STUDIES TOWARD THE TOTAL SYNTHESIS OF ARTOCARPOL A, D, E AND STRUCTURALLY RELATED ANALOGUES

by

Peggy Paduraru
BSc, Polytechnic University of Bucharest, 1999
MSc, Polytechnic University of Bucharest, 2000

THESIS SUBMITTED IN PARTIAL FULFILLMENT OF
THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

In the Department of Chemistry

SIMON FRASER UNIVERSITY

Summer 2006

APPROVAL

Name: Peggy Paduraru

Degree: Doctor of Philosophy

Title of Thesis: Studies Toward the Total Synthesis of Artocarpol A, D, E and Structurally Related Analogues

Examining Committee:

Chair: Dr. M.H. Eikerling (Assistant Professor)

Dr. P.D. Wilson (Associate Professor)
Senior Supervisor

Dr. B.M. Pinto (Professor)
Committee Member

Dr. E. Plettner (Associate Professor)
Committee Member

Dr. R.A. Britton (Assistant Professor)
Internal Examiner

Dr. T.G. Back (Professor)
External Examiner
Chemistry Department
University of Calgary

Date Approved: June 2, 2006

ABSTRACT

The work described in this thesis concerns studies toward the total synthesis of artocarpol A, D and E as well as the synthesis of structurally related analogues. The artocarpol family of natural products was isolated from the root bark of a breadfruit tree, *Artocarpus rigida* (Moraceae). Notably, artocarpol A has a particularly interesting molecular structure as well as potent anti-inflammatory activity and so it represents an important target for total synthesis. Artocarpol A, C, D, E, F, G and I share a common structural feature, a functionalized dibenz[*b,f*]oxepin ring system. Moreover, in the case of artocarpol A the dibenz[*b,f*]oxepin moiety is fused to a tricyclic system (a condensed 4,5,6-polycyclic system that features four contiguous stereogenic centres at the ring-junctions). Based on retrosynthetic analysis of this target compound, a novel synthetic route was devised and model studies were undertaken. The known 11*H*-dibenzo[*b,f*]oxepin-10-one was efficiently synthesized in five steps in order to test the validity of the two key steps in the proposed route. The first key step involved a cross-aldol condensation reaction between the unsubstituted oxepinone and citral that was coupled to a subsequent electrocyclization reaction. The second key step, involved an intramolecular [2+2] photocycloaddition reaction that resulted in the construction of the complete polycyclic ring system of artocarpol A and installed the four stereogenic centres in the correct relative sense. The structure of this complex polycyclic artocarpol

A analogue was elucidated by detailed NMR studies and by X-ray crystallography. A series of related 2*H*-chromenes and pyrans were also prepared by modification of a known synthetic procedure and were employed as additional substrates for this photocycloaddition reaction. An analogue of artocarpol D was also prepared from senecialdehyde. An alternative strategy was also developed for the synthesis of analogues of artocarpol A, D and E that employed alkylation reactions of the parent oxepinone with geranyl and prenyl bromide as key steps. The synthesis of a dimethoxy-substituted dibenzo[*b,f*]oxepinone was also completed. However, this appropriately functionalized substrate proved to be unsuitable for the proposed total syntheses. Thus, the corresponding dinitro-substituted oxepinone was identified as an alternative substrate for synthesis and preliminary investigations were undertaken.

To my daughter Jasmine, my husband Dragos, and my parents Janetta and Nicolae Moga.

Fiicei mele Jasmine, sotului meu Dragos, si parintilor mei Janetta si Nicolae Moga.

ACKNOWLEDGEMENT

My senior supervisor, Dr. Peter Wilson, is thanked for his advice, guidance and mentoring over the course of my doctoral studies. I am grateful to Dr. Wilson for the training in the technical and philosophical aspects of organic synthesis which I received during my time in his research group. Dr. Wilson is also thanked for his proofreading of this thesis.

The other members of my supervisory committee, Dr. Mario Pinto and Dr. Erika Plettner, are thanked for their suggestions and encouragement throughout my studies.

Mr. Neil Draper and Mr. Michael Katz (Simon Fraser University) are thanked for obtaining data and solving the X-ray crystal structures that are presented in this thesis.

My past and present lab colleagues (Jay Cadieux, Arun Narine, Hongjuan Hu, Michael Lyle, Jeremy Pettigrew, Darren McMurtrie, Patrick Chen, Jason Lamontagne and Brendan Whelan) are thanked for their friendship and numerous helpful discussions over the years.

The technical assistance of Mrs. Marcy Tracey (NMR), Mr. Greg Owen (MS), Mr. Philip Ferreira (MS), Mr. Simon Wong (MS) and Mr. M.K. Yang (CHN microanalysis) is gratefully acknowledged.

Finally, Simon Fraser University is thanked for financial support.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF SCHEMES

LIST OF TABLES

LIST OF ABBREVIATIONS

°	degree(s)
(±)-	racemic
1D	one dimensional
^{13}C NMR	carbon nuclear magnetic resonance
^{1}H NMR	proton nuclear magnetic resonance
aq.	aqueous
OAc	acetate
Anal.	analytical
Ar	aryl
Calcd	calculated
cat.	catalytic (amount)
cm^{-1}	wavenumbers (IR spectroscopy)
CI	chemical ionization
COSY	^{1}H-^{1}H correlation NMR spectroscopy
δ	chemical shift (NMR)
d	doublet (NMR spectroscopy)
dd	doublet of doublets (NMR spectroscopy)
dt	doublet of triplets (NMR spectroscopy)
DME	1,2-dimethoxyethane

DMF	*N,N*-dimethylformamide
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
ε	molar extinction coefficient (UV/visible spectroscopy)
EC_{50}	median effective concentration
ef	evaporative film (IR spectroscopy)
EI	electron impact
equiv	equivalent(s)
ether	diethyl ether
Et_3N	triethylamine
Et_2O	diethyl ether
EtOH	ethanol
EtOAc	ethyl acetate
h	hour(s)
$h\nu$	irradiation
HMBC	heteronuclear multiple bond coherence
HMPA	hexamethylphosphoramide
HMPT	hexamethylphosphoroustriamide
HMQC	heteronuclear multiple quantum coherence spectroscopy
Hz	Hertz
IC_{50}	median inhibition concentration
i-Pr	isopropyl
IR	infrared
J	coupling constant

LDA	lithium *N,N*-diisopropylamide
lit.	literature value for a physical or spectroscopy property
m	multiplet
M	molarity
Me	methyl
mg	milligram
MHz	megahertz (NMR field strength)
MeOH	methanol
min	minute
mL	milliliter
μL	microliter
mol	mole(s)
MS	mass spectrometry
m/z	mass to charge ratio
n-BuLi	*n*-butyllithium
NOESY	nuclear Overhauser effect correlation spectroscopy
OAc	acetate
OMe	methoxy
ORTEP	Oakridge thermal ellipsoid plot
Ph	phenyl
PhH	benzene
PhMe	toluene
pKa	acid dissociation constant
PMB	*p*-methoxybenzyl

PPA	polyphosphoric acid
ppm	parts per million (NMR spectroscopy)
py	pyridine
q	quartet
rel.	relative
R_f	retention factor (thin layer chromatography)
s	singlet (NMR spectroscopy)
S_NAr	aromatic nucleophilic substitution reaction
t	triplet (NMR spectroscopy)
TBAF	tetra-*n*-butylammonium fluoride
t-BuOH	*tertiary*-butanol (1,1-dimethylethanol)
TMSCl	trimethylsilyl chloride
KO*t*-Bu	potassium *t*-butoxide
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
p-TsOH	*p*-toluenesulfonic acid monohydrate
UV	ultraviolet
v/v	volume by volume
w/v	weight by volume
w/w	weight by weight

CHAPTER 1: ISOLATION, CHARACTERIZATION AND PROPOSED BIOSYNTHESIS OF ARTOCARPOL A, D AND E

1.1 Thesis Introduction

The work described in this thesis concerns studies towards the total synthesis of artocarpol A, D and E as well as the synthesis of structurally related analogues. The artocarpol family of natural products was isolated from the root bark of a breadfruit tree, *Artocarpus rigida* (Moraceae). Artocarpol A has a particularly interesting molecular structure as well as potent anti-inflammatory activity and so it represents an important target for total synthesis. Artocarpol A, C, D, E, F, G and I share a common structural feature, a functionalised dibenz[*b,f*]oxepine ring system. Moreover, in the case of artocarpol A the dibenz[*b,f*]oxepine moiety is fused to a tricyclic system (a condensed 4, 5, 6-polycyclic system that features four contiguous stereogenic centres at the ring-junctions). Based on the retrosynthetic analysis of these natural products, two synthetic routes were devised for the total synthesis of the target compounds and model studies were undertaken.

1.2 Overview of the Artocarpol Family of Natural Products

A variety of natural products have been isolated from the root bark of *Artocarpus rigida* (Moraceae).[1,2] These natural products are represented by two

(1) Hano, Y.; Inami, R.; Nomura, T. *Heterocycles* **1990**, *31*, 2173.

general classes of compounds; isoprenoid substituted flavones and phenolic compounds, most of which contain an oxepine ring.

Following the isolation and characterization of artocarpol A (**1**) other new phenolic compounds containing an oxepine ring were also isolated from the same source.[3] Artocarpol D (**4**) and E (**5**) have identical aromatic phenol and prenyl substituents as artocarpol A (**1**) and also share a very similar core ring structures. In addition, artocarpol B (**2**) and C (**3**) are structurally related to artocarpol A (**1**) in that they feature an oxepine ring (Figure 1).[4]

---

(2) Hano, Y.; Inami, R.; Nomura, T. *Heterocycles* **1993**, *35*, 1341.

(3) Chung, M.-I.; Ko, H.-H.; Yen, M.-H.; Lin, C.-N.; Yang, S.-Z.; Tsao, L.-T.; Wang, J.-P. *Helv. Chim. Acta* **2000**, *83*, 1200.

(4) Ko, H.-H.; Lin, C.-N.; Yang, S.-Z. *Heterocycles* **2000**, *83*, 3000.

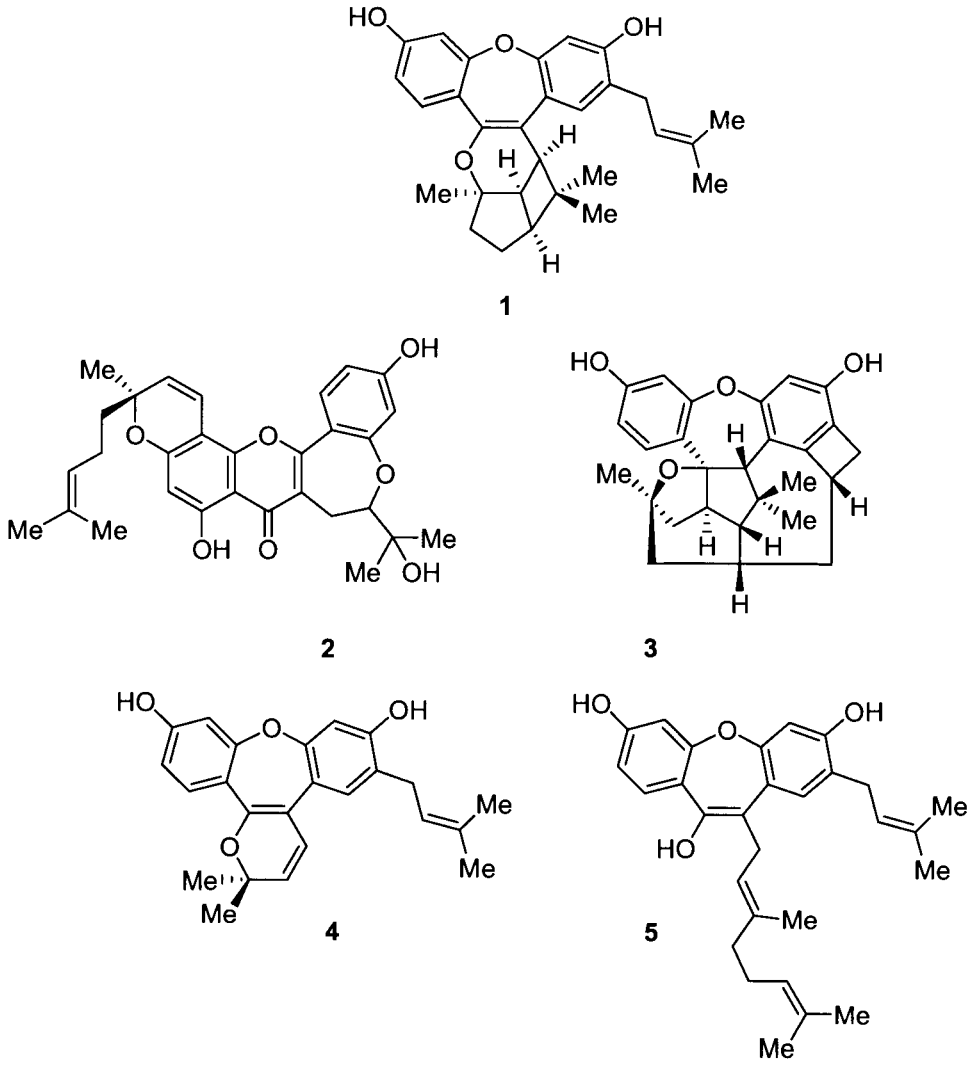


Figure 1 Structures of artocarpol A (1), B (2), C (3), D (4) and E (5).

Subsequent to the isolation of the above natural products, the isolation and structural characterization of five additional natural products was reported. The structure of artocarpol F (**6**) was elucidated based on information from ^{1}H, ^{1}H-COSY, and NOESY spectra as well as the molecular modelling program CS Chem 3D V3.5.1.[5] The structures of artocarpol G (**7**) and I (**9**) closely resembled

(5) Ko, H.-H.; Yang, S.-Z.; Lin, C.-N. *Tetrahedron Lett.* **2001**, *42*, 5269.

artocarpol A (**1**) but artocarpol H (**8**) and J (**10**) did not contain an oxepine ring.[6] Artocarpol J (**10**) could not be isolated in pure form and so it was converted to the corresponding peracetate compound for characterization purposes (Figure 2).[7]

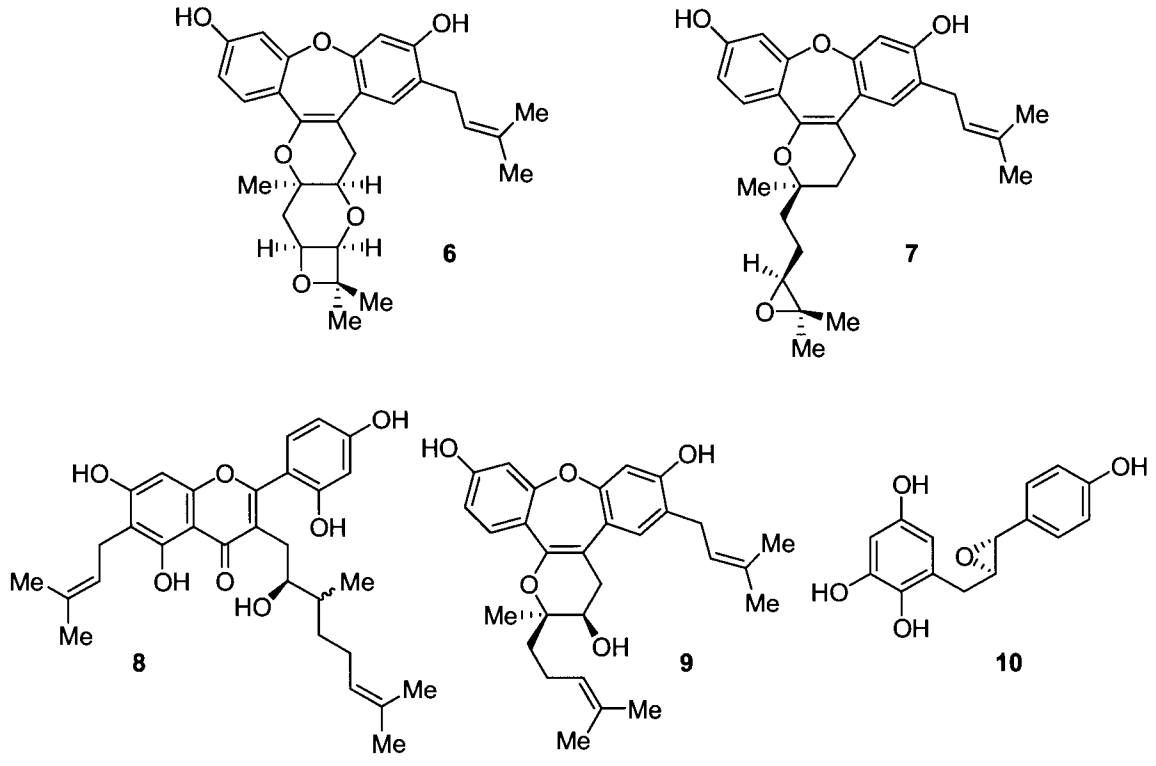


Figure 2 Structures of artocarpol F (6), G (7), H (8), I (9) and J (10).

In regard to the biological activity of these compounds, artocarpol A (**1**), C (**3**) and I (**9**), as well as the peracetate of artocarpol J (**10**), were found to display anti-inflammatory activity. Their activity was studied *in vitro* by measuring the inhibitory effect on a chemical-mediator released from mast cells, neutrophils,

(6) Lu, Y.-H.; Lin, C.-N.; Ko, H.-H.; Yang, S.-Z.; Tsao, L.-T.; Wang, J.-P. *Helv. Chim. Acta* **2002**, *85*, 1626.

(7) Lu, Y.-H.; Lin, C.-N.; Ko, H.-H.; Yang, S.-Z.; Tsao, L.-T.; Wang, J.-P. *Helv. Chim. Acta* **2003**, *86*, 2566.

macrophages, and microglial cells. These compounds inhibited superoxide-anion formation in a concentration-dependent manner (IC_{50} = 26.0 ± 5.6, IC_{50} = 17.1 ± 0.40 and IC_{50} = 20.5 ± 2.60 μM for the fMLP/CB-induced response).[4] These results, combined with other studies, showed that artocarpol C (**3**), I (**9**) and the peracetate of artocarpol J (**10**) attenuated the respiratory burst in neutrophils. Artocarpol C (**3**) also suppressed the release of β-glucuronidase and histamine from mast cells.[5,8]

Due to its particularly interesting molecular structure as well as potent anti-inflammatory activity, artocarpol A (**1**) was chosen as the primary target for total synthesis. Artocarpol D (**4**) and E (**5**) share similar structural features to artocarpol A (**1**) and so could be derived from common precursors. Therefore, artocarpol D (**4**) and E (**5**) were selected as additional targets.

1.3 Isolation and Characterization of Artocarpol A (1), D (4) and E (5)

Artocarpol A (**1**), D (**4**) and E (**5**) were obtained by extraction of *Artocarpus rigida* plant material with chloroform followed by column chromatography on silica gel.[3,4]

(8) Kuan, Y.-H.; Lin, R.-H.; Tsao, L.-T.; Lin, C.-N.; Wang, J.-P. *Br. J. Pharmacol.* **2005**, *145*, 460.

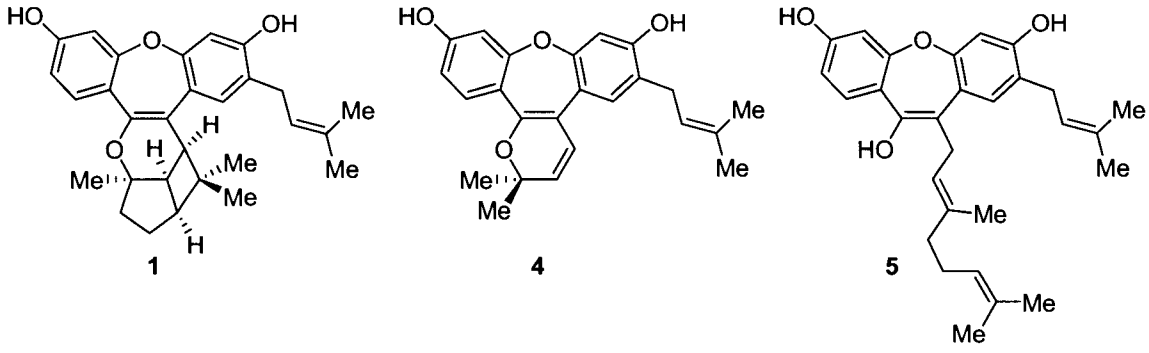


Figure 3 Structure of artocarpol A (1), D (4) and E (5).

The molecular structure of artocarpol A (**1**) was determined by detailed spectroscopic methods. High-resolution mass spectrometry of compound **1** showed a molecular ion (m/z 444.2394) corresponding to a compound having a molecular formula $C_{29}H_{32}O_4$. The presence of hydroxyl (phenolic) groups and aromatic rings was indicated by IR signals at 3399, 1620 and 1593 cm^{-1}. The ^1H NMR spectrum of compound **1** showed five aromatic proton signals with chemical shifts; δ = 6.51, 6.55, 6.80, 6.99, and 7.42 ppm and proton signals of a γ,γ-dimethylallyl group at chemical shifts; δ = 1.64, 1.70, 3.18 and 5.20 ppm (Table 1). Analysis of ^1H, ^1H-COSY, HMQC and HMBC data of **1** in conjugation with the EI-MS fragmentation pattern established the partial structures **a** and **b** (Figure 4).

Table 1 **^{1}H and ^{13}C NMR Spectra ($CDCl_3$) of Artocarpol A (1)[a]**

	δ(C)	δ(H)		δ(C)	δ(H)
H-C(1)	107.7	6.55 (s)	H-C(12)	122.6	5.20 (t, J = 6.8)
C(1a)	155.4		C(13)	134.1	
C(2)	153.7		Me(14)	17.8	1.64 (s)
C(3)	120.5		Me(15)	25.7	1.70 (s)
H-C(4)	106.5	6.51 (s)	H-C(16)	38.3	3.01 (d, J = 9.6)
C(4a)	130.7		H-C(17)	40.6	2.45 (t, J = 9.6)
H-C(5)	120.9	7.42 (d, J = 8.4)	C(18)	84.2	
C(5a)	122.3		Me(19)	25.3	1.27 (s)
H-C(6)	111.8	6.80 (dd, J = 8.4, 2.4)	CH_2(20)	25.1	1.62 (m), 1.75 (m)
C(7)	153.2[b]		CH_2(21)	41.0	1.57 (m), 2.02 (m)
H-C(8)	98.3	6.99 (d, J = 2.4)	H-C(22)	46.6	2.31 (dt, J = 8.8, 4.4)
C(8a)	153.1[b]		C(23)	40.1	
C(9)	153.3[b]		Me(24)	19.0	0.60 (s)
C(10)	119.7		Me(25)	33.3	0.86 (s)
CH_2(11)	27.4	3.18 (d, J = 6.8)			

[a] Numbering according to that indicated in Figure 5. [b] Assignments may be reversed.

The presence of the fused four, five, six membered ring structure was indicated by the characteristic signals at chemical shifts; δ = 0.60, 0.86, 1.27,

1.57, 1.62, 1.75, 2.02, 2.31, 2.54, and 3.01 ppm in the ^{1}H-NMR spectrum. This substructure is present in a number of natural products.[9] The connectivity of the partial structures **a**-**c** was deduced from HMBC data and the relative configuration of the stereogenic centres at C(16), C(17), C(18) and C(22) was determined from NOESY data (Figure 5).

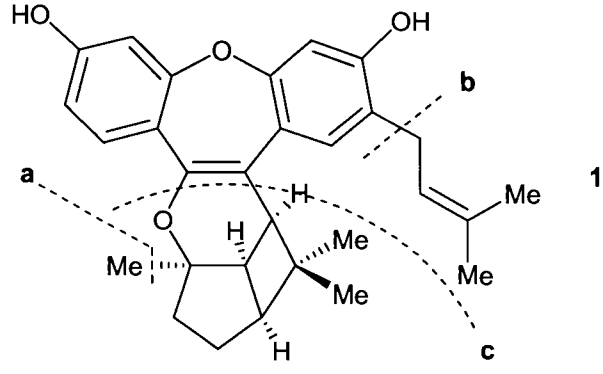


Figure 4 EI-MS fragmentation patterns of artocarpol A (1).

The molecular structure of artocarpol A (**1**) was finally determined by analysis of the ^{1}H- and ^{13}C-NMR and MS data of the corresponding diacetate derivative of this natural product. Therefore, artocarpol A (**1**) was characterized as *rel*-(10a*R*,12a*S*,12b*R*,13a*R*)-10a,11,12a,12b,13,13a-hexahydro-10a,13,13-trimethyl-2-(3-methylbut-2-enyl)-12*H*-5,10-dioxacyclobuta[*cd*]dibenzo[3,4:6,7] cyclohepta[1,2-*f*]indene-3,7-diol.

(9) Nomura, T.; Fukai, T.; Katayanagi, M. *Heterocycles* **1978**, *9*, 745.

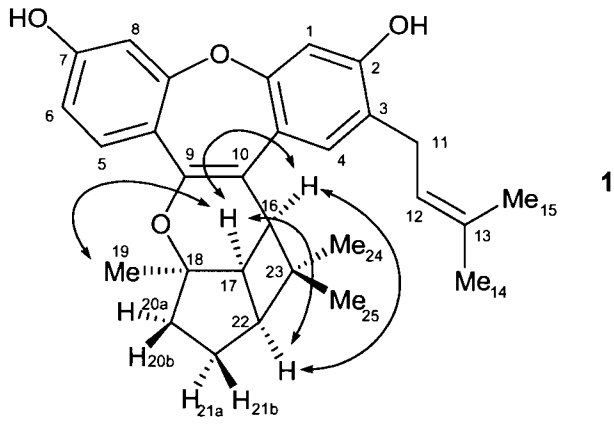


Figure 5 Some key NOESY interactions of artocarpol A (1).

Based on the use of similar spectroscopic techniques, artocarpol D (**4**) was characterized as 11,11-dimethyl-2-(3-methylbut-2-enyl)-11*H*-dibenzo[*b,f*]pyrano [2,3-*d*]oxepin-3,7-diol and artocarpol E (**5**) was characterized as 2-[(2*E*)-3,7-dimethylocta-2,6-dienyl]-2-(3-methylbut-2-enyl)dibenzo[*b,f*]oxepin-3,7,10-triol.

1.4 Proposed Biosynthesis Route to the Artocarpols

Seven of the isolated natural compounds from A*rtocarpus rigida*, artocarpol A (**1**), C (**3**), D (**4**), E (**5**), F (**6**), G (**7**) and I (**9**), share a common structural feature, an oxepine ring. Their common biogenetic synthesis from stilbene **11** was proposed by Lin and co-workers (Figure 6).[7] As shown below, subsequent reductive cleavage of the pyran ring of artocarpol D (**4**) could afford compound **12**.

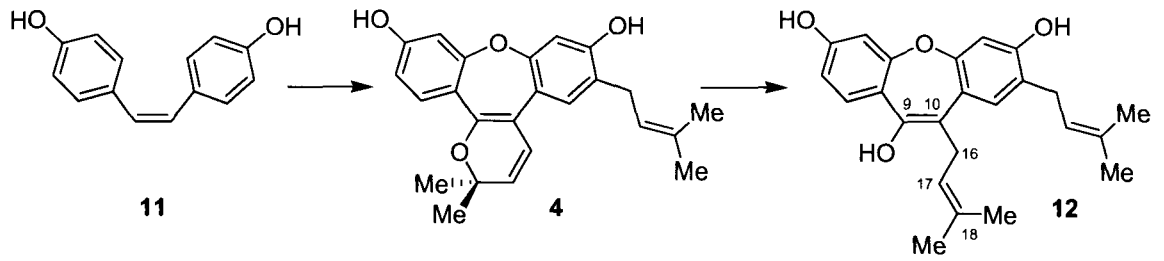


Figure 6 **Proposed biosynthesis of artocarpol D (4) from stilbenes (11): Synthesis of the intermediate 12 from artocarpol D (4).**

Prenylation of compound **12** at C(20) would then afford artocarpol E (**5**) which, in turn, could undergo oxidative cyclization to afford artocarpol I (**9**) (Figure 7). Subsequent cyclization and oxidation reactions between the C(17) hydroxyl group and the C(21)-C(22) double bond as well as C(23) of artocarpol I (**9**), respectively, could then afford artocarpol F (**6**) (Figure 7).

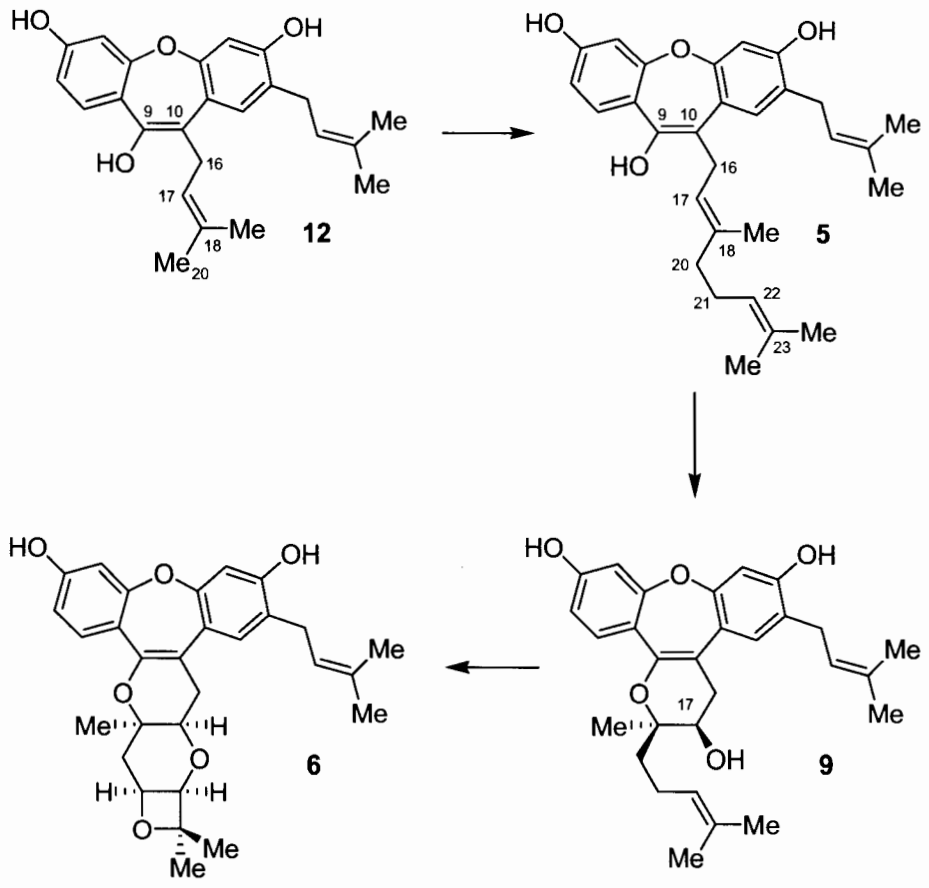


Figure 7 Proposed biosynthesis of artocarpol E (5), I (9) and F (6).

Artocarpol G (**7**) might be derived from artocarpol E (**5**) by cyclization reactions between the hydroxyl group at C(9) and the C(17)-C(18) double bond and on epoxidation of the C(22)-C(23) double bond. Artocarpol A (**1**) could result from cyclization reactions between the C(9) –hydroxyl and C(18), C(17) and between C(22), C(16), C(23) of artocarpol E (**5**). A rearrangement, between C(9) and C(16), and several cyclization reactions, between C(9) – OH and C(18), C(21) and C(13), between C(12) and C(4), between C(22) and C(16) and between C(23) and C(10) of artocarpol E (**5**) could led to artocarpol C (**3**) (Figure 8).[5]

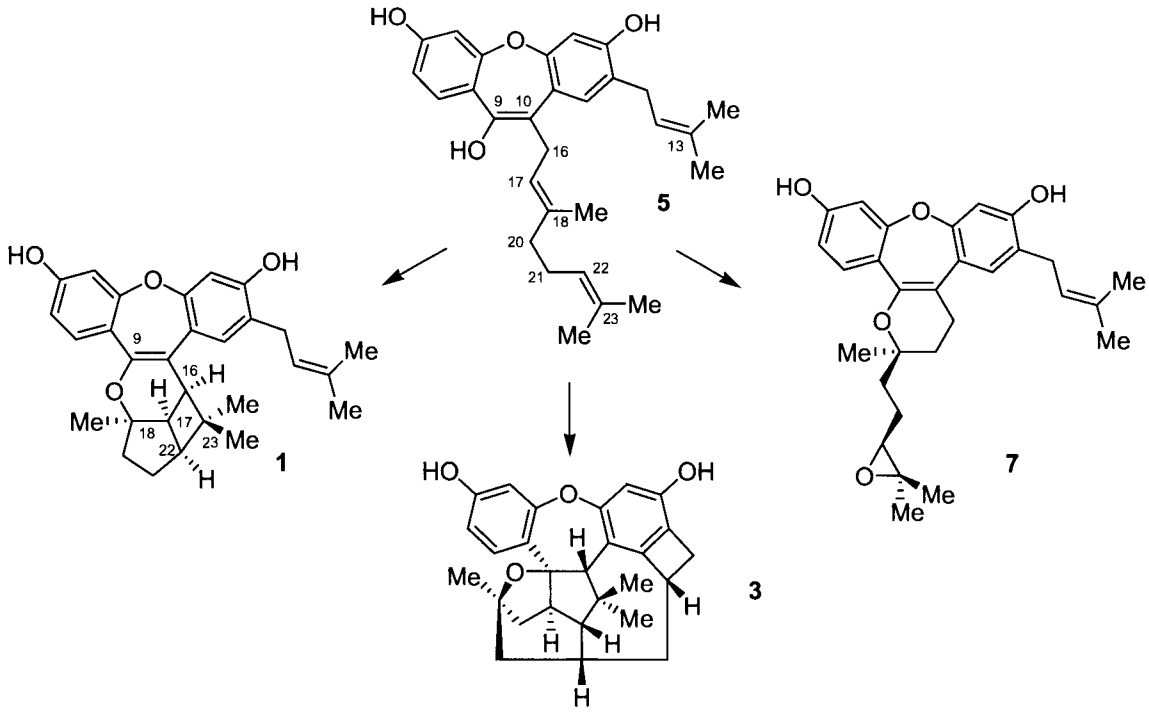


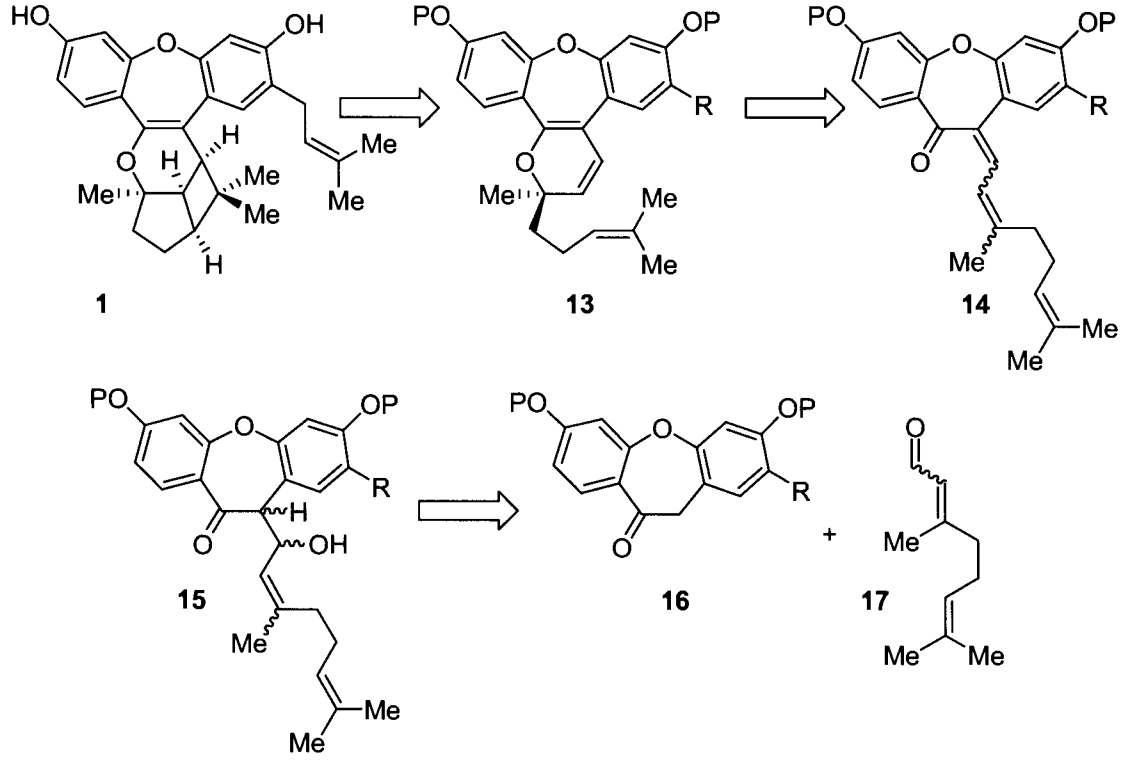
Figure 8 **Proposed biogenetic synthesis of artocarpol A (1), C (3) and G (7) from artocarpol E (5).**

CHAPTER 2: PROPOSED SYNTHESES OF ARTOCARPOL A, D AND E

2.1 Introduction

A retrosynthetic analysis of the fully functionalized ring structure of artocarpol A (**1**) is presented below.

Scheme 1 Retrosynthetic Analysis of Artocarpol A (1)



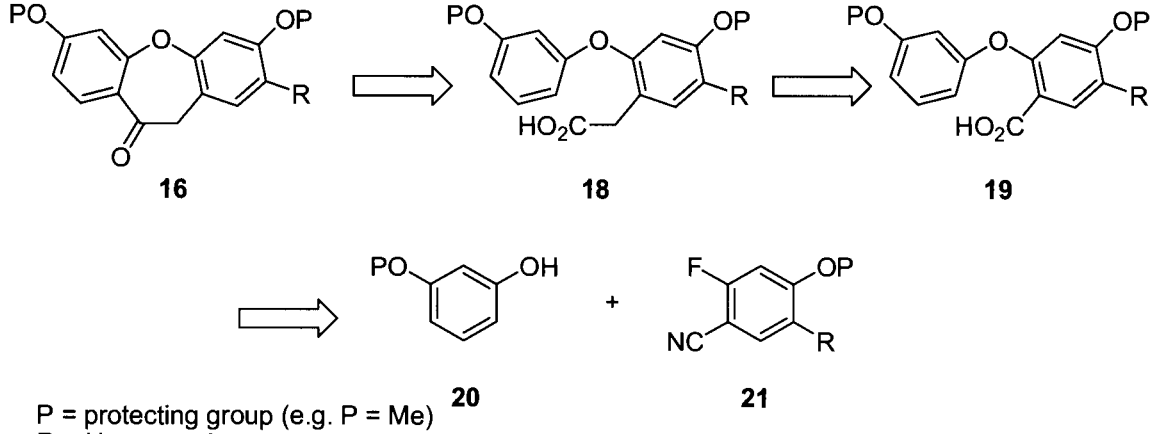
P = protecting group (*e.g.* P = Me)
R = H *or* prenyl

It was identified that the four and five membered rings could be installed *via* a [2+2] photocycloaddition reaction of the 2*H*-pyran derivative **13**. Based on steric arguments, in that the alkene moiety would be expected to approach from the top face of the molecule, the photocycloaddition reaction should also install

the remaining stereogenic centres of the natural product in the correct sense. The phenol protecting groups of the 2*H*-pyran **13** could be removed prior to or subsequent to this cyclization step. The 2*H*-pyran **13** could be synthesized *via* an electrocyclic ring closing reaction of the dienone **14**. In turn, the dienone **14** could be prepared by a dehydration reaction of the aldol product **15** which could result from the cross-aldol reaction of the substituted dibenzo[*b,f*]oxepin-10-one **16** with commercially available citral (**17**).

The functionalized dibenzo[*b,f*]oxepin-10-one **16** could be synthesized using a classical approach that would involve the Friedel-Crafts acylation reaction of the homologated phenoxybenzoic acid **18** (Scheme 2).

Scheme 2 Retrosynthetic Analysis of the Substituted Dibenzo[*b,f*]oxepin-10-one (16)



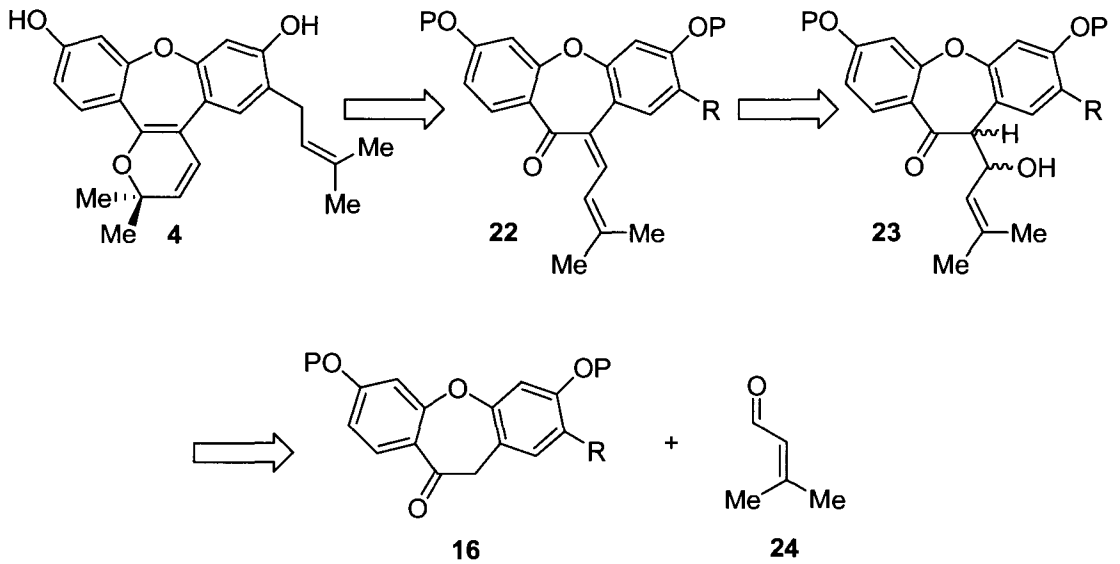
P = protecting group (e.g. P = Me)
R = H *or* prenyl

The biaryl ether linkage could in turn result from an aromatic nucleophilic substitution reaction of the fluorobenzene derivative **21** with the commercially available substituted phenol **20** (P = Me). Experimental investigation would be

necessary to determine the most appropriate point in proposed synthesis for the introduction of the prenyl substituent.

The advanced oxepinone intermediate **16** could also be used in the synthesis of other artocarpol natural products. For example, the 2*H*-pyran ring in artocarpol D (**4**) could be prepared from the electrocyclic ring-closing reaction of the dienone **22** which in turn could be obtained by an elimination reaction of the aldol coupling product **23**. The latter compound could be obtained from the advanced oxepinone intermediate **16** and senecialdehyde (**24**) which is a commercially available α,β-unsaturated aldehyde (Scheme 3).

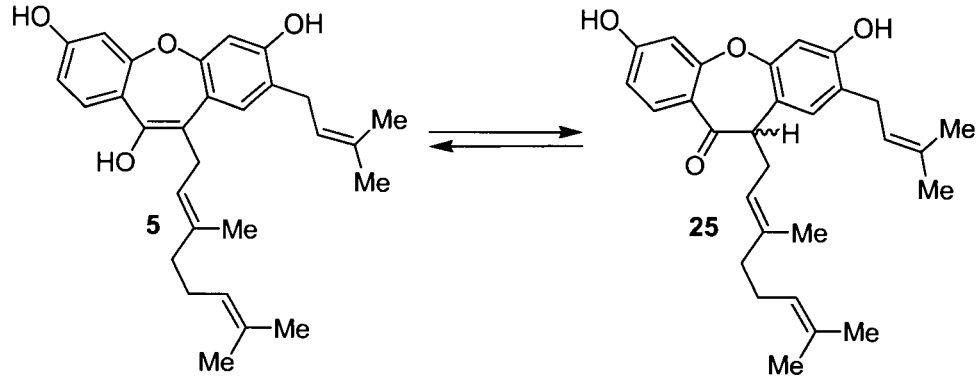
Scheme 3 Retrosynthetic Analysis of Artocarpol D (4)

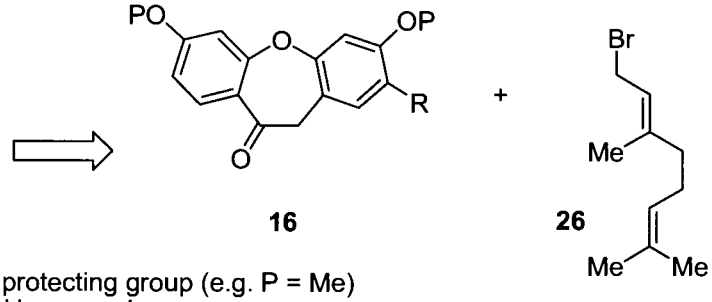


P = protecting group (e.g. P = Me)
R = H *or* prenyl

A different synthetic strategy was designed for the synthesis of artocarpol E (**5**). The keto-tautomer form of artocarpol E (**25**) could be obtained *via* an alkylation reaction of the advanced oxepinone intermediate **16** with geranyl bromide (**26**) (Scheme 4).

Scheme 4 Retrosynthetic Analysis of Artocarpol E (5)

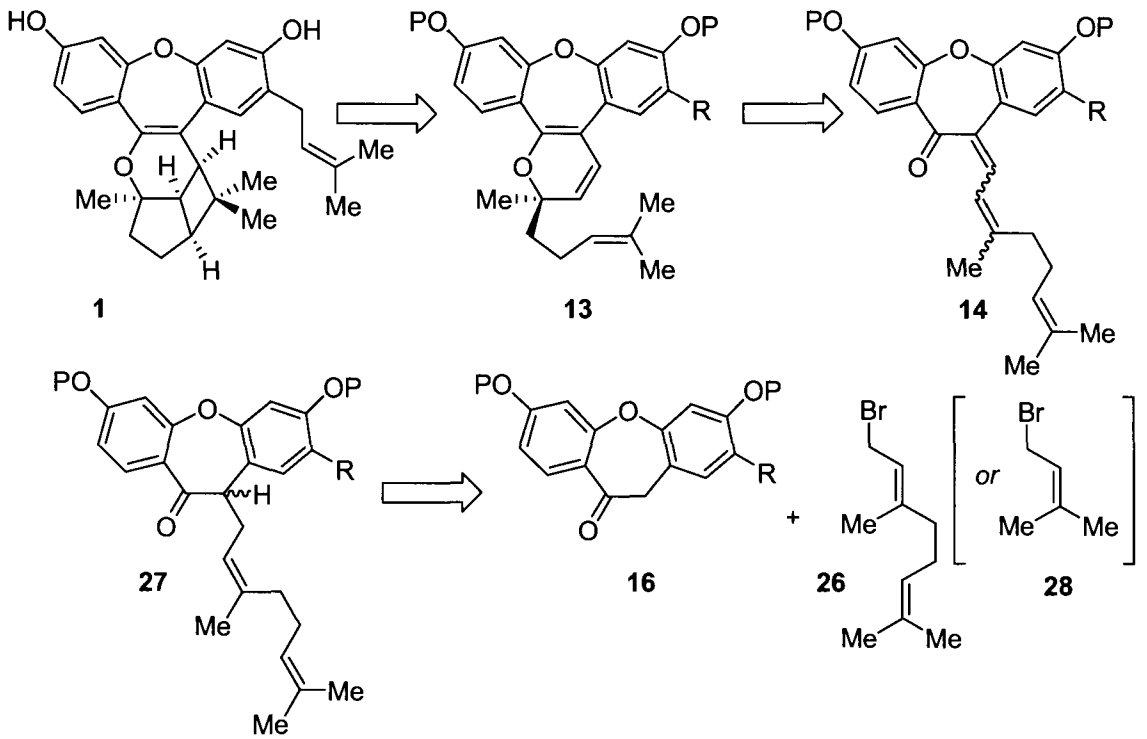




P = protecting group (e.g. P = Me)
R = H *or* prenyl

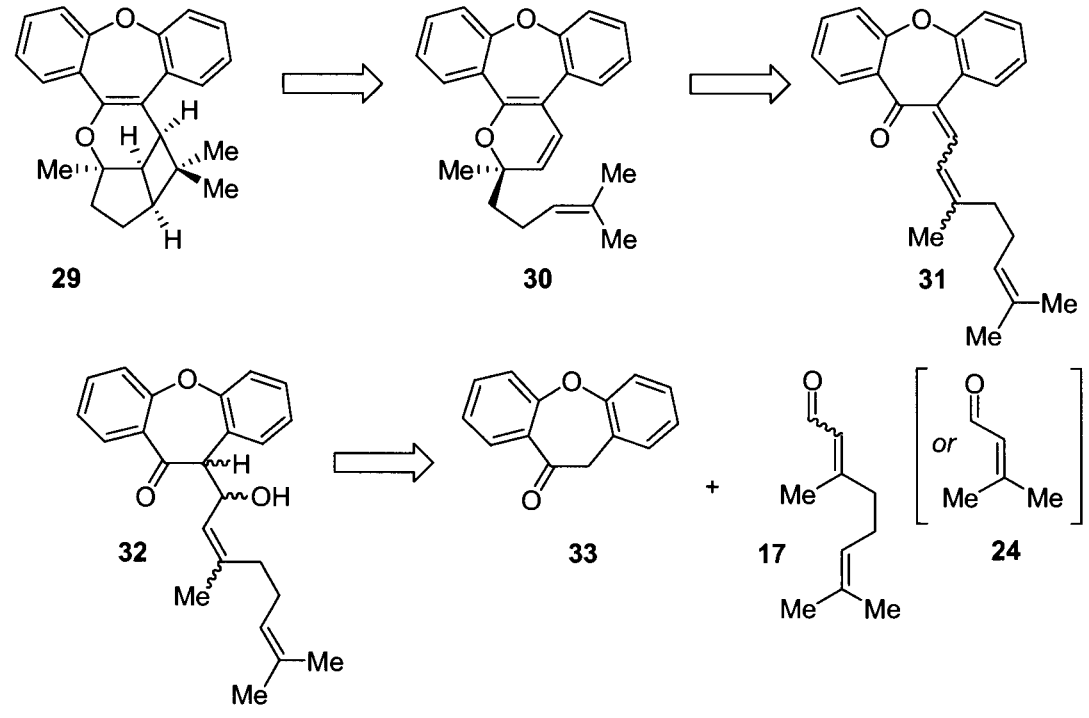
Of note, this alkylation synthetic strategy could also be applied in the synthesis of artocarpol A (**1**) and D (**4**). Alkylation of the advanced oxepinone intermediate **16** with geranyl bromide (**26**), in case of artocarpol A (**1**), should afford ketone **27** which could be oxidated to install the α,β-double bond. Once the dienone **14** had been obtained, the synthesis would follow the same steps as previously proposed (Scheme 5). Alkylation of the advanced oxepinone intermediate **16** with prenyl bromide (**28**) rather than geranyl bromide (**26**) should afford a substrate that would be suitable for the synthesis of artocarpol D (**4**).

Scheme 5 Alternative Retrosynthetic Analysis of Artocarpol A (1) and D (4)



In order to test the validity of the first synthetic pathway proposed for the synthesis of artocarpol A (**1**), model studies were planned using the known unsubstituted oxepinone **33**. The cross-aldol reaction of the oxepinone **33** should afford the aldol product **32** which could undergo an elimination reaction to afford the dienone **31**. The electrocyclization reaction to the 2*H*-pyran **30** followed by a [2+2] photocycloaddition reaction should complete the synthesis of the artocarpol A analogue **29** that contains the same core ring structure as artocarpol A (**1**) that would lack only the aromatic substituents. In a similar manner, the synthesis of an analogue of artocarpol D (**4**) could also be undertaken.

Scheme 6 Retrosynthetic Analysis of Artocarpol A Analogue (29)



The cross-aldol reaction of the oxepinone **33** with citral (**17**), an electrocyclization reaction of dienone **31** and a [2+2] photocycloaddition reaction of the 2*H*-pyran **30** were identified as key steps in the total synthesis of the artocarpol A analogue (**29**). In addition, the former two steps are suitable for the synthesis of an analogue of artocarpol D from senecialdehyde (**24**). In the following sections these proposed key steps are discussed in more detail.

2.2 The Cross-Aldol Condensation Reaction of the Oxepinone (33) with Citral (17)

The aldol reaction is among the most useful tools for carbon-carbon bond formation. [10] Interestingly, there has been no report on the use of a dibenzo[*b,f*]oxepin-10-one in an aldol reaction. However, there are a few cases

(10) Mahrwald, R. *Modern Aldol Reactions*; Wiley-VCH: Weinheim, 2004; Vol. 1.

where the α–carbon of oxepinones have been involved in alkylation reactions. Due to the lack of data concerning the ability of these ketones to participate in an aldol reaction, the study of cross-aldol reaction of the model oxepinone **33** with citral (**17**) was of particular interest in the synthesis of the artocarpol A analogue **29**.

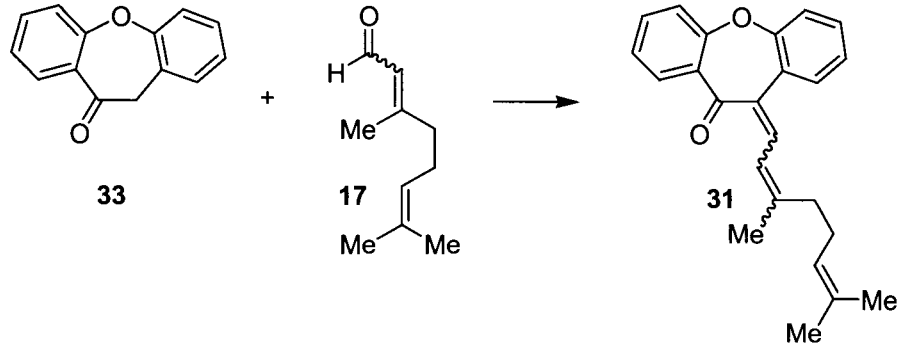
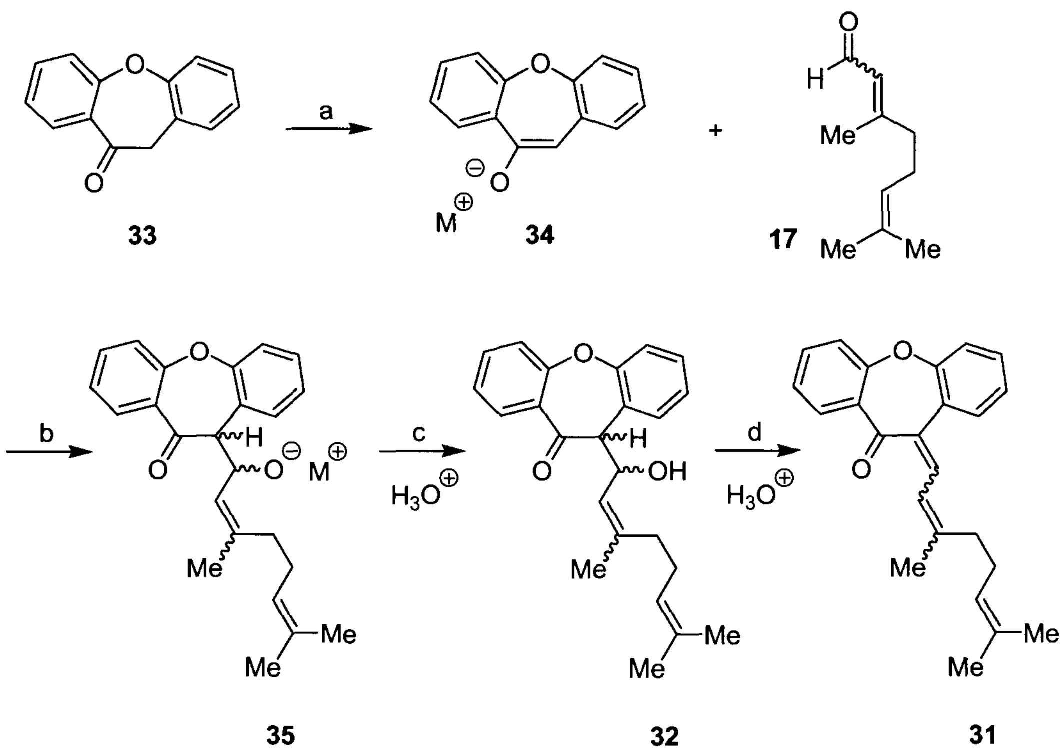


Figure 9 **Proposed cross-aldol condensation reaction of oxepinone (33) with citral (17).**

In the proposed cross-aldol reaction, the oxepinone **33** should be deprotonated in basic media in order to generate the enolate **34** which should then act as a nucleophile and react with citral (**17**) (Scheme 7). After a protonation step, the product of this reaction would be the β-hydroxycarbonyl compound **32** which could subsequently undergo the elimination of water to afford the α,β-unsaturated carbonyl compound **31**. This overall process is referred to as an "aldol condensation reaction".[10]

Scheme 7 Steps in the Cross-Aldol Reaction of the Oxepinone (33) with Citral (17)



Procedures: a) irreversible enolate formation; b) addition of the preformed enolate to the aldehyde; c) protonation; d) dehydration.

However, the enolate **34** could also react with the oxepinone **33** to afford the ketone self-condensation product but the process should be inhibited due to steric factors. Similarly, citral (**17**) could be deprotonated and react with itself. The self-condensation product of citral (**17**) has been reported.[11]

The proposed steps in the cross-aldol reaction of the oxepinone **33** with citral (**17**) are based on the use of a preformed enolate **34** (Scheme 7). The chemistry of preformed enolates emerged with the discovery of lithium *N,N*-diisopropylamide (LDA). The lithium and magnesium salts of diisopropylamine

(11) Holst, P. B.; Anthoni, U.; Cristophersen, C.; Nielsen, P. H.; Bock, K. *Acta Chem. Scand.* **1994**, *48*, 765.

were first developed in the nineteen-fifties.[12] Because of its behaviour as a soluble and strong non-nucleophilic base, LDA has become a widely used reagent.[13] LDA and related bases; for example, lithium hexamethyldisilazane, lithium *N*-isopropylcyclohexylamide and lithium 2,2,6,6-tetramethylpiperidide turned out to be the reagents of choice for conversion of a variety of carbonyl compound into their enolates in an irreversible reaction which enabled the successful synthesis of cross-aldol products. Therefore, LDA was the first base used in our model studies for the cross-aldol reaction.

Of note, commercially available citral (**17**) is a mixture of *E* and *Z* isomers. Moreover, two stereogenic centres are generated in the cross-aldol reaction making possible the synthesis of structural isomers of the aldol product **31**. In the elimination reaction of the aldol products two stereogenic centres are removed and the number of possible aldol condensation products is reduced to four. These four geometrical isomers are α,β- and σ,γ-double bond isomers, respectively. All of the isomers, in principle, could be converted to the desired 2*H*-pyran **30** *via* isomerization and cyclization reactions.

(12) Hamell, M.; Levine, R. *J. Org. Chem.* **1950**, *15*, 162.

(13) Wittig, G. *Topics in Current Chemistry*; Springer-Verlag: New York, 1976; Vol. 67.

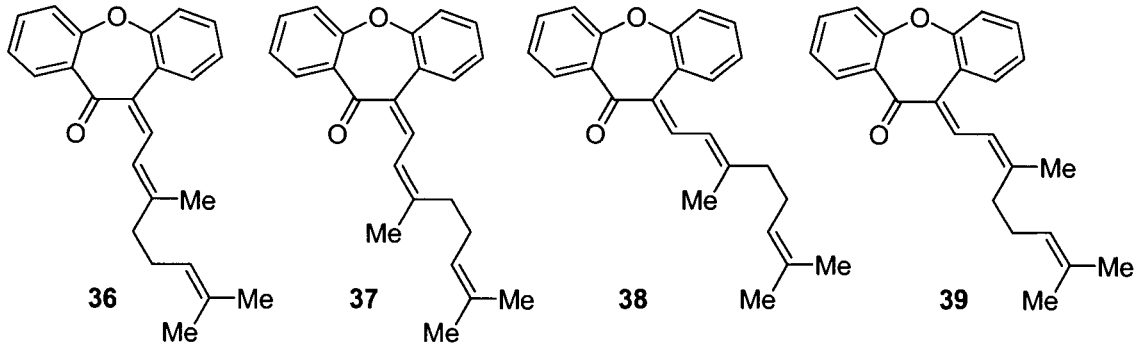


Figure 10 **Possible aldol condensation products in the reaction of the oxepinone (33) with citral (17): The dienone isomers (36, 37, 38 and 39).**

2.3 The Electrocyclization Reaction

2.3.1 Introduction

The second step in the proposed synthesis of the artocarpol A analogue (**29**) is the electrocyclization reaction of the dienone **31** to the 2*H*-pyran **30**. The electrocyclization process involves six electrons and an oxygen atom, therefore it is referred to as an oxa-6π electrocyclization.

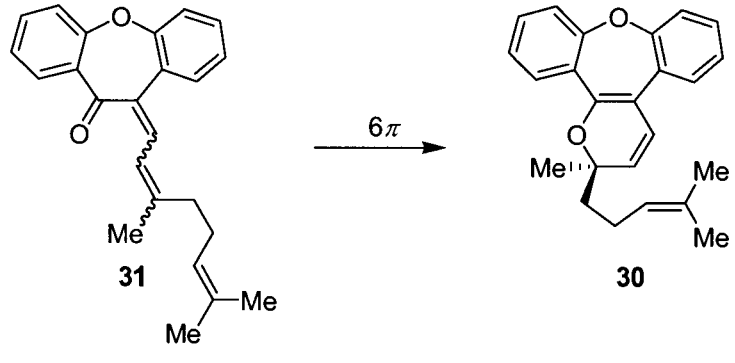
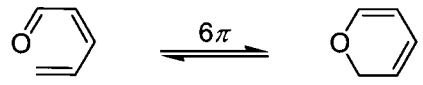


Figure 11 **Proposed electrocyclization reaction of dienone (31) to 2*H*-pyran (30).**

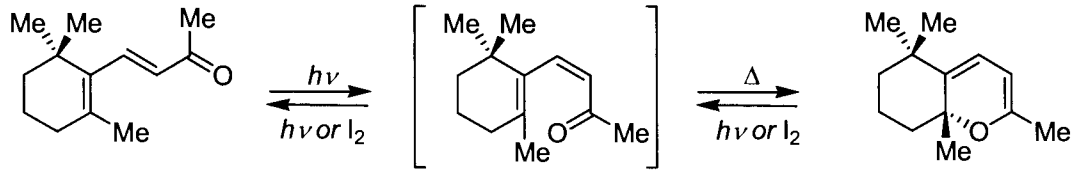
Oxa-6π electrocyclizations are essentially thermo-neutral reactions and have low activation energies which makes them highly reversible (Figure 12).[14]



dienal 2*H*-pyran

Figure 12 Oxa-6π electrocyclization reaction: Conversion of a dienal to a 2*H*-pyran.

Though postulated before, the first authentic 2*H*-pyran was reported in 1957 when the photochemical isomerization reactions of *trans*-β-ionone (**40**) were investigated.[15] When a solution of *trans*-β-ionone (**40**) in ethanol was irradiated with a low intensity mercury arc lamp, several compounds were isolated. One of these compounds was identified as the 2*H*-pyran **42** that formed *via* the isomerization of the α,β-double bond to the *cis*-isomer **41** and subsequently underwent electrocyclization.



40 **41** **42**

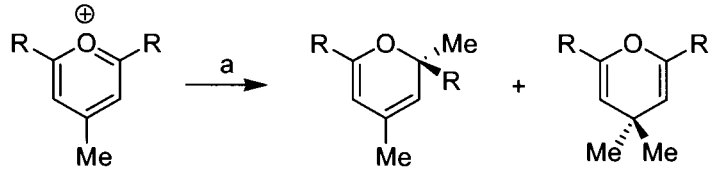
Figure 13 Photochemical isomerization of *trans*-β-ionone (40) to the *cis*-isomer (41) and 2*H*-pyran (42).

(14) Beaudry, C. M.; Malerich, J. P.; Trauner, D. *Chem. Rev.* **2005**, *105*, 4757.

(15) Buchi, G.; Yang, N. C. *J. Am. Chem. Soc.* **1957**, *79*, 2318.

A comprehensive study of the 2*H*- and 4*H*-pyrans was reported in 1972 by Dreux and co-workers.[16,17] The 2*H*- and 4*H*-pyrans (**44** and **45**) were obtained from the reaction of the pyrilium salts **43** with a methyl Grignard reagent according to the procedure published by Balaban and co-workers (Scheme 8).[18]

Scheme 8 Synthesis of 2*H*- and 4*H*-Pyrans (44 and 45) from Pyrilium Salts (43)



43 **44** **45**

Reagents and conditions: a) MeMgI, Et_2O, -18 °C, 1 h.

The relative ratio of the 2*H*- and 4*H*-pyrans was found to be dependent on the substituents present on the ring. An increase in the size of the R groups inhibited partially the synthesis of the 2*H*-pyran **44** and favoured the formation of the 4*H*-pyran **45**. These studies also included NMR, IR and UV spectral data for a large number of 2*H*- and 4*H*-pyrans as well as for several dienone compounds that were obtained by thermal isomerization of the 2*H*-pyran derivatives.[19]

2.3.2 Studies of the Dienone/2*H*-Pyran Equilibrium

The proposed valence isomerization of *cis*-dienones and 2*H*-pyrans was unambiguously proven by Marvell and co-workers.[20] The 2*H*-pyran **42** was

(16) Safieddine, A.; Royer, J.; Dreux, J. *Bull. Soc. Chim. Fr.* **1972**, 703.

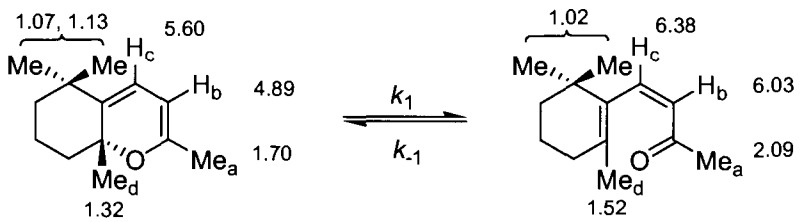
(17) Royer, J.; Dreux, J. *Bull. Soc. Chim. Fr.* **1972**, 707.

(18) Balaban, A. T.; Mihai, G.; Nenitzescu, C. D. *Tetrahedron* **1962**, *18*, 257.

(19) Royer, J.; Safieddine, A.; Dreux, J. *Bull. Soc. Chim. Fr.* **1972**, 1646.

(20) Marvell, E. N.; Caple, G.; Gosink, T. A.; Zimmer, G. *J. Am. Chem. Soc.* **1966**, *88*, 619.

obtained as previously described by irradiation of *trans*-β-ionone (**40**). The ^{1}H NMR spectrum of **42** was in complete agreement with the proposed 2*H*-pyran structure. However, the spectrum displayed several additional signals of another compound that could not be removed by further purification. An increase in the temperature of the NMR sample led to an increase in the intensity of the signals that were attributed to *cis*-β-ionone (**41**). This behaviour confirmed the predicted increase in the equilibrium content of the less stable isomer on increasing temperature. The total spectrum reverted to its original form when the sample was allowed to cool to room temperature.



42 **41**

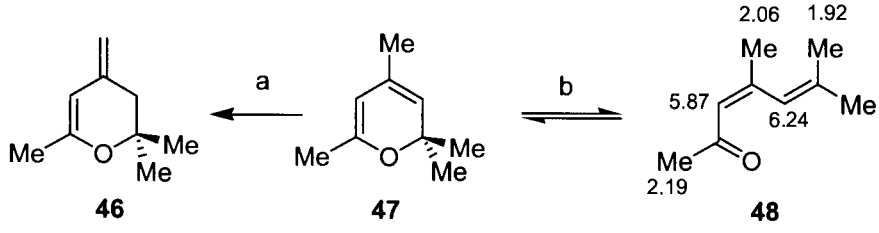
Figure 14 **^{1}H NMR spectral data for *cis*-β-ionone (41) and the corresponding 2*H*-pyran (42).**

The above process was repeated a number of times with a single sample with no apparent decomposition. Since both isomers were present in measurable concentration, their interconversion rates were determined directly. The ^{1}H NMR signals for H_b and H_c appeared at chemical shifts δ = 4.89 and 5.60 ppm for the 2*H*-pyran **42** and at δ = 6.03 and 6.38 ppm for *cis*-β-ionone (**41**), respectively. Integration of these separate and well-defined signals was used to measure the relative concentrations of the isomers at equilibrium. For cases

when the direct measurement of the isomerization rates was not possible, an indirect method was used.

2,2,4,6-Tetramethyl-2*H*-pyran (**47**) was also subjected to a similar study of the electrocyclization rate. Initially, carbon tetrachloride was used as the NMR solvent but the only observation was the conversion of the 2*H*-pyran **47** to the tetrahydropyran **46**. However, with anhydrous triethylamine as the solvent and using repetitive scanning, the peaks corresponding to *cis*-dienone **48** were identified (Scheme 9).[21]

Scheme 9 **Study of the 2,2,4,6-Tetramethyl-2*H*-pyran (47)/4,6-Dimethyl-3,5-heptadien-2-one (48) equilibrium. ^{1}H NMR Spectral Data for the *cis*-Dienone (48)**



Reagents and conditions: a) H^+; b) Et_3N.

Further investigations of the equilibrium reaction between dienones and the 2*H*-pyran isomers demonstrated the relationship between the electronic nature of the system and the position of the equilibrium. It was noted that electron-withdrawing substituents in the 2-position generally favoured the closed 2*H*-pyran form.[22,23]

---

(21) Marvell, E. N.; Gosink, T. A. *J. Org. Chem.* **1972**, *37*, 3036.

(22) Gosink, T. A. *J. Org. Chem.* **1974**, *39*, 1942.

(23) Duperrier, A.; Dreux, J. *Tetrahedron Lett.* **1970**, *36*, 3127.

2.3.3 Synthesis of Natural Products *via* Electrocyclization Reactions

Although oxa-6π electrocyclizations are common in Nature the resultant 2*H*-pyrans often undergo further transformations.[14]

An example of this is the biosynthesis of torreyanic acid (**51**) which was isolated from the endophytic fungus *Pestalotiopsis microspore* by Clardy and co-workers (Figure 15).[24]

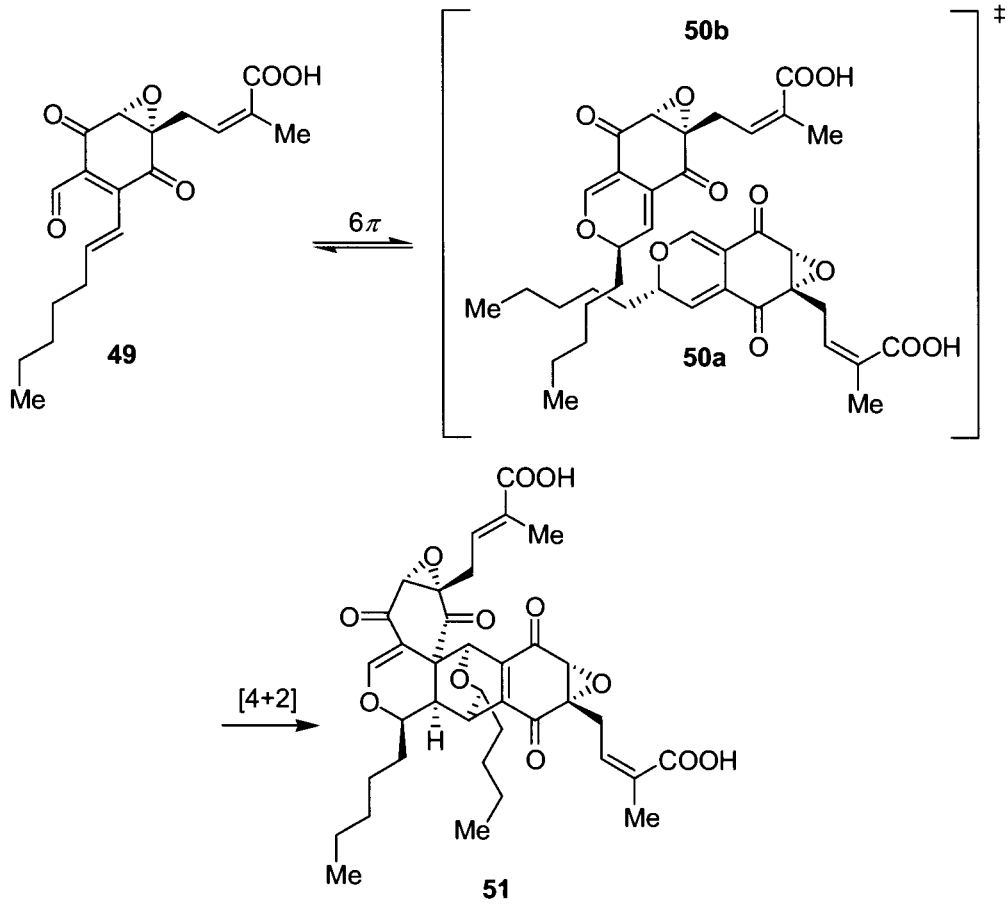
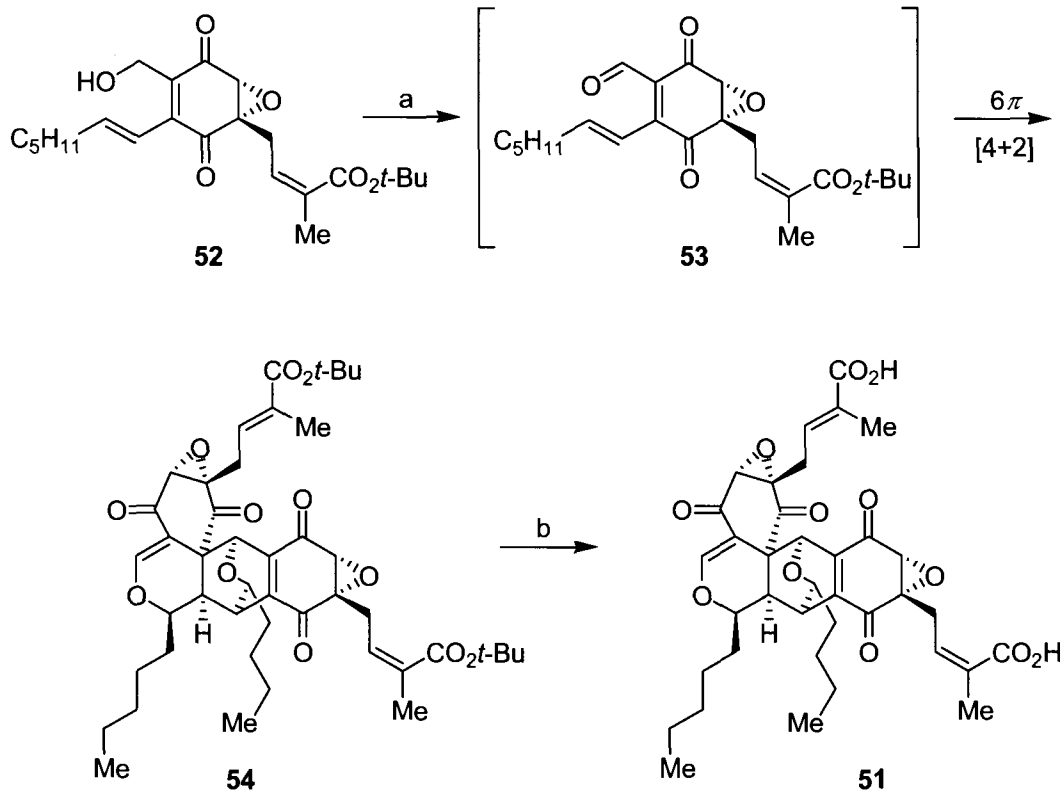


Figure 15 Torreyanic acid (51): Proposed biosynthesis.

(24) Lee, J. C.; Strobel, G. A.; Lobkovsky, E.; Clardy, J. *J. Org. Chem.* **1996**, *61*, 3232.

This complex natural product was proposed to arise from the Diels-Alder dimerization reaction of two diastereoisomeric 2*H*-pyrans, compounds **50a** and **50b**, which are in equilibrium with each other *via* the dienal **49** (Figure 15). The proposed biosynthetic route to torreyanic acid (**51**) was later supported by Porco and co-workers who adopted this concept to synthesize the natural product (Scheme 10).[25]

Scheme 10 Synthesis of Torreyanic Acid (51)



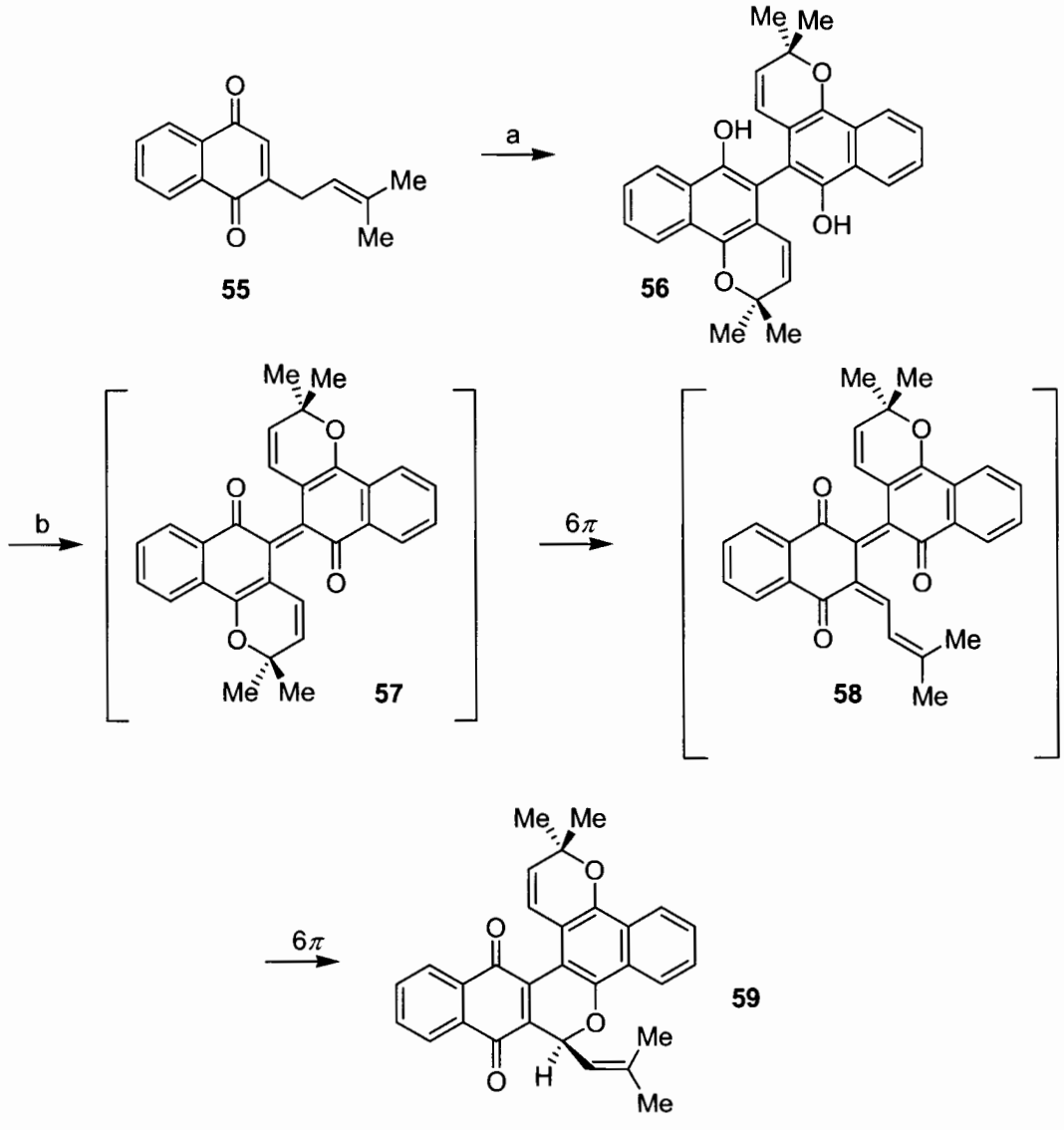
Reagents and conditions: a) Dess-Martin periodinane, CH_2Cl_2, 1.5 h, 80%; b) TFA/ CH_2Cl_2, 0 °C, 2 h, 100%.

Treatment of the enantiomerically pure quinone epoxide **52** with Dess-Martin periodinane led to the formation of the aldehyde **53** which underwent the

(25) Li, C.; Johnson, R. P.; Porco, J. J. A. *J. Am. Chem. Soc.* **2003**, *125*, 5095.

proposed electrocyclization–dimerization reactions to afford compound **54** as a single diastereoisomer. Deprotection of the carboxylic acid moieties then afforded torreyanic acid (**51**).

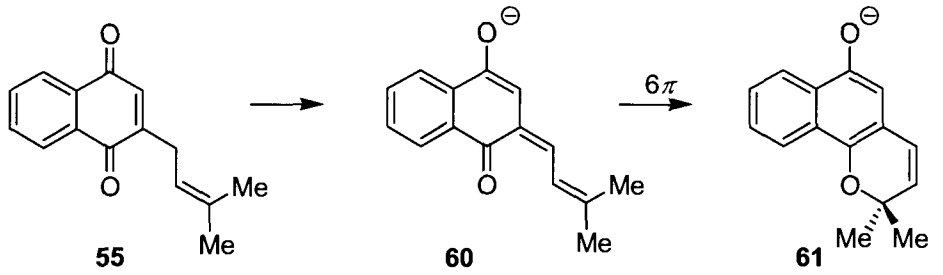
Scheme 11 Synthesis of Tecomaquinone I (59)



Reagents and conditions: a) pyridine, $Cu(OAc)_2$, b) $Cu(OAc)_2$, Et_2O.

A series of electrocyclization reactions was used by Thomson in the synthesis of tecomaquinone I (**59**).[26] Dissolution of deoxylapachol **55** in pyridine followed by reaction in presence of copper(II) acetate afforded the natural product tectol (**56**) (Scheme 11). Further oxidation of tectol with either copper(II) acetate or DDQ gave tecomaquinone I (**59**). The postulated intermediate **57** was the original structure proposed for teicomaquinone I. However, subsequent electrocyclic ring opening of compound **57** to afford **58**, followed by ring closure involving a different carbonyl group, led to the natural product **59**. In addition, the transformation of deoxylapachol **55** to tectol (**56**) probably proceeded *via* the 6π-electrocyclization of compound **60** which afforded the phenolate **61**. Oxidative coupling of the resultant phenolate **61** then afforded the natural product tectol (**56**).

Scheme 12 Electrocyclization Reaction Involved in the Synthesis of Tecomaquinone I (59)



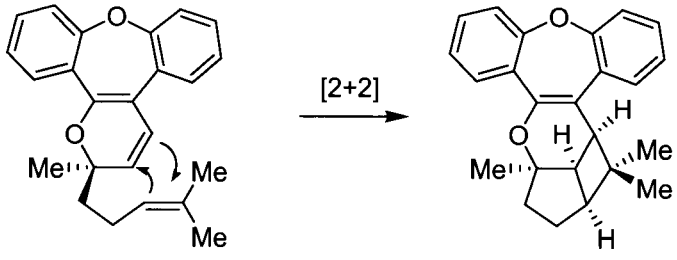
In summary, oxa-6π-electrocyclization reactions have been used in the synthesis of numerous natural products. The equilibrium between the dienone structure and the 2*H*-pyran has been studied and shown to be highly dependent on the electronic properties of the substituents present on the system. In the

(26) Khanna, R. N.; Sharma, P. K.; Thomson, R. H. *J. Chem. Soc. Perkin Trans. 1* **1987**, 1821.

synthesis of artocarpol A analogue **29** experimental results would establish which of the two compounds, the dienone **31** or the 2*H*-pyran **30**, is more stable. Of note, the proposed cross-aldol reaction and the electrocyclization could also occur in a tandem fashion to generate directly the 2*H*-pyran **30** from the oxepinone **33** and citral (**17**).

2.4 The [2+2] Photocycloaddition Reaction

The third proposed key step in the synthesis of the artocarpol A analogue **29** is the [2+2] photocycloaddition reaction of the 2*H*-pyran derivative **30**. This should establish, in one-step, the fused four and five membered rings of the artocarpol A analogue **29** as well install the remaining three stereogenic centres of the natural product (Figure 16).



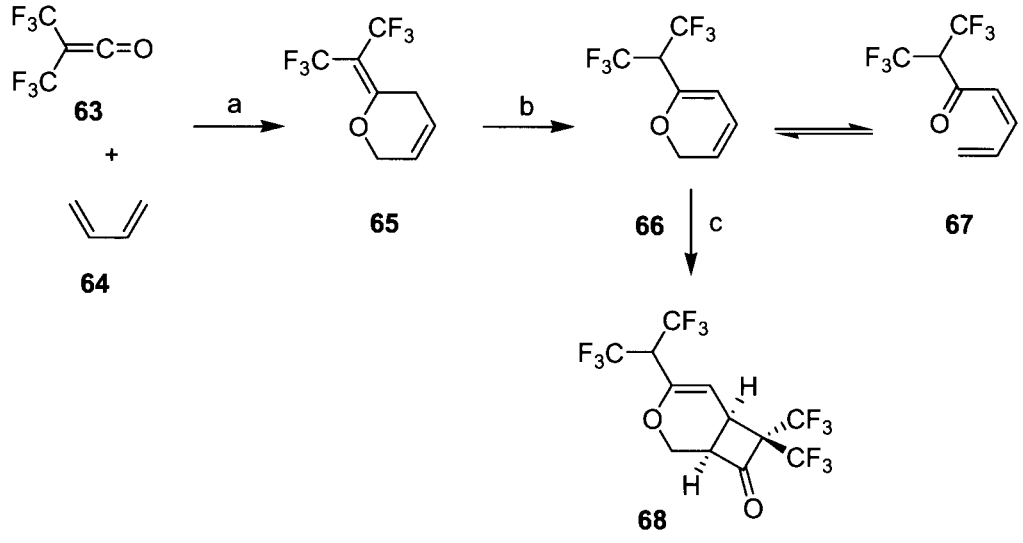
30 **29**

Figure 16 **Proposed synthesis of the artocarpol A analogue (29) *via* [2+2] photocycloaddition reaction of the 2*H*-pyran (30).**

When this research project was initiated there were no examples of [2+2] photocycloaddition reactions of 2*H*-pyran derivatives with alkenes. However,

there was precedent for the reaction of a 2*H*-pyran **66** with a ketene **63** in a [2+2] cycloaddition reaction under thermal conditions (Scheme 13).[27]

Scheme 13 The [2+2] Cycloaddition Reaction of the 2*H*-Pyran (66) with a Ketene Derivative (63)



Reagents and conditions: a) phenothiazine, 60 h, 100 °C; b) hexane, phenothiazine, 16 h, 70 °C; c) ketene 63, **hydroquinone, 16 h, 100 °C.**

The ketene derivative **63** reacted in a [2+4] cycloaddition reaction with butadiene (**64**) to afford the pyran **65**. Isomerization of the exocyclic double bond of the pyran **65** in basic medium afforded an equilibrium mixture containing the 2*H*-pyran **66** and the dienone **67**. This mixture was then reacted with the ketene derivative **63** in presence of hydroquinone at 100 °C to afford the [2+2] cycloaddition adduct **68** (Scheme 13).

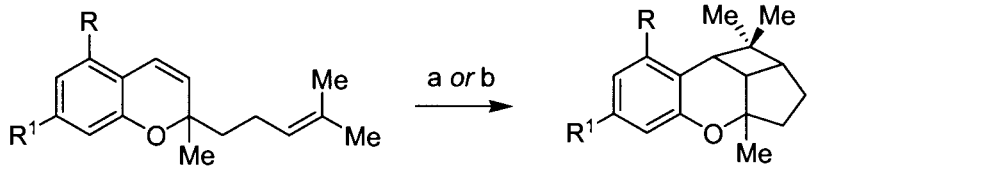
The [2+2] photocycloaddition reaction of the 2*H*-pyran proposed in the total synthesis of the artocarpol A analogue **29** has been successfully applied to 2*H*-chromenes in order to generate the fused four, five, six ring structure of the

(27) England, D. C.; Krespan, C. G. *J. Org. Chem.* **1970**, *35*, 3300.

natural products cannabicyclol (**72**) and rhododaurichromanic acids A (**75**) and B (**76**). 2*H*-Chromenes have the same ring structure as the 2*H*-pyrans but are also fused to a benzene ring.

Cannabicyclol (**71**), a member of the cannabinoid family of natural products, was synthesized *via* the [2+2] photocycloaddition reaction of an acetone:*t*-butanol (1:1) solution of cannabichromene **69** (Scheme 14).[28,29] The structurally related 2*H*-chromene **70** underwent a similar reaction in benzene and afforded the cyclic adduct **72** (Scheme 14).[30]

Scheme 14 The [2+2] Photocycloaddition Reaction of 2*H*-Chromene Derivatives (69 and 70)



69, R = OH, R^1 = *n*-C_5H_{11}
70, R = R^1 = H

71, R = OH, R^1 = *n*-C_5H_{11} (*Method a*)
72, R = R^1 = H (*Method b*)

Reagents and conditions: a) hν, PhH, benzophenone, 4 h, 25%; b) hν, t-BuOH, acetone, 4.5 h, 45%.

Rhododaurichromanic acids A (**75**) and B (**76**) were isolated recently from the leaves and twigs of *Rhododendron dauricum* (Ericaceae) together with the known compound daurichromenic acid (**73**).[31] Examination of the 1D and 2D NMR spectra allowed for the chemical structure of the compounds (**75** and **76**) to

(28) Crombie, L.; Ponsford, R. *Tetrahedron Lett.* **1968**, 5771.

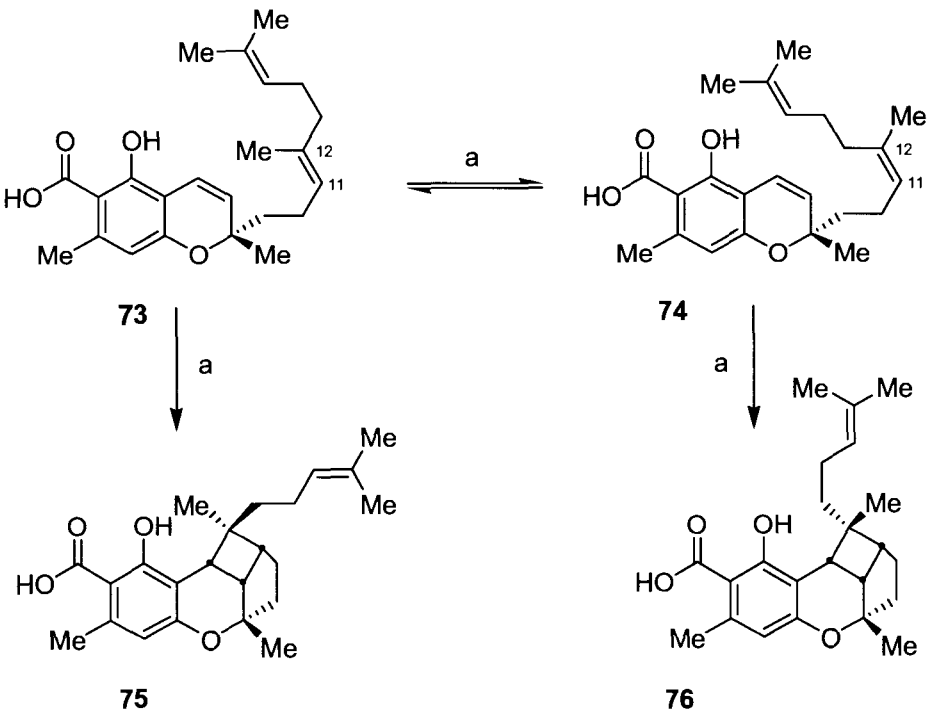
(29) Crombie, L.; Ponsford, R. *J. Chem. Soc.* **1971**, 796.

(30) Yamaguchi, S.; Shouji, N.; Kuroda, K. *Bull. Chem. Soc. Jpn* **1995**, *68*, 305.

(31) Kashiwada, Y.; Yamazaki, K.; Ikeshiro, Y.; Yamagishi, T.; Fujioka, T.; Mihashi, K.; Mizuki, K.; Cosentino, L. M.; Fowke, K.; Morris-Natschke, S. L.; Lee, K.-H. *Tetrahedron* **2001**, *57*, 1559.

be determined but further support came from the photochemical transformation of daurichromenic acid (**73**). A solution of compound **73** in hexane was irradiated with a low-pressure mercury lamp for 12 h to afford rhododaurichromanic acids A (**75**) and B (**76**). Of note, the synthesis of rhododaurichromanic acid B (**76**) was explained by the initial isomerization of the C(11)-C(12) double bond to afford chromene (**74**) followed by a [2+2] photocycloaddition reaction (Scheme 15).[31]

Scheme 15 Photochemical Isomerization and [2+2] Cycloaddition of Daurichromenic Acid (73)

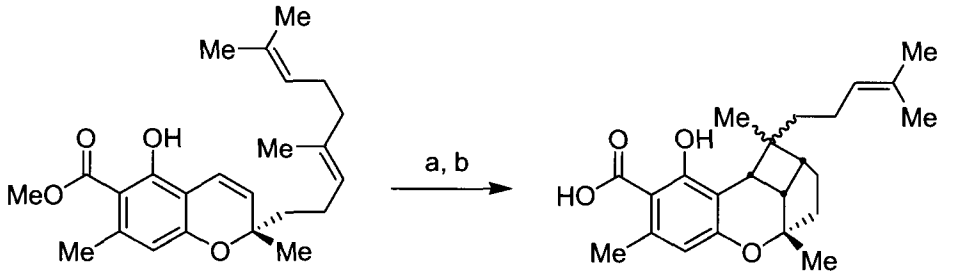


Reagents and conditions: a) hν, n-hexane, 12 h, 75 **(15%),** 76 **(21%).**

Interestingly, both daurichromenic acid (**73**) and rhododaurichromanic acid A (**75**) showed potent anti-HIV activity.[31] Since these initial biological investigations, several syntheses of daurichromenic acid (**73**) and analogues

have been reported.[32,33,34] Two of these syntheses also included the [2+2] photochemical cycloaddition reaction of daurichromenic acid (**73**) or the methyl ester derivative **77** to afford either directly, or after an additional saponification step, rhododaurichromanic acids (**75**) and (**76**) (Scheme 16).[32,33]

Scheme 16 [2+2] Photocycloaddition of the Daurichromenic Acid Methyl Ester (77): Synthesis of Rhododaurichromanic Acids A (75) and B (76)



77 **75 + 76**

Reagents and conditions: a) hν, hexane, room temperature, 65 h, 79%; b) NaOH, MeOH, H_2O, THF, room temperature, 20 h, 75:76 **(1:1, 94%).**

Thus, it was anticipated, in view of the structural relationship between 2*H*-pyrans and 2*H*-chromenes, that the proposed [2+2] photocycloaddition reaction for the synthesis of the artocarpol A analogue **29** should be possible.

2.5 Synthesis and Reactions of the Dibenzo[*b,f*]oxepine System

2.5.1 Introduction

The synthesis of the appropriate oxepinone for the synthesis of artocarpol A analogues was required. However, the oxepine ring in its native as well as in

(32) Kurdyumov, A. V.; Hsung, R. P.; Ihlen, K.; Wang, J.-P. *Org. Lett.* **2003**, *5*, 3935.

(33) Kang, Y.; Mei, Y.; Du, Y.; Jin, Z. *Org. Lett.* **2003**, *5*, 4481.

(34) Hu, H.; Harrison, T. J.; Wilson, P. D. *J. Org. Chem.* **2004**, *69*, 3782.

its reduced form occurs only in a small number of natural products and the synthesis of these substances have received limited attention.

The first important family of natural products containing an oxepine ring that have been isolated is represented by the cularine alkaloids. The cularines are a group of isoquinoline alkaloids that include, as the largest subgroup, the simple cularines **78** as well as highly oxidized members; the 4-hydroxycularines **79**, the oxocularines **80**, the dioxocularines **81** and the aristocularines **82** that contain oxepine rings (Figure 17).[35]

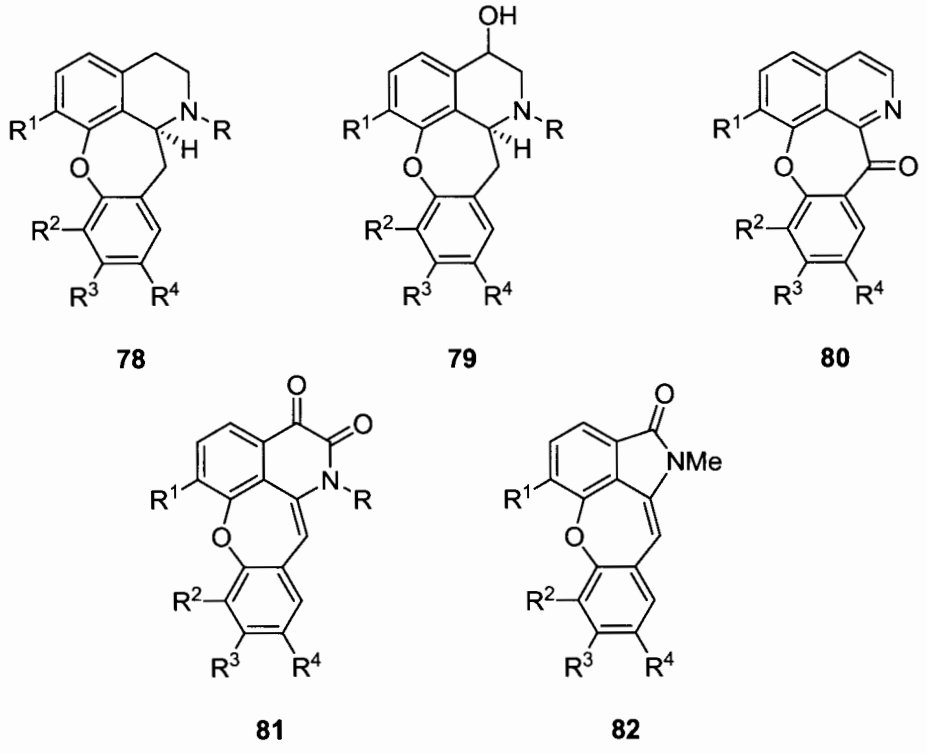


Figure 17 **General structures of cularine alkaloids: Cularines (78), 4-hydroxycularines (79), oxocularines (80), dioxocularines (81) and aristocularines (82).**

(35) Garcia, A.; Catedo, L.; Dominguez, D. *Tetrahedron* **1995**, *51*, 8585.

2.5.2 Synthesis of the Functionalized Dibenzo[*b,f*]oxepine Ring System

The dibenzo[*b,f*]oxepine system has been of interest to the field of medicinal chemistry due to the occurrence of the ring systems in several drug candidates. Even though the synthesis of dibenzoxepines represents a growing field due to the requirements of medicinal chemistry investigations, a limited number of approaches for their synthesis have been developed to date. The two most common approaches are; a) intramolecular C–O bond formation *via* the Ullmann ether r or aromatic nucleophilic substitution (S_NAr) reactions and b) cyclodehydration or intramolecular Friedel-Crafts acylation reaction of intermediates with a preformed biaryl ether bond (Figure 18). The choice of which of these two procedures or their sequence is largely dependent on the nature of the aromatic substituents.

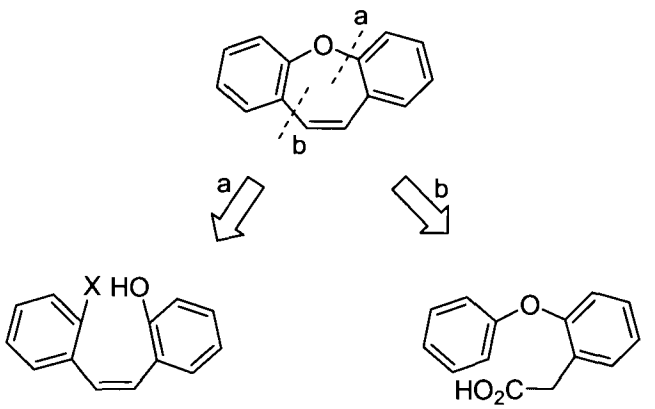


Figure 18 Common disconnections of the dibenzoxepine ring system: a) Biaryl ether bond formation and b) Cyclodehydration.

The synthesis of dibenzo[*b,f*]oxepines having specific substitution patterns on the nucleus has been difficult due to the limited commercial availability of

functionalized phenoxybenzoic acids. Most methods used for the formation of the biaryl ether bond were based on the Ullmann reactions or the aromatic nucleophilic substitution reactions of fluoroarenes with phenols/phenoxides.[36] The classical Ullmann reaction employs a mixture of metallic copper with copper(I *or* II) oxides but more recently copper(II) oxide has been the preferred reagent for this transformation. One of the main drawbacks of the Ullmann reaction (high reaction temperatures and low tolerance for the presence of functional groups) can be avoided by the appropriate choice of the copper reagent. For example, an Ullmann coupling reaction between the phenolic component **84** and 2-bromobenzoic acid (**83**) was the first step in the synthesis of the oxepinone **88** which is an extremely potent antioxidant isolated from *Saccharomyces cerevisiae*. A substoichiometric mixture of metallic copper and copper(I) iodide was used to promote the reaction. Homologation of the resultant benzoic acid **85** was achieved through a well-established reduction, halogenation, cyanation and hydrolysis protocol (Scheme 17). In many of the reported syntheses of dibenzoxepine compounds the ring system was closed either by Friedel-Crafts acylation or cyclodehydration reactions. The reagent of choice for the cyclodehydration reaction was, in general, polyphosphoric acid but other systems have also been used.[37,38] For example, in the synthesis of oxepinone **88** the annulation process was attempted in presence of several acids such as polyphosphoric and methanesulfonic acids. In every case the reaction

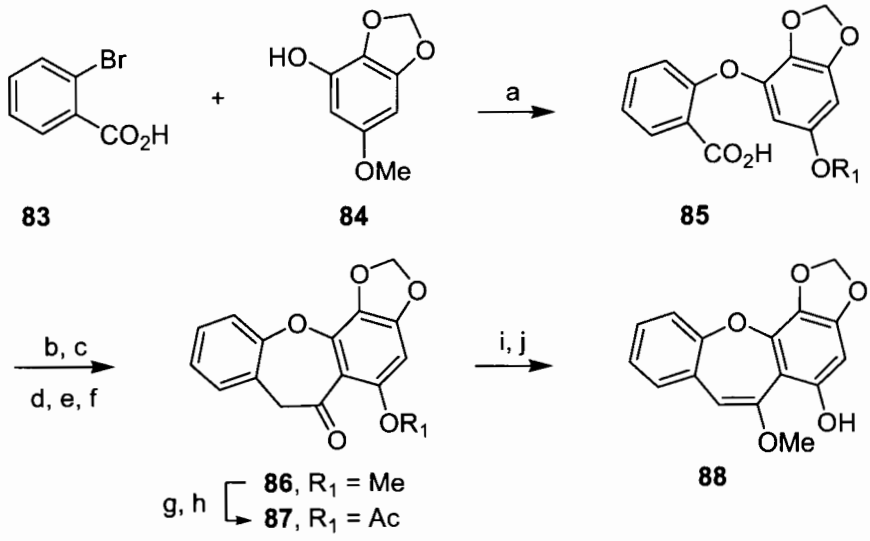
(36) Manske, R. H. F. *J. Am. Chem. Soc.* **1950**, *72*, 55.

(37) Rosowsky, A. *Seven-Membered Heterocyclic Compounds Containing Oxygen and Sulfur*; John Wiley and Sons, Inc.: New York, 1972; Vol. 26.

(38) Manske, R. H. F.; Ledingham, A. E. *J. Am. Chem. Soc.* **1950**, *72*, 4797.

resulted in decomposition of the starting material. After extensive experimentation, the dibenzo[*b,f*]oxepin derivative **86** was obtained under rather unusual conditions involving the use of trifluoroacetic anhydride and boron trifluoride diethyletherate (Scheme 17).[39]

Scheme 17 Synthesis of the Antioxidant 1-Hydroxy-3,4-methylendioxy-11-methoxydibenzo[*b,f*]oxepine (88)



Reagents and conditions: a) CuI, Cu (30 mol%), K_2CO_3, 1-methyl-2-pyrrolidinone, 120 °C; b) $NaBH_4$, $BF_3{\cdot}Et_2O$, THF, 0 °C to room temperature; c) PBr_3, CH_2Cl_2, 0 °C; d) NaCN, DMSO, 80 °C; e) NaOH (aq.), EtOH, THF, 110 °C; f) $(CF_3CO)_2O$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C; g) BBr_3, DMS, CH_2Cl_2, 0 °C; h) KO*t*-Bu, AcCl, THF, -78 °C; i) $CH(OMe)_3$, camphorsulfonic acid, MeOH, 80 °C; j) $NaHCO_3$ (aq), MeOH.

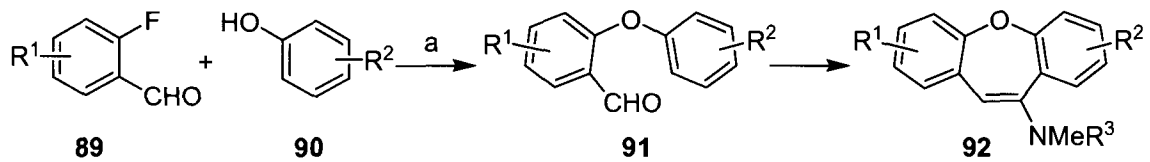
The aromatic nucleophilic substitution reaction of appropriate *ortho*-substituted aryl fluorides with phenols under mild alkaline conditions offers an alternative to the Ullmann coupling reaction. Depending on the availability of these substrates, as well as the compatibility and endurance of the chemical functional groups, either of these methods can be used. In the synthesis of

(39) Jinno, S.; Okita, T. *Heterocycles* **1999**, *51*, 303.

dibenzo[*b,f*]oxepines most of these S_NAr reactions involve heating the reactants in the presence of an inorganic base.

Dibenzo[*b,f*]oxepines **92** bearing different aminomethyl side chains and aromatic substituents, were prepared at Novartis for structure-activity studies for the treatment of neurodegenerative diseases. The phenoxyphenyl-benzaldehyde derivatives **91** were obtained in a nucleophilic aromatic substitution reaction of the *ortho*-fluorobenzaldehydes **89** and phenols **90** using potassium carbonate as base (Scheme 18). Further functional group interconversions and intramolecular ring-closing reactions allowed for the synthesis of the targeted 10-aminomethyl-dibenzo[*b,f*]oxepines **92**.[40,41]

Scheme 18 Biaryl Ether Bond Formation *via* S_NAr Reactions in the Synthesis of 10-Aminomethyldibenzoxepines (92)



89 **90** **91** **92**

Reagents and conditions: a) K_2CO_3, *N,N*-dimethylacetamide, 110 °C.

Another useful method for the facile preparation of biaryl ethers, biaryl thioethers and biaryl amines was developed at the Eli Lilly laboratories.[42] The method involved the use of potassium fluoride – alumina complex and 18-crown-

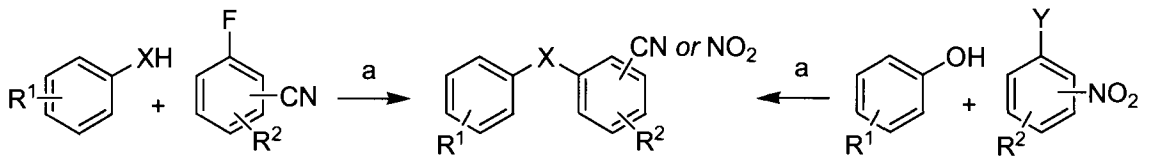
(40) Zimmermann, K.; Waldmeier, P. C.; Tatton, W. G. *Pure Appl. Chem.* **1999**, *71*, 2039.

(41) Zimmermann, K.; Roggo, S.; Kragten, E.; Furst, P.; Waldmeier, P. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1195.

(42) Sawyer, J. S.; Schmittling, E. A.; Palkowitz, J. A.; Smith, I. W. J. *J. Org. Chem.* **1998**, *63*, 6338.

6 in acetonitrile at reflux for the condensation of phenols, thiophenols and certain anilines with fluorobenzonitriles and halonitrobenzenes (Scheme 19).

Scheme 19 Synthesis of Biaryl Ethers, Thioethers and Amines Mediated by $KF{\cdot}Al_2O_3$ and 18-Crown-6



93 **84** **95** **96** **97**

X = O, S, NMe, or NH

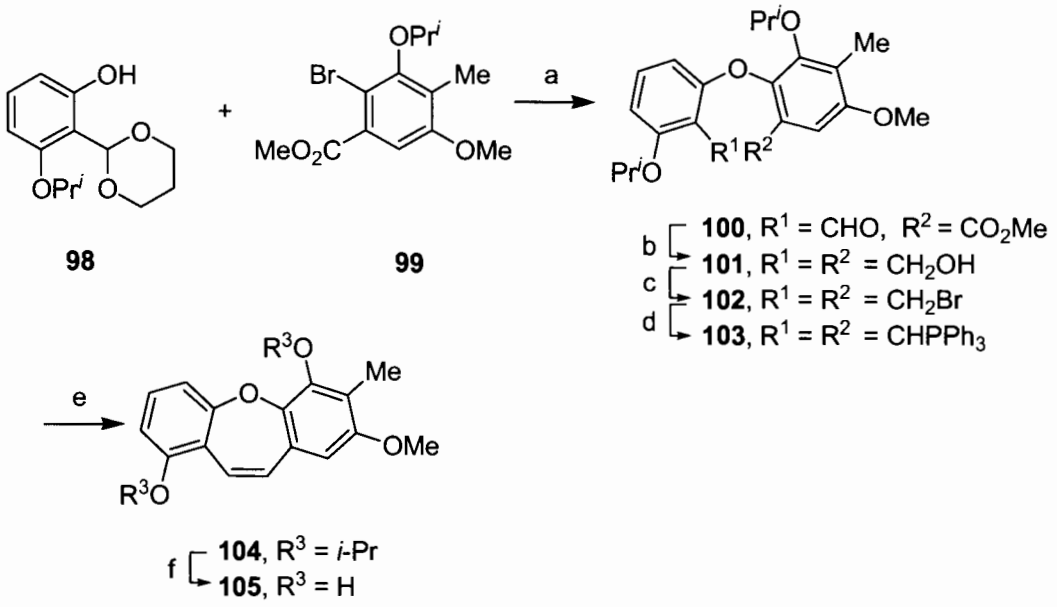
Y = F, Cl, Br, I

Reagents and conditions: a) $KF{\cdot}Al_2O_3$, 18-crown-6, MeCN, reflux.

As an alternative to the cyclodehydration or Friedel-Crafts intramolecular cyclization methods, the ring formation reaction in the case of the synthesis of Pacharin (**105**), a biologically active natural product isolated from the hearthwood of *Bauhinia racemosa Lank*, was achieved by an intramolecular Wittig reaction.[43] Following a condensation reaction between the complex phenol **98** and the bromoarene **99** that was mediated by copper(II) oxide and further functional group transformations, the *bis*-ylide **103** was prepared (Scheme 20). The *bis*-ylide **103** was then employed as a substrate for the intramolecular Wittig reaction. Of note, in this case one of the ylide moieties was reacted with oxygen to afford an aldehyde. Subsequent deprotection afforded pacharin (**105**).

(43) Comber, M. F.; Sargent, M. V. *J. Chem. Soc. Perkin Trans. 1* **1990**, 1371.

Scheme 20 Synthesis of the Biologically Active Natural Product Pacharin (105)

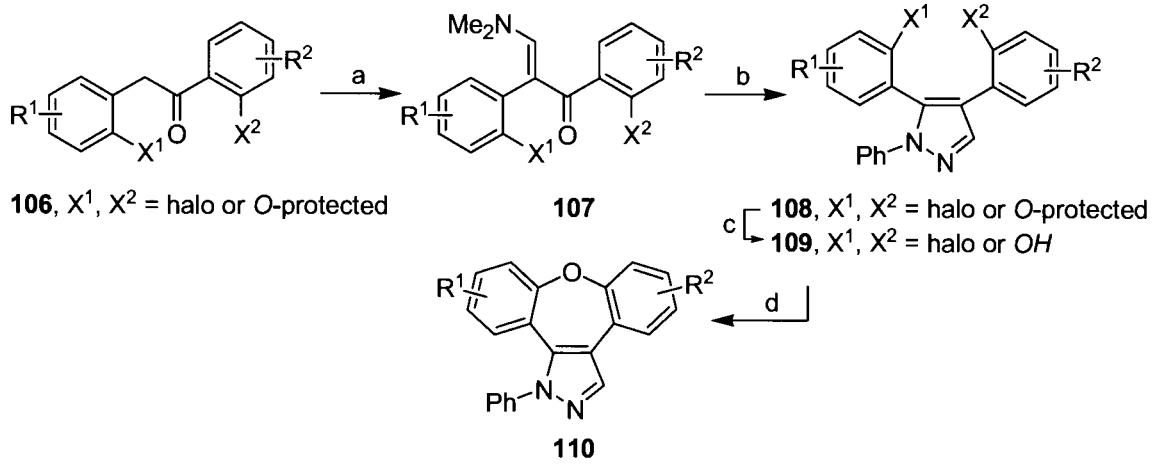


Reagents and conditions: a) CuO, K_2CO_3, pyridine, reflux, then HCl, THF; b) $LiAlH_4$, Et_2O, 0 °C to room temperature; c) PBr_3, CH_2Cl_2, pyridine; d) Ph_3P, DMF, then LiOMe, MeOH; e) O_2; f) BCl_3, CH_2Cl_2, -10 °C to 0 °C.

In a few cases, the formation of the biaryl ether bond has been used as the last step in the synthesis of functionalized oxepines. An example of this strategy was illustrated by the synthesis of polyheterocyclic dibenzoxepines **110** (Scheme 21). The substrates for the Ullmann reaction, the halohydroxy diarylpyrazoles **109**, were obtained from the deoxybenzoins **106** by aminomethylation followed by reaction with hydrazine and subsequent deprotection (Scheme 21). A large number of copper species were screened as reagents to facilitate the biaryl ether bond formation reaction. Many of the methods employed suffered from drawbacks, such as long reaction times and high temperatures, mainly due to the insolubility of copper reagents in the

reaction medium. As a result of these studies, the CuBr·SMe_2 complex was found to be the most suitable reagent for this transformation.[44]

Scheme 21 Synthesis of Heterocyclofused Dibenzoxepines (110): Late Stage Biaryl Ether Bond Formation



106, X^1, X^2 = halo or *O*-protected

107

108, X^1, X^2 = halo or *O*-protected

109, X^1, X^2 = halo or *OH*

110

Reagents and conditions: a) dimethyl formamide dimethyl acetal, PhMe, 90 °C; b) NH_2NHPh, H_2O, MeOH, pH 4; c) KO*t*-Bu, DMF, 0 °C or KOH, MeOH, H_2O, 70 °C or NaOH, MeOH, H_2O, TEBA (cat.), 140 °C (sealed tube); d) CuBr·SMe_2, NaH, pyridine, 120 °C.

2.5.3 Reactions of the Dibenzo[*b,f*]oxepine System

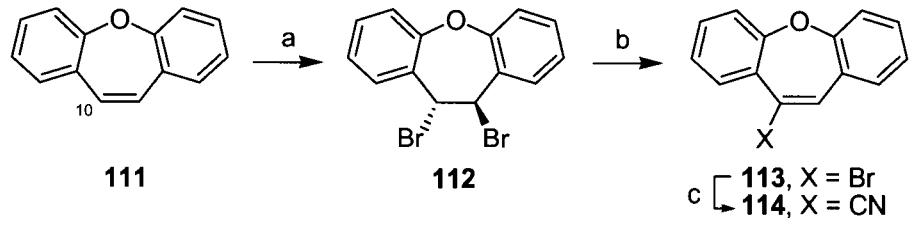
The reactions of the parent dibenz[*b,f*]oxepin **111** were attempted in connection with studies regarding the relative reactivities of the five possible sites that could undergo monosubstitution processes. At that time, the self-consistent field molecular orbital method was being used to predict the orientation of electrophilic aromatic substitutions in alternant polycyclic aromatic compounds. The dibenz[*b,f*]oxepin **111** was well-suited for this purpose since the relative

(44) Olivera, R.; SanMartin, R.; Churruca, F.; Dominguez, E. *J. Org. Chem.* **2002**, *67*, 7215.

reactivities at the five possible sites for monosubstitution processes were difficult to predict from classical resonance theory.[45]

The results of nitration, bromination and deuteration of the dibenzo[*b,f*]oxepin **111** established that the electrophilic substitution took place predominantly at the C(10) position (Scheme 22). The results contradicted two sets of orbital calculations which predicted the C(10) position to have the lowest reactivity for substitution processes. The lack of aromatic character of the dibenz[*b,f*]oxepin **111** was demonstrated, in this case, by its chemical properties.

Scheme 22 Reaction of Dibenz[*b,f*]oxepine (111) with Bromine



Reagents and conditions: a) Br_2, $CHCl_3$, Et_2O, 0 °C, 61%; b) KO*t*-Bu, t-BuOH, 64%; c) CuCN, DMF, pyridine, reflux, 71%.

Since the dibenz[*b,f*]oxepin **111** has been the parent molecule of a large number of clinically active psychotropic drugs possessing central nervous system depressant activity, its molecular structure has been the subject of several studies. It was believed that the pharmacological action of the tricyclic dibenzo derivatives was in part related to the conformation that this class of compounds can adopt.

(45) Bavin, P. M. G.; Bartle, K. D.; Jones, D. W. *J. Heterocycl. Chem.* **1968**, *5*, 327.

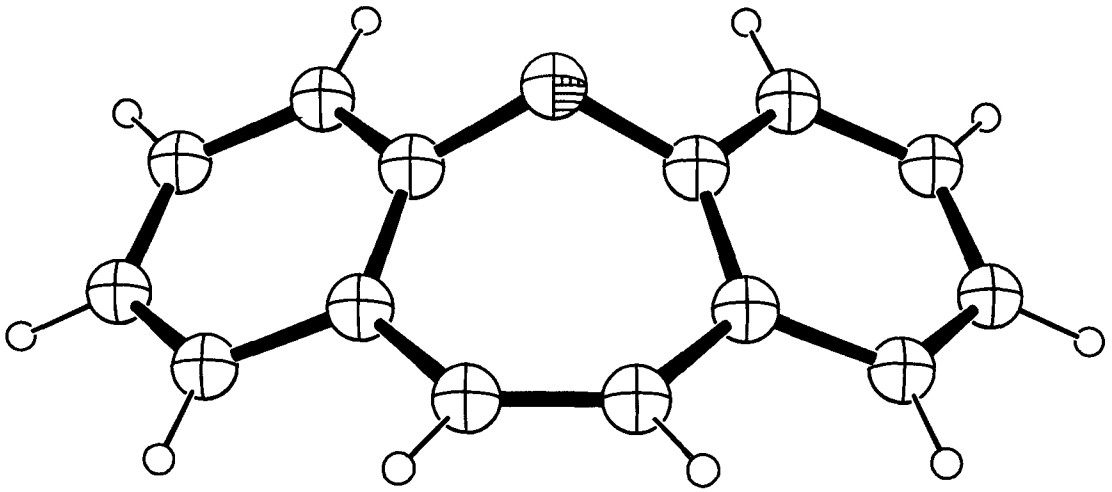


Figure 19 **X-ray crystal structure of the dibenz[*b,f*]oxepine (111). The thermal ellipsoids are drawn at a 30% probability level.**

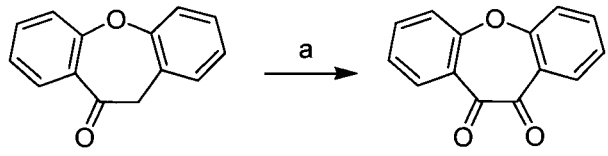
X-ray analysis of the dibenz[*b,f*]oxepin **111** revealed the overall saddle shape of the molecule with the central heterocyclic ring in boat conformation flanked by planar benzene rings, the latter having a "mutual inclination" (Figure 19).[46]

The dibenzo[*b,f*]oxepinone system bears a carbonyl functional group at C(10), therefore either C(10) or the α-carbon can participate in reactions. The two reported reactions involving the α-carbon are oxidation and alkylation. Oxidation of the unsubstituted dibenzo[*b,f*]oxepin-10-one **33** with selenium dioxide afforded the diketo derivative **115**, a key compound for several heterocyclization reactions (Scheme 23).[47]

(46) Drake, J. A. G.; Jones, D. W. *Acta Cryst.* **1982**, *B38*, 200.

(47) Mathys, F.; Prelog, V.; Woodward, R. B. *Helv. Chim. Acta* **1956**, 1095.

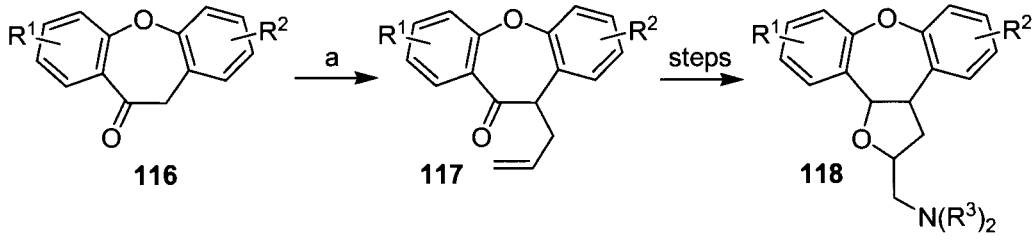
Scheme 23 Oxidation of Dibenzo[*b,f*]oxepin-10-one (33) to the Diketo-Derivative (115)



Reagents and conditions: a) SeO_2

Alkylation of the α-carbon of the substituted dibenzo[*b,f*]oxepin-10-ones **116** has been reported for the synthesis of derivatives that incorporate a fused heterocycle at the C(10)-C(11) bond (dibenzofurooxepines) (Scheme 24).[48] This synthesis was patented by Janssen Pharmaceutica and the first step involved the alkylation of dibenzo[*b,f*]oxepin-10-one derivatives **116** with allyl bromide. The alkylated products **117** was subjected to further functional group transformations and a cyclization reaction to afford the target tetracyclic compounds **118**.

Scheme 24 Synthesis of C(10)-C(11)-Fused Heterocycles from Dibenzo[*b,f*]oxepin-10(11)-one Derivatives (116)



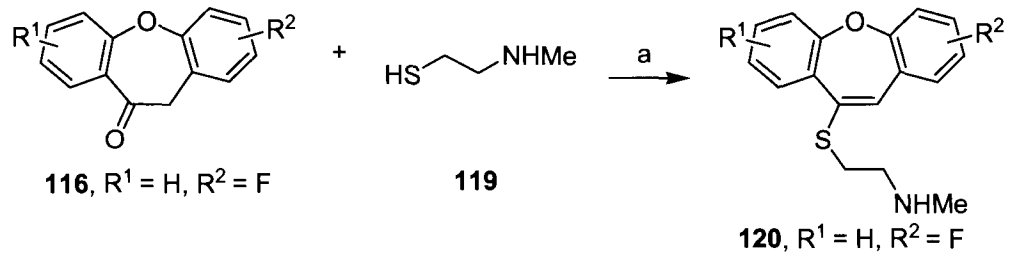
Reagents and conditions: a) allyl bromide, KO*t*-Bu, 80 °C.

Reactions involving the carbonyl carbon of the substituted dibenzo[*b,f*]oxepin-10(11)-one **116** have also been reported in several syntheses

(48) Gil-Lopetegui, P.; Fernandez-Gadea, F. J.; Meert, T. F. *PCT Int. Appl*, WO 9738991.

of dibenzo[*b,f*]oxepine derivatives that have industrial applications.[40,49,50] For example, in the synthesis of fluradoline derivatives (**120**), the carbonyl carbon of the dibenzoxepinone derivative **116** was reacted with the cysteamine derivative **119** under dehydrating conditions (Scheme 25). Fluradoline, that has a fluorine substituent *para* to the biaryl ether bond, has both analgesic and antidepressant activity as it blocks the uptake of norepinephrine and serotonin.[51]

Scheme 25 Synthesis of Fluradoline (120)



116, R^1 = H, R^2 = F **119** **120**, R^1 = H, R^2 = F

Reagents and conditions: a) $BF_3 \cdot Et_2O$, HOAc, 65 °C.

In summary, due to their numerous pharmaceutical and industrial applications, the synthesis of dibenzo[*b,f*]oxepines has been investigated. However, most of the existing synthetic annulation methods rely either on a cyclodehydration of appropriate precursors or on intramolecular biaryl ether bond formation reactions using either Ullmann coupling or S_NAr reactions. Once the ring system is formed there is a limited number of reactions available which can afford highly functionalized dibenzo[*b,f*]oxepine derivatives. Thus, in order to complete the total synthesis of the target natural products, appropriate functional groups should be installed at a relatively early stage.

(49) Bondinell, W. E.; Miller, W. H.; Heerding, D.; Samanem, J. M. *PCT Int. Appl*, WO 9915508.

(50) Boris, A.; Guthrie, R. W.; Kierstead, R. W. *US Patent*, US 4595689.

(51) Ong, H. H.; Flynn, M. J. *US Patent*, US 4496582.

CHAPTER 3: SYNTHESIS OF ARTOCARPOL A, D AND E ANALOGUES

3.1 Introduction

In order to test the validity of the proposed total syntheses of artocarpol A (**1**), D (**4**) and E (**5**), the simplest unsubstituted dibenzo[*b,f*]oxepin-10-one **33** was selected as a model compound. The successful application of the proposed chemistry to this oxepinone should afford the artocarpol A analogue **29**, the artocarpol D analogue **121** and the artocarpol E analogue **122** (Figure 20).

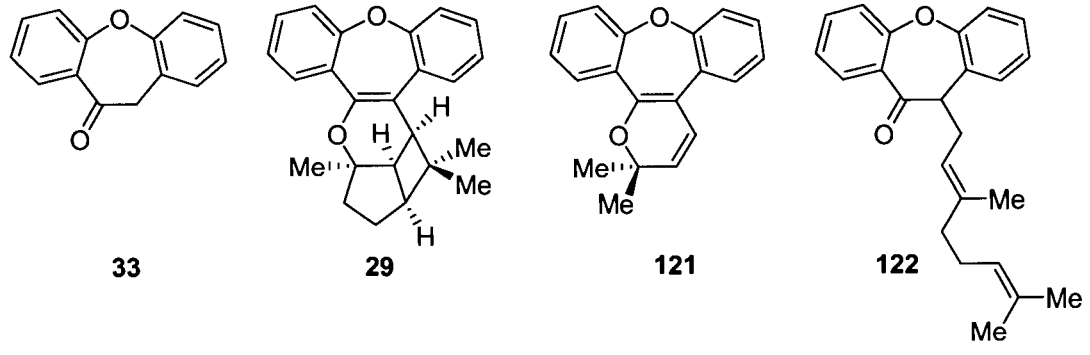


Figure 20 **Structures of the model dibenzo[*b,f*]oxepin-10-one (33) and artocarpol A, D and E analogues (29, 121, 122).**

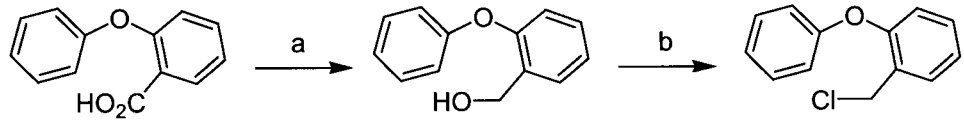
3.2 Synthesis of the 11*H*-Dibenzo[*b,f*]oxepin-10-one (33)

The synthesis of the known compound, 11*H*-dibenzo[*b,f*]oxepin-10-one **33**, began from the commercially available 2-phenoxybenzoic acid (**123**) which was homologated *via* a reduction, chlorination, cyanation and hydrolysis sequence. This homologation sequence has been commonly used in the

synthesis of dibenzoxepine derivatives and was previously applied in the synthesis of the oxepinone **33**.[52,53]

Accordingly, 2-phenoxybenzoic acid (**123**) was reduced with lithium aluminum hydride to afford the corresponding benzylic alcohol **124**. The reduction was complete at room temperature after 24 h. However, under gentle reflux, the reaction time was reduced to 2 h and afforded pure product. The benzyl alcohol **124** was then reacted with thionyl chloride and pyridine to afford the benzyl chloride **125** (Scheme 26).[53]

Scheme 26 Synthesis of 2-Phenoxybenzyl Chloride (125)



123 **124** **125**

Reagents and conditions: a) $LiAlH_4$, THF, 0 °C then reflux, 4 h, 90%; b) $SOCl_2$, pyridine, PhH, reflux, 24 h, 98%.

The one carbon unit was introduced *via* a substitution reaction of the benzyl chloride **125** with sodium cyanide in dimethyl sulfoxide according to a literature procedure.[54] This reaction afforded 2-phenoxybenzyl nitrile (**126**) as a green oil in 90% yield. The nitrile **126** was then hydrolyzed in aqueous ethanol with potassium hydroxide at reflux. Purification of the crude product by

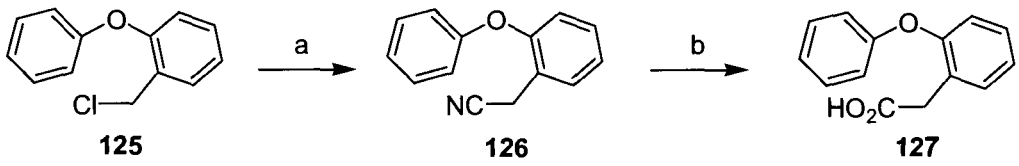
(52) Olivera, R.; SanMartin, R.; Churruca, F.; Dominguez, D. *Org. Prep. Proced. Int.* **2004**, *36*, 299.

(53) Atkinson, D. C.; Godfrey, K. E.; Meek, B.; Saville, J. F.; Stillings, M. R. *J. Med. Chem.* **1983**, *26*, 1353.

(54) Yoshioka, M.; Osawa, H.; Fukuzawa, S. *Bull. Chem. Soc. Jpn* **1982**, *55*, 877.

recrystallization from a mixture of hexanes and ether afforded the homologated acid, 2-phenoxyphenylacetic acid **127** (Scheme 27).[55]

Scheme 27 Synthesis of 2-Phenoxyphenylacetic Acid (127)

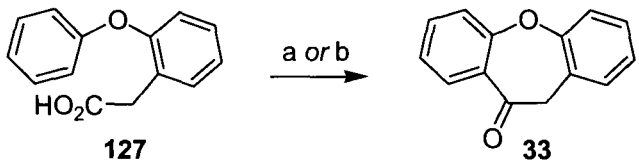


125 **126** **127**

Reagents and conditions: a) NaCN, DMSO, room temperature, 24 h, 90%; b) KOH, EtOH, H_2O, reflux, 4 h, 85%.

Two commonly used cyclization methods were then attempted to prepare the oxepinone ring. According to a literature procedure, the synthesis of the acid chloride derivative of 2-phenoxyphenyl acetic acid (**127**) followed by an intramolecular Friedel-Crafts reaction in presence of aluminum trichloride afforded the desired oxepinone **33**.[55] Thus, on performing these reactions, the pure oxepinone **33** was isolated in 56% yield after purification by flash chromatography (Scheme 28).[56]

Scheme 28 Synthesis of 11*H*-Dibenzo[*b,f*]oxepin-10-one (33)



127 **33**

Reagents and conditions: a) $SOCl_2$, CH_2Cl_2 then $AlCl_3$, CH_2ClCH_2Cl, 2 h, 56%; b) PPA, 100 °C, 4 h, 84%.

---

(55) Ong, H. H.; Profitt, J. A.; Anderson, V. B.; Spaulding, T. C.; Wilker, J. C.; Geyer III, H. M.; Kruse, H. *J. Med. Chem.* **1980**, *23*, 494.

(56) Harris, T. W.; Smith, H. E.; Mobley, P. L.; Manier, D. H.; Sulser, F. *J. Med. Chem.* **1982**, *25*, 855.

Following a second published route for the synthesis of the oxepinone **33**, the cyclodehydration reaction of 2-phenoxyphenylacetic acid (**127**) in presence of polyphosphoric acid at 100 °C was attempted. Slow addition of ice and water during the work-up of the reaction mixture and purification of the crude product by recrystallization from hexanes afforded the pure oxepinone **33** as yellow crystals in 84% yield (Scheme 28). The yield was significantly better than previously reported for these reaction conditions (53%).

The reported literature methods for the synthesis of the oxepinone **33** were modified in order to achieve shorter reaction times, better yields and simpler purification. On a larger scale, only two purification steps were required using this synthetic route and both of these involved recrystallization. After all the optimizations were concluded, gram quantities of 11*H*-dibenzo[*b,f*]oxepin-10-one **33** could be efficiently synthesized.

3.3 Study of the Cross-Aldol Condensation Reaction of 11*H*-Dibenzo[*b,f*]oxepin-10-one (33) with Citral (17) and Senecialdehyde (24)

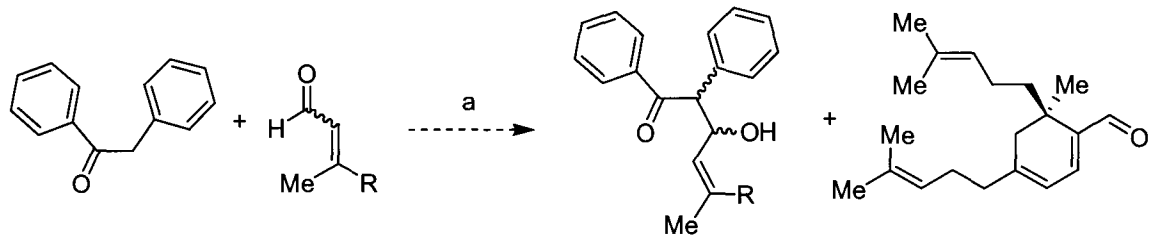
3.3.1 Introduction

In order to prepare the polycyclic ring systems of artocarpol A (**1**) and D (**4**), a study of the cross-aldol reaction of oxepinone **33** with citral (**17**) and senecialdehyde (**24**) was undertaken. However, an initial screen of reaction conditions for the proposed cross-aldol was made with the commercially available acyclic ketone, deoxybenzoin (**128**).

3.3.2 Model Studies with Deoxybenzoin (128) as a Model Compound

The first reaction attempted with deoxybenzoin (**128**) involved the use of lithium *N,N*-diisopropylamide (LDA) (Scheme 29). This base was generated *in situ* at 0 °C from *n*-butyllithium and *N,N*-diisopropylamine. The enolate formation and electrophile addition reactions were performed at -78 °C. With citral (**17**) as the electrophile (2 equiv), the only isolable reaction product was the cyclic aldehyde **131** which was formed *via* a conjugate addition reaction with itself (Figure 21). Slow addition of the electrophile, different reaction temperatures (-78 °C to room temperature) or an increase of the aldehyde/ketone ratio did not influence the outcome of the reaction. The reaction of deoxybenzoin (**128**) with senecialdehyde (**24**) resulted in the formation of a complex mixture of reaction products which could not be separated or characterized.

Scheme 29 Attempted Cross-Aldol Reaction of Deoxybenzoin (128) with Citral (17) and Senecialdehyde (24) in the Presence of LDA



128 **17**, R = $(CH_2)_2CH=C(Me)_2$; **24**, R = Me **129**, R = $(CH_2)_2CH=C(Me)_2$; **130**, R = Me **131**

Reagents and conditions: a) LDA, THF, -78 °C.

The cyclic aldehyde **131** had been previously reported as an undesired product in reactions involving citral (**17**).[11] Deprotonation of the γ-proton of one molecule of citral can afford the extended enolate **132** which can then add in a

conjugate fashion to another molecule of citral (**17**) to afford the adduct **133** (Figure 21). An intramolecular aldol reaction of the adduct **133** then leads to intermediate **134** which can undergo elimination of water to afford the cyclic aldehyde **131** as the final product on work-up.

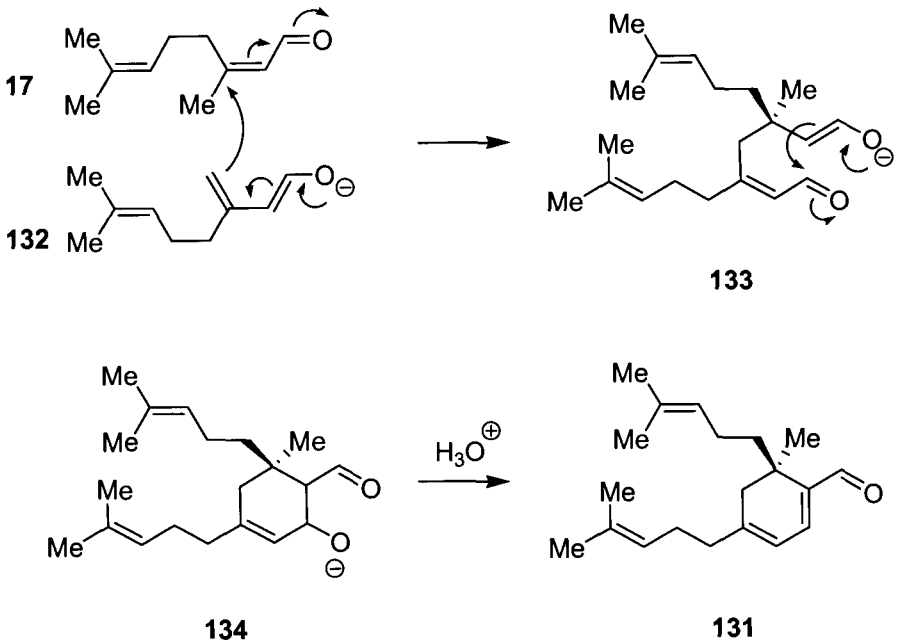


Figure 21 **Mechanism of the self condensation of citral (17): Synthesis of the cyclic aldehyde (131).**

The values of the chemical shifts in the ^{1}H NMR spectrum of the cyclic aldehyde **131** were consistent with the reported literature values (Figure 22). However, the carbon signals in the ^{13}C NMR spectrum were shifted by ~0.3 ppm from the reported values (Figure 23).[11]

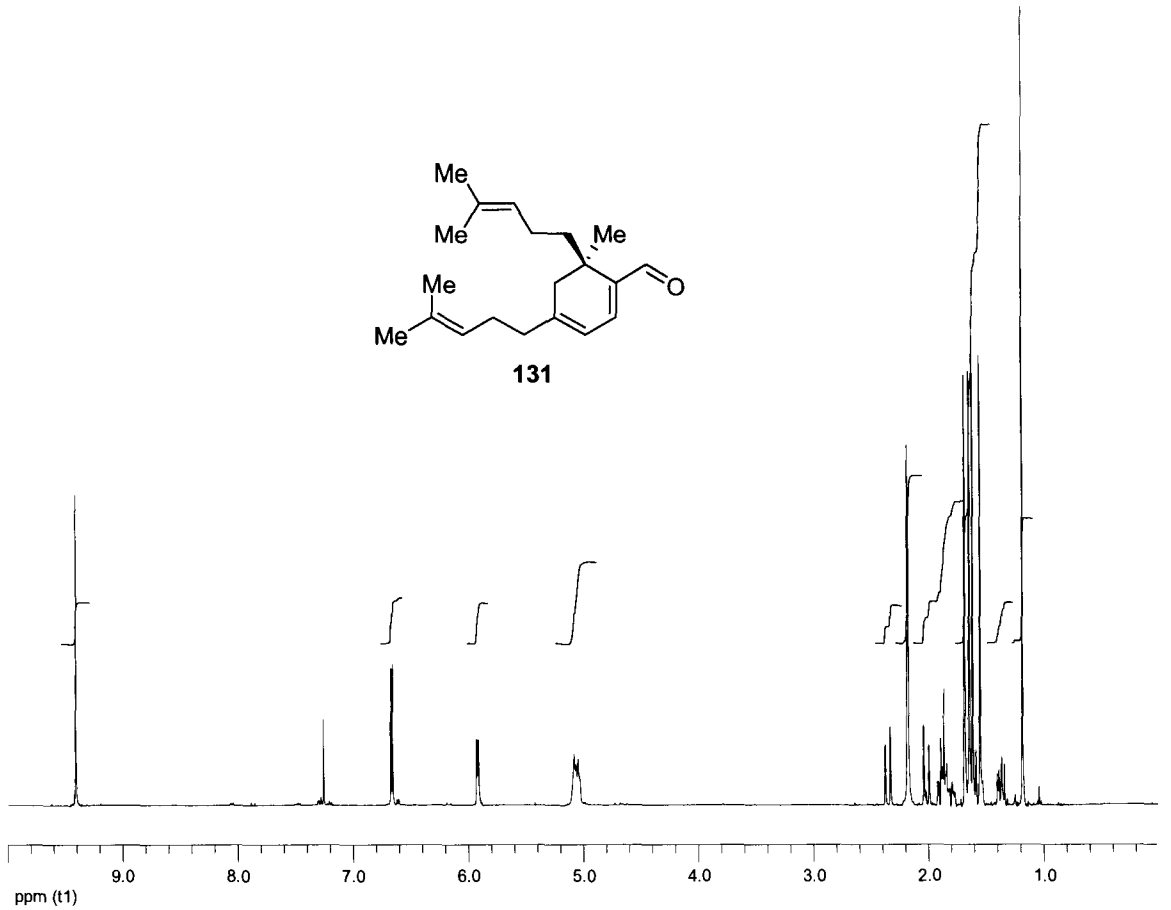


Figure 22 **Detail from the ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of the cyclic aldehyde (131).**

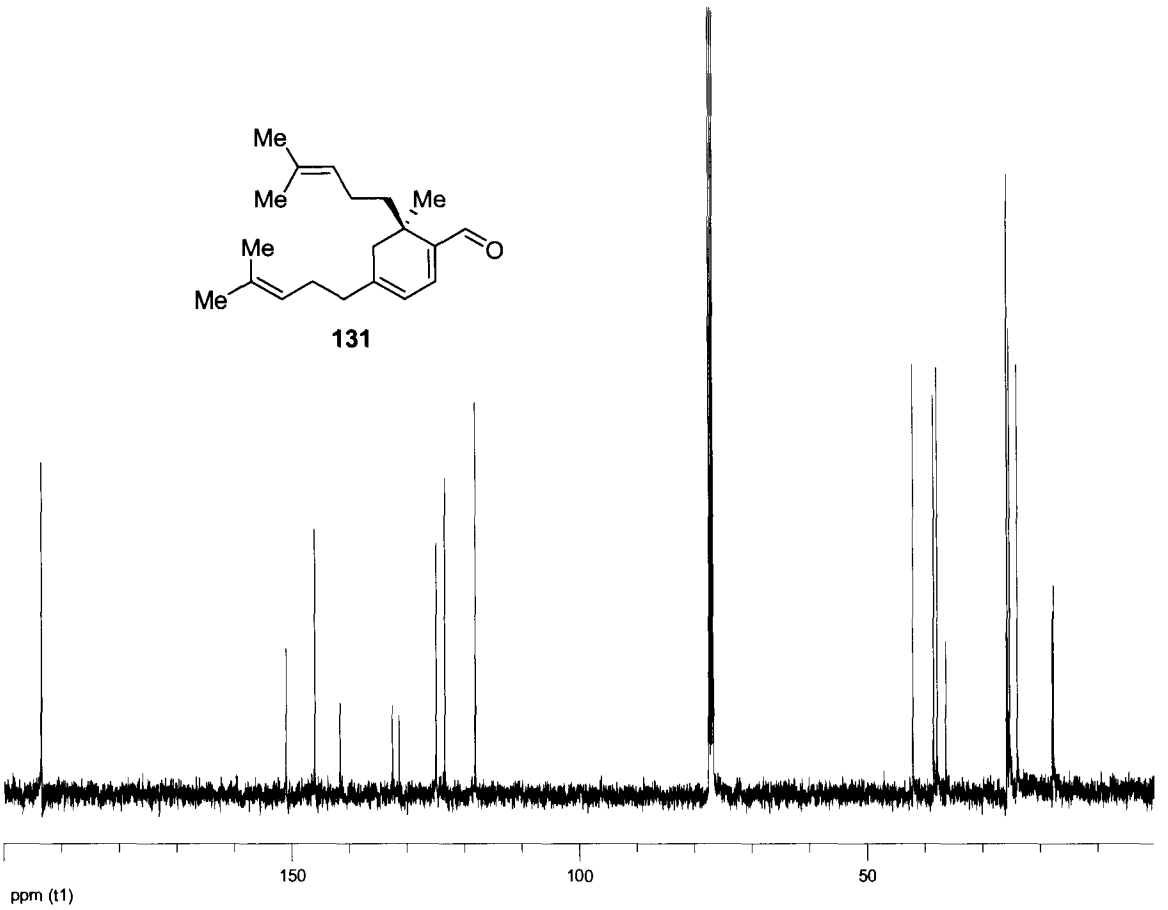


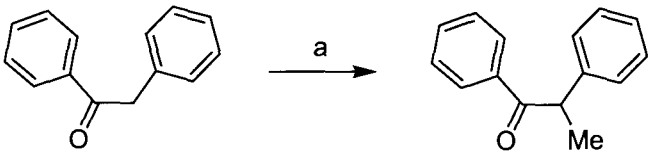
Figure 23 **Detail from the ^{13}C NMR spectrum ($CDCl_3$, 101 MHz) of the cyclic aldehyde (131).**

A possible explanation for the absence of cross-aldol products could have been due to lack of reactivity of the ketone enolate or that the ketone was not deprotonated under the reaction conditions. To clarify this aspect, the presumed lithium enolate of deoxybenzoin (**128**) was prepared in presence of LDA and reacted with trimethylsilyl chloride. However, in this case, the product could not be isolated due to decomposition. The lithium enolate of deoxybenzoin (**128**) was then reacted with methyl iodide.[57] The known mono-alkylated product, 1,2-

(57) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473.

diphenylpropan-1-one (**135**), was obtained exclusively in a very good yield (97%) when the reaction was allowed to reach 0 °C (Scheme 30).[58]

Scheme 30 Alkylation Reaction of Deoxybenzoin (128) with Methyl Iodide

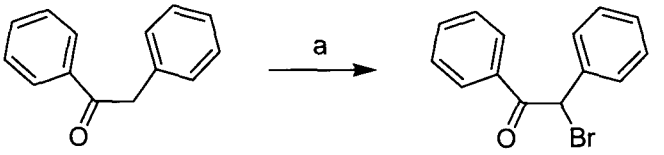


128 **135**

Reagents and conditions: a) LDA, THF, MeI, -78 °C to 0 °C, 1 h, 97%.

The α-carbon was also found to be the most reactive site on reaction with bromine which afforded the known compound, 2-bromo-1,2-diphenylethanone **136** (Scheme 31).[59]

Scheme 31 Bromination Reaction of Deoxybenzoin (128)



128 **136**

Reagents and conditions: a) Br_2, $CHCl_3$, reflux, 20 min, 94%.

Since the above studies showed that the enolate (or corresponding enol) was generated under these conditions, it was probably the lack of appropriate enolate reactivity with the α,β-unsaturated aldehyde which prevented the formation of any cross-aldol products. Of note, the enolate of deoxybenzoin might also be able to deprotonate the α,β-unsaturated aldehyde citral (**17**)

(58) Turro, N. J.; Mattay, J. *J. Am. Chem. Soc.* **1981**, *103*, 4200.

(59) Moreno, I.; Tellitu, I.; Dominguez, E.; SanMartin, R. *Eur. J. Org. Chem.* **2002**, 2126.

therefore preventing the cross-aldol reaction. A way of enhancing the appropriate reactivity of the ketone enolate could be achieved by coordination to a different metal than lithium. Thus, the titanium tetrachloride/amine systems (Evans protocol) was selected as a means to effect this reaction.[60]

The cross-aldol reaction of deoxybenzoin (**128**) with citral (**17**) was attempted in presence of titanium tetrachloride and triethylamine following a literature procedure.[61] Analysis of the thin layer chromatography plate of the reaction mixture suggested the presence of two new compounds. Examination of the ^{1}H NMR spectrum of the crude material confirmed the formation of new compounds together with unreacted starting materials. However, attempted purification of the crude products by flash chromatography resulted in the decomposition of the reaction products and only unreacted starting materials were recovered.

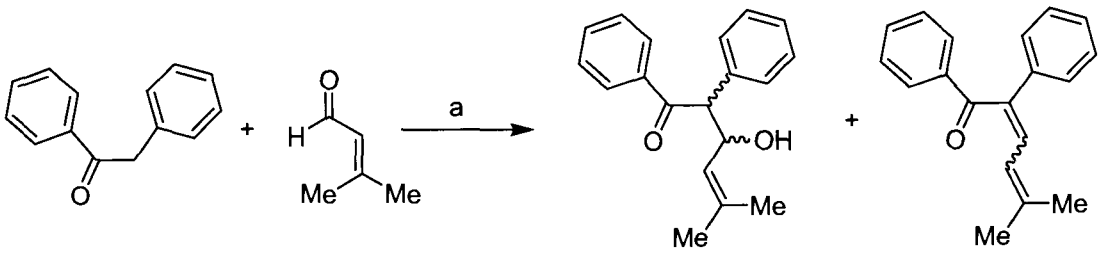
It was subsequently found that the titanium tetrachloride/triethylamine reagent promoted the cross-aldol reaction of deoxybenzoin (**128**) and senecialdehyde (**24**). Depending on the deoxybenzoin/senecialdehyde ratio, the aldol product **130** (at a ratio of 1:3) or the condensation product **137** (at a ratio of 1:1.3) could be isolated in 79% and 68%, respectively (Scheme 32).

---

(60) Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215.

(61) Yoshida, Y.; Hayashi, R.; Sumihara, H.; Tanabe, Y. *Tetrahedron Lett.* **1997**, *38*, 8727.

Scheme 32 The Titanium Tetrachloride / Triethylamine-Mediated Cross-Aldol Reaction of Deoxybenzoin (128) with Senecialdehyde (24)



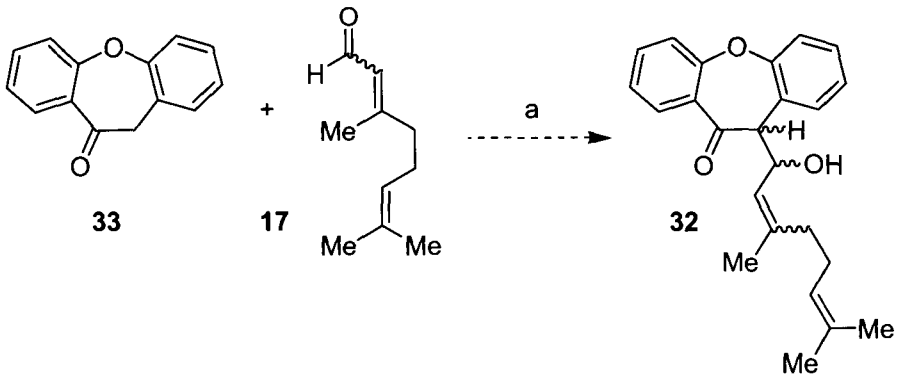
128 **24** **130** **137**

Reagents and conditions: a) $TiCl_4$, Et_3N, CH_2Cl_2, -78 °C, 3 h (see text).

3.3.3 Preliminary Studies with Dibenzo[*b,f*]oxepin-10-one (33)

The initial attempts to couple the 11*H*-dibenzo[*b,f*]oxepin-10-one **33** with citral (**17**) in a cross-aldol reaction were performed with lithium *N,N*-diisopropyl amide (LDA) at -78 °C and the only product isolated was the cyclic aldehyde **131** which resulted from the self condensation reaction of citral (**17**). The absence of cross-aldol products prompted several experiments to be performed in order to investigate the reactivity of the oxepinone **33**.

Scheme 33 Attempted Cross-Aldol Reaction of Oxepinone (33) with Citral (17) in the Presence of LDA

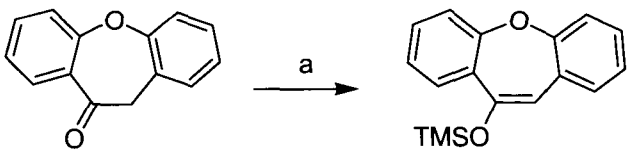


33 **17** **32**

Reagents and conditions: a) LDA, THF, -78 °C.

For the cross-aldol reaction to be successful, LDA had to be able to react with the oxepinone **33** and generate the enolate. In order to confirm that the enolate had formed, the oxepinone **33** was reacted with LDA at -78 °C. And after 30 min, trimethylsilyl chloride was added to the reaction mixture which was then allowed to warm to room temperature.[62] The silyl enol ether **138** was isolated in 98% yield. This established that the oxepinone **33** could be deprotonated to generate the corresponding enolate (Scheme 34).

Scheme 34 Synthesis of the Silyl Enol Ether (138)



33 **138**

Reagents and conditions: a) LDA, TMSCl, THF, -78 °C to 0 °C, 3 h, 98%.

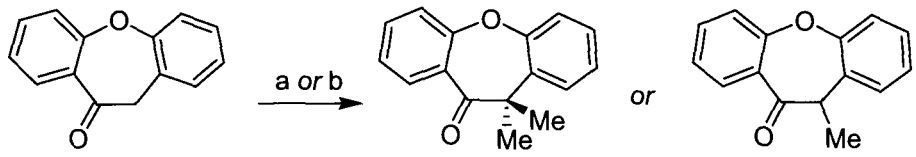
During the synthesis of the silyl enol ether **138** a very important experimental observation was made. After reacting the lithium enolate of the oxepinone **33** with trimethylsilyl chloride for 6 h at -78 °C, no product was formed (as indicated by thin layer chromatography). However, on allowing the reaction mixture to gradually warm to room temperature, and after a few hours at room temperature, analysis of the reaction mixture by thin layer chromatography confirmed the disappearance of the starting material and the formation of a new compound. This was subsequently identified as the silyl enol ether **138**. The

(62) Davis, F. A.; Sheppard, A. C.; Chen, B.-C.; Haque, M. S. *J. Am. Chem. Soc.* **1990**, *112*, 6679.

experiment was repeated under careful temperature control and the first appearance of reaction product was noticed at -25 °C.

A similar temperature influence was seen in the reaction of the lithium enolate of the oxepinone **33** with methyl iodide (Scheme 35). The reaction was monitored by thin layer chromatography and the appearance of the product, the dialkylated ketone **139**, was first noticed at -18 °C.

Scheme 35 Alkylation Reaction of the Oxepinone (33) with Methyl Iodide



33 **139** **140**

Reagents and conditions: a) LDA, MeI, THF, - 78 °C to 0 °C, 1 h, 139 **(80%); b) *n*-Bu_4NHSO_4, NaOH, MeI, CH_2Cl_2, room temperature, 1 h,** 140 **(60%).**

The monoalkylated product **140** was exclusively formed under basic phase transfer conditions, conditions reported for a similar alkylation reaction of a substituted oxepinone (Scheme 35).[63]

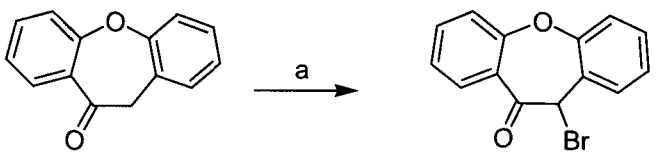
In conjunction to other objectives, it can be noted that one of the aromatic rings in artocarpol A (**1**) is substituted with a prenyl group. There are several methods to introduce a prenyl substituent on an aromatic ring and one of them involves reaction of an aryl bromide with *n*-butyl lithium and cuprous iodide followed by reaction with prenyl bromide.[64]

(63) Acton, D.; Hill, G.; Tait, B. S. *J. Med. Chem.* **1983**, *26*, 1131.

(64) Terashima, K.; Takaya, Y.; Niwa, M. *Bioorg. Med. Chem.* **2002**, *10*, 1619.

The bromination reaction of the oxepinone **33** was expected to introduce an aromatic bromine substituent which could undergo a prenylation reaction. However, the reaction afforded the α-brominated product **141** exclusively. This further indicated the oxepinone was prone to enolization.

Scheme 36 Bromination of the Oxepinone (33)

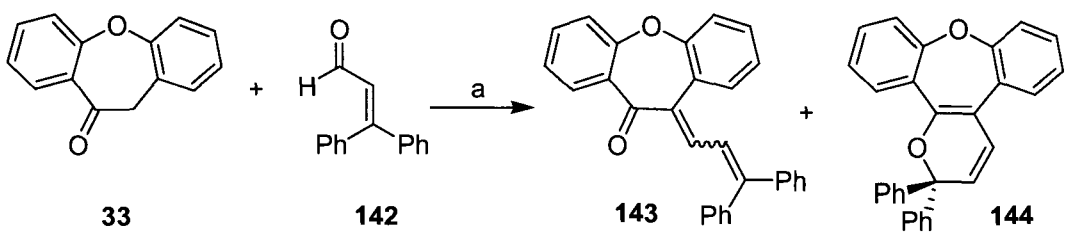


33 **141**

Reagents and conditions: a) Br_2, $CHCl_3$, reflux, 15 min, 63%.

One of the possible reasons for the absence of cross-aldol products, the reactivity of the α-carbon, was proven by the successful synthesis of the methyl alkylated products **139** and **140** and the α-brominated product **141**. A second potential reason for the lack of cross-aldol products, the deprotonation of the γ-proton of the α,β-unsaturated aldehyde by the enolate of the ketone was then investigated. The lithium enolate of the oxepinone **33** was reacted with 3,3-diphenyl acrylaldehyde **142**, an α,β-unsaturated aldehyde lacking γ-protons.

Scheme 37 The Cross-Aldol Reaction of the Oxepinone (33) with 3,3-Diphenyl Acrylaldehyde (142)



33 **142** **143** **144**

Reagents and conditions: a) LDA, THF, -78 °C to room temperature, 24 h, 143 **(80%).**

When the temperature of the reaction was allowed to rise from -78 °C to room temperature, the crystalline cross-aldol condensation product **143** was isolated in 80% yield as a single geometrical isomer (Scheme 37).

Analysis of the ^{1}H NMR spectrum of the product revealed the presence of two doublets at δ = 7.64 ppm and δ = 6.91 ppm (Figure 24). The two signals were assigned to *H*-1' and *H*-2', respectively. The remarkable chemical shift value of the β-proton of the dienone system (*H*-1' in this case) became a diagnostic tool in later experiments. In the ^{1}H NMR spectrum of the dienone **143** there was no evidence of the presence of the corresponding 2*H*-pyran isomer **144**. Probably, either steric hindrance or the extended conjugation involving the aromatic rings prevented the electrocyclic reaction of the dienone **143**. The geometry of the α,β-double bond could not be determined but it was assumed to be *trans* due to steric reasons. The *trans*-configuration of the α,β-double bond would also prevent the desired cyclization reaction.

The successful cross-aldol condensation reaction of the oxepinone **33** with the α,β-unsaturated aldehyde **142** confirmed the hypothesis of the competitive deprotonation of the γ-proton of the more reactive α,β-unsaturated aldehyde citral (**17**) by the lithium enolate of the oxepinone **33**.

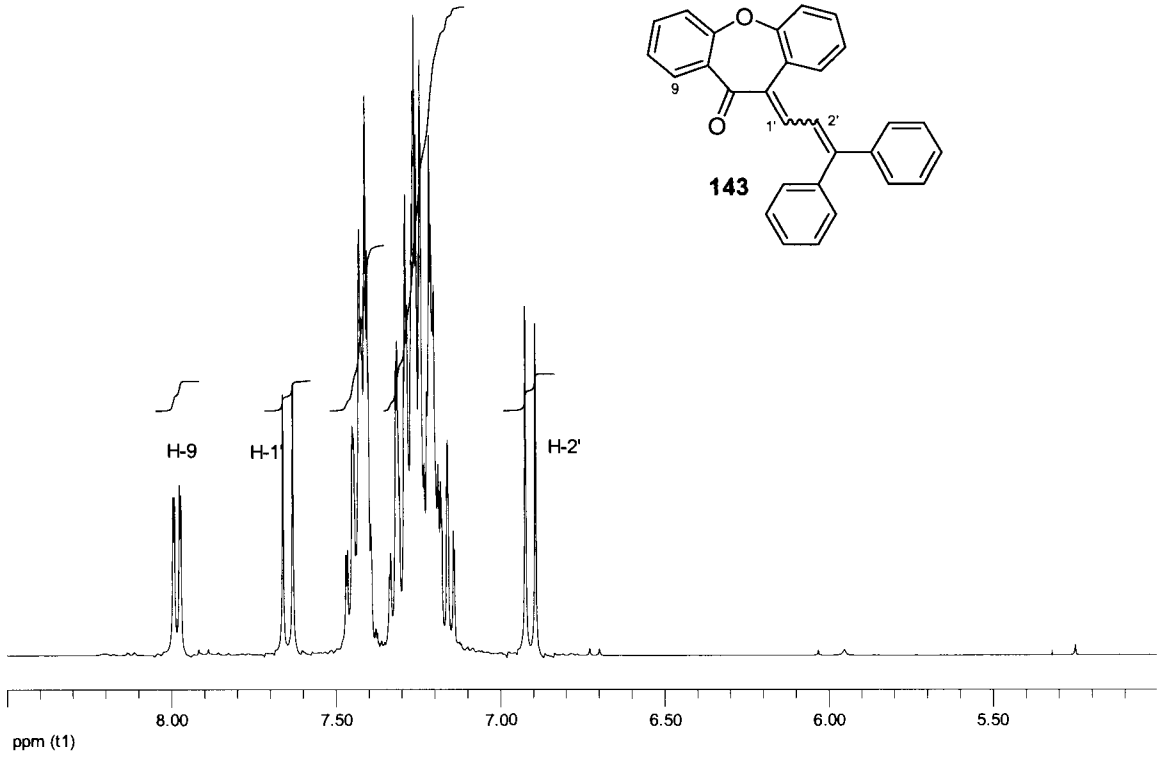
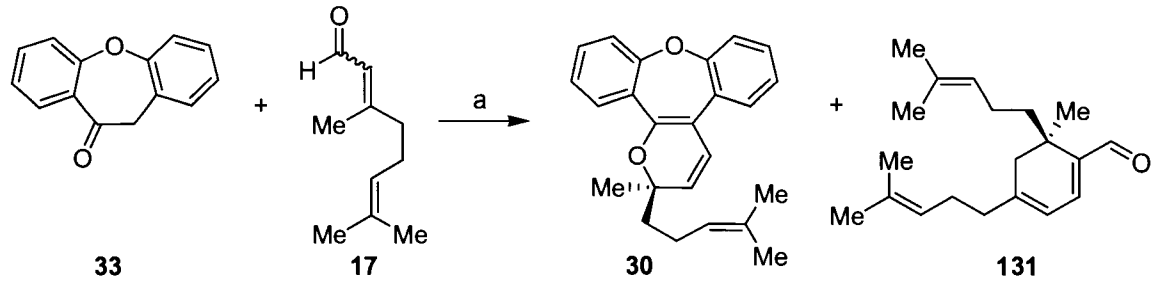


Figure 24 **Detail from the ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of the diphenyl dienone (143).**

The unsuccessful initial attempts to effect the cross-aldol of the oxepinone **33** with citral (**17**) in presence of LDA involved quenching the reaction at -78 °C. Since in subsequent reactions involving the oxepinone **33** it was found that a higher temperature than -78 °C was necessary to form products, the cross-aldol reaction of the oxepinone **33** with citral (**17**) in presence of LDA was repeated under different temperature conditions. The addition of the oxepinone **33** to LDA, and citral (**17**) to the resultant enolate was still performed at -78 °C but the reaction mixture was allowed to gradually warm to room temperature (Scheme 38).

Scheme 38 Synthesis of the 2*H*-Pyran (30) in the Presence of LDA

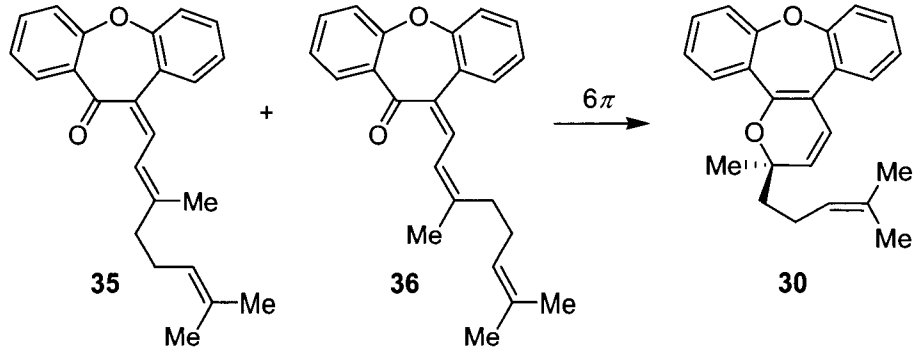


33 17 30 131

Reagents and conditions: a) LDA, THF, -78 °C to room temperature, 10 h, 30 **(18%),** 131 **(24%).**

In this case, the reaction afforded the desired 2*H*-pyran **30** in 18% yield along with the cyclic aldehyde **131** in 24% yield. The 2*H*-pyran **30** was probably formed *via* the proposed electrocyclization reaction of the aldol condensation products **35** and **36** (Scheme 39). These latter dienones have the correct geometrical orientation of the α,β-double bond to undergo the electrocyclization reaction. The other two possible aldol condensation products, the dienones (**38** and **39**), have a *trans* α,β-double bond. This would have prevented the electrocyclization to the 2*H*-pyran **30** (Figure 10).

Scheme 39 Electrocyclization Reaction of the Cross-Aldol Condensation Products (38 and 39) to the 2*H*-Pyran (30)



35 36 30

The 2*H*-pyran **30** was isolated from the reaction mixture by flash chromatography as a yellow oil. A characteristic pair of doublets corresponding to *H*-4 at δ = 6.32 ppm and *H*-3 at δ = 5.55 ppm was observed for this compound by ^{1}H NMR spectroscopy (Figure 25). Another isolated signal, typical for the side chain, was a multiplet at δ = 5.14-5.18 ppm which was assigned to *H*-3'.

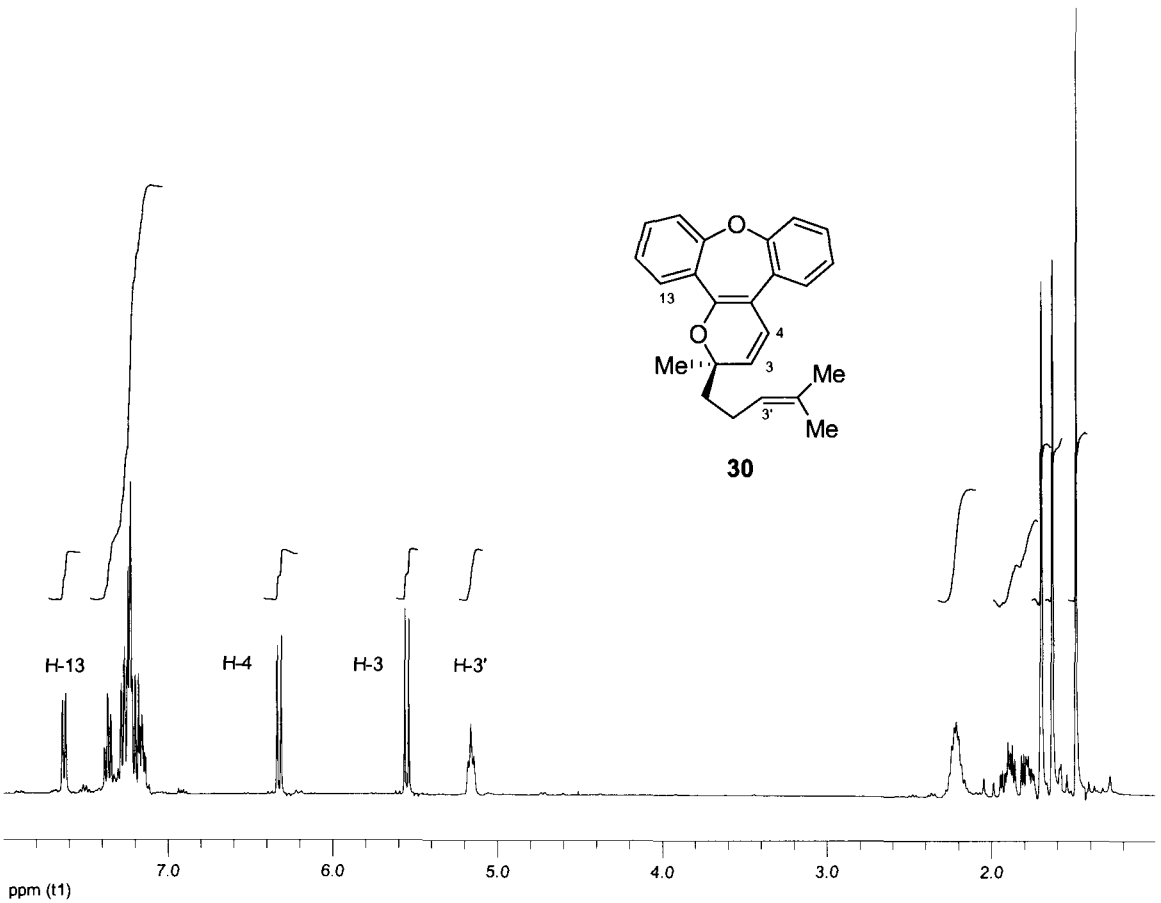


Figure 25 **Detail from the ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of the 2*H*-pyran (30).**

In deuterated benzene, the ^{1}H NMR signals corresponding to *H*-3 (δ = 5.19 ppm) and *H*-3' (δ = 5.12-5.17 ppm) could not be clearly resolved whereas in deuterated chloroform all the diagnostic protons, *H*-4, *H*-3 and *H*-3' gave

separate, well defined signals. However, deuterated benzene was better suited as the NMR solvent for later equilibration studies. The aromatic protons appeared grouped together except for a well resolved doublet of doublets at δ = 7.72 ppm which was assigned to *H*-13. This signal was characteristic for the dibenzoxepinone system in general.

Encouraged by the successful synthesis of the 2*H*-pyran (**30**) in presence of LDA, further modifications of the reaction conditions and/or amide base were attempted in order to increase the yield of the reaction.

3.3.4 The Cross-Aldol Reaction in Presence of Metal-Amide Bases

Different reaction conditions were subsequently investigated in order to effect the cross-aldol reaction of the oxepinone **33** with citral (**17**) using LDA (Scheme 40, Table 2).

Scheme 40 Cross-Aldol Reaction in Presence of Lithium-Amide Bases

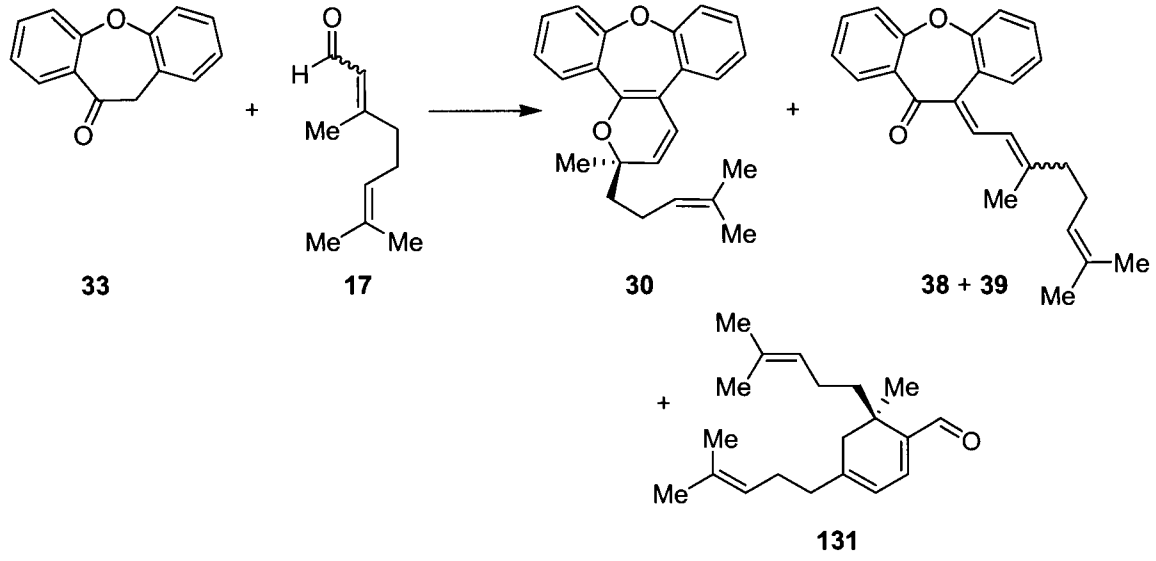


Table 2 The Cross-Aldol Reaction in the Presence of LDA: Reaction Conditions Corresponding to Scheme 40

Entry	Base, Solvent and Additional Reagents	Reaction Temperature	Reaction Products
1	LDA, tetrahydrofuran	-78 °C for 6 h then room temperature for 10 days	2*H*-pyran **30** (20%), cyclic aldehyde **131** (20%)
2	LDA, tetrahydrofuran	-78 °C for 30 min., room temperature for 2 h then reflux 2 days	2*H*-pyran **30** (17%), cyclic aldehyde **131** (23%)
3	LDA Hexamethylphosphor-amide (HMPA), tetrahydrofuran	-78 °C for 6 h then room temperature for 12 days	2*H*-pyran **30** (10%), cyclic aldehyde **131** (20%)

On increasing the reaction time at room temperature from 10 h to 10 days the yield of the reaction was not significantly influenced (Table 2, entry 1). Decreasing the reaction time at -78 °C (30 min as opposed to 6 h) and allowing the reaction mixture to warm to room temperature for 2 h followed by heating at

reflux resulted in the formation of the 2*H*-pyran in a similar yield (17%) (Table 2, entry 2).

A rate study of LDA-mediated ester enolization reactions by Collumn and co-workers revealed important solvation effects.[65] Among the systems studied were LDA/THF and LDA/HMPA/THF and the addition of HMPA was found to increase the rate of reaction. However, the addition of HMPA to the cross-aldol reaction of the oxepinone **33** with citral (**17**) did not seem to influence the rate of the reaction (Table 2, entry 3). The reaction was monitored for 12 days and no significant changes were observed by thin layer chromatography. After 12 days the 2*H*-pyran was isolated in 10% yield.

Cerium enolates prepared from cerium (III) chloride and lithium enolates were found by Imamoto and co-workers to undergo reaction with ketones or aldehydes to afford the corresponding β-hydroxyketones in high yields.[66] The use of the cerium enolate of the oxepinone **33** in the cross-aldol reaction with citral (**17**) did not cause an increase in the overall yield of the reaction (Table 3, entry 1). However, two new cross-aldol products were isolated from this reaction, the dienones **38** and **39**. The geometrical isomers **38** and **39** have the same *trans* α,β-double bond and opposite geometry of the σ,γ-double bond. These compounds, which were isolated in 14% yield, were not separated at this stage.

---

(65) Sun, X.; Collum, D. B. *J. Am. Chem. Soc.* **2000**, *122*, 2452.

(66) Imamoto, T.; Kusumoto, T.; Yokoyama, M. *Tetrahedron Lett.* **1983**, *24*, 5233.

Table 3 Other Reaction Conditions Corresponding to Scheme 40

Entry	Base and Additional Reagents	Reaction Temperature	Reaction Products
1	LDA, $CeCl_3$, tetrahydrofuran	- 78 °C to room temperature then reflux for 3 days	2*H*-pyran **30** (6%), dienones **38** + **39** (14%)
2	Lithium tetramethylpiperidide, HMPA, tetrahydrofuran	-78 °C to room temperature then room temperature for 10 h	2*H*-pyran **30** (traces), cyclic aldehyde **131** (^{1}H NMR analysis)
3	Lithium hexamethyldisilazide, HMPA, tetrahydrofuran	-78 °C to room temperature then room temperature for 10 h	cyclic aldehyde **131** (^{1}H NMR analysis)

Lithium 2,2,6,6-tetramethylpiperidide and lithium hexamethyldisilazide have been employed as strong, hindered and non-nucleophilic bases to generate lithium enolates and found to afford cross-aldol products in higher yields than LDA.[67,68] The use of these two bases together with HMPA according to published procedures afforded the cyclic ketone **131** and only traces of the 2*H*-pyran.[69,70]

In summary, the use of the lithium-amide type bases promoted the cross-aldol reaction of the oxepinone **33** with citral (**17**). However, the best yield of the reaction was rather low (20%) (Table 2, entry 1). The yield of the cross-aldol reaction was similar when the cerium enolate was employed and two new

(67) Campbell, M.; Snieckus, V. *Encyclopedia of Reagents for Organic Chemistry*; John Wiley & Sons: New York, 1995.

(68) Olofson, R. A.; Dougherty, C. M. *J. Am. Chem. Soc.* **1973**, *95*, 582.

(69) Smith, I. A. B.; Richmond, R. E. *J. Org. Chem.* **1981**, *46*, 4814.

(70) Murray, W.; Wachter, M.; Barton, D.; Forero-Kelly, Y. *Synthesis* **1991**, 18.

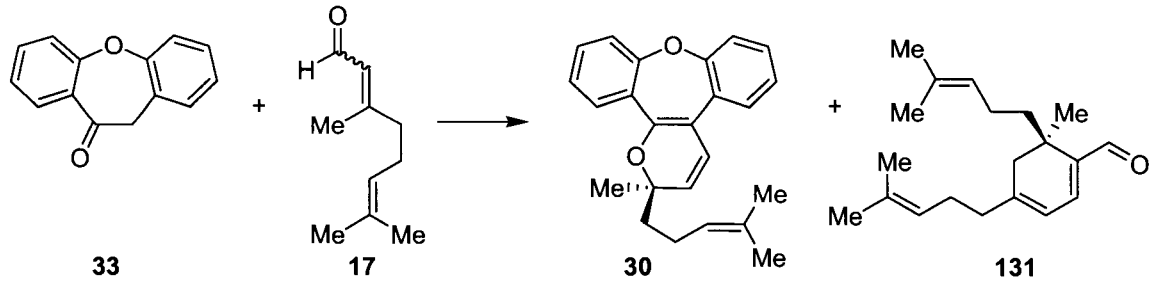
compounds, the dienones **38** and **39** were isolated. The outcome of these reactions seemed to be influenced by temperature and time. The reaction had to proceed at room temperature at least 10 h in order to isolate the 2*H*-pyran **30**. These observations suggested that thermodynamic rather than kinetic reaction conditions would favour the formation of the cross-aldol products and the 2*H*-pyran.

3.3.5 The Cross-Aldol Reaction in the Presence of Alkoxides and Inorganic Bases

Alkoxide-type bases and inorganic bases are also known to promote aldol reactions. Potassium *tert*-butoxide has been used as a catalyst in the cross-aldol reaction of an aliphatic aldehyde with an aromatic ketone affording the cross-aldol product in a high yield.[71] These reaction conditions were employed in the cross-aldol reaction of the oxepinone **33** with citral (**17**). In this case, the 2*H*-pyran was formed but isolated in a low yield (10%) (Table 4, entry 1).

(71) Arai, S.; Shirai, Y.; Ishida, T.; Shioiri, T. *Tetrahedron* **1999**, *55*, 6375.

Scheme 41 Cross-Aldol Reaction in Presence of Alkoxides and Inorganic Bases



33 17 30 131

Table 4 Reaction Conditions Corresponding to Scheme 41

Entry	Base and Additional Reagents	Reaction Temperature	Reaction Products
1	Potassium *tert*-butoxide (KO*t*-Bu), tetrahydrofuran	room temperature for 20 h	2*H*-pyran **30** (10%), cyclic aldehyde **131** (25%)
2	KOH, 18-crown-6, benzene, water	room temperature for 20 h	cyclic aldehyde **131** (20%)
3	NaOH, ethanol, water	room temperature for 48 h	cyclic aldehyde **131** (20%)
4	LiOH, tetrahydrofuran, water	reflux for 5 days	2*H*-pyran **30** (7%), cyclic aldehyde **131** (8%)

The use of potassium hydroxide under phase transfer catalysis conditions or aqueous sodium hydroxide in ethanol has also been reported to promote cross-aldol reactions.[72] On application of these reaction conditions to the present system, exclusive formation of the cyclic aldehyde **131** resulted (Table 4, entries 2 and 3).

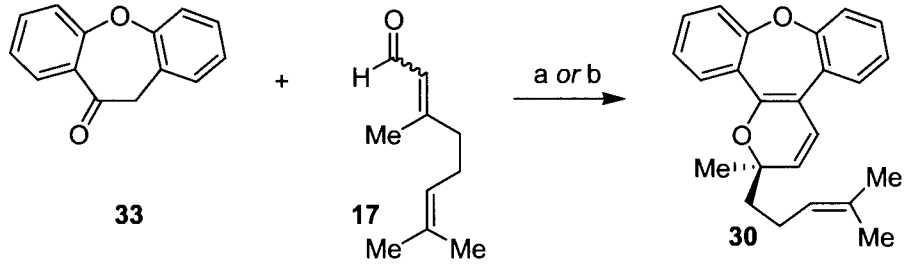
(72) Pathak, V. N.; Pathak, R.; Gupta, R.; Oza, C. K. *Synth. Commun.* **1997**, *27*, 1811.

Subsequently, it was found that the cross-aldol reaction of the oxepinone **33** with citral (**17**) in presence of lithium hydroxide, at reflux in a mixture of tetrahydrofuran and water, afforded the 2*H*-pyran **30** in 7% yield. These results further suggested that a weaker base under thermodynamic conditions was more efficient in promoting the desired cross-aldol reaction and that alternative methods should be explored.

3.3.6 Evans and Mukaiyama Protocols for Cross-Aldol Reaction

The Evans protocol (titanium tetrachloride/amine system) was successfully employed for the coupling of deoxybenzoin **128** and senecialdehyde (**24**) (Scheme 32). Identical reaction conditions were employed to effect the cross-aldol reaction of the oxepinone **33** with citral (**17**) (Scheme 42). Analysis of the thin layer chromatography plate of the reaction mixture revealed the presence of new products which could not be isolated.

Scheme 42 Synthesis of the 2*H*-Pyran (30) *via* the Titanium Tetrachloride / Amine-Mediated Cross-Aldol Reaction: The Evans Protocol



Reagents and conditions: a) $TiCl_4$, Et_3N, CH_2Cl_2, -78 °C, 3 h; b) $TiCl_4$, (i-Pr)$_2$NEt, CH_2Cl_2, -78 °C to room temperature, 20 h; b) PhMe, p-TsOH, reflux, 6 h, 12%.

It has been reported that the titanium tetrachloride/amine system promotes the synthesis of aldol products and not aldol condensation products.[61]

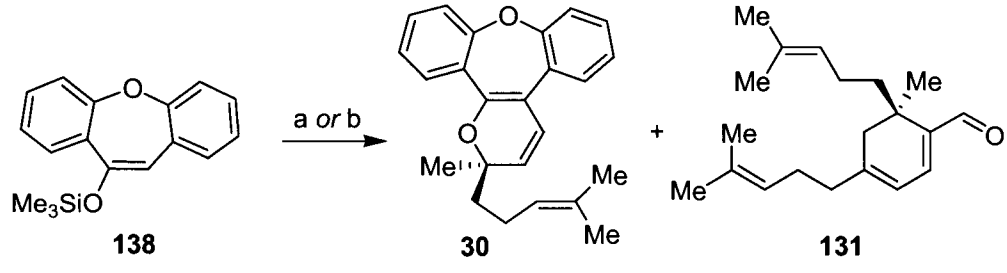
With the assumption that the cross-aldol products might not be stable to purification, several changes were made to the reaction conditions in order to favour the elimination of water from the presumed aldol products. The α,β-unsaturated aldehyde was still used in excess (3 equiv.) and diisopropylethylamine rather than triethylamine was added to the reaction mixture containing the oxepinone **33** and titanium tetrachloride in dichloromethane. No attempts were made to purify the products that resulted after the work-up of the reaction mixture. Instead, the mixture of products was diluted with toluene and heated at reflux in presence of *p*-toluenesulfonic acid for 6 h. The crude product was purified and the 2*H*-pyran **30** was isolated in 12% yield. No self-condensation product was isolated (Scheme 42).

Several decades ago, it was found that upon addition of titanium tetrachloride, trimethylsilyl enol ethers of ketones reacted with ketones or aldehydes at room temperature to give the aldol type addition products.[73] Since then, the scope of the reaction has been greatly extended and the method has became known as the Mukaiyama aldol reaction. One of the most important advantages of the procedure over classical aldol methods was that it allowed for the selective synthesis of cross-aldol products with none of the self-condensation products being formed. Since publication of the first paper in 1973, there have been numerous changes in the experimental procedures associated with the Mukaiyama aldol reaction.

(73) Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, 1011.

The Mukaiyama protocol could not be used in case of deoxybenzoin **128** because the corresponding silyl enol ether could not be isolated. However, following the successful isolation of the silyl enol ether of the oxepinone **33**, the Mukaiyama protocol was attempted with this substrate. The silyl enol ether **138** and citral (**17**) were initially reacted according to the original experimental procedure that involved the addition of a solution of the silyl enol ether in dichloromethane to a flask containing titanium tetrachloride, citral (**17**) and dichloromethane at room temperature.[73] Under these reaction conditions, both the 2*H*-pyran **30** and the cyclic aldehyde **131** were obtained in low yield (Scheme 43).

Scheme 43 The Cross-Aldol Reaction *via* the Silyl Enol Ether Derivative (138): Mukaiyama Protocol



Reagents and conditions: a) $TiCl_4$, citral (17), CH_2Cl_2, room temperature, 3 days, 30 (8%), 131 (7%); b) $TiCl_4$, citral (17), CH_2Cl_2, -78 °C to room temperature, 3 days, 30 (6%).

In a second attempted reaction, a solution of titanium tetrachloride in dichloromethane was added to a mixture of citral (**17**) and silyl enol ether **138** in dichloromethane at -78 °C.[74] The yield of the cross-aldol reaction under these conditions was still low (6%).

(74) Lalic, G.; Petrovski, Z.; Galonic, D.; Matovic, R.; Saicic, R. N. *Tetrahedron* **2001**, *57*, 583.

3.3.7 The Cross-Aldol Condensation Reaction in Presence of Amines

Considering the various reaction conditions attempted above, it was noted that the cross-aldol reaction of the oxepinone **33** with citral (**17**) proceeded with the highest yield in the presence of LDA under thermodynamic conditions. During the extended course of the reaction at room temperature it was possible that the diisopropylamine could have actually catalyzed the cross-aldol reaction. To test this hypothesis, the oxepinone **33** was reacted with citral (**17**) in presence of a stoichiometric amount of diisopropylamine. The reaction mixture was stirred at room temperature for 10 days and purification by column chromatography afforded the 2*H*-pyran **30** in 6% yield as well as the dienones (**38** and **39**) in 10% yield. Since diisopropylamine alone was able to mediate the cross-aldol reaction, a series of small scale reactions, which were monitored by thin layer chromatography, were performed to study the potential of several structurally different amines and reaction conditions.

In the first instance, the oxepinone **33** (~5 mg), citral (**17**) (1 drop) and various amines (1 drop or ~10 mg) were stirred in tetrahydrofuran, at room temperature for three days. The thin layer chromatogram shown below was developed in a mixture of petroleum ether/dichloromethane (1:2) (Figure 26).

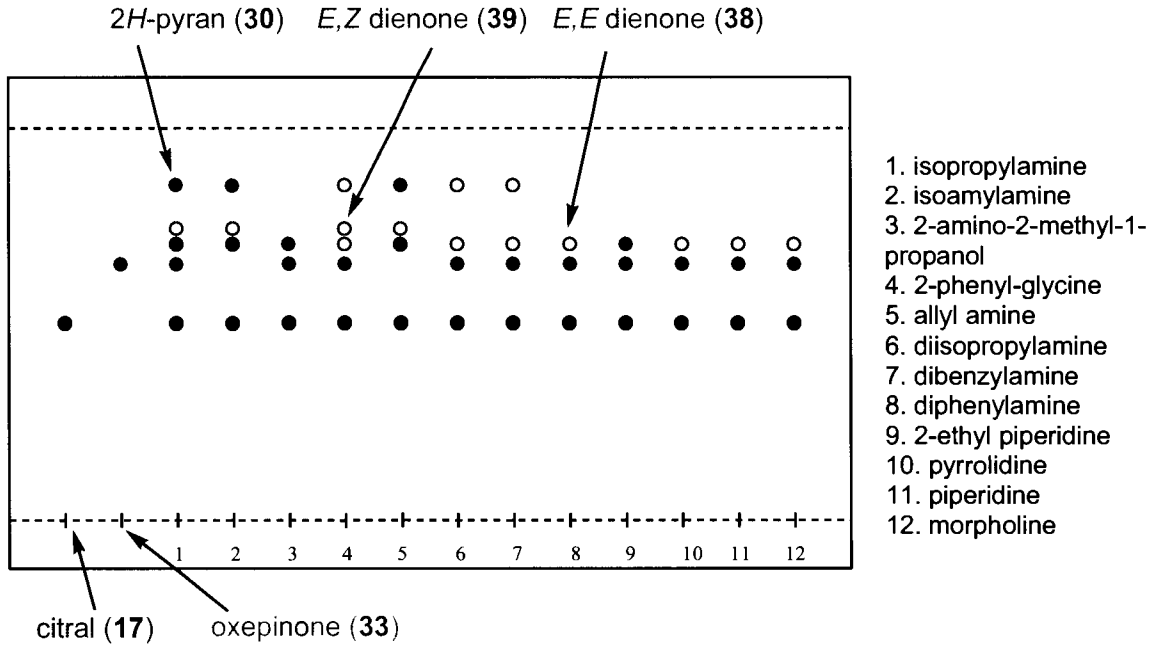


Figure 26 **Thin layer chromatogram corresponding to the study of the cross-aldol reaction: Survey of amines.**

The first five experiments were performed with primary amines. The 2*H*-pyran **30** was present as a major product in reactions that employed isopropylamine, isoamylamine and allylamine. Under these conditions, the cross-aldol condensation products (**38** and **39**) were also present. However, only in the case of isoamylamine and allylamine was the oxepinone **33** consumed. According to the intensity of the TLC spots, the desired products 2*H*-pyran **30** and dienones (**38** and **39**) were formed to a lesser extent in presence of 2-phenylglycine. 2-Amino-2-methyl-1-propanol seemed to favour the synthesis of the *E,E* dienone **38** which was the only cross-aldol product detected.

In the case of non-cyclic secondary amines, diphenylamine seemed to be the least effective, affording only a faint spot that corresponded to the dienone

38. However, diisopropylamine and dibenzylamine afforded trace amounts of all three of these desired products.

The last group of amines investigated in this study included secondary cyclic amines which are known to be effective promoters of cross-aldol reactions.[10] The results for this group were homogeneous in that the dienone **38** was the only cross-aldol product detected. The amount of the dienone **38** seemed to be higher for 2-ethyl piperidine as compared to pyrrolidine, piperidine and morpholine.

This survey of amines suggested that primary amines were the most efficient promoters of the desired cross-aldol reaction. However, these experiments allowed only for qualitative analysis and so preparative scale experiments involving the two most successful primary amines, as well as several other amines, were performed. The results of the experiments are shown below (Table 5).

When a mixture of oxepinone **33**, citral (**17**) and isopropylamine was stirred in tetrahydrofuran (at room temperature for four days) the 2*H*-pyran **30** and a mixture of the dienones (**38** and **39**) were isolated in 7% and 34%, respectively (Table 5, entry 1). Although the overall yield of the cross-aldol reaction was 41%, the yield of the desired 2*H*-pyran product was still low. Considering the dehydration step necessary for the synthesis of the dienone products from the aldol products, the effect of increasing the temperature of the process as well as removal of water from the reaction medium was investigated.

Table 5 Cross-Aldol Reaction in Presence of Primary Amines: Reaction Conditions and Yields of Isolated Products

Entry	Amine used	Reaction Conditions	Reaction Products
1	isopropylamine	tetrahydrofuran, room temperature, 4 days	2*H*-pyran **30** (7%), dienones **38** and **39** (34%)
2	isopropylamine	toluene, reflux, 4 days, Dean-Stark trap	2*H*-pyran **30** (27%), dienones **38** and **39** (14%)
3	allylamine	toluene, reflux, 4 days, Dean-Stark trap	2*H*-pyran **30** (42%), dienones **38** and **39** (10%)
4	(±)-methylbenzylamine	toluene, room temperature, 2 days	2*H*-pyran **30** (7%), dienones **38** and **39** (34%)
5	(±)-methylbenzylamine	toluene, reflux, 4 days, Dean-Stark trap	2*H*-pyran **30** (26%), dienones **38** and **39** (18%)
6	benzylamine	toluene, reflux, 4 days, Dean-Stark trap	2*H*-pyran **30** (18%), dienones **38** and **39** (21%)
7	isopropylamine	tetrahydrofuran, $MgSO_4$, reflux, 8 h	2*H*-pyran **30** (40%), dienones **38** and **39** (20%), cyclic aldehyde **131** (15%)
8	allylamine	tetrahydrofuran, $MgSO_4$, reflux, 8 h	2*H*-pyran **30** (50%), dienones **38** and **39** (27%), cyclic aldehyde **131** (20%)

Accordingly, a mixture of the oxepinone **33**, citral (**17**) and isopropylamine was heated at reflux in toluene with concomitant removal of water *via* a Dean-Stark trap. Toluene rather than tetrahydrofuran was used as a solvent in order to allow for a higher reaction temperature and after four days at reflux, the 2*H*-pyran

30 was isolated in 27% yield along with the dienones (**38** and **39**) which were isolated in 14% yield (Table 5, entry 2). Under these conditions, the overall yield of the cross-aldol reaction was not improved but the 2*H*-pyran **30** became the major product.

Another successful amine from the TLC survey, allylamine, was employed in a similar experiment which afforded the 2*H*-pyran **30** in a significantly higher yield (42%) as well as the dienones (**38** and **39**) in 10% yield (Table 5, entry 3). The overall yield of the cross-aldol reaction was, in this case, the highest obtained thus far (52%).

The steric requirements of the process were briefly investigated using (±)-methylbenzylamine and benzylamine. (±)-Methylbenzylamine was used under two sets of reaction conditions (in toluene at room temperature and under reflux with the removal of water) (Table 5, entries 4 and 5). The results of the two experiments were similar to previous observations; under reflux and on removal of water, a higher overall yield was obtained as well as a higher yield of the 2*H*-pyran **30**. The overall yield of the cross-aldol reaction for (±)-methylbenzylamine was 44%, lower than for allylamine but similar to isopropylamine. Benzylamine was employed only under the reflux conditions and a decrease in the overall yield of the process to 39% was observed (Table 5, entry 6). The results from these last three experiments suggested the size of the alkyl group attached to the amine functional group was not an important factor for the outcome of the reaction. However, a higher reaction temperature than room temperature as well

as the removal of water from the reaction medium seemed to have a positive influence on both the overall yield of the reaction and the product distribution.

An alternative method to remove water from the reaction medium was then tested. Two experiments that involved the cross-aldol reaction of the oxepinone **33** with citral (**17**) were conducted with isoamylamine and allylamine, under reflux in tetrahydrofuran and in the presence of anhydrous magnesium sulfate (Table 5, entries 7 and 8). The yield of the 2*H*-pyran product **30** increased with isopropylamine to 40% as compared to 27% on heating in toluene at reflux in a Dean-Stark trap (Table 5, entries 2 and 7). An increase in yield for the 2*H*-pyran **30** was also observed for allylamine (from 42 to 50%) as well as an increase in the overall yield of the reaction (from 52 to 77%) (Table 5, entries 3 and 8). Under the last set of conditions, a shorter reaction time (8 hours as opposed to four days, as indicated by monitoring the reaction by TLC) was required for disappearance of the limiting substrate, the oxepinone **33**.

Table 6 Cross-Aldol Reaction in Presence of Secondary Cyclic Amines: Conditions and Yields of Isolated Products

Entry	Amine used	Reaction Conditions	Reaction Products
1	piperidine	ethanol, reflux, 18 h	2*H*-pyran **30** (7%), cyclic aldehyde **131** (18%)
2	pyrrolidine	benzene, glacial acetic acid, reflux, 3 days	2*H*-pyran **30** (9%), cyclic aldehyde **131** (15%)
3	L-proline	dimethylsulfoxide, reflux, 4 h	2*H*-pyran **30** (10%), cyclic aldehyde **131** (15%)

Since the involvement of cyclic secondary amines in cross-aldol reactions *via* enamine intermediates has been reported in various syntheses, one known set of reaction conditions was used for the cross-aldol reaction of the oxepinone **33** with citral (**17**).[75] This reaction involved heating the ketone and the aldehyde with a catalytic amount of piperidine in ethanol at reflux (Table 6, entry 1). Under these reaction conditions, the 2*H*-pyran **30** was isolated in a low yield (7%). A subsequent experiment employing the cyclic secondary amine, pyrrolidine, in the cross-aldol reaction was also attempted (Table 6, entry 2). The reaction conditions involved the addition of pyrrolidine to the oxepinone **33** and citral (**17**) in the presence of an acid catalyst in benzene at reflux. This resulted in the formation of the 2*H*-pyran **30** albeit in low yield.[10]

It has been reported that L-proline is a versatile catalyst for the enantioselective reaction of both acyclic and cyclic ketones as aldol donors with aromatic and aliphatic aldehydes.[76] Thus, the oxepinone **33** and citral (**17**) were heated at reflux in dimethyl sulfoxide with a catalytic amount of L-proline. This afforded the 2*H*-pyran **30** in 10% yield. The catalyst load was subsequently increased to a stoichiometric quantity but this did not result in an increase in the yield.

It was noted from these latter experiments with cyclic secondary amines that a lower yield of the 2*H*-pyran product **30** was obtained and no dienone products were formed.

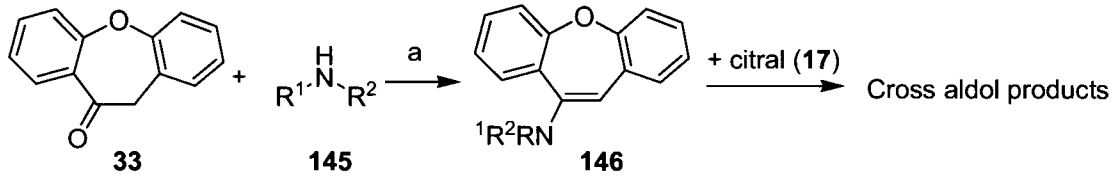
---

(75) Kuhn, R.; Hensel, H. R. *Chem. Ber.* **1953**, *86*, 1333.

(76) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, I. C. F. *J. Am. Chem. Soc.* **2001**, *123*, 5260.

Several attempts were then made to synthesize enamines of the oxepinone **33** (Scheme 44).[77]

Scheme 44 Proposed Enamine Route to the Cross-Aldol Products



Reagents and conditions: a) *p*-TsOH, PhH, reflux, Dean-Stark trap or $MgSO_4$

In all instances, the oxepinone **33** was almost entirely recovered on reaction with pyrrolidine, morpholine, piperidine and *L*-proline, in presence of *p*-toluenesulfonic acid as catalyst, and no enamine products **146** were formed. In view of this fact and that in certain cases these enamines might not be stable to silica gel or work-up procedures, a small scale experiment containing the oxepinone **33**, morpholine and *p*-toluenesulfonic acid was performed in deuterated benzene. The reaction mixture was monitored by ^1H NMR spectroscopy but no reaction products were observed. Thus, it appears that this reaction does not occur *via* enamine intermediates.

The use of allylamine in the condensation reaction of the oxepinone **33** with citral (**17**) along with the use of anhydrous magnesium sulfate, under reflux in tetrahydrofuran, was found to be the optimal conditions. In this case, the 2*H*-pyran **30** was obtained in a good yield (50%) together with the cross-aldol condensation products, the dienones (**38** and **39**) (27%) and the cyclic aldehyde

(77) Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 11273.

131 (20%). These reaction conditions were used as the starting point for two additional series of studies.

The first study was intended to test the efficiency of several drying agents. The commonly used drying agents magnesium sulfate, sodium sulfate, calcium oxide and molecular sieves were used in a series of small scale reactions together with isopropylamine, allylamine or isoamylamine (Figure 27). A potassium fluoride-alumina complex (37 w/w %) and anhydrous copper sulfate were also used as dehydrating agents.

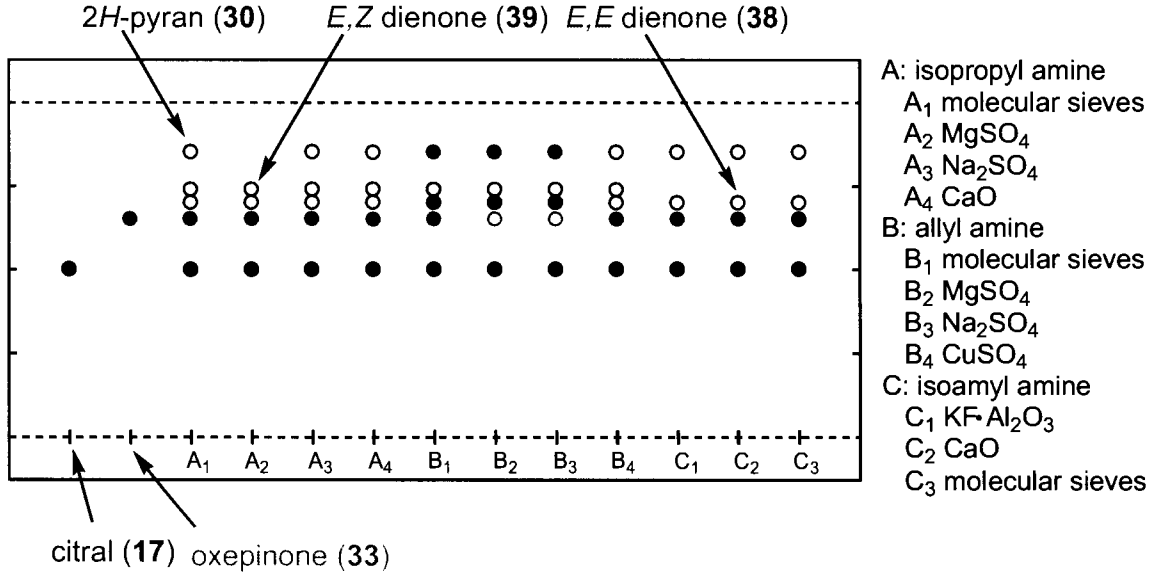


Figure 27 **Thin layer chromatogram corresponding to the study of the cross-aldol reaction: Survey of drying agents.**

Analysis of the thin layer chromatogram of the reaction mixture which was eluted with a mixture of petroleum ether/dichloromethane (1:2) showed that the 2*H*-pyran **30** was the major product in three instances. These conditions involved the use of the allyl amine and either molecular sieves, magnesium

sulfate or sodium sulfate as the drying agent (Figure 27, experiments B_{1-3}). Cross-aldol products were detected in the remaining experiments but according to the intensity of the corresponding spots on the chromatogram their amount was significantly less than in the case of allylamine. Therefore the allylamine/magnesium sulfate system was used in the final series of experiments which was designed to determine the influence of the solvent on the cross-aldol reaction (Figure 28).

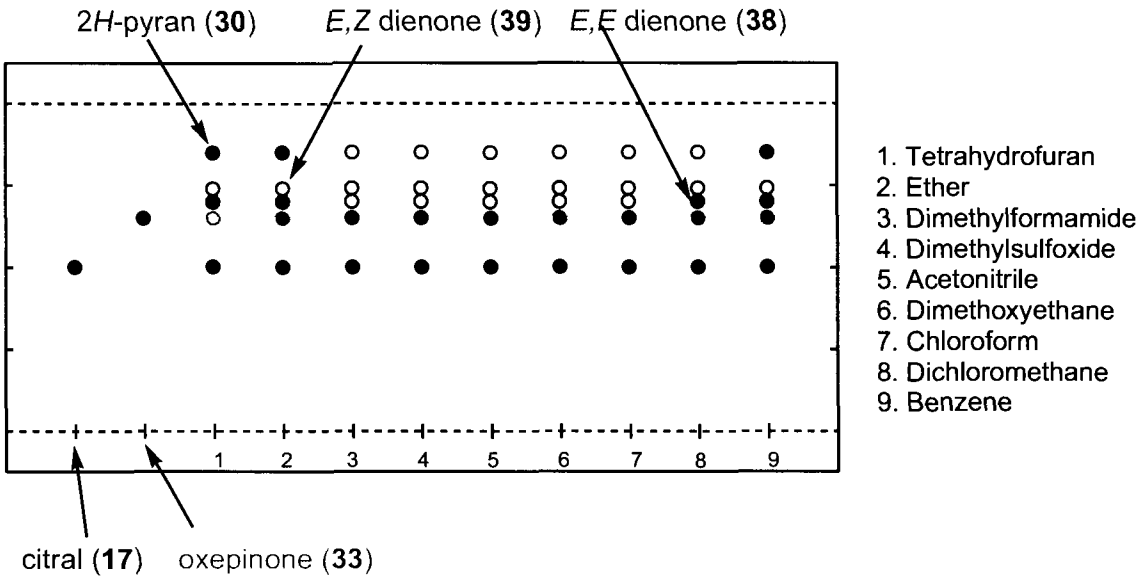


Figure 28 **Thin layer chromatogram corresponding to the study of the cross-aldol reaction: Survey of solvents.**

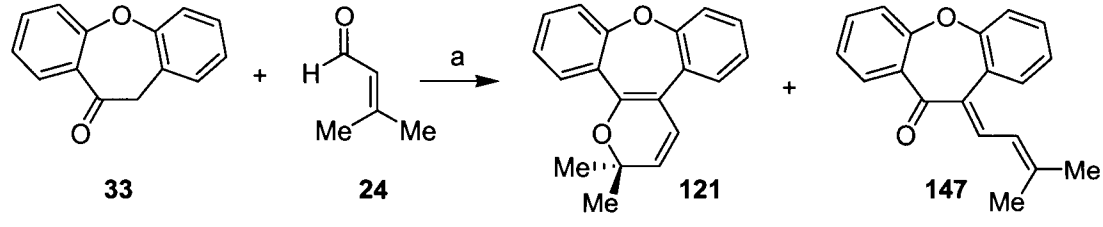
Analysis of the thin layer chromatogram showed that the 2*H*-pyran **30** was the major product in the experiments that involved the use of tetrahydrofuran, ether and benzene as reaction solvents (Figure 28). The use of the polar aprotic solvents dimethylformamide, dimethylsulfoxide, acetonitrile or dimethoxyethane afforded the cross-aldol products in trace amounts. A similar result was obtained

using the chlorinated solvents, chloroform and dichloromethane. It was concluded that tetrahydrofuran was the best solvent for the cross-aldol reaction since none of the other solvents seemed to be more efficient.

3.3.8 Synthesis of the Artocarpol D Analogue (121)

The optimal reaction conditions for promoting the cross-aldol reaction between the oxepinone **33** and citral (**17**) with titanium tetrachloride/tri-*n*-butylamine and allylamine/magnesium sulfate were also used in the cross-aldol reaction of the oxepinone **33** with senecialdehyde (**24**). Accordingly, the artocarpol D analogue **121** and the dienone isomer **147** were synthesized in the presence of titanium tetrachloride and tri-*n*-butylamine according to the Evans protocol (Scheme 45). The artocarpol D analogue **121** and the dienone **147** were obtained in similar yields (21 and 18% , respectively).

Scheme 45 Synthesis of the Artocarpol D Analogue (121) *via* the Titanium Tetrachloride/Tributylamine-Mediated Cross-Aldol Reaction



33 **24** **121** **147**

Reagents and conditions: a) $TiCl_4$, *n*-Bu_3N, CH_2Cl_2, -18 °C to room temperature, 24 h, 121 **(21%),** 147 **(18%).**

The characteristic pair of doublets for the 2*H*-pyran was observed in the ^1H NMR spectrum of the artocarpol D analogue **121** (Figure 29). The doublet at δ = 5.18 ppm, assigned to *H*-3, was coupled (J = 10 Hz) to the doublet at δ = 6.10 ppm which was assigned to *H*-4. The most downfield proton, the aromatic proton

H-13, appeared as a doublet of doublets at δ = 7.69 ppm. The two methyl groups were found to be equivalent and were assigned to the singlet signal at δ = 1.29 ppm.

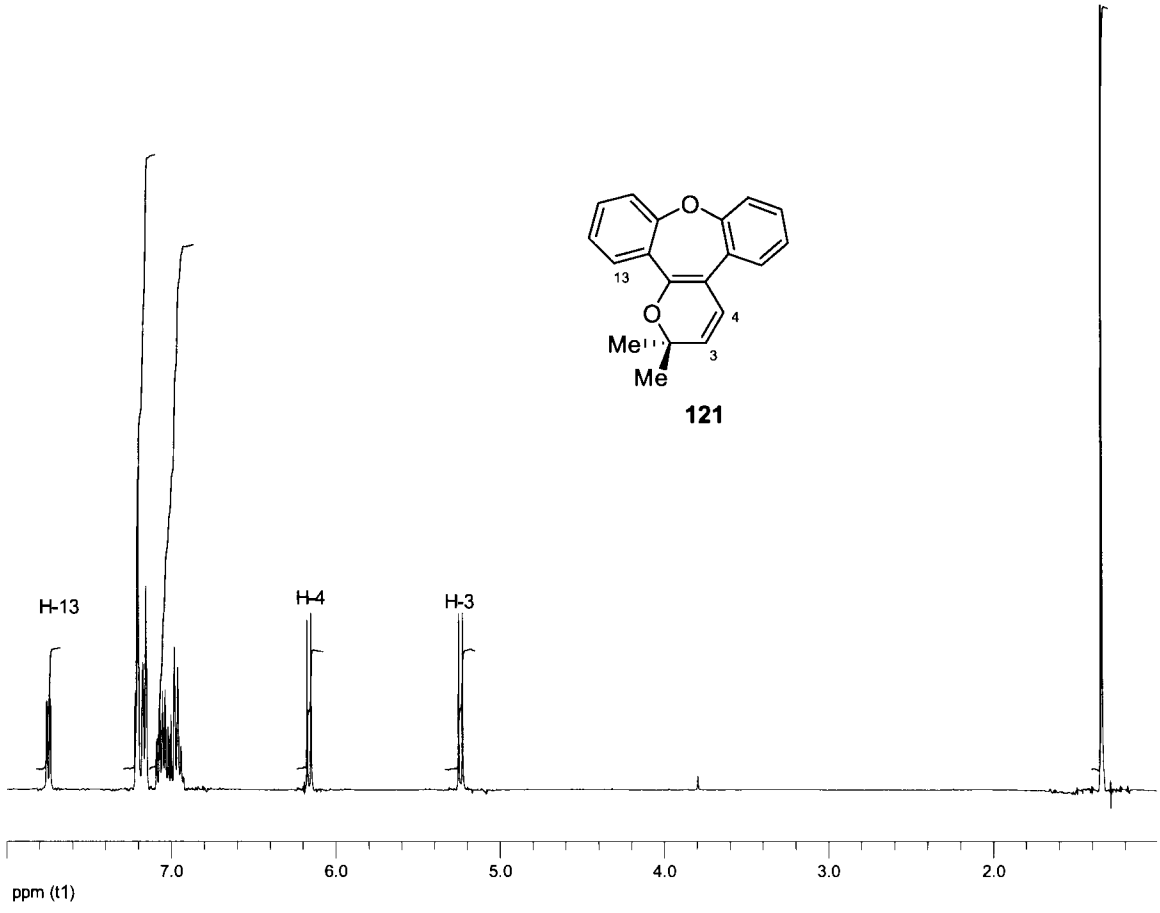


Figure 29 **Detail from the ^{1}H NMR spectrum (C_6D_6, 400 MHz) of the artocarpol D analogue (121).**

The ^{1}H NMR spectrum of the *E*-dienone **147** revealed the non-equivalence of the methyl groups which appeared as two singlets. An NOE contact between the doublet at δ = 6.18 ppm (assigned to *H*-2') and the singlet at δ = 1.52 ppm allowed for the assignment of the methyl groups. The singlet at δ = 1.38 ppm was assigned to *Me*-3' and the singlet at δ = 1.52 ppm to *Me*-4'. As

was previously seen for the diphenyl dienone **143**, the β-proton (*H*-1') appeared as a doublet at δ = 8.12 ppm and the aromatic proton *H*-9 was assigned to a doublet of doublets at δ = 8.31 ppm (Figure 30).

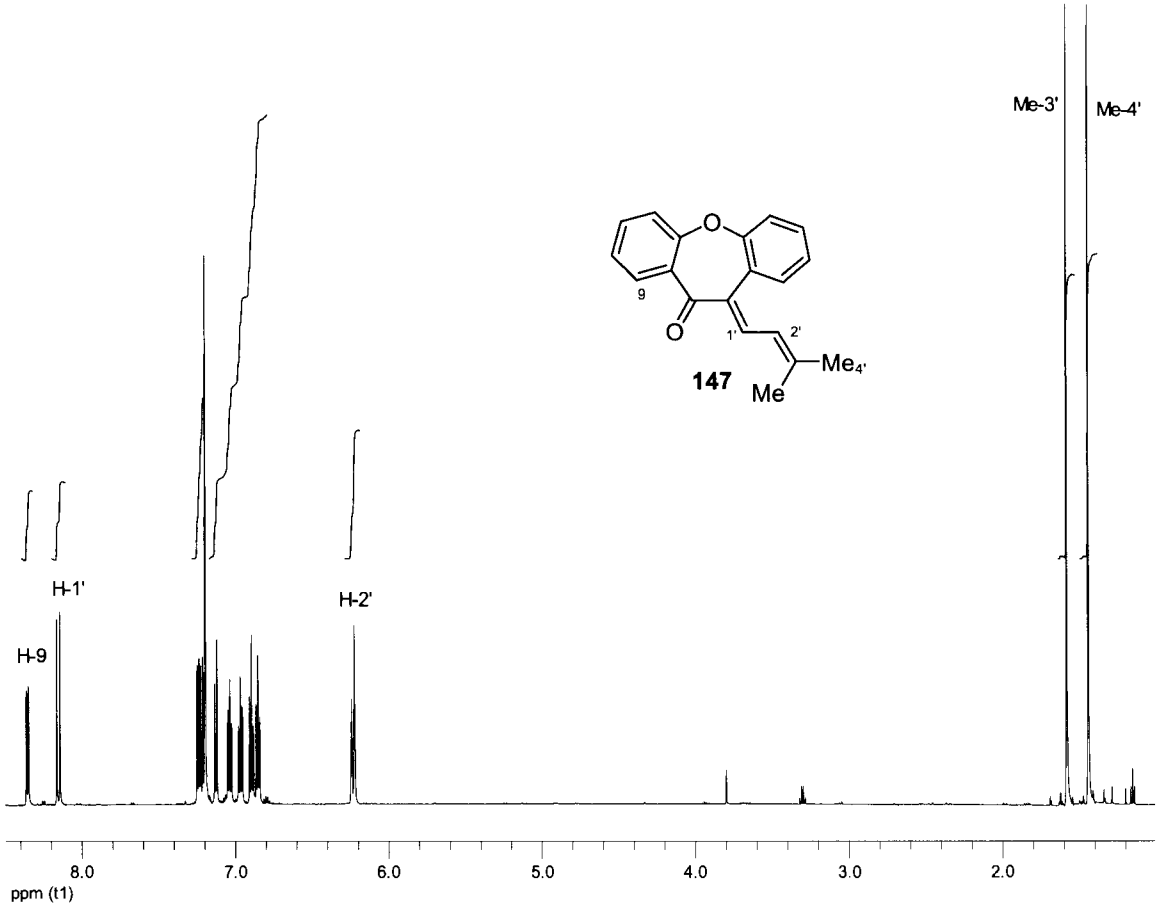


Figure 30 **Detail from the ^{1}H NMR spectrum (C_6D_6, 400 MHz) of the *E*-dienone (147).**

The geometry of the α,β-double bond of the dienone **147** was assigned according to the contacts observed in the NOE spectrum. The presence of a contact between *H*-2' and protons in the aromatic region as well as the absence of a contact between *H*-1' and aromatic protons established the *E* configuration of the double bond (Figure 31).

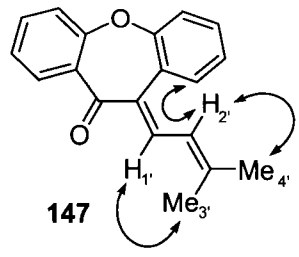
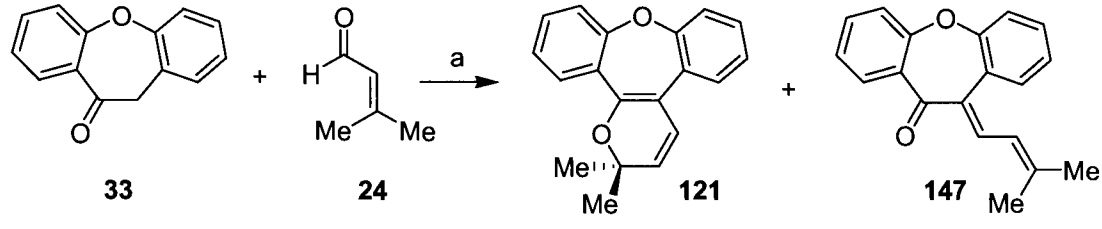


Figure 31 Contacts observed in the NOESY spectrum of the *E*-dienone (147).

The optimized allylamine/magnesium sulfate cross-aldol reaction conditions were also employed in the reaction of the oxepinone **33** with senecialdehyde (**24**) to afford the same artocarpol D analogue **121** and the dienone **147** in 40 and 26% yield, respectively. The overall yield of the cross-aldol reaction was higher in the case of the allylamine/magnesium sulfate system (66%) as compared with the Evans protocol (39%).

Scheme 46 Synthesis of the Artocarpol D Analogue (121) in Presence of Allyl Amine and Anhydrous Magnesium Sulfate



Reagents and conditions: a) allyl amine, $MgSO_4$, THF, reflux, 8 h, 121 **(40%),** 147 **(26%)**

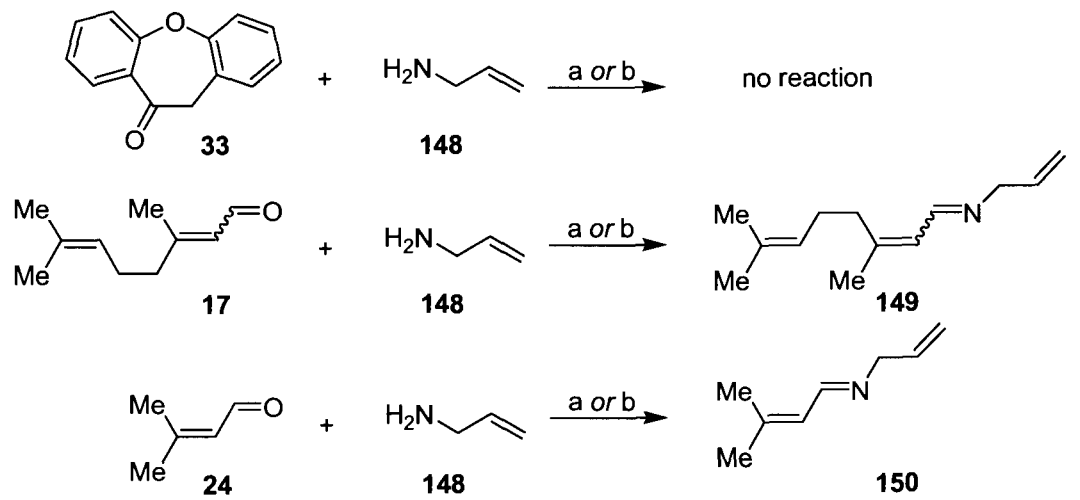
3.3.9 Investigation of the Amine-Mediated Cross-Aldol Reaction Mechanism

The development of the rather unusual reaction conditions for the cross-aldol reaction of the oxepinone **33** with citral (**17**) and senecialdehyde (**24**) that

involved the use of a primary amine and a drying agent prompted an investigation of the mechanism of the reaction.

Thus, oxepinone **33**, citral (**17**) and senecialdehyde (**24**) were reacted separately with allyl amine (**148**). The experiments were conducted in deuterated chloroform by mixing equimolecular quantities of these substrates. Analysis of the ^{1}H NMR spectrum of the reaction of the oxepinone **33** with allyl amine (**148**) indicated that no reaction had occurred. However, the α,β-unsaturated aldehydes, citral (**17**) and senecialdehyde (**24**), reacted rapidly with allylamine (**148**) to afford the corresponding imines **149** and **150** quantitatively (Scheme 47).

Scheme 47 Reaction of Allyl Amine with Oxepinone (33), Citral (17) and Senecialdehyde (24)



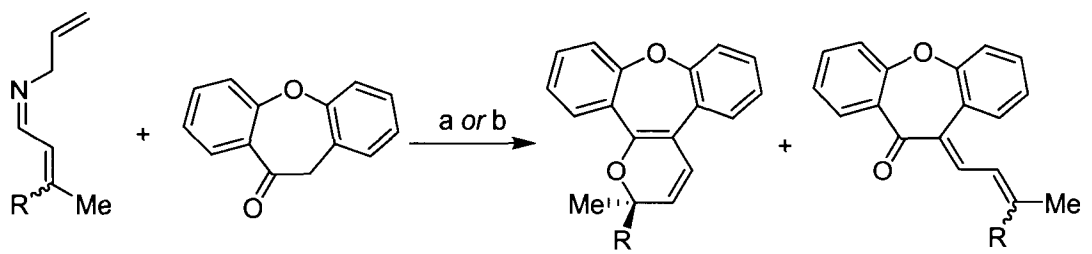
Reagents and conditions: a) $CDCl_3$, room temperature; b) PhH, room temperature, 1 h, 149 **(95%),** 150 **(97%).**

On a preparative scale, the imines (**149** and **150**) were isolated from the reaction mixture by bulb-to-bulb distillation and were fully characterized. They

were also found to be stable for days at low temperature (-25 °C) and in the absence of air.

The successful reaction of the α,β-unsaturated aldehydes (**17** and **24**) with allylamine (**148**) and the absence of products in the reaction of allylamine (**148**) with the oxepinone **33** suggested the involvement of the imine species (**149** and **150**) in the cross-aldol reaction. Consequently, the preformed imines (**149** and **150**) were reacted with the oxepinone **33** in tetrahydrofuran at reflux. The products isolated from these reactions were identical to the products isolated from the reaction of the oxepinone **33** with the α,β-unsaturated aldehydes **17** and **24** in presence of allylamine and magnesium sulfate (Scheme 48). The only differences in these reactions were the absence of the cyclic aldehyde **131** by-product and that a longer reaction time (48 h *vs* 8 h) was required.

Scheme 48 Reaction of the Oxepinone (33) with the Imines (149) and (150).



149, R = R_1 **33** **30**, R = R_1, 40% **38** + **39**, R = R_1, 19%
150, R = Me **121**, R = Me, 17% **147**, R = Me, 56%

R_1 = $(CH_2)_2CH=C(Me)_2$

Reagents and conditions: a) $MgSO_4$, THF, reflux, 48 h.

The significant difference in the reaction time of the oxepinone/aldehyde reaction in presence of amine/magnesium sulfate and the oxepinone/imine reaction, prompted an additional experiment. This involved repeating the

reaction of the oxepinone **33** with imines **149** and **150** in the presence of anhydrous magnesium sulfate and a trace amount of water. The yields obtained were identical to the former experiment but the reaction time was reduced from 48 to 8 h. These results suggested the involvement of water molecules (that would have been generated during the imine formation reaction) in the mechanism of the cross-aldol reaction (Figure 32).

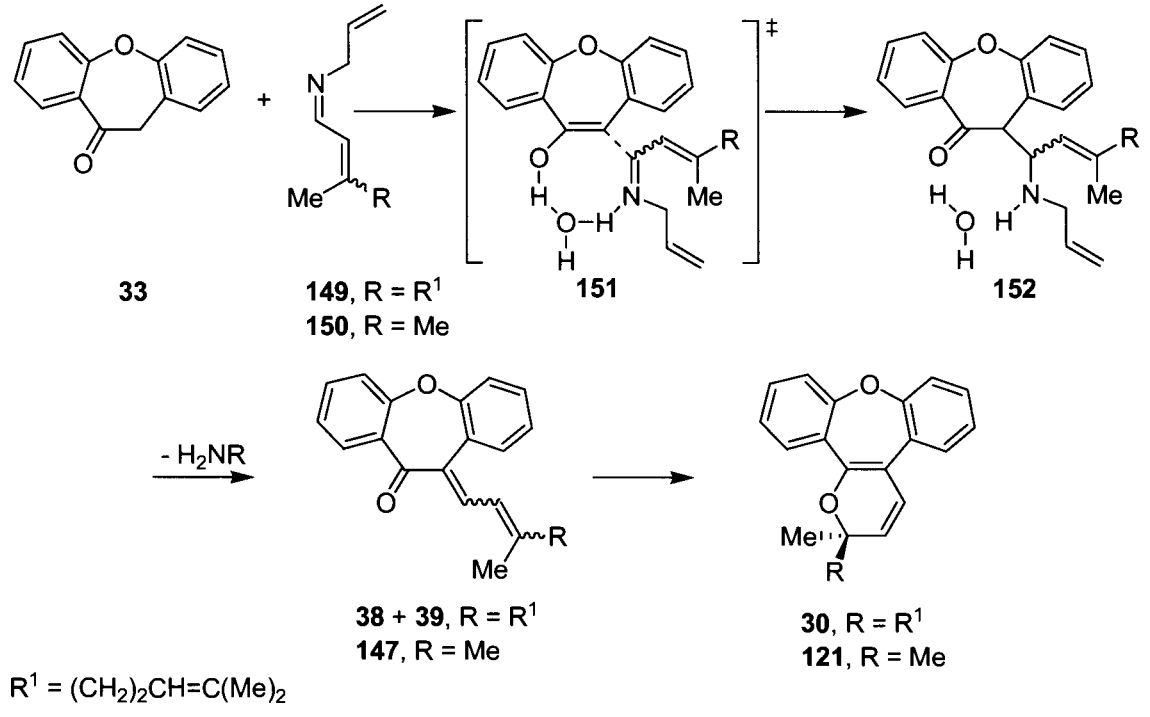


Figure 32 **Proposed mechanism for the formation of the dienones (38, 39 and 147) and 2*H*-pyrans (30 and 121).**

It was subsequently postulated that a water molecule could be engaged in a transition state **151** for the reaction of the enol form of the oxepinone **33** and the imine (**149** or **150**) (Figure 32). The water molecule might facilitate a proton transfer process between the enol and the imine. Of note, as the imine **149** is

inherently more difficult to deprotonate than the corresponding α,β-unsaturated aldehyde, the absence of self-condensation of citral can also be rationalized.

3.3.10 The Equilibrium Between the *E/Z* Dienones and the 2*H*-Pyran

Depending on the configuration of the two double bonds, there were four possible products which could have formed in the cross-aldol condensation reaction; the *Z,E*-isomer **36**, the *Z,Z*-isomer **37**, the *E,E*-isomer **38** and the *E,Z*-isomer **39** (Figure 33). The first two dienones have the correct orientation of the α,β-double bond to undergo an electrocyclic reaction to afford the 2*H*-pyran **30**.

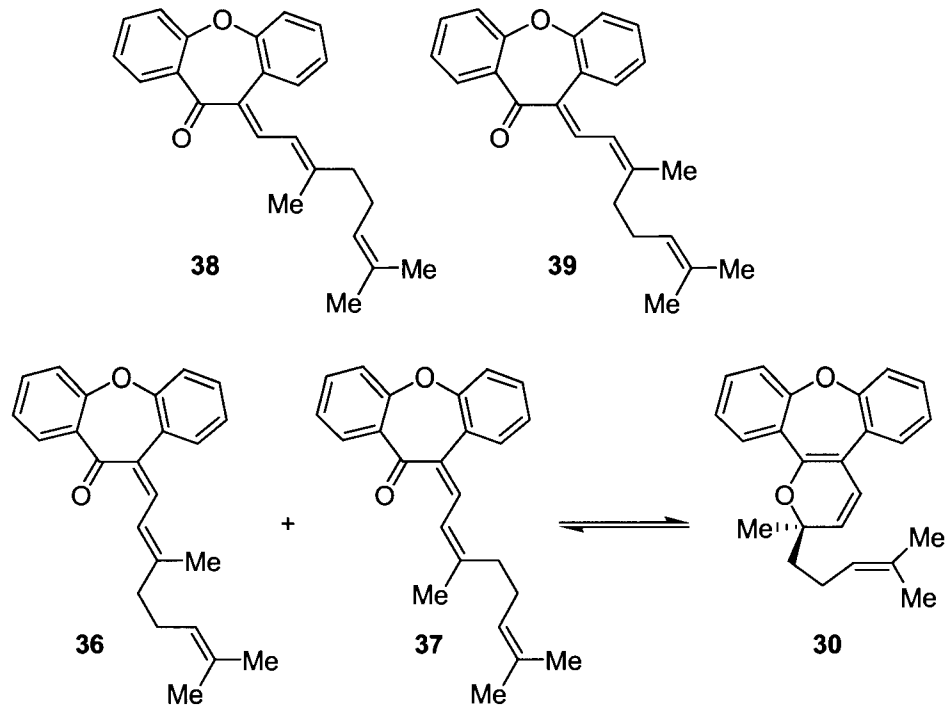


Figure 33 **Structure of the possible cross-aldol condensation products (36, 37, 38, 39) and the equilibrium between the *Z*-dienones (36 and 37) and the 2*H*-pyran (30).**

During the course of these studies, only the *E,E*- and the *E,Z*-isomers (**38** and **39**) were identified and isolated. The separation of these two isomers by column chromatography was problematic due to their similar retention factor (R_f). The separation of the isomers was not possible in most of the solvent systems tested. However, repetitive chromatography using chloroform as the eluant allowed for the separation of these isomers. In chloroform, the *E,Z*-isomer **39** had a retention factor 0.68 and the *E,E*-isomer **38** a retention factor 0.63.

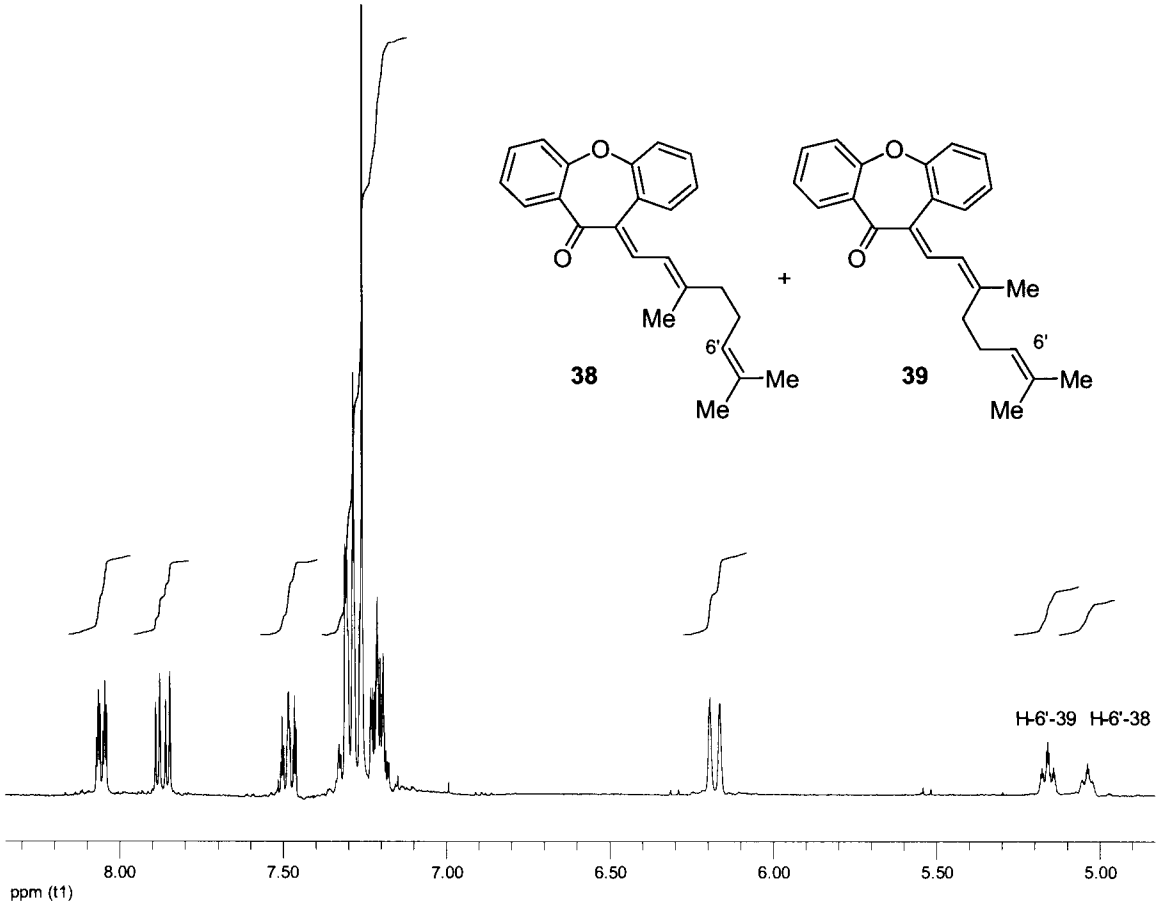


Figure 34 **Detail from the ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of the mixture *E,E*- and *E,Z*-dienones (38 and 39).**

In the ^{1}H NMR spectrum of both of these dienones the absence of the characteristic signals for the 2*H*-pyran in the 6.5 – 5.0 ppm region was noted. A signal corresponding to *H*-6' of the dienone was found in this region of the spectrum but the value was slightly different for the two isomers. In the ^{1}H NMR spectrum of the *E*,*Z*-dienone **39** the *H*-6' signal appeared at δ = 5.10 ppm and for the *E*,*E* dienone **38** the *H*-6' signal appeared at δ = 4.96 ppm. Integration of these signals was used to determine the relative ratios of the geometrical isomers (Figure 34).

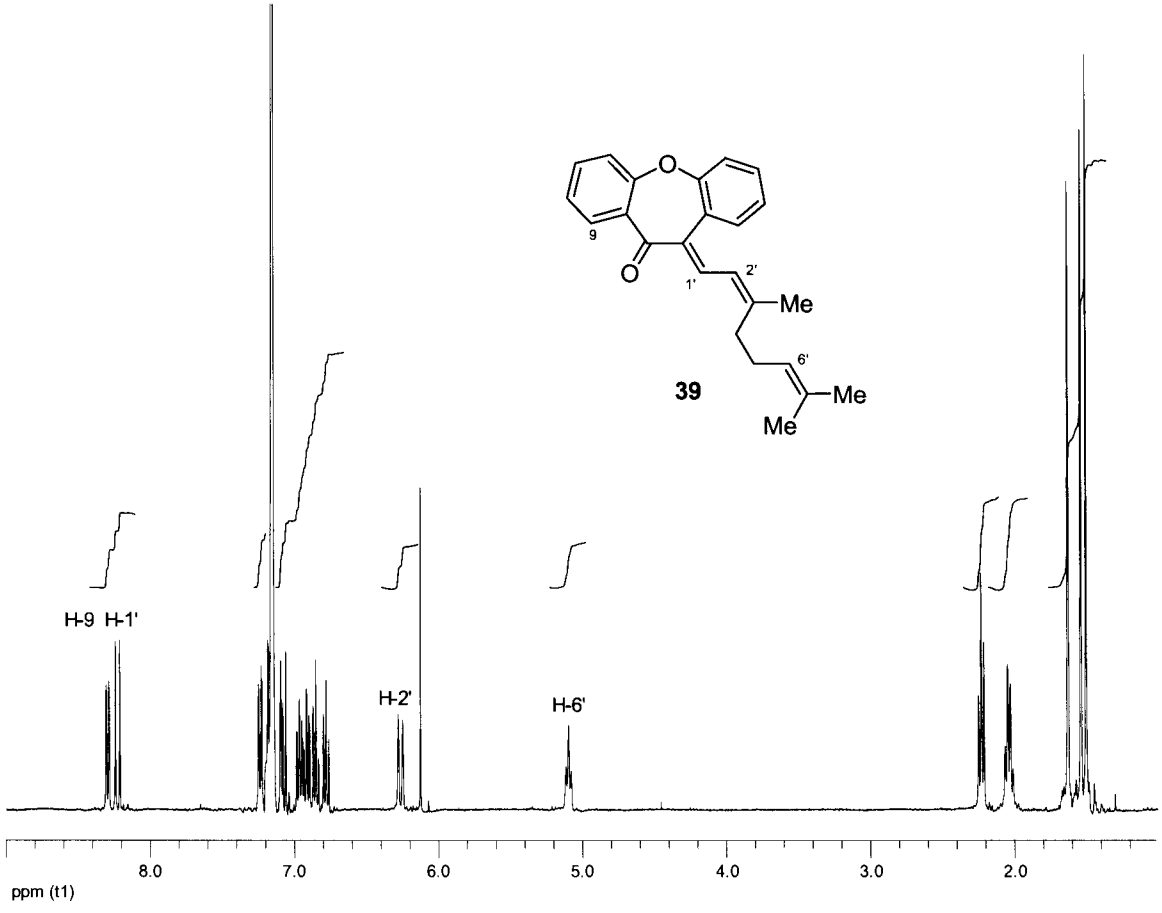


Figure 35 **Detail from the ^{1}H NMR spectrum (C_6D_6, 400 MHz) of the *E*,*Z*-dienone (39).**

The difference in chemical shift was of particular interest since *H*-6' was quite remote from the α,β-double bond. Moreover, the terminal methyl groups which were even further from the α,β-double bond displayed differences in the chemical shifts between the two isomers. The difference could be possibly explained by different conformational preferences for these two compounds.

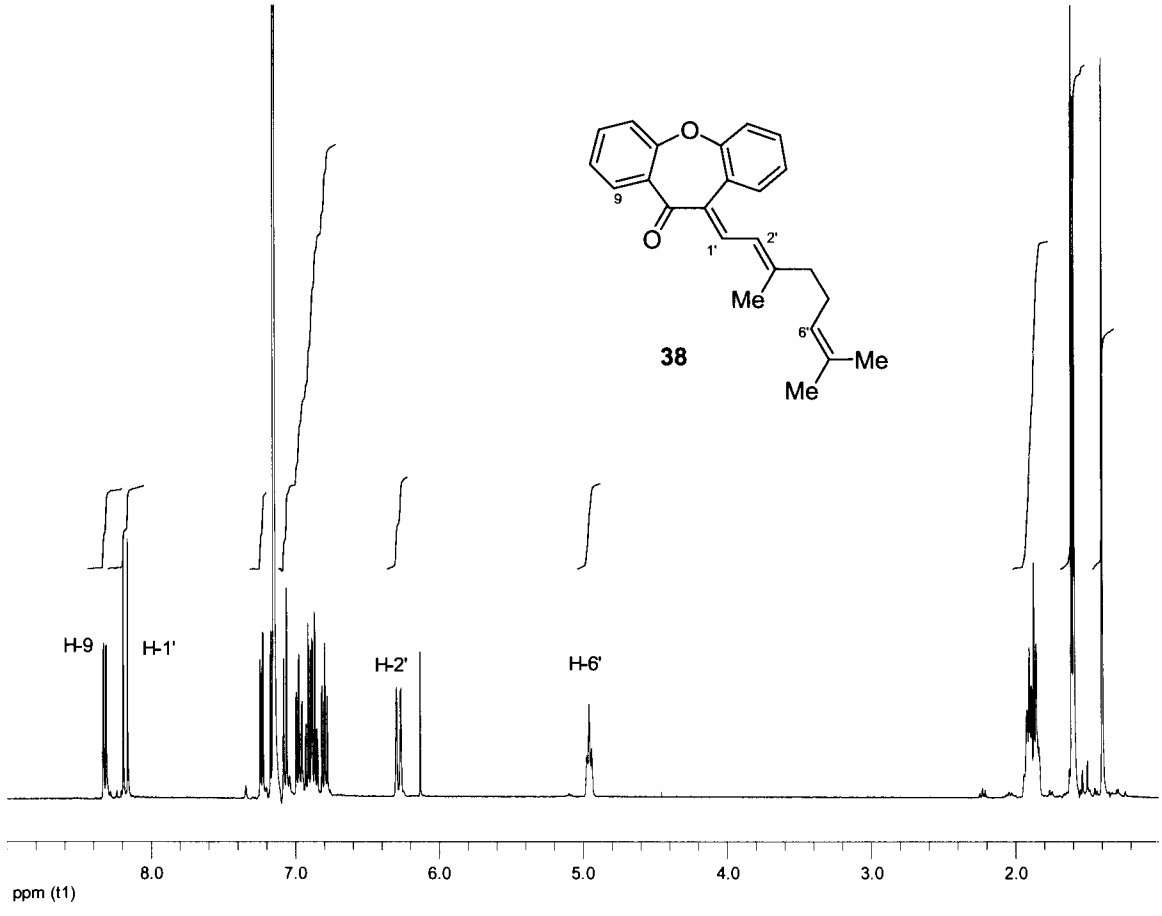


Figure 36 **Detail from the ^{1}H NMR spectrum (C_6D_6, 400 MHz) of the *E,E* dienone (38).**

The ^{1}H NMR signal corresponding to *H*-2' appeared to δ = 6.28 ppm for the *E,Z*-dienone **39** and at δ = 6.26 ppm for the *E,E* dienone **38** (Figure 37). Another difference in the chemical shifts could also be noted for *H*-1' which

appeared at δ = 8.18 ppm in the case of the *E*,*Z*-dienone **39** and at δ = 8.22 ppm for the *E*,*E* dienone **38**.

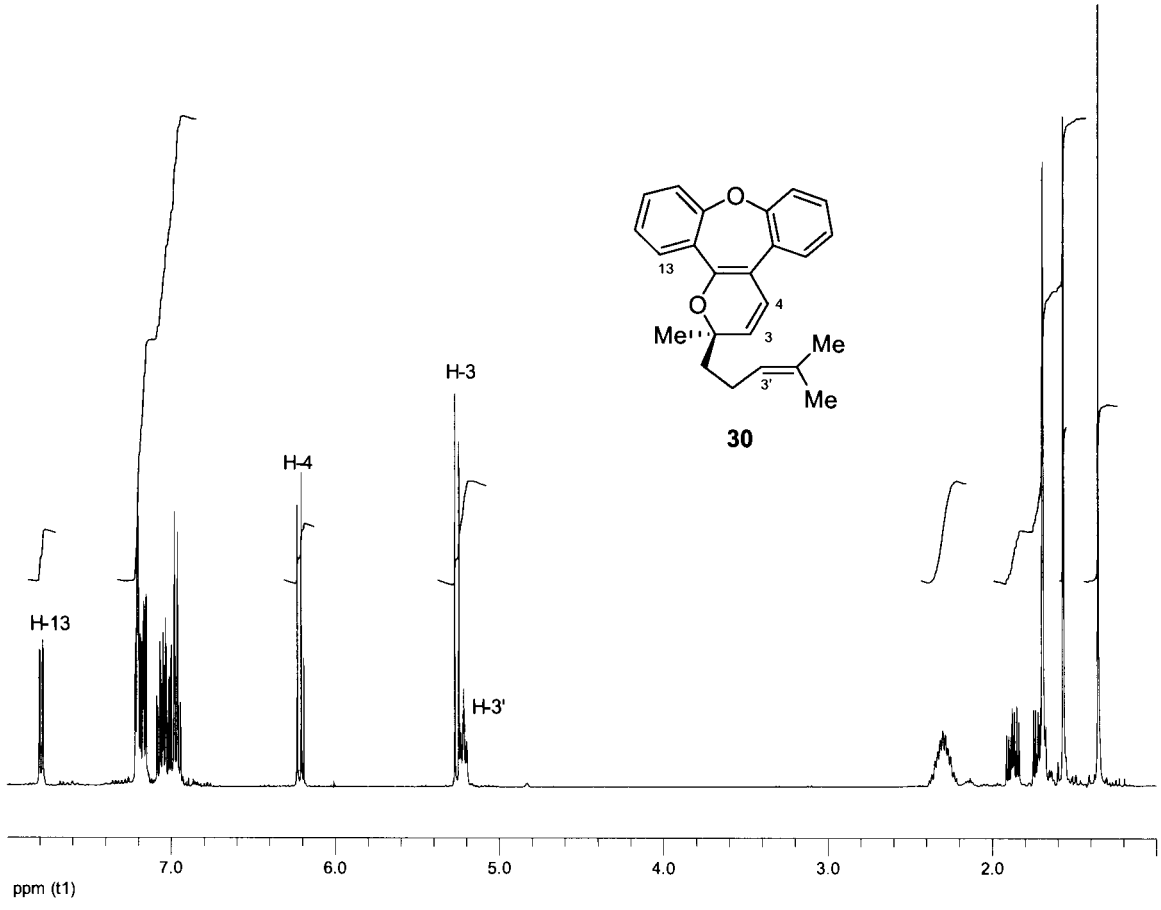


Figure 37 **Detail from the ^{1}H NMR spectrum (C_6D_6, 400 MHz) of the 2*H*-pyran (30).**

The geometry of the double bonds was assigned according to the contacts observed in the NOESY spectra of the two dienone isomers (**38** and **39**). For both dienones, the α,β-double bond was determined to have a *E* configuration because of the absence of NOE contacts between *H*-1' and any aromatic protons. The contact between *H*-2' and aromatic protons, present in both compounds, suggested a favoured *s-trans* conformation of the diene.

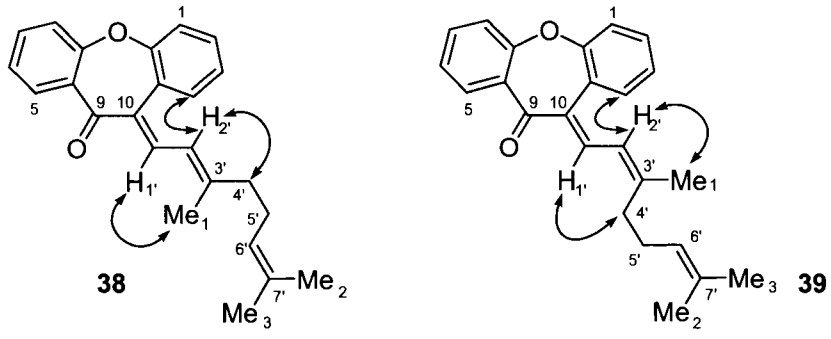
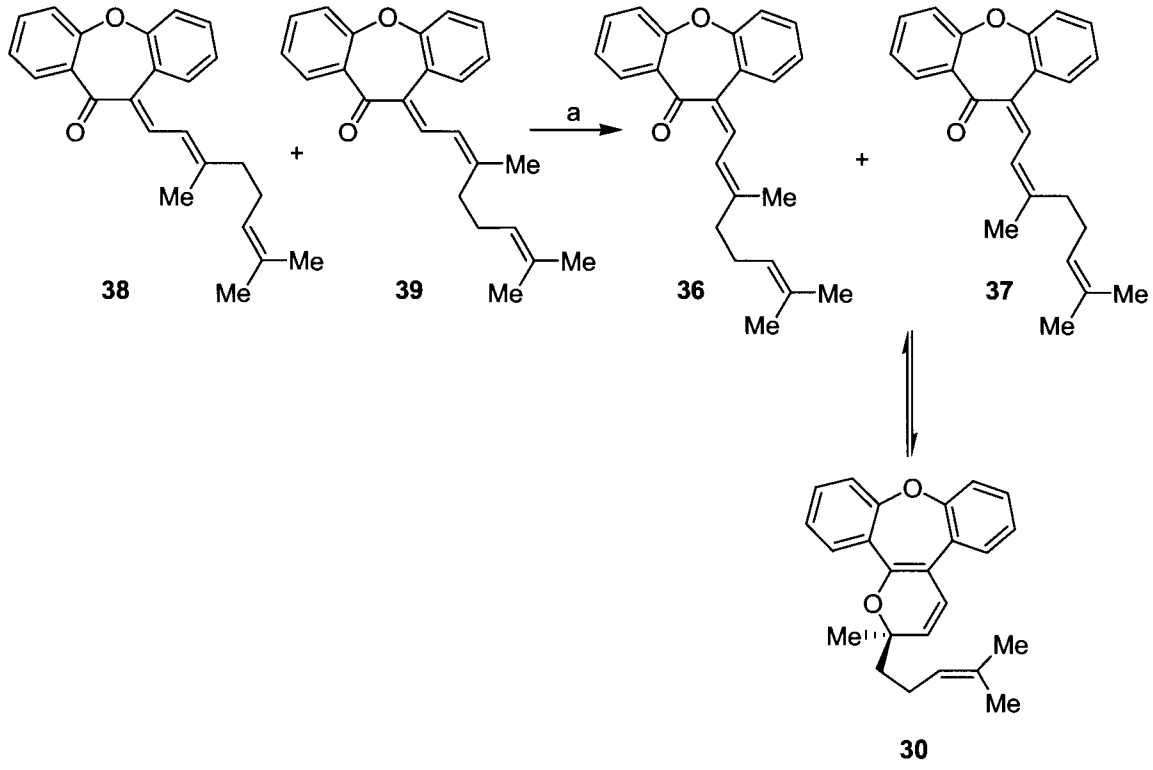


Figure 38 **Contacts observed in the NOESY spectrum of the *E,E*-dienone (38) and of the *E,Z*-dienone (39).**

For the *E,E*-dienone **38**, NOE contacts between *H*-2' and a methylene group as well as between *H*-1' and a methyl group, proved the *E* configuration of the γ,σ-double bond. Similarly, the geometry of the γ,σ double bond in compound **39** was proved by NOE contacts between *H*-2' and a methyl group as well as between *H*-1' and a methylene group.

The electrocyclic reaction of the dienone products to the 2*H*-pyran derivative required the α,β-double bond to have an *cis*-configuration. However, the *Z*-dienones **36** and **37** were not isolated. This suggested a fast *Z*-dienone $\leftrightarrow$ 2*H*-pyran interconversion. A mixture of the two *E*-dienones (**38** and **39**) was subsequently subjected to the optimized aldol condensation reaction conditions and the 2*H*-pyran **30** was isolated in 80% yield (Scheme 49). Thus, it appears that the *E*-dienones (**38** and **39**) could undergo the electrocyclic ring closing reaction to the 2*H*-pyran **30** only after the isomerization of the α,β-double bond to the *Z*-configuration (Scheme 49, Figure 33).

Scheme 49 Isomerization of the *E*-Dienones (38 and 39) to the *Z*-Dienones (36 and 37): The Electrocyclic Reaction of the *Z*-Dienones to the 2*H*-Pyran (30)



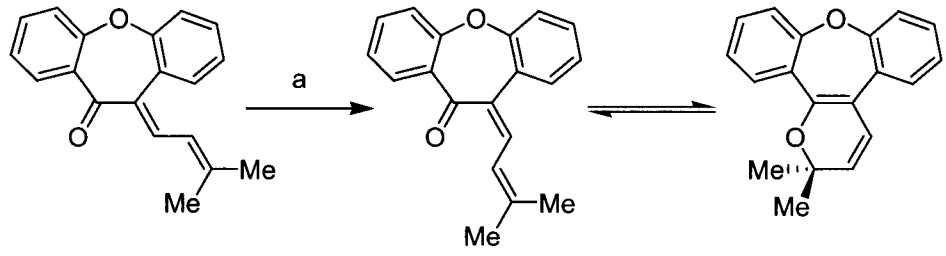
Reagents and conditions: a) allylamine, $MgSO_4$, THF, reflux, 8 h, 80%.

The isomerization/electrocyclization process did not necessarily require heat or the presence of other reagents. The analysis of ^{1}H NMR spectra of a sample containing a mixture of the *E*-dienones **38** and **39** in deuterated chloroform, revealed peaks characteristic to the 2*H*-pyran derivative **30**. However, in an NMR solvent, at room temperature, the process was significantly slower. A sample of the 2*H*-pyran **30** in deuterated chloroform was stable and no dienone could be detected after four days.

A similar behaviour was observed for the artocarpol D analogue **121**. The *E*-dienone **147** was the only dienone isomer isolated from the cross-aldol

reaction of the oxepinone **33** with senecialdehyde (**24**) (Scheme 46). The *E*-dienone **147** could be cyclized to the 2*H*-pyran **121** in a NMR solvent and in a reaction setting as well in 80% yield (Scheme 50).

Scheme 50 Isomerization of the *E*-Dienone (147) to the *Z*-Dienone (153): The Electrocyclic Reaction of the *E*-Dienone to the 2*H*-Pyran (121)



147 **153** **121**

Reagents and conditions: a) allyl amine, $MgSO_4$, THF, reflux, 8 h, 80%.

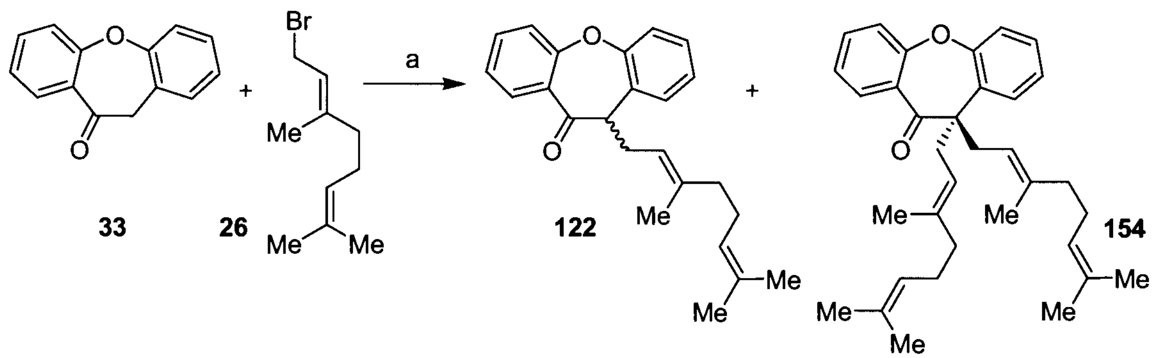
The electrocyclization of the dienone compounds (**38**, **39** and **147**) allowed for an increase of the overall yield of the 2*H*-pyran products. The overall yield of the 2*H*-pyran **30** became 72% and that of the 2*H*-pyran **121** became 61%.

3.4 An Alternative to the Aldol Condensation Reaction: Synthesis of the 2*H*-Pyran (30) and the Artocarpol D and E Analogue (121 and 122)

An alternative proposed synthesis of the artocarpol A (**1**) involved an initial alkylation reaction of an oxepinone derivative (Section 2.1, Scheme 5). The preliminary studies of the reactivity of the oxepinone **33** demonstrated the possibility to successfully alkylate the α-carbon. Thus, an alkylation, selenation and oxidation sequence was tested for the synthesis of the 2*H*-pyran **30**. Following the successful synthesis of the 2*H*-pyran **30**, the two routes would

share a common last step in the synthesis of the artocarpol A analogue **29**, the [2+2] photocycloaddition reaction (Scheme 6).

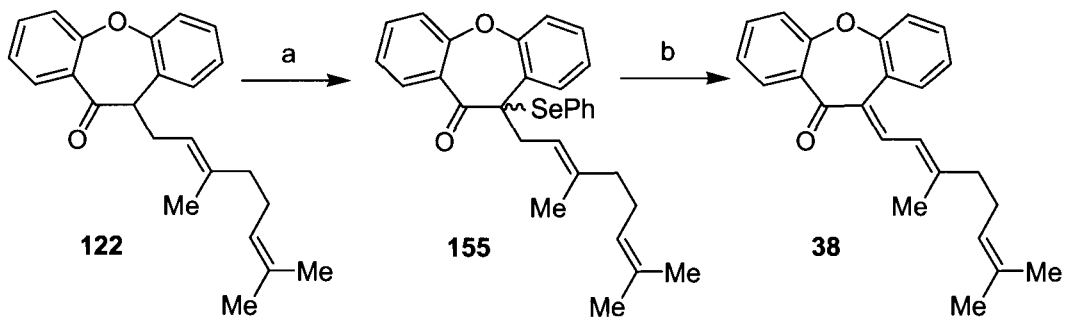
Scheme 51 Alkylation of the Oxepinone (33) with Geranyl Bromide (25): Synthesis of an Artocarpol E Analogue (122)



Reagents and conditions: a) LDA, THF, -18 °C to 0 °C, 4 h, 122 **(43%),** 154 **(12%).**

In the first step of this route, the required C(10)-substituent was introduced *via* an alkylation reaction of the oxepinone **33** with geranyl bromide **26** (Scheme 51). In this reaction, the desired mono-alkylated product **122** was obtained in 43% yield together with the dialkylated side-product **154** (Scheme 51). The mono-alkylated product **122** represents the keto-form of an analogue of artocarpol E (**5**).

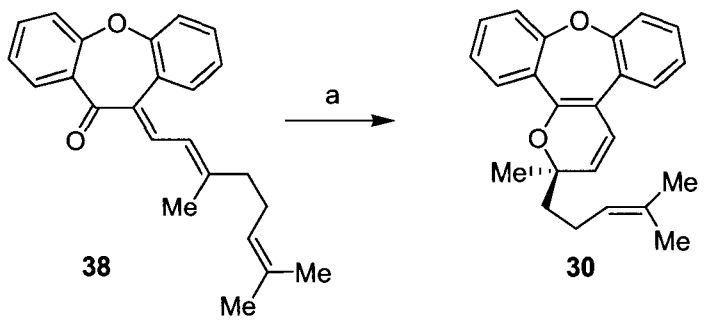
Scheme 52 Synthesis of the *E,E*-Dienone (38) *via* Selenation and Oxidation of the Alkylated Oxepinone (122)



Reagents and conditions: a) LDA, PhSeCl, -78 °C, 5 min; b) pyridine, H_2O_2, CH_2Cl_2, 10 min, 40% (over two steps).

The mono-alkylated ketone **122** was subsequently deprotonated with LDA and reacted with phenylselenyl chloride. The selenide **155** was then oxidized with hydrogen peroxide in the presence of pyridine. The product of the reaction was isolated by flash chromatography and it was characterized as the *E,E*-dienone **38** (Scheme 52). The isomerization and electrocyclic reaction of the *E,E*-dienone **38** in presence of allylamine and magnesium sulfate afforded the 2*H*-pyran **30** (Scheme 53). The spectroscopic data for the *E,E*-dienone **38** and the 2*H*-pyran **30** obtained *via* this route were identical to the data for the compounds synthesized *via* the cross-aldol reaction.

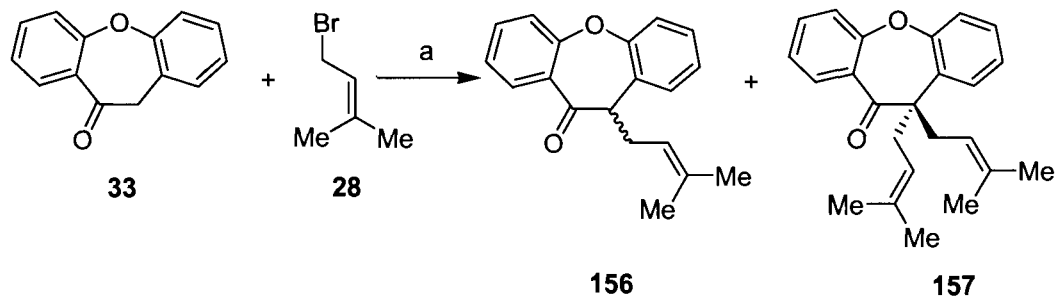
Scheme 53 Isomerization and Electrocyclic Reaction of the *E,E*-Dienone (38) to the 2*H*-Pyran (30)



Reagents and conditions: a) allyl amine, $MgSO_4$, THF, reflux, 8 h, 83%.

An analogous strategy was applied to the synthesis of the artocarpol D analogue **121**. However, the reaction between the oxepinone **33** and prenyl bromide **28** was less selective and the mono- and dialkylated products were isolated as a 1:1 mixture (Scheme 54).

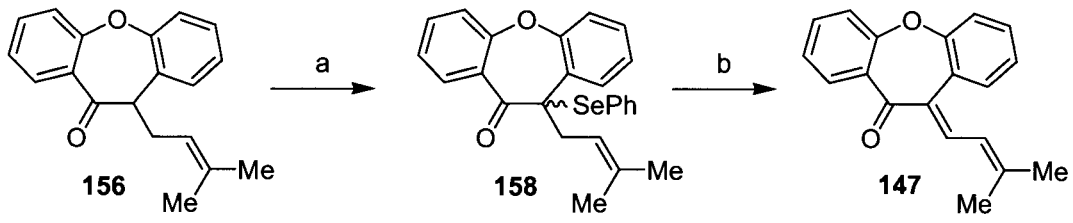
Scheme 54 Alkylation of the Oxepinone (33) with Prenyl Bromide (28)



Reagents and conditions: a) LDA, THF, -18 °C to 0 °C, 4 h, 156 **(30%),** 157 **(30%).**

The mono-alkylated oxepinone **156** was subsequently deprotonated with LDA and reacted with phenylselenyl chloride. Oxidation of the resultant selenide **158** with hydrogen peroxide afforded the *E*-dienone **147** (Scheme 55).

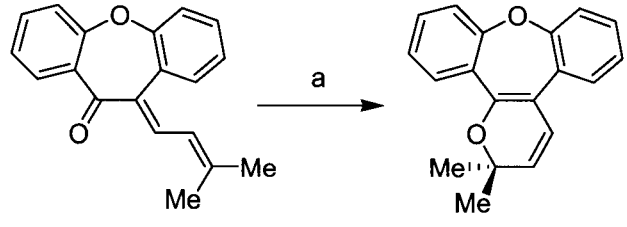
Scheme 55 Synthesis of the *E*-Dienone (147) *via* Selenation and Oxidation of the Alkylated Oxepinone (156)



Reagents and conditions: a) LDA, PhSeCl, -78 °C, 5 min; b) Pyridine, H_2O_2, CH_2Cl_2, 10 min, 37% (over two steps).

The *E*-dienone **147** underwent isomerization and an electrocyclization reaction to the artocarpol D analogue **121** in presence of allylamine and magnesium sulfate.

Scheme 56 Isomerization and Electrocyclic Reaction of the *E*-Dienone (147) to the Artocarpol D Analogue (121)



Reagents and conditions: a) allylamine, $MgSO_4$, THF, reflux, 8 h, 80%.

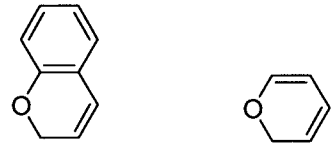
In summary, the alkylation, selenation and oxidation route afforded the desired 2*H*-pyran derivatives **30** and **121**. However, this involved several low yielding steps and the overall yield of the processes were 14 and 9%, respectively, from the oxepinone **33**.

3.5 Study of the [2+2] Photocycloaddition Reaction

3.5.1 Introduction

An important step in the proposed total synthesis of artocarpol A (**1**) and analogues involved the [2+2] photocycloaddition reaction of 2*H*-pyran derivatives. A general introduction to this type of reaction and examples of a 2*H*-pyran and 2*H*-chromenes that undergo [2+2] photocycloaddition reactions were discussed in Chapter 2 (Section 2.4).

2*H*-Chromenes are structurally related to 2*H*-pyrans and are sometimes referred to as benzopyrans (Figure 39). Therefore, the synthesis of 2*H*-chromenes which could undergo [2+2] photocycloaddition reactions became of interest. There are many published methods for the synthesis of 2*H*-chromenes and the procedure published by Talley was further developed for this purpose.[78,79]



2*H*-chromene 2*H*-pyran

Figure 39 Structures of 2*H*-chromene and 2*H*-pyran.

Model studies of the [2+2] photocycloaddition reaction of 2*H*-chromenes were undertaken in order to determine the optimal reaction conditions that would

(78) Hu, H. PhD. Thesis, Simon Fraser University, Burnaby, 2004.

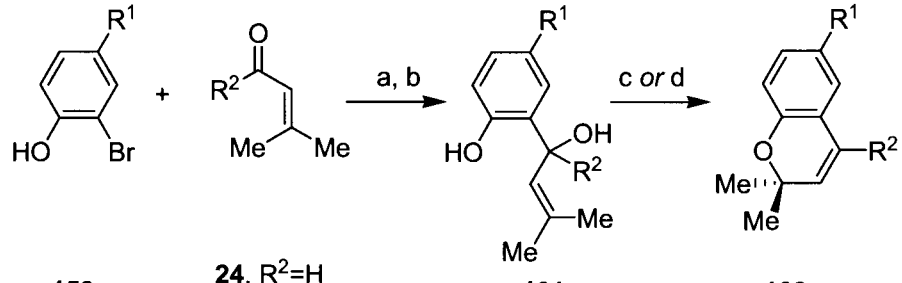
(79) Talley, J. J. *Synthesis* **1983**, 845.

be applied to a similar reaction of the 2*H*-pyran **30** which was expected to afford the artocarpol A analogue **29**.

3.5.2 Method Development for the Synthesis of 2*H*-Chromene Derivatives

Parallel to the study of the cross-aldol reaction of the oxepinone **33** and α,β-unsaturated aldehydes, a facile method for the synthesis of a series of 2*H*-chromenes was developed based on a published procedure.[79] This reported procedure involved initial treatment of an ethereal solution of substituted *o*-bromophenols **159** with 2 equiv *n*-butyllithium at room temperature. Treatment of the resultant dianion with either senecialdehyde (**24**) or mesityl oxide (**160**) afforded the corresponding allylic alcohols **161**. The 2*H*-chromene derivatives **162** were obtained from the dehydration reaction of allylic alcohols **161** under acid catalysis or simply by thermolysis by means of a distillation procedure (Scheme 57).

Scheme 57 Synthesis of 4- and 6-Substituted 2,2-Dimethyl-2*H*-chromenes (163) by Talley and Co-Workers



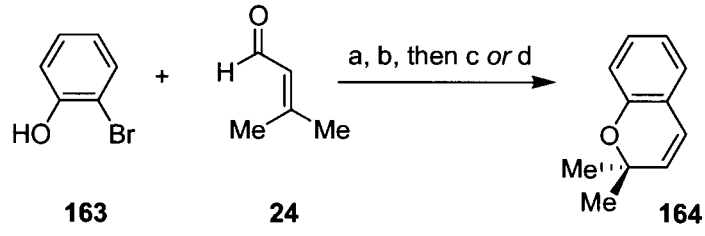
159 **24**, R^2=H; **160**, R^2=CH_3 **161** **162**

R^1 = H, CH_3, OCH_3 *or* Cl

Reagents and conditions: a) *n*-BuLi, Et_2O, 0 °C to room temperature; b) Et_2O, -20 °C; c) *p*-TsOH, PhMe, 60 °C; d) distillation.

The above procedure was applied to the synthesis of the 2*H*-chromene **164**. Both acid catalysis and distillation were employed as the last step of the reaction sequence. The acid-catalyzed reaction with *p*-toluenesulfonic acid afforded the 2*H*-chromene in 53% yield whereas distillation of the crude product obtained in the previous step led to decomposition of the products. The reported yield (75%) for the preparation of 2*H*-chromene **164** could not be duplicated.[79]

Scheme 58 Synthesis of the 2*H*-Chromene (164) *via* the Talley Procedure

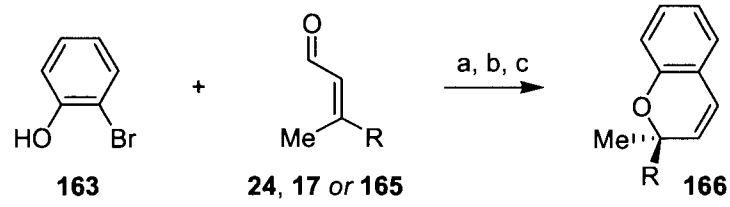


163 **24** **164**

Reagents and conditions: a) *n*-BuLi, Et_2O, 0 °C to room temperature; b) Et_2O, -20 °C; c) *p*-TsOH, PhMe, 60 °C, 20 h, 53%; d) distillation.

The synthesis of 2*H*-chromenes suitable as substrates for the [2+2] photocycloaddition reaction required the use of α,β-unsaturated aldehydes or ketones containing at least one additional double bond. Therefore, citral (**17**) and farnesal (**165**) were selected. The conditions used for the synthesis of the 2*H*-chromene **164** were then employed in the reaction of *o*-bromophenol **163** with citral (**17**) and farnesal (**165**). In these cases, the corresponding 2*H*-chromene derivatives (**70** and **167**) were obtained in 15 and 18 % yield, respectively, with the use of *p*-toluenesulfonic acid as the catalyst in the last step of the process. Due to the low yield of these reactions and difficulties in the purification of the final compounds, the reaction conditions were modified.

Scheme 59 Synthesis of 2*H*-Chromenes Derivatives from o-Bromophenol (163)



163 **24**, **17** *or* **165** **166**

24, R = Me
17, R = $(CH_2)_2CH=C(Me)_2$
165, R = $(CH_2)_2CH=C(Me)(CH_2)_2CH=C(Me)_2$

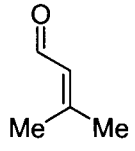
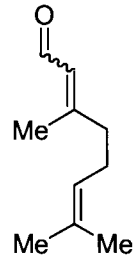
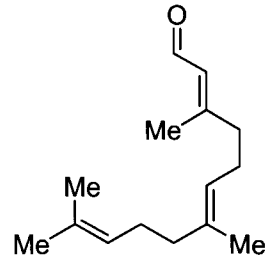
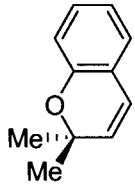
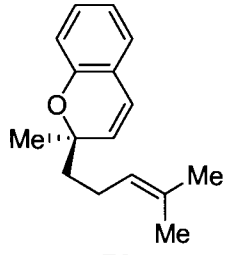
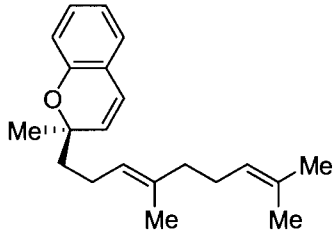
Reagents and conditions: a) *n*-BuLi, Et_2O, -18 °C; b) α,β-unsaturated aldehyde, Et_2O, -78 °C; c) PhMe, reflux, 20 h.

The new experimental conditions involved generation of the dianion at -18 °C rather than at 0 °C with an excess of *n*-butyllithium (3 equiv instead of 2 equiv as reported in the original procedure). The reaction mixture was not allowed to warm to room temperature and it was kept at -18 °C for 2 h. The α,β-unsaturated aldehyde (1.5 equiv) was then was added to the reaction mixture at -78 °C (as compared to -20°C in the original procedure). The work-up of the reaction mixture was identical to that reported. However, the resultant oil was dissolved in toluene and heated at reflux for 20 h without the addition of an acid catalyst (Scheme 59).

The reaction of *o*-bromophenol (**163**) with senecialdehyde (**24**) under these new set of conditions afforded the 2*H*-chromene **164** in 70% yield, a significant improvement from the 53% yield obtained with the reported reaction conditions. The use of these reaction conditions in the reaction of the *o*-bromophenol (**163**) with citral (**17**) and farnesal (**165**) allowed for the synthesis of

the 2*H*-chromene derivatives **70** and **167** in 65 and 45% yield, respectively (Table 7).

Table 7 **Details of the Synthesis of 2*H*-Chromene Derivatives from *o*-Bromophenol (163)**

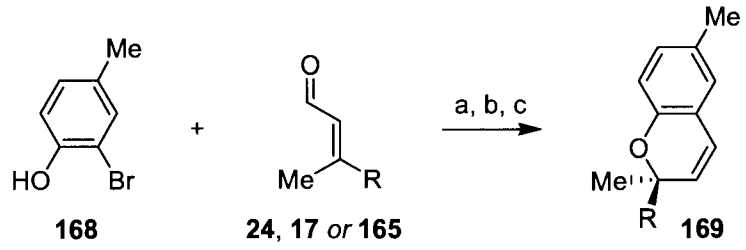
Aldehyde	 Senecialdehyde **24**	 Citral **17**	 Farnesal **165**
Product	 **164**	 **70**	 **167**
Yield (%)	70	65	45

The optimized reaction conditions were also employed in the successful coupling of two other *o*-bromophenol derivatives (2-bromo-4-methylphenol **168** and 1-bromo-2-naphtol **173**) (

Scheme 60 and

Scheme 61). The 2*H*-chromene derivatives were obtained in moderate but reproducible yield (Table 8 and Table 9).

Scheme 60 **Synthesis of 2*H*-Chromene Derivatives from 2-Bromo-4-methyl phenol (168)**

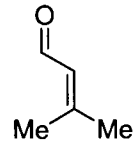
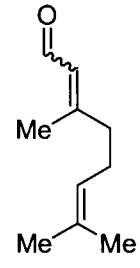
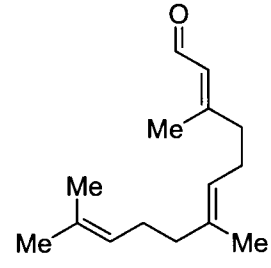
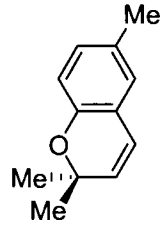
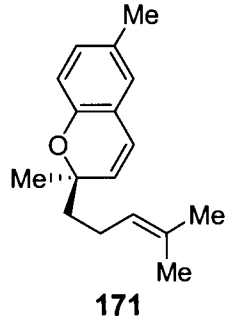
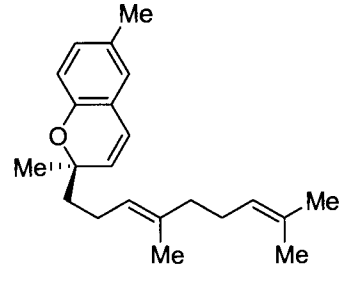


168 **24, 17 *or* 165** **169**

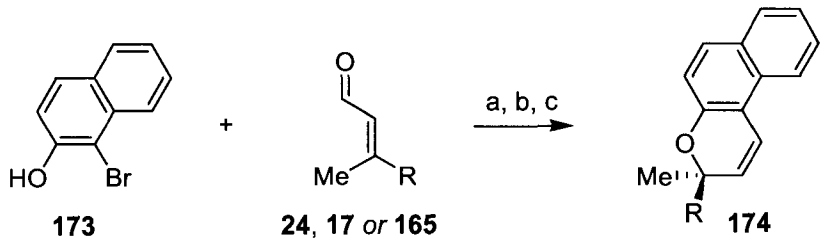
24, R = Me
17, R = $(CH_2)_2CH=C(Me)_2$
165, R = $(CH_2)_2CH=C(Me)(CH_2)_2CH=C(Me)_2$

Reagents and conditions: a) *n*-BuLi, Et_2O, -18 °C; b) α,β-unsaturated aldehyde, Et_2O, -78 °C; c) PhMe, reflux, 20 h.

Table 8 **Details of the Synthesis of 2*H*-Chromene Derivatives from 2-Bromo-4-methyl phenol (168)**

Aldehyde	 Senecialdehyde **24**	 Citral **17**	 Farnesal **165**
Product	 **170**	 **171**	 **172**
Yield (%)	50	54	40

Scheme 61 Synthesis of 2*H*-Chromene Derivatives from 1-Bromo-2-naphtol (173)

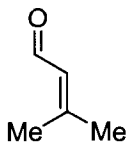
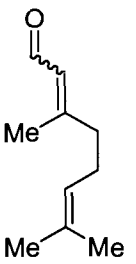
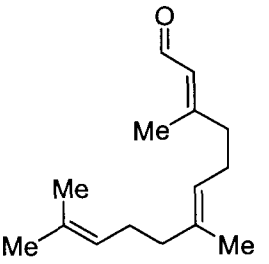
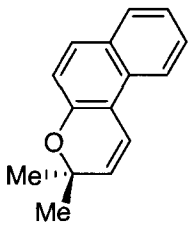
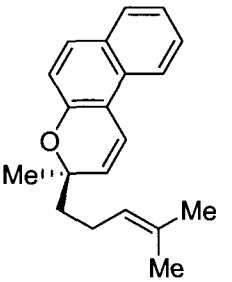
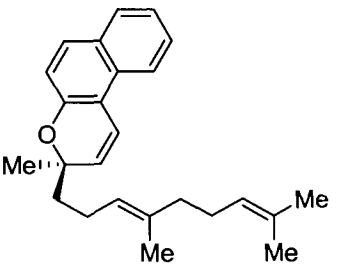


173 **24**, **17** *or* **165** **174**

24, R = Me
17, R = $(CH_2)_2CH=C(Me)_2$
165, R = $(CH_2)_2CH=C(Me)(CH_2)_2CH=C(Me)_2$

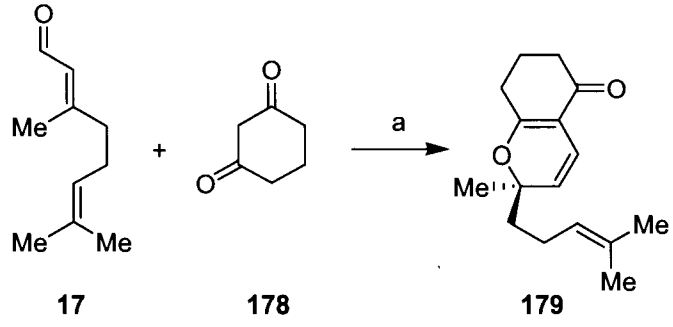
Reagents and conditions: a) *n*-BuLi, Et_2O, -18 °C; b) α,β-unsaturated aldehyde, Et_2O, -78 °C; c) PhMe, reflux.

Table 9 Details of the Synthesis of 2*H*-Chromene Derivatives from 1-Bromo-2-naphtol (173)

Aldehyde	 Senecialdehyde **24**	 Citral **17**	 Farnesal **165**
Product	 **175**	 **176**	 **177**
Yield (%)	47	51	60

The optimization of the reported procedure for the synthesis of 4- and 6-substituted 2,2-dimethyl-2*H*-chromenes allowed for the synthesis of a series of structurally different 2*H*-chromenes. Moreover, a 5,6,7,8-tetrahydrochromene derivative **179** was synthesized from citral (**17**) and 1,3-cyclohexanedione (**178**) in the presence of a catalytic amount of 1,2-ethanediammonium diacetate according to a procedure reported by Tietze and co-workers (Scheme 62).[80] Of note, these reaction conditions have also been used to prepare derivatives of a related natural product, daurichromenic acid.[34,78] The chromene derivative **179** represented an additional substrate for the subsequent [2+2] photocycloaddition reaction.

Scheme 62 Synthesis of the 5,6,7,8-Tetrahydrochromene Derivative (179)



17 **178** **179**

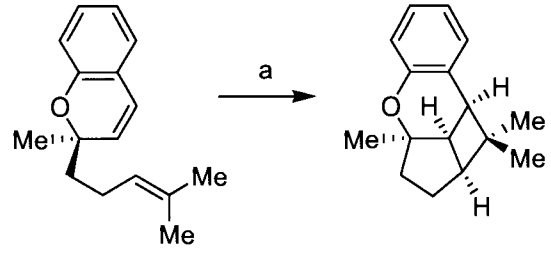
Reagents and conditions: a) $^{+}NH_3(CH_2)_2{}^{+}NH_3(AcO^{-})_2$, MeOH, 3 h, 62%.

3.5.3 The [2+2] Photocycloaddition Reactions of 2*H*-Chromene Derivatives

2-Methyl-2-(4-methylpent-3-enyl)-2*H*-chromene **70** had been reported to undergo [2+2] photocyclization reactions when irradiated in benzene, using a high-pressure mercury lamp (Scheme 63).[30]

(80) Tietze, L.-F.; Kiedrowski, G. V.; Berger, B. *Synthesis* **1982**, 683.

Scheme 63 Reported [2+2] Photocycloaddition Reaction of the 2*H*-Chromene (70)



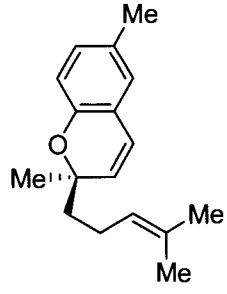
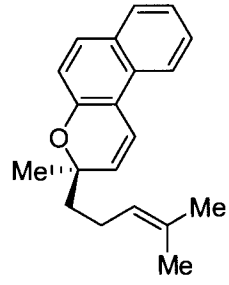
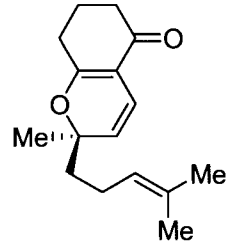
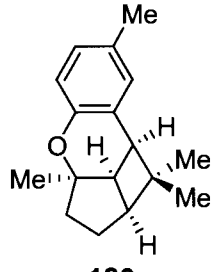
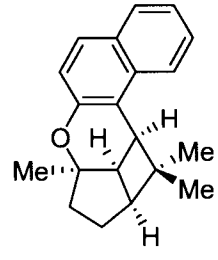
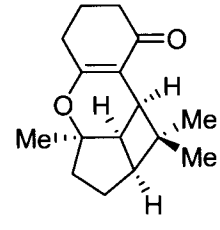
70 **72**

Reagents and conditions: a) benzophenone, PhH, hν, 4 h, 25%.

The reported reaction conditions were optimized by removal of the oxygen from the reaction media prior to irradiation and by employment of a quartz reaction flask as well as a shorter reaction time. This afforded the cycloadduct **72** in 54% yield which was a significant improvement to that reported (25%).

The optimized reaction conditions were then employed in the [2+2] photocycloaddition reaction of the 2*H*-chromene derivatives **171** and **176** and the tetrahydro-2*H*-chromene **179**. This afforded the cyclic adducts **180**, **181** and **182** (Table 10).

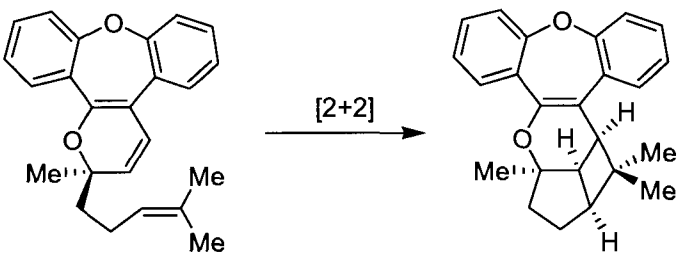
Table 10 **Synthesis of [2+2] Photocycloaddition Products from 2*H*-Chromene Derivatives**

Substrate	 **171**	 **176**	 **179**
Product	 **180**	 **181**	 **182**
Yield (%)	30	41	62

3.5.4 [2+2] Photocycloaddition Reaction of the 2*H*-Pyran (30) and Synthesis of the Artocarpol A Analogue (29)

The [2+2] photocycloaddition reaction of the 2*H*-pyran **30** was the last step in the proposed synthesis of the complex polycyclic ring structure of artocarpol A analogue (**29**) (Scheme 64).

Scheme 64 Proposed [2+2] Photocycloaddition Reaction of the 2*H*-Pyran (30) to the Artocarpol A Analogue (29)



30 **29**

The first attempts to cyclize the 2*H*-pyran **30** resulted in a very complex mixture of reaction products. The reaction conditions employed were based on the model studies performed with the 2*H*-chromenes. A benzene solution of the 2*H*-pyran **30** that contained benzophenone (1 equiv) was degassed and irradiated in a quartz vessel. In the ^{1}H NMR spectrum of the crude reaction mixture, several characteristic peaks corresponding to the two *E*-dienones (**38** and **39**) and to the unreacted 2*H*-pyran **30** were identified. The presence of the peaks corresponding to the sensitizer, benzophenone, in the aromatic region and overlapping peaks in the high field region (δ = 1-3 ppm) complicated the identification of any other reaction products.

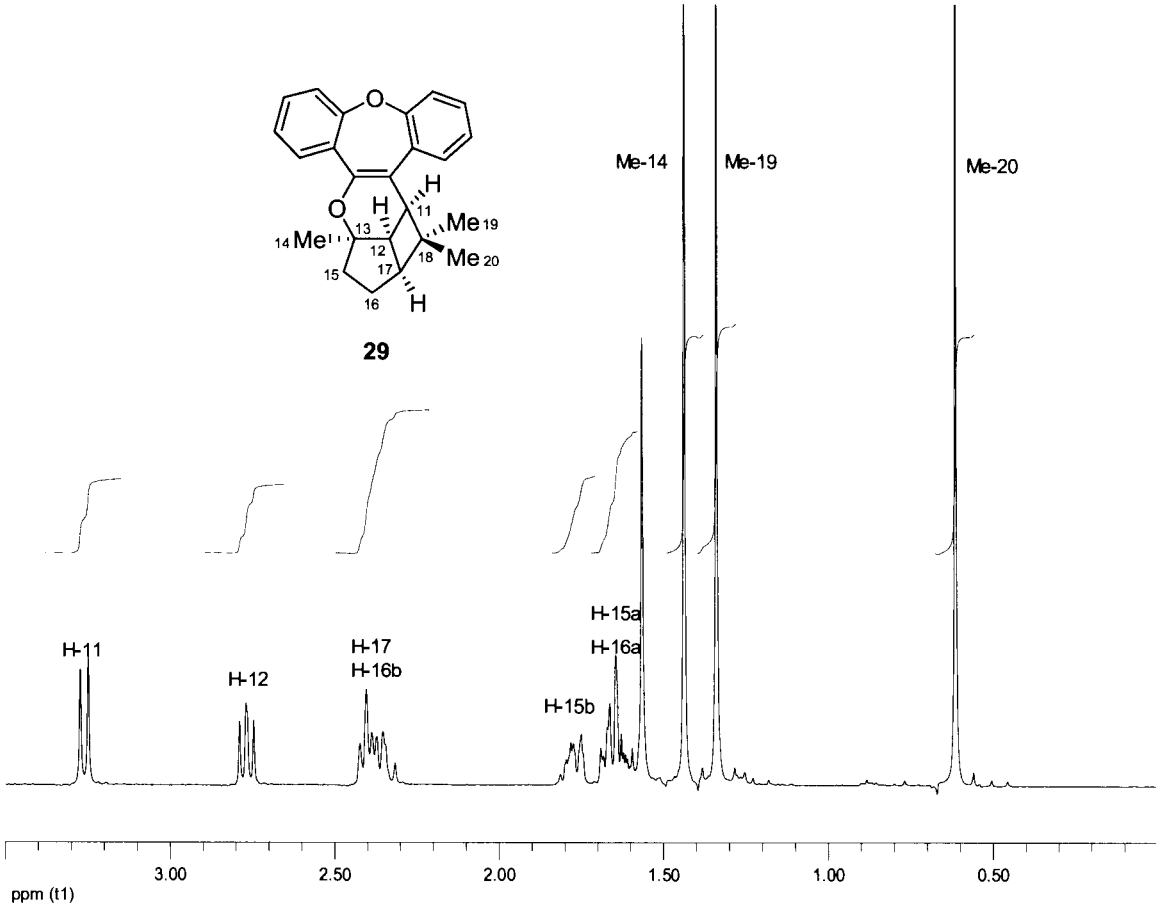
The highest running spot on the thin layer chromatography plate had an R_f value that corresponded to the 2*H*-pyran **30** and was separated by flash chromatography. Analysis of the ^{1}H NMR spectrum showed that this material comprised a mixture of 2*H*-pyran **30** and the photocycloaddition product **29** in a 1:3 ratio. Several solvent systems were employed as eluent but the two compounds could not be separated by flash chromatography. However, the mixture of compounds solidified on storage. Since the 2*H*-pyran **30** was known

to be an oil, it was assumed that the artocarpol A analogue **29** was a solid and so purification efforts were concentrated towards recrystallization.

Fractional recrystallization of the 2*H*-pyran **30** and cycloaddition product **29** mixture from hexanes afforded the pure artocarpol A analogue **29** as white crystals with a melting point in the range 184-186 °C. Repetitive fractional recrystallization was necessary for a better separation of the components. The yield was calculated using the mixture and the ratio of compounds and a 51% yield of the artocarpol A analogue **29** was determined. However, due to small losses during separation procedure, the artocarpol A analogue was isolated in 45% yield.

The structure of the artocarpol A analogue **29** was fully assigned on the basis of a series of 1D and 2D NMR experiments. The most high field signal in the ^{1}H NMR spectrum appeared at a chemical shift of δ = 0.61 ppm and corresponded to one of the methyl substituents (Figure 40). A similar singlet was present in the ^{1}H NMR spectrum of artocarpol A (**1**) at δ = 0.60 ppm (Section 1.3, Table 1).[3] Furthermore, in all of the ^{1}H NMR spectra of the [2+2] photocycloaddition products synthesized from 2*H*-chromene derivatives a singlet was present at a chemical shift δ ~ 0.70 ppm. A chemical shift value of ~0.70 has been previously assigned to other cyclobutane methyl substituents and was found to be characteristic of this four, five, six fused ring system.[29] The singlets at δ = 1.34 ppm and δ = 1.44 ppm were assigned to *Me*-19 and *Me*-14, respectively, based on the NOE contacts (Figure 43). The remaining singlet at δ

= 0.61 was assigned to *Me*-20. The proton (*H*-11), assigned based on multiplicity and chemical shift, was used as a diagnostic proton.



29

Figure 40 Detail from the ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of the artocarpol A analogue (29).

The signals corresponding to the remaining non-aromatic protons were assigned based on the 2D NMR spectra. In the ^{1}H-^{1}H COSY spectrum, coupling between *H*-11 and *H*-12 was observed (J = 9 Hz). Another ^{1}H-^{1}H COSY correlation indicated coupling between *H*-12 and the proton(s) from the multiplet at δ = 2.32-2.42 ppm which was presumably *H*-16 (Figure 41).

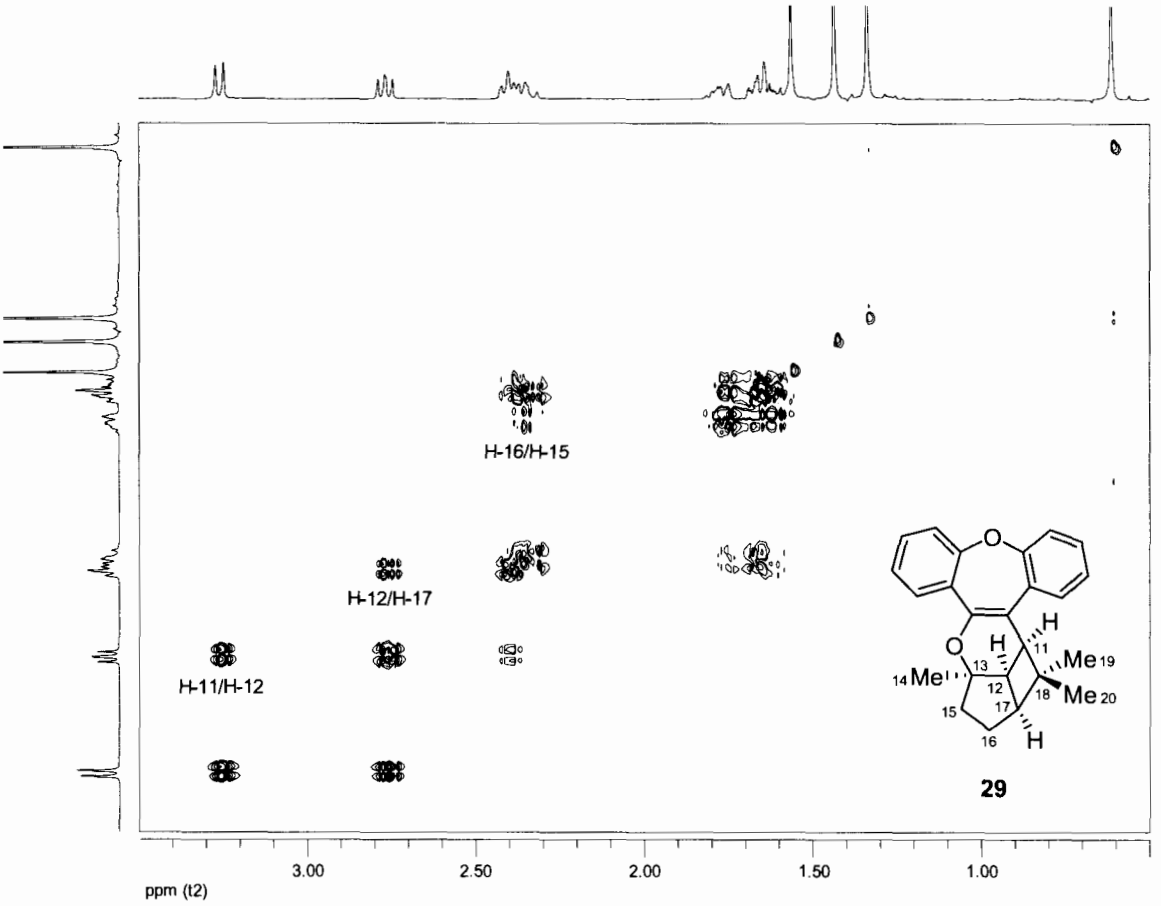


Figure 41 **Detail from the ^{1}H-^{1}H COSY ($CDCl_3$, 400 MHz) spectrum of the *artocarpol A* analogue (29).**

Data from the HMQC spectrum was used to identify the protons at *H*-15, *H*-16 and C(17) (Figure 42). Of significant importance was the discovery that the two protons in the multiplet at δ = 2.32-2.42 ppm were attached to different carbons. Similarly, the multiplet at δ = 1.60-1.69 ppm contained protons that were attached to different carbons. Since one of the carbons correlated with the multiplet at δ = 2.32-2.42 ppm and it was a tertiary carbon, it was assigned as C(17).

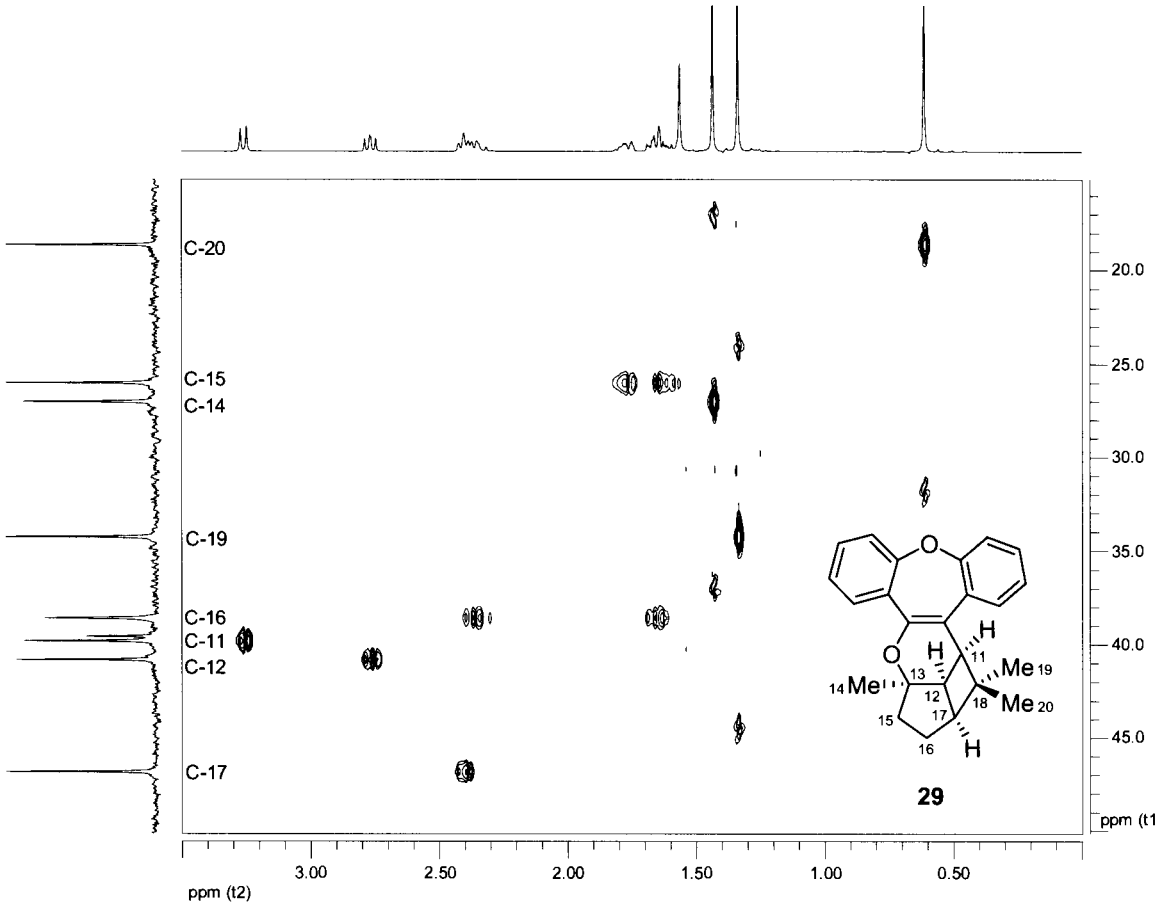
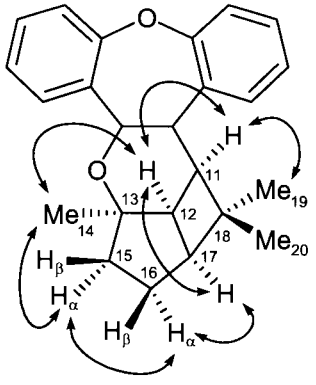


Figure 42 **Detail from the HMQC spectrum ($CDCl_3$) of the artocarpol A analogue (29).**

The final assignment of the diastereotopic protons *H*-15 and *H*-16 was based on the NOE contacts (Figure 43). The protons *H*-15$_\alpha$ and *H*-16$_\alpha$ were found to be part of the multiplet at δ = 1.60-1.69 ppm according to the observed NOE contacts with *Me*-14 and *H*-17. It is worth mentioning that the 0.7 ppm difference in chemical shift of the two diastereotopic protons at C(16) was the same as recorded in the ^{1}H NMR spectrum of artocarpol A (**1**) (Section 1.3, Table 1). Importantly, the NOE contacts between *H*-12 and *H*-11 as well as between

Me-14 and *H*-17 placed all four of these substituents on the same face of the molecule.



29

Figure 43 **Contacts observed in the NOESY spectrum of the artocarpol A analogue (29).**

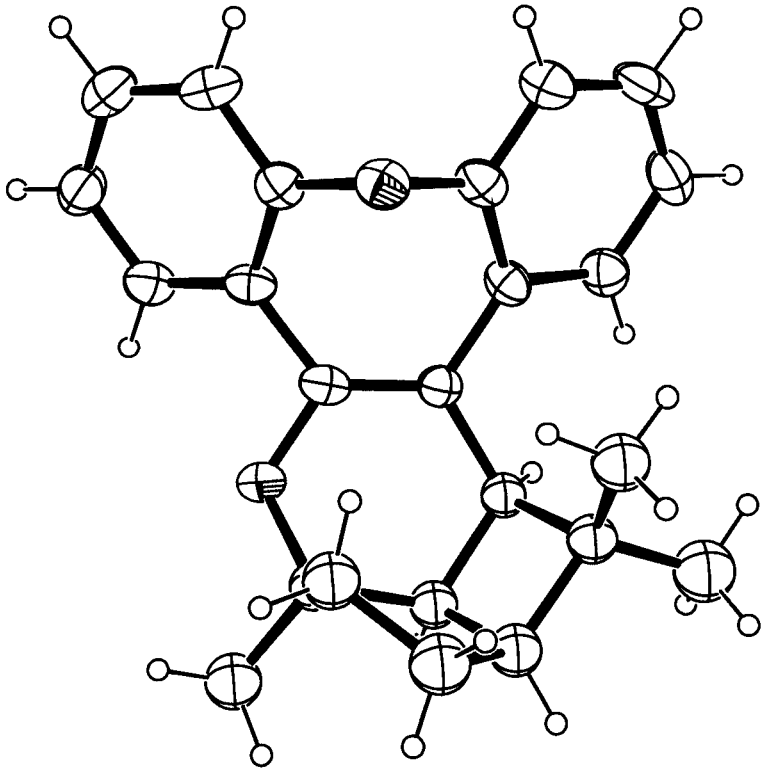
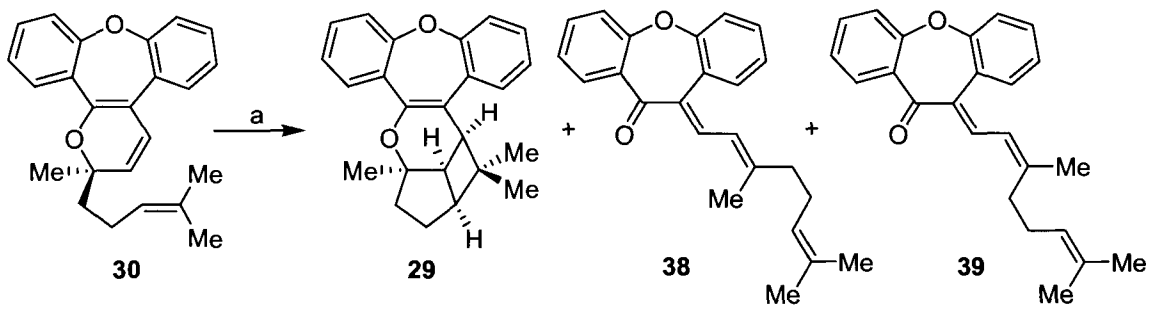


Figure 44 **X-ray crystal structure of the artocarpol A analogue (29). The thermal ellipsoids are drawn at a 30% probability level.**

The structural assignment of the artocarpol A analogue **29** was confirmed by X-ray crystallography. The crystal structure determination confirmed the relative stereochemistry at C(11), C(12), C(13) and C(17). The four, five and six membered rings formed a "cup-like" shape and the oxygen heteroatoms were both out from the planes of the oxepinone ring system (pointing in opposite directions). The oxepinone ring structure was non-planar and the benzene rings were oriented in the opposite direction to the "cup" like structure. Interestingly, the two enantiomers of the compound crystallized together forming one unit cell.

Scheme 65 The [2+2] Photocycloaddition and Ring-Opening Reaction of the 2*H*-pyran (30)



30 **29** **38** **39**

Reagents and conditions: a) benzophenone, PhH, hν, 24 h, 29 **(45%),** 38 **+** 39 **(10%),** 30 **(15%).**

The two other compounds separated by flash chromatography from the [2+2] photocycloaddition reaction mixture were identified as the two isomeric *E*-dienones (**38** and **39**). These two compounds were probably formed *via* the photochemical ring-opening reaction of the 2*H*-pyran **30** to form the *Z*-dienones (**36** and **37**) followed by isomerization of the α,β-double bond to the *trans*-configuration (Scheme 65).

Individual identification of the four compounds isolated from this reaction allowed for the analysis of the complex crude reaction mixture by analysis of the ^{1}H NMR spectrum. The TLC spots corresponding to the 2*H*-pyran **30**, artocarpol A analogue **29** and *E*-dienones **38** and **39** were grouped together and it was possible to easily isolate the four compounds from the rest of unidentified reaction products and from the sensitizer.

One of the undesired side reactions of the photochemical reaction of the 2*H*-pyran **30** was the ring-opening process that led to the *E*-dienones (**38** and **39**). In order to minimize the side reaction and to increase the yield of the artocarpol A analogue **29**, the effect of several different reaction conditions on the relative ratio of products was investigated (Table 11). The analysis of the ^{1}H NMR spectrum of the fraction containing the four compounds was used to obtain the relative ratios listed below (Table 11). It was found in the previous [2+2] photocycloaddition reaction studies on the 2*H*-chromene derivatives that it was important to remove oxygen from the reaction medium. Therefore all reactions were conducted in absence of oxygen. Deoxygenation of the reaction mixtures was performed by either a freeze-pump-thaw technique or by bubbling dry nitrogen through the solution for 2 h. Since both techniques gave similar results, the second procedure was chosen for experimental simplicity.

Table 11 Study of the [2+2] Photocycloaddition Reaction of the 2*H*-Pyran (30)

Entry	Solvent	Sensitizer	Irradiation Source	Glass Type	Time (h)	Product Distribution (relative ratios)		
						30	**29**	**38 + 39**
1	benzene	benzophenone	medium pressure	quartz	7	1.7	1	1.2
2	benzene	benzophenone	medium pressure	quartz	24	2	5	1
3	benzene	acetophenone	medium pressure	quartz	7	2.5	1	2.5
4	benzene	benzophenone	medium pressure	pyrex	7	3.2	1	3.2
5	benzene	no	medium pressure	quartz	7	2.5	0	1
6	acetone	acetone	medium pressure	pyrex	7	1.1	1	1.1
7	acetone	acetone	medium pressure	quartz	7	1	5	4
8	acetone	acetone	low pressure	quartz	7	2.2	1	1
9	hexanes	no	low pressure	quartz	7	5	0	1

Technical specification of the low pressure and medium-pressure mercury lamp can be found in the reference handbooks.[81,82]

The study of the photocycloaddition reaction allowed for a better understanding of the experimental conditions that influenced the outcome of the

(81) Gould, I. R. *Handbook of Organic Photochemistry*; CRC Press, Inc.: Boca Raton, Florida, 1989.

(82) Murov, S. L. *Handbook of Photochemistry*; Marcel Dekker, Inc.: New York, 1973.

reaction. The presence of a sensitizer seemed to be absolutely necessary to promote the [2+2] photocycloaddition. Three different sensitizers, benzophenone, acetophenone and acetone were used in the study and their spectral characteristics are listed below (Table 12). The extinction coefficients listed for the sensitizers are given for the wavelengths that correspond to the output of the UV lamps used in the experiments.[82] The UV/VIS spectrum of the 2*H*-pyran **30** showed absorption maxima at 249 (ε 13564) and 352 (ε 6721).

Table 12 Spectroscopic Properties of the Sensitizers Used in the Study of the [2+2] Photocycloaddition Reaction of the 2*H*-Pyran (30)

Compound	τ_T (μsec)	ε_{254}	ε_{313}	ε_{366}
acetone	0.94	7	3	~ 0
acetophenone	3.5	10^3	4×10^1	5
benzophenone	12	1.7×10^4	5×10^1	7×10^1

τ_T = lifetime of lowest excited triplet state

ε_{254} = extinction coefficient at 254 nm (in solution at room temperature)

ε_{313} = extinction coefficient at 313 nm (in solution at room temperature)

ε_{366} = extinction coefficient at 366 nm (in solution at room temperature)

In the absence of a sensitizer there was no cycloadduct present in the reaction mixture (Table 11, entries 5 and 9). Compared to benzophenone and acetophenone, acetone was easier to remove from the reaction mixture and caused the consumption of more of the starting material as well as decreased the reaction time (Table 11, entry 7). However, the propensity for ring-opening reaction of the 2*H*-pyran **30** to afford the *E*-dienones (**38** and **39**) was increased

(Table 11, entry 7). Acetone also caused other side reactions to occur that led to more complex reaction mixtures which were difficult to purify. The irradiation source used in most of the experiments was a medium pressure mercury lamp.

Pyrex glass reaction vessels were also used in several experiments to filter some of the incident wavelengths of light under 360 nm.[83] The photochemical reaction gave the same four products in both pyrex and quartz but the [2+2] photocycloaddition product was the major component of the mixture when a quartz reaction flask was used rather than pyrex (Table 11, entries 6 and 7). Quartz glass allows transmission of 50% of the incident wavelength of light under 200 nm and 90% of the incident wavelength of light under 240 nm.[83]

The photochemical reaction of the 2*H*-pyran **30** was also dependent on the reaction time. When a sample was irradiated for 24 hours, the ratio of the artocarpol A analogue **29** increased significantly as compared to the reaction irradiated for 7 hours (Table 11, entries 1 and 2). Irradiation of the sample for longer then 24 hours did not change the product ratio.

3.6 Conclusions

The synthesis of the known 11*H*-dibenzo[*b,f*]oxepin-10-one **33** was optimized and the oxepinone was isolated in 57% overall yield and in five steps from commercially available starting materials. The oxepinone **33** was used as a model compound to test the key cross-aldol and [2+2] photocyclization steps proposed for the synthesis of artocarpol A (**1**).

---

(83) Horspool, W.; Armesto, D. *Organic Photochemistry: A Comprehensive Treatment*; Ellis Horwood Limited, PTR Prentice Hall: Chichester, England, New York, 1992.

The cross-aldol condensation reaction of the oxepinone **33** with citral (**17**) was studied and optimized to afford the 2*H*-pyran derivative **30** as the main product from four other possible condensation products. The 2*H*-pyran derivative **30** was isolated in 50% yield. However, the other aldol condensation products isolated were resubjected to the aldol reaction conditions to afford the 2*H*-pyran derivative **30** in 80% yield. Therefore, the overall yield for the 2*H*-pyran derivative **30** was 72%. Similarly, the cross-aldol reaction of the oxepinone **33** with senecialdehyde (**24**) afforded the artocarpol D analogue **121** in 61% overall yield.

The equilibrium between the 2*H*-pyran compounds (**30** and **121**) and the dienone compounds (**38**, **39** and **147**) was found to favour the 2*H*-pyran compounds.

The synthesis of the artocarpol A analogue **29** was completed in one additional step *via* a [2+2] photocycloaddition reaction of the 2*H*-pyran **30** derivative in 51% yield (62% based on recovered starting material). Thus, in two steps from known compounds the complete polycyclic ring system of artocarpol A (**1**) was prepared and the relative stereochemistry of the four stereogenic centres was established.

An alkylation reaction of the oxepinone (**33**) with geranyl bromide (**26**) afforded an analogue of artocarpol E (**5**) (as the corresponding keto-form). Subsequent dehydrogenation of this compound afforded the *E,E*-dienone (**38**) which had been previously prepared by the aldol condensation route. Similarly,

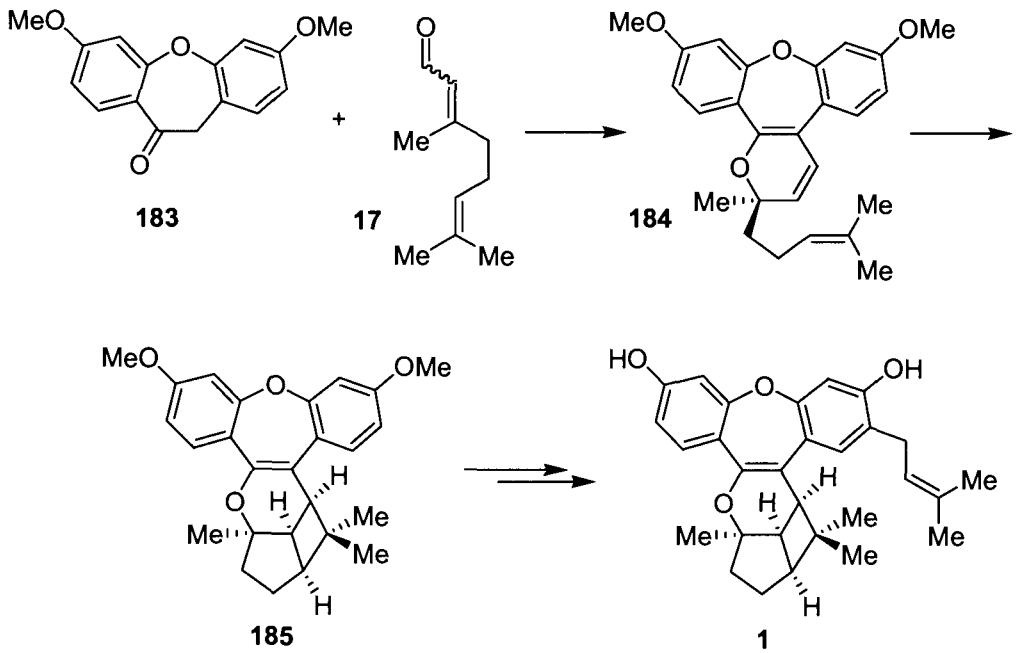
the artocarpol D analogue (**121**) could be accessed by this alternative route but the overall yield was lower.

CHAPTER 4: SYNTHESIS AND REACTIONS OF 3,7-DIMETHOXY-11*H*-DIBENZO[*b,f*]OXEPIN-10-ONE

4.1 Introduction

The artocarpol A analogue **29** had been successfully synthesized as a result of detailed studies regarding the cross-aldol condensation reaction of the oxepinone **33** with citral (**17**) and the [2+2] photocycloaddition reaction of the 2*H*-pyran **30**. The analogue **29** had the same ring structure as the natural product but lacked the three substituents of the aromatic rings of artocarpol A (**1**). Since no viable means to introduce these substituents on the oxepinone **33** or the artocarpol A analogue **29** were identified, the synthesis of 3,7-dimethoxy-11*H*-dibenzo[*b,f*]oxepin-10-one **183** was targeted (Scheme 66).

Scheme 66 Proposed Synthesis of the Dimethoxy-Artocarpol A Analogue (185) from the 3,7-Dimethoxy-11*H*-dibenzo[*b*,*f*]oxepin-10-one (183)



The dimethoxy-oxepinone **183** could undergo the aldol condensation with citral (**17**) and subsequent photocyclization reactions to afford the dimethoxy-artocarpol A analogue **185**. Moreover, deprotection of the methoxy substituents and subsequent *ortho*-prenylation of one of the aromatic rings could afford artocarpol A (**1**) (Scheme 66). The exact sequence to perform the photocycloaddition, deprotection and prenylation steps would be identified by experiment.

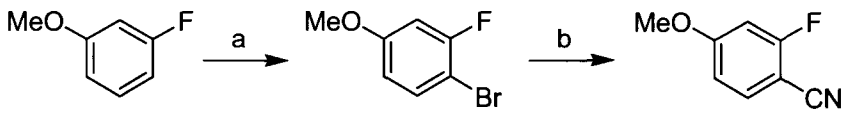
In the synthesis of the unsubstituted oxepinone derivative **33**, the commercially available 2-phenoxybenzoic acid **121** was used as starting material. However, there were no commercially available 2-phenoxybenzoic derivatives that have the required substitution pattern for the synthesis of the dimethoxy-

oxepinone **183**. Thus, the synthesis of the aromatic precursors necessary to form the biaryl ether bond had to be addressed.

4.2 Synthesis of the 3,7-Dimethoxy-11*H*-dibenzo[*b*,*f*]oxepin-10-one (183)

The synthesis of the dimethoxy-oxepinone **183** began from commercially available 3-fluoroanisole **186** which was reacted with bromine in chloroform. This electrophilic aromatic substitution reaction afforded a mixture of two known monobrominated products in a 3:1 ratio. The components of the mixture could not be separated by fractional distillation (Scheme 67).[84]

Scheme 67 Synthesis of 2-Fluoro-4-methoxybenzonitrile (188)



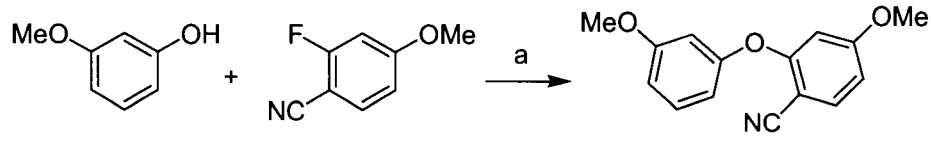
186 **187** **188**

Reagents and conditions: a) Br_2, $CHCl_3$, room temperature, 1 h, then reflux, 1 h; b) CuCN, DMF, 185 °C, 18h, 76% (over two steps).

Thus, the mixture of monobrominated products was reacted with copper cyanide in dimethylformamide to afford a mixture of two nitrile products. These products were then separated by fractional recrystallization from hexanes/ether. The desired compound, 2-fluoro-4-methoxybenzonitrile **188**, was crystallized from the reaction mixture and was isolated as pure white needles. The correct substitution pattern of the product was confirmed by *H-H*- and *H-F*-coupling patterns and constants in the ^{1}H NMR spectrum.

(84) Kelly, S. M. *Helv. Chim. Acta* **1984**, *67*, 1572.

Scheme 68 Synthesis of 2-(3'-Methoxyphenoxy)-4-methoxybenzonitrile (190)



189 **188** **190**

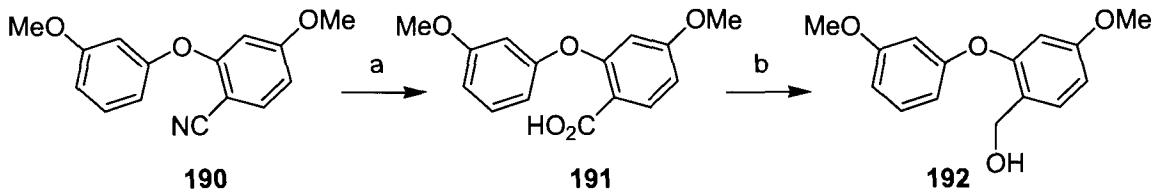
Reagents and conditions: a) 18-crown-6, $KF{\cdot}Al_2O_3$, MeCN, reflux, 20 h, 95%.

The coupling reaction of 2-fluoro-4-methoxybenzonitrile **188** and 3-methoxyphenol **189** was achieved on reaction with potassium fluoride-alumina and a catalytic amount of 18-crown-6 at reflux in acetonitrile.[42] The potassium fluoride reagent was prepared by mixing potassium fluoride and basic alumina in water at room temperature.[85] The method was extremely successful and afforded the pure benzonitrile **190** in 95% yield (Scheme 68).

The hydrolysis reaction of the nitrile **190** was initially attempted in presence of potassium hydroxide in 80% aqueous ethanol but the yield of the reaction was low (40%). A much better yield was obtained by the slow addition of 30 w/w % hydrogen peroxide to a mixture of the nitrile **190**, potassium hydroxide, methanol and ethanol at 0 °C followed by heating at reflux.[42] The addition of the hydrogen peroxide caused an extremely exothermic reaction and so initial cooling of the reaction mixture was essential (Scheme 69).

(85) Schmittling, A.; Sawyer, J. S. *Tetrahedron Lett.* **1991**, *32*, 7207.

Scheme 69 Synthesis of [2-(3'-Methoxyphenoxy)-4-methoxyphenyl]methanol (192)

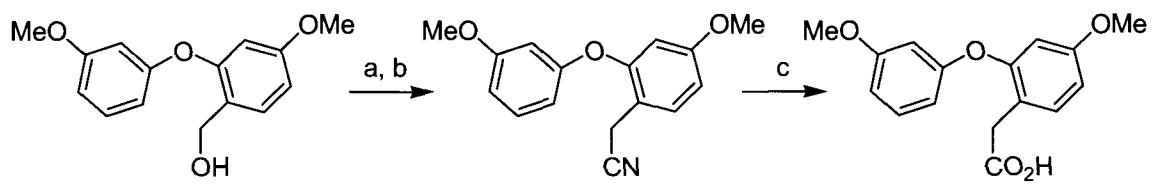


190 **191** **192**

Reagents and conditions: a) KOH, H_2O_2, MeOH, EtOH, 0 °C then reflux, 20 h, 97%; b) $LiAlH_4$, THF, 0 °C, then reflux, 3 h, 93%.

The benzyl alcohol **192** was obtained from the benzoic acid **191** on reduction with lithium aluminum hydride in tetrahydrofuran (Scheme 69).

Scheme 70 Synthesis of 2-[2-(3'-Methoxyphenoxy)-4-methoxyphenyl]acetic acid (194)



192 **193** **194**

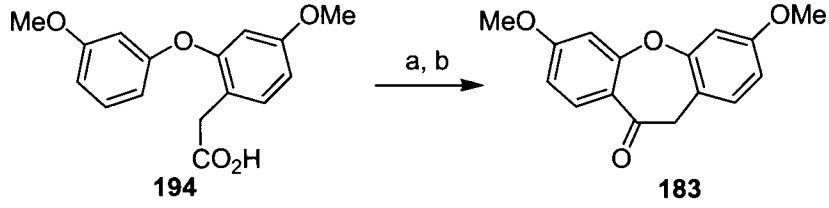
Reagents and conditions: a) HCl, CH_2Cl_2; b) NaCN, DMSO, room temperature, 20 h, 70%; c) EtOH, H_2O, KOH, reflux, 18 h, 85%.

The subsequent step in the homologation sequence required the synthesis of the benzyl chloride from the benzyl alcohol **192**. This transformation proved to be extremely facile and brief shaking of a dichloromethane solution of the benzyl alcohol **192** with concentrated hydrochloric acid afforded the corresponding benzyl chloride quantitatively. Attempted purification of a sample of this benzyl chloride by column chromatography, for characterization purposes, resulted in decomposition. Therefore, following a brief work-up, the chloride was immediately used in the next step. This involved reaction with sodium cyanide

and afforded the nitrile **193** which was then hydrolyzed to the corresponding carboxylic acid **194** under basic conditions (Scheme 70).

In the synthesis of the unsubstituted oxepinone **33**, the ring closure reaction was achieved by heating 2-phenoxyphenylacetic acid **121** in polyphosphoric acid at ~100 °C. Application of the same reaction conditions for the dimethoxy-derivative **194** resulted in extensive decomposition and a low yield (10%) of the desired oxepinone **183** was obtained. Consequently, another common ring closure method, that involved the corresponding acyl chloride and aluminum trichloride, was examined (Scheme 71).

Scheme 71 Synthesis of 3,7-Dimethoxy-11*H*-dibenzo[*b,f*]oxepin-10-one (183)



194 183

Reagents and conditions: a) $SOCl_2$, CH_2Cl_2, 100 °C, 5 min; b) $AlCl_3$, $ClCH_2CH_2Cl$, room temperature, 2 h, 84%.

The reaction of 2-[2-(3'-methoxyphenoxy)-4-methoxyphenyl]acetic acid (**194**) with thionyl chloride in dichloromethane afforded the corresponding acyl chloride which was used in the next step without purification. An intramolecular Friedel-Crafts acylation reaction was achieved in presence of a stoichiometric amount of aluminum trichloride at room temperature and afforded 3,7-dimethoxy-11*H*-dibenzo[*b*,*f*]oxepin-10-one (**183**) in good yield (84%) as a light brown solid that had a melting point in the range 93-96 °C (Scheme 71).

Analysis of the ^{1}H NMR spectrum of the dimethoxy-oxepinone **183** revealed two singlets each corresponding to three protons at δ = 3.79 ppm and at δ = 3.89 ppm. The signals were assigned to the non-equivalent methyl ethers. The two proton singlet at δ = 3.97 ppm was assigned to *H*-11 and was found to be slightly upfield as compared to the corresponding *H*-11 protons of the oxepinone **33** at δ = 4.10 ppm. In the aromatic region, *H*-9 at δ = 8.00 ppm and *H*-1 at δ = 7.18 ppm were assigned based on multiplicity, coupling constant and chemical shift (Figure 45).

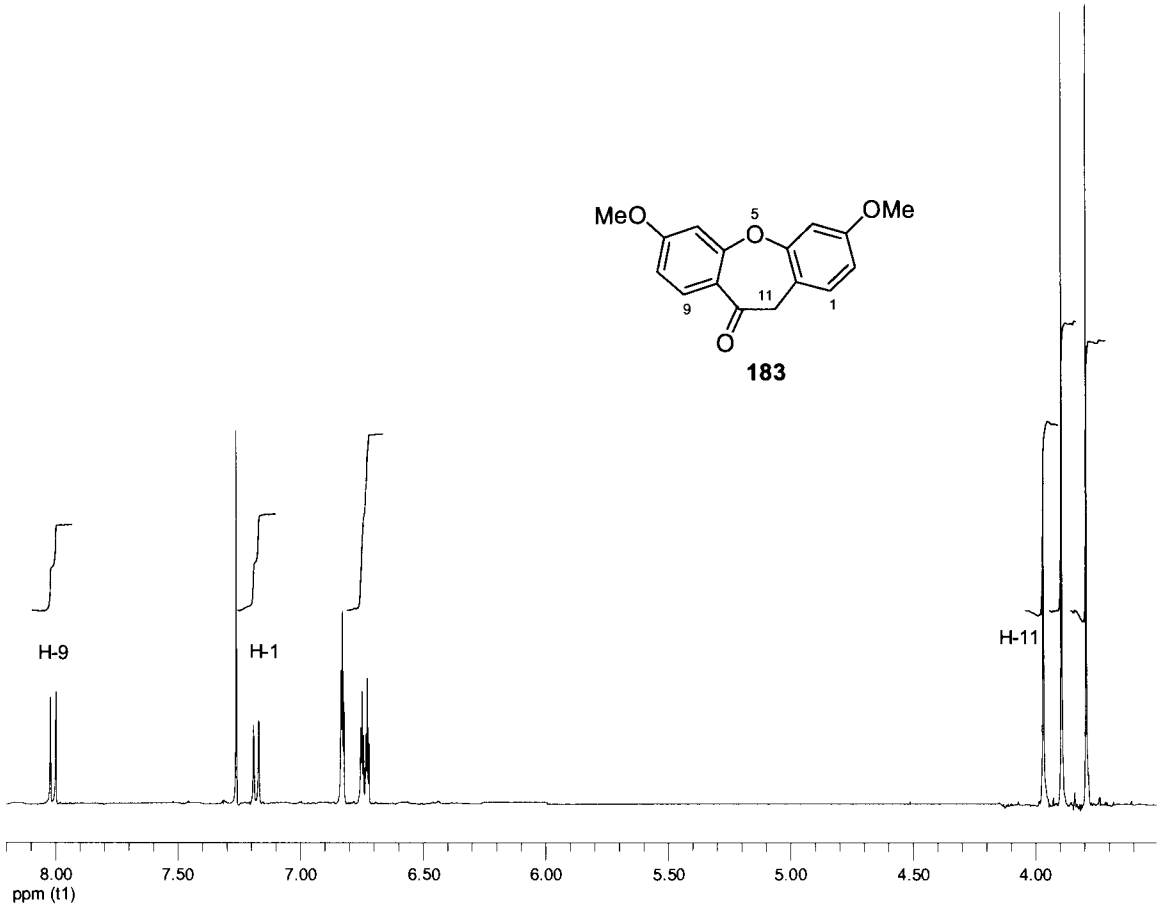


Figure 45 **Detail from the ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of the 3,7-dimethoxy-11*H*-dibenzo[*b,f*]oxepin-10-one (183).**

The ^{13}C NMR spectrum of the dimethoxy-oxepinone **183** was also consistent with the assigned structure. Of particular note, the aromatic carbon atoms directly linked to the oxygen atoms appeared as a separate group in the region δ = 157.7-164.9 ppm and the carbonyl carbon was observed as an isolated signal at δ = 190.0 ppm (Figure 46).

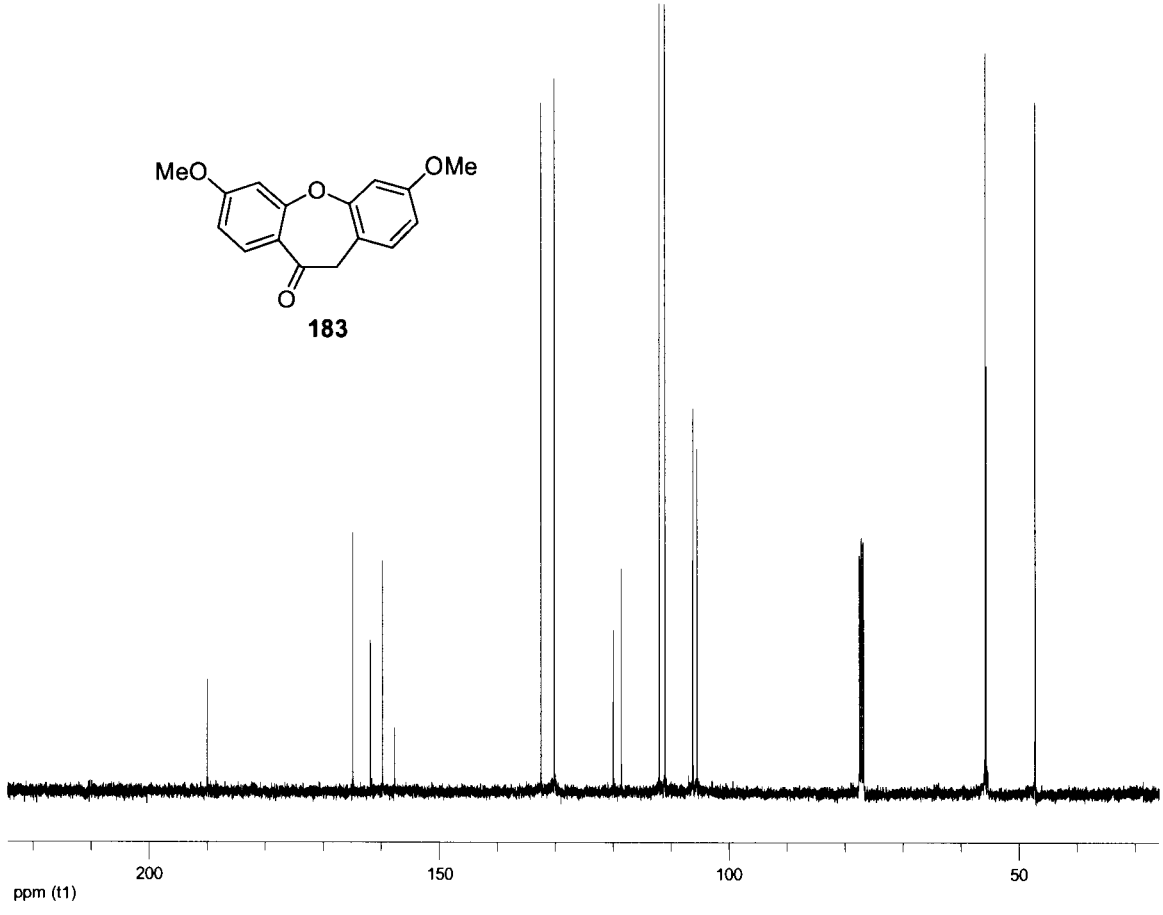


Figure 46 **Detail from the ^{13}C NMR spectrum ($CDCl_3$, 101 MHz) of the 3,7-dimethoxy-11*H*-dibenzo[*b,f*]oxepin-10-one (183).**

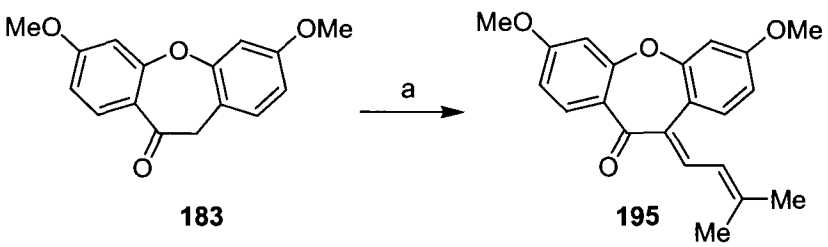
4.3 Reactions of 3,7-Dimethoxy-11*H*-dibenzo[*b*,*f*]oxepin-10-one (183) and Derivatives

In the previous studies of the cross-aldol reaction of the unsubstituted oxepinone **33** with citral (**17**) and senecialdehyde (**24**), two sets of reaction conditions afforded the corresponding cross-aldol products in good yield. These were the Evans protocol involving titanium tetrachloride and amines as well as the amine-mediated reaction. These methods were employed in the reaction of the dimethoxy-oxepinone **183** with citral (**17**) and senecialdehyde (**24**).

4.3.1 Evans Protocol for the Cross-Aldol Reaction

The cross-aldol reaction of the dimethoxy-oxepinone **183** with citral (**17**) in presence of titanium tetrachloride and tri-*n*-butylamine afforded a complex mixture which could not be separated. However, the reaction of dimethoxy-oxepinone **183** with senecialdehyde (**24**) in presence of titanium tetrachloride and tributylamine afforded the *E*-dienone **195** as a single product in 40% yield (Scheme 72).

Scheme 72 Synthesis of *E*-Dimethoxy-Dienone (195) *via* Titanium Tetrachloride/Tributylamine Mediated Cross-Aldol Reaction



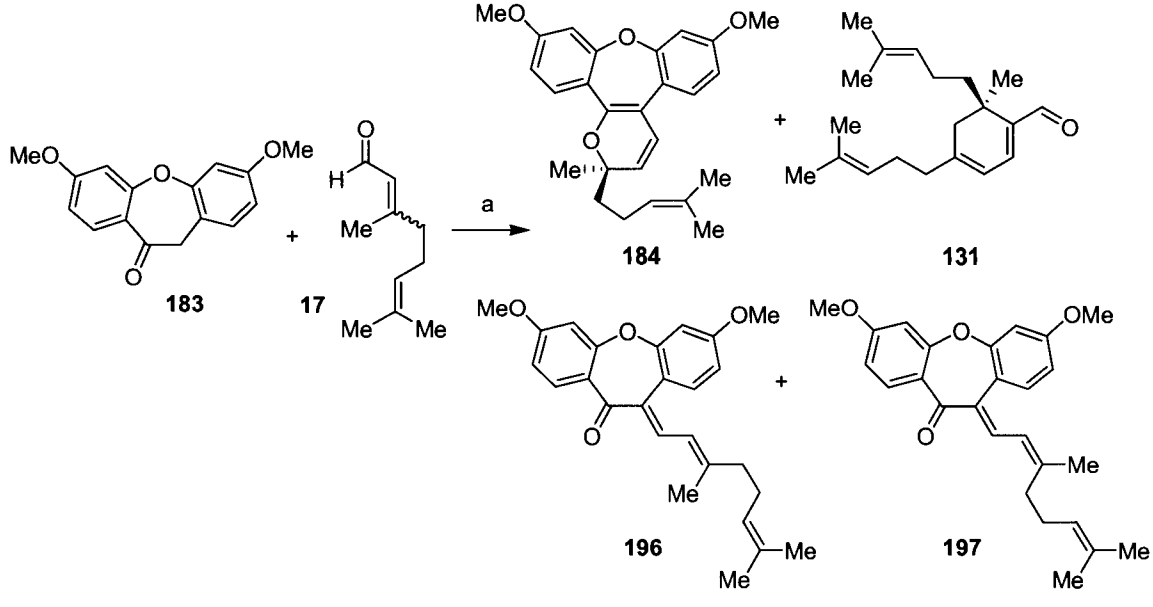
183 **195**

Reagents and conditions: a) 24, $TiCl_4$, *n*-Bu_3N, CH_2Cl_2, **-18 °C, 4 h, then room temperature, 18 h, 40%.**

4.3.2 The Amine-Mediated Aldol Reaction

The optimized conditions for the amine-mediated cross-aldol reaction involving allylamine and anhydrous magnesium sulfate in tetrahydrofuran at reflux were expected to be efficient in promoting the cross-aldol reaction of dimethoxy-oxepinone **183** with citral (**17**). Indeed, the dimethoxy-oxepinone **183** reacted in a similar manner with citral (**17**) as was observed with the oxepinone **33**. The dimethoxy-2*H*-pyran derivative **184**, the cyclic aldehyde **131** and an inseparable mixture of the two isomeric dienones **196** and **197** were isolated from the reaction mixture (Scheme 73).

Scheme 73 Isolated Products in the Cross-aldol Reaction of 3,7-Dimethoxy-11*H*-dibenzo[*b,f*]oxepin-10-one (183) with Citral (17)



Reagents and conditions: a) allyl amine, $MgSO_4$, THF, reflux, 5 days, 184 **(10%),** 131 **(23%),** 196 **+** 197 **(48%).**

The difference in reactivity between the unsubstituted oxepinone **33** and the dimethoxy-oxepinone **183** was evident in the product distribution. The 2*H*-

pyran **30** was the main product of the cross-aldol reaction of the oxepinone **33** with citral (**17**). However, the corresponding dimethoxy-2*H*-pyran **184** was found to be the minor product of this cross-aldol reaction and the dimethoxy-2*H*-pyran **184** was isolated in only 10% yield which was significantly lower than the 50% yield obtained for the unsubstituted derivative **30**. Another difference was in the relative stability of the 2*H*-pyran compounds. The dimethoxy-2*H*-pyran **184** was found to be unstable and converted to the dimethoxy-dienone derivatives **196** and **197** upon standing for a few minutes in an NMR solvent. Even in the absence of a solvent, the isomerization and electrocyclic ring-opening process degraded a pure sample of the dimethoxy-2*H*-pyran **184** in a few hours.

Due to its instability, the separation of the dimethoxy-2*H*-pyran **184** from the dienones **196** and **197** proved to be a challenging task. Flash chromatography using petroleum ether:dichloromethane (1:2) as the eluant afforded the pure dimethoxy-2*H*-pyran **184** but the rapid decomposition process prevented the complete characterization of the compound. Nevertheless, the 2*H*-pyran **184** product was characterized by NMR spectroscopy. The ^{1}H NMR spectrum of the compound displayed the characteristic pair of doublets corresponding to *H*-4 at δ = 6.23 ppm and *H*-3 at δ = 5.25 ppm (Figure 47). The singlets at δ = 3.17 ppm and δ = 3.25 ppm were assigned to the non-equivalent aromatic methyl ethers. The presence of the two singlets corresponding to the methoxy groups and the absence of two aromatic protons were the only noted differences in the ^{1}H NMR spectra of the two 2*H*-pyran compounds (**30** and **184**).

Furthermore, the mass spectrum was consistent with a product corresponding to the molecular formula $C_{26}H_{28}O_4$.

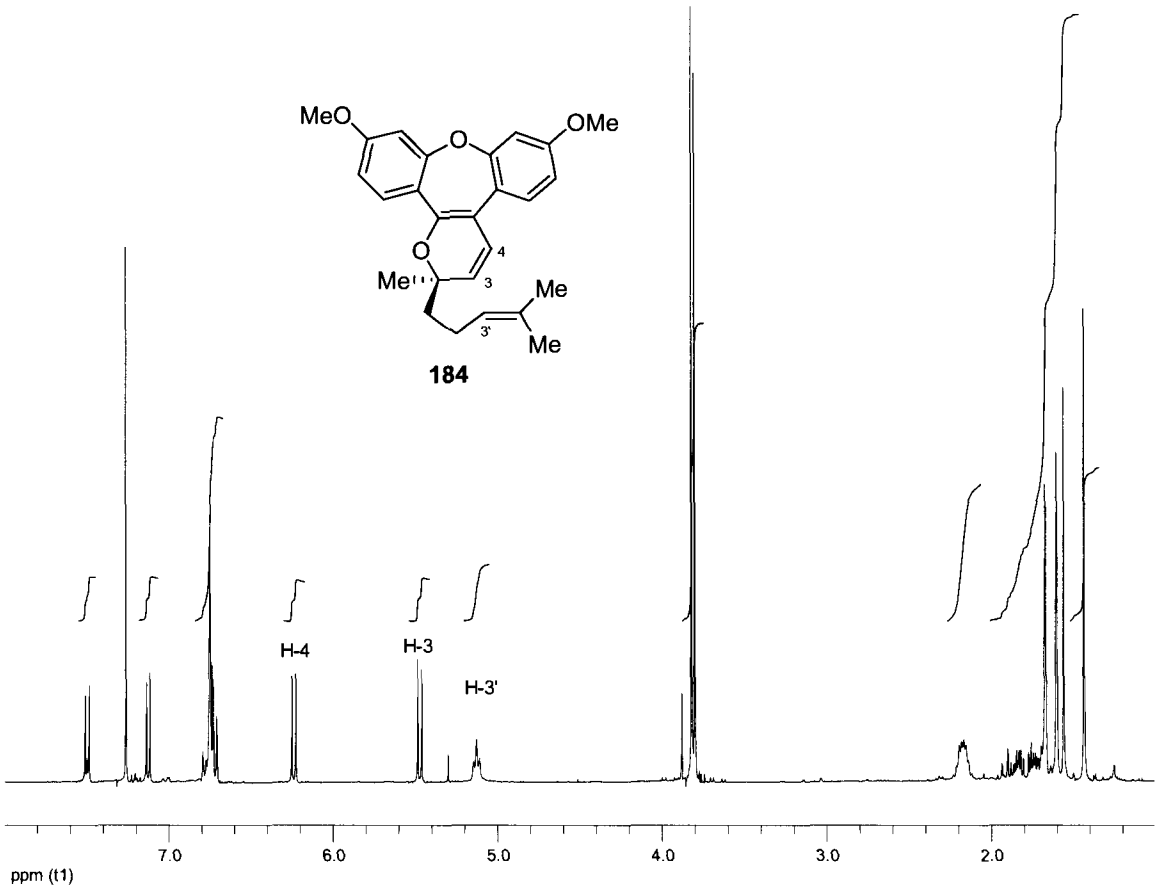


Figure 47 Detail from the ^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of the dimethoxy-2*H*-pyran (184).

A mixture of dienones (**196** and **197**) was separated from the cyclic aldehyde **131** by-product with difficulty by flash chromatography. Despite numerous efforts, the two isomers could not be separated. However, analysis of the ^{1}H NMR spectrum revealed the presence of two compounds and by analogy to the unsubstituted dienones (**38** and **39**), the compounds were characterized as being isomeric at the γ,δ-double bond. The signals corresponding to *H*-1' and *H*-

2' of the two isomers were only partially resolved but the multiplet corresponding to *H*-6' gave two well resolved signals at δ = 4.99-5.02 ppm and δ = 5.12-5.16 ppm, in a 1:1 ratio (Figure 48). A similar chemical shift difference was noted in the case of the unsubstituted *E*,*Z*-dienone **38** and *E*,*E*-dienone **39**.

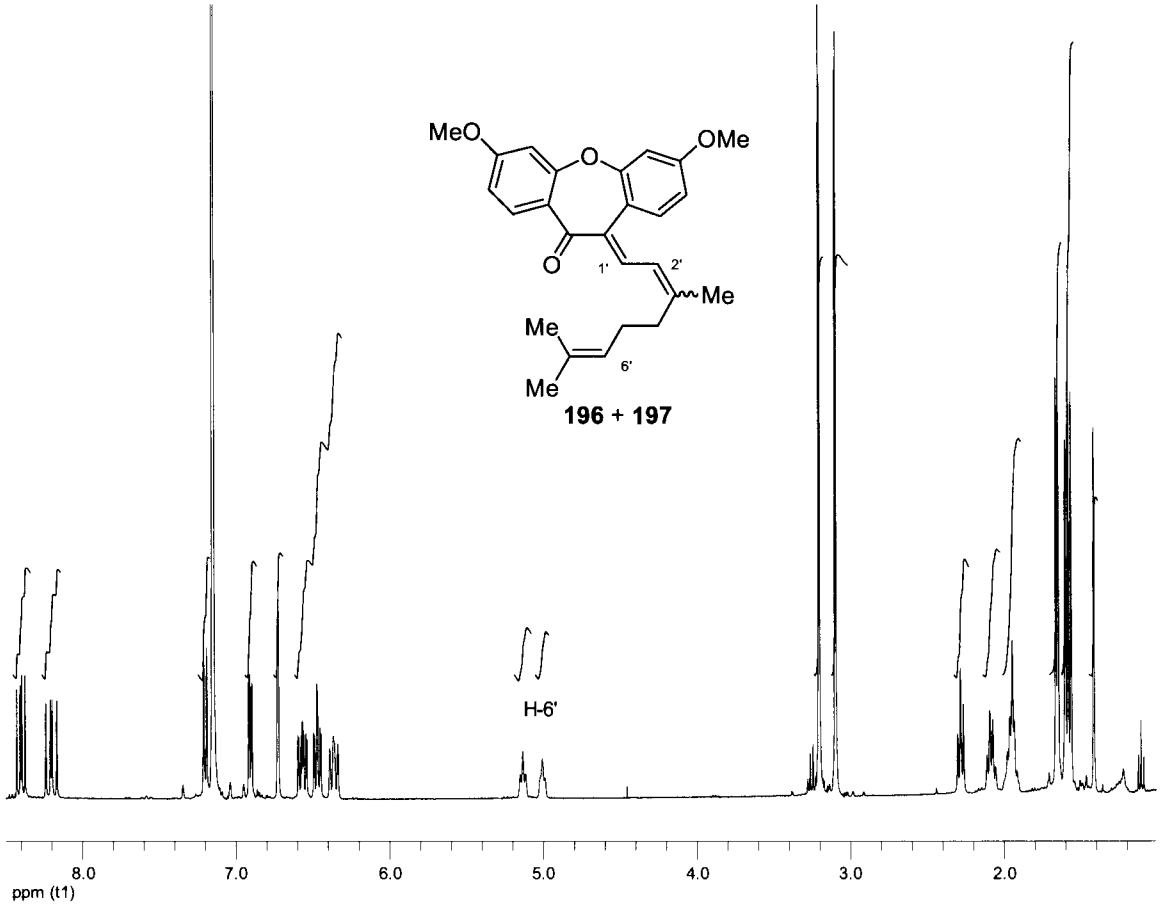


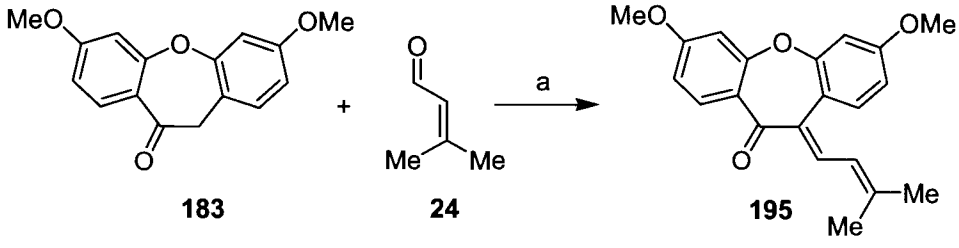
Figure 48 **Detail from the ^{1}H NMR spectrum (C_6D_6, 500 MHz) of the mixture of dimethoxy-dienones (196 and 197).**

The spectrum also displayed six singlet signals corresponding to the aliphatic methyl groups and four singlets corresponding to the methoxy groups. The chemical shift difference between the signals of the methoxy groups was

small, δ = 0.01 ppm, but still noticeable although these substituents are eleven and twelve carbon atoms away from the isomeric double bonds.

Similarly, the cross-aldol reaction of dimethoxy-oxepinone **183** and senecialdehyde (**24**) was performed with allyl amine and magnesium sulfate in tetrahydrofuran at reflux and afforded the *E*-dimethoxy-dienone **195** in 37% yield. The ^{1}H NMR spectrum of the reaction mixture showed no evidence of the desired 2*H*-pyran product.

Scheme 74 Synthesis of *E*-Dimethoxy-Dienone (195) *via* Amine-Mediated Cross-Aldol Reaction of Dimethoxy-Oxepinone (183) and Senecialdehyde (24)



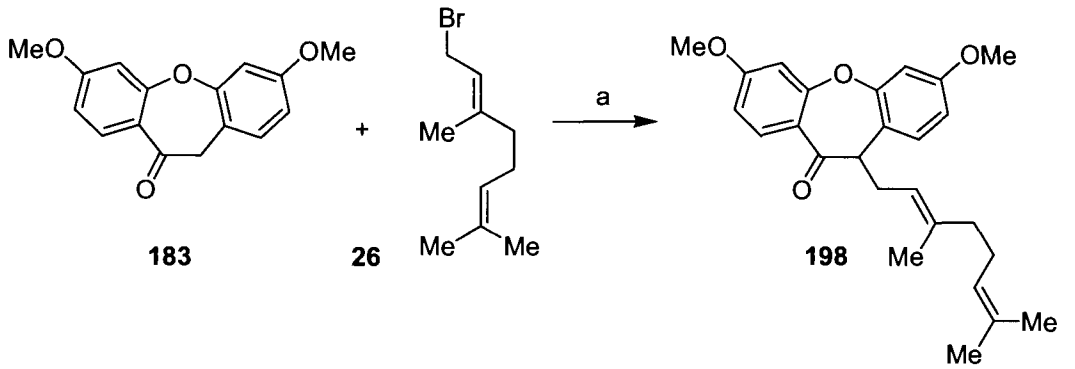
183 **24** **195**

Reagents and conditions: a) allyl amine, $MgSO_4$, THF, reflux, 37%.

4.3.3 The Alkylation, Selenation and Oxidation Route

Although it was impossible to separate the mixture of the two dienones (**196** and **197**) obtained in the cross-aldol reaction, the pure *E,E*-dimethoxy dienone **196** was synthesized *via* the alkylation, selenation and oxidation strategy (Scheme 75). Reaction of the lithium enolate derived from the dimethoxy-oxepinone **183** with geranyl bromide **26** afforded the mono-alkylated product **198** (Scheme 75).

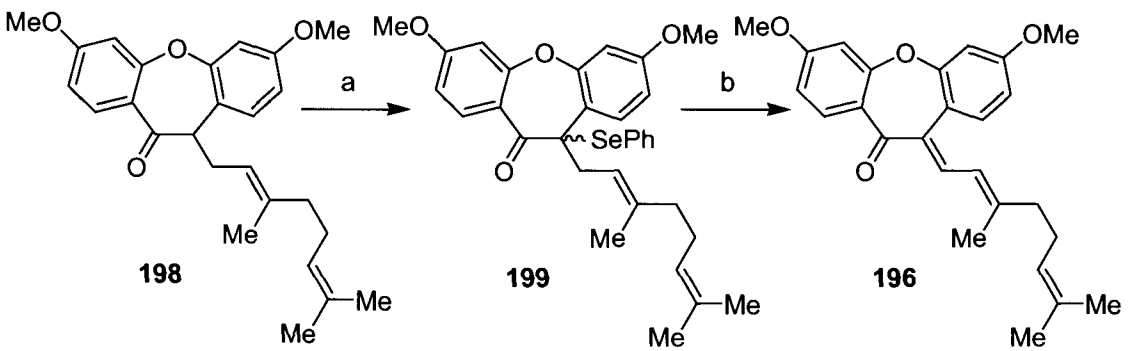
Scheme 75 Alkylation of the Dimethoxy-Oxepinone (183) with Geranyl Bromide (26): Synthesis of an Artocarpol E Analogue (198)



Reagents and conditions: a) LDA, THF, -18 °C to 0 °C, 4 h, 45%.

The alkylated dimethoxy-oxepinone **198**, an additional analogue of artocarpol E (**5**), was deprotonated with LDA and reacted with phenylselenyl chloride. Oxidation of the resultant selenide with hydrogen peroxide in the presence of pyridine afforded the *E,E*-dimethoxy-dienone **196** which was fully characterized as a single geometrical isomer (Scheme 76).

Scheme 76 Synthesis of the *E,E*-Dienone (196) *via* Selenation and Oxidation of the Alkylated Dimethoxy-Oxepinone (198)



Reagents and conditions: a) LDA, PhSeCl, -78 °C, 58%; c) pyridine, H_2O_2, CH_2Cl_2, 95%.

Comparison of the ^{1}H NMR spectrum of the dimethoxy-dienone (**196** and **197**) mixture and the ^{1}H NMR spectrum of the *E,E*-dimethoxy-dienone **196** confirmed the earlier characterization of the mixture of compounds. A pair of doublets at δ = 8.17 ppm and δ = 6.37 ppm had the same coupling constant value (J = 12 Hz) and were assigned to the diene protons *H*-1' and *H*-2'. A multiplet at δ = 4.99-5.02 ppm was assigned to the remaining olefinic proton (*H*-6') (Figure 49).

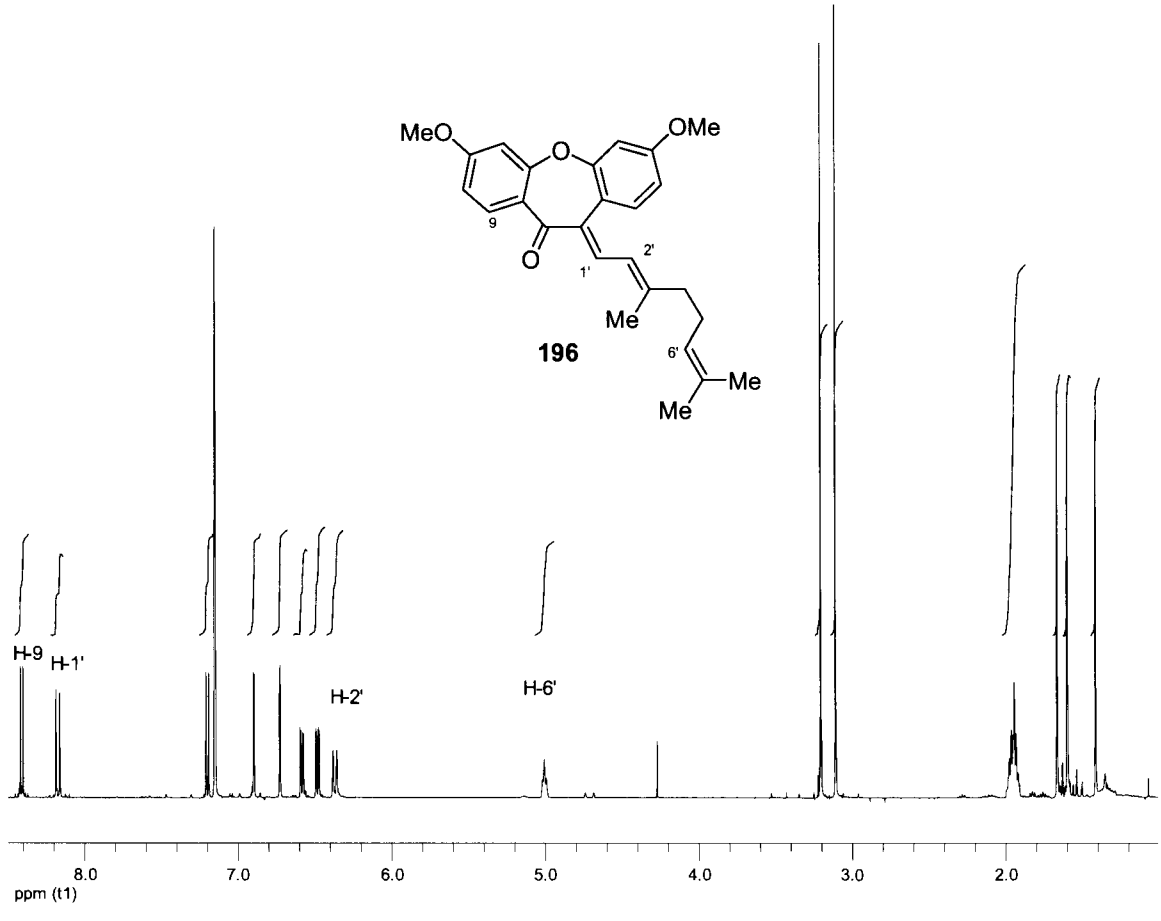


Figure 49 **Detail from the ^{1}H NMR spectrum (C_6D_6, 500 MHz) of the *E,E*-dimethoxy-dienone (196).**

The configuration of the double bonds was established by NOE contacts. Irradiation of the *H*-2' proton gave NOE contacts with an aromatic proton with a methylene group and with the diene proton *H*-1'. The NOE contact between *H*-2' and a methylene group supported the *trans*-configuration of the γ,δ-double bond. In another experiment, irradiation of the *H*-1' proton showed a weak contact with protons corresponding to a methyl group and the absence of any other contacts. The NOE contact of *H*-2' with an aromatic proton and the absence of a similar contact for *H*-1' confirmed both the *E* configuration of the α,β-double bond and the preferred *s-trans* configuration of the diene (Figure 50).

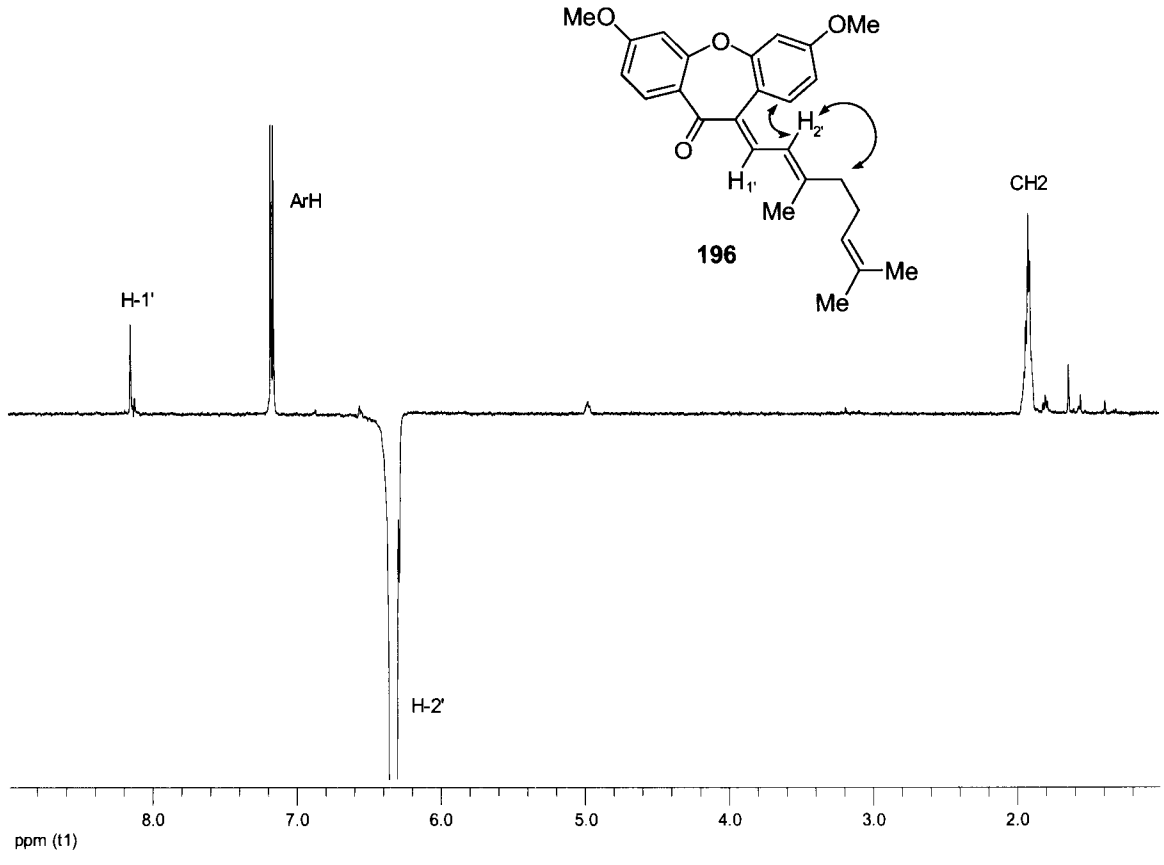
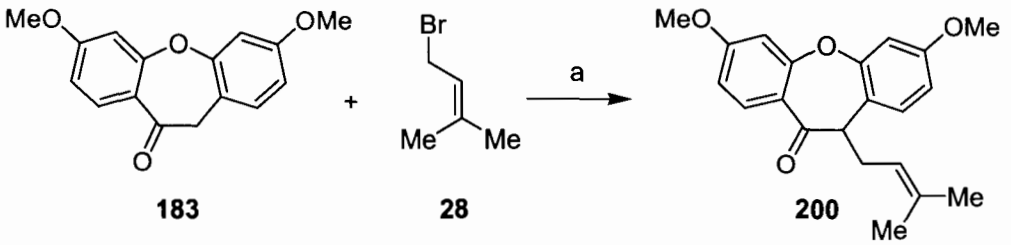


Figure 50 **Detail of the NOE spectrum (C_6D_6, 500 MHz) of the *E,E*-dimethoxy-dienone (196).**

The alkylation, selenation and oxidation sequence of reactions was also applied successfully to the synthesis of the *E*-dimethoxy-dienone **195**. The alkylation reaction of the dimethoxy-oxepinone **183** with prenyl bromide **28** afforded the monoalkylated product **200** in 73% yield (Scheme 77).

Scheme 77 Alkylation of the Dimethoxy-Oxepinone (183) with Prenyl Bromide (28)

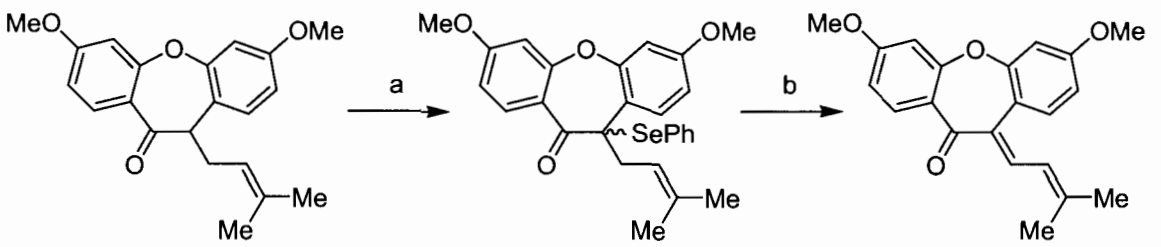


183 **28** **200**

Reagents and conditions: a) LDA, THF, -18 °C then 0 °C, 4 h, 73%.

The mono-alkylated dimethoxy-oxepinone **200** was then deprotonated and reacted with phenylselenyl chloride. The resultant crude selenide **201** was then oxidized with hydrogen peroxide in presence of pyridine. The *E*-dimethoxy-dienone **195** was obtained in 60% overall yield from the alkylated product **200** (Scheme 78).

Scheme 78 Synthesis of the *E*-dienone (195) *via* Selenation and Oxidation of the Alkylated Dimethoxy-Oxepinone (200)



200 **201** **195**

Reagents and conditions: a) LDA, PhSeCl, -78 °C; b) Pyridine, H_2O_2, CH_2Cl_2, 60% (over two steps).

The alkylation, selenation and oxidation route allowed for the synthesis and characterization of the *E,E*-dimethoxy-dienone **196**, derived from citral (**17**) as a single isomer and the synthesis of the *E*-dimethoxy-dienone **195**, derived from senecialdehyde (**24**). However, due to the low yielding alkylation step, the overall yield of the *E,E*-dimethoxy-dienone **196** was low (25%). The amine-promoted method gave a better yield (48%) but afforded a mixture of *E,E*- and *E,Z*-dimethoxy-dienones (**196** and **197**). The *E*-dimethoxy-dienone **195**, derived from senecialdehyde (**24**), was synthesized *via* the Evans protocol, the amine-catalyzed synthetic route and the alkylation, selenation and oxidation route. These three methods afforded similar overall yields (40, 37 and 44%, respectively).

4.3.4 Attempted Electrocyclization Reaction of the Dimethoxy-Dienone Compounds

The equilibrium between the *E/Z* dienones **38** and **39** and the corresponding 2*H*-pyran **30** had been analyzed and discussed earlier (see Chapter 3, Section 3.3.10). The overall yield of the unsubstituted 2*H*-pyran derivative **30** was increased due to the ability of the dienones **38** and **39** to undergo isomerization and electrocyclization reactions. A similar isomerization/electrocyclization reaction of the *E,E*-dimethoxy-dienone **196** was attempted in order to increase the overall yield of the dimethoxy-2*H*-pyran **184**.

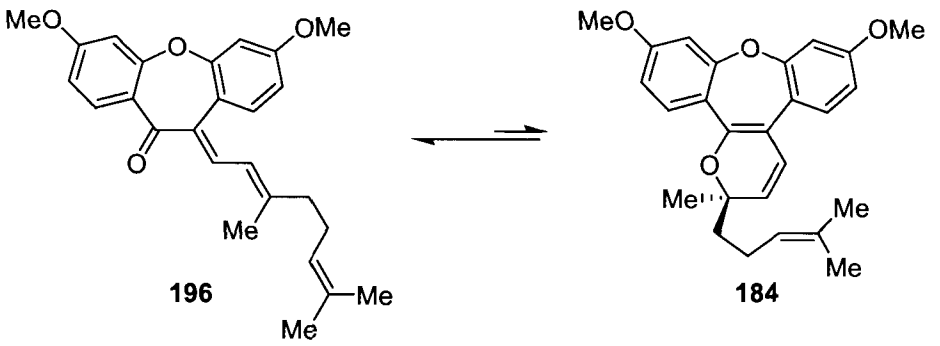


Figure 51 Isomerization and electrocyclization reaction of the *E,E*-dimethoxy-dienone (196) to afford the dimethoxy-2*H*-pyran (184).

A number of different reaction conditions were surveyed to effect the isomerization/electrocyclization reaction of the *E,E*-dimethoxy-dienone **196** and all gave similar results (Table 13).

Scheme 79 Attempted Electrocyclization of the *E,E*-Dimethoxy-Dienone (196) to the Dimethoxy-2*H*-pyran (184)

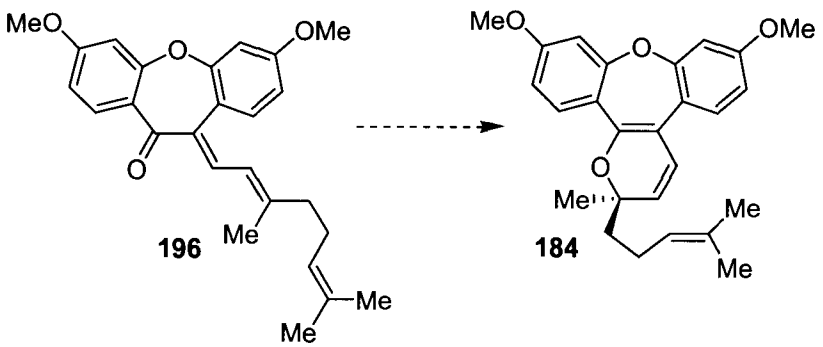


Table 13 Experimental Conditions Corresponding to Scheme 79

Entry	Reagents and conditions	Result
1	allyl amine, $MgSO_4$, THF, reflux	trace of **184**
2	*p*-TsOH, PhH, reflux	decomposition
3	H_2SO_4, PhH, reflux	decomposition

Entry	Reagents and conditions	Result
4	KOH, EtOH, reflux	no reaction
5	benzophenone, *hν*, PhH	trace of **184**

In the first instance, the reaction conditions successfully applied for the electrocyclization of the unsubstituted *E*-dienones **38** and **39** were employed in the similar electrocyclic transformation of the *E,E*-dimethoxy-dienone **196**. These reaction conditions involved the use of allylamine and anhydrous magnesium sulfate in tetrahydrofuran at reflux and afforded traces of the dimethoxy-2*H*-pyran **184** and unreacted starting material. An acid-catalyzed electrocyclization process, in presence of *p*-toluenesulfonic acid or sulfuric acid, afforded decomposition products and the unreacted *E,E*-dimethoxy-dienone **196** was also recovered (Table 13, entries 2 and 3). The *E,E*-dimethoxy-dienone **196** did not react under base catalysis with potassium hydroxide in ethanol at reflux (Table 13, entry 4).

The last method attempted involved the photochemical isomerization and cyclization of the *E,E*-dimethoxy-dienone **196**. This reaction was expected to afford the dimethoxy-2*H*-pyran **184** which could have reacted in an intramolecular [2+2] photocycloaddition reaction to afford the dimethoxy-artocarpol A analogue **185**. Thus, this strategy should have allowed for the trapping of the unstable dimethoxy-2*H*-pyran **184** *via* the intramolecular [2+2] photocycloaddition reaction. However, analysis of the ^{1}H NMR spectrum showed

the presence of only trace amounts of the dimethoxy-2*H*-pyran **184** as well as the unreacted *E,E*-dimethoxy-dienone **196** and no evidence of cyclic compound being formed.

In summary, the preference of the dimethoxy-oxepinone derivative to exist in the dienone form rather than in the 2*H*-pyran form was further confirmed by the unsuccessful attempts to effect an electrocyclization reaction of the *E,E*-dimethoxy-dienone **196** (Scheme 79). The stability of the *E,E*-dimethoxy-dienone **196** was probably due to the presence of extended conjugation of the system between the methoxy group at C(7) and the ketone functional group. In case of the electrocyclized product, the dimethoxy-2*H*-pyran **184**, this conjugation is absent and therefore the equilibrium favours the most stable form, the *E,E*-dimethoxy-dienone **196** (Figure 51).

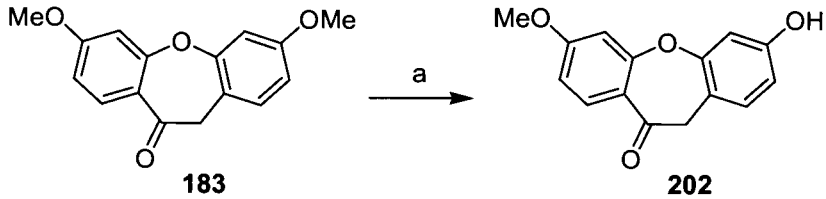
The electrocyclization reaction of the *E*-dimethoxy-dienone **195**, derived from senecialdehyde (**24**), was attempted under the same reaction conditions but none of the dimethoxy-2*H*-pyran compound was formed.

4.3.5 Partial Deprotection of the Dimethoxy-Oxepinone (183)

The proposed synthesis of the artocarpol A (**1**) from the dimethoxy-oxepinone **183** would involve the deprotection of the two methoxy substituents at a late stage in the synthesis. However, the deprotection of the methoxy substituents with boron tribromide was tested on the dimethoxy-oxepinone **183**

and in order to examine the reaction of this deprotected oxepinone in the cross-aldol reaction with citral (**17**) and senecialdehyde (**24**).[86,87*]

Scheme 80 Partial Deprotection of the Dimethoxy-Oxepinone (183) to the Hydroxy-Methoxy Oxepinone (202)



183 **202**

Reagents and conditions: a) BBr_3, CH_2Cl_2, -78 °C 1h, then room temperature, 20 h, 66%.

The dimethoxy-oxepinone **183** was reacted with boron tribromide in dichloromethane to afford a new compound. In the ^1H NMR spectrum of this material, the absence of the singlet peak at δ = 3.79 ppm, assigned to one of the methoxy groups of the starting material, was noted. The appearance of a singlet corresponding to one proton at δ = 8.64 ppm, assigned to a phenolic proton was also noted. The signal corresponding to the second methoxy substituent, singlet at δ = 3.93 ppm, was still present. On further analysis using mass spectroscopy the partial deprotection of the dimethoxy-oxepinone **183** was confirmed and the product was assigned as the hydroxyl-methoxy oxepinone **202**.

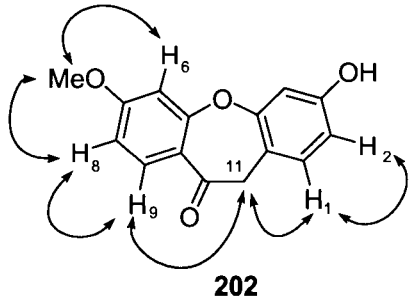
The complete characterization of the hydroxyl-methoxy oxepinone **202** was achieved by analysis of a series of 1D NOE experiments. The signals

(86) Zhu, Z.; Swager, T. M. *Org. Lett.* **2001**, *3*, 3471.

(87) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Chemistry*; 3rd ed.; John Wiley and Sons, Inc.: New York, 1999.

* The amine-mediated cross-aldol reaction of the hydroxy-methoxy oxepinone **202** with citral (**17**) did not afford any cross-aldol products.

corresponding to *H*-9 and *H*-1 were identified in the ^{1}H NMR spectrum based on chemical shift and multiplicity. Irradiation of *H*-1 gave contacts with a doublet of doublets at δ = 6.73 ppm, that was assigned to *H*-2, as well as to the methylene protons *H*-11 at δ = 3.96 ppm. Irradiation of *H*-9 resulted in contacts with the methylene protons *H*-11 and with a proton from the multiplet at δ = 6.81-6.83 ppm, which was assigned to *H*-8. Irradiation of the methoxy protons resulted in NOE contacts with *H*-8 and with the doublet at δ = 6.93 ppm, that was assigned to *H*-6. The absence of a NOE contact between the methoxy protons and *H*-2 confirmed that selective deprotection of the 3-O*Me* group had occurred and not of the 7-O*Me* group (Figure 52).



202

Figure 52 Contacts observed in the NOE spectrum of the hydroxyl-methoxy oxepinone (202).

The latter reaction was repeated at an elevated temperature and also with a large excess of boron tribromide. However, the partially deprotected compound **202** was the only compound formed.

4.4 Conclusions

The 3,7-dimethoxy-11*H*-dibenzo[*b*,*f*]oxepin-10-one **183** was successfully synthesized in ten steps and in 33% overall yield from commercially available 2-fluoroanisole **186**. The only purification method used, for three of the intermediates, was recrystallization. The rest of the reactions afforded pure compounds. The results were reproducible on a large scale that allowed for the synthesis of gram quantities of dimethoxy-oxepinone **183**.

Several reactions involving the dimethoxy-oxepinone **183** were investigated and resulted in the synthesis of new compounds. A notable difference was observed in the cross-aldol reaction with citral (**17**) and senecialdehyde (**24**) as compared with the unsubstituted oxepinone **33**. These results confirmed the important influence of the aromatic substituents on the reactivity of the dibenzoxepinone system.

Although the synthesis of the dimethoxy-artocarpol A **185** analogue could not be achieved, cross-coupled products of the dimethoxy-oxepinone **183** with citral (**17**) and senecialdehyde (**24**) were synthesized *via* two different methods. Of note, an analogue of artocarpol E (**5**) was also prepared by the alkylation reaction of this oxepinone (**183**) with geranyl bromide (**26**).

CHAPTER 5: TOWARDS THE SYNTHESIS OF 3,7-DINITRO-11*H*-DIBENZO[*b*,*f*]OXEPIN-10-ONE

5.1 Introduction

The synthesis of a second, closely related artocarpol A analogue was intended from the dimethoxy-oxepinone **183**. However, the dimethoxy-oxepinone **183** behaved in a significantly different manner to the unsubstituted system **33** in the reaction with citral (**17**) and the corresponding dimethoxy-2*H*-pyran compound, **184** could not be efficiently synthesized. The presence of the electron releasing dimethoxy-substituents resulted in a shift in the equilibrium to favour the dimethoxy-dienones **196** and **197** rather than the desired dimethoxy-2*H*-pyran **184** (Figure 51).

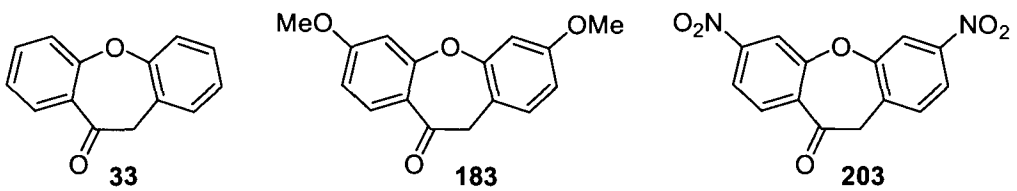
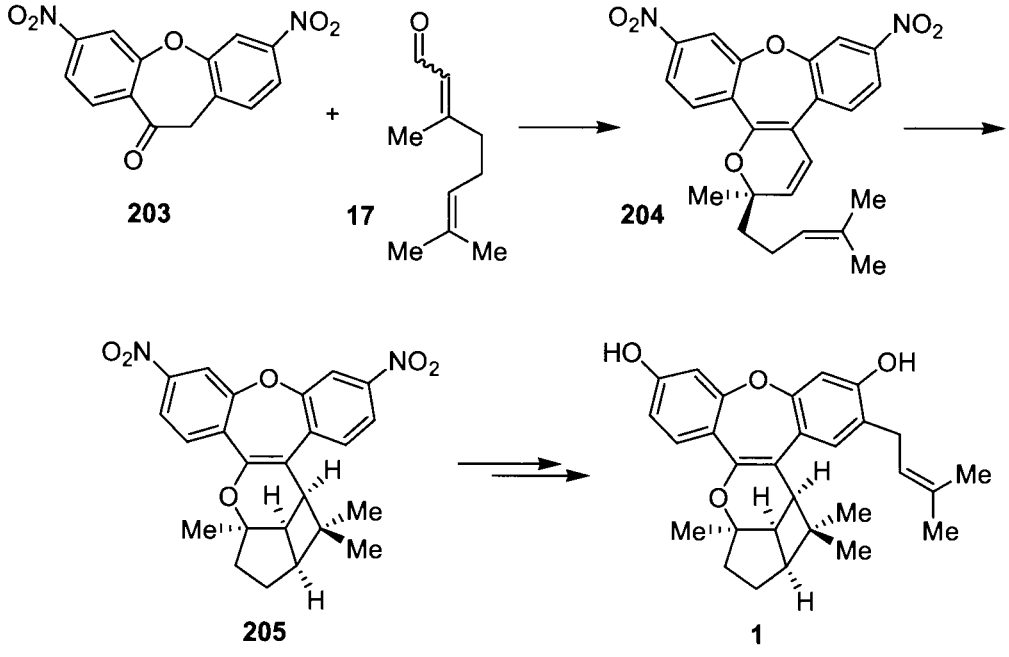


Figure 53 Unsubstituted, dimethoxy- and dinitro- substituted oxepinones (33, 183 and 203) used in the synthesis towards artocarpol A analogues.

The negative influence of the methoxy-substituents on the stability of the corresponding 2*H*-pyran **184** suggested a possible opposite effect might be obtained with electron-withdrawing substituents. Therefore, the dinitro-oxepinone **203** was selected as the next appropriate target. This change should stabilize the desired dinitro-2*H*-pyran compound **204** since extended conjugation

would be possible for the 2*H*-pyran compound and not for the dienone isomers. Thus, it was expected that this effect would be opposite to that observed in the dimethoxy-oxepinone.

Scheme 81 Proposed Synthesis of a Dinitro-Artocarpol A analogue (205) from Dinitro-Oxepinone (203)



The reaction of the dinitro-oxepinone **203** with citral (**17**) was expected to afford the cross-aldol dinitro-2*H*-pyran product **204**. The [2+2] photochemical cycloaddition reaction of the dinitro-2*H*-pyran **204** should then afford the dinitro-artocarpol A analogue **205**. Standard synthetic techniques involving reduction of the nitro groups, diazotization and hydrolysis reactions should allow for the functional group transformation of the nitro-substituents to the required hydroxyl-substituents (Scheme 81).

Two additional methoxy-nitro substituted oxepinone derivatives **206** and **207** could also be obtained in principle from intermediates used in the synthesis

of the dimethoxy-oxepinone **183** and dinitro-oxepinone **203** (Figure 54). These substituted oxepinones would allow for the synthesis of other artocarpol A analogues.

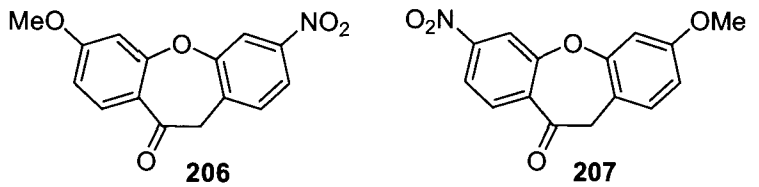


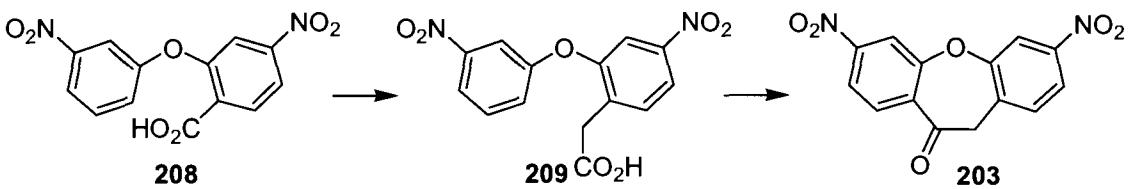
Figure 54 **Disubstituted oxepinone derivatives: 7-Methoxy-3-nitro- and 3-methoxy-7-nitro-11*H*-dibenzo[*b*,*f*]oxepin-10-one (206 and 207)**

5.2 The Intramolecular Friedel-Crafts Cyclization Approach

5.2.1 Synthesis of the Benzoic Acid Derivative (228)

The synthesis of the dinitro-oxepinone **203** was designed analogously to that of the unsubstituted and dimethoxy-substituted oxepinones (**33** and **183**).

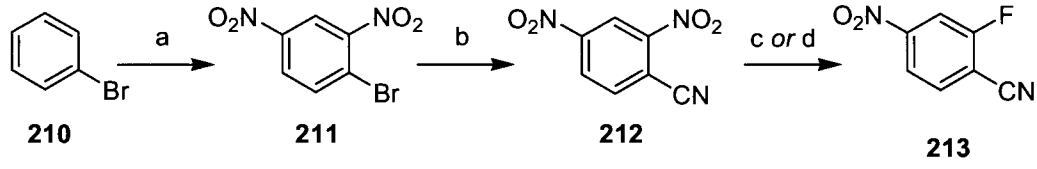
Scheme 82 **Proposed Friedel-Crafts Acylation Approach for the Synthesis of Dinitro-Oxepinone (203)**



As for the dimethoxy-oxepinone **183**, the precursors for the biaryl ether formation step had to be prepared. Subsequently, homologation of the benzoic acid derivative **208** should afford the intermediate **209** which would function as a precursor for an intramolecular Friedel-Crafts acylation reaction (Scheme 82).

The synthesis of the dinitro-oxepinone **203** started from commercially available bromobenzene **210**. 1-Bromo-2,4-dinitrobenzene **211** was isolated as the single product from the reaction between bromobenzene **210** and a mixture of sulfuric and nitric acid (Scheme 83). The melting point was in agreement with previously published data on this compound and NMR data indicated the desired substitution pattern.[88] The nitrile derivative **212** was obtained according to a published method that involved displacement of the bromine substituent on reaction with copper cyanide in dimethylformamide at 150 °C (Scheme 83).[84]

Scheme 83 Synthesis of 2-Fluoro-4-nitrobenzonitrile (213) from Bromobenzene (210)



210 **211** **212** **213**

Reagents and conditions: a) H_2SO_4, HNO_3, room temperature, 1 h then reflux, 3 h, 97%; b) CuCN, DMF, 150 °C, 4 h, 85%; c) KF, DMF, 120 °C, 7 h, 40%; d) *n*-Bu_4NF, THF, -78 °C then room temperature, 2 h, 88%.

The next step of the synthesis required the displacement of one nitro group of 2,4-dinitrobenzonitrile **212** with fluoride ion.[89] To achieve this goal, several different sources of fluoride ion were tested. When 2,4-dinitrobenzonitrile **212** was reacted with potassium fluoride in dimethylformamide at 120 °C according to the method reported by Sasaki and co-workers, the fluoride **213** was obtained in 40% yield.[90] The use of excess tetramethylammonium fluoride (3

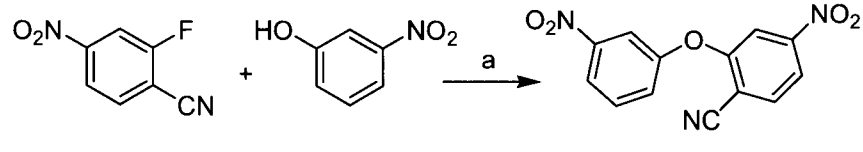
(88) Lerch, U.; Moffatt, J. G. *J. Org. Chem.* **1971**, *36*, 3861.

(89) Clark, J. H.; Wails, D.; Jones, C. W.; Smith, H. E.; Boechat, N.; Mayer, L. U.; Mendonca, J. S. *J. Chem. Res.* **1994**, 2783.

(90) Sasaki, M.; Takeuchi, K.; Sato, H.; Takatsu, H. *Mol. Cryst. Liq. Cryst.* **1984**, *109*, 169.

equiv) as a fluoride source has been reported to replace both nitro groups of 2,4-dinitrobenzonitrile **212** in 100% yield.[91] The same investigators also reported the synthesis of 2-fluoro-4-nitrobenzonitrile **213** from the dinitro compound **212** on employment of 1.2 equiv of tetramethylammonium fluoride. However, the reaction of 2,4-dinitrobenzonitrile **212** with freshly prepared and dried tetramethylammonium fluoride in dimethyl sulfoxide at 80 °C failed to afford any product. [92] In contrast, a solution of tetra-*n*-butylammonium fluoride in tetrahydrofuran was found to react immediately with 2,4-dinitrobenzonitrile **212** at room temperature and afforded the desired 2-fluoro-4-nitrobenzonitrile **213** together with unidentified by-products. Through a series of experiments, it was found that when the tetrabutylammonium fluoride solution was added to the substrate in tetrahydrofuran at -78 °C and the reaction was allowed to warm to room temperature, the amount of impurities contaminating the product were minimized (Scheme 83). The chemical shifts and coupling patterns of the aromatic protons in the ^{1}H NMR spectrum of 2-fluoro-4-nitrobenzonitrile **213** were in agreement with the desired aromatic substitution pattern.

Scheme 84 Synthesis of 2-(3'-Nitrophenoxy)-4-nitrobenzonitrile (215)



213 **214** **215**

Reagents and conditions: a) 18-crown-6, KF·Al_2O_3, MeCN, reflux, 20 h, 80%.

(91) Boechat, N.; Clark, J. H. *J.Chem. Soc. Chem. Commun.* **1993**, 921.

(92) Clark, J. H. *Chem. Rev.* **1980**, *80*, 429.

The formation of the required biaryl ether linkage was attempted under the same conditions as used in the dimethoxy series. The reaction of 2-fluoro-4-nitrobenzonitrile (**213**) with commercially available 3-nitrophenol (**214**) on heating at reflux in acetonitrile with potassium fluoride-alumina and a catalytic amount of 18-crown-6 was complete after 20 hours (Scheme 84). In the first instance, the work-up procedure was identical to that applied for the dimethoxy-oxepinone. However, a low mass recovery suggested that the nitrile product **215** was absorbed on the potassium-fluoride alumina residue. Therefore, the work-up procedure was modified. This involved continuous extraction (soxhlet) of the solid residue from the reaction mixture with dichloromethane. Accordingly, the nitrile product **215** was isolated as a white powder in 80% yield.

The structure of the nitrile derivative **215** was further confirmed by X-ray crystallography. This crystal structure proved the desired substitution pattern of the biaryl ether derivative **215** (Figure 55).

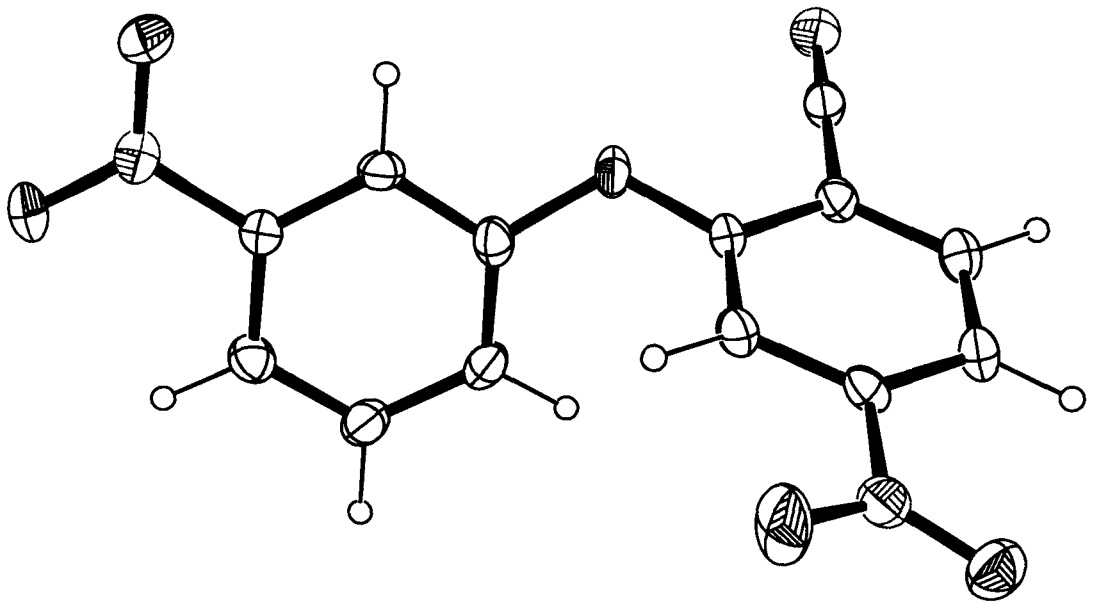


Figure 55 X-ray crystal structure of 2-(3'-nitrophenoxy)-4-nitrobenzonitrile (215). The thermal ellipsoids are drawn at a 30% probability level.

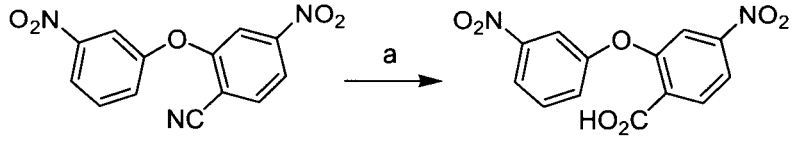
The hydrolysis of the nitrile derivative **215** was initially attempted under basic conditions. The previously used hydrolysis conditions: potassium hydroxide and 80% aqueous ethanol or potassium hydroxide, hydrogen peroxide, ethanol and methanol, led to the decomposition of the nitrile starting material **215**.

Therefore, acidic hydrolysis procedures were performed with hydrochloric acid (6 M), a mixture of sulfuric acid:water (2:1) and with an aqueous mixture of sulfuric acid and acetic acid.[93] From preliminary trials it was found that hydrolysis of the nitrile derivative **215** gave the best results when it was performed in a 2:1 mixture of concentrated sulfuric acid and water at 150 °C. Rapid heating of the

(93) Hays, S. J.; Caprathe, B. W.; Gilmore, J. L.; Amin, N.; Emmerling, M. R.; Michael, W.; Nadimpalli, R.; Nath, R.; Raser, K. J.; Stafford, D.; Watson, D.; Wang, K.; Jaen, J. C. *J. Med. Chem.* **1998**, *41*, 1060.

reaction mixture, as reported for this procedure, resulted in considerable decomposition of the starting material and caused difficulties in product separation. Gradual heating of the reaction to 150 °C and steady heating at this temperature for 2 to 3 hours allowed for the synthesis of 2-(3'-nitrophenoxy)-4-nitrobenzoic acid (**208**) in 92% yield.[94]

Scheme 85 Hydrolysis of 2-(3'-Nitrophenoxy)-4-nitrobenzonitrile (215) to the Corresponding Acid Derivative (208)



215 **208**

Reagents and conditions: a) H_2SO_4, H_2O, 150 °C, 2 h, 92%.

5.2.2 Attempted Homologation of the Benzoic Acid Derivative (208) *via* a Reduction, Halogenation, Cyanation and Hydrolysis Sequence

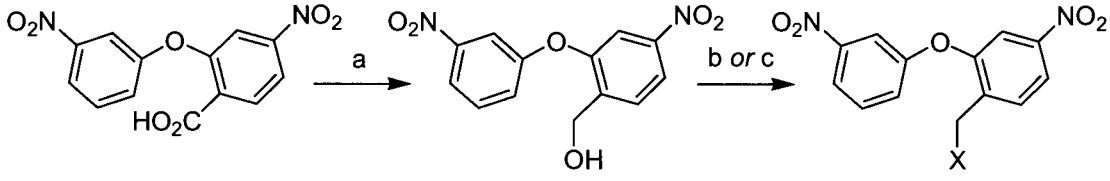
As discussed earlier, the reduction, halogenation, cyanation and hydrolysis sequence is a commonly used method to homologate benzoic acid derivatives. The homologated acid could then in principle undergo an intramolecular Friedel-Crafts reaction to complete the formation of the desired dibenzoxepine **203** (Scheme 82).

Thus, 2-(3'-nitrophenoxy)-4-nitrobenzoic acid (**208**) was reduced to the alcohol **216** using either lithium aluminum hydride or borane. Both reducing agents were efficient in small scale experiments and afforded the desired product

(94) Sannie, M. C.; Lapin, M. H. *Bull. Soc. Chim. Fr.* **1950**, 322.

in a quantitative yield. However, when lithium aluminum hydride was used in reactions involving gram quantities of the substrate, the yield decreased to 40%. In contrast, borane/tetrahydrofuran complex gave high yields and reproducible results on a large scale (Scheme 86).

Scheme 86 Synthesis of the Chloro- and Bromo-Benzyl Derivatives (217 and 218)

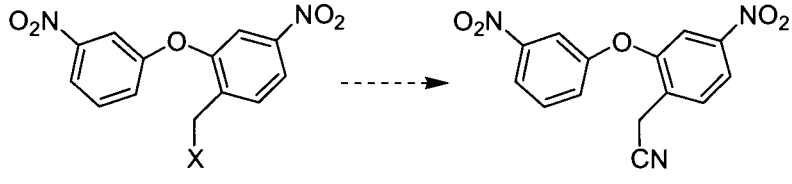


208 **216** **217**, X = Cl
218, X = Br

Reagents and conditions: a) BH_3, THF, 0 °C then room temperature, 20 h, 93%; b) $SOCl_2$, pyridine, PhH, reflux, 3 h, 89%; c) PBr_3, CH_2Cl_2, 0 °C, 1 h, 72%.

The reaction of the benzylic alcohol **216** with thionyl chloride in presence of pyridine afforded the benzyl chloride **217** derivative in good yield. The bromo-derivative **218** was also prepared in 72% yield by reacting the benzylic alcohol **216** with phosphorus tribromide (Scheme 86).

Scheme 87 Attempted Synthesis of the Nitrile Derivative (219)



217, X = Cl
218, X = Br

219

When sodium cyanide was added to a solution of the benzyl chloride **217** in dimethyl sulfoxide, an immediate colour change from colourless to red was observed.[54] Thin layer chromatography of the reaction mixture revealed the total

consumption of the starting material but no products could be isolated. Therefore, the solvent was changed from dimethyl sulfoxide to a mixture of ethanol, dioxane and water according to a published procedure by Nagai and co-workers but identical results were obtained (Table 14).[95]

Table 14 Experimental Conditions Corresponding to Scheme 87

Entry	Reagents and conditions
1	NaCN, DMSO
2	NaCN, EtOH, dioxane, H_2O
3	KCN, EtOH, H_2O, reflux
4	KCN, 18-crown-6, MeCN

Unfortunately, none of the desired product was isolated using two additional published procedures (Table 14, entries 3 and 4).[96,97] The synthesis of the nitrile derivative **219** from the benzyl bromide **218** was also attempted, albeit also unsuccessfully.

As the halogen substitution process with a nitrile group was unsuccessful, the direct conversion of the benzyl alcohol **216** to the desired nitrile compound was attempted (Scheme 88).

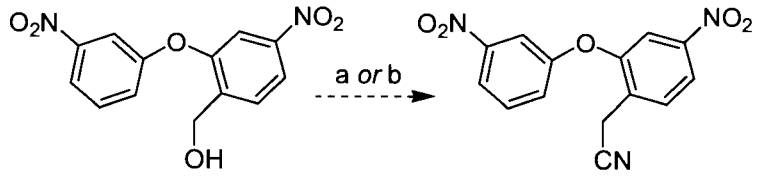
---

(95) Nagai, Y.; Irie, A.; Nakamura, H.; Hino, K.; Uno, H.; Nishimura, H. *J. Med. Chem.* **1982**, *25*, 1065.

(96) Polivka, Z.; Holubek, J.; Svatek, E.; Metysova, J. *Collect. Czech. Chem. Commun.* **1981**, *46*, 2222.

(97) Wright, S. W.; McClure, L. D. *Org. Prep. Proced. Int.* **1994**, *26*, 602.

Scheme 88 Attempted Direct Conversion of the Benzyl Alcohol (216) to the Benzyl Nitrile (219)



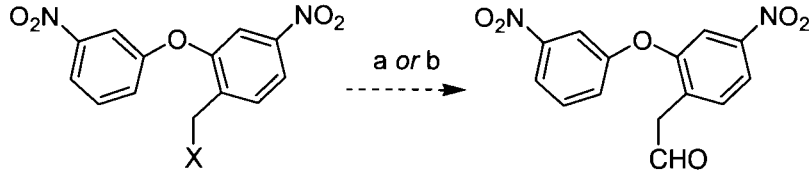
216 **219**

Reagents and conditions: a) NaCN, TMSCl, NaI (cat.), DMF, MeCN; b) TFAA, CH_2Cl_2 then NaCN, THF, HMPT.

However, reaction with sodium cyanide and trimethylsilyl chloride and a catalytic amount of sodium iodide in dimethyl formamide and acetonitrile or with trifluoroacetic anhydride and sodium cyanide did not afford the product.[98,99]

Additional attempts were made to prepare the corresponding aldehyde **220** from the chloro- and bromo-derivatives (**217** and **218**) *via* reaction with lithium metal (Bouveault reaction) as well as with magnesium and on subsequent reaction with dimethyl formamide.[100,101] These attempts were also unsuccessful.

Scheme 89 Attempted Synthesis of the Homologated Aldehyde Derivative (220)



217, X = Cl
218, X = Br

220

Reagents and conditions: a) Li, DMF, THF, ultrasound; b) Mg, Et_2O then DMF.

---

(98) Davis, R.; Untch, K. G. *J. Org. Chem.* **1981**, *46*, 2985.

(99) Camps, F.; Gasol, V.; Guerrero, A. *Synth. Commun.* **1988**, *18*, 445.

(100) Bouveault, L. *Bull. Soc. Chim. Fr.* **1904**, *31*, 1306.

(101) Petrier, C.; Gemal, A. L.; Luche, J.-L. *Tetrahedron Lett.* **1982**, *23*, 3361.

5.2.3 Homologation of the Benzoic Acid Derivative (208) *via* the Arndt-Eistert Protocol

The Arndt-Eistert protocol is a procedure for the conversion of an acid to its next higher homologue or to a derivative of a homologated carboxylic acid, such as an ester or amide. The procedure, which is applicable to both aliphatic and aromatic acids, usually involves three steps (Figure 56). First, the acid is converted to a more reactive derivative, either an acid chloride or an anhydride (Figure 56, step 1). In the second step, the acid derivative is reacted with diazomethane to afford a diazoketone (Figure 56, step 2). The last step in this procedure, also known as the Wolff rearrangement, is the rearrangement of the diazoketone in the presence of a suitable reagent and catalyst (Figure 56, step 3).[102]

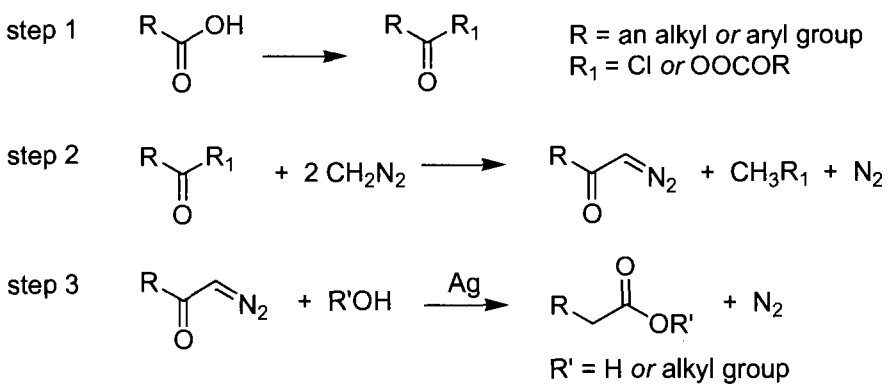


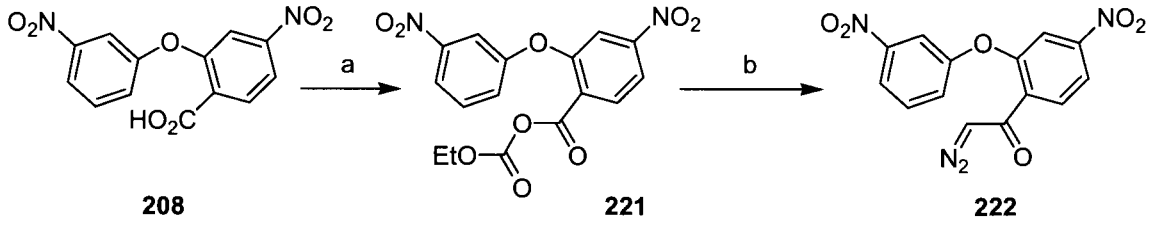
Figure 56 Overview of the Arndt-Eistert protocol.

When the Arndt-Eistert sequence of steps was applied to 2-(3'-nitrophenoxy)-4-nitrobenzoic acid **208**, the mixed anhydride **221** obtained on reaction with ethyl chloroformate reacted faster and more cleanly with

(102) Arndt, F. *Org. Reactions*; John Wiley and Sons, Inc: New York, 1963; Vol. 1.

diazomethane than the corresponding acid chloride. Of note, diazomethane was synthesized from *N*-methyl-*N*-nitrosourea and aqueous potassium hydroxide, according to a literature procedure and was used as a solution in diethyl ether.[103]

Scheme 90 Synthesis of the Diazoketone (222)

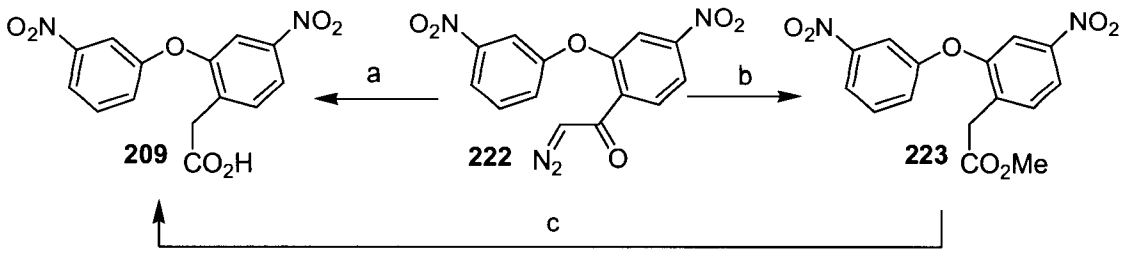


Reagents and conditions: a) Et_3N, EtOCOCl, THF, 0 °C, 15 min; b) CH_2N_2, room temperature, 4 h.

Both the mixed anhydride **221** and the diazoketone **222** were used without purification. The diazoketone **222** was initially diluted with methanol and reacted with triethylamine and silver benzoate in the dark at room temperature. The crude reaction mixture was purified by flash chromatography to afford the methyl ester **223** in 50% yield. A better yield (67%) was obtained by decreasing the reaction temperature to -18 °C (Scheme 91).

(103) Arndt, F. *Org. Syntheses*; John Wiley and Sons, Inc.: New York, 1943; Vol. 2.

Scheme 91 Synthesis of the Homologated Acid (209) and Methyl Ester (223) *via* the Wolff Rearrangement of the Diazoketone (222)



Reagents and conditions: a) Et_3N, $PhCO_2Ag$, THF, H_2O, dark, 30 min, 72% (over three steps); b) Et_3N, $PhCO_2Ag$, MeOH, -18 °C, dark, 30 min, 67% (over three steps); c) HCl (6 M), reflux, 5 h, 90%.

The methyl ester **223** was then hydrolyzed under acidic conditions to afford the homologated acid derivative **209**. The acid derivative **209** could also be obtained directly from the diazoketone **222** by changing the reaction solvent from methanol to a mixture of tetrahydrofuran and water. Under these reaction conditions, the homologated acid derivative **209** was isolated in pure form in 72% yield (Scheme 91).

5.2.4 The Intramolecular Cyclization Reaction

The previous cyclization reactions were performed either *via* the Friedel-Crafts reaction of the acid chloride, in case of the dimethoxy-oxepinone **183** or by cyclodehydration of a carboxylic acid in presence of polyphosphoric acid, in case of the unsubstituted oxepinone **33**. These two sets of reaction conditions were the first methods employed to accomplish the intramolecular cyclization of the 2-[2-(3'-nitrophenoxy)-4-nitrophenyl]acetic acid **209** to the dinitro-oxepinone **203** (Scheme 92).

Scheme 92 Intramolecular Cyclization of the Acid Derivative (209) to the Dinitro-Oxepinone (203)

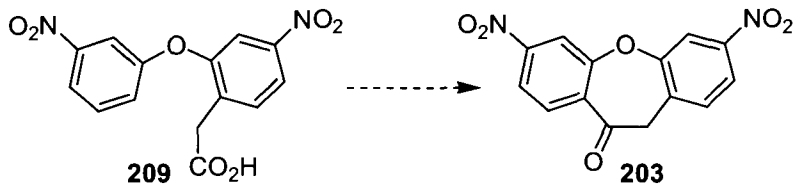


Table 15 Experimental Conditions Corresponding to Scheme 92

Entry	Reagents and conditions
1	$SOCl_2$, CH_2Cl_2 then $AlCl_3$, $ClCH_2CH_2Cl$
2	PPA, 100 °C
3	PPA, 150 °C
4	P_2O_5, H_3PO_4, PhMe, reflux
5	TFAA, BF_3·Et_2O, CH_2Cl_2

Treatment of the acid **209** with thionyl chloride in dichloromethane was expected to result in the synthesis of the corresponding acid chloride derivative which was not isolated.[55] The Friedel-Crafts intramolecular acylation reaction of this crude chloride was attempted in presence of aluminum trichloride as catalyst at either -18 °C, 0 °C, room temperature as well as at reflux. The changes in temperature did not appear to alter the outcome of the reaction which resulted only in the degradation of the starting material (Table 15, entry 1).

The acid **209** was then reacted under the cyclodehydration conditions (in polyphosphoric acid at 100 °C). Under these reaction conditions the starting

material was recovered (Table 15, entry 2). Therefore the reaction was performed at a higher temperature (150 °C) (Table 15, entry 3). At 150 °C the acid **209** decomposed and no evidence of the product was detected by thin layer chromatography.

Similarly, polyphosphoric acid was prepared from phosphorus pentoxide and concentrated phosphoric acid according to the procedure reported by Sindelar and co-workers.[104] Unfortunately, the starting material **209** did not react under these conditions (Table 15, entry 4).

A more unusual ring closing method has been reported to involve the reaction of a phenoxyacetic acid derivative with trifluoroacetic anhydride and boron trifluoride-etherate (Table 15, entry 5).[39] These reaction conditions were found to provide a general approach for the intramolecular cyclization of unstable compounds under acidic conditions but were not effective for the present system.

5.3 Miscellaneous Methods Attempted for the Synthesis of the 3,7-Dinitro- and Nitro,methoxy-11*H*-dibenzo[*b,f*]oxepin-10-one (203, 206 and 207)

Several other methods were attempted for the synthesis of the 3,7-dinitro-11*H*-dibenzo[*b,f*]oxepin-10-one **203** and either 7-methoxy-3-nitro- or 3-methoxy-7-nitro-11*H*-dibenzo[*b,f*]oxepin-10-one (**206** and **207**) (Figure 54).

Intramolecular C-H insertion reactions of α-diazocarbonyl compounds have proved to be a reliable method for the synthesis of carbocycles and

(104) Sindelar, K.; Jilek, J. O.; Pomykacek, J.; Sedivy, Z.; Protiva, M. *Collect. Czech. Chem. Commun.* **1978**, *43*, 471.

heterocycles. The catalysts of choice for these transformations is rhodium (II) acetate (Figure 57).[105]

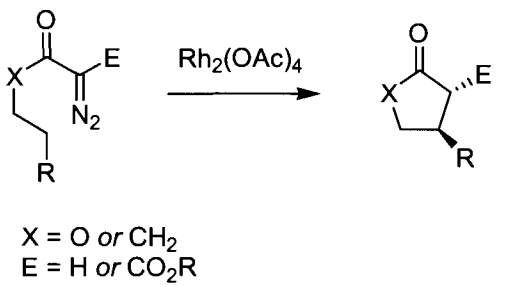
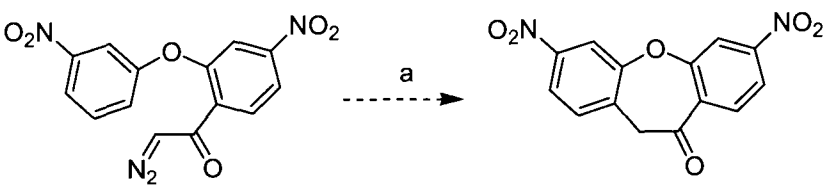


Figure 57 Stereoselective cyclization *via* intramolecular C-H insertion of a Rh-carbene complex.

Thus, the intramolecular C-H insertion of the diazoketone **222** in presence of rhodium diacetate was attempted under the reaction conditions reported by Ratcliffe and co-workers but none of the desired product was isolated (Scheme 93).[106]

Scheme 93 Attempted C-H Insertion of the Diazoketone (222) in Presence of Rhodium Diacetate as Catalyst



222 **203**

Reagents and conditions: a) $Rh_2(OAc)_4$, PhH, 80 °C.

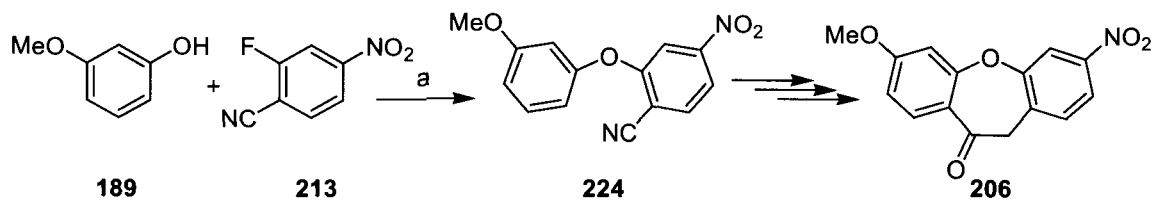
The synthesis of the 7-methoxy-3-nitro substituted oxepinone **206** was also planned to follow a reduction, chlorination, cyanation and hydrolysis

(105) Yoshikai, N.; Nakamura, E. *Adv. Synth. Catal.* **2003**, 1159.

(106) Ratcliffe, R. W.; Salzmann, T. N.; Christensen, B. G. *Tetrahedron Lett.* **1980**, *21*, 31.

strategy. Accordingly, the required benzyl alcohol was prepared. The known biaryl ether derivative **224** was first prepared according to a reported procedure, in presence of potassium fluoride/alumina and 18-crown-6.[42] This biaryl ether was obtained in 90% yield as a yellow solid with a melting point in the range 63-65 °C (Scheme 94).

Scheme 94 Synthesis of 2-(3'-Methoxy-phenoxy)-4-nitro-benzonitrile (224): Proposed Synthesis of 7-Methoxy-3-nitro-11*H*-dibenzo[*b,f*]oxepin-10-one (206)



189 **213** **224** **206**

Reagents and conditions: a) 18-crown-6, KF·Al_2O_3, MeCN, reflux, 20 h, 90%.

The product, 2-(3'-methoxy-phenoxy)-4-nitro-benzonitrile (**224**) was initially characterized based on NMR data. The methoxy peak appeared as a singlet at a chemical shift δ = 3.84 ppm and the aromatic protons were observed between 6.7 and 8.0 ppm (Figure 58).

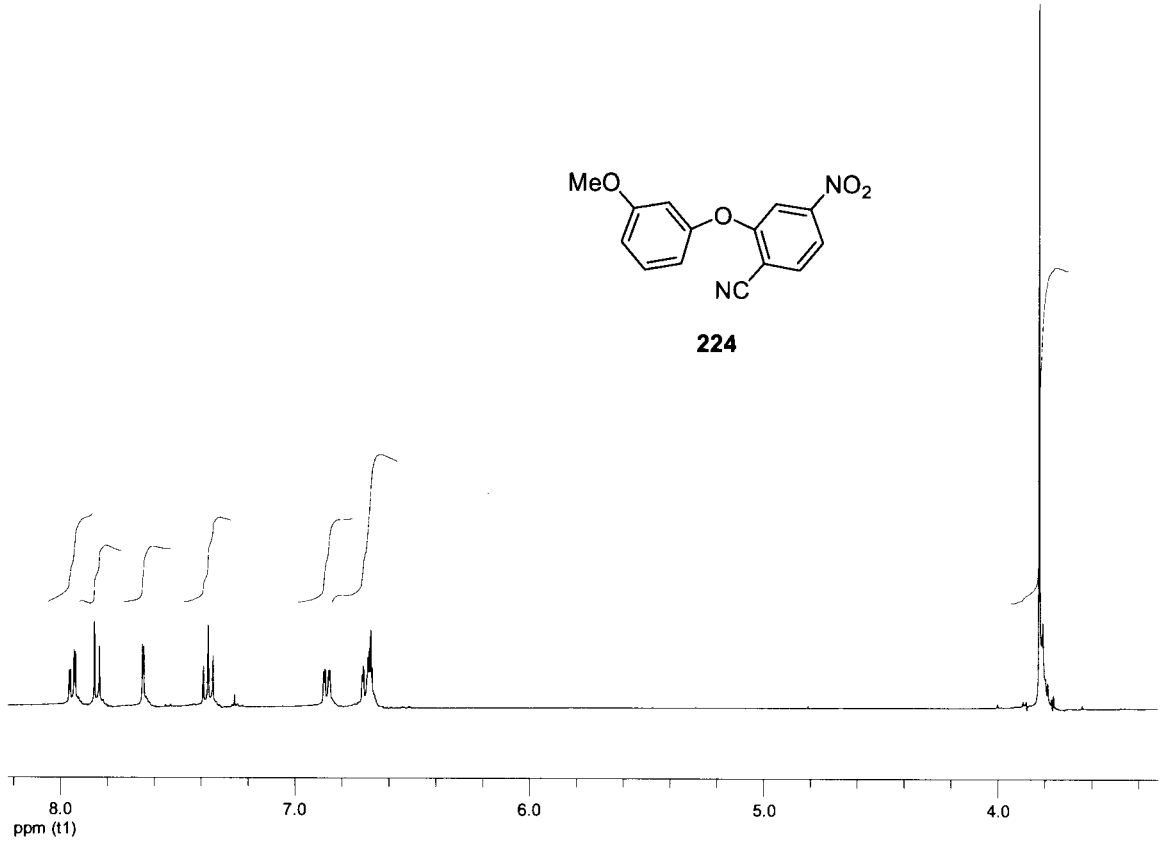


Figure 58 **Detail from the ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of 2-(3'-methoxy-phenoxy)-4-nitrobenzonitrile (224).**

However, the melting point and the ^{1}H NMR data of 2-(3'-methoxy-phenoxy)-4-nitro-benzonitrile **224** did not agree with the reported literature values.[42] In the ^{13}C NMR spectrum the peak corresponding to the methoxy group at δ = 55.7 ppm as well as peaks corresponding to the carbon atoms connected to oxygen atoms in the region δ = 151.3-161.7 ppm were observed. The presence of the nitrile group was confirmed by the strong absorption peak at 2236 cm^{-1} in the IR spectrum. The compound also passed elemental analysis as a proof of purity and there was no doubt regarding the accurate formula of the compound.

The correct substitution pattern of the starting materials involved in the synthesis of the nitrile **224** was previously proven (see section 5.2.1) in that the exact substitution of the 2-fluoro-4-nitrobenzonitrile **213** was proved by the X-ray crystallographic analysis of 2-(3'-nitrophenoxy)-4-nitrobenzonitrile **215** (Figure 55). The second reactant in the reaction, 3-methoxy phenol **189** was commercially available and was also prepared from resorcinol. Considering all the evidence, the initial structural assignment of the nitrile compound **224** was confirmed and the work reported by Sawyer and co-workers appears to be in error.[42]

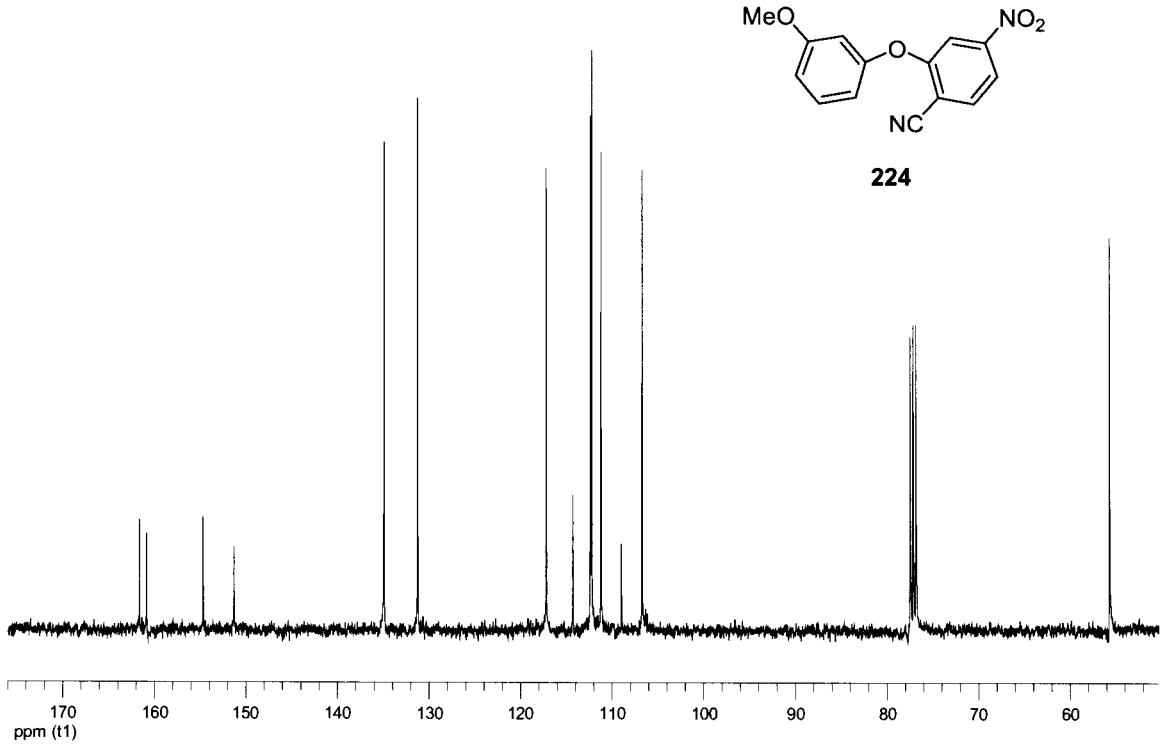
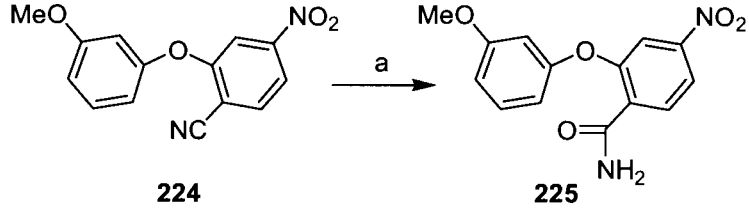


Figure 59 **Detail from the ^{13}C NMR spectrum ($CDCl_3$, 400 MHz) of 2-(3'-methoxy-phenoxy)-4-nitro-benzonitrile (224).**

One carbon homologation of 2-(3'-methoxy-phenoxy)-4-nitro-benzonitrile (**224**) followed by intramolecular cyclization was expected to afford 7-methoxy-3-nitro-11*H*-dibenzo[*b*,*f*]oxepin-10-one **206** (Scheme 94). Hydrolysis of the nitrile derivative **224** in basic media afforded the amide **225** as a yellow solid with a melting point in the range 180-181 °C (Scheme 95). However, the amide **225** could not be further hydrolyzed. The hydrolysis of the nitrile derivative **224** was also attempted under acid catalysis but decomposition of the starting material occurred.

Scheme 95 Synthesis of 2-(3'-Methoxyphenoxy)-4-nitrobenzamide (248)

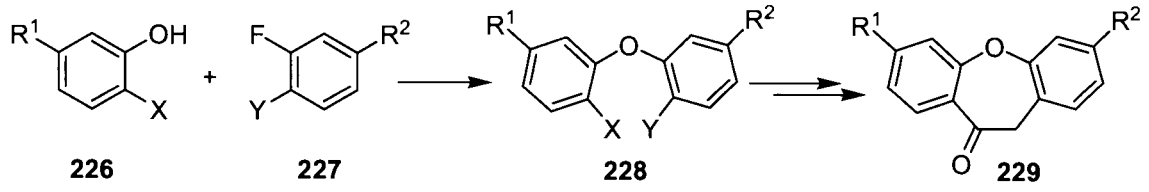


224 **225**

Reagents and conditions: a) KOH, H_2O_2, MeOH, EtOH, 50 °C, 10 min, 60%.

Since the deactivation of the aromatic ring due to the nitro substituents prevented the intramolecular Friedel-Crafts alkylation or dehydration reactions, an alternative strategy was considered (Scheme 96). This strategy would involve the coupling of a disubstituted phenol **226** with a disubstituted fluorobenzene **227** to afford the biaryl ether compound **228**. The substituents X and Y of the biaryl ether compound **228** should be functional groups capable of reacting in an intramolecular reaction to afford the di-substituted oxepinone **229**.

Scheme 96 Proposed Alternative Strategy for the Synthesis of Methoxy-Nitro Substituted Oxepinone (229)

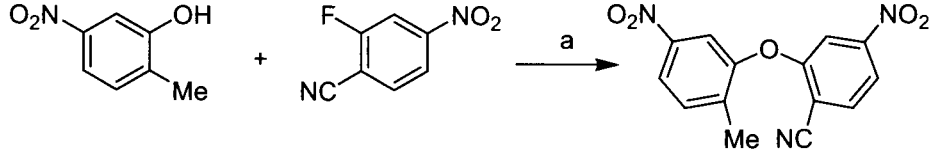


226 **227** **228** **229**

R^1 = OMe *or* NO_2
R^2 = OMe *or* NO_2
X, Y = functional groups

According to this strategy, 2-(2'-methyl-5'-nitrophenoxy)-4-nitrobenzonitrile **231** was obtained by reaction of 2-fluoro-4-nitrobenzonitrile **213** with commercially available 2-methyl-5-nitrophenol **230** (Scheme 97).

Scheme 97 Synthesis of 2-(2'-Methyl-5'-nitrophenoxy)-4-nitrobenzonitrile (250)

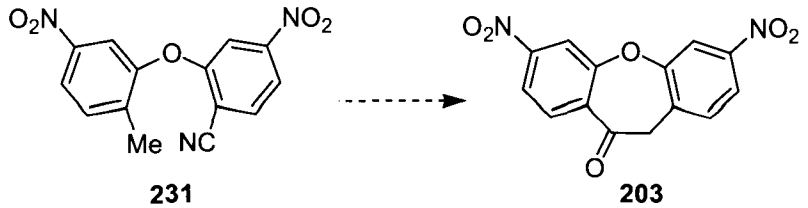


230 **213** **231**

Reagents and conditions: a) 18-crown-6, KF·Al_2O_3, MeCN, reflux, 4 h, 95%.

Deprotonation of the methyl group was expected to generate a carbanion which could have added to the nitrile group and after work-up afford the dinitro-oxepinone **203** (Scheme 98). The deprotonation step was attempted with potassium *tert*-butoxide, sodium hydroxide and LDA. However, none of the desired product was isolated.

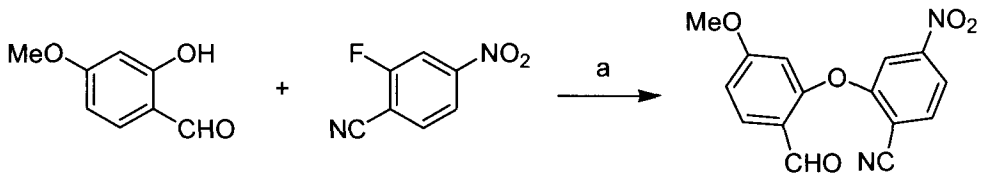
Scheme 98 Proposed Alternative Synthesis of Dinitro-Oxepinone (203)



231 **203**

2-Fluoro-4-nitrobenzonitrile **213** was then coupled with commercially available 2-hydroxy-4-methoxybenzaldehyde (**232**). The methoxy-nitro biaryl ether derivative **233** was obtained quantitatively (Scheme 99). Functional group transformation of the aromatic carbonyl to the benzyl bromide was expected to afford a substrate for an intramolecular Grignard addition reaction.

Scheme 99 Synthesis of 2-(2'-Formyl-5'-methoxyphenoxy)-4-nitrobenzonitrile (233)

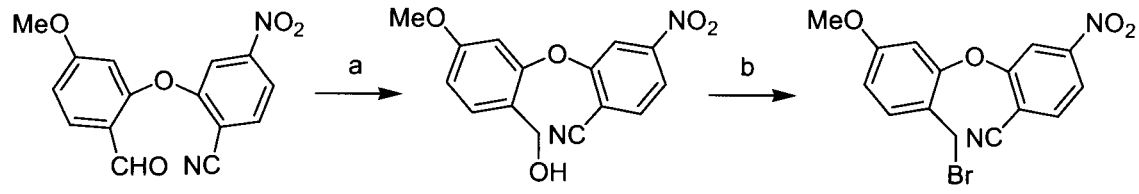


232 **213** **233**

Reagents and conditions: a) 18-crown-6, KF·Al_2O_3, MeCN, reflux, 2 h, 99%.

Reduction of the aldehyde functional group of the biaryl compound **233** with sodium borohydride afforded the benzylic alcohol **234** which was transformed into the benzyl bromide **235** in presence of phosphorus tribromide (Scheme 100).

Scheme 100 Synthesis of 2-(2'-(Hydroxymethyl)- (234) and 2-(2'-(Bromomethyl)-5'-methoxyphenoxy)-4-nitrobenzonitrile (235)

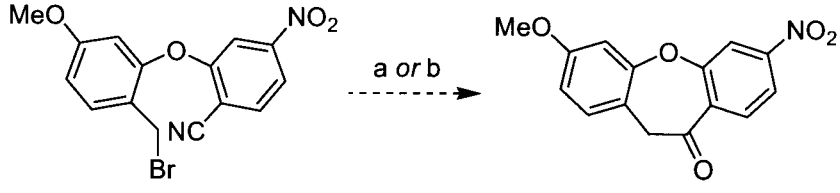


233 **234** **235**

Reagents and conditions: a) $NaBH_4$, MeOH, 91%; b) PBr_3, CH_2Cl_2, 0 °C, 5 min, 90%.

The benzyl bromide **235** was then reacted with magnesium to prepare a Grignard reagent which was expected to add to the nitrile in an intramolecular fashion but again no addition product was detected (Scheme 101).

Scheme 101 Attempted Grignard and Organosamarium Reactions for the Synthesis of 3-Methoxy-7-nitro-11*H*-dibenzo[*b,f*]oxepin-10-one (255)



235 **207**

Reagents and conditions: a) Mg, THF; b) SmI_2, THF.

Alternatively, reaction of the benzyl bromide **235** with samarium(II) iodide was expected to afford the corresponding benzylsamarium derivative *in situ* which could add to the nitrile functional group (Scheme 101).[107] This strategy was also unsuccessful. In both the Grignard and the benzylsamarium approach, the reduction product was observed.

(107) Hamann-Gaudinet, B.; Namy, J.-L.; Kagan, H. B. *Tetrahedron Lett.* **1997**, *38*, 6585.

5.4 Conclusions

Progress had been made towards the synthesis of the 3,7-dinitro-11*H*-dibenzo[*b,f*]oxepin-10-one **203** derivative. The presence of the two nitro-substituents had a notable influence on the reactivity of the system and homologation of the benzoic acid could not be achieved *via* the reduction, halogenation, cyanation and hydrolysis sequence. Instead, the Arndt-Eistert protocol was employed and the synthesis of the homologated 2-(2'-(3'-nitrophenoxy)-4-nitrophenyl)acetic acid **208** was achieved in 39% yield over eight steps starting from the commercially available bromobenzene **210**.

For the last step in the synthesis of the dinitro-oxepinone **203**, the Friedel-Crafts intramolecular acylation and the cyclodehydration reaction were attempted on the homologated acid derivative **208**. The deactivation effect of the nitro substituents prevented the ring forming reaction and the synthesis of the dinitro-oxepinone **203**. Alternative methods were also employed to synthesize other disubstituted oxepinone derivatives. The attempts resulted in the synthesis of new compounds but the final closure of the dibenzoxepine ring could not be achieved.

5.5 Future Work

The successful synthesis of the unsubstituted artocarpol A, D and E analogues will enable the biological activity of these compounds to be determined. This will establish whether the phenolic and prenyl substituents are required for biological activity. In addition, the biological activity of the dimethoxy artocarpol E analogue (**198**) could be determined.

The attempts to synthesize dimethoxy artocarpol A analogue (**185**) demonstrated that electron donating groups (*i.e.* methoxy) prevent the synthesis of the corresponding 2*H*-pyran derivative. A solution to this problem was thought to be the alternative use of electron withdrawing groups (*i.e.* nitro). However, electron withdrawing groups prevented the ring closure reaction of the corresponding oxepinone precursors due to deactivation of the aromatic rings towards a Friedel-Crafts acylation process (Figure 60). Therefore, an alternative approach to facilitate the ring closure reaction of the dinitro-oxepinone could involve a nucleophilic aromatic substitution process as opposed to an electrophilic aromatic substitution process.

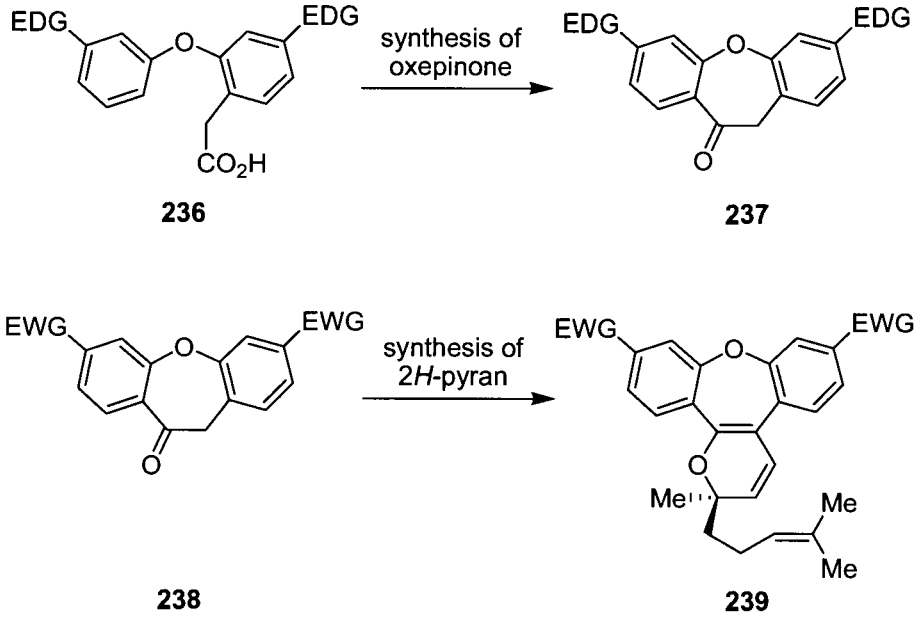
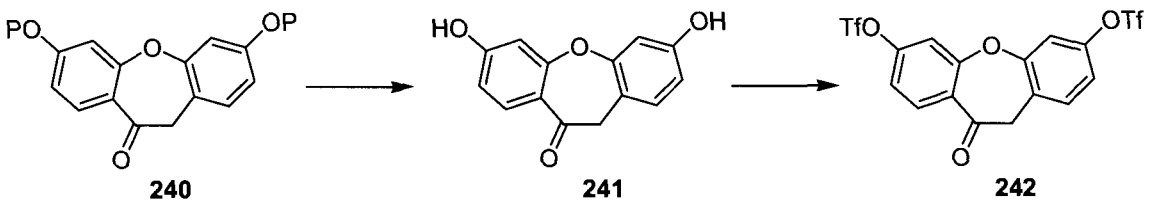


Figure 60 **Electron donating groups facilitate the Friedel-Crafts acylation reaction. Electron withdrawing groups should assist the synthesis of the 2*H*-pyran.**

An additional problem associated with the dimethoxy series of reaction intermediates was that it was not possible to deprotect both methoxy groups of the oxepinone in order to generate the diphenol derivative **241**. This problem could be circumvented by the use of a different protecting group. Thus, the corresponding *p*-methoxybenzyl derivative **240** (P = PMB) could be employed as it can be readily removed under mild reaction conditions. Furthermore, the resultant diphenol derivative **241** could be converted to the corresponding ditriflate **242**. The presence of these electron withdrawing groups should have a positive effect on the synthesis of the corresponding 2*H*-pyran derivatives and allow for the total synthesis of the natural products (Figure 61).



240 **241** **242**

Figure 61 **Deprotection of the oxepinone (240, P = PMB) and conversion to the ditriflate derivative (242).**

CHAPTER 6: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA

6.1 General Experimental Details

All non-aqueous reactions were performed under an atmosphere of dry nitrogen, in oven- or flame-dried glassware, unless otherwise indicated. Reaction temperatures stated were those of the external bath. Diethyl ether (ether) and tetrahydrofuran (THF) were dried over sodium/benzophenone ketyl and distilled under an atmosphere of dry nitrogen immediately prior to use. Benzene, dichloromethane, toluene, triethylamine, *N,N*-diisopropylamine and pyridine were dried over calcium hydride and distilled under an atmosphere of dry nitrogen immediately prior to use. All other solvents and reagents were purified by standard techniques or used as supplied.[108] Brine refers to a saturated aqueous solution of sodium chloride. Silica gel column chromatography ("flash chromatography") was carried out using Merck silica gel 60 (230 to 400 mesh).[109] Melting points were measured on a Gallenkamp capillary melting point apparatus and are uncorrected. All proton and carbon nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR, respectively) were recorded using a Bruker AMX 400 FT spectrometer (operating frequencies: ^{1}H, 400.13 MHz; ^{13}C, 100.61 MHz) and a Varian 500 spectrometer (operating

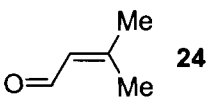
(108) Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*; 4th ed.; Butterworth-Heinemann: Oxford, **1997**.

(109) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

frequencies: ^{1}H, 499.77 MHz; ^{13}C, 125.68 MHz) at ambient temperature. Chemical shifts (δ) for all compounds are listed in parts per million downfield from tetramethylsilane using the NMR solvent as an internal reference. The reference values used for deuterated chloroform ($CDCl_3$) were 7.26 and 77.16 ppm for ^{1}H and ^{13}C NMR spectra, respectively. The reference values used for deuterated benzene (C_6D_6) were 7.15 and 128.02 ppm, respectively. The reference values used for deuterated acetone (acetone-D_6) were 2.05 and 30.8 ppm, respectively. Infrared spectra (IR) were recorded as either KBr discs (KBr) or evaporated films (ef) using a Perkin Elmer 599B IR spectrophotometer. Mass spectra (MS) were recorded on a Hewlett Packard 5985 GC-mass spectrometer and a Varian 4000 GC/MS/MS. The modes of ionization used were electron impact (EI) or chemical ionization (CI) with isobutane or methanol, respectively. Microanalyses were performed on a Carlo Erba Model 1106 CHN analyzer.

6.2 Experimental Procedures and Characterization Data Concerning Chapter 3

6.2.1 Senecialdehyde (24)[110]



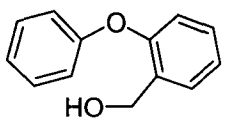
24

A solution of 3-methyl-but-2-enol (5.01 g, 58.1 mmol) in dichloromethane (10 mL) was added dropwise to a suspension of pyridinium dichromate (32.7 g, 87.1 mmol) in dichloromethane (50 mL) at 0 °C. The resultant mixture was stirred at room temperature for 20 h, diluted with ether (100 mL) and then filtered

(110) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

through a pad of celite. The filter-cake was washed with ether (20 mL) and the combined filtrates were concentrated under reduced pressure. Purification of the crude product by distillation afforded pure the aldehyde **24** (4.24 g, 87%) as a colourless oil. **B.p.** 132-133 °C, 760 mm (lit.[111] 133-135 °C, 760 mm); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.97 (s, 3H, *Me*), 2.16 (s, 3H, *Me*), 5.87 (d, J = 8 Hz, 1H, *H*-2), 9.94 (d, J = 8 Hz, 1H, C*H*O); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 18.9, 27.2, 128.1, 160.6, 191.0; **IR** (ef) 2980, 2845, 1681, 1634, 1616, 1378, 1198, 1131, 1047, 835 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 86 (5), 85 (M + H, 100).

6.2.2 2-Phenoxybenzyl alcohol (124)



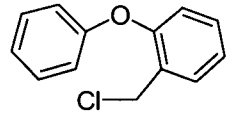
124

2-Phenoxybenzoic acid **123** (15.04 g, 70.00 mmol) was added over a period of 30 min to a suspension of lithium aluminum hydride (4.02 g, 110 mmol) in tetrahydrofuran (50 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and then was heated at reflux for 4 h. The resultant mixture was cooled to 0 °C and was diluted with water (10 mL) and then an aqueous solution of sodium hydroxide (15 w/v %, 5 mL). The reaction mixture was stirred for 2 h at room temperature, the two phases were separated and the organic phase was dried over anhydrous magnesium sulfate and filtered. The filter-cake was washed with ether (50 mL) and the combined filtrates were concentrated under reduced pressure to afford the pure benzyl alcohol **124** (12.72 g, 90%) as

(111) Riley, R. G.; Silverstein, R. M. *J. Org. Chem.* **1974**, *39*, 1957.

a pale yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.09 (broad s, 1H, O*H*), 4.75 (s, 2H, CH_2), 6.87-7.47 (m, 9H, Ar*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 61.3, 118.5, 118.7, 123.5, 123.9, 129.1, 129.4, 130.0, 132.0, 154.8, 157.3; **IR** (ef) 3416 (broad), 3038, 2870, 1580, 1493, 1162, 874, 806, 691 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 200 (M, 8), 199 (21), 183 (M - OH, 100).

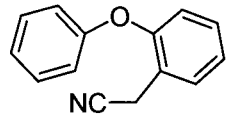
6.2.3 2-Phenoxybenzyl chloride (125)[53]



125

Thionyl chloride (6.5 mL, 89 mmol) was added to a solution of 2-phenoxybenzyl alcohol **124** (12.72 g, 63.60 mmol) and pyridine (5.1 mL, 64 mmol) in benzene (200 mL) at 0 °C. The reaction mixture was heated at reflux for 24 h and then cooled to room temperature. The resultant mixture was filtered and the filter-cake was washed with benzene (50 mL). The combined filtrates were then concentrated under reduced pressure to afford the pure benzyl chloride **125** (13.65 g, 98%) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.71 (s, 2H, CH_2), 6.87-7.50 (m, 9H, Ar*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 41.2, 118.8, 118.9, 123.6, 123.8, 128.8, 130.0, 130.2, 131.1, 155.2, 157.3; **IR** (ef) 3038, 2968, 1583, 1455, 750, 691 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 220 [M (^{37}C) + H, 32], 218 [M (^{35}C) + H, 7], 184 (100).

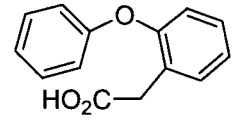
6.2.4 (2-Phenoxyphenyl)acetonitrile (126)[54]



126

A solution of 2-phenoxybenzyl chloride **125** (13.61 g, 62.20 mmol) in dimethyl sulfoxide (10 mL) was added to a mixture of sodium cyanide (4.58 g, 93.4 mmol) and dimethyl sulfoxide (10 mL) at room temperature. After 24 h, the reaction mixture was diluted with water (20 mL) and extracted with ether (2 x 30 mL). The combined organic extracts were washed with water (4 x 25 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the pure benzyl nitrile **126** (11.71 g, 90%) as a green oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.79 (s, 2H, CH_2), 6.85-7.51 (m, 9H, Ar*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 18.9, 117.8, 118.3, 119.0, 121.3, 123.9, 124.0, 129.81, 129.84, 130.1, 154.9, 156.4; **IR** (ef) 3043, 2928, 2251, 1585, 1455, 751 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 266 (M + *i*-butane, 48), 210 (M + H, 100).

6.2.5 (2-Phenoxyphenyl)acetic acid (127)[55]

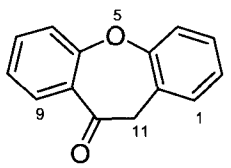


127

A solution of (2-phenoxyphenyl)acetonitrile **126** (5.62 g, 26.9 mmol) and potassium hydroxide (4.29 g, 76.7 mmol) in aqueous ethanol (80 v/v %, 100 mL) was heated at reflux for 4 h. The reaction mixture was allowed to cool to room temperature and then was concentrated under reduced pressure. The solid residue was dissolved in water (50 mL) and extracted with ether (2 x 20 mL).

The aqueous fraction was then acidified to pH ~ 1 with concentrated hydrochloric acid. The precipitated solid was filtered, washed with water (2 x 20 mL) and air-dried. Purification of the crude product by recrystallization from hexanes:ether (5:1) afforded the pure acid **127** (5.23 g, 85%) as a yellow solid. **M.p.** 85-88 °C, hexanes/ether (lit.[55] 89-91 °C, cyclohexane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.72 (s, 2H, C*H*$_2$), 6.85-7.32 (m, 9H, Ar*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 35.6, 118.7, 118.8, 123.4, 123.7, 125.2, 129.1, 129.9, 131.6, 155.5, 157.2, 177.1; **IR** (KBr) 2923, 2828 (broad), 2733, 1711, 1582, 1486, 1103, 753, 689 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 229 (M + H, 100), 183 (20); **Anal.** Calcd. for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.90; H, 5.26.

6.2.6 11*H*-Dibenzo[*b,f*]oxepin-10-one (33)



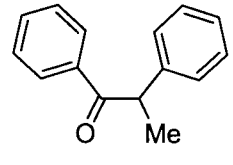
33

Method 1:[55] Thionyl chloride (0.77 mL, 10.5 mmol) was added to a solution of 2-phenoxyphenylacetic acid **127** (200 mg, 0.7 mmol) in dichloromethane (5 mL). The reaction mixture was heated at 80 °C for 5 min and then was concentrated under reduced pressure. The residue dissolved in 1,2-dichloroethane (10 mL) and then was added dropwise to a mixture of aluminum chloride (130 mg, 1.0 mmol) in 1,2-dichloroethane (5 mL). The resultant mixture was stirred at room temperature for 2 h and then was poured on to crushed ice (50 mL). The organic material was extracted into ethyl acetate (2 x 30 mL), washed with brine (30 mL), dried over anhydrous magnesium sulfate and

concentrated under reduced pressure to afford the pure oxepinone **33** (82 mg, 56%) as a yellow solid. **M.p.** 47-50 °C, ethyl acetate (lit. 53-54 °C, hexanes).

Method 2: (2-Phenoxyphenyl)acetic acid **127** (4.21 g, 18.5 mmol) was added in small portions to polyphosphoric acid (95.1 g, 257 mmol) at ~100 °C. The reaction mixture was heated for 4 h and then was allowed to cool to room temperature. The resultant mixture was diluted slowly with ice-cold water (50 mL) and then was extracted with ether (2 x 25 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium carbonate (2 x 25 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification of the crude product by recrystallization from hexanes afforded the pure oxepinone **33** (3.26 g, 84%) as a yellow solid. **M.p.** 48-50 °C, hexanes (lit. 53-54 °C, hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.10 (s, 2H, C*H*$_2$), 7.18-7.58 (m, 7H, Ar*H*), 8.06 (dd, *J* = 8, 2 Hz, 1H, *H*-9); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 48.4, 120.5, 121.7, 123.9, 126.4, 126.6, 128.6, 129.9, 130.6, 135.0, 157.0, 160.4, 190.4; **IR** (KBr) 3080, 2985, 1690, 1602, 1307, 947, 892, 786 cm^{-1}; **MS** (EI, 70 eV) *m/z* (rel. intensity) 210 (M, 100), 181 (91).

6.2.7 1,2-Diphenylpropan-1-one (135)[57]

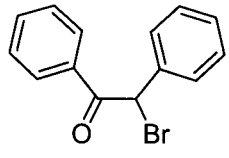


135

A solution of LDA was prepared by reacting a solution of *N,N*-diisopropylamine (0.30 mL, 2.1 mmol) in THF (5 mL) with *n*-butyllithium (0.80 mL,

2.5 M in hexanes, 2.0 mmol) at 0 °C for 30 min. A solution of deoxybenzoin **128** (200 mg, 1.02 mmol) in THF (5 mL) was added to the preformed solution of LDA at -78 °C. After 30 min, a solution of methyl iodide (434 mg, 3.06 mmol) in tetrahydrofuran (5 mL) was added. The reaction was stirred at 0 °C for 1 h and then was diluted with brine (15 mL) and ether (25 mL). The organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the pure monoalkylated ketone **135** (208 mg, 97%) as a brown solid. **M.p.** 51-53 °C, THF/ether (lit.[57] 51-52 °C, ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.51 (d, J = 7 Hz, 3H, *Me*), 4.66 (q, J = 7 Hz, 1H, *H*-2), 7.15-7.46 (m, 8H, Ar*H*), 7.92-7.94 (m, 2H, Ar*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 19.6, 48.0, 127.0, 127.9, 128.6, 128.8, 128.9, 129.1, 132.9, 136.6, 200.5; **IR** (KBr) 3064, 2987, 2247, 1673, 1596, 1448, 1216, 907, 733 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 211 (M + H, 13), 210 (100).

6.2.8 2-Bromo-1,2-diphenylethanone (136)[59]

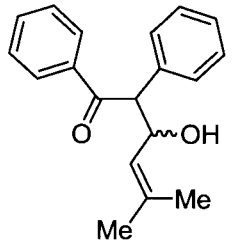


136

Bromine (80 μL, 1.7 mmol) was added dropwise to a solution of deoxybenzoin **128** (215 mg, 1.10 mmol) in chloroform (5 mL) at room temperature. The reaction mixture was heated at reflux for 20 min, then cooled to room temperature and concentrated under reduced pressure. Purification of the crude product by recrystallization from hexanes afforded the pure bromo-ketone **136** (284 mg, 94%) as a white solid. **M.p.** 44-48 °C, hexanes (lit.[59] 44-46

°C, hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.38 (s, 1H, *H*-2), 7.33-7.57 (m, 8H, Ar*H*), 7.99 (d, *J* = 8 Hz, 2H, Ar*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 51.2, 126.8, 128.2, 128.9, 129.3, 129.8, 131.6, 133.8, 134.3, 136.0, 191.2; **IR** (KBr) 2958, 1692, 1495, 1445, 1214, 1214, 1074, 988, 846, 755 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 277 [M (^{81}Br) + H, 99], 275 [M (^{79}Br) + H, 100), 195 (99).

6.2.9 3-Hydroxy-5-methyl-1,2-diphenylhex-4-en-1-one (130)[61]

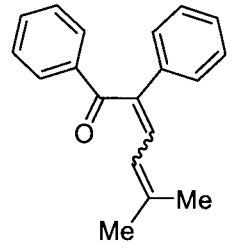


130

Titanium tetrachloride (1.6 mL, 1.0 M in dichloromethane, 1.6 mmol) and triethylamine (290 μL, 2.11 mmol) were successively added to a solution of deoxybenzoin **128** (207 mg, 1.06 mmol) in dichloromethane (10 mL) at -78 °C. After 30 min, a solution of senecialdehyde (**24**) (266 mg, 3.17 mmol) in dichloromethane (5 mL) was added. The reaction mixture was stirred at -78 °C for 3 h and was then diluted with water (15 mL) and ether (25 mL). The organic layer was washed with water (20 mL) and brine (15 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification of the crude product by flash chromatography using hexanes/ether (1:1) as the eluant afforded the pure hydroxyketone **130** (234 mg, 79%) as a white solid. **M.p.** 112-113 °C, hexanes/ether; **^{1}H NMR** (400 MHz, C_6D_6) δ 1.48 (s, 3H, *Me*), 1.63 (s, 3H, *Me*), 2.24 (broad s, 1H, O*H*), 4.57 (d, *J* = 7 Hz, 1H, *H*-4), 5.17-5.22 (m, 1H,

H-3), 5.29 (d, *J* = 10 Hz, 1H, *H*-2), 6.87-7.08 (m, 6H, Ar*H*), 7.38 (d, *J* = 7 Hz, 2H, Ar*H*), 7.88 (d, *J* = 9 Hz, 2H, Ar*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 18.6, 26.0, 59.4, 70.0, 124.7, 127.8, 128.7, 128.8, 129.0, 129.7, 133.3, 135.3, 136.8, 137.0, 200.3. **IR** (KBr) 3509, 3085, 2963, 1667, 1448, 750, 696 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 263 (M – H_2O, 20), 197 (100); **Anal.** Calcd. for $C_{19}H_{20}O_2$: C, 81.40; H, 7.19. Found: C, 81.20; H, 7.28.

6.2.10 2(*E*/*Z*)-5-Methyl-1,2-diphenylhexa-2,4-dien-1-one (137)[61]

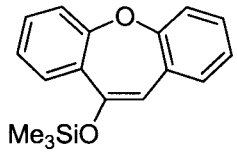


137

Titanium tetrachloride (1.6 mL, 1.0 M in dichloromethane, 1.6 mmol) and triethylamine (290 μL, 2.11 mmol) were successively added to a solution of deoxybenzoin (**128**) (200 mg, 1.0 mmol) in dichloromethane (10 mL) at -78 °C. After 30 min, a solution of senecialdehyde (**24**) (111 mg, 1.32 mmol) in dichloromethane (5 mL) was added and the reaction mixture was stirred at -78 °C for 3 h. The resultant mixture was diluted with water (15 mL) and ether (25 mL). The organic layer was washed with water (20 mL) and brine (15 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification of the crude product by flash chromatography using hexanes/ether (1:1) as the eluant afforded the pure dienone **137** (182 mg, 68%) as a clear oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.82 (s, 6H, 2 x *Me*), 6.09 (apparent d, *J* = 12 Hz,

1H, *H*-4), 7.26-7.50 (m, 9H, Ar*H*), 7.71-7.73 (m, 2H, *H*-3, Ar*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 19.3, 27.1, 122.4, 127.6, 128.2, 128.3, 129.7, 130.4, 131.7, 136.6, 138.10, 138.14, 139.2, 147.1, 197.5; **IR** (KBr) 3085, 2963, 1658, 1462, 740, 697 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 263 (M + 1, 50), 247 (100); **Anal.** Calcd. for $C_{19}H_{18}O$: C, 86.99; H, 6.92. Found: C, 87.05; H, 7.00.

6.2.11 (Dibenzo[*b,f*]oxepin-10-yloxy)trimethylsilane (138)[62]

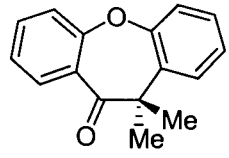


138

A solution of LDA was prepared by reacting a solution of *N,N*-diisopropylamine (160 μL, 1.14 mmol) in THF (5 mL) with *n*-butyllithium (0.50 mL, 2.5 M in hexanes, 1.2 mmol) at 0 °C for 30 min. A solution of the oxepinone **33** (201 mg, 0.95 mmol) in THF (5 mL) was added to the preformed solution of LDA at -78 °C. After 30 min, trimethylsilyl chloride (175 μL, 1.37 mmol) was added and the reaction was stirred at 0 °C for 3 h. The resultant mixture was diluted with triethylamine (1 mL) and pentane (20 mL). The organic layer was washed with a saturated aqueous solution of sodium bicarbonate (3 x 10 mL) and brine (2 x 20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the trimethyl silyl enol ether **138** (264 mg, 98%) as a brown oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.31 (s, 9H, 3 x *Me*), 6.20 (s, 1H, *H*-11), 7.05-7.54 (m, 8H, Ar*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 0.4, 77.3, 111.7, 121.0, 121.3, 124.8, 125.0, 127.1, 128.1, 128.8, 130.9, 156.1, 157.3; **IR** (ef) 3078, 2959, 2360,

1685, 1624, 1447, 1032, 919, 754 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 339 (17), 283 (M + H, 100), 211 (20).

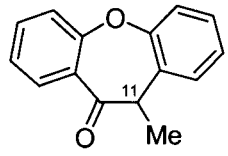
6.2.12 11,11-Dimethyl-11*H*-dibenzo[*b*,*f*]oxepin-10-one (139)



139

A solution of LDA was prepared by reacting a solution of *N,N*-diisopropyl amine (0.55 mL, 4.0 mmol) in THF (5 mL) with *n*-butyllithium (1.50 mL, 2.5 M in hexanes, 3.7 mmol) at 0 °C for 30 min. A solution of the oxepinone **33** (389 mg, 1.85 mmol) in THF (5 mL) was added to the preformed solution of LDA at -78 °C. After 30 min, a solution of methyl iodide (788 mg, 5.55 mmol) in THF (5 mL) was added and the reaction mixture was stirred at 0 °C for 1 h. Brine (15 mL) and ether (25 mL) were then added, the organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification of the crude product by flash chromatography using hexanes/ether (2:1) as the eluant afforded the dialkylated ketone **139** (352 mg, 80%) as a brown solid. **M.p.** 82-85 °C, hexanes/ether. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.67 (s, 6H, 2 x *Me*), 7.17-7.42 (m, 6H, Ar*H*), 7.52-7.57 (m, 1H, Ar*H*), 8.06-8.09 (m, 1H, Ar*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 23.5, 51.1, 121.0, 121.7, 123.4, 124.9, 126.0, 127.3, 128.7, 131.6, 132.7, 134.5, 156.5, 157.9, 195.4; **IR** (KBr) 1679, 1442, 1294, 1235, 889, 761 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 239 (M + H, 100); **Anal.** Calcd. for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.39; H, 5.81.

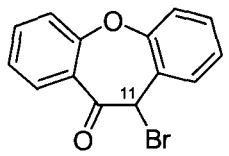
6.2.13 11-Methyl-11*H*-dibenzo[*b*,*f*]oxepin-10-one (140)[63]



140

A solution of tetra-*n*-butylammonium hydrogen sulfate (735 mg, 2.17 mmol) and sodium hydroxide (173 mg, 4.33 mmol) in water (10 mL) was added to a solution of the oxepinone **33** (455 mg, 2.17 mmol) and methyl iodide (270 μL, 4.33 mmol) in dichloromethane (15 mL). The reaction mixture was stirred for 1 h and then dichloromethane (20 mL) and water (20 mL) were added. The organic layer was washed with water (50 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Purification of the crude product by flash chromatography using petroleum ether/dichloromethane (2:1) as the eluant afforded the pure monoalkylated product **140** (290 mg, 60%) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.64 (d, J = 7 Hz, 3H, *Me*), 4.42 (q, J = 7 Hz, 1H, *H*-11), 7.16-7.32 (m, 5H, Ar*H*), 7.38-7.40 (m, 1H, Ar*H*), 7.52-7.56 (m, 1H, Ar*H*), 8.06 (dd, J = 8, 2 Hz, 1H, Ar*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ11.7, 47.9, 120.4, 121.3, 123.7, 126.3, 126.4, 126.6, 128.2, 130.5, 130.6, 134.6, 156.8, 160.0, 192.3; **IR** (ef) 3071, 2982, 1689, 1600, 1467, 953, 874, 751 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 225 (M + H, 100).

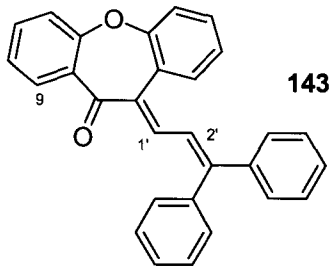
6.2.14 11-Bromo-11*H*-dibenzo[*b*,*f*]oxepin-10-one (141)[59]



141

Bromine (80 μL, 1.7 mmol) was added dropwise to a solution of the oxepinone **33** (206 mg, 0.98 mmol) in chloroform (5 mL). The resultant mixture was stirred at reflux for 15 min, cooled to room temperature and concentrated under reduced pressure. Purification of the crude product by recrystallization from hexanes/chloroform (1:1) afforded the pure bromoketone **141** (180 mg, 63%) as a white solid. **M.p.** 84-86 °C, hexanes/chloroform; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.62 (s, 1H, *H*-11), 7.23-7.46 (m, 6H, Ar*H*), 7.60-7.64 (m, 1H, Ar*H*), 8.13 (dd, J = 8, 2 Hz, 1H, Ar*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 53.2, 121.7, 122.0, 123.0, 124.0, 125.0, 126.3, 130.1, 131.2, 131.9, 135.7, 156.6, 158.8, 185.5; **IR** (KBr) 3073, 1672, 1445, 1324, 1216, 907, 772 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 291 (M + 1, 97), 290 (24), 289 (100), 211 (29), 209 (31); **Anal.** Calcd. for $C_{14}H_9BrO_2$: C, 58.16; H, 3.14. Found: C, 58.23; H, 3.14.

6.2.15 11(*E*)-11-[3',3'-Diphenylprop-2-enylidene]-11*H*-dibenzo[*b*,*f*]oxepin-10-one (143)

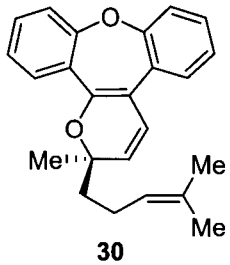


143

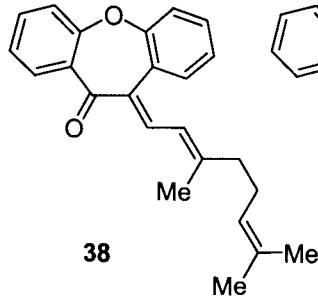
A solution of LDA was prepared by reacting a solution of *N,N*-diisopropylamine (120 μL, 0.86 mmol) in THF (5 mL) with *n*-butyllithium (2.5 M in hexanes, 0.35 mL, 0.85 mmol) at 0 °C for 30 min. A solution of the oxepinone **33** (119 mg, 0.56 mmol) in THF (5 mL) was then added to the preformed solution of LDA at -78 °C. After 30 min, a solution of 3,3-diphenylacrylaldehyde **142** (176 mg, 0.85 mmol) in THF (5 mL) was added and the reaction was allowed to warm to room temperature overnight. The resultant mixture was diluted with brine (15 mL) and ether (25 mL). The organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification of the crude product by flash chromatography using petroleum ether:dichloromethane (4:1) as the eluant afforded the pure dienone **143** (179 mg, 80%) as a yellow solid. **M.p.** 164-168 °C, petroleum ether/dichloromethane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.91 (d, J = 12 Hz, 1H, *H*-2'), 7.14-7.33 (m, 12H, Ar*H*), 7.39-7.47 (m, 5H, Ar*H*), 7.64 (d, J = 12 Hz, 1H, *H*-1'), 7.97-7.99 (dd, J = 8, 2 Hz, 1H, *H*-9); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 121.3, 121.4, 123.6, 125.0, 125.6, 128.5, 128.7, 128.9, 129.3, 129.7, 130.8, 131.8, 132.5, 134.7, 138.5, 138.6, 138.9, 141.9, 153.5, 157.2, 160.7, 188.2; **IR** (KBr) 3056, 3025, 1648, 1600,

1443, 1293, 1102, 893, 767, 697 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 402 (30), 401 (M + H, 100); **Anal.** Calcd. for $C_{29}H_{20}O_2$: C, 86.98; H, 5.03. Found: C, 86.72; H, 5.11.

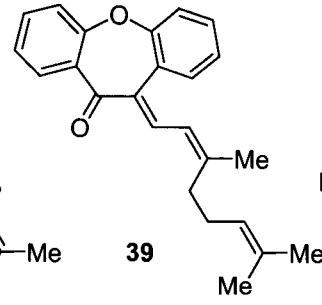
6.2.16 Experimental procedures for the cross-aldol condensation of the 11*H*-dibenzo[*b,f*]oxepin-10-one (33) with citral (17)



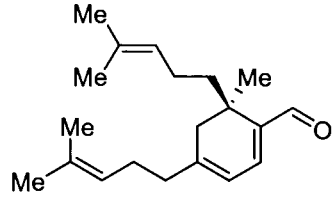
30



38



39



131

Method 1: A solution of LDA was prepared by reacting a solution of *N,N*-diisopropylamine (46 μL, 0.33 mmol) with *n*-butyllithium (140 μL, 2.5 M in hexanes, 0.35 mmol) in THF (5 mL) at 0 °C for 30 min. A solution of the oxepinone **33** (52 mg, 0.25 mmol) in THF (5 mL) was then added to the preformed LDA solution at -78 °C. After 30 min, a solution of citral (**17**) (76 mg, 0.50 mmol) in THF (5 mL) was added and the reaction mixture was stirred at -78 °C for 6 h. The resultant mixture was allowed to warm to room temperature overnight (10 h) and then brine (10 mL) and ether (15 mL) were added. The organic layer was washed with brine (3 x 10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification of the crude product by flash chromatography using hexanes:chloroform (3:1) as the eluant afforded the 2*H*-pyran **30** (16 mg, 18%) as a yellow oil and the cyclic aldehyde **131** (34 mg, 24%) as an orange oil.

Method 2: A solution of LDA was prepared by reacting a solution of *N,N*-diisopropylamine (46 μL, 0.33 mmol) with *n*-butyllithium (140 μL, 2.5 M in hexanes, 0.35 mmol) in THF (5 mL) at 0 °C for 30 min. A solution of the oxepinone **33** (50 mg, 0.25 mmol) in THF (5 mL) was then added to the preformed LDA solution at -78 °C. After 30 min, a solution of citral (**17**) (78 mg, 0.50 mmol) in THF (5 mL) was added and the reaction mixture was stirred at -78 °C for 6 h. The resultant mixture was allowed to warm to room temperature overnight (10 h) and then brine (10 mL) and ether (15 mL) were added. The organic layer was washed with brine (3 x 10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification of the crude product by flash chromatography using hexanes:chloroform (3:1) as the eluant afforded the 2*H*-pyran **30** (18 mg, 20%) as a yellow oil and the cyclic aldehyde **131** (32 mg, 20%) as an orange oil.

Method 3: A solution of LDA was prepared by reacting a solution of *N,N*-diisopropylamine (46 μL, 0.33 mmol) in THF (5 mL) with *n*-butyllithium (140 μL, 2.5 M in hexanes, 0.35 mmol) at 0 °C for 30 min. A solution of the oxepinone **33** (53 mg, 0.25 mmol) in THF (5 mL) was added to the preformed solution of LDA at -78 °C. After 30 min, a solution of citral (**17**) (76 mg, 0.50 mmol) in THF (5 mL) was added and the reaction mixture was stirred at -78 °C for 30 min. The resultant mixture was then allowed to warm to room temperature over 2 h. The reaction mixture was then heated at reflux for 48 h, cooled to room temperature and diluted with brine (10 mL) and ether (15 mL). The organic layer was washed with brine (3 x 10 mL), dried over anhydrous sodium sulfate and concentrated

under reduced pressure. Purification of the crude product by flash chromatography using hexanes:chloroform (3:1) as the eluant afforded the 2*H*-pyran **30** (15 mg, 17%) as a yellow oil and the cyclic aldehyde **131** (33 mg, 23%) as an orange oil.

Method 4: A solution of LDA was prepared by reacting a solution of *N,N*-diisopropylamine (42 μL, 0.29 mmol) with *n*-butyllithium (135 μL, 2.5 M in hexanes, 0.33 mmol) in THF (5 mL) at 0 °C for 30 min. Hexamethylphosphoramide (52 μL, 0.31 mmol) and a solution of the oxepinone **33** (52 mg, 0.25 mmol) in THF (5 mL) were added to the preformed solution of LDA at -78 °C. After 30 min, a solution of citral (**17**) (76 mg, 0.50 mmol) in THF (5 mL) was added. The reaction mixture was stirred at -78 °C for 6 h and then was allowed to warm to room temperature overnight. After stirring at room temperature for twelve days, the reaction mixture was diluted with brine (10 mL) and ether (15 mL). The organic layer was washed with brine (3 x 10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification of the crude product by flash chromatography using hexanes:chloroform (3:1) as the eluant afforded the 2*H*-pyran **30** (9 mg, 20%) as a yellow oil and the cyclic aldehyde **131** (17 mg, 20%) as an orange oil.

Method 5:[66] A solution of LDA was prepared by reacting a solution of *N,N*-diisopropylamine (140 μL, 1.00 mmol) in THF (5 mL) with *n*-butyllithium (0.40 mL, 2.5 M in hexanes, 1.0 mmol) at 0 °C for 30 min. A solution of the oxepinone **33** (203 mg, 0.96 mmol) in THF (5 mL) was added to the preformed solution of LDA at -78 °C. Cerium chloride heptahydrate (410 mg, 1.54 mmol)

was dried under reduced pressure at 160 °C for 2 h and then was cooled to room temperature. The reaction mixture was then transferred to a suspension of dried cerium chloride in tetrahydrofuran (3 mL) at -78 °C and after 30 min a solution of citral (**17**) (153 mg, 1.00 mmol) in THF (5 mL) was added. The resultant mixture was then allowed to warm to room temperature and then was heated at reflux for three days. The reaction mixture was cooled to room temperature and then was diluted with brine (10 mL) and ether (15 mL). The organic layer was washed with brine (3 x 10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification of the crude product by flash chromatography using petroleum ether:dichloromethane (4:1) as the eluant afforded the 2*H*-pyran **30** (20 mg, 6%) as a yellow oil and an inseparable mixture (1:1.5) of the dienones **38** and **39** (45 mg, 14%) as an orange oil.

Method 6:[69] A solution of lithium 2,2,6,6-tetramethylpiperidide was prepared by reacting a solution of 2,2,6,6 tetramethylpiperidine (100 μL, 0.59 mmol) in THF (5 mL) with *n*-butyllithium (240 μL, 2.5 M in hexanes, 0.60 mmol) at 0 °C for 30 min. Hexamethylphosphoramide (0.26 mL, 1.5 mmol) was added dropwise to the lithium 2,2,6,6-tetramethylpiperidide solution. After 30 min, the reaction was cooled to -78 °C and a solution of the oxepinone **33** (106 mg, 0.50 mmol) and citral (**17**) (153 mg, 1.00 mmol) in THF (5 mL) were added sequentially over 30 min. The reaction mixture was allowed to warm to room temperature overnight and then was diluted with water (10 mL) and ether (25 mL). The organic layer was washed with water (15 mL) and brine (15 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The

only species identified in the ^{1}H NMR spectrum of the crude reaction mixture were the cyclic aldehyde **131** and the unreacted oxepinone **33**. No further purification was performed.

Method 7:[70] A solution of lithium hexamethyldisilazide was prepared by reacting a solution of hexamethyldisilazane (250 μL, 1.19 mmol) in THF (5 mL) with *n*-butyllithium (0.5 mL, 2.5 M in hexanes, 1.3 mmol) at 0 °C for 30 min. Hexamethylphosphoramide (0.25 mL, 1.5 mmol) was added dropwise to the lithium hexamethyldisilazide solution. After 30 min, the reaction was cooled to -78 °C and a solution of the oxepinone **50** (209 mg, 1.0 mmol) in THF (5 mL) followed by a solution of citral (**17**) (199 mg, 1.3 mmol) in THF (5 mL) were added. The reaction mixture was allowed to warm to room temperature, stirred for 2 h and then was diluted with water (10 mL) and ether (25 mL). The organic layer was washed with water (3 x 15 mL) and brine (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The only species identified in the ^{1}H NMR spectrum of the crude reaction mixture were the cyclic aldehyde **131** and the unreacted oxepinone **33**. No further purification was performed.

Method 8:[71] Potassium *t*-butoxide (214 mg, 0.19 mmol) was added to a solution of the oxepinone **33** (123 mg, 0.58 mmol) and citral (**17**) (109 mg, 0.72 mmol) in THF (10 mL). The reaction mixture was stirred at room temperature for twenty h and then diluted with hydrochloric acid (1 M, 3 mL) and ether (25 mL). The organic layer was washed with water (25 mL) and brine (25 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure.

Purification of the crude product by flash chromatography using hexanes:ether (4:1) as the eluant afforded the 2*H*-pyran **30** (20 mg, 10%) as a yellow oil and the cyclic aldehyde **131** (52 mg, 25%) as an orange oil.

Method 9:[72] An aqueous solution of potassium hydroxide (50 w/v %, 2 mL) was added dropwise to a mixture of the oxepinone **33** (108 mg, 0.51 mmol) and 18-crown-6 (146 mg, 0.55 mmol) in benzene (15 mL). After 30 min, a solution of citral (**17**) (86 mg, 0.56 mmol) in benzene (1 mL) was added dropwise. The reaction mixture was stirred at room temperature for 20 h and then was diluted with water (10 mL) and benzene (20 mL). The organic layer was washed with water (5 x 10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification of the crude product by flash chromatography using hexanes:ether (4:1) as the eluant afforded the cyclic aldehyde **131** (32 mg, 20%) as an orange oil and the unreacted oxepinone **33** (78 mg) as a yellow solid.

Method 10: A mixture of the oxepinone **33** (52 mg, 0.3 mmol) and citral (**17**) (50 mg, 0.33 mmol) in ethanol (5 mL) was added to a solution of sodium hydroxide (98 mg, 2.5 mmol) in water (3 mL). The reaction mixture was stirred at room temperature for 48 h and then was diluted with ether (15 mL). The organic layer was washed with water (3 x 30 mL) and brine (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification of the crude product by flash chromatography using hexanes:chloroform (3:1) as the eluant afforded the cyclic aldehyde **131** (19 mg, 20%) as an orange oil.

Method 11: The oxepinone **33** (184 mg, 0.88 mmol) and lithium hydroxide monohydrate (147 mg, 3.50 mmol) were added to a mixture of citral (**17**) (399 mg, 2.63 mmol), THF (15 mL) and water (5 mL). The reaction mixture was heated at reflux for five days, cooled to room temperature and then diluted with water (20 mL) and ether (20 mL). The organic layer was washed with water (3 x 10 mL) and brine (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification of the crude product by flash chromatography using petroleum ether:dichloromethane (4:1) as the eluant afforded the 2*H*-pyran **30** (21 mg, 7%) as a yellow oil and the cyclic aldehyde **131** (54 mg, 8%) as an orange oil.

Method 12: Titanium tetrachloride (1.00 mL, 0.8 M in dichloromethane, 0.8 mmol) and diisopropylethylamine (185 μL, 1.06 mmol) were added in turn to a solution of the oxepinone **33** (112 mg, 0.53 mmol) in dichloromethane (5 mL) at -78 °C. After 30 min, a solution of citral (**17**) (258 mg, 1.69 mmol) in dichloromethane (5 mL) was added. The mixture was stirred at -78 °C for 6 h and then was allowed to warm slowly to room temperature overnight. The reaction mixture was then diluted with water (10 mL) and ether (25 mL), the organic layer was washed with water (15 mL) and brine (2 x 15 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was dissolved with toluene (15 mL) and *p*-toluenesulfonic acid monohydrate (67 mg, 0.35 mmol) was added and the reaction mixture was heated at reflux for 6 h. After cooling to room temperature, the resultant mixture was diluted with a saturated aqueous solution of sodium bicarbonate (5 mL) and

ether (20 mL). The organic layer was washed with water (15 mL) and brine (15 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification of the crude product by flash chromatography using petroleum ether:dichloromethane (4:1) as the eluant afforded the 2*H*-pyran **30** (22 mg, 12%) as a yellow oil and oxepinone **33** (32 mg) as yellow solid.

Method 13:[73] A solution of the silyl enol ether **138** (75 mg, 0.27 mmol) in dichloromethane (3 mL) was added to a solution of titanium tetrachloride (360 μL, 0.8 M in dichloromethane, 0.3 mmol) and citral (**17**) (42 mg, 0.28 mmol) in dichloromethane (5 mL). The reaction mixture was stirred for three days at room temperature and then was diluted with water (15 mL) and ether (25 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification of the crude product by flash chromatography using hexanes:chloroform (3:1) as the eluant afforded the 2*H*-pyran **30** (7 mg, 8%) as a yellow oil, the cyclic aldehyde **131** (6 mg, 7%) as an orange oil and the unreacted oxepinone **33** (29 mg) as a yellow solid.

Method 12: [74] A solution of titanium tetrachloride (360 μL, 0.8 M in dichloromethane, 0.3 mmol) was added to a mixture of citral (**17**) (40 mg, 0.26 mmol) and silyl enol ether **138** (73 mg, 0.26 mmol) in dichloromethane (5 mL) at -78 °C. The reaction mixture was stirred at room temperature for three days and then was diluted with water (20 mL) and ether (20 mL). The organic layer was washed with water (3 x 10 mL) and brine (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification of the crude product by flash chromatography using hexanes:chloroform (3:1) as eluant

afforded the 2*H*-pyran **30** (5 mg, 6%) as a yellow oil and the unreacted oxepinone **33** (34 mg) as a yellow solid.

Method 13: The oxepinone **33** (142 mg, 0.68 mmol), citral (**17**) (301 mg, 1.98 mmol) and isopropylamine (173 μL, 2.03 mmol) were stirred in tetrahydrofuran (20 mL) at room temperature. The reaction mixture was stirred at room temperature for four days and then was diluted with ether (20 mL). The organic layer was washed with a saturated aqueous solution of ammonium chloride (10 mL), hydrochloric acid (10 v/v %, 10 mL) and brine (2 x 15 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification of the crude product by flash chromatography using petroleum ether:dichloromethane (4:1) as the eluant afforded the 2*H*-pyran **30** (6 mg, 7%) as a yellow oil and a mixture (2:3) of the dienones **38** and **39** (30 mg, 34%) as an orange oil.

Method 14: The oxepinone **33** (142 mg, 0.68 mmol), citral (**17**) (301 mg, 1.98 mmol) and isopropylamine (173 μL, 2.03 mmol) were heated at reflux in toluene (20 mL) with azeotropic removal of water. After four days, the reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was diluted with ether (20 mL), washed with hydrochloric acid (1 M, 15 mL), water (2 x 15 mL) and brine (2 x 15 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification of the crude product by flash chromatography using petroleum ether:dichloromethane (4:1) as the eluant afforded the 2*H*-pyran **30** (63 mg, 27%)

as a yellow oil and an inseparable mixture (2:3) of the dienones **38** and **39** (33 mg, 14%) as an orange oil.

Method 15: The oxepinone **33** (205 mg, 0.98 mmol), citral (**17**) (475 mg, 3.13 mmol) and allylamine (1.0 mL, 3.1 mmol) were heated at reflux in toluene (25 mL) with azeotropic removal of water. After four days, the reaction was cooled to room temperature and concentrated under reduced pressure. The residue was diluted with ether (25 mL), washed with hydrochloric acid (1 M, 15 mL), water (2 x 15 mL) and brine (2 x 15 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification of the crude product by flash chromatography using petroleum ether:dichloromethane (4:1) as the eluant afforded the 2*H*-pyran **30** (142 mg, 42%) as a yellow oil and an inseparable mixture (2:3) of the dienones **38** and **39** (34 mg, 10%) as an orange oil.

Method 16: The oxepinone **33** (55 mg, 0.26 mmol) and (±)-methylbenzylamine (66 μL, 0.44 mmol) were added in turn to a solution of citral (**17**) (80 mg, 0.52 mmol) in benzene (10 mL). The reaction mixture was stirred at room temperature for 48 h and then was diluted with ether (20 mL). The organic layer was washed with a saturated aqueous solution of ammonium chloride (10 mL), hydrochloric acid (10 v/v %, 10 mL) and brine (2 x 15 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification of the crude product by flash chromatography using petroleum ether:dichloromethane (4:1) as the eluant afforded the 2*H*-pyran **30** (6 mg, 7%)

as a yellow oil and a mixture (2:3) of the dienones **38** and **39** (30 mg, 34%) as an orange oil.

Method 17: The oxepinone **33** (218 mg, 1.04 mmol), citral (**17**) (473 mg, 3.11 mmol) and (±)-methylbenzylamine (260 μL, 1.75 mmol) were heated at reflux in toluene (25 mL) with azeotropic removal of water. After four days, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was diluted with ether (25 mL), washed with hydrochloric acid (1 M, 15 mL), water (2 x 15 mL) and brine (2 x 15 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification of the crude product by flash chromatography using petroleum ether:dichloromethane (4:1) as the eluant afforded the 2*H*-pyran **30** (93 mg, 26%) as a yellow oil and a mixture (2:3) of the dienones **38** and **39** (64 mg, 18%) as an orange oil.

Method 18: The oxepinone **33** (107 mg, 0.51 mmol), citral (**17**) (232 mg, 1.53 mmol) and benzylamine (165 μL, 1.51 mmol) were heated at reflux in toluene (20 mL) with azeotropic removal of water. After 48 h, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was diluted with ether (20 mL), washed with hydrochloric acid (1 M, 15 mL), water (2 x 15 mL) and brine (2 x 15 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification of the crude product by flash chromatography using petroleum ether:dichloromethane (4:1) as the eluant afforded the 2*H*-pyran **30** (31 mg, 18%) as a yellow oil and a mixture (2:3) of the dienones **38** and **39** (36 mg, 21%) as an orange oil.

Method 19: A mixture of citral (**17**) (1.41 g, 9.27 mmol), isopropylamine (1.0 mL, 9.3 mmol), oxepinone **33** (324 mg, 1.54 mmol) and magnesium sulfate (2.0 g) in THF (20 mL) was heated at reflux for 8 h. The reaction mixture was allowed to cool to room temperature and then was filtered. The filter-cake was washed with ether (10 mL) and the combined filtrates were concentrated under reduced pressure. Purification of the crude product by flash chromatography using petroleum ether:dichloromethane (3:1) as the eluant afforded the 2*H*-pyran **30** (213 mg, 40%) as a yellow oil, an inseparable mixture (2:3) of the dienones **38** and **39** (107 mg, 20%) as an orange oil and the cyclic aldehyde **131** (400 mg, 15%) as an orange oil.

Method 20: A mixture of citral (**17**) (796 mg, 5.24 mmol), allylamine (0.40 mL, 5.3 mmol), oxepinone **33** (183 mg, 0.87 mmol) and magnesium sulfate (1.0 g) in THF (20 mL) was heated at reflux for 8 h. The reaction mixture was allowed to cool to room temperature and then was filtered. The filter-cake was washed with ether (10 mL) and the combined filtrates were concentrated under reduced pressure. Purification of the crude product by flash chromatography using petroleum ether:dichloromethane (3:1) as the eluant afforded the 2*H*-pyran **30** (145 mg, 50%) as a yellow oil, the cyclic aldehyde **131** (149 mg, 20%) as an orange oil and a mixture (2:3) of the dienones **38** and **39** (82 mg, 27%) as an orange oil. The two dienones **38** and **39** were then separated by repeated flash chromatography using chloroform as the eluant.

Method 21:[75] Piperidine (2 drops) was added to a mixture of the oxepinone **33** (107 mg, 0.51 mmol) and citral (**17**) (147 mg, 0.97 mmol) in

ethanol (10 mL). The reaction mixture was then heated at reflux for 18 h, cooled to room temperature and concentrated under reduced pressure. The residue was diluted with ether (25 mL) and washed with hydrochloric acid (1 M, 15 mL), water (20 mL) and brine (20 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification of the crude product by flash chromatography using hexanes:ether (4:1) as the eluant afforded the 2*H*-pyran **30** (12 mg, 7%) as a yellow oil and the cyclic aldehyde **131** (50 mg, 18%) as an orange oil.

Method 22: Pyrrolidine (80 μL, 1.0 mmol) and glacial acetic acid (55 μL, 1.0 mmol) were added to a mixture of the oxepinone **33** (50 mg, 0.24 mmol) and citral (**17**) (47 mg, 0.31 mmol) in benzene (6 mL). The reaction mixture was stirred at room temperature for three days and then was diluted with hydrochloric acid (1 M, 10 mL) and ether (20 mL). The organic layer was washed with water (15 mL) and brine (2 x 10 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Purification of the crude product by flash chromatography using hexanes:chloroform (4:1) as the eluant afforded the 2*H*-pyran **30** (8 mg, 9%) as a yellow oil, the cyclic aldehyde **131** (13 mg, 15%) as an orange oil and the unreacted oxepinone **33** (21 mg) as a yellow solid.

Method 23:[76] Citral (**17**) (94 mg, 0.68 mmol) and L-proline (6 mg, 0.05 mmol) were added to a solution of the oxepinone **33** (120 mg, 0.57 mmol) in dimethyl sulfoxide (10 mL). The reaction mixture was heated at 120 °C for 4 h, cooled to room temperature and then diluted with saturated aqueous solution of ammonium chloride (10 mL) and ethyl acetate (35 mL). The organic layer was

washed with water (4 x 20 mL) and brine (20 mL), dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. Purification of the crude product by flash chromatography using hexanes:chloroform (4:1) as the eluant afforded the 2*H*-pyran **30** (20 mg, 10%) as a yellow oil, the cyclic aldehyde **131** (27 mg, 15%) as an orange oil and the unreacted oxepinone **33** (49 mg) as a yellow solid.

Method 24: A mixture (1:1.5) of the dienones **38** and **39** (137 mg, 0.40 mmol), allylamine (90 μL, 1.2 mmol) and magnesium sulfate (0.30 g) in THF (10 mL) was heated at reflux for 8 h. The reaction mixture was allowed to cool to room temperature and then was filtered. The filter-cake was washed with ether (10 mL) and the combined filtrates were concentrated under reduced pressure. Purification of the crude product by flash chromatography using petroleum ether:dichloromethane (2:1) as the eluant afforded the 2*H*-pyran **30** (110 mg, 80%) as a yellow oil.

Method 25: A mixture of the oxepinone **33** (210 mg, 1.0 mmol) and imine **149** (1.09 g, 5.71 mmol) in THF (20 mL) was heated at reflux for 48 h. The reaction mixture was allowed to cool to room temperature and then was concentrated under reduced pressure. Purification of the crude product by flash chromatography using petroleum ether:dichloromethane (3:1) as the eluant afforded the 2*H*-pyran **30** (135 mg, 40%) as a yellow oil and a mixture (2:35) of the dienones **38** and **39** (67 mg, 19%) as an orange oil.

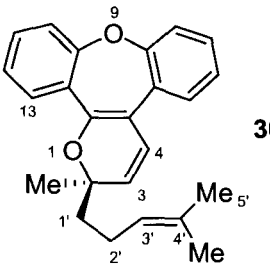
Method 26: General conditions for the TLC experiment (base-survey). The oxepinone **33** (~5 mg), citral (**17**) (1 drop) and an amine (1 drop or ~10 mg)

were stirred in THF (1 mL) at room temperature for three days. Thin layer chromatography was performed at 3 h intervals (during the day, 9 in total), using petroleum ether:dichloromethane (1:2) as the eluant.

Method 27: General conditions for the TLC experiment (drying agents-survey). The oxepinone **33** (~5 mg), citral (**17**) (1 drop), an amine (1 drop) and a drying agent (~200 mg) were stirred in THF (1 mL) at room temperature for 24 h. Thin layer chromatography was performed at using petroleum ether:dichloromethane (1:2) as the eluant.

Method 28: General conditions for the TLC experiment (solvent-survey). The oxepinone **33** (~5 mg), citral (**17**) (1 drop), allylamine (1 drop) and magnesium sulfate (~200 mg) were stirred in a solvent (1 mL) at room temperature for 10 h. Thin layer chromatography was performed at 2 h intervals (5 in total) using petroleum ether:dichloromethane (1:2) as the eluant.

6.2.17 2-Methyl-2-(4'-methyl-pent-3'-enyl)-2*H*-1,9-dioxa-tribenzo[*a*,*c*,*e*]cycloheptene (30)

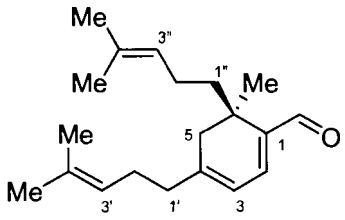


30

^{1}H NMR (400 MHz, C_6D_6) δ 1.28 (s, 3H, *Me*-2 *or Me*-5'), 1.49 (s, 3H, *Me*-2 *or Me*-5'), 1.67-1.84 (m, 2H, 2 x *H*-1'), 1.68 (d, *J* = 1 Hz, 3H, *Me*-4'), 2.14-2.32 (m, 2H, 2 x *H*-2'), 5.12-5.17 (m, 1H, *H*-3'), 5.19 (d, *J* = 10 Hz, 1H, *H*-3), 6.15 (d, *J* =

10 Hz, 1H, *H*-4), 6.87-7.01 (m, 4H, Ar*H*), 7.08-7.14 (m, 3H, Ar*H*), 7.72 (dd, *J* = 8, 2 Hz, 1H, *H*-13); **^{13}C NMR** (101 MHz, C_6D_6) δ 17.6, 23.2, 25.5, 25.8, 41.2, 78.9, 112.2, 121.1, 121.3, 123.8, 124.7, 124.9, 125.3, 125.5, 126.9, 129.0, 131.1, 131.5, 131.0, 147.9, 157.4, 158.7; **IR** (ef) 3073, 2852, 1727, 1644, 1557, 1013, 869, 752 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 345 (M + H, 100), 261 (8); **UV** λ_{max} ($CHCl_3$) 249 (ε 13564), 352 (ε 6721); **Anal.** Calcd. for $C_{24}H_{24}O_2$: C, 83.69; H, 7.02. Found: C, 83.40; H, 7.07.

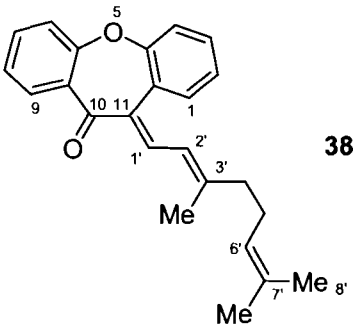
6.2.18 6-Methyl-4,6-*bis*-(4'-methyl-pent-3'-enyl)-cyclohexa-1,3-dienecarbaldehyde (131)[11]



131

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (s, 3H, *Me*), 1.32-1.41 (m, 1H), 1.55 (s, 3H, *Me*), 1.62 (s, 3H, *Me*), 1.65 (s, 3H, *Me*), 1.69 (s, 3H, *Me*), 1.77-2.04 (m, 4H), 2.18-2.19 (m, 4H), 2.33-2.38 (m, 1H), 5.03-5.10 (m, 2H, *H*-3', *H*-3"), 5.92 (d, *J* = 6 Hz, 1H, *H*-3), 6.67 (d, *J* = 6 Hz, 1H, *H*-2), 9.41 (s, 1H, C*H*O); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 17.7, 17.9, 24.0, 25.4, 25.8, 36.4, 37.9, 38.5, 42.1, 118.1, 123.4, 124.9, 131.3, 132.5, 141.6, 146.0, 151.0, 193.5; **IR** (ef) 2963, 2711, 1680, 1560, 732 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 287 (M + H, 35), 229 (100).

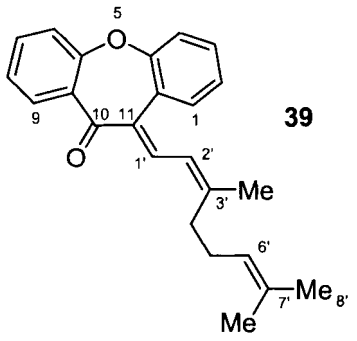
6.2.19 2'(*E*),11(*E*)-11-[3',7'-Dimethylocta-2',6'-dienylidene]-11*H*-dibenzo[*b*,*f*]oxepin-10-one (38)



38

^{1}H NMR (500 MHz, C_6D_6) δ 1.40 (s, 3H, *Me*-7'), 1.59 (d, *J* = 1 Hz, 3H, *Me*-3' *or Me*-8'), 1.61 (d, *J* = 1, 3H, *Me*-3' *or Me*-8'), 1.83-1.92 (m, 4H, 2 x *H*-4', 2 x *H*-5'), 4.96 (apparent t, *J* = 7 Hz, 1H, *H*-6'), 6.28 (dd, *J* = 12, 1 Hz, 1H, *H*-2'), 6.77-7.25 (m, 7H, Ar*H*), 8.18 (d, *J* = 12 Hz, 1H, *H*-1'), 8.32 (dd, *J* = 8, 1.5 Hz, 1H, *H*-9); **^{13}C NMR** (126 MHz, C_6D_6) δ 17.4, 17.6, 25.7, 26.5, 40.9, 121.3, 121.4, 121.9, 124.0, 125.0, 125.3, 127.4, 129.3, 130.1, 131.8, 132.3, 132.7, 134.3, 136.1, 136.9, 152.5, 157.9, 161.2, 187.8; **IR** (ef) 2970, 2918, 1652, 1557, 1445, 1293, 1102, 890, 772 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 345 (M + H, 100), 251 (52), 127 (48); **Anal.** Calcd. for $C_{24}H_{24}O_2$: C, 83.69; H, 7.02. Found: C, 83.50; H, 7.08.

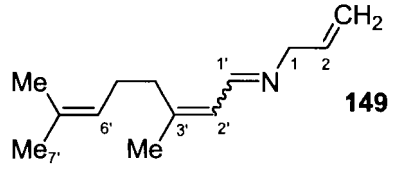
6.2.20 2'(*Z*),11(*E*)-11-[3',7'-Dimethylocta-2,6-dienylidene]-11*H*-dibenzo[*b*,*f*]oxepin-10-one (39)



39

^{1}H NMR (400 MHz, C_6D_6) δ 1.50 (d, J = 1 Hz, 3H, *Me*-3' *or Me*-8'), 1.54 (s, 3H, *Me*-3' *or Me*-8'), 1.63 (s, 3H, *Me*-7'), 2.01-2.06 (m, 2H, 2 x *H*-5'), 2.21-2.25 (m, 2H, 2 x *H*-4'), 5.10 (apparent t, J = 7 Hz, 1H, *H*-6'), 6.26 (apparent d, J = 12 Hz, 1H, *H*-2'), 6.76-7.23 (m, 7H, Ar*H*), 8.22 (d, J = 12 Hz, 1H, *H*-1'), 8.29 (dd, J = 8, 2 Hz, 1H, *H*-9); **^{13}C NMR** (101 MHz, C_6D_6) δ 17.7, 24.9, 25.8, 27.4, 33.3, 121.3, 121.4, 122.7, 123.8, 125.0, 125.3, 127.4, 129.3, 130.1, 132.3, 132.5, 132.7, 134.3, 135.9, 136.7, 152.7, 157.9, 161.2, 187.8; **IR** (ef) 2969, 2917, 1655, 1555, 1445, 1103, 895, 772 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 345 (M + H, 100); **Anal.** Calcd. for $C_{24}H_{24}O_2$: C, 83.69; H, 7.02. Found: C, 83.90; H, 7.09.

6.2.21 *N*-(3',7'-Dimethylocta-2',6'-dienylidene)prop-2-en-1-amine (149)

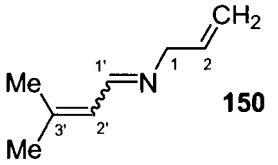


149

Anhydrous magnesium sulfate (1.1 g) and allyl amine (0.90 mL, 12 mmol) were added to a solution of citral (**17**) (1.46 g, 9.61 mmol) in benzene (30 mL). The reaction mixture was stirred at room temperature for 1 h and then was

filtered. The filter-cake was washed with benzene (20 mL) and the combined filtrates were concentrated under reduced pressure. Purification of the crude product by bulb-to-bulb distillation afforded the pure imine **149** (1.74 g, 95%) as a colourless oil. **B.p.** 152-154 °C, oven temperature; **^{1}H NMR** (400 MHz, C_6D_6) δ 1.46 (s, 3H, *Me*), 1.57 (dd, *J* = 4, 1 Hz, 3H, *Me*), 1.61 (s, 3H, *Me*), 1.92-2.13 (m, 4H, 2 x *H*-4', 2 x *H*-5'), 4.03 (d, *J* = 5 Hz, 2H, 2 x *H*-1), 5.04-5.08 (m, 2H, 2 x *H*-3), 5.22-5.29 (m, 1H, *H*-6'), 6.01-6.11 (m, 1H, *H*-2), 6.29-6.34 (m, 1H, *H*-2'), 8.09 (dt, *J* = 9, 1 Hz, 0.5 H, *H*-1'$_{cis/trans}$), 8.15 (dt, *J* = 9, 1 Hz, 0.5 H, *H*-1'$_{cis/trans}$); **^{13}C NMR** (101 MHz, C_6D_6) δ 16.9, 17.7, 24.1, 25.7, 26.5, 27.2, 32.7, 40.3, 64.1, 64.2, 115.0, 123.9, 124.0, 126.0, 127.1, 131.8, 132.3, 137.3, 148.4, 148.6, 159.2, 159.4; **IR** (ef) 3079, 2806, 1649, 1615, 1449, 1202, 1104, 917 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 192 (M + H, 100); **Anal.** Calcd. for $C_{13}H_{21}N$: C, 81.61; H, 11.06; N, 7.32. Found: C, 81.33; H, 11.04; N, 7.20.

6.2.22 *N*-(3'-Methylbut-2'-enylidene)prop-2-en-1-amine (150)

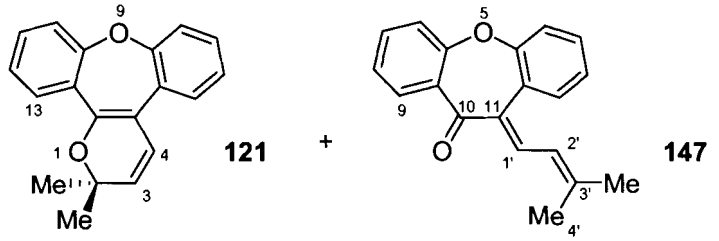


150

Anhydrous magnesium sulfate (1.0 g) and allylamine (1.50 mL, 20.3 mmol) were added to a solution of senecialdehyde (**24**) (1.42 g, 17.0 mmol) in benzene (30 mL). The reaction mixture was stirred at room temperature for 1 h and then was filtered. The filter-cake was washed with benzene (20 mL) and the combined filtrates were concentrated under reduced pressure. Purification of the crude product by bulb-to-bulb distillation afforded the pure imine **150** (2.02 g,

97%) as a colourless oil. **B.p.** 112-113 °C, oven temperature; **^{1}H NMR** (400 MHz, C_6D_6) δ 1.50 (s, 6H, 2 x *Me*), 4.01-4.02 (m, 2H, *H*-1), 5.05 (d, *J* = 10 Hz, 1H, *H*-3_{cis}), 5.25 (d, *J* = 17 Hz, 1H, *H*-3_{trans}), 6.00-6.10 (m, 1H, *H*-2), 6.22 (d, *J* = 9 Hz, 1H, *H*-1'), 8.03 (d, *J* = 9 Hz, 1H, *H*-2'); **^{13}C NMR** (101 MHz, C_6D_6) δ 18.3, 26.2, 64.1, 115.0, 126.5, 137.3, 144.9, 159.4; **IR** (ef) 3080, 2807, 1660, 1615, 1445, 1205, 990, 915, 815 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 125 (10), 124 (M + H, 100).

6.2.23 2,2-Dimethyl-2*H*-1,9-dioxa-tribenzo[*a*,*c*,*e*]cycloheptene (artocarpol D analogue) (121) and 11(*E*)-11-[3-Methyl-but-2-enylidene]-11*H*-dibenzo[*b*,*f*]oxepin-10-one (147)



Method 1: A mixture of senecialdehyde (**24**) (412 mg, 4.90 mmol), allylamine (400 μL, 5.34 mmol), oxepinone **33** (171 mg, 0.81 mmol) and magnesium sulfate (1.0 g) in THF (20 mL) was heated at reflux for 8 h. The reaction mixture was allowed to cool to room temperature and then was filtered. The filter-cake was washed with ether (10 mL) and the combined filtrates were concentrated under reduced pressure. Purification of the crude product by flash chromatography using petroleum ether:dichloromethane (3:1) as the eluant afforded the artocarpol D analogue **121** (92 mg, 40%) as a yellow oil and the dienone **147** (59 mg, 26%) as an orange oil.

Method 2: A mixture of the dienone **147** (130 mg, 0.47 mmol), allylamine (100 μL, 1.34 mmol) and magnesium sulfate (0.30 g) in THF (10 mL) was heated at reflux for 8 h. The reaction mixture was allowed to cool to room temperature and then was filtered. The filter-cake was washed with ether (10 mL) and the combined filtrates were concentrated under reduced pressure. Purification of the crude product by flash chromatography using petroleum ether:dichloromethane (2:1) as the eluant afforded the artocarpol D analogue **121** (105 mg, 80%) as a yellow oil.

Method 3: A mixture of the oxepinone **33** (102 mg, 0.49 mmol) and imine **150** (187 mg, 1.52 mmol) in THF (20 mL) was heated at reflux for 48 h. The reaction mixture was allowed to cool to room temperature and then was concentrated under reduced pressure. Purification of the crude product by flash chromatography using petroleum ether:dichloromethane (2:1) as the eluant afforded the artocarpol D analogue **121** (23 mg, 17%) as a yellow oil and the dienone **147** (75 mg, 56%) as an orange oil.

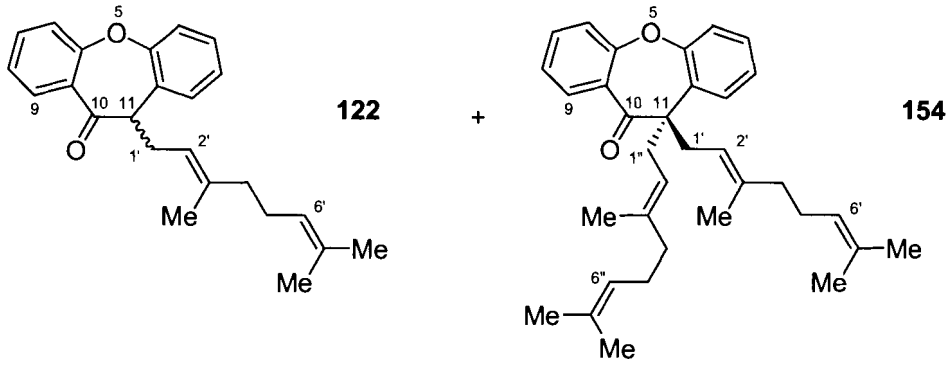
Method 4: Titanium tetrachloride (1.1 mL, 1 M in dichloromethane, 1.1 mmol) and tri-*n*-butylamine (275 μL, 1.15 mmol) were added successively to a solution of the oxepinone **33** (152 mg, 0.72 mmol) in dichloromethane (10 mL) at -18 °C. After 30 min, senecialdehyde (**24**) (200 μL, 2.07 mmol) was added. The reaction mixture was stirred at -18 °C for 4 h and then was allowed to gradually warm to room temperature overnight. The reaction mixture was then diluted with water (10 mL) and ether (25 mL), the organic layer was washed with brine (2 x 15 mL), dried over anhydrous sodium sulfate and concentrated under reduced

pressure. Purification of the crude product by flash chromatography using petroleum ether:dichloromethane (2:3) as the eluant afforded the artocarpol D analogue **147** (42 mg, 21%) as a yellow oil and the dienone **121** (36 mg, 18%) as an orange oil.

Artocarpol D analogue **121**: **^{1}H NMR** (400 MHz, C_6D_6) δ 1.29 (s, 6H, 2 x *Me*-2), 5.18 (d, *J* = 10 Hz, 1H, *H*-3), 6.10 (d, *J* = 10 Hz, 1H, *H*-4), 6.87-7.04 (m, 4H, Ar*H*), 7.10-7.14 (m, 3H, Ar*H*), 7.69 (dd, *J* = 8, 1.5 Hz, 1H, *H*-13); **^{13}C NMR** (101 MHz, C_6D_6) δ 27.1, 76.3, 112.6, 121.1, 121.4, 123.4, 124.9, 125.4, 126.7, 127.1, 128.3, 128.4, 129.0, 131.0, 131.1, 147.7, 157.4, 158.7; **IR** (ef) 3072, 2978, 1642, 1555, 1491, 1085, 884, 664 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 277 (M + H, 100); **Anal.** Calcd. for $C_{19}H_{16}O_2$: C, 82.58; H, 5.84. Found: C, 82.20; H, 5.91.

Dienone **147**: **^{1}H NMR** (400 MHz, C_6D_6) δ 1.38 (s, 3H, *Me*), 1.52 (s, 3H, *Me*), 6.18 (d, *J* = 12 Hz, 1*H*, *H*-2'), 6.78-7.01 (m, 5H, Ar*H*), 7.16-7.20 (m, 2H, Ar*H*), 8.12 (d, *J* = 12 Hz, 1H, *H*-1'), 8.31 (dd, *J* = 8, 1.5 Hz, 1H, *H*-9); **^{13}C NMR** (101 MHz, C_6D_6) δ 18.8, 26.7, 121.3, 121.4, 122.2, 125.0, 125.3, 129.3, 130.1, 132.3, 132.6, 134.3, 135.8, 136.9, 149.0, 158.0, 161.2, 187.8; **IR** (ef) 3073, 2907, 1649, 1610, 1550, 1102, 899, 635 cm^{-1}; **MS** (CI) m/z (rel. intensity) 277 (M + H, 100); **Anal.** Calcd. for $C_{19}H_{16}O_2$: C, 82.58; H, 5.84. Found: C, 82.43; H, 5.73.

6.2.24 2'(*E*)-11-(3,7-Dimethylocta-2,6-dienyl)-11*H*-dibenzo[*b*,*f*]oxepin-10-one (122) and 2'(*E*),2''(*E*)-11,11-*bis*-(3,7-dimethyl-octa-2,6-dienyl)-11*H*-dibenzo[*b*,*f*]oxepin-10-one (154)



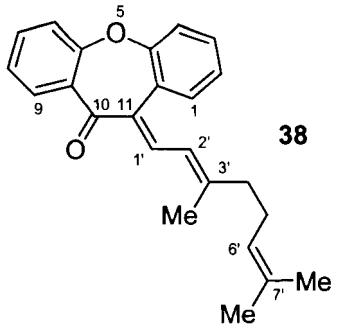
A solution of LDA was prepared by reacting a solution of *N,N*-diisopropylamine (160 μL, 1.14 mmol) in THF (5 mL) with *n*-butyllithium (0.50 mL, 2.5 M in hexanes, 1.2 mmol) at 0 °C. A solution of the oxepinone **33** (201 mg, 0.96 mmol) in THF (5 mL) was added to the preformed solution of LDA at -18 °C. After 30 min, a solution of geranyl bromide (**26**) (320 mg, 1.47 mmol) in THF (5 mL) was added and the reaction mixture was allowed to warm to 0 °C over 4 h. The reaction mixture was then diluted with water (15 mL) and ether (25 mL). The organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification of the crude product by flash chromatography using hexanes:ether (4:1) as the eluant afforded the monoalkylated product **122** (143 mg, 43%) as a yellow oil and dialkylated product **154** (53 mg, 12%) as a yellow oil.

Monoalkylated ketone **122**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.56 (s, 3H, *Me*), 1.59 (s, 3H, *Me*), 1.62 (s, 3H, *Me*), 1.92-2.02 (m, 4H, 2 x *H*-4', 2 x *H*-5'), 2.72-2.78 (m, 1H, *H*-1'), 2.90-2.96 (m, 1H, *H*-1'), 4.18 (t, *J* = 8 Hz, 1H, *H*-11),

4.99-5.01 (m, 1H, *H*-6'), 5.11 (apparent t, *J* = 7 Hz, 1H, *H*-2'), 7.17-7.28 (m, 5H, Ar*H*), 7.38 (d, *J* = 8 Hz, 1H, Ar*H*), 7.53-7.56 (m, 1H, Ar*H*), 8.03 (dd, *J* = 8, 2 Hz, 1H, *H*-9); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 16.2, 17.8, 25.8, 26.7, 39.8, 56.3, 120.7, 121.1, 121.3, 123.6, 124.2, 124.4, 126.2, 126.3, 128.4, 129.3, 130.8, 131.5, 134.7, 137.7, 156.7, 159.5, 192.3; **IR** (ef) 3070, 2973, 2917, 2847, 1688, 1600, 1470, 1448, 1112, 756 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 347 (M + H, 100); **Anal.** Calcd. for $C_{24}H_{26}O_2$: C, 83.20; H, 7.56. Found: C, 83.29; H, 7.31.

Dialkylated ketone **154**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.51 (s, 6H, 2 x *Me*), 1.55 (s, 6H, 2 x *Me*), 1.65 (s, 6H, 2 x *Me*), 1.88-2.00 (m, 8H), 2-81-2.86 (m, 2H), 2.92-2.97 (m, 2H), 4.98-5.02 (m, 4H, *H*-2' + *H*-2" + *H*-6' + *H*-6"), 7.16-7.24 (m, 2H, Ar*H*), 7.25-7.29 (m, 2H, Ar*H*), 7.31-7.37 (m, 2H, Ar*H*), 7.50-7.54 (m, 1H, Ar*H*), 7.95 (dd, *J* = 8, 2 Hz, 1H, *H*-9); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 16.3, 17.8, 25.8, 26.7, 30.4, 40.1, 59.1, 120.0, 120.6, 121.9, 123.5, 124.4, 125.9, 126.3, 128.5, 129.4, 130.8, 131.4, 131.5, 134.1, 137.6, 156.9, 157.6, 195.6; **IR** (ef) 2966, 2916, 2855, 1678, 1600, 1473, 1445, 1289, 758 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 483 (M + H, 31), 347 (100); **Anal.** Calcd. for $C_{34}H_{42}O_2$: C, 84.60; H, 8.77. Found: C, 84.78; H, 8.58.

6.2.25 2'(*E*),11(*E*)-11-[3',7'-Dimethylocta-2',6'-dienylidene]-11*H*-dibenzo[*b*,*f*]oxepin-10-one (28) from 2'(*E*)-11-(3,7-Dimethylocta-2,6-dienyl)-11*H*-dibenzo[*b*,*f*]oxepin-10-one (122)

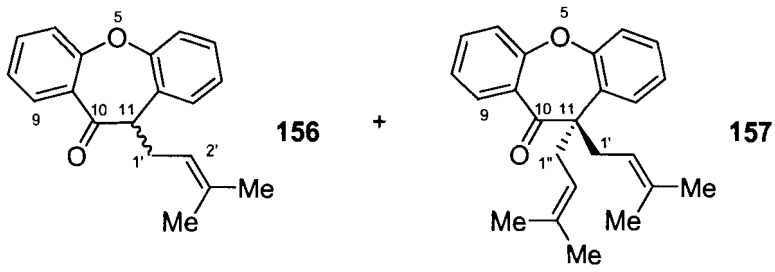


38

A solution of LDA was prepared by reacting a solution of *N,N*-diisopropylamine (120 μL, 0.86 mmol) in THF (5 mL) with *n*-butyllithium (0.40 mL, 2.5 M in hexanes, 1.0 mmol) at 0 °C. A solution of the monoalkylated oxepinone **122** (255 mg, 0.74 mmol) in THF (10 mL) was then added to the preformed solution of LDA at -78 °C. After 30 min, a solution of phenylselenyl chloride (188 mg, 0.96 mmol) in THF (5 mL) was added slowly and the reaction mixture was immediately poured into a mixture of hydrochloric acid (0.5 M, 20 mL), ether (10 mL) and pentane (10 mL). The organic layer was washed with water (20 mL), a saturated aqueous solution of sodium bicarbonate (20 mL) and brine (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification of the crude product by flash chromatography using petroleum ether:chloroform (2:1) as the eluant afforded unreacted phenylselenium chloride (71 mg) as an orange solid and the crude selenide (231 mg, 62%) as a brown oil. Pyridine (32 μL, 0.40 mmol) and hydrogen peroxide (30 w/w %, 0.10 mL, 0.9 mmol) were added in turn to a solution of the crude selenide (99 mg, 0.20 mmol) in dichloromethane (10 mL). After 10 min, the reaction mixture was diluted with

an aqueous solution of sodium bicarbonate (7 w/v%, 15 mL) and then was extracted with dichloromethane (2 x 20 mL). The combined organic layers were washed with aqueous hydrochloric acid (1 M, 15 mL) and brine (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification of the crude product by flash chromatography using petroleum ether:dichloromethane (1:1) as the eluant afforded the pure *E,E*-dienone **38** (53 mg, 73%) as a yellow oil. The spectral data was found to be in agreement with that reported above.

6.2.26 11-(3-Methylbut-2-enyl)-11*H*-dibenzo[*b,f*]oxepin-10-one (156) and 11,11-*bis*-(3-methylbut-2-enyl)-11*H*-dibenzo[*b,f*]oxepin-10-one (157)



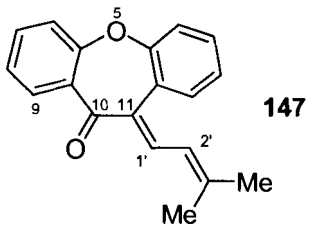
A solution of LDA was prepared by reacting a solution of *N,N*-diisopropylamine (250 μL, 1.79 mmol) in THF (5 mL) with *n*-butyllithium (0.75 mL, 2.5 M in hexanes, 1.8 mmol) at 0 °C. A solution of the oxepinone **33** (304 mg, 1.45 mmol) in THF (5 mL) was added to the preformed solution of LDA at -18 °C. After 30 min, a solution of prenyl bromide (**28**) (270 mg, 1.81 mmol) in THF (5 mL) was added and the reaction mixture was allowed to warm to 0 °C over 4 h. The reaction mixture was then diluted with water (15 mL) and ether (25 mL). The organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification of the crude

product by flash chromatography using hexanes:ether (4:1) as the eluant afforded monoalkylated product **156** (121 mg, 30%) as a yellow oil and dialkylated product **157** (148 mg, 30%) as a yellow oil.

Monoalkylated ketone **156**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.60 (s, 3H, *Me*), 1.64 (s, 3H, *Me*), 2.69-2.76 (m, 1H, *H*-1'), 2.91-2.98 (m, 1H, *H*-1'), 4.18 (t, *J* = 8 Hz, 1H, *H*-11), 5.09-5.11 (m, 1H, *H*-2'), 7.16-7.29 (m, 5H, Ar*H*), 7.28 (dd, *J* = 8, 1 Hz, 1H, Ar*H*), 7.52-7.57 (m, 1H, Ar*H*), 8.03 (dd, *J* = 8, 2 Hz, 1H, *H*-9); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 17.9, 26.1, 30.5, 58.9, 120.0, 120.6, 121.9, 123.5, 126.0, 126.2, 128.6, 129.3, 130.7, 131.5, 134.0, 134.2, 156.9, 157.6, 195.5; **MS** (CI) *m/z* (rel. intensity) 279 (M + H, 100).

Dialkylated ketone **157**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.51 (s, 3H, *Me*), 1.62 (s, 3H, *Me*), 2.78-2.83 (m, 2H), 2.90-2.96 (m, 2H), 4.94-4.98 (m, 2H, *H*-2', *H*-2''), 7.16-7.37 (m, 6H, Ar*H*), 7.50-7.54 (m, 1H, Ar*H*), 7.97 (dd, *J* = 8, 2 Hz, 1H, *H*-9); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 17.9, 26.1, 30.5, 58.9, 119.7, 120.6, 121.9, 123.5, 126.0, 126.2, 128.6, 129.3, 130.7, 131.5, 134.0, 134.2, 156.9, 157.6, 195.5; **MS** (CI) *m/z* (rel. intensity) 347 (M + H, 100).

6.2.27 11(*E*)-11-[3'-Methylbut-2'-enylidene]-11*H*-dibenzo[*b*,*f*]oxepin-10-one (147) from 11-(3-Methylbut-2-enyl)-11*H*-dibenzo[*b*,*f*]oxepin-10-one (156)



147

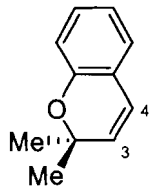
A solution of LDA was prepared by reacting a solution of *N,N*-diisopropylamine (63 μL, 0.45 mmol) in THF (5 mL) with *n*-butyllithium (200 μL, 2.5 M in hexanes, 0.50 mmol) at 0 °C. A solution of the monoalkylated oxepinone **156** (100 mg, 0.36 mmol) in THF (10 mL) was then added to the preformed solution of LDA at -78 °C. After 30 min, a solution of phenylselenyl chloride (85 mg, 0.44 mmol) in THF (5 mL) was added slowly and the reaction mixture was immediately poured into a mixture of hydrochloric acid (0.5 M, 20 mL), ether (10 mL) and pentane (10 mL). The organic layer was washed with water (20 mL), a saturated aqueous solution of sodium bicarbonate (20 mL) and brine (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification of the crude product by flash chromatography using petroleum ether:chloroform (2:1) as the eluant afforded unreacted phenylselenium chloride (15 mg) as an orange solid and the crude selenide. Pyridine (32 μL, 0.40 mmol) and aqueous hydrogen peroxide (30 w/w %, 0.10 mL, 0.9 mmol) were added in turn to a solution of the crude selenide in dichloromethane (10 mL). After 10 min, the reaction mixture was diluted with an aqueous solution of sodium bicarbonate (7 w/v%, 15 mL) and then was extracted with dichloromethane (2 x 20 mL). The combined organic layers were washed

with hydrochloric acid (1 M, 15 mL) and brine (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification of the crude product by flash chromatography using petroleum ether:dichloromethane (1:1) as the eluant afforded the pure *E*-dienone **147** (37 mg, 37%) as a yellow oil. The spectral data was found to be in agreement with that reported above.

6.2.28 General experimental procedure for the synthesis of 2*H*-chromenes

n-Butyllithium (3.0 mmol) was added dropwise to a solution of an *ortho*-bromophenol (1.0 mmol) in ether (5 mL) at -18 °C. After 2 h, the reaction mixture was cooled to -78 °C and a solution of the aldehyde (1.5 mmol) in ether (5 mL) was added dropwise. The reaction was stirred at -78 °C for 3 h and then was diluted with a saturated aqueous solution of ammonium chloride (10 mL) and ether (20 mL). The organic layer was washed with brine (2 x 10 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resultant crude product was diluted with toluene (20 mL) and heated at reflux for 20 h. The reaction mixture was then cooled to room temperature and was concentrated under reduced pressure. Purification of the resultant residue by flash chromatography using hexanes:chloroform (3:1) as the eluant afforded the pure 2*H*-chromenes.[79]

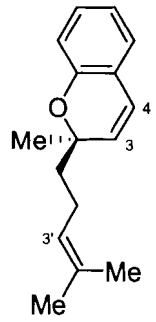
6.2.29 2,2-Dimethyl-2*H*-chromene (164)



164

Light yellow oil, 70% yield. **^{1}H NMR** (400 MHz, C_6D_6) δ 1.26 (s, 6H, 2 x *Me*), 5.22 (d, *J* = 10 Hz, 1H, *H*-3), 6.08 (d, *J* = 10 Hz, 1H, *H*-4), 6.70-6.97 (m, 4H, Ar*H*); **^{13}C NMR** (101 MHz, C_6D_6) δ 28.0, 76.0, 116.8, 121.0, 121.6, 123.0, 129.5, 129.7, 130.6, 153.7; **IR** (ef) 2974, 1712, 1603, 1487, 1358, 1261, 1165, 1120, 959, 772 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 162 (M + H, 12), 161 (100), 160 (35), 145 (25); **Anal.** Calcd. for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.17; H, 7.73.

6.2.30 2-Methyl-2-(4-methylpent-3-enyl)-2*H*-chromene (70)

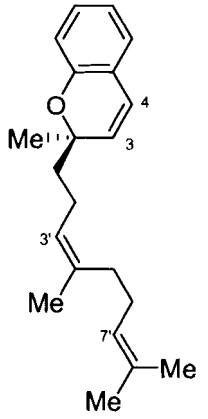


70

Yellow oil, 65% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.39 (s, 3H, *Me*), 1.57 (s, 3H, *Me*), 1.61-1.78 (m, 2H, 2 x *H*-1'), 1.66 (s, 3H, *Me*), 2.06-2.17 (m, 2H, 2 x *H*-2'), 5.10 (apparent t, *J* = 7 Hz, 1H, *H*-3'), 5.56 (d, *J* = 10 Hz, *H*-3), 6.35 (d, *J* = 10 Hz, *H*-4), 6.75-6.83 (m, 2H, Ar*H*), 6.95 (dd, *J* = 7, 2 Hz, 1H, Ar*H*), 7.08 (td, *J* = 8, 2 Hz, 1H, Ar*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 17.7, 22.9, 25.8, 26.7, 41.5, 78.6, 116.3, 120.6, 121.3, 123.0, 124.3, 126.5, 129.2, 129.8, 131.8, 153.4; **IR**

(ef) 2968, 2923, 2253, 1603, 1454, 1236, 901, 733 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 229 (M + H, 100), 173 (9), 145 (23); **UV** λ_{max} ($CHCl_3$) 240 (ε 3300), 266 (ε 3705), 310 (ε 3214); **Anal.** Calcd. for $C_{16}H_{20}O$: C, 84.16; H, 8.83. Found: C, 84.27; H, 8.97.

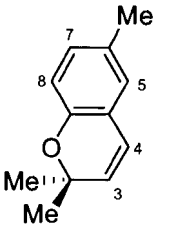
6.2.31 2-Methyl-2-(4',8'-dimethylnona-3',7'-dienyl)-2*H*-chromene (167)



167

Yellow oil, 45% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.40 (s, 3H, *Me*), 1.57 (s, 3H, *Me*), 1.59 (s, 3H, *Me*), 1.67 (s, 3H, *Me*), 1.69-1.79 (m, 2H, 2 x *H*-1'), 1.93-2.20 (m, 6H, 2 x *H*-2', 2 x *H*-5', 2 x *H*-6'), 5.06-5.13 (m, 2H, *H*-3', *H*-7'), 5.56 (d, *J* = 10 Hz, *H*-3), 6.35 (d, *J* = 10 Hz, *H*-4), 6.75-6.83 (m, 2H, Ar*H*), 6.95 (dd, *J* = 7, 2 Hz, 1H, Ar*H*), 7.09 (td, *J* = 8, 2 Hz, 1H, Ar*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 16.1, 17.8, 22.8, 25.8, 26.7, 26.8, 39.8, 41.5, 78.6, 116.3, 120.6, 121.3, 123.0, 124.1, 124.5, 126.5, 129.2, 129.8, 131.5, 135.5, 153.4; **IR** (ef) 2974, 2922, 1641, 1602, 1486, 1454, 1113, 752 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 297 (M + H, 100), 215 (30), 145 (48); **Anal.** Calcd. for $C_{21}H_{28}O$: C, 85.08; H, 9.52. Found: C, 84.75; H, 9.76.

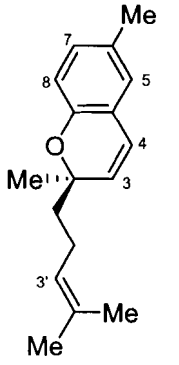
6.2.32 2,2,6-Trimethyl-2*H*-chromene (170)



170

Light yellow oil, 50% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.42 (s, 6H, 2 x *Me*), 2.45 (s, 3H, *Me*), 5.59 (d, *J* = 10 Hz, 1H, *H*-3), 6.28 (d, *J* = 10 Hz, 1H, *H*-4), 6.68 (d, *J* = 8 Hz, 1H, *H*-8), 6.76-6.79 (m, 1H, *H*-5), 6.91 (dd, *J* = 8, 2 Hz, *H*-7); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 20.7, 28.0, 76.0, 116.2, 121.2, 122.5, 126.9, 129.6, 131.0, 150.8; **IR** (ef) 2976, 2928, 1632, 1486, 1359, 1261, 1152, 857, 811, 763 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 175 (M + H, 100), 174 (19), 159 (23); **Anal.** Calcd. for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 83.00; H, 8.12.

6.2.33 2,6-Dimethyl-2-(4-methylpent-3-enyl)-2*H*-chromene (171)

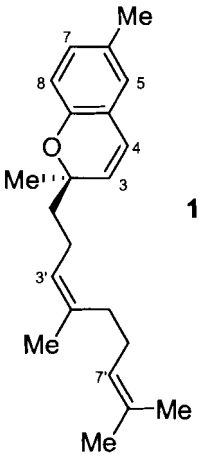


171

Light yellow oil, 54% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.38 (s, 3H, *Me*), 1.55-1.77 (m, 2H, 2 x *H*-1'), 1.58 (s, 3H, *Me*), 1.66 (s, 3H, *Me*), 2.07-2.17 (m, 2H, 2 x *H*-2'), 2.24 (s, 3H, *Me*), 5.09 (apparent t, *J* = 7 Hz, 1H, *H*-3'), 5.55 (d, *J* = 10 Hz, 1H, *H*-3), 6.31 (d, *J* = 10 Hz, 1H, *H*-4), 6.66 (d, *J* = 8 Hz, 1H, *H*-8), 6.77 (d, *J*

= 2 Hz, 1H, *H*-5), 6.89 (dd, *J* = 8, 2 Hz, 1H, *H*-7); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 17.8, 20.7, 22.9, 25.8, 26.5, 41.3, 78.4, 116.0, 121.0, 123.0, 126.9, 129.6, 129.8, 130.0, 131.8, 151.1; **IR** (ef) 3025, 2970, 2922, 2861, 1632, 1486, 1249, 1152, 811 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 243 (M + H, 5), 176 (12), 175 (100), 159 (13); **UV** λ_{max} ($CHCl_3$) 242 (ε 6092), 266 (ε 3945), 318 (ε 3438); **Anal.** Calcd. for $C_{17}H_{22}O$: C, 84.25; H, 9.15. Found: C, 83.97; H, 9.24.

6.2.34 2,6-Dimethyl-2-(4',8'-dimethylnona-3',7'-dienyl)-2*H*-chromene (172)

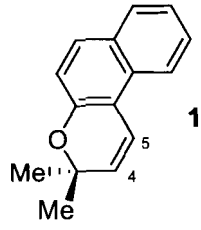


172

Yellow oil, 40% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.38 (s, 3H, *Me*), 1.57 (s, 3H, *Me*), 1.59 (s, 3H, *Me*), 1.68 (s, 3H, *Me*), 1.62-1.78 (m, 2H, 2 x *H*-1'), 1.93-2.18 (m, 6H, 2 x *H*-2', 2 x *H*-5', 2 x *H*-6'), 2.24 (s, 3H, *Me*), 5.06-5.13 (m, 2H, *H*-3', *H*-7'), 5.55 (d, *J* = 10 Hz, 1H, *H*-3), 6.31 (d, *J* = 10 Hz, 1H, *H*-4), 6.67 (d, *J* = 8 Hz, 1H, *H*-8), 6.77 (d, *J* = 2 Hz, 1H, *H*-5), 6.89 (dd, *J* = 8, 2 Hz, 1H, *H*-7); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 16.1, 17.8, 20.7, 22.8, 25.8, 26.5, 26.8, 39.8, 41.3, 78.4, 116.0, 121.1, 123.0, 124.2, 124.5, 126.9, 129.6, 129.8, 130.0, 131.5, 135.4, 151.1; **IR** (ef) 2964, 2922, 2855, 1638, 1486, 1444, 1255, 811 cm^{-1}; **MS** (CI) *m/z*

(rel. intensity) 311 (M + H, 93), 229 (47), 159 (100); **Anal.** Calcd. for $C_{22}H_{30}O$: C, 85.11; H, 9.74. Found: C, 84.88; H, 9.70.

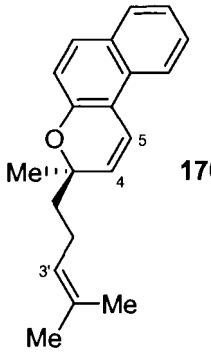
6.2.35 3,3-Dimethyl-3*H*-benzo[*f*]chromene (175)



175

Colourless oil, 47% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.50 (s, 6H, 2 x *Me*), 5.72 (d, *J* = 10 Hz, 1H, *H*-4), 7.03 (d, *J* = 10 Hz, 1H, *H*-5), 7.07 (d, *J* = 9 Hz, 1H, Ar*H*), 7.31-7.35 (m, 1H, Ar*H*), 7.46-7.50 (m, 1H, Ar*H*), 7.65 (d, *J* = 9 Hz, 1H, Ar*H*), 7.75 (d, *J* = 8 Hz, 1H, Ar*H*), 7.95 (d, *J* = 9 Hz, 1H, Ar*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 27.7, 76.2, 113.9, 118.4, 118.6, 121.4, 123.5, 126.6, 128.7, 129.3, 129.4, 129.5, 130.0, 151.1; **IR** (KBr) 3064, 2974, 1635, 1512, 1384, 1280, 1164, 1119, 991 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 211 (M + H, 100), 210 (10), 195 (7); **Anal.** Calcd. for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 85.40; H, 6.80.

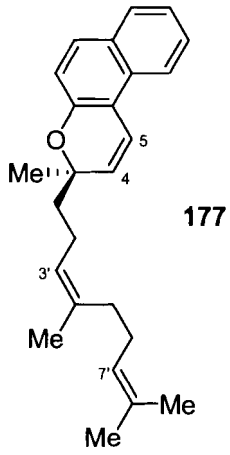
6.2.36 3-Methyl-3-(4-methylpent-3-enyl)-3*H*-benzo[*f*]chromene (176)



176

Yellow oil, 51% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.45 (s, 3H, *Me*), 1.58 (s, 3H, *Me*), 1.66 (s, 3H, *Me*), 1.69-1.84 (m, 2H, 2 x *H*-1'), 2.11-2.21 (m, 2H, 2 x *H*-2'), 5.10 (apparent t, *J* = 7 Hz, 1H, *H*-3'), 5.68 (d, *J* = 10 Hz, *H*-4), 7.04-7.07 (m, 2H, *H*-5, Ar*H*), 7.30-7.34 (m, 1H, Ar*H*), 7.44-7.49 (m, 1H, Ar*H*), 7.64 (d, *J* = 9 Hz, 1H, Ar*H*), 7.73 (d, *J* = 8 Hz, 1H, Ar*H*), 7.94 (d, *J* = 9 Hz, 1H, Ar*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 17.8, 22.9, 25.8, 26.2, 41.0, 78.5, 113.6, 118.5, 118.8, 121.3, 123.4, 124.3, 126.6, 128.6, 128.8, 129.2, 129.4, 130.0, 131.9, 151.3; **IR** (ef) 3058, 2968, 2923, 1628, 1590, 1454, 1242, 1087, 984, 733 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 279 (M + H, 100), 278 (13), 195 (32); **UV** λ_{max} ($CHCl_3$) 244 (ε 14906), 252 (ε 14293), 303 (ε 4504), 316 (ε 4545), 349 (ε 4197); **Anal.** Calcd. for $C_{20}H_{22}O$: C, 86.29; H, 7.97. Found: C, 86.41; H, 8.08.

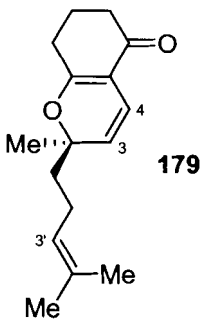
6.2.37 3-Methyl-3-(4',8'-dimethylnona-3',7'-dienyl)-3*H*-benzo[*f*]chromene (177)



177

Yellow oil, 60% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.45 (s, 3H, *Me*), 1.57 (s, 3H, *Me*), 1.58 (s, 3H, *Me*), 1.67 (s, 3H, *Me*), 1.70-1.85 (m, 2H, C*H*$_2$), 1.93-2.21 (m, 6H, 3 x C*H*$_2$), 5.06-5.14 (m, 2H, *H*-3', *H*-7'), 5.68 (d, *J* = 10 Hz, *H*-4), 7.04-7.07 (m, 2H, *H*-5, Ar*H*), 7.30-7.34 (m, 1H, Ar*H*), 7.44-7.49 (m, 1H, Ar*H*), 7.64 (d, *J* = 9 Hz, 1H, Ar*H*), 7.73 (d, *J* = 8 Hz, 1H, Ar*H*), 7.94 (d, *J* = 9 Hz, 1H, Ar*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 16.1, 17.8, 22.8, 25.8, 26.2, 26.8, 39.8, 41.0, 78.5, 113.6, 118.6, 118.8, 121.3, 123.4, 124.1, 124.5, 126.6, 128.6, 128.7, 129.2, 129.4, 130.0, 131.5, 135.5, 151.3; **IR** (ef) 3058, 2968, 2923, 1628, 1512, 1448, 1377, 1087, 811, 740 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 347 (M + H, 100), 265 (15), 195 (82); **Anal.** Calcd. for $C_{25}H_{30}O$: C, 86.66; H, 8.73. Found: C, 86.48; H, 8.89.

6.2.38 2-Methyl-2-(4-methyl-3-pentenyl)-5-oxo-5,6,7,8-tetrahydro-2*H*-chromene (179)[80]



179

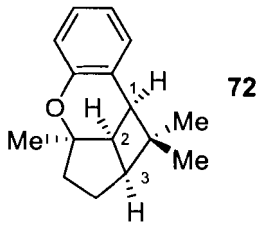
1,2-ethylenediammonium diacetate was prepared by stirring 1,2-ethylenediamine (50 μL, 0.75 mmol) with glacial acetic acid (0.50 mL, 8.73 mmol). A solution of citral **17** (1.35 g, 8.88 mmol) in methanol (5 mL) and 1,3-cyclohexanedione **178** (1.00 g, 8.91 mmol) were then added to a solution of 1,2-ethanediammonium diacetate in methanol (15 mL). The reaction mixture was stirred at room temperature for 3 h and then was concentrated under reduced pressure. The residue was diluted with ether (30 mL), washed with a saturated aqueous solution of sodium bicarbonate (2 x 10 mL), water (10 mL) and brine (15 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification of the crude product by flash chromatography using hexanes:ether (3:1) as the eluant afforded pure chromene **179** (1.36 g, 62%) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.35 (s, 3H, *Me*), 1.52-1.60 (m, 1H), 1.58 (s, 3H, *Me*), 1.67 (s, 3H, *Me*), 1.70-1.75 (m, 1H), 1.93-2.06 (m, 4H), 2.35-2.41 (m, 4H), 5.08 (apparent t, J = 7 Hz, 1H, *H*-3'), 5.17 (d, J = 10 Hz, 1H, *H*-3), 6.45 (d, J = 10 Hz, 1H, *H*-4); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 17.8, 20.8, 22.7, 25.8, 27.6, 28.7, 36.6, 41.9, 82.5, 110.5, 116.6, 121.8, 123.8, 132.1, 172.1, 194.9; **IR** (ef) 2927, 1663, 1589, 1410, 1330, 1071, 919 cm^{-1}; **MS** (CI) *m/z* (rel.

intensity) 247 (M + H, 100), 145 (11), 137 (13); **UV** λ_{max} ($CHCl_3$) 257 (ε 11307), 306 (ε 3567).

6.2.39 General experimental procedure for the [2+2] photocycloaddition reaction of the 2*H*-chromenes

A solution of the substrate (~0.40 mmol) and benzophenone (0.40 mmol) in benzene (20 mL) was deoxygenated on purging with dry nitrogen for 2 h at room temperature. The flask was then sealed and irradiated using a Hanovia 450 W high-pressure mercury lamp. The reaction mixture was concentrated under reduced pressure and the crude product was purified by flash chromatography.

6.2.40 1a,2,3,3a,7,8b-Hexahydro-1,1,3a-trimethyl-1*H*-bicyclo[3.2.0]hept-5-en[4,5,6-bc]chromene (72)

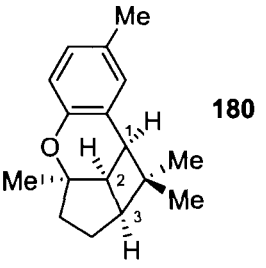


72

Reaction time: 2 h; glass type: quartz; eluant for flash chromatography: hexanes/chloroform (2:1); light yellow oil, 54% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.71 (s, 3H, *Me*), 1.37 (s, 3H, *Me*), 1.38 (s, 3H, *Me*), 1.55-2.01 (m, 4H, 2 x CH_2), 2.39-2.43 (m, 1H, *H*-3), 2.64 (dd, J = 10, 8 Hz, 1H, *H*-2), 3.05 (d, J = 10 Hz, 1H, *H*-1), 6.82-6.90 (m, 3H, Ar*H*), 7.07-7.12 (m, 1H, Ar*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 19.5, 25.6, 27.1, 35.0, 38.2, 39.3, 39.6, 40.2, 46.7, 83.8, 118.4, 120.5, 124.8, 127.2, 129.7, 153.7; **IR** (ef) 3078, 2949, 2866, 1580, 1486, 1238, 1150,

1108, 941, 757 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 229 (M + H, 22), 145 (79), 81 (100).

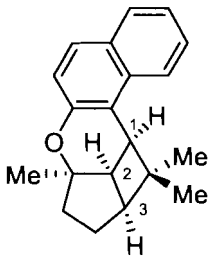
6.2.41 1a,2,3,3a,7,8b-Hexahydro-1,1,3a,7-tetramethyl-1*H*-bicyclo[3.2.0]hept-5-en[4,5,6-bc]chromene (180)



180

Reaction time: 3 h; glass type: quartz; eluant for flash chromatography: hexanes/chloroform (4:1); light yellow oil, 30% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.71 (s, 3H, *Me*), 1.35 (s, 3H, *Me*), 1.36 (s, 3H, *Me*), 1.52-1.78 (m, 4H, 2 x CH_2), 2.26 (s, 3H, Ar-*Me*), 2.38-2.42 (m, 1H, *H*-3), 2.59-2.63 (m, 1H, *H*-2), 3.01 (d, J = 10 Hz, 1H, *H*-1), 6.69-6.76 (m, 2H, Ar*H*), 6.87-6.91 (m, 1H, Ar*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 19.5, 25.6, 27.1, 35.0, 38.2, 39.2, 39.5, 40.2, 45.7, 83.8, 118.4, 120.5, 121.1, 124.8, 127.2, 129.7, 153.7; **IR** (ef) 3001, 2946, 1493, 1456, 1231, 1146, 811, 751 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 243 (M + H, 92), 159 (43), 81 (100); **Anal.** Calcd. for $C_{17}H_{22}O$: C, 84.25; H, 9.15. Found: C, 84.40; H, 9.25.

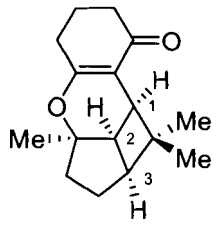
6.2.42 Cyclic adduct (181)



181

Reaction time: 8 h; glass type: pyrex; eluant for flash chromatography: hexanes/chloroform (3:1); white crystals, 41% yield. **M.p.** 109-110 °C, hexanes/chloroform; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.68 (s, *Me*), 1.45 (s, *Me*), 1.61 (s, *Me*), 1.65-1.82 (m, 2H), 2.03-2.11 (m, 2H), 2.52 (m, 1H, *H*-3), 2.75 (dd, *J* = 10, 8 Hz, 1H, *H*-2), 3.58 (d, *J* = 10 Hz, 1H, *H*-1), 7.08 (d, *J* = 9 Hz, 1H, Ar*H*), 7.29-7.33 (m, 1H, Ar*H*), 7.40-7.45 (m, 1H, Ar*H*), 7.61-7.65 (m, 2H, Ar*H*), 7.74 (d, *J* = 8 Hz, 1H, Ar*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 18.9, 25.8, 27.6, 34.3, 38.0, 38.6, 38.7, 40.0, 46.9, 83.3, 120.3, 123.7, 123.6, 125.9, 127.9, 128.5, 133.9, 151.2; **IR** (KBr) 2955, 2859, 1619, 1596, 1464, 1386, 1237, 997 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 279 (M + H, 65), 195 (100); **Anal.** Calcd. for $C_{20}H_{22}O$: C, 86.29; H, 7.97. Found: C, 86.04; H, 8.04.

6.2.43 1a,2,3,3a,5,6-Hexahydro-1,1,3a-trimethyl-1*H*-bicyclo[3.2.0]hept-5-eno[4,5,6-bc]chromen-(7*H*,8b*H*)-one (182)



182

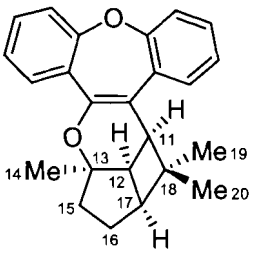
Reaction time: 3 h; glass type: pyrex; eluant for flash chromatography: hexanes:chloroform (4:1); yellow oil, 62% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.71 (s, 3H, *Me*), 1.32 (s, 3H, *Me*), 1.34 (s, 3H, *Me*), 1.49-1.59 (m, 1H), 1.64-2.00 (m, 6H), 2.29-2.49 (m, 5H), 2.80 (d, J = 9 Hz, 1H, *H*-1); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 17.8, 21.2, 26.0, 27.6, 29.5, 33.8, 35.1, 37.4, 38.0, 38.5, 40.0, 47.0, 85.4, 113.3, 170.0, 198.9; **IR** (ef) 2945, 1694, 1653, 1618, 1458, 1179, 1075, 1003, 878 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 247 (M + H, 100), 163 (42); **Anal.** Calcd. for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 77.89; H, 9.00.

6.2.44 General experimental procedure for the [2+2] photocycloaddition reaction of the 2*H*-pyran (30)

A solution of the 2*H*-pyran **30** (~0.40 mmol) and sensitizer (0.40 mmol) in a suitable solvent (40 mL) was deoxygenated on purging with dry nitrogen for 2 h. The flask was then sealed and irradiated using a Hanovia 450 W high- or low-pressure mercury lamp. The reaction mixture was then concentrated under reduced pressure. Purification of the crude product by flash chromatography using petroleum ether/dichloromethane (3:1) as the eluant afforded a fraction containing a mixture of the artocarpol A analogue **29**, unreacted 2*H*-pyran **30** and

the dienones **38** and **39**. The relative ratio of these components of the mixture was determined by analysis of the crude ^{1}H NMR spectrum.

6.2.45 Artocarpol A analogue (29)[30]



29

A solution of the 2*H*-pyran **30** (145 mg, 0.42 mmol) and benzophenone (75 mg, 0.48 mmol) in benzene (80 mL) was deoxygenated on purging with dry nitrogen for 2 h. The quartz Schlenk flask was then sealed and irradiated for 24 h using a Hanovia 450 W high-pressure mercury lamp. The reaction mixture was then concentrated under reduced pressure and the crude product was purified by flash chromatography using petroleum ether:dichloromethane (3:1) as the eluant. The first fraction (99 mg) collected contained a mixture (3:1) of the artocarpol A analogue **29** and the unreacted 2*H*-pyran **30**. The second fraction (15 mg, 10%) collected contained a mixture (1:1) of the dienones **38** and **39**. The first fraction was then purified by repetitive fractional recrystallization from hexanes to afford the artocarpol A analogue **29** (66 mg, 45%) as white crystals and the unreacted 2*H*-pyran **30** (22 mg, 15%) as a yellow oil. **M.p.** 184-186 °C, hexanes; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.61 (s, 3H, *Me*-20), 1.34 (s, 3H, *Me*-19), 1.44 (s, 3H, *Me*-14), 1.60-1.69 (m, 2H, *H*-15$_\alpha$, *H*-16$_\alpha$), 1.74-1.81 (m, 1H, *H*-15$_\beta$), 2.32-2.42 (m, 2H, *H*-16$_\beta$, *H*-17), 2.77 (apparent t, J = 9 Hz, 1H, *H*-12), 3.26 (d, J = 9 Hz, 1H, *H*-11),

7.06-7.31 (m, 7H, Ar*H*), 7.56 (dd, *J* = 8, 2 Hz, 1H, *H*-5); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 18.6, 26.0, 27.0, 34.3, 38.6, 39.6, 39.8, 40.8, 46.8, 83.6, 114.1, 120.3, 121.0, 124.8, 126.5, 127.0, 127.5, 129.8, 130.3, 132.7, 147.8, 157.2, 158.4; **IR** (KBr) 3073, 2953, 2858, 1618, 1484, 1217, 1139, 1016, 909, 772 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 345 (M + H, 66), 249 (27), 97 (27), 81 (100); **Anal.** Calcd. for $C_{24}H_{24}O_2$: C, 83.69; H, 7.02. Found: C, 83.55; H, 7.03.

6.2.46 X-Ray crystallographic analysis of the artocarpol A analogue (29)

A single crystal, a colourless block that had the dimensions 0.14 × 0.20 × 0.28 mm^3, was mounted on a glass fibre using epoxy adhesive. The data for this crystal of the artocarpol A analogue **29** was acquired at 293 K on a *Rigaku Raxis-Rapid-Auto* curved image plate area detector with graphite monochromated Cu Kα radiation. Indexing for the crystal was performed using three, 50° oscillations that were exposed for 350 seconds. A sweep of data was then collected using ω scans from 50.0° to 230.0° in 20.0° steps, at χ = 50.0° and ϕ = 0.0°. A second sweep of data was collected using ω scans from 50.0° to 230.0° in 20.0° steps, at χ = 50.0° and ϕ = 90.0°. A third sweep of data was collected using ω scans from 50.0° to 230.0° in 20.0° steps, at χ = 50.0° and ϕ = 180.0°. A fourth sweep of data was collected using ω scans from 50.0° to 230.0° in 20.0° steps, at χ = 50.0° and ϕ = 270.0°. A final sweep of data was collected using ω scans from 50.0° to 230.0° in 20° steps, at χ = 0.0° and ϕ = 0.0°. The following data range was recorded: 6.96° ≤ 2θ ≤ 134.71° and a total of 45 images were collected. The exposure rate was 80.0 sec/° and in each case, the crystal-

to-detector distance was 127.40 mm. A numerical absorption correction was then applied which resulted in the following transmission range: 0.31 - 0.9191.[112] The coordinates and anisotropic displacement parameters for the non-hydrogen atoms were then refined. Of note, hydrogen atoms were placed in calculated positions (d C-H 0.95 Å) and their coordinate shifts were linked with those of the respective carbon atoms during refinement. Isotropic thermal parameters for the hydrogen atoms were initially assigned proportionately to the equivalent isotropic thermal parameters of their respective carbon atoms. Subsequently, the isotropic thermal parameters for the hydrogen atoms were constrained to have identical shifts during refinement. The programs used for all absorption corrections, data reduction and processing were from the *Rigaku Raxis-Rapid-Auto* package. The structure was refined using *CRYSTALS*.[113] Complex scattering factors for neutral atoms were used in the calculation of structure factors.[114] An *ORTEP* representation of the artocarpol A analogue **29** is provided below (Figure 62). Crystallographic data, fractional atomic coordinates and equivalent isotropic thermal displacement parameters, selected bond lengths as well as selected bond angles are also listed below, Table 16,

---

• The X-ray crystallography data was obtained and solved by Mr Neil Draper (Simon Fraser University).

(112) De Meulenaer, J.; Tompa, H. *Acta Cryst.* **1965**, *19*, 1014.

(113) Watkin, D. J.; Prout, C. K.; Carruthers, J. R.; Betteridge, P. W.; Cooper, R. I. *CRYSTALS*; Chemical Crystallography Laboratory, University of Oxford: Oxford, England, 2003.

(114) *International Tables for X-Ray Crystallography*; Kynoch Press: Birmingham, England, 1952.

Table 17, Table 18, and Table 19, respectively).

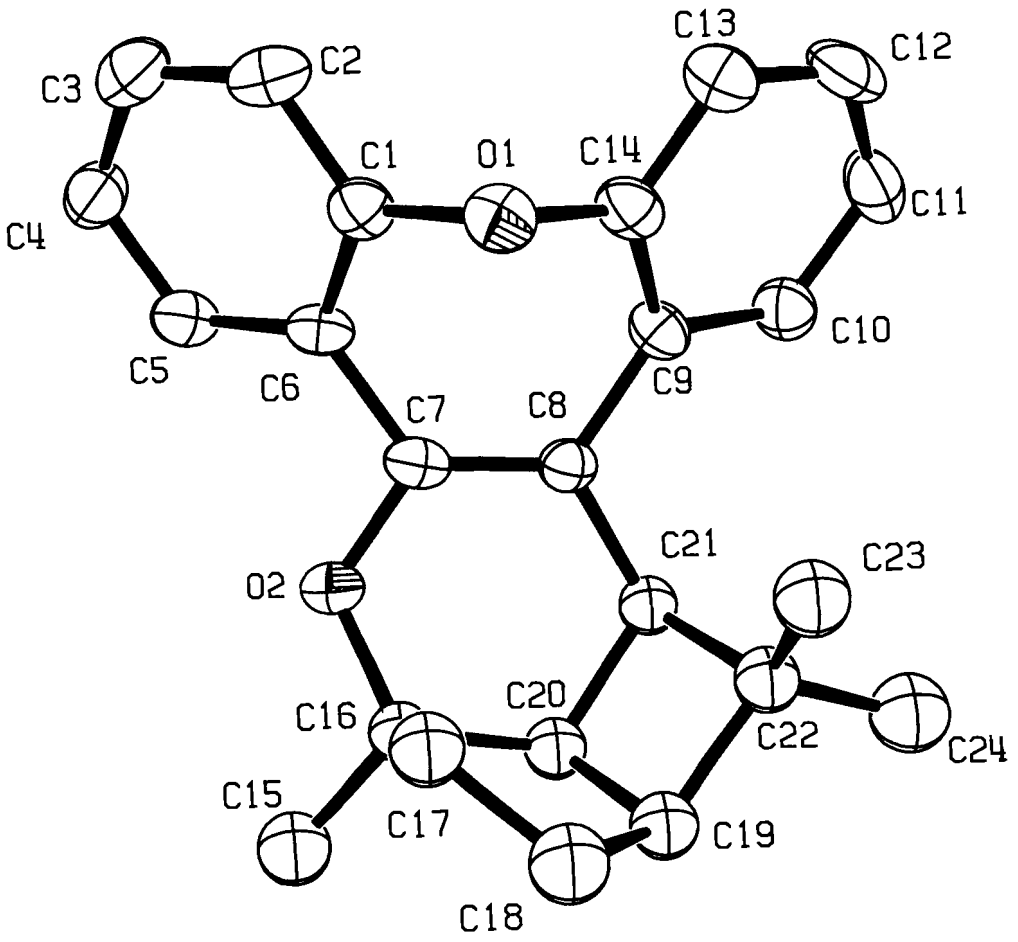


Figure 62 **X-ray crystal structure of the artocarpol A analogue (29). The thermal ellipsoids are drawn at a 30% probability level and the hydrogen atoms have been removed for clarity.**

Table 16 **Summary of Crystallographic Data for the Artocarpol A Analogue (29)**

Empirical formula	$C_{48}H_{48}O_4$
FW (g mol^{-1})	688.91

Temperature (K)	293
Wavelength (Cu $K\alpha$, Å)	1.54180
Crystal system	triclinic
Space group	*P1*
a (Å)	8.1515(13)
b (Å)	12.725(3)
c (Å)	17.876(5)
α (°)	86.452(11)
β (°)	86.161(15)
γ (°)	89.860(10)
Z	2
U (Å^3)	1846.5(7)
D_{calc} (g cm^{-3})	1.239
2θ limits (°)	6.96-134.71
Reflections collected	19255
Independent reflections	6109
Reflections observed [$I > 1.6\sigma(I)$]	2829
Goodness-of-fit on F	1.6012
R_1, R_w [$I > 2.5\sigma(I)$]	0.0751, 0.0644

Table 17 Fractional Atomic Coordinates (Å) and Equivalent Isotropic Thermal Displacement Parameters [*U*(iso), (Å^2)] for the Artocarpol A Analogue (29)

Atom	*x*	*y*	*z*	*U* (iso)
O1	-0.0733(4)	0.1569(3)	0.2754(2)	0.0567
O2	0.0900(4)	0.4165(3)	0.3650(2)	0.0545
O3	0.6368(4)	-0.3435(3)	0.2721(2)	0.0586
O4	0.4496(4)	-0.0825(3)	0.3626(2)	0.0552
C1	-0.1583(6)	0.1943(4)	0.3389(3)	0.0488
C2	-0.2738(7)	0.1305(5)	0.3783(4)	0.0643
C3	-0.3500(8)	0.1627(6)	0.4435(4)	0.0697
C4	-0.3144(7)	0.2607(5)	0.4687(3)	0.0638
C5	-0.2012(6)	0.3244(5)	0.4283(3)	0.0542
C6	-0.1214(6)	0.2934(4)	0.3612(3)	0.046
C7	0.0030(6)	0.3604(4)	0.3175(3)	0.0448
C8	0.0265(6)	0.3722(4)	0.2421(3)	0.0441
C9	-0.0705(6)	0.3132(4)	0.1927(3)	0.0467
C10	-0.1138(6)	0.3546(5)	0.1224(3)	0.0579
C11	-0.1968(7)	0.2970(6)	0.0734(3)	0.0704
C12	-0.2379(7)	0.1935(6)	0.0931(4)	0.0743

C13	-0.1992(7)	0.1489(5)	0.1613(4)	0.066
C14	-0.1171(6)	0.2070(5)	0.2086(3)	0.0516
C15	0.7045(7)	-0.3052(5)	0.3352(3)	0.0507
C16	0.8074(7)	-0.3705(5)	0.3744(4)	0.0632
C17	0.8669(7)	-0.3389(5)	0.4405(4)	0.0699
C18	0.8233(7)	-0.2414(5)	0.4648(3)	0.0649
C19	0.7213(7)	-0.1770(5)	0.4248(3)	0.0591
C20	0.6594(6)	-0.2062(4)	0.3577(3)	0.044
C21	0.5495(6)	-0.1392(4)	0.3144(3)	0.0479
C22	0.5477(6)	-0.1280(4)	0.2395(3)	0.0425
C23	0.6565(6)	-0.1868(4)	0.1886(3)	0.0439
C24	0.7178(7)	-0.1448(5)	0.1180(3)	0.0581
C25	0.8129(7)	-0.2003(6)	0.0691(4)	0.0691
C26	0.8499(7)	-0.3045(6)	0.0878(4)	0.0753
C27	0.7913(7)	-0.3497(5)	0.1565(4)	0.0658
C28	0.6978(6)	-0.2915(4)	0.2044(3)	0.0487
C29	0.1486(6)	0.4499(4)	0.2060(3)	0.0467
C30	0.2637(6)	0.5001(4)	0.2589(3)	0.0519
C31	0.2585(7)	0.4468(5)	0.3376(3)	0.0526

C32	0.3655(7)	0.3501(5)	0.3293(4)	0.0669
C33	0.4985(7)	0.3821(6)	0.2682(4)	0.0791
C34	0.4153(6)	0.4570(5)	0.2138(3)	0.0592
C35	0.3003(6)	0.4123(5)	0.1573(3)	0.055
C36	0.4341(6)	-0.0480(4)	0.2045(3)	0.0455
C37	0.3058(7)	0.0011(4)	0.2580(3)	0.052
C38	0.2888(7)	-0.0525(5)	0.3365(3)	0.0546
C39	0.1828(7)	-0.1498(5)	0.3288(4)	0.0692
C40	0.0666(7)	-0.1151(6)	0.2686(4)	0.0745
C41	0.1653(7)	-0.0402(5)	0.2137(3)	0.0575
C42	0.2939(7)	-0.0851(5)	0.1552(3)	0.0531
C43	0.3153(7)	0.5183(6)	0.3945(4)	0.0774
C44	0.2162(8)	0.0191(5)	0.3943(3)	0.075
C45	0.3129(7)	0.2961(5)	0.1446(4)	0.0731
C46	0.3200(8)	0.4747(6)	0.0815(4)	0.089
C47	0.2945(8)	-0.0224(5)	0.0806(3)	0.0765
C48	0.2849(7)	-0.2019(5)	0.1423(4)	0.0717
H21	-0.2989	0.064	0.3605	0.082(3)
H31	-0.428	0.1182	0.4717	0.087(3)

H41	-0.3682	0.2833	0.5136	0.082(3)
H51	-0.1775	0.3912	0.446	0.072(3)
H101	-0.0872	0.4258	0.1076	0.072(3)
H111	-0.2256	0.3281	0.0264	0.091(3)
H121	-0.2934	0.1532	0.0595	0.097(3)
H131	-0.2287	0.078	0.1756	0.084(3)
H161	0.8379	-0.437	0.3566	0.082(3)
H171	0.9378	-0.3831	0.4685	0.092(3)
H181	0.8624	-0.219	0.5101	0.085(3)
H191	0.6932	-0.11	0.4426	0.075(3)
H241	0.6924	-0.0738	0.1037	0.075(3)
H251	0.8529	-0.1682	0.022	0.089(3)
H261	0.915	-0.3445	0.0539	0.095(3)
H271	0.8162	-0.421	0.1702	0.081(3)
H291	0.0931	0.5037	0.1785	0.060(3)
H301	0.2583	0.5747	0.2578	0.066(3)
H321	0.4138	0.3313	0.3752	0.085(3)
H322	0.3033	0.2924	0.3151	0.085(3)
H331	0.5873	0.4159	0.2888	0.100(3)

H332	0.5382	0.3222	0.2434	0.100(3)
H341	0.4864	0.511	0.1916	0.075(3)
H361	0.4971	0.0058	0.1769	0.056(3)
H371	0.3124	0.0757	0.2573	0.068(3)
H391	0.1222	-0.1688	0.3749	0.090(3)
H392	0.2482	-0.2077	0.3138	0.090(3)
H401	-0.027	-0.0807	0.2902	0.094(3)
H402	0.0321	-0.1742	0.2437	0.094(3)
H411	0.1003	0.0145	0.1925	0.074(3)
H431	0.4246	0.5404	0.3798	0.094(3)
H432	0.2456	0.5782	0.3968	0.094(3)
H433	0.3129	0.4818	0.4426	0.094(3)
H441	0.1106	0.0423	0.3809	0.093(3)
H442	0.2065	-0.0179	0.4422	0.093(3)
H443	0.2864	0.0782	0.3961	0.093(3)
H451	0.4103	0.2838	0.1141	0.090(3)
H452	0.3174	0.2574	0.1916	0.090(3)
H453	0.2201	0.2739	0.1202	0.090(3)
H461	0.4132	0.4499	0.0531	0.112(3)

H462	0.3343	0.5472	0.0894	0.112(3)
H463	0.2243	0.466	0.055	0.112(3)
H471	0.2082	-0.0464	0.0527	0.096(3)
H472	0.397	-0.0316	0.0532	0.096(3)
H473	0.2789	0.0501	0.0888	0.096(3)
H481	0.1955	-0.2144	0.1126	0.086(3)
H482	0.2695	-0.2412	0.1892	0.086(3)
H483	0.3846	-0.2228	0.1169	0.086(3)

Table 18 Bond Lengths (Å) for the Artocarpol A Analogue (29)

O1-C1	1.400(7)
O1-C14	1.385(6)
O2-C7	1.375(6)
O2-C31	1.471(6)
O3-C15	1.402(6)
O3-C28	1.404(6)
O4-C21	1.381(6)
O4-C38	1.463(6)
C1-C2	1.374(7)

C1-C6	1.384(7)
C2-C3	1.369(9)
C3-C4	1.389(9)
C4-C5	1.368(7)
C5-C6	1.405(7)
C6-C7	1.476(7)
C7-C8	1.348(7)
C8-C9	1.466(7)
C8-C29	1.491(7)
C9-C10	1.399(7)
C9-C14	1.412(7)
C10-C11	1.386(8)
C11-C12	1.378(9)
C12-C13	1.369(8)
C13-C14	1.365(8)
C15-C16	1.374(7)
C15-C20	1.387(7)
C16-C17	1.389(8)
C17-C18	1.377(9)

C18-C19	1.370(7)
C19-C20	1.402(7)
C20-C21	1.461(7)
C21-C22	1.340(7)
C22-C23	1.466(7)
C22-C36	1.510(7)
C23-C24	1.399(7)
C23-C28	1.391(7)
C24-C25	1.359(8)
C25-C26	1.386(9)
C26-C27	1.378(8)
C27-C28	1.360(8)
C29-C30	1.542(7)
C29-C35	1.556(8)
C30-C31	1.522(7)
C30-C34	1.548(8)
C31-C32	1.516(8)
C31-C43	1.503(8)
C32-C33	1.524(8)

C33-C34	1.512(8)
C34-C35	1.557(8)
C35-C45	1.513(8)
C35-C46	1.526(8)
C36-C37	1.528(8)
C36-C42	1.579(7)
C37-C38	1.520(7)
C37-C41	1.546(7)
C38-C39	1.530(8)
C38-C44	1.510(8)
C39-C40	1.526(8)
C40-C41	1.516(8)
C41-C42	1.563(8)
C42-C47	1.512(7)
C42-C48	1.520(8)

Table 19 Bond Angles (°) for the Artocarpol A Analogue (29)

C1-O1-C14	113.3(4)
C7-O2-C31	116.1(4)

C15-O3-C28	112.9(4)
C21-O4-C38	116.1(4)
O1-C1-C2	118.7(5)
O1-C1-C6	119.3(5)
C2-C1-C6	122.0(5)
C1-C2-C3	119.6(6)
C2-C3-C4	120.3(6)
C3-C4-C5	119.6(6)
C4-C5-C6	121.3(6)
C5-C6-C1	117.1(5)
C5-C6-C7	122.1(5)
C1-C6-C7	120.7(5)
C6-C7-O2	110.2(5)
C6-C7-C8	126.9(5)
O2-C7-C8	122.8(5)
C7-C8-C9	121.8(5)
C7-C8-C29	120.6(5)
C9-C8-C29	117.6(5)
C8-C9-C10	122.8(5)

C8-C9-C14	123.3(5)
C10-C9-C14	113.7(5)
C9-C10-C11	123.1(6)
C10-C11-C12	119.7(6)
C11-C12-C13	119.8(6)
C12-C13-C14	119.6(6)
C9-C14-O1	118.4(5)
C9-C14-C13	124.1(6)
O1-C14-C13	117.4(6)
O3-C15-C16	117.9(6)
O3-C15-C20	119.3(5)
C16-C15-C20	122.6(6)
C15-C16-C17	119.8(6)
C16-C17-C18	119.0(6)
C17-C18-C19	120.5(6)
C18-C19-C20	122.0(6)
C19-C20-C15	116.1(5)
C19-C20-C21	123.0(5)
C15-C20-C21	121.0(5)

C20-C21-O4	109.6(5)
C20-C21-C22	126.9(5)
O4-C21-C22	123.4(5)
C21-C22-C23	123.2(5)
C21-C22-C36	119.3(5)
C23-C22-C36	117.4(5)
C22-C23-C24	122.9(5)
C22-C23-C28	122.4(5)
C24-C23-C28	114.5(5)
C23-C24-C25	123.3(6)
C24-C25-C26	119.6(6)
C25-C26-C27	119.2(6)
C26-C27-C28	119.6(6)
O3-C28-C23	119.6(5)
O3-C28-C27	116.7(6)
C23-C28-C27	123.7(6)
C8-C29-C30	116.1(5)
C8-C29-C35	120.5(5)
C30-C29-C35	90.2(4)

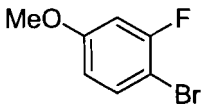
C29-C30-C31	114.1(4)
C29-C30-C34	90.3(4)
C31-C30-C34	107.6(5)
C30-C31-O2	111.6(4)
C30-C31-C32	104.3(5)
O2-C31-C32	110.6(4)
C30-C31-C43	112.4(5)
O2-C31-C43	104.9(5)
C32-C31-C43	113.2(5)
C31-C32-C33	105.3(5)
C32-C33-C34	105.3(5)
C30-C34-C33	105.7(5)
C30-C34-C35	89.9(4)
C33-C34-C35	119.4(5)
C29-C35-C34	89.5(4)
C29-C35-C45	117.5(4)
C34-C35-C45	117.4(5)
C29-C35-C46	111.7(5)
C34-C35-C46	110.6(5)

C45-C35-C46	109.0(6)
C22-C36-C37	116.3(5)
C22-C36-C42	120.0(4)
C37-C36-C42	90.4(4)
C36-C37-C38	114.6(5)
C36-C37-C41	90.8(4)
C38-C37-C41	107.4(5)
C37-C38-O4	111.0(4)
C37-C38-C39	104.7(5)
O4-C38-C39	110.9(5)
C37-C38-C44	112.6(5)
O4-C38-C44	104.8(5)
C39-C38-C44	112.9(5)
C38-C39-C40	104.2(5)
C39-C40-C41	105.7(4)
C37-C41-C40	105.7(5)
C37-C41-C42	90.4(4)
C40-C41-C42	119.7(5)
C41-C42-C36	88.3(4)

C41-C42-C47	111.0(5)
C36-C42-C47	111.8(5)
C41-C42-C48	117.7(5)
C36-C42-C48	117.3(5)
C47-C42-C48	109.3(5)

6.3 Experimental Procedures and Characterization Data Concerning Chapter 4

6.3.1 1-Bromo-2-fluoro-4-methoxybenzene (187)[84]

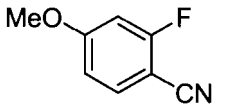


187

A solution of bromine (1.28 g, 8.00 mmol) in chloroform (3 mL) was added dropwise to a solution of 2-fluoroanisole **186** (1.00 g, 7.93 mmol) in chloroform (5 mL) at room temperature. The reaction mixture was stirred at room temperature for 1 h and then was heated at a gentle reflux for 1 h. The resultant mixture was cooled to room temperature and diluted with chloroform (20 mL). The organic layer was washed with brine (2 x 25 mL) and an aqueous solution of sodium hydroxide (10 w/v %, 2 x 15 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure to afford the crude product **187** (1.72 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.79 (s, 3H, O*Me*), 3.88 (s, 0.6 H, O*Me*), 6.56-6.71 (m, 2.3H, Ar*H*), 7.40-7.48 (m, 1.05H, Ar*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 55.9, 56.5, 99.3, 99.5, 100.4, 100.7, 102.8, 103.1, 108.4, 108.6, 111.5, 133.4, 158.4,

160.3, 160.4, 160.9; **IR** (ef) 3098, 3013, 2838, 1608, 1495, 1240, 1058, 949, 849, 795, 729, 619 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 207 [M (^{81}Br) + H, 94), 205 [M (^{79}Br) + H, 100).

6.3.2 2-Fluoro-4-methoxybenzonitrile (188)[84]



188

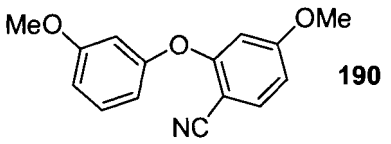
A mixture of 1-bromo-2-fluoro-4-methoxybenzene **187** (770 mg, 3.77 mmol), anhydrous copper cyanide (672 mg, 7.50 mmol) and dimethylformamide (7 mL) was heated at 185 °C for 18 h. The reaction mixture was then allowed to cool to room temperature. A stock solution was prepared from anhydrous $FeCl_3$ (30 g), concentrated hydrochloric acid (2 mL) and water (300 mL). The reaction mixture was then added to the stock solution (20 mL) and the resultant mixture was stirred for 40 min at 50-60 °C. The resultant mixture was extracted with ether (3 x 25 mL) and the combined organic layers were washed with brine (2 x 25 mL), dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. Purification of the crude product by recrystallization from hexanes:ether (4:1) afforded the pure nitrile **188** (431 mg, 76%) as white needles. **M.p.** 55-57 °C, hexanes/ether (lit.[84] 59-60 °C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.87 (s, 3H, O*Me*), 6.71 (dd, *J* = 11, 2 Hz, 1H, *H*-3), 6.76 (dd, *J* = 9, 2 Hz, 1H, *H*-5), 7.60 (apparent t, *J* = 8 Hz, 1H, *H*-6); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 56.2, 93.2 (d, *J* = 16 Hz), 102.4 (d, *J* = 23 Hz), 111.4, 114.5, 134.3, 164.8 (d, *J* =

258 Hz), 164.9 (d, J = 11 Hz) ; **IR** (KBr) 3103, 2988, 2228, 1621, 1506, 1450, 1102, 846 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 152 (M + H, 100).

6.3.3 Potassium fluoride - alumina complex[85]

A mixture of potassium fluoride (37 g) and basic alumina (63 g) in water (100 mL) was stirred at room temperature for 15 min. The reaction mixture was then concentrated under reduced pressure and the white powder was dried in an oven at 120 °C for three days and then stored in the oven at 120 °C.

6.3.4 2-(3'-Methoxyphenoxy)-4-methoxybenzonitrile (190)[42]

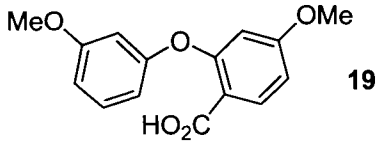


190

A mixture of 3-methoxyphenol **189** (7.96 g, 64.2 mmol), 2-fluoro-4-methoxybenzonitrile **188** (9.11 g, 60.3 mmol), 18-crown-6 (1.59 g, 6.02 mmol), and potassium fluoride-alumina (37 w/w %, 22 g) in acetonitrile (50 mL) was heated at reflux for 20 h. The reaction mixture was cooled to room temperature, diluted with ether (250 mL) and water (200 mL) and then was shaken vigorously. The organic layer was washed with a saturated aqueous solution of potassium chloride (200 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the nitrile **190** (15.38 g, 95%) as a colourless oil. Purification of a sample of this material (578 mg) by flash chromatography using petroleum ether/dichloromethane (1:2) as the eluant afforded an analytically pure sample of the product **190** (562 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.75 (s, 3H,

O*Me*), 3.80 (s, 3H, O*Me*), 6.37 (d, *J* = 2 Hz, 1H, *H*-3), 6.63-6.67 (m, 3H, Ar*H*), 6.75-6.78 (m, 1H, Ar*H*), 7.27-7.31 (m, 1H, Ar*H*), 7.56 (d, *J* = 9 Hz, 1H, *H*-6); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 55.3, 55.6, 95.5, 103.3, 106.0, 108.8, 110.6, 111.9, 116.3, 130.4, 134.7, 155.9, 161.0, 161.1, 164.2; **IR** (ef) 3081, 2845, 2222, 1610, 1432, 1294, 1032, 968, 845, 682 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 256 (M + H, 100), 152 (21), 105 (14); **Anal.** Calcd. for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.64; H, 5.19; N, 5.31.

6.3.5 2-(3'-Methoxyphenoxy)-4-methoxybenzoic acid (191)[42]

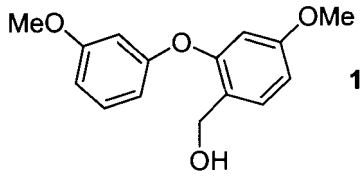


191

Potassium hydroxide (50.6 g, 368 mmol) and hydrogen peroxide (30 w/w %, 18 mL) were added slowly to a solution of 2-(3'-methoxyphenoxy)-4-methoxybenzonitrile **190** (4.58 g, 18.0 mmol) in methanol (11.5 mL) and ethanol (46 mL) at 0 °C. The reaction mixture was then heated at reflux for 20 h, cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in an aqueous solution of sodium hydroxide (5 M, 45 mL), extracted with ether (100 mL) and acidified with concentrated hydrochloric acid to pH ~1. The resultant brown precipitate was collected by vacuum filtration and was purified by recrystallization from hexanes/ether (2:1) to afford the pure benzoic acid **191** (4.77 g, 97%) as white crystals. **M.p.** 125-147 °C, hexanes/ether; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.76 (s, 3H, O*Me*), 3.79 (s, 3H, O*Me*), 6.37 (d, *J* = 2 Hz, 1H, *H*-3), 6.64-6.66 (m, 2H, Ar*H*), 6.49 (dd, *J* = 9, 2 Hz,

1H, *H*-5), 6.75-6.77 (m, 1H, Ar*H*), 7.26-7.30 (m, 1H, Ar*H*), 8.12 (d, *J* = 9 Hz, 1H, *H*-6); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 55.6, 55.8, 104.4, 106.0, 109.3, 110.8, 112.0, 112.6, 130.6, 135.1, 156.2, 159.0, 161.3, 164.9, 167.4; **IR** (KBr) 3448 (broad), 2845, 1692, 1491, 1445, 1284, 1027, 965 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 275 (M + H, 100), 257 (14); **Anal.** Calcd. for $C_{15}H_{14}O_5$: C, 65.69; H, 5.15. Found: C, 65.34; H, 5.09.

6.3.6 (2-(3'-Methoxyphenoxy)-4-methoxyphenyl)methanol (192)

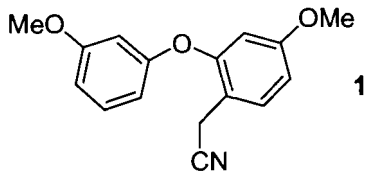


192

The benzoic acid **191** (12.8 g, 46.7 mmol) was added over a period of 40 min to a suspension of lithium aluminum hydride (3.00 g, 78.9 mmol) in THF (120 mL) at 0 °C. The reaction mixture was then allowed to warm to room temperature and was heated at reflux for 3 h. The resultant mixture was cooled to 0 °C and diluted with water (15 mL), an aqueous solution of sodium hydroxide (15%, 10 mL) and water (15 mL). The reaction mixture was stirred for 1 h at room temperature and then was filtered. The filter-cake was washed with ether (50 mL), the filtrate was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to afford the pure benzyl alcohol **192** (11.2 g, 93%) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.77 (broad s, 1H, O*H*), 3.74 (s, 3H, O*Me*), 3.78 (s, 3H, O*Me*), 4.65 (s, 2H, CH_2), 6.46 (d, *J* = 3 Hz, 1H, *H*-3), 6.54-6.57 (m, 2H, Ar*H*), 6.64-6.69 (m, 2H, Ar*H*), 7.20-7.24 (m, 1H, Ar*H*), 7.34

(d, J = 8 Hz, 1H, *H*-6); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 55.4, 55.5, 60.7, 104.5, 105.4, 109.0, 109.2, 110.5, 124.5, 130.3, 130.4, 155.5, 158.3, 160.5, 161.1; **IR** (ef) 3439 (broad), 3070, 2940, 2834, 1620, 1504, 1487, 1285, 1048, 914, 850, 768 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 260 (M + H, 16), 243 (100), 211 (11), 165 (13); **Anal.** Calcd. for $C_{15}H_{16}O_4$: C, 69.22; H, 6.20. Found: C, 69.27; H, 6.35.

6.3.7 2-[2-(3'-Methoxyphenoxy)-4-methoxyphenyl]acetonitrile (193)

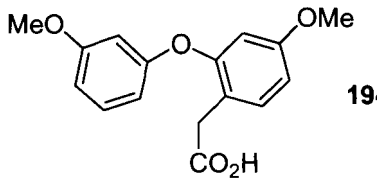


193

A solution of the benzyl alcohol **192** (9.37 g, 36.2 mmol) in dichloromethane (50 mL) was briefly shaken in a separatory funnel with concentrated hydrochloric acid (50 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the crude chloride. A solution of the crude chloride in dimethyl sulfoxide (10 mL) was added to a suspension of sodium cyanide (2.65 g, 54.1 mmol) in dimethyl sulfoxide (20 mL). The resultant mixture was stirred at room temperature for 20 h, diluted with water (20 mL) and extracted with ethyl acetate (2 x 35 mL). The combined organic extracts were washed with water (5 x 30 mL) and brine (35 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford pure nitrile **193** (6.78 g, 70%) as a yellow solid. Purification of a sample of the crude product (350 mg) by flash chromatography using hexanes/ether (2:3) as the eluant afforded an analytically pure sample of product **193** (320 mg). **M.p.** 38-40 °C, hexanes/ether; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.69

(s, 2H, 2 x *H*-2), 3.74 (s, 3H, O*Me*), 3.79 (s, 3H, O*Me*), 6.45 (d, *J* = 3 Hz, 1H, *H*-3), 6.55-6.58 (m, 2H, Ar*H*), 6.66-6.70 (m, 2H, Ar*H*), 7.21-7.24 (m, 1H, Ar*H*), 7.37 (d, *J* = 9 Hz, 1H, *H*-6); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 18.0, 55.41, 55.44, 104.8, 105.0, 109.1, 109.4, 110.7, 113.2, 117.9, 130.2, 130.4, 155.3, 157.3, 160.7, 161.1; **IR** (ef) 3076, 3007, 2836, 2251, 1623, 1415, 1331, 1030, 971, 917, 853, 687 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 270 (M + H, 100), 243 (15); **Anal.** Calcd. for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.09; H, 5.69; N, 5.22.

6.3.8 2-(2-(3'-Methoxyphenoxy)-4-methoxyphenyl)acetic acid (194)[55]

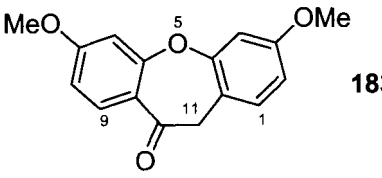


194

The nitrile **193** (6.38 g, 23.7 mmol) was added to a solution of potassium hydroxide (6.05 g, 108 mmol) in aqueous ethanol (80 v/v%, 50 mL). The resultant mixture was heated at reflux for 18 h, cooled to room temperature, diluted with water (100 mL) and acidified with concentrated hydrochloric acid to pH ~1. The precipitated solid was filtered under vacuum, washed with water (2 x 25 mL) and air-dried. Purification of the crude product by recrystallization from hexanes:ether (4:1) afforded the pure acid **194** (5.80 g, 85%) as white crystals. **M.p.** 78-80 °C, hexanes/ether; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.64 (s, 2H, 2 x *H*-2), 3.72 (s, 3H, O*Me*), 3.75 (s, 3H, O*Me*), 6.44 (d, *J* = 3 Hz, 1H, *H*-3), 6.53-6.55 (m, 2H, Ar*H*), 6.63-6.67 (m, 2H, Ar*H*), 7.17-7.21 (m, 2H, Ar*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 35.0, 55.4, 55.5, 104.6, 105.2, 109.2, 109.4, 110.8, 117.3, 130.3,

132.0, 156.0, 158.1, 160.3, 161.1, 178.2; **IR** (KBr) 3199 (broad), 1717, 1580, 1511, 1406, 1036, 917, 839, 687 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 289 (M + H, 100), 243 (7); **Anal.** Calcd. for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.40; H, 5.77.

6.3.9 3,7-Dimethoxy-11*H*-dibenzo[*b*,*f*]oxepin-10-one (183)[55]

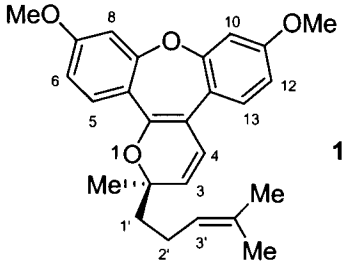


183

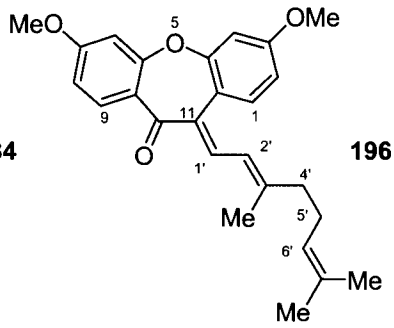
Thionyl chloride (0.77 mL, 11 mmol) was added to a solution of benzoic acid **194** (505 mg, 1.75 mmol) in dichloromethane (5 mL). The reaction mixture was heated on a steam bath for 5 min and then was concentrated under reduced pressure. The residue was dissolved in 1,2-dichloroethane (10 mL) and was added dropwise to a suspension of aluminum chloride (234 mg, 1.75 mmol) in 1,2-dichloroethane (5 mL). The resultant mixture was stirred at room temperature for 2 h and then was poured onto crushed ice (50 mL). The organic material was extracted with ethyl acetate (2 x 30 mL), washed with brine (30 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure to afford the pure dimethoxy-oxepinone **183** (399 mg, 84%) as a light brown solid. **M.p.** 93-96 °C, ethyl acetate; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.79 (s, 3H, O*Me*), 3.89 (s, 3H, O*Me*), 3.97 (s, 2H, 2 x *H*-11), 6.72-6.75 (m, 2H, Ar*H*), 6.82-6.83 (m, 2H, Ar*H*), 7.18 (d, *J* = 8 Hz, 1H, *H*-1), 8.00 (d, *J* = 9 Hz, 1H, *H*-9); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 47.2, 55.7, 55.8, 105.5, 106.3, 111.1, 112.1, 118.6, 120.0, 130.2, 132.4, 157.7, 159.8, 161.9, 164.9, 190.0; **IR** (KBr) 1664,

1605, 1506, 1274, 1161, 1126, 1017, 805 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 271 (M + H, 100); **Anal.** Calcd. for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.19; H, 5.14.

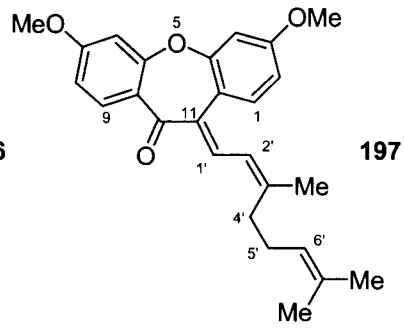
6.3.10 7,11-Dimethoxy-2-methyl-2-(4'-methyl-pent-3'-enyl)-2*H*-1,9-dioxa-tribenzo[*a*,*c*,*e*]cycloheptene (184) and 2'(*E*/*Z*),11(*E*)-11-[3',7'-dimethyl-octa-2',6'-dienylidene]-3,7-dimethoxy-11*H*-dibenzo[*b*,*f*]oxepin-10-one(196 + 197)



184



196



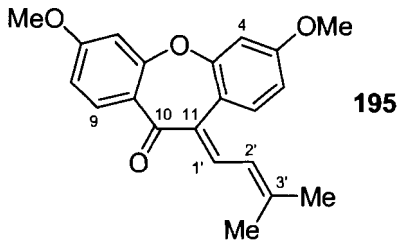
197

A mixture of citral (**17**) (235 mg, 1.55 mmol), allylamine (120 μL, 1.60 mmol), dimethoxy-oxepinone **183** (139 mg, 0.51 mmol) and anhydrous magnesium sulfate (0.5 g) in THF (8 mL) was heated at reflux for five days. The reaction mixture was allowed to cool to room temperature and then was filtered. The filter-cake was washed with ether (10 mL) and the combined filtrates were concentrated under reduced pressure. Purification of the crude product by flash chromatography using petroleum ether/dichloromethane (1:2) as the eluant afforded the dimethoxy-2*H*-pyran **184** (21 mg, 10%) as a yellow oil and a mixture of three compounds (204 mg). Purification of this mixture by flash chromatography using ether:hexanes (3:2) as the eluant afforded a mixture (1:1) of the dienones **196** and **197** (105 mg, 51%) as a yellow oil and the cyclic aldehyde **131** (90 mg, 20%) as an orange oil.

2*H*-pyran **184**: **^{1}H NMR** (500 MHz, C_6D_6) δ 1.34 (s, 3H, *Me*), 1.54 (s, 3H, *Me*), 1.65 (s, 3H, *Me*), 1.68-1.91 (m, 2H, 2 x *H*-1'), 2.19-2.38 (m, 2H, 2 x *H*-2'), 3.17 (s, 3H, O*Me*), 3.25 (s, 3H, O*Me*), 5.17-5.22 (m, 1H, *H*-3'), 5.25 (d, *J* = 10 Hz, 1H, *H*-3), 6.23 (d, *J* = 10 Hz, 1H, *H*-4), 6.64-6.68 (m, 2H, Ar*H*), 6.80 (d, *J* = 3 Hz, 1H, Ar*H*), 6.86 (d, *J* = 3 Hz, 1H, Ar*H*), 7.08 (d, *J* = 9 Hz, 1H, Ar*H*), 7.71 (d, *J* = 9 Hz, 1H, Ar*H*); **MS** (CI) *m/z* (rel. intensity) 405 (M + H, 100).

Mixture of the dienones **196** and **197**: **^{1}H NMR** (500 MHz, C_6D_6) δ 1.42, 1.56, 15.8, 1.60, 1.65, 1.66 (6 x s, 18H, 6 x *Me*), 1.90-2.00 (m, 4H, CH_2), 2.06-2.11 (m, 2H, CH_2), 2.26-2.30 (m, 2H, CH_2), 3.09, 3.10 (2 x s, 6H, 2 x O*Me*), 3.20, 3.21 (2 x s, 6H, 2 x O*Me*), 4.99-5.02 (m, 1H, *H*-2' of the *E,E*-isomer), 5.12-5.16 (m, 1H, *H*-2' of the *E,Z*-isomer), 6.34-6.60 (m, 6H), 6.72-6.73 (m, 2H, Ar*H*), 6.91 (dd, *J* = 7, 3 Hz, 2H, Ar*H*), 7.20 (dd, *J* = 8, 1 Hz, 2H, Ar*H*), 8.18 (d, *J* = 12 Hz, 1H, *H*-1' of the *E,E*-isomer), 8.22 (d, *J* = 12 Hz, 1H, *H*-1' of the *E,Z*-isomer), 8.39 (d, *J* = 9 Hz, 1H, *H*-9 of the *E,Z*-isomer), 8.42 (d, *J* = 9 Hz, 1H, *H*-9 of the *E,E*-isomer); **IR** (ef) 3012, 2927, 2839, 1715, 1651, 1520, 1414, 1096, 1028 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 405 (M + H, 100); **Anal.** Calcd. for $C_{26}H_{28}O_4$: C, 77.20; H, 6.98. Found: C, 77.03; H, 7.09.

6.3.11 11(*E*)-3,7-Dimethoxy-11-[3'-methyl-but-2-enylidene]-11*H*-dibenzo[*b*,*f*]oxepin-10-one (195)[61]

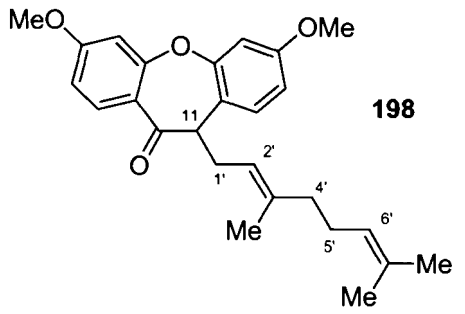


195

Titanium tetrachloride (0.70 mL, 1 M in dichloromethane, 0.7 mmol) and tri-*n*-butylamine (140 μL, 0.51 mmol) were successively added to a solution of the dimethoxy-oxepinone **183** (110 mg, 0.4 mmol) in dichloromethane (5 mL) at -18 °C. After 30 min, a solution of senecialdehyde (**24**) (43 mg, 0.51 mmol) in dichloromethane (5 mL) was added, the mixture was stirred at -18 °C for 4 h and then was allowed to gradually warm to room temperature overnight. The resultant mixture was diluted with water (10 mL) and ether (25 mL), the organic layer was washed with brine (2 x 15 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification of the crude product by flash chromatography using dichloromethane as the eluant afforded the pure dimethoxy-dienone **195** (55 mg, 40%) as a light yellow oil. **^{1}H NMR** (500 MHz, C_6D_6) δ 1.46 (s, 3H, *Me*), 1.58 (s, 3H, *Me*), 3.10 (s, 3H, O*Me*), 3.20 (s, 3H, O*Me*), 6.34 (d, *J* = 12 Hz, 1H, *H*-2'), 6.53 (dd, *J* = 9, 2 Hz, 1H, Ar*H*), 6.59 (dd, *J* = 9, 2 Hz, 1H, Ar*H*), 6.79 (d, *J* = 2 Hz, 1H, Ar*H*), 6.97 (d, *J* = 3 Hz, 1H, Ar*H*), 7.16 (m, 1H, Ar*H*), 8.18 (d, *J* = 12 Hz, 1H, *H*-1'), 8.47 (d, *J* = 9 Hz, 1H, *H*-9); **^{13}C NMR** (126 MHz, C_6D_6) δ 18.8, 26.7, 55.0, 55.1, 106.0, 107.0, 111.6, 121.5, 122.4, 127.3, 127.5, 133.2, 134.1, 135.3, 136.2, 147.3, 158.5, 160.7, 162.6, 164.8, 187.2; **IR** (ef) 3005, 2838, 1651, 1503, 1413, 1162, 1114, 1025, 756 cm^{-1}; **MS**

(CI) *m/z* (rel. intensity) 337 (M + H, 100); **Anal.** Calcd. for $C_{21}H_{20}O_4$: C, 74.98; H, 5.99. Found: C, 74.81; H, 6.14.

6.3.12 2'(*E*)-11-(3',7'-Dimethylocta-2',6'-dienyl)-3,7-dimethoxy-11*H*-dibenzo[*b*,*f*]oxepin-10-one (198)

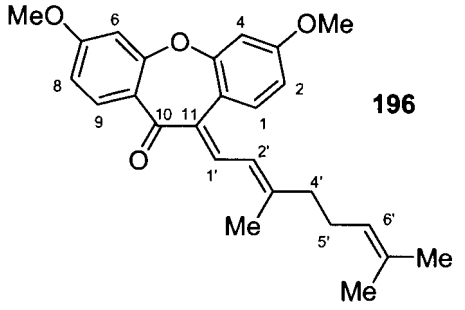


198

A solution of LDA was prepared by reacting a solution of *N,N*-diisopropylamine (190 μL, 1.36 mmol) in THF (5 mL) with *n*-butyllithium (0.55 mL, 2.5 M in hexanes, 1.3 mmol) at 0 °C for 30 min. A solution of the dimethoxy-oxepinone **183** (302 mg, 1.11 mmol) in THF (5 mL) was then added to the preformed solution of LDA at -18 °C. After 30 min, a solution of geranyl bromide **26** (378 mg, 1.74 mmol) in THF (5 mL) was added and reaction mixture was allowed to warm to 0 °C over 4 h. The resultant mixture was diluted with water (15 mL) and ether (25 mL). The organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification of the crude product by flash chromatography using chloroform as the eluant afforded the pure monoalkylated ketone **198** (202 mg, 45%) as a yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.56 (s, 3H, *Me*), 1.58 (s, 3H, *Me*), 1.63 (s, 3H, *Me*), 1.91-1.99 (m, 4H, 2 x *H*-4', 2 x *H*-5'), 2.73-2.67 (m, 1H, *H*-1'), 2.81-2.87 (m, 1H, *H*-1'), 3.79 (s, 3H, O*Me*), 3.89 (s, 3H, O*Me*), 4.01 (t, *J* = 8 Hz, 1H,

H-11), 5.00 (t, *J* = 7 Hz, 1H, *H*-6'), 5.09 (t, *J* = 7 Hz, 1H, *H*-2'), 6.72-6.77 (m, 2H, Ar*H*), 6.82 (dd, *J* = 6, 2 Hz, 2H, Ar*H*), 7.10 (d, *J* = 9 Hz, 1H, Ar*H*), 7.98 (d, *J* = 9 Hz, 1H, Ar*H*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 16.2, 17.8, 25.7, 26.1, 26.7, 39.8, 55.6, 55.8, 77.4, 105.0, 106.3, 110.9, 112.1, 119.5, 121.3, 121.4, 124.3, 129.1, 131.4, 132.6, 137.4, 157.4, 159.6, 161.0, 164.7, 191.8; **IR** (ef) 2963, 2907, 1684, 1566, 1413, 1032, 911, 756, 733 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 407 (M + H, 100); **Anal.** Calcd. for $C_{26}H_{30}O_4$: C, 76.82; H, 7.44. Found: C, 76.55; H, 7.60.

6.3.13 2'(*E*),11(*E*)-11-(3',7'-Dimethyl-octa-2',6'-dienylidene)-3,7-dimethoxy-11*H*-dibenzo[*b*,*f*]oxepin-10-one (196)



196

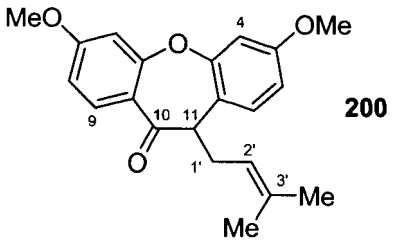
A solution of LDA was prepared by reacting a solution of *N,N*-diisopropylamine (100 μL, 0.71 mmol) in THF (5 mL) with *n*-butyllithium (0.35 mL, 2.5 M in hexanes, 0.88 mmol) at 0 °C for 30 min. A solution of the dimethoxy-oxepinone **183** (162 mg, 0.60 mmol) in THF (10 mL) was then added to the preformed solution of LDA at -78 °C. After 30 min, a solution of phenylselenyl chloride (137 mg, 0.72 mmol) in THF (5 mL) was slowly added and the reaction mixture was immediately poured into a mixture of hydrochloric acid (0.5 M, 20 mL), ether (10 mL) and pentane (10 mL). The organic layer was washed with water (20 mL), a saturated aqueous solution of sodium bicarbonate (20 mL) and

brine (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification of the crude product by flash chromatography using petroleum ether/chloroform (1:1) as the eluant afforded unreacted phenyl selenium chloride (30 mg) as an orange solid and a mixture of selenides products (208 mg, 58%) as a brown oil.

Pyridine (53 μL, 0.66 mmol) and hydrogen peroxide (30 w/w %, 100 μL, 0.90 mmol) were added to a solution of the selenide (185 mg, 0.33 mmol) in dichloromethane (10 mL). The reaction mixture was then diluted with an aqueous solution of sodium bicarbonate (7 w/v %, 15 mL) and extracted with dichloromethane (2 x 20 mL). The combined organic extracts were washed with dilute hydrochloric acid (10 v/v %, 15 mL), brine (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification of the crude product by flash chromatography using petroleum ether/dichloromethane (1:1) as the eluant afforded the pure *E,E*-dimethoxy-dienone **196** (128 mg, 95%) as a yellow oil. **^{1}H NMR** (500 MHz, C_6D_6) δ 1.42 (s, 3H, *Me*), 1.60 (s, 3H, *Me*), 1.67 (s, 3H, *Me*), 1.91-1.98 (m, 4H, 2 x *H*-4', 2 x *H*-5'), 3.11 (s, 3H, O*Me*), 3.21 (s, 3H, O*Me*), 4.99-5.02 (m, 1H, *H*-6'), 6.37 (dd, *J* = 12, 1 Hz, 1H, *H*-2'), 6.48 (dd, *J* = 9, 2 Hz, 1H, *H*-2), 6.58 (dd, *J* = 9, 3 Hz, 1H, *H*-8), 6.73 (d, *J* = 3 Hz, 1H, *H*-4), 6.89 (d, *J* = 3 Hz, 1H, *H*-6), 7.20 (d, *J* = 9 Hz, 1H, *H*-1), 8.17 (d, *J* = 12 Hz, 1H, *H*-1'), 8.41 (d, *J* = 9 Hz, 1H, *H*-9); **^{13}C NMR** (126 MHz, C_6D_6) δ 17.1, 17.4, 25.5, 26.4, 29.9, 40.7, 54.8, 105.7, 106.7, 111.3, 111.4, 121.3, 121.9, 122.9, 123.8, 131.5, 133.0, 133.9, 135.1, 136.2, 150.5, 158.3, 160.5, 162.3, 164.5, 186.9; **IR**

(ef) 3013, 2928, 2839, 1720, 1651, 1504, 1414, 1096, 1026 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 405 (M + H, 100).

6.3.14 3,7-Dimethoxy-11-(3'-methylbut-2'-enyl)-11*H*-dibenzo[*b*,*f*]oxepin-10-one (200)

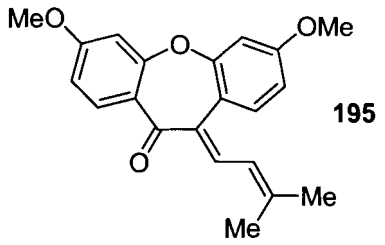


200

A solution of LDA was prepared by reacting a solution of *N,N*-diisopropylamine (200 μL, 1.43 mmol) in THF (5 mL) with *n*-butyllithium (0.60 mL, 2.5 M in hexanes, 1.5 mmol) at 0 °C for 30 min. A solution of dimethoxy-oxepinone **183** (300 mg, 1.11 mmol) in THF (5 mL) was then added to the preformed solution of LDA at -18 °C. After 30 min, a solution of prenyl bromide (**28**) (208 mg, 1.39 mmol) in THF (5 mL) was added and the reaction was allowed to warm to 0 °C over 4 h. The resultant mixture was diluted with water (15 mL) and ether (25 mL). The organic layer was then washed with brine (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification of the crude product by flash chromatography using chloroform as the eluant afforded the pure monoalkylated ketone **200** (272 mg, 73%) as a yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.59 (s, 3H, *Me*), 1.64 (s, 3H, *Me*), 2.64-2.71 (m, 1H, *H*-1'), 2.82-2.89 (m, 1H, *H*-1'), 3.79 (s, 3H, O*Me*), 3.89 (s, 3H, O*Me*), 4.01 (t, *J* = 8 Hz, 1H, *H*-11), 5.09 (t, *J* = 7 Hz, 1H, *H*-2'), 6.72-6.83 (m, 4H, Ar*H*), 7.11 (d, *J* = 9 Hz, 1H, Ar*H*), 7.98 (d, *J* = 9 Hz, 1H, *H*-9); **^{13}C NMR** (126

MHz, $CDCl_3$) δ 17.9, 25.8, 26.1, 55.3, 55.5, 55.7, 105.0, 106.2, 110.9, 112.0, 119.4, 121.3, 121.4, 128.8, 132.5, 133.7, 157.4, 159.5, 160.9, 164.6, 191.7; **IR** (ef) 3075, 2837, 1686, 1564, 1411, 1030, 910, 729 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 339 (M + H, 100), 338 (53).

6.3.15 11(*E*)-3,7-Dimethoxy-11-(3'-methylbut-2'-enylidene)-11*H*-dibenzo[*b*,*f*]oxepin-10-one (195)

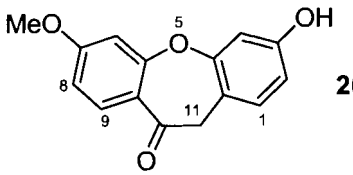


195

A solution of LDA was prepared by reacting a solution of *N,N*-diisopropylamine (63 μL, 0.45 mmol) in THF (5 mL) with *n*-butyllithium (200 μL, 2.5 M in hexanes, 0.50 mmol) at 0 °C for 30 min. A solution of the monoalkylated ketone **200** (100 mg, 0.30 mmol) in THF (10 mL) was added to the preformed solution of LDA at -78 °C. After 30 min, a solution of phenyl selenium chloride (83 mg, 0.44 mmol) in THF (5 mL) was slowly added and the reaction mixture was immediately poured over a mixture of hydrochloric acid (0.5 M, 20 mL), ether (10 mL) and pentane (10 mL). The organic layer was washed with water (20 mL), a saturated aqueous solution of sodium bicarbonate (20 mL) and brine (20 mL), dried over anhydrous sodium sulfate and then concentrated under reduced pressure. Purification of the crude product by flash chromatography using petroleum ether:chloroform (2:1) as the eluant afforded phenyl selenium chloride (10 mg) as an orange solid and a mixture of selenides as a brown oil.

Pyridine (32 μL, 0.39 mmol) and hydrogen peroxide (30 w/w %, 100 μL, 0.90 mmol) were added to a solution of the crude selenide in dichloromethane (10 mL). The reaction mixture was diluted with an aqueous solution of sodium bicarbonate (7 w/v %, 15 mL) and then was extracted with dichloromethane (2 x 20 mL). The combined organic layers were washed with dilute hydrochloric acid (10%, 15 mL) and brine (20 mL), dried over anhydrous sodium sulfate and then concentrated under reduced pressure. Purification of the crude product by flash chromatography using petroleum ether:dichloromethane (1:1) as the eluant afforded the pure *E*-dienone **195** (75 mg, 60%) as a yellow oil.

6.3.16 3-Hydroxy-7-methoxy-11*H*-dibenzo[*b*,*f*]oxepin-10-one (202)[86]



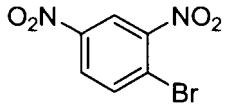
202

Boron tribromide (190 μL, 2.00 mmol) was added to a solution of the dimethoxy-oxepinone **183** (118 mg, 0.44 mmol) in dichloromethane (15 mL) at -78 °C. After 1 h, the reaction mixture was allowed to warm to room temperature. After 20 h, the reaction was poured onto crushed ice (10 mL) and the mixture was extracted with ethyl acetate (2 x 20 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification of the crude product by flash chromatography using dichloromethane/ethyl acetate (3:1) as the eluant afforded the pure hydroxymethoxyoxepinone **202** (75 mg, 66%) as a light brown solid.

M.p. 153-156 °C, dichloromethane:ethyl acetate; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.89 (s, 3H, O*Me*), 3.96 (s, 2H, 2 x *H*-11), 5.14 (s, 1H, O*H*), 6.66 (dd, *J* = 8, 2 Hz, 1H, *H*-2), 6.73 (dd, *J* = 9, 2 Hz, 1H, *H*-8), 6.78-6.81 (m, 3H, Ar*H*), 7.12 (d, *J* = 8 Hz, 1H, *H*-1), 8.00 (d, *J* = 9 Hz, 1H, *H*-9); **^{1}H NMR** (400 MHz, acetone-d_6) δ 3.91 (s, 2H, 2 x *H*-11), 3.93 (s, 3H, O*Me*), 6.73 (dd, *J* = 8, 2 Hz, 1H, *H*-2), 6.81-6.83 (m, 2H, *H*-8, *H*-4), 6.93 (d, *J* = 3 Hz, 1H, *H*-6), 7.18 (d, *J* = 8 Hz, 1H, *H*-1), 7.93 (d, *J* = 9 Hz, 1H, *H*-9), 8.64 (s, 1H, O*H*); **^{13}C NMR** (101 MHz, acetone-d_6) δ 47.5, 56.3, 106.3, 108.3, 111.9, 114.2, 118.4, 120.7, 131.0, 132.7, 158.5, 158.7, 162.8, 165.8, 189.8; **IR** (KBr) 3273 (broad), 3015, 2841, 1656, 1553, 1514, 1434, 1334, 1017, 820 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 257 (M + H, 100); **Anal.** Calcd. for $C_{15}H_{12}O_4$: C, 70.31; H, 4.72. Found: C, 70.51; H, 4.82.

6.4 Experimental Procedures and Characterization Data Concerning Chapter 5

6.4.1 1-Bromo-2,4-dinitrobenzene (211)[115]



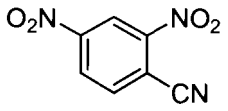
211

Concentrated sulfuric acid (40 mL) and then bromobenzene **210** (10.0 mL, 100 mmol) were added dropwise to concentrated nitric acid (40 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 h and then was heated at a gentle reflux for 3 h. The resultant mixture was cooled to room temperature and poured onto crushed ice (100 mL). The pure bromide **211** was isolated by

(115) Vogel, A. I. *Practical Organic Chemistry*; 3rd ed.; Longman: New York, 1956.

vacuum filtration (22.8 g, 97%) as a yellow solid. A sample of this material was then recrystallized from methanol to afford the analytically pure product **211**. **M.p.** 69-71 °C, methanol (lit.[88] 72-73 °C, methanol); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.00 (d, J = 9 Hz, 1H, *H*-6), 8.29 (dd, J = 9, 3 Hz, 1H, *H*-5), 8.70 (d, J = 3 Hz, 1H, *H*-3); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 121.0, 122.0, 127.3, 130.6, 147.0, 149.8; **IR** (KBr) 3104, 1962, 1796, 1701, 1609, 1034, 898, 833 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 249 [M (^{81}Br) + H, 100], 246 [M (^{79}Br) + H, 100].

6.4.2 2,4-Dinitrobenzonitrile (212)[84]



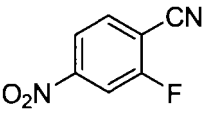
212

A mixture of 1-bromo-2,4-dinitrobenzene **211** (22.4 g, 90.6 mmol), anhydrous copper cyanide (16.2 g, 181 mmol) and dimethylformamide (30 mL) was heated at 150 °C for 4 h. The reaction mixture was then cooled to room temperature and was added to a solution of anhydrous iron trichloride (30 g), concentrated hydrochloric acid (2 mL) in water (300 mL). The resultant mixture was stirred for 40 min at 50-60 °C and then was extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with brine (2 x 250 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Purification of the crude product by recrystallization from ethanol afforded the pure nitrile **212** (14.9 g, 85%) as a yellow solid. **M.p.** 102-104 °C, ethanol (lit.[116] 103.5-105 °C, ether/petroleum ether); **^{1}H NMR** (500 MHz, $CDCl_3$)

(116) Aitken, R. A.; Karodia, N. *Eur. J. Org. Chem.* **1999**, 251.

δ 8.19 (d, J = 8 Hz, 1H, *H*-6), 8.67 (dd, J = 8, 2 Hz, 1H, *H*-5), 9.16 (d, J = 2 Hz, 1H, *H*-3); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 113.3, 113.4, 121.1, 128.7, 137.3, 149.3, 150.0; **IR** (KBr) 3108, 3078, 2240, 1600, 1536, 1349, 919, 836, 740 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 194 (M + H, 42), 89 (32), 74 (100).

6.4.3 2-Fluoro-4-nitrobenzonitrile (213)[90]



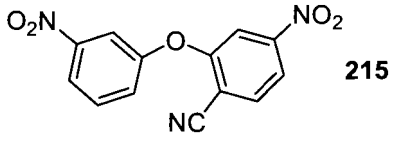
213

Method 1: A solution of tetra-*n*-butylammoniumfluoride in THF (36 mL, 1.0 M, 36 mmol) was added dropwise to a solution of 2,4-dinitrobenzonitrile **212** (5.39 g, 28 mmol) in THF (60 mL) at -78 °C. The reaction mixture was stirred at room temperature for 2 h and then was diluted with ether (40 mL) and water (40 mL). The organic layer was washed with water (40 mL) and brine (40 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification of the crude product by flash chromatography using chloroform as the eluant afforded the pure nitrile **213** (4.05 g 88%) as a yellow solid. **M.p.** 64-67 °C, chloroform (lit.[90] 68.7-70.2 °C, methanol).

Method 2:[90] Potassium fluoride (124 mg, 2.13 mmol) was added to a solution of 2,4-dinitrobenzonitrile **212** (317 mg, 1.64 mmol) in dimethylformamide (10 mL). The resultant mixture was stirred at 120 °C for 7 h and then was diluted with water (20 mL) and extracted with ethyl acetate (3 x 25 mL). The organic layer was washed with water (3 x 25 mL) and brine (3 x 25 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure.

Purification of the crude product by flash chromatography using hexanes/ethyl acetate (3:1) as the eluant afforded the pure nitrile **213** (109 mg, 40%) as a yellow solid. **M.p.** 65-67 °C, hexanes/ethyl acetate (lit.[90] 68.7-70.2 °C, methanol); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.88 (dd, J = 8, 6 Hz, 1H, *H*-6), 8.12 (dd, J = 8, 2 Hz, 1H, *H*-5), 8.18 (ddd, J = 8, 2, 1 Hz, 1H, *H*-3); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 107.8 (d, J = 16 Hz), 112.1, 112.5 (d, J = 25 Hz), 120.0 (d, J = 4 Hz), 134.9, 151.3 (d, J = 8 Hz), 163.01 (d, J = 264 Hz); **IR** (KBr) 3109, 2241, 1612, 1423, 1354, 943, 897, 814, 742 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 223 (100), 166 (M + H, 100), 153 (55), 137 (95).

6.4.4 2-(3'-Nitrophenoxy)-4-nitrobenzonitrile (215)[42]



215

A mixture of 3-nitrophenol **214** (4.21 g, 30.3 mmol), 2-fluoro-4-nitrobenzonitrile **213** (5.03 g, 30.3 mmol), 18-crown-6 (799 mg, 3.03 mmol), and potassium fluoride-alumina (37 w/w %, 10.5 g) in acetonitrile (50 mL) was heated at reflux for 20 h. The resultant mixture was cooled to room temperature and concentrated under reduced pressure. The residue was then diluted with an aqueous solution of sodium hydroxide (1 M, 20 mL). The precipitate was collected by vacuum filtration and was washed with a saturated aqueous solution of potassium chloride (50 mL). Purification of the crude product by continuous extraction (soxhlet) in dichloromethane followed by concentration under reduced pressure afforded the pure nitrile **215** (6.90 g, 80%) as a white solid. **M.p.** 191-

194 °C, dichloromethane; **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 7.54 (ddd, *J* = 8, 2, 1 Hz, 1H, Ar*H*), 7.70, 7.73 (m, 2H), 7.95 (d, *J* = 9 Hz, 1H, Ar*H*), 8.00 (apparent t, *J* = 2 Hz, 1H, Ar*H*), 8.08 (dd, *J* = 8, 2 Hz, 1H, Ar*H*), 8.20 (ddd, *J* = 8, 2, 1 Hz, 1H, Ar*H*); **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 110.4, 112.5, 114.1, 115.7, 119.1, 121.4, 126.6, 132.0, 135.9, 150.0, 151.1, 159.5. **IR** (KBr) 3109, 3047, 2230, 1540, 1352, 899, 829, 735 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 286 (M + H, 100); **Anal.** Calcd. for $C_{13}H_7N_3O_5$: C, 54.74; H, 2.47; N, 14.73. Found: C, 54.88; H, 2.40; N, 14.52.

6.4.5 X-Ray Crystallographic Analysis of 2-(3'-Nitrophenoxy)-4-nitrobenzonitrile (215)

A single crystal of 2-(3'-nitrophenoxy)-4-nitrobenzonitrile **215**, a colourless plate that had the dimensions 0.30 x 0.35 x 0.35 mm^3, was mounted on a glass fibber using epoxy adhesive. The data for the crystal was acquired at 293 K on an Enraf Nonius CAD4F diffractometer using graphite monochromated Mo Kα radiation. The following data range was recorded: $4° \leq 2\theta \leq 54°$. The data reduction included corrections for Lorentz and polarization effects. Final unit-cell dimensions were determined based on the following well-centred reflections: 22 reflections with range $12.5° \leq 2\theta \leq 20.5°$.

The coordinates and anisotropic displacement parameters for the non-hydrogen atoms were refined. Hydrogen atoms were located in subsequent fourier maps, their coordinate shifts were linked with those of the respective carbon atoms during refinement. Isotropic thermal parameters for the hydrogen atoms were initially assigned proportionately to the equivalent isotropic thermal

parameters of their respective carbon atoms. Subsequently the isotropic thermal parameters for the C-H hydrogen atoms were constrained to have identical shifts during refinement. The program used for all absorption corrections, data reduction, and processing were from the NRCVAX Crystal Structure System.[117] The structure was refined using CRYSTALS.[113]

An *ORTEP* representation of the 2-(3'-nitrophenoxy)-4-nitrobenzonitrile **215** is provided below (Figure 63). Crystallographic data, fractional atomic coordinates and equivalent isotropic thermal displacement parameters, selected bond lengths and selected bond angles are also listed below, Table 20, Table 21, Table 22 and Table 23).

---

* The X-ray crystallography data was obtained and solved by Mr. Michael Katz (Simon Fraser University).

(117) Gabe, E. J.; Page, Y. L.; Charland, J. P.; Lee, F. L.; White, P. S. *J. Appl. Crystallogr.* **1989**, *22*, 384.

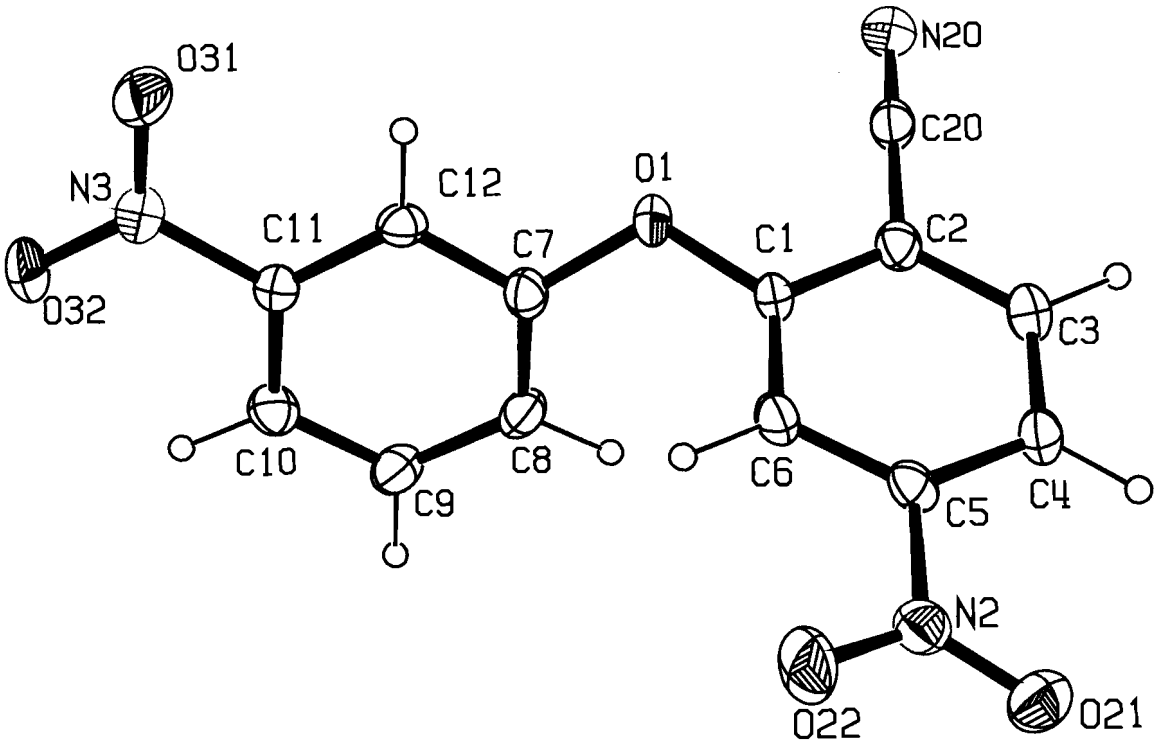


Figure 63 **X-ray crystal structure of 2-(3'-nitrophenoxy)-4-nitrobenzonitrile (215). The thermal ellipsoids are drawn at a 30% probability level.**

Table 20 **Summary of Crystallographic Data for the 2-(3'-Nitrophenoxy)-4-nitrobenzonitrile (215)**

Empirical formula	$C_{13}H_7N_3O_5$
FW (g mol^{-1})	285.81
Temperature (K)	293
Crystal system	monoclinic
Space group	*Cc*
a (Å)	7.873(3)
b (Å)	7.957(4)

c (Å)	19.650(4)
α (°)	90.02(3)
β (°)	101.52(2)
γ (°)	89.99(4)
Z	4
V (Å^3)	1206.2(8)
D_{calc} (g cm^{-3})	6.278
2θ limits (°)	$4° \leq 2\theta \leq 54°$
Reflections collected	1951
Independent reflections	1951
Reflections observed [$I > 2.0\sigma(I)$]	1134
Goodness-of-fit on F	1.3253
R_1, R_w [$I > 2.0\sigma(I)$]	0.0413, 0.0336

Table 21 **Fractional Atomic Coordinates (Å) and Equivalent Isotropic Thermal Displacement Parameters [U(iso), (Å^2)] for the 2-(3'-Nitrophenoxy)-4-nitrobenzonitrile (215)**

Atom	*x*	*y*	*z*	*U* (iso)
O1	0.0889(4)	0.1328(4)	0.97094(15)	0.0548
O21	-0.3106(4)	0.5145(4)	0.73424(16)	0.0575

O22	-0.4213(4)	0.3507(5)	0.80062(19)	0.0784
O31	-0.1199(5)	-0.2465(4)	1.13115(17)	0.0607
O32	-0.2451(4)	-0.0930(4)	1.19649(15)	0.0542
N2	-0.2969(5)	0.4147(5)	0.78158(19)	0.0446
N3	-0.1680(5)	-0.1106(5)	1.14851(17)	0.0428
N2O	0.5073(5)	0.1798(5)	0.94609(19)	0.0541
C1	0.0572(6)	0.2299(5)	0.9124(2)	0.0375
C2	0.2010(5)	0.2743(5)	0.88517(19)	0.0363
C3	0.1798(6)	0.3666(6)	0.8239(2)	0.0418
C4	0.0167(5)	0.4154(5)	0.78984(19)	0.0390
C5	-0.1223(5)	0.3653(5)	0.81791(19)	0.0353
C6	-0.1077(5)	0.2731(5)	0.8783(2)	0.0390
C7	-0.0091(5)	0.1604(6)	1.0221(2)	0.0373
C8	-0.0528(6)	0.3178(5)	1.0412(2)	0.0405
C9	-0.1373(6)	0.3352(6)	1.0962(2)	0.0440
C10	-0.1781(5)	0.1964(6)	1.1311(2)	0.0416
C11	-0.1316(5))	0.0403(5)	1.11037(19	0.0317
C12	-0.0470(6)	0.0176(5)	1.0562(2)	0.0336
C20	0.3721(6)	0.2233(5)	0.9197(2)	0.0394

H31	0.2841	0.4000	0.8041	0.053(5)
H41	0.0026	0.4861	0.7464	0.080(5)
H61	-0.2140	0.2344	0.8960	0.060(5)
H81	-0.0167	0.4177	1.0169	0.036(5)
H91	-0.1742	0.4505	1.1094	0.044(5)
H101	-0.2402	0.2045	1.1710	0.064(5)
H121	-0.0140 -	0.0977	1.0421	0.056(5)

Table 22 Bond Lengths (Å) for 2-(3'-Nitrophenoxy)-4-nitrobenzonitrile (215)

O1-C1	1.367(4)
O1-C7 .	1.401(5)
O21-N2 .	1.212(4)
O22-N2 .	1.227(5)
O31-N3 .	1.217(4)
O32-N3 .	1.227(4)
N2-C5 .	1.470(5)
N3-C11 .	1.474(5)
N20-C20 .	1.141(5)
C1-C2	1.391(5)

C1-C6	1.380(6)
C2-C3	1.392(5)
C2-C20	1.440(6)
C3-C4	1.380(6)
C5-C6	1.380(5)
C7-C8	1.371(5)
C7-C12	1.382(5)
C8-C9	1.383(6)
C9-C10	1.372(6)
C10-C11	1.379(5)
C11-C12	1.376(5)

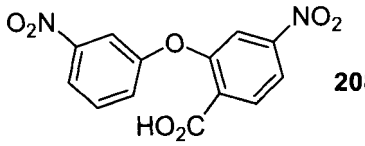
Table 23 Bond Angles (°) for 2-(3'-Nitrophenoxy)-4-nitrobenzonitrile (215)

C1-O1-C7	118.8(3)
O22-N2-O21	123.5(4)
O22-N2-C5	117.8(4)
O21-N2-C5	118.6(4)
O32-N3-O31	123.1(4)
O32-N3-C11	118.3(4)

O31-N3-C11	118.6(4)
O1-C1-C2	116.2(4)
O1-C1-C6	123.0(4)
C2-C1-C6	120.6(4)
C1-C2-C3	120.0(4)
C1-C2-C20	120.3(4)
C3-C2-C20	119.7(4)
C2-C3-C4	120.5(4)
C3-C4-C5	117.4(4)
N2-C5-C4	117.9(4)
N2-C5-C6	117.9(4)
C4-C5-C6	124.1(4)
C1-C6-C5	117.3(4)
O1-C7-C8	123.0(4)
O1-C7-C12	115.0(4)
C8-C7-C12	121.8(4)
C7-C8-C9	119.5(4)
C8-C9-C10	120.4(4)
C9-C10-C11	118.4(4)

N3-C11-C10	119.6(4)
N3-C11-C12	117.4(4)
C10-C11-C12	123.0(4)
C7-C12-C11	116.9(4)
C2-C20-N20	178.5(5)

6.4.6 2-(3'-Nitrophenoxy)-4-nitrobenzoic acid (208)[94]

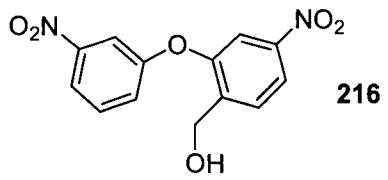


208

2-(3'-Nitrophenoxy)-4-nitrobenzonitrile **215** (5.03 g, 17.6 mmol) was added to a mixture of concentrated sulfuric acid (30 mL) and water (15 mL). The resultant mixture was stirred at 150 °C for 2 h and then was cooled to room temperature and poured onto crushed ice (50 mL). The precipitate was collected by vacuum filtration, washed with water and dried under reduced pressure to afford the pure benzoic acid **208** (4.93 g, 92%) as a light yellow solid. **M.p.** 118-119 °C, hexanes:ether; **^{1}H NMR** (500 MHz, acetone-d_6) δ 7.53 (ddd, J = 8, 2, 1 Hz, 1H, *H*-6'), 7.72 (apparent t, J = 8 Hz, 1H, *H*-5'), 7.85 (apparent t, J = 2 Hz, 1H, *H*-2'), 8.03-8.06 (m, 2H, Ar*H*), 8.22-8.27 (m, 2H, Ar*H*); **^{13}C NMR** (126 MHz, acetone-d_6) δ 14.5, 18.7, 20.2, 21.6, 26.0, 32.0, 33.0, 35.1, 151.3, 152.9, 156.7, 159.8, 166.0; **IR** (KBr) 3478, 3102, 1711, 1532, 1474, 1352, 828, 736 cm^{-1}; **MS**

(CI) *m/z* (rel. intensity) 305 (M + H, 52), 287 (100), 261 (82); **Anal.** Calcd. for $C_{13}H_8N_2O_7$: C, 51.33; H, 2.62; N, 8.97. Found: C, 51.67; H, 2.88; N, 8.97.

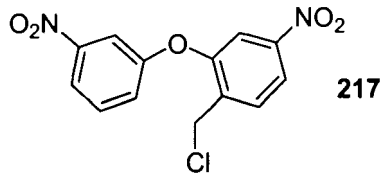
6.4.7 [2-(3'-Nitrophenoxy)-4-nitrophenyl]methanol (216)



216

Borane tetrahydrofuran complex (10.0 mL, 1.0 M in tetrahydrofuran, 10 mmol) was added to a solution of 2-(2'-(3-nitrophenoxy)-4-nitrophenyl)acetic acid **208** (1.02 g, 3.35 mmol) in THF (30 mL) at 0 °C. The resultant mixture was stirred at room temperature for 20 h and then was cooled to 0 °C and diluted with hydrochloric acid (1.0 M, 10 mL) and ether (25 mL). The organic layer was washed with water (2 x 30 mL) and brine (30 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the pure benzyl alcohol **216** (900 mg, 93%) as a yellow solid. **M.p.** 93-96 °C, ether; **^{1}H NMR** (500 MHz, acetone-d_6) δ 4.69 (t, *J* = 5 Hz, 1H, O*H*), 4.85 (d, *J* = 5 Hz, 2H, CH_2), 7.56 (dd, *J* = 8, 2 Hz, 1H, *H*-6'), 7.73 (apparent t, *J* = 8 Hz, 1H, *H*-5'), 7.77 (d, *J* = 2 Hz, 1H, *H*-2'), 7.88-7.89 (m, 1H, Ar*H*), 7.95 (d, *J* = 9 Hz, 1H, Ar*H*), 8.07 (dd, *J* = 8, 2 Hz, 1H, Ar*H*), 8.13 (dd, *J* = 9, 2 Hz, 1H, Ar*H*); **^{13}C NMR** (101 MHz, acetone-d_6) δ 60.2, 115.2, 115.4, 120.7, 121.3, 126.6, 130.7, 133.2, 143.5, 149.7, 151.4, 154.7, 158.9; **IR** (KBr) 3547, 3098, 1532, 1360, 888, 829, 743 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 290 (M, 32), 273 (M - OH, 100); **Anal.** Calcd. for $C_{13}H_{10}N_2O_6$: C, 53.80; H, 3.47; N, 9.65. Found: C, 53.94; H, 3.61; N, 9.44.

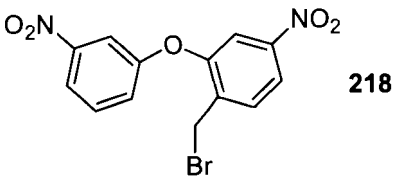
6.4.8 1-[2'-[(Chloromethyl)-5'-nitrophenoxy]-3-nitrobenzene (217)[53]



217

Thionyl chloride (320 μL, 4.38 mmol) was added to a solution of (2-(3'-nitrophenoxy)-4-nitrophenyl)methanol **216** (900 mg, 3.10 mmol) and pyridine (250 μL, 3.09 mmol) in benzene (25 mL) at 0 °C. The resultant mixture was heated at reflux for 3 h, cooled to room temperature and filtered. The filter-cake was washed with benzene (25 mL) and the combined filtrates were concentrated under reduced pressure. Purification of the crude product by flash chromatography using chloroform as the eluant afforded the pure benzyl chloride **217** (853 mg, 89%) as a light brown solid. **M.p.** 64-66 °C, chloroform; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.73 (s, 2H, C*H*$_2$), 7.42 (dd, *J* = 8, 2 Hz, 1H, Ar*H*), 7.62 (t, *J* = 8 Hz, 1H, Ar*H*), 7.70 (d, *J* = 2 Hz, 1H, Ar*H*), 7.74 (d, *J* = 9 Hz, 1H, Ar*H*), 7.91 (apparent t, *J* = 2 Hz, 1H, Ar*H*), 8.07 (dd, *J* = 9, 2 Hz, 1H, Ar*H*), 8.11 (dd, *J* = 8, 2 Hz, 1H, Ar*H*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 39.7, 113.5, 114.4, 119.6, 119.8, 125.3, 131.3, 132.0, 135.8, 149.0, 149.6, 154.7, 156.5; **IR** (KBr) 3078, 1600, 1532, 1418, 1347, 1244, 964, 828, 804 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 311 [M (^{37}C) + H, 32], 309 [M (^{35}C) + H, 100], 273 (25); **Anal.** Calcd. for $C_{13}H_9ClN_2O_5$: C, 50.58; H, 2.94; N, 9.08. Found: C, 50.70; H, 3.08; N, 8.94.

6.4.9 1-[2'-(Bromomethyl)-5'-nitrophenoxy]-3-nitrobenzene (218)



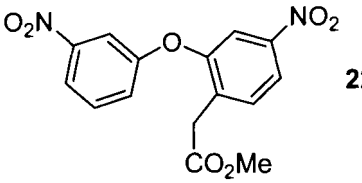
218

Phosphorous tribromide (60 μL, 0.64 mmol) was added to a solution of [2-(3'-nitrophenoxy)-4-nitrophenyl]methanol **216** (416 mg, 1.43 mmol) in dichloromethane (10 mL) at 0 °C. After 1 h, the reaction mixture was poured onto crushed ice (25 mL) and diluted with ether (25 mL). The organic layer was washed with a saturated aqueous solution of sodium bicarbonate (20 mL), water (20 mL) and brine (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the bromide **218** (364 mg, 72%) as a white solid. A sample of this material (50 mg) was purified by flash chromatography using hexanes/ether (2:1) as the eluant to afford analytically pure product **218** (45 mg). **M.p.** 77-79 °C, hexanes/ether; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.60 (s, 2H, CH_2), 7.44 (dd, J = 8, 2 Hz, 1H, ArH), 7.62 (t, J = 8 Hz, 1H, ArH), 7.66-7.69 (m, 2H, ArH), 7.91 (apparent t, J = 2 Hz, 1H, ArH), 8.01 (dd, J = 8, 2 Hz, 1H, ArH), 8.08 (dd, J = 8, 1 Hz, 1H, ArH); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 25.5, 113.4, 114.5, 119.5, 119.8, 125.4, 131.2, 132.3, 136.2, 148.9, 149.6, 154.8, 156.4; **IR** (KBr) 3107, 1530, 1416, 1351, 1244, 963, 828 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 355 [M (^{81}Br) + H, 99], 353 [M (^{79}Br) + H, 100]; **Anal.** Calcd. for $C_{13}H_9BrN_2O_5$: C, 44.22; H, 2.57; N, 7.93. Found: C, 44.30; H, 2.60; N, 8.01.

6.4.10 Diazomethane[102]

N-Nitrosomethylurea (684 mg, 6.6 mmol) was added in small portions to a mixture of ether (30 mL) and an aqueous solution of potassium hydroxide (40%, 10 mL) at 0 °C. After 15 min, the yellow ether layer was then transferred with a plastic pipette into an Erlenmeyer flask than contained pellets of potassium hydroxide.

6.4.11 Methyl 2-[2-(3'-nitrophenoxy)-4-nitrophenyl]acetate (223)[102]

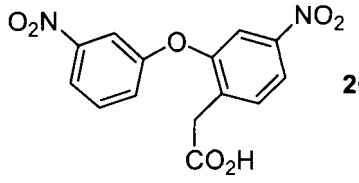


223

Triethylamine (230 μL, 1.65 mmol) and ethyl chloroformate (160 μL, 1.67 mmol) were added to a solution of 2-(3'-nitrophenoxy)-4-nitrobenzoic acid **208** (505 mg, 1.66 mmol) in THF (15 mL) at 0 °C. After 15 min, a solution of diazomethane in ether was added dropwise until a yellow colour persisted for several min. After 4 h, the resultant mixture was diluted with hexanes (15 mL) and ethyl acetate (15 mL). The organic layer was washed with a saturated aqueous solution of sodium bicarbonate (20 mL), water (20 mL) and brine (20 mL), dried over anhydrous sodium sulfate and then was concentrated under reduced pressure to afford the crude product. Triethylamine (0.70 mL, 5.0 mmol) and silver benzoate (63 mg, 0.27 mmol) were added to this material in methanol (15 mL) at -18 °C and the reaction mixture was stirred in the dark for 30 min. The resultant mixture was diluted with ethyl acetate (25 mL), the organic layer

was washed with a saturated aqueous solution of sodium bicarbonate (15 mL), a saturated aqueous solution of ammonium chloride (15 mL) and brine (20 mL), dried over anhydrous sodium sulfate and then concentrated under reduced pressure. Purification of the crude product by flash chromatography using hexanes/ether (1:2) as the eluant afforded the pure methyl ester **223** (370 mg, 67%) as a white solid. **M.p.** 60-61 °C, hexanes/ether; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.66 (s, 3H, Me), 3.83 (s, 2H, C*H*$_2$), 7.39 (ddd, *J* = 8, 2, 1 Hz, 1H, *H*-6'), 7.54 (d, *J* = 9 Hz, 1H, *H*-6), 7.59 (apparent t, *J* = 8 Hz, 1H, *H*-5'), 7.69 (d, *J* = 2 Hz, 1H, *H*-3), 7.87 (apparent t, *J* = 2 Hz, 1H, *H*-2'), 8.05 (dd, *J* = 8, 2 Hz, 1H, *H*-5), 8.07 (ddd, *J* = 8, 2, 1 Hz, 1H, *H*-4'); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 35.8, 52.5, 113.4, 114.2, 119.4, 119.5, 125.1, 131.1, 132.8, 133.3, 148.4, 149.6, 155.1, 156.7, 170.2; **IR** (KBr) 3106, 2954, 1749, 1412, 1078, 895, 828 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 333 (M + H, 100), 319 (35); **Anal.** Calcd. for $C_{15}H_{12}N_2O_7$: C, 54.22; H, 3.64; N, 8.43. Found: C, 54.15; H, 3.72; N, 8.56.

6.4.12 2-[2-(3'-Nitrophenoxy)-4-nitrophenyl]acetic acid (209)



209

Method 1:[103] Triethylamine (250 μL, 1.80 mmol) and ethyl chloroformate (160 μL, 1.67 mmol) were added to a solution of 2-(3'-nitrophenoxy)-4-nitrobenzoic acid **208** (502 mg, 1.65 mmol) in THF (15 mL) at 0 °C. After 15 min, a solution of diazomethane in ether was added dropwise until a yellow colour

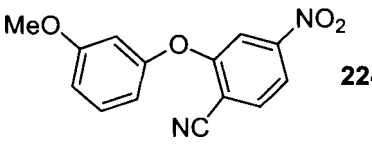
persisted for several minutes. After 4 h, the resultant mixture was diluted with hexanes (15 mL) and ethyl acetate (15 mL). The organic layer was washed with a saturated solution of sodium bicarbonate (20 mL), water (20 mL) and brine (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford a crude product. Triethylamine (0.50 mL, 3.6 mmol) and silver benzoate (45 mg, 0.20 mmol) were added to this material in a mixture of tetrahydrofuran (10 mL) and water (3 mL). The resultant mixture was stirred at room temperature, in absence of light for 30 min and then was diluted with ethyl acetate (25 mL). The organic layer was washed with a saturated solution of sodium bicarbonate (15 mL), a saturated solution of ammonium chloride (15 mL) and brine (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the pure acid **209** (378 mg, 72%) as a light brown solid. **M.p.** 130-132 °C, ethyl acetate.

Method 2:[118] A mixture of the methylester **223** (4.24 g, 12.8 mmol) and hydrochloric acid (6 M, 40 mL) was heated at reflux for 5 h. The resultant mixture was cooled to room temperature and poured onto crushed ice (50 mL). The solid precipitate was collected by vacuum filtration, washed with water and dried under reduced pressure to afford the pure product **209** (3.65, 90%) as a brown solid. **M.p.** 130-133 °C, water; **^{1}H NMR** (500 MHz, acetone-d_6) δ 3.94 (s, 2H, CH_2), 7.59 (dd, J = 8, 2 Hz, 1H, *H*-6'), 7.73-7.79 (m, 3H, Ar*H*), 7.92 (apparent t, J = 2, 1H, *H*-2'), 8.08-8.11 (m, 2H, Ar*H*); **^{13}C NMR** (126 MHz, acetone-d_6) δ

(118) Zhu, J.; Beugelmans, R.; Bourdet, S.; Chastanet, J.; Roussi, G. *J. Org. Chem.* **1995**, *60*, 6389.

36.9, 115.2, 115.7, 120.9, 127.2, 133.2, 135.0, 136.4, 150.1, 151.4, 157.1, 158.8, 172.3; **IR** (KBr) 3473, 3111, 1713, 1603, 1538, 1354, 965, 830 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 275 (M – CO_2H, 100), 227 (63); **Anal.** Calcd. for $C_{14}H_{10}N_2O_7$: C, 52.84; H, 3.17; N, 8.80. Found: C, 52.51; H, 3.31; N, 8.86.

6.4.13 2-(3'-Methoxyphenoxy)-4-nitrobenzonitrile (224)[42]

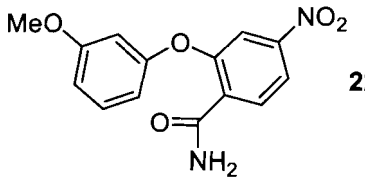


224

A mixture of 3-methoxyphenol **189** (92 mg, 0.74 mmol), 2-fluoro-4-nitrobenzonitrile **213** (118 mg, 0.71 mmol), 18-crown-6 (19 mg, 0.07 mmol), and potassium fluoride-alumina (37 w/w %, 500 mg) in acetonitrile (15 mL) was heated at reflux for 20 h. The resultant mixture was allowed to cool to room temperature and then was diluted with ether (25 mL) and water (20 mL). The resultant mixture was shaken vigorously and then the organic layer was washed with a saturated aqueous solution of potassium chloride (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the nitrile **224** (173 mg, 90%) as a yellow solid. Purification of a sample of this material (50 mg) by flash chromatography using dichloromethane as the eluant afforded the analytically pure product **206** (47 mg). **M.p.** 63-65 °C, dichloromethane. (lit.[42] 90-92 °C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.84 (s, 3H, O*Me*), 6.68-6.72 (m, 2H), 6.87 (dd, *J* = 8, 2 Hz, 1H, Ar*H*), 7.38 (apparent t, *J* = 8 Hz, 1H, Ar*H*), 7.67 (d, *J* = 2 Hz, 1H), 7.85 (d, *J* = 8 Hz, 1H, Ar*H*), 7.96 (dd, *J* = 8, 2 Hz, 1H, Ar*H*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 55.7, 106.8, 109.0, 111.2, 112.3,

112.4, 114.3, 117.2, 131.3, 134.9, 151.3, 154.7, 160.9, 161.7; **IR** (KBr) 3109, 3047, 2230, 1540, 1352, 899, 829, 735 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 271 (M + H, 100); **Anal.** Calcd. for $C_{14}H_{10}N_2O_4$: C, 62.22; H, 3.73; N, 10.37. Found: C, 62.15; H, 3.83; N, 10.13.

6.4.14 2-(3'-Methoxyphenoxy)-4-nitrobenzamide (225)[42]

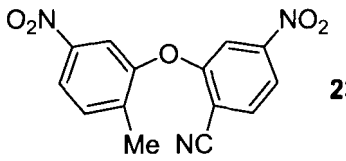


225

Potassium hydroxide (451 mg, 8.05 mmol) and hydrogen peroxide (30 w/w %, 2 mL) were added slowly to a solution of 2-(3'-methoxyphenoxy)-4-nitrobenzonitrile **224** (109 mg, 0.40 mmol) in a mixture of methanol (2 mL) and ethanol (8 mL). The resultant mixture was heated in a water bath at 50 °C for 10 min and then was concentrated under reduced pressure. The residue was dissolved in an aqueous solution of sodium hydroxide (5 M) and then acidified with concentrated hydrochloric acid to pH ~1. The resultant precipitate was collected by vacuum filtration, washed with water and air-dried to afford the pure amide **225** (69 mg, 60%) as a yellow solid. **M.p.** 180-181 °C, water; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.84 (s, 3H, O*Me*), 5.97 (broad s, 1H, N*H*), 6.67-6.71 (m, 2H, Ar*H*), 6.86-6.88 (m, 1H, Ar*H*), 7.38 (apparent t, *J* = 8 Hz, 1H, Ar*H*), 7.59 (broad s, 1H, N*H*), 7.66 (d, *J* = 2 Hz, 1H, Ar*H*), 7.99 (dd, *J* = 9, 2 Hz, 1H, Ar*H*), 8.44 (d, *J* = 9 Hz, 1H, Ar*H*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 55.8, 106.8, 111.9, 112.4, 112.5, 117.7, 131.4, 134.0, 150.7, 150.7, 154.9, 156.8, 161.7, 164.5; **IR** (KBr) 3458,

3163, 1691, 1595, 1349, 1137, 876, 815 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 289 (M + H, 100); **Anal.** Calcd. for $C_{14}H_{12}N_2O_5$: C, 58.33; H, 4.20; N, 9.72. Found: C, 58.51; H, 4.18; N, 9.63.

6.4.15 2-(2'-Methyl-5'-nitrophenoxy)-4-nitrobenzonitrile (231)[42]

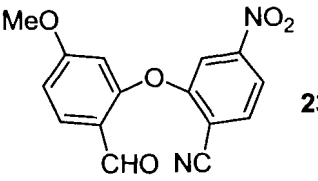


231

A mixture of 2-methyl-5-nitrophenol **230** (199 mg, 1.30 mmol), 2-fluoro-4-nitrobenzonitrile **213** (213 mg, 1.28 mmol), 18-crown-6 (36 mg, 0.13 mmol), and potassium fluoride-alumina (37 w/w %, 500 mg) in acetonitrile (20 mL) was heated at reflux for 4 h. The resultant mixture was allowed to cool to room temperature, diluted with ethyl acetate (25 mL) and water (20 mL) and then the resultant mixture was shaken vigorously. The organic layer was washed with an aqueous solution of sodium hydroxide (1 M, 20 mL), a saturated aqueous solution of potassium chloride (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the pure product **231** (365 mg, 95%) as a white powder. **M.p.** 143-145 °C, ethyl acetate; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.39 (s, 3H, C*H*$_3$), 7.56-7.57 (m, 2H, Ar*H*), 7.87 (d, *J* = 2 Hz, 1H, *H*-3), 7.95 (d, *J* = 9 Hz, 1H, *H*-6), 8.08 (dd, *J* = 9, 2 Hz, 1H, *H*-3'), 8.14 (dd, *J* = 8, 2 Hz, 1H, *H*-5); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 16.6, 109.5, 111.1, 113.7, 115.4, 118.5, 121.5, 133.0, 135.5, 138.4, 147.5, 151.4, 152.2, 159.3; **IR** (KBr) 3109, 3080, 2235, 1601, 1531, 1352, 1248, 1181, 828, 739 cm^{-1}; **MS** (CI) *m/z* (rel. intensity)

300 (M + H, 100), 270 (25); **Anal.** Calcd. for $C_{14}H_9N_3O_5$: C, 56.19; H, 3.03; N, 14.04. Found: C, 56.03; H, 3.13; N, 13.94.

6.4.16 2-(2'-Formyl-5'-methoxyphenoxy)-4-nitrobenzonitrile (233)[42]

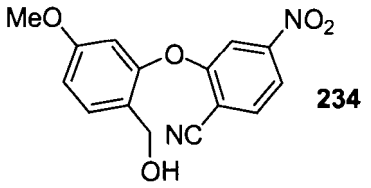


233

A mixture of 2-hydroxy-4-methoxybenzaldehyde **232** (137 mg, 0.89 mmol), 2-fluoro-4-nitrobenzonitrile **213** (147 mg, 0.88 mmol), 18-crown-6 (20 mg, 0.08 mmol), and potassium fluoride-alumina (37 w/w %, 351 mg) in acetonitrile (20 mL) was heated at reflux for 2 h. The resultant mixture was cooled to room temperature, diluted with ethyl acetate (25 mL) and water (20 mL) and then the resultant mixture was shaken vigorously. The organic layer was then washed with a saturated aqueous solution of potassium chloride (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the pure aldehyde **233** (262 mg 99%) as a yellow solid. **M.p.** 134-135 °C, acetonitrile/ether; **^{1}H NMR** (500 MHz, acetone-d_6) δ 3.83 (s, 3H, O*Me*), 6.97 (d, *J* = 2 Hz, 1H, *H*-6'), 7.12 (dd, *J* = 9, 2 Hz, 1H, *H*-4'), 7.75 (d, *J* = 2 Hz, 1H, *H*-3'), 8.00 (d, *J* = 9 Hz, 1H, *H*-6), 8.14-8.16 (m, 1H, *H*-5), 8.22 (d, *J* = 9 Hz, 1H, *H*-3), 10.15 (s, 1H, C*H*O); **^{13}C NMR** (126 MHz, acetone-d_6) δ 57.7, 108.6, 111.1, 113.4, 114.6, 115.9, 120.1, 123.3, 134.5, 137.4, 158.8, 161.8, 168.0, 188.4; **IR** (KBr) 3097, 2861, 2232, 1690, 1673, 1349, 1090, 824 cm^{-1}; **MS** (CI) *m/z* (rel.

intensity) 299 (M + H, 100), 268 (40); **Anal.** Calcd. for $C_{15}H_{10}N_2O_5$: C, 60.41; H, 3.38; N, 9.39. Found: C, 60.72; H, 3.48; N, 9.02.

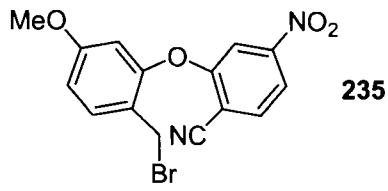
6.4.17 2-[2-(Hydroxymethyl)-5'-methoxyphenoxy]-4-nitrobenzonitrile (234)



234

Sodium borohydride (46 mg, 1.2 mmol) was added to a solution of 2-(2'-formyl-5-methoxyphenoxy)-4-nitrobenzonitrile **233** (101 mg, 0.34 mmol) in methanol (10 mL). The reaction mixture was concentrated under reduced pressure and then diluted with ethyl acetate (30 mL). The resultant mixture was washed with water (20 mL) and brine (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the pure benzyl alcohol **234** (92 mg, 91%) as a light yellow solid. **M.p.** 140-143 °C, ethyl acetate; **^{1}H NMR** (500 MHz, acetone-d_6) δ 3.82 (s, 3H, O*Me*), 4.15 (t, *J* = 6 Hz, 1H, O*H*), 4.58 (d, *J* = 6, 2H, CH_2), 6.85 (d, *J* = 3 Hz, 1H, *H*-6'), 6.98 (dd, *J* = 9, 3 Hz, 1H, *H*-4'), 7.55 (d, *J* = 2 Hz, 1H, *H*-3), 7.58 (d, *J* = 9 Hz, 1H, *H*-3'), 8.06 (dd, *J* = 8, 2 Hz, 1H, *H*-5), 8.14 (d, *J* = 9 Hz, *H*-6); **^{13}C NMR** (126 MHz, acetone-d_6) δ 57.0, 60.2, 108.5, 109.9, 112.4, 114.1, 116.1, 119.0, 128.1, 132.7, 137.1, 153.2, 153.7, 162.5, 162.7; **IR** (KBr) 3404 (broad), 3112, 2232, 1621, 1413, 1241, 1100, 846 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 300 (M, 50), 283 (100); **Anal.** Calcd. for $C_{15}H_{12}N_2O_5$: C, 60.00; H, 4.03; N, 9.33. Found: C, 60.11; H, 4.12; N, 9.15.

6.4.18 2-[2'-(Bromomethyl)-5'-methoxyphenoxy]-4-nitrobenzonitrile (235)



235

Phosphorous tribromide (16 μL, 0.20 mmol) was added to a solution of 2-[2'-(hydroxymethyl)-5'-methoxyphenoxy]-4-nitrobenzonitrile **234** (100 mg, 0.34 mmol) in dichloromethane (10 mL) at 0 °C. After 5 min, the reaction was poured onto crushed ice (25 mL) and diluted with ether (25 mL). The organic layer was then washed with a saturated aqueous solution of sodium bicarbonate (20 mL), water (20 mL) and brine (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the bromide **235** (108 mg, 90%) as a yellow solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.82 (s, 3H, O*Me*), 4.51 (s, 2H, CH_2), 6.55 (d, *J* = 3 Hz, 1H, *H*-6'), 6.87 (dd, *J* = 9, 3 Hz, 1H, *H*-4'), 7.46 (d, *J* = 8.9 Hz, 1H, *H*-3'), 7.69 (d, *J* = 2 Hz, 1H, *H*-3), 7.88 (d, *J* = 9 Hz, 1H, *H*-6), 8.00 (dd, *J* = 9, 2 Hz, 1H, *H*-5); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 27.3, 55.8, 107.0, 108.9, 111.6, 112.4, 114.1, 117.7, 122.3, 132.9, 134.9, 151.2, 152.7, 160.2, 161.6; **IR** (KBr) 3116, 2838, 2232, 1619, 1413, 1351, 816 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 365 [M (^{81}Br) + H, 100], 363 [M (^{79}Br) + H, 100].

REFERENCES

(1) Hano, Y.; Inami, R.; Nomura, T. *Heterocycles* **1990**, *31*, 2173.

(2) Hano, Y.; Inami, R.; Nomura, T. *Heterocycles* **1993**, *35*, 1341.

(3) Chung, M.-I.; Ko, H.-H.; Yen, M.-H.; Lin, C.-N.; Yang, S.-Z.; Tsao, L.-T.; Wang, J.-P. *Helv. Chim. Acta* **2000**, *83*, 1200.

(4) Ko, H.-H.; Lin, C.-N.; Yang, S.-Z. *Heterocycles* **2000**, *83*, 3000.

(5) Ko, H.-H.; Yang, S.-Z.; Lin, C.-N. *Tetrahedron Lett.* **2001**, *42*, 5269.

(6) Lu, Y.-H.; Lin, C.-N.; Ko, H.-H.; Yang, S.-Z.; Tsao, L.-T.; Wang, J.-P. *Helv. Chim. Acta* **2002**, *85*, 1626.

(7) Lu, Y.-H.; Lin, C.-N.; Ko, H.-H.; Yang, S.-Z.; Tsao, L.-T.; Wang, J.-P. *Helv. Chim. Acta* **2003**, *86*, 2566.

(8) Kuan, Y.-H.; Lin, R.-H.; Tsao, L.-T.; Lin, C.-N.; Wang, J.-P. *Br. J. Pharmacol.* **2005**, *145*, 460.

(9) Nomura, T.; Fukai, T.; Katayanagi, M. *Heterocycles* **1978**, *9*, 745.

(10) Mahrwald, R. *Modern Aldol Reactions*; Wiley-VCH: Weinheim, 2004; Vol. 1.

(11) Holst, P. B.; Anthoni, U.; Cristophersen, C.; Nielsen, P. H.; Bock, K. *Acta Chem. Scand.* **1994**, *48*, 765.

(12) Hamell, M.; Levine, R. *J. Org. Chem.* **1950**, *15*, 162.

(13) Wittig, G. *Topics in Current Chemistry*; Springer-Verlag: New York, 1976; Vol. 67.

(14) Beaudry, C. M.; Malerich, J. P.; Trauner, D. *Chem. Rev.* **2005**, *105*, 4757.

(15) Buchi, G.; Yang, N. C. *J. Am. Chem. Soc.* **1957**, *79*, 2318.

(16) Safieddine, A.; Royer, J.; Dreux, J. *Bull. Soc. Chim. Fr.* **1972**, 703.

(17) Royer, J.; Dreux, J. *Bull. Soc. Chim. Fr.* **1972**, 707.

(18) Balaban, A. T.; Mihai, G.; Nenitzescu, C. D. *Tetrahedron* **1962**, *18*, 257.

(19) Royer, J.; Safieddine, A.; Dreux, J. *Bull. Soc. Chim. Fr.* **1972**, 1646.

(20) Marvell, E. N.; Caple, G.; Gosink, T. A.; Zimmer, G. *J. Am. Chem. Soc.* **1966**, *88*, 619.

(21) Marvell, E. N.; Gosink, T. A. *J. Org. Chem.* **1972**, *37*, 3036.

(22) Gosink, T. A. *J. Org. Chem.* **1974**, *39*, 1942.

(23) Duperrier, A.; Dreux, J. *Tetrahedron Lett.* **1970**, *36*, 3127.

(24) Lee, J. C.; Strobel, G. A.; Lobkovsky, E.; Clardy, J. *J. Org. Chem.* **1996**, *61*, 3232.

(25) Li, C.; Johnson, R. P.; Porco, J. J. A. *J. Am. Chem. Soc.* **2003**, *125*, 5095.

(26) Khanna, R. N.; Sharma, P. K.; Thomson, R. H. *J. Chem. Soc. Perkin Trans. 1* **1987**, 1821.

(27) England, D. C.; Krespan, C. G. *J. Org. Chem.* **1970**, *35*, 3300.

(28) Crombie, L.; Ponsford, R. *Tetrahedron Lett.* **1968**, 5771.

(29) Crombie, L.; Ponsford, R. *J. Chem. Soc.* **1971**, 796.

(30) Yamaguchi, S.; Shouji, N.; Kuroda, K. *Bull. Chem. Soc. Jpn* **1995**, *68*, 305.

(31) Kashiwada, Y.; Yamazaki, K.; Ikeshiro, Y.; Yamagishi, T.; Fujioka, T.; Mihashi, K.; Mizuki, K.; Cosentino, L. M.; Fowke, K.; Morris-Natschke, S. L.; Lee, K.-H. *Tetrahedron* **2001**, *57*, 1559.

(32) Kurdyumov, A. V.; Hsung, R. P.; Ihlen, K.; Wang, J.-P. *Org. Lett.* **2003**, *5*, 3935.

(33) Kang, Y.; Mei, Y.; Du, Y.; Jin, Z. *Org. Lett.* **2003**, *5*, 4481.

(34) Hu, H.; Harrison, T. J.; Wilson, P. D. *J. Org. Chem.* **2004**, *69*, 3782.

(35) Garcia, A.; Catedo, L.; Dominguez, D. *Tetrahedron* **1995**, *51*, 8585.

(36) Manske, R. H. F. *J. Am. Chem. Soc.* **1950**, *72*, 55.

(37) Rosowsky, A. *Seven-Membered Heterocyclic Compounds Containing Oxygen and Sulfur*; John Wiley and Sons, Inc.: New York, 1972; Vol. 26.

(38) Manske, R. H. F.; Ledingham, A. E. *J. Am. Chem. Soc.* **1950**, *72*, 4797.

(39) Jinno, S.; Okita, T. *Heterocycles* **1999**, *51*, 303.

(40) Zimmermann, K.; Waldmeier, P. C.; Tatton, W. G. *Pure Appl. Chem.* **1999**, *71*, 2039.

(41) Zimmermann, K.; Roggo, S.; Kragten, E.; Furst, P.; Waldmeier, P. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1195.

(42) Sawyer, J. S.; Schmittling, E. A.; Palkowitz, J. A.; Smith, I. W. J. *J. Org. Chem.* **1998**, *63*, 6338.

(43) Comber, M. F.; Sargent, M. V. *J. Chem. Soc. Perkin Trans. 1* **1990**, 1371.

(44) Olivera, R.; SanMartin, R.; Churruca, F.; Dominguez, E. *J. Org. Chem.* **2002**, *67*, 7215.

(45) Bavin, P. M. G.; Bartle, K. D.; Jones, D. W. *J. Heterocycl. Chem.* **1968**, *5*, 327.

(46) Drake, J. A. G.; Jones, D. W. *Acta Cryst.* **1982**, *B38*, 200.

(47) Mathys, F.; Prelog, V.; Woodward, R. B. *Helv. Chim. Acta* **1956**, 1095.

(48) Gil-Lopetegui, P.; Fernandez-Gadea, F. J.; Meert, T. F. *PCT Int. Appl*, WO 9738991.

(49) Bondinell, W. E.; Miller, W. H.; Heerding, D.; Samanem, J. M. *PCT Int. Appl*, WO 9915508.

(50) Boris, A.; Guthrie, R. W.; Kierstead, R. W. *US Patent*, US 4595689.

(51) Ong, H. H.; Flynn, M. J. *US Patent*, US 4496582.

(52) Olivera, R.; SanMartin, R.; Churruca, F.; Dominguez, D. *Org. Prep. Proced. Int.* **2004**, *36*, 299.

(53) Atkinson, D. C.; Godfrey, K. E.; Meek, B.; Saville, J. F.; Stillings, M. R. *J. Med. Chem.* **1983**, *26*, 1353.

(54) Yoshioka, M.; Osawa, H.; Fukuzawa, S. *Bull. Chem. Soc. Jpn* **1982**, *55*, 877.

(55) Ong, H. H.; Profitt, J. A.; Anderson, V. B.; Spaulding, T. C.; Wilker, J. C.; Geyer III, H. M.; Kruse, H. *J. Med. Chem.* **1980**, *23*, 494.

(56) Harris, T. W.; Smith, H. E.; Mobley, P. L.; Manier, D. H.; Sulser, F. *J. Med. Chem.* **1982**, *25*, 855.

(57) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473.

(58) Turro, N. J.; Mattay, J. *J. Am. Chem. Soc.* **1981**, *103*, 4200.

(59) Moreno, I.; Tellitu, I.; Dominguez, E.; SanMartin, R. *Eur. J. Org. Chem.* **2002**, 2126.

(60) Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215.

(61) Yoshida, Y.; Hayashi, R.; Sumihara, H.; Tanabe, Y. *Tetrahedron Lett.* **1997**, *38*, 8727.

(62) Davis, F. A.; Sheppard, A. C.; Chen, B.-C.; Haque, M. S. *J. Am. Chem. Soc.* **1990**, *112*, 6679.

(63) Acton, D.; Hill, G.; Tait, B. S. *J. Med. Chem.* **1983**, *26*, 1131.

(64) Terashima, K.; Takaya, Y.; Niwa, M. *Bioorg. Med. Chem.* **2002**, *10*, 1619.

(65) Sun, X.; Collum, D. B. *J. Am. Chem. Soc.* **2000**, *122*, 2452.

(66) Imamoto, T.; Kusumoto, T.; Yokoyama, M. *Tetrahedron Lett.* **1983**, *24*, 5233.

(67) Campbell, M.; Snieckus, V. *Encyclopedia of Reagents for Organic Chemistry*; John Wiley & Sons: New York, 1995.

(68) Olofson, R. A.; Dougherty, C. M. *J. Am. Chem. Soc.* **1973**, *95*, 582.

(69) Smith, I. A. B.; Richmond, R. E. *J. Org. Chem.* **1981**, *46*, 4814.

(70) Murray, W.; Wachter, M.; Barton, D.; Forero-Kelly, Y. *Synthesis* **1991**, 18.

(71) Arai, S.; Shirai, Y.; Ishida, T.; Shioiri, T. *Tetrahedron* **1999**, *55*, 6375.

(72) Pathak, V. N.; Pathak, R.; Gupta, R.; Oza, C. K. *Synth. Commun.* **1997**, *27*, 1811.

(73) Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, 1011.

(74) Lalic, G.; Petrovski, Z.; Galonic, D.; Matovic, R.; Saicic, R. N. *Tetrahedron* **2001**, *57*, 583.

(75) Kuhn, R.; Hensel, H. R. *Chem. Ber.* **1953**, *86*, 1333.

(76) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, I. C. F. *J. Am. Chem. Soc.* **2001**, *123*, 5260.

(77) Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 11273.

(78) Hu, H. PhD. Thesis, Simon Fraser University, Burnaby, 2004.

(79) Talley, J. J. *Synthesis* **1983**, 845.

(80) Tietze, L.-F.; Kiedrowski, G. V.; Berger, B. *Synthesis* **1982**, 683.

(81) Gould, I. R. *Handbook of Organic Photochemistry*; CRC Press, Inc.: Boca Raton, Florida, 1989.

(82) Murov, S. L. *Handbook of Photochemistry*; Marcel Dekker, Inc.: New York, 1973.

(83) Horspool, W.; Armesto, D. *Organic Photochemistry: A Comprehensive Treatment*; Ellis Horwood Limited, PTR Prentice Hall: Chichester, England, New York, 1992.

(84) Kelly, S. M. *Helv. Chim. Acta* **1984**, *67*, 1572.

(85) Schmittling, A.; Sawyer, J. S. *Tetrahedron Lett.* **1991**, *32*, 7207.

(86) Zhu, Z.; Swager, T. M. *Org. Lett.* **2001**, *3*, 3471.

(87) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Chemistry*; 3rd ed.; John Wiley and Sons, Inc.: New York, 1999.

(88) Lerch, U.; Moffatt, J. G. *J. Org. Chem.* **1971**, *36*, 3861.

(89) Clark, J. H.; Wails, D.; Jones, C. W.; Smith, H. E.; Boechat, N.; Mayer, L. U.; Mendonca, J. S. *J. Chem. Res.* **1994**, 2783.

(90) Sasaki, M.; Takeuchi, K.; Sato, H.; Takatsu, H. *Mol. Cryst. Liq. Cryst.* **1984**, *109*, 169.

(91) Boechat, N.; Clark, J. H. *J.Chem. Soc. Chem. Commun.* **1993**, 921.

(92) Clark, J. H. *Chem. Rev.* **1980**, *80*, 429.

(93) Hays, S. J.; Caprathe, B. W.; Gilmore, J. L.; Amin, N.; Emmerling, M. R.; Michael, W.; Nadimpalli, R.; Nath, R.; Raser, K. J.; Stafford, D.; Watson, D.; Wang, K.; Jaen, J. C. *J. Med. Chem.* **1998**, *41*, 1060.

(94) Sannie, M. C.; Lapin, M. H. *Bull. Soc. Chim. Fr.* **1950**, 322.

(95) Nagai, Y.; Irie, A.; Nakamura, H.; Hino, K.; Uno, H.; Nishimura, H. *J. Med. Chem.* **1982**, *25*, 1065.

(96) Polivka, Z.; Holubek, J.; Svatek, E.; Metysova, J. *Collect. Czech. Chem. Commun.* **1981**, *46*, 2222.

(97) Wright, S. W.; McClure, L. D. *Org. Prep. Proced. Int.* **1994**, *26*, 602.

(98) Davis, R.; Untch, K. G. *J. Org. Chem.* **1981**, *46*, 2985.

(99) Camps, F.; Gasol, V.; Guerrero, A. *Synth. Commun.* **1988**, *18*, 445.

(100) Bouveault, L. *Bull. Soc. Chim. Fr.* **1904**, *31*, 1306.

(101) Petrier, C.; Gemal, A. L.; Luche, J.-L. *Tetrahedron Lett.* **1982**, *23*, 3361.

(102) Arndt, F. *Org. Reactions*; John Wiley and Sons, Inc: New York, 1963; Vol. 1.

(103) Arndt, F. *Org. Syntheses*; John Wiley and Sons, Inc.: New York, 1943; Vol. 2.

(104) Sindelar, K.; Jilek, J. O.; Pomykacek, J.; Sedivy, Z.; Protiva, M. *Collect. Czech. Chem. Commun.* **1978**, *43*, 471.

(105) Yoshikai, N.; Nakamura, E. *Adv. Synth. Catal.* **2003**, 1159.

(106) Ratcliffe, R. W.; Salzmann, T. N.; Christensen, B. G. *Tetrahedron Lett.* **1980**, *21*, 31.

(107) Hamann-Gaudinet, B.; Namy, J.-L.; Kagan, H. B. *Tetrahedron Lett.* **1997**, *38*, 6585.

(108) Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*; 4th ed.; Butterworth-Heinemann: Oxford, **1997**.

(109) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(110) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

(111) Riley, R. G.; Silverstein, R. M. *J. Org. Chem.* **1974**, *39*, 1957.

(112) De Meulenaer, J.; Tompa, H. *Acta Cryst.* **1965**, *19*, 1014.

(113) Watkin, D. J.; Prout, C. K.; Carruthers, J. R.; Betteridge, P. W.; Cooper, R. I. *CRYSTALS*; Chemical Crystallography Laboratory, University of Oxford: Oxford, England, 2003.

(114) *International Tables for X-Ray Crystallography*; Kynoch Press: Birmingham, England, 1952.

(115) Vogel, A. I. *Practical Organic Chemistry*; 3rd ed.; Longman: New York, 1956.

(116) Aitken, R. A.; Karodia, N. *Eur. J. Org. Chem.* **1999**, 251.

(117) Gabe, E. J.; Page, Y. L.; Charland, J. P.; Lee, F. L.; White, P. S. *J. Appl. Crystallogr.* **1989**, *22*, 384.

(118) Zhu, J.; Beugelmans, R.; Bourdet, S.; Chastanet, J.; Roussi, G. *J. Org. Chem.* **1995**, *60*, 6389.

---

i