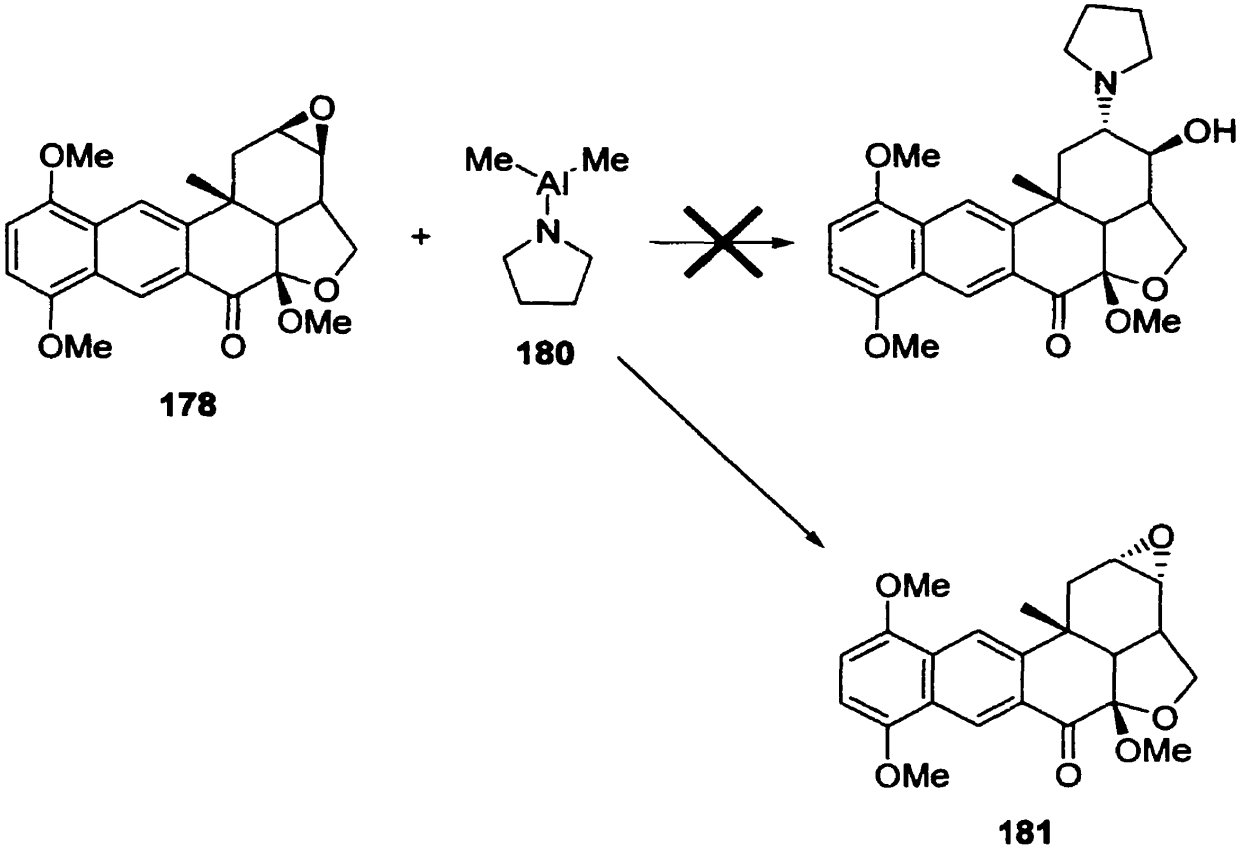


Figure 4.2: X-ray crystal structure of epoxide **181**

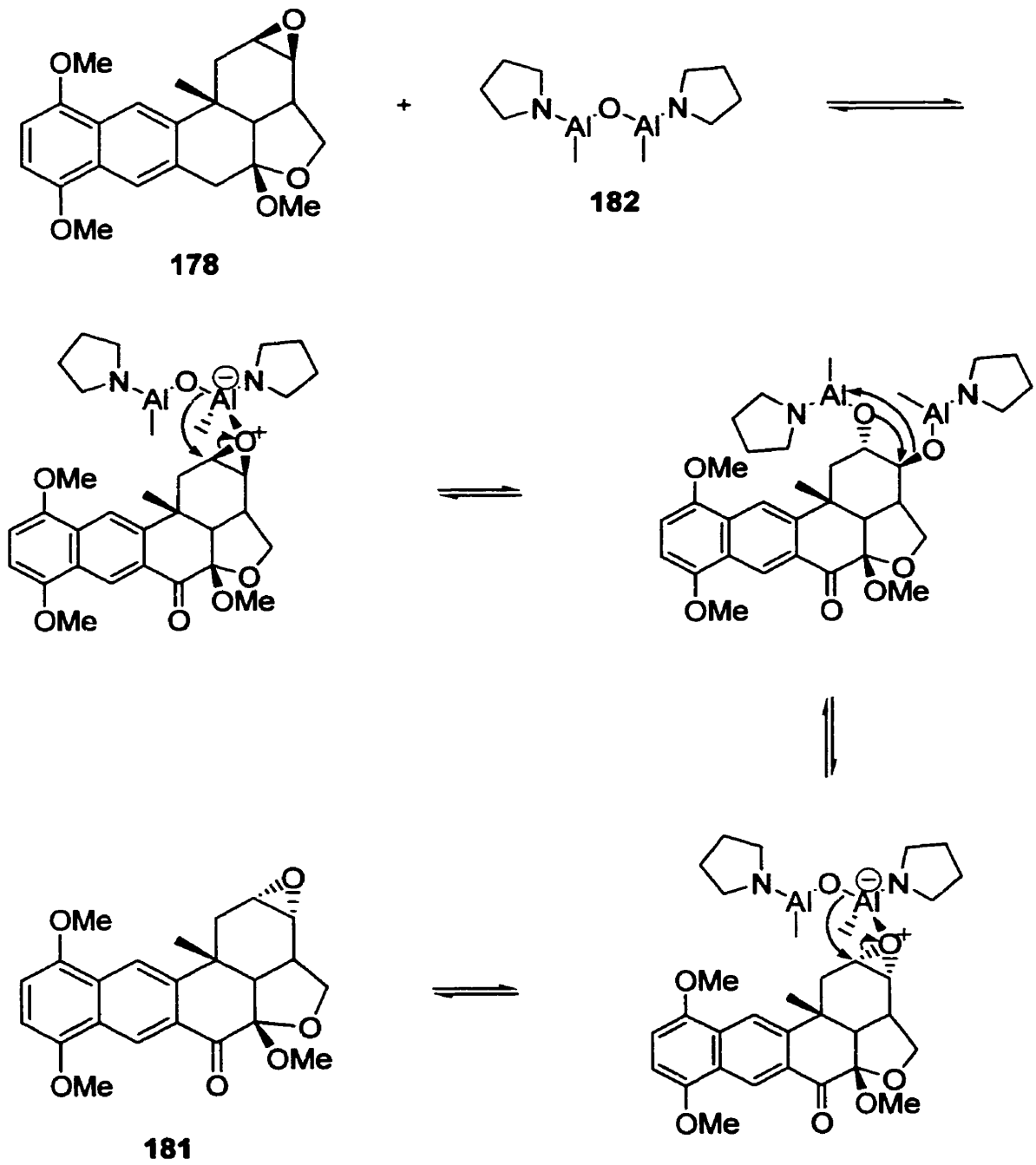
Me_3Al is a poor route to oxygen bridged aluminum species,[127] we were not surprised to see all our efforts to generate **182** *in situ* fail, and it seems to us that the actual catalytic species will have to be identified before such an interesting synthetic transformation can be put to further use.

Scheme 4.5

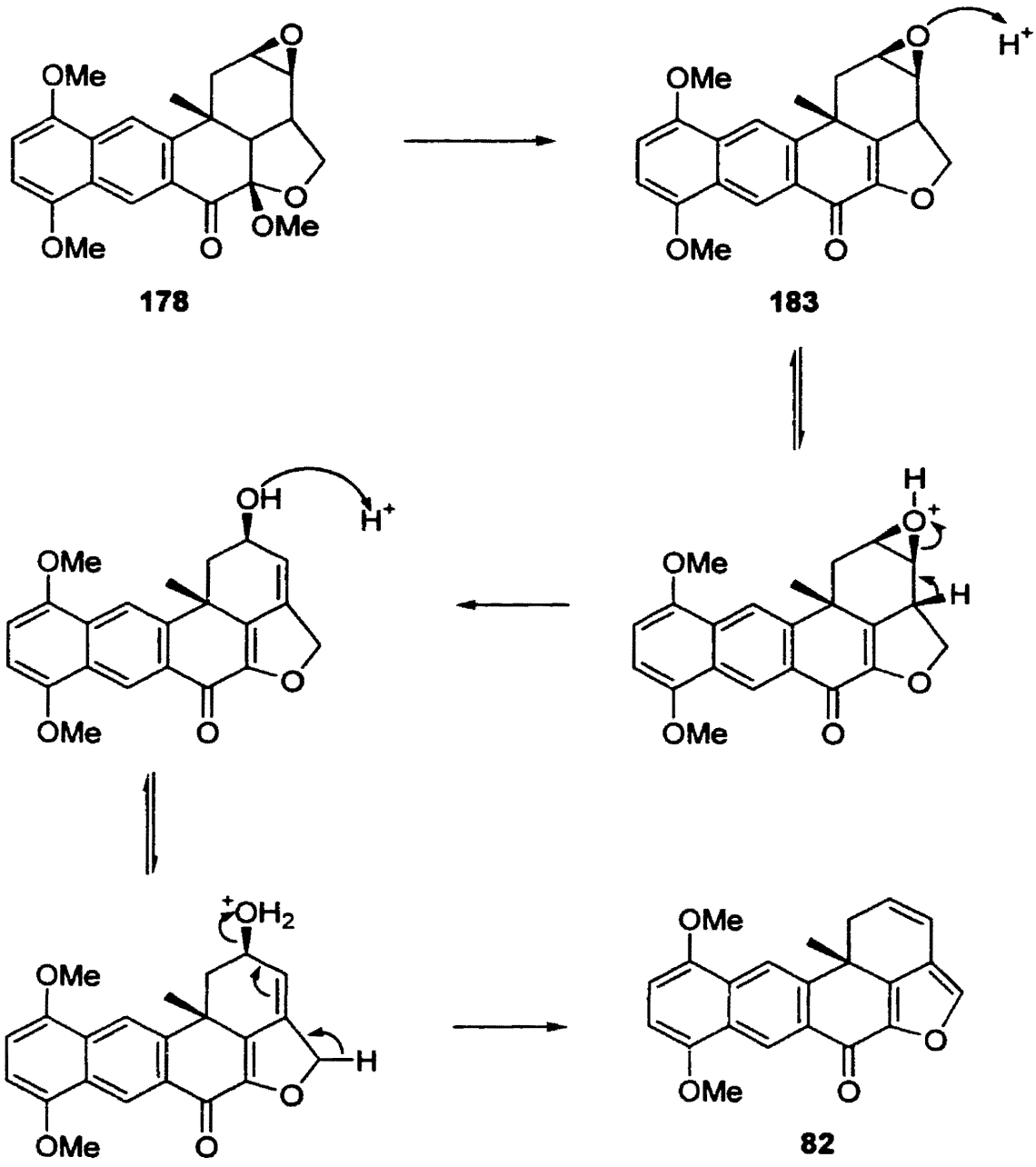


Attempts to open epoxide **178** using strong acids (TFA, BF_3) led to substantial decomposition of the starting material, as well as to the formation of compound **82**. Careful control of the reaction conditions only allowed us to isolate **183**, and we believe that the process to form **82** (Scheme 4.7) begins with loss of methanol, followed by epoxide ring opening to form an allylic alcohol, which is then quickly dehydrated to give

Scheme 4.6



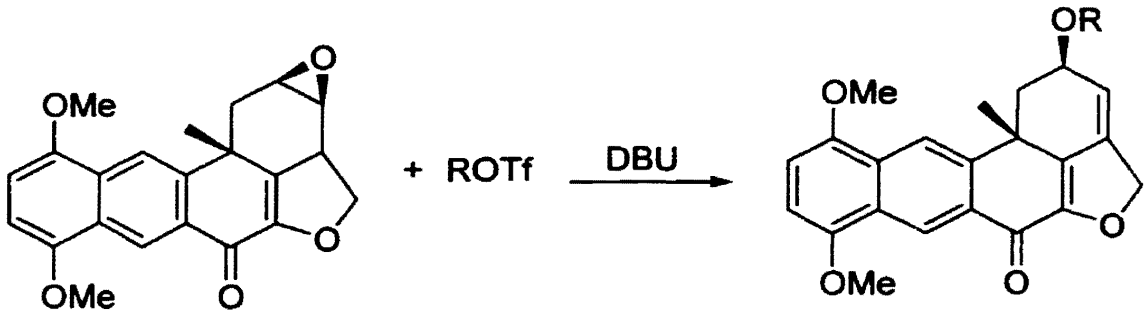
Scheme 4.7



pentacycle **82**. Since **183** could be isolated, its reactivity was also investigated. Thus, no reaction took place upon treatment with $LiClO_4$,[124] and while **183** and TMSOTf did react in the presence of DBU,[122] the epoxide ring opening occurred with undesired regiochemistry to give silylated allylic alcohol **184a** (Scheme 4.8). Similar results were

obtained when the bulkier TIPSOTf was used, indicating that the regiochemistry of the ring opening is determined by the relative acidity of the α-hydrogens, rather than by any steric factors.

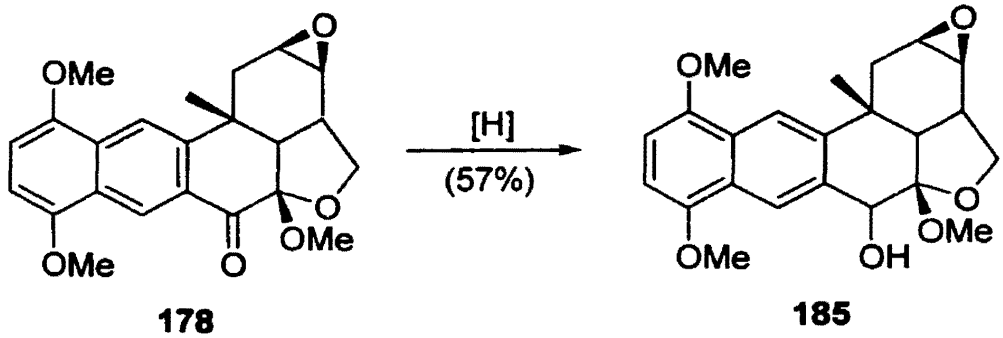
Scheme 4.8



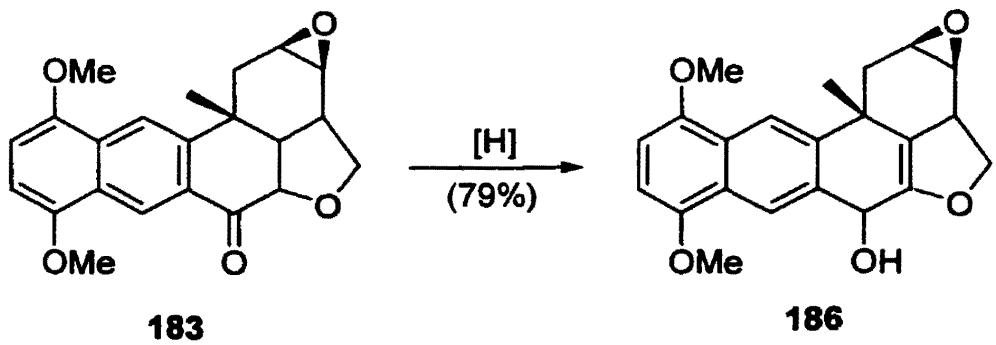
183

184a: R = TMS
184b: R = TIPS

Scheme 4.9



178 **185**



183 **186**

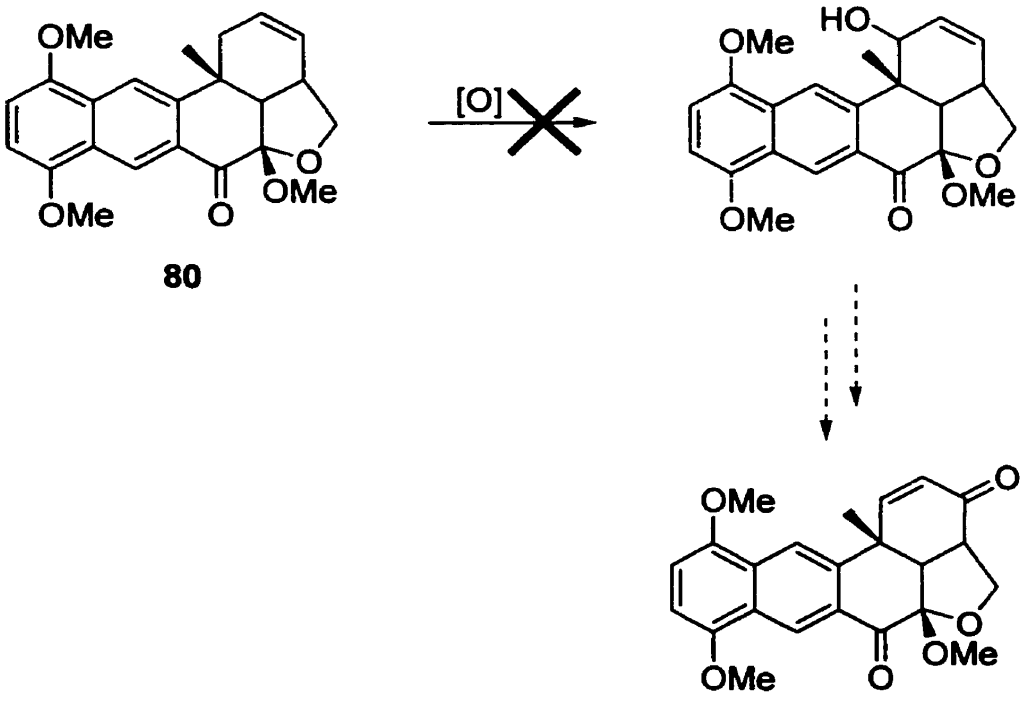
Finally, the reduction of **178** and **183** with metal hydrides was also examined (Scheme 4.9), and while attempts to open the epoxide rings using LAH[128] caused decomposition of the starting materials into complex mixtures of unidentified products, DIBAL,[129] Red-Al[130] or Super Hydride[131] reduced only the carbonyl moieties of epoxides **178** and **183** to yield **185** and **186**, respectively. Presumably steric hindrance is once again responsible for the unusual lack of reactivity exhibited by both epoxides, and we thus focused our efforts to functionalize ring A on other oxidative methods.

4.3. Permanganate Oxidation and the α-Ketol Rearrangement

Allylic oxidation followed by transposition and oxidation to an enone was investigated as a way of functionalizing ring A (Scheme 4.10), but when both PCC[132] and SeO_2/TBHP[133] failed to oxidize **80** we turned our attention to the use of $KMnO_4$ to differentiate between C-2 and C-3. Oxidation of alkenes using $KMnO_4$ is widely known to produce glycols, but reactions conducted in mildly acidic medium result in further oxidation of the cyclic manganese ester leading to α-hydroxyketones.[134] Thus reaction between **80** and $KMnO_4$ in acidic acetone-water mixture gave hydroxyketone **187** in fairly good yields (Scheme 4.11). While the formation of **187** instead of **188** was quite unfortunate, as the latter could be much more easily converted to **38**, the complete regioselectivity of the reaction was not entirely surprising, since that arrangement relieves a 1,3 diaxial interaction between the manganese ester and the C-12b methyl group and also leaves the newly formed hydroxyl group in a quasi-equatorial position. Still, it is well documented in the literature that α-hydroxyketones can be isomerized in the presence of acid[135] or base,[136] and it was our hope that conditions could be found to

convert **187** into **188**, or at least to establish an equilibrium between both isomeric hydroxyketones. Thus **187** was treated with NaOH in methanol, but surprisingly only diketone **189** was produced (Scheme 4.12), presumably due to air oxidation, since no measures were taken to exclude oxygen from the reaction. The use of milder reaction conditions such as KCN in EtOH-water[136] did not overcome the problem, with essentially the same results being observed. Conducting the base catalyzed rearrangement under inert atmosphere also failed to produce **188** to any extent. Instead, an intramolecular aldol reaction affords intermediate **190**, which then undergoes an α-ketol rearrangement with migration of an alkyl group to give compound **191**, which had its structure determined by X-ray crystallography (Figure 4.3).

Scheme 4.10



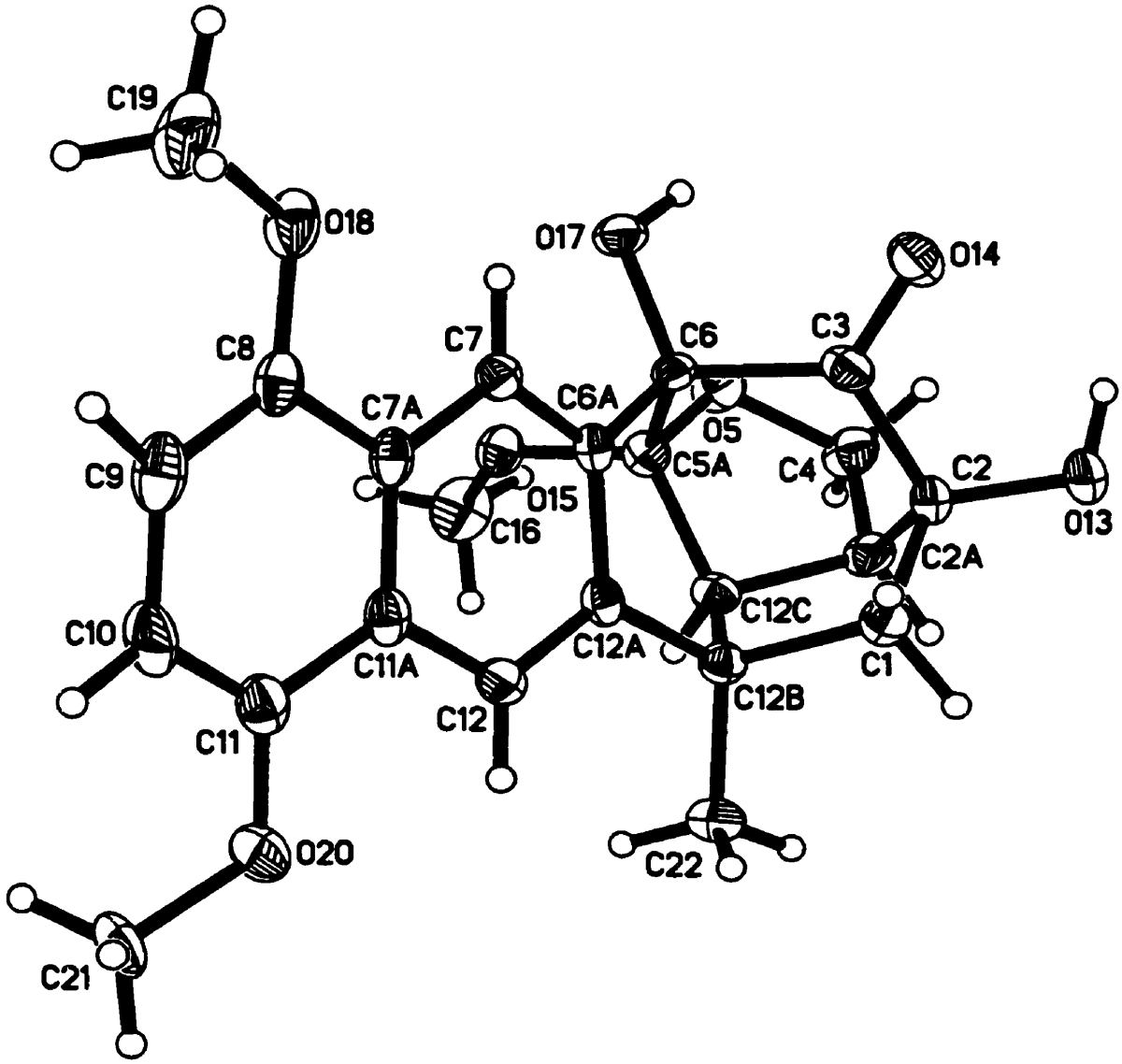
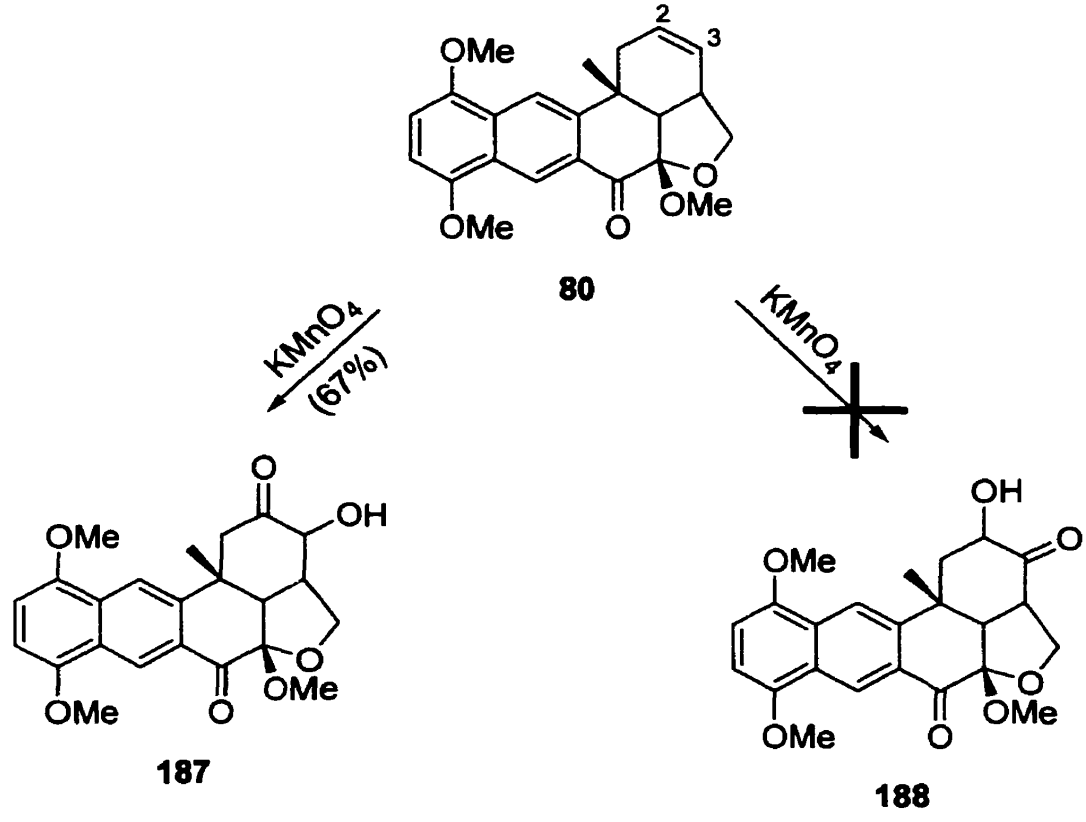


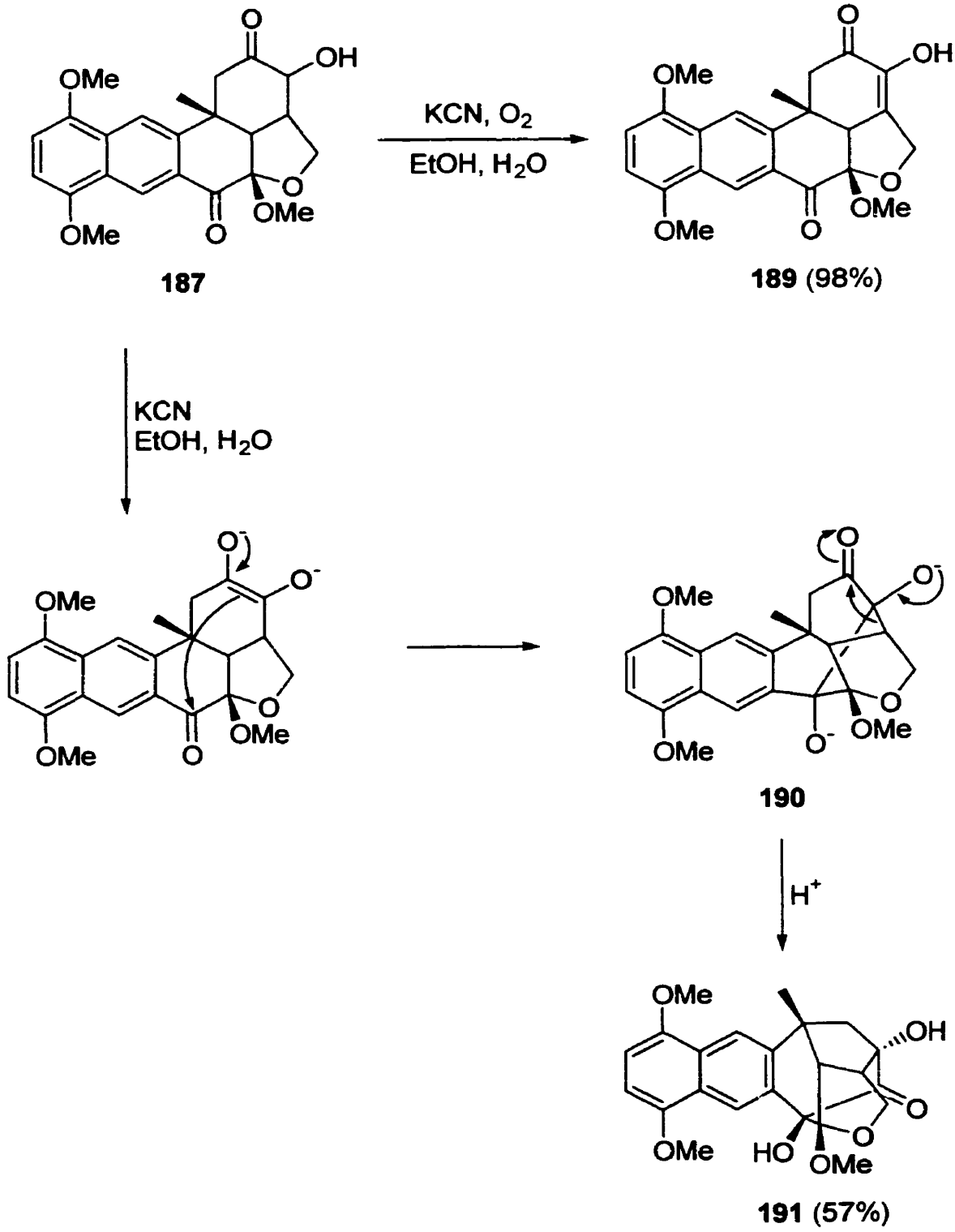
Figure 4.3: X-ray crystal structure of compound **191**

Scheme 4.11



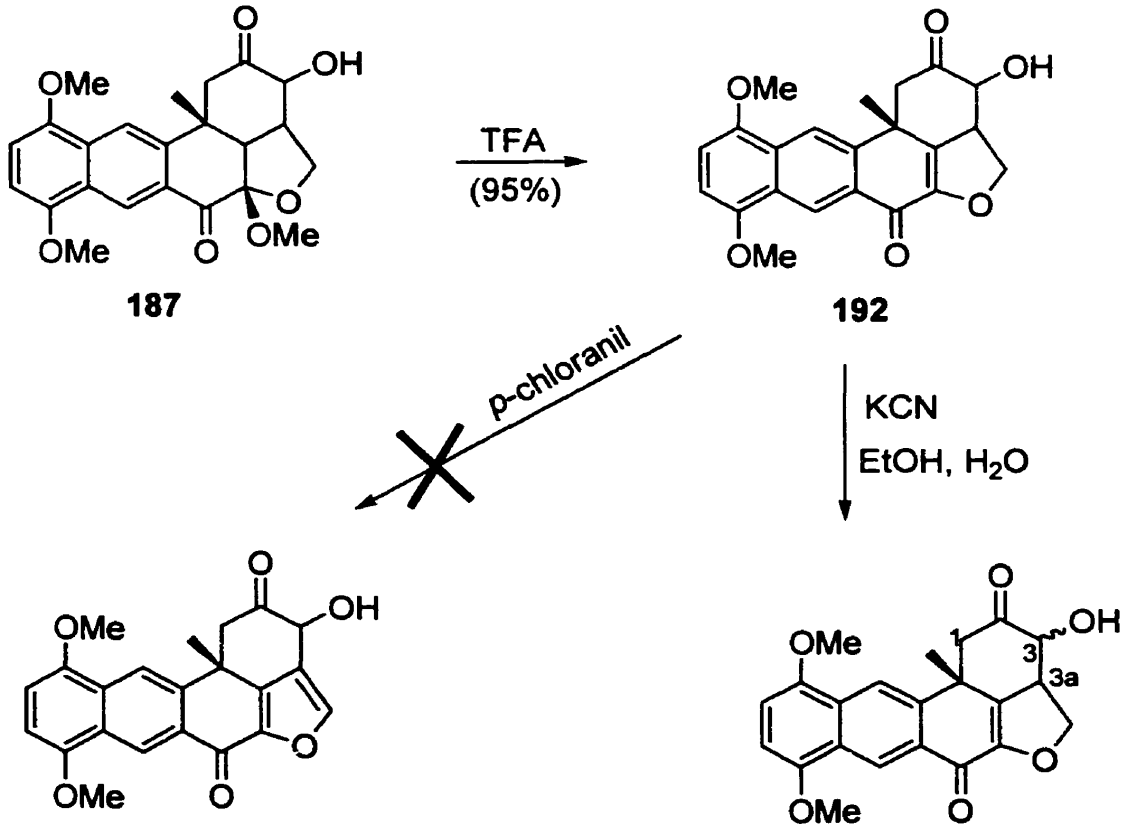
Since **188** could not be obtained by treatment of **187** with bases, we also investigated the use of acid to catalyze such rearrangement.[135] While no reaction took place when dilute acid was used, treatment with neat TFA caused elimination of methanol to give compound **192** (Scheme 4.13), but the hydroxyketone moiety remained unchanged. Since the structure of hydroxyketone **192** is much more planar than that of **187**, we believed that the former could not undergo the intramolecular aldol reaction, and we therefore decided to examine the reaction between **192** and KCN in the absence of oxygen. As expected, no carbonyl condensations took place, with an inseparable mixture of two compounds being produced instead. One of the products was promptly identified as the starting material **192**, and the other has been proposed to be its OH-epimer, based

Scheme 4.12


OMe
OH
O
OMe
OMe
O
KCN, O2
EtOH, H2O
187
189 (98%)
KCN
EtOH, H2O
O-
190
H+
HO
191 (57%)

on both 1D and 2D ^{1}H NMR experiments. Although the important C-3 signal of the newly formed compound is obscured by overlap with the methoxy peaks and C-3a is a multiplet, the C-1 protons clearly showed no vicinal coupling for either of the protons, thus supporting our epimerization hypothesis. In a final attempt, we hoped that the aromatization of ring E could provide some thermodynamic drive to the ketol rearrangement, but treatment of **192** with *p*-chloranil[102] led only to the decomposition of the starting material. Although frustrating, such decomposition was not unexpected, as a similar case was recorded in our investigations towards the synthesis of xestoquinone (**39**).[137] Apparently, conjugation with an additional unsaturated moiety on ring A is necessary for the aromatization of the furan ring to proceed.

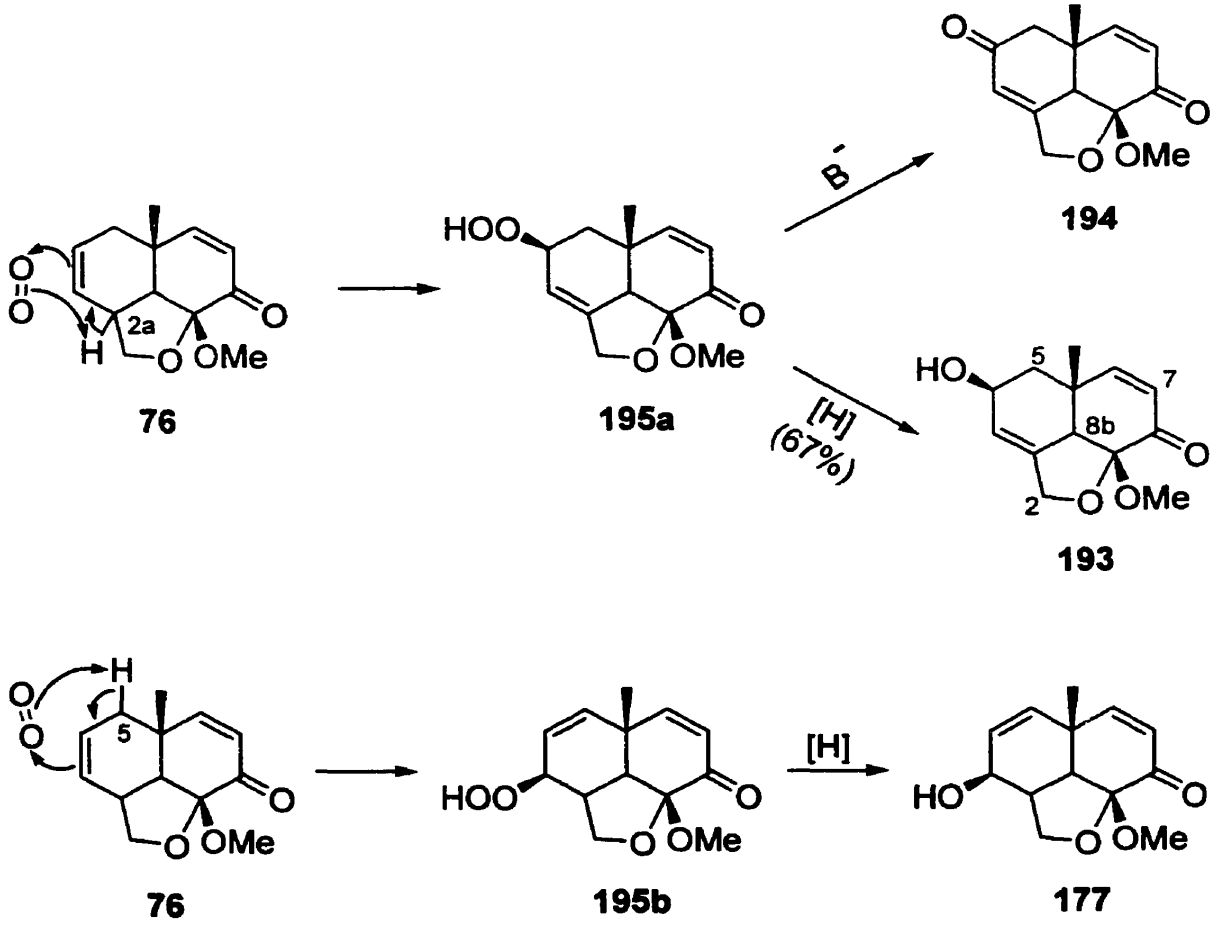
Scheme 4.13



4.4. The Singlet Oxygen Ene Reaction

The functionalization of ring A of compound **76** using singlet oxygen[138] was also investigated. The pathway envisaged (Scheme 4.14) was that of an ene reaction,[139] and it seemed to us that hydrogen abstraction was likely to occur at the secondary C-5 to give the desired allylic alcohol **177** rather than at the tertiary C-2a. Once again our hopes were foiled, as reactions in MeCN, THF and CH_2Cl_2 all gave allylic alcohol **193** as the only product, which we assumed to be the β alcohol, as the β face is much more accessible. Singlet oxygen reactions are reportedly sensitive to the polarity of the solvent,[138] and we were thus led to investigate the product distributions in non-polar solvents. Surprisingly

Scheme 4.14



enough, reaction between singlet oxygen and **76** in CCl_4 produced naphthofurandione **194** as the major product, along with minor quantities of **193**. The formation of an enone in singlet oxygen oxidations requires the presence of a base to quench the intermediate hydroperoxide **195a**,[140] and our results thus indicate that contamination of the solvent must have occurred. Since the extent of the contamination – and thus of its effects on the regioselectivity of the reaction – was not known, the experiment was repeated using freshly distilled CCl_4. Unfortunately once again only alcohol **193** was isolated. Allylic alcohol **177** was finally obtained when **76** was reacted with singlet oxygen in benzene using TPP as the sensitizer. The product consisted of a mixture of alcohols **193** and **177**, the latter unfortunately being present only in minor quantities (less than 5% yield). Coupled with the difficulty encountered in the separation of the isomeric alcohols, such poor yields effectively made any route based on tricycle **177** impractical.

Our attention then turned to the reactions of alcohol **193**. Due to the directive effect of the hydroxyl group, treatment with *m*-CPBA gave β epoxide **196** (Scheme 4.15), which was then reacted with $LiClO_4$,[124] in the hope that the epoxide moiety would rearrange into a ketone. When no reaction took place, we reasoned that a free hydroxyl group might coordinate the lithium cation and prevent any further reaction. To avoid such problems, acetate **197** and methyl ether **198** were prepared, and **197** gave crystals suitable for x-ray analysis (Figure 4.4), which confirmed our assumptions regarding the relative stereochemistry of compounds **193** and **196-200**. Upon treatment with $LiClO_4$, however, both **197** and **198** were unfortunately as unreactive as parent compound **196.** Compound **198** was also subjected to treatment with neat TFA and, surprisingly, no reaction took place. Even elimination of methanol (from C-8a and C-8b) did not occur, leading us to

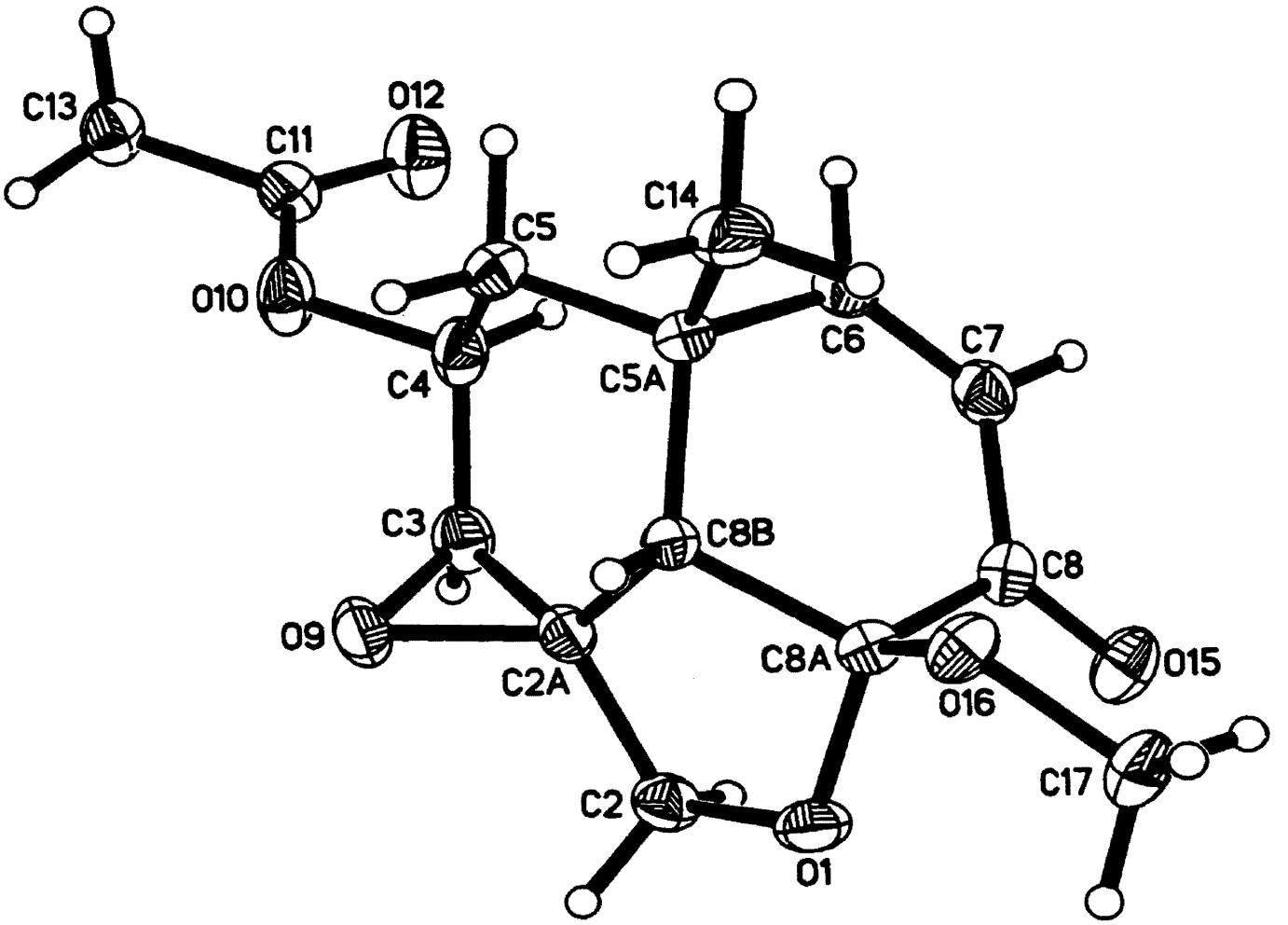
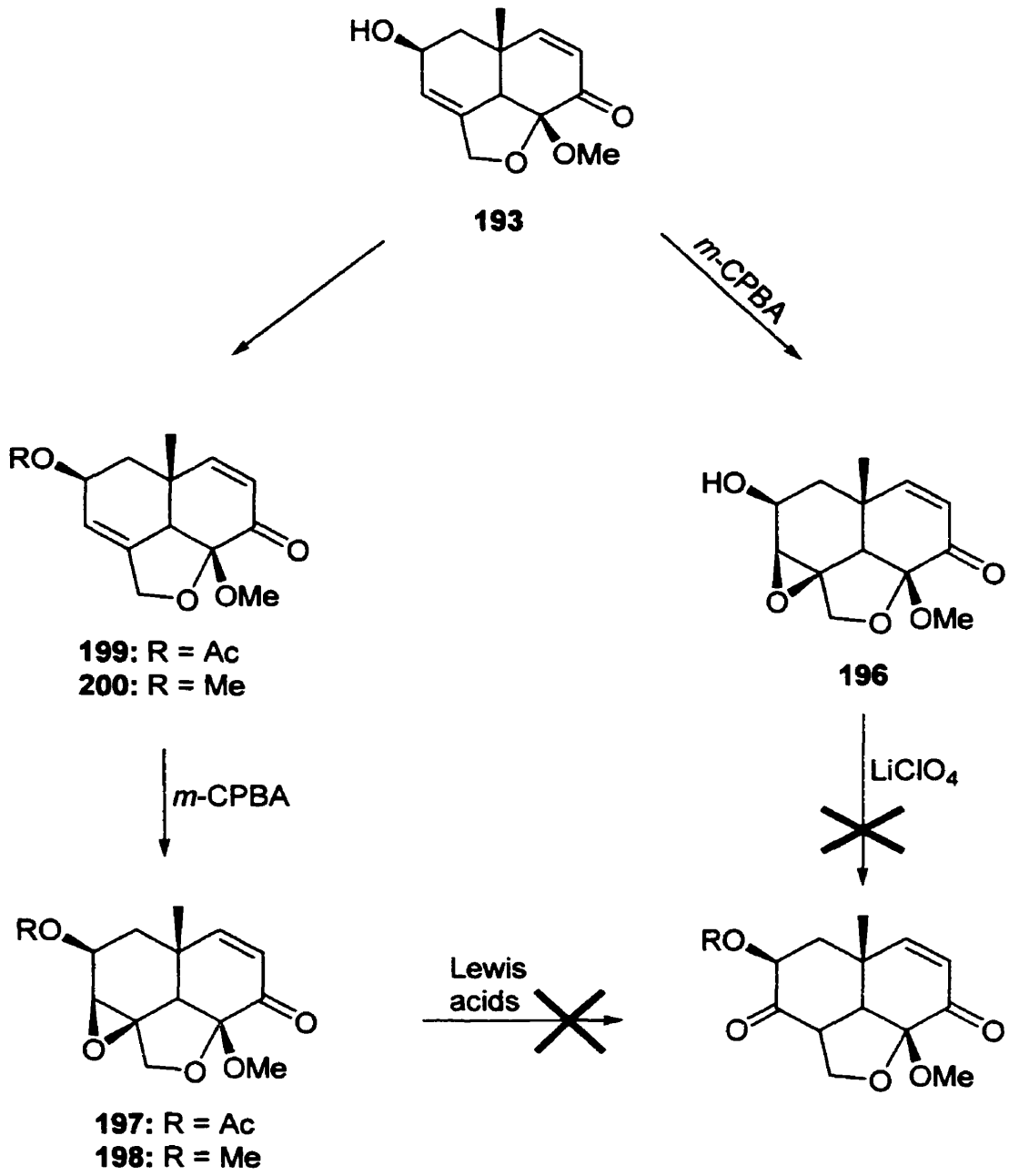


Figure 4.4: X-ray crystal structure of acetate **197**

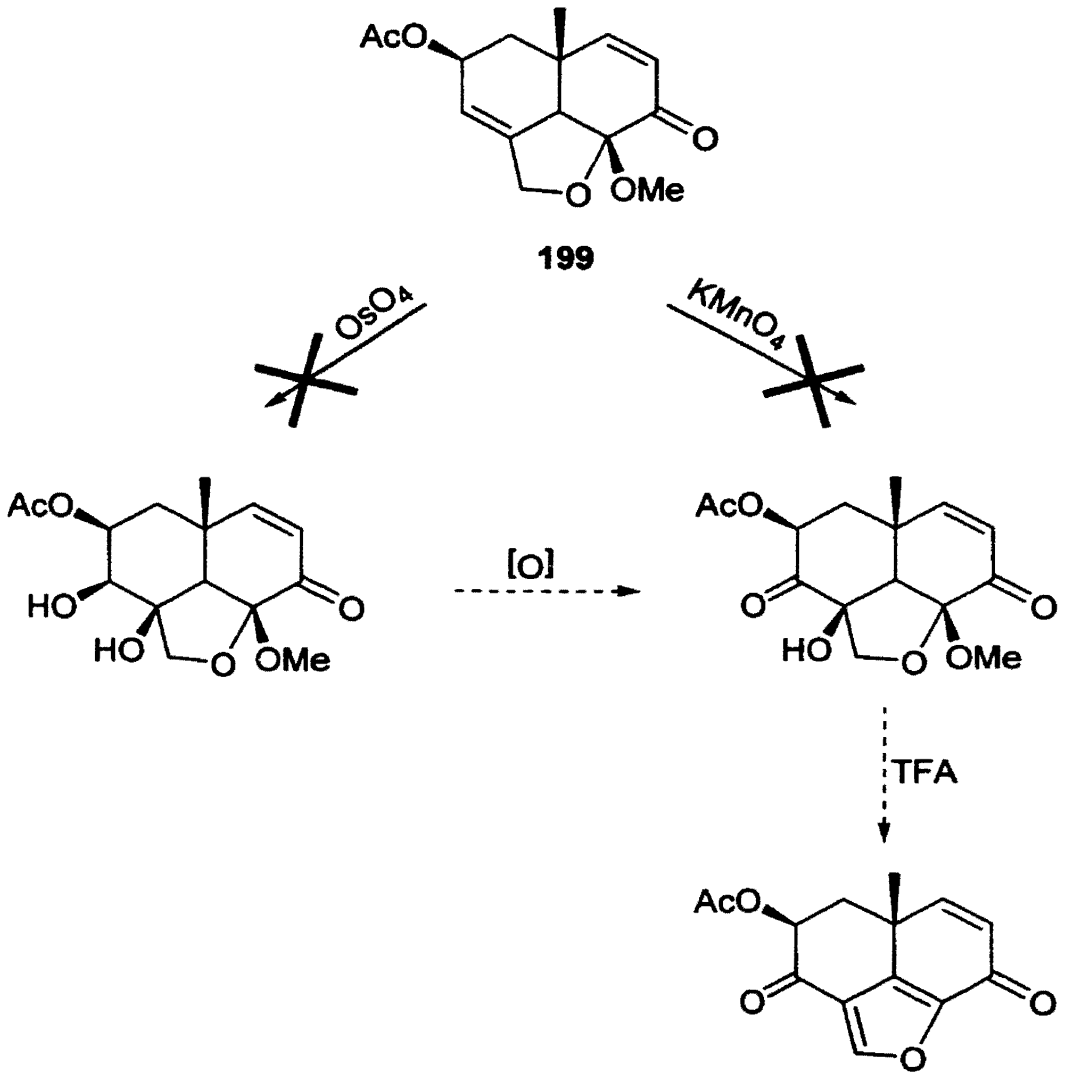
Scheme 4.15



believe that the same unfavorable geometry is again responsible for the unusual stability of epoxides **196**, **197** and **198**. In light of the previous results, a less subtle approach to epoxide ring opening was taken by reacting ether **198** with BF_3 etherate.[141] Such

conditions, however, proved to be too harsh, and the starting material decomposed into a complex mixture of unidentified products.

Scheme 4.16



Intermediate **199** was also used in attempts to install the carbonyl at C-3. Initial studies focused on its oxidation with $KMnO_4$ under acidic conditions[134] (Scheme 4.16). Given that the substrate is a trisubstituted olefin, the reaction could only proceed with the

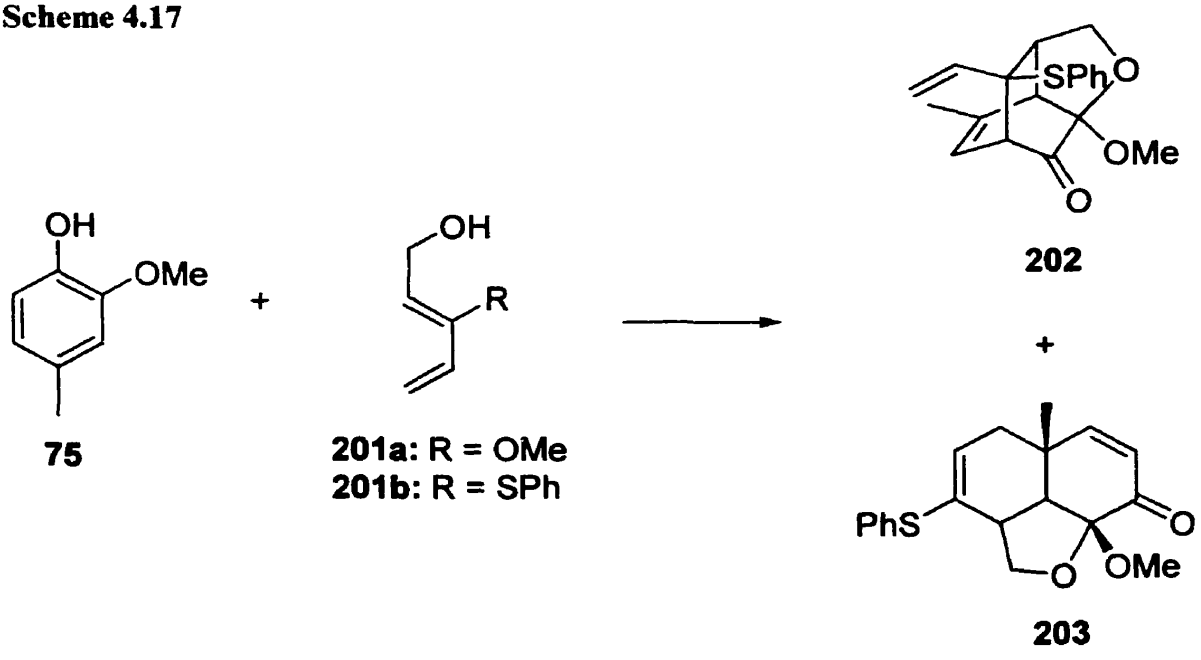
desired regiochemistry, and, in addition, the hydroxyl group at C-2a would also considerably simplify the generation of an aromatic ring E, since treatment with TFA would cause elimination of methanol and also dehydration to yield a furan ring. Unfortunately, no reaction took place, presumably because the steric crowding around the vinyl moiety prevents the formation of the cyclic manganese ester. Alternatively, dihydroxylation of compound **199** with OsO_4[142] was also attempted, as oxidation of the C-3 hydroxyl group to a ketone was thought to be a straightforward matter. Once again, however, only starting material was recovered, and we believe that steric crowding can one more time account for the observed lack of reactivity.

4.5. A New Dienol for the IMDA Reaction

While we were investigating the functionalization of ring A by oxidative methods, a different approach to the synthesis of halenaquinone (**38**) was also been pursued in our laboratory.[143] Our new route was based on the use of a more functionalized dienol, containing an oxygenated functionality at C-3. Initial studies using dienol **201a** had been unsuccessful,[76] but the use of a dienol containing an oxygen equivalent at C-3 eventually led to the synthesis of **38**. Thus, diene **201b**[144] was used in the IMDA step, and, in this manner, both bridged adduct **202** and naphthofuranone **203** were obtained (Scheme 4.17). Initially we attempted to purify compounds **202** and **203** by column chromatography, but while tricycle **203** could be easily isolated, it was next to impossible to separate adduct **202** from the excess diene present. Thus a crude mixture of **201b**, **202** and **203** was redissolved in 1,2,4-trimethylbenzene and refluxed for 2 days to give exclusively the desired adduct **203**. The steric effects of the thiophenyl substituent in **201b**, however,

take their toll on the yields (ca. 36%), which are considerably lower than the 56% usually obtained when dienol **91** is used.[49] Nevertheless, we were quite pleased with the successful preparation of **203**, as it represented a major breakthrough in our efforts towards the synthesis of both **38** and **2.** According to the procedure developed for the synthesis of xestoquinone (**39**),[48] we proceeded to react tricycle **203** with isobenzofuran **78** (Scheme 4.18) to obtain bridged pentacycle **204**, which upon reflux with NaOMe in MeOH caused the aromatization of ring C to give the expected naphthalene **205**. Conversion of **205** into enone **206** was done by the customary treatment with TFA, and aromatization of ring E by reflux with *p*-chloranil[102] in xylenes. Subsequent hydrolysis of sulfide **207** with moist acetic acid and $TiCl_4$ produced Harada's intermediate **48**,[38] thus completing our synthesis of **38**.[143]

Scheme 4.17



75

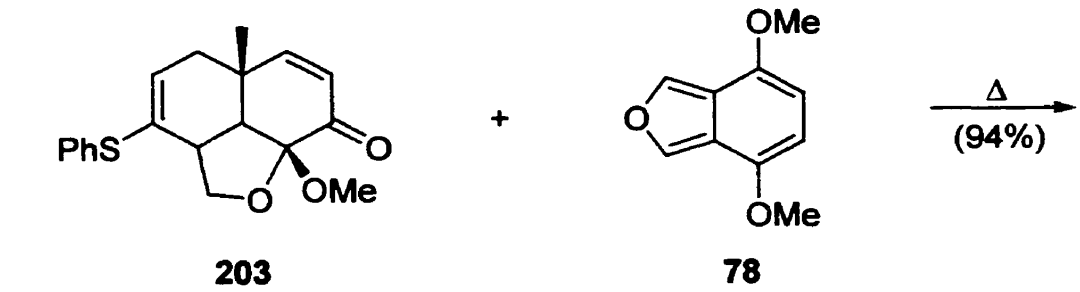
201a: R = OMe
201b: R = SPh

202

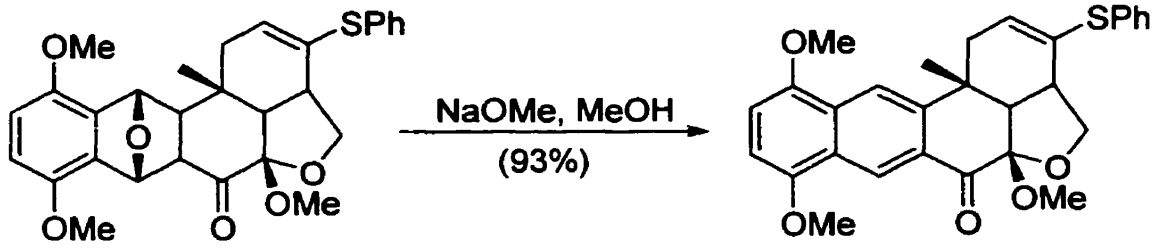
+

203

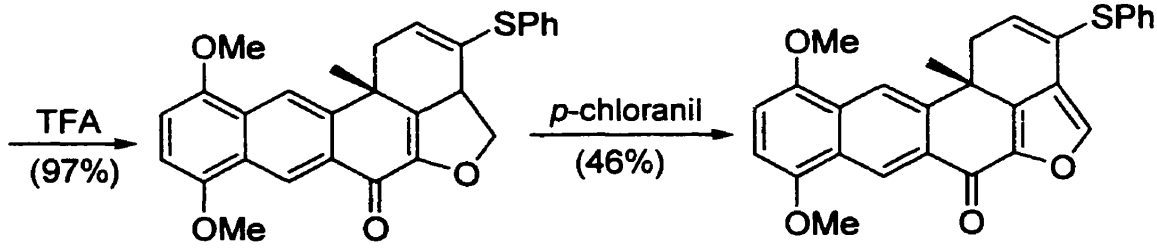
Scheme 4.18



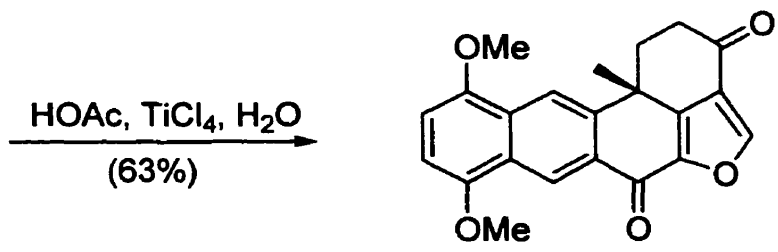
203 **78**



204 **205**

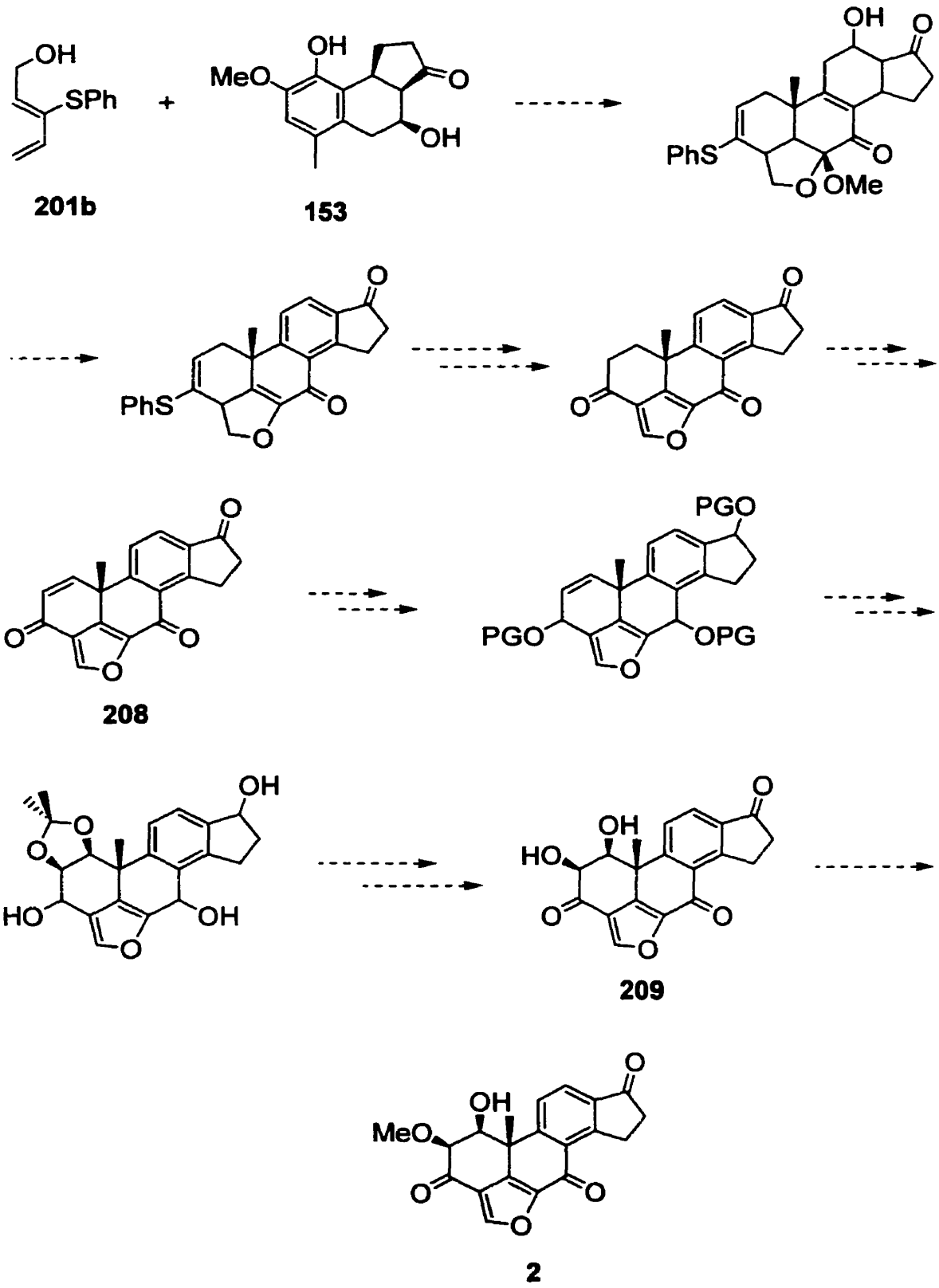


206 **207**



48

Scheme 4.19


OH
SPh
+
MeO
OH
O
OH
201b
153
OH
O
PhS
O
O
OMe
PhS
O
O
O
O
O
O
O
208
PGO
PGO
OPG
O
OH
O
HO
OH
O
OH
HO
O
O
O
209
O
OH
MeO
O
O
O
2

4.6. Conclusion

The use of the IMDA methodology provided us with a fast and convenient way of assembling the ABE fragment of viridin (**2**) and related natural products, thus enabling us to explore both ABE→ABCDE and BCD→ABCDE routes to the preparation of the carbon skeleton of **2**. The latter approach delivered a synthesis of the pentacyclic framework of **2** that is relatively short and high yielding, yet flexible enough to be adapted to other members of the viridin family of steroidal antibiotics.

Attempts to functionalize ring A of model compounds by oxidative methods failed to produce the desired substitution pattern, but several new compounds were isolated and characterized in the process. Many of those compounds can be classified as xestoquinone (**39**) derivatives, and, like most of the structurally related marine quinones, may possess interesting biological activity.

Finally, the use of dienol **201** to create a ketone on ring A not only allowed us to complete the synthesis of **38**, but also constitutes a significant advancement in a future synthesis of viridin (**2**) and related fungal metabolites. Also, from the hydrolysis of **207** we learned that furan ring E is considerably more stable than previously thought, and further functionalization of ring A is now known not to require strictly neutral conditions. The challenges however remain considerable, as illustrated by our proposed synthesis of **2** (Scheme 4.19). Particularly sensitive steps are the selective introduction of a double bond on ring A to form enone **208** and the selective methylation of intermediate **209**. In addition, one still needs to be concerned with the opening of furan ring E via 1,4 addition[23] and also with the facile epimerization of the methoxyl group α to the carbonyl

on the ring A of **2**.[5] Still, we believe that the path has already been laid and that success will ultimately be within reach. These investigations have already commenced.

CHAPTER 5 – EXPERIMENTAL PROCEDURES

5.1. General Conditions

All reactions, unless otherwise stated, were performed under an inert atmosphere (Ar or N_2) using dry solvents. Benzene and toluene were distilled from sodium, THF from potassium and diethyl ether from Na/K alloy, all using benzophenone ketyl as an indicator. Dichloromethane, chloroform, hexane, DMF and 1,1,2,2-tetrachloroethane were distilled from CaH_2. Commercially available reagents were used without further purification.

For TLC analysis, E. Merck 5554 pre-coated silica gel 60 F_{254} aluminum sheets were used, and the plates were developed with iodine or an oxidizing acidic solution of $NH_4Ce(SO_4)_2$ and $(NH_4)_6Mo_7O_{24}.H_2O$. Flash chromatography was carried out using silica gel 60 (230-400 mesh), and the solvent mixtures used as eluent are indicated in each case.

Melting points were measured with a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Spectrum RX I FTIR spectrometer; liquids and oils as neat films between NaCl plates and solids in KBr discs, and only the strongest bands are listed. NMR spectra were obtained on Bruker AC-200, AM-250, AM-300 and AMX-500 instruments, with ^1H and ^{13}C chemical shifts determined relative to the residual solvent signal and ^{19}F chemical shifts determined relative to $CFCl_3$ ($\delta = 0$) as an external standard. All ^1H NMR spectra were considered as first order and coupling constants are therefore reported as measured. ^1H and ^{13}C NMR signals were assigned based on JMOD, COSY and HMQC data, as well as on comparison with the spectra of similar compounds previously synthesized in our laboratory. Mass

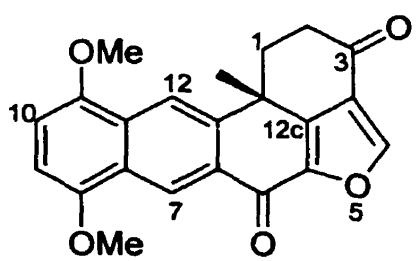
spectra were run at the McMaster Regional Centre for Mass Spectrometry, McMaster University, Hamilton, Ontario, and elemental analyses were performed by MHW Laboratories, Phoenix, Arizona.

Regarding known compounds, only the reference to the reported preparation and characterization data is given, unless the compound has been prepared via a significantly modified or previously unreported route, in which case both the experimental procedure and ^{1}H NMR data have been included.

5.2. Reaction Conditions and Experimental Data

Halenaquinol dimethyl ether (48)[38]

To a solution of sulfide **207** (14 mg, 0.031 mmol) in glacial acetic acid (2 mL) were added neat $TiCl_4$ (1 mL) and water (50 μL), and the resulting mixture was refluxed overnight. After being diluted with CH_2Cl_2, the reaction mixture was washed with saturated aqueous $NaHCO_3$ solution and the organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue (50% Et_2O in hexane) gave known pentacycle **48** (7 mg, 0.019 mmol, 63% yield), whose ^{1}H NMR spectrum was identical with the previously published data for (+) **48**.



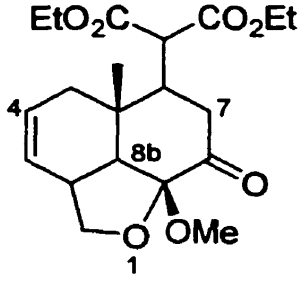
48

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.66 (s, 3H, R-C<u>H</u>$_3$), 2.32 (dt, J = 4.6, 13.1 Hz, 1H, H-1), 2.79-3.07 (m, 3H, H-1, H-2), 3.97 (s, 3H, Ar-OC<u>H</u>$_3$), 3.98 (s, 3H, Ar-OC<u>H</u>$_3$), 6.72,

6.83 (both d, J = 8.4 Hz, 1H, H-9, H-10), 8.21 (s, 1H, H-4), 8.29 (s, 1H, H-12), 9.29 (s, 1H, H-7).

Synthesis of Diethyl 2-(8a-methoxy-5a-methyl-8-oxo-2a,5,5a,6,7,8,8a,8b-octahydro-2*H*-naphtho[1,8-*bc*]furan-6-yl)-malonate (86)

To a solution of naphthofuranone **76**[49] (130 mg, 0.59 mmol), diethyl malonate (500 mg, 3.13 mmol) and HMPA (1 mL) in THF (20 mL) was added solid NaH (60% in mineral oil, 85 mg, 2.13 mmol) and the resulting suspension was stirred at room temperature for 4 h. The reaction mixture was then diluted with Et_2O, quenched with saturated NH_4Cl solution and after separation of the layers the aqueous phase was extracted with Et_2O. The combined organic layers were dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. Column chromatography (20% Et_2O in hexane) gave diester **86** as a colorless oil (203 mg, 0.53 mmol, 90% yield).



86

IR: 2980, 1732, 1465, 1369, 1303, 1214, 1063 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.95 (s, 1H, R-C$\underline{H}_3$), 1.21 (t, J = 7.4 Hz, 6H, R-$CO_2CH_2C\underline{H}_3$, overlapping the other R-$CO_2CH_2C\underline{H}_3$), 1.23 (t, J = 7.4 Hz, R-$CO_2CH_2C\underline{H}_3$), 1.68 (br d, J = 18.1 Hz, 1H, H-5), 1.97 (br d, J = 18.1 Hz, 1H, H-5), 2.49-2.57 (m, 2H, H-7), 2.70-2.93 (m, 3H, H-2a, H-6, H-8b), 3.15 (s, 3H, R-O$C\underline{H}_3$), 3.73

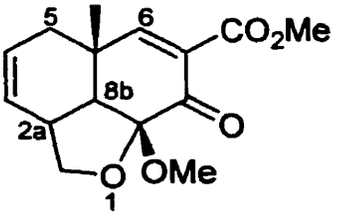
(d, J = 6.3 Hz, 1H, R-C<u>H</u>$(CO_2Et)_2$), 3.80 (dd, J = 2.4, 8.3 Hz, 1H, H-2), 3.99 (dd, J = 6.9, 8.3 Hz, 1H, H-2), 4.15 (m, 4H, R-$CO_2C\underline{H}_2CH_3$), 5.56 (m, 2H, H-3, H-4).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.99, 14.02 (R-$CO_2CH_2\underline{C}H_3$), 24.9 (R-$\underline{C}H_3$), 33.5, 34.4, 37.9 (C-5, C-5a, C-7), 38.0, 40.1 (C-2a, C-6), 50.8, 52.5, 55.7 (C-8b, R-O$\underline{C}H_3$, R-$\underline{C}H(CO_2Et)_2$), 61.67, 61.72 (R-$CO_2\underline{C}H_2CH_3$), 72.6 (C-2), 104.8 (C-8a), 124.6, 127.3 (C-3, C-4), 168.91, 168.92 (R-$\underline{C}O_2CH_2CH_3$), 205.6 (C-8).

Anal. Calc. for $C_{20}H_{28}O_7$: C, 63.14; H, 7.42. Found: C, 63.35; H, 7.27.

Synthesis of 7-Carbomethoxy-8a-methoxy-5a-methyl-2a,5,5a,8,8a,8b-hexahydro-2*H*-naphtho[1,8-*bc*]furan-8-one (90)

To a solution of iodide **98** (401 mg, 1.16 mmol) in THF (30 mL) were added MeOH (250 μL), 2,6-lutidine (300 μL), $Pd(OAc)_2$ (14 mg, 0.06 mmol) and dppp (25 mg, 0.06 mmol), and the reaction mixture was placed under a CO atmosphere (750 psi) in a pressure reactor, which was then heated at 60°C for 48 h. The resulting solution was diluted with Et_2O and washed with water. The aqueous layer was extracted with Et_2O, the combined organic phases were dried (Na_2SO_4) and the solvent was removed under reduced pressure. Flash chromatography (50% Et_2O in hexane) gave **90** as a light yellow solid (203 mg, 0.73 mmol, 63% yield).



90

mp: 80-82°C.

IR: 2952, 1744, 1722, 1436, 1275, 1131 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.25 (s, 3H, R-C$\underline{H}_3$), 1.80 (br d, J = 16.7 Hz, 1H, H-5), 2.02 (dd, J = 4.4, 16.7 Hz, 1H, H-5), 2.57 (dd, J = 1.3, 9.0 Hz, 1H, H-8b), 2.98 (m, 1H, H-2a), 3.25 (s, 3H, R-OC$\underline{H}_3$), 3.79 (s, 3H, R-$CO_2C\underline{H}_3$), 3.86 (dd, J = 1.8, 8.6 Hz, 1H, H-2), 4.13 (dd, J = 6.6, 8.6 Hz, 1H, H-2), 5.72 (br s, 2H, H-3 and H-4), 7.60 (s, 1H, H-6).

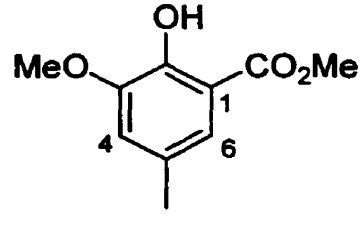
^{13}C NMR (63 MHz, $CDCl_3$) δ: 27.3 (R-$\underline{C}H_3$), 34.2 (C-5a), 36.4 (C-5), 36.8 (C-2a), 50.4, 52.3, 53.9 (R-O$\underline{C}H_3$, R-$CO_2\underline{C}H_3$, C-8b), 73.3 (C-2), 105.2 (C-8a), 124.8, 128.4 (C-3, C-4), 131.3 (C-7), 163.6 (R-$\underline{C}O_2$Me), 164.4 (C-6), 188.3 (C-8).

HRMS (EI) *m/z*: Required for $C_{15}H_{18}O_5$: 278.1154; Found: 278.1150.

Anal. Calc. for $C_{15}H_{18}O_5$: C, 64.74; H, 6.52. Found: C, 64.60; H, 6.39.

Synthesis of Methyl 2-hydroxy-3-methoxy-5-methylbenzoate (92)[145]

To a solution of benzoic acid **129** (308 mg, 1.69 mmol) in MeOH (25 mL) was added H_2SO_4 (2 mL) and the resulting solution was stirred at room temperature for 3 days. The reaction mixture was partitioned between a Na_2CO_3 solution and Et_2O, the aqueous phase was further extracted with Et_2O and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography (20% EtOAc in hexane) gave benzoate **92** as a white solid (297 mg, 1.51 mmol, 89% yield).



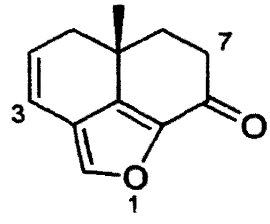
92

mp: 88-90°C (lit. 90-91°C).

^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.29 (s, 3H, Ar-C$\underline{H}_3$), 3.89 (s, 3H, Ar-$CO_2C\underline{H}_3$), 3.94 (s, 3H, Ar-OC$\underline{H}_3$), 6.86 (d, J = 1.4 Hz, 1H, H-4), 7.23 (d, J = 1.4 Hz, 1H, H-6), 10.79 (s, 1H, Ar-O$\underline{H}$).

Attempted Cope Rearrangement of 1-Carbomethoxy-3-methoxy-8-methyl-2-oxo-10-vinyl-4-oxatricyclo[4.3.1.$0^{3,7}$]dec-8-ene (93)

A solution of bridged adduct **93** (210 mg, 0.75 mmol) in 1,1,2,2-tetrachloroethane (5 mL) was heated to reflux for 24 h, after which the solvent was removed under vacuum and the resulting brown residue purified by column chromatography (20% EtOAc in hexane) to give, in order of elution, 5a-methyl-5a,6,7,8-tetrahydro-5*H*-naphtho[1,8-*bc*]furan-8-one (**94**) as a light yellow oil (38 mg, 0.20 mmol, 27% yield) and also 7-carbomethoxy-5a-methyl-5a,8-dihydro-5*H*-naphtho[1,8-*bc*]furan-8-one (**95**)[5951] as a yellow solid (62 mg, 0.25 mmol, 33% yield).



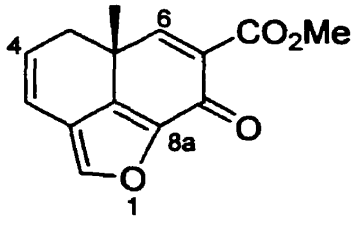
94

IR: 2928, 1674, 1425, 1341, 1052, 840 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.20 (s, 3H, R-C$\underline{H}_3$), 2.00 (t, J = 2.5 Hz, 2H, H-6, overlapping the other H-6), 2.04 (d, J = 3.4 Hz, H-6), 2.14 (br d, J = 16.8 Hz, 1H, H-5), 2.29 (dd, J = 6.2, 16.8 Hz, 1H, H-5), 2.48 (dt, J = 3.4, 17.6 Hz, 1H, H-7), 2.77 (t, J = 8.8 Hz, 1H, H-7), 5.86 (m, 1H, H-4), 6.40 (dd, J = 3.2, 9.5 Hz, 1H, H-3), 7.33 (s, 1H, H-2).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.4 (R-$\underline{C}H_3$), 30.3 (C-5a), 36.1, 38.1, 38.9 (C-5, C-6, C-7), 116.7 (C-3), 120.6 (C-2a), 128.6 (C-4), 140.8 (C-2), 143.2, 145.7 (C-8a, C-8b), 184.6 (C-8).

HRMS (EI) *m/z*: Required for $C_{12}H_{12}O_2$: 188.0837; Found: 188.0849.

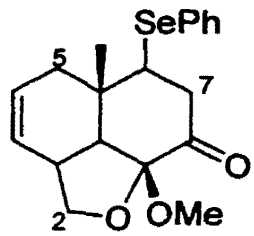


95

^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.41 (s, 3H, R-C$\underline{H}_3$), 2.44 (m, 2H, H-5), 3.89 (s, 3H, $RCO_2C\underline{H}_3$), 5.94 (ddd, J = 2.6, 5.6, 9.7 Hz, 1H, H-4), 6.58 (ddd, J = 1.2, 2.9, 9.7 Hz, 1H, H-3), 7.52 (s, 1H, H-2), 7.64 (s, 1H, H-6).

Synthesis of 8a-Methoxy-5a-methyl-6-phenylseleno-2a,5,5a,6,7,8,8a,8b-octahydro-2*H*-naphtho[1,8-*bc*]furan-8-one (96)

To a solution of Ph_2Se_2 (312 mg, 1.00 mmol) in EtOH (8 mL) was added finely ground $NaBH_4$ (70 mg, 1.85 mmol) and, after evolution of gas ceased, a degassed solution of naphthofuranone **76**[49] (104 mg, 0.47 mmol) in EtOH (2 mL). After stirring for 30 min at room temperature, the reaction mixture was quenched with AcOH (200 μL) and partitioned between water and EtOAc. The aqueous phase was further extracted with EtOAc and the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (20% EtOAc in hexane) gave selenide **96** as a colorless oil (18 mg, 48 μmol, 10% yield).



96

IR: 2939, 1735, 1476, 1438, 1123, 1059 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.13 (s, 3H, R-C$\underline{H}_3$), 1.75 (dm, J = 17.4 Hz, 1H, H-5), 2.28 (br dd, J = 4.2, 17.4 Hz, 1H, H-5), 2.75 (d, J = 9.0 Hz, 2H, H-8b, overlapping H-8b), 2.83 (dd, J = 6.8, 18.7 Hz, H-7,), 3.07 (dd, J = 8.6, 18.7 Hz, 2H, H-7, overlapping H-2a), 3.29 (s, 3H, R-OC$\underline{H}_3$), 3.81 (dd, J = 8.4, 11.1 Hz, 2H, H-6, overlapping H-2), 3.85(t, J = 8.0 Hz, H-2), 4.11 (t, J = 8.0 Hz, 1H, H-2), 5.45-5.64 (m, 2H, H-3, H-4), 7.28 (m, 3H, R-Se-$C_6\underline{H}_5$), 7.57 (m, 2H, R-Se-$C_6\underline{H}_5$).

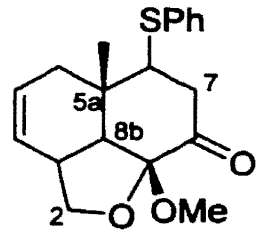
^{13}C NMR (75 MHz, $CDCl_3$) δ: 25.9 (R-$\underline{C}H_3$), 33.9 (C-7), 36.4 (C-5a), 37.7 (C-2a), 44.8 (C-5), 46.9, 50.8, 56.1 (R-O$\underline{C}H_3$, C-6, C-8b), 73.4 (C-2), 106.9 (C-8a), 124.7, 127.3, 127.5, 129.0, 134.6 (C-3, C-4, C-2', C-3', C-4'), 130.0 (C-1'), 204.8 (C-8).

HRMS (EI) *m/z*: Required for $C_{19}H_{22}O_3Se$: 378.0734; Found 378.0732.

Synthesis of 8a-Methoxy-5a-methyl-6-phenylthio-2a,5,5a,6,7,8,8a,8b-octahydro-2*H*-naphtho[1,8-*bc*]furan-8-one (97)

To a suspension of NaH (60% in mineral oil, 100 mg, 2.5 mmol) in THF (10 mL), were added thiophenol (1mL) and, after the evolution of gas ceased, a solution of naphthofuranone **76**[49] (250 mg, 1.14 mmol) in THF (5mL). The reaction mixture was stirred for 2 h, quenched with NH_4Cl solution and extracted with Et_2O. The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure.

Column chromatography (20% Et_2O in hexane) gave sulfide **97** as an off white solid (368 mg, 1.12 mmol, 98% yield).



97

mp: 60-63°C.

IR: 2925, 1736, 1480, 1438, 1125, 1062 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.13 (s, 3H, R-C$\underline{H}_3$), 1.73 (dm, J = 17.4 Hz, 1H, H-5), 2.36 (br dd, J = 4.5, 17.4 Hz, 1H, H-5), 2.66 (dd, J = 7.2, 18.3 Hz, 2H, H-7, overlapping H-8b), 2.68 (d, J = 9.0 Hz, H-8b), 3.01 (dd, J = 8.4, 18.3 Hz, 2H, H-7, overlapping H-2a), 3.30 (s, 3H, R-OC$\underline{H}_3$), 3.75 (dd, J = 7.2, 8.4 Hz, 1H, H-6), 3.85(dd, J = 3.7, 8.3 Hz, 1H, H-2), 4.12 (t, J = 8.3 Hz, 1H, H-2), 5.51-5.68 (m, 2H, H-3, H-4), 7.18-7.51 (m, 5H, R-S-$C_6\underline{H}_5$).

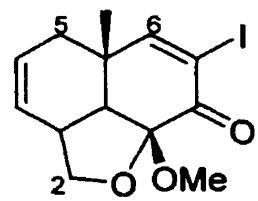
^{13}C NMR (50 MHz, $CDCl_3$) δ: 24.9 (R-$\underline{C}H_3$), 33.5 (C-7), 36.3 (C-5a), 37.7 (C-2a), 44.2 (C-5), 49.7 (C-6), 50.8, 56.3 (R-O$\underline{C}H_3$, C-8b), 73.6 (C-2), 105.5 (C-8a), 124.6, 127.1, 127.6, 129.0, 132.0 (C-3, C-4, C-2', C-3', C-4'), 135.5 (C-1'), 204.8 (C-8).

Anal. Calc. for $C_{19}H_{22}O_3S$: C, 69.06; H, 6.71. Found: C, 69.22; H, 6.93.

Synthesis of 7-Iodo-8a-methoxy-5a-methyl-2a,5,5a,8,8a,8b-hexahydro-2*H*-naphtho[1,8-*bc*]furan-8-one (98)

To a solution of naphthofuranone **76**[49] (2.20 g, 10.0 mmol) in CH_2Cl_2 (200 mL) were added solid iodine (5.60 g, 22.0 mmol) and pyridine (4 mL). The reaction mixture was stirred for two days, after which it was washed with cold HCl (1 M) and then with a

solution of ascorbic acid. The organic phase was dried (Na_2SO_4) and the solvent removed under reduced pressure to give iodide **98** as a yellow solid (3.44 g, 9.94 mmol, 99% yield). The ^1H NMR spectrum recorded was in complete agreement with the data previously reported.[59]



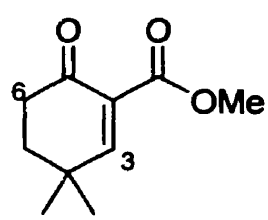
98

mp: 81-83°C (lit 81-82°C).

^1H NMR (250 MHz, $CDCl_3$) δ: 1.25 (s, 3H, R-C$\underline{H}_3$), 1.98 (m, 2H, H-5), 2.64 (d, J = 10.1 Hz, 1H, H-8b), 3.02 (m, 1H, H-2a), 3.27 (s, 3H, R-OC$\underline{H}_3$), 3.78 (dd, J = 2.9, 8.6 Hz, 1H, H-2), 4.15 (dd, J = 7.2, 8.6 Hz, 1H, H-2), 5.77 (br s, 2H, H-3, H-4), 7.36 (s, 1H, H-6).

Synthesis of 2-Carbomethoxy-4,4-dimethyl-2-cyclohexen-1-one (100a)

Compound **100a** was prepared as a colorless oil (124 mg, 0.68 mmol, 68% yield) from iodide **99**[64b] (250 mg, 1.00 mmol) using MeOH (250 μL), 2,6-lutidine (300 μL), $Pd(OAc)_2$ (10 mg, 0.04 mmol) and dppp (18 mg, 0.04 mmol) in THF (30 mL) according to the procedure described for the synthesis of compound **90**. The ^1H NMR spectrum recorded was in complete agreement with the data reported in the literature.[54e]

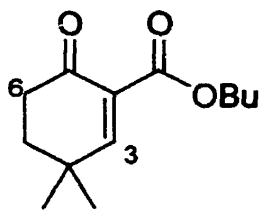


100a

^1H NMR (300 MHz, $CDCl_3$) δ: 1.24 (s, 6H, R-C$\underline{H}_3$), 1.90 (m, 2H, H-5), 2.54 (m, 2H, H-6), 3.80 (s, 3H, R-$CO_2C\underline{H}_3$), 7.36 (t, J = 1.0 Hz, 1H, H-3).

Synthesis of 2-Carbobutoxy-4,4-dimethyl-2-cyclohexen-1-one (100b)

Compound **100b** was prepared as a yellow oil (172 mg, 0.77 mmol, 62% yield) from iodide **99**[64b] (310 mg, 1.24 mmol) using *n*-BuOH (300 μL), 2,6-lutidine (300 μL), $Pd(OAc)_2$ (15 mg, 0.07 mmol) and dppp (29 mg, 0.07 mmol) in THF (25 mL) according to the procedure described for the synthesis of compound **90**.



100b

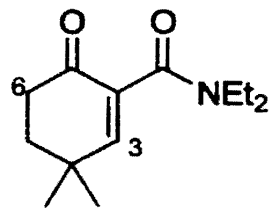
IR: 2961, 1741, 1713, 1690, 1467, 1272 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.93 (t, J = 7.2 Hz, 3H, R-$CO_2(CH_2)_3C\underline{H}_3$), 1.22 (s, 6H, R-$C\underline{H}_3$), 1.42 (m, 2H, R-$CO_2(CH_2)_2C\underline{H}_2Me$), 1.63 (m, 2H, R-$CO_2CH_2C\underline{H}_2Et$), 1.88 (m, 2H, H-5), 2.52 (m, 2H, H-6), 4.18 (t, J = 6.7 Hz, 2H, R-$CO_2C\underline{H}_2Pr$), 7.27 (t, J = 0.9 Hz, 1H, H-3).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.6 (R-$CO_2(CH_2)_3\underline{C}H_3$), 19.0 (R-$CO_2(CH_2)_2\underline{C}H_2Me$), 27.3 (R-$\underline{C}H_3$), 30.5, 35.1, 35.3 (C-5, C-6, R-$CO_2CH_2\underline{C}H_2Et$), 33.3 (C-4), 65.0 (R-$CO_2\underline{C}H_2Pr$), 130.3 (C-2), 163.6 (R$\underline{C}O_2Bu$), 164.9 (C-3), 194.4 (C-1).

Synthesis of 2-Diethylaminocarbonyl-4,4-dimethyl-2-cyclohexen-1-one- (100c)

Compound **100c** was prepared as a light brown oil (143 mg, 0.64 mmol, 64% yield) from iodide **99**[64b] (250 mg, 1.00 mmol) using $HNEt_2$ (300 μL), 2,6-lutidine (300 μL), $Pd(OAc)_2$ (10 mg, 0.04 mmol) and dppp (16 mg, 0.04 mmol) in THF (30 mL) according to the procedure described for the synthesis of compound **90**.



100c

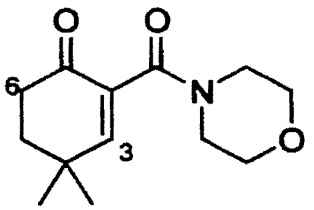
IR: 2964, 1683, 1636, 1430, 1362, 1284 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.05 (t, J = 7.1 Hz, 3H, R-CON($CH_2C\underline{H}_3$)$_2$), 1.14 (t, J = 7.1 Hz, 3H, R-CON($CH_2C\underline{H}_3$)$_2$), 1.18 (s, 6H, R-C$\underline{H}_3$), 1.88 (m, 2H, H-5), 2.49 (m, 2H, H-6), 3.09 (q, J = 7.1 Hz, 2H, R-CON($C\underline{H}_2CH_3$)$_2$), 3.40 (q, J = 7.1 Hz, 2H, R-CON($C\underline{H}_2CH_3$)$_2$), 6.63 (s, 1H, H-3).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 12.9, 14.1 (RCON($CH_2\underline{C}H_3$)$_2$), 27.6 (R-$\underline{C}H_3$), 32.9 (C-4), 34.4, 35.7 (C-5, C-6), 39.2, 43.1 (RCON($\underline{C}H_2CH_3$)$_2$), 135.9 (C-2), 156.4 (C-3), 166.9 (R-$\underline{C}ONEt_2$), 195.7 (C-1).

Synthesis of 4,4-Dimethyl-2-morpholinocarbonyl-2-cyclohexen-1-one (100d)

Compound **100d** was prepared as a yellow oil (753 mg, 3.17 mmol, 77% yield) from iodide **99**[64b] (1.03 g, 4.12 mmol) using morpholine (1.5 mL), 2,6-lutidine (1.5 mL), $Pd(OAc)_2$ (42 mg, 0.19 mmol) and dppp (78 mg, 0.19 mmol) in THF (50 mL) according to the procedure described for the synthesis of compound **90**.



100d

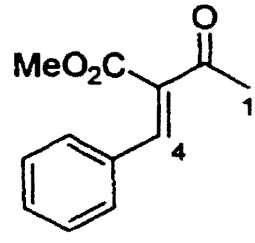
IR: 2960, 1682, 1634, 1434, 1360, 1114 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.20 (s, 6H, R-C$\underline{H}_3$), 1.90 (t, J = 6.8 Hz, 2H, H-5), 2.51 (t, J = 6.8 Hz, 2H, H-6), 3.20 (t, J = 4.8 Hz, 2H, RN(C$\underline{H}_2$CH$_2$)$_2$O), 3.62 (t, J = 4.8 Hz, 2H, RN(CH$_2$C$\underline{H}_2$)$_2$O), 3.68 (br s, 4H, RN(C$\underline{H}_2$C$\underline{H}_2$)$_2$O), 6.76 (s, 1H, H-3).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 27.4 (R-$\underline{C}$H$_3$), 33.0 (C-4), 34.3 (C-5), 35.5 (C-6), 42.0, 47.4 (RN($\underline{C}$H$_2$CH$_2$)$_2$O), 66.6, 66.7 (RN(CH$_2\underline{C}$H$_2$)$_2$O), 134.9 (C-2), 158.4 (C-3), 165.7 (R$\underline{C}$ON(CH$_2$CH$_2$)$_2$O), 195.3 (C-1).

Synthesis of (*Z*)-3-carbomethoxy-4-phenyl-3-buten-2-one (102)

Compound **102** was prepared as a light orange oil (117 mg, 0.57 mmol, 51% yield) from iodide **101**[64a] (306 mg, 1.12 mmol) using MeOH (300 μL), 2,6-lutidine (300 μL), $Pd(OAc)_2$ (9 mg, 0.04 mmol) and dppp (17 mg, 0.04 mmol) in THF (20 mL) according to the procedure described for the synthesis of compound **90**. The ^{1}H NMR spectrum recorded was in complete agreement with the data reported in the literature.[146]

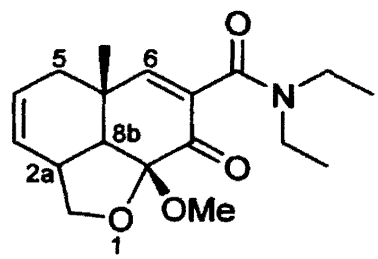


102

^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.42 (s, 3H, R-COC$\underline{H}_3$), 3.84 (s, 3H, R-CO$_2$C$\underline{H}_3$), 7.42 (m, 5H, R-C$_6\underline{H}_5$), 7.58 (s, 1H, H-3).

Synthesis of 7-Diethylaminocarbonyl-8a-methoxy-5a-methyl-2a,5,5a,8,8a,8b-hexahydro-2*H*-naphtho[1,8-*bc*]furan-8-one (103a)

Compound **103a** was prepared as a light brown solid (293 mg, 0.92 mmol, 62% yield) from iodide **98** (511 mg, 1.48 mmol) using MeOH (400 μL), 2,6-lutidine (500 μL), $Pd(OAc)_2$ (15 mg, 0.07 mmol) and dppp (30 mg, 0.07 mmol) in THF (25 mL) according to the procedure described for the synthesis of compound **90**.



103a

mp: 55-58°C.

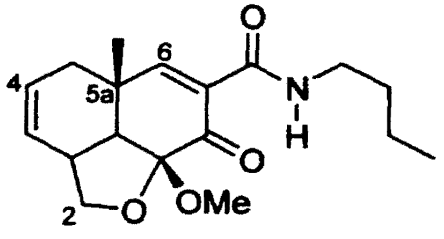
IR: 2972, 1692, 1635, 1458, 1433, 1049 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.11 (t, J = 7.1 Hz, 3H, $R_2NCH_2C\underline{H}_3$), 1.18 (t, J = 7.1 Hz, 3H, $R_2NCH_2C\underline{H}_3$), 1.27 (s, 3H, R-$C\underline{H}_3$), 1.96 (br d, J = 16.5 Hz, 1H, H-5), 2.04 (br d, J = 16.5 Hz, 1H, H-5), 2.65 (dd, J = 0.9, 9.3 Hz, 1H, H-8b), 3.04 (m, 1H, H-2a), 3.20 (q, J = 7.1 Hz, 2H, $R_2NC\underline{H}_2CH_3$), 3.32 (s, 3H, R-$OC\underline{H}_3$), 3.45 (m, 2H, $R_2NC\underline{H}_2CH_3$), 3.81 (dd, J = 3.0, 8.6 Hz, 1H, H-2), 4.15 (dd, J = 7.2, 8.6 Hz, 1H, H-2), 5.79 (m, 2H, H-3 and H-4), 6.75 (s, 1H, H-6).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 12.8, 14.2 (R-$N(CH_2\underline{C}H_3)_2$), 28.1 (R-$\underline{C}H_3$), 34.9 (C-5a), 37.2, 37.4, 39.2, 42.7 (C-2a, C-5, R-$N(\underline{C}H_2CH_3)_2$), 50.6, 53.5 (R-$O\underline{C}H_3$, C-8b), 73.3 (C-2), 103.2 (C-8a), 125.6, 129.7 (C-3, C-4), 136.6 (C-7), 156.0 (C-6), 165.4 (R$\underline{C}ONEt_2$), 188.2 (C-8).

Synthesis of 7-Butylaminocarbonyl-8a-methoxy-5a-methyl-2a,5,5a,8,8a,8b-hexahydro-2*H*-naphtho[1,8-*bc*]furan-8-one (103b)

Compound **103b** was prepared as a light yellow solid (120 mg, 0.37 mmol, 43% yield) from iodide **98** (300 mg, 0.87 mmol) using *n*-$BuNH_2$ (200 μL), 2,6-lutidine (300 μL), $Pd(OAc)_2$ (6 mg, 0.03 mmol) and dppp (12 mg, 0.03 mmol) in THF (20 mL) according to the procedure described for the synthesis of compound **90**.



103b

mp: 61-62°C.

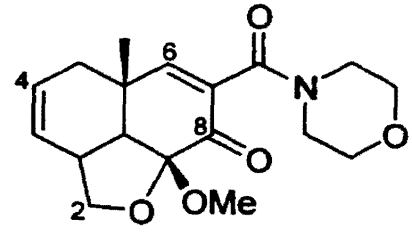
IR: 3359, 2959, 1694, 1661, 1532, 1458, 1048 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.90 (t, J = 7.3 Hz, 3H, $RNH(CH_2)_3C\underline{H}_3$), 1.26 (s, 3H, R-$C\underline{H}_3$), 1.34 (m, 2H, $RNH(CH_2)_2C\underline{H}_2Me$), 1.52 (m, 2H, $RNHCH_2C\underline{H}_2Et$), 1.87 (br d, J = 16.4 Hz, 1H, H-5), 2.03 (br d, J = 16.4 Hz, 1H, H-5), 2.58 (d, J = 8.9 Hz, 1H, H-8b), 2.98 (m, 1H, H-2a), 3.25 (s, 3H, R-$OC\underline{H}_3$), 3.31 (m, 2H, $RNHC\underline{H}_2Pr$), 3.76 (dd, J = 3.1, 8.5 Hz, 1H, H-2), 4.12 (dd, J = 7.2, 8.5 Hz, 1H, H-2), 5.74 (m, 2H, H-3 and H-4), 7.85 (s, 1H, H-6), 8.09 (br s, 1H, $RN\underline{H}Bu$).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.8 ($RNH(CH_2)_3\underline{C}H_3$), 20.2 ($RNH(CH_2)_2C\underline{H}_2Me$), 28.1 (R-$\underline{C}H_3$), 31.4 ($RNHCH_2C\underline{H}_2Et$), 34.8 (C-5a), 37.2, 37.5, 39.3 (C-2a, C-5, $RNH\underline{C}H_2Pr$), 50.5, 52.9 (R-$O\underline{C}H_3$, C-8b), 73.2 (C-2), 104.4 (C-8a), 125.7, 129.2 (C-3, C-4), 130.0 (C-7), 162.0 ($R\underline{C}ONEt_2$), 166.9 (C-6), 192.2 (C-8).

Synthesis of 8a-Methoxy-5a-methyl-7-morpholinocarbonyl-2a,5,5a,8,8a,8b-hexahydro-2*H*- naphtho[1,8-*bc*]furan-8-one (103c)

Compound **103c** was prepared as a light brown oil (266 mg, 0.80 mmol, 55% yield) from iodide **98** (502 mg, 1.45 mmol) using morpholine (400 μL), 2,6-lutidine (500 μL), $Pd(OAc)_2$ (15 mg, 0.07 mmol) and dppp (30 mg, 0.07 mmol) in THF (30 mL) according to the procedure described for the synthesis of compound **90**.



103c

IR: 2963, 1692, 1639, 1435, 1275, 1114 cm^{-1}.

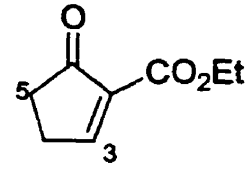
^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.20 (s, 3H, R-C$\underline{H}_3$), 1.85 (br d, J = 16.5 Hz, 1H, H-5), 2.01 (br d, J = 16.5 Hz, 1H, H-5), 2.58 (d, J = 9.0 Hz, 1H, H-8b), 2.99 (m, 1H, H-2a), 3.21 (s, 5H, R-OC$\underline{H}_3$, overlapping RN(C$\underline{H}_2$CH_2)$_2$O), 3.49-3.70 (m, 6H, RCON(C$\underline{H}_2$C$\underline{H}_2$)$_2$O), 3.75 (dd, J = 2.8, 8.5 Hz, 1H, H-2), 4.05 (dd, J = 7.2, 8.5 Hz, 1H, H-2), 5.72 (m, 2H, H-3 and H-4), 6.86 (s, 1H, H-6).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 27.8 (R-$\underline{C}H_3$), 35.0 (C-5a), 37.1, 37.3, 42.2, 47.0 (C-2a, C-5, RCON($\underline{C}H_2CH_2$)$_2$O), 50.6, 53.5 (R-O$\underline{C}H_3$, C-8b), 66.5, 66.7 (RCON(CH$_2\underline{C}$H$_2$)$_2$O) 73.0 (C-2), 103.3 (C-8a), 125.4, 129.4 (C-3, C-4), 135.4 (C-7), 158.7 (C-6), 164.3 (R$\underline{C}$ONEt$_2$), 187.6 (C-8).

Synthesis of 2-Carboethoxy-2-cyclopenten-1-one (105a)

Compound **105a** was prepared as a yellow oil (137 mg, 0.89 mmol, 58% yield) from iodide **104a**[64a] (320 mg, 1.54 mmol) using EtOH (300 μL), 2,6-lutidine (500 μL),

$Pd(OAc)_2$ (15 mg, 0.07 mmol) and dppp (30 mg, 0.07 mmol) in THF (30 mL) according to the procedure described for the synthesis of compound **90**. The ^1H NMR spectrum recorded was in complete agreement with the data reported in the literature.[147]

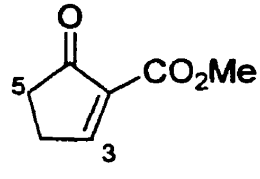


105a

^1H NMR (200 MHz, $CDCl_3$) δ: 1.35 (t, J = 6.9 Hz, 3H, R-$C\underline{H}_3$), 2.56 (m, 2H, H-4), 2.75 (m, 2H, H-5), 4.30 (q, J = 6.9 Hz, 2H, R-$CO_2C\underline{H}_2$Me), 8.40 (t, J = 3.3 Hz, 1H, H-3).

Synthesis of 2-Carbomethoxy-2-cyclopenten-1-one (105b)

Compound **105b** was prepared as a light yellow oil (130 mg, 0.93 mmol, 55% yield) from iodide **104a**[64a] (352 mg, 1.69 mmol) using MeOH (300 μL), 2,6-lutidine (500 μL), $Pd(OAc)_2$ (17 mg, 0.08 mmol) and dppp (31 mg, 0.08 mmol) in THF (30 mL) according to the procedure described for the synthesis of compound **90**. The ^1H NMR spectrum recorded was in complete agreement with the data reported in the literature.[147]



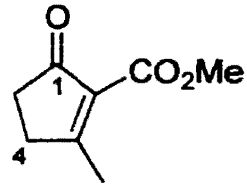
105b

^1H NMR (200 MHz, $CDCl_3$) δ: 2.50 (m, 2H, H-4), 2.71 (m, 2H, H-5), 3.79 (s, 3H, R-$CO_2C\underline{H}_3$), 8.41 (t, J = 3.2 Hz, 1H, H-3).

Synthesis of 2-Carbomethoxy-3-methyl-2-cyclopenten-1-one (105c)

Compound **105c** was prepared as a light yellow oil (131 mg, 0.85 mmol, 42% yield) from iodide **104c**[64a] (450 mg, 2.03 mmol) using MeOH (300 μL), 2,6-lutidine (600

μL), $Pd(OAc)_2$ (22 mg, 0.10 mmol) and dppp (41 mg, 0.10 mmol) in THF (50 mL) according to the procedure described for the synthesis of compound **90**. The ^1H NMR spectrum recorded was in complete agreement with the data reported in the literature.[148]

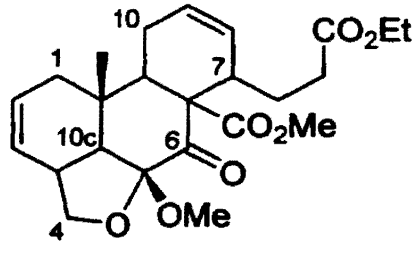


105c

^1H NMR (300 MHz, $CDCl_3$) δ: 2.39 (s, 3H, R-$C\underline{H}_3$), 2.52 (m, 2H, H-4), 2.70 (m, 2H, H-5), 3.85 (s, 3H, R-$CO_2C\underline{H}_3$).

Synthesis of 6a-Carbomethoxy-7-(2-carbomethoxyethyl)-5a-methoxy-10b-methyl-3a,4,5a,6,6a,7,10,10a,10b,10c-decahydro-1*H*-phenanthro[10,1-*bc*]furan-6-one (107)

To a solution of naphthofuranone **90** (87 mg, 0.31 mmol) and ester **85** (280 mg, 2.0 mmol) in CH_2Cl_2 (5 mL) was added anhydrous $ZnCl_2$ (30 mg, 0.22 mmol) and the resulting mixture was stirred at room temperature for 3 days. The reaction was diluted with CH_2Cl_2, washed with water and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure to give a light brown oil that could not be obtained in pure form, despite repeated chromatography. The lack of a pure sample, combined with the small amount of material available (16 mg, 37 μmol, 12% yield), limited the characterization to ^1H NMR.



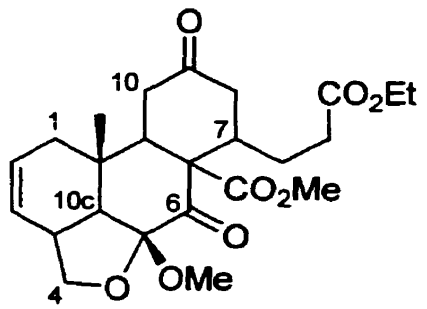
107

^{1}H NMR (250 MHz, $CDCl_3$) δ: 0.95 (s, 3H, R-C$\underline{H}_3$), 1.58 (br d, J = 16.9 Hz, 1H, H-1), 2.09-2.56 (m, 9H, H-1, H-10, H-10a, H-10c, R-C$\underline{H}_2$C$\underline{H}_2$$CO_2$Me), 2.77 (t, J = 7.5 Hz, 1H, H-7), 3.05 (m, 1H, H-3a), 3.23 (s, 3H, R-OC$\underline{H}_3$), 3.63 (s, 3H, R-CO_2C$\underline{H}_3$), 3.67 (s, 3H, R-CO_2C$\underline{H}_3$), 3.80 (dd, J = 3.9, 8.4 Hz, 1H, H-4), 4.05 (t, J = 8.4 Hz, 1H, H-4), 5.55 (dt, J = 2.6, 9.6 Hz, 1H, H-9), 5.67 (m, 2H, H-2, H-3), 5.94 (m, 1H, H-8).

Synthesis of 7-(2-Carboethoxyethyl)-6a-carbomethoxy-5a-methoxy-10b-methyl-3a,4,5a,6,6a,7,8,9,10,10a,10b,10c-dodecahydro-1*H*-phenanthro[10,1-*bc*]furan-6,9-dione (113)

A mixture of NEt_3 (1 mL) and anhydrous $ZnCl_2$ (20 mg, 0.15 mmol) was stirred for several hours until a homogeneous suspension was formed. A solution of enone **87** (348 mg, 2.04 mmol) in benzene (0.5 mL) was then added, followed by TMSCl (1 mL). The reaction mixture was stirred at room temperature overnight, after which the solvents were removed under reduced pressure and the residue was redissolved in CH_2Cl_2 (5 mL), with analysis by GC/MS showing no starting enone **87** left, and also the appearance of silyl ether **106**, with a molecular peak of *m/z* 242. A solution of ester **90** (97 mg, 0.35 mmol) in CH_2Cl_2 (2 mL) and more anhydrous $ZnCl_2$ (20 mg, 0.15 mmol) were added, and the reaction was stirred at room temperature for 3 days. The reaction mixture was treated with excess TBAF (1 mL 1M solution in THF, 1 mmol) for 1 h and washed with saturated solution of NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 and the combined organic phases were dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography (30-45% EtOAc in hexane) to give tetracycle **113** as

a yellow oil (54 mg, 0.12 mmol, 34% yield). Compound **113** unfortunately underwent decomposition during storage, thus preventing any further characterization.

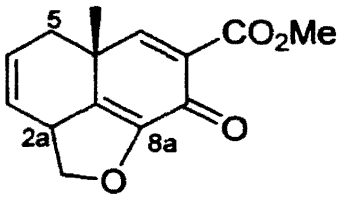


113

^{1}H NMR (250 MHz, $CDCl_3$) δ: 0.99 (s, 3H, R-C$\underline{H}_3$), 1.23 (t, J = 7.1 Hz, 3H, R-$CO_2CH_2C\underline{H}_3$), 1.56 (br d, J = 16.1 Hz, 1H, H-1), 1.95 (br d, J = 16.1 Hz, 1H, H-1), 2.07-2.68 (m, 10H, H-7, H-8, H-10, H-10a, H-10c, R-C$\underline{H}_2C\underline{H}_2CO_2$Et), 2.74 (m, 1H, H-10), 3.07 (m, 1H, H-3a), 3.19 (s, 3H, R-OC$\underline{H}_3$), 3.68 (s, 3H, R-$CO_2C\underline{H}_3$), 3.78 (dd, J = 3.3, 8.4 Hz, 1H, H-4), 4.03 (t, J = 8.4 Hz, 1H, H-4), 4.10 (q, J = 7.1 Hz, 2H, R-$CO_2C\underline{H}_2CH_3$), 5.64 (br s, 2H, H-2, H-3).

Synthesis of 7-Carbomethoxy-5a-methyl-2a,5,5a,8-tetrahydro-2*H*-naphtho[1,8-*bc*]furan-8-one (114)

To a solution of ester **90** (770 mg, 2.77 mmol) in CH_2Cl_2 (20 mL) cooled to -40°C was added TFA (0.5 mL), and after 2.5 hours at that temperature, solid $NaHCO_3$ (0.5 g) was also added. The reaction mixture was washed with saturated Na_2CO_3 solution and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4) and the solvent was removed under reduced pressure to give, after column chromatography (30% EtOAc in hexane), ester **114** as a light yellow solid in quantitative yield (681 mg, 2.77 mmol).



114

mp: 109-112°C.

IR: 3445, 2956, 1731, 1664, 1435, 1272, 1145, 1008 cm^{-1}.

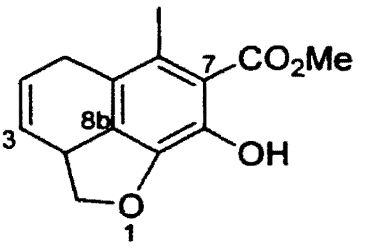
^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.35 (s, 3H, R-C$\underline{H}_3$), 2.18 (br d, J = 16.6 Hz, 1H, H-5), 2.47 (dd, J = 3.1, 16.6 Hz, 1H, H-5), 3.86 (s, 3H, R-$CO_2C\underline{H}_3$), 3.93 (br t, J = 10.2 Hz, 1H, H-2a), 4.08 (dd, J = 8.6, 10.2 Hz, 1H, H-2), 4.13 (dd, J = 8.6, 10.2 Hz, 1H, H-2), 5.75 (br s, 2H, H-3 and H-4), 7.58 (s, 1H, H-6).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 21.1 (R-$\underline{C}H_3$), 36.8 (C-5a), 38.8 (C-5), 40.1 (C-2a), 51.9 (R-$CO_2\underline{C}H_3$), 76.2 (C-2), 124.7, 126.2 (C-3, C-4), 131.0, 138.7, 147.1 (C-7, C-8a, C-8b), 164.7 (R-$\underline{C}O_2$Me), 164.4 (C-6), 172.9 (C-8).

HRMS (EI) *m/z*: Required for $C_{14}H_{14}O_4$: 246.0892; Found: 246.0858.

Synthesis of 7-Carbomethoxy-6-methyl-2a,5-dihydro-2*H*-naphtho[1,8-*bc*]furan-8-ol (115)

Ester **114** (350 mg, 1.26 mmol) was treated with neat TFA (3 mL) at room temperature for 5 min., after which the reaction mixture was diluted with CH_2Cl_2 and washed with saturated Na_2CO_3 solution. The organic layer was dried (Na_2SO_4) and the solvent removed under reduced pressure. Column chromatography (40% Et_2O in hexane) gave phenol **115** as a dark yellow oil (127 mg, 0.52 mmol, 41%).



115

IR: 3430, 1656, 1648, 1438, 1344, 1000, 944 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.37 (s, 3H, Ar-C$\underline{H}_3$), 3.20 (m, 2H, H-5), 3.95 (s, 4H, Ar-OC$\underline{H}_3$, overlapping H-2a), 4.12 (dd, J = 7.5, 12.8 Hz, 1H, H-2), 4.95 (dd, J = 7.5, 8.3 Hz, 1H, H-2), 5.94 (dm, J = 9.7 Hz, 1H, H-3), 6.07 (dm, J = 9.7 Hz, 1H, H-4), 9.98 (s, 1H, Ar-O$\underline{H}$).

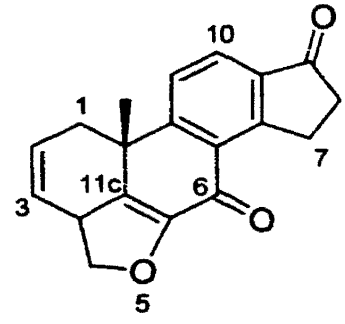
^{13}C NMR (63 MHz, $CDCl_3$) δ: 17.1 (Ar-$\underline{C}H_3$), 27.4 (C-5), 39.3 (C-2a), 52.0 (Ar-O$\underline{C}H_3$), 78.2 (C-2), 113.5 (C-7), 122.8, 125.9, 130.4, 133.7 (C-5a, C-6, C-8, C-8b), 124.3, 129.1 (C-3, C-4), 145.0 (C-8a) 172.2 (Ar-$\underline{C}O_2Me$).

LRMS (EI) *m/z*: 246 (M^+, 25), 215 (24), 214 (100), 185 (14), 171 (13), 158 (13), 129 (25), 128 (26), 127 (13), 115 (30).

Synthesis of 11b-Methyl-1,3a,4,6,7,8,9,11b-octahydrocyclopenta[7,8]phenanthro [10,1-bc]furan-6,9-dione (126)

Method 1: A solution of hydroxyketone **157** (159 mg, 0.46 mmol) and *p*-TsOH (45 mg, 0.26 mmol) in benzene (15 mL) was heated at 50°C for 4 hours, after which the reaction mixture was diluted with CH_2Cl_2 and washed once with $NaHCO_3$ solution. The aqueous phase was extracted with CH_2Cl_2 and the combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Flash chromatography (20% EtOAc in hexane) gave pentacycle **126** as a light yellow oil (64 mg, 0.22 mmol, 48% yield).

Method 2: A solution of bridged adduct **158** (22 mg, 67 μmol) in 1,1,2,2-tetrachloroethane (3 mL) was heated to reflux for 2 days. The solvent was removed under high vacuum and the residue was purified by column chromatography (20% EtOAc in hexane) to give pentacycle **126** as a light yellow oil (12 mg, 0.41 μmol, 61% yield).



126

IR: 2926, 1710, 1659, 1591, 1319, 1188, 725 cm^{-1}.

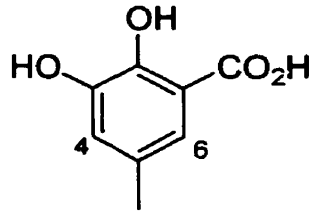
^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.51 (s, 3H, R-C$\underline{H}_3$), 2.18 (dd, J = 3.1, 17.8 Hz, 1H, H-1), 2.67 (t, J = 5.7 Hz, 2H, H-7), 2.74 (dd, J = 2.3, 17.8 Hz, H-1), 3.67 (t, J = 5.7, 5.7 Hz, 2H, H-8), 4.00 (dt, J = 2.6, 10.3 Hz, 1H, H-3a), 4.06 (dd, J = 8.1, 10.7 Hz, 1H, H-4), 4.87 (dd, J = 8.1, 9.8 Hz, 1H, H-4), 5.74 (s, 2H, H-2, H-3), 7.55 (d, J = 8.1 Hz, 1H, H-11), 7.89 (d, J = 8.1 Hz, 1H, H-10).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.8 (R-$\underline{C}H_3$), 28.3 (C-8), 36.5 (C-7), 37.8 (C-11b), 41.0 (C-3a), 42.4 (C-1), 76.1 (C-4), 125.8, 126.1, 126.4, 126.6 (C-2, C-3, C-10, C-11), 128.1, 129.6 (C-6a, C-9a), 136.9, 138.6 (C-5a, C-11c), 147.1 (C-6b), 157.8 (C-11a), 177.0 (C-6), 206.6 (C-9).

HRMS (EI) ***m/z*:** Required for $C_{19}H_{16}O_3$: 292.1099; Found: 292.1104.

Synthesis of 2,3-Dihydroxy-5-methylbenzoic acid (129)[87]

To a cooled (-78°C) solution of benzoic acid **131** (13.0 g, 71.4 mmol) in CH_2Cl_2 (500 mL) was added neat BBr_3 (53.8 g, 215 mmol) dropwise. After warming up to room temperature, the solution was stirred overnight and then quenched with MeOH. The solvent was removed under reduced pressure and the solids were redissolved in MeOH and rotoevaporated dry three times. Sublimation of the crude product (120°C, high vacuum) gave acid **129** as a white solid (10.5 g, 62.5 mmol, 87% yield).

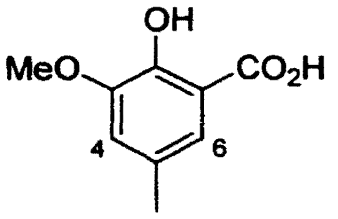


129

^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.11 (s, 3H, Ar-C<u>H</u>$_3$), 6.78 (d, J = 1.7 Hz, 1H, C-3), 7.05(d, J = 1.7 Hz, 1H, C-5), 10.49 (br s, R-O<u>H</u>).

Synthesis of 2-Hydroxy-3-methoxy-5-methylbenzoic acid (131)[88]

Phenol **75** (10.0 g, 72.5 mmol) and solid oven-dried K_2CO_3 (30.0 g, 217 mmol) were mixed and placed in a high pressure vessel under a CO_2 atmosphere (800 psi). The reaction vessel was kept at 200°C for 4.5 h and subsequently allowed to cool down to room temperature. The pressure was released, the contents of the reaction vessel were dissolved in water (400 mL) and the resulting solution was extracted once with ether, boiled with activated carbon, filtered and acidified to pH 1 with HCl. The precipitated acid **131** (13.0 g, 71.4 mmol, 98% yield) was collected by filtration, dried in a vacuum dessicator over P_2O_5 and used without further purification.

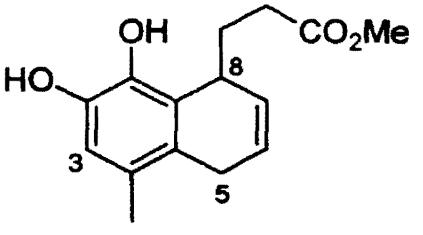


131

^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.32 (s, 3H, Ar-C<u>H</u>$_3$), 3.91 (s, 3H, Ar-OC<u>H</u>$_3$), 6.93 (d, J = 1.7 Hz, 1H, C-3), 7.31(d, J = 1.7 Hz, 1H, C-5), 10.35 (br s, R-O<u>H</u>).

Synthesis of 8-(2-Carbomethoxyethyl)-1,2-dihydroxy-4-methyl-4,8-dihydronaphthalene (132)

To a cooled (0°C) solution of benzoic acid **129** (2.00 g, 11.9 mmol), diene **85** (8.00 g, 57.1 mmol) and BHT (one crystal, approx. 5 mg) in THF (30 mL) was added solid PIFA (6.14 g, 14.3 mmol) portionwise over a period of 2 minutes. After 30 minutes, the reaction was removed from the ice bath and stirred another 3.5 hours at room temperature. The reaction mixture was then concentrated under reduced pressure, diluted with ether and washed with saturated solution of $NaHCO_3$. The aqueous layer was extracted with ether and the combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Distillation of the excess diene and iodobenzene gave a red viscous oil, which was purified to a colorless solid (2.75 g, 10.5 mmol, 88% yield) by column chromatography (20% Et_2O in hexane).



132

mp: 76-79°C.

IR: 3402, 2951, 1708, 1619, 1439, 1363, 1298 cm^{-1}.

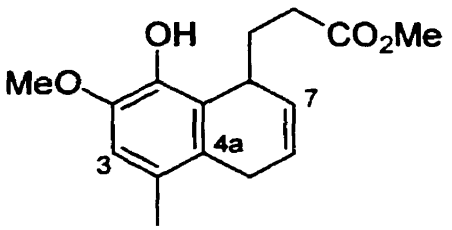
^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.78 (m, 1H, R-C<u>H</u>$_2$-CH_2-CO_2Me), 2.02 (m, 1H, R-C<u>H</u>$_2$-CH_2-CO_2Me), 2.13 (s, 3H, Ar-C<u>H</u>$_3$), 2.38 (dt, J = 5.3, 17.6 Hz, 1H, R-C<u>H</u>$_2$-CO_2Me), 2.53 (ddd, J = 5.1, 10.5, 17.6 Hz, 1H, R-C<u>H</u>$_2$-CO_2Me), 3.14 (m, 2H, H-5), 3.59 (m, 1H, H-8), 3.74 (s, 3H, R -CO_2-C<u>H</u>$_3$), 5.98 (br s, 2H, H-6, H-7), 6.66 (s, 1H, H-3), 7.18 (br s, Ar-O<u>H</u>).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.9 (Ar-<u>C</u>H_3), 27.5 (R-<u>C</u>H_2-CH_2-CO_2Me), 30.0, 32.0 (R-<u>C</u>H_2-CO_2Me, C-5), 33.2 (C-8), 52.3 (R-CO_2<u>C</u>H_3), 114.5 (C-3), 124.3, 124.4, 127.0 (C-4, C-4a, C-8a), 125.6, 126.8 (C-6, C-7), 139.0, 142.1 (C-1, C-2), 176.6 (R-<u>C</u>O_2Me).

Anal. Calc. for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92. Found: C, 68.48; H, 6.70.

Synthesis of 8-(2-Carbomethoxyethyl)-1-hydroxy-2-methoxy-4-methyl-5,8-dihydronaphthalene (133)

To a solution of catechol **132** (2.14 g, 8.17 mmol) in CH_2Cl_2 (150 mL) was added oven dried K_2CO_3 (11.3 g, 81.8 mmol) and the resulting suspension was stirred for 30 min. The reaction mixture was cooled down (0°C), Me_3OBF_4 (2.42 g, 18.3 mmol) was added and the flask was purged with N_2. The reaction was allowed to warm up to room temperature, and stirring was continued for 20 h. After quenching with dilute HCl (0.1 M), the layers were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Column chromatography (20% EtOAc in hexane) gave phenol **133** as a light yellow oil (2.16 g, 7.82 mmol, 96% yield).



133

IR: 3462, 2946, 1732, 1488, 1436, 1299, 1161 cm^{-1}.

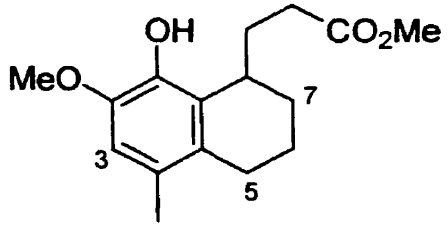
^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.93-2.32 (m, 7H, R-($C\underline{H}_2$)$_2$-CO_2Me, overlapping Ar-$C\underline{H}_3$), 2.17 (s, Ar-$C\underline{H}_3$), 3.13 (m, 2H, H-5), 3.58 (s, 3H, R-$CO_2C\underline{H}_3$), 3.83 (m, 4H, H-8, overlapping Ar-$OC\underline{H}_3$), 3.85 (s, Ar-$OC\underline{H}_3$), 5.63 (s, Ar-O$\underline{H}$), 5.87 (dm, J = 10.1 Hz, 1H, H-6), 5.99 (dm, J = 10.1 Hz, 1H, H-7), 6.60 (s, 1H, H-3).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 19.2 (Ar-$\underline{C}H_3$), 27.5 (R-$\underline{C}H_2$-CH_2-CO_2Me), 30.1, 30.2 (R-$\underline{C}H_2$-CO_2Me, C-5), 33.5 (C-8), 51.3 (R-$CO_2\underline{C}H_3$), 56.0 (Ar-O$\underline{C}H_3$), 110.6 (C-3), 123.8, 126.0, 126.4 (C-4, C-4a, C-8a), 125.4, 128.2 (C-6, C-7), 140.7 (C-1), 144.0 (C-2), 174.6 (R-$\underline{C}O_2Me$).

Anal. Calc. for $C_{16}H_{20}O_4$: C, 69.55; H, 7.30. Found: C, 69.31; H, 7.05.

Synthesis of 8-(2-Carbomethoxyethyl)-1-hydroxy-2-methoxy-4-methyl-5,6,7,8-tetrahydronaphthalene (134)

To a cooled (0°C) solution of phenol **133** (429 mg, 1.55 mmol) in CH_2Cl_2 (120 mL) was added $AlCl_3$ (1.5 g) and the resulting mixture was allowed to warm up to room temperature and stirred overnight. The reaction mixture was washed with cold HCl (1 M) and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography (20% ether in hexane) to give tetrahydronaphthalene **134** as a colorless oil (207 mg, 0.74 mmol, 48% yield).



134

IR: 3460, 2937, 1738, 1487, 1300, 1250, 833 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.58-1.87 (m, 5H, H-6, H-7, R-C$\underline{H}_2$CH_2CO_2Me), 2.06 (m, 1H, R-C$\underline{H}_2$CH_2CO_2Me), 2.15 (s, 3H, Ar-C$\underline{H}_3$), 2.36-2.55 (m, 3H, H-5, R-CH$_2$C$\underline{H}_2CO_2$Me), 2.64 (br d, J = 16.8 Hz, 1H, H-5), 3.03 (m, 1H, H-8), 3.68 (s, 3H, R-CO_2C$\underline{H}_3$), 3.84 (s, 3H, Ar-OC$\underline{H}_3$), 5.85 (br s, 1H, Ar-O$\underline{H}$), 6.59 (s, 1H, H-3).

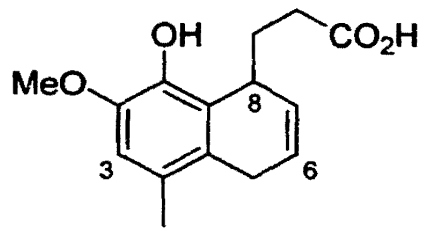
^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 17.7 (C-6), 19.4 (Ar-$\underline{C}H_3$), 25.1, 26.3, 28.9, 32.5 (C-5, C-7, R-$\underline{C}H_2\underline{C}H_2CO_2$Me), 31.6 (C-8), 51.6 (R$CO_2\underline{C}H_3$), 56.1 (Ar-O$\underline{C}H_3$), 110.7 (C-3), 126.8, 127.3, 127.8 (C-4, C-4a, C-8a), 141.2 (C-1), 143.7 (C-2), 174.8 (R-$\underline{C}O_2$Me).

HRMS (EI) *m/z*: Required for $C_{16}H_{22}O_4$: 278.1518; Found: 278.1529.

Synthesis of 6-Methoxy-4-methyl-3,9,10,10a-tetrahydro-7-oxacyclohepta[*de*] naphthalen-8-one (136)

To a degassed solution of phenol **133** (2.11 g, 7.64 mmol) in MeOH (50 mL) was added a solution of NaOH (6 g) in water (50 mL), also degassed. The resulting solution was stirred for 30 min, extracted with ether to remove unreacted starting material, acidified to pH 1 with HCl and finally extracted with EtOAc. The combined EtOAc phases were dried (Na_2SO_4), filtered and the solvents were removed under reduced pressure to give crude acid **135**, which was used without further purification. Compound **135** was then redissolved in CH_2Cl_2 (50 mL), trifluoroacetic anhydride (25 mL) was added and the resulting solution was stirred overnight. The reaction mixture was

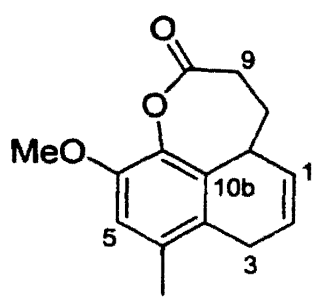
concentrated under reduced pressure and column chromatography (20% EtOAc in hexane) gave lactone **136** (1.62 g, 6.63 mmol, 87% yield) as a colorless solid.



135

^{1}H NMR (300 MHz, CDCl$_3$/DMSO-d6) δ: 1.91-2.29 (m, 7H, R-(C<u>H</u>$_2$)$_2$-CO$_2$H, overlapping Ar-C<u>H</u>$_3$), 2.17 (s, Ar-C<u>H</u>$_3$), 3.12 (m 2H, H-5), 3.79 (m, 1H, H-8), 3.84 (s, 3H, Ar-OC<u>H</u>$_3$), 5.89 (br d, J = 10.0 Hz, 1H, H-6), 5.98 (br d, J = 10.0 Hz, 1H, H-7), 6.61 (s, 1H, H-3)

^{13}C NMR (75.5 MHz, CDCl$_3$/DMSO-d6) δ: 18.6 (Ar-<u>C</u>H$_3$), 26.9 (C-5), 29.7, 29.8 (R-(<u>C</u>H$_2$)$_2$-CO$_2$H), 32.9 (C-8), 55.5 (Ar-O<u>C</u>H$_3$), 110.5 (C-3), 123.9, 125.1, 125.6 (C-4, C-4a, C-8a), 124.7, 127.7 (C-6, C-7), 140.3 (C-1), 143.8 (C-2), 175.7 (R-<u>C</u>O$_2$H).



136

mp: 116-119°C.

IR: 2941, 1761, 1608, 1488, 1455, 1318, 1137 cm^{-1}.

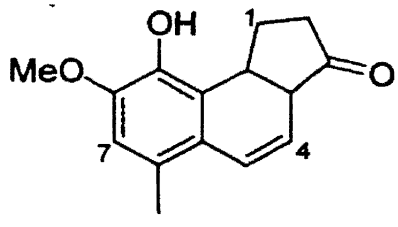
^{1}H NMR (300 MHz, CDCl$_3$) δ: 2.21 (s, 3H, Ar-C<u>H</u>$_3$), 2.36-2.58 (m, 4H, H-9, H-10), 3.17 (br s, 2H, H-3), 3.66 (m, 1H, H-10a), 3.81 (s, 3H, Ar-OC<u>H</u>$_3$), 5.80 (dm, J = 10.1 Hz, 1H, H-2), 5.87 (dm, J = 10.1 Hz, 1H, H-1), 6.72 (s, 1H, H-5).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.8 (Ar-$\underline{C}H_3$), 27.3 (C-10), 30.9 (C-9), 33.2 (C-10a), 34.3 (C-3), 56.4 (Ar-O$\underline{C}H_3$), 113.4 (C-5), 124.1, 126.7 (C-1, C-2), 124.6, 127.5 (C-4, C-10b), 134.1 (C-3a), 138.0 (C-6a), 147.5 (C-6), 171.9 (C-8).

Anal. Calc. for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.61; H, 6.49.

Synthesis of 9-Hydroxy-8-methoxy-6-methyl-2,3,3a,9b-tetrahydro-1*H*-benz[*e*]inden-3-one (137)

To a solution of lactone **136** (366 mg, 1.50 mmol) in CH_2Cl_2 (50 mL) was added $AlCl_3$ (1 g), and the resulting reaction mixture was stirred for 1 h 45 min. Water was added, the phases separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Column chromatography (20% Et_2O in hexane) gave benzindanone **137** as a white solid (99 mg, 0.40 mmol, 27% yield).



137

mp: 112-114°C.

IR: 3500, 2935, 1766, 1604, 1487, 1315, 1134 cm^{-1}.

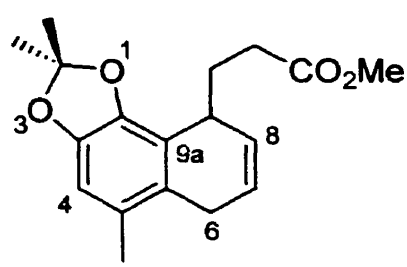
^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.93-2.37 (m, 7H, H-1, H-2, overlapping Ar-C$\underline{H}_3$), 2.32 (s, Ar-C$\underline{H}_3$), 2.62 (m, 1H, H-3a), 3.22 (m, 1H, H-9b), 3.84 (s, 3H, Ar-OC$\underline{H}_3$), 5.79 (m, 1H, H-4), 5.85-5.91, 6.51 (dd, J = 3.3, 9.9 Hz, 1H, H-5), 6.65 (s, 1H, H-7).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.9 (Ar-$\underline{C}H_3$), 26.8 (C-1), 29.4 (C-9b), 31.1 (C-2), 56.0, 56.1 (Ar-O$\underline{C}H_3$, C-3a), 112.7 (C-7), 122.3, 123.0 (C-4, C-5), 123.3, 127.4, 129.2 (C-5a, C-6, C-9a), 137.7, 148.1 (C-8, C-9), 212.0 (C-3).

Anal. Calc. for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.81; H, 6.43.

Synthesis of Methyl 3-(2,2,5-trimethyl-6,9-dihydronaphtho[1,2-*d*][1,3]dioxol-9-yl) propanoate (141)

To a solution of catechol **132** (1.00 g, 3.81 mmol), in MeOH (5 mL) and dimethoxypropane (15 mL) was added *p*-TsOH (1 g) and the resulting solution was stirred at room temperature for 2 days. The reaction mixture was partitioned between water and EtOAc, and the aqueous phase was extracted with more EtOAc. The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash chromatography (20% Et_2O in hexane) gave acetonide **141** as a light yellow solid (1.07 g, 3.54 mmol, 93% yield).



141

mp: 60-62°C.

IR: 2949, 1739, 1478, 1375, 1244, 1007, 843 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.64, 1.66 (2 s, 6H, $(ArO)_2C(C\underline{H}_3)_2$), 1.90-2.29 (m, 7H, R-$(C\underline{H}_2)_2$-$CO_2Me$, overlapping Ar-$C\underline{H}_3$), 2.14 (s, Ar-$C\underline{H}_3$), 3.10 (m, 2H, H-6), 3.58 (s,

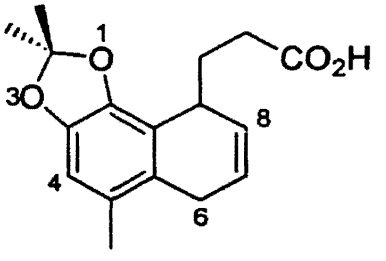
3H, R-$CO_2C\underline{H}_3$), 3.64 (m, 1H, H-9), 5.80 (dm, J = 10.3 Hz, 1H, H-7), 5.99 (dm, J = 10.3 Hz, 1H, H-8), 6.50 (s, 1H, H-4).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.5 (Ar-$C\underline{H}_3$), 25.8 ($(ArO)_2C(\underline{C}H_3)_2$), 27.5, 30.0, 30.1 (R-$(\underline{C}H_2)_2$-$CO_2Me$, C-6), 33.6 (C-9), 51.4 (R-$CO_2\underline{C}H_3$), 108.4 (C-4), 117.3 ($(ArO)_2\underline{C}(CH_3)_2$), 119.3, 125.7, 127.7 (C-5, C-5a, C-9a), 125.9, 127.3 (C-7, C-8), 142.7, 144.8 (C-3a, C-9b), 174.5 (R-$\underline{C}O_2CH_3$).

Anal. Calc. for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.74; H, 7.16.

Synthesis of 3-(2,2,5-Trimethyl-6,9-dihydronaphtho[1,2-*d*][1,3]dioxol-9-yl)propanoic acid (142)

To a solution of NaOH (500 mg) in MeOH (30 mL) was added solid ester **141** (230 mg, 0.76 mmol) and the resulting solution was stirred at room temperature for 4 days. The base was neutralized with NH_4Cl and the reaction mixture was diluted with water and subsequently extracted with Et_2O. The combined organic layers were dried ($MgSO_4$), filtered and removal of the solvent under reduced pressure gave acid **142** (203 mg, 0.70 mmol, 92% yield) as a light yellow solid that was used without further purification.



142

mp: 108-113°C.

IR: 2935, 1709, 1479, 1375, 1245, 1006, 843 cm^{-1}.

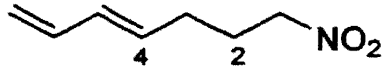
^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.64, 1.65 (2 s, 6H, $(ArO)_2C(C\underline{H}_3)_2$), 1.88-2.32 (m, 7H, R-$(C\underline{H}_2)_2$-$CO_2Me$, overlapping Ar-$C\underline{H}_3$), 2.14 (s, Ar-$C\underline{H}_3$), 3.12 (m, 2H, H-6), 3.65 (m, 1H, H-9), 5.79 (dm, J = 10.3 Hz, 1H, H-7), 6.00 (dm, J = 10.3 Hz, 1H, H-8), 6.49 (s, 1H, H-4), 11.12 (br s, R-$CO_2\underline{H}$).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.5 (C-6), 25.8, 25.9 ($(ArO)_2C(\underline{C}H_3)_2$), 27.5, 29.7, 30.0 (R-$(\underline{C}H_2)_2$-$CO_2Me$, C-6), 33.5 (C-9), 108.5 (C-4), 117.3 ($(ArO)_2\underline{C}(CH_3)_2$), 119.1, 125.6, 127.8 (C-5, C-5a, C-9a), 126.1, 127.1 (C-7, C-8), 142.8, 144.8 (C-3a, C-9b), 179.9 (R-$\underline{C}O_2H$).

Anal. Calc. for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 71.06; H, 7.07.

Synthesis of 1-Nitrohepta-4,6-diene (146)[96]

To a solution of 1-iodohepta-4,6-diene (2.46 g, 11.1 mmol) in dry ether (15 mL) was added solid $AgNO_2$ (2.18 g, 14.2 mmol) and the resulting suspension was stirred in the dark at room temperature for three days. The silver salts were then removed by filtration and evaporation of the solvent under reduced pressure gave a red oil, which was purified by column chromatography (hexane) to give compound **146** as a slightly yellow liquid (1.06 g, 7.51 mmol, 68% yield).



146

IR: 2932, 1553, 1435, 1382, 1007, 906 cm^{-1}.

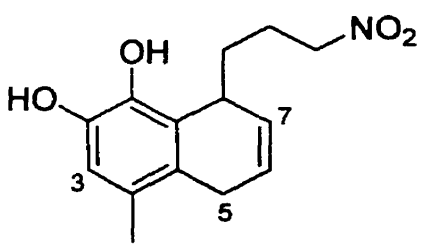
^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.04-2.23 (m, 4H, H-2 and H-3), 4.39 (t, J = 6.8 Hz, 2H, H-1), 5.03 (d, J = 10.3 Hz, 1H, H-7) 5.15 (dd, J = 1.7, 17.0 Hz, 1H, H-7), 5.63 (dt, J = 7.1, 15.0 Hz, 1H, H-4), 6.10 (dd, J = 10.3, 15.0 Hz, 1H, H-5), 6.30 (dt, J = 10.3, 17.0 Hz, 1H, H-6).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 26.7, 28.9 (C-2, C-3), 74.7 (C-1), 116.3 (C-7), 131.4, 133.0, 136.5 (C-4, C-5, C-6).

Anal. Calc. for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.41; H, 7.77; N, 9.89.

Synthesis of 4-Methyl-8-(3-nitropropyl)-5,8-dihydronaphthalene-1,2-diol (148)

To a cooled (0°C) solution of benzoic acid **129** (828 mg, 4.93 mmol), diene **146** (3.50 g, 24.8 mmol) and BHT (one crystal, approx. 3 mg) in THF (40 mL) was added solid PIFA (2.50g, 5.81 mmol) portionwise over a period of 2 minutes. After 30 minutes, the reaction was removed from the ice bath and stirred another 3.5 hours at room temperature. The reaction mixture was then concentrated under reduced pressure, diluted with ether and washed with saturated solution of $NaHCO_3$. The aqueous layer was extracted with ether and the combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Distillation of the excess diene and iodobenzene gave a red viscous oil, which was purified to a light yellow oil (1.12 g, 4.27 mmol, 86% yield) by column chromatography (20% EtOAc in hexane).



148

IR: 3496, 2919, 1620, 1550, 1382, 1295, 1194, 735 cm^{-1}.

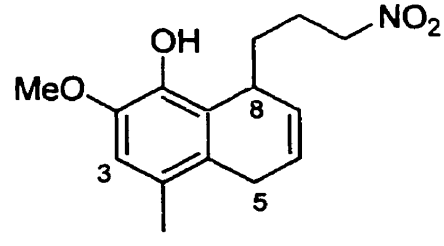
^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.63-2.09 (m, 4H, R-($C\underline{H}_2$)$_2$-CH_2-NO_2), 2.12 (s, 3H, Ar-$C\underline{H}_3$), 3.13 (m, 2H, H-5), 3.76 (m, 1H, H-8), 4.29 (t, J = 6.9 Hz, 2H, R-$C\underline{H}_2$-NO_2), 5.20 (s, br, 2H, Ar-O$\underline{H}$), 5.85-5.91, 5.99-6.05 (m, 2H, H-6, H-7), 6.57 (s, 1H, H-3).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.9 (Ar-$\underline{C}H_3$), 23.7, 27.5, 31.7 (C-5, R-($\underline{C}H_2$)$_2$-CH_2-NO_2), 33.5 (C-8), 75.9 (R-$\underline{C}H_2$-NO_2), 115.0 (C-3), 124.9, 126.5, 127.0 (C-4, C-4a, C-8a), 125.6, 127.8 (C-6, C-7), 139.4, 140.2 (C-1, C-2).

HRMS (EI) ***m/z*:** Required for $C_{14}H_{17}NO_4$: 263.1157; Found: 263.1142.

Synthesis of 2-Methoxy-4-methyl-8-(3-nitropropyl)-5,8-dihydronaphthalen-1-ol (149)

To a solution of catechol **148** (200 mg, 0.76 mmol) in CH_2Cl_2 (20 mL) was added oven dried K_2CO_3 (1.07 g, 7.74 mmol) and the resulting suspension was stirred for 30 min. The reaction mixture was cooled down (0°C), Me_3OBF_4 (230 mg, 1.55 mmol) was added and the flask was purged with N_2. The reaction was allowed to warm up to room temperature, and stirring was continued for 20 h. After quenching with dilute HCl (0.1 M), the layers were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Column chromatography (20% EtOAc in hexane) gave phenol **149** as a light yellow oil (215 mg, quantitative yield).



149

IR: 3504, 2939, 1618, 1551, 1489, 1381, 1301 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.62-2.15 (m, 4H, R-($\underline{C}H_2$)$_2$-CH_2-NO_2), 2.18 (s, 3H, Ar-$\underline{C}H_3$), 3.13 (m, 2H, H-5), 3.78 (m, 1H, H-8), 3.85 (s, 3H, Ar-O$\underline{C}H_3$) 4.27 (t, J = 7.0 Hz,

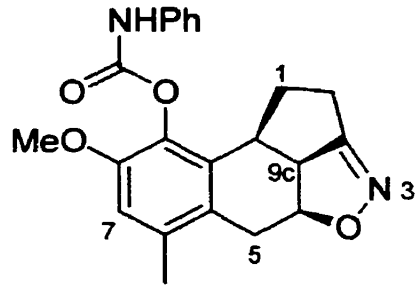
2H, R-C$\underline{H}_2$-NO_2), 5.60 (s, 1H, Ar-O$\underline{H}$), 5.85-5.91, 5.97-6.03 (m, 2H, H-6, H-7), 6.61 (s, 1H, H-3).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.2 (Ar-$\underline{C}H_3$), 23.7, 27.4, 31.7 (C-5, R-($\underline{C}H_2$)$_2$-CH_2-NO_2), 33.5 (C-8), 56.0 (Ar-O$\underline{C}H_3$), 75.9 (R-$\underline{C}H_2$-NO_2), 110.6 (C-3), 123.8, 126.1, 126.2 (C-4, C-4a, C-8a), 125.4, 128.0 (C-6, C-7), 140.5 (C-1), 143.9 (C-2).

Anal. Calc. for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 65.12; H, 6.81; N, 4.96.

Synthesis of 8-Methoxy-6-methyl-1,2,4a,5,9b,9c-hexahydrobenzo[4,5]indeno[1,7-*cd*] isoxazol-9-yl-*N*-phenylcarbamate (150)

Phenol **149** (215 mg, 0.78 mmol) was dissolved in benzene (15 mL), and to the resulting solution were added NEt_3 (320 μL, 2.22 mmol) and phenyl isocyanate (350 μL, 3.11 mmol). The reaction mixture was protected from light and stirred at room temperature for 24 hours, after which it was filtered and the benzene was removed under reduced pressure to give a mixture that consisted mostly of product **150** and aniline. The crude residue was treated with deoxygenated NaOH (1 g in 20 mL 1:1 water:methanol) for 45 minutes. The resulting suspension was filtered and the filtrate was acidified with HCl (1 M) and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography (30% EtOAc in hexane) to give isooxazoline **152** as a white crystalline solid (68 mg, 0.26 mmol, 33% yield).



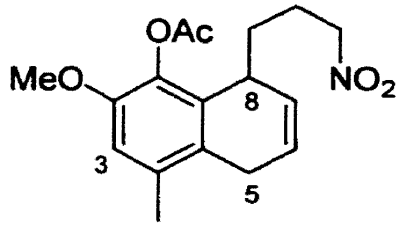
150

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.55 (m, 1H, H-1), 2.25 (s, 4H, Ar-C$\underline{H}_3$, overlapping H-5), 2.38-2.72 (m, 3H, H-1, H-2), 3.10 (dd, J = 6.2, 14.5 Hz, 1H, H-5), 3.75 (s, 3H, Ar-OC$\underline{H}_3$), 3.89 (m, 2H, H-9b, H-9c), 4.63 (m, 1H, H-4a), 6.67 (s, 1H, H-7), 6.95-7.60 (m, 6H, ArOCONHC$_6\underline{H}_5$, ArOCON$\underline{H}$C$_6$H$_5$).

Synthesis of 8-Methoxy-6-methyl-1,2,4a,5,9b,9c-hexahydrobenzo[4,5]indeno[1,7-*cd*] isoxazol-9-ol (152)

Phenol **149** (1.16 g, 4.41 mmol) was dissolved in pyridine (2 mL) and Ac_2O (10 mL), and the resulting solution was stirred at room temperature for 3 hours. The mixture was concentrated under reduced pressure, diluted with CH_2Cl_2, washed with dilute HCl (1:50) and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and concentrated to give crude acetate **151** as an orange oil, which was used without further purification. Acetate **151** was then dissolved in benzene (90 mL), and to the resulting solution were added NEt_3 (0.7 mL, 5.03 mmol) and *para*-chlorophenyl isocyanate (2.50 g, 16.3 mmol). The reaction mixture was protected from light and stirred at room temperature for 20 hours, after which more *para*-chlorophenyl isocyanate (600 mg, 3.91 mmol) was added and the stirring continued for 2 hours. The reaction mixture was filtered, the benzene removed under reduced pressure and the residue treated with degassed NaOH (2 g in 50 mL 1:1 water:methanol)

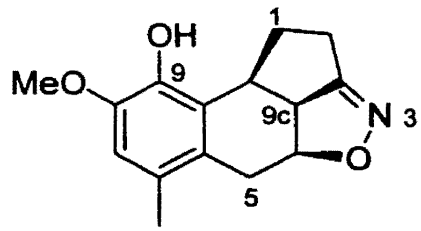
for 30 minutes. The resulting suspension was filtered and the filtrate was acidified with HCl (1 M) and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, concentrated and purified by column chromatography (30% EtOAc in hexane) to give isooxazoline **152** as a white crystalline solid (969 mg, 3.74 mmol, 85%).



151

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.63-2.10 (m, 4H, R-($C\underline{H}_2$)$_2$-CH_2-NO_2), 2.22 (s, 3H, Ar-$C\underline{H}_3$), 2.33 (s, 3H, $\underline{H}_3CCO_2R$) 3.15 (m, 2H, H-5), 3.55 (m, 1H, H-8), 3.80 (s, 3H, Ar-$OC\underline{H}_3$) 4.27 (t, J = 6.8 Hz, 2H, R-$C\underline{H}_2$-NO_2), 5.80-5.86, 6.00-6.05 (m, 2H, H-5, H-6), 6.72 (s, 1H, H-3).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 19.7 (Ar-$\underline{C}H_3$), 20.6 ($H_3\underline{C}CO_2R$) 23.3, 27.5, 32.4 (C-5, R-($\underline{C}H_2$)$_2$-CH_2-NO_2), 34.1 (C-8), 55.9 (Ar-$O\underline{C}H_3$), 75.7 (R-$\underline{C}H_2$-NO_2), 112.3 (C-3), 125.7, 127.3 (C-6, C-7), 126.1, 130.4, 133.9, 135.3 (C-1, C-4, C-4a, C-8a), 148.7 (C-2), 169.0 ($H_3C\underline{C}O_2R$).



152

mp: 198-200°C (dec.).

IR: 3448, 2963, 1728, 1686, 1456, 1251, 1100, 1056 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.53 (m, 1H, H-1), 2.25 (s, 4H, Ar-$C\underline{H}_3$, overlapping H-5), 2.57 (m, 1H, H-2), 2.70 (m, 2H, H-1, H-2), 3.11 (dd, J = 6.4, 14.7 Hz, 1H, H-5), 3.86

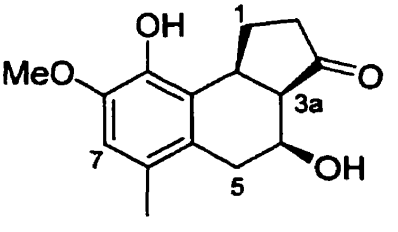
(s, 3H, Ar-OC$\underline{H}_3$), 3.94 (m, 2H, H-9b, H-9c), 4.66 (m, 1H, H-4a), 5.61 (s, 1H, Ar-O$\underline{H}$), 6.60 (s, 1H, H-7).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.5 (Ar-$\underline{C}H_3$), 26.7, 26.9 (C-1, C-2), 30.2 (C-9c), 37.9 (C-5), 53.3 (C-9b), 56.0 (Ar-O$\underline{C}H_3$), 81.3 (C-4a), 110.8 (C-7),124.5, 125.2, 126.7 (C-5a, C-6, C-9a), 140.6 (C-9), 144.0 (C-8), 171.0 (C-2a).

Anal. Calc. for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.38; H, 6.46; N, 5.34.

Synthesis of 4,9-Dihydroxy-8-methoxy-6-methyl-2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*] inden-3-one (153)

To a solution of oxazoline **152** (889 mg, 3.43 mmol) in THF (35 mL), MeOH (100 mL) and water (25 mL) were added H_3BO_3 (940 mg, 15.2 mmol) and Pd/C (10%, 90 mg). The reaction flask was evacuated and refilled with H_2 5 times, and stirring was continued overnight. The reaction mixture was filtered through a plug of celite, the organic solvents were removed under reduced pressure and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to give hydroxyketone **153** as a colorless solid (891 mg, 3.40 mmol, 99% yield).



153

mp: 136-137°C.

IR: 3449, 2940, 1731, 1612, 1488, 1306, 912, 731 cm^{-1}.

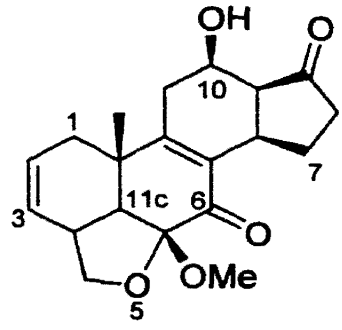
^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.05-2.59 (m, 8H, H-1, H-2, H-5, overlapping Ar-C$\underline{H}_3$), 2.18 (s, Ar-C$\underline{H}_3$), 2.74 (dd, J = 4.9, 9.0 Hz, 1H, H-3a), 2.88 (dd, J = 4.3, 16.2 Hz, 1H, H-5), 3.27 (br s, R-O$\underline{H}$), 3.87 (s, 4H, Ar-OC$\underline{H}_3$, overlapping H-9b), 4.19 (qn, J = 4.6 Hz, 1H, H-4), 5.79 (br s, Ar-O$\underline{H}$), 6.64 (s, 1H, H-7).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 19.5 (Ar-$\underline{C}H_3$), 28.3 (C-1), 33.4 (C-5), 36.8 (C-9b), 38.6 (C-2), 50.9 (C-3a), 56.0 (Ar-O$\underline{C}H_3$), 67.9 (C-4), 111.2 (C-7), 123.3, 125.4, 127.1 (C-5a, C-6, C-9a), 141.4, 144.1 (C-8, C-9).

Anal. Calc. for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92. Found: C, 68.53; H, 6.84.

Diels-Alder reaction between 2,4-pentadienol (91) and benzindanone 153

To a solution of benzindanone **153** (870 mg, 3.32 mmol), alcohol **91** (2.80 g, 33 mmol) and BHT (1 crystal) in THF (30 mL), was added solid $NaHCO_3$ (670 mg, 7.98 mmol) and the resulting suspension was heated to 50°C. A solution of PIFA (1.70 g, 3.95 mmol) in THF (10 mL) was then added to the reaction mixture via a syringe pump over a period of 4 h. Removal of the solvent, iodobenzene and excess **91** under vacuum, followed by column chromatography (30% EtOAc in hexane) gave 12-methoxy-10-methyl-16-vinyl-13-oxapentacyclo[10.4.1.$0^{1,9}$.$0^{2,6}$.$0^{11,15}$]heptadeca-6,9-diene-5,17-dione (**155**) as a colorless solid (332 mg, 1.02 mmol, 31% yield) and a mixture of two diastereomeric forms of 10-hydroxy-5a-methoxy-11b-methyl-1,3a,4,5a,6,6b,7,8,9,9a,10,11,11b,11c-tetradecahydrocyclopenta[7,8]phenanthro[10,1-*bc*]furan-6,9-dione (**154**) as a light yellow oil (376 mg, 1.09 mmol, 33% yield). Both diastereomers were separated by preparative HPLC (10% *i*-PrOH in hexane).



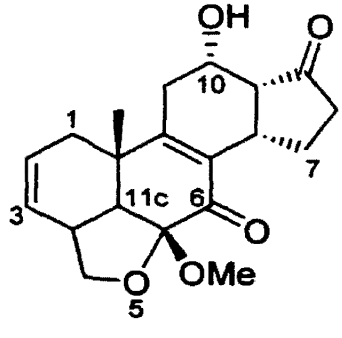
154a

IR: 3476, 2946, 1736, 1682, 1457, 1253, 1038 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.17 (s, 3H, R-C$\underline{H}_3$), 1.85 (dq, J = 2.9, 16.3 Hz, 1H, H-1), 1.91-2.29 (m, 6H, H-1, H-7, H-8, H-11), 2.56-2.68 (m, 3H, H-8, H-9a, overlapping H-11c), 2.65 (d, J = 10.4 Hz, H-11c), 3.06 (m, 1H, H-3a), 3.39 (t, J = 8.1 Hz, 1H, H-4), 3.51 (s, 3H, R-OC$\underline{H}_3$), 3.60 (m, 1H, H-6b), 4.02 (m, 1H, H-10), 4.22 (t, J = 8.4 Hz, 1H, H-4), 5.63 (dt, J = 2.6, 9.7 Hz, 1H, H-3), 5.83 (m, 1H, H-2).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 26.8 (C-7), 29.7 (R-$\underline{C}H_3$), 32.8 (C-8), 34.7 (C-1), 36.4 (C-11b), 36.9 (C-6b), 37.6 (C-11), 39.0 (C-3a), 50.3, 50.8, 51.5 (R-O$\underline{C}H_3$, C-9a, C-11c), 66.8 (C-10), 73.0 (C-4), 104.3 (C-5a), 126.6 (C-2), 128.4 (C-3), 134.4 (C-6a), 157.3 (C-11a), 192.1 (C-6), 223.5 (C-9).

Anal. Calc. for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found (mixture of both diastereomers): C, 69.94; H, 6.86.

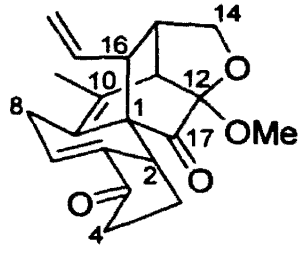


154b

IR: 3480, 2941, 1733, 1682, 1457, 1295, 1163, 1043 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.13 (s, 3H, R-C$\underline{H}_3$), 1.70 (br d, J = 16.4 Hz, 1H, H-1), 1.79 (m, 1H, H-7), 2.01 (dm, J = 16.4 Hz, H-1), 1.98-2.33 (m, 6H, H-6b, H-7, H-8, H-11, overlapping H-1), 2.48 (dd, J = 1.9, 8.7 Hz, 1H, H-11c), 2.62-2.75 (m, 2H, H-8, H-9a), 3.03 (m, 1H, H-3a), 3.19 (s, 3H, R-OC$\underline{H}_3$), 3.63 (m, 1H, H-10), 3.86 (d, J = 8.4 Hz, 1H, H-4), 4.04 (dd, J = 6.6, 8.4 Hz, 1H, H-4), 5.69 (m, 2H, H-2, H-3).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.3 (R-$\underline{C}H_3$), 26.6 (C-7), 33.1 (C-8), 36.3 (C-11b), 36.8, 37.0 (C-1, C-11), 36.9 (C-6b), 37.2 (C-3a), 49.4, 50.8 (R-O$\underline{C}H_3$, C-9a), 52.9 (C-11c), 67.1 (C-10), 72.7 (C-4), 103.3 (C-5a), 124.3, 127.9 (C-2, C-3), 132.9 (C-6a), 159.7 (C-11a), 190.4 (C-6), 223.6 (C-9).



155

mp: 178-179°C.

IR: 2949, 1731, 1714, 1459, 1218, 1025, 929 cm^{-1}.

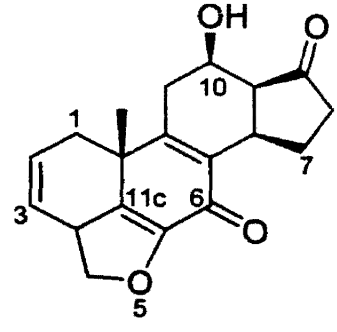
^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.91 (d, J = 1.8 Hz, 3H, R-C$\underline{H}_3$), 2.11 (m, 2H, H-3), 2.39 (br t, J = 3.2 Hz, 2H, H-15, overlapping H-4), 2.43 (ddd, J = 7.6, 10.3, 19.0 Hz, H-4), 2.59 (br d, J = 18.1 Hz, 1H, H-8), 2.64 (d, J = 10.0 Hz, 1H, H-16), 2.73 (ddd, J = 4.7, 10.0, 19.0 Hz, 1H, H-4), 2.99 (m, 1H, H-2), 3.10 (d, J = 4.4 Hz, 1H, H-11), 3.40 (dd, J = 7.0, 18.1 Hz, 1H, H-8), 3.48 (s, 3H, R-OC$\underline{H}_3$), 3.92 (d, J = 8.2 Hz, 1H, H-14), 4.16 (dd, J = 3.2, 8.2 Hz, 1H, H-14), 5.13 (dd, J = 1.4, 10.0 Hz, 2H, RCH=C$\underline{H}_2$, overlapping the other RCH=C$\underline{H}_2$), 5.16 (dd, J = 1.4, 17.0 Hz, RCH=C$\underline{H}_2$), 5.54 (dt, J = 10.0, 17.0 Hz, 1H, RC$\underline{H}$=CH_2), 6.56 (dt, J = 6.4, 6.8 Hz, 1H, H-7).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.3 (R-$\underline{C}H_3$), 19.2 (C-3), 27.6 (C-8),37.1 (C-2), 38.4 (C-4), 43.7 (C-15), 47.1 (C-16), 49.9 (C-11), 51.4 (R-O$\underline{C}H_3$), 60.4 (C-1), 74.0 (C-14), 100.6 (C-12), 117.1 (RCH=$\underline{C}H_2$), 126.1 (C-7), 127.9, 130.7 (C-9, C-10), 138.1 (R$\underline{C}$H=CH_2), 142.3 (C-6), 197.1 (C-17), 205.9 (C-5).

Anal. Calc. for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.70; H, 6.75.

Synthesis of 10-Hydroxy-11b-methyl-1,3a,4,6,6b,7,8,9,9a,10,11,11b-dodecahydrocyclopenta[7,8]phenanthro[10,1-*bc*]furan-6,9-dione (157)

Pentacycle **154** (70 mg, 0.20 mmol) was dissolved in neat TFA (3 mL) and stirred at room temperature for 15 min. The TFA was removed under reduced pressure and the residue was dissolved in EtOAc (1 mL) and subsequently treated with solid $NaHCO_3$ (100 mg), filtered and concentrated under reduced pressure. Purification by column chromatography (65% EtOAc in hexane) gave dienone **157** (51 mg, 0.16 mmol, 80% yield) as a light yellow solid. Both diastereomers were separated by preparative HPLC (10% *i*-PrOH in hexane).



157a

IR: 3468, 2930, 1738, 1634, 1458, 1201, 1154, 730 cm^{-1}.

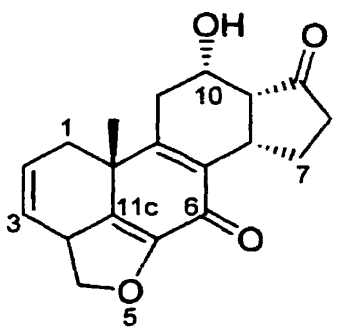
^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.27 (s, 3H, R-$\underline{C}H_3$), 1.66 (br s, R-O$\underline{H}$), 1.94-2.22 (m, 3H, H-1, H-7, H-11), 2.26-2.40 (m, 2H, H-8, H-11), 2.45-2.63 (m, 3H, H-1, H-7, H-9a),

2.68 (br dd, J = 4.0, 17.6 Hz, 1H, H-8), 3.61 (br dd, J = 7.2, 15.8 Hz, 1H, H-6b), 3.94 (m, 1H, H-3a), 4.03 (dd, J = 8.0, 10.7 Hz, 1H, H-4), 4.31 (m, 1H, H-10), 4.86 (dd, J = 8.0, 9.6 Hz, 1H, H-4), 5.70 (dm, J = 9.7 Hz, 1H, H-3), 5.77 (dt, J = 2.0, 9.7 Hz, 1H, H-2).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.1 (R-$\underline{C}H_3$), 28.0 (C-7), 32.4 (C-8), 35.7 (C-6b), 38.7 (C-11b), 38.8 (C-11), 40.0 (C-1), 40.8 (C-3a), 50.0 (C-9a), 66.2 (C-10), 76.2 (C-4), 125.8, 126.6 (C-2, C-3), 133.1 (C-11c), 139.0 (C-5a), 146.9 (C-6a), 156.4 (C-11a), 176.8 (C-6), 223.3 (C-9).

HRMS (EI) *m/z*: Required for $C_{19}H_{20}O_4$: 312.1361; Found: 312.1341.

Anal. Calc. for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found (mixture of both diastereomers): C, 72.89; H, 6.53.



157b

IR: 3462, 2925, 1734, 1634, 1459, 1201, 1156, 731 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.25 (s, 3H, R-C$\underline{H}_3$), 1.63 (br s, R-O$\underline{H}$), 2.00-2.23 (m, 3H, H-1, H-7, H-11), 2.27-2.39 (m, 3H, H-8, H-9a, H-11), 2.54 (dd, J = 4.3, 16.7 Hz, 1H, H-1), 2.63 (dd, J = 4.4, 7.6 Hz, 1H, H-8), 2.77 (dd, J = 5.3, 8.6 Hz, 1H, H-7), 3.77 (m, 1H, H-10), 3.90-4.04 (m, 2H, H-3a, H-6b), 4.09 (dd, J = 8.7, 9.7 Hz, 1H, H-4), 4.85 (dd, J = 9.7, 10.3 Hz, 1H, H-4), 5.73 (m, 2H, H-2, H-3).

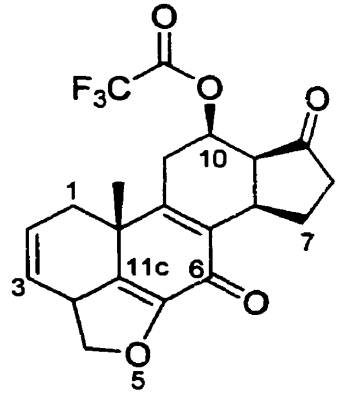
^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.2 (R-$\underline{C}H_3$), 27.4 (C-7), 29.7 (C-11b), 32.0 (C-8), 36.8 (C-6b), 38.1 (C-11), 40.2, 40.9 (C-1, C-3a), 50.5 (C-9a), 67.2 (C-10), 76.3 (C-4), 125.6,

127.2 (C-2, C-3), 133.0 (C-11c), 139.4 (C-5a), 147.2 (C-6a), 157.8 (C-11a), 176.4 (C-6), 224.8 (C-9).

HRMS (EI) *m/z*: Required for $C_{19}H_{20}O_4$: 312.1361; Found: 312.1356.

Synthesis of 10-Trifluoroacetoxy-11b-methyl-1,3a,4,6,6b,7,8,9,9a,10,11,11b-dodecahydrocyclopenta[7,8]phenanthro[10,1-*bc*]furan-6,9-dione (158)

To a solution of dienone **157** (50 mg, 0.16 mmol) in TFAA (1 mL) was added NEt_3 (1 mL) and the resulting solution was stirred at room temperature overnight. The reaction mixture was partitioned between dilute HCl (0.1 M) and CH_2Cl_2, and the aqueous phase was further extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum. Flash chromatography (20% EtOAc in hexane) gave trifluoroacetate **158** (61 mg, 0.15 mmol, 94% yield) as a light yellow oil. Both diastereomers were separated by preparative HPLC (10% *i*-PrOH in hexane).



158a

IR: 2926, 1789, 1712, 1591, 1220, 1156 cm^{-1}.

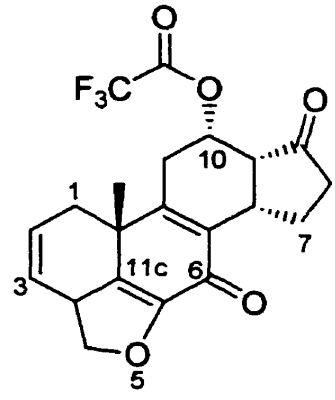
^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.26 (s, 3H, R-C<u>H</u>$_3$), 1.70 (m, 1H, H-7), 1.88 (br d, J = 16.7 Hz, 1H, H-1), 2.33-2.47 (m, 3H, H-1, H-7, H-8), 2.64 (dd, J = 3.3, 9.4 Hz, 1H, H-9a), 2.72-2.87 (m, 2H, H-11), 2.95 (m, 1H, H-8), 3.52 (m, 1H, H-6b), 3.97 (m, 1H, H-3a),

4.09 (t, J = 9.4 Hz, 1H, H-4), 4.89 (dd, J = 8.6, 10.1 Hz, 1H, H-4), 5.67-5.80 (m, 3H, H-2, H-3, H-10).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.7 (R-$\underline{C}H_3$), 28.4 (C-7), 29.0 (C-11b), 29.6 (C-8), 34.0 (C-6b), 38.8, 40.2, 41.0 (C-1, C-3a, C-11), 47.2 (C-9a), 72.5 (C-10), 76.4 (C-4), 125.5, 127.0 (C-2, C-3), 129.9 (q, J = 130 Hz, R-OCO$\underline{C}F_3$), 133.4 (C-11c), 140.0 (C-5a), 147.0 (C-6a), 153.2 (C-11a), 167.7 (R-O$\underline{C}$OCF$_3$), 176.8 (C-6), 217.4 (C-9).

^{19}F NMR (280 MHz, $CDCl_3$) δ: -75.67 (R-OCOC$\underline{F}_3$).

HRMS (EI) *m/z*: Required for $C_{21}H_{19}F_3O_5$: 408.1184; Found: 408.1166.



158b

IR: 2927, 1734, 1690, 1645, 1458, 1200, 1128 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.26 (s, 3H, R-C$\underline{H}_3$), 1.64-1.81 (m, 2H, H-7), 2.03 (br d, J = 16.8 Hz, 1H, H-1), 2.34 (m, 1H, H-8), 2.46 (dd, J = 4.4, 16.8 Hz, 1H, H-1), 2.56 (br d, J = 18.4 Hz, 1H, H-11), 2.69 (dd, J = 3.4, 9.4 Hz, 1H, H-9a), 2.86 (m, 1H, H-8), 2.98 (d, J = 3.8, 18.4 Hz, 1H, H-11), 3.58 (m, 1H, H-6b), 3.98 (m, 1H, H-3a), 4.06 (dd, J = 8.2, 10.6 Hz, 1H, H-4), 4.89 (t, J = 9.1 Hz, 1H, H-4), 5.68 (m, 1H, H-10), 5.72 (dm, J = 9.8 Hz, 1H, H-2), 5.79 (br d, J = 9.8 Hz, 1H, H-3).

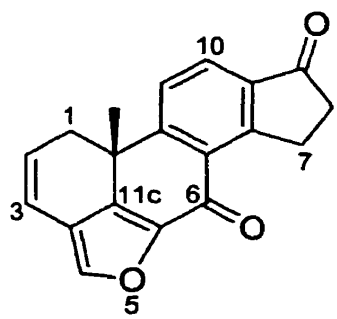
^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.5 (R-$\underline{C}H_3$), 28.5 (C-7), 29.0 (C-11b), 29.8 (C-8), 34.3 (C-6b), 38.7, 38.8, 40.8 (C-1, C-3a, C-11), 47.3 (C-9a), 72.7 (C-10), 76.5 (C-4), 125.5,

126.9 (C-2, C-3), 129.9 (q, J = 130 Hz, R-OCO<u>C</u>F$_3$), 133.9 (C-11c), 139.5 (C-5a), 147.1 (C-6a), 152.5 (C-11a), 167.8 (R-O<u>C</u>OCF$_3$), 176.2 (C-6), 216.9 (C-9).

^{19}F NMR (280 MHz, CDCl$_3$) δ: -75.71 (R-OCOC<u>F</u>$_3$).

Synthesis of 11b-Methyl-1,6,7,8,9,11b-hexahydrocyclopenta[7,8]phenanthro[10,1-*bc*] furan-6,9-dione (159)

A solution of pentacycle **126** (40 mg, 0.14 mmol) and *p*-chloranil (40 mg, 0.16 mmol) in xylenes (15 mL) was refluxed for 36 hours, after which the solvent was removed under reduced pressure and the residue was purified by flash chromatography (20% EtOAc in hexane) to give furan **159** (24 mg, 83 μmol, 60% yield) as a light brown oil.



159

IR: 2925, 1706, 1670, 1638, 1589, 1081 cm^{-1}.

^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.51 (s, 3H, R-C<u>H</u>$_3$), 2.56 (br d, J = 16.6 Hz, 1H, H-1), 2.75 (t, J = 5.8 Hz, 2H, H-7), 2.97 (dd, J = 6.2, 16.6 Hz, H-1), 3.72 (dt, J = 5.8, 19.7 Hz, 1H, H-8), 3.86 (dt, J = 5.8, 19.7 Hz, 1H, H-8), 6.07 (m, 1H, H-2), 6.30 (dd, J = 2.9, 9.7 Hz, 1H, H-3), 7.56 (s, 2H, H-4, overlapping H-11), 7.96 (d, J = 8.0 Hz, 1H, H-10).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 28.4 (C-7), 31.5 (R-<u>C</u>H$_3$), 35.0 (C-1), 36.3 (C-11b), 36.5 (C-8), 117.9 (C-3), 120.8 (C-3a), 125.2 (C-2), 127.1 (C-11), 128.2 (C-10), 131.0, 137.2

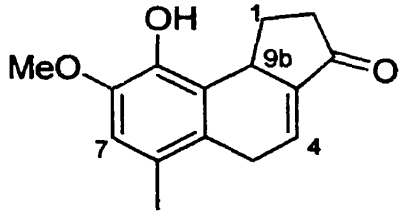
(C-6a, C-11c), 141.5 (C-4), 143.0, 144.3 (C-5a, C-9a), 157.5, 158.5 (C-6b, C-11a), 173.6 (C-6), 206.7 (C-9).

HRMS (EI) *m/z*: Required for $C_{19}H_{14}O_3$: 290.0943; Found: 290.0915.

Synthesis of 9-Hydroxy-8-methoxy-6-methyl-2,3,5,9b-tetrahydro-1*H*-benz[*e*]inden-3-one (162)

Compound **162** was initially isolated as one of the products from the treatment of compound **161** (or **164**) with KH. In order to verify the identity of compound **162** and fully characterize it, **162** was also prepared according to the procedure described below.

To a solution of hydroxyketone **153** (32 mg, 0.12 mmol) in benzene (5 mL) was added *p*-TsOH (150 mg, 0.87 mmol) and the resulting suspension was sealed under vacuum in a Young's tube. After stirring at room temperature for 3 days, the reaction mixture was washed with a saturated solution of Na_2CO_3 and the aqueous phase was extracted with Et_2O. The combined organic phases were dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure to give benzindanone **162** (27 mg, 0.11 mmol, 91% yield) as a dark orange oil, which was not further purified.



162

IR: 3428, 2938, 1721, 1670, 1488, 1300, 1117 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.66 (m, 1H, H-1), 2.22 (s, 3H, Ar-C<u>H</u>$_3$), 2.42 (m, 2H, H-2), 3.26 (m, 2H, H-1 overlapping H-5), 3.31 (ddd, J = 2.3, 8.8, 22.8 Hz, H-5), 3.52 (dt,

J = 5.3, 22.8 Hz, 1H, H-5), 3.82 (m, 1H, H-9b), 3.88 (s, 3H, Ar-OC$\underline{H}_3$), 5.72 (s, 1H, Ar-O$\underline{H}$), 6.66 (s,1H, H-7), 6.84 (m, 1H, H-4).

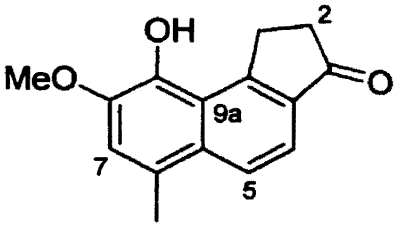
^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.8 (Ar-$\underline{C}H_3$), 28.81, 28.82 (C-1, C-5), 38.0 (C-2), 38.6 (C-9b), 56.1 (Ar-O$\underline{C}H_3$), 111.1 (C-7), 122.9, 124.0, 126.4 (C-5a, C-6, C-9a), 127.4 (C-4), 139.4, 142.3, 144.5 (C-3a, C-8, C-9), 205.9 (C-3).

HRMS (EI) *m/z*: Required for $C_{15}H_{16}O_3$: 244.1099; Found: 244.1096.

Synthesis of 9-Hydroxy-8-methoxy-6-methyl-2,3-dihydro-1*H*-benz[*e*]inden-3-one (163)

Compound **163** was initially isolated as one of the products from the treatment of compound **161** (or **164**) with KH, and also from subjecting **153** to Mitsunobu conditions. In order to verify the identity of compound **163** and fully characterize it, **163** was also prepared according to the procedure described below.

To a solution of hydroxyketone **153** (50 mg, 0.19 mmol) in toluene (10 mL) was added *p*-TsOH (150 mg, 0.87 mmol) and the resulting suspension was heated in a steam bath for 8 hours. The reaction mixture was partitioned between Et_2O and a saturated solution of Na_2CO_3 and the aqueous phase was extracted with Et_2O. The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (30% Et_2O in hexane) to give benzindanone **163** (21 mg, 87 μmol, 46% yield) as a yellow solid.



163

mp: 168-172°C.

IR: 3176, 2925, 1674, 1586, 1464, 1336 cm^{-1}.

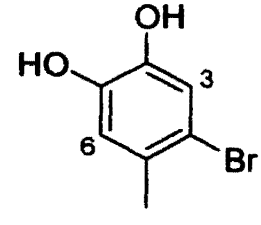
^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.66 (s, 3H, Ar-C$\underline{H}_3$), 2.77 (m, 2H, H-1), 3.81 (m, 2H, H-2), 4.02 (s, 3H, Ar-OC$\underline{H}_3$), 6.12 (s, 1H, Ar-O$\underline{H}$), 7.23 (s, 1H, H-7), 7.61 (d, J = 8.8 Hz, 1H, H-5),), 7.82 (d, J = 8.8 Hz, 1H, H-4).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.9 (Ar-$\underline{C}H_3$), 28.7 (C-1), 36.3 (C-2), 57.0 (Ar-O$\underline{C}H_3$), 116.4, 117.5, 124.3, (C-4, C-5, C-7), 121.4, 126.7, 131.1, 134.5 (C-3a, C-5a, C-6, C-9a), 141.4, 142.2, 156.5 (C-8, C-9, C-9b), 207.6 (C-3).

HRMS (EI) *m/z*: Required for $C_{15}H_{14}O_3$: 242.0943; Found: 242.0934.

Synthesis of 4-Bromo-5-methyl-1,2-benzenediol (167)[149]

To a cooled (0°C) solution of 4-methylcatechol (5.00 g, 40.3 mmol) in CH_2Cl_2 (100 mL) was added bromine (7.00 g, 43.8 mmol) dropwise, and the resulting solution was allowed to warm up to room temperature while stirring overnight. The reaction mixture was washed with Na_2CO_3 and $Na_2S_2O_3$ solutions, dried ($MgSO_4$) and filtered. Removal of the solvent under reduced pressure gave catechol **167** as a gray solid (7.33 g, 36.1 mmol, 90% yield) which was used without further purification.

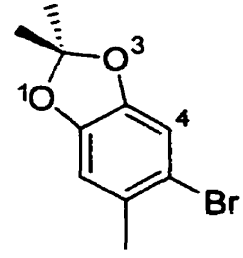


167

^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.26 (s, 3H, Ar-C$\underline{H}_3$), 5.25 (br s, Ar-O$\underline{H}$), 6.76 (s, 1H, H-3), 7.05 (s, 1H, H-6).

Synthesis of 5-bromo-2,2,6-trimethyl-1,3-benzodioxole (168)

A solution of catechol **167** (2.03g, 10.0 mmol) and a catalytic amount of *p*-TsOH in 2,2-dimethoxypropane (30 mL) was refluxed overnight, after which the reaction mixture was concentrated under reduced pressure, dried under high vacuum and purified by kugelrohr distillation to give acetonide **168** (1.47 g, 6.05 mmol, 61% yield) as a light yellow liquid.



168

IR: 2990, 1674, 1491, 1377, 1236, 857 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.66 (s, 6H, R-C<u>H</u>$_3$), 2.29 (s, 3H, Ar-C<u>H</u>$_3$), 6.27 (s, 1H, H-4), 6.90 (s, 1H, H-7).

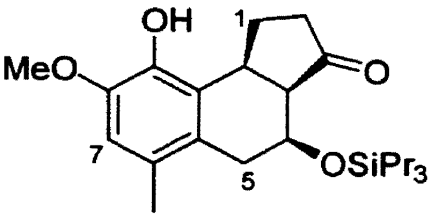
^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.7 (Ar-<u>C</u>H$_3$), 25.7 (R-<u>C</u>H$_3$), 110.3, 112.1 (C-4, C-7), 113.9 (C-2), 118.7 (C-5), 129.8 (C-6), 146.3, 146.9 (C-3a, C-7a).

HRMS (EI) *m/z*: Required for $C_{10}H_{11}BrO_2$: 241.9922; Found: 241.9933.

Synthesis of 9-Hydroxy-8-methoxy-6-methyl-4-(triisopropylsiloxy)-2,3,3a,4,5, 9b-hexahydro-1*H*-benz[*e*]inden-3-one (173)

To a solution of hydroxyketone **153** (1.05 g, 4.01 mmol) and 2,6-lutidine (1.08 g, 10.1 mmol) in CH_2Cl_2 (20 mL) was added TIPSOTf (1.47 g, 4.80 mmol) and the resulting solution was stirred at room temperature for 2 days. The reaction mixture was diluted with CH_2Cl_2, washed with dilute HCl (0.1 M) and the organic phase was dried

($MgSO_4$), filtered and concentrated under reduced pressure. Purification by flash chromatography gave silyl ether **173** (1.22 g, 2.93 mmol, 73% yield) as a colorless thick oil and disilylated product **174** (392 mg, 0.68 mmol, 17% yield) as a colorless solid.



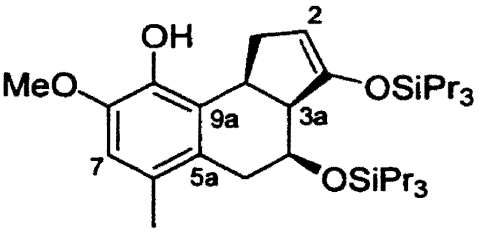
173

IR: 3449, 2946, 1736, 1490, 1308, 1059 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.85-1.03 (m, 21H, R-C<u>H</u>(C<u>H</u>$_3$)$_2$), 2.10 (m, 1H, H-1), 2.17 (s, 3H, Ar-C<u>H</u>$_3$), 2.30-2.41 (m, 3H, H-1, H-2), 2.56 (br dd, J = 3.0, 16.8 Hz, 1H, H-5), 2.88 (m, 2H, H-3a, overlapping H-5), 2.93 (dd, J = 3.1, 16.8 Hz, H-5), 3.56 (m, 1H, H-9b), 3.87 (s, 3H, Ar-OC<u>H</u>$_3$), 4.76, 4.85 (m, 1H, H-4), 5.62 (s, 1H, Ar-O<u>H</u>), 6.61 (s, 1H, H-7).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 12.8 (R-<u>C</u>HMe$_2$), 17.9, 18.1 (R-CH(<u>C</u>H$_3$)$_2$), 19.6 (Ar-<u>C</u>H$_3$), 28.6 (C-1), 34.6 (C-5), 35.5 (C-9b), 39.4 (C-2), 50.9 (C-3a), 56.0 (Ar-O<u>C</u>H$_3$), 67.9 (C-4), 110.6 (C-7), 123.7, 126.9, 128.6 (C-5a, C-6, C-9a), 141.5, 143.9 (C-8, C-9).

HRMS (EI) *m/z*: Required for $C_{24}H_{38}O_4Si$: 418.2539; Found: 418.2541.



174

mp: 71-73°C.

IR: 3553, 2944, 2866, 1649, 1465, 1198 cm^{-1}.

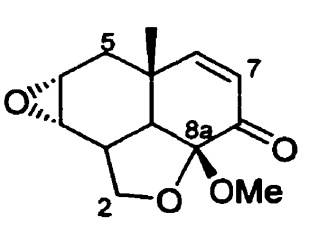
^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.85-1.32 (m, 42H, R-C<u>H</u>(C<u>H</u>$_3$)$_2$), 2.18 (s, 3H, Ar-C<u>H</u>$_3$), 2.28 (m, 1H, H-1), 2.44 (m, 2H, H-1, overlapping H-5), 2.50 (br d, J = 18.5 Hz, 1H, H-5), 2.90-3.03 (m, 2H, H-3a, H-5), 3.53 (m, 1H, H-9b), 3.85 (s, 3H, Ar-OC<u>H</u>$_3$), 4.49, 4.59 (m, 1H, H-4), 4.79 (br s, 1H, H-2), 5.51 (s, 1H, Ar-O<u>H</u>), 6.55 (s, 1H, H-7).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 12.4, 12.9 (R-<u>C</u>HMe$_2$), 17.92, 17.97, 18.04, 18.20 (R-CH(<u>C</u>H$_3$)$_2$), 19.8 (Ar-<u>C</u>H$_3$), 34.8 (C-1), 35.98 (C-5), 36.04 (C-9b), 50.1 (C-3a), 56.0 (Ar-O<u>C</u>H$_3$), 66.4, 66.6 (C-4), 105.2, 105.4 (C-2), 110.1 (C-7), 125.3, 125.9, 126.5 (C-5a, C-6, C-9a), 141.7, 143.7 (C-8, C-9), 153.6 (C-3).

HRMS (EI) *m/z*: Required for $C_{33}H_{58}O_4Si_2$: 574.3873; Found: 574.3874.

Synthesis of 3,4-Epoxy-8a-methoxy-5a-methyl-2a,3,4,5,5a,8,8a,8b-octahydro-2*H*-naphtho[1,8-*bc*]furan-8-one (176)

A solution of naphthofuranone **76**[49] (650 mg, 2.95 mmol) and *m*-CPBA (1.3 g, 57-86%) in $CHCl_3$ was stirred under reflux for 24 hours. The reaction mixture was then washed with saturated solutions of $Na_2S_2O_3$ and Na_2CO_3, and the combined aqueous phases were extracted with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure to give a 6:1 mixture of the β and α epoxides as a yellow oil (680 mg, 2.88 mmol, 98% yield). Separation of the epoxides was done by column chromatography (20% Et_2O in hexane).



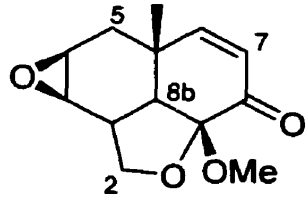
α-176

IR: 2960, 1727, 1689, 1456, 1250, 1100, 1055 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.19 (s, 3H, R-C$\underline{H}_3$), 1.87 (d, J = 15.2 Hz, 1H, H-5), 2.12 (dd, J = 3.7, 15.2 Hz, 1H, H-5), 2.40 (d, J = 10.3 Hz, 1H, H-8b), 2.88 (ddt, J = 2.1, 7.0, 10.3 Hz, 1H, H-2a), 3.08 (dd, J = 2.1, 4.4 Hz, 1H, H-3), 3.25 (t, J = 4.3 Hz, 1H, H-4), 3.37 (s, 3H, R-OC$\underline{H}_3$), 3.81 (dd, J = 6.7, 8.9 Hz, 1H, H-2), 4.22 (dd, J = 7.3, 8.9 Hz, 1H, H-2), 5.92 (d, J = 10.2 Hz, 1H, H-7), 6.54 (d, J = 10.2 Hz, 1H, H-6).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 32.1 (R-$\underline{C}H_3$), 33.3 (C-5a), 35.3, 36.9 (C-2a, C-5), 48.7, 50.4, 50.7, 50.8 (R-O$\underline{C}H_3$, C-3, C-4, C-8b), 69.4 (C-2), 103.1 (C-8a), 123.8 (C-7), 159.4 (C-6), 191.1 (C-8).

Anal Calc. for $C_{13}H_{16}O_4$:C, 66.09; H, 6.83. Found: C, 65.84; H, 6.72.



β-176

IR: 2958, 2835, 1729, 1692, 1448, 1049 cm^{-1}.

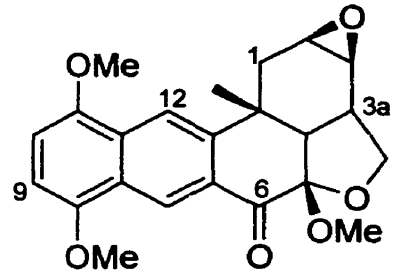
^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.27 (s, 3H, R-C$\underline{H}_3$), 2.50 (m, 2H, H-5), 2.39 (d, J = 9.4 Hz, 1H, H-8b), 2.85 (m, 1H, H-2a), 2.91 (m, 1H, H-3), 3.09 (q, J = 3.5 Hz, 1H, H-4), 3.19 (s, 3H, R-OC$\underline{H}_3$), 3.84 (dd, J = 3.0, 9.2 Hz, 1H, H-2), 4.07 (t, J = 8.7 Hz, 1H, H-2), 5.90 (d, J = 10.2 Hz, 1H, H-7), 6.52 (d, J = 10.2 Hz, 1H, H-6).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 30.4 (R-$\underline{C}H_3$), 34.5 (C-5a), 36.6, 37.2 (C-2a, C-5), 50.8, 51.0, 51.6, 52.6 (R-O$\underline{C}H_3$, C-3, C-4, C-8b), 69.6 (C-2), 102.5 (C-8a), 125.9 (C-7), 158.7 (C-6), 190.7 (C-8).

Anal Calc. for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 65.86; H, 6.67.

Synthesis of 2,3-Epoxy-5a,8,11-trimethoxy-12b-methyl-2,3,3a,4,5a,6,12b,12c-octahydro-1*H*-benzo[6,7]phenanthro[10,1-*bc*]furan-6-one (178)

Sodium metal (380 mg) was added to methanol (30 mL) and the resulting mixture was stirred until gas evolution had ceased and no more solids were visible, at which time it was added to a solution of bridged adduct **179** (390 mg, 0.94 mmol) in methanol (130 mL). After overnight reflux, the solvent was removed under reduced pressure, and the remaining solids partitioned between HCl (1 M) and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried (Na_2SO_4), filtered and concentrated to give, after column chromatography (30% EtOAc in hexane), epoxide **180** as a greenish-yellow solid (351 mg, 0.89 mmol, 94%).



178

mp: 208-210°C.

IR: 2937, 1705, 1469, 1269, 1088, 1049, 734 cm^{-1}.

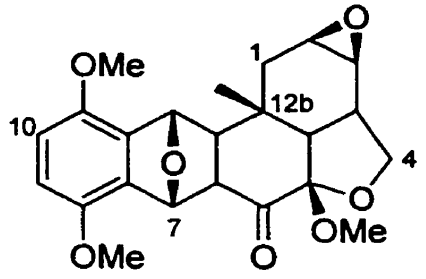
^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.76 (s, R-C$\underline{H}_3$; partially overlapping H-1), 1.80 (dd, J = 2.0, 16.0 Hz, H-1), 1.99 (br d, J = 16.0 Hz, 1H, H-1), 2.63 (d, J = 8.4 Hz, 1H, H-12c), 3.08 (d, J = 4.2 Hz, 1H, H-3), 3.18 (s, R-OC$\underline{H}_3$; overlapping H-3a, H-2), 3.93 (s, 3H, Ar-OC$\underline{H}_3$), 3.96 (s, 3H, Ar-OC$\underline{H}_3$), 4.02 (dd, J = 1.3, 9.1 Hz, 1H, H-4), 4.18 (dd, J = 5.8, 9.1 Hz, 1H, H-4), 6.69, 6.80 (d, J = 8.4 Hz, 1H, H-9, H-10), 8.18 (s, 1H, H-12), 8.68 (s, 1H, H-7).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 27.4 (R-$\underline{C}H_3$), 34.8 (C-12b), 36.8 (C-3a), 38.0 (C-1), 50.0, 52.4, 52.7, 53.3 (R-O$\underline{C}H_3$, C-2, C-3, C-12c), 55.6, 55.7 (Ar- O$\underline{C}H_3$), 70.6 (C-4), 103.8, 106.3 (C-9, C-10), 104.5 (C-5a), 117.9, 123.2 (C-7, C-12), 124.6, 128.3, 131.2, 145.9 (C-6a, C-7a, C-11a, C-12a), 149.1, 150.5 (C-8, C-11), 192.9 (C-6).

Anal. Calc. for $C_{23}H_{24}O_6$: C, 69.68; H, 6.10; Found C, 69.56; H, 6.04.

Synthesis of 2,3,7,12-Diepoxy-5a,8,11-trimethoxy-12b-methyl-2,3,3a,4,5a,6,6a,7,12, 12a,12b,12c-dodecahydro-1*H*-benzo[6,7]phenanthro[10,1-*bc*]furan-6-one (179)

A solution of crude epoxide **176** (425 mg, 1.80 mmol) and isobenzofuran **78** (320 mg, 1.80 mmol) in toluene (15 mL) was refluxed for 12 hours, after which the solvent was removed under reduced pressure and the crude material purified by column chromatography (30% EtOAc in hexane) to give **179** as a white crystalline solid (468 mg, 1.13 mmol, 63% yield).



179

mp: 128-132°C.

IR: 2944, 1739, 1501, 1463, 1261, 1078, 735 cm^{-1}.

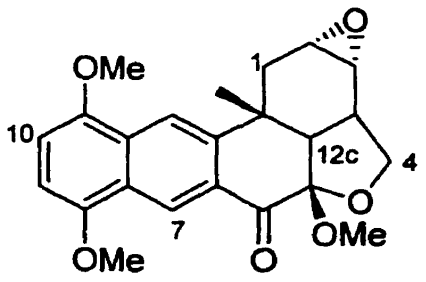
^{1}H NMR (300 MHz, C_6D_6, 340 K) δ: 0.94 (s, 3H, R-C$\underline{H}_3$), 1.19 (dd, J = 2.2, 15.5 Hz, 1H, H-1), 1.97 (dd, J = 5.9, 15.5 Hz, 1H, H-1), 2.20 (d, J = 9.6 Hz, 1H, H-12a), 2.22 (d, J = 9.8 Hz, 1H, H-12c), 2.31 (d, J = 3.9 Hz, 1H, H-3), 2.67 (q, J = 9.1 Hz, 1H, H-3a), 2.89 (d, J = 9.6 Hz, 1H, H-6a), 3.12 (t, J = 8.7 Hz, 1H, H-4), 3.38, 3.40, 3.46 (s, R-OC$\underline{H}_3$, Ar-

$OC\underline{H}_3$; overlapping H-2), 3.76 (t, J = 8.9 Hz, 1H, H-4), 5.43 (s, 1H, H-12), 6.31 (s, 1H, H-7), 6.43 (s, 2H, H-9, H-10).

Anal. Calc. for $C_{23}H_{26}O_7$: C, 66.65; H, 6.32; Found C, 66.56; H, 6.04.

Synthesis of 2,3-α-Epoxy-5a,8,11-trimethoxy-12b-methyl-2,3,3a,4,5a,6,12b,12c-octahydro-1*H*-benzo[6,7]phenanthro[10,1-*bc*]furan-6-one (181)

To a solution of Me_3Al (2 M in hexane, 10 mL, 20.0 mmol) in CH_2Cl_2 (10 mL) was added pyrrolidine (1.46 g, 20.5 mmol) and the resulting solution was stirred for 30 min., after which a solution of epoxide **178** (205 mg, 0.52 mmol) in CH_2Cl_2 (10 mL) was also added. The reaction mixture was stirred at room temperature for 36 h and quenched with saturated NH_4Cl solution. The aqueous layer was extracted with CH_2Cl_2 and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash chromatography (30% EtOAc in hexane) gave starting material **178** (170 mg, 0.43 mmol, 83% yield) and inverted epoxide **181** (19 mg, 0.05 mmol, 9% yield). These results are not typical, and could only be reproduced when reagent from one particular old bottle of trimethylaluminum was used. For more information see Chapter 4.



181

mp: 88°C (dec. without melting).

IR: 2958, 1702, 1628, 1596, 1467, 1333, 1268 cm^{-1}.

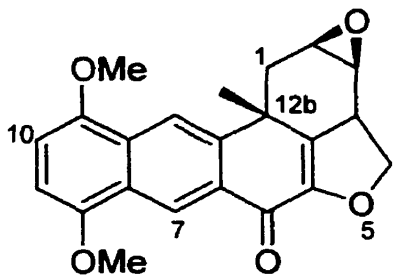
^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.54 (s, 3H, R-C$\underline{H}_3$), 1.94 (m, 2H, H-1), 2.63 (d, J = 9.4 Hz, 1H, H-12c), 3.02 (m, 1H, H-3a), 3.27 (s, 4H, R-OC$\underline{H}_3$, overlapping H-2), 3.94, 3.97 (s, 7H, Ar-OC$\underline{H}_3$, overlapping H-3), 4.13 (dd, J = 3.3, 8.5 Hz, 1H, H-4), 4.22 (dd, J = 6.9, 1H, 8.5 Hz, H-4), 6.69, 6.80 (d, 2H, J = 8.4 Hz, H-9, H-10), 8.17 (s, 1H, H-12), 8.72 (s, 1H, H-7).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 28.9 (R-$\underline{C}H_3$), 34.6 (C-12b), 35.6 (C-12c), 37.7 (C-1), 50.4, 50.7, 52.8, 55.6, 55.7, 55.8 (R-O$\underline{C}H_3$, Ar-O$\underline{C}H_3$, C-2, C-3, C-3a), 70.6 (C-4), 103.7, 106.1 (C-9, C-10), 104.8 (C-5a), 117.4, 123.3 (C-7, C-12), 124.7, 128.3, 131.2 (C-6a, C-7a, C-11a), 144.7, 149.0, 150.6 (C-8, C-11, C-12a), 192.3 (C-6).

Anal. Calc. for $C_{23}H_{24}O_6$: C, 69.68; H, 6.10. Found: C, 69.68; H, 5.94.

Synthesis of 2,3-Epoxy-8,11-dimethoxy-12b-methyl-2,3,3a,4,6,12b-hexahydro-1*H*-benzo[6,7]phenanthro[10,1-*bc*]furan-6-one (183)

To a cooled (0°C) solution of epoxide **178** (100 mg, 0.25 mmol) in CH_2Cl_2 (10 mL) was added TFA (1 mL) and the resulting solution was stirred for 2 h. After quenching with saturated aqueous Na_2CO_3, the phases were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure to a light brown oil. Column chromatography (35% EtOAc in hexane) gave demethoxylated epoxide **183** as a bright yellow solid (88 mg, 0.24 mmol, 96% yield).



183

mp: 154°C (dec. without melting).

IR: 2937, 1668, 1466, 1398, 1268, 1091, 1063, 726 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.69 (s, 3H, R-C$\underline{H}_3$), 1.87 (dd, J = 2.1, 15.3 Hz, 1H, H-1), 2.98 (dd, J = 1.6, 15.3 Hz, 1H, H-1), 2.63 (d, J = 8.4 Hz, 1H, H-12c), 3.21 (d, J = 3.5 Hz, 1H, H-3), 3.33 (m, 1H, H-2), 3.90 (t, J = 11.2 Hz, 1H, H-3a) 3.95 (s, 3H, Ar-OC$\underline{H}_3$), 3.98 (s, 3H, Ar-OC$\underline{H}_3$), 4.32 (dd, J = 9.5, 11.0 Hz, 1H, H-4), 4.98 (dd, J = 9.5, 11.3 Hz, 1H, H-4), 6.68, 6.79 (d, J = 8.4 Hz, 1H, H-9, H-10), 8.32 (s, 1H, H-12), 9.17 (s, 1H, H-7).

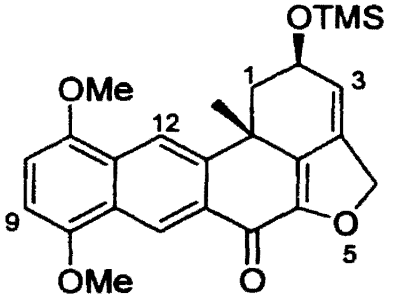
^{13}C NMR (75 MHz, $CDCl_3$) δ: 27.6 (R-$\underline{C}H_3$), 36.5 (C-12b), 39.2 (C-1), 40.6 (C-3a), 54.4 55.6, 55.7, 55.8 (Ar- O$\underline{C}H_3$, C-2, C-3), 72.9 (C-4), 103.2, 105.8 (C-9, C-10), 119.5, 122.9 (C-7, C-12), 124.7, 127.8, 128.8, 137.3 (C-6a, C-7a, C-11a, C-12a), 146.4, 147.5, 148.6 (C-8, C-11, C-12c), 150.6 (C-5a), 176.1 (C-6).

HRMS (EI) *m/z*: Required for $C_{22}H_{20}O_5$: 364.1310; Found: 364.1295

General procedure for the synthesis of 8,11-Dimethoxy-12b-methyl-2-trialkylsiloxy-2,4,6,12b-tetrahydro-1*H*-benzo[6,7]phenanthro[10,1-*bc*]furan-6-ones (184)

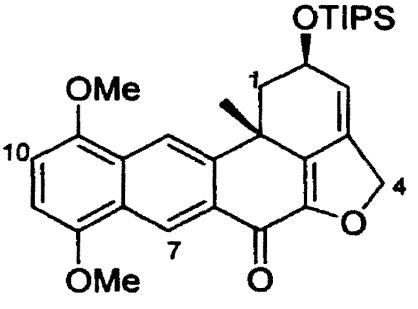
To a solution of epoxide **183** (130 mg, 0.36 mmol) in benzene (8 mL) and CH_2Cl_2 (2 mL) were added DBU (0.3 mL) and TMSOTf (150 μL). The resulting solution was stirred for 24 h at room temperature, after which it was diluted with CH_2Cl_2, washed with dilute HCl (0.1 M), dried ($MgSO_4$), filtered and concentrated under reduced pressure to

give crude silyl ether **184a** as a yellow oil. The same procedure was followed in the synthesis of **184b**, and all attempts to purify these compounds by flash chromatography led only to desilylation and subsequent dehydration to give pentacycle **82**.



184a

^{1}H NMR (250 MHz, $CDCl_3$) δ: 0.23 (s, 9H, R-Si($C\underline{H}_3$)$_3$), 1.68 (s, 3H, R-$C\underline{H}_3$), 1.88 (dd, J = 4.7, 14.0 Hz, 1H, H-1), 2.67 (br d, J = 14.0 Hz, 1H, H-1), 3.96, 3.99 (s, 3H each, Ar-$OC\underline{H}_3$), 4.66 (m, 1H, H-2), 5.15 (m, 2H, H-4), 5.76 (m, 1H, H-3), 6.68, 6.80 (d, J = 8.3 Hz, 1H each, H-9, H-10), 8.22 (s, 1H, H-12), 9.18 (s, 1H, H-7).

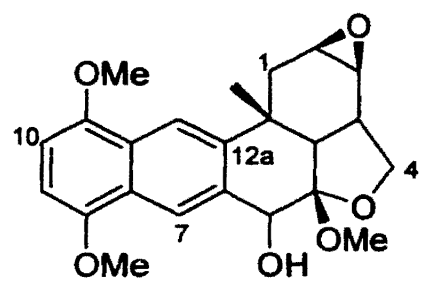


184b

^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.82-1.05 (m, 21H, R-C$\underline{H}$($C\underline{H}_3$)$_2$), 1.69 (s, 3H, R-$C\underline{H}_3$), 1.87 (dd, J = 4.7, 13.7 Hz, 1H, H-1), 2.72 (br d, J = 13.7 Hz, 1H, H-1), 3.95, 3.99 (s, 3H each, Ar-$OC\underline{H}_3$), 4.72 (m, 1H, H-2), 5.15 (m, 2H, H-4), 5.79 (m, 1H, H-3), 6.67, 6.80 (d, J = 8.3 Hz, 1H each, H-9, H-10), 8.21 (s, 1H, H-12), 9.17 (s, 1H, H-7).

Synthesis of 2,3-Epoxy-5a,8,11-trimethoxy-12b-methyl-2,3,3a,4,5a,6,12b,12c-octahydro-1*H*-benzo[6,7]phenanthro[10,1-*bc*]furan-6-ol (185)

To a cooled (0°C) solution of epoxide **178** (100 mg, 0.25 mmol) in THF (10 mL) was added sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al, 65% by weight in toluene, 400 μL, 270 mg, 1.34 mmol) and the resulting mixture was allowed to warm up to room temperature while stirring overnight, after which it was diluted with EtOAc, washed with HCl (0.1 M), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash chromatography (40% hexane in EtOAc) followed by crystallization from EtOAc gave alcohol **185** as colorless needles (57 mg, 0.14 mmol, 57% yield).



185

mp: 184°C (dec. without melting).

IR: 3472, 2940, 1603, 1464, 1266, 1087 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.74 (s, 3H, R-C$\underline{H}_3$), 1.94 (dd, J = 2.2, 16.3 Hz, 1H, H-1), 2.16 (dd, J = 2.8, 16.3 Hz, 1H, H-1), 2.46 (d, J = 9.2 Hz, 1H, H-12c), 3.03 (d, J = 9.2 Hz, 2H, H-3, overlapping H-3a), 3.06 (m, H-3a), 3.25 (s, 3H, R-OC$\underline{H}_3$), 3.33 (m, 1H, H-2), 3.95 (s, 3H, Ar-OC$\underline{H}_3$), 3.97 (s, 3H, Ar-OC$\underline{H}_3$), 4.03 (dd, J = 2.2, 9.3 Hz, 1H, H-4), 4.27 (dd, J = 6.7, 9.3 Hz, 1H, H-4), 5.00 (d, J = 1.0 Hz, 1H, H-6), 6.69 (s, 2H, H-9, H-10), 8.13 (s, 1H, H-12), 8.41 (d, J = 1.0 Hz, 1H, H-7).

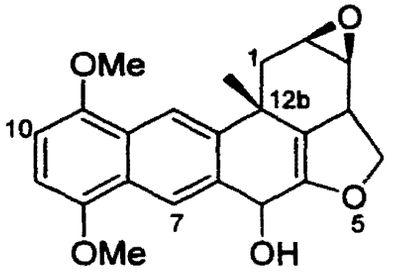
^{13}C NMR (75 MHz, $CDCl_3$) δ: 31.1 (R-$\underline{C}H_3$), 35.8 (C-12b), 36.2 (C-1), 37.8 (C-3a), 49.5, 50.0, 53.0, 54.0 (R-O$\underline{C}H_3$, C-2, C-3, C-12c), 55.8 (Ar-O$\underline{C}H_3$), 72.5 (C-4), 73.4 (C-

6), 103.3, 103.5 (C-9, C-10), 109.9 (C-5a), 117.3, 119.3 (C-7, C-12), 125.1, 125.9, 135.1, 142.3 (C-6a, C-7a, C-11a, C-12a), 149.4, 149.7 (C-8, C-11).

HRMS (EI) *m/z*: Required for $C_{23}H_{26}O_6$: 398.1729; Found: 398.1737.

Synthesis of 2,3-Epoxy-8,11-dimethoxy-12b-methyl-2,3,3a,4,5a,6,12b,12c-octahydro-1*H*-benzo[6,7]phenanthro[10,1-*bc*]furan-6-ol (186)

To a cooled (0°C) solution of epoxide **183** (50 mg, 0.14 mmol) in THF (10 mL) was added lithium triethylborohydride (Super Hydride®, 1 M in THF, 0.5 mL, 0.50 mmol) and the resulting mixture was allowed to warm up to room temperature while stirring overnight, after which it was diluted with EtOAc, washed with NaOH solution (1 M), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash chromatography (20% hexane in EtOAc) gave **186** as a brown solid of acceptable purity (42 mg, 0.11 mmol, 79% yield).



186

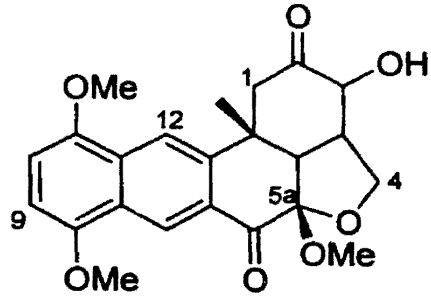
^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.63 (s, 3H, R-C$\underline{H}_3$), 1.73 (dd, J = 2.1, 15.2 Hz, 1H, H-1), 2.26 (br d, J = 6.5 Hz, 1H, R-O$\underline{H}$), $\underline{2}$.80 (dd, J = 1.4, 15.2 Hz, 1H, H-1), 3.08 (d, J = 3.6 Hz, 1H, H-2), 3.25 (br s, 1H, H-3), 3.71 (t, J = 10.7 Hz, 1H, H-3), 3.95 (s, 3H, Ar-OC$\underline{H}_3$), 3.98 (s, 3H, Ar-OC$\underline{H}_3$), 4.22 (dd, J = 9.3, 10.4 Hz, 1H, H-4), 4.88 (dd, J = 9.3, 10.9 Hz, 1H, H-4), 5.37 (br d, J = 6.5 Hz, 1H, H-6), 6.64 (d, J = 8.3 Hz, 1H, H-10), 6.68 (d, J = 8.3 Hz, 1H, H-9), 8.22 (s, 1H, H-12), 8.43 (d, J = 1.0 Hz, 1H, H-7).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 28.3 (R-$\underline{C}H_3$), 35.4 (C-12b), 39.4 (C-3a), 40.1 (C-1), 54.7 (C-3), 55.6 (Ar-O$\underline{C}H_3$), 55.7 (C-2), 63.4 (C-6), 72.9 (C-4), 102.6, 103.2 (C-9, C-10), 114.1 (C-12c), 119.2, 123.4 (C-7, C-12), 125.1, 126.1, 133.3, 142.9 (C-6a, C-7a, C-11a, C-12a), 148.3, 148.9, 149.3 (C-5a, C-8, C-11).

HRMS (EI) *m/z*: Required for $C_{22}H_{22}O_5$: 366.1467; Found: 366.1465.

Synthesis of 3-Hydroxy-5a,8,11-trimethoxy-12b-methyl-2,3,3a,4,5a,6,12b,12c-octahydro-1*H*-benzo[6,7]phenanthro[10,1-*bc*]furan-2,6-dione (187)

To a solution of pentacycle **80** (1.02 g, 2.68 mmol) in acetone (120 mL) were added HOAc (3 mL) and a solution of $KMnO_4$ (1.10 g, 6.96 mmol) in water (40 mL). The resulting mixture was stirred at room temperature for 20 h, filtered through Celite and the organic solvent was removed under reduced pressure. The aqueous layer was made basic by addition of $NaHCO_3$ and was then extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Column chromatography (30% EtOAc in hexane) gave ketol **187** (739 mg, 1.79 mmol, 67% yield) as a bright yellow solid.



187

mp: 107-110°C.

IR: 3468, 2960, 1724, 1712, 1628, 1464, 1091 cm^{-1}.

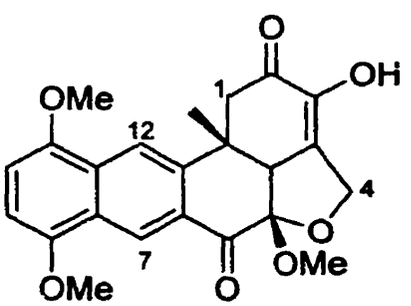
^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.57 (s, 3H, R-C$\underline{H}_3$), 2.41 (dd, J = 0.9, 15.5 Hz, 1H, H-1), 2.81 (d, J = 15.5 Hz, 2H, H-1, overlapping H-3a), 3.92 (d, J= 8.3 Hz, 1H, H-12c), 3.39 (s, 4H, R-OC$\underline{H}_3$, overlapping R-O$\underline{H}$), 3.96 (s, 6H, Ar-OC$\underline{H}_3$), 4.07 (dd, J = 3.1, 10.2 Hz, 2H, H-3, overlapping H-4), 4.12 (dd, J = 4.3, 9.1 Hz, H-4), 4.24 (d, J = 9.1 Hz, H-4), 6.74, 6.83 (d, J = 8.4 Hz, 2H, H-9, H-10), 8.08 (s, 1H, H-12), 8.76 (s, 1H, H-7).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 29.5 (R-$\underline{C}H_3$), 40.4 (C-12b), 48.7, 50.7, 51.2 (C-3a, C-12c, R-O$\underline{C}H_3$), 55.7, 55.8 (Ar-O$\underline{C}H_3$), 56.7 (C-1), 70.6 (C-4), 73.6 (C-3), 101.4 (C-5a), 104.2, 106.6 (C-9, C-10), 116.6, 124.0 (C-7, C-12), 124.9 (C-6a), 128.4, 131.1 (C-7a, C-11a), 142.4, 149.0, 150.5 (C-8, C-11, C12a), 194.1 (C-6), 209.1 (C-2).

Anal. Calc. for $C_{23}H_{24}O_7$: C, 66.98; H, 5.87. Found: C, 66.78; H, 6.07.

Synthesis of 3-Hydroxy-5a,8,11-trimethoxy-12b-methyl-2,4,5a,6,12b,12c-hexahydro-1*H*-benzo[6,7]phenanthro[10,1-*bc*]furan-2,6-dione (189)

To a solution of hydroxyketone **187** (100mg, 0.24 mmol) in EtOH (8 mL) was added a solution of KCN (60 mg, 0.92 mmol) in water (3 mL). The reaction mixture was refluxed for 0.5 h, stirred at room temperature overnight and finally diluted with CH_2Cl_2. The resulting solution was washed with dilute Na_2CO_3, and the organic phase was dried ($MgSO_4$), filtered and concentrated under vacuum to give crude **189** as a brown oily solid (97 mg, 0.24 mmol, 98% yield), which was not further purified.



189

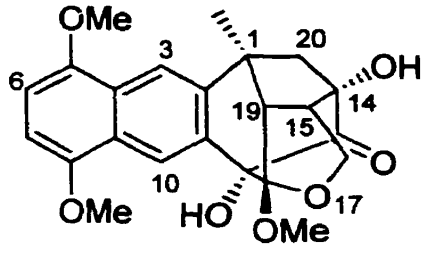
IR: 3402, 2925, 1673, 1626, 1465, 1382, 1264, 1092 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.55 (s, 3H, R-C$\underline{H}_3$), 2.80 (d, J = 16.7 Hz, 1H, H-1), 3.57 (d, J = 16.7 Hz, 1H, H-1), 3.64 (t, J= 2.6 Hz, 1H, H-12c), 3.71 (s, 3H, R-OC$\underline{H}_3$), 3.94 (s, 6H, Ar-OC$\underline{H}_3$), 4.51 (dd, J = 2.8, 15.6 Hz, 1H, H-4), 4.73 (dd, J = 2.5, 15.6 Hz, 1H, H-4), 5.84 (br s, R-O$\underline{H}$), 6.68, 6.79 (d, J = 8.4 Hz, 2H, H-9, H-10), 8.06 (s, 1H, H-12), 8.98 (s, 1H, H-7).

^{13}C NMR (63 MHz, $CDCl_3$) δ: 32.2 (R-$\underline{C}H_3$), 41.4 (C-12b), 47.8 (C-1), 52.4, 53.7 (C-12c, R-O$\underline{C}H_3$), 55.7, 55.8 (Ar-O$\underline{C}H_3$), 66.0 (C-4), 102.5 (C-5a), 103.9, 107.1 (C-9, C-10), 118.9, 126.0 (C-7, C-12), 125.0 (C-3a), 128.2, 128.6, 128.8 (C-6a, C-7a, C-11a), 140.2, 140.3 (C-8, C-11), 148.6, 150.8 (C-3, C-12a), 192.0, 192.6 (C-2, C-6).

Synthesis of 12,14-Dihydroxy-5,8,18-trimethoxy-1-methyl-17-oxahexacyclo [12.5.1.$0^{2,11}$.$0^{4,9}$.$0^{12,18}$.$0^{15,19}$]icosa-2,4,6,8,10-pentaen-13-one (191)

To a deoxygenated solution of hydroxyketone **187** (150 mg, 0.36 mmol) in EtOH (10 mL) was added an also deoxygenated solution of KCN (100 mg, 1.54 mmol) in water (5 mL). The resulting solution was stirred for 0.5 h and then quenched (CAUTION: HCN formed, do it in the fumehood!) with deoxygenated dilute HCl (0.1 M). A stream of N_2 was then bubbled through the solution for 15 min (also in the fumehood), after which the reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude brown solid. Column chromatography (50% EtOAc in hexane) and crystallization from EtOAc (slow evaporation) gave compound **191** as shiny yellow crystals (86 mg, 57% yield).



191

mp: 237-238°C.

IR: 3480, 2958, 1722, 1627, 1602, 1462, 1336, 1263 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$/DMSO-d6) δ**:** 1.51 (d, J = 12.7 Hz, 1H, H-20), 1.71 (s, 3H, R-C$\underline{H}_3$), 2.12 (d, J = 12.7 Hz, 1H, H-20), 2.69 (d, J = 6.3 Hz, 1H, H-19), 2.98 (s, 4H, R-OC$\underline{H}_3$, overlapping H-15), 3.71, 3.74 (s, 7H, Ar-OC$\underline{H}_3$, overlapping H-16), 3.94 (dd, J = 4.5, 9.4 Hz, 1H, H-16), 6.46, 6.51 (d, J = 8.4 Hz, 2H, H-6, H-7), 7.85, 8.29 (s, 2H, H-3, H-10).

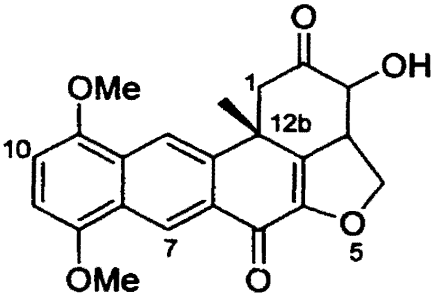
^{13}C NMR (75 MHz, $CDCl_3$/DMSO-d6) δ**:** 26.7 (R-$\underline{C}H_3$), 39.2 (C-20), 47.8 (C-1), 49.2, 50.2, -51.5 (C-15, C-19, R-O$\underline{C}H_3$), 55.0, 55.1 (Ar-O$\underline{C}H_3$), 55.9 (C-1), 65.7 (C-16), 85.0 (C-14), 86.2 (C-12), 102.7, 103.2 (C-6, C-7), 111.2 (C-18), 114.1, 117.6 (C-3, C-10), 124.5, 125.0, 132.5, 141.1 (C-2, C-4, C-9, C-11), 148.5, 149.0 (C-5, C-8), 207.5 (C13).

HRMS (EI) *m/z*: Required for $C_{23}H_{24}O_7$: 412.1522; Found: 412.1522.

Synthesis of 3-Hydroxy-8,11-dimethoxy-12b-methyl-2,3,3a,4,6,12b-hexahydro-1*H*-benzo[6,7]phenanthro[10,1-*bc*]furan -2,6-dione (192)

To a solution of ketol **187** (100 mg, 0.24 mmol) in CH_2Cl_2 (5 mL) was added TFA (5 mL) and the resulting solution was stirred at room temperature for 2 h, after which it was diluted with CH_2Cl_2, washed with saturated $NaHCO_3$ solution, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Flash chromatography (30%

EtOAc in hexane) gave demethoxylated product **192** as a yellow solid (87 mg, 0.23 mmol, 95% yield).



192

mp: 144-147°C.

IR: 3472, 2962, 1722, 1662, 1626, 1464, 1268 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.58 (s, 3H, R-C$\underline{H}_3$), 2.59 (d, J = 13.1 Hz, 1H, H-1), 3.25 (d, J = 13.1 Hz, 1H, H-1), 3.52 (dt, J= 5.7, 9.7 Hz, 1H, H-3a), 3.92 (s, 3H, Ar-OC$\underline{H}_3$), 3.95 (s, 3H, Ar-OC$\underline{H}_3$), 4.22 (d, J = 9.7 Hz, 1H, H-3), 4.73 (dd, J = 5.7, 10.2 Hz, 2H, H-4, overlapping the other H-4), 4.83 (t, J = 9.8 Hz, H-4), 6.65, 6.77 (d, J = 8.4 Hz, 2H, H-9, H-10), 8.23 (s, 1H, H-12), 9.11 (s, 1H, H-7).

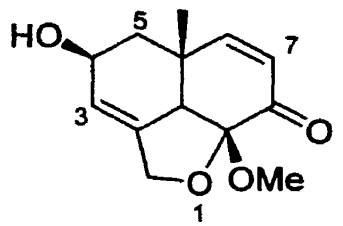
^{13}C NMR (75 MHz, $CDCl_3$) δ: 27.2 (R-$\underline{C}H_3$), 40.1 (C-3a), 47.8 (C-12b), 52.6 (C-1), 55.6, 55.7 (Ar-O$\underline{C}H_3$), 74.6 (C-4), 78.6 (C-3), 103.7, 106.3 (C-9, C-10), 119.3, 123.5 (C-7, C-12), 124.9, 127.8, 128.8, 132.6 (C-6a, C-7a, C-11a, C-12a), 142.9 (C-12c), 148.5, 148.7 (C-8, C-11), 150.6 (C-5a), 176.3 (C-6), 206.6 (C-2).

HRMS (EI) *m/z*: Required for $C_{22}H_{20}O_6$: 380.1260; Found: 380.1249.

Synthesis of 4-Hydroxy-8a-methoxy-5a-methyl-4,5,5a,8,8a,8b-hexahydro-2*H*-naphtho[1,8-*bc*]furan-8-one (193)

A solution of naphthofuranone **76**[49] (1.40 g, 6.36 mmol) and a catalytic amount of Rose Bengal in MeCN (10 mL) was irradiated with a 600 W tungsten lamp for 5 h,

during which a stream of oxygen was constantly bubbled through the liquid. The formed hydroperoxide was quenched by the addition of Me_2S (5 mL) and the solvents were removed under reduced pressure to give a red oil, which was purified to colorless crystals (1.00 g, 4.24 mmol, 67% yield) by column chromatography (30% EtOAc in hexane).



193

IR: 3436, 2932, 1680, 1459, 1240, 1026 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.35 (s, 3H, R-C$\underline{H}_3$), 1.53 (dd, J = 10.5, 13.0 Hz, 1H, H-5), 2.13 (dd, J = 5.6, 13.0 Hz, 1H, H-5), 2.89 (m, 1H, H-8b), 3.42 (s, 3H, R-OC$\underline{H}_3$), 4.14 (m, 2H, H-4, overlapping H-2), 4.18 (dm, J = 12.4 Hz, H-2), 4.55 (dm, J = 12.4 Hz, 1H, H-2), 5.57 (br s, 1H, H-3), 5.87 (d, J = 10.2 Hz, 1H, H-7), 6.54 (dd, J = 1.6, 10.2 Hz, 1H, H-6).

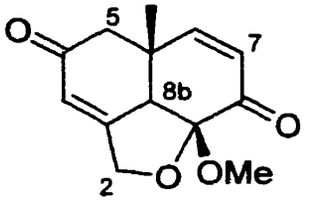
^{13}C NMR (63 MHz, $CDCl_3$) δ: 27.9 (R-$\underline{C}H_3$), 37.6 (C-5a), 45.4 (C-5), 50.4, 51.9 (R-O$\underline{C}H_3$, C-8b), 66.2 (C-4), 67.8 (C-2), 101.2 (C-8a), 123.1, 126.4 (C-3, C-7), 137.3 (C-2a), 154.4 (C-6), 193.1 (C-8).

Anal. Calc. for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 65.91; H, 6.84.

Synthesis of 8a-Methoxy-5a-methyl-4,5,5a,8,8a,8b-hexahydro-2*H*-naphtho[1,8-*bc*]furan-4,8-dione (194)

A solution of naphthofuranone **76**[49] (353 mg, 1.60 mmol) and a catalytic amount of TPP in CCl_4 (5 mL) was irradiated with a 600 W tungsten lamp for 5 h, during which a stream of oxygen was constantly bubbled through the liquid. The formed hydroperoxide

was quenched by the addition of Me_2S (5 mL) and the solvents were removed under reduced pressure. Column chromatography (30% EtOAc in hexane) gave diketone **194** as yellow crystals (274 mg, 1.17 mmol, 73% yield). Such results are not reproducible, and are believed to be due to a contamination of the solvent by a base.



194

mp: 140-142°C.

IR: 2968, 1684, 1668, 1460, 1257, 1028 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.46 (s, 3H, R-C$\underline{H}_3$), 2.55 (s, 2H, H-5), 3.31 (m, 1H, H-8b), 3.52 (s, 3H, R-OC$\underline{H}_3$), 4.38 (dt, J = 2.0, 16.4 Hz, 1H, H-2), 4.81 (dt, J = 1.7, 16.4 Hz, 1H, H-2), 5.96 (m, 2H, H-3, overlapping H-7), 5.97 (d, J = 10.3 Hz, H-7), 6.57 (dd, J = 1.4, 10.3 Hz, 1H, H-6).

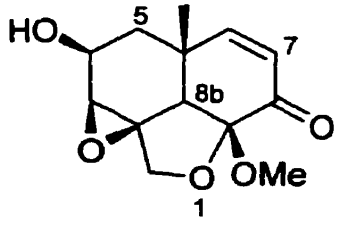
^{13}C NMR (63 MHz, $CDCl_3$) δ: 28.2 (R-$\underline{C}H_3$), 39.5 (C-5a), 49.8 (C-5), 52.4, 52.5 (R-O$\underline{C}H_3$, C-8b), 67.8 (C-2), 101.6 (C-8a), 122.5, 127.2 (C-3, C-7), 154.5 (C-6), 161.3 (C-2a), 191.7, 195.6 (C-4, C-8).

HRMS (EI) *m/z*: Required for $C_{13}H_{14}O_4$: 234.0892; Found: 234.0893.

Synthesis of 2a,3-Epoxy-4-hydroxy-8a-methoxy-5a-methyl-2a,3,4,5,5a,8,8a,8b-octahydro-2*H*-naphtho[1,8-*bc*]furan-8-one (196)

To a solution of allylic alcohol **193** (150 mg, 0.64 mmol) in CH_2Cl_2 (10 mL) was added *m*-CPBA (300 mg, 57-86%), and the resulting solution was stirred for 6 h. The reaction mixture was then washed with saturated solutions of $Na_2S_2O_3$ and Na_2CO_3, and

the combined aqueous phases were extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to give, after column chromatography (30% EtOAc in hexane), epoxide **196** as a colorless solid (126 mg, 0.50 mmol, 78% yield).



196

mp: 134-135°C.

IR: 3454, 2945, 1686, 1459, 1247, 1033, 848 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ**:** 1.27 (s, 3H, R-C$\underline{H}_3$), 1.59 (dd, J = 11.7, 13.2 Hz, 1H, H-5), 1.75 (dd, J = 5.4, 13.2 Hz, 1H, H-5), 1.91 (br s, R-O$\underline{H}$), 2.65 (br s, 1H, H-8b), 3.28 (br s, 1H, H-3), 3.46 (s, 3H, R-OC$\underline{H}_3$), 3.78 (d, J = 10.8 Hz, 1H, H-2), 3.89 (m, 1H, H-4), 4.05 (d, J = 10.8 Hz, 1H, H-2), 6.05 (d, J = 10.3 Hz, 1H, H-7), 6.52 (dd, J = 2.0, 10.3 Hz, 1H, H-6).

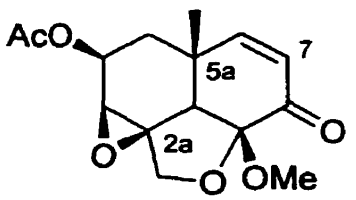
^{13}C NMR (75.5 MHz, $CDCl_3$) δ**:** 28.5 (R-$\underline{C}H_3$), 36.8 (C-5a), 39.0 (C-5), 48.9 (R-O$\underline{C}H_3$), 52.0 (C-3), 59.6 (C-8b), 66.3 (C-4), 66.6 (C-2), 67.1 (C-2a), 101.4 (C-8a), 126.9 (C-7), 156.1 (C-6), 192.5 (C-8).

Anal. Calc. for $C_{13}H_{16}O_5$: C, 61.90; H, 6.39. Found: C, 62.20; H, 6.22.

Synthesis of 2a,3-Epoxy-4-acetoxy-8a-methoxy-5a-methyl-2a,3,4,5,5a,8,8a,8b-octahydro-2*H*-naphtho[1,8-*bc*]furan-8-one (197)

To a solution of allylic acetate **199** (100 mg, 0.36 mmol) in CH_2Cl_2 (10 mL) was added *m*-CPBA (600 mg, 57-86%), and the resulting solution was stirred for 96 h. The

reaction mixture was then washed with saturated solutions of $Na_2S_2O_3$ and Na_2CO_3, and the combined aqueous phases were extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to give, after column chromatography (30% EtOAc in hexane), epoxide **197** as a colorless solid (106 mg, quantitative yield).



197

mp: 70-74°C.

IR: 2940, 1738, 1691, 1456, 1374, 1240, 1034 cm^{-1}.

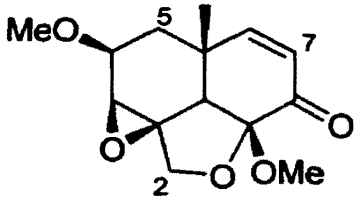
^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.26 (d, J = 10.3 Hz, 4H, H-5, overlapping R-C$\underline{H}_3$), 1.28 (s, R-C$\underline{H}_3$), 1.73 (d, J = 10.3 Hz, 4H, H-5), 1.73 (s, 3H, R-CO C$\underline{H}_3$), 2.68 (br s, 1H, H-8b), 3.30 (br s, 1H, H-3), 3.46 (s, 3H, R-OC$\underline{H}_3$), 3.77 (d, J = 11.2 Hz, 1H, H-2), 4.04 (d, J = 11.2 Hz, 1H, H-2), 4.99 (m, 1H, H-4), 6.08 (d, J = 10.0 Hz, 1H, H-7), 6.57 (dd, J = 1.3, 10.0 Hz, 1H, H-6).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 21.0 (R-CO$\underline{C}H_3$), 28.5 (R-$\underline{C}H_3$), 34.8 (C-5), 36.5 (C-5a), 49.0 (R-O$\underline{C}H_3$), 52.1, 56.7 (C-3, C-8b), 66.0 (C-2a), 66.5 (C-2), 68.6 (C-4), 101.3 (C-8a), 127.3 (C-7), 155.6 (C-6), 170.6 (R-$\underline{C}OCH_3$), 192.5 (C-8).

HRMS (EI) *m/z*: Required for $C_{15}H_{18}O_6$: 294.1103; Found: 294.1095.

Synthesis of 2a,3-Epoxy-4,8a-dimethoxy-5a-methyl-2a,3,4,5,5a,8,8a,8b-octahydro-2*H*-naphtho[1,8-*bc*]furan-8-one (198)

To a solution of methyl ether **200** (40 mg, 0.16 mmol) in CH_2Cl_2 (10 mL) was added *m*-CPBA (100 mg, 57-86%), and the resulting solution was stirred for 72 h. The reaction mixture was then washed with saturated solutions of $Na_2S_2O_3$ and Na_2CO_3, and the combined aqueous phases were extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure to give, after column chromatography (30% EtOAc in hexane), epoxide **198** as a slightly yellow oil (35 mg, 0.13 mmol, 81% yield).



198

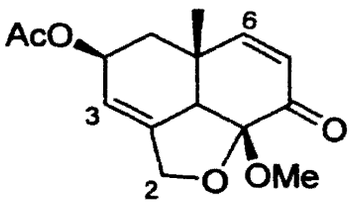
IR: 2632, 1689, 1456, 1246, 1103, 1037, 843 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.27 (s, 3H, R-C<u>H</u>$_3$), 1.66 (m, 2H, H-5), 2.66 (br s, 1H, H-8b), 3.32 (br s, 1H, H-3), 3.42 (s, 3H, R-OC<u>H</u>$_3$), 3.45 (s, 3H, R-OC<u>H</u>$_3$), 3.47 (m, 1H, H-4), 3.77 (d, J = 10.9 Hz, 1H, H-2), 4.04 (d, J = 10.9 Hz, 1H, H-2), 6.03 (d, J = 10.3 Hz, 1H, H-7), 6.50 (dd, J = 1.3, 10.3 Hz, 1H, H-6).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 28.7 (R-<u>C</u>H$_3$), 35.3 (C-5), 36.4 (C-5a), 48.9, 51.9 (R-O<u>C</u>H$_3$), 56.4, 56.7 (C-3, C-8b), 65.7 (C-2a), 66.7 (C-2), 74.5 (C-4), 101.4 (C-8a), 126.8 (C-7), 156.2 (C-6), 192.5 (C-8).

Synthesis of 4-Acetoxy-8a-methoxy-5a-methyl-4,5,5a,8,8a,8b-hexahydro-2*H*-naphtho[1,8-*bc*]furan-8-one (199)

To a solution of allylic alcohol **193** (700 mg, 2.97 mmol) in pyridine (2 mL) were added acetic anhydride (2 mL) and a catalytic amount of DMAP. After stirring overnight, the reaction mixture was partitioned between dilute HCl (1 M) and CH_2Cl_2, the phases were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Column chromatography (30% EtOAc in hexane) gave acetate **199** as a light yellow oil (803 mg, 2.89 mmol, 97% yield).



199

IR: 2944, 1736, 1688, 1460, 1374, 1239, 1025 cm^{-1}.

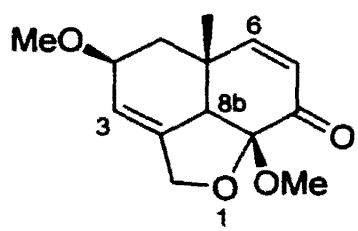
^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.38 (s, 3H, R-C$\underline{H}_3$), 1.63 (dd, J = 10.6, 13.0 Hz, 1H, H-5), 2.07 (s, 3H, R-O_2CC$\underline{H}_3$), 2.23 (ddd, J = 0.8, 5.9, 13.0 Hz, 1H, H-5), 2.96 (m, 1H, H-8b), 3.47 (s, 3H, R-OC$\underline{H}_3$), 4.23 (dm, J = 12.7 Hz, H-2), 4.60 (dm, J = 12.7 Hz, 1H, H-2), 5.20 (m, 1H, H-4), 5.55 (br s, 1H, H-3), 5.93 (d, J = 10.2 Hz, 1H, H-7), 6.61 (dd, J = 1.7, 10.2 Hz, 1H, H-6).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.1 (R-O_2C$\underline{C}H_3$), 28.2 (R-$\underline{C}H_3$), 37.4 (C-5a), 41.1 (C-5), 50.6 (C-8b), 52.0 (R-O$\underline{C}H_3$), 67.8 (C-2), 68.8 (C-4), 101.2 (C-8a), 119.1 (C-3), 126.7 (C-7), 139.4 (C-2a), 153.8 (C-6), 170.5 (R-$O_2\underline{C}CH_3$), 192.7 (C-8).

HRMS (EI) *m/z*: Required for $C_{15}H_{18}O_5$: 278.1154; Found: 278.1126.

Synthesis of 4,8a-Dimethoxy-5a-methyl-4,5,5a,8,8a,8b-hexahydro-2*H*-naphtho[1,8-*bc*]furan-8-one (200)

To a solution of alcohol **193** (150 mg, 0.64 mmol) in a mixture of THF (5 mL), HMPA (1 mL) and MeI (2 mL) was added KH (1.00 g of a 35% w/w suspension in mineral oil, 0.35 g, 8.75 mmol), and the resulting mixture was stirred at room temperature overnight. The reaction was partitioned between Et_2O and water and the aqueous layer was further extracted with Et_2O. The combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Flash chromatography gave methyl ether **200** as an oily colorless solid (98 mg, 0.39 mmol, 61% yield).



200

IR: 2935, 1682, 1461, 1366, 1086, 1030 cm^{-1}.

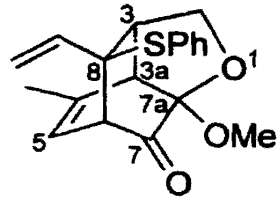
^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.31 (s, 3H, Ar-C$\underline{H}_3$), 1.47, (dd, J = 10.7, 13.2 Hz, 1H, H-5), 2.10 (dd, J = 5.9, 13.2 Hz, 1H, H-5), 2.85 (m, 1H, H-8b), 3.31, 3.39 (s, 6H, Ar-OC$\underline{H}_3$, R-OC$\underline{H}_3$), 3.66 (m, 1H, H-4), 4.14 (dq, J = 1.5, 12.2 Hz, 1H, H-2), 4.51 (dq, J = 2.1, 12.2 Hz, 1H, H-2), 5.60 (br s, 1H, H-3), 5.82 (d, J = 10.3 Hz, 1H, H-7), 6.49 (dd, J = 1.5, 10.3 Hz, 1H, H-6).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 27.9 (R-$\underline{C}H_3$), 37.2 (C-5a), 41.7 (C-5), 50.4, 51.8, 55.8 (R-O$\underline{C}H_3$, C-8b), 67.8 (C-2), 74.6 (C-4), 101.1 (C-8a), 120.1, 126.3 (C-3, C-7), 137.7 (C-2a), 154.2 (C-6), 192.9 (C-8).

Anal. Calc. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.02; H, 7.04.

Synthesis of 8a-Methoxy-5a-methyl-3-phenylthio-2a,5,5a,8,8a,8b-hexahydro-2*H*-naphtho[1,8-*bc*]furan-8-one (203)

To a cooled (0°C) solution of methylguaicol **75** (100 mg, 0.72 mmol), 3-phenylthio-penta-2,4-dien-1-ol (**201b**) (500 mg, 2.60 mmol) and BHT (1 crystal, aprox. 2 mg) in THF (15 mL), was added [bis(trifluoroacetoxy)iodo]benzene (375 mg, 0.87 mmol) and the resulting solution was stirred for 5 minutes, after which solid $NaHCO_3$ (150 mg, 1.79 mmol) was also added. After the reaction mixture was allowed to warm up to room temperature and stir overnight, it was partitioned between water and ether. The aqueous phase was extracted twice more with ether and the combined organic layers were dried ($MgSO_4$) and filtered through a plug of silica gel. After removal of the solvent under reduced pressure, the resulting dark orange oil containing compounds **201b**, **202** and **203** was dissolved in 1,2,4-trimethylbenzene and refluxed for 2 days. Removal of the solvent under vacuum followed by flash chromatography (30% ether in hexane) gave naphthofuranone **203** as a light yellow oil (86 mg, 0.26 mmol, 36% yield).



202

mp: 167-169°C.

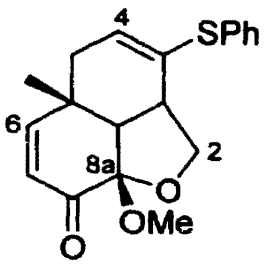
IR: 2949, 1738, 1441, 1217, 1082, 1030 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ**:** 2.03 (d, J = 1.5 Hz, 3H, R-C$\underline{H}_3$), 2.32 (m, 1H, H-3), 3.02 (d, J = 6.8 Hz, 1H, H-6), 3.21 (dd, J = 2.1, 4.4 Hz, 1H, H-3a), 3.52 (s, 3H, R-OC$\underline{H}_3$), 4.01 (dd, J = 3.2, 8.9 Hz, 1H, H-2), 4.06 (d, J = 8.9 Hz, 1H, H-2), 4.88 (d, J = 17.6 Hz, 1H, R-

CH=C$\underline{H}_2$), 5.09 (d, J = 11.0 Hz, 1H, R-CH=C$\underline{H}_2$), 5.97 (dm, J = 6.8 Hz, 1H, H-5), 6.06 (dd, J = 11.0, 17.6, 1H, R-C$\underline{H}$=CH$_2$), 7.26-7.48 (m, 5H, R-S-C$_6\underline{H}_5$).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 21.4 (R-$\underline{C}$H$_3$), 46.0 (C-3), 48.2 (C-3a), 51.5, 51.8 (C-6, R-O$\underline{C}$H$_3$), 58.0 (C-8), 69.4 (C-2), 100.9 (C-7a), 114.9 (R-CH=$\underline{C}$H$_2$), 122.3 (C-5), 128.6, 129.3, 136.6 (C-2',C-3',C-4'), 131.0 (C-1'), 138.4 (R-$\underline{C}$H=CH$_2$), 138.8 (C-4), 199.2 (C-7).

Anal. Calc. for $C_{19}H_{20}O_3S$: C, 69.48; H, 6.14. Found: C, 69.61; H, 6.11.



203

IR: 2940, 1691, 1477, 1439, 1063, 746 cm^{-1}.

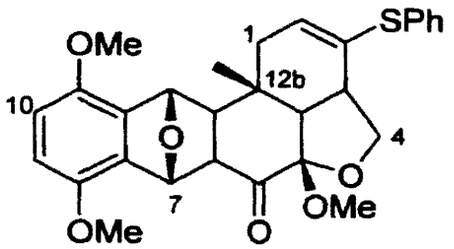
^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.22 (s, 3H, R-C$\underline{H}_3$), 1.95 (br d, J = 16.2 Hz, 1H, H-5), 2.14 (dd, J = 6.7, 16.2 Hz, 1H, H-5), 2.57 (dd, J = 1.7, 9.3 Hz, 1H, H-8b), 3.08 (m, 1H, H-2a), 3.29 (s, 3H, R-OC$\underline{H}_3$), 4.02 (dd, J = 7.5, 8.8 Hz, 1H, H-2), 4.09 (dd, J = 3.4, 8.8 Hz, 1H, H-2), 6.94 (dd, J = 3.1, 6.7 Hz, 1H, H-4), 6.05 (d, J = 10.1 Hz, 1H, H-7), 6.76 (d, J = 10.1 Hz, 1H, H-6), 7.25-7.40 (m, 5H, R-SC$_6\underline{H}_5$).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 27.7 (R-$\underline{C}$H$_3$), 35.0 (C-5a), 38.9, 40.8 (C-2a, C-5), 50.2 (R-O$\underline{C}$H$_3$), 54.4 (C-8b), 73.3 (C-2), 102.8 (C-8a), 127.1, 127.5, 127.6 (C-4, C-7, R-S$\underline{C}_6$H$_5$), 129.2, 131.9 (R-S$\underline{C}_6$H$_5$), 133.0, 135.5 (C-1', C-3), 158.5 (C-6), 190.5 (C-8).

Anal. Calc. for $C_{19}H_{20}O_3S$: C, 69.48; H, 6.14. Found: C, 69.30; H, 6.05.

Synthesis of 7,12-Epoxy-5a,8,11-trimethoxy-12b-methyl-3-phenylthio-3a,4,5a,6,6a,7, 12,12a,12b,12c-decahydro-1*H*-benzo[6,7]phenanthro[10,1-*bc*]furan-6-one (204)

A solution of naphthofuranone **203** (204 mg, 0.62 mmol) and isobenzofuran **78** (250 mg, 1.40 mmol) in toluene (20 mL) was refluxed for 21 hours, after which the solvent was removed under reduced pressure and the residue purified by flash chromatography (50% ether in hexane) to give adduct **204** as a white powder (295 mg, 0.58 mmol, 94% yield).



204

mp: 155-156°C.

IR: 2942, 1736, 1500, 1439, 1260, 1085 cm^{-1}.

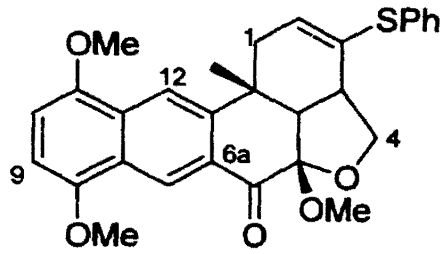
^{1}H NMR (300 MHz, $CDCl_3$) δ: Compound **11** is a fluxional molecule, and the proton NMR at room temperature consists of several very broad signals[4] with a few diagnostic peaks: 1.59 (s, R-C$\underline{H}_3$), 3.32 (s, R-OC$\underline{H}_3$), 3.78 (s, Ar-OC$\underline{H}_3$), 3.80 (s, Ar-OC$\underline{H}_3$), 6.64, 6.68 (both d, J = 9.0 Hz, H-9, H-10), 7.23-7.37 (m, 5H, R-SC$_6\underline{H}_5$).

Anal. Calc. for $C_{29}H_{30}O_6S$: C, 68.75; H, 5.97. Found: C, 68.68; H, 6.13.

Synthesis of 5a,8,11-Trimethoxy-12b-methyl-3-phenylthio-3a,4,5a,6,12b,12c-hexahydro-1*H*-benzo[6,7]phenanthro[10,1-*bc*]furan-6-one (205)

A solution of adduct **204** (403 mg, 0.80 mmol) and NaOMe (4.00 g, 74 mol) in MeOH (100 mL) was refluxed for 3 h, after which the solvent was removed under reduced pressure and the residue partitioned between ether and dilute HCl (3 M). The

organic phase was washed once with water and dried ($MgSO_4$). Removal of the solvent under reduced pressure and flash chromatography of the residue (35% EtOAc in hexane) gave the pentacycle **205** as a bright yellow solid (361 mg, 0.74 mmol, 93% yield).



205

mp: 165-166°C.

IR: 2938, 1704, 1628, 1471, 1267, 1090 cm^{-1}.

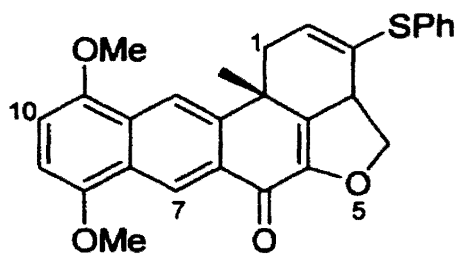
^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.65 (s, 3H, R-C$\underline{H}_3$), 2.02 (br dd, J = 6.4, 17.8 Hz, 1H, H-1), 2.18 (br d, J = 17.8 Hz, 1H, H-1), 2.79 (dd, J = 1.8, 8.4 Hz, 1H, H-12c), 3.07 (m, 1H, H-3a), 3.20 (s, 3H, R-OC$\underline{H}_3$), 3.95 (s, 3H, Ar-OC$\underline{H}_3$), 3.98 (s, 3H, Ar-OC$\underline{H}_3$), 4.05 (dd, J = 6.1, 8.8 Hz, 1H, H-4), 4.39 (d, J = 8.8 Hz, 1H, H-4), 6.06 (dd, J = 1.7, 6.4 Hz, 1H, H-2), 6.71, 6.82 (both d, J = 8.4 Hz, 1H, H-9, H-10), 7.24-7.44 (m, 5H, R-SC$_6\underline{H}_5$), 8.22 (s, 1H, H-12), 8.73 (s, 1H, H-7).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.6 (R-$\underline{C}H_3$), 35.4 (C-12b), 41.4, 41.5 (C-3a, C-1), 49.9 (R-O$\underline{C}H_3$), 55.5, 55.7, 55.8 (C-12c, Ar-O$\underline{C}H_3$), 71.7 (C-4), 103.8, 106.3 (C-9, C-10), 104.7 (C-5a), 117.5, 123.4 (C-7, C-12), 124.8, 128.4 (C-7a, C-11a), 127.3 (C-2), 129.2, 131.1, 131.3, 131.6, 132.7 (C-6a, R-S$\underline{C}_6H_5$), 133.6 (C-3), 145.0 (C-12a), 149.1, 150.7 (C-8, C-11), 192.6 (C-6).

Anal. Calc. for $C_{29}H_{28}O_5S$: C, 71.29; H, 5.78. Found: C, 71.30; H, 5.63.

Synthesis of 8,11-Dimethoxy-12b-methyl-3-phenylthio-3a,4,6,12b-dihydro-1*H*-benzo [6,7]phenanthro[10,1-*bc*]furan-6-one (206)

To a solution of compound **205** (153 mg, 0.31 mmol) in CH_2Cl_2 (10 mL) was added TFA (0.5 mL). The resulting solution was stirred for 15 min., after which the reaction mixture was diluted with CH_2Cl_2 and quenched with aqueous $NaHCO_3$ solution. The organic layer was washed with water, dried ($MgSO_4$) and the solvent removed under reduced pressure to give pentacycle **206** as a bright yellow solid (138 mg, 0.30 mmol, 97% yield) that was used without further purification.



206

mp: 202-204°C.

IR: 2934, 1664, 1627, 1464, 1268, 1091 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.66 (s, 3H, R-C$\underline{H}_3$), 2.36 (br d, J = 17.5 Hz, 1H, H-1), 3.06 (dd, J = 5.4, 17.5 Hz, 1H, H-1), 3.97 (s, 3H, Ar-OC$\underline{H}_3$), 3.99 (s, 3H, Ar-OC$\underline{H}_3$), 4.07 (m, 1H, H-3a), 4.33 (dd, J = 9.1, 10.6 Hz, 1H, H-4), 4.67 (dd, J = 9.1, 10.2 Hz, 1H, H-4), 6.08 (m, 1H, H-2), 6.70, 6.81 (both d, J = 8.4 Hz, 1H, H-9, H-10), 7.29-7.48 (m, 5H, R-S$C_6\underline{H}_5$), 8.35 (s, 1H, H-12), 9.22 (s, 1H, H-7).

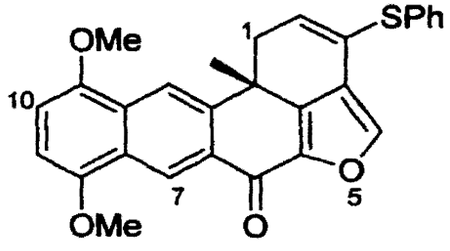
^{13}C NMR (75 MHz, $CDCl_3$) δ: 25.4 (R-$\underline{C}H_3$), 36.6 (C-12b), 43.6 (C-1), 44.2 (C-3a), 55.6, 55.7 (Ar-O$\underline{C}H_3$), 75.3 (C-4), 103.3, 105.8 (C-9, C-10), 119.3, 123.1 (C-7, C-12), 124.8, 127.6, 129.7, 132.2 (C-1', C-3, C-7a, C-11a), 127.9 (C-2), 129.3, 129.6, 131.8 (C-

2', C-3', C-4'), 132.9, 139.2 (C-6a, C-12a), 145.0, 146.9, 148.6, 150.7 (C-5a, C-8, C-11, C-12c), 176.2 (C-6).

Anal. Calc. for $C_{28}H_{24}O_4S$: C, 73.66; H, 5.30. Found: C, 73.85; H, 5.50.

Synthesis of 8,11-Dimethoxy-12b-methyl-3-phenylthio-6,12b-dihydro-1*H*-benzo[6,7]phenanthro[10,1-*bc*]furan-6-one (207)

A solution of pentacycle **206** (108 mg, 0.24 mmol) and *para*-choranil (249 mg, 1.01 mmol) in xylenes was refluxed for 2 days, after which the solvent was removed under vacuum and the residue purified by flash chromatography (50% EtOAc in hexane) to give furan **207** as a bright yellow oil (50 mg, 0.11 mmol, 46% yield).



207

IR: 2932, 1674, 1625, 1464, 1433, 1091, 724 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.59 (s, 3H, R-C$\underline{H}_3$), 2.79 (br d, J = 16.8 Hz, 1H, H-1), 3.27 (dd, J = 6.4, 16.8 Hz, 1H, H-1), 3.97 (s, 3H, Ar-OC$\underline{H}_3$), 3.98 (s, 3H, Ar-OC$\underline{H}_3$), 6.34 (m, 1H, H-2), 6.70, 6.81 (both d, J = 8.4 Hz, 1H, H-9, H-10), 7.20-7.44 (m, 6H, R-SC$_6\underline{H}_5$, overlapping H-4), 8.24 (s, 1H, H-12), 9.27 (s, 1H, H-7).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 32.2 (R-$\underline{C}H_3$), 35.3, 37.5 (C-1, C-12b), 55.68, 55.70 (Ar-O$\underline{C}H_3$), 103.5, 106.2 (C-9, C-10), 118.4, 121.7, 124.2, 124.3, 124.8 (C-3a, C-7, C-7a, C-11a, C-12), 127.2, 127.5, 128.7, 129.2, 130.2, 131.1, 131.8 (C-2, C-6a, C-12a, R-S$\underline{C}_6H_5$),

133.5 (C-3), 142.5 (C-4), 144.1, 144.9, 148.6, 150.8 (C-5a, C-8, C-11, C-12c), 172.6 (C-6).

HRMS (EI) *m/z*: Required for $C_{28}H_{22}O_4S$: 454.1239; Found: 454.1249.

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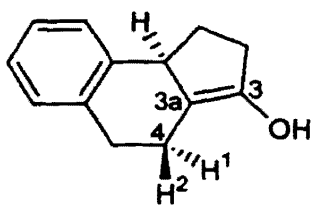
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APPENDIX – X-RAY CRYSTALLOGRAPHIC DATA

Compound 155

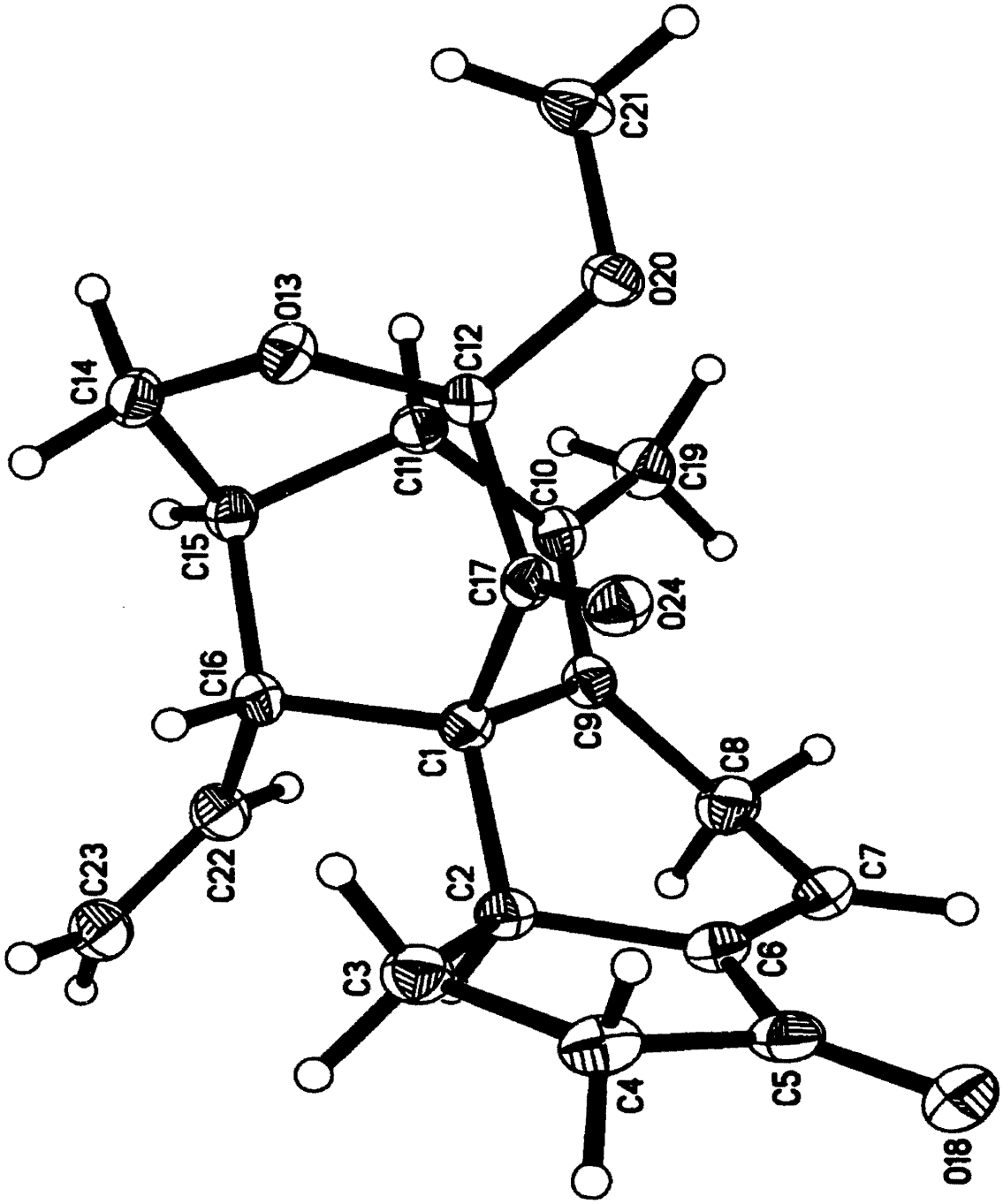


Table 1. Crystal data and structure refinement for rr965m.

Identification code	rr965m	
Empirical formula	C20 H22 O4	
Formula weight	326.38	
Temperature	150(1) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 13.3872(5) Å	α= 90°.
	b = 8.9215(3) Å	β= 104.0140(10)°.
	c = 14.1103(5) Å	γ = 90°.
Volume	1635.09(10) $Å^3$	
Z	4	
Density (calculated)	1.326 Mg/m^3	
Absorption coefficient	0.091 mm^{-1}	
F(000)	696	
Crystal size	0.43 x 0.28 x 0.20 mm^3	
Theta range for data collection	1.57 to 28.28°.	
Index ranges	-17<=h<=17, -11<=k<=11, -18<=l<=18	
Reflections collected	17568	
Independent reflections	4059 [R(int) = 0.0283]	
Completeness to theta = 28.28°	100.0 %	
Absorption correction	Sadabs	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4059 / 0 / 298	
Goodness-of-fit on F^2	2.117	
Final R indices [I>2sigma(I)]	R1 = 0.0493, wR2 = 0.1066	
R indices (all data)	R1 = 0.0584, wR2 = 0.1079	
Extinction coefficient	0.0005(6)	
Largest diff. peak and hole	0.705 and -0.219 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for rr965m. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	2547(1)	1834(2)	3956(1)	27(1)
C(2)	3370(1)	2907(2)	4531(1)	30(1)
C(3)	2973(1)	4314(2)	4981(1)	36(1)
C(4)	3401(1)	5689(2)	4560(1)	39(1)
C(5)	4107(1)	5130(2)	3948(1)	37(1)
C(6)	4023(1)	3475(2)	3884(1)	33(1)
C(7)	4383(1)	2549(2)	3305(1)	37(1)
C(8)	4115(1)	913(2)	3306(1)	38(1)
C(9)	2991(1)	733(2)	3330(1)	29(1)
C(10)	2312(1)	-247(2)	2826(1)	29(1)
C(11)	1225(1)	-41(2)	2935(1)	28(1)
C(12)	872(1)	1565(2)	2660(1)	27(1)
O(13)	52(1)	1875(1)	3126(1)	31(1)
C(14)	67(1)	725(2)	3858(1)	32(1)
C(15)	1116(1)	-20(2)	4001(1)	29(1)
C(16)	2000(1)	916(2)	4632(1)	28(1)
C(17)	1744(1)	2629(2)	3158(1)	26(1)
O(18)	4650(1)	5914(1)	3571(1)	50(1)
C(19)	2513(2)	-1472(2)	2170(1)	40(1)
O(20)	579(1)	1932(1)	1674(1)	32(1)
C(21)	-238(2)	1025(2)	1112(1)	41(1)
C(22)	2768(1)	-50(2)	5321(1)	36(1)
C(23)	3022(2)	94(3)	6271(1)	46(1)
O(24)	1786(1)	3933(1)	2928(1)	32(1)

Table 3. Bond lengths [Å] and angles [°] for rr965m.

C(1)-C(17)	1.529(2)
C(1)-C(9)	1.534(2)
C(1)-C(2)	1.535(2)
C(1)-C(16)	1.567(2)
C(2)-C(6)	1.498(2)
C(2)-C(3)	1.556(2)
C(3)-C(4)	1.533(2)
C(4)-C(5)	1.512(2)
C(5)-O(18)	1.2194(18)
C(5)-C(6)	1.482(2)
C(6)-C(7)	1.331(2)
C(7)-C(8)	1.504(2)
C(8)-C(9)	1.521(2)
C(9)-C(10)	1.336(2)
C(10)-C(19)	1.498(2)
C(10)-C(11)	1.510(2)
C(11)-C(12)	1.529(2)
C(11)-C(15)	1.547(2)
C(12)-O(20)	1.3904(17)
C(12)-O(13)	1.4371(17)
C(12)-C(17)	1.536(2)
O(13)-C(14)	1.4527(18)
C(14)-C(15)	1.522(2)
C(15)-C(16)	1.543(2)
C(16)-C(22)	1.503(2)
C(17)-O(24)	1.2126(17)
O(20)-C(21)	1.4347(19)
C(22)-C(23)	1.307(2)
C(17)-C(1)-C(9)	100.04(11)
C(17)-C(1)-C(2)	112.77(12)
C(9)-C(1)-C(2)	112.04(12)
C(17)-C(1)-C(16)	110.01(11)
C(9)-C(1)-C(16)	108.59(12)
C(2)-C(1)-C(16)	112.64(12)
C(6)-C(2)-C(1)	109.80(12)
C(6)-C(2)-C(3)	106.42(13)
C(1)-C(2)-C(3)	116.53(13)
C(4)-C(3)-C(2)	106.94(14)
C(5)-C(4)-C(3)	107.53(14)
O(18)-C(5)-C(6)	126.13(16)
O(18)-C(5)-C(4)	125.54(16)
C(6)-C(5)-C(4)	108.33(14)
C(7)-C(6)-C(5)	128.44(15)
C(7)-C(6)-C(2)	121.04(15)
C(5)-C(6)-C(2)	110.34(14)
C(6)-C(7)-C(8)	118.69(15)
C(7)-C(8)-C(9)	109.87(13)
C(10)-C(9)-C(8)	127.39(14)
C(10)-C(9)-C(1)	114.59(13)
C(8)-C(9)-C(1)	117.95(13)
C(9)-C(10)-C(19)	127.19(15)
C(9)-C(10)-C(11)	114.53(13)
C(19)-C(10)-C(11)	118.27(14)
C(10)-C(11)-C(12)	109.54(12)
C(10)-C(11)-C(15)	114.88(12)
C(12)-C(11)-C(15)	97.98(12)
O(20)-C(12)-O(13)	110.56(11)
O(20)-C(12)-C(11)	117.96(12)
O(13)-C(12)-C(11)	106.73(11)
O(20)-C(12)-C(17)	108.14(11)
O(13)-C(12)-C(17)	104.62(11)
C(11)-C(12)-C(17)	108.01(12)
C(12)-O(13)-C(14)	107.97(11)
O(13)-C(14)-C(15)	104.86(12)
C(14)-C(15)-C(11)	100.26(12)
C(14)-C(15)-C(16)	113.24(13)
C(11)-C(15)-C(16)	109.11(12)
C(22)-C(16)-C(15)	111.87(13)
C(22)-C(16)-C(1)	110.25(12)

C(15)-C(16)-C(1)	109.75(12)
O(24)-C(17)-C(1)	124.87(13)
O(24)-C(17)-C(12)	123.34(13)
C(1)-C(17)-C(12)	111.78(12)
C(12)-O(20)-C(21)	114.39(12)
C(23)-C(22)-C(16)	125.05(18)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for rr965m. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	24(1)	30(1)	26(1)	-1(1)	6(1)	1(1)
C(2)	26(1)	33(1)	29(1)	-1(1)	4(1)	-1(1)
C(3)	34(1)	36(1)	35(1)	-6(1)	7(1)	-2(1)
C(4)	35(1)	34(1)	45(1)	-4(1)	2(1)	-3(1)
C(5)	29(1)	44(1)	34(1)	0(1)	-3(1)	-8(1)
C(6)	23(1)	41(1)	32(1)	1(1)	2(1)	-3(1)
C(7)	23(1)	51(1)	36(1)	0(1)	7(1)	-4(1)
C(8)	29(1)	44(1)	41(1)	-4(1)	12(1)	4(1)
C(9)	29(1)	30(1)	29(1)	2(1)	9(1)	5(1)
C(10)	33(1)	29(1)	28(1)	1(1)	11(1)	3(1)
C(11)	30(1)	26(1)	27(1)	-2(1)	7(1)	-3(1)
C(12)	26(1)	30(1)	25(1)	0(1)	7(1)	-1(1)
O(13)	27(1)	32(1)	37(1)	3(1)	12(1)	2(1)
C(14)	31(1)	34(1)	33(1)	1(1)	12(1)	-4(1)
C(15)	32(1)	27(1)	30(1)	2(1)	11(1)	-1(1)
C(16)	30(1)	29(1)	26(1)	0(1)	9(1)	2(1)
C(17)	25(1)	28(1)	27(1)	-2(1)	11(1)	0(1)
O(18)	47(1)	51(1)	50(1)	2(1)	9(1)	-20(1)
C(19)	44(1)	35(1)	42(1)	-7(1)	16(1)	2(1)
O(20)	34(1)	35(1)	26(1)	2(1)	3(1)	-5(1)
C(21)	47(1)	37(1)	33(1)	-2(1)	-2(1)	-6(1)
C(22)	37(1)	36(1)	34(1)	5(1)	7(1)	1(1)
C(23)	41(1)	60(1)	36(1)	10(1)	7(1)	-4(1)
O(24)	31(1)	29(1)	36(1)	2(1)	6(1)	-2(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for rr965m.

	x	y	z	U(eq)
H(8X)	4552	428	3872	45
H(8Y)	4233	436	2725	45
H(2)	3800(11)	2299(16)	5064(11)	25(4)
H(3X)	2216(13)	4320(17)	4851(12)	35(4)
H(3Y)	3209(13)	4259(18)	5709(14)	52(5)
H(4X)	3795(13)	6380(20)	5038(13)	47(5)
H(4Y)	2891(15)	6280(20)	4149(13)	54(5)
H(7)	4784(12)	2928(18)	2852(12)	42(5)
H(11)	773(11)	-723(15)	2563(10)	25(4)
H(14X)	-499(11)	18(16)	3592(11)	27(4)
H(14Y)	-4(11)	1242(16)	4479(11)	28(4)
H(15)	1132(11)	-1025(16)	4277(10)	24(4)
H(16)	1707(11)	1605(16)	5017(10)	25(4)
H(19X)	3277(15)	-1620(20)	2182(13)	61(6)
H(19Y)	2089(14)	-1270(20)	1479(14)	54(5)
H(19Z)	2309(14)	-2430(20)	2367(14)	65(6)
H(21X)	-468(12)	1512(18)	434(13)	41(5)
H(21Y)	-41(14)	-10(20)	1063(14)	59(6)
H(21Z)	-813(16)	1050(20)	1430(14)	62(6)
H(22)	3066(14)	-880(20)	5007(14)	58(6)
H(23X)	3509(14)	-610(20)	6686(14)	55(5)
H(23Y)	2715(14)	890(20)	6582(13)	50(6)

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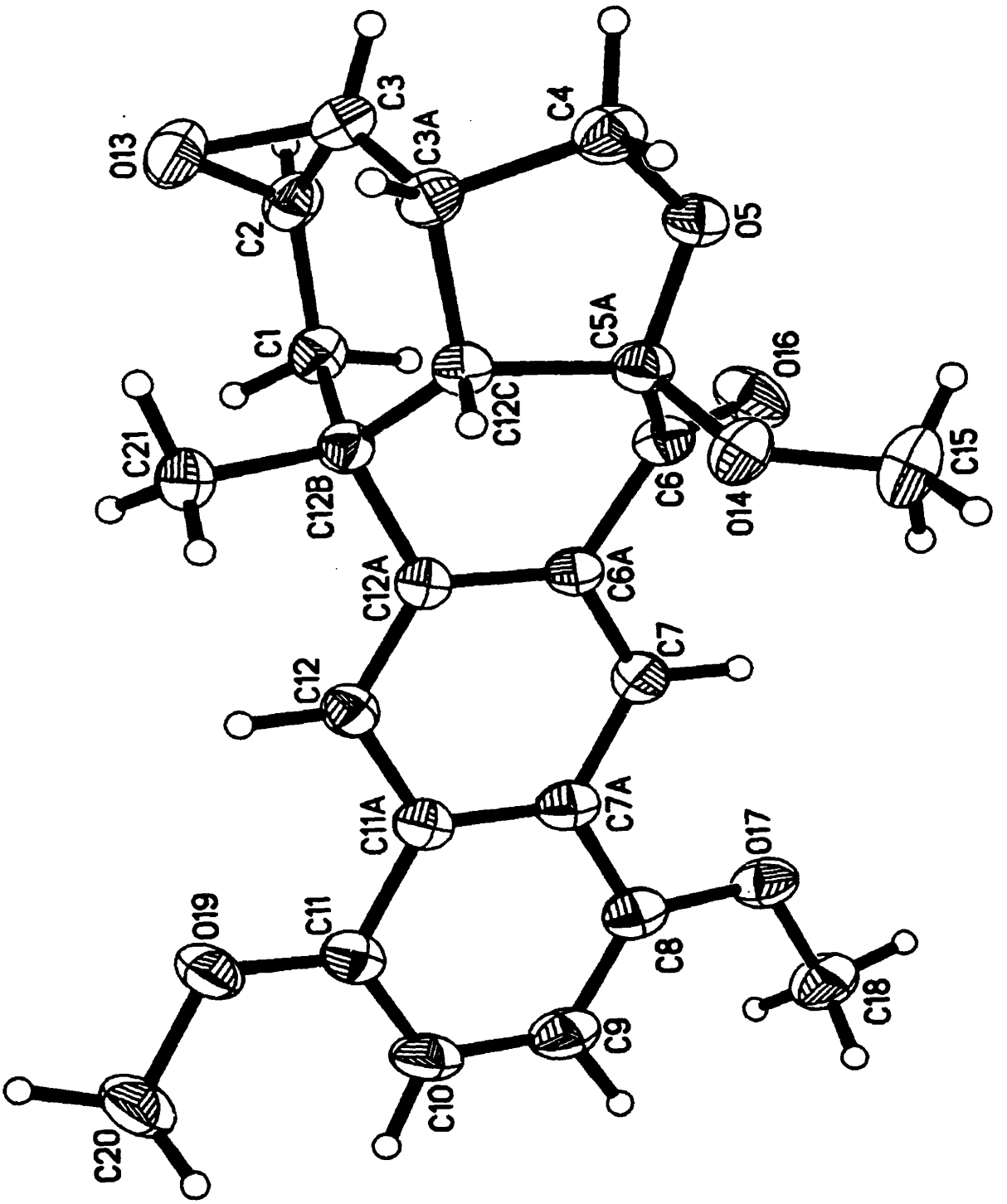


Table 1. Crystal data and structure refinement for rr900.

Identification code	rr900
Empirical formula	$C_{23}H_{24}O_6$
Formula weight	396.42
Temperature	180(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	Pca2(1)
Unit cell dimensions	a = 11.4340(10) Å alpha = 90° b = 16.963(2) Å beta = 90° c = 9.8120(10) Å gamma = 90°
Volume, Z	1903.1(3) $Å^3$, 4
Density (calculated)	1.384 Mg/m^3
Absorption coefficient	0.100 mm^{-1}
F(000)	840
Crystal size	0.84 x 0.40 x 0.26 mm
θ range for data collection	2.15 to 27.99°
Limiting indices	$0 \le h \le 15$, $-22 \le k \le 0$, $0 \le l \le 12$
Reflections collected	2421
Independent reflections	2421
Completeness to θ = 27.99°	100.0 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2421 / 0 / 358
Goodness-of-fit on F^2	2.128
Final R indices [$I>2\sigma(I)$]	R1 = 0.0322, wR2 = 0.0586
R indices (all data)	R1 = 0.0357, wR2 = 0.0589
Absolute structure parameter	0.5(9)
Extinction coefficient	0.0039(5)
Largest diff. peak and hole	0.223 and -0.197 $eÅ^{-3}$

Table 2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for rr900. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
C(1)	5080(2)	2140(1)	1423(3)	28(1)
C(2)	4285(2)	1582(1)	696(3)	30(1)
C(3)	3996(2)	820(1)	1285(3)	31(1)
C(3A)	4461(2)	555(1)	2633(3)	28(1)
C(4)	3460(2)	435(1)	3638(3)	31(1)
O(5)	3255(1)	1212(1)	4188(2)	29(1)
C(5A)	4368(2)	1525(1)	4443(3)	25(1)
C(6)	4290(2)	2433(1)	4441(3)	25(1)
C(6A)	5452(2)	2810(1)	4300(3)	23(1)
C(7)	5707(2)	3467(1)	5059(3)	25(1)
C(7A)	6848(2)	3787(1)	5069(3)	26(1)
C(8)	7150(2)	4455(1)	5893(3)	29(1)
C(9)	8283(2)	4711(1)	5913(3)	35(1)
C(10)	9142(2)	4337(1)	5133(3)	35(1)
C(11)	8883(2)	3711(1)	4308(3)	29(1)
C(11A)	7710(2)	3416(1)	4256(3)	26(1)
C(12)	7409(2)	2762(1)	3429(3)	26(1)
C(12A)	6302(2)	2451(1)	3440(3)	23(1)
C(12B)	5896(2)	1773(1)	2518(3)	24(1)
C(12C)	5230(2)	1166(1)	3399(3)	23(1)
O(13)	4803(1)	872(1)	151(2)	37(1)
O(14)	4804(1)	1303(1)	5747(2)	32(1)
C(15)	4152(3)	1572(2)	6902(3)	43(1)
O(16)	3387(1)	2785(1)	4648(2)	40(1)
O(17)	6242(1)	4781(1)	6609(2)	34(1)
C(18)	6504(2)	5465(1)	7412(3)	40(1)
O(19)	9673(1)	3312(1)	3520	35(1)
C(20)	10854(2)	3580(2)	3589(4)	46(1)
C(21)	6941(2)	1360(1)	1839(3)	31(1)

Table 3. Bond lengths [Å] and angles [°] for rr900.

C(1)-C(2)	1.493(3)	C(1)-C(12B)	1.554(3)
C(2)-O(13)	1.444(3)	C(2)-C(3)	1.455(3)
C(3)-O(13)	1.447(3)	C(3)-C(3A)	1.495(3)
C(3A)-C(4)	1.524(3)	C(3A)-C(12C)	1.553(3)
C(4)-O(5)	1.443(2)	O(5)-C(5A)	1.401(2)
C(5A)-O(14)	1.424(2)	C(5A)-C(6)	1.543(3)
C(5A)-C(12C)	1.547(3)	C(6)-O(16)	1.209(2)
C(6)-C(6A)	1.482(3)	C(6A)-C(7)	1.371(3)
C(6A)-C(12A)	1.423(3)	C(7)-C(7A)	1.413(3)
C(7A)-C(11A)	1.416(3)	C(7A)-C(8)	1.434(3)
C(8)-C(9)	1.366(3)	C(8)-O(17)	1.371(3)
C(9)-C(10)	1.398(3)	C(10)-C(11)	1.368(3)
C(11)-O(19)	1.369(3)	C(11)-C(11A)	1.432(3)
C(11A)-C(12)	1.417(3)	C(12)-C(12A)	1.372(3)
C(12A)-C(12B)	1.535(3)	C(12B)-C(21)	1.536(3)
C(12B)-C(12C)	1.545(3)	O(14)-C(15)	1.431(3)
O(17)-C(18)	1.434(3)	O(19)-C(20)	1.426(3)

C(2)-C(1)-C(12B)	116.21(17)	O(13)-C(2)-C(3)	59.90(14)
O(13)-C(2)-C(1)	117.14(19)	C(3)-C(2)-C(1)	120.82(19)
O(13)-C(3)-C(2)	59.70(14)	O(13)-C(3)-C(3A)	118.20(18)
C(2)-C(3)-C(3A)	122.53(19)	C(3)-C(3A)-C(4)	110.27(18)
C(3)-C(3A)-C(12C)	115.38(17)	C(4)-C(3A)-C(12C)	101.58(17)
O(5)-C(4)-C(3A)	104.01(16)	C(5A)-O(5)-C(4)	105.42(16)
O(5)-C(5A)-O(14)	112.19(16)	O(5)-C(5A)-C(6)	109.01(16)
O(14)-C(5A)-C(6)	106.62(16)	O(5)-C(5A)-C(12C)	108.09(16)
O(14)-C(5A)-C(12C)	105.55(16)	C(6)-C(5A)-C(12C)	115.43(17)
O(16)-C(6)-C(6A)	124.63(17)	O(16)-C(6)-C(5A)	122.82(18)
C(6A)-C(6)-C(5A)	112.26(16)	C(7)-C(6A)-C(12A)	121.64(18)
C(7)-C(6A)-C(6)	119.39(19)	C(12A)-C(6A)-C(6)	118.86(17)
C(6A)-C(7)-C(7A)	120.78(19)	C(7)-C(7A)-C(11A)	117.89(18)
C(7)-C(7A)-C(8)	121.98(19)	C(11A)-C(7A)-C(8)	120.11(18)
C(9)-C(8)-O(17)	125.6(2)	C(9)-C(8)-C(7A)	119.2(2)
O(17)-C(8)-C(7A)	115.19(17)	C(8)-C(9)-C(10)	120.9(2)
C(11)-C(10)-C(9)	121.6(2)	C(10)-C(11)-O(19)	125.1(2)
C(10)-C(11)-C(11A)	119.7(2)	O(19)-C(11)-C(11A)	115.20(19)
C(7A)-C(11A)-C(12)	120.16(18)	C(7A)-C(11A)-C(11)	118.42(19)
C(12)-C(11A)-C(11)	121.4(2)	C(12A)-C(12)-C(11A)	121.3(2)
C(12)-C(12A)-C(6A)	118.09(18)	C(12)-C(12A)-C(12B)	124.14(18)
C(6A)-C(12A)-C(12B)	117.66(16)	C(12A)-C(12B)-C(21)	111.25(17)
C(12A)-C(12B)-C(12C)	108.59(17)	C(21)-C(12B)-C(12C)	108.80(17)
C(12A)-C(12B)-C(1)	106.74(15)	C(21)-C(12B)-C(1)	110.50(19)
C(12C)-C(12B)-C(1)	110.94(16)	C(12B)-C(12C)-C(5A)	114.97(16)
C(12B)-C(12C)-C(3A)	116.97(18)	C(5A)-C(12C)-C(3A)	102.88(17)
C(2)-O(13)-C(3)	60.40(14)	C(5A)-O(14)-C(15)	116.42(18)
C(8)-O(17)-C(18)	116.79(18)	C(11)-O(19)-C(20)	116.15(19)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2$ x 10^3] for rr900.

The anisotropic displacement factor exponent takes the form:

$-2\pi^2 [(ha^*)^2 U_{11} + ... + 2hka^* b^* U_{12}]$

	U11	U22	U33	U23	U13	U12
C(1)	32(1)	26(1)	24(1)	3(1)	0(1)	0(1)
C(2)	34(1)	35(1)	21(1)	-1(1)	-4(1)	3(1)
C(3)	33(1)	31(1)	28(1)	-7(1)	-2(1)	-4(1)
C(3A)	33(1)	19(1)	31(1)	-4(1)	-1(1)	1(1)
C(4)	38(1)	24(1)	31(1)	1(1)	-3(1)	-5(1)
O(5)	29(1)	26(1)	32(1)	-4(1)	3(1)	-7(1)
C(5A)	25(1)	24(1)	26(1)	1(1)	-2(1)	-3(1)
C(6)	25(1)	25(1)	26(1)	-1(1)	-3(1)	0(1)
C(6A)	23(1)	22(1)	24(1)	2(1)	-3(1)	1(1)
C(7)	24(1)	24(1)	26(1)	0(1)	-1(1)	4(1)
C(7A)	29(1)	22(1)	26(1)	5(1)	-6(1)	-2(1)
C(8)	34(1)	25(1)	29(1)	2(1)	-6(1)	-1(1)
C(9)	40(1)	30(1)	35(1)	-4(1)	-7(1)	-9(1)
C(10)	29(1)	37(1)	39(1)	4(1)	-8(1)	-12(1)
C(11)	27(1)	32(1)	29(1)	9(1)	-2(1)	-4(1)
C(11A)	26(1)	25(1)	26(1)	7(1)	-3(1)	-2(1)
C(12)	24(1)	26(1)	27(1)	2(1)	0(1)	0(1)
C(12A)	24(1)	22(1)	24(1)	2(1)	-1(1)	1(1)
C(12B)	24(1)	25(1)	24(1)	-2(1)	0(1)	1(1)
C(12C)	23(1)	22(1)	25(1)	2(1)	-3(1)	1(1)
O(13)	48(1)	36(1)	28(1)	-6(1)	4(1)	0(1)
O(14)	39(1)	34(1)	22(1)	1(1)	-2(1)	3(1)
C(15)	58(2)	48(2)	25(1)	-1(1)	3(1)	5(1)
O(16)	24(1)	32(1)	63(1)	-4(1)	4(1)	4(1)
O(17)	35(1)	28(1)	38(1)	-8(1)	-7(1)	0(1)
C(18)	49(2)	32(1)	40(1)	-11(1)	-4(1)	-5(1)
O(19)	24(1)	39(1)	43(1)	0(1)	2(1)	-7(1)
C(20)	28(1)	52(2)	58(2)	-2(2)	5(1)	-12(1)
C(21)	28(1)	33(1)	33(1)	-6(1)	4(1)	2(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for rr900.

	x	y	z	U(eq)
H(1X)	5576(19)	2420(12)	780(20)	30(6)
H(1Y)	4550(20)	2529(13)	1860(30)	46(7)
H(2)	3703(19)	1806(13)	50(30)	36(6)
H(3)	3280(20)	616(13)	1060(30)	33(6)
H(3A)	4850(20)	104(15)	2510(30)	36(6)
H(4X)	2710(20)	267(11)	3150(20)	39(7)
H(4Y)	3709(18)	109(12)	4360(30)	31(6)
H(7)	5151(18)	3662(11)	5670(20)	23(6)
H(9)	8450(20)	5144(13)	6570(30)	34(6)
H(10)	9920(20)	4526(11)	5240(30)	34(6)
H(12)	8030(17)	2549(11)	2810(20)	23(5)
H(13C)	5766(19)	896(11)	3980(20)	22(5)
H(15X)	3340(30)	1538(18)	6760(40)	94(13)
H(15Y)	4320(30)	2110(20)	7100(40)	86(12)
H(15Z)	4450(30)	1285(18)	7730(40)	72(10)
H(18X)	6890(20)	5866(12)	6840(30)	38(7)
H(18Y)	5760(20)	5628(15)	7800(30)	48(8)
H(18Z)	7030(20)	5336(15)	8140(30)	49(8)
H(20X)	11280(20)	3239(16)	2820(30)	61(9)
H(20Y)	11170(20)	3493(14)	4540(30)	41(7)
H(20Z)	10890(20)	4113(15)	3260(30)	48(8)
H(21X)	7470(20)	1211(10)	2510(30)	26(5)
H(21Y)	7300(20)	1677(12)	1180(30)	38(7)
H(21Z)	6670(20)	889(13)	1320(30)	47(7)

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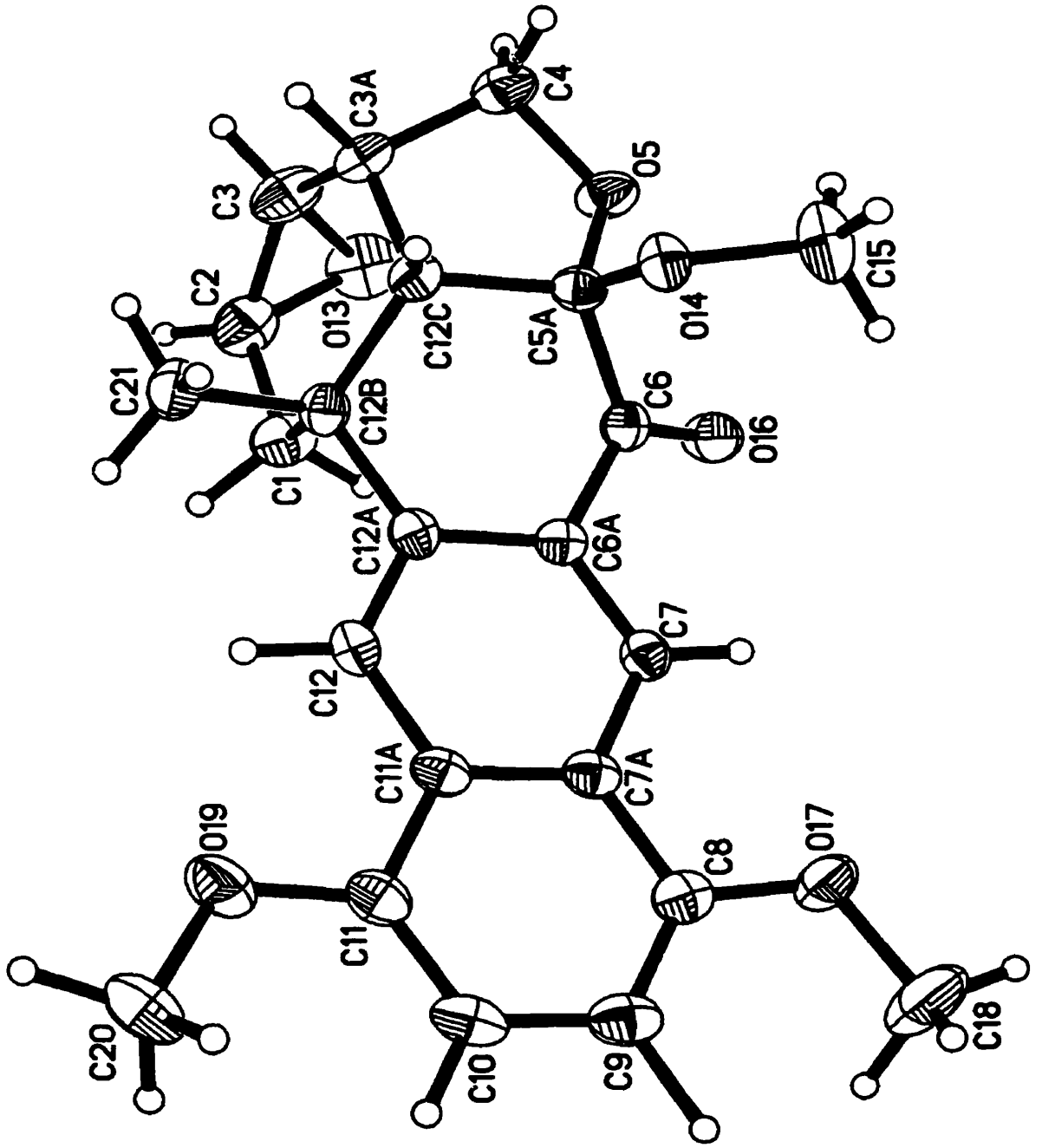


Table 1. Crystal data and structure refinement for rr899.

Identification code	rr899
Empirical formula	$C_{23}H_{24}O_6$
Formula weight	396.42
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 12.3753(11) Å alpha = 90° b = 14.1655(15) Å beta = 117.743(6)° c = 12.4277(13) Å gamma = 90°
Volume, Z	1928.2(3) $Å^3$, 4
Density (calculated)	1.366 Mg/m^3
Absorption coefficient	0.098 mm^{-1}
F(000)	840
Crystal size	0.40 x 0.38 x 0.36 mm
θ range for data collection	2.34 to 25.00°
Limiting indices	$0 \le h \le 14$, $0 \le k \le 16$, $-14 \le l \le 13$
Reflections collected	3563
Independent reflections	3399 (R_{int} = 0.0152)
Completeness to θ = 25.00°	100.0 %
Absorption correction	Face-indexed analytical
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3399 / 0 / 359
Goodness-of-fit on F^2	1.958
Final R indices [I>2σ(I)]	R1 = 0.0389, wR2 = 0.0669
R indices (all data)	R1 = 0.0556, wR2 = 0.0680
Extinction coefficient	0.0020(2)
Largest diff. peak and hole	0.351 and -0.166 $eÅ^{-3}$

Table 2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for rr899. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
C(1)	2097(2)	3969(2)	237(2)	40(1)
C(2)	2795(2)	4858(1)	789(2)	46(1)
C(3)	3389(2)	5012(2)	2106(2)	48(1)
C(3A)	3288(2)	4324(1)	2970(2)	36(1)
C(4)	4538(2)	3990(2)	3930(2)	42(1)
O(5)	4806(1)	3173(1)	3396(1)	38(1)
C(5A)	3714(2)	2676(1)	2778(2)	28(1)
C(6)	3715(2)	2117(1)	1731(2)	29(1)
C(6A)	2481(2)	1806(1)	816(2)	27(1)
C(7)	2346(2)	938(1)	286(2)	29(1)
C(7A)	1191(2)	590(1)	-551(2)	29(1)
C(8)	1024(2)	-331(1)	-1072(2)	33(1)
C(9)	-119(2)	-642(1)	-1866(2)	39(1)
C(10)	-1140(2)	-47(2)	-2170(2)	39(1)
C(11)	-1017(2)	839(1)	-1693(2)	36(1)
C(11A)	165(2)	1177(1)	-856(2)	30(1)
C(12)	332(2)	2080(1)	-307(2)	31(1)
C(12A)	1454(2)	2400(1)	529(2)	28(1)
C(12B)	1685(2)	3400(1)	1047(2)	30(1)
C(12C)	2651(2)	3381(1)	2408(2)	29(1)
O(13)	4098(1)	4712(1)	1520(1)	57(1)
O(14)	3545(1)	2003(1)	3542(1)	34(1)
C(15)	4556(2)	1379(2)	4166(2)	54(1)
O(16)	4648(1)	1882(1)	1707(1)	40(1)
O(17)	2086(1)	-838(1)	-692(1)	42(1)
C(18)	2000(3)	-1768(2)	-1157(3)	72(1)
O(19)	-1944(1)	1462(1)	-1923(1)	48(1)
C(20)	-3166(2)	1131(2)	-2616(2)	55(1)
C(21)	535(2)	3862(2)	983(2)	41(1)

Table 3. Bond lengths [Å] and angles [°] for rr899.

C(1)-C(2)	1.501(3)	C(1)-C(12B)	1.550(2)
C(2)-O(13)	1.450(3)	C(2)-C(3)	1.465(3)
C(3)-O(13)	1.440(2)	C(3)-C(3A)	1.497(3)
C(3A)-C(4)	1.524(3)	C(3A)-C(12C)	1.543(2)
C(4)-O(5)	1.447(2)	O(5)-C(5A)	1.3950(19)
C(5A)-O(14)	1.4279(19)	C(5A)-C(6)	1.525(2)
C(5A)-C(12C)	1.540(2)	C(6)-O(16)	1.2152(19)
C(6)-C(6A)	1.483(2)	C(6A)-C(7)	1.368(2)
C(6A)-C(12A)	1.424(2)	C(7)-C(7A)	1.409(2)
C(7A)-C(11A)	1.415(2)	C(7A)-C(8)	1.428(2)
C(8)-C(9)	1.367(2)	C(8)-O(17)	1.374(2)
C(9)-C(10)	1.416(3)	C(10)-C(11)	1.366(3)
C(11)-O(19)	1.367(2)	C(11)-C(11A)	1.426(2)
C(11A)-C(12)	1.418(2)	C(12)-C(12A)	1.367(2)
C(12A)-C(12B)	1.527(2)	C(12B)-C(21)	1.534(3)
C(12B)-C(12C)	1.552(2)	O(14)-C(15)	1.430(2)
O(17)-C(18)	1.422(3)	O(19)-C(20)	1.427(2)

C(2)-C(1)-C(12B)	115.62(16)	O(13)-C(2)-C(3)	59.20(13)
O(13)-C(2)-C(1)	113.74(18)	C(3)-C(2)-C(1)	121.22(18)
O(13)-C(3)-C(2)	59.88(13)	O(13)-C(3)-C(3A)	116.42(17)
C(2)-C(3)-C(3A)	122.57(18)	C(3)-C(3A)-C(4)	111.71(17)
C(3)-C(3A)-C(12C)	115.75(16)	C(4)-C(3A)-C(12C)	101.77(15)
O(5)-C(4)-C(3A)	104.80(15)	C(5A)-O(5)-C(4)	106.57(13)
O(5)-C(5A)-O(14)	112.02(13)	O(5)-C(5A)-C(6)	110.24(13)
O(14)-C(5A)-C(6)	106.18(13)	O(5)-C(5A)-C(12C)	108.17(14)
O(14)-C(5A)-C(12C)	105.24(13)	C(6)-C(5A)-C(12C)	114.95(14)
O(16)-C(6)-C(6A)	123.40(16)	O(16)-C(6)-C(5A)	122.83(15)
C(6A)-C(6)-C(5A)	113.49(14)	C(7)-C(6A)-C(12A)	121.01(16)
C(7)-C(6A)-C(6)	119.16(16)	C(12A)-C(6A)-C(6)	119.80(15)
C(6A)-C(7)-C(7A)	121.68(17)	C(7)-C(7A)-C(11A)	117.87(16)
C(7)-C(7A)-C(8)	122.56(17)	C(11A)-C(7A)-C(8)	119.55(16)
C(9)-C(8)-O(17)	125.65(17)	C(9)-C(8)-C(7A)	120.29(18)
O(17)-C(8)-C(7A)	114.05(15)	C(8)-C(9)-C(10)	119.76(18)
C(11)-C(10)-C(9)	121.68(18)	C(10)-C(11)-O(19)	126.03(17)
C(10)-C(11)-C(11A)	119.64(18)	O(19)-C(11)-C(11A)	114.31(17)
C(7A)-C(11A)-C(12)	119.32(15)	C(7A)-C(11A)-C(11)	119.06(16)
C(12)-C(11A)-C(11)	121.61(17)	C(12A)-C(12)-C(11A)	122.25(17)
C(12)-C(12A)-C(6A)	117.83(16)	C(12)-C(12A)-C(12B)	123.53(16)
C(6A)-C(12A)-C(12B)	118.17(15)	C(12A)-C(12B)-C(21)	112.74(15)
C(12A)-C(12B)-C(1)	105.18(14)	C(21)-C(12B)-C(1)	108.80(16)
C(12A)-C(12B)-C(12C)	109.94(13)	C(21)-C(12B)-C(12C)	106.85(15)
C(1)-C(12B)-C(12C)	113.45(15)	C(5A)-C(12C)-C(3A)	103.93(14)
C(5A)-C(12C)-C(12B)	117.04(14)	C(3A)-C(12C)-C(12B)	116.74(15)
C(3)-O(13)-C(2)	60.91(13)	C(5A)-O(14)-C(15)	114.29(15)
C(8)-O(17)-C(18)	117.74(18)	C(11)-O(19)-C(20)	117.72(17)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2$ x 10^3] for rr899.

The anisotropic displacement factor exponent takes the form:

$-2\pi^2 [(ha^*)^2 U_{11} + ... + 2hka^* b^* U_{12}]$

	U11	U22	U33	U23	U13	U12
C(1)	53(1)	36(1)	37(1)	1(1)	25(1)	-5(1)
C(2)	61(2)	34(1)	53(1)	5(1)	33(1)	-3(1)
C(3)	63(2)	32(1)	60(1)	-8(1)	38(1)	-10(1)
C(3A)	42(1)	32(1)	41(1)	-9(1)	25(1)	-3(1)
C(4)	41(1)	39(1)	46(1)	-15(1)	21(1)	-9(1)
O(5)	29(1)	39(1)	43(1)	-14(1)	15(1)	-7(1)
C(5A)	25(1)	31(1)	28(1)	-3(1)	11(1)	-4(1)
C(6)	27(1)	29(1)	31(1)	2(1)	14(1)	2(1)
C(6A)	28(1)	27(1)	26(1)	0(1)	13(1)	-2(1)
C(7)	28(1)	33(1)	28(1)	3(1)	14(1)	3(1)
C(7A)	33(1)	32(1)	23(1)	1(1)	13(1)	-5(1)
C(8)	42(1)	32(1)	29(1)	2(1)	20(1)	-4(1)
C(9)	49(1)	40(1)	29(1)	-3(1)	20(1)	-13(1)
C(10)	37(1)	51(1)	26(1)	-4(1)	13(1)	-17(1)
C(11)	32(1)	45(1)	28(1)	2(1)	13(1)	-4(1)
C(11A)	31(1)	34(1)	23(1)	2(1)	12(1)	-5(1)
C(12)	27(1)	34(1)	30(1)	7(1)	12(1)	4(1)
C(12A)	29(1)	29(1)	27(1)	4(1)	14(1)	1(1)
C(12B)	31(1)	27(1)	34(1)	3(1)	16(1)	1(1)
C(12C)	31(1)	29(1)	31(1)	-1(1)	18(1)	-2(1)
O(13)	58(1)	62(1)	66(1)	-2(1)	40(1)	-16(1)
O(14)	32(1)	36(1)	34(1)	7(1)	16(1)	6(1)
C(15)	46(2)	59(2)	59(2)	27(1)	27(1)	20(1)
O(16)	28(1)	50(1)	40(1)	-10(1)	15(1)	2(1)
O(17)	49(1)	28(1)	49(1)	-5(1)	23(1)	-1(1)
C(18)	67(2)	37(2)	112(3)	-26(2)	42(2)	-7(1)
O(19)	26(1)	59(1)	47(1)	-3(1)	7(1)	-3(1)
C(20)	29(1)	75(2)	48(1)	1(1)	6(1)	-7(1)
C(21)	38(1)	34(1)	47(1)	0(1)	16(1)	7(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for rr899.

	x	y	z	U(eq)
H(1X)	2611(17)	3560(14)	-13(16)	49(6)
H(1Y)	1319(17)	4116(12)	-540(17)	45(5)
H(2)	2593(17)	5445(15)	265(17)	56(6)
H(3)	3521(18)	5711(15)	2360(18)	65(7)
H(3A)	2854(14)	4653(12)	3361(14)	31(5)
H(4X)	5250(18)	4446(14)	4100(17)	57(6)
H(4Y)	4560(16)	3790(13)	4747(17)	53(6)
H(7)	3039(15)	580(11)	530(14)	23(4)
H(9)	-219(16)	-1403(13)	-2343(16)	50(5)
H(10)	-1969(16)	-292(12)	-2717(15)	39(5)
H(12)	-400(15)	2480(12)	-568(14)	36(5)
H(12C)	2228(13)	3157(10)	2859(13)	17(4)
H(15X)	4400(20)	1020(16)	4730(20)	80(8)
H(15Y)	4730(20)	928(19)	3600(20)	110(10)
H(15Z)	5340(30)	1790(20)	4450(30)	128(11)
H(18X)	1530(20)	-1718(17)	-2140(20)	90(9)
H(18Y)	1430(20)	-2180(17)	-970(20)	90(9)
H(18Z)	2840(20)	-1995(16)	-800(20)	80(8)
H(20X)	-3720(20)	1717(17)	-2630(20)	92(9)
H(20Y)	-3299(18)	948(15)	-3440(20)	65(7)
H(20Z)	-3300(20)	513(18)	-2230(20)	91(9)
H(21X)	223(17)	3461(14)	1444(17)	53(6)
H(21Y)	747(17)	4471(15)	1364(17)	53(6)
H(21Z)	-118(18)	3926(14)	131(18)	55(6)

Compound 197

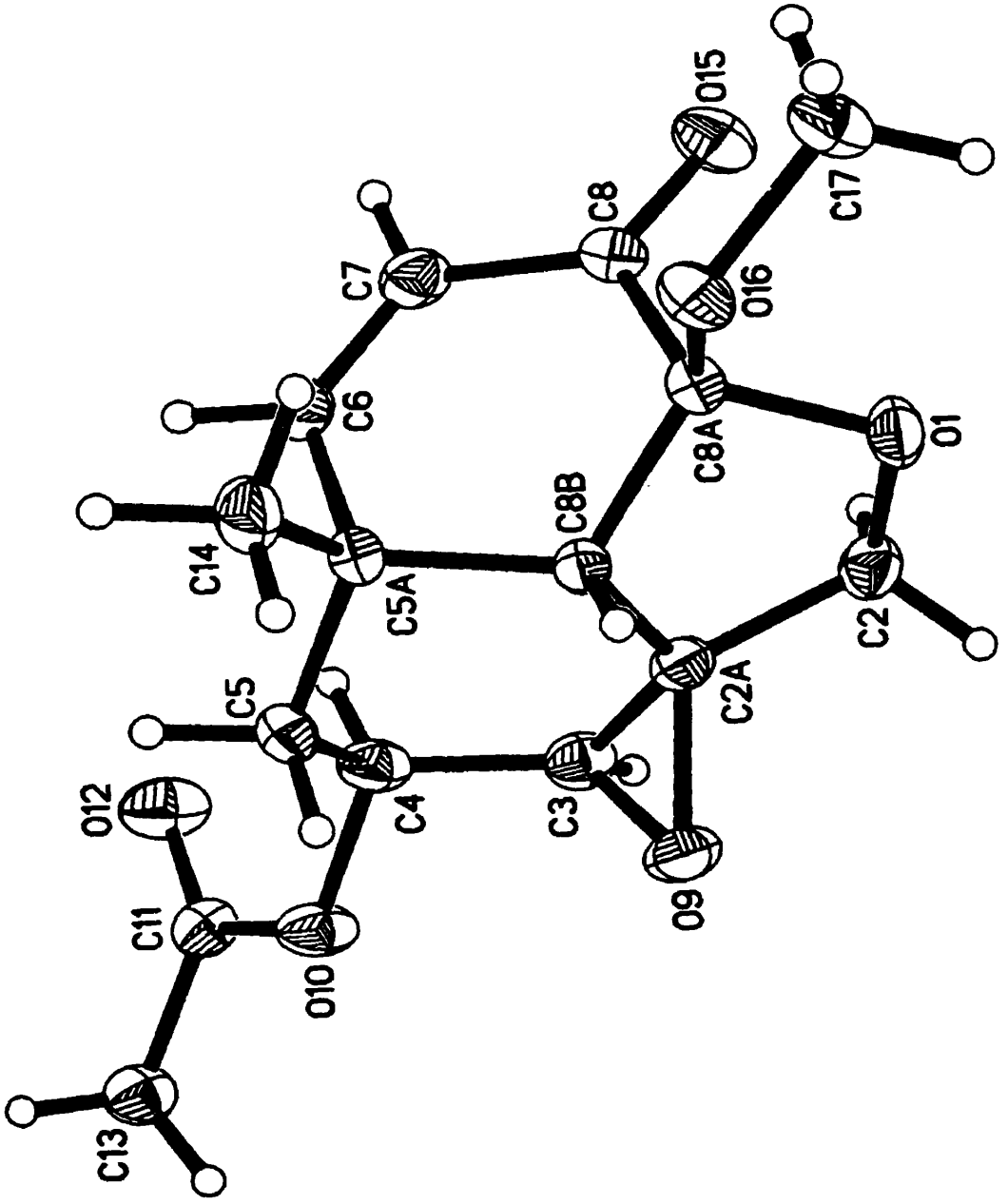


Table 1. Crystal data and structure refinement for rr909.

Identification code	rr909
Empirical formula	$C_{15}H_{18}O_6$
Formula weight	294.29
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	$P\bar{1}$
Unit cell dimensions	a = 7.5059(7) Å alpha = 86.967(7)° b = 7.8212(9) Å beta = 81.114(4)° c = 11.9450(12) Å gamma = 85.860(6)°
Volume, Z	690.39(12) $Å^3$, 2
Density (calculated)	1.416 Mg/m^3
Absorption coefficient	0.110 mm^{-1}
F(000)	312
Crystal size	0.82 x 0.48 x 0.48 mm
θ range for data collection	2.61 to 30.00°
Limiting indices	$0 \le h \le 10$, $-10 \le k \le 10$, $-16 \le l \le 16$
Reflections collected	4280
Independent reflections	3999 (R_{int} = 0.0101)
Completeness to θ = 30.00°	99.3 %
Absorption correction	Integration
Max. and min. transmission	0.9602 and 0.9367
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3999 / 0 / 263
Goodness-of-fit on F^2	2.646
Final R indices [$I>2\sigma(I)$]	R1 = 0.0365, wR2 = 0.0965
R indices (all data)	R1 = 0.0408, wR2 = 0.0971
Extinction coefficient	0.021(4)
Largest diff. peak and hole	0.404 and -0.179 $eÅ^{-3}$

Table 2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for rr909. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
O(1)	1107(1)	1878(1)	3391(1)	30(1)
C(2)	937(1)	2384(1)	2240(1)	30(1)
C(2A)	1125(1)	4305(1)	2148(1)	24(1)
C(3)	1593(1)	5294(1)	1084(1)	31(1)
C(4)	2677(1)	6821(1)	1096(1)	32(1)
C(5)	2502(1)	7568(1)	2256(1)	31(1)
C(5A)	2975(1)	6212(1)	3166(1)	25(1)
C(6)	4891(1)	5507(1)	2853(1)	30(1)
C(7)	5463(1)	3860(1)	2943(1)	31(1)
C(8)	4246(1)	2503(1)	3336(1)	26(1)
C(8A)	2245(1)	3049(1)	3756(1)	23(1)
C(8B)	1638(1)	4797(1)	3262(1)	21(1)
O(9)	-238(1)	5410(1)	1694(1)	33(1)
O(10)	2061(1)	8154(1)	322(1)	39(1)
C(11)	3314(1)	8833(1)	-467(1)	28(1)
O(12)	4862(1)	8286(1)	-628(1)	45(1)
C(13)	2527(2)	10343(2)	-1087(1)	34(1)
C(14)	2849(2)	7069(1)	4309(1)	35(1)
O(15)	4779(1)	996(1)	3369(1)	37(1)
O(16)	1952(1)	3090(1)	4937(1)	28(1)
C(17)	2205(2)	1490(1)	5557(1)	34(1)

Table 3. Bond lengths [Å] and angles [°] for rr909.

O(1)-C(8A)	1.4244(11)	O(1)-C(2)	1.4333(12)
C(2)-C(2A)	1.5160(13)	C(2A)-O(9)	1.4435(11)
C(2A)-C(3)	1.4616(13)	C(2A)-C(8B)	1.5166(12)
C(3)-O(9)	1.4523(12)	C(3)-C(4)	1.4946(15)
C(4)-O(10)	1.4553(11)	C(4)-C(5)	1.5152(15)
C(5)-C(5A)	1.5405(13)	C(5A)-C(6)	1.5014(13)
C(5A)-C(8B)	1.5352(12)	C(5A)-C(14)	1.5399(14)
C(6)-C(7)	1.3318(14)	C(7)-C(8)	1.4618(14)
C(8)-O(15)	1.2176(11)	C(8)-C(8A)	1.5452(13)
C(8A)-O(16)	1.3954(11)	C(8A)-C(8B)	1.5275(12)
O(10)-C(11)	1.3417(12)	C(11)-O(12)	1.1994(12)
C(11)-C(13)	1.4948(14)	O(16)-C(17)	1.4357(11)

C(8A)-O(1)-C(2)	106.42(7)	O(1)-C(2)-C(2A)	105.42(7)
O(9)-C(2A)-C(3)	59.98(6)	O(9)-C(2A)-C(2)	119.24(8)
C(3)-C(2A)-C(2)	124.57(8)	O(9)-C(2A)-C(8B)	116.63(7)
C(3)-C(2A)-C(8B)	122.87(8)	C(2)-C(2A)-C(8B)	106.65(7)
O(9)-C(3)-C(2A)	59.39(6)	O(9)-C(3)-C(4)	116.76(9)
C(2A)-C(3)-C(4)	118.05(8)	O(10)-C(4)-C(3)	108.82(8)
O(10)-C(4)-C(5)	107.76(8)	C(3)-C(4)-C(5)	113.34(8)
C(4)-C(5)-C(5A)	111.98(8)	C(6)-C(5A)-C(8B)	111.61(7)
C(6)-C(5A)-C(14)	107.25(8)	C(8B)-C(5A)-C(14)	110.28(8)
C(6)-C(5A)-C(5)	109.59(8)	C(8B)-C(5A)-C(5)	108.74(7)
C(14)-C(5A)-C(5)	109.35(8)	C(7)-C(6)-C(5A)	125.40(9)
C(6)-C(7)-C(8)	122.86(9)	O(15)-C(8)-C(7)	122.05(9)
O(15)-C(8)-C(8A)	120.42(9)	C(7)-C(8)-C(8A)	117.50(8)
O(16)-C(8A)-O(1)	110.11(7)	O(16)-C(8A)-C(8B)	108.85(7)
O(1)-C(8A)-C(8B)	104.76(7)	O(16)-C(8A)-C(8)	109.82(7)
O(1)-C(8A)-C(8)	109.85(7)	C(8B)-C(8A)-C(8)	113.34(7)
C(2A)-C(8B)-C(8A)	101.29(7)	C(2A)-C(8B)-C(5A)	115.22(7)
C(8A)-C(8B)-C(5A)	116.89(7)	C(2A)-O(9)-C(3)	60.63(6)
C(11)-O(10)-C(4)	117.40(8)	O(12)-C(11)-O(10)	123.22(9)
O(12)-C(11)-C(13)	125.54(9)	O(10)-C(11)-C(13)	111.24(9)
C(8A)-O(16)-C(17)	116.94(7)		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2$ x 10^3] for rr909.

The anisotropic displacement factor exponent takes the form:

$-2\pi^2 [(ha^*)^2 U_{11} + ... + 2hka^* b^* U_{12}]$

	U11	U22	U33	U23	U13	U12
O(1)	34(1)	24(1)	34(1)	0(1)	-6(1)	-10(1)
C(2)	31(1)	28(1)	34(1)	-6(1)	-9(1)	-5(1)
C(2A)	21(1)	26(1)	27(1)	-2(1)	-6(1)	-1(1)
C(3)	29(1)	37(1)	26(1)	1(1)	-5(1)	1(1)
C(4)	26(1)	36(1)	31(1)	12(1)	-3(1)	2(1)
C(5)	30(1)	24(1)	38(1)	8(1)	-7(1)	-4(1)
C(5A)	25(1)	20(1)	30(1)	2(1)	-7(1)	-4(1)
C(6)	24(1)	32(1)	35(1)	5(1)	-7(1)	-8(1)
C(7)	21(1)	35(1)	35(1)	2(1)	-4(1)	-1(1)
C(8)	27(1)	26(1)	24(1)	0(1)	-4(1)	3(1)
C(8A)	24(1)	20(1)	24(1)	0(1)	-3(1)	-3(1)
C(8B)	20(1)	20(1)	24(1)	0(1)	-3(1)	-2(1)
O(9)	24(1)	39(1)	36(1)	4(1)	-10(1)	1(1)
O(10)	26(1)	49(1)	38(1)	22(1)	-1(1)	2(1)
C(11)	28(1)	36(1)	21(1)	1(1)	-4(1)	-4(1)
O(12)	31(1)	60(1)	38(1)	13(1)	3(1)	4(1)
C(13)	34(1)	39(1)	29(1)	9(1)	-5(1)	-3(1)
C(14)	43(1)	27(1)	38(1)	-5(1)	-12(1)	-7(1)
O(15)	41(1)	27(1)	40(1)	1(1)	-1(1)	9(1)
O(16)	36(1)	24(1)	23(1)	2(1)	-1(1)	-1(1)
C(17)	40(1)	30(1)	31(1)	9(1)	-5(1)	0(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for rr909.

	x	y	z	U(eq)
H(2X)	1898(18)	1760(16)	1724(11)	37(3)
H(2Y)	-265(19)	2085(17)	2113(11)	43(4)
H(3)	1754(16)	4694(15)	347(11)	31(3)
H(4)	3920(18)	6488(16)	829(11)	36(3)
H(5X)	1319(19)	8023(16)	2470(11)	37(3)
H(5Y)	3284(18)	8514(18)	2230(11)	40(3)
H(6)	5762(18)	6364(17)	2581(12)	42(4)
H(7)	6690(20)	3476(18)	2763(12)	46(4)
H(8B)	538(16)	5145(15)	3771(10)	29(3)
H(13X)	1220(20)	10410(20)	-967(14)	62(5)
H(13Y)	2830(30)	11380(30)	-792(17)	88(6)
H(13Z)	3020(20)	10290(20)	-1877(16)	72(5)
H(14X)	1650(20)	7558(18)	4559(12)	45(4)
H(14Y)	3700(20)	7988(19)	4242(12)	47(4)
H(14Z)	3120(20)	6218(19)	4889(13)	49(4)
H(17X)	1410(20)	660(20)	5351(13)	58(4)
H(17Y)	3410(20)	957(19)	5429(13)	51(4)
H(17Z)	1890(20)	1759(18)	6333(13)	48(4)