TOTAL SYNTHESIS OF THE XYLOKETAL NATURAL PRODUCTS AND ALBOATRIN

by

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ABSTRACT

The isolation and structural characterization of seven closely related natural products, the xyloketals, from a mangrove fungus of the *Xylaria* species have been reported recently by Lin and co-workers. Of these natural products, all of which incorporate identical chiral nonracemic 5,6-bicyclic acetal moieties, xyloketal A has a unique and aesthetically pleasing C_3-symmetric molecular structure that was elucidated by detailed spectroscopic studies and by X-ray crystallography. Xyloketal A, B, C and D have also been shown to be potent inhibitors of acetylcholine esterase and so represent important lead compounds for the treatment of neurological diseases. In addition, xyloketal A, B and F have been shown to have L-calcium channel blocking activity. Thus, the total synthesis of these natural products, and structural analogues thereof, is of notable significance.

Towards these ends, a series of novel synthetic routes to prepare these compounds were developed. The initial route, in which the key synthetic transformation involved an inverse electron demand hetero Diels-Alder reaction between appropriately substituted *ortho*-quinone methides and dihydrofurans, afforded (±)-, (+)- and (–)-xyloketal D. In addition, demethyl analogues of xyloketal A and D were prepared. However, the application of this synthetic route to prepare the more structurally complex xyloketals was unsuccessful.

A second route, utilizing a phenylboronic acid-mediated condensation reaction as the key synthetic transformation, afforded a series of novel *tris*-2*H*-chromenes that represent structural analogues of the natural product xyloketal A. However, due to the

instability of a key synthetic intermediate, the total synthesis of xyloketal A was not completed by this route.

A third route was also investigated that featured a boron trifluoride diethyl etherate-promoted electrophilic aromatic substitution reaction as a key step. This synthetic route was used to complete total syntheses of xyloketal A, B, D, E, F and G. Moreover, demethyl analogues of xyloketal A, B, C, D, E and G were also prepared.

The application of the electrophilic aromatic substitution reaction towards the total synthesis of the structurally related and biologically active natural product alboatrin was also investigated. This led to the first asymmetric total synthesis of this natural product as well as a demethyl analogue.

To Nicolette and my parents, Carol and Alan.

"Chance favours the prepared mind"

Louis Pasteur, 1854

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LIST OF ABBREVIATIONS

$[\alpha]_D$	specific rotation
α	bottom face (steroid nomenclature)
β	top face (steroid nomenclature)
δ	chemical shift (NMR spectroscopy)
(+)-	dextrorotatory
(–)-	laevorotatory
(±)-	racemic
2D	two dimensional
Ac	acetyl
AcOH	acetic acid
Ac_2O	acetic anhydride
AIBN	2,2'-azo-*bis*-isobutyronitrile
amu	atomic mass units (mass spectroscopy)
Anal.	elemental analysis
aq	aqueous
Ar	aromatic group
atm	atmospheres
Å	Ångstrom (0.1 nm)

BINAP	[1,1'-binaphthalene]-2,2'-diyl*bis*(diphenylphosphine)
Bn	benzyl (phenylmethyl)
B.p.	boiling point
br	broad (spectroscopy)
brsm	based on recovered starting material
Calcd.	calculated (elemental analysis)
CAN	ceric ammonium nitrate
cat.	catalytic (amount)
CD	circular dichroism
CI	chemical ionization (mass spectroscopy)
cm^{-1}	wavenumbers (IR spectroscopy)
^{13}C NMR	carbon nuclear magnetic resonance spectroscopy
conc.	concentrated
COSY	^{1}H-^{1}H correlation spectroscopy
D	sodium *D*-line (589 nm)
d	doublet (NMR spectroscopy)
dd	doublet of doublets (NMR spectroscopy)
ddd	doublet of doublet of doublets (NMR spectroscopy)
dr	diastereoisomeric ratio

dt	doublet of triplets (NMR spectroscopy)
DIBAL-H	diisobutylaluminum hydride
DMAP	*N,N*-dimethyl-4-aminopyridine
DMF	*N,N*-dimethylformamide
DMS	dimethyl sulfide
ef	evaporated film (IR spectroscopy)
EI	electron impact ionization (mass spectroscopy)
equiv	equivalent(s)
Et	ethyl
EtOAc	ethyl acetate
EtOH	ethanol
Et_2O	diethyl ether (ether)
FAB-HRMS	fast atom bombardment high resolution mass spectroscopy
GC	gas chromatography
h	hour(s)
hfc	3-(heptafluoropropylhydroxymethylene)-(+)-camphorate
HMPA	hexamethylphosphoramide
HMQC	heteronuclear multiple quantum coherence spectroscopy
^{1}H NMR	proton nuclear magnetic resonance spectroscopy

HPLC	high performance liquid chromatography
HRMS	high-resolution mass spectroscopy
Hz	Hertz (cycles per second)
IC_{50}	median inhibition concentration
IR	infrared spectroscopy
J	coupling constant (NMR spectroscopy)
KBr	Potassium bromide disc (IR spectroscopy)
LDA	lithium *N,N*-diisopropylamide
lit.	literature value for a physical or spectroscopic property
m	multiplet (NMR spectroscopy)
M	molarity of a solution
M	molecular ion (mass spectroscopy)
M + H	molecular ion plus a proton (mass spectroscopy)
M + K	molecular ion plus potassium (mass spectroscopy)
M + Na	molecular ion plus sodium (mass spectroscopy)
$M - H_2O$	molecular ion minus water (mass spectroscopy)
M – OMe	molecular ion minus methoxide (mass spectroscopy)
MALDI-TOF	matrix assisted laser desorption ionization-time of flight (mass spectroscopy)
Me	methyl

MeCN	acetonitrile
Me_2CO	acetone
MeI	methyl iodide (iodomethane)
MeOH	methanol (methyl alcohol)
Me_2SO_4	dimethyl sulfate
mg	milligram
MHz	megahertz (NMR spectroscopy)
min	minute(s)
mL	millilitres
mm Hg	millimetres of mercury
mmol	millimole(s)
M.p.	melting point
mol	mole(s)
MS	mass spectroscopy
m/z	mass to charge ratio
μL	microlitre(s)
N/A	not applicable
n-BuLi	*n*-butyl lithium
NBS	*N*-bromosuccinimide

NMR	nuclear magnetic resonance spectroscopy
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
OAc	acetate
ORTEP	Oakridge thermal ellipsoid plot
PDC	pyridinium dichromate
Ph	phenyl
PhH	benzene
PhMe	toluene
ppm	parts per million (NMR spectroscopy)
PPTS	pyridinium *p*-toluenesulfonate
p-TsOH·H_2O	*p*-toluenesulfonic acid monohydrate
py	pyridine
q	quartet (NMR spectroscopy)
rel.	relative
R_f	retention factor (thin-layer chromatography)
s	singlet (NMR spectroscopy)
t	triplet (NMR spectroscopy)
TBS	*t*-butyldimethylsilyl

TBSCl	*t*-butyldimethylsilyl chloride
t-BuLi	*t*-butyl lithium
td	triplet of doublets (NMR spectroscopy)
TEA	triethylamine
Tebbe reagent	$(CH_3)_2(C_5H_5)_2CH_2AlClTi$
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
tq	triplet of quartets (NMR spectroscopy)
UV	ultra violet
v/v	volume by volume
w/v	weight by volume
w/w	weight by weight

CHAPTER ONE

Introduction to the Xyloketal Natural Products and Alboatrin

1.1 Thesis Introduction

This thesis concerns a series of novel syntheses of the seven membered xyloketal family of natural products that was isolated from a mangrove fungus of the *Xylaria* species. The chiral nonracemic and polycyclic molecular architecture of these compounds, in addition to the high symmetry of several members of the family, make these natural products attractive targets for total synthesis. In addition, several of these compounds were shown to have potent and notable biological activity. Therefore, these compounds could serve as potential lead compounds for drug discovery. Moreover, the syntheses described in this thesis should be easily adaptable for the synthesis of structural analogues for further biological evaluation. Also presented in this thesis is a novel total synthesis of the structurally related natural product alboatrin. Several racemic syntheses of this biologically active natural product have been reported in the literature to date. However, the synthesis reported herein is the first asymmetric total synthesis of the natural product.

1.2 The Xyloketal Natural Products

1.2.1 Isolation and Structural Characterization of the Xyloketal Natural Products

In 2001, Lin and co-workers reported the isolation and structural characterization of five structurally related natural products, xyloketal A (**1**), B (**2**), C (**3**), D (**4**) and E (**5**), from a South China Sea mangrove fungus of the *Xylaria* species (Figure 1.2.1.1).[1]

Subsequent to this initial report, an improved isolation procedure has been reported.[2] Moreover, Lin and co-workers have recently reported the isolation and structural characterization of two additional members of this family of natural products, xyloketal F (**6**) and G (**7**).[3,4]

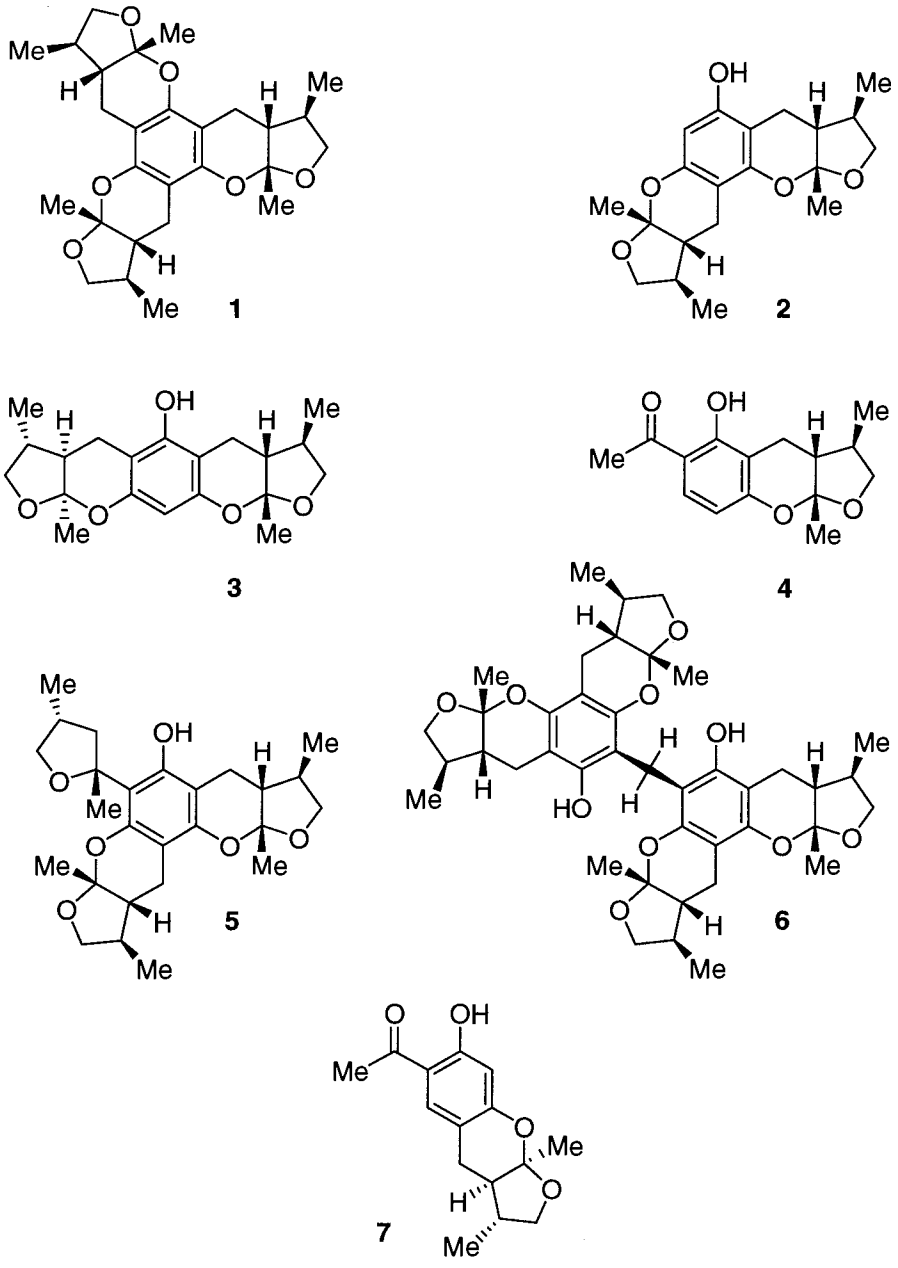


Figure 1.2.1.1 Molecular structures of xyloketal A (1), B (2), C (3), D (4), E (5), F (6) and G (7).

The molecular structures and relative stereochemistries of these natural products were determined by extensive spectroscopic studies and by X-ray crystallography. The absolute stereochemistries of xyloketal A (**1**), D (**4**), F (**6**) and G (**7**) were determined by interpretation of their CD spectra. The absolute stereochemistries of the remaining members of this family of natural products were assigned by analogy.

The xyloketals incorporate identical 5,6-bicyclic acetal moieties that are fused to an aromatic core. In all cases, the *cis*-ring junctions of the bicyclic acetals are *syn* to the methyl substituents at *C*-5 of the five-membered rings.* Xyloketal A (**1**) has a unique and remarkable C_3-symmetric molecular structure that incorporates three bicyclic acetal moieties. Xyloketal B (**2**) and the minor C_2-symmetric component, xyloketal C (**3**), incorporate two bicyclic acetal moieties. Xyloketal D (**4**) and the corresponding regioisomer, xyloketal G (**7**), are the simplest members of this family of natural products in that they only contain one bicyclic acetal moiety.

Xyloketal C (**3**) is relatively unstable as compared to the regioisomeric natural product, xyloketal B (**2**), and undergoes isomerization to afford the latter substance in solution.[1] It is reasonable to assume that this is a result of unfavourable dipole interactions which are minimized in the case of xyloketal B (**2**).

The isolation and structural characterization of xyloketal E (**5**), a derivative of xyloketal B (**2**), suggests that (4*R*)-2,4-dimethyl-4,5-dihydrofuran is a common biogenic precursor to all of these natural products. It is reasonable to conclude that this natural product is formed by a direct substitution reaction of the electron rich aromatic ring of

(*) The numbering scheme employed for the xyloketals, and analogues thereof, in this thesis is based upon that reported by Lin and co-workers (See: Ref. 1, 3 and 4).

xyloketal B (**2**) on protonation of the aforementioned dihydrofuran precursor. In addition, the semi-synthesis of the C_2-symmetric natural product, xyloketal F (**6**), from xyloketal B (**2**), on condensation with formaldehyde under acidic reaction conditions, further supports a common biogenic origin of all of these novel secondary metabolites.[3]

1.2.2 X-Ray Crystal Structures of the Xyloketals

The X-ray crystal structures of xyloketal A (**1**), C (**3**), D (**4**), E (**5**) and F (**6**) have been solved.[1,3] In the solid state, xyloketal A (**1**) adopts a bowl-shaped conformation (Figure 1.2.2.1). The other xyloketals also exhibit this puckered conformation which is presumably enforced by anomeric effects.

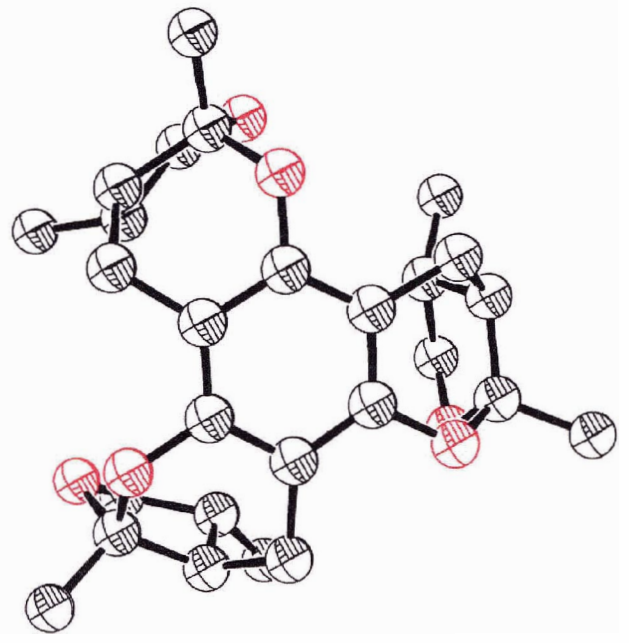


Figure 1.2.2.1 X-Ray crystal structure of xyloketal A (1) (the thermal ellipsoids are drawn at a 50% probability level and the hydrogen atoms have been omitted for clarity).

1.3 Biological Properties of the Xyloketal Natural Products

1.3.1 Acetylcholine Esterase Inhibition

During preliminary biological evaluation of the xyloketals, xyloketal A (**1**), B (**2**), C (**3**) and D (**4**) were shown to inhibit acetylcholine esterase with IC_{50} values of 29.9, 137.4, 109.3 and 425.6 μmol/L, respectively.[1,5] This enzyme is responsible for the metabolic saponification of the active neurotransmitter acetylcholine to inactive choline within the human nervous system. Patients suffering from the neurological disorder Alzheimer's disease show a depressed level of acetylcholine in their brain tissue. The only therapeutic strategy that has been shown to be widely useful in treating this disorder is to inhibit acetylcholine esterase.[6] This strategy increases the levels of acetylcholine in the brain by decreasing the metabolism of this compound at the neurotransmitter synapse and is referred to as the "cholinergic hypothesis".[7] Therefore, xyloketal A (**1**), B (**2**), C (**3**) and D (**4**) are potential lead compounds for drug discovery for the treatment of this disease.

1.3.2 L-Calcium Channel Inhibition

In subsequent biological evaluations, it was shown that xyloketal A (**1**), B (**2**) and F (**6**) block L-calcium channels by 21, 12 and 50%, respectively, at 0.03 μmol/L.[3] These channels are responsible for regulating the movement of calcium ions into and out of muscle cells. There is a high concentration of these channels in heart muscle and the movement of calcium ions is directly related to heart muscle contraction. As a result, calcium channel blockers have been widely targeted for the treatment of cardiovascular diseases such as angina and hypertension.[8] Therefore, xyloketal A (**1**), B (**2**) and F (**6**) are potential lead compounds for the treatment of various cardiovascular diseases.

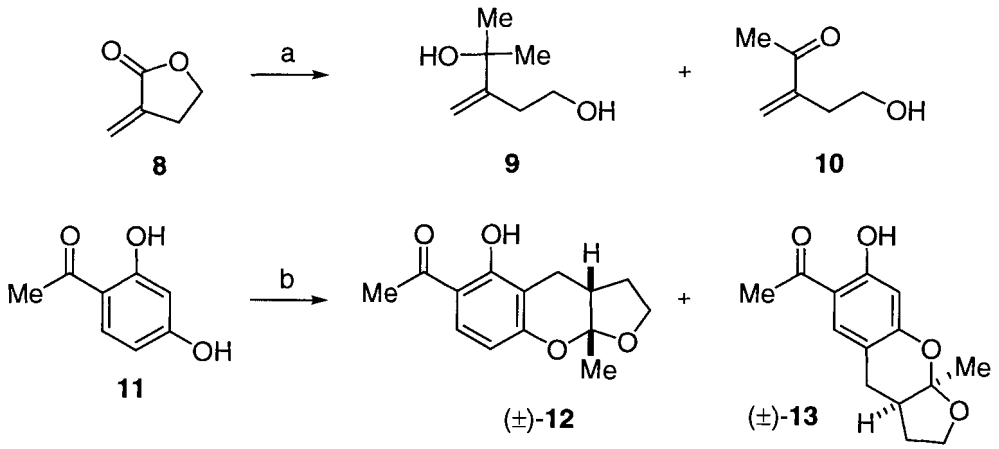
1.4 Literature Syntheses of the Xyloketal Natural Products and Analogues

Concurrent with the execution of the work described in this thesis, there have been several reports regarding the synthesis of members of the xyloketal family of natural products. A brief summary of these investigations is presented below.

1.4.1 Krohn's Synthesis of the Xyloketal D and G Analogues [(±)-12] and [(±)-13]

Krohn and co-workers have reported the synthesis of the xyloketal D analogue (±)-**12** and the xyloketal G analogue (±)-**13** (Scheme 1.4.1.1).[9]

Scheme 1.4.1.1 Krohn's Synthesis of the Xyloketal D and G Analogues [(±)-12] and [(±)-13]



Reagents and conditions: (a) MeLi, Et_2O, –30 to 0 °C, 90 min, 21% (**9**), 55% (**10**); (b) enone **10**, PhMe, reflux, 4 h, 83% [(±)-**12**], 8% [(±)-**13**].

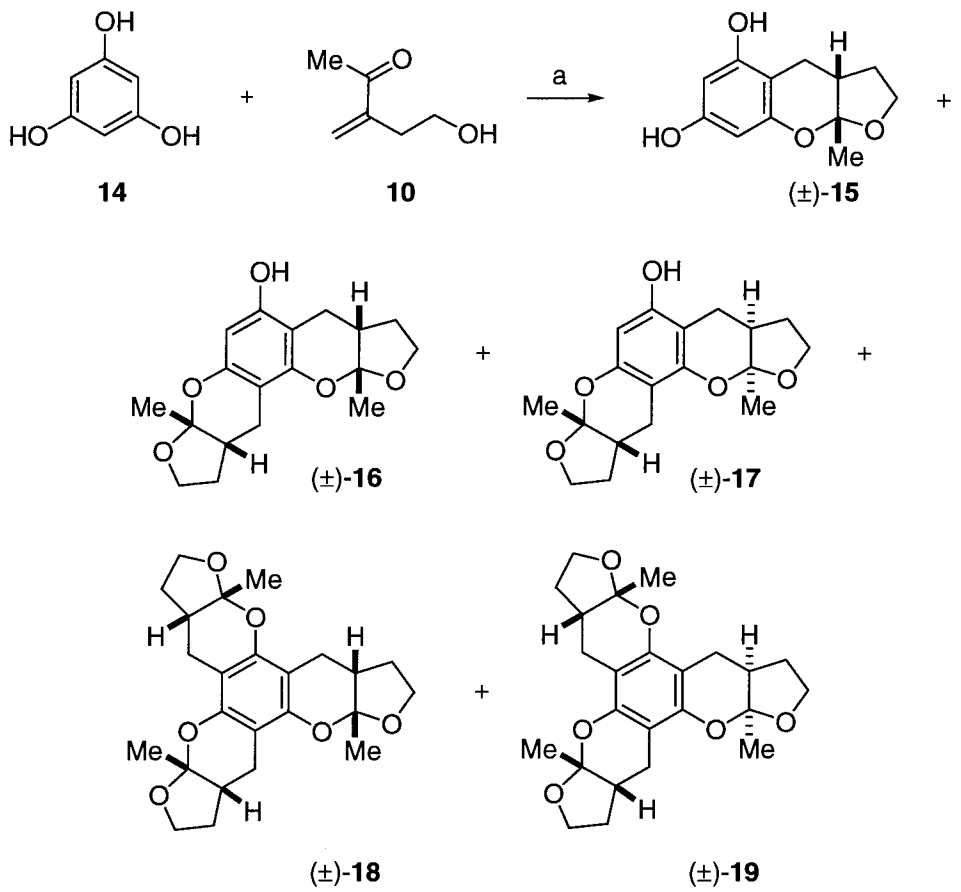
The key step in this synthesis involved a conjugate addition reaction of the 2,4-dihydroxyacetophenone (**11**) to the enone **10** followed by a spontaneous acetal formation process. The reaction was regioselective and favoured the formation of the xyloketal D analogue (±)-**12** rather than the xyloketal G analogue (±)-**13** (~10:1). In both analogues,

the *cis*-ring junction of the 5,6-bicyclic acetals was installed stereoselectively. The lactone starting material **8** was prepared in single step from commercially available butyrolactone.

1.4.2 Krohn's Synthesis of the Xyloketal A and B Analogues [(±)-18], [(±)-19], [(±)-16] and [(±)-17]

Krohn and co-workers have also extended the above reaction sequence to prepare the xyloketal A analogues (±)-**18** and (±)-**19** as well as the xyloketal B analogues (±)-**16** and (±)-**17**, from the enone **10** and 1,3,5-trihydroxybenzene [phloroglucinol (**14**)] (Scheme 1.4.2.1).[9]

Scheme 1.4.2.1 Krohn's Synthesis of the Xyloketal A and B Analogues [(±)-18], [(±)-19], [(±)-16] and [(±)-17]



Reagents and conditions: (a) Enone **10** (0.5 equiv), PhMe, reflux, 4 h, 50% [(±)-**15**], 27% [(±)-**16** and (±)-**17**], 6% [(±)-**18** and (±)-**19**] *or* enone **10** (3.0 equiv), PhMe, reflux, 4 h, 19% [(±)-**15**], 63% [(±)-**16** and (±)-**17**], 7% [(±)-**18** and (±)-**19**] *or* enone **10** (6.0 equiv), PhMe, reflux, 20 h, 7% [(±)-**15**], 22% [(±)-**16** and (±)-**17**], 58% [(±)-**18** and (±)-**19**].

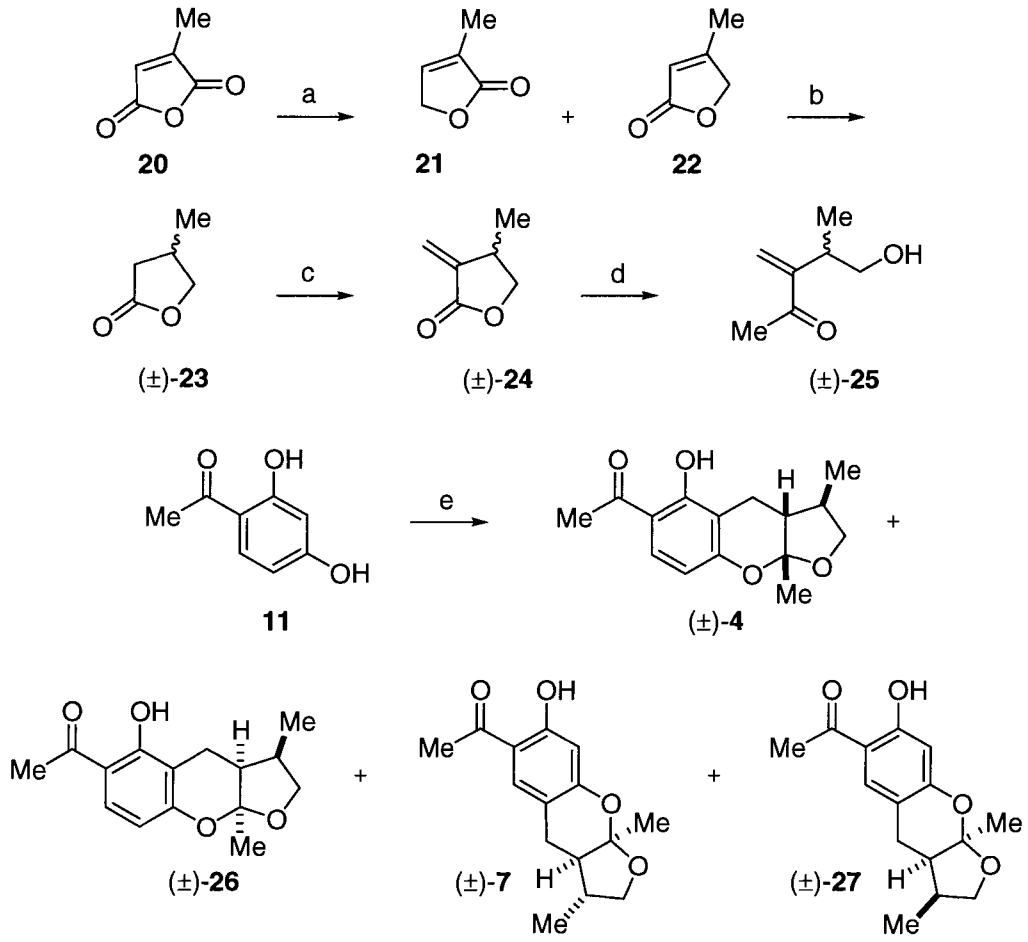
On variation of the number of equivalents of the enone **10** relative to phloroglucinol (**14**), it was found that the ratio of the resultant *mono*-, *bis*- and *tris*-adducts could be controlled. In all cases, the xyloketal B analogues (±)-**16** and (±)-**17** were isolated as an inseparable mixture (dr = 2:3) with the *syn,anti*-isomer (±)-**17** being the predominate reaction product. This product ratio varied slightly from the expected 1:1 statistical mixture. Of note, none of the regioisomeric *bis*-adducts, corresponding to the xyloketal C (**3**), were obtained. In the case of the xyloketal A analogues (±)-**18** and

(±)-**19**, an inseparable mixture (dr = 1:4) was formed. The unsymmetric *syn,syn,anti*-isomer (±)-**19** was the predominate reaction product isolated. Again, this varied to a small extent from the expected 1:3 statistical mixture.

1.4.3 Krohn's Synthesis of Racemic Xyloketal D [(±)-4] and G [(±)-7]

On completion of model studies, Krohn and co-workers synthesized the racemic enone (±)-**25** and used this material to prepare racemic xyloketal D [(±)-**4**] and G [(±)-**7**] (Scheme 1.4.3.1).[9]

Scheme 1.4.3.1 Krohn's Synthesis of Racemic Xyloketal D [(±)-4] and G [(±)-7]



Reagents and conditions: (a) $LiAlH_4$, 73% (**21**:**22**), 17:3; (b) H_2, 10% Pd/C, 72%; (c) NaH, HCO_2Et, EtOH, Et_2O, room temperature, 30 min then paraformaldehyde, Et_2O, reflux, 1 h, 63%; (d) MeLi, Et_2O, –50 to 0 °C, 90 min, 75%; (e) enone (±)-**25**, PhMe, reflux, 4h, 80%, dr = 17:3 [(±)-**4**:(±)-**26**], 9% [(±)-7:(±)-**27**].

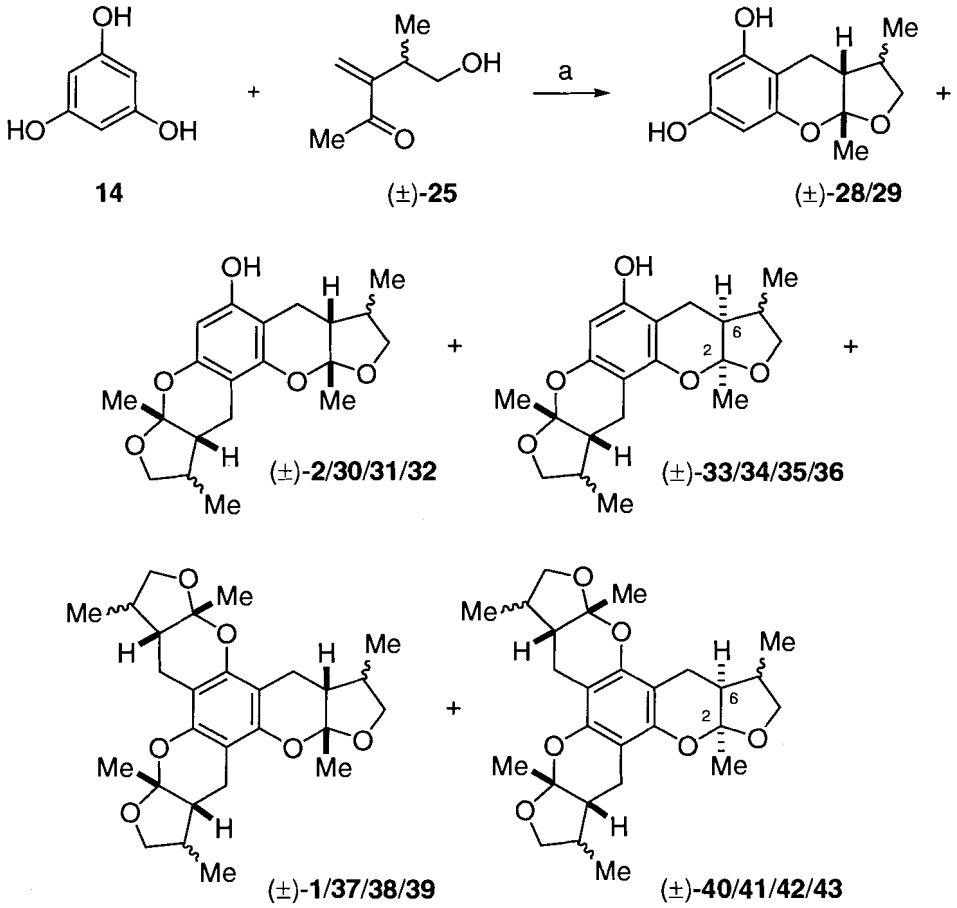
Although the four step synthesis of the enone (±)-**25** was concise the initial reduction step in this sequence led to the undesired formation of the regioisomer **21** as the major reaction product. The final step of the reaction sequence afforded xyloketal D [(±)-**4**] regioselectivity (~8:1) as had been observed with the model system. Furthermore, the bicyclic acetal moiety was *cis*-fused and good diastereoselectivity was observed relative to the stereogenic centre at *C*-5 (dr = 17:3). No comment was made on the selectivity between the formation of xyloketal G [(±)-**7**] and its epimer (±)-**27**. However,

it is reasonable to assume that a similar ratio was obtained as for that observed for xyloketal D [(±)-**4**] and its epimer (±)-**26**.

1.4.4 Krohn's Attempted Synthesis of Racemic Xyloketal A [(±)-1] and B [(±)-2]

Krohn and co-workers have also applied the above synthetic method towards the preparation of racemic xyloketal A [(±)-**1**] and B [(±)-**2**] from phloroglucinol (**14**) (Scheme 1.4.4.1).[9]

Scheme 1.4.4.1 Krohn's Attempted Synthesis of Racemic Xyloketal A [(±)-1] and B [(±)-2]



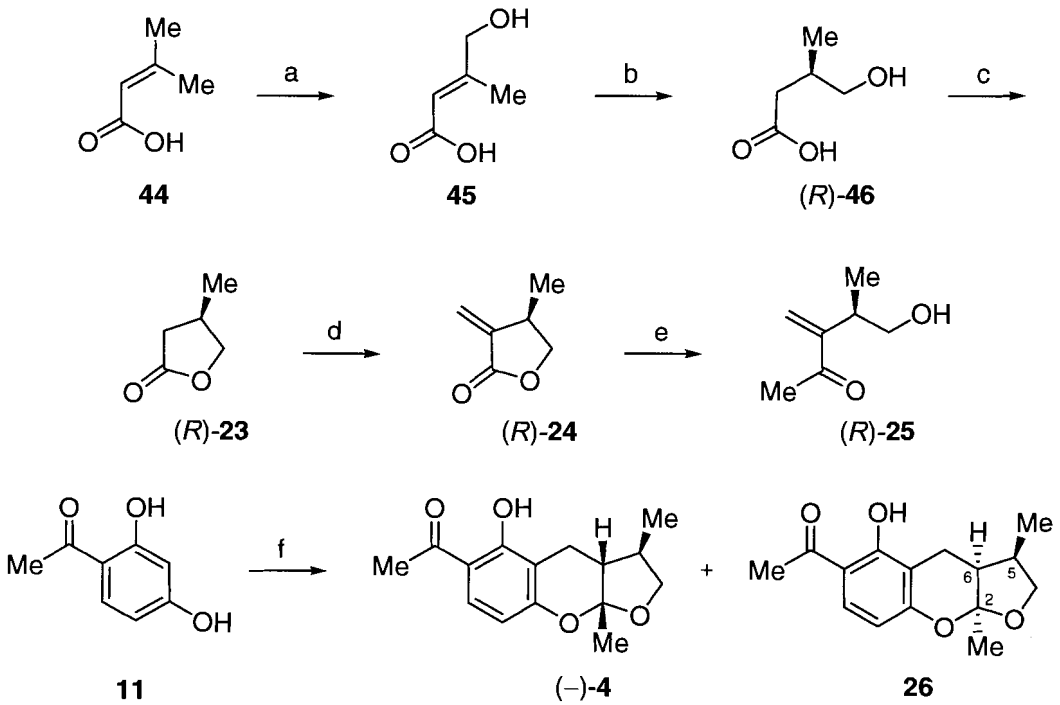
Reagents and conditions: (a) Enone (±)-**25** (1 equiv), PhMe, reflux, 4 h, 50% [(±)-**28** and (±)-**29**], 31% [(±)-**2** and (±)-**30-36**], 6% [(±)-**1** and (±)-**37-43**].

Reaction of the racemic enone (±)-**25** with phloroglucinol (**14**) afforded the *mono*-adducts (±)-**28** and (±)-**29**, the *bis*-adducts (±)-**2** and (±)-**30-36** as well as the *tris*-adducts (±)-**1** and (±)-**37-43**. The *mono*-adducts (±)-**28** and (±)-**29** were obtained as an inseparable mixture of epimers (dr = 17:3), which was similar to that observed for xyloketal D [(±)-**4**]. The *bis*-adducts (±)-**2** and (±)-**30-36** were also obtained as an inseparable mixture of eight compounds. In addition, the *tris*-adducts (±)-**1** and (±)-**37-43** were obtained in low yield (6%) and as an inseparable mixture of eight compounds.

1.4.5 Krohn's Asymmetric Synthesis of (–)-Xyloketal D [(–)-4]

Krohn and co-workers subsequently completed an asymmetric total synthesis of (–)-xyloketal D [(–)-**4**] (Scheme 1.4.5.1).[9,10]

Scheme 1.4.5.1 Krohn's Asymmetric Synthesis of (–)-Xyloketal D [(–)-4]



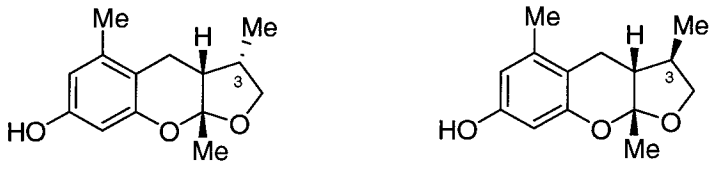
Reagents and conditions: (a) SeO_2, AcOH, reflux, 4 h, 37%; (b) H_2, (*R*)-BINAP-Ru(OAc)$_2$, MeOH, room temperature, 12 h, 100%, 93% ee; (c) HCl (aq), $CHCl_3$, reflux, 75%; (d) NaH, HCO_2Et, EtOH, Et_2O, room temperature, 30 min then paraformaldehyde, Et_2O, reflux, 1 h; (e) MeLi, Et_2O, –50 to 0 °C, 90 min, 54% (over two steps); (f) enone (*R*)-**25**, PhMe, reflux, 4 h, 81%, dr = 17:3 [(–)-**4**:**26**].

The absolute stereochemistry in this synthesis was introduced by an asymmetric hydrogenation reaction of the carboxylic acid **45** using a ruthenium/BINAP catalytic system. The resultant alcohol (*R*)-**46** was converted to the optically active lactone (*R*)-**23** which corresponded to an intermediate in the racemic synthesis discussed above. This material was then elaborated to afford (–)-xyloketal D [(–)-**4**] and the 2,6-epimer **26**, again in a 17:3 ratio. Of note, no comment was made regarding the possible formation of the optically active natural product xyloketal G (**7**).

1.5 Alboatrin

1.5.1 Isolation and Structural Characterization of Alboatrin (48)

In 1988, Ichihara and co-workers reported the isolation, structural characterization and total synthesis of the natural product alboatrin (**48**) from the fungus *Verticillium albo-atrum* (Figure 1.5.1.1).[11] The assigned structure **47** featured a 5,6-bicyclic acetal moiety that was fused to an aromatic core. At this time, the *C*-3 methyl substituent was assigned as being *anti* to the *cis*-ring junction of the bicyclic acetal.* No comment regarding the absolute stereochemistry of the natural product was made in this initial report.



Ichihara's assigned molecular structure (**47**)

Murphy's revised molecular structure (**48**)

Figure 1.5.1.1 Ichihara's assigned molecular structure (47) and Murphy's revised molecular structure (48) of alboatrin.

In 1999, Murphy and co-workers completed a total synthesis of the assigned structure of alboatrin (**47**).[12] The spectral data for their synthetic material did not match the data reported for the natural product. X-Ray crystal structure analysis of their synthetic material confirmed that the major reaction product corresponded to the structure reported by Ichihara and co-workers. However, their minor reaction product **48**, the *C*-3 epimer of the assigned structure for alboatrin (**47**), matched the spectral data of the natural product. Therefore, the molecular structure for alboatrin (**48**) was revised. Of

(*) The numbering scheme employed for alboatrin (**48**), and analogues thereof, is based upon that reported by Ichihara and co-workers (See: Ref. 11).

note, the correct molecular structure of alboatrin (**48**) incorporates an identical 5,6-bicyclic acetal moiety as to that found in the xyloketal family of natural products.

1.5.2 X-Ray Crystal Structure of Alboatrin (48)

Baldwin and co-workers have recently reported a total synthesis and X-ray crystal structure analysis of racemic alboatrin [(±)-**48**] (Figure 1.5.2.1).[13,14] Similar to the xyloketals, alboatrin (**48**) adopts a puckered conformation in the solid state.

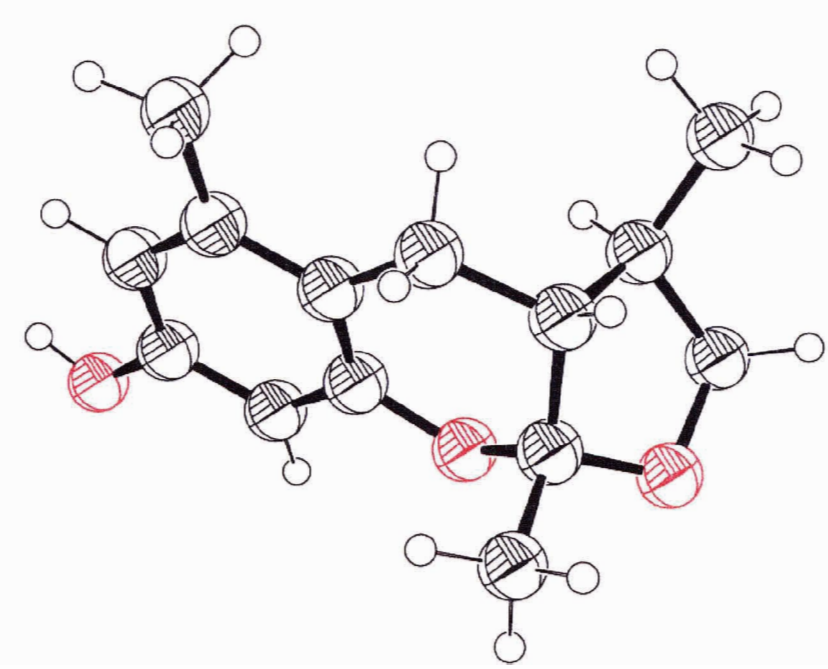


Figure 1.5.2.1 X-Ray crystal structure of alboatrin [(±)-48] (the thermal ellipsoids are drawn at a 50% probability level).

1.6 Biological Properties of Alboatrin

1.6.1 Root Growth Inhibition of Alfalfa

Alboatrin (**48**) is a phytotoxic metabolite associated with vascular-wilt disease of alfalfa.[11] It has been reported that alboatrin (**48**) inhibits the root growth of the host plant,

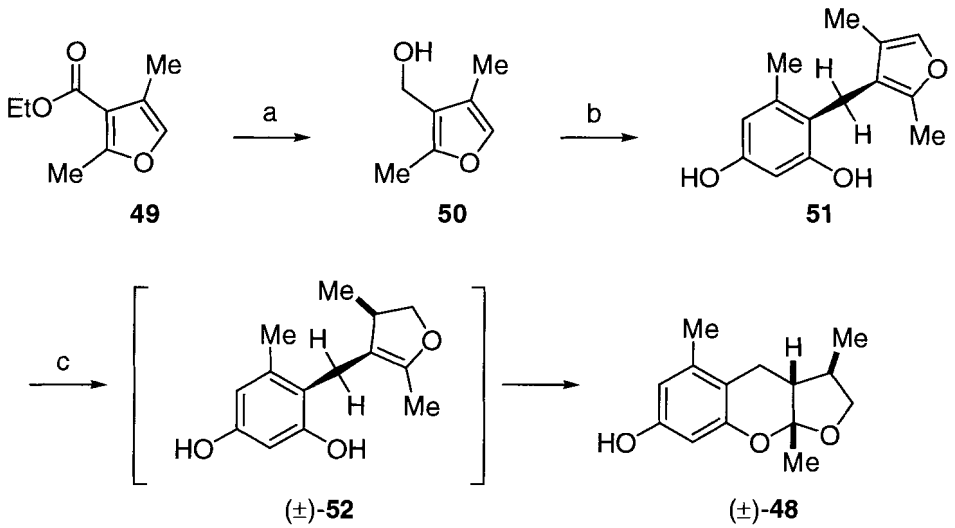
Maris Kabul, by 49% at a concentration of 50 ppm. This disease causes stunted growth, reduced quality, wilted and dead foliage as well as a reduction in life span of the plant.[15] This causes crop production to become uneconomical after two to three years in infected alfalfa fields. In addition, infected plants are more susceptible to death from environmental stresses such as the lack of precipitation and temperature.

1.7 Literature Syntheses of Alboatrin

1.7.1 Ichihara's Synthesis of Racemic Alboatrin [(±)-48]

Ichihara and co-workers described the first total synthesis of racemic alboatrin [(±)-**48**] concurrently with their report on the isolation of the natural product (Scheme 1.7.1.1).[11]

Scheme 1.7.1.1 Ichihara's Synthesis of Racemic Alboatrin [(±)-48]



Reagents and conditions: (a) $LiAlH_4$, Et_2O, 85%; (b) 1-methyl-3,5-dihydroxybenzene, $BF_3 \cdot Et_2O$, $CHCl_3$, 10%; (c) H_2, Pd/C, AcOH, 64%.

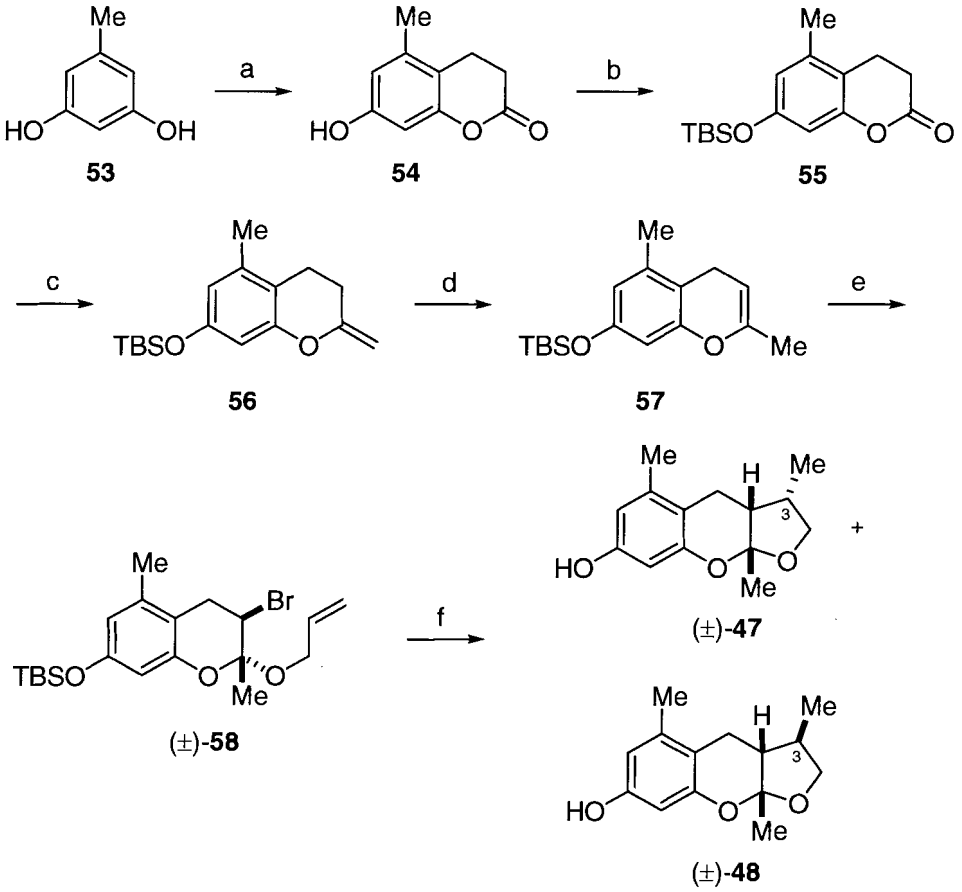
The key steps in this synthesis featured an electrophilic aromatic substitution process and a subsequent hydrogenation reaction. Presumably, the less substituted

double bond of the furan **51** was reduced selectively, based on steric factors, which led to the spontaneous formation of the bicyclic acetal moiety. The relative stereochemistry of the *C*-3 methyl substituent was *syn* to the bridgehead hydrogen atom of the acetal moiety. Of note, this racemic product was resolved by chiral HPLC to afford both enantiomers of alboatrin (**48**). The enantiomers were shown to exhibit similar biological activity.

1.7.2 Murphy's Synthesis of Racemic Alboatrin [(±)-48]

Murphy and co-workers have also reported a total synthesis of racemic alboatrin [(±)-**48**] (Scheme 1.7.2.1).[12]

Scheme 1.7.2.1 Murphy's Synthesis of Racemic Alboatrin [(±)-48]



Reagents and conditions: (a) Acrylic acid, Amberlyst 15® resin, PhMe, 4 h, 87%; (b) TBSCl, TEA, CH_2Cl_2, room temperature, 6 h, 97%; (c) Tebbe reagent, PhMe, –40 °C to room temperature, 4 h, 70%; (d) Amberlyst 15® resin, $CHCl_3$, 60 °C, 12 h, 100%; (e) allyl alcohol, NBS, CH_2Cl_2, 0 °C to room temperature, 6 h, 72%; (f) 1-ethylpiperidine hypophosphite, AIBN, PhH, 4 h, 77%, dr = 7:1 [(±)-**47**:(±)-**48**].

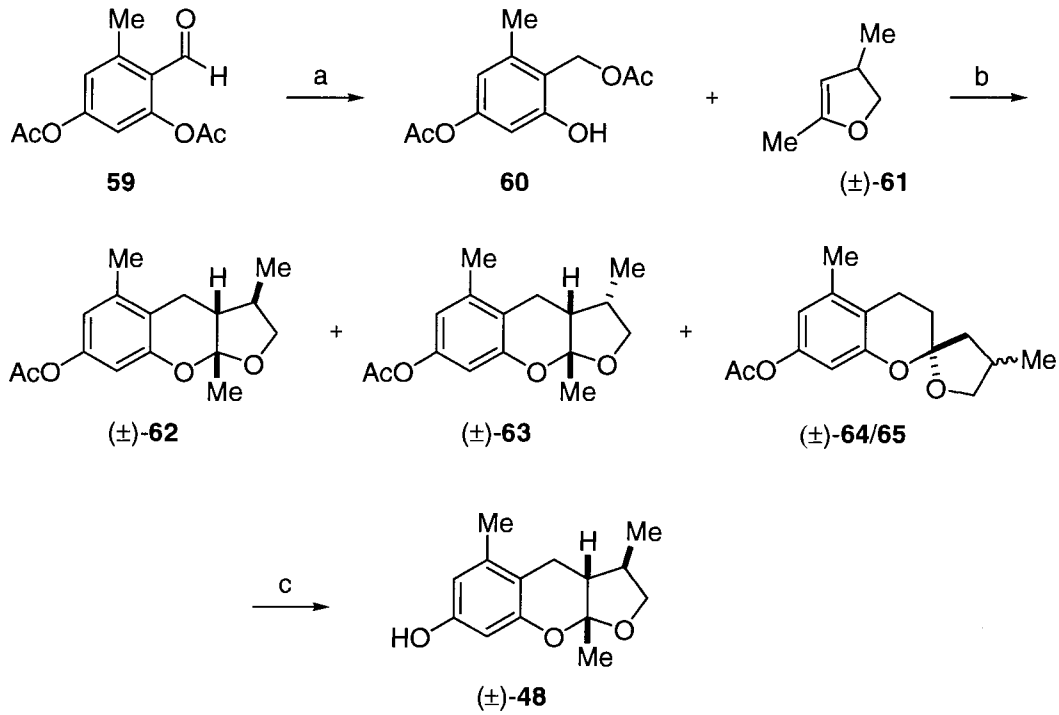
The key step in this synthesis was the use of a 1-ethylpiperidine hypophosphite-mediated radical cyclization process to install the 5,6-bicyclic acetal moiety. From the outset of this synthesis, it was expected that this reaction would afford predominately compound **47,** that was the original structure assigned to alboatrin (**48**), based on the steric arguments that are associated with 5-*exo*-trig radical cyclizations. As mentioned earlier, only on comparison of the spectral data of the major product of this reaction with

that reported for alboatrin (**48**) was it discovered that the minor reaction product corresponded to the correct molecular structure of alboatrin (**48**).

1.7.3 Baldwin's Synthesis of Racemic Alboatrin [(±)-48]

Recently, Baldwin and co-workers have reported an additional total synthesis of racemic alboatrin [(±)-**48**] (Scheme 1.7.3.1).[13,14]

Scheme 1.7.3.1 Baldwin's Synthesis of Racemic Alboatrin [(±)-48]



Reagents and conditions: (a) BH_3·DMS, THF, 0 °C to room temperature, 1 h, 84%; (b) PhH, reflux, 36 h, 68%, dr = 13:1 [(±)-**62**:(±)-**63**], 25%, dr = 3:2 [(±)-**64**:(±)-**65**]; (c) K_2CO_3, CH_2Cl_2:MeOH:H_2O (12:7:10), room temperature, 6 h, 90%.

The key step in this synthesis was an inverse electron demand hetero Diels-Alder reaction between an *ortho*-quinone methide and a dihydrofuran. This reaction proceeded in high yield and in good diastereoselectivity (dr = 13:1) for the desired reaction product (±)-**62**. However, during this key synthetic step, a substantial quantity (25%) of the

undesired spiroacetals (±)-**64** and (±)-**65** were also formed (*vide infra*). Of note, the known acetate **59** was prepared in two steps from 5-methyl-1,3-dihydroxybenzene [orcinol (**53**)]. This material was then converted to the *ortho*-quinone methide precursor **60** in a one pot reaction sequence that involved reduction of the formyl group and migration of the adjacent acetate. (±)-2,4-Dimethyl-4,5-dihydrofuran [(±)-**61**] was prepared by a four step procedure from simple precursors.

CHAPTER TWO

Towards the Synthesis of the Xyloketals: Diels-Alder Approach

2.1 Introduction

In this chapter, the application of a Diels-Alder reaction towards the synthesis of the xyloketal natural products is discussed.[†] The key feature of this synthetic route is based on the generation of *ortho*-quinone methides and subsequent reactions with appropriately functionalized dihydrofurans. Demethyl analogues of xyloketal A (**1**) and D (**4**) were prepared during the course of the optimization of appropriate reaction conditions. In addition, this synthetic route led to the completion of total syntheses of (±)-, (+)- and (–)-xyloketal D (**4**).

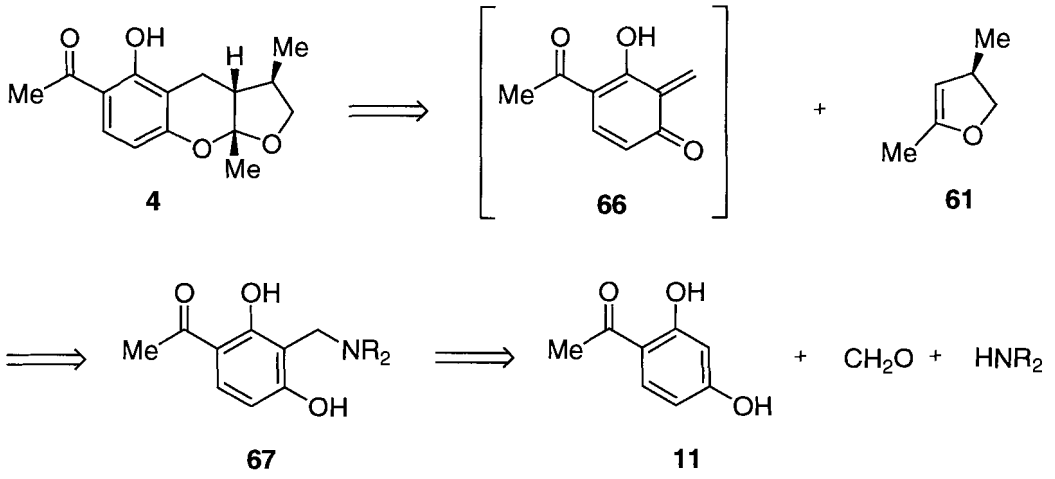
2.2 Retrosynthetic Analysis: Diels-Alder Approach

2.2.1 Retrosynthetic Analysis of Xyloketal D (4)

Retrosynthetic analysis of xyloketal D (**4**) suggested that it could be prepared by a [4+2] cycloaddition reaction of the *ortho*-quinone methide **66** and the dihydrofuran **61** (Scheme 2.2.1.1). It was anticipated that this inverse electron demand hetero Diels-Alder reaction would afford the target compound in a regio- and stereoselective manner.[16,17,18,19] There are a variety of precursors for the generation of *ortho*-quinone methides including Mannich bases.[20] The Mannich base **67** could be prepared from commercially available 2,4-dihydroxyacetophenone (**11**), a formaldehyde source and secondary amines.[21]

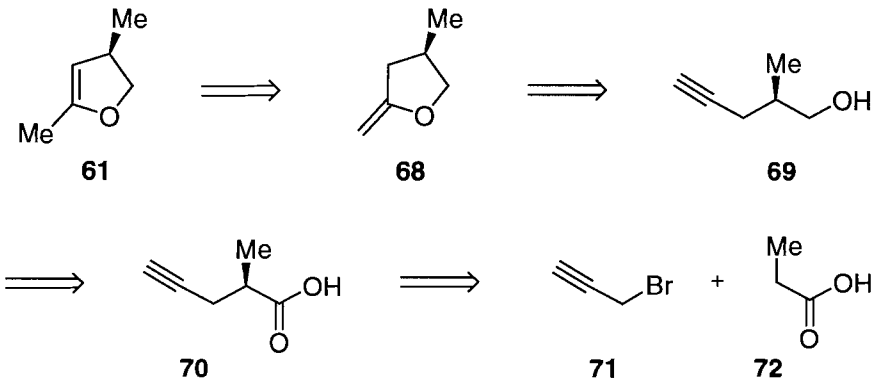
(†) The results discussed in this chapter have been reported in part, see: (a) *Total Synthesis of* (±)-*Xyloketal D and Model Studies Towards the Synthesis of* (–)-*Xyloketal A*. Pettigrew, J. D.; Bexrud, J. A.; Freeman, R. P.; Wilson, P. D. *Heterocycles* **2004**, *62*, 445; (b) *Total Synthesis of* (–)-*Xyloketal D and its Enantiomer – Confirmation of Absolute Stereochemistry*. Pettigrew, J. D.; Freeman, R. P.; Wilson, P. D. *Can. J. Chem.* **2004**, *82*, 1640.

Scheme 2.2.1.1 Retrosynthetic Analysis of Xyloketal D (4): Diels-Alder Approach



The required dihydrofuran **61** can be prepared *via* the thermal isomerization of the corresponding *exo*-cyclic double bond isomer **68** which in turn can be formed from the intramolecular 5-*exo*-dig cyclization of the alcohol **69** upon exposure to a base (Scheme 2.2.1.2).[22,23] The alcohol **69** can be prepared by reduction of the corresponding carboxylic acid **70**,[24] which in turn, is available on alkylation of the dianion of propionic acid (**72**) with propargyl bromide (**71**).[25]

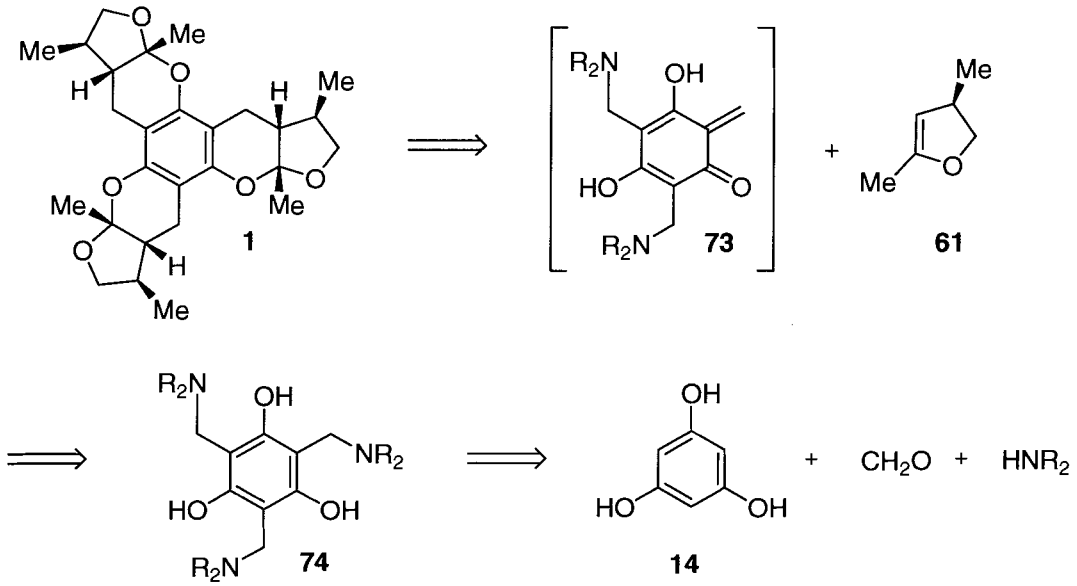
Scheme 2.2.1.2 Retrosynthetic Analysis of 2,4-Dimethyl-4,5-dihydrofuran (61)



2.2.2 Retrosynthetic Analysis of Xyloketal A (1)

In a similar fashion, it was envisioned that xyloketal A (**1**) could be prepared from the Mannich base **74** and three equivalents of the dihydrofuran **61** (Scheme 2.2.2.1). This direct synthetic process would involve the stepwise generation and subsequent cycloaddition reaction of a series of *ortho*-quinone methide reaction intermediates (*cf.* structure **73**). The Mannich base **74** could be prepared from commercially available phloroglucinol (**14**), a formaldehyde source and a secondary amine.[26,27]

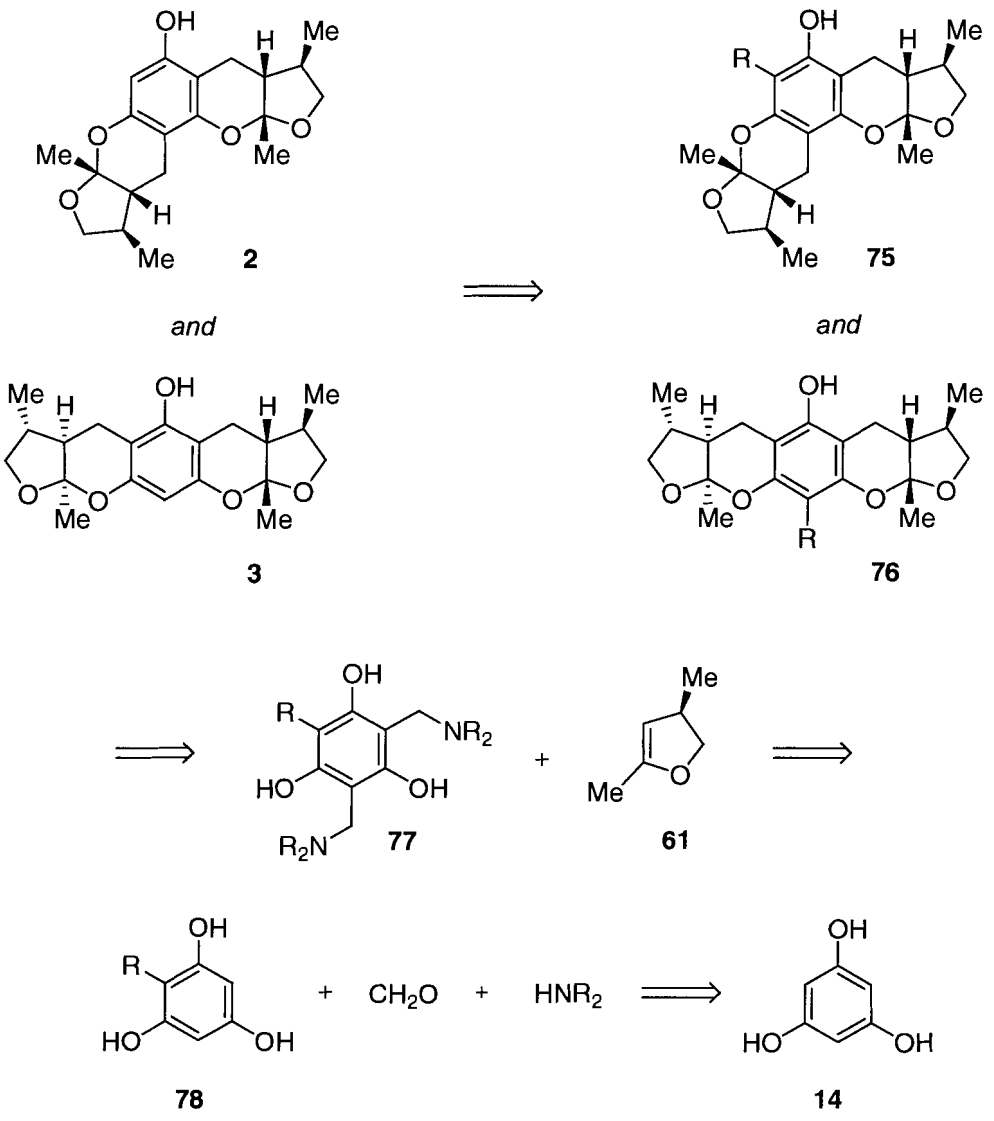
Scheme 2.2.2.1 Retrosynthetic Analysis of Xyloketal A (1): Diels-Alder Approach



2.2.3 Retrosynthetic Analysis of Xyloketal B (2) and C (3)

The application of this retrosynthetic scheme towards the synthesis of xyloketal B (**2**) and C (**3**) would require the preparation of a *bis*-Mannich base **77** (R = H) of phloroglucinol (**14**) (Scheme 2.2.3.1). It was expected that the synthesis of this compound would be difficult as the reactivity of the aromatic ring would presumably increase with an increasing number of electron donating substituents. As a result, the *bis*-adduct formed by the reaction of phloroglucinol (**14**) with two equivalents of formaldehyde and the secondary amine would be expected to react at a faster rate than phloroglucinol (**14**) or the corresponding *mono*-substituted intermediate. Therefore, it was anticipated that one of the aromatic positions of phloroglucinol (**14**) would need to be blocked (R = protecting group) with a readily removable functional group prior to the Mannich reaction. After the execution of the proposed Diels-Alder reactions, this group (R = protecting group) would then be removed to afford the desired natural products, xyloketal B (**2**) and C (**3**).

Scheme 2.2.3.1 Retrosynthetic Analysis of Xyloketal B (2) and C (3): Diels-Alder Approach

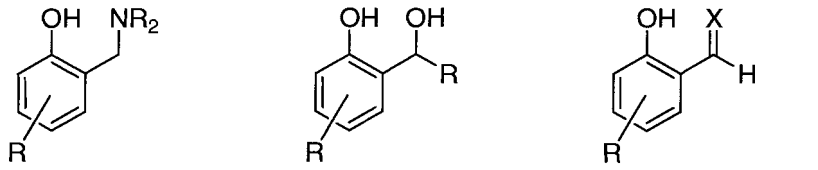


2.3 Brief Overview of *ortho*-Quinone Methide Chemistry

As the use of *ortho*-quinone methides in synthetic chemistry is not widespread, a brief overview of several of the key aspects associated with these species is presented below. More comprehensive reviews on the chemistry of *ortho*-quinone methides can be found in the chemical literature.[20,28]

2.3.1 Generation of *ortho*-Quinone Methides

The precursors used to generate *ortho*-quinone methides have a common structural motif, a phenol with a substituent in the *ortho* position that can be readily converted to an alkylidene usually by either the elimination of a leaving group or by coordination to an additive in the reaction mixture. Consequently, there are numerous ways to generate *ortho*-quinone methides. Three commonly employed precursors are *ortho*-hydroxyl Mannich bases **79**, *ortho*-hydroxyalkyl phenols **80** as well as salicylaldehydes and derivatives **81** (Figure 2.3.1.1).



79 **80** **81** (X = O, NR)

Figure 2.3.1.1 Common precursors for the generation of *ortho*-quinone methides.

When the Mannich bases **79** are used as the precursors of *ortho*-quinone methides, the amino group is generally converted into a good leaving group to facilitate the reaction. One common method for this process is an alkylation reaction of the nitrogen atom to form the corresponding ammonium salt **82** which readily undergoes an elimination reaction upon heating or on exposure to light (Figure 2.3.1.2).[29,30] Oxidation with hydrogen peroxide to generate the corresponding *N*-oxides **84**, which can undergo a thermal elimination process, has also been demonstrated.[30] In addition, it has been shown that *ortho*-quinone methides can be produced directly on photolysis of Mannich bases **79**.[31]

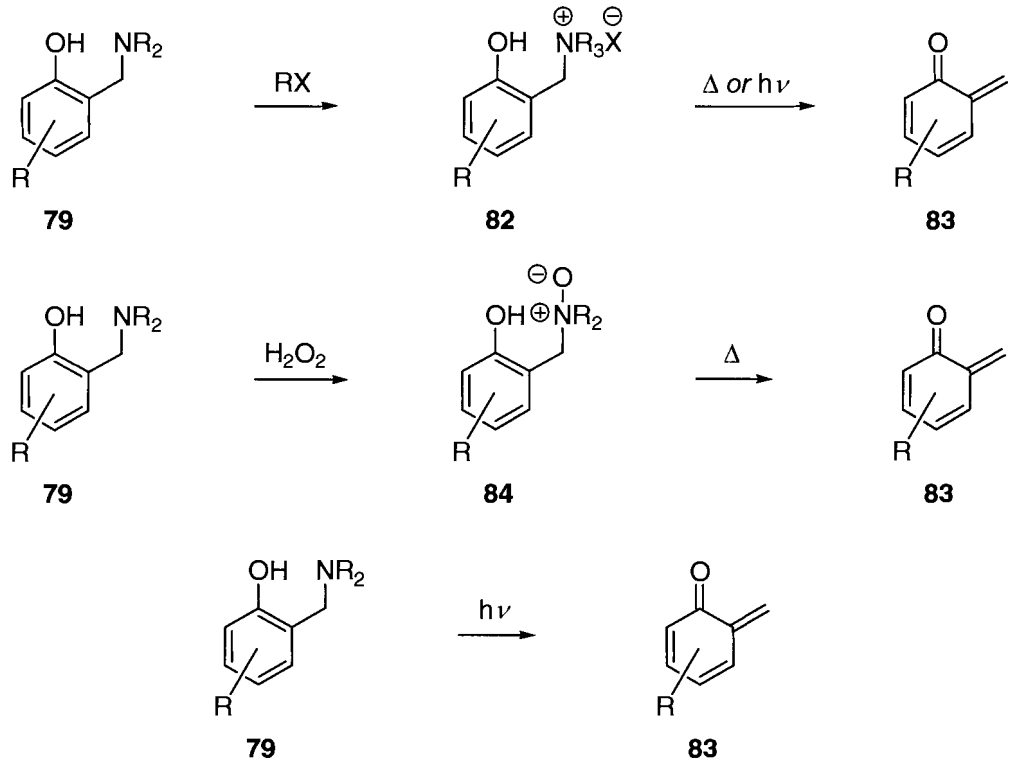


Figure 2.3.1.2 *ortho*-Quinone methide generation from Mannich bases (79).

Direct photolysis has also been used to generate *ortho*-quinone methides from *ortho*-hydroxyalkyl phenols **80** (Figure 2.3.1.3).[32] The hydroxyl group can also be chemically modified to facilitate its departure as a leaving group. For example, it has been demonstrated that the *ortho*-acetoxymethyl phenol **86** can be readily converted to an *ortho*-quinone methide upon heating.[13] In addition, cyclic borate esters **87** have been used to generate *ortho*-quinone methides under thermal or acidic conditions.[19] These types of readily available precursors allow for the introduction of substituents at the benzylic site of the *ortho*-quinone methide.

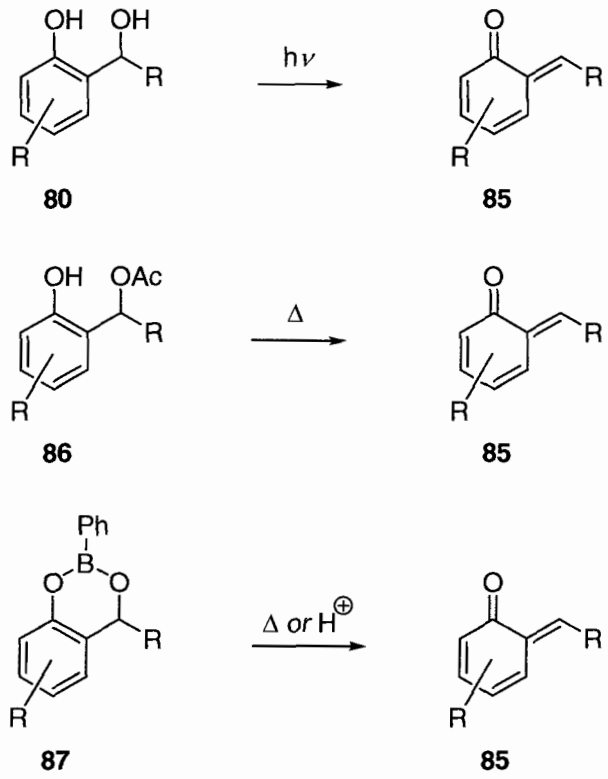


Figure 2.3.1.3 ***ortho*-Quinone methide generation from *ortho*-hydroxyalkyl phenols (80) and derivatives (86) and (89).**

It has also been reported that salicylaldehydes **88**, and derivatives thereof, can be used to generate *ortho*-quinone methides by co-ordination to additives in the reaction mixture (Figure 2.3.1.4). These additives have included both Lewis and Brønsted acids.[16,17] These types of precursors provide an additional benefit in that heteroatom substituents at the benzylic site provide a handle for further manipulations during target-oriented synthesis.

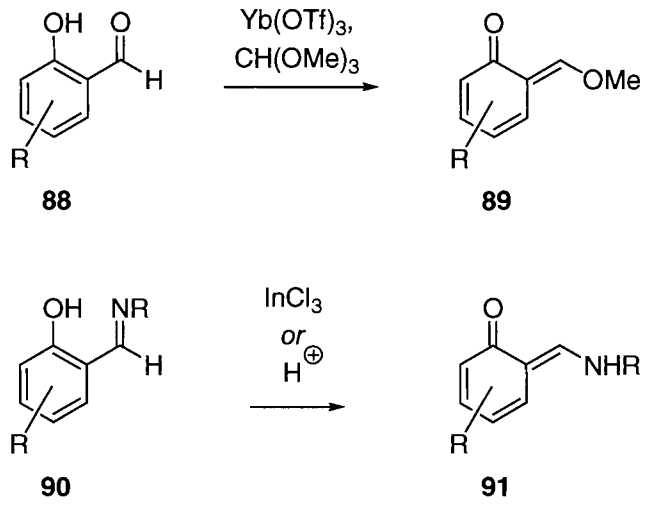
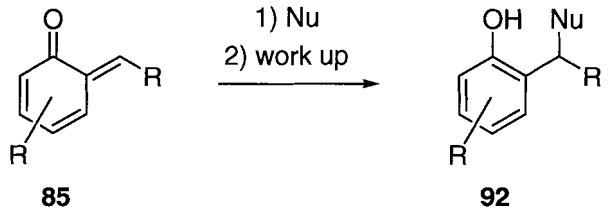


Figure 2.3.1.4 ***ortho*-Quinone methide generation from salicylaldehydes (80) and derivatives (90).**

In many cases, it has been possible to isolate the resultant *ortho*-quinone methides.[20] However, this is generally only so when the *ortho*-quinone methides are part of an extended π-system. It is more common to generate *ortho*-quinone methides *in situ* for direct use in the next step of an intended reaction sequence.

2.3.2 Reactions of *ortho*-Quinone Methides

Once generated, *ortho*-quinone methides can be utilized in a variety of reaction types. These extended π-systems are excellent acceptors of nucleophiles in 1,4/1,8-conjugate addition reactions that result in the restoration of aromaticity. A variety of nulceophiles, including carbanions,[33] nitriles,[33] amines,[29,34] alcohols,[29,34] thiols,[29] halogens[35] and phosphites,[36] have been shown to react with *ortho*-quinone methides (Figure 2.3.2.1).

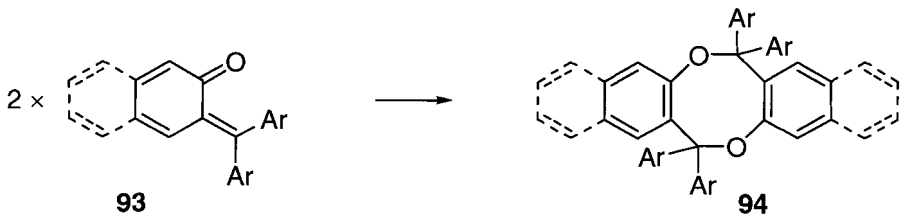


85 **92**

Nu = $R_3C^{\ominus}$, $NC^{\ominus}$, R_2NH, ROH, RSH, halogen, $P(OR)_3$

Figure 2.3.2.1 Nucleophilic addition reactions of *ortho*-quinone methides.

Of particular interest to the research described in this thesis is the extensive array of pericyclic reactions that are associated with *ortho*-quinone methides. For example, Soucek and co-workers have reported a series of net [4+4] dimerization reactions of *ortho*-quinone methides (Figure 2.3.2.2).[37]



93 **94**

Figure 2.3.2.2 Net [4+4] cycloaddition reactions of *ortho*-quinone methides.

However, the most common types of pericyclic reactions are [4+2] cycloaddition reactions and 6π electrocyclic rearrangements. *ortho*-Quinone methides are excellent dienes in inverse electron demand hetero Diels-Alder reactions. A variety of dienophiles have been employed in these reactions, including alkenes (**95**, X = alkyl, H),[38,39] enol ethers (**95**, X = OR),[16,17,31] enamines (**95**, X = NR_2),[40] dihydrofurans (**97**, n = 1)[13,14,16,17] and dihydropyrans (**97**, n = 2)[16,17] (Figure 2.3.2.3). In addition, these reactions are often highly regio- and stereoselective.

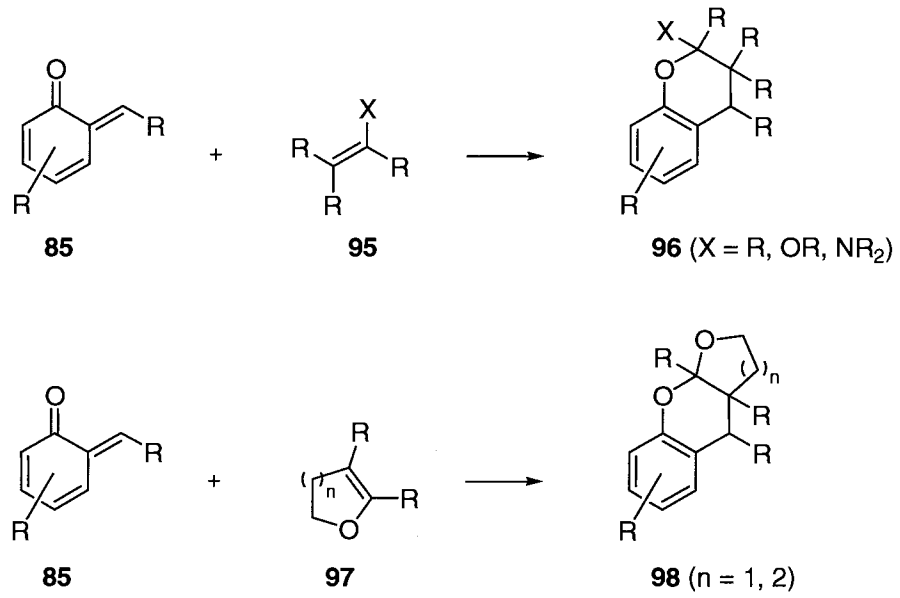


Figure 2.3.2.3 [4+2] Cycloaddition reactions of *ortho*-quinone methides.

In the absence of a suitable nucleophile or diene, certain *ortho*-quinone methides can undergo 6π electrocyclic rearrangements to form biaryl ethers **100**[41] and 2*H*-chromenes **102**[19,42,43] (Figure 2.3.2.4).

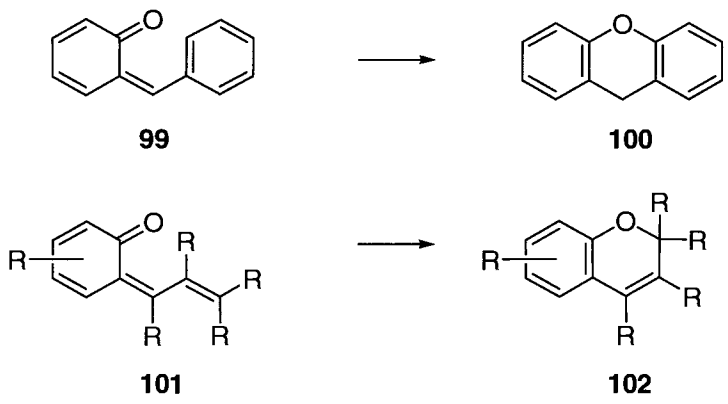


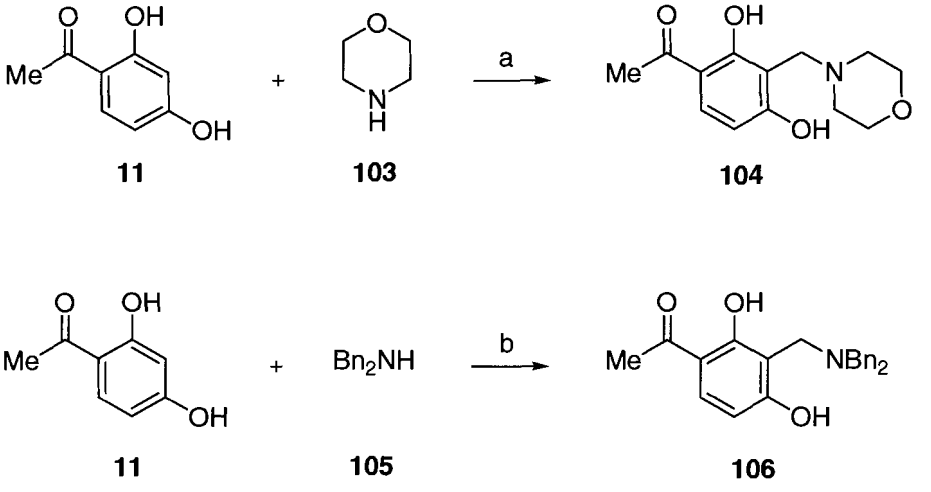
Figure 2.3.2.4 6π Electrocyclic rearrangements of *ortho*-quinone methides.

2.4 Synthesis of Mannich Bases as Precursors to *ortho*-Quinone Methides

2.4.1 Preparation of Mannich Bases for the Synthesis of Xyloketal D (4)

The synthesis of Mannich bases from 2,4-dihydroxyacetophenone (**11**), paraformaldehyde and secondary amines has been reported by Shigesmasa and co-workers.[21] Thus, the Mannich bases **104** and **106** were prepared in good yield and as single regioisomeric products by heating a solution of 2,4-dihydroxyacetophenone (**11**) and formaldehyde with morpholine (**103**) or dibenzylamine (**105**) in aqueous methanol (Scheme 2.4.1.1).

Scheme 2.4.1.1 Synthesis of Mannich Bases from 2,4-Dihydroxyacetophenone (11)



Reagents and conditions: (a) CH_2O, H_2O, MeOH, reflux, 3 h, 82%; (b) CH_2O, H_2O, MeOH, reflux, 48 h, 73%.

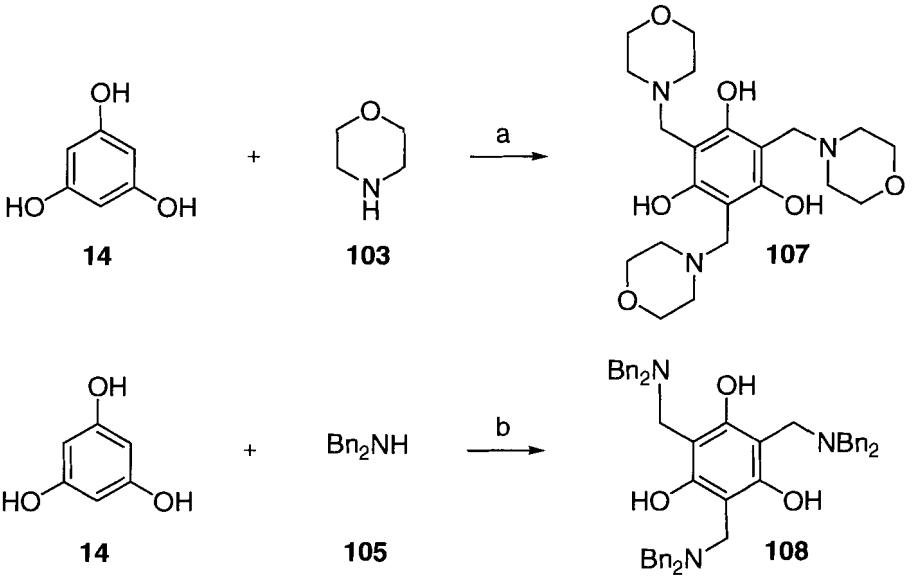
The structures of the reaction products and the regioselectivity of these aromatic substitution reactions were determined by analysis of the ^1H NMR spectra. The aromatic protons were strongly coupled ($J \sim 9$ Hz) which indicated that they were located on adjacent carbon atoms.[21] The origin of the high regioselectivity of this process is not

fully understood. However, these results are in agreement with the reported syntheses of other Mannich bases from 2,4-dihydroxyacetophenone (**11**).[21]

2.4.2 Preparation of Mannich Bases for the Synthesis of Xyloketal A (1)

Several triple Mannich bases of phloroglucinol (**14**) have been reported in the chemical literature.[26,27] The synthesis of the Mannich bases **107** and **108** proved to be exceedingly facile (Scheme 2.4.2.1). This involved the addition of an aqueous solution of formaldehyde to a solution of phloroglucinol (**14**) and the amine **103** or **105** in ethanol. Within several minutes, the reaction products **107** or **108** precipitated from the reaction mixture. The amorphous powders that were isolated were found to be analytically pure.

Scheme 2.4.2.1 Synthesis of Mannich Bases from Phloroglucinol (14)



Reagents and conditions: (a) CH_2O, H_2O, EtOH, room temperature, 18 h, 79%; (b) CH_2O, H_2O, EtOH, room temperature, 18 h, 93%.

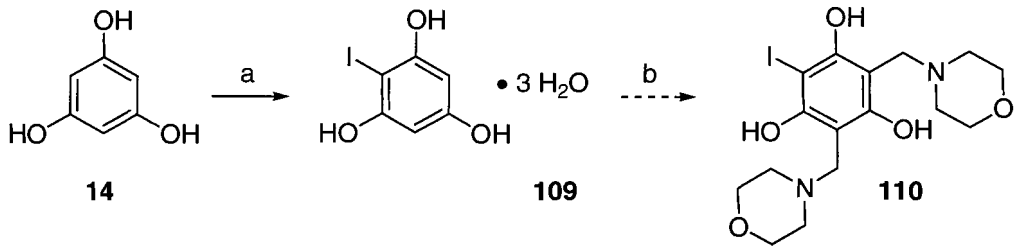
The ^1H NMR spectra of these compounds were very simple. This is a consequence of the inherent C_3-symmetry of the reaction products. The ^{13}C NMR spectra

contained two signals at approximately δ 99 and 156 ppm which corresponded to the hexasubstituted electron rich aromatic core.

2.4.3 Preparation of Mannich Bases for the Synthesis of Xyloketal B (2) and C (3)

As mentioned earlier, the direct formation of the *bis*-Mannich bases of phloroglucinol (**14**) would not be possible (See: Section 2.2.3). Thus, the synthesis of an appropriate *mono*-substituted derivative of phloroglucinol (**14**) was required. Initially, it was decided to employ an iodide substituent as a blocking group. It was anticipated that this functional group could be readily removed at a later stage of the proposed synthetic route by a variety of methods. For example, this could involve reduction with lithium aluminum hydride[44] or sodium borohydride[45] as well as by transmetallation followed by the introduction of a proton source such as water. Therefore, phloroglucinol (**14**) (1 equiv) was allowed to react with iodine (1 equiv) and sodium bicarbonate in a mixture of tetrahydrofuran and water to afford a mixture of the known *mono*- and *di*-iodides as well as the unreacted starting material **14** (Scheme 2.4.3.1).[46] The desired reaction product **109** was obtained by repetitive precipitation of the minor undesired compounds from a mixture of acetone and chloroform. Of note, this procedure afforded the trihydrate of iodophloroglucinol (**109**), as indicated by the large singlet at δ 2.94 ppm in the ^{1}H NMR spectrum.

Scheme 2.4.3.1 Attempted Synthesis of the *bis*-Mannich Base (110)

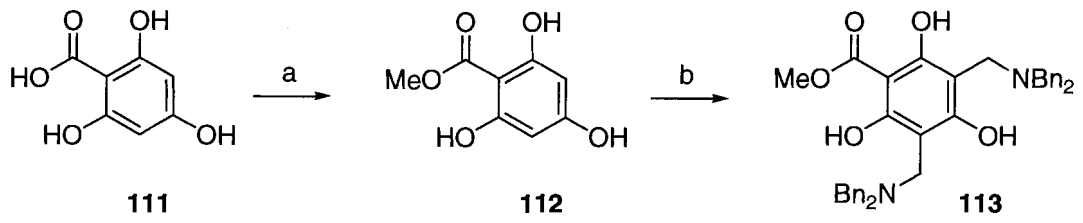


Reagents and conditions: (a) I_2, $NaHCO_3$, THF, H_2O, room temperature, 15 min, 87%; (b) morpholine (**103**), CH_2O, H_2O, EtOH, room temperature, 17 h.

Iodophloroglucinol trihydrate (**109**) was then treated with formaldehyde and morpholine (**103**) in aqueous ethanol and the resultant precipitate was isolated. Unexpectedly, this material was found to be the *tris*-Mannich base **107** of phloroglucinol (**14**) and not the desired *bis*-adduct **110**. Subsequent concentration of the filtrate afforded a complex mixture of products from which the desired Mannich base **110** could not be isolated. It was rationalized that the iodide moiety had been transferred in this reaction to afford a mixture of products of the generic formula $C_6H_3O_3I_n(CH_2NR_2)_{3-n}$, where n = 0, 1, 2 and 3. This transfer process of iodide between iodophloroglucinol (**109**), and derivatives thereof, has also been observed by other research groups.[46]

Given the above findings, an alternative blocking group was selected. It was decided to prepare a carboxylate methyl ester derivative of phloroglucinol (**14**). Of note, aromatic esters, which are located in the *ortho* or *para* positions to phenols, are known to undergo facile decarboxylation reactions on saponification.[47,48,49] Towards these ends, 2,4,6-trihydroxybenzoic acid (**111**) was allowed to react with dimethylsulfate in the presence of sodium bicarbonate to afford the methyl ester **112** according to a literature procedure (Scheme 2.4.3.2).[50]

Scheme 2.4.3.2 Synthesis of Mannich Base (113)



Reagents and conditions: (a) Me_2SO_4, $NaHCO_3$, DMF, room temperature, 6 days, 66%; (b) dibenzylamine (**105**), CH_2O, H_2O, EtOH, room temperature, 20 h, 44%.

This material was subsequently used to prepare the Mannich base **113** on reaction with formaldehyde and dibenzylamine (**105**) in aqueous ethanol. The precipitate from this reaction was impure and the filtrate contained substantial quantities of the desired reaction product **113**. Therefore, the crude reaction mixture was concentrated and the product **113** was isolated by flash chromatography.

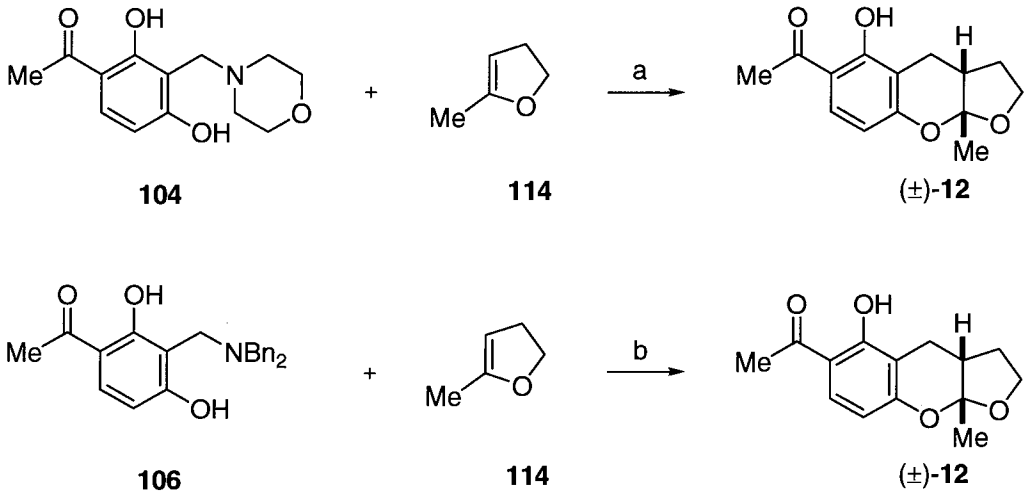
2.5 Model Studies: Diels-Alder Approach

2.5.1 Synthesis of (±)-11-Norxyloketal D [(±)-12]

In order to determine the feasibility of the proposed cycloaddition reaction for the synthesis of xyloketal D (**4**), commercially available 2-methyl-4,5-dihydrofuran (**114**) was employed as a model dieneophile. It was found on heating the Mannich base **104** (1 equiv) and the dihydrofuran **114** (3 equiv) with methyl iodide (1.05 equiv) in benzene at reflux for five days, that the xyloketal D analogue [(±)-**12**] could be isolated in 43% yield (Scheme 2.5.1.1). When the Mannich base **106** was subjected to the above reaction conditions the desired reaction product (±)-**12** was also obtained, but in slightly lower yield (38%). In addition, increasing the number of equivalents of methyl iodide employed lowered the yield of these reactions. This was caused by competing

methylation reactions of one or more of the phenol groups of the Mannich bases **104** and **106**.

Scheme 2.5.1.1 Synthesis of (±)-11-Norxyloketal D [(±)-12]: Diels-Alder Approach



Reagents and conditions: (a) MeI, PhH, reflux, 5 days, 43%; (b) MeI, PhH, reflux, 5 days, 38%.

The regioselectivity of the cycloaddition process, with respect to the two phenols, was determined on the basis of a peak at δ 13.09 ppm in the ^{1}H NMR spectrum that corresponded to the unreacted phenolic proton (Figure 2.5.1.1). This sharp downfield signal suggested that the phenol group was adjacent to the carbonyl group.[1,21]

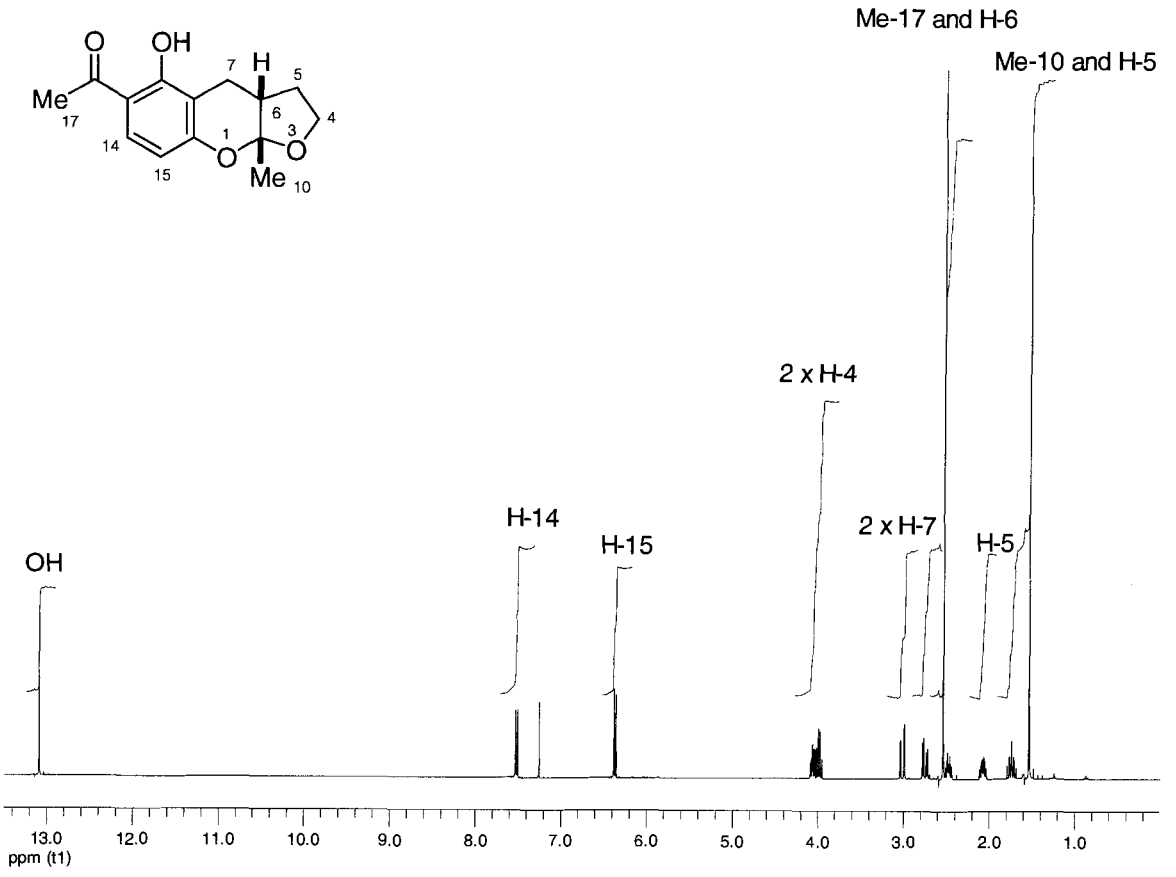


Figure 2.5.1.1 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of (±)-11-norxyloketal D [(±)-12].

The structure of the desired reaction product (±)-**12** was assigned from the COSY NMR spectrum (Figure 2.5.1.2). The multiplet at δ3.98 ppm was assigned to the protons adjacent to the acetal oxygen (*H*-4). This signal showed correlations to the two peaks that corresponded to the *H*-5 protons at δ 1.74 and 2.08 ppm. These signals were also coupled with *H*-6 at δ2.47 ppm. In addition, *H*-6 was coupled to *H*-7$_\beta$ at δ2.75 ppm and *H*-7$_\beta$ was coupled to *H*-7$_\alpha$ at δ3.02 ppm. The aromatic proton, *H*-15, was assigned to the upfield signal at δ 6.37 ppm in the aromatic region based on its *para*-relationship to the electron releasing hydroxyl group. The remaining aromatic proton at δ 7.52 ppm was

therefore assigned as *H*-14. The two methyl substituents, *Me*-10 and *Me*-17, corresponded to the signals at δ 1.54 and 2.54 ppm, respectively.

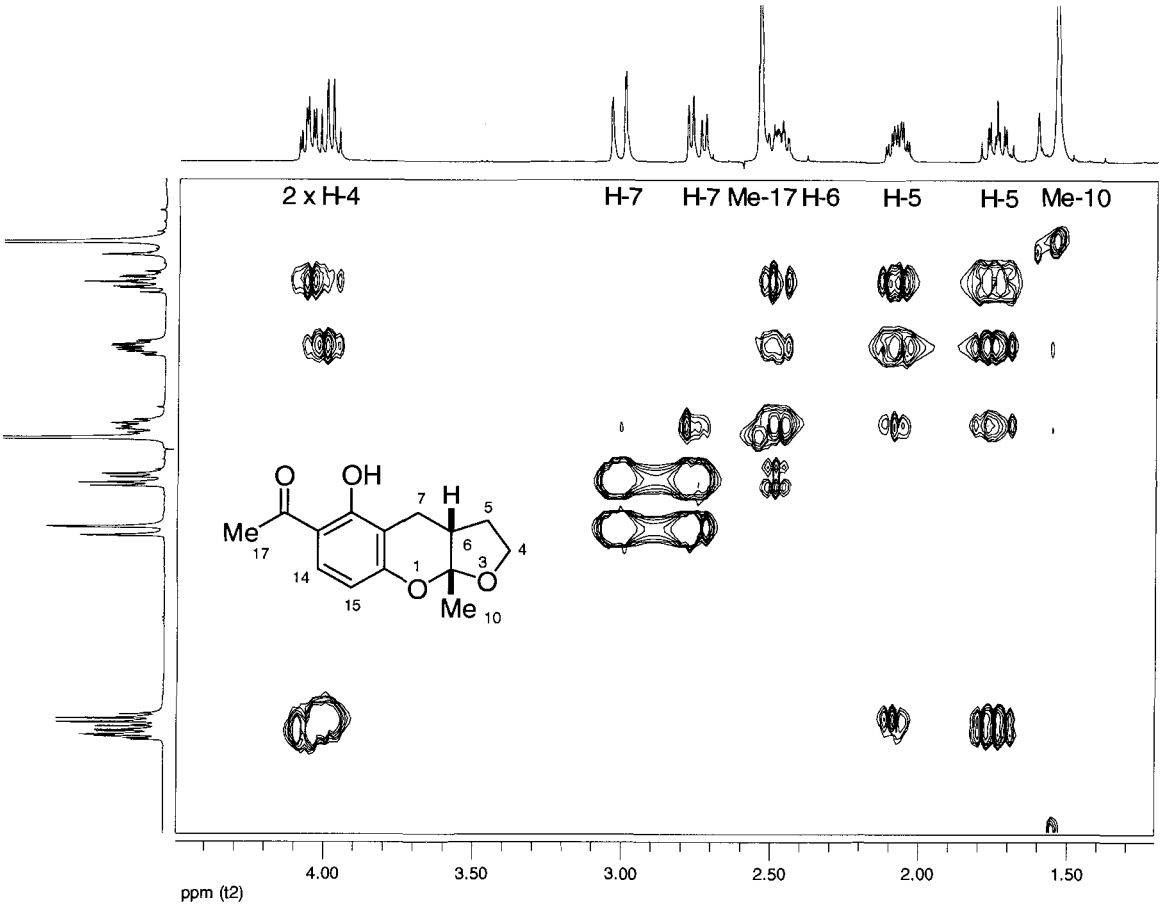


Figure 2.5.1.2 COSY NMR spectrum (400 MHz, $CDCl_3$) of (±)-11-norxyloketal D [(±)-12].

The ^{13}C NMR spectrum contained fourteen distinct signals that accounted for all of the carbons in the molecule (Figure 2.5.1.3). Furthermore, the ^{13}C NMR spectrum showed a characteristic signal that could be assigned to the acetal carbon, *C*-2, at δ 107 ppm.

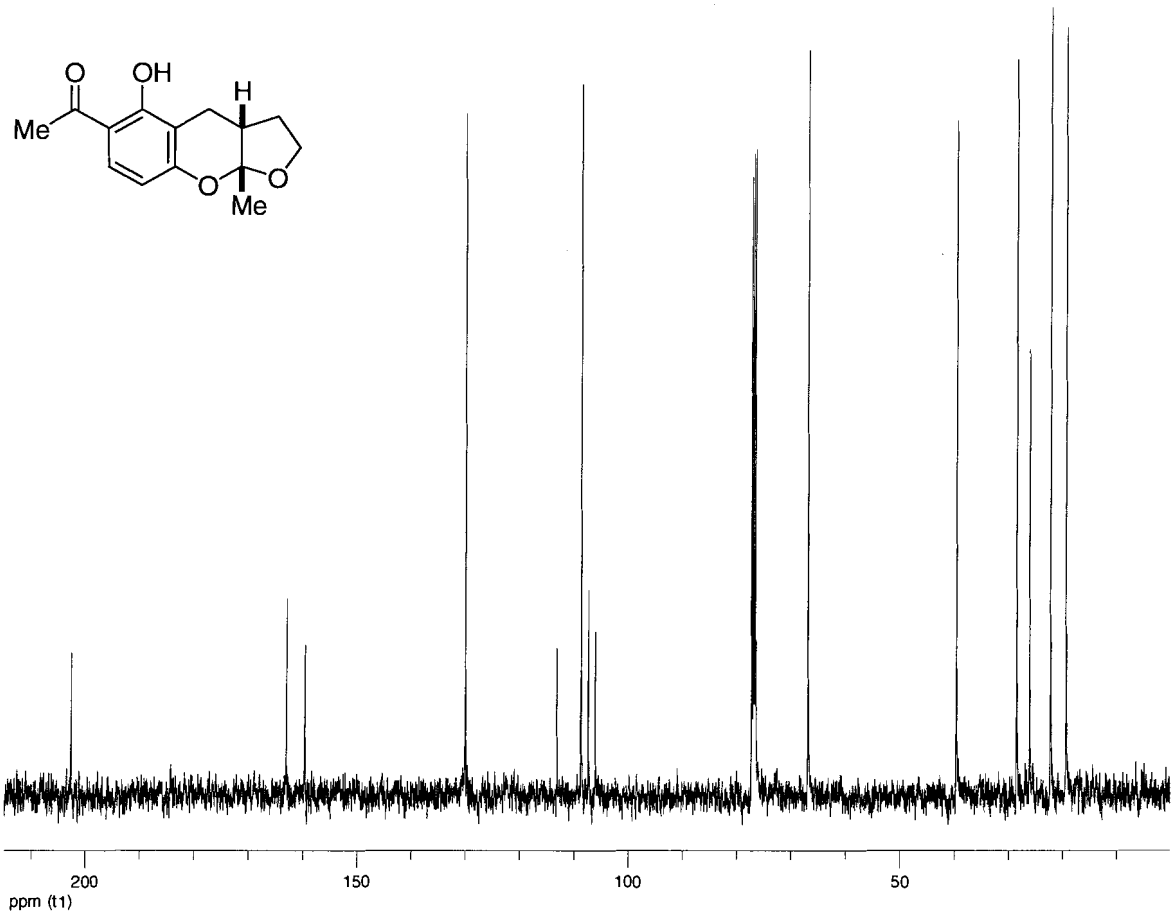
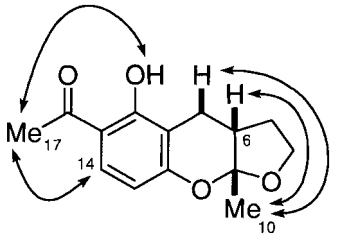


Figure 2.5.1.3 ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of (±)-11-norxyloketal D [(±)-12].

The stereochemistry of the ring junction was confirmed as being *cis* based on the observation of a nOe contact between *Me*-10 and *H*-6 (Figure 2.5.1.4). Also of note, a nOe contact was observed between the proton that had been assigned as *H*-7$_\beta$ (δ 2.75 ppm) and *Me*-10. In addition, nOe contacts were observed between *Me*-17, the O*H* and *H*-14 that confirmed the regioselectivity of the cycloaddition process and the assignment of the signals corresponding to the aromatic protons.



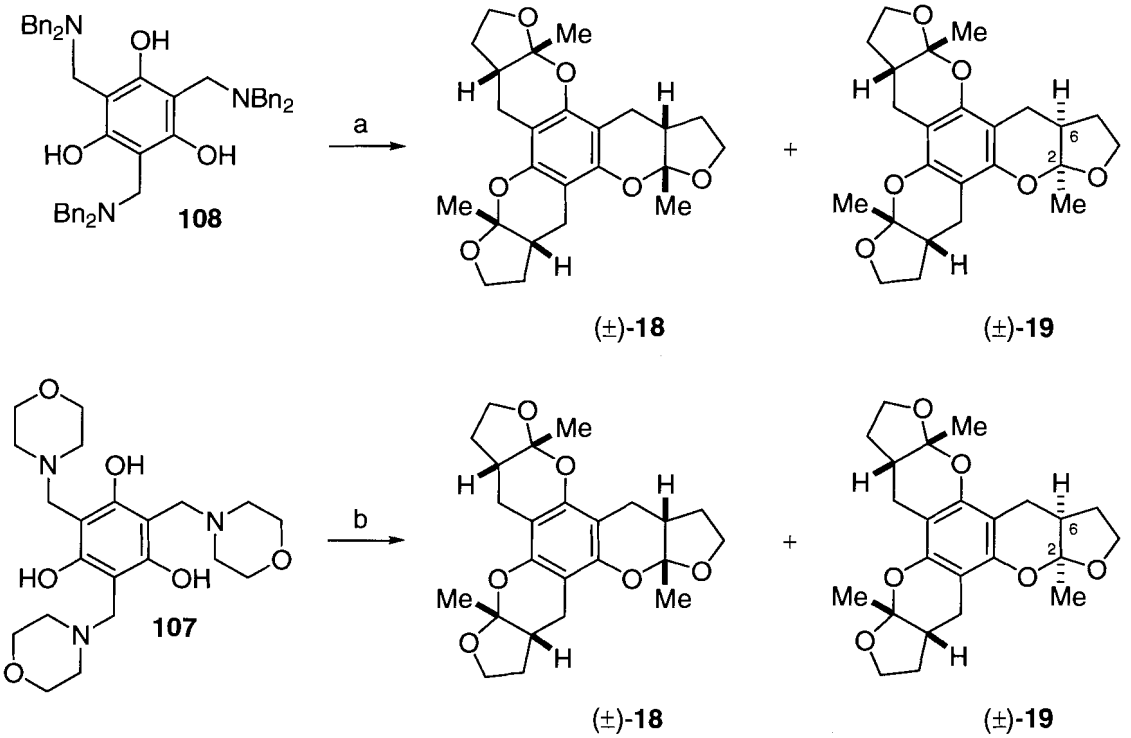
(±)-**12**

Figure 2.5.1.4 Observed nOe contacts for (±)-11-norxyloketal D [(±)-12].

2.5.2 Synthesis of (±)-11-Trinorxyloketal A [(±)-18] and (±)-2,6-*epi*-11,11',11''-Trinorxyloketal A [(±)-19].

The feasibility of using this cycloaddition strategy to prepare xyloketal A (**1**) was then demonstrated successfully in a model study (Scheme 2.5.2.1). A mixture of the Mannich base **108** (1 equiv), 2-methyl-4,5-dihydrofuran (**114**) (9 equiv) and methyl iodide (3 equiv) was heated at reflux for 24 h to afford an inseparable mixture (dr = 1:4) of the desired C_3-symmetric xyloketal A analogue (±)-**18** and the unsymmetric diastereoisomer (±)-**19** in 19% yield. The use of Mannich base **107** as the *ortho*-quinone methide precursor also afforded the desired reaction products (±)-**18** and (±)-**19** although in a slightly lower yield (14%).

Scheme 2.5.2.1 Synthesis of (±)-11-Trinorxyloketal A [(±)-18] and (±)-2,6-*epi*-11,11',11''-Trinorxyloketal A [(±)-19]: Diels-Alder Approach



Reagents and conditions: (a) 2-Methyl-4,5-dihydrofuran (**114**) (9 equiv), MeI (3 equiv), PhH, reflux, 24 h, 19%, dr = 1:4 [(±)-**18**:(±)-**19**]; (b) 2-methyl-4,5-dihydrofuran (**114**) (9 equiv), MeI (3 equiv), PhH, reflux, 24 h, 14%, dr = 1:4 [(±)-**18**:(±)-**19**].

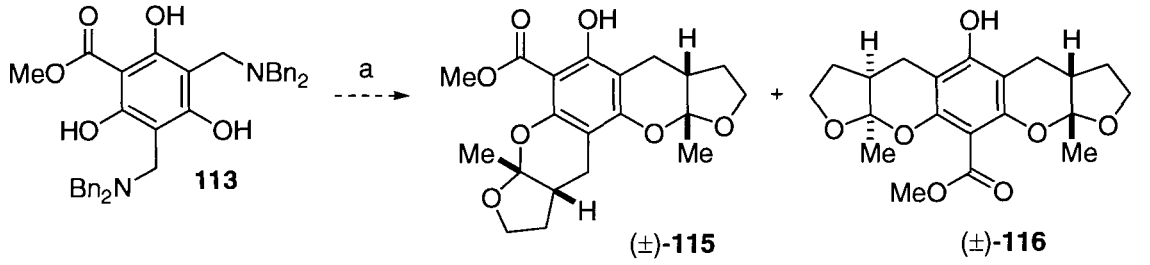
This mixture of compounds was fully characterized by spectroscopic methods. The ^{1}H NMR spectrum of the mixture showed four signals corresponding to *Me*-10 [one from the C_3-symmetric analogue (±)-**18** and three from the diastereoisomer (±)-**19**]. The relative intensities of these signals were used to determine the product ratio. The ^{13}C NMR spectrum also showed groups of either three or four signals corresponding to the C_3-symmetric isomer (±)-**18** and the unsymmetric isomer (±)-**19.** Of note, the mass spectrum (CI) contained the parent molecular ion (M + H) at 415 amu as well as daughter ions that could be attributed to fragmentation by *retro* Diels-Alder reactions. In addition, a large signal for an ion that corresponded to the dihydrofuran **114** was also observed.

The yield of this reaction (19%), although low, is indeed respectable when one considers that this direct process involves nine individual reactions (three alkylation reactions, three elimination reactions and three subsequent cycloaddition reactions). Furthermore, it was anticipated that the *C*-4 methyl substituent of the dihydrofuran **61** required to prepare xyloketal A (**1**) would control the diastereoselectivity of the proposed reaction in an absolute sense.

2.5.3 Attempted Synthesis of the Xyloketal B and C Analogues [(±)-115] and [(±)-116]

In a similar manner to that described previously for the synthesis of the xyloketal D analogue (±)-**12** and the xyloketal A analogues (±)-**18** and (±)-**19**, the Mannich base **113** (1 equiv) was allowed to react with the dihydrofuran **114** (6 equiv) and methyl iodide (2 equiv) in benzene at reflux for 24 h (Scheme 2.5.3.1). However, in this instance, a complex mixture of reaction products was obtained from which the desired reaction products (±)-**115** and (±)-**116** could not be isolated despite extensive chromatographic efforts.

Scheme 2.5.3.1 Attempted Synthesis of the Methyl Esters [(±)-115] and [(±)-116]: Diels-Alder Approach



Reagents and conditions: (a) 2-Methyl-4,5-dihydrofuran (**114**) (6 equiv), MeI (2 equiv), PhH, reflux, 24 h.

On the basis of this result, the application of the Mannich base **113** in the synthesis of xyloketal B (**2**) and C (**3**) was not investigated.

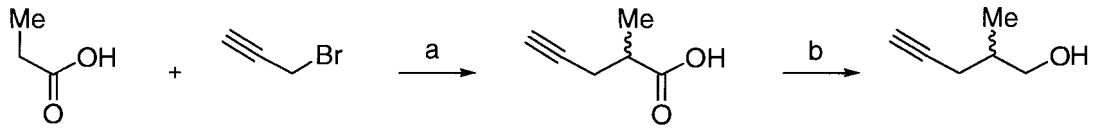
2.6 Synthesis of Racemic 2,4-Dimethyl-4,5-dihydrofuran

In order to undertake the total synthesis of the xyloketal natural products, the synthesis of the known racemic dihydrofuran (±)-**61** was accomplished by adaptation of literature procedures.

2.6.1 Preparation of Racemic 2,4-Dimethyl-4,5-dihydrofuran [(±)-61] Based on Literature Procedures

The synthesis of the dihydrofuran (±)-**61** began from propionic acid (**72**) and propargyl bromide (**71**). This involved generation of the corresponding dianion of propionic acid (**72**) with excess lithium *N,N*-diisopropylamide (2.3 equiv) in a mixture of hexamethylphosphoramide and tetrahydrofuran (Scheme 2.6.1.1). This dianion was then treated with propargyl bromide (**71**) (1.2 equiv) to afford the desired product (±)-**70** in good yield (68%).[25] This acid was subsequently reduced to the corresponding acetylenic alcohol (±)-**69** with lithium aluminum hydride.[24]

Scheme 2.6.1.1 Synthesis of the Alcohol [(±)-69] from Propionic Acid (72) and Propargyl Bromide (71)

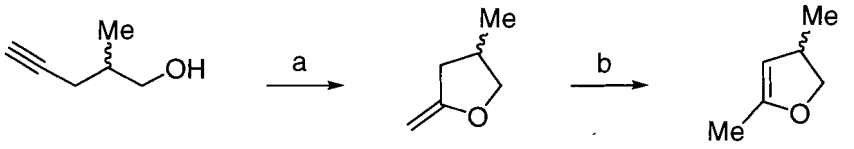


72 **71** (±)-**70** (±)-**69**

Reagents and conditions: (a) LDA, HMPA, THF, 0 °C to room temperature, 1 h then propargyl bromide (**71**), 0 °C to room temperature, 3 h, 68%; (b) $LiAlH_4$, THF, 0 °C to room temperature, 16 h, 82%.

The alcohol (±)-**69** was then heated at reflux with a substoichiometric amount of sodium amide (Scheme 2.6.1.2).[22,23] This induced a 5-*exo*-dig cyclization to afford the exocyclic dihydrofuran (±)-**68** which was isomerized to the desired 2,4-dimethyl-4,5-dihyrofuran [(±)-**61**] upon heating at reflux (~100 °C) in the absence of solvent.

Scheme 2.6.1.2 Synthesis of (±)-2,4-Dimethyl-4,5-dihydrofuran [(±)-61] from the Alcohol [(±)-69]



(±)-**69** (±)-**68** (±)-**61**

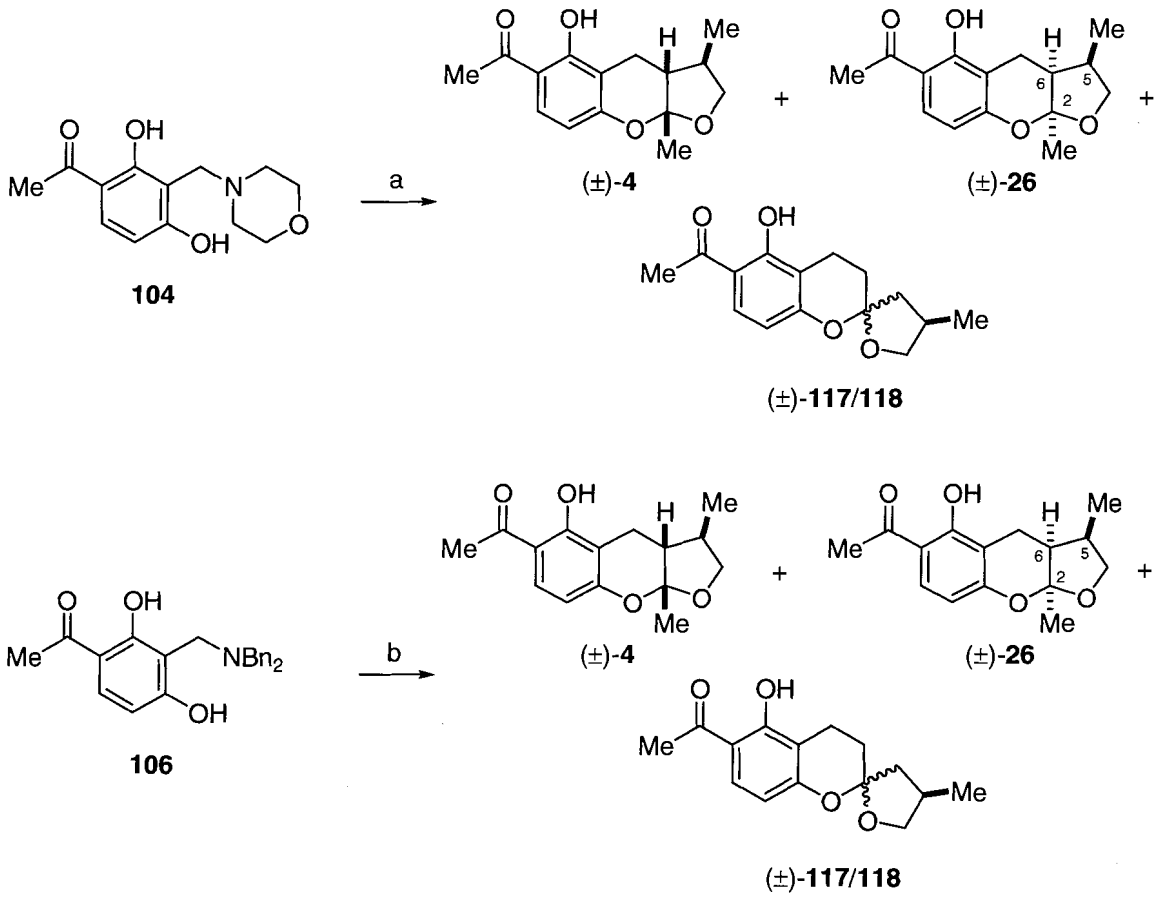
Reagents and conditions: (a) $NaNH_2$ (cat.), reflux, 2 h, 66 %; (b) reflux, 16 h, 87%.

2.7 Total Synthesis of Racemic Xyloketals: Diels-Alder Approach

2.7.1 Total Synthesis of (±)-Xyloketal D [(±)-4]

The cycloaddition reaction of the Mannich base **104** (1 equiv) with the dihydrofuran (±)-**61** (3 equiv) as described in the model studies afforded (±)-xyloketal D [(±)-**4**] and (±)-2,6-*epi*-xyloketal D [(±)-**26**] as well as the diastereoisomeric spiroacetals (±)-**117** and (±)-**118** as a mixture of products (11:1:3:3) in a combined yield of 54% (Scheme 2.7.1.1). Similar to the results observed in the model studies, the use of Mannich base **106** afforded these reaction products in a slightly lower combined yield (47%).

Scheme 2.7.1.1 Synthesis of (±)-Xyloketal D [(±)-4]: Diels-Alder Approach



Reagents and conditions: (a) (±)-2,4-Dimethyl-4,5-dihydrofuran [(±)-**61**] (3 equiv), MeI (1.05 equiv), PhH, reflux, 5 days, 54%, 11:1:3:3 [(±)-**4**:(±)-**26**:(±)-**117**:(±)-**118**]; (b) (±)-2,4-dimethyl-4,5-dihydrofuran [(±)-**61**] (3 equiv), MeI (1.05 equiv), PhH, reflux, 5 days, 47%, 11:1:3:3 [(±)-**4**:(±)-**26**:(±)-**117**:(±)-**118**].

It was possible to separate these reaction products by repetitive chromatography and the spectral data (^{1}H and ^{13}C NMR) for synthetic (±)-xyloketal D [(±)-**4**] were in agreement with those reported for the natural product (Figure 2.7.1.1).[1] Of note, the ^{1}H NMR signal of natural (–)-xyloketal D [(–)-**4**] centred at δ 2.15 ppm should have been

reported at δ 2.08 ppm.* Thus, the relative stereochemistry of the expected major reaction product was firmly established.

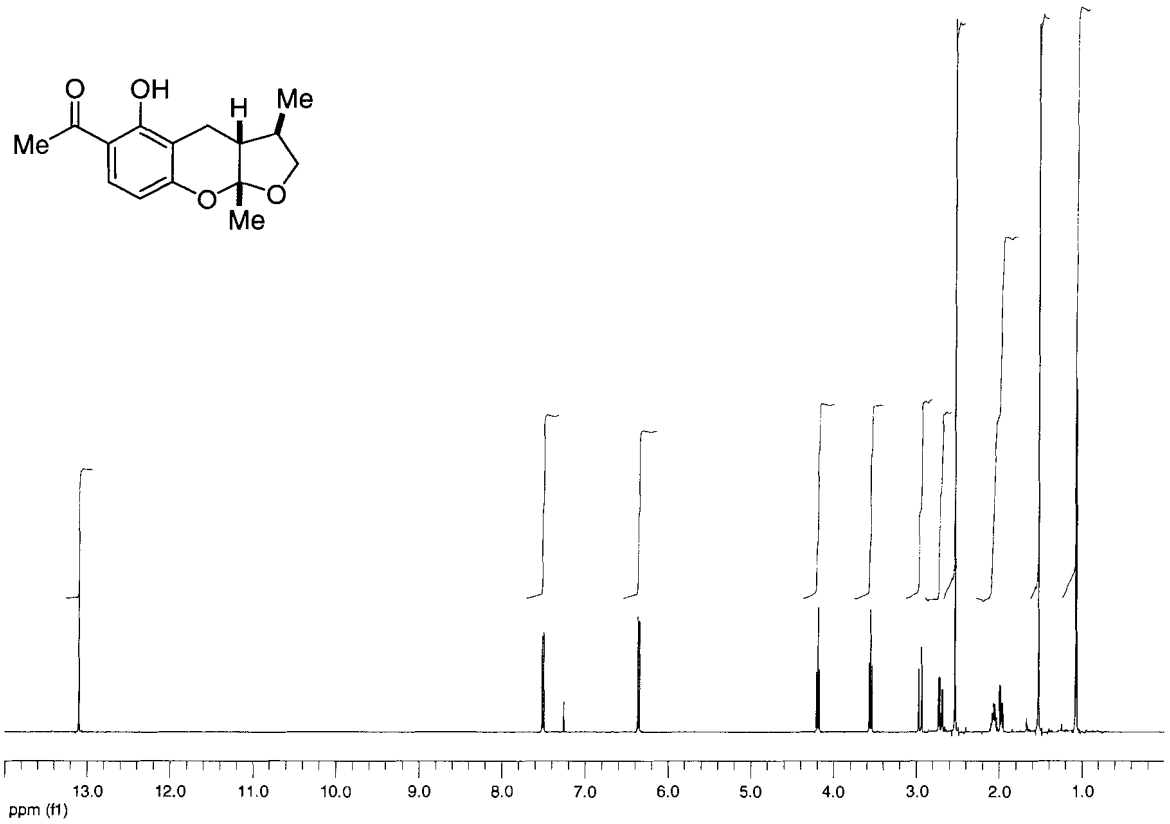


Figure 2.7.1.1 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of (±)-xyloketal D [(±)-4].

The formation of the spiroacetal by-products (±)-**117** and (±)-**118** in this reaction was attributed to the isomerization of the double bond of the dihydrofuran (±)-**61** to afford the corresponding exocyclic double bond isomer (±)-**68** which then underwent a subsequent Diels-Alder reaction.** It is of interest that a spiroacetal by-product was not identified in the cycloaddition reaction of 2-methyl-4,5-dihydrofuran (**114**). Thus, it

(*) Professor Lin kindly provided the ^{1}H and ^{13}C NMR spectra of the xyloketal D (**4**) for comparison purposes.

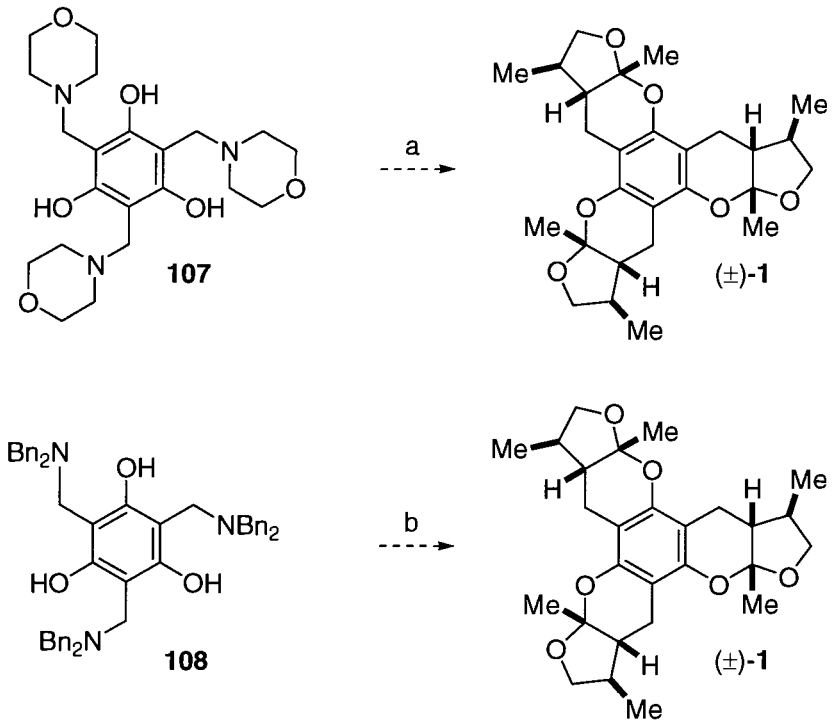
(**) Baldwin and co-workers have subsequently applied a similar synthetic approach towards the total synthesis of alboatrin (**48**) and have also observed the formation of undesired spiroacetal reaction products by a similar process (See: Ref. 13 and 14).

appears that the additional methyl substituent decreases the reactivity of the endocyclic double bond of the dihydrofuran (±)-**61** in this cycloaddition reaction, possibly as a result of steric hindrance.

2.7.2 Attempted Synthesis of (±)-Xyloketal A [(±)-1]

The cycloaddition reactions of the Mannich bases **107** and **108** (1 equiv) with the dihydrofuran (±)-**61** (9 equiv) to prepare (±)-xyloketal A [(±)-**1**] were attempted (Scheme 2.7.2.1). However, these reactions afforded highly complex mixtures of products from which the desired product (±)-**1** could not be isolated.

Scheme 2.7.2.1 Attempted Synthesis of (±)-Xyloketal A [(±)-1]: Diels-Alder Approach



Reagents and conditions: (a) (±)-2,4-Dimethyl-4,5-dihydrofuran [(±)-**61**] (9 equiv), MeI (3 equiv), PhH, reflux, 24 h; (b) (±)-2,4-dimethyl-4,5-dihydrofuran [(±)-**61**] (9 equiv), MeI (3 equiv), PhH, reflux, 24 h.

2.8 Synthesis of Chiral Nonracemic 2,4-Dimethyl-4,5-dihydrofuran

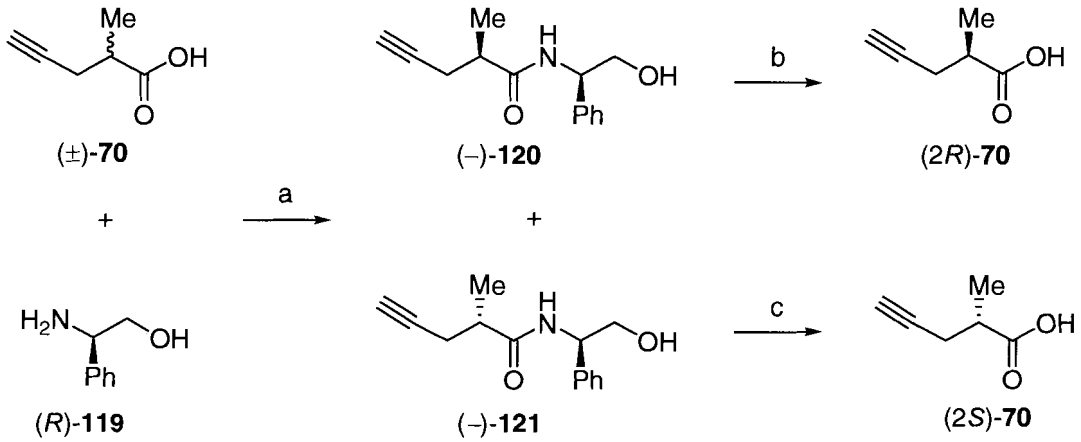
In order to complete an asymmetric synthesis of xyloketal D (**4**) and attempt the asymmetric synthesis of xyloketal A (**1**), it was decided to prepare optically active 2,4-dimethyl-4,5-dihydrofuran (**61**) and use this material in the Diels-Alder reactions. The use of chiral nonracemic dihydrofuran **61** in the synthesis of xyloketal D (**4**) would firmly establish the absolute stereochemistry of this natural product. Furthermore, this modification was expected to reduce the number of possible stereoisomeric reaction products produced in the triple Diels-Alder reactions and facilitate the isolation of the natural product, xyloketal A (**1**). Towards these ends, it was decided to investigate the resolution of one of the intermediates from the previously described racemic synthetic route.

2.8.1 Synthesis of (2*R*)-2-Methylpent-4-ynoic Acid [(2*R*)-70] and (2*S*)-2-Methyl-pent-4-ynoic Acid [(2*S*)-70] Employing a Resolution Procedure

A variety of methods were investigated in order to identify an efficient resolution procedure for the racemic carboxylic acid (±)-**70**. It was not possible to separate the diastereoisomeric salts that were formed between the carboxylic acid (±)-**70** and (*R*)-α-methylbenzylamine or (*R*)-(1-naphthyl)-ethylamine by fractional recrystallization. In addition, the racemic carboxylic acid (±)-**70** was condensed with (*R*)-phenylglycinol [(*R*)-**119**] to afford the corresponding diastereoisomeric oxazolines.[51] Unfortunately, these derivatives were found to be chromatographically inseparable. The racemic carboxylic acid (±)-**70** was also converted to the corresponding acid chloride and condensed with menthol, isomenthol and (2*R*)-butan-2-ol. All of the diastereoisomeric esters could not

be separated by fractional recrystallization or by chromatographic methods. The corresponding acid chloride of the carboxylic acid (±)-**70** was also condensed with an extensive series of chiral nonracemic amines including (*R*)-α-methylbenzylamine and (*R*)-(1-naphthyl)-ethylamine, the methyl esters of (*S*)-alanine, (*S*)-isoleucine, (*S*)-leucine, (*S*)-phenylalanine, (*S*)-proline, (*S*)-tryptophan and (*R*)-phenylglycine, as well as (*S*)-valinol and (1*S*,2*R*)-norephedrine. It was found that the diastereoisomeric amides (–)-**120** and (–)-**121** prepared from (*R*)-phenylglycinol [(*R*)-**119**] could be readily separated by flash chromatography on a multigram scale (Scheme 2.8.1.1).[52,53] Of note, the diastereoisomeric amides that were prepared from (*S*)-valinol were also chromatographically separable. However, the (*R*)-phenylglycinol-derived amides (–)-**120** and (–)-**121** were employed due to the ease of handling these compounds (UV chromophore for TLC analysis, high crystallinity and greater difference in R_f value). The chiral nonracemic carboxylic acids (2*R*)-**70** and (2*S*)-**70** were then prepared by hydrolysis of the diastereoisomeric amides (–)-**120** and (–)-**121**, respectively, under acidic reaction conditions.[54]

Scheme 2.8.1.1 Resolution of (±)-2-Methylpent-4-ynoic Acid [(±)-70] with (*R*)-Phenylglycinol [(*R*)-119]



Reagents and conditions: (a) $(COCl)_2$, CH_2Cl_2, DMF (cat.), 0 °C to room temperature, 2 h then (*R*)-phenylglycinol [(*R*)-**119**], TEA, CH_2Cl_2, 0 °C to room temperature, 16 h, 36% [(–)-**120**], 34% [(–)-**121**]; (b) 3 M H_2SO_4, *p*-dioxane, reflux, 7 h, 76% [(2*R*)-**70**]; (c) 3 M H_2SO_4, *p*-dioxane, reflux, 7 h, 86% [(2*S*)-**70**].

The amide (–)-**121** was a crystalline solid which on recrystallization from ethyl acetate afforded colourless needles that were suitable for X-ray crystal structure analysis (Figure 2.8.1.1). Inspection of the X-ray crystal structure revealed that this amide had the *S* configuration at the carboxylic acid stereogenic centre. Therefore, the amide (–)-**121** had an appropriate absolute stereochemistry to prepare the enantiomer of the natural product, (+)-xyloketal D [(+)-**4**], and the amide (–)-**120** had the appropriate absolute stereochemistry to prepare the natural product (–)-xyloketal D [(–)-**4**].

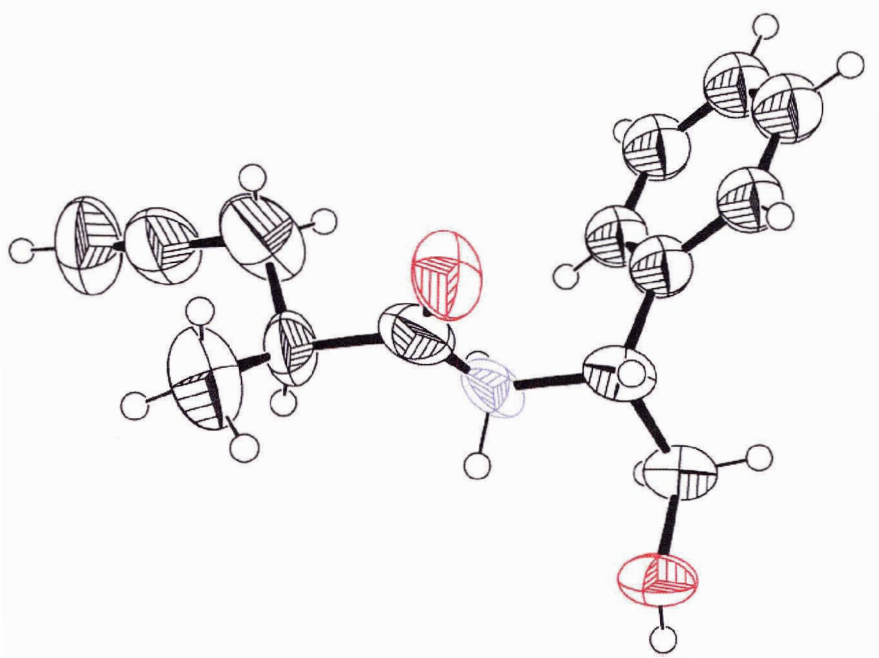
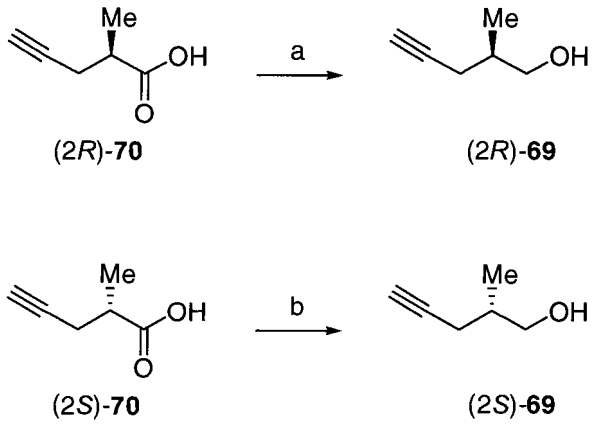


Figure 2.8.1.1 X-Ray crystal structure of the amide [(–)-121] (the thermal ellipsoids are drawn at a 50% probability level).

2.8.2 Synthesis of (2*R*)-2-Methylpent-4-yn-1-ol [(2*R*)-69] and (2*S*)-2-Methylpent-4-yn-1-ol [(2*S*)-69]

The chiral nonracemic carboxylic acids (2*R*)-**70** and (2*S*)-**70** were then reduced with lithium aluminum hydride to afford the corresponding alcohols (2*R*)-**69** and (2*S*)-**69** (Scheme 2.8.2.1).

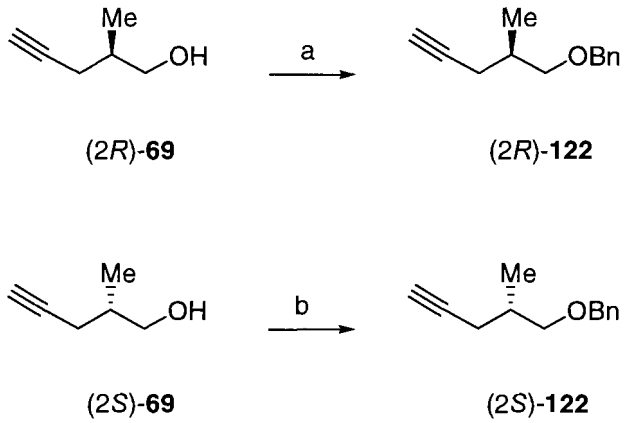
Scheme 2.8.2.1 Synthesis of the Alcohols [(2*R*)-69] and [(2*S*)-69] from the Corresponding Carboxylic Acids [(2*R*)-70] and [(2*S*)-70]



Reagents and conditions: (a) $LiAlH_4$, THF, 0 °C to room temperature, 16 h, 89%; (b) $LiAlH_4$, THF, 0 °C to room temperature, 16 h, 85%.

Of note, the chiral nonracemic alcohol (2*R*)-**69** is a known compound and has been prepared in six steps from commercially available (2*R*)-methyl-3-hydroxy-2-methylpropanoate.[55,56] However, the optical rotation of this compound has not been reported. The corresponding benzyl ether (2*R*)-**122** has also been prepared from this expensive starting material.[57,58] In this case, the optical rotation of this material has been reported. Therefore, a sample of the alcohol (2*R*)-**69** was converted to the benzyl ether (2*R*)-**122** (Scheme 2.8.2.2). The optical rotation of the product was identical in both sign and magnitude to the reported literature values. Thus, the absolute stereochemistry and high optical purity of the resolved alcohol (2*R*)-**69** was firmly established. A sample of the alcohol (2*S*)-**69** was also converted to the corresponding benzyl ether (2*S*)-**122** which proved to be the enantiomer of the known compound.

Scheme 2.8.2.2 Confirmation of Absolute Stereochemistry of the Alcohols [(2*R*)-69] and [(2*S*)-69] by the Synthesis of the Known Benzyl Ethers [(2*R*)-122] and [(2*S*)-122]

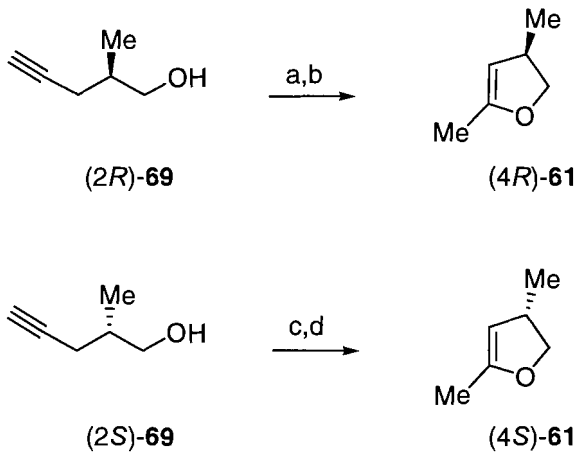


Reagents and conditions: (a) NaH, BnBr, DMF, THF, room temperature, 6 h, 90%; (b) NaH, BnBr, DMF, THF, room temperature, 6 h, 90%.

2.8.3 Synthesis of (4*R*)-2,4-Dimethyl-4,5-dihydrofuran [(4*R*)-61] and (4*S*)-2,4-Dimethyl-4,5-dihydrofuran [(4*R*)-61]

The chiral nonracemic alcohol (2*R*)-**69** was then used to prepare the dihydrofuran (4*R*)-**61** as described earlier for the racemic compound (Scheme 2.8.3.1). This compound would serve as the precursor of (–)-xyloketal D [(–)-**4**] and would allow for the confirmation of the absolute stereochemistry of the natural product. In an identical fashion, the alcohol (2*S*)-**69** was used to prepare the dihydrofuran (4*S*)-**61**. This compound would serve as the precursor of the enantiomer of the natural product, (+)-xyloketal D [(+)-**4**].

Scheme 2.8.3.1 Synthesis of the Dihydrofurans [(4*R*)-61] and [(4*S*)-61] from the Corresponding Alcohols [(2*R*)-69] and [(2*S*)-69]



Reagents and conditions: (a) $NaNH_2$ (cat.), reflux, 2 h; (b) reflux, 2 h, 44% (over two steps); (c) $NaNH_2$ (cat.), reflux, 2 h; (d) reflux, 2 h, 36% (over two steps).

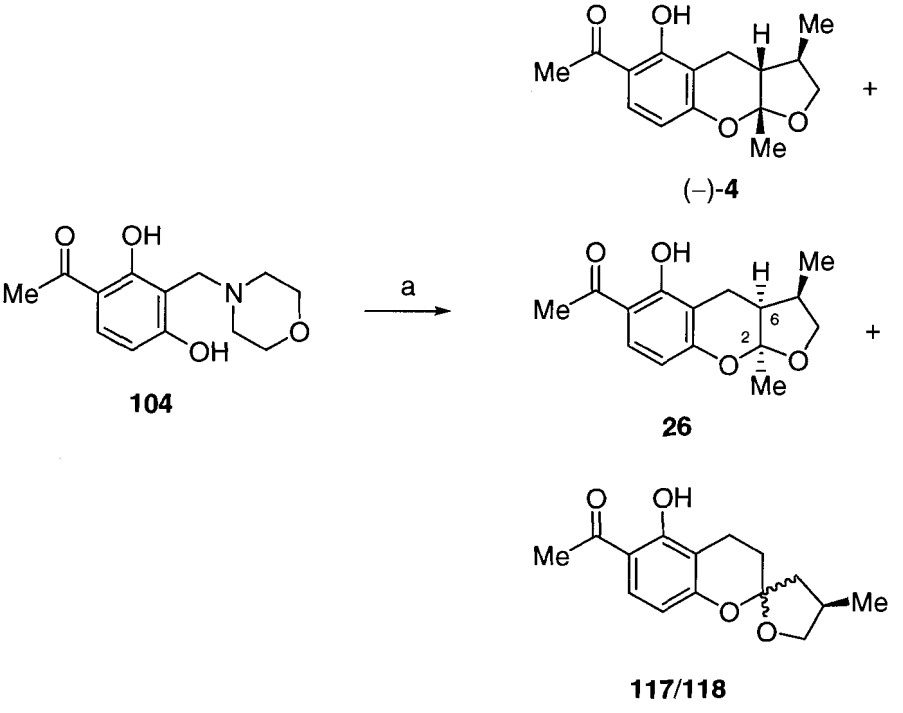
2.9 Synthesis of Chiral Nonracemic Xyloketals: Diels-Alder Approach

2.9.1 Synthesis of (–)-Xyloketal D [(–)-4]

The chiral nonracemic dihydrofuran (4*R*)-**61** (3 equiv) and the Mannich base **104** (1 equiv) were heated in benzene at reflux with methyl iodide (1 equiv) for eight days (Scheme 2.9.1.1). This reaction afforded a mixture (8:1:2:2) of (–)-xyloketal D [(–)-**4**], 2,6-*epi*-xyloketal D (**26**) and the diastereoisomeric spiroacetals **117** and **118** in a combined yield of 40%. The reaction was also repeated using dimethylsulfate (1 equiv) instead of methyl iodide. This reaction proceeded at a faster rate and afforded a mixture of reaction products (16:1:4:4) in a similar combined yield. A diastereoisomerically and analytically pure sample of the synthetic natural product, (–)-xyloketal D [(–)-**4**], was obtained by repetitive chromatography and recrystallization. An analytically pure sample of the diastereoisomeric spiroacetals **117** and **118** was also obtained as a mixture (dr = 4:5) by repetitive chromatography and recrystallization. Of note, the Mannich base **106**

was not employed as an *ortho*-quinone methide precursor as the use of this material had led to slightly poorer yields in both the model studies and when the racemic dihydrofuran (±)-**61** was employed as a reaction partner.

Scheme 2.9.1.1 Synthesis of (–)-Xyloketal D [(–)-4]: Diels-Alder Approach

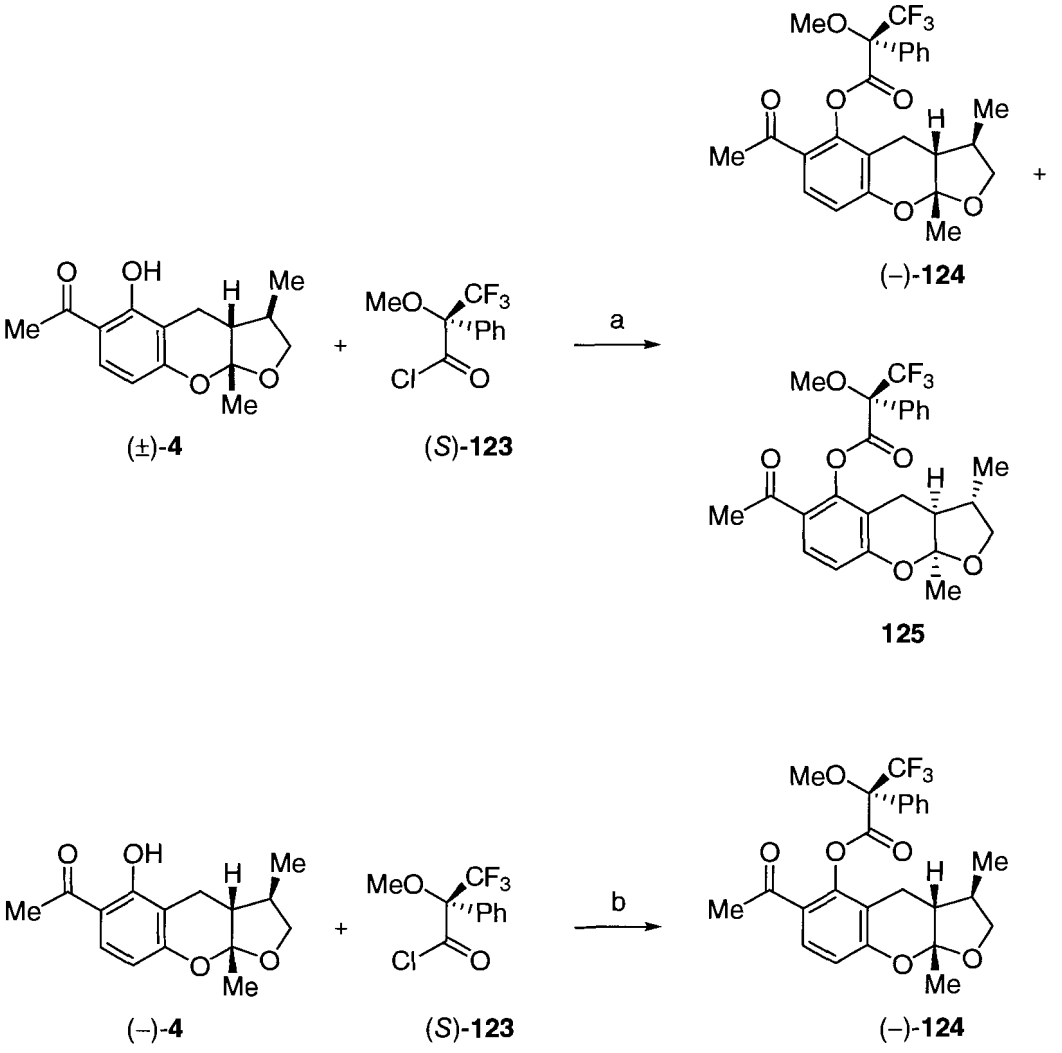


Reagents and conditions: (a) Dihydrofuran (4*R*)-**61** (3 equiv), MeI (1 equiv), PhH, reflux, 8 days, 40%, 8:1:2:2 [(–)-**4**:**26**:**117**:**118**] *or* dihydrofuran (4*R*)-**61** (3 equiv), Me_2SO_4 (1 equiv), PhH, reflux, 3 days, 37%, 16:1:4:4 [(–)-**4**:**26**:**117**:**118**].

The ^1H NMR and ^{13}C NMR spectra of synthetic (–)-xyloketal D [(–)-**4**] were identical to those of the natural product and to the racemic material prepared previously. The sign of the optical rotation of synthetic (–)-xyloketal D [(–)-**4**] was in agreement with that reported for the natural product.[1] This confirmed the absolute stereochemistry of the natural product that had been assigned previously by the interpretation of CD data.[1] However, the magnitude of the rotation was slightly lower than that reported for the natural product (92% ee based on the reported optical rotation of the natural product). In

order to determine the enantiomeric purity of synthetic (–)-xyloketal D [(–)-**4**], efforts were also made to separate the enantiomers of a sample of racemic xyloketal D [(±)-**4**]. This was not possible by analytical chiral HPLC (Daicel Chiralcel OD column) or by GC (Cyclosil-B column). Similarly, ^{1}H NMR spectroscopy using a chiral shift reagent [Eu(hfc)$_3$] was unsuccessful. Derivatization of the phenol moiety of racemic xyloketal D [(±)-**4**] with (*S*)-(+)-α-methoxy-α-trifluoromethyl-phenylacetyl chloride [(*S*)-**123**] afforded the corresponding Mosher's ester derivatives (Scheme 2.9.1.2).[59,60] In this case, the ^{1}H NMR (600 MHz) signals of the methoxy substituents were clearly resolved at δ 3.72 and 3.73 ppm. However, the ^{19}F NMR (470 MHz) signals of the Mosher's ester derivatives, although separate, were poorly resolved. Subsequent derivatization of synthetic (–)-xyloketal D [(–)-**4**] afforded the corresponding Mosher's ester as a single diastereoisomer with the signal for the methoxy substituent at δ 3.72 ppm. This indicated that the synthetic material was of high optical purity.

Scheme 2.9.1.2 Mosher's Ester Derivatization of (±)-Xyloketal D [(±)-4] and Synthetic (–)-Xyloketal D [(–)-4]



Reagents and conditions: (a) DMAP, THF, reflux, 3 h, 82%, dr = 1:1 [(–)-**124**:**125**]; (b) DMAP, THF, reflux, 2.5 h, 84%;

Interestingly, the melting point of synthetic (–)-xyloketal D [(–)-**4**] (71-73 °C) was significantly lower than that reported for the natural product (111-113 °C). Repeated recrystallization of the synthetic material from petroleum ether did not increase the melting point. Krohn and co-workers have reported that synthetic (–)-xyloketal D [(–)-**4**] (93% ee calculated from the reported optical rotation of the natural product and 93% ee based on the enantiomeric purity of a synthetic precursor) also had a lower melting point

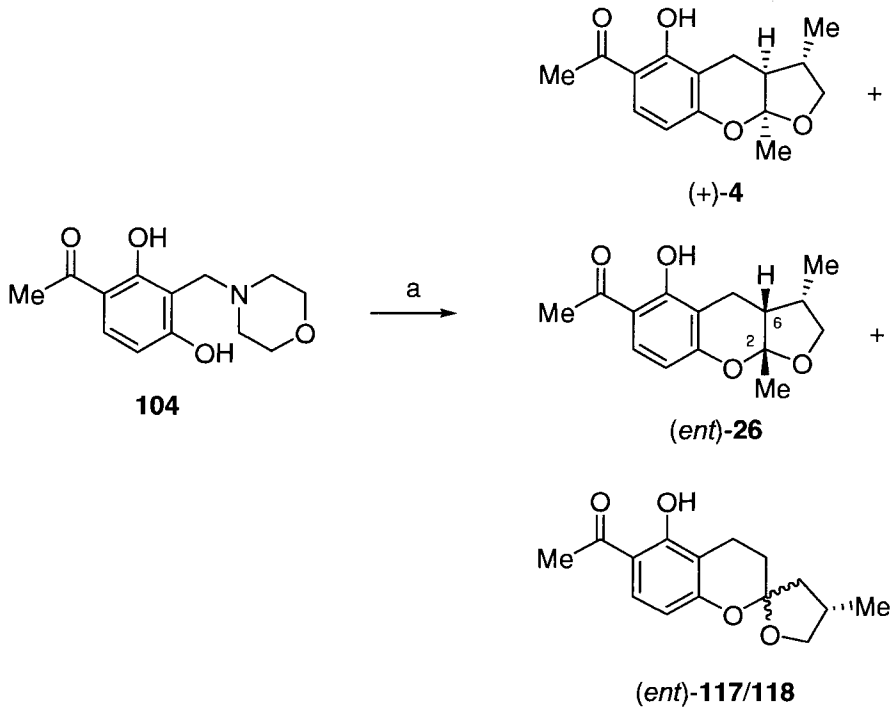
(87 °C).[9,10] They also reported that subsequent recrystallization from a mixture of ether and pentane afforded material which had a melting point of 110-111 °C.* Therefore, our sample of synthetic (–)-xyloketal D [(–)-**4**] was recrystallized from this solvent system. However, this procedure did not increase the melting point. Thus, it was concluded that this difference in melting point resulted from contamination with a trace amount of the enantiomer which had significantly depressed the melting point of our sample of synthetic (–)-xyloketal D [(–)-**4**].

2.9.2 Synthesis of (+)-Xyloketal D [(+)-4]

The Mannich base **104** (1 equiv) was also allowed to react with the enantiomeric chiral nonracemic dihydrofuran (4*S*)-**61** (3 equiv) in the presence of methyl iodide (1 equiv) or dimethylsulfate (1 equiv) using the two procedures described above (Scheme 2.9.2.1). These reactions afforded mixtures of (+)-xyloketal D [(+)-**4**], *ent*-2,6-*epi*-xyloketal D [(*ent*)-**26**] and the diastereoisomeric spiroacetals (*ent*)-**117** and (*ent*)-**118**.

(*) Professor Krohn graciously recorded the melting point of a sample of natural (–)-xyloketal D [(–)-**4**] which was provided to him by Professor Lin. This material was found to have a melting point of 107-108 °C (Büchi SMP-2 melting point apparatus).

Scheme 2.9.2.1 Synthesis of (+)-Xyloketal D [(+)-4]: Diels-Alder Approach



Reagents and conditions: (a) Dihydrofuran (4*S*)-**61** (3 equiv), MeI (1 equiv), PhH, reflux, 6 days, 46%, 13:1:3:3 [(+)-**4**:(*ent*)-**26**:(*ent*)-**117**:(*ent*)-**118**] *or* dihydrofuran (4*S*)-**61** (3 equiv), Me_2SO_4 (1 equiv), PhH, reflux, 3 days, 36%, 20:1:3:3 [(+)-**4**:(*ent*)-**26**:(*ent*)-**117**:(*ent*)-**118**].

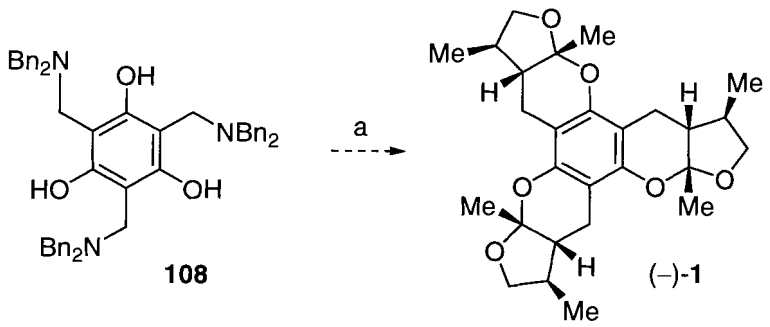
A diastereoisomerically and analytically pure sample of the enantiomeric natural product, (+)-xyloketal D [(+)-**4**], was also prepared and fully characterized following repetitive chromatography and recrystallization. The melting point and the magnitude of the optical rotation were in agreement with our synthetic (–)-xyloketal D [(–)-**4**].

2.9.3 Attempted Synthesis of (–)-Xyloketal A [(–)-1]

The total synthesis of (–)-xyloketal A [(–)-**1**] was also attempted (Scheme 2.9.3.1). The Mannich base **108** (1 equiv) and a large excess of the chiral nonracemic dihydrofuran (4*R*)-**61** (9 equiv) were heated in benzene at reflux with methyl iodide (3 equiv) as well as with dimethyl sulfate (3 equiv). Unfortunately, the natural product

could not be isolated from the complex mixtures of products that were produced in these reactions.

Scheme 2.9.3.1 Attempted Synthesis of (–)-Xyloketal A [(–)-1]: Diels-Alder Approach



Reagents and conditions: (a) Dihydrofuran (4*R*)-**61** (9 equiv), MeI (1 equiv), PhH, reflux, 24 h *or* dihydrofuran (4*R*)-**61** (9 equiv), Me_2SO_4 (1 equiv), PhH, reflux, 24 h.

It was anticipated that the stereochemistry of this attempted cycloaddition reaction would have been directed efficiently by the *C*-4 methyl substituent of the chiral nonracemic dihydrofuran (4*R*)-**61** [as was observed in the case of the syntheses of xyloketal D (**4**)]. Thus, it appears that the competing isomerization reaction of the dihydrofuran (4*R*)-**61** and the subsequent non-stereoselective cycloaddition reaction of the exocyclic dihydrofuran (4*R*)-**68** was a dominant complicating factor which prevented the isolation of (–)-xyloketal A [(–)-**1**].

2.10 Conclusions

The Mannich bases **104** and **106**, which were prepared in a single step from commercially available starting materials, were shown to be appropriate precursors for the generation of *ortho*-quinone methides which served as dienes for inverse electron demand hetero Diels-Alder reactions. When commercially available 2-methyl-4,5-

dihydrofuran (**114**) was employed in the reaction, a highly regio- and stereoselective reaction occurred to afford the xyloketal D analogue (±)-**12** as the sole reaction product. The synthesis of racemic 2,4-dimethyl-4,5-dihydrofuran [(±)-**61**] was accomplished according to adaptation of literature procedures. The use of this dihydrofuran led to the first total synthesis of (±)-xyloketal D [(±)-**4**] (9% overall yield in six steps from commercially available starting materials). This reaction exhibited excellent regioselectivity and good stereoselectivity (dr = 11:1). However, this process was complicated by the unexpected formation of the spiroacetals (±)-**117** and (±)-**118**. Both enantiomers of the dihydrofuran (4*R*)-**61** and (4*S*)-**61** were subsequently prepared, on resolution of the racemic carboxylic acid (±)-**69** precursor with (*R*)-phenylglycinol [(*R*)-**119**]. These compounds were used to prepare (–)- and (+)-xyloketal D [(–)-**4**] (3% overall yield in eight steps from commercially available starting materials) and [(+)-**4**] (3% overall yield in eight steps from commercially available starting materials), respectively and confirmed the absolute stereochemistry of the natural product.

The synthesis of the *tris*-Mannich bases **107** and **108** was found to be exceedingly facile. These compounds proved to be effective for the stepwise formation of *ortho*-quinone methides which were used to prepare the xyloketal A analogues (±)-**18** and (±)-**19**. Although the overall yield of these reaction was low (19%), the process involved nine individual reaction steps and the coupling of four reaction components. The application of this synthetic process for the synthesis of racemic or optically active xyloketal A (**1**) was unsuccessful. This result was attributed to thermal isomerization reactions of the dihydrofuran **61** and the subsequent formation of spiroacetal by-products.

The Mannich base **113**, required for the synthesis of xyloketal B (**2**) and C (**3**), was prepared in two steps from commercially available starting materials. However, this compound was found to be unsuitable as a precursor for the stepwise generation of the *ortho*-quinone methides in a model study. Therefore, no further efforts to synthesize these natural products were made by this approach.

CHAPTER THREE

Towards the Synthesis of Xyloketal A: Phenylboronic Acid-Mediated Reactions

3.1 Introduction

In this chapter the application of a phenylboronic acid-mediated reaction to the synthesis of xyloketal A (**1**), and analogues thereof, is described.[†] The key feature of this synthetic route is a triple condensation reaction of phloroglucinol (**14**) with α,β-unsaturated carbonyl compounds. This synthetic route did not afford xyloketal A (**1**) but a series of derivatives which represent structural analogues of the natural product were prepared.

3.2 Retrosynthetic Analysis: Phenylboronic Acid-Mediated Reactions

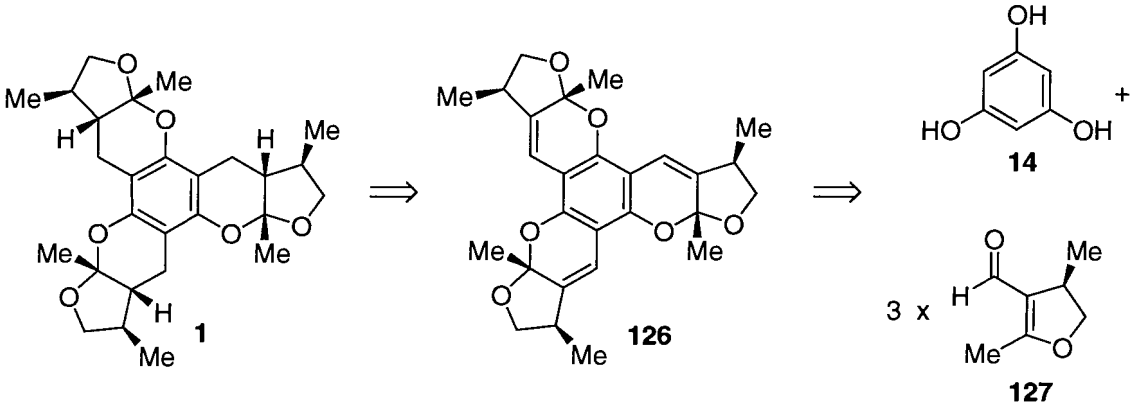
3.2.1 Retrosynthetic Analysis of Xyloketal A (1)

In addition to containing three ketal moieties, xyloketal A can be considered to be a *tris*-chromane. Therefore, retrosynthetic analysis of xyloketal A (**1**) suggested that it could be prepared from the C_3-symmetric 2*H*-chromene derivative **126** by a stereoselective hydrogenation reaction (Scheme 3.2.1.1). Here it would be expected that hydrogen would be added to the convex face of the molecule. There are a variety of methods for the synthesis of 2*H*-chromene derivatives.[61,62,63,64,65] Of particular relevance is the phenylboronic acid-mediated condensation reaction of phenols and α,β-unsaturated

(†) The results discussed in this chapter have been reported in part, see: (a) *Phenylboronic Acid Mediated Triple Condensation Reactions of Phloroglucinol and Unsaturated Carbonyl Compounds.* Pettigrew, J. D.; Cadieux, J. A.; So, S. S. S.; Wilson, P. D. *Org. Lett.* **2005**, *7*, 467; (b) *Total Synthesis of (–)-Xyloketal A.* Pettigrew, J. D.; Wilson, P. D. *Org. Lett.* **2006**, *8*, 1427.

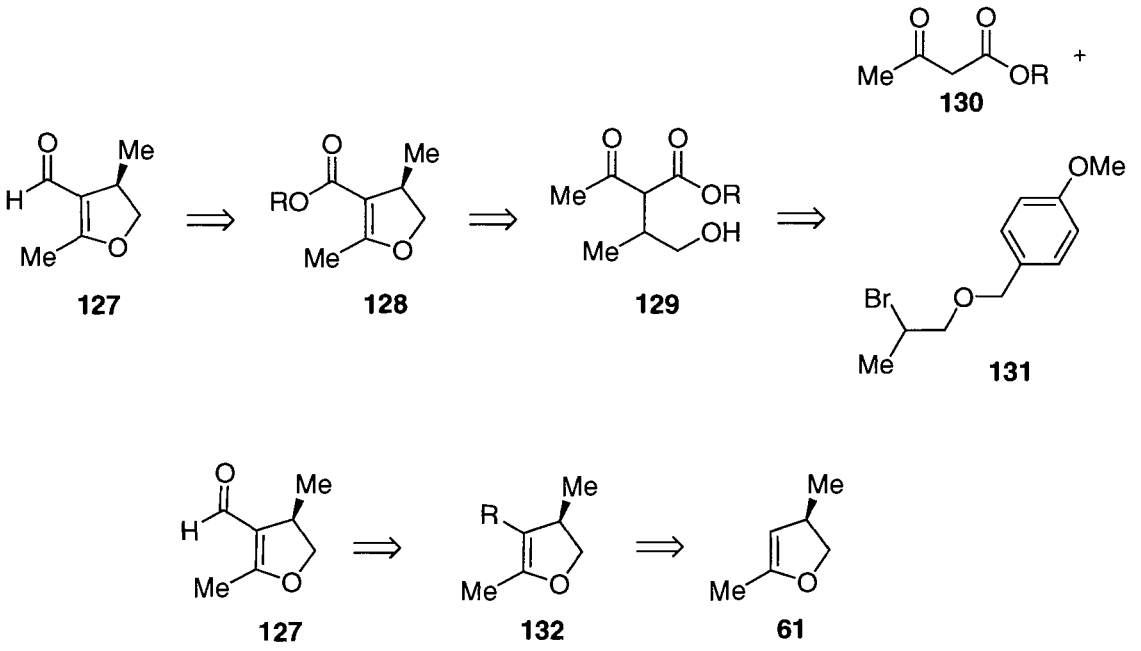
aldehydes.[42,43] Accordingly, the *tris*-chromene derivative **126** could be prepared from phloroglucinol (**14**) and three equivalents of the α,β-unsaturated aldehyde **127**. This process would involve three *ortho*-specific electrophilic aromatic substitution reactions followed by three subsequent dehydrative-cyclization reactions.[66,67,68]

Scheme 3.2.1.1 Retrosynthetic Analysis of Xyloketal A (1): Phenylboronic Acid-Mediated Reactions



The aldehyde **127**, which is a natural product isolated from the marine sponge fungi *A. cruciatus*,[69] could be prepared by reduction of the ester **128** (Scheme 3.2.1.2). This ester could be prepared by isomerization of the corresponding hydroxy ester **129** under acidic reaction conditions.[70,71] This latter compound, in principle, should be readily available from an ester of acetoacetate **130** and the bromide **131**. Alternatively, the aldehyde **127** could be prepared by elaboration of the dihydrofuran **61**.[72]

Scheme 3.2.1.2 Retrosynthetic Analyses of the Aldehyde (127)



3.3 Brief Overview of the Phenylboronic Acid-Mediated Reaction of Phenols and Aldehydes

A brief overview of the development and application of the phenylboronic acid-mediated reaction of phenols and aldehydes to afford 2*H*-chromenes is presented below.

3.3.1 Development and Application of the Phenylboronic Acid-Mediated Reaction

In 1992, Lau and co-workers reported the facile synthesis of cyclic borate esters from phenols, aldehydes and phenylboronic acid.[19] This regiospecific reaction afforded products which proved to be isolable *ortho*-quinone methide precursors as discussed previously (See: Section 2.3.1). This initial work was subsequently followed by a report on the extension of this reaction towards the total synthesis of several biologically active natural products, such as precocene I (**137**) and II (**138**) (Figure 3.3.1.1).[42] In this report, the authors used α,β-unsaturated aldehydes to generate the borate esters, which in the

presence of a small amount of propionic acid (**72**), spontaneously underwent further reactions to afford the corresponding *ortho*-quinone methides. These reactive species then underwent 6π electrocyclic rearrangements to afford 2*H*-chromenes in a one-pot reaction sequence.

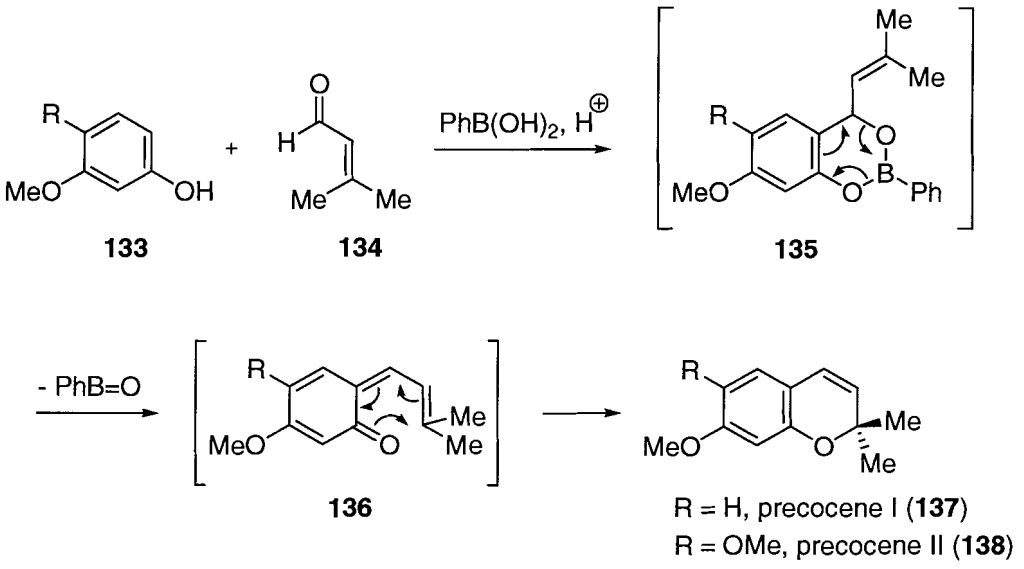
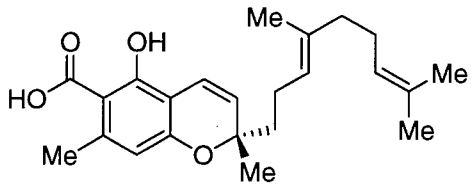


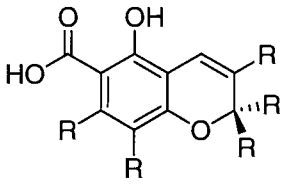
Figure 3.3.1.1 Synthesis of precocene I (137) and II (138).

Further studies by Snieckus and co-workers have shown that this synthetic method can be applied to napthols and phenanthrols.[43] In addition, it was demonstrated that this reaction is sensitive to the electronic nature of the aromatic system employed. For example, the use of electron rich *para*-methoxyphenol as a reaction substrate afforded the desired 2*H*-chromene when allowed to react with 3-methyl-2-butenal [senecialdehyde (**134**)]. In contrast, the use of *para*-bromophenol afforded the corresponding reaction product in poor yield and *para*-nitrophenol did not afford the desired product under the same reaction conditions.

Wilson and co-workers have also applied this synthetic method to the synthesis of analogues of the potent anti-HIV natural product daurichromenic acid (**139**) (Figure 3.3.1.2).[73]



Daurichromenic acid (**139**)



Daurichromenic acid analogues (**140**)

Figure 3.3.1.2 Application of the phenylboronic acid-mediated reaction for the synthesis of daurichromenic acid analogues (140) by Wilson and co-workers.

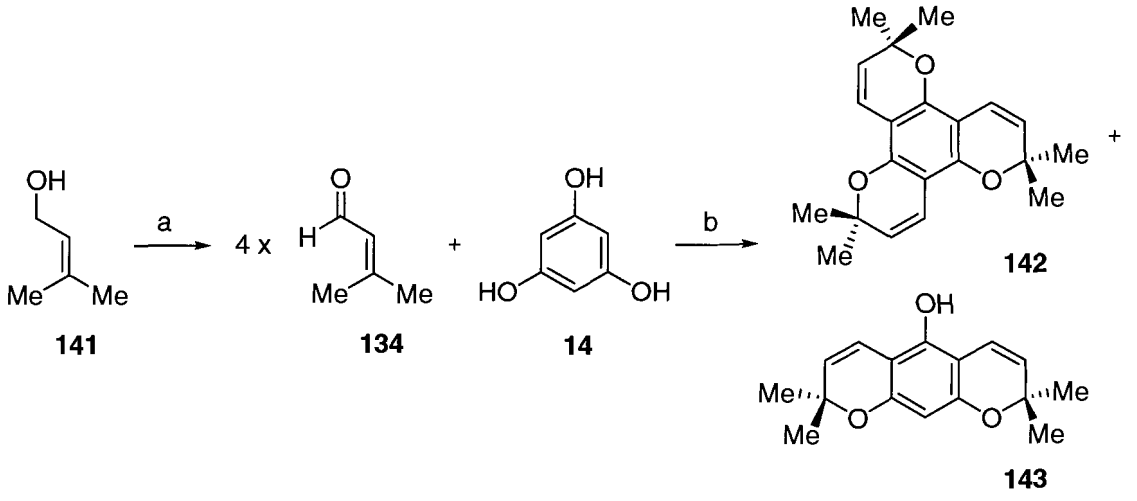
3.4 Formation of *tris*-2*H*-Chromenes

In order to optimize the reaction conditions for the preparation of *tris*-2*H*-chromenes from phloroglucinol (**14**), model studies were performed with senecialdehyde (**134**) as the α,β-unsaturated aldehyde reaction component.

3.4.1 Formation of *tris*-2*H*-Chromenes: Optimization of Reaction Conditions

Senecialdehyde (**134**) is commercially available but it is relatively expensive as compared to the corresponding alcohol **141**. Therefore, this model compound was prepared in a single step from the alcohol **141** by oxidation with pyridinium dichromate according to a literature procedure (Scheme 3.4.1.1).[74] Phloroglucinol (**14**) (1 equiv) was treated with this aldehyde (4 equiv), propionic acid (**72**) and phenylboronic acid in benzene at reflux with azeotropic removal of water to afford the chromene derivatives **142** and **143**. The results of these model studies are presented below (Table 3.4.1.1).

Scheme 3.4.1.1 Phenylboronic Acid-Mediated Reaction of Phloroglucinol (14) and Senecialdehyde (134)



Reagents and conditions: (a) PDC, CH_2Cl_2, room temperature, 16 h, 56%; (b) see below: Table 3.4.1.1.

Table 3.4.1.1 Reaction Conditions Corresponding to Scheme 3.4.1.1*

Entry	Reagents and Conditions	Yield of (142) (%)	Yield of (143) (%)
1	$PhB(OH)_2$ (0.25 equiv), propionic acid (**72**) (cat.), PhH, reflux, 22 h	55	39
2	$PhB(OH)_2$ (1 equiv), propionic acid (**72**) (cat.), PhH, reflux, 22 h	74	23
3	$PhB(OH)_2$ (2 equiv), propionic acid (**72**) (cat.), PhH, reflux, 22 h	81	11
4	$PhB(OH)_2$ (3 equiv), propionic acid (**72**) (cat.), PhH, reflux, 22 h	92	6
5	$PhB(OH)_2$ (3 equiv), PhH, reflux, 22 h	Trace	Trace
6	Propionic acid (**72**) (cat.), PhH, reflux, 22 h	Trace	Trace
7	$B(OH)_3$ (0.25 equiv), propionic acid (**72**) (cat.), PhH, reflux, 22 h	45	30

(*) All reactions were performed with four equivalents of the aldehyde **134** and one equivalent of phloroglucinol (**14**).

Entry	Reagents and Conditions	Yield of (142) (%)	Yield of (143) (%)
8	$B(OH)_3$ (1 equiv), propionic acid (**72**) (cat.), PhH, reflux, 22 h	50	25
9	$B(OH)_3$ (3 equiv), propionic acid (**72**) (cat.), PhH, reflux, 22 h	44	27

The initial reaction of phloroglucinol (**14**) and senecialdehyde (**134**) with phenylboronic acid (0.25 equiv), in the presence of propionic acid (**72**) (cat.) afforded a mixture of the condensation products **142** and **143** in good yield (entry 1). These reaction products had the core ring systems of xyloketal A (**1**) and C (**3**), respectively. It was then found that increasing the amount of phenylboronic acid used in this reaction led to an increase in the amount of the triple condensation product **142** that was formed, up to 92% (entries 2-4). It was also found that only trace amounts of these reaction products were formed when propionic acid (**72**) was omitted from the reaction (entry 5). This suggested that the cyclic borate esters formed during the course of the reaction were stable, although no attempts were made to isolate these intermediates. When phenylboronic acid was omitted from the reaction mixture only trace amounts of the products were formed that indicated a requirement for a suitable promoter in the reaction (entry 6). Given the high reactivity of phloroglucinol (**14**) towards electrophilic substitution processes, attempts were made to promote this reaction with the inexpensive but less reactive reagent, boric acid (entries 7-9). The reactions with boric acid afforded the reaction products **142** and **143** albeit in lower yields. Of note, boric acid was only sparingly soluble in benzene. Therefore, the similar yields observed in all of these latter reactions could reflect that the concentration of boric acid in solution was the same.

In the example where three equivalents of phenylboronic acid were employed, presumably three electrophilic aromatic substitution reactions occurred prior to the cyclization reactions (entry 4). The formation of significant quantities of the disubstituted product **143**, when less than three equivalents of phenylboronic acid were used, was attributed to the formation and subsequent cyclization reactions of intermediate **144** (Figure 3.4.1.1). The disubstituted product **143** cannot undergo a subsequent phenylboronic acid-directed electrophilic aromatic substitution reaction as the *ortho*-positions, with respect to the remaining phenol moiety, are blocked.[66,67,68] Of note, the unsymmetric disubstituted intermediate **145** or the product formed from subsequent cyclization reactions could react further with senecialdehyde (**134**) to afford the *tris*-adduct **142**.

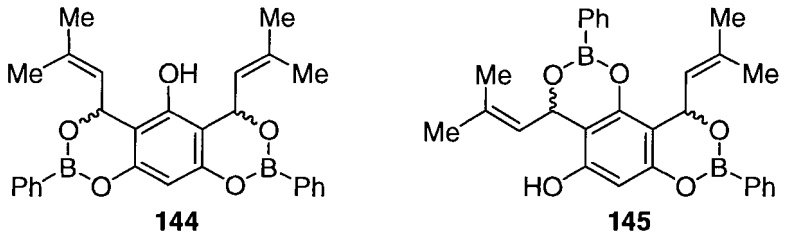
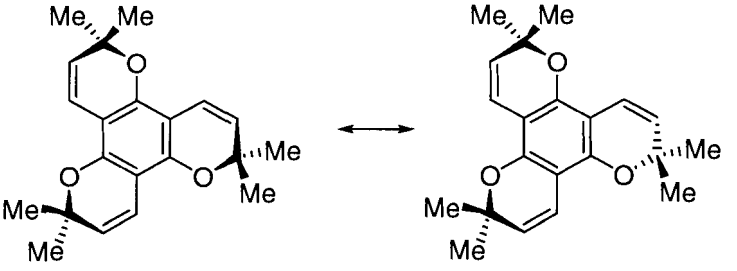


Figure 3.4.1.1 Molecular structures of the borate ester intermediates (144) and (145).

The two reaction products **142** and **143** were readily separated by flash chromatography. The ^{1}H NMR spectrum of the *tris*-2*H*-chromene **142** was very simple and showed two doublets corresponding to the chromene double bond protons at δ 5.43 and 6.59 ppm and a single sharp singlet corresponding to the methyl groups at δ 1.40 ppm. The appearance of one set of signals for the three chromene moieties indicated that the two possible conformers of the reaction product **142**, neither of which would be expected to show a single signal for the methyl groups, were rapidly interconverting on

the NMR timescale (Figure 3.4.1.2). Consequently, a time averaged spectra was observed. The ^{13}C NMR spectrum contained peaks at δ 103.4 and 149.1 ppm that corresponded to the two chemically inequivalent carbon atoms of the aromatic core. In addition, four signals for the chromene moieties were also observed. The mass spectrum (CI) showed large peaks at 325 and 324 amu that corresponded to the protonated molecular ion and the molecular ion, respectively.



146 147

Figure 3.4.1.2 Rapid interconversion of the two possible conformers (146) and (147) of the *tris*-2*H*-chromene (142).

The *bis*-2*H*-chromene product **143** showed an additional peak in the ^{1}H NMR spectrum at δ 6.46 ppm that corresponded to the remaining aromatic proton and two additional peaks at δ 99.0 and 147.6 ppm in the ^{13}C NMR spectrum for this less symmetrical aromatic core. This material also showed a molecular ion peak at 258 amu in the mass spectrum (CI).

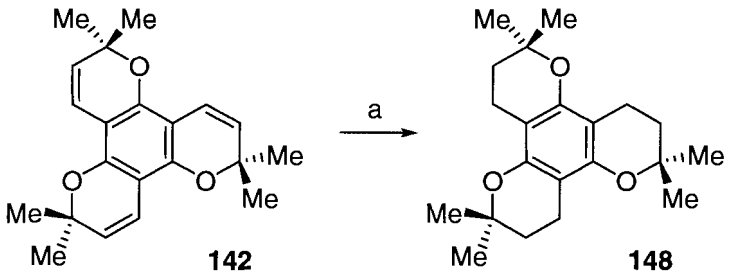
3.5 Hydrogenation of *tris*-2*H*-Chromenes

On having determined reaction conditions to prepare a model *tris*-2*H*-chromene in good yield, the conversion of this compound to the corresponding *tris*-2*H*-chromane was investigated.

3.5.1 Synthesis of the *tris*-Chromane (148)

The model compound **142** was subjected to standard hydrogenation reaction conditions (H_2, Pd/C) (Scheme 3.5.1.1).[42] This reaction afforded the analytically pure known *tris*-chromane **148** in excellent yield (96%).[75,76]

Scheme 3.5.1.1 Hydrogenation of the *tris*-2*H*-Chromene (148)



Reagents and conditions: (a) H_2, Pd/C, MeOH, room temperature, 20 h, 96%.

3.6 Phenylboronic Acid-Mediated Reactions of a Series of α,β-Unsaturated Carbonyl Compounds

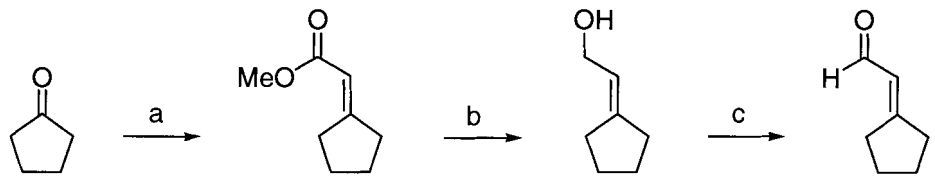
In order to examine the scope of the above reaction, it was decided to use a series of either commercially or readily available α,β-unsaturated carbonyl compounds as substrates for the phenylboronic acid-mediated reaction of phloroglucinol (**14**).

3.6.1 Synthesis of α,β-Unsaturated Aldehydes

An efficient three step procedure for the conversion of ketones to the corresponding dialkylideneacetaldehydes has been reported in the literature by Snowden and co-workers.[77] Following this procedure, a Horner-Wadsworth-Emmons reaction[78] between cyclopentanone (**149**) and trimethyl phosphonoacetate afforded the α,β-unsaturated ester **150** (Scheme 3.6.1.1). This material was then reduced to the corresponding allylic alcohol **151** with lithium aluminum hydride and this product was

subsequently oxidized with manganese dioxide to afford the known aldehyde **152**.[77] This procedure afforded the aldehyde **152** in 72% overall yield.

Scheme 3.6.1.1 Synthesis of Cyclopentylideneacetaldehyde (152) from Cyclopentanone (149)

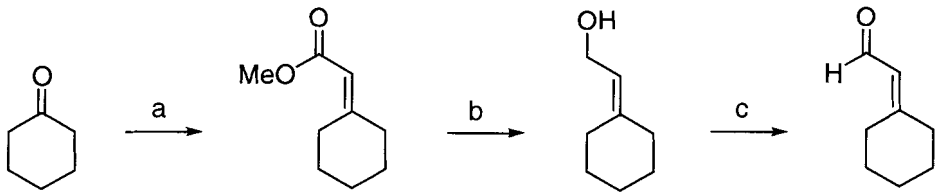


149 **150** **151** **152**

Reagents and conditions: (a) Trimethyl phosphonoacetate, NaH, THF, room temperature, 1 h then cyclopentanone (**149**), reflux, 24 h; (b) $LiAlH_4$, Et_2O, 0 °C to room temperature, 1 h; (c) MnO_2, CH_2Cl_2, room temperature, 6 h, 72% (over three steps).

This three step procedure was then used to prepare the known aldehyde **156** in 81% overall yield from cyclohexanone (**153**) (Scheme 3.6.1.2).[77,79]

Scheme 3.6.1.2 Synthesis of Cyclohexylideneacetaldehyde (156) from Cyclohexanone (153)

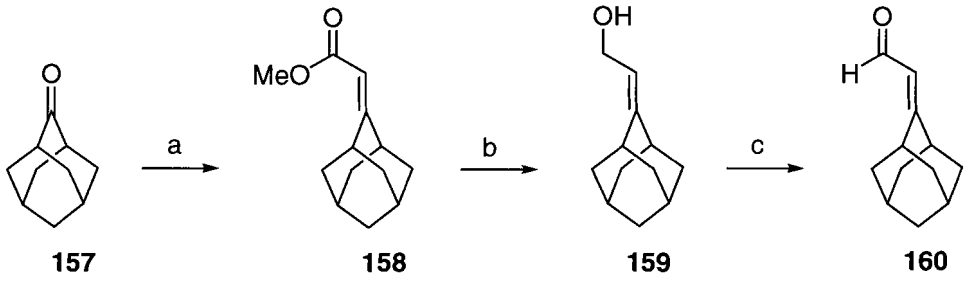


153 **154** **155** **156**

Reagents and conditions: (a) Trimethyl phosphonoacetate, NaH, THF, room temperature, 1 h then cyclohexanone (**153**), reflux, 24 h; (b) $LiAlH_4$, Et_2O, 0 °C to room temperature, 1 h; (c) MnO_2, CH_2Cl_2, room temperature, 3 h, 81% (over three steps).

In a similar manner, the adamantane derivative **160** was prepared in 83% overall yield from the commercially available ketone **157** (Scheme 3.6.1.3).[80]

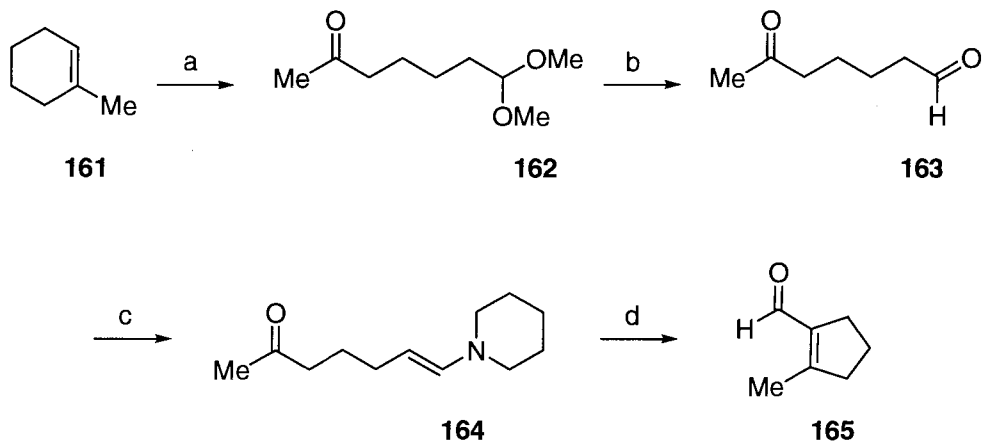
Scheme 3.6.1.3 Synthesis of Adamantylideneacetaldehyde (160) from 2-Adamantanone (157)



Reagents and conditions: (a) Trimethyl phosphonoacetate, NaH, THF, room temperature, 1 h then 2-adamantanone (**157**), reflux, 24 h, 95%; (b) $LiAlH_4$, Et_2O, 0 °C to room temperature, 1 h, 97%; (c) MnO_2, CH_2Cl_2, room temperature, 3 h, 90%.

The aldehyde **165**, which would lead to the synthesis of a carbocyclic analogue of xyloketal A (**1**), was prepared in 54% overall yield from methylcyclohexene (**161**) on a modification of the four step procedure (ozonolysis followed be reductive work-up, acetal hydrolysis, enamine formation and aldol cyclization) of Hudlicky's variant of the method of White and co-workers (Scheme 3.6.1.4).[81,82] An aqueous solution of sulfuric acid (3% v/v) was substituted for the aqueous solution of perchloric acid (3% v/v) that was used by Hudlicky and co-workers in the acetal hydrolysis step. This had no detrimental effect on the yield.

Scheme 3.6.1.4 Synthesis of 2-Methylcyclopentene-1-carboxaldehyde (165) from 1-Methylcyclohexene (161)

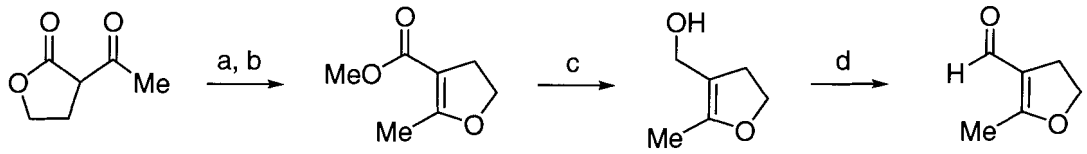


Reagents and conditions: (a) O_3, MeOH, CH_2Cl_2, –78 °C then Me_2S, *p*-TsOH·H_2O, –78 °C to room temperature, 3 h, 75%; (b) H_2SO_4, THF, 0 °C, 2 h, room temperature 1.5 h; (c) piperidine, Et_2O, 0 °C, 3 h; (d) AcOH, Et_2O, reflux, 6 h, 67% (over three steps).

The dihydrofuran aldehyde **169**, which would afford a demethyl analogue of xyloketal A (**1**), was prepared in three steps (Scheme 3.6.1.5). Commercially available α-acetyl-γ-butyrolactone (**166**) was converted to the ester **167** on saponification and subsequent dehydration under acidic conditions.[70,71] Direct conversion of this material to the corresponding aldehyde **169** with diisobutyl aluminum hydride in dichloromethane at –78 °C afforded a mixture of the unstable alcohol **168** and the unreacted ester **167**.[83] Therefore, a two step reaction sequence (reduction to the alcohol **168** with lithium aluminum hydride followed by oxidation to the aldehyde **169** with managanese dioxide) as described above was employed. Of note, although the reduction of the ester **167** proceeded in very high yield (>95%), the resultant alcohol **168** was found to be unstable. Therefore, the overall low yield of this process was attributed to the decomposition of this alcohol during oxidation to the corresponding aldehyde **169**. In an attempt to increase the overall yield of this process, the use of alternative oxidants was investigated. However, the use of pyridinium dichromate,[74] pyridinium dichromate and potassium

carbonate, Swern conditions[84] or sulfur trioxide pyridine complex[85] did not afford the desired reaction product **169**.

Scheme 3.6.1.5 Synthesis of 4-Formyl-5-methyl-2,3-dihydrofuran (169) from α-Acetyl-γ-butyrolactone (166)



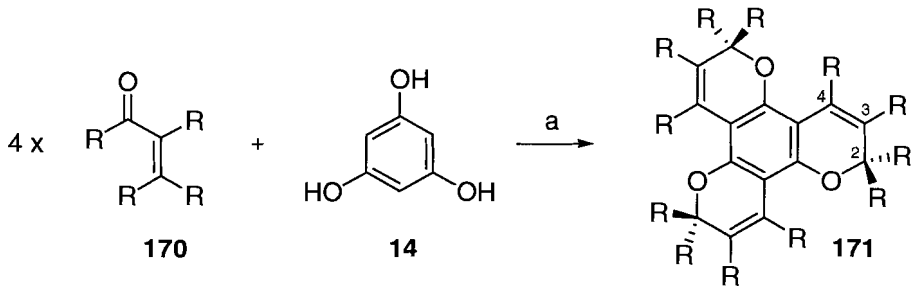
166 **167** **168** **169**

Reagents and conditions: (a) HCl (g), MeOH, reflux, 4 days then distill; (b) H_2SO_4 (cat.), distill, 19% (over two steps); (c) $LiAlH_4$, Et_2O, 0 °C to room temperature, 20 min; (d) MnO_2, CH_2Cl_2, room temperature, 54 h, 41% (over two steps).

3.6.2 Synthesis of *tris*-2*H*- and 4*H*-Chromenes

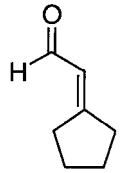
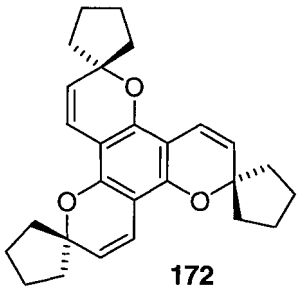
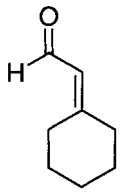
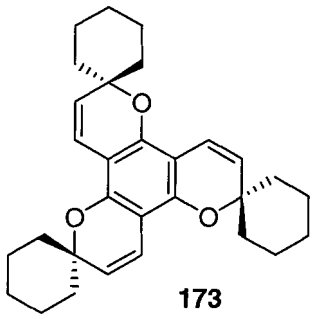
The optimized reaction conditions described above were employed systematically as part of an investigation into the scope of *tris*-2*H*-chromenes that can be prepared by this process. Accordingly, phloroglucinol (**14**) (1 equiv) was treated with a series of α,β-unsaturated carbonyl compounds **170** (4 equiv), phenylboronic acid (3 equiv) and propionic acid (**72**) (cat.) in benzene at reflux with azeotropic removal of water to afford the chromene derivatives **171** (Scheme 3.6.2.1). The results of these studies are presented below (Table 3.6.2.1).

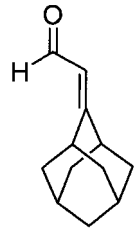
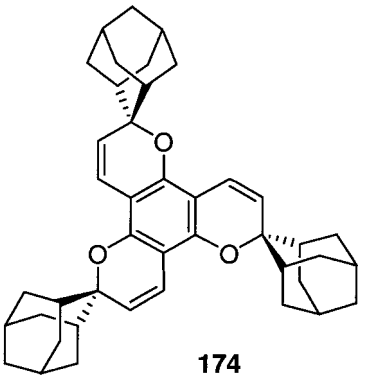
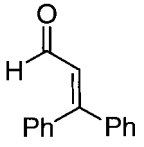
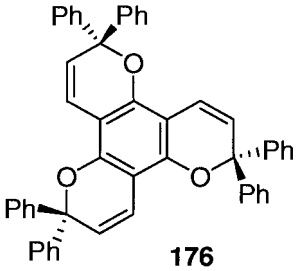
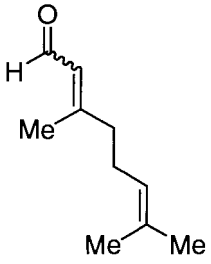
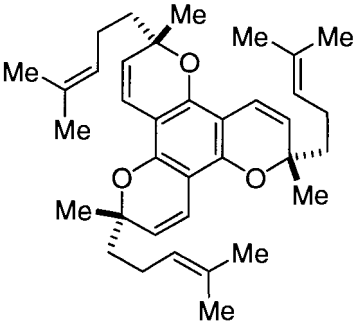
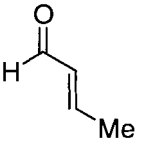
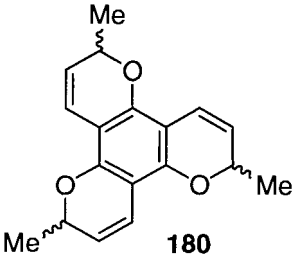
Scheme 3.6.2.1 Phenylboronic Acid-Mediated Reactions of Phloroglucinol (14) and α,β-Unsaturated Carbonyl Compounds (170)



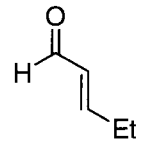
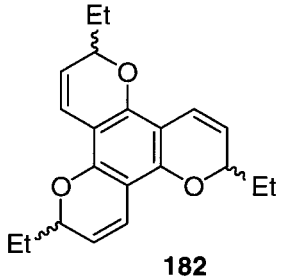
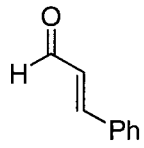
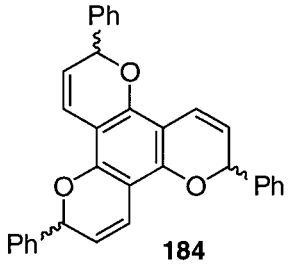
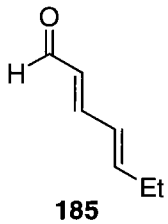
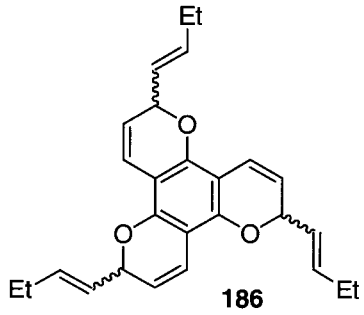
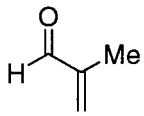
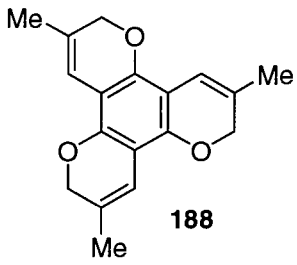
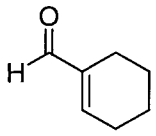
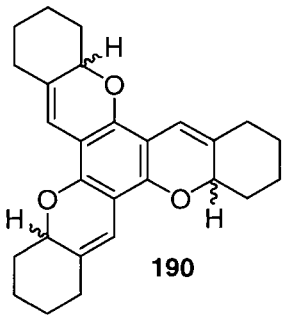
Reagents and conditions: (a) Carbonyl compound **170** (4 equiv), $PhB(OH)_2$ (3 equiv), propionic acid (**72**) (cat.), PhH, reflux.

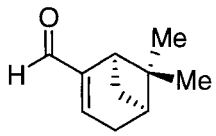
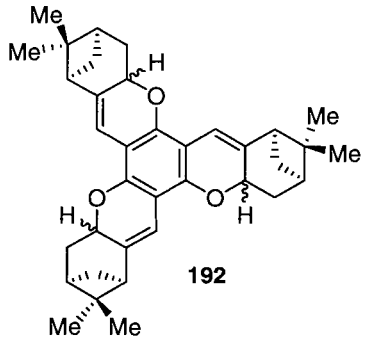
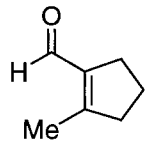
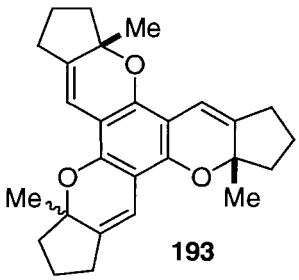
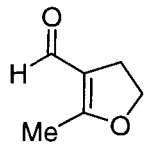
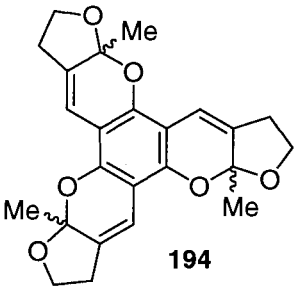
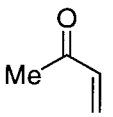
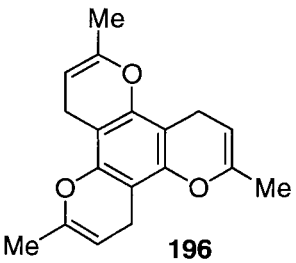
Table 3.6.2.1 Results Corresponding to Scheme 3.6.2.1

Entry	α,β-Unsaturated Carbonyl Compound	Chromene Derivative	Reaction Time	Yield (%)
1	 **152**	 **172**	4 h	57
2	 **156**	 **173**	135 min	52

Entry	α,β-Unsaturated Carbonyl Compound	Chromene Derivative	Reaction Time	Yield (%)
3	 **160**	 **174**	22 h	79
4	 **175**	 **176**	150 min	28*
5	 **177**	 (±)-**178**	4 h	61
6	 **179**	 **180**	150 min	0

(*) Isolated as the corresponding chromane following hydrogenation (H_2, Pd/C, MeOH, 18 h).

Entry	α,β-Unsaturated Carbonyl Compound	Chromene Derivative	Reaction Time	Yield (%)
7	 **181**	 **182**	24 h	0
8	 **183**	 **184**	22 h	0
9	 **185**	 **186**	105 min	0
10	 **187**	 **188**	19 h	0
11	 **189**	 **190**	4 h	0

Entry	α,β-Unsaturated Carbonyl Compound	Chromene Derivative	Reaction Time	Yield (%)
12	 **191**	 **192**	4 h	0
13	 **165**	 **193**	6 h	31*
14	 **169**	 **194**	105 min	0
15	 **195**	 **196**	6 h	14

Further examples of achiral 2,2-disubstituted chromenes were prepared when the reaction was performed with the three symmetric alkylidene aldehydes **152**, **156** and **160**

(*) Isolated as an inseparable mixture of two diastereoisomers (dr = 20:1, α:β).

(entries 1-3). In addition, when β-phenylcinnamaldehyde (**175**) was subjected to the reaction conditions, an unstable 2,2-disubstituted chromene derivative **176** was formed (entry 4). This instability was attributed to a 6π electrocyclic ring-opening reaction that afforded the corresponding *ortho*-quinone methides which could undergo further reactions. Therefore, the chromene **176** was immediately reduced (H_2, Pd/C, MeOH, 18 h) to afford the corresponding *tris*-chromane which proved to be a stable compound. It was appreciated that if an unsymmetric 2,2-disubstituted α,β-unsaturated aldehyde was employed in this reaction two possible diastereoisomers could be produced. To investigate the stereoselectivity of this process, the commercially available unsymmetric α,β-unsaturated aldehyde **177** (citral, E:Z = ~2:1) was employed as a reaction substrate (entry 5). The triple condensation product (±)-**178** was isolated in good yield. Interestingly, this chromene derivative was formed (based on inspection of the ^{1}H NMR spectrum of the crude reaction mixture) and isolated as a single C_3-symmetric diastereoisomer. Furthermore, unpublished research by the Wilson research group has shown that very high stereoselectivities can be obtained in this process with a variety of unsymmetric aldehydes.

A series of corresponding mono-substituted aldehydes were also used as reaction substrates. However, this led to the formation of a complex mixture of reaction products and the desired chromene products could not be isolated (entries 6-9). Similarly, the use of the aldehyde **187** did not lead to the formation of the 3-substituted chromene **188** nor were the 2,3-disubstituted chromene derivatives **190** and **192** prepared from the reactions of the aldehydes **189** and **191**, respectively (entries 10-12). Thus, it appears that the α,β-unsaturated aldehyde substrate needs to be 2,2-disubstituted.

Two attempts to prepare 2,2,3-trisubstituted *tris*-2*H*-chromenes were also performed. When the aldehyde **165** was employed as a reaction substrate, the desired carbocyclic xyloketal A analogue **193** was obtained in moderate yield (entry 13). In this case, the product was obtained as a mixture of diastereoisomers and the unsymmetric diastereoisomer was the major product (dr = 20:1, α:β). Unfortunately, the use of the dihydrofuran aldehyde **169** did not afford the desired demethyl xyloketal A analogue **194** possibly due to the instability of the aldehyde (entry 14).

Finally, the reaction of methyl vinyl ketone (**195**) with phloroglucinol (**14**) was performed in an attempt to prepare a 4-substituted *tris*-2*H*-chromene (entry 15). Unexpectedly, this resulted in the isolation of the isomeric 4*H*-chromene derivative **196**, in relatively low yield, from a complex mixture of reaction products. In this instance, the reaction substrate employed was an α,β-unsaturated ketone and presumably the isolated product was formed by a different reaction mechanism (Figure 3.6.2.1). Initial 1,4-addition of phloroglucinol (**14**) to methyl vinyl ketone (**195**) would afford the ketone **198**. The formation of a hemi-acetal of the ketone and one of the phenol moieties followed by a subsequent dehydration reaction would afford the 4*H*-chromene **200**. Repetition of this process would afford the observed reaction product **196**.

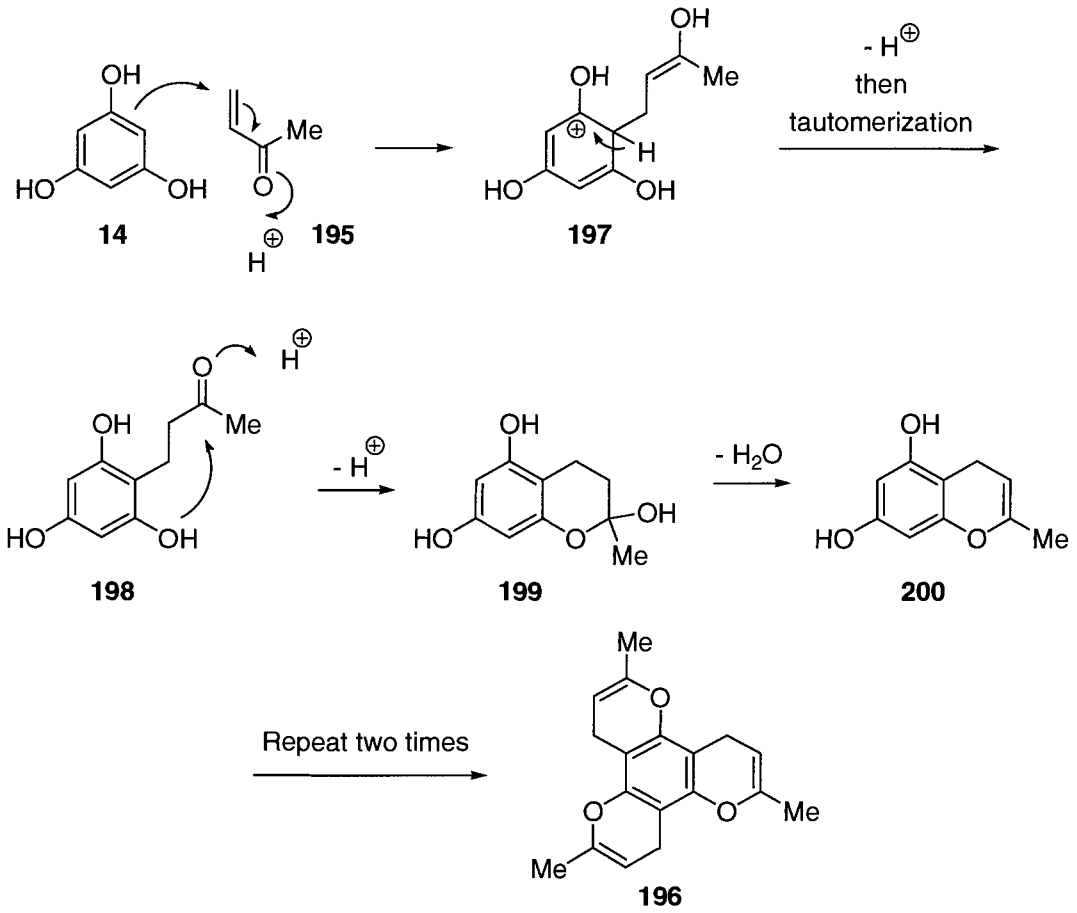


Figure 3.6.2.1 Proposed reaction mechanism for the formation of the *tris*-4*H*-chromene derivative (196).

Of final note, the corresponding double condensation reaction products were not isolated from any of the above condensation reactions.

3.6.3 X-Ray Crystal Structure Analysis of the *tris*-2*H*-Chromene (174)

The chromene derivative **174** proved to be a highly crystalline solid. Crystals that were suitable for X-ray crystallography were obtained on recrystallization from chloroform upon slow evaporation of the solvent (Figure 3.6.3.1). The unit cell was found to contain two molecules with the adamantyl group of one molecule positioned over the aromatic core of an adjacent molecule. It was noted that the chromene **174**

adopts an unsymmetric conformation in the solid state in which one of the adamantyl moieties is positioned below the plane of the aromatic core.

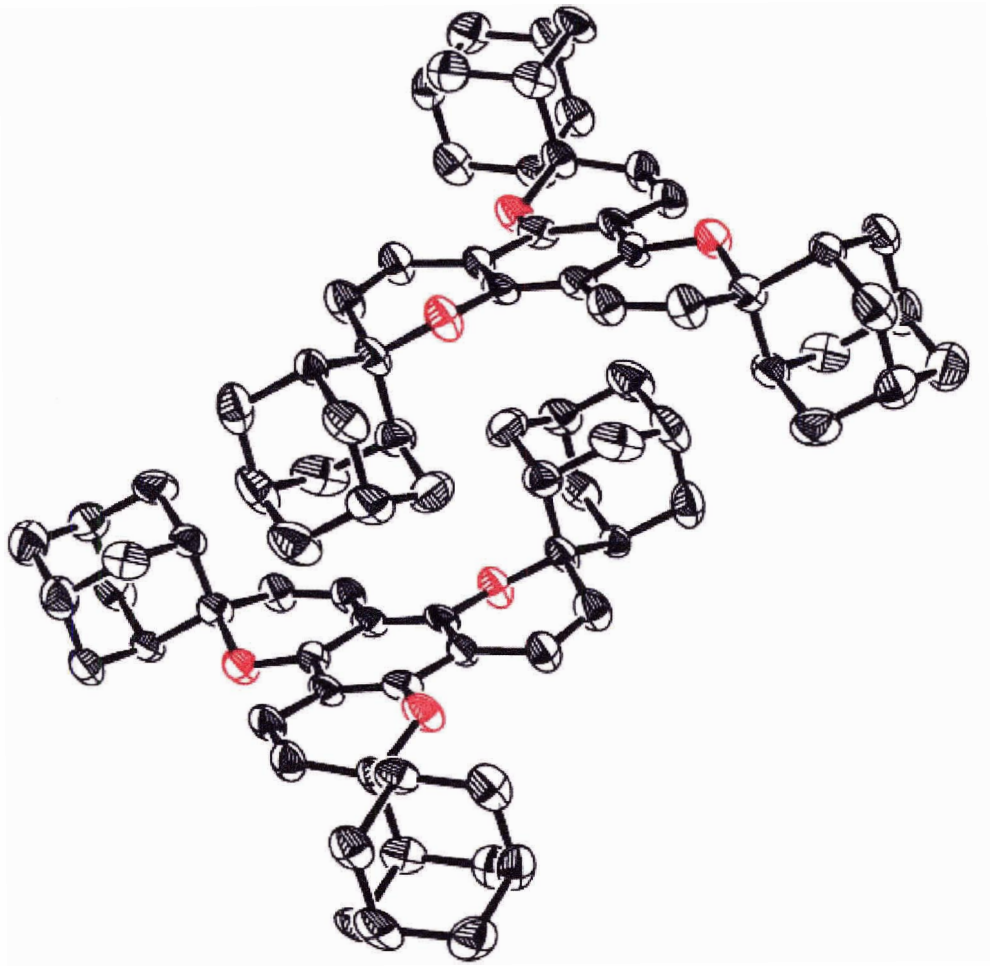


Figure 3.6.3.1 Unit cell of the X-ray crystal structure of the *tris*-2*H*-chromene (174) (the thermal ellipsoids are drawn at a 50% probability level and the hydrogen atoms have been omitted for clarity).

3.7 Synthesis of (4*R*)-2,4-Dimethyl-3-formyl-4,5-dihydrofuran

The synthesis of 2,4-dimethyl-3-formyl-4,5-dihydrofuran (**127**) for the preparation of xyloketal A (**1**) was subsequently investigated.

3.7.1 Attempted Synthesis of the Aldehyde (127) from an Acyclic Precursor

In principle, the synthetic process used for the preparation of 2-methyl-3-formyl-4,5-dihydrofuran (**169**) (See: Section 3.6.1) could be adapted to prepare the aldehyde **127** (Figure 3.7.1.1).[70,71] In the original synthesis, the lactone **166** was converted to the methyl ester **167** on reaction with hydrochloric acid in methanol. This process would have afforded the intermediate **202** which in turn cyclized to afford the hemi-acetal **204**. Subsequent elimination of water (or methanol) then would have afforded the reaction product **167**. It was anticipated that the synthesis of the lactone **201** or the ester **203** would provide the corresponding substrate for the synthesis of the fully substituted dihydrofuran **206**. The ester group of this compound could then be reduced to afford the desired aldehyde **127**.

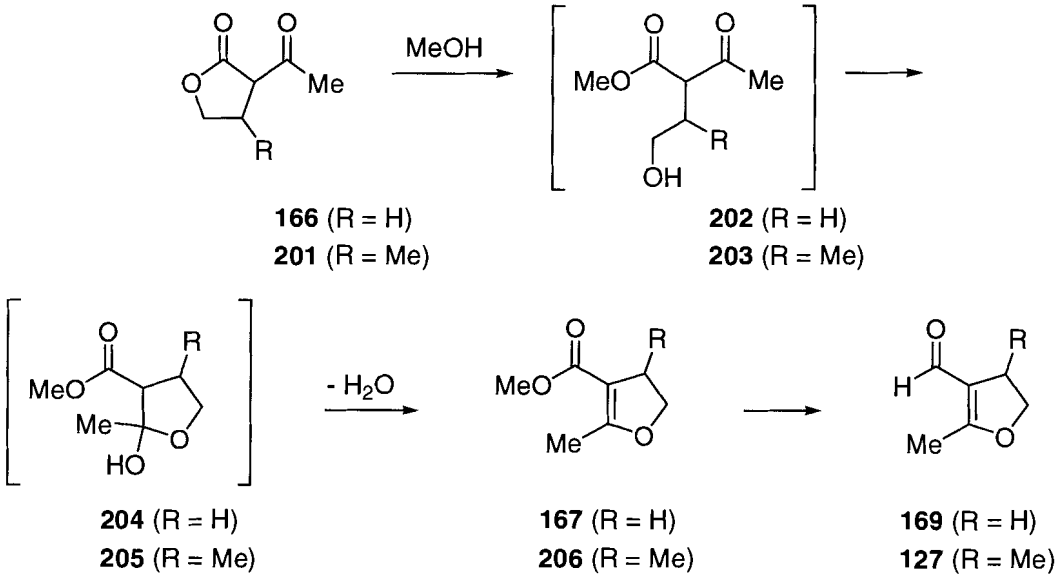
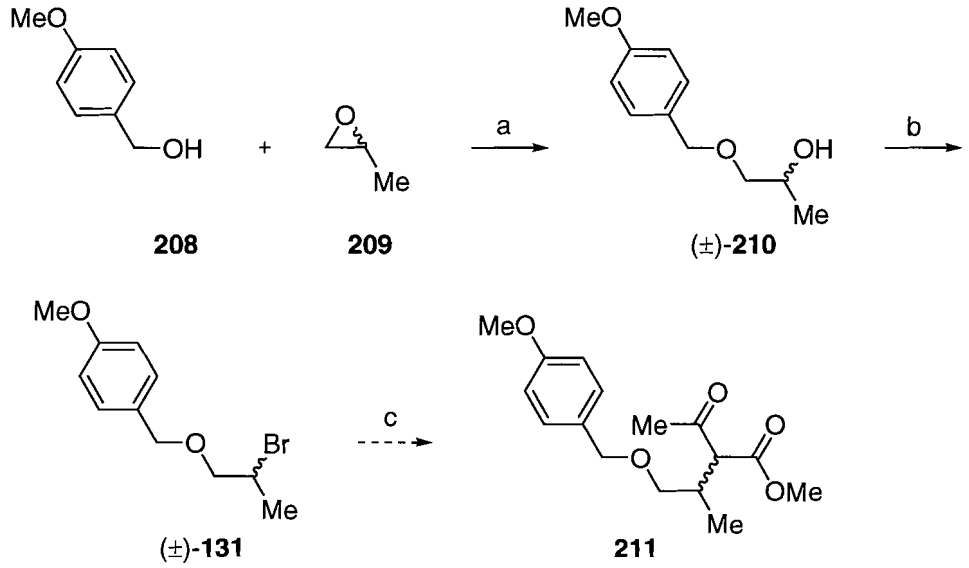


Figure 3.7.1.1 Intermediates involved in the formation of the dihydrofuran ester (169).

Towards this objective, propylene oxide (**209**) was allowed to react with *p*-methoxybenzyl alcohol (**208**) in the presence of sodium hydroxide to afford the

secondary alcohol (±)-**210** (Scheme 3.7.1.1).[86,87] This alcohol was then converted to the corresponding bromide (±)-**131** in good yield on reaction with triphenylphosphine, carbon tetrabromide and 2,6-lutidine.[88] A variety of methods were subsequently investigated to achieve reaction of this bromide with the anion of methyl acetoacetate (Table 3.7.1.1). The desired product of this reaction would be a protected version of the required alcohol **203**.

Scheme 3.7.1.1 Attempted Synthesis of the Ester (211) from Propylene Oxide (209)



Reagents and conditions: (a) NaOH, 65 °C, 24 h, 53%; (b) Ph_3P, CBr_4, 2,6-lutidine, THF, 56 h, 68%; (c) see below: Table 3.7.1.1.

Table 3.7.1.1 Reaction Conditions Corresponding to Scheme 3.7.1.1

Entry	Reagents and Conditions	Yield (%)
1	Methyl acetoacetate (1.25 equiv), Na (1.25 equiv), MeOH, reflux, 5.5 h	0
2	Methyl acetoacetate (5 equiv), Na (5 equiv), MeOH, reflux, 45 h	0

Entry	Reagents and Conditions	Yield (%)
3	Methyl acetoacetate (5 equiv), *n*-Bu_4NI (0.1 equiv), Na (5 equiv), MeOH, reflux, 45 h	0
4	Methyl acetoacetate (5 equiv), NaH (5 equiv), DMF, 100 °C, 21 h	0
5	Methyl acetoacetate (0.5 equiv), $CsCO_3$ (0.75 equiv), DMF, room temperature, 20 h	0

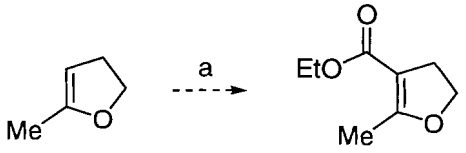
The reaction of the bromide (±)-**131** with several equivalents of the anion of methyl acetoacetate in the presence of sodium methoxide afforded complex mixtures of products from which the adduct **211** could not be isolated (entries 1 and 2).[89] The addition of tetrabutylammonium iodide (in order to generate a more reactive alkyl iodide) also afforded a complex mixture of products (entry 3).[90] Two different bases were employed to generate the anion of methyl acetoacetate. However, the use of sodium hydride[91] or cesium carbonate[92] failed to afford the desired reaction product **211** (entries 4 and 5). In view of these observations, an alternative route for the synthesis of the aldehyde **127** was investigated.

3.7.2 Elaboration of 2-Methyl-4,5-dihydrofuran (114)

Stetter and Lorenz have reported the direct conversion of 2,3-dihydrofuran to ethyl 2,3-dihydrofuran-4-carboxylate on reaction with ethyl chloroformate.[72] A similar reaction with 2,4-dimethyl-4,5-dihydrofuran (**61**) would directly afford the corresponding ester which could be converted to the aldehyde **127** (See: Section 3.6.1). To test if this process would be feasible, commercially available 2-methyl-4,5-dihydrofuran (**114**) was

allowed to react with ethyl chloroformate (Scheme 3.7.2.1). However, this reaction afforded a complex mixture of reaction products from which the desired reaction product **212** could not be isolated.

Scheme 3.7.2.1 Attempted Direct Synthesis of the Dihydrofuran Ester (212)

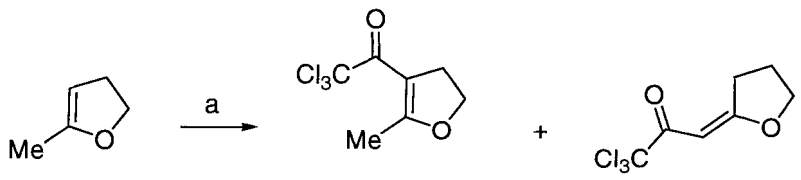


114 **212**

Reagents and conditions: (a) $ClCO_2Et$ (1.5 equiv), Et_2O, room temperature, 4 h.

An alternative reaction sequence to elaborate the model dihydrofuran **114** was then investigated. According to the work of Hojo and co-workers, this dihydrofuran was allowed to react with trichloroacetyl chloride and pyridine in dichloromethane at room temperature (Scheme 3.7.2.2).[93] This afforded the trichloroketone **213** and the regioisomeric ketone **214** in very high overall yield (98%). Presumably, the latter compound was formed *via* isomerization of the *endo*-cyclic dihydrofuran **114** to the corresponding *exo*-cyclic isomer under the reaction conditions. Of note, the trichloroketone **214** was isolated as a single geometrical isomer. The geometry of the double bond was not determined but it is reasonable to assume, based on electronic and steric considerations, that it is *trans*. To suppress the formation of the regioisomeric trichloroketone **214**, the reaction was repeated at –20 °C.[94] This reaction afforded the above products in a similar overall yield (95%) but with better regioselectivity (6:1) in favour of the desired reaction product **213**.

Scheme 3.7.2.2 Synthesis of the Trichloroketones (213) and (214) from 2-Methyl-4,5-dihydrofuran (114)

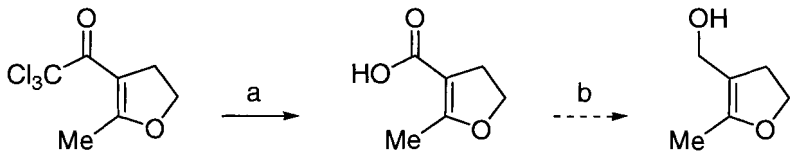


114 **213** **214**

Reagents and conditions: (a) Cl_3CCOCl, py, CH_2Cl_2, room temperature, 15 min, 62% (**213**), 36% (**214**) *or* Cl_3CCOCl, py, CH_2Cl_2, –20 °C to room temperature, 21 h, 79% (**213**), 16% (**214**).

The trichloroketone **213** was then converted to the corresponding carboxylic acid **215** on reaction with aqueous sodium hydroxide (Scheme 3.7.2.3).[70,95] However, the reduction of this material to the alcohol **168** with lithium aluminum hydride proved to be difficult and only trace amounts of this alcohol were obtained. This unexpected result was attributed to the formation of a relatively stable aluminum carboxylate salt which subsequently precipitated from solution and did not undergo reduction.

Scheme 3.7.2.3 Attempted Synthesis of the Alcohol (168) from the Carboxylic Acid (215)

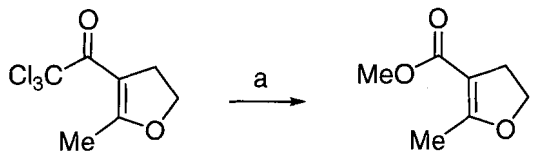


213 **215** **168**

Reagents and conditions: (a) NaOH, H_2O, room temperature, 2 h, 48%; (b) $LiAlH_4$, Et_2O, 0 °C to room temperature, 20 min.

Therefore, according to the work of de Buyck and co-workers, the ketone **213** was allowed to react with sodium bicarbonate in methanol to afford the previously prepared methyl ester **167** in high yield (Scheme 3.7.2.4).[96] Thus, a method for the elaboration of a dihydrofuran had been successfully identified and developed.

Scheme 3.7.2.4 Synthesis of the Ester (167) from the Trichloroketone (213)



213 167

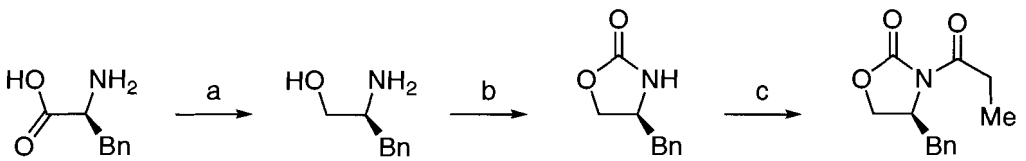
Reagents and conditions: (a) MeOH, $NaHCO_3$, reflux, 45 min, 96%.

3.7.3 Synthesis of Chiral Nonracemic (4*R*)-2,4-Dimethyl-3-formyl-4,5-dihydrofuran [(4*R*)-127]

A suitable procedure for the proposed synthesis of (4*R*)-2,4-dimethyl-3-formyl-4,5-dihydrofuran [(4*R*)-**127**] from (4*R*)-2,4-dimethyl-4,5-dihydrofuran [(4*R*)-**61**] was outlined in the previous section. However, at this stage, it was decided to prepare the dihydrofuran (4*R*)-**61** in an asymmetric fashion rather than using the relatively inefficient resolution procedure that was discussed previously (See: Section 2.8).

Towards these ends, the chiral oxazolidinone (4*S*)-**219** was prepared in three steps based on literature procedures (Scheme 3.7.3.1). Accordingly, commercially available (*S*)-phenylalanine [(*S*)-**216**] was reduced with lithium aluminum hydride to afford the alcohol (*S*)-**217**.[97,98] This material was then allowed to react with diethyl carbonate to afford the Evans auxiliary (4*S*)-**218**.[99,100] Attachment of the appropriate substrate was accomplished by reaction of the corresponding lithium amide of the auxiliary (4*S*)-**218**, prepared by deprotonation with *n*-butyl lithium, with propionyl chloride.[101] Of note, the oxazolidinone (4*S*)-**219**, and all of the intermediates *en route* to its preparation, had spectral data identical to those reported in the literature. In addition, the optical rotations of these compounds were in agreement, in both sense and magnitude, to the reported literature values. This confirmed the optical purity of these materials.

Scheme 3.7.3.1 Synthesis of the Chiral Oxazolidinone [(4*S*)-219] According to Literature Procedures

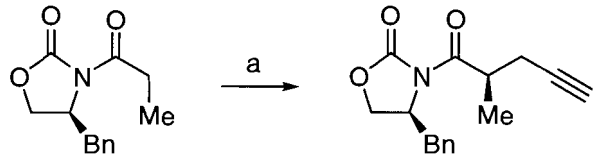


(*S*)-**216** (*S*)-**217** (4*S*)-**218** (4*S*)-**219**

Reagents and conditions: (a) $LiAlH_4$, THF, reflux, 5 h, room temperature, 15 h, 63%; (b) $(EtO)_2CO$, K_2CO_3, 135 °C, 1.5 h, 79%; (c) *n*-BuLi, THF, –78 °C, 25 min then EtCOCl, –78 °C, 35 min, room temperature, 45 min, 94%.

The conversion of the oxazolidinone (4*S*)-**219** to the acetylenic compound (+)-**220** was subsequently investigated (Scheme 3.7.3.2). Accordingly, the corresponding enolate of the oxazolidinone (4*S*)-**219** was generated and allowed to react with a propargyl halide under a variety of conditions. The results of these investigations are presented below (Table 3.7.3.1).

Scheme 3.7.3.2 Optimization of the Diastereoselective Alkylation Reaction of the Oxazolidinone [(4*S*)-219] with a Propargyl Halide



(4*S*)-**219** (+)-**220**

Reagents and conditions: (a) See below: Table 3.7.3.1.

Table 3.7.3.1 Reaction Conditions Corresponding to Scheme 3.7.3.2

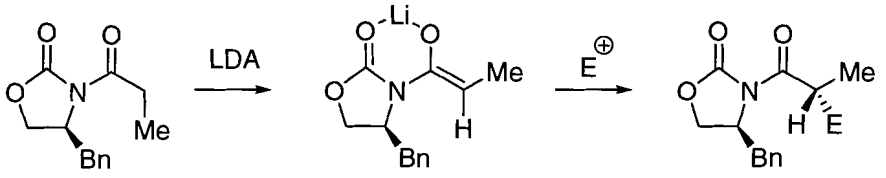
Entry	Reagents and Conditions	Yield (%)	dr
1	LDA (1.1 equiv), THF, –78 °C, 30 min then propargyl bromide (**71**) (1.5 equiv), –78 °C, 30 min, 0 °C, 2 h	49	7:1

Entry	Reagents and Conditions	Yield (%)	dr
2	LDA (1.1 equiv), THF, –78 °C, 30 min then propargyl bromide (**71**) (1.5 equiv), –78 to –20°C, 20 h	55	6:1
3	LDA (1.1 equiv), THF, –78 °C, 30 min then propargyl bromide (**71**) (4 equiv), –78 to 0°C, 23 h	53	6:1
4	LDA (1.5 equiv), THF, –78 °C, 30 min then propargyl bromide (**71**) (4 equiv), –78 to 0°C, 23 h	55	6:1
5	$TiCl_4$, CH_2Cl_2, 0 °C, 5 min then *N,N,N*-diisopropylethylamine (1.05 equiv), 0 °C, 5 min then propargyl chloride (2 equiv), 0 °C to room temperature, 18 h	0	N/A
6	$TiCl_4$, CH_2Cl_2, 0 °C, 5 min then *N,N,N*-diisopropylethylamine (1.05 equiv), 0 °C, 5 min then propargyl bromide (**71**) (2 equiv), 0 °C to room temperature, 18 h	0	N/A
7	LDA (1.5 equiv), THF, –78 °C, 30 min then HMPA –78 °C, 30 min then propargyl bromide (**71**) (4 equiv), –78 °C, 20 h	77	>20:1

In the first instance, the oxazolidinone (4*S*)-**219** was deprotonated with lithium *N,N*-diisopropylamide (1.1 equiv) in tetrahydrofuran at –78 °C and the resultant enolate was subsequently allowed to react with propargyl bromide (**71**) (1.5 equiv) at 0 °C for 2 h (entry 1).[102] This afforded the desired alkylated product (+)-**220** in moderate yield (49%) as a mixture of two diastereoisomers (dr = 7:1). It was attempted to improve the yield and diastereoselectivity of this process by repeating the above reaction and allowing it to warm slowly from –78 to –20 °C over 20 h (entry 2). In this case, the alkylated oxazolidinone (+)-**220** was isolated in 55% yield as a mixture of diastereoisomers (dr = 6:1). The use of an increased amount of lithium *N,N*-diisopropylamide (1.5 equiv) and

propargyl bromide (**71**) (4 equiv) did not significantly increase the yield and diastereoselectivity of the reaction (entries 3 and 4). The use of titanium tetrachloride and *N,N,N*-diisopropylethylamine to deprotonate the oxazolidinone (4*S*)-**219**, employing propargyl chloride or propargyl bromide (**71**) as alkylating agents, did not afford the desired compound (+)-**220** (entries 5 and 6).[103] However, it was subsequently found that use of hexamethylphosphoramide as an additive in this reaction led to an increase in both the yield and diastereoselectivity of the process (entry 7).[104,105,106] Accordingly, deprotonation of the oxazolidinone (4*S*)-**219** in a mixture of tetrahydrofuran and hexamethylphosphoramide (~10%) with lithium *N,N*-diisopropylamide (1.5 equiv), and on subsequent reaction with propargyl bromide (**71**) (4 equiv) at –78°C for 20 h, led to the formation of the desired reaction product (+)-**220** in good yield (77%) and as a single diastereoisomer.

The diastereoselectivity of the above reactions were determined by inspection of the crude ^{1}H NMR spectrum (400 MHz, $CDCl_3$). A doublet that corresponded to the methyl group of the major diastereoisomer (+)-**220** was observed at δ 1.29 ppm in addition to a signal corresponding to the minor diastereoisomer at δ 1.43 ppm. The absolute stereochemistry of the newly formed stereogenic centre was tentatively assigned as *R* based on consideration of the model proposed by Evans (Figure 3.7.3.1).[102] In this model, the electrophile approaches the less sterically hindered α-face of the predominate (*Z*)-lithium enolate (4*S*)-**221** to afford the major reaction product (2'*R*,4*S*)-**222**.



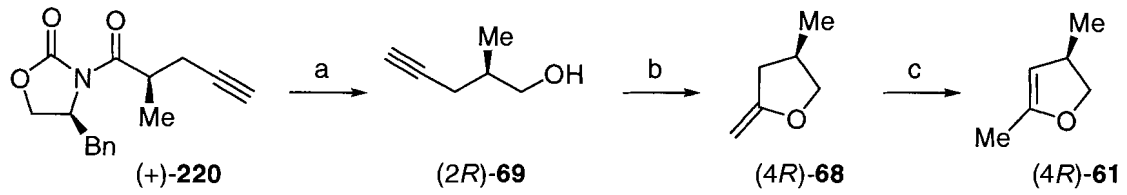
(4*S*)-**219** (4*S*)-**221** (2'*R*,4*S*)-**222**

Figure 3.7.3.1 Evans' stereochemical rationale for the alkylation reactions of the oxazolidinone [(4*S*)-219].

The increased diastereoselectivity observed when hexamethylphosphoramide was added to the reaction mixture can be attributed to the increased reactivity of the enolate at low temperature. The alkylation reaction of the enolate of the oxazolidinone (4*S*)-**219** occurred between –40 and –50 °C in tetrahydrofuran. In contrast, this reaction proceeded smoothly at –78 °C in tetrahydrofuran in the presence of hexamethylphosphoramide.

The alkylated oxazolidinone was then reduced with lithium aluminum hydride to afford the chiral nonracemic alcohol (2*R*)-**69** (Scheme 3.7.3.3).[102] Comparison of the sign of the optical rotation of this material with the material prepared by the resolution procedure, confirmed the absolute stereochemistry of the product. Furthermore, the high optical purity of this material was confirmed by comparison of the magnitude of the optical rotation to the material made by the resolution procedure. This acetylenic alcohol was subsequently converted to the *endo*-cyclic dihydrofuran (4*R*)-**68** on heating with a sub-stoichiometric amount of sodium amide followed by thermal-isomerization of the corresponding *exo*-cyclic dihydrofuran (4*R*)-**61** as previously discussed (See: Section 2.8.3).[22,23]

Scheme 3.7.3.3 Synthesis of the Dihydrofuran [(4*R*)-61] from the Oxazolidinone [(+)-220]

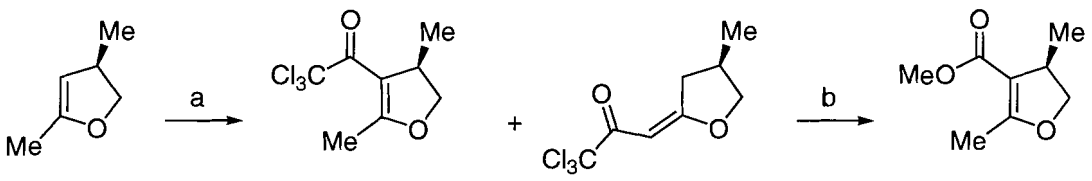


(+)-**220** (2*R*)-**69** (4*R*)-**68** (4*R*)-**61**

Reagents and conditions: (a) $LiAlH_4$, THF, 0 °C, 45 min, 73%; (b) $NaNH_2$, reflux, 4 h; (c) reflux, 18 h, 74% (over two steps).

In order to prepare the methyl ester (4*R*)-**206**, the dihydrofuran (4*R*)-**61** was allowed to react with trichloroacetyl chloride and pyridine at room temperature (Scheme 3.7.3.4).[93] As observed in the model studies, this afforded a readily separable mixture of the desired trichloroketone (4*R*)-**223** (45%) and a substantial quantity of the regioisomeric trichloroketone (4*R*)-**224** (46%). The ketone (4*R*)-**224** was isolated as a single geometric isomer which was again assumed to be the *trans* isomer. To suppress the formation of the undesired trichloroketone (4*R*)-**224**, the reaction was repeated at –78 °C. This resulted in the isolation of the desired trichloroketone (4*R*)-**223** in very good yield (93%).[94] Of note, the dihydrofuran (4*R*)-**61** used in this reaction was contaminated with approximately 7% of the *exo*-cyclic double bond isomer (4*R*)-**68**. Therefore, it is reasonable to conclude that at –78 °C the migration of the double bond from the *endo*-cyclic to the *exo*-cyclic position does not occur. Subsequent methanolysis of the trichloroketone (4*R*)-**223**, as previously described, afforded the methyl ester (4*R*)-**206** in excellent yield.[96]

Scheme 3.7.3.4 Synthesis of the Methyl Ester [(4*R*)-206] from the Dihydrofuran [(4*R*)-61]

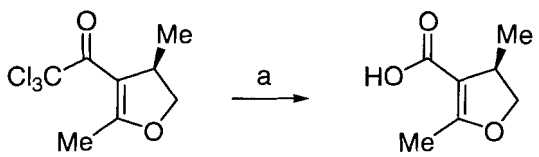


(4*R*)-**61** (4*R*)-**223** (4*R*)-**224** (4*R*)-**206**

Reagents and conditions: (a) Cl_3CCOCl, py, CH_2Cl_2, room temperature, 30 min, 45% [(4*R*)-**223**], 46% [(4*R*)-**224**] *or* Cl_3CCOCl, py, CH_2Cl_2, –78 °C to room temperature, 21 h, 93% [(4*R*)-**223**]; (b) trichloroketone (4*R*)-**223**, $NaHCO_3$, MeOH, reflux, 1 h, 98%.

It should also be noted that it was not possible to obtain satisfactory elemental analysis or a high-resolution mass spectrum of the ketone (4*R*)-**223** or the methyl ester (4*R*)-**206**. The ketone (4*R*)-**223** readily underwent hydrolysis upon storage. Attempted purification of the methyl ester (4*R*)-**206** by flash column chromatography resulted in partial loss of material and did not significantly increase the purity of the reaction product. Therefore, a sample of the trichloroketone (4*R*)-**223** was hydrolyzed to afford the carboxylic acid (4*R*)-**225** which proved to be stable and satisfactory elemental analysis was obtained (Scheme 3.7.3.5).[95]

Scheme 3.7.3.5 Synthesis of the Chiral Nonracemic Carboxylic Acid [(4*R*)-225] from the Trichloroketone [(4*R*)-223]



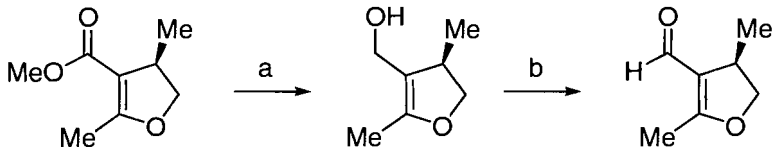
(4*R*)-**223** (4*R*)-**225**

Reagents and conditions: (a) $LiOH{\cdot}H_2O$, THF, H_2O, room temperature, 15 min, 88%.

The ester (4*R*)-**206** was converted to the aldehyde (4*R*)-**127** according to the procedure developed in the model studies (See: Section 3.6.1). Accordingly, the ester

(4*R*)-**206** was reduced to the alcohol (4*R*)-**226** with lithium aluminum hydride (Scheme 3.7.3.6). This material was then immediately converted to the desired aldehyde (4*R*)-**127** upon reaction with manganese dioxide in dichloromethane.

Scheme 3.7.3.6 Conversion of the Ester [(4*R*)-206] into the Aldehyde [(4*R*)-127]



(4*R*)-**206** (4*R*)-**226** (4*R*)-**127**

Reagents and conditions: (a) $LiAlH_4$, Et_2O, 0 °C to room temperature, 20 min; (b) MnO_2, CH_2Cl_2, room temperature, 46 h, 34% (over two steps).

Of note, the aldehyde (4*R*)-**127** obtained by this method was not particularly pure (~70%). Further purification by distillation or flash chromatography did not significantly increase the purity of the product. Derivatization of a portion of this material to the corresponding *N,N*-diphenyl hydrazone (which was expected to be a crystalline solid and aid in purification) was unsuccessful.[107] The sense of the optical rotation of the aldehyde (4*R*)-**127** was in agreement with that reported for the natural product.[69] Thus, the absolute stereochemistry of this natural product can be tentatively assigned as being *R*. Of note, this is the first total synthesis of this relatively simple natural product.

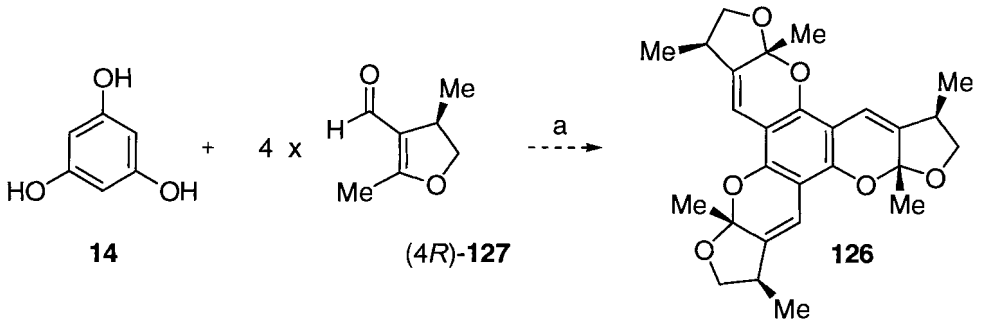
3.8 Attempted Synthesis of Xyloketal A: Phenylboronic Acid-Mediated Reaction

The application of the phenylboronic acid-mediated reaction to prepare (–)-xyloketal A [(–)-**1**] from chiral nonracemic (4*R*)-2,4-dimethyl-3-formyl-4,5-dihydrofuran [(4*R*)-**127**] was subsequently investigated.

3.8.1 Attempted Synthesis of the *tris*-2*H*-Chromene (126)

The chiral nonracemic aldehyde (4*R*)-**127** (4 equiv) was allowed to react with phloroglucinol (**14**) (1 equiv), phenylboronic acid (3 equiv) and propionic acid (**72**) (cat.) in benzene as previously described (Scheme 3.8.1.1). After 7 h, analysis by thin-layer chromatography indicated that the limiting reagent, phloroglucinol (**14**), had been consumed and a complex mixture of reaction products had formed. Inspection of the ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of the crude reaction mixture showed only trace amounts (<5%) of signals corresponding to 2*H*-chromene double bonds at δ ~6.6 ppm. Unfortunately, none of the desired reaction product **126** could be isolated from the reaction mixture.

Scheme 3.8.1.1 Attempted Synthesis of the *tris*-2*H*-Chromene (126)



Reagents and conditions: (a) $PhB(OH)_2$ (3 equiv), propionic acid (**72**) (cat.), PhH, reflux, 7 h.

3.9 Conclusions

An unprecedented phenylboronic acid-mediated triple condensation reaction of phloroglucinol (**14**) with a series of α,β-unsaturated aldehydes was developed. This experimentally simple reaction afforded novel C_3-symmetric chromene derivatives that represent structural analogues of the natural product xyloketal A (**1**). *tris*-2*H*-Chromenes with a 2,2-disubstitution or a 2,2,3-trisubstitution pattern were found to be stable. The

synthesis of derivatives that had alternative substitution patterns, proved to be less successful. In addition, the reduction of *tris*-2*H*-chromenes to the corresponding *tris*-chromanes proved to be an exceedingly facile process.

An asymmetric total synthesis of the chiral nonracemic dihydrofuran (4*R*)-**61** employing a chiral auxiliary to control the asymmetry of an alkylation reaction as a key step was developed in order to avoid the resolution procedure that was described previously. The elaboration of this material to the corresponding aldehyde (4*R*)-**127**, which constitutes the synthesis of this natural product, was also demonstrated. However, the subsequent reaction of this compound with phloroglucinol (**14**) did not provide the *tris*-2*H*-chromene derivative **126** required for the preparation of xyloketal A (**1**).

CHAPTER FOUR

Synthesis of the Xyloketals: Electrophilic Aromatic Substitution Reactions

4.1 Introduction

In this chapter the development and application of electrophilic aromatic substitution reactions for the synthesis of the xyloketal natural products is described.[†] An initial approach employing an appropriately substituted hydroxymethyl furan as the electrophile did not afford the natural products. However, the use of an appropriately substituted hydroxymethyl dihydrofuran in an exceedingly facile and diastereoselective boron trifluoride diethyl etherate-promoted electrophilic aromatic substitution reaction that was coupled to a bicyclic acetal formation reaction proved to be very successful. The optimization of this synthetic route led to syntheses of demethyl analogues of xyloketal A (**1**), B (**2**), C (**3**), D (**4**), E (**5**) and G (**7**). In addition, the asymmetric total syntheses of xyloketal A (**1**), B (**2**), D (**4**), E (**5**), F (**6**) and G (**7**) were completed.

4.2 Retrosynthetic Analysis: Electrophilic Aromatic Substitution Reactions with 2,4-Dimethyl-3-hydroxymethylfuran

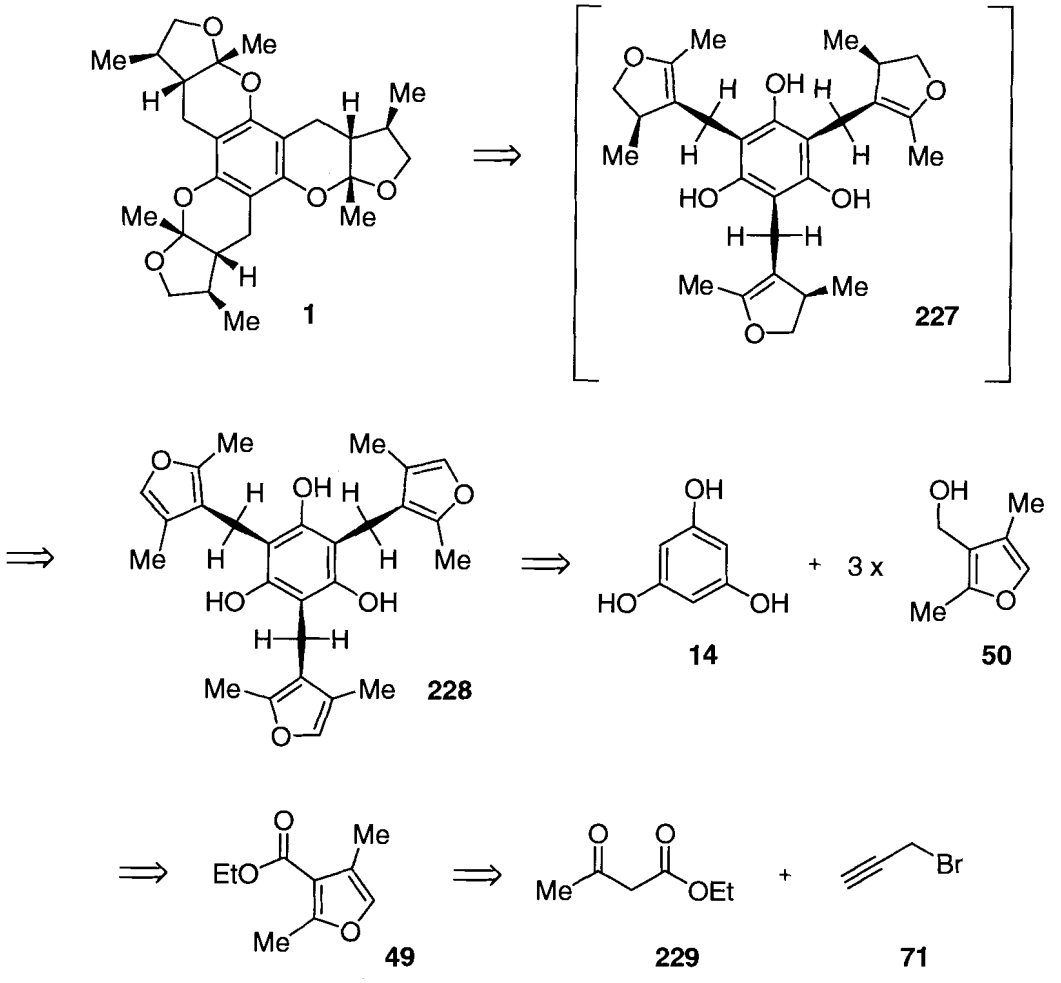
An initial approach, featuring a proposed electrophilic aromatic substitution reaction of phloroglucinol (**14**), for the total synthesis of xyloketal A (**1**) was based on the total synthesis of alboatrin (**48**) that was reported by Ichihara and co-workers.[11]

(†) The results discussed in this chapter have been reported in part, see: (a) *Synthesis of Xyloketal A, B, C, D, and G Analogues.* Pettigrew, J. D.; Wilson, P. D. *J. Org. Chem.* **2006**, *71*, 1620; (b) *Total Synthesis of (–)-Xyloketal A.* Pettigrew, J. D.; Wilson, P. D. *Org. Lett.* **2006**, *8*, 1427.

4.2.1 Retrosynthetic Analysis of Xyloketal A (1)

Xyloketal A (**1**) could be formed by three bicyclic acetal formation reactions of the intermediate **227** upon hydrogenation of the less substituted double bonds of compound **228** (Scheme 4.2.1.1). This compound could, in principle, be prepared by a triple electrophilic aromatic substitution of phloroglucinol (**14**) with an electrophile generated on ionization of the alcohol **50**. Of note, the yield of an analogous electrophilic aromatic substitution reaction used in the synthesis of alboatrin (**48**) was poor (~10%).[11] It is reasonable to assume that the low yield of this reaction was a result of multiple alkylation reactions of the electron rich phenolic precursor. In this system, however, exhaustive C-alkylation was required. The synthesis of the alcohol **50** has been reported from the ester **49** which in turn was prepared from ethyl acetoacetate (**229**) and propargyl bromide (**71**).[108]

Scheme 4.2.1.1 Retrosynthetic Analysis of Xyloketal A (1): Electrophilic Aromatic Substitution Reactions with 2,4-Dimethyl-3-hydroxymethylfuran (50)



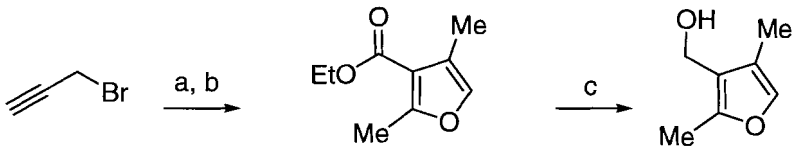
4.3 Attempted Synthesis of Xyloketal A: Electrophilic Aromatic Substitution Reactions with 2,4-Dimethyl-3-hydroxymethylfuran

4.3.1 Synthesis of 2,4-Dimethyl-3-hydroxymethylfuran (50)

The ester **49** was prepared in two steps from propargyl bromide (**71**) based on literature procedures (Scheme 4.3.1.1).[11,108] Accordingly, the bromide **71** was treated with dimethylsulfide to afford dimethylprop-2-ynylsulfonium bromide. This material

was then allowed to react with ethyl acetoacetate (**229**) in the presence of sodium ethoxide. This two step reaction sequence afforded the ester **49** in good overall yield (87%).

Scheme 4.3.1.1 Synthesis of the 2,4-Dimethyl-3-hydroxymethylfuran (50) from Propargyl Bromide (71)



71 **49** **50**

Reagents and conditions: (a) Me_2S, MeCN, room temperature, 24 h, 89%; (b) ethyl acetoacetate (**229**), Na, EtOH, reflux, 10 h, 98%; (c) $LiAlH_4$, Et_2O, 0 °C to room temperature, 20 min, 92%.

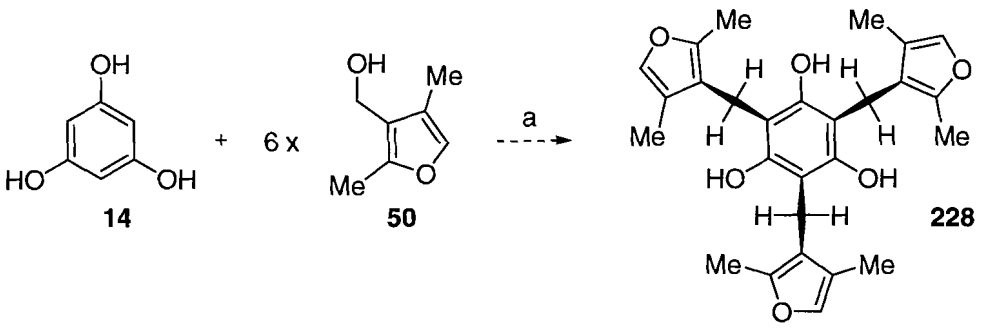
The initial attempt to reduce the ester **49** to the corresponding alcohol **50** according to a literature procedure with lithium aluminum hydride (1 equiv) proceeded in poor yield (13%).[109] In addition, a considerable amount of polymeric material was produced which suggested that the alcohol **50** was not a stable compound in the presence of the Lewis acidic aluminum salts. In subsequent reactions, it was found that increasing the number of equivalents of lithium aluminum hydride (4 equiv) and performing the reaction for a short period of time cleanly afforded the desired reaction product **50** in high yield (up to 92%).

4.3.2 Attempted Electrophilic Aromatic Substitution Reactions of Phloroglucinol (14) with 2,4-Dimethyl-3-hydroxymethylfuran (50)

A variety of reagents were screened in order to effect the triple electrophilic aromatic substitution reaction between phloroglucinol (**14**) and the hydroxymethyl furan **50** (Scheme 1.4.1.1). Accordingly, phloroglucinol (**14**) was allowed to react with the alcohol **50** (6 equiv, 2 equiv per phenolic site) in the presence of anhydrous magnesium

sulfate and a catalyst (20 mol%) in ether. The results of this extensive study are presented below (Table 4.3.2.1).

Scheme 4.3.2.1 Attempted Synthesis of the Hexasubstituted Benzene Derivative (50) from Phloroglucinol (228)



Reagents and conditions: (a) 20 mol% Catalyst (see below: Table 4.3.2.1), $MgSO_4$, Et_2O, room temperature, 15 min to 24 h.

Table 4.3.2.1 Catalysts Corresponding to Scheme 4.3.2.1

Entry	Catalyst	Result
1	$BF_3 \cdot Et_2O$	Complex mixture
2	$AlCl_3$	Complex mixture
3	$TiCl_4$	Complex mixture
4	BBr_3	Complex mixture
5	$MgCl_2$	Complex mixture
6	Alumina	No reaction
7	$ZnCl_2$	No reaction
8	Ti(*i*-PrO)$_4$	Complex mixture
9	HBF_4	Complex mixture
10	$SiCl_4$	Complex mixture
11	$InCl_3$	Complex mixture
12	Et_2AlCl	Complex mixture
13	$CuCl_2$	Complex mixture

Entry	Catalyst	Result
14	$SnCl_2$	Complex mixture
15	$FeCl_3$	Complex mixture
16	$CdCl_2$	No reaction
17	$MgBr_2 \cdot Et_2O$	No reaction
18	$NiCl_2$	No reaction
19	$MnCl_2 \cdot 4H_2O$	No reaction
20	$CoCl_2$	No reaction
21	NbF_5	Complex mixture
22	$NbCl_5$	Complex mixture
23	$NbBr_5$	Complex mixture
24	4Å Molecular sieves	No reaction
25	Silica gel	No reaction
26	$CrCl_3 \cdot 3THF$	Complex mixture
27	$GdCl_3 \cdot 6H_2O$	No reaction
28	$Sc(OTf)_3$	Complex mixture
29	HBF_4	Complex mixture
30	HCl	Complex mixture
31	$TsOH \cdot H_2O$	Complex mixture
32	PPTS	No reaction
34	AcOH	No reaction

The initial reaction conditions attempted were based on literature reports of the use of boron trifluoride diethyl etherate to promote electrophilic aromatic substitution reactions between allylic alcohols and phenols (entry 1).[11,110,111] However, these conditions afforded a complex mixture of reaction products from which the desired product **228** could not be isolated. In an attempt to identify suitable reaction conditions,

alternative solvents (THF, dioxane, DMF, DMSO), reaction temperatures (0 °C, –78 °C) and catalyst loadings (0.5%, 2%, 10%, 50%) were investigated. However, similar complex mixtures of reaction products were obtained.

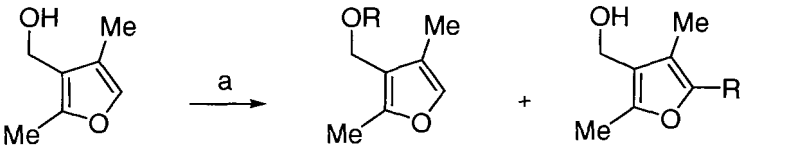
Further attempts to effect the desired reaction were focused on the identification of a suitable catalyst. An extensive series of Lewis acids (entries 2-28)[112,113,114,115] and Brønsted acids (entries 29-33)[116,117] were employed as potential promoters of the reaction. However, these reagents either caused the formation of complex mixtures of products or no reaction was observed.

Regardless of the reaction conditions employed, inspection of the crude ^{1}H NMR spectra of the complex mixtures that were formed in some of these reactions indicated that the *C*-5 position of the furan had taken part in the reaction. This suggested that the electron rich furan **50** acting as a competing site for electrophilic aromatic substitution under these reaction conditions. Thus, it was decided to temporarily block this site.

4.3.3 Attempted Derivatization of 2,4-Dimethyl-3-hydroxymethylfuran (50)

It was initially decided to employ a silicon protecting group, either a *t*-butyldimethylsilyl (TBS) or a trimethylsilyl (TMS), as the blocking group on the furan. It was anticipated that the dianion generated from the furan **50**, upon reaction with two or more equivalents of a strong base, could be allowed to react with a trialkylsilyl chloride to afford the desired C-silylated product **232** or **233** (Scheme 4.3.3.1).[118] Towards these objectives, the furan **50** (1 equiv) was metalated with either *n*-butyl lithium or *t*-butyl lithium ($\geq$ 2.2 equiv) and then a trialkylsilyl chloride. The results of these studies are presented below (Table 4.3.3.1).

Scheme 4.3.3.1 Attempted Direct C-Silylation of the Furan (50)



50 **230** (R = TBS) **232** (R = TBS)
231 (R = TMS) **233** (R = TMS)

Reagents and conditions: (a) See below: Table 4.3.3.1.

Table 4.3.3.1 Reagents and Conditions Corresponding to Scheme 4.3.3.1

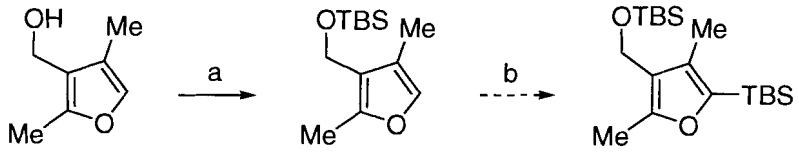
Entry	Reagents and Conditions	Yield of O-Silylated Product (230) or (231) (%)	Yield of C-Silylated Product (232) or (233) (%)
1	*n*-BuLi (2.2 equiv), THF, 0 °C, 2 h then TBSCl (1 equiv), 0 °C to room temperature, 18 h	52	0
2	*n*-BuLi (2.5 equiv), THF, room temperature, 2 h then TBSCl (1 equiv), room temperature, 18 h	57	0
3	*n*-BuLi (2.5 equiv), THF, reflux, 2 h then TBSCl (1 equiv), room temperature, 20 h	35	0
4	*n*-BuLi (5 equiv), THF, 0 °C, 2 h then TMSCl (8 equiv), 0 °C to room temperature, 22 h then acidic work-up	0	0
5	*t*-BuLi (2.2 equiv), THF, –78 °C to room temperature, 4 h then TBSCl (1 equiv), room temperature, 18 h	68	0

In the initial instance, a related procedure described by Keay and co-workers was employed. Thus, the furan **50** was deprotonated with *n*-butyl lithium (2.2 equiv) at 0 °C

for 2 h and then allowed to warm to room temperature in the presence of *t*-butyldimethylsilyl chloride (1 equiv) over 18 h (entry 1).[118] The product of this reaction was not the desired C-silylated **232** product but was the corresponding O-silylated compound **230** which was isolated in 52% yield. This suggested that the dianion had not formed. In an effort to generate the dianion of this furan, the reaction was repeated at room temperature and at reflux (entries 2 and 3). However, in these instances, the O-silylated product **230** was again isolated (57 and 35% yield, respectively). An attempt to form the trimethylsilyl derivative **233** according to the work reported by Schultz and co-workers (involving exhaustive silylation and selective cleavage of the resultant trimethylsiloxy moiety) did not afford the desired reaction product (entry 4).[119] This again suggested that the dianion had not formed. The final attempt to form the dianion of the furan **50** involved the use of *t*-butyl lithium. However, this also resulted in isolation of the O-silylated product **230** in modest yield (68%) (entry 5).

Since the dianion of the furan **50** could not be generated, the furan **50** was converted to the O-silylated product **230** under standard conditions[120] (Scheme 4.3.3.2). This material was then treated with *n*-butyl lithium followed by *t*-butyldimethylsilyl chloride. However, the desired product **234** was not formed and the starting material **230** was recovered.

Scheme 4.3.3.2 Attempted Two Step Synthesis of the C-Silylated Furan (234)

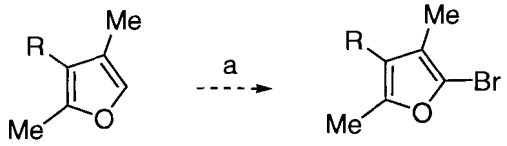


50 **230** **234**

Reagents and conditions: (a) TBSCl, imidazole, DMF, room temperature, 46 h, 99%; (b) *n*-BuLi, THF, 0 °C, 1 h *or* 5 h then TBSCl (1.2 equiv), 0 °C to room temperature, 20 h.

Given the unsuccessful installation of a silicon protecting group, it was decided to use a halogen as a blocking group as aromatic halides can be reduced under hydrogenation reaction conditions.[121] Thus, the alcohol **50** and the corresponding ester **49** were allowed to react with bromine and *N*-bromosuccinimide (Scheme 4.3.3.3).[122,123] Unfortunately, complex mixtures of products were formed in the reactions.

Scheme 4.3.3.3 Attempted Synthesis of the Brominated Furans (235) and (236)

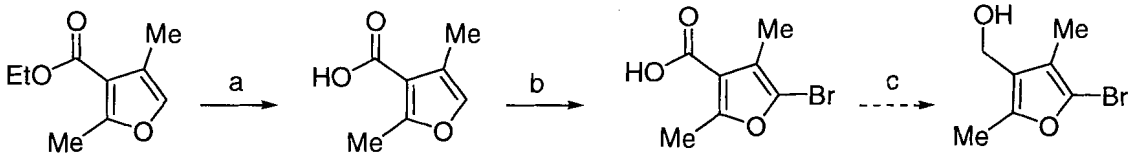


50 (R = CH_2OH) **235** (R = CH_2OH)
49 (R = CO_2Et) **236** (R = CO_2Et)

Reagents and conditions: (a) Br_2, $CHCl_3$, room temperature, 20 h *or* NBS, AcOH, room temperature, 2 h.

The ester **49** was subsequently converted to the corresponding carboxylic acid **237** (Scheme 4.3.3.4).[124] This material was then successfully converted to the bromofuran **238** upon treatment with bromine in acetic acid.[125]

Scheme 4.3.3.4 Attempted Synthesis of the Furan (235) from the Carboxylic Acid (237)



49 **237** **238** **235**

Reagents and conditions: (a) NaOH, H_2O, reflux, 3.5 h, 97%; (b) Br_2, AcOH, 0 °C to room temperature, 20 min, 54%; (c) $LiAlH_4$, Et_2O, 0 °C to room temperature, 15 min *or* BH_3·THF, THF, room temperature, 20 h *or* BH_3·DMS, THF, room temperature, 24 h.

Unfortunately, subsequent reduction of this carboxylic acid **238** with lithium aluminum hydride,[123] borane tetrahydrofuran complex[126] or borane dimethyl sulfide complex[127] resulted in the formation of complex mixtures of products from which the desired alcohol **235** could not be isolated.

4.4 Retrosynthetic Analysis of the Xyloketals: Electrophilic Aromatic Substitution Reactions with (4*R*)-2,4-Dimethyl-3-hydroxymethyl-4,5-dihydrofuran

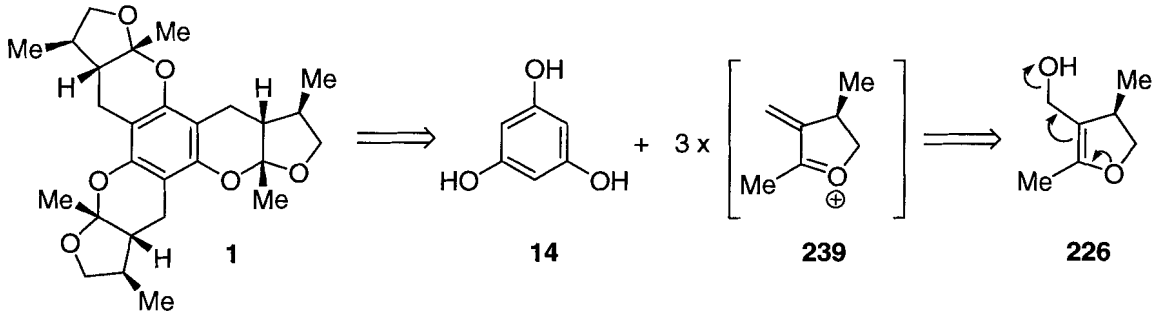
As a result of the above findings, an alternative approach to xyloketal A (**1**) and the other members of the xyloketal family of natural products was envisioned.

4.4.1 Retrosynthetic Analysis of Xyloketal A (1)

It was realized that a similar triple electrophilic aromatic substitution between phloroglucinol (**14**) and the reactive intermediate **239** would afford adducts that would then rearrange, under the reaction conditions, to afford the thermodynamically stable *cis*-fused bicyclic acetal moieties of xyloketal A (**1**) (Scheme 4.4.1.1). The reactive intermediate **239** in this reaction could, in principle, be generated by ionization of the alcohol **226** that had been prepared from the dihydrofuran **61** (See: Section 3.7.3). It was

expected that the stereochemistry of the acetal formation reactions would be controlled, based on steric arguments, by the *C*-4 methyl substituent of the parent alcohol **226**.

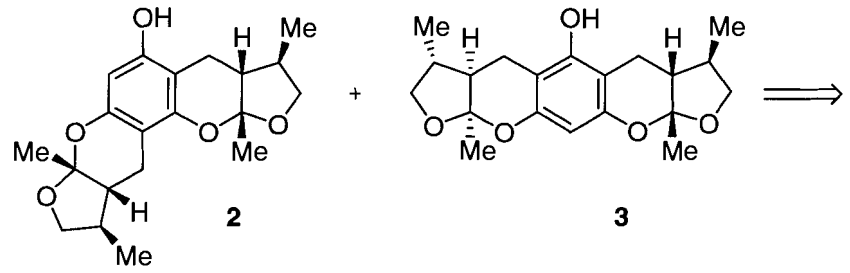
Scheme 4.4.1.1 Retrosynthetic Analysis of Xyloketal A (1): Electrophilic Aromatic Substitution Reactions with 2,4-Dimethyl-3-hydroxymethyl-4,5-dihydrofuran (226)

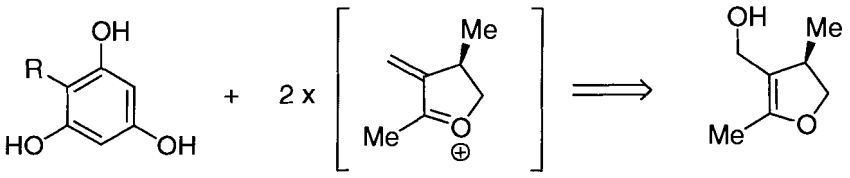


4.4.2 Retrosynthetic Analysis of Xyloketal B (2) and C (3)

In a similar manner, xyloketal B (**2**) and C (**3**) could be prepared on execution of a selective double electrophilic aromatic substitution reaction of phloroglucinol (**14**) (R = H) or with the previously prepared substituted triphenol **112** (R = CO_2Me) (Scheme 4.4.2.1). A subsequent decarboxylative saponification reaction of the latter products, would then afford the target compounds **2** and **3**.

Scheme 4.4.2.1 Retrosynthetic Analysis of Xyloketal B (2) and C (3): Electrophilic Aromatic Substitution Reactions with 2,4-Dimethyl-3-hydroxymethyl-4,5-dihydrofuran (226)





14 (R = H)
112 (R = CO_2Me)

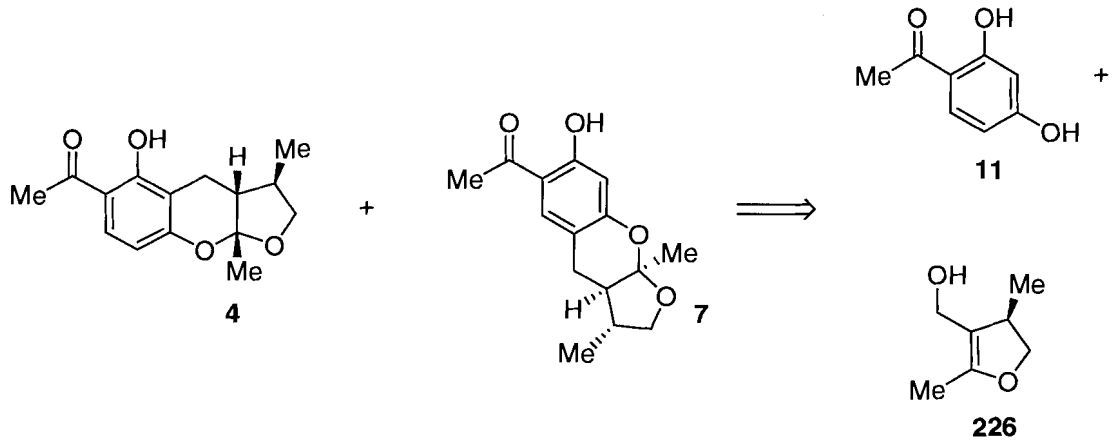
239

226

4.4.3 Retrosynthetic Analysis of Xyloketal D (4) and G (7)

Xyloketal D (**4**) and, in principle, the regioisomer, xyloketal G (**7**), could also be prepared from the corresponding aromatic phenol, 2,4-dihydroxyacetophenone (**11**), and the alcohol **226** (Scheme 4.4.3.1). In previous examples of electrophilic substitution reactions of the acetophenone **11**, only the regioisomeric products that corresponded to xyloketal D (**4**) were isolated (See: Section 2.4.1). However, Krohn and co-workers have reported that both xyloketal D (**4**) and G (**7**) can be prepared by a conjugate addition reaction of 2,4-dihydroxyacetophenone (**11**) and an enone.[9,10]

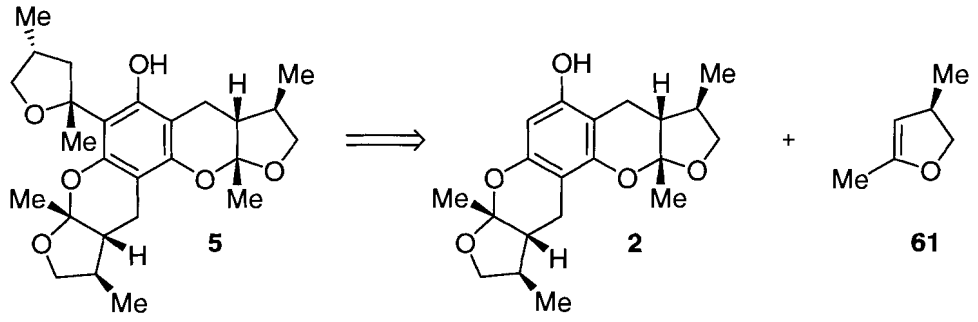
Scheme 4.4.3.1 Retrosynthetic Analysis of Xyloketal D (4) and G (7): Electrophilic Aromatic Substitution Reactions with 2,4-Dimethyl-3-hydroxymethyl-4,5-dihydrofuran (226)



4.4.4 Retrosynthetic Analysis of Xyloketal E (5) from Xyloketal B (2) and 2,4-Dimethyl-4,5-dihydrofuran (61)

It was anticipated that xyloketal B (**2**) could be subsequently converted to xyloketal E (**5**) on reaction with 2,4-dimethyl-4,5-dihydrofuran (**61**) under acidic conditions (Scheme 4.4.4.1).[128,129,130,131]

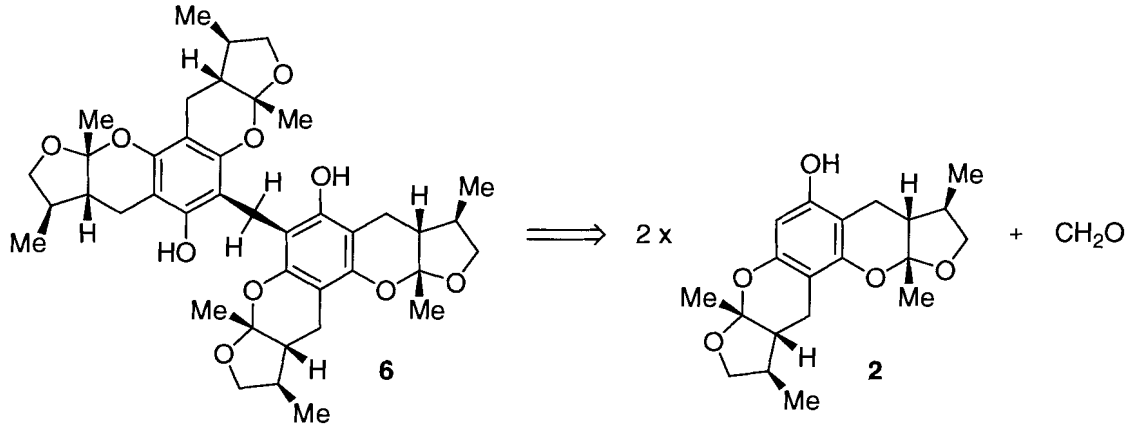
Scheme 4.4.4.1 Retrosynthetic Analysis of Xyloketal E (5) from Xyloketal B (2) and 2,4-Dimethyl-4,5-dihydrofuran (61)



4.4.5 Retrosynthetic Analysis of Xyloketal F (6) from Xyloketal B (2)

Xyloketal F (**6**)* could be made by reacting two equivalents of xyloketal B (**2**) with one equivalent of formaldehyde (Scheme 4.4.6.1).[132,133,134]

Scheme 4.4.5.1 Retrosynthetic Analysis of Xyloketal F (6) from Xyloketal B (2)

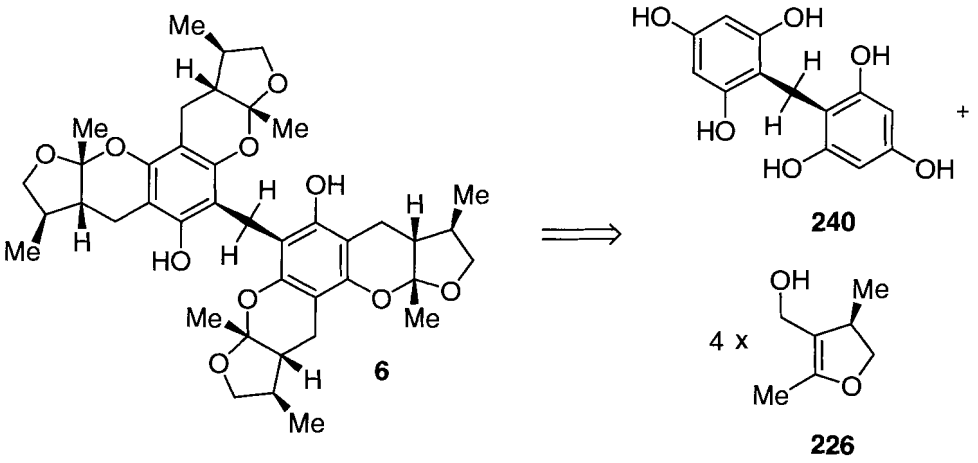


4.4.6 Retrosynthetic Analysis of Xyloketal F (6) from 2,4-Dimethyl-3-hydroxymethyl-4,5-dihydrofuran (226)

An alternative direct synthesis of xyloketal F (**6**) was also conceived. This would involve the execution of a quadruple electrophilic aromatic substitution reaction of the known hexaphenol **240** and the alcohol **226** (Scheme 4.4.6.1).[135,136]

(*) Professor Lin informed us of the molecular structure of xyloketal F (**6**) before it was reported in the chemical literature. As such, our initial investigation towards the synthesis of xyloketal F (**6**) from xyloketal B (**2**) was independently proposed and executed prior to his semi-synthesis of this natural product by a similar set of conditions(See: Ref. 3).

Scheme 4.4.6.1 Retrosynthetic Analysis of Xyloketal F (6) from 2,4-Dimethyl-3-hydroxymethyl-4,5-dihydrofuran (226)



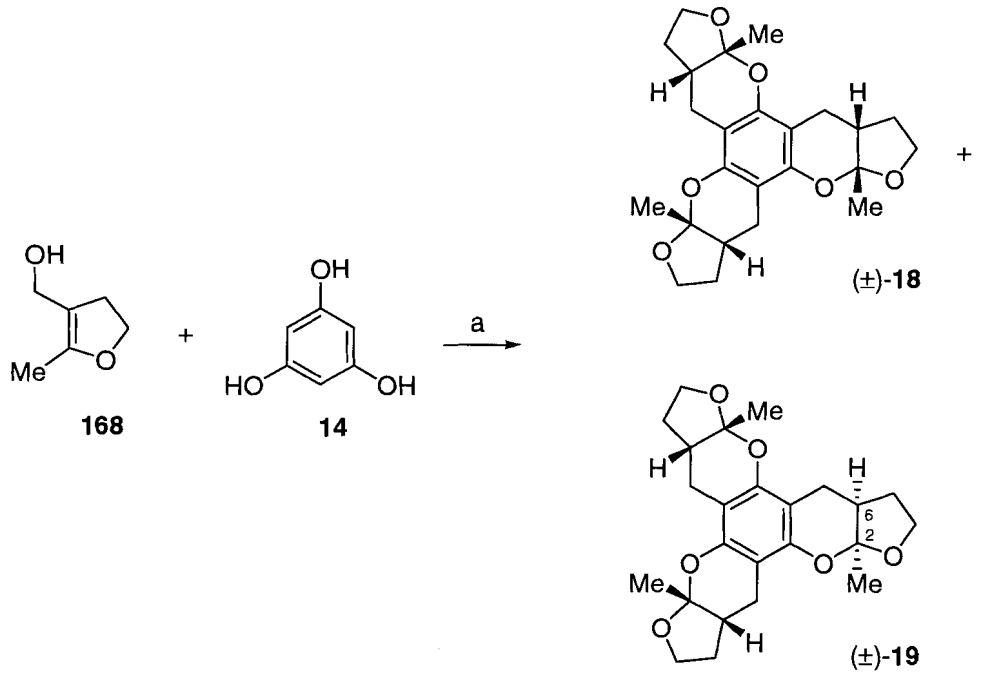
It was possible that this direct method would produce a mixture of three regioisomers including xyloketal F (**6**). However, it was expected that the other regioisomers, which have structures that are related to the unstable natural product xyloketal C (**3**), could be isomerized to give exclusively xyloketal F (**6**).

4.5 Model Studies: Electrophilic Aromatic Substitution Reactions with 2-Methyl-3-hydroxymethyl-4,5-dihydrofuran

4.5.1 Synthesis of (±)-11-Trinorxyloketal A [(±)-18] and (±)-2,6-*epi*-11,11',11''-Trinorxyloketal A [(±)-19]

In order to optimize the reaction conditions required for the total synthesis of the xyloketals, model studies were performed (Scheme 4.5.1.1). Accordingly, phloroglucinol (**14**) (1 equiv) was allowed to react with the alcohol **168** (6 equiv, 2 equiv per phenolic site) and a catalyst in the presence of anhydrous magnesium sulfate in ether. The results of these studies are presented below (Table 4.5.1.1).

Scheme 4.5.1.1 Synthesis of (±)-11-Trinorxyloketal A [(±)-18] and (±)-2,6-*epi*-11,11',11''-Trinorxyloketal A [(±)-19]: Electrophilic Aromatic Substitution Reactions with 2-Methyl-3-hydroxymethyl-4,5-dihydrofuran (168)



Reagents and condition: (a) See below: Table 4.5.1.1.

Table 4.5.1.1 Reagents and Conditions Corresponding to Scheme 4.5.1.1*

Entry	Reagents and Conditions	Yield of [(±)-18] and [(±)-19] (%)
1	$BF_3 \cdot Et_2O$ (2.7 equiv), $MgSO_4$, Et_2O, 0 °C, 15 min	36
2	$BF_3 \cdot Et_2O$ (2.7 equiv), $MgSO_4$, Et_2O, –78 °C, 15 min	35
3	$BF_3 \cdot Et_2O$ (1.3 equiv), $MgSO_4$, Et_2O, 0 °C, 15 min	69
4	$BF_3 \cdot Et_2O$ (1.0 equiv), $MgSO_4$, Et_2O, 0 °C, 15 min	93

(*) All reactions afforded an inseparable mixture of the xyloketal A analogues (±)-**18** and (±)-**19** (dr = 2:7).

Entry	Reagents and Conditions	Yield of [(±)-18] and [(±)-19] (%)
5	$BF_3 \cdot Et_2O$ (0.5 equiv), $MgSO_4$, Et_2O, 0 °C, 15 min	77
6	$BF_3 \cdot Et_2O$ (0.25 equiv), $MgSO_4$, Et_2O, 0 °C, 15 min	77
7	HF (cat), $MgSO_4$, Et_2O, 0 °C, 15 min	77
8	*p*-TsOH·H_2O (1.0 equiv), $MgSO_4$, Et_2O, 0 °C, 15 min	71
9	Acetic acid (2.7 equiv), $MgSO_4$, Et_2O, 0 °C to room temperature, 72 h	0
10	$MgSO_4$, Et_2O, 0 °C to room temperature, 4 h	0

The initial reaction conditions selected for the triple electrophilic aromatic substitution reaction of phloroglucinol (**14**) with the alcohol **168** were based on a report by Razdan and co-workers on the synthesis of Δ^1-tetrahydrocannabinol (THC) from *p*-mentha-2,8-dienol and olivetol.[110] A two-fold excess of the unstable alcohol **168** was employed per phenolic reaction site and the initial reaction involved stirring a mixture of the phloroglucinol (**14**) (1 equiv) and the alcohol **168** (6 equiv) in ether at 0 °C in the presence of anhydrous magnesium sulfate and boron trifluoride diethyl etherate (2.7 equiv) (entry 1). The xyloketal A analogues (±)-**18** and (±)-**19** were formed rapidly and the limiting starting material, phloroglucinol (**14**), was consumed in less than 15 min. These compounds were isolated, in pure form and in reasonable yield (36%), as an inseparable mixture of two diastereoisomers (dr = 2:7). The corresponding *mono*- and *bis*-adducts were not isolated from this reaction. In addition, no evidence for the

formation of these intermediates was observed by thin layer chromatography during the course of the reaction. It would be expected that these more substituted and electron-rich intermediates would react at a faster rate than the limiting starting material, phloroglucinol (**14**).

In order to improve the efficiency of this new reaction, the reaction was repeated at a lower temperature (–78 °C) (entry 2). However, the desired products were isolated in essentially the same yield and diastereoselectivity after 15 min. In this instance, as in the initial experiment, phloroglucinol (**14**) was completely consumed and highly polar or polymeric reaction by-products were also formed. Thus, it was decided to systematically decrease the number of equivalents of boron trifluoride diethyl etherate and explore the use of different acid promoters. On employing boron trifluoride diethyl etherate (1.3 equiv), at 0 °C, a dramatic improvement in the isolated yield of the xyloketal A analogues (±)-**18** and (±)-**19** (69%) was recorded (entry 3). Moreover, the use of one equivalent of boron trifluoride diethyl etherate (~0.3 equiv per phenolic reaction site) led to an exceptionally clean synthetic transformation and the isolation of the xyloketal A analogues (±)-**18** and (±)-**19** in excellent yield (93%) (entry 4). The isolated yield of these reaction products is truly remarkable in view of the fact that this transformation involves, minimally, six individual reactions. Decreasing the number of equivalents of boron trifluoride diethyl etherate further resulted in the isolation of the desired reaction products (±)-**18** and (±)-**19** in lower yields (entries 5 and 6). It was found that concentrated hydrofluoric acid (which could have been involved in the reactions described above) and *p*-toluenesulfonic acid also promoted this reaction in good yield (entries 7 and 8). None of the desired products were formed on performing the reactions

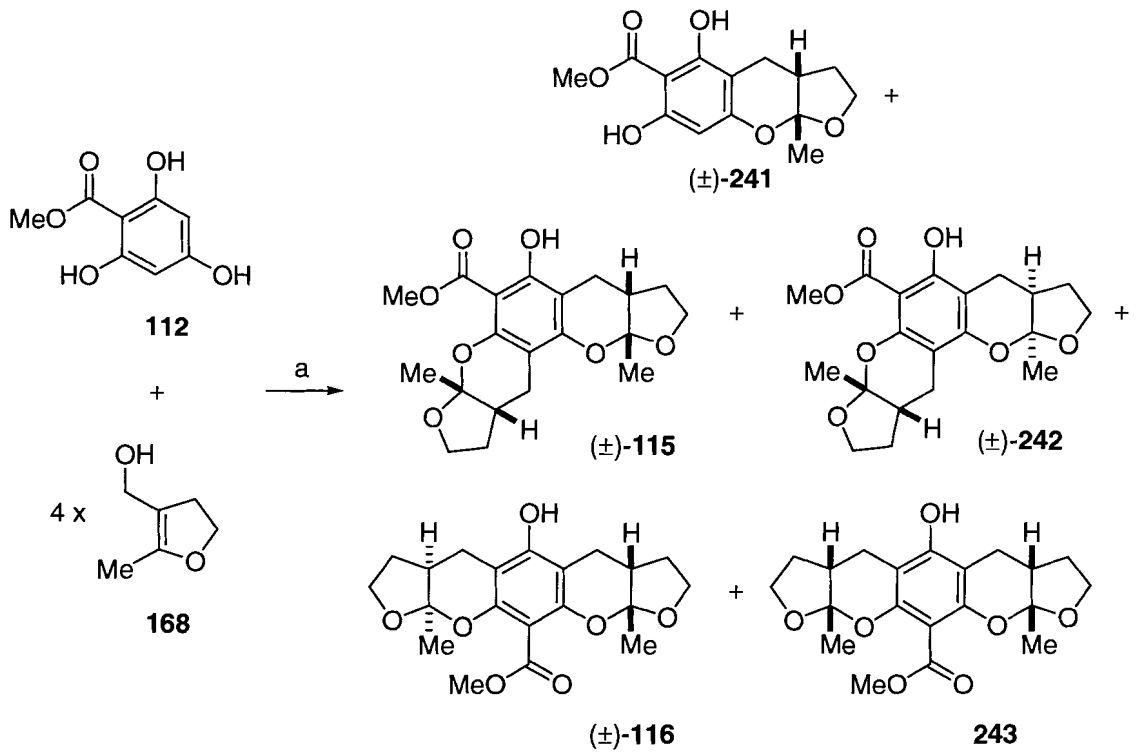
at room temperature in the absence of an acid promoter or in the presence of acetic acid (entries 9 and 10, respectively).

Of note, the desired C_3-symmetric diastereoisomer (±)-**18**, which has the same relative stereochemistry as xyloketal A (**1**), was the minor component in all of these reactions. This was indicated by the ^{1}H and ^{13}C NMR spectra which were dominated by the complex series of signals of the major unsymmetric diastereoisomer (±)-**19** (See: Section 2.5.2). However, it was anticipated that the stereochemistry of the *C*-4 methyl substituent of the chiral nonracemic alcohol (4*R*)-**226** would correctly direct the diastereoselectivity of the triple condensation reactions, in an absolute sense, on attempting the asymmetric total synthesis of (–)-xyloketal A [(–)-**1**].

4.5.2 Synthesis of (±)-11,11'-Dinorxyloketal B [(±)-16] and (±)-2,6-*epi*-11,11'-Dinorxyloketal B [(±)-17]

It was considered that analogues of xyloketal B (**2**) and C (**3**) could be prepared by decreasing the number of the equivalents of the alcohol **168** employed in the above optimized reaction with phloroglucinol (**14**). However, given the relative instability of this alcohol and the observed propensity for the preferential formation of the *tris*-adducts (±)-**18** and (±)-**19** [as well as to prepare analogues of xyloketal B (**2**) and C (**3**) in acceptable yield], it was decided to employ the ester **112** as a reaction substrate (Scheme 4.5.2.1). Accordingly, the ester **112** (1 equiv) was allowed to react with the alcohol **168** (4 equiv, 2 equiv per phenolic site) and boron trifluoride diethyl etherate in the presence of anhydrous magnesium sulfate in ether. The results of these studies are presented below (Table 4.5.2.1).

Scheme 4.5.2.1 Synthesis of the Methyl Ester Xyloketal B and C Analogues [(±)-115], [(±)-242], [(±)-116] and (243): Electrophilic Aromatic Substitution Reactions with 2-Methyl-3-hydroxymethyl-4,5-dihydrofuran (168)



Reagents and conditions: (a) See below: Table 4.5.2.1.

Table 4.5.2.1 Reagents and Conditions Corresponding to Scheme 4.5.2.1

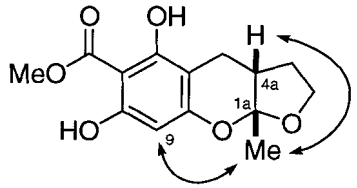
Entry	Reagents and Conditions	Yield of [(±)-241] (%)	Yield of [(±)-115:(±)-242:(±)-116:243] (%)	Product Ratio [(±)-115:(±)-242:(±)-116:243]
1	$BF_3 \cdot Et_2O$ (1.0 equiv), $MgSO_4$, Et_2O, 0 °C to room temperature, 4 h	6	50	6:6:1:1
2	$BF_3 \cdot Et_2O$ (1.0 equiv), $MgSO_4$, Et_2O, 0 °C to room temperature, 36 h	0	51	10:10:1:1

Entry	Reagents and Conditions	Yield of [(±)-241] (%)	Yield of [(±)-115:(±)-242:(±)-116:243] (%)	Product Ratio [(±)-115:(±)-242:(±)-116:243]
3	$BF_3 \cdot Et_2O$ (0.7 equiv), $MgSO_4$, Et_2O, 0 °C to room temperature, 46 h	0	58	10:10:1:1

In the first instance, the methyl ester **112** (1 equiv) was allowed to react with the alcohol **168** (4 equiv), boron trifluoride diethyl etherate (1 equiv) and magnesium sulfate in ether and the resultant mixture was allowed to warm from 0 °C to room temperature over 4 h (entry 1). On subsequent purification of the crude reaction mixture by flash chromatography, the *mono*-adduct (±)-**241** (6%) and a mixture (6:6:1:1) of the substituted xyloketal B analogues (±)-**115** and (±)-**242** as well as the substituted xyloketal C analogues (±)-**116** and **243** (50% combined yield) were isolated. On performing the above reaction for an extended period of time (36 h), a mixture (10:10:1:1) of the substituted xyloketal B analogues (±)-**115** and (±)-**242** as well as the substituted xyloketal C analogues (±)-**116** and **243** was isolated (51% combined yield) (entry 2). In this instance, none of the *mono*-adduct (±)-**241** was present in the crude reaction mixture and less of the unstable xyloketal C analogues (±)-**116** and **243** were formed. The xyloketal C analogues (±)-**116** and **243** presumably were converted to the xyloketal B analogues (±)-**115** and (±)-**242** during the extended reaction time. The substituted xyloketal B analogues (±)-**115** and (±)-**242** could also be separated from the substituted xyloketal C analogues (±)-**116** and **243**, in this instance, following further purification by flash chromatography. It was subsequently found that the above products could be prepared in

improved yield (58%) on decreasing the amount of boron trifluoride diethyl etherate employed in the process (0.7 equiv, ~0.3 equiv per phenolic reaction site) and on performing the reaction for 46 h (entry 3). Of note, the slower rate and lower isolated yields of these latter reactions as compared to that used to prepare the xyloketal A analogues (±)-**18** and (±)-**19** reflects the decreased reactivity of the less electron-rich phenol **112** as compared to phloroglucinol (**14**).

The ^{1}H and ^{13}C NMR spectra of the *mono*-adduct (±)-**241** were very similar to the xyloketal D analogue (±)-**12** (See: Section 2.5.1). Similar methods were used to determine the structure of the product. In particular, nOe contacts were observed between *Me*-1a and *H*-4a and between *Me*-1a and *H*-9 (Figure 4.5.2.1). Therefore, the relative stereochemistry and the regiochemistry of the product (±)-**241** were firmly established.



(±)-**241**

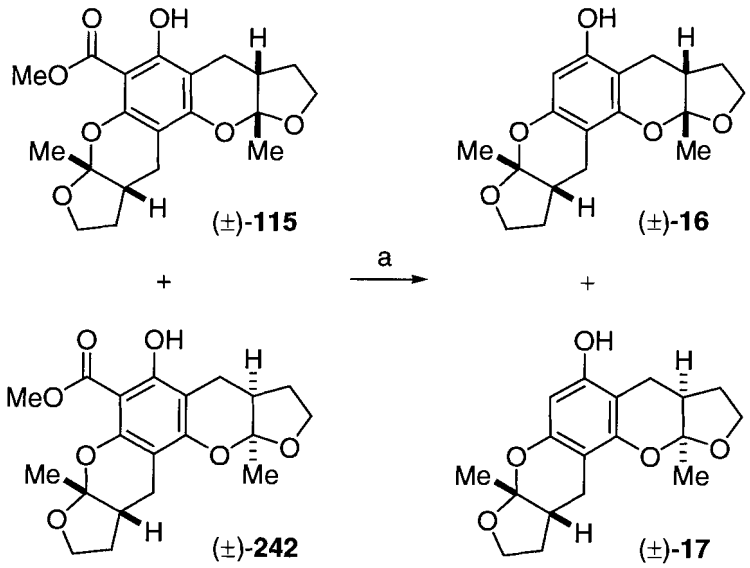
Figure 4.5.2.1 Observed nOe contacts for the methyl ester [(±)-241].

The regiochemistry of major reaction products (±)-**115** and (±)-**242** (dr = 1:1) was assigned based upon inspection of the ^{1}H and ^{13}C NMR spectra. The ^{1}H NMR spectrum contained two sharp down field signals (δ 11.99 and 12.00 ppm) indicating that the phenol moieties were hydrogen-bonded to an adjacent carbonyl group.[1,21] In addition, both the ^{1}H and ^{13}C NMR spectra contained groups of complex multiplets which could only result from the xyloketal B analogues (±)-**115** and (±)-**242** (the corresponding

xyloketal C analogues (±)-**116** and **243** contain a C_2-axis and a mirror plane, respectively, and would be expected to be less complex). Observed nOe contacts confirmed the expected relative stereochemistry of the major reaction products (±)-**115** and (±)-**242** as being *cis*.

The synthesis of the demethyl xyloketal B analogues (±)-**16** and (±)-**17** was subsequently accomplished on execution of a facile and high yielding decarboxylative saponification reaction (96%) of a mixture (dr = 1:1) of the substituted xyloketal B analogues (±)-**115** and (±)-**242** (Scheme 4.5.2.2).[47,48,49]

Scheme 4.5.2.2 Synthesis of the *bis*-Demethyl Xyloketal B Analogues [(±)-16] and [(±)-17]



Reagents and conditions: (a) NaOH, MeOH, H_2O, reflux, 6 h, 96%, dr = 1:1 [(±)-**115**:(±)-**242**].

Extensive analysis of 2D NMR spectral data confirmed the structure of the demethyl analogues of xyloketal B (**2**). The ^{1}H NMR spectrum contained signals at δ 6.16 and 6.17 ppm corresponding to the aromatic protons. In addition, signals at δ 5.88 and 5.92 ppm corresponding to nonhydrogen-bonded phenols were also observed.

Observed nOe contacts between the aromatic protons and the phenols as well as between the bridgehead methyl groups and the angular protons confirmed that the regio- and stereochemistry of the reaction products (±)-**16** and (±)-**17** had not been altered during the course of the final synthetic transformation (Figure 4.5.2.2).

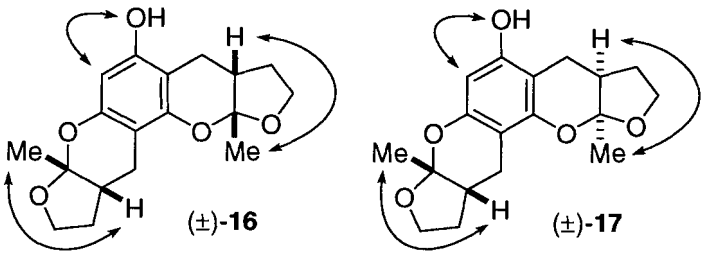
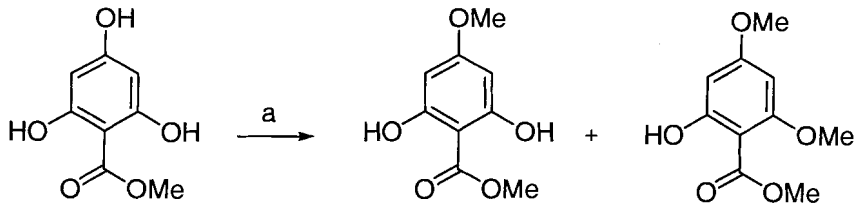


Figure 4.5.2.2 Observed nOe contacts for the *bis*-demethyl xyloketal B analogues [(±)-16] and [(±)-17].

4.5.3 Attempted Synthesis of the Xyloketal C Analogues [(±)-247] and (248)

Given that the reaction of neither phloroglucinol (**14**) nor the methyl ester **112** had provided practical syntheses of the demethyl analogues of xyloketal C (**3**), the use of an alternative phenol which could only undergo the desired *bis*-alkylation process with the appropriate regiochemistry was investigated. Thus, the phenol **244** was prepared according to literature procedures from the methyl ester **112** in moderate yield (39%) (Scheme 4.5.3.1).[137,138,139,140] Extending the reaction time from 23 h to 84 h did not result in an improvement in the yield of this reaction. In addition, a substantial amount of methyl 2,4-dimethoxy-6-hydroxy-benzoate (**245**) (28%) was also isolated in this instance.[141]

Scheme 4.5.3.1 Synthesis of the Methyl Esters (244) and (245)

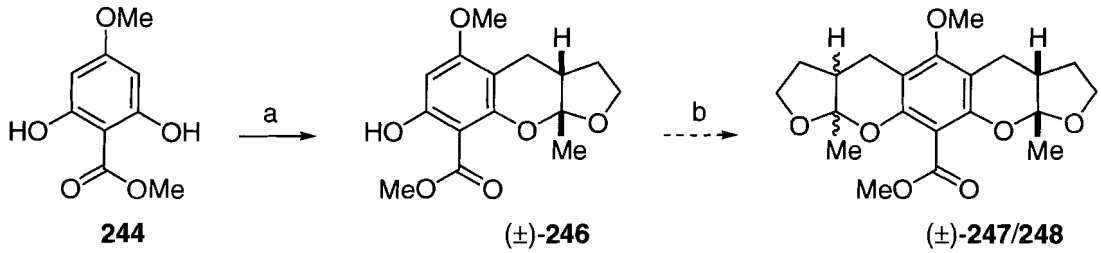


112 **244** **245**

Reagents and conditions: (a) MeI (1 equiv), K_2CO_3, acetone, room temperature, 23 h, 39% (**244**) *or* MeI (1 equiv), K_2CO_3, acetone, room temperature, 84 h, 39% (**244**), 28% (**245**).

The methoxy methyl ester **244** (1 equiv) was then allowed to react with the alcohol **168** (4 equiv), boron trifluoride diethyl etherate (1 equiv) and magnesium sulfate in ether and the resultant mixture was allowed to warm from 0 °C to room temperature over 50 h (Scheme 4.5.3.2). On subsequent purification of the crude reaction mixture by flash chromatography, only the *mono*-adduct (±)-**246** was obtained. When this material was re-subjected to the reaction conditions [alcohol **168** (5 equiv), $BF_3{\cdot}Et_2O$ (1 equiv), $MgSO_4$, Et_2O] no further reaction occurred to afford the desired xyloketal C analogues (±)-**247** and **248** and the unreacted starting material (±)-**246** was recovered. This result could be attributed to the increased steric crowding, as compared to the ester **112**, of the aromatic position by the methoxy substituent.

Scheme 4.5.3.2 Attempted Synthesis of the Methoxy Xyloketal C Analogues [(±)-247] and (248): Electrophilic Aromatic Substitution Reactions with 2-Methyl-3-hydroxymethyl-4,5-dihydrofuran (168)



244 (±)-**246** (±)-**247/248**

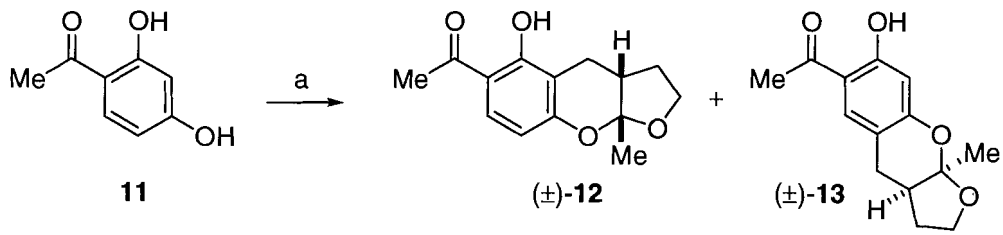
Reagents and conditions: (a) Alcohol **168** (4 equiv), $BF_3{\cdot}Et_2O$ (1 equiv), $MgSO_4$, Et_2O, 0 °C to room temperature, 50 h, 47%; (b) alcohol **168** (5 equiv), $BF_3{\cdot}Et_2O$ (1 equiv), $MgSO_4$, Et_2O, 0 °C to room temperature, 23 h.

As a result of this finding, no further investigations directed towards the total synthesis of the unstable natural product, xyloketal C (**3**), were made.

4.5.4 Synthesis of (±)-11-Norxyloketal D [(±)-12] and (±)-10-Norxyloketal G [(±)-13]

In a similar way to that described above, the synthesis of the xyloketal D and G analogues (±)-**12** and (±)-**13** was undertaken from the commercially available phenol, 2,4-dihydroxyacetophenone (**11**) (Scheme 4.5.4.1).

Scheme 4.5.4.1 Synthesis of (±)-11-Norxyloketal D [(±)-12] and (±)-10-Norxyloketal G [(±)-13]: Electrophilic Aromatic Substitution Reactions with 2-Methyl-3-hydroxymethyl-4,5-dihydrofuran (168)



11 (±)-**12** (±)-**13**

Reagents and conditions: (a) Alcohol **168** (2 equiv), $BF_3{\cdot}Et_2O$ (0.3 equiv), $MgSO_4$, Et_2O, 0 °C to room temperature, 46 h, 13% (41% brsm) [(±)-**12**], 11% (34% brsm) [(±)-**13**] *or* alcohol **169** (4 equiv), $BF_3{\cdot}Et_2O$ (0.3 equiv), $MgSO_4$, Et_2O, 0 °C to room temperature, 46 h, 17% (54% brsm) [(±)-**12**], 10% (32% brsm) [(±)-**13**].

Accordingly, the acetophenone **11** (1 equiv) was allowed to react with the alcohol **168** (2 equiv), boron trifluoride diethyl etherate (0.3 equiv) and magnesium sulfate in ether. On allowing the reaction mixture to warm from 0 °C to room temperature over 46 h and following purification of the crude reaction mixture by flash chromatography, the xyloketal D analogue (±)-**12** [13% (41% brsm)] and the xyloketal G analogue (±)-**13** [11% (34% brsm)] were isolated. A substantial quantity of the unreacted acetophenone **11** (62%) was also recovered. In view of the relative low reactivity of this less electron-rich phenol, the above reaction was repeated with an increased amount of the alcohol **168** (4 equiv). In this instance, the xyloketal D analogue (±)-**12** [17% (54% brsm)] and the xyloketal G analogue (±)-**13** [10% (32% brsm)] were isolated in slightly improved overall yield. In addition, the unreacted acetophenone **11** (68%) was also recovered from the crude reaction mixture.

The spectral data for the xyloketal D analogue (±)-**12** was identical to the material prepared by the Diels-Alder approach (See: Section 2.5.1). The structure of the xyloketal G analogue (±)-**13** was assigned on the basis of extensive analysis of 2D NMR data. The regiochemistry of this process was determined on inspection of the ^{1}H NMR spectrum. A sharp downfield signal at δ 12.37 ppm corresponding to the phenolic proton was observed. This suggested that the phenol group was adjacent to the carbonyl substituent.[1,21] In addition, the signals for the aromatic protons (δ 6.36 and 7.44 ppm) were singlets. As shown below, nOe contacts were observed that confirmed both the relative stereochemistry and the regiochemistry of this product (Figure 4.5.4.1).

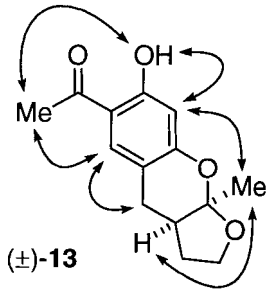
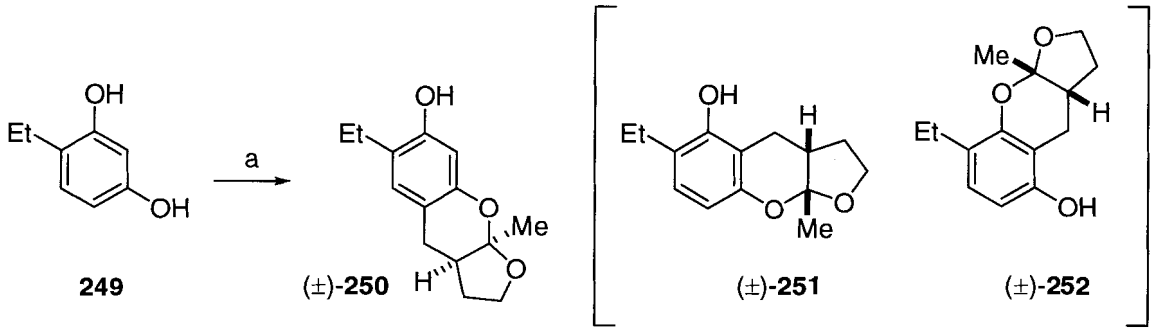


Figure 4.5.4.1 Observed nOe contacts for the demethyl xyloketal G analogue [(±)-13].

In view of the results of the above non-regioselective and low yielding reaction, it was decided to investigate the use of alternative phenols for the preparation of these natural product analogues. In the first instance, 4-ethyl resorcinol **(249)** (1 equiv) was allowed to react with the alcohol **168** (1.25 equiv), boron trifluoride diethyl etherate (1 equiv) and magnesium sulfate in ether (Scheme 4.5.4.2). This afforded the bicyclic acetal (±)-**250** in good yield (61%) as a single regioisomer corresponding to the structure of xyloketal G (**7**). The potential regioisomeric products (±)-**251** and (±)-**252** were not isolated.

Scheme 4.5.4.2 Synthesis of (1a*RS*,4a*RS*)-3,4,4a,1a-Tetrahydro-7-ethyl-8-hydroxy-1a-methyl-furo[*b*]chromane [(±)-250]: Electrophilic Aromatic Substitution Reactions with 2-Methyl-3-hydroxymethyl-4,5-dihydrofuran (168)



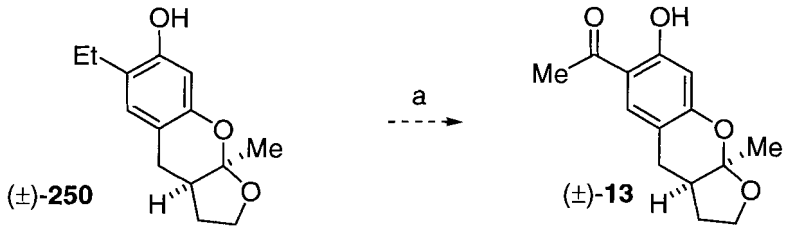
Reagents and conditions: (a) Alcohol **168** (1.25 equiv), $BF_3 \cdot Et_2O$ (1 equiv), $MgSO_4$, Et_2O, 0 °C to room temperature, 23 h, 61% [(±)-**250**].

The assignment of the regiochemistry of the above product was determined on inspection of the ^1H NMR spectrum. Of the three possible regioisomers, (±)-**250**, (±)-**251** and (±)-**252**, only the isomer (±)-**250** would be expected to have the observed pair of singlets for the aromatic protons.

Three attempts were made to oxidize this compound in a regioselective fashion (Scheme 4.5.4.3). In the first instance, the bicyclic acetal (±)-**250** was allowed to react with potassium permanganate in acetonitrile at room temperature for 21 h according to a procedure reported by Lee (entry 1).[142] However, this resulted in rapid decomposition of the starting material. Subsequently, the bicyclic acetal (±)-**250** was reacted with potassium permanganate and copper (II) sulfate pentahydrate in dichloromethane at reflux for 5 h according to the procedure of Noureldin and co-workers (entry 2).[143] These reaction conditions have been reported to be milder than initial reaction conditions that were employed. In addition, this reagent system has been shown to oxidize a benzylic ethyl moiety and not to oxidize a chromane. However, these reaction conditions resulted

in a complex mixture of compounds from which the desired product (±)-**13** could not be isolated. The final attempt to oxidize this compound with selenium dioxide in ethanol at reflux for 7 days according to the method reported by Fisher was made (entry 3).[144] However, these relatively mild reaction conditions resulted in slow decomposition of the starting material (±)-**250**.

Scheme 4.5.4.3 Attempted Synthesis of the Xyloketal G Analogue [(±)-13] from the Bicyclic Acetal [(±)-250]



Reagents and conditions: (a) See below: Table 4.5.4.1.

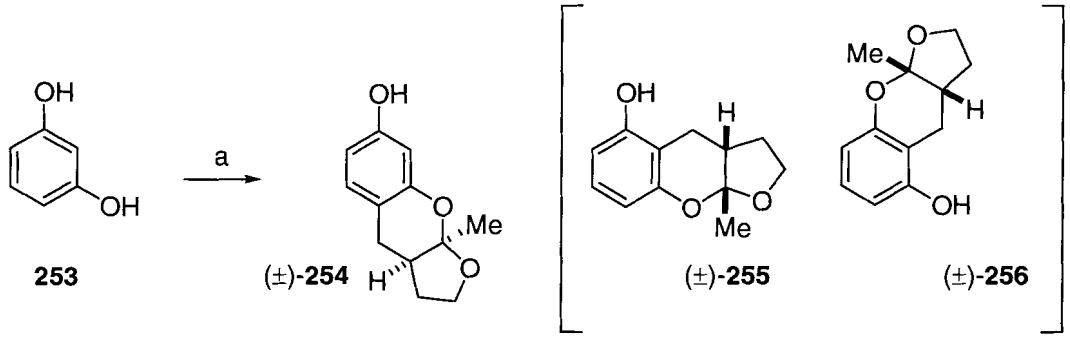
Table 4.5.4.1 Reagents and Conditions Corresponding to Scheme 4.5.4.3

Entry	Reagents and Conditions	Result
1	$KMnO_4$, MeCN, room temperature, 21 h	Decomposition
2	$KMnO_4$, $CuSO_4 \cdot 5H_2O$, CH_2Cl_2, reflux, 5 h	Complex mixture
3	SeO_2, EtOH, reflux, 7 days	Decomposition

The use of commercially available resorcinol (**253**) as a phenolic precursor was subsequently investigated. Accordingly, resorcinol (**253**) (1 equiv) was allowed to react with the alcohol **168** (1.25 equiv), boron trifluoride diethyl etherate (1 equiv) and magnesium sulfate in ether (Scheme 4.5.4.4). This afforded the bicyclic acetal (±)-**254**,

in moderate yield (35%) and as the single regioisomer that corresponded to the molecular structure of xyloketal G (**7**). The potential regioisomeric products (±)-**255** and (±)-**256** were not isolated.

Scheme 4.5.4.4 Synthesis of (1a*RS*,4a*RS*)-3,4,4a,1a-Tetrahydro-8-hydroxy-1a-methyl-furo[*b*]chromane [(±)-254]: Electrophilic Aromatic Substitution Reactions with 2-Methyl-3-hydroxymethyl-4,5-dihydrofuran (168)



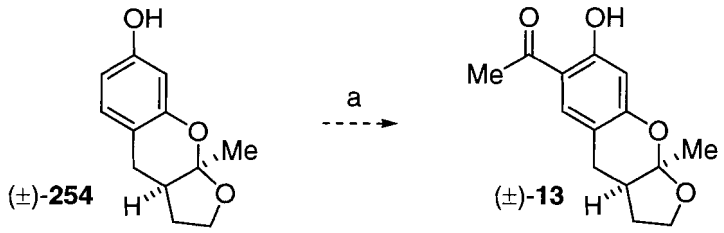
Reagents and conditions: (a) Alcohol **168** (1.25 equiv), $BF_3 \cdot Et_2O$ (1 equiv), $MgSO_4$, Et_2O, 0 °C to room temperature, 22 h, 35% [(±)-**254**].

Similar to the previous bicyclic acetal (±)-**250**, the regiochemistry of the reaction product (±)-**254** was determined by analysis of the coupling constants in the aromatic region of the ^1H NMR spectrum.

Two attempts were made to install a methyl ketone into this adduct (Scheme 4.5.4.5). In the first instance, this material was allowed to react with acetyl chloride and aluminum trichloride at 180 °C for 30 min according to a procedure described by Kim and co-workers.[145] This resulted in rapid and complete decomposition of the starting material (±)-**254**. In the second instance, the bicyclic acetal (±)-**254** was reacted with acetic anhydride and boron trifluoride diethyl etherate at room temperature for 22 h

according to the procedure of Mateeva and co-workers.[146] This resulted in the isolation of a thick red oil from which the desired reaction product (±)-**13** could not be isolated.

Scheme 4.5.4.5 Attempted Synthesis of the Xyloketal G Analogue [(±)-13] from the Bicyclic Acetal [(±)-245]



Reagents and conditions: (a) AcCl, $AlCl_3$, 180 °C, 30 min *or* Ac_2O, $BF_3{\cdot}Et_2O$, room temperature, 22 h.

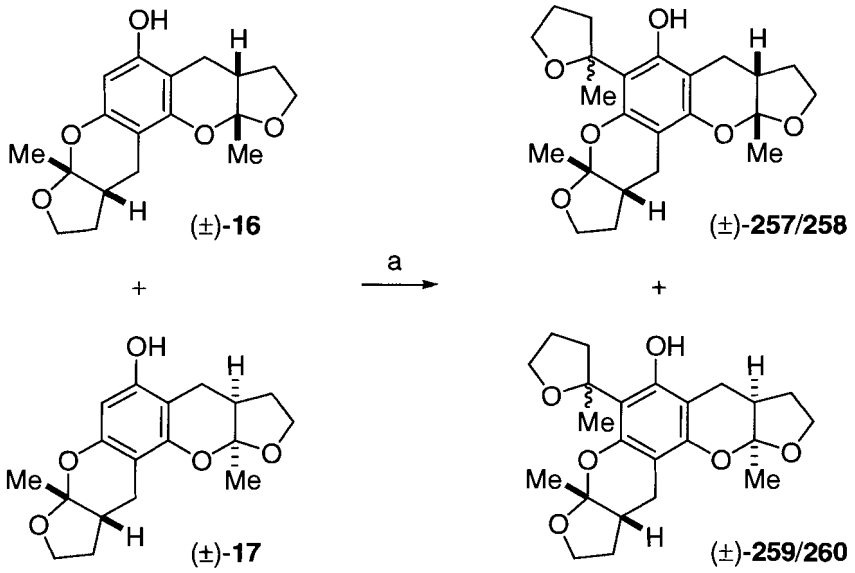
No further attempts were made to improve the syntheses of these analogues in view of the fact that xyloketal D (**4**) and G (**7**) are minor metabolites and that insignificant biological activity has been reported for these natural products.

4.5.5 Synthesis of (±)-11,11',20-Trinorxyloketal E [(±)-257], (±)-14-*epi*-11,11',20-Trinorxyloketal E [(±)-258], (±)-2,6-*epi*-11,11',20-Trinorxyloketal E [(±)-259] and (±)-2,6,14-*epi*-11,11',20-Trinorxyloketal E [(±)-260] from the Xyloketal B Analogues [(±)-16] and [(±)-17]

Various methods for electrophilic aromatic substitution reactions of phenols with dihydrofurans or dihydropyrans have been reported.[128,129,130,131] To investigate the possibility of the conversion of xyloketal B (**2**) into xyloketal E (**5**), model studies using a mixture (dr = 1:1) of the xyloketal B analogues (±)-**16** and (±)-**17** with commercially available 2-methyl-4,5-dihydrofuran (**114**) were performed. Thus, the two starting materials were allowed to react in the presence of pyridinium *p*-toluenesulfonate according to the procedure described by Cottet and co-workers (Scheme 4.5.5.1).[128] This

cleanly afforded an inseparable mixture (dr = 2:1:2:1) of the xyloketal E analogues (±)-**257**, (±)-**258**, (±)-**259** and (±)-**260**.

Scheme 4.5.5.1 Synthesis of the Xyloketal E Analogues [(±)-257], [(±)-258], [(±)-259] and [(±)-260] from the Xyloketal B Analogues [(±)-16] and [(±)-17]



Reagents and conditions: (a) 2-Methyl-4,5-dihydrofuran (**114**), PPTS, CH_2Cl_2, room temperature, 20 h, 73%, dr = 2:1:2:1 [(±)-**257**:(±)-**258**:(±)-**259**:(±)-**260**].

The ^{1}H NMR spectrum of this mixture did not show any signals corresponding to aromatic protons but did show four well resolved peaks corresponding to hydrogen-bonded phenols at δ 10.72, 10.75, 10.78 and 10.80 ppm. This confirmed that the reaction had occurred by the desired electrophilic aromatic substitution process and that acetals were not formed by reaction of the phenol moiety with the dihydrofuran **114**. The stereoselectivity of this process was difficult to rationalize. The starting material was a mixture (dr = 1:1) of the xyloketal B analogues (±)-**16** and (±)-**17**. Therefore, it is reasonable to assume that each isomer afforded a pair of diastereoisomers in a 2:1 ratio. However, the relative stereochemistry within each set was not determined. It was

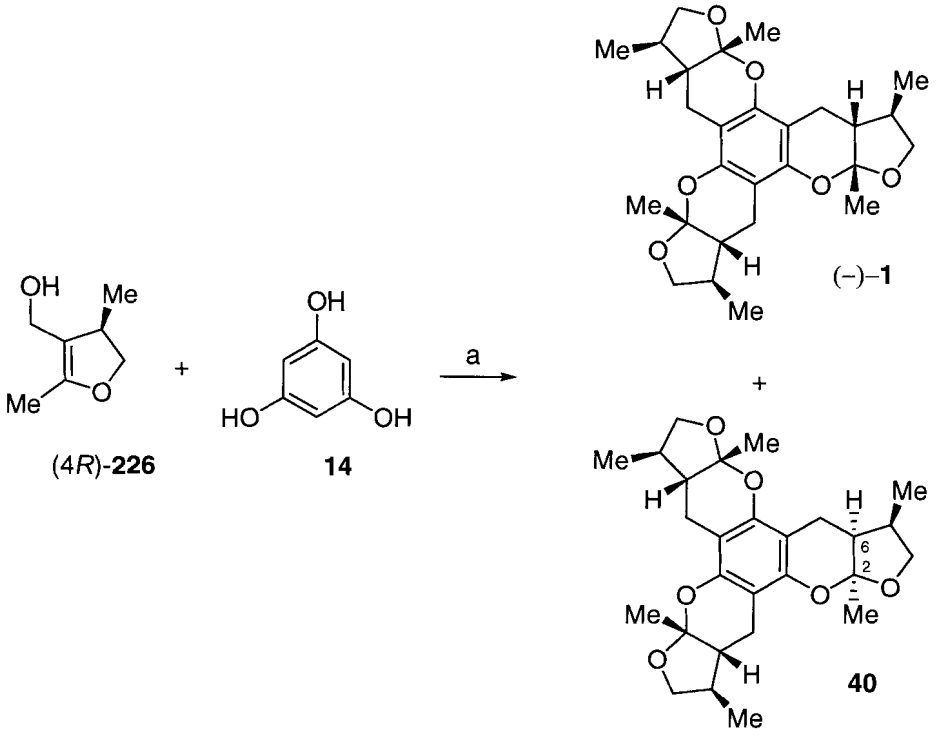
anticipated that the stereochemistry of chiral nonracemic xyloketal B (**2**) and/or the stereochemistry of chiral nonracemic 2,4-dimethyl-4,5-dihydrofuran (**61**) would direct the stereochemistry of this process on attempting the synthesis of the natural product xyloketal E (**5**).

4.6 Asymmetric Synthesis of the Xyloketals: Electrophilic Aromatic Substitution Reactions with (4*R*)-2,4-Dimethyl-3-hydroxymethyl-4,5-dihydrofuran

4.6.1 Total Synthesis of (–)-Xyloketal A [(–)-1]

As shown previously (See: Section 3.7.3), the chiral nonracemic ester (4*R*)-**206** could be cleanly reduced to the desired alcohol (4*R*)-**226** with lithium aluminum hydride. However, the latter compound was found to be somewhat unstable to isolation and purification and so it was used directly in the subsequent electrophilic aromatic substitution reactions. Therefore, phloroglucinol (**14**) (1 equiv) was allowed to react with the alcohol (4*R*)-**226** and boron trifluoride diethyl etherate (1 equiv) in the presence of anhydrous magnesium sulfate in ether (Scheme 4.6.1.1). The results of these studies are presented below (see Table 4.6.1.1).

Scheme 4.6.1.1 Total Synthesis of (–)-Xyloketal A [(–)-1]: Electrophilic Aromatic Substitution Reactions with (4*R*)-2,4-Dimethyl-3-hydroxymethyl-4,5-dihydrofuran [(4*R*)-226]



Reagents and conditions: (a) See below: Table 4.6.1.1.

Table 4.6.1.1 Reagents and Conditions Corresponding to Scheme 4.6.1.1

Entry	Equivalents of [(4*R*)-226]	Additional Reagents and Conditions	Yield (%)	dr [(–)-1:40]
1	6	$BF_3 \cdot Et_2O$ (1 equiv), $MgSO_4$, Et_2O, 0 °C, 20 min	85	5:2
2	6	$BF_3 \cdot Et_2O$ (1 equiv), $MgSO_4$, Et_2O, –78 °C, 20 min	79	4:1
3	4	$BF_3 \cdot Et_2O$ (1 equiv), $MgSO_4$, Et_2O, 0 °C, 2 h	14	5:2

In the first instance, a mixture of a two-fold excess [per phenolic reaction site of phloroglucinol (**14**)] of the alcohol (4*R*)-**226** and phloroglucinol (**14**) (1 equiv) in ether at 0 °C was stirred with boron trifluoride diethyl etherate (1 equiv) and anhydrous magnesium sulfate (entry 1). Within 20 minutes, an exceptionally clean synthetic transformation occurred that led to the isolation of a chromatographically inseparable mixture (dr = 5:2) of xyloketal A [(–)-**1**] and a single additional diastereoisomer, tentatively assigned as 2,6-*epi*-xyloketal A (**40**), in 85% yield. Although the diastereoselectivity of the overall process was not exceptional, the diastereoselectivity of each of the three individual ring formation reactions was certainly respectable (dr = ~9:1). Moreover, the ^{1}H NMR spectrum of the crude reaction mixture was dominated by signals that corresponded to the C_3-symmetric natural product. In order to improve the overall diastereoselectivity of this remarkable process, the above reaction was repeated at –78 °C (entry 2). This led to the isolation of a mixture of xyloketal A [(–)-**1**] and 2,6-*epi*-xyloketal A (**40**) in similar yield (79% yield). However, the diastereoselectivity of the overall process was increased (dr = 4:1). In this case, the diastereoselectivity of each of the three individual ring formation reactions had reached an impressive level (dr = ~19:1). The reaction was also repeated at 0 °C with four equivalents of the alcohol (4*R*)-**226** (entry 3). In this instance, a mixture (dr = 5:2) of xyloketal A [(–)-**1**] and 2,6-*epi*-xyloketal A (**40**) was isolated in 14% yield. In addition, no evidence for the formation of *mono*- or *bis*-addition products was recorded. This reflected the relative instability of the alcohol (4*R*)-**226** and the increased reactivity of the more electron-rich *mono*- and *bis*-addition products towards electrophilic aromatic substitution processes.

An analytically pure sample of synthetic (–)-xyloketal A [(–)-**1**] was subsequently obtained on crystallization from petroleum ether. The ^{1}H and ^{13}C NMR spectra of this material were identical to those recorded for the natural product (Figure 4.6.1.1).[1]

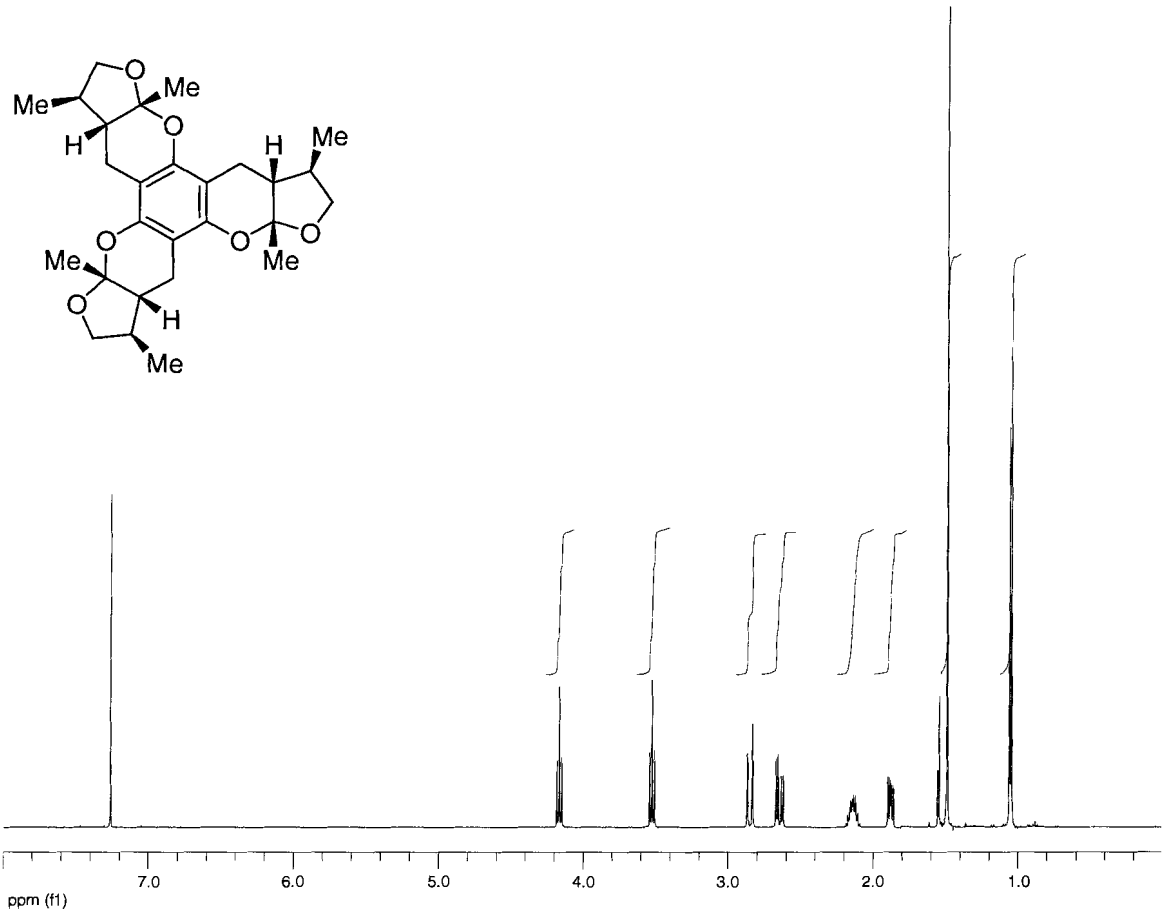


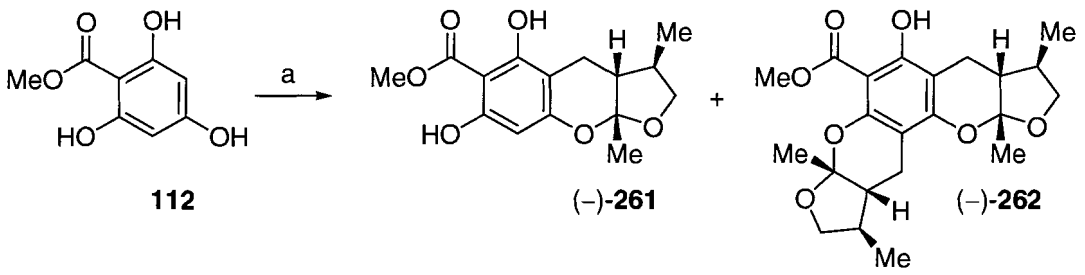
Figure 4.6.1.1 ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of (–)-xyloketal A [(–)-1].

The optical rotation (in both sense and magnitude) as well as the melting point of the synthetic material were in close agreement with those reported in the original isolation paper.[1] Thus, the absolute stereochemistry of the natural product was firmly established.

4.6.2 Total Synthesis of (–)-Xyloketal B [(–)-2]

According to the optimized reaction conditions from the model studies, the ester **112** (1 equiv) was allowed to react with the alcohol (4*R*)-**226** (4 equiv) and boron trifluoride diethyl etherate (0.7 equiv) in the presence of anhydrous magnesium sulfate (Scheme 4.6.2.1). After 38 h, a clean synthetic transformation occurred that led to the isolation of a chromatographically separable mixture of the *mono*-adduct (–)-**261** (17%) and the *bis*-adduct (–)-**262** (73%). It was subsequently found that extending the reaction time to 46 h afforded exclusively the *bis*-adduct (–)-**262** in very good yield (91%). Of note, a single diastereoisomer was obtained. Furthermore, none of the regioisomer corresponding to the thermodynamically unstable natural product xyloketal C (**3**) was isolated in these reactions.

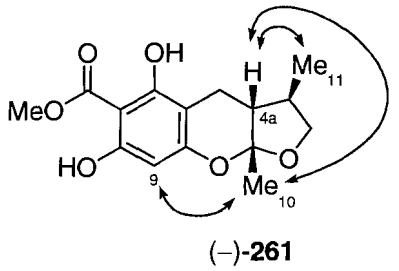
Scheme 4.6.2.1 Synthesis of the Xyloketal B Methyl Esters [(–)-261] and [(–)-262]: Electrophilic Aromatic Substitution Reactions with (4*R*)-2,4-Dimethyl-3-hydroxymethyl-4,5-dihydrofuran [(4*R*)-226]



Reagents and conditions: (a) Alcohol (4*R*)-**226** (4 equiv), $BF_3{\cdot}Et_2O$ (0.7 equiv), $MgSO_4$, Et_2O, 0 °C to room temperature, 38 h, 17% [(–)-**261**], 73% [(–)-**262**] *or* alcohol (4*R*)-**226** (4 equiv), $BF_3{\cdot}Et_2O$ (0.7 equiv), $MgSO_4$, Et_2O, 0 °C to room temperature, 46 h, 91% [(–)-**262**].

The spectral data for *mono*-adduct (–)-**261** was very similar to the spectral data of xyloketal D (**4**). Extensive analysis of the 2D NMR data led to the unambiguous assignment of the molecular structure of this compound. The regiochemistry of this product was confirmed by a nOe contact that was observed between *Me*-10$_\beta$ and *H*-9

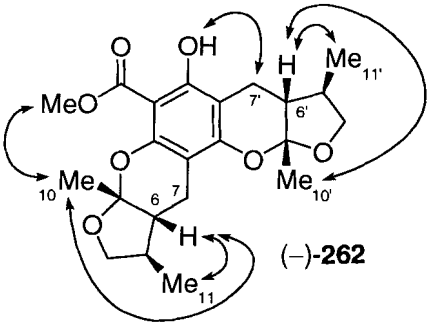
(Figure 4.6.2.1). In addition, nOe contacts were observed between *Me*-10$_\beta$, *H*-4a$_\beta$, and *Me*-11$_\beta$ which confirmed the *cis* relationship between these moieties.



(–)-**261**

Figure 4.6.2.1 Observed nOe contacts for the *mono*-adduct [(–)-261].

The ^{1}H NMR spectrum for the *bis*-adduct (–)-**262** contained signals that were well resolved. Therefore, based on analysis of the COSY NMR spectrum and the observed nOe contacts, unambiguous assignment of both the regio- and stereochemistry were made. This confirmed that the product had the desired substitution pattern for the synthesis of xyloketal B (**2**) (Figure 4.6.2.2).

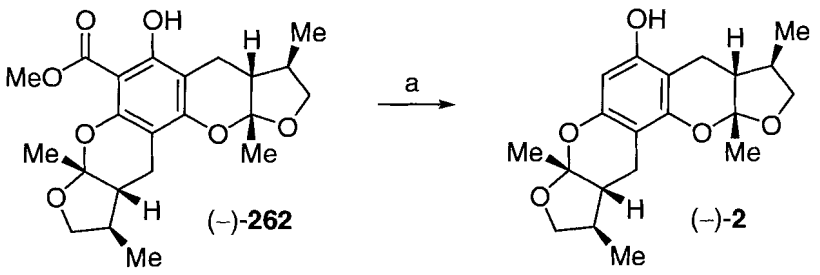


(–)-**262**

Figure 4.6.2.2 Observed nOe contacts for the *bis*-adduct [(–)-262].

The *bis*-adduct (–)-**262** was subsequently saponified and decarboxylated in a single step upon reaction with sodium hydroxide in aqueous methanol at reflux to afford (–)-xyloketal B [(–)-**2**] in excellent yield (95%) (Scheme 4.6.2.2).

Scheme 4.6.2.2 Total Synthesis of (–)-Xyloketal B [(–)-2] from the Xyloketal B Methyl Ester [(–)-262]



Reagents and conditions: (a) NaOH, H_2O, MeOH, reflux, 3.5 h, 95%.

The ^1H and ^{13}C NMR spectra of this material were slightly different to that reported for the natural product (Figure 4.6.2.3).[1] In particular, the signals corresponding to the phenol and aromatic protons had slightly different chemical shifts. It was subsequently found that the chemical shift of these signals varied depending on the concentration of the NMR sample. Thus, it is reasonable to assume that these differences arose from the degree of intermolecular hydrogen bonding at the different sample concentrations. Therefore, 2D NMR experiments were performed to confirm the molecular structure of the product. Of note, the ^1H NMR signal of natural xyloketal B (**2**) centred at δ4.10 ppm should have been reported at δ4.18 ppm by Lin and co-workers.*

(*) Professor Lin kindly provided the ^1H and ^{13}C NMR spectra of xyloketal B (**2**) for comparison purposes.

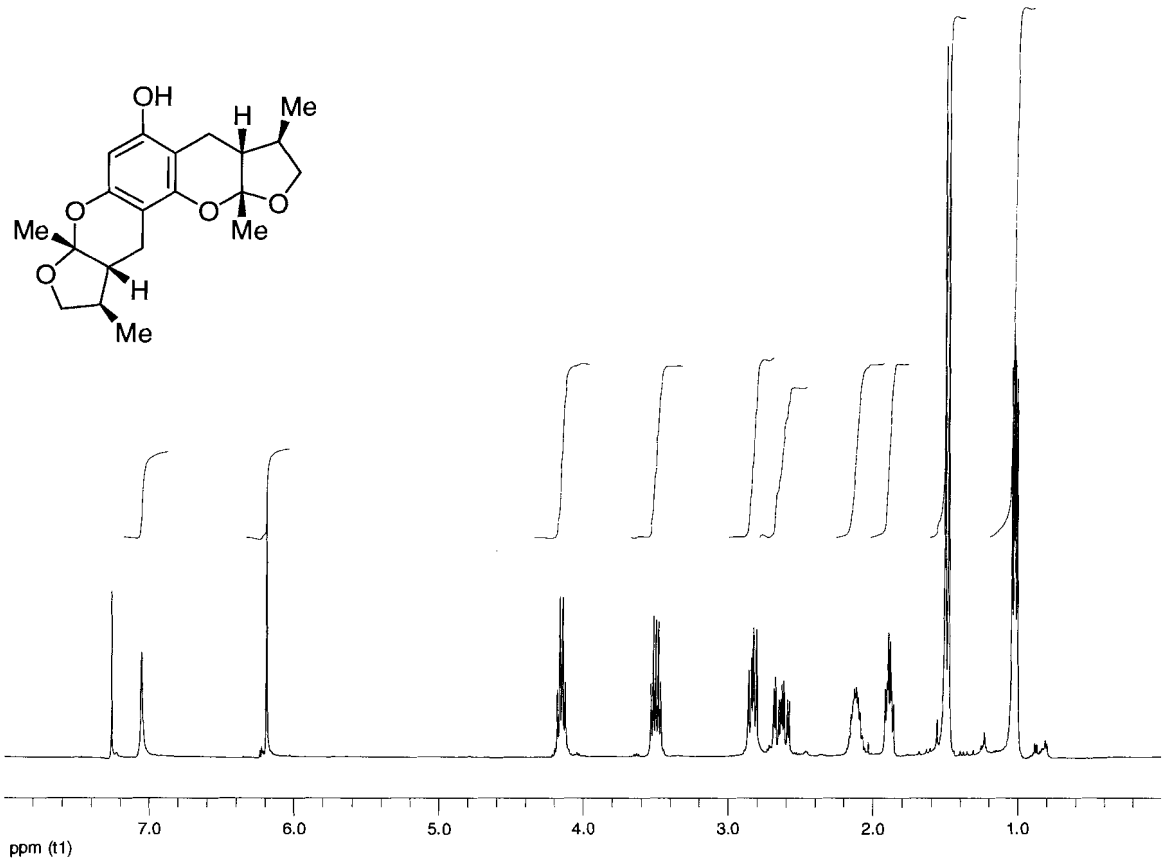


Figure 4.6.2.3 ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of (–)-xyloketal B [(–)-2].

The melting point of the synthetic material and the magnitude of the optical rotation were in close agreement with those reported in the original isolation paper.[1] However, the sign of the optical rotation of the synthetic (–)-xyloketal B [(–)-**2**] was opposite to that reported.[1] There are two possible explanations for this discrepancy. First, natural xyloketal B (**2**) could have the opposite absolute stereochemistry to that reported in the isolation paper.[1] However, the work described in this thesis and the results described by Krohn and co-workers have shown that the absolute stereochemistries of the other members of the xyloketal family of natural products were assigned correctly.[9,10] Since it is reasonable to assume that the xyloketal natural products result from a common biosynthetic pathway, this possibility is unlikely.[1,3,4]

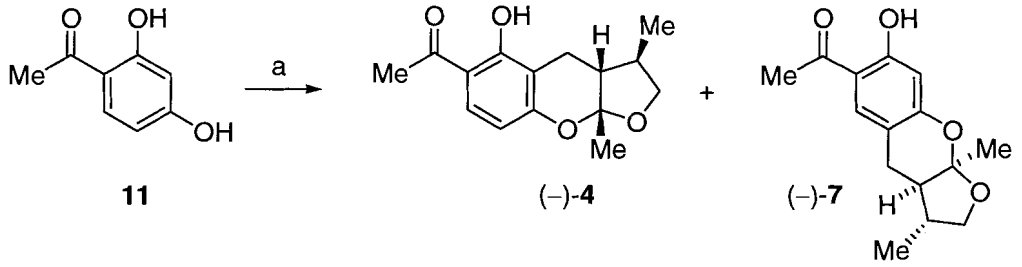
Alternatively, the sign of the reported optical rotation could have been reported incorrectly. Furthermore, Lin and co-workers have reported a semi-synthesis of (–)-xyloketal F [(–)-**6**] from natural xyloketal B (**2**).[3] However, when our synthetic (–)-xyloketal B [(–)-**2**] was allowed to react under similar reaction conditions (See: Section 4.6.5), (–)-xyloketal F [(–)-**6**] was also obtained. Thus, it appears that the optical rotation reported for the natural product is incorrect*

4.6.3 Total Synthesis of (–)-Xyloketal D [(–)-4] and G [(–)-7]

The application of the electrophilic aromatic substitution reactions towards the total synthesis of xyloketal D (**4**) and G (**7**) proceeded in a similar fashion to that described in the corresponding model studies. 2,4-Dihydroxyacetophenone **11** (1 equiv) was allowed to with the alcohol (4*R*)-**226** (4 equiv) in the presence of boron trifluoride diethyl etherate (0.3 equiv) to afford (–)-xyloketal D [(–)-**4**] [14% (51% brsm)] and (–)-xyloketal G [(–)-**7**] [8% (29% brsm)] that were separated by flash chromatography (Scheme 4.6.3.1).

(*) In an effort to clarify this inconsistency, Professor Lin agreed to record the optical rotation of natural xyloketal B (**2**). However, this information has not been reported to us.

Scheme 4.6.3.1 Total Synthesis of (–)-Xyloketal D [(–)-4] and G [(–)-7]: Electrophilic Aromatic Substitution Reactions with (4*R*)-2,4-Dimethyl-3-hydroxymethyl-4,5-dihydrofuran [(4*R*)-226]



Reagents and conditions: (a) Alcohol (4*R*)-**226** (4 equiv), $BF_3 \cdot Et_2O$ (0.3 equiv), $MgSO_4$, Et_2O, 0 °C to room temperature, 46 h, 14% (51% brsm) [(–)-**4**], 8% (29% brsm) [(–)-**7**].

All of the spectral data of (–)-xyloketal D [(–)-**4**] were identical to that of the natural product and to the material prepared by the Diels-Alder route as discussed previously (See: Section 2.9.1).[1] The melting point and optical rotation (both sign and magnitude) were identical to the material produced by the Diels-Alder approach but varied from the values reported for the natural product (See: Section 2.9.1).[1]

The ^1H and ^{13}C NMR data for (–)-xyloketal G [(–)-**7**] were identical to the natural product (Figure 4.6.3.1).[4] Furthermore, extensive 2D NMR analysis independently confirmed the molecular structure of this material.*

(*) The synthesis of (–)-xyloketal G [(–)-**7**] was completed prior to the publication of the isolation of the natural product (See: Ref. 4). Therefore, complete structure characterization of this reaction product was performed.

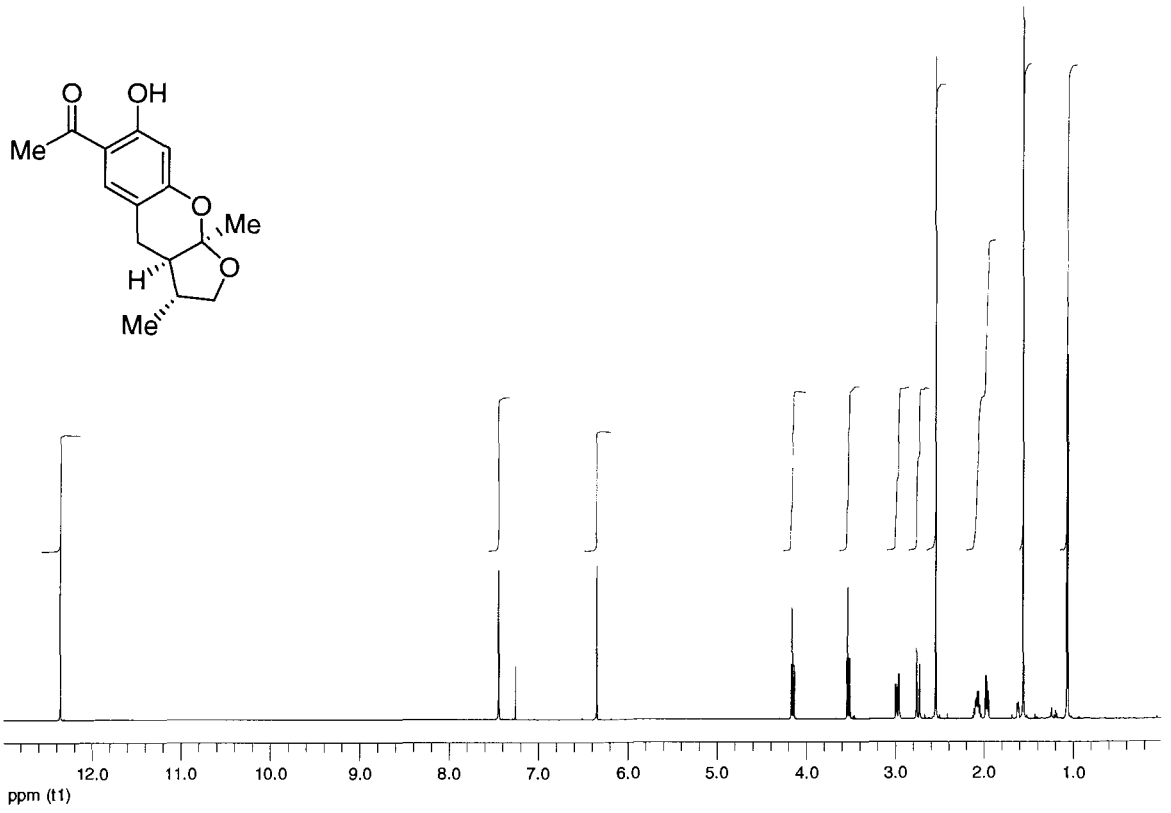


Figure 4.6.3.1 ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of (–)-xyloketal G [(–)-7].

The melting point and sign of the optical rotation of synthetic (–)-xyloketal G [(–)-7] were in agreement with the natural product.[4] However, the magnitude of the optical rotation was lower than that reported for the natural product.* No further attempts were made to investigate the cause of the depressed optical rotation in view of the fact that xyloketal G [(–)-7] is a minor metabolite and that no biological activity has been reported for this natural product.

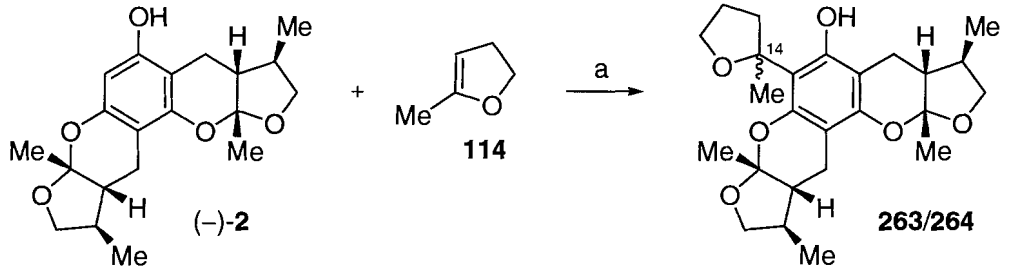
4.6.4 Total Synthesis of Xyloketal E (5) from (–)-Xyloketal B [(–)-2]

In the model studies towards the synthesis of xyloketal E (**5**), modest diastereoselectivity (dr = 2:1) was observed during the electrophilic aromatic substitution

(*) Professor Lin agreed to record the optical rotation for the natural xyloketal G [(–)-7]. However, this information has not been reported to us.

reaction of the xyloketal B analogues (±)-**16** and (±)-**17** with the achiral dihydrofuran **114**. However, it was not possible to separate the resultant mixture of products to determine if the relative stereochemistry of the major reaction products corresponded to xyloketal E (**5**). Therefore, further investigations into the stereoselectivity of this process were performed. Accordingly, synthetic (–)-xyloketal B [(–)-**2**] was allowed to react with commercially available 2-methyl-4,5-dihydrofuran (**114**) as previously described to afford the xyloketal E analogues **263** and **264** in good yield (78%) (Scheme 4.6.4.1). Interestingly, no diastereoselectivity (dr = 1:1) was observed in this reaction with chiral nonracemic (–)-xyloketal B [(–)-**2**].

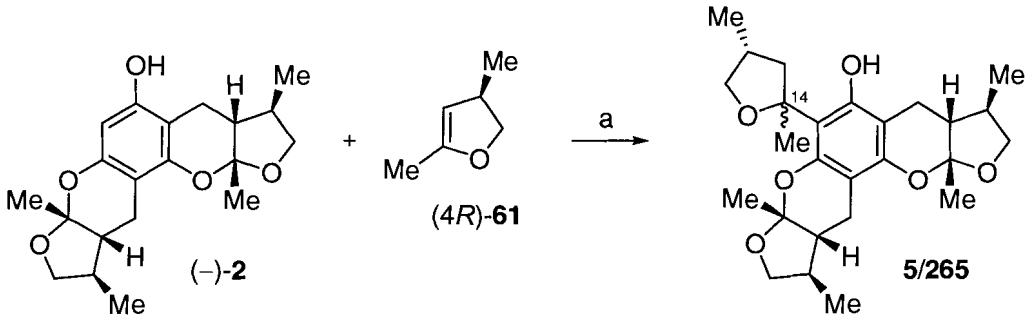
Scheme 4.6.4.1 Synthesis of Analogues of Xyloketal E (5) from (–)-Xyloketal B [(–)-2]



Reagents and conditions: (a) PPTS, CH_2Cl_2, room temperature, 22 h, 78%, dr = 1:1 (**263**:**264**).

The completion of the total synthesis of xyloketal E (**5**) involved the reaction of (–)-xyloketal B [(–)-**2**] with chiral nonracemic (4*R*)-2,4-dimethyl-4,5-dihydrofuran (4*R*)-**61** and pyridinium *p*-toluenesulfonate (Scheme 4.6.4.2). This afforded an inseparable mixture (dr = 2:9) of xyloketal E (**5**) and 14-*epi*-xyloketal E (**265**).

Scheme 4.6.4.2 Total Synthesis of the Xyloketal E (5) and 14-*epi*-Xyloketal E (265) from (–)-Xyloketal B [(–)-2]



Reagents and conditions: (a) PPTS, CH_2Cl_2, room temperature, 21 h, 82%, dr = 2:9 (**5**:**265**).

The diastereoslectivity of this process (dr = 2:9) was readily determined by inspection of the ^{1}H NMR spectra as the signals corresponding to the two hydrogen bonded phenol moieties of the reaction products **5** and **265** were well resolved at δ 10.81 and 10.86 ppm, respectively (Figure 4.6.4.1). Previous model studies had shown that the stereochemistry of (–)-xyloketal B [(–)-**2**] did not effect the diastereoselectivity of this process. Therefore, the product ratio was controlled by the *C*-4 methyl substituent of the dihydrofuran (4*R*)-**61** which led to the preferential formation of the undesired diastereoisomer of the natural product (which had been expected based on steric arguments). Therefore, it is reasonable to assume that the formation of the natural xyloketal E (**5**) is controlled by an enzyme or that 14-*epi*-xyloketal E (**265**) has not yet been isolated from the natural source.

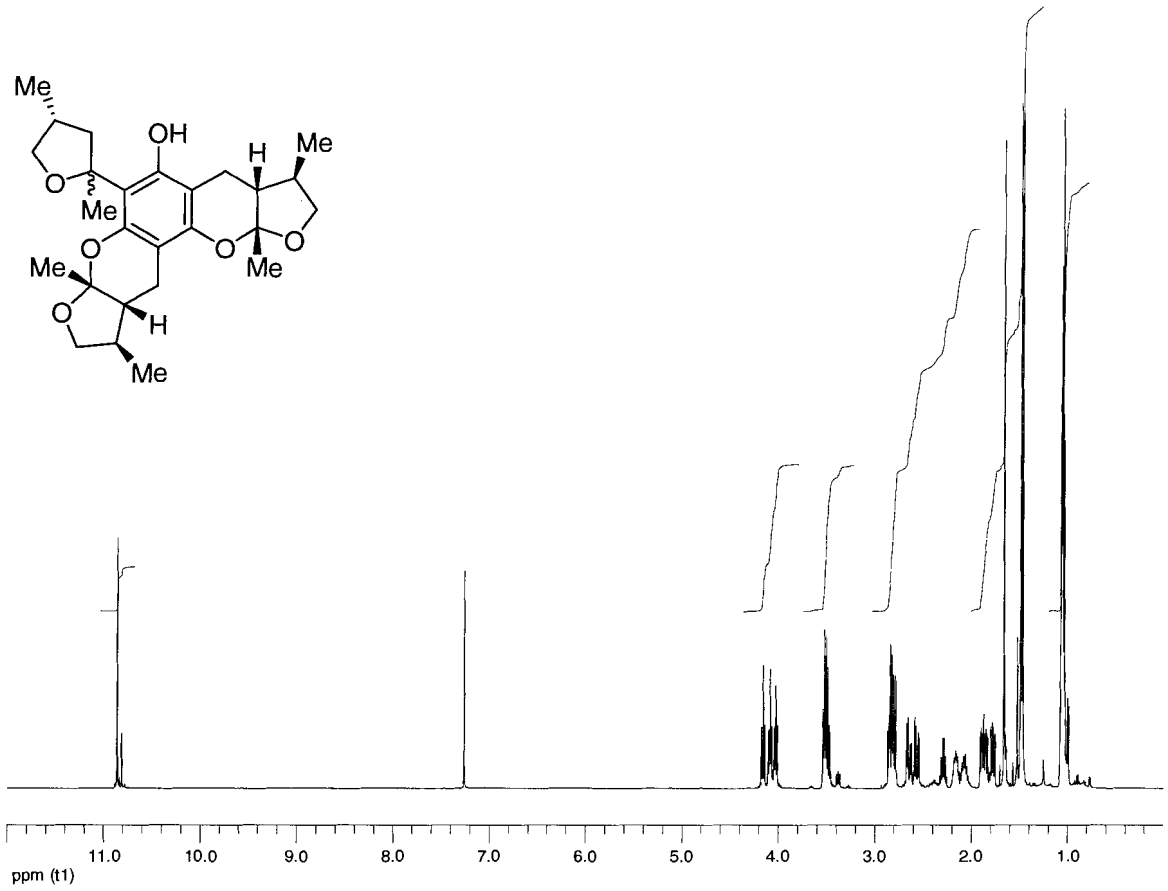
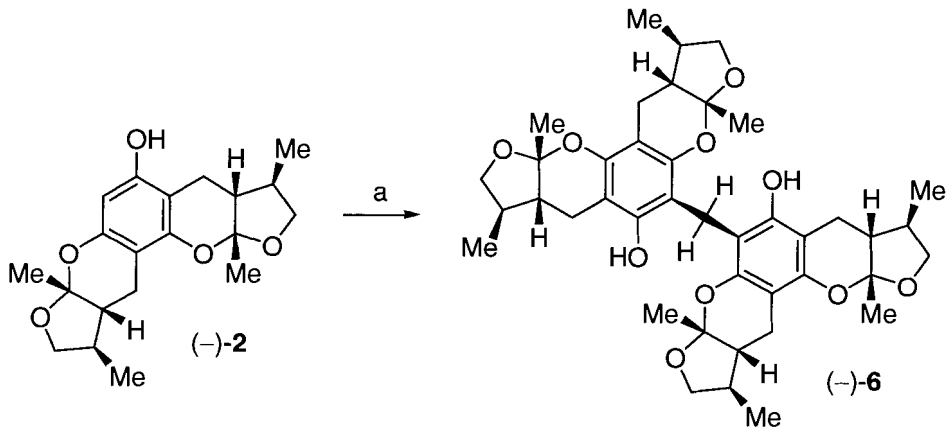


Figure 4.6.4.1 ^{1}**H NMR spectrum (500 MHz, $CDCl_3$) of xyloketal E (5) and 14-*epi*-xyloketal E (265).**

4.6.5 Two Alternative Syntheses of (–)-Xyloketal F [(–)-6]

The potentially biomimetic synthesis of xyloketal F [(–)-**6**] *via* the coupling of two equivalents of xyloketal B (**2**) was initially investigated. (–)-Xyloketal B [(–)-**2**] (2 equiv) was allowed to react with paraformaldehyde under mild acidic conditions at room temperature (Scheme 4.6.5.1).[128] This facile reaction cleanly afforded (–)-xyloketal F [(–)-**6**] in good yield (84%).

Scheme 4.6.5.1 Synthesis of (–)-Xyloketal F [(–)-6] from (–)-Xyloketal B [(–)-2]



Reagents and conditions: (a) Paraformaldehyde, PPTS, CH_2Cl_2, room temperature, 23 h, 84%.

The ^1H and ^{13}C NMR spectra of this material were identical to those recorded for the natural product (Figure 4.6.5.1).[3]

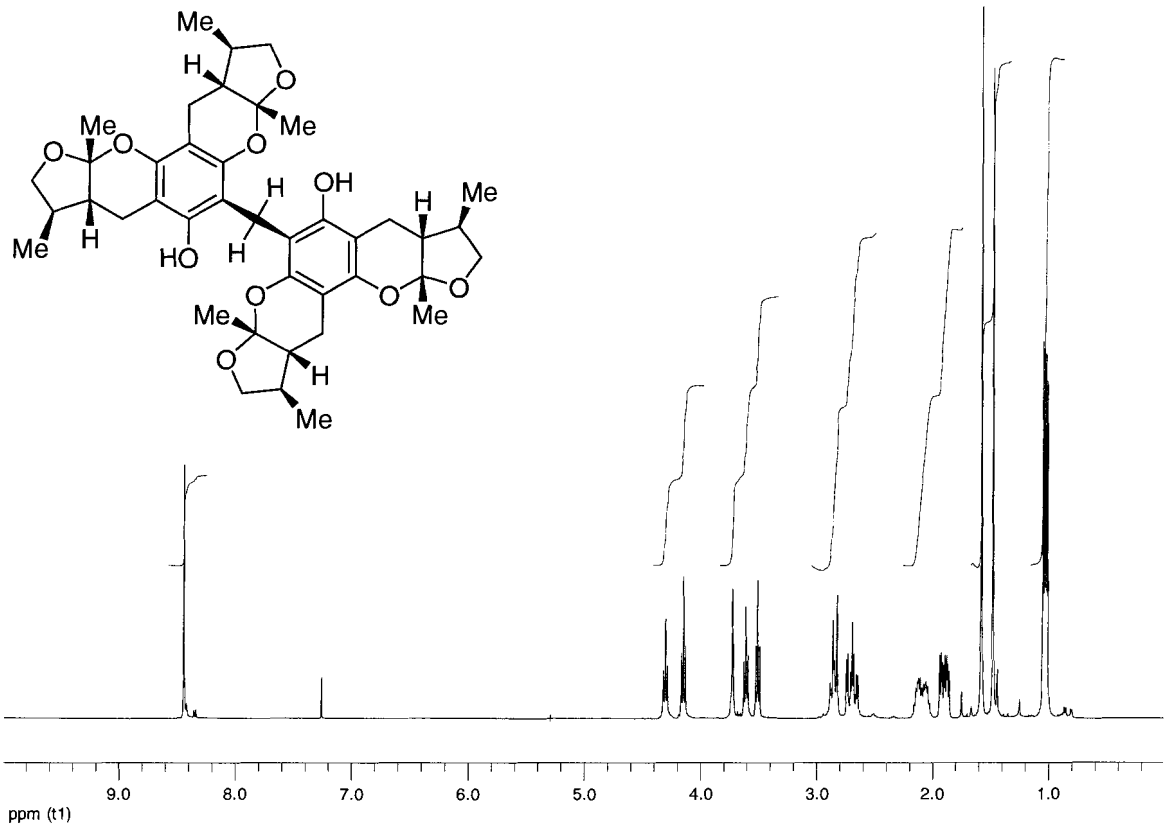
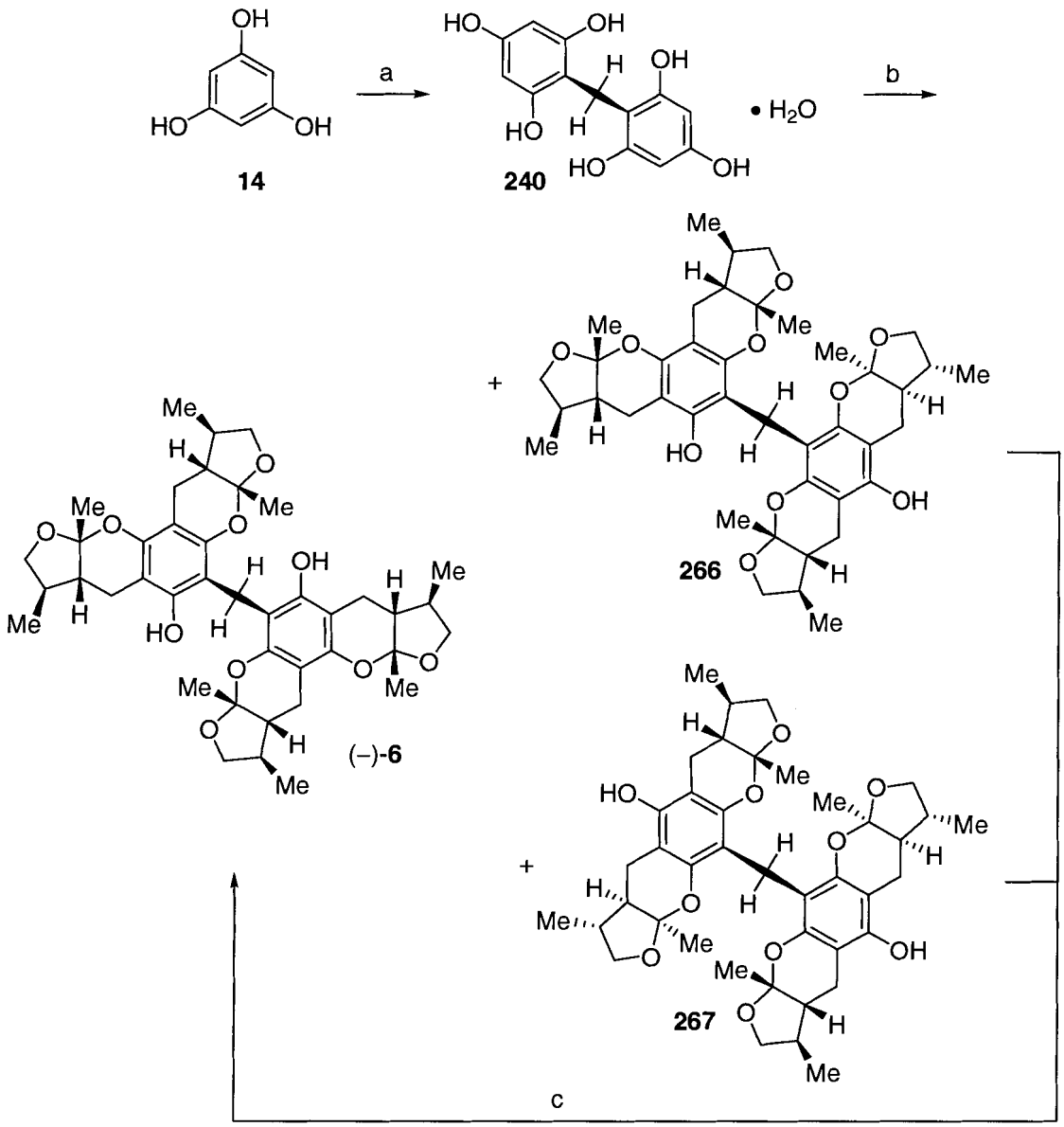


Figure 4.6.5.1 ^1H NMR spectrum (500 MHz, $CDCl_3$) of (–)-xyloketal F [(–)-6].

The melting point as well as the sign of the optical rotation of synthetic (–)-xyloketal F [(–)-**6**] were in close agreement with those reported in the original isolation paper.[3] However, the magnitude of the optical rotation was slightly lower than the value reported for the natural product.

An alternative and more direct synthesis of xyloketal F [(–)-**6**] was subsequently investigated. The known biaryl compound **240** was prepared in one step according to literature procedures from phloroglucinol (**14**) (Scheme 4.6.5.2).[135,136] Although the overall yield of this process was low (34%), the starting materials are readily available and inexpensive. In addition, the isolation of this product was straightforward. This material was then subjected to the electrophilic aromatic substitution reaction with the alcohol (4*R*)-**226** (8 equiv) and boron trifluoride diethyl etherate (1.3 equiv). Within 75 min, a clean synthetic transformation of this electron rich phenol had occurred to afford an inseparable mixture (10:7:3) of xyloketal F [(–)-**6**] and the regioisomers **266** and **267** in good combined yield (71%).

Scheme 4.6.5.2 Total Synthesis of (–)-Xyloketal F [(–)-6] from the Regioisomeric Adducts (266) and (267)



Reagents and conditions: (a) Paraformaldehyde (0.5 equiv), HCl, H_2O, 4 °C, 16 h, 34%; (b) alcohol (4*R*)-**226** (8 equiv), BF_3•Et_2O (1.3 equiv), $MgSO_4$, Et_2O, 0 °C to room temperature, 75 min, 71% [(–)-**6**:**266**:**267**], 10:7:3; (c) *p*-TsOH•H_2O, $CDCl_3$, 23 °C, 18 h, >99%.

Of note, the regioisomers **266** and **267** contain moieties that correspond to the molecular structure of xyloketal C (**3**). In addition, it should be noted that, a methyl ester precursor to xyloketal C (**3**) was not formed in the reaction of the relatively electron poor phenol **112** and the dihydrofuran (4*R*)-**226** (See: Section 4.6.2). In the latter case, the

reaction proceeded slowly and so the regioisomeric product, corresponding to xyloketal C (**3**), had sufficient time to undergo isomerization processes and afforded the more stable xyloketal B derivative (±)-**262**. However, when the electron rich phenol **240** was used as a substrate in the former case, the reaction proceeded relatively quickly and so there was presumably insufficient time for the isomerization process to occur.

From the beginning of these investigations, it was anticipated that a mixture of the three regioisomers (–)-**6**, **266** and **267** would be formed. However, it was also anticipated that the undesired regioisomers **266** and **267** would be unstable as compared to xyloketal F [(–)-**6**] and under appropriate conditions could be isomerized to the natural product. Therefore, a portion of this mixture of products (~7 mg) was dissolved in deuterated chloroform (~0.75 mL) and a crystal of *p*-toluenesulfonic acid monohydrate was added. Over the course of 18 h at 23 °C, the resultant mixture was shown to cleanly convert into (–)-xyloketal F [(–)-**6**] by ^{1}H NMR spectroscopy (Figure 4.6.5.2).

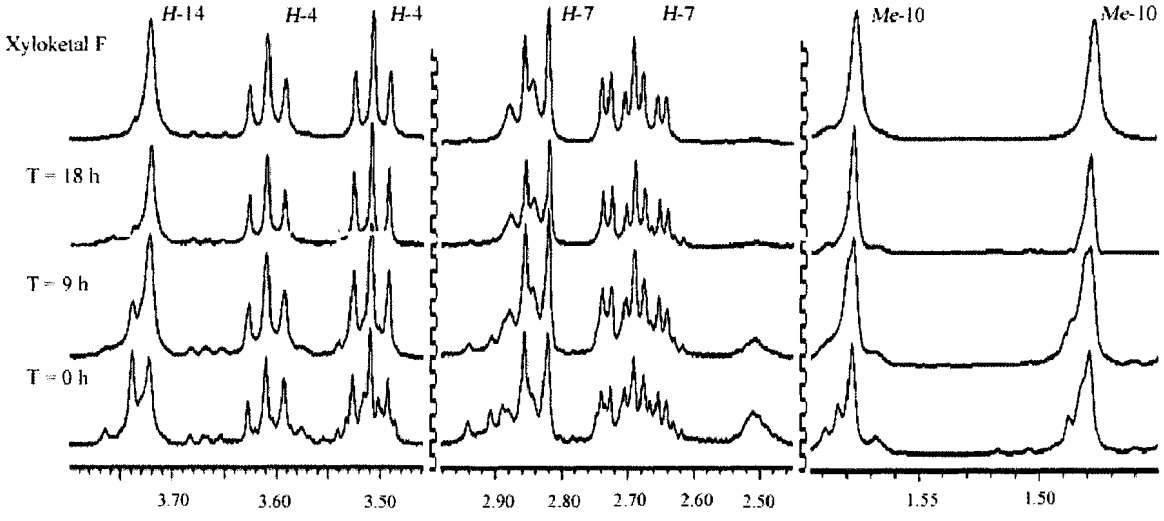


Figure 4.6.5.2 Selected regions of the ^{1}H NMR spectrum (500 MHz, $CDCl_3$) obtained during the isomerization of the regioisomeric adducts (266) and (267) to (–)-xyloketal F [(–)-6].

4.7 Conclusions

A series of demethyl analogues of xyloketal A (**1**), B (**2**), C (**3**), D (**4**), E (**5**) and G (**7**) were prepared in a notably direct manner from 2-methyl-3-hydroxymethyl-4,5-dihydrofuran (**168**) and a series of corresponding phenols *via* an electrophilic aromatic substitution reaction that was promoted by boron trifluoride diethyl etherate. In the case of the synthesis of the xyloketal A analogues (±)-**18** and (±)-**19**, the process was found to be highly efficient (up to 93% yield). This remarkable transformation involved six individual reactions (three electrophilic aromatic substitution reactions and three subsequent acetal formation reactions). Analogues of xyloketal B (**2**) and C (**3**) were prepared from methyl 2,4,6-trihydroxybenzoate (**112**) and analogues of xyloketal D (**4**) and G (**7**) were also prepared from 2,4-dihydroxyacetophenone (**11**). The lower isolated yields of the desired analogues, in these instances, reflected the decreased reactivity of these phenolic substrates towards electrophilic aromatic substitution reactions. The xyloketal B analogues (±)-**115** and (±)-**242** were subsequently converted to a mixture of the xyloketal E analogues (±)-**257**, (±)-**258**, (±)-**259** and (±)-**260**. Since all of these syntheses were non-diastereoselective, the synthesis of analogues of xyloketal F (**6**) was not attempted (a mixture of eight diastereoisomers would be expected).

The application of this potentially biomimetic synthetic method employing (4*R*)-2,4-dimethyl-3-hydroxymethyl-4,5-dihydrofuran [(4R)-**226**] and a variety of phenols led to the total synthesis of (–)-xyloketal A [(–)-**1**] (21% overall yield in nine steps from commercially available starting materials), (–)-xyloketal B [(–)-**2**] (19% overall yield twelve steps from commercially available starting materials), (–)-xyloketal D [(–)-**4**] [5% (17% brsm) overall yield in nine steps from commercially available starting materials],

xyloketal E (**5**) (3% overall yield in thirteen steps from commercially available starting materials), (–)-xyloketal F [(–)-**6**] (16% overall yield in thirteen steps *or* 8% overall yield in eleven steps from commercially available starting materials) and (–)-xyloketal G [(–)-**7**] [3% (10% brsm) in nine steps from commercially available starting materials].* The decreased reactivity of (4*R*)-2,4-dimethyl-3-hydroxymethyl-4,5-dihydrofuran [(4R)-**226**] as compared to 2-methyl-3-hydroxymethyl-4,5-dihydrofuran (**168**) used in the model studies, meant that this synthetic route was not applicable to the synthesis of xyloketal C (**3**). These syntheses are the first reported practical asymmetric syntheses of xyloketal A (**1**), B (**2**), E (**5**) and F (**6**). The spectral data of these natural products was in agreement with the data recorded for the isolated natural products.[1,3,4] There were some differences between the optical rotations and meting points of some of the synthetic compounds and the values reported for the isolated natural products. Professor Lin agreed to record the optical rotation for the natural xyloketals. However, this information has not been reported to us. The depressed melting points were attributed to trace amounts of the enantiomer which had significantly depressed the melting point of our sample of synthetic xyloketals.

In view of the general applicability and success of this route to the total synthesis of the xyloketal natural products, the synthesis of structural analogues can now be pursued. In particular, this synthetic route could be adapted to prepare; a) the enantiomeric series of compounds, b) derivatives with different aromatic cores, c) compounds with alternative heteroatom substitution (*i.e.* nitrogen, sulphur and selenium), d) 5,6-bicyclic acetal derivatives with alternative substitution patterns and e) 6,6-bicyclic

(*) For a discussion of this potentially biomimetic reaction, see: *Synthesis of Xyloketal A, B, C, D, and G Analogues*. Pettigrew, J. D.; Wilson, P. D. *J. Org. Chem.* **2006**, *71*, 1620.

acetal derivatives with various substitution patterns from the corresponding dihydropyran precursors. These analogues may show improved biological activity and enable the structure-activity relationships of the xyloketal natural products to be determined.

CHAPTER FIVE

Total Synthesis of (+)-Alboatrin

5.1 Introduction

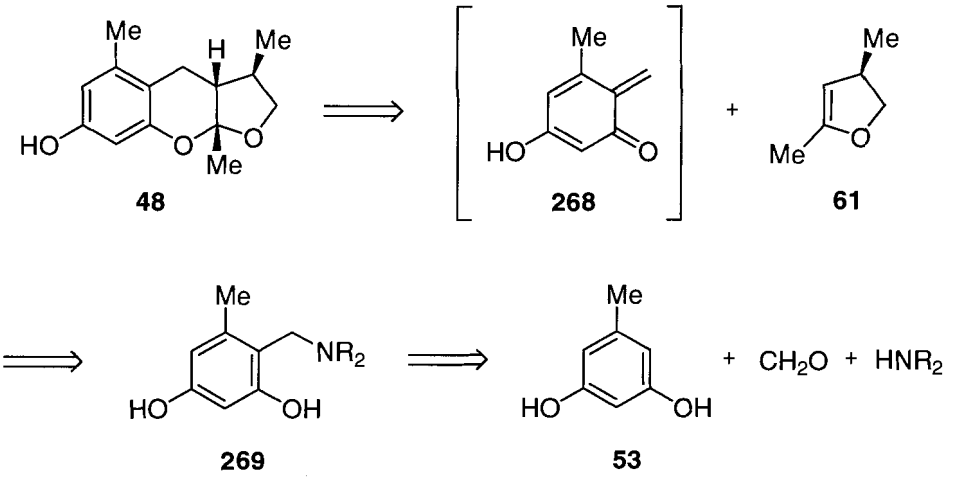
In this chapter the further application of the Diels-Alder approach and the electrophilic aromatic substitution reaction for the synthesis of alboatrin (**48**) is discussed. The latter process led to the successful synthesis of a demethyl analogue of alboatrin (**48**) during optimization of reaction conditions. In addition, the first asymmetric total synthesis of (+)-alboatrin [(+)-**48**] was also accomplished with this process that established the absolute stereochemistry of the natural product.

5.2 Attempted Synthesis of Alboatrin: Diels-Alder Approach

5.2.1 Retrosynthetic Analysis of Alboatrin (48)

In a similar manner to that conceived for the synthesis of the xyloketals, retrosynthetic analysis of alboatrin (**48**) suggested that it could be prepared by a [4+2] cycloaddition reaction of the *ortho*-quinone methide **268** and the dihydrofuran **61** (Scheme 5.2.1.1). The Mannich base **269**, which would serve as a precursor for the generation of the *ortho*-quinone methide **268** could, in principle, be prepared from commercially available orcinol (**53**), a formaldehyde source and a secondary amine.

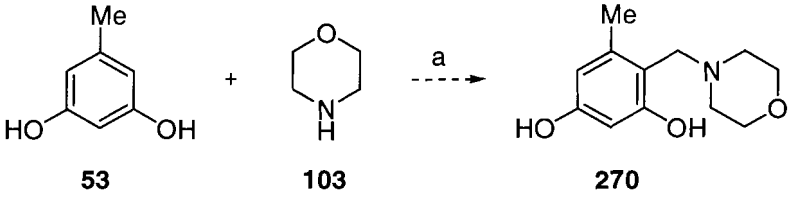
Scheme 5.2.1.1 Retrosynthetic Analysis of Alboatrin (48): Diels-Alder Approach



5.2.2 Attempted Synthesis of the Mannich Base (270) for the Synthesis of Alboatrin (48)

The synthesis of the desired Mannich base **270** from orcinol (**53**), aqueous formaldehyde and morpholine (**103**) was attempted (Scheme 5.2.2.1). The results of these studies are presented below (Table 5.2.2.1).

Scheme 5.2.2.1 Attempted Synthesis of the Mannich Base (270) from Orcinol (53)



Reagents and conditions: (a) See below: Table 5.2.2.1.

Table 5.2.2.1 Reagents and Conditions Corresponding to Scheme 5.2.2.1.

Entry	Reagents and Conditions	Equivalents of Morpholine (103)	Result
1	CH_2O (1.1 equiv), H_2O, MeOH, reflux, 3.5 h	1.1	Complex mixture

Entry	Reagents and Conditions	Equivalents of Morpholine (103)	Result
2	CH_2O (1.1 equiv), H_2O, MeOH, room temperature, 18 h	1.1	Complex mixture
3	CH_2O (0.2 equiv), H_2O, MeOH, reflux, 7 h	0.2	Complex mixture

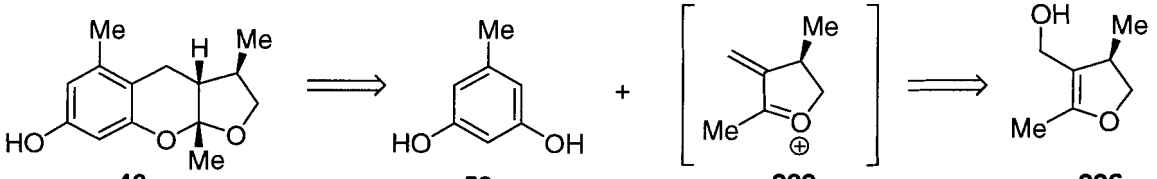
The initial reaction attempted involved identical conditions to that which had been used to make the precursors to xyloketal D (**4**) (See: Section 2.4.1).[21] This involved the reaction of orcinol (**53**) (1 equiv) with aqueous formaldehyde (1.1 equiv) and morpholine (**103**) (1.1 equiv) in methanol at reflux (entry 1). However, this afforded a complex mixture of reaction products. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture indicated that *mono*-, *bis*- and *tris*-adducts had formed. In an effort to suppress the formation of these undesired products, the reaction was performed at room temperature (entry 2). However, this afforded a similar mixture of products. Of note, Ichihara and co-workers have shown that related reactions of orcinol (**53**) afford complex mixtures of products from which the desired *mono*-adducts can be isolated in low yield.[11] Therefore, the number of equivalents of formaldehyde and morpholine (**103**) were decreased in attempt to limit the undesired multiple reactions (entry 3). Unfortunately, a complex mixture of reaction products was again obtained and so no further attempts to prepare the Mannich base **270** were made.

5.3 Total Synthesis of Alboatrin: Electrophilic Aromatic Substitution Reactions with (4*R*)-2,4-Dimethyl-3-hydroxymethyl-4,5-dihydrofuran

5.3.1 Retrosynthetic Analysis of Alboatrin: Electrophilic Aromatic Substitution Reactions with 2,4-Dimethyl-3-hydroxymethyl-4,5-dihydrofuran (226)

An alternative retrosynthetic analysis employing the successful electrophilic aromatic substitution reaction described earlier was also applied to the synthesis of alboatrin (**48**) (Scheme 5.3.1.1). In this instance, the reactive intermediate **239** could be allowed to react with orcinol (**53**) to afford alboatrin (**48**).

Scheme 5.3.1.1 Retrosynthetic Analysis of Alboatrin (48): Electrophilic Aromatic Substitution Reactions with 2,4-Dimethyl-3-hydroxymethyl-4,5-dihydrofuran (226)

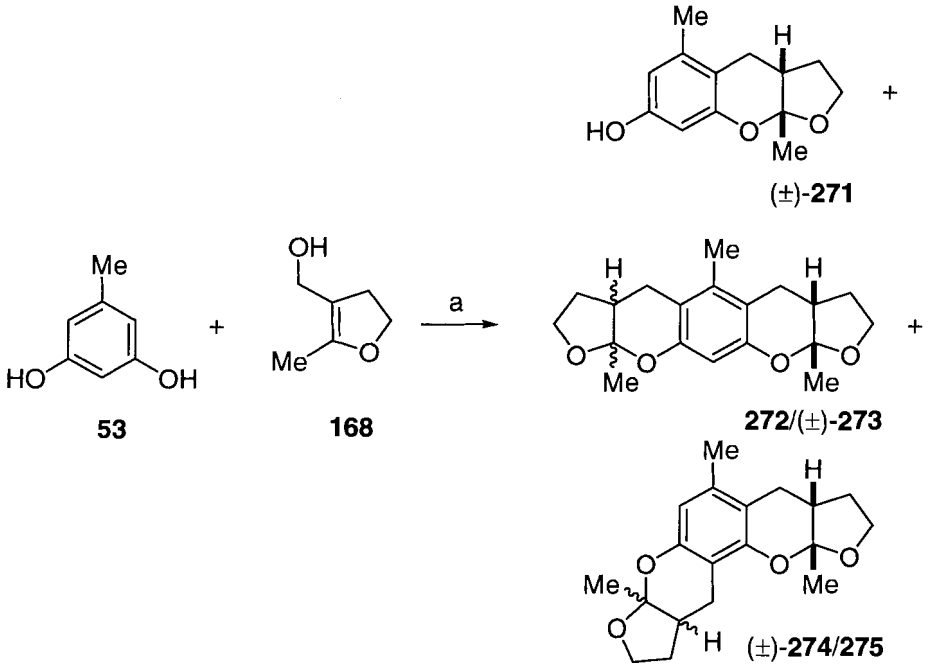


48 **53** **239** **226**

5.3.2 Model Studies: Electrophilic Aromatic Substitution Reactions with 2-Methyl-3-hydroxymethyl-4,5-dihydrofuran (168)

In order to optimize the reaction conditions for the preparation of alboatrin (**48**), model studies were performed (Scheme 5.3.2.1). Accordingly, orcinol (**53**) (1 equiv) was allowed to react with the alcohol **168** and boron trifluoride diethyl etherate in the presence of anhydrous magnesium sulfate in ether. The results of these studies are presented below (Table 5.3.2.1).

Scheme 5.3.2.1 Synthesis of 10-Noralboatrin [(±)-271]: Electrophilic Aromatic Substitution Reactions with 2-Methyl-3-hydroxymethyl-4,5-dihydrofuran (168)



Reagents and conditions: (a) See below: Table 5.3.2.1.

Table 5.3.2.1 Reagents and Conditions Corresponding to Scheme 5.3.2.1.*

Entry	Equivalents of the Alcohol (168)	Reagents and Conditions	Yield of [(±)-271] (%)	Yield of [272:(±)-273:(±)-274:(±)-275] (%)
1	1.25	$BF_3 \cdot Et_2O$ (1 equiv), $MgSO_4$, Et_2O, 0 °C to room temperature, 28 h	31	25
2	1.05	$BF_3 \cdot Et_2O$ (1 equiv), $MgSO_4$, Et_2O, 0 °C to room temperature, 24 h	34 (75 brsm)	8
3	0.3	$BF_3 \cdot Et_2O$ (1 equiv), $MgSO_4$, Et_2O, 0 °C to room temperature, 24 h	36	trace

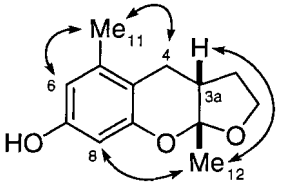
(*) The *bis*-adducts **272**, (±)-**273**, (±)-**274** and (±)-**275** were obtained as an inseparable mixture (3:3:1:1).

Entry	Equivalents of the Alcohol (168)	Reagents and Conditions	Yield of [(±)-271] (%)	Yield of [272:(±)-273:(±)-274:(±)-275] (%)
4	1.05	$BF_3 \cdot Et_2O$ (0.3 equiv), $MgSO_4$, Et_2O, 0 °C to room temperature, 45 h	48 (72 brsm)	34

During the attempted synthesis of the Mannich base **270** derived from orcinol (**53**), multiple electrophilic aromatic substitution reactions were observed. Thus, in the initial attempt, orcinol (**53**) (1 equiv) was allowed to react with the alcohol **168** (1.25 equiv) in the presence of boron trifluoride diethyl etherate (1 equiv) (entry 1). This afforded the desired *mono*-adduct (±)-**271** in modest yield (31%). In addition, a substantial amount of an inseparable mixture (3:3:1:1) of the *bis*-adducts **272**, (±)-**273**, (±)-**274** and (±)-**275** was also obtained (25% combined yield). Unexpectedly, none of the corresponding regioisomeric *mono*-adduct was obtained. In an effort to reduce the amount of the *bis*-adducts **272**, (±)-**273**, (±)-**274** and (±)-**275** formed, the quantity of the alcohol **168** was reduced (1.05 equiv) (entry 2). Although the amount of the *bis*-adducts **272**, (±)-**273**, (±)-**274** and (±)-**275** produced in this reaction was less (8%), a large amount of unreacted orcinol (**53**) was also recovered. The overall yield of the desired reaction was not significantly increased (34%). However, based on the amount of starting material **53** that was recovered, the yield of the desired reaction product (±)-**271** was 75%. Further reduction of the number of equivalents of the alcohol **168** (0.3 equiv) did not significantly increase the yield of the desired reaction product (±)-**271** (36%) (entry 3). It was subsequently found that reducing the number of equivalents of boron

trifluoride diethyl etherate (0.3 equiv), resulted in a significant increase in the yield of the desired reaction product (±)-**271** (48%) (entry 4). This increased yield was attributed to a reduction in the level of decomposition of the unstable alcohol **168**.

The structure of the single *mono*-adduct (±)-**271** was determined to have the desired relative stereo- and regiochemistry based upon extensive spectral studies. In particular, nOe contacts were observed between *Me*-12 and *H*-3a that supported the desired relative stereochemistry of the product (Figure 5.3.2.1). Furthermore, nOe contacts between *Me*-12 and *H*-8 and between *Me*-11, *H*-4 and *H*-6 indicated that the reaction product had the desired regiochemistry.



(±)-**271**

Figure 5.3.2.1 Observed nOe contacts for the alboatrin analogue [(±)-271].

The regiochemistry of the *bis*-adducts **272**, (±)-**273**, (±)-**274** and (±)-**275** was determined on the basis of the ^{1}H and ^{13}C NMR spectra. The aromatic region of the ^{1}H NMR spectrum contained four aromatic signals from which the product ratio could be determined (3:3:1:1). Inspection of the ^{13}C NMR spectrum revealed that the major reaction products, based on the intensities of the signals, had a high degree of symmetry and therefore they were the linear regioisomers **272** and (±)-**273** (Figure 5.3.2.2). Of note, this was the opposite regiochemistry to that which had been observed previously during the corresponding work towards xyloketal B (**2**) and C (**3**).

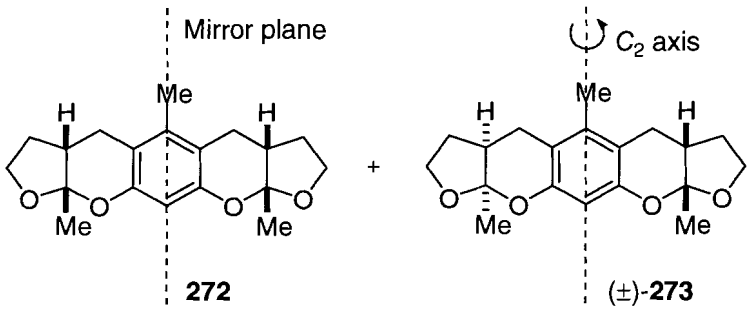
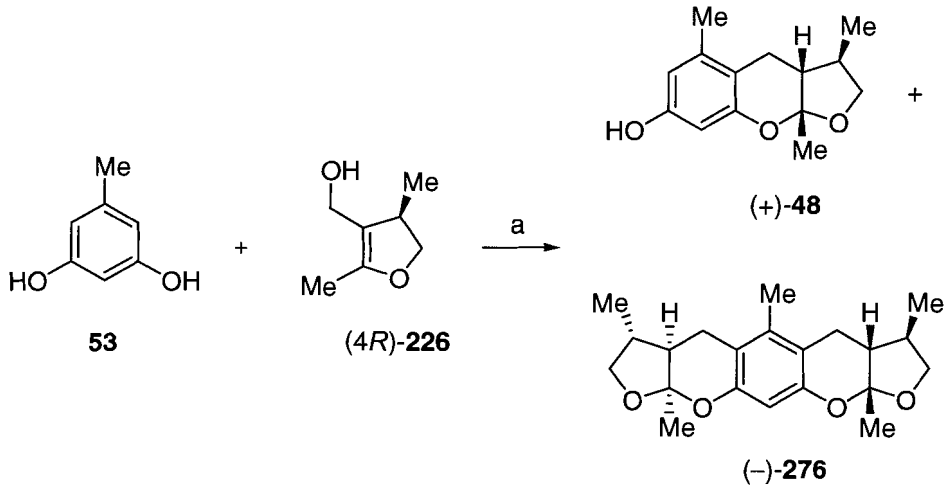


Figure 5.3.2.2 Symmetry elements present in the linear *bis*-adducts (272) and [(±)-273].

5.3.3 Total Synthesis of (+)-Alboatrin [(+)-48]

Having completed model studies and demonstrated the feasibility of the electrophilic aromatic substitution reactions for the total synthesis of alboatrin (**48**), the reaction between orcinol (**53**) (1 equiv) and the chiral nonracemic alcohol (4*R*)-**226** (1.05 equiv) in the presence boron trifluoride diethyl etherate (0.3 equiv) was performed (Scheme 5.3.3.1). This reaction afforded the desired natural product (+)-alboatrin [(+)-**48**] in moderate yield [36%, (78% brsm)]. In addition, a single regioisomeric *bis*-adduct (–)-**276** was also isolated in low yield (14%).

Scheme 5.3.3.1 Total Synthesis of (+)-Alboatrin [(+)-48]: Electrophilic Aromatic Substitution Reactions with (4*R*)-2,4-Dimethyl-3-hydroxymethyl-4,5-dihydrofuran [(4*R*)-226]



Reagents and conditions: (a) Alcohol (4*R*)-**226** (1.05 equiv), $BF_3 \cdot Et_2O$ (0.3 equiv), $MgSO_4$, Et_2O, 0 °C to room temperature, 48 h, 36% (78% brsm) [(+)-**48**], 14% [(–)-**276**].

The ^1H and ^{13}C NMR spectra of synthetic (+)-alboatrin [(+)-**48**] were identical to those recorded for the natural product (Figure 5.3.3.1).[11] The structural characterization of this material was also performed using 2D NMR methods for comparison purposes to our studies on the total synthesis of the xyloketals.

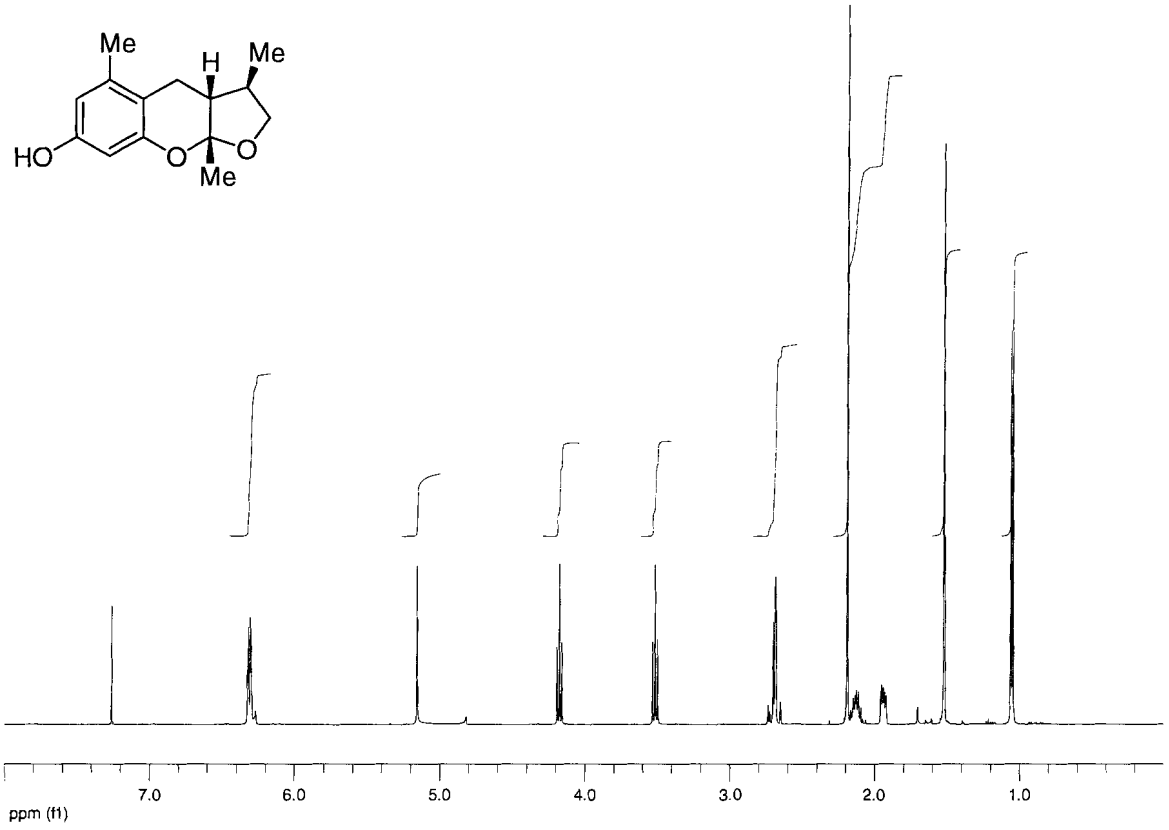
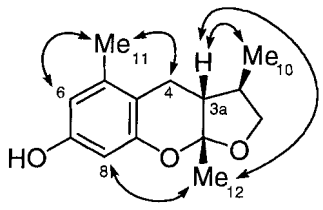


Figure 5.3.3.1 ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of (+)-alboatrin [(+)-48].

Thus, nOe contacts were observed between *Me*-10, *H*-3a and *Me*-12 that confirmed the relative stereochemistry of these substituents (Figure 5.3.3.2). The regiochemistry of this product was further confirmed on the basis of nOe contacts observed between *Me*-12 and *H*-8 and between *Me*-11, *H*-4 and *H*-6.



(+)-**48**

Figure 5.3.3.2 Observed nOe contacts for (+)-alboatrin [(+)-48].

The optical rotation (in both sense and magnitude) as well as the melting point of the synthetic material [(+)-**48**] were also in close agreement with those reported in the original isolation paper.[11] Thus, the absolute stereochemistry of the natural product is now firmly established.

The structure of the single regioisomeric *bis*-adduct (–)-**276** was also determined by 2D NMR analysis. The relative simplicity of the ^{1}H and ^{13}C NMR spectra confirmed the C_2-symmetry of the reaction product.

5.4 Conclusions

The application of the Diels-Alder approach towards the synthesis of alboatrin (**48**) was not successful. The preparation of the Mannich base **270** required for the generation of an appropriately substituted *ortho*-quinone methide proved to be exceedingly difficult as the result of competitive multiple electrophilic substitution reactions of the electron rich aromatic phenol, orcinol (**53**).

The use of the alcohol **168** as the source of a reactive intermediate in model studies for the electrophilic aromatic substitution reaction of orcinol (**53**) afforded the demethyl analogue (±)-**271** of alboatrin (**48**). It was noted that this phenolic substrate displayed a propensity to undergo multiple reactions to afford the *bis*-adducts **272**, (±)-**273**, (±)-**274** and (±)-**275**. However, careful control of the number of equivalents of the alcohol **168** and the boron trifluoride diethyl etherate employed in the reaction resulted in the isolation of the desired reaction product (±)-**271** in moderate yield [48% (72% brsm)]. The use of the chiral nonracemic alcohol (4*R*)-**226** in this electrophilic aromatic substitution process led to the first asymmetric total synthesis of (+)-alboatrin [(–)-**48**]

[12% (27% brsm) overall yield, 9 steps] and allowed for the absolute stereochemistry of this natural product to be assigned.

CHAPTER SIX

Experimental

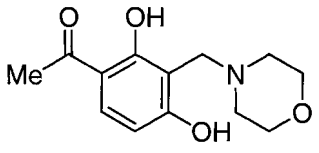
6.1 General Experimental Details

All non-aqueous reactions were performed under an atmosphere of dry nitrogen in oven- or flame-dried glassware. The reaction temperatures stated were those of the external bath. Diethyl ether (ether) and tetrahydrofuran were dried over sodium/benzophenone ketyl and distilled under an atmosphere of dry nitrogen immediately prior to use. Dichloromethane and benzene 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.[147] Silica gel column chromatography ("flash chromatography") was carried out using Merck silica gel 60 (230 to 400 mesh) unless stated otherwise.[148] Brine refers to a saturated aqueous solution of sodium chloride. Melting points (**M.p.**) were measured on a Gallenkamp capillary melting point apparatus and are uncorrected. Optical rotations ($[\alpha]_D$) were measured using a Perkin-Elmer 341 digital polarimeter. All proton, carbon and fluorine nuclear magnetic resonance spectra (**^{1}H NMR**, **^{13}C NMR** and **^{19}F NMR**, respectively) were recorded on 400 MHz (operating frequencies: ^{1}H, 400.13 MHz; ^{13}C, 100.61 MHz), 500 MHz (operating frequencies: ^{1}H, 499.77 MHz; ^{13}C, 125.68 MHz; ^{19}F, 470.22 MHz) and 600 MHz (operating frequencies: ^{1}H, 600.14 MHz) FT spectrometers at ambient temperature. The 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 δ 7.26 and 77.00 ppm for

^{1}H and ^{13}C NMR spectra, respectively. The reference values used for deuterated benzene (C_6D_6) were δ 7.15 and 128.02 ppm, respectively. The reference values used for deuterated acetone [$(CD_3)_2CO$] were δ 2.05 and 30.83 ppm, respectively. ^{19}F NMR spectra were recorded in deuterated chloroform ($CDCl_3$) and the chemical shifts (δ) for all compounds are listed in parts per million downfield from trifluoroacetic acid which was used as an external reference. Infrared spectra (**IR**) were recorded as evaporated films (ef) or as KBr discs (KBr) using a Perkin Elmer 599B IR spectrophotometer. Low-resolution mass spectra (**MS**) were recorded on a Varian 4000 GC/MS/MS. The mode of ionization used was electron impact (EI, 70 eV) or chemical ionization (CI) with methanol as the ionization gas. Matrix-assisted laser desorption/ionization time-of-flight mass spectra (MALDI-TOF) were recorded using 2,4-dihydroxybenzoic acid as the matrix. High-resolution mass spectra using fast atom bombardment (**FAB-HRMS**) were recorded on a Kratos Concept IH mass spectrometer. Microanalyses (**Anal.**) were performed on a Carlo Erba Model 1106 CHN analyzer.

6.2 Experimental Concerning Chapter Two

6.2.1 3-Morpholin-4-yl-methyl-2,4-dihydroxyacetophenone (104)[21]

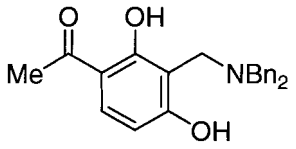


104

To a solution of 2,4-dihydroxyacetophenone (**11**) (504 mg, 3.31 mmol) in methanol (9 mL) at room temperature was added morpholine (**103**) (315 μL, 3.61 mmol) and an aqueous formaldehyde solution (290 μL, 37% w/v, 3.58 mmol). The reaction mixture was heated at reflux for 3 h and then concentrated *in vacuo* to afford a cream

coloured solid. Purification by flash chromatography using ether:hexanes (1:1) as the eluant afforded the *title compound* **104** (687 mg, 83%) as a white solid. $\mathbf{R}_f$ = 0.22, ether:hexanes (4:1); **M.p.** 100-102 °C, hexanes:ether; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.53 (s, 3H, *Me*), 2.65 (m, 4H, NC*H*$_2$), 3.78 (m, 4H, OC*H*$_2$), 3.87 (s, 2H, ArC*H*$_2$), 6.36 (d, J = 8.9 Hz, 1H, *H*-5), 7.57 (d, J = 8.9 Hz, 1H, *H*-6), 8.64 (broad s, 1H, 4-O*H*), 13.15 (s, 1H, 2-O*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 26.1, 53.0, 54.0, 66.78, 106.9, 108.5, 112.8, 131.9, 162.7, 166.0, 202.7; **IR** (ef) 3432, 2948, 2854, 1615, 1493, 1274, 1260, 1116, 1060, 817 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 252 (M + H, 100), 88 (24); **Anal.** Calcd. for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 61.84; H, 6.95; N, 5.25.

6.2.2 3-Dibenzylaminomethyl-2,4-dihydroxyacetophenone (106)[21]

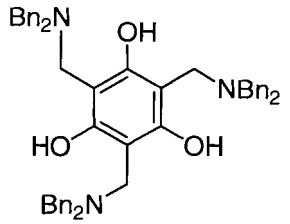


106

To a solution of 2,4-dihydroxyacetophenone (**11**) (502 mg, 3.30 mmol) in methanol (9 mL) at room temperature was added dibenzylamine (**105**) (690 μL, 3.60 mmol) and an aqueous formaldehyde solution (290 μL, 37% w/v, 3.58 mmol). The reaction mixture was heated at reflux for 48 h and then concentrated *in vacuo* to afford a yellow gum. Purification by flash chromatography using ether:hexanes (1:1) as the eluant afforded the *title compound* **106** (868 mg, 73%) as a thick yellow syrup. $\mathbf{R}_f$ = 0.61, ether:hexanes (4:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.53 (s, 3H, *Me*), 3.65 (m, 4H, NC*H*$_2$Ph), 3.90 (m, 2H, NC*H*$_2$Ar), 6.37 (d, J = 8.8 Hz, 1H, *H*-5), 7.31 (m, 3H, Ar*H*), 7.55 (d, J = 8.8 Hz, 1H, *H*-6), 13.17 (s, 1H, 2-O*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 26.2, 48.8, 58.1, 108.1, 108.5, 112.8, 128.0, 128.8, 129.8, 131.8, 136.4, 162.7, 166.1, 202.7;

IR (ef) 3072, 3029, 2924, 2830, 1622, 1494, 1368, 1270, 1059 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 362 (M + H, 2), 254 (2), 236 (3), 198 (100); **Anal.** Calcd. for $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41; N, 3.88. Found: C, 76.61; H, 6.56; N, 3.93.

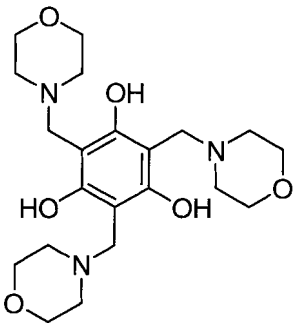
6.2.3 2,4,6-*tris*[Dibenzylaminomethyl]phloroglucinol (108)[26,27]



108

To a solution of phloroglucinol (**14**) (3.00 g, 23.8 mmol) in ethanol (100 mL) at room temperature were added dibenzylamine (**105**) (14.2 mL, 78.5 mmol) and an aqueous formaldehyde solution (6.0 mL, 37% w/v, 74 mmol). The reaction mixture was stirred for 18 h and then the resultant precipitate was collected by filtration, washed with ethanol (3 × 15 mL) and dried *in vacuo* to afford the *title compound* **108** (16.7 g, 93%) as a white powder. $\mathbf{R_f}$ = 0.70, hexanes:ether (1:4); **M.p.** 156-160 °C, ethanol; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.60 (s, 12H, 6 × PhCH_2), 3.78 (s, 6H, 3 × ArCH_2), 7.22-7.33 (m, 30H, Ar*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 49.2, 57.8, 99.5, 110.3, 127.4, 128.5, 129.6, 137.2, 155.9; **IR** (KBr) 3454, 3093, 3067, 3031, 2897, 2830, 2794, 1743, 1630, 1491, 1450, 1383, 1352, 1254, 1115 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 212 (96), 198 (100), 89 (18). **Anal.** Calcd for $C_{51}H_{51}N_3O_3$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.21; H, 7.04; N, 5.62.

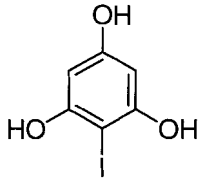
6.2.4 2,4,6-*tris*[3-Morpholin-4-yl-methyl]phloroglucinol (107)[26,27]



107

To a solution of phloroglucinol (**14**) (2.00 g, 15.9 mmol) in ethanol (100 mL) at room temperature were added morpholine (**103**) (4.30 mL, 49.2 mmol) and an aqueous formaldehyde solution (4.0 mL, 37% w/v, 49 mmol). The reaction mixture was stirred for 18 h and the resultant precipitate was collected by filtration, washed with ethanol (3 × 15 mL) and dried *in vacuo* to afford the *title compound* **107** (5.32 g, 79%) as a beige powder. $\mathbf{R}_f$ = 0.65, hexanes:ether (1:4); **M.p.** 150-151 °C, ethanol; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.58 (m, 12H, NCH_2), 3.72 (m, 18H, OCH_2 *and* ArCH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 52.8, 54.2, 66.3, 98.2, 156.2; **IR** (KBr) 3511, 2840, 1630, 1460, 1115 cm^{-1}; **MS** (EI) *m/z* (rel. intensity) 100 (100). **Anal.** Calcd for $C_{21}H_{33}N_3O_6$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.47; H, 8.01; N, 9.79.

6.2.5 Iodophloroglucinol Trihydrate (109)[46]

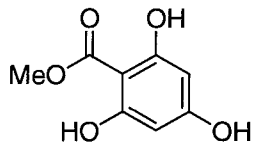


• 3 H_2O **109**

To a solution of phloroglucinol (**14**) (3.78 g, 30.0 mmol) in tetrahydrofuran (30 mL) and water (30 mL) at room temperature were added iodine (7.70 g, 30.3 mmol) and sodium bicarbonate (2.72 g, 32.4 mmol) and the resultant mixture was stirred for 15 min.

The reaction mixture was then diluted with water (40 mL), extracted with ether (3 × 80 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The resultant yellow oil was dissolved in acetone (5 mL) and chloroform (40 mL) and refrigerated at – 20 °C overnight. The resultant precipitate was removed by filtration and the filtrate was concentrated *in vacuo* to afford the impure *title compound* **109**. This process was repeated to afford the pure *title compound* **109** (6.83 g, 90%) as a yellow powder. $\mathbf{R}_f$ = 0.40, chloroform:methanol (17:3); **M.p.** 147-149 °C, acetone:chloroform; **^{1}H NMR** [400 MHz, $(CD_3)_2CO$] δ 2.94 (s, 6H, 3 × H_2O), 6.10 (s, 2H, Ar*H*), 8.33 (s, 1H, O*H*), 8.67 (s, 2H, 2 × O*H*); **^{13}C NMR** [101 MHz, $(CD_3)_2CO$] δ 64.3, 96.3, 160.0, 161.1; **IR** (ef) 3373, 1598, 1460, 1365, 1275, 1158 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 253 (M + H, 100).

6.2.6 Methyl 2,4,6-trihydroxybenzoate (112)[50]

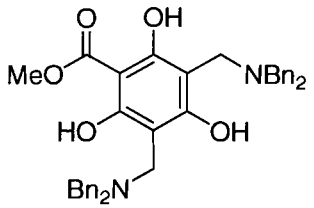


112

To a mixture of 2,4,6-trihydroxybenzoic acid (**111**) [90% (Aldrich), 10.0 g, 47.9 mmol] and sodium bicarbonate (5.41 g, 64.4 mmol) in *N*,*N*-dimethylformamide (30 mL) was added a solution of dimethyl sulfate (5.0 mL, 53 mmol) in *N*,*N*-dimethylformamide (5 mL). The resultant mixture was stirred at room temperature for six days and then ice (~100 g) was added. The reaction mixture was then extracted with ethyl acetate (3 × 150 mL). The combined organic layers were washed with water (200 mL), a saturated aqueous solution of sodium bicarbonate (200 mL), brine (200 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by flash chromatography using chloroform:methanol (9:1) as the eluant afforded the *title compound* **112** (5.84 g, 66%) as a white solid. $\mathbf{R}_f$ = 0.54, chloroform:methanol (9:1); **M.p.** 166-168 °C,

chloroform:methanol (lit.[50] 180-180.5 °C, ethyl acetate:cyclohexane); **^{1}H NMR** [500 MHz, $(CD_3)_2CO$] δ 4.04 (s, 3H, *Me*), 5.93 (s, 2H, Ar*H*), 9.31 (broad s, 1H, O*H*), 9.98 (broad s, 2H, O*H*); **^{13}C NMR** [101 MHz, $(CD_3)_2CO$] δ 53.9, 95.1, 97.3, 164.7, 166.6, 172.1; **IR** (ef) 3528, 3455, 3387, 3088, 3008, 2701, 2652, 1650, 1606, 1480, 1461, 1326, 1294, 1256, 1190 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 185 (M + H, 100).

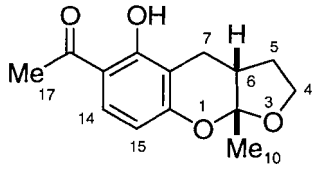
6.2.7 Methyl 2,4,6-trihydroxy-3,5-dibenzylaminomethylbenzoate (113)



113

To a solution of the methyl ester **112** (200 mg, 1.09 mmol) in methanol (7 mL) at room temperature were added dibenzylamine (**105**) (440 μL, 2.4 mmol) and an aqueous formaldehyde solution (200 μL, 37% w/v, 2.4 mmol). The reaction mixture was stirred for 20 h and then concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (1:1) as the eluant afforded the *title compound* **137** (289 mg, 44%) as a white solid. $\mathbf{R_f}$ = 0.40, hexanes:ether (1:1); **M.p.** 46-48 °C, hexanes:ether; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.65 (s, 8H, 4 × PhC*H*$_2$), 3.81 (s, 4H, 3 × ArC*H*$_2$), 3.98 (s, 3H, CO_2*Me*), 7.32 (m, 20H, Ar*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 48.7, 52.1, 57.5, 94.3, 99.7, 127.6, 128.5, 129.6, 136.5, 161.0, 162.7, 172.1; **IR** (ef) 3424, 3029, 2953, 2847, 1647, 1496, 1453, 1439, 1314, 1213, 1130 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 198 (100). **Anal.** Calcd for $C_{38}H_{38}N_2O_5$: C, 75.72; H, 6.35; N, 4.65. Found: C, 75.88; H, 6.26; N, 4.53.

6.2.8 (±)-11-Norxyloketal D [(±)-12][9]



(±)-**12**

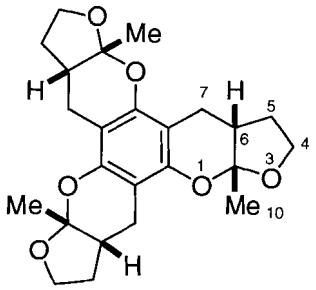
Method A: To a solution of the Mannich base **104** (199 mg, 0.793 mmol) in benzene (8 mL) at room temperature were added 2-methyl-4,5-dihydrofuran (**114**) (220 μL, 2.41 mmol) and methyl iodide (52 μL, 0.84 mmol). The resultant solution was heated at reflux until TLC analysis indicated that the Mannich base **104** had undergone complete reaction (5 days). The reaction mixture was then cooled to room temperature, filtered with ether (8 mL) and concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (16:1) as the eluant afforded the *title compound* (±)-**12** (86 mg, 43%) as a white solid.

Method B: To a solution of the Mannich base **106** (290 mg, 0.803 mmol) in benzene (8 mL) at room temperature were added 2-methyl-4,5-dihydrofuran (**114**) (220 μL, 2.41 mmol) and methyl iodide (52 μL, 0.84 mmol). The resultant solution was heated at reflux until TLC analysis indicated that the Mannich base **106** had undergone complete reaction (5 days). The reaction mixture was then cooled to room temperature, filtered with ether (8 mL) and concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (16:1) as the eluant afforded the *title compound* (±)-**12** (75 mg, 38%) as a white solid.

Title compound (±)-**12**: $\mathbf{R}_f$ = 0.25, hexanes:ether (4:1); **M.p.** 104-105 °C, hexanes:ether (lit.[9] 114-116 °C, pentane:ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.54 (s, 3H, *Me*-10), 1.74 (m, 1H, *H*-5), 2.08 (m, 1H, *H*-5), 2.47 (m, 1H, *H*-6$_\beta$), 2.54 (s, 3H, *Me*-

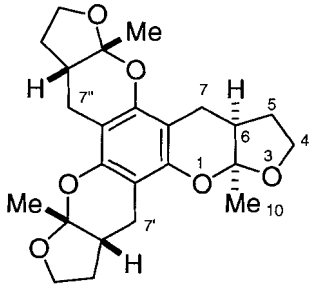
17), 2.75 (dd, J = 17.9, 6.4 Hz, 1H, H-7$_\beta$), 3.02 (dd, J = 17.9, 1.1 Hz, 1H, H-7$_\alpha$), 3.98 (apparent q, J = 8.5 Hz, 1H, H-4), 4.06 (apparent td, J = 9.5, 2.9 Hz, 1H, H-4), 6.37 (d, J = 8.9 Hz, 1H, H-15), 7.52 (d, J = 8.9 Hz, 1H, H-14), 13.10 (s, 1H, OH); **Observed nOe contacts** Me-11 to H-6$_\beta$, Me-11 to H-7$_\beta$; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 19.4 (C-7), 22.2 (C-10), 26.1 (C-17), 28.5 (C-5), 39.6 (C-6), 66.9 (C-4), 106.1, 107.4 (C-2), 108.8 (C-15), 113.1, 130.0 (C-14), 159.6, 162.9, 202.6; **IR** (ef) 3232 (br), 2987, 2930, 2897, 1622, 1491, 1420, 1370, 1330, 1271, 1177, 1107, 1085, 1004, 852 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 249 (M + H, 100), 231 (30); **Anal.** Calcd. for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.85; H, 6.61.

6.2.9 (±)-11-Trinorxyloketal A [(±)-18] and (±)-2,6-*epi*-11,11',11''-Trinorxyloketal A [(±)-19][9]



(±)-**18**

and



(±)-**19**

Method A: To a solution of the Mannich base **108** (754 mg, 1.00 mmol) in benzene (10 mL) at room temperature were added 2-methyl-4,5-dihydrofuran (**114**) (820 μL, 8.99 mmol) and methyl iodide (190 μL, 3.05 mmol). The resultant solution was heated at reflux until TLC analysis indicated that the Mannich base **108** had undergone complete reaction (24 h). The reaction mixture was then cooled to room temperature, filtered with ether (10 mL) and concentrated *in vacuo*. Purification by repetitive flash chromatography using hexanes:ether (1:1) then dichloromethane:ether (18:1) as eluants

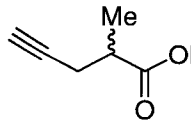
afforded an inseparable mixture (dr = 1:4) of the *title compounds* (±)-**18** and (±)-**19** (78 mg, 19%) as a solid white foam.

Method B: To a solution of the Mannich base **107** (170 mg, 0.40 mmol) in benzene (10 mL) at room temperature were added 2-methyl-4,5-dihydrofuran (**114**) (330 μL, 3.62 mmol) and methyl iodide (75 μL, 1.21 mmol). The resultant solution was heated at reflux until TLC analysis indicated that the Mannich base **114** had undergone complete reaction (24 h). The reaction mixture was then cooled to room temperature, filtered with ether (10 mL) and concentrated *in vacuo*. Purification by repetitive flash chromatography using hexanes:ether (1:1) then dichloromethane:ether (18:1) as eluants afforded an inseparable mixture (dr = 1:4) of the *title compounds* (±)-**18** and (±)-**19** (23 mg, 14%) as a solid white foam.

Recrystallization of the *title compounds* (±)-**18** and (±)-**19** from petroleum ether, on slow evaporation of the solvent, afforded an analytically pure mixture (dr = 1:4) of the *title compounds* (±)-**18** and (±)-**19** as a white solid. $\mathbf{R}_f$ = 0.43, ether:hexanes (4:1), 0.27, dichloromethane:ether (9:1); **M.p.** 145-147 °C, petroleum ether (lit.[9] 155-157 °C, petroleum ether for a mixture (dr = 1:4) of the *title compounds* (±)-**18** and (±)-**19**); **^{1}H NMR** (600 MHz, C_6D_6) δ 1.44 (s, 3H, *Me* of (±)-**19**), 1.45 (s, 3H, *Me* of (±)-**19**), 1.47 (s, 3H, *Me* of (±)-**19**), 1.48 (s, 9H, *Me* of (±)-**18**), 1.51 (m, 3H, *H*-5), 1.65 (m, 3H, *H*-5), 1.95 (m, 3H, *H*-6), 2.73 (m, 3H, *H*-7), 3.05 (m, 3H, *H*-7), 3.62 (m, 3H, *H*-4), 3.90 (m, 3H, *H*-4); **^{13}C NMR** (126 MHz, C_6D_6) δ 20.81, 20.84, 20.9, 22.8, 22.9, 23.1, 23.2, 29.3, 29.36, 40.6, 40.66, 40.69, 66.56, 66.57, 66.59, 99.4, 99.57, 99.63, 99.65, 106.8, 106.91, 106.95, 107.1, 150.8, 150.88, 150.89, 151.1; **IR** (ef) 2981, 2936, 2885, 2852, 1617, 1455, 1371,

1179, 1105, 1003 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 415 (M + H, 31), 414 (M, 15), 373 (10), 331 (100), 97 (9), 43 (32); **Anal.** Calcd. for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30. Found: C, 69.34; H, 7.30.

6.2.10 (±)-2-Methylpent-4-ynoic Acid [(±)-70][24,25]

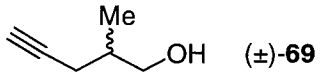


(±)-**70**

To a solution of *N,N*-diisopropylamine (44.0 mL, 312 mmol) in tetrahydrofuran (300 mL) at 0 °C was added *n*-butyl lithium (124 mL, 2.5 M in hexanes, 310 mmol). The resultant solution was stirred at 0 °C for 30 min and then propionic acid (**72**) (10.1 mL, 135 mmol) and hexamethylphosphoramide (23.5 mL, 134 mmol) were added. The reaction mixture was stirred at room temperature for 1 h and then cooled to 0 °C. A solution of propargyl bromide (**71**) (18.1 mL, 80 % w/w in toluene, 162 mmol) was then added dropwise. The resultant mixture was allowed to warm to room temperature and was stirred for 16 h. The reaction mixture was then acidified to pH ~2 with hydrochloric acid (3 M) and extracted with ether (3 × 150 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification of the resultant residue by distillation at reduced pressure afforded the *title compound* (±)-**70** (10.3 g, 68%) as a colourless oil. $\mathbf{R}_f$ = 0.48, hexanes:ethyl acetate (1:2); **B.p.** 103-106 °C, 5 mm Hg (lit.[24] 106.5-109.5 °C, 14-15 mm Hg); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.31 (d, J = 7.1 Hz, 3H, C*H*$_3$), 2.02 (t, J = 2.7 Hz, 1H, *H*CC), 2.40 (m, 1H, C*H*H), 2.57 (m, 1H, CH*H*), 2.71 (m, 1H, C*H*CO_2H), 10.73 (m, 1H, O*H*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 16.1, 22.3, 38.6, 70.1, 81.1, 181.3; **IR** (ef) 3293, 2978,

2668, 1701, 1420, 1295, 1240, 1200, 940, 659 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 113 (M + H, 100).

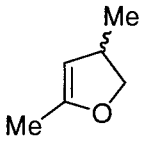
6.2.11 (±)-2-Methylpent-4-yn-1-ol [(±)-69][24]



(±)-**69**

To a suspension of lithium aluminum hydride (3.73 g, 98.2 mmol) in tetrahydrofuran (150 mL) at 0 °C was added a solution of the carboxylic acid (±)-**70** (5.51 g, 49.1 mmol) in tetrahydrofuran (150 mL) and the resultant suspension was stirred at room temperature for 16 h. Water (3.7 mL), an aqueous solution of sodium hydroxide (2 M, 3.7 mL) and water (11.2 mL) were then added in succession and the resultant mixture was filtered. The filter-cake was washed with ether (200 mL) and the combined organic filtrates were concentrated *in vacuo*. Purification by distillation at reduced pressure afforded the *title compound* (±)-**69** (3.98 g, 82%) as a colourless oil. $\mathbf{R}_f$ = 0.55, hexanes:ethyl acetate (1:2); **B.p**. 61-66 °C, ~20 mm Hg (lit.[24] 64-64.5 °C, 10 mm Hg); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.01 (d, J = 6.9 Hz, 3H, CH_3), 1.56 (broad s, 1H, O*H*), 1.90 (m, 1H, C*H*CH_3), 1.98 (t, J = 2.7 Hz, 1H, *H*CC), 2.21 (ddd, J = 16.8, 6.4, 2.7 Hz, 1H, CC*H*H), 2.29 (ddd, J = 16.8, 6.2, 2.7 Hz, 1H, CCH*H*), 3.59 (d, J = 6.1 Hz, 2H, CH_2O); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 16.0, 22.2, 34.8, 66.8, 69.6, 82.6; **IR** (ef) 3409, 2961, 2922, 2117, 1461, 1430, 1037, 651 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 99 (M + H, 100).

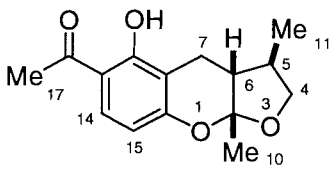
6.2.12 (±)-2,4-Dimethyl-4,5-dihydrofuran [(±)-61][22,23]



(±)-**61**

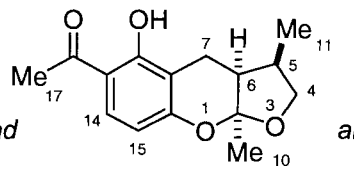
The alcohol (±)-**69** (3.95 g, 40.3 mmol) and sodium amide (150 mg, 3.84 mmol) were heated at reflux for 2 h. Direct distillation of the reaction mixture afforded the exocyclic double bond isomer (±)-**68** as a colourless liquid (2.60 g, 66%). A sample of this material (1.20 g, 12.2 mmol) was heated at reflux for 16 h and then distilled to afford the *title compound* (±)-**61** (1.04 g, 87%) as a colourless liquid. **B.p.** ~100 °C, ~760 mm Hg; **^{1}H NMR** (400 MHz, C_6D_6) δ 0.84 (d, J = 6.6 Hz, 3H, *Me*-4), 1.68 (apparent t, J = 1.5 Hz, 3H, *Me*-2), 2.76 (m, 1H, *H*-4), 3.71 (dd, J = 8.7, 6.5 Hz, 1H, *H*-5), 4.21 (dd, J = 9.5, 8.6 Hz, 1H, *H*-5), 4.43 (m, 1H, *H*-3); **^{13}C NMR** (101 MHz, C_6D_6) δ 13.6, 20.9, 37.9, 77.2, 101.4, 155.0; **IR** (ef) 2961, 2875, 1674, 1453, 1383, 1243, 1043, 1008, 886 cm^{-1}. **MS** (CI) *m/z* (rel. intensity) 99 (M + H, 100).

6.2.13 (±)-Xyloketal D [(±)-4], (±)-2,6-*epi*-Xyloketal D [(±)-26] and the Diastereoisomeric (±)-Spiroacetals [(±)-117] and [(±)-118][9]



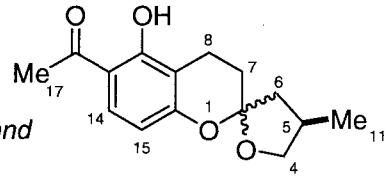
(±)-**4**

and



(±)-**26**

and



(±)-**117/118**

Method A: To a solution of the Mannich base **104** (177 mg, 0.704 mmol) in benzene (7 mL) at room temperature were added the dihydrofuran (±)-**61** (207 mg, 2.11 mmol) and methyl iodide (46 μL, 0.74 mmol). The resultant solution was heated at reflux until TLC analysis indicated that the Mannich base **104** had undergone complete

reaction (5 days). The reaction mixture was then cooled to room temperature, filtered with ether (7 mL) and concentrated *in vacuo*. Purification by flash chromatography using dichloromethane:ether (40:1) as the eluant afforded a mixture (11:1:3:3) of the *title compounds* (±)-**4**, (±)-**26**, (±)-**117** and (±)-**118** (99 mg, 54%) as a yellow oil. Further purification by flash chromatography using hexanes:ether (4:1) as the eluant on TLC grade silica gel afforded an inseparable mixture (dr = 11:1) of the *title compounds* (±)-**4** and (±)-**26** as a pale cream solid and an inseparable mixture (dr = 1:1) of the *title compounds* (±)-**117** and (±)-**118** as a pale cream solid.

Method B: To a solution of the Mannich base **106** (255 mg, 0.706 mmol) in benzene (7 mL) at room temperature were added the dihydrofuran (±)-**61** (207 mg, 2.11 mmol) and methyl iodide (46 μL, 0.74 mmol). The resultant solution was heated at reflux until TLC analysis indicated that the Mannich base **106** had undergone complete reaction (5 days). The reaction mixture was then cooled to room temperature, filtered with ether (7 mL) and concentrated *in vacuo*. Purification by flash chromatography using dichloromethane as the eluant afforded a mixture (11:1:3:3) of the *title compounds* (±)-**4**, (±)-**26**, (±)-**117** and (±)-**118** (86 mg, 47%) as a yellow oil. Further purification by flash chromatography using hexanes:ether (4:1) as the eluant on TLC grade silica gel afforded an inseparable mixture (dr = 11:1) of the *title compounds* (±)-**4** and (±)-**26** as a pale cream solid and an inseparable mixture (dr = 1:1) of the *title compounds* (±)-**117** and (±)-**118** as a pale cream solid.

Title compound (±)-**4**: Recrystallization of the *title compounds* (±)-**4** and (±)-**26** from petroleum ether, on slow evaporation of the solvent, afforded an analytically pure

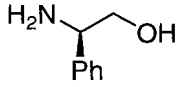
sample of (±)-xyloketal D [(±)-**4**]. $\mathbf{R}_f$ = 0.24, hexanes:ether (14:1); **M.p.** 66-67 °C, petroleum ether (lit.[9] 82 °C, ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.08 (d, J = 6.5 Hz, 3H, *Me*-11), 1.52 (s, 3H, *Me*-10), 1.98 (ddd, J = 11.3, 6.3, 1.2 Hz, 1H, *H*-6), 2.06 (m, 1H, *H*-5), 2.53 (s, 3H, *Me*-17), 2.71 (dd, J = 17.9, 6.2 Hz, 1H, *H*-7), 2.96 (d, J = 18.0 Hz, 1H, *H*-7), 3.56 (apparent t, J = 8.4 Hz, 1H, *H*-4), 4.20 (apparent t, J = 8.3 Hz, 1H, *H*-4), 6.36 (d, J = 8.9 Hz, 1H, *H*-15), 7.52 (d, J = 8.9 Hz, 1H, *H*-14), 13.10 (s, 1H, O*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 15.8, 18.0, 22.7, 26.1, 35.1, 47.0, 74.3, 106.1, 108.3, 108.8, 113.1, 130.0, 159.5, 162.9, 202.7; **IR** (ef) 3399, 2968, 2898, 1621, 1491, 1421, 1382, 1370, 1332, 1272, 1117, 1070, 1006 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 263 (M + H, 100) **Anal.** Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.88; H, 6.85.

Title compound (±)-**26**: **^{1}H NMR** [400 MHz, $CDCl_3$ (additional signals observed for the *title compound* (±)-**26**)] δ 0.80 (d, J = 7.1 Hz, 3H, *Me*-11), 3.68 (q, J = 5.0 Hz, 1H, *H*-4).

Title compounds (±)-**117** and (±)-**118** (dr = 1:1): Recrystallization of the *title compounds* (±)-**117** and (±)-**118** from petroleum ether, on slow evaporation of the solvent, afforded analytically pure colourless needles. $\mathbf{R}_f$ = 0.32, hexanes:ether (4:1); **M.p.** 57-59 °C, petroleum ether; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.10 (d, J = 6.6 Hz, 3H, *Me*-11), 1.18 (d, J = 6.6 Hz, 3H, *Me*-11), 1.55 (dd, J = 12.8, 9.5 Hz, 1H, *H*-6), 2.00 (m, 5H, 2 × *H*-5, *H*-6 *and* 2 × *H*-7), 2.28 (dd, J = 13.4, 9.5 Hz, 1H, *H*-6), 2.36 (dd, J = 12.9, 7.3 Hz, 1H, *H*-6), 2.46 (m, 1H, *H*-7), 2.54 (s, 3H, *Me*-17), 2.55 (s, 3H, *Me*-17), 2.78 (m, 5H, *H*-7 *and* 4 × *H*-8), 3.54 (t, J = 7.7 Hz, 1H, *H*-4), 3.64 (t, J = 8.4 Hz, 1H, *H*-4), 4.09 (t, J = 7.9 Hz, 1H, *H*-4), 4.21 (t, J = 7.9 Hz, 1H, *H*-4), 6.34 (d, J = 8.9 Hz, 1H, *H*-15), 6.37

(d, J = 9.0 Hz, 1H, *H*-15), 7.50 (d, J = 8.9 Hz, 1H, *H*-14), 7.51 (d, J = 8.9 Hz, 1H, *H*-14), 13.01 (s, 1H, O*H*), 13.02 (s, 1H, O*H*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 16.3, 16.5, 17.6, 18.0, 26.2, 29.3, 29.6, 31.9, 33.0, 45.2, 45.3, 75.0, 75.4, 108.1, 108.9, 109.0, 110.0, 110.1, 113.16, 113.24, 129.58, 129.62, 159.6, 162.2, 202.7, 202.8; **IR** (ef) 3423, 2958, 2878, 1626, 1488, 1419, 1369, 1331, 1270, 1247, 1136, 1060, 1018, 853 cm^{-1}; MS (CI) *m/z* (rel. intensity) 263 (M + H, 100), 111 (12); **Anal.** Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.47; H, 7.16.

6.2.14 (*R*)-Phenylglycinol [(±)-119][149,150]

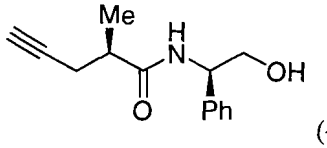


(*R*)-**119**

To a suspension of lithium aluminum hydride (11.0 g, 289 mmol) in tetrahydrofuran (500 mL) at 0 °C was added (*R*)-phenylglycine (20.0 g, 132 mmol) in portions over 1 h. The resultant mixture was heated at reflux for 8 h and then stirred for an additional 15 h at room temperature. A saturated aqueous solution of potassium carbonate (70 mL) was then added slowly over 3 h. The resultant mixture was filtered, the filter-cake was washed ethyl acetate (3 × 150 mL) and the combined filtrates were concentrated *in vacuo*. Purification by recrystallization from ethyl acetate:hexanes (3:1) afforded the *title compound* (±)-**119** (14.6 g, 80%) as yellow needles. **M.p.** 74-75 °C, ethyl acetate:hexanes (lit.[150] 75-78 °C); $[\alpha]_D^{20}$ = – 29.8 (*c* 6.37, methanol) [lit.[150] $[\alpha]_D^{20}$ = – 27.1 (*c* 5.36, methanol)]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.13 (s, 3H, O*H and* NH_2), 3.56 (dd, J = 10.8, 8.3 Hz, 1H, C*H*HOH), 3.74 (dd, J = 10.8, 4.4 Hz, 1H, CH*H*OH), 4.04 (dd, J = 8.3, 4.4 Hz, 1H, NC*H*), 7.30 (m, 5H, Ar*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ

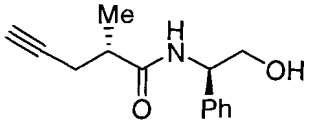
57.6, 68.3, 126.7, 127.8, 128.9, 143.0; **IR** (KBr) 3330, 3058, 2910, 1605, 1496, 1453, 1198, 1079, 1050 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 138 (M + H, 100).

6.2.15 (2*R*)-*N*-[(1*R*)-1-Phenyl-2-hydroxyethyl]-2-methyl-4-pentynamide [(–)-120] and (2*S*)-*N*-[(1*R*)-1-Phenyl-2-hydroxyethyl]-2-methyl-4-pentynamide [(–)-121][52,53]



(–)-**120**

and



(–)-**121**

To a solution of the racemic carboxylic acid (±)-**70** (5.40 g, 48.2 mmol) in dichloromethane (100 mL) at 0 °C were added oxalyl chloride (5.5 mL, 58 mmol) and *N*,*N*-dimethylformamide (2 drops). The resultant solution was allowed to warm to room temperature over 2 h and then was concentrated *in vacuo* to afford the corresponding acid chloride. A solution of this acid chloride in dichloromethane (50 mL) was then added to a stirred solution of (*R*)-phenylglycinol [(*R*)-**119**] (6.60 g, 48.2 mmol) and triethylamine (8.0 mL, 58 mmol) in dichloromethane (150 mL) at 0 °C. The resultant solution was allowed to warm to room temperature over 16 h and then water (50 mL) was added. The reaction mixture was extracted with ethyl acetate (3 × 50 mL) and the combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by flash chromatography using petroleum ether:ethyl acetate (1:2) as the eluant afforded the *title compounds* (–)-**120** (4.01 g, 36%) and (–)-**121** (3.82 g, 34%) as white solids.

Title compound (–)-**120**: $\mathbf{R}_f$ = 0.37, petroleum ether:ethyl acetate (1:2); **M.p.** 78-82 °C, petroleum ether:ethyl acetate; $[\alpha]_D^{24}$ = – 63 (*c* 1.31, chloroform); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.25 (d, *J* = 6.5 Hz, 3H, *Me*), 2.07 (t, *J* = 2.6 Hz, 1H, *H*CC), 2.30 (broad

s, 1H, O*H*), 2.38 (m, 1H, C*H*CO), 2.51 (m, 2H, CCH_2), 3.91 (d, J = 4.6 Hz, 2H, CH_2O), 5.10 (dt, J = 7.0, 4.8 Hz, 1H, PhC*H*), 6.32 (broad d, J = 4.9 Hz, 1H, N*H*), 7.34 (m, 5H, Ar*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 17.1, 23.1, 40.4, 55.6, 66.2, 70.2, 82.1, 126.6, 127.7, 128.7, 138.9, 175.0; **IR** (ef) 3314, 3286, 1650, 1544, 1052, 758, 702 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 232 (M + H, 100); **Anal.** Calcd. for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.86; H, 7.35; N, 5.87.

Title compound (–)-**121**: $\mathbf{R_f}$ = 0.27, petroleum ether:ethyl acetate (1:2); **M.p.** 90-93 °C, petroleum ether:ethyl acetate; $[\alpha]_D^{23}$ = – 33 (*c* 0.80, chloroform); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.29 (d, J = 6.7 Hz, 3H, *Me*), 2.01 (t, J = 2.7 Hz, 1H, *H*CC), 2.32 (broad s, 1H, O*H*), 2.39 (ddd, J = 15.8, 6.2, 2.8 Hz, 1H, CC*H*H), 2.51 (m, 2H, CCH*H* and C*H*CO), 3.90 (m, 2H, CH_2O), 5.08 (dt, J = 6.8, 4.8 Hz, 1H, PhC*H*), 6.37 (d, J = 4.3 Hz, 1H, N*H*), 7.32 (m, 5H, Ar*H*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 17.2, 23.2, 40.4, 55.8, 66.4, 70.4, 82.0, 126.7, 127.8, 128.8, 138.8, 175.1; **IR** (ef) 3282, 1645, 1545, 1038, 699 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 232 (M + H, 100); **Anal.** Calcd. for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.45; H, 7.54; N, 5.77.

6.2.16 X-Ray Crystallographic Analysis of (2*S*)-*N*-[(1*R*)-1-Phenyl-2-hydroxyethyl]-2-methyl-4-pentynamide [(–)-121]*

A single crystal of the amide (–)-**121**, a colourless needle, was mounted on a glass fibre using epoxy adhesive. The data for this crystal was acquired at 293 K on a *Rigaku RAXIS-RAPID* curve image plate area detector with graphite monochromatic Cu Kα radiation. Indexing for the crystal was performed using three, 5° oscillations that were

(*) The data for this X-ray crystal structure was obtained by Dr. K. Jantunen (Simon Fraser University). The X-ray crystal structure was solved by Mr. M. Katz (Simon Fraser University).

exposed for 425 seconds. The following data range was collected: $7.95° \leq 2\theta \leq 144.56°$ and a total of twenty seven images were collected. A sweep of data was then collected using ω scans from 50.0° to 230.0° in 20° steps at $\chi = 50.0°$ and $\phi = 0.0°$. A second sweep of data was collected using ω scans from 50.0° to 230.0° in 20° steps at $\chi = 50.0°$ and $\phi = 90.0°$. A final sweep of data was collected using ω scans from 50.0° to 230.0° in 20° steps at $\chi = 50.0°$ and $\phi = 180.0°$. The exposure rate was 90 sec/° and in each case, the crystal to detector distance was 127.40 mm. For the amide (–)-**121**, coordinates and anisotropic displacement parameters for the non-carbon and hydrogen atoms were refined; carbon atoms, not including the phenyl ring, were refined using isotropic thermal parameters. Hydrogen atoms were placed in calculated positions (C-H 0.95 Å) or detected and their coordinate shifts were linked with those of the respective carbon, nitrogen or oxygen atoms during refinement. Isotropic thermal parameters for the hydrogen atoms were initially assigned proportionately to the equivalent isotropic thermal parameters of their respective carbon, nitrogen or oxygen atoms. Subsequently, the isotropic thermal parameters for the C-H hydrogen atoms were constrained to have identical shifts during refinement. The programs used for all absorption corrections, data reduction, and processing of the amide (–)-**121** were from *Rigaku CrystalClear* package. The structure was refined using CRYSTALS.[151] An ORTEP representation of the amide (–)-**121** is provided below (Figure 6.2.16.1). Crystallographic data, fractional atomic coordinates and equivalent isotropic thermal displacement parameters, selected bond lengths as well as selected bond angles for the amide (–)-**121** are also listed below (Table 6.2.16.1, Table 6.2.16.2, Table 6.2.16.3 and Table 6.2.16.4, respectively).

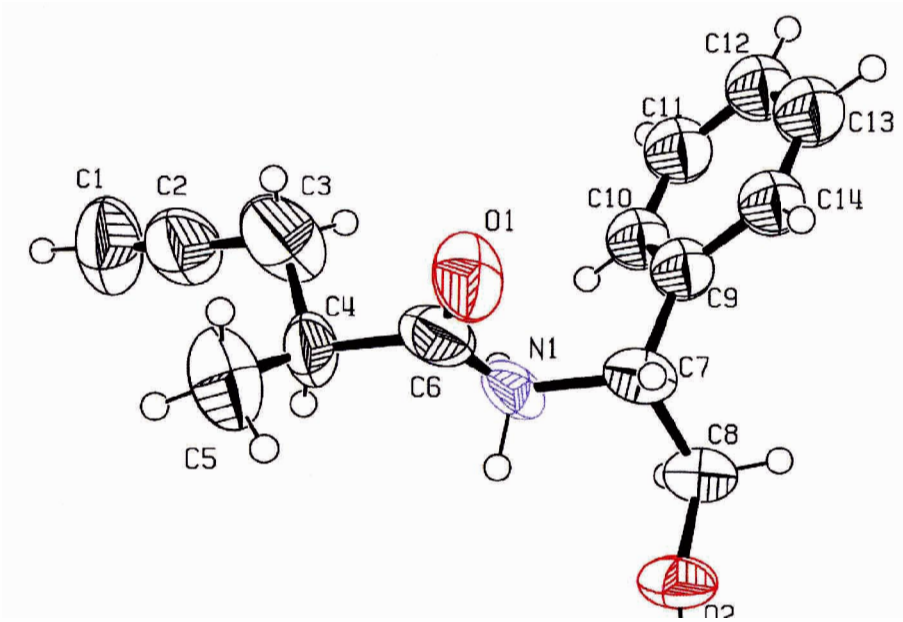


Figure 6.2.16.1 ORTEP representation of the amide [(–)-121] (the thermal ellipsoids are drawn at a 50% probability level).

Table 6.2.16.1 Summary of Crystallographic Data for the Amide [(–)-121]

Empirical Formula	$C_{14}H_{17}NO_2$
FW (g mol^{-1})	231.29
Temperature (K)	293
Wavelength (Cu *Kα*, Å)	1.5419
Crystal system	Orthorhombic
Space group	P*212121*
a (Å)	5.084
b (Å)	13.729
c (Å)	18.937
α (°)	90
β (°)	90
γ (°)	90

Z	4
U (Å^3)	1321.94226(4)
D_{calc} (g cm^{-3})	1.162
2θ limits (°)	11.35-83.95
Reflections collected	2334
Independent reflections	2334
Reflections observed [$I > 2.0\sigma(I)$]	805
Goodness-of-fit on F	1.0142
R_1, R_w [$I > 2.0\sigma(I)$]	0.0866, 0.1370

Table 6.2.16.2 Fractional Atomic Coordinates (Å) and Equivalent Isotropic Thermal Displacement Parameters [U(iso), (Å^2)] for the Amide [(–)-121]

Atom	X	Y	Z	U (iso)	Occupancy
O1	1.1607(16)	0.5001(7)	-0.1155(4)	0.0828	1
O2	0.5838(14)	0.7086(5)	-0.0130(4)	0.0668	1
N1	0.7319(17)	0.5297(6)	-0.0890(5)	0.0567	1
C1	0.586(4)	0.2885(11)	-0.3186(7)	0.117	1
C2	0.688(4)	0.3245(10)	-0.2721(8)	0.0975	1
C3	0.836(3)	0.3656(9)	-0.2109(7)	0.1114	1
C4	0.829(3)	0.4761(9)	-0.2076(5)	0.0734	1
C5	0.998(3)	0.5227(9)	-0.2627(6)	0.105	1
C6	0.931(3)	0.5037(10)	-0.1337(6)	0.0731	1
C7	0.791(2)	0.5486(7)	-0.0131(5)	0.0572	1
C8	0.576(2)	0.6143(7)	0.0186(6)	0.0589	1
C9	0.803(2)	0.4554(8)	0.0298(5)	0.059(3)	1
C10	0.618(2)	0.3799(8)	0.0181(5)	0.062(4)	1
C11	0.624(2)	0.2955(8)	0.0602(6)	0.076(4)	1
C12	0.813(2)	0.2861(8)	0.1114(6)	0.070(4)	1
C13	0.987(3)	0.3593(8)	0.1248(6)	0.074(4)	1
C14	0.985(2)	0.4429(8)	0.0842(5)	0.063(3)	1

Atom	X	Y	Z	U (iso)	Occupancy
H11	0.4808	0.258	-0.3629	0.174(11)	1
H21	0.448	0.7431	-0.0125	0.129(11)	1
H31	1.013	0.3439	-0.2123	0.224(11)	1
H32	0.7531	0.3416	-0.1694	0.224(11)	1
H41	0.6451	0.4913	-0.2159	0.118(11)	1
H51	1.0148	0.5942	-0.248	0.199(11)	1
H52	1.1597	0.4935	-0.2595	0.200(11)	1
H53	0.9127	0.52	-0.3058	0.199(11)	1
H71	0.9562	0.5807	-0.0147	0.073(11)	1
H81	0.6062	0.6192	0.0681	0.089(11)	1
H82	0.4141	0.5823	0.0064	0.089(11)	1
H101	0.4935	0.3868	-0.0151	0.065(11)	1
H111	0.5068	0.2462	0.0501	0.081(11)	1
H121	0.8231	0.2312	0.1415	0.071(11)	1
H131	1.1171	0.3559	0.1614	0.078(11)	1
H141	1.1105	0.4899	0.0896	0.065(11)	1
H12	0.6597	0.5866	-0.1073	0.069	0.5
H13	0.6066	0.4804	-0.09	0.069	0.5

Table 6.2.16.3 Bond Lengths (Å) for the Amide [(–)-121]

Atoms	Bond Length (Å)
O1-C6	1.217(13)
O2-C8	1.427(10)
O2-H21	0.838
N1-C6	1.369(12)
N1-C7	1.490(11)
N1-H12	0.93
N1-H13	0.93
C1-C2	1.135(16)
C1-H11	1.078

Atoms	Bond Length (Å)
C2-C3	1.493(18)
C3-C4	1.519(14)
C3-H31	0.95
C3-H32	0.95
C4-C5	1.494(14)
C4-C6	1.541(15)
C4-H41	0.972
C5-H51	1.024
C5-H52	0.915
C5-H53	0.926
C7-C8	1.539(13)
C7-C9	1.517(13)
C7-H71	0.949
C8-H81	0.953
C8-H82	0.96
C9-C10	1.417(13)
C9-C14	1.395(13)
C10-C11	1.408(13)
C10-H101	0.896
C11-C12	1.370(13)
C11-H111	0.923
C12-C13	1.364(14)
C12-H121	0.947
C13-C14	1.382(13)
C13-H131	0.958
C14-H141	0.914

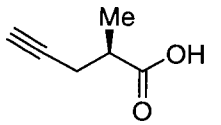
Table 6.2.16.4 Bond Angles (°) for the Amide [(–)-121]

Atoms	Bond Angles (°)
C8-O2-H21	119

Atoms	Bond Angles (°)
C6-N1-C7	119.5(9)
C6-N1-H12	106.3
C7-N1-H12	107
C6-N1-H13	107.7
C7-N1-H13	106.6
H12-N1-H13	109.5
C2-C1-H11	176.5
C1-C2-C3	175.7(20)
C2-C3-C4	113.5(11)
C2-C3-H31	109.8
C4-C3-H31	109.6
C2-C3-H32	106.7
C4-C3-H32	107.7
H31-C3-H32	109.5
C3-C4-C5	112.7(11)
C3-C4-C6	106.0(10)
C5-C4-C6	109.6(11)
C3-C4-H41	103.2
C5-C4-H41	110.5
C6-C4-H41	114.7
C4-C5-H51	105.6
C4-C5-H52	106.4
H51-C5-H52	109.2
C4-C5-H53	109.1
H51-C5-H53	108.4
H52-C5-H53	117.6
C4-C6-N1	112.2(11)
C4-C6-O1	124.8(12)
N1-C6-O1	123.0(12)
N1-C7-C8	109.5(9)

Atoms	Bond Angles (°)
N1-C7-C9	112.2(9)
C8-C7-C9	108.3(9)
N1-C7-H71	103.2
C8-C7-H71	111.7
C9-C7-H71	112
C7-C8-O2	110.4(8)
C7-C8-H81	108
O2-C8-H81	110.1
C7-C8-H82	104.3
O2-C8-H82	109.8
H81-C8-H82	114
C7-C9-C10	120.4(10)
C7-C9-C14	121.7(11)
C10-C9-C14	117.8(11)
C9-C10-C11	119.8(11)
C9-C10-H101	120
C11-C10-H101	120.1
C10-C11-C12	119.7(11)
C10-C11-H111	118.1
C12-C11-H111	122.1
C11-C12-C13	121.2(12)
C11-C12-H121	122.7
C13-C12-H121	116
C12-C13-C14	120.2(12)
C12-C13-H131	123.2
C14-C13-H131	116.6
C9-C14-C13	121.3(11)
C9-C14-H141	117.4
C13-C14-H141	121.2

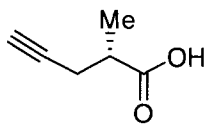
6.2.17 (2*R*)-2-Methylpent-4-ynoic Acid [(2*R*)-70][52,54]



(2*R*)-**70**

To a solution of the amide (–)-**120** (5.44 g, 23.5 mmol) in *p*-dioxane (60 mL) at room temperature was added sulfuric acid (3 M, 60 mL). The resultant solution was heated at reflux for 7 h and then was cooled to 0 °C. The reaction mixture was basified to pH ~10 with an aqueous solution of sodium hydroxide (50% w/w), diluted with water (50 mL) and extracted with dichloromethane (3 × 50 mL). The aqueous layer was acidified to pH ~2 with sulfuric acid (3 M) and then extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by distillation at reduced pressure afforded the *title compound* (2*R*)-**70** (2.01 g, 76%) as a colourless oil. $\mathbf{R}_f$ = 0.48, hexanes:ethyl acetate (1:2); **B.p.** 103-106 °C, 5 mm Hg; $[\alpha]_D^{20}$ = + 6.5 (*c* 1.50, chloroform); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.31 (d, J = 7.1 Hz, 3H, C*H*$_3$), 2.02 (t, J = 2.7 Hz, 1H, *H*CC), 2.40 (m, 1H, C*H*H), 2.57 (m, 1H, CH*H*), 2.71 (m, 1H, C*H*CO$_2$H), 10.73 (m, 1H, O*H*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 16.1, 22.3, 38.6, 70.1, 81.1, 181.3; **IR** (ef) 3293, 2978, 2668, 1701, 1420, 1295, 1240, 1200, 940, 659 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 113 (M + H, 100).

6.2.18 (2*S*)-2-Methylpent-4-ynoic Acid [(2*S*)-70][52,54]

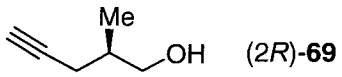


(2*S*)-**70**

To a solution of the amide (–)-**121** (4.56 g, 19.7 mmol) in *p*-dioxane (50 mL) at room temperature was added sulfuric acid (3 M, 50 mL). The resultant solution was heated at reflux for 7 h and then was cooled to 0 °C. The reaction mixture was basified to

pH ~10 with an aqueous solution of sodium hydroxide (50% w/w), diluted with water (50 mL) and extracted with dichloromethane (3 × 50 mL). The aqueous layer was acidified to pH ~2 with sulfuric acid (3 M) and then extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by distillation at reduced pressure afforded the *title compound* (2*S*)-**70** (1.91 g, 86%) as a colourless oil. $\mathbf{R}_f$ = 0.48, hexanes:ethyl acetate (1:2); **B.p.** 103-106 °C, 5 mm Hg; $[\alpha]_D^{20}$ = – 6.5 (*c* 1.50, chloroform); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.31 (d, J = 7.1 Hz, 3H, CH_3), 2.02 (t, J = 2.7 Hz, 1H, *H*CC), 2.40 (m, 1H, C*H*H), 2.57 (m, 1H, CH*H*), 2.71 (m, 1H, C*H*CO_2H), 10.73 (m, 1H, O*H*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 16.1, 22.3, 38.6, 70.1, 81.1, 181.3; **IR** (ef) 3293, 2978, 2668, 1701, 1420, 1295, 1240, 1200, 940, 659 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 113 (M + H, 100).

6.2.19 (2*R*)-2-Methylpent-4-yn-1-ol [(2*R*)-69][55,56]

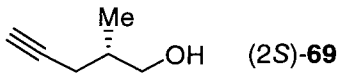


(2*R*)-**69**

To a suspension of lithium aluminum hydride (0.79 g, 20.8 mmol) in tetrahydrofuran (35 mL) at 0 °C was added a solution of the carboxylic acid (2*R*)-**70** (1.17 g, 10.4 mmol) in tetrahydrofuran (10 mL) and the resultant suspension was stirred at room temperature for 16 h. Water (0.8 mL), an aqueous solution of sodium hydroxide (2 M, 0.8 mL) and water (2.4 mL) were then added in succession and the resultant mixture was filtered. The filter-cake was washed with ether (100 mL) and the combined organic filtrates were concentrated *in vacuo*. Purification by distillation at reduced pressure afforded the *title compound* (2*R*)-**69** (0.91 g, 89%) as a colourless oil. $\mathbf{R}_f$ = 0.55, hexanes:ethyl acetate (1:2); **B.p.** 61-66 °C, ~20 mm Hg; $[\alpha]_D^{20}$ = + 10.9 (*c* 1.10,

chloroform); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.01 (d, J = 6.9 Hz, 3H, CH_3), 1.56 (broad s, 1H, O*H*), 1.90 (m, 1H, $CHCH_3$), 1.98 (t, J = 2.7 Hz, 1H, *H*CC), 2.21 (ddd, J = 16.8, 6.4, 2.7 Hz, 1H, CC*H*H), 2.29 (ddd, J = 16.8, 6.2, 2.7 Hz, 1H, CCH*H*), 3.59 (d, J = 6.1 Hz, 2H, CH_2O); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 16.0, 22.2, 34.8, 66.8, 69.6, 82.6; **IR** (ef) 3409, 2961, 2922, 2117, 1461, 1430, 1037, 651 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 99 (M + H, 100).

6.2.20 (2*S*)-2-Methylpent-4-yn-1-ol [(2*S*)-69][55,56]

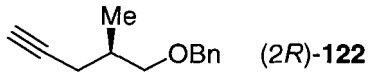


(2*S*)-**69**

To a suspension of lithium aluminum hydride (1.07 g, 28.0 mmol) in tetrahydrofuran (35 mL) at 0 °C was added a solution of the carboxylic acid (2*S*)-**70** (1.57 g, 14.0 mmol) in tetrahydrofuran (10 mL) and the resultant suspension was stirred at room temperature for 16 h. Water (1.1 mL), an aqueous solution of sodium hydroxide (2 M, 1.1 mL) and water (3.3 mL) were then added in succession and the resultant mixture was filtered. The filter-cake was washed with ether (100 mL) and the combined organic filtrates were concentrated *in vacuo*. Purification by distillation at reduced pressure afforded the *title compound* (2*S*)-**69** (1.17 g, 85%) as a colourless oil. $\mathbf{R}_f$ = 0.55, hexanes:ethyl acetate (1:2); **B.p.** 61-66 °C, ~20 mm Hg; $[\alpha]_D^{20}$ = – 11.1 (*c* 1.10, chloroform); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.01 (d, J = 6.9 Hz, 3H, CH_3), 1.56 (broad s, 1H, O*H*), 1.90 (m, 1H, $CHCH_3$), 1.98 (t, J = 2.7 Hz, 1H, *H*CC), 2.21 (ddd, J = 16.8, 6.4, 2.7 Hz, 1H, CC*H*H), 2.29 (ddd, J = 16.8, 6.2, 2.7 Hz, 1H, CCH*H*), 3.59 (d, J = 6.1 Hz, 2H, CH_2O); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 16.0, 22.2, 34.8, 66.8, 69.6, 82.6; **IR**

(ef) 3409, 2961, 2922, 2117, 1461, 1430, 1037, 651 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 99 (M + H, 100).

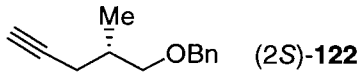
6.2.21 (2*R*)-Benzyl-(2-methylpent-4-ynyl)ether [(2*R*)-122][57,58]



(2*R*)-**122**

To a suspension of sodium hydride (81 mg, 60% w/w in mineral oil, 2.0 mmol, pre-washed with hexanes) in *N*,*N*-dimethylformamide (4.0 mL) at 0 °C were added a solution of the alcohol (2*R*)-**69** (181 mg, 1.84 mmol) in tetrahydrofuran (1 mL) and benzyl bromide (230 μL, 1.93 mmol). The resultant mixture was stirred at room temperature for 6 h. The reaction mixture was diluted then with ether (10 mL) and washed with water (3 × 10 mL) and brine (10 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (50:1) as the eluant afforded the *title compound* (2*R*)-**122** (313 mg, 90%) as a colourless oil. $\mathbf{R}_f$ = 0.77, hexanes:ether (4:1); $[\alpha]_D^{20}$ = + 16.1 (*c* 1.40, chloroform) [lit.[57] $[\alpha]_D^{20}$ = + 16 (*c* 1.20, chloroform); lit.[58] $[\alpha]_D^{20}$ = + 16.3 (*c* 0.95, chloroform)]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.03 (d, *J* = 6.8 Hz, 3H, *Me*), 1.95 (t, *J* = 2.6 Hz, 1H, *H*CC), 2.02 (m, 1H, C*H*CH_3), 2.21 (ddd, *J* = 16.7, 6.9, 2.6 Hz, 1H, CC*H*H), 2.35 (ddd, *J* = 16.7, 5.5, 2.7 Hz, 1H, CCH*H*), 3.39 (d, *J* = 6.5 Hz, 2H, CH_2O), 4.52 (s, 2H, OCH_2Ph), 7.33 (m, 5H, Ar*H*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 16.4, 22.5, 32.9, 69.3, 73.0, 74.1, 82.7, 127.5, 127.5, 128.3, 138.5; **IR** (ef) 3289, 3031, 2857, 2117, 1496, 1454, 1112, 749 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 189 (M + H, 78), 171 (17), 111 (M – Ph, 100).

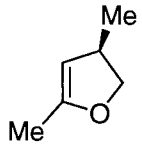
6.2.22 (2*S*)-Benzyl-(2-methylpent-4-ynyl)ether [(2*S*)-122]



(2*S*)-**122**

To a suspension of sodium hydride (144 mg, 60% w/w in mineral oil, 1.47 mmol, pre-washed with hexanes) in *N*,*N*-dimethylformamide (4.0 mL) at 0 °C were added a solution of the alcohol (2*S*)-**69** (144 mg, 1.47 mmol) in tetrahydrofuran (1 mL) and benzyl bromide (184 μL, 1.54 mmol). The resultant mixture was stirred at room temperature for 6 h. The reaction mixture was diluted then with ether (10 mL) and washed with water (3 × 10 mL) and brine (10 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (50:1) as the eluant afforded the *title compound* (2*S*)-**122** (248 mg, 90%) as a colourless oil. $\mathbf{R}_f$ = 0.77, hexanes:ether (4:1); $[\alpha]_D^{20}$ = – 15.9 (*c* 1.05, chloroform); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.03 (d, *J* = 6.8 Hz, 3H, *Me*), 1.95 (t, *J* = 2.6 Hz, 1H, *H*CC), 2.02 (m, 1H, C*H*CH_3), 2.21 (ddd, *J* = 16.7, 6.9, 2.6 Hz, 1H, CC*H*H), 2.35 (ddd, *J* = 16.7, 5.5, 2.7 Hz, 1H, CCH*H*), 3.39 (d, *J* = 6.5 Hz, 2H, CH_2O), 4.52 (s, 2H, OCH_2Ph), 7.33 (m, 5H, Ar*H*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 16.4, 22.5, 32.9, 69.3, 73.0, 74.1, 82.7, 127.5, 127.5, 128.3, 138.5; **IR** (ef) 3289, 3031, 2857, 2117, 1496, 1454, 1112, 749 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 189 (M + H, 78), 171 (17), 111 (M – Ph, 100).

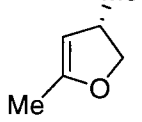
6.2.23 (4*R*)-2,4-Dimethyl-4,5-dihydrofuran [(4*R*)-61][22,23]



(4*R*)-**61**

The alcohol (2*R*)-**69** (0.91 g, 9.3 mmol) and sodium amide (50 mg, 1.3 mmol) were heated at reflux for 2 h. Direct distillation of the reaction mixture at atmospheric pressure afforded the exocyclic dihydrofuran (4*R*)-**68** as a colourless oil. This material was heated at reflux for 2 h and then distilled at atmospheric pressure to afford the *title compound* (4*R*)-**69** (0.40 g, 44%) as a colourless oil. **B.p.** 97-103 °C, ~760 mm Hg; $[\alpha]_D^{24}$ = – 118 (*c* 0.82, chloroform); **^{1}H NMR** (400 MHz, C_6D_6) δ 0.84 (d, *J* = 6.6 Hz, 3H, *Me*-4), 1.68 (apparent t, *J* = 1.5 Hz, 3H, *Me*-2), 2.76 (m, 1H, *H*-4), 3.71 (dd, *J* = 8.7, 6.5 Hz, 1H, *H*-5), 4.21 (dd, *J* = 9.5, 8.6 Hz, 1H, *H*-5), 4.43 (m, 1H, *H*-3); **^{13}C NMR** (101 MHz, C_6D_6) δ 13.6, 20.9, 37.9, 77.2, 101.4, 155.0; **IR** (ef) 2961, 2875, 1674, 1453, 1383, 1243, 1043, 1008, 886 cm^{-1}. **MS** (CI) *m/z* (rel. intensity) 99 (M + H, 100).

6.2.24 (4*S*)-2,4-Dimethyl-4,5-dihydrofuran [(4*S*)-61][22,23]

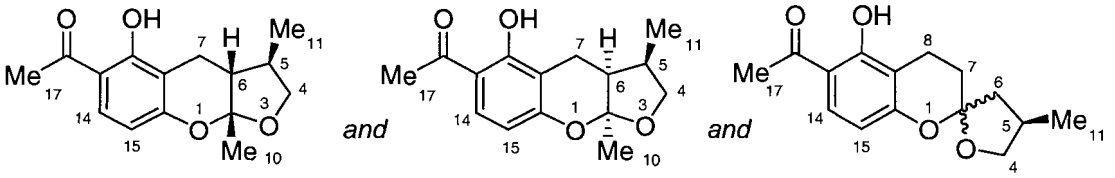


(4*S*)-**61**

The alcohol (2*S*)-**69** (1.17 g, 11.9 mmol) and sodium amide (60 mg, 1.5 mmol) were heated at reflux for 2 h. Direct distillation of the reaction mixture at atmospheric pressure afforded the exocyclic dihydrofuran (4*S*)-**68** as a colourless oil. This material was heated at reflux for 2 h and then distilled at atmospheric pressure to afford the *title compound* (4*S*)-**61** (0.42 g, 36%) as a colourless oil. **B.p.** 97-103 °C, ~760 mm Hg; $[\alpha]_D^{24}$ = + 120 (*c* 0.44, chloroform); **^{1}H NMR** (400 MHz, C_6D_6) δ 0.84 (d, *J* = 6.6 Hz,

3H, *Me*-4), 1.68 (apparent t, J = 1.5 Hz, 3H, *Me*-2), 2.76 (m, 1H, *H*-4), 3.71 (dd, J = 8.7, 6.5 Hz, 1H, *H*-5), 4.21 (dd, J = 9.5, 8.6 Hz, 1H, *H*-5), 4.43 (m, 1H, *H*-3); **^{13}C NMR** (101 MHz, C_6D_6) δ 13.6, 20.9, 37.9, 77.2, 101.4, 155.0; **IR** (ef) 2961, 2875, 1674, 1453, 1383, 1243, 1043, 1008, 886 cm^{-1}. **MS** (CI) *m/z* (rel. intensity) 99 (M + H, 100).

6.2.25 (–)-Xyloketal D [(–)-4], 2,6-*epi*-Xyloketal D (26) and the Diastereoisomeric Spiroacetals (117) and (118)[1,9,10]



(–)-**4** **26** **117/118**

Method A: To a solution of the dihydrofuran (4*R*)-**61** (295 mg, 3.01 mmol) in benzene (10 mL) at room temperature were added the Mannich base **104** (251 mg, 1.00 mmol) and methyl iodide (65.0 μL, 1.05 mmol). The resultant solution was then heated at reflux until TLC analysis indicated that the Mannich base **104** had undergone complete reaction (8 days). The reaction mixture was then cooled to room temperature, filtered with ether (10 mL) and concentrated *in vacuo*. Purification by flash chromatography using dichloromethane as the eluant afforded a mixture (8:1:2:2) of the *title compounds* (–)-**4**, **26**, **117** and **118** (105 mg, 40%) as a yellow solid. Repetitive flash chromatography using hexanes:ether (4:1) as the eluant on TLC grade silica gel afforded a mixture (dr = 20:1) of the *title compounds* (–)-**4** and **26** as a pale cream solid and a separate mixture (dr = 4:5) of the *title compounds* **117** and **118** as a pale cream solid.

Method B: To a solution of the dihydrofuran (4*R*)-**61** (121 mg, 1.23 mmol) in benzene (5 mL) at room temperature were added the Mannich base **104** (103 mg, 0.41 mmol) and dimethyl sulfate (41 μL, 0.43 mmol). The resultant solution was heated at

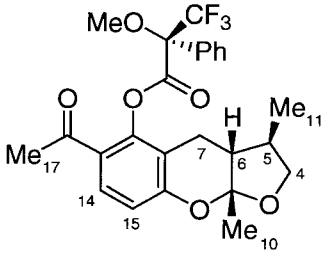
reflux until TLC analysis indicated that the Mannich base **104** had undergone complete reaction (3 days). The reaction mixture was then cooled to room temperature and decanted. The remaining solid residue was extracted with dichloromethane (3 × 5 mL) and the combined organic extracts were concentrated *in vacuo*. Purification by flash chromatography using dichloromethane:ether (19:1) as the eluant afforded a mixture (16:1:4:4) of the *title compounds* (–)-**4**, **26**, **117** and **118** (40 mg, 37%) as a yellow solid.

Title compound (–)-**4**: An analytically pure sample of the *title compound* (–)-**4**, as pale pink prisms, was prepared by recrystallization from petroleum ether. $\mathbf{R}_f$ = 0.24, hexanes:ether (4:1); **M.p.** 71-73 °C, petroleum ether *and* 68-71 °C, ether:pentane (lit.[1] 111-113 °C; lit.[9] 110-111 °C, ether:pentane; lit.[10] 110-111 °C); $[\alpha]_D^{20}$ = – 110 (*c* 0.102, chloroform) [lit.[1] $[\alpha]_D^{25}$ = – 119.5 (*c* 0.113, chloroform); lit.[9] $[\alpha]_D^{25}$ = – 118 (*c* 0.10, chloroform); lit.[10] $[\alpha]_D^{25}$ = – 118 (*c* 0.10, chloroform)]; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.07 (d, *J* = 6.5 Hz, 3H, *Me*-11), 1.53 (s, 3H, *Me*-10), 1.98 (ddd, *J* = 11.3, 6.5, 1.1 Hz, 1H, *H*-6), 2.08 (m, 1H, *H*-5), 2.55 (s, 3H, *Me*-17), 2.72 (dd, *J* = 17.9, 6.5 Hz, 1H, *H*-7), 2.97 (d, *J* = 18.0, 1H, *H*-7), 3.57 (apparent t, *J* = 8.4 Hz, 1H, *H*-4), 4.20 (apparent t, *J* = 8.3 Hz, 1H, *H*-4), 6.36 (d, *J* = 8.9 Hz, 1H, *H*-15), 7.52 (d, *J* = 8.9 Hz, 1H, *H*-14), 13.12 (s, 1H, O*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 15.8, 18.0, 22.7, 26.1, 35.1, 47.0, 74.3, 106.2, 108.3, 108.8, 113.2, 130.0, 159.5, 162.9, 202.6; **IR** (ef) 3399, 2967, 2927, 2884, 1620, 1491, 1421, 1382, 1370, 1332, 1272, 1117, 1070, 1006 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 263 (M + H, 100); **Anal.** Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.52; H, 6.98.

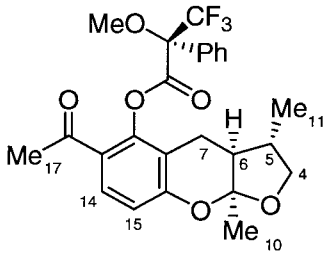
Title compound **26**: **^{1}H NMR** [400 MHz, $CDCl_3$ (additional signals observed for the *title compound* **26**] δ 0.80 (d, J = 7.1 Hz, 3H, *Me*-11), 3.68 (q, J = 5.0 Hz, 1H, *H*-4).

Title compounds **117** and **118** (dr = 4:5): An analytically pure sample of a mixture (dr = 4:5) of the *title compounds* **117** and **118**, as colourless needles, was also prepared by recrystallization from petroleum ether. $\mathbf{R}_f$ = 0.32, hexanes:ether (4:1); **M.p.** 60-61 °C, petroleum ether; $[\alpha]_D^{20}$ = + 26.9 (*c* 0.71, chloroform); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.10 (d, J = 6.6 Hz, 3H, *Me*-11), 1.18 (d, J = 6.6 Hz, 3H, *Me*-11), 1.55 (dd, J = 12.8, 9.5 Hz, 1H, *H*-6), 2.00 (m, 5H, 2 × *H*-5, *H*-6 *and* 2 × *H*-7), 2.28 (dd, J = 13.4, 9.5 Hz, 1H, *H*-6), 2.36 (dd, J = 12.9, 7.3 Hz, 1H, *H*-6), 2.46 (m, 1H, *H*-7), 2.54 (s, 3H, *Me*-17), 2.55 (s, 3H, *Me*-17), 2.78 (m, 5H, *H*-7 *and* 4 × *H*-8), 3.54 (t, J = 7.7 Hz, 1H, *H*-4), 3.64 (t, J = 8.4 Hz, 1H, *H*-4), 4.09 (t, J = 7.9 Hz, 1H, *H*-4), 4.21 (t, J = 7.9 Hz, 1H, *H*-4), 6.34 (d, J = 8.9 Hz, 1H, *H*-15), 6.37 (d, J = 9.0 Hz, 1H, *H*-15), 7.50 (d, J = 8.9 Hz, 1H, *H*-14), 7.51 (d, J = 8.9 Hz, 1H, *H*-14), 13.01 (s, 1H, O*H*), 13.02 (s, 1H, O*H*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 16.3, 16.5, 17.6, 18.0, 26.2, 29.3, 29.6, 31.9, 33.0, 45.2, 45.3, 75.0, 75.4, 108.1, 108.9, 109.0, 110.0, 110.1, 113.16, 113.24, 129.58, 129.62, 159.6, 162.2, 202.7, 202.8; **IR** (ef) 3423, 2958, 2878, 1626, 1488, 1419, 1369, 1331, 1270, 1247, 1136, 1060, 1018, 853 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 263 (M + H, 100), 111 (12); **Anal.** Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.58; H, 6.99.

6.2.26 Xyloketal D-(*R*)-α-methoxy-α-trifluoromethyl-phenylacetate [(–)-124] and *ent*-Xyloketal D-(*R*)-α-methoxy-α-trifluoromethyl-phenylacetate (125)[59]



(–)-**124** *and*

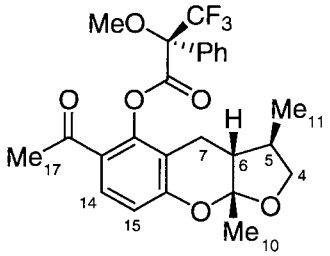


125

To a solution of (±)-xyloketal D [(±)-**4**], that contained a trace amount of the 2,6-epimer (±)-**26**, (24 mg, 0.093 mmol) in tetrahydrofuran (2 mL) were added *N,N*-dimethyl-4-aminopyridine (13 mg, 0.11 mmol) and a freshly prepared sample of (*S*)-α-methoxy-α-trifluoromethyl-phenylacetyl chloride (34 μL, 0.18 mmol). The resultant mixture was heated at reflux for 3 h and then allowed to cool to room temperature. The reaction mixture was then diluted with ether (25 mL) and was washed with hydrochloric acid (1 M, 7 mL), a saturated aqueous solution of sodium bicarbonate (7 mL) and water (7 mL). The organic layer was then dried over anhydrous sodium sulfate and concentrated *in vacuo*. Filtration of the resultant residue through a pad of silica gel using hexanes:ether (2:1) as the eluant afforded a mixture (dr = 1:1) of the *title compounds* (–)-**124** and **125** (36 mg, 82%) as a solid pale yellow foam. $\mathbf{R}_f$ = 0.16, hexanes:ether (2:1); **M.p.** 37-41 °C, hexanes:ether; $[\alpha]_D^{20}$ = + 13.8 (*c* 1.76, chloroform); **^{1}H NMR** (600 MHz, $CDCl_3$) δ0.95 (d, *J* = 6.4 Hz, 3H, *Me*-11), 0.97 (d, *J* = 6.6 Hz, 3H, *Me*-11), 1.51 (s, 3H, *Me*-10), 1.53 (s, 3H, *Me*-10), 1.85 (m, 2H, 2 × *H*-6), 1.99 (m, 2H, 2 × *H*-5), 2.46 (s, 3H, *Me*-17), 2.48 (s, 3H, *Me*-17), 2.54 (m, 4H, 4 × *H*-7), 3.50 (m, 2H, 2 × *H*-4), 3.72 (s, 3H, O*Me*), 3.73 (s, 3H, O*Me*), 4.14 (apparent t, *J* = 8.4 Hz, 2H, *H*-4), 4.16 (apparent t, *J* = 8.5 Hz, 1H, *H*-4), 6.81 (d, *J* = 8.5 Hz, 2H, 2 × *H*-15), 7.46 (m, 6H, ArH), 7.64 (d, *J* = 8.6

Hz, 2H, 2 × *H*-14), 7.79 (m, 4H, ArH); **^{13}C NMR** (126 MHz, $CDCl_3$, observed signals) δ 15.5, 15.7, 18.6, 18.7, 22.8, 23.1, 28.50, 28.52, 35.0, 35.1, 46.8, 47.0, 55.70, 55.73, 74.2, 108.3, 108.4, 113.3, 113.6, 114.88, 114.90, 122.0, 122.1, 123.2, 123.3, 124.3, 124.4, 128.2, 128.3, 128.4, 128.5, 129.79, 129.81, 129.83, 129.85, 131.0, 131.1, 147.6, 147.7, 157.68, 157.72, 164.4, 164.5, 196.09, 196.13; **^{19}F NMR** (470 MHz, $CDCl_3$) δ 3.85 (s), 3.91 (s); **IR** (ef) 2948, 1764, 1686, 1485, 1264, 1171, 1116, 1052, 1004 cm^{-1}; **MS** (MALDI-TOF) *m/z* (rel. intensity) 517 (M + K, 22), 501 (M + Na, 82), 479 (M + H, 100) *and* (CI) *m/z* (rel. intensity) 479 (M + H, 13), 263 (68), 189 (20), 163 (100); **Anal.** Calcd. for $C_{25}H_{25}F_3O_6$: C, 62.76; H, 5.27; Found: C, 62.82; H, 5.37.

6.2.27 Xyloketal D (*R*)-α-methoxy-α-trifluoromethyl-phenylacetate [(–)-124][59]

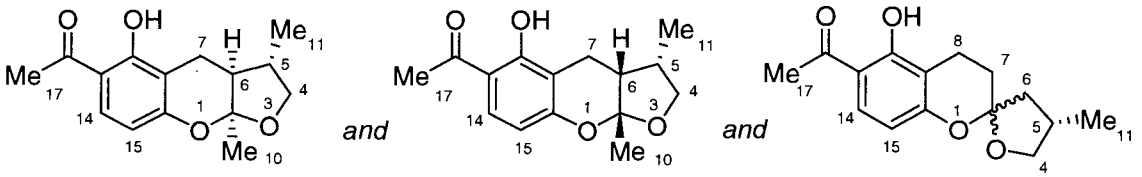


(–)-**124**

To a solution of synthetic (–)-xyloketal D [(–)-**4**] (15 mg, 0.058 mmol) in tetrahydrofuran (1.8 mL) were added *N,N*-dimethyl-4-aminopyridine (10 mg, 0.082 mmol) and a freshly prepared sample of (*S*)-α-methoxy-α-trifluoromethyl-phenylacetyl chloride (22 μL, 0.12 mmol). The resultant mixture was heated at reflux for 2.5 h and then allowed to cool to room temperature. The reaction mixture was then diluted with ether (25 mL) and was washed with hydrochloric acid (1 M, 7 mL), a saturated aqueous solution of sodium bicarbonate (7 mL) and water (7 mL). The organic layer was then dried over anhydrous sodium sulfate and concentrated *in vacuo*. Filtration of the resultant residue through a pad of silica gel using hexanes:ether (2:1) as the eluant

afforded the *title compound* (–)-**124** (23 mg, 84%) as a solid white foam. $\mathbf{R}_f$ = 0.16, hexanes:ether (2:1); **M.p.** 92-93 °C, on evaporation from chloroform; $[\alpha]_D^{20}$ = – 36.6 (*c* 1.10, chloroform); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 0.95 (d, *J* = 6.5 Hz, 3H, *Me*-11), 1.53 (s, 3H, *Me*-10), 1.85 (m, 1H, *H*-6), 1.99 (m, 1H, *H*-5), 2.46 (s, 3H, *H*-17), 2.54 (m, 2H, *H*-7), 3.50 (apparent t, *J* = 8.5 Hz, 1H, *H*-4), 3.72 (s, 3H, O*Me*), 4.14 (apparent t, *J* = 8.5 Hz, 1H, *H*-4), 6.81 (d, *J* = 8.5 Hz, 1H, *H*-15), 7.47 (m, 3H, Ar*H*), 7.64 (d, *J* = 8.5 Hz, 1H, *H*-14), 7.80 (m, 2H, Ar*H*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 15.5, 18.6, 23.1, 28.6, 35.0, 47.0, 55.7 (apparent d, *J* = 1.1 Hz), 74.2, 84.8 (q, *J* = 28 Hz), 108.4, 113.5, 114.91, 122.2, 123.2 (q, *J* = 289 Hz), 128.2 (apparent d, *J* = 1.1 Hz), 128.4, 129.8, 129.9, 130.9, 147.7, 157.7, 164.5, 196.1; **^{19}F NMR** (470 MHz, $CDCl_3$) δ 3.85 (s); **IR** (ef) 2948, 1764, 1686, 1485, 1264, 1171, 1116, 1052, 1004 cm^{-1}; **MS** (MALDI-TOF) m/z (rel. intensity) 517 (M + K, 65), 501 (M + Na, 100), 479 (M + H, 85); **Anal.** Calcd. for $C_{25}H_{25}F_3O_6$: C, 62.76; H, 5.27; Found: C, 62.84; H, 5.37.

6.2.28 (+)-Xyloketal D [(+)-4], 2,6-*epi*-ent-Xyloketal D [(*ent*)-26] and the Diastereoisomeric Spiroacetals [(*ent*)-117] and [(*ent*)-118]



(+)-**4** (*ent*)-**26** (*ent*)-**117/118**

Method A: To a solution of the dihydrofuran (4*S*)-**61** (237 mg, 2.42 mmol) in benzene (8 mL) at room temperature were added the Mannich base **104** (202 mg, 0.804 mmol) and methyl iodide (52 μL, 0.84 mmol). The resultant solution was then heated at reflux until TLC analysis indicated that the Mannich base **104** had undergone complete reaction (6 days). The reaction mixture was then cooled to room temperature, filtered

with ether (8 mL) and concentrated *in vacuo*. Purification by flash chromatography using dichloromethane as the eluant afforded a mixture (13:1:3:3) of the *title compounds* (+)-**4**, (*ent*)-**26**, (*ent*)-**117** and (*ent*)-**118** (96 mg, 46%) as a yellow solid. Repetitive flash chromatography using hexanes:ether (4:1) as the eluant on TLC grade silica gel afforded a mixture (dr = 14:1) of the *title compounds* (+)-**4** and (*ent*)-**26** as a pale cream solid and a separate mixture (dr = 4:5) of the *title compounds* (*ent*)-**117** and (*ent*)-**118** as a pale cream solid.

Method B: To a solution of the dihydrofuran (4*S*)-**61** (198 mg, 2.02 mmol) in benzene (8 mL) at room temperature were added the Mannich base **104** (170 mg, 0.67 mmol) and dimethyl sulfate (67 μL, 0.70 mmol). The resultant solution was heated at reflux until TLC analysis indicated that the Mannich base **104** had undergone complete reaction (3 days). The reaction mixture was then cooled to room temperature and decanted. The remaining solid residue was extracted with dichloromethane (3 × 5 mL) and the combined organic extracts were concentrated *in vacuo*. Purification by flash chromatography using dichloromethane:ether (19:1) as the eluant afforded a mixture (20:1:3:3) of the *title compounds* (+)-**4**, (*ent*)-**26**, (*ent*)-**117** and (*ent*)-**118** (64 mg, 36%) as a yellow solid.

Title compound (+)-**4**: An analytically pure sample of the *title compound* (+)-**4**, as pale pink prisms, was prepared by recrystallization from petroleum ether. $\mathbf{R}_f$ = 0.24, hexanes:ether (4:1); **M.p.** 70-71 °C, petroleum ether; $[\alpha]_D^{20}$ = + 113 (*c* 0.122, chloroform); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.07 (d, *J* = 6.5 Hz, 3H, *Me*-11), 1.53 (s, 3H, *Me*-10), 1.98 (ddd, *J* = 11.3, 6.5, 1.1 Hz, 1H, *H*-6), 2.08 (m, 1H, *H*-5), 2.55 (s, 3H, *Me*-17), 2.72 (dd, *J* = 17.9, 6.5 Hz, 1H, *H*-7), 2.97 (d, *J* = 18.0, 1H, *H*-7), 3.57 (apparent

t, J = 8.4 Hz, 1H, *H*-4), 4.20 (apparent t, J = 8.3 Hz, 1H, *H*-4), 6.36 (d, J = 8.9 Hz, 1H, *H*-15), 7.52 (d, J = 8.9 Hz, 1H, *H*-14), 13.12 (s, 1H, O*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 15.87, 18.0, 22.7, 26.1, 35.1, 47.0, 74.3, 106.2, 108.3, 108.8, 113.2, 130.0, 159.5, 162.9, 202.6; **IR** (ef) 3399, 2967, 2927, 2884, 1620, 1491, 1421, 1382, 1370, 1332, 1272, 1117, 1070, 1006 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 263 (M + H, 100)); **Anal.** Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.72; H, 6.79.

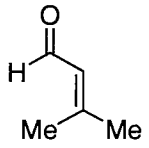
Title compound (*ent*)-**26**: **^{1}H NMR** [400 MHz, $CDCl_3$ (additional signals observed for the *title compound* (*ent*)-**26**)] δ 0.80 (d, J = 7.1 Hz, 3H, *Me*-11), 3.68 (q, J = 5.0 Hz, 1H, *H*-4).

Title compounds (*ent*)-**117** and (*ent*)-**118** (dr = 4:5): An analytically pure sample of a mixture (dr = 4:5) of the *title compounds* (*ent*)-**117** and (*ent*)-**118**, as colourless needles, was also prepared by recrystallization from petroleum ether. $\mathbf{R}_f$ = 0.32, hexanes:ether (4:1); **M.p.** 59-61 °C, petroleum ether; $[\alpha]_D^{20}$ = – 26.7 (*c* 1.05, chloroform); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.10 (d, J = 6.6 Hz, 3H, *Me*-11), 1.18 (d, J = 6.6 Hz, 3H, *Me*-11), 1.55 (dd, J = 12.8, 9.5 Hz, 1H, *H*-6), 2.00 (m, 5H, 2 × *H*-5, *H*-6, *and* 2 × *H*-7), 2.28 (dd, J = 13.4, 9.5 Hz, 1H, *H*-6), 2.36 (dd, J = 12.9, 7.3 Hz, 1H, *H*-6), 2.46 (m, 1H, *H*-7), 2.54 (s, 3H, *Me*-17), 2.55 (s, 3H, *Me*-17), 2.78 (m, 5H, *H*-7 *and* 4 × *H*-8), 3.54 (t, J = 7.7 Hz, 1H, *H*-4), 3.64 (t, J = 8.4 Hz, 1H, *H*-4), 4.09 (t, J = 7.9 Hz, 1H, *H*-4), 4.21 (t, J = 7.9 Hz, 1H, *H*-4), 6.34 (d, J = 8.9 Hz, 1H, *H*-15), 6.37 (d, J = 9.0 Hz, 1H, *H*-15), 7.50 (d, J = 8.9 Hz, 1H, *H*-14), 7.51 (d, J = 8.9 Hz, 1H, *H*-14), 13.01 (s, 1H, O*H*), 13.02 (s, 1H, O*H*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 16.3, 16.5, 17.6, 18.0, 26.2, 29.3, 29.6, 31.9, 33.0, 45.2, 45.3, 75.0, 75.4, 108.1, 108.9, 109.0, 110.0, 110.1, 113.16, 113.24,

129.58, 129.62, 159.6, 162.2, 202.7, 202.8; **IR** (ef) 3423, 2958, 2878, 1626, 1488, 1419, 1369, 1331, 1270, 1247, 1136, 1060, 1018, 853 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 263 (M + H, 100), 111 (12)); **Anal.** Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.53; H, 7.02.

6.3 Experimental Concerning Chapter Three

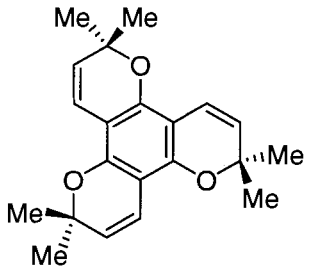
6.3.1 3-Methyl-but-2-enal [Senecialdehyde (134)][74,152]



134

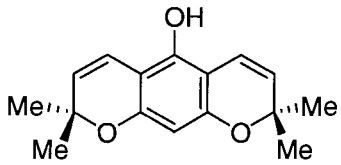
To a solution of 3-methyl-but-2-enol (**141**) (7.00 g, 81.3 mmol) in dichloromethane (100 mL) was added pyridinium dichromate (39.9 g, 106 mmol) at 0 °C. The reaction was stirred at room temperature for 16 h and then filtered through celite. The filter-cake was washed with ether (50 mL) and the combined filtrates were concentrated *in vacuo*. Purification of the crude product by distillation at reduced pressure afforded the *title compound* **134** (3.81 g, 56%) as a colourless oil. $\mathbf{R_f}$ = 0.41, hexanes:ether (1:1); **B.p.** ~50 °C, ~35 mm Hg (lit.[152] 133-135 °C, 760 mm Hg); **^{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) 85 (M + H, 100).

6.3.2 2,2,6,6,10,10-Hexamethyl-2*H*,6*H*,10*H*-dipyrano[6,5-*f*,6',5'-*h*]chromene (142) and 2,2,8,8-Tetramethyl-2*H*,8*H*-pyrano[5,6-*g*]chromen-5-ol (143)



142

and



143

Method A: A mixture of phloroglucinol (**14**) (38 mg, 0.30 mmol, 1 equiv), senecialdehyde (**134**) (109 mg, 1.30 mmol, 4 equiv), phenylboronic acid (9 mg, 0.07 mmol, 0.25 equiv), propionic acid (**72**) (4 drops) and benzene (10 mL) in a Dean-Stark trap was heated at reflux for 22 h. The resultant solution was cooled to room temperature and on filtration through a pad of silica gel with ether (125 mL) was concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (4:1) as the eluant afforded the *title compound* **142** (53 mg, 55%) as a white solid and the *title compound* **143** (30 mg, 39%) as a waxy yellow solid.

Method B: A mixture of phloroglucinol (**14**) (38 mg, 0.30 mmol, 1 equiv), senecialdehyde (**134**) (104 mg, 1.24 mmol, 4 equiv), phenylboronic acid (38 mg, 0.31 mmol, 1 equiv), propionic acid (**72**) (4 drops) and benzene (10 mL) in a Dean-Stark trap was heated at reflux for 22 h. The resultant solution was cooled to room temperature and on filtration through a pad of silica gel with ether (125 mL) was concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (4:1) as the eluant afforded the *title compound* **142** (72 mg, 74%) as a white solid and the *title compound* **143** (18 mg, 23%) as a waxy yellow solid.

Method C: A mixture of phloroglucinol (**14**) (38 mg, 0.30 mmol, 1 equiv), senecialdehyde (**134**) (103 mg, 1.23 mmol, 4 equiv), phenylboronic acid (74 mg, 0.61

mmol, 2 equiv), propionic acid (**72**) (4 drops) and benzene (10 mL) in a Dean-Stark trap was heated at reflux for 22 h. The resultant solution was cooled to room temperature and on filtration through a pad of silica gel with ether (125 mL) was concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (4:1) as the eluant afforded the *title compound* **142** (79 mg, 81%) as a white solid and the *title compound* **143** (9 mg, 11%) as a waxy yellow solid.

Method D: A mixture of phloroglucinol (**14**) (38 mg, 0.30 mmol, 1 equiv), senecialdehyde (**134**) (103 mg, 1.23 mmol, 4 equiv), phenylboronic acid (110 mg, 0.90 mmol, 3 equiv), propionic acid (**72**) (4 drops) and benzene (10 mL) in a Dean-Stark trap was heated at reflux for 22 h. The resultant solution was cooled to room temperature and on filtration through a pad of silica gel with ether (125 mL) was concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (4:1) as the eluant afforded the *title compound* **142** (89 mg, 92%) as a white solid and the *title compound* **143** (5 mg, 6%) as a waxy yellow solid.

Method E: A mixture of phloroglucinol (**14**) (38 mg, 0.30 mmol, 1 equiv), senecialdehyde (**134**) (103 mg, 1.23 mmol, 4 equiv), phenylboronic acid (110 mg, 0.90 mmol, 3 equiv) and benzene (10 mL) in a Dean-Stark trap was heated at reflux for 22 h after which time TLC analysis indicated only trace amounts of the *title compound* **142** and the *title compound* **143** had formed.

Method F: A mixture of phloroglucinol (**14**) (38 mg, 0.30 mmol, 1 equiv), senecialdehyde (**134**) (104 mg, 1.24 mmol, 4 equiv), propionic acid (**72**) (4 drops) and benzene (10 mL) in a Dean-Stark trap was heated at reflux for 22 h after which time TLC

analysis indicated only trace amounts of the *title compound* **142** and the *title compound* **143** had formed.

Method G: A mixture of phloroglucinol (**14**) (38 mg, 0.30 mmol, 1 equiv), senecialdehyde (**134**) (107 mg, 1.27 mmol, 4 equiv), boric acid (5 mg, 0.08 mmol, 0.25 equiv), propionic acid (**72**) (4 drops) and benzene (10 mL) in a Dean-Stark trap was heated at reflux for 22 h. The resultant mixture was cooled to room temperature and on filtration through a pad of silica gel with ether (125 mL) was concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (4:1) as the eluant afforded the *title compound* **142** (44 mg, 45%) as a white solid and the *title compound* **143** (23 mg, 30%) as a waxy yellow solid.

Method H: A mixture of phloroglucinol (**14**) (38 mg, 0.30 mmol, 1 equiv), senecialdehyde (**134**) (109 mg, 1.29 mmol, 4 equiv), boric acid (19 mg, 0.31 mmol, 1 equiv), propionic acid (**72**) (4 drops) and benzene (10 mL) in a Dean-Stark trap was heated at reflux for 22 h. The resultant mixture was cooled to room temperature and on filtration through a pad of silica gel with ether (125 mL) was concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (4:1) as the eluant afforded the *title compound* **142** (49 mg, 50%) as a white solid and the *title compound* **143** (19 mg, 25%) as a waxy yellow solid.

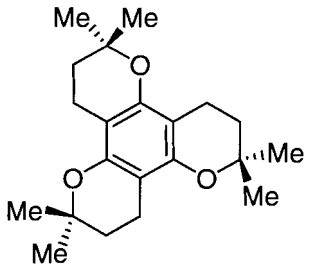
Method I: A mixture of phloroglucinol (**14**) (38 mg, 0.30 mmol, 1 equiv), senecialdehyde (**134**) (104 mg, 1.24 mmol, 4 equiv), boric acid (56 mg, 0.91 mmol, 3 equiv), propionic acid (**72**) (4 drops) and benzene (10 mL) in a Dean-Stark trap was heated at reflux for 22 h. The resultant mixture was cooled to room temperature and on filtration through a pad of silica gel with ether (125 mL) was concentrated *in vacuo*.

Purification by flash chromatography using hexanes:ether (4:1) as the eluant afforded the *title compound* **142** (43 mg, 44%) as a white solid and the *title compound* **143** (21 mg, 27%) as a waxy yellow solid.

Title compound **142**: $\mathbf{R_f}$ = 0.59, hexanes:ether (4:1); **M.p.** 110-113 °C, hexanes:ether; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.40 (s, 18H, C*H*$_3$), 5.43 (d, J = 9.9 Hz, 3H, ArCHC*H*), 6.59 (d, J = 9.9 Hz, 3H, ArC*H*CH); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 27.9, 76.5, 103.4, 116.8, 125.8, 149.1; **IR** (ef) 2972, 2928, 2853, 1626, 1590, 1463, 1425, 1366, 1242, 1177, 1136 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 325 (M + H, 100), 324 (M, 76), 309 (19); **Anal.** Calcd. for $C_{21}H_{24}O_3$: C, 77.75; H, 7.46. Found: C, 77.49; H, 7.82.

Title compound **143**: $\mathbf{R_f}$ = 0.27, hexanes:ether (4:1); **M.p.** 107-109 °C, hexanes:ether; **^{1}H NMR** (400 MHz, C_6D_6) δ 1.24 (s, 12H, C*H*$_3$), 5.14 (d, J = 9.9 Hz, 2H, ArCHC*H*), 6.23 (d, J = 9.9 Hz, 2H, ArC*H*CH), 6.46 (s, 1H, Ar*H*); **^{13}C NMR** (101 MHz, C_6D_6) δ 27.8, 76.1, 99.0, 103.5, 116.2, 126.6, 147.6, 155.4; **IR** (ef) 3353, 2978, 2928, 1638, 1613, 1563, 1481, 1360, 1139, 1106, 1071 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 258 (M, 21), 243 (100), 114 (13); **Anal.** Calcd. for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found: C, 74.24; H, 7.02.

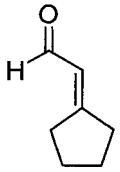
6.3.3 2,2,6,6,10,10-Hexamethyl-3,4,7,8,11,12-hexahydro-2*H*,6*H*,10*H*-dipyrano[6,5-*f*,6',5'-*h*]chromene (148)[75,76]



148

A mixture of the chromene **142** (200 mg, 0.62 mmol) and palladium on charcoal (199 mg, 10% w/w) in methanol (20 mL) under an atmosphere of hydrogen (balloon pressure) was stirred at room temperature for 20 h. The resultant mixture was filtered through a pad of celite with dichloromethane (3 × 20 mL) and then concentrated *in vacuo* to afford the *title compound* **148** (197 mg, 96%) as a white solid. $\mathbf{R}_f$ = 0.64, hexanes:ether (4:1); **M.p.** 96-97 °C, 95% ethanol (lit.[75] 103.5-104.5 °C, 95% ethanol); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.29 (s, 18H, CH_3), 1.71 (t, J = 6.8 Hz, 6H, $ArCH_2CH_2$), 2.55 (t, J = 6.8 Hz, 6H, $ArCH_2CH_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 16.7, 26.9, 32.5, 73.4, 100.3, 149.9; **IR** (ef) 2973, 2934, 2853, 1614, 1447, 1382, 1367, 1322, 1260, 1157, 1119, 1041 cm^{-1}; **MS** (EI) *m/z* (rel. intensity) 330 (M, 70), 275 (86), 219 (100); **Anal.** Calcd. for $C_{21}H_{30}O_3$: C, 76.33; H, 9.15. Found: C, 76.30; H, 9.13.

6.3.4 Cyclopentylideneacetaldehyde (152)[77]



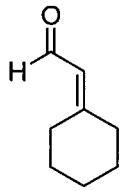
152

To a suspension of sodium hydride (2.20 g, 60% w/w in mineral oil, 55.0 mmol) in tetrahydrofuran (80 mL) at room temperature was added a solution of trimethyl phosphonoacetate (8.50 mL, 52.5 mmol). The resultant mixture was stirred for 1 h and

then cyclopentanone (**149**) (4.40 mL, 49.7 mmol) was added. The reaction mixture was heated at reflux for 24 h and then cooled to 0 °C after which a saturated aqueous solution of ammonium chloride (50 mL) was added. The resultant mixture was extracted with ether (2 × 50 mL) and the combined organic extracts were washed with brine (2 × 50 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by distillation at reduced pressure (B.p. 115-120 °C, ~2 mm Hg) afforded the corresponding α,β-unsaturated ester. A solution of this material (5.90 g, 42.1 mmol) in ether (20 mL) was added to a suspension of lithium aluminum hydride (2.60 g, 68.6 mmol) in ether (100 mL) at 0 °C and the resultant mixture was allowed to warm to room temperature over 1 h. Water (2.6 mL), an aqueous solution of sodium hydroxide (2 M, 2.6 mL) and water (7.8 mL) were then added in succession and the resultant mixture was filtered. The filter-cake was washed with ether (3 × 50 mL) and the combined filtrates were concentrated *in vacuo* to afford the corresponding alcohol. To a solution of this material (4.70 g, 42.0 mmol) in dichloromethane (200 mL) at room temperature was added manganese dioxide (32.9 g, 378 mmol) and the resultant mixture stirred for 6 h. The reaction mixture was filtered through a pad of celite, the filter-cake was washed with dichloromethane (3 × 50 mL) and the combined filtrates were concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (2:1) as the eluant afforded the *title compound* **152** (3.97 g, 72% over three steps) as a clear oil. $\mathbf{R_f}$ = 0.42, hexanes:ether (1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.72 (m, 2H, CH_2), 1.83 (m, 2H, CH_2), 2.54 (t, J = 7.2 Hz, 2H, CH_2C), 2.80 (t, J = 7.2 Hz, 2H, CH_2C), 5.97 (m, 1H, C*H*CHO), 9.85 (d, J = 8.0 Hz, 1H, C*H*O); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 25.0, 26.4, 30.3, 35.9, 123.2, 173.8, 191.7; **IR**

(ef) 2962, 2874, 1671, 1625, 1446, 1090 cm^{-1}; **MS** (EI) m/z (rel. intensity) 110 (M, 13), 109 (9), 85 (11), 67 (14), 46 (83), 45 (75), 29 (100).

6.3.5 Cyclohexylideneacetaldehyde (156)[77,79]

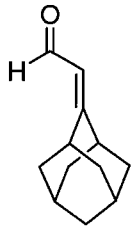


156

To a suspension of sodium hydride (2.20 g, 60% w/w in mineral oil, 55.0 mmol) in tetrahydrofuran (100 mL) at room temperature was added a solution of trimethyl phosphonoacetate (8.50 mL, 52.5 mmol). The resultant mixture stirred for 1 h and then cyclohexanone (**153**) (5.20 mL, 50.2 mmol) was added. The reaction mixture was heated at reflux for 24 h and then cooled to 0 °C after which a saturated aqueous solution of ammonium chloride (50 mL) was added. The resultant mixture was extracted with ether (2 × 50 mL) and the combined organic extracts were washed with brine (2 × 50 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by distillation at reduced pressure (B.p. 120-130 °C, ~2 mm Hg) afforded the corresponding α,β-unsaturated ester. A solution of this material (4.00 g, 25.9 mmol) in ether (25 mL) was added to a suspension of lithium aluminum hydride (1.00 g, 26.4 mmol) in ether (80 mL) at 0 °C. The resultant mixture was allowed to warm to room temperature over 1 h and then was cooled to 0 °C. Water (1.0 mL), an aqueous solution of sodium hydroxide (2 M, 1.0 mL) and water (3.0 mL) were then added in succession and the resultant mixture was filtered. The filter-cake was washed with ether (3 × 50 mL) and the combined filtrates were concentrated *in vacuo* to afford the corresponding alcohol. To a solution of this material (3.27 g, 25.9 mmol) in dichloromethane (150 mL) at room

temperature was added manganese dioxide (33.0 g, 380 mmol) and the resultant mixture was stirred for 3 h. The reaction mixture was filtered through a pad of celite, the filter-cake was washed with dichloromethane (3 × 50 mL) and the combined filtrates were concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (2:1) as the eluant afforded the *title compound* **156** (2.62 g, 81% over three steps) as a clear oil. $\mathbf{R}_f$ = 0.45, hexanes:ether (1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.69 (m, 6H, CH_2), 2.29 (t, J = 6.4 Hz, 2H, CH_2C), 2.71 (t, J = 6.4 Hz, 2H, CH_2C), 5.82 (d, J = 8.2 Hz, 1H, CHCHO), 10.01 (d, J = 8.2 Hz, 1H, C*H*O); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 26.3, 28.2, 28.5, 29.7, 38.1, 125.4, 168.1, 190.6; **IR** (ef) 2934, 1856, 2773, 1674, 1625, 1449, 1194, 1141, 1120 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 125 (M + H, 100), 123 (45), 95 (22), 81 (27), 65 (15), 53 (21).

6.3.6 Adamantylideneacetaldehyde (160)[77,80]



160

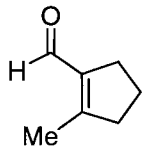
To a suspension of sodium hydride (731 mg, 60% w/w in mineral oil, 18.3 mmol) in tetrahydrofuran (70 mL) at room temperature was added a solution of trimethyl phosphonoacetate (2.80 mL, 17.3 mmol). The resultant mixture was stirred for 1 h and then 2-adamantanone (**157**) (2.50 g, 16.6 mmol) was added. The reaction mixture was heated at reflux for 24 h and then cooled to 0 °C after which a saturated aqueous solution of ammonium chloride (50 mL) was added. The resultant mixture was extracted with ether (2 × 50 mL) and the combined organic extracts were washed with brine (2 × 50

mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (9:1) as the eluant afforded the corresponding α,β-unsaturated ester (3.26 g, 95%) as a colourless solid. $\mathbf{R}_f$ = 0.50, hexanes:ether (9:1); **M.p.** 46-47 °C, hexanes:ether; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.82 (m, 6H, C*H*), 1.95 (m, 6H, C*H*), 2.41 (s, 1H, C*H*C), 3.66 (s, 3H, CO_2CH_3), 4.05 (s, 1H, C*H*C), 5.57 (s, 1H, $CHCO_2CH_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 28.0, 33.0, 36.9, 39.3, 40.2, 41.5, 50.8, 108.3, 167.5, 172.6; **IR** (ef) 2995, 2912, 2845, 1710, 1640, 1444, 1382, 1326, 1236, 1205, 1160 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 207 (M + H, 100), 175 (11).

A solution of the above material (3.26 g, 15.8 mmol) in ether (10 mL) was added to a suspension of lithium aluminum hydride (600 mg, 15.8 mmol) in ether (50 mL) at 0 °C and the resultant mixture was allowed to warm to room temperature over 1 h. Water (0.6 mL), an aqueous solution of sodium hydroxide (2 M, 0.6 mL) and water (1.8 mL) were then added in succession and the resultant mixture was filtered. The filter-cake was washed with ether (3 × 25 mL) and the combined filtrates were concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (1:1) as the eluant afforded the corresponding α,β-unsaturated alcohol (2.72 g, 97%) as a clear oil. $\mathbf{R}_f$ = 0.25, hexanes:ether (1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.69 (m, 2H, C*H*), 1.79 (m, 4H, C*H*), 1.88 (m, 4H, C*H*), 1.94 (m, 2H, C*H*), 2.36 (m, 1H, C*H*C), 2.85 (m, 1H, C*H*C), 4.11 (d, J = 7.0 Hz, 2H, CH_2OH), 5.35 (t, J = 7.0 Hz, 1H, $CHCH_2OH$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 28.4, 32.4, 37.1, 39.1, 39.7, 40.4, 58.1, 115.5, 152.6; **IR** (ef) 3427 (br), 3064, 2920, 2850, 1596, 1513, 1358 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 177 (M, 5), 161 (M – OH, 100), 41 (9), 39 (11).

To a solution of the above material (2.00 g, 11.3 mmol) in dichloromethane (70 mL) at room temperature was added manganese dioxide (20.0 g, 230 mmol) and the resultant mixture was stirred for 3 h. The reaction mixture was then filtered through a pad of celite, the filter-cake was washed with dichloromethane (3 × 20 mL) and the combined filtrates were concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (3:1) as the eluant afforded the *title compound* **160** (1.77 g, 90%) as a colourless solid. $\mathbf{R}_f$ = 0.55, hexanes:ether (1:1); **M.p.** 48-49 °C, hexanes:ether; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.90 (m, 6H, C*H*), 2.01 (m, 6H, C*H*), 2.51 (s, 1H, C*H*C), 3.61 (s, 1H, C*H*C), 5.78 (d, J = 8.4 Hz, 1H, C*H*CHO), 10.00 (d, J = 8.4 Hz, 1H, CHC*H*O); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 28.1, 33.4, 36.7, 39.7, 40.0, 41.6, 121.4, 176.9, 190.0; **IR** (ef) 2913, 2850, 1669, 1622, 1450, 1196, 1132 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 175 (M + H, 100), 39 (15).

6.3.7 2-Methylcyclopentene-1-carboxaldehyde (165)[81,82]

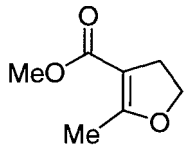


165

Ozone was bubbled into a solution of methylcyclohexene (**161**) (18.0 mL, 152 mmol) in dichloromethane (40 mL) and methanol (75 mL) at –78 °C until a blue colour developed. The resultant solution was degassed by bubbling nitrogen through it and then was poured into a mixture of dimethyl sulfide (40 mL) and *p*-toluenesulfonic acid monohydrate (400 mg, 2.11 mmol). After 16 h at room temperature, the resultant mixture was diluted with dichloromethane (200 mL) and then washed with hydrochloric acid (3 M, 75 mL), water (75 mL) and brine (75 mL). The organic layer was dried over

anhydrous sodium sulfate and concentrated *in vacuo*. Purification by distillation at reduced pressure (B.p. ~140 °C, 4 mm Hg) afforded 1,1-dimethoxyheptan-6-one (19.7 g, 75%) as a colourless oil. To a solution of this material (5.00 g, 28.7 mmol) in tetrahydrofuran (50 mL) at 0 °C was added an aqueous solution of sulfuric acid (50 mL, 3% v/v). The reaction mixture was stirred at 0 °C for 2 h and then at room temperature for 1.5 h. The resultant mixture was diluted with dichloromethane (150 mL) and then washed with a saturated aqueous solution of sodium bicarbonate (2 × 25 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford 6-ketoheptanal (3.68 g). To a solution of this material in ether (75 mL) at 0 °C was added piperidine (3.1 mL, 32 mmol). After 3 h, the reaction mixture was washed with brine (50 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford the corresponding ketoenamine (5.20 g). A solution of this material (5.20 g, 26.6 mmol) and acetic acid (3.7 mL) in ether (70 mL) was heated at reflux for 6 h. The resultant mixture was allowed to cool to room temperature and a saturated aqueous solution of sodium bicarbonate (35 mL) was added. The organic layer was washed with brine (35 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by distillation at reduced pressure afforded the *title compound* **165** (2.11 g, 67% over three steps) as a colourless oil. $\mathbf{R}_f$ = 0.60, hexanes:ether (1:1); **B.p.** 80-85 °C, 1 mm Hg (lit.[81] 30-75 °C, 0.05 mm Hg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.85 (m, 2H, CH_2), 2.14 (m, 3H, CH_3), 2.56 (m, 4H, CH_2), 9.99 (s, 1H, C*H*O); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 14.4, 20.8, 30.1, 41.0, 138.2, 163.6, 188.7; **IR** (ef) 2959, 2861, 1664, 1449, 1381, 1259 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 111 (M + H, 100), 99 (8), 61 (64), 43 (90).

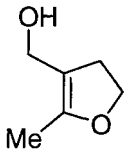
6.3.8 Methyl-2-methyl-4,5-dihydrofuran-3-carboxylate (167)[70,71]



167

A solution of α-acetyl-γ-butyrolactone (**166**) (70.0 mL, 0.650 mmol) and hydrogen chloride (11.2 g, 0.307 mmol) in methanol (600 mL) was heated at reflux for 4 days. The resultant mixture was allowed to cool to room temperature and a saturated aqueous solution of sodium bicarbonate (1.6 L) was added. The resultant mixture was extracted with ether (9 × 150 mL) and the combined organic layers were washed with water (2 × 200 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Distillation (B.p. 50-123 °C, ~15 mm Hg) of the resultant oil afforded the impure *title compound* **167** (35.6 g) as a clear oil. Redistillation of this material, in the presence of concentrated sulfuric acid (4 drops), afforded the *title compound* **167** (17.8 g, 19%) as colourless crystals. $\mathbf{R}_f$ = 0.63, ether; **B.p.** 78-84 °C, ~15 mm Hg (lit.[70] 72-73 °C, ~12 mm Hg); **M.p.** 28-29 °C (lit.[71] 31.5-32.5 °C, petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.17 (s, 3H, *Me*), 2.87 (apparent t, J = 9.6 Hz, 2H, OCH_2CH_2), 3.70 (s, 3H, CO_2Me), 4.39 (apparent t, J = 9.6 Hz, 2H, OCH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 13.8, 29.5, 50.6, 70.2, 101.7, 166.5, 168.7; **IR** (ef) 2952, 1705, 1651, 1438, 1388, 1334, 1229, 1084, 998 cm^{-1}; **MS** (EI) *m/z* (rel. intensity) 143 (M + H, 38), 142 (M, 18), 43 (100).

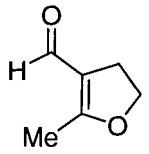
6.3.9 2-Methyl-3-hydroxymethyl-4,5-dihydrofuran (168)



168

A solution of the ester **167** (1.88 g, 13.2 mmol) in ether (15 mL) was added to a suspension of lithium aluminum hydride (753 mg, 19.8 mmol) in ether (40 mL) at 0 °C. The resultant mixture was allowed to warm to room temperature over 20 min and then was cooled to 0 °C. Water (0.75 mL), an aqueous solution of sodium hydroxide (2 M, 0.75 mL) and water (2.25 mL) were then added in succession and the resultant mixture was filtered. The filter-cake was washed with ether (3 × 50 mL) and the combined filtrates were concentrated *in vacuo* to afford the *title compound* **168** (1.45 g, 96%) as pale yellow oil. This material proved to be unstable to purification (Kugelrohr distillation or flash chromatography on silica gel) and to storage. Thus, the crude *title compound* **168** (>95% pure) was used immediately in subsequent experiments. $\mathbf{R}_f$ = 0.31, ether; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.64 (s, 1H, O*H*), 1.78 (t, J = 1.8 Hz, 3H, *Me*), 2.72 (apparent t, J = 9.4 Hz, 2H, OCH_2CH_2), 4.18 (d, J = 5.3 Hz, 2H, CH_2OH), 4.29 (apparent t, J = 9.4 Hz, 2H, OCH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 11.1, 31.4, 57.9, 68.3, 106.8, 151.1; **IR** (ef) 3335 (broad), 2917, 2817, 1693, 1378, 1215, 998, 972 cm^{-1}; **MS** (EI) *m/z* (rel. intensity) 115 (M + H, 27), 97 (M – H_2O, 23), 43 (100).

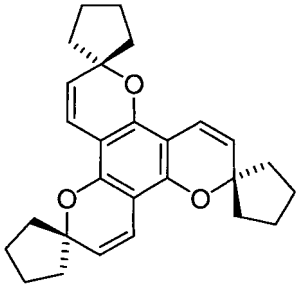
6.3.10 2-Methyl-3-formyl-4,5-dihydrofuran (169)[153]



169

A suspension of the alcohol **168** [prepared from the corresponding ester **167** (2.50 g, 17.6 mmol)] and manganese dioxide (24.3 g, 27.9 mmol) in dichloromethane (100 mL) was stirred at room temperature for 54 h. The reaction mixture was then filtered through a pad of celite, the filter-cake was washed with dichloromethane (3 × 100 mL) and the combined filtrates were concentrated *in vacuo*. Purification by distillation at reduced pressure afforded the *title compound* **169** (0.80 g, 41%) as a pale yellow oil. **B.p.** 95-100 °C, ~2 mm Hg; **^{1}H NMR** (400 MHz, C_6D_6) δ 1.45 (s, 3H, *Me*), 2.47 (apparent t, J = 9.5 Hz, OCH_2CH_2), 3.67 (apparent t, J = 9.5 Hz, OCH_2), 9.61 (s, 1H, *CH*O); **^{13}C NMR** (101 MHz, C_6D_6) δ 11.9, 27.2, 71.6, 115.7, 173.7, 184.1; **IR** (ef) 2975, 2930, 1651, 1393, 1237, 972; **MS** (EI) *m/z* (rel. intensity) 112 (M, 67), 84 (100).

6.3.11 2,6,10-Tricyclopentylidene-2*H*,6*H*,10*H*-dipyrano[6,5-*f*,6',5'-*h*]chromene (172)

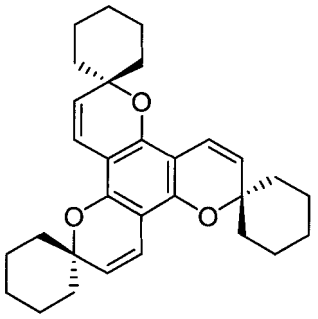


172

A mixture of phloroglucinol (**14**) (38 mg, 0.30 mmol), cyclopentylideneacetaldehyde (**152**) (139 mg, 1.26 mmol), phenylboronic acid (113 mg, 0.93 mmol), propionic acid (**72**) (4 drops) and benzene (10 mL) in a Dean-Stark trap was heated at reflux for 4 h. The resultant solution was cooled to room temperature and on

filtration through a pad of silica gel with ether (125 mL) was concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (99:1) as the eluant afforded the *title compound* **172** (69 mg, 57%) as a solid white foam. $\mathbf{R}_f$ = 0.28, hexanes:ether (99:1); **M.p.** 41-44 °C, hexanes:ether; **^{1}H NMR** (400 MHz, C_6D_6) δ 1.32 (m, 6H, CH_2), 1.45 (m, 6H, CH_2), 1.83 (m, 6H, CH_2), 2.15 (m, 6H, CH_2), 5.32 (d, J = 10.0 Hz, 3H, ArCHC*H*), 6.87 (d, J = 9.9 Hz, 3H, ArC*H*CH); **^{13}C NMR** (101 MHz, C_6D_6) δ 23.8, 39.4, 87.8, 104.9, 118.4, 124.8, 149.7; **IR** (ef) 2959, 1638, 1592, 1445, 1373, 1154, 1009 cm^{-1}; **MS** (EI) *m/z* (rel. intensity) 402 (M, 54), 57 (54), 44 (100), 18 (49), 14 (66); **FAB-HRMS** Calcd. for $C_{27}H_{30}O_3$: 402.2195. Found: 402.2198.

6.3.12 2,6,10-Tricyclohexylidene-2*H*,6*H*,10*H*-dipyrano[6,5-*f*,6',5'-*h*]chromene (173)

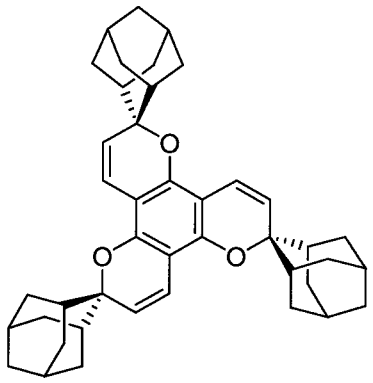


173

A mixture of phloroglucinol (**14**) (38 mg, 0.30 mmol), cyclohexylideneacetaldehyde (**156**) (152 mg, 1.23 mmol), phenylboronic acid (114 mg, 0.94 mmol), propionic acid (**72**) (4 drops) and benzene (10 mL) in a Dean-Stark trap was heated at reflux for 135 min. The resultant solution was cooled to room temperature and on filtration through a pad of silica gel with ether (125 mL) was concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (99:1) as the eluant afforded the *title compound* **173** (69 mg, 52%) as a solid white foam. $\mathbf{R}_f$ = 0.38, hexanes:ether (99:1); **M.p.** 50-52 °C, hexanes:ether; **^{1}H NMR** (400 MHz, C_6D_6) δ 1.10 (m, 3H, CH_2),

1.31 (m, 12H, CH_2), 1.49 (m, 3H, CH_2), 1.76 (m, 6H, CH_2), 2.01 (m, 6H, CH_2), 5.32 (d, J = 9.9 Hz, 3H, ArCHCH), 6.96 (d, J = 9.9 Hz, 3H, ArCHCH); **^{13}C NMR** (101 MHz, C_6D_6) δ 21.9, 25.7, 36.2, 77.4, 104.8, 117.9, 126.0, 149.8; **IR** (ef) 3052, 2931, 2857, 1637, 1591, 1447, 1372, 1272, 1187, 1139 cm^{-1}; **MS** (EI) *m/z* (rel. intensity) 444 (M, 5), 91 (5), 56 (5), 55 (10), 18 (100); **Anal.** Calcd. for $C_{30}H_{36}O_3$: C, 81.04; H, 8.16. Found: C, 80.92; H, 8.34.

6.3.13 2,6,10-Triadamantylidene-2*H*,6*H*,10*H*-dipyrano[6,5-*f*,6',5'-*h*]chromene (174)



174

A mixture of phloroglucinol (**14**) (38 mg, 0.30 mmol), adamantylideneacetaldehyde (**160**) (214 mg, 1.22 mmol), phenylboronic acid (112 mg, 0.92 mmol), propionic acid (**72**) (4 drops) and benzene (10 mL) in a Dean-Stark trap was heated at reflux for 22 h. The resultant solution was cooled to room temperature and on filtration through a pad of silica gel with chloroform (200 mL) was concentrated *in vacuo*. Purification by flash chromatography using chloroform as the eluant afforded the *title compound* **174** (141 mg, 79%) as a white solid. $\mathbf{R}_f$ = 0.79 (chloroform); **M.p.** 234-235 °C, chloroform; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.52 (m, 3H, CH), 1.55 (m, 3H, CH), 1.69 (m, 3H, CH), 1.73 (m, 9H, CH), 1.87 (m, 6H, CH), 1.94 (m, 3H, CH), 1.97 (m, 3H, CH), 2.11 (m, 6H, CH), 2.30 (m, 3H, CHC), 2.34 (m, 3H, CHC), 6.00 (d, J = 10.0 Hz,

3H, ArCHC*H*), 6.75 (d, J = 10.0 Hz, 3H, ArC*H*CH); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 26.9, 27.3, 32.7, 33.8, 35.8, 38.0, 80.7, 105.3, 117.9, 124.1, 148.9; **IR** (ef) 2902, 2855, 1633, 1588, 1445, 1189, 1133, 1097 cm^{-1}; **MS** (MALDI-TOF) *m/z* (rel. intensity) 640 (M + K, 16), 623 (M + Na, 19), 601 (M + H, 100); **FAB-HRMS** Calcd. for $C_{42}H_{48}O_3$: 600.3603. Found: 600.3606.

6.3.14 X-Ray Crystallographic Analysis of 2,6,10-Triadamantylidene-2*H*,6*H*,10*H*-dipyrano[6,5-*f*,6',5'-*h*]chromene (174)*

A single crystal of the chromene **174**, a yellow block that had the dimensions 0.43 × 0.42 × 0.04 mm, was mounted on a glass fibre using epoxy adhesive. The data for this crystal was acquired at 293 K on an Enraf Nonius CAD4F diffractometer with graphite monochromatic Mo Kα radiation. The following data range was recorded: $4^\circ \leq 2\theta \leq 45^\circ$. The data was corrected by integration for the effects of absorption using a Gaussian method with the following transmission range: 0.974433 – 0.993929. Data reduction for the crystal of the chromene **174** included corrections for Lorentz and polarization effects. Final unit-cell dimensions were determined based on the following well-centred reflections: 40 reflections with range $22^\circ \leq 2\theta \leq 24^\circ$.

For the chromene **174**, coordinates and anisotropic displacement parameters for the non-carbon and hydrogen atoms were refined; carbon atoms were refined using isotropic thermal parameters. Hydrogen atoms were placed in calculated positions (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

(*) The data for this X-ray crystal structure was obtained and solved by Mr. M. Katz (Simon Fraser University).

carbon atoms. Subsequently the isotropic thermal parameters for the C-H hydrogen atoms were constrained to have identical shifts during refinement. The programs used for all absorption corrections, data reduction and processing of the chromene **174** were from the NRCVAX Crystal Structure System.[154] The structure was refined using CRYSTALS.[151] An ORTEP representation of the chromene **174** is provided below (Figure 6.3.14.1). Crystallographic data, fractional atomic coordinates and equivalent isotropic thermal displacement parameters, selected bond lengths as well as selected bond angles for the chromene **174** are also listed below (Table 6.3.14.1, Table 6.3.14.2, Table 6.3.14.3 and Table 6.3.14.4, respectively).

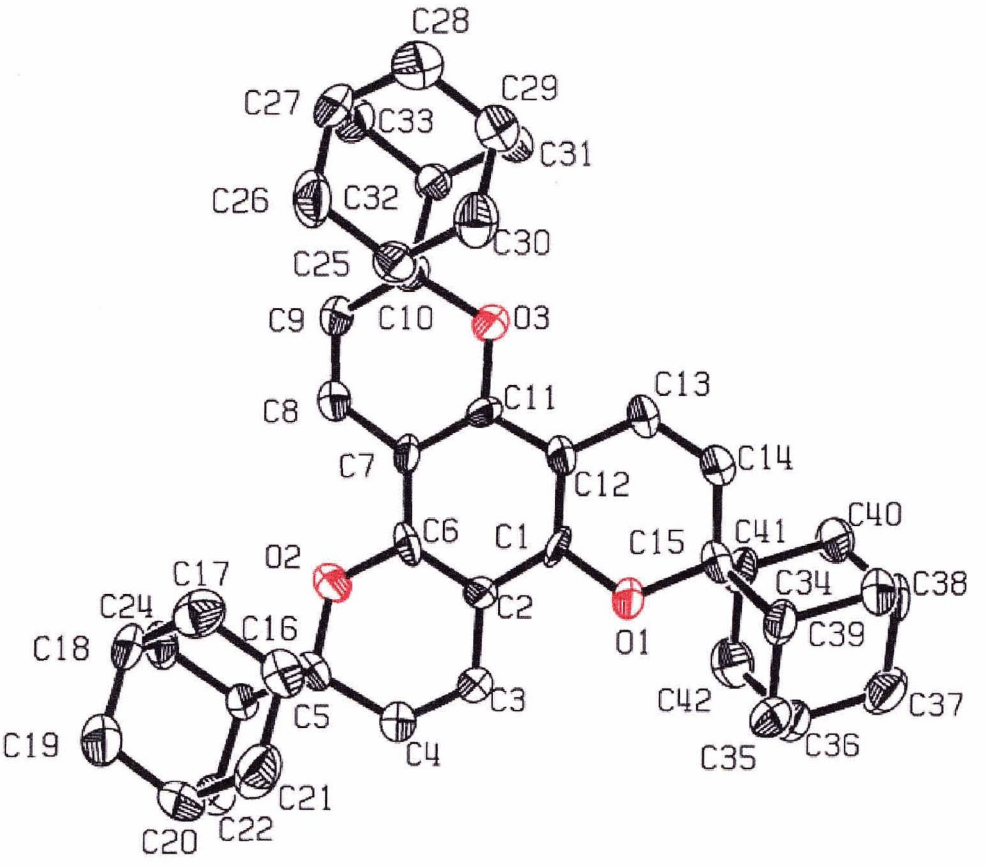


Figure 6.3.14.1 ORTEP representation of the chromene (174) (the thermal ellipsoids are drawn at a 50% probability level and the hydrogen atoms have been omitted for clarity).

Table 6.3.14.1 Summary of Crystallographic Data for the Chromene (174)

Empirical Formula	$C_{42}H_{48}O_3$
FW (g mol^{-1})	600.84
Temperature (K)	293
Wavelength (Mo *Kα*, Å)	0.71073
Crystal system	Triclinic
Space Group	P$\bar{1}$
a (Å)	9.533(2)
b (Å)	11.808(3)

c (Å)	15.530(3)
α (°)	109.000(18)
β (°)	91.953(18)
γ (°)	106.166(19)
Z	2
U (Å^3)	1572.6(7)
D_{calc} (g cm^{-3})	1.269
2θ limits (°)	4-45
Reflections collected	4632
Independent reflections	4632
Reflections observed [$I > 2.5\sigma(I)$]	2523
Goodness-of-fit on F	1.9364
R_1, R_w [$I > 2.5\sigma(I)$]	0.0667, 0.0909

Table 6.3.14.2 Fractional Atomic Coordinates (Å) and Equivalent Isotropic Thermal Displacement Parameters [U(iso), (Å^2)] for the Chromene (174)*

Atom	X	Y	Z	U (iso)
O1	0.5924(4)	0.3281(3)	0.2032(2)	0.0469
O2	0.5841(4)	0.2156(3)	0.4700(2)	0.0447
O3	0.1788(4)	0.0117(3)	0.2307(2)	0.0437
C1	0.5199(6)	0.2522(5)	0.2484(3)	0.0353
C2	0.5934(5)	0.2728(5)	0.3348(3)	0.0359
C3	0.7438(6)	0.3483(5)	0.3701(3)	0.0459
C4	0.7974(6)	0.3718(5)	0.4568(4)	0.0495
C5	0.6944(6)	0.3344(5)	0.5229(3)	0.0425
C6	0.5184(6)	0.2065(5)	0.3858(3)	0.0366
C7	0.3796(6)	0.1189(5)	0.3548(3)	0.0347
C8	0.2998(6)	0.0383(5)	0.4034(3)	0.041
C9	0.1599(6)	-0.0297(5)	0.3730(3)	0.0436

(*) The occupancies for all atoms listed in this table are 1.0.

Atom	X	Y	Z	U (iso)
C10	0.0761(6)	-0.0176(5)	0.2935(3)	0.0392
C11	0.3138(5)	0.1008(4)	0.2688(3)	0.0329
C12	0.3806(6)	0.1669(5)	0.2133(3)	0.0362
C13	0.3137(6)	0.1624(5)	0.1271(3)	0.0458
C14	0.3943(6)	0.2220(5)	0.0763(4)	0.0467
C15	0.5591(6)	0.2838(5)	0.1028(3)	0.0429
C16	0.6197(6)	0.4346(5)	0.5646(4)	0.0465
C17	0.5069(6)	0.3905(6)	0.6249(4)	0.0559
C18	0.5835(7)	0.3676(6)	0.6998(4)	0.0556
C19	0.6980(7)	0.4861(6)	0.7590(4)	0.0675
C20	0.8140(7)	0.5319(6)	0.7034(4)	0.0627
C21	0.7388(8)	0.5562(5)	0.6243(4)	0.0672
C22	0.8869(6)	0.4313(6)	0.6603(4)	0.0579
C23	0.7702(5)	0.3103(5)	0.5987(3)	0.0367
C24	0.6588(6)	0.2672(5)	0.6595(4)	0.0485
C25	-0.0002(6)	0.0834(5)	0.3242(3)	0.0409
C26	-0.1186(7)	0.0446(6)	0.3829(4)	0.059
C27	-0.2356(6)	-0.0789(6)	0.3260(4)	0.0554
C28	-0.3044(7)	-0.0629(7)	0.2429(4)	0.0651
C29	-0.1882(7)	-0.0267(6)	0.1848(4)	0.057
C30	-0.0756(7)	0.0982(5)	0.2424(4)	0.0528
C31	-0.1136(6)	-0.1271(5)	0.1528(3)	0.0476
C32	-0.0397(6)	-0.1442(5)	0.2340(3)	0.0372
C33	-0.1590(6)	-0.1795(5)	0.2934(4)	0.0547
C34	0.6179(6)	0.4032(5)	0.0781(3)	0.0418
C35	0.7817(6)	0.4632(5)	0.1124(4)	0.0519
C36	0.8660(6)	0.3722(6)	0.0695(4)	0.0509
C37	0.8422(6)	0.3358(6)	-0.0337(4)	0.0574
C38	0.6787(7)	0.2742(6)	-0.0706(3)	0.0537
C39	0.5952(7)	0.3669(5)	-0.0269(3)	0.0486

Atom	X	Y	Z	U (iso)
C40	0.6198(7)	0.1586(5)	-0.0458(3)	0.0542
C41	0.6453(6)	0.1928(5)	0.0598(3)	0.043
C42	0.8110(6)	0.2547(5)	0.0936(4)	0.0539
H31	0.8045	0.3845	0.3326	0.068(8)
H41	0.9001	0.409	0.4776	0.072(8)
H81	0.349	0.0333	0.4556	0.070(8)
H91	0.1098	-0.086	0.4019	0.074(8)
H131	0.2127	0.1164	0.1057	0.069(8)
H141	0.3475	0.2269	0.0232	0.077(8)
H161	0.571	0.449	0.5166	0.049(3)
H171	0.4612	0.4533	0.6513	0.062(3)
H172	0.4341	0.3151	0.5875	0.062(3)
H181	0.513	0.3394	0.736	0.056(3)
H191	0.7438	0.4719	0.8082	0.066(3)
H192	0.652	0.5494	0.7832	0.066(3)
H201	0.8867	0.6072	0.741	0.063(3)
H211	0.6945	0.6199	0.6511	0.070(3)
H212	0.8077	0.583	0.5867	0.070(3)
H221	0.9332	0.4162	0.7088	0.060(3)
H222	0.9588	0.4594	0.6248	0.060(3)
H231	0.8165	0.2477	0.5731	0.036(3)
H241	0.708	0.2546	0.7081	0.049(3)
H242	0.5867	0.1907	0.6233	0.049(3)
H251	0.0708	0.161	0.3598	0.045(3)
H261	-0.0727	0.0349	0.4342	0.057(3)
H262	-0.1651	0.1081	0.4039	0.057(3)
H271	-0.3088	-0.102	0.3624	0.060(3)
H281	-0.3472	0.0031	0.2642	0.070(3)
H282	-0.3785	-0.1383	0.2069	0.070(3)
H291	-0.2325	-0.0173	0.1328	0.066(3)

Atom	X	Y	Z	U (iso)
H301	-0.1254	0.1591	0.2646	0.053(3)
H302	-0.0046	0.1252	0.206	0.053(3)
H311	-0.1864	-0.2041	0.118	0.049(3)
H312	-0.0425	-0.1045	0.1151	0.049(3)
H321	0.0068	-0.2079	0.2133	0.033(3)
H331	-0.1146	-0.1882	0.3456	0.057(3)
H332	-0.2305	-0.257	0.2581	0.057(3)
H341	0.5663	0.4612	0.1052	0.037(3)
H351	0.817	0.5359	0.0959	0.050(3)
H352	0.7975	0.4868	0.1774	0.050(3)
H361	0.9679	0.4115	0.092	0.056(3)
H371	0.878	0.4084	-0.0502	0.060(3)
H372	0.8946	0.278	-0.0596	0.060(3)
H381	0.6649	0.2519	-0.1355	0.052(3)
H391	0.6287	0.4396	-0.0435	0.058(3)
H392	0.4933	0.3269	-0.0491	0.058(3)
H401	0.6687	0.099	-0.0743	0.053(3)
H402	0.5171	0.1234	-0.0669	0.053(3)
H411	0.6103	0.1194	0.0754	0.041(3)
H421	0.8633	0.198	0.0648	0.056(3)
H422	0.8275	0.2754	0.1584	0.056(3)

Table 6.3.14.3 Bond Lengths (Å) for the Chromene (174)

Atoms	Bond Lengths (Å)
O1-C1	1.368(5)
O1-C15	1.465(6)
O2-C5	1.456(6)
O2-C6	1.389(6)
O3-C10	1.457(6)
O3-C11	1.379(5)

Atoms	Bond Lengths (Å)
C1-C2	1.406(7)
C1-C12	1.387(7)
C2-C3	1.438(7)
C2-C6	1.372(7)
C3-C4	1.335(7)
C4-C5	1.528(7)
C5-C16	1.526(8)
C5-C23	1.505(7)
C6-C7	1.387(7)
C7-C8	1.469(7)
C7-C11	1.380(7)
C8-C9	1.327(7)
C9-C10	1.516(7)
C10-C25	1.521(8)
C10-C32	1.556(7)
C11-C12	1.399(6)
C12-C13	1.442(7)
C13-C14	1.346(7)
C14-C15	1.514(7)
C15-C34	1.542(7)
C15-C41	1.529(8)
C16-C17	1.544(7)
C16-C21	1.537(8)
C17-C18	1.489(8)
C18-C19	1.496(8)
C18-C24	1.527(8)
C19-C20	1.515(8)
C20-C21	1.547(9)
C20-C22	1.521(9)
C22-C23	1.532(7)

Atoms	Bond Lengths (Å)
C23-C24	1.535(7)
C25-C26	1.539(7)
C25-C30	1.521(7)
C26-C27	1.529(8)
C27-C28	1.517(8)
C27-C33	1.523(8)
C28-C29	1.510(8)
C29-C30	1.524(8)
C29-C31	1.507(9)
C31-C32	1.519(7)
C32-C33	1.541(7)
C34-C35	1.519(7)
C34-C39	1.536(7)
C35-C36	1.515(8)
C36-C37	1.508(8)
C36-C42	1.513(8)
C37-C38	1.524(8)
C38-C39	1.526(8)
C38-C40	1.502(8)
C40-C41	1.548(7)
C41-C42	1.535(8)

Table 6.3.14.4 Bond Angles (°) for the Chromene (174)

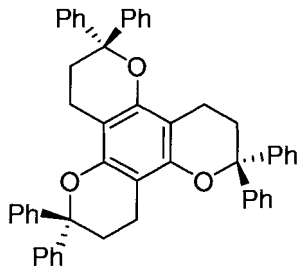
Atoms	Bond Angles (°)
C1-O1-C15	118.3(4)
C5-O2-C6	117.0(4)
C10-O3-C11	117.5(4)
O1-C1-C2	115.0(4)
O1-C1-C12	121.9(4)
C2-C1-C12	123.0(4)

Atoms	Bond Angles (°)
C1-C2-C3	125.5(4)
C1-C2-C6	116.7(4)
C3-C2-C6	117.6(5)
C2-C3-C4	120.2(5)
C3-C4-C5	120.2(5)
C4-C5-O2	107.2(4)
C4-C5-C16	110.6(5)
O2-C5-C16	110.0(4)
C4-C5-C23	113.4(5)
O2-C5-C23	106.0(4)
C16-C5-C23	109.4(4)
O2-C6-C2	121.0(4)
O2-C6-C7	115.3(4)
C2-C6-C7	123.4(4)
C6-C7-C8	125.5(4)
C6-C7-C11	117.4(4)
C8-C7-C11	117.0(4)
C7-C8-C9	119.9(5)
C8-C9-C10	121.1(5)
C9-C10-O3	108.7(4)
C9-C10-C25	112.8(4)
O3-C10-C25	109.4(4)
C9-C10-C32	112.2(4)
O3-C10-C32	104.3(4)
C25-C10-C32	109.1(4)
C7-C11-O3	121.4(4)
C7-C11-C12	122.9(4)
O3-C11-C12	115.6(4)
C11-C12-C1	116.5(4)
C11-C12-C13	126.2(5)

Atoms	Bond Angles (°)
C1-C12-C13	117.1(5)
C12-C13-C14	120.3(5)
C13-C14-C15	121.2(5)
C14-C15-O1	108.4(4)
C14-C15-C34	113.6(5)
O1-C15-C34	104.5(4)
C14-C15-C41	111.9(4)
O1-C15-C41	109.4(4)
C34-C15-C41	108.7(4)
C5-C16-C17	109.9(5)
C5-C16-C21	108.4(5)
C17-C16-C21	109.4(5)
C16-C17-C18	109.6(5)
C17-C18-C19	110.2(5)
C17-C18-C24	110.4(5)
C19-C18-C24	108.6(5)
C18-C19-C20	110.8(5)
C19-C20-C21	109.1(6)
C19-C20-C22	110.2(5)
C21-C20-C22	107.5(5)
C16-C21-C20	109.3(5)
C20-C22-C23	109.8(5)
C22-C23-C5	110.2(4)
C22-C23-C24	107.5(4)
C5-C23-C24	110.5(4)
C23-C24-C18	109.6(5)
C10-C25-C26	108.7(5)
C10-C25-C30	111.4(4)
C26-C25-C30	108.2(5)
C25-C26-C27	110.5(4)

Atoms	Bond Angles (°)
C26-C27-C28	109.2(5)
C26-C27-C33	107.8(5)
C28-C27-C33	109.0(5)
C27-C28-C29	110.5(5)
C28-C29-C30	108.7(5)
C28-C29-C31	109.8(5)
C30-C29-C31	110.0(5)
C29-C30-C25	109.7(5)
C29-C31-C32	111.1(4)
C10-C32-C31	109.4(4)
C10-C32-C33	108.1(4)
C31-C32-C33	108.0(5)
C32-C33-C27	111.2(5)
C15-C34-C35	110.0(5)
C15-C34-C39	109.1(4)
C35-C34-C39	108.5(5)
C34-C35-C36	110.5(5)
C35-C36-C37	109.5(5)
C35-C36-C42	109.9(5)
C37-C36-C42	108.7(5)
C36-C37-C38	110.4(4)
C37-C38-C39	108.9(5)
C37-C38-C40	110.1(5)
C39-C38-C40	108.6(5)
C34-C39-C38	109.8(5)
C38-C40-C41	110.2(4)
C40-C41-C15	107.9(5)
C40-C41-C42	108.7(5)
C15-C41-C42	110.8(4)
C41-C42-C36	109.9(5)

6.3.15 2,2,6,6,10,10-Hexaphenyl-3,4,7,8,11,12-hexahydro-2*H*,6*H*,10*H*-dipyrano[6,5-*f*,6',5'-*h*]chromane (176-*6H*)

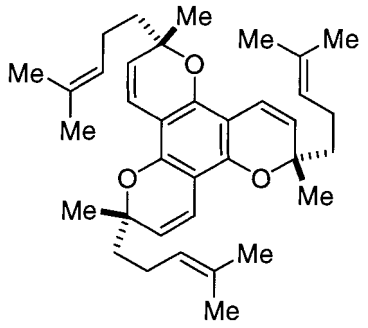


176-*6H*

A mixture of phloroglucinol (**14**) (38 mg, 0.30 mmol), *β*-phenylcinnamaldehyde (**175**) (250 mg, 1.20 mmol), phenylboronic acid (111 mg, 0.91 mmol), propionic acid (**72**) (4 drops) and benzene (10 mL) in a Dean-Stark trap was heated at reflux for 150 min. The resultant mixture was cooled to room temperature and concentrated *in vacuo* to afford the chromene **176** as a brown gum. Palladium on charcoal (210 mg, 10% w/w) was then added to a solution of the crude chromene **176** in methanol (20 mL). The reaction mixture was stirred under an atmosphere of hydrogen (balloon pressure) for 18 h. The resultant mixture was filtered through a pad of celite with dichloromethane (3 × 20 mL) and then the combined filtrates were concentrated *in vacuo*. The resultant residue was dissolved in ether (10 mL) and on filtration through a pad of silica gel with ether (125 mL) was concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (9:1) as the eluant afforded the *title compound* **176-*6H*** (59 mg, 28%) as a pale pink solid. $\mathbf{R}_f$ = 0.24, hexanes:ether (9:1); **M.p.** >245 °C, hexanes:ether; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.66 (t, J = 5.7 Hz, 6H, $ArCH_2CH_2$), 2.72 (t, J = 5.7 Hz, 6H, $ArCH_2CH_2$), 7.20 (m, 18H, Ar*H*), 7.34 (m, 12H, Ar*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 17.6, 31.5, 81.3, 102.3, 125.8, 126.8, 128.2, 144.9, 149.8; **IR** (ef) 2975, 1629, 1617, 1560, 1482, 1360, 1139, 1106, 1071 cm^{-1}; **MS** (EI) *m/z* (rel. intensity) 702 (M, 3), 675

(5), 180 (56), 90 (44), 82 (30), 77 (49), 57 (32), 44 (100), 39 (86), 18 (50); **FAB-HRMS** Calcd. for $C_{51}H_{42}O_3$: 702.3134. Found: 702.3128.

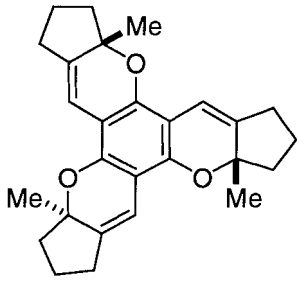
6.3.16 (2*RS*,6*RS*,10*RS*)-2,6,10-Trimethyl-2,6,10-tri-(4'-methylpent-3'-enyl)-2*H*,6*H*,10*H*-dipyrano[6,5-*f*,6',5'-*h*]chromene [(±)-178]



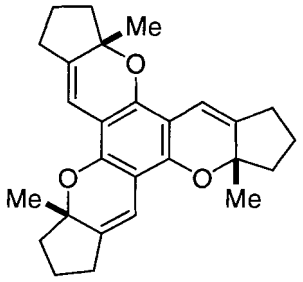
(±)-**178**

A mixture of phloroglucinol (**14**) (38 mg, 0.30 mmol), citral (**177**) (*E*:*Z* = ~2:1, 210 μL, 1.23 mmol), phenylboronic acid (113 mg, 0.93 mmol), propionic acid (**72**) (4 drops) and benzene (10 mL) in a Dean-Stark trap was heated at reflux for 4 h. The resultant solution was cooled to room temperature and on filtration through a pad of silica gel with ether (125 mL) was concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (99:1) as the eluant afforded the *title compound* (±)-**178** (97 mg, 61%) as a colourless oil. $\mathbf{R}_f$ = 0.26, hexanes:ether (99:1); **^{1}H NMR** (400 MHz, C_6D_6) δ 1.28 (apparent dd, J = 4.1, 2.4 Hz, 9H, CH_3), 1.51 (s, 9H, CH_3), 1.63 (s, 9H, CH_3), 1.69 (m, 6H, CH_2), 2.21 (m, 6H, CH_2), 5.11 (m, 3H, CHCMe$_2$), 5.20 (d, J = 10.0 Hz, 3H, ArCHCH), 6.93 (d, J = 10.0 Hz, 3H, ArCHCH); **^{13}C NMR** (101 MHz, C_6D_6) δ 17.6, 23.2, 25.8, 26.5, 41.6, 79.1, 103.5, 117.8, 124.87, 124.93, 131.3, 150.1; **IR** (ef) 2969, 2924, 2851, 1639, 1593, 1451, 1375, 1152, 1129 cm^{-1}; **MS** (EI) *m/z* (rel. intensity) 528 (M, 100), 446 (46), 69 (67), 45 (30); **Anal.** Calcd. for $C_{36}H_{48}O_3$: C, 81.77; H, 9.15. Found: C, 82.01; H, 9.31.

6.3.17 (1a-*RS*,6a-*SR*,11a-*SR*)-3,4,4a,1a,8,9,8a,6a,12,13,14a,11a-Dodecahydro-1a,6a,11a-trimethyl-tricyclopenta[*b*,*b*',*b*"]-1a*H*,6a*H*,11a*H*-dipyrano[6,5-*i*,6',5'-*k*]chromene (193-*α*) and (1a-*RS*,6a-*RS*,11a-*RS*)-3,4,4a,1a,8,9,8a,6a,12,13,14a,11a-Dodecahydro-1a,6a,11a-trimethyl-tricyclopenta[*b*,*b*',*b*"]-1a*H*,6a*H*,11a*H*-dipyrano[6,5-*i*,6',5'-*k*]chromene (193-*β*)



193-*α* *and*

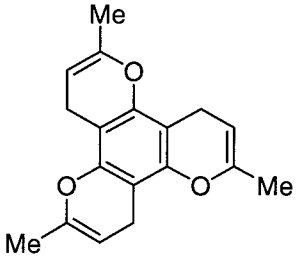


193-*β*

A mixture of phloroglucinol (**14**) (38 mg, 0.30 mmol), 2-methylcyclopent-1-enecarboxaldehyde (**165**) (134 mg, 1.22 mmol), phenylboronic acid (112 mg, 0.92 mmol), propionic acid (**72**) (4 drops) and benzene (10 mL) in a Dean-Stark trap was heated at reflux for 6 h. The resultant solution was cooled to room temperature and on filtration through a pad of silica gel with ether (125 mL) was concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (49:1) as the eluant afforded an inseparable mixture (dr = 20:1) of the *title compounds* **193-*α*** and **193-*β*** (37 mg, 31%) as a yellow solid. $\mathbf{R}_f$ = 0.26, hexanes:ether (49:1); **M.p.** 196 °C (dec.), hexanes:ether; ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 1.26 (s, 6H, 2 × C*H*$_3$ of **193-*α***), 1.28 (s, 3H, 1 × C*H*$_3$ of **193-*α***), 1.29 (s, 9H, 3 × C*H*$_3$ of **193-*β***), 1.72 (m, 3H, C*H*$_2$), 1.84 (m, 3H, C*H*$_2$), 2.01 (m, 3H, C*H*$_2$), 2.10 (m, 3H, C*H*$_2$), 2.51 (m, 6H, C*H*$_2$), 6.39 (apparent t, *J* = 2.1 Hz, 3H, 3 × ArC*H* of **195-*β***), 6.40 (apparent t, *J* = 2.1 Hz, 1H, 1 × ArC*H* of **193-*α***), 6.42 (apparent t, *J* = 2.1 Hz, 1H, 1 × ArC*H* of **193-*α***), 6.43 (apparent t, *J* = 2.1 Hz, 1H, 1 × ArC*H* of **193-*α***); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 21.3, 21.4, 21.5, 22.2, 22.4, 22.6, 22.8, 27.7, 27.8, 27.89, 27.94, 39.30, 39.34, 39.39, 39.42, 83.1, 83.3, 83.4, 106.0, 106.1, 106.4, 110.17, 110.20,

110.25, 139.3, 139.6, 147.0, 147.1, 147.4; **IR** (ef) 2963, 1667, 1595, 1431, 1366, 1151, 1125 cm^{-1}; **MS** (EI) *m/z* (rel. intensity) 402 (M, 7), 307 (8), 132 (6), 96 (6), 85 (6), 79 (15), 67 (18), 55 (27), 43 (40), 28 (100); **FAB-HRMS** Calcd. for $C_{27}H_{30}O_3$: 402.2195. Found: 402.2196.

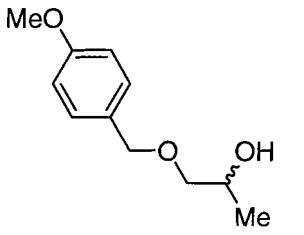
6.3.18 2,6,10-Trimethyl-4*H*,8*H*,12*H*-dipyrano[6,5-*f*;6',5'-*h*]chromene (196)



196

A mixture of phloroglucinol (**14**) (63 mg, 0.50 mmol), methyl vinyl ketone (**195**) (160 μL, 1.98 mmol), phenylboronic acid (184 mg, 1.51 mmol), propionic acid (**72**) (7 drops) and benzene (16 mL) in a Dean-Stark trap was heated at reflux for 6 h. The resultant solution was cooled to room temperature and on filtration through a pad of silica gel with ether (125 mL) was concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (99:1) as the eluant afforded the *title compound* **196** (20 mg, 14%) as a white solid. $\mathbf{R_f}$ = 0.57, hexanes:ether, 99:1; **M.p.** 111 °C (dec.), hexanes:ether; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.82 (d, J = 1.1 Hz, 9H, CH_3), 3.15 (m, 6H, $ArCH_2$), 4.65 (m, 3H, $ArCH_2CH$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 19.1, 19.2, 95.3, 101.5, 147.2, 147.9; **IR** (ef) 2928, 1707, 1621, 1467, 1379, 1326, 1303, 1184, 1101 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 283 (M + H, 100); **FAB-HRMS** Calcd. for $C_{18}H_{18}O_3$: 282.1256. Found: 282.1259.

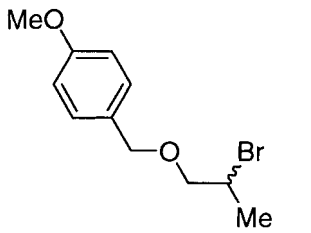
6.3.19 (±)-1-(4-Methoxybenzyloxy)propan-2-ol [(±)-210][86,87]



(±)-**210**

Propylene oxide (**209**) (7.3 mL, 10 mmol) was slowly added to a suspension of *p*-methoxybenzyl alcohol (**208**) (65 mL, 520 mmol) and sodium hydroxide (145 mg, 3.63 mmol) at 65 °C and the resultant mixture was stirred for 24 h. Purification by direct distillation of the reaction mixture at reduced pressure afforded the *title compound* (±)-**210** (10.3 g, 53%) as a colourless oil. **B.p.** 169-171 °C, 15 mm Hg; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.14 (d, J = 6.4 Hz, 3H, *Me*), 2.08 (s, 1H, O*H*), 3.25 (dd, J = 9.4, 8.3 Hz, 1H, OC*H*H), 3.44 (dd, J = 9.4, 3.5 Hz, 1H, OCH*H*), 3.25 (s, 3H, O*Me*), 3.99 (m, 1H, HOC*H*), 4.49 (s, 2H, ArCH_2O), 6.88 (d, J = 8.6 Hz, 2H, Ar*H*), 7.27 (d, J = 8.6 Hz, 2H, Ar*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 18.6, 55.1, 66.3, 72.8, 75.4, 113.7, 129.2, 130.0, 159.1; **IR** (ef) 3451, 2969, 2933, 2904, 2860, 2837, 1613, 1514, 1248, 1087, 1035 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 195 (M + H, 8), 121 (100), 45 (7).

6.3.20 (±)-1-(4-Methoxybenzyloxy)-2-bromopropane [(±)-131][88]

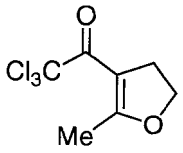


(±)-**131**

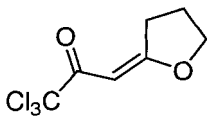
To a mixture of the alcohol (±)-**210** (9.16 g, 46.7 mmol), 2,6-lutidene (1.30 mL, 11.7 mmol) and triphenylphosphine (15.31 g, 58.4 mmol) in tetrahydrofuran (115 mL) at room temperature was added carbon tetrabromide (18.6 g, 56.0 mmol). After 56 h, the

reaction mixture was diluted with hexanes (150 mL) and filtered. The filter-cake was washed with ether:hexanes (1:1, 200 mL) and the combined filtrates were concentrated *in vacuo*. Distillation at reduced pressure afforded the *title compound* (±)-**131** (8.22 g, 68%) as a yellow oil. **B.p.** 157-165 °C, 2 mm Hg; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.70 (d, J = 6.7 Hz, 3H, *Me*), 3.55 (dd, J = 10.3, 6.6 Hz, 1H, OC*H*H), 3.66 (dd, J = 10.3, 6.2 Hz, 1H, OCH*H*), 3.81 (s, 3H, O*Me*), 4.18 (m, 1H, BrC*H*), 4.52 (s, 2H, ArCH_2O), 6.88 (d, J = 8.6 Hz, 2H, Ar*H*), 7.27 (d, J = 8.6 Hz, 2H, Ar*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 22.7, 46.9, 55.3, 72.8, 75.3, 113.8, 129.3, 129.9, 159.3; **IR** (ef) 2956, 2931, 2859, 2836, 1613, 1513, 1248, 1080, 1035 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 260 [M (^{81}Br), 3], 259 [M (^{81}Br) – H, 5], 258 [M (^{79}Br), 4], 257 [M (^{79}Br) – H, 5], 179 (M – Br, 6), 149 (19), 121 (100), 39 (20); **Anal.** Calcd. for $C_{11}H_{15}BrO_2$: C, 50.98; H, 5.83. Found: C, 50.72; H, 5.91.

6.3.21 2-Methyl-3-trichloroacetyl-4,5-dihydrofuran (213) and 1,1,1-Trichloro-3-[4-dihydrofuran-2'*E*-ylidene]propane-2-one (214)[93,94]



213 *and*



214

Method A: To a solution of 2-methyl-4,5-dihydrofuran (**114**) (0.60 mL, 6.5 mmol) and pyridine (0.79 mL, 10 mmol) in dichloromethane (8 mL) at room temperature was added trichloroacetyl chloride (1.1 mL, 10 mmol) dropwise (CAUTION: exothermic process). The reaction mixture was stirred for 15 min and then a saturated aqueous solution of sodium bicarbonate (10 mL) was added. The resultant mixture was diluted with chloroform (10 mL), washed with water (3 × 5 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification of the resultant oil by flash

chromatography using hexanes:ether (2:1) as the eluant afforded the *title compound* **213** (931 mg, 62%) as a pale yellow oil and the *title compound* **214** (542 mg, 36%) as a pale yellow solid.

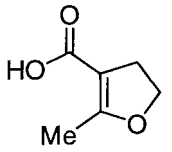
Method B: To a solution of 2-methyl-4,5-dihydrofuran (**114**) (0.20 mL, 2.2 mmol) and pyridine (0.26 mL, 3.3 mmol) in dichloromethane (5 mL) at –20 °C was added a solution of trichloroacetyl chloride (0.36 mL, 3.3 mmol) dropwise (CAUTION: exothermic process). The reaction mixture was allowed to warm to room temperature over 21 h and then a saturated aqueous solution of sodium bicarbonate (10 mL) was added. The resultant mixture was diluted with chloroform (10 mL), washed with water (2 × 10 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification of the resultant oil by flash chromatography using hexanese:ether (2:1) as the eluant afforded the *title compound* **213** (393 mg, 79%) as a pale yellow oil and *title compound* **214** (80 mg, 16%) as a pale yellow solid.

Title compound **213**:[94] $\mathbf{R}_f$ = 0.57, hexanes:ether (2:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.35 (t, J = 1.0 Hz, 3H, *Me*), 3.30 (apparent tq, J = 9.2, 1.1 Hz, 2H, OCH_2CH_2), 4.56 (apparent t, J = 9.3 Hz, 2H, OCH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 16.2, 30.6, 72.3, 97.4, 104.0, 177.3, 180.2; **IR** (ef) 2979, 2907, 1766, 1682, 1674, 1567, 1386, 1242, 1115 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 235 [M (3 × ^{37}Cl) + H, 3], 233 [M (^{35}Cl + 2 × ^{37}Cl) + H, 31], 231 [M (2 × ^{35}Cl + ^{37}Cl) + H, 100], 229 [M (3 × ^{35}Cl) + H, 88], 196 (8), 165 (22), 111 (22), 43 (30).

Title compound **214**: $\mathbf{R}_f$ = 0.32, hexanes:ether (2:1); **M.p.** 47-49 °C, hexanes:ether; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.14 (m, 2H, OCH_2CH_2), 3.17 (apparent td, J = 7.8, 1.5 Hz, 2H, $OCCH_2$), 4.35 (apparent t, J = 7.3 Hz, 2H, OCH_2), 6.23 (t, J = 1.5

Hz, 1H, C*H*COCCl$_3$); **^{13}C NMR** (101 MHz, CDCl$_3$) δ 23.1, 31.9, 73.3, 89.7, 97.4, 181.0, 184.3; **IR** (ef) 3073, 3006, 2972, 2911, 1680, 1591, 1391, 1246, 1110, 1028 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 235 [M (3 × ^{37}Cl) + H, 1], 233 [M (^{35}Cl + 2 × ^{37}Cl) + H, 8], 231 [M (2 × ^{35}Cl + ^{37}Cl) + H, 26], 229 [M (3 × ^{35}Cl) + H, 27], 165 (45), 111 (100), 69 (23), 39 (44); **Anal.** Calcd. for $C_7H_7Cl_3O_2$: C, 36.64; H, 3.07. Found: C, 36.82; H, 3.25.

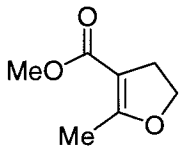
6.3.22 2-Methyl-4,5-dihydrofuran-3-carboxylic Acid (215)[70,95]



215

A mixture of the trichloroketone **213** (524 mg, 2.29 mmol) and an aqueous solution of sodium hydroxide (1 M, 3.4 mL, 3.4 mmol) was stirred at room temperature for 2 h and then cooled to 0 °C. The pH was adjusted to ~3 with hydrochloric acid (1 M) and the resultant precipitate was collected and washed with water (2 × 5 mL) and then dried *in vacuo* to afford the *title compound* **215** (140 mg, 48%) as a beige powder. $\mathbf{R_f}$ = 0.53, ether; **M.p.** 136-139 °C, water (lit.[70] 153-154 °C, benzene); **^{1}H NMR** (400 MHz, CDCl$_3$) δ2.21 (s, 3H, *Me*), 2.90 (apparent t, J = 9.4 Hz, 2H, OCH$_2$C*H*$_2$), 4.44 (apparent t, J = 9.5 Hz, 2H, OC*H*$_2$); **^{13}C NMR** (101 MHz, CDCl$_3$) δ 14.2, 29.3, 70.8, 101.8, 171.3, 171.9; **IR** (ef) 3484, 3000, 2904, 2859, 1654, 1229 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 129 (M + H, 100), 111 (15), 85 (75), 43 (50).

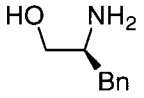
6.3.23 Methyl-2-methyl-4,5-dihydrofuran-3-carboxylate (167)[70,71,96]



167

To a solution of the trichloroketone **213** (216 mg, 0.939 mmol) in methanol (5 mL) was added sodium bicarbonate (75 mg, 0.89 mmol) and the resultant mixture was heated at reflux for 45 min. The reaction mixture was then allowed to cool to room temperature and water (20 mL) was added. The resultant mixture was extracted with ether (9 × 10 mL) and the combined organic extracts were washed with water (2 × 15 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the *title compound* **167** (128 mg, 96%) as a white solid. $\mathbf{R}_f$ = 0.43, hexanes:ether (2:1); **M.p.** 28-29 °C, ether (lit.[70] 31.5-32.5 °C, petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.17 (s, 3H, *Me*), 2.87 (apparent t, J = 9.6 Hz, 2H, OCH_2CH_2), 3.70 (s, 3H, CO_2Me), 4.39 (apparent t, J = 9.6 Hz, 2H, OCH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 13.8, 29.5, 50.6, 70.2, 101.7, 166.5, 168.7; **IR** (ef) 2952, 1705, 1651, 1438, 1388, 1334, 1229, 1084, 998 cm^{-1}; **MS** (EI) *m/z* (rel. intensity) 143 (M + H, 38), 142 (M, 18), 43 (100).

6.3.24 (*S*)-Phenylalaninol [(*S*)-217][97,99]

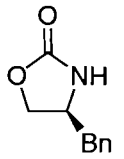


(*S*)-**217**

To a suspension of lithium aluminum hydride (26.6 g, 675 mmol) in tetrahydrofuran (700 mL) at 0 °C was added (*S*)-phenylalanine [(*S*)-**216**] (74.3 g, 450 mmol) in portions over 80 min. The resultant mixture was heated at reflux for 5 h and then stirred for an additional 15 h at room temperature before being diluted with ether (600 mL) and cooled to 0 °C. Water (26 mL), an aqueous solution of sodium hydroxide

(2 M, 26 mL) and water (78 mL) were then added in succession and the resultant mixture was filtered. The filter-cake was washed with ether (3 × 100 mL) and the combined filtrates were concentrated *in vacuo*. Purification by recrystallization from ethyl acetate afforded the *title compound* (*S*)-**217** (43.1 g, 93%) as colourless needles. **M.p.** 87-88 °C, ethyl acetate (lit.[99] 88.5-91 °C, ethyl acetate); $[\alpha]_D^{20} = -23.7$ (*c* 0.88, ethanol) [lit.[99] $[\alpha]_D = -24.7$ (*c* 1.03, ethanol)]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.88 (s, 3H, O*H* *and* NH_2), 2.52 (dd, *J* = 13.5, 8.6 Hz, 1H, C*H*HPh), 2.79 (dd, *J* = 13.5, 5.2 Hz, 1H, CH*H*Ph), 3.12 (m, 1H, NC*H*), 3.39 (dd, *J* = 10.6, 7.2 Hz, 1H, C*H*HOH), 3.64 (dd, *J* = 10.6, 3.9 Hz, 1H, CH*H*OH), 7.25 (m, 5H, Ar*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 40.6, 54.1, 66.0, 126.3, 128.5, 129.1, 138.6; **IR** (ef) 3355, 3289, 2918, 2847, 1584, 1495, 1454, 1059 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 152 (M + H, 100), 117 (13), 42 (7).

6.3.25 (*S*)-4-(Phenylmethyl)-2-oxazolidinone [(4*S*)-218][99,155]

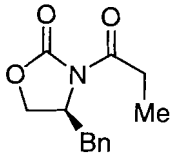


(4*S*)-**218**

A round bottom flask, that was fitted with a Vigreux column, a distillation head and a receiving flask, was charged with the amino alcohol (*S*)-**217** (43.0 g, 285 mmol), potassium carbonate (3.95 g, 28.5 mmol) and diethyl carbonate (71 mL, 586 mmol). The resultant mixture was heated at 135 °C. After the generation of ethanol had ceased (~90 min), the reaction mixture was allowed to cool to room temperature, was diluted with dichloromethane (250 mL) and washed with water (250 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification by recrystallization from ethyl acetate:hexanes (2:1) afforded the *title compound* (4*S*)-**218**

(39.9 g, 79%) as colourless plates. **M.p.** 86-87 °C, ethyl acetate:hexanes (lit.[99] 84.5-86.5 °C, ethyl acetate:hexanes); $[\alpha]_D^{20} = -62$ (*c* 1.18, chloroform) [lit.[155] $[\alpha]_D^{20} = -62$ (*c* 1.00, chloroform)]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.87 (d, J = 6.9 Hz, 2H, CH_2Ph), 4.12 (m, 2H, NC*H and* OCH*H*), 4.45 (apparent t, J = 8.3 Hz, 1H, OC*H*H), 5.53 (s, 1H, N*H*), 7.17 (m, 2H, Ar*H*), 7.30 (m, 3H, Ar*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 41.0, 53.5, 69.2, 126.9, 128.6, 128.9, 135.7, 159.7; **IR** (ef) 3287, 2922, 1754, 1711, 1406, 1064, 1096, 1021 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 178 (M + H, 100).

6.3.26 (4*S*)-4-Benzyl-3-propionyloxazolidin-2-one [(4*S*)-219][101]

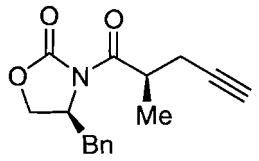


(4*S*)-**219**

To a solution of the oxazolidinone (4*S*)-**218** (39.7 g, 224 mmol) in tetrahydrofuran (650 mL) at –78 °C was added *n*-butyl lithium (90 mL, 2.5 M in hexanes, 225 mmol). The resultant mixture was allowed to stir for 15 min and then propionyl chloride (22 mL, 250 mmol) was added. The reaction mixture was stirred at –78 °C for 30 min and then was allowed to warm to room temperature over 45 min after which a saturated solution of ammonium chloride (135 mL) was added. The resultant mixture was concentrated *in vacuo* and the residue was then extracted with dichloromethane (3 × 150 mL). The combined organic extracts were washed with sodium hydroxide (1 M, 150 mL), brine (150 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The resultant crystalline solid was pulverized and triturated with cold hexanes (200 mL). Filtration and drying of the solid *in vacuo* afforded the *title compound* (4*S*)-**219** (48.9 g, 94%) as a white powder. **M.p.** 42-46 °C, hexanes (lit.[101] 44-46 °C, hexanes); $[\alpha]_D^{20} = +92$ (*c* 1.38,

ethanol) [lit.[101] $[\alpha]_D^{20}$ = + 92.9 (*c* 1.01, ethanol)]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.20 (t, J = 7.3 Hz, 3H, *Me*), 2.77 (dd, J = 13.3, 9.7 Hz, 1H, CH*H*Ph), 2.95 (m, 2H, CH_2Me), 3.29 (dd, J = 13.3, 3.2 Hz, 1H, C*H*HPh), 4.18 (m, 2H, OCH_2), 4.67 (m, 1H, NC*H*), 7.30 (m, 5H, Ar*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 8.2, 29.0, 37.7, 55.0, 66.1, 127.2, 128.8, 129.3, 135.2, 153.4, 173.9; **IR** (ef) 3029, 2982, 2941, 1790, 1706, 1455, 1352, 1249, 1210 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 234 (M + H, 100), 178 (8).

6.3.27 (2'*R*,4*S*)-4-Benzyl-3-[2'-methylpent-4'-ynoyl]oxazolidin-2-one [(+)-220]



(+)-**220**

Method A:[102] To a solution of *N*,*N*-diisopropylamine (2.7 mL, 19 mmol) in tetrahydrofuran (15 mL) at 0 °C was added *n*-butyl lithium (7.6 mL, 2.5 M in hexanes, 19 mmol, 1.1 equiv). The reaction mixture was stirred for 30 min and then cooled to –78 °C. A solution of (4*S*)-4-benzyl-3-propionyloxazolidin-2-one [(4*S*)-**219**] (3.98 g, 17.1 mmol, 1 equiv) in tetrahydrofuran (5 mL) was added and the resultant mixture was stirred for 30 min. Propargyl bromide (**71**) (2.9 mL, 80% w/w in toluene, 26 mmol, 1.5 equiv) was then added dropwise. The reaction mixture was then stirred at –78 °C for 30 min and subsequently at 0 °C for 2 h. A saturated aqueous solution of ammonium chloride (10 mL) and water (10 mL) were then added. The resultant mixture was extracted with ether (3 × 30 mL) and the combined organic extracts were washed with water (3 × 30 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification of the resultant oil by flash chromatography using hexanes:ether (2:1) as the eluant afforded

the *title compound* (+)-**220** (2.27 g, 49%) as a brown solid and as a mixture of two diastereoisomers (dr = 7:1).

Method B:[102] To a solution of *N,N*-diisopropylamine (1.4 mL, 10 mmol) in tetrahydrofuran (10 mL) at 0 °C was added *n*-butyl lithium (3.8 mL, 2.5 M in hexanes, 9.5 mmol, 1.1 equiv). The reaction mixture was stirred for 30 min and then cooled to −78 °C. A solution of (4*S*)-4-benzyl-3-propionyloxazolidin-2-one [(4*S*)-**219**] (2.00 g, 8.58 mmol, 1 equiv) in tetrahydrofuran (3 mL) was added and the resultant mixture was stirred for 30 min. Propargyl bromide (**71**) (1.5 mL, 80% w/w in toluene, 13 mmol, 1.5 equiv) was then added dropwise and the reaction mixture was allowed to warm from −78 to −20 °C over 20 h. A saturated aqueous solution of ammonium chloride (5 mL) and water (5 mL) were then added. The resultant mixture was extracted with ether (3 × 20 mL) and the combined organic extracts were washed with water (3 × 20 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification of the resultant oil by flash chromatography using hexanes:ethyl acetate (3:1) as the eluant afforded the *title compound* (+)-**220** (1.27 g, 55%) as a yellow solid and as a mixture of two diastereoisomers (dr = 6:1).

Method C:[102] To a solution of *N,N*-diisopropylamine (1.4 mL, 10 mmol) in tetrahydrofuran (10 mL) at 0 °C was added *n*-butyl lithium (3.8 mL, 2.5 M in hexanes, 9.5 mmol, 1.1 equiv). The reaction mixture was stirred for 30 min and then cooled to −78 °C. A solution of (4*S*)-4-benzyl-3-propionyloxazolidin-2-one [(4*S*)-**219**] (2.00 g, 8.58 mmol, 1 equiv) in tetrahydrofuran (3 mL) was added and the resultant mixture was stirred for 30 min. Propargyl bromide (**71**) (3.8 mL, 80% w/w in toluene, 34 mmol, 4 equiv) was then added dropwise and the reaction mixture was allowed to warm from −78

to 0 °C over 23 h. A saturated aqueous solution of ammonium chloride (5 mL) and water (5 mL) were then added. The resultant mixture was extracted with ether (3 × 20 mL) and the combined organic extracts were washed with water (3 × 20 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification of the resultant oil by flash chromatography using hexanes:ethyl acetate (3:1) as the eluant afforded the *title compound* (+)-**220** (1.24 g, 53%) as a yellow solid and as a mixture of two diastereoisomers (dr = 6:1).

Method D:[102] To a solution of *N,N*-diisopropylamine (1.9 mL, 14 mmol) in tetrahydrofuran (10 mL) at 0 °C was added *n*-butyl lithium (5.0 mL, 2.5 M in hexanes, 13 mmol, 1.5 equiv). The reaction mixture was stirred for 30 min and then cooled to −78 °C. A solution of (4*S*)-4-benzyl-3-propionyloxazolidin-2-one [(4*S*)-**219**] (2.00 g, 8.58 mmol, 1 equiv) in tetrahydrofuran (3 mL) was added and the resultant mixture was stirred for 30 min. Propargyl bromide (**71**) (3.8 mL, 80% w/w in toluene, 34 mmol, 4 equiv) was then added dropwise and the reaction mixture was allowed to warm from −78 to 0 °C over 23 h. A saturated aqueous solution of ammonium chloride (5 mL) and water (5 mL) were then added. The resultant mixture was extracted with ether (3 × 20 mL) and the combined organic extracts were washed with water (3 × 20 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification of the resultant oil by flash chromatography using hexanes:ethyl acetate (3:1) as the eluant afforded the *title compound* (+)-**220** (1.27 g, 55%) as a yellow solid and as a mixture of two diastereoisomers (dr = 6:1).

Method E:[103] To a solution of (*S*)-4-benzyl-3-propionyl-oxazolidin-2-one [(4*S*)-**219**] (1.17 g, 5.02 mmol) in dichloromethane (20 mL) at 0 °C was added titanium

tetrachloride (0.57 mL, 5.2 mmol) and the resultant mixture was allowed to stir for 5 min after which time *N,N,N*-diisopropylethylamine (0.91 mL, 5.2 mmol) was added. After 1 h, propargyl chloride (0.72 mL, 10 mmol) was then added. The resultant mixture was stirred at 0 °C for 6 h and then allowed to warm to room temperature over 18 h. TLC analysis indicated that none of the desired product had formed.

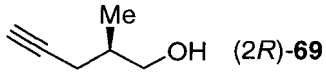
Method F:[103] To a solution of (*S*)-4-benzyl-3-propionyl-oxazolidin-2-one (4*S*)-**219**] (1.16 g, 4.98 mmol) in dichloromethane (20 mL) at 0 °C was added titanium tetrachloride (0.57 mL, 5.2 mmol) and the resultant mixture was allowed to stir for 5 min after which time *N,N,N*-diisopropylethylamine (0.91 mL, 5.2 mmol) was added. After 1 h, propargyl bromide (**71**) (1.1 mL, 80% w/w in toluene, 10 mmol) was then added. The resultant mixture was stirred at 0 °C for 6 h and then allowed to warm to room temperature over 18 h. TLC analysis indicated that none of the desired product had formed.

Method G:[104,105,106] To a solution of *N,N*-diisopropylamine (31 mL, 220 mmol) in tetrahydrofuran (170 mL) at 0 °C was added *n*-butyl lithium (81 mL, 2.5 M in hexanes, 200 mmol). The reaction mixture was stirred for 30 min and then cooled to –78 °C. Hexamethylphosphoramide (25 mL) and a solution of (4*S*)-4-benzyl-3-propionyl-oxazolidin-2-one [(4*S*)-**219**] (32.5 g, 139 mmol) in tetrahydrofuran (50 mL) were then added. The resultant mixture was stirred for 30 min and then propargyl bromide (**71**) (62 mL, 80% w/w in toluene, 560 mmol) was added dropwise. The reaction mixture was stirred at –78 °C for 20 h and then a saturated aqueous solution of ammonium chloride (80 mL) and water (80 mL) were added. The resultant mixture was extracted with ether (3 × 200 mL) and the combined organic extracts were washed with water (6 × 15 mL),

dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification of the resultant oil by flash chromatography using hexanes:ethyl acetate (2:1) as the eluant afforded the *title compound* (+)-**220** (29.1 g, 77%) as a brown solid and as a single diastereoisomer. This material was recrystallized from ether:hexanes (2:1) to afford the *title compound* (+)-**220** as a cream coloured solid.

Title compound (+)-**220**: $\mathbf{R}_f$ = 0.34, hexanes:ethyl acetate (2:1); **M.p.** 52-54 °C, ether:hexanes; $[\alpha]_D^{20}$ = + 56.2 (*c* 1.18, chloroform); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.29 (d, *J* = 6.8 Hz, 3H, *Me*), 2.03 (apparent t, *J* = 2.7 Hz, 1H, CC*H*), 2.49 (ddd, *J* = 16.8, 6.6, 2.7 Hz, 1H, C*H*HCC), 2.61 (ddd, *J* = 16.8, 6.7, 2.7 Hz, 1H, CH*H*CC), 2.78 (dd, *J* = 13.4, 9.5 Hz, 1H, C*H*HPh), 3.31 (dd, *J* = 13.4, 3.2 Hz, 1H, CH*H*Ph), 3.95 (m, 1H, C*H*Me), 4.20 (m, 2H, CH_2O), 4.70 (m, 1H, C*H*N), 7.30 (m, 5H, *Ph*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 16.4, 22.4, 37.1, 37.7, 55.1, 66.0, 70.0, 81.2, 127.2, 128.8, 129.3, 135.1, 152.9, 174.9; **IR** (ef) 3288, 3029, 2987, 2977, 2917, 1779, 1698, 1389, 1350, 1244, 1209 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 272 (M + H, 100), 217 (22), 135 (14), 39 (27); **Anal.** Calcd. for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.80; H, 6.46; N, 5.33.

6.3.28 (2*R*)-2-Methylpent-4-yn-1-ol [(2*R*)-69][55,56,102]

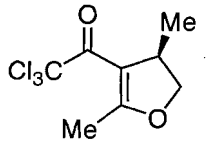


(2*R*)-**69**

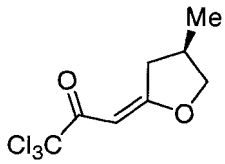
To a suspension of lithium aluminum hydride (11.3 g, 298 mmol) in tetrahydrofuran (300 mL) at 0 °C was added a solution of the oxazolidinone (+)-**220** (26.8 g, 99.0 mmol) in tetrahydrofuran (65 mL) and the resultant suspension was stirred for 45 min. Water (11 mL), an aqueous solution of sodium hydroxide (2 M, 11 mL) and an additional quantity of water (34 mL) were then added. The resultant mixture was

filtered and the filter-cake was washed with ether (3 × 150 mL). The combined filtrates were concentrated *in vacuo* and the resultant oil was purified by distillation at reduced pressure to afford the *title compound* (2*R*)-**69** (7.1 g, 73%) as a colourless oil. $\mathbf{R}_f = 0.47$, ethyl acetate:hexanes (2:1); **B.p.** 67-72 °C, ~12 mm Hg; $[\alpha]_D^{20}$ = + 11.4 (*c* 1.10, chloroform); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.01 (d, J = 6.9 Hz, 3H, CH_3), 1.56 (broad s, 1H, O*H*), 1.90 (m, 1H, C*H*CH_3), 1.98 (t, J = 2.7 Hz, 1H, *H*CC), 2.21 (ddd, J = 16.8, 6.4, 2.7 Hz, 1H, CC*H*H), 2.29 (ddd, J = 16.8, 6.2, 2.7 Hz, 1H, CCH*H*), 3.59 (d, J = 6.1 Hz, 2H, CH_2O); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 16.0, 22.2, 34.8, 66.8, 69.6, 82.6; **IR** (ef) 3409, 2961, 2922, 2117, 1461, 1430, 1037, 651 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 99 (M + H, 100).

6.3.29 (4*R*)-2,4-Dimethyl-3-trichloroacetyl-4,5-dihydrofuran [(4*R*)-223] and (4'*R*)-1,1,1-Trichloro-3-[4'-methyldihydrofuran-2'*E*-ylidene]propane-2-one [(4*R*)-224][93,94]



(4*R*)-**223** *and*



(4*R*)-**224**

Method A: To a solution of the dihydrofuran (2*R*)-**61** (699 mg, 7.13 mmol) and pyridine (0.87 mL, 11 mmol) in dichloromethane (5 mL) at room temperature was added trichloroacetyl chloride (1.2 mL, 11 mmol) dropwise (CAUTION: exothermic process). The reaction mixture was stirred for 30 min and then a saturated aqueous solution of sodium bicarbonate (10 mL) was added. The resultant mixture was diluted with dichloromethane (20 mL), was washed with water (2 × 10 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification of the resultant oil by flash chromatography using hexanes:ether (19:1) as the eluant afforded the *title compound*

(4*R*)-**223** (788 mg, 45%) as a pale yellow oil and the *title compound* (4*R*)-**224** (790 mg, 46%) as a pale yellow solid.

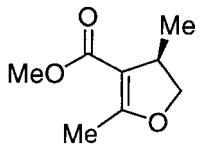
Method B: To a solution of the dihydrofuran (2*R*)-**61** (4.58 g, 46.7 mmol) and pyridine (5.6 mL, 70 mmol) in dichloromethane (90 mL) at –78 °C was added a solution of trichloroacetyl chloride (7.8 mL, 70 mmol) in dichloromethane (10 mL). The reaction mixture was allowed to warm to room temperature over 21 h and then a saturated aqueous solution of sodium bicarbonate (50 mL) was added. The resultant mixture was washed with water (2 × 50 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification of the resultant oil by flash chromatography using dichloromethane:ether (19:1) as the eluant afforded the *title compound* (4*R*)-**223** (10.5 g, 93%) as a pale yellow oil.

Title compound (4*R*)-**223**: $\mathbf{R}_f$ = 0.41, hexanes:ether (9:1); $[\alpha]_D^{20}$ = + 44.1 (*c* 1.20, chloroform); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.28 (d, *J* = 6.4 Hz, 3H, *Me*-4), 2.29 (s, 3H, *Me*-2), 3.57 (m, 1H, C*H*Me), 4.21 (dd, *J* = 8.9, 2.3 Hz, 1H, OC*H*H), 4.48 (apparent t, *J* = 8.5 Hz, 1H, OCH*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 16.2, 21.2, 37.6, 79.4, 108.6, 111.6, 176.7, 178.3; **IR** (ef) 2972, 2929, 2896, 1801, 1687, 1558, 1387, 1374, 1322, 1248, 1182 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 249 [M (3 × ^{37}Cl) + H, 3], 247 [M (^{35}Cl + 2 × ^{37}Cl) + H, 31], 245 [M (2 × ^{35}Cl + ^{37}Cl) + H, 100], 243 [M (3 × ^{35}Cl) + H, 86], 180 (17), 125 (33), 83 (7) 39 (34).

Title compound (4*R*)-**224**: $\mathbf{R}_f$ = 0.15, hexanes:ether (19:1); **M.p.** 39-40 °C, hexanes:ether; $[\alpha]_D^{20}$ = + 51.5 (*c* 1.41, chloroform); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.15 (d, *J* = 6.8 Hz, 3H, *Me*), 2.62 (m, 1H, C*H*Me), 2.86 (ddd, *J* = 19.0, 6.8, 1.5 Hz, 1H,

C*H*HCHMe), 3.43 (ddd, J = 19.0, 8.1, 1.4 Hz, 1H, CH*H*CHMe), 3.95 (dd, J = 8.8, 6.7 Hz, 1H, C*H*HO), 4.45 (dd, J = 8.8, 6.7 Hz, 1H, CH*H*O), 6.30 (apparent t, J = 1.5 Hz, 1H, C*H*COCCl$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 17.5, 31.4, 40.0, 79.2, 90.3, 97.6, 181.0, 184.3; **IR** (ef) 2967, 2906, 1694, 1600, 1391, 1365, 1237, 1102 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 249 [M (3 × ^{37}Cl) + H, 3], 247 [M (1 × ^{35}Cl + 2 × ^{37}Cl) + H, 31], 245 [M (2 × ^{35}Cl + 1 × ^{37}Cl) + H, 100], 243 [M (3 × ^{35}Cl) + H, 84], 210 (414), 180 (6), 125 (6), 39 (14); **Anal.** Calcd. for $C_8H_9Cl_3O_2$: C, 39.46; H, 3.73. Found: C, 39.26; H, 3.85.

6.3.30 (4*R*)-Methyl-2,4-dimethyl-4,5-dihydrofuran-3-carboxylate [(4*R*)-206][96]

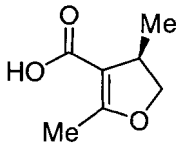


(4*R*)-**206**

To a solution of the trichloroketone (4*R*)-**223** (10.1 g, 41.6 mmol) in methanol (250 mL) was added sodium bicarbonate (1.33 g, 15.8 mmol) and the resultant mixture was heated at reflux for 1 h. The reaction mixture was then allowed to cool to room temperature and water (650 mL) was added. The resultant mixture was extracted with ether (9 × 80 mL) and the combined organic extracts were washed with water (2 × 75 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the *title compound* (4*R*)-**206** (6.34 g, 98%) as a yellow oil. Attempted purification of this material by flash column chromatography using hexanes:ether (9:1) as the eluant resulted in partial loss of material and did not significantly increase the purity of the reaction product. $\mathbf{R}_f$ = 0.32, hexanes:ether (9:1); $[\alpha]_D^{20}$ = + 27.2 (*c* 1.10, chloroform); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.14 (d, J = 6.7 Hz, 3H, *Me*-4), 2.14 (s, 3H, *Me*-2), 3.18 (m, 1H, C*H*Me), 3.67 (s, 3H, CO_2*Me*), 3.95 (dd, J = 8.9, 5.1 Hz, 1H, OC*H*H), 4.41 (apparent t, J

= 9.0 Hz, 1H, OCH*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 14.2, 19.9, 36.8, 50.5, 77.7, 107.6, 166.5, 168.6; **IR** (ef) 2955, 1800, 1700, 1648, 1436, 1387, 1340, 1185 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 157 (M + H, 100), 125 (7), 39 (12).

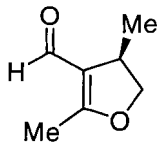
6.3.31 (4*R*)-2,4-Dimethyl-4,5-dihydrofuran-3-carboxylic Acid [(4*R*)-225][95]



(4*R*)-**225**

To a solution of the trichloroketone (4*R*)-**223** (711 mg, 293 mmol) in tetrahydrofuran (5 mL) and water (5 mL) was added lithium hydroxide dihydrate (248 mg, 5.90 mmol) at room temperature. After 15 min, the pH was adjusted to ~ 3 with concentrated hydrochloric acid and the resultant mixture was extracted with chloroform (3 × 15 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford the *title compound* (4*R*)-**225** (363 mg, 88%) as a waxy yellow solid. $\mathbf{R}_f$ = 0.50, ethyl acetate:hexanes (2:1); **M.p.** 35-36 °C, ethyl acetate:hexanes; $[\alpha]_D^{20}$ = + 46.0 (*c* 1.12, chloroform); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.21 (d, J = 6.7 Hz, 3H, *Me*-4), 2.21 (d, J = 1.1 Hz, 3H, *Me*-2), 3.25 (m, 1H, C*H*Me), 4.02 (dd, J = 9.1, 5.2 Hz, 1H, OC*H*H), 4.49 (apparent t, J = 9.3 Hz, 1H, OCH*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 14.6, 19.9, 36.6, 78.2, 107.4, 171.2, 171.9; **IR** (ef) 3434 (br), 2963, 2903, 2643, 2588, 1671, 1619, 1441, 1387, 1331, 1229 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 143 (M + H, 100); **Anal.** Calcd. for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 59.41; H, 7.23.

6.3.32 (4*R*)-2,4-Dimethyl-4,5-dihydrofuran-3-carboxaldehyde [(4*R*)-127][69]

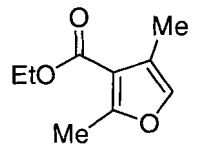


(4*R*)-**127**

A solution of the ester (4*R*)-**206** (656 mg, 4.21 mmol) in ether (10 mL) was added to a suspension of lithium aluminum hydride (243 mg, 6.39 mmol) in ether (20 mL) at 0 °C. The resultant mixture was allowed to warm to room temperature over 20 min and then was cooled to 0 °C. Water (0.24 mL), an aqueous solution of sodium hydroxide (2 M, 0.24 mL) and water (0.72 mL) were then added in succession and the resultant mixture was filtered. The filter-cake was washed ether (3 × 25 mL) and the combined filtrates were concentrated *in vacuo* to afford the alcohol **226** as pale yellow oil. A suspension of this material and manganese dioxide (13.1 g, 151 mmol) in dichloromethane (70 mL) was stirred at room temperature for 46 h. The reaction mixture was then filtered through a pad of celite, the filter-cake was washed with dichloromethane (3 × 50 mL) and the combined filtrates were concentrated *in vacuo*. Purification by distillation at reduced pressure afforded the impure *title compound* (4*R*)-**127** (180 mg, ~70 % pure, 34% over two steps) as a pale yellow oil. Attempted further purification did not significantly increase the purity of the product. $[\alpha]_D^{20}$ = + 26.5 (*c* 1.04, chloroform) [lit.[69] $[\alpha]_D^{20}$ = + 38.9 (*c* 0.61, chloroform)]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.19 (d, *J* = 6.7 Hz, 3H, *Me*-4), 2.15 (s, 3H, *Me*-2), 3.32 (m, 1H, *H*-4), 4.04 (dd, *J* = 9.2, 5.2 Hz, 1H, *H*-5), 4.53 (apparent t, *J* = 9.2 Hz, 1H, *H*-5), 9.69 (s, 1H, C*H*O); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 12.4, 19.2, 34.8, 79.2, 174.6, 185.0; **IR** (ef) 2966, 2930, 2902, 1754, 1683, 1652, 1632, 1453, 1393, 1243 cm^{-1}. **MS** (CI) *m/z* (rel. intensity) 127 (M + H, 100), 39 (12).

6.4 Experimental Concerning Chapter Four

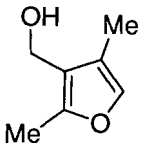
6.4.1 Ethyl-2,4-dimethyl-3-furanoate (49)[108,156]



49

To a solution of propargyl bromide (**71**) (24.0 mL, 80% w/w in toluene, 216 mmol) in acetonitrile at room temperature was added dimethyl sulfide (16.0 mL, 216 mmol) and the reaction mixture was stirred for 24 h. The resultant precipitate was collected and washed with ether (3 × 75 mL) and then dried *in vacuo* to afford dimethyl-2-propynyl sulfonium bromide (34.7 g, 89%) as a colourless crystalline solid. A portion of this material (24.0 g, 133 mmol) was added to a solution of sodium ethoxide (133 mmol) and ethyl acetoacetate (16.9 mL, 133 mmol) in ethanol (250 mL) at 0 °C. The resultant mixture was heated at reflux for 10 h and then allowed to cool to room temperature. The solvent was removed by distillation at atmospheric pressure and the residue was suspended in ether (300 mL). The resultant mixture was filtered and the filtrate was concentrated *in vacuo*. Purification by distillation at reduced pressure afforded the *title compound* **49** (21.9 g, 98%) as a colourless oil. $\mathbf{R}_f$ = 0.64, hexanes:ether (1:1); **B.p.** 73-79 °C, ~2 mm Hg (lit.[156] 100 °C, 16 mm Hg); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.35 (t, J = 7.0 Hz, 3H, CH_2*Me*), 2.13 (d, J = 1.2 Hz, 3H, *Me*-4), 2.53 (s, 3H, *Me*-2), 4.27 (q, J = 7.2 Hz, 3H, *C*H_2Me), 7.02 (d, J = 1.2 Hz, 1H, *H*-5); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 9.9, 14.2, 59.7, 113.4, 121.1, 137.5, 159.9, 164.8; **IR** (ef) 2981, 2876, 1707, 1638, 1611, 1406, 1069 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 169 (M + H, 100).

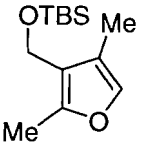
6.4.2 2,4-Dimethyl-3-hydroxymethylfuran (50)[109]



50

A solution of the ester **49** (7.51 g, 44.7 mmol) in ether (15 mL) was added to a suspension of lithium aluminum hydride (6.79 g, 179 mmol) in ether (75 mL) at 0 °C. The resultant mixture was allowed to warm to room temperature over 20 min and then was cooled to 0 °C. Water (7 mL), an aqueous solution of sodium hydroxide (2 M, 7 mL) and water (20.5 mL) were then added in succession. The resultant mixture was filtered and the filter-cake was washed with ether (3 × 60 mL) and then the combined filtrates were concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (1:1) as the eluant afforded the *title compound* **50** (5.16 g, 92%) as a cream coloured solid. $\mathbf{R}_f$ = 0.26, hexanes:ether (1:1); **M.p.** 34-35 °C, hexanes:ether; **^{1}H NMR** (400 MHz, C_6D_6) δ 1.85 (d, J = 1.1 Hz, 3H, *Me*-4), 1.96 (s, 3H, *Me-2*), 4.12 (s, 2H, CH_2OH), 6.88 (apparent d, J = 0.9 Hz, 1H, *H*-5); **^{13}C NMR** (101 MHz, C_6D_6) δ 8.2, 11.5, 55.0, 119.9, 120.8, 137.3, 149.8; **IR** (ef) 3357, 2938, 2884, 1635, 1571, 1443, 1408, 1279, 1118 cm^{-1}; **MS** (EI) *m/z* (rel. intensity) 127 (M + H, 36), 109 (M – OH, 100).

6.4.3 2,4-Dimethyl-3-*t*-butyldimethylsilyloxymethylfuran (230)



230

Method A:[118] To a solution of the alcohol **50** (63 mg, 0.50 mmol) in tetrahydrofuran (4 mL) at 0 °C was added *n*-butyl lithium (0.44 mL, 2.5 M in hexanes,

1.1 mmol). After 2 h, a solution of *t*-butyldimethylsilyl chloride (77 mg, 0.51 mmol) in tetrahydrofuran (3 mL) was added and the resultant mixture was allowed to warm to room temperature over 18 h. The reaction mixture was then diluted with ether (10 mL), was washed with a saturated aqueous solution of ammonium chloride (3 × 10 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (1:1) as the eluant afforded the *title compound* **230** (62 mg, 52%) as a colourless oil.

Method B: To a solution of the alcohol **50** (31 mg, 0.25 mmol) in tetrahydrofuran (2 mL) at room temperature was added *n*-butyl lithium (0.25 mL, 2.5 M in hexanes, 0.63 mmol). After 2 h, a solution of *t*-butyldimethylsilyl chloride (37 mg, 0.25 mmol) in tetrahydrofuran (2 mL) was added and the resultant mixture was stirred for 18 h. The reaction mixture was then diluted with ether (10 mL), was washed with a saturated aqueous solution of ammonium chloride (3 × 10 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (1:1) as the eluant afforded the *title compound* **230** (34 mg, 57%) as a colourless oil.

Method C: To a solution of the alcohol **50** (38 mg, 0.30 mmol) in tetrahydrofuran (3 mL) at room temperature was added *n*-butyl lithium (0.30 mL, 2.5 M in hexanes, 0.75 mmol). The resultant mixture was heated at reflux for 2 h. After cooling to room temperature, a solution of *t*-butyldimethylsilyl chloride (46 mg, 0.31 mmol) in tetrahydrofuran (3 mL) was added and the resultant mixture was allowed to stir 20 h. The reaction mixture then was diluted with ether (10 mL), was washed with a saturated aqueous solution of ammonium chloride (3 × 10 mL), dried over anhydrous

sodium sulfate and concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (9:1) as the eluant afforded the *title compound* **230** (25 mg, 35%) as a colourless oil.

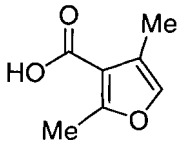
Method D: To a solution of the alcohol **50** (64 mg, 0.51 mmol) in tetrahydrofuran (5 mL) at –78 °C was added *t*-butyl lithium (0.65 mL, 1.7 M in pentane, 1.11 mmol) and the resultant mixture was allowed to warm to room temperature over 4 h. A solution of *t*-butyldimethylsilyl chloride (75 mg, 0.51 mmol) in tetrahydrofuran (3 mL) was then added and the reaction mixture was stirred at room temperature for 18 h. The resultant mixture was then diluted with ether (10 mL), was washed with a saturated aqueous solution of ammonium chloride (3 × 10 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (9:1) as the eluant afforded the *title compound* **230** (81 mg, 68%) as a colourless oil.

Method E:[120] To a solution of the alcohol **50** (101 mg, 0.80 mmol) and *t*-butyldimethylsilyl chloride (130 mg, 0.87 mmol) in *N,N*-dimethylformamide (3 mL) at room temperature was added imidazole (190 mg, 2.75 mmol). After 46 h, the reaction mixture was diluted with ethyl acetate (20 mL) and washed with brine (4 × 15 mL). The combined aqueous layers were extracted with ethyl acetate (4 × 25 mL) and the combined organic layers were then dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (9:1) as the eluant afforded the *title compound* **230** (192 mg, 99%) as a colourless oil.

Title compound **230**: $\mathbf{R}_f$ = 0.63, hexanes:ether (9:1); **^{1}H NMR** (500 MHz, C_6D_6) δ 0.03 (s, 6H, 2 × Si*Me*), 0.95 (s, 9H, 3 × Si*t-Bu*), 1.94 (s, 3H, *Me*-4), 2.05 (s, 3H, *Me*-2),

4.37 (s, 2H, CH_2O), 6.91 (s, 1H, Ar*H*); **^{13}C NMR** (126 MHz, C_6D_6) δ –5.2, 8.6, 11.8, 18.4, 26.1, 56.3, 119.7, 120.9, 137.3, 148.9; **IR** (ef) 2953, 2928, 2853, 1569, 1476, 1413, 1255, 1063 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 241 (M + H, 100), 183 (38), 109 (92); **Anal.** Calcd. for $C_{13}H_{24}O_2Si$: C, 64.95; H, 10.06. Found: C, 64.73; H, 9.86.

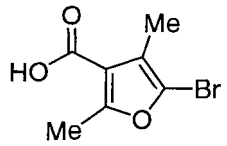
6.4.4 2,4-Dimethyl-3-furanoic Acid (237)[124]



237

The ester **49** (6.04 g, 36.0 mmol) and an aqueous solution of sodium hydroxide (125 mL, 5% w/v) were heated at reflux for 3.5 h and then cooled to room temperature. The pH was adjusted to ~ 2 with hydrochloric acid (1 M) and the resultant mixture was extracted with chloroform (3 × 120 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by flash chromatography using ether as the eluant afforded the *title compound* **237** (4.90 g, 97%) as a white solid. Purification by crystallization from petroleum ether afforded fine colourless needles. $\mathbf{R}_f$ = 0.57, ether; **M.p.** 118-119 °C, petroleum ether (lit.[124] 122 °C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.16 (s, 3H, *Me*-4), 2.58 (s, 3H, *Me-2*), 7.06 (s, 1H, *H*-5), 10.27 (s, 1H, CO_2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 9.9, 14.6, 112.8, 121.5, 137.9, 162.0, 170.8; **IR** (ef) 3590, 2978, 2929, 1673, 1611, 1562, 1441, 1312, 1281, 1118, 916 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 141 (M + H, 100).

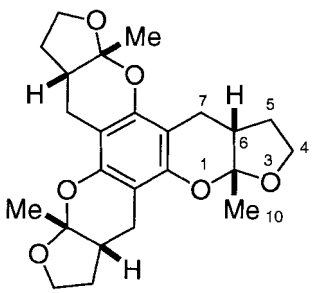
6.4.5 2,4-Dimethyl-5-bromo-3-furanoic Acid (238)[125]



238

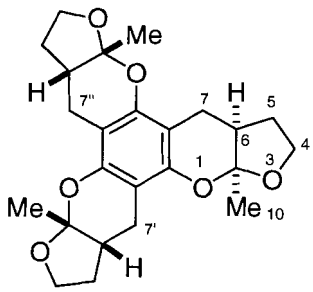
To a solution of the carboxylic acid **237** (200 mg, 1.43 mmol) in acetic acid (2 mL) at 0 °C was added bromine (108 μL, 2.13 mmol) and the resultant mixture was allowed to warm to room temperature over 20 min. The reaction mixture was then concentrated *in vacuo* and the residue was poured onto crushed ice (~3 g). The resultant solid was collected by filtration, rinsed with cold water (3 × 2 mL) and dried *in vacuo*. Purification by recystalization from water afforded the *title compound* **238** (169 mg, 54%) as a yellow solid. $\mathbf{R}_f$ = 0.33, hexanes:ether (1:1); **M.p.** 147 °C (dec.), water [lit.[125] 154 °C (dec.), water]; **^{1}H NMR** [400 MHz, $(CD_3)_2CO$] δ 2.09 (s, 3H, *Me*-4), 2.53 (s, 3H, *Me-2*), 11.14 (s, 1H, CO_2H); **^{13}C NMR** [101 MHz, $(CD_3)_2CO$] δ 11.8, 15.2, 117.0, 120.4, 122.2, 162.5, 165.4; **IR** (ef) 3348, 2919, 2852, 1680, 1606, 1562, 1442, 1297, 1115 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 221 [M (^{81}Br) + H, 100], 219 [M (^{79}Br) + H, 100], 141 (92).

6.4.6 (±)-11-Trinorxyloketal A [(±)-18] and (±)-2,6-*epi*-11,11',11''-Trinorxyloketal A [(±)-19][9,11,110,111]



(±)-**18**

and



(±)-**19**

Method A: To a suspension of phloroglucinol (**14**) (38 mg, 0.30 mmol, 1 equiv), the alcohol **168** [prepared from the corresponding ester **167** (260 mg, 1.83 mmol, 6

equiv)] and anhydrous magnesium sulfate (0.25 g) in ether (5 mL) at 0 °C was added boron trifluoride diethyl etherate (0.10 mL, 0.80 mmol, 2.7 equiv). The resultant mixture was stirred at 0 °C for 15 min. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 10 mL). The combined filtrates were washed with water (3 × 10 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by flash chromatography using ether:hexanes (3:1) as the eluant afforded a mixture (dr = 2:7) of the *title compounds* (±)-**18** and (±)-**19** (45 mg, 36%) as a solid white foam.

Method B: To a suspension of phloroglucinol (**14**) (38 mg, 0.30 mmol, 1 equiv), the alcohol **168** [prepared from the corresponding ester **167** (254 mg, 1.79 mmol, 6 equiv)] and anhydrous magnesium sulfate (0.25 g) in ether (5 mL) at -78 °C was added boron trifluoride diethyl etherate (0.10 mL, 0.80 mmol, 2.7 equiv). The resultant mixture was stirred at -78 °C for 15 min. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 10 mL). The combined filtrates were washed with water (3 × 10 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by flash chromatography using ether:hexanes (3:1) as the eluant afforded a mixture (dr = 2:7) of the *title compounds* (±)-**18** and (±)-**19** (43 mg, 35%) as a solid white foam.

Method C: To a suspension of phloroglucinol (**14**) (38 mg, 0.30 mmol, 1 equiv), the alcohol **168** [prepared from the corresponding ester **167** (254 mg, 1.79 mmol, 6 equiv)] and anhydrous magnesium sulfate (0.25 g) in ether (5 mL) at 0 °C was added boron trifluoride diethyl etherate (50 μL, 0.40 mmol, 1.3 equiv). The resultant mixture was stirred at 0 °C for 15 min. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 10 mL). The combined filtrates were washed with water (3 ×

10 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by flash chromatography using ether:hexanes (3:1) as the eluant afforded a mixture (dr = 2:7) of the *title compounds* (±)-**18** and (±)-**19** (85 mg, 69%) as a solid white foam.

Method D: To a suspension of phloroglucinol (**14**) (38 mg, 0.30 mmol, 1 equiv), a solution of the alcohol **168** in ether [(3.0 mL, 1.8 mmol, 6 equiv) prepared from the corresponding ester **167** (854 mg, 6.01 mmol) in ether (10.0 mL)] and anhydrous magnesium sulfate (0.25 g) in ether (2 mL) at 0 °C was added boron trifluoride diethyl etherate (38 μL, 0.30 mmol, 1 equiv). The resultant mixture was stirred at 0 °C for 15 min. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 10 mL). The combined filtrates were washed with water (3 × 10 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by flash chromatography using ether:hexanes (3:1) as the eluant afforded a mixture (dr = 2:7) of the *title compounds* (±)-**18** and (±)-**19** (115 mg, 93%) as a solid white foam.

Method E: To a suspension of phloroglucinol (**14**) (38 mg, 0.30 mmol, 1 equiv), a solution of the alcohol **168** [(3.0 mL, 1.8 mmol, 6 equiv) prepared from the corresponding ester **167** (854 mg, 6.01 mmol) in ether (10.0 mL)] and anhydrous magnesium sulfate (0.25 g) in ether (2 mL) at 0 °C was added boron trifluoride diethyl etherate (19 μL, 0.15 mmol, 0.5 equiv). The resultant mixture was stirred at 0 °C for 15 min. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 10 mL). The combined filtrates were washed with water (3 × 10 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by flash chromatography using ether:hexanes (3:1) as the eluant afforded a mixture (dr = 2:7) of the *title compounds* (±)-**18** and (±)-**19** (95 mg, 77%) as a solid white foam.

Method F: To a suspension of phloroglucinol (**14**) (38 mg, 0.30 mmol, 1 equiv), a solution of the alcohol **168** [(3.0 mL, 1.8 mmol, 6 equiv) prepared from the corresponding ester **167** (854 mg, 6.01 mmol) in ether (10.0 mL)] and anhydrous magnesium sulfate (0.25 g) in ether (2 mL) at 0 °C was added boron trifluoride diethyl etherate (9 μL, 0.08 mmol, 0.25 equiv). The resultant mixture was stirred at 0 °C for 15 min. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 10 mL). The combined filtrates were washed with water (3 × 10 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by flash chromatography using ether:hexanes (3:1) as the eluant afforded a mixture (dr = 2:7) of the *title compounds* (±)-**18** and (±)-**19** (95 mg, 77%) as a solid white foam.

Method G: To a suspension of phloroglucinol (**14**) (38 mg, 0.30 mmol, 1 equiv), a solution of the alcohol **168** [(3.0 mL, 1.8 mmol, 6 equiv) prepared from the corresponding ester **167** (860 mg, 6.06 mmol) in ether (10.0 mL)] and anhydrous magnesium sulfate (0.25 g) in ether (2 mL) at 0 °C was added an aqueous solution of hydrogen fluoride (1 drop, 48% w/v). The resultant mixture was stirred at 0 °C for 15 min. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 10 mL). The combined filtrates were washed with water (3 × 10 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by flash chromatography using ether:hexanes (3:1) as the eluant afforded a mixture (dr = 2:7) of the *title compounds* (±)-**18** and (±)-**19** (88 mg, 71%) as a solid white foam.

Method H: To a suspension of phloroglucinol (**14**) (38 mg, 0.30 mmol, 1 equiv), a solution of the alcohol **168** [(3.0 mL, 1.8 mmol, 6 equiv) prepared from the corresponding ester **167** (860 mg, 6.06 mmol) in ether (10.0 mL)] and anhydrous

magnesium sulfate (0.25 g) in ether (2 mL) at 0 °C was added *p*-toluenesulfonic acid monohydrate (57 mg, 0.30 mmol, 1 equiv). The resultant mixture was stirred at 0 °C for 15 min. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 10 mL). The combined filtrates were washed with water (3 × 10 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by flash chromatography using ether:hexanes (3:1) as the eluant afforded a mixture (dr = 2:7) of the *title compounds* (±)-**18** and (±)-**19** (96 mg, 77%) as a solid white foam.

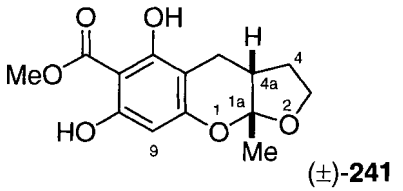
Method I: To a suspension of phloroglucinol (**14**) (38 mg, 0.30 mmol, 1 equiv), a solution of the alcohol **168** [(3.0 mL, 1.8 mmol, 6 equiv) prepared from the corresponding ester **167** (860 mg, 6.06 mmol) in ether (10.0 mL)] and anhydrous magnesium sulfate (0.25 g) in ether (2 mL) at 0 °C was added acetic acid (17 μL, 0.30 mmol). The resultant mixture was stirred at allowed to warm up to room temperature and was stirred for 72 h. TLC analysis indicated that none of the desired reaction products (±)-**18** and (±)-**19** had formed.

Method J: A suspension of phloroglucinol (**14**) (38 mg, 0.30 mmol, 1 equiv), the alcohol **168** [prepared from the corresponding ester **167** (254 mg, 1.79 mmol, 6 equiv)] and anhydrous magnesium sulfate (0.25 g) in ether (5 mL) at 0 °C was allowed to warm to room temperature over 4.5 h. TLC analysis indicated that none of the desired reaction products (±)-**18** and (±)-**19** had formed.

Recrystallization from petroleum ether, on slow evaporation of the solvent, afforded an analytically pure mixture (dr = 2:7) of the *title compounds* (±)-**18** and (±)-**19** as a white solid. $\mathbf{R}_f$ = 0.32, ether:hexanes (3:1); **M.p.** 139-143 °C, petroleum ether [lit.[9] 155-157 °C, petroleum ether for a mixture (dr = 1:4) of the *title compounds* (±)-**18** and

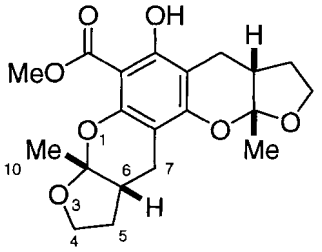
(±)-**19**]; **^{1}H NMR** (400 MHz, C_6D_6) δ 1.44 (s, 3H, *Me*-10 of (±)-**19**), 1.45 (s, 3H, *Me*-10 of (±)-**19**), 1.47 (s, 3H, *Me*-10 of (±)-**19**), 1.48 (s, 9H, *Me*-10 of (±)-**18**), 1.51 (m, 3H, *H*-5), 1.65 (m, 3H, *H*-5), 1.94 (m, 3H, *H*-6), 2.74 (m, 3H, *H*-7), 3.05 (m, 3H, *H*-7), 3.62 (m, 3H, *H*-4), 3.90 (m, 3H, *H*-4); **^{13}C NMR** (101 MHz, C_6D_6) δ 20.8, 20.9, 22.9, 23.0, 23.2, 23.3, 29.4, 29.5, 66.57, 66.59, 99.7, 99.8, 106.9, 107.0, 107.1, 107.2, 150.86, 150.93, 151.0, 151.1; **IR** (ef) 2981, 2936, 2885, 2852, 1617, 1455, 1371, 1179, 1105, 1003 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 415 (M + H, 31), 414 (M, 15), 373 (10), 331 (100), 97 (9), 43 (32); **Anal.** Calcd. for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30. Found: C, 69.34; H, 7.48.

6.4.7 (1a*RS*,4a*RS*)-3,4,4a,1a-Tetrahydro-6,8-dihyroxy-1a-methyl-furo[*b*]chromane-7-methylcarboxylate [(±)-241], (±)-11,11'-Dinorxyloketal B-13-methylcarboxylate [(±)-115], (±)-2,6-*epi*-11,11'-Dinorxyloketal B-13-methylcarboxylate [(±)-242], (±)-11,11'-Dinorxyloketal C-13-methylcarboxylate [(±)-116] and (±)-2,6-*epi*-11,11'-Dinorxyloketal C-13-methylcarboxylate (243)



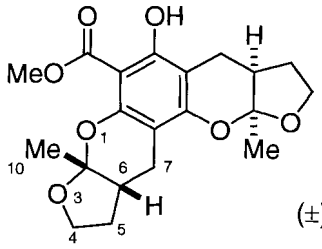
(±)-**241**

and



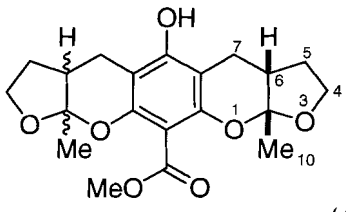
and

(±)-**115**



(±)-**242**

and



(±)-**116/243**

Method A: To a suspension of the methyl ester **112** (165 mg, 0.896 mmol, 1 equiv), a solution of the alcohol **168** [(3.6 mL, 3.6 mmol, 4 equiv) prepared from the corresponding ester **167** (1.42 g, 10.0 mmol) in ether (10.0 mL)] and anhydrous

magnesium sulfate (0.75 g) in ether (10 mL) at 0 °C was added boron trifluoride diethyl etherate (115 μL, 0.916 mmol, 1 equiv). The resultant mixture was allowed to warm to room temperature and was stirred for 4 h. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 15 mL). The combined filtrates were washed with water (3 × 20 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by flash chromatography using dichloromethane:ether (19:1) as the eluant afforded the *title compound* (±)-**241** (15 mg, 6%) as a white solid and a mixture (6:6:1:1) of the *title compounds* (±)-**115**, (±)-**242**, (±)-**116** and **243** (169 mg, 50%) as a solid white foam.

Method B: To a suspension of the methyl ester **112** (166 mg, 0.90 mmol, 1 equiv), a solution of the alcohol **168** [(3.6 mL, 3.6 mmol, 4 equiv) prepared from the corresponding ester **167** (1.42 g, 10.0 mmol) in ether (10.0 mL)] and anhydrous magnesium sulfate (0.75 g) in ether (10 mL) at 0 °C was added boron trifluoride diethyl etherate (115 μL, 0.916 mmol, 1 equiv). The resultant mixture was allowed to warm to room temperature and was stirred for 36 h. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 15 mL). The combined filtrates were washed with water (3 × 20 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by flash chromatography using dichloromethane:ether (12:1) as the eluant afforded a mixture (10:10:1:1) of the *title compounds* (±)-**115**, (±)-**242**, (±)-**116** and **243** (174 mg, 51%) as a solid white foam. Further purification by flash chromatography using dichloromethane:ether (19:1) as the eluant afforded a mixture (dr = 1:1) of the analytically pure *title compounds* (±)-**115** and (±)-**242** as a solid white foam.

Method C: To a suspension of the methyl ester **112** (139 mg, 0.76 mmol, 1 equiv), a solution of the alcohol **168** [(4 mL, 3.0 mmol, 4 equiv) prepared from the corresponding ester **167** (1.07 g, 7.5 mmol) in ether (10.0 mL)] and anhydrous magnesium sulfate (0.75 g) in ether (10 mL) at 0 °C was added boron trifluoride diethyl etherate (63 μL, 0.50 mmol, 0.7 equiv). The resultant mixture was allowed to warm to room temperature and was stirred for 46 h. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 15 mL). The combined filtrates were washed with water (3 × 20 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by flash chromatography using dichloromethane:ether (12:1) as the eluant afforded a mixture (10:10:1:1) of the *title compounds* (±)-**115**, (±)-**242**, (±)-**116** and **243** (165 mg, 58%) as a solid white foam. Further purification by flash chromatography using dichloromethane:ether (19:1) as the eluant afforded a mixture (dr = 1:1) of the analytically pure *title compounds* (±)-**115** and (±)-**242** as a solid white foam.

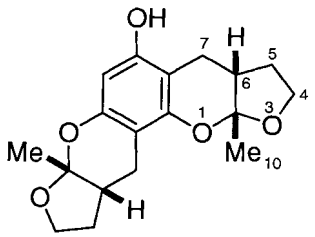
Title compound (±)-**241**: $\mathbf{R}_f$ = 0.46, ether:hexanes (19:1); **M.p.** 94-95 °C, dichloromethane:ether; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.52 (s, 3H, *Me*), 1.74 (m, 1H, *H*-4$_\alpha$), 2.05 (m, 1H, *H*-4$_\beta$), 2.43 (m, 1H, *H*-4a$_\beta$), 2.67 (dd, J = 17.2, 6.4 Hz, 1H, *H*-5$_\beta$), 2.88 (dd, J = 17.2, 1.3 Hz, 1H, *H*-5$_\alpha$), 3.95 (apparent q, J = 8.5 Hz, 1H, *H*-3), 4.02 (s, 3H, CO_2*Me*), 4.03 (m, 1H, *H*-3), 5.96 (s, 1H, *H*-9), 8.96 (broad s, 2H, O*H*); **Observed nOe contacts** *Me* to *H*-4a$_\beta$, *Me* to *H*-5$_\beta$, *Me* to *H*-9, *H*-4a$_\beta$ to *H*-4$_\beta$, *H*-4a$_\beta$ to *H*-5$_\beta$; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 19.4 (*C*-5), 22.2 (*Me*), 28.4 (*C*-4), 39.7 (*C*-4a), 52.4 (CO_2*Me*), 66.8 (*C*-3), 93.5, 96.3 (*C*-9), 98.0, 107.5, 160.2, 169.8; **IR** (ef) 3423 (br), 2981, 2955, 2897, 1667, 1642, 1591, 1435, 1308, 1269, 1157, 1106 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 281

(M + H, 100), 249 (M – OMe, 10), 197 (28), 97 (8), 43 (10); **Anal.** Calcd. for $C_{14}H_{16}O_6$: C, 59.99; H, 5.75. Found: C, 60.10; H, 5.82.

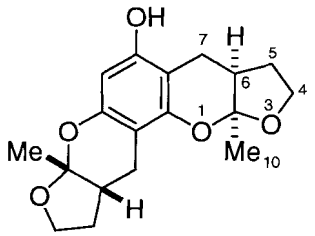
Title compounds (±)-**115** and (±)-**242** (dr = 1:1): $\mathbf{R}_f$ = 0.21, ether:hexanes (19:1); **M.p.** 137-138 °C, dichloromethane:ether; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.51 (s, 3H, *Me*-10), 1.52 (s, 3H, *Me*-10), 1.53 (s, 6H, 2 × *Me*-10), 1.73 (m, 4H, *H*-5$_\alpha$), 2.05 (m, 4H, *H*-5$_\beta$), 2.41 (m, 4H, *H*-6$_\beta$), 2.63 (apparent dt, J = 17.0, 7.0 Hz, 2H, *H*-7$_\beta$), 2.70 (apparent dt, J = 17.3, 7.0 Hz, 2H, *H*-7$_\beta$), 2.83 (apparent ddd, J = 17.0, 8.1, 2.2 Hz, 2H, *H*-7$_\alpha$), 2.93 (apparent ddd, J = 17.3, 3.6, 1.5 Hz, 2H, *H*-7$_\alpha$), 3.90 (s, 2 × 3H, CO_2*Me*), 3.98 (m, 8H, *H*-4), 11.99 (s, 1H, O*H*), 12.00 (s, 1H, O*H*); **Observed nOe contacts** *Me*-10 to *H*-6$_\beta$, *Me*-10 to 2 × *H*-7$_\beta$, *H*-6$_\beta$ to *H*-5$_\beta$, *H*-6$_\beta$ to 2 × *H*-7$_\beta$; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 19.7 (*C*-7), 19.8 (*C*-7), 20.26 (*C*-7), 20.30 (*C*-7), 22.5 (*Me*-10), 22.6 (*Me*-10), 22.8 (*Me*-10), 22.9 (*Me*-10), 28.58 (*C*-5), 28.62 (*C*-5), 29.4 (*C*-5), 29.5 (*C*-5), 39.8 (*C*-6), 40.07 (C-6), 40.14 (*C*-6), 52.1 (CO_2*Me*), 66.81 (*C*-4), 66.84 (*C*-4), 96.18, 96.22, 98.3, 98.4, 99.5, 107.5, 107.6, 107.76, 107.83, 153.7, 153.8, 156.3, 156.4, 160.79, 160.81, 172.1; **IR** (ef) 3425 (broad), 2981, 2898, 2852, 1648, 1615, 1338, 1227, 1177, 1105, 1002 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 377 (M + H, 8), 376 (M, 4), 345 (15), 293 (100), 85 (11), 43 (17); **Anal.** Calcd. for $C_{20}H_{24}O_7$: C, 63.82; H, 6.43. Found: C, 63.93; H, 6.54.

Title compounds (±)-**115**, (±)-**242**, (±)-**116** and **243** (10:10:1:1): **M.p.** 48-51 °C, dichloromethane:ether; **^{1}H NMR** [500 MHz, $CDCl_3$ (additional signals observed for the *title compounds* (±)-**116** and **243**)] δ 1.20 (s, 3H, *Me*-10), 1.22 (s, 3H, *Me*-10), 1.59 (m), 1.87 (m), 3.56 (m); **Anal.** Calcd. for $C_{20}H_{24}O_7$: C, 63.82; H, 6.43. Found: C, 63.58; H, 6.60.

6.4.8 (±)-11,11'-Dinorxyloketal B [(±)-16] and (±)-2,6-*epi*-11,11'-Dinorxyloketal B [(±)-17][9,47,48,49]



(±)-**16** *and*

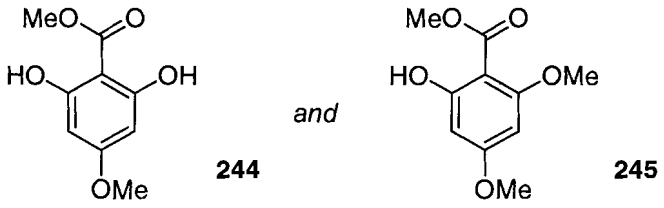


(±)-**17**

To a suspension of the esters (±)-**115** and (±)-**242** (dr = 1:1, 57 mg, 0.15 mmol) in methanol (2 mL) and water (2 mL) was added an aqueous solution of sodium hydroxide (2 M, 0.75 mL). The resultant mixture was heated at reflux for 6 h and then allowed to cool to room temperature. The reaction mixture was then diluted with ethyl acetate (30 mL). The resultant solution was washed with a saturated aqueous solution of ammonium chloride (2 × 8 mL), brine (8 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by flash chromatography using dichloromethane:ether (17:3) as the eluant afforded a mixture (dr = 1:1) of the *title compounds* (±)-**16** and (±)-**17** (46 mg, 96%) as a white solid. $\mathbf{R}_f$ = 0.29, ether:hexanes (17:3); **M.p.** 236 °C (dec.), dichloromethane:ether [lit.[9] 244-245 °C (dec.), for a mixture (dr = 1:1) of the *title compounds* (±)-**16** and (±)-**17**]; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.52 (s, 3H, *Me*-10), 1.53 [2 × (s, 3H, *Me*-10)], 1.54 (s, 3H, *Me*-10), 1.79 (m, 4H, *H*-5$_\alpha$), 2.04 (m, 4H, *H*-5$_\beta$), 2.42 (m, 4H, *H*-6$_\beta$), 2.64 (dd, *J* = 17.1, 6.3 Hz, 2H, *H*-7$_\beta$), 2.73 (m, 2H, *H*-7$_\beta$), 2.88 (m, 4H, *H*-7$_\alpha$), 3.94 (m, 4H, *H*-4$_\beta$), 4.03 (m, 4H, *H*-4$_\alpha$), 5.88 (s, 1H, O*H*), 5.92 (s, 1H, O*H*), 6.16 (s, 1H, *H*-13), 6.17 (s, 1H, *H*-13); **Observed nOe contacts** *Me*-10 to *H*-6$_\beta$, *Me*-10 to 2 × *H*-7$_\beta$, *H*-6$_\beta$ to *H*-5$_\beta$, *H*-6$_\beta$ to 2 × *H*-7$_\beta$, *H*-5$_\beta$ to *H*-7$_\beta$, *H*-5$_\beta$ to *H*-4$_\beta$, *H*-5$_\alpha$ to *H*-7$_\alpha$, *H*-5$_\alpha$ to *H*-4$_\alpha$, *H*-13 to O*H*; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 20.0 (*C*-7), 20.08 (*C*-7), 20.12 (*C*-7), 22.5 (*Me*), 22.6 (*Me*), 22.8 (*Me*), 28.9 (*C*-5), 29.00 (*C*-5), 29.04 (*C*-5), 40.0 (*C*-6), 40.1

(*C*-6), 40.3 (*C*-6), 66.69 (*C*-4), 66.71 (*C*-4), 66.8 (*C*-4), 95.91 (*C*-13), 95.94 (*C*-13), 98.5, 98.7, 99.4, 99.5, 106.67 106.72, 106.8, 106.9, 151.9, 152.13, 152.16, 152.2, 153.2, 153.3; **IR** (ef) 3364 (br), 2981, 2933, 2896, 2848, 1618, 1509, 1453, 1381, 1175, 1131, 1106, 1082, 1002 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 319 (M + H, 15), 318 (M, 30), 277 (32), 235 (5), 180 (8), 85 (18), 43 (100); **Anal.** Calcd. for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97. Found: C, 67.55; H, 7.09.

6.4.9 Methyl 2,6-Dihydroxy-4-methoxybenzoate (244) and Methyl 2,4-Dimethoxy-6-hydroxybenzoate (245)[137,138,139,140,141]



Method A: To a suspension of the ester **112** (207 mg, 1.13 mmol) and potassium carbonate (308 mg, 2.23 mmol) in acetone (10 mL) at room temperature was added methyl iodide (70 μL, 1.1 mmol). The resultant mixture was stirred at room temperature for 23 h and then was filtered. The filter-cake was washed with acetone (2 × 5 mL) and the combined filtrates were concentrated *in vacuo*. Purification by flash chromatography using chloroform as the eluant afforded the *title compound* **244** (84 mg, 39%) as a white solid.

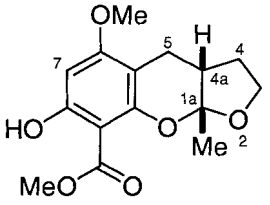
Method B: To a suspension of the ester **112** (207 mg, 1.13 mmol) and potassium carbonate (318 mg, 2.30 mmol) in acetone (10 mL) at room temperature was added methyl iodide (70 μL, 1.1 mmol). The resultant mixture was stirred at room temperature for 84 h and then was filtered. The filter-cake was washed with acetone (2 × 5 mL) and the combined filtrates were concentrated *in vacuo*. Purification by flash chromatography

using chloroform as the eluant afforded the *title compound* **244** (85 mg, 39%) as a white solid and the *title compound* **245** (67 mg, 28%) as a white solid.

Title compound **244**: $\mathbf{R}_f$ = 0.27, chloroform; **M.p.** 114-116 °C, chloroform (lit.[137] 115-116 °C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.79 (s, 3H, O*Me*), 4.03 (s, 3H, CO_2*Me*), 6.03 (s, 2H, Ar*H*), 9.94 (broad s, 2H, O*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 52.5, 55.4, 93.9, 94.4, 162.4, 166.4, 169.6; **IR** (ef) 3416, 3098, 3018, 2958, 2848, 1679, 1650, 1583, 1345, 1256, 1154, 1105, 1073, 1033 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 199 (M + H, 100).

Title compound **245**: $\mathbf{R}_f$ = 0.21, chloroform; **M.p.** 108-110 °C, chloroform (lit.[141] 107-109 °C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.79 (s, 3H, O*Me*), 3.82 (s, 3H, O*Me*), 3.91 (s, 3H, CO_2*Me*), 5.96 (s, 1H, Ar*H*), 6.10 (s, 1H, Ar*H*), 12.04 (s, 1H, O*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 52.1, 55.4, 56.0, 91.5, 93.4, 96.5, 162.1, 165.3, 165.9, 171.6; **IR** (ef) 2918, 2853, 1640, 1613, 1434, 1333, 1312, 1275 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 213 (M + H, 100), 181 (M – OMe, 6).

6.4.10 (1a*RS*,4a*RS*)-3,4,4a,1a-Tetrahydro-6-methoxy-8-hydroxy-1a-methyl-furo[*b*]chromane-9-methylcarboxylate [(±)-246]

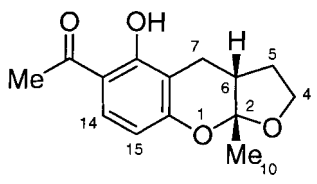


(±)-**246**

To a suspension of the ester **245** (137 mg, 0.69 mmol, 1 equiv), the alcohol **168** [(399 mg, 2.8 mmol, 4 equiv) prepared from the corresponding ester **167**] and anhydrous magnesium sulfate (0.51 g) in ether (9 mL) at 0 °C was added boron trifluoride diethyl etherate (90 μL, 0.69 mmol, 1.0 equiv). The resultant mixture was allowed to warm to room temperature and was stirred for 50 h. The reaction mixture was then filtered and

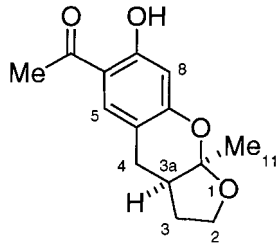
the filter-cake was washed with ethyl acetate (3 × 10 mL). The combined filtrates were washed with water (3 × 10 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by flash chromatography using dichloromethane:ether (19:1) as the eluant afforded the *title compound* (±)-**246** (96 mg, 47%) as a white solid. $\mathbf{R}_f$ = 0.49, dichloromethane:ether (19:1); **M.p.** 184-186 °C, dichloromethane:ether; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.51 (s, 3H, *Me*-1a$_\beta$), 1.79 (m, 1H, *H*-4$_\alpha$), 2.04 (m, 1H, *H*-4$_\beta$), 2.39 (m, 1H, *H*-4a$_\beta$), 2.60 (dd, J = 17.0, 6.5 Hz, 1H, *H*-5$_\beta$), 2.80 (dd, J = 17.0, 1.8 Hz, 1H, *H*-5$_\alpha$), 3.81 (s, 3H, O*Me*), 3.90 (s, 3H, CO_2*Me*), 3.92 (m, 1H, *H*-3$_\beta$), 4.01 (m, 1H, *H*-3$_\alpha$), 6.08 (s, 1H, *H*-7), 11.80 (s, 1H, O*H*); **Observed nOe contacts** *Me*-1a$_\beta$ to *H*-4a$_\beta$, *Me*-1a$_\beta$ to *H*-5$_\beta$, *H*-4a$_\beta$ to *H*-5$_\beta$, *H*-4a$_\beta$ to *H*-4$_\beta$, *H*-4$_\beta$ to *H*-4$_\alpha$, *H*-4$_\alpha$ to *H*-4a$_\beta$, *H*-5$_\beta$ to *H*-5$_\alpha$, *H*-7 to O*H*, *H*-7 to O*Me*; **^{13}C NMR** (126 MHz, $CDCl_3$) δ20.1 (*C*-5), 22.6 (*Me*-1a), 29.2 (*C*-4), 39.9 (*C*-4a), 52.1 (CO_2*Me*), 55.5 (O*Me*), 66.8 (*C*-3), 91.9 (*C*-7), 96.6, 99.8, 107.7, 155.1, 162.7, 163.7, 171.8; **IR** (ef) 3247 (broad), 2934, 2847, 1632, 1594, 1435, 1328, 1305, 1257, 1162, 997 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 295 (M + H, 22), 263 (M – OMe, 7), 211 (100), 43 (8); **Anal.** Calcd. for $C_{15}H_{18}O_6$: C, 61.22; H, 6.16. Found: C, 61.06; H, 6.12.

6.4.11 (±)-11-Norxyloketal D [(±)-12] and (±)-10-Norxyloketal G [(±)-13][9]



(±)-**12**

and



(±)-**13**

Method A: To a suspension of 2,4-dihydroxyacetophenone (**11**) (227 mg, 1.49 mmol, 1 equiv), a solution of the alcohol **168** [(4.0 mL, 3.0 mmol, 2 equiv) prepared from

the corresponding ester **167** (1.07 g, 7.53 mmol) in ether (10.0 mL)] and anhydrous magnesium sulfate (1.0 g) in ether (10 mL) at 0 °C was added boron trifluoride diethyl etherate (63 μL, 0.50 mmol, 0.3 equiv). The resultant mixture was allowed to warm to room temperature and was stirred for 46 h. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 15 mL). The combined filtrates were washed with water (3 × 20 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by flash chromatography using a gradient of dichloromethane:ether (100:0 then 98:2) as the eluant afforded the *title compound* (±)-**12** [57 mg, 13% (41% brsm)] as a white solid (on evaporation from petroleum ether), the *title compound* (±)-**13** [48 mg, 11% (34% brsm)] as a white solid (also on evaporation from petroleum ether) and the unreacted acetophenone **11** (142 mg, 62%).

Method B: To a suspension of the 2,4-dihydroxyacetophenone (**11**) (230 mg, 1.51 mmol, 1 equiv), a solution of the alcohol **168** [(7.5 mL, 6.0 mmol, 4 equiv) prepared from the corresponding ester **167** (1.14 g, 8.03 mmol) in ether (10.0 mL)] and anhydrous magnesium sulfate (1.0 g) in ether (10 mL) at 0 °C was added boron trifluoride diethyl etherate (63 μL, 0.50 mmol, 0.3 equiv). The resultant mixture was allowed to warm to room temperature and was stirred for 46 h. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 15 mL). The combined filtrates were washed with water (3 × 20 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by flash chromatography using a gradient of dichloromethane:ether (99:1 then 98:2) as the eluant afforded the *title compound* (±)-**12** [63 mg, 17% (54% brsm)] as a white solid (on evaporation from petroleum ether), the *title compound* (±)-**13**

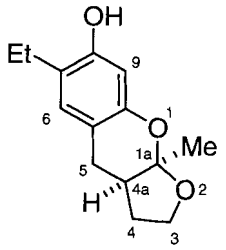
[37 mg, 10% (32% brsm)] as a white solid (also on evaporation from petroleum ether) and the unreacted acetophenone **11** (158 mg, 68%).

Title compound (±)-**12**: $\mathbf{R}_f$ = 0.48, dichloromethane:ether (99:1); **M.p.** 103-105 °C, petroleum ether [lit.[9] 114-116 °C]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.54 (s, 3H, *Me*-10), 1.74 (m, 1H, *H*-5), 2.08 (m, 1H, *H*-5), 2.47 (m, 1H, *H*-6$_\beta$), 2.54 (s, 3H, *Me*-17), 2.75 (dd, J = 17.9, 6.4 Hz, 1H, *H*-7$_\beta$), 3.02 (dd, J = 17.9, 1.1 Hz, 1H, *H*-7$_\alpha$), 3.98 (apparent q, J = 8.5 Hz, 1H, *H*-4), 4.06 (apparent td, J = 9.5, 2.9 Hz, 1H, *H*-4), 6.37 (d, J = 8.9 Hz, 1H, *H*-15), 7.52 (d, J = 8.9 Hz, 1H, *H*-14), 13.10 (s, 1H, O*H*); **Observed nOe contacts** *Me*-11 to *H*-6$_\beta$, *Me*-11 to *H*-7$_\beta$; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 19.4, 22.2, 26.1, 28.5, 39.6, 66.9, 106.1, 107.4, 108.7, 113.1, 130.0, 159.6, 162.9, 202.6; **IR** (ef) 3232 (br), 2987, 2930, 2897, 1622, 1491, 1420, 1370, 1330, 1271, 1177, 1107, 1085, 1004, 852 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 249 (M + H, 100), 231 (30); **Anal.** Calcd. for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.38; H, 6.81.

Title compound (±)-**13**: $\mathbf{R}_f$ = 0.35, dichloromethane:hexanes (99:1); **M.p.** 131-133 °C, petroleum ether [lit.[9] 134-135 °C]; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.58 (s, 3H, *Me*-11), 1.73 (m, 1H, *H*-3$_\alpha$), 2.05 (m, 1H, *H*-3$_\beta$), 2.48 (m, 1H, *H*-3a$_\beta$), 2.54 (s, 3H, *Me*-13), 2.77 (dd, J = 16.3, 1.2 Hz, 1H, *H*-4$_\alpha$), 3.00 (dd, J = 16.3, 5.4 Hz, 1H, *H*-4$_\beta$), 3.97 (m, 2H, 2 × *H*-2), 6.36 (s, 1H, *H*-8), 7.44 (s, 1H, *H*-5), 12.37 (s, 1H, O*H*); **Observed nOe contacts** *Me*-11 to *H*-3a$_\beta$, *Me*-11 to *H*-4$_\beta$, *Me*-11 to *H*-8, *H*-3a$_\beta$ to *H*-3$_\beta$, *H*-3a$_\beta$ to *H*-4$_\beta$, *H*-4$_\beta$ to *H*-4$_\alpha$, *H*-4$_\beta$ to *H*-5, *H*-4$_\alpha$ to *H*-5, *H*-5 to *Me*-13, *Me*-13 to O*H*, O*H* to *H*-8, *H*-3$_\beta$ to *H*-2, *H*-3$_\beta$ to *H*-3$_\alpha$, *H*-3$_\alpha$ to *H*-2; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 23.0 (*C*-11), 25.3 (*C*-4), 26.2 (*C*-13), 28.0 (*C*-3), 40.7 (*C*-3a), 66.9 (*C*-2), 104.5 (*C*-8), 108.1, 110.4, 114.4, 132.2 (*C*-5), 160.4, 163.3, 202.3; **IR** (ef) 3399 (br), 2988, 2927, 2899, 1650, 1615, 1494, 1390,

1364, 1284, 1160, 1099, 1074, 1000 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 249 (M + H, 100), 248 (M, 26), 231 (30), 165 (7), 43 (59); **Anal.** Calcd. for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.60; H, 6.65.

6.4.12 (1a*RS*,4a*RS*)-3,4,4a,1a-Tetrahydro-7-ethyl-8-hydroxy-1a-methyl-furo[*b*]chromane [(±)-250]

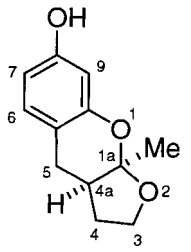


(±)-**250**

To a suspension of 4-ethyl-resorcinol (**249**) (332 mg, 2.41 mmol, 1 equiv), a solution of the alcohol **168** [(6.0 mL, 3.0 mmol, 1.25 equiv) prepared from the corresponding ester **167** (713 mg, 5.0 mmol) in ether (10.0 mL)] and anhydrous magnesium sulfate (1.0 g) in ether (12 mL) at 0 °C was added boron trifluoride diethyl etherate (0.30 mL, 2.4 mmol, 1.0 equiv). The resultant mixture was allowed to warm to room temperature and was stirred for 23 h. The reaction mixture was then filtered and the filter-cake was washed with ether (2 × 10 mL). The combined filtrates were washed with water (3 × 10 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by flash chromatography using dichloromethane:ether (19:1) as the eluant afforded the *title compound* (±)-**250** (341 mg, 61%) as a white solid. $\mathbf{R}_f$ = 0.25, dichloromethane:ether (9:1); **M.p.** 124-125 °C, dichloromethane:ether; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.20 (apparent t, J = 7.6 Hz, 3H, CH_2*Me*), 1.59 (s, 3H, *Me*-1a$_\beta$), 1.80 (m, 1H, *H*-4$_\alpha$), 2.03 (m, 1H, *H*-4$_\beta$), 2.48 (m, 1H, *H*-4a$_\beta$), 2.56 (m, 2H, C*H*$_2$Me), 2.69 (apparent d, J = 16.1 Hz, 1H, *H*-5$_\alpha$), 2.96 (dd, J = 16.2, 5.7 Hz, 1H, *H*-5$_\beta$), 3.91 (apparent

q, J = 8.3 Hz, 1H, H-3$_\beta$), 4.01 (apparent td, J = 8.8, 3.4 Hz, 1H, H-3$_\alpha$), 5.93 (s, 1H, OH), 6.56 (s, 1H, H-9), 6.80 (m, 1H, H-6); **Observed nOe contacts** Me-1a$_\beta$ to H-4a$_\beta$, Me-1a$_\beta$ to H-5$_\beta$, Me-1a$_\beta$ to H-9, Me-1a$_\beta$ to OH, H-4a$_\beta$ to H-4$_\beta$, H-4a$_\beta$ to H-3$_\beta$, H-4$_\beta$ to H-4$_\alpha$, H-4$_\beta$ to H-3$_\beta$, H-4$_\beta$ to Me-1a$_\beta$, H-4$_\alpha$ to H-3$_\alpha$, H-9 to OH, H-6 to H-5$_\alpha$, H-6 to CH_2Me, H-6 to CH$_2Me$; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 14.3 (CH$_2Me$), 22.4 (CH$_2$Me), 23.6 (Me-1a), 25.6 (C-5), 28.8 (C-4), 41.4 (C-4a), 66.8 (C-3), 103.7 (C-9), 107.5, 111.1, 123.0 (C-6), 129.1, 151.7, 153.3; **IR** (ef) 3359 (br), 2973, 2931, 2893, 2867, 2847, 1625, 1606, 1513, 1447, 1382, 1189, 1102, 1008 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 235 (M + H, 100), 151 (8), 97 (40), 43 (20); **Anal.** Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.56; H, 7.63.

6.4.13 (1a*RS*,4a*RS*)-3,4,4a,1a-Tetrahydro-8-hydroxy-1a-methyl-furo[*b*]chromane [(±)-254]

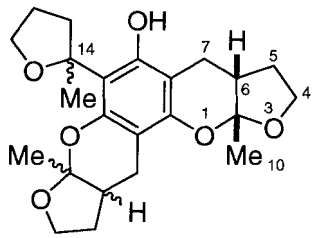


(±)-**254**

To a suspension of resorcinol (**253**) (140 mg, 1.25 mmol, 1 equiv), the alcohol **168** [(235 mg, 1.65 mmol,1.3 equiv) prepared from the corresponding ester **167**] and anhydrous magnesium sulfate (1.00 g) in ether (15 mL) at 0 °C was added boron trifluoride diethyl etherate (160 μL, 1.25 mmol, 1.0 equiv). The resultant mixture was allowed to warm to room temperature and was stirred for 22 h. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 10 mL). The combined filtrates were washed with water (3 × 10 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by flash chromatography using

dichloromethane:ether (19:1) as the eluant afforded the *title compound* (±)-**254** (89 mg, 35%) as a white solid. $\mathbf{R}_f$ = 0.25, dichloromethane:ether (19:1); **M.p.** 106-108 °C, hexanes; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.58 (s, 3H, *Me*-1a$_\beta$), 1.78 (m, 1H, *H*-4), 2.04 (m, 1H, *H*-4), 2.46 (m, 1H, *H*-4a$_\beta$), 2.73 (apparent d, J = 16.2 Hz, 1H, *H*-5$_\alpha$), 2.97 (dd, J = 16.2, 5.7 Hz, 1H, *H*-5$_\beta$), 3.94 (m, 1H, *H*-3), 4.01 (m, 1H, *H*-3), 5.59 (s, 1H, O*H*), 6.41 (m, 1H, *H*-7), 6.49 (m, 1H, *H*-9), 6.93 (d, J = 8.1 Hz, 1H, *H*-6); **Observed nOe contacts** *Me*-1a$_\beta$ to *H*-4a$_\beta$, *Me*-1a$_\beta$ to *H*-5$_\beta$, *Me*-1a$_\beta$ to O*H*, *Me*-1a$_\beta$ to *H*-9; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 23.4, 25.6, 28.7, 41.3, 66.8, 103.9, 107.5, 108.4, 111.4, 129.8, 154.0, 155.7; **IR** (ef) 3380 (br), 2980, 2938, 2898, 2843, 1623, 1597, 1509, 1458, 1381, 1301, 1226, 1153, 1110 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 207 (M + H, 100), 189 (13), 97 (31), 43 (30); **Anal.** Calcd. for $C_{12}H_{14}O_3$: C, 69.68; H, 6.84. Found: C, 69.48; H, 6.96.

6.4.14 (±)-11,11',20-Trinorxyloketal E [(±)-257], (±)-14-*epi*-11,11',20-Trinorxyloketal E [(±)-258], 2,6-*epi*-11,11',20-Trinorxyloketal E [(±)-259] and (±)-2,6,14-*epi*-11,11',20-Trinorxyloketal E [(±)-260][128]

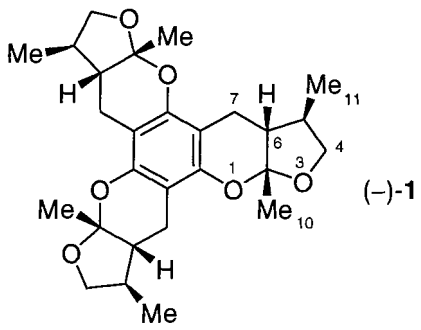


(±)–**257/258/259/260**

To a solution of the xyloketal B analogues (±)-**16** and (±)-**17** (dr = 1:1, 40 mg, 0.16 mmol) and 2-methyl-4,5-dihydrofuran (**114**) (42 μL, 0.46 mmol, 2.9 equiv) in dichloromethane (4 mL) was added pyridinium *p*-toluenesulfonate (7 mg, 0.03 mmol) and the resultant solution was stirred at room temperature for 20 h. The reaction mixture was then diluted with dichloromethane (25 mL), was washed with brine (3 × 5 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by flash

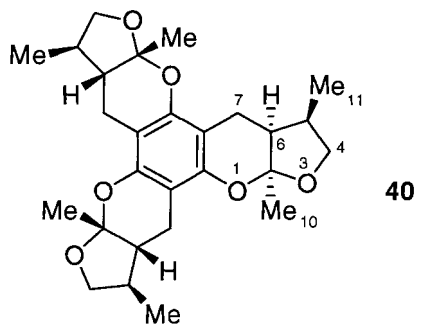
chromatography using dichloromethane:ether (9:1) as the eluant afforded an inseparable mixture (dr = 2:1:2:1) of the *title compounds* (±)-**257**, (±)-**258**, (±)-**259** and (±)-**260** (37 mg, 72%) as a white solid. $\mathbf{R}_f$ = 0.55, dichloromethane:ether (9:1); **M.p.** 119-124 °C, dichloromethane:ether; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.486, 1.491, 1.498, 1.504, 1.515, 1.520, 1.53, 1.540, 1.544, 1.55 (10 × s, 9H total), 1.61-1.99 (m, 4H), 2.03 (m, 2H), 2.25-2.63 (m, 5H), 2.70 (m, 1H), 2.87 (m, 2H, 2 × *H*-7), 3.90 (m, 4H), 4.03 (m, 2H), 10.72, 10.75, 10.78, 10.80 (4 × s, 1H total, 4 × O*H*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 20.0, 20.16, 20.22, 20.3, 20.4, 22.3, 22.5, 22.6, 22.7, 22.8, 22.9, 25.3, 27.6, 27.7, 28.9, 29.1, 39.57, 39.64, 40.0, 40.1, 40.2, 66.6, 67.76, 67.83, 88.34, 88.42, 88.44, 98.4, 98.6, 98.9, 99.0, 106.28, 106.32, 106.50, 106.52, 106.8, 107.0, 107.1, 110.0, 110.1, 110.2, 148.52, 148.55, 148.6, 150.1, 150.3, 152.2, 152.36, 152.43, 152.5; **IR** (ef) 3170 (br), 2977, 2940, 2894, 1621, 1455, 1439, 1379, 1328, 1105, 1003 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 319 (55), 235 (28), 97 (47), 85 (100), 43 (43); **Anal.** Calcd. for $C_{23}H_{30}O_6$: C, 68.64; H, 7.51. Found: C, 68.73; H, 7.54.

6.4.15 (–)-Xyloketal A [(–)-1] and 2,6-*epi*-Xyloketal A (40)[1]



(–)-**1**

and



40

Method A: To a suspension of phloroglucinol (**14**) (42 mg, 0.33 mmol, 1 equiv), a solution of the alcohol (4*R*)-**226** in ether [(4.0 mL, 2.0 mmol, 6 equiv) prepared from the corresponding ester (4*R*)-**206** (783 mg, 5.02 mmol) in ether (10.0 mL)] and anhydrous

magnesium sulfate (0.30 g) in ether (3 mL) at 0 °C was added boron trifluoride diethyl etherate (42 μL, 0.33 mmol, 1 equiv). The resultant mixture was stirred at 0 °C for 20 min. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 10 mL). The combined filtrates were washed with water (2 × 10 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by flash chromatography using dichloromethane:ether (19:1) as the eluant afforded a mixture (dr = 5:2) of the *title compounds* (–)-**1** and **40** (128 mg, 85%) as a colourless oil.

Method B: To a suspension of phloroglucinol (**14**) (42 mg, 0.33 mmol, 1 equiv), a solution of the alcohol (4*R*)-**226** in ether [(4.0 mL, 2.0 mmol, 6 equiv) prepared from the corresponding ester (4*R*)-**206** (783 mg, 5.02 mmol) in ether (10.0 mL)] and anhydrous magnesium sulfate (0.30 g) in ether (3 mL) at –78 °C was added boron trifluoride diethyl etherate (42 μL, 0.33 mmol, 1 equiv). The resultant mixture was stirred at 0 °C for 20 min. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 10 mL). The combined filtrates were washed with water (2 × 10 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by flash chromatography using dichloromethane:ether (19:1) as the eluant afforded a mixture (dr = 4:1) of the *title compounds* (–)-**1** and **40** (119 mg, 79%) as a colourless oil.

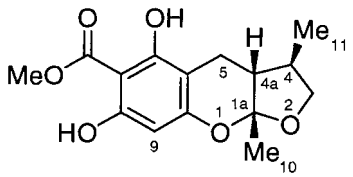
Method C: To a suspension of phloroglucinol (**14**) (32 mg, 0.25 mmol, 1 equiv), a solution of the alcohol (4*R*)-**226** in ether [(2.0 mL, 1.0 mmol, 4 equiv) prepared from the corresponding ester (4*R*)-**206** (783 mg, 5.02 mmol) in ether (10.0 mL)] and anhydrous magnesium sulfate (0.25 g) in ether (2 mL) at 0 °C was added boron trifluoride diethyl etherate (32 μL, 0.25 mmol, 1 equiv). The resultant mixture was allowed to warm to room temperature over 2 h. The reaction mixture was then filtered and the filter-cake

was washed with ether (3 × 10 mL). The combined filtrates were washed with water (2 × 10 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by flash chromatography using dichloromethane:ether (19:1) as the eluant afforded a mixture (dr = 5:2) of the *title compounds* (–)-**1** and **40** (16 mg, 14%) as a colourless oil.

Title compound (–)-**1**: Crystallization of the *title compounds* (–)-**1** and **40** from petroleum ether, on slow evaporation of the solvent, afforded the analytically pure (–)-xyloketal A (–)-**1** as colourless shards and as a single diastereoisomer. $\mathbf{R}_f$ = 0.45, dichloromethane:ether (19:1); **M.p.** 158-160 °C, petroleum ether (lit.[1] 164-166 °C); $[\alpha]_D^{20}$ = – 6.3 (*c* 0.43, chloroform) [lit.[1] $[\alpha]_D^{20}$ = – 4.88 (*c* 0.205, chloroform)]; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.05 (d, *J* = 6.6 Hz, 9H, *Me*-11), 1.49 (s, 9H, *Me*-10), 1.88 (dd, *J* = 10.9, 6.4 Hz, 3H, *H*-6), 2.13 (m, 3H, *H*-5), 2.64 (dd, *J* = 17.6, 6.8 Hz, 3H, *H*-7), 2.85 (apparent d, *J* = 17.6 Hz, 3H, *H*-7), 3.53 (apparent t, *J* = 8.4 Hz, 3H, *H*-4), 4.16 (apparent t, *J* = 8.4 Hz, 3H, *H*-4); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 16.0, 18.9, 22.9, 35.5, 47.5, 74.0, 98.9, 107.3, 149.7; **IR** (ef) 2955, 2934, 2876, 1615, 1455, 1378, 1205, 1115, 1008 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 457 (M + H, 34), 401 (M, 15), 359 (100), 111 (33), 43 (33); **Anal.** Calcd. for $C_{27}H_{36}O_6$: C, 71.03; H, 7.95. Found: C, 71.10; H, 8.11.

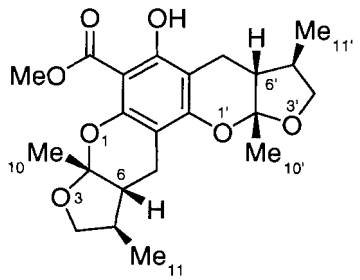
Title compound **40**: **^{1}H NMR** [500 MHz, $CDCl_3$ (additional signals observed for the *title compound* **40**)] δ 0.83 (d, *J* = 7.1 Hz, 3H, *Me*-11), 1.45 (s, 3H, *Me*-10), 1.50 (s, 3H, *Me*-10), 1.51 (s, 3H, *Me*-10), 2.35 (m, 1H, *H*-5 *or H*-6), 2.50 (m, 1H, *H*-5 *or H*-6), 2.68 (m, 1H, *H*-7), 2.84 (m, 1H, *H*-7), 3.55 (m, 1H, *H*-4), 4.09 (t, *J* = 8.1 Hz, 1H, *H*-4).

6.4.16 (–)-(1a*R*,4*R*,4a*R*)-3,4,4a,1a-Tetrahydro-6,8-dihydroxy-1a,4-dimethylfuro[*b*]-7-chromane Methylcarboxylate [(–)-261] and (–)-13-Xyloketal B Methylcarboxylate [(–)-262]



(–)-**261**

and



(–)-**262**

Method A: To a suspension of the methyl ester **112** (139 mg, 0.755 mmol, 1 equiv), a solution of the alcohol (4*R*)-**226** in ether [(3.0 mL, 3.0 mmol, 4 equiv) prepared from the corresponding ester (4*R*)-**206** (1.57 g, 10.1 mmol) in ether (10.0 mL)] and anhydrous magnesium sulfate (0.75 g) in ether (12 mL) at 0 °C was added boron trifluoride diethyl etherate (63 μL, 0.50 mmol, 0.7 equiv). The resultant mixture was allowed to warm to room temperature over 38 h. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 10 mL). The combined filtrates were washed with water (3 × 15 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by flash chromatography using dichloromethane followed by dichloromethane:ether (19:1) as the eluant afforded the *title compound* (–)-**261** (37 mg, 17%) as a white solid and the *title compound* (–)-**262** (222 mg, 73%) as a solid white foam.

Method B: To a suspension of the methyl ester **112** (138 mg, 0.750 mmol, 1 equiv), a solution of the alcohol (4*R*)-**226** in ether [(3.0 mL, 3.0 mmol, 4 equiv) prepared from the corresponding ester (4*R*)-**206** (1.57 g, 10.1 mmol) in ether (10.0 mL)] and anhydrous magnesium sulfate (0.75 g) in ether (12 mL) at 0 °C was added boron trifluoride diethyl etherate (63 μL, 0.50 mmol, 0.7 equiv). The resultant mixture was

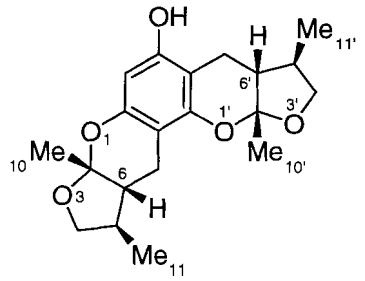
allowed to warm to room temperature over 46 h. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 15 mL). The combined filtrates were washed with water (3 × 20 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by flash chromatography using dichloromethane:ether (19:1) as the eluant afforded the *title compound* (–)-**262** (277 mg, 91%) as a solid white foam.

Title compound (–)-**261**: This compound was recrystallized from petroleum ether to afford colourless needles. $\mathbf{R}_f$ = 0.32, dichloromethane; **M.p.** 85-87 °C, petroleum ether; $[\alpha]_D^{20}$ = – 59.8 (*c* 0.48, chloroform); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.06 (d, *J* = 6.5 Hz, 3H, *Me*-4$_\beta$), 1.51 (s, 3H, *Me*-1a$_\beta$), 1.93 (ddd, *J* = 11.2, 6.4, 1.0 Hz, 1H, *H*-4a$_\beta$), 2.08 (m, 1H, *H*-4$_\alpha$), 2.62 (dd, *J* = 17.4, 6.4 Hz, 1H, *H*-5$_\beta$), 2.84 (dd, *J* = 17.5, 1.1 Hz, 1H, *H*-5$_\alpha$), 3.54 (apparent t, *J* = 8.6 Hz, 1H, *H*-3$_\beta$), 4.03 (s, 3H, CO_2*Me*), 4.18 (apparent t, *J* = 8.5 Hz, 1H, *H*-3$_\alpha$), 5.97 (s, 1H, *H*-9), 8.71 (broad s, 1H, O*H*), 10.78 (broad s, 1H, O*H*); **Observed nOe contacts** *Me*-4$_\beta$ to *H*-4a$_\beta$, *Me*-4$_\beta$ to *H*-4$_\alpha$, *Me*-4$_\beta$ to *H*-5$_\alpha$, *Me*-4$_\beta$ to *H*-3$_\beta$, *Me*-1a$_\beta$ to *H*-9, *Me*-1a$_\beta$ to *H*-4a$_\beta$, *Me*-1a$_\beta$ to *H*-5$_\beta$, *H*-9 to CO_2*Me*, *H*-9 to *Me*-1a$_\beta$; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 15.9, 18.0, 22.7, 35.0, 47.1, 52.4, 74.2, 93.5, 96.4, 98.1, 108.4, 160.2, 169.8; **IR** (ef) 3435 (br), 2962, 2929, 2897, 1673, 1648, 1591, 1441, 1308, 1268, 1162, 1139, 1116, 1073, 1005 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 295 (M + H, 100), 263 (M – OMe, 12), 197 (17), 111 (21), 43 (9); **Anal.** Calcd. for $C_{15}H_{18}O_6$: C, 61.22; H, 6.16. Found: C, 61.41; H, 6.06.

Title compound (–)-**262**: This compound was evaporated from petroleum ether to afford a solid white foam. $\mathbf{R}_f$ = 0.56, dichloromethane:ether (19:1); **M.p.** 127-129 °C,

petroleum ether; $[\alpha]_D^{20} = -6.7$ (*c* 0.48, chloroform); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.05 (d, *J* = 6.6 Hz, 3H, *Me*-11$_\beta$), 1.08 (d, *J* = 6.5 Hz, 3H, *Me*-11'$_\beta$), 1.49 (s, 3H, *Me*-10$_\beta$), 1.52 (s, 3H, *Me*-10'$_\beta$), 1.88 (ddd, *J* = 10.5, 6.8, 1.3 Hz, 1H, *H*-6$_\beta$), 1.94 (ddd, *J* = 11.0, 6.3, 0.7 Hz, 1H, *H*-6'$_\beta$), 2.08 (m, 2H, *H*-5$_\alpha$ *and H*-5'$_\alpha$), 2.60 (dd, *J* = 17.4, 6.9 Hz, 1H, *H*-7$_\beta$), 2.66 (dd, *J* = 17.5, 6.5 Hz, 1H, *H*-7'$_\beta$), 2.77 (dd, *J* = 17.3, 1.3 Hz, 1H, *H*-7$_\alpha$), 2.89 (apparent d, *J* = 17.5 Hz, 1H, *H*-7'$_\alpha$), 3.49 (apparent t, *J* = 8.4 Hz, 1H, *H*-4$_\beta$), 3.56 (apparent t, *J* = 8.4 Hz, 1H, *H*-4'$_\beta$), 3.90 (s, 3H, CO_2*Me*), 4.18 (apparent q, *J* = 8.1 Hz, 2H, *H*-4$_\alpha$ *and H*-4'$_\alpha$), 12.03 (s, 1H, O*H*); **Observed nOe contacts** CO_2*Me* to O*H*, CO_2*Me* to *Me*-10$_\beta$, O*H* to *H*-7'$_\alpha$, *H*-7$_\alpha$ to *H*-7$_\beta$, *H*-7'$_\alpha$ to *H*-7'$_\beta$, *Me*-10$_\beta$ to *H*-6$_\beta$, *Me*-10$_\beta$ to *H*-7$_\beta$, *Me*-10'$_\beta$ to *H*-6'$_\beta$, *Me*-10'$_\beta$ to *H*-7'$_\beta$, *Me*-11$_\beta$ to *H*-4$_\beta$, *Me*-11$_\beta$ to *H*-5$_\beta$, *Me*-11$_\beta$ to *H*-6$_\beta$, *Me*-11$_\beta$ to *H*-7$_\alpha$, *Me*-11'$_\beta$ to *H*-4'$_\beta$, *Me*-11'$_\beta$ to *H*-5$_\beta$, *Me*-11'$_\beta$ to *H*-6'$_\beta$, *Me*-11'$_\beta$ to *H*-7'$_\alpha$; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 16.0 (*C*-11 *or C*-11'), 16.1 (*C*-11 *or C*-11'), 18.3 (*C*-7'), 19.0 (*C*-7), 22.9 (*C*-10 *or C*-10'), 23.0 (*C*-10 *or C*-10'), 35.1 (*C*-5 *or C*-5'), 36.0 (*C*-5 *or C*-5'), 47.2 (*C*-6'), 47.5 (*C*-6), 52.1 (CO_2*Me*), 74.0 (*C*-4 *or C*-4'), 74.2 (*C*-4 *or C*-4'), 96.2, 98.3, 99.2, 108.2, 108.5, 153.4, 156.4, 160.8, 172.2; **IR** (ef) 3367 (br), 2964, 2925, 2852, 1644, 1620, 1433, 1334, 1229, 1115, 1008 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 405 (M + H, 11), 404 (M, 3), 373 (M – OMe, 15), 333 (5), 307 (100), 111 (20), 99 (50), 43 (24); **Anal.** Calcd. for $C_{22}H_{28}O_7$: C, 65.33; H, 6.98. Found: C, 65.27; H, 6.99.

6.4.17 (–)-Xyloketal B [(–)-2][1]

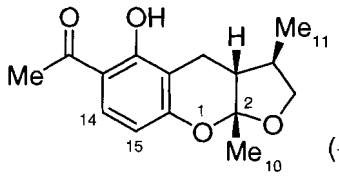


(±)-**2**

To a suspension of the ester (–)-**262** (299 mg, 0.740 mmol) in methanol (9 mL) and water (9 mL) was added an aqueous solution of sodium hydroxide (2 M, 3.7 mL). The resultant mixture was heated at reflux for 3.5 h then was allowed to cool to room temperature. The resultant mixture was diluted with ethyl acetate (50 mL) and was washed with a saturated aqueous solution of ammonium chloride (2 × 20 mL), brine (20 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by flash chromatography using dichloromethane:ether (9:1) as the eluant afforded the *title compound* (–)-**2** (243 mg, 95%) as a solid white foam. $\mathbf{R}_f$ = 0.24, dichloromethane:ether (9:1); **M.p.** 85-86 °C, chloroform (lit.[1] 84-86 °C); $[\alpha]_D^{20}$ = – 8.5 (*c* 0.34, chloroform) [lit.[1] $[\alpha]_D^{20}$ = + 8.2 (*c* 0.061, chloroform)]; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.02 (d, *J* = 6.5 Hz, 3H, *Me*-11$_\beta$), 1.04 (d, *J* = 6.6 Hz, 3H, *Me*-11'$_\beta$), 1.48 (s, 3H, *Me*-10$_\beta$), 1.50 (s, 3H, *Me*-10'$_\beta$), 1.88 (m, 2H, *H*-6$_\beta$ *and H*-6'$_\beta$), 2.12 (m, 2H, *H*-5$_\alpha$ *and H*-5'$_\alpha$), 2.61 (dd, *J* = 17.4, 6.6 Hz, 1H, *H*-7), 2.68 (dd, *J* = 17.2, 6.5 Hz, 1H, *H*-7'), 2.83 (apparent d, *J* = 17.4 Hz, 1H, *H*-7), 2.84 (apparent d, *J* = 17.0 Hz, 1H, *H*-7'), 3.48 (apparent t, *J* = 8.5 Hz, 1H, *H*-4$_\beta$), 3.52 (apparent t, *J* = 8.4 Hz, 1H, *H*-4'$_\beta$), 4.14 (apparent q, *J* = 8.5 Hz, 2H, *H*-4$_\alpha$ *and H*-4'$_\alpha$), 6.19 (s, 1H, *H*-13), 7.05 (s, 1H, O*H*); **Observed nOe contacts** *H*-6$_\beta$ to *H*-4$_\beta$, *H*-6$_\beta$ to *H*-7$_\alpha$, *H*-6$_\beta$ to *H*-7$_\beta$, *H*-6$_\beta$ to *Me*-10$_\beta$, *H*-6$_\beta$ to *Me*-11$_\beta$, *H*-6'$_\beta$ to *H*-4'$_\beta$, *H*-6'$_\beta$ to *H*-7$_\alpha$, *H*-6'$_\beta$ to *H*-7$_\beta$, *H*-6'$_\beta$ to *Me*-10'$_\beta$, *H*-6'$_\beta$ to *Me*-11'$_\beta$; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 15.7 (*C*-11),

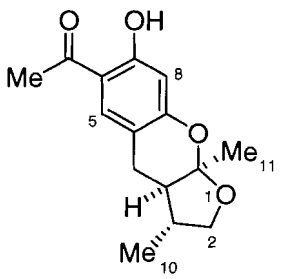
15.9 (*C*-11'), 18.4 (*C*-7'), 18.5 (*C*-7), 22.7 (*C*-10), 22.9 (*C*-10'), 35.1 (*C*-5'), 35.3 (*C*-5), 47.4 (*C*-6'), 47.6 (*C*-6), 73.8 (*C*-4 *and* *C*-4'), 95.8 (*C*-13), 98.6 (*C*-8'), 98.9 (*C*-8), 107.3 (*C*-2), 107.5 (*C*-2'), 151.6 (*C*-9), 151.8 (*C*-9'), 153.4 (*C*-12); **IR** (ef) 3391 (br), 2949, 2936, 2897, 2851, 1629, 1609, 1505, 1455, 1385, 1339, 994 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 347 (M + H, 61), 249 (21), 111 (42), 99 (100), 43 (41); **FAB-HRMS** Calcd. for $C_{20}H_{26}O_5$: 346.1780. Found: 346.1787.

6.4.18 (–)-Xyloketal D [(–)-4] and (–)-Xyloketal G [(–)-7][1,4,9,10]



(–)-**4**

and



(–)-**7**

To a suspension of 2,4-dihydroxyacetophenone (**11**) (227 mg, 0.1.49 mmol, 1 equiv), a solution of the alcohol (4*R*)-**226** in ether [(6.0 mL, 6.0 mmol, 4 equiv) prepared from the corresponding ester (4*R*)-**206** (1.57 g, 10.1 mmol) in ether (10.0 mL)] and anhydrous magnesium sulfate (1.0 g) in ether (9 mL) at 0 °C was added boron trifluoride diethyl etherate (63 μL, 0.50 mmol, 0.3 equiv). The resultant mixture was allowed to warm to room temperature over 46 h. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 15 mL). The combined filtrates were washed with water (3 × 20 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by flash chromatography using dichloromethane:ether (9:1) as the eluant afforded a mixture (3:2) of the *title compounds* (–)-**4** and (–)-**7** [95 mg, 24%, (86% brsm)] as a yellow oil and the unreacted acetophenone **11** (163 mg, 71%). Further purification by flash chromatography using hexanes:ether (4:1) as the eluant afforded the

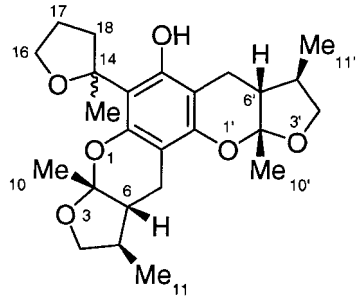
title compound (–)-**4** [56 mg, 14%, (51% brsm)] as a solid white foam and the *title compound* (–)-**7** [32 mg, 8%, (29% brsm)] as a white solid.

Title compound (–)-**4**: This compound was recrystallized from pentane:ether to afford colourless prisms. $\mathbf{R}_f$ = 0.27, hexanes:ether (4:1); **M.p.** 79-81 °C, pentane:ether (lit.[1] 111-113 °C, lit.[9] 110-111 °C, pentane:ether, lit.[10] 110-111 °C); $[\alpha]_D^{20}$ = – 110.2 (*c* 0.61, chloroform) [lit.[1] $[\alpha]_D^{25}$ = – 119.5 (*c* 0.113, chloroform), lit.[9] $[\alpha]_D^{25}$ = – 118 (*c* 0.10, chloroform), lit.[10] $[\alpha]_D^{25}$ = – 118 (*c* 0.10, chloroform)]; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.07 (d, *J* = 6.5 Hz, 3H, *Me*-11$_\beta$), 1.52 (s, 3H, *Me*-10$_\beta$), 1.97 (ddd, *J* = 11.2, 6.4, 0.7 Hz, 1H, *H*-6$_\beta$), 2.05 (m, 1H, *H*-5), 2.54 (s, 3H, *Me*-17), 2.71 (dd, *J* = 17.0, 6.5 Hz, 1H, *H*-7), 2.96 (apparent d, *J* = 18.0 Hz, 1H, *H*-7), 3.56 (apparent t, *J* = 8.5 Hz, 1H, *H*-4), 4.19 (apparent t, *J* = 8.4 Hz, 1H, *H*-4), 6.35 (d, *J* = 8.9 Hz, 1H, *H*-15), 7.50 (d, *J* = 8.9 Hz, 1H, *H*-14), 13.10 (s, 1H, O*H*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 15.7 (*C*-11), 18.0 (*C*-7), 22.7 (*C*-10), 26.1 (*C*-17), 35.1 (*C*-5), 46.9 (*C*-6), 74.3 (*C*-4), 106.1 (*C*-8), 108.2 (*C*-2), 108.7 (*C*-15), 113.1 (*C*-13), 130.0 (*C*-14), 159.5 (*C*-9), 162.9 (*C*-12), 202.6 (*C*-16); **IR** (ef) 3232 (br), 2955, 2930, 2898, 1616, 1490, 1419, 1332, 1272, 1117, 1070, 1006 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 263 (M + H, 100), 245 (7), 111 (6), 43 (18); **Anal.** Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.72; H, 6.95.

Title compound (–)-**7**: This compound was recrystallized from petroleum ether:ether to afford colourless flakes. $\mathbf{R}_f$ = 0.16, hexanes:ether (4:1); **M.p.** 137-139 °C, petroleum ether:ether [lit.[4] 144 °C]; $[\alpha]_D^{20}$ = – 19.1 (*c* 0.11, chloroform) [lit.[4] $[\alpha]_D^{20}$ = – 111 (*c* 0.1, chloroform)]; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.06 (d, *J* = 6.5 Hz, 3H, *Me*-10$_\beta$), 1.56 (s, 3H, *Me*-11$_\beta$), 1.97 (ddd, *J* = 11.0, 5.7, 1.7 Hz, 1H, *H*-3a$_\beta$), 2.08 (m, 1H, *H*-

3_α), 2.54 (s, 3H, *Me*-13), 2.76 (dd, J = 16.6, 1.2 Hz, 1H, *H*-4), 2.97 (ddd, J = 16.5, 5.7, 0.8 Hz, 1H, *H*-4), 3.53 (apparent t, J = 8.4 Hz, 1H, *H*-2_β), 4.16 (apparent t, J = 8.4 Hz, 1H, *H*-2_α), 6.35 (s, 1H, *H*-8), 7.45 (s, 1H, *H*-5), 12.35 (s, 1H, O*H*); **Observed nOe contacts** *H*-$3a_\beta$ to *Me*-10_β, *H*-$3a_\beta$ to *Me*-11_β, *H*-$3a_\beta$ to *H*-2_β; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 16.0 (*C*-10), 23.4 (*C*-11), 23.8 (*C*-4), 26.2 (*C*-13), 34.6 (*C*-3), 48.1 (*C*-3a), 74.1 (*C*-2), 104.6 (*C*-8), 108.9 (*C*-9a), 110.3 (*C*-4a), 114.4 (*C*-6), 132.1 (*C*-5), 160.2 (*C*-8a), 163.3 (*C*-7), 202.2 (*C*-12); **IR** (ef) 3440 (br), 2961, 2891, 2871, 1644, 1614, 1494, 1387, 1364, 1286, 1205, 1166, 1114, 1103 cm^{-1}**MS** (CI) *m/z* (rel. intensity) 263 (M + H, 100), 245 (5), 111 (14), 43 (10); **Anal.** Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.60; H, 7.07.

6.4.19 20-Norxyloketal E (263) and 14-*epi*-20-Norxyloketal E (264)[128]

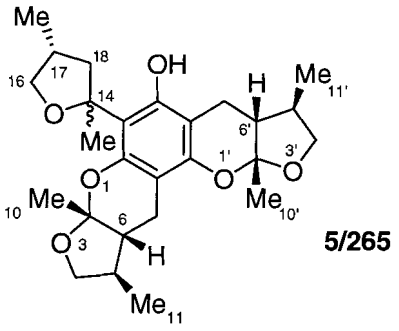


263/264

To a solution of synthetic (–)-xyloketal B [(–)-**2**] (21 mg, 0.061 mmol) and 2-methyl-4,5-dihydrofuran (**114**) (20 μL, 0.22 mmol, 3.6 equiv) in dichloromethane (2 mL) was added pyridinium *p*-toluenesulfonate (3 mg, 0.01 mmol) and the resultant solution was stirred at room temperature for 22 h. The reaction mixture was then diluted with dichloromethane (20 mL), was washed with brine (3 × 5 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by flash chromatography using dichloromethane:ether (9:1) as the eluant afforded an inseparable mixture (dr = 1:1) of

the *title compounds* **263** and **264** (20 mg, 78%) as a colourless oil. $\mathbf{R}_f$ = 0.66, dichloromethane:ether (9:1); $[\alpha]_D^{20}$ = – 2.6 (*c* 0.34, chloroform); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.04 (d, *J* = 6.6 Hz, 6H, 2 × *Me*-11), 1.06 (d, *J* = 6.2 Hz, 3H, *Me*-11), 1.07 (d, *J* = 6.5 Hz, 3H, *Me*-11), 1.47 (s, 3H, *Me*-10), 1.48 (s, 3H, *Me*-10), 1.49 (s, 3H, *Me*-10), 1.50 (s, 3H, *Me*-10), 1.54 (s, 6H, 2 × *Me*-19), 1.89 (m, 8H), 2.06 (m, 2H), 2.17 (m, 2H), 2.25 (m, 1H), 2.33 (m, 1H), 2.45 (m, 1H), 2.55 (m, 3H), 2.65 (m, 2H), 2.81 (m, 2H, *H*-7), 2.85 (m, 2H, *H*-7), 3.48 (apparent t, *J* = 8.2 Hz, 2H, *H*-4), 3.52 (apparent t, *J* = 8.4 Hz, 2H, *H*-4), 3.86 (dd, *J* = 15.3, 8.4 Hz, 2H, *H*-16), 4.04 (m, 2H, *H*-16), 4.08 (apparent t, *J* = 8.4 Hz, 2H, *H*-4), 4.16 (apparent t, *J* = 8.4 Hz, 2H, *H*-4), 10.73 (s, 1H, O*H*), 10.80 (s, 1H, O*H*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 16.1, 16.2, 16.28, 16.31, 18.83, 18.85, 18.9, 22.5, 22.8, 23.0, 25.3, 25.4, 27.76, 27.79, 35.4, 35.7, 39.7, 40.1, 47.58, 47.64, 47.7, 47.77, 47.79, 67.79, 67.83, 73.8, 73.9, 74.0, 88.3, 88.4, 98.2, 98.8, 107.32, 107.34, 107.5, 107.6, 110.1, 148.28, 148.34, 150.2, 152.3, 152.4; **IR** (ef) 3178 (br), 2957, 2923, 2884, 1622, 1456, 1381, 1112, 1008 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 431 (M + H, 6), 430 (M, 16), 375 (8), 346 (14), 291 (12), 111 (8), 85 (7), 43 (100); **FAB-HRMS** Calcd. for $C_{25}H_{34}O_6$: 430.2355. Found: 430.2356.

6.4.20 Xyloketal E (5) and 14-*epi*-Xyloketal E (265)[1,128]

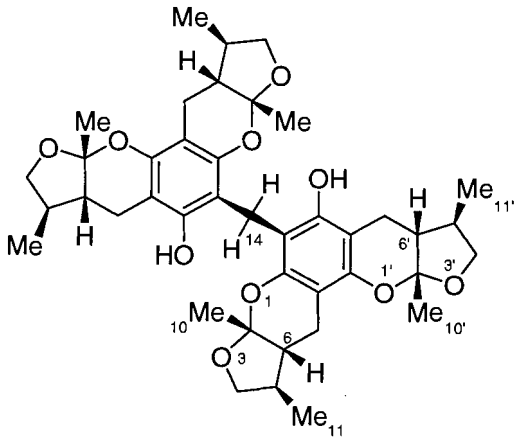


5/265

To a solution of synthetic (–)-xyloketal B [(–)-**2**] (35 mg, 0.10 mmol) and (4*R*)-2,4-dimethyl-4,5-dihydrofuran [(4*R*)-**61**] (25 mg, 0.25 mmol, 2.5 equiv) in dichloromethane (3 mL) was added pyridinium *p*-toluenesulfonate (3 mg, 0.01 mmol) and the resultant solution was stirred at room temperature for 21 h. The reaction mixture was then diluted with dichloromethane (20 mL), was washed with brine (3 × 5 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by flash chromatography using dichloromethane:ether (19:1) as the eluant afforded an inseparable mixture (dr = 2:9) of the *title compounds* **5** and **265** (37 mg, 82%) as a colourless oil. $\mathbf{R}_f$ = 0.47, dichloromethane:ether (99:1); $[\alpha]_D^{20}$ = – 2.4 (*c* 0.33, chloroform) [lit.[1] $[\alpha]_D^{25}$ = + 5.35 (*c* 0.113, chloroform) for *title compound* **5**]; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.00 (d, *J* = 6.5 Hz, 3H, *Me*-20 of **5**), 1.06 (m, 9H, 2 × *Me*-11 *and Me*-20), 1.47 (s, 3H, *Me*-10), 1.49 (s, 3H, *Me*-10), 1.53 (s, 3H, *Me*-19 of **5**), 1.66 (s, 3H, *Me*-19 of **265**), 1.77 (dd, *J* = 13.2, 7.8 Hz, 1H), 1.87 (m, 2H), 2.06 (m, 1H), 2.16 (m, 1H), 2.28 (m, 1H of **265**), 2.38 (m, 1H of **5**), 2.56 (dd, *J* = 17.4, 6.6 Hz, 1H, *H*-7), 2.66 (dd, *J* = 17.4, 6.7 Hz, 1H, *H*-7), 2.82 (m, 3H), 3.38 (dd, *J* = 10.1, 8.3 Hz, 1H of **5**), 3.50 (m, 3H, 2 × *H*-4 *and H*-16), 4.03 (apparent t, *J* = 7.6 Hz, 1H), 4.08 (apparent t, *J* = 7.6 Hz, 1H of **5**), 4.09 (apparent t, *J* = 8.3 Hz, 1H), 4.16 (apparent t, *J* = 8.4 Hz, 1H), 10.81 (s, 1H, O*H* of **5**), 10.86 (s, 1H, O*H* of **265**); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 15.5, 16.1, 16.2, 16.3, 17.4, 18.8, 18.9, 18.9,

22.4, 22.7, 22.9, 23.0, 28.4, 28.9, 32.7, 33.9, 35.4, 35.7, 47.57, 47.63, 47.7, 47.9, 49.3, 73.8, 73.9, 74.0, 74.2, 89.1, 89.5, 98.2, 98.3, 98.8, 107.28, 107.32, 107.4, 107.6, 109.5, 110.7, 148.1, 148.2, 150.11, 150.14, 152.0, 153.0; **IR** (ef) 3180 (br), 2962, 2923, 2878, 1616, 1455, 1371, 1204, 1107, 1004 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 445 (M + H, 34), 444 (M, 72), 389 (36), 348 (34), 347 (16), 292 (10), 111 (21), 99 (49), 43 (100); **FAB-HRMS** Calcd. for $C_{26}H_{36}O_6$: 444.2512. Found: 444.2513.

6.4.21 (–)-Xyloketal F [(–)-6][3]

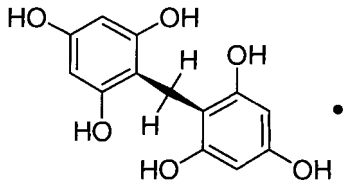


(–)-**6**

To a mixture of synthetic (–)-xyloketal B [(–)-**2**] (70 mg, 0.20 mmol) and paraformaldehyde (10 mg, 0.33 mmol) in dichloromethane (3 mL) was added pyridinium *p*-toluenesulfonate (52 mg, 0.21 mmol) and the resultant mixture was allowed to stir at room temperature for 23 h. The reaction mixture was then diluted with dichloromethane (20 mL), was washed with brine (3 × 5 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by flash chromatography using dichloromethane:ether (19:1) as the eluant afforded the *title compound* (–)-**6** (60 mg, 84%) as a white solid. $\mathbf{R}_f$ = 0.45, dichloromethane:ether (19:1); **M.p.** 158-159 °C, chloroform (lit.[3] 160-162 °C, ethyl acetate:petroleum ether); $[\alpha]_D^{20}$ = – 42.3 (*c* 0.57,

methanol) [lit.[3] $[\alpha]_D^{20}$ = – 50.6 (*c* 0.2, methanol)]; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.02 (d, *J* = 6.5 Hz, 6H, *Me*-11$_\beta$), 1.04 (d, *J* = 6.6 Hz, 6H, *Me*-11'$_\beta$), 1.48 (s, 6H, *Me*-10$_\beta$), 1.58 (s, 6H, *Me*-10'$_\beta$), 1.87 (dd, *J* = 11.0, 6.6 Hz, 2H, *H*-6$_\beta$), 1.91 (dd, *J* = 11.0, 6.5 Hz, 2H, *H*-6'$_\beta$), 2.06 (m, 2H, *H*-5$_\alpha$ *or H*-5'$_\alpha$), 2.12 (m, 2H, *H*-5$_\alpha$ *or H*-5'$_\alpha$), 2.66 (dd, *J* = 17.7, 6.6 Hz, 2H, *H*-7'), 2.71 (dd, *J* = 17.7, 6.5 Hz, 2H, *H*-7), 2.83 (apparent d, *J* = 17.6 Hz, 2H, *H*-7'), 2.87 (apparent d, *J* = 17.5 Hz, 2H, *H*-7), 3.51 (apparent t, *J* = 8.5 Hz, 2H, *H*-4), 3.61 (apparent t, *J* = 8.6 Hz, 2H, *H*-4'), 3.73 (s, 2H, *H*-14), 4.15 (apparent t, *J* = 8.4 Hz, 2H, *H*-4), 4.30 (apparent t, *J* = 8.4 Hz, 2H, *H*-4'), 8.44 (s, 2H, O*H*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 15.78 (*C*-11'), 15.80 (*C*-11), 17.1 (*C*-14), 18.8 (*C*-7' *or C*-7), 19.1 (*C*-7' *or C*-7), 22.2 (*C*-10'), 22.8 (*C*-10), 35.1 (*C*-5), 35.2 (*C*-5'), 47.3 (*C*-6' *or C*-6), 47.4 (*C*-6' *or C*-6), 73.9 (*C*-4), 74.4 (*C*-4'), 97.9 (*C*-8'), 100.0 (*C*-8), 106.0 (*C*-13), 107.4 (*C*-2), 109.2 (*C*-2'), 148.0 (*C*-9'), 150.1 (*C*-9), 152.5 (*C*-12); **IR** (ef) 3353, 2957, 2933, 2888, 2851, 1615, 1460, 1382, 1340, 1205, 1115, 1078, 1004 cm^{-1}; **MS** (MALDI-TOF) *m/z* (rel. intensity) 744 (M + K, 8), 727 (M + Na, 26), 704 (M, 11), 608 (62), 509 (100), 412 (83), 360 (45), 317 (49); **FAB-HRMS** Calcd. for $C_{41}H_{52}O_{10}$: 704.3560. Found: 704.3544.

6.4.22 *bis*-(2,4,6-Trihydroxyphenyl)methane Monohydrate (240)[135,136]

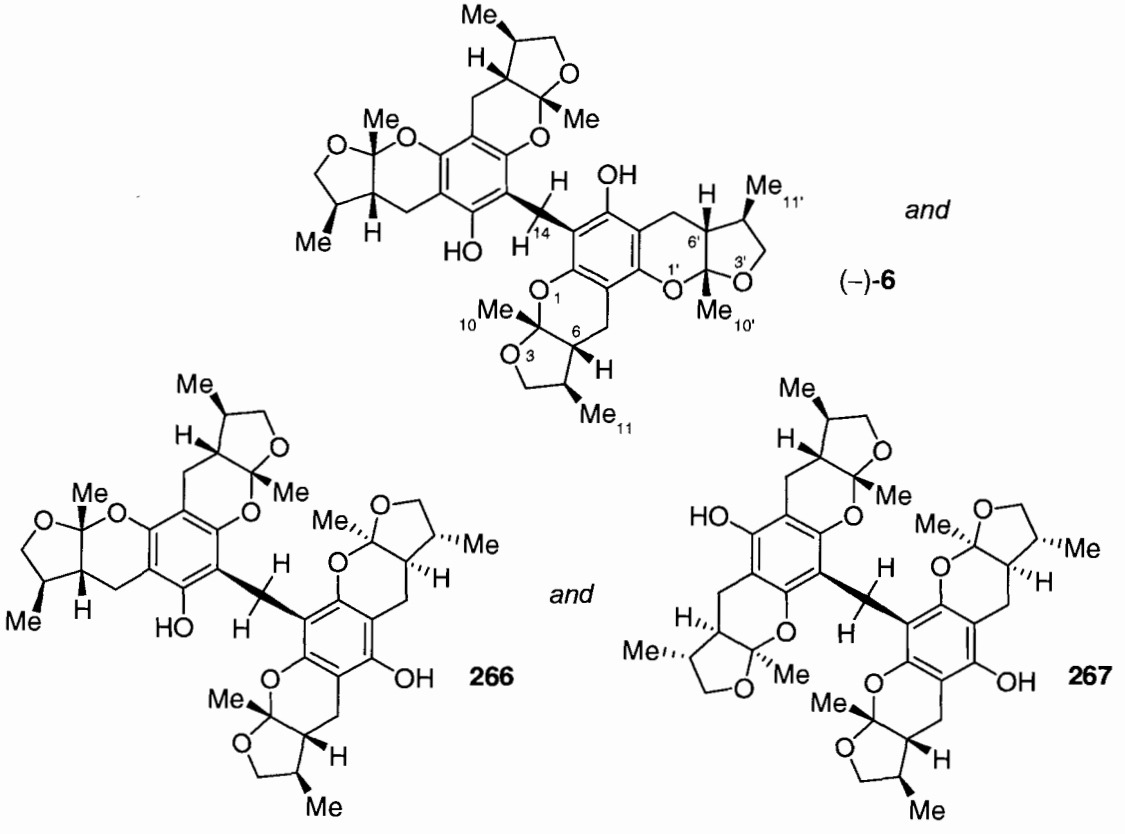


240

To a solution of phloroglucinol (**14**) (1.26 g, 10.0 mmol) and concentrated hydrochloric acid (5 mL) in water (200 mL) at 0 °C was added an aqueous solution of formaldehyde (0.40 mL, 37% w/w, 4.9 mmol) and the resultant mixture was stirred at 4 °C for 16 h. The reaction product was collected *via* vacuum filtration, washed with ice

cold water (3 × 15 mL) and dried *in vacuo*. Purification by flash chromatography using ether as the eluant afforded the *title compound* **240** (474 mg, 34%) as a beige solid. $\mathbf{R}_f$ = 0.25, ether; **M.p.** 218 °C (dec.), ether [lit.[135] 230 °C (dec.) for the dihydrate]; **^{1}H NMR** [500 MHz, $(CD_3)_2CO$] δ 3.25 (s, 2H, H_2O), 3.69 (s, 2H, CH_2), 6.00 (s, 4H, Ar*H*), 8.08 (s, 2H, 4-O*H*), 9.02 (s, 4H, 2-O*H and* 6-O*H*); **^{13}C NMR** [101 MHz, $(CD_3)_2CO$] δ 18.0, 97.4, 107.6, 157.5, 159.0; **IR** (ef) 3209 (br), 1627, 1521, 1479, 1146, 1076, 1005 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 223 (5), 167 (6), 140 (7), 139 (6), 127 (34), 126 (25), 59 (18), 43 (100).

6.4.23 (–)-Xyloketal F [(–)-6] and the Regioisomers (266) and (267)



To a suspension of the hexaphenol **240** (31 mg, 0.15 mmol, 1 equiv), the alcohol (4*R*)-**226** [prepared from the corresponding ester (4*R*)-**206** (191 mg, 1.22 mmol, 8 equiv)]

and anhydrous magnesium sulfate (0.50 g) in ether (5 mL) at 0 °C was added boron trifluoride diethyl etherate (25 μL, 0.20 mmol, 1.3 equiv). The resultant mixture was allowed to warm to room temperature over 75 min. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 5 mL). The combined filtrates were washed with water (3 × 5 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by flash chromatography using dichloromethane:ether (19:1) as the eluant afforded an inseparable mixture (10:7:3) of the *title compounds* (–)-**6**, **266** and **267** (74 mg, 71%) as a solid white foam.

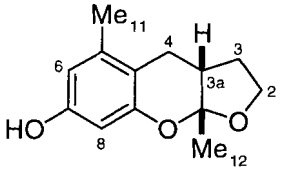
To a solution of this mixture of products (6.9 mg, 0.098 mmol) in deuterated chloroform (0.75 mL) at 23 °C was added *p*-toluenesulfonic acid monohydrate (one crystal). The resultant mixture was then monitored by ^{1}H NMR spectroscopy (500 MHz) at two-hour intervals. After 18 h, the ^{1}H NMR spectrum indicated quantitative conversion to the *title compound* (–)-**6**.

Title compounds (–)-**6**, **266** and **267** (10:7:3): $\mathbf{R}_f$ = 0.45, dichloromethane:ether (19:1); **M.p.** 135-141 °C, dichloromethane:ether; $[\alpha]_D^{20}$ = – 17 (*c* 0.57, methanol); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 0.80 (d, *J* = 5.8 Hz, 3H, *Me*-11), 0.83 (d, *J* = 7.4 Hz, 3H, *Me*-11), 0.86 (d, *J* = 7.2 Hz, 3H, *Me*-11), 1.01 (d, *J* = 6.2 Hz, 6H, *Me*-11), 1.04 (d, *J* = 6.6 Hz, 6H, *Me*-11), 1.44 (s, 3H, *Me*-10), 1.48 (s, 6H, *Me*-10 of (–)-**6**), 1.56 (s, 3H, *Me*-10), 1.58 (s, 6H, *Me*-10 of (–)-**6**), 1.63 (s, 3H, *Me*-10), 1.67 (s, 3H, *Me*-10), 1.89 (m, 4H, *H*-6), 2.08 (m, 4H, *H*-5), 2.50 (m, 4H, *H*-7 of **266** *or* **267**), 2.68 (m, 4H, *H*-7), 2.85 (m, 4H, *H*-7), 3.51 (m, 2H, *H*-4), 3.60 (m, 2H, *H*-4), 3.73 (s, 2H, *H*-14 of (–)-**6**), 3.74 (s, 2H, *H*-14 of **266**), 3.76 (s, 2H, *H*-14 of **267**), 4.14 (m, 2H, *H*-4), 4.30 (m, 2H, *H*-4), 8.34 (s, 1H, O*H* of **266**), 8.36 (s, 1H, O*H* of **266**), 8.42 (s, 2H, O*H* of **267**), 8.44 (s, 2H, O*H* of (–)-**6**); **^{13}C**

NMR (126 MHz, $CDCl_3$) δ 15.5, 15.7, 15.77, 15.79, 15.89, 15.91, 16.0, 17.06, 17.13, 17.7, 18.1, 18.5, 18.76, 18.79, 18.8, 19.1, 19.3, 22.1, 22.17, 22.24, 22.5, 22.6, 22.8, 22.86, 22.94, 24.2, 34.9, 35.07, 35.14, 35.23, 35.26, 35.32, 35.33, 35.4, 35.5, 47.3, 47.4, 47.45, 47.48, 73.92, 73.93, 73.94, 73.98, 74.41, 74.43, 74.46, 74.5, 97.8, 98.8, 100.0, 100.1, 106.00, 106.03, 107.2, 107.3, 107.38, 107.42, 107.6, 109.1, 109.17, 109.24, 147.96, 147.99, 148.0, 148.1, 149.7, 150.0, 151.0, 152.1, 152.2, 152.3, 152.4; **IR** (ef) 3353, 2957, 2933, 2888, 2851, 1615, 1460, 1382, 1340, 1205, 1115, 1078, 1004 cm^{-1}; **MS** (MALDI-TOF) *m/z* (rel. intensity) 744 (M + K, 29), 727 (M + Na, 35), 703 (M, 15), 608 (87), 509 (100), 412 (65), 360 (99), 317 (16); **FAB-HRMS** Calcd. for $C_{41}H_{52}O_{10}$: 704.3560. Found: 704.3550.

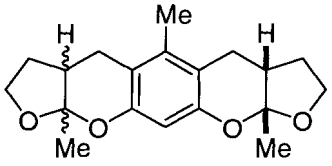
6.5 Experimental Concerning Chapter Five

6.5.1 (±)-10-Noralboatrin [(±)-271] and the (±)-*bis*-Adducts (272), [(±)-273], [(±)-274] and [(±)-275]



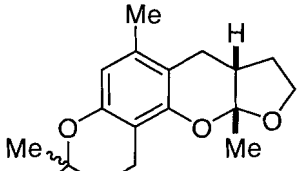
(±)-**271**

and



(±)-**272/273**

and



(±)-**274/275**

Method A: To a suspension of orcinol (**53**) (185 mg, 1.49 mmol, 1 equiv), the alcohol **168** [prepared from the corresponding ester **167** (267 mg, 1.88 mmol, 1.3 equiv)] and anhydrous magnesium sulfate (1.01 g) in ether (15 mL) at 0 °C was added boron trifluoride diethyl etherate (190 μL, 1.51 mmol, 1 equiv). The resultant mixture was

allowed to warm to room temperature over 28 h in the dark. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 10 mL). The combined filtrates were washed with water (3 × 10 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by flash chromatography using dichloromethane:ether (19:1) as the eluant afforded a mixture (3:3:1:1) of the *title compounds* **272**, (±)-**273**, (±)-**274** and (±)-**275** (75 mg, 25%) as a colourless oil and the *title compound* (±)-**271** (102 mg, 31%) as a solid white foam.

Method B: To a suspension of orcinol (**53**) (237 mg, 1.91 mmol, 1 equiv), a solution of the alcohol **168** in ether [(4.0 mL, 2.0 mmol, 1.05 equiv) prepared from the corresponding ester **167** (711 mg, 5.00 mmol) in ether (10.0 mL)] and anhydrous magnesium sulfate (1.02 g) in ether (10 mL) at 0 °C was added boron trifluoride diethyl etherate (240 μL, 1.91 mmol, 1 equiv). The resultant mixture was allowed to warm to room temperature over 24 h in the dark. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 10 mL). The combined filtrates were washed with water (3 × 10 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by flash chromatography using dichloromethane:ether (9:1) as the eluant afforded a mixture (3:3:1:1) of the *title compounds* **272**, (±)-**273**, (±)-**274** and (±)-**275** (25 mg, 8%) as a colourless oil, the *title compound* (±)-**271** [141 mg, 34% (75% brsm)] as a solid white foam and unreacted orcinol (**53**) (131 mg).

Method C: To a suspension of orcinol (**53**) (554 mg, 4.47 mmol, 1 equiv), a solution of the alcohol **168** in ether [(3.0 mL, 1.5 mmol, 0.3 equiv) prepared from the corresponding ester **167** (711 mg, 5.00 mmol) in ether (10.0 mL)] and anhydrous magnesium sulfate (1.04 g) in ether (11 mL) at 0 °C was added boron trifluoride diethyl

etherate (190 μL, 1.51 mmol, 0.3 equiv). The resultant mixture was allowed to warm to room temperature over 24 h in the dark. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 10 mL). The combined filtrates were washed with water (3 × 10 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by flash chromatography using dichloromethane:ether (9:1) as the eluant, afforded the *title compound* (±)-**271** (120 mg, 36%) as a solid white foam.

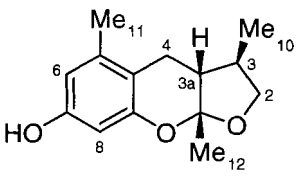
Method D: To a suspension of orcinol (**53**) (186 mg, 1.50 mmol, 1 equiv), a solution of the alcohol **168** in ether [(2.0 mL, 1.6 mmol, 1.07 equiv) prepared from the corresponding ester **167** (1.14 g, 8.03 mmol) in ether (10.0 mL)] and anhydrous magnesium sulfate (1.02 g) in ether (10 mL) at 0 °C was added boron trifluoride diethyl etherate (63 μL, 0.50 mmol, 0.3 equiv). The resultant mixture was allowed to warm to room temperature over 45 h in the dark. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 10 mL). The combined filtrates were washed with water (3 × 10 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by flash chromatography using dichloromethane:ether (9:1) as the eluant afforded a mixture (3:3:1:1) of the *title compounds* **272**, (±)-**273**, (±)-**274** and (±)-**275** (85 mg, 34%) as a colourless oil, the *title compound* (±)-**271** [159 mg, 48% (72% brsm)] as a solid white foam and unreacted orcinol (**53**) (62 mg).

Title compound (±)-**271**: $\mathbf{R}_f$ = 0.29, dichloromethane:ether (9:1); **M.p.** 148-149 °C, dichloromethane:ether; ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 1.54 (s, 3H, *Me*-12), 1.80 (m, 1H, *H*-3$_\alpha$), 2.05 (m, 1H, *H*-3$_\beta$), 2.17 (s, 3H, *Me*-11), 2.46 (m, 1H, *H*-3a$_\beta$), 2.74 (m, 2H, *H*-4), 3.94 (apparent q, J = 8.2 Hz, 1H, *H*-2$_\beta$), 4.04 (td, J = 8.3, 3.2 Hz, 1H, *H*-2$_\alpha$), 5.71 (broad s, 1H, O*H*), 6.32 (d, J = 2.5 Hz, 1H, *H*-6), 6.38 (d, J = 2.5 Hz, 1H, *H*-8);

Observed nOe contacts *Me*-12 to *H*-3a$_\beta$, *Me*-12 to *H*-8, *Me*-11 to *H*-4, *Me*-11 to *H*-6, *H*-3a$_\beta$ to *H*-3$_\beta$, *H*-3$_\beta$ to *H*-2$_\beta$; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 19.3 (*Me*-11), 22.7 (*Me*-12), 23.0 (*C*-4), 29.0 (*C*-3), 40.8 (*C*-3a), 66.7 (*C*-2), 101.7 (*C*-8), 106.5, 109.6, 109.9 (*C*-6), 138.2, 153.8, 155.0; **IR** (ef) 3369 (br), 2981, 2943, 2897, 2848, 1620, 1600, 1494, 1467, 1382, 1334, 1145, 1109, 1012 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 221 (M + H, 27), 220 (M, 53), 203 (100), 179 (79), 97 (12), 43 (64); **Anal.** Calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.78; H, 7.52.

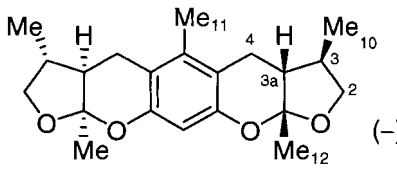
Title compounds **272**, (±)-**273**, (±)-**274** and (±)-**275** (3:3:1:1): $\mathbf{R_f}$ = 0.45, dichloromethane:ether (9:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.486, (s, 6H, *Me*-12), 1.490 (s, 6H, *Me*-12), 1.51 (s, 6H, *Me*-12), 1.80 (m, 2H, *H*-3), 2.02 (m, 2H, *H*-3), 2.08, (s, 3H, *Me*-11), 2.14 (s, 3H, *Me*-11), 2.19 (s, 3H, *Me*-11), 2.41 (m, 2H, *H*-3a), 2.71 (apparent d, J = 5.9 Hz, 4H, *H*-4), 2.74 (apparent d, J = 9.0 Hz, 4H, *H*-4), 2.78 (apparent d, J = 4.3 Hz, 4H, *H*-4), 2.91 (apparent d, J = 17.3 Hz, 4H, *H*-4), 3.92 (m, 2H, *H*-2), 4.02 (m, 2H, *H*-2), 6.02 (s, 1H, Ar*H*), 6.24 (d, J = 2.9 Hz, 1H, Ar*H*), 6.25 (d, J = 2.1 Hz, 1H, Ar*H*), 6.31 (s, 1H, Ar*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 14.6, 20.0, 20.3, 21.1, 22.2, 22.3, 22.6, 22.9, 23.3, 23.6, 23.8, 28.8, 29.0, 29.1, 40.0, 40.7, 66.5, 66.6, 102.9, 105.7, 105.8, 106.1, 107.9, 109.6, 110.4, 110.07, 110.14, 110.3, 135.17, 135.23, 137.5, 152.2, 152.3, 153.8, 154.4; **IR** (ef) 2980, 2929, 2895, 2845, 1608, 1591, 1471, 1381, 1326, 1109, 1006 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 330 (M + MeOH – H_2O, 11), 317 (M + H, 45), 329 (49), 316 (M, 49), 299 (15), 275 (100), 97 (7), 43 (83); **Anal.** Calcd. for $C_{19}H_{24}O_4$: C, 72.13; H, 7.65. Found: C, 72.22; H, 7.73.

6.5.2 (+)-Alboatrin [(+)-48] and the (–)-*bis*-Adduct [(–)-276][11,12,13,14]



(+)-**48**

and



(–)-**276**

To a suspension of orcinol (**53**) (118 mg, 0.95 mmol, 1 equiv), a solution of the alcohol (4*R*)-**226** in ether [(1.0 mL, 1.0 mmol, 1.05 equiv) prepared from the corresponding ester (4*R*)-**206** (1.57 g, 10.0 mmol) in ether (10.0 mL)] and anhydrous magnesium sulfate (0.75 g) in ether (9 mL) at 0 °C was added boron trifluoride diethyl etherate (40 μL, 0.32 mmol, 0.34 equiv). The resultant mixture was allowed to warm to room temperature over 48 h in the dark. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 10 mL). The combined filtrates were washed with water (3 × 10 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by flash chromatography using dichloromethane:ether (9:1) as the eluant afforded the *title compound* (–)-**276** (24 mg, 14%) (that was contaminated with a trace amount of isomeric by-products) as a solid white foam, the *title compound* (+)-**48** [79 mg, 36% (78% brsm)] as a solid yellow foam and unreacted orcinol (**53**) (64 mg).

Title compound (+)-**48**: This compound was recrystallized from ether:petroleum ether (1:1) on slow evaporation of the solvent to afford colourless prisms. $\mathbf{R}_f$ = 0.29, dichloromethane:ether (9:1); **M.p.** 145-147 °C, ether:petroleum ether (lit.[11] 146-149 °C); $[\alpha]_D^{20}$ = + 5.5 (*c* 0.58, chloroform) [lit.[11] $[\alpha]_D^{22.5}$ = + 8.8 (*c* 0.5, chloroform)]; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.05 (d, *J* = 6.6 Hz, 3H, Me-10$_\beta$), 1.52 (s, 3H, *Me*-12$_\beta$), 1.94 (ddd, *J* = 11.0, 5.7, 2.3 Hz, 1H, *H*-3a$_\beta$), 2.12 (m, 1H, *H*-3$_\alpha$), 2.19 (s, 3H, *Me*-11), 2.68 (dd, *J* = 17.0, 2.1 Hz, 1H, *H*-4), 2.70 (dd, *J* = 17.0, 5.6 Hz, 1H, *H*-4), 3.51 (apparent t, *J* = 8.6 Hz,

1H, *H*-2$_\beta$), 4.17 (apparent t, J = 8.6 Hz, 1H, *H*-2$_\alpha$), 4.91 (s, 1H, O*H*), 6.27 (d, J = 2.2 Hz, 1H, *H*-8), 6.29 (d, J = 2.3 Hz, 1H, *H*-6); **Observed nOe contacts** *Me*-12 to *H*-3a$_\beta$, *Me*-12 to *H*-8, *Me*-12 to *H*-2$_\beta$, *Me*-11 to *H*-4, *Me*-11 to *H*-6, *Me*-10 to *H*-2$_\beta$, *Me*-10 to *H*-3a$_\beta$; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 15.9, 19.4, 21.5, 22.9, 35.4, 48.2, 73.9, 101.7, 107.2, 109.5, 109.7, 138.2, 153.7, 154.8; **IR** (ef) 3379 (broad), 2955, 1622, 1599, 1495, 1461, 1383, 1336, 1149, 1118, 1003 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 235 (M + H, 100), 217 (13), 179 (82), 137 (11), 111 (63), 99 (9), 43 (15); **Anal.** Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.78; H, 7.96.

Title compound (–)-**276**: This compound was recrystallized from ether:petroleum ether (1:1) on slow evaporation of the solvent to afford colourless blocks. $\mathbf{R_f}$ = 0.50, dichloromethane:ether (9:1); **M.p.** 189-190 °C, ether:petroleum ether; $[\alpha]_D^{20}$ = – 11.3 (*c* 0.84, chloroform); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.05 (d, J = 6.6 Hz, 6H, Me-10$_\beta$), 1.49 (s, 6H, *Me*-12$_\beta$), 1.91 (apparent dt, J = 11.0, 4.3 Hz, 2H, *H*-3a$_\beta$), 2.13 (s, 3H, *Me*-11), 2.14 (m, 2H, *H*-3$_\alpha$), 2.73 (apparent d, J = 3.4 Hz, 4H, *H*-4), 3.50 (apparent t, J = 8.5 Hz, 2H, *H*-2$_\beta$), 4.17 (apparent t, J = 8.4 Hz, 2H, *H*-2$_\alpha$), 6.25 (s, 1H, Ar*H*); **Observed nOe contacts** *H*-3a$_\beta$ to *Me*-10, *H*-3a$_\beta$ to *Me*-12$_\beta$, *H*-3a$_\beta$ to *H*-4, *H*-3a$_\beta$ to *H*-2$_\beta$; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 14.8, 16.0, 22.4, 22.7, 35.5, 48.3, 73.9, 103.2, 106.7, 110.0, 135.1, 152.3; **IR** (ef) 2955, 2936, 2891, 1610, 1590, 1474, 1381, 1327, 1115, 1005 cm^{-1}; **MS** (CI) *m/z* (rel. intensity) 345 (M + H, 86), 247 (100), 235 (26), 111 (61), 43 (21); **Anal.** Calcd. for $C_{21}H_{28}O_4$: C, 73.23; H, 8.19. Found: C, 73.55; H, 8.25.

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